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

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Aims To assess the proportion of patients with heart failure and reduced ejection fraction (HFrEF) who are eligible for sacubitril/valsartan (LCZ696) based on the European Medicines Agency/Food and Drug Administration (EMA/FDA) label, the PARADIGM-HF trial and the 2016 ESC guidelines, and the association between eligibility and outcomes.

Methods and results Outpatients with HFrEF in the ESC-EORP-HFA Long-Term Heart Failure (HF-LT) Registry between March 2011 and November 2013 were considered. Criteria for LCZ696 based on EMA/FDA label, PARADIGM-HF and ESC guidelines were applied. Of 5443 patients, 2197 and 2373 had complete information for trial and guideline eligibility assessment, and 84%, 12% and 12% met EMA/FDA label, PARADIGM-HF and guideline criteria, respectively. Absent PARADIGM-HF criteria were low natriuretic peptides (21%), hyperkalemia (4%), hypotension (7%) and sub-optimal pharmacotherapy (74%); absent Guidelines criteria were LVEF>35% (23%), insufficient NP levels (30%)

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and sub-optimal pharmacotherapy (82%); absent label criteria were absence of symptoms (New York Heart Association class I). When a daily requirement of ACEi/ARB ≥ 10 mg enalapril (instead of ≥ 20 mg) was used, eligibility rose from 12% to 28% based on both PARADIGM-HF and guidelines. One-year heart failure hospitalization was higher (12% and 17% vs. 12%) and all-cause mortality lower (5.3% and 6.5% vs. 7.7%) in registry eligible patients compared to the enalapril arm of PARADIGM-HF.

Conclusions Among outpatients with HFrEF in the ESC-EORP-HFA HF-LT Registry, 84% met label criteria, while only 12% and 28% met PARADIGM-HF and guideline criteria for LCZ696 if requiring ≥ 20 mg and ≥ 10 mg enalapril, respectively. Registry patients eligible for LCZ696 had greater heart failure hospitalization but lower mortality rates than the PARADIGM-HF enalapril group.

Keywords Sacubitril/valsartan • LCZ696 • Angiotensin receptor–neprilysin inhibitor • Eligibility • Registry • Prognosis

Introduction

Sacubitril/valsartan (LCZ696) is the first agent of the angiotensin receptor–neprilysin inhibitor (ARNI) drug class.[1] In PARADIGM-HF (Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure), LCZ696 compared to enalapril reduced the risk of the primary outcome [cardiovascular death or heart failure (HF) hospitalization] by 20%. Notably, the risks of all-cause and cardiovascular mortality and of HF hospitalization were also significantly reduced by ARNI.[2]

Following the results of the PARADIGM-HF trial, both the U.S. Food and Drug Administration (FDA) and European Medicines Agency (EMA) approved LCZ696 for symptomatic patients with HF and reduced ejection fraction (HFrEF). The EMA guidance referenced the inclusion/exclusion criteria of PARADIGM-HF which some may interpret as suggesting patients offered LCZ696 should also meet PARADIGM-HF criteria. Interestingly, the FDA permitted a more liberal use of LCZ696 compared with the EMA.[3] The inclusion criteria in PARADIGM-HF were complex, requiring symptomatic HF [New York Heart Association (NYHA) class II–IV], left ventricular ejection fraction (LVEF) ≤ 40% (later amended to ≤ 35%), but also elevated plasma levels of natriuretic peptides (NPs), a dose of angiotensin-converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB) equivalent to ≥ 10 mg of enalapril daily for the run-in and ≥ 20 mg of enalapril daily for randomization, and therapy with a beta-blocker (BB) as tolerated according to guidelines. Thus, the 2016 European Society of Cardiology (ESC) guidelines on HF, considering the single trial and strict inclusion criteria of PARADIGM-HF, recommended ARNI as a replacement for an ACEi only in outpatients with LVEF ≤ 35% who remain symptomatic (NYHA class II–IV) despite optimal treatment with an ACEi/ARB (at equivalent of 20 mg enalapril daily dose), a BB and an MRA as tolerated and with NP levels above those required in PARADIGM-HF (class I, level B).[4]

Given the efficacy of LCZ696 and the potential implications of widespread implementation, for both improved HF outcomes and increased costs, we assessed in a large and unselected, European-wide real-world HF population eligibility for LCZ696 according to EMA and FDA labels, the PARADIGM-HF and the ESC guideline criteria, and compared outcomes in registry vs. trial patients.

Methods

ESC-EORP-HFA HF-LT Registry HFrEF cohort: baseline characteristics and comparability with the PARADIGM-HF population

The ESC-EURObservational Research Programme (EORP)-Heart Failure Association (HFA) Heart Failure Long-Term (HF-LT) Registry has been previously described.[5,6] Briefly, it is a prospective, multicentre, observational study enrolling patients presenting with HF to a broad range of cardiology centres. In this analysis, 28 countries were included. Chronic HF outpatients and acute HF inpatients requiring intravenous HF therapy are included. The only exclusion criterion for enrolment in the registry is age < 18 years. Patients are followed up in accordance with the usual practice of the centres, except for a mandatory follow-up visit, or telephone follow-up for those unwilling or unable to attend a visit, at 1 year performed to collect information on morbidity and mortality.

In the current analysis, only outpatients with HFrEF registered between March 2011 and November 2013 were considered. The index date was defined as the baseline outpatient visit where data on baseline characteristics, laboratory tests and medications were collected. We compared the baseline characteristics of the ESC-EORP-HFA HF-LT Registry outpatients with HFrEF according to the availability of data for assessment of eligibility and the presence/absence of eligibility for LCZ696 with those of the PARADIGM-HF population.[2,7]

Patient eligibility for LCZ696 based on EMA/FDA label, PARADIGM-HF and 2016 ESC guidelines

