

ORIGINAL CLINICAL SCIENCE

“Real-world prognostic performance of different severe and advanced heart failure definitions: Data from the Swedish Heart Failure Registry”



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KEYWORDS:

Severe heart failure;
Advanced heart failure;
Heart failure with
reduced ejection
fraction;
RCT design;

BACKGROUND: A valid definition of severe heart failure (HF) is essential for earlier identification, timely referral for advanced therapies, and to optimize clinical trial design.

OBJECTIVES: To assess the prevalence, prognostic performance, and 1-year outcomes associated with different definitions of severe and advanced HF (AdvHF) in patients with heart failure with reduced ejection fraction (HFrEF).

METHODS: We included 15,153 patients with EF <40%, HF duration >6 months, and no prior left ventricular assist device or heart transplant, from the Swedish Heart Failure Registry. Several

Abbreviations: AdvHF, Advanced HF; AIC, Akaike information criterion; AF, Atrial fibrillation; ARNI, Angiotensin-receptor-neprilysin-inhibitors; AUC, Area under the curve; BIC, Bayesian information criterion; BB, Beta-blockers; CRT, Cardiac resynchronization therapy; CV, Cardiovascular; CI, Confidence intervals; CKD, Chronic kidney disease; d-MCS, Durable mechanical circulatory support; EF, Ejection fraction; ESC, European Society of Cardiology; HF, Heart failure; HFA, Heart Failure Association; HHF, Heart failure hospitalizations; HFrEF, Heart failure with reduced ejection fraction; HTx, Heart transplantation; ICD, Implantable cardioverter defibrillator; IDI, Integrated discrimination improvement; LVAD, Left ventricular assist devices; MRA, Mineralocorticoid receptor antagonists; NRI, Net reclassification improvement; NYHA, NT-proBNP, New York Heart Association N-terminal pro-B-type natriuretic peptide; RCTs, Randomized control trials; RASI, Renin-angiotensin system inhibitors; SwedeHF), Swedish Heart Failure Registry; OR, Odds ratios; OMT, Optimal medical therapy; VIFs, Variance inflation factors

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definitions of severe/AdvHF were evaluated: a simplified Heart Failure Association (HFA) definition (NYHA III–IV, EF < 30%, ≥2 HF hospitalizations in 12 months), the GALACTIC-Severe-definition (NYHA III–IV, EF < 30%, ≥1 hospitalization in 6 months), and variations adding/removing criteria such as NT-proBNP levels and diuretic dose to the HFA-AdvHF definition. Predictive performance and 1-year outcomes were analyzed.

RESULTS: The HFA-definition identified 6.4% of patients, with a 1-year cardiovascular death/HF hospitalization risk of 70% and all-cause mortality of 45% (AUC = 0.72). The GALACTIC-Severe definition identified 12.6% of patients with slightly lower but still substantial event rates (59% and 38%, respectively; AUC = 0.73). Definitions incorporating NT-proBNP ≥2000 pg/ml had the highest prognostic accuracy (AUC = 0.75).

CONCLUSIONS: The HFA-AdvHF definition selected a smaller, high-risk group, while the GALACTIC-Severe criteria identified a broader population, with a lower, but still high risk. NT-proBNP, HF hospitalization history, and diuretic dose might represent valuable enrichment tools for future trials.

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Introduction

Heart failure (HF) affects over 64 million people globally,¹ with ~10–15% progressing to advanced HF (AdvHF), characterized by severe symptoms, severely impaired functional capacity, recurrent HF hospitalizations (HHF), and high mortality.² As HF prevalence and patient longevity increase, the burden of AdvHF is expected to escalate.³

Treatment options for AdvHF remain limited. Therapies proven effective in stable, chronic HF with reduced EF (HFrEF) show reduced benefit or have not been tested in advanced stages. The LIFE trial, demonstrated poor tolerability of angiotensin-receptor-neprilysin-inhibitors (ARNI) and no outcome benefit over valsartan in AdvHF.⁴ Similarly, ambulatory oral and intravenous inotropes have not improved outcomes and often increased mortality,^{5–8} except for omecamtiv mecarbil, which provided only a modest benefit (8% reduction in cardiovascular [CV] mortality or HHF).

Accordingly, guidelines recommend referral for heart transplantation (HTx) or durable mechanical circulatory support (D-MCS) unless a palliative strategy is chosen.⁹ However, organ shortage, comorbidities and delayed referrals often reduce eligibility for advanced therapies. Thus, earlier identification of high-risk patients and the development of innovative treatment strategies are critical to improve their prognosis.

To address this gap, a new HF stage, stage C2 (severe HF), intermediate between symptomatic HF (Stage C) and AdvHF (Stage D), has been recently proposed to identify high-risk patients earlier in the disease trajectory.^{10,11} In a recent post-hoc analysis of the GALACTIC-HF trial, patients with severe HF, defined by New York Heart Association [NYHA] class III–IV, ejection fraction [EF] < 30%, ≥1 HF within 6 months, experienced a 20% reduction in CV mortality/HHF with omecamtiv mecarbil, while no benefit was observed in the non-severe subgroup.¹² Accordingly, the COMET-HF trial (NCT06736574) has been started to investigate omecamtiv mecarbil in a selected severe HF cohort.

Despite efforts to better characterize the subpopulation of HF patients at higher risk of events, real-world data

validating their risk profile remain limited, and no studies have specifically examined Stage C2. A standardized definition of severe HF is essential for accurate patient identification, timely referral to AdvHF centers, and robust clinical trial design, as therapeutic response may vary significantly according to disease severity. Designing randomized control trials (RCTs) in high-risk HF patients poses additional challenges: 1) high comorbidity burden and competing risks may lead to neutral results; 3) low disease prevalence, high mortality and greater loss-to-follow-up rates may hinder enrollment. Real-world data can address these challenges and improve RCT design.

This study aimed to evaluate the prevalence, prognostic performance, and outcomes associated with various definitions of severe and AdvHF, in a large real-world cohort with heart failure with reduced ejection fraction (HFrEF). The goal is to inform RCT design and optimize referral to AdvHF centers.

Methods

Data sources

We analyzed data from the Swedish Heart Failure Registry (SwedeHF), a nationwide continuous health quality and research registry established in 2000, enrolling both in- and outpatients with HF regardless of EF.^{13,14} At discharge from the hospital or at the outpatient visit (i.e. the index date), approximately 80 variables are recorded and entered into an electronic database managed by the Uppsala Clinical Research Centre (Uppsala, Sweden). Participation in the registry is voluntary for Swedish healthcare centers but aims to achieve the most comprehensive nationwide coverage possible. In 2022, 69 out of 76 Swedish hospitals participated in SwedeHF, covering ~32% of prevalent HF cases in Sweden.¹⁵ Patients are included into the registry upon a clinical HF diagnosis until 2017, which was thereafter defined by specific ICD-10 codes (I50.0, I50.1, I50.9, I42.0, I42.6, I42.7, I25.5, I11.0, I13.0, I13.2). The

inclusion and exclusion criteria remained otherwise unchanged over time.

