JACC: HEART FAILURE VOL. 13, NO. 10, 2025

ORIGINAL RESEARCH

Timing of Cardiac Resynchronization Therapy Following Stable Medical Therapy in Patients With Heart Failure

Alessandro Villaschi, MD,[a,b] Christian Basile, MD,[a,c] Lina Benson, MSc,[a,d] Paolo Gatti, MD, PhD,[d,e] William T. Abraham, MD,[f] Michael Böhm, MD,[g] Biykem Bozkurt, MD, PhD,[h] Javed Butler, MD, MPH MBA,[i,j] Gianluigi Condorelli, MD, PhD,[b,k] Cecilia Linde, MD, PhD,[d] Marco Metra, MD,[l] Wilfried Mullens, MD, PhD,[m,n] Peter Mol, PharmD, PhD,[o] Shelley Zieroth, MD,[p] Raffaele Scorza, MD, PhD,[a] Lars H. Lund, MD, PhD,[d] Fredrik Gadler, MD, PhD,[d] Gianluigi Savarese, MD, PhD[a]

ABSTRACT

BACKGROUND Guidelines' recommendations for cardiac resynchronization therapy (CRT) implantation in selected patients with heart failure (HF) exist. However, data on the best timing for CRT implantation after the achievement of stable medical therapy (SMT) and its association with outcomes are currently lacking.

OBJECTIVES The aim of this study was to investigate the timing of CRT implantation after the achievement of SMT, associated patient profiles, and clinical outcomes in a real-world HF population.

METHODS Patients with HF treated with SMT derived from the Swedish ICD and Pacemaker Registry who received CRT between 2007 and 2020 were included in the study. Patient characteristics associated with a shorter or longer time to CRT implantation were assessed using multivariable logistic regression, and associations between the time from SMT to CRT implantation and clinical outcomes (mortality and morbidity) were analyzed using multivariable Cox regression.

RESULTS Of the 9,409 patients, 43.8% received CRT at <3 months of achieving SMT, 34.9% between 3 and 9 months, and 21.3% after 9 months. The time from SMT to CRT implantation decreased significantly over the study period. Independent determinants of shorter time to implantation included recent HF hospitalization, previous implantation of a defibrillator, and greater use of guideline-directed medical therapy, whereas a history of HF >6 months and ischemic heart disease were associated with a longer time. After adjustments, there was a 9% lower risk of cardiovascular death with a shorter time from SMT to CRT implantation of <3 months vs 3-9 months ($P = 0.045$). A delayed time of >9 months vs 3-9 months was associated with a 13% higher risk of cardiovascular death/HF hospitalization, a 12% higher risk of cardiovascular death ($P = 0.040$), and an 11% higher risk of first HF hospitalization ($P = 0.013$).

CONCLUSIONS Time from the achievement of SMT to CRT implantation decreased over the study period. Delayed CRT implantation beyond 3 months was associated with higher cardiovascular mortality compared with earlier implantation after GDMT optimization. (JACC Heart Fail. 2025;13:102515) © 2025 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

From the [a]Department of Clinical Science and Education, Södersjukhuset, Karolinska Institutet, Stockholm, Sweden; [b]Department of Biomedical Sciences, Humanitas University, Pieve Emanuele, Milan, Italy; [c]Department of Advanced Biomedical Sciences, University of Naples "Federico II", Naples, Italy; [d]Division of Cardiology, Department of Medicine, Karolinska Institutet, Stockholm, Sweden; [e]Internal Medicine Unit, Södertälje Hospital, Södertälje, Sweden; [f]Division of Cardiovascular Medicine, The Ohio State University, Columbus, Ohio, USA; [g]Department of Internal Medicine III, Saarland University, Homburg,

ISSN 2213-1779 https://doi.org/10.1016/j.jchf.2025.102515

ABBREVIATIONS AND ACRONYMS

ARNI = angiotensin receptor neprilysin inhibitor

BB = beta-blocker

CRT = cardiac resynchronization therapy

GDMT = guideline-directed medical therapy

HF = heart failure

HFrEF = heart failure with reduced ejection fraction

ICD = implantable cardiac defibrillator

LVEF = left ventricular ejection fraction

MRA = mineralocorticoid receptor antagonist

OMT = optimal medical therapy

SGLT2 = sodium-glucose cotransporter 2

SMT = stable medical therapy

RASi = renin-angiotensin system inhibitor

Cardiac resynchronization therapy (CRT) has been proven to reduce morbidity and mortality and improve quality of life in selected populations with heart failure with reduced ejection fraction (HFrEF).[1-3] Therefore, CRT has a class I recommendation, level of evidence A, in international guidelines for patients with HFrEF, left bundle branch block, and QRS complex duration ≥150 ms who remain symptomatic despite pharmacological optimal medical therapy (OMT).[3]

Despite the strong guidelines' recommendations, CRT implantation rates remain low in daily clinical practice.[4-6] Delays in referral and implantation may be detrimental, in particular when considering that reverse remodeling induced by guideline-directed medical therapy (GDMT) is limited in patients with a wide QRS complex.[7,8] Early CRT implantation after the diagnosis of left bundle branch block–associated nonischemic cardiomyopathy (ie, <9 months after the diagnosis) was previously reported to be linked with a higher likelihood of left ventricular ejection fraction (LVEF) improvement.[9] CRT implantation in patients with no history of or at their first hospitalization for heart failure (HF) was associated with better outcome as compared with later implantation, suggesting that it should occur as early as possible, when indicated.[10,11]

However, many barriers to implementation still exist.[12,13] Delays in the optimization of GDMT due to either physician inertia or tolerability issues are frequent, which may further delay device implantation, as OMT is expected before device implantation.[14,15] In patients with a CRT indication after the achievement of stable medical therapy (SMT), timely referral should be performed. However, data on the best timing for CRT implantation and its association with outcomes are currently lacking.

The aim of the present study was to describe in patients with HFrEF who received CRT: 1) how the time from the achievement of SMT to CRT implantation has changed over time; 2) which patient profiles were associated with different time from SMT to implantation; 3) HFrEF pharmacological therapy at the time of implantation; and 4) the association between different time from SMT to CRT implantation and mortality/morbidity.

METHODS

DATA SOURCES. The study population was derived from the Swedish ICD and Pacemaker Registry, which has been previously described.[16] Briefly, it is an ongoing nationwide registry enrolling patients from all device implanting centers in Sweden since 1989, with data on implantable cardiac defibrillator (ICD) implantations entered online since 2004. Coverage approximates 95% to 98% of the total pacemaker and ICD implantations (including also CRT). Informed consent for data entry is required.

For the present study, the Swedish ICD and Pacemaker Registry was linked with 1) the Swedish National Prescribed Drug Register, providing data on pharmacological therapy; 2) LISA (Longitudinal Integration Database for Health Insurance and Labour Market Studies) and Total Population Register, providing socioeconomic data; 3) the Swedish NPR (National Patient Register), providing data on comorbidities, previous HF diagnosis, and HF hospitalizations coded using the International Classification of Diseases-10th Revision (ICD-10) (Supplemental Table 1); and 4) the Cause of Death Register, providing information on time/cause of death, through the Swedish personal identification number. The present analysis requiring the linkage of the above-reported registries was approved by the Swedish Ethical Review Authority.

STUDY POPULATION. Patients undergoing first CRT implantation between January 1, 2017, and December

Germany; [h]Department of Cardiology, Baylor College of Medicine, Houston, Texas, USA; [i]Baylor Scott and White Research Institute, Dallas, Texas, USA; [j]Department of Medicine, University of Mississippi, Jackson, Mississippi, USA; [k]IRCCS Humanitas Research Hospital, Rozzano, Milan, Italy; [l]ASST Spedali Civili di Brescia, Department of Medical and Surgical Specialties, Radiological Sciences and Public Health, University of Brescia, Brescia, Italy; [m]Department of Cardiology, Ziekenhuis Oost-Limburg, Genk, Belgium; [n]Biomedical Research Institute, Faculty of Medicine and Life Sciences, LCRC, UHasselt-Hasselt University, Diepenbeek, Belgium; [o]Department of Clinical Pharmacy and Pharmacology, University Medical Center Groningen, University of Groningen, Groningen, the Netherlands; and the [p]Section of Cardiology, Max Rady College of Medicine, University of Manitoba, Winnipeg, Manitoba, Canada.

