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RESEARCH ARTICLE

Heart failure in Europe: Guideline-directed medical therapy use and decision making in chronic and acute, pre-existing and de novo, heart failure with reduced, mildly reduced, and preserved ejection fraction – the ESC EORP Heart Failure III Registry

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†ESC EORP HF III National Leaders and Investigators are listed in Appendices.

[Correction added on 30 September 2024, after first online publication: The copyright line was changed.]

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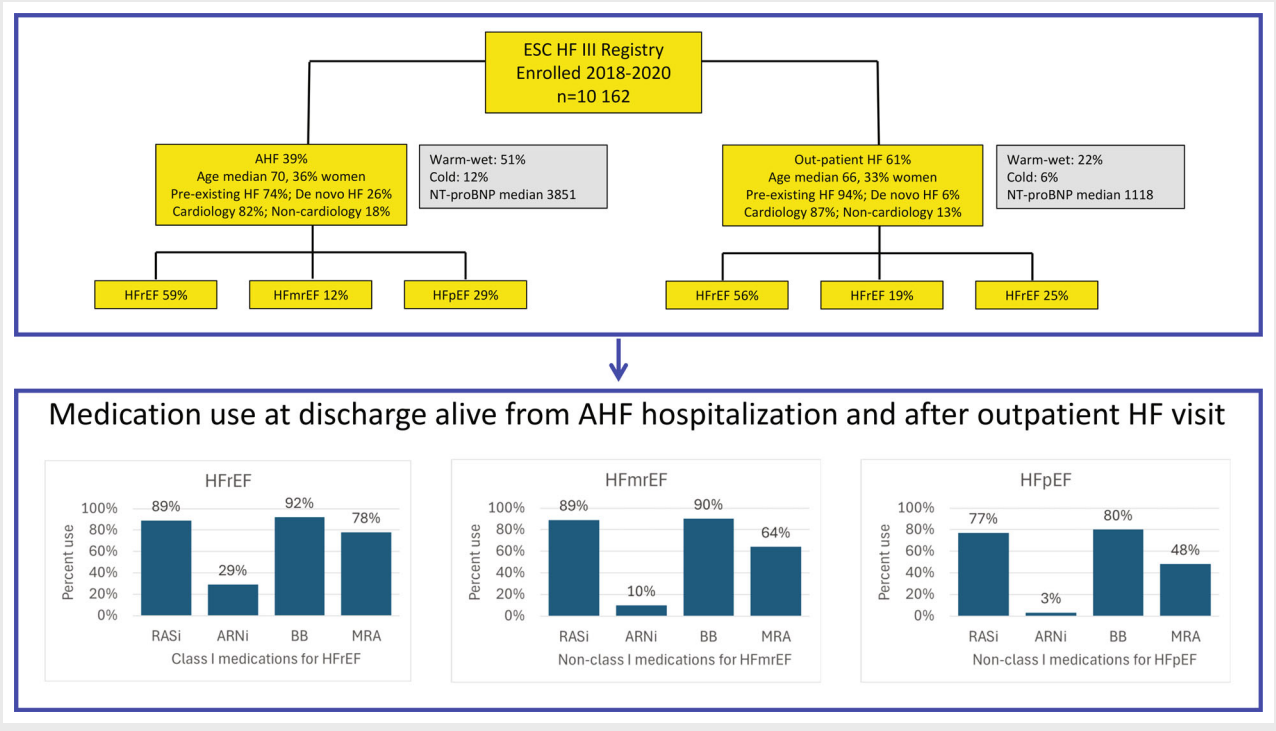
Aims We analysed baseline characteristics and guideline-directed medical therapy (GDMT) use and decisions in the European Society of Cardiology (ESC) Heart Failure (HF) III Registry.

Methods and results Between 1 November 2018 and 31 December 2020, 10 162 patients with acute HF (AHF, 39%, age 70 [62–79], 36% women) or outpatient visit for HF (61%, age 66 [58–75], 33% women), with HF with reduced (HFrEF, 57%), mildly reduced (HFmrEF, 17%) or preserved (HFpEF, 26%) ejection fraction were enrolled from 220 centres in 41 European or ESC-affiliated countries. With AHF, 97% were hospitalized, 2.2% received intravenous treatment in the emergency department, and 0.9% received intravenous treatment in an outpatient clinic. AHF was seen by most by a general cardiologist (51%) and outpatient HF most by a HF specialist (48%). A majority had been hospitalized for HF before, but 26% of AHF and 6.1% of outpatient HF had de novo HF. Baseline use, initiation and discontinuation of GDMT varied according to AHF versus outpatient HF, de novo versus pre-existing HF, and by ejection fraction. After the AHF event or outpatient HF visit, use of any renin–angiotensin system inhibitor, angiotensin receptor–neprilysin inhibitor, beta-blocker, mineralocorticoid receptor antagonist and loop diuretics was 89%, 29%, 92%, 78%, and 85% in HFrEF; 89%, 9.7%, 90%, 64%, and 81% in HFmrEF; and 77%, 3.1%, 80%, 48%, and 80% in HFpEF.

Conclusion Use and initiation of GDMT was high in cardiology centres in Europe, compared to previous reports from cohorts and registries including more primary care and general medicine and regions more local or outside of Europe and ESC-affiliated countries.