Eligibility for LCZ696 in the ESC-EORP-HFA HF-LT Registry was assessed based on EMA/FDA label, the PARADIGM-HF eligibility criteria and the 2016 ESC HF guidelines.[2,4] According to the EMA label, LCZ696 is indicated for 'adult patients with symptomatic chronic HFrEF", while according to the FDA label, LCZ696 is indicated for 'chronic HF (NYHA class II–IV) and reduced ejection fraction'. Thus,

patients were considered eligible for LCZ696 based on the EMA/FDA label if they were outpatients (inpatients were not included in any analysis in this manuscript) with LVEF ≤ 40% and NYHA class II–IV. In this study, for PARADIGM-HF, patients were considered eligible if they had: (i) symptomatic HF (NYHA class II–IV); (ii) LVEF ≤ 40%; (iii) elevated plasma levels of NPs [B-type natriuretic peptide (BNP) ≥ 150 pg/mL or N-terminal pro-B-type natriuretic peptide (NT-proBNP) ≥ 600 pg/mL; or alternatively BNP ≥ 100 pg/mL or NT-proBNP ≥ 400 pg/mL if they had been hospitalized for HF within the previous 12 months]; (iv) a dose of ACEi/ARB equivalent to ≥ 10 mg of enalapril daily for run-in and ≥ 20 mg of enalapril daily for randomization, and therapy with a BB according to guidelines. MRAs were not required, but the trial protocol specified that an MRA should also be considered in all patients, taking account of renal function, serum potassium, and tolerability. Therefore, MRA use was not considered a criterion for LCZ696 eligibility in our analysis, though proportions of patients with and without MRA receipt were reported. Furthermore and uniquely, the registry records all the details required to assess PARADIGM-HF criteria, even including history of angioedema. Thus, the exclusion criteria in PARADIGM-HF that were considered as ineligibility criteria in the present analysis included (i) severe chronic kidney disease (estimated glomerular filtration rate < 30 mL/min/1.73 m^2), (ii) intolerance to ACEi due to angioedema, (iii) a current or recent (within the last 3 months) cardiovascular medical condition (myocardial infarction, stroke, transient ischaemic attack) or surgical (including heart surgery and vascular surgery) or interventional procedure (percutaneous coronary intervention or carotid angioplasty), (iv) hyperkalaemia (serum potassium > 5.2 mmol/L for screening or > 5.4 mmol/L for run-in and randomization), or (v) symptomatic hypotension and/or systolic blood pressure < 100 mmHg for screening and < 95 mmHg for run-in and randomization. When not explicitly stated otherwise, in this study the criteria for randomization were used for parameters that were different for screening, run-in and randomization. The registry captures not only use and dosing of drugs, but also reasons for non-use. Thus, uniquely, tolerability and contraindications, even history of angioedema, were available for our analyses.

In this study, for ESC guidelines, patients were considered eligible if they had: (i) symptomatic HF (NYHA class II–IV), (ii) LVEF ≤ 35%, (iii) (current or prior, not tolerated) use of an ACEi/ARB, (iv) (current or prior, not tolerated) use of a BB, (v) (current or prior, not tolerated) use of an MRA, (vi) elevated NPs (same levels as above), and (vii) daily dose of an ACEi/ARB equal to an enalapril equivalent of ≥ 20 mg.

As PARADIGM-HF run-in required only 10 mg daily, in the present study, a daily dose of an ACEi/ARB ≥ 10 mg of enalapril equivalent was also evaluated as potential alternative to the last criterion for PARADIGM-HF and ESC eligibility.

We analysed the study population with no missing data for the detailed variables required to assess eligibility. We compared baseline characteristics of the entire population vs. the population of patients with complete information on eligibility to evaluate any potential differences due to data not missing at random. Finally, we analysed the impact of the individual criteria on eligibility and the impact of all criteria when applied one after the other in a sequential manner.

Risk of outcomes in PARADIGM-HF vs. ESC-EORP-HFA HF-LT Registry

We calculated crude risk during the 1-year follow-up for HF hospitalization and all-cause mortality in the overall HFrEF cohort of the ESC-EORP-HFA HF-LT Registry, as well as in the subgroups, defined by the fulfilment or not of EMA/FDA label, ESC guidelines and PARADIGM-HF eligibility criteria for LCZ696 use. Outcome risk was compared vs. the enalapril arm of the PARADIGM-HF population (we did not use the LCZ696 arm since none in the registry were treated with LCZ696) in order to investigate differences in outcomes occurrence in trial vs. real-world setting.[7]

Statistical analysis

Design and statistical analyses were performed by EORP. For baseline characteristics as well as outcome variables, numerical data are presented as mean ± standard deviation or median [interquartile range] and categorical data are presented as numbers (percentages). All analyses were performed with SAS statistical software version 9.4 (SAS Institute, Inc., Cary, NC, USA).

Results

ESC-EORP-HFA HF-LT Registry HFrEF cohort: baseline characteristics according to eligibility and comparability with the PARADIGM-HF trial population

The baseline characteristics of the 5443 HFrEF outpatients of the ESC-EORP-HFA HF-LT registry are shown in *Table 1*. Mean age was 64 ± 13 years, 22% female, approximately half had a history of hypertension and one third had diabetes.

Patients in the registry were similar to those in PARADIGM-HF regarding age, gender distribution, body mass index, prevalence of diabetes, systolic blood pressure and LVEF (*Table 1*). Notably, ischaemic heart disease was the most common underlying cause of HF in both populations (48% in the registry vs. 60% in PARADIGM-HF). Fewer patients in the registry were in NYHA class II–IV compared with the PARADIGM-HF trial (84% vs. 95%). Indeed, 16% in the registry were in NYHA class I, which was an exclusion criterion for the PARADIGM-HF trial run-in but not for randomization, when 5% in PARADIGM-HF has improved to NYHA class I. Regarding HF pharmacotherapy, in the ESC-EORP-HFA HF-LT HFrEF outpatient population vs. PARADIGM-HF trial, patients were less likely to use an ACEi, more likely to use an MRA and a loop diuretic, whereas no differences existed in use of BBs and ARBs (*Table 1*).

ESC-EORP-HFA HF-LT Registry patient eligibility for LCZ696 based on EMA/FDA label, PARADIGM-HF and 2016 ESC guideline criteria

Among the 5443 outpatients with HFrEF, 84% where symptomatic (NYHA class II–IV) and thus met the regulatory criteria. Complete data for variables needed to define LCZ696 eligibility according to PARADIGM-HF and the 2016 ESC HF guidelines were available in 2197 (40%) and 2373 (44%) patients, respectively (*Tables 2* and *3*).

