ESC HEART FAILURE
ESC Heart Failure 2022; **9**: 164–177
Published online 22 November 2021 in Wiley Online Library (wileyonlinelibrary.com) **DOI:** 10.1002/ehf2.13705

ORIGINAL ARTICLE

Eligibility of patients with heart failure with preserved ejection fraction for sacubitril/valsartan according to the PARAGON-HF trial

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Abstract

Aims In the heart failure (HF) with preserved ejection fraction (HFpEF) PARAGON-HF trial, sacubitril/valsartan vs. valsartan improved mortality/morbidity in patients with left ventricular ejection fraction (LVEF) below median (57%). We assessed eligibility for sacubitril/valsartan based on four scenarios.

Methods and results Eligibility was assessed in the Karolinska-Rennes study (acute HFpEF, LVEF $\geq$ 45%, and N-terminal pro-B-type natriuretic peptide $\geq$300 pg/mL subsequently assessed as outpatients including echocardiography) in (i) a trial scenario (all trial criteria); (ii) a pragmatic scenario (selected trial criteria); (iii) LVEF below lower limit of normal range ($<$54% in women and $<$52% in men); and (iv) LVEF below mean of normal range ($<$64% in women and $<$62% in men). Among 425 patients [age 78 (72–83) years, 57% women, 28% LVEF $\leq$ 57% (median in PARAGON-HF), the *trial scenario*, identified 34% as eligible. Left atrial enlargement and/or left ventricular hypertrophy were present in 99%. Inclusion criteria not met were diuretic treatment and New York Heart Association class. Important exclusion criteria were estimated glomerular filtration rate $<$30 mL/min/1.73 m^2, haemoglobin $<$10 g/day, and cancer. In the *pragmatic scenario*, 63% were eligible. In LVEF below lower limit of normal range, 5.4% were eligible, and in LVEF below mean of normal range, 41% were eligible. In patients with LVEF $\leq$ 57%, eligibility was 42%, 69%, 21%, and 91% according to the *trial scenario*, *pragmatic scenario*, *LVEF below lower limit of normal range*, and *LVEF below mean of normal range*, respectively.

Conclusions In real-world HFpEF (LVEF $\geq$ 45%) with N-terminal pro-B-type natriuretic peptide and cardiac structure/function assessed, eligibility for sacubitril/valsartan was according to PARAGON-HF complete criteria 34%, pragmatic criteria 63%, LVEF below lower limit of normal range 5.4%, and LVEF below mean of normal range 41%. Cardiac structural impairment was almost ubiquitous. Ineligibility was more due to exclusion criteria than failing to meet inclusion criteria.

Keywords Heart failure with preserved ejection fraction; Heart failure with mid-range ejection fraction; Heart failure with mildly reduced ejection fraction; Heart failure with borderline ejection fraction; PARAGON-HF; Sacubitril/valsartan; Eligibility; Echocardiography; Structural heart disease; Trial design

Received: 8 August 2021; Revised: 4 October 2021; Accepted: 29 October 2021
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Clinical Trial Registration: ClinicalTrials.gov NCT00774709.

Introduction

Half of the heart failure (HF) population consists of patients with left ventricular ejection fraction (LVEF) $\geq$50% or LVEF 41–49%, that is, HF with preserved (HFpEF) or mildly reduced (HFmrEF) LVEF, respectively. The remaining half has LVEF $\leq$ 40%, that is, HF with reduced LVEF (HFrEF). Mortality in HF is high regardless of LVEF, but the risk of cardiovascular (CV) events is lower with higher LVEF.[1] There have been great advances in HFrEF therapy.[1] In HFpEF, apart from the very recent results from the EMPEROR-Preserved trial on the sodium/glucose cotransporter-2 inhibitor empagliflozin,[2]

previous randomized controlled trials (RCTs) have failed to show any treatment benefit.[3–6] According to guidelines, treatment of patients with HFpEF is therefore currently limited to improving symptoms and treating risk factors and co-morbidities. However, recent *post hoc* analyses of HFpEF RCTs, where HFmrEF was included, suggest that HFrEF treatments may improve outcomes also in HFmrEF.[7–9]

The PARAGON-HF trial [Prospective Comparison of ARNI (angiotensin receptor–neprilysin inhibitor) with ARB (angiotensin receptor blocker) Global Outcomes in HF with Preserved Ejection Fraction] studied the efficacy and safety of sacubitril/valsartan vs. valsartan in patients with HFpEF (defined as LVEF $\geq$ 45%). The primary outcome was the composite of CV mortality and total HF hospitalizations. PARAGON-HF missed statistical significance for the primary endpoint {rate ratio (RR), 0.87 [95% confidence interval (CI) 0.75–1.01]; P = 0.06}.[10] However, there was a significant treatment–LVEF interaction. The primary PARAGON-HF publication[10] did not present the P-value for the interaction, but with LVEF equal to or below median (≤57%), the RR was 0.78 (95% CI 0.64–0.95), whereas with LVEF above median (>57%), the RR was 1.00 (95% CI 0.81–1.23).[10] In a *post hoc* analysis of effect across the LVEF spectrum using PARADIGM-HF and PARAGON-HF combined, there was a significant treatment–LVEF interaction (P = 0.02). The effect of LVEF on the efficacy of sacubitril/valsartan did not differ between sexes, but the benefit persisted to a higher LVEF in women compared with men ($P_{\text{interaction}}$ = 0.032).[11] This suggests that the benefits of sacubitril/valsartan observed in patients with HFrEF in PARADIGM-HF[12] could extend to patients with mildly reduced (i.e. lower than normal) LVEF and to women.

In RCTs, inclusion/exclusion criteria are applied to ensure enrolment of the targeted study population, to enrich for modifiable events, and to reduce the risk of competing events, and in PARAGON-HF, to ensure the presence of HF, because the diagnosis can be difficult in the presence of a preserved or normal LVEF. The strict selection criteria might reduce external validity of trial findings, affecting drug labels, guideline recommendations, payer reimbursement, and clinical implementation. The PARAGON-HF trial had numerous selection criteria, in particular the presence of left atrial enlargement (LAE) or left ventricular hypertrophy (LVH), which are often unavailable in clinical datasets.[13] Recently, the Food and Drug Administration (FDA) updated the label for sacubitril/valsartan to '… adult patients with chronic heart failure. Benefits are most clearly evident in patients with left ventricular ejection fraction (LVEF) below normal'.[14] Finally, of relevance for clinicians and payers is how a new drug will be implemented clinically, which often reflects a pragmatic simplified approach to a combination of trial, guideline, and label characteristics and criteria.

Therefore, in a well-characterized HFpEF observational cohort, overall and in women and men separately, and in patients with LVEF $\leq$ 57% and >57% separately, we aimed to (i) assess eligibility for sacubitril/valsartan according to strict and pragmatic PARAGON-HF inclusion/exclusion criteria and LVEF below normal, (ii) compare patient characteristics according to the eligibility status, and (iii) investigate the prevalence of LVEF $\leq$ 57% and 'below normal' defined as LVEF below the lower limit of the normal range (<54% in women and <52% in men) and LVEF below the mean of normal range (<64% in women and <62% in men) according to the American Society of Echocardiography and the European Association of Cardiovascular Imaging.[15]

Methods

Patients

The Karolinska-Rennes (KaRen) study was a prospective, multicentre, international, non-interventional study recruiting patients between 28 June 2007 and 29 December 2011, presenting with acute signs and symptoms of HF according to the Framingham criteria, LVEF $\geq$ 45% by echocardiography, and elevated natriuretic peptides [B-type natriuretic peptide >100 ng/L or N-terminal pro-B-type natriuretic peptide (NT-proBNP) >300 ng/L]. Exclusion criteria included primary restrictive or obstructive cardiomyopathy or pericardial constriction, any CV disorder with an indication for surgical or percutaneous intervention (e.g. valve disease requiring intervention, even if such intervention was not offered because of, e.g. frailty or age), existing cardiac resynchronization therapy, renal disease requiring dialysis, or pulmonary disease requiring chronic supplemental oxygen. Patients in a stable state after 4–8 weeks returned for detailed echocardiography and clinical examination and were subsequently followed up by phone for 18 months.[16] Echocardiography was assessed using Vivid 7 ultrasound systems (GE Healthcare, Horten, Norway) and analysed in a dedicated core lab in Rennes, France.

Statistics

Eligibility according to PARAGON-HF in KaRen was assessed in the whole cohort, separately in women and men, and separately in LVEF $\leq$ 57% and >57%. Calculations are reported as number and percentages representing the remaining cohort after applying the respective inclusion/exclusion criteria. The criteria were not ordered and were not mutually exclusive; that is, the percentage shown for each criterion is the percentage eligible considering only that criterion, disregarding all other criteria.

