Heart failure treatment in patients with cardiac implantable electronic devices: Opportunity for improvement

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BACKGROUND Heart failure and reduced ejection fraction (HFrEF) is the predominant indication for cardiac resynchronization therapy (CRT) and implantable cardioverter-defibrillator (ICD) implantation. The care gap and opportunity to optimize guideline-directed medical therapy (GDMT) is unclear.

OBJECTIVE We sought to define uptake, eligibility, dose, and adherence to GDMT in patients with CRT/ICD and HFrEF.

METHODS MEDLINE was searched from 2000 to July 2021 for major randomized trials, registries, and cohort studies evaluating GDMT in this population. Thirty-eight studies focused on medical therapy in patients with CRT/ICD devices (CRT = 23, ICD = 11, and both = 4).

RESULTS In the pivotal device trials, ACEI/ARB and beta-blocker use was high (mean 94%, range 41%–99%; and 83%, range 27%–97%, respectively), but mineralocorticoid receptor antagonists were modest (mean 45%, range 32%–61%), in keeping with guidelines of that era. Similar results were found in observational registries. CRT was associated with beta-blocker uptitration, while the effects on ACEI/ARB were less consistent. For beta blockers, 57%–68% of patients were uptitrated, increasing the mean percent of target dose achieved by 24% from baseline to follow-up. In one study, adherence increased, for ACEI/ARB from 37% to 55% and beta blockers 34% to 58%. Only 1 study assessed potential eligibility at implant for sacubitril-valsartan (72%) or ivabradine (28%), and no study examined sodium-glucose cotransporter-2 inhibitors. Increased uptake, titration, and dose was associated with reduced mortality, hospitalization, and device therapies.

CONCLUSION Patients with HFrEF and ICD/CRT are undertreated with respect to GDMT, and there is opportunity to optimize therapy to improve morbidity and mortality.

KEYWORDS Heart failure with reduced ejection fraction; Medical therapy; CRT; Optimization

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Introduction

The treatment of heart failure (HF) with reduced ejection fraction (HFrEF) has transformed in the past decade. Quadruple therapy including newer drug classes modulates 5 different pathways and leads to an average of 6 life-years gained, compared to conventional therapy with angiotensin-converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARBs) and beta blockers alone.[1] Newer therapies include mineralocorticoid receptor antagonists (MRAs),[2] angiotensin receptor–neprilysin inhibitors (ARNIs),[3] sodium-glucose cotransporter-2 (SGLT2) inhibitors,[4] and ivabradine.[5] Strategies are needed to screen, identify, and treat patients with HFrEF to improve symptoms, morbidity, and mortality.

Patients with cardiac implantable electronic devices, particularly implantable cardioverter-defibrillators (ICDs) and cardiac resynchronization therapy (CRT), present a clearly defined population with HFrEF in the healthcare system. Optimization of medical therapy may be possible for several reasons: suboptimal therapy prior to implant,[6,7] advances in guideline-recommended therapy since initial implant, improved medication tolerability after implant,[8–10] and decline in left ventricular ejection fraction (LVEF) and symptoms during follow-up. Electrophysiologists involved in longitudinal device care are key providers in the circle of care. If the care gap is significant, quality improvement initiatives could improve outcomes. This systematic review has 2 key objectives. The first is to describe medical therapy in patients with ICD and CRT in major randomized controlled trials, registries, and cohort studies. Our second objective is to define the opportunity to

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KEY FINDINGS

- In the pivotal device trials, angiotensin-converting enzyme inhibitor / angiotensin receptor blocker (ACEI/ARB) and beta-blocker use was high but mineralocorticoid receptor agonist (MRA) use was modest, in keeping with guidelines of that era.
- Most contemporary registries report similar uptake for these 3 classes.
- Greater uptake and titration and higher doses of medical therapy were reported in patients with heart failure after cardiac resynchronization therapy implantation, more so for beta blockers compared to ACEI/ARBs or MRAs. This in turn was consistently associated with reduced hospitalization and mortality.
- Eligibility for newer therapies in the device population was rarely studied, but appears significant from the single study identified.

optimize conventional pharmacological therapies and eligibility for newer evidence-based therapies.

Methods

The population of interest was patients with ICD and CRT. The outcome of interest was medical therapy for HFrEF (ACEI, ARB, beta blocker, MRA, ARNI, SGLT2 inhibitors). MEDLINE was searched from 2000 to July 2021, limited to adult humans without language restriction. Search terms were selected by consensus and iterative database queries. Medical subject headings (MeSH) were identified from keyword mapping and published literature. Study selection is displayed in Figure 1, and the search strategy is provided in Supplemental Data. The evidence is presented as a narrative synthesis owing to heterogeneity in outcomes and reporting. Besides reviewing the identified studies focusing on optimization of medical therapy in patients with CRT and/or ICD devices (n = 38), we also provide a brief review of major randomized clinical trials (n = 19) and registries (n = 19) that have reported the baseline medical therapies in patients with electronic devices. Results are presented as weighted averages (min-max) unless otherwise indicated. The terms "usage" and "uptake" are used to refer to the individual and population-level medication utilization, respectively.

Results

Baseline medical therapy in randomized controlled trials

Nineteen randomized controlled trials were included, 7 involving ICD alone, 2 CRT with pacemaker alone, and the remaining 10 CRT with defibrillator (Figure 2).[11–29] Inclusion criteria ranged from NYHA class I to class IV and LVEF ≤40% to ≤30%. In the CRT trials, the reported rates of ACEI/ARB and beta-blocker baseline use were 94% (41%–99.8%) and 83% (27%–97%), respectively. The respective proportions in ICD trials were 87% (68%–96%) and 84% (50%–92%). MRA use was infrequently reported, being 45% (32%–61%) in CRT studies and 59% in a single ICD trial.

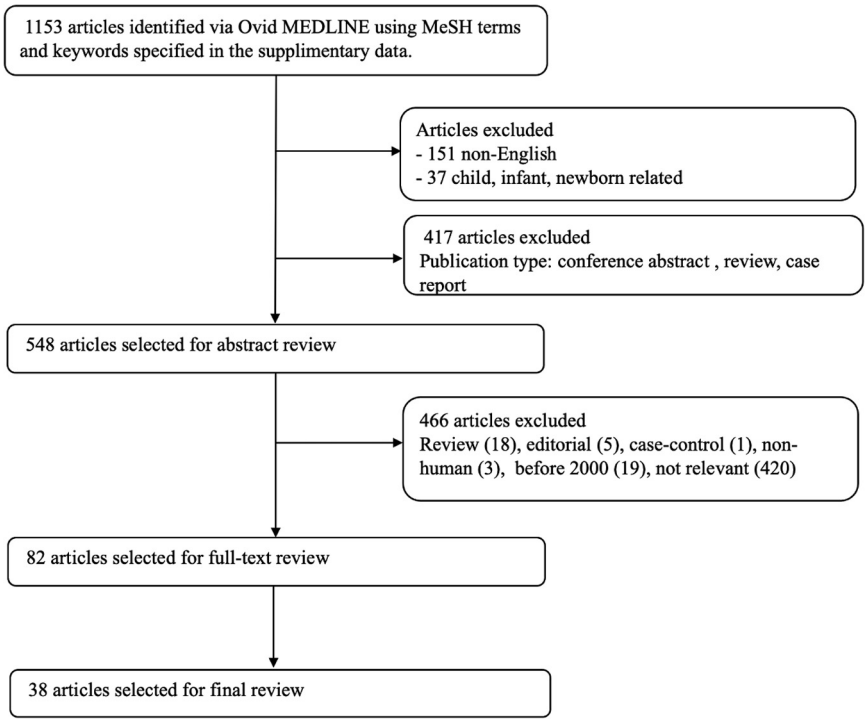

Figure 1 Literature flow diagram. MeSH = medical subject headings.