Eligible patients based on PARADIGM-HF and the ESC guidelines had similar characteristics (*Table 1*). Baseline characteristics

Table 1 Baseline characteristics in ESC-EORP-HFA HF-LT Registry outpatients with heart failure with reduced ejection fraction and in PARADIGM-HF patients

	ESC-EORP-HFA HF-LT Registry population					PARADIGM-HF population[b]
	Missing data (% of outpatient HFrEF cohort)	HFrEF overall	Complete information (PARADIGM-HF criteria)	Eligible according to 2016 ESC guidelines[a]	Eligible according to PARADIGM-HF run-in criteria	
Baseline, *n*		5443	2197 (40% of overall)	282 (12% of complete info on ESC guideline criteria)	616 (28% complete info on PARADIGM-HF criteria)	8399
Age (years)	0%	63.8 ± 12.6	63.4 ± 12.8	62.4 ± 12.4	65.0 ± 11.6	63.8 ± 11.4
Age ≤ 65 years	0%	53%	54%	56%	50%	–
BMI (kg/m^2)	0%	27.8 ± 4.9	27.8 ± 4.9	29.0 ± 4.9	28.4 ± 4.8	28.2 ± 5.5
Female sex	0%	22%	20%	17%	21%	22%
Diabetes	0%	32%	34%	40%	37%	35%
Chronic obstructive pulmonary disease	0%	15%	16%	17%	17%	13%
Hypertension	0%	56%	58%	66%	64%	71%
NYHA class	0%					
I		16%	14%	0%	0%	5%
II		55%	59%	70%	71%	70%
III		26%	25%	30%	27%	24%
IV		2%	2%	0%	2%	1%
Unknown		0%	0%	0%	0%	0%
LVEF	0%					
≤ 15%		5%	6%	6%	5%	29.5 ± 6.2
15–20%		13%	14%	16%	15%	
21–25%		18%	18%	24%	18%	
26–30%		28%	27%	30%	31%	
31–35%		24%	24%	24%	22%	
36–40%		12%	11%	0%	9%	
Primary aetiology	0%					
IHD		48%	47%	51%	46%	60%
Hypertension		4%	4%	4%	5%	–
DCM		35%	39%	36%	39%	
Valve disease		4%	4%	3%	4%	–
Tachycardia-related myopathy		1%	1%	0%	1%	–
Other		7%	6%	6%	5%	–
eGFR (mL/min/1.73 m^2)	11%					
≥ 60		56%	58%	64%	62%	70.0 ± 20.0
45–59		23%	22%	22%	24%	
30–44		15%	14%	12%	14%	
< 30		7%	6%	2%	0%	

Table 1 Continued

	ESC-EORP-HFA HF-LT Registry population					PARADIGM-HF population[b]
	Missing data (% of outpatient HFrEF cohort)	HFrEF overall	Complete information (PARADIGM-HF criteria)	Eligible according to 2016 ESC guidelines[a]	Eligible according to PARADIGM-HF run-in criteria	
Serum K^+	12%	4.5 ± 0.5	4.5 ± 0.5	4.5 ± 0.5	4.5 ± 0.5	4.5 ± 0.5
BNP (pg/mL)	88%	348 [128–862]	343 [128–862]	545 [290–935]	422 [236–836]	–
NT-proBNP (pg/mL)	68%	1608 [646–3939]	1614 [650–3982]	2181 [1073–3853]	2054 [1055–4534]	1631 (885–3154) for LCZ696 1594 [886–3305] for enalapril
SBP (mmHg)	0%	120.8 ± 19.8	120.7 ± 19.8	123.9 ± 21.3	126.2 ± 18.5	121 ± 15
Implantable cardioverter-defibrillator	0%	23%	24%	31%	22%	15%
Cardiac resynchronization therapy	0%	18%	19%	22%	21%	7%
Haemoglobin	16%	13.5 ± 1.8	13.7 ± 1.7	13.8 ± 1.6	13.8 ± 1.7	–
HbA_{1c}	72%	6.8 ± 1.5	6.7 ± 1.5	6.7 ± 1.4	6.7 ± 1.5	–
Non-CV drugs, *n*	38%	2.2 ± 1.6	2.3 ± 1.6	2.2 ± 1.7	2.2 ± 1.6	–
HF pharmacotherapy						
ACEi	0%	69%	70%	92%	81%	78%
ACEi according to PARADIGM-HF run-in[c]	32%	42%	44%	88%	73%	–
ARB	0%	21%	22%	10%	19%	23%
ARB according to PARADIGM-HF run-in[c]	79%	11%	10%	7%	16%	–
BB	0%	90%	91%	95%	97%	93%
MRA	0%	63%	65%	83%	68%	56%
Loop diuretics	17%	96%	97%	96%	96%	80%
Thiazide	17%	11%	10%	10%	13%	–

Continuous data presented as mean ± standard deviation or median [interquartile range], as appropriate. Categorical data presented as proportions.

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BB, beta-blocker; BMI, body mass index; BNP, B-type natriuretic peptide; CV, cardiovascular; DCM, dilated cardiomyopathy; eGFR, estimated glomerular filtration rate; EORP, EURObservational Research Programme; ESC, European Society of Cardiology; HbA_{1c}, glycated haemoglobin; HF, heart failure; HFA, Heart Failure Association; HF-LT, Heart Failure Long-Term; HFrEF, heart failure with reduced ejection fraction; IHD, ischaemic heart disease; K^+, potassium; LCZ696, sacubitril/valsartan; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; SBP, systolic blood pressure.

[a]Patients with (i) LVEF ≤ 35%, (ii) NYHA class II–IV, (iii) plasma BNP ≥ 150 pg/mL (or NT-proBNP ≥ 600 pg/mL) or a BNP ≥ 100 pg/mL (or NT-proBNP ≥ 400 pg/mL) and a hospitalization for HF within the last 12 months, (iv) current or prior treatment with an ACEi/ARB at minimum ESC guideline dose equivalent to enalapril 20 mg daily and BB and MRA (or contraindicated or not tolerating BB and/or MRA).

[b]Data adapted from McMurray *et al.*2

[c]Minimum daily dose equivalent to 10 mg of enalapril.