Akshay Desai, MD, served as acting Editor-in-Chief and main adjudicator for this paper.

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

Manuscript received March 31, 2025; revised manuscript received May 12, 2025, accepted May 14, 2025.

31, 2020, as registered in the Swedish ICD and Pacemaker Registry, with a previous HF diagnosis (ie, at least 1 ICD-10 code for HF in the main position) (Supplemental Table 1) as identified from the Swedish NPR, and currently treated with SMT (definition reported later) were included in the study. The *index date* was defined as the date of CRT implantation. Exclusion criteria were age <18 years, missing data on socioeconomic variables, no GDMT (ie, renin-angiotensin system inhibitors [RASis] or angiotensin receptor neprilysin inhibitors [ARNIs], mineralocorticoid receptor antagonists [MRAs], and beta-blockers [BBs]) dispensation within 4 months before device implantation, or CRT implantation >24 months after SMT.

DEFINITION OF AND TIME FROM SMT TO CRT IMPLANTATION. We considered the following HFrEF GDMT: RASi/ARNI, MRA, and BB. Sodium-glucose cotransporter 2 (SGLT2) inhibitors were not considered part of GDMT because they were not recommended for HF during the study period.[17]

The *date of SMT achievement* was defined as the date of the latest increase in use/dose of one of the HF drugs still dispensed within 4 months before CRT implantation. Time from SMT to CRT implantation was analyzed as a continuous variable and as a 3-level categorical variable: <3, 3-9, and >9 months.

STATISTICAL ANALYSIS. Patient characteristics were compared across the 3 strata of time from SMT achievement to CRT implantation (<3, 3-9, and >9 months) using the Kruskal-Wallis test and reported as median (Q1-Q3) if continuous variables and compared using the chi-square test and reported as number and percentage if categorical variables.

Multivariable logistic regression models were fitted to investigate patient characteristics independently associated with a shorter/longer time to CRT implantation (ie, <3 months vs 3-9 months vs >9 months, with 3-9 months as the reference category); the covariates included in the models are marked with superscript a in **Table 1**. The results are displayed as odds ratios with 95% CIs.

The associations between the time from SMT to CRT implantation and outcomes (ie, a composite of cardiovascular death or first HF hospitalization and its individual components) were investigated using univariable and multivariable (including the variables marked with superscript b in **Table 1** as covariates) Cox proportional hazards regression, where the exposure was separately modeled as a restricted cubic spline (with 3 knots and 3 months as the reference) and as a linear variable. A likelihood ratio test was performed to compare the 2 models and assess the nonlinearity of the spline model. Additional models were performed including time from SMT to CRT implantation as a categorical variable (using 3-9 months as the reference category) rather than a continuous variable, and unadjusted survivor functions were estimated using the Kaplan-Meier method. The results of Cox regression models were reported as HRs and 95% CIs. Consistency of the results across subgroups was assessed by including an interaction term between the time from SMT achievement to CRT implantation (reported as a categorical variable) and the variables defining the subgroups of interest. The proportional hazards assumption was tested via Schoenfeld residuals and was met. Incidence rates per 100 patient-years with 95% CIs were also calculated for each outcome according to the strata of time from SMT to CRT implantation. Time to incident outcome was calculated starting from the index date (ie, day of CRT implantation).

Analyses were censored at death, emigration, 10 years after the index date, or at the end of study follow-up (ie, December 31, 2021), whichever occurred first. In a sensitivity analysis, censoring was performed at 5 rather than 10 years to evaluate the consistency of the associations observed in the main analysis during the earlier period when attrition and competing risks may be lower. There were no missing data in the data set used for this analysis. The 3- to 9-month time period was selected as the reference for the analysis, as it corresponds to the window in which LVEF and CRT indication reassessment, as well as implantation, typically occur in clinical practice. Statistical analyses were performed in Stata 18 (StataCorp LLC), and a 2-sided value of $P < 0.05$ was considered statistically significant.

RESULTS

Of the 12,475 patients with a previous HF diagnosis and first CRT implantation between January 1, 2007, and December 31, 2020, 9,409 fulfilled the selection criteria for this study and were therefore included in the analysis (Supplemental Figure 1).

PATIENT CHARACTERISTICS AT CRT IMPLANTATION, ALSO ACCORDING TO THE TIME FROM SMT ACHIEVEMENT. In the overall population of HF patients undergoing CRT implantation, the median age was 72 years (Q1-Q3: 65-78 years) and 24.1% were female. The median time since HF diagnosis was 31 months (Q1-Q3: 9-96 months), and 26% had already received a pacemaker or ICD before CRT. Double GDMT was prescribed in 39.6% of patients, whereas

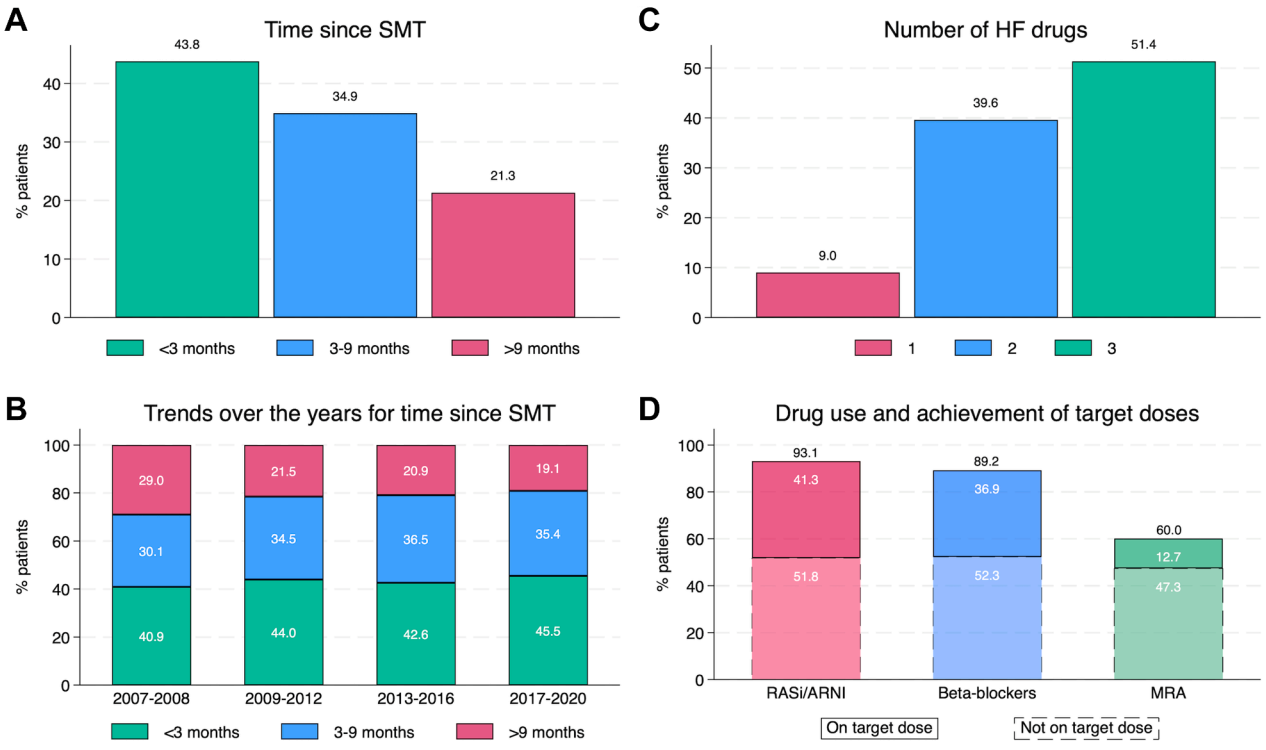
TABLE 1 Baseline Characteristics Stratified by Time From the Achievement of SMT