Patients are not required to sign informed consent for inclusion, although they are notified about the registration and can opt out.

For this study, SwedeHF was linked through the personal identification number, that all Swedish residents have, with (I) the Cause of Death Register to obtain information on cause-specific death, (II) the National Patient Register, which provided data on additional comorbidities, HHF, left ventricular assist devices (LVAD) implantation and HTx, and (III) Statistic Sweden for obtaining socioeconomic variables.

This study and the related linkage across registries received approval from the Swedish Ethical Review Authority and conform to the Declaration of Helsinki.

Study cohort

We included patients enrolled in SwedeHF between 1 January 2011 and 31 December 2022 with EF <40%, HF duration >6 months, no previous history of LVAD implantation or HTx, and no missing data for NYHA and NT-proBNP (N-terminal pro-B-type natriuretic peptide). Given the limited torsemide use in Sweden, patients with unreported loop diuretic preparations were assumed as receiving furosemide if the daily dose was ≥ 20 mg/day. Those with <20 mg/day were excluded due to the uncertainty in differentiating loop diuretic types. Patients with missing loop diuretic doses were also excluded. If multiple records existed for a patient, the most recent was selected (Fig. S1, Supplemental material).

HFrEF was defined as EF <40% rather than $\leq 40\%$ according to the recent Universal Definition and Classification of HF, since EF in SwedeHF has been mostly reported as a categorical variable (i.e. <30%, 30–39%, 40–49%, $\geq 50\%$) during the study period. We selected patients with HF history >6 months to ensure sufficient time for optimizing treatment, as severe and AdvHF are defined by persistent severe symptoms despite optimal medical therapy (OMT).¹⁶

Definitions of advanced and severe HF (Table 1, supplemental material)

The Heart Failure Association (HFA) - European Society of Cardiology (ESC) definition of AdvHF requires 4 simultaneous criteria despite OMT¹: severe and persistent symptoms,² severe cardiac dysfunction,³ ≥ 2 episodes of congestion, low-output syndrome or malignant arrhythmias requiring unplanned visits or hospitalizations in the past year,⁴ severely impaired exercise capacity. Given our focus on HFrEF and the available data in SwedeHF, we adapted the HFA-definition as follows¹: NYHA class III-IV,² EF <30%,³ ≥ 2 HHF within the previous 12 months. This adapted definition ("HFA-AdvHF definition") served as the reference in our analysis, as the HFA-definition is endorsed

by both American and European HF Guidelines and represents the most widely accepted.

Alternative definitions were assessed by systematically removing one criterion from the HFA-AdvHF definition, resulting in three 2-variable definitions: 1) NYHA III-IV + EF <30%, 2) NYHA III-IV + ≥ 2 HHF within 12 months, 3) EF <30% + ≥ 2 HHF within 12 months.

We also tested the severe HF definition from the post-hoc analysis of the GALACTIC-HF trial,¹² considering EF $\leq 30\%$, NYHA class III-IV, ≥ 1 HHF within 6 months, which we re-adapted to our data as¹ NYHA class III-IV,² EF <30%,³ ≥ 1 HHF within 6 months ("GALACTIC-Severe-definition").

Recognizing the prognostic and trial-selection value of NT-proBNP, we incorporated it in the HFA-AdvHF definition. Since no specific NT-proBNP levels have been universally established to define severe and AdvHF, we considered two cut-offs: ≥ 800 pg/ml as in the LIFE Trial,¹⁷ $\geq 2,000$ pg/ml representing both the median value in our cohort and in other RCTs enrolling AdvHF patients.⁴ This yielded two additional 4-variable definitions: 1) NYHA III-IV + EF <30% + ≥ 2 HHF within 12 months + NT-proBNP ≥ 800 , 2) NYHA III-IV + EF <30% + ≥ 2 HHF within 12 months + NT-proBNP $\geq 2,000$.

Given that high-dose diuretics reflect disease severity¹⁸ and are used as an enrichment criterion in RCTs,¹⁹ we also tested a definition incorporating daily loop diuretic dosage into the HFA-AdvHF definition. We converted loop diuretic doses to furosemide equivalents (40 mg furosemide = 10 mg torsemide = 1 mg bumetanide), and we investigated two cut-offs based on prior studies, i.e. furosemide equivalent doses >40 and >80 mg/day.²⁰ By adding these variables to the HFA-AdvHF definition, we generated two additional 4-variable definitions: 1) NYHA III-IV + EF <30% + ≥ 2 HHF within 12 months + furosemide equivalent dose >40 mg/day, 2) NYHA III-IV + EF <30% + ≥ 2 HHF within 12 months + furosemide equivalent dose >80 mg/day.

All the severity criteria included in these definitions were assessed at the index date.

Outcomes

The primary outcome was 1-year risk of CV death or first HHF. Secondary outcomes included 1-year risk of all-cause death, non-CV death, CV death, first HHF, LVAD implantation, HTx and the composite of death/HTx/LVAD. Follow-up was censored at 1 year unless death occurred earlier.

Statistical analysis

Continuous variables were presented as median and inter-quartile range, while categorical variables as numbers and percentages. Patients with missing values for EF, NYHA class, NTproBNP or diuretic dosage were excluded from the population, as these variables were required to define disease severity. Since all the remaining variables were used solely for descriptive purposes in the study population

