Circulation: Heart Failure

ORIGINAL ARTICLE

Baseline Characteristics of Patients With Heart Failure and Preserved Ejection Fraction in the PARAGON-HF Trial

BACKGROUND: To describe the baseline characteristics of patients with heart failure and preserved left ventricular ejection fraction enrolled in the PARAGON-HF trial (Prospective Comparison of Angiotensin Receptor Neprilysin Inhibitor With Angiotensin Receptor Blocker Global Outcomes in HFpEF) comparing sacubitril/valsartan to valsartan in reducing morbidity and mortality.

METHODS AND RESULTS: We report key demographic, clinical, and laboratory findings, and baseline therapies, of 4822 patients randomized in PARAGON-HF, grouped by factors that influence criteria for study inclusion. We further compared baseline characteristics of patients enrolled in PARAGON-HF with those patients enrolled in other recent trials of heart failure with preserved ejection fraction (HFpEF). Among patients enrolled from various regions (16% Asia-Pacific, 37% Central Europe, 7% Latin America, 12% North America, 28% Western Europe), the mean age of patients enrolled in PARAGON-HF was 72.7±8.4 years, 52% of patients were female, and mean left ventricular ejection fraction was 57.5%, similar to other trials of HFpEF. Most patients were in New York Heart Association class II, and 38% had ≥1 hospitalizations for heart failure within the previous 9 months. Diabetes mellitus (43%) and chronic kidney disease (47%) were more prevalent than in previous trials of HFpEF. Many patients were prescribed angiotensin-converting enzyme inhibitors or angiotensin receptor blockers (85%), β-blockers (80%), calcium channel blockers (36%), and mineralocorticoid receptor antagonists (24%). As specified in the protocol, virtually all patients were on diuretics, had elevated plasma concentrations of N-terminal pro-B-type natriuretic peptide (median, 911 pg/mL; interquartile range, 464–1610), and structural heart disease.

CONCLUSIONS: PARAGON-HF represents a contemporary group of patients with HFpEF with similar age and sex distribution compared with prior HFpEF trials but higher prevalence of comorbidities. These findings provide insights into the impact of inclusion criteria on, and regional variation in, HFpEF patient characteristics.

CLINICAL TRIAL REGISTRATION: URL: https://www.clinicaltrials.gov. Unique identifier: NCT01920711.

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Key Words: angiotensin receptor antagonists ■ endopeptidases ■ heart failure, diastolic ■ clinical trial

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WHAT IS NEW?

- This is a contemporary description of an international cohort of patients with heart failure and preserved ejection fraction in a large clinical trial, PARAGON-HF (Prospective Comparison of Angiotensin Receptor Neprilysin Inhibitor With Angiotensin Receptor Blocker Global Outcomes in Heart Failure and Preserved Left Ventricular Ejection Fraction).
- We find a high prevalence of comorbidities, including diabetes mellitus, renal dysfunction, atrial fibrillation.

WHAT ARE THE CLINICAL IMPLICATIONS?

- Patients with heart failure with preserved ejection fraction are at substantially increased risk of morbidity and mortality.
- These data provide insight into the clinical characteristics of patients with heart failure with preserved ejection fraction, stringently defined by the entry criteria of the PARAGON-HF trial.
- These data will serve as a detailed description of the baseline characteristics of this trial that allow for comparison to other cohorts, including real-world cohorts and registries of patients with heart failure with preserved ejection fraction.

The clinical syndrome of heart failure with preserved ejection fraction (HFpEF) is characterized broadly by signs and symptoms of heart failure and in the absence of a reduced left ventricular ejection fraction.[1] Precise definition and diagnostic clinical criteria for HFpEF remain controversial but, for the purposes of inclusion in clinical trials, have become more stringent in recent years because of concerns about enrolling patients with other causes of dyspnea and edema misdiagnosed as heart failure.[2]

The PARAGON-HF trial (Prospective Comparison of Angiotensin Receptor Neprilysin Inhibitor With Angiotensin Receptor Blocker Global Outcomes in Heart Failure and Preserved Left Ventricular Ejection Fraction) is a large, double-blind randomized controlled clinical outcomes trial testing the hypothesis that sacubitril/valsartan, an angiotensin receptor neprilysin inhibitor would be superior to valsartan in reducing morbidity and mortality in patients with HFpEF.[3] Sacubitril/valsartan simultaneously blocks the angiotensin II type I receptor and inhibits the enzyme neprilysin, a protease that plays a role in the breakdown of several vasoactive peptides, including the biologically active natriuretic peptides. Compared with enalapril, sacubitril/valsartan conclusively reduced morbidity and mortality among patients with heart failure with reduced ejection fraction (HFrEF) in PARADIGM-HF (Prospective Comparison of ARNI With ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure).[4] In a phase II trial of HFpEF, PARAMOUNT-HF (Prospective Comparison of ARNI With ARB on Management of Heart Failure With Preserved Ejection Fraction),[5] sacubitril/valsartan compared with valsartan, reduced NT-proBNP (N-terminal pro-B-type natriuretic peptide) at 12 weeks and reduced both left atrial volume and New York Heart Association (NYHA) class at 36 weeks compared with valsartan.[4] These data provided the rationale for the design of PARAGON-HF, which was also heavily influenced by the experience gained from previous trials of HFpEF. In this report, we describe the baseline characteristics of patients enrolled in PARAGON-HF and compare them to patients enrolled in other clinical trials of patients with HFpEF and with the recently completed PARADIGM-HF trial.

METHODS

The data, analytic methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure.

Patients and Study Design

PARAGON-HF is a randomized, double-blind, parallel group, active-controlled, 2-arm event-driven trial comparing the efficacy and safety of sacubitril/valsartan versus valsartan in patients with HFpEF. PARAGON-HF enrolled patients with signs and symptoms of heart failure (NYHA class II–IV), left ventricular ejection fraction of ≥45, increased plasma concentrations of NT-proBNP (degree of elevation depending on history of heart failure hospitalization within 9 months and presence or absence of atrial fibrillation), and evidence of structural heart disease (increased left atrial size or left ventricular hypertrophy). Before randomization, patients entered sequential single-blind run-in periods ensuring that both treatments were tolerated at half the target doses. The primary end point for the trial is cardiovascular death and total number of (first and recurrent) heart failure hospitalizations. The trial is event-driven and will stop when at least 1847 primary events are reached. The study was approved by institutional review boards at individual study sites, and all patients signed written informed consent. The details of the study design are published.[3]

