ESC European Society of Cardiology

European Heart Journal (2020) **41**, 2356–2362
doi:10.1093/eurheartj/ehaa184

FASTTRACK CLINICAL RESEARCH
ACC.20

A putative placebo analysis of the effects of sacubitril/valsartan in heart failure across the full range of ejection fraction

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Received 25 January 2020; revised 7 February 2020; editorial decision 29 February 2020; accepted 27 March 2020; online publish-ahead-of-print 28 March 2020

See page 2363 for the editorial comment on this article (doi: 10.1093/eurheartj/ehaa281)

Aims The PARADIGM-HF and PARAGON-HF trials tested sacubitril/valsartan against active controls given renin–angiotensin system inhibitors (RASi) are ethically mandated in heart failure (HF) with reduced ejection fraction and are used in the vast majority of patients with HF with preserved ejection fraction. To estimate the effects of sacubitril/valsartan had it been tested against a placebo control, we made indirect comparisons of the effects of sacubitril/valsartan with putative placebos in HF across the full range of left ventricular ejection fraction (LVEF).

Methods and results We analysed patient-level data from the PARADIGM-HF and PARAGON-HF trials ($n = 13\,194$) and the CHARM-Alternative and CHARM-Preserved trials ($n = 5050$, candesartan vs. placebo). The rate ratio (RR) of sacubitril/valsartan vs. putative placebo was estimated by the product of the RR for sacubitril/valsartan vs. RASi and the RR for RASi vs. placebo. Total HF hospitalizations and cardiovascular death were analysed using the negative binomial method. Treatment effects were estimated using cubic spline methods by ejection fraction as a continuous measure. Across the range of LVEF, sacubitril/valsartan was associated with a RR 0.54 [95% confidence interval (CI) 0.45–0.65] for the recurrent primary endpoint compared with putative placebo ($P < 0.001$). Treatment benefits of sacubitril/valsartan vs. putative placebo varied non-linearly with LVEF with attenuation of effects observed at LVEF above 60%. When analyzing data from PARADIGM-HF and CHARM-Alternative, the estimated risk reduction of sacubitril/valsartan vs. putative placebo was 48% (95% CI 35–58%); $P < 0.001$. When analyzing data from PARAGON-HF and CHARM-Preserved (with LVEF ≥ 45%), the estimated risk reduction of sacubitril/valsartan vs. putative placebo was 29% (95% CI 7–46%); $P = 0.013$. Across the full range of LVEF, consistent effects were observed for time-to-first endpoints: first primary endpoint (RR 0.72, 95% CI 0.64–0.82), first HF hospitalization (RR 0.67, 95% CI 0.58–0.78), cardiovascular death (RR 0.76, 95% CI 0.64–0.89), and all-cause death (RR 0.83, 95% CI 0.71–0.96); all $P < 0.02$.

Conclusion This putative placebo analysis reinforces the treatment benefits of sacubitril/valsartan on risk of adverse cardiovascular events across the full range of LVEF, with most pronounced effects observed at a LVEF up to 60%.

Keywords Placebo • Sacubitril/valsartan • Statistics • Trials

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Presentation at the American College of Cardiology Annual Scientific Sessions & the World Congress of Cardiology Congress, 29 March 2020, Chicago, IL, USA.

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Introduction

The angiotensin receptor neprilysin inhibitor (ARNI), sacubitril/valsartan, was tested against active comparators in paired, similarly designed trials of heart failure (HF) that covered the spectrum of left ventricular ejection fraction (LVEF).[1] Trials were designed to test the value of neprilysin inhibition, added to standard background therapy, inclusive of renin–angiotensin system inhibitors (RASi). The PARADIGM-HF (Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure) trial[2] compared sacubitril/valsartan against enalapril, as angiotensin-converting enzyme inhibitors (ACEi) are ethically mandated background therapy, represent the regulatory gold standard, and are supported by Class I, level of evidence A recommendations by international guidelines in HF with reduced ejection fraction (HFrEF).[3,4] The PARAGON-HF (Prospective Comparison of ARNI with ARB Global Outcomes in HF With Preserved Ejection Fraction) trial[5] compared sacubitril/valsartan against valsartan, as RASi are used in the vast majority of patients with HF with preserved ejection fraction (HFpEF) to achieve blood pressure control and to treat comorbidities (such as diabetes mellitus, chronic kidney disease, and coronary artery disease) to goals recommended by clinical practice guidelines.[3,4] While these trials inform the incremental efficacy and safety of ARNI compared with RASi, regulators and clinicians may be interested in understanding the combined effects of ARNI when compared with placebo. We employed established statistical approaches to estimate treatment effects of ARNI against a putative placebo comparator, leveraging data from two large clinical trial programmes evaluating sacubitril/valsartan and the angiotensin receptor blocker (ARB), candesartan, across the full range of LVEF.

