ANALYSIS PLAN

Applicability of past and ongoing steroidal and non-steroidal mineralocorticoid receptor antagonist trials in real-world patients with heart failure with reduced, mildly reduced, and preserved ejection fraction

---

Benedikt N Beer[1,2,3], Felix Lindberg[1], Lina Benson[1], Gianluigi Savarese[1]

Affiliations:

1. Department of Clinical Science and Education, Södersjukhuset, Karolinska Institutet, Stockholm, Sweden
2. Department of Cardiology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany
3. German Center für Cardiovascular Research (DZHK), Partner Site Hamburg/Lübeck/Kiel, Hamburg, Germany

Table of Content

Abbreviations

ACEi, angiotensin-converting enzyme inhibitor;
ACS, acute coronary syndrome;
AFib, atrial fibrillation;
AFlu, atrial flutter;
AIDS, acquired immunodeficiency syndrome;
AKI, acute kidney injury;
ALAT, alanine aminotransferase;
AMI, acute myocardial infarction;
Apodos, Swedish multi-dose drug dispensing system with all medication for a given time in one bag;
ARB, angiotensin II receptor blocker;
ARNi, angiotensin receptor/neprilysin inhibitor;
ASAT, aspartate aminotransferase;
ATC, Anatomical Therapeutic Chemical classification;
BMI, body mass index;
BNP, brain natriuretic peptide;
BP, blood pressure;
CABG, coronary artery bypass graft;
CKD-EPI 2021, Chronic Kidney Disease Epidemiology Collaboration (2021 update) formula;
CoD, Cause of Death Register;
CONFIRMATION-HF, Determine the Efficacy and Safety of Finerenone and SGLT2i in Combination in Hospitalized Patients with Heart Failure study;
COPD, chronic obstructive pulmonary disease;
CRT, cardiac resynchronisation therapy;
CV, cardiovascular;
CYP3A4, cytochrome P450 3A4;
DBP, diastolic blood pressure;
E, Early diastolic transmitral flow velocity (E wave in echocardiography);
é, Early diastolic mitral annular velocity (é wave in echocardiography);
eGFR, estimated glomerular filtration rate;
EMPHASIS-HF, Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure;
EPHESUS, Eplerenone Post–Acute Myocardial Infarction Heart Failure Efficacy and Survival study;
FINALITY-HF, Evaluate Finerenone on Clinical Efficacy and Safety in Patients with Heart Failure Who Are Intolerant or Not Eligible for Treatment with Steroidal Mineralocorticoid Receptor Antagonists study;
FINEARTS-HF, Finerenone in Heart Failure with Mildly Reduced or Preserved Ejection Fraction study;
GOLD, Global Initiative for Chronic Obstructive Lung Disease classification;
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;
i.v., intravenous;
ICD, implantable cardioverter-defibrillator;
ICD-10-SE, International Statistical Classification of Diseases, 10th revision, Swedish version;

IQR, interquartile range;
KCCQ, Kansas City Cardiomyopathy Questionnaire;
LAA, left atrial area;
LAD, left atrial diameter;
LAVI, left atrial volume index;
LISA, Longitudinal Integrated Database for Health Insurance and Labour Market Studies;
LVAD, left ventricular assist device;
LVEF, left ventricular ejection fraction;
LVMI, left ventricular mass index;
MDRD, Modification of Diet in Renal Disease (unspecified version) formula;
MDRD-6, Modification of Diet in Renal Disease (6 variables version) formula;
MI, myocardial infarction;
MRA, mineralocorticoid receptor antagonist;
n (%), total number of patients (relative number of patients);
NPDR, National Prescribed Drug Register;
NPR, National Patient Register;
NT-proBNP, N-terminal prohormone of brain natriuretic peptide;
NYHA, New York Heart Association classification;
O_2, oxygen;
OPS, classification for the encoding of operations, procedures and general medical measures;
PCI, percutaneous coronary intervention;
RACE, RAte Control vs Electrical Cardioversion for Persistent Atrial Fibrillation classification;
RALES, Randomized Aldactone Evaluation study;
RCT, randomised controlled trial;
REDEFINE-HF, Determine the Efficacy and Safety of Finerenone on Morbidity and Mortality Among Hospitalized Heart Failure Patients study;
RIFLE, Risk, Injury, Failure, Loss, End-stage kidney disease classification;
SBP, systolic blood pressure;
SPIRIT-HF, Spironolactone In The Treatment of Heart Failure study;
SPIRRIT-HFpEF, Spironolactone Initiation Registry Randomized Interventional Trial in Heart Failure With Preserved Ejection Fraction;
SGLT2i, sodium/glucose cotransporter 2 inhibitor;
SR, sinus rhythm;
SwedeHF, Swedish Heart Failure Registry, database 4;
TIA, transient ischaemic attack;
TOPCAT, Aldosterone Antagonist Therapy for Adults With Heart Failure and Preserved Systolic Function study;
ULORSAK, leading cause of death diagnosis according to ICD-10-SE;
VT, ventricular tachycardia;
WHF, worsening heart failure

1 Background & aim

Steroidal mineralocorticoid receptor antagonists (sMRA) are core pillars in the treatment of patients with heart failure (HF) with reduced ejection fraction (HFrEF), while the evidence for HF with mildly reduced (HFmrEF) and preserved ejection fraction (HFpEF) is more ambiguous.[1,2] The novel non-steroidal MRAs (nsMRAs) present a new opportunity to target the MR in HF, with potentially lesser risk of adverse drug reactions such as hyperkalaemia.[3]

We aim to assess the eligibility of a real-world HF population to past and ongoing MRA trials to explore their generalisability, and to identify key inclusion and exclusion criteria to inform future trial design.

2 Methods

2.1 Data sources

Data from 5 different Swedish registries will be used. The study population will be derived from the Swedish Heart Failure Registry (SwedeHF), managed by the Uppsala Clinical Research Center (Uppsala, Sweden), founded in 2000 and implemented nationwide in 2003.[4,5] Physician-judged HF is the only inclusion criterion, since April 2017 defined by the International Statistical Classification of Diseases, 10th revision, Swedish version (ICD-10-SE) codes I11.0, I13.0, I13.2, I25.5, I42.0, I42.6-7 or I50. Approximately 80 variables are recorded at the hospitalisation discharge or outpatient visit that prompts a registration. Until December 2023, 129,240 unique patients had been registered in SwedeHF, with 59% coverage of prevalent HF in Sweden in 2023.[6] The Swedish personal identification number allows for linkage between SwedeHF and other national registries: The Longitudinal Integrated Database for Health Insurance and Labour Market Studies (LISA), managed by Statistics Sweden, will provide socioeconomic variables.[7] The National Patient Register (NPR) collects data on diagnoses and procedures from in-patient stays since 1964 (nationwide since 1987) and from specialist out-patient care (but not primary care) since 2001, and was used to supplement comorbidity variables and cause-specific hospitalisation outcomes according to ICD-10-SE.[8] The National Prescribed Drug Register (NPDR) was implemented in July 2005, and provides information based on the Anatomical Therapeutic Chemical classification (ATC) codes on prescribed drugs that were dispensed in pharmacies.[9] Information on cause-specific death was collected through the National Cause of Death Register (CoD).[10] The NPR, NPDR and CoD are all managed by the National Board of Health and Welfare.

2.2 Patients

Patients from SwedeHF with a diagnosis of HF and a registry entry from January 1, 2017 (year following the prior European Society of Cardiology [ESC] HF guideline) to December 31, 2023 (censoring of registry) will be included. For patients with multiple SwedeHF entries, the latest registration (‘index registration’) will be selected to achieve a more contemporary population. Four different patient groups will be used as the denominator of eligibility rates: the overall HF population (i.e. any left ventricular ejection fraction [LVEF]), HFpEF (i.e. LVEF $\geq$ 50%), HFmrEF (i.e. LVEF 40-49%), and HFrEF (i.e. LVEF $<$ 40%). Of note, SwedeHF mostly comprises of categorical LVEF data based on these cut-offs. An LVEF of 40% is, thus, categorised as HFmrEF in accordance with prior European guidelines[11] before they were updated.[1,12]

2.3 Eligibility criteria definitions

Eight completed or ongoing MRA trials will be considered in this analysis: TOPCAT[13], SPIRRIT-HFpEF[14], SPIRIT-HF[15], FINEARTS-HF[16], RALES[17], EMPHASIS-HF[18], FINALITY-HF[19], and REDEFINE-HF[20]. From each trial, eligibility criteria will be extracted and adapted to the SwedeHF setting. An overview of all inclusion and exclusion criteria of the original randomised controlled trials (RCTs) of interest is given in Table 2. From Table 3 to Table 10, the operationalised adaption to the SwedeHF setting of each of these criteria based on data availability is provided, and detailed reasoning is provided.

2.4 Statistical analysis

Baseline characteristics of the overall parent population of each trial as well as stratified by eligibility for this trial vs ineligibility will be presented (Table 11). Categorical variables will be shown as absolute and relative frequencies, continuous variables as median with interquartile range. Comparison of these two strata will be performed by the Mann-Whitney U-test for continuous and by the $\chi 2$ test for categorical variables, respectively. The percentage of missing data will be reported. Missing data will then be handled by single imputation.[21] The variables included in the imputation model are displayed in Table 11.

For each trial, patients will be considered as potentially eligible and therefore included in the denominator of the eligibility calculation, if they meet an EF phenotype (HFrEF, HFmrEF, or HFpEF) considered in the trial. This means that all patients with HFrEF will be included in the eligibility calculations for RALES[17], EMPHASIS-HF[18], and FINALITY-HF[19], whereas all patients with HFmrEF or HFpEF will be included in the eligibility calculations for TOPCAT[13], SPIRRIT-HFpEF[14], SPIRIT-HF[15], FINEARTS-HF[16], and REDEFINE-HF[20]. Eligibility will be calculated for each criterion individually, for variable groups and clusters (Table 12), and for all trial criteria simultaneously ('strict scenario', Table 3 to Table 10). The numerators in the eligibility calculations will consist of those patients in the denominator (i.e. potentially eligible) who fulfil all criteria, as adapted to the SwedeHF setting from each trial.

The same approach will be applied to a 'pragmatic scenario': the pragmatic criteria are based on physiological reasoning (estimated glomerular filtration rate [eGFR] and potassium). There will be only one pragmatic scenario across all trials, using the least exclusive threshold (i.e. the lowest eGFR and the highest potassium). However, no prior sMRA use will be employed as an additional pragmatic criterion for FINALITY-HF[19], as this trial specifically targets patients with sMRA intolerance.

In addition, the estimates of the proportion of patients eligible to any MRA trial will be reported. These estimates will be provided for strict and pragmatic eligibility in the overall HF population as well as for HFrEF, HFmrEF, and HFpEF separately. The number of patients being eligible for any trial up to all trials (both scenarios) will be assessed and presented as a histogram.

Finally, incidence rates of the following outcomes will be reported for patients eligible for any trial vs no trial and compared as incidence rate ratios with 95% confidence intervals: composite of HF hospitalisation and cardiovascular death, HF hospitalisation, cardiovascular death, all-cause death, non-cardiovascular death, cardiovascular hospitalisation, non-cardiovascular hospitalisation.

A subanalysis is planned for patients with an index registration in the years 2022 and 2023, as the latest ESC HF guideline of 2021[1] made MRA a foundational pillar of pharmacological treatment in HFrEF in contrast to the prior[11] sequential treatment approach.

Statistical analyses will be performed in the statistical software R. Two-sided p-values < 0.05 will denote statistical significance.

3 Tables

Table 1: PICO of all trials

Trial	Population (P)	Intervention (I)	Control (C)	Efficacy outcome (O)
TOPCAT[13]	HFmrEF / HFpEF (LVEF ≥ 45%)	Spironolactone	Placebo	• Primary (composite, time-to-event): CV death, non-fatal cardiac arrest, HF hospitalisation • Secondary (separate endpoints): all-cause death, all-cause hospitalisation, MI, stroke
SPIRRIT-HFpEF[14]	HFmrEF / HFpEF (LVEF ≥ 40%)	Spironolactone / eplerenone	Usual care without spironolactone / eplerenone (open label)	• Primary (composite, incidence rate): CV death, HF hospitalisation • Secondary (composite, time-to-event): CV death, HF hospitalisation • Secondary (composite, incidence rate): all-cause death, all-cause hospitalisation • Secondary (composite, time-to-event):CV death, HF hospitalisation • Secondary (separate endpoints, incidence rate): HF hospitalisation, all-cause hospitalisation • Secondary (separate endpoints, time-to-event): CV death, HF hospitalisation, all-cause death, all-cause hospitalisation
SPIRIT-HF[15]	HFmrEF / HFpEF (LVEF ≥ 40%)	Spironolactone	Placebo	• Primary (composite, incidence rate): CV death, HF hospitalisation • Secondary (separate endpoints, incidence rate): HF hospitalisation, non-fatal CV hospitalisation, all-cause hospitalisation, CV death, all-cause death

Trial	Population (P)	Intervention (I)	Control (C)	Efficacy outcome (O)
FINEARTS-HF[16]	HFmrEF / HFpEF (LVEF ≥ 40%)	Finerenone	Placebo	• Primary (composite, incidence rate): WHF (HF hospitalisation or urgent HF visit), CV death • Secondary (hierarchical): 1) incidence rate HF events, 2) KCCQ and NYHA, 3) composite kidney outcome (time-to-event) • Secondary (separate endpoints): all-cause mortality, CV death
RALES[17]	HFrEF (LVEF ≤ 35%)	Spironolactone	Placebo	• Primary (time to-event): all-cause death • Secondary (separate endpoints): cardiac death, cardiac hospitalisation, NYHA class • Secondary (composite, time-to-event): cardiac death, cardiac hospitalisation • Secondary (composite, time-to-event): all-cause death, all-cause hospitalisation • Secondary (composite, time-to-event): all-cause death, cardiac hospitalisation
EMPHASIS-HF[18]	HFrEF (LVEF ≤ 35%)	Eplerenone	Placebo	• Primary (composite, time-to-event): CV death, HF hospitalisation • Secondary (composite, time-to-event): all-cause death, HF hospitalisation • Secondary (separate endpoints): all-cause death, CV death, all-cause hospitalisation, HF hospitalisation, CV hospitalisation, MI, stroke, ICD implantation, CRT implantation • Secondary (composite): all-cause death, all-cause hospitalisation • Secondary (composite): HF death, HF hospitalisation
FINALITY-HF[19]	HFrEF (LVEF ≤ 40%)	Finerenone	Placebo	• Primary (composite, time-to-event): CV death, HF event

Trial	Population (P)	Intervention (I)	Control (C)	Efficacy outcome (O)
				• Secondary (composite, timing and incidence rate): HF events, CV death • Secondary (separate endpoints, time-to-event): CV death, all-cause death • Secondary: KCCQ • Secondary (time-to-event): composite renal endpoint (eGFR, dialysis, transplantation)
REDEFINE-HF[20]	HFmrEF / HFpEF (LVEF ≥ 40%)	Finerenone	Placebo	• Primary (composite, incidence rate): HF event, CV death • Secondary (composite, time-to-event): CV death, HF event • Secondary (incidence rate): HF event • Secondary: KCCQ • Secondary (separate endpoints, time-to-event): CV death, all-cause death

Table 2: Overview of enrolment criteria (all trials)

	Inclusion criteria (all must be true)	**Exclusion criteria** (none must be true)
TOPCAT[13]	- Male or female - Age ≥ 50 years - HF, defined by one symptom at the time of screening (paroxysmal nocturnal dyspnoea, orthopnoea, dyspnoea on mild or moderate exertion) and one sign present in the last 12 months (any rales post cough, jugular venous pressure ≥ 10 cmH_2O, lower extremity oedema, chest X-ray demonstrating pleural effusion, pulmonary congestion or cardiomegaly) - LVEF ≥ 45% - ≥ 1 hospitalisation in the previous year with HF as a major component; transient HF in the context of MI does not qualify OR BNP in the previous 30 days ≥ 100 pg/ml or NT-proBNP ≥ 360 pg/ml (not explained by another condition) - Controlled SBP (target SBP < 140 mmHg); subjects with SBP ≤ 160 mmHg are eligible for enrolment if on 3 or more medications to control BP - Serum potassium < 5.0 mmol/l - Women: pregnancy and nursing ruled out - Willing to comply with scheduled visits - Written informed consent	- Severe systemic illness with life expectancy judged < 3 years - Chronic pulmonary disease requiring home O_2, oral steroid therapy or hospitalisation for exacerbation within 12 months, or significant chronic pulmonary disease in the opinion of the investigator - Known infiltrative or hypertrophic obstructive cardiomyopathy or known pericardial constriction - Primary haemodynamically significant uncorrected valvular heart disease, obstructive or regurgitant, or any valvular disease expected to lead to surgery during the trial - AFib with a resting heart rate > 90 bpm - MI in past 90 days - CABG surgery in past 90 days - PCI in past 30 days - Heart transplant recipient - Currently implanted LVAD - Stroke in past 90 days - SBP > 160 mm Hg - Known orthostatic hypotension - Gastrointestinal disorder that could interfere with study drug absorption - Use of any aldosterone antagonist or potassium sparing medication in last 7 days - Known intolerance to aldosterone antagonists - Current lithium use - Current participation (including prior 30 days) in any other therapeutic trial

	Inclusion criteria (all must be true)	**Exclusion criteria** (none must be true)
		- Any condition that, in the opinion of the investigator, may prevent the subject from adhering to the trial protocol - Serum potassium ≥ 5.5 mmol/l) in the past 6 months or serum potassium ≥ 5.0 mmol/l within the past 2 weeks - Severe renal dysfunction, defined as an eGFR (MDRD) < 30 ml/min; also, all subjects with serum creatinine ≥ 2.5 mg/dl independent from eGFR - Known chronic hepatic disease, defined as ASAT and ALAT levels > 3.0 times the upper limit of normal as read at the local lab
SPIRRIT-HFpEF[14]	- Age ≥ 50 years - Stable HF defined by symptoms and signs of HF as judged by local investigator. Patients may be enrolled as an out-patient or in-hospital at, or close to, the time of hospital discharge. - LVEF ≥ 40% - Most recent NT-proBNP > 300 ng/l (or BNP > 100 pg/ml) in SR OR most recent NT-proBNP > 750 ng/l (or BNP > 250 pg/ml) in AFib (adjustments may be made for BMI) OR NT-proBNP > 1200 ng/l (or BNP > 400 pg/ml) within the last 12 months even if most recent value is lower - Regular use of loop diuretics daily or most days of the week) - NYHA class II–IV - Written informed consent	- Previously enrolled in this study - Known LVEF < 40% ever - Current absolute indication or contraindication for MRA in judgement of investigator. In the absence of absolute indication, patients currently treated with an MRA may have the MRA discontinued and then be included in the trial, according to investigator judgement. - Known chronic liver disease - Probable alternative explanations for symptoms such as: a) Known primary cardiomyopathy, i.e. hypertrophic with obstruction, constrictive, restrictive, infiltrative or congenital (hypertrophic without current obstruction and other primary cardiomyopathies are allowed) b) Primary valve disease (to exclude a patient, the valve disease must be primary AND the primary cause of the symptoms) c) Significant chronic pulmonary disease defined by requirement for home O_2 d) Symptomatic anaemia (haemoglobin < 10 g/dl) as likely cause of the symptoms

	Inclusion criteria (all must be true)	**Exclusion criteria** (none must be true)
		e) Right-sided HF not due to left-sided HF - Heart transplant or LVAD recipient. - CRT device - SBP < 90 mmHg or > 160 mmHg at baseline - Potassium > 5.0 mmol/l (most recent, not older than 30 days) - eGFR (MDRD) < 30 ml/min/1.73 m^2 (most recent, not older than 30 days) - Current dialysis - Current lithium use - Actual or potential for pregnancy - Participation in another interventional clinical trial where an MRA is studied. Co-enrolment in trials and observational studies of other medical and device interventions is permitted. - Not suitable in the opinion of the investigator due to severe or terminal comorbidity with poor prognosis, or characteristics that may interfere with adherence to trial protocol.
SPIRIT-HF[15]	- Male or female - Age ≥ 50 years - Current HF symptoms (NYHA ≥ II) - HF symptom(s) ≥ 30 days prior to randomisation - LVEF ≥ 40% at screening measured by echocardiography and evidence of structural/ functional abnormalities (at least one of the following criteria): LAVI > 34 ml/m^2 // E/é mean ≥ 13 // mean e' (septal and lateral) < 9 cm/s - NT-proBNP > 300 pg/ml (SR) or > 900 pg/ml (AFib); only if NT-proBNP is NOT available: BNP > 80 / 250 pg/ml (SR/AFib)	- Potassium level ≥ 5.5 mmol/L in prior two weeks - Sodium level < 135 mmol/l prior to randomisation - Severe renal dysfunction: eGFR < 30 ml/min/1.73m^2 (MDRD) or serum creatinine level ≥ 1,8 mg/dl (> 160 µmol/ml) - History of anuria or acute renal failure (as defined by the RIFLE criteria for AKI) within the past two weeks - ACS (including MI) and elective PCI within prior 30 days - Cardiac surgery, other major CV surgery or urgent PCI within the prior 3 months

	Inclusion criteria (all must be true)	**Exclusion criteria** (none must be true)
	- HF hospitalisation or treatment with i.v. diuretics for WHF within 12 months prior to randomisation - Controlled SBP (target SBP < 140 mmHg); subjects with SBP ≤ 160 mmHg are eligible for enrolment if on 3 or more medications to control BP - Serum potassium < 5.0 mmol/l - Written informed consent	- Current acute decompensated HF requiring augmented therapy with i.v. diuretics, i.v. vasodilators and/or i.v. inotropic drugs. Patients are eligible after initial stabilisation. - Probable alternative diagnoses accounting for the patient's HF symptoms (i.e., dyspnoea, fatigue) such as significant pulmonary disease (incl. primary pulmonary hypertension), anaemia or obesity. Specifically, patients with the following are not eligible: a) Severe pulmonary disease including COPD or severe bronchial asthma (i.e. requiring home O_2, chronic nebuliser therapy, chronic oral steroid therapy) b) anaemia (haemoglobin < 10 g/dl males and < 9.5 g/dl females) c) BMI > 40 kg/m^2 - Evidence of right sided HF in the absence of left-sided structural heart disease - Specific aetiologies such as infiltrative, genetic hypertrophic cardiomyopathy, pericardial constriction, sarcoidosis, amyloidosis and any other storage diseases - Clinically significant congenital heart disease underlying HF - Life-threatening or uncontrolled dysrhythmia, including symptomatic or sustained VT and uncontrolled persistent or permanent AFib or AFlu (wit heart rate > 100 bpm, RACE II) during randomisation visit. - Presence of significant (i.e. more than moderate) valvular heart disease expected to lead to surgery during the trial - Stroke, TIA, carotid surgery or carotid angioplasty within the prior 3 months

	Inclusion criteria (all must be true)	**Exclusion criteria** (none must be true)
		- Coronary or carotid artery disease or valvular heart disease likely to require surgical or percutaneous intervention within the 6 months after randomisation - Patients with prior major organ transplant or intent to transplant (on transplant list) or with current ventricular assist device therapy - Evidence of hepatic disease: ASAT or ALAT values exceeding 3x the upper limit of normal or bilirubin >1.5 mg/dl - Evidence of present bilateral renal artery stenosis - Known intolerance or history of hypersensitivity to the active substance (spironolactone) or to any of the excipients of the Investigational Medicinal Product or placebo - Present use of any aldosterone antagonist, potassium supplements or potassium sparing diuretics at the time of enrolment - Required treatment with prohibited comedications according to the summary of product characteristics with the exception of ACEi or ARB (i.e. potassium chloride, triamterene, amiloride, abirateron) - Use of other investigational drugs at the time of enrolment or within 30 days or 5 half-lives before enrolment, whichever is longer - Any condition that may prevent the subject from adhering to the study protocol (e.g., history of non-compliance to medical regimens, patients who are considered potentially unreliable, patients with a history of addiction). - History or presence of any other disease (i.e. including malignancies) with a life expectancy of < 1 year

