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. Newer therapies include mineralocorticoid receptor antagonists (MRAs), angiotensin receptor-neprilysin inhibitors (ARNIs), sodium-glucose cotransporter-2 (SGLT2) inhibitors, and ivabradine. 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, advances in guideline-recommended therapy since initial implant, improved medication tolerability after implant, 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...
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). 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.
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. Overall triple therapy usage was reported in a single retrospective French study (n = 243), which increased from

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.
26% to 32% at 3 months after CRT implant ($P < .001$). 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 therapies79 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 up-titration, 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...
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 decreased from 59% to 50%. In that study, more patients were adherent at baseline to ACEI/ARB, beta blocker, and MRA, which declined to 94%, 95%, and 77%, respectively, at 4 years. 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).

### Medical therapy adherence

Two studies reported medication adherence following CRT. 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. 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).

### Eligibility for contemporary medical therapy

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

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

1Medication usage rates are reported at follow-up time.
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,3 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 2: Studies examining baseline and follow-up medical therapy following cardiac resynchronization therapy / implantable cardioverter-defibrillator implantation

| Study, year | Location | Center design | Follow-up (mo) | LVEF (%) | ACEI/ARB, p (%) | Beta blocker, n (%) | MRA, n (%) |
|-------------|----------|---------------|---------------|----------|----------------|-------------------|------------|
| Baseline    | Follow-up (mo) |               | LVEF (%) |                         |                  |                   |            |
| Jorsal, 2020 | Denmark | Single-retro | 6 | 25±6 | 171 (94) | 167 (92) | 131 (96) | 67 (49) |
| Rinkuniene, 2017 | Lithuania | Single-retro | 12 | 20±6 | 69 (81) | 64 (81) | 75 (88) | 47 (55) |
| Nebata, 2016 | Japan | Single-retro | 6 | 28±6 | 55 (87) | 47 (81) | 63 (100) | 47 (55) |
| Witt, 2015 | Denmark | Single-retro | 53 (6) | 24±3 | 74 (90) | 62 (90) | 76 (91) | 47 (58) |
| Mantziari, 2012 | UK | Single-retro | 6 | 24±6 | 85 (98) | 70 (98) | 1517 (94) | 47 (58) |
| Aranda, 2005 | US | Single-retro | 11 | 18±6 | 136 (97) | 113 (61) | 100% | 44 (85) |
| Onofrio, 2016 | Italy | Multi-prosp | 12 | 31±9 | 664 (67) | 2518 (53) | 72 (80) | 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.
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 optimal criteria for newer therapies 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.”56,77