Graphical Abstract



The ESC Heart Failure III Registry enrolled 10 162 patients between 2018 and 2020, with acute heart failure (HF) and in the outpatient setting, with pre-existing and de novo HF, in cardiology and non-cardiology settings, including patients with HF with reduced (HFrEF), mildly reduced (HFmrEF) and preserved ejection fraction (HFpEF). The figures show patient distribution and medical treatment after discharge from hospital or after the outpatient visit. ARNi, angiotensin receptor–neprilysin inhibitor; BB, beta-blocker; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-B-type natriuretic peptide; RASi, renin–angiotensin system inhibitor.

Keywords Heart failure • Ejection fraction • Registry • Guideline-directed medical therapy • Implementation • Quality of care

Introduction

Heart failure (HF) affects more than 64 million people worldwide and is increasing in prevalence,[1–3] especially HF with preserved ejection fraction (HFpEF).[4] Mortality and risk of HF hospitalization remain high and quality of life and functional capacity are poor.[1,2,5]

Since the first heart transplantation in 1967, there has been remarkable development of medical therapy beyond diuretics and digitalis. Current class I guideline-directed medical therapy (GDMT) in the form of the four foundational classes—angiotensin-converting enzyme inhibitors (ACEi), angiotensin receptor blockers (ARB), angiotensin receptor–neprilysin inhibitors (ARNi), beta-blockers, mineralocorticoid receptor antagonists (MRA) and sodium–glucose cotransporter 2/1 inhibitors (SGLT2/1i)—antagonizes or modulates neurohormonal activation and additionally has favourable effects on the heart, kidney, vasculature and on inflammation and metabolism. The clinical effects extend to important improvements in quality of life and reductions in the risk of hospitalization for HF, and cardiovascular (CV) or all-cause mortality. While for many decades GDMT was available only for patients with HF with reduced ejection fraction (HFrEF), SGLT2/1i are now recommended across the ejection fraction (EF) spectrum, and the remaining three foundational drug classes may also be considered in HF with mildly reduced ejection fraction (HFmrEF).[6,7]

Despite these advances, outcomes over time have been suggested both to be improving and to be worsening.[8–10] The major reason is poor implementation of existing therapy.[11,12] Implementation science analyses have described quality indicators and reasons for poor initiation, up-titration, adherence, and persistence.[13–19] However, there have been no comprehensive studies of therapeutic decision making (i.e. changes in medical therapy) according to acute and outpatient HF care, chronic and de novo HF, and across the different EF categories. The rationale and design of the European Society of Cardiology (ESC) HF III Registry have been described.[20] Here we present the first co-primary analysis from the HF III Registry, providing a comprehensive analysis of contemporary HF characteristics and GDMT decisions.

Methods

Rationale and design

The aim is to provide a comprehensive data set for both discovery and implementation science.[21] Extensive baseline data including medical history, clinical characteristics, biomarkers and laboratory tests, imaging, and therapy are collected, as well as the course of and diagnostic and therapeutic decisions during the baseline AHF event and outpatient HF visit, and changes in therapy and outcomes over 1 year of follow-up. This allows further discovery of clinical and biological characteristics of patients with HF, enabling development of novel interventions, as well as implementation science, characterizing treatment decisions and implementation of GDMT in various settings and over time.

Oversight

The HF III Registry is sponsored by the ESC EURObservational Research Programme (EORP; https://www.escardio.org/Research/Registries-&-surveys/Observational-research-programme). The HF III Chairperson wrote the protocol with input from the EORP Oversight Committee (*Appendix 1*) and from the HF III Executive Committee (*Appendix 2*). National coordinators (the Steering Committee, *Appendix 3*) coordinated national activities and liaised with the Chairman, the sponsor team at EORP, and local investigators (*Appendix 4*).

Setting

The HF III Registry enrolled patients with HF in European, Mediterranean and some non-European countries. The registry complies with the 1975 Declaration of Helsinki; the locally appointed ethics committees approved the research protocol, and informed consent was obtained from all patients. The target enrolment was 10 000 patients. Detailed data elements and time points have been described.[21] Data were entered manually by investigators and/or coordinators into a registry specific electronic case report form, managed by EORP. Data were validated by EORP and out-of-range, missing or incomplete data were queried by EORP to local sites.

Access to data and data availability

Direct access to the HF III Registry dataset is limited to the EORP HF III Data Management and Statistical Analysis teams. Country-specific datasets may be provided to the national cardiology societies upon request to EORP.

