Sacubitril–valsartan as a treatment for apparent resistant hypertension in patients with heart failure and preserved ejection fraction

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Aims

Patients with heart failure and preserved ejection fraction (HFpEF) frequently have difficult-to-control hypertension. We examined the effect of neprilysin inhibition on ‘apparent resistant hypertension’ in patients with HFpEF in the PARAGON-HF trial, which compared the effect of sacubitril–valsartan with valsartan.

Methods and results

In this post hoc analysis, patients were categorized according to systolic blood pressure at the end of the valsartan run-in (n = 4795). ‘Apparent resistant hypertension’ was defined as systolic blood pressure ≥140 mmHg (≥135 mmHg if diabetes) despite treatment with valsartan, a calcium channel blocker, and a diuretic. ‘Apparent mineralocorticoid receptor antagonist (MRA)-resistant’ hypertension was defined as systolic blood pressure ≥140 mmHg (≥135 mmHg if diabetes) despite the above treatments and an MRA. The primary outcome in the PARAGON-HF trial was a composite of total hospitalizations for heart failure and death from cardiovascular causes. We examined clinical endpoints and the safety of sacubitril–valsartan according to the hypertension category. We also examined reductions in blood pressure from the end of valsartan run-in to Weeks 4 and 16 after randomization. Overall, 731 patients (15.2%) had apparent resistant hypertension and 135 (2.8%) had apparent MRA-resistant hypertension. The rate of the primary outcome was higher in patients with apparent resistant hypertension [17.3; 95% confidence interval (CI) 15.6–19.1 per 100 person-years] compared to those with a controlled systolic blood pressure (13.4; 12.7–14.3 per 100 person-years), with an adjusted rate ratio
of 1.28 (95% CI 1.05–1.57). The reduction in systolic blood pressure at Weeks 4 and 16, respectively, was greater with sacubitril–valsartan vs. valsartan in patients with apparent resistant hypertension [−4.8 (-7.0 to -2.5) and 3.9 (-6.6 to -1.3) mmHg] and apparent MRA-resistant hypertension [−8.8 (-14.0 to -3.5) and -6.3 (-12.5 to -0.1) mmHg]. The proportion of patients with apparent resistant hypertension achieving a controlled systolic blood pressure by Week 16 was 47.9% in the sacubitril–valsartan group and 34.3% in the valsartan group [adjusted odds ratio (OR) 1.78, 95% CI 1.30–2.43]. In patients with apparent MRA-resistant hypertension, the respective proportions were 43.6% vs. 28.4% (adjusted OR 2.63, 95% CI 1.18–5.89).

**Conclusion**

Sacubitril–valsartan may be useful in treating apparent resistant hypertension in patients with HFpEF, even in those who continue to have an elevated blood pressure despite treatment with at least four antihypertensive drug classes, including an MRA.

**Clinical trial registration**

PARAGON-HF: ClinicalTrials.gov Identifier NCT01920711.

**Graphical Abstract**

Almost one in six patients with heart failure and preserved ejection fraction had apparent resistant hypertension in PARAGON-HF and this was associated with worse clinical outcomes; neprilysin inhibition reduced systolic blood pressure significantly in these patients.

**Keywords**

Heart failure • Preserved ejection fraction • Sacubitril–valsartan • Blood pressure

**Introduction**

The links between hypertension and heart failure with preserved ejection fraction (HFpEF) are well known, with left ventricular hypertrophy, arterial stiffening, and renal impairment likely contributing to the development of this syndrome. Ninety percent or more of patients with HFpEF in contemporary trials have a history of hypertension. Moreover, many patients developing HFpEF remain hypertensive and treatment of this comorbidity is one of the few recommended therapies for individuals with this heart failure phenotype. Recent evidence suggests that not only do many HFpEF patients remain hypertensive but also a considerable proportion may
have hypertension that is difficult to control, despite use of multiple antihypertensive agents. Indeed, it appears that ‘resistant hypertension’ is as common in patients with HFpEF as in individuals with hypertension more generally, with 10–20% of patients affected.6,7 Resistant hypertension is formally defined as blood pressure persistently above target, despite the use of three antihypertensive agents of different classes, including an angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB), a calcium channel blocker, and a diuretic, although there is some variation between USA and European guidelines.8,9

Neprilysin inhibition offers an additional approach to reducing blood pressure. Indeed, the first clinical trial using the combined angiotensin receptor–neprilysin inhibitor, sacubitril–valsartan, was conducted in patients with uncomplicated mild-to-moderate hypertension.10 Sacubitril–valsartan 194/206 mg (LCZ696 200 mg) once daily was compared with valsartan 320 mg once daily (the doses selected gave equivalent plasma exposure of valsartan, due to greater bioavailability with the combination drug). After 8 weeks of treatment, sitting systolic pressure was reduced by 6.01 [95% confidence interval (CI) -9.01 to -3.02] mmHg with sacubitril–valsartan, compared with valsartan (P < 0.0001). Sacubitril–valsartan was subsequently developed as a treatment for heart failure using a twice rather than once daily dosing regimen. In the first study of this agent in patients with HFpEF, sacubitril–valsartan 97/103 mg twice daily was compared to valsartan 160 mg twice daily in a phase 2 randomized trial of 266 patients.11 Although change in blood pressure was not the primary endpoint, this trial showed that, after 12 weeks of treatment, sacubitril–valsartan reduced systolic pressure by 6.4 mmHg, compared with valsartan (P = 0.001). The same treatment regimens were then compared in a phase 3 morbidity/mortality trial in patients with HFpEF, the Prospective Comparison of ARNI With ARB Global Outcomes in Heart Failure With Preserved Ejection Fraction trial (PARAGON-HF).12 Although not a hypertension trial, >95% of patients in PARAGON-HF had a history of hypertension and, overall, sacubitril–valsartan reduced systolic pressure by 5.2 (4.4–6.0) mmHg compared with valsartan after 4 weeks.13 However, the effect of sacubitril–valsartan in resistant hypertension is of special interest, given the difficulty of controlling blood pressure in these patients and the need for new treatments.19

The large PARAGON-HF dataset allowed post hoc exploration of the prevalence of ‘apparent resistant hypertension’, the association between ‘apparent resistant hypertension’ and outcomes in HFpEF, and the effect of neprilysin inhibition on blood pressure in these patients. We studied blood pressure control in individuals receiving all three recommended classes of antihypertensive therapy. We also examined a further group of patients with ‘apparent mineralocorticoid receptor antagonist (MRA)-resistant hypertension’ receiving, in addition, an MRA, which has recently become the preferred fourth-line agent as a result of the PATHWAY-2 trial.15

Methods

The design and primary results of the PARAGON-HF trial are published.12,16,17 The ethics committee of each participating institution approved the protocol, and all patients gave written informed consent. Novartis is committed to sharing, with qualified external researchers, access to patient-level data and supporting clinical documents from eligible studies. These requests are reviewed and approved by an independent review panel, based on scientific merit. All data provided are anonymized to respect the privacy of patients who have participated in the trial in line with applicable laws and regulations. The criteria and process for obtaining trial data are described at www.clinicalstudydatarequest.com (last accessed 24 July 2021).

Study patients

The trial eligibility criteria included New York Heart Association (NYHA) functional Class II–IV, a left ventricular ejection fraction (LVEF) of 45% or higher, an elevated natriuretic peptide concentration (with the level varying according to whether or not there had been a recent hospitalization for heart failure and the presence or absence of atrial fibrillation or flutter), evidence of structural heart disease, and treatment with a diuretic. Exclusion criteria included systolic blood pressure >180 mmHg; in addition, patients with a systolic blood pressure >150–180 mmHg were excluded unless receiving at least three antihypertensive drugs. Other exclusion criteria at screening included systolic blood pressure <110 mmHg, estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m², and serum potassium >5.2 mmol/L.

