STUDY PROTOCOL

Effectiveness and safety of cardiac glycosides in HFrEF: target trial emulation and transportability of DIG and DIGIT-HF effects to a contemporary real-world population

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1 Background

Digoxin may be considered to reduce hospitalisations in patients with heart failure (HF) with reduced ejection fraction (HFrEF) and sinus rhythm according to the European Society of Cardiology (ESC) guidelines.[1] The recommendation is primarily based on the secondary outcomes of the DIG trial from 1997, whose primary outcome all-cause mortality was shown to be neutral.[2] In the recently published DIGIT-HF trial, the pharmacologically similar agent digitoxin reduced the risk of the primary outcome of all-cause mortality or HF hospitalisation in HFrEF.[3] This finding has sparked renewed interest in both cardiac glycosides, and digoxin is currently investigated at low doses and with a HF-specific primary outcome in the DECISION trial in patients with HFrEF or HF with mildly reduced EF (HFmrEF).[4,5]

The present study aims to contextualise evidence on the use of cardiac glycosides in HFrEF in a contemporary Swedish real-world HF population. We aim to:

1) Estimate the effectiveness and safety of digoxin vs standard of care without digoxin in a contemporary Swedish real-world population of patients meeting all eligibility criteria from the DIG trial by transporting a causal effect model, learned in DIG individual patient data, to the registry-based real-world population.[2,6] In addition, a target trial emulation will emulate a DIG-like trial, applying all eligibility criteria from DIG with the only exception of excluding patients in sinus rhythm and including atrial fibrillation/flutter instead. The transportation and the emulation study will then be merged to contextualise the interpretation of the upcoming DECISION trial, which includes patients irrespective of heart rhythm.[5]

2) Estimate the effectiveness and safety of digitoxin versus standard of care in a contemporary Swedish real-world population of patients meeting all eligibility criteria from the DIGIT-HF trial by transporting a causal effect model, learned in DIGIT-HF individual patient data, to the registry-based real-world population.[3]

The overall aim of this study is thus to synthesise existing trial evidence on both digoxin and digitoxin and to assess its applicability to a contemporary real-world HFrEF population in Sweden *(Figure 1)*. The study will also establish a novel method of generalisation, merging transportability studies with target trial emulation. Together with the upcoming DECISION trial, this study will inform the decision whether to use cardiac glycosides and which one to use in Sweden and comparable countries.

2 Methods

2.1 Real-world data sources

SwedeHF was founded in 2000 and implemented nationwide in 2003.[7] Physician-diagnosed HF is the only inclusion criterion – since April 2017 defined by the ICD-10-SE (International Statistical Classification of Diseases, 10th revision, Swedish version) codes I11.0, I13.0, I13.2, I25.5, I42.0, I42.3, I42.5-9, I43, I50, J81, and K76.1 in the main position of the National Patient Register (NPR).[8] Around 80 variables are recorded at the hospitalisation discharge or out-patient visit that prompts a registration. These variables are entered in an electronic database that is managed by the Uppsala Clinical Research Center (Uppsala, Sweden). As of January 14, 2025, 130,011 unique patients had been registered in SwedeHF, with 60% coverage of prevalent heart failure in 2024.[9] Informed consent is not mandatory, but patients are informed about data collection in registries for the purpose of research and have a right to opt-out.

The personal identification number held by all Swedish residents enables 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.[10] The NPR contains data on diagnoses according to ICD-10-SE from in-patient stays since 1964 (nationwide 1987) and from specialist out-patient care (but not primary care) since 2001, and will be

used to supplement comorbidity variables available in SwedeHF.[11] The National Prescribed Drug Register (NPDR) was implemented in July 2005 and will provide information on prescribed drugs that were dispensed in pharmacies including their Anatomical Therapeutic Chemical classification (ATC) codes.[12] Information on the occurrence and cause of death according to ICD-10-SE codes will be collected from the National Cause of Death Register (CoDR).[13] The NPR, NPDR, and CoDR are all managed by the National Board of Health and Welfare.

2.2 Randomised data sources

Individual patient data of the DIG trial will be requested from the National Heart, Lung, and Blood Institute.[14] Individual patient data of the DIGIT-HF trial will be requested from the principal investigator.[3]

2.3 Ethics

The use of data from the Swedish registries is covered by ethics approval Dnr 2024-04229-01, issued by Etikprövningsnämnd Göteborg. Access to the DIG and DIGIT-HF data including legal and ethical aspects is currently under evaluation and will be reported in good time. If access to DIG or DIGIT-HF data will not be possible, all other parts of this study will be performed, nonetheless.

2.4 Digoxin study (DIG)

2.4.1 Population

Patients in the SwedeHF registry will be assessed for eligibility if they have at least one SwedeHF registration between January 1, 2017 (the year following publication of the 2016 ESC Heart Failure Guidelines), and December 31, 2024 (administrative censoring of SwedeHF).[8,15] Eligibility will be evaluated according to the original DIG trial criteria, with the exception of the heart rhythm criterion, such that patients will be considered irrespective of the presence of atrial fibrillation or flutter.[6] Prior use of digoxin will not constitute an exclusion criterion, in accordance with the design of the DIG trial.[6] All DIG eligibility criteria and their translation into the observational real-world data are listed in *Table 1*. Eligibility assessment is based on the imputed data (exception: all patients with missing EF or information on atrial fibrillation/flutter will be excluded).

For patients with multiple SwedeHF registrations during the study period, eligibility will be assessed sequentially, starting with the earliest registration. If a patient is found to be ineligible at a given registration, the next subsequent registration will be evaluated. This process will continue until a registration meeting all eligibility criteria is identified, which will be defined as the index registration, or until all registrations have been assessed and the patient is deemed ineligible *(Figure 2)*.

Among eligible patients, heart rhythm will be classified based on information available at the index registration and on documented prior diagnoses. The presence of atrial fibrillation or flutter will be defined as either a recorded diagnosis at the index registration or a prior documented diagnosis of atrial fibrillation or flutter. Patients without evidence of atrial fibrillation or flutter will be assumed to be in sinus rhythm. Eligible patients in sinus rhythm will constitute the DIG transport population (resembling exactly the DIG trial), whereas eligible patients with atrial fibrillation or flutter will constitute the emulation population (emulating DIG as though it would have included patients with atrial fibrillation or flutter) *(Figure 2)*. Detailed definitions of variables regarding patient characteristics are outlined in *Table 2.*

Patients will be censored after 36 months of follow-up, at the first occurrence of emigration from Sweden, or at administrative censoring of the registry data (December 31, 2024).

2.4.2 Intervention

The transported effect is based on the intervention from DIG: randomisation to treatment with digoxin in addition to standard of care without digoxin. The process of randomisation and dose titration is described elsewhere.[2,6]

In the target trial emulation, the intervention is the clinical decision for initiating or continuation of treatment with digoxin at index registration in SwedeHF in addition to standard of care without digoxin *(Table 3)*.

2.4.3 Comparator

The transported effect is based on the intervention from DIG: randomisation to treatment with placebo in addition to standard of care without digoxin.[2,6]

In the target trial emulation, the comparator is the decision not to initiate or continue treatment with digoxin at index registration in SwedeHF but maintaining standard of care *(Table 3).*

2.4.4 Outcomes

The primary outcome will be a composite of all-cause mortality or first HF hospitalisation, assessed as the risk difference of the composite event by 36 months. The cumulative incidence curves of the composite event will also be reported. The 36-month restricted mean survival difference will be reported as a secondary measure. Using hazard ratios for the transportation study should be avoided: due to the unlikeliness of the proportional hazards assumption and non-collapsibility, hazard ratios are likely to depend on the censoring distribution in the data and are complex to model if both conditional and marginal models need to be used, with poor properties under model misspecification.[16,17]

Secondary and exploratory outcomes will be evaluated, reported in *Table 4*. For all analyses, follow-up will be truncated at 36 months after index to ensure sufficient statistical power while minimising the risk of treatment cross-over. Estimands according to the International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) E9 are defined in detail in *Table 5*.[18]

2.4.5 Statistical analysis

We are interested in the SwedeHF population that is eligible according to the original DIG trial criteria, with the exception of the heart rhythm criterion, such that patients will be considered irrespective of the presence of atrial fibrillation or flutter. This population is split in two subpopulations based on the presence/absence of atrial fibrillation or flutter. Two different analyses will be run: a transportation study for eligible patients with sinus rhythm and a target trial emulation for eligible patients with atrial fibrillation or flutter.[19,20] These two analyses are then merged into a single estimate: the enriched treatment effect *(Figure 1)*.

Baseline characteristics of the overall non-weighted and non-imputed study population will be presented as well as stratified by rhythm *(Table 2)*. Baseline characteristics of the overall non-weighted and non-imputed emulation population will be presented stratified by decision for digoxin treatment vs non-treatment at index *(Table 2)*. Categorical variables will be shown as absolute and relative frequencies, and continuous variables as median with interquartile range, together with the frequency of missing data. Balance between groups will be evaluated by SMDs (successful balance will be achieved by SMDs $\leq$0.10).[21]

For both sub-analyses, transportation and emulation, we include baseline covariates that are considered potential confounders based on subject-matter knowledge. Variables included as covariates for nuisance parameter calculations are indicated in *Table 2*.

Several nuisance parameters will be estimated addressing confounding, informative censoring, and propensity to meet the eligibility criteria of DIG. The positivity assumption of receiving the treatment and participating in the trial, will be assessed. Diagnostics will include score distributions, covariate balance before and after weighting, weight summaries, and effective sample size. The corresponding weights will be truncated at the 1% and 99% percentile.

If major non-overlap or weight instability is observed, the primary estimand will be redefined to the overlap-supported target population, and the full target-population estimate will be reported as secondary.

Whenever flexible models will be used in nuisance parameter estimation, cross-fitting will be applied to prevent overfitting bias and regularisation bias.[22]

Missingness in the registry data will be handled using multiple imputation by chained equations (20 imputed datasets), generated with a flexible machine learning-imputation method to preserve assumptions regarding aforementioned nuisance estimation (covariates of the model are marked in *Table 2*).[23] Missingness in the randomised data source will be handled with the same approach, using all available variables in the dataset. To avoid cross-fold leakage, all imputation procedures are incorporated within the cross-fitting scheme and estimated separately on each auxiliary sample used for the nuisance and final regression stages.

The overall analysis will target the average treatment effect (ATE) for decision for digoxin treatment vs decision for non-treatment with digoxin on outcomes reported in *Table 4*. We will use a one-step estimator for the enriched treatment effect, which in this case reduces to a weighted average of augmented inverse probability of censoring weighting (AIPCW) for the population with atrial fibrillation/flutter (i.e. the emulation part of the digoxin study) and an AIPCW-type transport estimator for the population without atrial fibrillation/flutter (i.e. the transportation part of the digoxin study).[24-27] All estimates will be reported along 95% confidence intervals, in compliance to the cross-fitting procedure, the variances will be estimated within the cross-fit using the influence function variance for one-step corrections. Two-sided p values < 0.05 will denote statistical significance.

