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Heart failure—does it matter whether LVEF is reduced?

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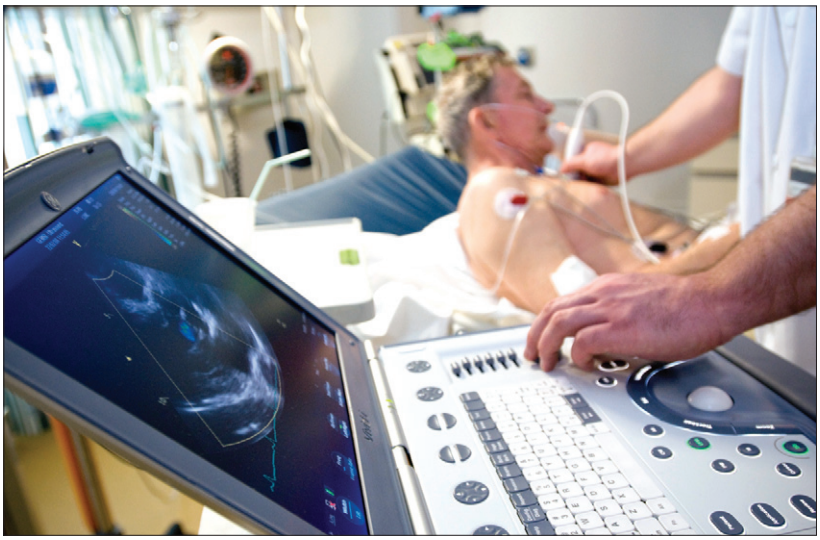
Heart failure is the result of many diseases, often acting in concert. Despite great advances in the management of some phenotypes, particularly those associated with a reduced left ventricular ejection fraction (LVEF) or valve disease, progress has been less certain for others, including those with preserved (or normal) LVEF.[1–3] The pathophysiology of heart failure with preserved ejection fraction is highly heterogeneous, ranging from restriction, through impaired diastolic relaxation, long-axis left ventricular systolic dysfunction, to predominant right ventricular dysfunction. All can coexist and vary in severity over time and with cardiovascular stress. At rest, echocardiography can be normal.[4]

Cohort studies suggest that patients with heart failure with preserved and reduced ejection fraction have similar prognoses, yet randomised trials consistently show that event rates are lower in those with preserved ejection fraction.[1–3] This finding might reflect both the exclusion from trials of patients with serious comorbidities and the inclusion of patients without objective evidence of heart failure. Exclusion of patients with comorbidities might be important in a proof-of-concept trial, both to increase the probability that symptoms and events are due to heart failure and because the treatment could have adverse effects on non-cardiac disease. However, patients free of serious comorbidity might be rare, explaining why trials of heart failure with preserved ejection fraction recruit slowly even though the disease is common.[1,3] Low event rates necessitate larger, longer trials. Caution is also needed in extrapolating the results of such trials to the wider population of patients with heart failure with preserved ejection fraction.

Currently, heart failure with preserved ejection fraction is predominantly a diagnosis of exclusion, which is unsatisfactory. Breathlessness, particularly in elderly people, can have many causes other than heart failure.[5] Robust, practical diagnostic criteria are needed. The desire to show that cardiac dysfunction was the probable cause of both symptoms and risk led to the adoption in the late 1980s of reduced LVEF as a key selection criterion for heart failure trials.[6] Had measurement of natriuretic peptides been widely available, they would almost certainly have taken precedence over imaging because of their simplicity, easy accessibility, low cost and operator dependency, and prognostic superiority over conventional echocardiographic measurements.[7] The great diagnostic advantage of natriuretic peptides is that they are increased in most types of heart failure; imaging is needed only to provide the probable cause.



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False-positive natriuretic peptide results probably do not exist, but interpretation of plasma concentrations needs knowledge of body mass, heart rhythm, and renal function. Cardiac dysfunction reported on imaging when plasma concentrations of natriuretic peptides are normal suggests that images were misread or at the limits of the normal range, or that treatment has been effective and prognosis is good.

If therapeutic response is dictated by the cardiac phenotype, then it makes sense to base treatment on imaging. However, if therapeutic response is dictated by the neuroendocrine adaptation to disease, which might be similar across cardiac phenotypes, then it makes sense to base treatment on blood markers of such activation. This strategy could be appropriate for angiotensin-converting-enzyme (ACE) inhibitors, angiotensin-receptor blockers (ARB), and aldosterone-receptor antagonists.

What then for angiotensin receptor neprilysin inhibitors? Neprilysin inhibitors were investigated as alternatives or adjuncts to ACE inhibitors almost 20 years ago;[8] their small and inconsistent effects in hypertension deterred large-scale investment. A trial of omapatrilat, a dual inhibitor of ACE and neprilysin, suggested that the drug might be superior to ACE inhibitors alone in patients with heart failure with reduced ejection fraction if systolic blood pressure was greater than 120 mm Hg, but there was a small increase in the risk of angioneurotic oedema, probably due to combined neprilysin and ACE inhibition,[9] that discouraged commercial development.

LCZ696 is valsartan plus a neprilysin inhibitor, which decouple after absorption. There is no current indication for neprilysin inhibition. For heart failure with reduced ejection fraction, ARBs seem effective at high doses, although whether they are as effective as ACE inhibitors is uncertain.[10,11] Inhibition of bradykinin degradation, which increases production of vasodilator prostaglandins, could be key to the efficacy of ACE inhibitors, as attested by the powerful interaction with aspirin.[12] ARBs might have less effect in heart failure with preserved ejection fraction than with reduced ejection fraction, whereas the effect of ACE inhibitors might be similar, although the data for disease with preserved ejection fraction are not robust.[1–3,13] Accordingly, LCZ696 may be safer than omapatrilat, but less effective.

The PARAMOUNT[14] study, reported in *The Lancet*, assessed 301 patients with heart failure and a preserved ejection fraction based on a clinical diagnosis of heart failure, the absence of left ventricular systolic dysfunction, and, importantly, an increased plasma concentration of NT-proBNP that provided objective evidence of cardiac dysfunction. The threshold, 400 pg/mL, could have been set lower for sinus rhythm and higher for atrial fibrillation, an alternative cause of raised NT-proBNP. ACE inhibitors were withdrawn at randomisation. The primary aim was to assess the effects of LCZ696 compared with valsartan on plasma concentrations of NT-proBNP at 12 weeks, with an extension phase to 36 weeks. LCZ696 caused a greater reduction in NT-proBNP compared with valsartan at 12 weeks (ratio LCZ696/valsartan 0·77, 95% CI 0·64–0·92, p=0·005), but the effect was lost by 36 weeks, which could reflect a difference in rate of onset but similar overall efficacy for the interventions. However, symptoms improved and left atrial volume fell more with LCZ696 than with valsartan. The effect of LCZ696 on NT-proBNP appeared greater if systolic blood pressure was higher than 140 mm Hg or if the patient was diabetic.

