ESC European Society of Cardiology

Europace (2023) **25**, 1–12
https://doi.org/10.1093/europace/euad192

CLINICAL RESEARCH

Prognosis of CRT-treated and CRT-untreated unselected population with LBBB in Stockholm County

Paolo Gatti [1]*, Stefan Lind [2], Ingibjörg Kristjánsdóttir [1], Ava Azari[1], Gianluigi Savarese [1,2], Matteo Anselmino [3], Cecilia Linde [1,2], and Fredrik Gadler [1,2]

[1]Division of Cardiology, Department of Medicine, Karolinska Institutet, Norrbacka S1:02, Eugeniavägen 27-31, 171 76 Stockholm, Sweden; [2]Department of Cardiology, Karolinska Universitetssjukhuset, Stockholm, Sweden; and [3]Division of Cardiology, Department of Medical Sciences, University of Turin, Azienda Ospedaliero Universitaria (A.O.U.) Città della Salute e della Scienza di Torino, 10126 Turin, Italy

Received 13 April 2023; accepted after revision 23 May 2023; online publish-ahead-of-print 5 July 2023

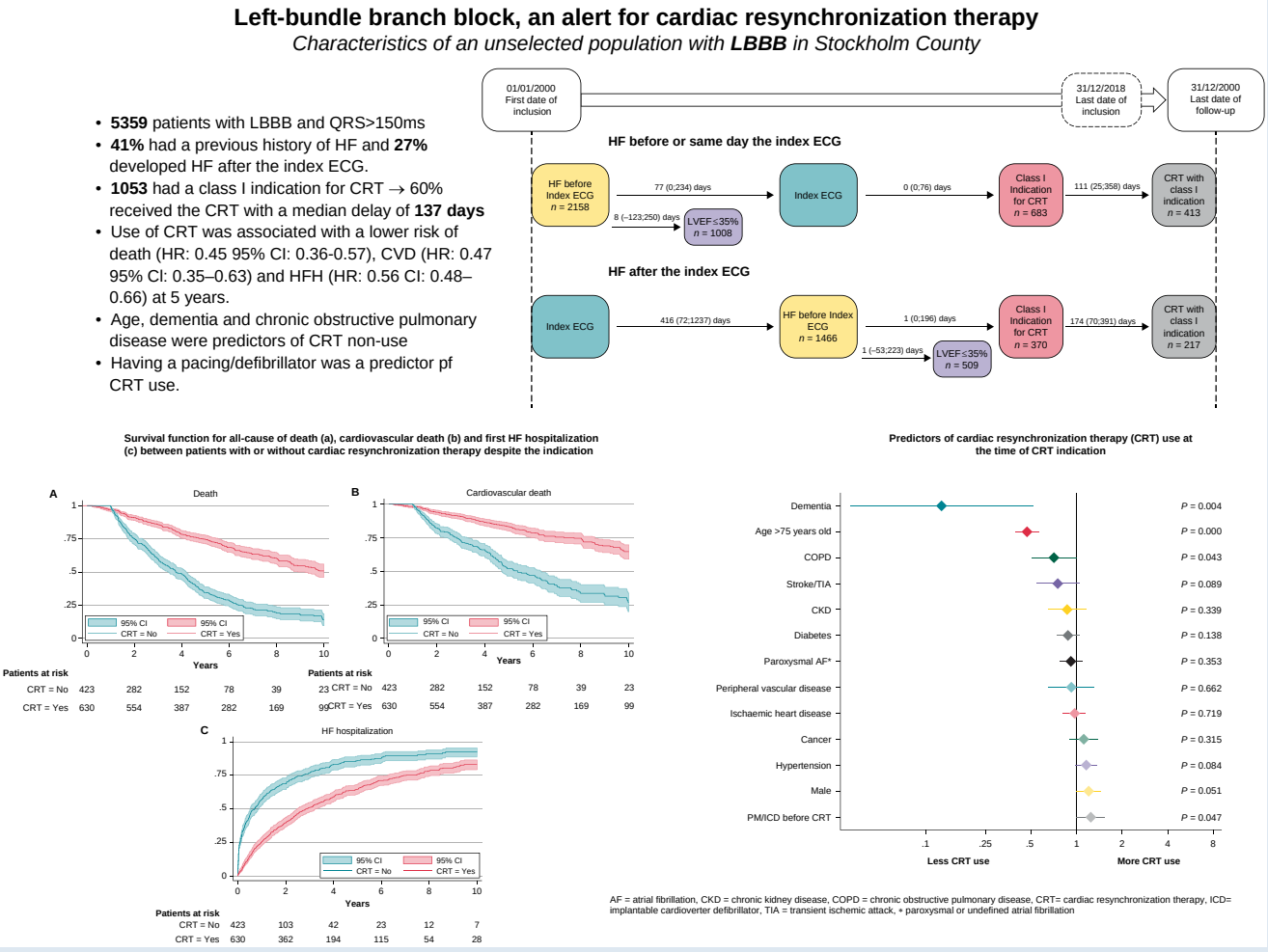
Aims Left bundle branch block (LBBB) might be the first finding of cardiovascular diseases but also the prerequisite for cardiac resynchronization therapy (CRT) in heart failure (HF) with reduced ejection fraction (HFrEF). The prognosis for patients with LBBB and the implications of CRT in an unselected real-world setting are the focus of our study.

Methods and results A central electrocardiogram (ECG) database and national registers have been screened to identify patients with LBBB. Predictors of HF and the use of CRT were identified with Cox models. The hazard ratios (HRs) of death, cardiovascular death (CVD), and HF hospitalization (HFH) were estimated according to CRT use. Of 5359 patients with LBBB and QRS > 150 ms, median age 76 years, 36% were female. At the time of index ECG, 41% had a previous history of HF and 27% developed HF. Among 1053 patients with a class I indication for CRT, only 60% received CRT with a median delay of 137 days, and it was associated with a lower risk of death [HR: 0.45, 95% confidence interval (CI): 0.36–0.57], CVD (HR: 0.47, 95% CI: 0.35–0.63), and HFH (HR: 0.56, 95% CI: 0.48–0.66). The age of over 75 years and the diagnosis of dementia and chronic obstructive pulmonary disease were predictors of CRT non-use, while having a pacing/defibrillator device independently predicted CRT use.

Conclusion In an unselected LBBB population, CRT is underused but of great value for HF patients. Therefore, it is crucial to find ways of better implementing and understanding CRT utilization and characteristics that influence the management of our patients.

* Corresponding author. Tel: +46 70 295 5285, *E-mail address*: paolo.gatti@ki.se

Graphical Abstract



Keywords LBBB • Heart failure • CRT

What's new?

- Present the prognosis and characteristics of a large unselected population with left bundle branch block.
- Describe the state of the art of cardiac resynchronization therapy utilization in a real-world setting.
- Identify possible factors associated with cardiac resynchronization therapy underutilization.

Introduction

In the general population, the prevalence of left bundle branch block (LBBB) is 0.19–0.82% and increases with age.[1] It is more common in the presence of hypertension, heart failure (HF), and coronary heart disease and is associated with an impaired prognosis.[2,3,4] Left bundle branch block further aggravates HF through delayed contraction of the left ventricle wall, but LBBB may also *per se* impair cardiac function over time and cause HF.[5] Cardiac resynchronization therapy (CRT) partly restores the left ventricle activation pattern in LBBB and improves symptoms and prognosis. Therefore, CRT has a class I indication in current guidelines but is underused.[6]

The diagnosis of LBBB is easily obtained with routine 12-lead electrocardiogram (ECG) recording.[7] We identified and characterized patients with LBBB with and without HF through a large central ECG database in Stockholm. We further identified patients with HF with reduced ejection fraction (HFrEF) with a CRT indication and compared outcomes in those with indications who were or were not treated with CRT and studied clinical predictors of use vs. non-use of CRT.

