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RESEARCH ARTICLE

Cardiac resynchronization therapy for enabling guideline-directed medical therapy optimization in heart failure

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Aims We aimed to assess whether cardiac resynchronization therapy (CRT) might serve as an enabler for guideline-directed medical therapy (GDMT) optimization.

Methods and results Patients with heart failure with reduced ejection fraction (HFrEF) enrolled in the Swedish Heart Failure Registry between January 2009 and August 2022 were considered. Patients receiving a CRT close to the index registration were the cases, whereas controls had not received a CRT despite having an indication. Overall, 1543 (25%) HFrEF cases and 4537 (75%) controls were analysed in the intention-to-treat analysis. At baseline, beta-blockers, angiotensin-converting enzyme inhibitor (ACEi), angiotensin receptor blocker (ARB) or angiotensin receptor–neprilysin inhibitor (ARNi), mineralocorticoid receptor antagonist (MRA) and loop diuretic use was 84% versus 86%, 89% versus 88%, 57% versus 46% and 62% versus 59% in patients receiving versus not receiving CRT, respectively. At 1.5-year follow-up, patients receiving a CRT more likely experienced an improved use/dose of beta-blocker therapy (46% vs. 35%) and decreased loop diuretic use/dose (30% vs. 24%) versus controls. These associations were consistent after adjustments (odds ratio [OR] 1.83, 95% confidence interval [CI] 1.58–2.13, and OR 1.26, 95% CI 1.07–1.48, respectively), and confirmed in the per-protocol analysis (i.e. after excluding controls who received a CRT during follow-up). A significant association between CRT and the likelihood of ACEi/ARB/ARNi and MRA optimization (OR 1.22, 95% CI 1.04–1.44, and OR 1.25, 95% CI 1.05–1.50, respectively) was observed in the per-protocol analysis.

Conclusions In this large nationwide real-world population with HFrEF, CRT implantation was associated with enabled use/dose of heart failure GDMT and decreased loop diuretic need (use/dose).

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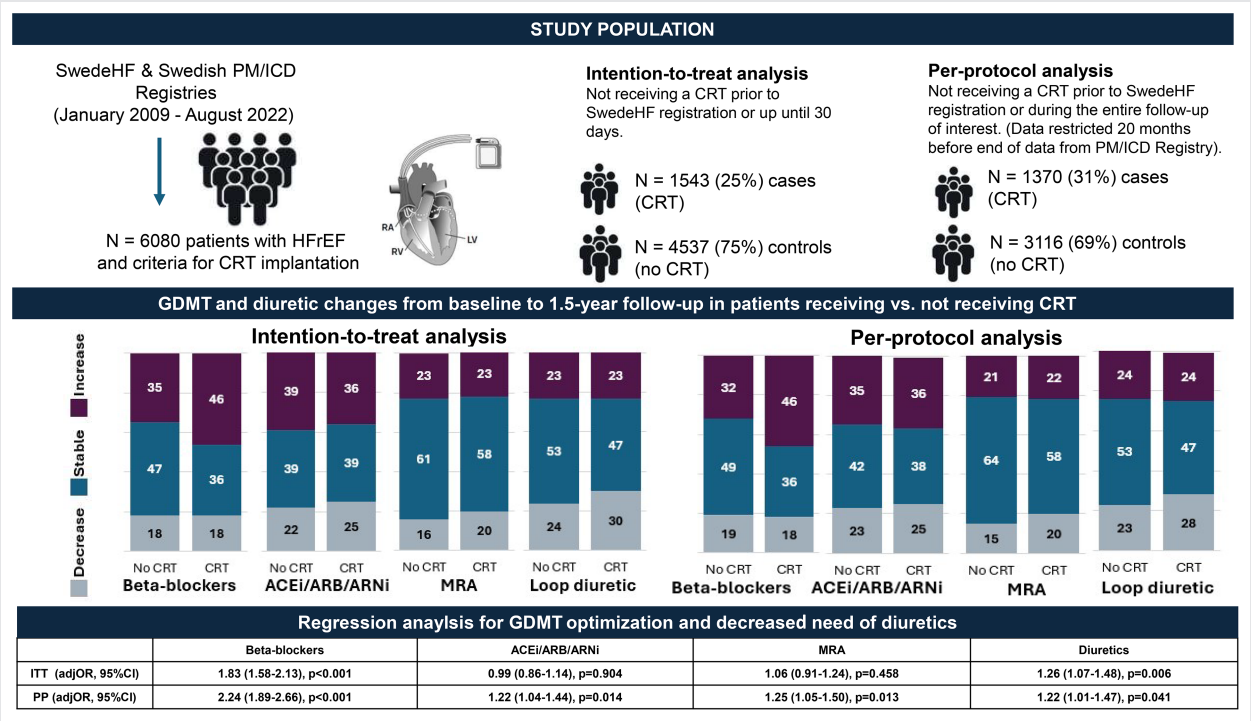
Graphical Abstract



Regression anaylsis for GDMT optimization and decreased need of diuretics

	Beta-blockers	ACEi/ARB/ARNi	MRA	Diuretics
ITT (adjOR, 95%CI)	1.83 (1.58-2.13), p<0.001	0.99 (0.86-1.14), p=0.904	1.06 (0.91-1.24), p=0.458	1.26 (1.07-1.48), p=0.006
PP (adjOR, 95%CI)	2.24 (1.89-2.66), p<0.001	1.22 (1.04-1.44), p=0.014	1.25 (1.05-1.50), p=0.013	1.22 (1.01-1.47), p=0.041

Cardiac resynchronization therapy (CRT) as an enabler for guideline-directed medical therapy (GDMT) in the Swedish Heart Failure Registry (SwedeHF). The figure summarizes the selection of the study population, changes in GDMTs and loop diuretic use/doses from baseline to 1.5-year follow-up in patients receiving versus not receiving CRT, and reports the results of the regression model for the association between CRT and GDMT optimization (i.e. increased vs. stable/decreased use/doses) and decrease in loop diuretic need (use/dose). Both intention-to-treat (ITT) and per-protocol (PP) results are reported. ACEi, angiotensin-converting enzyme inhibitor; adjOR, adjusted odds ratio; ARB, angiotensin receptor blocker; ARNi, angiotensin receptor–neprilysin inhibitor; CI, confidence interval; HFrEF, heart failure with reduced ejection fraction; ICD, implantable cardiac defibrillator; MRA, mineralocorticoid receptor antagonist; PM, pacemaker.

Keywords Cardiac resynchronization therapy • Guideline-directed medical therapy • Optimization • Loop diuretics • Heart failure

Introduction

Guideline-directed medical therapy (GDMT) reduces morbidity and mortality in patients with heart failure (HF) with reduced ejection fraction (HFrEF).[1] However, initiation and up-titration towards target doses is often suboptimal in daily clinical practice.[2–5]

The 2021 European Society of Cardiology (ESC) HF guidelines recommend cardiac resynchronization therapy (CRT) for patients with HF in sinus rhythm and with wide QRS duration (with a different class of recommendation according to QRS duration and morphology) who remain symptomatic and maintain a left ventricular ejection fraction ≤35% despite optimal medical therapy.[1] Optimal medical therapy may be insufficiently implemented before implantation due to actual or perceived tolerability issues.[6–8] In previous studies, only a minority of patients implanted with CRT have been reported to be on maximal doses of GDMT before CRT.[8]

Cardiac resynchronization therapy-induced left ventricular reverse remodelling leads to improved systolic function and cardiac output, and consequently lower mortality and morbidity, with improvements in functional capacity and quality of life.[9–12] Therefore, it may enable GDMT optimization through multiple mechanisms, including an increase in systolic blood pressure (SBP), improvement in renal function secondary to better perfusion and reduced venous congestion,[10,11,13] by protecting from bradycardia, and by improving general and HF-related well-being.

Thus, the aim of this study was to evaluate whether CRT might play a role as enabler for GDMT optimization and for reducing loop diuretic need, by comparing patterns in HFrEF treatment use at versus post-CRT implantation with those from a control cohort with an indication not followed by the implantation of a CRT, in the nationwide HFrEF population from the Swedish HF Registry (SwedeHF) linked with the Swedish Pacemaker and Implantable

Cardiac Defibrillator Registry, and other Swedish administrative registries.

Methods

Data sources

The study population was extracted from the SwedeHF, which has been previously described.[14] Briefly, it is an ongoing nationwide quality registry started in 2000 that includes in- and out-of-hospital patients with HF, regardless of ejection fraction.[14] Ejection fraction is collected in most patients as a categorical variable (i.e. <40%, 40–49%, >50%), and therefore we defined HFrEF as ejection fraction <40% and not as ≤40% according to HF guidelines.[1]

For this study, SwedeHF was linked with (1) the Swedish Pacemaker and Implantable Cardiac Defibrillator Registry (http://www.pacemakerregistret.se) that provided information on the date of CRT implantation. This registry collects data on pacemaker implants from 1989 and on implantable cardiac defibrillator implants from 2004, with more than 40 contributing centres covering >95–98% of the total implantations in Sweden; (2) the National Patient Register that provided data on comorbidities; (3) the National Prescribed Drug Register that provided information on all prescribed drugs dispensed in pharmacies; (4) the longitudinal integrated database for health insurance and labour market studies and the Register of the Total Population that provided data on the socioeconomic factors.