Statistical analysis

Data are descriptive and presented with percentage and median (interquartile range). Comparisons between groups were performed

Table 1 Enrolment and clinical care setting by acute heart failure versus outpatient heart failure

Variable	AHF ($n = 3913$, 39%)	Outpatient HF ($n = 6217$, 61%)	Missing data	*p*-value
EF category			1.1%	<0.001
HFrEF, EF ≤40%	58%	56%		
HFmrEF, EF 41–49%	12%	19%		
HFpEF, EF ≥50%	29%	25%		
Type of visit			2.4%	NA
Outpatient		100%		
Of acute, % hospitalized	97%			
Of acute, % emergency department i.v. therapy	2.2%			
Of acute, % outpatient clinic i.v. therapy	0.9%			
Specialty of the enrolling physician			0.1%	<0.001
Cardiology	82%	87%		
HF specialist	24%	48%		
Other cardiology specialist	6.3%	3.0%		
General cardiologist	51%	36%		
Non-cardiology	18%	13%		
Internal medicine specialist	8.2%	6.6%		
General practitioner	2.6%	3.5%		
Other	7.3%	2.8%		
HF history			0.7%	<0.001
Yes, without previous hospitalization	18%	30%		
Yes, with previous hospitalization	57%	64%		
De novo HF	26%	6.1%		

AHF, acute heart failure; EF, ejection fraction; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; i.v., intravenous.
EF is from most recent before visit; if not available then at presentation this visit; if not available then at discharge (AHF only).

using a χ^2-test for categorical variables and a Kruskal–Wallis test for continuous variables. All analyses were performed using SAS statistical software version 9.4 (SAS Institute Inc, Cary, NC, USA) and R version 4.3.0.

Results

Patient enrolment and clinical setting according to acute heart failure versus outpatient heart failure and ejection fraction category

Between 1 November 2018 and 31 December 2020, 10 162 patients were enrolled from 220 centres in 41 countries. *Table 1* shows the clinical setting of enrolment for AHF versus outpatient HF, with 39% as AHF and 61% as outpatient. Among AHF, 97% were hospitalized, 2.2% received intravenous treatment in the emergency department, and 0.9% received intravenous treatment in the outpatient clinic or infusion centre. In the outpatient setting, most patients were cared for by a HF specialist, whereas in the AHF setting, by a general cardiologist. A majority had been hospitalized for HF before, but fully 26% of AHF had de novo HF and 6.1% of outpatient HF had de novo HF.

Table 2 shows the clinical setting for HFrEF versus HFmrEF versus HFpEF, with 57% HFrEF (EF ≤40%), 17% HFmrEF (with the more recent definition, namely EF 41–49% rather than 40–49%[22]), and 26% HFpEF (EF ≥50%). Patients with HFpEF less commonly received HF specialist care than patients with HFrEF or HFmrEF, more commonly had de novo HF, and less commonly had been previously hospitalized for HF.

Patient baseline characteristics according to acute heart failure versus outpatient heart failure and ejection fraction category

Figure 1 shows selected and *Table 3* shows comprehensive baseline characteristics according to AHF versus outpatient HF. Patients with AHF versus outpatient were older (70 vs. 66 years), and slightly more commonly women (36% vs. 33%). In AHF, 80% had New York Heart Association (NYHA) class III–IV versus 32% in outpatient HF. HF aetiology was similar, with 51% and 52% ischaemic aetiology in AHF and outpatient HF, respectively. In AHF, previous CV interventions were less common and both CV and non-CV comorbidities were more common (consistent with higher age in AHF). Patients with AHF also had higher blood pressure (but the same proportions with systolic blood pressure ≤110 mmHg at 29% and 28%, respectively) and heart rate, more atrial fibrillation, distinctly more signs and symptoms of HF, and lower haemoglobin and estimated glomerular filtration rate and considerably higher

Table 2 Enrolment and clinical care setting by ejection fraction category

Variable	HFrEF ($n = 5699$, 57%)	HFmrEF ($n = 1673$, 17%)	HFpEF ($n = 2647$, 26%)	Missing data	*p*-value
Type of visit				0.3%	<0.001
Outpatient HF	61%	71%	58%		
AHF	39%	29%	42%		
Specialty of the enrolling physician				0.1%	<0.001
Cardiology	86%	85%	83%		
HF specialist	40%	44%	33%		
Other cardiology specialist	4.4%	4.1%	4.1%		
General cardiologist	42%	36%	45%		
Non-cardiology	14%	15%	17%		
Internal medicine specialist	5.1%	8.9%	10%		
General practitioner	3.0%	3.7%	3.2%		
Other	5.4%	2.8%	3.6%		
HF history				0.7%	<0.001
Yes, without previous hospitalization	24%	26%	28%		
Yes, with previous hospitalization	64%	63%	54%		
De novo HF	12%	11%	18%		

AHF, acute heart failure; EF, ejection fraction; HF, heart failure; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction.
EF is from most recent before visit; if not available then at presentation this visit; if not available then at discharge (AHF only).

N-terminal pro-B-type natriuretic peptide (NT-proBNP) (3851 [1349–9988] in AHF vs. 1118 [494–2679] pg/ml in outpatient HF). The warm/wet haemodynamic profile was present in 51% in AHF and 22% in out-patient HF, and 12% were cold/dry or cold/wet in AHF and 6.0% in out-patient HF.

Figure 1 and *Table 4* show baseline characteristics according to EF category. Patients with HFpEF were distinctly older and more commonly women, with less commonly a previous myocardial infarction and ischaemic HF aetiology. Comorbidities were similarly common in the three EF categories except venous thromboembolism and cognitive dysfunction which were more common in HFpEF. Blood pressure was lowest and natriuretic peptides highest in HFrEF.

Guideline-directed medical therapy use at presentation and treatment decisions and changes

Baseline use, initiation and discontinuation of GDMT varied according to AHF versus outpatient HF, de novo versus pre-existing HF, and EF category.