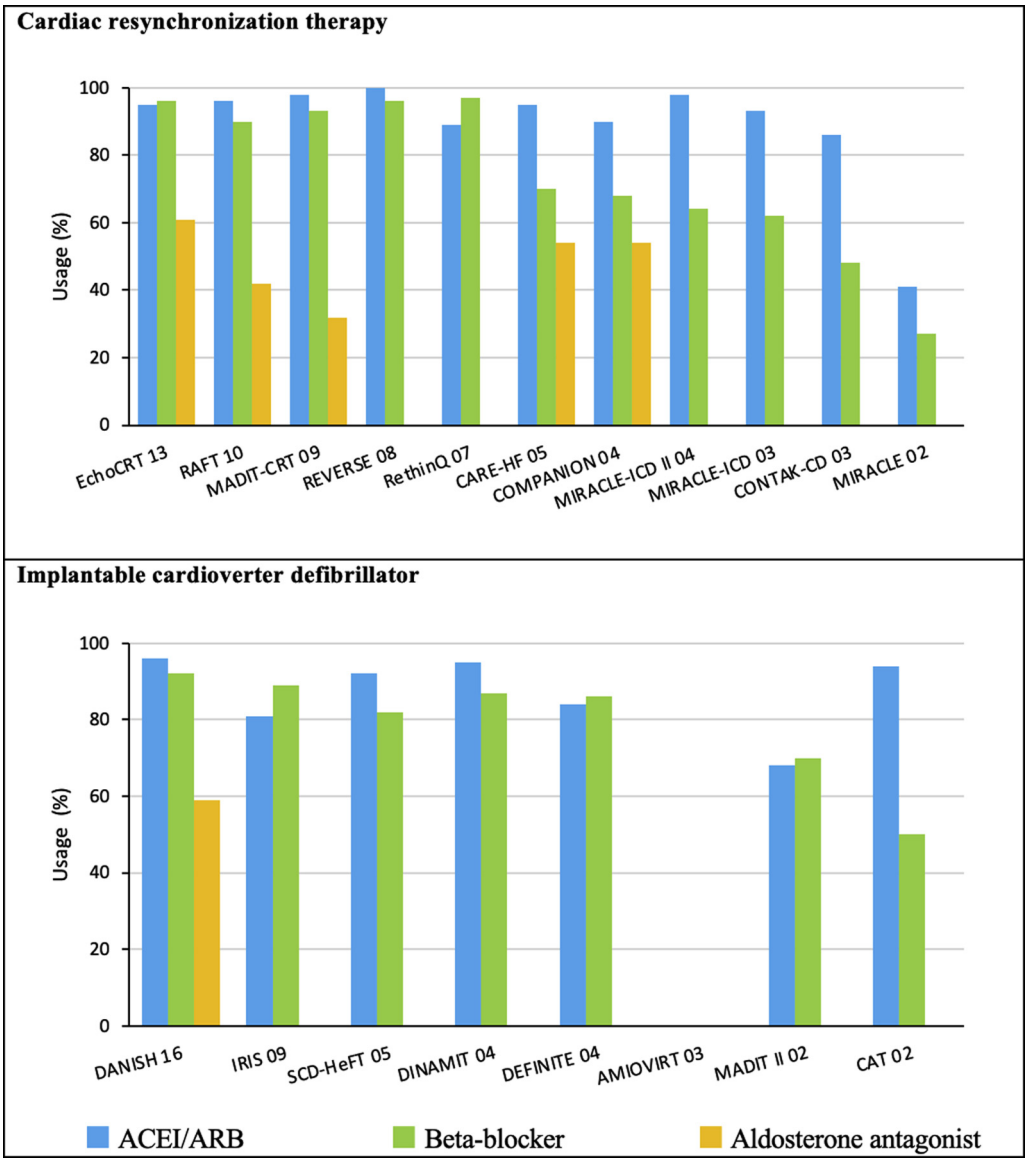

Figure 2 Baseline medical therapy in randomized controlled trials of cardiac resynchronization therapy/implantable cardioverter-defibrillators. ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker.

Baseline medical therapy in registries and cohort studies

Baseline medical therapy in major registries and cohort studies of CRT and ICD (n = 19) is presented in Figure 3.[30–48] CRT studies reported ACEI/ARB and beta-blocker baseline use in 78% (52%–100%) and 80% (70%–87%). Uptake was similar in ICD studies, 78% (59%–99%) and 85% (53%–97%), respectively. As with the randomized trials, MRA was infrequently reported, 49% (43%–56%) overall in CRT and 38% (21%–56%) in ICD studies.

Medical therapy usage and associated outcomes

Thirty-eight studies focused on specific aspects of medication optimization and associated outcomes following CRT (n = 27) and ICD (n = 15) implantation,[8–10,49–63] 21 of which were single-center and retrospective (Tables 1 and 2). These 38 studies are the main focus of this review. Sample size ranged from 50 to 7932 patients, with a mean/median follow-up duration from 6 to 70 months. Baseline usage of ACEI/ARB, beta blocker, and MRA in patients with CRT was 85% (54%–98%), 86% (67%–93%), and 46% (21%–78%) and in patients with ICD was 75% (24%–87%), 78% (24%–89%), and 36% (23%–38%), respectively. At follow-up, utilization increased to 92% (86%–100%), 92% (80%–97%), and 61% (49%–83%), respectively, in CRT patients. Nine studies reported both baseline and follow-up medications (Table 2). Usage significantly increased for beta blockers in 5 of 8 CRT studies,[8,50,53,54,64] for ACEI/ARB in 1 of 7,[64] and for MRA in 1 of 4 CRT studies.[50] Overall triple therapy usage was reported in a single retrospective French study (n = 243), which increased from

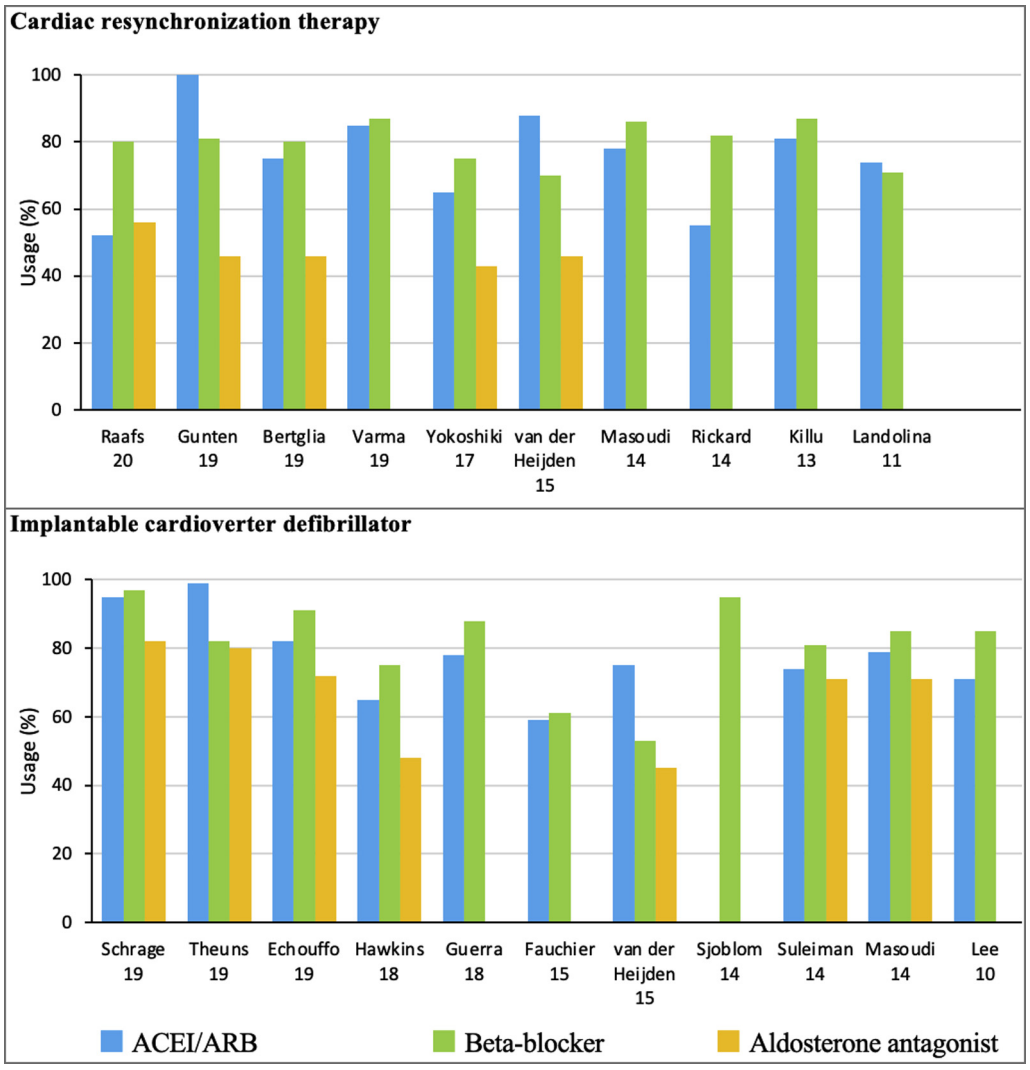

Figure 3 Baseline medical therapy in major registries and cohort studies of cardiac resynchronization therapy/implantable cardioverter-defibrillators. ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker.