Concomitant methodological papers are being written to further detail the methodology and will be publicly available before the publication of this study. Moreover, a statistical analysis plan will be publicly available, specifying modelling hypothesis (nuisance) and reproducibility matter.

As a negative control analysis in the target trial emulation, we will assess the association between decision for digoxin treatment vs non-treatment at index and hospitalisation for cancer – an outcome not biologically plausibly affected by digoxin but sharing similar confounding structure. A statistically significant association would be indicative of residual confounding. No negative control analysis is required for the transportation study, since confounding in DIG is handled by randomisation.

To analyse potential subgroup heterogeneity in the association between decision for vs against digoxin use and outcomes, we will assess exploratively the interaction with:

- age (≥ 75 vs < 75 years),
- sex,
- EF (< 30% vs 30-39%),
- New York Heart Association (NYHA) class (III/IV vs I/II),
- HF aetiology (ischaemic vs non-ischaemic),
- presence of cardiac pacing devices,
- heart rate (≥ 70 vs < 70 bpm),
- systolic blood pressure (>120 vs ≤120 mmHg),
- body mass index (≥30 vs <30 kg/m^2),
- arterial hypertension,
- diabetes,
- estimated glomerular filtration rate (>60 vs ≤60 ml/min/1.73m^2),
- beta-blocker therapy,
- mineralocorticoid receptor antagonist therapy (MRA),
- angiotensin receptor/neprilysin inhibitor therapy (ARNi),
- SGLT2i therapy,
- triple therapy (angiotensin-converting enzyme inhibitor [ACEi] or angiotensin II receptor blocker [ARB] or ARNi, plus MRA and beta-blocker therapy),
- quadruple therapy (triple therapy plus SGLT2i),
- N-terminal prohormone of brain natriuretic peptide (NT-proBNP) (≥ vs < median),
- and in-patient vs out-patient status at index.

Subgroup analyses will depend on data availability: for the emulation study, variables need to be available only in SwedeHF; for the transportation study, variables need to be available in both SwedeHF and DIG. We will report results according to each subanalysis and for the enriched treatment effect.

Sensitivity analyses will be performed to assess the impact of changing standard of care over time, in particular the addition of sodium/glucose cotransporter 2 inhibitors (SGLT2i) to standard of care in 2021 (stratification by guideline periods 2022-2024 vs 2017-2021).[1,15] Another sensitivity analysis will be performed according to prior use of digoxin.

In summary, we estimate the ATE of decision for digoxin treatment vs non-treatment at index using an AIPCW-type estimator, transporting the intention-to-treat effect of the DIG trial for patients without atrial fibrillation/flutter and emulating the intention-to-treat effect of a trial with the same eligibility criteria as DIG but with atrial fibrillation/flutter.

2.5 Digitoxin study (DIGIT-HF)

2.5.1 Population

Patients in the SwedeHF registry will be assessed for eligibility if they have at least one SwedeHF registration between January 1, 2017 (the year following publication of the 2016 ESC Heart Failure Guidelines), and December 31, 2024 (administrative censoring of SwedeHF).[8,15] Eligibility will be evaluated according to the original DIGIT-HF trial criteria.[3] All DIGIT-HF eligibility criteria and their translation into the observational real-world data are listed in *Table 6.* Eligibility assessment is based on the imputed data (exception: patients with missing EF will be excluded).

For patients with multiple SwedeHF registrations during the study period, eligibility will be assessed sequentially, starting with the earliest registration. If a patient is found to be ineligible at a given registration, the next subsequent registration will be evaluated. This process will continue until a registration meeting all eligibility criteria is identified, which will be defined as the index registration, or until all registrations have been assessed and the patient is deemed ineligible *(Figure 3)*. Detailed definitions of variables regarding patient characteristics are outlined in *Table 2.*

Since DIGIT-HF included both patients with sinus rhythm and atrial fibrillation/flutter, it will not be necessary to perform separate emulation and transportation studies which would then be combined to an enriched treatment effect.

Patients will be censored after 36 months of follow-up, at the first occurrence of emigration from Sweden, or at administrative censoring of the registry data (December 31, 2024).

2.5.2 Intervention

The transported effect is based on the intervention from DIGIT-HF: randomisation to treatment with digitoxin in addition to standard of care. The process of randomisation and dose titration is described elsewhere.[3]

2.5.3 Comparator

The transported effect is based on the intervention from DIGIT-HF: randomisation to treatment with placebo in addition to standard of care.[3]

2.5.4 Outcomes

The primary outcome will be a composite of all-cause mortality or first HF hospitalisation, assessed as the risk difference of the composite event by 36 months. The cumulative incidence curves of the composite event will also be reported. The 36-month restricted mean survival difference will be reported as a secondary measure. Using hazard ratios for the transportation study should be avoided: due to the unlikeliness of the proportional hazards assumption and non-collapsibility, hazard ratios are likely to depend on the censoring distribution in the data and are complex to model if both conditional and marginal models need to be used, with poor properties under model misspecification.[16,17]

Secondary and exploratory outcomes will be evaluated, reported in *Table 4*. For these analyses, follow-up will be truncated at 36 months after index to ensure sufficient statistical power while minimising the risk of treatment cross-over. Estimands according to ICH E9 are defined in detail in *Table 5*.[18]

2.5.5 Statistical analysis

We are interested in the SwedeHF population that is eligible according to the original DIGIT-HF trial criteria. A one-step transportation analysis will be used since DIGIT-HF did not exclude patients based on heart rhythm. In addition, emulation is not feasible since 1) digitoxin is not available on the Swedish market and 2) even using digoxin as a proxy is not possible as this drug is used almost exclusively in patients with atrial fibrillation/flutter but not with sinus rhythm, thereby violating the positivity assumption.

Baseline characteristics of the overall non-weighted and non-imputed study population will be presented as well as stratified by rhythm *(Table 2)*. Categorical variables will be shown as absolute and relative frequencies, and continuous variables as median with interquartile range, together with the frequency of missing data. Balance between groups will be evaluated by SMDs (successful balance will be achieved by SMDs ≤ 0.10).[21]

We include baseline covariates that are considered potential confounders based on subject-matter knowledge. Variables included in the imputation models and those considered as covariates for nuisance parameter calculations are indicated in *Table 2*.

Several nuisance parameters will be estimated addressing confounding, informative censoring, and propensity to meet the eligibility criteria of DIGIT-HF. The positivity assumption for receiving the treatment and participating in the trial will be assessed. Diagnostics will include score distributions, covariate balance before and after weighting, weight summaries, and effective sample size. The corresponding weights will be truncated at the 1% and 99% percentile.

If major non-overlap or weight instability is observed, the primary estimand will be redefined to the overlap-supported target population, and the full target-population estimate will be reported as secondary.

Whenever flexible models will be used in nuisance parameter estimation, cross-fitting will be applied to prevent overfitting bias and regularisation bias.[22]

Missingness in the data will be handled using multiple imputation by chained equations (20 imputed datasets), generated with a flexible machine learning-imputation method to preserve assumptions regarding aforementioned nuisance estimation (covariates of the model are marked in *Table 2*).[23] Missingness in the randomised data source will be handled with the same approach, using all available variables in the dataset. To avoid cross-fold leakage, all imputation procedures are incorporated within the cross-fitting scheme and estimated separately on each auxiliary sample used for the nuisance and final regression stages.

All estimates will be reported along 95% confidence intervals, in compliance to the cross-fitting procedure, the variances will be estimated within the cross-fit using the influence function variance for one-step corrections.

Concomitant methodological papers are being written to further detail the methodology and will be publicly available before the publication of this study. Moreover, a statistical analysis plan will be publicly available, specifying modelling hypothesis (nuisance) and reproducibility matter.

The overall analysis will target the ATE for decision for digitoxin treatment vs decision for non-treatment with digitoxin on outcomes reported in *Table 4*. We will use a one-step estimator for the transported treatment effect which reduces to an AIPCW-type transport estimator.[24-27] All estimates will be reported along 95% confidence intervals. Two-sided p values < 0.05 will denote statistical significance.

No negative control analysis is required for this transportation study, since confounding in DIGIT-HF is handled sufficiently by randomisation.

To analyse potential subgroup heterogeneity in the association between decision for vs against digitoxin use and outcomes, we will assess exploratively the interaction with:

- age (≥70 vs <70 years),
- sex,
- EF (<30% vs 30-39%),
- NYHA class (III/IV vs II),

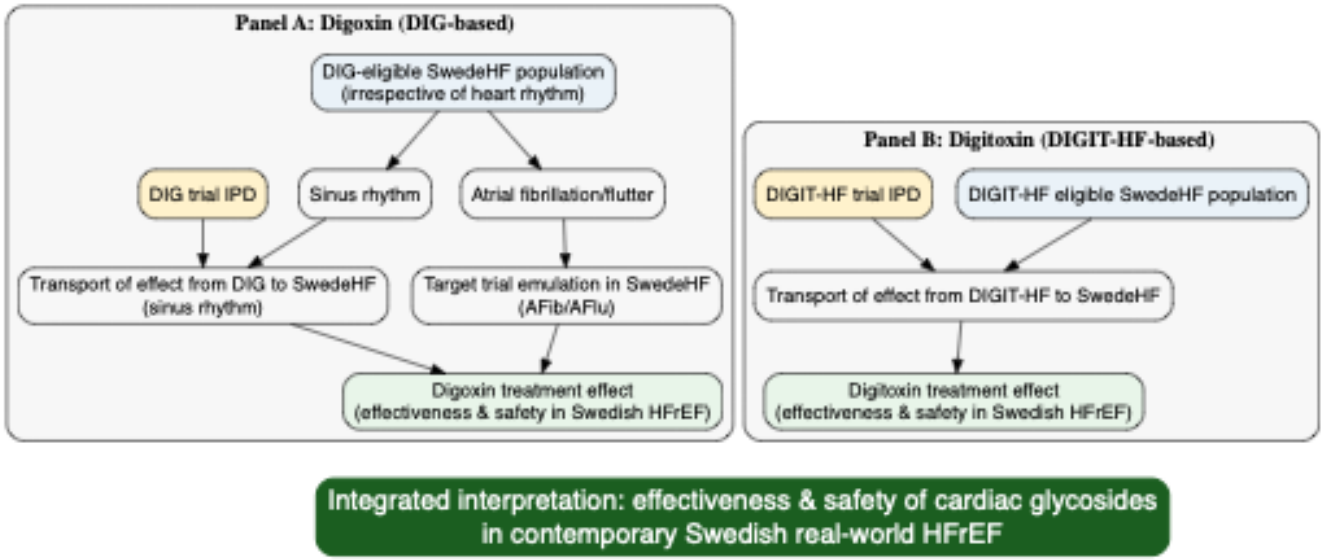
- atrial fibrillation or flutter,
- HF aetiology (ischaemic vs non-ischaemic),
- presence of cardiac devices,
- heart rate (≥75 vs <75 bpm),
- systolic blood pressure (>120 vs ≤120 mmHg),
- body mass index (≥30 vs <30 kg/m^2),
- arterial hypertension,
- diabetes,
- estimated glomerular filtration rate (>60 vs ≤60 ml/min/1.73m^2),
- beta-blocker therapy,
- MRA therapy,
- ARNi therapy,
- SGLT2i therapy,
- triple therapy (ACEi or ARB or ARNi, plus MRA and beta-blocker therapy),
- and quadruple therapy (triple therapy plus SGLT2i).