	Inclusion criteria (all must be true)	**Exclusion criteria** (none must be true)
		- Subjects who are legally detained in an official institution. - Subjects who may be dependent on the sponsor, the investigator or the trial sites. - Pregnant (positive pregnancy test) or nursing women - Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception during study participation and until 2 months after the last dose of study drug
FINEARTS-HF[16]	- Age ≥ 40 years - HF with NYHA class II–IV, ambulatory or hospitalised primarily for HF - On diuretic treatment for at least 30 days prior to randomisation - LVEF of ≥ 40% measured by any modality within the prior 12 months; if several values are available, the most recent one shall be reported. If LVEF was not measured in the past 12 months, a new measurement may be done at screening - Structural heart abnormalities based on any local imaging measurement within the last 12 months, latest at screening, defined by at least 1 of the following findings: a) LAD ≥ 3.8 cm b) LAA ≥ 20 cm^2 c) LAVI > 30 ml/m^2 d) LVMI ≥ 115 g/m^2 (♂) / 95 g/m^2 (♀) e) septal thickness or posterior wall thickness ≥ 1.1 cm - NT-proBNP ≥ 300 pg/ml (BNP ≥ 100 pg/ml) in SR and patient does not have an ongoing diagnosis of paroxysmal AFib	- eGFR < 25 mL/min/1.73 m^2 - Serum/plasma potassium > 5.0 mmol/l - Acute inflammatory heart disease (e.g., acute myocarditis) within prior 90 days - MI or any event which could have reduced the LVEF within prior 90 days - CABG surgery in the prior 90 days - PCI in the prior 30 days - Stroke or TIA within prior 90 days - Probable alternative primary cause of participants' HF symptoms, specifically: a) Severe pulmonary disease requiring home O_2 or chronic oral steroid therapy b) History of primary pulmonary arterial hypertension c) Haemoglobin < 10 g/dl d) Valvular heart disease considered to be clinically significant e) BMI > 50 kg/m^2 - SBP ≥ 160 mmHg if not on treatment with ≥ 3 blood pressure lowering medications or ≥ 180 mmHg

	Inclusion criteria (all must be true)	**Exclusion criteria** (none must be true)
	OR NT-proBNP ≥ 900 pg/ml (BNP ≥ 300 pg/ml) in AFib (or if AFib status is unknown or if patient has an ongoing diagnosis of paroxysmal AFib); values obtained at the following time: a) Within 90 days prior to randomisation if patient had been hospitalised for HF requiring initiation or change in HF therapy or if patient had an urgent visit for HF requiring i.v. diuretic therapy, both within 90 days prior to randomisation OR b) Within 30 days prior to randomisation if patient has not been hospitalised for HF nor had an urgent HF visit within the past 90 days. - Male or female - Women of childbearing potential: negative pregnancy test and adequate contraception - Written informed consent	irrespective of treatments on 2 consecutive measurements at least 2-minute apart - Life-threatening or uncontrolled arrhythmias at screening and/or randomisation including but not limited to sustained VT and AFib or AFlu with resting ventricular rate > 110 bpm - Symptomatic hypotension with mean SBP < 90 mmHg - Any primary cause of HF scheduled for surgery, e.g., valve disease such as severe aortic stenosis or severe mitral regurgitation - History of peripartum cardiomyopathy, chemotherapy induced cardiomyopathy, viral myocarditis, right HF in absence of left-sided structural disease, pericardial constriction, genetic hypertrophic cardiomyopathy or infiltrative cardiomyopathy including amyloidosis - Presence of LVAD - History of hyperkalaemia or acute renal failure during MRA treatment for > 7 consecutive days, leading to permanent discontinuation of the MRA treatment - Pregnant (positive pregnancy test) or nursing women - Known hypersensitivity to the study intervention (active substance or excipients) - Hepatic insufficiency classified as Child-Pugh C - Addison’s disease - Requirement of any i.v. vasodilating drug (e.g., nitrates, nitroprusside), any i.v. natriuretic peptide (e.g., nesiritide, carperitide), any i.v. positive inotropic agents or mechanical support (intra-aortic balloon pump, endotracheal intubation, mechanical ventilation or any ventricular assist device) within prior 24 hours

	Inclusion criteria (all must be true)	**Exclusion criteria** (none must be true)
		- Participants who require treatment with more than one ACEi, ARB or ARNi; or two simultaneously at randomisation - Continuous (at least 90 days) treatment with an MRA (e.g., spironolactone, eplerenone, canrenone, esaxerenone) within prior 12 months. Last intake at least 30 days before randomisation. - Concomitant treatment with any renin inhibitor or potassium-sparing diuretic that cannot be stopped prior to randomisation and for the duration of the treatment period - Concomitant systemic therapy with potent CYP3A4 inhibitors (e.g., itraconazole, ritonavir, indinavir, cobicistat, clarithromycin) or moderate or potent CYP3A4 inducers, that cannot be discontinued 7 days prior to randomisation and for the duration of the treatment period. - Any other condition or therapy, which would make the participant unsuitable for this study and will not allow participation for the full planned study period (e.g., active malignancy or other condition limiting life expectancy to < 12 months) - Previous assignment to treatment during this study - Participation in another interventional clinical study (e.g., Phase 1 to 3 clinical studies) or treatment with another investigational medicinal product within prior 30 days prior - Close personal affiliation with the investigational site - Known current alcohol and/or illicit drug abuse that may interfere with the participant’s safety and/or compliance

	Inclusion criteria (all must be true)	**Exclusion criteria** (none must be true)
		- Participant is in custody by order of an authority or a court of law.
RALES[17]	- HF diagnosis ≥ 6 weeks prior to enrolment - NYHA class IV in 6 months prior to enrolment - NYHA class III or IV at enrolment - Treatment with ACEi if tolerated - Treatment with a loop diuretic - LVEF ≤ 35% in 6 months prior to enrolment with no clinically significant intercurrent event - Written informed consent	- Treatment with potassium-sparing diuretics - Primary operable valvular heart disease (other than mitral or tricuspid regurgitation with clinical symptoms due to left ventricular systolic heart failure) - Congenital heart disease - Unstable angina - Primary hepatic failure - Active cancer - Any life-threatening disease other than HF - History of heart transplantation or on waiting list - Serum creatinine concentration > 2.5 mg/dl - Serum potassium concentration > 5 mmol/l
EMPHASIS-HF[18]	- Written informed consent - Male or female, ≥ 55 years of age - Chronic systolic HF of either ischaemic or non-ischaemic aetiology a) Duration: at least 4 weeks b) LVEF: ≤ 30% by echocardiography, contrast ventriculography, magnetic resonance imaging or nuclear imaging, based on local (most recent measurement within 6 months prior to randomisation), or LVEF 31-35% in addition to QRS duration >130 ms c) Functional Capacity: Currently NYHA II (in the investigator's opinion) d) Treatments (for ACEi, ARB and beta-blockers, optimal target or maximal tolerated dose unless contraindicated): ACEi and/or ARB, beta-blocker, diuretic if clinically indicated to reduce fluid retention	- Severe chronic systolic HF (symptoms at rest despite optimal medical therapy) - MI complicated by left ventricular systolic dysfunction and clinical HF within 30 days prior to randomisation - Stroke within 30 days prior to randomisation - Cardiac surgery within 30 days prior to randomisation - PCI within 30 days prior to randomisation - MRA for > 7 consecutive days without permanent discontinuation for ≥ 3 months prior to randomisation, or history of clinically significant hyperkalaemia or renal impairment during a previous exposure to an MRA - Required treatment with eplerenone, spironolactone or potassium canrenoate and either have prior NYHA class IV HF with an LVEF ≤ 0.35 (as in the RALES trial) or HF or diabetes and an LVEF < 0.40 after acute MI (as in EPHESUS trial)

	Inclusion criteria (all must be true)	**Exclusion criteria** (none must be true)
	- Serum potassium (K+) level ≤ 5.0 mmol/l within 24 hours prior to randomisation - eGFR (MDRD-6) ≥ 30 ml/min/1.73m^2 within 24 hours prior to randomisation - Randomisation must occur ≤ 6 months from the date of CV hospitalisation (HF, AMI, angina pectoris, cardiac arrhythmia, stroke / cerebral vascular accident, other reasons [e.g., hypotension, peripheral vascular disease]; elective procedures are not eligible unless ICD or CRT implantation); if the subject is clinically stable, he or she may be randomised during admission for a CV reason OR if no recent CV hospitalisation, then: plasma BNP concentration ≥ 250 pg/ml or NT-proBNP ≥ 500 pg/ml for males and ≥ 750 pg/ml for females, within 15 days of randomisation - Women: a) negative serum pregnancy within 72 hours prior to the first dose of study drug, except if she previously had a total hysterectomy or is > 65 years old b) use of an adequate form of contraception (abstinence will not be considered an acceptable form of contraception) if child-bearing potential - Subjects previously treated with an MRA for > 7 consecutive days will be allowed if they fulfil the following criteria: a) no history of clinically significant hyperkalaemia or renal impairment during earlier MRA use b) MRA must have been discontinued for at least 3 months prior to randomisation	- Uncontrolled hypertension (SBP > 180 mmHg and/or a DBP > 110 mmHg) - Symptomatic hypotension or SBP < 85 mmHg - Required treatment with potassium-sparing diuretics - History of hypersensitivity to eplerenone or spironolactone - Evidence of cardiogenic shock - Primary cause of HF is surgically amenable valve disease, pericardial disease or an obstructive or restrictive cardiomyopathy - Intra-aortic balloon pump or other mechanical assist device - Patients awaiting cardiac transplantation - Serum potassium > 5.0 mmol/l within 24 hours prior to randomisation - eGFR (MDRD-6) < 30 ml/min/1.73m^2 within 24 hours prior to randomisation - Concomitant use of potent CYP3A4 inhibitors, such as but not limited to: a) Ketoconazole b) Itraconazole c) Nefazodone d) Troleandomycin e) Clarithromycin f) Ritonavir g) Nelfinavir - Concomitant use of CYP3A4 inducers, such as but not limited to: a) St. John’s Wort b) Rifampin c) Carbamazepine

	Inclusion criteria (all must be true)	**Exclusion criteria** (none must be true)
	- Subjects previously treated with an MRA for ≤ 7 consecutive days will be allowed if washout period ≥ 48 hours - Inoperable valve disease as primary cause of HF	d) Phenytoin e) Phenobarbitol - Haemoglobin < 10g/dl - Preexisting significant hepatic disease (e.g., known positive serology for viral hepatitis) or ASAT and/or ALAT > 3 times the upper limits of normal - Status-post gastric bypass surgery, partial gastrectomy or other surgery of the gastrointestinal tract that may interfere with the absorption of eplerenone - Preexisting serious conditions (e.g., cancer, AIDS; patients with a previous history of cancer will be eligible if in the opinion of the investigator life expectancy is anticipated to be > 5 years - Patients unable to give written informed consent - Progressively fatal disease (except congestive HF) and/or life expectancy < 3 years - Patients receiving immunosuppressive or antineoplastic therapy - History of alcohol and/or any other drug abuse that in the opinion of the investigator will make the patient unreliable - Previous participation in this trial - Patients likely to require treatment during the trial period with drugs not permitted by this protocol - Women who are either pregnant, lactating or of childbearing potential and not using an acceptable method of contraception - Donation of blood or blood products for transfusion at any time during the trial or until 30 days after completion of treatment

	Inclusion criteria (all must be true)	**Exclusion criteria** (none must be true)
		- Participation in any other trial involving investigational or marketed products (including devices) concomitantly or within 30 days prior to entry in the trial - Other severe acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with trial participation or investigational product administration or may interfere with the interpretation of trial results and, in the judgment of the investigator, would make the subject inappropriate for entry into this trial
FINALITY-HF[19]	- Electronic or written informed consent (personally or through a legally authorised representative) - Age ≥ 18 years or legal age of majority - Symptomatic HFrEF - Not on steroidal MRA due to history of intolerance, contraindication or ineligibility for treatment - Women: negative pregnancy test and agreement to use adequate contraception during trial	- Treatment with non-steroidal MRA - eGFR < 25 ml/min/1.73m² and/or serum/plasma potassium > 5.0 mmol/l - Type 1 acute MI, coronary revascularisation, valve replacement/repair or implantation of a cardiac resynchronisation therapy device within 30 days or planned - Prior or planned heart transplant - Haemodynamically significant (severe) uncorrected primary cardiac valvular disease considered by the investigator to be the primary cause of HF - Symptomatic bradycardia or second- or third-degree heart block without a pacemaker - Cardiomyopathy due to known acute inflammatory heart disease, infiltrative diseases, accumulation diseases, muscular dystrophies, cardiomyopathy with reversible causes, hypertrophic obstructive cardiomyopathy, complex congenital heart disease or pericardial constriction - Probable alternative cause of participant's HF

	Inclusion criteria (all must be true)	**Exclusion criteria** (none must be true)
		- Concomitant systemic therapy with potent CYP3A4 inhibitors, or moderate or potent CYP3A4 inducers - Any other condition or therapy which would make the participant unsuitable for the study - Concurrent participation in another interventional clinical study using an investigational agent
REDEFINE-HF[20]	- Provide electronic or written informed consent (personally or through a legally authorised representative) - Age ≥ 18 years - Current hospitalisation or recently discharged with the primary diagnosis of HF - HF signs and symptoms at the time of hospital admission - Imaging evidence of LVEF ≥ 40% - NT-proBNP ≥ 1000 pg/ml or BNP ≥ 250 pg/ml for patients without AFib; or NT-proBNP ≥ 2000 pg/ml or BNP ≥ 500 pg/ml for patients with AFib	- MRA treatment - Documented prior history of severe hyperkalaemia in the setting of MRA use - eGFR < 25 ml/min/1.73m² or serum/plasma potassium > 5.0 mmol/l at screening - AMI, coronary revascularisation, valve replacement/repair or implantation of a cardiac resynchronisation therapy device within 30 days - Haemodynamically significant (severe) uncorrected primary cardiac valvular disease - Cardiomyopathy due to known acute inflammatory heart, infiltrative diseases, accumulation diseases, muscular dystrophies, cardiomyopathy with reversible causes, known hypertrophic obstructive cardiomyopathy, complex congenital heart disease or known pericardial constriction - Probable alternative cause of participant's HF symptoms - Concomitant systemic therapy with potent CYP3A4 inhibitors or moderate CYP3A4 inducers or potent CYP3A4 inducers

Table 3: Operationalisation of TOPCAT criteria

	TOPCAT[13] criterion	Study variable	ID	Definition / operationalisation
Inclusion criteria (all must be true)	Male or female	Male or female	ID1	SwedeHF[1]: shf_sex
	Age ≥ 50 years	Age ≥ 50 years	ID2	SwedeHF: shf_age
	HF, defined by one symptom at the time of screening (paroxysmal nocturnal dyspnoea, orthopnoea, dyspnoea on mild or moderate exertion) and one sign present in the last 12 months (any rales post cough, jugular venous pressure ≥ 10 cmH_2O, lower extremity oedema, chest X-ray demonstrating pleural effusion, pulmonary congestion or cardiomegaly)	Presence of HF	ID3	Assumed 100% eligibility. Reasoning: Inclusion in SwedeHF is based on these or very similar criteria.
	LVEF ≥ 45%	LVEF ≥ 40%	ID4	SwedeHF: shf_ef Reasoning: LVEF in SwedeHF is registered as a categorical variable (< 30%, 30-39%, 40-49%, ≥ 50%).
	a) ≥ 1 hospitalisation in the previous year with HF as a major component; transient HF in the context of MI does not qualify OR b) BNP in the previous 30 days ≥ 100 pg/ml or NT-proBNP ≥ 360 pg/ml (not explained by another condition)	a) ≥ 1 hospitalisation for HF without AMI in prior 1 year OR b) NT-proBNP ≥ 360 pg/ml	a) ID5 b) ID6	a) New variable (non-AMI hospitalisation): - HF hospitalisation: NPR (in-patients): ICD-10-SE codes (same as in sos_out_hosphf) I11.0, I13.0, I13.2, I25.5, I42.0, I42.3, I42.5-9, I43, I50, J81, K76.1 OR R57.0 / position: main diagnosis / timeframe: -1 – 0 years BUT NOT within the same hospitalisation

[1] The definitions of variables already in SwedeHF can be found at: https://kiheartfailure.github.io/shfdb4/

TOPCAT[13] criterion	Study variable	ID	Definition / operationalisation
			- AMI: NPR (in-patients): ICD-10-SE codes I21-22 / position: all diagnoses / timeframe: -1 – 0 years b) SwedeHF: shf_ntprobnp
Controlled SBP (target SBP < 140 mmHg); subjects with SBP ≤ 160 mmHg are eligible for enrolment if on 3 or more medications to control BP	SBP < 140 mmHg or 140-160 mmHg while on ≥ 3 antihypertensive agents	ID7	SwedeHF: shf_bpsys New variable: - NPDR: ATC codes C01D (count as 1), C02A-K (count as 1), C02L (count as 2), C03A-D (count as 1), C03E (count as 2), C03X (count as 1), C04 (count as 1), C07A (count as 1), C07B-C (count as 2), C07D (count as 3), C07E-F (count as 2), C08C-E (count as 1), C08G (count as 2), C09A (count as 1), C09B (count as 2), C09C (count as 1), C09DA-B (count as 2), C09DX01 (count as 3) OR C09DX04 (count as 2) / Apodos included / timeframe: -120 – +5 days Reasoning: A lookback is supposed to ensure capture of currently used medication as filling in a prescription at least every 3 months is necessary even for long-term medication. An additional month lookback is supposed to account for stockpiling and (temporary) incompliance. An additional 5 days follow-up ensures to capture prescriptions during the index registration, which reflect eligibility during the respective registration.
Serum potassium < 5.0 mmol/l	Potassium < 5.0 mmol/l	ID8	SwedeHF: shf_potassium

	TOPCAT[13] criterion	Study variable	ID	Definition / operationalisation
	Women: pregnancy and nursing ruled out	Pregnancy or nursing	ID9	Assumed 0%. Reasoning: Data on pregnancy and nursing are not available in the dataset.
	Willing to comply with scheduled visits	Willing to comply with scheduled visits	ID10	Assumed 100%. Reasoning: Cannot be concluded from retrospective registry data – and will very likely only affect a small proportion of patients. In addition, partly redundant given the informed consent criterion. Only the will of the patient is assessed here, not the expected adherence of the patient judged by the reviewer (e.g. based on prior conditions).
	Written informed consent	Informed consent	ID11	Given 100%. Reasoning: Written informed consent in an RCT equals the non-opt-out of SwedeHF patients.
Exclusion criteria (none must be true)	Severe systemic illness with life expectancy judged < 3 years	Limited life expectancy due to metastatic cancer or primary cancer with very poor prognosis	ID12	New variable: - NPR (in- and out-patients): ≥ 2 registrations of ICD-10-SE codes C15, C16, C22, C25, C34, C45, C71 OR C77-79 / position: main diagnosis / timeframe: -6 – 0 months Reasoning: Life expectancy is very difficult to estimate, even in personal contact with the patient as during screening for a randomised controlled trial. This assessment is even more difficult in registries without borrowing information from the future which would introduce a bias of its own. However, diagnosis

TOPCAT[13] criterion	Study variable	ID	Definition / operationalisation
			of metastatic or aggressive cancer appears as a rational surrogate and has been used before.
Chronic pulmonary disease requiring home O_2, oral steroid therapy or hospitalisation for exacerbation within 12 months or significant chronic pulmonary disease in the opinion of the investigator	a) COPD GOLD group E OR b) Severe bronchial asthma OR c) Primary pulmonary hypertension	a) ID13 b) ID14 c) ID15	a) New variable: - COPD diagnosis: NPR (in- and out-patients): ≥ 2 diagnoses of J41-44 / position: all diagnoses / timeframe: -5 – 0 years - GOLD E group: ≥ 2 moderate COPD exacerbations OR ≥ 1 severe COPD exacerbations in the past 1 year -- count of moderate COPD exacerbations (NPDR): dispensation of oral glucocorticoids, ATC code H02AB / Apodos excluded / interval between dispensations < 4 weeks counts as 1 event / timeframe: -1 – 0 years -- count of severe COPD exacerbations (NPR, in-patients, previously named sos_com_hospcopd1yr): hospitalisation for ICD-10-SE J12-18, J20-22, J41-44 OR J96 / position: main diagnosis / timeframe: -1 – 0 years b) New variable: - Bronchial asthma diagnosis: NPR (in- and out-patients): ≥ 2 diagnoses of J45-46 / position: all diagnoses / timeframe: -5 – 0 years - Asthma severity: NPR (in-patients): ≥ 1 hospitalisation for ICD-10-SE J45-46 / position: main position / timeframe: -5 – 0 years c) New variable (PAH diagnosis):

TOPCAT[13] criterion	Study variable	ID	Definition / operationalisation
			- NPR (in- and out-patients): ≥ 1 registration of ICD-10-SE I27.0 / position: main position / timeframe: -5 – 0 years AND New variable (PDE5 inhibitors): - NPDR: ATC codes G04BE03 OR G04BE08 / Apodos included / timeframe: -120 - +5 days Reasoning: a) The most frequent reason for home O_2 and oral glucocorticoids with a respiratory indication is COPD. Identification of severe COPD patients based on home O_2 is not feasible, but the abovementioned definition has been used before successfully. b) Bronchial asthma is frequent, and its severe presentation counts as a "significant pulmonary disease" even if usually not treated with home O_2. The definition of severe asthma by the recent need for hospitalisation is most feasible. c) Primary pulmonary hypertension is (relatively) rare, but if present it is always regarded as a "significant pulmonary disease" due to its generally poor prognosis. The validity of the diagnosis is enhanced by including ongoing phosphodiesterase 5 inhibitor therapy in the variable. A lookback is supposed to ensure

TOPCAT[13] criterion	Study variable	ID	Definition / operationalisation
			capture of currently used medication as filling in a prescription at least every 3 months is necessary even for long-term medication. An additional month lookback is supposed to account for stockpiling and (temporary) incompliance. An additional 5 days follow-up ensures to capture prescriptions during the index registration, which reflect eligibility during the respective registration.
Known chronic hepatic disease, defined as ASAT and ALAT levels > 3.0 times the upper limit of normal as read at the local lab	Chronic liver disease	ID16	SwedeHF/NPR (in- and out-patients): sos_com_liver (ICD-10-SE B18, I85, I86.4, I98.2, K70, K71.0, K71.1, K71.3-7, K72-4, K76.0 OR K76.2-9 / position: all diagnoses / timeframe: -5 – 0 years) Reasoning: ASAT and ALAT are not available in SwedeHF. However, these chronic hepatic conditions are likely to come along with elevated transaminases.
Primary haemodynamically significant uncorrected valvular heart disease, obstructive or regurgitant, or any valvular disease expected to lead to surgery during the trial	Valve intervention / surgery in prior 3 months	ID66	New variable: - NPR (in-patients): OPS codes FG, FJE, FJF, FC OR FM / timeframe: -3 – 0 months Reasoning: Retrospective identification of patients with expected heart valve correction in the registry is not feasible. At the same time, borrowing time from the future (after index registration) creates a bias of its own. Thus, we ruled to exclude recent valve correction instead.