Table 2 The individual and sequential impact of each eligibility criterion according to PARADIGM-HF in ESC-EORP-HFA HF-LT Registry outpatient population with complete information for eligibility assessment

	ESC-EORP-HFA HF-LT Registry population with complete information on PARADIGM-HF criteria	
	Individually, *n* (%)	**Sequentially, *n* (cum. %)**
ESC-EORP-HFA HF-LT Registry HFrEF outpatient population with complete data on eligibility	2197 (100)	2197 (100)
Inclusion criteria		
1 Age ≥ 18 years	2197 (100)	2197 (100)
2 LVEF ≤ 40%	2197 (100)	2197 (100)
3 NYHA class II–IV	1881 (86)	1881 (86)
4 Plasma BNP ≥ 150 pg/mL (or NT-proBNP ≥ 600 pg/mL) or a BNP ≥ 100 pg/mL (or NT-proBNP ≥ 400 pg/mL) and a hospitalization for HF within last 12 months	1732 (79)	1542 (70)
Exclusion criteria		
1 eGFR < 30 mL/min/1.73 m^2	2066 (94)	1427 (65)
2 Patients with acute HF	2197 (100)	1427 (65)
3 Patients with angioedema or history of angioedema	2193 (100)	1425 (65)
4 Patients with a current or recent (within last 3 months) CV medical condition (MI, stroke, TIA) or surgical (including heart surgery, carotid, vascular surgery) and interventional procedure (PCI or carotid angioplasty)	1970 (90)	1247 (57)
5 Patients with hyperkalaemia (serum K^+ > 5.4 mmol/L)	2110 (96)	1200 (55)
6 Symptomatic hypotension and/or a SBP < 95 mmHg	2039 (93)	1109 (50)
Pharmacotherapy		
1 Current or prior treatment with an ACEi/ARB + BB	1936 (88)	985 (45)
a Current or prior treatment with an ACEi/ARB + BB + MRA	1407 (64)	751 (34)
2 Current or prior treatment with minimum PARADIGM-HF dose of an ACEi/ARB equivalent to enalapril 10 mg/day + BB	1236 (56)	616 (28)
a Current or prior treatment with minimum PARADIGM-HF dose of an ACEi/ARB equivalent to enalapril 10 mg/day + BB + MRA	874 (40)	461 (21)
3 Current or prior treatment with a stable dose of an ACEi/ARB equivalent to enalapril 20 mg/day + BB	565 (26)	259 (12)
a Current or prior treatment with a stable dose of an ACEi/ARB equivalent to enalapril 20 mg/day + BB + MRA	388 (18)	189 (9)

Adult HFrEF outpatients are used as denominator for all percentage calculation.
ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BB, beta-blocker; BNP, B-type natriuretic peptide; CV, cardiovascular; eGFR, estimated glomerular filtration rate; EORP, EURObservational Research Programme; ESC, European Society of Cardiology; HF, heart failure; HFA, Heart Failure Association; HF-LT, Heart Failure Long-Term; HFrEF, heart failure with reduced ejection fraction; K^+, potassium; LVEF, left ventricular ejection fraction; MI, myocardial infarction; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; SBP, systolic blood pressure; TIA, transient ischaemic attack.

were also similar between patients who had no missing data for the variables required to assess eligibility and the entire population (*Table 1*).

Eligibility based on the EMA/FDA label is shown in *Figure 1*. The individual and sequential impact of each eligibility criterion according to PARADIGM-HF is shown in *Table 2* and *Figure 1*. Of HFrEF outpatients with complete data to assess eligibility, the vast majority met criteria for NYHA class II–IV and NPs, estimated glomerular filtration rate, potassium and systolic blood pressure levels. Regarding HF pharmacotherapy, 1936 (88%) of HFrEF outpatients were receiving (or had received when the outpatient visit began) treatment with an ACEi/ARB and a BB. When the criterion for a minimum daily dose of ACEi/ARB equivalent to enalapril 10 mg daily and a BB was included, 1236 (56%) patients met this criterion, whereas when a minimum daily dose of ACEi/ARB equivalent to enalapril 20 mg was considered, 565 (26%) patients met the criterion. Finally, when all the PARADIGM-HF criteria for eligibility were simultaneously considered, only 259 (12%) patients were candidates for LCZ696 if a minimum dose of ACEi/ARB at least equivalent to enalapril 20 mg daily was considered as a requirement and 616 (28%) if a dose at least equal to 10 mg daily was required.

Table 3 **The individual and sequential impact of each eligibility criterion according to the 2016 ESC guideline criteria in the ESC-EORP-HFA HF-LT Registry population with complete information for eligibility assessment**

	ESC-EORP-HFA HF-LT Registry population with complete information on 2016 ESC guideline criteria	
	Individually, *n* (%)	**Sequentially, *n* (cum. %)**
ESC-EORP-HFA HF-LT Registry HFrEF outpatient population	2373	2373
ESC guideline inclusion criteria		
1 NYHA class II–IV	2035 (86)	2035 (86)
2 LVEF ≤ 35%	1827 (77)	1827 (77)
3 Current or prior treatment with an ACEi/ARB	1897 (80)	1703 (72)
4 Current or prior treatment with an ACEi/ARB + BB (or contraindicated or not tolerating BB)	1865 (79)	1674 (71)
5 Current or prior treatment with an ACEi/ARB + BB + MRA (or contraindicated or not tolerating BB and/or MRA)	1539 (65)	1392 (59)
6 Plasma BNP ≥ 150 pg/mL (or NT-proBNP ≥ 600 pg/mL) or a BNP ≥ 100 pg/mL (or NT-proBNP ≥ 400 pg/mL) and a hospitalization for HF within last 12 months	1667 (70)	1150 (48)
7 Current or prior treatment with an ACEi/ARB at minimum PARADIGM-HF dose equivalent to enalapril 10 mg daily + BB + MRA (or contraindicated or not tolerating BB and/or MRA)	942 (40)	669 (28)
a Current treatment with an ACEi/ARB not reaching minimum PARADIGM-HF dose equivalent to enalapril 10 mg daily but who are in up-titration + BB + MRA (or contraindicated or not tolerating BB and/or MRA)	152 (6)	139 (6)
8 Current or prior treatment with an ACEi/ARB at minimum ESC guideline dose equivalent to enalapril 20 mg daily + BB + MRA (or contraindicated or not tolerating BB and/or MRA)	419 (18)	282 (12)
a Current treatment with an ACEi/ARB not reaching minimum ESC guideline dose equivalent to enalapril 20 mg daily but who are in up-titration + BB + MRA (or contraindicated or not tolerating BB and/or MRA)	332 (14)	302 (13)

Adult HFrEF outpatients are used as denominator for all percentage calculation.
ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BB, beta-blocker; BNP, B-type natriuretic peptide; EORP, EURObservational Research Programme; ESC, European Society of Cardiology; HF, heart failure; HFA, Heart Failure Association; HF-LT, Heart Failure Long-Term; HFrEF, heart failure with reduced ejection fraction; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association.