Baseline characteristics were collected at screening, and several of these were assessed again at randomization. We report baseline characteristics at screening for all variables unless otherwise stated, as screening represents a truer baseline because of the sequential run-in periods before randomization. Because plasma concentrations of NT-proBNP required for enrollment in PARAGON-HF differed based on the presence or absence of atrial fibrillation (AF) at screening, and whether or not patients had been hospitalized for heart failure within 9 months, we grouped baseline characteristics based on these measures. In addition, we grouped baseline characteristics based on region of origin: Asia-Pacific/Other, Central Europe, Latin America, North America, or Western Europe. Finally, we compared baseline characteristics from PARAGON-HF with those of other HFpEF trials, including those patients enrolled

in the Americas in TOPCAT (Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist),[6] I-PRESERVE (Irbesartan in Heart Failure With Preserved Ejection Fraction),[7] CHARM-Preserved (Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity),[8] and PEP-CHF (Perindopril in Elderly People With Chronic Heart Failure),[9] and with patients with HFrEF enrolled in the PARADIGM-HF trial.[4] Assessment in TOPCAT was confined to those patients enrolled in the Americas because of concern about enrollment of patients without clinical heart failure in those enrolled in Russia and the Republic of Georgia.[2] The MAGGIC (Meta-Analysis Global Group in Chronic Heart Failure) risk score,[10] a validated risk score in heart failure, was calculated. Baseline characteristics are compared using *t* tests or ANOVA for continuous variables and χ^2 test for categorical variables.

RESULTS

Between July 18, 2014, and December 16, 2016, 11 302 patients were screened for inclusion in the study in 43 countries. The most common reasons for screen failure were insufficient NT-proBNP (61%), elevated potassium (10%), estimated glomerular filtration rate below inclusion cutoff (6%), alternative diagnoses other than HFpEF (6%), and elevated liver function tests (4%). Five thousand seven hundred and fifty-four patients who fulfilled inclusion and exclusion criteria entered valsartan run-in, and of these, 544 did not complete the valsartan run-in phase. Subsequently, 5210 entered the sacubitril/valsartan run-in phase, and of these, 388 did not complete the sacubitril/valsartan run-in phase. The most common reasons for run-in failure were predefined safety adverse events (65%) including predefined safety criteria for blood pressure, serum potassium, and renal function, subject decision (15%), protocol deviation (12%), noncompliance (5%), and death (2%). Ultimately, 4822 patients were randomized to sacubitril/valsartan or valsartan.

Baseline characteristics of randomized patients are shown in Table 1, and signs and symptoms of heart failure in randomized patients are shown in Figure. Their median age was 73±8.4 years, 52% were women, most were in NYHA functional class II, and the mean left ventricular ejection fraction was 58±7.9%. Only 48% of patients had had a prior heart failure hospitalization and of these almost 80% had been in the previous 9 months. Nearly all (98%) patients had dyspnea on effort, and many had fatigue (59%), edema (45%), orthopnea (22%), jugular venous distension (17%), rales (11%), paroxysmal nocturnal dyspnea (7.6%), and dyspnea at rest (4.6%). AF or flutter (32%) based on an ECG at the time of screening, diabetes mellitus (43%), and chronic kidney disease (47%) were all common. As required by the protocol, almost all patients were on diuretics and had structural heart disease, including left atrial enlargement in 99.6%, at screening. ACE (angiotensin-converting enzyme) inhibitors or angiotensin receptor blocker (ARB) (85%), β-blocker (80%), and mineralocorticoid receptor antagonist (27%) were commonly prescribed. The median MAGGIC risk score was 20 (interquartile range, 16–24).

Patients who fulfilled inclusion criteria, entered run-in, but were not randomized, were slightly older, were slightly higher NYHA class, had lower systolic blood pressure, were more likely to have been hospitalized for heart failure, had higher NT-proBNP, lower estimated glomerular filtration rate, and had less use of ACE inhibitors, ARBs, and β-blockers (Table 1).

Patients with AF (Table I in the Data Supplement) were older, more likely to be men, and had features suggesting more advanced heart failure, such as worse NYHA class, higher heart rate and lower blood pressure, substantially higher plasma concentrations of NT-proBNP (per protocol requirement), and MAGGIC risk score. Patients with a history of hospitalization for heart failure within the previous 9 months (Table II in the Data Supplement) were younger, had higher NYHA class and were more likely to be prescribed mineralocorticoid receptor antagonists (MRAs) but had lower plasma concentrations of NT-proBNP (reflecting the lower threshold required for inclusion), and the MAGGIC risk score was slightly, but significantly, lower.

Patients in North America and Western Europe tended to be older (Table III in the Data Supplement), and more likely to have AF. North Americans were mostly likely to have diabetes mellitus; BMI was highest in North America and lowest in Asia. There were substantial differences in concomitant therapy by region. MRA use was nearly twice as high in Asia as in other regions. Although ACE inhibitor or ARB use was similar overall between regions, the proportion of ACE inhibitor to ARB varied widely. Nitrate use was highest in North America, and anticoagulant use was highest in Western Europe. The MAGGIC risk score was lowest in Central Europe and highest in North America and Western Europe.

In comparison with other trials of HFpEF (Table 2), patients enrolled in PARAGON-HF were of similar age, with the exception of CHARM-Preserved, which allowed inclusion of younger patients. More patients were in NYHA class II compared with previous trials. Entry blood pressure was similar to that in other trials except TOPCAT-Americas, which required patients to have systolic blood pressure <130 mm Hg at entry, and PEP-CHF, in which blood pressure was higher. Left ventricular ejection fraction was similar to prior trials except for PEP-CHF, in which it was higher. The prevalence of diabetes mellitus and chronic kidney disease were similar to that observed in TOPCAT-Americas but higher than in other trials.

Characteristics differed substantially from patients with HFrEF enrolled in PARADIGM-HF (Table IV in the Data Supplement). Patients enrolled in PARAGON-HF were older and much more likely to be women. Plasma concentrations of NT-proBNP were substantially higher in PARADIGM-HF perhaps, in part, because of different threshold values for inclusion. Patients in PARAGON-HF

