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Associations between Cardiac Resynchronization Therapy and Clinical Outcomes According to the Atrial Fibrillation Status in Patients with Heart Failure with Reduced Ejection Fraction

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Title	Associations between Cardiac Resynchronization Therapy and Clinical Outcomes According to the Atrial Fibrillation Status in Patients with Heart Failure with Reduced Ejection Fraction.
Research question & Objectives	To evaluate in a real-world cohort of patients with HFrEF the association between patient characteristics and likelihood of CRT use, as well as between CRT and clinical outcomes, according to the presence or history of AF.
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1. Abstract

Evidence on the effectiveness of cardiac resynchronization therapy (CRT) in patients with heart failure with reduced ejection fraction (HFrEF) and atrial fibrillation (AF) is limited. We aim to evaluate in a real-world cohort of patients with HFrEF the association between patient characteristics and likelihood of CRT use, as well as between CRT and clinical outcomes, according to the presence or history of AF. Patients in the Swedish HF Registry who met the guidelines' recommendation for CRT implantation between 2014 and 2022 were included. Linkage to other Swedish registries is performed to complement these data (Swedish Implantable Cardioverter Defibrillator and Pacemaker [ICD/PM] Registry, Longitudinal Integrated Database for Health Insurance and Labour Market Studies [LISA], National Patient Register [NPR], National Prescribed Drug Register [NPDR], National Cause of Death Register). Multivariable logistic regression analysis, including interaction terms between AF and each covariate, is performed to identify the independent predictors of CRT use. The primary endpoint is the composite of time to first HF hospitalization (HFH) or cardiovascular (CV) mortality. Secondary endpoints are the individual components of the primary endpoint, all-cause mortality, and total number of HFHs. The association between CRT use and clinical outcomes is assessed using Cox or negative binomial regression models with overlap weighting (OW) and multivariable adjustments, including interaction terms between AF and CRT.

2. Amendments and updates

n/a

3. Milestones

The research group has continuous access to the data used for this study. A statistical analysis plan was completed on 25 April 2025. The analyst (Renzo Laborante) gained access to the dataset on 26 April 2025. The statistical analysis plan was formatted according to the HARPER protocol (finalised on 1 August 2025) to provide standardised reporting.

Table 1 Milestones

Milestone	**Date**
Anticipated completion of analyses	5 August 2025
Anticipated submission of manuscript	01 September 2025

4. Rationale and background

What is known about the condition: HF is a major global health burden, associated with significant morbidity and mortality. It affects nearly 64 million individuals worldwide[1]. In recent decades, substantial progress has been achieved in the management of patients with HFrEF through both pharmacological and device-based therapies [2-4]. Among these, CRT represents a cornerstone treatment for HFrEF patients in sinus rhythm with electrical dyssynchrony, despite optimised medical therapy[4]. However, certain patient subgroups, such as those with comorbidities or with AF, are often underrepresented or excluded from randomized controlled trials evaluating CRT, leaving its effectiveness in these populations uncertain[5]. A major determinant of the success of CRT is the effective delivery of biventricular pacing. Patho-physiologically, the presence of AF may attenuate the response to CRT through a combination of reduced biventricular pacing and loss of atrioventricular synchrony [6].

What is known about the exposure of interest: CRT clearly improves symptoms and reduces morbidity and mortality, compared with medical therapy or ICD alone, in HFrEF patients with sinus rhythm and prolonged QRS duration (≥130 ms with left bundle branch block [LBBB] or ≥150 ms with non-LBBB morphology)[4].

Gaps in knowledge: Although up to 60% of patients with HFrEF have a history of AF, evidence regarding CRT efficacy in this patient subset remains limited. Major randomized controlled trials often excluded those with AF at the time of randomization or included only a small proportion of patients with a prior history of AF [6,7]. A recent patient-level meta-analysis of randomized clinical trials found no prognostic benefit of CRT in patients with a history of AF. However, the analysis was markedly underpowered due to the limited number of patients with AF included [8]. Similarly, evidence from observational studies is conflicting[9]. Thus, it remains unclear whether advances in pharmacological and interventional management of AF, alongside the development of more effective CRT programming algorithms, have improved the efficacy of CRT in this subset of patients[10].

What is the expected contribution of this study? This study is expected to assess in a real-world cohort of patients with HFrEF the association between patient characteristics and likelihood of CRT use, as well as between CRT and clinical outcomes, according to the presence or history of AF.

Research question and objectives

Table 2 Primary and secondary research questions and objective

A. Primary research questions and objectives

Objective:	To evaluate the association between CRT use and the risk of the composite of cardiovascular death or first HF hospitalization, according to the presence or history of AF.

Hypothesis:	CRT is associated with a lower risk of cardiovascular death or first HF hospitalization, regardless of the presence or history of AF.
Population ***(mention key inclusion-exclusion criteria):***	HFrEF patients enrolled in SwedeHF between 1 January 2014 and 31 August 2022 who are either treated with CRT within 1 year or 30 days after registration in SwedeHF or meet class I or IIa indications for CRT according to the current European HF guidelines (HF duration > 6 months and QRS ≥150 ms) are included. Patients who undergo His ablation prior to or at index time are excluded.
Exposure:	CRT implantation (within 1 year prior to, or up to 30 days after, registration in SwedeHF).
Comparator:	No CRT implantation (prior to or within 30 days after registration in SwedeHF).
Outcome:	Time to cardiovascular death or first HF hospitalisation.
Time ***(when follow up begins and ends):***	Index date (i.e, date of CRT implantation or first registration in SwedeHF for control) with censoring at the earliest of 31 December 2023, emigration from Sweden or at death.
Setting:	The index visit can be both in- and outpatient care settings.
Main measure of effect:	Hazard ratio.

B. Secondary research questions and objectives

Objective:	To evaluate the association between CRT use and the risk of first HF hospitalization, according to the presence or history of AF.
Hypothesis:	CRT is associated with a lower risk of first HF hospitalization, regardless of the presence or history of AF.
Population ***(mention key inclusion-exclusion criteria):***	HFrEF patients enrolled in SwedeHF between 1 January 2014 and 31 August 2022 who are either treated with CRT within 1 year or 30 days after registration in SwedeHF or meet class I or IIa indications for CRT according to the current European HF guidelines (HF duration > 6 months and QRS ≥150 ms) are included. Patients who undergo His ablation prior to or at index time are excluded.

