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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Study Ongoing

Administrative details

EU PAS number

EUPAS1000001109

Study ID

1000001109

DARWIN EU® study

No

Study countries

France

Sweden

Study description

Digoxin may be considered to reduce hospitalisations in patients with heart failure with reduced ejection fraction (HFrEF) and sinus rhythm according to ESC guidelines, based primarily on secondary outcomes of the 1997 DIG trial, whose neutral primary outcome was all-cause mortality. The recently published DIGIT-HF trial demonstrated that the pharmacologically similar agent digitoxin significantly reduced the risk of all-cause mortality or HF hospitalisation. This has renewed interest in both cardiac glycosides, and digoxin is currently being investigated at low doses in patients with HFrEF or HF with mildly reduced ejection fraction, irrespective of heart rhythm, in the DECISION trial.

This study contextualises evidence on cardiac glycosides in a contemporary Swedish real-world HF population. Aim 1: to estimate the effectiveness and safety of digoxin versus standard of care without digoxin by transporting the causal effect estimated in DIG individual patient data to the SwedeHF population in sinus rhythm, combined with a target trial emulation in patients with atrial fibrillation/flutter; both analyses are merged into a single enriched treatment effect. Aim 2: to estimate the effectiveness and safety of digitoxin versus standard of care by transporting the causal effect estimated in DIGIT-HF individual patient data to a DIGIT-HF-eligible SwedeHF population.

Data sources comprise the SwedeHF registry (index registrations 2017–2024), linked to the LISA database, the National Patient Register, the National Prescribed Drug Register, and the Cause of Death Register. The primary outcome is the risk difference of all-cause mortality or first HF hospitalisation at 36 months, estimated using AIPCW-based one-step estimators with cross-fitting. Findings are intended to inform the decision on whether, and which, cardiac glycoside to use in Sweden and comparable countries.

Study status

Ongoing

Research institutions and networks

Institutions

Karolinska Institutet

Sweden

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Institution | Educational Institution

Centre for Research in Epidemiology and Statistics (Paris, France)

Networks

More-EUROPA (Horizon Europe)

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Study timelines

Date when funding contract was signed
Planned: 05/02/2026

Actual: 05/02/2026

Study start date
Planned: 08/04/2026

Actual: 08/04/2026

Data analysis start date
Planned: 07/09/2026

Date of final study report
Planned: 01/03/2027

Sources of funding

- EU institutional research programme
- Other public funding (e.g. hospital or university)

More details on funding

This work is supported by the Horizon Europe programme (project number 101095479 - More-EUROPA). Dr Beer is supported by a grant of the Deutsche Forschungsgemeinschaft (DFG, German Research Foundation; grant number 535014557).

Study protocol

Cardiac glycosides_Study Protocol_2026-09-02.pdf (811.47 KB)

Regulatory

Was the study required by a regulatory body?

No

Is the study required by a Risk Management Plan (RMP)?

Not applicable

Methodological aspects

Study type

Study type list

Study topic:

Human medicinal product

Study type:

Non-interventional study

Scope of the study:

Effectiveness study (incl. comparative)

Safety study (incl. comparative)

Data collection methods:

Secondary use of data

Study design:

Retrospective cohort study transporting causal effects from the DIG & DIGIT-HF trials to a contemporary Swedish HFrEF population, combined with target trial emulation for DIG-eligible patients with atrial fibrillation/flutter, to assess effectiveness and safety of digoxin and digitoxin.

Main study objective:

To estimate the effectiveness and safety of digoxin and digitoxin, versus standard of care without cardiac glycosides, in a contemporary Swedish real-world HFrEF population, by transporting causal treatment effects estimated in the DIG and DIGIT-HF randomised trials to the SwedeHF-based target population.

Specifically:

For digoxin: to estimate the treatment effect in patients meeting DIG trial eligibility criteria, combining (a) a transportability analysis for patients in sinus rhythm, resembling the original DIG trial population, with (b) a target trial emulation for patients with atrial fibrillation/flutter (a population excluded from the original DIG trial). These two components are merged into a single enriched treatment effect estimate.

For digitoxin: to estimate the treatment effect in patients meeting DIGIT-HF trial eligibility criteria by transporting the DIGIT-HF causal effect to the SwedeHF-eligible population, without the need for a separate emulation component, since DIGIT-HF did not restrict enrolment by heart rhythm.

Interventions:
Digoxin study: In the transport population (sinus rhythm), the intervention corresponds to the DIG trial's randomised allocation to digoxin in addition to standard of care, with randomisation and dose titration as described in the original DIG trial. In the emulation population (atrial fibrillation/flutter), the intervention corresponds to the observed clinical decision to initiate or continue digoxin treatment at the SwedeHF index registration, in addition to standard of care.
Digitoxin study: The intervention corresponds to the DIGIT-HF trial's randomised allocation to digitoxin in addition to standard of care, with randomisation and dose titration as described in the original DIGIT-HF trial.