Table 1. Baseline Characteristics

	Patients Who Entered Run-In But Were Not Randomized, N=917	Randomized Patients, N=4822	*P* Value
Demographics			
Age, y	74±8	73±8	0.004
Female sex	52%	52%	0.66
NYHA classification			<0.001
II	65%	72%	
III	34%	27%	
IV	1%	1%	
Race			0.007
Asian	13%	13%	
Black	3%	2%	
White	81%	82%	
Native American	0.3%	1%	
Other	3%	3%	
Physical examination			
Sitting pulse rate, beats per min	71±13	70±12	<0.001
Sitting systolic BP, mm Hg	132±17	136±15	<0.001
Sitting diastolic BP, mm Hg	74±11	76±11	<0.001
BP category			<0.001
Systolic BP ≤110	9%	4%	
Systolic BP 111–130	41%	35%	
Systolic BP 131–150	38%	46%	
Systolic BP ≥151	12%	15%	
BMI, kg/m^2	29.7±5.6	30.2±5.0	0.003
Obese (BMI >30 kg/m^2)	44%	49%	0.003
Medical history			
Prior heart failure hospitalization	55%	48%	<0.001
Heart failure hospitalization within 9 mo	45%	38%	<0.001
Hypertension	92%	96%	<0.001
Coronary artery disease	41%	43%	0.22
Myocardial infarction	22%	23%	0.85
Atrial fibrillation/atrial flutter	35%	32%	0.13
Left bundle branch block	7%	7%	0.71
Diabetes mellitus	43%	43%	0.82
Stroke	10%	10%	0.83
Current smoker	7%	7%	0.80
Chronic obstructive pulmonary disease	15%	14%	0.56
Laboratory values			
N-terminal pro-B-type natriuretic peptide, pg/mL, plasma/serum (median, IQR)	1062 (998–1129)	885 (863–908)	<0.001
Ejection fraction (%), mean±SD	57±8	58±8	0.19
eGFR, mL/min per 1.73 m^2, mean±SD	58±20	63±19	<0.001
eGFR category, mL/min per 1.73 m^2			<0.001
<45	28%	18%	
≥45, <60	31%	29%	
≥60	41%	53%	

(*Continued*)

Table 1. Continued

	Patients Who Entered Run-In But Were Not Randomized, N=917	Randomized Patients, N=4822	*P* Value
Medical therapies at baseline			
Diuretic	874 (95%)	4638 (96%)	0.21
Mineralocorticoid receptor antagonists	290 (32%)	1301 (27%)	0.004
ACE inhibitors	312 (34%)	1931 (40%)	<0.001
Angiotensin receptor blockers	321 (35%)	2185 (45%)	<0.001
Digoxin	89 (10%)	447 (9%)	0.68
β-blockers	684 (75%)	3866 (80%)	<0.001
Calcium channel blockers	285 (31%)	1736 (36%)	0.004
Nitrate	182 (20%)	808 (17%)	0.023
Anticoagulant	242 (26%)	1277 (26%)	0.95
Aspirin	353 (38%)	1928 (40%)	0.40
Statin lipid-lowering medication	525 (57%)	2999 (62%)	0.005
Nonstatin lipid-lowering medication	48 (5%)	270 (6%)	0.66
Combined statin/nonstatin medication	540 (59%)	3087 (64%)	0.003
Antiplatelet agent (excluding aspirin)	115 (13%)	633 (13%)	0.63
ADP antagonist	115 (13%)	633 (13%)	0.63
Automated implantable cardioverter defibrillator	0.3%	0.4%	
MAGGIC risk score	n/a	20±6	
Patients with LA enlargement by any criteria (site-reported)	n/a	99.6%	

ACE indicates angiotensin-converting enzyme; ADP, adenosin diphosphate; BMI, body mass index; BP, blood pressure; eGFR, estimated glomerular filtration rate; HHF, hospitalization for heart failure; IQR, interquartile range; LA, left atrial; MAGGIC, Meta-Analysis Global Group in Chronic Heart Failure; n/a, data not available; and NYHA, New York Heart Association.

were more likely to be prescribed an ARB rather than an ACE inhibitor before screening, but overall use of either an ACE inhibitor or ARB was similar. Prescription of β-blockers was similar in the two trials, but patients in PARAGON-HF were much less likely to be prescribed an MRA. The overall MAGGIC risk score for mortality was similar for PARAGON-HF and PARADIGM-HF.

DISCUSSION

PARAGON-HF is the most contemporary and largest outcomes trial for HFpEF conducted to date, with more stringent entry criteria than previous trials. The baseline characteristics of patients enrolled in PARAGON-HF are generally consistent with those in prior trials of HFpEF,

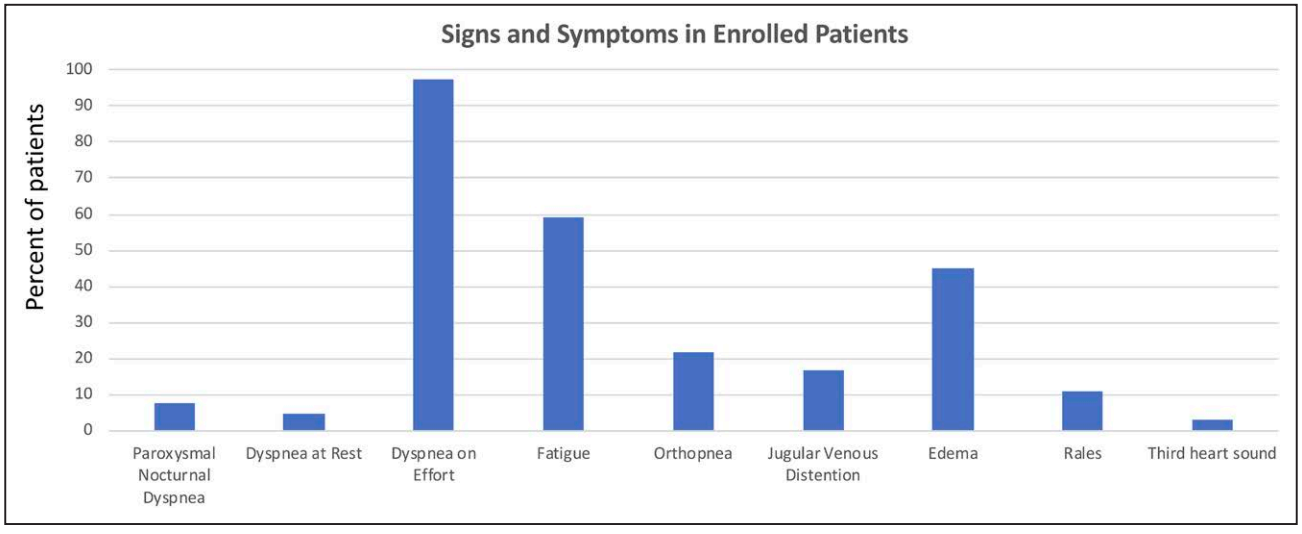

Figure. Heart failure signs and symptoms in enrolled patients.

