ESC European Society of Cardiology

European Journal of Heart Failure (2022) **24**, 672–677
doi:10.1002/ejhf.2439

SHORT REPORT

Natriuretic peptide-based inclusion criteria in heart failure with preserved ejection fraction clinical trials: insights from PARAGON-HF

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Received 9 August 2021; revised 14 January 2022; accepted 21 January 2022; online publish-ahead-of-print 14 February 2022

Aim Natriuretic peptides (NPs) are now routinely incorporated as key inclusion criteria in clinical trials of heart failure with preserved ejection fraction (HFpEF) as objective measures of risk. An early amendment in PARAGON-HF required all participants to have elevated NP concentrations, but some were enrolled pre-amendment, providing a unique opportunity to understand the influence of enrolment pathway in HFpEF clinical trials.

Methods and results Among 4796 participants in PARAGON-HF, 193 (4.0%) did not meet the final NP-based enrolment criteria (N-terminal pro-B-type natriuretic peptide >300 pg/ml for patients in sinus rhythm or >900 pg/ml for patients in atrial fibrillation/flutter). These patients had lower rates of the primary endpoint of total heart failure hospitalizations and cardiovascular death as compared with patients meeting final enrolment criteria (8.6 [6.7–11.2] events per 100 patient-years vs. 14.0 [13.4–14.7] events per 100 patient-years; $p = 0.01$). The rate ratio for the treatment effect comparing sacubitril/valsartan with valsartan was 0.85 (95% confidence interval 0.74–0.99; $p = 0.04$) in those who met final criteria.

Conclusions Natriuretic peptides are an important tool in HFpEF clinical trials to objectively affirm diagnoses and enrich clinical event rates.

Keywords Clinical trials • Heart failure with preserved ejection fraction • Natriuretic peptides

Introduction

Heart failure with preserved ejection fraction (HFpEF) is a heterogeneous disease and to date there is a lack of a uniform definition.[1] Virtually all contemporary trials in this population have utilized elevation in natriuretic peptide (NP) concentrations as inclusion criteria to affirm heart failure diagnoses and identify patients likely to be at higher risk of clinical events. The NP requirement was, in part, a response to the failings of the TOPCAT (Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist) trial of spironolactone in HFpEF, which permitted entry on the basis of either elevated NPs or recent heart failure hospitalization. The lack of uniform requirement for elevation in NPs led to the ability to enrol patients who had just been hospitalized, many of whom may not have had heart failure[2] leading to dramatically lower event rates in these patients.

Prior to the unblinding of TOPCAT in 2014, the PARAGON-HF (Prospective Comparison of ARNI with ARB Global Outcomes in HF with Preserved Ejection Fraction) trial was designed to also allow two potential pathways for inclusion. The original entry criteria required either a heart failure hospitalization within 9 months or elevation in NPs. In response to the TOPCAT results in 2014, the

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PARAGON-HF trial, which had already commenced enrolment, amended the inclusion criteria to require elevated N-terminal pro-B-type natriuretic peptide (NT-proBNP) concentrations in all participants. By the time the amendment was fully implemented, there were patients enrolled who met the original, but not final, inclusion criteria. In this analysis we compared patients who met or who did not meet final enrolment criteria in terms of baseline characteristics, clinical event rates, and treatment effects of sacubitril/valsartan.

Methods

The design and results of PARAGON-HF have been previously reported.[3,4] In brief, PARAGON-HF was a global, randomized, double-blind, parallel group, active-controlled, event-driven trial that enrolled patients with New York Heart Association (NYHA) class II–IV symptoms, ejection fraction ≥45%, evidence of structural heart disease (left atrial enlargement or left ventricular hypertrophy), and elevated NP. The primary outcome was a composite of total hospitalizations for heart failure and cardiovascular death. Patients were randomized to sacubitril/valsartan (target dose 97/103 mg twice daily) or valsartan (target dose 160 mg twice daily) and followed for a median of 35 months. All patients provided written informed consent. The study protocol was approved by local institutional review boards at participating sites.