Table 1 Baseline Characteristics

Variables	Overall	4-Variable Definitions			3-Variable Definitions		2-Variable Definitions		
		HFA-AdvHF + NT-proBNP≥2.000 pg/ml	HFA-AdvHF + NT-proBNP≥800 pg/ml	HFA-AdvHF + furosemide-equivalent > 80 mg/day	HFA-AdvHF + furosemide-equivalent > 40 mg/day	GALACTIC-Severe def. (NYHA III-IV + EF < 30 + ≥1HHF within 6 months)	HFA-AdvHF def. (NYHA III-IV + EF < 30 + ≥2HHF within 12 months)	EF < 30% + ≥2HHF within 12 months	NYHA III-IV + ≥2HHF within 12 months
Patients, n (%)	15,153	839 (5,5%)	934 (6,2%)	368 (2,4%)	620 (4,1%)	1,911 (12,6%)	964 (6,4%)	1,310 (8,6%)	3,534 (23,4%)
<i>Demographic</i>									
Age (years), median [IQR]	75 [67-81]	76 [69-82]	75 [67- 82]	74 [67- 81]	75 [68- 81]	76 [69- 82]	75 [67- 81]	75 [67,-81]	76 [68-82]
Female sex, n (%)	3722 (25%)	178 (21%)	196 (21%)	60 (16%)	110 (18%)	429 (22%)	202 (21%)	288 (22%)	816 (23%)
Index year, n (%)									
≤ 2017	6476 (43%)	561 (67%)	602 (64%)	269 (73%)	432 (70%)	1195 (63%)	617 (64%)	814 (62%)	1834 (52%)
>2017	8677 (57%)	278 (33%)	332 (36%)	99 (27%)	188 (30%)	716 (37%)	347 (36%)	496 (38%)	1700 (48%)
Caregiver at registration, n (%)									
Out-patient	13,542 (89%)	505 (60%)	583 (62%)	196 (53%)	359 (58%)	1227 (64%)	607 (63%)	866 (66%)	2850 (81%)
In-patient	1611 (11%)	334 (40%)	351 (38%)	172 (47%)	261 (42%)	684 (36%)	357 (37%)	444 (34%)	684 (19%)
Location of follow-up, n (%)									
Hospital	11,969 (80%)	651 (80%)	733 (80%)	279 (78%)	474 (78%)	1488 (80%)	759 (80%)	1053 (82%)	2,830 (82%)
Primary care	2569 (7%)	145 (18%)	153 (17%)	64 (18%)	110 (18%)	322 (17%)	157 (17%)	196 (15%)	544 (16%)
Other	348 (2%)	22 (3%)	27 (3%)	15 (4%)	22 (4%)	51 (3%)	27 (3%)	35 (3%)	82 (2%)
<i>Clinical variables</i>									
NYHA class, n (%)									
I	1273 (8%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	35 (3%)	0 (0%)
II	6737 (44%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	311 (24%)	0 (0%)
III	6702 (44%)	704 (84%)	786 (84%)	296 (80%)	512 (83%)	1664 (87%)	812 (84%)	812 (62%)	3233 (91%)
IV	441 (3%)	135 (16%)	148 (16%)	72 (20%)	108 (17%)	247 (13%)	152 (16%)	152 (12%)	301 (9%)
EF, n (%)									
30-39%	8656 (57%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	533 (36%)
<30%	6497 (43%)	839 (100%)	934 (100%)	368 (100%)	620 (100%)	1911 (100%)	964 (100%)	1310 (100%)	3534 (100%)
BMI (kg/m2), median [IQR]	27 [24,-30]	25 [22,-29]	26 [23-30]	27 [24-30]	27 [23-30]	26 [23,-29]	26 [23-30]	26 [23-29]	26 [23-30]
MAP (mmHg), median [IQR]	87 [79-96]	80 [73-88]	80 [73-88]	80 [73-87]	80 [73-87]	82 [74-90]	80 [73-89]	82 [73-90]	82 [73-90]
Heart rate (bpm), median [IQR]	70 [62-80]	73 [66-84]	73 [66-83]	72 [66-84]	73 [66-82]	74 [66-84]	73 [66-83]	72 [65-82]	72 [65-82]
Creatinine, median (IQR)	102 [83-129]	127 [100-167]	124 [98-163]	142 [112-180]	133 [106-171]	116 [91-152]	123 [96-161]	119 [94-157]	112 [89-145]
eGFR									
<30 ml/min/1.73 m ²	951 (6%)	134 (16%)	136 (15%)	82 (22%)	111 (18%)	237 (12%)	136 (14%)	170 (13%)	364 (10%)
30-59 ml/min/1.73 m ²	6049 (40%)	452 (54%)	490 (53%)	208 (57%)	353 (57%)	920 (48%)	501 (52%)	657 (50%)	1675 (48%)
≥60 ml/min/1.73 m ²	8079 (54%)	248 (30%)	303 (33%)	78 (21%)	154 (25%)	740 (39%)	322 (34%)	476 (37%)	1474 (42%)
Potassium (mmol/L), median [IQR]	4,3 [4,0-4,6]	4,2 [3,9-4,5]	4,2 [3,9-4,5]	4,1 [3,7-4,5]	4,2 [3,8-4,5]	4,2 [3,9-4,5]	4,2 [3,9-4,5]	4,2 [3,9-4,5]	4,3 [4,0-4,6]
NT-proBNP (pg/ml), median [IQR]	2066 [818-5,066]	7886 [4,461-15,741]	6916 [3,560-14,200]	7843 [3,995-17,400]	7130 [3,642-14,304]	6000 [2,761-12,286]	6639 [3,296-13,875]	5976 [2,860-12,652]	4471 [2,000-12,900]

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Table 1 (Continued)

Variables	Overall	4-Variable Definitions		3-Variable Definitions		2-Variable Definitions	
		HFA-AdvHF + NT-proBNP≥2,000 pg/ml	HFA-AdvHF + NT-BNP≥800 pg/ml	HFA-AdvHF + furosemide- equivalent > 80 mg/day	HFA-AdvHF + furosemide- equivalent > 40 mg/day	HFA-AdvHF def. (NYHA III-IV + EF < 30 + ≥2HHF within 12 months)	NYHA III-IV + ≥2HHF within 12 months
Medical history, n (%)							
≥1 HHF within 6 months	5119 (34%)	789 (94%)	877 (94%)	350 (95%)	586 (95%)	901 (94%)	1408 (94%)
≥2 HHF within 12 months	2103 (14%)	839 (100%)	934 (100%)	368 (100%)	620 (100%)	964 (100%)	1497 (100%)
Atrial fibrillation	9009 (59%)	598 (71%)	659 (71%)	262 (71%)	452 (73%)	668 (69%)	1076 (72%)
Smoke							
Current	1314 (10%)	67 (10%)	75 (10%)	27 (9%)	46 (9%)	78 (10%)	107 (9%)
Former	5970 (48%)	332 (48%)	370 (48%)	150 (48%)	255 (49%)	383 (48%)	597 (48%)
Never	5276 (42%)	293 (42%)	322 (42%)	134 (43%)	219 (42%)	332 (42%)	527 (43%)
Hypertension	10,617 (70%)	599 (71%)	670 (72%)	263 (71%)	451 (73%)	686 (71%)	1127 (75%)
Diabetes	4821 (32%)	354 (42%)	397 (43%)	180 (49%)	297 (48%)	411 (43%)	670 (45%)
Peripheral artery disease	1588 (10%)	126 (15%)	134 (14%)	56 (15%)	91 (15%)	136 (14%)	221 (15%)
Ischemic heart disease	9665 (64%)	628 (75%)	694 (74%)	285 (77%)	475 (77%)	710 (74%)	1100 (73%)
Valvular disease	4098 (27%)	324 (39%)	353 (38%)	142 (39%)	242 (39%)	358 (37%)	575 (38%)
Cerebrovascular disease	2675 (18%)	191 (23%)	207 (22%)	79 (21%)	140 (23%)	209 (22%)	328 (22%)
COPD	2088 (14%)	144 (17%)	167 (18%)	66 (18%)	112 (18%)	174 (18%)	298 (20%)
Cancer within 3 years	1971 (13%)	105 (13%)	115 (12%)	48 (13%)	81 (13%)	116 (12%)	188 (13%)
Liver disease	417 (3%)	46 (5%)	50 (5%)	23 (6%)	35 (6%)	50 (5%)	76 (5%)
Anemia	4354 (31%)	382 (48%)	414 (46%)	176 (50%)	283 (47%)	419 (46%)	686 (48%)
Concomitant medications, n (%)							
Beta blocker	14,192 (94%)	782 (93%)	874 (94%)	343 (93%)	580 (94%)	904 (94%)	1397 (93%)
RASI/ ARNI	14,033 (93%)	704 (84%)	792 (85%)	296 (81%)	513 (83%)	821 (86%)	1254 (84%)
MRA	8851 (58%)	468 (56%)	541 (58%)	198 (54%)	347 (56%)	564 (59%)	858 (57%)
Digoxin	1735 (11%)	135 (16%)	151 (16%)	54 (15%)	98 (16%)	155 (16%)	229 (15%)
Diuretic type							
No diuretic	6477 (43%)	98 (12%)	116 (12%)	0 (0%)	0 (0%)	125 (13%)	186 (12%)
Bumetanide	61 (< 1%)	4 (< 1%)	5 (1%)	2 (1%)	3 (< 1%)	5 (1%)	7 (< 1%)
Furosemide	8585 (57%)	734 (87%)	809 (87%)	366 (99%)	615 (99%)	830 (86%)	1296 (87%)
Torsemide	30 (< 1%)	3 (< 1%)	4 (< 1%)	0 (0%)	2 (< 1%)	4 (< 1%)	8 (1%)
Furosemide equivalent dose (mg/day), median [IQR]	30 [0-60]	80 [40-160]	80 [40-160]	160 [120-245]	120 [80-160]	80 [40-145]	80 [40-160]
Furosemide equivalent dose							
0-80 mg/day	13,410 (88%)	505 (60%)	574 (61%)	0 (0%)	252 (41%)	596 (62%)	916 (61%)
> 80 mg/day	1743 (12%)	334 (40%)	360 (39%)	368 (100%)	368 (59%)	368 (38%)	581 (39%)
Nitrate	1643 (11%)	127 (15%)	146 (16%)	63 (17%)	102 (16%)	147 (15%)	253 (17%)
Antiplatelet	5013 (33%)	255 (31%)	288 (31%)	109 (30%)	182 (29%)	297 (31%)	464 (31%)
Anticoagulant	8666 (57%)	522 (62%)	575 (62%)	227 (62%)	397 (64%)	590 (61%)	940 (63%)
Statin	8986 (59%)	455 (54%)	510 (55%)	188 (51%)	341 (55%)	524 (54%)	829 (55%)
Procedures, n (%)							
Coronary revascularization	6665 (44%)	425 (51%)	468 (50%)	196 (53%)	327 (53%)	480 (50%)	747 (50%)