26% to 32% at 3 months after CRT implant ($P < .001$).[56] Sacubitril/valsartan use was reported in 23%–44% of patients with CRT and 19% with ICD in 2 recent studies.[58,65]

Twenty-three studies reported the association between usage rates and outcomes at 3 months to 6 years post CRT/ICD implant (Table 3). Higher usage was associated with reduced risk of death and HF hospitalization for ACEI/ARB and beta blocker,[51,66] death for both medications,[59,67–70] and death for sacubitril-valsartan.[58] Conversely, lower usage of ACEI/ARB and/or beta blockers was associated with increased risk of death, hospitalization, or cardiac transplant.[55,60,61,71–73] Finally, in the aforementioned French study, triple therapy was associated with significantly improved survival compared to single therapy (HR 0.59 [0.36–0.97]).

In ICD studies, absence of ACEI/ARB,[74,75] beta blocker,[76–78] and both beta-blocker and MRA therapies[79] were significant predictors of appropriate ICD therapies.

Medical therapy titration

Twelve studies (12 following CRT, 2 of which included ICD patients) examined optimization in terms of dose defined using various metrics, including proportion of patients with uptitration, mean dose expressed as percent of target dose, proportion achieving target dose, and the outcomes associated with dose change (Table 3). Results were similar to those for usage rates. Beta blockers consistently and significantly increased in dose after device implant, while results for ACEI/ARB and MRA were mixed. For beta-blockade, the proportion of patients uptitrated ranged from 57% to 68%.[9,10,80] This translated into an increase in mean target dose by 24% from baseline to follow-up, with 20%–58% achieving maximum target dose.[57,80] One study examined a specific beta-blocker titration program assisted by remote monitoring, which increased the proportion of patients with target dose from 23% to 76% at 6 months post-CRT.[80] ACEI/ARB also increased in mean target dose by 13%, with 32%–37% achieving maximum target dose.[8,57] The

Table 1 Studies examining baseline or follow-up medical therapy following cardiac resynchronization therapy / implantable cardioverter-defibrillator implantation

Study, year	N	Location	Center Design	Follow-up (mo)	LVEF (%)	ACEI/ARB, n (%)	Beta blocker, n (%)	MRA, n (%)	Sacubitril/ valsartan, n (%)
CRT									
Martens, 2020[10]	162	Belgium	Single-retro	37	26 ± 7	144 (89)	149 (92)	120 (74)	-
Chun, 2020[58]	175	Korea	Single-retro	30	-	48 (96)	42 (84)	39 (78)	22 (44)
Shah, 2020[63]	7932	US	Multi-retro	6	-	-	-	-	-
Hu, 2019[60]	376	China	Single-retro	57 (6)	53 ± 4	54 (90)†	54 (90)†	50 (83)†	-
DeVore, 2018[65]	319	US	CHAMP-HF	24	29	172 (54)	-	-	73 (23)
Massoullie, 2018[56]	243	France	Multi-retro	23		199 (82)	170 (70)	86 (35)	-
Fontaine, 2018[73]	294	US	Single-retro	52	23 ± 10	209 (71)	263 (89)	62 (21)	-
Martens, 2017[9]	650	Belgium	Single-retro	37	30 ± 10	556 (86)	578 (89)	404 (62)	-
D'Onofrio, 2017[80]	254	Italy	Multi-prosp	6	27	159 (63)	217 (85)	63 (25)	-
Jin, 2017[100]	201	China	Single-retro	6	29 ± 8	52 (88)	55 (93)	-	-
Schmidt, 2014[62]	185	Switzerland	Single-retro	45 (24)	26 ± 8	-	-	-	-
Shen, 2013[71]	136	US	Single-prosp	17	21	123 (90)	122 (90)	49 (36)	-
Mantziari, 2012[52]	91	UK	Single-retro	6	24 ± 6	85 (93)	61 (67)	58 (64)	-
					24 ± 6	86 (98)	70 (80)	-	-
Kreuz, 2012[61]	239	Germany	Single-retro	43	26 ± 10	171 (95)	171 (95)	97 (54)	-
Friedman, 2012[76]	269	US	Single-prosp	18	24 ± 7	223 (83)	245 (91)	99 (37)	-
Voigt, 2010[55]	177	US	Single-retro	20	22 ± 9	142 (80)	129 (73)	42 (24)	-
Heywood, 2010[57]	2610	US	Multi-prosp	n/r	24 ± 7	2057 (79)	2288 (88)	1035 (40)	-
Desai, 2010[68]	209	US	Single-prosp	34	28 ± 7	146 (70)	158 (76)	-	-
Adlbrecht, 2009[81]	205	Austria	Single-retro	17	27	-	-	-	-
Bai, 2008[59]	542	US	Single-retro	27	20	443 (82)	372 (69)	-	-
ICD									
Massoullie, 2018[56]	135	France	Multi-retro	23	-	106 (79)	97 (72)	46 (34)	-
DeVore, 2018[65]	1727	US	CHAMP-HF	24	29	1005 (58)	-	-	321(19)
Ruwald, 2018[72]	2935	Denmark	Multi-retro	26	27	2251 (77)	2260 (77)	-	-
AlJaroudi, 2015[74]	1509	US	Multi-prosp	30	20	1213 (80)	1286 (85)	405 (27)	-
Chichareon, 2015[79]	115	Thailand	Single-retro	22	24	89 (74)	108 (89)	28 (23)	-
Desai, 2010[68]	320	US	Single-prosp	34	30 ± 7	199 (62)	216 (68)	-	-
Obeyesekere, 2010[75]	126	Australia	Single-prosp	19	23 ± 7	108 (86)	104 (83)	-	-
Verma, 2010[77]	421	Canada	Single-retro	25	27 ± 9	330 (78)	374 (89)	-	-
Heywood, 2010[57]	4394	US	Multi-prosp	n/r	24 ± 7	3586 (82)	3889 (89)	1665 (38)	-
Pietrasik, 2009[66]	671	US	MADIT-II	20	-	516(77)	422(63)	-	-
Lai, 2008[67]	965	US	Single-retro	32	-	494 (51)†	575 (60)†	-	-
Tandri, 2006[70]	1382	US	Single-prosp	70	33 ± 11	332 (24)	332 (24)	-	-
Pinski, 2000[69]	1628	US	Multi-prosp	17	33 ± 14	982 (60)	510 (31)	-	-

Follow-up times in parentheses show the time at which the distribution of medication is analyzed.

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; BB = beta blocker; LVEF = left ventricular ejection fraction; MRA = mineralocorticoid receptor antagonist; Prosp = prospective; Retro = retrospective; UK = United Kingdom; US = United States.

†Medication usage rates are reported at follow-up time.

mean target dose for MRA, evaluated in only 1 study, decreased from 59% to 50%. In that study, more patients received spironolactone after CRT, but the greater usage included relatively low doses, which reduced the mean.[50]

Dose titration was consistently associated with improved symptoms and survival (Table 4). For symptoms, mean NYHA score improved by 24% in patients with beta-blocker uptitration after CRT compared to those without titration (16%).[54] For outcomes, higher ACEI/ARB and beta-blocker dose following implant was independently associated with reduced mortality[8,52,62,81] and the composite of death or hospitalization.[9] In absolute terms, high- vs low-dose ACEI/ARB was associated with mean survival of 22.9 vs 19.2 months.[52] Beta-blocker titration was also associated with lower risk of appropriate ICD therapy.[10]

Medical therapy adherence

Two studies reported medication adherence following CRT.[8,63] A Danish cohort of 826 consecutive patients defined adherence as continuation at annual intervals. All patients were adherent at baseline to ACEI/ARB, beta blocker, and MRA, which declined to 94%, 95%, and 77%, respectively, at 4 years.[8] Conversely, a large US cohort defined adherence by proportion of days covered ≥80% using pharmacy claims. Adherence to ACEI/ARB and beta blockers increased, respectively, from 37% to 55% and from 34% to 58% at 12 months post-CRT (n = 7932, all $P < .001$).[63]

Eligibility for contemporary medical therapy

Only 1 study evaluated eligibility for newer medical therapies.[49] In a single-center Danish cohort (n = 182), the

Table 2 Studies examining baseline and follow-up medical therapy following cardiac resynchronization therapy / implantable cardioverter-defibrillator implantation

