

Improving Guideline-Directed Medical Therapy for Patients with Heart Failure with Reduced Ejection Fraction: A Review of Implementation Strategies

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Highlights

- Use of guideline-directed medical therapy (GDMT) for patients with heart failure with reduced ejection fraction (HFrEF) remains sub-optimal, despite clear evidence that these medications reduce morbidity and mortality
- In our review of published work describing approaches to improve we found that many studies were limited to single-center experiences and had small sample sizes.
- Among studies with positive results, successful implementation strategies often included the use of multidisciplinary teams, dedicated GDMT titration algorithms, and clinician audit with feedback.
- Large, rigorous trials are needed to understand what interventions are most effective at improving the use and titration of GDMT in HFrEF.

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Abstract

Despite recent advances in guideline-directed medical therapy (GDMT) for patients with heart failure with reduced ejection fraction (HFrEF), achievement of target GDMT utilization and up-titration to goal doses continue to be modest. In recent years, a number of different interventional approaches to improve GDMT have been published, but many are limited by single-center experiences with small sample sizes. However, strategies including use of multidisciplinary teams, dedicated GDMT titration algorithms, and clinician audit with feedback have shown promise. There remains a critical need for large, rigorous trials to assess the utility of different interventions to improve use and titration of GDMT in HFrEF. Here, we review existing literature in GDMT implementation for HFrEF, and discuss future directions and considerations within the field.

Lay Summary

- Guideline-directed medical therapies (GDMT) for heart failure with reduced ejection fraction are recommended to reduce rates of death and heart failure hospitalization: despite this, many patients are not on all four core GDMT medications, or remain on low doses
- In this review of studies evaluating different strategies to improve GDMT initiation and up-titration, we found that using multidisciplinary teams with nurses, pharmacists, and care managers, or algorithms to guide GDMT use helped to improve GDMT initiation
- Larger studies are needed to understand how to best improve GDMT use to prevent heart-failure related clinical events

Introduction

Heart failure with reduced ejection fraction (HFrEF) affects approximately 6.5 million people in the United States, and is associated with high levels of morbidity and mortality, with projected mortality at 6 years approaching 50%¹. Use of guideline-directed medical therapy (GDMT) in HFrEF reduces the high morbidity and mortality associated with HFrEF²⁻⁴. These medications include four groups of medications: 1) β -blockers; 2) renin-angiotensin system (RAS) inhibitors such as angiotensin-converting enzyme inhibitor (ACEi); angiotensin receptor blocker (ARB); and angiotensin-receptor neprilysin inhibitor (ARNI); 3) mineralocorticoid receptor antagonist (MRA), and 4) sodium-glucose co-transporter 2 inhibitors (SGLT2i). Based on their proven efficacy, these medications represent foundational therapies with Class 1 recommendations for patients with HFrEF^{4,5}.

Despite the data to support GDMT in HFrEF, 'real-world' use of these medications is relatively modest, with significant room for optimization^{6,7}. In the United States, registry data indicate that 33% of eligible patients are not prescribed a RAS inhibitor (ACEi/ARB/ARNI), 25% are not prescribed a β -blocker, and 55% are not prescribed an MRA⁸. Furthermore, of patients prescribed these therapies, only a small percentage are on target doses of any given medication, and only 1% of all eligible patients with HFrEF are simultaneously on target doses of RAS inhibitor, β -blocker and MRA⁶. SGLT2i, a newer class of medications in this landscape, remain infrequently used in eligible patients⁹⁻¹¹.

The low rates of GDMT use in HFrEF significantly reduces the potential benefit of these medications on a population level. Projections suggest that optimal use of SGLT2i could prevent an additional 34,000 heart failure-related deaths in the United States, and that 28,000 deaths could be prevented with optimal ARNI use^{12,13}. The combined magnitude of clinical benefit with use of β -blocker, ARNI, MRA, and SGLT2i is projected to extend life expectancy by >6 additional years for a 55-year old patient with HFrEF compared with ACE and β -blocker alone¹⁴. In one study of high-intensity care, patients with rapid up-titration to maximally tolerated

doses of GDMT within 2 weeks of discharge from a HF hospitalization experienced a 34% reduction in HF readmissions or all-cause death at 180 days.¹⁵ Thus, there exists an imperative to improve GDMT implementation to prevent patient morbidity and mortality while simultaneously reducing strain on the healthcare system by reducing hospitalizations and urgent visits for heart failure decompensations¹⁶.

As a result of the low rates of GDMT use despite clear safety and efficacy data, there are ongoing calls to understand barriers to GDMT use and subsequently improve optimization of GDMT^{17,18}. There have been multiple attempts at improving use of GDMT with HFrEF, largely at the individual site level and with varied success in terms of improvement in GDMT prescription rates. Increasingly, there is interest in understanding what strategies improve GDMT usage in the real world¹⁹. By studying potential interventions and rigorously evaluating their effectiveness on a population level, it may become possible to identify which strategy, or strategies, could be most effective to increase GDMT use across the country. Here, we provide a framework for understanding reported clinician-based barriers to GDMT use, discuss previously reported strategies to improve GDMT implementation, and outline a potential path forward to improve prescription of GDMT.

Challenges in Prescribing GDMT

Barriers to GDMT prescription likely vary depending on local resources and care structures, though data shows that GDMT implementation rates are similarly low across care provided by multiple types of clinicians²⁰. Here, we briefly review the most commonly reported barriers to the prescription of GDMT at the patient, physician, and system levels. Though important, a comprehensive review of patient level barriers, such as medication adherence, poor health literacy, insurance coverage, or other psychosocial, cultural, or economic factors is out of the scope of this review.