The positive signals from PARAMOUNT will surely trigger a definitive trial. However, what will the comparator be? Valsartan, a drug not known to be effective for heart failure with preserved ejection fraction? This comparison would show whether there was an advantage to adding a neprilysin inhibitor, but would not provide evidence that valsartan was useful in patients with heart failure with preserved ejection fraction. ACE inhibitors, which seem to have some effect in disease with preserved ejection fraction?[2,13] An increase in diuretic dose—perhaps the best method of improving symptoms in a congested patient? Or simply placebo? A placebo-controlled design would be the easiest to interpret, but could be confounded by the widespread use of renin–angiotensin–aldosterone system antagonists in patients with heart failure with preserved ejection fraction, often for problems such as hypertension and peripheral oedema. Such background treatment might not easily be withdrawn, rendering enrolment difficult.

Another trial, in patients with heart failure with reduced ejection fraction and raised plasma natriuretic peptides,[15] will show whether LCZ696 is superior to

enalapril. If trials in disease with both preserved and reduced ejection fraction are positive (and use the same comparator), cardiac phenotype could become less important than plasma concentration of natriuretic peptides for management of heart failure. However, if LCZ696 proves ineffective in heart failure with preserved ejection fraction, then more attention should be paid to targeting of comorbid disease, to the individual phenotypes, to the causes underlying disease with preserved ejection fraction, or to the ageing process itself, which could be the ultimate determinant of prognosis in these patients.

*John G F Cleland, Andrew L Clark
Department of Cardiology, Castle Hill Hospital, Hull York Medical School, University of Hull, Kingston-upon-Hull HU6 5JQ, UK
j.g.cleland@hull.ac.uk

JGFC has received honoraria from Novartis related to heart failure research; and was chief investigator for the PEP-CHF study comparing perindopril with placebo, and an investigator in I-PRESERVE and CHARM. ALC declares that he has no conflicts of interest.

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The battle against stent thrombosis—to protect and to serve

I have done the state some service, and they know't.

Othello by William Shakespeare

Late on Sunday, Sept 3, 2006, Edoardo Camenzind took the podium at the end of a European Society of Cardiology (ESC) session in Barcelona, Spain, to present a meta-analysis of data from the pivotal drug-eluting stent approval trials with long-term follow-up. The main finding was that first generation drug-eluting stents were associated with higher rates of death and myocardial infarction than bare-metal stents—an effect most pronounced with the Cypher sirolimus-eluting stent (C-SES).[1] A similar risk of adverse mortality was detected in a second meta-analysis presented in the same session,[2] and in the aftermath of heated debate—the repercussions of which were felt far beyond the confines of the meeting—the controversy came to be known as the "ESC Firestorm".

The proposed mechanism for increased risk of death or myocardial infarction with drug-eluting stents was an increased rate of late stent thrombosis,[3] mediated at a pathophysiological level by impaired healing of the stented arterial segment.[4] The fallout from this controversy had two important consequences: an abrupt fall in the use of drug-eluting stent therapy in many jurisdictions,[5] and a non-evidence based recommendation for prolongation of dual antiplatelet therapy by guideline-writing authorities.[6]

Born from the embers of that firestorm, the Patient Related OuTcomes with Endeavor versus Cypher


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The angiotensin receptor neprilysin inhibitor LCZ696 in heart failure with preserved ejection fraction: a phase 2 double-blind randomised controlled trial

*Scott D Solomon, Michael Zile, Burkert Pieske, Adriaan Voors, Amil Shah, Elisabeth Kraigher-Krainer, Victor Shi, Toni Bransford, Madoka Takeuchi, Jianjian Gong, Martin Lefkowitz, Milton Packer, John J V McMurray, for the Prospective comparison of ARNI with ARB on Management Of heart failUre with preserved ejectioN fracTion (PARAMOUNT) Investigators**

Summary

Background Heart failure with preserved ejection fraction is associated with substantial morbidity and mortality, but effective treatments are lacking. We assessed the efficacy and safety of LCZ696, a first-in-class angiotensin receptor neprilysin inhibitor (ARNI), in patients with this disorder.

Methods PARAMOUNT was a phase 2, randomised, parallel-group, double-blind multicentre trial in patients with New York Heart Association (NYHA) class II–III heart failure, left ventricular ejection fraction 45% or higher, and NT-proBNP greater than 400 pg/mL. Participants were randomly assigned (1:1) by central interactive voice response system to LCZ696 titrated to 200 mg twice daily or valsartan titrated to 160 mg twice daily, and treated for 36 weeks. Investigators and participants were masked to treatment assignment. The primary endpoint was change in NT-proBNP, a marker of left ventricular wall stress, from baseline to 12 weeks; analysis included all patients randomly assigned to treatment groups who had a baseline and at least one postbaseline assessment. This trial is registered at Clinicaltrials.gov, number NCT00887588.

Findings 149 patients were randomly assigned to LCZ696 and 152 to valsartan; 134 in the LCZ696 group and 132 in the valsartan group were included in analysis of the primary endpoint. NT-proBNP was significantly reduced at 12 weeks in the LCZ696 group compared with the valsartan group (LCZ696: baseline, 783 pg/mL [95% CI 670–914], 12 weeks, 605 pg/mL [512–714]; valsartan: baseline, 862 pg/mL [733–1012], 12 weeks, 835 [710–981]; ratio LCZ696/valsartan, 0·77, 95% CI 0·64–0·92, p=0·005). LCZ696 was well tolerated with adverse effects similar to those of valsartan; 22 patients (15%) on LCZ696 and 30 (20%) on valsartan had one or more serious adverse event.

Interpretation In patients with heart failure with preserved ejection fraction, LCZ696 reduced NT-proBNP to a greater extent than did valsartan at 12 weeks and was well tolerated. Whether these effects would translate into improved outcomes needs to be tested prospectively.

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*Investigators listed in appendix

Cardiovascular Division, Brigham and Women's Hospital, Boston, MA, USA (Prof S D Solomon MD, A Shah MD, E Kraigher-Krainer MD, M Takeuchi MS); **Medical University of South Carolina, Charleston, SC, USA** (Prof M Zile MD); **University of Graz, Graz, Austria** (Prof B Pieske MD); **University of Groningen, Groningen, Netherlands** (Prof A Voors MD); **Novartis Pharmaceuticals, East Hanover, NJ, USA** (V Shi MD, T Bransford MD, J Gong PhD, M Lefkowitz MD); **University of Texas Southwestern, Dallas, TX, USA** (Prof M Packer MD); **and University of Glasgow, Glasgow, UK** (Prof J J V McMurray MD)

Correspondence to:
Dr Scott D Solomon, Cardiovascular Division, Brigham and Women's Hospital, Boston, MA 02115, USA
ssolomon@rics.bwh.harvard.edu

See Online for appendix

Introduction

Heart failure with preserved ejection fraction accounts for up to half of heart failure cases,[1,2] is associated with substantial morbidity and mortality,[3–5] and to date no treatments have improved clinical outcomes.[6] Pathophysiological mechanisms that have been implicated in the disorder include abnormal diastolic function with resultant increased ventricular filling pressures,[7,8] increased vascular stiffness, and subtle abnormalities of systolic function despite relatively preserved ejection fraction.[9–12] These individuals also have an impaired natriuretic and renal endocrine response to acute volume expansion early in the development of this syndrome.[13] Several pharmacological treatments have been tested in clinical trials, including β blockers,[14] calcium-channel blockers,[15] angiotensin-converting enzyme (ACE) inhibitors,[16] and angiotensin receptor blockers (ARBs),[17–19] with none showing definitive benefit.