Natriuretic peptide amendment

In May 2015, the study protocol was amended to require elevated NP for all patients. Prior to the amendment, patients could be enrolled based on either elevated NT-proBNP at the screening visit (>300 pg/ml for patients in sinus rhythm on screening visit electrocardiogram or >900 pg/ml for patients in atrial fibrillation/flutter) or heart failure hospitalization within the prior 9 months. The amendment added a minimum screening visit NT-proBNP concentration for patients with recent hospitalization, which was at a lower level than patients without hospitalization: >200 pg/ml for patients in sinus rhythm or >600 pg/ml in atrial fibrillation/flutter. Screening visit NT-proBNP samples (n = 4757, 99% of patients) were collected at individual sites and analysed to determine study eligibility at nine regional laboratories owned by or affiliated with the central laboratory (Clinical Reference Laboratory, Lenexa, KS, USA) with the Roche proBNP II (Roche Diagnostics, Penzberg, Germany) or the Siemens Immulite 1000 (Siemens, Munich, Germany) assays.

Statistical analysis

Baseline characteristics of patients who met or did not meet the final inclusion criteria were described using median (interquartile range) for continuous variables, and number (proportion) for categorical variables. Baseline characteristics of patients who met or did not meet the final inclusion criteria were compared using appropriate non-parametric tests. Rates of the primary outcome, total heart failure hospitalizations and cardiovascular death, were compared using the model of Lin et al. as pre-specified in PARAGON-HF,[5] and displayed using Nelson–Aalen curves. Treatment effect modification was assessed by the interaction term of randomized treatment group and final inclusion criteria group. Cardiovascular death was analysed in similar fashion by using the log-rank rest and cumulative incidence curves. A 2-sided p-value of <0.05 was considered significant. Statistical analysis was performed using STATA 16.1 (College Station, TX, USA) and R 3.6 (Foundation for Statistical Computing, Vienna, Austria).

TOPCAT (Americas region)

We applied the inclusion criteria from PARAGON-HF to patients enrolled in the Americas region of the TOPCAT trial who had available NT-proBNP data at baseline. TOPCAT was a randomized clinical trial comparing spironolactone with placebo in patients with HFpEF.[6] Due to substantial regional variation in enrolled populations, study conduct, protocol adherence, this analysis evaluated only patients enrolled in the Americas region. Baseline characteristics and rates of clinical events were compared between patients who did and did not meet PARAGON-HF final inclusion criteria using appropriate parametric and non-parametric tests.

Results

Baseline characteristics

Of the 4796 patients enrolled, 193 (4.0%) did not meet the final enrolment criteria. This group included four patients whose NT-proBNP at screening was unknown. The remaining 189 patients had NT-proBNP concentrations below the protocol-specified minimum based on atrial fibrillation and heart failure hospitalization status. By design, patients who did not meet final enrolment criteria were more likely to have been previously hospitalized for heart failure within 9 months (80% vs. 37%, $p = 0.001$) and had lower screening visit NT-proBNP (median 135 vs. 952 pg/ml, $p < 0.001$) (*Table 1*). Furthermore, patients not meeting final enrolment criteria were younger (67 vs. 74 years, $p < 0.001$), with higher body mass index (33 vs. 30 kg/m^2, $p < 0.001$), ejection fraction (60% vs. 57%, $p = 0.008$), and estimated glomerular filtration rate (71 vs. 60 ml/min/1.73 m^2, $p < 0.001$), and less prevalent atrial fibrillation (16% vs. 33%, $p < 0.001$). The proportion of patients not meeting final enrolment criteria was numerically higher in Central Europe but did not differ significantly by region. Median screening visit was 281 days earlier in participants not meeting final criteria ($p < 0.001$). Baseline characteristics were balanced between the sacubitril/valsartan and valsartan groups (online supplementary *Table S1*).