Exposure:	CRT implantation (within 1 year prior to, or up to 30 days after, registration in SwedeHF).
Comparator:	No CRT implantation (prior to or within 30 days after registration in SwedeHF).
Outcome:	Time to first HF hospitalization.
Time ***(when follow up begins and ends):***	Index date (i.e, date of CRT implantation or first registration in SwedeHF for control) with censoring at the earliest of 31 December 2023, emigration from Sweden or at death.
Setting:	The index visit can be both in- and outpatient care settings.
Main measure of effect:	Hazard ratio.

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Objective:	To evaluate the association between CRT use and the risk of cardiovascular death, according to the presence or history of AF.
Hypothesis:	CRT is associated with a lower risk of cardiovascular death, regardless of the presence or history of AF.
Population ***(mention key inclusion-exclusion criteria):***	HFrEF patients enrolled in SwedeHF between 1 January 2014 and 31 August 2022 who are either treated with CRT within 1 year or 30 days after registration in SwedeHF or meet class I or IIa indications for CRT according to the current European HF guidelines (HF duration > 6 months and QRS ≥150 ms) are included. Patients who undergo His ablation prior to or at index time are excluded.
Exposure:	CRT implantation (within 1 year prior to, or up to 30 days after, registration in SwedeHF).
Comparator:	No CRT implantation (prior to or within 30 days after registration in SwedeHF).
Outcome:	Time to cardiovascular death.
Time ***(when follow up begins and ends):***	Index date (i.e, date of CRT implantation or first registration in SwedeHF for control) with censoring at the earliest of 31 December 2023, emigration from Sweden or at death.

Setting:	The index visit can be both in- and outpatient care settings.
Main measure of effect:	Hazard ratio.

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Objective:	To evaluate the association between CRT use and the risk of all-cause death, according to the presence or history of AF.
Hypothesis:	CRT is associated with a lower risk of all-cause death, regardless of the presence or history of AF.
Population ***(mention key inclusion-exclusion criteria):***	HFrEF patients enrolled in SwedeHF between 1 January 2014 and 31 August 2022 who are either treated with CRT within 1 year or 30 days after registration in SwedeHF or meet class I or IIa indications for CRT according to the current European HF guidelines (HF duration > 6 months and QRS ≥150 ms) are included. Patients who undergo His ablation prior to or at index time are excluded.
Exposure:	CRT implantation (within 1 year prior to, or up to 30 days after, registration in SwedeHF).
Comparator:	No CRT implantation (prior to or within 30 days after registration in SwedeHF).
Outcome:	Time to all-cause death
Time ***(when follow up begins and ends):***	Index date (i.e, date of CRT implantation or first registration in SwedeHF for control) with censoring at the earliest of 31 December 2023, emigration from Sweden or at death.
Setting:	The index visit can be both in- and outpatient care settings.
Main measure of effect:	Hazard ratio

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Objective:	To evaluate the association between CRT use and the risk of total HF hospitalizations, according to the presence or history of AF.
Hypothesis:	CRT is associated with a lower risk of total HF hospitalizations, regardless of the presence or history of AF.

Population ***(mention key inclusion-exclusion criteria):***	HFrEF patients enrolled in SwedeHF between 1 January 2014 and 31 August 2022 who are either treated with CRT within 1 year or 30 days after registration in SwedeHF or meet class I or IIa indications for CRT according to the current European HF guidelines (HF duration > 6 months and QRS ≥150 ms) are included. Patients who undergo His ablation prior to or at index time are excluded.
Exposure:	CRT implantation (within 1 year prior to, or up to 30 days after, registration in SwedeHF).
Comparator:	No CRT implantation (prior to or within 30 days after registration in SwedeHF).
Outcome:	Total HF hospitalizations
Time ***(when follow up begins and ends):***	Index date (i.e, date of CRT implantation or first registration in SwedeHF for control) with censoring at the earliest of 31 December 2023, emigration from Sweden or at death.
Setting:	The index visit can be both in- and outpatient care settings.
Main measure of effect:	Incidence rate ratio

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Objective:	To evaluate the association between patient characteristics and the likelihood of CRT use, according to the presence or history of AF.
Hypothesis:	AF influences the likelihood of receiving CRT implantation and the associations between other patient characteristics and the likelihood of CRT use.
Exposure:	History of or concomitant AF (present vs absent) and other patient characteristics
Outcome:	CRT use.
Main measure of effect:	Odds ratio for CRT use associated with AF and other patient characteristics, from a multivariable logistic regression model.

