ESC European Society of Cardiology

European Heart Journal (2021) **42**, 3741–3752
doi:10.1093/eurheartj/ehab499

CLINICAL RESEARCH
Heart failure and cardiomyopathies

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

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Received 8 February 2021; revised 21 April 2021; editorial decision 6 July 2021; accepted 16 July 2021; online publish-ahead-of-print 15 August 2021

See page 3753 for the editorial comment on this article (doi:10.1093/eurheartj/ehab489)

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

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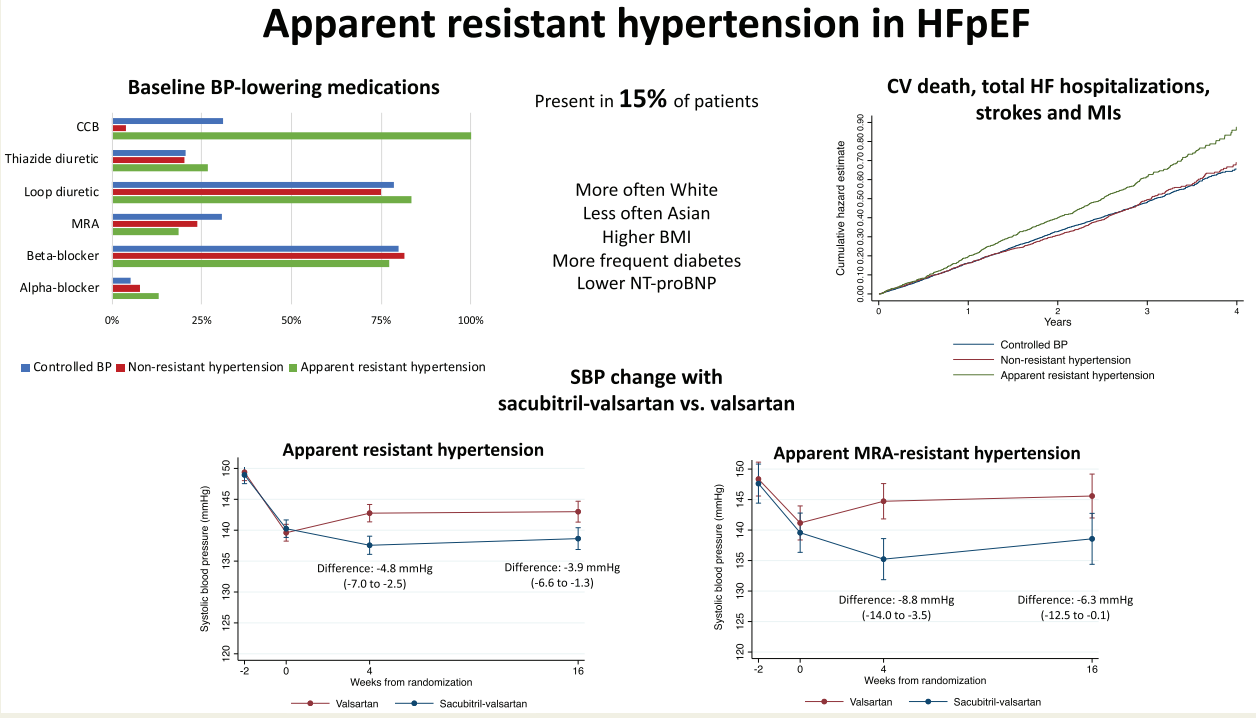
of 1.28 (95% CI 1.05–1.57). The reduction in systolic blood pressure at Weeks 4 and 16, respectively, was greater with sacubitril–valsartan vs. valsartan in patients with apparent resistant hypertension [-4.8 (-7.0 to -2.5) and 3.9 (-6.6 to -1.3) mmHg] and apparent MRA-resistant hypertension [-8.8 (-14.0 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.[1–3] Ninety percent or more of patients with HFpEF in contemporary trials have a history of hypertension.[1–3] 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.[4,5] 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.[14]

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 m^2, 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 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 ≥140 mmHg (≥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 ≥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.[8] Finally, we also examined patients with more refractory, 'apparent MRA-resistant' hypertension, defined as: systolic blood pressure ≥140 mmHg (≥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 χ^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 (±11.0), 149.1 (±11.2), and 123.6 (±9.2) mmHg, respectively. Systolic blood pressure in patients with apparent MRA-resistant hypertension was 148.0 (±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*).

