Baseline Characteristics of Patients with Heart Failure and Preserved Ejection Fraction: The PARAGON-HF Trial

Scott D. Solomon, MD[1], Adel R Rizkala, PharmD[2], Martin P. Lefkowitz, MD[2], Victor C Shi, MD[2], JianJian Gong, PhD[2], Nagesh Anavekar, MD[3], Stefan D. Anker, MD[4,5], Juan L. Arango, MD[6], Jose L. Arenas, MD[7], Dan Atar, MD[8], Turia Ben-Gal, MD[9], Sergey A. Boytsov, MD[10], Chen-Huan Chen, MD[11], Vijay K. Chopra, MD[12], John Cleland, MD[13,14], Josep Comin-Colet, MD, PhD[15], Hans-Dirk Duengen, MD[16], Luis E. Echeverría Correa, MD[17], Gerasimos Filippatos, MD[18], Andreas J. Flammer, MD[19], Michel Galinier, MD[20], Armando Godoy, MD[21,22,23], Eva Goncalvesova, MD[24], PhD, Stefan Janssens, MD[25], Tzvetana Katova, MD[26], Jose F. Kerr Saraiva, MD[27], Lars Køber, MD[28], Małgorzata Lelonek, MD[29], Gerard Linssen, MD[30], Lars H. Lund, MD, PhD[31], Eileen O. Meara, MD[32], Bela Merkely, MD[33]; Davor Milicic, MD, PhD[34], Byung-Hee Oh, MD[35], Sergio V. Perrone, MD[36], Naresh Ranjith, MD[37], Yoshihiko Saito, MD[38], Sanjiv Shah, M[39], Petar M. Seferovic, MD[40], Michele Senni, MD[41], Antonio S. Sibulo, Jr., MD[42], David Sim, MD[43], Nancy K. Sweitzer, MD, PhD[44], Jyrki Taurio, MD[45], Dragos Vinereanu, MD[46], Bojan Vrtovec, MD[47], Jiří Widimský, Jr., MD[48], Mehmet B. Yilmaz, MD[49], Jingmin Zhou, MD[50], Robert Zweiker, MD[51], Inder S Anand, MD, D Phil[52], Junbo Ge, MD[53], Carolyn S.P. Lam, MBBS, PhD[54], Aldo P. Maggioni, MD[55], Felipe Martinez, MD[56], Milton Packer, MD[57], Marc A. Pfeffer, MD, PhD[1], Burkert Pieske, MD[16], Margaret M. Redfield, MD[58], Jean L. Rouleau, MD[32] Dirk J. Van Veldhuisen MD[59], Faiez Zannad, MD[60], Michael R. Zile, MD[61], John J.V. McMurray, MD[62].

Affiliations:
1 Cardiovascular Division, Brigham and Women's Hospital, Harvard Medical School (SDS, MAP, ASD), Boston, MA, USA; 2 Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA; 3 Faculty of Medicine, Dentistry and Health Sciences, University of Melbourne, Melbourne, Australia; 4 Division of Cardiology and Metabolism, Department of Cardiology (CVK) and Berlin-Brandenburg Center for Regenerative Therapies (BCRT), Deutsches Zentrum für Herz-Kreislauf-Forschung (DZHK) Berlin, Charité Universitätsmedizin Berlin, Germany; 5 Department of Cardiology and Pneumology, University of Göttingen Medical Center, Göttingen, Germany; 6 Guatemalan Heart Institute, Guatemala, Guatemala; 7 Centro de Atención e Investigación Cardiovascular del Potosi SC and Hospital Ángeles San Luis, México; 8 Department of Cardiology B, Oslo University Hospital, and University of Oslo, Oslo, Norway; 9 Heart Failure Unit, Cardiology Department, "Rabin" Medical Center, Petah Tikva, Israel; 10 National Research Center for Cardiology of the Ministry of Health of the Russian Federation, Moscow, Russia; 11

