ESC European Society of Cardiology

European Heart Journal (2023) **44**, 2982–2993
https://doi.org/10.1093/eurheartj/ehad344

FASTTRACK CLINICAL RESEARCH
Heart failure and cardiomyopathies

Sacubitril/valsartan in heart failure with mildly reduced or preserved ejection fraction: a pre-specified participant-level pooled analysis of PARAGLIDE-HF and PARAGON-HF

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Received 18 April 2023; revised 16 May 2023; accepted 17 May 2023; online publish-ahead-of-print 19 May 2023

See the editorial comment for this article 'Targeting sacubitril/valsartan for heart failure with mildly reduced or preserved ejection fraction', by S.J. Greene and G.C. Fonarow, https://doi.org/10.1093/eurheartj/ehad427.

Abstract

Aims The PARAGLIDE-HF trial demonstrated reductions in natriuretic peptides with sacubitril/valsartan compared with valsartan in patients with heart failure (HF) with mildly reduced or preserved ejection fraction who had a recent worsening HF event, but was not adequately powered to examine clinical outcomes. PARAGON-HF included a subset of PARAGLIDE-HF-like patients who were recently hospitalized for HF. Participant-level data from PARAGLIDE-HF and PARAGON-HF were pooled to better estimate the efficacy and safety of sacubitril/valsartan in reducing cardiovascular and renal events in HF with mildly reduced or preserved ejection fraction.

Methods and results Both PARAGLIDE-HF and PARAGON-HF were multicentre, double-blind, randomized, active-controlled trials of sacubitril/valsartan vs. valsartan in patients with HF with mildly reduced or preserved left ventricular ejection fraction (LVEF >40% in PARAGLIDE-HF and ≥45% in PARAGON-HF). In the pre-specified primary analysis, we pooled participants in PARAGLIDE-HF (all of whom were enrolled during or within 30 days of a worsening HF event) with a 'PARAGLIDE-like' subset of PARAGON-HF (those hospitalized for HF within 30 days). We also pooled the entire PARAGLIDE-HF and PARAGON-HF populations for a broader context. The primary endpoint for this analysis was the composite of total worsening HF events (including first and recurrent HF hospitalizations and urgent visits) and cardiovascular death. The secondary endpoint was the pre-specified renal composite endpoint for both studies (≥50% decline in estimated glomerular filtration rate from baseline, end-stage renal disease, or renal death). Compared with valsartan, sacubitril/valsartan significantly reduced total worsening HF events and cardiovascular death in both the primary pooled analysis of participants with recent worsening HF [$n = 1088$; rate ratio (RR) 0.78; 95% confidence interval (CI) 0.61–0.99; $P = 0.042$] and in the pooled analysis of all participants ($n = 5262$; RR 0.86; 95% CI: 0.75–0.98; $P = 0.027$). In the pooled analysis of all participants, first nominal statistical significance was reached by Day 9 after randomization, and treatment benefits were larger in those with LVEF ≤60% (RR 0.78; 95% CI 0.66–0.91)

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compared with those with LVEF >60% (RR 1.09; 95% CI 0.86–1.40; $P_{interaction} = 0.021$). Sacubitril/valsartan was also associated with lower rates of the renal composite endpoint in the primary pooled analysis [hazard ratio (HR) 0.67; 95% CI 0.43–1.05; $P = 0.080$] and the pooled analysis of all participants (HR 0.60; 95% CI 0.44–0.83; $P = 0.002$).

Conclusion In pooled analyses of PARAGLIDE-HF and PARAGON-HF, sacubitril/valsartan reduced cardiovascular and renal events among patients with HF with mildly reduced or preserved ejection fraction. These data provide support for use of sacubitril/valsartan in patients with HF with mildly reduced or preserved ejection fraction, particularly among those with an LVEF below normal, regardless of care setting.

Structured Graphical Abstract

Key Question

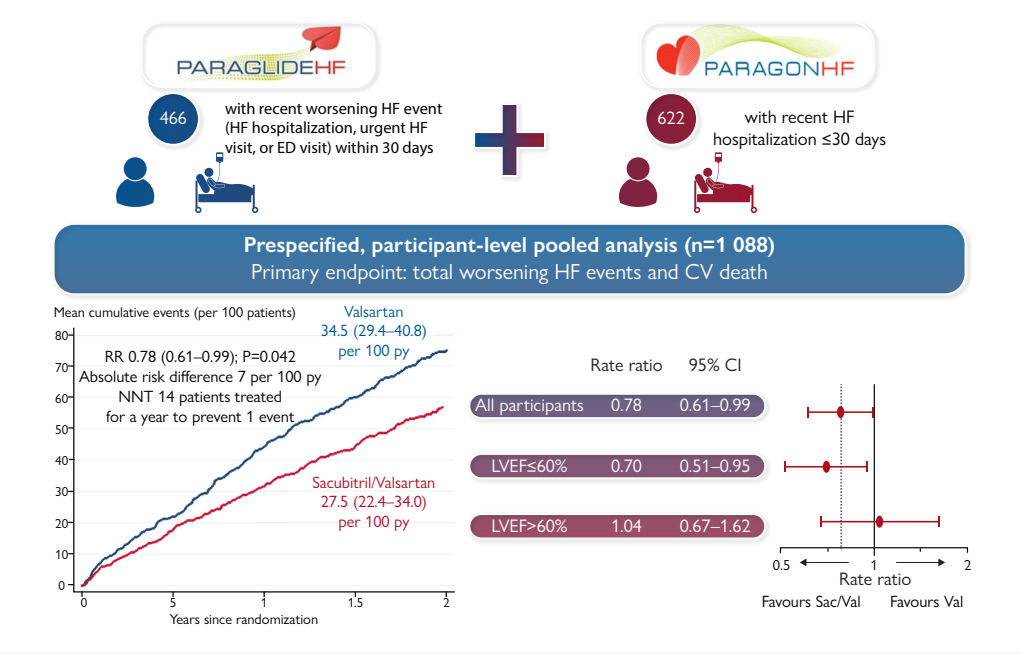
What is the efficacy and safety of sacubitril/valsartan compared with valsartan on cardiovascular and renal outcomes in patients with heart failure (HF) with mildly reduced or preserved ejection fraction?

Key Finding

In a prespecified, participant-level pooled analysis of PARAGLIDE-HF and the PARAGON-HF subset that was recently hospitalized for HF, sacubitril/valsartan significantly reduced total worsening HF events and cardiovascular death (rate ratio 0.78; 95% confidence interval 0.61-0.99; P = 0.042). Treatment benefits tended to be larger in those with left ventricular ejection fraction (LVEF) ≤ 60%.

Take Home Message

These data strengthen the current evidence base supporting the use of sacubitril/valsartan in patients with heart failure with mildly reduced or preserved ejection fraction, particularly among those with an LVEF below normal, regardless of care setting.



A pre-specified participant-level pooled analysis of PARAGLIDE-HF and PARAGON-HF. The primary endpoint for the pooled analysis was total worsening HF events and cardiovascular death. CI, confidence interval; CV, cardiovascular; ED, emergency department; NNT, number needed to treat; RR, rate ratio.

