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Heart Failure (W Tang, Section Editor)

Novel Strategies to Improve Prescription of Guideline-Directed Medical Therapy in Heart Failure

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Abstract

Purpose of review To examine the emerging data for novel strategies being studied to improve use and dose titration of guideline-directed medical therapy (GDMT) for patients with heart failure (HF).
Recent findings There is mounting evidence to employ novel multi-pronged strategies to address HF implementation gaps.
Summary Despite high-level randomized evidence and clear national society recommendations, a large gap persists in use and dose titration of guideline-directed medical therapy (GDMT) in patients with heart failure (HF). Accelerating the safe implementation of GDMT has proven to reduce the morbidity and mortality associated with HF but remains an ongoing challenge for patients, clinicians, and health systems. In this review, we examine the emerging data for novel strategies to improve the use of GDMT including the use of

multidisciplinary team-based approaches, nontraditional patient encounters, patient messaging/engagement, remote patient monitoring, and electronic health record (EHR)-based clinical alerts. While societal guidelines and implementation studies have focused on heart failure with reduced ejection fraction (HFrEF), expanding indications and evidence for the use of sodium glucose cotransporter2 (SGLT2i) will necessitate implementation efforts across the LVEF spectrum.

Introduction

In recent years, newer heart failure (HF) medical therapies have proven efficacious when added to established therapies, significantly expanding the armamentarium to reduce the morbidity and mortality associated with HF. This is particularly true for patients with heart failure with reduced ejection fraction (HFrEF). High-level, randomized evidence has been incorporated into both European and American society recommendations for guideline-directed medical therapy (GDMT) [1, 2]. Unfortunately, adoption and dose titration of these therapies remain poor in national registries representative of the contemporary implementation of GDMT [3]. The etiology of these pervasive gaps in the use and optimization of pharmacotherapy for HFrEF patients is multifactorial. The sequential implementation of evidence-based therapies is woefully inadequate and opportunities for improvement exist at the level of the patient, the provider, and the healthcare system. Clinician competency, therapeutic inertia, low healthcare literacy, concerns for adverse events, inadequate access to multidisciplinary resources, uneven insurance coverage, and unpredictable out-pocket costs contribute to the slow uptake of GDMT [4]. Novel approaches are needed to improve the appropriate use of GDMT and enhance HF care in this high-risk patient population.

Comprehensive four-drug therapy with beta-blocker, angiotensin receptor-neprilysin inhibitor (ARNI), mineralocorticoid receptor antagonist (MRA), and sodium-glucose cotransporter-2 inhibitor (SGLT2i) provide the backbone of contemporary pharmacologic therapies recommended and have the highest societal guideline recommendations as of 2022 [1]. Optimal implementation of comprehensive four-drug therapy has been projected to significantly reduce the morbidity and mortality associated with HFrEF [5–8]. Yet, until the recently published safety, tolerability, and efficacy of up-titration of guideline-directed medical therapies for acute heart failure (STRONG-HF) trial, large-scale post-hospital discharge quality initiatives have not demonstrated a reproducible and durable increase in medication use/titration nor shown to improve clinical outcomes [9, 10, 11••, 12]. Despite multiple proposed strategies for the sequencing of HF medical therapy, challenges of transforming clinical practice persist [13–17]. Electronic health record (EHR)-embedded alerts, patient registries, and multidisciplinary team-based approaches are being incorporated at numerous centers to help define and ameliorate this gap [18•, 19, 20]. The advent of multiple remote patient monitoring devices, more robust integrated healthcare system data, and machine learning may be pathways to improving care. In this review, we summarize proven and evolving strategies to improve prescribing and dose titration of GDMT in modern heart failure care (Fig. 1).

Strategies

EHR-embedded optimization and large-scale quality initiatives

EHR-based data and tools are an increasingly recognized avenue to identify and address gaps in the use of GDMT [18•]. Several recent randomized trials have utilized EHR-embedded alerts or educational tools to improve