Methods

Putative placebo analysis

To estimate the effects of RASi against placebo, we analysed patient-level data from PARADIGM-HF/PARAGON-HF trials and the CHARM (Candesartan in Heart failure—Assessment of Reduction in Mortality and morbidity)-Alternative/CHARM-Preserved trials. We employed an established method of indirect comparisons[6–8] that has been previously applied to estimate the effects of ARNI vs. putative placebo in HFrEF.[9] Treatment estimates of sacubitril/valsartan vs. putative placebo were estimated as the product of sacubitril/valsartan vs. RASi (derived from the PARADIGM-HF and PARAGON-HF trials) and RASi vs. placebo (derived from the CHARM-Alternative and CHARM-Preserved trials). The 95% confidence interval (CI) was estimated based on the square root of the sum of both squared standard errors of the logarithmic rate ratios (RRs). This approach relies on the assumption that the relative effects of sacubitril/valsartan vs. enalapril or valsartan would be comparable to that when compared with candesartan.

PARADIGM-HF and PARAGON-HF

PARADIGM-HF[2] and PARAGON-HF[5] were global, randomized, active-controlled clinical trials comparing sacubitril/valsartan vs. RASi in HF. Both trials enrolled symptomatic patients with HF and New York Heart Association (NYHA) class II-IV; PARADIGM-HF and PARAGON-HF patients had to be on RASi and diuretic therapy, respectively, during the month prior to enrolment. PARADIGM-HF patients were also required to be on a β-blocker (unless contraindicated or not tolerated) and a mineralocorticoid receptor antagonist (if indicated). Patients were required to have elevated natriuretic peptides (with variable thresholds based on recent HF hospitalization and history of atrial fibrillation/flutter). PARAGON-HF additionally required patients to have evidence of structural heart disease (left atrial enlargement or left ventricular hypertrophy). PARADIGM-HF enrolled patients with an LVEF of 40% or less and PARAGON-HF included patients with LVEF of 45% or greater. Patients who tolerated run-in periods (sequential titration phases of RASi followed by ARNI) were subsequently randomized to sacubitril/valsartan vs. enalapril (in PARADIGM-HF) or valsartan (in PARAGON-HF). The primary endpoint of PARADIGM-HF was time to first cardiovascular death or HF hospitalization and that of PARAGON-HF was total (first and recurrent) HF hospitalizations and cardiovascular death. Endpoints were centrally adjudicated by an independent clinical endpoints committee. PARADIGM-HF enrolled patients from 2009 to 2012 with median follow-up of 27 months. PARAGON-HF enrolled patients from 2014 to 2016 with median follow-up of 35 months. Pooling of individual patient-level data from both trials was prespecified to interpolate between LVEF 40–45% (a range not covered by eligibility criteria in either trial).

CHARM programme

This analysis focused on patients enrolled in CHARM-Alternative and CHARM-Preserved. We excluded CHARM-Added as patients enrolled in this trial were already treated with ACEi, and thus do not reflect an untreated patient population (free from RASi). CHARM-Alternative[10] enrolled symptomatic HF patients with NYHA Class II–IV and LVEF ≤40% who were intolerant to an ACEi. CHARM-Preserved[11] enrolled patients with HF and NYHA Class II–IV symptoms and LVEF >40%. Initially, in CHARM-Preserved, ACEi were not allowed as concomitant treatment, but after publication of the Heart Outcomes Prevention Evaluation trial results, their use was optional in appropriate patients. The CHARM programme enrolled patients between 1999 and 2001 and median follow-up was 34 months (for CHARM-Alternative) and 37 months (for CHARM-Preserved). The primary endpoint was time-to-first cardiovascular death or hospitalization for HF. Endpoints were centrally adjudicated by a clinical endpoints committee.