TOPCAT[13] criterion	Study variable	ID	Definition / operationalisation
Known infiltrative or hypertrophic obstructive cardiomyopathy or known pericardial constriction	a) Chronic constrictive pericarditis OR b) Hypertrophic-obstructive cardiomyopathy OR c) Amyloidosis-induced cardiomyopathy OR d) Sarcoidosis-induced cardiomyopathy	a) ID18 b) ID19 c) ID20 d) ID21	a) New variable: - NPR (in- and out-patients): ICD-10-SE I31.1 / position: all diagnoses / timeframe: -5 – 0 years b) New variable: - NPR (in- and out-patients): ICD-10-SE I42.1 / position: all diagnoses / timeframe: -5 – 0 years c) New variable: - NPR (in- and out-patients): ICD-10-SE E85 / position: all diagnoses / timeframe: -5 – 0 years d) New variable: - NPR (in- and out-patients): ICD-10-SE D86 / position: all diagnoses / timeframe: -5 – 0 years <u>Reasoning</u>: Infiltrative cardiomyopathy does not have a distinct ICD code. However, cardiac amyloidosis is the most frequent sub-entity. In this study, an amyloidosis code in the presence of HF (which is true for all SwedeHF patients) is considered to denote amyloidosis-induced cardiomyopathy. The same is applied for sarcoidosis.
AFib with a resting heart rate > 90 bpm	AFib or AFlu with a resting heart rate > 90 bpm	ID22	SwedeHF/NPR (in- and out-patients): shf_sos_com_af (ICD-10-SE I48 / position: all diagnoses / timeframe: -5 – 0 years) SwedeHF (heart rate): shf_heartrate

TOPCAT[13] criterion	Study variable	ID	Definition / operationalisation
			Reasoning: The SwedeHF variable for AFib also includes AFlu. However, the overlap as well as the risk of misclassification is significant, and we assume there is only a very small minority of HF patients with AFlu but without AFib. Thus, no further distinction between these two entities is needed.
Myocardial infarction in past 90 days	AMI in prior 3 months	ID23	New variable: - NPR (in-patients): ICD-10-SE I21 OR I22 / position: all diagnoses / timeframe: -3 – 0 months Reasoning: AMI without hospitalisation is unlikely. Thus, to increase specificity of the diagnosis, only in-patients are considered. However, MI does not have to be in main position as in patients with secondary MI caused by another entity the latter might be put into main position.
CABG in past 90 days	CABG in prior 3 months	ID24	New variable: - NPR (in-patients): OPS codes FNA, FNB, FNC, FND OR FNE / timeframe: -3 – 0 months
PCI in past 30 days	PCI in prior 30 days	ID25	New variable: - NPR (in- and out-patients): OPS codes DF009, DF019, DF020, FNG02, FNG05 OR FNG22 / timeframe: -30 – 0 days Reasoning: Elective PCIs can also be performed in out-patients.
Heart transplant recipient	Heart transplant recipient	ID26	New variable:

TOPCAT[13] criterion	Study variable	ID	Definition / operationalisation
			- NPR (in- and out-patients): ICD-10-SE codes Z94.1 OR Z94.3 OR OPS codes FQA-B / position: all diagnoses / timeframe: -5 – 0 years Reasoning: Patients who have received a heart transplantation will seek medical attention for follow-up frequently, with near to certainty within a 5-years period. A non-restricted lookback might reduce specificity by including more cases with miscoding.
Currently implanted LVAD	Currently implanted LVAD	ID27	New variable: - NPR (in-patients): OPS codes FXL40, FXL50 OR FXL60 / timeframe: -5 – 0 years Reasoning: Any LVAD implantation in the past is assumed to be a current LVAD since explantations are rare.
Stroke in past 90 days	Stroke in prior 3 months	ID28	New variable: - NPR (in- and out-patients): ICD-10-SE codes I60-64 / position: main diagnosis / timeframe -3 – 0 months Reasoning: Only acute strokes in the prior 90 days are supposed to be registered. Choosing the main position and excluding the codes I69.0-4 (late effects of stroke) increases specificity in this regard.
SBP > 160 mmHg	SBP > 160 mmHg	ID29	SwedeHF: shf_bpsys
Known orthostatic hypotension	SBP < 85 mmHg	ID30	SwedeHF: shf_bpsys

TOPCAT[13] criterion	Study variable	ID	Definition / operationalisation
			Reasoning: This criterion is not feasible to assess retrospectively as there is no respective SwedeHF variable. However, severe arterial hypotension at rest can be used as a surrogate parameter; the cut-off is adapted from EMPHASIS-HF.
Gastrointestinal disorder that could interfere with study drug absorption	Non-infectious inflammatory bowel disease	ID32	New variable: - NPR (in- and out-patients): ICD-10-SE codes K50-52 / position: all diagnoses / timeframe: -5 – 0 years Reasoning: Non-infectious inflammatory bowel disease is frequent, and consecutive malabsorption may be underdiagnosed (and not coded). Thus, it is also considered an exclusion criterion even in the absence of codes for malabsorption. On the other hand, severe malnutrition (ICD-10-SE codes E40-43) is not considered as the underlying condition of these codes may not be malabsorption only but also cardiac cachexia, a frequent entity in terminal HF patients.
Use of any aldosterone antagonist or potassium sparing medication in last 7 days	a) MRA in prior 3 months OR b) Non-MRA potassium-sparing diuretics	a) ID33 b) ID34	a) Assumed 0%. b) Assumed 0%. Reasoning: a) The original trial was performed to evaluate efficacy and safety of MRA in patients with HF at a time when this indication was not established, yet. Exclusion of MRA made sense

TOPCAT[13] criterion	Study variable	ID	Definition / operationalisation
			to exclude use because of other indications. Nowadays, in a contemporary population, exclusion of MRA would result in artificially low eligibility rates as patients are treated based on the results of, among others, this trial. Therefore, it is reasonable to account for this aspect by setting this exclusion criterion to 0%. b) Non-MRA potassium-sparing diuretics are rarely used in Sweden. In addition, fast wash-out would be possible and would not pose an actual barrier to RCT enrolment.
Known intolerance to aldosterone antagonists	MRA intolerance	ID35	Assumed 0%. Reasoning: Allergies against MRA are rare and other intolerances usually rather subjective. In addition, this information cannot be retrieved retrospectively.
Current lithium use	Lithium use in prior 3 months	ID36	New variable: - NPDR: ATC code N05AN01 / Apodos included / timeframe: -120 – +5 days Reasoning: A lookback is supposed to ensure capture of currently used medication as filling in a prescription at least every 3 months is necessary even for long-term medication. An additional month lookback is supposed to account for stockpiling and (temporary) incompliance. An additional 5 days follow-up ensures to capture prescriptions during the index

TOPCAT[13] criterion	Study variable	ID	Definition / operationalisation
			registration, which reflect eligibility during the respective registration.
Current participation (including prior 30 days) in any other therapeutic trial	Current participation in any other therapeutic trial	ID37	Assumed 0%. Reasoning: Data unknown.
Any condition that, in the opinion of the investigator, may prevent the subject from adhering to the trial protocol	Any condition which may reduce adherence	ID38	New variable: - NPR (in- and out-patients): ICD-10-SE codes F01-7, F09-16, F18-25 OR F28-30 / position: all diagnoses / timeframe: -1 – 0 years Reasoning: The included conditions are likely to impair the participant's adherence to the trial protocol. These are: dementia, organic amnesic syndrome, delirium, other mental disorder or personality and behavioural disorders due to brain disease, unspecified mental disorder, mental disorders due to psychoactive substances, schizophrenia, manic episode, and bipolar affective disorder.
Serum potassium ≥ 5.5 mmol/l) in the past 6 months or serum potassium ≥ 5.0 mmol/l within the past 2 weeks	Potassium ≥ 5.0 mmol/l	ID39	SwedeHF: shf_potassium Reasoning: Laboratory data outside of SwedeHF is not available and most patients do not have multiple SwedeHF registration within such short periods as 2 weeks.
Severe renal dysfunction: a) eGFR (MDRD) < 30 ml/min/1.73m^2 or b) serum creatinine ≥ 2.5 mg/dl (independent from eGFR)	a) eGFR (CKD-EPI 2021) < 30 ml/min/1.73m^2 OR	a) ID40 b) ID41	a) SwedeHF: shf_gfrckdepi b) SwedeHF: shf_crea

TOPCAT[13] criterion	Study variable	ID	Definition / operationalisation
	b) Serum creatinine ≥ 2.5 mg/dl (independent from eGFR)		

If not explicitly stated otherwise, the time of assessment of each variable is the index registration.

Table 4: Operationalisation of SPIRRIT-HFpEF criteria

	SPIRRIT-HFpEF[14]	Study variable	ID	Definition / operationalisation
Inclusion criteria (all must be true)	Age ≥ 50 years	Age ≥ 50 years	ID2	SwedeHF: shf_age
	Stable HF defined by symptoms and signs of HF as judged by local investigator. Patients may be enrolled as an out-patient or in-hospital at, or close to, the time of hospital discharge.	Presence of HF	ID3	Assumed 100% eligibility. Reasoning: Patients are registered in SwedeHF, all of whom with a mandatory diagnosis of HF.
	LVEF ≥ 40%	LVEF ≥ 40%	ID4	SwedeHF: shf_ef
	a) Most recent NT-proBNP > 300 ng/l (or BNP > 100 pg/ml) in SR OR b) Most recent NT-proBNP > 750 ng/l (or BNP > 250 pg/ml) in AFib (adjustments may be made for BMI) OR c) NT-proBNP > 1,200 ng/l (or BNP > 400 pg/ml) within the last 12 months even if most recent value is lower	a) NT-proBNP > 300 ng/l without AFib or AFlu OR b) NT-proBNP > 750 ng/l with AFib or AFlu OR c) NT-proBNP > 1,200 ng/l in prior 1 year	a) ID42 b) ID43 c) ID44	a) and b) - SwedeHF: shf_ntprobnp - SwedeHF: shf_sos_com_af c) New variable: - SwedeHF: shf_ntprobnp / timeframe: -1 – 0 years Reasoning: Only NT-proBNP is registered in SwedeHF, not BNP. In addition, criterion c) employs previous SwedeHF registrations; inclusion of laboratory data outside of SwedeHF is not feasible.
	Regular use of loop diuretics (daily or most days of the week)	Daily use of loop diuretics	ID45	SwedeHF: shf_loopdiureticusage Reasoning: The variable in SwedeHF can distinguish daily from pro re nata medication;

	SPIRRIT-HFpEF[14]	Study variable	ID	Definition / operationalisation
				there is no category “most days of the week”, however.
	NYHA class II–IV	NYHA class II–IV	ID46	SwedeHF: shf_nyha
	Written informed consent	Informed consent	ID11	Given 100%. Reasoning: Written informed consent in an RCT equals the non-opt-out of SwedeHF patients.
Exclusion criteria (none must be true)	Previously enrolled in this study	Previously enrolled in the same trial	ID47	Given 0%. Reasoning: This cross-sectional study addresses the eligibility of SwedeHF patients to enrolment in RCTs. Only one registration per personal number is used; thus, an individual can only be counted once.
	Known LVEF < 40% ever	Known LVEF < 40% ever	ID48	New variable: - SwedeHF: shf_ef / timeframe: -infinite – 0 years Reasoning: Consideration of LVEF registered outside of SwedeHF is not feasible.
	Current a) absolute indication or b) contraindication for MRA in judgement of investigator. In the absence of absolute indication, patients currently treated with an MRA may have the MRA discontinued and then be included in the trial, according to investigator judgement.	a) Hyperaldosteronism OR b) MRA intolerance	a) ID49 b) ID35	a) New variable: - NPR (in- and out-patients): ICD-10-SE code E26 / position: all diagnoses / timeframe: -5 – 0 years b) Assumed 0%. Reasoning: a) Hyperaldosteronism may constitute an absolute indication for MRA.

SPIRRIT-HFpEF[14]	Study variable	ID	Definition / operationalisation
			b) As for contraindications, allergies are rare and other intolerances usually rather subjective, not constituting an absolute contraindication. Severe renal dysfunction may also be a contraindication, but these patients are excluded by the respective separate criterion and are, thus, not included in the present criterion.
Known chronic liver disease	Chronic liver disease	ID16	SwedeHF/NPR (in- and out-patients): sos_com_liver (ICD-10-SE B18, I85, I86.4, I98.2, K70, K71.0, K71.1, K71.3-7, K72-4, K76.0 OR K76.2-9 / position: all diagnoses / timeframe: -5 – 0 years)
Probable alternative explanations for symptoms such as: a) Known primary cardiomyopathy, i.e., hypertrophic with obstruction, constrictive, restrictive, infiltrative or congenital (hypertrophic without current obstruction and other primary cardiomyopathies are allowed) b) Primary valve disease (to exclude a patient, the valve disease must be primary AND the primary cause of the symptoms) c) Significant chronic pulmonary disease defined by requirement for home O_2	a) 1. Hypertrophic-obstructive cardiomyopathy OR 2. Chronic constrictive pericarditis OR 3. Restrictive cardiomyopathy OR 4. Amyloidosis-induced cardiomyopathy	a) 1. ID19 2. ID18 3. ID50 4. ID20 5. ID51 b) ID66	a) 1. New variable: NPR (in- and out-patients): ICD-10-SE I42.1 / position: all diagnoses / timeframe: -5 – 0 years 2. New variable: NPR (in- and out-patients): ICD-10-SE I31.1 / position: all diagnoses / timeframe: -5 – 0 years 3. New variable: NPR (in- and out-patients): ICD-10-SE I42.5 / position: all diagnoses / timeframe: -5 – 0 years 4. New variable: NPR (in- and out-patients): ICD-10-SE E85 / position: all diagnoses / timeframe: -5 – 0 years

SPIRRIT-HFpEF[14]	Study variable	ID	Definition / operationalisation
d) Symptomatic anaemia (haemoglobin < 10 g/dl) as likely cause of the symptoms e) Right-sided HF not due to left-sided HF	OR 5. Congenital cardiac malformations OR b) Valve intervention / surgery in prior 3 months OR c) COPD GOLD group E OR d) Haemoglobin < 10 g/dl OR e) Right-sided HF not due to left-sided HF	c) ID13 d) ID52 e) ID53	5. New variable: NPR (in- and out-patients): ICD-10-SE Q20-26 / position: all diagnoses / timeframe: -infinite – 0 years b) New variable: - NPR (in-patients): OPS codes FG, FJE, FJF, FC OR FM / timeframe: -3 – 0 months c) New variable: - COPD diagnosis: NPR (in- and out-patients): ≥ 2 diagnoses of J41-44 / position: all diagnoses / timeframe: -5 – 0 years - GOLD E group: ≥ 2 moderate COPD exacerbations OR ≥ 1 severe COPD exacerbations in the past 1 year -- count of moderate COPD exacerbations (NPDR): dispensation of oral glucocorticoids, ATC code H02AB / Apodos excluded / interval between dispensations < 4 weeks counts as 1 event / timeframe: -1 – 0 years -- count of severe COPD exacerbations (NPR, in-patients, previously named sos_com_hospcopd1yr): hospitalisation for ICD-10-SE J12-18, J20-22, J41-44 OR J96 / position: main diagnosis / timeframe: -1 – 0 years d) SwedeHF: shf_hb e) Assumed 0%.

SPIRRIT-HFpEF[14]	Study variable	ID	Definition / operationalisation
			Reasoning: a) Infiltrative cardiomyopathy does not have a distinct ICD code. However, cardiac amyloidosis is the most frequent sub-entity. In this study, an amyloidosis code in the presence of HF (which is true for all SwedeHF patients) is considered to denote amyloidosis-induced cardiomyopathy. Congenital malformations might not be coded frequently but rather only the resulting HF. Thus, an infinite lookback is necessary. Specificity both regarding diagnosis position and lookback is unlikely to become a problem as these codes are very specific themselves and only used of the diagnosis is ensured. b) Primary valve disease causing HF symptoms is likely to be addressed interventionally or surgically in the majority of patients. A retrospective assessment of this criterion is not feasible in the registry data, thus, we ruled to assess recent procedures only to avoid borrowing information from the future. A distinction between primary and secondary to HF valve disease is not feasible and, therefore, disregarded. c) Direct assessment of home O_2 use is not feasible in registry data; however, the most frequent pulmonary cause for home O_2 use is severe COPD. Thus, severe COPD defined as GOLD group E is assessed as a surrogate.

SPIRRIT-HFpEF[14]	Study variable	ID	Definition / operationalisation
			d) Retrospective assessment of the likelihood of anaemia causing HF symptoms is not feasible. However, severe anaemia is known to cause or worsen HF symptoms frequently. Thus, this study uses only the severe anaemia (haemoglobin < 10 mg/dl) criterion. e) Isolated right HF is difficult to assess in SwedeHF and with ICD codes. As only a small minority of patients presents with this condition, we decided to assume 0%.
Heart transplant or LVAD recipient	a) Heart transplant recipient OR b) Currently implanted LVAD	a) ID26 b) ID27	a) New variable: - NPR (in- and out-patients): ICD-10-SE codes Z94.1 <u>OR</u> Z94.3 <u>OR</u> OPS codes FQA-B / position: all diagnoses / timeframe: -5 – 0 years b) New variable: - NPR (in-patients): OPS codes FXL40, FXL50 <u>OR</u> FXL60 / timeframe: -5 – 0 years <u>Reasoning</u>: a) Patients who have received a heart transplantation will seek medical attention for follow-up frequently, with near to certainty within a 5-years period. A non-restricted lookback might reduce specificity by including more cases with miscoding. b) Any LVAD implantation in the past is assumed to be a current LVAD since explantations are rare and heart transplantation as the more frequent

SPIRRIT-HFpEF[14]	Study variable	ID	Definition / operationalisation
			way of LVAD discontinuation is assessed in the same original trial criterion anyway.
Cardiac resynchronisation therapy device	Implanted CRT	ID54	SwedeHF: shf_device
SBP < 90 mmHg or > 160 mmHg at baseline	SBP < 90 mmHg or > 160 mmHg	ID55	SwedeHF: shf_bpsys
Potassium > 5.0 mmol/l (most recent, not older than 30 days)	Potassium > 5.0 mmol/l	ID56	SwedeHF: shf_potassium
eGFR (MDRD) < 30 ml/min/1.73m^2 (most recent, not older than 30 days)	eGFR (CKD-EPI 2021) < 30 ml/min/1.73m^2	ID40	SwedeHF: shf_gfrckdepi
Current dialysis	Current dialysis	ID57	New variable: - NPR (in- and out-patients): ICD-10-SE Z49 OR Z99.2 OR OPS codes DR012-014, DR016, DR024, DR055-056, DR060-061 OR TJA33 / position: all diagnoses / timeframe: -1 – 0 years Reasoning: Codes exclusively used for acute dialysis were excluded to avoid exclusion of patients due to short-term (e.g., postoperative) dialysis during the lookback. In addition, other types of renal replacement therapy (e.g., haemofiltration) are not part of this variable as the trial's wording is "dialysis" rather than "renal replacement therapy". A lookback of 1 year allows for exclusion of all current dialysis patients but avoids exclusion of most previous dialysis patients with recovered renal function (or after renal transplantation).
Current lithium use	Lithium use in prior 3 months	ID36	New variable: - NPDR: ATC code N05AN01 / Apodos included / timeframe: -120 – +5 days

SPIRRIT-HFpEF[14]	Study variable	ID	Definition / operationalisation
			Reasoning: A lookback is supposed to ensure capture of currently used medication as filling in a prescription at least every 3 months is necessary even for long-term medication. An additional month lookback is supposed to account for stockpiling and (temporary) incompliance. An additional 5 days follow-up ensures to capture prescriptions during the index registration, which reflect eligibility during the respective registration.
Actual or potential for pregnancy	Pregnancy or nursing	ID9	Assumed 0%. Reasoning: Data on pregnancy and nursing are not available in the dataset.
Participation in another interventional clinical trial where an MRA is studied. Co-enrolment in trials and observational studies of other medical and device interventions is permitted.	Current participation in any other therapeutic trial	ID37	Assumed 0%. Reasoning: Data unknown.
Not suitable in the opinion of the investigator due to a) severe or terminal comorbidity with poor prognosis, or b) characteristics that may interfere with adherence to trial protocol.	a) Limited life expectancy due to metastatic cancer or primary cancer with very poor prognosis OR b) Any condition which may reduce adherence	a) ID12 b) ID38	a) New variable: - NPR (in- and out-patients): ≥ 2 registrations of ICD-10-SE codes C15, C16, C22, C25, C34, C45, C71 OR C77-79 / position: main diagnosis / timeframe: -6 – 0 months b) New variable: - NPR (in- and out-patients): ICD-10-SE codes F01-7, F09-16, F18-25 OR F28-30 / position: all diagnoses / timeframe: -1 – 0 years

SPIRRIT-HFpEF[14]	Study variable	ID	Definition / operationalisation
			Reasoning: a) Life expectancy is very difficult to estimate, even in personal contact with the patient as during screening for a randomised controlled trial. This assessment is even more difficult in registries without borrowing information from the future which would introduce a bias of its own. However, diagnosis of metastatic or aggressive cancer appears as a rational surrogate and has been used before. b) The included conditions are likely to impair the participant's adherence to the trial protocol. These are: dementia, organic amnesic syndrome, delirium, other mental disorder or personality and behavioural disorders due to brain disease, unspecified mental disorder, mental disorders due to psychoactive substances, schizophrenia, manic episode, and bipolar affective disorder.

If not explicitly stated otherwise, the time of assessment of each variable is the index registration.

Table 5: Operationalisation of SPIRIT-HF criteria

	SPIRIT-HF[15]	Study variable	ID	Definition / operationalisation
Inclusion criteria (all must be true)	Male or female	Male or female	ID1	SwedeHF: shf_sex
	Age ≥ 50 years	Age ≥ 50 years	ID2	SwedeHF: shf_age
	Current HF symptoms (NYHA ≥ II)	NYHA class II–IV	ID46	SwedeHF: shf_nyha
	HF symptom(s) ≥ 30 days prior to randomisation	Previous HF diagnosis ≥ 30 days ago	ID58	SwedeHF: sos_durationhf
	LVEF ≥ 40% at screening measured by echocardiography and evidence of structural/ functional abnormalities (at least one of the following criteria): LAVI > 34 ml/m^2 // E/é mean ≥ 13 // mean e' (septal and lateral) < 9 cm/s	LVEF ≥ 40%	ID4	SwedeHF: shf_ef Reasoning: LVEF in SwedeHF is registered as a categorical variable (< 30%, 30-39%, 40-49%, ≥ 50%). More specific echocardiographic parameters are not available. However, if the HF diagnosis is valid (given in SwedeHF), the presence of at least one of these structural or functional criteria is very likely.
	HF hospitalisation or treatment with i.v. diuretics for worsening HF within 12 months prior to randomisation	≥ 1 HF hospitalisation in prior 1 year	ID59	SwedeHF/NPR: shf_sos_prevhfh1yr Reasoning: Worsening HF with need for i.v. diuretic treatment is very likely to cause a HF hospitalisation in Sweden. Thus, only using the HF hospitalisation data is sufficient.
	NT-proBNP > 300 pg/ml (SR) or > 900 pg/ml (AFib); only if NT-proBNP is NOT available: BNP > 80 / 250 pg/ml (SR/AFib)	a) NT-proBNP > 300 ng/l without AFib or AFlu OR	a) ID42 b) ID60	SwedeHF: shf_ntprobnp SwedeHF: shf_sos_com_af

SPIRIT-HF[15]	Study variable	ID	Definition / operationalisation
	b) NT-proBNP > 900 pg/ml with AFib or AFlu		
Controlled SBP (target SBP < 140 mmHg); subjects with SBP ≤ 160 mmHg are eligible for enrolment if on 3 or more medications to control BP	SBP < 140 mmHg or 140-160 mmHg while on ≥ 3 antihypertensive agents	ID7	SwedeHF: shf_bpsys NPDR: ATC codes C01D (count as 1), C02A-K (count as 1), C02L (count as 2), C03A-D (count as 1), C03E (count as 2), C03X (count as 1), C04 (count as 1), C07A (count as 1), C07B-C (count as 2), C07D (count as 3), C07E-F (count as 2), C08C-E (count as 1), C08G (count as 2), C09A (count as 1), C09B (count as 2), C09C (count as 1), C09DA-B (count as 2), C09DX01 (count as 3) OR C09DX04 (count as 2) / Apodos included / timeframe: -120 – +5 days Reasoning: A lookback is supposed to ensure capture of currently used medication as filling in a prescription at least every 3 months is necessary even for long-term medication. An additional month lookback is supposed to account for stockpiling and (temporary) incompliance. An additional 5 days follow-up ensures to capture prescriptions during the index registration, which reflect eligibility during the respective registration.
Serum potassium < 5.0 mmol/l	Potassium < 5.0 mmol/l	ID8	SwedeHF: shf_potassium
Written informed consent	Informed consent	ID11	Given 100%. Reasoning: Written informed consent in an RCT equals the non-opt-out of SwedeHF patients.

	SPIRIT-HF[15]	Study variable	ID	Definition / operationalisation
Exclusion criteria (none must be true)	Potassium level ≥ 5.5 mmol/L in prior two weeks	Potassium ≥ 5.5 mmol/l in prior 2 weeks	ID61	Assumed 0%. Reasoning: Laboratory data outside of SwedeHF are not available, i.e. potassium levels during the two weeks prior to the index registration are unknown.
	Sodium level < 135 mmol/l prior to randomisation	Sodium < 135 mmol/l	ID62	SwedeHF: shf_sodium
	Severe renal dysfunction: a) eGFR < 30 ml/min/1.73m^2 (MDRD) or b) serum creatinine level ≥ 1,8 mg/dl (> 160 µmol/ml)	a) eGFR (CKD-EPI 2021) < 30 ml/min/1.73m^2 OR b) Serum creatinine ≥ 1.8 mg/dl (independent from eGFR)	a) ID40 b) ID63	a) SwedeHF: shf_gfrckdepi b) SwedeHF: shf_crea
	History of anuria or acute renal failure (as defined by the RIFLE criteria for AKI) within the past two weeks	Acute renal failure in prior 2 weeks	ID64	New variable: - NPR (in- and out-patients): ICD-10-SE code N17 / position: main diagnosis / timeframe: -14 – 0 days Reasoning: ICD codes do not allow for applying the RIFLE classification; the code N17 encompasses acute kidney failure in general, which is likely to contain the (by far more frequent) RIFLE categories Risk and Injury, too. Choosing the position “main diagnosis” is supposed to select only those patients with leading and, thus, probably severe acute kidney failure comparable to the RIFLE definition.