Patient Level Barriers

On the individual patient level, described barriers to GDMT prescription by clinicians include the cost of branded drugs, and reticence to change therapies or add additional medications to a regimen that they may be tolerating, especially for patients with perceived frailty²¹. Prior work has shown that patients with lower levels of kidney function, older age, and lower blood pressure are less likely to receive GDMT, despite the fact that they may also be more likely to benefit from its use.²² Though beta-blockers, ACEi and MRAs are all available as generic drugs, ARNI and SGLT2i use can have significant out-of-pocket costs for patients, even with insurance coverage. In 2018, the estimated annual out-of-pocket expense for an ARNI and an SGLT2i together was estimated to be \$895 for a patient with Medicare: for a patient without insurance, the annual cost was \$10,802 if they did not qualify for a drug's subsidy program. These costs have remained high, and the median out-of-pocket cost for use of all four pillars of HF GDMT for a patient with Medicare in 2022 was estimated to be \$2,217.²³ For patients with multiple chronic medical conditions requiring medical therapy, both cost and reticence to take a large number of medications may contribute to low prescription rates. In addition to cost concerns, patients who are older, have lower blood pressure, or renal insufficiency are less likely to be prescribed or to have escalation in doses of their GDMT^{6, 24}. Similarly, patients with recent hospitalizations for heart failure and worse functional class are also less likely to receive initiation or up-titration of these medications, though they arguably stand to have the greatest absolute benefit^{6, 24}. In an analysis of 3,518 patients from the CHAMP-HF registry, risk factors for underuse of GDMT included worse functional class, recent HF hospitalization, older age, and lower blood pressure²⁴.

Clinician and System Level Barriers

On a clinician level, barriers to prescription of GDMT may include lack of familiarity with the newer drugs, lack of time, and lack of resources to navigate prior authorizations and other

insurance issues²⁵⁻²⁷. A review of different studies assessing barriers to physician adherence for both specialists and clinicians found that the single most commonly reported barrier was awareness of guidelines²⁶. Though not explicitly assessed, this may be a particular issue for non-HF specialists who may have less exposure to HF-specific guidelines. Clinicians may not always be cognizant of their own knowledge gaps: one survey of 467 cardiologists found that though 92% of respondents reported that they were adherent to ESC guidelines, fewer than 25% of the same respondents made treatment decisions that followed guidelines when provided hypothetical patient cases²⁸. Even when clinicians are aware of the guidelines, other barriers exist: one survey of cardiology clinicians found that over half (53.4%) felt that time was a major barrier to following guidelines, and a similar proportion (48.4%) of survey respondents reported that their workload prevented them from fully following guideline recommendations²⁵. Another survey of cardiologists evaluating barriers to prescribing cardiovascular medications found that clinicians feel that they have inadequate time with patients to discuss new therapies and spend too much of their time communicating with insurance companies if authorization is needed. Of survey participants, 55% indicated that it was difficult to attain payer approval for cardiovascular drugs. Furthermore, 78% of clinicians noted that the associated administrative burden with expensive therapies represented a substantial barrier to prescription²⁹.

Search Strategy for Prior Studies Targeting GDMT Initiation

The focus of this literature review was to review studies which evaluated clinician-based GDMT prescription strategies focused on improving the utilization of GDMT using various methods. In order to assess prior studies targeting GDMT initiation, we performed a literature review of published papers in PubMed focusing on GDMT implementation in heart failure, and summarize the findings here. Our search strategy was broad, and search terms included “guideline directed medical therapy,” “initiation,” “implementation,” “heart failure,” “beta blocker,” “heart failure,”

“mineralocorticoid receptor antagonist,” and “angiotensin converting enzyme inhibitor.” There were no specific restrictions placed on the years for which manuscripts had been published. Overall, studies tended to be small, non-randomized, and were typically single-site. Of 42 studies found and reviewed, the majority (29 studies, 69%) were performed at a single site, and 40% (17 studies) of studies included fewer than 300 patients. Relatively few studies (12, 29%) were randomized, many studies conducted as before-after analyses (20, 48%) (**Table**). There was significant variation in terms of both intervention type, and outcome measurement, with some studies reporting only changes in a single class of GDMT, and others reporting changes for multiple class types. We broadly separated interventions into 7 categories: clinician education, clinician reminders, clinician financial incentives, clinician benchmark and audit reporting, nurse/pharmacist/multidisciplinary team-led interventions, patient engagement, and multifaceted interventions to explore the reported success of each intervention type.

Clinician Education

Programs focusing on clinician education reported mixed success: in one study, training sessions for general primary care practitioners addressing optimal GDMT therapies, led by HF specialists, and a review of possible implementation strategies, led by quality improvement experts, resulted in significantly higher increases in ACEi use significantly (18% difference between intervention and control groups, $p < 0.0001$), but had no significant impact on beta blocker use³⁰. Another study of 10 peer review groups found that a small group sessions reviewing HF guidelines did not significantly change rates of ACEi prescription or dose in the 6 months following the sessions³¹. Many other studies successfully use clinician education as a part of a multi-pronged strategy that included audit and feedback and decision support tools or algorithms for GDMT titration, but have not evaluated education efforts in isolation^{32, 33}.

Therefore, though clinician education is important, it may be insufficient to improve GDMT implementation in isolation.

Clinician Reminders

Studies evaluating the utility of clinician reminders to improve GDMT implementation or escalation have had mixed results.³⁴⁻³⁸ Though there are multiple reasons for the mixed success of this intervention, factors associated with successful increases in GDMT implementation following clinician reminders include offering reminders at times during patient care when prescription modification would naturally occur, and allowing clinicians to participate in the process of designing and then optimizing alerts and reminders to be maximally effective during clinical care.

One RCT of 169 HFrEF patients examined the efficacy of 1) clinician and patient reminders to start and increase beta-blockers vs. 2) a nursing-led initiative to start and up-titrate β -blockers vs. 3) a control arm and found that at 12 months, 67% of patients in the nurse facilitator group were initiated or up-titrated β -blockers compared with only 16% of those in the “reminder” group and 27% of those in the control arm³⁹. Strikingly, patients whose clinicians received reminders in the patients electronic health record to increase their beta blocker therapy were actually less likely to receive escalation of this medication than providers who received no reminder at all.