Methods

Data sources and study population

We queried the data from the central electronic ECG database MUSE (General Electric Healthcare) between 2000 and 2018 in an estimated population of almost 1 000 000 individuals. All ECGs from three hospitals (Karolinska Hospital-Solna, Karolinska Hospital-Huddinge, and Södertalje Hospital), from ambulances and elective ECGs in the larger Norrtälje area, were retrospectively considered. The ECGs from 432 108 unique adult subjects (>18 years of age) were retrieved and analysed by the MUSE system. Our selection criteria were LBBB with QRS duration ≥

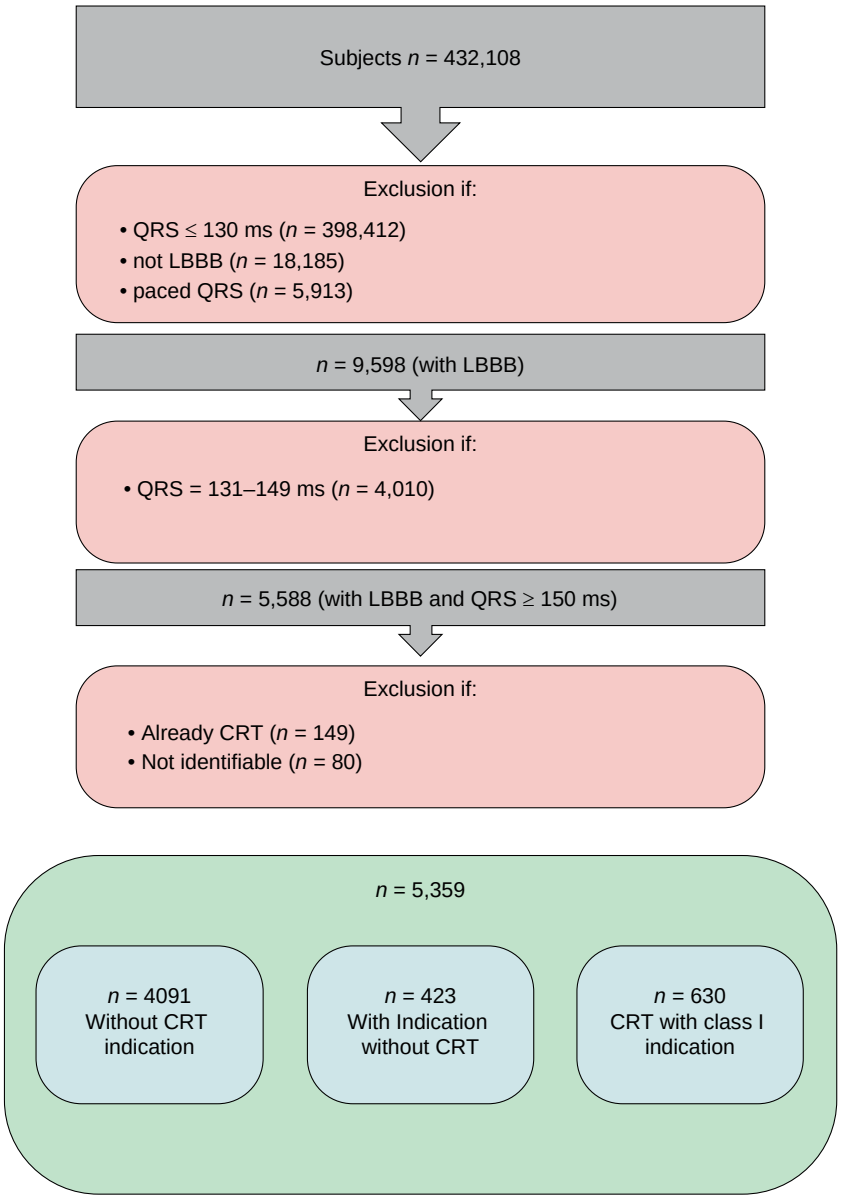


Figure 1 Flowchart of cohort selection from adults in the MUSE ECG database from 2000 to 2018. CRT, cardiac resynchronization therapy; ECG, electrocardiogram; EF, ejection fraction; HF, heart failure; LBBB, left bundle branch block; *n*, number.

150 ms without right ventricular pacing or CRT. Our *index ECG date* was the first ECG fulfilling these criteria. Thus, 5359 patients were identified (*Figure 1*).

To obtain clinical characteristics, outcomes, and information about CRT or pacemaker (PM) treatment, we linked patients' data with three national registries [the Swedish Pacemaker and ICD Registry (annual report accessible online http://www.pacemakerregistret.se), the Swedish National Patient Registry (including hospitalizations and outpatient visits), and the Cause of Death Registry] between 2000 and 2020 using the personal identification number used in all permanent residents in Sweden. New York Heart Association (NYHA) class, NT-proBNP, and HF medication at index ECG were not available.

Echocardiographic data were not stored digitally in the Stockholm area during this study period; therefore, such data were collected in patients with a history of HF or who developed HF by one investigator (P.G.) from electronic health records using written echo assessments of left ventricular ejection fraction (LVEF) and left ventricular end-diastolic diameter (LVEDD), when available, using a structured approach: the date of the first echocardiographic exam with LVEF ≤ 35% was considered if the LVEF was stable, below, or equal to 35% during follow-up or till CRT use; the last echocardiographic exam was considered if the LVEF was never observed below 35% or recovered over 35% during follow-up or till CRT use.

Timelines, definitions, and ethical considerations

Index ECGs were obtained from 1 January 2000 to 31 December 2018, and the ICD-10 codes were collected starting from one year before index ECG to the last available follow-up or the end of the study (31 December 2020).

We defined *LBBB morphology* as wide QRS, predominantly upright QRS with wide R and/or R′ in lateral leads (I and V6), and predominantly negative QRS in leads V1 and V2 with wide Q or S waves.