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Table 1 (Continued)

Variables	Overall	4-Variable Definitions		3-Variable Definitions		2-Variable Definitions	
		HFA-AdvHF + NT-proBNP ≥ 2,000 pg/ml	HFA-AdvHF + NT-proBNP ≥ 800 pg/ml	HFA-AdvHF + furosemide-equivalent > 80 mg/day	HFA-AdvHF + furosemide-equivalent > 40 mg/day	GALACTIC-Severe def. (NYHA III-IV + EF < 30 + ≥ 1HHF within 6 months)	HFA-AdvHF def. (NYHA III-IV + EF < 30 + ≥ 2HHF within 12 months)
HF devices	4077 (27%)	351 (42%)	403 (43%)	164 (45%)	281 (46%)	645 (34%)	420 (44%)
CRT-P	707 (4%)	76 (9%)	82 (9%)	27 (7%)	54 (9%)	120 (6%)	82 (9%)
CRT-D	1744 (12%)	180 (22%)	204 (22%)	91 (25%)	147 (24%)	321 (17%)	213 (22%)
ICD	1626 (11%)	95 (11%)	117 (12%)	46 (13%)	80 (13%)	204 (11%)	125 (13%)
Socioeconomic characteristics, n (%)							
Family type							
Cohabiting	8382 (55%)	465 (55%)	508 (54%)	211 (57%)	357 (58%)	1019 (53%)	524 (54%)
Living alone	6760 (45%)	374 (45%)	426 (46%)	157 (43%)	263 (42%)	889 (47%)	440 (46%)
Education level							
Compulsory school	5639 (38%)	360 (44%)	390 (43%)	154 (42%)	272 (45%)	791 (43%)	399 (42%)
Secondary school	6369 (43%)	340 (41%)	381 (42%)	156 (43%)	248 (41%)	773 (42%)	395 (42%)
University	2910 (20%)	123 (15%)	145 (16%)	53 (15%)	91 (15%)	297 (16%)	151 (16%)
Income > median	7583 (50%)	335 (40%)	379 (41%)	143 (39%)	241 (39%)	757 (40%)	394 (41%)

ARNI, angiotensin receptor-neprilysin inhibitor; BML, body mass index; COPD, chronic obstructive pulmonary disease; EF, ejection fraction; eGFR, estimated glomerular filtration rate (calculated by the Chronic Kidney Disease Epidemiology Collaboration formula); IQR, interquartile range; KRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; MAP, mean arterial pressure; RAS-i, renin angiotensin converting enzyme inhibitors

and were not included in any inferential analysis, no method for handling missing data was applied. The proportion of missing values for each variable is reported in [Table S2, Supplemental material](#).

Patient characteristics across different definitions are presented ([Table 1](#)) for descriptive purposes only, no formal statistical comparisons between definitions were performed.

Univariable logistic regression models were applied to evaluate the association between each severity criterion (NYHA class, EF, history of HHF, NT-proBNP levels, and furosemide equivalent dose) and the primary outcome. Odds ratios (OR) and 95% confidence intervals (CI) were estimated. A multivariable logistic regression model was then performed to assess their independent prognostic significance. Variance inflation factors (VIFs) were also calculated to assess multicollinearity, with VIF values interpreted as follows: 1 indicating no correlation, 1–5 indicating moderate correlation, and > 5 indicating high correlation.

Agreement between all the possible pairs of definitions was evaluated using Cohen's kappa statistic.²¹ Kappa values were interpreted according to the Landis and Koch criteria (< 0.00 poor agreement, 0.00–0.20 slight agreement, 0.21–0.40 fair agreement, 0.41–0.60 moderate agreement, 0.61–0.80 substantial agreement, and 0.81–1.00 perfect agreement).

1-year crude event rates for primary and secondary outcomes were calculated for each severity criterion and all the above-mentioned definitions ([Table S1, Supplemental material](#)) as the percentage of patients experiencing the event within the first year of follow-up.

The predictive performance of each 2-, 3- and 4-variable definitions ([Table S1, Supplemental material](#)) was assessed and compared with the HFA-AdvHF definition (reference) using different metrics: the Bayesian information criterion (BIC), the Akaike information criterion (AIC), the area under the curve (AUC), the Net reclassification improvement (NRI) and Integrated discrimination improvement (IDI) as well as the Brier score. More details about these metrics are reported in Supplements.

No additional statistical adjustments were made. This approach aligns with clinical practice, where HF staging and RCT inclusion typically rely solely on predefined criteria.

Statistical analyses were performed by Stata 17.0 (Stata Corp LLC, College Station, TX, USA). A p-value < 0.05 was considered statistically significant.