Linkage between these registries was made possible by the personal identification number, which all residents in Sweden have.[15] The data source and definition for each variable is reported in online supplementary *Table Appendix S1*.[16] More information on linkage and data management were made available online.[17]

This analysis including the linkage across several registries was approved by the Swedish Ethical Review Authority and complies with the Declaration of Helsinki. Individual patient consent was not required, but patients were informed of entry into SwedeHF and the Swedish Pacemaker and Implantable Cardiac Defibrillator Registry and could opt out.

Study population

Patients with HFrEF and a registration in SwedeHF within 1 year before or 30 days after a first CRT implantation were considered as cases. The timing of inclusion was restricted from 1 January 2009, since ESC guidelines for CRT were first published in 2007 and ESC HF guidelines were then updated in 2008,[18,19] to 31 August 2022, due to data availability (online supplementary *Figure Appendix S1*). Recommendations for CRT slightly changed over time until the 2021 ESC HF guidelines (online supplementary *Table S2*). A control population with a potential indication but not implanted with a CRT prior to or up until 30 days after the SwedeHF registration, was selected during the same time period if fulfilling the following criteria: HFrEF, QRS ≥130 ms and left bundle branch block or QRS ≥150 ms and no left bundle branch block.[1] Both patients with sinus rhythm and atrial fibrillation were included as controls since initial recommendations for CRT were not restricted to patients in sinus rhythm. A minimal HF duration of 3 months was required to have ensured GDMT optimization.

If the same patient was registered in SwedeHF more than once, we selected the first record where the control was potentially eligible (online supplementary *Figure Appendix S1*).

Definitions

The date of inclusion (baseline) in the current study was defined as the date of CRT implantation for the CRT population and the index date (i.e. registration in SwedeHF) for the controls.

A patient was defined as receiving GDMT and loop diuretics at baseline if there was a dispensed prescription in the National Prescribed Drug Register 4 months prior up until the day before the date of inclusion (i.e. CRT implantation for the CRT population and registration in SwedeHF for the controls). GDMT and loop diuretic use at 1.5-year follow-up was defined as a dispensed prescription registered in the National Prescribed Drug Register 18 ±2 months after the date of inclusion. Thus, a minimum follow-up to ensure re-evaluation of GDMT at 1.5 year was set at 20 (18 + 2) months, and patients who died before (2691 controls [28%] and 491 cases [17%]) or with a shorter follow-up were excluded (online supplementary *Figure Appendix S1*).

From the National Prescribed Drug Register the dispensation closest to date of inclusion (for baseline use) and 1.5-year follow-up (for follow-up use) was chosen if multiple dispensations were registered during the defined time window. Additional information about the dose calculation is reported in online supplementary *Table Appendix S1*.

For the purpose of the current analysis, use and dose of the following GDMTs were examined at inclusion and at follow-up: (1) beta-blockers; (2) angiotensin-converting enzyme inhibitors (ACEi), angiotensin receptor blockers (ARB) or angiotensin receptor–neprilysin inhibitor (ARNi), and (3) mineralocorticoid receptor antagonists (MRA). Sodium–glucose cotransporter 2 inhibitors were not evaluated as data collection occurred mostly before their indication for HFrEF treatment.[1] For each medication, the achieved fractional dose (%) of the target dose was categorized as: 0%-not treated, <25%, 25–49%, 50–74%, 75–99%, 100-target dose. Target doses for GDMT were defined as in the current HF guidelines[1] (online supplementary *Table S3*). Furthermore, the dispensed prescription of loop diuretics was assessed at inclusion and at follow-up. Furosemide-equivalent doses were reported and categorized into four categories (i.e. not treated; 1–40; 41–80; >80 mg).

The change in use/dose of medications between baseline and 1.5-year follow-up was defined as: (1) stable: if the patient was not on medication at baseline nor at follow-up or was stable in achieved % target dose; (2) increased: if the patient was not on medication at baseline and was on medication at follow-up, or increased in the achieved % of target dose; for ACEi/ARB/ARNi a switch from ACEi/ARB to ARNi was considered as an increase; (3) decreased: if the patient was on medication at baseline and was not on medication at follow-up, or decreased in achieved % of target dose; for ACEi/ARB/ARNi a switch from ARNi to ACEi/ARB was considered as a decrease. For loop diuretics, the same categories (i.e. stable, increased, or decreased) were defined based on furosemide-equivalent doses at baseline and follow-up.

For facilitating statistical modelling, increased use of GDMT (i.e. optimization) was compared with stable/decreased use, whereas for loop diuretics decreased use was compared with stable/increased use.

Statistical analysis

Baseline characteristics were presented as frequencies and percentages if categorical, and as median [1st–3rd quartile] if continuous, and compared by chi-square and Kruskal–Wallis tests, respectively, for CRT users (cases) versus non-users (controls).

The proportion of patients with increased, decreased or stable use of GDMT/loop diuretics were compared among CRT users and non-users by chi-square test.

Table 1 Baseline characteristics of the study population stratified by cardiac resynchronization therapy groups

Variable	Intention-to-treat			Per-protocol		
	No CRT	CRT	*p*-value	No CRT	CRT	*p*-value
n (%)	4537 (75)	1543 (25)		3116 (69)	1370 (31)	
Demographics						
Calendar year*			0.141			0.715
2009–2013	1389 (31)	510 (33)		1127 (36)	510 (37)	
2014–2018	1823 (40)	614 (40)		1403 (45)	614 (45)	
2019–2022	1325 (29)	419 (27)		586 (19)	246 (18)	
Sex*			<0.001			<0.001
Female	1281 (28)	337 (22)		892 (29)	304 (22)	
Male	3256 (72)	1206 (78)		2224 (71)	1066 (78)	
Age (years)*			<0.001			<0.001
<70	1418 (31)	563 (36)		874 (28)	514 (38)	
70–80	1917 (42)	736 (48)		1273 (41)	642 (47)	
>80	1202 (26)	244 (16)		969 (31)	214 (16)	
Clinical variables, ECG, echo and laboratory findings						
Duration of HF (months)*			0.746			0.568
3–9	1035 (23)	338 (22)		712 (23)	295 (22)	
10–18	523 (12)	177 (11)		360 (12)	155 (11)	
≥19	2979 (66)	1028 (67)		2044 (66)	920 (67)	
Previous HF hospitalization <1 year*	2025 (45)	648 (42)	0.076	1397 (45)	579 (42)	0.118
Systolic blood pressure (mmHg)*			<0.001			<0.001
<110	816 (18)	416 (28)		522 (17)	369 (28)	
≥110	3627 (82)	1065 (72)		2535 (83)	950 (72)	
Mean arterial pressure (mmHg)			<0.001			<0.001
≤90	2504 (56)	924 (62)		1682 (55)	832 (63)	
>90	1946 (44)	558 (38)		1381 (45)	488 (37)	
Heart rate (bpm)*			0.085			0.009
≤60	1121 (25)	329 (23)		798 (26)	287 (22)	
>60	3338 (75)	1111 (77)		2266 (74)	1004 (78)	
NYHA class*			<0.001			<0.001
I–II	2269 (61)	647 (51)		1563 (62)	551 (50)	
III–IV	1475 (39)	610 (49)		953 (38)	559 (50)	
ECG atrial rhythm			<0.001			<0.001
Sinus	3051 (67)	368 (26)		2046 (66)	343 (27)	
Atrial fibrillation	1284 (28)	211 (15)		906 (29)	200 (16)	
PM/other	202 (4)	828 (59)		164 (5)	723 (57)	
QRS width (ms)	156 [146–168]	152 [136–168]	<0.001	154 [144–166]	152 [136–168]	<0.001
LBBB	3710 (82)	385 (64)	<0.001	2476 (79)	365 (64)	<0.001
LVEF (%)			<0.001			<0.001
30–39	2295 (51)	637 (41)		1648 (53)	539 (39)	
<30	2242 (49)	906 (59)		1468 (47)	831 (61)	
eGFR (ml/min/1.73 m^2)*			0.115			0.499
≥60	2634 (59)	841 (57)		1760 (57)	743 (56)	
<60	1827 (41)	643 (43)		1313 (43)	581 (44)	
NT-proBNP (pg/ml)*			0.246			0.278
≤1080	1048 (34)	309 (31)		656 (33)	259 (30)	
1081–3110	1023 (33)	343 (34)		646 (32)	289 (33)	
>3110	1051 (34)	354 (35)		701 (35)	322 (37)	
Follow-up referral HF nurse clinic*	3313 (76)	1135 (76)	0.561	2110 (70)	983 (75)	0.002
Follow-up referral specialty*			<0.001			<0.001
Primary care/other	857 (19)	90 (6)		726 (24)	77 (6)	
Hospital	3584 (81)	1432 (94)		2316 (76)	1273 (94)	
Comorbidities						
Diabetes*	1301 (29)	453 (29)	0.632	861 (28)	404 (29)	0.216
Atrial fibrillation/flutter*	1968 (43)	813 (53)	<0.001	1379 (44)	724 (53)	<0.001
Ischaemic heart disease*	2709 (60)	969 (63)	0.034	1894 (61)	870 (64)	0.091
Hypertension*	2788 (61)	909 (59)	0.083	1894 (61)	793 (58)	0.073