More recent research evaluating clinician reminders to improve GDMT initiation has been more promising. The largest and most recent study in this space, Building Electronic Tools to Enhance and Reinforce Cardiovascular Recommendations for Heart Failure (Better Care-HF) was a 3-arm cluster randomized trial of 180 cardiologists, who were randomized to either 1) continue usual care 2) receive a message each month in their electronic health record system listing patients eligible for MRA, and 3) receive an alert during a patient visit alerting that they were eligible for but not receiving an MRA. Both monthly messages and alerts during patient

visits included direct links to order an MRA, and recent information on lab values and vital signs that might influence clinician decision-making. At the end of the trial, new MRA prescribing occurred in 29.6% of patients whose clinicians received alerts, 15.6% of patients whose clinicians received a monthly message, and 11.7% of patients whose clinicians received neither (RR 2.53 for alerts, $p < 0.0001$ and RR 1.67, $p = 0.002$).⁴⁰ These findings emphasize the importance of providing such reminders at maximally impactful times (i.e., when clinicians are already considering patient medications). Similarly, the Pragmatic Trial Of Messaging to Providers about Treatment of Heart Failure (PROMPT-HF) studied GDMT prescription rates for 1310 patients whose clinicians were randomized to either receive alerts in the electronic medical record or to proceed with usual care, did find that patients whose clinicians received alerts were more than 40% more likely to receive GDMT ($p = 0.03$). Notably, this alert feature was designed with input from clinicians across multiple focus groups and modified iteratively with feedback on design, user friendliness, and hindrance to clinical care. As a result, this alert included relevant information including recent potassium and creatinine values, blood pressure, heart rate, current GDMT and relevant allergies, in addition to a link to order new therapies.⁴¹ Clinician input into the development of reminders and alerts to initiate or escalate GDMT may therefore be an important component of ensuring usability and increased uptake.

Clinician Financial Incentives

Clinician financial incentives similarly do not appear to improve GDMT implementation rates^{42,}⁴³, unless incorporated as part of a multifaceted strategy. Riggio et al found a 15.7% increase in ACEi use when they combined financial incentives as part of a multipronged approach that also included a discharge order set, clinician audit feedback, and educational lectures, but it is not clear that this was driven by financial incentives⁴⁴. Another cohort study of 4304 inpatients found that financial incentives for physicians, in the form of Medicare and Medicaid's pay-for-

performance demonstration project, did not lead to significant improvement in GDMT use⁴³. Another study offered a hospital-wide bonus system if the institution was within the top 10% nationally for heart failure measures, including GDMT use, also did not find significant changes in GDMT use⁴².

Clinician Benchmark Reporting and Audits

A summary of systematic reviews for implementation of cardiovascular guidelines funded by the National Heart Lung and Blood Institute found that audit and feedback on guideline adherence was a promising strategy to improve implementation of clinical practice guidelines, including blood pressure, obesity, and cholesterol management¹⁸. However, in individual studies, physician feedback appears to have mixed efficacy in improving GDMT use in HFrEF. One study in which a clinical pharmacist provided monthly reports to physicians identifying instances of “unreasonable omission” in their discharge prescription patterns for 716 HFrEF hospitalizations found that such “omissions” of medications fell steadily over the 12-month study from 24.5%, 13.1% and 9.1% for ACEi/ARB, β -blockers and MRA, respectively, to zero instances at the end of the study ($p<0.01$)⁴⁵. Similarly, a pre-post analysis in which 21 clinicians were trained on GDMT and their prescription rates were reported back to them at two hospitals found significant improvements in ACEi (3% increase, from 77% to 80%, $p=0.008$) and β -blocker (10% increase, from 46% to 56%, $p<0.0001$) use⁴⁶. Another study, which gave clinicians a “report card” on their adherence to guidelines for their heart failure patients found that there was no significant difference in beta-blocker or MRA use after the intervention, though patients were more likely to have a documented contraindication to an ACE inhibitor ($p=0.02$)⁴⁷. A study using audit and feedback, education, and chart reminders found no significant changes in ACEi use, but did find increased rates of beta-blocker usage (48.3% to 67.9%, $p<0.001$)⁴⁸. Thus, audit and feedback of GDMT prescription rates to clinicians appear to have a mixed

impact on GDMT initiation and up-titration, though it is possible that certain forms of feedback may be more or less effective. Ultimately, coupling individual clinician metrics on GDMT initiation rates alongside strategies to address barriers to prescription may represent an effective strategy.

Nurses, Pharmacists, and Multidisciplinary Teams

The presence of specialized teams of pharmacists and navigators on inpatient HF teams has been associated with numerically higher rates of GDMT implementation.⁴⁹ In one study of 94 inpatients randomized to teams rounding with or without a HF nurse and clinical pharmacist, RAAS inhibitor use increased from 68.4% to 85.2% ($p=0.17$), and β -blockers use from 75 to 90% ($p=0.12$). Though these results were complicated by small sample size, the difference was not statistically significant⁵⁰. Another study of 400 patients admitted at a single site reported significant improvements in GDMT when pharmacists were available in the inpatient setting. In this study, presence of an inpatient pharmacist was associated with up to 105% increase in MRA use (from 11.1 to 22.7%) for patients pre-admission compared with discharge when a pharmacist was present inpatient ($p<0.001$ pre-post), as compared to a 38% increase in MRA use (from 12.2 to 16.8%) for teams without a rounding pharmacist ($p=0.027$ pre-post)⁵¹.