Left ventricular ejection fractions were based site-assessed measures at entry in all trials. The primary endpoint for this analysis was total HF hospitalizations and cardiovascular death. We analysed additional endpoints using time-to-first event analyses: composite of cardiovascular death or first HF hospitalization, each of its components, and all-cause mortality. Relative treatment effects were modelled using Poisson regression models (for time-to-first event analyses) and negative binomial models (for recurrent event analyses). In addition, to remain consistent with the protocol-specified approach to handling recurrent events in PARAGON-HF,[2] we separately analyzed the primary endpoint using a semiparametric proportional rates method developed by Lin, Wei, Yang, and Ying. Treatment effects (sacubitril/valsartan vs. putative placebo) were estimated using restricted cubic spline methods by LVEF as a continuous measure. We further analysed treatment effects separately in HFrEF (with data from PARADIGM-HF and CHARM-Alternative) and HFpEF (with data from PARAGON-HF and CHARM-Preserved). For this indirect comparison, to keep criteria consistent between trials, we restricted CHARM-Preserved to LVEF ≥45% (excluding 450 patients). We additionally carried out a sensitivity analysis evaluating treatment effects relative to an alternative LVEF cut-point (above and below 60%). All statistical analyses were performed using STATA 14.1 (College Station, TX, USA).

Table 1 Selected trial design elements and baseline characteristics

	CHARM-Alternative (*n* = 2028)	PARADIGM-HF (*n* = 8399)	CHARM-Preserved (*n* = 3023)	PARAGON-HF (*n* = 4796)
Comparison	Candesartan vs. placebo	Sacubitril/valsartan vs. enalapril	Candesartan vs. placebo	Sacubitril/valsartan vs. valsartan
Enrolment window	1999–2001	2009–12	1999–2000	2014–16
Median follow-up (months)	34	27	37	35
Age (years)	66.1 ± 10.8	63.8 ± 11.4	66.7 ± 11.1	72.7 ± 8.4
Women	646 (31.9%)	1832 (21.8%)	1212 (40.1%)	2479 (51.7%)
Body mass index (kg/m^2), mean ± SD	27.4 ± 4.9	28.2 ± 5.5	29.2 ± 5.8	30.2 ± 5.0
Systolic blood pressure (mmHg), mean ± SD	130.1 ± 18.7	121.4 ± 15.3	136.2 ± 18.4	130.6 ± 15.5
Heart rate (b.p.m.), mean ± SD	74.4 ± 13.6	72.4 ± 12.0	71.3 ± 12.5	70.4 ± 12.3
Left ventricular ejection fraction (%), mean ± SD	29.9 ± 7.4	29.5 ± 6.2	54.0 ± 9.4	57.5 ± 7.9
New York Heart Association class				
1	0 (0%)	389 (4.6 %)	0 (0%)	137 (2.9 %)
2	966 (47.6%)	5919 (70.6%)	1836 (60.7%)	3706 (77.3%)
3	989 (48.8%)	2018 (24.1%)	1140 (37.7%)	932 (19.4%)
4	73 (3.6 %)	60 (0.7 %)	47 (1.6 %)	19 (0.4 %)
Atrial fibrillation	515 (25.4%)	3091 (36.8%)	881 (29.1%)	1552 (32.5%)
Diabetes mellitus	548 (27.0%)	2907 (34.6%)	857 (28.3%)	2062 (43.0%)
Prior stroke	175 (8.6 %)	725 (8.6 %)	268 (8.9 %)	508 (10.6%)
Prior MI	1247 (61.5%)	3634 (43.3%)	1340 (44.3%)	1083 (22.6%)
Prior hospitalization for HF	1385 (68.3%)	5274 (62.8%)	2076 (68.7%)	2306 (48.1%)
Diuretics	1733 (85.5%)	6738 (80.2%)	2259 (74.7%)	4585 (95.6%)
MRA[a]	103 (5.1 %)	4671 (55.6%)	144 (4.8 %)	1239 (25.8%)
ACEi/ARB[b]	3 (0.1 %)	8379 (99.8%)	576 (19.1%)	4139 (86.3%)
β-blocker	1106 (54.5%)	7811 (93.0%)	1684 (55.7%)	3821 (79.7%)

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; HF, heart failure; MI, myocardial infarction; MRA, mineralocorticoid receptor antagonist; SD, standard deviation.
[a]In CHARM trials, spironolactone was the MRA captured in this category.
[b]In CHARM trials, only prior ACEi use was permitted.