Table 1 (Continued)

Variable	Intention-to-treat			Per-protocol		
	No CRT	CRT	*p*-value	No CRT	CRT	*p*-value
Peripheral artery disease*	391 (9)	140 (9)	0.621	267 (9)	121 (9)	0.817
PCI	1069 (24)	417 (27)	0.007	707 (23)	363 (26)	0.007
CABG	1464 (32)	600 (39)	<0.001	1021 (33)	531 (39)	<0.001
Stroke*	579 (13)	221 (14)	0.128	413 (13)	202 (15)	0.197
Valvular disease*	925 (20)	344 (22)	0.120	651 (21)	306 (22)	0.295
Malignant cancer within 3 years*	507 (11)	158 (10)	0.332	368 (12)	141 (10)	0.154
COPD*	530 (12)	184 (12)	0.833	386 (12)	161 (12)	0.582
Liver disease*	81 (2)	39 (3)	0.088	64 (2)	36 (3)	0.276
Dementia	43 (1)	<10	0.012	36 (1)	<10	0.008
Severe bleeding*	774 (17)	238 (15)	0.147	541 (17)	214 (16)	0.164
Musculoskeletal/connective tissue diseases within 3 years*	1350 (30)	475 (31)	0.466	948 (30)	422 (31)	0.827
Charlson comorbidity index			0.694			0.958
1	1207 (27)	393 (25)		788 (25)	347 (25)	
2–3	1896 (42)	639 (41)		1287 (41)	558 (41)	
4–7	1311 (29)	466 (30)		945 (30)	425 (31)	
≥8	123 (3)	45 (3)		96 (3)	40 (3)	
Other treatments						
SGLT2i	234 (5)	83 (5)	0.786	46 (1)	28 (2)	0.212
Calcium channel blockers*	514 (11)	122 (8)	<0.001	342 (11)	103 (8)	<0.001
Antiplatelet*	1990 (44)	604 (39)	0.001	1396 (45)	544 (40)	0.002
Anticoagulant*	1978 (44)	709 (46)	0.115	1342 (43)	627 (46)	0.100
Insulin	526 (12)	222 (14)	0.004	365 (12)	202 (15)	0.006
Oral glucose lowering	903 (20)	296 (19)	0.564	497 (16)	220 (16)	0.962
Lipid lowering*	2543 (56)	893 (58)	0.223	1714 (55)	792 (58)	0.087
Digoxin*	441 (10)	166 (11)	0.260	313 (10)	157 (11)	0.170
Nitrate*	1040 (23)	313 (20)	0.034	738 (24)	290 (21)	0.071
Antiarrhythmic*	221 (5)	132 (9)	<0.001	141 (5)	118 (9)	<0.001
Type of CRT						
CRT-P		579 (38)			516 (38)	
CRT-D		964 (62)			854 (62)	
Previous ICD	301 (7)	135 (9)	0.006	203 (7)	114 (8)	0.035
Previous PM	503 (11)	388 (25)	<0.001	373 (12)	341 (25)	<0.001
Socioeconomics				1714 (55)	840 (61)	
Family situation*			0.001	1400 (45)	530 (39)	
Cohabitating	2553 (56)	945 (61)		2655 (85)	1160 (85)	0.677
Living alone	1981 (44)	598 (39)				<0.001
Children*	3874 (85)	1315 (85)	0.908	1349 (44)	458 (34)	
Education*			<0.001	1217 (40)	601 (45)	
Compulsory school	1793 (40)	515 (34)		487 (16)	290 (21)	
Secondary school	1867 (42)	680 (45)				<0.001
University	789 (18)	324 (21)		1135 (36)	368 (27)	
Income*			<0.001	1036 (33)	450 (33)	
1st tertile within year	1580 (35)	424 (27)		943 (30)	552 (40)	
2nd tertile within year	1493 (33)	511 (33)		1164 (33)	511 (33)	
3rd tertile within year	1461 (32)	608 (39)		1075 (31)	608 (39)	

Data are presented as *n* (%), or median [interquartile range].
CABG, coronary artery bypass grafting; COPD, chronic obstructive pulmonary disease; CRT, cardiac resynchronization therapy; CRT-D, cardiac resynchronization therapy-defibrillator; CRT-P, cardiac resynchronization therapy-pacemaker; ECG, electrocardiogram; eGFR, estimated glomerular filtration rate; HF, heart failure; ICD, implantable cardiac defibrillator; LBBB, left bundle branch block; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; PM, pacemaker; SGLT2i, sodium–glucose cotransporter 2 inhibitor.
*Included in multiple imputation and regression models.

Changes in treatments use from baseline to follow-up, that is optimization versus no optimization for GDMT and decrease versus no decrease for loop diuretic use/dose, were compared in cases versus controls by logistic regression models fitted as follows: (1) unadjusted, (2) adjusted for variables indicated in *Table 1* (marked with *) together with the baseline medication use. Variables for adjustments were chosen based on clinical relevance and excluded from the models in presence of collinearity.

As control patients could receive CRT during follow-up, we performed both an intention-to-treat analysis, that is CRT status defined

Table 2 Baseline and 1.5-year follow-up use and achieved % target dose of medications in the intention-to-treat and per-protocol population stratified by cardiac resynchronization therapy groups

Variable	Intention-to-treat				Per-protocol			
	Baseline		Follow-up		Baseline		Follow-up	
	No CRT	CRT	No CRT	CRT	No CRT	CRT	No CRT	CRT
n (%)	4537 (75)	1543 (25)	4537 (75)	1543 (25)	3116 (69)	1370 (31)	3116 (69)	1370 (31)
Beta-blocker (% of target dose)								
Not treated	655 (14)	247 (16)	633 (14)	180 (12)	475 (15)	219 (16)	476 (15)	161 (12)
<25	393 (9)	137 (9)	267 (6)	58 (4)	271 (9)	114 (8)	200 (6)	51 (4)
25–49	1077 (24)	336 (22)	847 (19)	187 (12)	732 (23)	302 (22)	622 (20)	165 (12)
50–74	1121 (25)	313 (20)	1010 (22)	314 (20)	782 (25)	277 (20)	714 (23)	271 (20)
75–99	237 (5)	85 (6)	276 (6)	96 (6)	156 (5)	78 (6)	184 (6)	85 (6)
100	1054 (23)	425 (28)*	1504 (33)	708 (46)*	700 (22)	380 (28)*	920 (30)	637 (46)*
Beta-blocker (% of target dose)	50 [25–75]	50 [25–100]	50 [25–100]	75 [25–100]*	50 [25–75]	50 [25–100]*	50 [25–100]	75 [25–100]*
ACEi/ARB/ARNi (% of target dose)								
Not treated	545 (12)	170 (11)	670 (15)	206 (13)	420 (13)	152 (11)	503 (16)	185 (14)
<25	456 (10)	111 (7)	355 (8)	99 (6)	333 (11)	106 (8)	271 (9)	93 (7)
25–49	911 (20)	248 (16)	631 (14)	195 (13)	649 (21)	228 (17)	476 (15)	182 (13)
50–74	1269 (28)	460 (30)	1103 (24)	401 (26)	869 (28)	414 (30)	781 (25)	369 (27)
75–99	141 (3)	49 (3)	127 (3)	53 (3)	92 (3)	44 (3)	80 (3)	49 (4)
100	1215 (27)	505 (33)*	1651 (36)	589 (38)	753 (24)	426 (31)*	1005 (32)	492 (36)*
ACEi/ARB/ARNi (% of target dose)	50 [25–100]	50 [25–100]*	50 [25–100]	50 [25–100]*	50 [25–75]	50 [25–100]*	50 [25–100]	50 [25–100]*
MRA (% of target dose)								
Not treated	2469 (54)	664 (43)	2297 (51)	675 (44)	1854 (59)	599 (44)	1743 (56)	612 (45)
<50	268 (6)	115 (7)	297 (7)	107 (7)	180 (6)	108 (8)	199 (6)	101 (7)
50–99	1551 (34)	626 (41)	1512 (33)	560 (36)	932 (30)	547 (40)	937 (30)	487 (36)
100	249 (5)	138 (9)*	431 (9)	201 (13)*	150 (5)	116 (8)*	237 (8)	170 (12)*
MRA (% of target dose)	0 [0–50]	50 [0–50]*	0 [0–50]	50 [0–50]*	0 [0–50]	25 [0–50]*	0 [0–50]	25 [0–50]*
Loop diuretic (furosemide equivalent dose)								
Not treated	1840 (41)	582 (38)	2089 (46)	742 (48)	1240 (40)	507 (37)	1349 (43)	620 (45)
≤40 mg	1686 (37)	589 (38)	1332 (29)	426 (28)	1118 (36)	522 (38)	932 (30)	394 (29)
41–80 mg	807 (18)	271 (18)	797 (18)	256 (17)	608 (20)	248 (18)	608 (20)	246 (18)
>80 mg	204 (4)	101 (7)*	319 (7)	119 (8)	150 (5)	93 (7)*	227 (7)	110 (8)
Loop diuretic (furosemide equivalent dose, mg)	40 [0–40]	40 [0–40]*	40 [0–40]	20 [0–40]	40 [0–40]	40 [0–40]	40 [0–60]	40 [0–60]

Data are presented as *n* (%), or median [interquartile range].
ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNi, angiotensin receptor–neprilysin inhibitor; CRT, cardiac resynchronization therapy; MRA, mineralocorticoid receptor antagonist.
*Statistically significant differences between CRT users versus non-users.

as at the index date according to the time window provided above, and a per-protocol analysis where we excluded controls who received a CRT >30 days after the index registration and during follow-up. In the per-protocol analysis, we restricted the study population to patients registered until 27 December 2020 to allow a 20-month time period before end of data collection in the Swedish Pacemaker and Implantable Cardiac Defibrillator Registry for ensuring the assessment of crossover, that is later implantation of CRT (online supplementary *Figure Appendix S1*).