LCZ696 is a first-in-class angiotensin receptor neprilysin inhibitor that comprises the molecular moieties of the neprilysin (neutral endopeptidase 24.11) inhibitor prodrug AHU377 and the ARB valsartan in one compound.[20] AHU377 is metabolised by enzymatic cleavage to LBQ657, the active inhibitor of neprilysin. Neprilysin degrades biologically active natriuretic peptides, including atrial natriuretic peptide (ANP), B-type natriuretic peptide (BNP), and C-type natriuretic peptide, but not the biologically inert NT-proBNP, which is not a substrate for this enzyme.[21] By augmenting the active natriuretic peptides, neprilysin inhibition increases generation of myocardial cyclic guanosine 3′5′ monophosphate, which improves myocardial relaxation and reduces hypertrophy. Natriuretic peptides also stimulate diuresis, natriuresis, and vasodilation, and might have additional antifibrotic and antisympathetic effects.[22,23] However, neprilysin also contributes to the breakdown of angiotensin,[24] which is the rationale for dual-acting compounds that both inhibit this enzyme and block the action or generation of angiotensin. One such compound, omapatrilat, which inhibited both neprilysin and ACE,[25] lowered blood

pressure more than did ACE inhibition alone.[26] However, the development of omapatrilat (and similar compounds) was discontinued because of an increased risk of angio-oedema likely caused by accumulation of bradykinin secondary to both neprilysin and ACE inhibition.[25] Because LCZ696 blocks the angiotensin receptor without inhibiting ACE, it is expected to have a lower risk of angio-oedema than omapatrilat, has shown greater blood pressure reduction in patients with hypertension compared with valsartan with similar tolerability,[27] and is currently being tested in a large outcomes trial in heart failure with reduced ejection fraction (NCT01035255).

LCZ696 might also have potential therapeutic value in heart failure with preserved ejection fraction. We therefore undertook a randomised trial comparing LCZ696 with valsartan to assess the safety and efficacy of LCZ696 in patients with this disorder.

Methods

Patients

PARAMOUNT was a randomised, double-blind, parallel-group, active controlled trial undertaken in 65 centres and 13 countries. Patients were recruited between Nov 2, 2009, and March 31, 2011, and the study ended on Jan 24, 2012. Men and women aged 40 years or older with a left ventricular ejection fraction (LVEF) of 45% or higher and a documented history of heart failure with associated signs or symptoms (dyspnoea on exertion, orthopnoea, paroxysmal dyspnoea, and peripheral oedema) were eligible. Patients were required to have NT-proBNP greater than 400 pg/mL at screening, be on diuretic therapy, and have a systolic blood pressure less than 140 mm Hg, or 160 mm Hg or less if on three or more blood pressure drugs at randomisation, have an estimated glomerular filtration rate (eGFR) of at least 30 mL/min per 1·73 m² at screening (calculated by the Modification of Diet in Renal Disease formula), and a potassium concentration of no more than 5·2 mmol/L.

Patients were excluded if they had previous LVEF less than 45% at any time, isolated right heart failure due to pulmonary disease, dyspnoea due to non-cardiac causes such as pulmonary disease, anaemia, or severe obesity, primary valvular or myocardial diseases, or coronary artery or cerebrovascular disease needing revascularisation within 3 months of screening or likely to need revascularisation during the trial. The number of patients enrolled with atrial fibrillation was limited to roughly 25% of the total. The study protocol was submitted to individual sites' institutional review boards or ethics committees and all enrolled patients provided written informed consent. A data safety monitoring committee oversaw the programme and reviewed trial data for patient safety at regular intervals.

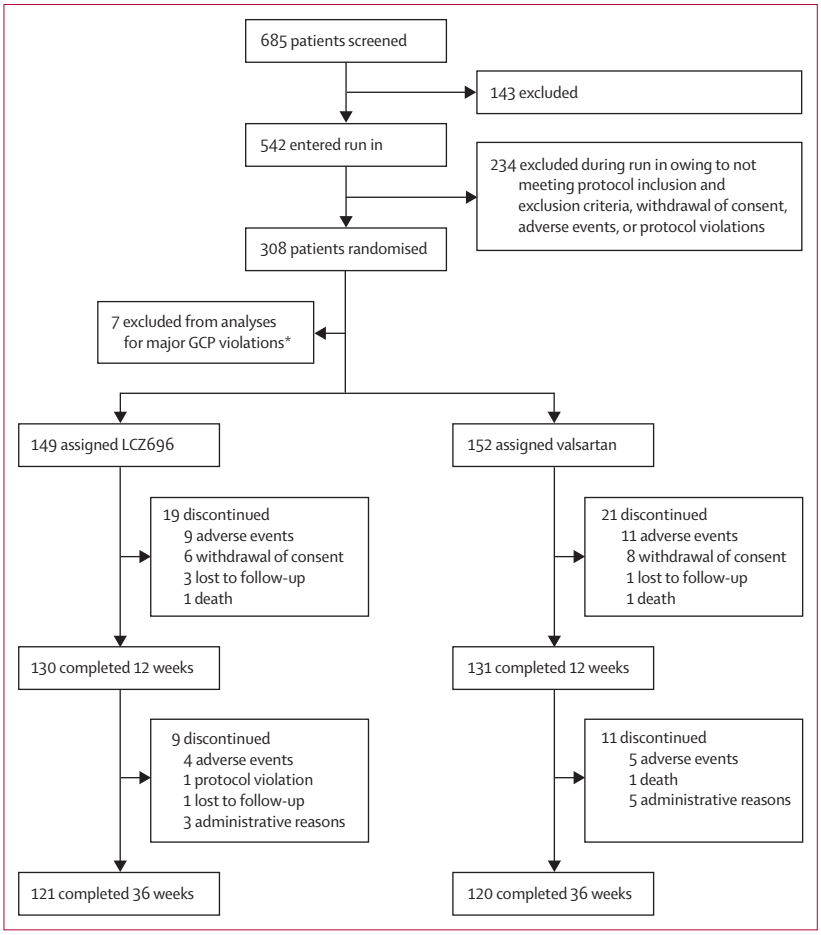

Figure 1: **Trial profile**
GCP=good clinical practice. *Three assigned to LCZ696 and four to valsartan.