Sensitivity analyses will be performed to assess the impact of changing standard of care over time, in particular the addition of SGLT2i to standard of care in 2021 (stratification by guideline periods 2022-2024 vs 2017-2021).[1,15] Another sensitivity analysis will be performed according to prior use of digoxin.

In summary, we estimate the ATE of decision for digitoxin treatment vs non-treatment at index using an AIPCW-type estimator, transporting the intention-to-treat effect of the DIGIT-HF trial for patients with the same eligibility criteria as DIGIT-HF in SwedeHF.

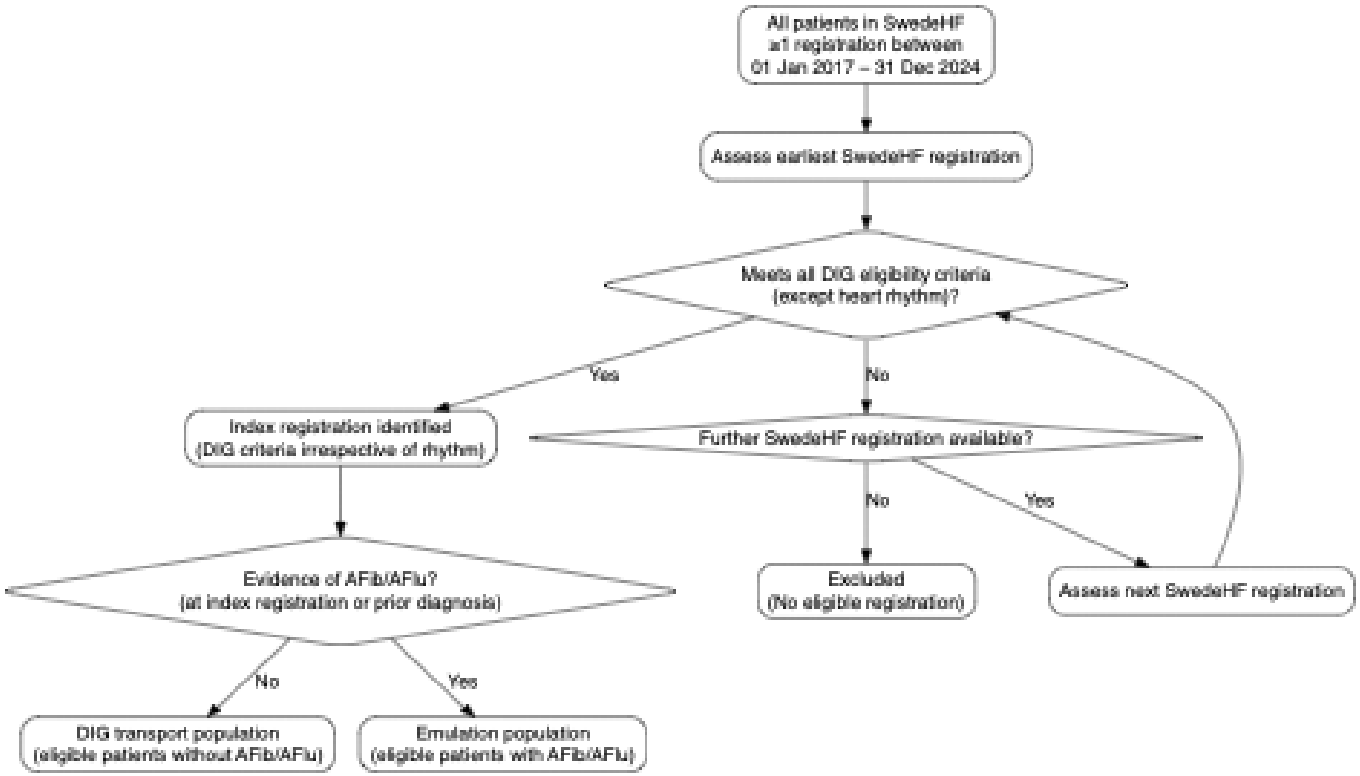
3 Figures

Figure 1: Study design integrating transportability and target trial emulation for digoxin and digitoxin in a Swedish real-world HFrEF population



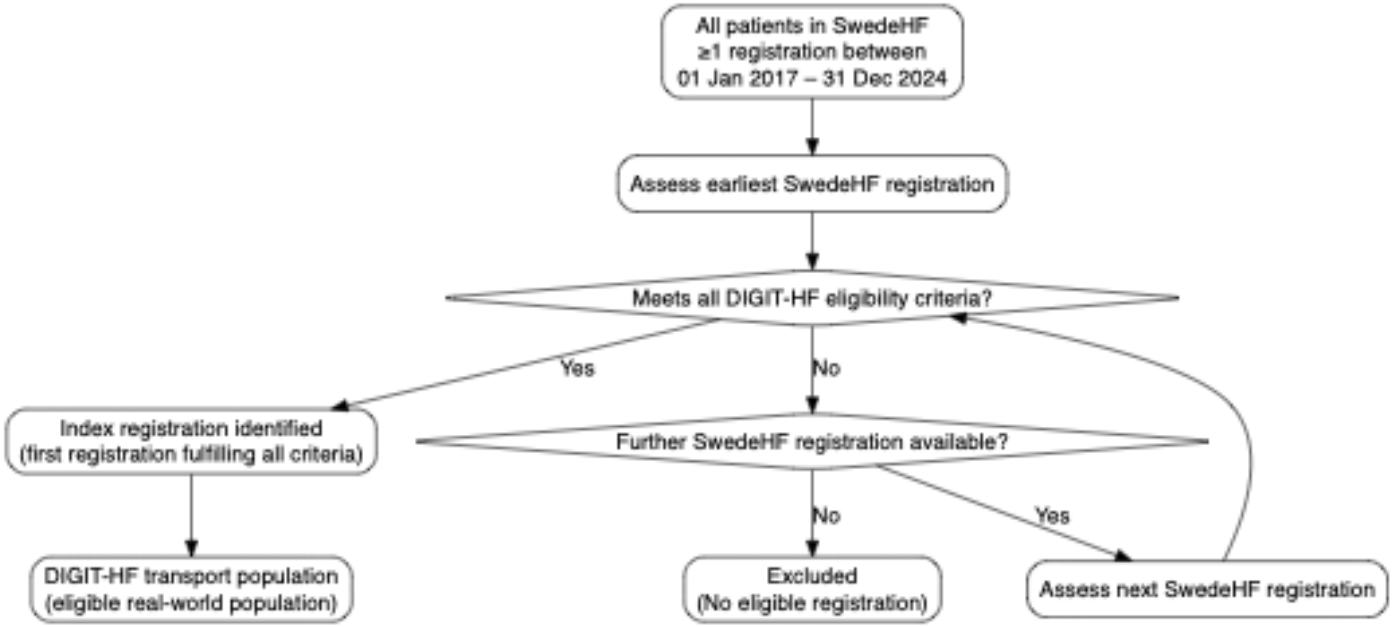
Panel A shows the digoxin study: the treatment effect in sinus rhythm is obtained by transporting the effect from the DIG trial to the DIG-eligible SwedeHF population, while in patients with AFib/AFlu a DIG-analogous target trial emulation is performed within SwedeHF. These two components are combined to yield an enriched digoxin treatment effect reflecting effectiveness and safety in the Swedish real-world HFrEF population irrespective of heart rhythm. Panel B shows the digitoxin study, in which the effect from DIGIT-HF is transported to the DIGIT-HF-eligible SwedeHF population. Together, these analyses provide complementary evidence on the effectiveness and safety of cardiac glycosides in a contemporary Swedish population with HFrEF. **Abbreviations:** AFib/AFlu, atrial fibrillation or flutter; HFrEF, heart failure with reduced ejection fraction; IPD, individual patient data; SwedeHF, Swedish Heart Failure Registry.

Figure 2: Populations and index of the digoxin study



This figure highlights the selection process of the index registration of the digoxin study as well as the division into the two subpopulations “transport population” and “emulation population” according to heart rhythm. **Abbreviations:** AFib/AFlu, atrial fibrillation or flutter; SwedeHF, Swedish Heart Failure Registry.

Figure 3: Population and index of the digitoxin study



This figure highlights the selection process of the index registration of the digitoxin study. **Abbreviations:** SwedeHF, Swedish Heart Failure Registry.

4 Tables

Table 1: DIG trial eligibility criteria

DIG trial	Observational study	Definition / Comment	Variable label (SHFDB5)
Inclusion criteria			
Clinical heart failure diagnosis, based on past or present clinical signs or symptoms or radiological evidence of pulmonary congestion	Heart failure	All patients in SwedeHF have a physician-judged heart failure diagnosis.	-
EF ≤45%	EF <40%	Collected in the SwedeHF CRF. Latest recorded EF at index registration (not necessarily measured at index registration, but also possible before) (in-patients: status at discharge; out-patients: status after visit). Comment: SwedeHF applies the previous ESC Heart Failure Guidelines, including EF 40% into the HFmrEF category, and most EF data are captured in the categorical variable. We thus decide to only include HFrEF according to the SwedeHF definition (≤39%).	shf_ef
Sinus rhythm	No prior or current atrial fibrillation or flutter, n (%)	Diagnosis in SwedeHF or NPR. NPR: ICD-10-SE code I48 (setting: in- and out-patients; position: all diagnoses; timeframe: -5 – 0 years). SwedeHF: physician-based diagnosis at index registration or in latest ECG at the time of the index registration (but not necessarily during index).	shf_sos_com_af
Written informed consent	Written informed consent	Not required by Swedish law: possibility to opt-out of quality registries such as SwedeHF (§ 2 kap. 7	-

DIG trial	Observational study	Definition / Comment	Variable label (SHFDB5)
		Patientdatalag [2008:355]); administrative registries mandated by law.	
Exclusion criteria			
Age <21 years	Age <21 years	Collected in the SwedeHF CRF at index registration.	shf_age
Missing EF data	Missing EF data	Collected in the SwedeHF CRF at index registration.	shf_ef
Myocardial infarction, cardiac surgery, or PTCA within 4 weeks	a) AMI in prior 28 days OR b) CABG in prior 28 days OR c) PCI in prior 28 days OR d) Valve intervention / surgery in prior 28 days	a) NPR: ICD-10-SE I21 or I22 (setting: in-patients; position: all diagnoses; timeframe: -28 – 0 days). b) NPR: OPS codes FNA, FNB, FNC, FND, or FNE (setting: in-patients; timeframe: -28 – 0 days). c) NPR: OPS codes DF009, DF019, DF020, FNG02, FNG05, or FNG22 (setting: in- and out-patients; timeframe: -28 – 0 days). d) NPR: OPS codes FG, FJE, FJF, FC, or FM (setting: in-patients; timeframe: -28 – 0 days)	a) new variable: sos_com_ami b) new variable: sos_com_cabg2 c) new variable: sos_com_pci2 d) new variable: sos_com_valve
Need for cardiac surgery (e.g. severe valvular disease, planned CABG) or PTCA in the near future (eligible after the procedures)	Need for cardiac surgery or intervention in the near future.	Assumed 0%. Comment: Not possible to assess in the registries without using future information and thus introducing bias.	-
Unstable or refractory angina <1 month	Unstable angina pectoris in prior 30 days	NPR: ICD-10-SE I20.0 (setting: in- and out-patients; position: all diagnoses; timeframe: -28 – 0 days)	new variable: sos_com_angina2
II-III° AV block without a pacemaker	a) AV block II° or III° BUT NOT b) Pacemaker, CRT-D/P, or ICD	a) NPR: ICD-10-SE I44.1 or I44.2 (setting: in- and out-patients; position: all diagnoses; timeframe: -365 – 0 days) b) Collected in the SwedeHF CRF at index registration.	a) new variable: sos_com_avblock b) shf_device