Analyses were also separately performed in patients with SBP <110 mmHg, as the proportion of patients with SBP <110 mmHg was unbalanced between CRT users and non-users, which might have influenced the prescription of GDMT. An additional sensitivity analysis was performed including only patients with a class I recommendation for CRT based on QRS width and morphology according to the 2021 HF guidelines (online supplementary *Table S2*).

Potential outliers were evaluated using Cook's distance, and multicollinearity was assessed using the variance inflation factor. No action was deemed necessary.

For the subset of patients with an available repeated registration in SwedeHF at 18 ± 2 month follow-up after the index date, changes in SBP and estimated glomerular filtration rate (eGFR) were presented descriptively by CRT status and the respective trajectories in medication use.

Missing data in multivariable models were handled by multiple imputation by chained equations (with 10 generated databases), with Rubin's rules used for combining estimates and standard errors across the imputed datasets.[20] Frequencies of missing data for each variable are reported in online supplementary *Table Appendix S1*.

All analyses were performed using R version 4.3.1. The R code for data handling and statistical analyses is on https://github.com/KIHeartFailure/crt-gdmt. The level of significance was set to 5%, two-sided.

Results

A flow chart reporting patient selection is reported in online supplementary *Figure Appendix S1*. Overall, 6080 patients were included. The median (Q1–Q3) age was 74 (67–80) years and 27% were female.

Intention-to-treat analysis

In the intention-to-treat analysis, 1543 (25%) patients who received a CRT (62% with CRT-defibrillator and 38% with CRT-pacemaker) and 4537 (75%) controls were included.

Patient characteristics in cardiac resynchronization therapy users versus non-users

Patients who received a CRT were younger, more likely male, with higher New York Heart Association class, lower SBP and lower ejection fraction as compared with CRT non-users. There were no significant differences in heart rate, N-terminal pro-B-type natriuretic peptide concentrations and eGFR (*Table 1*).

Baseline medication use

At baseline, of CRT versus non-CRT users, 84% versus 86% received a beta-blocker, 89% versus 88% an ACEi/ARB/ARNi, and 57% versus 46% an MRA, respectively (*Table 2*). Patients receiving CRT were more likely prescribed with target doses of beta-blockers (28% vs. 23%), ACEi/ARB/ARNi (33% vs. 27%) and MRA (9% vs. 5%). Patients receiving versus not receiving a CRT were more likely on loop diuretics (62% vs. 59%) and more likely on a furosemide-equivalent dose >80 mg (*Table 2*).

Changes in medications from baseline to follow-up

Sankey plots for changes in use and achieved % target doses of GDMTs and doses (mg) of loop diuretics from baseline to 1.5-year follow-up are reported in *Figure 1*. A higher proportion of patients not on beta-blockers at baseline were initiated with beta-blockers and up-titrated to 100% of target dose at 1.5-year follow-up in the CRT group. On the other hand, in both groups there were few patients on target doses that required suspicion of GDMTs. In the CRT group versus controls, a higher proportion of patients experienced a meaningful reduction in diuretic doses (i.e., reduction >40 mg/day) (*Figure 1*).

Overall, 591 (12.7%) patients switched from an ACEi/ARB to ARNi, of whom 177 (15.5%) versus 414 (11.8%) in cases versus controls, respectively.

A statistically significant higher proportion of patients achieved at 1.5 year an optimized use of beta-blocker therapy (46% vs. 35%, $p < 0.001$), a decrease in loop diuretic need (i.e. decrease in loop diuretic dose or withdrawn) (30% vs. 24%, $p < 0.001$), and a slight decrease in MRA use (20% vs. 16%, $p = 0.008$) if they were versus were not implanted with a CRT (*Figure 2A*).

After adjustments (*Figure 3*, left panel), patients receiving a CRT were confirmed to be more likely optimized for beta-blocker therapy (odds ratio [OR] 1.83, 95% confidence interval [CI] 1.58–2.13), whereas no significant associations were shown between CRT implantation and changes in ACEi/ARB/ARNi and MRA use. Patients implanted with a CRT were confirmed to have significant less need (use/dose) of loop diuretics (OR 1.26, 95% CI 1.07–1.48).

In patients with SBP <110 mmHg (baseline characteristics reported in online supplementary *Tables S4* and *S5*), receiving a CRT was independently associated with optimization of beta-blockers (online supplementary *Table S6*, *Figure S2*). The sensitivity analysis including patients with a class I recommendation for CRT is reported in online supplementary *Table S7*.

Changes in systolic blood pressure and estimated glomerular filtration rate from baseline to follow-up

Changes in SBP and eGFR from baseline to follow-up is descriptively reported in a subset of patients ($n = 528$ and $n = 533$, respectively) (online supplementary *Table S8*). Among patients not receiving a CRT, we observed a slight decrease in SBP after optimization of beta-blockers and ACEi/ARB/ARNi. These changes were not reported or were less pronounced for patients who received a CRT and were optimized for the same drugs. A similar trend was reported for changes in eGFR after optimization of ACEi/ARB/ARNi and MRA. Similarly, in patients non-optimized with GDMT, a descriptive long-term less decrease in SBP and eGFR after CRT implantation (as compared with controls) was reported (online supplementary *Table S8*).

Per-protocol analysis

After the exclusion of control patients who received a CRT during the follow-up, the per-protocol analysis included 3116 (69%) controls without CRT and 1370 (31%) CRT users.

Baseline characteristics and medication use

Differences in baseline characteristics and baseline medication use among the two study groups were similar to those reported in the intention-to-treat analysis (*Tables 1* and *2*).

Changes in medications from baseline to follow-up

Patterns for use and doses of GDMTs and loop diuretics are reported in *Figures 2B* and *4*. Similarly to the intention-to-treat analysis, more patients were initiated and up-titrated with beta-blockers at 1.5-year follow-up in the CRT group as compared with controls. It resulted in 46% of patients (vs. 28% at baseline) achieving the target dose in the CRT group. On the other hand, among controls, 30% achieved the target dose at follow-up (vs. 22% at baseline) (*Figure 4*, *Table 2*). Of those on renin–angiotensin system inhibitors, 149 (13.9%) versus 176 (7.0%) among cases