Clinical event rates

Mean follow-up time was 2.9 years in patients who met final enrolment criteria and 3.5 years in those who did not. Participants who did not meet the final enrolment criteria had lower rates of the primary endpoint, total heart failure hospitalizations and cardiovascular death: 8.6 (95% confidence interval [CI] 6.7–11.2) events per 100 patient-years in those not meeting final criteria vs. 14.0 (95% CI 13.4–14.7) events per 100 patient-years in those meeting final criteria (rate ratio 0.60, 95% CI 0.40–0.89; $p = 0.01$). Lower event rates were observed regardless of atrial fibrillation (rate ratio 0.61, 95% CI 0.28–1.32 in atrial fibrillation vs. 0.57, 95% CI 0.36–0.92 without atrial fibrillation; $p_{interaction} = 0.83$). Rates of cardiovascular death were also significantly lower in participants who did not meet final enrolment criteria: 1.6 (95% CI 0.9–2.9) events per 100 patient-years vs. 3.1 (95% CI 2.8–3.4) events per

Table 1 Baseline characteristics of participants in the PARAGON-HF trial who did or did not meet final natriuretic peptide-based enrolment criteria

	Final criteria (n = 4603)	Not final criteria (n = 193)	p-value
Age, years	74 (67–79)	67 (60–72)	<0.001
Female sex	2380 (51.7)	99 (51.3)	0.91
Race			0.31
Asian	593 (12.9)	14 (7.3)	
Black	99 (2.2)	3 (1.6)	
Other	165 (3.6)	15 (7.8)	
White	3746 (81.4)	161 (83.4)	
Region			0.35
Asia/Pacific and other	744 (16.2)	18 (9.3)	
Central Europe	1623 (35.3)	92 (47.7)	
Latin America	352 (7.6)	18 (9.3)	
North America	534 (11.6)	25 (13.0)	
Western Europe	1350 (29.3)	40 (20.7)	
Diabetes	1969 (42.8)	93 (48.2)	0.14
Stroke	492 (10.7)	16 (8.3)	0.28
Hypertension	4393 (95.4)	191 (99.0)	0.02
Prior myocardial infarction	1039 (22.6)	44 (22.8)	0.94
Ischaemic aetiology of HF	1639 (35.6)	84 (43.8)	0.021
New York Heart Association functional class			0.15
I	126 (2.7)	11 (5.7)	
II	3558 (77.3)	148 (76.7)	
III	900 (19.6)	32 (16.6)	
IV	17 (0.4)	2 (1.0)	
Prior HF hospitalization (within 9 months)	1685 (36.6)	155 (80.3)	0.001
Body mass index, kg/m^2	30 (26–34)	33 (29–36)	<0.001
Left ventricular ejection fraction, %	57 (50–62)	60 (54–65)	0.008
ACEi/ARB	3969 (86.2)	170 (88.1)	0.46
Mineralocorticoid receptor antagonist	1184 (25.7)	55 (28.5)	0.39
Diuretic agent	4404 (95.7)	181 (93.8)	0.21
Beta-blocker	3679 (79.9)	142 (73.6)	0.032
Atrial fibrillation at screening visit	1523 (33.2)	29 (15.6)	<0.001
Systolic blood pressure, mmHg	130 (120–140)	130 (120–138)	0.92
Diastolic blood pressure, mmHg	75 (67–81)	78 (70–81)	0.002
Estimated glomerular filtration rate, ml/min/1.73 m^2	60 (48–74)	71 (58–85)	<0.001
N-terminal pro-B-type natriuretic peptide, pg/ml	952 (498–1658)	135 (86–194)	<0.001

Values are median (interquartile range), or n (%).
ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; HF, heart failure.