Randomisation and masking

Eligible patients were enrolled into a 2-week, single-blind, placebo run-in period, during which time they continued their background treatments. ACE inhibitors and ARBs were required to be discontinued 24 h before randomisation. After 2 weeks, all patients who fulfilled the criteria for enrolment were randomly assigned (1:1) to treatment with either LCZ696 or valsartan. Treatment assignment was done with a computer-generated random sequence with a block size of four, stratified by previous use of ACE inhibitor or ARB and region. There were no constraints on the number of patients randomly assigned into either stratum. Assignment used a central interactive voice response system with randomisation codes generated by the sponsor. The system assigned a randomisation number to each patient, which linked the patient to a treatment group and specified a unique drug number for study drug to be dispensed. Placebo and active treatments were identical in appearance. Study investigators and participants were masked to treatment for the duration of the trial.

Procedures

After randomisation, patients were started on LCZ696 50 mg twice daily or valsartan 40 mg twice daily and

titrated to their final doses of LCZ696 200 mg twice daily or valsartan 160 mg twice daily over a period of 2–4 weeks. The LCZ696 doses and the corresponding valsartan doses provide similar systemic exposure to valsartan and AT1 blockade.[20,27] Background therapy was at the discretion of treating physicians. The double-dummy design continued for 36 weeks, encompassing a 12-week main study period and 24-week extension period.

The primary study endpoint was change from baseline in NT-proBNP assessed at 12 weeks. Secondary endpoints included changes in echocardiographic measures (left ventricular volumes and ejection fraction, left atrial volume, measures of diastolic function) and change in blood pressure, as well as change in New York Heart Association (NYHA) class, clinical composite assessment, and quality of life (Kansas City cardiomyopathy questionnaire; KCCQ).[28]

NT-proBNP was measured at screening, randomisation, week 4, week 12, and week 36 or at end of study or at early termination visits. Screening NT-proBNP was established by table-top device at point of care, local laboratory, or central laboratory. Assessment of NT-proBNP for efficacy was measured at a central laboratory (Quest Diagnostics, Valencia, CA, USA) with the Elecsys NT-proBNP immunoassay (Roche Diagnostics, Indianapolis, IN, USA).

Echocardiography was done at screening, randomisation, at week 12, and week 36 or at end of study or early termination visits. Analyses were done at a core laboratory (Brigham and Women's Hospital, Boston, MA, USA). Measurements were made in triplicate in accordance with the recommendations of the American Society of Echocardiography[29] and as previously described.[30]

The clinical composite assessment was based on a composite of the NYHA functional classification, patient global assessment, and major adverse clinical events.[31] Patients were classified as improved if at the endpoint visit they had improvement in NYHA functional classification or in patient global assessment (or both) but did not have a major adverse cardiovascular event. Patients were judged to be worse if at the endpoint visit they had a major adverse cardiac event during double-blind treatment or reported worsening of their NYHA class or patient global assessment.

Statistical analysis

A sample size of 290 patients randomly assigned to two groups, ensured at least 80% power to detect a 25% reduction in the ratio of the 12-week NT-proBNP over baseline NT-proBNP between the LCZ696 group and the valsartan group, using a two-sided *t* test on the logarithm of this ratio, with an α level of 0·05. In this calculation we assumed a common SD of 0·83 for the log-scale of the ratio and a dropout rate of 10%. This sample size required 132 patients completing the trial in each group.

Stata (version 11.0) was used for all analyses. We analysed the primary efficacy variable using an ANCOVA model with treatment and randomisation stratification (previous use of an ACE inhibitor or ARB, and region) as fixed factors and the baseline log-transformed NT pro-BNP as a covariate. The primary

	LCZ696 (n=149)	Valsartan (n=152)
Mean age (years)	70·9 (9·4)	71·2 (8·9)
Women	85 (57%)	85 (56%)
NYHA class		
Class I	1 (1%)	1 (1%)
Class II	120 (81%)	119 (78%)
Class III	28 (19%)	32 (21%)
Previous admission to hospital for heart failure	59 (40%)	68 (45%)
History of atrial fibrillation	60 (40%)	65 (43%)
Atrial fibrillation at screening	40 (27%)	45 (30%)
History of hypertension	142 (95%)	140 (92%)
History of diabetes	61 (41%)	53 (35%)
History of myocardial infarction	32 (21%)	30 (20%)
Mean eGFR (mL/min per 1·73 m²)	67 (19·4)	64 (21·3)
eGFR <60 mL/min per 1·73 m²	56 (38%)	69 (45%)
Median sitting SBP (mm Hg)	136 (130–145)	136 (126–145)
Median sitting DBP (mm Hg)	80 (74–85)	78 (70–84)
Mean heart rate (beats per min)	69 (12)	70 (14)
Mean BMI (kg/m²)	30·1 (5·5)	29·8 (6·1)
NT-proBNP (pg/mL)		
Median	828 (460–1341)	939 (582–1490)
Geometric mean	794 (681–925)	870 (740–1022)
Baseline treatments		
ACE inhibitors	83 (56%)	80 (53%)
ARBs	57 (38%)	62 (41%)
ACE inhibitors or ARBs	139 (93%)	141 (93%)
Diuretics	149 (100%)	152 (100%)
β blockers	117 (79%)	121 (80%)
Aldosterone antagonists	28 (19%)	35 (23%)
Baseline echocardiographic measures		
Left ventricular ejection fraction	58% (7·3)	58% (8·1)
Left ventricular ejection fraction ≥50%	113 (76%)	125 (82%)
E′ (cm/s)	7·8 (2·7)	7·3 (2·9)
E/E′	12·4 (8·1)	13·0 (7·0)
E/A	1·1 (0·54)	1·1 (0·65)
Left atrial dimension (cm)	3·7 (0·45)	3·7 (0·54)
Left atrial volume (mL)	65·6 (22·7)	67·4 (28·4)
Left atrial volume index (mL/m²)	35·2 (12·3)	36·3 (14·7)
Left ventricular end-diastolic volume (mL)	111 (26·6)	116 (33·1)
Left ventricular end-systolic volume (mL)	46·9 (15·9)	49·7 (22·0)
Left ventricular mass (g)	145 (40·5)	150 (43·8)
Left ventricular mass index (g/m²)	77·5 (20·4)	80·7 (23·8)
Relative wall thickness	0·38% (0·09)	0·38% (0·08)
Tricuspid regurgitant velocity (m/s)	2·50 (0·39)	2·55 (0·38)

Data are n (%), mean (SD), median (IQR), or geometric mean (95% CI). NYHA=New York Heart Association. eGFR=estimated glomerular filtration rate. SBP=systolic blood pressure. DBP=diastolic blood pressure. BMI=body-mass index. ACE=angiotensin-converting enzyme. ARB=angiotensin receptor blocker. E′=lateral mitral relaxation velocity. E/E′=mitral inflow to mitral relaxation velocity ratio. E/A=early to late mitral inflow velocity ratio.

	NT-proBNP (pg/mL) at 12 weeks			NT-proBNP (pg/mL) at 36 weeks		
	n	Baseline	12 weeks	n	Baseline	36 weeks
LCZ696	134	783 (670–914)	605 (512–714)	115	763 (646–901)	496 (401–613)
Valsartan	132	862 (733–1012)	835 (710–981)	116	822 (688–983)	607 (484–760)
Ratio of change (LCZ696/valsartan)	..	..	0·77 (95% CI 0·64–0·92), p=0·005	..	..	0·85 (95% CI 0·65–1·09), p=0·20

Data for NT-proBNP are geometric mean (95% CI).