Because there were some missing data for variables to be considered for eligibility assessment, and to avoid bias due to data missing not at random, the main analysis was per-

formed on an imputed dataset. Missing data were handled by multiple imputations using the R package 'mice'[17] with 10 datasets generated and 10 iterations. Variables included in the imputation models are specified in Supporting Information, *Table S2*. For the eligibility calculations, because one specific value is needed for each patient, the median was used for the continuous variables and the mode for categorical variables. If multiple modes existed, the lower value was used. For consistency, eligibility calculations were also performed on a complete case dataset, where only patients with non-missing information for all eligibility variables were included and in patients in whom missing values for eligibility variables were assumed to be eligible for inclusion. Patient characteristics were compared in eligible vs. non-eligible patients by Wilcoxon–Mann–Whitney test and χ^2 test for continuous and categorical variables, respectively. The eligibility analysis was performed considering four scenarios: (i) a *trial scenario*, where all the PARAGON-HF selection criteria that could be investigated in our dataset were applied, (ii) a *pragmatic scenario* including only those PARAGON-HF trial criteria that are more likely to influence real-world treatment decisions, that is, inclusion criteria: age ≥50 years, New York Heart Association (NYHA) II–IV, and elevated NT-proBNP criteria (defined as in the trial), and exclusion criteria: systolic blood pressure <110 mmHg, estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2, and two LVEF 'below normal' scenarios including patients with chronic (symptomatic) HFpEF (NYHA II–IV)[14] with LVEF 'below normal' defined as (iii) *below lower limit of normal range (*<54% in women and <52% in men) and (iv) *below mean of normal range* (<64% in women and <62% in men). Normal ranges of LVEF (54–74% in women and 52–72% in men) are according to the American Society of Echocardiography and the European Association of Cardiovascular Imaging.[15]

To describe patients in the lower LVEF range, who may be more likely to benefit from and receive sacubitril/valsartan, patient characteristics independently associated with LVEF below the lower limit of normal range (<54% in women and <52% in men) and below the mean of normal range (<64% in women and <62% in men) and with LVEF ≤ 57% (median in PARAGON-HF) were assessed by multivariable logistic regression models, with covariates selected based on clinical relevance [sex, age, NYHA class, eGFR, median NT-proBNP, diabetes, hypertension, ischaemic heart disease, atrial fibrillation/flutter, renin–angiotensin–aldosterone system inhibitor, mineralocorticoid receptor antagonist (MRA), and beta-blocker]. Results are presented as odds ratios (ORs) and corresponding 95% CIs.

All analyses were performed using R Version 3.6.1. The R code for all data handling and statistical analyses is available at https://github.com/linabe/eligibilityparagonkaren. The level of significance was set to 5%, two sided. No adjustments for multiple comparisons were made.

Ethical considerations

The KaRen study conforms to the International Conference on Harmonization and Good Clinical Practice guidelines and the Declaration of Helsinki. The study was approved by the French and Swedish ethics committees. All patients provided a written informed consent.

Results

Patient characteristics

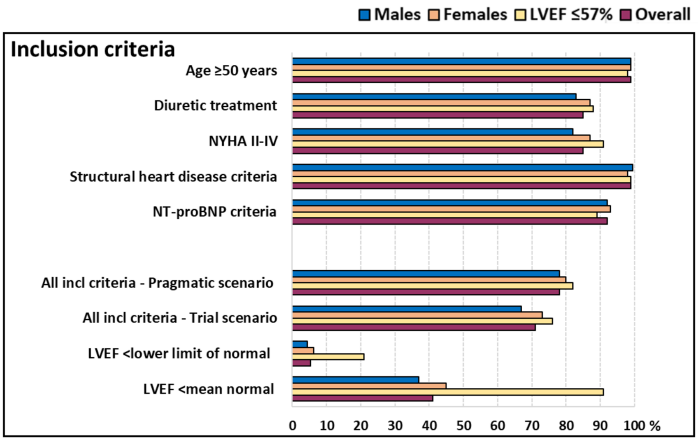
Of the 539 KaRen patients, the present analysis is based on the 425 who underwent echocardiographic assessment at the 4–8 weeks of visit. Median age was 78 (72–83) years, and 57% were women. In 28%, LVEF was ≤57%, in 8% below lower limit of normal range, and in 46% below mean of normal range (Supporting Information, *Table S1*).

Eligibility according to four scenarios

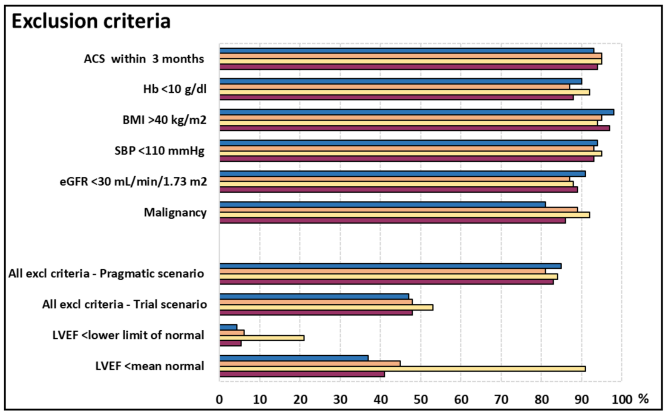
Eligibility based on (i) PARAGON-HF trial criteria, (ii) PARAGON-HF pragmatic criteria, and symptomatic HF (NYHA II–IV) and LVEF below normal assessed as (iii) LVEF below lower limit of normal range and (iv) LVEF below mean of normal range in the whole cohort and separately in women vs. men and in LVEF ≤ 57% vs. >57% is presented in *Figure 1* and Supporting Information, *Table S2*. Overall, in the imputed dataset, considering both inclusion and exclusion criteria, 34% were eligible according to the *trial scenario*, 63% according to the *pragmatic scenario*, 5.4% according to the *LVEF below lower limit of normal range criteria*, and 41% according to the *LVEF below mean of normal range criteria*. Applying only the inclusion criteria, eligibility in the *trial scenario* was 71% and in the *pragmatic scenario* 78%. The most likely met inclusion criteria were age ≥50 years (99%), structural heart disease (99%), and elevated NT-proBNP (93%). Inclusion criteria less likely to be met were diuretic treatment (85% eligible) and NYHA Classes II–IV (85% eligible). When applying only the exclusion criteria, 48% were eligible according to the *trial scenario* and 83% according to the *pragmatic scenario*. Major exclusion criteria affecting eligibility were eGFR < 30 mL/min/1.73 m^2 (89% eligible after applying this exclusion criterion), haemoglobin <10 g/dL (88% eligible), and malignancies within 5 years (86% eligible).

In women, the *trial scenario* was met in 36%, the *pragmatic scenario* in 64%, the *LVEF below lower limit of normal range criteria* in 6.2%, and *LVEF below mean of normal range criteria* in 45%, and in men in 31%, 62%, 4.3%, and 37%, respectively. In patients with LVEF ≤ 57%, eligibility was 42% according to *trial scenario*, 69% according to the

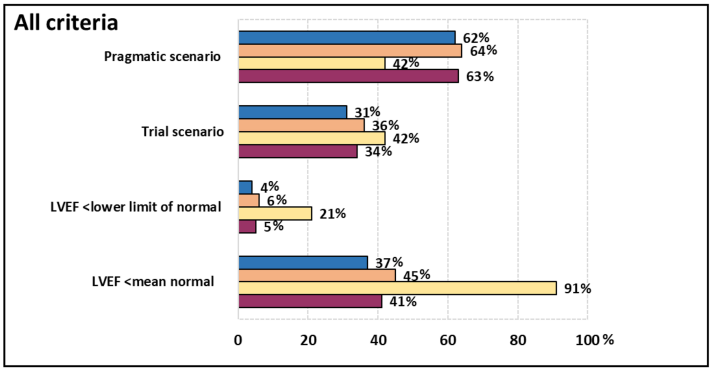
Figure 1 Inclusion criteria met and exclusion criteria not met in men (blue), women (pink), left ventricular ejection fraction (LVEF) ≤57% (yellow), and the whole KaRen cohort (purple). Inclusion criteria: age: ≥50 years; diuretic treatment: required for heart failure ≥30 days prior to enrolment; New York Heart Association (NYHA) Class: II–IV; structural heart disease: left atrial volume index ≥29 mL/m^2 or septal thickness or posterior wall thickness ≥1.1 cm; N-terminal pro-B-type natriuretic peptide (NT-proBNP): >300 pg/mL for patients in sinus rhythm or >600 pg/mL for patients in atrial fibrillation. Exclusion criteria: acute coronary syndrome (ACS) within 3 months; haemoglobin (Hb): <10 g/dL; body mass index (BMI): >40 kg/m^2; systolic blood pressure (SBP): >150 and <180 mmHg unless receiving three or more antihypertensive drugs; estimated glomerular filtration rate (eGFR): <30 mL/min/1.73 m^2; malignancy: within the past 5 years (except localized basal or squamous cell carcinoma of the skin or localized prostate cancer).



Age: ≥50 years; Diuretic treatment: required for HF ≥30 days prior to enrolment; NYHA class: II-IV; Structural heart disease: Left atrial volume index ≥29 mL/m^2 or septal thickness or posterior wall thickness ≥1.1 cm; NT-proBNP: >300 pg/ml for patients in sinus rhythm or >600 pg/ml for patients in AF



Acute coronary syndrome within 3 months; Hemoglobin: <10 g/dL; Body mass index: >40 kg/m2; Systolic blood pressure: >150 mmHg and <180 mmHg unless receiving 3 or more antihypertensive drugs; Estimated glomerular filtration rate: <30 mL/min/1.73m2; Malignancy: within the past 5 years (except localized basal or squamous cell carcinoma of the skin or localized prostate cancer



pragmatic scenario, 21% according to the *LVEF below lower limit of normal range criteria*, and 91% in the *LVEF below mean of normal range criteria*. Detailed data on eligibility based on each individual inclusion/exclusion criteria of PARAGON-HF trial are reported in Supporting Information, *Table S2*.