RESULTS

Between 1 January 2011 and 31 December 2022, 165,347 patients were enrolled in SwedeHF. After applying selection criteria of this study, 15,153 patients were included ([Figure S1, Supplemental material](#)). The median age was 75 (IQR 67–81) years, and 25% were female ([Table 1](#)). Median NT-proBNP was 2066 pg/ml (IQR 818–5066), with 47% classified as NYHA III–IV, 43% having EF < 30%, 14% having experienced ≥ 2 HHF within 12 months prior to

baseline, and 34% ≥ 1 HHF within 6 months. Among them, 89% were outpatients, and 80% received follow-up in specialty care. Common comorbidities included history of ischemic heart disease (64%), atrial fibrillation (AF) (59%), chronic kidney disease (CKD) (46%). 94% received beta-blockers (BB), 93% renin-angiotensin system inhibitors (RASi) or angiotensin receptor/neprilysin inhibitors (ARNi), and 58% mineralocorticoid receptor antagonists (MRA). 27% had an HF device (16% cardiac resynchronization therapy [CRT] and 11% an implantable cardioverter defibrillator [ICD]). 57% received loop diuretics with a median furosemide equivalent dose of 30 mg/day (IQR 0–60 mg/day).

Prevalence of severe/AdvHF according to different definitions

Overall, 6.4% of patients met the HFA-AdvHF-definition, while 22.7% met only 2 HFA criteria, 39.3% 1 criterion, and 31.6% fulfilled none ([Figure 1](#)). The distribution of additional HFA criteria among those who fulfilled at least one is detailed in [Figure 2](#).

12.6% met the GALACTIC-Severe definition. Fewer patients fulfilled the 4-variable definitions compared with the HFA-AdvHF-definition, with a prevalence ranging from 6.2% (HFA-AdvHF definition + NT-proBNP ≥ 800 ng/ml) to 2.4% (HFA-AdvHF definition + furosemide dose > 80 mg/daily) ([Table 1](#)). In contrast, the prevalence of all the 2-variable definitions surpassed that of the HFA. Among these, the combination of NYHA III–IV with EF < 30% had the highest prevalence, encompassing 23.4% of patients.

Patient characteristics according to different definitions

HFA-AdvHF-definition

Median age was 75 (IQR 67–81), and 21% were female. Compared with the overall population, a higher proportion were inpatients (36%), although referral rates to specialty care follow-up were similar (80%). They exhibited a higher burden of comorbidities, including AF (69%) and ischemic

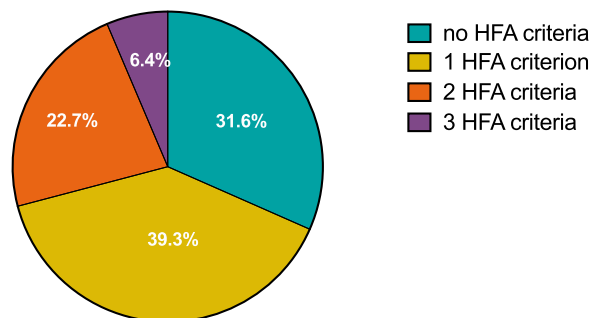


Figure 1 Distribution of patients according to the number of HFA criteria for the AdvHF definition (NYHA class III–IV, EF < 30%, ≥ 2 HHF within 12 months). AdvHF, advanced heart failure; EF, ejection fraction; HFA, Heart Failure Association; HHF, heart failure hospitalization; NYHA, New York Heart Association.

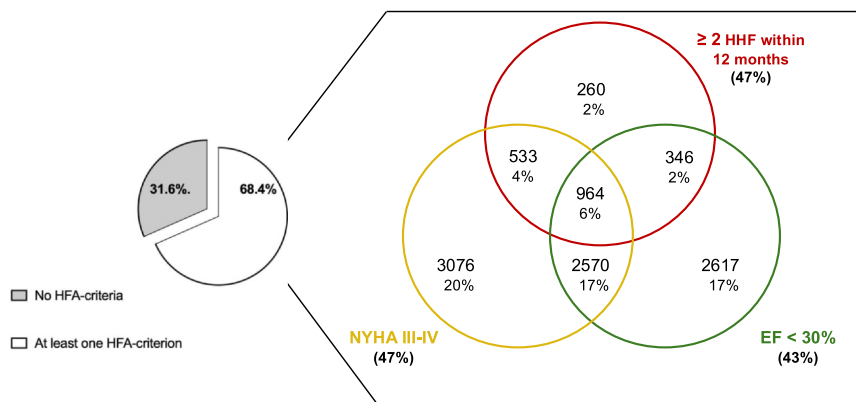


Figure 2 Distribution of the HFA criteria for the AdvHF definition in the study population. AdvHF, advanced heart failure; EF, ejection fraction; HFA, Heart Failure Association; HHF, heart failure hospitalization; NYHA, New York Heart Association.

heart disease (74%). They were less likely to receive RASI/ARNI (86%), but more likely to have HF devices (44%), MRA (59%), digoxin (16%) and loop diuretics (87%), with a median furosemide equivalent dose of 80 mg/daily (IQR 40–145). Median NT-proBNP was 6639 pg/ml (IQR 3296–13,875) and 16% had NYHA IV.

GALACTIC-Severe definition

Compared with patients meeting the HFA-AdvHF definition, those fulfilling the GALACTIC-Severe criteria had a lower prevalence of NYHA IV (13%), lower median NT-proBNP level (6000 pg/ml, [IQR 2761–12,286]) and were less likely to have HF devices (34%). Treatment patterns were similar, with 94% receiving BB, 87% RASI/ARNI, 57% MRA and 85% loop diuretics, with a median furosemide equivalent dose of 80 [IQR 40–120] mg/daily. These patients had a lower prevalence of CKD (61%), ischemic heart disease (71%), as well as of all the other comorbidities, except for cancer (14%) and hypertension (72%), which showed no significant differences.

4-variable definitions

Compared with patients meeting the GALACTIC-Severe and HFA-AdvHF definitions, these patients had a higher comorbidity burden, were more frequently inpatients at the index date, and were more likely to have an HF device. Those meeting the HFA-definition+furosemide > 80 mg/day had the highest prevalence of NYHA IV (20%) and CKD (79%), along with the lowest use of RASI/ARNI (81%) and MRA (54%).

2-variable definitions

Patients fulfilling these definitions were more likely to be female and outpatients, had lower NYHA IV prevalence and lower median NT-proBNP levels as compared with those meeting the HFA-AdvHF definition. In particular, those defined by NYHA III-IV + EF < 30% had lower NT-proBNP (4471 pg/ml, IQR 2.000–9.372) and required lower furosemide (40 mg/day, IQR 20–80). Additionally, they

were less likely to have NYHA IV (9%), CKD (58%), an HF device (35%) and to be on MRA (57%), although their use of RASI/ARNI was higher (90%).

Agreement between alternative definitions

Overall agreement between alternative definitions ranged from moderate to substantial (Table 2). The highest concordance was observed among the 4-variable definitions, between these definitions (except those including daily diuretic dose) and the HFA-AdvHF definition, and between the HFA-AdvHF definition and the 2-variable definition including EF and previous HHF. The GALACTIC-Severe definition demonstrated moderate agreement with most definitions, including the HFA-AdvHF-definition (k-value 0.5923), but only fair agreement with the 4-variable definition including furosemide-equivalent dose > 80 mg/day. Likewise, only slight to fair agreement has been documented between 2-variable definitions including HHF ("NYHA + HHF", "EF + HHF") and 4-variable definitions that incorporated daily diuretic dose.