SPIRIT-HF[15]	Study variable	ID	Definition / operationalisation
a) ACS (including MI) within prior 30 days b) Elective PCI within prior 30 days	a) ACS (including MI) in prior 30 days OR b) PCI in prior 30 days	a) ID65 b) ID25	a) New variable: - NPR (in- and out-patients): ICD-10-SE codes I20-23 OR I24.8-9 / position: main diagnosis / timeframe: -30 – 0 days b) New variable: - NPR (in- and out-patients): OPS codes DF009, DF019, DF020, FNG02, FNG05 OR FNG22 / timeframe: -30 – 0 days Reasoning: a) Main diagnosis position was chosen to avoid excluding most patients with chronic angina pectoris which is less likely to be in main position compared to acute angina pectoris (as in ACS). b) All PCIs are captured as this trial's criterion also addresses ACS with potential acute PCIs.
a) Cardiac surgery or other major CV surgery in prior 3 months b) Urgent PCI within the prior 3 months	a) 1. CABG in prior 3 months OR 2. Valve intervention / surgery in prior 3 months b) In-patient PCI in prior 3 months	a) 1. ID24 2. ID66 b) ID67	a) 1. New variable: NPR (in-patients): OPS codes FNA, FNB, FNC, FND OR FNE / timeframe: -3 – 0 months 2. New variable: NPR (in-patients): OPS codes FG, FJE, FJF, FC OR FM / timeframe: -3 – 0 months b) New variable: - NPR (in-patients): OPS codes DF009, DF019, DF020, FNG02, FNG05 OR FNG22 / timeframe: -3 – 0 months

SPIRIT-HF[15]	Study variable	ID	Definition / operationalisation
			Reasoning: a) Major CV surgery is CABG or valve surgery in the vast majority of all cases. Distinguishing valve surgery from interventions is not feasible within the NPR using OPS codes; thus, both are included. b) The urgency of any PCI cannot be reconstructed in the registry data. However, including in-patients only is supposed to exclude as many elective PCIs as possible from this criterion. Filtering for the combination with AMI, however, would exclude patients with urgent PCI in the absence of AMI (e.g., unstable angina pectoris because of a progressive coronary artery disease).
Current acute decompensated HF requiring augmented therapy with i.v. diuretics, i.v. vasodilators and/or i.v. inotropic drugs. Patients are eligible after initial stabilisation.	Acute non-stabilised HF	ID68	Assumed 0%. Reasoning: The index registration captures out-patients at their visit to specialised care; and out-patients will not need receive i.v. inotropes or vasodilators and almost never i.v. diuretics in Sweden. In-patients are captured at discharge from hospitalisation and, thus, after stabilisation and then eligible for enrolment. Therefore, this study assumes that (virtually) 0% of SwedeHF patients meet this criterion.
Probable alternative diagnoses accounting for the patient's HF symptoms (i.e., dyspnoea, fatigue) such as significant pulmonary disease (incl. primary pulmonary	a) 1. COPD GOLD group E OR	a) 1. ID13	a) 1. New variable: - COPD diagnosis: NPR (in- and out-patients): ≥ 2 diagnoses of J41-44 / position: all diagnoses / timeframe: -5 – 0 years

SPIRIT-HF[15]	Study variable	ID	Definition / operationalisation
hypertension), anaemia or obesity. Specifically, patients with the following are not eligible: a) Severe pulmonary disease including COPD or severe bronchial asthma (i.e. requiring home O_2, chronic nebuliser therapy, chronic oral steroid therapy) b) anaemia (haemoglobin < 10 g/dl males and < 9.5 g/dl females) c) BMI > 40 kg/m^2	2. Severe bronchial asthma OR 3. Primary pulmonary hypertension OR b) Haemoglobin < 10 g/dl OR c) BMI > 40 kg/m^2	2. ID14 3. ID15 b) ID52 c) ID69	- GOLD E group: ≥ 2 moderate COPD exacerbations OR ≥ 1 severe COPD exacerbations in the past 1 year -- count of moderate COPD exacerbations (NPDR): dispensation of oral glucocorticoids, ATC code H02AB / Apodos excluded / interval between dispensations < 4 weeks counts as 1 event / timeframe: -1 – 0 years -- count of severe COPD exacerbations (NPR, in-patients, previously named sos_com_hospcopd1yr): hospitalisation for ICD-10-SE J12-18, J20-22, J41-44 OR J96 / position: main diagnosis / timeframe: -1 – 0 years 2. New variable: - Bronchial asthma diagnosis: NPR (in- and out-patients): ≥ 2 diagnoses of J45-46 / position: all diagnoses / timeframe: -5 – 0 years - Asthma severity: NPR (in-patients): ≥ 1 hospitalisation for ICD-10-SE J45-46 / position: main position / timeframe: -5 – 0 years 3. New variable (PAH diagnosis): - NPR (in- and out-patients): ≥ 1 registration of ICD-10-SE I27.0 / position: main position / timeframe: -5 – 0 years AND New variable (PDE5 inhibitors):

SPIRIT-HF[15]	Study variable	ID	Definition / operationalisation
			- NPDR: ATC codes G04BE03 OR G04BE08 / Apodos included / timeframe: -120 - +5 days b) SwedeHF: shf_hb c) SwedeHF: shf_bmi Reasoning: The probability of these alternative diagnoses to cause HF (-like) symptoms cannot be concluded from the registry data. In addition, the mentioned (severe) pulmonary diseases are incorporated in this criterion which are deemed to represent most severe pulmonary disease cases.
Evidence of right sided HF in the absence of left-sided structural heart disease	Right-sided HF not due to left-sided HF	ID53	Assumed 0%. Reasoning: Isolated right HF is difficult to assess in SwedeHF and with ICD codes. As only a small minority of patients presents with this condition, we decided to assume 0%.
Specific aetiologies such as infiltrative, genetic hypertrophic cardiomyopathy, pericardial constriction, sarcoidosis, amyloidosis and any other storage diseases	a) Chronic constrictive pericarditis OR b) Hypertrophic cardiomyopathy with or without obstruction OR	a) ID18 b) ID70 c) ID20 d) ID21	a) New variable: - NPR (in- and out-patients): ICD-10-SE I31.1 / position: all diagnoses / timeframe: -5 – 0 years b) New variable: - NPR (in- and out-patients): ICD-10-SE I42.1 OR I42.2 / position: all diagnoses / timeframe: -5 – 0 years c) New variable: - NPR (in- and out-patients): ICD-10-SE E85 / position: all diagnoses / timeframe: -5 – 0 years

SPIRIT-HF[15]	Study variable	ID	Definition / operationalisation
	c) Amyloidosis-induced cardiomyopathy OR d) Sarcoidosis-induced cardiomyopathy		d) New variable: - NPR (in- and out-patients): ICD-10-SE D86 / position: all diagnoses / timeframe: -5 – 0 years Reasoning: Infiltrative cardiomyopathy does not have a distinct ICD code. However, cardiac amyloidosis is the most frequent sub-entity. In this study, an amyloidosis code in the presence of HF (which is true for all SwedeHF patients) is considered to denote amyloidosis-induced cardiomyopathy. The same is applied for sarcoidosis. Other storage diseases are very rare and, therefore, not considered here.
Clinically significant congenital heart disease underlying heart failure	Congenital cardiac malformations	ID51	New variable: - NPR (in- and out-patients): ICD-10-SE Q20-26 / position: all diagnoses / timeframe: -infinite – 0 years Reasoning: Congenital malformations might not be coded frequently but rather only the resulting HF. Thus, an infinite lookback is necessary. Specificity both regarding diagnosis position and lookback is unlikely to become a problem as these codes are very specific themselves and only used of the diagnosis is ensured. The causal relationship with HF cannot be investigated in the registry data. However, only major congenital malformations likely to be a cause of HF were selected.
Life-threatening or uncontrolled dysrhythmia, including	a) Symptomatic or sustained VT	a) ID71	a) Assumed 0%.

SPIRIT-HF[15]	Study variable	ID	Definition / operationalisation
a) symptomatic or sustained VT and b) uncontrolled persistent or permanent AFib or AFlu (with heart rate > 100 bpm, RACE II) during randomisation visit	OR b) AFib or AFlu with heart rate > 100 bpm	b) ID72	b) - SwedeHF: shf_sos_com_af - SwedeHF: shf_heartrate Reasoning: a) VT and other life-threatening arrythmia are not captured in a SwedeHF registration. In addition, only few patients are expected to present with this condition during a SwedeHF registration (out-patients and in-patients at discharge). Therefore, VT is disregarded. b) If AFib/AFlu is paroxysmal, persistent or permanent is unknown and therefore disregarded.
Presence of significant (i.e., more than moderate) valvular heart disease expected to lead to surgery during the trial	Valve intervention / surgery in prior 3 months	ID66	New variable: - NPR (in-patients): OPS codes FG, FJE, FJF, FC OR FM / timeframe: -3 – 0 months Reasoning: Retrospective identification of patients with expected heart valve correction in the registry is not feasible. At the same time, borrowing time from the future (after index registration) creates a bias of its own. Thus, we ruled to exclude recent valve correction instead.
Stroke, TIA, carotid surgery or carotid angioplasty within the prior 3 months	a) Stroke in prior 3 months OR b) TIA in prior 3 months	a) ID28 b) ID73	a) New variable: - NPR (in- and out-patients): ICD-10-SE codes I60-64 (OR) / position: main diagnosis / timeframe -3 – 0 months b) New variable:

SPIRIT-HF[15]	Study variable	ID	Definition / operationalisation
	OR c) Surgery or angioplasty of brachiocephalic trunk, common carotid artery or its branches in prior 3 months	c) ID74	- NPR (in- and out-patients): ICD-10-SE code G45 / position: all diagnoses / timeframe -3 – 0 months c) Assumed 0% Reasoning: a) Only acute strokes in the prior 3 months are supposed to be registered. Choosing the main position and excluding the codes I69.0-4 (late effects of stroke) increases specificity in this regard. b) and c) TIAs and carotid surgery or angioplasty may also occur if a different main diagnosis is present (while strokes are usually the main diagnosis themselves if they occur). Thus, all positions are considered. c) OPS codes not available in the dataset.
a) Coronary or b) carotid artery disease or c) valvular heart disease likely to require surgical or percutaneous intervention within the 6 months after randomisation	a) 1. CABG in prior 3 months OR 2. PCI in prior 30 days OR b) Surgery or angioplasty of	a) 1. ID24 2. ID25 b) ID74 c) ID66	a) 1. New variable: NPR (in-patients): OPS codes FNA, FNB, FNC, FND OR FNE / timeframe: -3 – 0 months 2. New variable: NPR (in- and out-patients): OPS codes DF009, DF019, DF020, FNG02, FNG05 OR FNG22 / timeframe: -30 – 0 days b) Assumed 0%. c) New variable:

SPIRIT-HF[15]	Study variable	ID	Definition / operationalisation
	brachiocephalic trunk, common carotid artery or its branches in prior 3 months OR c) Valve intervention / surgery in prior 3 months		- NPR (in-patients): OPS codes FG, FJE, FJF, FC OR FM / timeframe: -3 – 0 months Reasoning: a) Similar to other criteria of this study, the likelihood of imminent surgery / intervention cannot be assessed retrospectively in registry data; to avoid borrowing information from the future and hereby introducing new bias, we ruled to assess recent procedures only. b) OPS codes not available in the dataset. c) Retrospective identification of patients with expected heart valve correction in the registry is not feasible. At the same time, borrowing time from the future (after index registration) creates a bias of its own. Thus, we ruled to exclude recent valve correction instead.
Patients with a) prior major organ transplant or intent to transplant (on transplant list) OR b) with current ventricular assist device therapy	a) 1. Kidney, lung or liver transplant recipient OR 2. Heart transplant recipient OR	a) 1. ID79 2. ID26 3. ID138 b) ID27	a) 1. New variable: - NPR (in- and out-patients): ICD-10-SE codes Z94.0 OR Z94.2-4 / position: all diagnoses / timeframe: -5 – 0 years 2. New variable: - NPR (in- and out-patients): ICD-10-SE codes Z94.1 OR Z94.3 OR OPS codes FQA-B / position: all diagnoses / timeframe: -5 – 0 years 3. Assumed 0%.

SPIRIT-HF[15]	Study variable	ID	Definition / operationalisation
	3. Heart transplant waiting list OR b) Currently implanted LVAD		b) New variable: - NPR (in-patients): OPS codes FXL40, FXL50 OR FXL60 / timeframe: -5 – 0 years Reasoning: a) Patients who have received a major organ transplantation will seek medical attention for follow-up frequently, with near to certainty within a 5-years period. A non-restricted lookback might reduce specificity by including more cases with miscoding. Identification of patients on transplant waiting lists is not feasible in the registry data. b) Any LVAD implantation in the past is assumed to be a current LVAD since explantations are rare. Other ventricular assist devices than LVAD are very rare, too, and therefore not assessed.
Evidence of hepatic disease: ASAT or ALAT values exceeding 3x the upper limit of normal or bilirubin >1.5 mg/dl	Chronic liver disease	ID16	SwedeHF/NPR (in- and out-patients): sos_com_liver (ICD-10-SE B18, I85, I86.4, I98.2, K70, K71.0, K71.1, K71.3-7, K72-4, K76.0 OR K76.2-9 / position: all diagnoses / timeframe: -5 – 0 years) Reasoning: ASAT, ALAT and bilirubin are not available in SwedeHF. However, these chronic hepatic conditions are likely to come along with elevated transaminases.
Evidence of present bilateral renal artery stenosis	Renal artery atherosclerosis	ID80	New variable:

SPIRIT-HF[15]	Study variable	ID	Definition / operationalisation
			- NPR (in- and out-patients): ICD-10-SE code I70.1 / position: all diagnoses / timeframe: -5 – 0 years
Known intolerance or history of hypersensitivity to the active substance (spironolactone) or to any of the excipients of the Investigational Medicinal Product or placebo	MRA intolerance	ID35	Assumed 0%. Reasoning: Allergies against MRA are rare and other intolerances usually rather subjective. In addition, this information cannot be retrieved retrospectively.
Present use of any a) aldosterone antagonist, b) potassium supplements or c) potassium-sparing diuretics at the time of enrolment	a) MRA in prior 3 months OR b) Potassium supplementation in prior 3 months OR c) Non-MRA potassium-sparing diuretics	a) ID33 b) ID81 c) ID34	a) Assumed 0%. b) New variable: - NPDR: ATC code A12B / Apodos included / timeframe: -120 – +5 days c) Assumed 0%. Reasoning: a) The original trial was performed to evaluate efficacy and safety of MRA in patients with HF at a time when this indication was not established, yet. Exclusion of MRA made sense to exclude use because of other indications. Nowadays, in a contemporary population, exclusion of MRA would result in artificially low eligibility rates as patients are treated based on the results of, among others, this trial. Therefore, it is reasonable to account for this aspect by setting this exclusion criterion to 0%.

SPIRIT-HF[15]	Study variable	ID	Definition / operationalisation
			b) A lookback is supposed to ensure capture of currently used medication as filling in a prescription at least every 3 months is necessary even for long-term medication. An additional month lookback is supposed to account for stockpiling and (temporary) incompliance. An additional 5 days follow-up ensures to capture prescriptions during the index registration, which reflect eligibility during the respective registration. c) Non-MRA potassium-sparing diuretics are rarely used in Sweden. In addition, the short period of 7 days would allow for fast wash-out and would not pose an actual barrier to RCT enrolment.
Required treatment with prohibited co-medications according to the summary of product characteristics with the exception of ACEi or ARB (i.e. potassium chloride, triamterene, amiloride, abiraterone)	a) Abiraterone use in prior 3 months OR b) Potassium supplementation in prior 3 months OR c) MRA in prior 3 months	a) ID82 b) ID81 c) ID33	a) Assumed 0%. b) New variable: - NPDR: ATC code A12B / Apodos included / timeframe: -120 – +5 days c) Assumed 0%. <u>Reasoning</u>: a) Amiloride and triamterene are not available in Sweden. Abiraterone is only very rarely used and thus assumed to be 0%. b) A lookback is supposed to ensure capture of currently used medication as filling in a prescription at least every 3 months is necessary

SPIRIT-HF[15]	Study variable	ID	Definition / operationalisation
			even for long-term medication. An additional month lookback is supposed to account for stockpiling and (temporary) incompliance. An additional 5 days follow-up ensures to capture prescriptions during the index registration, which reflect eligibility during the respective registration. c) The original trial was performed to evaluate efficacy and safety of MRA in patients with HF at a time when this indication was not established, yet. Exclusion of MRA made sense to exclude use because of other indications. Nowadays, in a contemporary population, exclusion of MRA would result in artificially low eligibility rates as patients are treated based on the results of, among others, this trial. Therefore, it is reasonable to account for this aspect by setting this exclusion criterion to 0%.
Use of other investigational drugs at the time of enrolment or within 30 days or 5 half-lives before enrolment, whichever is longer	Current participation in any other therapeutic trial	ID37	Assumed 0%. Reasoning: Data not available; the expected prevalence is very low, however.
Any condition that may prevent the subject from adhering to the study protocol (e.g., history of non-compliance to medical regimens, patients who are considered potentially unreliable, patients with a history of addiction).	Any condition which may reduce adherence	ID38	New variable: - NPR (in- and out-patients): ICD-10-SE codes F01-7, F09-16, F18-25 OR F28-30 / position: all diagnoses / timeframe: -1 – 0 years Reasoning: The included conditions are likely to impair the participant's adherence to the trial protocol. These are: dementia, organic amnesic syndrome, delirium, other mental disorder or

SPIRIT-HF[15]	Study variable	ID	Definition / operationalisation
			personality and behavioural disorders due to brain disease, unspecified mental disorder, mental disorders due to psychoactive substances, schizophrenia, manic episode, and bipolar affective disorder.
History or presence of any other disease (i.e., including malignancies) with a life expectancy of < 1 year	Limited life expectancy due to metastatic cancer or primary cancer with very poor prognosis	ID12	New variable: - NPR (in- and out-patients): ≥ 2 registrations of ICD-10-SE codes C15, C16, C22, C25, C34, C45, C71 OR C77-79 / position: main diagnosis / timeframe: -6 – 0 months Reasoning: Life expectancy is very difficult to estimate, even in personal contact with the patient as during screening for a randomised controlled trial. This assessment is even more difficult in registries without borrowing information from the future which would introduce a bias of its own. However, diagnosis of metastatic or aggressive cancer appears as a rational surrogate and has been used before.
Subjects who are legally detained in an official institution.	Detained person	ID84	Assumed 0%. Reasoning: Data not available; and very low estimated prevalence.
Subjects who may be dependent on the sponsor, the investigator or the trial sites.	Person dependent on investigator, sponsor or trial site	ID85	Assumed 0%. Reasoning: Data not available; and very low estimated prevalence.
Pregnant (positive pregnancy test) or nursing women	Pregnancy or nursing	ID9	Assumed 0%.

SPIRIT-HF[15]	Study variable	ID	Definition / operationalisation
			Reasoning: Data on pregnancy and nursing are not available in the dataset.
Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception during study participation and until 2 months after the last dose of study drug	Use of highly effective contraception	ID86	Assumed 100%, i.e. 0% ineligibility. Reasoning: The probability of potential pregnancy also taking the kind of contraception into account cannot be assessed in the registry data with sufficient validity.

If not explicitly stated otherwise, the time of assessment of each variable is the index registration.

Table 6: Operationalisation of FINEARTS-HF criteria

	FINEARTS-HF[16]	Study variable	ID	Definition / operationalisation
Inclusion criteria (all must be true)	Male or female	Male or female	ID1	SwedeHF: shf_sex
	Age ≥ 40 years	Age ≥ 40 years	ID87	SwedeHF: shf_age
	HF with NYHA class II–IV, ambulatory or hospitalised primarily for HF	NYHA class II–IV	ID46	SwedeHF: shf_nyha Reasoning: The HF diagnosis is given by the inclusion in SwedeHF which encompasses both out- and in-patients.
	On diuretic treatment for at least 30 days prior to randomisation	Current use of any diuretics	ID88	SwedeHF: shf_diuretic Reasoning: A current use of diuretics according to SwedeHF approximates the original criterion close enough.
	LVEF of ≥ 40% measured by any modality within the prior 12 months; if several values are available, the most recent one shall be reported. If LVEF was not measured in the past 12 months, a new measurement may be done at screening	LVEF ≥ 40%	ID4	SwedeHF: shf_ef Reasoning: In SwedeHF, the most recent LVEF is entered in the database at each registration, not necessarily measured at the time of this registration. However, as at least one follow-up per year is planned, this latest value meets the trial's "in the past 12 months" criterion.
	Structural heart abnormalities based on any local imaging measurement within the last 12 months, latest at screening, defined by at least 1 of the following findings: LAD ≥ 3.8 cm, LAA ≥ 20 cm^2, LAVI > 30 ml/m^2, LVMI ≥ 115 g/m^2 (♂) /	Structural cardiac abnormalities: LAD, LAA, LAVI, LVMI, wall thickness	ID89	Assumed 100%. Reasoning: These data are not available, but at least on criterion is likely to be present given a qualified HF diagnosis within SwedeHF.

FINEARTS-HF[16]	Study variable	ID	Definition / operationalisation
95 g/m^2 (♀) or septal thickness or posterior wall thickness ≥ 1.1 cm			
NT-proBNP ≥300 pg/mL (BNP ≥100 pg/mL) in SR and patient does not have an ongoing diagnosis of paroxysmal AFib or NT-proBNP ≥900 pg/mL (BNP ≥300 pg/mL) in AFib (or if AFib status is unknown or if patient has an ongoing diagnosis of paroxysmal AFib) for participants obtained at the following time: • Within 90 days prior to randomisation if patient had been hospitalised for HF requiring initiation or change in HF therapy or if patient had an urgent visit for HF requiring i.v. diuretic therapy, both within 90 days prior to randomisation OR • Within 30 days prior to randomisation if patient has not been hospitalised for HF nor had an urgent HF visit within the past 90 days.	a) NT-proBNP > 300 ng/l without AFib or AFlu OR b) NT-proBNP > 750 ng/l with AFib or AFlu	a) ID42 b) ID43	a) and b) - SwedeHF: shf_ntprobnp - SwedeHF: shf_sos_com_af <u>Reasoning</u>: Only NT-proBNP is registered in SwedeHF, not BNP. In addition, laboratory data outside of SwedeHF is not available; consequently, the time of the respective SwedeHF registration is chosen.
Women of childbearing potential: negative pregnancy test and adequate contraception	a) Pregnancy AND b) Use of highly effective contraception	a) ID90 b) ID86	a) Assumed 0%. b) Assumed 100%. <u>Reasoning</u>: a) Codes not available in the dataset.