Consistency analysis

In consistency analyses, patients with and without missing data did not substantially differ in eligibility. Calculations on the complete case dataset (n = 84) displayed a slightly higher eligibility applying the *trial scenario* (39%) and similar applying the *pragmatic scenario* (62%), the *LVEF below lower limit of normal range criteria* (8.3%), and the *LVEF below mean of normal range criteria* (52%) compared with the analyses on the imputed dataset (34%, 63%, 5.4%, and 41%, respectively). As expected, eligibility in patients with missing eligibility data assumed as eligible (n = 425) was slightly higher, 38% according to the *trial scenario*, 70% according to the *pragmatic scenario*, 22.4% according to the *LVEF below lower limit of normal range criteria*, and 51% according to the *LVEF below mean of normal range criteria* (Supporting Information, *Table S2*).

Characteristics in eligible vs. non-eligible patients

Clinical characteristics in eligible vs. non-eligible patients according to the four scenarios are presented in *Table 1*. According to the *trial scenario*, eligible patients had higher NT-proBNP, larger atrial volumes, and a more preserved kidney function expressed as higher eGFR. Haemoglobin presented as median was higher, but anaemia was more prevalent in eligible patients compared with the non-eligible patients. Eligible patients were less likely to have diabetes or history of cancer. The use of angiotensin-converting enzyme inhibitors or ARBs, beta-blockers, MRAs, and diuretics was more common in eligible patients compared with the non-eligible patients. In the *pragmatic scenario*, eligible vs. non-eligible patients were older and had higher systolic blood pressure, but otherwise, clinical characteristics were consistent with those observed in the *trial scenario*. Regarding treatments, MRAs and diuretics were more likely used in eligible patients, but there were no differences for use of angiotensin-converting enzyme inhibitors/ARBs and beta-blockers. Eligible patients according to the *LVEF below lower limit of normal range criteria* had higher heart rate and lower potassium but did not significantly differ in any other aspect. Eligible patients fulfilling the *LVEF below mean of normal range criteria* had higher body mass index and heart rate and were more symptomatic reflected by higher NYHA class, NT-proBNP, and rales/dyspnoea and more often on diuretics (*Table 1*).

Predictors of left ventricular ejection fraction below lower limit and below mean of normal range and ≤57%

In the whole cohort (LVEF ≥ 45%), *LVEF below lower limit of normal range (8%)* was as expected uncommon and was not significantly associated with any specific characteristics (*Figure 2A*). *LVEF below mean of normal range (46%)* was independently associated with higher odds of beta-blockers [OR 1.80 (95% CI 1.08–3.01); P = 0.026] (*Figure 2B*), while LVEF ≤ 57% (28%) was associated with lower odds of MRA treatment [OR 0.40 (95% CI 0.19–0.84); P = 0.018] and higher odds of beta-blocker treatment [OR 2.37 (95% CI 1.32–4.25); P = 0.004] (*Figure 2C*). In women, the use of beta-blockers [OR 2.46 (95% CI 1.09–5.53); P = 0.031] was independently associated with LVEF ≤ 57% (Supporting Information, *Table S3*). In men, NYHA Classes III–IV vs. I–II [OR 2.52 (95% CI 1.16–5.50); P = 0.021] and less use of MRAs [OR 0.27 (95% CI 0.08–0.89); P = 0.035] were independently associated with LVEF ≤ 57%.

Discussion

In a well-characterized HFpEF cohort including detailed clinical, biomarker, and echocardiographic data, 34% met the PARAGON-HF trial eligibility criteria for treatment with sacubitril/valsartan. If eligibility criteria more likely to influence treatment use in clinical practice were considered, defined as >50 years old with increased NT-proBNP, systolic blood pressure >110 mmHg, and eGFR > 30 mL/min/1.73 m^2, then 63% were eligible. Among our patients, all of whom had LVEF ≥ 45%, only 5.4% had an LVEF below lower limit of normal range, however, increasing to 41% when defined as LVEF below mean of normal range. Importantly, almost all patients had structural heart disease, suggesting that for clinicians to determine eligibility for sacubitril/valsartan based on PARAGON-HF, meeting the structural heart disease criteria can be assumed. Ineligibility was more due to severe co-morbidities than to insufficiently severe HF. The major inclusion criteria limiting eligibility were absence of diuretic treatment and not fulfilling NYHA Classes II–IV, whereas eGFR < 30 mL/min/1.73 m^2, haemoglobin <10 g/dL, and cancer were the major exclusion criteria limiting the eligibility. Eligibility in patients with LVEF ≤ 57% was 42% in the trial scenario, 69% in the pragmatic scenario, 21% in LVEF below lower limit of normal range, and 91% in LVEF below mean of normal range. Eligibility was overall slightly higher in women than men.

Recently, the FDA approved an extended label for sacubitril/valsartan, to '… adult patients with chronic heart failure. Benefits are most clearly evident in patients with left ventricular ejection fraction (LVEF) below normal'.[14] Therefore, in

Table 1 Baseline characteristics in eligible vs. non-eligible patients according to *trial scenario*, *pragmatic scenario*, *LVEF below lower limit of normal range* (<54% in women and <52% in men), and *LVEF below mean of normal range* (<64% in women and <62% in men)

	Trial scenario (imputed data)			Pragmatic scenario (imputed data)			LVEF below lower limit of normal range (imputed data)			LVEF below mean of normal range (imputed data)		
	Eligible	Not eligible	*P*-value	Eligible	Not eligible	*P*-value	Eligible	Not eligible	*P*-value	Eligible	Not eligible	*P*-value
n	144 (33.9)	281 (66.1)		268 (63.1)	157 (36.9)		23 (5.5)	402 (94.5)		176	249	
Sex (male)	57 (39.6)	127 (45.2)	0.316	114 (42.5)	70 (44.6)	0.757	8 (34.8)	176 (43.8)	0.528	68 (38.6)	116 (46.6)	0.126
Age (years)	79.0 [73.0, 83.0]	78.0 [70.0, 83.0]	0.092	79.0 [73.0, 84.0]	76.0 [66.0, 81.0]	<0.001	77.0 [71.0, 81.0]	78.0 [72.0, 83.0]	0.373	79.0 [73.0, 83.0]	78.0 [70.0, 83.0]	0.185
Heart failure index year 2012–2016	2 (1.4)	3 (1.1)	1.000	3 (1.1)	2 (1.3)	1.000	0 (0.0)	5 (1.2)	1.000	1 (0.6)	4 (1.6)	0.602
LVEF 40–49%	3 (2.6)	6 (2.6)	1.000	4 (1.8)	5 (4.1)	0.374	8 (36.4)	1 (0.3)	<0.001	8 (5.8)	1 (0.5)	0.008
LVEF ≥ 57%	76 (66.1)	170 (74.9)	0.113	154 (70.3)	92 (74.8)	0.448	0 (0.0)	246 (76.9)	<0.001	53 (38.1)	193 (95.1)	<0.001
LVEF ≥ 52% men and ≥54% women	107 (93.0)	208 (91.6)	0.806	206 (94.1)	109 (88.6)	0.113	0 (0.0)	315 (98.4)	<0.001	117 (84.2)	198 (97.5)	<0.001
LVEF ≥ 62% men and ≥64% women	59 (51.3)	124 (54.6)	0.640	113 (51.6)	70 (56.9)	0.405	0 (0.0)	183 (57.2)	<0.001	0 (0.0)	183 (90.1)	<0.001
LVEF (%)	63.0 [56.0, 66.5]	63.0 [57.5, 68.0]	0.236	63.0 [57.0, 68.0]	64.0 [57.5, 67.5]	0.546	50.0 [47.0, 51.0]	64.0 [58.0, 68.0]	<0.001	56.0 [54.0, 60.0]	66.0 [64.0, 69.0]	<0.001
NYHA class												
I	0 (0.0)	49 (19.6)	<0.001	0 (0.0)	49 (35.5)	<0.001	0 (0.0)	49 (13.3)	0.209	0 (0.0)	49 (22.1)	<0.001
II	107 (75.9)	136 (54.4)		183 (72.3)	60 (43.5)		16 (69.6)	227 (61.7)		110 (65.1)	133 (59.9)	
III	34 (24.1)	55 (22.0)		62 (24.5)	27 (19.6)		7 (30.4)	82 (22.3)		54 (32.0)	35 (15.8)	
IV	0 (0.0)	10 (4.0)		8 (3.2)	2 (1.4)		0 (0.0)	10 (2.7)		5 (3.0)	5 (2.3)	
NYHA Classes III–IV	34 (24.1)	65 (26.0)	0.771	70 (27.7)	29 (21.0)	0.185	7 (30.4)	92 (25.0)	0.738	59 (34.9)	40 (18.0)	<0.001
Atrial fibrillation or flutter on ECG	53 (76.8)	80 (73.4)	0.738	87 (74.4)	46 (75.4)	1.000	11 (78.6)	122 (74.4)	0.980	70 (77.8)	63 (71.6)	0.437
Left atrial diameter (mm)	46.0 [42.5, 50.0]	45.0 [41.0, 49.0]	0.210	46.0 [42.0, 50.0]	44.0 [40.8, 48.2]	0.015	47.5 [44.2, 51.5]	45.0 [41.8, 49.0]	0.087	45.0 [42.0, 50.5]	45.0 [41.0, 49.0]	0.159
Left atrial volume (mL)	91.0 [74.8, 111.0]	83.0 [69.0, 102.0]	0.023	88.0 [72.5, 111.0]	83.0 [67.5, 99.0]	0.012	96.5 [85.5, 111.8]	85.0 [70.0, 106.0]	0.018	88.0 [72.0, 108.0]	84.0 [70.0, 104.0]	0.275
Interventricular septal thickness (mm)	11.0 [10.0, 13.0]	11.0 [10.0, 13.0]	0.412	11.0 [10.0, 13.0]	11.0 [10.0, 13.0]	0.349	11.0 [9.2, 13.0]	11.0 [10.0, 13.0]	0.366	11.0 [10.0, 12.0]	11.0 [10.0, 13.0]	0.758
Posterior wall thickness in diastole (mm)	11.0 [10.0, 12.0]	11.0 [10.0, 12.0]	0.387	11.0 [10.0, 12.0]	10.0 [9.0, 12.0]	0.111	10.5 [9.0, 12.0]	11.0 [10.0, 12.0]	0.297	11.0 [10.0, 12.0]	11.0 [10.0, 12.0]	0.820
Left atrial volume indexed (mL/m^2)	50.0 [40.6, 62.5]	44.9 [37.3, 55.4]	0.009	48.9 [39.1, 60.6]	44.9 [34.5, 52.2]	0.014	49.3 [43.4, 63.4]	46.4 [37.9, 57.2]	0.122	45.9 [38.5, 58.7]	47.5 [38.0, 58.1]	0.729
Systolic blood pressure (mmHg)	140.0 [125.0, 150.0]	140.0 [120.0, 155.0]	0.855	140.0 [125.0, 153.5]	134.5 [110.8, 150.0]	0.001	131.0 [120.0, 150.5]	140.0 [120.0, 150.0]	0.665	140.0 [125.0, 150.0]	140.0 [120.0, 150.8]	0.442