Results

We analysed individual patient-level data from the PARADIGM-HF and PARAGON-HF trials (*n* = 13 195, sacubitril/valsartan vs. RASi) and the CHARM-Alternative and CHARM-Preserved trials (*n* = 5051, candesartan vs. placebo); *Table 1*. While patients enrolled in CHARM-Alternative were on average older than in PARADIGM-HF, patients enrolled in CHARM-Preserved were younger than in PARAGON-HF. Patients in the more contemporary PARADIGM-HF/PARAGON-HF trials had lower systolic blood pressures and rates of prior myocardial infarction, higher rates of atrial fibrillation, and diabetes mellitus and were more frequently NYHA functional class II compared with patients enrolled in CHARM. Mean LVEF was 39.7 ± 15.1% in PARADIGM-HF/PARAGON-HF and 44.3 ± 14.7% in the CHARM programme; LVEF was broadly represented in both clinical trial programmes (Supplementary material online, *Figure S1*). Rates of use of ACEi/ARB, β-blockers, and mineralocorticoid receptor antagonists were markedly higher in both PARADIGM-HF and PARAGON-HF compared with the corresponding CHARM trials.

During follow-up, incidence rates of recurrent primary endpoints were higher in CHARM-Alternative [1524 events; 29.1 (26.6–31.7) per 100 patient-years] compared with in PARADIGM-HF [3179 events; 17.1 (16.3–18.1) per 100 patient-years]. Risks of recurrent primary endpoints were more comparable between CHARM-Preserved [1308 events; 14.8 (13.5–16.2) per 100 patient-years] and PARAGON-HF [1903 events; 13.7 (12.8–14.8) per 100 patient-years].

In the overall trial programmes, sacubitril/valsartan reduced the recurrent primary endpoint by 21% (95% CI 13–29%) compared with RASi, while candesartan led to a 31% (95% CI 19–41%) event reduction compared with placebo (both $P < 0.001$). Applying indirect comparisons, sacubitril/valsartan reduced the recurrent primary endpoint by 46% (95% CI 35–55%) compared with putative placebo ($P < 0.001$). In examining PARADIGM-HF as the active comparator trial and CHARM-Alternative as the reference trial, the estimated risk reduction of sacubitril/valsartan vs. putative placebo was 48% (95% CI 35–58%); $P < 0.001$. In examining PARAGON-HF as the active comparator trial and CHARM-Preserved (restricted to LVEF ≥ 45%, excluding 450 patients to keep criteria consistent between trials) as the reference trial, the estimated risk reduction of sacubitril/valsartan vs. putative placebo was 29% (95% CI 7–46%); $P = 0.013$ (*Figure 1*). Qualitatively similar results were obtained when analyzing