Associations between individual severity criteria and outcomes

In univariable analyses, each severity criterion was associated with a higher risk of the primary outcome (CV death/first HHF) (Figure 3). NT-proBNP > 800 pg/ml showed the strongest association (OR 5.23; 95%CI 4.65–5.89), followed by ≥ 2 HHF within 12 months and a furosemide dose > 80 mg/daily. Multivariable analysis confirmed the independent predictive role of all criteria (Figure 3), with VIF values indicating minimal collinearity (Table S3, Supplemental material).

1-year event rates across various definitions (Fig. 4, Table S4 Supplemental material)

Patients meeting the HFA-AdvHF definition had a 1-year risk of CV death/HHF of 70%. One-year all-cause mortality was 45%, with 79% of deaths being CV-related. CV

Table 2 Pairwise Agreement between Alternative Severe and AdvHF Definitions Calculated using Cohen's Kappa

	HFA-AdvHF def. + NT- proBNP ≥2000 pg/ml	HFA-AdvHF def. + NT- proBNP ≥800 pg/ml	HFA-AdvHF def. + furosemide- equivalent > 80 mg/day	HFA-AdvHF def. + furosemide- equivalent > 40 mg/day	HFA-AdvHF definition	GALACTIC-- Severe definition	NYHA + EF	NYHA + HHF	EF + HHF
HFA-AdvHF def. + NT-proBNP ≥2000 pg/ml	-	0.9431*	0.5378*	0.7547*	0.9263*	0.5383	0.3231*	0.6968*	0.7650*
HFA-AdvHF def. + NT-proBNP ≥800 pg/ml	0.9431*	-	0.5369*	0.7685*	0.9831*	0.5819	0.3552*	0.7494*	0.8194*
HFA-AdvHF def. + furosemide-equivalent > 80 mg/day	0.5378*	0.5369*	-	0.7369*	0.5363*	0.2777	0.1513*	0.3701*	0.4165*
HFA-AdvHF def. + furosemide-equivalent > 40 mg/day	0.7547*	0.7685*	0.7369*	-	0.7714*	0.4277	0.2460*	0.5603*	0.6215*
HFA-AdvHF definition	0.9263*	0.9831*	0.5363*	0.7714*	-	0.5923	0.3652*	0.7653*	0.8358*
GALACTIC-Severe definition	0.5383	0.5819	0.2777	0.4277	0.5923	-	0.6436	0.4700	0.5091
NYHA + EF	0.3231*	0.3552*	0.1513*	0.2460*	0.3652*	0.6436	-	0.2838*	0.3111*
NYHA + HHF	0.6968*	0.7494*	0.3701*	0.5603*	0.7653*	0.4700	0.2838*	-	0.6550*
EF + HHF	0.7650*	0.8194*	0.4165*	0.6215*	0.8358*	0.5091	0.3111*	0.6550	-

* Kappa value among nested definitions

EF, ejection fraction; HHF, heart failure hospitalization; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart

Agreement according to Kappa values: <0.00 poor, 0.00–0.20 slight, 0.21–0.40 fair, 0.41–0.60 moderate, 0.61–0.80 substantial, and 0.81–1.00 almost perfect

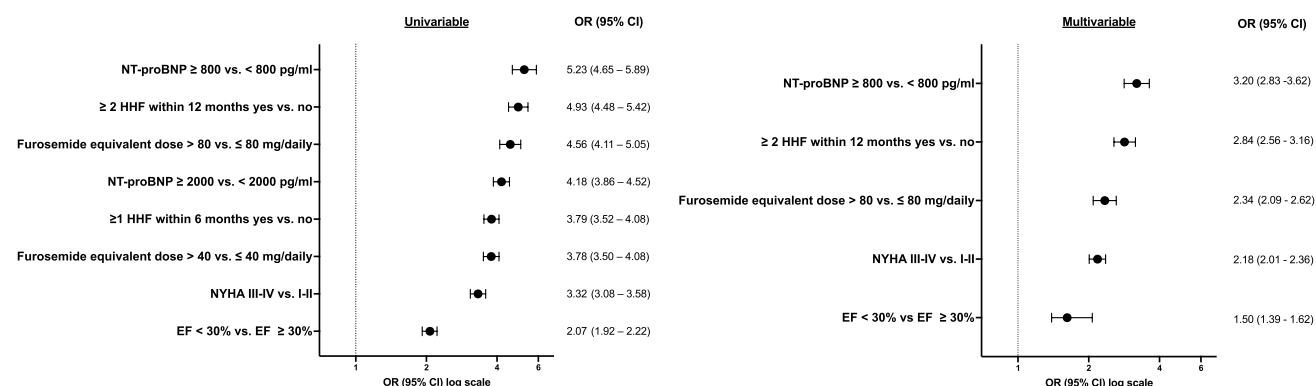


Figure 3 Severity criteria and their association with the primary outcome (1-year CV death or first HHF) in univariable and multivariable analysis. CV, cardiovascular; EF, ejection fraction; HHF, heart failure hospitalization; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association.

mortality alone was 36%, and 59% of patients experienced at least 1 HHF.

Those meeting the GALACTIC-Severe definition had a lower, yet still substantial risk of primary outcome (59%), with an all-cause mortality rate of 38% (76% CV), a CV mortality of 29% and 49% experiencing at least 1 HHF. Rates of advanced therapies use were low across both groups: among HFA-defined patients, 3.1% underwent HTx and 1.9% received an LVAD, compared with 1.9% and 1.4%, respectively, among those meeting the GALACTIC-Severe-definition.

Compared with patients meeting the HFA-AdvHF definition, those fulfilling any 4-variable definition had higher event rates for both primary and secondary outcomes, except for LVAD and HTx, which were less frequent. Notably, while all 4-variable definitions were associated with a higher CV event rate than the HFA-definition, only

those including NT-proBNP ≥2000 pg/ml or furosemide > 40 mg/daily showed a higher CV/non-CV events ratio.

In contrast, all 2-variable definitions had lower event rates for all outcomes as compared with the HFA-AdvHF-definition. Their CV/non-CV events ratios were also lower, except in the subgroups defined by EF < 30% and ≥2 HHF within 12 months.

Performance of the different definitions

Table 3. summarizes the prognostic performance metrics across the various definitions.