Study treatment

Patients entered two sequential single-blind run-in periods, first receiving valsartan 80 mg twice daily (i.e. half the target dose for heart failure and half the maximum recommended dose for hypertension) for 1–2 weeks and then sacubitril–valsartan 49/51 mg twice daily for 2–4 weeks. Patients had to be free of symptoms of hypotension and have a systolic blood pressure of at least 100 mmHg to progress through each step of the run-in and to randomization. Participants were then randomized 1:1:1 to treatment with either sacubitril–valsartan (target dose 97/103 mg twice daily) or valsartan (target dose 160 mg twice daily). Valsartan 103 mg in sacubitril–valsartan gives plasma exposure equivalent to 160 mg of the standard valsartan formulation (and 51 mg the same as 80 mg).

Blood pressure measurement

Investigators were asked to measure blood pressure in the sitting position after 5 min of rest using an automated, validated device (e.g. OMRON) or a standard sphygmomanometer with an appropriately sized cuff on the non-dominant arm. Investigators were also asked to ensure patients had not taken caffeine or smoked within the 30 min preceding the blood pressure measurement and that the measurement was made in a quiet room, with the patient comfortably seated, back resting against their chair.

Trial outcomes

The median follow-up duration in the PARAGON-HF trial was 35 months [interquartile range (IQR) 30–41]. The primary outcome was a composite of first and recurrent hospitalizations for heart failure and death from cardiovascular causes. Secondary outcomes included in this study were the time to the first occurrence of a decline in renal function (defined as a reduction of 50% of more in eGFR, development of end-stage renal disease or death due to renal failure) and time to death from any cause. We also examined the prespecified exploratory composite of cardiovascular death, total non-fatal heart failure hospitalizations, total non-fatal strokes and total non-fatal myocardial infarctions. Safety outcomes analysed were hypotension (systolic blood pressure <100 mmHg), elevation of serum creatinine, and elevation of serum potassium. Because sacubitril–valsartan did not reduce the risk of the primary outcome in the trial overall, the effect of randomized therapy on clinical outcomes was not analysed in the hypertension subgroups.
Statistical analysis
A total of 4796 patients were randomized in the PARAGON-HF trial. Inclusion, definitions, and outcomes analysed in this study are summarized in Supplementary material online, Figure S1. In this study, the primary definition of ‘apparent resistant hypertension’ was a systolic blood pressure $\geq 140$ mmHg ($\geq 135$ mmHg in those with diabetes) at the end of the valsartan run-in, despite concomitant treatment with a calcium channel blocker and diuretic (thiazide or thiazide-like, loop, or potassium-sparing other than an MRA), as well as valsartan.$^{12,16,17}$ Concomitant medications were at the start of the run-in period, i.e. prior to the visit at which the patient was defined as having resistant hypertension. An alternative definition was also used in supplementary analyses: systolic blood pressure $\geq 130$ mmHg at the end of valsartan run-in despite concomitant treatment with a calcium channel blocker and diuretic, as well as valsartan, reflecting the American Heart Association recommendations.$^6$ Finally, we also examined patients with more refractory, ‘apparent MRA-resistant’ hypertension, defined as: systolic blood pressure $\geq 140$ mmHg ($\geq 135$ mmHg in those with diabetes) at the end of valsartan run-in, despite concomitant treatment with a calcium channel blocker, diuretic and an MRA, as well as valsartan (i.e. at least four classes of blood pressure-lowering therapy, including an MRA). Other patients were considered to have non-resistant hypertension if systolic blood pressure remained above the respective thresholds, but the definition of apparent resistant hypertension was not fulfilled (i.e. patients were not on the specified blood pressure-lowering drug combination) and considered to have a ‘controlled blood pressure’ if systolic blood pressure was below the respective thresholds at the end of the valsartan run-in (irrespective of concomitant medications and accepting that many of these patients had effectively treated hypertension). Baseline characteristics were compared using $t$-tests, ANOVA, Wilcoxon rank-sum test, and $\chi^2$ tests where appropriate. Reduction in systolic blood pressure from the end of the valsartan run-in to Weeks 4 and 16 after randomization, on sacubitril–valsartan vs. valsartan, was analysed using a mixed model for repeated measures (including all values up to Week 16, including baseline value and interaction of treatment and visit with a random intercept and slope per patient), and the between treatment group differences at Week 16 following randomization were presented as least square means difference and 95% CI. In the event of death prior to Week 16, blood pressure measurements were included up until the time at which the death occurred and were recorded as missing thereafter. The proportion of patients with controlled systolic blood pressure at 16 weeks, defined as reduction in systolic blood pressure to below $140$ mmHg in patients without diabetes and to below $135$ mmHg in patients with diabetes (and as a reduction in systolic blood pressure to below $130$ mmHg using the alternative definition of apparent resistant hypertension), was examined and the odds of a reduction were estimated using logistic regression. The primary composite outcome and one of its components, total heart failure hospitalizations, were examined using a semiparametric proportional rates method.$^{18}$ Cardiovascular death, all-cause death, and the renal outcome were examined using Cox proportional hazards regression. Cumulative first events were displayed using Kaplan–Meier curves. The Nelson-Aalen non-parametric estimator for cumulative hazard rate function, which accounts for patients who are censored due to competing events (i.e. cardiovascular death), was used to display the hazard of recurrent events. The proportional hazards assumptions were checked and met for all models. All models examining the primary and secondary trial outcomes included randomized treatment and were stratified by region. The multivariable models for the primary and secondary trial outcomes also included sex, age, heart rate, body mass index, N-terminal pro-B-type natriuretic peptide (NT-proBNP) (log), NYHA class, LVEF, eGFR, prior hospitalization for heart failure, myocardial infarction, diabetes, cigarette smoking history (current or former), and atrial fibrillation. Safety outcomes were compared across the hypertension categories using a logistic regression model, adjusted for region, with a test for interaction. Multivariable models for systolic blood pressure change included age, sex, body mass index, cigarette smoking history (current or former), and region. All analyses were conducted using STATA version 16 (StataCorp LLC, College Station, TX, USA). A $P$-value of $<0.05$ was considered statistically significant.

Results
One patient without a recorded systolic blood pressure measurement at the end of the valsartan run-in period was excluded. Of the 4795 patients included, 731 (15.2%) had apparent resistant hypertension, 1268 (26.4%) had hypertension that was not resistant, and 2796 (58.3%) had a controlled blood pressure. A total of 135 patients (2.8%) had apparent MRA-resistant hypertension. The mean (standard deviation) systolic blood pressures at the end of the valsartan run-in in patients with apparent resistant hypertension, non-resistant hypertension, and a controlled blood pressure were 149.2 ($\pm 11.0$), 149.1 ($\pm 11.2$), and 123.6 ($\pm 9.2$) mmHg, respectively. Systolic blood pressure in patients with apparent MRA-resistant hypertension was 148.0 ($\pm 9.7$) mmHg. Data on patients with apparent resistant hypertension using the alternative definition are given in Supplementary material online, Table S1.

We examined adherence to randomized therapy, as measured by pill count, and persistence with non-randomized blood pressure-lowering therapy. Adherence to sacubitril–valsartan and valsartan was high throughout the trial. The mean total daily doses of blood pressure-lowering therapies are presented in Table 1, and doses of calcium channel blocker and MRA were similar at 6 months and 1 year after randomization. At the final visit, target dose of the study drug was reached in 87.4% of patients with apparent resistant hypertension who were continuing therapy and was similar irrespective of randomized group. At 6 months and 1 year, a calcium channel blocker was prescribed in 88.3% and 86.7% of patients with apparent resistant hypertension and any diuretic in 95.7% and 95.0%, respectively. The study drug was discontinued in 25.4% of patients with apparent resistant hypertension for reasons other than death.