	<3 mo (n = 4,119, 43.8%)	3-9 mo (n = 3,285, 34.9%)	>9 mo (n = 2,005, 21.3%)	Total (N = 9,409, 100%)	*P* Value
Age, y[a,b]	71 (64-77)	72 (65-78)	73 (65-79)	72 (65-78)	<0.001
Female[a,b]	1,009 (24.5)	795 (24.2)	468 (23.3)	2,272 (24.1)	0.610
Socioeconomic status					
Living alone[a,b]	1,592 (38.7)	1,267 (38.6)	744 (37.1)	3,603 (38.3)	0.467
Children[a,b]	3,529 (85.7)	2,800 (85.2)	1,763 (87.9)	8,092 (86.0)	0.017
Education level[a,b]					0.183
Compulsory school	1,404 (34.1)	1,203 (36.6)	727 (36.3)	3,334 (35.4)	
Secondary school	1,861 (45.2)	1,422 (43.3)	885 (44.1)	4,168 (44.3)	
University	854 (20.7)	660 (20.1)	393 (19.6)	1,907 (20.3)	
Income above median[a,b]	2,146 (52.1)	1,652 (50.3)	940 (46.9)	4,738 (50.4)	<0.001
HF history					
Months since HF diagnosis[a,b]	23.00 (5.49-89.13)	24.77 (8.74-91.46)	51.41 (22.11-113.07)	31.21 (8.64-96.39)	<0.001
Last HFH within 6 mo[a,b]	1,727 (41.9)	931 (28.3)	435 (21.7)	3,093 (32.9)	<0.001
Previous pacemaker[a]	219 (5.3)	192 (5.8)	152 (7.6)	563 (6.0)	0.002
Previous ICD[a]	831 (20.2)	627 (19.1)	427 (21.3)	1,885 (20.0)	0.143
CRT-D[b]	2,305 (56.0)	1,822 (55.5)	984 (49.1)	5,111 (54.3)	<0.001
Year of CRT implantation[a,b]					<0.001
2007-2008	432 (10.5)	318 (9.7)	306 (15.3)	1,056 (11.2)	
2009-2012	1,002 (24.3)	787 (24.0)	490 (24.4)	2,279 (24.2)	
2013-2016	1,159 (28.1)	993 (30.2)	568 (28.3)	2,720 (28.9)	
2017-2020	1,526 (37.0)	1,187 (36.1)	641 (32.0)	3,354 (35.6)	
Months since SMT	1.35 (0.72-2.04)	4.86 (3.71-6.47)	14.42 (11.37-18.56)	3.48 (1.51-7.85)	<0.001
Comorbidities					
Hypertension[a,b]	2,421 (58.8)	2,019 (61.5)	1,227 (61.2)	5,667 (60.2)	0.039
Chronic kidney disease[a,b]	603 (14.6)	557 (17.0)	393 (19.6)	1,553 (16.5)	<0.001
Diabetes mellitus[a,b]	1,228 (29.8)	976 (29.7)	625 (31.2)	2,829 (30.1)	0.475
Valvular heart disease[a,b]	901 (21.9)	729 (22.2)	454 (22.6)	2,084 (22.1)	0.791
Ischemic heart disease[a,b]	2,471 (60.0)	1,995 (60.7)	1,349 (67.3)	5,815 (61.8)	<0.001
Previous MI	1,746 (42.4)	1,355 (41.2)	962 (48.0)	4,063 (43.2)	<0.001
Atrial fibrillation[a,b]	2,018 (49.0)	1,666 (50.7)	1,132 (56.5)	4,816 (51.2)	<0.001
Previous stroke/TIA[a,b]	715 (17.4)	562 (17.1)	404 (20.1)	1,681 (17.9)	0.010
Peripheral artery disease[a,b]	360 (8.7)	312 (9.5)	214 (10.7)	886 (9.4)	0.051
History of cancer[a,b]	523 (12.7)	459 (14.0)	282 (14.1)	1,264 (13.4)	0.180
Liver disease[a,b]	62 (1.5)	77 (2.3)	44 (2.2)	183 (1.9)	0.023
Alcohol abuse[a,b]	99 (2.4)	89 (2.7)	47 (2.3)	235 (2.5)	0.622
Dementia[a,b]	22 (0.5)	15 (0.5)	10 (0.5)	47 (0.5)	0.895
Depressive disorder[a,b]	152 (3.7)	95 (2.9)	76 (3.8)	323 (3.4)	0.106
Drugs					
Number of HF drugs	3 (2-3)	3 (2-3)	2 (2-3)	3 (2-3)	<0.001
Beta-blockers[a,b]	3,742 (90.8)	2,914 (88.7)	1,735 (86.5)	8,391 (89.2)	<0.001
Beta-blocker target dose[c]	1,485 (36.1)	1,207 (36.7)	776 (38.7)	3,468 (36.9)	0.129
RASi[a,b]	3,329 (80.8)	2,708 (82.4)	1,701 (84.8)	7,738 (82.2)	<0.001
ARNI[a,b]	568 (13.8)	340 (10.4)	116 (5.8)	1,024 (10.9)	<0.001
RASi/ARNI target dose[c]	1,656 (40.2)	1,420 (43.2)	806 (40.2)	3,882 (41.3)	0.018
MRA[a,b]	2,677 (65.0)	1,961 (59.7)	1,011 (50.4)	5,649 (60.0)	<0.001
MRA target dose[c]	554 (13.4)	411 (12.5)	229 (11.4)	1,194 (12.7)	0.076
Loop diuretics[a,b]	2,876 (69.8)	2,179 (66.3)	1,337 (66.7)	6,392 (67.9)	0.002
DHP CCB[a,b]	390 (9.5)	240 (7.3)	194 (9.7)	824 (8.8)	0.001
Antiarrhythmic drugs[a,b]	381 (9.2)	283 (8.6)	214 (10.7)	878 (9.3)	0.043
Digoxin[a,b]	650 (15.8)	441 (13.4)	345 (17.2)	1,436 (15.3)	<0.001
Anticoagulant medications[a,b]	2,056 (49.9)	1,579 (48.1)	1,040 (51.9)	4,675 (49.7)	0.025
SGLT2[a,b]	67 (1. 6)	56 (1.7)	22 (1.1)	145 (1.5)	0.184

Values are median (Q1-Q3) or n (%), unless otherwise indicated. [a]Variables included in multivariable logistic regression models for predictors. [b]Variables included in multivariable Cox regression models for survival analysis. [c]Number of patients at the target dose, defined as ≥100% of the recommended target dose; proportions are calculated as the number of patients at the target dose divided by the total number of patients in the subgroup.

ARNI = angiotensin receptor neprilysin inhibitor; CRT = cardiac resynchronization therapy; CRT-D = cardiac resynchronization therapy with defibrillator; DHP CCB = dihydropyridine calcium channel blocker; HF = heart failure; HFH = heart failure hospitalization; ICD = implantable cardiac defibrillator; MI = myocardial infarction; MRA = mineralocorticoid receptor antagonist; RASi = renin-angiotensin system inhibitor; SGLT2 = sodium-glucose cotransporter 2; SMT = stable medical therapy; TIA = transient ischemic attack.

FIGURE 1 Time From SMT to CRT Implantation and GDMT



(A) Overall distribution of the time from SMT to CRT implantation in the entire population. (B) Distribution of the time from SMT to CRT implantation according to the year of implantation. (C) Number of HF drugs at the time of CRT implantation. (D) Proportion of patients receiving each class of GDMT. ARNI = angiotensin receptor neprilysin inhibitor; CRT = cardiac resynchronization therapy; GDMT = guideline-directed medical therapy; HF = heart failure; MRA = mineralocorticoid receptor antagonist; RASi = renin-angiotensin system inhibitor; SMT = stable medical therapy.

51.4% were receiving triple GDMT. RASi/ARNI were prescribed in 93.1%, ARNI in 10.9% (30.4% between 2017 and 2020), and BB and MRA in 89.2% and 60%, respectively. The target dose was achieved in 41.3%, 36.9%, and 12.7% of the study population for RASi/ARNI, BB, and MRA, respectively (**Table 1**, **Figure 1**).