Figure 2 and online supplementary *Figure S1* show medication use and, importantly, medication decisions and changes, presented in bar graphs for six medication classes (ACEi/ARB/ARNi, ARNi alone, BB, MRA, SGLT2/1i, and loop diuretics). *Figure 2* is for all patients (AHF and outpatient HF and de novo and pre-existing) and online supplementary *Figure S1* are separately according to outpatient HF and AHF (where opportunities for medication changes differ), separately for de novo HF (where use at presentation presumably reflect non-HF indications and decisions reflect the new HF diagnosis) and pre-existing HF. All figures show HFrEF, HFmrEF, and HFpEF separately (where indications for GDMT are different). In the *Figure 2* bar graphs, percentages are shown for continued use (i.e. both before and after the encounter) and for started, and these add up to use after the encounter. In the online supplementary *Appendix S1* bar graphs percentages are shown for all four potential scenarios: use at presentation and continued, not used at presentation but initiated at the AHF event or outpatient HF visit (these two are analogous to *Figure 2*), as well as used at presentation but stopped at the AHF or outpatient HF event, and not treated either before or after the event (these two add up to non-use after the encounter). GDMT was much more commonly started than stopped, generally used at presentation more in outpatient HF, pre-existing HF and with lower EF; started more commonly in AHF, de novo HF, and with lower EF, and used somewhat more after outpatient HF visits, pre-existing HF, and encounters with lower EF.

As an example, among patients enrolled with de novo AHF, beta-blockers were used at presentation and continued in 38% in HFrEF, 42% in HFmrEF, and 48% in HFpEF, started in 53%, 36%, and 32%, respectively, and stopped in 0.2%, 3.0% and 2.5%, respectively. ARNi was used after the visit in 9.1–38% of HFrEF, depending on whether pre-existing or not and whether AHF or outpatient HF. The equivalent for SGLT2/1i over the entire EF spectrum was 0.7–8.4% (enrolment occurred in 2018–2020) and for MRAs in HFrEF 69–79%. The key percentages reflecting quality of care were use of EF-specific GDMT after the encounter, and these were in HFrEF: RASi 89%, ARNi 29%, beta-blocker 92%, MRA 78%, and oral loop diuretics 85%; HFmrEF oral loop diuretics 81%, and HFpEF oral loop diuretics 80%.