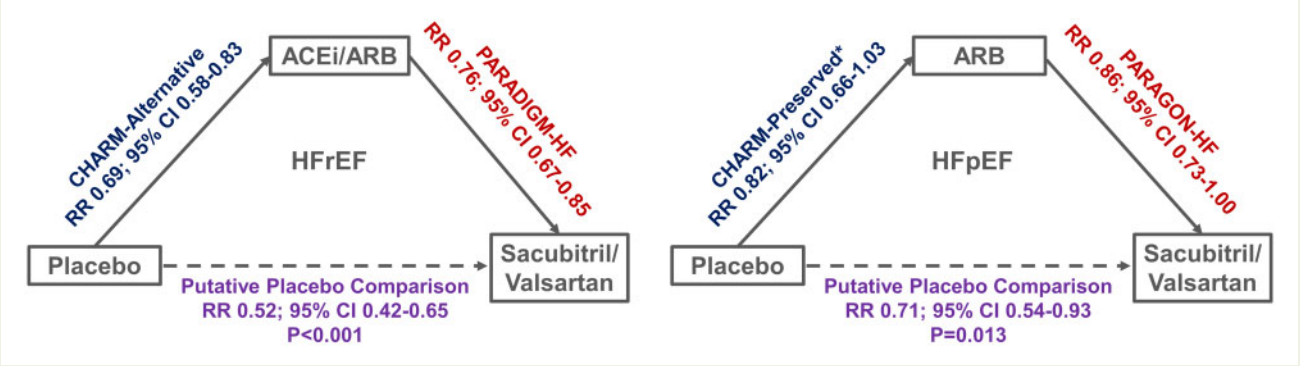
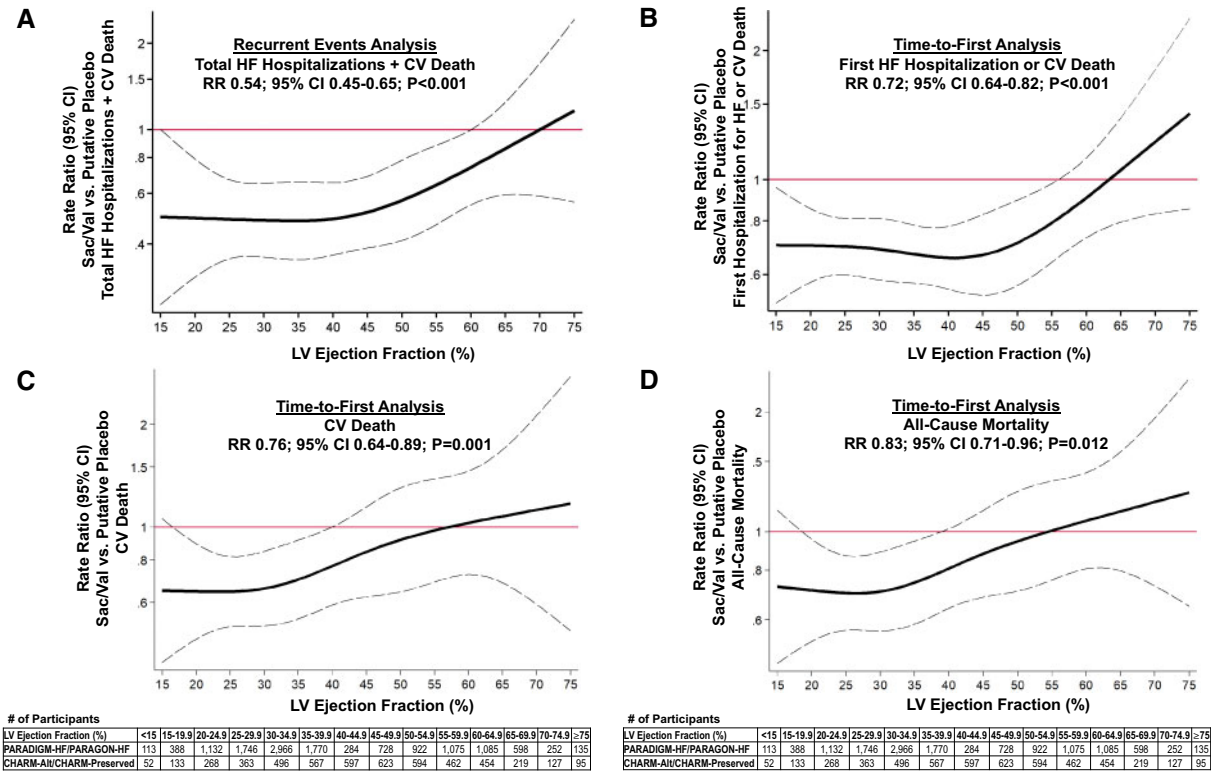


Figure 1 Schematic of the indirect comparisons used to estimate the effects of sacubitril/valsartan vs. putative placebo. The CHARM programme compared candesartan vs. placebo. PARADIGM-HF and PARAGON-HF compared sacubitril/valsartan vs. a renin–angiotensin system inhibitor. Solid lines represent direct comparisons performed in clinical trials, whereas the dashed lines represent indirect comparisons estimating the effects of sacubitril/valsartan vs. putative placebo. The endpoint was the recurrent primary endpoint of total heart failure hospitalizations and cardiovascular death, analysed using negative binomial methods. *Restricted to CHARM-Preserved patients with ejection fraction ≥45%; excluding 450 patients with left ventricular ejection fraction <45% to keep consistent with eligibility criteria in PARAGON-HF. ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CI, confidence interval; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; RR, rate ratio.



# of Participants

LV Ejection Fraction (%)	<15	15-19.9	20-24.9	25-29.9	30-34.9	35-39.9	40-44.9	45-49.9	50-54.9	55-59.9	60-64.9	65-69.9	70-74.9	≥75
PARADIGM-HF/PARAGON-HF	113	388	1,132	1,746	2,966	1,770	284	728	922	1,075	1,085	598	252	135
CHARM-Alt/CHARM-Preserved	52	133	268	363	496	567	597	623	594	462	454	219	127	95

# of Participants

LV Ejection Fraction (%)	<15	15-19.9	20-24.9	25-29.9	30-34.9	35-39.9	40-44.9	45-49.9	50-54.9	55-59.9	60-64.9	65-69.9	70-74.9	≥75
PARADIGM-HF/PARAGON-HF	113	388	1,132	1,746	2,966	1,770	284	728	922	1,075	1,085	598	252	135
CHARM-Alt/CHARM-Preserved	52	133	268	363	496	567	597	623	594	462	454	219	127	95