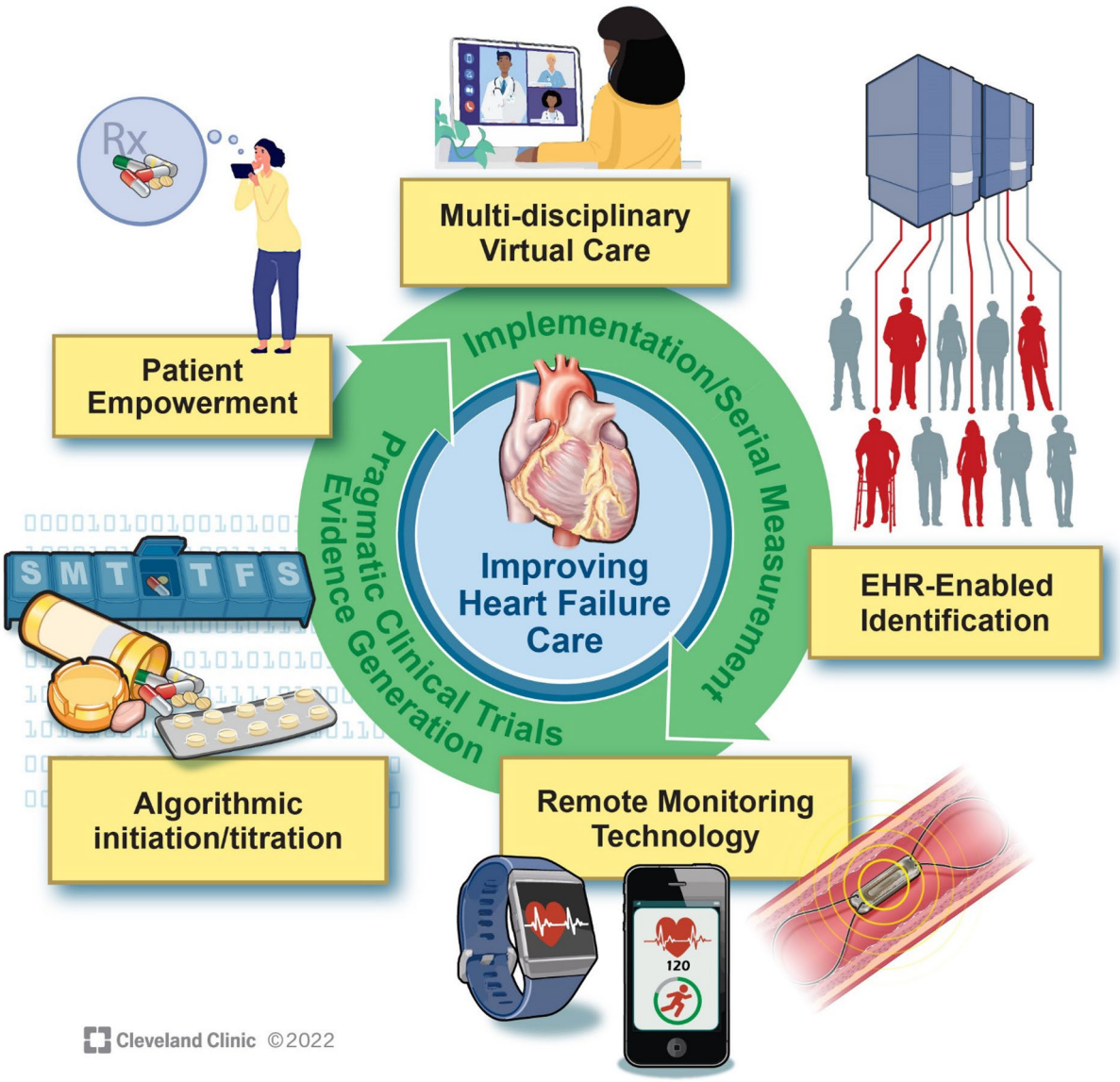

Fig. 1 Health system approaches to improving heart failure care.

medication prescription in HF (Table 1). Historically, clinical alerts have not consistently demonstrated a durable impact on cardiovascular care and can contribute to "alert fatigue" [10, 21]. However, multiple recent trials with tailored clinical alerts and patient-centered education initiatives have increased GDMT prescription. The Pragmatic trial Of Messaging to Providers about Treatment of Heart Failure (PROMPT-HF) study was an EHR-based, cluster-randomized trial which randomized 100 high-volume providers of HFrEF patients in the Yale-New Haven Health system to either usual care or receiving focused alerts within the electronic medical record. The investigators demonstrated an improvement in the primary outcome of an increase in the number