Department of Medicine, National Yang-Ming University, Taipei, Taiwan, Republic of China; 12 Heart Failure Unit, Medanta Medicity, Gurugram, Haryana, India; 13 Robertson Centre for Biostatistics & Clinical Trials, Institute of Health & Well-being, University of Glasgow, United Kingdom; 14 National Heart and Lung Institute, Royal Brompton and Harefield Hospitals, Imperial College, London, United Kingdom; 15 Community Heart failure Program, Department of Cardiology, Bellvitge University Hospital and IDIBELL, University of Barcelona, Barcelona, Spain; 16 Department of Internal Medicine, Cardiology Charité, Universitaetsmedizin Berlin, Campus Virchow Klinikum Berlin, Germany; 17 Heart Failure Unit and Cardiac Transplant Program; Fundación Cardiovascular de Colombia, Floridablanca, Santander, Colombia; 18 National and Kapodistrian University of Athens, Attikon University Hospital and University of Cyprus, School of Medicine, Greece; 19 Department of Cardiology, University Heart Center Zurich, University Hospital Zurich, Zurich, Switzerland; 20 Department of Cardiology, Rangueil University Hospital, Toulouse, France; 21 Universidad Nacional Mayor de San Marcos, Lima, Perú; 22 Instituto Nacional Cardiovascular INCOR, Lima, Perú; 23 Scentia Clinical and Epidemiological Research Institute, Trujillo, Perú; 24 Department of Heart Failure/Transplantation, National Cardiovacular Institute, Bratislava, Slovakia; 25 Department of Cardiology, University Hospitals Leuven, Leuven, Belgium; 26 Clinic of Cardiology, National Cardiology Hospital, Sofia, Bulgaria; 27 Disciplina de Cardiologia Faculdade de Medicina, Pontifícia Universidade Católica de Campinas, Sao Paulo, Brazil; 28 Rigshospitalet, Copenhagen University Hospital, Heart Centre, Department of Cardiology, Copenhagen, Denmark; 29 Department of Noninvasive Cardiology, Medical University of Lodz, Lodz, Poland; 30 Department of Cardiology, Hospital Group Twente, Almelo and Hengelo, the Netherlands; 31 Department of Medicine, Karolinska Institutet, and Heart and Vascular Theme, Karolinska University Hospital, Stockholm, Sweden; 32 Institut de Cardiologie de Montréal, Université de Montréal, Montréal, Québec, Canada; 33 Heart and Vascular Center, Semmelweis University, Budapest, Hungary;34 Department of Cardiovascular Diseases, University Hospital Center Zagreb, Zagreb, Croatia; 35 Seoul National University Hospital, Seoul National University College of Medicine, Seoul, Korea; 36 Instituto Fleni, Mendoza, Argentina; 37 Department of Cardiology, City Hospital, Durban, South Africa; 38 First Department of Internal Medicine, Nara Medical University, Kashihara, Nara, Japan; 39 Division of Cardiology, Department of Medicine, Northwestern University Feinberg School of Medicine, Chicago, IL, USA; 40 University of Belgrade School of Medicine, Belgrade University Medical Center, Belgrade, Serbia; 41 Cardiology Division, Cardiovascular Department, Hospital Papa Giovanni XXIII, Bergamo, Italy; 42 St LukesHeart Institute, Philippines; 43 National Heart Centre Singapore, Singapore; 44 Sarver Heart Center, University of Arizona College of Medicine, Tucson, AZ, USA; 45 Tampere University Hospital, Tampere, Finland; 46 University of Medicine and Pharmacy Carol Davila, University and Emergency Hospital of Bucharest, Bucharest, Romania; 47 University Medical Centre, Ljubljana, Slovenia; 48 First faculty of Medicine, Charles University Prague, Prague,