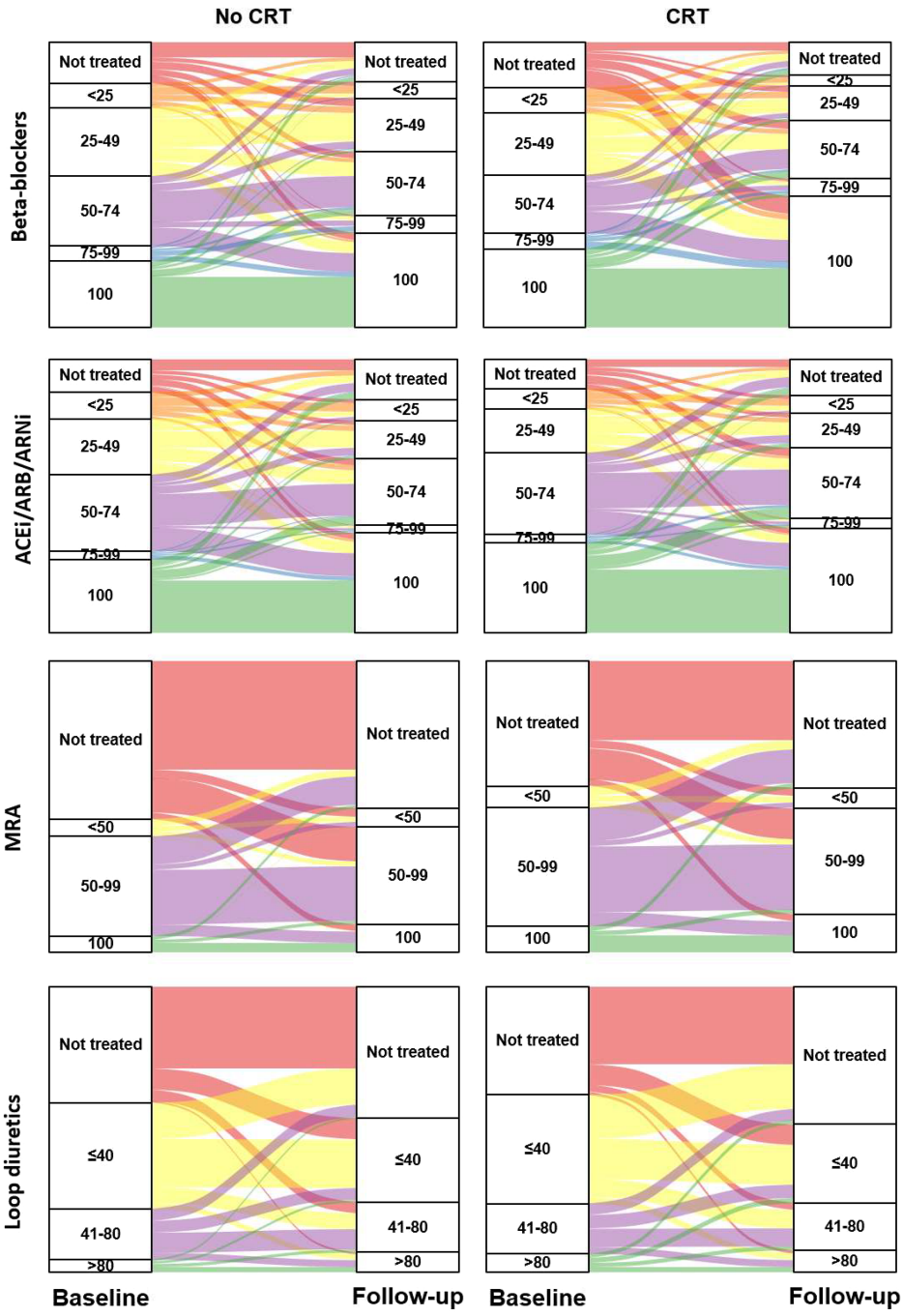


Figure 1 Sankey plots for changes in achieved % of target doses for beta-blockers, angiotensin-converting enzyme inhibitors (ACEi)/angiotensin receptor blockers (ARB)/angiotensin receptor–neprilysin inhibitor (ARNi), mineralocorticoid receptor antagonists (MRA) and doses of loop diuretics (furosemide-equivalent) from baseline to 1.5-year follow-up, stratified by cardiac resynchronization therapy (CRT) (intention-to-treat analysis).

versus controls, respectively, were switched to ARNi. Diuretic use/dose changes between baseline and follow-up were consistent with the intention-to-treat analysis.

After adjustments, receiving a CRT was independently and significantly associated with better optimized use of all GDMTs (OR 2.24, 95% CI 1.89–2.66 for beta-blockers; OR 1.22, 95% CI 1.04–1.44 for ACEi/ARB/ARNi; OR 1.25, 95% CI 1.05–1.50 for MRA) (*Figure 3*, right panel). Receiving a CRT was also associated with a decrease in loop diuretic need (use/dose) (OR 1.22, 95% CI 1.01–1.47).

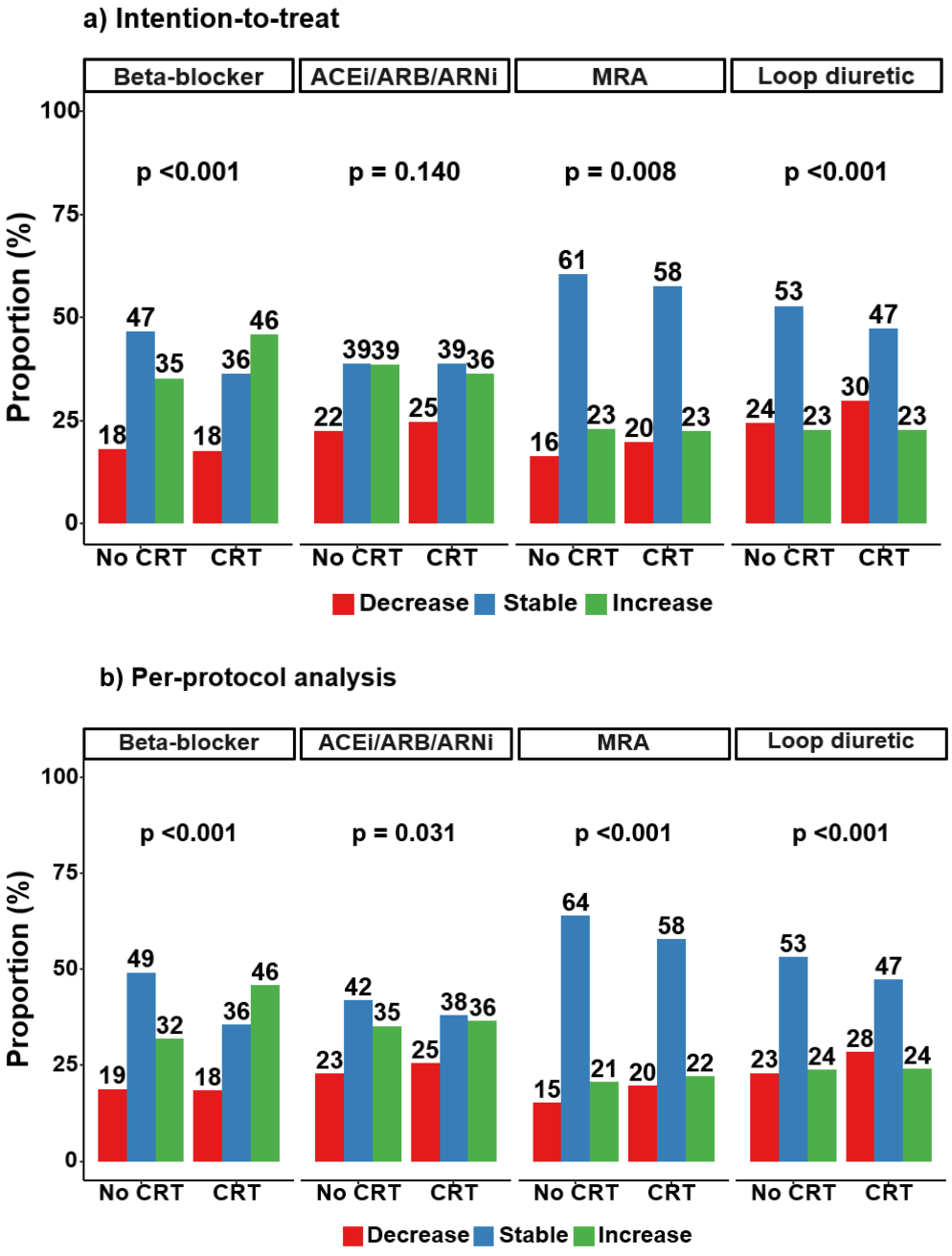


Figure 2 Changes in guideline-directed medical therapy (GDMT) from baseline to follow-up. Proportion of patients with decrease, stable or increase in the use/dose of GDMTs and loop diuretics stratified by cardiac resynchronization therapy (CRT) in the (*A*) intention-to-treat and (*B*) per-protocol analysis. ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNi, angiotensin receptor–neprilysin inhibitor; MRA, mineralocorticoid receptor antagonist.

The association for ACEi/ARB/ARNi was no longer statistically significant in the sensitivity analysis in patients with SBP <110 mmHg (controls $n = 522$; cases $n = 369$) despite a similar trend and an even higher point estimates (OR 1.41, 95% CI 0.98–2.04) (online supplementary *Figure S3*, *Table S9*).

Online supplementary *Table S10* reports the sensitivity analysis for patients with a class I recommendation for CRT, and online supplementary *Table S11* changes in SBP and eGFR from baseline to 1.5-year follow-up in the per-protocol population.

Discussion

To the best of our knowledge, this is the largest and one of few studies investigating whether CRT implantation may act as an