The respective impact of eligibility criteria according to the ESC guidelines is shown in *Table 3* and *Figure 1* . Of 2373 HFrEF patients with complete data to assess ESC criteria, a vast majority again met clinical criteria, somewhat fewer met concomitant therapy criteria, and only a small minority met the ACEi/ARB dose criteria. Indeed, only 419 (18%) patients were on current treatment or had been previously treated with ACEi/ARB at a daily dosage ≥ 20 mg enalapril, whereas in 332 (14%) up-titration was still ongoing. When a minimum daily dose of ACEi/ARB equal to enalapril 10 mg was considered, 942 (40%) patients met this criterion, with additional 152 (6%) patients in the up-titration phase. Finally, when all the ESC guideline criteria for eligibility were simultaneously considered, only 282 (12%, same as for PARADIGM-HF eligibility) patients were candidates for LCZ696 if a dose of ACEi/ARB at least equivalent to enalapril 20 mg daily was considered as a requirement and 669 (28%, same as for PARADIGM-HF eligibility) if a dose of ACEi/ARB at least equal to enalapril 10 mg daily was required.

Risk of outcomes in PARADIGM-HF vs. ESC-EORP-HFA HF-LT Registry

Among the 5443 HFrEF outpatients of the registry, 139 (2.6%) were lost to follow-up leaving 5304 (97%) patients for outcomes analysis.

In the enalapril (control) arm of the PARADIGM-HF trial,[2,7] the 1-year HF hospitalization rate was 12%. HF hospitalization rates were higher in the overall outpatient HFrEF cohort and in all the outpatient sub-categories of the ESC-EORP-HFA HF-LT Registry (*Figure 2A*). The corresponding risk was 13%, 15%, 17%, 15%, 12%, and 14% for HFrEF outpatients overall, EMA/FDA label eligible, ESC eligible and ineligible, and PARADIGM-HF eligible and ineligible, respectively. The 1-year all-cause mortality rate in the enalapril arm of PARADIGM-HF was 7.7%.[2] The rate of death in the overall HFrEF cohort was 8.8% but differed considerably across outpatient sub-categories of the ESC-EORP-HFA HF-LT Registry (*Figure 2B*). Namely, all-cause mortality rates were 8.7%,

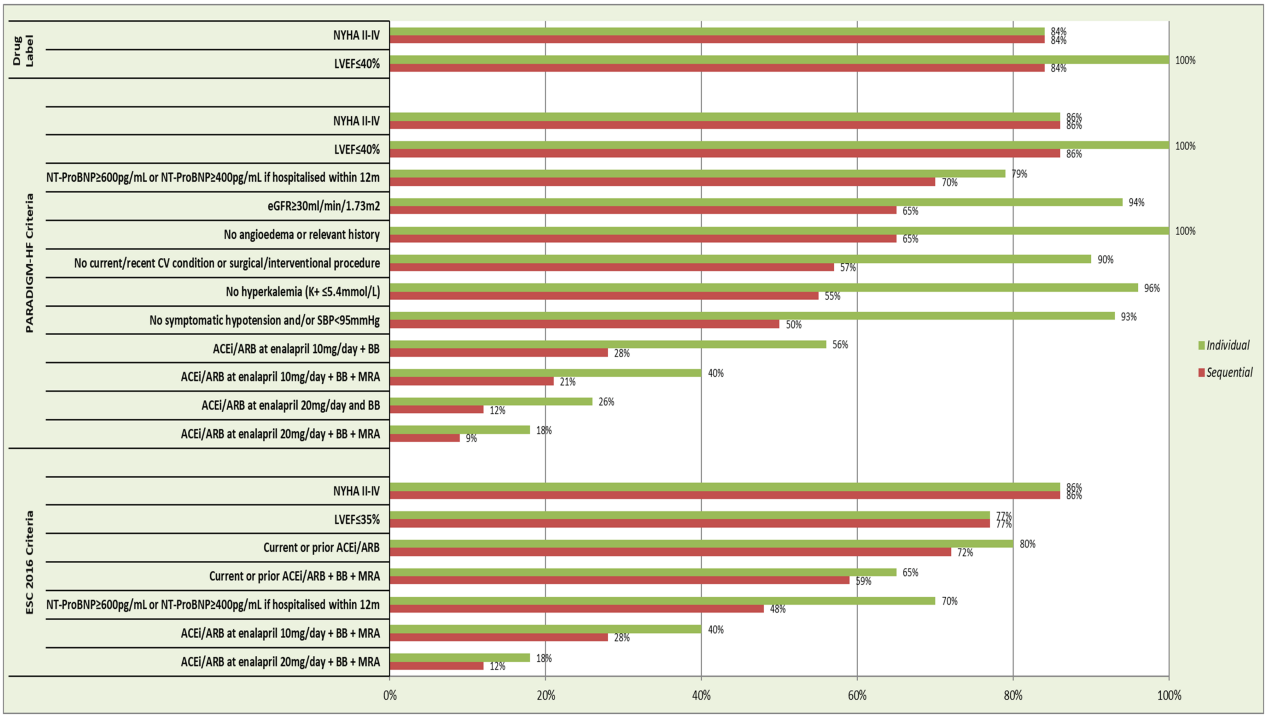

Figure 1 Fulfilment of (*A*) drug label, (*B*) 2016 ESC guidelines on heart failure and (*C*) PARADIGM-HF criteria for sacubitril/valsartan (LCZ696) eligibility among ESC-EORP-HFA HF-LT Registry heart failure with reduced ejection fraction outpatients: individual and sequential impact of criteria. Proportions of 28% and 12% for both PARADIGM-HF and ESC guidelines represent the main findings based on requiring 10 or 20 mg enalapril daily, respectively. ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BB, beta-blocker; CV, cardiovascular; 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; SBP, systolic blood pressure.

6.5%, 9.0%, 5.3%, and 8.7% in EMA/FDA label eligible, ESC guideline eligible and ineligible, and PARADIGM-HF eligible and ineligible, respectively. Among registry patients considered ineligible for LCZ696 based on PARADIGM-HF criteria, the ones considered ineligible due to low levels of NPs had considerably lower HF hospitalization (4.9% vs. 18%) and all-cause mortality rates (1.8% vs. 12%) compared with patients ineligible due to all other criteria (*Figure 3*).