Two recent studies have drawn attention to all-cause hospitalizations (i.e., including non-HF hospitalizations) as key opportunities for multidisciplinary teams to assist with optimizing GDMT for patients with HFrEF admitted to non-cardiology services. Following an observational period documenting usual care, the single-center IMPLEMENT-HF pilot study utilized a virtual multidisciplinary “GDMT team” of pharmacists and physicians who provided optimization suggestions to treatment teams for patients with HFrEF who were hospitalized for non-cardiac reasons, using a pre-specified algorithm for GDMT escalation. The primary outcome in this non-

randomized pilot study was a GDMT optimization score (+1 point for new medications or up-titrations, and -1 for discontinuations or down-titrations). Investigators found that 89 hospitalized patients whose team received recommendations from the GDMT treatment team had higher associated increases in GDMT prescription patterns without any serious adverse events (β -blockers 72% to 88%, $p=0.01$, ARNI 6% to 17%, $p=0.03$, MRA 16% to 29%, $p=0.05$, and triple therapy 9% to 26%, $p<0.01$, with overall increase in GDMT score of 0.58 [CI 0.09 to 1.07, $p=0.02$]), compared with 29 patients who received usual care during the observational period. There was no significant change in GDMT prescriptions among usual care patients⁵². A more recent pilot trial confirmed these observational findings among contemporary patients with HFrEF eligible to receive multiple GDMT, including novel SGLT2i. Among 20 medical teams randomized to a clinician-level multidisciplinary intervention or usual care, 52 patients who received the intervention had higher use of ACEI/ARB/ARNI (71% vs. 49%; $p=0.04$), and nominally higher for MRA (41% vs. 21%; $p=0.05$) and SGLT2i (26% vs. 14%; $p=0.19$) by discharge, compared with 39 patients who received usual care. A modified optimal medical therapy score which accounted for use and target dosing of GDMT was higher following intervention (+0.44) compared with usual care (-0.31), with absolute difference +0.75 (adjusted estimate 0.86 ± 0.42 ; $p=0.04$)⁵³.

In the outpatient setting, the use of clinics dedicated to GDMT initiation and up-titration, typically staffed by nurses and/or pharmacists, has been associated with markedly higher appropriate use of GDMT^{39, 54–58}. The Safety, Tolerability and Efficacy of Rapid Optimization, Helped by NT-proBNP Testing, of Heart Failure Therapies (STRONG-HF) was a recent RCT of 1078 patients that found that close outpatient follow-up following a HF hospitalization, including 4 visits over 2 months to follow a protocol-based escalation of GDMT, led to markedly higher rates of each maximal therapy for GDMT class (55% vs 2% for renin-angiotensin blockers, 29% vs 4% for beta blockers, and 84 vs 46% for MRAs)⁵⁹. These titration clinics may be valuable even for

patients already established in cardiology clinics: In one prospective pilot RCT, 25 patients already followed in a HF clinic who were randomized to an additional nursing-led GDMT clinic vs standard of care reached their maximally tolerated β -blockers dose in 90 vs 166 days ($p=0.0005$), and a higher proportion of patients were able to achieve maximal dose β -blockers (82% vs 45%, $p=0.04$)⁵⁴. A smaller VA-based pharmacist-led GDMT titration program successfully implemented an algorithm-based protocol to increase RAAS inhibitor and BB use over 14 months (7% and 3.5% increase in those achieving >50% of target ACEi and BB dose, $p<0.001$ and 0.2, respectively), in which >85% (N=88 of 103) of encounters were telehealth visits⁵⁸. There have been some other, less encouraging, results and at least one study reported that of 1533 patients at 14 Danish nursing-led HF clinics, target dose of β -blockers had only been reached by 21%: patients not reaching target dose were more likely to be female, elderly, and to have NYHA III-IV HF⁶⁰. Other programs have used telehealth visits, with phone calls and remote blood work every 2 weeks, to successfully escalate GDMT⁶¹.

The use of GDMT titration algorithms has been used successfully in many settings, and is often driven by nursing staff or pharmacists with physician oversight, either in person or remotely. A recent case-control study used a sequential GDMT titration algorithm based on laboratory, BP and symptoms. The study was deployed by “navigators” (typically individuals with bachelor’s or master’s degrees, without prior clinical training) under the supervision of pharmacy and nursing staff. In this case-control study of 1028 patients, those who participated had increased use of RAAS antagonists (70.1% to 86.3%, $p<0.001$) and β -blockers (77.2% to 91.9%, $p<0.001$) but not MRAs. Doses were also higher in the group in the intervention arm. In the standard care arm there were no changes in proportion of patients on GDMT, nor was there significant up-titration of therapy⁶². Another study found that a cardiologist-designed algorithm for ACEi initiation for inpatients with HFrEF increased ACEi use by 27% ($p=0.003$)⁶³. In each of these

instances, initiation of the algorithm was preceded by an investigation to understand barriers to GDMT implementation or escalation, with algorithms designed to overcome these barriers.

Though many algorithms are followed by dedicated GDMT teams, their use by primary care clinicians also appears tentatively promising^{64–67}. These have included documented plans for future escalation of GDMT with explicit titration goals that were visible to all members of the care team. Though one small inpatient study found no significant change with this intervention⁶⁴, another larger study found that this strategy improved β -blocker use by 14.3% ($p=0.006$) albeit without a significant change in RAAS use⁶⁵. Overall, leveraging GDMT titration algorithms, especially when they are applied by dedicated nursing clinicians or pharmacists, appears to be one of the most consistently successful strategies to improve GDMT prescription and up-titration rates. Many of these algorithms can be coupled with remote blood pressure and laboratory value monitoring, making it possible to escalate GDMT without requiring an in-person visit.

Multifaceted Interventions

Among the most successful interventions are those that, in addition to engaging stakeholders in iterative planning, pursue multifaceted approaches to improve GDMT implementation. In theory, these multifaceted approaches increase awareness of the importance of GDMT, offer opportunities for all stakeholders and leadership to demonstrate their commitment, and provide complimentary efforts towards improved GDMT use^{32, 44}. Even if individual changes make only small impacts, multiple impacts together are able to have not only been additive, but potentially have multiplicative results. For instance, the Registry to Improve the Use of Evidence-Based Heart Failure Therapies in the Outpatient Setting (IMPROVE HF) utilized a multi-pronged strategy that incorporated chart audits, a clinician support tool, recommended improvement

strategies for pharmacotherapy and educational opportunities for providers in a pre-post study of 34,810 patients at 167 outpatient cardiology practices. These interventions resulted in increased MRA and β -blocker use at 24 months (MRA increased 25.1% from 34.5% to 60.3%, $p < 0.001$, β -blockers use increased 6.2%, from 86% to 92.2%, $p < 0.001$), though without significant changes in ACEi use³³.