Table 2: **NT-proBNP at baseline, 12 weeks, and 36 weeks and ratio of change in NT-proBNP at 12 and 36 weeks**

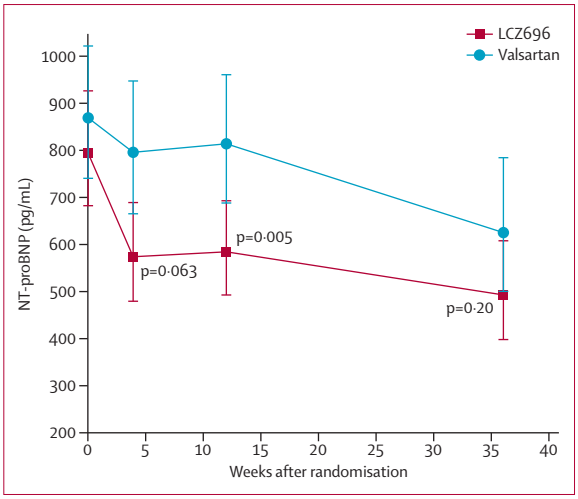

Figure 2: **NT-proBNP at 4, 12, and 36 weeks in the LCZ696 and valsartan groups**

treatment comparison was reported as the ratio of the geometric means of NT-proBNP between groups. The primary 12-week analysis was prespecified as last observation carried forward and included all patients randomly assigned to treatment groups who had a baseline and at least one postbaseline assessment. We did several additional analyses for the primary endpoint for sensitivity, including a completer-only analysis, and a multiple imputation analysis to account for patients without 12-week follow-up studies. All 36-week analyses were based on completers only. Statistical testing was done at the two-sided significance level of 0·05 and estimated geometric means for the ratios, estimated effect sizes, and their 95% CIs were calculated. We analysed all other continuous variables in ANCOVA models adjusting for baseline values, stratification variables, and treatment, and analysed categorical variables with a logistic regression model for binary variables and a Cochran-Mantel-Haenszel test for responses of more than two levels, using the randomisation stratification. Logarithmic transformation was used for biomarker data, including NT-proBNP, to address their skewed distribution. Analysis of the primary endpoint was done in prespecified subgroups.

This trial is registered at ClinicalTrials.gov, NCT00887588.

Role of the funding source

PARAMOUNT was designed jointly by the academic steering committee and the sponsor, which funded the trial. The sponsor was responsible for study management, data collection, and data analysis; all analyses were replicated by an independent statistician at the Brigham and Women's Hospital. The report was drafted by the first author and revised by all authors who have read and agree to the report as written and the decision to submit for publication. The first author had full access to and takes full responsibility for the integrity of the data.

Results

We screened 685 patients, of whom 308 were eligible for randomisation on the basis of inclusion and exclusion criteria (figure 1). Seven patients from one site were excluded before unmasking because of major data irregularities, leaving 301 valid study patients, of whom 149 were randomly assigned to LCZ696 and 152 to valsartan. Baseline characteristics were similar between treatment groups (table 1). Patients were elderly and most were female, overweight, and in NYHA functional class II. Atrial fibrillation was present in 85 (28%) patients. Mean LVEF was 58% (SD 7·7) and LVEF was 50% or greater in 238 (79%) patients. Blood pressure was well controlled (median sitting pressure 136/79 mm Hg). Baseline NT-proBNP was raised (geometric mean 830·6 pg/mL, 95% CI 744–928). All patients were on diuretic drugs at baseline and most patients had been taking an ACE inhibitor or ARB before enrolment. Echocardiographic assessment at baseline showed reduced mitral annular relaxation velocity, raised E/e′, and enlarged left atria, consistent with mild increase in cardiac filling pressures.

The primary endpoint, change in NT-proBNP from baseline to 12 weeks, was significantly different in the LCZ696 group compared with the valsartan group (ratio of change LCZ696/valsartan 0·77, 95% CI 0·64–0·92, p=0·005; table 2) with a greater reduction in the LCZ696-treated patients. Analysis of the primary endpoint in completers only (p=0·007) or with multiple imputation for missing values (p=0·01) yielded similar results. The effect of LCZ696 on NT-proBNP occurred fairly early, although an early reduction in NTpro-BNP after 4 weeks of treatment in the LCZ696 group compared with the valsartan group was not significant (p=0·063; figure 2). The reduction in NT-proBNP at 12 weeks was