Discussion

Real-world outpatients with HFrEF enrolled in the large, multi-site ESC-EORP-HFA HF-LT Registry were overall comparable to those randomized in the PARADIGM-HF trial. In the registry, 84% met the EMA/FDA drug label criteria. Most criteria for LCZ696 eligibility set by PARADIGM-HF and the ESC guidelines were individually met. However, when all criteria were considered simultaneously, only 12% of HFrEF outpatients were eligible, based on either the PARADIGM-HF or ESC criteria. Notably, the most difficult criterion was the use of ACEi/ARB at a minimum daily dose equivalent to 20 mg of enalapril (required for randomization in PARADIGM-HF). If the criterion of 10 mg enalapril daily dose (required for run-in in PARADIGM-HF) was alternatively considered, then 28% of patients were eligible by both PARADIGM-HF and ESC criteria.

Heart failure trials are selective, and patients are generally younger and have better outcomes compared to real-world patients.[8] However, the HFrEF outpatient cohort of the ESC-EORP-HFA HF-LT Registry was comparable to the PARADIGM-HF population. This suggests that the PARADIGM-HF population was relatively representative of real-world HFrEF patients, although the ESC-EORP-HFA HF-LT Registry is more selective than many real-world registries and cohorts because it is voluntary and investigators tend to have a greater research interest, even though centres are selected to represent a broad range of HF care.[5,6]

The exact proportion of real-world HFrEF outpatients who are eligible for LCZ696 based on the PARADIGM-HF and ESC guideline criteria remains debatable, as only 4 out of 10 patients of the ESC-EORP-HFA HF-LT Registry had complete entries for the detailed variables required for defining eligibility (although most other cohorts miss many of the criteria completely, e.g. history of angioedema). However, the baseline characteristics of patients with complete entries were similar to those of the entire ESC-EORP-HFA HF-LT Registry HFrEF population, suggesting that data were missing reasonably at random and thus that our results

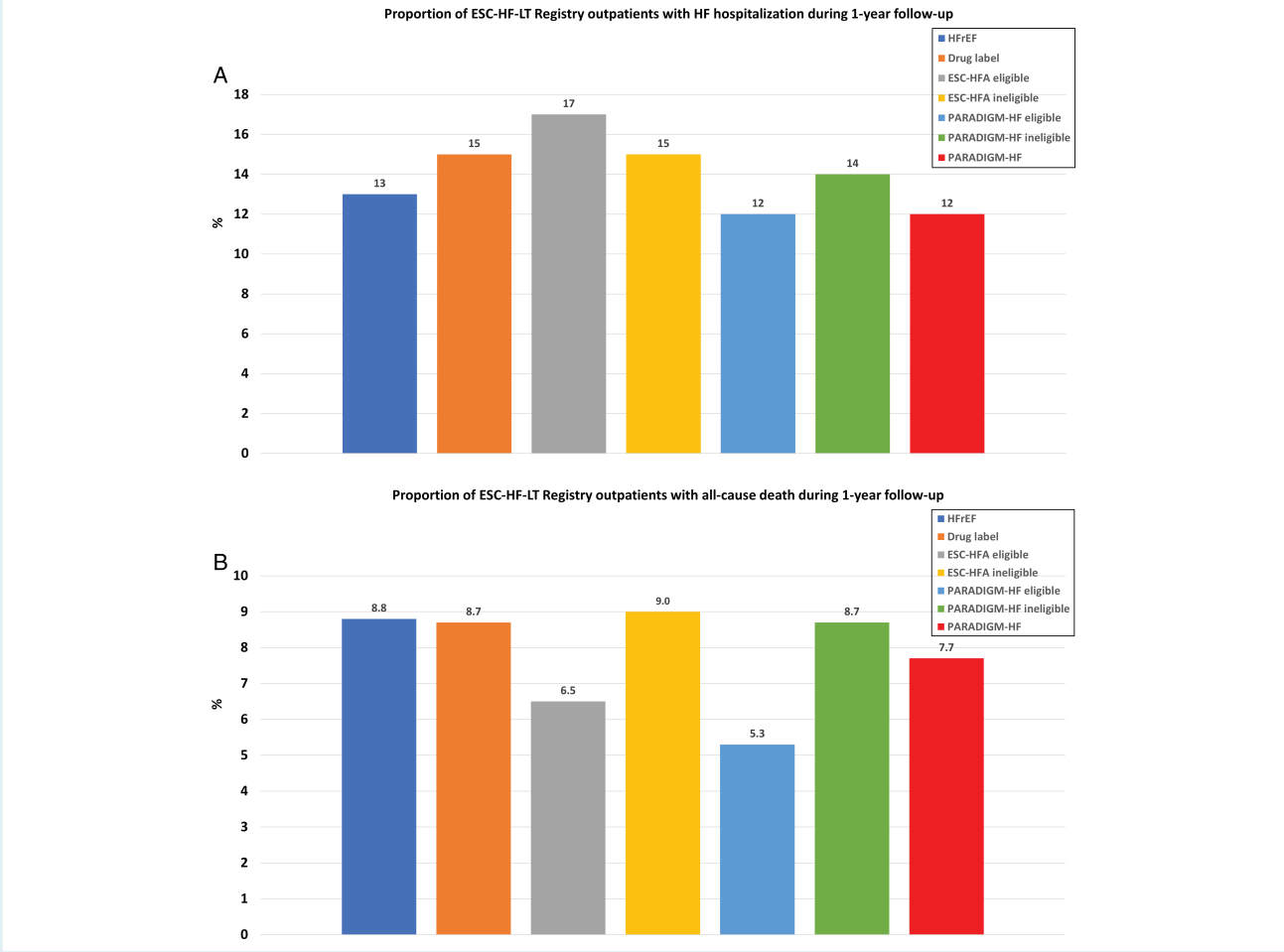

Figure 2 One-year heart failure hospitalization rates (*A*) and all-cause mortality rates (*B*) among different groups of heart failure with reduced ejection fraction (HFrEF) outpatients enrolled in the ESC-EORP-HFA HF-LT Registry and in patients enrolled in PARADIGM-HF.