However, a sub-study within the Get With The Guidelines HF (GWTG-HF) registry, which compared site-level personalized audit and feedback with on-demand reports and tools, did not find a significant difference in use of β -blockers, ACEi, and MRA. However, the offered comparator arm was very similar to the intervention⁶⁸. These results were complicated by the fact that all hospitals enrolled in the study, in both arms, were also voluntary participants in the American Heart Association quality reporting program, and therefore already more likely to be early adopter of innovations to improve quality outcomes. These results may therefore not be generalizable across all US hospitals.

Most recently, the results of the Care Optimization Through Patient and Hospital Engagement Clinical Trial for Heart Failure (CONNECT-HF) trial were reported as neutral for an innovative QI intervention⁶⁹. CONNECT-HF was a large clinical trial of 5647 patients at 161 hospitals across the country. Patients were randomized to either usual care or to audit and feedback for HF quality metrics (including use of GDMT) to identify gaps, followed by a site-based analysis of gaps in care to create a personalized intervention plan for each site. CONNECT-HF announced no change in rates of all-cause death or hospitalization for heart failure, and additionally found no significant difference in percent of patients achieving $\geq 50\%$ of target dose of β -blockers or RAAS inhibitor. However, patients who used optional smartphone digital applications did show modest but statistically significant improvements in HF quality measures, including GDMT use.⁷⁰

CONNECT-HF faced numerous challenges, including the fact that it was conducted during COVID-19, which limited both enrollment and trial resources. It also enrolled fewer patients than initially planned and therefore experienced mid-enrollment changes to study design, including reduction in size, early trial cessation, and reduced use of smartphone patient check-ins (which became optional and non-randomized). Patients were screened and enrolled prior to hospital discharge, with limited feedback and interactions between hospital-based providers or longitudinal outpatient care providers during 1-year follow-up.

Patient Engagement

Engagement of patients, in which they are encouraged to ask providers about opportunities to improve their HF care, is another effective strategy to improve GDMT prescription rates. The benefits of engagement patients were demonstrated in the recently published Electronically Delivered, Patient-Activation Tool for Intensification of Medications for Chronic Heart Failure with reduced Ejection Fraction (EPIC-HF) trial. In EPIC-HF, patients who were randomized to receive a 3-minute video and one-page checklist reviewing ways to escalate their GDMT three times over the week preceding an appointment were significantly more likely to experience initiation or intensify their GDMT (49% vs 30%, $p=0.001$), largely driven by up-titration in beta-blocker use (22.1% vs 11% with dose increase, $p=0.02$). These findings also suggest that empowering patients to advocate for GDMT initiation and/or up-titration may be a viable part of a multipronged strategy to improve GDMT use ⁷¹.

The CONNECT-HF trial also offered insight into how digital technologies may be leveraged to engage patients in their health following a HF hospitalization. The CONNECT-HF Digital Sub-study enrolled 2,431 patients from sites randomized to offering the digital application, which was designed to engage patients and promote health education, self-monitoring, self-management

of evidence-based HF_rEF therapies, and patient adherence to weight reporting and medication use. Approximately 20% (N=420) offered digital applications actually used the application within 1 week of hospital discharge. When matched to non-digital users from the usual care group, digital users had higher composite HF quality of care scores (48.0% vs 43.6%; + 4.76% [3.27–6.24]; P = 0.001) and 24% lower risk of HF rehospitalization or all-cause mortality at one year (hazard ratio 0.76 [0.59 to 0.97; p=0.027])⁷⁰. While these results show promise in improving guideline-recommended therapies and clinical outcomes by engaging patients through digital applications, their overall modest use among patients who demonstrated the ability to use mobile applications in this sub-study highlighted particular challenges with implementation and longitudinal use of digital applications following hospitalizations for HF among patients with HF_rEF.

Path Forward

There have been a number of reported interventions to increase GDMT use. However, much of the published data to date are limited by the single-center nature of the trial, non-randomized study design, and small sample size. Though their findings are important to real-world experiences, these prior studies may also have limited applicability to other contexts/environments. Most strategies discussed have had mixed success within different environments and settings, making generalizability challenging. Furthermore, heterogeneous interventions make comparisons across studies difficult.

In aggregate, the more successful strategies appear to include multidisciplinary teams with nurses, nurse practitioners, and/or pharmacists who follow algorithms to rapidly initiate and escalate GDMT (**Figure 1**).^{62, 64–67, 72, 73} Audit of local performance with feedback and strategies to improve GDMT also appears promising, especially when incorporated with other interventions

31–33, 44–48, 68, 69, 74, as does engagement of patients in their own care⁷¹. Though this will need to be explored in future research, we envision a future successful research implementation effort would be multifaceted and include 1) a multidisciplinary team that included nurses, pharmacists, and care managers to help titrate GDMT and to navigate costly medications for patients 2) a GDMT algorithm designed by HF specialists to support the titration of GDMT by other clinicians and 3) efforts to engage patients in their own medical care. These interventions could be conducted in person or remotely via telemedicine visits depending on local needs. Ideally, any study in this space would be large and conducted at multiple centers, in order to best understand the true potential of these interventions to improve GDMT prescription rates. Because individual sites will face unique barriers to GDMT implementation, these trials should also include opportunities for personalization and iterative site-based improvement, facilitating head to head testing of different methods to understand which interventions work best in which contexts (**Figure 2**). Though most studies took place in the United States, some trials were performed in Europe, Australia, New Zealand, Taiwan, and India. It is likely that some barriers to GDMT escalation, including lack of time or lack of familiarity with newer medications are observed across many countries. Others, such as insurance approval, may be specific to certain countries. This makes it likely that not all interventions will be equally effective in all countries, which future work should acknowledge. Additional disparities in HF care for patients from racial and ethnic minorities further warrant dedicated studies to understand how to improve implementation among these vulnerable populations.⁷⁵