Keywords Angiotensin receptor–neprilysin inhibitor • Heart failure with mildly reduced ejection fraction • Heart failure with preserved ejection fraction • Sacubitril/valsartan

Introduction

The PARAGLIDE-HF trial evaluated sacubitril/valsartan against valsartan in a high-risk, broad population of patients with heart failure (HF) with mildly reduced or preserved ejection fraction and a recent worsening HF event.[1] While the primary objective of PARAGLIDE-HF was to evaluate changes in natriuretic peptide levels, the trial was not adequately powered to assess clinical outcomes. The larger PARAGON-HF trial examined sacubitril/valsartan against the same active comparator (valsartan) among patients with HF and left ventricular ejection fraction (LVEF) ≥ 45%,[2] and suggested potential benefits in select populations, including those with an LVEF below normal[3] and women.[4] PARAGON-HF included a subset of 'PARAGLIDE-HF-like' patients who were recently hospitalized for HF.[5] A pooled analysis of PARAGLIDE-HF and PARAGON-HF was pre-specified in the PARAGLIDE-HF statistical analysis plan before unblinding to better

estimate the composite therapeutic effects of sacubitril/valsartan on cardiovascular and renal outcomes. This comprehensive pooled analysis provides a more robust evidence base to guide clinical decision-making about the use of sacubitril/valsartan in HF with mildly reduced or preserved ejection fraction.

Methods

Design of PARAGLIDE-HF and PARAGON-HF

Detailed study designs, protocols, and the primary results of PARAGLIDE-HF[1,6] and PARAGON-HF[2,7,8] have been previously published. Key design elements are summarized in Supplementary data online, *Table S1*. Both trials were multicentre, double-blind, randomized, active-controlled trials of sacubitril/valsartan vs. valsartan in patients with HF, LVEF >40% (PARAGLIDE-HF) or LVEF ≥45% (PARAGON-HF), and elevated natriuretic peptides. Patients in PARAGLIDE-HF were enrolled during (once haemodynamically stabilized) or soon after (within 30 days) a worsening HF event, while PARAGON-HF allowed screening but did not allow randomization during hospitalization for worsening HF. PARAGLIDE-HF also had broader eligibility enrolling patients to a lower screening estimated glomerular filtration rate (eGFR) (20 mL/min/1.73 m^2 vs. 30 mL/min/1.73 m^2 in PARAGON-HF) and included populations excluded in PARAGON-HF such as class 3 obesity (body mass index >40 kg/m^2), *de novo* HF, and patients with HF with improved LVEF.

PARAGON-HF only randomized patients tolerating half-target doses of both study drugs during sequential single-blind run-in periods, while PARAGLIDE-HF did not employ a run-in period. Eligible participants were randomized 1:1 to either sacubitril/valsartan (target dose, 97 mg/103 mg twice daily) or valsartan (target dose, 160 mg twice daily) in both trials.

Data harmonization and pooling

We conducted two pooled analyses using participant-level data from both PARAGON-HF and PARAGLIDE-HF. The primary analysis pooled participants in PARAGLIDE-HF and a subset in PARAGON-HF who were 'PARAGLIDE-HF-like' enrolled within 30 days of an episode of worsening HF.[5] For broader context, a secondary analysis pooled the entire PARAGLIDE-HF and PARAGON-HF populations.

Clinical outcomes

The primary endpoint of these pooled analyses was a composite of total (first and recurrent) worsening HF events (which included hospitalizations and urgent ambulatory visits for HF) and cardiovascular death. The secondary endpoint was the pre-specified renal composite endpoint for both studies (≥50% decline in eGFR from baseline, end-stage renal disease, or renal death). Glomerular filtration rate was estimated using the Modification of Diet in Renal Disease study equation in both trials.[9] In addition, we examined total HF hospitalizations and cardiovascular death (the primary endpoint of PARAGON-HF).

Clinical endpoints were adjudicated by the same clinical endpoints committee in both trials (Brigham and Women's Hospital, Boston, MA). In the primary pooled analysis, treatment effects of sacubitril/valsartan on the primary endpoint were examined across key subgroups of interest based on age, sex, race, LVEF, eGFR, history of atrial fibrillation or flutter, body mass index, baseline use of renin–angiotensin system inhibitors (RASi), mineralocorticoid receptor antagonists, and β-blockers.

Definitions of adverse events [symptomatic hypotension, hyperkalemia (defined as serum potassium ≥5.5 mEq/L) and worsening renal function (defined as an increase in serum creatinine of ≥0.5 mg/dL AND worsening of the eGFR by at least 25%)] were applied from the PARAGLIDE-HF trial and harmonized between both trials. Mortality outcomes (all-cause and cardiovascular) were additionally examined for safety. Unknown or undetermined death was considered non-cardiovascular death in both trials.

Statistical analysis

All pooled effect sizes are reported as point estimates with accompanying 95% confidence intervals (CI). Total (first and recurrent) cardiovascular endpoints were analysed using the Lin-Wei-Yang-Ying model proportional rates model,[10] stratified by trial, region, and setting of randomization (in-hospital vs. out-of-hospital) with robust variance estimates. Renal and mortality outcomes were analysed as time-to-first events using Cox proportional hazard models applying the same stratification variables. Proportional hazards assumptions of the Cox proportional hazards models were tested on the basis of Schoenfeld residuals, and no significant violations of this assumption were identified ($P > 0.20$ for all models). Safety outcomes were assessed as binary events using logistic regression models without stratification. Statistical heterogeneity in treatment effects for the primary endpoint was assessed by each component trial and across 10 subgroups with interaction testing. Cumulative incidence of the primary endpoint was visualized using the Nelson–Aalen estimator, and that of the renal composite endpoint was visualized using the Kaplan–Meier estimator. We further identified the time to when first statistical significance was reached for the primary endpoint; rate ratios (RR) and 95% CI were iteratively estimated with truncated data at each day post-randomization.

Given different follow-up timeframes in both trials (median follow-up of 2.9 years in PARAGON-HF and 0.5 years in PARAGLIDE-HF), in pooled analyses of the two trials, PARAGON-HF participants thus disproportionately contributed to risk estimates in late follow-up. As such, a sensitivity analysis was conducted for the primary endpoint truncating follow-up at fixed standardized time-points (1 and 2 years). To account for potential competing risks of non-cardiovascular death, an additional sensitivity analysis was conducted examining the endpoint of total worsening HF events and all-cause death.

The pooled analysis, including designation of the primary and secondary endpoints, was pre-specified in the PARAGLIDE-HF statistical analysis plan and pre-registered with PROSPERO (CRD42023410574). The pooled analyses were conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.[11] To ensure pooling of only high quality studies, formal assessment found a low risk of bias in both PARAGLIDE-HF and PARAGON-HF (see Supplementary data online, *Table S2*). Written informed consent was obtained from each participant, and the study protocols were approved by the ethics committees or institutional review boards at all sites in both trials. STATA, version 16 (StataCorp, College Station, TX), was used for statistical analyses, and two-sided *P*-values <0.05 were considered statistically significant. No adjustments were made for multiple testing.