DIG trial	Observational study	Definition / Comment	Variable label (SHFDB5)
Cor pulmonale	Cor pulmonale	Assumed 0%. Comment: Not possible to assess within the registries but overall expected low prevalence.	-
Constrictive pericarditis (eligible after surgery)	Chronic constrictive pericarditis	NPR: ICD-10-SE I31.1 (setting: in- and out-patients; position: all diagnoses; timeframe: -1,826 – 0 days) Comment: Patients with constrictive pericarditis more than 5 years ago are likely not to get respective codes in the NPR anymore thereafter if they received surgical treatment. However, within the 5-year timeframe, all patients with the diagnosis are considered ineligible.	new variable: sos_com_pericarditis
Acute myocarditis	Acute myocarditis	NPR: ICD-10-SE I40 (setting: in- and out-patients; position: all diagnoses; timeframe: -90 – 0 days)	new variable: sos_com_myocarditis
Hypertrophic cardiomyopathy	Hypertrophic cardiomyopathy with or without obstruction	NPR: ICD-10-SE I42.1 or I42.2 (setting: in- and out-patients; position: all diagnoses; timeframe: -1,826 – 0 days)	new variable: sos_com_hcardiomyopathy
Amyloid cardiomyopathy	Amyloidosis-induced cardiomyopathy	NPR: ICD-10-SE E85 (setting: in- and out-patients; position: all diagnoses; timeframe: -1,826 – 0 days)	new variable: sos_com_acardiomyopathy
Complex congenital heart disease	Congenital cardiac malformations	NPR: ICD-10-SE Q20-26 (setting: in- and out-patients; position: all diagnoses; timeframe: -infinite – 0 days)	new variable: sos_com_congenital
Pre-excitation syndrome	Pre-excitation syndrome	NPR: ICD-10-SE code I45.6 (setting: in- and out-patients; position: all diagnoses; timeframe: -1,826 – 0 days)	new variable: sos_com_preexcitation
Current treatment with i.v. inotropic agents	Acute non-stabilised heart failure	Assumed 0%. Comment: The index registration captures out-patients at their visit to specialised care; and out-patients will not need to receive i.v. inotropes or vasodilators and almost never i.v. diuretics in Sweden. In-patients are captured at discharge from	-

DIG trial	Observational study	Definition / Comment	Variable label (SHFDB5)
		hospitalisation and, thus, after stabilisation and then eligible for enrolment. Therefore, this study assumes that (virtually) 0% of SwedeHF patients meet this criterion.	
Potassium <3.2 mmol/l or >5.5 mmol/l	Potassium <3.2 mmol/l or >5.5 mmol/l	Collected in the SwedeHF CRF at index registration (if in-patient visit: at discharge if available, otherwise at admission).	shf_potassium
Listed for heart transplantation	Heart transplant waiting list	Assumed 0%. Comment: Identification of patients on transplant waiting lists is not feasible in the registry data.	-
Sick sinus syndrome without pacemaker	a) Sick sinus syndrome BUT NOT b) Pacemaker, CRT-D/P, or ICD	a) NPR: ICD-10-SE I49.5 (setting: in- and out-patients; position: all diagnoses; timeframe: -365 – 0 days) b) Collected in the SwedeHF CRF at index registration.	a) new variable: sos_com_sicksinus b) shf_device
Recognisable non-cardiac causes of chronic heart failure	Non-cardiac causes of chronic heart failure	Assumed 0%. Comment: This rather vague term cannot be assessed with sufficient preciseness. It remains unclear which specific conditions (potentially also depending on severity) would result in exclusion.	-
Significant renal insufficiency (creatinine >3 mg/dl)	a) Serum creatinine ≥3.0 mg/dl (independent of eGFR) OR b) Current dialysis	a) Collected in the SwedeHF CRF at index registration. b) NPR: ICD-10-SE Z49 or Z99.2 or OPS codes DR012-014, DR016, DR024, DR055-056, DR060-061, or TJA33 (setting: in- and out-patients; position: all diagnoses; timeframe: -365 – 0 days)	a) shf_crea b) new variable: sos_com_dialysis2
Severe liver disease	Liver cirrhosis	NPR: ICD-10-SE codes I85, I86.4, I98.2, K70.3-4, K71.7, K72.1, K74.6, or K76.6-7 (setting: in- and out-	new variable: sos_com_livercirrhosis

DIG trial	Observational study	Definition / Comment	Variable label (SHFDB5)
		patients; position: main diagnosis; timeframe: -1,826 – 0 days)	
Any non-cardiac disease that shortens life expectancy to <3 years (e.g. most cancers)	Diagnosis of malignancies (exception: basal-cell carcinoma, squamous-cell carcinoma or carcinoma-in-situ, localised prostate cancer) in prior 5 years or still ongoing	NPR: ICD-10-SE code C (malignant tumours without in-situ) BUT NOT C44 (non-melanoma malignant skin cancers) AND NOT C61.9 in the absence of any other C code (localised prostate cancer) (setting: in- and out-patients; position: main diagnosis; timeframe: -1,826 – 0 days). Comment: C61.9 with any other C code is likely to capture metastasised prostate cancer and is thus included in this variable.	new variable: sos_com_cancer
Patient is unlikely to comply with the protocol requirements for follow-up and drug adherence (e.g. chronic alcoholism, no fixed address)	Any condition which may reduce adherence	NPR: ICD-10-SE codes F01-7, F09-16, F18-25, or F28-30 (setting: in- and out-patients; position: all diagnoses; timeframe: -365 – 0 days) Comment: 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.	new variable: sos_com_redadhere

Eligibility is assessed based on the imputed data (exception: patients with missing information on EF or of atrial fibrillation/flutter will be excluded). **Abbreviations**: AMI, acute myocardial infarction; AV, atrio-ventricular; CABG, coronary artery bypass graft; CRF, case report form; CRT-D/P, cardiac resynchronisation therapy (D: with a defibrillator; P: only with pacemaker); EF, ejection fraction; eGFR, estimated glomerular filtration rate; ESC, European Society of Cardiology; HFmrEF, heart failure with mildly reduced ejection fraction; HFrEF, heart failure with reduced ejection fraction; i.v., intravenous; ICD-10-SE, International Statistical Classification of Diseases, 10th revision, Swedish version; NPR, National Patient Register; OPS, classification for the encoding of

operations, procedures and general medical measures; PCI, percutaneous coronary intervention; PTCA, percutaneous transluminal coronary angiography; SHFDB5, Swedish Heart Failure Registry, database version 5; SwedeHF, Swedish Heart Failure Registry.

Table 2: Patient characteristics (digoxin & digitoxin studies)

Label	Definition / Comment	Variable label (SHFDB5)
Sociodemographics		
Age (years), median [IQR] *,†,‡,§	Collected in the SwedeHF CRF at index registration.	shf_age
Sex *,†,‡,§ - female, n (%) - male, n (%)	Collected in the SwedeHF CRF at index registration.	shf_sex
Disposable income (SEK) grouped by year, median [IQR] *,‡	Status on Dec 31 of the year prior to the index registration acquired from the LISA database.	scb_dispincome
Education *,‡ - compulsory school, n (%) - secondary school, n (%) - university, n (%)	Status on Dec 31 of the year prior to the index registration acquired from the LISA database.	scb_education
Marital status * - single / widowed / divorced, n (%) - married, n (%)	Status on Dec 31 of the year prior to the index registration acquired from the LISA database.	scb_maritalstatus
Family status *,‡ - living alone, n (%) - cohabitating, n (%)	Status on Dec 31 of the year prior to the index registration acquired from the LISA database.	scb_famtype
Clinical variables of heart failure		
Ejection fraction (%) *,†,‡,§ - 30-39%, n (%) - < 30%, n (%)	Collected in the SwedeHF CRF; latest recorded EF at index registration (not necessarily measured at index registration but possibly before).	shf_ef
NYHA *,†,‡,§ - class I, n (%) - class II, n (%) - class III, n (%) - class IV, n (%)	Collected in the SwedeHF CRF at index registration.	shf_nyha

Label	Definition / Comment	Variable label (SHFDB5)
Duration of heart failure (days), median [IQR] *,‡,§	Time from first in-patient discharge or out-patient visit with registration of a HF code in the NPR to index registration: ICD-10-SE codes I11.0, I13.0, I13.2, I25.5, I42.0, I42.3, I42.5-9, I43, I50, J81, K76.1, R57.0, or ICD-9-SE codes 414W, 425E, 425F, 425G, 425H, 425W, 425X, or 428 (setting: in- and out-patients; position: all diagnoses; timeframe: -infinite – 0 days).	sos_durationhf
≥ 1 HF hospitalisation in prior year, n (%) *,‡	Any HF hospitalisation either in the NPR or in SwedeHF. NPR: 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 (setting: in-patients; position: main diagnosis; timeframe: -1 – 0 years). SwedeHF: any registration with shf_location = In-patient.	shf_sos_prevhfh1yr
Primary aetiology of heart failure *,†,‡,§ - ischaemic cardiomyopathy, n (%) - non-ischaemic aetiology, n (%)	Collected in the SwedeHF CRF at index registration.	shf_primaryetiology
Comorbidities & cardiovascular risk factors		
Atrial fibrillation/flutter, n (%) *,‡,§	Diagnosis in SwedeHF or NPR. NPR: ICD-10-SE code I48 (setting: in- and out-patients; position: all diagnoses; timeframe: -5 – 0 years). SwedeHF: physician-based diagnosis at index registration or in latest ECG at the time of the index registration (but not necessarily during index).	shf_sos_com_af
Latest ECG, n (%) * - sinus rhythm, n (%) - atrial fibrillation, n (%) - other, n (%)	SwedeHF: diagnosis in latest ECG at the time of the index registration (but not necessarily during index).	shf_ekg
Patterns of atrial fibrillation *,‡ - paroxysmal atrial fibrillation, n (%) - persistent atrial fibrillation, n (%)	NPR: ICD-10-SE codes I48.0 (paroxysmal) or I48.1 (persistent) (setting: in- and out-patients; position: all diagnoses; timeframe: -1,826 – 0 days). Comment: only the latest code counts (e.g. a prior registration of I48.0 can be overruled by a newer registration of I48.1).	new variable: sos_com_af2