	FINEARTS-HF[16]	Study variable	ID	Definition / operationalisation
				b) The probability of potential pregnancy also taking the kind of contraception into account cannot be assessed in the registry data with sufficient validity.
	Written informed consent	Informed consent	ID11	Given 100%. Reasoning: Written informed consent in an RCT equals the non-opt-out of SwedeHF patients.
Exclusion criteria (none must be true)	eGFR < 25 mL/min/1.73 m²	eGFR (CKD-EPI 2021) < 25 ml/min/1.73m²	ID91	SwedeHF: shf_gfrckdepi
	Serum/plasma potassium > 5.0 mmol/l	Potassium ≥ 5.0 mmol/l	ID39	SwedeHF: shf_potassium
	Acute inflammatory heart disease (e.g., acute myocarditis) within prior 90 days	a) Acute myocarditis in prior 3 months OR b) Acute endocarditis in prior 3 months OR c) Acute pericarditis in prior 3 months	a) ID92 b) ID93 c) ID94	a) New variable: - NPR (in- and out-patients): ICD-10-SE codes I01.2 OR I40 / position: all diagnoses / timeframe: -3 – 0 months b) New variable: - NPR (in- and out-patients): ICD-10-SE codes A39.5, A52.0, B37.6, I01.1, I09.1, I33, I38 OR I39 / position: all diagnoses / timeframe: -3 – 0 months c) New variable: - NPR (in- and out-patients): ICD-10-SE code I30 / position: all diagnoses / timeframe: -3 – 0 months

FINEARTS-HF[16]	Study variable	ID	Definition / operationalisation
			Reasoning: Acute and not specified diagnoses are captured but not chronic ones.
MI or any event which could have reduced the LVEF within prior 90 days	AMI in prior 3 months	ID23	New variable: - NPR (in-patients): ICD-10-SE I21 OR I22 / position: all diagnoses / timeframe: -3 – 0 months Reasoning: AMI without hospitalisation is unlikely. Thus, to increase specificity of the diagnosis, only in-patients are considered. However, MI does not have to be in main position as in patients with secondary MI caused by another entity, the latter might be put into main position. Other acute entities likely to reduce LVEF are much less frequent and not feasible to identify in registry data.
CABG surgery in the prior 90 days	CABG in prior 3 months	ID24	New variable: - NPR (in-patients): OPS codes FNA, FNB, FNC, FND OR FNE / timeframe: -3 – 0 months
PCI in the prior 30 days	PCI in prior 30 days	ID25	New variable: - NPR (in- and out-patients): OPS codes DF009, DF019, DF020, FNG02, FNG05 OR FNG22 / timeframe: -30 – 0 days Reasoning: Elective PCIs can also be performed in out-patients.
Stroke or TIA within prior 90 days	a) Stroke in prior 3 months OR	a) ID28 b) ID73	a) New variable: - NPR (in- and out-patients): ICD-10-SE codes I60-64 (OR) / position: main diagnosis / timeframe -3 – 0 months b) New variable:

FINEARTS-HF[16]	Study variable	ID	Definition / operationalisation
	b) TIA in prior 3 months		- NPR (in- and out-patients): ICD-10-SE code G45 / position: all diagnoses / timeframe -3 – 0 months Reasoning: a) Only acute strokes in the prior 3 months are supposed to be registered. Choosing the main position and excluding the codes I69.0-4 (late effects of stroke) increases specificity in this regard. b) TIAs may also occur if a different main diagnosis is present (while strokes are usually the main diagnosis themselves if they occur). Thus, all positions are considered.
Probable alternative primary cause of participants' HF symptoms, specifically: a) Severe pulmonary disease requiring home O_2 or chronic oral steroid therapy b) History of primary pulmonary arterial hypertension c) Haemoglobin < 10 g/dl d) Valvular heart disease considered to be clinically significant e) BMI > 50 kg/m^2	a) COPD GOLD group E OR b) Primary pulmonary hypertension OR c) Haemoglobin < 10 g/dl OR	a) ID13 b) ID15 c) ID52 d) ID66 e) ID95	a) New variable (COPD GOLD E): - COPD diagnosis: NPR (in- and out-patients): ≥ 2 diagnoses of J41-44 / position: all diagnoses / timeframe: -5 – 0 years - GOLD E group: ≥ 2 moderate COPD exacerbations OR ≥ 1 severe COPD exacerbations in the past 1 year -- count of moderate COPD exacerbations (NPDR): dispensation of oral glucocorticoids, ATC code H02AB / Apodos excluded / interval between dispensations < 4 weeks counts as 1 event / timeframe: -1 – 0 years -- count of severe COPD exacerbations (NPR, in-patients, previously named sos_com_hospcopd1yr): hospitalisation for ICD-

FINEARTS-HF[16]	Study variable	ID	Definition / operationalisation
	d) Valve intervention / surgery in prior 3 months OR e) BMI > 50 kg/m^2		10-SE J12-18, J20-22, J41-44 OR J96 / position: main diagnosis / timeframe: -1 – 0 years b) New variable (PAH diagnosis): - NPR (in- and out-patients): ≥ 1 registration of ICD-10-SE I27.0 / position: main position / timeframe: -5 – 0 years AND New variable (PDE5 inhibitors): - NPDR: ATC codes G04BE03 OR G04BE08 / Apodos included / timeframe: -120 - +5 days c) SwedeHF: shf_hb d) New variable: - NPR (in-patients): OPS codes FG, FJE, FJF, FC OR FM / timeframe: -3 – 0 months e) SwedeHF: shf_bmi_ Reasoning: a) The most frequent reason for home O_2 and oral glucocorticoids with a respiratory indication is COPD. Identification of severe COPD patients based on home O_2 is not feasible, but the abovementioned definition has been used before successfully.

FINEARTS-HF[16]	Study variable	ID	Definition / operationalisation
			b) Primary pulmonary hypertension is (relatively) rare, but if present it is always regarded as a "significant pulmonary disease" due to its generally poor prognosis. The validity of the diagnosis is enhanced by including ongoing phosphodiesterase 5 inhibitor therapy in the variable. A lookback is supposed to ensure capture of currently used medication as filling in a prescription at least every 3 months is necessary even for long-term medication. An additional month lookback is supposed to account for stockpiling and (temporary) incompliance. An additional 5 days follow-up ensures to capture prescriptions during the index registration, which reflect eligibility during the respective registration. c) – d) Expected valve correction would be a good surrogate for clinically relevant valve disease. However, retrospective identification of patients with expected heart valve correction in the registry is not feasible. At the same time, borrowing time from the future (after index registration) creates a bias of its own. Thus, we ruled to exclude recent valve correction instead. e) -

FINEARTS-HF[16]	Study variable	ID	Definition / operationalisation
			Overall, the retrospective assessment of these entities' probability to cause participants' HF symptoms is not possible – and rather subjective in the first place. Thus, this aspect was disregarded.
SBP ≥ 160 mmHg if not on treatment with ≥ 3 blood pressure lowering medications or ≥ 180 mmHg irrespective of treatments on 2 consecutive measurements at least 2-minute apart	a) SBP ≥ 160 mmHg while on < 3 antihypertensive agents OR b) SBP ≥ 180 mmHg	a) ID96 b) ID97	a) SwedeHF: shf_bpsys New variable: - NPDR: ATC codes C01D (count as 1), C02A-K (count as 1), C02L (count as 2), C03A-D (count as 1), C03E (count as 2), C03X (count as 1), C04 (count as 1), C07A (count as 1), C07B-C (count as 2), C07D (count as 3), C07E-F (count as 2), C08C-E (count as 1), C08G (count as 2), C09A (count as 1), C09B (count as 2), C09C (count as 1), C09DA-B (count as 2), C09DX01 (count as 3) <u>OR</u> C09DX04 (count as 2) / Apodos included / timeframe: -120 – +5 days b) SwedeHF: shf_bpsys <u>Reasoning</u>: a) A lookback is supposed to ensure capture of currently used medication as filling in a prescription at least every 3 months is necessary even for long-term medication. An additional month lookback is supposed to account for stockpiling and (temporary) incompliance. An additional 5 days follow-up ensures to capture prescriptions during the index registration, which

FINEARTS-HF[16]	Study variable	ID	Definition / operationalisation
			reflect eligibility during the respective registration. b) -
Life-threatening or uncontrolled arrhythmias at screening and/or randomisation including but not limited to a) sustained VT and b) AFib or AFlu with resting ventricular rate > 110 bpm	a) Symptomatic or sustained VT OR b) AFib or AFlu with heart rate > 110 bpm	a) ID71 b) ID98	a) Assumed 0%. b) - SwedeHF: shf_sos_com_af - SwedeHF: shf_heartrate <u>Reasoning</u>: a) VT and other life-threatening arrythmia are not captured in a SwedeHF registration. In addition, only few patients are expected to present with this condition during a SwedeHF registration (out-patients and in-patients at discharge). Therefore, VT is disregarded. b) -
Symptomatic hypotension with mean SBP < 90 mmHg	SBP < 90 mmHg	ID99	SwedeHF: shf_bpsys <u>Reasoning</u>: Hypotension-related symptoms are not captured during a SwedeHF registration; thus, this aspect is disregarded.
Any primary cause of HF scheduled for surgery, e.g., valve disease such as severe aortic stenosis or severe mitral regurgitation	a) Valve intervention / surgery in prior 3 months OR	a) ID66 b) ID24	a) New variable: - NPR (in-patients): OPS codes FG, FJE, FJF, FC <u>OR</u> FM / timeframe: -3 – 0 months b) New variable: - NPR (in-patients): OPS codes FNA, FNB, FNC, FND <u>OR</u> FNE / timeframe: 0 – 3 months

FINEARTS-HF[16]	Study variable	ID	Definition / operationalisation
	b) CABG in prior 3 months		<u>Reasoning</u>: a) First, a distinction between primary and secondary to HF valve disease is not feasible and, thus, disregarded. Second, retrospective identification of patients with expected heart valve correction in the registry is not feasible. At the same time, borrowing time from the future (after index registration) creates a bias of its own. Thus, we ruled to exclude recent valve correction instead. b) If cardiac surgery is already scheduled at the time of the SwedeHF registration is not available in the registry data. Borrowing information from the future would create a bias on its own. Thus, we ruled to address recent procedures only.
History of a) peripartum cardiomyopathy, b) chemotherapy induced cardiomyopathy, c) viral myocarditis, d) right HF in absence of left-sided structural disease, e) pericardial constriction,	a) Peripartum cardiomyopathy OR b) Chemotherapy-induced cardiomyopathy OR c) History of viral myocarditis	a) ID102 b) ID103 c) ID104 d) ID53 e) ID18	a) Assumed 0%. b) - New variable: NPR (in- and out-patients): ICD-10-SE codes C / position: main diagnosis / timeframe: -5 – 0 years AND - New variable: NPR (in- and out-patients): ICD-10-SE code I42.7 / position: all diagnoses / timeframe: -5 – 0 years c) New variable:

FINEARTS-HF[16]	Study variable	ID	Definition / operationalisation
f) genetic hypertrophic cardiomyopathy or g) infiltrative cardiomyopathy including amyloidosis	OR d) Right-sided HF not due to left-sided HF OR e) Chronic constrictive pericarditis OR f) Hypertrophic cardiomyopathy with or without obstruction OR g) 1. Amyloidosis-induced cardiomyopathy OR 2. Sarcoidosis-induced cardiomyopathy	 f) ID70 g) 1. ID20 2. ID21	- NPR (in- and out-patients): ICD-10-SE codes I40 <u>OR</u> I41.1 / position: all diagnoses / timeframe: -5 – 0 years d) Assumed 0%. e) New variable: - NPR (in- and out-patients): ICD-10-SE I31.1 / position: all diagnoses / timeframe: -5 – 0 years f) New variable: - NPR (in- and out-patients): ICD-10-SE I42.1 <u>OR</u> I42.2 / position: all diagnoses / timeframe: -5 – 0 years g) 1. New variable: NPR (in- and out-patients): ICD-10-SE E85 / position: all diagnoses / timeframe: -5 – 0 years 2. New variable: NPR (in- and out-patients): ICD-10-SE D86 / position: all diagnoses / timeframe: -5 – 0 years <u>Reasoning</u>: a) Code not available in the dataset. b) ICD code I42.7 considers cardiomyopathy caused by drugs and other external factors, i.e. including but not exclusively chemotherapy-induced cardiomyopathy. The specificity is

FINEARTS-HF[16]	Study variable	ID	Definition / operationalisation
			increased by an additional cancer diagnosis within the past 5 years. However, distinguishing chemotherapy-induced from radiation-induced cardiomyopathy remains not feasible, even if the latter rather establishes as a long-term side effect later than 5 years. c) The ICD code I40 does not provide cause-specific information (I41.1 is specific for a viral aetiology) but is used frequently and should be considered. Thus, the criterion used in this study does not encompass viral myocarditis only. However, if not specifically classified for a different cause, a viral aetiology is usually the most probable one. d) Isolated right HF is difficult to assess in SwedeHF and with ICD codes. As only a small minority of patients presents with this condition, we decided to assume 0%. e-f) – g) Infiltrative cardiomyopathy does not have a distinct ICD code. However, cardiac amyloidosis is the most frequent sub-entity. In this study, an amyloidosis code in the presence of HF (which is true for all SwedeHF patients) denotes amyloidosis-induced cardiomyopathy. The same is applied for sarcoidosis. Other storage diseases are very rare and, therefore, not considered here.

FINEARTS-HF[16]	Study variable	ID	Definition / operationalisation
Presence of LVAD	Currently implanted LVAD	ID27	New variable: - NPR (in-patients): OPS codes FXL40, FXL50 OR FXL60 / timeframe: -5 – 0 years Reasoning: Any LVAD implantation in the past is assumed to be a current LVAD since explantations are rare.
History of hyperkalaemia or acute renal failure during MRA treatment for > 7 consecutive days, leading to permanent discontinuation of the MRA treatment	a) History of MRA-induced hyperkalaemia leading to MRA discontinuation OR b) History of MRA-induced acute renal failure leading to MRA discontinuation	a) ID105 b) ID106	a) Assumed 0%. b) Assumed 0%. Reasoning: a) and b) This information cannot be retrieved from the registries.
Pregnant (positive pregnancy test) or nursing women	Pregnancy or nursing	ID9	Assumed 0%. Reasoning: Data on pregnancy and nursing are not available in the dataset.
Known hypersensitivity to the study intervention (active substance or excipients)	MRA intolerance	ID35	Assumed 0%. Reasoning: Allergies are rare and other intolerances usually rather subjective. In addition, this data cannot be retrieved from the registries.
Hepatic insufficiency classified as Child-Pugh C	Liver cirrhosis	ID108	New variable: - NPR (in- and out-patients): ICD-10-SE codes I85, I86.4, I98.2, K70.3-4, K71.7, K72.1, K74.6

FINEARTS-HF[16]	Study variable	ID	Definition / operationalisation
			OR K76.6-7 / position: main diagnosis / timeframe: -5 – 0 years Reasoning: The Child-Pugh classification is not mirrored in the Swedish version of ICD-10 and cannot be calculated based on the available registry data. Thus, in this study diagnosis of liver cirrhosis in general and associated diagnoses (oesophageal or gastric varices, hepatoportal hypertension, liver failure, hepatorenal syndrome) are used. The decision to exclude diagnoses in other than first position is supposed to select more serious cases of cirrhosis to capture a similar patient population compared to Child-Pugh class C.
Addison's disease	Addison's disease	ID109	New variable: - NPR (in- and out-patients): ICD-10-SE codes E27.1-2 (OR) / position: all diagnoses / timeframe: -5 – 0 years
Requirement of any i.v. vasodilating drug (e.g., nitrates, nitroprusside), any i.v. natriuretic peptide (e.g., nesiritide, carperitide), any i.v. positive inotropic agents or mechanical support (intra-aortic balloon pump, endotracheal intubation, mechanical ventilation or any ventricular assist device) within prior 24 hours	Intensive care treatment in prior 24 hours	ID110	Assumed 0%. Reasoning: SwedeHF registrations happen in out-patient care as well as at discharge from hospitalisation. Thus, no intensive care treatments are performed in these patients in the prior 24 hours.
Participants who require treatment with more than one ACEi, ARB or ARNi; or two simultaneously at randomisation	Simultaneous use ≥ 1 agent of the classes ACEi / ARB / ARNi	ID111	- SwedeHF: shf_acei - SwedeHF: shf_arb - SwedeHF: shf_arni

FINEARTS-HF[16]	Study variable	ID	Definition / operationalisation
Continuous (at least 90 days) treatment with an MRA (e.g., spironolactone, eplerenone, canrenone, esaxerenone) within prior 12 months. Last intake at least 30 days before randomisation	MRA in prior 3 months	ID33	Assumed 0%. Reasoning: The original trial was performed to evaluate efficacy and safety of MRA in patients with HF at a time when this indication was not established, yet. Exclusion of MRA made sense to exclude use because of other indications. Nowadays, in a contemporary population, exclusion of MRA would result in artificially low eligibility rates as patients are treated based on the results of, among others, this trial. Therefore, it is reasonable to account for this aspect by setting this exclusion criterion to 0%.
Concomitant treatment with any renin inhibitor or potassium-sparing diuretic that cannot be stopped prior to randomisation and for the duration of the treatment period	a) Renin inhibitor use in prior 3 months OR b) Non-MRA potassium-sparing diuretics	a) ID112 b) ID34	a) New variable: - NPDR: ATC code C09XA / Apodos included / timeframe: -120 - +5 days b) Assumed 0%. Reasoning: a) A lookback is supposed to ensure capture of currently used medication as filling in a prescription at least every 3 months is necessary even for long-term medication. An additional month lookback is supposed to account for stockpiling and (temporary) incompliance. An additional 5 days follow-up ensures to capture prescriptions during the index registration, which reflect eligibility during the respective registration.

FINEARTS-HF[16]	Study variable	ID	Definition / operationalisation
			b) Non-MRA potassium-sparing diuretics are rarely used in Sweden. In addition, fast wash-out would be possible and would not pose an actual barrier to RCT enrolment.
Concomitant systemic therapy with potent CYP3A4 inhibitors (e.g., itraconazole, ritonavir, indinavir, cobicistat, clarithromycin) or moderate or potent CYP3A4 inducers, that cannot be discontinued 7 days prior to randomisation and for the duration of the treatment period.	a) Treatment with CYP3A4 inhibitors in prior 3 months OR b) Treatment with CYP3A4 inducers in prior 3 months	a) ID113 b) ID114	a) New variable: - NPDR: ATC codes N06AX06, J05AR10, J05AE03, J05AE30, J05AP53 <u>OR</u> J05AE04 / Apodos included / timeframe: -120 - +5 days b) New variable: - NPDR: ATC codes J04AB02, J04AM02, J04AM05, J04AM06, N03AF01, N03AB02 <u>OR</u> N03AB04 / Apodos included / timeframe: -120 - +5 days <u>Reasoning</u>: a) Included agents: nefazodone, ritonavir or nelfinavir / disregarded because of usually just short-term use: ketoconazole, itraconazole, clarithromycine. b) Included agents: rifampicin, carbamazepine, phenytoin / disregarded because of usually just short-term use: phenobarbital a) and b) i) Only systemically administered drugs are included, i.e., no topical formulations like shampoos. ii) A lookback is supposed to ensure capture of currently used medication as filling in a

FINEARTS-HF[16]	Study variable	ID	Definition / operationalisation
			prescription at least every 3 months is necessary even for long-term medication. An additional month lookback is supposed to account for stockpiling and (temporary) incompliance. An additional 5 days follow-up ensures to capture prescriptions during the index registration, which reflect eligibility during the respective registration. iii) Of note, St. John's wort was deregistered in Sweden 15 December 2009 as a drug but may still be available in other ways that are not covered by ATC codes. iv) ATC codes of drugs deregistered before the start of SwedeHF are not considered.
Any other condition or therapy, which would make the participant unsuitable for this study and will not allow participation for the full planned study period (e.g., active malignancy or other condition limiting life expectancy to < 12 months)	Limited life expectancy due to metastatic cancer or primary cancer with very poor prognosis	ID12	New variable: - NPR (in- and out-patients): ≥ 2 registrations of ICD-10-SE codes C15, C16, C22, C25, C34, C45, C71 OR C77-79 / position: main diagnosis / timeframe: -6 – 0 months Reasoning: Life expectancy is very difficult to estimate, even in personal contact with the patient as during screening for a randomised controlled trial. This assessment is even more difficult in registries without borrowing information from the future which would introduce a bias of its own. However, diagnosis of metastatic or aggressive cancer appears as a rational surrogate and has been used before.

FINEARTS-HF[16]	Study variable	ID	Definition / operationalisation
Previous assignment to treatment during this study	Previous assignment to treatment within the same trial	ID115	Given 0%. Reasoning: This cross-sectional study addresses the eligibility of SwedeHF patients to enrolment in RCTs once. As only one registration per personal identification number is assessed, each individual cannot be counted more than once.
Participation in another interventional clinical study (e.g., Phase 1 to 3 clinical studies) or treatment with another investigational medicinal product within prior 30 days prior	Current participation in any other therapeutic trial	ID37	Assumed 0%. Reasoning: Data unknown; and estimated actual prevalence very low.
Close personal affiliation with the investigational site	Person dependent on investigator, sponsor or trial site	ID85	Assumed 0%. Reasoning: Data unknown; and estimated actual prevalence very low.
Known current alcohol and/or illicit drug abuse that may interfere with the participant's safety and/or compliance	Any condition which may reduce adherence	ID38	New variable: - NPR (in- and out-patients): ICD-10-SE codes F01-7, F09-16, F18-25 OR F28-30 / position: all diagnoses / timeframe: -1 – 0 years Reasoning: The included conditions are likely to impair the participant's adherence to the trial protocol. These are: dementia, organic amnesic syndrome, delirium, other mental disorder or personality and behavioural disorders due to brain disease, unspecified mental disorder, mental disorders due to psychoactive substances, schizophrenia, manic episode, and bipolar affective disorder.

FINEARTS-HF[16]	Study variable	ID	Definition / operationalisation
Participant is in custody by order of an authority or a court of law.	Detained person	ID84	Assumed 0%. Reasoning: Data not available; and very low estimated prevalence.

Table 7: Operationalisation of RALES criteria

	RALES[17]	Study variable	ID	Definition / operationalisation
Inclusion criteria (all must be true)	HF diagnosis ≥ 6 weeks prior to enrolment	Previous HF diagnosis ≥ 42 days ago	ID116	SwedeHF: sos_durationhf
	NYHA class IV in 6 months prior to enrolment	NYHA class IV in prior 6 months	ID117	Assumed 100%. Reasoning: It is not feasible to assess this criterion in the registries. The first follow-up registration in SwedeHF is intended to be scheduled 6 months after the first registration and then yearly. Thus, more granular data on NYHA is not available – and each of these registrations represents a snapshot only but do not take into account the time between registrations. Using only the index registration, however, is not a potential solution as there is an additional, specific NYHA criterion at index including both classes III and IV. Thus, patients meeting this NYHA class III or IV at index are assumed to have had NYHA class IV in the prior 6 months.
	NYHA class III or IV at enrolment	NYHA class III or IV	ID118	SwedeHF: shf_nyha
	Treatment with ACEi if tolerated	Treatment with ACEi or ARB or ARNi if tolerated	ID119	Assumed 100%. Reasoning: Taking into account the time of the RALES trial, this criterion would need to be adjusted to the presence by adding ARB and ARNi. The prescription of these agents in patients with HFrEF is > 90% in the more recent years.[22] In addition, the reason for non-treatment with these agents cannot be taken from the registry data, but tolerability issues (e.g., symptomatic hypotension) are

	RALES[17]	Study variable	ID	Definition / operationalisation
				likely according to clinical experience. Thus, the present study assumes 100% eligibility for this criterion.
	Treatment with a loop diuretic	Current use of loop diuretic	ID120	SwedeHF: shf_loopdiuretic
	LVEF ≤ 35% in 6 months prior to enrolment with no clinically significant intercurrent event	LVEF < 40%	ID145	SwedeHF: shf_ef Reasoning: LVEF in SwedeHF is registered as a categorical variable (< 30%, 30-39%, 40-49%, ≥ 50%). As SwedeHF does not register LVEF in high temporal resolution, the latest registered LVEF during the index registration is used.
	Written informed consent	Informed consent	ID11	Given 100%. Reasoning: Written informed consent in an RCT equals the non-opt-out of SwedeHF patients.
Exclusion criteria (none must be true)	Treatment with potassium-sparing diuretics	Non-MRA potassium-sparing diuretics	ID34	Assumed 0%. Reasoning: Non-MRA potassium-sparing diuretics are rarely used in Sweden. In addition, fast wash-out would be possible and would not pose an actual barrier to RCT enrolment.
	Primary operable valvular heart disease (other than mitral or tricuspid regurgitation with clinical symptoms due to left ventricular systolic HF)	Valve intervention / surgery in prior 3 months	ID66	New variable: - NPR (in-patients): OPS codes FG, FJE, FJF, FC OR FM / timeframe: -3 – 0 months Reasoning: Retrospective identification of patients with expected heart valve correction in the registry is not feasible. At the same time, borrowing time from the future (after index registration) creates a bias of its own. Thus, we ruled to exclude recent valve correction instead.