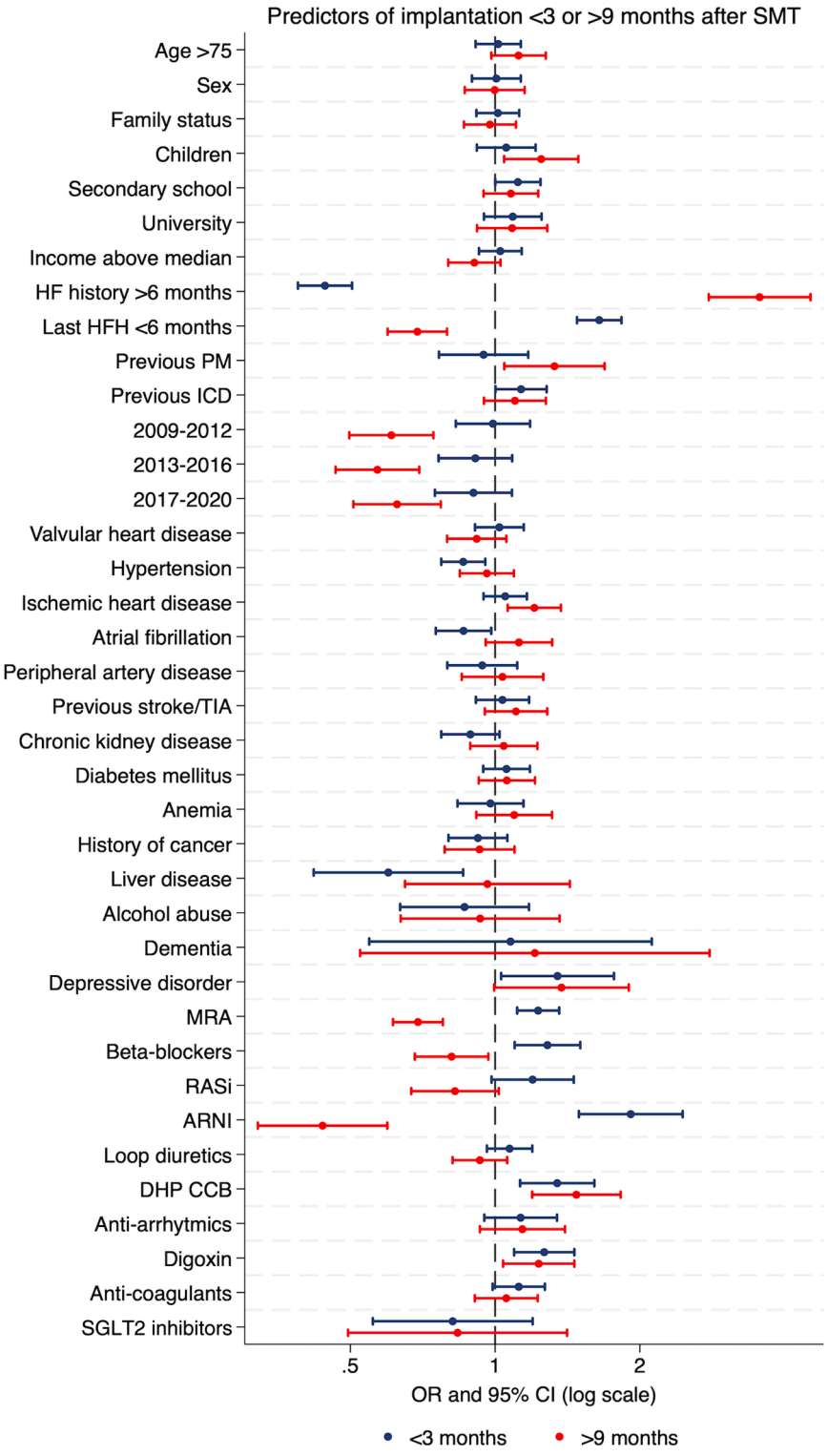
The median time from SMT achievement to CRT implantation was 3.5 months (Q1-Q3: 1.5-7.8 months), and the most recent change in GDMT was an increase in treatment dose in 75.4% of patients. Time from SMT to CRT implantation significantly differed across the study period, being longest in 2007 to 2008 (3.8 months [Q1-Q3: 1.6-10.9 months]) and shortest in 2017 to 2020 (3.3 months [Q1-Q3: 1.4-7.0 months]) (**Figure 1**, Supplemental Table 2); 43.8% of patients received CRT at <3 months, 34.9% 3-9 months, and 21.3% >9 months after achieving SMT.

Patients receiving later CRT implantation (>9 months vs 3-9 months) after SMT achievement were older, had a longer HF history, and were less likely to be hospitalized for HF in the 6 months before CRT implantation. Ischemic heart disease, atrial fibrillation, previous stroke or transient ischemic attack, and chronic kidney disease were more prevalent in this group; the use of HF drugs was less, although the use of digoxin and loop diuretic agents was more likely. Conversely, patients receiving earlier CRT implantation (<3 months vs 3-9 months) were younger, more likely to be hospitalized for HF in the 6 months before implantation, and had an overall lower comorbidity burden. They were receiving more GDMT with higher doses, but they were also slightly more likely to be taking loop diuretic agents and digoxin than patients in the 3- to 9-month group.

PATIENT PROFILES ASSOCIATED WITH EARLIER/LATER CRT IMPLANTATION AFTER SMT ACHIEVEMENT. Overall, more recent (in 2009-2020) vs earlier CRT implantation was associated with a shorter time from SMT achievement to the actual device implantation (**Figure 2**, Supplemental Table 3).

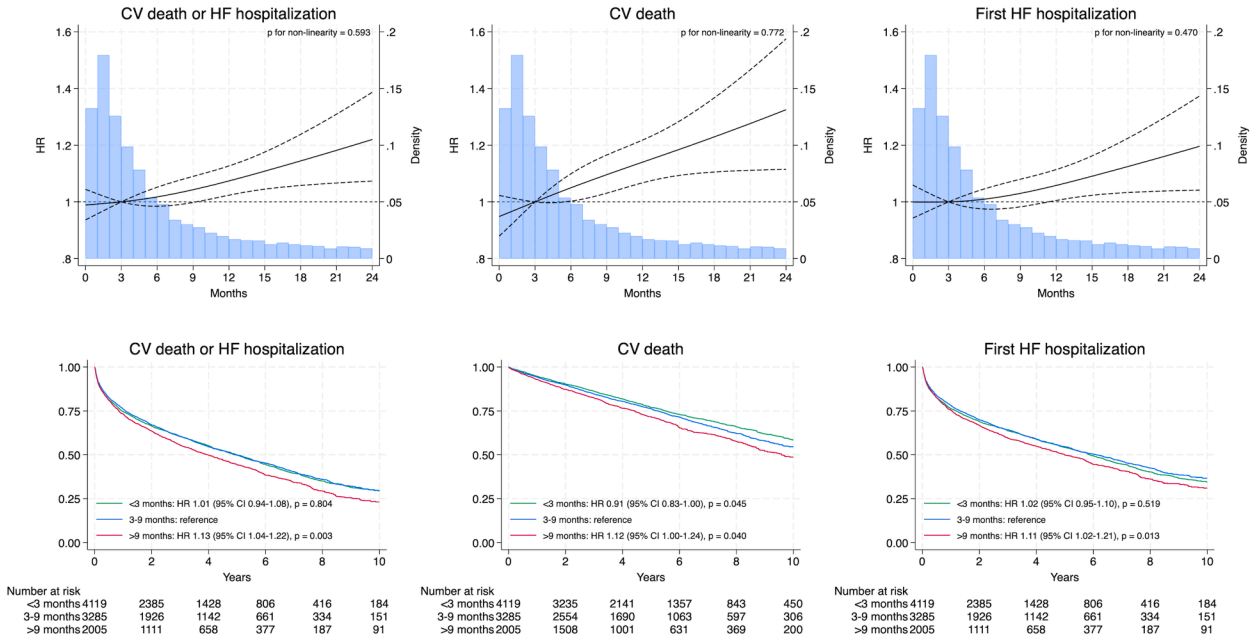
Key patient characteristics independently associated with a shorter time from SMT to CRT implantation (<3 months vs 3-9 months) were having an

FIGURE 2 **Patient Characteristics Independently Associated With the Time From SMT to CRT Implantation**



Adjusted ORs and 95% CIs are calculated using 3-9 months as the reference category. DHP CCB = dihydropyridine calcium channel blocker; HFH = heart failure hospitalization; ICD = implantable cardiac defibrillator; PM = pacemaker; SGLT2 = sodium-glucose cotransporter 2; TIA = transient ischemic attack; other abbreviations as in Figure 1.