(*Continues*)

Table 1 (continued)

	Trial scenario (imputed data)			Pragmatic scenario (imputed data)			LVEF below lower limit of normal range (imputed data)			LVEF below mean of normal range (imputed data)		
	Eligible	Not eligible	*P*-value	Eligible	Not eligible	*P*-value	Eligible	Not eligible	*P*-value	Eligible	Not eligible	*P*-value
Diastolic blood pressure (mmHg)	72.0 [67.0, 80.0]	73.0 [63.0, 80.0]	0.506	75.0 [65.0, 80.0]	70.0 [60.0, 80.0]	0.233	70.0 [63.5, 83.5]	73.0 [65.0, 80.0]	0.883	75.0 [65.0, 80.0]	73.0 [65.0, 80.0]	0.723
Mean arterial pressure (mm)	95.7 [86.7, 101.7]	96.7 [83.3, 104.3]	0.927	96.7 [86.7, 103.6]	93.3 [81.8, 103.3]	0.012	96.7 [86.7, 104.2]	96.7 [86.7, 103.3]	0.877	96.7 [86.7, 103.3]	95.0 [85.0, 103.3]	0.542
Mean arterial pressure ≥90 mmHg	100 (73.0)	167 (64.5)	0.108	178 (71.2)	89 (61.0)	0.047	13 (56.5)	254 (68.1)	0.357	116 (69.9)	151 (65.7)	0.437
Heart rate (b.p.m. on ECG)	67.0 [59.0, 78.0]	68.0 [58.0, 78.5]	0.869	68.0 [60.0, 78.0]	67.0 [57.0, 79.0]	0.414	77.0 [64.5, 88.5]	67.0 [58.0, 77.0]	0.008	70.0 [61.2, 85.8]	65.0 [56.0, 72.8]	<0.001
Heart rate ≥70	56 (42.1)	108 (43.7)	0.845	105 (43.9)	59 (41.8)	0.772	15 (68.2)	149 (41.6)	0.026	85 (52.5)	79 (36.2)	0.002
eGFR (mL/min/1.73 m^2)	58.9 [45.4, 72.2]	54.3 [35.3, 71.5]	0.013	57.5 [43.8, 71.4]	52.7 [27.9, 74.2]	0.011	44.6 [33.1, 77.6]	56.9 [40.1, 71.6]	0.555	54.9 [36.3, 71.2]	56.9 [41.1, 73.1]	0.300
eGFR categorized												
eGFR < 30	0 (0.0)	47 (18.7)	<0.001	0 (0.0)	47 (33.1)	<0.001	5 (22.7)	42 (11.4)	0.283	21 (12.8)	26 (11.6)	0.894
eGFR 30–59	71 (51.4)	98 (39.0)		134 (54.3)	35 (24.6)		8 (36.4)	161 (43.9)		72 (43.9)	97 (43.1)	
eGFR ≥ 60	67 (48.6)	106 (42.2)		113 (45.7)	60 (42.3)		9 (40.9)	164 (44.7)		71 (43.3)	102 (45.3)	
eGFR ≥ 60 vs. <60	67 (48.6)	106 (42.2)	0.274	113 (45.7)	60 (42.3)	0.574	9 (40.9)	164 (44.7)	0.900	71 (43.3)	102 (45.3)	0.767
Haemoglobin (g/L)	130.0 [120.0, 133.5]	121.5 [107.8, 134.0]	0.003	126.0 [110.0, 134.0]	127.0 [110.0, 133.8]	0.910	120.0 [110.0, 130.0]	127.0 [110.0, 134.8]	0.251	122.0 [110.0, 133.0]	129.0 [110.0, 135.0]	0.323
Anaemia	92 (68.1)	125 (50.4)	0.001	138 (56.3)	79 (57.2)	0.947	11 (52.4)	206 (56.9)	0.857	85 (52.8)	132 (59.5)	0.232
NT-proBNP (pg/mL)	1560.0 [716.8, 2812.8]	1173.0 [467.8, 2427.5]	0.004	1590.0 [716.8, 2842.8]	819.0 [367.0, 1860.5]	<0.001	1580.5 [932.2, 2740.5]	1332.5 [507.5, 2625.0]	0.250	1584.0 [692.0, 2887.0]	1154.0 [462.5, 2323.0]	0.005
NT-proBNP ≥ median	74 (57.8)	94 (45.2)	0.033	121 (57.1)	47 (37.9)	0.001	11 (61.1)	157 (49.4)	0.467	85 (57.0)	83 (44.4)	0.028
Potassium (mmol/L)	4.1 [3.8, 4.4]	4.1 [3.8, 4.5]	0.110	4.1 [3.8, 4.4]	4.1 [3.8, 4.5]	0.395	4.0 [3.6, 4.1]	4.1 [3.8, 4.5]	0.045	4.1 [3.8, 4.4]	4.1 [3.8, 4.5]	0.059
RAAS blocker	109 (76.2)	181 (65.3)	0.030	180 (67.7)	110 (71.4)	0.488	12 (52.2)	278 (70.0)	0.117	118 (67.0)	172 (70.5)	0.518
MRA	48 (33.6)	49 (17.7)	<0.001	73 (27.4)	24 (15.6)	0.008	2 (8.7)	95 (23.9)	0.152	34 (19.3)	63 (25.8)	0.149
Diuretic	143 (100.0)	214 (77.3)	<0.001	241 (90.6)	116 (75.3)	<0.001	20 (87.0)	337 (84.9)	1.000	158 (89.8)	199 (81.6)	0.029
Nitrate	25 (17.5)	17 (6.1)	<0.001	32 (12.0)	10 (6.5)	0.098	1 (4.3)	41 (10.3)	0.567	17 (9.7)	25 (10.2)	0.974
Antiplatelet	50 (35.0)	89 (32.1)	0.634	96 (36.1)	43 (27.9)	0.108	9 (39.1)	130 (32.7)	0.686	62 (35.2)	77 (31.6)	0.494
Anticoagulant	86 (60.1)	135 (48.7)	0.034	144 (54.1)	77 (50.0)	0.474	16 (69.6)	205 (51.6)	0.144	96 (54.5)	125 (51.2)	0.567
Statin	57 (39.9)	109 (39.4)	1.000	101 (38.0)	65 (42.2)	0.452	14 (60.9)	152 (38.3)	0.053	76 (43.2)	90 (36.9)	0.230
Beta-blocker	113 (79.0)	175 (63.2)	0.001	188 (70.7)	100 (64.9)	0.266	18 (78.3)	270 (68.0)	0.425	129 (73.3)	159 (65.2)	0.096
Calcium channel blocker	36 (25.2)	79 (28.5)	0.540	67 (25.2)	48 (31.2)	0.226	7 (30.4)	108 (27.2)	0.922	49 (27.8)	66 (27.0)	0.945
Smoking never	92 (63.9)	178 (63.8)	1.000	172 (64.7)	98 (62.4)	0.720	13 (56.5)	257 (64.2)	0.598	112 (63.6)	158 (64.0)	1.000
BMI (kg/m^2)	28.8 [24.8, 31.6]	27.4 [24.1, 32.9]	0.621	28.5 [24.9, 32.0]	27.6 [23.5, 31.8]	0.298	28.0 [26.2, 31.9]	28.2 [24.2, 32.0]	0.399	29.0 [24.9, 33.7]	27.4 [24.1, 31.4]	0.032