The overarching aim is to synthesise existing randomised evidence on both cardiac glycosides and assess its applicability to present-day Swedish clinical practice, thereby informing the decision on whether, and which, cardiac glycoside should be used in Sweden and comparable healthcare settings.

Study Design

Non-interventional study design
Cohort

Study drug and medical condition

Study drug International non-proprietary name (INN) or common name

DIGOXIN

Anatomical Therapeutic Chemical (ATC) code

(C01AA05) digoxin

digoxin

(C01AA04) digitoxin

digitoxin

Medical condition to be studied

Heart failure with reduced ejection fraction

Population studied

Short description of the study population

The study population comprises two components: (1) individual patient data from two randomised controlled trials, and (2) a contemporary real-world cohort drawn from Swedish national registers, to which the trial-based causal effects are transported.

Trial populations: Individual patient data from the DIG trial (digoxin vs placebo, HFrEF with sinus rhythm, USA/Canada) and the DIGIT-HF trial (digitoxin vs placebo, HFrEF irrespective of heart rhythm, Germany/Austria/Serbia) provide the randomised source populations from which treatment effects are estimated and subsequently transported.

Real-world population: Patients registered in the Swedish Heart Failure Registry (SwedeHF) with at least one registration between 1 January 2017 and 31 December 2024, linked to national Swedish registers (LISA, National Patient

Register, National Prescribed Drug Register, Cause of Death Register). Two eligible subpopulations are derived by applying trial-specific eligibility criteria to SwedeHF, using the earliest qualifying registration as the index date:

Digoxin study: Patients meeting all DIG trial eligibility criteria (HFrEF with EF ≤39%), irrespective of heart rhythm. This population is split into a transport population (sinus rhythm, resembling the original DIG trial) and an emulation population (atrial fibrillation/flutter).
Digitoxin study: Patients meeting all DIGIT-HF trial eligibility criteria (HFrEF, NYHA III–IV with EF ≤39% or NYHA II with EF ≤30%, on evidence-based HF therapy for ≥6 months), irrespective of heart rhythm.

Real-world patients are followed for up to 36 months from index, with censoring at emigration or administrative end of registry data (31 December 2024).

Age groups

- **Adult and elderly population (≥18 years)**
  - Adults (18 to < 65 years)
    - Adults (18 to < 46 years)
    - Adults (46 to < 65 years)
  - Elderly (≥ 65 years)
    - Adults (65 to < 75 years)
    - Adults (75 to < 85 years)
    - Adults (85 years and over)

Study design details

Setting

Persons/place: Adult patients with heart failure with reduced ejection fraction (HFrEF) registered in the Swedish Heart Failure Registry (SwedeHF), a nationwide quality register covering hospital in-patient and specialist out-patient HF care across Sweden, linked to the LISA database, National Patient Register, National Prescribed Drug Register, and Cause of Death Register.

Time period: Patients with at least one SwedeHF registration between 1 January 2017 and 31 December 2024 (administrative censoring). For patients with multiple registrations, eligibility is assessed sequentially from the earliest registration; the first registration meeting all criteria defines the index date. Follow-up extends up to 36 months from index, with censoring at emigration or 31 December 2024.

Selection criteria and treatment-arm split:

Digoxin study: Eligibility criteria derived from the DIG trial (USA/Canada, published 1997), applied to SwedeHF irrespective of heart rhythm (HFrEF, EF ≤39%; key exclusions include recent MI/revascularisation, significant renal/hepatic impairment, active malignancy, reduced adherence). Split by rhythm:

Transport population: sinus rhythm; treatment arms per DIG randomisation (digoxin vs placebo).
Emulation population: atrial fibrillation/flutter; arms per observed clinical decision (digoxin vs no digoxin).

Digitoxin study: Eligibility criteria derived from the DIGIT-HF trial (Germany/Austria/Serbia, published 2025), applied to SwedeHF irrespective of heart rhythm (HFrEF, NYHA III–IV with EF ≤39% or NYHA II with EF ≤30%, on

evidence-based HF therapy ≥6 months; similar exclusions plus amiodarone use, glycoside/AFib combination). Arms per DIGIT-HF randomisation (digitoxin vs placebo); no emulation arm, as digitoxin is unavailable in Sweden.

Comparators

Digoxin study:

Transport population (sinus rhythm): Comparator is the DIG trial's randomised placebo arm in addition to standard of care without digoxin.
Emulation population (atrial fibrillation/flutter): Comparator is the observed clinical decision against initiating or continuing digoxin at index registration, while maintaining standard of care.