Role of the funding source

Both trials were funded by Novartis Pharmaceuticals Corporation. For this pooled analysis, individual-participant level data access for both trials were obtained, and data were analysed independently at Brigham and Women's Hospital (Boston, MA). The first and last author drafted the manuscript and all authors were responsible for the decision to submit.

Results

The primary pooled analysis of recent worsening HF included 1088 participants ($n = 466$ from PARAGLIDE-HF and $n = 622$ who were 'PARAGLIDE-HF-like' in PARAGON-HF). The secondary pooled analysis included all 5262 participants from both trials.

Baseline characteristics

PARAGLIDE-HF enrolled patients exclusively in the USA and Canada and accordingly enrolled a higher proportion of Black participants compared with the PARAGLIDE-like subset of PARAGON-HF, which included slightly older participants who were more frequently White or Asian (see Supplementary data online, *Table S3*). Participants in

PARAGLIDE-HF also had lower baseline LVEF, higher screening natriuretic peptide levels, worse kidney function, and higher body mass index than PARAGLIDE-like participants in PARAGON-HF. With regard to background medical therapy, PARAGLIDE-HF participants were less frequently treated before randomization with a RASi and had greater use of sodium glucose cotransporter-2 inhibitors (SGLT2i) (see Supplementary data online, *Table S3*). Similar differences in baseline characteristics were observed when comparing the entire PARAGLIDE-HF and PARAGON-HF cohorts (see Supplementary data online, *Table S4*). Baseline clinical profiles and medication use were well-balanced between study arms in both the primary pooled analysis (*Table 1*) and the pooled analysis of all participants (see Supplementary data online, *Table S5*).

Cardiovascular and renal outcomes

The median follow-up for the primary pooled analysis was 2.2 (25th–75th percentiles 0.5–3.0) years, while the median follow-up for the pooled analysis of all participants was 2.8 (25th–75th percentiles 2.4–3.4) years. In the primary pooled analysis of patients with recent worsening HF, compared with valsartan, sacubitril/valsartan significantly reduced total worsening HF events and cardiovascular death (event rate 27.5 vs. 34.5 per 100 patient-years; RR 0.78; 95% CI 0.61–0.99; $P = 0.042$) (*Figure 1* and *Table 2*). Sacubitril/valsartan also reduced the PARAGON-HF primary endpoint of total HF hospitalizations and cardiovascular death (RR 0.76; 95% CI 0.60–0.97; $P = 0.029$). The absolute risk difference in total worsening HF events and cardiovascular death between sacubitril/valsartan and valsartan arms was 7 per 100 patient-years suggesting one event could be prevented per 14 patients treated for a year with sacubitril/valsartan. A significant risk reduction for the primary endpoint was also observed in the pooled analysis including all trial participants (event rate 14.5 vs. 16.8 per 100 patient-years; RR 0.86; 95% CI: 0.75–0.98; $P = 0.027$) (*Table 3*). Time to first nominal statistical significance for the primary endpoint was reached at 267 days in follow-up in the primary pooled analysis (RR 0.72; 95% CI 0.52–1.00; $P = 0.048$) and at 9 days in the pooled analysis of all participants (RR 0.20; 95% CI 0.06–0.69; $P = 0.011$).

Consistent risk reductions in the primary endpoint were observed with sacubitril/valsartan vs. valsartan in both component trials included in these pooled analyses (see Supplementary data online, *Table S6*). Treatment effects in the primary pooled analysis were also consistent across subgroups defined by demographics, comorbidities, and background HF therapies (*Figure 2*). In the pooled analysis of all participants, treatment benefits were larger in those with LVEF ≤60% (LVEF ≤60%: RR 0.78; 95% CI 0.66–0.91; LVEF >60% 1.09; 95% CI 0.86–1.40; $P_{interaction} = 0.021$; *Figure 3*) and in women (women: RR 0.74; 95% CI 0.61–0.90; men: RR 0.98; 95% CI 0.82–1.18; $P_{interaction} = 0.039$), but there was no evidence for heterogeneity in relative treatment effects by recent worsening HF event within 30 days ($P_{interaction} = 0.47$).

Sacubitril/valsartan was also associated with lower rates of the renal composite endpoint compared with valsartan in the primary pooled analysis [6.1% vs. 8.8%; hazard ratio (HR) 0.67; 95% CI 0.43–1.05; $P = 0.080$] and the pooled analysis of all participants (2.3% vs. 3.8%; HR 0.60; 95% CI 0.44–0.83; $P = 0.002$) (*Figure 4*).

Safety outcomes

In the primary pooled analysis, sacubitril/valsartan reduced risks of worsening renal function (OR 0.71; 95% CI 0.54–0.94) compared with valsartan (*Table 2*). In the pooled analysis of all participants, sacubitril/valsartan increased risks of symptomatic hypotension compared with valsartan [odds ratio (OR) 1.50; 95% CI 1.31–1.72], but had lower risks of worsening renal function (OR 0.72; 95% CI 0.63–0.82) (*Table 3*). Mortality did not significantly differ between study arms in either pooled analysis.

Sensitivity analyses

With complete follow-up from both trials in the primary pooled analysis, 639 total primary events were captured. To standardize the duration of follow-up, a sensitivity analysis truncating follow-up at 2 years yielded 509 total primary events with consistent treatment effects (RR 0.74; 95% CI 0.56–0.97; $P = 0.030$). Truncating follow-up further at 1 year yielded 331 total primary events and also demonstrated consistent treatment effects (RR 0.72; 95% CI 0.53–0.98; $P = 0.036$). An additional sensitivity analysis performed to account for competing risks on non-cardiovascular death yielded consistent findings: sacubitril/valsartan significantly reduced the risk of total worsening HF events and all-cause death in the primary pooled analysis (RR 0.77; 95% 0.61–0.97; $P = 0.028$) and in the pooled analysis of all participants (RR 0.87; 95% CI 0.77–0.99; $P = 0.030$).

Discussion

In this pre-specified, participant-level pooled analysis of PARAGLIDE-HF and PARAGON-HF, sacubitril/valsartan reduced cardiovascular and renal events compared with valsartan among patients with HF with mildly reduced or preserved ejection fraction who were either enrolled in-hospital, recently hospitalized, or in ambulatory care. These benefits appeared to accrue rapidly with statistically significant reductions in cardiovascular events first observed within 1–2 weeks of treatment initiation. These pooled analyses affirm previous observations of treatment heterogeneity by LVEF, such that cardiovascular benefits were most apparent in patients with an LVEF below normal. In addition, sacubitril/valsartan was associated with lower rates of a renal composite endpoint compared with valsartan. Sacubitril/valsartan resulted in higher rates of symptomatic hypotension, but lower risks of worsening renal function when compared with valsartan. Taken together, these pooled analyses reinforce the overall benefit of sacubitril/valsartan in patients with HF with mildly reduced or preserved ejection fraction, especially among those with an LVEF below normal, and irrespective of care setting (*Structured Graphical Abstract*).