Table 1 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[a] (mmHg)	123.6 ± 9.2	149.1 ± 11.2	149.2 ± 11.0	<0.001	<0.001	<0.001
Diastolic blood pressure[a] (mmHg)	72.7 ± 10.0	80.4 ± 10.5	78.7 ± 10.7	<0.001	<0.001	<0.001
Pulse pressure[a] (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				<0.001	0.052	<0.001
American Indian/Alaska native	27 (1.0)	18 (1.4)	6 (0.8)			
Asian	414 (14.8)	145 (11.4)	48 (6.6)			
Black/African American	59 (2.1)	24 (1.9)	19 (2.6)			
Native Hawaiian/Pacific Islander	1 (0.0)	0 (0.0)	0 (0.0)			
Other	69 (2.5)	37 (2.9)	22 (3.0)			
White	2226 (79.6)	1044 (82.3)	636 (87.0)			
Cigarette smoking (current or former)	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/m^2)	30.0 ± 5.0	30.2 ± 5.1	31.2 ± 4.8	<0.001	0.32	<0.001
Body mass index (>30 kg/m^2)	1320 (47.2)	611 (48.2)	422 (57.7)	<0.001	0.55	<0.001
eGFR (mL/min/1.73 m^2)	62 ± 19	64 ± 19	63 ± 20	0.019	0.005	0.34
eGFR (<60 mL/min/1.73 m^2)	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				0.76	0.40	0.95
I	75 (2.7)	40 (3.2)	22 (3.0)			
II	2152 (77.0)	990 (78.1)	563 (77.0)			
III	557 (19.9)	231 (18.2)	144 (19.7)			
IV	10 (0.4)	7 (0.6)	2 (0.3)			
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[b]	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[b]	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[b]	4.9 ± 3.3	4.9 ± 3.0	5.1 ± 3.1	0.46	0.70	0.31
Alpha-blocker[c]	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.

[a]At the end of valsartan run-in.

[b]In 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.

[c]Doxazosin, 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 0.8–1.7 per 100 person-years) compared to those with a controlled blood pressure (0.6; 95% CI 0.4–0.8 per 100 person-years), with an adjusted rate ratio of 1.72 (95% CI 1.04–2.86).

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			
Number of events	1305	603	446
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)

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.