Czech Republic; 49 Department of Cardiology Cumhuriyet University, Faculty of Medicine, Sivas, Turkey; 50 Department of Cardiology, Tongji Hospital, Tongji University School of Medicine, Shanghai, China; 51 Department of Cardiology, Medical University Graz, Graz, Austria; 52 University of Minnesota, Minneapolis, MN; 53 Shanghai Institute of Cardiovascular Diseases, Zhongshan Hospital, Fudan University, Shanghai, China; 54 National Heart Centre Singapore & Duke-National University of Singapore, Singapore; 55 ANMCO, Florence, Italy; 56 Universidad Nacional of Cordoba, Cordoba, Argentina; 57 Baylor University Medical Center, Dallas, TX, USA; 58 Mayo Clinic, Rochester, MN, USA; 59 University Medical Center Groningen, University of Groningen, Groningen, The Netherlands; 60 Inserm CIC 1433 and Université de Lorraine, CHRU Nancy, France; 61 Medical University of South Carolina, Charleston, SC, USA; 62 BHF Cardiovascular Research Centre, University of Glasgow, Glasgow, Scotland.

Address Correspondence to:

Scott D. Solomon, MD
Cardiovascular Division
Brigham and Women's Hospital
75 Francis St
Boston, MA 02115
email: ssolomon@bwh.harvard.edu
tel. 857-307-1960
fax. 857-307-1944

Abstract

Background: To describe the baseline characteristics of patients with heart failure and preserved left ventricular ejection fraction (HFpEF) enrolled in the PARAGON-HF (Prospective Comparison of ARNI with ARB Global Outcomes in HFpEF) trial 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 4,822 patients randomized in PARAGON-HF, stratified 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 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 $\pm$ 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 NYHA Class II, and 38% had one or more hospitalizations for heart failure within the previous 9 months. Diabetes (43%) and chronic kidney disease (47%) were more prevalent than in previous trials of HFpEF. Many patients were prescribed ACE inhibitors or ARBs (85%), beta-blockers (80%), calcium-channel blockers (36%), and MRA (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 [IQR 464, 1610]), and structural heart disease.

Conclusions: PARAGON-HF represents a contemporary group of patients with HFpEF with similar age and sex distribution compared to 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 Information: https://clinicaltrials.gov/ct2/show/NCT01920711

Introduction

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 is a large, double-blind randomized controlled clinical outcomes trial testing the hypothesis that sacubitril/valsartan, an angiotensin receptor neprilysin inhibitor (ARNIO) 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 to enalapril, sacubitril/valsartan conclusively reduced morbidity and mortality amongst patients with HFrEF in PARADIGM-HF[4]. In a phase II trial of HFpEF, PARAMOUNT-HF, sacubitril/valsartan compared with valsartan, reduced NT-proBNP at 12 weeks, and reduced both left atrial volume and New York Heat Association (NYHA) class at 36 weeks compared to valsartan[5]. 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, two-arm event driven trial comparing the efficacy and safety of sacubitril/valsartan versus valsartan in patients with heart failure and preserved ejection fraction. PARAGON-HF enrolled patients with signs and symptoms of heart failure (NYHA Class II to IV), left ventricular ejection fraction (LVEF) of 45% or greater, increased plasma concentrations of B-type natriuretic peptides (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). Prior to randomization, patients entered sequential single-blind run-in periods ensuring that both treatments were tolerated at half the target doses. The primary endpoint 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 prior to randomization. Because plasma concentrations of NT-proBNP required for enrollment in PARAGON-HF differed based on the presence or absence of atrial fibrillation at screening, and whether or not patients had been hospitalized for heart failure within 9 months, we stratified baseline characteristics based on these measures. In addition, we stratified 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[6], I-Preserve[7], CHARM-Preserved[8] and PEP-CHF[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 risk score[10], a validated risk score in heart failure, was calculated and compared amongst trials. Baseline characteristics are compared using t-tests or analysis of variance for continuous variables and Chi-squared 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%), eGFR below inclusion cutoff (6%), alternative diagnoses other than HFpEF (6%) and elevated LFTs (4%). 5754 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 (hypotension, hyperkalemia, and renal dysfunction; 62%), subject decision (12%), protocol deviation (12%), non-compliance (6%), and death (5%). 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 1. Their median age was 73 ± 8.4 years, 52% were women, most were in NYHA functional class II and the mean LVEF 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 (33%) based on an ECG at the time of screening, diabetes (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 92%, at screening. ACE