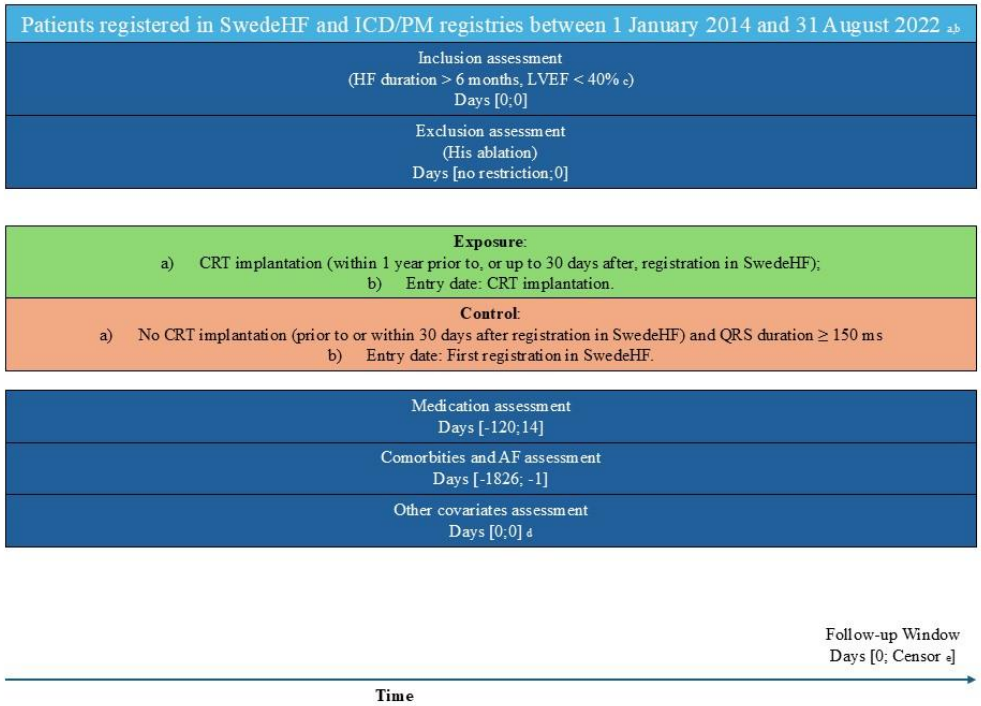
5. Research methods

5.1. Study design

Research design (e.g. cohort, case-control, etc.): observational cohort study

Rationale for study design choice: The necessary real-world high-quality data are readily available within SwedeHF and other national registries with possible linkage by the unique personal identification number of all Swedish inhabitants ("personnummer").

5.2. Study design diagram



[a] 31 August 2022 is the last date available for ICD/PM Registry.

[b] If multiple SwedeHF registrations exist, the registration closest to CRT implantation (i.e., within 1 year after or 30 days before CRT implantation) is selected.

[c] Latest available LVEF on entry date; the measurement may have been performed before, however.

[d] Covariates from LISA refer to the year prior to baseline. Comorbidities derived from ICD-9 are recorded starting from 1987.

[e] Earliest of: death, emigration from Sweden; registry censoring (31 December 2023 for main analyses and 31 August 2022 for cross-over sensitivity analysis).

AF: atrial fibrillation; CRT: cardiac resynchronization therapy; LVEF: left ventricular ejection fraction

5.3. Setting

5.3.1. Context and rationale for definition of time 0 (and other primary time anchors) for entry to the study population

The index date is defined as the date of CRT implantation for the CRT group, to capture the clinical impact of the exposure from its earliest stage. For the control group, the index date corresponds to the date of hospital discharge or outpatient visit that leads to registration in SwedeHF, coinciding with the emergence of the indication for CRT implantation. If multiple SwedeHF registrations are available, the registration occurring closest to the date of CRT implantation is selected, provided it falls within the window of up to 30 days prior to or within 1 year following the implantation, to ensure that baseline characteristics reflect the clinical status at the time of implantation as accurately as possible.

Table 3 Operational Definition of Time 0 (index date) and other primary time anchors

Study population name(s)	**Time Anchor Description (e.g. time 0)**	**Number of entries**	**Type of entry**	**Washout window**	**Care Setting[1]**	**Code Type[2]**	**Diagnosis position**	**Incident with respect to…**	**Measurement characteristics/ validation**	**Source of algorithm**
Study population (HFrEF)	Date of CRT implantation for CRT group and registration in SwedeHF (date of hospital discharge or outpatient visit that prompts the registration) for control group	single entry	incident & prevalent	n/a	IP & OP	ICD-10/ICD-9	HFrEF: main	n/a	n/a	own

[1] IP = inpatient, OP = outpatient, ED = emergency department, OT = other, n/a = not applicable

[2]See appendix for listing of clinical codes for each study parameter

5.3.2. Context and rationale for study inclusion criteria:

Table 4. Operational Definitions of Inclusion Criteria

Criterion	Details	Order of application	Assessment window	Care Settings[1]	Code Type[2]	Diagnosis position[3]	Applied to study populations:	Measurement characteristics/ validation	Source for algorithm
SwedeHF registration	Registration with HF in SwedeHF / until April 2017 physician-judged, since then ICD based	after	[0, 0]	IP & OP	n/a	main	study & control	n/a	n/a
1 January 2014 – 31 August 2022	1 January 2014/ 31 August 2022 is registry censoring for ICD/PM registry	n/a	[0, 0]	IP & OP	n/a	n/a	study & control	n/a	n/a
CRT implantation	Derived from the ICD/PM registry, provided it occurs between 2014 and 2022 and within one year before or up to 30 days after registration in SwedeHF	after	[0, 0]	IP	n/a	n/a	study: presence / control: absence	n/a	own
QRS duration	Derived from SwedeHF; Included if ≥ 150 ms	after	[0, 0]	IP & OP	n/a	n/a	control	n/a	n/a

HF duration	From NPR; inclusion if > 6 months, as surrogate of optimal medical therapy	after	[0, 0]	IP & OP	ICD-10-SE	any	study & control	n/a	n/a

[1] IP = inpatient, OP = outpatient, ED = emergency department, OT = other, n/a = not applicable
[2] See appendix for listing of clinical codes for each study parameter
[3] Specify whether a diagnosis code is required to be in the primary position (main reason for encounter)

5.3.3. Context and rationale for study exclusion criteria

Table 5. Operational Definitions of Exclusion Criteria

Criterion	**Details**	**Order of application**	**Assessment window**	**Care Settings[1]**	**Code Type[2]**	**Diagnosis position[3]**	**Applied to study populations:**	**Measurement characteristics/ validation**	**Source for algorithm**
Left ventricular ejection fraction	exclusion if ≥ 40%	after	[0, 0]	IP & OP	n/a	n/a	study & control	n/a	n/a
His ablation	From NPR (i.e., FPB20, FPB22, FPE00 and FPE20)	after	[no restriction, 0]	IP	ICD-10-SE	any	study & control	n/a	own

[1] IP = inpatient, OP = outpatient, ED = emergency department, OT = other, n/a = not applicable
[2] See appendix for listing of clinical codes for each study parameter
[3] Specify whether a diagnosis code is required to be in the primary position (main reason for encounter)

5.4. Variables

5.4.1. Context and rationale for exposure(s) of interest

CRT clearly improves symptoms and reduces morbidity and mortality, compared with medical therapy or ICD alone, in HFrEF patients with sinus rhythm and prolonged QRS duration (≥130 ms with LBBB or ≥150 ms with non-LBBB morphology)[4]. Although up to 60% of patients with HFrEF have a history of or concomitant AF, evidence regarding CRT efficacy in this patient subset remains limited. Major randomized controlled trials often excluded those with AF at the time of randomization or included only a small proportion of patients with a prior history of AF [6,7].