100 patient-years (hazard ratio 0.50, 95% CI 0.27–0.90; p = 0.02). This lower event rate for the primary endpoint was virtually unchanged when applying criteria of NT-proBNP >300 ng/L in sinus rhythm and >900 ng/L in atrial fibrillation, without taking into account hospitalization status: 8.9 (95% CI 7.4–10.5) events per 100 patient-years in those not meeting this NP-based criteria vs. 14.3 (95% CI 13.7–15.0) events per 100 patient-years in those meeting NP-based criteria (rate ratio 0.61, 95% CI 0.79–0.47).

Treatment effect of sacubitril/valsartan versus valsartan

In patients who met final enrolment criteria, sacubitril/valsartan reduced the primary endpoint of total heart failure hospitalizations and cardiovascular death (rate ratio 0.85, 95% CI 0.74–0.99; p = 0.04). In those who did not meet final criteria, there was no evidence of sacubitril/valsartan treatment effect (rate ratio 1.27, 95% CI 0.59–2.73; p = 0.54). There was no statistically significant interaction between treatment group and final enrolment criteria for the primary endpoint ($p_{interaction}$ = 0.39) (*Figure 1*).

Application of PARAGON-HF inclusion criteria to the TOPCAT trial

Among 359 patients in the Americas region of the TOPCAT trial with NT-proBNP data available at baseline, 290 patients would have met final criteria for PARAGON-HF (based on NT-proBNP,

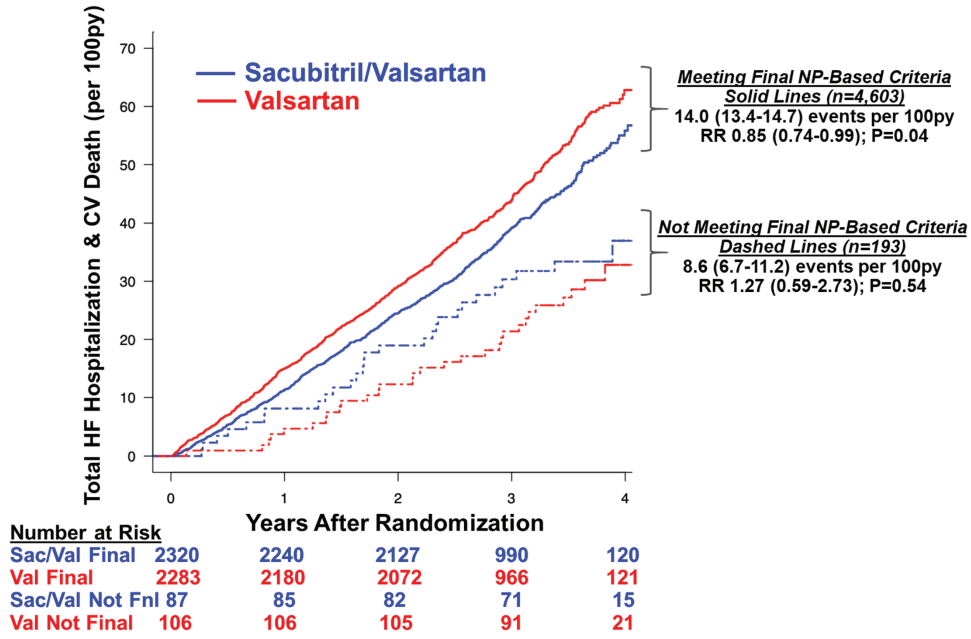

Figure 1 Total heart failure (HF) hospitalizations and cardiovascular (CV) death by inclusion criteria group and treatment arm in the PARAGON-HF trial. Primary outcomes in patients meeting final criteria versus patients not meeting final criteria. Event rates are presented as events per 100 patient-years (95% confidence interval) for the primary outcome. RR, rate ratio; Sac/Val, sacubitril/valsartan; Val, valsartan.