Study, year	N	Location	Center design	Follow-up (mo)	LVEF (%)	ACEI/ARB, n (%)	Beta blocker, n (%)	MRA, n (%)	LVEF (%)	ACEI/ARB, n (%)	Beta blocker, n (%)	MRA, n (%)
CRT					**Baseline**						**Follow-Up**	
Jorsal, 2020[49]	182	Denmark	Single-retro	6	25 ± 6	171 (94)	167 (92)	83 (46)	36±10	128 (94)	131 (96)	67 (49)
Rinkuniene, 2017[50]	85	Lithuania	Single-retro	12	20 ± 6	69 (81)	69 (81)	47 (55)	31±9	75 (88)	82 (97)†	60 (71)†
Nebata, 2016[64]	63	Japan	Single-retro	6	28 ± 8	55 (87)	43 (68)	35 (56)	-	63 (100)†	61 (97)†	46 (73)
Witt, 2015[8]	826	Denmark	Single-retro	53 (6)	24	747 (90)	620 (75)	475 (58)	-	753 (91)	724 (88)†	490 (59)
Penn, 2015[51]	1820	US	MADIT-CRT	12	29 ± 3	1784 (98)	1693 (93)	n/r	-	1517 (94)	1533 (95)	n/r
Mantziari, 2012[52]	91	UK	Single-retro	6	24 ± 6	85 (93)	61 (67)	58 (64)	24±6	86 (98)	70 (80)	-
Hitz, 2012[53]	140	Switzerland	Single-retro	43 (36)	-	136 (97)	113 (81)	-	-	100%	95%†	-
Aranda, 2005[54]	50	US	Single-retro	11	18 ± 6	-	36 (69)	-	25±12	-	44 (85)†	-
ICD												
D'Onofrio, 2016[101]	987	Italy	Multi-prosp	12	31 ± 9	664 (67)	792 (80)	-	-	518 (53)	712 (72)	-

No sacubitril/valsartan medication usage is reported in these studies.
Follow-up time in parentheses shows the time at which the distribution of medication is analyzed.
Abbreviations are the same as in Table 1.
†$P < .05$ for comparison from baseline to follow-up.

majority of patients had an indication for sacubitril-valsartan, ivabradine, or both at baseline. The proportion eligible varied according to the criteria applied: 72% by 2016 ESC guidelines but irrespective of ACE-I/ARB dosage, 43% by strict 2016 ESC guidelines,[82] 56% by PARADIGM-HF trial criteria.[3] These proportions approximately halved when applied in patients 6 months following implant, respectively, 32%, 17%, and 24%. Moreover, 18% of the patients without an indication at baseline developed an indication for optimization during follow-up.

Discussion

Our review highlights several key findings. In the pivotal device trials, ACEI/ARB and beta-blocker use was high but MRA was modest, in keeping with guidelines of that era. However, most contemporary registries report similar uptake for these 3 classes. Greater uptake and titration and higher doses of medical therapy were reported in patients with HF after CRT implantation, more so for beta blockers compared to ACEI/ARBs or MRAs. This in turn was consistently associated with reduced hospitalization and mortality. Eligibility for newer therapies in the device population was rarely studied but appears significant from the single study identified.

Underutilization of medical therapy

We observed variability in baseline medical therapy among major cohorts and registries (Figures 1 and 2). Similar findings were reported in the US National Cardiovascular Data Registry; only 44%–76% of patients with HFrEF across health regions had filled HF medication prescriptions within the 90 days prior to primary prevention ICD implantation.[7] Understanding these care gaps requires careful adjudication and granular patient-level data, since physiologic intolerance (blood pressure, heart rate, potassium, renal function) is the most common limiting factor.[83] For example, in patients attending a hospital-based multidisciplinary HF clinic, target dose achievement was higher once adjusted for physiological limitation (ACEI/ARB from 24% to 63%, beta blocker from 30% to 68%, MRA from 39% to 59%, ARNI from 51% to 63%).[84]

Measuring the quality of medical therapy

The concepts of uptake and dose are interrelated and tend to improve in parallel at the population and individual level. However, increased population uptake may reduce the population average dose if lower doses are prescribed in more patients.[50] This highlights the importance of carefully defining metrics for quality improvement. Measurement of adherence is equally nuanced. Based on our results, when complete adherence was required at baseline, subsequent compliance inevitably appeared to decline.[8] However, adherence dramatically improved when described by proportion of days covered. The percent change increased by approximately 20%–30% when considered as total days covered, and 45%–70% when defined by individuals with ≥80% of days covered.[63]

Table 3 Usage of medical therapy and associated outcomes following cardiac resynchronization therapy / implantable cardioverter-defibrillator implantation

Study, year	Follow-up (mo)	Usage measurement	Outcome	Associated outcomes
Chun, 2020[58]	30	Sacubitril/valsartan in CRT nonresponders: 22/50 (44%)	Mortality	5% vs 36%, $P = .02$.
Hu, 2019[60]	57	ACEI/ARB + BB vs single/none	Mortality HFH	4% vs 8%, $P = .53$ 2% vs 23%, $P = .04$
DeVore, 2018[65]	24	Sacubitril/valsartan use associated number advanced practice providers		aOR 1.08 (1.03–1.14)
Massoullie, 2018[56]	23	Dual therapy 38% base vs 41% 3 mo Triple therapy 26% base vs 32% 3 mo	Mortality	HR 0.59 (0.36–0.97), $P = .04$
Ruwald, 2018[72]	26	BB vs no-BB therapy	HFH Death VA	HR 0.43 (0.34–0.54), $P < .001$ HR 0.24 (0.18–0.33), $P < .001$ HR 0.53 (0.39–0.72), $P < .001$
Fontaine, 2018[73]	52	Lack of ACEI/ARB	Death	HR 2.51 (1.0–6.3), $P = .05$ in African Americans
Jin, 2017[100]	6	ACEI/ARB, 88% vs 69% use super-responders vs not super-response	Super response	OR 0.33 (CI: 0.13–0.82), $P < .01$
Zeitler, 2017[78]	31	Absence of BB therapy	Shocks	OR 1.61 (1.23–2.12), $P < .01$
Aljaroudi, 2015[74]	30	ACEI/ARB therapy	Shocks	RR 0.61 (0.43–0.86), $P = .005$
Chichareon, 2015[79]	22	Lack of BB and MRA therapy	ICD therapy	BB OR 0.23 (0.07–0.82) $P = .02$ MRA OR 0.33 (0.11–0.99) $P = .04$
Penn, 2015[51]	12	ACEI/ARB, 96% super-responders vs 88% nonresponders	Death or HFH	HR 0.58 (0.42–0.80), $P = .001$
Shen, 2013[71]	17	BB vs no-BB therapy	Mortality	12% vs 36%
Kreuz, 2012[61]	43	Lack of BB therapy	Mortality	HR 2.3 (1.6-3.8), $P = .003$
Friedman, 2012[76]	18	Absence of BB therapy	ICD therapy	HR 6.34 (2.28–17.65), $P < .001$
Voigt, 2010[55]	20	15% unexplained BB absence	Death or transplant	HR 3.1 (1.1–9.3), $P = .04$ Mean transplant-free survival: 21 vs 17 mo, $P = .003$
Desai, 2010[68]	34	ACEI/ARB use	Death	RR 0.l (0.04–0.20), $P < .0001$
Obeyesekere, 2010[75]	19	Lack of ACEI/ARB	ICD therapy	OR 0.06 (0.01–0.37), $P < .01$ No difference transplant rates
Verma, 2010[77]	25	Absence of BB therapy in ischemic and dilated cardiomyopathy	ICD therapy	HR 4.0 (1.5–10.5), $P = .006$ HR 1.9 (1.1–4.8) $P = .04$
Pietrasik, 2009[66]	20	BB and ACEI use	HF events	BB HR 0.51, $P = .017$ ACEI HR 0.64, $P = .071$ Combination 0.36, $P < .001$
Bai, 2008[59]	27	BB use	Death	aOR 0.33 (0.16–0.67), $P = .002$
Lai, 2008[67]	32	BB and ACEI/ARB use	Death	13% and 17% vs 24% non-use
Tandri, 2006[70]	70	BB and ACEI use	Death	BB 0.43 (0.27–0.78), $P < .001$ ACEI 0.78 (0.60–0.95), $P = .05$
Pinski, 2000[69]	17	ACEI use during hospitalization	Death	ACEI 0.71 (0.50–0.99), $P = .04$

ACEI = angiotensin-converting enzyme inhibitor; aOR = adjusted odds ratio; ARB = angiotensin receptor blocker; BB = beta blocker; CRT = cardiac resynchronization therapy; HFH = heart failure hospitalization; HR = hazard ratio; RR = relative risk; ICD = implantable cardioverter-defibrillator; MRA = mineralocorticoid receptor antagonist; VA = ventricular arrhythmia.