FIGURE 3 **Associations Between the Time From SMT to CRT Implantation and Outcomes**



The *P* value for nonlinearity is derived from a likelihood ratio test comparing the spline model with the linear model. HRs are adjusted for variables marked with superscript b in Table 1 and are calculated using 3-9 months as the reference category. CV = cardiovascular; other abbreviations as in Figure 1.

ICD, higher education level, and no history of hypertension, atrial fibrillation, or liver disease. HF duration ≤6 months, HF hospitalization in the previous 6 months, and treatment with MRA, BB, or ARNI were also linked with earlier implantation (<3 months vs 3-9 months vs >9 months).

In contrast, having a pacemaker and a history of ischemic heart disease were independently associated with a longer time from SMT achievement to CRT implantation (>9 months vs 3-9 months).

ASSOCIATIONS BETWEEN THE TIME FROM SMT TO CRT IMPLANTATION AND. Over a median follow-up of 5.5 years (Q1-Q3: 3.0-8.5 years), there was a crude and independent linear relationship between increasing time from SMT to CRT implantation and a higher risk of the composite of cardiovascular death or HF hospitalization (HR: 1.011; 95% CI: 1.006-1.016; $P < 0.001$). The same applied to cardiovascular death (HR: 1.020; 95% CI: 1.013-1.026; $P < 0.001$) and HF hospitalization separately (HR: 1.008; 95% CI: 1.003-1.014; $P = 0.001$), with no significant difference between spline and linear models ($P > 0.05$ for all tests of nonlinearity) outcomes (Figure 3, Table 2, Supplemental Figure 2, Supplemental Table 4).

However, when assessing time from SMT to CRT implantation as a categorical variable, crude risks of the composite of cardiovascular death or HF hospitalization and HF hospitalization alone were similar with a time from SMT achievement to CRT implantation of <3 or 3-9 months, whereas they were significantly higher with a time of >9 months. The unadjusted risk of cardiovascular death was significantly higher with a time from SMT achievement to CRT implantation of <3 months compared with 3-9 months and >9 months. After multivariable adjustments, the results were consistent, with a 9% lower risk of cardiovascular death with a time from SMT to CRT implantation of <3 months compared with 3-9 months (adjusted HR: 0.91 [95% CI: 0.83-1.00]; $P = 0.045$) and a 13% higher risk of cardiovascular death/HF hospitalization (adjusted HR: 1.13 [95% CI: 1.04-1.22]; $P = 0.003$), a 12% higher risk of cardiovascular death (adjusted HR: 1.12 [95% CI: 1.00-1.24]; $P = 0.040$), and an 11% higher risk of first HF hospitalization (adjusted HR: 1.11 [95% CI: 1.02-1.21]; $P = 0.013$) with a time of >9 months compared with 3-9 months.

SENSITIVITY AND SUBGROUP ANALYSES. When follow-up was censored at 5 years, the results were consistent except for similar crude and adjusted risks of cardiovascular death with a time from SMT to CRT

TABLE 2 Results of Cox Proportional Hazards Regression Models Investigating the Association Between the Time From SMT to CRT Implantation and Clinical Outcomes

	Univariable			Multivariable		
	HR	95% CI	*P* Value	HR	95% CI	*P* Value
Linear model						
HF hospitalization or CV death	1.011	1.006-1.016	**<0.001**	1.009	1.004-1.014	**0.001**
CV death	1.020	1.013-1.026	**<0.001**	1.014	1.007-1.021	**<0.001**
First HF hospitalization	1.008	1.003-1.014	**0.001**	1.007	1.002-1.012	**0.009**
<3 mo vs 3-9 mo						
HF hospitalization or CV death	1.02	0.95-1.08	0.628	1.01	0.94-1.08	0.804
CV death	0.90	0.82-0.98	**0.021**	0.91	0.83-1.00	**0.045**
First HF hospitalization	1.04	0.97-1.11	0.283	1.02	0.95-1.10	0.519
>9 mo vs 3-9 mo						
HF hospitalization or CV death	1.17	1.09-1.26	**<0.001**	1.13	1.04-1.22	**0.003**
CV death	1.20	1.08-1.32	**0.001**	1.12	1.00-1.24	**0.040**
First HF hospitalization	1.15	1.06-1.25	**0.001**	1.11	1.02-1.21	**0.013**

HRs and 95% CIs are displayed for 1-month increase for the linear model. **Bold** indicates $P < 0.05$.
CV = cardiovascular; other abbreviations as in Table 1.

implantation of <3 and 3-9 months (Supplemental Table 5, Supplemental Figure 3).

The results were consistent for all the outcomes across all the tested subgroups, including history of atrial fibrillation, sex, ischemic heart disease, and different GDMT regimens (Supplemental Tables 6 to 8, Supplemental Figure 4).

DISCUSSION

This is the first study evaluating time from the achievement of SMT, probably reflecting maximum tolerated medical treatment, to CRT implantation and patient profiles linked with a shorter or longer time to implantation, as well as analyzing clinical outcomes in patients receiving earlier vs later implantation, using data from a large population with HF from a nationwide registry.

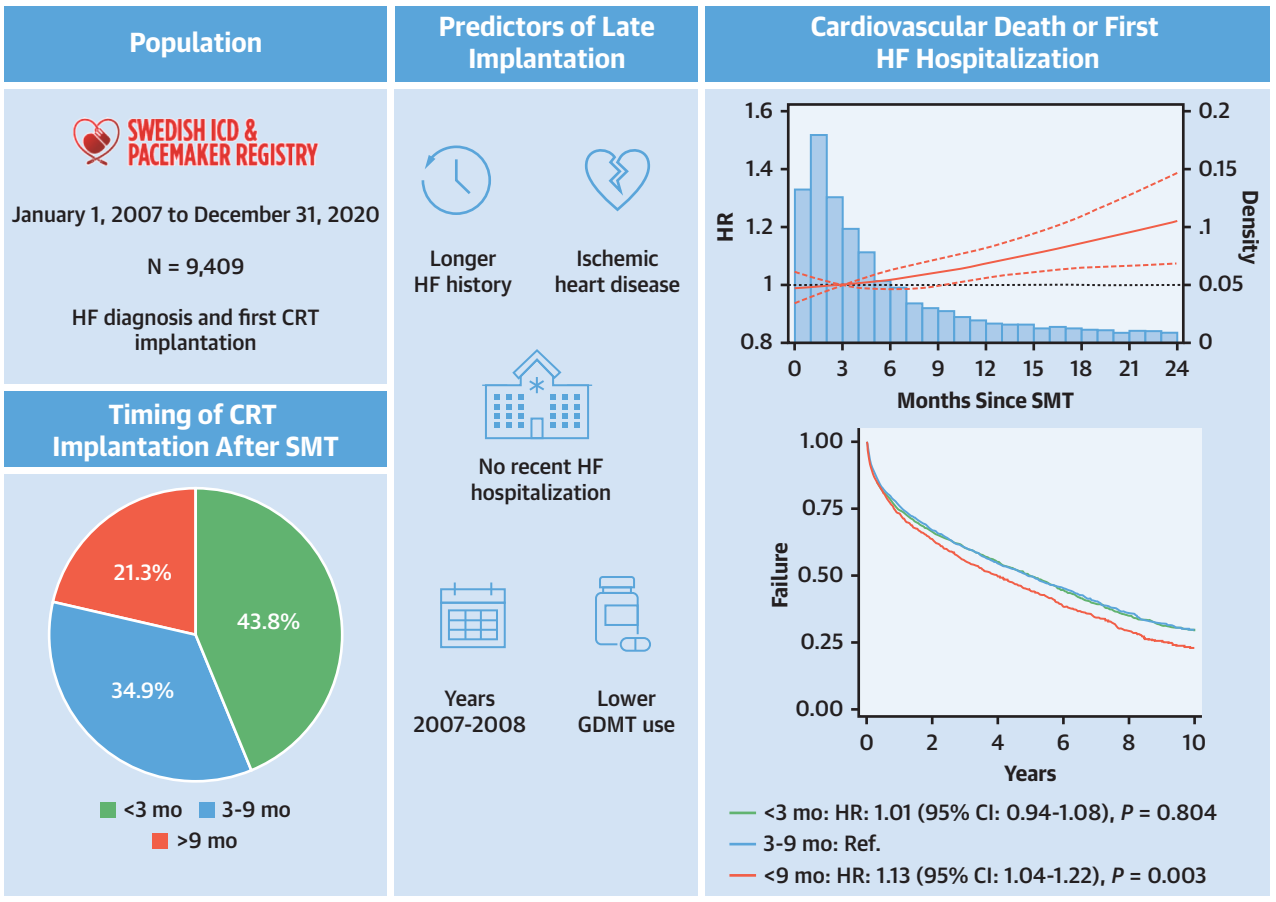
In our cohort of ~9,500 patients undergoing CRT implantation, key findings were as follows: 1) the median time from SMT achievement to CRT implantation was 3.5 months (Q1-Q3: 1.5-7.8 months), with ~21% of patients undergoing implantation >9 months after reaching SMT; 2) the time from SMT to CRT implantation slightly, but significantly, decreased over the study period; and 3) the risk of cardiovascular death or HF hospitalization increased with a longer time from SMT to CRT implantation, with a higher risk of cardiovascular death regardless of whether CRT implantation was delayed beyond 3 months after SMT (**Central Illustration**).