Table 2. Comparison of PARAGON-HF With Other HFpEF Trials

	PARAGON-HF (N=4822)	TOPCAT-Americas (N=1767)	I-PRESERVE (N=4128)	CHARM-Preserved (N= 3023)	PEP-CHF (N=850)
Age, y	73±8	72 (64–79)	72±7	67±11	75 (72–79)
Female sex	52%	50%	60%	40%	56%
NYHA classification					
II	72%	59%	22%	61%	I/II=76%
III	27%	35%	77%	38%	
IV	0.6%	1%	3%	2%	III/IV=25%
Race					
Asian	13%	1%	1%	2%	n/a
Black	2%	17%	2%	4%	n/a
White	82%	78%	93%	92%	n/a
Native American	1%	0.6%		0%	n/a
Other	3%	4%	4%	2%	n/a
Sitting pulse rate, beats per min	70±12	68 (61–76)	71±10	71±12	73 (66–82)
Sitting systolic blood pressure, mm Hg	136±15	129 (118–138)	136±15	136±18	139 (129–150)
Sitting diastolic blood pressure, mm Hg	77±11	70 (62–80)	79±9	78±11	80 (74–86)
Ejection fraction, %	58±8	58 (53–64)			64 (56–66)
Body mass index, kg/m^2	30±5	33 (28–38)	30±5	29±6	28 (25–30)
Prior heart failure hospitalization	48%	58.9%	23%	68.7%	
HHF within 9 mo	38%		44% within 6 mo		
Hypertension	96%	90%	89%	64%	79%
Coronary artery disease	43%	32%	13%	33%	CABG 20%; PCI 8%
Myocardial infarction	23%	20%	23.5%	44%	27%
Atrial fibrillation/atrial flutter at screening	32%	34%	29%	29%	21%
History of AF	52%	42%	29%	29%	
Left bundle branch block	7%		8%		
Diabetes mellitus	43%	45%	27%	28%	21%
Stroke	10%	9%	10%	9%	
Current smoker	7%	7%		14%	
Glomerular filtration rate, estimated, mL/min (serum)	61.3 (49–75)	61 (49–77)	73±23		
<45	18%	17.7%			
≥45, <60	30%	31%	31%		
≥60	53%	52%			
Diuretic	96%	89%	Loop 83%; Thiazide 52%	75%	Loop 46%; Thiazide 55%
Mineralocorticoid receptor antagonists	24%		15%	12%	
ACE inhibitors	40%	50%	26%	19%	
Angiontensin receptor blockers	45%	31%			
Digoxin	9%		14%	28%	12%
β-blockers	75%	79%	59%	56%	55%
Calcium channel blockers	36%	39%	40%	31%	33%
Nitrate	17%	17%	27%	33%	51%
Anticoagulant	27%		19%	10%	16%
Aspirin	40%	58%		58%	66%
Statin lipid-lowering medication	62%	65%			

(*Continued*)

Table 2. Continued

	PARAGON-HF (N=4822)	TOPCAT-Americas (N=1767)	I-PRESERVE (N=4128)	CHARM-Preserved (N= 3023)	PEP-CHF (N=850)
Nonstatin lipid-lowering medication	6%	13%	31%	42%	34%
Antiplatelet agent (excluding aspirin)	13%		59%	5%	
ADP antagonist	13%				
Automated implantable cardioverter defibrillator	0.4%	2%		0.8%	

ACE indicates angiotensin-converting enzyme; ADP, adenosin diphosphate; AF, atrial fibrillation; CABG, coronary artery bypass graft; CHARM-Preserved, Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity-Preserved; HFpEF, heart failure with preserved left ventricular ejection fraction; HHF, hospitalization for heart failure; I-PRESERVE, Irbesartan in Heart Failure With Preserved Ejection Fraction; NYHA, New York Heart Association; PARAGON-HF, Prospective Comparison of Angiotensin Receptor Neprilysin Inhibitor With Angiotensin Receptor Blocker Global Outcomes in Heart Failure and Preserved Left Ventricular Ejection Fraction; PCI, percutaneous coronary intervention; PEP-CHF, Perindopril in Elderly People With Chronic Heart Failure; and TOPCAT, Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist.

although are reflective of the somewhat more stringent inclusion criteria than in prior trials, designed to exclude low-risk patients who might have little to gain from a novel intervention and to include patients with a higher rate of events.

Similar to other HFpEF trials and epidemiological studies, those enrolled in PARAGON-HF were, on average, older than patients enrolled in trials of HFrEF, and included a much higher proportion of women. The prevalence of comorbidities was high, including prior hypertension, diabetes mellitus, coronary artery disease, and AF. Despite capping enrollment of patients with AF, 32% had atrial fibrillation at enrollment and more than half had a history of AF, suggesting that paroxysmal AF is extremely common in HFpEF.

All patients enrolled in PARAGON-HF after protocol amendment 2 were required to have increased plasma concentration of NT-proBNP, with thresholds based on whether or not they had AF at screening and whether or not they had been hospitalized for heart failure within the prior 9 months. Before this amendment, which occurred early during the course of recruitment, patients could be enrolled without an increased NT-proBNP if they had been hospitalized in the previous 9 months. After the amendment, patients were required to have NT-proBNP >200 pg/mL if in sinus rhythm or >600 pg/mL if in AF, if they had been hospitalized; if they had not been hospitalized for heart failure in the previous 9 months, they were required to have an NT-proBNP >300 pg/mL if in sinus rhythm, and >900 pg/mL if in AF. Only 136 patients (<3%) were enrolled who did not fulfill these NT-proBNP criteria. Because patients enrolled with a history of HF hospitalization could be included with a lower NT-proBNP, on average, the NT-proBNP and risk profile for this group was slightly lower than those in the subgroup that had not been hospitalized.

Patients who fulfilled PARAGON-HF inclusion criteria and entered run-in but were not randomized were slightly older, sicker, and more comorbid than patients who were randomized. Not surprisingly, the most frequent reasons for failing run-in were adverse events, such as hypotension, hyperkalemia, and renal dysfunction per protocol-defined safety criteria, which would be expected to be more likely in a frailer population. The run-in was designed to maximize adherence to study medication during the double-blind period, but ultimately excludes some patients who may have trouble tolerating the therapy at target doses.

In general, patients with AF were more likely to have other characteristics suggestive of higher risk, and their MAGGIC risk scores were higher. The NT-proBNP requirement was tripled for patients with AF to avoid the criticism that increased NT-proBNP reflected AF rather than heart failure. Although some risk factors were less prominent in patients who had had a heart failure hospitalization within 9 months, this was likely because of the fact that these patients had a lower NT-proBNP. Nevertheless, prior analyses suggest that these groups should carry a similar risk of events,[11] and patients with both atrial fibrillation and elevation in NT-proBNP are likely to be at higher overall risk. Importantly, despite strong recommendations in guidelines <60% of patients with AF were reported to be treated with anticoagulants, which may reflect strong regional differences in the use of anticoagulants in this population.

Regional differences in characteristics of patients with HFpEF have been noted previously.[12] Patients in Central Europe were slightly younger and tended to have less renal dysfunction and lower NT-proBNP than in other regions. There were some substantial differences in concomitant medication use by region. Patients in North America and Western Europe were less likely to use MRAs than other regions. ACE inhibitor use was particularly low in Asia. Overall those in Central Europe had the lowest MAGGIC risk scores, and those in North America and Western Europe had the highest risk scores.