Algorithm to define duration of exposure effect:

CRT use at the index date is considered long-term treatment, following an intention-to-treat approach. Potential treatment cross-over is addressed by conducting a cross-over sensitivity analysis, excluding patients in the control group who undergone CRT implantation during follow-up.

Table 6. Operational Definitions of Exposure

Exposure group name(s)	Details	Washout window	Assessment Window	Care Setting[1]	Code Type[2]	Diagnosis position[3]	Applied to study populations:	Incident with respect to…	Measurement characteristics/ validation	Source of algorithm
CRT	Derived from the ICD/PM registry, provided it occurs between 2014 and 2022	after	[0, 0]	IP	n/a	n/a	study: presence / control: absence	n/a	n/a	own

	and within one year before or up to 30 days after registration in SwedeHF.									

[1] IP = inpatient, OP = outpatient, ED = emergency department, OT = other, n/a = not applicable
[2] See appendix for listing of clinical codes for each study parameter
[3] Specify whether a diagnosis code is required to be in the primary position (main reason for encounter)

5.4.2. Context and rationale for outcome(s) of interest

The association of CRT with a lower risk of adverse cardiovascular events, regardless of the history of or concomitant AF, is expected based on the aforementioned trials [2,6], advancements in the management of AF, and the development of more effective CRT programming algorithms that may ensure an adequate rate of biventricular capture also in this subset of patients [10].

Table 7. Operational Definitions of Outcome

Outcome name	Details	Primary outcome?	Type of outcome	Washout window	Care Settings[1]	Code Type[2]	Diagnosis Position[3]	Applied to study populations:	Measurement characteristics/ validation	Source of algorithm
Time to first HF hospitalisation	see Appendix	yes	time-to-event	n/a	IP	ICD-10-SE	main	study & control	n/a	own
Time to cardiovascular death	see Appendix	no	time-to-event	n/a	IP & OP	ICD-10-SE	n/a	study & control	n/a	own

Total number of HF hospitalisations	see Appendix	no	count	n/a	IP	ICD-10-SE	main	study & control	n/a	own
Time to all-cause death	see Appendix	no	time-to-event	n/a	IP & OP	ICD-10-SE	n/a	study & control	n/a	own

[1] IP = inpatient, OP = outpatient, ED = emergency department, OT = other, n/a = not applicable
[2] See appendix for listing of clinical codes for each study parameter
[3] Specify whether a diagnosis code is required to be in the primary position (main reason for encounter)

5.4.3. Context and rationale for follow up

Follow-up is defined until the censoring date of the SwedeHF (31 December 2023) to ensure sufficient statistical power. For the cross-over sensitivity analysis, which involves the removal of patients in the control group who receive CRT during follow-up, censoring is applied as of 31 August 2022, corresponding to the censoring date of the ICD/PM registry. Beyond this point, it would not be possible to identify CRT implantations occurring in the control group.

Table 8. Operational Definitions of Follow Up

Follow up start	(day) 1	
Follow up end[1]	Select all that apply	Specify
Date of outcome	no	n/a
Date of death	yes	n/a
End of observation in data	yes	31 December 2023 31 August 2022 (for cross-over sensitivity analysis)
Day X following index date *(specify day)*	no	n/a

End of study period (specify date)	yes	31 December 2023 31 August 2022 (for cross-over sensitivity analysis)
End of exposure *(specify operational details,* *e.g. stockpiling algorithm, grace period)*	no	explantation of CRT is not assessed
Date of add to/switch from exposure *(specify algorithm)*	no	n/a
Other date *(specify)*	yes	day of emigration from Sweden

[1] Follow up ends at the first occurrence of any of the selected criteria that end follow up.

5.4.4. Context and rationale for covariates (confounding variables and effect modifiers, e.g. risk factors, comorbidities, comedications)

To minimise the influence of confounding factors, two different statistical methods are used: multivariate adjustment and calculation of the propensity score (dependent variable: CRT) with overlap weighting (OW). The balance of baseline covariates between CRT users and non-users is assessed using standardised mean differences in the weighted population, with values <10% indicating acceptable balance. Covariates included in the imputation and multiple regression models are labelled with *. In- or out-patient status depends on the status at registration in SwedeHF registry.

Table 9. Operational Definitions of Covariates

Sources of baseline variables.

Variable	Data source	Time period
Exposure		
CRT * and CRT type	ICD & PM Registry	Registration
Baseline characteristics		
Index year*	SwedeHF/ ICD & PM Registry	Registration
Sex*	SwedeHF/ ICD & PM Registry	Registration
Age*	SwedeHF/ ICD & PM Registry	Registration

QRS duration*	SwedeHF	Registration
LBBB*	SwedeHF	Registration
EF*	SwedeHF	Registration
HF duration*	NPR	No time restriction
Follow-up location*	SwedeHF	Registration
Follow-up HF unit*	SwedeHF	Registration
NYHA class*	SwedeHF	Registration
SBP*	SwedeHF	Registration
DAP	SwedeHF	Registration
MAP*	SwedeHF	Registration
HR*	SwedeHF	Registration
eGFR*	SwedeHF	Registration
NT-pro BNP*	SwedeHF	Registration
RASi/ARNI*	NPDR: ATC C09A, C09B, C09C, C09D	Between 4 months before and 14 days after registration
BB*	NPDR: ATC C07	Between 4 months before and 14 days after registration
MRA*	NPDR: ATC C03DA	Between 4 months before and 14 days after registration
Loop diuretic*	NPDR: ATC C03C	Between 4 months before and 14 days after registration
SGLT2i*	NPDR: ATC A10BK, A10BD16, A10BD15, A10BD20, A10BD23, A10BD27, A10BD25, A10BD21, A10BD29, A10BD24	Between 4 months before and 14 days after registration
CCB*	NPDR: ATC C08	Between 4 months before and 14 days after registration
Antiplatelet*	NPDR: ATC B01AC	Between 4 months before and 14 days after registration
Anticoagulant*	NPDR: ATC B01AA, B01AB, B01AE, B01AF, B01AX05	Between 4 months before and 14 days after registration