inhibitors or ARB (85%), beta-blocker (80%) and mineralocorticoid receptor antagonist (24%) were commonly prescribed. The median MAGGIC risk score was 20 (IQR 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 eGFR, and had less use of ACEi, ARBs and beta-blockers (Table 1).

Patients with AF (Table S1) 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 S2) were younger, had higher NYHA class and were more likely to be prescribed 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 S3), and more likely to have AF. North Americans were mostly likely to have diabetes; 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. While 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 to previous trials. Entry blood pressure was similar to that in other trials except TOPCAT-Americas, which required patients to have SBP < 130mmHg at entry, and PEP-CHF, in which blood pressure was higher. LVEF was similar to prior trials except for PEP-CHF, in which it was higher. The prevalence of diabetes and CKD 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 S4). 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, due to different threshold values for inclusion. Patients in PARAGON-HF were more likely to be prescribed an ARB rather than an ACE inhibitor prior to screening but overall use of either an ACE-I or ARB was similar. Prescription of beta-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, 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, coronary artery disease, and AF. Despite capping enrolment of patients with AF, 33% 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 following 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. Prior to 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. Following 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 SR, 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 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 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. While some risk factors were less prominent in patients who had had a heart failure hospitalization within 9 months, this was likely due to 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 anti-coagulants, 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 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 increased in NT-proBNP and evidence of structural heart disease, or may reflect different regional distribution including more patients enrolled in the US. 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 due to 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 ACEi an ARB or an ARNI, a beta-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 amongst 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 epidemiologic cohorts, although some differences in characteristics likely are due to 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.

Source of Funding

The PARAGON-HF Trial is funded by Novartis

DISCLOSURES

Dr. Solomon, Dr. Anavekar, Dr. Boytsov, Dr. Duengen, Prof. Galinier, Prof. Lelonek, Dr. Lund, Dr. Shah, and Dr. 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 & 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. 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 speaker's bureau of Novartis. Prof. 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/BMS 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; Professor 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. 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, 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, NovoNordisk, 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 BWH regarding 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. Veldhuisen has received board membership fees from Novartis. Dr. 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 co-principal investigator of ATMOSPHERE (a trial using aliskiren) and co-principal investigator of the PARADIGM-HF and PARAGON-HF trials (using sacubitril/valsartan); and his employer, Glasgow University, has been paid by Novartis for his time spent in these roles. Dr. Chopra, Dr. Goncalvesova, Dr. Oh, Dr. Senni, Dr. Widimsky, Dr. Zile, and Dr. Zweiker have consulted for Novartis. Dr. Ben Gal, Dr Seferovic, and Dr. Taurio have received lecture fees from Novartis. Dr Sibulo and Dr. Zhou have received research grants from Novartis. Dr. Rizkala, Dr. Lefkowitz, Dr. Shi, and Dr. Gong are employees of Novartis. Dr. Arenas, Dr. Linssen, Dr. Saito, and Dr. Vrtovec have nothing to disclose.