The PARAGLIDE-HF trial demonstrated reductions in its primary endpoint (change in natriuretic peptides) and identified potential benefits on a hierarchical clinical composite but was not powered for clinical outcomes. PARAGON-HF also suggested clinical benefits in a broader population of patients with chronic HF, but did not meet statistical significance.[2] As such, there might be residual uncertainties about clinical benefit when interpreting either trial in isolation. Pooling PARAGLIDE-HF added ~50% more total primary events to the PARAGON-HF subset with recent worsening HF and 10% more total primary events to the overall PARAGON-HF trial. Greater power allowed for more precision and substantiated favourable treatment effects with sacubitril/valsartan on cardiovascular and renal outcomes among patients with HF with mildly reduced or preserved ejection fraction. Similar to treatment heterogeneity observed in PARAGON-HF on clinical outcomes by baseline LVEF,[3] larger treatment effects with sacubitril/valsartan were seen on changes in natriuretic peptides and on a hierarchical composite outcome (analysed as a win ratio) among individuals with LVEF ≤60% in PARAGLIDE-HF. Pooled analyses lend further support that the clinical benefits of sacubitril/valsartan are

Table 1 Baseline characteristics in the primary pooled analysis of patients with recent worsening heart failure in PARAGLIDE-HF and PARAGON-HF

	Sacubitril/valsartan ($n = 541$)	Valsartan ($n = 547$)	*P*-value
Demographics			
Age (years)	70.5 ± 10.4	71.2 ± 10.2	0.30
Male sex	262 (48.4)	251 (45.9)	0.40
Race			0.40
White	421 (77.8)	433 (79.2)	
Black or African American	55 (10.2)	59 (10.8)	
Asian	52 (9.6)	49 (9.0)	
Other	13 (2.4)	6 (1.1)	
Medical history			
Left ventricular ejection fraction (%)	56.6 ± 8.1	56.1 ± 8.0	0.33
Left ventricular ejection fraction ≤ 60%	389 (71.9)	412 (75.3)	0.20
Hypertension	523 (96.7)	522 (95.4)	0.29
Atrial fibrillation or flutter	299 (55.3)	327 (59.8)	0.13
Screening vital signs and laboratory measures			
Systolic blood pressure (mmHg)	130.8 ± 17.8	131.7 ± 17.5	0.41
Heart rate (b.p.m.)	74.9 ± 16.1	74.1 ± 15.2	0.41
Body mass index (kg/m^2)	32.1 ± 7.5	32.1 ± 7.2	0.90
eGFR (mL/min/1.73 m^2)	58.5 ± 20.2	59.8 ± 20.8	0.30
Serum potassium (mmol/L)	4.4 ± 0.5	4.4 ± 0.5	0.90
NT-proBNP (pg/mL)	1195 (535–2252)	1138 (505–2197)	0.70
Medication use			
ACEi or ARB	452 (83.5)	454 (83.0)	0.81
MRA	164 (30.3)	157 (28.7)	0.56
β-blocker	441 (81.5)	432 (79.0)	0.29
SGLT2i	31 (5.7)	31 (5.7)	0.96
Loop diuretic	529 (97.8)	542 (99.1)	0.08

Presented as *n* (%), mean ± standard deviation, or median (25th–75th percentile, as appropriate.
ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; MRA, mineralocorticoid receptor antagonist; eGFR, estimated glomerular filtration rate; NT-proBNP, N-terminal pro-brain natriuretic peptide; SGLT2i, sodium-glucose cotransporter-2 inhibitor.

expected to be greatest in those with an LVEF below normal. While LVEF is a continuous biological measure, categorization adds simplicity to its interpretation and ultimately how it is applied in clinical practice.

In-hospital optimization of medical therapy for HF is now supported as a class I recommendation by global clinical practice guidelines.[12,13] In a prior trial of patients with HF with reduced ejection fraction, sacubitril/valsartan significantly reduced levels of natriuretic peptides[14] and cardiovascular events[15] when implemented during hospitalization for acute decompensated HF. The current pooled analysis of the two trials consistently supports the early implementation of sacubitril/valsartan after an episode of worsening HF among patients with HF with mildly reduced or preserved ejection fraction. The pooled analysis of all participants showed consistent relative treatment benefits of sacubitril/valsartan irrespective of recency of worsening HF. In light of markedly higher event rates experienced by patients early after worsening HF, absolute benefits with sacubitril/valsartan may be expected to be especially pronounced in this setting. Indeed, in our primary pooled analysis of those with recent worsening HF, the absolute risk difference between sacubitril/valsartan and valsartan arms was 7 per 100 patient-years suggesting approximately one primary event could be prevented per 14 patients treated for a year with sacubitril/valsartan.

In addition to the cardiovascular benefits, nominally lower rates of renal composite outcomes were observed with sacubitril/valsartan in the PARAGON-HF trial,[16] but these results were outside of the formal testing hierarchy and absolute event rates were low. PARAGLIDE-HF enrolled a population of patients with HF after a recent worsening