Patient characteristics
Patients with apparent resistant hypertension were more often White and less often Asian and had a higher body mass index and eGFR, compared to patients with a controlled blood pressure, although all these differences were small (Table 1). Patients with apparent resistant hypertension were much more likely to have diabetes (60.5% vs. 35.6%) but had a lower median NT-proBNP level (744 vs. 962 pg/mL) than those with a controlled blood pressure (Table 1). Patients with apparent resistant hypertension were more often treated with a diuretic, calcium channel blocker and alpha-blocker than those with a controlled blood pressure but less often treated with an MRA. Age, NYHA class distribution, and the proportions of patients with a prior heart failure hospitalization or stroke were similar, irrespective of hypertension category. The distribution of baseline characteristics was similar in patients meeting the alternative definition of apparent resistant hypertension (Supplementary material online, Table S1).
| Baseline characteristics of patients according to hypertension category |
|---------------------------------------------------------------|
| **Controlled blood pressure (n = 2796)**                        |
| **Non-resistant hypertension (n = 1268)**                       |
| **Apparent resistant hypertension (n = 731)**                   |
| **Global P-value**                                             |
| **Non-resistant hypertension vs. controlled BP P-value**        |
| **Apparent resistant hypertension vs. controlled BP P-value**   |
|---------------------------------------------------------------|
| **Systolic blood pressure (mmHg)**                             | 123.6 ± 9.2 | 149.1 ± 11.2 | 149.2 ± 11.0 | <0.001 | <0.001 | <0.001 |
| **Diastolic blood pressure (mmHg)**                            | 72.7 ± 10.0 | 80.4 ± 10.5 | 78.7 ± 10.7 | <0.001 | <0.001 | <0.001 |
| **Pulse pressure (mmHg)**                                      | 50.9 ± 10.6 | 68.7 ± 14.0 | 70.5 ± 14.2 | <0.001 | <0.001 | <0.001 |
| **Age (years)**                                                | 72.6 ± 8.5  | 73.2 ± 8.4  | 72.5 ± 8.2  | 0.11   | 0.058  | 0.68   |
| **Women**                                                      | 1419 (50.8)| 689 (54.3)  | 370 (50.6)  | 0.09   | 0.034  | 0.95   |
| **Race**                                                       |             |             |             |        |        |        |
| American Indian/Alaska native                                  | 27 (1.0)    | 18 (1.4)    | 5 (0.8)     | <0.001 | 0.27   | 0.31   |
| Asian                                                          | 414 (14.8)  | 145 (11.4)  | 48 (6.6)    | <0.001 | 0.034  | <0.001 |
| Black/African American                                         | 59 (2.1)    | 24 (1.9)    | 19 (2.6)    | <0.001 | 0.034  | <0.001 |
| Native Hawaiian/Pacific Islander                               | 1 (0.0)     | 0 (0.0)     | 0 (0.0)     | <0.001 | 0.034  | <0.001 |
| Other                                                          | 69 (2.5)    | 37 (2.9)    | 22 (3.0)    | <0.001 | 0.034  | <0.001 |
| **White**                                                      | 2226 (79.6)| 1044 (82.3)| 636 (87.0)  | <0.001 |        |        |
| **Cigarette smoking**                                          | 1106 (39.9)| 472 (37.4)  | 276 (37.8)  | 0.27   | 0.14   | 0.31   |
| **Left ventricular ejection fraction (%)**                     | 57.6 ± 8.0  | 57.3 ± 7.9  | 57.6 ± 7.5  | 0.36   | 0.17   | 1.00   |
| **Heart rate (b.p.m.)**                                        | 70.7 ± 12.3 | 70.6 ± 12.3 | 69.2 ± 11.9 | 0.010  | 0.88   | 0.003  |
| **Body mass index (kg/m²)**                                    | 30.0 ± 5.0  | 30.2 ± 5.1  | 31.2 ± 4.8  | <0.001 | 0.32   | <0.001 |
| **Body mass index (>30 kg/m²)**                                | 1320 (47.2)| 611 (48.2)  | 422 (57.7)  | <0.001 | 0.55   | <0.001 |
| **eGFR (mL/min/1.73 m²)**                                      | 62 ± 19     | 64 ± 19     | 63 ± 20     | 0.019  | 0.005  | 0.34   |
| **eGFR (<60 mL/min/1.73 m²)**                                  | 1400 (50.1)| 579 (45.7)  | 362 (49.5)  | 0.033  | 0.010  | 0.79   |
| **NT-proBNP (pg/mL)**                                          | 962 (488–1625)| 847 (458–1606)| 744 (408–1560)| <0.001| 0.026  | <0.001 |
| **NYHA class**                                                 |             |             |             |        |        |        |
| I                                                              | 75 (2.7)    | 40 (3.2)    | 22 (3.0)    | <0.001 | <0.001 | <0.001 |
| II                                                             | 2152 (77.0)| 990 (78.1)  | 563 (77.0)  | <0.001 | 0.43   | 0.43   |
| III                                                            | 557 (19.9)  | 231 (18.2)  | 144 (19.7)  | <0.001 |        | <0.001 |
| IV                                                             | 10 (0.4)    | 7 (0.6)     | 2 (0.3)     | <0.001 |        |        |
| **Diabetes**                                                   | 996 (35.6)| 623 (49.1)  | 442 (60.5)  | <0.001 | <0.001 | <0.001 |
| **Prior heart failure hospitalization**                        | 1350 (48.3)| 614 (48.4)  | 341 (46.6)  | 0.70   | 0.93   | 0.43   |
| **Stroke**                                                     | 290 (10.4)  | 127 (10.0)  | 91 (12.4)   | 0.20   | 0.71   | 0.11   |
| **Calcium channel blocker**                                    | 867 (31.0)  | 49 (3.9)    | 731 (100.0) | <0.001 | <0.001 | <0.001 |
| **Total daily amlodipine-equivalent dose**                     | 6.9 ± 2.9   | 7.4 ± 2.6   | 7.4 ± 3.2   | 0.015  | 0.34   | 0.004  |
| **Thiazide or thiazide-like diuretic**                         | 572 (20.5)  | 257 (20.3)  | 195 (26.7)  | <0.001 | 0.89   | <0.001 |
| **Loop diuretic**                                              | 2192 (78.4)| 950 (74.9)  | 609 (83.3)  | <0.001 | 0.014  | 0.003  |
| **Mineralocorticoid receptor antagonist**                      | 858 (30.7)  | 300 (23.7)  | 135 (18.5)  | <0.001 | <0.001 | <0.001 |
| **Total daily dose**                                           | 27.5 ± 13.8 | 27.0 ± 13.5 | 30.4 ± 17.2 | 0.06   | 0.61   | 0.032  |
| **Other potassium-sparing diuretic**                           | 37 (1.3)    | 15 (1.2)    | 9 (1.2)     | 0.93   | 0.71   | 0.85   |
| **Beta-blocker**                                               | 2236 (80.0)| 1033 (81.5)| 564 (77.2)  | 0.07   | 0.27   | 0.094  |
| **Total daily bisoprolol-equivalent dose**                     | 4.9 ± 3.3   | 4.9 ± 3.0   | 5.1 ± 3.1   | 0.46   | 0.70   | 0.31   |
| **Alpha-blocker**                                              | 148 (5.3)   | 99 (7.8)    | 95 (13.0)   | <0.001 | 0.002  | <0.001 |

Data are presented as mean ± standard deviation or median (interquartile range) for continuous measures and n (%) for categorical measures. Medications are at the run-in. Global P-value is for the comparison of all three groups. BP, blood pressure; eGFR, estimated glomerular filtration rate; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association.

*At the end of valsartan run-in.