Table 1. Notable recent trials in heart failure quality improvement

	Trial	Format	*N*	Primary findings	Strengths	Limitations	Implications
Multidisciplinary	STRONG-HF [11••]	Multinational, randomized, parallel group implementation trial	1078	Rapid up-titration of GDMT after HF admission significant reduced all-cause death or HF readmission at 180 days	Specific targets and timeline of intervention; similar rates of serious adverse events with usual care	Unblinded; causes of readmission were not adjudicated; SGLT2i not included	4 clinic visits within 2 weeks post-discharge in the intensive treatment arm requires significant patient, provider, and system commitment. Follow-up performed by HF experts
	CONNECT-HF [10]	Cluster-randomized, multicenter, implementation, post-discharge QI	5647	No difference in composite of mortality or HF readmission; Hospitals randomized to receive extensive HF-related education	Large, multicenter	Did not provide recommendations or automate orders/referrals	No difference in outcomes detected with hospitals who were provided HF education and quality initiative information; Limits buy-in from health systems
	PACT-HF [26]	Stepped-wedge cluster randomized; single-center	2494	No difference in all-cause readmission, ED visit, or death at 3 months; Patient-centered transitional care model vs usual care	Significant resource commitment with transitional care; patients, providers, and policy-makers involved	Single healthcare system; did not assess adherence to discharge (DC) recommendations	No difference in primary outcome(s) with transitional care model which included nurse-led self-care education, DC summary, close follow-up, ± home-care visits

Table 1. (continued)

	Trial	Format	*N*	Primary findings	Strengths	Limitations	Implications
	Remote Optimization. Desai et al. [32]	Case–control study for algorithmic, multidisciplinary GDMT optimization	1028 (19% in optimization group)	Significant increase in dose or use of BB and RAAS antagonists (but not MRA) with navigator driven remote medication optimization vs usual care	Clinical navigator driven algorithmic intervention; remote-care; multidisciplinary approach	Non-randomized; short-term follow-up; single-center	Potentially scalable; would require dedicated navigator, pharmacist, and HF cardiologist efforts
EHR-based	PROMPT-HF [22•]	Single-center, randomized, pragmatic, EHR-based; outpatient	100 providers; 1310 patients	Increase in GDMT prescriptions (primarily with BB) at 30 days. Providers randomized to receive targeted prompts vs usual care	Provides framework for rapid, lower cost EHR-based, pragmatic randomized trials	Single-system; Detected changes quite modest (mostly beta-blocker)	Relatively low-cost and scalable; requires integrated EHR; Average of 14 prompts per provider to prescribe 1 additional class of GDMT
	REVEAL-HF [25]	Single-center, randomized, pragmatic, EHR-based	3124	No difference in composite of all-cause mortality at 1 yr and HFH within 30 days; Providers randomized to receive prognostic information vs usual care	Easy to integrate within existing EHR	Did not provide recommendations or automate orders/referrals	No benefit detected to providing 1 year mortality estimates

Table 1. (continued)

	Trial	Format	*N*	Primary findings	Strengths	Limitations	Implications
	IMPLEMENT-HF pilot study [44]	Prospective pilot study; EHR-based	118	Increase in prescriptions at time of discharge for BB, ARNI, and MRA; Primary team provided with algorithmic recommendations from pharmacist–physician GDMT Team	Increase in GDMT score in the intervention arm; proof-of-concept	Small, single-center pilot quality study	Requires dedicated HF Cardiologist and Pharmacist effort
	EPIC-HF [9]	Single-center; randomized; patient-centered	306	Increase in GDMT intensification at 30 days; 3-min video and 1 page checklist provided electronically to patients prior to clinic visit	Patient-engagement, readily scalable at centers with integrated EHR and patient messaging capability	Single system. Patients already scheduled with Cardiology were enrolled	Relatively low cost and scalable for patients with technology literacy
Virtual RCT	CHIEF-HF [62]	Completely remote, patient-centered	476	Canagliflozin use improved KCCQ symptom score at 12 weeks	Similar QOL improvement with both HFrEF and HFpEF; all-remote trial with no in-person interaction	Subjective symptom assessment and QOL measures	Virtual implementation of GDMT shown to be safe and effective, trial design efficient/cost-effective. Fitbit devices to monitor activity level

Table 1. (continued)

	Trial	Format	*N*	Primary findings	Strengths	Limitations	Implications
Remote monitoring	CHAMPION [42]	Single-blind, randomized trial with CardioMEMS device	550	Reduction in HF hospitalization at 6 months with the addition of ambulatory PA pressure monitoring	Success with remote monitoring device	Single-blinded; industry-funded	Scalability has some limitations given invasive procedure that requires dedicated resources to receive and act on hemodynamic data but likely underutilized for eligible patients