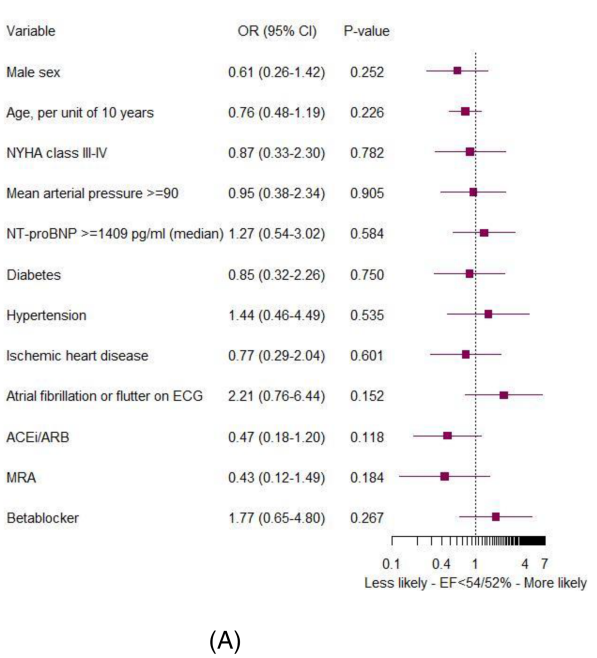
(*Continues*)

Table 1 (continued)

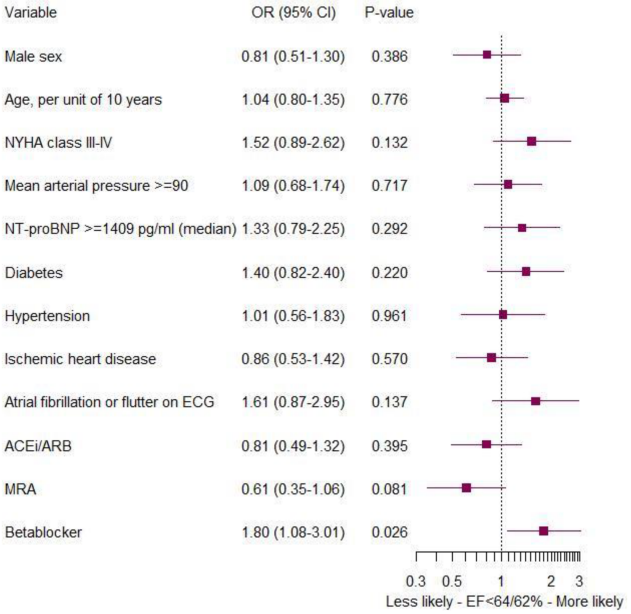
	Trial scenario (imputed data)			Pragmatic scenario (imputed data)			LVEF below lower limit of normal range (imputed data)			LVEF below mean of normal range (imputed data)		
	Eligible	Not eligible	*P*-value	Eligible	Not eligible	*P*-value	Eligible	Not eligible	*P*-value	Eligible	Not eligible	*P*-value
BMI categorized												
BMI < 30	81 (58.7)	155 (61.8)	0.005	149 (60.1)	87 (61.7)	0.598	12 (54.5)	224 (61.0)	0.832	91 (54.8)	145 (65.0)	0.044
BMI 30–40	57 (41.3)	81 (32.3)		91 (36.7)	47 (33.3)		9 (40.9)	129 (35.1)		65 (39.2)	73 (32.7)	
BMI ≥ 40	0 (0.0)	15 (6.0)		8 (3.2)	7 (5.0)		1 (4.5)	14 (3.8)		10 (6.0)	5 (2.2)	
BMI ≥ 30	57 (41.3)	96 (38.2)	0.630	99 (39.9)	54 (38.3)	0.836	10 (45.5)	143 (39.0)	0.703	75 (45.2)	78 (35.0)	0.053
Hypertension	110 (78.0)	206 (79.8)	0.763	199 (79.3)	117 (79.1)	1.000	20 (90.9)	296 (78.5)	0.262	135 (80.4)	181 (78.4)	0.718
Diabetes	31 (22.0)	92 (35.4)	0.008	68 (27.1)	55 (36.7)	0.057	8 (36.4)	115 (30.3)	0.721	59 (35.1)	64 (27.5)	0.126
Ischaemic heart disease	44 (31.4)	84 (32.6)	0.906	84 (33.6)	44 (29.7)	0.492	6 (28.6)	122 (32.4)	0.903	54 (32.5)	74 (31.9)	0.980
Coronary event prev 4–8 weeks	0 (0.0)	25 (9.7)	<0.001	14 (5.6)	11 (7.4)	0.600	0 (0.0)	25 (6.6)	0.450	9 (5.4)	16 (6.9)	0.687
PCI/CABG	24 (17.4)	48 (18.6)	0.872	46 (18.5)	26 (17.6)	0.912	6 (27.3)	66 (17.6)	0.394	35 (21.2)	37 (16.0)	0.234
Peripheral vessel disease	15 (10.6)	40 (15.5)	0.232	36 (14.3)	19 (12.8)	0.786	5 (22.7)	50 (13.3)	0.350	27 (16.1)	28 (12.1)	0.326
Stroke	14 (9.9)	29 (11.2)	0.834	28 (11.2)	15 (10.0)	0.845	5 (22.7)	38 (10.0)	0.129	26 (15.5)	17 (7.3)	0.014
Stroke event prev 4–8 weeks	0 (0.0)	5 (1.9)	0.236	2 (0.8)	3 (2.0)	0.558	1 (4.5)	4 (1.1)	0.656	3 (1.8)	2 (0.9)	0.712
Valvular heart disease	29 (20.6)	38 (14.3)	0.137	45 (17.6)	22 (14.5)	0.486	2 (9.1)	65 (16.9)	0.507	25 (14.9)	42 (17.6)	0.558
Valvular surgery	1 (0.7)	3 (1.2)	1.000	3 (1.2)	1 (0.7)	1.000	0 (0.0)	4 (1.1)	1.000	0 (0.0)	4 (1.7)	0.236
Lung disease	34 (24.1)	72 (27.7)	0.511	73 (29.1)	33 (22.0)	0.150	6 (27.3)	100 (26.4)	1.000	45 (26.8)	61 (26.2)	0.983
Liver disease	0 (0.0)	7 (2.7)	0.117	3 (1.2)	4 (2.7)	0.487	0 (0.0)	7 (1.8)	1.000	1 (0.6)	6 (2.6)	0.268
Cancer	0 (0.0)	61 (23.5)	<0.001	36 (14.3)	25 (16.7)	0.629	1 (4.5)	60 (15.8)	0.259	16 (9.5)	45 (19.3)	0.011
Syncope	14 (10.0)	23 (8.9)	0.852	25 (10.0)	12 (8.1)	0.638	1 (4.8)	36 (9.5)	0.729	13 (7.8)	24 (10.3)	0.487
Peripheral oedema	40 (28.4)	84 (32.9)	0.409	81 (32.0)	43 (30.1)	0.773	6 (26.1)	118 (31.6)	0.745	62 (36.7)	62 (27.3)	0.060
Pulmonary rales	21 (14.9)	30 (11.8)	0.463	36 (14.2)	15 (10.5)	0.362	4 (17.4)	47 (12.6)	0.730	29 (17.2)	22 (9.7)	0.041
Jugular venous distension	9 (6.4)	23 (9.0)	0.466	22 (8.7)	10 (7.0)	0.685	2 (8.7)	30 (8.0)	1.000	15 (8.9)	17 (7.5)	0.753
Dyspnoea at exercise	101 (72.1)	177 (69.1)	0.610	194 (76.7)	84 (58.7)	<0.001	19 (82.6)	259 (69.4)	0.269	130 (76.9)	148 (65.2)	0.016

BMI, body mass index; CABG, coronary artery bypass grafting; ECG, electrocardiogram; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; RAAS, renin–angiotensin–aldosterone system inhibitor.
Continuous variables presented as median [Q1, Q3] and categorical variables as numbers (%).

Figure 2 (A) Adjusted associations between baseline characteristics and left ventricular ejection fraction (LVEF) below lower limit of normal range (<54% in women/<52% in men) in the whole KaRen cohort. (B) Adjusted associations between baseline characteristics and LVEF below mean of normal range (<64% in women/<62% in men) in the whole KaRen cohort. (C) Adjusted associations between baseline characteristics and LVEF ≤ 57% in the whole KaRen cohort. Covariates: sex, age, NYHA class, eGFR, median NT-proBNP, diabetes, hypertension, ischaemic heart disease, atrial fibrillation/flutter, renin–angiotensin–aldosterone system inhibitor, mineralocorticoid receptor antagonists, and beta-blocker. ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CI, confidence interval; ECG, electrocardiogram; EF, ejection fraction; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; OR, odds ratio.