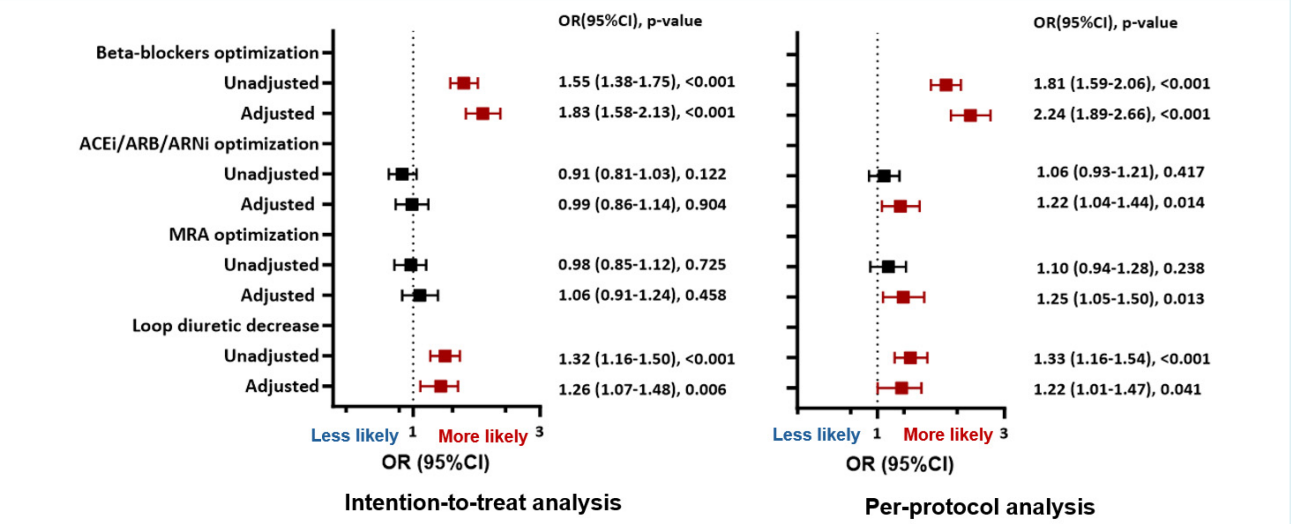


Figure 3 Regression analysis for cardiac resynchronization therapy (CRT) as an enabler for guideline-directed medical therapy (GDMT). Forest plot for the association between CRT versus no CRT implantation and optimization in GDMT/decrease in loop diuretic use/doses (left panel, intention-to-treat analysis; right panel, per-protocol analysis). The multivariable model was adjusted for all variables marked with * in *Table 1* and baseline medications. ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNi, angiotensin receptor–neprilysin inhibitor; CI, confidence interval; MRA, mineralocorticoid receptor antagonist; OR, odds ratio.

enabler for GDMT optimization in patients with HFrEF.[21–24] The analyses were performed using data from a large contemporary nationwide registry.

The main findings of our analysis are the following (*Graphical Abstract*): (i) a large proportion of patients were prescribed with GDMT before CRT implantation, with target doses achieved in a minority of patients, and more likely in those receiving CRT; (ii) CRT was independently associated with beta-blocker optimization over the follow-up in both the intention-to-treat and per-protocol analyses. CRT was independently associated with ACEi/ARB/ARNi and MRA therapy optimization in the per-protocol analysis; and (iii) CRT was independently associated with a decrease in loop diuretic use/dose.

Guideline-directed medical therapy prescription before cardiac resynchronization therapy implantation

Current HF guidelines recommend optimization of GDMT before CRT implantation.[1] Beyond its benefits in terms of mortality/morbidity and quality of life in patients with HFrEF, optimal GDMT can induce cardiac remodelling with a consequent improvement in ejection fraction, which might lead to no further indication for a CRT.[25] In our real-world nationwide population, a high proportion of patients received GDMT before CRT implantation. Only a minority instead received the target doses of these medications before implantation, that is 28% for beta-blockers, 33% for ACEi/ARB/ARNi and 9% for MRA. These percentages are consistent with reports from recent registries including patients with HFrEF with or without devices,[3,8] and are even higher if compared with less contemporary data.[8,26,27]

The expected long time required for GDMT up-titration might delay CRT implantation. Furthermore, patients with wide QRS, especially left bundle branch block, might have significantly less left ventricular functional recovery than those with narrow QRS, even after 3–6 months of medical therapy.[28,29]

Optimization of guideline-directed medical therapy after cardiac resynchronization therapy

In the present analysis, we observed a significant optimization of beta-blocker therapy after CRT implantation versus baseline in terms of use (88% vs. 84%) and doses (46% vs. 28% receiving the target dose). The prescription of ACEi/ARB/ARNi and MRA at follow-up slightly decreased (87% vs. 89% and 66% vs. 67%, respectively), but the proportion of patients achieving the target dose increased with CRT (38% vs. 33% and 13% vs. 9%, respectively) (*Table 2*).

As a comparison, among 826 consecutive patients receiving a CRT in a tertiary centre in Denmark, a significant increase in daily doses of beta-blockers and ACEi/ARB was shown after 6 months as compared with pre-implantation.[30] The opportunity of GDMT optimization after CRT was also highlighted in other smaller studies.[22,27,31] The lack of a control group in all these studies prevents the possibility of excluding a merely optimization of GDMT during follow-up that is not related to device implantation but rather to the overall improving acceptance of guideline recommendations over time. Thus, we compared GDMT optimization in patients receiving a CRT with a control group of patients fulfilling criteria for CRT implantation according to guidelines, but without a CRT device. Controls were older as compared with cases and older age,

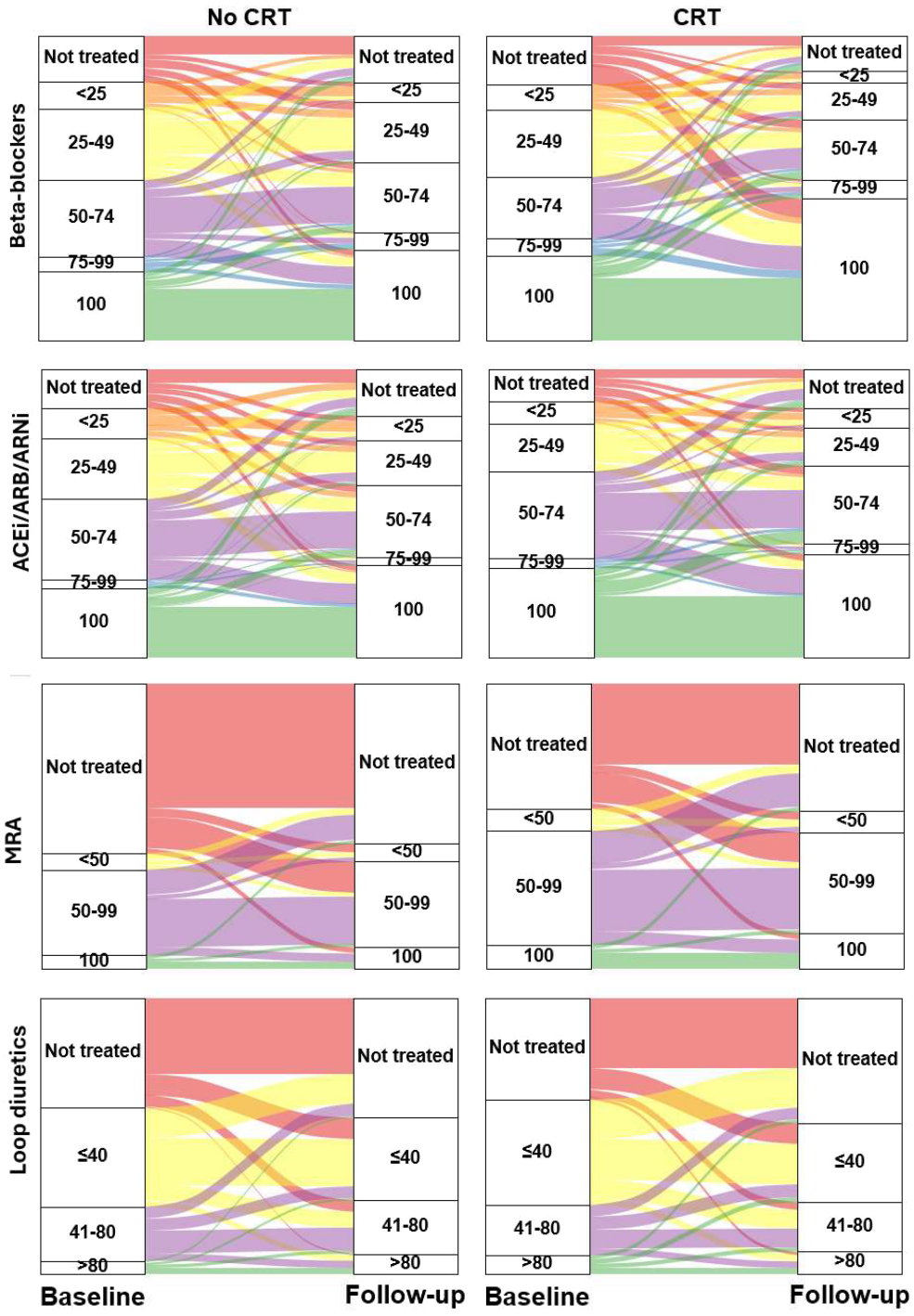


Figure 4 Sankey plots for changes in achieved % of target doses for beta-blockers, angiotensin-converting enzyme inhibitors (ACEi)/angiotensin receptor blockers (ARB)/angiotensin receptor–neprilysin inhibitor (ARNi), mineralocorticoid receptor antagonists (MRA) and doses of loop diuretics from baseline to 1.5-year follow-up, stratified by cardiac resynchronization therapy (CRT) (per-protocol analysis).

especially >80 years, has been associated with lower proportions of achieved target doses, lower adherence, and higher discontinuation rates for GDMT.[32] Similarly, other patient characteristics that were imbalanced between cases and controls might have influenced the results (e.g. follow-up referral in specialty or primary care). Additionally, both recommendations for CRT and GDMT changed during our study period. This might lead to different options for GDMT optimization in the later as compared to the earlier years.

Thus, we performed extensive adjustments in order to mitigate the role of these and other potential confounders.