Label	Definition / Comment	Variable label (SHFDB5)
- no atrial fibrillation or non-classified pattern, n (%)		
Arterial hypertension, n (%) *,†,‡,§	Diagnosis in SwedeHF or NPR. SwedeHF: Collected in the SwedeHF CRF at index registration. NPR: ICD-10-SE codes I10-15 (setting: in- and out-patients; position: all diagnoses; timeframe: -5 – 0 years).	shf_sos_com_hypertension
Valvular disease, n (%) *,‡	Diagnosis in SwedeHF or NPR. SwedeHF: Collected in the SwedeHF CRF at index registration. NPR: ICD-10-SE codes I05-08, I34-39, Q22, Q23.0-3, Q23.8-9, or Z95.2-4 (setting: in- and out-patients; position: all diagnoses; timeframe: -5 – 0 years).	shf_sos_com_valvular
Ischaemic heart disease, n (%) *	Diagnosis in SwedeHF or NPR. SwedeHF: Collected in the SwedeHF CRF at index registration. NPR: ICD-10-SE codes I20-25 or ICD-9-SE codes 410-4 (setting: in- and out-patients; position: all diagnoses; timeframe: -infinite – 0 years).	shf_sos_com_ihd
History of myocardial infarction, n (%) *,†,‡	NPR: ICD-10-SE codes I21, I22, I25.2, or ICD-9-SE codes 410 or 412 (setting: in- and out-patients; position: all diagnoses; timeframe: -infinite – 0 years).	sos_com_mi
Diabetes mellitus, n (%) *,†,‡	Diagnosis in SwedeHF or NPR. SwedeHF: Collected in the SwedeHF CRF at index registration. NPR: ICD-10-SE codes E10-4 (setting: in- and out-patients; position: all diagnoses; timeframe: -5 – 0 years)	shf_sos_com_diabetes
Dialysis, n (%) *,‡	NPR: ICD-10-SE codes Z49.0-2 or Z99.2 (setting: in- and out-patients; position: all diagnoses; timeframe: -5 – 0 years), or KVÅ codes DR012, DR013, DR014, DR016, DR020, DR024, TJA33, DR055, DR056, DR060, DR061, or QF006 (timeframe: -5 – 0 years).	sos_com_dialysis
COPD, n (%) *,‡,§	NPR: ICD-10-SE codes J40-4 (setting: in- and out-patients; position: all diagnoses; timeframe: -5 – 0 years).	sos_com_copd
Smoking * - current smoker, n (%) - former smoker, n (%) - never smoked, n (%)	Collected in the SwedeHF CRF at index registration.	shf_smoke
Liver disease, n (%) *,‡	NPR: ICD-10-SE codes B18, I85, I86.4, I98.2, K70, K71.0, K71.1, K71.3-7, K72-4, K76.0, K76.2-9 (setting: in- and out-patients; position: all diagnoses; timeframe: -5 – 0 years).	sos_com_liver

Label	Definition / Comment	Variable label (SHFDB5)
Peripheral artery disease, n (%) *,‡,§	NPR: ICD-10-SE codes I70-3 (setting: in- and out-patients; position: all diagnoses; timeframe: -5 – 0 years).	sos_com_pad
History of stroke, n (%) *,‡,§	NPR: ICD-10-SE codes I60-4, I69.0-4, or ICD-9-SE codes 430-4 or 438 (setting: in- and out-patients; position: all diagnoses; timeframe: -infinite – 0 years).	sos_com_stroke
Anaemia, n (%) *	Calculated from SwedeHF data: haemoglobin < 120 g/l (women) or < 130 g/l (men).	shf_anemia
Anxiety or depression, n (%) *,‡	Collected in the SwedeHF CRF at index registration.	shf_anxiety
Cancer, n (%) *,‡,§	NPR: ICD-10-SE code C (setting: in- and out-patients; position: main diagnosis; timeframe: -3 – 0 years).	sos_com_cancer3y
BMI (kg/m^2), median [IQR] *,†,‡,§	Calculated as weight/height^2, using the respective variables in SwedeHF; if no height had been registered, it was imputed. Weight was captured at discharge in in-patients; if missing, it was replaced by weight at admission.	shf_bmi
Charlson Comorbidity Index, median [IQR] *	Calculated as an adapted score for all patients in SwedeHF based on NPR data according to Ludvigsson et al.[28] (in-patients: status at discharge; out-patients: status after visit).	sos_com_charlsonci
Vital signs		
Systolic blood pressure (mmHg), median [IQR] *,†,‡,§	Collected in the SwedeHF CRF at index registration (if in-patient visit: at discharge if available, otherwise at admission).	shf_bpsys
Diastolic blood pressure (mmHg), median [IQR] *,†,‡,§	Collected in the SwedeHF CRF at index registration (if in-patient visit: at discharge if available, otherwise at admission).	shf_bpdia
Mean arterial pressure (mmHg), median [IQR] *	Collected in the SwedeHF CRF at index registration (if in-patient visit: at discharge if available, otherwise at admission).	shf_map
Heart rate (bpm), median [IQR] *,†,‡,§	Collected in the SwedeHF CRF at index registration (if in-patient visit: at discharge if available, otherwise at admission).	shf_heartrate
Laboratory parameters		
Haemoglobin (g/l), median [IQR] *,‡,§	Collected in the SwedeHF CRF at index registration (if in-patient visit: at discharge if available, otherwise at admission).	shf_hb
Potassium, median [IQR] *,†,‡,§	Collected in the SwedeHF CRF at index registration (if in-patient visit: at discharge if available, otherwise at admission).	shf_potassium

Label	Definition / Comment	Variable label (SHFDB5)
Sodium, median [IQR] *,‡,§	Collected in the SwedeHF CRF at index registration (if in-patient visit: at discharge if available, otherwise at admission).	shf_sodium
Creatinine (µmol/l), median [IQR] *	Collected in the SwedeHF CRF at index registration (if in-patient visit: at discharge if available, otherwise at admission).	shf_crea
eGFR (ml/min/1.73 m²), median [IQR] *,†,‡,§	Collected in the SwedeHF CRF at index registration (if in-patient visit: at discharge if available, otherwise at admission; CKD-EPI 2021).	shf_gfrckdepi
NT-proBNP (pg/ml), median [IQR] *,‡	Collected in the SwedeHF CRF at index registration (if in-patient visit: at discharge if available, otherwise at admission).	shf_ntprobnp
Cardiocirculatory treatment		
Beta-blocker, n (%) *,‡,§	Collected in the SwedeHF CRF at index registration.	shf_bbl
ACEi, n (%) *,†,‡,§	Collected in the SwedeHF CRF at index registration.	shf_acei
ARB, n (%) *,‡,§	Collected in the SwedeHF CRF at index registration.	shf_arb
ARNi, n (%) *,‡,§	Collected in the SwedeHF CRF at index registration.	shf_arni
MRA, n (%) *,†,‡,§	Collected in the SwedeHF CRF at index registration.	shf_mra
SGLT2i, n (%) *,‡,§	Collected in the SwedeHF CRF at index registration.	shf_sglt2
Diuretic (all), n (%) *,†	Collected in the SwedeHF CRF at index registration.	shf_diuretic
Loop diuretic, n (%) *,‡,§	Collected in the SwedeHF CRF at index registration.	shf_loopdiuretic
Prior digoxin use, n (%) *,†,‡,§	NPDR: ATC code C01AA05 (ApoDos included; timeframe: -120 – -1 days)	new variable: sos_lm_digoxin
Sinus node inhibitor, n (%) *,‡,§		shf_sinusnodei
Nitrate, n (%) *,†,‡	Collected in the SwedeHF CRF at index registration.	shf_nitrate
Anticoagulant, n (%) *,‡	Collected in the SwedeHF CRF at index registration.	shf_anticoagulantia
Platelet inhibitor, n (%) *,‡	Collected in the SwedeHF CRF at index registration.	shf_asaantiplatelet
Statin, n (%) *,‡	Collected in the SwedeHF CRF at index registration.	shf_statin
Cardiac devices *,†,‡,§ - no device, n (%) - pacemaker, n (%) - CRT-P, n (%) - CRT-D, n (%) - ICD, n (%)	Collected in the SwedeHF CRF at index registration.	shf_device

Label	Definition / Comment	Variable label (SHFDB5)
Index registration & follow-up		
Year of index event, median [IQR] *,†,‡,§	Collected in the SwedeHF CRF at index registration.	shf_indexyear
Place of index registration *,‡ - in-patient, n (%) - out-patient, n (%)	Collected in the SwedeHF CRF at index registration.	shf_location
Planned follow-up setting *,‡ - primary care, n (%) - speciality care, n (%)	Collected in the SwedeHF CRF at index registration.	shf_followuplocation_cat
Planned follow-up in a heart failure nurse clinic, n (%) *,‡	Collected in the SwedeHF CRF at index registration.	shf_followuphfunit

Variables collected in SwedeHF represent the status at the end of the index registration (i.e. discharge in in-patients), if not explicitly stated otherwise. **Abbreviations:** ACEi, angiotensin-converting enzyme inhibitor; 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; ATC, anatomic therapeutical drug classification; bpm, beats per minute; BMI, body mass index; COPD, chronic obstructive pulmonary disease; CRF, case report form; CRT-P/D, cardiac resynchronisation therapy pacemaker/defibrillator; ECG, electrocardiogram; EF, ejection fraction; eGFR, estimated glomerular filtration rate; ICD, implantable cardioverter-defibrillator; ICD-10-SE, International Classification of Diseases, 10th revision, Swedish version; ICD-9-SE, International Classification of Diseases, 9th revision, Swedish version; IQR, interquartile range; LISA, Longitudinal Integrated Database for Health Insurance and Labour Market Studies; 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; OPS, classification for the encoding of operations, procedures and general medical measures; SGLT2i, sodium/glucose cotransporter 2 inhibitor; SHFDB5, Swedish Heart Failure Registry, database version 5; SwedeHF, Swedish Heart Failure Registry. Displayed baseline characteristics without imputed data. / *, included in imputation model of SwedeHF data; †, used for the nuisance models of the DIG transportation study (requires availability of respective variable both in SwedeHF and in DIG); ‡, used for the nuisance models of the DIG emulation study (requires availability of respective variable only in SwedeHF); §, used for the nuisance models of the DIGIT-HF transportation study (requires availability of respective variable both in SwedeHF and in DIGIT-HF).

Table 3: Treatment strategy (digoxin study: emulation)

Target trial	Observational study	Definition / Comment	Variable label (SHFDB5)
Treatment arm			
Standard of care for heart failure plus: digoxin, titrated based on individual factors.	Decision for treatment with digoxin at index registration	We assume that standard of care is provided. Titration cannot be assessed in the registries.	SwedeHF: shf_digoxin
Comparator arm			
Standard of care for heart failure plus: completely inert placebo.	Decision against treatment with digoxin at index registration	We assume that standard of care is provided.	SwedeHF: shf_digoxin

Abbreviations: ApoDos, Swedish multi-dose drug dispensing system with all medication for a given time in one bag; ATC, anatomic therapeutical drug classification; SHFDB5, Swedish Heart Failure Registry, database version 5; SwedeHF, Swedish Heart Failure Registry.