Take home figure Estimated treatment effects of sacubitril/valsartan vs. putative placebo across the full range of left ventricular ejection fraction. (*A*) Recurrent event analysis using a negative binomial model, for total heart failure hospitalizations and cardiovascular death. (*B–D*) Time-to-first analyses using Poisson regression models for first heart failure hospitalization or cardiovascular death, cardiovascular death, and all-cause mortality, respectively. Treatment effects were estimated using cubic spline methods by LV ejection fraction as a continuous measure. Density of patients at given left ventricular ejection fraction ranges is displayed in the table. CI, confidence interval; CV, cardiovascular; LV, left ventricular; RR, rate ratio.

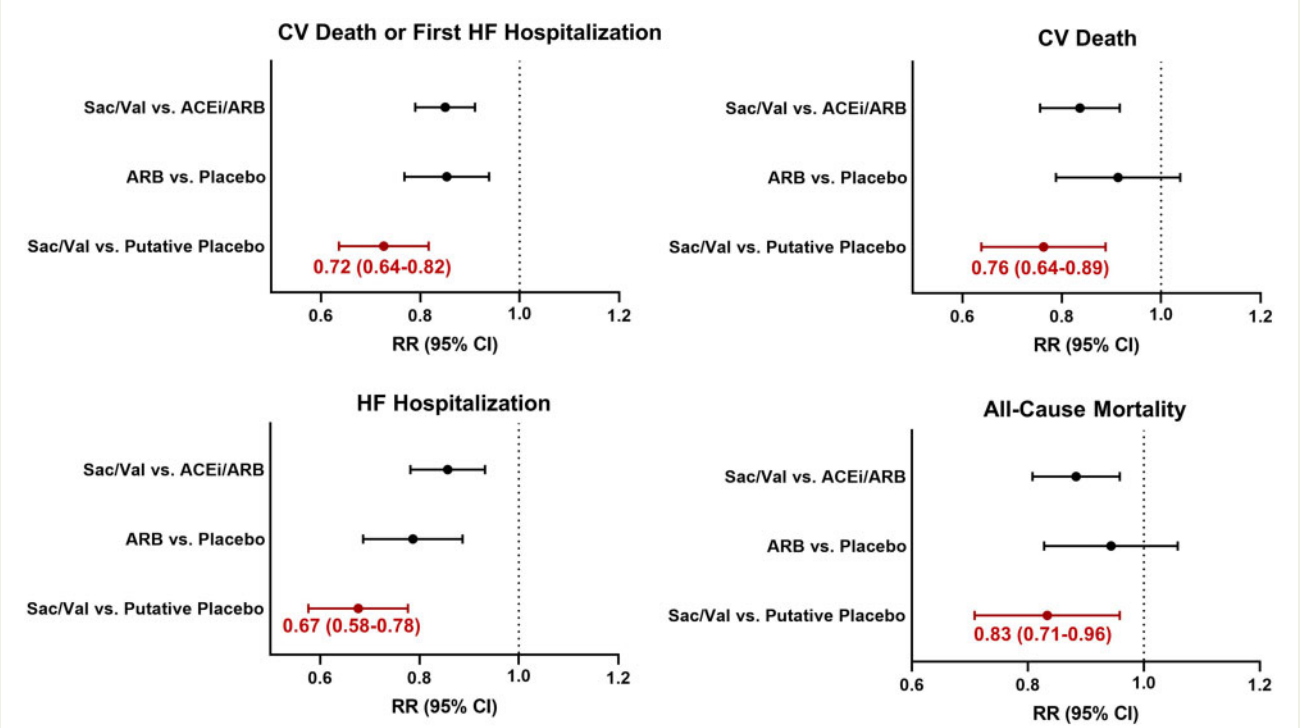


Figure 2 Forest plot of indirect comparisons used to estimate the effects of sacubitril/valsartan vs. putative placebo across a broad range of endpoints. PARADIGM-HF and PARAGON-HF compared sacubitril/valsartan vs. a renin–angiotensin system inhibitor. The CHARM programme compared candesartan vs. placebo. Black lines represent direct comparisons performed in clinical trials, whereas the red lines represent indirect comparisons estimating the effects of sacubitril/valsartan vs. putative placebo. All endpoints were analysed using time-to-first event analyses. ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CI, confidence interval; CV, cardiovascular; HF, heart failure; RR, rate ratio.

the recurrent primary endpoint with the semiparametric proportional rates method instead of the negative binomial method (Supplementary material online, Results).