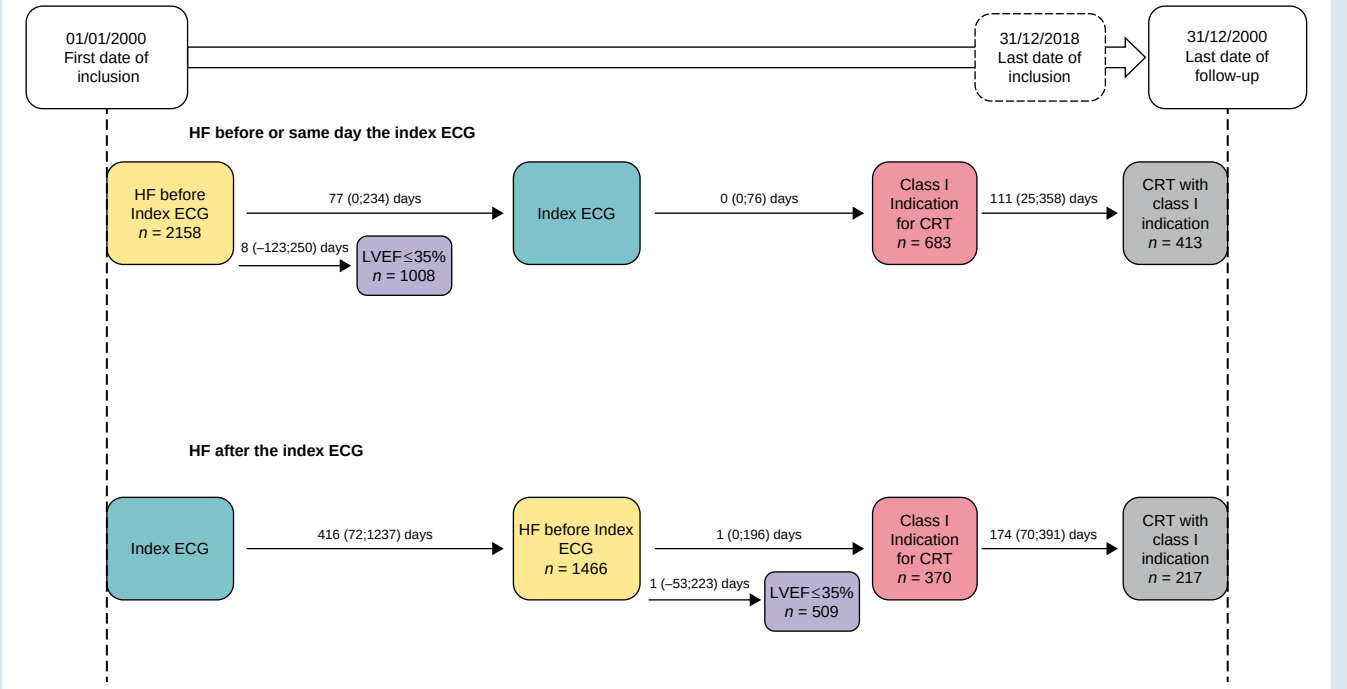


Figure 2 Timeline of index ECG, first HF diagnosis, LVEF below 35%, indication for CRT, and CRT in patients with HF before or after index ECG. Index ECG = first ECG with QRS ≥ 150 ms and LBBB morphology, without paced QRS. CRT indication = if ECG with QRS ≥ 150 ms and LBBB morphology, without paced QRS, HF duration ≥ 90 days, LVEF ≤ 35%, without previous history of permanent AF and follow-up ≥ 12 months. AF, atrial fibrillation; CRT, cardiac resynchronization therapy; ECG, electrocardiogram; HF, heart failure; LBBB, left bundle branch block; LVEF, left ventricular ejection fraction; *n*, number.

We defined *HFrEF* as a clinical HF diagnosis according to ICD-10 combined with stable LVEF ≤ 35%.

We estimated the *date of class I indication for CRT* (referring to the current 2021 EHRA/ESC pacing guidelines[6]) during follow-up of our cohort based on index ECG date and the first date of HF diagnosis with stable LVEF ≤ 35% (if present), whichever came last and, if not treated with CRT, under the condition of available follow-up of >12 months (survival of >12 months) and no previous history of permanent atrial fibrillation (AF) (persistent AF was not excluded).

The list of ICD-10 codes used to identify the clinical variables for the analysis is available in Supplementary material online, *Table S1*. The Charlson comorbidity index was calculated as follows: age 50–59 years = 1 point (pt), 60–69 years = 2 pts, 70–79 years = 3 pts, and ≥80 years = 4 pts; myocardial infarction (MI) = 1 pt; HF = 1 pt; peripheral vascular disease (PVD) = 1 pt; stroke or transient ischaemic attack (TIA) = 1 pt; dementia = 1 pt; chronic obstructive pulmonary disease (COPD) = 1 pt; musculoskeletal and connective disease (MSD) = 1 pt; peptic ulcer = 1 pt; liver disease = 2 pts; diabetes mellitus = 1 pt; chronic kidney disease (CKD) = 2 pts; history of cancer = 2 pts; hemiplegia = 2 pts; acquired immunodeficiency syndrome (AIDS); or human immunodeficiency virus (HIV) infection = 6 pts.

The local ethics committee approved the study protocol including data extraction and journal reading.

Statistical analysis

Categorical variables were presented as absolute numbers (%) and continuous variables as medians (interquartile ranges). Baseline characteristics were compared across groups by the Mann–Whitney test (if continuous) and by the χ^2 test (if categorical).

Univariable and multivariable Cox regression models were fitted to investigate patient characteristics independently associated with the development of HF after LBBB and CRT use after class I indication. Age was transformed into a binary variable using the integer number around the median (75 years old). Results were reported as hazard ratios (HRs) with 95% confidence intervals (CIs).

The outcomes considered coprimary endpoints were as follows: time to death for any cause, time to cardiovascular death (CVD), and time to first HF hospitalization (HFH).

Univariable and multivariable Cox proportional hazard regression models were fitted to compare the crude and adjusted risk of outcomes in patients with an indication for CRT, according to CRT use. Incidence per 1000 patient-years was calculated at 95% CI. A proportional hazard model for the subdistribution of the HR (SHR) was fitted to assess the cumulative incidence of CVD and HFH with all-cause death as a competing risk.

The proportional hazard assumption of the model was checked using the Schoenfeld residual method. Any violation of the proportional hazard assumption of the model was also considered and adjusted in the analysis splitting the time into two bands of 5 years. Data were censored on 31 December 2020 (end of study) or death.

All variables included in the multivariable regression models are reported in Supplementary material online, *Table S2*.

All analyses were performed using Stata/IC version 16.1. The level of significance was set to 5%, two-sided.

Results

A total of 5359 patients [1905 (35.6%) women, median age 76 (67–83) years] were included. Echocardiographic data were available in 3153 (86%).

Heart failure patients

In total, 3624 (68%) had a history of HF. Concerning index ECG date, 2158 (41%) subjects had a previous history of HF, 1466 (27%) developed HF after index ECG (*Figure 2*), and 1735 (32%) never developed HF.

Those who developed HF [1466 (27%)] did so after 416 (72–1237) days. They were younger and with less prevalence of comorbidities

Table 1 Characteristics of patients by the time of HF diagnosis

	Total $n = 5359$	No HF $n = 1735$	HF before index ECG $n = 2158$	HF after index ECG $n = 1466$	*P*-value
Days from index ECG to HF			−77 (−234–0)	416 (72–1237)	<0.001
LVEF, %[a]			33 (25–47)	40 (30–50)	<0.001
LVEF categories[a]					<0.001
≤35%			1008 (58%)	509 (43%)	
36–50%			441 (26%)	417 (35%)	
>50%			279 (16%)	256 (22%)	
LVEDD, mm[b]			56 (49–62)	54 (49–60)	<0.001
Age, years	76 (67–83)	73 (64–82)	77 (69–85)	75 (66–82)	<0.001
Age categories					<0.001
<60 years	728 (14%)	305 (18%)	216 (10%)	207 (14%)	
60–69 years	1093 (20%)	394 (23%)	405 (19%)	294 (20%)	
70–79 years	1588 (30%)	488 (28%)	620 (29%)	480 (33%)	
≥80 years	1950 (36%)	548 (32%)	917 (42%)	485 (33%)	
ECG QRS duration, ms	158 (152–168)	158 (152–164)	160 (154–170)	158 (152–168)	<0.001
Index ECG rhythm (AF)	769 (14%)	143 (8%)	433 (20%)	193 (13%)	<0.001
Type of AF history					<0.001
Paroxysmal AF	208 (14%)	52 (20%)	104 (12%)	52 (16%)	
Persistent AF	30 (2%)	9 (3%)	14 (2%)	7 (2%)	
Permanent AF	191 (13%)	25 (10%)	143 (17%)	23 (7%)	
Undefined AF	1011 (70%)	173 (67%)	600 (70%)	238 (74%)	
CKD	426 (8%)	65 (4%)	290 (13%)	71 (5%)	<0.001
Diabetes mellitus	1503 (28%)	350 (20%)	713 (33%)	440 (30%)	<0.001
Hypertension	2101 (39%)	599 (35%)	975 (45%)	527 (36%)	<0.001
Stroke/TIA	290 (5%)	101 (6%)	112 (5%)	77 (5%)	0.65
PVD	299 (6%)	72 (4%)	148 (7%)	79 (5%)	0.001
Cancer	904 (17%)	330 (19%)	376 (17%)	198 (14%)	<0.001
COPD	332 (6%)	54 (3%)	217 (10%)	61 (4%)	<0.001
Liver disease	59 (1%)	27 (2%)	25 (1%)	7 (0%)	0.014
Ischaemic heart disease	1598 (30%)	272 (16%)	931 (43%)	395 (27%)	<0.001
MI	563 (11%)	94 (5%)	302 (14%)	167 (11%)	<0.001
Dementia	158 (3%)	63 (4%)	72 (3%)	23 (2%)	0.001
AIDS	8 (0%)	1 (0%)	6 (0%)	1 (0%)	0.13
Peptic ulcer	62 (1%)	19 (1%)	28 (1%)	15 (1%)	0.72
Musculoskeletal disease	324 (6%)	77 (4%)	169 (8%)	78 (5%)	<0.001
Hemiplegia	36 (1%)	18 (1%)	10 (0%)	8 (1%)	0.073
Charlson comorbidity index	4 (3–6)	4 (2–5)	5 (4–7)	4 (3–5)	<0.001
Other pacing devices					<0.001
PM	999 (87%)	319 (96%)	357 (78%)	323 (90%)	
ICD	153 (13%)	14 (4%)	102 (22%)	37 (10%)	

AF, atrial fibrillation; AIDS, acquired immunodeficiency syndrome; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; ECG, electrocardiogram; HF, heart failure; ICD, implantable cardioverter defibrillator; LVEF, left ventricular ejection fraction; LVEDD, left ventricular end-diastolic diameter; MI, myocardial infarction; PM, pacemaker; PVD, peripheral vascular disease; TIA, transient ischaemic attack.