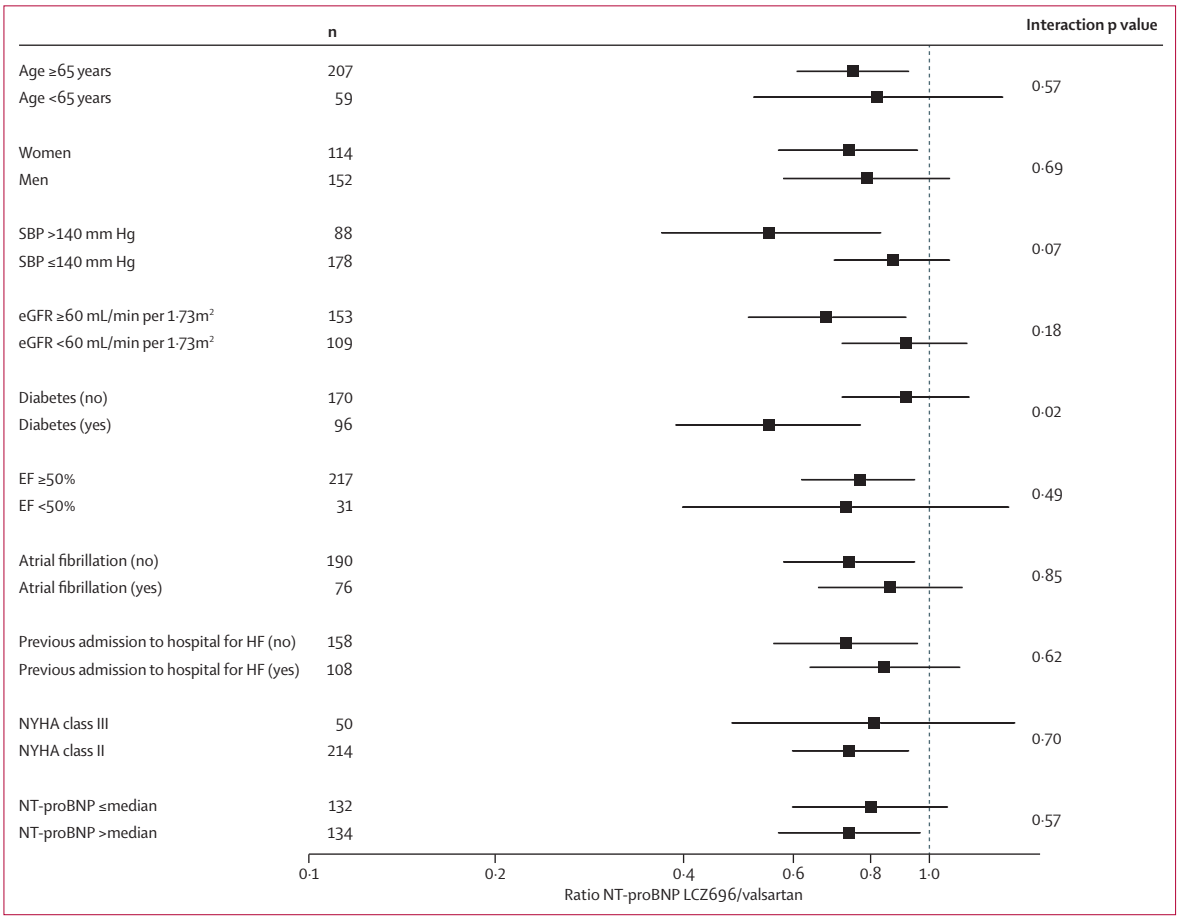

Figure 3: **Change in NT-proBNP in prespecified subgroups**
p values shown are for test for heterogeneity. SBP=systolic blood pressure. eGFR=estimated glomerular filtration rate. EF=ejection fraction. HF=heart failure. NYHA=New York Heart Association.

noted in all prespecified subgroups (figure 3). Of these subgroups, only patients with diabetes had a differentially greater reduction in NT-proBNP when treated with LCZ696 compared with patients without diabetes (interaction p=0·02).

After 12 weeks of treatment, blood pressure was reduced by 9·3 (SD 14)/4·9 (10) mm Hg in the LCZ696 group and 2·9 (17)/2·1 (11) mm Hg in the valsartan group (p=0·001 for systolic and p=0·09 for diastolic blood pressure differences). LCZ696 was associated with a greater reduction in NT-proBNP than was valsartan even after adjustment for the change in blood pressure between the two groups (p=0·01). Moreover, change in blood pressure correlated poorly with change in NT-proBNP (r=0·104, p=0·1). We measured no significant changes in left ventricular size or function, diastolic function, left ventricular mass, or tricuspid regurgitant velocity from baseline to 12 weeks between treatment groups (table 3).

Although NT-proBNP remained reduced from baseline at 36 weeks in the LCZ696 group (figure 2), the difference between treatment groups at 36 weeks was no longer significant (p=0·20; table 2). At 36 weeks, blood pressure was reduced by 7·5 (15)/5·1 (10·8) in the LCZ696 group versus 1·5 (16)/0·34 (11·5) in the valsartan group (p=0·006 for systolic and p=0·001 for diastolic blood pressure differences). Left atrial volume was reduced significantly in the LCZ696 group after 36 weeks of treatment (p=0·003), as was left atrial dimension (p=0·034). The change in left atrial size was most apparent in patients without atrial fibrillation at baseline. No other echocardiographic measures, including LVEF, ventricular volumes, or measures of diastolic function, differed between treatment groups at 36 weeks. NYHA class improvement at 12 weeks did not differ significantly between groups (p=0·11), but we noted an improvement in NYHA class at 36 weeks in the LCZ696 group compared with the valsartan group (p=0·05, figure 4). Clinical composite assessment after 12 weeks (p=0·19) and 36 weeks (p=0·17) of treatment did not differ significantly between groups (figure 4). There was no difference in KCCQ score between treatment groups at either timepoint.

Target dose was achieved in 121 (81%) patients in the LCZ696 group and in 119 (78%) in the valsartan group. The use of concomitant blood-pressure lowering drugs,

	12 weeks							36 weeks						
	LCZ696			Valsartan			p value	LCZ696			Valsartan			p value
	n	Baseline	Δ from baseline	n	Baseline	Δ from baseline		n	Baseline	Δ from baseline	n	Baseline	Δ from baseline	
Ejection fraction	114	58·2% (7·6)	1·06% (5·0)	118	58·0% (8·0)	1·04% (4·9)	0·85	94	58·3% (7·7)	2·7% (6·5)	111	58·1% (8·0)	3·07% (5·9)	0·69
Lateral mitral annular relaxation velocity (e′; cm/s)	97	7·7 (2·7)	0·57 (1·7)	106	7·2 (2·9)	0·55 (1·5)	0·56	84	7·6 (2·7)	0·55 (2·3)	96	7·3 (2·8)	0·92 (2·0)	0·40
Mitral inflow velocity to mitral annular relaxation velocity ratio (E/e′)	96	12·6 (8·4)	−1·3 (3·4)	106	13·0 (7·3)	−1·3 (4·3)	0·71	83	12·3 (5·5)	−1·3 (3·1)	95	12·7 (6·2)	−1·0 (4·7)	0·42
Early to late mitral inflow velocity ratio (E/A)	72	1·1 (0·56)	−0·09 (0·36)	78	1·1 (0·66)	−0·08 (0·67)	0·90	60	1·1 (0·51)	−0·05 (0·39)	68	1·1 (0·65)	−0·03 (0·61)	0·43
Left atrial width (cm)	116	3·7 (0·42)	−0·07 (0·25)	114	3·7 (0·53)	−0·02 (0·22)	0·07	99	3·7 (0·43)	−0·15 (0·31)	108	3·7 (0·53)	−0·08 (0·30)	0·03
Left atrial volume (mL)	113	67·0 (23·2)	−3·2 (12·2)	119	68·1 (28·1)	−1·3 (12·5)	0·18	96	65·3 (22·5)	−4·6 (13·7)	112	68·3 (29·3)	0·37 (15·9)	0·003
Left atrial volume index (mL/m²)	110	35·9 (12·5)	−0·98 (7·6)	118	36·5 (14·4)	−0·41 (6·8)	0·45	90	35·0 (11·7)	−2·6 (7·3)	106	36·8 (14·8)	0·31 (9·3)	0·007
Left ventricular end-diastolic volume (mL)	114	110·3 (26·4)	−2·90 (10·5)	118	113·1 (31·3)	−3·27 (12·3)	0·99	94	111·8 (26·3)	−10·4 (14·4)	111	114·3 (31·5)	−12·7 (17·3)	0·39
Left ventricular end-systolic volume (mL)	114	46·5 (15·7)	−3·3 (6·5)	118	48·5 (20·9)	−2·7 (8·9)	0·97	95	46·9 (15·8)	−6·9 (9·1)	111	48·8 (20·6)	−8·70 (11·0)	0·31
Left ventricular mass index (kg/m²)	112	77·4 (20·7)	−1·2 (13·0)	112	78·8 (21·5)	−4·2 (11·8)	0·10	91	76·6 (19·8)	−2·8 (14·0)	100	79·5 (22·7)	−1·9 (19·2)	0·35
Relative wall thickness	116	0·38% (0·09)	−0·002% (0·045)	114	0·37% (0·07)	0·001% (0·033)	0·76	98	0·37% (0·07)	0·01% (0·06)	107	0·37% (0·07)	0·01% (0·06)	0·96
Tricuspid regurgitant velocity (m/s)	45	2·5 (0·36)	0·008 (0·25)	42	2·5 (0·33)	0·09 (0·33)	0·19	35	2·6 (0·44)	−0·01 (0·24)	42	2·52 (0·34)	0·06 (0·35)	0·38

Data are mean (SD). Baseline data are presented for follow-up values.