of GDMT classes prescribed at 30 days and GDMT dose with targeted, integrated prompts within the EHR [22•]. The modest improvement in GDMT classes prescribed required providers to receive an average of 14 different alerts to increase one additional GDMT class prescription [22•]. Of note, more patients were prescribed beta-blockers at baseline than any other class, yet beta-blockers were the only class of GDMT with a statistically significant improvement in prescription with provider prompts. Whether these modest medication changes in the short term will prove sustainable is uncertain. Additionally, cardiology providers were more likely to escalate GDMT than non-cardiology providers. Although somewhat exploratory secondary outcomes, the improvement in GDMT prescriptions did not result in significant differences in ED visits, hospitalization, or mortality [22•]. PROMPT-HF, as compared to other similar studies, provided targeted, actionable prompts to high-volume providers, rather than more passive and ubiquitous best-practice alerts (BPAs) examined in other trials. Furthermore, the pragmatic design structure allowed for cheap and rapid patient enrollment and participation. Although encouraging from a clinical design perspective, this randomized trial within one health care system utilizing one EHR is unlikely to be applicable and scalable to all healthcare centers. We believe the use of provider alerts may achieve more substantial gains if these prompts are combined with actionable and automated (opt-out) orders within the EHR to facilitate evidence-based care and minimize provider workflow interruption. Automated referrals to dedicated clinical teams focused on medication optimization may improve uptake; however, this would necessitate clinical resourcing beyond EHR builds. Similarly, a prognostic BPA that was linked to an advanced heart failure or palliative care consultation may be more powerful than simple prognostic information.

In addition to providing targeted alerts for providers, electronic information may also be used to educate and empower patients on the importance of medical therapy in HFrEF. The Electronically Delivered, Patient-Activation Tool for Intensification of Medications for Chronic Heart Failure with Reduced Ejection Fraction (EPIC-HF) trial leveraged a patient education video delivered electronically to patients who had scheduled cardiology visits. This patient-focused intervention demonstrated an improvement in medication prescription at 30 days after randomization [9]. Intensification of GDMT in EPIC-HF was primarily driven by increasing the dose of already provided medications, with the most prominent effect being with evidence-based beta-blockers. Relatively few patients were prescribed new medications in the intervention or usual care arms of the study [9].

Furthermore, patients who fail titration pathways or have de-escalation of GDMT may signal advanced heart failure and merit systematic referral to advanced heart failure physicians and/or palliative care providers [1]. EHR-based tools and algorithms that incorporate de-escalation/intolerance of medical therapy and other markers of HF risk have been studied. A recent retrospective analysis by McGilvray et al. demonstrated the use of a machine learning (ML) algorithm to identify patients at increased risk of clinical decompensation and need for advanced therapies [23]. Unfortunately, how to change clinical care based on the identification

of risk remains a challenge. The recently published Risk Evaluation And its Impact on ClinicAL Decision Making and Outcomes in Heart Failure (REVEAL-HF) trial provided an additional alert of validated risk assessment. Trial results found no difference in mortality at 1 year or HF hospitalizations at 30 days. Similarly, in this population, there was no significant difference between groups in discharge medication prescription, palliative care involvement, or ICD implantation [24, 25].

Heart failure quality initiatives, often enabled by EHR data, are ubiquitous at many healthcare centers, yet there has been limited data for improvement in meaningful clinical outcomes. A large, cluster-randomized clinical trial of post-discharge quality improvement intervention showed no significant difference in outcomes (death/rehospitalization) or heart failure quality of care score [10]. Similarly, the PACT-HF randomized trial provided self-care education, detailed patient instructions, and transitional post-discharge visits but revealed no significant differences in the composite of all-cause readmission, ED visit, or death at 3 months [26]. Encouragingly, in the recently published multinational, open-label, and parallel-group randomized trial examining safety, tolerability, and efficacy of up-titration of guideline-directed medical therapy for acute heart failure (STRONG-HF), patients were randomized to usual care or "intensive" medical therapy titration [11••, 12]. "Usual care" followed usual local practice, while high-intensity care involved the up-titration of treatments to 100% of recommended doses within 2 weeks of discharge for ACEi/ARB/ARNI, beta-blocker, and MRA across the LVEF spectrum. It is important to note that the intensive management arm protocolized four outpatient visits with a HF specialist in the 2 months post-discharge along with serial measurement of laboratory values including NT-proBNP. The trial was stopped early due to clear benefit in reduction of the primary endpoint of all-cause death or heart failure readmission within 180 days. Additionally, there was an improvement in patient-reported quality of life and documented NYHA class in the intensive arm compared to usual care. STRONG-HF provides a useful framework for how implantation studies should be performed. The investigators had specific targets to achieve within a clear timeline, which likely contributed to the marked improvements in medical therapy in the "intensive" arm. Furthermore, allowing for 180-day follow-up provided enough time after dose escalation (within 2 weeks post-discharge) to take effect and see meaningful improvement in clinical outcomes. Of note, given the timing of study design and execution, SGLT2i was not part of the intensive titration algorithm and recent evidence suggests the addition of this agent could add incremental benefit [27, 28].