In spline analyses (*Take home figure*), treatment benefits with respect to the recurrent primary endpoint of sacubitril/valsartan vs. putative placebo varied non-linearly with LVEF; $P_{interaction} = 0.03$ for LVEF above vs. below 50%. Sensitivity analysis selecting an alternative LVEF cut-point demonstrated that the effect of sacubitril/valsartan vs. putative placebo were robust at LVEF ≤ 60% [RR 0.50 (0.41–0.61); $P < 0.001$] but not in patients with LVEF >60% [RR 1.00 (0.59–1.69); $P = 1.00$]. In the aggregate analysis across the full range of LVEF, consistent effects were observed for time-to-first endpoints: first primary endpoint [RR 0.72 (0.64–0.82)], first HF hospitalization [RR 0.67 (0.58–0.78)], cardiovascular death [RR 0.76 (0.64–0.89)], and all-cause mortality [RR 0.83 (0.71–0.96)]; all $P < 0.02$; *Figure 2*. Treatment benefits of sacubitril/valsartan vs. putative placebo on first and recurrent primary endpoints extended to a higher LVEF compared with its effects on cardiovascular death and all-cause mortality (*Take home figure*).

Discussion

As supported by clinical practice guidelines,[3,4] RASi are established in the treatment of HFrEF. Given the high-risk nature of HF, withholding standard of care therapy (e.g. RASi) in a placebo-controlled trial was considered unethical in the evaluation of sacubitril/valsartan in HFrEF. While guidelines support management of prevalent comorbidities of HFpEF,[3,4] there is currently no pharmacological standard of care for this cohort of patients. Renin–angiotensin system inhibitors are widely used among patients with HFpEF, mostly in the treatment of hypertension. Since the addition of sacubitril/valsartan to background ACEi may increase risks of angioedema, a placebo-controlled trial could not be practically carried out and an active control (valsartan) was instead selected as the comparator in PARAGON-HF. As such, we conducted a comprehensive putative placebo analysis to estimate the treatment effects of sacubitril/valsartan if a placebo was selected across key cardiovascular endpoints. We uniquely leveraged pooled, patient-level data from the only clinical trials examining ARNI and RASi across the full range of LVEF. These data reinforce the robust clinical benefits of sacubitril/valsartan in HF. In the aggregate analysis across the full range of LVEF, we estimate treatment effects of 46% reductions in total HF hospitalizations and cardiovascular death. However, we detected notable non-linearity in the treatment effects with event reductions waning at higher LVEF, especially above 60%. Event reductions for the recurrent primary endpoint were estimated to be 48% (when assessing PARADIGM-HF and CHARM-Alternative) and 29% (when assessing PARAGON-HF and CHARM-

Preserved). Across the spectrum of LVEF, consistent reductions were observed for all cardiovascular events and mortality endpoints analysed.

Ideally, active-controlled and reference trials are similarly designed in the same era of background therapy with comparable reference drugs and dosing. However, as CHARM is the only clinical trial programme which evaluated a RASi in symptomatic HF across the full range of LVEF with long-term outcomes, this was selected as the historical reference comparator. While the SOLVD (Studies of Left Ventricular Dysfunction) Treatment trial could have been used as a comparator for PARADIGM-HF, patients were enrolled in this trial from 1986 to 1989 and CHARM-Alternative reflects a more conservative treatment effect estimate (as candesartan displayed relatively less benefit than enalapril as compared with placebo).[12] As such, the RASi evaluated in the active-controlled trials (PARADIGM-HF and PARAGON-HF) differed from that studied in the reference trials (CHARM-Alternative and CHARM-Preserved). While irbesartan, another ARB, has been studied in HFpEF,[13] the agent has not been studied in a comparable trial in HFrEF. However, it is reassuring that valsartan 160 mg twice daily (as tested in PARAGON-HF) and candesartan 32 mg once daily (as tested in CHARM) both have similarly potent biological activity in blood pressure lowering[14] and both represent target doses in contemporary guidelines.[15] It is further reassuring that the primary endpoints (either first or total HF hospitalization and/or cardiovascular death) were common across trials, and events were adjudicated under similar rigorous procedures by independent clinical endpoints committees.