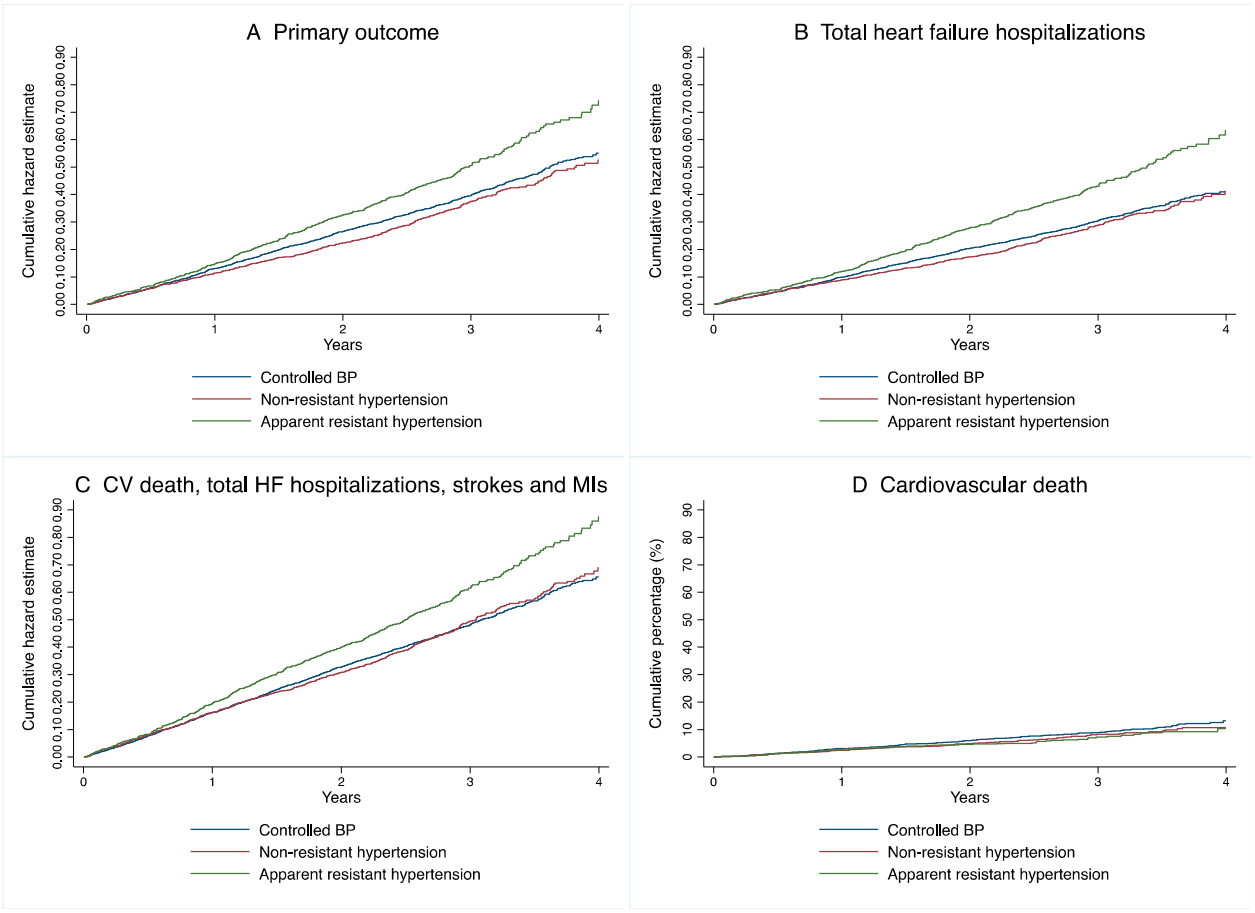


Figure 1 Hazard and survival curves according to hypertension category. (*A*) Primary outcome. (*B*) Total heart failure hospitalizations. (*C*) Cardiovascular death, total heart failure hospitalizations, strokes, and myocardial infarctions. (*D*) Cardiovascular death. BP, blood pressure; CV, cardiovascular; HF, heart failure; MI, myocardial infarction.

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

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.