Table 4: Outcomes (digoxin & digitoxin studies)

Observational study	Definition / Comment	Variable label (SHFDB5)
Effectiveness & safety: primary outcome		
All-cause death or HF hospitalisation (time to first event)	Composite of: a) CoD: all ICD-10-SE codes (ULORSAK; timeframe: 1 – 1,096 days). b) NPR: 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 (setting: in-patients; position: main diagnosis; timeframe: 1 – 1,096 days).	event: sos_out_deathhosphf time: sos_outtime_death, sos_outtime_hosphf
Effectiveness & safety: secondary outcomes		
Cardiovascular death or HF hospitalisation (time to first event)	Composite of: a) CoD: ICD-10-SE codes I, J81, K76.1, R57.0, or G45 (ULORSAK; timeframe: 1 – 1,096 days). b) NPR: 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 (setting: in-patients; position: main diagnosis; timeframe: 1 – 1,096 days).	event: sos_out_deathcvhosphf time: sos_outtime_death, sos_outtime_hosphf
All-cause death (time to event)	CoD: all ICD-10-SE codes (ULORSAK; timeframe: 1 – 1,096 days).	event: sos_out_death time: sos_outtime_death
Cardiovascular death (time to event)	CoD: ICD-10-SE codes I, J81, K76.1, R57.0, or G45 (ULORSAK; timeframe: 1 – 1,096 days).	event: sos_out_deathcv time: sos_outtime_death
Non-cardiovascular death (time to event)	CoD: all ICD-10-SE codes BUT NOT I, J81, K76.1, R57.0, or G45 (ULORSAK; timeframe: 1 – 1,096 days).	event: sos_out_deathnoncv time: sos_outtime_death
HF death (time to event)	CoD: 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 (ULORSAK; timeframe: 1 – 1,096 days).	event: sos_deathcause time: sos_outtime_death
Sudden cardiac death (time to event)	CoD: ICD-10-SE code I46.1 (ULORSAK; timeframe: 1 – 1,096 days).	event: sos_out_deathscd time: sos_outtime_death
HF hospitalisation (time to first event)	NPR: 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 (setting: in-patients; position: main diagnosis; timeframe: 1 – 1,096 days).	event: sos_out_hosphf time: sos_outtime_hosphf
Non-HF hospitalisation (time to first event)	NPR: all ICD-10-SE codes BUT NOT I11.0, I13.0, I13.2, I25.5, I42.0, I42.3, I42.5-9, I43, I50, J81, K76.1, or R57.0 (setting: in-patients; position: main diagnosis; timeframe: 1 – 1,096 days).	new event variable: sos_out_hospnonhf new time variable: sos_outtime_hospnonhf

Observational study	Definition / Comment	Variable label (SHFDB5)
Cardiovascular hospitalisation (time to first event)	NPR: ICD-10-SE codes I, J81, K76.1, G45, or R57.0 (setting: in-patients; position: main diagnosis; timeframe: 1 – 1,096 days).	event: sos_out_hospcv time: sos_outtime_hospcv
Non-cardiovascular hospitalisation (time to first event)	NPR: all ICD-10-SE codes BUT NOT I, J81, K76.1, G45, or R57.0 (setting: in-patients; position: main diagnosis; timeframe: 1 – 1,096 days).	event: sos_out_hospnoncv time: sos_outtime_hospnoncv
All-cause hospitalisation (time to first event)	NPR: all ICD-10-SE codes (setting: in-patients; position: all diagnoses; timeframe: 1 – 1,096 days).	event: sos_out_hospany time: sos_outtime_hospany
Effectiveness & safety: exploratory outcomes		
All-cause death or HF hospitalisation (total number of events)	Composite of: a) CoD: all ICD-10-SE codes (ULORSAK; timeframe: 1 – 1,096 days). b) NPR: 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 (setting: in-patients; position: main diagnosis; timeframe: 1 – 1,096 days).	a) event: sos_out_death time: sos_outtime_death b) new variable: sos_out_counthosphf3yr
HF hospitalisation (total number of events)	NPR: 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 (setting: in-patients; position: main diagnosis; timeframe: 1 – 1,096 days).	new variable: sos_out_counthosphf3yr
All-cause hospitalisation (total number of events)	NPR: all ICD-10-SE codes (setting: in-patients; position: all diagnoses; timeframe: 1 – 1,096 days).	new variable: sos_out_counthospany3yr
Negative control outcome		
Cancer hospitalisation (time to first event)	NPR: ICD-10-SE code C (setting: in-patients; position: main diagnosis; timeframe: 1 – 1,096 days).	event: sos_out_hospcancer time: sos_outtime_hospcancer

All effectiveness and safety outcomes will be assessed in both the digoxin and the digitoxin study (depending on data availability). The negative control outcome will be assessed only in the target trial emulation, since confounding in the DIG and DIGIT-HF trials is sufficiently addressed by randomisation. **Abbreviations:** CoD, National Cause of Death Register; HF, heart failure; ICD-10-SE, International Classification of Diseases, 10th revision, Swedish version; NPR, National Patient Register; SHFDB5, Swedish Heart Failure Registry, database version 5; ULORSAK, cause of death (as an ICD-10-SE code).

Table 5: Definitions of estimands (digoxin & digitoxin studies)

All outcomes	
Population	• Digoxin study (transportation): patients with HFrEF in SwedeHF eligible for DIG trial • Digoxin study (emulation): patients with HFrEF in SwedeHF with concomitant atrial fibrillation/flutter (eligible for DIG trial with exception of heart rhythm eligibility criterion) • Digoxin study (enriched): patients with HFrEF in SwedeHF eligible for DIG trial irrespective of heart rhythm eligibility criterion • Digitoxin study (transportation): patients with HFrEF in SwedeHF eligible for DIGIT-HF trial
Intervention	• Digoxin study (transportation): randomisation to treatment with digoxin in addition to SoC without digoxin • Digoxin study (emulation): clinical decision for initiating or continuing treatment with digoxin at index registration in SwedeHF in addition to SoC without digoxin • Digitoxin study (transportation): randomisation to treatment with digitoxin in addition to SoC
Comparator	• Digoxin study (transportation): randomisation to treatment with placebo in addition to SoC without digoxin • Digoxin study (emulation): decision against initiating or continuing treatment with digoxin at index registration in SwedeHF but maintaining SoC • Digitoxin study (transportation): randomisation to treatment with placebo in addition to SoC
All-cause death or HF hospitalisation (time to first event)	
Objective	To demonstrate that the investigational treatment plus SoC is superior to SoC alone regarding time to all-cause death or first HF hospitalisation.
Intercurrent event: treatment discontinuation	treatment policy strategy
Intercurrent event: treatment cross-over	treatment policy strategy
Intercurrent event: change of pharmacological or device background therapy	treatment policy strategy
Intercurrent event: emigration[1]	hypothetical
Summary measure	risk difference (cumulative incidence) of all-cause death or HF hospitalisation by 36 months
Estimand type	ATE
Cardiovascular death or HF hospitalisation (time to first event)	

[1] Emigration can be assessed in SwedeHF with the variable censdtm, which is the date of emigration, death, or the last follow-up (i.e. administrative registry censoring, here December 31, 2024), whichever comes first. A patient with censdtm 2024-12-31 who has not died is thus emigrated.

Objective	To explore the effect of the investigational treatment in addition to SoC vs SoC alone regarding time to cardiovascular death or first HF hospitalisation.
Intercurrent event: treatment discontinuation	treatment policy strategy
Intercurrent event: treatment cross-over	treatment policy strategy
Intercurrent event: change of pharmacological or device background therapy	treatment policy strategy
Intercurrent event: non-cardiovascular death	competing event strategy
Intercurrent event: emigration	hypothetical
Summary measure	risk difference (cumulative incidence) of cardiovascular death or HF hospitalisation by 36 months
Estimand type	ATE
All-cause death (time to event)	
Objective	To explore the effect of the investigational treatment in addition to SoC vs SoC alone regarding time to all-cause death.
Intercurrent event: treatment discontinuation	treatment policy strategy
Intercurrent event: treatment cross-over	treatment policy strategy
Intercurrent event: change of pharmacological or device background therapy	treatment policy strategy
Intercurrent event: emigration	hypothetical
Summary measure	risk difference (cumulative incidence) of all-cause death by 36 months
Estimand type	ATE
Cardiovascular death (time to event)	
Objective	To explore the effect of the investigational treatment in addition to SoC vs SoC alone regarding time to cardiovascular death.
Intercurrent event: treatment discontinuation	treatment policy strategy
Intercurrent event: treatment cross-over	treatment policy strategy
Intercurrent event: change of pharmacological or device background therapy	treatment policy strategy
Intercurrent event: non-cardiovascular death	competing event strategy
Intercurrent event: emigration	hypothetical
Summary measure	risk difference (cumulative incidence) of cardiovascular death by 36 months
Estimand type	ATE
Non-cardiovascular death (time to event)	

Objective	To explore the effect of the investigational treatment in addition to SoC vs SoC alone regarding time to non-cardiovascular death.
Intercurrent event: treatment discontinuation	treatment policy strategy
Intercurrent event: treatment cross-over	treatment policy strategy
Intercurrent event: change of pharmacological or device background therapy	treatment policy strategy
Intercurrent event: cardiovascular death	competing event strategy
Intercurrent event: emigration	hypothetical
Summary measure	risk difference (cumulative incidence) of non-cardiovascular death by 36 months
Estimand type	ATE
HF death (time to event)	
Objective	To explore the effect of the investigational treatment in addition to SoC vs SoC alone regarding time to HF death.
Intercurrent event: treatment discontinuation	treatment policy strategy
Intercurrent event: treatment cross-over	treatment policy strategy
Intercurrent event: change of pharmacological or device background therapy	treatment policy strategy
Intercurrent event: non-HF death	competing event strategy
Intercurrent event: emigration	hypothetical
Summary measure	risk difference (cumulative incidence) of HF-death by 36 months
Estimand type	ATE
Sudden cardiac death (time to event)	
Objective	To explore the effect of the investigational treatment in addition to SoC vs SoC alone regarding time to sudden cardiac death.
Intercurrent event: treatment discontinuation	treatment policy strategy
Intercurrent event: treatment cross-over	treatment policy strategy
Intercurrent event: change of pharmacological or device background therapy	treatment policy strategy
Intercurrent event: non-sudden cardiac death	hypothetical
Intercurrent event: emigration	hypothetical
Summary measure	risk difference (cumulative incidence) of sudden cardiac death by 36 months
Estimand type	ATE