1In patients taking the drug, amlodipine-equivalent dose is calculated for amlodipine, felodipine, and lercanidipine; bisoprolol-equivalent dose is calculated for bisoprolol, atenolol, metoprolol, carvedilol, and nebivolol; and mineralocorticoid receptor antagonist dose is calculated for spironolactone and eplerenone.

2Doxazosin, prazosin, bunazosin, terazosin, naftopidil, or urapidil.
Patients with apparent MRA-resistant hypertension were younger, had a higher body mass index, lower natriuretic peptide level, and more often had a diabetes than patients with a controlled blood pressure (Supplementary material online, Table SII). Patients with apparent MRA-resistant hypertension were more often treated with a diuretic, calcium channel blocker and alpha-blocker than those with a controlled blood pressure.

Outcomes according to hypertension category

The rate of the primary composite outcome was higher in patients with apparent resistant hypertension (17.3; 95% CI 15.6–19.1 per 100 person-years) compared to those with a controlled blood pressure (13.4; 12.7–14.3 per 100 person-years), with an adjusted rate ratio of 1.28 (95% CI 1.05–1.57) (Table 2 and Figure 1). The greater risk of the primary composite outcome in patients with apparent resistant hypertension was driven by a higher rate of heart failure hospitalization whereas the risk of death from cardiovascular causes (and from any cause) was not different between these groups.

The rate of the prespecified exploratory composite outcome of cardiovascular death, total heart failure hospitalizations, total strokes, and total myocardial infarctions was also higher in patients with apparent resistant hypertension (20.8; 95% CI 19.0–22.8 per 100 person-years) compared to those with a controlled blood pressure (16.3; 95% CI 15.4–17.2 per 100 person-years), with an adjusted rate ratio of 1.30 (95% CI 1.08–1.55).

The risk of the composite renal outcome was significantly higher in patients with apparent resistant hypertension (1.2; 95% CI 0.4–0.8 per 100 person-years), with an adjusted rate ratio of 1.72 (95% CI 1.04–2.86).

Unadjusted models include randomized treatment and are stratified by region. Adjusted models include randomized treatment, sex, age, heart rate, body mass index, N-terminal pro-B-type natriuretic peptide (log), New York Heart Association class, left ventricular ejection fraction, estimated glomerular filtration rate, prior hospitalization for HF, MI, diabetes, cigarette smoking, and atrial fibrillation, and are stratified by region. Rates are per 100 person-years.

CI, confidence interval; CV, cardiovascular; HF, heart failure; MI, myocardial infarction.

Table 2  Outcomes according to hypertension category referent to patients without controlled blood pressure

|                                | Controlled blood pressure (n = 2796) | Non-resistant hypertension (n = 1268) | Apparent resistant hypertension (n = 731) |
|--------------------------------|-------------------------------------|--------------------------------------|------------------------------------------|
| Primary outcome                |                                     |                                      |                                          |
| Number of events               | 1078                                | 455                                  | 370                                      |
| Event rate (95% CI)            | 13.4 (12.7–14.3)                    | 12.4 (11.3–13.6)                     | 17.3 (15.6–19.1)                         |
| Unadjusted rate ratio (95% CI) | 1.00                                | 1.00 (0.84–1.18)                     | 1.35 (1.10–1.67)                         |
| Adjusted rate ratio (95% CI)   | 1.00                                | 0.93 (0.78–1.09)                     | 1.28 (1.05–1.57)                         |
| Total HF hospitalizations      |                                     |                                      |                                          |
| Number of events               | 818                                 | 353                                  | 316                                      |
| Event rate (95% CI)            | 10.2 (9.5–10.9)                     | 9.6 (8.6–10.6)                       | 14.7 (13.2–16.5)                        |
| Unadjusted rate ratio (95% CI) | 1.00                                | 1.03 (0.86–1.25)                     | 1.53 (1.21–1.93)                        |
| Adjusted rate ratio (95% CI)   | 1.00                                | 0.96 (0.79–1.15)                     | 1.42 (1.14–1.78)                        |
| CV death, total HF hospitalizations, MIs, strokes | 1305 | 603 | 446 |
| Number of events               |                                     |                                      |                                          |
| Event rate (95% CI)            | 16.3 (15.4–17.2)                    | 16.4 (15.1–17.8)                     | 20.8 (19.0–22.8)                        |
| Unadjusted rate ratio (95% CI) | 1.00                                | 1.09 (0.94–1.26)                     | 1.35 (1.12–1.63)                        |
| Adjusted rate ratio (95% CI)   | 1.00                                | 1.02 (0.88–1.19)                     | 1.30 (1.08–1.55)                        |
| CV death                       |                                     |                                      |                                          |
| Number of events               | 260                                 | 102                                  | 54                                       |
| Event rate (95% CI)            | 3.2 (2.9–3.7)                       | 2.8 (2.3–3.4)                        | 2.5 (1.9–3.3)                           |
| Unadjusted hazard ratio (95% CI)| 1.00                                | 0.88 (0.70–1.11)                     | 0.80 (0.60–1.08)                        |
| Adjusted hazard ratio (95% CI) | 1.00                                | 0.83 (0.66–1.05)                     | 0.81 (0.60–1.10)                        |
| Death from any cause           |                                     |                                      |                                          |
| Number of events               | 414                                 | 180                                  | 97                                       |
| Event rate (95% CI)            | 5.2 (4.7–5.7)                       | 4.9 (4.2–5.7)                        | 4.5 (3.7–5.5)                           |
| Unadjusted hazard ratio (95% CI)| 1.00                                | 0.96 (0.80–1.14)                     | 0.89 (0.71–1.11)                        |
| Adjusted hazard ratio (95% CI) | 1.00                                | 0.90 (0.75–1.08)                     | 0.89 (0.70–1.12)                        |
| Renal outcome                  |                                     |                                      |                                          |
| Number of events               | 45                                  | 27                                   | 25                                       |
| Event rate (95% CI)            | 0.6 (0.4–0.8)                       | 0.7 (0.5–1.1)                        | 1.2 (0.8–1.7)                           |
| Unadjusted hazard ratio (95% CI)| 1.00                                | 1.38 (0.86–2.24)                     | 2.19 (1.34–3.58)                        |
| Adjusted hazard ratio (95% CI) | 1.00                                | 1.19 (0.73–1.94)                     | 1.72 (1.04–2.86)                        |
The rate of all the outcomes of interest was similar in patients with non-resistant hypertension and those with a controlled blood pressure (Table 2 and Figure 1).

A broadly similar pattern was seen using the alternative definition of apparent resistant hypertension (Supplementary material online, Table SIII and Figure SII) and in apparent MRA-resistant hypertension, although the relatively small number of patients in the latter group precluded formal analysis of outcomes (Supplementary material online, Table SIV and Figure SIII).

Effect of sacubitril–valsartan (compared with valsartan) on systolic blood pressure in patients with resistant hypertension

Systolic blood pressure declined between the end of the valsartan 80 mg b.i.d. run-in period and the end of the subsequent sacubitril–valsartan 49/51 mg b.i.d. run-in period, in all three groups of patients without a controlled blood pressure (Table 3 and Figure 2). After randomization, blood pressure remained lower in patients assigned to 97/103 mg of sacubitril–valsartan b.i.d. In those assigned to valsartan 160 mg b.i.d., systolic blood pressure rose above the level at the randomization visit but remained below the level at the end of the valsartan 80 mg b.i.d. run-in period (Table 3 and Figure 2).

As a result, systolic blood pressure was reduced more by sacubitril–valsartan (97/103 mg b.i.d.) than by valsartan (160 mg b.i.d.) at both 4 and 16 weeks after randomization, compared to the end of valsartan run-in, in patients with apparent resistant hypertension (Table 3 and Figure 2), with differences between the treatment groups of -4.8 (-7.0 to -2.5) mmHg at Week 4 and -3.9 (-6.6 to -1.3) mmHg at Week 16.