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

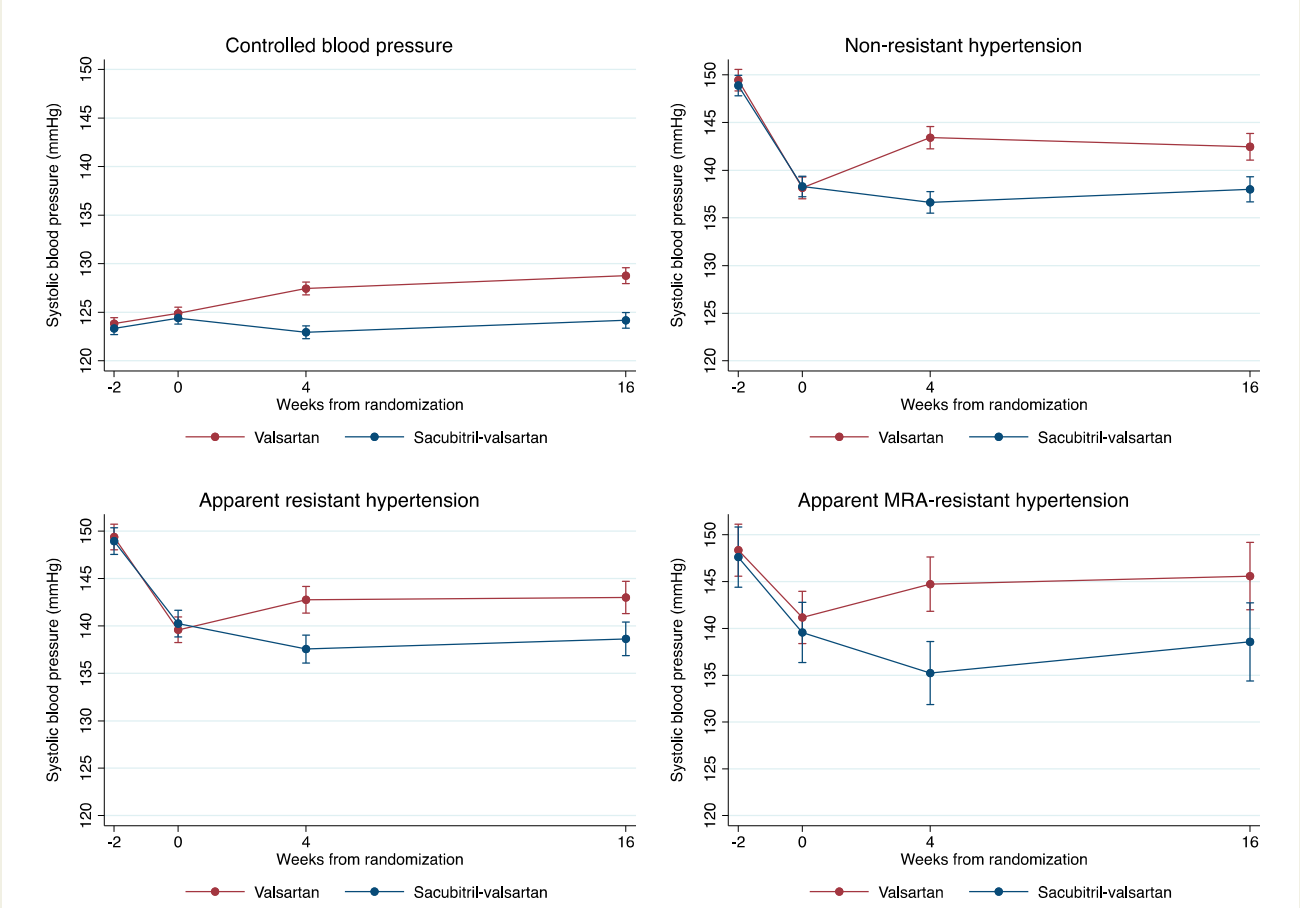


Figure 2 Change in systolic blood pressure in patients with controlled blood pressure, 'non-resistant', 'apparent resistant', and 'apparent mineralocorticoid receptor antagonist-resistant' hypertension. Week -2 = end of the open run-in period of treatment with valsartan 80 mg twice daily and Week 0 = 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

	Controlled blood pressure		Non-resistant hypertension		Apparent resistant hypertension		Interaction *P*-value
	Valsartan	Sacubitril–valsartan	Valsartan	Sacubitril–valsartan	Valsartan	Sacubitril–valsartan	
Hypotension	208 (14.8)	314 (22.5)	38 (6.2)	50 (7.6)	11 (2.9)	16 (4.5)	0.55
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,[20,21] these studies did not raise safety concerns and ARBs are, therefore, another useful antihypertensive therapy in HFpEF. The same is true of spironolactone.[22] 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%.[23,24] 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.[25] 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.[26] The possibility that neprilysin 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 and sacubitril–valsartan in patients with uncomplicated hypertension, including elderly individuals who comprise the majority of people with HFpEF).[10,13,27,28]