HF hospitalisation (time to first event)	
Objective	To explore the effect of the investigational treatment in addition to SoC vs SoC alone regarding time to first HF hospitalisation.
Intercurrent event: treatment discontinuation	treatment policy strategy
Intercurrent event: treatment cross-over	treatment policy strategy
Intercurrent event: change of pharmacological or device background therapy	treatment policy strategy
Intercurrent event: all-cause death	competing event strategy
Intercurrent event: emigration	hypothetical
Summary measure	risk difference (cumulative incidence) of HF-hospitalisation by 36 months
Estimand type	ATE
Non-HF hospitalisation (time to first event)	
Objective	To explore the effect of the investigational treatment in addition to SoC vs SoC alone regarding time to first non-HF hospitalisation.
Intercurrent event: treatment discontinuation	treatment policy strategy
Intercurrent event: treatment cross-over	treatment policy strategy
Intercurrent event: change of pharmacological or device background therapy	treatment policy strategy
Intercurrent event: all-cause death	competing event strategy
Intercurrent event: emigration	hypothetical
Summary measure	risk (cumulative incidence) of non-HF hospitalisation by 36 months
Estimand type	ATE
Cardiovascular hospitalisation (time to first event)	
Objective	To explore the effect of the investigational treatment in addition to SoC vs SoC alone regarding time to first cardiovascular hospitalisation.
Intercurrent event: treatment discontinuation	treatment policy strategy
Intercurrent event: treatment cross-over	treatment policy strategy
Intercurrent event: change of pharmacological or device background therapy	treatment policy strategy
Intercurrent event: all-cause death	competing event strategy
Intercurrent event: emigration	hypothetical
Summary measure	risk difference (cumulative incidence) of cardiovascular hospitalisation by 36 months

Estimand type	ATE
Non-cardiovascular hospitalisation (time to first event)	
Objective	To explore the effect of the investigational treatment in addition to SoC vs SoC alone regarding time to first non-cardiovascular hospitalisation.
Intercurrent event: treatment discontinuation	treatment policy strategy
Intercurrent event: treatment cross-over	treatment policy strategy
Intercurrent event: change of pharmacological or device background therapy	treatment policy strategy
Intercurrent event: all-cause death	competing event strategy
Intercurrent event: emigration	hypothetical
Summary measure	risk difference (cumulative incidence) of non-cardiovascular hospitalisation by 36 months
Estimand type	ATE
All-cause hospitalisation (time to first event)	
Objective	To explore the effect of the investigational treatment in addition to SoC vs SoC alone regarding time to first all-cause hospitalisation.
Intercurrent event: treatment discontinuation	treatment policy strategy
Intercurrent event: treatment cross-over	treatment policy strategy
Intercurrent event: change of pharmacological or device background therapy	treatment policy strategy
Intercurrent event: all-cause death	competing event strategy
Intercurrent event: emigration	hypothetical
Summary measure	risk difference (cumulative incidence) of all-cause hospitalisation by 36 months
Estimand type	ATE
All-cause death or HF hospitalisation (total number of events)	
Objective	To explore the effect of the investigational treatment in addition to SoC vs SoC alone regarding the cumulative event burden of all-cause death and HF hospitalisations.
Intercurrent event: treatment discontinuation	treatment policy strategy
Intercurrent event: treatment cross-over	treatment policy strategy
Intercurrent event: change of pharmacological or device background therapy	treatment policy strategy
Intercurrent event: emigration	hypothetical
Summary measure	difference in the expected cumulative number of all-cause death or hospitalisations by 36 months

Estimand type	ATE
HF hospitalisation (total number of events)	
Objective	To explore the effect of the investigational treatment in addition to SoC vs SoC alone regarding the cumulative event burden of HF hospitalisations.
Intercurrent event: treatment discontinuation	treatment policy strategy
Intercurrent event: treatment cross-over	treatment policy strategy
Intercurrent event: change of pharmacological or device background therapy	treatment policy strategy
Intercurrent event: all-cause death	treatment policy strategy
Intercurrent event: emigration	hypothetical
Summary measure	difference in the expected cumulative number of HF-hospitalisations by 36 months
Estimand type	ATE
All-cause hospitalisation (total number of events)	
Objective	To explore the effect of the investigational treatment in addition to SoC vs SoC alone regarding the cumulative event burden of all-cause hospitalisations.
Intercurrent event: treatment discontinuation	treatment policy strategy
Intercurrent event: treatment cross-over	treatment policy strategy
Intercurrent event: change of pharmacological or device background therapy	treatment policy strategy
Intercurrent event: all-cause death	treatment policy strategy
Intercurrent event: emigration	hypothetical
Summary measure	difference in the expected cumulative number of all-cause hospitalisations by 36 months
Estimand type	ATE
Cancer hospitalisation (time to first event)	
Objective	To assess possible residual confounding (there is no biologically plausible effect of the investigational treatment on this outcome).
Intercurrent event: treatment cross-over	treatment policy strategy
Intercurrent event: change of pharmacological or device background therapy	treatment policy strategy
Intercurrent event: non-cancer hospitalisation	hypothetical (rationale: any non-cancer hospitalisation increases probability to find cancer through in-patient diagnostics)
Intercurrent event: emigration	hypothetical

Summary measure	difference in the expected cumulative number of All-cause hospitalisations by 36 months
Estimand type	ATE

The estimands were defined according to ICH E9.[18] The 36-month (i.e. 1,096 days) restricted mean survival time difference will be reported exploratively for all estimands in addition to the primary summary measure. **Abbreviations**: ATE, average treatment effect; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; SoC, standard of care.

Table 6: DIGIT-HF trial eligibility criteria

DIGIT-HF trial	Observational study	Definition / Comment	Variable label (SHFDB5)
Inclusion criteria			
Signed written informed consent	Written informed consent	Not required by Swedish law: possibility to opt-out of quality registries such as SwedeHF (§ 2 kap. 7 Patientdatalag [2008:355]); administrative registries mandated by law.	-
Male or female sex	Male or female sex	Collected in the SwedeHF CRF at index registration.	shf_sex
Age ≥18 years	Age ≥18 years	Collected in the SwedeHF CRF at index registration.	shf_age
Patients capable of understanding the investigational nature, potential risks, and benefits of the clinical trial	Patients capable of understanding the investigational nature, potential risks, and benefits of the clinical trial	Cannot be assessed in the registry; partly covered by the exclusion criterion of reduced adherence (see below).	-
Patients with chronic HF NYHA class III-IV and EF ≤40% or patients with HF NYHA class II and EF ≤30%	a) HF diagnosis b) NYHA class III-IV with EF ≤39%; or NYHA class II with EF ≤30 %	a) All patients in SwedeHF have a physician-judged heart failure diagnosis. b) Collected in the SwedeHF CRF. Latest recorded EF at index registration (not necessarily measured at index registration, but also possible before) (in-patients: status at discharge; out-patients: status after visit). <u>Comment</u>: SwedeHF applies the previous ESC Heart Failure Guidelines, including EF 40% into the HFmrEF category, and most EF data are captured in the categorical variable. We thus decide to only include HFrEF according to the SwedeHF definition (≤39%).	a) - b) shf_nyha , shf_ef

DIGIT-HF trial	Observational study	Definition / Comment	Variable label (SHFDB5)
Evidence-based HF therapy ≥6 months upon discretion of the treating physician	≥2 of 3 foundational HFrEF pharmacotherapies according to 2016 ESC Guidelines[15] for ≥180 days. These are: a) Beta-blockers b) ACEi/ARB/ARNi c) MRA	a) NPDR: ATC code C07 (ApoDos included), dispensed ≥2 times in timeframe -180 – -1 days b) NPDR: ATC codes C09A-D (ApoDos included), dispensed ≥2 times in timeframe -180 – -1 days c) NPDR: ATC code C03DA (ApoDos included), dispensed ≥2 times in timeframe -180 – -1 days Comment: The original trial criterion allowed treatment at the discretion of the treating physician and did not require a fixed combination of drug classes. To approximate this flexible, clinician-driven concept in registry data, we defined evidence-based therapy as the use of ≥2 out of 3 foundational HFrEF drug classes for ≥180 days prior to index. This approach reflects receipt of guideline-directed HF therapy without assuming full triple therapy in all patients, while not capturing individual clinical judgement or contraindications.	a) new variable: sos_lm_bbl2 b) new variable: sos_lm_rasiarni2 c) new variable: sos_lm_mra2
Women without childbearing potential (detailed definition elsewhere)[3]	Women without childbearing potential	Assumed 100%. Comment: Not sufficiently possible to assess in registry data, especially regarding reliant use of contraception or sexual practice. However, we – instructed patients are likely to comply, e.g. regarding contraceptive measures, thus assumed to be 100% for this study.	-

DIGIT-HF trial	Observational study	Definition / Comment	Variable label (SHFDB5)
Exclusion criteria			
Recent (<2 months ago): myocardial infarction, coronary revascularisation, surgery or catheter intervention for valvular heart disease, acute coronary syndrome, stroke or cerebral ischaemia, or start of HF device therapy potentially improving EF or HF symptoms (e.g. CRT, CCM, baroreflex-activation therapy)	a) AMI in prior 60 days OR b) CABG in prior 60 days OR c) PCI in prior 60 days OR d) Valve intervention / surgery in prior 60 days OR e) Stroke or TIA in prior 60 days OR f) CRT implantation in prior 60 days	a) NPR: ICD-10-SE codes I21 or I22 (setting: in-patients; position: all diagnoses; timeframe: -60 – 0 days). b) NPR: OPS codes FNA, FNB, FNC, FND, or FNE (setting: in-patients; timeframe: -60 – 0 days). c) NPR: OPS codes DF009, DF019, DF020, FNG02, FNG05, or FNG22 (setting: in- and out-patients; timeframe: -60 – 0 days). d) NPR: OPS codes FG, FJE, FJF, FC, or FM (setting: in-patients; timeframe: -60 – 0 days) e) NPR: ICD-10-SE codes I60-4, I69.0-4, or G45 (setting: in-patients; position: all diagnoses; timeframe: -60 – 0 days). f) NPR: OPS codes FPE26 or FPG36 (setting: in- and out-patients; timeframe: -60 - 0 days)	a) new variable: sos_com_ami2 b) new variable: sos_com_cabg3 c) new variable: sos_com_pci3 d) new variable: sos_com_valve2 e) new variable: sos_com_stroketia2 f) new variable: sos_com_crt2
Scheduled surgery or catheter intervention for valvular heart disease, scheduled coronary revascularisation, or scheduled HF device therapy potentially improving EF or HF symptoms (e.g.	Scheduled cardiac surgery or intervention in the near future	Assumed 0%. Comment: Not possible to assess in the registries without using future information and thus introducing bias.	-