In patients with apparent MRA-resistant hypertension, the absolute reduction in systolic blood pressure was also larger with sacubitril–valsartan, compared with valsartan: -8.8 (-14.0 to -3.5) mmHg and -6.3 (-12.5 to -0.1) mmHg at Weeks 4 and 16, respectively (Table 3 and Figure 2).

Proportion of patients with resistant hypertension achieving systolic blood pressure control with sacubitril–valsartan (compared with valsartan)

The proportion of patients with apparent resistant hypertension achieving a controlled systolic blood pressure by Week 16 was...
significantly greater in participants assigned to sacubitril–valsartan (47.9%) than in those assigned to valsartan (34.3%), with an adjusted odds ratio (OR) of 1.78 (95% CI 1.30–2.43) (Table 3). The relative proportion of responders was greatest in patients with apparent MRA-resistant hypertension (43.6% vs. 28.4%), with an adjusted OR of 2.63 (95% CI 1.18–5.89).

### Safety and tolerability of sacubitril–valsartan in patients with resistant hypertension

Hypotension was more common with sacubitril–valsartan than with valsartan, although the excess in patients with apparent resistant hypertension was small (Table 4). Conversely, elevation of serum creatinine and potassium was less common with sacubitril–valsartan than with valsartan, in patients with apparent resistant hypertension. The pattern of adverse events was broadly similar using the alternative definition of apparent resistant hypertension and in those with apparent MRA-resistant hypertension (Supplementary material online, Tables SV and SVI).

### Discussion

As defined in this study, ‘apparent resistant hypertension’ was common in patients with HFpEF, affecting 15% of all individuals at the end of the valsartan run-in period in PARAGON-HF and 37% of those whose systolic blood pressure remained elevated at that time point. Patients with ‘apparent resistant hypertension’, as defined in this study, had a greater risk of the primary composite of hospitalization for heart failure and cardiovascular death and the prespecified exploratory composite of hospitalization for heart failure, myocardial infarction, stroke, and cardiovascular death. When added to an ARB (valsartan), a calcium channel blocker, and a diuretic (and even to these three agents plus an MRA), neprilysin inhibition lowered systolic blood pressure significantly and increased the proportion of patients with controlled hypertension (Graphical abstract). Given the overall safety profile of sacubitril–valsartan, compared with valsartan, and better renal function, switching from an ACE inhibitor or ARB to sacubitril–valsartan may offer an effective and safe approach to controlling resistant hypertension in patients with HFpEF. This possibility merits further investigation in prospective hypertension trial with a more rigorous definition of resistant hypertension.

Although HFpEF is widely recognized as a hypertensive phenotype, little is known about the prevalence of hypertension in HFpEF and how best to lower blood pressure in patients with this syndrome.1–5 In a pooled analysis (n = 8466) of the three largest morbidity/mortality trials in HFpEF before PARAGON-HF, 46% of participants had a systolic blood pressure ≥140 mmHg (or ≥135 mmHg in individuals with diabetes) and 70% a systolic blood pressure ≥130 mmHg, indicating that hypertension remains a highly prevalent and sub-optimally treated problem in these patients.19 In terms of therapy, diuretics are often needed to control sodium and water retention in HFpEF, making them a first-line treatment for comorbid hypertension. While ARBs did not improve HFpEF outcomes in two large randomized

### Table 3: Changes in systolic blood pressure and blood pressure control in patients with ‘non-resistant’, ‘apparent resistant’, and ‘apparent mineralocorticoid receptor antagonist-resistant’ hypertension

|                          | Controlled blood pressure | Non-resistant hypertension | Apparent resistant hypertension | Apparent MRA-resistant hypertension |
|--------------------------|---------------------------|----------------------------|---------------------------------|-------------------------------------|
|                          | Valsartan | Sacubitril–valsartan | Valsartan | Sacubitril–valsartan | Valsartan | Sacubitril–valsartan | Valsartan | Sacubitril–valsartan |
| SBP at end of valsartan run-in (mmHg) | 123.9 ± 9.1 | 123.3 ± 9.2 | 149.4 ± 11.1 | 148.8 ± 11.3 | 149.4 ± 11.0 | 148.9 ± 11.1 | 148.1 ± 9.8 | 148.0 ± 9.5 |
| Change from end of valsartan run-in to Week 4 | +3.6 ± 0.4 | -0.4 ± 0.4 | -6.0 ± 0.7 | -12.3 ± 0.6 | -6.6 ± 0.8 | -11.4 ± 0.8 | -3.6 ± 1.7 | -12.4 ± 2.0 |
| Between treatment group difference | -4.0 (-5.0 to -3.0) | -6.2 (-8.0 to -4.4) | -4.8 (-7.0 to -2.5) | -8.8 (-14.0 to -3.5) |
| Change from end of valsartan run-in to Week 16 | +4.9 ± 0.4 | +0.8 ± 0.4 | -7.0 ± 0.8 | -10.9 ± 0.7 | -6.4 ± 0.9 | -10.3 ± 1.0 | -2.8 ± 2.1 | -9.1 ± 2.4 |
| Between treatment group difference | -4.1 (-5.3 to -2.9) | -3.9 (-6.0 to -1.8) | -3.9 (-6.6 to -1.3) | -6.3 (-12.5 to -0.1) |
| SBP controlled by Week 16, n (%) | 964 (71.1) | 1103 (81.7) | 216 (37.5) | 304 (47.5) | 127 (34.3) | 163 (47.9) | 21 (28.4) | 24 (43.6) |
| Adjusted odds ratio (95% CI) for SBP control | 1.80 (1.49–2.16) | 1.52 (1.20–1.92) | 1.78 (1.30–2.43) | 2.63 (1.18–5.89) |

SBP is shown as mean ± standard deviation and changes are shown as estimate ± standard error. All models include SBP at the end of valsartan run-in, age, sex, body mass index, cigarette smoking, and region. Models examining SBP change also include SBP at all other time points up to Week 16 and an interaction term between treatment and time. CI, confidence interval; MRA, mineralocorticoid receptor antagonist; SBP, systolic blood pressure.
Figure 2. Change in systolic blood pressure in patients with controlled blood pressure, ‘non-resistant’, ‘apparent resistant’, and ‘apparent mineralocorticoid receptor antagonist-resistant’ hypertension. Week -2 = end of the open run-in period of treatment with valsartan 80 mg twice daily and Week 0 = end of the open run-in period of treatment with sacubitril–valsartan 49/51 mg. Thereafter, patients randomized to double-blind treatment with valsartan 160 mg twice daily or sacubitril–valsartan 97/103 mg twice daily. Models include systolic blood pressure at the end of the valsartan run-in, age, sex, body mass index, cigarette smoking, and region, as well as systolic blood pressure at all other time points up to Week 16 and an interaction term between treatment and time. MRA, mineralocorticoid receptor antagonist.