RALES[17]	Study variable	ID	Definition / operationalisation
Congenital heart disease	Congenital cardiac malformations	ID51	New variable: - NPR (in- and out-patients): ICD-10-SE Q20-26 / position: all diagnoses / timeframe: -infinite – 0 years Reasoning: Congenital malformations might not be coded frequently but rather only the resulting HF. Thus, an infinite lookback is necessary. Specificity both regarding diagnosis position and lookback is unlikely to become a problem as these codes are very specific themselves and only used of the diagnosis is ensured.
Unstable angina	ACS (including MI) in prior 30 days	ID65	New variable: - NPR (in- and out-patients): ICD-10-SE codes I20-23 OR I24.8-9 / position: main diagnosis / timeframe: -30 – 0 days Reasoning: Main diagnosis position was chosen to avoid excluding most patients with chronic angina pectoris which is less likely to be in main position compared to acute angina pectoris (= as in ACS).
Primary hepatic failure	Liver cirrhosis	ID108	New variable: - NPR (in- and out-patients): ICD-10-SE codes I85, I86.4, I98.2, K70.3-4, K71.7, K72.1, K74.6 OR K76.6-7 / position: main diagnosis / timeframe: -5 – 0 years Reasoning: Liver cirrhosis is used as a surrogate parameter as acute primary hepatic failure without a chronic (cirrhosis) component (e.g., due to acute intoxication) is likely very rare in the SwedeHF population. Hepatic failure is not defined by RALES but presumably refers to advanced hepatic disease such as advanced liver cirrhosis. The decision to use main

RALES[17]	Study variable	ID	Definition / operationalisation
			diagnosis position only is supposed to i) select more severe cirrhosis and ii) select mostly primary cirrhosis (as secondary to HF cirrhosis would likely be in secondary position with HF in main).
Active cancer	Cancer diagnosis in prior 3 years	ID122	SwedeHF/NPR (in- and out-patients): sos_com_cancer3y (ICD-10-SE code C / position: main diagnosis / timeframe: -3 – 0 years) Reasoning: A cancer diagnosis within the prior 3 years captures active cancer well for even a remission within a 3-years period would still need to be considered an active disease.
Any life-threatening disease other than HF	Limited life expectancy due to metastatic cancer or primary cancer with very poor prognosis	ID12	New variable: - NPR (in- and out-patients): ≥ 2 registrations of ICD-10-SE codes C15, C16, C22, C25, C34, C45, C71 OR C77-79 / position: main diagnosis / timeframe: -6 – 0 months Reasoning: Life expectancy is very difficult to estimate, even in personal contact with the patient as during screening for a randomised controlled trial. This assessment is even more difficult in registries without borrowing information from the future which would introduce a bias of its own. However, diagnosis of metastatic or aggressive cancer appears as a rational surrogate and has been used before.
History of heart transplantation or on waiting list	a) Heart transplant recipient OR	a) ID26 b) ID138	a) New variable: - NPR (in- and out-patients): ICD-10-SE codes Z94.1 OR Z94.3 OR OPS codes FQA-B / position: all diagnoses / timeframe: -5 – 0 years b) Assumed 0%.

RALES[17]	Study variable	ID	Definition / operationalisation
	b) Heart transplant waiting list		Reasoning: Patients who have received a heart transplantation will seek medical attention for follow-up frequently, with near to certainty within a 5-years period. A non-restricted lookback might reduce specificity by including more cases with miscoding. Identification of patients on transplant lists is not feasible in the registry data.
Serum creatinine concentration > 2.5 mg/dl	Serum creatinine ≥ 2.5 mg/dl (independent from eGFR)	ID41	SwedeHF: shf_crea
Serum potassium concentration > 5 mmol/l	Potassium > 5 mmol/l	ID56	SwedeHF: shf_potassium

If not explicitly stated otherwise, the time of assessment of each variable is the index registration.

Table 8: Operationalisation of EMPHASIS-HF criteria

	EMPHASIS-HF[18]	Study variable	ID	Definition / operationalisation
Inclusion criteria (all must be true)	Written informed consent	Informed consent	ID11	Given 100%. Reasoning: Written informed consent in an RCT equals the non-opt-out of SwedeHF patients.
	Male or female	Male or female	ID1	SwedeHF: shf_sex
	≥ 55 years of age	Age ≥ 55 years	ID123	SwedeHF: shf_age
	a) Chronic systolic HF of either ischaemic or non-ischaemic aetiology b) Duration: at least 4 weeks c) LVEF: ≤ 30% by echocardiography, contrast ventriculography, magnetic resonance imaging or nuclear imaging, based on local (most recent measurement within 6 months prior to randomisation), or LVEF 31-35% in addition to QRS duration > 130 ms d) Functional Capacity: Currently NYHA II (in the investigator's opinion) e) Treatments (for ACEi, ARB and beta-blockers, optimal target or maximal tolerated dose unless contraindicated): ACEi and/or ARB, beta-blocker, diuretic if clinically indicated to reduce fluid retention	a) Presence of HF AND b) Previous HF diagnosis ≥ 28 days ago AND c) LVEF < 40% AND d) NYHA class II AND e) Previous HF treatment: (ACEi, ARB or ARNi) AND beta-blocker	a) ID3 b) ID128 c) ID145 d) ID124 e) ID125	a) Given 100%. b) SwedeHF: sos_durationhf c) SwedeHF: shf_ef d) SwedeHF: shf_nyha e) - SwedeHF: shf_rasiarni - SwedeHF: shf_bbl Reasoning: a) This criterion encompasses HF of any origin, i.e. 100%. The diagnosis of HF is ensured upon registration to SwedeHF. b) HF duration is a categorical variable in SwedeHF that only distinguishes < 6 vs ≥ 6 months. In addition, HF symptoms are only captured for SwedeHF registrations. However, excluding all patients without

EMPHASIS-HF[18]	Study variable	ID	Definition / operationalisation
			previous SwedeHF registration is not feasible, e.g., because SwedeHF does not capture incident but prevalent HF. Thus, this study assesses if a HF diagnosis has been coded any time before the index registration in any diagnosis position, but not earlier than 28 days ago. However, codes earlier than 5 years ago are disregarded to increase diagnostic specificity: HF that is not coded within a 5-year period is less likely to be a correct diagnosis. c) LVEF in SwedeHF is registered as a categorical variable (< 30%, 30-39%, 40-49%, ≥ 50%). EMPHASIS-HF aims for patients with HFrEF, thus, the threshold was set to 40%. d) - e) As ARNi belong to the same pillar of pharmacological HFrEF treatment but were not existent at the time of EMPHASIS-HF, it is also included in the present study. Tolerated target doses for these agents are not assessed as the registry data do not provide information on tolerability. Contraindications are not assessed as they are rather rare with the exception of severe

EMPHASIS-HF[18]	Study variable	ID	Definition / operationalisation
			renal dysfunction which is addressed in a separate criterion.
Serum potassium (K+) level ≤ 5.0 mmol/l within 24 hours prior to randomisation	Potassium ≤ 5.0 mmol/l	ID126	SwedeHF: shf_potassium Reasoning: Potassium is registered only once for each SwedeHF registration and access to laboratory data outside of SwedeHF is not feasible. Thus, the time criterion needs to be disregarded.
eGFR (MDRD-6) ≥ 30 ml/min/1.73m^2 within 24 hours prior to randomisation	eGFR (CKD-EPI 2021) ≥ 30 ml/min/1.73m^2	ID127	SwedeHF: shf_gfrckdepi Reasoning: eGFR is registered only once for each SwedeHF registration and access to laboratory data outside of SwedeHF is not feasible. Thus, the time criterion is disregarded.
a) Randomisation must occur ≤ 6 months from the date of CV hospitalisation (HF, acute MI, angina pectoris, cardiac arrhythmia, stroke / cerebral vascular accident, other reasons [e.g., hypotension, peripheral vascular disease]; elective procedures are not eligible unless ICD or CRT implantation); b) if the subject is clinically stable, he or she may be randomised during admission for a CV reason OR	a) CV hospitalisation in prior 6 months OR b) In-patient OR c) NT-proBNP ≥ 500 pg/ml (males) or ≥ 750 pg/ml (females)	a) ID129 b) ID78 c) ID130	a) - New variable: NPR (in-patients): ICD-10-SE codes I, J81, K76.1, G45 OR R57.0 / position: main diagnosis / timeframe: -6 – 0 months b) - SwedeHF: shf_location c) - SwedeHF: shf_ntprobnp - SwedeHF: shf_sex Reasoning:

EMPHASIS-HF[18]	Study variable	ID	Definition / operationalisation
b) if no recent CV hospitalisation, then: plasma BNP concentration ≥ 250 pg/ml or NT-proBNP ≥ 500 pg/ml for males and ≥ 750 pg/ml for females, within 15 days of randomisation			a) Established codes for CV hospitalisation as outcome are used with a different timeframe of a 6-years lookback. Main position assures that the hospitalisation was driven by the respective CV cause. b) – c) BNP is not available, NT-proBNP is used. Furthermore, laboratory data are registered only once per SwedeHF registrations, these registrations usually do not occur multiple times within 15 days, and access to laboratory data outside of SwedeHF is not feasible. Thus, the time criterion is disregarded and only the index registration considered.
Women: a) Negative serum pregnancy within 72 hours prior to the first dose of study drug, except if she previously had a total hysterectomy or is > 65 years old b) Use of an adequate form of contraception (abstinence will not be considered an acceptable form of contraception) if child-bearing potential	a) Pregnancy AND b) Use of highly effective contraception	a) ID90 b) ID86	a) Assumed 0%. b) Assumed 100%. <u>Reasoning</u>: a) Codes not available in the dataset. b) Contraception (and its adequate application) is not feasible to assess in the registry.
Subjects previously treated with an MRA for > 7 consecutive days will be allowed if they fulfil the following criteria:	[No] MRA in prior 3 months	ID33	Assumed 0% use, i.e. 100% eligibility.

EMPHASIS-HF[18]	Study variable	ID	Definition / operationalisation
a) no history of clinically significant hyperkalaemia or renal impairment during earlier MRA use b) MRA must have been discontinued for at least 3 months prior to randomisation			Reasoning: The original trial was performed to evaluate efficacy and safety of MRA in patients with HF at a time when this indication was not established, yet. Exclusion of MRA made sense to exclude use because of other indications. Nowadays, in a contemporary population, exclusion of MRA would result in artificially low eligibility rates as patients are treated based on the results of, among others, this trial. Therefore, it is reasonable to account for this aspect by setting this exclusion criterion to 0%.
Subjects previously treated with an MRA for ≤ 7 consecutive days will be allowed if washout period ≥ 48 hours	[No] MRA in prior 3 months	ID33	Assumed 0% use, i.e. 100% eligibility. Reasoning: The original trial was performed to evaluate efficacy and safety of MRA in patients with HF at a time when this indication was not established, yet. Exclusion of MRA made sense to exclude use because of other indications. Nowadays, in a contemporary population, exclusion of MRA would result in artificially low eligibility rates as patients are treated based on the results of, among others, this trial. Therefore, it is reasonable to account for this aspect by setting this exclusion criterion to 0%.
Inoperable valve disease as primary cause of HF	-	-	Not applicable.

EMPHASIS-HF[18]	Study variable	ID	Definition / operationalisation
			Reasoning: In the clinical trial protocol published by Pfizer and provided in the supplement of the main publication (protocol A6141079, final protocol amendment, 1 June 2010; used as the primary source here), this criterion is listed as an independent criterion, i.e. must independently be true in addition to all other inclusion criteria.[18] However, this is counterintuitive; e.g., patients with HF of ischaemic aetiology (see first inclusion criterion) usually do not meet the criterion of HF primarily due to valve disease at the same time (even though there might be an overlap in few patients). Moreover, a previous publication on the rationale and design of EMPHASIS-HF lists this criterion as an alternative eligible aetiology of HF: "[a] diagnosis of chronic HF and LVSD of either ischaemic or non-ischaemic aetiology or inoperable valve disease".[23] As a consequence of this phrasing, all aetiologies of HF would be eligible (one could even argue that HF due to valve disease is a subtype of non-ischaemic HF and, thus, already included hereby). This is very likely the intended meaning of this criterion and the trial was most likely conducted this way. Therefore, the criterion "Inoperable valve disease as primary cause of HF" is disregarded in the

	EMPHASIS-HF[18]	Study variable	ID	Definition / operationalisation
				context of the present study as it merely highlights that inclusion of patients with inoperable valve disease was possible.
Exclusion criteria (none must be true)	Severe chronic systolic HF (symptoms at rest despite optimal medical therapy)	NYHA class IV	ID131	SwedeHF: shf_nyha
	MI complicated by left ventricular systolic dysfunction and clinical HF within 30 days prior to randomisation	AMI in prior 30 days	ID132	New variable: - NPR (in-patients): ICD-10-SE I21 OR I22 / position: all diagnoses / timeframe: -30 – 0 days Reasoning: AMI without hospitalisation is unlikely. Thus, to increase specificity of the diagnosis, only in-patients are considered. However, AMI does not have to be in main position as in patients with secondary MI caused by another entity, the latter might be put into main position.
	Stroke within 30 days prior to randomisation	Stroke in prior 30 days	ID133	New variable: - NPR (in- and out-patients): ICD-10-SE codes I60-64 / position: main diagnosis / timeframe -30 – 0 days Reasoning: Only acute strokes in the prior 30 days are supposed to be registered. Choosing the main position and excluding the codes I69.0-4 (late effects of stroke) increases specificity in this regard.
	Cardiac surgery within 30 days prior to randomisation	a) CABG in prior 30 days	a) ID134	a) New variable:

EMPHASIS-HF[18]	Study variable	ID	Definition / operationalisation
	OR b) Valve intervention / surgery in prior 30 days	 b) ID135	- NPR (in-patients): OPS codes FNA, FNB, FNC, FND OR FNE / timeframe: -30 – 0 days b) New variable: - NPR (in-patients): OPS codes FG, FJE, FJF, FC OR FM / timeframe: -30 – 0 days
PCI within 30 days prior to randomisation	PCI in prior 30 days	ID25	New variable: - NPR (in- and out-patients): OPS codes DF009, DF019, DF020, FNG02, FNG05 OR FNG22 / timeframe: -30 – 0 days
MRA for > 7 consecutive days without permanent discontinuation for ≥ 3 months prior to randomisation or history of clinically significant hyperkalaemia or renal impairment during a previous exposure to an MRA	-		Not applicable. Reasoning: The exact opposite statement of this exclusion criterion is an inclusion criterion already. Thus, there is a 100% overlap of these criteria.
Required treatment with eplerenone, spironolactone or potassium canrenoate and either have prior NYHA class IV HF with an LVEF ≤ 0.35 (as in the RALES trial) or HF or diabetes and an LVEF < 0.40 after acute MI (as in EPHESUS trial)	MRA in prior 3 months	ID33	Assumed 0%. Reasoning: If a treatment with MRA (eplerenone, spironolactone, potassium canrenoate) would be required (and possible), these drugs would already be administered. However, “No MRA in prior 3 months” is an inclusion criterion already. The other following criteria (“and either […]”) do not need to be assessed, consequently. In addition gerading MRA use: The original trial was performed to evaluate efficacy and safety of MRA in patients with HF at a time when this

EMPHASIS-HF[18]	Study variable	ID	Definition / operationalisation
			indication was not established, yet. Exclusion of MRA made sense to exclude use because of other indications. Nowadays, in a contemporary population, exclusion of MRA would result in artificially low eligibility rates as patients are treated based on the results of, among others, this trial. Therefore, it is reasonable to account for this aspect by setting this exclusion criterion to 0%.
Uncontrolled hypertension (SBP > 180 mmHg and/or a DBP > 110 mmHg)	SBP > 180 mmHg or DBP > 110 mmHg	ID136	- SwedeHF: shf_bpsys - SwedeHF: shf_bpdia
Symptomatic hypotension or SBP < 85 mmHg	SBP < 85 mmHg	ID30	SwedeHF: shf_bpsys Reasoning: Hypotension-related symptoms are not captured during a SwedeHF registration; thus, this aspect is disregarded.
Required treatment with potassium-sparing diuretics	Non-MRA potassium-sparing diuretics	ID34	Assumed 0%. Reasoning: Non-MRA potassium-sparing diuretics are rarely used in Sweden. In addition, fast wash-out would be possible and would not pose an actual barrier to RCT enrolment.
History of hypersensitivity to eplerenone or spironolactone	MRA intolerance	ID35	Assumed 0%. Reasoning: Allergies against MRA are rare and other intolerances or hypersensitivities usually rather subjective. In addition, this

EMPHASIS-HF[18]	Study variable	ID	Definition / operationalisation
			information cannot be retrieved retrospectively.
Evidence of cardiogenic shock	Current evidence of cardiogenic shock	ID137	Assumed 0%. Reasoning: SwedeHF registrations occur in out-patient care and at discharge from hospital for in-patients. Thus, evidence of cardiogenic shock during the registration is very unlikely.
Primary cause of HF is surgically amenable valve disease, pericardial disease or an obstructive or restrictive cardiomyopathy	a) Surgically amenable valve disease OR b) Chronic constrictive pericarditis OR c) Hypertrophic-obstructive cardiomyopathy OR d) Restrictive cardiomyopathy	a) – b) ID18 c) ID19 d) ID50	a) Not applicable. b) New variable: - NPR (in- and out-patients): ICD-10-SE I31.1 / position: all diagnoses / timeframe: -5 – 0 years c) New variable: - NPR (in- and out-patients): ICD-10-SE I42.1 / position: all diagnoses / timeframe: -5 – 0 years d) New variable: - NPR (in- and out-patients): ICD-10-SE I42.5 / position: all diagnoses / timeframe: -5 – 0 years Reasoning: a) This exclusion criterion is corresponding to the inclusion criterion “Inoperable valve disease as primary cause of HF” and was taken from the clinical trial protocol

EMPHASIS-HF[18]	Study variable	ID	Definition / operationalisation
			published by Pfizer and provided in the supplement of the main publication (protocol A6141079, final protocol amendment, 1 June 2010; used as the primary source here).[18] However, similarly, this criterion is not listed in the previous publication on the rationale and design of the EMPHASIS-HF trial.[23] Because of this inconsistency this criterion is disregarded in the context of the present study. b-d) -
Intra-aortic balloon pump or other mechanical assist device	Currently implanted LVAD	ID27	New variable: - NPR (in-patients): OPS codes FXL40, FXL50 OR FXL60 / timeframe: -5 – 0 years Reasoning: SwedeHF registrations occur in out-patient care and at discharge from hospital for in-patients. Thus, use of short-term mechanical circulatory support devices during the registration is very unlikely. On the other hand, durable devices like LVAD can be present; other durable ventricular assist devices are very rare and, thus, disregarded.
Patients awaiting cardiac transplantation	Heart transplant waiting list	ID138	Assumed 0%. Reasoning: Identification of patients on transplant lists is not feasible in the registry data.

EMPHASIS-HF[18]	Study variable	ID	Definition / operationalisation
Serum potassium > 5.0 mmol/l within 24 hours prior to randomisation	Potassium > 5 mmol/l	ID56	SwedeHF: shf_potassium
eGFR (MDRD-6) < 30 ml/min/1.73m^2 within 24 hours prior to randomisation	eGFR (CKD-EPI 2021) < 30 ml/min/1.73m^2	ID40	SwedeHF: shf_gfrckdepi
Concomitant use of potent CYP3A4 inhibitors, such as but not limited to: ketoconazole, itraconazole, nefazodone, troleandomycin, clarithromycin, ritonavir, nelfinavir	Treatment with CYP3A4 inhibitors in prior 3 months	ID113	New variable: - NPDR: ATC codes N06AX06, J05AR10, J05AE03, J05AE30, J05AP53 OR J05AE04 / Apodos included / timeframe: -120 - +5 days Reasoning: Included agents: nefazodone, ritonavir or nelfinavir / disregarded because of usually just short-term use: ketoconazole, itraconazole, clarithromycine. A lookback is supposed to ensure capture of currently used medication as filling in a prescription at least every 3 months is necessary even for long-term medication. An additional month lookback is supposed to account for stockpiling and (temporary) incompliance. An additional 5 days follow-up ensures to capture prescriptions during the index registration, which reflect eligibility during the respective registration.
Concomitant use of CYP3A4 inducers, such as but not limited to: St. John's Wort, rifampicin, carbamazepine, phenytoin, phenobarbital	Treatment with CYP3A4 inducers in prior 3 months	ID114	New variable: - NPDR: ATC codes J04AB02, J04AM02, J04AM05, J04AM06, N03AF01, N03AB02 OR N03AB04 / Apodos included / timeframe: -120 - +5 days

EMPHASIS-HF[18]	Study variable	ID	Definition / operationalisation
			Reasoning: Included agents: rifampicin, carbamazepine, phenytoin / disregarded because of usually just short-term use: phenobarbital i) Only systemically administered drugs are included, i.e. no topical formulations like shampoos. ii) A lookback is supposed to ensure capture of currently used medication as filling in a prescription at least every 3 months is necessary even for long-term medication. An additional month lookback is supposed to account for stockpiling and (temporary) incompliance. An additional 5 days follow-up ensures to capture prescriptions during the index registration, which reflect eligibility during the respective registration. iii) St. John's wort was deregistered in Sweden 15 December 2009 as a drug but may still be available in other ways that are not covered by ATC codes. iv) ATC codes of drugs deregistered before the start of SwedeHF are not considered.
Haemoglobin < 10 g/dl	Haemoglobin < 10 g/dl	ID52	SwedeHF: shf_hb
Preexisting significant hepatic disease (e.g., known positive serology for viral hepatitis) or ASAT and/or ALAT > 3 times the upper limits of normal	Chronic liver disease	ID16	SwedeHF/NPR (in- and out-patients): sos_com_liver (ICD-10-SE B18, I85, I86.4, I98.2, K70, K71.0, K71.1, K71.3-7, K72-4, K76.0 OR K76.2-9 / position: all diagnoses / timeframe: -5 – 0 years)

EMPHASIS-HF[18]	Study variable	ID	Definition / operationalisation
			Reasoning: ASAT and ALAT are not available in SwedeHF. However, these chronic hepatic conditions are likely to come along with elevated transaminases.
Status-post gastric bypass surgery, partial gastrectomy or other surgery of the gastrointestinal tract that may interfere with the absorption of eplerenone	Post-surgery malabsorption	ID31	Assumed 0%. Reasoning: Post-surgery malabsorption is rather difficult to assess in the registries. One would need a combination of respective surgical procedures and malabsorption codes. However, the validity of the malabsorption diagnosis may be rather low. Thus, as only very few patients actually have this condition, we decided to assume 0% for the study population.
Preexisting serious conditions (e.g., cancer, AIDS; patients with a previous history of cancer will be eligible if in the opinion of the investigator life expectancy is anticipated to be > 5 years)	a) Limited life expectancy due to metastatic cancer or primary cancer with very poor prognosis OR b) AIDS	a) ID12 b) ID139	a) New variable: - NPR (in- and out-patients): ≥ 2 registrations of ICD-10-SE codes C15, C16, C22, C25, C34, C45, C71 OR C77-79 / position: main diagnosis / timeframe: -6 – 0 months b) New variable: - NPR (in- and out-patients): ICD-10-SE codes B20.0, B20.2, B20.4, B20.6, B21.0-2, B22.0 OR B22.2 / position: all diagnoses / timeframe: -5 – 0 years Reasoning: a) Life expectancy is very difficult to estimate, even in personal contact with the

EMPHASIS-HF[18]	Study variable	ID	Definition / operationalisation
			patient as during screening for a randomised controlled trial. This assessment is even more difficult in registries without borrowing information from the future which would introduce a bias of its own. However, diagnosis of metastatic or aggressive cancer appears as a rational surrogate and has been used before. b) The used ICD codes reflect AIDS-defining illnesses, not just every HIV infection.
Patients unable to give written informed consent	Informed consent	ID11	Given 100%. Reasoning: Patients are informed about their inclusion in registries with the opportunity to opt-out of the non-mandatory ones.
Progressively fatal disease (except congestive HF) and/or life expectancy < 3 years	Limited life expectancy due to metastatic cancer or primary cancer with very poor prognosis	ID12	New variable: - NPR (in- and out-patients): ≥ 2 registrations of ICD-10-SE codes C15, C16, C22, C25, C34, C45, C71 OR C77-79 / position: main diagnosis / timeframe: -6 – 0 months Reasoning: Life expectancy is very difficult to estimate, even in personal contact with the patient as during screening for a randomised controlled trial. This assessment is even more difficult in

EMPHASIS-HF[18]	Study variable	ID	Definition / operationalisation
			registries without borrowing information from the future which would introduce a bias of its own. However, diagnosis of metastatic or aggressive cancer appears as a rational surrogate and has been used before.
Patients receiving immunosuppressive or antineoplastic therapy	a) Use of immunosuppressants in prior 3 months OR b) Use of antineoplastic agents in prior 3 months	a) ID140 b) ID141	a) New variable: - NPDR: ATC code L04 / Apodos included / timeframe: -120 - +5 days b) New variable: - NPDR: ATC code L01 / Apodos included / timeframe: -120 - +5 days Reasoning: A lookback is supposed to ensure capture of currently used medication as filling in a prescription at least every 3 months is necessary even for long-term medication. An additional month lookback is supposed to account for stockpiling and (temporary) incompliance. An additional 5 days follow-up ensures to capture prescriptions during the index registration, which reflect eligibility during the respective registration.
History of alcohol and/or any other drug abuse that in the opinion of the investigator will make the patient unreliable	Any condition which may reduce adherence	ID38	New variable: - NPR (in- and out-patients): ICD-10-SE codes F01-7, F09-16, F18-25 OR F28-30 / position: all diagnoses / timeframe: -1 – 0 years

EMPHASIS-HF[18]	Study variable	ID	Definition / operationalisation
			Reasoning: The included conditions are likely to impair the participant's adherence to the trial protocol. These are: dementia, organic amnesic syndrome, delirium, other mental disorder or personality and behavioural disorders due to brain disease, unspecified mental disorder, mental disorders due to psychoactive substances, schizophrenia, manic episode, and bipolar affective disorder.
Previous participation in this trial	Previously enrolled in the same trial	ID47	Assumed 0%. Reasoning: Data unknown but estimated prevalence very low.
Patients likely to require treatment during the trial period with drugs not permitted by this protocol	a) Expected need for additional MRA treatment OR b) Non-MRA potassium-sparing diuretics OR c) Treatment with CYP3A4 inhibitors in prior 3 months OR	a) ID142 b) ID34 c) ID113 d) ID114 e) ID140 f) ID141	a) Given/assumed 0%. b) Assumed 0%. c) New variable: - NPDR: ATC codes N06AX06, J05AR10, J05AE03, J05AE30, J05AP53 OR J05AE04 / Apodos included / timeframe: -120 - +5 days d) New variable: - NPDR: ATC codes J04AB02, J04AM02, J04AM05, J04AM06, N03AF01, N03AB02 OR N03AB04 / Apodos included / timeframe: -120 - +5 days e) New variable:

EMPHASIS-HF[18]	Study variable	ID	Definition / operationalisation
	d) Treatment with CYP3A4 inducers in prior 3 months OR e) Use of immunosuppressants in prior 3 months OR f) Use of antineoplastic agents in prior 3 months		- NPDR: ATC code L04 / Apodos included / timeframe: -120 - +5 days f) New variable: - NPDR: ATC code L01 / Apodos included / timeframe: -120 - +5 days Reasoning: In general: The prohibited drugs are stated in the clinical trial protocol published by Pfizer and provided in the supplement of the main publication (protocol A6141079, final protocol amendment, 1 June 2010; used as the primary source here).[18] a) To our knowledge, there is no indication for MRA treatment that could not be met by eplerenone (given 0%). This might have been different before studies evaluating eplerenone further justifying this original trial criterion; in this case, as "expected need" is rather vague and subjective, this study assumes 0%. b) Non-MRA potassium-sparing diuretics are rarely used in Sweden. In addition, fast wash-out would be possible and would not pose an actual barrier to RCT enrolment. c) – f) "Expected need" is a rather vague and subjective term which cannot be

EMPHASIS-HF[18]	Study variable	ID	Definition / operationalisation
			assessed in retrospective registry data. However, it can be assumed that ongoing treatment at index registration justifies also expected future need for this treatment. A lookback is supposed to ensure capture of currently used medication as filling in a prescription at least every 3 months is necessary even for long-term medication. An additional month lookback is supposed to account for stockpiling and (temporary) incompliance. An additional 5 days follow-up ensures to capture prescriptions during the index registration, which reflect eligibility during the respective registration. c) – f) These criteria are already considered separately (see above). However, the trialists decided to include them in this composite criterion as well. c) Included agents: nefazodone, ritonavir or nelfinavir / disregarded because of usually just short-term use: ketoconazole, itraconazole, clarithromycine d) Included agents: rifampicin, carbamazepine, phenytoin / disregarded because of usually just short-term use: phenobarbital. More detailed reasoning: see above.