Differences in baseline characteristics between patients enrolled in PARAGON-HF and those enrolled in prior HFpEF trials, such as the higher prevalence of diabetes mellitus and renal dysfunction, may be, to some extent, a result of the more stringent entry criteria in PARAGON-HF, which required patients to have an increase in NT-proBNP and evidence of structural heart disease or may reflect differ-

ent regional distribution, including more patients enrolled in the United States. Diagnostic awareness and thresholds for renal dysfunction and diabetes mellitus may also have changed. The MAGGIC risk score, a well-validated comprehensive measure of mortality risk in heart failure, was similar to that observed in TOPCAT-Americas and slightly higher than that observed in CHARM-Preserved. Interestingly, the PARAGON-HF MAGGIC risk score was similar to that observed in PARADIGM-HF, a trial of HFrEF, probably because of the greater average age of participants in PARAGON-HF. MRA use was higher than in previous trials, which may be a result of the TOPCAT trial which showed relatively favorable results for spironolactone or may reflect inclusion of more Asian patients, in whom MRA use was especially high (40%).

Guidelines recommend that patients with HFrEF should generally receive an ACE inhibitor, an ARB or an ARNI, a β-blocker, and an MRA and indicate that there is no robust evidence that any of these agents is effective for patients with HFpEF. Accordingly, it might be thought that large differences in treatment patterns would be observed between HFrEF and HFpEF, yet the similarities seem as striking as the differences, an observation that has also been observed in registries.[13] This might reflect a failure to distinguish among phenotypes in clinical practice, or the use of these agents to treat comorbid conditions, such as hypertension, ischemic heart disease, or atrial fibrillation.

In summary, PARAGON-HF is the largest clinical outcomes trial in HFpEF conducted to date. Patient characteristics are largely similar to those enrolled in other HFpEF trials, and in HFpEF epidemiological cohorts, although some differences in characteristics likely are because of the more stringent enrollment criteria in PARAGON-HF than prior trials, as well as some clear regional differences. PARAGON-HF will determine whether sacubitril/valsartan, which has previously been shown to benefit patients with HFrEF, will also reduce morbidity and mortality in HFpEF.

ARTICLE INFORMATION

Received January 29, 2018; accepted June 5, 2018.

Guest Editor for this article was Walter J. Paulus, MD, PhD.

The Data Supplement is available at http://circheartfailure.ahajournals.org/lookup/suppl/doi:10.1161/CIRCHEARTFAILURE.118.004962/-/DC1.

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Sources of Funding

The PARAGON-HF trial is funded by Novartis.

Disclosures

Drs Solomon, Anavekar, Boytsov, Duengen, Galinier, Lelonek, Lund, Shah, and Vinereanu have received research grants from Novartis and have consulted for Novartis. Dr Anker reports personal fees from Bayer, Boehringer Ingelheim, Vifor, V-Wave, Impulse Dynamics, Novartis, Servier, and Stealth Peptides all for registry and clinical trial related committee work and lecture fees. Dr Anker also reports having received research grants for investigator-initiated trials from Vifor and Abbott Vascular. Dr Arango has received funds for clinical studies and has consulted for Novartis. Dr Arenas reports investigator fees from Novartis, MSD, Amgen, Sanofi, Takeda, Janssen and Novo Nordisk paid to his institution and reports speaker fees from MSD and Novartis. Dr Atar has received speaker or consultancy fees from Novartis, MSD, AstraZeneca, Bayer, Pfizer/BMS and Boehringer Ingelheim. Dr Chen has consulted for Novartis and is on the speakers' bureau of Novartis. Dr Cleland has received research grants from Amgen, Bayer, Medtronic, Novartis, and Stealth Biopharmaceuticals, has consulted and lectured for Amgen, Bayer, Medtronic, Novartis, Philips, Stealth Biopharmaceuticals, and Vifor. Dr Comin-Colet has received unrestricted research grants and consultancy honoraria from Novartis. Dr Echeverria has received lecture and consultancy fees from Novartis. Dr Filippatos reports honoraria as committee member of trials sponsored by Novartis during the conduct of the study and honoraria as committee member of trials or registries sponsored by Bayer, Servier, Medtronic, outside the submitted work. Dr Flammer has received research support, consultancy fees and speaker honoraria from Novartis. Dr Godoy has received lecture fees from Pfizer, Sanofi, Menarini, and Tecnofarma and fees for serving as principal investigator for Novartis, AstraZeneca and Merck. Dr Janssens has received research grants from Novartis and has a consultancy agreement with Novartis through the University of Leuven, Belgium. Dr Katova has received speaker fees from Novartis, Servier, Astra Zeneca, Egis, Berlin Chemie, and Pfizer. Dr Saraiva reports consulting fees and grant support from Amgen, Novo Nordisk, Eli Lilly, AstraZeneca, Novartis, Sanofi-Aventis, Boehringer Ingelheim. Dr Koeber has received speaker honoraria from Novartis and Astra Zeneca. Dr O'Meara has served as a consultant for Amgen, Bayer, Novartis and Servier, and as a speaker for AstraZeneca, Bayer, Novartis, Pfizer/Bristol-Myers Squibb and Servier. Dr O'Meara's institution, the Montreal Heart Institute, has received payments for her participation in clinical trials by Novartis, Bayer, AstraZeneca, Cardiorentis, Merck, Servier, and Amgen. Dr Merkely has received speaker fees and consultancy fees from Sanofi-Aventis, Medtronic, Abbott, and Biotronik. Dr Milicic has lectured and consulted for Novartis. Dr Perrone has received fees from Novartis for conferences, clinical research programs and to integrate an advisory group. Dr Ranjith has consulted for Novartis and Bayer. Dr Sim has received honorarium from Novartis. Dr Sweitzer has received research grants from Novartis and Merck. Dr Vrtovec reports investigator fees paid to his institution. Dr Yilmaz has received institutional research grants from Novartis, Bayer, Amgen and has consulted Novartis, Bayer, Amgen via institutional contracts. Dr Anand has received consulting fees from Amgen, ARCA Biopharma, AstraZeneca, Boehringer Ingelheim, LivaNova, Novartis, and Zensun. Dr Ge has received honoraria from Novartis. Dr Lam has received consulting fees from Novartis, Bayer, Takeda, Merck, AstraZeneca, Janssen Research & Development, LLC, Menarini, Boehringer Ingelheim, and Abbott Diagnostics; research support from Bayer, Boston Scientific, Thermofisher, Medtronic, and Vifor Pharma; and is supported by a Clinical Scientist Award from the National Medical Research Council Singapore. Dr Maggioni is a member of the executive/steering committees of Novartis, Bayer, and Cardiorentis. Dr Martinez is a member of the PARAGON-HF steering committee and has consulted for Novartis and Astra Zeneca. Dr Packer has received personal fees from Akcea, AstraZeneca, Amgen, Bayer, Boehringer Ingelheim, Cardiorentis, Celyad, Daiichi Sankyo, Gilead, Novo Nordisk, Pfizer, Relypsa, Sanofi, Takeda, and ZS Pharma. Dr Pfeffer has received grant support from Novartis and Sanofi; consulting fees from AstraZeneca, Bayer, Boehringer Ingelheim, DalCor, Genzyme, Gilead, GlaxoSmithKline, Janssen, Lilly, Medicines Company, Merck, Novartis, Novo Nordisk, Relypsa, Sanofi, Teva, and Thrasos; owns stock options for DalCor; and is listed on a patent awarded to Brigham and Women's Hospital on the use of inhibitors of the renin-angiotensin system in myocardial infarction (licensed by Novartis, with Dr Pfeffer's share irrevocably assigned to charity). Dr Pieske has relationships with Novartis, Bayer Healthcare, Stealth Peptides, Daiichi-Sankyo, Vifor, AstraZeneca, and Bristol-Myers Squibb; and is a consultant for Merck, Sharp, and Dohme. Dr Redfield has served as an unpaid consultant for Novartis. Dr Saito has received consultancy fees from Novartis and investigator fees from Novartis paid to his institution. Dr Veldhuisen has received board membership fees from Novartis. Dr Zannad has received consulting fees from Novartis. and has served as a steering committee member of the PARAGON-HF trial. Dr McMurray has served as an executive committee member and coprincipal investigator of ATMOSPHERE (Efficacy and Safety of Aliskiren and Aliskiren/Enalapril Combination on Morbidity-Mortality in Patients With Chronic Heart Failure) and coprincipal 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. Drs Chopra, Goncalvesova, Oh, Senni, Widimsky, Zile, and Zweiker have consulted for Novartis. Drs Ben-Gal, Seferovic, and Taurio have received lecture fees from Novartis. Drs Sibulo and Zhou have received research grants from Novartis. Drs Rizkala, Lefkowitz, Shi, and Gong are employees of Novartis. The other authors report no conflicts.