[a]Echocardiogram searched in the patients' records: the first constant LVEF ≤ 35% during follow-up or till CRT use was recorded; otherwise, the last LVEF > 35% during follow-up or till CRT use was recorded.

[b]Collected from the same echocardiogram used to collect the LVEF.

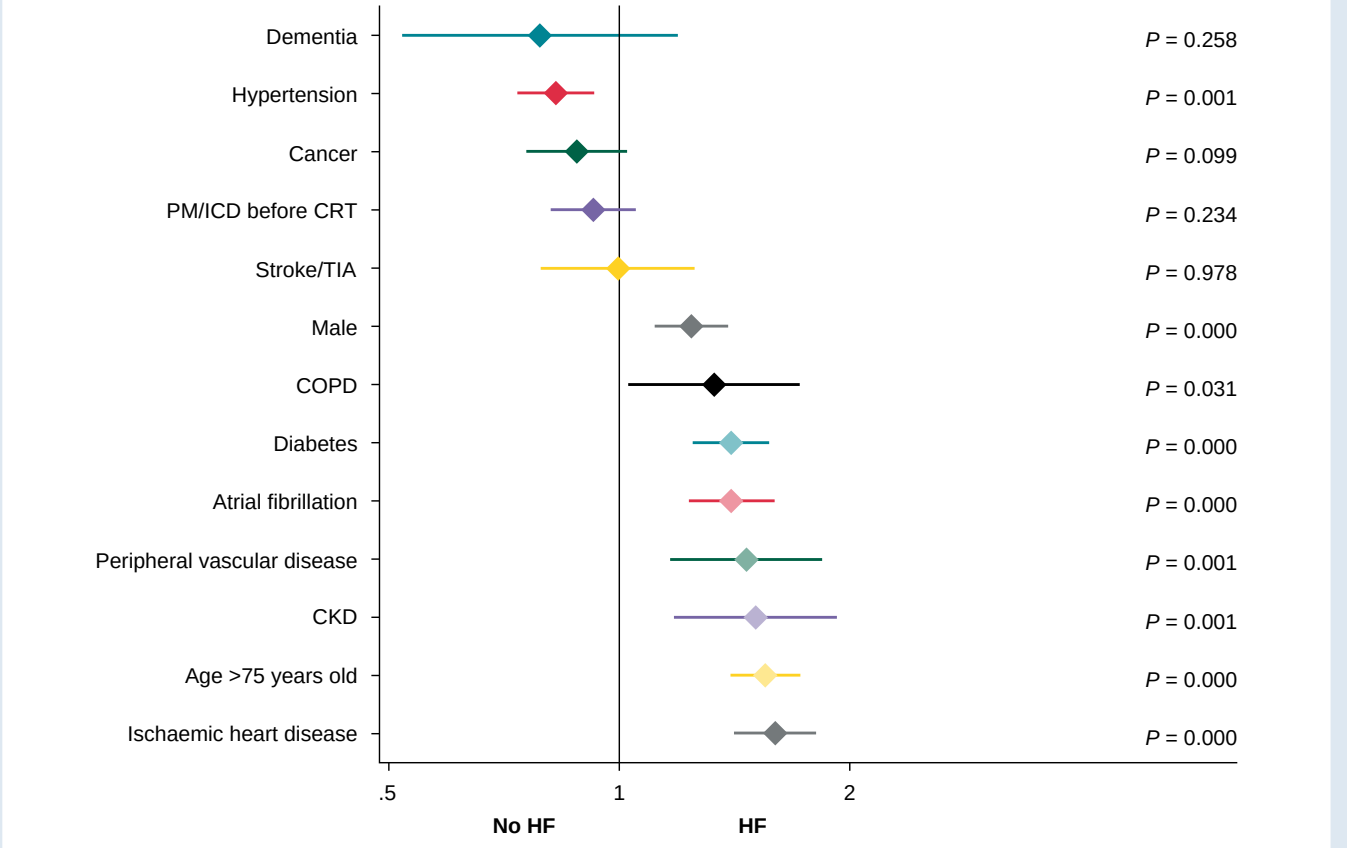


Figure 3 Predictors of developing HF after LBBB with QRS ≥ 150 ms. CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CRT, cardiac resynchronization therapy; HF, heart failure; ICD, implantable cardioverter defibrillator; LBBB, left bundle branch block; PM, pacemaker; TIA, transient ischaemic attack.

compared with those who had a previous history of HF but comparable to those who never developed HF (*Table 1*). The prevalence of HFrEF was higher in those who had a previous history of HF compared with those who developed HF after index ECG (58% vs. 43%).

At the time of index ECG, among patients without a previous diagnosis of HF, male sex, older age (>75 years old), and the diagnosis of COPD, diabetes, AF, PVD, CKD, and ischaemic heart disease were independent predictors of developing HF, while the presence of hypertension was an independent predictor of not developing HF (*Figure 3*); HRs are reported in Supplementary material online, *Table S3*.

Cardiac resynchronization therapy indication

As expected, most patients [4091 patients (76%)] did not meet the criteria for class I CRT indication (42% without HF diagnosis, 27% with an LVEF above 35%; 19% had a follow-up of <12 months, and in another 12%, it was not possible to confirm the indication) nor were they treated with CRT during the study period. In 214 patients who received CRT (4%), it was not possible to establish the class of indication because the echocardiographic data were missing or the available value of LVEF was over 35%. Of 1053 (20%) with a class I CRT indication, 630 (60%) were treated with CRT and 423 (40%) were not (*Figure 1*). The patient characteristics of those with class I CRT indication with or without CRT are reported in *Table 2*. Of those treated with CRT, 47% received CRT without defibrillation function (CRT-P) and 53% CRT with defibrillation function (CRT-D), and the median delay from indication to CRT use was 137 (35–378) days.

At the time of indication for CRT, among the variables tested in our models (see Supplementary material online, *Table S2*), the diagnosis of dementia, the age of over 75 years old, and the diagnosis of COPD were independent predictors of CRT non-use, while the presence of a PM or an implantable cardioverter defibrillator (ICD) was an independent predictor of CRT utilization (*Figure 4*); HRs are reported in Supplementary material online, *Table S4*.