Eligibility and timing of newer medical therapies

Only 1 study, from Denmark, specifically examined ARNI eligibility in patients with devices, with several key findings.[49] First, a large proportion of patients were eligible for changing ACEI/ARB to ARNI. Second, this eligibility varied from 43% to 72% depending on the criteria applied. Third, eligibility approximately halved when applied to patients alive at 6 months with persistent symptoms (17% to 32%). Finally, 18% developed an indication for ARNI during follow-up, confirming the importance of reevaluating medical therapies post–device implant.

The new medication classes, notably ARNI and SGLT2 inhibitors, have further reduced morbidity and mortality in patient with HFrEF.[3,4] The recently updated American College of Cardiology and Canadian Cardiovascular Society guidelines both recommend quadruple therapy (ARNI, beta blocker, MRA, SGLT2 inhibitor) for almost all patients with HFrEF.[85,86] However, the optimal time for medication switching (ARNI) or addition (SGLT2 inhibitors) after device implant is unclear. A patient may no longer fulfill guideline criteria for newer therapies owing to improvement in LVEF or symptoms post-CRT. Therefore, starting the optimization immediately after implantation might not be cost-effective in responders. Conversely, postponing optimization in patients who will later be considered CRT nonresponders denies them a survival benefit. Mortality was significantly reduced within 30 days in PARADIGM-HF—time is of the essence and no patient with HF is truly "stable."[87]

Table 4 Dose and adherence to medical therapy and associated outcomes following cardiac resynchronization therapy / implantable cardioverter-defibrillator implantation

Study, year	Main endpoints	Main result	Associated outcomes or secondary result
CRT			
Martens, 2020[10]	*Dose uptitration* Mean % target dose Baseline vs 6 mo	BB uptitration 33% vs 79%	Every 1% uptitration associated lower risk-appropriate ICD therapy OR 0.982 (0.965–0.999), $P = .042$
Martens, 2017[9]	*Dose uptitration* Mean % target dose Baseline vs 6 mo	ACEI/ARB 30% vs 70%, $P < .001$ BB 30% vs 75%, $P < .001$	Reduced death/HF hospitalization ACEI/ARB aHR 0.54 (0.32–0.91), $P = .02$ BB aHR 0.63 (0.41–0.99), $P = .04$
Mantziari, 2012[52]	*Dose uptitration* Mean % of target Baseline vs 6 mo	ACEI 64% vs 71%, $P = .01$ ARB 50% vs 50%, $P = .57$. ACEI/ARB 55% vs 62%, $P = .03$	Worse survival, ACEI/ARB dose <50% vs 50%–99% vs 100% target: 19.2 mo vs 22.1 mo vs 22.9 mo, $P < .01$ and $P = .007$
D'Onofrio, 2017[80]	*Dose uptitration* Median % of target Proportion at target Baseline vs 6 mo	BB 25% vs 100% BB 20% vs 58% $P < .001$.	Proportion at target dose, remote vs in-clinic titration: 76% vs 38% at 6 mo
Adlbrecht, 2009[81]	*Dose uptitration* Proportion at target HF clinic care vs Cardio-internist	ACEI/ARB and BB 73% vs 27, $P < .001$	Significant predictor survival without cardiac hospitalization HR 2.08 (1.17–3.71), $P = .013$
Aranda, 2005[54]	*Dose uptitration* BB increase vs no increase	Functional class improvement: 24% vs 16%	-
Rinkuniene, 2017[50]	*Dose* Mean % of target Baseline vs 1 y	BB 23% vs 30% MRA 59% vs 50%	-
Nebata, 2016[64]	*Dose* Mean daily dose Proportion at target Baseline vs 6 mo	BB 5.6 ± 7.0 vs 13.2 ± 7.8 mg, $P < .001$ BB 13% vs 40%	Uptitration BB dose independent predictor cardiac events HR 0.92 (0.87–0.98), $P < .01$
Witt, 2015[8]	*Dose* Mean % of target Baseline vs 6 mo Adherence	ACEI/ARB 74% vs 78%, $P = .02$ BB 43% vs 53%, $P < .001$ Adherence: BB 95%, ACEI/ARB 94%	High vs low dose associated lower mortality ACEI/ARB aHR 0.55 vs 0.68 BB aHR 0.50 vs 0.65
Schmidt, 2014[62]	*Dose* Mean % of target 24 mo	Super-responders vs not ACEI/ARB 68% vs 52%, $P < .01$; BB 59% vs 42%, $P < .01$	Higher doses independently associated lower mortality HR 0.98, $P = .001$
Hitz, 2012[53]	*Dose* Mean % of target Baseline vs 3 y	BB 55% vs 68%, $P < .02$ ACEI/ARB 78% vs 79%	Responder BB 58% vs 72%, $P = .01$ Nonresponder BB 57% vs 56%, $P =$ ns Responder ACEI/ARB 83% vs 78%, $P =$ ns Nonresponder 80% vs 87%, $P =$ ns
Heywood, 2010[57]	*Dose* Proportion at or above target dose	CRT-D, CRT-P, no-CRT: BB 20%, 17%, 15% ACEI/ARB 32%, 31%, 35% MRA 73%, 72%, 77%	Use of CRT-P/CRT-D associated delivery of BB at or above target dose: OR 1.54 (1.03–2.3), $P = .03$/OR 1.35 (1.07 to 1.71), $P = .01$
Shah, 2019[63]	*Adherence* Pre, post 12 mo	Proportion days covered ACEI 58% vs 71%, $P < .001$ BB 57% vs 75%, $P < .001$	Proportion days covered ≥80% ACEI 37% vs 55%, (47% change), $P < .001$. BB 34% vs 58% (71% change), $P < .001$
ICD			
Heywood, 2010[57]	Proportion treated at or above target dose ICD vs no ICD	BB 20% vs 15% ACEI/ARB 33% vs 35% MRA 70% vs 77%	ICD use not associated delivery at or above target doses (BB, ACEI, and MRA, $P = .07$, $P = .3$, and $P = .5$)
D'Onofrio, 2016[101]	*Dose uptitration* Proportion at target Baseline vs 6 mo	Standard BB titration 7% vs 13%, $P < .05$ Remote titration 6% vs 10%	BB effective dose and adoption of remote monitoring improved HF clinical composite score, OR 0.58 (0.39–0.86), $P = .006$, OR 0.65 (0.50–0.86), $P = .003$

ns = nonsignificant; CRT-D = CRT with defibrillator; CRT-P = CRT with pacemaker; other abbreviations are the same as Table 3.

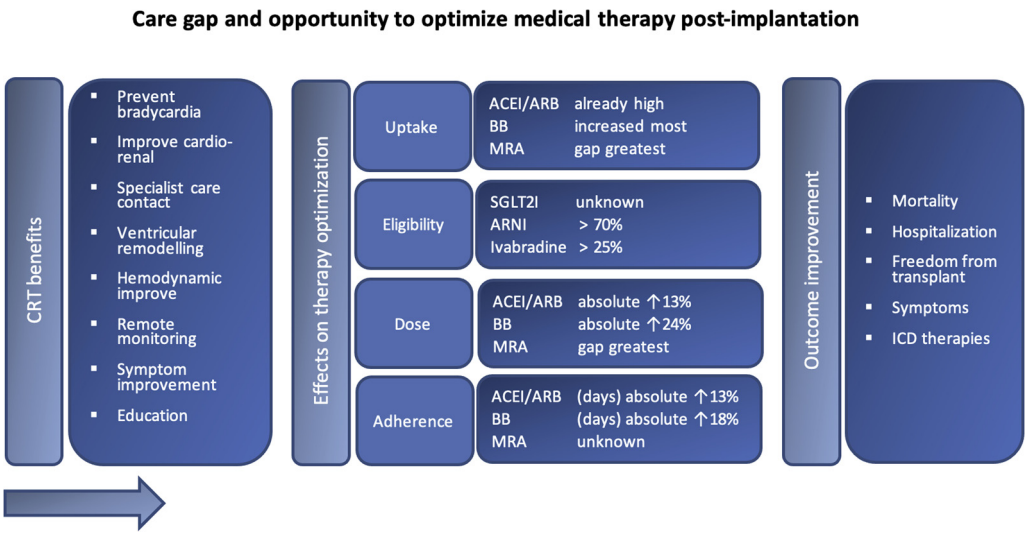

Figure 4 Overview of the benefits and association of cardiac implantable electronic devices with uptake, dose, and adherence of medical therapy and eligibility for newer therapies. ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; ARNI = angiotensin receptor–neprilysin inhibitor; BB = beta blocker; CRT = cardiac resynchronization therapy; ICD = implantable cardioverter-defibrillator; MRA = mineralocorticoid receptor antagonist; SGLT2I = sodium-glucose cotransporter-2 inhibitor.