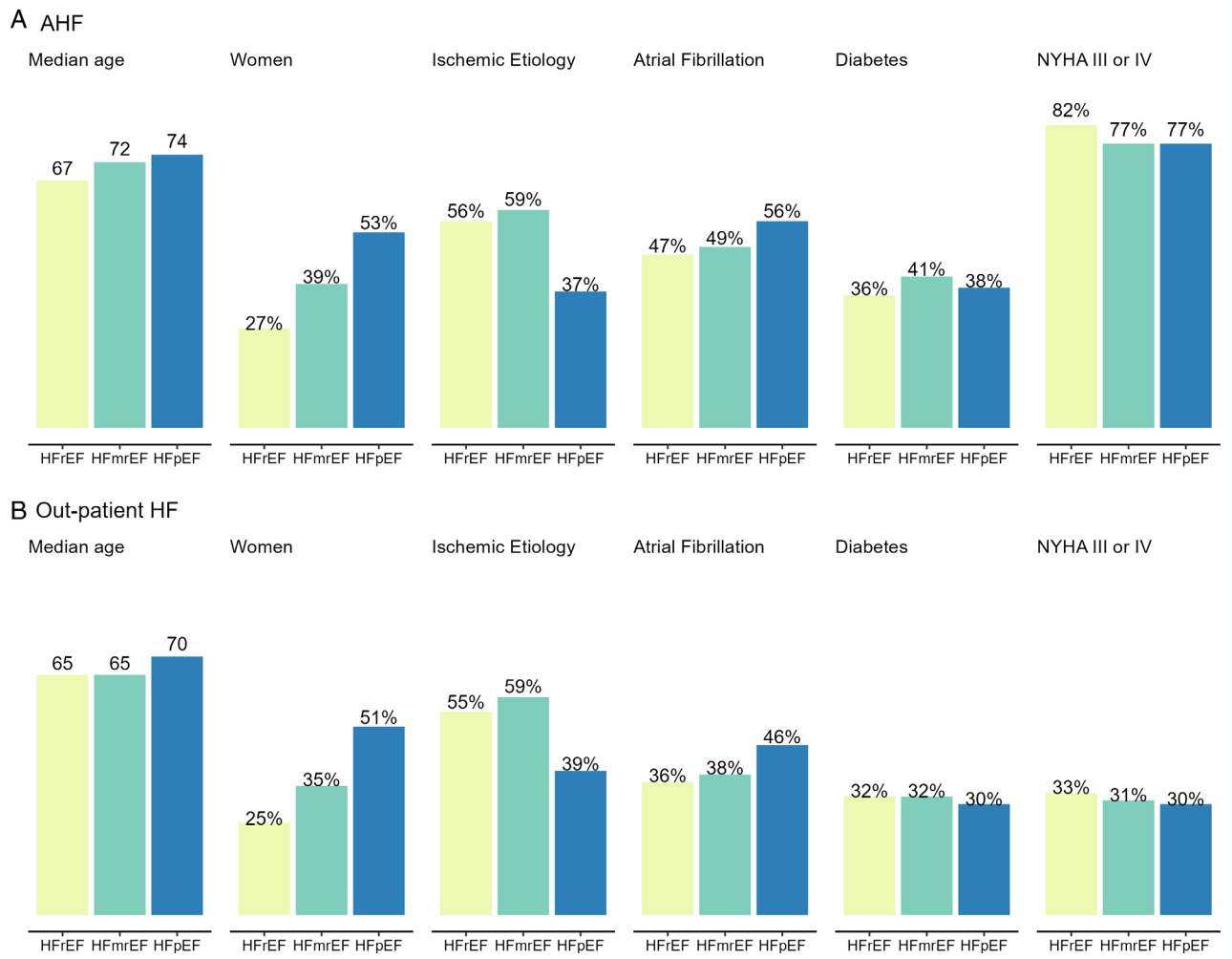


Figure 1 Selected baseline characteristics according to ejection fraction category in acute heart failure (AHF) (*A*) and outpatient heart failure (HF) (*B*). HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; NYHA, New York Heart Association.

Discussion

The large and contemporary ESC HF III Registry reports patient characteristics and therapy for 10 162 patients enrolled from 220 cardiology centres with a range of size and specialty focus, in 41 European Union (EU) or ESC-affiliated countries. Importantly, we describe both acute and outpatient HF care, in pre-existing and de novo HF, and for all three EF categories. Uniquely, in all these scenarios, we also report GDMT use both prior to and after the encounter, reflecting therapeutic decision making and GDMT implementation. The key findings were: outpatient enrolment represented 61% and worsening or acute HF represented 39%; HFrEF represented 57%, HFmrEF 17% and HFpEF 26%, and de novo HF was common in the AHF (26%) but not outpatient setting (6.1%); and treatment decisions at hospital discharge and outpatient clinic visits led to GDMT treatment in HFrEF: RASi 89%, ARNi 29%, beta-blocker 92%, MRA 78%, and oral loop diuretics 85%; HFmrEF oral loop diuretics 81%, and HFpEF oral loop diuretics 80% (*Graphical Abstract*).

Setting of heart failure care in cardiology centres in Europe

The ESC HF III Registry is representative of diverse cardiology centres in EU and ESC-affiliated countries. Patients are thus different, less rigorously selected and more generalizable than patients enrolled in randomized trials, but more selected and less generalizable than patients in epidemiological surveys.[21] Uniquely, the HF III Registry captures a vast majority of European countries as well as numerous non-EU but ESC-affiliated countries, making it representative of a large proportion of HF patients worldwide.

Age (66–70 years) and sex distribution (about 30–40% women) was similar to other selective registries such as the previous

Table 3 Baseline clinical characteristics prior to and at enrolment (at acute or outpatient presentation)

Variable	AHF ($n = 3913$, 39%)	Outpatient HF ($n = 6217$, 61%)	Missing data	*p*-value
Age (years), median (IQR)	70 (62–79)	66 (58–75)	0.0%	<0.001
Women (%)	36%	33%	0.1%	0.006
BMI (kg/m^2), median (IQR)	28 (24–31)	28 (25–31)	4.4%	0.67
EF last known prior to enrolment			8.9%	<0.001
≤40%	59%	56%		
41–49%	12%	19%		
≥50%	29%	25%		
EF at enrolment			13%	<0.001
≤40%	62%	54%		
41–49%	13%	20%		
≥50%	25%	26%		
NYHA class at enrolment			5.2%	<0.001
I–II	20%	68%		
III–IV	80%	32%		
Primary underlying HF aetiology			2.0%	<0.001
Ischaemic	51%	52%		
Dilated cardiomyopathy of unknown cause	13%	17%		
Other	36%	31%		
Medical history				
Myocardial infarction	39%	38%	0.5%	0.51
Stroke/transient ischaemic attack	9.5%	8.9%	0.5%	0.35
Atrial fibrillation history			0.6%	<0.001
Permanent/persistent	37%	28%		
Paroxysmal	13%	11%		
Diabetes			0.7%	<0.001
Non-insulin treated	21%	21%		
Insulin-treated	16%	11%		
Arterial hypertension	73%	65%	0.5%	<0.001
Peripheral vascular disease	14%	11%	1.0%	<0.001
Venous thromboembolism	3.8%	2.7%	0.5%	<0.001
CRT	4.6%	9.4%	1.5%	<0.001
ICD	7.8%	16%	1.5%	<0.001
Any of the following non-cardiovascular conditions	32%	26%	1.2%	<0.001
Chronic obstructive pulmonary disease	15%	11%	1.2%	<0.001
Dialysis	1.4%	1.4%	1.2%	0.89
Hepatic dysfunction	4.7%	3.2%	1.2%	<0.001
Current active cancer	3.6%	2.6%	1.2%	0.007
Depression	5.5%	5.5%	1.2%	0.95
Cognitive dysfunction	5.7%	2.1%	1.2%	<0.001
Rheumatoid arthritis	1.2%	1.2%	1.2%	0.74
Sleep apnoea	4.0%	5.0%	1.4%	0.03
Physical signs and symptoms at presentation				
Systolic blood pressure, mmHg, median (IQR)	130 (110–148)	122 (110–139)	1.3%	<0.001
Systolic blood pressure ≤110 mmHg	29%	28%	1.3%	0.52
Diastolic blood pressure, mmHg, median (IQR)	80 (70–90)	75 (66–80)	1.5%	<0.001
Heart rate (bpm), median (IQR)	87 (74–102)	70 (64–80)	1.0%	<0.001
Pulmonary rales	68%	18%	1.3%	<0.001
Peripheral oedema	65%	25%	1.1%	<0.001
Dyspnoea at rest	66%	14%	1.0%	<0.001
Orthopnoea	55%	14%	1.4%	<0.001
Jugular venous pulse (>6 cm from right atrium)	36%	12%	5.2%	<0.001
Laboratory at presentation				
Haemoglobin (g/dl), median (IQR)	13 (11–14)	13 (12–15)	9.8%	<0.001
eGFR (ml/min/1.73 m^2), median (IQR)	55 (38–74)	65 (48–83)	10%	<0.001
Potassium (mmol/L), median (IQR)	4.3 (3.9–4.7)	4.5 (4.2–4.8)	12%	<0.001
BNP (pg/ml), median (IQR)	842 (352–1963)	406 (188–676)	83%	<0.001
NT-proBNP (pg/ml), median (IQR)	3851 (1349–9988)	1118 (494–2679)	49%	<0.001
NT-proBNP >1000 pg/ml	80%	53%	49%	<0.001