Outcomes

In patients with a class I indication for CRT, after a median follow-up time of 4.0 (2.2–7.6) years from the date of indication, the incidence rate of all-cause of death, CVD, and first HFH for those *not* implanted with CRT compared with those implanted with CRT was 180/1000 person-years (95% CI: 161–203) vs. 62/1000 person-years (95% CI: 55–71), 113/1000 person-years (95% CI: 98–131) vs. 39/1000 person-years (95% CI: 33–47), and 553/1000 person-years (95% CI: 497–616) vs. 216/1000 person-years (95% CI: 197–238), respectively (*Figure 5*). After multiple adjustments, CRT use was associated with a lower overall risk of all-cause of death at 10 years from the indication [HR = 0.67 (95% CI: 0.45–0.99)]; CRT use was also associated with a reduced risk of CVD and first HFH at 5 years from the indication as individual endpoints [HR = 0.47 (95% CI: 0.35–0.63); HR = 0.56 (95% CI: 0.48–0.66)], but no significant risk reduction was

Table 2 Baseline characteristics of patients with an indication for CRT by use or not of CRT

Population with an indication for CRT	Total $n = 1053$	Without CRT $n = 423$	With CRT $n = 630$	*P*-value
Age, years	73 (65–81)	78 (72–85)	69 (62–76)	<0.001
Age categories				<0.001
<60 years	152 (14%)	23 (5%)	129 (20%)	
60–79 years	265 (25%)	65 (15%)	200 (32%)	
70–79 years	350 (33%)	141 (33%)	209 (33%)	
≥80 years	286 (27%)	194 (46%)	92 (15%)	
HF history				0.53
HF before index ECG	683 (65%)	270 (64%)	413 (66%)	
HF after index ECG	370 (35%)	153 (36%)	217 (34%)	
LVEF, %[a]	27 (23–33)	30 (23–33)	27 (20–30)	0.001
LVEF categories[a]				
≤35%	1053 (100%)	423 (100%)	630 (100%)	
LVEDD, mm[b]	60 (56–65)	59 (53–63)	62 (58–67)	<0.001
Index ECG QRS duration, ms	160 (154–170)	160 (154–168)	162 (154–172)	0.001
Index ECG rhythm (AF)	166 (16%)	67 (16%)	99 (16%)	0.97
Type of AF history				<0.001
History of paroxysmal AF	79 (7%)	27 (6%)	52 (8%)	
History of persistent AF	9 (1%)	2 (0%)	7 (1%)	
History of permanent AF	46 (4%)	0 (0%)	46 (7%)	
History of undefined AF	268 (25%)	128 (30%)	140 (22%)	
CKD	117 (11%)	63 (15%)	54 (9%)	0.001
Diabetes mellitus	384 (36%)	155 (37%)	229 (36%)	0.95
Hypertension	511 (48%)	213 (50%)	298 (47%)	0.35
Stroke/TIA	83 (8%)	43 (10%)	40 (6%)	0.025
PVD	76 (7%)	40 (9%)	36 (6%)	0.022
Cancer	199 (19%)	90 (21%)	109 (17%)	0.11
COPD	89 (8%)	51 (12%)	38 (6%)	<0.001
Liver disease	8 (1%)	4 (1%)	4 (1%)	0.57
Ischaemic heart disease	488 (46%)	211 (50%)	277 (44%)	0.064
MI	185 (18%)	82 (19%)	103 (16%)	0.21
Dementia	22 (2%)	20 (5%)	2 (0%)	<0.001
AIDS	3 (0%)	2 (0%)	1 (0%)	0.35
Peptic ulcer	14 (1%)	3 (1%)	11 (2%)	0.15
Musculoskeletal disease	111 (11%)	51 (12%)	60 (10%)	0.19
Hemiplegia	8 (1%)	5 (1%)	3 (0%)	0.20
CRT-P	293 (28%)	0 (0%)	293 (47%)	
CRT-D	337 (32%)	0 (0%)	337 (53%)	
Charlson comorbidity index	5 (4–7)	6 (5–7)	4 (3–6)	<0.001
Devices (not CRT)				0.004
PM	122 (12%)	59 (14%)	63 (10%)	
ICD	68 (6%)	16 (4%)	52 (8%)	

AF, atrial fibrillation; AIDS, acquired immunodeficiency syndrome; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease, CRT, cardiac resynchronization therapy; CRT-D, cardiac resynchronization therapy with defibrillation function; CRT-P, cardiac resynchronization therapy without defibrillation function; ECG, electrocardiogram; HF, heart failure; ICD, implantable cardioverter defibrillator; LVEF, left ventricular ejection fraction; LVEDD, left ventricular end-diastolic diameter; MI, myocardial infarction; PM, pacemaker; PVD, peripheral vascular disease; TIA, transient ischaemic attack.

[a]Echocardiogram searched in the patients' records: the first constant LVEF ≤ 35% was recorded; otherwise, the last LVEF > 35% was recorded.

[b]Collected from the same echocardiogram used to collect the LVEF.

observed at 10 years from indication. Crude and adjusted HRs are reported in *Table 3*.

Sensitivity analysis

In patients with a class I indication for CRT, considering non-CVD as a competing risk, the results were consistent: the use of CRT was associated with a lower risk of CVD and first HFH in the first 5 years from the indication (see Supplementary material online, *Figure S1*).

Discussion

In this analysis, we describe a large and unselected cohort of LBBB patients with a wide QRS duration (≥150 ms). As previously shown from several epidemiological studies, LBBB conduction abnormality is associated with comorbidities and worse prognosis and its prevalence increases with age and varies in accordance with cardiovascular disease profiles.[8,9] Furthermore, LBBB not only is easy to be diagnosticated but also has important therapeutic implications. In HF, electrical dyssynchrony further aggravates the HF condition.[10,11] Conversely, LBBB may cause left ventricular dysfunction and eventually HF over time, a condition that can be reversed by CRT.[5]

In terms of comorbidities, significant differences, as expected, were visible between those who had HF at the time of LBBB development compared with those who did not develop HF or developed HF after LBBB diagnosis.

In our cohort, 41% of patients had a previous history of HF. Although there are difficulties in comparison due to different populations' selection criteria and definitions, these results are in line with previous findings in patients with LBBB.[1,9] Left bundle branch block is associated with HF and several comorbidities, and older age and male sex were associated with a higher risk of developing HF.[12]

As many clinical trials demonstrated the CRT benefit in terms of morbidity, mortality, and quality of life, it was also confirmed in this and other large unselected material, as many studies showed how CRT is still largely underused in Europe and Sweden. The magnitude of the problem varies based on eligibility criteria and population selection.[13,14] Lund *et al.*[15] reported that CRT underutilization varies, depending on different consistency analyses, from 69 to 79% based on class I and IIa indications from 2013 EHRA. Linde *et al.*[16] estimated that two-thirds of eligible HFrEF patients were not receiving CRT. In our study, the percentage of underuse was relatively lower (40%). This finding is mainly explained by our selection criteria that were limited, different from other studies, solely class I indication (HF with EF ≤ 35%, LBBB, and QRS ≥ 150 ms, without a history of permanent AF and survival of at least 12 months), based on the recent 2021 EHRA guidelines on cardiac pacing that had extended the indications in regard to symptoms but restricted the indications regarding morphology and QRS duration.[6] Furthermore, the region is also well-supplied with hospital care and three CRT-implanting hospitals and our results cannot be extended to regions with worse healthcare access. We think that having limited the analysis to class I indication, a setting where CRT is proven to be beneficial without any doubt and that includes the majority of CRT device implantation in Europe,[17] underlines, even more, that a big room for improvement is present in terms of therapy implementation. Notably, accurate data on NYHA class were not retrievable from our sources, and thus, all the patients with HF and LVEF ≤ 35% were considered symptomatic. However, although the recent 2022 American HF guidelines required NYHA class II-III or ambulatory IV to fulfil class I indication[18] and less strength of evidence for CRT and NYHA class I is reported in 2021 EHRA/ESC guidelines on cardiac pacing[6] and 2021 ESC/HFA guidelines on chronic HF,[19] we assume that the majority of HF patients with LVEF ≤ 35% in our cohort, in accordance with NYHA class distribution in HFrEF, had NYHA class II or more.[20,21] Different from previous studies, where the indication was estimated

Table 3 Crude and adjusted HRs in patients with an indication for CRT between those with CRT and without CRT for all-cause of death, CVD, and first HFH at 5 and 10 years from the indication

CRT vs. not CRT	All-cause of death				CVD				First HFH			
	5 years	95% CI	*P*-value	10 years	95% CI	*P*-value	5 years	95% CI	*P*-value	10 years	95% CI	*P*-value
Crude HR	0.30	0.24–0.36	<0.001	0.40	0.28–0.58	<0.001	0.30	0.23–0.39	<0.001	0.38	0.25–0.59	<0.001	0.43	0.37–0.50	<0.001	1.12	0.59–2.12	0.741
Adjusted HR	0.45	0.36–0.57	<0.001	0.67	0.45–0.99	0.047	0.47	0.35–0.63	<0.001	0.67	0.41–1.10	0.110	0.56	0.48–0.66	<0.001	1.34	0.68–2.65	0.402

CI, confidence interval; CRT, cardiac resynchronization therapy; CVD, cardiovascular death; HFH, heart failure hospitalization; HR, hazard ratio; vs., versus.