Association between medical therapy optimization and outcomes

In the identified cohort studies, higher doses of medical therapy post-CRT were associated with improved outcomes after multivariable adjustment.[8,9,52,62] While it is possible that dose increases led to improved outcomes, cause and effect cannot be inferred from nonrandomized observational studies. However, this aligns with published randomized controlled trial evidence of high- vs low-dose therapies, which consistently demonstrates a dose-response relationship in ventricular remodeling and outcomes.[88–90]

We also observed lower rates of ventricular arrhythmia and ICD therapies associated with higher doses of ACEI/ARB and particularly beta blockade. The benefits were elegantly highlighted in a Belgian cohort where every 1% beta-blocker dose uptitration was independently associated with 2% lower odds of a first appropriate therapy.[10] Similarly, absence of beta blocker or ACEI/ARB was a significant predictor of appropriate therapy.[74–79] In the landmark clinical trials, the incidence of sudden cardiac death is reduced 20%–75% by ACEI/ARB,[91] 19%–44% by beta blockers,[91] 20%–30% by MRA,[92] 20% by ARNI,[3] and 16% by SGLT2 inhibitors.[93] Moreover, in the PARADIGM-HF trial sacubitril-valsartan reduced risk of sudden cardiac death in patients irrespective of device status.[94]

Possible mechanisms for improved medication optimization post-CRT

An overview of the association of cardiac implantable electronic devices with uptake, dose, and adherence of medical therapies and eligibility for newer therapies is presented in Figure 4. Medication tolerability may improve after CRT owing to multiple hemodynamic and neurohormonal factors: prevention of bradycardia, higher blood pressure, ventricular remodeling with increased cardiac output, reduced cardiorenal impairment, and improved symptoms.[12,95] The same factors that improve uptake, titration, and dose may well increase adherence. Optimization capability may also be increased by specialized healthcare exposure, remote monitoring, and education after CRT implantation. In our review, ICD therapy in the IMPROVE-HF registry was not associated with delivery of medications at target doses, including beta blockers.[57] Although the enablement of renin-angiotensin-aldosterone blockade might be limited, pacing support should facilitate beta-blocker titration.

Approach for medication optimization

Owing to the timeframe of the studies identified, optimization of newer agents and quadruple therapy could not be assessed. However, further consideration should be given to strategies for medication optimization after device implantation. The goal of maximum tolerated quadruple therapy in the minimum time period, based on the recent guidelines, requires multiple titrations. Single or, in less frail patients, multiple therapies may be changed together.[96] In our opinion, a collaborative team approach is needed, where every healthcare contact is an opportunity to improve, whether nurse practitioner, pharmacist, primary care physician, general cardiologist, HF specialist, or electrophysiologist. These should be complemented by remote titration,[80,97] as well as novel strategies such as electronic patient-activation tools, directly involving patients in the optimization process.[98] The provider mix, level of service integration, and enabling technologies depend in part on health system infrastructure and reimbursement models. The arrival of novel survival-prolonging therapies and updated guidelines means no provider can be a bystander in delivering patient-centered care. This is particularly relevant to the SGLT2 inhibitors, which

require no titration, have an adverse event profile similar to placebo, and require very little monitoring.[4,99]

Limitations

Several limitations merit consideration. The heterogeneous measures of medication dose, eligibility, and associated outcomes all prevented meta-analysis. Most of the included studies were small, single center, and retrospective. This highlights the need for systematic, granular electronic data collection to address focused quality objectives proven to improve patient outcomes. Very few studies examined eligibility for newer therapies, which should be a future goal for research.

Conclusion

Optimization of medical therapy following device implantation is feasible and associated with improved outcomes. Further studies are needed to define and understand the care gaps, particularly for newer therapies including ARNI and SGLT2 inhibitors. Device follow-up and remote monitoring extends the circle of care and provides an opportunity for optimization. The most important action is just that—to take an action.

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Authorship

All authors attest they meet the current ICMJE criteria for authorship.

Ethics Statement

The systematic review presented in this manuscript adhered to the PRISMA guidelines.

Appendix

Supplementary data

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.hroo.2021.09.010.

References

1. Vaduganathan M, Claggett BL, Jhund PS, et al. Estimating lifetime benefits of comprehensive disease-modifying pharmacological therapies in patients with heart failure with reduced ejection fraction: a comparative analysis of three randomised controlled trials. Lancet 2020;396:121–128.
2. Zannad F, McMurray JJ, Krum H, et al. Eplerenone in patients with systolic heart failure and mild symptoms. N Engl J Med 2011;364:11–21.
3. McMurray JJ, Packer M, Desai AS, et al. Angiotensin-neprilysin inhibition versus enalapril in heart failure. N Engl J Med 2014;371:993–1004.
4. McMurray JJV, Solomon SD, Inzucchi SE, et al. Dapagliflozin in patients with heart failure and reduced ejection fraction. N Engl J Med 2019;381:1995–2008.
5. Swedberg K, Komajda M, Bohm M, et al. Ivabradine and outcomes in chronic heart failure (SHIFT): a randomised placebo-controlled study. Lancet 2010;376:875–885.
6. Hauptman PJ, Swindle JP, Masoudi FA, Burroughs TE. Underutilization of beta-blockers in patients undergoing implantable cardioverter-defibrillator and cardiac resynchronization procedures. Circ Cardiovasc Qual Outcomes 2010;3:204–211.
7. 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.
8. 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.
9. Martens P, Verbrugge FH, Nijst P, et al. Feasibility and association of neurohumoral blocker up-titration after cardiac resynchronization therapy. J Card Fail 2017;23:597–605.
10. Martens P, Dupont M, Mullens W. Reduced occurrence of appropriate therapy for ventricular arrhythmias after beta-blocker uptitration following implant of a primary prevention CRT-defibrillator. Acta Cardiol 2020;75:49–53.
11. Abraham WT, Fisher WG, Smith AL, et al. Cardiac resynchronization in chronic heart failure. N Engl J Med 2002;346:1845–1853.
12. Bristow MR, Saxon LA, Boehmer J, et al. Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. N Engl J Med 2004;350:2140–2150.
13. Cleland JG, Daubert JC, Erdmann E, et al. The effect of cardiac resynchronization on morbidity and mortality in heart failure. N Engl J Med 2005;352:1539–1549.
14. Linde C, Abraham WT, Gold MR, et al. Randomized trial of cardiac resynchronization in mildly symptomatic heart failure patients and in asymptomatic patients with left ventricular dysfunction and previous heart failure symptoms. J Am Coll Cardiol 2008;52:1834–1843.
15. Young JB, Abraham WT, Smith AL, et al. Combined cardiac resynchronization and implantable cardioversion defibrillation in advanced chronic heart failure: the MIRACLE ICD Trial. JAMA 2003;289:2685–2694.
16. Abraham WT, Young JB, Leon AR, et al. Effects of cardiac resynchronization on disease progression in patients with left ventricular systolic dysfunction, an indication for an implantable cardioverter-defibrillator, and mildly symptomatic chronic heart failure. Circulation 2004;110:2864–2868.
17. Higgins SL, Hummel JD, Niazi IK, et al. Cardiac resynchronization therapy for the treatment of heart failure in patients with intraventricular conduction delay and malignant ventricular tachyarrhythmias. J Am Coll Cardiol 2003;42:1454–1459.
18. Moss AJ, Hall WJ, Cannom DS, et al. Cardiac-resynchronization therapy for the prevention of heart-failure events. N Engl J Med 2009;361:1329–1338.
19. Tang AS, Wells GA, Talajic M, et al. Cardiac-resynchronization therapy for mild-to-moderate heart failure. N Engl J Med 2010;363:2385–2395.
20. Beshai JF, Grimm RA, Nagueh SF, et al. Cardiac-resynchronization therapy in heart failure with narrow QRS complexes. N Engl J Med 2007;357:2461–2471.
21. Ruschitzka F, Abraham WT, Singh JP, et al. Cardiac-resynchronization therapy in heart failure with a narrow QRS complex. N Engl J Med 2013;369:1395–1405.
22. Hohnloser SH, Kuck KH, Dorian P, et al. Prophylactic use of an implantable cardioverter-defibrillator after acute myocardial infarction. N Engl J Med 2004;351:2481–2488.
23. Steinbeck G, Andresen D, Seidl K, et al. Defibrillator implantation early after myocardial infarction. N Engl J Med 2009;361:1427–1436.
24. Moss A, Zareba W, Hall W, et al. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. N Engl J Med 2002;346:877–883.
25. Bardy GH, Lee KL, Mark DB, et al. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. N Engl J Med 2005;352:225–237.