AHF, acute heart failure; BMI, body mass index; BNP, B-type natriuretic peptide; CRT, cardiac resynchronization therapy; EF, ejection fraction; eGFR, estimated glomerular filtration rate; HF, heart failure; ICD, implantable cardioverter defibrillator; IQR, interquartile range; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association.

Table 4 Baseline clinical characteristics by ejection fraction category

Variable	HFrEF (*n* = 5699, 57%)	HFmrEF (*n* = 1673, 17%)	HFpEF (*n* = 2647, 26%)	Missing data	*p*-value
Age (years), median (IQR)	66 (58–74)	67 (58–76)	72 (63–80)	0.0%	<0.001
Women (%)	26%	36%	52%	0.1%	<0.001
BMI (kg/m^2), median (IQR)	27 (25–31)	28 (25–31)	28 (25–32)	4.2%	<0.001
NYHA class at enrolment				5.0%	<0.001
I–II	48%	56%	51%		
III–IV	52%	44%	49%		
Primary underlying HF aetiology				1.8%	<0.001
Ischaemic	55%	59%	38%		
Dilated cardiomyopathy of unknown cause	22%	10%	4.9%		
Other	23%	32%	57%		
Medical history					
Myocardial infarction	45%	44%	22%	0.3%	<0.001
Stroke/transient ischaemic attack	9.0%	9.8%	9.1%	0.4%	0.62
Atrial fibrillation history				0.4%	<0.001
Permanent/persistent	29%	32%	35%		
Paroxysmal	11%	8.8%	16%		
Diabetes				0.5%	0.003
Non-insulin treated	20%	22%	22%		
Insulin-treated	14%	12%	11%		
Arterial hypertension	62%	72%	78%	0.3%	<0.001
Peripheral vascular disease	11%	14%	14%	0.8%	<0.001
Venous thromboembolism	2.9%	2.6%	3.9%	0.4%	0.01
CRT	11%	4.2%	2.8%	1.3%	<0.001
ICD	20%	6.8%	3.1%	1.4%	<0.001
Any of the following non-cardiovascular conditions	29%	27%	30%	1.0%	0.18
Chronic obstructive pulmonary disease	12%	14%	12%	1.0%	0.15
Dialysis	1.5%	1.0%	1.3%	1.0%	0.20
Hepatic dysfunction	3.9%	3.6%	3.9%	1.0%	0.91
Current active cancer	2.7%	3.4%	3.3%	1.0%	0.18
Depression	5.7%	4.8%	5.7%	1.0%	0.37
Cognitive dysfunction	2.9%	3.3%	4.8%	1.0%	<0.001
Rheumatoid arthritis	1.2%	0.9%	1.5%	1.0%	0.22
Sleep apnoea	4.7%	4.3%	4.7%	1.2%	0.75
Vital signs at presentation					
Systolic blood pressure, mmHg, median (IQR)	120 (109–136)	130 (116–145)	130 (120–145)	1.1%	<0.001
Systolic blood pressure ≤110 mmHg	36%	20%	18%	1.1%	<0.001
Diastolic blood pressure, mmHg, median (IQR)	72 (65–80)	80 (70–90)	80 (70–85)	1.3%	<0.001
Heart rate (bpm), median (IQR)	76 (66–90)	76 (67–90)	75 (65–88)	0.9%	<0.001
Laboratory at presentation					
Haemoglobin (g/dl), median (IQR)	13 (12–15)	13 (12–14)	13 (12–14)	9.7%	<0.001
eGFR (ml/min/1.73 m^2), median (IQR)	61 (44–80)	65 (47–83)	59 (41–77)	9.9%	<0.001
Potassium (mmol/L), median (IQR)	4.4 (4.1–4.8)	4.4 (4.1–4.9)	4.4 (4.0–4.7)	12%	<0.001
BNP (pg/ml), median (IQR)	653 (250–1480)	467 (307–784)	479 (216–1092)	83%	<0.001
NT-proBNP (pg/ml), median (IQR)	2057 (779–5907)	1256 (481–3621)	1260 (610–3267)	49%	<0.001
NT-proBNP >1000 pg/ml	68%	56%	59%	49%	<0.001

AHF, acute heart failure; BMI, body mass index; BNP, B-type natriuretic peptide; CRT, cardiac resynchronization therapy; EF, ejection fraction; eGFR, estimated glomerular filtration rate; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; ICD, implantable cardioverter defibrillator; IQR, interquartile range; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association. EF is from most recent before visit; if not available then at presentation this visit; if not available then at discharge (AHF only).