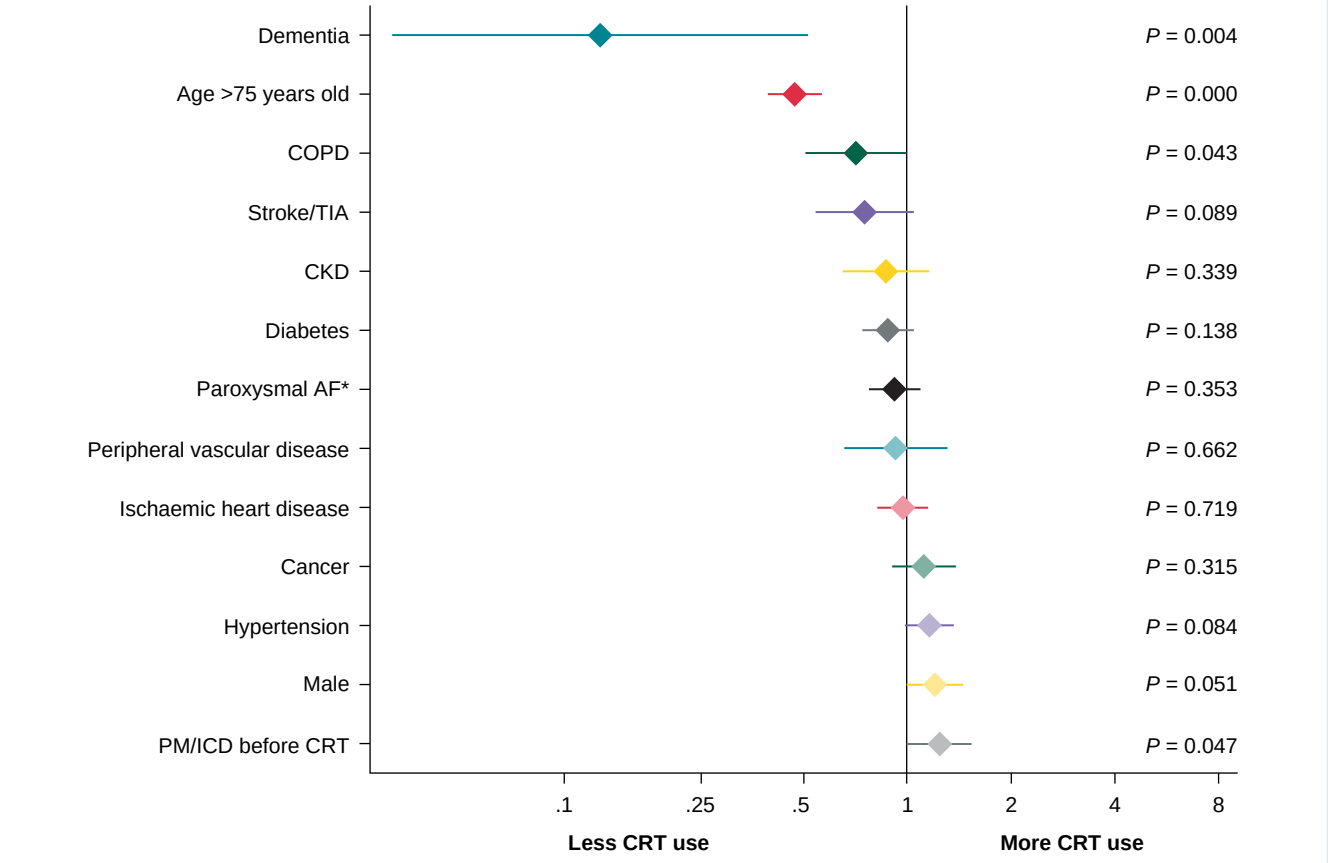


Figure 4 Predictors of CRT use at the time of CRT indication. AF, atrial fibrillation; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CRT, cardiac resynchronization therapy; ICD, implantable cardioverter defibrillator; PM, pacemaker; TIA, transient ischaemic attack. *Paroxysmal or undefined AF.

based on a baseline time point data collection, the strength of our longitudinal data, which could partially explain the lower prevalence of CRT underuse, was the possibility to estimate the time when the indication was met during follow-up. This allowed us to restrict the indication only to those who lived >1 year and exclude those who had only a temporary indication. Furthermore, it was possible to calculate the delay from the indication to CRT use. A recently published large national perspective on the timing of CRT after HFH emphasized the association of total mortality and delay of CRT from the first HFH.[22] Our results showed also how CRT implementation is affected by a substantial delay. Therefore, strong efforts have to be undertaken to timely adopt CRT when indicated. Interestingly, we evaluated the predictors of CRT utilization based on clinical characteristics at the time of indication; this might give more pragmatic evidence of what influences doctors' decisions. First of all, the older age (>75 years old) was an independent factor of CRT non-use. It is important to underline how CRT in older age is associated with survival benefits irrespective of age.[23] Therefore, there is no evidence of holding back a beneficial therapy when indicated even in older patients. Thus, CRT is beneficial both for patients' reported outcomes and for treatment facilitation, which is even more relevant in the elderly.[24] Dementia was also associated with CRT underuse, but perhaps this should not be the case, as a diminished risk for hospital care is relevant also in this patient group. On the other side, little evidence is available for patients with dementia; therefore, CRT has to be evaluated case by case, considering that patient acceptance might play a relatively bigger role. While many comorbidities were not associated with differences in CRT use in the multivariable analysis, COPD was still an independent factor associated with CRT underuse. In our analysis, males have a slightly higher likelihood of CRT use. Although not statistically significant, considering the different adherence to class I indication showed by Normand *et al.*[17] and the results showed by Chatterjee *et al.*[25] on CRT-D, this finding could be relevant and not attributable to chance. The presence of a PM or an ICD was associated with CRT use. These findings can be explained by the fact that patients with a device had more frequent and specialized medical contacts such as with device follow-up clinics with higher awareness of CRT. However, it was not possible for us to adjust for this factor. Furthermore, the bias of patient acceptance for device therapy and its associated limitation has to be considered.[26] In the previous analysis of the Swedish HF registry, surprisingly, even after adjusting for NYHA class and organizational factors, a strong association was found between AF and a lower risk of CRT underuse.[15] This finding was not confirmed in our analysis, where the history of AF was available at the time of CRT indication and patients with persistent and permanent AF were not considered having a class I indication for CRT if not implanted.