Insulin*	NPDR: ATC A10A	Between 4 months before and 14 days after registration
Oral antidiabetic*	NPDR: ATC A10B	Between 4 months before and 14 days after registration
Lipid lowering*	NPDR: ATC C10	Between 4 months before and 14 days after registration
Digoxin*	NPDR: ATC C01AA05	Between 4 months before and 14 days after registration
Nitrate*	NPDR: ATC C01DA	Between 4 months before and 14 days after registration
Antiarrhythmic*	NPDR: ATC C01BD01, C01BD07, C01BC04, C01BC03, C07AA07, C01BA03	Between 4 months before and 14 days after registration
ICD (control group)	ICD & PM Registry	Registration
PM (control group)	ICD & PM Registry	Registration
Prior ICD/PM (CRT group)	ICD & PM Registry	Registration
Diabetes*	NPR: ICD-10 E10-4	Within 5 years
AF*	NPR: ICD-9/10 427D, I48 and SwedeHF (electrocardiogram showing AF)	Within 5 years for ICD 10 and since 1987 for ICD 9
AF type	NPR: ICD-9/10 427D	Within 5 years for ICD 10 and since 1987 for ICD 9
Ischemic heart disease*	NPR: ICD-9/10 410-4, I20-5, Z951, Z955 Procedure FNA, FNB, FNC, FND, FNE, FNF, FNH, FNG	Within 5 years for ICD 10 and since 1987 for ICD 9
Hypertension*	NPR: ICD-10 I10-5	Within 5 years
PAD*	NPR: ICD-10 I70-3	Within 5 years
PCI	NPR: Procedure FNG	Within 5 years
CABG	NPR: ICD-9/10 Z951, Z955 Procedure FNA, FNB, FNC, FND, FNE, FNF, FNH	Within 5 years for ICD 10 and since 1987 for ICD 9
Stroke*	NPR: ICD-9/10 430-4, 438, I60-4, I690-4	Within 5 years for ICD 10 and since 1987 for ICD 9
Valvular disease*	NPR: ICD-10 I05-8, I34-9, Q22, Q230-3, Q230-3, Q235-9, Z952-4	Within 5 years

Cancer within 3 years*	NPR: ICD-10 C	Within 3 years
COPD*	NPR: ICD-10 J40-4	Within 5 years
Liver disease*	NPR: ICD-10 B18, I85, I864, I982, K70, K710, K711, K713-7, K72-4, K760, K762-9	Within 5 years
Dementia*	NPR: ICD-10 F00-4, R54	Within 5 years
Bleeding*	NPR: ICD-10 S064, S065, S066, I850, I983, K226, K250, K252, K254, K256, K260, K262, K264, K266, K270, K272, K274, K276, K280, K284, K286, K290, K625, K661, K920, K921, K922, H431, N02, R04, R58, T810, D629 Procedure DR029	Within 5 years
Muscoloskeletal diseases within 3 years*	NPR: ICD-10 M	Within 3 years
Family type*	LISA	From the year before registration
Children*	RTP	From the year before registration
Education*	LISA	From the year before registration
Income*	LISA	From the year before registration

Abbreviations: AF, atrial fibrillation; ARNI, angiotensin receptor/neprilysin inhibitor; ATC, Anatomical Therapeutic Chemical classification; BB, beta-blocker; CABG, coronary artery bypass grafting; CCB, calcium channel blocker; COPD, chronic obstructive pulmonary disease; CRT, cardiac resynchronization therapy; DBP, diastolic blood pressure; EF, ejection fraction; eGFR, estimated glomerular filtration rate; HF, heart failure; HR, heart rate; ICD, implantable cardioverter-defibrillator; ICD-10-SE, International Statistical Classification of Diseases, 10th revision, Swedish version; LBBB, left bundle branch block; LISA, Longitudinal Integrated Database for Health Insurance and Labour Market Studies; MAP, mean arterial pressure; MRA, mineralocorticoid receptor antagonist; NPDR, National Prescribed Drug Register; NPR, National Patient Register; NT-pro BNP, N-terminal pro b-type natriuretic peptide; NYHA, New York Heart Association classification; PAD, peripheral artery disease; PCI, percutaneous coronary intervention; PM, pace-maker; RASi, renin–angiotensin system inhibitor; RTP, Registry of Total Population; SBP, systolic blood pressure; SGLT2i, Sodium-Glucose Transport Protein 2; SwedeHF, Swedish heart failure.

[a] Hospitalizations are derived from diagnoses in main position, in-patient care.

* Covariates included in multiple regression and imputation models.

5.5. Data analysis

5.5.1. Context and rationale for analysis plan

Missing baseline data, but not outcomes, are handled by multiple imputations using chained equations. Multivariable and OW regression models are performed to minimise confounding. Effectiveness outcomes were chosen based on previous trials, expected treatment asssociation on the assessed conditions as well as taking power into account.