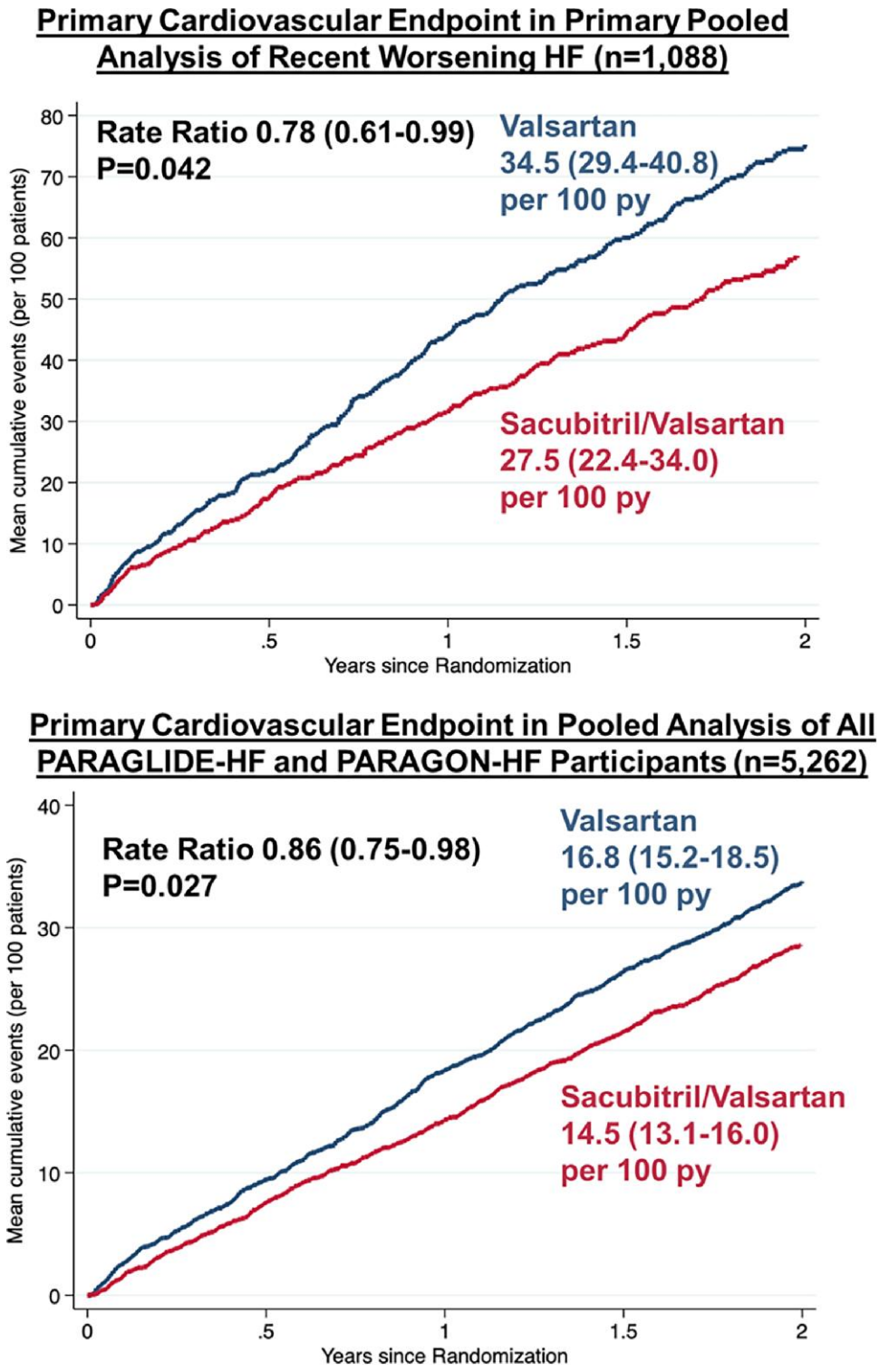


Figure 1 Cumulative incidence of total heart failure hospitalizations, urgent HF visits, and cardiovascular death. The cumulative incidence of the primary endpoint by study arm in both pooled analyses was visualized using the Nelson–Aalen estimator. Treatment effects of sacubitril/valsartan vs. valsartan are summarized as rate ratios with accompanying 95% confidence intervals. HF, heart failure; py, patient-years.

HF event with lower baseline eGFR; these patients faced high near-term risks for kidney disease progression. The pooled analysis examined a pre-specified renal composite endpoint, inclusive of ≥50% eGFR decline, end-stage renal disease, or renal death. A substantial and meaningful decline in eGFR from baseline has been closely linked with the subsequent development of kidney failure, and is considered a valid surrogate endpoint in regulatory decision-making in clinical trials of kidney disease progression.[17] In the pooled analyses, sacubitril/

Table 2 Efficacy and safety outcomes in the primary pooled analysis of patients with recent worsening heart failure in PARAGLIDE-HF and PARAGON-HF

	Sacubitril/valsartan ($n = 541$)		Valsartan ($n = 547$)			
	Events	Event rate per 100 py (95% CI)	Events	Event rate per 100 py (95% CI)	Effect Estimate (95% CI)	*P*-value
CV outcomes					Rate ratio	
Total HF hospitalizations, urgent HF visits, and CV death	281	27.5 (22.4–34.0)	358	34.5 (29.4–40.8)	0.78 (0.61–0.99)	0.042
Total HF hospitalizations and CV death	259	25.4 (20.8–31.2)	335	32.5 (27.5–38.6)	0.76 (0.60–0.97)	0.029
Renal outcomes					Hazard ratio	
≥50% decline in eGFR, ESRD, or renal death	33	3.3 (2.3–4.6)	48	4.8 (3.6–6.3)	0.67 (0.43–1.05)	0.080
Safety outcomes					Odds ratio	
Symptomatic hypotension	113 (20.9%)		92 (16.8%)		1.31 (0.96–1.77)	0.09
Hyperkalemia	100 (18.5%)		99 (18.1%)		1.03 (0.75–1.40)	0.87
Worsening renal function	113 (20.9%)		148 (27.1%)		0.71 (0.54–0.94)	0.017
Mortality outcomes					Hazard ratio	
All-cause death	67	6.5 (5.1–8.3)	88	8.5 (6.9–10.4)	0.77 (0.56–1.06)	0.11
CV death	48	4.7 (3.5–6.2)	61	5.9 (4.6–7.6)	0.81 (0.55–1.18)	0.26

Total (first and recurrent) CV endpoints were analysed using the proportional rates model (LWYY), stratified by trial, region, and setting of randomization with robust variance estimate. Renal and mortality outcomes were analysed as time-to-first events using Cox's proportional hazard model with the same stratification variables.
Safety outcomes were assessed as binary events using logistic regression models. Hyperkalemia was defined as potassium ≥5.5 mEq/L. Worsening renal function as an adverse event was defined as an increase in serum creatinine of ≥0.5 mg/dL and worsening of the eGFR by at least 25%.
CI, confidence interval; CV, cardiovascular; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; HF, heart failure; py, patient-years.

Table 3 Efficacy and safety outcomes in the pooled analysis of all participants randomized in PARAGLIDE-HF and PARAGON-HF

	Sacubitril/valsartan ($n = 2640$)		Valsartan ($n = 2622$)			
	Events	Event rate per 100 py (95% CI)	Events	Event rate per 100 py (95% CI)	Effect Estimate (95% CI)	*P*-value
CV outcomes					Rate ratio	
Total HF hospitalizations, urgent HF visits, and CV death	1028	14.5 (13.1–16.0)	1181	16.8 (15.2–18.5)	0.86 (0.75–0.98)	0.027
Total HF hospitalizations and CV death	975	13.7 (12.5–15.1)	1108	15.7 (14.3–17.4)	0.87 (0.76–0.99)	0.040
Renal outcomes					Hazard ratio	
≥50% decline in eGFR, ESRD, or renal death	60	0.8 (0.7–1.1)	99	1.4 (1.2–1.7)	0.60 (0.44–0.83)	0.002
Safety outcomes					Odds ratio	
Symptomatic hypotension	618 (23.4%)		443 (16.9%)		1.50 (1.31–1.72)	<0.001
Hyperkalemia	361 (13.7%)		404 (15.4%)		0.87 (0.75–1.01)	0.07
Worsening renal function	480 (18.2%)		619 (23.6%)		0.72 (0.63–0.82)	<0.001
Mortality outcomes					Hazard ratio	
All-cause death	359	5.0 (4.6–5.6)	375	5.3 (4.8–5.9)	0.95 (0.82–1.10)	0.49
CV death	214	3.0 (2.6–3.4)	230	3.3 (2.9–3.7)	0.93 (0.77–1.12)	0.42

Total (first and recurrent) CV endpoints were analysed using the proportional rates model (LWYY), stratified by trial, region, and setting of randomization with robust variance estimate. Renal and mortality outcomes were analysed as time-to-first events using Cox's proportional hazard model with the same stratification variables.
Safety outcomes were assessed as binary events using logistic regression models. Hyperkalemia was defined as potassium ≥5.5 mEq/L. Worsening renal function as an adverse event was defined as increase in serum creatinine of ≥0.5 mg/dL and worsening of the eGFR by at least 25%.
CI, confidence interval; CV, cardiovascular; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; HF, heart failure; py, patient-years.