Outcomes

Patients with broad LBBB QRS morphology in sinus rhythm and symptomatic HFrEF are the perfect candidates for CRT, and although landmark clinical trials have been conducted more than two decades ago, CRT is still one of the most beneficial, with a lower number needed

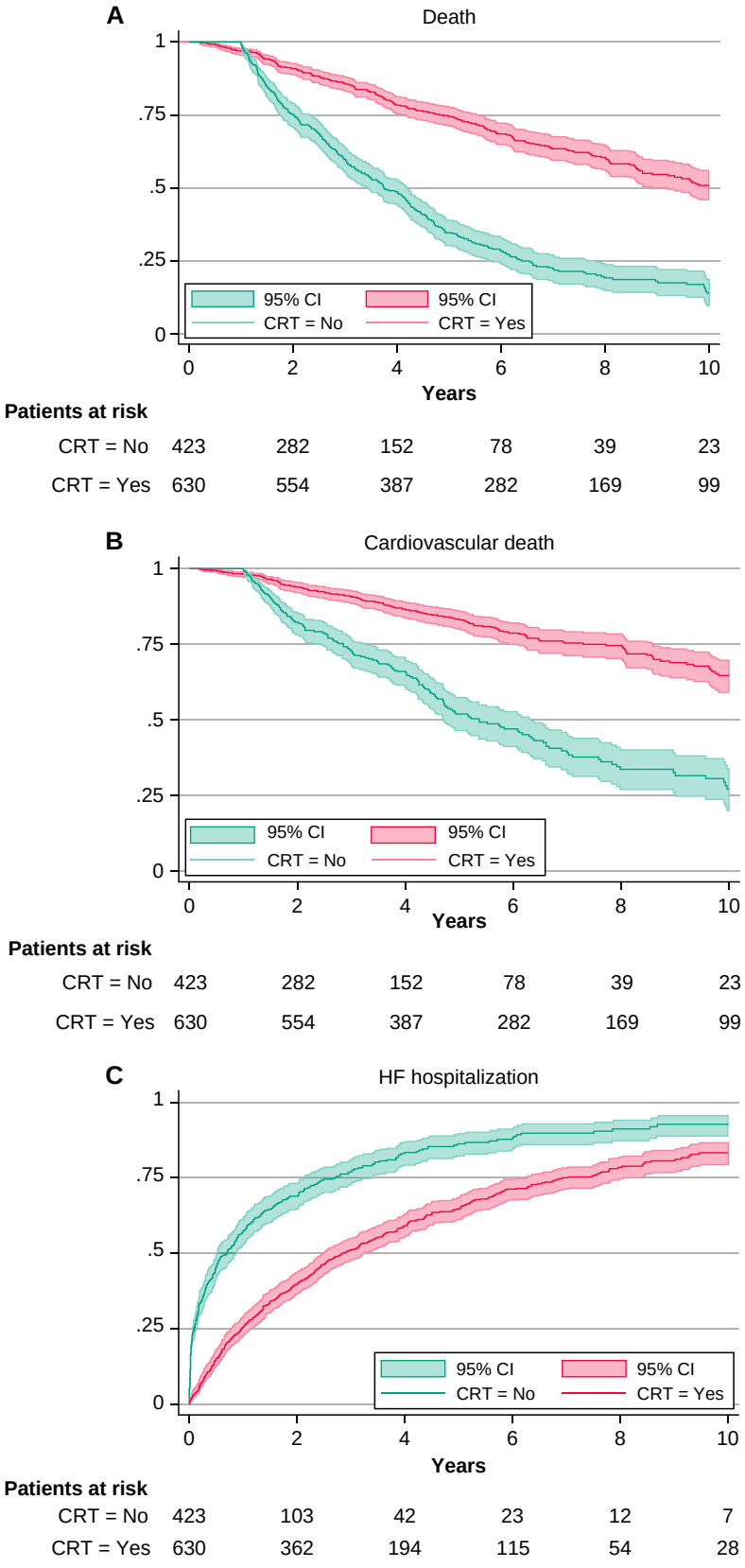


Figure 5 Survival function for all-cause of death (*A*), CVD (*B*), and first HFH (*C*) between patients with or without CRT despite the indication. With CRT (grey), without CRT (green). CI, confidence interval; CRT, cardiac resynchronization therapy; CVD, cardiovascular death; HFH, heart failure hospitalization.

to treat medications available for these patients.[27] Our study showed that independent of age, sex, and comorbidities, CRT use is associated with lower all-cause mortality and cardiovascular mortality and less HFH in the first 5 years after the indication and, importantly, also after 10 years for the overall mortality. These results are consistent in the sensitivity analysis where non-CVD is accounted as a competing risk. Notably, as previously shown by Noordzij *et al*.,[28] models without the competing risk effect overestimate the outcome rate affected by the competing risk but the efficacy of CRT is still clearly present. Therefore, the competing risk of death on specific causes of death, which is relevant in the elderly and with constant improvement of medical treatment, has to be and is studied in clinical trials such as the RESET-CRT trial (NCT03494933) to determine whether the benefit overwhelms the risk of an expensive therapy like CRT-P vs. CRT-D.[29] These findings are crucial to stress furthermore the importance of not withholding a therapy when indicated and considering new strategies that may lead patients' features to survival benefits like device remote monitoring.[30] Although some together with older age might be associated with lower CRT response, this should not lead to CRT underutilization as shown in the recent EHRA document by Mullens *et al*.[14]

Limitations

Our analysis is affected by several limitations. The observational design of the current study implies that causality could be extrapolated. Potential residual and unknown confounders despite a large adjustment have to be accounted for. Important information like medical treatment and socioeconomic characteristics were not available in our database, and we could not account for them, but we planned to implement and further analyse these aspects. Our results are not generalizable to non-LBBB or shorter QRS duration. Our study is limited to the Stockholm region, and the extrapolation of data like the CRT-P/CRT-D ratio may not be representative of other populations. The absence of medical treatment, NT-proBNP, and laboratory finding information is a major limitation since it was not possible to include them in the adjustments.

A selection bias in patients who received or did not receive CRT cannot be ruled out and may affect the outcome of our study. The definition of CRT indication and the characteristics were extrapolated by the available variable, and misclassification could not be completely excluded. Furthermore, it was not possible to exclude patients with persistent AF from class I indication for CRT because of the retrospective data and the overtime overlapping diagnosis with paroxysmal AF. The presence of undefined AF in our criteria for class I indication for CRT has to be considered since it implies a proportion of misclassification in accordance with the recent 2021 ESC-EHRA guideline indication. The expected relatively low numbers and the quality of the data sources should have unlikely impacted our results. The selection of a broad timeframe could increase the heterogeneity in CRT indications during the study period but, beyond allowing a longer follow-up, gives a broad perspective of CRT utilization. The succession of different CRT recommendations over the years limits the extrapolation of results to a single timeframe and affects the results. Therefore, a time-adjusted analysis was adopted. Many variables are based on ICD codes, and misclassification cannot be completely ruled out, but the longitudinal structure of our data allowed us to account for variation during the study period and reduce the misclassification and risk of missing data. Missing data were present, especially regarding echocardiographic parameters; under the assumption of random missingness, we think that this had a limited effect on the results.

Conclusions

Left bundle branch block is a marker of worse prognosis, but it is also a characteristic, in HFrEF patients, that could indicate that a very beneficial therapy is available (CRT). Our study and others indicate that CRT is beneficial but still affected by significant underuse. Therefore, it is crucial to find ways of better implementing CRT utilization and to better understand the characteristics that influence the management of our patients.

Supplementary material

Supplementary material is available at *Europace* online.

Funding

Unrestricted grant Medtronic, Institutional research funds.

Conflict of interest: P.G. reports no conflict of interest related to this work. S.L. reports no conflict of interest related to this work. I.K. reports no conflict of interest related to this work. A.A. reports no conflict of interest related to this work. G.S. reports research support from Vifor Pharma, Cytokinetics, Boehringer Ingelheim, Boston Scientific, AstraZeneca, Novartis, Merck, Pharmacosmos, Bayer, and Horizon 2022 funding; consulting fees from TEVA, MIUR (Ministero dell'Istruzione, Universita´ e Ricerca), Medical Education Global Solutions, Atheneum, Genesis, Vifor Pharma, and Agence Recherche (ANR); payment or honoraria from Servier, Roche, Cytokinetics, Translational Medicine Academy Foundation (TMA), Medtronic, Medical Education Global Solutions, Dynamicom Education, AstraZeneca, Vifor Pharma, and Novartis; and participation in Advisory Board for AstraZeneca, Edwards, Uppsala Clinical Research Center (UCR), Vifor, and Servier, all outside the present work. M.A. reports no conflict of interest related to this work. C.L. reports receiving research support from the Swedish Heart Lung Foundation, Swedish Royal Society of Science, and Stockholm County Council; consulting fees from AstraZeneca and Roche Diagnostics; and speaker honoraria from Novartis, Astra, Bayer, Vifor Pharma, Medtronic, and Impulse Dynamics and serves on advisory boards for Astra Zeneca, all outside the present work. F.G. reports no conflict of interest related to this work

Data availability

Data cannot be shared for ethical/privacy reasons.