Table 10. Primary, secondary, and subgroup analysis specification

A. Primary analysis

Hypothesis:	CRT is associated with a lower risk of cardiovascular death or first HF hospitalization, regardless of the presence or history of AF.
Exposure contrast:	CRT vs. no-CRT (no placebo).
Outcome:	Time to cardiovascular death or first HF hospitalization.
Analytic software:	STATA.
Model(s): ***(provide details or code)***	Multivariable and OW Cox proportional hazards regression models.
Confounding adjustment method	***Name method and provide relevant details, e.g. bivariate, multivariable, propensity score matching (specify matching algorithm ratio and caliper), propensity score weighting (specify weight formula, trimming, truncation), propensity score stratification (specify strata definition), other.***
	Overlap weighting by propensity scores (PS) assigns a weight of 1-PS to treated units and PS to untreated units without the need for trimming/truncation as there cannot be extreme weights. A multivariable and OW Cox proportional hazards regression models are used to evaluate the association between CRT and outcome. An

	interaction term between CRT and AF history or presence is included in the models to assess whether the association between CRT and outcome differs by AF status. The proportional hazards assumption is verified using Schoenfeld residuals.
Missing data methods	***Name method and provide relevant details, e.g. missing indicators, complete case, last value carried forward, multiple imputation (specify model/variables), other.***
	Multiple imputation by chained equations (mi package in STATA), 10 imputed datasets.
Subgroup Analyses	***List all subgroups***
	a) the exposure variable is categorized into three levels (i.e., no-CRT, CRT-P, and CRT-D), with no-CRT serving as the reference category, to independently assess the association of CRT-P and CRT-D with clinical outcomes as compared with no-CRT, including an interaction term between CRT and AF. For this analysis, adjustment for potential confounding is performed using only a multivariable model, as the propensity score is specifically calculated for CRT use defined as a binary variable (CRT vs. no-CRT). b) AF is categorized into four levels (i.e., no-AF, paroxysmal AF, persistent AF, and permanent AF), with no-AF as the reference category, to assess whether the association between CRT use and clinical outcomes varies according to AF subtypes. Patients with AF of unknown type are excluded from this analysis.

B. Secondary Analysis

Hypothesis:	CRT is associated with a lower risk of cardiovascular death, regardless of the presence or history of AF.

Exposure contrast:	CRT vs. no-CRT (no placebo).
Outcome:	Time to cardiovascular death
Analytic software:	STATA.
Model(s): ***(provide details or code)***	Multivariable and OW Cox proportional hazards regression models.
Confounding adjustment method	***Name method and provide relevant details, e.g. bivariate, multivariable, propensity score matching (specify matching algorithm ratio and caliper), propensity score weighting (specify weight formula, trimming, truncation), propensity score stratification (specify strata definition), other.***
	Overlap weighting by propensity scores (PS) assigns a weight of 1-PS to treated units and PS to untreated units without the need for trimming/truncation as there cannot be extreme weights. A multivariable and OW Cox proportional hazards regression models are used to evaluate the association between CRT and outcome. An interaction term between CRT and AF history or presence is included in the models to assess whether the association between CRT and outcome differs by AF status. The proportional hazards assumption is verified using Schoenfeld residuals.
Missing data methods	***Name method and provide relevant details, e.g. missing indicators, complete case, last value carried forward, multiple imputation (specify model/variables), other.***
	Multiple imputation by chained equations (mi package in STATA), 10 imputed datasets.
Subgroup Analyses	***List all subgroups***
	a) the exposure variable is categorized into three levels (i.e., no-CRT, CRT-P, and CRT-D), with no-CRT serving as the reference category, to independently assess the association of CRT-P and CRT-D with clinical outcomes as compared with no-CRT, including an interaction term between CRT and AF. For this analysis,

	adjustment for potential confounding is performed using only a multivariable model, as the propensity score is specifically calculated for CRT use defined as a binary variable (CRT vs. no-CRT). b) AF is categorized into four levels (i.e., no-AF, paroxysmal AF, persistent AF, and permanent AF), with no-AF as the reference category, to assess whether the association between CRT use and clinical outcomes varies according to AF subtypes. Patients with AF of unknown type are excluded from this analysis.

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Hypothesis:	CRT is associated with a lower risk of first HF hospitalization, regardless of the presence or history of AF.
Exposure contrast:	CRT vs. no-CRT (no placebo).
Outcome:	Time to first HF hospitalization
Analytic software:	STATA.
Model(s): ***(provide details or code)***	Multivariable and OW Cox proportional hazards regression models.
Confounding adjustment method	***Name method and provide relevant details, e.g. bivariate, multivariable, propensity score matching (specify matching algorithm ratio and caliper), propensity score weighting (specify weight formula, trimming, truncation), propensity score stratification (specify strata definition), other.***
	Overlap weighting by propensity scores (PS) assigns a weight of 1-PS to treated units and PS to untreated units without the need for trimming/truncation as there cannot be extreme weights. A multivariable and OW Cox proportional hazards regression models are used to evaluate the association between CRT and outcome. An interaction term between CRT and AF history or presence is included in the models to assess whether the association between CRT and outcome differs by AF status. The proportional hazards assumption is verified using Schoenfeld residuals.

Missing data methods	***Name method and provide relevant details, e.g. missing indicators, complete case, last value carried forward, multiple imputation (specify model/variables), other.***
	Multiple imputation by chained equations (mi package in STATA), 10 imputed datasets.
Subgroup Analyses	***List all subgroups***
	a) the exposure variable is categorized into three levels (i.e., no-CRT, CRT-P, and CRT-D), with no-CRT serving as the reference category, to independently assess the association of CRT-P and CRT-D with clinical outcomes as compared with no-CRT, including an interaction term between CRT and AF. For this analysis, adjustment for potential confounding is performed using only a multivariable model, as the propensity score is specifically calculated for CRT use defined as a binary variable (CRT vs. no-CRT). b) AF is categorized into four levels (i.e., no-AF, paroxysmal AF, persistent AF, and permanent AF), with no-AF as the reference category, to assess whether the association between CRT use and clinical outcomes varies according to AF subtypes. Patients with AF of unknown type are excluded from this analysis.