Table 4. Safety of sacubitril–valsartan compared with valsartan in patients according to hypertension category

| Hypertension                                                                 | Controlled blood pressure | Non-resistant hypertension | Apparent resistant hypertension | Interaction P-value |
|-------------------------------------------------------------------------------|---------------------------|----------------------------|--------------------------------|---------------------|
| Hypotension                                                                  | Valsartan | Sacubitril–valsartan | Valsartan | Sacubitril–valsartan | Valsartan | Sacubitril–valsartan |                                    |
| Elevated serum creatinine (mg/dL)                                            |            |                      |            |                      |            |                      |                                    |
| >2.0                                                                          | 185 (13.2) | 146 (10.5)           | 69 (11.3) | 64 (9.7)             | 74 (19.5) | 51 (14.5)            | 0.71                              |
| >2.5                                                                          | 51 (3.6)   | 54 (3.9)             | 27 (4.4)  | 21 (3.2)             | 31 (8.2)  | 22 (6.2)             | 0.41                              |
| >3.0                                                                          | 18 (1.3)   | 26 (1.9)             | 9 (1.5)   | 6 (0.9)              | 13 (3.4)  | 6 (1.7)              | 0.09                              |
| Elevated serum potassium (mmol/L)                                            |            |                      |            |                      |            |                      |                                    |
| >5.5                                                                          | 217 (15.5) | 187 (13.4)           | 77 (12.6) | 77 (11.7)            | 67 (17.7) | 51 (14.5)            | 0.87                              |
| >6.0                                                                          | 59 (4.2)   | 42 (3.0)             | 21 (3.4)  | 19 (2.9)             | 21 (5.5)  | 14 (4.0)             | 0.91                              |
controlled morbidity/mortality trials, these studies did not raise safety concerns and ARBs are, therefore, another useful antihypertensive therapy in HfPEF. The same is true of spironolactone. Thereafter, evidence is lacking. There is no large randomized placebo-controlled experience with beta-blockers, with only 314 patients with an LVEF >50% enrolled in the landmark trials, and a recent analysis of non-randomized beta-blocker use in TOPCAT showed that this treatment was associated with a higher risk of heart failure hospitalization in patients with an LVEF >50%. Dihydropyridine calcium channel blockers cause peripheral oedema and heart failure to develop significantly more often in hypertensive patients treated with alpha-adrenoceptor blockers than with other blood pressure-lowering drugs. Indeed, in the setting of increased pulmonary blood flow, dihydropyridine calcium channel blockers can cause pulmonary oedema as a result of pre-capillary vasodilation in the pulmonary circulation, and it is of interest that the two blood pressure groups with the highest rates of use of calcium channel blockers (controlled blood pressure and apparent resistant hypertension) had the highest rates of heart failure hospitalization in the present study. The possibility that nephrilysin inhibition might be an effective, as well as safe, blood pressure-reducing therapy in HfPEF suggests that this approach may be a valuable addition to the antihypertensive options available for these patients (and consistent with early studies of sacubitril–valsartan in patients with uncomplicated hypertension, including elderly individuals who comprise the majority of people with HfPEF).

However, the focus of the current report is ‘apparent resistant hypertension’, and nephrilysin inhibition also reduced blood pressure in patients remaining hypertensive despite treatment with the recommended combination of an ARB, a calcium channel blocker, and a diuretic; indeed, 77% of these patients were also treated with a beta-blocker and 13% with an alpha-blocker. Spironolactone has also been shown to reduce blood pressure in HfPEF patients with resistant hypertension. Specifically, in TOPCAT, 403 HfPEF patients (23%) enrolled in the Americas had ‘resistant hypertension’, defined as a systolic blood pressure between 140 and 160 mmHg, despite treatment with three or more antihypertensive medications. After 4 months, systolic blood pressure was reduced by 5.3 mmHg compared with placebo, in keeping with the superior blood pressure reduction exhibited with spironolactone, compared with other treatments, in patients with resistant hypertension in the PATHWAY-2 trial. In TOPCAT, spironolactone also increased the proportion of patients achieving blood pressure control significantly (OR 1.77, 95% CI 1.16–2.69). In our analysis of the 731 patients in PARAGON-HF qualifying because of a high risk faced by these patients, we believe that this incremental antihypertensive action of nephrilysin inhibition on top of an MRA could be of considerable clinical importance, if confirmed. This benefit is likely to reflect the complementary and additive mechanisms of action of the two drugs, with spironolactone treating sodium and water retention and nephrilysin inhibition augmenting natriuretic and other vasodilator peptides (e.g. adrenomedullin), as well as possibly reducing sympathetic activation. The elevation in natriuretic peptides may be particularly relevant in this patient subgroup who had the lowest baseline levels of these peptides, probably reflecting the high prevalence of obesity in these patients. In addition to more effective blood pressure lowering, sacubitril–valsartan reduces arterial stiffness and left ventricular mass more than an ARB, other actions likely to be valuable in patients with HfPEF.

Importantly, the renal safety profile of sacubitril–valsartan in this study was favourable, irrespective of the definition of resistant hypertension used. In fact, elevation of serum creatinine and potassium generally occurred less frequently in patients with apparent resistant hypertension taking sacubitril–valsartan than it did in those taking valsartan. This is particularly important in patients taking both an ARB and MRA, where the risk of decline in renal function and/or hyperkalaemia is accentuated.

Examining clinical outcomes, it was of interest that patients with ‘non-resistant’ hypertension were at lower risk than patients with ‘apparent resistant hypertension’, despite a similar baseline systolic blood pressure and, in fact, had a risk similar to patients with a controlled blood pressure. The greater risk of the primary composite outcome seen for patients with ‘apparent resistant hypertension’ was driven predominantly by heart failure hospitalization, consistent with heart failure being a blood pressure sensitive endpoint in hypertension trials. We do not know what the explanation for this is, although our data suggest several possibilities. The prevalence of obesity was higher in the ‘apparent resistant hypertension’ group, compared with both the ‘non-resistant’ hypertension and controlled blood pressure groups (who had a similar prevalence of obesity) and more obese HfPEF patients have higher heart failure hospitalization rates. Baseline use of an MRA was lowest in patients with apparent resistant hypertension and highest in those with a controlled blood pressure group, and MRA therapy may reduce the risk of heart failure hospitalization in HfPEF. Conversely, the use of alpha-adrenoceptor antagonists was much higher among patients with apparent resistant hypertension than in the other groups, and alpha-blockers increase the risk of heart failure hospitalization in patients with hypertension. It is possible that there were other differences between these groups for which we did not have data. For example, patients with apparent resistant hypertension may have had a longer history of disease, a longer time sub-optimally treated in the early course of their disease, unidentified end-organ damage, or differences in diurnal blood pressure profile.

Two additional observations are worthy of comment, although are not based on randomized comparisons. First, the decline in systolic blood pressure after switching from valsartan 80 mg b.i.d. to sacubitril–valsartan 49/51 mg b.i.d. (i.e. from the first to the second consecutive run-in period) seemed to be larger than the blood pressure difference between valsartan 80 and 160 mg b.i.d. However, systolic pressure did appear to decrease with 160 mg b.i.d. of valsartan compared to 80 mg b.i.d. of valsartan.
This study had some limitations. Certain patients were excluded from PARAGON-HF including those with a systolic blood pressure >180 mmHg and an eGFR <30 mL/min/1.73 m². Similarly, patients with a systolic blood pressure of >150 and <180 mmHg were only eligible for enrolment if receiving at least three antihypertensive agents, which may have increased the proportion of patients who fulfilled the definition of apparent resistant hypertension in this study. Blood pressure measured at trial follow-up visits was not standardized and repeated in the same way as in dedicated hypertension trials and we did not perform ambulatory blood pressure monitoring or out-of-office measurements, which would be required to confirm true resistant hypertension. We did not have information on treatment adherence or time between administration of antihypertensive medication and measurements of blood pressure, but drug adherence in patients with heart failure has previously been found to be much better than in people with hypertension. Because of the way we measured blood pressure, because we did not know the doses of all classes of blood pressure-lowering drugs or whether these were at maximally tolerated doses, and because we could not confirm adherence, we could not exclude pseudo-resistance; therefore, the term ‘apparent resistant hypertension’ was used to describe this group, although the proportion of patients in this category was consistent with other studies of patients classified as having resistant hypertension. Also, as our trial had sequential run-in periods, the patients randomized to valsartan 160 mg b.i.d. had just discontinued sacubitril–valsartan 49.5/1 mg b.i.d. As the effect of sacubitril–valsartan was borderline statistical significance in the overall trial, we did not have the power to examine the effect of sacubitril–valsartan in each hypertension subgroup.