References

1. Søndergaard MM, Riis J, Bodker KW, Hansen SM, Nielsen J, Graff C *et al.* Associations between left bundle branch block with different PR intervals, QRS durations, heart rates and the risk of heart failure: a register-based cohort study using ECG data from the primary care setting. *Open Heart* 2021;**8**:e001425.
2. Francia P, Balla C, Paneni F, Volpe M. Left bundle-branch block—pathophysiology, prognosis, and clinical management. *Clin Cardiol* 2007;**30**:110–5.
3. Schneider JF, Thomas HE, Kreger BE, McNamara PM, Kannel WB. Newly acquired left bundle-branch block: the Framingham study. *Ann Intern Med* 1979;**90**:303–10.
4. Rasmussen PV, Skov MW, Ghouse J, Pietersen A, Hansen SM, Torp-Pedersen C *et al.* Clinical implications of electrocardiographic bundle branch block in primary care. *Heart* 2019;**105**:1160–7.
5. Vaillant C, Martins RP, Donal E, Leclercq C, Thébault C, Behar N *et al.* Resolution of left bundle branch block-induced cardiomyopathy by cardiac resynchronization therapy. *J Am Coll Cardiol* 2013;**61**:1089–95.
6. Glikson M, Nielsen JC, Kronborg MB, Michowitz Y, Auricchio A, Barbash IM *et al.* 2021 ESC guidelines on cardiac pacing and cardiac resynchronization therapy. *Europace* 2022;**24**:71–164.
7. Lund LH, Jurga J, Edner M, Benson L, Dahlström U, Linde C *et al.* Prevalence, correlates, and prognostic significance of QRS prolongation in heart failure with reduced and preserved ejection fraction. *Eur Heart J* 2013;**34**:529–39.
8. Eriksson P, Hansson PO, Eriksson H, Dellborg M. Bundle-branch block in a general male population: the study of men born 1913. *Circulation* 1998;**98**:2494–500.
9. Wang B, Wang Z, Yang X, Han X, Yang Y, Chu H *et al.* Prevalence and incidence of intraventricular conduction disturbances among Chinese adults: results from the Kailuan study. *Front Cardiovasc Med* 2022;**9**:959781.
10. Silvet H, Amit J, Padmanabhan S. Increased QRS-duration reduces survival in patients with left ventricular dysfunction: results form a cohort of 2263 patients. *J Am Coll Cardiol* 1999;**33**:145A.
11. Baldasseroni S, Opasich C, Gorini M, Lucci D, Marchionni N, Marini M *et al.* Left bundle-branch block is associated with increased 1-year sudden and total mortality rate in 5517 outpatients with congestive heart failure: a report from the Italian network on congestive heart failure. *Am Heart J* 2002;**143**:398–405.

12. Zannad F, Huvelle E, Dickstein K, van Veldhuisen DJ, Stellbrink C, Køber L *et al.* Left bundle branch block as a risk factor for progression to heart failure. *Eur J Heart Fail* 2007;**9**:7–14.
13. Tymińska A, Ozierański K, Brociek E, Kapłon-Cieślicka A, Balsam P, Marchel M *et al.* Fifteen-year differences in indications for cardiac resynchronization therapy in international guidelines—insights from the heart failure registries of the European Society of Cardiology. *J Clin Med* 2022;**11**:3236.
14. Mullens W, Auricchio A, Martens P, Witte K, Cowie MR, Delgado V *et al.* Optimized implementation of cardiac resynchronization therapy: a call for action for referral and optimization of care. *Europace* 2021;**23**:1324–42.
15. 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**:1270–9.
16. Linde C, Ståhlberg M, Benson L, Braunschweig F, Edner M, Dahlström U *et al.* Gender, underutilization of cardiac resynchronization therapy, and prognostic impact of QRS prolongation and left bundle branch block in heart failure. *Europace* 2015;**17**:424–31.
17. Normand C, Linde C, Blomström-Lundqvist C, Stellbrink C, Gasparini M, Anker SD *et al.* Adherence to ESC cardiac resynchronization therapy guidelines: findings from the ESC CRT Survey II. *Europace* 2020;**22**:932–8.
18. Heidenreich PA, Bozkurt B, Aguilar D, Allen LA, Byun JJ, Colvin MM *et al.* 2022 AHA/ACC/HFSA guideline for the management of heart failure. *J Am Coll Cardiol* 2022;**79**:e263–421.
19. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M *et al.* 2021 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J* 2021;**42**:3599–726.
20. Greene SJ, Butler J, Spertus JA, Hellkamp AS, Vaduganathan M, DeVore AD *et al.* Comparison of New York Heart Association class and patient-reported outcomes for heart failure with reduced ejection fraction. *JAMA Cardiol* 2021;**6**:522–31.
21. Savarese G, Becher PM, Lund LH, Seferovic P, Rosano GMC, Coats AJS. Global burden of heart failure: a comprehensive and updated review of epidemiology. *Cardiovasc Res* 2022;**118**:3272–3287.
22. Leyva F, Zegard A, Patel P, Stegemann B, Marshall H, Ludman P *et al.* Timing of cardiac resynchronization therapy implantation. *Europace* 2023;**25**:euad059.
23. Verbrugge FH, Dupont M, De Vusser P, Rivero-Ayerza M, Van Herendael H, Vercammen J *et al.* Response to cardiac resynchronization therapy in elderly patients (≥70 years) and octogenarians. *Eur J Heart Fail* 2013;**15**:203–10.
24. Stolfo D, Lund LH, Becher PM, Orsini N, Thorvaldsen T, Benson L *et al.* Use of evidence-based therapy in heart failure with reduced ejection fraction across age strata. *Eur J Heart Fail* 2022;**24**:1047–62.
25. Chatterjee NA, Borgquist R, Chang Y, Lewey J, Jackson VA, Singh JP *et al.* Increasing sex differences in the use of cardiac resynchronization therapy with or without implantable cardioverter-defibrillator. *Eur Heart J* 2017;**38**:1485–94.
26. Januszkiewicz Ł, Barra S, Providencia R, Conte G, de Asmundis C, Chun JKR *et al.* Long-term quality of life and acceptance of implantable cardioverter-defibrillator therapy: results of the European Heart Rhythm Association survey. *Europace* 2022;**24**:860–7.
27. Srivastava PK, Claggett BL, Solomon SD, McMurray JJV, Packer M, Zile MR *et al.* Estimated 5-year number needed to treat to prevent cardiovascular death or heart failure hospitalization with angiotensin receptor-neprilysin inhibition vs standard therapy for patients with heart failure with reduced ejection fraction: an analysis of data from the PARADIGM-HF trial. *JAMA Cardiol* 2018;**3**:1226–31.
28. Noordzij M, Leffondré K, van Stralen KJ, Zoccali C, Dekker FW, Jager KJ. When do we need competing risks methods for survival analysis in nephrology? *Nephrol Dial Transplant* 2013;**28**:2670–7.
29. Schrage B, Lund LH, Melin M, Benson L, Uijl A, Dahlström U *et al.* Cardiac resynchronization therapy with or without defibrillator in patients with heart failure. *Europace* 2022;**24**:48–57.
30. Kolk MZH, Narayan SM, Clopton P, Wilde AAM, Knops RE, Tjong FVY. Reduction in long-term mortality using remote device monitoring in a large real-world population of patients with implantable defibrillators. *Europace* 2023;**25**:969–77.