Hypothesis:	CRT is associated with a lower risk of all-cause death, regardless of the presence or history of AF.
Exposure contrast:	CRT vs. no-CRT (no placebo).
Outcome:	Time to all-cause death.
Analytic software:	STATA.
Model(s): ***(provide details or code)***	Multivariable and OW Cox proportional hazards regression models.
Confounding adjustment method	***Name method and provide relevant details, e.g. bivariate, multivariable, propensity score matching (specify matching algorithm ratio and caliper), propensity score weighting (specify weight formula, trimming, truncation), propensity score stratification (specify strata definition), other.***
	Overlap weighting by propensity scores (PS) assigns a weight of 1-PS to treated units and PS to untreated units without the need for trimming/truncation as there cannot be extreme weights. A multivariable and OW Cox proportional hazards regression models are used to evaluate the association between CRT and outcome. An interaction term between CRT and AF history or presence is included in the models to assess whether the association between CRT and outcome differs by AF status. The proportional hazards assumption is verified using Schoenfeld residuals.
Missing data methods	***Name method and provide relevant details, e.g. missing indicators, complete case, last value carried forward, multiple imputation (specify model/variables), other.***
	Multiple imputation by chained equations (mi package in STATA), 10 imputed datasets.
Subgroup Analyses	***List all subgroups***
	a) the exposure variable is categorized into three levels (i.e., no-CRT, CRT-P, and CRT-D), with no-CRT serving as the reference category, to independently assess the association of CRT-P and CRT-D with clinical

	outcomes as compared with no-CRT, including an interaction term between CRT and AF. For this analysis, adjustment for potential confounding is performed using only a multivariable model, as the propensity score is specifically calculated for CRT use defined as a binary variable (CRT vs. no-CRT). b) AF is categorized into four levels (i.e., no-AF, paroxysmal AF, persistent AF, and permanent AF), with no-AF as the reference category, to assess whether the association between CRT use and clinical outcomes varies according to AF subtypes. Patients with AF of unknown type are excluded from this analysis.

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Hypothesis:	CRT is associated with a lower number of total HF hospitalisations.
Exposure contrast:	CRT vs. no-CRT (no placebo).
Outcome:	Total number of HF hospitalizations.
Analytic software:	STATA.
Model(s): ***(provide details or code)***	Negative binomial regression with log of time as offset in the model.
Confounding adjustment method	***Name method and provide relevant details, e.g. bivariate, multivariable, propensity score matching (specify matching algorithm ratio and caliper), propensity score weighting (specify weight formula, trimming, truncation), propensity score stratification (specify strata definition), other.***
	Overlap weighting by propensity scores (PS) assigns a weight of 1-PS to treated units and PS to untreated units without the need for trimming/truncation as there cannot be extreme weights. Multivariable and OW negative binomial regression models are used to estimate incidence rate ratio, including the log of FUP time as an offset. An

	interaction term between CRT and AF history or presence is included in the models to assess whether the association between CRT and outcome differs by AF status.
Missing data methods	***Name method and provide relevant details, e.g. missing indicators, complete case, last value carried forward, multiple imputation (specify model/variables), other.***
	Multiple imputation by chained equations (mi package in STATA), 10 imputed datasets.
Subgroup Analyses	***List all subgroups***
	a) the exposure variable is categorized into three levels (i.e., no-CRT, CRT-P, and CRT-D), with no-CRT serving as the reference category, to independently assess the association of CRT-P and CRT-D with clinical outcomes as compared with no-CRT, including an interaction term between CRT and AF. For this analysis, adjustment for potential confounding is performed using only a multivariable model, as the propensity score is specifically calculated for CRT use defined as a binary variable (CRT vs. no-CRT). b) AF is categorized into four levels (i.e., no-AF, paroxysmal AF, persistent AF, and permanent AF), with no-AF as the reference category, to assess whether the association between CRT use and clinical outcomes varies according to AF subtypes. Patients with AF of unknown type are excluded from this analysis.

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Hypothesis:	History of or concomitant AF influences the likelihood of CRT implantation.
Exposure contrast:	CRT vs. no-CRT (no placebo).
Outcome:	CRT implantation.
Analytic software:	STATA.

Model(s): ***(provide details or code)***	Multivariable logistic regression model.
Confounding adjustment method	***Name method and provide relevant details, e.g. bivariate, multivariable, propensity score matching (specify matching algorithm ratio and caliper), propensity score weighting (specify weight formula, trimming, truncation), propensity score stratification (specify strata definition), other.***
	A multivariable logistic regression model is used to assess the association of each covariate with CRT use, adjusting for potential confounders. An interaction term between AF and other covariates is included to assess if AF modifies the association of each covariate with CRT use.
Missing data methods	***Name method and provide relevant details, e.g. missing indicators, complete case, last value carried forward, multiple imputation (specify model/variables), other.***
	Multiple imputation by chained equations (mi package in STATA), 10 imputed datasets.
Subgroup Analyses	***List all subgroups***
	N.A.

Sensitivity analyses – rationale, strengths and limitations

Two different sensitivity analyses are planned:

a) a cross-over sensitivity analysis, aimed at assessing the association between CRT use and clinical outcomes after excluding patients in the control group who received CRT implantation during follow-up. For this analysis, registry censoring is applied as of 31 August 2022, corresponding to the latest date available in the ICD/PM registry.

b) a contemporary-cohort sensitivity analysis (2017–2022), designed to evaluate the association between CRT use and clinical outcomes in a setting reflecting

current clinical practice, by restricting the analysis to patients enrolled in 2017 or later. This period corresponds to the timeframe following the publication of the 2016 European heart failure guidelines[11].

Falsification analysis

A falsification analysis is run to test the association between CRT use and the composite outcome of time to first hospitalization for trauma or genitourinary tract infection. As such an association would be pathophysiologically implausible, its presence would suggest residual confounding.

5.6. Data sources

5.6.1. Context and rationale for data sources

Reason for selection:

a) Swedish Heart Failure Registry (SwedeHF): quality, coverage, availability and easy linkage to other registries / previous extensive experience with the registry in this research group

b) Longitudinal Integrated Database for Health Insurance and Labour Market Studies (LISA): quality, coverage, availability and easy linkage to other registries / national registry without any adequate alternative

c) National Patient Registry (NPR): quality, coverage, availability and easy linkage to other registries / national registry without any adequate alternative

d) National Prescribed Drug Registry (NPDR): quality, coverage, availability and easy linkage to other registries / national registry without any adequate alternative

e) National Cause of Death Registry (CoD): quality, coverage, availability and easy linkage to other registries / national registry without any adequate alternative

f) Swedish Implantable Cardioverter Defibrillator (ICD)- and Pacemaker- (PM) registry: quality, coverage, availability and easy linkage to other registries / national registry without any adequate alternative