Conclusion

Implementation research can bridge the gap between clinical trial (with tremendous and highly focused infrastructure to create the most similar experience for each enrolled participant) to real-world situations. To date, literature in this space in the HF community has been largely

limited to cohort or pre/post study designs, with mixed results that have been complicated by small trial sizes. As a result, there remains a critical need to understand the best ways to increase initiation and escalation of GDMT in the HF community. However, certain interventions appear to have promise. Incorporation of non-physician care providers such as pharmacists and nurses, use of algorithms to guide initiation and titration, and audit and feedback of current metrics all appear to be promising, especially when used as part of a multi-pronged approach. Automated alerts for GDMT initiation may be helpful if they are designed with feedback from major stakeholders to ensure tolerability and functionality. Future efforts to evaluate these interventions should consider including all or many of these elements, alongside opportunities for sites to personalize interventions to be consistent with their own culture and infrastructure. Such trials may benefit from a pragmatic design, with embedded opportunities for local stakeholders to iteratively adapt and improve their interventions in response to local outcomes.

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Journal Pre-proof

	Author	Year	Country	Setting	Study Design	Patient Size	Intervention	Impact on GDMT
Provider: Audit/Feedback	Shukkoor et al ⁴⁵	2020	India	Inpatient, single site	Pre-Post	716	Monthly reports to physicians of discharge prescription patterns, including rates of "unreasonable omission of GDMT"	Rate of "unreasonable omission" of medications decreased from 24.5%/13.1%/9.1% for RAS, BB and MRA to zero instances for any drug over 12 months (p=0.00)
	Cancian et al ⁴⁶	2013	Italy	Outpatient primary care, 21 sites	Pre-Post	1905	Review of system-wide utilization of GDMT with report of data to physicians; Educational materials offered	ACEi use up 3%, p=0.008, BB up 10%, p<0.0001
	Matthews et al ⁴⁷	2007	United States	Outpatient, single site	Pre-Post	265	Outpatient providers were given "score cards" identifying gaps in HF GDMT for their patients at time of hospital discharge; Offered educational material on titration of GDMT	No significant differences in prescriptions of ACEi, BB, or MRA
	Goff ⁴⁸	2005	United States	Outpatient primary care	Pre-Post	3141	Review of stem-wide utilization of GDMT with report of data to physicians	BB use up 19.6%, p<0.001, no significant change in ACE
Provider: Education	Asch et al ³⁰	2005	United States	Inpatient, multisite	Clustered with control organizations	489	Training sessions led by QI and HF specialists.	ACEi use up 18% p<0.0001, with no change in BB use

	Kasje et al ³¹	2006	The Netherlands	Outpatient primary care, single site	Cluster RCT	508	Physicians received education on current heart failure guidelines in small groups	No significant change
Nursing and Pharmacist Support	Ansari et al (see also MDT) ³⁹	2003	United States	Outpatient primary care, single site	RCT	119	3 arms: provider education on BB use, provider reminder when patient was eligible BB, and dedicated nurse to initiate and escalate BB dose	No significant change in BB use with provider reminders; Nursing intervention associated with 40% increase in BB initiation or up-titration, p<0.001
	Di Palo et al ⁵⁰	2017	United States	Inpatient, single site	Case Control	120	NP and pharmacist provided recommendations for target GDMT doses and supporting literature for providers caring for patients with HF	No significant change
	Blizzard et al ⁵¹	2019	United States	Inpatient, single site	Time-Based Cohort	400	Pharmacists added to rounding inpatient HF consult team	MRA up 105%, p<0.001
	Bhatt et al ⁵²	2021	United States	Outpatient, single site	Cohort	118	IMPLEMENT HF pilot study. Utilized a virtual multidisciplinary "GDMT team" of pharmacists and physicians provided optimization suggestions to treatment teams for 118 patients based on an algorithm.	BB up 16%, p=0.01, ARNI up 11%, p=0.03, MRA up 13%, p=0.05, and triple therapy up 17%, p<0.01. No significant change with usual use.

	Driscoll et al ⁵⁴	2014	United States	Outpatient, single site	Cohort	28	Use of a nursing-led titration clinic of patients already followed in an outpatient HF clinic	Faster up-titration of BB use (90 vs 166 days, $p=0.0005$), and a higher percentage of patients on maximal dose BB (82% vs 45%, $p=0.04$)
	Jain et al ⁵⁵	2005	United Kingdom	Outpatient, single site	Pre-Post	234	Nurse and pharmacist led, protocol driven clinics for escalation of GDMT	12% increase in patients on medium or high-dose ACEi or ARB ($p<0.01$), 41% increase in BB ($p<0.001$), 28% increase in MRA ($p<0.001$)
	Mao et al ⁵⁶	2015	Taiwan	Inpatient, single site	RCT	349	Outpatient multidisciplinary team	Significantly higher rates of ACEi (92 vs 82.9%), and BB use (77% vs 54.9%) in patients with the multidisciplinary team
	Mclachlan et al ⁶¹	2021	New Zealand	Outpatient, single site	Pre-Post	52	Telehealth NP pilot program in NZ designed to escalate GDMT during the Covid-19 Pandemic used telephone visits. Patients had blood collected and phone visits every 2 weeks, and monitored their own weight, HR and BP at home.	At study end 75% were optimally tolerated (on >50% target dose RAS, BB and MRA) within 2 months, with 88%, 74% and 62% on >50% of target dose for RAS, BB, and MRA, respectively.