Table 1. Baseline Characteristics

	Patients Who Entered Run-in But were not Randomized N = 917	Randomized patients N = 4822	*p*
Demographics			
Age	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%	
Caucasian	81%	82%	
Native American	0.3%	1%	
Other	3%	3%	
Physical Examination			
Sitting Pulse Rate (beats/min)	71 ± 13	70 ± 12	<0.001
Sitting Systolic Blood Pressure (mmHg)	132 ±17	136± 15	<0.001
Sitting Diastolic Blood Pressure (mmHg)	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 or greater	12%	15%	
Body Mass Index (kg/m2)	29.7 ±5.6	30.2 ± 5.0	0.003
Obese (BMI > 30 kg/m2)	44%	49%	0.003
Medical History			
Prior Heart Failure Hospitalization,	55%	48%	<0.001
HHF within 9 Months	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	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 proB-type natriuretic peptide (pg/mL), Plasma/Serum (median, IQR)	Median 1062 (998, 1129)	Median 885 (863, 908)	<0.001
Ejection Fraction (%), mean ± SD	57 ±8	58 ± 8	0.19

Estimated glomerular filtration rate (mL/min/1.73m^2), mean ± SD	58 ±20	63 ±19	<0.001
eGFR category			<0.001
< 45 mL/min/1.73m^2	28%	18%	
≥ 45, < 60 mL/min/1.73m^2	31%	29%	
≥ 60 mL/min/1.73m^2	41%	53%	
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
Beta-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
Non-Statin Lipid Lowering Medication	48 (5%)	270 (6%)	0.66
Combined statin/non-statin 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%	
Patients with wall thickness >= 1.2mm by any criteria (site-reported)	n/a		
Structural heart disease by any criteria (site)	n/a		

n/a data not available

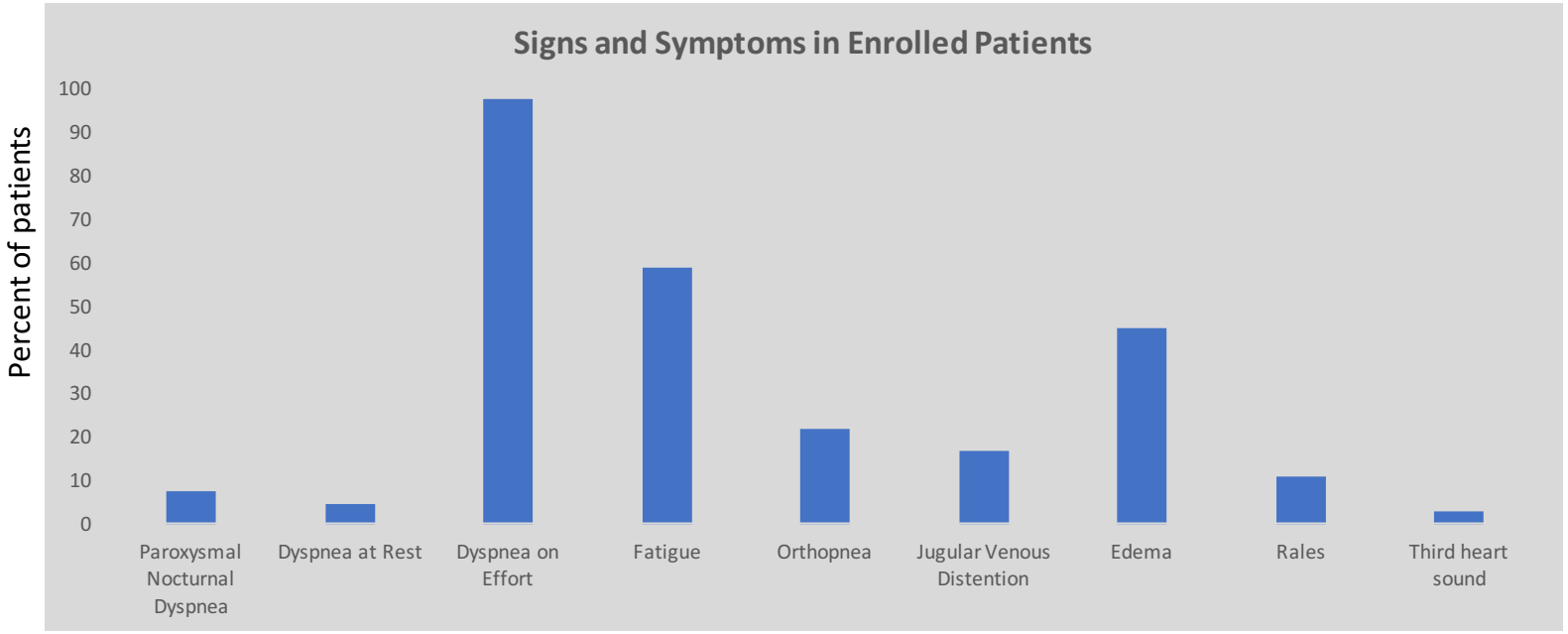
Table 2. Comparison of PARAGON with other HFpEF trials