After extensive adjustments, CRT was found to be associated with ~2-fold higher likelihood of beta-blocker optimization. These results on CRT enabling beta-blocker optimization are expected since CRT protects from bradycardia. In addition, beta-blocker optimization may be required to obtain a higher degree of CRT pacing in patients with supraventricular tachycardia, premature ventricular contractions, or as rate control strategy in atrial fibrillation. Finally, beta-blockers more than the other GDMT agents may be associated with fatigue and diminished well-being, and since these are substantially improved by CRT, beta-blocker increases may also be especially enabled by CRT. CRT seemed not to be associated with ACEi/ARB/ARNi and MRA optimization in the intention-to-treat analysis, which might have been explained by physicians, after haemodynamic improvement, prioritizing beta-blocker optimization in order to increase the percentage of biventricular pacing as stated above. Also, a substantial improvement in ejection fraction (e.g. >40%) after CRT reverse remodelling might have prevented the optimization itself.[1] However, the most likely explanation seems that the results in the intention-to-treat analysis were confounded and diluted by a high proportion of controls (~23%) finally receiving a CRT during the follow-up of interest. Indeed, after the exclusion of these patients (per-protocol analysis), we found that CRT was independently associated with both ACEi/ARB/ARNi and MRA optimization. Importantly, results were consistent regardless of baseline SBP, supporting the hypothesis that CRT may improve cardiac output and allow further GDMT optimization. This hypothesis may be supported by the less pronounced decrease in SBP and eGFR after neurohormonal blocker optimization, which we observed at follow-up in patients receiving versus not receiving a CRT. Consistently, a significant increase in SBP in patients with advanced HFrEF receiving CRT than those in the medication group was described in the COMPANION trial.[11]

Decrease in loop diuretic use/dose after cardiac resynchronization therapy implantation

We showed that CRT implantation was significantly and independently associated with a decrease in loop diuretic use/dose during follow-up. Consistently, CRT response has been previously associated with diuretic dose reduction.[22] Diuretic therapy as well as an increase in diuretic doses has been associated with a higher risk of events.[33] Thus, our results are in line with the proven reduction in the risk of HF hospitalizations with CRT, reverse cardiac remodelling, including improvement in ejection fraction, decrease in left ventricular volumes, reduction in mitral regurgitation, leading to a reduction in pulmonary hypertension, volume overload, congestion and symptoms.[1] Also, the haemodynamic improvement after CRT implantation may lead to an improvement in renal function resulting in a lower diuretic requirement.[34] Less need of diuretics might lead to better blood pressure and renal function, allowing for longer-term treatment optimization.

Limitations

Several limitations deserve acknowledgement. First, this was an observational study, and as such, although we performed extensive adjustments, it is prone to residual confounding. Second, the exclusion of patients who died before the follow-up of interest might have led to a selection bias. Third, a minimal HF duration of 3 months was required to assume, but we cannot ensure that GDMT optimization had been performed at the baseline, in particular in the control arm. Reasons behind limited GDMT optimization at baseline were not assessed. For example, only about a quarter of patients were on the target beta-blocker dose (100%) despite >70% with heart rate >60 bpm. However, rates of GDMT prescription are consistent, or even higher, in our as compared with other cohorts, supporting our assumption that optimal medical treatment was used at the baseline. Low cardiac output, hypotension as well as clinical inertia might explain the lack of further optimization. Fourth, misclassification of medical therapy doses cannot be excluded: a patient could have a dispensed prescription without assuming the pill. Fifth, CRT response is the foundational basis behind the hypothesis of CRT as an enabler for GDMT optimization. However, we did not assess CRT response in our study, precluding the possibility of ascertaining whether the lack of up-titration was due to lack of CRT response. Of note, CRT response itself with a significant improvement/complete normalization of ejection fraction might have prevent physicians from a further optimization of GDMT, but less likely from diuretic discontinuation/down-titration. Sixth, data on QRS morphology and width were not available/reliable in a proportion of patients in the CRT group since registration in SwedeHF might have occurred after CRT implantation and therefore the QRS was paced. Thus, we did not adjust for this parameter in the multivariable models, but a sensitivity analysis was performed for patients with a class I recommendation for CRT according to the 2021 ESC HF guidelines (online supplementary material). Seventh, follow-up data on SBP and eGFR were available in few patients, limiting the possibility of reporting causes of lack of up-titration. Eighth, patients not receiving CRT despite an indication might also be less rigorously followed up and up-titrated with GDMTs. Finally, generalizability of our results is partially limited because patients enrolled in SwedeHF have different characteristics compared with the overall HF population.[35,36]

Conclusion

In a nationwide cohort of patients with HFrEF, CRT implantation was associated with optimization of beta-blockers, ACEi/ARB/ARNi and MRA with a stronger magnitude for the association with beta-blockers. CRT implantation was also linked with lower need (use/dose) of loop diuretics which may preserve renal function and blood pressure.

Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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Conflict of interest: D.T. reports speaker fees from Alnylam Pharmaceutics, AstraZeneca, Bayer, Boehringer Ingelheim, Pfizer, Roche Diagnostics, outside the submitted work. C.Lj. reports reimbursements for lectures from AstraZeneca, Pfizer, Novartis, Boehringer Ingelheim, Novo Nordisk and Pharmacosmos, outside the submitted work. G.R. reports grants, institutional and personal fees from Anlylam, CSL Vifor, Boehringer Ingelheim, AstraZeneca, Servier, Novartis, Medtronic, Bayer, Roche, Menariniall, outside the submitted work. J.B. reports consultancies for Abbott, Adaptyx, ADI Analog, American Regent, Amgen, AskBio, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol Myers Squibb, Cardiac Dimension, Cardior, CSL Vifor, CVRx, Cytokinetics, Daxor, Diastol, Edwards, Element Sciences, Faraday, Idorsia, Impulse Dynamics, Imbria, Innolife, Intellia, Inventiva, Levator, Lexicon, Eli Lilly, Mankind, Medtronic, Merck, New Amsterdam, Novartis, Novo Nordisk, Pfizer, Pharmacosmos, Pharmain, Prolaio, Pulnovo, Regeneron, Renibus, Repreive, Roche, Rycarma, Saillent, Salamandra, Salubris, SC Pharma, SQ Innovation, Secretome, Sequanna, Transmural, TekkunLev, Tenex, Tricog, Ultromic, Zoll. L.H.L. reports grants, consulting, honoraria to author's institution from Alleviant, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Novo Nordisk, Owkin, Pharmacosmos, outside the submitted work. G.S. reports grants and personal fees from CSL Vifor, Boehringer Ingelheim, AstraZeneca, Servier, Novartis, Cytokinetics, Pharmacosmos, Medtronic, Bayer, personal fees from Roche, Abbott, Edwards Lifescience, TEVA, Menarini, INTAS, GETZ, and grants from Boston Scientific, Merck, outside the submitted work. All other authors have nothing to disclose.