	Desai et al ⁶²	2020	United States	Outpatient, single site	Cohort	1028	Remotely administered GDMT titration algorithm	RAS antagonists use up 16.2%, p<0.001, and BB use up 14.7%, <0.001; no change in MRAs
	McCarren ⁷⁶	2013	United States	Outpatient, multisite	Cluster RCT	220	Pharmacists given list of patients on suboptimal therapy (all given guidelines and asked to improve GDMT use)	1.9x increase in rates of GDMT prescription (pooled), 95% CI 1.1-3.2
	Mejhert ⁷⁷	2004	Sweden	Outpatient, single site	RCT	208	Nurse-led titration of GDMT	ACEi use up 14%, p<0.05
	Kasper ⁷⁸	2002	United States	Outpatient, single site	RCT	200	Nursing-led implementation of GDMT algorithm to make recommendations to primary team	No significant difference in prescription rates of ACEi, or BB vs control
	Guder ⁷⁹	2015	Germany	Outpatient, # sites not specified	RCT	390	Nursing-led implementation of GDMT algorithm	ACEi use up 4.9% (p<0.05), BB use up 7.6% (p<0.001), no significant difference in ACEi or MRA
	Warden ⁸⁰	2014	United States	Outpatient, single site	Pre-Post	150	Pharmacists reviewed patient charts and suggested opportunities to increase GDMT	ACEi use up 13%, p=0.02
	Martinez ⁸¹	2013	United States	Outpatient, single site	Pre-Post	144	Pharmacist-led GDMT clinic	ACEi use 22% higher, p=0.007, BB use up 24.3%, p=0.012

	Crissinger ⁸²	2015	United States	Outpatient, single site	Cohort	899	NP and pharmacist-led GDMT titration	Use of optimal disease of ACEi/ARB and BB together 44% higher (p=0.02) with use of multidisciplinary HF rounding team
	Mebazaa et al ⁵⁹	2022	14 Countries	Outpatient, multicenter	Randomized	1078	Frequent up-titration of GDMT following hospitalization for HF using a pre-specified algorithm	Patients randomized to intense titration were more likely to receive maximal doses of all forms of GDMT (55% vs 2% for renin-angiotensin blockers, 29% vs 4% for beta blockers, and 84 vs 46% for MRAs)
Care model: Algorithms/Clinical Pathways	Braun et al ³⁵	2011	Germany	Primary Care, single site	Pre-Post	190	Pop-up window with summarized HF guidelines	No change in ACEi, BB use up 12.3% (p=0.03), MRA up 9.2% (p=0.04)
	Thilly et al ⁶³	2003	France	Inpatient, 20 sites	Cluster RCT	370	Cardiologists created their own algorithm on initiating inpatient ACEi use in HFrEF. (Prior to intervention surveys were completed to understand problems in HF care)	ACEi use up 27% (p=0.003)

	Panella ⁶⁴	2005	Italy	Inpatient, single site	RCT	68	Displayed planned pathway for each patient and patient goals	No significant change
	Garin ⁶⁵	2012	Switzerland	Inpatient, single site	Pre-Post	363	Displayed clinical pathway with goals for advancement of GDMT	BB use up 14.3%, p=0.006, no significant difference in ACEi
	Hickey ⁶⁶	2016	Australia	Outpatient, 3 sites	Cohort	335	Communication system to connect inpatient and outpatient providers to form a plan for GDMT titration	No significant difference in ACEi; BB use up 13%, p=0.045
	Allen et al ⁷¹	2021	United States	Outpatient, single site	RCT	306	EPIC-HF study: HFREF patients were randomized to receive a 3 minute video and a one-page checklist to encourage them to "make one positive change" with their cardiology provider	BB increased 11.1% (p=0.02), 64% more likely to receive initiation or intensification of GDMT p=0.001
	Whellan ⁷²	2001	United States	United States, single site	Pre-Post	117	Schedule of follow-up visits and phone calls planned prior to patient discharge	BB use up 24%, p=0.01, no significant change in ACEi
	Ranjan ⁷³	2003	United States	Inpatient, single site	Cohort	371	Clinical pathway	ACEi use up 33%, p<0.001
Patient: Education/Reminders	Butler et al ³⁶	2006	United States	Inpatient, single site	Pre-Post	1275	Reminder for quality measures in EMR, with direct option to prescribe	No significant change
Provider Reminders and Algorithms	Reingold and Kulstad et al ³⁴	2007	United States	Inpatient, single site	Pre-Post	171	Streamlined HF orderset encouraged GDMT initiation	ACEi increased 58%, p=0.008

	Oujiri et al ³⁸	2011	United States	Inpatient, single site	Pre-Post	153	Trial of mandatory admission and discharge facesheets	ACEi increased 18%, p=0.01
	Baker et al ³⁷	2011	United States	Outpatient primary care, single sites	Pre-Post	276	Paper and electronic reminders of individual patient GDMT opportunities	No significant change in ACEi use; BB use up 2.9%, p=0.004
	Ghazi et al ⁴¹	2022	United States	Outpatient internal medicine and cardiology clinicians, single site	RCT	1310	EMR alert with recent vitals and lab values, current GDMT therapies, and allergies	Increase in GDMT by 41%, p=0.03
	Lindenauer et al ⁴²	2007	United States	Inpatient, multisite	Pre-Post	Provider-based	Hospital-wide bonuses for systems in the top 10% for HF measures, including GDMT	No significant difference in ACEi use between groups with and without bonus structure
	Esse et al ⁴³	2013	United States	Inpatient, multisite	Cohort	4304	Financial incentives for physicians with increased use of GDMT	No significant change
	Mukhopadhyay ⁴⁰	2023	United States	Outpatient cardiology clinics, single site	Cluster RCT	2211	3 arms: EMR alerts for patients eligible for MRA during routine clinical care, monthly messages reviewing all patients eligible MRA initiation, and routine care	Increased rates of MRA prescribing for both alerts during clinical care (RR 2.53 vs usual care, p<0.0001) and with monthly messaging (RR 1.67, p=0.002)
Provider: Financial Incentives	Fonarow ³³	2010	United States	Outpatient, multisite	Pre-Post	34810	Multi-pronged strategy including chart audits with feedback, clinician support tools, structured improvement strategies, and education opportunities	BB use up 6.2%, p<0.001, MRA use up 25.1% p<0.001. No change in ACEi