GDMT BEFORE CRT IMPLANTATION. The use of multiple HF drugs with the recommendation to achieve their target doses, is the cornerstone of the treatment of patients with HFrEF worldwide.[3,18] The achievement of OMT is recommended before CRT implantation, as GDMT in patients with de novo HFrEF may lead to positive left ventricular remodeling and LVEF recovery up to >35%, despite its lower efficacy when a conduction delay is present.[7,8,19] Although there is increasing consensus on OMT being the maximum tolerated dose of multiple HF drugs rather than the use or achievement of target doses of all the foundational HF drugs.[20] the exact definition of OMT remains challenging. The attempt to reach full GDMT, as well as the consequent delays due to related tolerability and organizational issues, might challenge timely referral for CRT implantation.

During our study period, 3 GDMT classes were used. In our cohort, half of the patients at the time of CRT implantation were receiving triple GDMT (RASi/ARNI + BB + MRA) and >90% were receiving BB or RASi/ARNI before CRT implantation, which is consistent with good implementation of RASi and BB in patients with HFrEF in Sweden.[21] However, consistent with others,[14] our study shows that GDMT implementation takes time, with most patients receiving CRT >2 years after their initial HF diagnosis, even in more recent years. Despite being higher than in other cohorts,[22] MRA use was likely suboptimal (ie, ~60%), as was ARNI use (~30% between 2017 and 2020) and overall target dose achievement for drugs requiring uptitration,[23] especially in patients with delayed CRT implantation.

Less intense GDMT use in patients undergoing later CRT implantation may be explained either by delays in implantation in an attempt to first achieve better GDMT or by both being markers of poorer care and clinical inertia. However, overall worse clinical status cannot be entirely ruled out, which might have led physicians to delay CRT implantation for other unmeasured reasons, ie, residual confounding that could not be addressed through statistical adjustments.[23] Whether our patients were eligible for further GDMT optimization or were on maximum tolerated treatment remains uncertain, particularly because doses were quite far from the recommended targets. However, many factors including HF duration, uptitration efforts before implantation, and the use of multidrug regimens even in the era of sequential GDMT initiation might suggest that, at least in a proportion of patients, OMT was achieved.[17] Moreover, it should be noted that a lower extent of reverse remodeling with GDMT should be expected in patients with HF with conduction diseases than in

CENTRAL ILLUSTRATION **Timing of CRT Implantation After the Achievement of SMT**



Villaschi A, et al. JACC Heart Fail. 2025;13(10):102515.

CRT = cardiac resynchronization therapy; GDMT = guideline-directed medical therapy; HF = heart failure; ICD = implantable cardiac defibrillator; Ref. = reference; SMT = stable medical therapy.

those without, thus prompting for early referral for CRT implantation even when GDMT is not fully optimized.[8,9] Therefore, even though multiple factors may lead to delays in CRT implantation, poorer care and underestimation of CRT benefits appear to be among the most relevant contributors.

TIME FROM SMT TO CRT IMPLANTATION AND TEMPORAL TRENDS. Despite guidelines' recommendations highlighting the need for OMT before CRT implantation, how long a patient should be receiving OMT before considering CRT remains uncertain.[3] In our study, which is the first to systematically evaluate the time from SMT to CRT implantation in the real world, almost 80% of patients received CRT in the first 9 months. The median delay to CRT implantation was 3.5 months, aligning with the frequently applied 3-month cutoff, derived from trial indications and European guidelines for ICD implantation.[3] Over time, a progressive decrease in median time from SMT to CRT implantation was observed, likely reflecting better CRT availability, expertise, and overall acceptance, because our study period started in 2007, with CRT first recommended for HFrEF in 2005.[24] Although the reduction in time from SMT to CRT implantation continued even after the introduction of ARNI, there was no corresponding increase in HF history duration, despite recommendations to achieve OMT before implantation.[17,25]

A gradual increase in awareness of the importance of timely referral seems a reasonable explanation. Faster GDMT implementation across the entire HF spectrum, replicating the results of the STRONG-HF (Safety, Tolerability and Efficacy of Rapid Optimization, Helped by NT-proBNP testinG, of Heart Failure Therapies) study in acute HF, may lead to earlier referral for CRT implantation during the course of the disease.[26]

PATIENT PROFILES ASSOCIATED WITH EARLIER/LATER CRT IMPLANTATION AFTER THE ACHIEVEMENT OF SMT. We observed differences in patient profiles associated with earlier vs later CRT implantation. After adjustments, patients who underwent implantation >9 months after SMT achievement were more likely to have a longer HF duration and a history of ischemic heart disease but were less likely to have a history of HF hospitalization within 6 months before implantation and GDMT use. An erroneous perception of a lower expected benefit from CRT in ischemic patients may have contributed.[27] Other reasons for late referral may include less disease severity and fewer symptoms, as seen with longer HF duration, lower likelihood of previous hospitalization, and care in less specialized centers (ie, less GDMT use).[28-30] Profiles of patients undergoing early implantation (<3 months) possibly confirmed better care (ie, more GDMT use and previous ICD implantation) but also higher baseline risk (recent HF hospitalization and higher digoxin use with less atrial fibrillation history). However, using recent HF hospitalization as an opportunity to tackle therapeutic inertia and optimize GDMT might also facilitate timely evaluation for CRT implantation, which is suggested by our results linking better GDMT use, shorter time to CRT implantation, and previous hospitalization within 6 months before implantation.[23]

OUTCOME ASSOCIATED WITH THE TIME FROM THE ACHIEVEMENT OF SMT TO CRT IMPLANTATION. Delays in CRT implantation were independently associated with higher mortality/morbidity, both when considering time to CRT as a continuous and as a categorical variable. In the latter case, the highest risk was observed in patients receiving CRT >9 months after the achievement of SMT while differences between <3-months and 3- to 9-month periods were significant, although slightly more modest. Our results were consistent across subgroups and consistency analyses, supporting the temporal robustness of our findings. The association between delays in CRT implantation and increased mortality mirrors previous findings on HF pharmacotherapy optimization, ie, an estimated 1% absolute mortality increase per month when HF drugs are completely withheld.[31] These data suggest that timely referral for CRT implantation may be as important as GDMT implementation. Moreover, although achieving successful remodeling might take months after initiating GDMT, the potential for LVEF improvement is highest in the first 3 months after diagnosis[19] but lower in patients with conduction diseases.[7,8] Therefore, as supported by our analysis where not all patients were receiving full GDMT, referral to CRT should be considered as soon as further GDMT optimization is not feasible, and delays, whether from SMT or HF diagnosis, should be avoided given their detrimental effect on patients' prognosis.[11,32] Finally, observing an association between earlier CRT implantation and lower mortality/morbidity on top of recent pharmacotherapy suggests that despite improvements in GDMT and HF outcomes,[33,34] the benefit of CRT demonstrated in randomized clinical trials remains relevant.

STUDY STRENGTHS AND LIMITATIONS. The main strengths of our study are the large sample size, the use of a nationwide registry with high coverage, the long study period including patients implanted in addition to different background GDMT, the long follow-up period, and the lack of missing data.