EMPHASIS-HF[18]	Study variable	ID	Definition / operationalisation
Women who are either pregnant, lactating or of childbearing potential and not using an acceptable method of contraception	Pregnancy or nursing	ID9	Assumed 0%. Reasoning: Data on pregnancy and nursing are not available in the dataset.
Donation of blood or blood products for transfusion at any time during the trial or until 30 days after completion of treatment	Blood donation during the trial	ID143	Assumed 0%. Reasoning: Not possible to assess in the registry data; and can be avoided in all patients, it is rather an instruction than an inclusion criterion.
Participation in any other trial involving investigational or marketed products (including devices) concomitantly or within 30 days prior to entry in the trial	Current participation in any other therapeutic trial	ID37	Assumed 0%. Reasoning: Data unknown; and actual prevalence very low.
Other severe acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with trial participation or investigational product administration or may interfere with the interpretation of trial results and, in the judgment of the investigator, would make the subject inappropriate for entry into this trial	-	-	Not applicable. Reasoning: This criterion is extremely vague and subjective. As a consequence, it cannot be operationalised for this study at all.

If not explicitly stated otherwise, the time of assessment of each variable is the index registration.

Table 9: Operationalisation of FINALITY-HF criteria

	FINALITY-HF[19]	Study variable	ID	Definition / operationalisation
Inclusion criteria (all must be true)	Electronic or written informed consent (personally or through a legally authorised representative)	Informed consent	ID11	Given 100%. Reasoning: Written informed consent in an RCT equals the non-opt-out of SwedeHF patients.
	Age ≥ 18 years or legal age of majority	Age ≥ 18 years	ID144	SwedeHF: shf_age
	Symptomatic HFrEF	LVEF < 40%	ID145	SwedeHF: shf_ef Reasoning: LVEF in SwedeHF is registered as a categorical variable (< 30%, 30-39%, 40-49%, ≥ 50%). Thus, HFrEF needs to be defined by < 40% rather than ≤ 40%. HF diagnosis (incl. signs and symptoms) is verified by the clinician upon first registration to SwedeHF.
	Not on steroidal MRA due to history of intolerance, contraindication or ineligibility for treatment	[No] Steroidal MRA in prior 3 months	ID107	New variable: - NPDR: ATC code C03DA01-4 / Apodos included / timeframe: -120 - +5 days Reasoning: A lookback is supposed to ensure capture of currently used medication as filling in a prescription at least every 3 months is necessary even for long-term medication. An additional month lookback is supposed to account for stockpiling and (temporary) incompliance. An additional 5 days follow-up ensures to capture prescriptions during the index registration, which reflect eligibility during the respective registration. The reason why a steroidal MRA was not administered cannot be assessed in registry data, however, including

	FINALITY-HF[19]	Study variable	ID	Definition / operationalisation
				MRA allergy and intolerance as potential reasons.
	Women: negative pregnancy test and agreement to use adequate contraception during trial	a) [No] Pregnancy AND b) Use of highly effective contraception	a) ID90 b) ID86	a) Assumed 0%, i.e. 100% eligibility. b) Assumed 100%. Reasoning: a) Codes not available in the dataset. b) The probability of potential pregnancy also taking the kind of contraception into account cannot be assessed in the registry data with sufficient validity.
Exclusion criteria (none must be true)	Treatment with non-steroidal MRA	Non-steroidal MRA in prior 3 months	ID146	New variable: - NPDR: ATC code C03DA05 / Apodos included / timeframe: -120 – +5 days Reasoning: A lookback is supposed to ensure capture of currently used medication as filling in a prescription at least every 3 months is necessary even for long-term medication. An additional month lookback is supposed to account for stockpiling and (temporary) incompliance. An additional 5 days follow-up ensures to capture prescriptions during the index registration, which reflect eligibility during the respective registration.
	eGFR < 25 ml/min/1.73m²	eGFR (CKD-EPI 2021) < 25 ml/min/1.73m²	ID91	SwedeHF: shf_gfrckdepi

FINALITY-HF[19]	**Study variable**	**ID**	**Definition / operationalisation**
Serum/plasma potassium > 5.0 mmol/l	Potassium > 5.0 mmol/l	ID56	SwedeHF: shf_potassium
Type 1 acute MI, coronary revascularisation, valve replacement/repair or implantation of a CRT device within 30 days or planned	a) AMI in prior 30 days OR b) 1. PCI in prior 30 days OR 2. CABG in prior 30 days OR c) CRT implantation in prior 30 days OR d) Valve intervention / surgery in prior 30 days	a) ID132 b) 1. ID25 2. ID134 c) ID17 d) ID135	a) New variable: - NPR (in-patients): ICD-10-SE I21 OR I22 / position: all diagnoses / timeframe: -30 – 0 days b) 1. New variable: NPR (in- and out-patients): OPS codes DF009, DF019, DF020, FNG02, FNG05 OR FNG22 / timeframe: -30 – 0 days 2. New variable: NPR (in-patients): OPS codes FNA, FNB, FNC, FND OR FNE / timeframe: -30 – 0 days c) New variable: NPR (in- and out-patients): OPS code FPE26 OR FPG36 / timeframe: -30 - 0 days d) NPR (in-patients): OPS codes FG, FJE, FJF, FC OR FM / timeframe: -30 – 0 days Reasoning: a) AMI without hospitalisation is unlikely. Thus, to increase specificity of the diagnosis, only in-patients are considered. However, MI does not have to be in main position as in patients with secondary MI caused by another entity, the latter might be put into main position. The type of AMI (especially type 1 vs. 2) cannot be assessed in the registry data.

FINALITY-HF[19]	Study variable	ID	Definition / operationalisation
			b) - d) A planned procedure cannot be assessed in registry data. Borrowing information from the future, i.e. actually performed procedures after baseline, reduces a bias of its own. Thus, we ruled just to address recently performed procedures.
Prior or planned heart transplant	a) Heart transplant recipient OR b) Heart transplant waiting list	a) ID26 b) ID138	a) New variable: - NPR (in- and out-patients): ICD-10-SE codes Z94.1 OR Z94.3 OR OPS codes FQA-B / position: all diagnoses / timeframe: -5 – 0 years b) Assumed 0%. Reasoning: a) Patients who have received a heart transplantation will seek medical attention for follow-up frequently, with near to certainty within a 5-years period. A non-restricted lookback might reduce specificity by including more cases with miscoding. b) Patients on the waiting list cannot be identified in the registries and, thus, 0% is assumed.
Haemodynamically significant (severe) uncorrected primary cardiac valvular disease considered by the investigator to be the primary cause of HF	Valve intervention / surgery in prior 3 months	ID66	New variable: - NPR (in-patients): OPS codes FG, FJE, FJF, FC OR FM / timeframe: -3 – 0 months Reasoning: Severe primary valve disease is likely to be addressed by surgery or

FINALITY-HF[19]	Study variable	ID	Definition / operationalisation
			interventions. However, retrospective identification of patients with expected heart valve correction in the registry is not feasible. At the same time, borrowing time from the future (after index registration) creates a bias of its own. Thus, we ruled to exclude recent valve correction instead.
Symptomatic bradycardia or second- or third-degree heart block without a pacemaker	Heart rate < 40 bpm	ID121	SwedeHF: shf_heartrate
Cardiomyopathy due to known acute inflammatory heart disease, infiltrative diseases, accumulation diseases, muscular dystrophies, cardiomyopathy with reversible causes, hypertrophic obstructive cardiomyopathy, complex congenital heart disease or pericardial constriction	a) Acute myocarditis in prior 3 months OR b) 1. Amyloidosis-induced cardiomyopathy OR 2. Sarcoidosis-induced cardiomyopathy OR	a) ID92 b) 1. ID20 2. ID21 c) ID101 d) ID100 e) ID19 f) ID51	a) New variable: - NPR (in- and out-patients): ICD-10-SE codes I01.2 OR I40 / position: all diagnoses / timeframe: -3 – 0 months b) 1. New variable: NPR (in- and out-patients): ICD-10-SE E85 / position: all diagnoses / timeframe: -5 – 0 years 2. New variable: NPR (in- and out-patients): ICD-10-SE D86 / position: all diagnoses / timeframe: -5 – 0 years c) Assumed 0%. d) Assumed 0%. e) New variable: - NPR (in- and out-patients): ICD-10-SE I42.1 / position: all diagnoses / timeframe: -5 – 0 years

FINALITY-HF[19]	Study variable	ID	Definition / operationalisation
	c) Cardiomyopathy due to muscular dystrophies OR d) Cardiomyopathy due to reversible causes OR e) Hypertrophic-obstructive cardiomyopathy OR f) Congenital cardiac malformations OR g) Chronic constrictive pericarditis	g) ID18	f) New variable: - NPR (in- and out-patients): ICD-10-SE Q20-26 / position: all diagnoses / timeframe: -infinite – 0 years g) New variable : - NPR (in- and out-patients): ICD-10-SE I31.1 / position: all diagnoses / timeframe: -5 – 0 years <u>Reasoning</u>: a) - b) Infiltrative cardiomyopathy does not have a distinct ICD code. However, cardiac amyloidosis is the most frequent sub-entity. In this study, an amyloidosis code in the presence of HF (which is true for all SwedeHF patients) is considered to denote amyloidosis-induced cardiomyopathy. The same is applied for sarcoidosis. Other storage diseases are very rare and, therefore, not considered here. c) Codes not available in the dataset. d) Rather vague term; myocarditis would be the most frequent reversible cause but is already a separate variable, thus 0% can be presumed. e) - g) -

FINALITY-HF[19]	Study variable	ID	Definition / operationalisation
Probable alternative cause of participant's HF	Probable alternative HF aetiology	ID83	Assumed 0%. Reasoning: Very subjective criterion which cannot be operationalised in an objective manner.
Concomitant systemic therapy with potent CYP3A4 inhibitors, or moderate or potent CYP3A4 inducers	a) Treatment with CYP3A4 inhibitors in prior 3 months OR b) Treatment with CYP3A4 inducers in prior 3 months	a) ID113 b) ID114	a) New variable: - NPDR: ATC codes N06AX06, J05AR10, J05AE03, J05AE30, J05AP53 OR J05AE04 / Apodos included / timeframe: -120 - +5 days b) New variable: - NPDR: ATC codes J04AB02, J04AM02, J04AM05, J04AM06, N03AF01, N03AB02 OR N03AB04 / Apodos included / timeframe: -120 - +5 days Reasoning: a) Included agents: nefazodone, ritonavir or nelfinavir / disregarded because of usually just short-term use: ketoconazole, itraconazole, clarithromycine b) Included agents: rifampicin, carbamazepine, phenytoin / disregarded because of usually just short-term use: phenobarbital a) and b) i) Only systemically administered drugs are included, i.e. no topical formulations like shampoos.

FINALITY-HF[19]	Study variable	ID	Definition / operationalisation
			ii) A lookback is supposed to ensure capture of currently used medication as filling in a prescription at least every 3 months is necessary even for long-term medication. An additional month lookback is supposed to account for stockpiling and (temporary) incompliance. An additional 5 days follow-up ensures to capture prescriptions during the index registration, which reflect eligibility during the respective registration. iii) Of note, St. John's wort was deregistered in Sweden 15 December 2009 as a drug but may still be available in other ways that are not covered by ATC codes. iv) ATC codes of drugs deregistered before the start of SwedeHF are not considered.
Any other condition or therapy which would make the participant unsuitable for the study	Any condition which may reduce adherence	ID38	New variable: - NPR (in- and out-patients): ICD-10-SE codes F01-7, F09-16, F18-25 OR F28-30 / position: all diagnoses / timeframe: -1 – 0 years Reasoning: The included conditions are likely to impair the participant's adherence to the trial protocol. These are: dementia, organic amnesic syndrome, delirium, other mental disorder or personality and behavioural disorders due to brain disease, unspecified mental disorder, mental disorders due to psychoactive substances, schizophrenia, manic episode, and bipolar affective disorder.

FINALITY-HF[19]	Study variable	ID	Definition / operationalisation
Concurrent participation in another interventional clinical study using an investigational agent	Current participation in any other therapeutic trial	ID37	Assumed 0%. Reasoning: Data unknown but estimated prevalence very low.

If not explicitly stated otherwise, the time of assessment of each variable is the index registration.

Table 10: Operationalisation of REDEFINE-HF criteria

	REDEFINE-HF[20]	Study variable	ID	Definition / operationalisation
Inclusion criteria (all must be true)	Provide electronic or written informed consent (personally or through a legally authorised representative)	Informed consent	ID11	Given 100%. Reasoning: Written informed consent in an RCT equals the non-opt-out of SwedeHF patients.
	Age ≥ 18 years	Age ≥ 18 years	ID144	SwedeHF: shf_age
	Current hospitalisation or recently discharged with the primary diagnosis of HF	In-patient	ID78	SwedeHF: shf_location Reasoning: REDEFINE-HF aims to assess patients hospitalised for acute HF during a current respective hospitalisation or after recent (although not more specifically defined) discharge. However, a second registration in SwedeHF few days after discharge will happen very rarely. As a consequence, only in-patients are considered eligible.
	HF signs and symptoms at the time of hospital admission	Presence of HF	ID3	Given 100%. Reasoning: Inclusion in SwedeHF is based on these criteria.
	Imaging evidence of LVEF ≥ 40%	LVEF ≥ 40%	ID4	SwedeHF: shf_ef
	a) NT-proBNP ≥ 1000 pg/ml or BNP ≥ 250 pg/ml for patients without AFib OR b) NT-proBNP ≥ 2000 pg/ml or BNP ≥ 500 pg/ml for patients with AFib	a) NT-proBNP ≥ 1000 pg/ml without AFib or AFlu OR	a) ID77 b) ID76	- SwedeHF: shf_ntprobnp - SwedeHF: shf_sos_com_af Reasoning: Only NT-proBNP is registered in SwedeHF, not BNP.

	REDEFINE-HF[20]	Study variable	ID	Definition / operationalisation
		b) NT-proBNP ≥ 2000 pg/ml with AFib or AFlu		
Exclusion criteria (none must be true)	MRA treatment	MRA in prior 3 months	ID33	Assumed 0%. Reasoning: The original trial was performed to evaluate efficacy and safety of MRA in patients with HF at a time when this indication was not established, yet. Exclusion of MRA made sense to exclude use because of other indications. Nowadays, in a contemporary population, exclusion of MRA would result in artificially low eligibility rates as patients are treated based on the results of, among others, this trial. Therefore, it is reasonable to account for this aspect by setting this exclusion criterion to 0%.
	Documented prior history of severe hyperkalaemia in the setting of MRA use	History of MRA-induced hyperkalaemia	ID75	Assumed 0%. Reasoning: This information cannot be retrieved from the registries.
	eGFR < 25 ml/min/1.73m² or serum/plasma potassium > 5.0 mmol/l at screening	a) eGFR (CKD-EPI 2021) < 25 ml/min/1.73m^2 OR b) Potassium > 5.0 mmol/l	a) ID91 b) ID56	a) SwedeHF: shf_gfrckdepi b) SwedeHF: shf_potassium
	AMI, coronary revascularisation, valve replacement/repair or implantation of a	a) ACS (including MI) in prior 30 days	a) ID65	a) New variable:

REDEFINE-HF[20]	**Study variable**	**ID**	**Definition / operationalisation**
cardiac resynchronisation therapy device within 30 days	OR b) 1. PCI in prior 30 days OR 2. CABG in prior 30 days OR c) Valve intervention / surgery in prior 30 days OR d) CRT implantation in prior 30 days	b) 1. ID25 2. ID134 c) ID135 d) ID17	- NPR (in- and out-patients): ICD-10-SE codes I20-23 <u>OR</u> I24.8-9 / position: main diagnosis / timeframe: -30 – 0 days b) 1. New variable: - NPR (in- and out-patients): OPS codes DF009, DF019, DF020, FNG02, FNG05 <u>OR</u> FNG22 / timeframe: -30 – 0 days 2. New variable: - NPR (in-patients): OPS codes FNA, FNB, FNC, FND <u>OR</u> FNE / timeframe: -30 – 0 days c) New variable: NPR (in-patients): OPS codes FG, FJE, FJF, FC <u>OR</u> FM / timeframe: -30 – 0 days d) New variable: - NPR (in- and out-patients): OPS code FPE26 <u>OR</u> FPG36 / timeframe: -30 - 0 days <u>Reasoning</u>: a) Main diagnosis position was chosen to avoid excluding most patients with chronic angina pectoris which is less likely to be in main position compared to acute angina pectoris (= as in ACS). b) All PCIs are captured as this trial's criterion also addresses ACS with potential acute PCIs.

REDEFINE-HF[20]	Study variable	ID	Definition / operationalisation
			c) – d) -
Haemodynamically significant (severe) uncorrected primary cardiac valvular disease	Valve intervention / surgery in prior 3 months	ID66	New variable: - NPR (in-patients): OPS codes FG, FJE, FJF, FC OR FM / timeframe: -3 – 0 months Reasoning: Severe primary valve disease is likely to be addressed by surgery or interventions. However, retrospective identification of patients with expected heart valve correction in the registry is not feasible. At the same time, borrowing time from the future (after index registration) creates a bias of its own. Thus, we ruled to exclude recent valve correction instead.
Cardiomyopathy due to known acute inflammatory heart, infiltrative diseases, accumulation diseases, muscular dystrophies, cardiomyopathy with reversible causes, known hypertrophic obstructive cardiomyopathy, complex congenital heart disease or known pericardial constriction	a) Acute myocarditis in prior 3 months OR b) 1. Amyloidosis-induced cardiomyopathy OR 2. Sarcoidosis-induced cardiomyopathy	a) ID92 b) 1. ID20 2. ID21 c) ID101 d) ID100	a) New variable: - NPR (in- and out-patients): ICD-10-SE codes I01.2 OR I40 / position: all diagnoses / timeframe: -3 – 0 months b) 1. New variable: - NPR (in- and out-patients): ICD-10-SE E85 / position: all diagnoses / timeframe: -5 – 0 years 2. New variable: - NPR (in- and out-patients): ICD-10-SE D86 / position: all diagnoses / timeframe: -5 – 0 years c) Assumed 0%.

REDEFINE-HF[20]	Study variable	ID	Definition / operationalisation
	OR c) Cardiomyopathy due to muscular dystrophies OR d) Cardiomyopathy due to reversible causes OR e) Hypertrophic-obstructive cardiomyopathy OR f) Congenital cardiac malformations OR g) Chronic constrictive pericarditis	e) ID19 f) ID51 g) ID18	d) Assumed 0%. e) New variable: - NPR (in- and out-patients): ICD-10-SE I42.1 / position: all diagnoses / timeframe: -5 – 0 years f) New variable: - NPR (in- and out-patients): ICD-10-SE Q20-26 / position: all diagnoses / timeframe: -infinite – 0 years g) New variable : - NPR (in- and out-patients): ICD-10-SE I31.1 / position: all diagnoses / timeframe: -5 – 0 years <u>Reasoning</u>: a) - b) Infiltrative cardiomyopathy does not have a distinct ICD code. However, cardiac amyloidosis is the most frequent sub-entity. In this study, an amyloidosis code in the presence of HF (which is true for all SwedeHF patients) is considered to denote amyloidosis-induced cardiomyopathy. The same is applied for sarcoidosis. Other storage diseases are very rare and, therefore, not considered here. c) Codes not available in the dataset.

REDEFINE-HF[20]	Study variable	ID	Definition / operationalisation
			d) Rather vague term; myocarditis would be the most frequent reversible cause but is already a separate variable, thus 0% can be presumed. e) - f) Congenital malformations might not be coded frequently but rather only the resulting HF. Thus, an infinite lookback is necessary. Specificity both regarding diagnosis position and lookback is unlikely to become a problem as these codes are very specific themselves and only used of the diagnosis is ensured. The causal relationship with HF cannot be investigated in the registry data. However, only major congenital malformations likely to be a cause of HF were selected. g) -
Probable alternative cause of participant's HF symptoms	Probable alternative HF aetiology	ID83	Assumed 0%. <u>Reasoning</u>: Very subjective criterion which cannot be operationalised in an objective manner.
Concomitant systemic therapy with potent CYP3A4 inhibitors or moderate CYP3A4 inducers or potent CYP3A4 inducers	a) Treatment with CYP3A4 inhibitors in prior 3 months OR	a) ID113 b) ID114	a) New variable: - ATC codes N06AX06, J05AR10, J05AE03, J05AE30, J05AP53 <u>OR</u> J05AE04 / Apodos included / timeframe: -120 - +5 days b) New variable:

REDEFINE-HF[20]	Study variable	ID	Definition / operationalisation
	b) Treatment with CYP3A4 inducers in prior 3 months		- NPDR: ATC codes J04AB02, J04AM02, J04AM05, J04AM06, N03AF01, N03AB02 OR N03AB04 / Apodos included / timeframe: -120 - +5 days Reasoning: a) Included agents: nefazodone, ritonavir or nelfinavir / disregarded because of usually just short-term use: ketoconazole, itraconazole, clarithromycine b) Included agents: rifampicin, carbamazepine, phenytoin / disregarded because of usually just short-term use: phenobarbital a) and b) i) Only systemically administered drugs are included, i.e. no topical formulations like shampoos. ii) A lookback is supposed to ensure capture of currently used medication as filling in a prescription at least every 3 months is necessary even for long-term medication. An additional month lookback is supposed to account for stockpiling and (temporary) incompliance. An additional 5 days follow-up ensures to capture prescriptions during the index registration, which reflect eligibility during the respective registration. iii) Of note, St. John's wort was deregistered in Sweden 15 December 2009 as a drug but may

REDEFINE-HF[20]	Study variable	ID	Definition / operationalisation
			still be available in other ways that are not covered by ATC codes. iv) ATC codes of drugs deregistered before the start of SwedeHF are not considered.