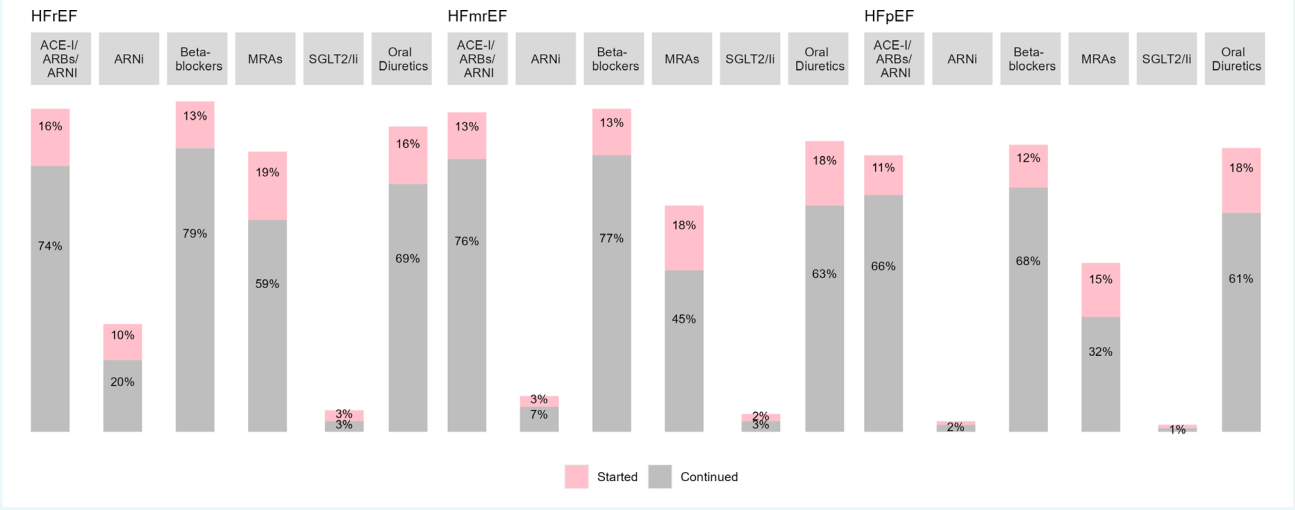


Figure 2 Medication use and medication decisions and changes for combinations of ejection fraction categories, acute heart failure versus outpatient heart failure, and de novo versus pre-existing heart failure. Bars show treatment at presentation (before acute heart failure event and before outpatient heart failure clinic visit), treatment decisions, and treatment at discharge for acute heart failure and after the clinic visit for outpatient heart failure. The sum of the bars is the percentage treated after the encounter, reflecting treatment decisions and implementation of guideline-directed medical therapy in Europe. ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNi, angiotensin receptor–neprilysin inhibitor; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; MRA, mineralocorticoid receptor antagonist; SGLT2/1i, sodium–glucose cotransporter 2/1 inhibitor.

ESC HF Long-Term Registry,[23] CHAMP-HF,[24] and ASIAN-HF,[25] but patients were younger and more commonly male with a somewhat greater proportion of HFrEF than in more generalizable cohorts and registries such as the Swedish HF registry,[26] the UK national HF audit,[27] and the US Get With The Guidelines-HF registry,[28] where age was around 75–80 years and about half of patients were women. Slightly more than half of patients had HFrEF and 39% were enrolled in the AHF setting, consistent with participating centres being hospital-based and to some extent referral centres. Although it is increasingly common to treat AHF and worsening HF in the emergency department of in outpatient clinics where intravenous diuretics are given, only 2.2% and 0.9% of AHF patients were enrolled in these settings, respectively. The COVID-19 pandemic affected patterns of HF and CV care during the latter part of HF III enrolment (2020), with fewer hospital admissions for HF.[29] This may have affected enrolment of patients with AHF or worsening HF in HF III, but it is not clear that it affected care of those patients enrolled.

These data are useful for planning HF clinical trials because the investigators and sites in the present HF III analysis are those who are also likely to enrol patients into HF trials. However, participating investigators and centres have an interest in cardiology and HF, and thus patients and treatment are not representative of more generalized or population-wide HF care, where patients are older, with more comorbidities, more commonly with HFpEF, worse GDMT, and more non-CV events and outcomes.[30,31]

Clinical characteristics in acute heart failure and outpatient heart failure and in HFrEF, HFmrEF, and HFpEF

Patients with AHF versus outpatient visits were more commonly treated by general cardiologists and more commonly had de novo HF, suggesting that outpatient HF visits are mostly patients with established HF and that many patients do not receive a diagnosis until hospitalized. The clinical characteristics and haemodynamic profiles suggest that congestion was common and considerable in AHF, but far from universal, highlighting the variability and complexity of presentation and signs and symptoms of patients with AHF.