Limitations include the observational design, with residual confounding avoiding inference of any causal relationship. Therefore, our data should be considered as hypothesis-generating, advocating for future prospective studies in the field. Different data sources should also be explored, as our analysis was based on administrative data from a single country, which limited data granularity and generalizability to other health care systems and populations. We focused on time from the last change in medical therapy, which we defined as SMT, rather than on the achievement of OMT, as data characteristics prevented us from ascertaining whether the use of GDMT observed in our cohort truly represented OMT. However, the use of multidrug regimens, long time from HF diagnosis, and previous uptitration efforts support such a possibility. Data on NYHA functional class, QRS complex duration and morphology, electrocardiogram, LVEF, and symptoms and their trajectories over time were not available in the analyzed registries. As a result, patient characterization may be suboptimal and statistical adjustments could not address certain potentially important confounders, thus preventing us from entirely ruling out residual

confounding due to unmeasured and unknown factors. Although we assumed that all patients diagnosed with HF who received CRT were implanted because of an indication for HFrEF, this may not be true in few cases, as other indications have been proposed over the years.[3] However, the results were consistent across the entire study period. The clinical indication for CRT may have also emerged months after achieving the observed doses of GDMT, particularly in patients who underwent CRT implantation >9 months. However, this seems unlikely, as, when the indication for CRT emerges in suboptimally treated patients, adjustments in pharmacological therapy should generally precede CRT implantation. Moreover, because patients who received CRT later were healthy enough to survive until implantation whereas eligible patients who died while waiting for CRT were not included because of study design, the magnitude of the association between the time to CRT implantation and mortality/morbidity might be underestimated. Our study did not include a comparator group of patients who initiated GDMT but improved their LVEF sufficiently to obviate the need for CRT; therefore, it remains unclear whether some patients who received CRT early might have had further LVEF improvement, avoiding CRT implantation altogether, thus limiting our ability to assess the potential downside of early referral in the absence of fully optimized medical therapy. Treatment with SGLT2 inhibitors was not included among GDMT, and the proportion of patients included in the post-ARNI era was small, thus limiting the generalizability of our findings to even more contemporary cohorts. However, once these treatments are initiated and an indication for CRT persists, it is unlikely they would prevent observing an earlier vs later benefit with CRT. In addition, the overall effect of SGLT2 inhibitors on LVEF has been shown to be quite limited.[35]

CONCLUSIONS

Time from the achievement of SMT to CRT implantation progressively decreased over the study period, which may highlight better CRT availability, acceptance, and awareness of the benefits provided by appropriate device therapy. Delayed CRT implantation was independently associated with higher morbidity and mortality, regardless of the year of implantation and therefore of the different background GDMT, especially in patients waiting for >9 months. Notably, even delayed CRT implantation beyond 3 months was possibly associated with higher cardiovascular mortality as compared with earlier implantation after GDMT optimization. Overall, our findings suggest that prompt referral for CRT implantation after achieving SMT should be considered to further improve clinical outcomes, even in the context of more recent pharmacotherapy.

ACKNOWLEDGMENT The authors thank all staff members at care units in Sweden who report to the Swedish ICD and Pacemaker Registry for their contributions.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

This study received support through grants from Medtronic, the Horizon Europe programme (project number 101095479 - MoreEUROPA), and the Swedish Heart and Lung Foundation (project number 20220680) awarded to the institution of Dr Savarese. Dr Böhm has received research support from Deutsche Forschungsgemeinschaft (SFB-TTR 219, S-01); and speaking honoraria from Abbott, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol Myers Squibb, Cytokinetics, Medtronic, Novartis, Servier, and Vifor Pharma; and has participated in advisory boards of Amgen, Bayer, Boehringer Ingelheim, Cytokinetics, Medtronic, Novartis, Pfizer, Recor Medical, Servier, and Vifor Pharma. Dr Bozkurt has served in consultation or advisory committee roles for Abiomed, American Regent, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Cytokinetics, Daiichi Sankyo, Johnson and Johnson, Hanger Institute, Merck, Occlutech, Regeneron, Roche, Sanofi, scPharmaceuticals, Vifor Pharma, and Zoll Medical/Respicardia; and has served on the clinical event committee of Abbott Vascular and the data safety monitoring committees of Cardurion, LivaNova, Novo Nordisk, and Renovacor. Dr Butler has served as a consultant for Abbott, American Regent, Amgen, Applied Therapeutics, AskBio, Astellas, AstraZeneca, Bayer, Boehringer Ingelheim, Boston Scientific, Bristol Myers Squibb, Cardiac Dimension, CardioCell, Cardior, CSL Behring, CVRx, Cytokinetics, Daxor, Edwards Lifesciences, Element Science, Faraday Pharmaceuticals, Foundry, G3P Pharmaceuticals, Innolife, Impulse Dynamics, Imbria Pharmaceuticals, Inventiva, Ionis Pharmaceuticals, Lexicon Pharmaceuticals, Eli Lilly, LivaNova, Janssen, Medtronic, Merck, Occlutech, Owkin, Novartis, Novo Nordisk, Pfizer, Pharmacosmos, Pharmain, Prolaio, Regeneron, Renibus Therapeutics, Roche, Salamandra, Sanofi, SC Pharma, Secretome, Sequana Medical, SQ Innovation, Tenex Health, Tricog Health, Ultromics, Vifor Pharma, and Zoll Medical. Dr Linde has received research support from the Swedish Heart Lung Foundation, the Swedish Society of Medical Sciences, the Stockholm County Council; consulting fees from AstraZeneca and Roche Diagnostics; and speaker honoraria from Novartis, AstraZeneca, Bayer, Vifor Pharma, Medtronic, and Impulse Dynamics; and has served on the advisory board of AstraZeneca. Dr Metra has received consulting honoraria for participation in steering committees, advisory boards, or speeches from Abbott Vascular, Amgen, AstraZeneca, Bayer, Edwards Lifesciences, Fresenius Medical Care, Novartis, and Servier (all outside of the submitted work). Dr Zieroth has received research grant support from, has served on the advisory boards of, or has speaker engagements with Abbott, AstraZeneca, Bayer, Bristol Myers Squibb, Boehringer Ingelheim, CSL Vifor, Cytokinetics, Edwards Lifesciences, Eli Lilly, GlaxoSmithKline, Medtronic, Merck, Novartis, Novo Nordisk, and Pfizer; and has served on the clinical trial committees for studies sponsored by AstraZeneca, Boehringer Ingelheim, Cytokinetics, Merck, Novartis, Pfizer, and Salubris Biotherapeutics. Dr Lund has received grants, consulting fees, and honoraria from Myocardia, AstraZeneca, Boehringer Ingelheim/Eli Lilly, Novartis,

Bayer, Vifor Pharma, Sanofi/Lexicon Pharmaceuticals, Servier, Abbott, Pharmacosmos, Medscape, Radcliffe, TMA, Orion Pharma, and Alleviant (all outside of the submitted work); and reports ownership of AnaCardio. Dr Savarese has received grants and personal fees from CSL Vifor, Boehringer Ingelheim, AstraZeneca, Servier, Novartis, Cytokinetics, Pharmacosmos, Medtronic, and Bayer; personal fees from Roche, Abbott, Edwards Lifesciences, Teva Pharmaceuticals, Menarini, INTAS Pharmaceuticals, GETZ Pharma, Laboratori Guidotti; and grants from Boston Scientific and Merck (all outside of the submitted work). All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

ADDRESS FOR CORRESPONDENCE: Dr Gianluigi Savarese, Department of Clinical Science and Education, Södersjukhuset, Karolinska Institutet, Sjukhusbacken 10, 118 83 Stockholm, Sweden. E-mail: gianluigi.savarese@ki.se. X handle: @GianluSava.

PERSPECTIVES

COMPETENCY IN PATIENT CARE AND MEDICAL KNOWLEDGE: Findings from this large national registry suggest that earlier CRT implantation is associated with a lower risk of morbidity and mortality whereas delayed CRT implantation (beyond 9 months) is associated with worse outcomes.

TRANSLATIONAL OUTLOOK: Although guidelines strongly recommend CRT for eligible patients, the actual timing of CRT post-OMT has remained unclear, and future prospective studies in diverse cohorts should better identify the optimal one.