may be representative of the entire registry population. Among HFrEF patients in the registry, only 12% were eligible for LCZ696 when the ESC guideline criteria were applied. This percentage was identical when the PARADIGM-HF criteria were used. When the ACEi/ARB dose criterion (20 mg daily), which was most rare to be met, was set to half dose, the proportion of patients eligible significantly increased to 28% with either the PARADIGM-HF or the ESC guideline criteria. Low rates of eligibility have been previously reported in smaller studies with fewer and less generalizable centres: the proportion of patients considered suitable for LCZ696 according to the FDA drug label ranged between 50% and 71% of patients, whereas the respective proportion when the PARADIGM-HF criteria (20 mg daily ACEi/ARB dose) were applied decreased to 21–39%.[1,9–11] However, if the 10 mg ACEi/ARB dose criterion was alternatively used, rates of eligibility again significantly rose.[9–11] The only exception seems to come from the Swedish Heart Failure Registry[12]; symptomatic (NYHA class II–IV) HFrEF patients were prescribed enalapril ≥ 10 mg or equivalent in 74.4% and enalapril ≥ 20 mg or equivalent in 50.0% of cases. When patients with complete data to assess eligibility were analysed, 75.5% of patients prescribed enalapril ≥ 10 mg or equivalent and 77.4% of patients prescribed enalapril ≥ 20 mg or equivalent fulfilled all criteria for LCZ696.[12] This underscores the potential for better integration of evidence-based treatment in HFrEF and it has been shown that enrolment in the Swedish Heart Failure Registry is associated with considerably improved mortality, and that this improvement is precisely explained by better use of HF therapy.[13]

Regulatory authorities (both EMA and FDA) do not consider NP levels for LCZ696 eligibility. Several criteria in PARADIGM-HF and other trials are simply for enrichment and do not necessarily suggest lack of efficacy outside these criteria or lack of generalizability. However, for LCZ696, NP levels were used in the trial, in guidelines and by some countries and payers, so they are still relevant for stakeholders trying to interpret real-world implementation. Furthermore, and considering the big difference that we showed in outcome rates among patients fulfilling the NP vs. all other exclusion criteria, it is conceivable that the risk/benefit ratio is different in patients not having sufficiently high NP criteria, and even probable that cost-effectiveness is quantitatively different.[11] NPs do

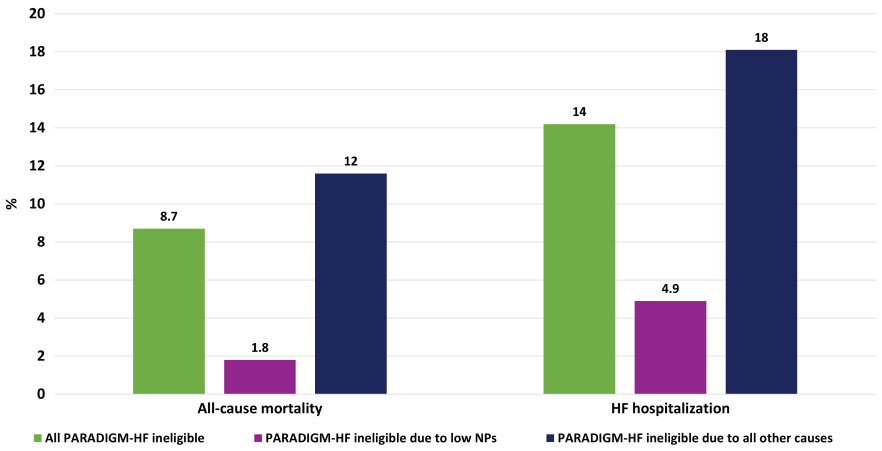

Figure 3 One-year heart failure (HF) hospitalization and all-cause mortality rates of ESC-EORP-HFA HF-LT Registry outpatients ineligible for PARADIGM-HF due to low natriuretic peptides (NPs) vs. other criteria.

not appear to be routinely measured in real-world HFrEF outpatients once the diagnosis has been established, as demonstrated by the high number of missing entries in the present study and other registries.[14] Eight out of 10 patients with NP entries in the registry fulfilled the guideline (and PARADIGM-HF) criteria, and expanding the indication of LCZ696 to patients with lower NP levels, as permitted by the EMA/FDA label, may not be cost-effective,[11] even though the efficacy of LCZ696 appears to be potentially and counterintuitively greater in NYHA class I–II vs. NYHA class III–IV patients, the NYHA class sub-groups representing the only statistically significant interaction in PARADIGM-HF.[2]

The ESC guideline criterion, which was most rare to be met, was the requirement of an ACEi/ARB use at a minimum daily dose equal to enalapril 20 mg daily. Indeed, only 18% of patients were on current or prior treatment with a BB, an MRA and an ACEi/ARB at this dose. When minimum daily dose of ACEi/ARB equal to enalapril 10 mg was considered, 40% of patients fulfilled it. When these two criteria were considered on top of all the other eligibility criteria, the proportion of HFrEF patients suitable for LCZ696 was 12% and 28%, respectively, similar to that observed also in smaller populations.[9,11] The respective rates when all PARADIGM-HF criteria were assessed were identical. This may raise concerns regarding the representativeness and generalizability of the PARADIGM-HF trial. The run-in period (which was not randomized) was designed to minimize patient drop-out but may have limited eligibility based on the trial criteria and the subsequent guideline recommendations.

Importantly, ACEi/ARB are not always tolerated and rarely used at their maximum recommended doses,[15] thus hindering the guideline-recommended introduction of LCZ696. Multiple retrospective analyses of the PARADIGM-HF trial have demonstrated associations between LCZ696 use and favourable secondary outcomes, such as renal function preservation in patients with HF and diabetes and reduced risk of hyperkalaemia during treatment with MRAs.[16,17] These findings, combined with the results of a sub-analysis that suggests the superiority of LCZ696 over enalapril at lower than their target doses,[18] have sprouted significant controversy regarding the optimal timing of LCZ696 initiation. Some experts have advocated that LCZ696 should be initiated in all patients with HFrEF who can tolerate an ACEi/ARB, irrespective of the dose.[19] The need for presence of symptoms as a prerequisite for drug initiation has also been downplayed on the grounds that one of the most significant effects of LCZ696 is the decreased risk of sudden cardiac death,[19] which often affects asymptomatic or oligosymptomatic HF patients. Although the efficacy of LCZ696 was the same regardless of dose of LCZ696 vs. enalapril achieved, the 20 mg dose was, nevertheless, required for randomization in PARADIGM-HF.