All 4-variable definitions showed significantly superior discrimination compared with the reference HFA-AdvHF definition (AUC 0.7155 [0.70647 – 0.72451]; all $p < 0.001$). Their AUCs ranged from 0.7301 (0.72112 –

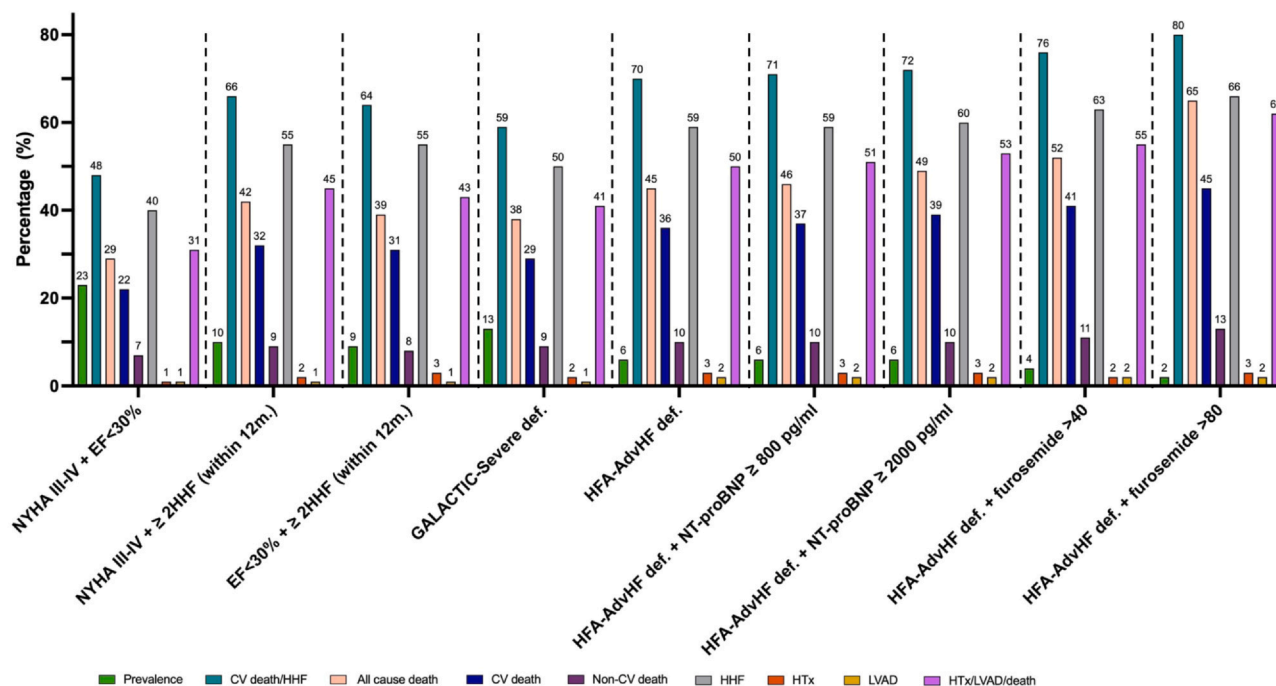


Figure 4 1-year event rates associated with different definitions of severe and AdvHF. AdvHF, advanced heart failure; CV, cardiovascular; EF, ejection fraction; HFA, Heart Failure Association; HTX heart transplantation; LVAD, left ventricular assist device, NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association.

0.73902) for the HFA-AdvHF definition + furosemide equivalent dose > 40 mg/day to 0.7507 (0.74225 – 0.75920) for the HFA AdvHF definition + NT-proBNP ≥2000 pg/ml.

Beyond discrimination, 4-variable definitions were also associated with better overall model performance, as reflected by lower AIC and BIC values (indicating better model fit), higher NRI, and IDI values (reflecting superior discrimination and reclassification), and lower Brier scores (indicating improved calibration). Among the 4-variable definitions, those incorporating NT-proBNP ≥2000 pg/ml consistently delivered the best overall performance. In contrast, all 2-variable definitions performed worse than the HFA-definition, with the combination of EF < 30% and ≥2 HHF within 12 months (AUC 0.6570 [0.64768 – 0.66628], $p < 0.01$) showing the poorest performance across metrics.

The GALACTIC-Severe definition demonstrated a modest but significantly higher discrimination than the HFA-AdvHF definition by an AUC of 0.7273 (.71850 - 0.73602) and an NRI value of 0.194 (0.164 – 0.225). It also demonstrated a slightly improved model fit by lower AIC and BIC, despite similar IDI and Brier scores.

Discussion

Large registries provide valuable insights into patient profiling and risk stratification, particularly for less prevalent sub-populations, as patients with severe and AdvHF, who are often underrepresented in smaller cohorts. Our analysis of one of the largest real-world HFrEF cohorts worldwide provides key findings in this setting, which might contribute

to refining RCT design and optimizing referrals to AdvHF centers. In particular, we showed that:

- I) The HFA-AdvHF definition (NYHA III-IV, EF < 30; ≥2 HHF within 12 months) identified a small, high-risk HFrEF subgroup (70% 1-year risk of CV death/HHF, 45% 1-year mortality). The GALACTIC-Severe definition (NYHA III-IV, EF < 30; and ≥1 HHF within 6 months) demonstrated moderate agreement with the HFA-AdvHF definition and outperformed it across most performance parameters. Since it was less restrictive, doubled patient identification, maintaining high, although lower risk when compared to the HFA-AdvHF definition (59% 1-year CV death/HHF, 38% 1-year mortality).
- II) No single criterion (e.g., NYHA class, EF, HHF, NT-proBNP, diuretic dose) fully captured severe and AdvHF complexity. Combining multiple criteria, improved predictive accuracy and event rates while reducing patient eligibility.

Profiling severe and AdvHF for patient characteristics and outcome

Data on severe HF epidemiology and outcomes are lacking, and only limited data exist on AdvHF. In our study, the simplified HFA-AdvHF definition was met by 6% of patients with HFrEF and identified a population with a 70% 1-year risk of CV death or HHF and 45% all-cause mortality (79% CV-related). These findings align with prior studies, however focusing specifically on HFrEF.^{3,22}

Metrics

4-variable Definitions

3-variable definitions

2-variable definitions

† p-value < 0.01 De Long test comparing the AUC of the reference definition (HFA-AdvHF definition) with the AUC of the other definitions
* Statistical significance of the comparison of the AIC of the reference definition (HFA-AdvHF definition) with the AIC of the other definitions.
‡ Statistical significance of the comparison of the BIC of the reference definition (HFA-AdvHF definition) with the BIC of the other definitions.
‡‡ Statistical significance of the comparison of the NRI and IDI of the reference definition (HFA-AdvHF definition) with those of the other definitions.
AUC, area under the curve; AIC, Akaike information criterion; BIC, Bayesian information criterion; EF, ejection fraction; HFA, Heart Failure Association; HHF, heart failure hospitalization; IDI, integrated discrimination improvement; NRI, Net reclassification index; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association

The HFA-definition selects a too high-risk group for AdvHF referrals, potentially missing the optimal window for advanced therapies. Given LVAD advancements and broader indications for earlier use, early identification is critical. An intermediate stage (C2, severe HF) has been proposed between symptomatic HF (stage C) and AdvHF (stage D), but no validated definition exists.¹⁰ In our cohort, applying the GALACTIC-Severe definition doubled patient identification while maintaining high risk of events (38% 1-year mortality, 76% CV-related), suggesting that avoiding a second HHF requirement could facilitate earlier access to AdvHF care. Despite the poor prognosis of AdvHF, consistent with prior observational studies,^{3,23} HTx and LVAD utilization remained low in our cohort, likely due to older median age (75 years) and high comorbidity burden.