Table 3: **Changes in echocardiographic measures at 12 weeks and 36 weeks**

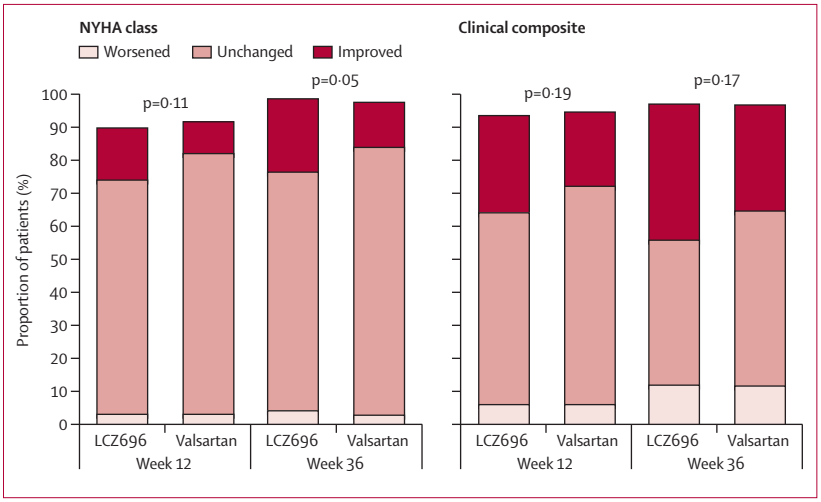

Figure 4: **Changes in NYHA and clinical composite assessment showing percentage of patients who have worsened, remained unchanged, or improved for each measure**
NYHA=New York Heart Association.

particularly loop diuretics, was greater in the valsartan group during the trial, although β-blocker use was similar. In the LCZ696 group, 22 patients (15%) had one or more serious adverse events, including one death; in the valsartan group, 30 patients (20%) had one or more serious adverse events, including two deaths (table 4). The number of patients with hypotension, renal dysfunction, or hyperkalaemia did not differ between groups. Over 36 weeks, eGFR decreased to a greater extent in the valsartan group (LCZ696, −1·6 mL/min per 1·73 m² *vs* valsartan, −5·2 mL/min per 1·73 m²; p=0·007) and urinary albumin creatinine ratio increased to a greater extent in the LCZ696 group (LCZ696, 1·9 mg/mmol at baseline, 2·9 mg/mmol at week 36; valsartan, 2·0 mg/mmol at baseline, 2·0 mg/mmol at week 36; p=0·02). Angio-oedema occurred in one patient on LCZ696, who did not need admission to hospital, and no patients on valsartan.

Discussion

We found that in patients with heart failure with preserved ejection fraction, the angiotensin receptor neprilysin inhibitor LCZ696 reduced NT-proBNP to a greater extent than did valsartan after 12 weeks of treatment (panel). The reduction in NT-proBNP in patients receiving LCZ696 became evident at 4 weeks and appeared to be sustained to 36 weeks, although the between-group difference was no longer significant. Additionally, we noted a reduction in left atrial size, indicative of reverse left atrial remodelling, in patients randomly assigned to LCZ696 after 36 weeks compared with those assigned to valsartan. NYHA class improved significantly at 36 weeks in patients on LCZ696

	LCZ696 (n=149)	Valsartan (n=152)	p value
Any serious adverse event	22 (15%)	30 (20%)	0·32
Deaths	1 (1%)	2 (1%)	0·99
All cardiac	9 (6%)	12 (8%)	0·69
Heart failure	4 (3%)	6 (4%)	0·77
Acute coronary syndrome	4 (3%)	4 (3%)	0·74
Arrhythmia	2 (1%)	2 (1%)	0·63
Renal	2 (1%)	3 (2%)	0·98
Any adverse event	96 (64%)	111 (73%)	0·14
Adverse events of Interest			
Symptomatic hypotension	28 (19%)	27 (18%)	0·88
Renal dysfunction	3 (2%)	7 (5%)	0·34
Hyperkalaemia	12 (8%)	9 (6%)	0·50
Discontinuation for any adverse event	15 (10%)	17 (11%)	0·90
Abnormal laboratory values			
Potassium >5·5 mmol/L	24 (16%)	16 (11%)	0·21
Potassium ≥6·0 mmol/L	5 (3%)	6 (4%)	0·97
≥50% decrease in eGFR	5 (3%)	4 (3%)	0·98

eGFR=estimated glomerular filtration rate.

Table 4: **Adverse events and abnormal laboratory values**

compared with those on valsartan, and LCZ696 was well tolerated overall. These hypothesis-generating findings suggest that LCZ696 might have beneficial effects in patients with heart failure with preserved ejection fraction and that further testing of this compound could be warranted in patients with this disorder.

Present treatment of heart failure with preserved ejection fraction remains both symptom-based and empiric,[6] with no specific treatment approved for this indication. Although ACE inhibitors and ARBs have been associated with symptom improvement, increased functional capacity, and reduction in admission to hospital in these patients,[16,17] existing guidelines state that no treatment has convincingly been shown to reduce morbidity or mortality.[32] Augmentation of the actions of natriuretic peptides could offer an alternative approach to the treatment of the disorder. ANP and BNP are secreted in response to cardiac myocyte stretch as a result of increased myocardial wall tension and act to defend the heart from volume and pressure overload, a protective mechanism recently shown to be deficient early in the development of heart failure with preserved ejection fraction.[33] Neprilysin inhibition, by blocking the breakdown of natriuretic peptides, should augment this endogenous defence mechanism and could be beneficial in heart failure with both reduced and preserved ejection fraction. In addition to their vasodilatory, natriuretic, and diuretic effects, ANP and BNP inhibit the renin–angiotensin–aldosterone system (RAAS), sympathetic nervous system, and release of antidiuretic hormone, improve myocardial relaxation and vagal tone, and are antifibrotic and antihypertrophic.[22,23] Importantly, however, simultaneous inhibition of the generation or action of angiotensin II is needed because neprilysin also degrades angiotensin II, and inhibition of this enzyme can increase circulating and tissue angiotensin II.