References

1. 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: Developed by the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). With the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur J Heart Fail* 2022;**24**:4–131. https://doi.org/10.1002/ejhf.2333
2. Savarese G, Lindberg F, Christodorescu RM, Ferrini M, Kumler T, Toutoutzas K, *et al.* Physician perceptions, attitudes, and strategies towards implementing guideline-directed medical therapy in heart failure with reduced ejection fraction. A survey of the Heart Failure Association of the ESC and the ESC Council for Cardiology Practice. *Eur J Heart Fail* 2024;**26**:1408–1418. https://doi.org/10.1002/ejhf.3214
3. Savarese G, Lindberg F, Cannata A, Chioncel O, Stolfo D, Musella F, *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. https://doi.org/10.1002/ejhf.3295
4. Tomasoni D, Pagnesi M, Colombo G, Chiarito M, Stolfo D, Baldetti L, *et al.* Guideline-directed medical therapy in severe heart failure with reduced ejection fraction: An analysis from the HELP-HF registry. *Eur J Heart Fail* 2024;**26**:327–337. https://doi.org/10.1002/ejhf.3081
5. Savarese G, Kishi T, Vardeny O, Adamsson Eryd S, Bodegard J, Lund LH, *et al.* Heart failure drug treatment-inertia, titration, and discontinuation: A multinational observational study (EVOLUTION HF). *JACC Heart Fail* 2023;**11**:1–14. https://doi.org/10.1016/j.jchf.2022.08.009
6. Greene SJ, Butler J, Albert NM, DeVore AD, Sharma PP, Duffy CI, *et al.* Medical therapy for heart failure with reduced ejection fraction: The CHAMP-HF registry. *J Am Coll Cardiol* 2018;**72**:351–366. https://doi.org/10.1016/j.jacc.2018.04.070
7. 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: A joint position statement from the Heart Failure Association (HFA), European Heart Rhythm Association (EHRA), and European Association of Cardiovascular Imaging (EACVI) of the European Society of Cardiology. *Eur J Heart Fail* 2020;**22**:2349–2369. https://doi.org/10.1002/ejhf.2046
8. Heywood JT, Fonarow GC, Yancy CW, Albert NM, Curtis AB, Gheorghiade M, *et al.* Comparison of medical therapy dosing in outpatients cared for in cardiology practices with heart failure and reduced ejection fraction with and without device therapy: Report from IMPROVE HF. *Circ Heart Fail* 2010;**3**:596–605. https://doi.org/10.1161/CIRCHEARTFAILURE.109.912683
9. Cleland JG, Abraham WT, Linde C, Gold MR, Young JB, Claude Daubert J, *et al.* An individual patient meta-analysis of five randomized trials assessing the effects of cardiac resynchronization therapy on morbidity and mortality in patients with symptomatic heart failure. *Eur Heart J* 2013;**34**:3547–3556. https://doi.org/10.1093/eurheartj/eht290
10. Nelson GS, Berger RD, Fetics BJ, Talbot M, Spinelli JC, Hare JM, *et al.* Left ventricular or biventricular pacing improves cardiac function at diminished energy cost in patients with dilated cardiomyopathy and left bundle-branch block. *Circulation* 2000;**102**:3053–3059. https://doi.org/10.1161/01.cir.102.25.3053
11. Bristow MR, Saxon LA, Boehmer J, Krueger S, Kass DA, De Marco T, *et al.*; Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) Investigators. Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. *N Engl J Med* 2004;**350**:2140–2150. https://doi.org/10.1056/NEJMoa032423
12. St John Sutton M, Linde C, Gold MR, Abraham WT, Ghio S, Cerkvenik J, *et al.*; REVERSE Study Group. Left ventricular architecture, long-term reverse remodeling, and clinical outcome in mild heart failure with cardiac resynchronization: Results from the REVERSE trial. *JACC Heart Fail* 2017;**5**:169–178. https://doi.org/10.1016/j.jchf.2016.11.012
13. Mullens W, Dauw J, Gustafsson F, Mebazaa A, Steffel J, Witte KK, *et al.* Integration of implantable device therapy in patients with heart failure. A clinical consensus statement from the Heart Failure Association (HFA) and European Heart Rhythm Association (EHRA) of the European Society of Cardiology (ESC). *Eur J Heart Fail* 2024;**26**:483–501. https://doi.org/10.1002/ejhf.3150
14. Savarese G, Vasko P, Jonsson A, Edner M, Dahlstrom U, Lund LH. The Swedish Heart Failure Registry: A living, ongoing quality assurance and research in heart failure. *Ups J Med Sci* 2019;**124**:65–69. https://doi.org/10.1080/03009734.2018.1490831
15. Ludvigsson JF, Otterblad-Olausson P, Pettersson BU, Ekbom A. The Swedish personal identity number: Possibilities and pitfalls in healthcare and medical research. *Eur J Epidemiol* 2009;**24**:659–667. https://doi.org/10.1007/s10654-009-9350-y
16. Ludvigsson JF, Appelros P, Askling J, Byberg L, Carrero JJ, Ekstrom AM, *et al.* Adaptation of the Charlson comorbidity index for register-based research in Sweden. *Clin Epidemiol* 2021;**13**:21–41. https://doi.org/10.2147/CLEP.S282475
17. SwedeHF database 4 (SHFDB4). https://github.com/KIHeartFailure/shfdb4. Accessed 20/03/25
18. Vardas PE, Auricchio A, Blanc JJ, Daubert JC, Drexler H, Ector H, *et al.*; European Society of Cardiology; European Heart Rhythm Association. Guidelines for cardiac pacing and cardiac resynchronization therapy: The task force for cardiac pacing and cardiac resynchronization therapy of the European Society of Cardiology. Developed in collaboration with the European Heart Rhythm Association. *Eur Heart J* 2007;**28**:2256–2295. https://doi.org/10.1093/eurheartj/ehm305
19. Dickstein K, Cohen-Solal A, Filippatos G, McMurray JJ, Ponikowski P, Poole-Wilson PA, *et al.*; ESC Committee for Practice Guidelines (CPG). ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2008: The task force for the diagnosis and treatment of acute and chronic heart failure 2008 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association of the ESC (HFA) and endorsed by the European Society of Intensive Care Medicine (ESICM). *Eur Heart J* 2008;**29**:2388–2442. https://doi.org/10.1093/eurheartj/ehn309
20. van Buuren S, Groothuis-Oudshoorn K. mice: Multivariate imputation by chained equations in R. *J Stat Softw* 2011;**45**:1–67. https://doi.org/10.18637/jss.v045.i03
21. Martens P, Verbrugge FH, Nijst P, Bertrand PB, Dupont M, Tang WH, *et al.* Feasibility and association of neurohumoral blocker up-titration after cardiac resynchronization therapy. *J Card Fail* 2017;**23**:597–605. https://doi.org/10.1016/j.cardfail.2017.03.001
22. Schmidt S, Hurlimann D, Starck CT, Hindricks G, Luscher TF, Ruschitzka F, *et al.* Treatment with higher dosages of heart failure medication is associated with improved outcome following cardiac resynchronization therapy. *Eur Heart J* 2014;**35**:1051–1060. https://doi.org/10.1093/eurheartj/eht514

23. Mullens W, Grimm RA, Verga T, Dresing T, Starling RC, Wilkoff BL, *et al.* Insights from a cardiac resynchronization optimization clinic as part of a heart failure disease management program. *J Am Coll Cardiol* 2009;**53**:765–773. https://doi.org/10.1016/j.jacc.2008.11.024
24. Mullens W, Kepa J, De Vusser P, Vercammen J, Rivero-Ayerza M, Wagner P, *et al.* Importance of adjunctive heart failure optimization immediately after implantation to improve long-term outcomes with cardiac resynchronization therapy. *Am J Cardiol* 2011;**108**:409–415. https://doi.org/10.1016/j.amjcard.2011.03.060
25. Schneider PM, Pellegrini CN, Wang Y, Fein AS, Reynolds MR, Curtis JP, *et al.* Prevalence of guideline-directed medical therapy among patients receiving cardiac resynchronization therapy defibrillator implantation in the National Cardiovascular Data Registry during the years 2006 to 2008. *Am J Cardiol* 2014;**113**:2052–2056. https://doi.org/10.1016/j.amjcard.2014.03.049
26. Roth GA, Poole JE, Zaha R, Zhou W, Skinner J, Morden NE. Use of guideline-directed medications for heart failure before cardioverter-defibrillator implantation. *J Am Coll Cardiol* 2016;**67**:1062–1069. https://doi.org/10.1016/j.jacc.2015.12.046
27. Jorsal A, Pryds K, McMurray JJV, Wiggers H, Sommer A, Nielsen JC, *et al.* Optimizing heart failure treatment following cardiac resynchronization therapy. *Clin Res Cardiol* 2020;**109**:638–645. https://doi.org/10.1007/s00392-019-01553-4
28. Sze E, Samad Z, Dunning A, Campbell KB, Loring Z, Atwater BD, *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. https://doi.org/10.1016/j.jacc.2017.11.020
29. Huang HT, Huang JL, Lin PL, Lee YH, Hsu CY, Chung FP, *et al.* Clinical impacts of sacubitril/valsartan on patients eligible for cardiac resynchronization therapy. *ESC Heart Fail* 2022;**9**:3825–3835. https://doi.org/10.1002/ehf2.14107
30. Witt CT, Kronborg MB, Nohr EA, Mortensen PT, Gerdes C, Nielsen JC. Optimization of heart failure medication after cardiac resynchronization therapy and the impact on long-term survival. *Eur Heart J Cardiovasc Pharmacother* 2015;**1**:182–188. https://doi.org/10.1093/ehjcvp/pvv016
31. Massoullie G, Chouki C, Mulliez A, Rossignol P, Ploux S, Pereira B, *et al.* Effect of optimization of medical treatment on long-term survival of patients with heart failure after implantable cardioverter defibrillator and cardiac resynchronization device implantation (from the French National EGB Database). *Am J Cardiol* 2018;**121**:725–730. https://doi.org/10.1016/j.amjcard.2017.12.013
32. Garred CH, Zahir D, Butt JH, Ravn PB, Bruhn J, Gislason GH, *et al.* Adherence and discontinuation of optimal heart failure therapies according to age: A Danish nationwide study. *J Am Heart Assoc* 2022;**11**:e026187. https://doi.org/10.1161/JAHA.122.026187
33. Metra M, Tomasoni D, Adamo M, Bayes-Genis A, Filippatos G, Abdelhamid M, *et al.* Worsening of chronic heart failure: Definition, epidemiology, management and prevention. A clinical consensus statement by the Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail* 2023;**25**:776–791. https://doi.org/10.1002/ejhf.2874
34. Boerrigter G, Costello-Boerrigter LC, Abraham WT, Sutton MG, Heublein DM, Kruger KM, *et al.* Cardiac resynchronization therapy improves renal function in human heart failure with reduced glomerular filtration rate. *J Card Fail* 2008;**14**:539–546. https://doi.org/10.1016/j.cardfail.2008.03.009
35. Lund LH, Carrero JJ, Farahmand B, Henriksson KM, Jonsson A, Jernberg T, *et al.* Association between enrolment in a heart failure quality registry and subsequent mortality – a nationwide cohort study. *Eur J Heart Fail* 2017;**19**:1107–1116. https://doi.org/10.1002/ejhf.762
36. Lainscak M, Savarese G. Real-world heart failure registries: Fact or fiction? *EClinicalMedicine* 2025;**82**:103172. https://doi.org/10.1016/j.eclinm.2025.103172