In PARADIGM-HF there was considerable and similar drop-out in both parts of the run-in, but the run-in began with enalapril and was not randomized. Thus, those eliminated during the enalapril run-in phase may have been frailer or less suitable trial subjects than those eliminated during LCZ696 run-in, who had already demonstrated tolerance to enalapril 20 mg daily. Furthermore, there was a greater risk of symptomatic hypotension in the LCZ696 arm than in the enalapril arm.[2] Although LCZ696 dose titration to the target dose seemed to be feasible in the majority (> 80%) of patients with systolic blood pressure > 100 mmHg enrolled in another randomized study,[20] more than 90% of the study participants had tolerated an ACEi/ARB prior to screening, whereas an open-label 5-day run-in phase of LCZ696 50 mg twice daily was also included. Another randomized trial assessing the feasibility and safety of pre-discharge vs. post-discharge initiation of LCZ696 in HFrEF patients hospitalized for HF decompensation was recently presented.[21] Importantly, 24% of the study patients were ACEi/ARB naïve. Although no significant differences were reported between the two study groups during the 10-week follow-up period regarding the incidence of hyperkalaemia, hypotension, heart failure, dizziness or renal impairment, a trend towards higher rates of tolerating LCZ696 at high doses of 100 or 200 mg twice daily was noted with post-discharge vs. pre-discharge initiation

of the medication (68 vs. 62.5%, $P = 0.07$). This could raise concern as to whether pressure for earlier or wider administration of the drug could ultimately result in sub-optimal dosing regimens. However, concerns that LCZ696 may be unsafe in hospitalized or ACEi/ARB naïve patients were dispelled by the recently published PIONEER-HF trial,[22] and it is possible that guideline indications and reimbursement for LCZ696 will be soon expanded. Although LCZ696 led to significantly greater decrease in NPs post-discharge and in significant decrease in the incidence of the exploratory composite endpoint (including death, rehospitalization for HF, implantation of a left ventricular assist device, and inclusion on the list of patients eligible for heart transplantation) compared with enalapril, PARADIGM-HF remains the only LCZ696 outcomes trial and there may be delays before PIONEER-HF affects guidelines, reimbursement and practice.

Debate regarding extrapolation of trial results continues. As history has shown, what is logically hypothesized is not always correct; for example, all traditional HF medications have been proven ineffective in patients with HFpEF,[23] whereas the use of BB or digoxin in patients with HF and/or atrial fibrillation is also currently challenged.[24,25] Moreover, potential safety issues related to long-term LCZ696 use should also be highlighted.[26] Finally, many argue that data pertaining to the post-market, non-trial setting use of LCZ696 should also be examined, even though this would be non-randomized data, prior to considering use of the drug in a wider population. This piece of information may be greatly valued as the observed proportion of HF patients eligible for LCZ696 is very close to the theoretical estimate of 10% among all HF patients.[27] We should also look into contemporary registry data to evaluate penetration of LCZ696 into clinical practice, with particular emphasis on eligibility criteria (if information available), safety and drug discontinuation. We do not make an argument regarding who should receive LCZ696, or whether clinicians should follow the label, the trial, or guidelines, or what are appropriate payer restrictions. The aim of our study was completely different: LCZ696 is beneficial to patients but has been variably implemented worldwide and poorly implemented in certain areas. We hypothesized that the trial criteria and guidelines may explain the extent of implementation, and therefore the eligibility numbers in our analyses may be helpful in understanding LCZ696 implementation and HF quality of care more generally. However, poor implementation may also be due to complex reimbursement schemes or other administrative hurdles. A major purpose of a quality registry is to assess use of and potential reasons for poor use of evidence-based interventions. There is indeed evidence that HF registries can improve survival by improving use of treatment,[13] and there are studies assessing in detail reasons for non-use of MRAs and cardiac resynchronization therapy.[28,29] Actual implementation of ARNI will be assessed in the current ongoing ESC HF III Registry. The present analysis is intended to assess but by no means justify or reinforce potential reasons for LCZ696 underuse.

The risk of outcomes in the HFrEF population enrolled in the ESC-EORP-HFA HF-LT Registry was heterogeneous among groups. Risk of HF hospitalization in the registry was distinctly higher than in the enalapril arm of the PARADIGM-HF trial. This lower risk in PARADIGM-HF could potentially be explained by the stricter selection that inevitably occurs in trials, the higher risk profile (i.e. higher prevalence of end-stage renal disease and more use of loop diuretics) and the less regular follow-up in the registry vs. the PARADIGM-HF and other trial populations.[30] However, this consideration is not supported by the fact that the sub-populations of HFrEF patients enrolled in the ESC-EORP-HFA HF-LT Registry that were eligible for LCZ696 both by PARADIGM-HF and ESC guideline criteria had better outcome in terms of survival compared to patients in the enalapril arm of PARADIGM-HF, although they had similar baseline characteristics. This could be possibly explained either by the effect of unrecognized confounders or, although it is far-fetched, by the under-reporting of adverse events (such as hospitalizations), which has been recognized as a significant drawback of clinical trials.[31]

The risk of outcomes in the HFrEF outpatient cohort of the ESC-EORP-HFA HF-LT Registry was also higher than in other registry populations.[32] This may be explained by the different risk of outcomes across the countries participating in the registry (i.e. risk of all-cause mortality ranged from 6.9% in Southern Europe to 15.6% in North Africa), and thus by geographical differences in HF severity, pharmacotherapy use and clinical practice.[6] Since baseline characteristics were similar to PARADIGM-HF, it may be expected that if LCZ696 were administered to eligible patients from countries and centres such as those enrolled in the ESC-EORP-HFA HF-LT Registry, the benefits may be similar to those observed in the trial.

Limitations

Our study included only centres which had elected to participate in the ESC-EORP-HFA HF-LT Registry, and thus results may not be generalizable to those seen in different units or centres. Furthermore, although baseline characteristics of patients with no missing data for relevant variables needed for our analysis did not differ from those of the entire cohort, non-randomness in missing data, leading to bias, cannot be excluded. Although the ESC-EORP-HFA HF-LT Registry is generalizable, it had low representation of women, as is common also in clinical trials.

Conclusion

Real-world HFrEF patients enrolled in the ESC-EORP-HFA HF-LT Registry had similar demographic and clinical characteristics, but different use of HF treatment and different outcomes compared with those randomized in the PARADIGM-HF trial. Of these HFrEF patients, 84% met regulatory criteria for LCZ696, whereas only 12% were eligible for LCZ696 if 20 mg enalapril equivalent was required (28% if only 10 mg enalapril equivalent was required), based on either the PARADIGM-HF or the ESC guideline criteria. The most difficult criterion was the use of ACEi/ARB at a daily dose equivalent to $\geq$ 20 mg of enalapril. Our findings highlight the need for better strategies to integrate evidence-based treatments in a real-world HF setting.

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Appendix

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