We chose NT-proBNP as the primary endpoint in PARAMOUNT because raised natriuretic peptide concentrations are associated with adverse outcomes in patients with heart failure,[34] including those with preserved ejection fraction,[35,36] and reductions in NT-proBNP have been associated with improved outcomes in heart failure.[34] Although both ANP and BNP undergo degradation by neprilysin, the biologically inert NT-proBNP, cleaved from proBNP along with BNP, is not a substrate for neprilysin degradation, and changes in this marker still reflect reduction in left ventricular wall stress even in the setting of neprilysin inhibition.[37] Although physiological negative feedback of the natriuretic system might play a part in healthy patients,[38] these mechanisms are unlikely to be particularly important in patients with heart failure, since increases of natriuretic peptides

Panel: Research in context

Systematic review

Heart failure is a major and increasing clinical problem that is associated with substantial morbidity and mortality. It is the leading cause of admission to hospital in individuals older than 65 years. Nearly half of all patients with heart failure have normal or nearly normal ejection fraction; this disorder is termed heart failure with preserved ejection fraction. The prevalence of disorder with preserved ejection fraction is rising more rapidly than that of disease with reduced ejection fraction. By contrast with the many studies that have shown a benefit of pharmacological treatment in heart failure with reduced ejection fraction, a recent meta-analysis and systematic review concluded that renin–angiotensin system inhibitors are not associated with consistent reductions in hospital admissions or mortality in disease with preserved ejection fraction.[19] Similarly, the 2012 European Society of Cardiology guidelines notes that no treatment has convincingly been shown to reduce morbidity or mortality.[32] Heart failure with preserved ejection fraction is therefore a disease with a major unmet need. LCZ696 is a first-in-class angiotensin receptor neprilysin inhibitor that has previously been studied in hypertension[27] and is currently under investigation in an outcomes trial in disease with reduced ejection fraction (NCT01035255); it has not been previously studied in heart failure with preserved ejection fraction.

Interpretation

We undertook a phase 2 study of LCZ696 compared with valsartan in 301 patients with heart failure with preserved ejection. The study met its primary endpoint. LCZ696 reduced NT-proBNP to a greater extent than did valsartan after 12 weeks. NT-proBNP is a marker of left ventricular stress and reductions in NT-proBNP have been associated with improved outcomes in patients with heart failure. Although these differences in NT-proBNP were no longer significant at week 36, we did note significantly greater reductions in left atrial volumes at week 36 for LCZ696 compared with valsartan. An enlarged left atrium is a characteristic finding in heart failure with preserved ejection and is reflective of sustained increases in left ventricular filling pressures. LCZ696 was well tolerated overall and its side-effect profile was similar to that of valsartan in this study. The results of this study are based on biomarkers and surrogate endpoints; whether the observed effects will translate into improved clinical outcomes needs prospective testing in an appropriately sized outcomes study.

continue as heart failure worsens and natriuretic peptides are potent predictors of outcomes in heart failure. Moreover, maximum titrated infusions of both nesiritide and nitroglycerin that result in similar haemodynamic findings are associated with similar levels of reduction in BNP and NT-proBNP,[37] suggesting that reduction of these markers in patients with heart failure is mainly due to the improvement in left ventricular wall stress.

We noted a relatively rapid reduction in NT-proBNP, apparent as early as 4 weeks, in patients receiving LCZ696. This reduction was sustained at 12 weeks, the primary trial endpoint, and at 36 weeks. Although reductions in NT-proBNP in the LCZ696 group were similar in all prespecified subgroups, patients with diabetes might have had a more favourable response, although we cannot rule out that this finding represented the play of chance. Although this finding would need to be replicated in future studies, previous studies have shown that other agents that augment cGMP, known to be the active mediator of the beneficial vasodilatory and natriuretic effects of the natriuretic peptides, could improve cardiac mechanics in patients with diabetic cardiomyopathy.[39]

We recorded small changes in NT-proBNP in the valsartan group at 4 and 12 weeks. After 36 weeks of treatment, NT-proBNP concentrations fell in the valsartan group, although not to the level of those in the LCZ696 group, in whom NT-proBNP remained reduced. We cannot establish whether the late reduction in NT-proBNP in the valsartan group, although not to the extent of that in the LCZ696 group, was secondary to beneficial haemodynamic actions of valsartan that were slower in onset, or was related to increased use of concomitant blood pressure drugs in the valsartan group. Nevertheless, the early reduction in NT-proBNP in the LCZ696 group could have contributed to other beneficial effects noted in this group during the extended follow-up, including reduction in left atrial size. We postulated that cardiac structural changes would need longer follow-up time to manifest than would biomarker changes; hence, we followed up patients on study drug for 36 weeks for these secondary endpoints. Left atrial size has been one of the most powerful predictors of outcome in heart failure, including heart failure with preserved ejection fraction,[40,41] and is generally thought to reflect sustained increase in left ventricular filling pressure, which might be more robust than Doppler-derived measures of diastolic function that are subject to greater variability.[41] The reported reduction in left atrial size offers support to the notion that LCZ696 had a sustained physiological benefit to 36 weeks.

Although the trial was not powered to examine clinical status endpoints or cardiovascular endpoints, we recorded significant improvement in NYHA class at 36 weeks; any clinical benefit of LCZ696 needs to be prospectively confirmed in an adequately sized trial. As expected, LCZ696 reduced blood pressure more than did valsartan alone; however, regression models accounting for the blood pressure changes suggested that the benefit for reduction in NT-proBNP and reduction in left atrial size were independent of the blood-pressure lowering effect.

LCZ696 had similar tolerability in this study to the comparator, valsartan, as was also shown in a larger hypertension trial.[27] This trial was not designed or powered to assess clinical outcomes, although we recorded numerically fewer adverse events in patients receiving LCZ696. An ongoing study in approximately 8000 patients with reduced ejection fraction heart failure, PARADIGM-HF (NCT01035255), will provide more comprehensive safety and efficacy data, although further data for heart failure with preserved ejection fraction will be needed to establish safety and efficacy in this population. Finally, although we believe this population is representative of patients with the disease, we noted a high incidence of β-blocker and RAAS inhibitor use at baseline. Moreover, because increase in NT-proBNP was an entry criterion for our study, this measure was higher in this population than in previous trials in this disorder.

In summary, we found that in patients with heart failure and preserved ejection fraction, the angiotensin receptor neprilysin inhibitor LCZ696 reduced NT-proBNP to a greater extent than did valsartan at 12 weeks, and was associated with left atrial reverse remodelling at 36 weeks and improvement in NYHA class at 36 weeks, consistent with the hypothesis that LCZ696 reduced left ventricular pressures and wall stress. These findings suggest that LCZ696 could have favourable effects in patients with this disorder, and that further testing of the drug in this patient population might be warranted.

Contributors

SDS participated in study concept and design, study operations, analysis and interpretation of data, and drafted the report. MZ, BP, AV, VS, MP, and JJVM participated in study concept and design, study operations, interpretation of data, and editing of the report. AS and EK-K participated in study operations, data analysis, interpretation of data, and editing of the report. TB participated in study operations, interpretation of data, and editing of the report. MT participated in data analysis, interpretation of data, and editing of the report. JG and ML participated in study concept and design, data analysis, interpretation of data, and editing of the report.

Conflicts of interest

SDS, MZ, BP, AV, AS, MP, and JJVM have received research support and have consulted for Novartis. VS, TB, JG and ML are employees of Novartis. EK-K and MT declare that they have no conflicts of interest.

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