(A)



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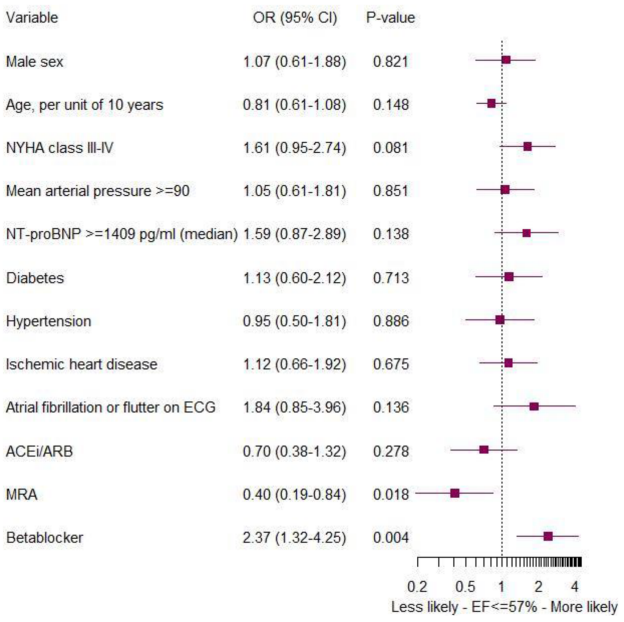

(C)

addition to the trial and pragmatic criteria, we assessed eligibility also based on this label, using criteria for normal based on the current American Society of Echocardiography recommendations[18] in patients with NYHA Classes II–IV. Given this label, the use of below normal may become a more commonly considered criterion in clinical practice than the arbitrary LVEF value of 57%, the median LVEF in PARAGON. Because the lower limit of normal is lower than the median in PARAGON-HF and also lower than the median in KaRen, very few patients with HFpEF were eligible when the LVEF was below the lower limit of normal range, increasing substantially when set to LVEF below mean of normal range. PARADIGM-HF and its LVEF criterion was ≤40%, and PARAGON-HF and our cohort had LVEF ≥ 45%. With LVEF digit preference at 5% intervals, there are likely few patients with LVEF 41–44%; thus, by extending the label from 'reduced LVEF' (≤40%) to LVEF 'below normal', and defining below normal as below the lower limit of normal, there is a relatively small proportion of additional patients with HF who have become eligible, but given that HF is so common, it is still a substantial number. By interpreting the label to also including patients below the LVEF mean of normal range, the number of patients would increase markedly.

Eligibility

Study populations in HF trials might not reflect 'real-world' HF characteristics as patients are selected using inclusion/exclusion criteria for enrichment purposes, compared with unselected HFpEF patients often being older and with multiple co-morbidities. In KaRen, the median age of eligible patients according to the trial scenario was 79 years. This is similar to the Swedish Heart Failure Registry (SwedeHF)[13] and the American Get With the Guidelines—Heart Failure registry (GWTG-HF)[19] where mean age was 77 and 79 years, respectively, whereas mean age in PARAGON-HF was 74 years.[20] In an analysis of the SwedeHF including 16 306 patients with LVEF ≥ 40%, 22% were eligible according to a PARAGON-HF trial scenario and 52% in a pragmatic scenario.[13] In a similar analysis in 106 440 patients in the GWTG-HF registry, only 10% met all trial inclusion/exclusion criteria while 71% met a broader set of criteria.[19] However, in these registries, echocardiographic variables (except for LVEF) were not available and subsequently not considered among the inclusion criteria. The KaRen study has the advantage of enrolling 'real-world' patients but also collecting detailed echocardiographic and clinical characteristics, whereas registries might enrol larger and more unselected populations but lack this granularity. Notably, in KaRen, despite requiring also echocardiographic criteria, we found a somewhat higher eligibility (34% trial criteria) and (63% pragmatic scenario) compared with in SwedeHF. This finding is supported by a recent report from a smaller prospective national registry including imaging variables where 170 out of 427 (40%) patients were eligible when applying a strict set of PARAGON-HF selection criteria.[21]

In PARAGON-HF, LAE (83%) and diastolic dysfunction (53%) were common, while left ventricular (LV) structural abnormalities (46%), especially concentric hypertrophy, were less prevalent.[22] This is in part consistent with previous HFpEF trials, except that PARAGON-HF patients had slightly greater LV wall thickness, smaller LV size, and larger LAE presumably explained by requirement for either LAE or increased LV wall thickness or LAE as an inclusion criterion.[22] In KaRen, LAE was reported in 79%, LVH in 72%, and diastolic dysfunction in 39% of the population.[23] Overall, 99% of the KaRen patients had structural heart disease, that is, LAE and/or LVH according to the PARAGON-HF definition; hence, this criterion is almost ubiquitous in 'real-world' HFpEF patients, implying that the vast majority of these patients have structural heart disease. Although structural cardiac HFpEF parameters such as left atrial (LA) volume and LV mass should be part of clinical echocardiography for patients with suspected or manifest HF, there may be circumstances when a detailed echocardiographic assessment is unavailable, in geriatric wards or in outpatient clinics with restricted access to echocardiography. In such situations, our results demonstrate that simpler criteria may suffice to identify eligible HFpEF patients.[24,25]

Ineligibility

Overall, ineligibility, and the discrepancy between the proportion of patients fulfilling the trial vs. the pragmatic scenario selection criteria, was more due to severe concomitant co-morbidities than not severe enough HF. In particular, among the inclusion criteria limiting eligibility, ongoing diuretic treatment (85% eligible) and NYHA Classes II–IV (85%; 62% in NYHA II) were the most noticeable. These criteria are easily assessed in clinical practice and may aid in identifying HFpEF patients in whom treatment may be beneficial and simplify screening procedures in future clinical trials.

Major exclusion criteria were linked with severe co-morbidities such as severe renal disease (eGFR < 30 mL/min/1.73 m^2), anaemia (haemoglobin <10 g/dL), and history of cancer. In the heterogeneous HFpEF patient group, often suffering from multiple co-morbidities, this may be of importance as many of these patients will never be included in clinical trials but may still be considered for treatment. Information on treatment effects of novel therapies is limited in a large proportion of HFpEF patients with high concomitant CV risk.[26]

Patients with HFpEF are at high risk for CV and HF events, especially the weeks after hospitalization.[27] When assessing eligibility based on trial inclusion/exclusion criteria for sacubitril/valsartan in HF populations after a hospitalization with acute decompensated HF, the eligibility has been low

at 2–12%.[19,28–30] The limitation in eligibility may be due to the high proportion of coexisting co-morbidities such as renal dysfunction and hyperkalaemia or a minimum daily dose of angiotensin-converting enzyme inhibitor/ARB, or excluding patients with ongoing HF hospitalizations as in PARADIGM-HF. The angiotensin-converting enzyme inhibitor/ARB criterion is strictly limited to HFrEF patients and is likely not applied in practice in HFmrEF and HFpEF, but the others are of interest also in these patient groups. However, as demonstrated in PARAGON-HF, sacubitril/valsartan actually reduced the risk of renal events and slowed the decline of eGFR and therefore might be beneficial in patients with impaired kidney function.[31] Finally, the use of potassium binders might facilitate the use of medications affecting kidney function and/or potassium.[32] Therefore, these exclusion criteria in PARAGON-HF may not be absolute limitations to the use of sacubitril/valsartan.

PARAGON-HF subgroups left ventricular ejection fraction ≤57% and women

In a pre-specified subgroup analysis in PARAGON-HF, the efficacy of sacubitril/valsartan varied across the LVEF spectrum. A greater treatment benefit was observed in patients with LVEF below or equal to median (≤57%) with a markedly higher relative risk reduction of the primary endpoint of 22% compared with 13% in the overall trial.[10] This finding might support the use of sacubitril/valsartan for reducing mortality and the risk of HF hospitalizations in HFmrEF and the lower range of HFpEF patients.[11] Neurohormonal activation is present, even if at a lower extent, in mildly reduced HF or HFmrEF, and also in HFpEF[33] and might explain the beneficial effects of sacubitril/valsartan in patients with LVEF ≤ 57% and lend support to the recently extended FDA label for sacubitril/valsartan in patients with LVEF below normal. Indeed, our patients with LVEF below the mean of the normal range vs. above displayed more symptomatic HF in form of higher NT-proBNP and higher NYHA class.