However, the focus of the current report is 'apparent resistant hypertension', and neprilysin 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.[6] After 4 months, systolic blood pressure was reduced by 5.53 (standard error 1.95) mmHg with spironolactone 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.[15] In TOPCAT, spironolactone also increased the proportion of patients achieving blood pressure control significantly (OR 1.77, 95% CI 1.16–2.69).[6] In our analysis of the 731 patients in PARAGON-HF qualifying because of a similar blood pressure threshold, neprilysin inhibition reduced systolic blood pressure by 3.9 (-6.6 to -1.3) mmHg at 4 months. Neprilysin inhibition also increased the proportion of patients with a controlled blood pressure significantly (OR 1.78, 95% CI 1.30–2.43). More importantly, neprilysin inhibition also reduced systolic blood pressure [by 6.3 (-12.5 to -0.1) mmHg] in the 135 patients treated with an MRA in addition to an ARB, a calcium channel blocker, and a diuretic (i.e. with at least four drugs), resulting in a more than doubling of the proportion of patients attaining blood pressure control with neprilysin inhibition (OR 2.63, 95% CI 1.18–5.89). Given the superior efficacy of spironolactone as a treatment for resistant hypertension, and the high risk faced by these patients, we believe that this incremental antihypertensive action of neprilysin 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 neprilysin inhibition augmenting natriuretic and other vasodilator peptides (e.g. adrenomedullin), as well as possibly reducing sympathetic activation.[29] 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.[30–32] 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.[33,34]

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.[35,36]

Examining clinical outcomes, it was of interest that patents 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.[37] 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.[23] 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.[25] 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 m^2. 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.[38–40] 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 49/51 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.

Funding

A.M.J. is supported by a British Heart Foundation Clinical Research Training Fellowship (FS/18/14/33330) and J.J.V.M. is supported by a British Heart Foundation Centre of Research Excellence Grant (RE/18/6/34217).