Strengths of data source(s):

a) Swedish Heart Failure Registry (SwedeHF): leading HF registry in Scandinavia with c. 80 registered variables, 59% coverage and linkage to other national registries

b) Longitudinal Integrated Database for Health Insurance and Labour Market Studies (LISA): national registry with near to complete coverage and quality assurance

c) National Patient Registry (NPR): national registry with near to complete coverage, easy linkage to other registries

d) National Prescribed Drug Registry (NPDR): national registry with near to complete coverage, easy linkage to other registries

e) National Cause of Death Registry (CoD): national registry with near to complete coverage, easy linkage to other registries

f) Swedish Implantable Cardioverter Defibrillator (ICD)- and Pacemaker- (PM) registry: national registry with near to complete coverage, easy linkage to other registries

Limitations of data source(s):

a) Swedish Heart Failure Registry (SwedeHF): not full coverage, recruitment in primary care not from the beginning

b) Longitudinal Integrated Database for Health Insurance and Labour Market Studies (LISA): not full coverage of some parameters, especially education in immigrants / yearly updates

c) National Patient Registry (NPR): no data from primary care, causes of hospital admissions reported within routine, not adjudicated

d) National Prescribed Drug Registry (NPDR): prescribed and dispensed drugs, but no information on actual use of medication

e) National Cause of Death Registry (CoD): causes are reported by physicians in death certificates, not adjudicated

f) Swedish Implantable Cardioverter Defibrillator (ICD)- and Pacemaker- (PM) registry: not full coverage of some parameters, variation in code registration across healthcare centers and individual physicians

Data source provenance/curation:

a) Swedish Heart Failure Registry (SwedeHF): Uppsala Clinical Research Center (Uppsala, Sweden)

b) Longitudinal Integrated Database for Health Insurance and Labour Market Studies (LISA): Statistics Sweden

c) National Patient Registry (NPR): National Board of Health and Welfare (Sweden)

d) National Prescribed Drug Registry (NPDR): National Board of Health and Welfare (Sweden)

e) National Cause of Death Registry (CoD): National Board of Health and Welfare (Sweden)

f) Swedish Implantable Cardioverter Defibrillator (ICD)- and Pacemaker- (PM) registry: cardiology clinics performing electronic implantable device procedures in Sweden, overseen by Karolinska University Hospital Solna and coordinated nationally by the Swedish Society of Cardiology

Table 12. Metadata about data sources and software

Data Source(s):	SwedeHF	ICD/PM registry	LISA	NPR	NPDR	CoD
Study Period:	1 January 2014 – 31 August 2022	1 January 2014- 31 August 2022	2013 – 2021	1 January 2009 for ICD-10/ 1	3 September 2013 – 14 September 2022	2 January 2014 – 31 December 2023

				January 1987 for ICD-9– 30 August 2022		
Eligible Cohort Entry Period:	1 January 2014 – 31 August 2022	1 January 2014 – 31 August 2022	1 January 2014 – 31 August 2022	1 January 2014 – 31 August 2022	1 January 2014 – 31 August 2022	1 January 2014 – 31 August 2022
Data Version (or date of last update):	24 April 2025	24 April 2025	24 April 2025	24 April 2025	24 April 2025	24 April 2025
Type(s) of data:	clinical data (focus: HF)	data on implantable electronic device	socioeconomic data	comorbidities	prescribed medication	cause-specific death
Data linkage:	personal identification number	personal identification number	personal identification number	personal identification number	personal identification number	personal identification number
Conversion to CDM*:	no	no	no	no	no	no
Software for data management:	R	R	R	R	R	R

*CDM = Common Data Model

5.7. Data management

Detailed information on data management is provided and updated regularly on GitHub: https://github.com/KIHeartFailure/swedehf-af-crt.

5.8. Quality control

Quality assurance is managed within the respective registries. However, there is known a risk of misclassification of comorbidities within the NPR. To enhance sensitivity in identifying a history of AF, we therefore used a composite definition based on either an electrocardiographic diagnosis recorded in SwedeHF or a diagnostic code from the NPR.

5.9. Study size and feasibility

This retrospective study is based on observational data and a formal study size calculation was not deemed necessary. Inclusion and exclusion criteria are chosen with respect to a careful and clinically meaningful definition of the study population while still achieving a sufficient study size for the analysis.

Table 13. Power and sample size

n/a

6. Limitation of the methods

Our study has limitations that are in need of acknowledgment when interpreting the results. First, as this is an observational study, causality cannot be established. Although extensive adjustments and a falsification analysis are planned, residual confounding cannot be fully ruled out. The classification of AF subtypes should be interpreted with caution, as these categories are not fixed and may change over time, with patients potentially transitioning from one subtype to another during

follow-up [12]. Finally, patients recruited into SwedeHF exhibit a lower comorbidity burden and better outcomes than the broader Swedish HF population [13]. Therefore, the generalizability of our findings to a less selected, more comorbid HF cohort requires validation in further studies.

7. Protection of human subjects

No individual informed consent is necessary for data collection in the national registries and SwedeHF according to Swedish law. However, patients are informed and allowed to opt out. This study was approved by the Swedish Ethical Review Authority (Etikprövningsmyndigheten; study identifier 2021-04326, 2021-06332-02, 2023-05468-02, 2024-02299-02).

8. Reporting of adverse events

n/a

9. Appendices

Definitions and sources of outcome variables.

Outcome	Source
Death (all-cause)	NPR; CDR a
Death (cardiovascular)	CDR: ICD-10 I, J81, K761, R570, G45 a
Hospitalization for HF	NPR: ICD-10 I110, I130, I132, I255, I420, I423, I425, I426, I427, I428, I429, I43, I50, J81, K761, R570 b
Hospitalization for trauma	NPR: ICD-10 S, T0, T10-4[a]
Hospitalization for genito-urinary tract infection	NPR: ICD-10 S, T0, T10-4[a]

Abbreviations: CDR, Cause of Death Registry; ICD-10, International Statistical Classification of Diseases, 10th revision, Swedish version; NPR, National Patient Register.

a Cause of death is derived from the underlying cause of death.
b Hospitalizations are derived from diagnoses in main position, in patient care.

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