In KaRen, the PARAGON-HF NT-proBNP criterion (>200 pg/mL in sinus rhythm or >600 pg/mL in atrial fibrillation), which reflects LV filling pressures, was fulfilled in 92% of the population. Additionally, NT-proBNP was higher in the sacubitril/valsartan eligible KaRen population than in PARAGON-HF (1590 vs. 911 ng/L, respectively). This implies a slightly more severe HF syndrome, which may be due to the inclusion criterion requiring an episode of acute HF within 4–8 weeks, in addition to higher age or lower body mass index among KaRen patients compared with PARAGON-HF patients. Among PARAGON-HF patients, 62% had a previous HF hospitalization within 9 months, with a lower NT-proBNP in patients with vs. without previous HF hospitalization (840 vs. 944 pg/mL; $P < 0.001$).[20]

Limitations

The sample size in KaRen study is limited compared with large registries. Inclusion criteria stated LVEF ≥ 45%, thus excluding patients with LVEF 41–44%. This may have resulted in a lower proportion of patients in Karen defined as *below lower limit of normal LVEF* (i.e. <52% in men and <54% in women) when using the lower limit of normal LVEF as cut-off compared with HFpEF in general. Further, there was a difference in the timing of assessment after an acute HF event in KaRen (at 4–8 weeks) vs. PARAGON-HF (up to 9 months). Patients with a recent acute HF hospitalization can display higher natriuretic peptides, worse kidney function, and possibly a lower LVEF, which might not reflect the actual values in the chronic state. In KaRen, enrolment required LVEF ≥ 45% assessed at the acute HF; however, the present analysis is based on the assessment performed after treatment optimization and in stable condition after 1–2 months. Still, this might still have impacted on eligibility estimates. The small sample size did not suffice to make subgroup analyses of sex in patients with LVEF below normal. In KaRen, there were some missing data for patient characteristics, which represented inclusion/exclusion criteria for PARAGON-HF, and to reduce confounding due to missing data, we used multiple imputations. There were also some slight differences in inclusion/exclusion criteria in our analysis compared with the trial definition, such as definition of renal and hepatic disease. Some criteria were not possible to apply as data were not available, such as LA length and LA area. Further, LVEF is commonly reported in 5% ranges, which may result in incorrect estimates. Especially in HFpEF patients, with significant concentric remodelling, hypertrophic cardiomyopathy, or small LV volumes, there may be a significant systolic dysfunction with reduced stroke volume despite a normal LVEF. Still, it is the mode most commonly used in clinical practice when assessing LV function and subsequently classifying the same as preserved or reduced. Treatment with sacubitril/valsartan is currently approved for patients with chronic HF with LVEF below normal in the USA, while Karen was a smaller registry study in Europe; thus, the populations may differ in some aspects.

Conclusions

In the KaRen HFpEF study, 34% met the PARAGON-HF trial selection criteria and 63% met a pragmatic set of inclusion/exclusion criteria more likely to influence treatment decisions in clinical practice. Reflecting the recent extended FDA label including HFpEF patients with LVEF below normal, only 5.4% met the LVEF below lower limit of normal range criteria due to a low proportion of patients with LVEF ≥ 45% but below the lower limit of normal range. However, eligibility in-

creased applying LVEF below mean of the normal range demonstrating a substantial proportion of patients within the lower normal LVEF span. Patients in the lower normal LVEF span also had more symptomatic HF. Ineligibility was more due to the presence of exclusion criteria than not fulfilling inclusion criteria and therefore more likely related to severe co-morbidities rather than not having severe enough HF. Structural alterations in form of LAE and/or LVH were nearly universal and had no impact on determining eligibility, suggesting that these can be assumed present in HFpEF patients with a recent HF hospitalization and increased NT-proBNP concentrations.

Acknowledgements

The authors are grateful to Gunilla Förstedt and Eva Wallgren at Karolinska University Hospital for blood sampling, laboratory analysis, and taking care of patients and Kambiz Shahgaldi and Maria Westerlind for echocardiogram assessments.

Conflict of interest

C.H. reports consulting fees from Novartis and Roche Diagnostics and speaker and honoraria from MSD, supported by the Swedish Research Council (Grant 20180899). C.L. reports research grants, speaker honoraria, and consulting fees from Medtronic, Abbot, Impulse Dynamics, Novartis, Bayer, Vifor, MicroPort, Boston Scientific, AstraZeneca, and Orion Pharma. G.S. reports financial support from Novartis for the current research; grants and personal fees from Vifor and AstraZeneca; grants and non-financial support from Boehringer Ingelheim; personal fees from Società Prodotti Antibiotici, Roche, Servier, GENESIS, Cytokinetics, and Medtronic; and grants from Boston Scientific, outside the submitted work. L.H.L. reports personal fees from Sanofi and Lexicon, during the conduct of the study; personal fees from Merck, Bayer, Pharmacosmos, Abbott, Medscape, and Myokardia; grants and personal fees from Vifor Fresenius, AstraZeneca, Relypsa, Boehringer Ingelheim, and Novartis, outside the submitted work; and grants from Boston Scientific. E.D. reports echocardiographic core lab for Abbott and consulting fees for GE Healthcare, Abbott, AstraZeneca, Novartis, and Pfizer. A.L. is employed by Novartis Sweden.

Funding

The KaRen study was supported by grants from Fédération Française de Cardiologie/Société Française de Cardiologie, France, and Medtronic Bakken Research Center, Maastricht, the Netherlands. This study was supported by Novartis and the Swedish Research Council (Vetenskapsrådet; Grant 20180899). No funding agency had any role in the design and conduct of the study and in the collection, management, analysis, or interpretation of the data.

Supporting information

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

Table S1. Patient characteristics in the whole KaRen cohort, in females/males and in patients with LVEF ≤/>57%. Continuous variables presented as median [Q1,Q3] and categorical variables as numbers (%).
Table S2. Eligibility in KaRen cohort based on each individual inclusion/exclusion criteria of PARAGON-HF-trial. Eligibility estimates reported as numbers and percentages after applying the respective inclusion/exclusion criteria on the 1) imputed dataset in the whole Karen cohort, separate in females and males and in patients with LVEF ≤57% and >57% and in 2) complete cases (patients with non-missing information for all eligibility variables) and in 3) missing as eligible (patients with missing observations for any of the eligibility variables were assumed to be eligible). The criteria were not ordered and mutually exclusive. Variables included in the pragmatic scenario are marked in bold. (The number prior to the respective criteria are indicating the numbers in Table 1 in reference (9).
Table S3. Characteristics associated with LVEF ≤57% in females and males in the KaRen population.

References

1. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Bohm M, Burri H, Butler J, Celutkiene J, Chioncel O, Cleland JGF, Coats AJS, Crespo-Leiro MG, Farmakis D, Gilard M, Heymans S, Hoes AW, Jaarsma T, Jankowska EA, Lainscak M, Lam CSP, Lyon AR, McMurray JJV, Mebazaa A, Mindham R, Muneretto C, Francesco Piepoli M, Price S, Rosano GMC, Ruschitzka F, Kathrine Skibelund A, ESC Scientific Document Group. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: developed by the Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure of the European Society of Cardiology (ESC) with the special contribu-