Conflict of interest: P.S.J. has received personal fees from Novartis AstraZeneca, personal fees and grants Boehringer Ingelheim and his employer, the University of Glasgow and has received remuneration from AstraZeneca for work on the DAPA-HF and DELIVER trials. I.S.A. has received personal fees from Novartis, Amgen, ARCA, AstraZeneca, Boehringer Ingelheim, Boston Scientific, LivaNova, and Zensun. H.-D.D. has received grants and personal fees from Novartis, Bayer, Amgen, Boehringer Ingelheim, and CSL Behring. L.H.L. has received personal fees from Merck, Bayer, Pharmacosmos, Abbott, Medscape, Myokardia, Sanofi, Lexicon, and Radcliffe cardiology, grants and personal fees from Vifor-Fresenius, AstraZeneca, Boehringer Ingelheim, and Novartis, and grants from Boston Scientific. C.S.P.L. is supported by a Clinician Scientist Award from the National Medical Research Council of Singapore, has received research support from AstraZeneca, Bayer, Boston Scientific, and Roche Diagnostics, has served as consultant or on the Advisory Board/Steering Committee/Executive Committee for Actelion, Amgen, Applied Therapeutics, AstraZeneca, Bayer, Boehringer Ingelheim, Boston Scientific, Cytokinetics, Darma Inc., Janssen Research & Development LLC, Medscape, Merck, Novartis, Novo Nordisk, Radcliffe Group Ltd, Roche Diagnostics, Sanofi, Us2.ai, and WebMD Global LLC and serves as co-founder and non-executive director of Us2.ai. M.P.L. is an employee of Novartis. A.P.M. has received personal fees from Novartis, Bayer, AstraZeneca, and Fresenius. J.L.R. has received personal fees from Novartis, AstraZeneca, Abbott, Bayer, Aventis, and Myokardia/BMS. M.A.P. has received grants from Novartis and personal fees from Astra Zeneca, Boehringer Ingelheim, Eli Lilly Alliance, Corvidia, DalCor, GlaxoSmithKline, Lexicon, NHLBI CONNECTs (Master Protocol Committee), Novartis, Novo Nordisk, Peerbridge, and Sanofi. Y.S. has received grants from MEXT KAKENHI, Health Labour Sciences Research, and AMED, grants and personal fees from Otsuka Pharmaceutical Co. Ltd, Ono Pharmaceutical Co. Ltd, Daiichi Sankyo Co. Ltd, Mitsubishi Tanabe Pharma Corporation, Bristol-Myers Squibb Company, Kowa Pharmaceutical Co. Ltd, Teijin Pharma Ltd, Novartis Pharma, Pfizer Japan Inc., and Bayer Yakuhin, Ltd, personal fees from Alnylam Japan K.K., AstraZeneca., Tsumura & Co., Toa Eiyo Ltd, Nippon Shinyaku Co. Ltd, Nippon Boehringer Ingelheim Co. Ltd, and Mochida Pharmaceutical Co. Ltd, grants from Takeda Pharmaceutical Co. Ltd, Actelion Pharmaceuticals Japan Ltd, Kyowa Kirin Co. Ltd, Shionogi & Co. Ltd, Dainippon Sumitomo Pharma Co. Ltd, Chugai Pharmaceutical Co. Ltd, Eli Lilly Japan K.K., Nihon Medi-Physics Co. Ltd, and Fuji Yakuhin Co. Ltd, and research support from Amgen Astellas BioPharma K.K. Actelion Pharmaceuticals Japan Ltd, Novartis, Bayer Yakuhin Ltd, and Roche Diagnostics. J.F.S. has received grants from Novartis, Novo Nordisk, AstraZeneca, and Boehringer Ingelheim. M.S. has consulted for Novartis, Abbott, Merck, Bayer, Vifor, Boehringer, and AstraZeneca. M.R.Z. has received personal fees from Novartis. O.V. has received grants from AstraZeneca and Bayer and personal fees from Novartis. M.O.W. has received grants from The Swedish Heart Association, The Swedish Society of Medicine, Region Östergötland, Sweden, and personal fees from MSD, Lilly, and Novo Nordisk, and has organized a professional regional meeting in Sweden sponsored by Lilly, Rubin Medical, Sanofi, Novartis, and Novo Nordisk. M.B.Y. has received grants from Novartis, Amgen, Bayer, and Dalcor Pharmaceuticals. S.D.S. has received grants from Novartis, Actelion, Alnylam, Amgen, AstraZeneca, Bellerophon, Bayer, BMS, Celladon, Cytokinetics, Eidos, Gilead, GSK, Ionis, Lilly, Lone Star Heart, Mesoblast, MyoKardia, NIH/NHLBI, Neurotronik, Novartis, Novo Nordisk, Respicardia, Sanofi Pasteur, and Theracos and and personal fees from Abbott, Actelion, Akros, Alnylam, Amgen, Arena, AstraZeneca, Bayer, Boeringer-Ingelheim, BMS, Cardior, Cardurion, Corvia, Cytokinetics, Daiichi Sankyo, Gilead, GSK, Ironwood, Lilly, Merck, Myokardia, Novartis, Roche, Takeda, Theracos, Quantum Genetics, Cardurion, AoBiome, Janssen, Cardiac Dimensions, Sanofi Pasteur, Tenaya, Dinaqor, Tremeau, CellProThera, Moderna, and American Regent. J.J.V.M.'s employer, Glasgow University, has been paid by Novartis for his serving as an executive committee member and co–principal investigator of the ATMOSPHERE (Efficacy and Safety of Aliskiren and Aliskiren/Enalapril Combination on Morbidity–Mortality in Patients With Chronic Heart Failure), PARADIGM-HF (Prospective Comparison of ARNI With ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure), and PARAGON-HF (Prospective Comparison of ARNI With ARB Global Outcomes in Heart Failure With Preserved Ejection Fraction) trials and as an executive/steering