These analyses further inform decision-making surrounding use of sacubitril/valsartan in HF. Estimation of the placebo-controlled response of a novel therapy is especially relevant in a disease entity, such as HFpEF that lacks a definitive standard of care. These data reinforce that the beneficial effects of sacubitril/valsartan on HF events and cardiovascular mortality appear to extend up to an LVEF below normal, including in 'HF with mid-ranged ejection fraction'. Sacubitril/valsartan is currently approved for use in HFrEF and is undergoing regulatory review for use at higher LVEF. Defining single LVEF thresholds for use is challenging given the inherent imprecision and variability in LVEF assessment and since certain subgroups (such as women) may derive benefits to a higher LVEF.[16] Costs, access, and ease of implementation will further modify the ultimate application of this therapy in HF at higher ranges of LVEF.

However, certain limitations of applying a historical reference trial should be acknowledged. Consistent with the differences in enrolment periods between the active-controlled (2009–16) and historical reference trials (1999–2001), there were marked differences in comorbidity profiles and background therapies of enrolled subjects. Since we only evaluate within-trial comparisons, balance in these parameters (as a function of randomization) was maintained without concern for confounding. Despite these substantial differences, observed risk of total HF events and cardiovascular death between CHARM-Preserved and PARAGON-HF was relatively comparable. Furthermore, we evaluated relative treatment effects as these estimates may be more similar across trials with varying designs, populations, and durations of follow-up compared with estimates of absolute treatment effects. Left ventricular ejection fraction captured was site-assessed (and not centrally measured); data quality may vary across global sites. Certain trial design features may have contributed to highly selected patient populations, including inclusion of only ACEi-intolerant patients in CHARM-Alternative and of patients who tolerated sequential run-in phases in PARADIGM-HF and PARAGON-HF. These factors introduce uncertainty around the exact estimate of treatment effect of sacubitril/valsartan vs. putative placebo and limit the generalizability of our findings.

This putative placebo analysis across the full range of LVEF complement and extend previous primary clinical trial findings, supporting the robust clinical benefits of sacubitril/valsartan in HF, with most pronounced effects observed at an ejection fraction up to 60%.

Supplementary material

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

Funding

The CHARM programme was funded by AstraZeneca. The PARADIGM-HF and PARAGON-HF trials were funded by Novartis.

Conflict of interest: M.V. was supported by the KL2/Catalyst Medical Research Investigator Training award from Harvard Catalyst (NIH/NCATS Award UL 1TR002541) and serves on advisory boards for Amgen, AstraZeneca, Baxter Healthcare, Bayer AG, Boehringer Ingelheim, Cytokinetics, and Relypsa. P.S.J. discloses speaker fees from Novartis, AstraZeneca; advisory board fees from Cytokinetics; and research grants from Boehringer Ingelheim. P.S.J. employer, University of Glasgow, has been paid by Novartis for time spent working on PARADIGM-HF and PARAGON-HF trials by Novartis and DAPA-HF by AstraZeneca. B.L.C. has received consultancy fees from Boehringer Ingelheim, Gilead, AOBiome, and Corvia. M.P. has received personal fees from Akcea, AstraZeneca, Amgen, Actavis, AbbVie, Bayer, Boehringer Ingelheim, Cardiorentis, Daiichi Sankyo, Johnson and Johnson, Novo Nordisk, Pfizer, Sanofi, Synthetic Biologics, and Theravance. J.W. reports personal fees from Novartis. P.S. reports personal fees from Novartis, Vifor Pharma, Respicardia , Boehringer Ingelheim, Abbott, and Medtronic. A.R., V.S., and M.L. are employees of Novartis. J.J.V.M. has served as an executive committee member and co-principal investigator of the PARADIGM-HF and PARAGON-HF trials; and his employer, Glasgow University, has been paid by Novartis for his time spent in these roles. S.D.S. has received research grants from Alnylam, Amgen, AstraZeneca, Bellerophon, Celladon, Gilead, GlaxoSmithKline, Ionis Pharmaceutics, Lone Star Heart, Mesoblast, MyoKardia, NIH/NHLBI, Novartis, Sanofi Pasteur, and Theracos; and has consulted for Alnylam, Amgen, AstraZeneca, Bayer, Bristol-Myers Squibb, Corvia, Gilead, GlaxoSmithKline, Ironwood, Merck, Novartis, Pfizer, Takeda, and Theracos.

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