tion of the Heart Failure Association (HFA) of the ESC. *Eur Heart J* 2021; **2021**: 3599–3726.
2. Anker SD, Butler J, Filippatos G, Ferreira JP, Bocchi E, Bohm M, Brunner-La Rocca HP, Choi DJ, Chopra V, Chuquiure-Valenzuela E, Giannetti N, Gomez-Mesa JE, Janssens S, Januzzi JL, Gonzalez-Juanatey JR, Merkely B, Nicholls SJ, Perrone SV, Pina IL, Ponikowski P, Senni M, Sim D, Spinar J, Squire I, Taddei S, Tsutsui H, Verma S, Vinereanu D, Zhang J, Carson P, Lam CSP, Marx N, Zeller C, Sattar N, Jamal W, Schnaidt S, Schnee JM, Brueckmann M, Pocock SJ, Zannad F, Packer M, EMPEROR-Preserved Trial Investigators. Empagliflozin in heart failure with a preserved ejection fraction. *N Engl J Med* 2021; **385**: 1451–1461.
3. 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. Spironolactone for heart failure with preserved ejection fraction. *N Engl J Med* 2014; **370**: 1383–1392.
4. Yusuf S, Pfeffer MA, Swedberg K, Granger CB, Held P, McMurray JJV, Michelson EL, Olofsson B, Östergren J. Effects of candesartan in patients with chronic heart failure and preserved left-ventricular ejection fraction: the CHARM-Preserved Trial. *Lancet* 2003; **362**: 777–781.
5. Cleland JG, Tendera M, Adamus J, Freemantle N, Polonski L, Taylor J. The perindopril in elderly people with chronic heart failure (PEP-CHF) study. *Eur Heart J* 2006; **27**: 2338–2345.
6. Massie BM, Carson PE, McMurray JJ, Komajda M, McKelvie R, Zile MR, Anderson S, Donovan M, Iverson E, Staiger C, Ptaszynska A. Irbesartan in patients with heart failure and preserved ejection fraction. *N Engl J Med* 2008; **359**: 2456–2467.
7. Lund LH, Claggett B, Liu J, Lam CS, Jhund PS, Rosano GM, Swedberg K, Yusuf S, Granger CB, Pfeffer MA, McMurray JJV, Solomon SD. Heart failure with mid-range ejection fraction in CHARM: characteristics, outcomes and effect of candesartan across the entire ejection fraction spectrum. *Eur J Heart Fail* 2018; **20**: 1230–1239.
8. Solomon SD, Claggett B, Lewis EF, Desai A, Anand I, Sweitzer NK, O'Meara E, Shah SJ, McKinlay S, Fleg JL, Sopko G, Pitt B, Pfeffer MA. Influence of ejection fraction on outcomes and efficacy of spironolactone in patients with heart failure with preserved ejection fraction. *Eur Heart J* 2016; **37**: 455–462.
9. Cleland JGF, Bunting KV, Flather MD, Altman DG, Holmes J, Coats AJS, Manzano L, McMurray JJV, Ruschitzka F, van Veldhuisen DJ, von Lueder TG, Bohm M, Andersson B, Kjekshus J, Packer M, Rigby AS, Rosano G, Wedel H, Hjalmarson A, Wikstrand J, Kotecha D, Beta-blockers in Heart Failure Collaborative Group. Beta-blockers for heart failure with reduced, mid-range, and preserved ejection fraction: an individual patient-level analysis of double-blind randomized trials. *Eur Heart J* 2018; **39**: 26–35.
10. Solomon SD, McMurray JJV, 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, Claggett B, Jhund PS, Boytsov SA, Comin-Colet J, Cleland J, Dungen HD, Goncalvesova E, Katova T, Kerr Saraiva JF, Lelonek M, Merkely B, Senni M, Shah SJ, Zhou J, Rizkala AR, Gong J, Shi VC, Lefkowitz MP, Investigators P-H, Committees. Angiotensin–neprilysin inhibition in heart failure with preserved ejection fraction. *N Engl J Med* 2019; **381**: 1609–1620.
11. Solomon SD, Vaduganathan M, Claggett BL, Packer M, Zile M, Swedberg K, Rouleau J, Pfeffer MA, Desai A, Lund LH, Kober L, Anand I, Sweitzer N, Linssen G, Merkely B, Luis Arango J, Vinereanu D, Chen CH, Senni M, Sibulo A, Boytsov S, Shi V, Rizkala A, Lefkowitz M, McMurray JJV. Sacubitril/valsartan across the spectrum of ejection fraction in heart failure. *Circulation* 2020; **141**: 352–361.
12. 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.
13. Savarese G, Hage C, Benson L, Schrage B, Thorvaldsen T, Lundberg A, Fudim M, Linde C, Dahlström U, Rosano GMC, Lund LH. Eligibility for sacubitril/valsartan in heart failure across the ejection fraction spectrum: real-world data from the Swedish Heart Failure Registry. *J Intern Med* 2021; **289**: 369–384.
14. ENTRESTO [prescribing information]. East Hanover NNPCF.
15. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, Flachskampf FA, Foster E, Goldstein SA, Kuznetsova T, Lancellotti P, Muraru D, Picard MH, Rietzschel ER, Rudski L, Spencer KT, Tsang W, Voigt JU. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr* 2015; **28**: 1–39.14.
16. Donal E, Lund LH, Linde C, Edner M, Lafitte S, Persson H, Bauer F, Ohrvik J, Ennezat PV, Hage C, Lofman I, Juilliere Y, Logeart D, Derumeaux G, Gueret P, Daubert JC. Rationale and design of the Karolinska-Rennes (KaRen) prospective study of dyssynchrony in heart failure with preserved ejection fraction. *Eur J Heart Fail* 2009; **11**: 198–204.
17. van Buuren S, Groothuis-Oudshoorn K. mice: Multivariate Imputation by Chained Equations in R. *J Stat Softw* 2011; **45**: 1–67.
18. Lang R, Badano L, Mor-Avi V. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging* 2015; **16**: 233–270.
19. Sayeed S, Fudim M, Devore AD, Xu H, Matsouaka RA, Heidenreich PA, Yancy CW, Fonarow GC, Hernandez AF. PARAGON-HF clinical trial eligibility in a population of patients hospitalized with heart failure. *J Card Fail* 2019; **25**: 1009–1011.
20. Solomon SD, Rizkala AR, Lefkowitz MP, Shi VC, Gong J, Anavekar N, Anker SD, Arango JL, Arenas JL, Atar D, Ben-Gal T, Boytsov SA, Chen CH, Chopra VK, Cleland J, Comin-Colet J, Duengen HD, Echeverria Correa LE, Filippatos G, Flammer AJ, Galinier M, Godoy A, Goncalvesova E, Janssens S, Katova T, Kober L, Lelonek M, Linssen G, Lund LH, O'Meara E, Merkely B, Milicic D, Oh BH, Perrone SV, Ranjith N, Saito Y, Saraiva JF, Shah S, Seferovic PM, Senni M, Sibulo AS Jr, Sim D, Sweitzer NK, Taurio J, Vinereanu D, Vrtovec B, Widimsky J Jr, Yilmaz MB, Zhou J, Zweiker R, 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, McMurray JJV. Baseline characteristics of patients with heart failure and preserved ejection fraction in the PARAGON-HF trial. *Circ Heart Fail* 2018; **11**: e004962.
21. Rettl R, Dachs TM, Duca F, Binder C, Dusik F, Seirer B, Schonauer J, Kronberger C, Camuz Ligios L, Hengstenberg C, Derkits N, Kastner J, Badr Eslam R, Bonderman D. What type of patients did PARAGON-HF select? Insights from a real-world prospective cohort of patients with heart failure and preserved ejection fraction. *J Clin Med* 2020; **9**: 3669.
22. Shah AM, Cikes M, Prasad N, Li G, Getchevski S, Claggett B, Rizkala A, Lukashevich I, O'Meara E, Ryan JJ, Shah SJ, Mullens W, Zile MR, Lam CSP, McMurray JJV, Solomon SD, Investigators P-H. Echocardiographic features of patients with heart failure and preserved left ventricular ejection fraction. *J Am Coll Cardiol* 2019; **74**: 2858–2873.
23. Persson H, Donal E, Lund LH, Matan D, Oger E, Hage C, Daubert JC, Linde C, KaRen I. Importance of structural heart disease and diastolic dysfunction in heart failure with preserved ejection fraction assessed according to the ESC guidelines—a substudy in the Ka (Karolinska) Ren (Rennes) study. *Int J Cardiol* 2019; **274**: 202–207.

24. Landolfo M, Piani F, Esposti DD, Cosentino E, Bacchelli S, Dormi A, Borghi C. Effects of sacubitril valsartan on clinical and echocardiographic parameters of outpatients with heart failure and reduced ejection fraction. *Int J Cardiol Heart Vasc* 2020; **31**: 100656.
25. Suo Y, Yuan M, Li H, Zhang Y, Li Y, Fu H, Han F, Ma C, Wang Y, Bao Q, Li G. Sacubitril/valsartan improves left atrial and left atrial appendage function in patients with atrial fibrillation and in pressure overload-induced mice. *Front Pharmacol* 2019; **10**: 1285.
26. Savarese G, Settergren C, Schrage B, Thorvaldsen T, Lofman I, Sartipy U, Mellbin L, Meyers A, Farsani SF, Brueckmann M, Brodovicz KG, Vedin O, Asselbergs FW, Dahlstrom U, Cosentino F, Lund LH. Comorbidities and cause-specific outcomes in heart failure across the ejection fraction spectrum: a blueprint for clinical trial design. *Int J Cardiol* 2020; **313**: 76–82.
27. Vaduganathan M, Jhund PS, Claggett BL, Packer M, Widimsky J, Seferovic P, Rizkala A, Lefkowitz M, Shi V, McMurray JJV, Solomon SD. A putative placebo analysis of the effects of sacubitril/valsartan in heart failure across the full range of ejection fraction. *Eur Heart J* 2020; **41**: 2356–2362.
28. Daly A, Coughlan JJ, Mross T, Wafer M, O'Connor A, Liston R. Assessing suitability for sacubitril-valsartan therapy in an Irish cohort: challenges and opportunities. *Ir J Med Sci* 2019; **188**: 1169–1174.
29. Carballo D, Stirnemann J, Garin N, Marti C, Serratrice J, Carballo S. Eligibility for sacubitril–valsartan in patients with acute decompensated heart failure. *ESC Heart Fail* 2020; **7**: 1282–1290.
30. Kapelios CJ, Lainscak M, Savarese G, Laroche C, Seferovic P, Ruschitzka F, Coats A, Anker SD, Crespo-Leiro MG, Filippatos G, Piepoli MF, Rosano G, Zanolla L, Aguiar C, Murin J, Leszek P, McDonagh T, Maggioni AP, Lund LH, Heart Failure Long-Term Registry Investigators. Sacubitril/valsartan eligibility and outcomes in the ESC-EORP-HFA Heart Failure Long-Term Registry: bridging between European Medicines Agency/Food and Drug Administration label, the PARADIGM-HF trial, ESC guidelines, and real world. *Eur J Heart Fail* 2019; **21**: 1383–1397.
31. Mc Causland FR, Lefkowitz MP, Claggett B, Anavekar NS, Senni M, Gori M, Jhund PS, McGrath MM, Packer M, Shi V, van Veldhuisen DJ, Zannad F, Comin-Colet J, Pfeffer MA, McMurray JJV, Solomon SD. Angiotensin-neprilysin inhibition and renal outcomes in heart failure with preserved ejection fraction. *Circulation* 2020; **142**: 1236–1245.
32. Rosano GMC, Tamargo J, Kjeldsen KP, Lainscak M, Agewall S, Anker SD, Ceconi C, Coats AJS, Drexel H, Filippatos G, Kaski JC, Lund L, Niessner A, Ponikowski P, Savarese G, Schmidt TA, Seferovic P, Wassmann S, Walther T, Lewis BS. Expert consensus document on the management of hyperkalaemia in patients with cardiovascular disease treated with renin angiotensin aldosterone system inhibitors: coordinated by the Working Group on Cardiovascular Pharmacotherapy of the European Society of Cardiology. *Eur Heart J Cardiovasc Pharmacother* 2018; **4**: 180–188.
33. Vergaro G, Aimo A, Prontera C, Ghionzoli N, Arzilli C, Zyw L, Taddei C, Gabutti A, Poletti R, Giannoni A, Mammini C, Spini V, Passino C, Emdin M. Sympathetic and renin-angiotensin-aldosterone system activation in heart failure with preserved, mid-range and reduced ejection fraction. *Int J Cardiol* 2019; **296**: 91–97.