DIGIT-HF trial	Observational study	Definition / Comment	Variable label (SHFDB5)
CRT, CCM, baroreflex-activation therapy)			
Active myocarditis	Acute myocarditis	NPR: ICD-10-SE code I40 (setting: in- and out-patients; position: all diagnoses; timeframe: -90 – 0 days)	new variable: sos_com_myocarditis
Complex congenital heart disease; this does not include: mild to moderate valve disease, uncomplicated shunts (isolated patent foramen ovale, small atrial or ventricular septum defects without associated lesions), repaired secundum or sinus venosus atrial septal defects or ventricular septal defects without residua, previously ligated or occluded ductus arteriosus	Congenital cardiac malformations	NPR: ICD-10-SE codes Q20-26 (setting: in- and out-patients; position: all diagnoses; timeframe: -infinite – 0 years)	new variable: sos_com_congenital
High-urgency listing for heart transplantation or scheduled therapy with left ventricular assist device	a) Heart transplant waiting list OR b) Scheduled therapy with left ventricular assist device	Both assumed 0%. Comment: Identification of patients on transplant waiting lists is not feasible in the registry data. The same is true for scheduled surgery without using future data and thus introducing bias.	-
Heart rate <60 bpm (except if functional CRT in place)	Heart rate <60 bpm (except if functional CRT in place)	Collected in the SwedeHF CRF at index registration (if in-patient visit: at discharge if available, otherwise at admission).	shf_heartrate, shf_device
SA-/AV-block >I°, sick sinus syndrome, or carotid sinus syndrome (except if pacemaker protected)	a) AV-block >I°, sick sinus syndrome incl. SA-block, or idiopathic peripheral autonomic neuropathy incl.	a) NPR: ICD-10-SE codes I44.1-2, I49.5, or G90.0 (setting: in- and out-patients; position: all diagnoses; timeframe: -1,826 – 0 days)	a) new variable: sos_com_avblock2 b) shf_device

DIGIT-HF trial	Observational study	Definition / Comment	Variable label (SHFDB5)
	carotid sinus syndrome (except if pacemaker protected) b) unless an ICD or CRT-D implanted	b) Collected in the SwedeHF CRF at index registration.	
Proven or suspected accessory atrio-ventricular pathways (e.g. WPW syndrome)	Pre-excitation syndrome	NPR: ICD-10-SE code I45.6 (setting: in- and out-patients; position: all diagnoses; timeframe: -1,826 – 0 days)	new variable: sos_com_preexcitation
History of symptomatic or sustained (≥30 s) ventricular arrhythmia unless an ICD implanted	a) History of symptomatic or sustained (≥30 s) ventricular arrhythmia b) unless an ICD or CRT-D implanted	a) NPR: ICD-10-SE codes I47.2 or I49.0 (setting: in- and out-patients; position: all diagnoses; timeframe: -1,826 – 0 days) b) Collected in the SwedeHF CRF at index registration. Comment: Symptom burden and duration cannot be assessed in the registries. However, it is unlikely that asymptomatic or very brief episodes would be registered.	a) new variable: sos_com_ventarr b) shf_device
Current ventricular tachycardia or fibrillation (i.e. patients presenting with a running ventricular tachycardia or fibrillation; if ventricular arrhythmias are terminated and an ICD is implanted, inclusion is allowed)	Current ventricular tachycardia or fibrillation unless terminated and an ICD or CRT-D implanted	Assumed 0%. Comment: SwedeHF registrations capture the end of an out-patient visit or the status at discharge from hospitalisation. It is highly unlikely that patients with unresolved arrhythmias of life-threatening nature would be discharged and not implanted an ICD.	-
Hypertrophic-obstructive cardiomyopathy	Hypertrophic-obstructive cardiomyopathy	NPR: ICD-10-SE code I42.1 (setting: in- and out-patients; position: all diagnoses; timeframe: -1,826 – 0 days)	new variable: sos_com_hocardiomyopathy
Cor pulmonale	Cor pulmonale	Assumed 0%.	-

DIGIT-HF trial	Observational study	Definition / Comment	Variable label (SHFDB5)
		Comment: Not possible to assess within the registries but overall expected low prevalence.	
Constrictive pericarditis	Chronic constrictive pericarditis	NPR: ICD-10-SE I31.1 (setting: in- and out-patients; position: all diagnoses; timeframe: -1,826 – 0 days) Comment: Patients with constrictive pericarditis more than 5 years ago are likely not to get respective codes in the NPR anymore thereafter if they received surgical treatment. However, within the 5-year timeframe, all patients with the diagnosis are considered ineligible.	new variable: sos_com_pericarditis
Thoracic aortic aneurysm (defined as diameter ≥45 mm)	Thoracic aortic aneurysm (defined as diameter ≥45 mm)	Assumed 0%. Comment: The diameter cannot be assessed in the registries. Without the diameter restriction, this criterion would exclude patients with a registered aneurysm of 40-44 mm as well. We thus decide to assume 0% prevalence.	-
Severe liver disease	Liver cirrhosis	NPR: ICD-10-SE codes I85, I86.4, I98.2, K70.3-4, K71.7, K72.1, K74.6, or K76.6-7 (setting: in- and out-patients; position: main diagnosis; timeframe: -1,826 – 0 days)	new variable: sos_com_livercirrhosis
Severe renal disease	a) Serum creatinine ≥3.0 mg/dl (independent of eGFR) OR	a) Collected in the SwedeHF CRF at index registration. b) NPR: ICD-10-SE Z49 or Z99.2 or OPS codes DR012-014, DR016, DR024, DR055-056,	a) shf_crea b) new variable: sos_com_dialysis2

DIGIT-HF trial	Observational study	Definition / Comment	Variable label (SHFDB5)
	b) Current dialysis	DR060-061, or TJA33 (setting: in- and out-patients; position: all diagnoses; timeframe: -365 – 0 days)	
Persistent hypokalaemia (<3.2 mmol/l)	Potassium <3.2 mmol/l	Collected in the SwedeHF CRF at index registration.	shf_potassium
Hypercalcaemia or hypomagnesaemia, if clinically suspected and verified by laboratory testing (e. g. hyperparathyroidism, neoplasia-induced hypercalcaemia, signs of neuromuscular hyperexcitability)	Hypercalcaemia or hypomagnesaemia	Assumed 0%. Comment: Electrolyte disturbances can only be assessed for potassium and sodium in the registries. However, hypercalcaemia or hypomagnesaemia are likely rare and can often easily be corrected, resulting in later eligibility.	-
Present (within 6 weeks before baseline/day 0 visit) and continuous treatment with amiodarone. Single or short-term (up to 3 days) not continuous administration of amiodarone immediately before or during study treatment are acceptable	Amiodarone in prior 120 days	NPDR: ATC code C01BD01 (ApoDos included; timeframe: -120 – 0 days) Comment: To account for stockpiling, lookback in the registry has to be increased to 120 days.	new variable: sos_lm_amiodarone
Scheduled direct current cardioversion in the next 24h (e.g. patients not on cardiac glycosides with new onset of atrial fibrillation).	Scheduled cardioversion	Assumed 0%. Comment: Scheduled procedures cannot be assessed in the registries without using future data, which would introduce bias. In addition, as SwedeHF registrations capture the end of an out-patient visit or the status at discharge from hospitalisation, indicated cardioversions are likely to have already been performed and less likely to still be planned for the next day.	-

DIGIT-HF trial	Observational study	Definition / Comment	Variable label (SHFDB5)
Presence of both treatment with cardiac glycosides and AFib	a) Prior digoxin treatment AND b) Atrial fibrillation or flutter	a) NPDR: ATC code C01AA05 (ApoDos included; timeframe: -120 – -1 days) b) Diagnosis in SwedeHF or NPR. NPR: ICD-10-SE code I48 (setting: in- and out-patients; position: all diagnoses; timeframe: -1,826 – 0 days). SwedeHF: physician-based diagnosis at index registration or in latest ECG at the time of the index registration (but not necessarily during index).	a) new variable: sos_lm_digoxin b) shf_sos_com_af
Simultaneous intravenous treatment with calcium salts	Intravenous treatment with calcium salts	Assumed 0%. Comment: SwedeHF registrations capture the end of an out-patient visit or the status at discharge from hospitalisation. As intravenous calcium is almost exclusively administered in hospitalised patients, the prevalence at this timepoint can be assumed to be 0%.	-
Evidence of cardiac glycosides intolerance or known hypersensitivity to any component of investigational drug	Allergy or intolerance against cardiac glycosides	Assumed 0%. Reasoning: Allergies against cardiac glycosides are rare and other intolerances usually rather subjective. In addition, this information cannot be retrieved from the registries.	-
Suspected intoxication with cardiac glycosides	Suspected intoxication with cardiac glycosides	Assumed 0%.	-

DIGIT-HF trial	Observational study	Definition / Comment	Variable label (SHFDB5)
		Comment: This information cannot be retrieved from the registries. However, since only current intoxication is relevant, these patients become eligible as soon as the intoxication is resolved. We can thus assume that 0% of patients would be permanently ineligible based on this criterion.	
Unlikely compliance with protocol requirements	Any condition which may reduce adherence	NPR: ICD-10-SE codes F01-7, F09-16, F18-25, or F28-30 (setting: in- and out-patients; position: all diagnoses; timeframe: -365 – 0 days) Comment: 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.	new variable: sos_com_redadhere
Pregnant and lactating women	Pregnant or lactating women	Assumed 0%. Reasoning: Data not available; the expected prevalence is very low, however.	-
Use of other investigational drugs or devices at the time of enrolment or within 30 days prior to enrolment or 5 half-lives for investigational drugs, whichever is longer	Current participation in any other therapeutic trial	Assumed 0%. Reasoning: Data not available; the expected prevalence is very low, however.	-
Life expectancy <12 months (e.g. due to active cancer)	Diagnosis of malignancies (exception: basal-cell	NPR: ICD-10-SE code C (malignant tumours without in-situ) BUT NOT C44 (non-	new variable: sos_com_cancer

DIGIT-HF trial	Observational study	Definition / Comment	Variable label (SHFDB5)
	carcinoma, squamous-cell carcinoma or carcinoma-in-situ, localised prostate cancer) in prior 5 years or still ongoing	melanoma malignant skin cancers) AND NOT C61.9 in the absence of any other C code (localised prostate cancer) (setting: in- and out-patients; position: main diagnosis; timeframe: -1,826 – 0 days). Comment: C61.9 with any other C code is likely to capture metastasised prostate cancer and is thus included in this variable.	

Eligibility is assessed based on the imputed data (exception: patients with missing information on EF will be excluded). **Abbreviations**: ACEi, angiotensin-converting enzyme inhibitor; 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; ATC, anatomic therapeutical drug classification; AV, atrio-ventricular; bpm, beats per minute; CABG, coronary artery bypass graft; CCM, cardiac contractility modulation; CRF, case report form; CRT (-D), cardiac resynchronisation therapy (with a defibrillator); EF, ejection fraction; ESC, European Society of Cardiology; HF, heart failure; HFmrEF, heart failure with mildly reduced 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; MRA, mineralocorticoid receptor antagonist; NPDR, National Prescribed Drug Register; NPR, National Patient Register; NYHA, New York Heart Association classification; OPS, classification for the encoding of operations, procedures and general medical measures; PCI, percutaneous coronary intervention; SA, sino-atrial; SHFDB5, Swedish Heart Failure Registry, database version 5; SwedeHF, Swedish Heart Failure Registry; TIA, transient ischaemic attack; WPW syndrome, Wolff-Parkinson-White syndrome.

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