	PARAGON (n = 4822)	TOPCAT Americas (n = 1767)	I-Preserve (n = 4128)	CHARM-Preserved (n= 3023)	PEP-CHF (n = 850)
Age	73 ± 8	72 (64, 79)	72±7	67 ± 11	75 (72, 79)
Female Sex	52%	50%	60%	40%	56%
NYHA Classification:2=CLASS II; 3=CLASS III; 4=CLASS IV;					
2	72%	59%	22%	61%	I/II =76%
3	27%	35%	77%	38%	
4	0.6%	1%	3%	2%	III/IV =25%
Race					
ASIAN	13%	1%	1%	2%	n/a
BLACK	2%	17%	2%	4%	n/a
CAUCASIAN	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/min):	70 ± 12	68 (61, 76)	71±10	71±12	73 (66, 82)
Sitting Systolic Blood Pressure (mmHg):	136± 15	129 (118, 138)	136±15	136±18	139 (129, 150)
Sitting Diastolic Blood Pressure (mmHg):	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/m2):	30 ± 5	33 (28, 38)	30±5	29±6	28 (25, 30)
Prior Heart Failure Hospitalization:0=N; 1=Y;	48%	58.9%	23%	68.7%	
HHF > 9 Month prior to Screening	38%		44% within 6 months		
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	33%	34%	29%	29%	21%
History of AF	52%	42%	29%	29%	
Left Bundle Branch Block	7%		8%		
Diabetes	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%	Loop8 3% 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%
Beta 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%			
Non-Statin 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%	

Figure 1. Heart failure signs and symptoms in enrolled patients



REFERENCES

[1] Komajda M, Lam CS. Heart failure with preserved ejection fraction: a clinical dilemma. Eur Heart J. 2014;35:1022-32.

[2] Pfeffer MA, Claggett B, Assmann SF, Boineau R, Anand IS, Clausell N, Desai AS, Diaz R, Fleg JL, Gordeev I, Heitner JF, Lewis EF, O'Meara E, Rouleau JL, Probstfield JL, Shaburishvili T, Shah SJ, Solomon SD, Sweitzer NK, McKinlay SM, Pitt B. Regional variation in patients and outcomes in the Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist (TOPCAT) trial. Circulation. 2015;131:34-42.

[3] Solomon SD, Rizkala AR, Gong J, Wang W, Anand IS, Ge J, Lam CSP, Maggioni AP, Martinez F, Packer M, Pfeffer MA, Pieske B, Redfield MM, Rouleau JL, Van Veldhuisen DJ, Zannad F, Zile MR, Desai AS, Shi VC, Lefkowitz MP, McMurray JJV. Angiotensin Receptor Neprilysin Inhibition in Heart Failure With Preserved Ejection Fraction: Rationale and Design of the PARAGON-HF Trial. JACC Heart Fail. 2017;5:471-482.

[4] McMurray JJ, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, Rouleau JL, Shi VC, Solomon SD, Swedberg K, Zile MR; PARADIGM-HF Investigators and Committees. Angiotensin-neprilysin inhibition versus enalapril in heart failure. N Engl J Med. 2014;371:993-1004.