recent heart failure hospitalization, and atrial fibrillation status) and 69 would have been ineligible. Patients not meeting PARAGON-HF inclusion criteria had markedly lower NT-proBNP (median 539 pg/ml vs. 1215 pg/ml, $p < 0.001$). These patients experienced lower rates of heart failure hospitalization or cardiovascular death (5.7 [95% CI 3.2–10.3] events per 100 patient-years vs. 10.9 [95% CI 8.7–13.6] events per 100 patient-years; hazard ratio 0.53, 95% CI 0.28–1.00; $p = 0.05$) and heart failure hospitalization alone (3.1 [95% CI 1.4–6.9] events per 100 patient-years vs. 7.5 [95% CI 5.7–9.9] events per 100 patient-years with final criteria; HR 0.42, 95% CI 0.18–0.99; $p = 0.047$) (online supplementary *Table S2*). These results were consistent with findings in PARAGON-HF.

Discussion

In PARAGON-HF, a small subgroup of 193 patients were enrolled before a protocol amendment requiring elevated NPs in all patients. Participants not meeting final inclusion criteria had lower rates of clinical events and did not appear to benefit from sacubitril/valsartan, though treatment interaction analysis was underpowered to show a statistical difference. These results underscore the value of NP-based criteria in enrolling a population with higher, potentially modifiable heart failure events.

Given the challenges of diagnosing HFpEF, clinical trials have relied on stringent definitions with objective parameters to ensure enrolment of subjects who have the disease and are at risk for heart failure-related hospitalization and death. NPs are neurohormones released from the atrial and ventricular myocardium in response to volume expansion and pressure overload.[7,8] Upon binding to their receptors, NPs induce diuresis, natriuresis, and vasodilatation by regulating the renin–angiotensin–aldosterone system and the sympathetic nervous system resulting in improved myocardial relaxation and reduced myocardial fibrosis.[9,10] Elevated NP concentration has proven to be a helpful biomarker for congestion in patients with undifferentiated dyspnoea.[11] As such, NPs have been included as a criterion for the diagnosis of heart failure in current clinical practice guidelines in conjunction with other clinical information.[9]

In addition to their role in heart failure diagnosis, elevated NPs are known to be associated with adverse cardiovascular outcomes in HFpEF[12,13] even in populations with classically lower distribution of NP concentrations, such as Black and obese patients.[14] Here, the incidence of the primary outcome in patients who met final NP-based criteria was 60% greater compared to those who did not meet those criteria. Concordantly, patients meeting final inclusion criteria had a higher prevalence of comorbidities including older age, renal dysfunction, and atrial fibrillation. Previous studies have also shown the value of NP-based inclusion criteria to enrich clinical event rates.[5] Regional variations in TOPCAT suggest that clinical diagnostic criteria were not consistently applied, accounting for the marked difference in population risk profiles seen.[6,15] Furthermore, analysis from the I-PRESERVE and TOPCAT studies have shown that absolute rates of primary outcomes in HFpEF are lower when NT-proBNP concentration is <400 pg/ml which suggests that also establishing a minimum NP threshold may help to ensure adequately high event rates.[16]

The benefits of NP-based inclusion criteria in confirming the diagnosis of heart failure and ensuring high event rates are counterbalanced by some limitations. In up to 30% of patients believed to have HFpEF, NP concentrations are not confirmatory of the diagnosis.[17] NP concentrations are also lower in patients with HFpEF compared to heart failure with reduced ejection fraction[18–20] and their values differ in certain populations such as obesity, atrial fibrillation, race/ethnicity, age, and sex.[14,17,21–23] Applying a single NP threshold as an inclusion criterion may lead to underrepresentation of some groups.[14] Refining NP thresholds in these groups or using multiple biomarkers could minimize these limitations but adds complexity to the enrolment process. In PARAGON-HF, a higher NP threshold was used in atrial fibrillation because patients in atrial fibrillation have higher NPs relative to their risk of heart failure events.