26. Bansch D, Antz M, Boczor S, et al. Primary prevention of sudden cardiac death in idiopathic dilated cardiomyopathy: the Cardiomyopathy Trial (CAT). Circulation 2002;105:1453–1458.
27. Strickberger SA, Hummel JD, Bartlett TG, et al. Amiodarone versus implantable cardioverter-defibrillator: randomized trial in patients with nonischemic dilated cardiomyopathy and asymptomatic nonsustained ventricular tachycardia–AMIOVIRT. J Am Coll Cardiol 2003;41:1707–1712.
28. Kadish A, Dyer A, Daubert JP, et al. Prophylactic defibrillator implantation in patients with nonischemic dilated cardiomyopathy. N Engl J Med 2004; 350:2151–2158.
29. Kober L, Thune JJ, Nielsen JC, et al. Defibrillator implantation in patients with nonischemic systolic heart failure. N Engl J Med 2016;375:1221–1230.
30. Landolina M, Gasparini M, Lunati M, et al. Long-term complications related to biventricular defibrillator implantation: rate of surgical revisions and impact on survival: insights from the Italian Clinical Service Database. Circulation 2011; 123:2526–2535.
31. van der Heijden AC, Borleffs CJ, Buiten MS, et al. The clinical course of patients with implantable cardioverter-defibrillators: extended experience on clinical outcome, device replacements, and device-related complications. Heart Rhythm 2015;12:1169–1176.
32. Killu AM, Wu JH, Friedman PA, et al. Outcomes of cardiac resynchronization therapy in the elderly. Pacing Clin Electrophysiol 2013;36:664–672.
33. Masoudi FA, Mi X, Curtis LH, et al. Comparative effectiveness of cardiac resynchronization therapy with an implantable cardioverter-defibrillator versus defibrillator therapy alone: a cohort study. Ann Intern Med 2014; 160:603–611.
34. Varma N, Boehmer J, Bhargava K, et al. Evaluation, management, and outcomes of patients poorly responsive to cardiac resynchronization device therapy. J Am Coll Cardiol 2019;74:2588–2603.
35. Rickard J, Cheng A, Spragg D, et al. Durability of the survival effect of cardiac resynchronization therapy by level of left ventricular functional improvement: fate of "nonresponders". Heart Rhythm 2014;11:412–416.
36. Yokoshiki H, Shimizu A, Mitsuhashi T, et al. Survival and heart failure hospitalization in patients with cardiac resynchronization therapy with or without a defibrillator for primary prevention in Japan - analysis of the Japan Cardiac Device Treatment Registry Database. Circ J 2017;81:1798–1806.
37. Bertaglia E, Arena G, Pecora D, et al. The VALID-CRT risk score reliably predicts response and outcome of cardiac resynchronization therapy in a real-world population. Clin Cardiol 2019;42:919–924.
38. Raafs AG, Linssen GCM, Brugts JJ, et al. Contemporary use of devices in chronic heart failure in the Netherlands. ESC Heart Fail 2020;7:1771–1780.
39. Gunten SV, Theuns DA, Kuhne M, Reichlin T, Sticherling C, Schaer B. Predictors for early mortality and arrhythmic events in patients with cardiac resynchronization therapy with defibrillator: A two center cohort study. Cardiol J 2019; 26:711–716.
40. Fauchier L, Marijon E, Defaye P, et al. Effect of age on survival and causes of death after primary prevention implantable cardioverter-defibrillator implantation. Am J Cardiol 2015;115:1415–1422.
41. Lee DS, Krahn AD, Healey JS, et al. Evaluation of early complications related to de novo cardioverter defibrillator implantation insights from the Ontario ICD database. J Am Coll Cardiol 2010;55:774–782.
42. Sjoblom J, Kalm T, Gadler F, et al. Efficacy of primary preventive ICD therapy in an unselected population of patients with reduced left ventricular ejection fraction. Europace 2014;17:255–261.
43. Suleiman M, Goldenberg I, Haim M, et al. Clinical characteristics and outcomes of elderly patients treated with an implantable cardioverter-defibrillator or cardiac resynchronization therapy in a real-world setting: data from the Israeli ICD Registry. Heart Rhythm 2014;11:435–441.
44. Hawkins NM, Grubisic M, Andrade JG, et al. Long-term complications, reoperations and survival following cardioverter-defibrillator implant. Heart 2018; 104:237–243.
45. Guerra F, Palmisano P, Dell'Era G, et al. Cardiac resynchronization therapy and electrical storm: results of the OBSERVational registry on long-term outcome of ICD patients (OBSERVO-ICD). Europace 2018;20:979–985.
46. Schrage B, Uijl A, Benson L, et al. Association between use of primary-prevention implantable cardioverter-defibrillators and mortality in patients with heart failure: a prospective propensity score-matched analysis from the Swedish Heart Failure Registry. Circulation 2019;140:1530–1539.
47. Theuns D, Van Boven N, Schaer BA, et al. Predicting early mortality among implantable defibrillator patients treated with cardiac resynchronization therapy. J Card Fail 2019;25:812–818.
48. Echouffo-Tcheugui JB, Masoudi FA, Bao H, Curtis JP, Heidenreich PA, Fonarow GC. Body mass index and outcomes of cardiac resynchronization with implantable cardioverter-defibrillator therapy in older patients with heart failure. Eur J Heart Fail 2019;21:1093–1102.
49. Jorsal A, Pryds K, McMurray JJV, et al. Optimizing heart failure treatment following cardiac resynchronization therapy. Clin Res Cardiol 2020; 109:638–645.
50. Rinkuniene D, Krivickiene A, Laukaitiene J, Jurkevicius R. Pharmacological treatment changes of chronic heart failure during cardiac resynchronization therapy: a 1-year follow-up study. Int J Cardiol 2017;238:92–96.
51. Penn J, Goldenberg I, McNitt S, et al. Changes in drug utilization and outcome with cardiac resynchronization therapy: a MADIT-CRT substudy. J Card Fail 2015;21:541–547.
52. Mantziari L, Guha K, Khalique Z, McDonagh T, Sharma R. Relation of dosing of the renin-angiotensin system inhibitors after cardiac resynchronization therapy to long-term prognosis. Am J Cardiol 2012;109:1619–1625.
53. Hitz L, Kuhne MS, Sticherling C, Osswald S, Schaer BA. Adjustments of heart failure medication after implantation of a cardiac resynchronization therapy defibrillator. Minerva Med 2012;103:361–367.
54. Aranda JM Jr, Woo GW, Conti JB, Schofield RS, Conti CR, Hill JA. Use of cardiac resynchronization therapy to optimize beta-blocker therapy in patients with heart failure and prolonged QRS duration. Am J Cardiol 2005;95:889–891.
55. Voigt A, Shalaby A, Adelstein E, Saba S. Beta-blocker utilization and outcomes in patients receiving cardiac resynchronization therapy. Clin Cardiol 2010; 33:E1–E5.
56. Massoullie G, Chouki C, Mulliez A, 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.
57. Heywood JT, Fonarow GC, Yancy CW, 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.
58. Chun KH, Oh J, Yu HT, et al. The role of sacubitril/valsartan in the management of cardiac resynchronization therapy non-responders: a retrospective analysis. ESC Heart Fail 2020;7:4404–4407.
59. Bai R, Di Biase L, Elayi C, et al. Mortality of heart failure patients after cardiac resynchronization therapy: identification of predictors. J Cardiovasc Electrophysiol 2008;19:1259–1265.
60. Hu YR, Hua W, Jin H, et al. Does 'super-responder' patients to cardiac resynchronization therapy still have indications for neuro-hormonal antagonists? Evidence from long-term follow-up in a single center. J Geriatr Cardiol 2019; 16:251–258.
61. Kreuz J, Horlbeck F, Linhart M, et al. Independent predictors of mortality in patients with advanced heart failure treated by cardiac resynchronization therapy. Europace 2012;14:1596–1601.
62. Schmidt S, Hurlimann D, Starck CT, 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.
63. Shah BR, DerSarkissian M, Tsintzos SI, et al. Adherence to heart failure management medications following cardiac resynchronization therapy. Curr Med Res Opin 2020;36:199–207.
64. Nabeta T, Inomata T, Iida Y, et al. Prognostic significance of beta-blocker uptitration in conjunction with cardiac resynchronization therapy in heart failure management. Heart Vessels 2016;31:1109–1116.
65. DeVore AD, Hill CL, Thomas L, et al. Patient, provider, and practice characteristics associated with sacubitril/valsartan use in the United States. Circ Heart Fail 2018;11:e005400.
66. Pietrasik G, Goldenberg I, McNitt S, Polonsky B, Moss AJ, Zareba W. Efficacy of medical therapy for the reduction of heart failure events in patients with implanted cardioverter defibrillators. J Cardiovasc Electrophysiol 2009; 20:395–400.
67. Lai HM, Aronow WS, Kruger A, et al. Effect of beta blockers, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, and statins on mortality in patients with implantable cardioverter-defibrillators. Am J Cardiol 2008;102:77–78.
68. Desai H, Aronow WS, Ahn C, et al. Incidence of appropriate cardioverter-defibrillator shocks and mortality in patients with heart failure treated with combined cardiac resynchronization plus implantable cardioverter-defibrillator therapy versus implantable cardioverter-defibrillator therapy. J Cardiovasc Pharmacol Ther 2010;15:37–40.
69. Pinski SL, Yao Q, Epstein AE, et al. Determinants of outcome in patients with sustained ventricular tachyarrhythmias: the antiarrhythmics versus implantable defibrillators (AVID) study registry. Am Heart J 2000;139:804–813.
70. Tandri H, Griffith LS, Tang T, et al. Clinical course and long-term follow-up of patients receiving implantable cardioverter-defibrillators. Heart Rhythm 2006; 3:762–768.
71. Shen X, Nair CK, Aronow WS, Hee T, Esterbrooks DJ. Effect of carvedilol versus metoprolol CR/XL on mortality in patients with heart failure treated