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Circulation
Heart Failure

Baseline Characteristics of Patients With Heart Failure and Preserved Ejection Fraction in the PARAGON-HF Trial

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Circ Heart Fail. 2018;11:
doi: 10.1161/CIRCHEARTFAILURE.118.004962
Circulation: Heart Failure is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 1941-3289. Online ISSN: 1941-3297

SUPPLEMENTAL MATERIAL

Table S1. Baseline characteristics stratified by History of AF/Flutter

	In sinus rhythm at Screening	In atrial fibrillation/flutter at Screening	p-value
	n=3246	n=1560	
Demographics			
Age	72 ± 9	74 ± 8	<0.001
Female Sex	1752 (54%)	730 (47%)	<0.001
NYHA Classification:2=CLASS II; 3=CLASS III; 4=CLASS IV;			<0.001
2	2393 (74%)	1066 (68%)	
3	834 (26%)	483 (31%)	
4	19 (0.6%)	11 (0.7%)	
Race			0.004
Asian	398 (12%)	207 (13%)	
Black	84 (3%)	18 (1%)	
Caucasian	2629 (81%)	1290 (83%)	
Native American	41 (1%)	10 (0.6%)	
Other	93 (3%)	35 (2%)	
Physical Examination			
Sitting Pulse Rate (beats/min):	68 ± 10	75 ± 12	<0.001
Sitting Systolic Blood Pressure (mmHg):	137 ± 15	134 ± 15	<0.001
Sitting Diastolic Blood Pressure (mmHg):	76 ± 10	78 ± 11	<0.001

Body Mass Index (kg/m2):	30 ± 5	30 ± 5	0.31
Medical History			
Prior Heart Failure Hospitalization at any time;	1501 (46%)	804 (52%)	<0.001
HHF within 9 Months prior to Screening	1206 (37%)	637 (41%)	0.01
Hypertension	3106 (96%)	1485 (95%)	0.42
coronary artery disease	1586 (49%)	474 (30%)	<0.001
Myocardial Infarction	872 (27%)	211 (14%)	<0.001
History of AF	945 (29.1%)	1538 (98.6%)	<0.001
Left Bundle Branch Block	193 (6%)	66 (4%)	0.01
Diabetes	1444 (45%)	608 (39%)	<0.001
Stroke	297 (9%)	198 (13%)	<0.001
Current Smoker	255 (8%)	97 (6%)	0.04
Laboratory Values			
N-Terminal ProB-type Natriuretic Peptide (pg/mL), Plasma/Serum (geo mean, 95% CI)	654 (634, 673)	1664 (1620, 1708)	<0.001
Ejection Fraction (%):	58 ± 8	57 ± 8	0.003
Estimated Glomerular Filtration Rate, (mL/min)	64 ± 20	62 ± 18	<0.001
eGFR Category			
< 45	574 (18%)	286 (18%)	<0.001
>= 45, < 60	902 (28%)	513 (33%)	
>= 60	1769 (55%)	761 (49%)	
Medical Therapy at Baseline			
Diuretic	3115 (96%)	1509 (97%)	0.19
Mineralocorticoid Receptor Antagonists	710 (22%)	449 (29%)	<0.001
ACE-inhibitor	1293 (40%)	634 (41%)	0.59
Angiotensin Receptor Blockers	1514 (47%)	665 (43%)	0.009
Digoxin	66 (2%)	379 (24%)	<0.001

Beta Blockers	2570 (79.2%)	1285 (82.4%)	0.009
CCB	1210 (37%)	517 (33%)	0.005
Nitrate	585 (18%)	219 (14%)	<0.001
Anticoagulant	478 (15%)	794 (51%)	<0.001
Aspirin	1667 (51%)	255 (16%)	<0.001
Statin Lipid Lowering Medication	2152 (66%)	839 (54%)	<0.001
Non-Statin Lipid Lowering Medication	210 (7%)	59 (4%)	<0.001
Antiplatelet Agent (excluding Aspirin)	556 (17%)	75 (5%)	<0.001
ADP Antagonist	556 (17%)	75 (5%)	<0.001
Automated Implantable Cardioverter Defibrillator	11 (0.3%)	7 (0.4%)	0.56
MAGGIC Risk Score	20 ± 6	21 ± 6	<0.001