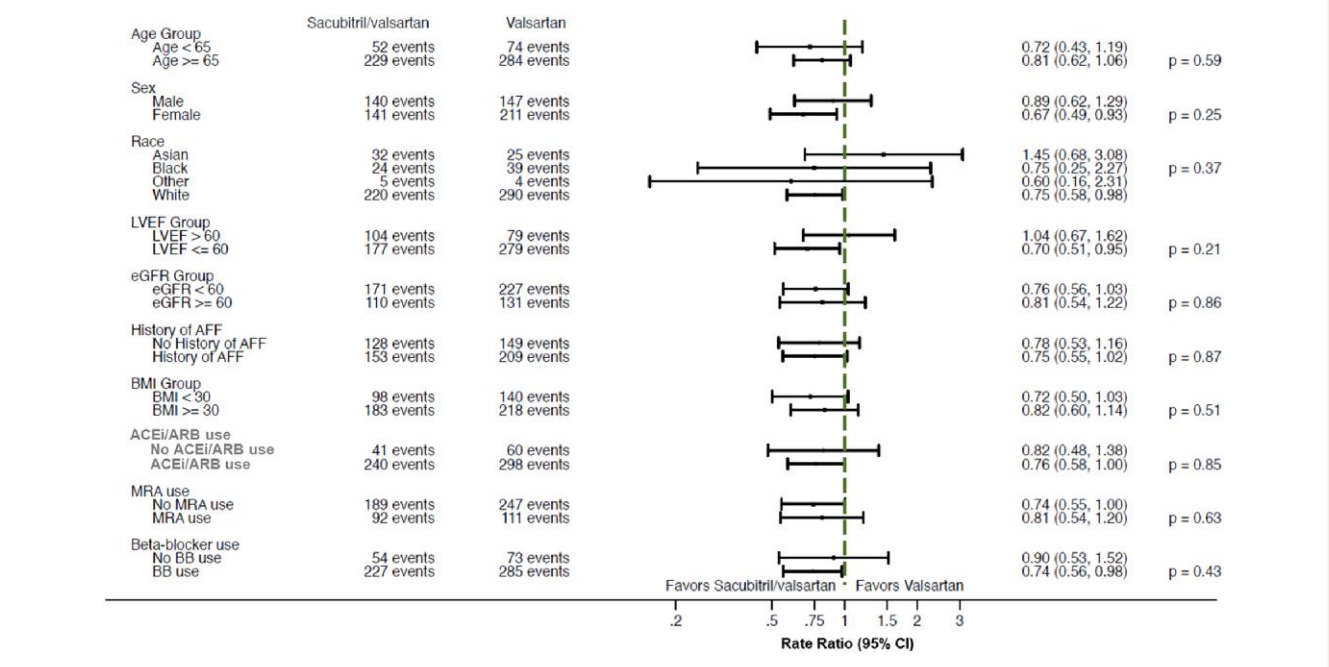


Figure 2 Treatment effects on primary endpoint across key subgroups in the primary pooled analysis of patients with recent worsening heart failure in PARAGLIDE-HF and PARAGON-HF. Treatment effects of sacubitril/valsartan vs. valsartan for the primary endpoint (total worsening heart failure events and cardiovascular death) are summarized as rate ratios with accompanying 95% confidence intervals. ACEi, angiotensin converting enzyme inhibitor; AFF, atrial fibrillation or flutter; ARB, angiotensin receptor blocker; BB, beta-blocker; BMI, body mass index; CI, confidence interval; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist.

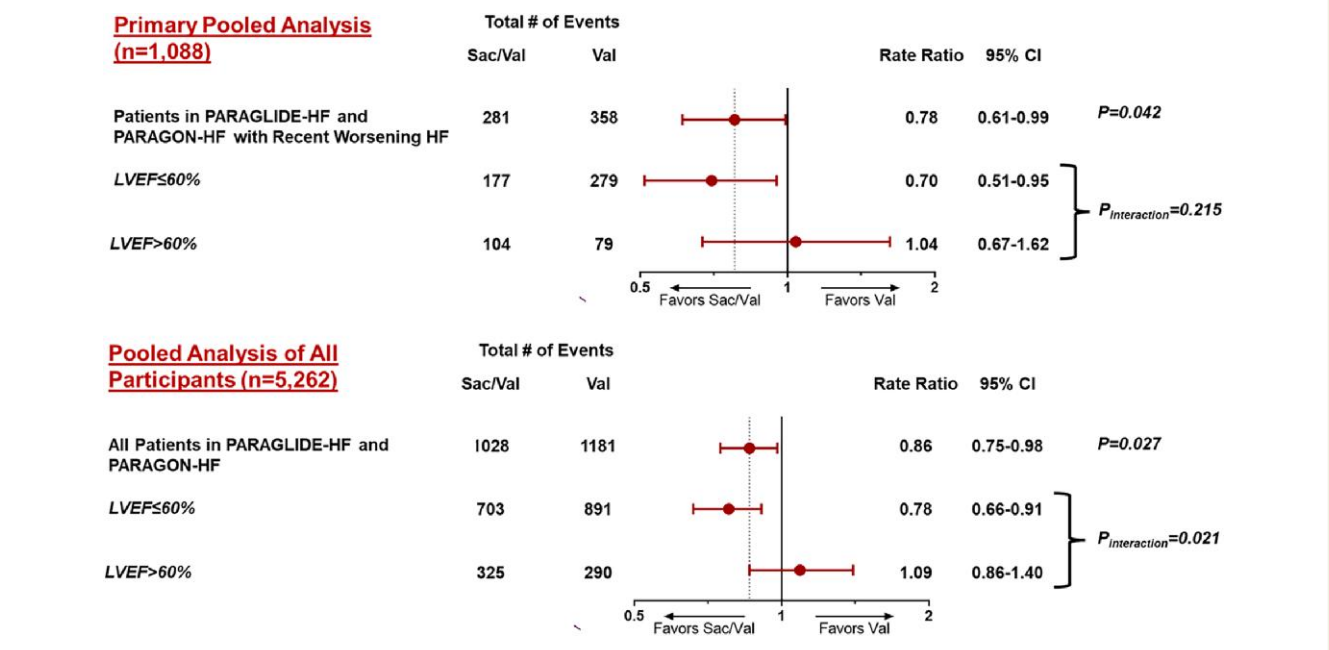


Figure 3 Treatment effect of sacubitril/valsartan vs. valsartan on the primary endpoint by left ventricular ejection fraction. CI, confidence interval; LVEF, left ventricular ejection fraction.

valsartan resulted in approximately a 40% lower risk of this renal composite endpoint supporting the nephroprotective effects of sacubitril/valsartan compared with RASi in HF. In contrast, improvements in this renal composite endpoint were either not observed or less apparent in previous placebo-controlled trials of RASi,[18–20] mineralocorticoid receptor antagonists,[21] and SGLT2i[22,23] in patients with HF with mildly reduced or preserved ejection fraction. It is also important to note that sacubitril/valsartan demonstrated these renal benefits