[5] Solomon SD, Zile M, Pieske B, Voors A, Shah A, Kraigher-Krainer E, Shi V, Bransford T, Takeuchi M, Gong J, Lefkowitz M, Packer M, McMurray JJ; Prospective comparison of ARNI with ARB on Management Of heart failUre with preserved ejectioN fracTion (PARAMOUNT) Investigators. The angiotensin receptor neprilysin inhibitor LCZ696 in heart failure with preserved ejection fraction: a phase 2 double-blind randomised controlled trial. Lancet. 2012;380:1387-95.

[6] Pitt B, Pfeffer MA, Assmann SF, Boineau R, Anand IS, Claggett B, Clausell N, Desai AS, Diaz R, Fleg JL, Gordeev I, Harty B, Heitner JF, Kenwood CT, Lewis EF, O'Meara E, Probstfield JL, Shaburishvili T, Shah SJ, Solomon SD, Sweitzer NK, Yang S, McKinlay SM; TOPCAT Investigators. Spironolactone for heart failure with preserved ejection fraction. N Engl J Med. 2014;370:1383-92.

[7] Massie BM, Carson PE, McMurray JJ, Komajda M, McKelvie R, Zile MR, Anderson S, Donovan M, Iverson E, Staiger C, Ptaszynska A; I-PRESERVE Investigators. Irbesartan in patients with heart failure and preserved ejection fraction. N Engl J Med. 2008 Dec 4;359(23):2456-67.

[8] Yusuf S, Pfeffer MA, Swedberg K, Granger CB, Held P, McMurray JJ, Michelson EL, Olofsson B, Ostergren J; CHARM Investigators and Committees. Effects of candesartan in patients with chronic heart failure and preserved left-ventricular ejection fraction: the CHARM-Preserved Trial. Lancet. 2003;362:777-81.

[9] Cleland JG, Tendera M, Adamus J, Freemantle N, Polonski L, Taylor J; PEP-CHF Investigators. The perindopril in elderly people with chronic heart failure (PEP-CHF) study. Eur Heart J. 2006;27:2338-45.

[10] Pocock SJ, Ariti CA, McMurray JJ, Maggioni A, Køber L, Squire IB, Swedberg K, Dobson J, Poppe KK, Whalley GA, Doughty RN; Meta-Analysis Global Group in Chronic Heart Failure. Predicting survival in heart failure: a risk score based on 39 372 patients from 30 studies. Eur Heart J. 2013;34:1404-13.

[11] Kristensen SL, Jhund PS, Køber L, McKelvie RS, Zile MR, Anand IS, Komajda M, Cleland JGF, Carson PE, McMurray JJV. Relative Importance of History of Heart Failure Hospitalization and N-

Terminal Pro-B-Type Natriuretic Peptide Level as Predictors of Outcomes in Patients With Heart Failure and Preserved Ejection Fraction. JACC Heart Fail. 2015;3:478-486.

[12] Kristensen SL, Køber L, Jhund PS, Solomon SD, Kjekshus J, McKelvie RS, Zile MR, Granger CB, Wikstrand J, Komajda M, Carson PE, Pfeffer MA, Swedberg K, Wedel H, Yusuf S, McMurray JJ. International geographic variation in event rates in trials of heart failure with preserved and reduced ejection fraction. Circulation. 2015;131:43-53.

[13] Chioncel O, Lainscak M, Seferovic PM, Anker SD, Crespo-Leiro MG, Harjola VP, Parissis J, Laroche C, Piepoli MF, Fonseca C, Mebazaa A, Lund L, Ambrosio GA, Coats AJ, Ferrari R, Ruschitzka F, Maggioni AP, Filippatos G. Epidemiology and one-year outcomes in patients with chronic heart failure and preserved, mid-range and reduced ejection fraction: an analysis of the ESC Heart Failure Long-Term Registry. Eur J Heart Fail. 2017;19:1574-1585.