Table S2. Baseline characteristics stratified by History of HHF at 9 Month

	No hospitalization for heart failure within 9 months before screening	Hospitalized for heart failure in 9 months before screening	
	n=2972	n=1850	
Demographics			
Age	73 ± 8	72 ± 9	<0.001
Female Sex	1576 (53%)	915 (50%)	0.02
NYHA Classification:2=CLASS II; 3=CLASS III; 4=CLASS IV;			<0.001
2	2207 (74%)	1263 (68%)	
3	755 (25%)	567 (31%)	
4	10 (0.3%)	20 (1%)	
Race			0.06
Asian	353 (12%)	254 (14%)	
Black	55 (2%)	47 (3%)	
Caucasian	2444 (82%)	1488 (80%)	
Native American	38 (1%)	13 (0.7%)	
Other	81 (3%)	48 (3%)	
Physical Examination			
Sitting Pulse Rate (beats/min):	70 ± 12	71 ± 12	<0.001
Sitting Systolic Blood Pressure (mmHg):	136 ± 15	136 ± 15	0.32
Sitting Diastolic Blood Pressure (mmHg):	77 ± 11	76 ± 11	0.53
Body Mass Index (kg/m2):	30 ± 5	30 ± 5	0.06
Medical History			
Prior Heart Failure Hospitalization:0=N; 1=Y;	462 (16%)	1850 (100%)	<0.001
Hypertension	2831 (95%)	1774 (96%)	0.30

coronary artery disease	1255 (42%)	811 (44%)	0.27
Myocardial Infarction	671 (23%)	415 (22%)	0.91
Atrial Fibrillation/Atrial Flutter at Screening	923 (31%)	637 (35%)	0.01
History of AF	1480 (50%)	1012 (55%)	<0.001
Left Bundle Branch Block	161 (5%)	99 (5%)	0.92
Diabetes	1214 (41%)	849 (46%)	<0.001
Stroke	291 (10%)	204 (11%)	0.17
Current Smoker	203 (7%)	150 (8%)	0.11
Laboratory Values			
N-Terminal ProB-type Natriuretic Peptide (pg/mL), Plasma/Serum	944 (496, 1572)	840 (393, 1695)	<0.001
Ejection Fraction (%):	58 ± 8	57 ± 8	0.02
Glomerular Filtration Rate, Estimated (mL/min), Serum:	62.83 ± 18.71	64.39 ± 20.48	0.007
GFR Category			0.05
< 45	527 (18%)	338 (18%)	
>= 45, < 60	914 (31%)	507 (27%)	
>= 60	1531 (52%)	1004 (54%)	
Medical Therapy at Baseline			
Diuretic	2842 (96%)	1796 (97%)	0.01
MRA	604 (20%)	559 (30%)	<0.001
ACE-inhibitor	1162 (39%)	769 (42%)	0.09
ARB	1379 (46%)	806 (44%)	0.05
Digoxin	259 (9%)	188 (10%)	0.09
BB	2355 (79.2%)	1511 (81.7%)	0.039
CCB	1081 (36%)	655 (35%)	0.50
Nitrate	481 (16%)	327 (18%)	0.18
Anticoagulant	763 (26%)	514 (28%)	0.11

Aspirin	1191 (40%)	737 (40%)	0.87
Statin Lipid Lowering Medication	1872 (63%)	1127 (61%)	0.15
Non-Statin Lipid Lowering Medication	179 (6%)	91 (5%)	0.10
Antiplatelet Agent (excluding Aspirin)	394 (13%)	239 (13%)	0.74
ADP Antagonist	394 (13%)	239 (13%)	0.74
Automated Implantable Cardioverter Defibrillator	14 (0.5%)	4 (0.2%)	0.16
MAGGIC Risk Score	20 ± 5 20 [17, 24]	20 ± 6 19 [15, 24]	<0.001

Table S3. Baseline characteristics stratified by Region*

	Asia-Pacific/Other	**Central Europe**	**Latin America**	**North America**	**Western Europe**	
	n=761	n=1804	n=370	n=560	n=1327	
Demographics						
Age	72 ± 9	71 ± 8	72 ± 9	74 ± 8	76 ± 7	<0.001
Female Sex	379 (50%)	933 (52%)	222 (60%)	264 (47%)	693 (52%)	0.003
NYHA Classification:2=CLASS II; 3=CLASS III; 4=CLASS IV;						0.004
2	543 (71%)	1260 (70%)	290 (78%)	396 (71%)	981 (74%)	
3	211 (28%)	534 (30%)	75 (20%)	163 (29%)	339 (26%)	
4	7 (0.9%)	10 (0.6%)	5 (1%)	1 (0.2%)	7 (0.5%)	
Race						<0.001
Asian	591 (78%)	0 (0.0%)	1 (0.3%)	8 (1%)	7 (0.5%)	
Black	9 (1%)	0 (0.0%)	16 (4%)	74 (13%)	3 (0.2%)	
Caucasian	130 (17%)	1803 (99%)	213 (58%)	469 (84%)	1317 (99%)	
Native American	0 (0%)	0 (0.0%)	46 (12%)	5 (0.9%)	0 (0%)	
Other	31 (4%)	1 (0.1%)	94 (25%)	3 (0.5%)	0 (0%)	
Physical Examination						
Sitting Pulse Rate (beats/min):	72 ± 12	71 ± 11	70 ± 12	68 ± 11	69 ± 12	<0.001
Sitting Systolic Blood Pressure (mmHg):	133 ± 16	137 ± 13	134 ± 15	133 ± 15	139 ± 17	<0.001
Sitting Diastolic Blood Pressure (mmHg):	73 ± 11	80 ± 9	77 ± 11	72 ± 11	75.45 ± 10.83	<0.001
Body Mass Index (kg/m2):	28 ± 5	31 ± 5	30 ± 5	32 ± 5	30 ± 5	<0.001
Medical History						