In summary, we have examined the efficacy and safety of sacubitril–valsartan in treating apparent resistant hypertension in patients with HFpEF, when compared with valsartan alone. Our findings suggest that sacubitril–valsartan is effective in reducing blood pressure not only in patients with apparent resistant hypertension but also in those who have more refractory, or apparent MRA-resistant hypertension, with an elevated systolic blood pressure despite treatment with at least four antihypertensive drug classes, including an MRA.

Supplementary material

Supplementary material is available at European Heart Journal online.

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committee member of the PARADISE-MI (Prospective ARNI vs. ACE Inhibitor Trial to Determine Superiority in Reducing Heart Failure Events After MI) and PERSPECTIVE (Efficacy and Safety of LCZ696 Compared to Valsartan on Cognitive Function in Patients With Chronic Heart Failure and Preserved Ejection Fraction) trials (with sacubitril–valsartan) and for meetings/presentations related to these trials, aliskiren, and sacubitril–valsartan. Novartis has also paid for his travel and accommodation for some of these meetings. 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References

1. Slivnick J, Lampert BC. Hypertension and heart failure. Heart Fail Clin 2019;15:531–541.
2. Gladden JD, Chaanine AH, Redfield MM. Heart failure with preserved ejection fraction. Annu Rev Med 2018;69:65–79.
3. Tadic M, Cupidil C, Frydas A, Grassi G. The role of arterial hypertension in development heart failure with preserved ejection fraction: just a risk factor or something more? Heart Fail Rev 2018;23:631–639.
4. Gupta T, Rezan T, Krim SR. Managing hypertension in patients with heart failure. Curr Opin Cardiol 2019;34:359–366.
5. Shah SJ. Gheorghade M. Heart failure with preserved ejection fraction: treat now by treating comorbidities. JAMA 2008;300:431–433.
6. Rossignol P, Claggett BL, Liu J, Vardeny O, Piet B, Zannad F, Solomon S. Spironolactone and resistant hypertension in heart failure with preserved ejection fraction. Am J Hypertens 2018;31:407–414.
7. Jin C-N, Liu M, Sun J-P, Fang F, Wen Y-N, Yu C-M, Lee APW. The prevalence and prognosis of resistant hypertension in patients with heart failure. PLoS One 2014;9:e114958.
8. Carey RM, Calhoun DA, Bakris GL, Brook RD, Dennison-Himmelfarb CR, Egan BM, Flick JM, Gidding SS, Judd E, Lakkand LA, Laffer CL, Newton-Cheh C, Smith SM, Taler SJ, Tector SC, Turan TN, White WB. American Heart Association Professional/Public Education and Publications Committee of the Council on Hypertension; Council on Cardiovascular and Stroke Nursing; Council on Clinical Cardiology; Council on Genomic and Precision Medicine; Council on Peripheral Vascular Disease; Council on Quality of Care and Outcomes Research; and Stroke Council. Resistant hypertension: detection, evaluation, and management; a scientific statement from the American Heart Association. Hypertension 2018;72:e53–e90.
9. Williams B, Mancia G, Spiering W, Agabiti Roselli E, Azizi M, Burnier M, Clement DL, Coca a, de Simone G, Dominiczak A, Kahan T, Mahfoud F, Redon J, Rulope L, Zanchetti A, Kerns M, Kjeldsen SE, Kreutz R, Laurent S, Lip GTH, McNaman R, Narkiewicz K, Rutschitzka F, Schmieder RE, Shlyakhto E, Tiscaus G, Abeyans V, Desormais J;ESC Scientific Document Group. 2018 ESC/ESH Guidelines for the management of arterial hypertension. Eur Heart J 2018;39:3021–3104.
10. Rulope LM, Dukat A, Böhm M, Laccourcière Y, Gong J, Leftkowitz 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.
11. Solomon SD, Zile M, Pieske B, Voors A, Shah A, Kraigher-Kainer E, Shi V, Bransford T, Takeuchi M, Gong J, Leftkowitz M, Packer M, McMurray JJ. Prospective comparison of ARNI with ARB on Management Of heart failure with preserved ejection fraction (PARAMOUNT) Investigators. The angiotensin receptor neprilysin inhibitor LCZ696 in heart failure with preserved ejection fraction: a phase 2 double-blind randomised controlled trial. Lancet 2012;380:1387–1395.
12. Solomon SD, McMurray JJV, Anand IS, Ge J, Lam CSP, Maggioni AP, Martinez F, Packer M, Pfeffer MA, Pieske B, Redfield MM, Routes J, van Velden DJ, Zannad F, Zile MR, Desai AS, Claggett B, Jhund PS, Boystadt SA, Comin-Colet J, Cleland J, Düngen H-D, Goncalvesova E, Katova T, Kerr Saravia JF, Lelonek M, Merkely B, Senni M, Shah SJ, Zhou J, Rziala AR, Gong J, Shi VC, Leftkowitz M, PARAGON-HF Investigators and Committees. Angiotensin–neprilysin inhibition in heart failure with preserved ejection fraction. N Engl J Med 2019;381:1609–1620.
13. Sekaraj S, Claggett BL, Böhm M, Anker SD, Vladianathan M, Zannad F, Pieske B, Lam CSP, Anand IS, Shi VC, Leftkowitz MP, McMurray JVF, Solomon SD. Systolic blood pressure in heart failure with preserved ejection fraction treated with sacubitril/valsartan. J Am Coll Cardiol 2020;75:1644–1656.
Sacubitril–valsartan for resistant hypertension in HFpEF

14. Hiremath S, Sapir-Pichhadze R, Nakhlia M, Gabor JY, Khan NA, Kyper LM, Ruzicka M, Tobe SW, Tran K, Rabi DM, Daskalopoulou SS. Hypertension Canada's 2020 evidence review and guidelines for the management of resistant hypertension. Can J Cardiol 2020;36:625–634.

15. Williams B, MacDonald TM, Morant S, Webb DJ, Sever P, Michines G, Ford I, Cruickshank JK, Caufield MJ, Salbury J, Mackenzie I, Padmanabhan S, Brown MJ. British Hypertension Society's PATHWAY Studies Group. Spironolactone versus placebo, bisoprolol, and doxazosin to determine the optimal treatment for drug-resistant hypertension (PATHWAY-2): a randomised, double-blind, crossover trial. Lancet 2015;386:2059–2068.

16. Solomon SD, Rizkala AR, Gong J, Wang W, Anand IS, Ge J, Lam CSP, Maggioni AP, Martinez F, Packer M, Pfeffer MA, Pieck B, Redfield MM, Rouleau JL, Van Veldhuisen DJ, Zannad F, Zile MR, Desai AS, Shi VC, Lefkowitz MP, McMurray JJV. Angiotensin receptor neprilysin inhibition in heart failure with preserved ejection fraction: rationale and design of the PARAGON-HF trial. JACC Heart Fail 2017;5:471–482.

17. Solomon SD, Rizkala AR, Lefkowitz MP, Shi VC, Gong J, Anavekar N, Anker SD, Arango JL, Arenas JL, Atar D, Ben-Gal T, Boysoyan SA, Chen C-H, Chopra VK, Cleland J, Comin-Colet J, Duengens H-D, Echeverria Correa LE, Filippatos G, Flammer AJ, Galimier M, Godoy A, Goncalvesova E, Janssens E, Katsoa S, Katsoa T, Keber L, Lelonek M, Linssen G, Lund L, O'Meara E, Merkely B, Milicic D, Oh B-H, Perrone SV, Ranjit N, Saito Y, Saravia JF, Shah S, Seferovic PM, Senni M, Sibullo AS, Sim D, Swierzewski NK, Taurio J, Vancreau D, Vrtovec B, Widimsky J, Yilmaz MB, Zhou J, Zoecker R, Anand IS, Ge J, Lam CSP, Maggioni AP, Martinez F, Packer M, Pfeffer MA, Pieck B, Redfield MM, Rouleau JL, Van Veldhuisen DJ, Zannad F, Zile MR, McMurray JJV. Baseline characteristics of patients with heart failure and preserved ejection fraction in the PARAGON-HF trial. Circ Heart Fail 2018;11:e004962.