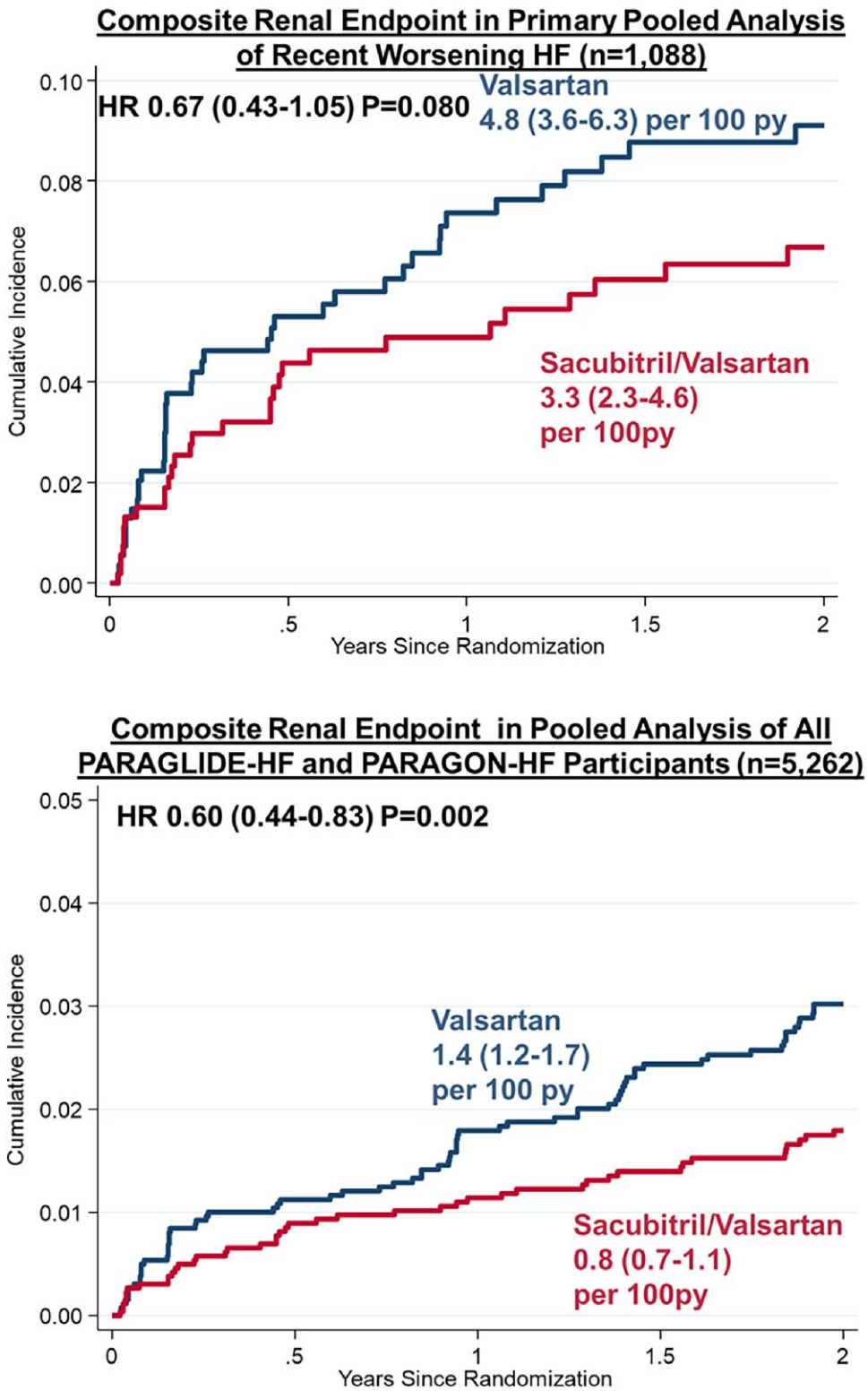


Figure 4 Cumulative incidence of the composite renal endpoint. The cumulative incidence of the composite renal endpoint (time to first occurrence of ≥50% decline in estimated glomerular filtration rate, end-stage renal disease, or renal death) was visualized using the Kaplan–Meier estimator. Treatment effects of sacubitril/valsartan vs. valsartan are summarized as hazard ratios with accompanying 95% confidence intervals. HR, hazard ratios; HF, heart failure.

against an active comparator of RASi, which is known to be nephroprotective in other clinical settings such as diabetic kidney disease. The lower risks of worsening renal function (as an adverse event) may also facilitate the implementation of this therapy, even among patients after a worsening HF event who face high risks of renal events.

The pooled experience also more comprehensively summarizes the expected safety of use of sacubitril/valsartan in clinical practice. PARAGON-HF enrolled a selected population of participants who had to tolerate half-target doses of both valsartan and sacubitril/valsartan before randomization. PARAGLIDE-HF in contrast did not have a pre-randomization run-in period and enrolled higher risk, less selected participants, many of whom had no prior exposure to RASi. Furthermore, as a function of less stringent eligibility criteria, PARAGLIDE-HF enrolled patients with a higher burden of certain comorbidities (such as obesity and chronic kidney disease). Based on data from this pooled experience of patients with broad clinical risk profiles, clinical implementation of sacubitril/valsartan should be accompanied by heightened vigilance for potential adverse effects, namely symptomatic hypotension. Alteration of concomitant diuretics or other blood pressure lowering therapies and provision of anticipatory behavioural guidance may attenuate these risks.

Based on the results of PARAGON-HF, sacubitril/valsartan received indications for use in patients with HF with mildly reduced ejection fraction and select patients with preserved ejection fraction in the USA and multiple other countries. In addition, current US HF guidelines recommend consideration of sacubitril/valsartan in select patients with HF with mildly reduced or preserved ejection fraction (class IIb).[12] In contrast, recent European Society of Cardiology HF guidelines do not provide specific recommendations for its use in those with HF with preserved ejection fraction.[13] In those countries where sacubitril/valsartan has been approved for use in chronic HF at higher LVEF, initial uptake has been variable.[24] These mixed guideline recommendations and variable clinical practice patterns may reflect residual uncertainties about the role of sacubitril/valsartan in HF with mildly reduced or preserved ejection fraction. These pooled analyses may bolster the confidence in cardiovascular and renal event reduction with sacubitril/valsartan in patients with HF with mildly reduced or preserved ejection fraction, particularly in those with LVEF below normal.

Strengths and limitations

These pre-specified pooled analyses were strengthened by participant-level data access to both component trials that allowed for the harmonization of endpoint and subgroup definitions. Furthermore, endpoints were adjudicated in a similarly rigorous standardized manner by the same clinical endpoints committee in both trials. Nevertheless, several limitations are noteworthy. First, although PARAGON-HF and PARAGLIDE-HF were similar in many respects, these trials differed in other aspects, including duration of follow-up. Sensitivity analysis, however, truncating follow-up at standardized earlier timepoints yielded consistent treatment benefits. Second, the pooled analyses focused on cardiovascular and renal endpoints; patient-reported outcomes such as Kansas City Cardiomyopathy Questionnaire were not collected in PARAGLIDE-HF to allow pooling. Third, while renal death as a component of the renal composite endpoint was specifically adjudicated in PARAGON-HF, we relied on investigator-reported information in PARAGLIDE-HF. Finally, relatively few patients in either trial were treated with an SGLT2i at baseline, which is now recommended in this population.[12]

Conclusions

These pre-specified pooled analyses of PARAGLIDE-HF and PARAGON-HF including over 5000 participants worldwide strengthen the current evidence base supporting the use of sacubitril/valsartan in patients with HF with mildly reduced or preserved ejection fraction, especially among those with an LVEF below normal, and irrespective of care setting.