Prior Heart Failure Hospitalization:0=N; 1=Y;	408 (54%)	895 (50%)	152 (41%)	277 (50%)	580 (44%)	<0.001
HHF within 9 Month prior to Screening	327 (43%)	756 (42%)	116 (31%)	213 (38%)	438 (33%)	<0.001
Hypertension	694 (91%)	1770 (98%)	355 (96%)	542 (97%)	1244 (94%)	<0.001
coronary artery disease	311 (41%)	892 (49%)	99 (27%)	272 (49%)	492 (37%)	<0.001
Myocardial Infarction	172 (23%)	427 (24%)	81 (22%)	132 (24%)	274 (21%)	0.35
Atrial Fibrillation/Atrial Flutter at Screening	255 (33.6%)	559 (31%)	110 (30%)	160 (29%)	476 (36%)	0.005
History of AF	340 (45%)	923 (51.2%)	134 (36.2%)	327 (58.4%)	768 (57.9%)	<0.001
Left Bundle Branch Block	27 (4%)	99 (6%)	25 (7%)	24 (4%)	85 (6%)	0.03
Diabetes	334 (44%)	802 (45%)	142 (38%)	276 (49%)	509 (38%)	<0.001
Stroke	94 (12%)	190 (11%)	20 (5 %)	69 (12%)	122 (9%)	0.002
Current Smoker	67 (9%)	155 (9%)	23 (6%)	38 (7%)	70 (5%)	0.003
Laboratory Values						
N-Terminal ProB-type Natriuretic Peptide (pg/mL), Plasma/Serum	942 (887, 1001)	826 (792, 861)	858 (775, 950)	890 (827, 957)	946 (905, 988)	0.05
Ejection Fraction (%):	58.27 ± 8.19	56.14 ± 7.54	58.65 ± 8.85	58.64 ± 7.32	58.26 ± 7.91	<0.001
Glomerular Filtration Rate, Estimated (mL/min), Serum:	64.62 ± 20.00	66.04 ± 19.63	64.87 ± 19.30	58.62 ± 19.19	60.83 ± 18.22	<0.001
GFR Category						<0.001
< 45	137 (18%)	251 (14%)	55 (15%)	149 (27%)	273 (21%)	
>= 45, < 60	200 (26%)	502 (28%)	103 (28%)	187 (33%)	429 (32%)	
>= 60	424 (56%)	1050 (58%)	212 (57%)	224 (40%)	625 (47%)	
Medical Therapy at Baseline						
Diuretic	694 (91%)	1760 (98%)	354 (96%)	545 (97%)	1285 (97%)	<0.001
Mineralocorticoid Receptor Antagonists	301 (40%)	446 (25%)	82 (22%)	99 (18%)	235 (18%)	<0.001
ACE-inhibitors	178 (23%)	896 (50%)	103 (28%)	213 (38%)	541 (41%)	<0.001
Angiotensin Receptor Blockers	414 (54%)	768 (43%)	235 (64%)	184 (33%)	584 (44 %)	<0.001
Digoxin	71 (9.3%)	196 (11%)	35 (10%)	20 (4%)	125 (9%)	<0.001

Beta Blockers	539 (70.8%)	1575 (87.3%)	264 (71.4%)	450 (80.4%)	1038 (78.2%)	<0.001
CCB	246 (32%)	721 (40%)	113 (31%)	222 (40%)	434 (33%)	<0.001
Nitrate	214 (28 %)	212 (12%)	28 (8%)	160 (29%)	194 (15 %)	<0.001
Anticoagulant	127 (17%)	494 (27%)	56 (15%)	148 (26%)	452 (34%)	<0.001
Aspirin	365 (48%)	670 (37%)	160 (43%)	305 (55%)	428 (32%)	<0.001
Statin Lipid Lowering Medication	507 (67%)	1106 (61%)	191 (52%)	413 (74%)	782 (59%)	<0.001
Non-Statin Lipid Lowering Medication	36 (5%)	93 (5%)	16 (4%)	53 (10%)	72 (5%)	<0.001
Antiplatelet Agent (excluding Aspirin)	169 (22%)	229 (13%)	44 (12%)	83 (15%)	108 (8 %)	<0.001
ADP Antagonist	169 (22%)	229 (13%)	44 (12%)	83 (15%)	108 (8 %)	<0.001
Automated Implantable Cardioverter Defibrillator	2 (0.3%)	2 (0.1%)	1 (0.3%)	4 (0.7%)	9 (0.7%)	0.07
MAGGIC Risk Score	21 ± 6	19 ± 6	19 ± 5	22 ± 5	21 ± 5	<0.001

*Region Asia-Pacific/Other includes patients enrolled in Australia, China, India, Israel, Japan, South Korea, Philippines, Singapore, South Africa, and Taiwan. Region Central Europe includes patients enrolled in Bulgaria, Croatia, Czech Republic, Greece, Hungary, Poland, Romania, Russia, Serbia, Slovakia, Slovenia, and Turkey. Region Latin America includes patient enrolled in Argentina, Brazil, Colombia, Guatemala, Mexico, and Peru. Region North America includes patients enrolled in Canada and the United States. Region Western Europe includes patients randomized in Austria, Belgium, Denmark, Finland, France, Germany, Italy, Netherlands, Norway, Spain, Sweden, Switzerland, and the United Kingdom.

Table S4. Differences in Baseline characterics between PARAGON-HF (HFpEF) and PARADIGM-HF (HFrEF)

Demographics	PARAGON-HF	PARADIGM-HF
Age	73 ± 8	64 ± 11
Female Sex	52%	22%
NYHA Classification:2=CLASS II; 3=CLASS III; 4=CLASS IV;		
2	72%	71%
3	27%	24%
4	0.6%	0.7%
Race		
Asian	13%	18%
Black	2%	5%
Caucasian	82%	66%
Native American	1%	
Other	3%	11%
Physical Examination		
Sitting Pulse Rate (beats/min):	70 ± 12	72 ± 12
Sitting Systolic Blood Pressure (mmHg):	136± 15	121 ± 15
Sitting Diastolic Blood Pressure (mmHg):	77 ± 11	78 ± 11
Body Mass Index (kg/m2):	30 ± 5	28 ± 6
Medical History		
Prior Heart Failure Hospitalization:0=N; 1=Y;	48%	63%
HHF > 9 Month prior to Screening	38%	--
Hypertension	96%	71%
coronary artery disease	43%	55%

Myocardial Infarction	23%	43%
Atrial Fibrillation/Atrial Flutter at Screening	33%	--
History of AF	52%	37%
Left Bundle Branch Block	7%	20%
Diabetes	43%	35%
Stroke	10%	9%
Current Smoker	7%	14%
Laboratory Values		
N-Terminal ProB-type Natriuretic Peptide (pg/mL), Plasma/Serum (geometric mean, 95% CI)	885 (864, 908)	1748 (1712, 1785)
Ejection Fraction (%):	58 ± 8	29%
Glomerular Filtration Rate, Estimated (mL/min), Serum:	63± 19	68 ± 19
< 45	18%	10%
>= 45, < 60	30%	25%
>= 60	53%	65%
Medical Therapies at Baseline		
Diuretic	96%	80%
Mineralocorticoid Receptor Antagonists	24%	56%?
ACE-inhibitor	40%	78%
Angiotensin Receptor Blockers	45%	23%
Digoxin	9%	30%
Beta Blockers	80.2%	93.0%
Calcium Channel Blockers	36.0%	--
Nitrate	17%	--
Anticoagulant	27%	32%

Aspirin	40 %	52%
Statin Lipid Lowering Medication	62%	56%
Non-Statin Lipid Lowering Medication	6%	--
Antiplatelet Agent (excluding Aspirin)	13%	10%
ADP Antagonist	13%	--
Automated Implantable Cardioverter Defibrillator	0.4%	14.8%
MAGGIC Risk Score	20 ± 6	20 (16, 24)
Patients with LA Enlargement by any criteria (site)	92%	--
Patients with wall thickness >= 1.2mm by any criteria (site)	53%	--
Structural heart disease by any criteria (site)	99.6%	--