### Table 3

| Study, year | Follow-up (mo) | Usage measurement | Outcome | Associated outcomes |
|------------|----------------|-------------------|---------|---------------------|
| Chun, 202048 | 30 | Sacubitril/valsartan in CRT nonresponders: 22/50 (44%) | Mortality | 5% vs 36%, P = .02. |
| Hu, 201960 | 57 | ACEI/ARB + BB vs single/none | Mortality | 4% vs 8%, P = .53 |
| DeVore, 201865 | 24 | Sacubitril/valsartan use associated number advanced practice providers | HFF | 2% vs 23%, P = .04 |
| Massoullie, 201856 | 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, 201872 | 26 | BB vs no-BB therapy | HFF | HR 0.43 (0.34–0.54), P < .001 |
| Fontaine, 201874 | 52 | Lack of ACEI/ARB | Super response | OR 0.33 (CI: 0.13–0.82), P < .01 |
| Zeitler, 201778 | 31 | Absence of BB therapy | Shocks | OR 1.61 (1.23–2.12), P < .01 |
| Aljaroudi, 201574 | 30 | ACEI/ARB therapy | Shocks | RR 0.61 (0.43–0.86), P = .005 |
| Chicheareon, 201579 | 22 | Lack of BB and MRA therapy | ICD therapy | BB OR 0.23 (0.07–0.82) P = .02 |
| Penn, 201551 | 12 | ACEI/ARB, 96% super-responders vs 88% nonresponders | Death or HFF | HR 0.58 (0.42–0.80), P = .001 |
| Shen, 201371 | 17 | BB vs no-BB therapy | Mortality | 12% vs 36% |
| Kreuz, 201241 | 43 | Lack of BB therapy | Mortality | HR 2.3 (1.6–3.8), P = .003 |
| Friedman, 201276 | 18 | Absence of BB therapy | ICD therapy | HR 6.34 (2.28–17.65), P < .001 |
| Voigt, 201075 | 20 | 15% unexplained BB absence | Death or transplant | HR 5.1 (1.9–14.3), P = .04 |
| Desai, 201068 | 34 | ACEI/ARB use | Death | RR 0.1 (0.04–0.20), P < .0001 |
| Obeyesekere, 201075 | 19 | Lack of ACEI/ARB | ICD therapy | OR 0.06 (0.01–0.37), P < .01 |
| Verma, 201047 | 25 | Absence of BB therapy in ischemic and dilated cardiomyopathy | ICD therapy | HR 4.0 (1.5–10.5), P = .006 |
| Pietrasik, 200986 | 20 | BB and ACEI use | HF events | HR 1.9 (1.1–4.8) P = .04 |
| Bai, 200859 | 27 | BB use | Death | aOR 0.33 (0.16–0.67), P = .002 |
| Lai, 200847 | 32 | BB and ACEI/ARB use | Death | 13% and 17% vs 24% non-use |
| Tandri, 200660 | 70 | BB and ACEI use | Death | BB 0.43 (0.27–0.78), P < .001 |
| Pinski, 200049 | 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.
| Study, year | Main endpoints | Main result | Associated outcomes or secondary result |
|-------------|----------------|-------------|----------------------------------------|
| **CRT**     | **Dose uptitration** | BB uptitration 33% vs 79% | Every 1% uptitration associated lower risk-appropriate ICD therapy OR 0.982 (0.965–0.999), P = .002 |
| Martens, 2020 | Mean % target dose | ACEI/ARB 30% vs 70%, P < .001 | Reduced death/HF hospitalization ACEI/ARB aHR 0.54 (0.32–0.91), P = .02 |
| Martens, 2017 | Mean target dose | BB 30% vs 75%, P < .001 | BB aHR 0.63 (0.41–0.99), P = .04 |
| Mantziari, 2012 | Mean target dose | ACEI 64% vs 71%, P = .01 | 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 | Proportion at target | BB 25% vs 100% | Proportion at target dose, remote vs in-clinic titration: 76% vs 38% at 6 mo |
| Adlbrecht, 2009 | Proportion at target | ACEI/ARB and BB | Significant predictor survival without cardiac hospitalization HR 2.08 (1.17–3.71), P = .013 |
| Aranda, 2005 | Proportion at target | Functional class improvement: BB 73% vs 27%, P < .001 | - |
| Rinkuniene, 2017 | BB increase vs no increase | BB 24% vs 16% | - |
| Nebata, 2016 | Mean % of target | BB 6.6 ± 7.0 vs 13.2 ± 7.8 mg, P < .001 | Uptitration BB dose independent predictor cardiac events HR 0.92 (0.87–0.98), P < .01 |
| Witt, 2015 | Adherence | BB 43% vs 53%, P < .001 | High vs low dose associated lower mortality ACEI/ARB aHR 0.55 vs 0.68 |
| Schmidt, 2014 | BB 95%, ACEI/ARB 94% | BB aHR 0.50 vs 0.65 | Higher doses independently associated lower mortality HR 0.98, P = .001 |
| Hitz, 2012 | Super-responders vs not | ACEI/ARB 68% vs 52%, P < .01; BB 59% vs 42%, P < .01 | - |
| Heywood, 2010 | Proportion at target dose | BB 20% vs 15%, P = .01 | Nonresponder BB 58% vs 72%, P = ns |
| Shah, 2019 | Adherence | ACEI/ARB 32% vs 31%, 35% | Nonresponder BB 57% vs 56%, P = ns |
| Heywood, 2010 | MRA 73%, 72%, 77% | MRA 70% vs 77% | Responder ACEI/ARB 83% vs 78%, P = ns |
| D’Onofrio, 2016 | Proportion days covered | ACEI 58% vs 71%, P < .001 | Nonresponder 80% vs 87%, P = ns |
| | BB 57% vs 75%, P < .001 | BB 55% vs 68%, P < .02 | 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 |
| | Pre, post 12 mo | Proportion days covered ≥80% | Proportion days covered ≥80% ACEI 37% vs 55%, (47% change), P < .001. BB 34% vs 58% (71% change), P < .001 |
| **ICD**     | **Proportion treated at or above target dose ICD vs no ICD** | BB 20% vs 15% | ICD use not associated delivery at or above target doses (BB, ACEI, and MRA, P = .07, P = .3, and P = .5) |
| | **Proportion at target** | ACEI/ARB 33% vs 35% | 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 |
| | **Baseline vs 6 mo** | MRA 70% vs 77% | - |

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

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. Similarly, absence of beta blocker or ACEI/ARB was a significant predictor of appropriate therapy. In the landmark clinical trials, the incidence of sudden cardiac death is reduced 20%–75% by ACEI/ARB, 19%–44% by beta blockers, 20%–30% by MRA, 20% by ARNI, and 16% by SGLT2 inhibitors. Moreover, in the PARADIGM-HF trial sacubitril-valsartan reduced risk of sudden cardiac death in patients irrespective of device status.

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 therapy 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. 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. 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. 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, as well as novel strategies such as electronic patient-activation tools, directly involving patients in the optimization process. 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.\textsuperscript{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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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.

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