18. Claggett B, Pocock S, Wei LJ, Pfeffer MA, McMurray JJV. Solomon SD. Comparison of time-to-first event and recurrent-event methods in randomized clinical trials. Circulation 2018;138:570–577.

19. Shen L, Ranth R, Cosmi D, Kristensen SL, Petrie MC, Cosmi F, Latino R, Keber L, Anand IS, Carson PE, Granger CB, Komajda M, McKeilve RS, Solomon SD, Staszewsky L, Swedberg K, Huynh T, Zile MR, Jhund PS, McMurray JJV. Insulin treatment and clinical outcomes in patients with diabetes and heart failure with preserved ejection fraction. Eur J Heart Fail 2019;21:974–984.

20. Yusuuf S, Pfeffer MA, Swedberg K, Granger CB, Held P, McMurray JJV, Michelson EL, Olasson B, Ostergren J. CHARM Investigators and Committees. Effects of candesartan in patients with chronic heart failure and preserved left-ventricular ejection fraction: the CHARM-Preserved Trial. Lancet 2003;362:777–781.

21. Massie BM, Carson PE, McMurray JJV, Komajda M, McKeilve R, Zile MR, Anderson S, Donovan M, Iversen E, Staiger C, Piazynska A. I-PRESERVE Investigators. Irbesartan in patients with heart failure and preserved ejection fraction. N Engl J Med 2008;359:2456–2467.

22. Pitt B, Pfeffer MA, Assmann SF, Boineau R, Anand IS, Claggett B, Clausell N, Desai AS, Diaz R, Fglg J, Gordelev I, Harty B, Heitner JF, Kenwood CT, Lewis EF, O'Meara E, Probstfield JL, Shabunihvili T, Shah SJ, Solomon SD, Swierzewski K, Yun S, Yung SY, McMurray JJV. Spironolactone for heart failure with preserved ejection fraction. N Engl J Med 2014;370:1383–1392.

23. Silverman DN, Plante TB, Infeld M, Cailas PW, Jurasech SP, Dougherty GB, Meyer M. Association of β-blocker use with heart failure hospitalizations and cardiovascular disease mortality among patients with heart failure with a preserved ejection fraction. JAMA Netw Open 2019;2:e1916598.

24. Cleland GF, Bunting KV, Flather MD, Altman DG, Holmes J, Coats AJ, Manzano L, McMurray JJV, Ruschitzka F, Van Veldhuisen DJ, Van Luntert G, Bohm M, Anderson B, Kjekshus J, Packer M, Rigby AS, Rosano G, Wedel H, Hjalmarson A, Wikstrand J, Kotecha D. Beta-blockers in Heart Failure Collaborative Group. Beta-blockers for heart failure with reduced, mid-range, and preserved ejection fraction: an individual-patient-level analysis of double-blind randomized trials. Eur Heart J 2018;39:26–35.

25. ALLHAT Collaborative Research Group. Major cardiovascular events in hypertensive patients randomized to doxazosin vs chlorthalidone: the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). JAMA 2000;283:1967–1975.

26. Humbert VH Jr, Munn NJ, Hawkins RF. Noncardiogenic pulmonary edema complicating massive diabetosis overdose. Chest 1991;99:258–259.

27. Zhao Y, Yu H, Zhao X, Ma R, Li N, Yu J. The effects of LCZ696 in patients with hypertension compared with angiotensin receptor blockers: a meta-analysis of randomized controlled trials. J Cardiovasc Pharmacol Ther 2017;22:447–457.

28. 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.

29. Casale R, Messeri FH, Kadoh B, Rulope LM, Kario K. Role of nephrilysin inhibitor combinations in hypertension: insights from hypertension and heart failure trials. Eur Heart J 2015;36:1967–1973.

30. Dassi-Fulghen P, Sarzani R, Rappelli A. The natriuretic peptide system in obesity-related hypertension: new pathophysiological aspects. J Nephrol 1998;11:296–300.

31. Clerico A, Giannini A, Vittorini S, Emdin M. The paradox of low BNP levels in obesity. Can J Cardiol 2012;17:81–96.

32. Neelad J, Winders BR, Ayers CR, Das SR, Chang AY, Berry JD, Khera A, McGuire DK, Vega GL, De Lemos JA, Turer AT. Higher natriuretic peptide levels associate with a favorable adipose tissue distribution profile. J Am Coll Cardiol 2013;62:572–580.

33. Schmieder RE, Wagner F, Mayr M, Delles C, Ott C, Keicher C, Hrabak-Paar M, Heye T, Aichner S, Kheder Y, Yates D, Albrecht D, Langeninkel T, Freyhardt P, Jania R, Bremerich J. The effect of sacubitril/valsartan compared to olmesartan on cardiovascular remodeling in subjects with essential hypertension: the results of a randomized, double-blind, active-controlled study. Eur Heart J 2017;38:3308–3317.

34. Suzuki K, Claggett B, Minamisawa N, Nochioka K, Mitchell GF, Anand IS, Zannad F, Shah SJ, Lefkowitz M, Shi V, Pfeffer MA, McMurray JJV, Solomon SD. Pulse pressure, prognosis, and influence of sacubitril/valsartan in heart failure with preserved ejection fraction. Hypertension 2021;71:546–536.

35. Damman K, Gori M, Claggett B, Jhund PS, Senni M, Lefkowitz MP, Prescott MF, Shi VC, Rauoleau JL, Swedberg K, Zile MR, Packer M, Desai AS, Solomon SD, McMurray JJV. Renal effects and associated outcomes during angiotensin-nephrilysin inhibition in heart failure. JACC Heart Fail 2018;6:489–498.

36. Jeng KS, Zannad F, Claggett B, Mc Causland FR, Ferreira JP, Desai A, Barkoudah E, McMurray JJV, Pfeffer MA, Solomon SD. Cardiovascular and renal outcomes of mineralocorticoid receptor antagonist use in PARAGON-HF. JACC Heart Fail 2021;9:13–24.

37. Mandiwala TM, Basa SS, Khalid U, Pickett JK, Przybylowicz R, Shah T, Namibi V, Virani SS, Deswal A. Obesity and the paradox of mortality and heart failure hospitalization in heart failure with preserved ejection fraction. Int J Obes 2020;44:1561–1567.

38. Tomaszewski M, White C, Patel P, Masca N, Damaris R, Hepworth J, Samani NJ, Gupta P, Madras W, Stanley A, Williams B. High rates of non-adherence to anti-hypertensive treatment revealed by high-performance liquid chromatography-tandem mass spectrometry (HP LC-MS/MS) urine analysis. Heart 2014;100:855–861.

39. Simpson J, Jackson CE, Hoig C, Jhund PS, Tomaszewski M, Gardner RS, Tsorlalis Y, Pennie MC, McMurray JJV, Squire IB, Gupta P. Adherence to prescribed medications in patients with heart failure: insights from liquid chromatography–tandem mass spectrometry-based urine analysis. Eur J Heart J Cardiovasc Pharmacother 2021;7:296–301.

40. Sweeney M, Cole GD, Papari P, Hadjiphippou S, Taitt U, Mayet J, Chapman N, Pym CM. Urinary drug metabolite testing in chronic heart failure patients indicates high levels of adherence with long-prolonging therapies. ESC Heart Fail 2021;8:2334–2337.