Acknowledgements

None.

Supplementary data

Supplementary data is available at *European Heart Journal* online.

Declarations

Disclosure of Interest

M.V. has received research grant support, served on advisory boards, or had speaker engagements with American Regent, Amgen, AstraZeneca, Bayer AG, Baxter Healthcare, Boehringer Ingelheim, Chiesi, Cytokinetics, Lexicon Pharmaceuticals, Merck, Novartis, Novo Nordisk, Pharmacosmos, Relypsa, Roche Diagnostics, Sanofi, and Tricog Health, and participates on clinical trial committees for studies sponsored by AstraZeneca, Galmed, Novartis, Bayer AG, Occlutech, and Impulse Dynamics. R.J.M. receives research support and/or honoraria from Novartis, Abbott, American Regent, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Boston Scientific, Cytokinetics, Fast BioMedical, Gilead, Innolife, Eli Lilly, Medtronic, Medable, Merck, Novo Nordisk, Pharmacosmos, Relypsa, Respicardia, Roche, Sanofi, Vifor, Windtree Therapeutics, and Zoll. B.L.C. reports personal consulting for Alnylam, Cardurion, Corvia, Cytokinetics, Intellia, and Rocket. J.H.W., K.M.W., and M.L. are employees of Novartis. A.F.H. reports research grants from American Regent, Amgen, AstraZeneca, Bayer, Bayer, Boehringer Ingelheim, Cytokinetics, Merck, Novartis, Somologic, Verily and consulting from Amgen, AstraZeneca, Bayer, Bristol-Myers Squib Boehringer Ingelheim, Boston Scientific, Cytokinetics, Merck, Novartis, and Novo Nordisk. D.A.M. is a member of the TIMI Study Group, which has received institutional research grant support through Brigham and Women's Hospital from Abbott, Abiomed, Amgen, Anthos Therapeutics, ARCA Biopharma, Inc., AstraZeneca, Bayer HealthCare Pharmaceuticals, Inc., Daiichi-Sankyo, Eisai, Intarcia, Ionis Pharmaceuticals, Inc., Janssen Research and Development, LLC, Merck, Novartis, Pfizer, Quark Pharmaceuticals, Regeneron Pharmaceuticals, Inc., Roche, Siemens Healthcare Diagnostics, Inc., Softcell Medical Limited, and Zora Biosciences; he has received consulting fees from Abbott Laboratories, ARCA Biopharma, Inflammatix, Merck & Co, Novartis, and Roche Diagnostics. R.C.S. serves on the steering committee for the PARAGLIDE trial sponsored by Novartis. E.J.V. reports grants from Novartis, Amgen, Phillips, and NHLBI/NIH. A.S.D. reports institutional grant support from Abbott, Alnylam, AstraZeneca, Bayer, Novartis, Pfizer and consulting fees from Abbott, Alnylam, AstraZeneca, Avidity, Axon Therapeutics, Bayer, Biofourmis, Boston Scientific, Cytokinetics, GlaxoSmithKline, Medpace, Merck, New Amsterdam, Novartis, Parexel, Regeneron, River2Renal Roche, Veristat, Verily, Zydus. S.Z. received research grant support, served on advisory boards

for, or speaker engagements with Abbott, Akcea AstraZeneca, Amgen, Alnylam, Bayer, BMS, Boehringer Ingelheim, Eli Lilly, GSK, Janssen, Merck, Novartis, Novo-Nordisk, Otsuka, Pfizer, Roche, Servier and Vifor Pharma; and serves on a clinical trial committee or as a national lead for studies sponsored by AstraZeneca, Bayer, Boehringer Ingelheim, Merck, Novartis and Pfizer. J.J.V.M. has received funding to his institution, Glasgow University, for his work on clinical trials, consulting, and other activities from Alnylam, Amgen, AstraZeneca, Bayer, Bristol Myers Squibb, Cardurion, Cytokinetics, GlaxoSmithKline, Novartis, Pfizer, and Theracos; and has received personal lecture fees from the Corpus, Abbott, Hickma, Sun Pharmaceuticals, and Medsca. E.B. reports grant support to his institution from Novartis for the conduct of the PIONEER-HF trial [Comparison of Sacubitril/Valsartan Versus Enalapril on Effect on NT-proBNP (N-terminal pro-B type natriuretic peptide) in Patients Stabilized From an Acute HF Episode], for serving on the Executive Committee of the PARADISE-MI [Prospective ARNI (angiotensin receptor–neprilysin inhibitor) vs. ACE (angiotensin-converting enzyme) Inhibitor Trial to Determine Superiority in Reducing Heart Failure Events After Myocardial Infarction] trial and the Steering Committee of the PARAGLIDE-HF trial, and for participation in an Advisory Board Meeting. In addition, he reports receiving grant support through his institution from AstraZeneca, Daiichi Sankyo, and Merck, and consultancies with Amgen, Bristol Myers Squibb, Boehringer Ingelheim/Lilly, Cardurion, and Verve. S.D.S. has received research grants from Actelion, Alnylam, Amgen, AstraZeneca, Bellerophon, Bayer, Bristol Myers Squibb, Celladon, Cytokinetics, Eidos, Gilead, GlaxoSmithKline, Ionis, Lilly, Mesoblast, MyoKardia, National Institutes of Health/NHLBI, Neurotronik, Novartis, NovoNordisk, Respicardia, Sanofi Pasteur, Theracos, US2.AI; and has consulted for Abbott, Action, Akros, Alnylam, Amgen, Arena, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol Myers Squibb, Cardior, Cardurion, Corvia, Cytokinetics, Daiichi-Sankyo, GlaxoSmithKline, Lilly, Merck, Myokardia, Novartis, Roche, Theracos, Quantum Genomics, Cardurion, Janssen, Cardiac Dimensions, Tenaya, Sanofi-Pasteur, Dinaqor, Tremeau, CellProThera, Moderna, American Regent, and Sarepta. The remaining authors report no relevant disclosures to this work.

Data Availability

The sponsor of these trials (Novartis) is committed to sharing access to patient-level data and supporting clinical documents from eligible studies with qualified external researchers. 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 trial data availability is according to the criteria and process described at https://www.novartis.com/sites/novartis_com/files/clinical-trial-data-transparency.pdf.

Funding

PARAGLIDE-HF and PARAGON-HF were funded by Novartis Pharmaceuticals Corporation.

Ethical Approval

Written informed consent was obtained from each participant, and the study protocols were approved by the ethics committees or institutional review boards at all sites in both PARAGLIDE-HF and PARAGON-HF.

Pre-registered Clinical Trial Number

The pre-registered clinical trial number is PROSPERO CRD42023410574.

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