In most registries and cohorts, HFrEF represents roughly half of patients, and HFmrEF and HFpEF together the other half. HFpEF appears to be increasing the most.[32] The recent change in the definition of HFmrEF from 40–49% to 41–49%[22] has had a considerable effect on reducing the size of the HFmrEF proportion. This is due to digit bias, where EF is often reported in increments of 5%. In the ESC HF Long-Term Registry, 21% had HFmrEF defined as 40–49%, 7% had EF 'exactly' 40%, and thus these 7% were reclassified as HFrEF, leaving only 14% with HFmrEF with the new 41–49% definition.[33] In the present HF III, the distribution of HFrEF, HFmrEF, and HFpEF was 57%, 17% and 26%, thus still a meaningful proportion with HFmrEF. The proportions who have changed EF over time prior to enrolment in HF III is not reported but will be available in future follow-up analysis of HF III.

The different EF categories have previously been extensively characterized and were largely confirmed in the present analysis, suggesting that on average, HFrEF and HFmrEF are similar in most characteristics, including age, predominance of men and underlying ischaemic heart disease, with the main difference being that HFrEF is more severe, with higher NYHA class, NT-proBNP and CV and HF event rates than HFmrEF.[4] In contrast, patients with HFpEF are older, more commonly women, with more commonly atrial fibrillation, and other comorbidities.

Implementation of guideline-directed medical therapy

A key objective of HF III is assessment of quality of care and adherence to the ESC HF guidelines. Patients were enrolled in 2018–2020, during which time the 2016 ESC HF guidelines were applicable, with class I recommendations for ACEi/ARB/ARNi, beta-blockers and MRAs.[34] In the present analysis, we provide detailed data on these three fundamental drug categories. SGLT2/1i were emerging as beneficial in reducing HF events in patients with diabetes but not yet indicated specifically for HF.

In HFrEF, use of ACEi/ARB/ARNi and beta-blockers was highly variable depending on EF, pre-existing versus de novo HF, and acute versus outpatient setting. However, after enrolment in HF III and optimization during the baseline encounter (whether in-hospital or as outpatient), use of these drug classes reached nearly 90% at discharge from an AHF event and over 90% after an outpatient visit. Use of ARNi in HFrEF was far less than one third prior to enrolment, and was initiated in about 10% at the baseline encounter, resulting in about 30% use after an outpatient encounter and 10–20% use after an AHF encounter. The 29% use of ARNi was relatively modest, despite several years having passed since the pivotal PARADIGM-HF trial and the 2016 guidelines recommending ARNi in HFrEF. The present study was conducted in 2018–2020 and cannot meaningfully assess SGLT2i use, but very recent data suggest that SGLT2i implementation[35–38] has been more rapid than ARNi in the present HF III as well as in other cohorts and registries.[37–40] There are several potential explanations. Traditional HFrEF treatments such as ACEi and beta-blockers were also slow to be implemented. The design of PARADIGM-HF and recommendations in ensuing guidelines was to first treat with ACEi and then switch to ARNi, which may delay initiation of ARNi. ARNi is also more expensive than ACEi/ARB. In contrast, before they were shown effective in dedicated HF trials, SGLT2i had already received attention for their dramatic and unexpected effects on HF outcomes in CV outcome trials, and both the HF and primary care communities were primed for rapid implementation of SGLT2i once the HF trials were published. MRA use in HFrEF was higher, with more than 70% regardless of the type of encounter, which is considerably higher than that reported in other registries,[16,27,28] and may reflect a greater comfort with medication side effects[41,42] among the HF III providers as compared to those in other more general settings.

In 2016, there were no specific recommendations for any disease-modifying treatment in HFmrEF or HFpEF. Still, a vast majority of patients in HF III received ACEi/ARB and beta-blockers. It is unknown if indications have been primarily HF or some comorbidity such as hypertension, chronic kidney disease or diabetic kidney disease. Post-hoc analyses of randomized HFpEF trials[43,44] and the 2021 guidelines[6] suggest that use in HFmrEF may be reasonable, whereas in HFpEF (EF ≥50%) there appears to be no benefit at all from ARBs or beta-blockers.[43,44]

Conclusions

The current first co-primary analysis of the HF III Registry presents detailed and important contemporary baseline data on HF in the EU and ESC-affiliated countries. The data may serve as reference material for readers and investigators wishing to understand contemporary HF characteristics according to EF category, acute versus outpatient setting and de novo versus pre-existing HF. It also provides detailed data on GDMT use and decision making in these different clinical settings. Overall, implementation of GDMT in HF III is at a high level, with greater percentage use of GDMT medications than in most other large registries and cohorts[5,30,45–54] and an improvement since the previous ESC HF Long-Term Registry.[12] The present data are useful for multiple stakeholders, including patients and patient organizations, clinicians, investigators, and professional societies, payers and health economics assessors, and the pharmaceutical industry.

Supplementary Information

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

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Appendix 1

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