If not explicitly stated otherwise, the time of assessment of each variable is the index registration.

Table 11: Patient characteristics of SwedeHF population

Label	Variable name	Register
Sociodemographics		
Age (years), median (IQR) *	shf_age	SwedeHF
Sex * - female, n (%) - male, n (%)	shf_sex	SwedeHF
Disposable income (SEK) * - ≥ median, n (%) - < median, n (%)	scb_dispincome_catmed	LISA
Education * - compulsory school, n (%) - secondary school, n (%) - university, n (%)	scb_education	LISA
Family situation * - single/widowed/divorced, n (%) - living alone, n (%)	scb_maritalstatus, scb_famtype	LISA
Clinical variables		
Left ventricular ejection fraction (%) * - LVEF 30-39%, n (%) - LVEF < 30%, n (%)	shf_ef, shf_ef_cat	SwedeHF
Duration of heart failure (months) *	sos_durationhf_months	NPR
NYHA - class I, n (%) * - class II, n (%) * - class III, n (%) * - class IV, n (%) * - classes I & II, n (%) - class III & IV, n (%)	shf_nyha, shf_nyha_cat	SwedeHF
Dyspnoea	shf_outofbreath	SwedeHF
Weight at admission (kg), median (IQR)	shf_weight	SwedeHF
BMI (kg/m^2) - continuous, median (IQR) * - obese (BMI ≥ 30), n (%)	shf_bmi, shf_bmi_cat	SwedeHF
Comorbidities & cardiovascular risk factors		
Valvular disease, n (%) *	sos_com_valvular	NPR
Liver disease, n (%) *	sos_com_liver	NPR
Cancer (past 3 years) , n (%) *	sos_com_cancer3y	NPR
Arterial hypertension, n (%) *	sos_com_hypertension	NPR
Atrial fibrillation/flutter, n (%) *	sos_com_af	NPR
Diabetes mellitus, n (%) *	sos_com_diabetes	NPR
COPD, n (%) *	sos_com_copd	NPR
Smoking * - current smoker, n (%) - former smoker, n (%)	shf_smoke	SwedeHF

Label	Variable name	Register
- never smoked, n (%)		
Ischaemic heart disease, n (%) *	sos_com_ihd	NPR
History of stroke/TIA, n (%) *	sos_com_stroketia	NPR
Anaemia, n (%) *	shf_anemia	NPR
Charlson Comorbidity Index, median, median (IQR)	sos_com_charlsonci	NPR
Vital signs		
Systolic blood pressure (mmHg), median (IQR) *	shf_bpsys	SwedeHF
Diastolic blood pressure (mmHg), median (IQR) *	shf_bpdia	SwedeHF
Mean arterial pressure - continuous (mmHg), median (IQR) - > 90 mmHg, n (%) - ≤ 90 mmHg, n (%)	shf_map, shf_map_cat	SwedeHF
Heart rate - continuous (bpm), median (IQR) * - > 70 bpm, n (%) - ≤ 70 bpm, n (%)	shf_heartrate, shf_heartrate_cat	SwedeHF
Laboratory parameters		
Haemoglobin (g/l), median (IQR) *	shf_hb	SwedeHF
Potassium - continuous (mmol/l), median (IQR) * - normokalaemia (3.5-5.0 mmol/l), n (%) - hyperkalaemia (> 5.0 mmol/l), n (%) - hypokalaemia (< 3.5 mmol/l), n (%)	shf_potassium, shf_potassium_cat	SwedeHF
Sodium - continuous (mmol/l), median (IQR) * - normonatraemia (135-145 mmol/l), n (%) - hypernatraemia (> 145 mmol/l), n (%) - hyponatraemia (< 135 mmol/l), n (%)	shf_sodium, shf_sodium_cat	SwedeHF
eGFR (ml/min/1.73 m²) - continuous, median (IQR) * - eGFR > 60, n (%) - eGFR 30-60, n (%) - eGFR < 30, n (%)	shf_gfrckdepi, shf_gfrckdepi_cat30_60	SwedeHF
NT-proBNP (pg/ml)	shf_ntprobnp, shf_ntprobnp_catmed	SwedeHF

Label	Variable name	Register
- continuous, median (IQR) * - ≥ median, n (%) - < median, n (%)		
Cardiocirculatory treatment		
Beta-blocker, n (%) *	shf_bbl	SwedeHF
Beta-blocker agent, n (%)	shf_bblsub	SwedeHF
ACEi/ARB/ARNi, n (%) *	shf_rasiarni	SwedeHF
MRA, n (%) *	shf_mra	SwedeHF
MRA substance, n (%)	shf_mrasub	SwedeHF
MRA dosage/24h (mg), median (IQR)	shf_mradose	SwedeHF
SGLT2i, n (%) *	shf_sglt2	SwedeHF
Diuretic, n (%) *	shf_diuretic	SwedeHF
Digoxin, n (%) *	shf_digoxin	SwedeHF
Nitrate, n (%) *	shf_nitrate	SwedeHF
Anticoagulant, n (%) *	shf_anticoagulantia	SwedeHF
Platelet inhibitor, n (%) *	shf_asaantiplatelet	SwedeHF
Statin, n (%) *	shf_statin	SwedeHF
Pacemaker, n (%) *	shf_device	SwedeHF
Index registration & follow-up		
Year of index registration - continuous, median (IQR) * - 2017-2021, n (%) - 2022-2023, n (%)	shf_indexyear, shf_indexyear_cat	SwedeHF
Place of index registration * - inpatient care, n (%) - outpatient care, n (%)	shf_location	SwedeHF
Place of planned follow-up * - primary care, n (%) - speciality care, n (%)	shf_followuplocation_cat	SwedeHF
Planned follow-up in a heart failure nurse clinic, n (%) *	shf_followuphfunit	SwedeHF

*, included in imputation model / displayed baseline characteristics without imputed data

Table 12: Grouping and clustering of all enrolment criteria

Cluster	Variable cluster	Group	Variable group	Variable	Variable label
C1	Sociodemographics	G1	Sex	ID1	Male or female
		G2	Age	ID2	Age ≥ 50 years
				ID87	Age ≥ 40 years
				ID123	Age ≥ 55 years
				ID144	Age ≥ 18 years
C2	Heart failure & cardiocirculatory system	G3	Presence of HF	ID3	Presence of HF
		G4	LVEF	ID4	LVEF ≥ 40%
				ID48	Known LVEF < 40% ever
				ID145	LVEF < 40%
		G5	Structural or functional cardiac abnormalities (other than LVEF)	ID51	Congenital cardiac malformations
				ID89	Structural cardiac abnormalities: LAD, LAA, LAVI, LVMI, wall thickness
		G6	Previous CV hospitalisation	ID5	≥ 1 hospitalisation for HF without AMI in prior 1 year
				ID59	≥ 1 HF hospitalisation in prior 1 year
				ID129	CV hospitalisation in prior 6 months or in-patient
		G7	NT-proBNP	ID6	NT-proBNP ≥ 360 pg/ml
				ID42	NT-proBNP > 300 ng/l without AFib or AFlu
				ID43	NT-proBNP > 750 ng/l with AFib or AFlu
				ID44	NT-proBNP > 1,200 ng/l in prior 1 year
				ID60	NT-proBNP > 900 pg/ml with AFib or AFlu
				ID130	NT-proBNP ≥ 500 pg/ml (males) or ≥ 750 pg/ml (females)
				ID77	NT-proBNP ≥ 1000 pg/ml without AFib or AFlu
				ID76	NT-proBNP ≥ 2000 pg/ml with AFib or AFlu

Cluster	Variable cluster	Group	Variable group	Variable	Variable label
		G8	Blood pressure	ID7	SBP < 140 mmHg or 140-160 mmHg while on ≥ 3 antihypertensive agents=
				ID29	SBP > 160 mmHg
				ID30	SBP < 85 mmHg
				ID55	SBP < 90 mmHg or > 160 mmHg
				ID96	SBP ≥ 160 mmHg while on < 3 antihypertensive agents
				ID97	SBP ≥ 180 mmHg
				ID99	SBP < 90 mmHg
				ID136	SBP > 180 mmHg or DBP > 110 mmHg
		G9	Valvular disease	ID66	Valve intervention / surgery in prior 3 months
				ID135	Valve intervention / surgery in prior 30 days
		G10	Cardiomyopathy	ID19	Hypertrophic-obstructive cardiomyopathy
				ID20	Amyloidosis-induced cardiomyopathy
				ID21	Sarcoidosis-induced cardiomyopathy
				ID50	Restrictive cardiomyopathy
				ID70	Hypertrophic cardiomyopathy with or without obstruction
				ID102	Peripartum cardiomyopathy
				ID103	Chemotherapy-induced cardiomyopathy
				ID101	Cardiomyopathy due to muscular dystrophies
				ID100	Cardiomyopathy due to reversible causes
		G11	Heart rhythm and frequency	ID22	AFib or AFlu with a resting heart rate > 90 bpm
				ID71	Symptomatic or sustained VT
				ID72	AFib or AFlu with heart rate > 100 bpm
				ID98	AFib or AFlu with heart rate > 110 bpm
				ID121	Heart rate < 40 bpm

Cluster	Variable cluster	Group	Variable group	Variable	Variable label
		G12	Myocardial ischaemia	ID23	AMI in prior 3 months
				ID65	ACS (including MI) in prior 30 days
				ID132	AMI in prior 30 days
		G13	Coronary revascularisation	ID24	CABG in prior 3 months
				ID25	PCI in prior 30 days
				ID67	In-patient PCI in prior 3 months
				ID134	CABG in prior 30 days
		G14	Heart transplant	ID26	Heart transplant recipient
				ID138	Heart transplant waiting list
		G15	Ventricular assist device	ID27	Currently implanted LVAD
		G16	NYHA class	ID46	NYHA class II–IV
				ID117	NYHA class IV in prior 6 months
				ID118	NYHA class III or IV
				ID124	NYHA class II
				ID131	NYHA class IV
		G17	Right-sided HF	ID53	Right-sided HF not due to left-sided HF
		G18	Cardiac resynchronisation therapy	ID54	Implanted CRT
				ID17	CRT implantation in prior 30 days
		G19	HF duration	ID58	Previous HF diagnosis ≥ 30 days ago
				ID116	Previous HF diagnosis ≥ 42 days ago
				ID128	Previous HF diagnosis ≥ 28 days ago
		G20	Acute HF	ID68	Acute non-stabilised HF
		G21	Cardiac inflammatory disease	ID92	Acute myocarditis in prior 3 months
				ID93	Acute endocarditis in prior 3 months
				ID94	Acute pericarditis in prior 3 months
				ID18	Chronic constrictive pericarditis
				ID104	History of viral myocarditis
		G22	Cardiogenic shock	ID137	Current evidence of cardiogenic shock

Cluster	Variable cluster	Group	Variable group	Variable	Variable label
		G23	Probable alternative HF aetiology	ID83	Probable alternative HF aetiology
C3	Renal disease & electrolytes	G24	Potassium	ID8	Potassium < 5.0 mmol/l
				ID39	Potassium ≥ 5.0 mmol/l
				ID56	Potassium > 5.0 mmol/l
				ID61	Potassium ≥ 5.5 mmol/l in prior 2 weeks
				ID105	History of MRA-induced hyperkalaemia leading to MRA discontinuation
				ID75	History of MRA-induced hyperkalaemia
				ID126	Potassium ≤ 5.0 mmol/l
		G25	Sodium	ID62	Sodium < 135 mmol/l
		G26	Renal function	ID40	eGFR (CKD-EPI 2021) < 30 ml/min/1.73m^2
				ID41	Serum creatinine ≥ 2.5 mg/dl (independent from eGFR)
				ID57	Current dialysis
				ID63	Serum creatinine ≥ 1.8 mg/dl (independent from eGFR)
				ID64	Acute renal failure in prior 2 weeks
				ID80	Renal artery atherosclerosis
				ID91	eGFR (CKD-EPI 2021) < 25 ml/min/1.73m^2
				ID106	History of MRA-induced acute renal failure leading to MRA discontinuation
				ID127	eGFR (CKD-EPI 2021) ≥ 30 ml/min/1.73m^2
C4	Non-cardiac comorbidities & limited life expectancy	G27	Pulmonary disease	ID13	COPD GOLD group E
				ID14	Severe bronchial asthma
				ID15	Primary pulmonary hypertension
		G28	Hepatic disease	ID16	Chronic liver disease
				ID108	Liver cirrhosis

Cluster	Variable cluster	Group	Variable group	Variable	Variable label
		G29	Organ transplant recipient (other than heart)	ID79	Kidney, lung or liver transplant recipient
		G30	Stroke or TIA	ID28	Stroke in prior 3 months
				ID73	TIA in prior 3 months
		G31		ID74	Surgery or angioplasty of brachiocephalic trunk, common carotid artery or its branches in prior 3 months
				ID133	Stroke in prior 30 days
		G32	Gastrointestinal disease	ID31	Post-surgery malabsorption
				ID32	Non-infectious inflammatory bowel disease
		G33	Hyperaldosteronism	ID49	Hyperaldosteronism
		G34	Anaemia	ID52	Haemoglobin < 10 g/dl
		G35	Obesity	ID69	BMI > 40 kg/m^2
				ID95	BMI > 50 kg/m^2
		G36	Addison's disease	ID109	Addison's disease
		G37	Cancer	ID122	Cancer diagnosis in prior 3 years
		G38	AIDS	ID139	AIDS
		G39	Limited life expectancy	ID12	Limited life expectancy due to metastatic cancer or primary cancer with very poor prognosis
C5	RCT-specific aspects	G40	Other trial enrolments	ID47	Previously enrolled in the same trial
				ID115	Previous assignment to treatment within the same trial
				ID37	Current participation in any other therapeutic trial
		G41	Adherence	ID10	Willing to comply with scheduled visits
				ID38	Any condition which may reduce adherence
		G42	Informed consent	ID11	Informed consent
		G43	Blood donation during the trial	ID143	Blood donation during the trial
C6	Vulnerable groups	G44	Pregnancy or nursing	ID9	Pregnancy or nursing

Cluster	Variable cluster	Group	Variable group	Variable	Variable label
				ID86	Use of highly effective contraception
				ID90	Pregnancy
		G45	Other vulnerable groups	ID84	Detained person
				ID85	Person dependent on investigator, sponsor or trial site
C7	Medication	G46	MRA use	ID33	MRA in prior 3 months
				ID146	Non-steroidal MRA in prior 3 months
				ID107	Steroidal MRA in prior 3 months
		G47	Intolerance / allergy	ID35	MRA intolerance
		G48	Comedication (no diuretics)	ID36	Lithium use in prior 3 months
				ID81	Potassium supplementation in prior 3 months
				ID82	Abiraterone use in prior 3 months
				ID111	Simultaneous use ≥ 1 agent of the classes ACEi / ARB / ARNi
				ID112	Renin inhibitor use in prior 3 months
				ID113	Treatment with CYP3A4 inhibitors in prior 3 months
				ID114	Treatment with CYP3A4 inducers in prior 3 months
				ID119	Treatment with ACEi or ARB or ARNi if tolerated
				ID125	Previous HF treatment: (ACEi, ARB or ARNi) AND beta-blocker
				ID140	Use of immunosuppressants in prior 3 months
				ID141	Use of antineoplastic agents in prior 3 months
				ID142	Expected need for additional MRA treatment
		G49	Comedication with diuretics	ID45	Daily use of loop diuretics

Cluster	Variable cluster	Group	Variable group	Variable	Variable label
				ID88	Current use of any diuretics
				ID34	Non-MRA potassium-sparing diuretics
				ID120	Current use of loop diuretic
C8	Treatment setting	G50	Intensive care	ID110	Intensive care treatment in prior 24 hours
		G51	Location: in- vs out-patient care	ID78	In-patient

Table 13: Clinical outcomes

Outcome variable	Definition
Count of all-cause hospitalisations in 3-year follow-up	NPR (in-patients): all ICD-10-SE codes / position: all diagnoses / timeframe: +1 – 1,096 days
Count of HF hospitalisation in 3-year follow-up	NPR (in-patients): ICD-10-SE codes I11.0, I13.0, I13.2, I25.5, I42.0, I42.3, I42.5-9, I43, I50, J81, K76.1 OR R57.0 / position: main diagnosis / timeframe: +1 – 1,096 days
Count of CV hospitalisation in 3-year follow-up	NPR (in-patients): ICD-10-SE codes I, J81, K76.1, G45 OR R57.0 / position: main diagnosis / timeframe: +1 – 1,096 days
Count of non-CV hospitalisation in 3-year follow-up	NPR (in-patients): NO ICD-10-SE codes I, J81, K76.1, G45 AND R57.0 / position: main diagnosis / timeframe: +1 – 1,096 days
All-cause death in 3-year follow-up	CoD: all ICD-10-SE codes as ULORSAK / timeframe: +1 – 1,096 days
CV death in 3-year follow-up	CoD: ICD-10-SE codes I, J81, K76.1, R57.0 OR G45 as ULORSAK / timeframe: +1 – 1,096 days
Non-CV death in 3-year follow-up	CoD: NO ICD-10-SE codes I, J81, K76.1, R57.0 AND G45 as ULORSAK / timeframe: +1 – 1,096 days

4 References

1. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, Burri H, Butler J, Čelutkienė J, Chioncel O, et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: Developed by the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) With the special contribution of the Heart Failure Association (HFA) of the ESC. *European Heart Journal*. 2021;42:3599-3726. doi: 10.1093/eurheartj/ehab368
2. Heidenreich PA, Bozkurt B, Aguilar D, Allen LA, Byun JJ, Colvin MM, Deswal A, Drazner MH, Dunlay SM, Evers LR, et al. 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation*. 2022;145:e895-e1032. doi: 10.1161/CIR.0000000000001063
3. Kolkhof P, Delbeck M, Kretschmer A, Steinke W, Hartmann E, Bärfacker L, Eitner F, Albrecht-Küpper B, Schäfer S. Finerenone, a Novel Selective Nonsteroidal Mineralocorticoid Receptor Antagonist Protects From Rat Cardiorenal Injury. *Journal of Cardiovascular Pharmacology*. 2014;64:69-78. doi: 10.1097/fjc.0000000000000091
4. Savarese G, Vasko P, Jonsson Å, Edner M, Dahlström U, Lund LH. The Swedish Heart Failure Registry: a living, ongoing quality assurance and research in heart failure. *Upsala Journal of Medical Sciences*. 2019;124:65-69. doi: 10.1080/03009734.2018.1490831
5. Benson L. SwedeHF database 4 (SHFDB4). https://kiheartfailure.github.io/shfdb4/. Accessed 09.07.2025.
6. SWEDEHEART Annual Report 2023: SwedeHF Appendix. https://www.ucr.uu.se/rikssvikt/om-rikssvikt/arsrapporter/arsrapporter/2023-swedeheart-annual-report-swedehf-appendix-nytt. 2024. Accessed 13.02.2025.
7. Ludvigsson JF, Svedberg P, Olén O, Bruze G, Neovius M. The longitudinal integrated database for health insurance and labour market studies (LISA) and its use in medical research. *European Journal of Epidemiology*. 2019;34:423-437. doi: 10.1007/s10654-019-00511-8
8. National Patient Register. Socialstyrelsen. https://www.socialstyrelsen.se/en/statistics-and-data/registers/national-patient-register/. 2024. Accessed 16.09.2024.
9. Ohlin MO, Petter. Statistical register's production and quality - National Prescribed Drug Register. Socialstyrelsen. https://www.socialstyrelsen.se/en/statistics-and-data/registers/national-prescribed-drug-register/. 2021.
10. National Cause of Death Register. Socialstyrelsen. https://www.socialstyrelsen.se/globalassets/sharepoint-dokument/dokument-webb/ovrigt/production-and-quality-dors.pdf. 2022. Accessed 18.09.2024.
11. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, Falk V, González-Juanatey JR, Harjola V-P, Jankowska EA, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *European Heart Journal*. 2016;37:2129-2200. doi: 10.1093/eurheartj/ehw128
12. Bozkurt B, Coats AJS, Tsutsui H, Abdelhamid CM, Adamopoulos S, Albert N, Anker SD, Atherton J, Böhm M, Butler J, et al. Universal definition and classification of heart failure: a report of the Heart Failure Society of America, Heart Failure Association of the European Society of Cardiology, Japanese Heart Failure Society and Writing Committee of the Universal Definition of Heart Failure. *European Journal of Heart Failure*. 2021;23:352-380. doi: 10.1002/ejhf.2115
13. Pitt B, Pfeffer MA, Assmann SF, Boineau R, Anand IS, Claggett B, Clausell N, Desai AS, Diaz R, Fleg JL, et al. Spironolactone for Heart Failure with Preserved Ejection Fraction. *New England Journal of Medicine*. 2014;370:1383-1392. doi: 10.1056/NEJMoa1313731

14. Lund LH, James S, DeVore AD, Anstrom KJ, Fudim M, Aaronson KD, Dahlström U, Desvigne-Nickens P, Fleg JL, Yang S, et al. The Spironolactone Initiation Registry Randomized Interventional Trial in Heart Failure with Preserved Ejection Fraction (SPIRRIT-HFpEF): Rationale and design. *European Journal of Heart Failure*. 2024;26:2453-2463. doi: 10.1002/ejhf.3453
15. Pieske B. Spironolactone In The Treatment of Heart Failure (SPIRIT-HF). https://clinicaltrials.gov/study/NCT04727073. 2021. Accessed 16.01.2025.
16. Solomon SD, McMurray JJV, Vaduganathan M, Claggett B, Jhund PS, Desai AS, Henderson AD, Lam CSP, Pitt B, Senni M, et al. Finerenone in Heart Failure with Mildly Reduced or Preserved Ejection Fraction. *New England Journal of Medicine*. 2024;391:1475-1485. doi: 10.1056/NEJMoa2407107
17. Pitt B, Zannad F, Remme WJ, Cody R, Castaigne A, Perez A, Palensky J, Wittes J. The Effect of Spironolactone on Morbidity and Mortality in Patients with Severe Heart Failure. *New England Journal of Medicine*. 1999;341:709-717. doi: 10.1056/NEJM199909023411001
18. Zannad F, McMurray JJV, Krum H, Veldhuisen DJv, Swedberg K, Shi H, Vincent J, Pocock SJ, Pitt B. Eplerenone in Patients with Systolic Heart Failure and Mild Symptoms. *New England Journal of Medicine*. 2011;364:11-21. doi: 10.1056/NEJMoa1009492
19. A Study to Evaluate Finerenone on Clinical Efficacy and Safety in Patients with Heart Failure Who Are Intolerant or Not Eligible for Treatment with Steroidal Mineralocorticoid Receptor Antagonists (FINALITY-HF). Colorado Prevention Center. https://clinicaltrials.gov/study/NCT06033950. 2023. Accessed 29.01.2025.
20. A Study to Determine the Efficacy and Safety of Finerenone on Morbidity and Mortality Among Hospitalized Heart Failure Patients (REDEFINE-HF). Colorado Prevention Center. https://clinicaltrials.gov/study/NCT06008197. 2023. Accessed 30.01.2025.
21. van Buuren S, Groothuis-Oudshoorn K. mice: Multivariate Imputation by Chained Equations in R. *Journal of Statistical Software*. 2011;45:1 - 67. doi: 10.18637/jss.v045.i03
22. SWEDEHEART Annual Report 2023: SwedeHF Appendix. https://www.ucr.uu.se/swedeheart/dokument-sh/arsrapporter-sh/arsrapport-2023/09-swedeheart-annual-report-2023-swedehf-appendix. 2024. Accessed 25.11.2024.
23. Zannad F, McMurray JJV, Drexler H, Krum H, van Veldhuisen DJ, Swedberg K, Shi H, Vincent J, Pitt B. Rationale and design of the Eplerenone in Mild Patients Hospitalization And SurvIval Study in Heart Failure (EMPHASIS-HF). *European Journal of Heart Failure*. 2010;12:617-622. doi: 10.1093/eurjhf/hfq049