Our analysis also highlights the importance of researchers learning from contemporary clinical trials and modifying study protocols, as necessary. For example, in the COMMANDER-HF trial, after adding a minimum of 800 pg/ml of NT-proBNP as an inclusion criterion, primary endpoint event rates increased by 30%.[24] Without the amendment, the trial would have needed to recruit 1000 more patients in order to have sufficient power.[24]

This study has several limitations. First, this analysis was post-hoc, and the proportion of patients who did not meet final inclusion criteria was small (4%), which reduced statistical power to detect differences between groups, especially treatment interactions. Some of these patients may have been enrolled in violation of the protocol rather than prior to amendment implementation. In addition, the timing of protocol amendment implementation varied by site.

In conclusion, in PARAGON-HF, 4% of patients were enrolled before a protocol amendment was introduced requiring elevated NPs in all patients. These patients did not meet final inclusion criteria, had lower rates of total heart failure hospitalizations and cardiovascular death, and did not benefit from sacubitril/valsartan as compared to patients meeting final NP concentration criteria. These results highlight the importance of requiring elevated NPs for inclusion in HFpEF clinical trials to assure heart failure diagnosis, reducing subjectivity of eligibility criteria interpretation, and enriching clinical risk.

Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Funding

PARAGON-HF was sponsored by Novartis.

Conflict of interest: M.A.P. has no disclosures. J.W.C. was supported by the NHLBI T32 postdoctoral training grant T32HL094301. B.C. received consultancy fees from Boehringer Ingelheim, Gilead, AOBiome, Novartis, Myokardia, and Corvia. M.P. has received personal fees from Akcea Therapeutics, AstraZeneca, Amgen, Actavis, AbbVie, Bayer, Boehringer Ingelheim, Cardiorentis, Daiichi Sankyo, Johnson & Johnson, Novo Nordisk, Pfizer, Relypsa, Sanofi, Synthetic Biologics, and Theravance. M.Z. has received research funding from Novartis; and has been a consultant for Novartis, Abbott, Boston Scientific, CVRx, EBR, Endotronics, Ironwood, Merck, Medtronic, and MyoKardia V Wave. M.A.P. has been a consultant for AstraZeneca, DalCor Pharmaceuticals, GlaxoSmithKline, Innovative Science Solutions, Novo Nordisk, Pharmascience, Sanofi, Jazz, MyoKardia, Servier, Takeda, and Corvidia; has received research support from Novartis; and has stock options in DalCor Pharmaceuticals. M.L., V.S. and A.R. are employees of Novartis. J.J.V.M. has received consulting payments through Glasgow University from Bayer, Cardiorentis, Amgen, Theracos, AbbVie, DalCor Pharmaceuticals, Pfizer, Merck, AstraZeneca, GlaxoSmithKline, Bristol-Myers Squibb, Vifor-Fresenius, Kidney Research UK, Novartis, and Theracos. S.D.S. has received research grants from Actelion, Alnylam, Amgen, AstraZeneca, Bellerophon, Bayer, BMS, Celladon, Cytokinetics, Eidos, Gilead, GSK, Ionis, Lilly, Mesoblast, MyoKardia, NIH/NHLBI, Neurotronik, Novartis, NovoNordisk, Respicardia, Sanofi Pasteur, Theracos, and has consulted for Abbott, Action Akros, Alnylam, Amgen, Arena, AstraZeneca, Bayer, Boehringer Ingelheim, BMS, Cardior, Cardurion, Corvia, Cytokinetics, GSK, Ironwood, Lilly, Merck, Myokardia, Novartis, Roche, Takeda, Theracos, Quantum Genetics, Janssen, Cardiac Dimensions, Tenaya, Sanofi-Pasteur, Dinaqor, Tremeau, CellProThera, Moderna, American Regent. M.V. receives research grants from and/or serves on advisory boards for American Regent, Amgen, AstraZeneca, Baxter Healthcare, Bayer AG, Boehringer Ingelheim, Cytokinetics, Lexicon Pharmaceuticals, Pharmacosmos, Relypsa, Roche Diagnostics, and Sanofi; has participated in speaking engagements for Novartis and Roche Diagnostics, and participates in clinical endpoint committees for studies sponsored by Galmed and Novartis.

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