with cardiac resynchronization therapy: a COX multivariate regression analysis. Am J Ther 2013;20:247–253.
72. Ruwald AC, Gislason GH, Vinther M, et al. Importance of beta-blocker dose in prevention of ventricular tachyarrhythmias, heart failure hospitalizations, and death in primary prevention implantable cardioverter-defibrillator recipients: a Danish nationwide cohort study. Europace 2018;20:f217–f224.
73. Fontaine JM, Franklin SM, Essilfie G, Ahiable LE. Cardiac resynchronization therapy: a comparative analysis of mortality in African Americans and Caucasians. Pacing Clin Electrophysiol 2018;41:536–545.
74. AlJaroudi WA, Refaat MM, Habib RH, et al. Effect of angiotensin-converting enzyme inhibitors and receptor blockers on appropriate implantable cardiac defibrillator shock in patients with severe systolic heart failure (from the GRADE Multicenter Study). Am J Cardiol 2015;115:924–931.
75. Obeyesekere MN, Chan W, Stub D, et al. Left ventricular ejection fraction and absence of ACE inhibitor/angiotensin II receptor blocker predicts appropriate defibrillator therapy in the primary prevention population. Pacing Clin Electrophysiol 2010;33:696–704.
76. Friedman DJ, Altman RK, Orencole M, et al. Predictors of sustained ventricular arrhythmias in cardiac resynchronization therapy. Circ Arrhythm Electrophysiol 2012;5:762–772.
77. Verma A, Sarak B, Kaplan AJ, et al. Predictors of appropriate implantable cardioverter defibrillator (ICD) therapy in primary prevention patients with ischemic and nonischemic cardiomyopathy. Pacing Clin Electrophysiol 2010; 33:320–329.
78. Zeitler EP, Al-Khatib SM, Friedman DJ, et al. Predicting appropriate shocks in patients with heart failure: patient level meta-analysis from SCD-HeFT and MADIT II. J Cardiovasc Electrophysiol 2017;28:1345–1351.
79. Chichareon P, Krittayaphong R, Yindeengam A. Prevalence and predictors of appropriate implantable cardioverter defibrillator therapy in chronic left ventricular dysfunction patients for primary prevention of sudden cardiac death in Siriraj Hospital. J Med Assoc Thai 2015;98:14–20.
80. D'Onofrio A, Palmisano P, Rapacciuolo A, et al. Effectiveness of a management program for outpatient clinic or remote titration of beta-blockers in CRT patients: The RESTORE study. Int J Cardiol 2017;236:290–295.
81. Adlbrecht C, Hulsmann M, Gwechenberger M, et al. Outcome after device implantation in chronic heart failure is dependent on concomitant medical treatment. Eur J Clin Invest 2009;39:1073–1081.
82. Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur J Heart Fail 2016;18:891–975.
83. Diamant MJ, Virani SA, MacKenzie WJ, Ignaszewski A, Toma M, Hawkins NM. Medical therapy doses at hospital discharge in patients with existing and de novo heart failure. ESC Heart Fail 2019;6:774–783.
84. Jarjour M, Henri C, de Denus S, et al. Care gaps in adherence to heart failure guidelines: clinical inertia or physiological limitations? JACC Heart Fail 2020;8:725–738.
85. Maddox TM, Januzzi JL Jr, Allen LA, et al. 2021 Update to the 2017 ACC Expert Consensus Decision Pathway for Optimization of Heart Failure Treatment: answers to 10 pivotal issues about heart failure with reduced ejection fraction: a report of the American College of Cardiology Solution Set Oversight Committee. J Am Coll Cardiol 2021;77:772–810.
86. McDonald M, Virani S, Chan M, et al. CCS/CHFS Heart Failure Guidelines Update: defining a new pharmacologic standard of care for heart failure with reduced ejection fraction. Can J Cardiol 2021;37:531–546.
87. Pascual-Figal D, Bayes-Genis A. The misperception of 'stable' heart failure. Eur J Heart Fail 2018;20:1375–1378.
88. Packer M, Poole-Wilson PA, Armstrong PW, et al. Comparative effects of low and high doses of the angiotensin-converting enzyme inhibitor, lisinopril, on morbidity and mortality in chronic heart failure. ATLAS Study Group. Circulation 1999;100:2312–2318.
89. Konstam MA, Neaton JD, Dickstein K, et al. Effects of high-dose versus low-dose losartan on clinical outcomes in patients with heart failure (HEAAL study): a randomised, double-blind trial. Lancet 2009;374:1840–1848.
90. Bristow MR, Gilbert EM, Abraham WT, et al. Carvedilol produces dose-related improvements in left ventricular function and survival in subjects with chronic heart failure. MOCHA Investigators. Circulation 1996;94:2807–2816.
91. Adamson PB, Gilbert EM. Reducing the risk of sudden death in heart failure with beta-blockers. J Card Fail 2006;12:734–746.
92. Rossello X, Ariti C, Pocock SJ, et al. Impact of mineralocorticoid receptor antagonists on the risk of sudden cardiac death in patients with heart failure and left-ventricular systolic dysfunction: an individual patient-level meta-analysis of three randomized-controlled trials. Clin Res Cardiol 2019;108:477–486.
93. Yan Y, Liu B, Du J, et al. SGLT2i versus ARNI in heart failure with reduced ejection fraction: a systematic review and meta-analysis. ESC Heart Fail 2021;8:2210–2219.
94. Rohde LE, Chatterjee NA, Vaduganathan M, et al. Sacubitril/valsartan and sudden cardiac death according to implantable cardioverter-defibrillator use and heart failure cause: a PARADIGM-HF analysis. JACC Heart Fail 2020; 8:844–855.
95. European Heart Rhythm Association (EHRA), European Society of Cardiology (ESC), Heart Rhythm Society, et al. 2012 EHRA/HRS expert consensus statement on cardiac resynchronization therapy in heart failure: implant and follow-up recommendations and management. Europace 2012; 14:1236–1286.
96. Miller RJ, Howlett JG, Fine NM. A novel approach to medical management of heart failure with reduced ejection fraction. Can J Cardiol 2021; 37:632–643.
97. Desai AS, Maclean T, Blood AJ, et al. Remote optimization of guideline-directed medical therapy in patients with heart failure with reduced ejection fraction. JAMA Cardiol 2020;5:1430–1434.
98. Allen LA, Venechuk G, McIlvennan CK, et al. An electronically delivered patient-activation tool for intensification of medications for chronic heart failure with reduced ejection fraction: the EPIC-HF Trial. Circulation 2021; 143:427–437.
99. Packer M, Anker SD, Butler J, et al. Effect of empagliflozin on the clinical stability of patients with heart failure and a reduced ejection fraction: the EMPEROR-Reduced Trial. Circulation 2021;143:326–336.
100. Jin H, Gu M, Hua W, et al. Predictors of super-response to cardiac resynchronization therapy: the significance of heart failure medication, pre-implant left ventricular geometry and high percentage of biventricular pacing. J Geriatr Cardiol 2017;14:737–742.
101. D'Onofrio A, Stabile G, Capucci A, et al. Association between remote implantable cardioverter defibrillator monitoring and beta-blocker utilization: an analysis from the EFFECT study. J Telemed Telecare 2016;22:383–390.