	Riggio ⁴⁴	2009	United States	Inpatient, single-site	Pre-Post	4728	Discharge order set to increase GDMT, provider audit feedback, financial bonuses, educational lectures	ACEi use up 15.7% p<0.00
Multipronged Interventions	Scott ³²	2004	Australia	Inpatient and Outpatient, 3 sites	Pre-Post	914	Inpatient chart reminders, educational meetings, discharge order set, communication between inpatient and outpatient teams	ACEi use up 15%, p=0.04, BB use up 21%, p=0.01
	DeVore ⁶⁸	2015	United States	Inpatient and Outpatient multisite	Cluster randomized	71829	Personalized audit and feedback, with suggestions and guidance for improvement, vs usual GWTG normal on-demand reports and tools	No significant change
	DeVore ⁶⁹	2021	United States	Inpatient and Outpatient, multisite	RCT	5647	Education, audit, and feedback with evaluation of gaps sites and individualized intervention plans	No significant difference in percent of patients at ≥ 50% of target BB or RASS dose
	Qian ⁷⁴	2011	United States	Inpatient, single site	Pre-Post	5000	EMR flagged eligible patients not on ACEi/ARB: pharmacists confirmed that patient eligibility and contacted primary team every 24 hours	ACEi use up 9.2%, p<0.0002

Table: Implementation Trials in GDMT. Angiotensin converting enzyme inhibitor (ACEi); BB (beta-blockers); Guideline-directed Medical therapy (GDMT); Get with the guidelines (GWTG); Heart failure (HF); Randomized Controlled trial (RCT)

Guideline-Directed Medical Therapy in Heart Failure with Reduced Ejection Fraction

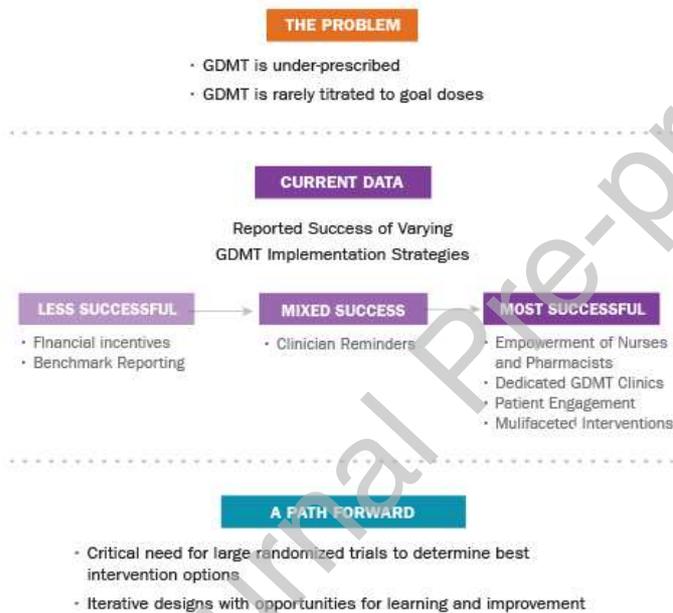
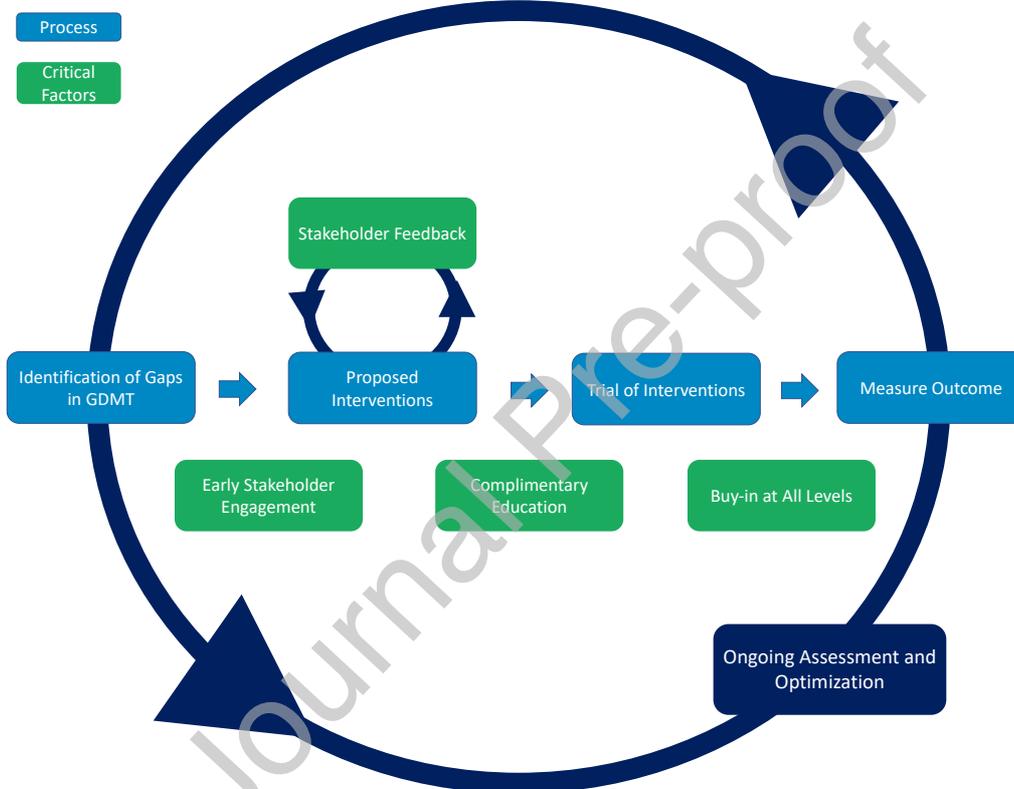


Figure 1: Improving Initiation of Guideline Directed Medical Therapy: The Current Status and Available Data. GDMT: Guideline Directed Medical Therapy (Visual Take-Home Graphic)

Iterative Improvement in GDMT: A Site-Based Model**Figure 2: A Paradigm for Iterative Site-Based Improvement.** Guideline-directed Medical therapy (GDMT)



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