REFERENCES

1. Wells G, Parkash R, Healey JS, et al. Cardiac resynchronization therapy: a meta-analysis of randomized controlled trials. *CMAJ*. 2011;183:421-429.

2. Freemantle N, Tharmanathan P, Calvert MJ, Abraham WT, Ghosh J, Cleland JGF. Cardiac resynchronisation for patients with heart failure due to left ventricular systolic dysfunction—a systematic review and meta-analysis. *Eur J Heart Fail*. 2006;8:433-440.

3. McDonagh TA, Metra M, Adamo M, et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J*. 2021;42:3599-3726.

4. Nieminen MS, Brutsaert D, Dickstein K, et al. EuroHeart Failure Survey II (EHFS II): a survey on hospitalized acute heart failure patients: description of population. *Eur Heart J*. 2006;27:2725-2736.

5. Raatikainen MJP, Arnar DO, Zeppenfeld K, et al. Statistics on the use of cardiac electronic devices and electrophysiological procedures in the European Society of Cardiology countries: 2014 report from the European Heart Rhythm Association. *Europace*. 2015;17:i1-i75.

6. Lyons KJ, Ezekowitz JA, Liang L, et al. Impact of current versus previous cardiac resynchronization therapy guidelines on the proportion of patients with heart failure eligible for therapy. *JACC Heart Fail*. 2017;5:388-392.

7. Straw S, McGinlay M, Gierula J, et al. Impact of QRS duration on left ventricular remodelling and survival in patients with heart failure. *J Cardiovasc Med (Hagerstown)*. 2021;22:848-856.

8. Sze E, Samad Z, Dunning A, et al. Impaired recovery of left ventricular function in patients with cardiomyopathy and left bundle branch block. *J Am Coll Cardiol*. 2018;71:306-317.

9. Wang NC, Li JZ, Adelstein EC, et al. New-onset left bundle branch block-associated idiopathic nonischemic cardiomyopathy and time from diagnosis to cardiac resynchronization therapy: the NEOLITH II study. *Pacing Clin Electrophysiol*. 2018;41:143-154.

10. Goldstein SA, Mentz RJ, Hellkamp AS, et al. Timing of cardiac resynchronization therapy device implantation in heart failure patients and its association with outcomes. *Clin Cardiol*. 2018;42:256-263.

11. Leyva F, Zegard A, Patel P, et al. Timing of cardiac resynchronization therapy implantation. *Europace*. 2023;25:euad059.

12. Lund LH, Braunschweig F, Benson L, Ståhlberg M, Dahlström U, Linde C. Association between demographic, organizational, clinical, and socio-economic characteristics and underutilization of cardiac resynchronization therapy: results from the Swedish Heart Failure Registry. *Eur J Heart Fail*. 2017;19:1270-1279.

13. Gatti P, Linde C, Benson L, et al. What determines who gets cardiac resynchronization therapy in Europe? A comparison between ESC-HF-LT registry, SwedeHF registry, and ESC-CRT Survey II. *Eur Heart J Qual Care Clin Outcomes*. 2023;9:741-748.

14. Savarese G, Kishi T, Vardeny O, et al. Heart failure drug treatment-inertia, titration, and discontinuation: a multinational observational study (EVOLUTION HF). *JACC Heart Fail*. 2023;11:1-14.

15. Dhande M, Rangavajla G, Canterbury A, et al. Guideline-directed medical therapy and the risk of death in primary prevention defibrillator recipients. *JACC Clin Electrophysiol*. 2022;8:1024-1030.

16. Gadler F, Valzania C, Linde C. Current use of implantable electrical devices in Sweden: data from the Swedish pacemaker and implantable cardioverter-defibrillator registry. *Europace*. 2015;17:69-77.

17. Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure: the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J*. 2016;37:2129-2200.

18. Heidenreich PA, Bozkurt B, Aguilar D, et al. 2022 AHA/ACC/HFSA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2022;79(17):e263-e421.

19. Veltmann C, Duncker D, Doering M, et al. Therapy duration and improvement of ventricular function in de novo heart failure: the Heart Failure Optimization Study. *Eur Heart J*. 2024;45:2771-2781.

20. Abraham WT, Psotka MA, Fiuzat M, et al. Standardized definitions for evaluation of heart failure therapies: scientific expert panel from the Heart Failure Collaboratory and Academic Research Consortium. *Eur J Heart Fail*. 2020;22:2175-2186.

21. D'Amario D, Rodolico D, Rosano GMC, et al. Association between dosing and combination use of medications and outcomes in heart failure with reduced ejection fraction: data from the Swedish Heart Failure Registry. *Eur J Heart Fail*. 2022;24:871-884.

22. Greene SJ, Butler J, Albert NM, et al. Medical therapy for heart failure with reduced ejection fraction: the CHAMP-HF registry. *J Am Coll Cardiol*. 2018;72:351-366.

23. Savarese G, Lindberg F, Cannata A, et al. How to tackle therapeutic inertia in heart failure with reduced ejection fraction: a scientific statement of the Heart Failure Association of the ESC. *Eur J Heart Fail*. 2024;26:1278-1297.

24. Swedberg K, Members ATF, Cleland J, et al. Guidelines for the diagnosis and treatment of chronic heart failure: executive summary (update 2005): the Task Force for the Diagnosis and Treatment of Chronic Heart Failure of the European Society of Cardiology. *Eur Heart J*. 2005;26:1115-1140.

25. Ezekowitz JA, O'Meara E, McDonald MA, et al. 2017 comprehensive update of the Canadian Cardiovascular Society Guidelines for the Management of Heart Failure. *Can J Cardiol*. 2017;33:1342-1433.

26. Mebazaa A, Davison B, Chioncel O, et al. Safety, tolerability and efficacy of up-titration of guideline-directed medical therapies for acute heart failure (STRONG-HF): a multinational, open-label, randomised, trial. *Lancet*. 2022;400:1938-1952.

27. Sudesh S, Abraham WT, Cleland JGF, et al. Cardiac resynchronization therapy in ischemic versus nonischemic cardiomyopathy: patient-level meta-analysis of 7 randomized clinical trials. *JACC Heart Fail*. 2024;12:1915-1924.

28. Wikstrom G, Blomström-Lundqvist C, Andren B, et al. The effects of aetiology on outcome in patients treated with cardiac resynchronization therapy in the CARE-HF trial. *Eur Heart J*. 2009;30:782-788.

29. Sutton MG, Plappert T, Hilpisch KE, Abraham WT, Hayes DL, Chinchoy E. Sustained reverse left ventricular structural remodeling with cardiac resynchronization at one year is a function of etiology: quantitative Doppler echocardiographic evidence from the Multicenter InSync Randomized Clinical Evaluation (MIRACLE). *Circulation*. 2006;113:266-272.

30. Mustafa U, Atkins J, Mina G, et al. Outcomes of cardiac resynchronisation therapy in patients with heart failure with atrial fibrillation: a systematic review and meta-analysis of observational studies. *Open Heart*. 2019;6:e000937.

31. Zaman S, Zaman SS, Scholtes T, et al. The mortality risk of deferring optimal medical therapy in heart failure: a systematic comparison against norms for surgical consent and patient information leaflets. *Eur J Heart Fail*. 2017;19:1401-1409.

32. Verbrugge FH, Dupont M, Vercammen J, et al. Time from emerging heart failure symptoms to cardiac resynchronisation therapy: impact on clinical response. *Heart*. 2013;99:314-319.

33. Nakamaru R, Kohsaka S, Shiraishi Y, et al. Temporal trends in heart failure management and outcomes: insights from a Japanese multicenter registry of tertiary care centers. *J Am Heart Assoc*. 2023;12:e031179.

34. Lindberg F, Benson L, Dahlstrom U, Lund LH, Savarese G. Trends in heart failure mortality in Sweden between 1997 and 2022. *Eur J Heart Fail*. 2024;27:366-376.

35. Carluccio E, Biagioli P, Reboldi G, et al. Left ventricular remodeling response to SGLT2 inhibitors in heart failure: an updated meta-analysis of randomized controlled studies. *Cardiovasc Diabetol*. 2023;22:235.

KEY WORDS cardiac resynchronization therapy, heart failure, medical therapy, morbidity, mortality, registry, real world

APPENDIX For supplemental figures and tables, please see the online version of this paper.