Digitoxin study:

Comparator is the DIGIT-HF trial's randomised placebo arm in addition to standard of care.

In all analyses, "standard of care" reflects contemporary Swedish guideline-directed HFrEF background therapy (e.g. beta-blockers, ACEi/ARB/ARNi, MRA, SGLT2i), which may evolve over the study period (2017–2024); this temporal change is addressed via a pre-specified sensitivity analysis stratifying by guideline period (2017–2021 vs 2022–2024, reflecting the introduction of SGLT2i to standard of care).

No active comparator arms are included, as none of the underlying trials compared digoxin or digitoxin against another active cardiac glycoside or alternative HF-specific pharmacotherapy.

Outcomes

Primary outcome: All-cause mortality or first HF hospitalisation (composite, time-to-first-event), assessed as the risk difference (cumulative incidence) at 36 months. Cumulative incidence curves and the 36-month restricted mean survival time difference are also reported. Hazard ratios are avoided due to non-collapsibility and unlikely proportional hazards.

Secondary outcomes (time-to-first-event, risk difference at 36 months): cardiovascular death or HF hospitalisation; all-cause death; cardiovascular death; non-cardiovascular death; HF death; sudden cardiac death; HF hospitalisation; non-HF hospitalisation; cardiovascular hospitalisation; non-cardiovascular hospitalisation; all-cause hospitalisation.

Exploratory outcomes (total number of events): difference in expected cumulative counts at 36 months for all-cause death or HF hospitalisation; HF hospitalisation; all-cause hospitalisation.

Negative control outcome: Cancer hospitalisation (time to first event), assessed only in the digoxin target trial emulation, to detect residual confounding.

Outcome ascertainment: For the transportability components (DIG sinus-rhythm population; full DIGIT-HF population), the treatment effect is estimated from outcomes observed within the respective trial's individual patient data, then transported to the SwedeHF target population using its baseline covariate distribution; SwedeHF itself contributes covariates, not outcomes, to this component. For the target trial emulation component (DIG-eligible patients with atrial fibrillation/flutter), outcomes are ascertained directly from linked Swedish registers (National Patient Register, Cause of Death Register, SwedeHF), harmonised to match trial outcome definitions. All outcomes are assessed over

36 months from index, per ICH E9 estimand specifications.

Data analysis plan

Treatment effects are estimated as risk differences (cumulative incidence) at 36 months, using augmented inverse probability of censoring weighting (AIPCW)-type one-step estimators. For the transportability components (DIG sinus-rhythm population; full DIGIT-HF population), trial-based causal effects are transported to the SwedeHF target population by standardising to its covariate distribution; internal validity is preserved by trial randomisation, while external validity (transportability) relies on the positivity and no-unmeasured-effect-modifier assumptions. For the target trial emulation component (DIG-eligible patients with atrial fibrillation/flutter), confounding is addressed via weighting on estimated propensity and censoring models, with a negative control outcome used to assess residual confounding. The digoxin study's transportability and emulation estimates are combined into a single enriched treatment effect. Nuisance parameters are estimated with flexible/machine-learning models under a cross-fitting scheme to avoid overfitting bias; missing data are handled via multiple imputation. Sensitivity analyses address changes in background HF therapy over time (guideline-period stratification) and prior digoxin use. Subgroup analyses assess treatment-effect heterogeneity across clinical and demographic variables.

Full methodological detail, including formal estimand definitions (ICH E9), diagnostics, and sensitivity analyses, is provided in the attached study protocol.

Data management

ENCePP Seal

The use of the ENCePP Seal has been discontinued since February 2025. The ENCePP Seal fields are retained in the display mode for transparency but are no longer maintained.

Data sources

Data source(s)

Swedish Cause of Death Register

Sweden National Prescribed Drugs Register / Läkemedelsregistret

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Data source(s), other

Swedish Heart Failure Registry (SwedeHF)

Swedish National Patient Register (NPR)

Swedish Longitudinal Integrated Database for Health Insurance and Labour (LISA)

Swedish Total Population Register

DIG (DOI: 10.1056/NEJM19970220336080)

DIGIT-HF (DOI: 10.1056/NEJMoa2415471)

Data sources (types)

Administrative healthcare records (e.g., claims)

Clinical trial

Death registry

Disease registry

Pharmacy dispensing records

Population registry

Use of a Common Data Model (CDM)

CDM mapping

No

Data quality specifications

Check conformance

Yes

Check completeness

Yes

Check stability

Yes

Check logical consistency

Yes

Data characterisation

Data characterisation conducted

Not applicable