Defining severe and AdvHF for clinical and research applications

Real-world data informs RCT design by refining selection criteria, determining sample size, and optimizing power calculations. In the absence of a universally accepted definition of severe and AdvHF, we evaluated several definitions based on varying combinations of severity criteria. Each factor (NYHA class III-IV, EF <30%, HHF, NT-proBNP, diuretic dose) was independently associated with increased risk of the primary outcome, with minimal collinearity observed among them. Incorporating multiple variables consistently improved the performance of the definitions in terms of model fit, discrimination and calibration. These findings suggest that each criterion may capture different aspects of disease severity, and no single factor is sufficient to fully characterize the high-risk stage of HF.

Among all definitions tested, the 4-variable model incorporating NT-proBNP $\geq 2,000$ pg/ml consistently demonstrated the strongest performance, achieving the highest AUC, lowest AIC, BIC, Brier score, and strongest NRI and IDI values. NT-proBNP emerged as a more powerful predictor than diuretic dose, with model performance improving as NT-proBNP thresholds increased.

The GALACTIC-Severe-definition demonstrated moderate agreement with the HFA-definition and outperformed it across most metrics, including AUC, AIC, BIC, and NRI, although IDI and Brier score showed no significant differences.

Balancing prevalence against event rates for RCT design and clinical implications

Our findings highlight the difficulties of developing a simpler yet effective definition of severe and AdvHF. While incorporating multiple severity criteria increases event rates, it delays patient identification for referral and reduces eligibility in the context of trial design. Indeed, while stringent inclusion criteria in RCT can enhance risk stratification, they may limit generalizability, complicate enrolment and escalate trial costs. Thus, our data can be used to

identify the optimal trade-off between eligibility and desired event rates tailored to the specific intervention.

The HFA-AdvHF definition identified 6.4% of patients, with a 70% 1-year risk of CV death or HHF, while the GALACTIC-Severe-definition identified 12.6%, with a slightly lower risk, i.e. 60% risk of primary outcome. Even though CV events were more frequent than non-CV events, the latter were still significant and should be considered when enrolling patients in RCTs or considering them for advanced treatment strategies.

As compared with recent HFREF RCTs (e.g., PARADIGM-HF, DAPA-HF and EMPEROR-REDUCED; [Table S5, Supplemental material](#)), our cohort had significantly higher event rates, as those trials did not focus on AdvHF.^{24–26} In contrast, the event rate in our cohort was closer to, but still higher than, that observed in the VICTORIA and GALACTIC-HF trials, which targeted higher-risk patients with higher NT-proBNP levels and recent HHF.^{27,28} Our findings support the use of NT-proBNP and HHF history as enrichment criteria to increase CV event rates and improve trial efficiency by minimizing competing risks. NT-proBNP was more effective than diuretic dose in predicting CV events, and among 4-variable models, only those including NT-proBNP ≥ 2000 pg/ml or furosemide > 40 mg/day showed a higher CV/non-CV event ratio than the HFA-definition.

Consistent with the known real-world vs. RCT event rate disparities, our study population had higher event rates than the MEDAMACS, LIFE and ROADMAP trials, which specifically targeted AdvHF patients ([Table S6, Supplemental material](#)).^{4,29,30}

Notably, 2-variable models including ≥ 2 HHF within 12 months + EF <30% or NYHA III-IV increased eligibility while maintaining high CV event risk.

Limitations

Some limitations must be acknowledged. First, while SwedeHF data are comprehensive, they may not fully capture AdvHF patient diversity, particularly those treated outside Sweden or in non-specialty settings. This limits generalizability to different healthcare systems. While having a validation cohort could have mitigated this limitation, the availability of such cohorts in the context of large registries is limited. Second, although we applied the most recognized criteria to define severe and AdvHF, the use of registry data limited the inclusion of certain variables, such as functional capacity, intolerance to HF therapy, prior inotrope use, episodes of ventricular arrhythmias or need for ambulatory intravenous diuretics, since unavailable for most or the entire study period. Nevertheless, the severity criteria we used reflect those most commonly available and routinely employed in clinical practice and RCT design. While the registry is generalizable, both trial inclusion and AdvHF referrals may intentionally (and in some cases appropriately) focus on younger patients, and the present data may be less applicable to such situations. Finally, while the HFA-AdvHF

definition encompasses patients across the entire EF spectrum, our analysis specifically focused on HFrEF. This decision was guided by the generally distinct therapeutic approaches required for HFrEF and HF with preserved EF, which are also separately investigated in RCTs.

Conclusions

In this large real-world HFrEF cohort, the HFA-AdvHF definition identified a small subset of high-risk patients, while the GALACTIC-Severe-definition captured twice as many patients with only slightly lower but still high CV event risk. A less restrictive definition, like the GALACTIC-Severe one, may improve referral timing to AdvHF centers when prognosis can still be positively influenced. However, further validation is required, particularly within a targeted population eligible for LVAD or HTx. For RCT design, NT-proBNP, HHF history and diuretic dosage can help tailoring risk levels, balancing potential risk against enrollment feasibility.

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Conflicts of interests

G.S. reports grants and personal fees from CSL Vifor, Boehringer Ingelheim, AstraZeneca, Servier, Novartis, Cytokinetics, Pharmacosmos, Medtronic, Bayer, and personal fees from Roche, Abbott, Edwards Lifescience, TEVA, Menarini, INTAS, GETZ, Laboratori Guidotti, and grants from Boston Scientific, Merck, all outside the submitted work.

L.H.L. reports grants, consulting or speaker fees from AstraZeneca, Novartis, Bayer, Pharmacosmos, Boehringer Ingelheim, Amgen, Novo Nordisk, outside the submitted work.

C.H. reports consulting fees from Novartis, Roche Diagnostics and AnaCardio, research grants from Bayer and speaker and honoraria from AstraZeneca and Novartis, outside the submitted work.

FL reports consulting fees from AstraZeneca, outside the submitted work.

Oscar Braun has received honoraria for advisory board and speaker fees from Abbot, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol Meyers Squibb, Novartis, Novo Nordisk and Pfizer, outside the submitted work.

BB reports advisory or consultation from ABIOMED / Johnson and Johnson, Bayer, Boehringer Ingelheim, Cardurion, Cytokinetics, Eli Lilly, Medtronic, Merck, Idorsia, Novo Nordisk, Regeneron, Renovacor, Roche, Salubris, Sanofi-Aventis, scPharmaceuticals, Vifor, Respircardia/ Zoll, outside the submitted work.

M.M. reports personal consulting honoraria of minimal amount from Abbott, Amgen, Bayer, Edwards Therapeutics, LivaNova and Vifor Pharma for participation in advisory board meetings and executive committees of clinical trials, outside the submitted work. GB reports personal fees from Abbott, AstraZeneca, Boehringer Ingelheim, Novartis and Novo-Nordisk, outside the submitted work.

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Appendix A. Supporting information

Supplemental data associated with this article can be found in the online version at [doi:10.1016/j.healun.2026.03.008](https://doi.org/10.1016/j.healun.2026.03.008).

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