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. Glasgow University has also been paid by Novartis for J.J.V.M. serving on an advisory board; by Bayer for serving as a steering committee member of the PANACHE (A Trial to Study Neladenoson Bialanate Over 20 Weeks in Patients With Chronic Heart Failure With Preserved Ejection Fraction) trial using neladenoson bialanate (BAY 1067197); by Cardiorentis for serving as a steering committee member and endpoint committee chair for the TRUE-AHF (Trial of Ularitide Efficacy and Safety in Acute Heart Failure) trial and attending meetings related to this trial; by Cardiorentis for travel and accommodation to attend some of these meetings; by Amgen for serving as a steering committee member for the ATOMIC-HF (Study to Evaluate the Safety and Efficacy of IV Infusion Treatment With Omecamtiv Mecarbil in Subjects With Left Ventricular Systolic Dysfunction Hospitalized for Acute Heart Failure) and COSMIC-HF (Chronic Oral Study of Myosin Activation to Increase Contractility in Heart Failure) trials and attending meetings related to these trials; by Amgen for travel and accommodation for some of these meetings; by Oxford University (which received a grant from Bayer, which manufactures acarbose) for serving as a steering committee member for the ACE (Acarbose Cardiovascular Evaluation) trial (using acarbose) and attending meetings related to this trial; by Theracos for serving as principal investigator for the BEST (Bypass Surgery vs. Everolimus-Eluting Stent Implantation for Multivessel Coronary Artery Disease) trial and attending meetings related to this trial; by Theracos for travel and accommodation to attend some of these meetings; by AbbVie (which manufactures atrasentan) for serving as a steering committee member for the SONAR (Study of Diabetic Nephropathy With Atrasentan) trial (using atrasentan) and to attend meetings related to this trial; by AbbVie for travel and accommodation to attend some of these meetings; by DalCor Pharmaceuticals for serving as a steering committee member for the Dal-GenE (Effect of Dalcetrapib vs. Placebo on CV Risk in a Genetically Defined Population With a Recent ACS) trial and to attend meetings related to this trial; by Pfizer for serving on the data safety monitoring committee for the SPIRE (The Evaluation of Bococizumab (PF-04950615; RN316) in Reducing the Occurrence of Major Cardiovascular Events in High Risk Subjects) trial and to attend meetings related to this trial; by Merck for serving on the data safety monitoring committee for the MK-3102 program for the VICTORIA (A Study of Vericiguat in Participants With Heart Failure With Reduced Ejection Fraction) trial and for attending meetings related to this trial; by AstraZeneca (which markets dapagliflozin) for serving as a principal investigator of DAPA-HF (Study to Evaluate the Effect of Dapagliflozin on the Incidence of Worsening Heart Failure or Cardiovascular Death in Patients With Chronic Heart Failure) and a co-principal investigator of DELIVER (Dapagliflozin Evaluation to Improve the Lives of Patients With Preserved Ejection Fraction Heart Failure; trials using dapagliflozin on heart failure) and to attend meetings related to these trials; by AstraZeneca for travel and accommodation to attend meetings; by GlaxoSmithKline for serving as a co-principal investigator and steering committee member, respectively, for the Harmony-Outcomes trial (albiglutide) and 2 trials, ASCEND-D (Anemia Studies in Chronic Kidney Disease: Erythropoiesis Via a Novel Prolyl Hydroxylase Inhibitor Daprodustat-Dialysis) and ASCEND-ND (Anemia Studies in Chronic Kidney Disease: Erythropoiesis Via a Novel Prolyl Hydroxylase Inhibitor Daprodustat-Non-Dialysis), using daprodustat, and to attend meetings related to these trials; by GlaxoSmithKline for travel and accommodation to attend some of the meetings; by Bristol-Myers Squibb for serving as a steering committee member for the STAND-UP (Evaluate the Safety and Efficacy of 48-Hour Infusions of HNO (Nitroxyl) Donor in Hospitalized Patients With Heart Failure) clinical trial (using an HNO donor) on heart failure and to attend meetings related to this trial; by Kings College Hospital (which has received a grant from KRUK and Vifor-Fresenius, which manufacture intravenous iron) for serving as a steering committee member for the PIVOTAL (Proactive IV Iron Therapy in Haemodialysis Patients) trial (using intravenous iron) and for running the endpoint adjudication committee for this trial and to attend meetings related to PIVOTAL and for travel and accommodation to attend some of the meetings. All payments were made through consultancies with Glasgow University, and J.J.V.M. has not received any personal payments in relation to the trials or drugs. All other authors declared no conflict of interest.

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