The data supporting EHR-based alerting, patient messaging, and large-scale quality initiatives targeting HF care have been mixed. As evidence grows, the appropriate form of patient identification, teams for intervention, and agents to maximize clinical benefit may become clearer. Importantly, racial, socioeconomic, and sex-specific disparities persist in contemporary HF care [29–31]. EHR-based registries may help systems address systemic barriers to access to the device and medical therapy through a better understanding of practice variation across health systems.

Remote monitoring and virtual care

Remote patient monitoring combined with non-traditional patient encounters like virtual or phone-based visits has been an effective means of improving GDMT in selected populations [32]. The COVID-19 pandemic led to a marked decrease in clinic visits and necessitated the health system to rapidly move to telemedicine-based care. The pandemic also catalyzed new entrants and significant investment into the virtual cardiovascular care space. Access to telemedicine can occur through audio-only or synchronous two-way audio–video conferencing. The latter requires access to broadband internet, an internet-capable device, and sufficient technology literacy to execute the visit. Reducing the inconvenience and cost associated with in-person traditional visits may allow for improved patient satisfaction, improve rural access to care, and enable more patient touch points in the implementation of GDMT; however, awareness of limitations based on technological literacy and access to broadband have to be considered [33–37]. Whether these non-traditional visits and virtual care models continue to grow in the future will likely evolve based on legislative and reimbursement structures [34].

Additionally, virtual or remote care including remote monitoring and application-based tools has garnered significant interest as potential means to accelerate safe and effective medication optimization. With remote data acquisition and interpretation, clinicians can be notified of changes in patient status, especially as it relates to congestion, allowing for early intervention in the cascade of acute or worsening heart failure [38]. Wearable or implantable electronic devices and invasive pressure monitors may be able to reduce barriers to cardiovascular care by remotely assessing symptoms, activity level, and volume status to help reduce the risk of decompensation [19, 39]. Remote monitoring of PA pressure, LA pressure, chest impendence, IVC size, and others have been developed [40, 41]. In a sub-analysis of the CHAMPION (CardioMEMS Heart Sensor Allows Monitoring of Pressure to Improve Outcomes in Class III Heart Failure), the active monitoring group experienced a higher frequency of medication adjustments including significant increases in the doses of neurohormonal antagonists, targeted intensification of diuretics and vasodilators in patients with higher PA pressures, and preservation of renal function despite diuretic intensification [42]. Additionally, novel insights into the hemodynamic effects of heart failure medical therapy could be studied with the expansion of remotely transmitted hemodynamic data like CardioMEMS [43]. The breadth of emerging technology in remote HF care is reviewed extensively elsewhere [39]. It is worth noting that the incorporation of patient data into electronic health records presents logistical and data privacy challenges and the resourcing of who will gather, interpret, and act on clinical data will be an ongoing challenge as new technologies and platforms emerge.

Multidisciplinary teams: overcoming barriers and seizing opportunities

Dedicated longitudinal follow-up within an integrated health care system has proven efficacious in improving GDMT prescription. Recent

case–control studies have demonstrated improvement in care with multidisciplinary teams of heart failure cardiologists, pharmacists, and clinical navigators both in the ambulatory and hospitalized settings (Table 1) [32, 44]. Current American and European heart failure guidelines endorse the use of a multidisciplinary team, including physicians, nurses, pharmacists, dieticians, and social workers, to optimize the care of patients with heart failure [1, 45, 46]. The expansion of medications used to treat HF has reinforced the need for multi-disciplinary teams to expand implementation efforts, reduce barriers, and manage the complexity of HF pharmacotherapy. Current barriers exist with the incorporation of four medications for one disease state which include polypharmacy, cost, medication, and comorbidity interactions.

Cost and complex therapy regimens can prove to be significant barriers to the adoption of quadruple therapy, especially in the aging population where HF remains the leading cause of hospitalization [47]. A study by Unlu and colleagues sought to characterize the number of medication changes around older patients (> 65 years of age) with recent heart failure hospitalizations [48]. The majority of the population was ≥ 75 years old, with a median of 5–6 comorbidities and the majority taking at least 5 medications. Interestingly, over half of the population took more than 10 medications and this tended to increase overtime. The potential for drug interactions, adverse drug effects, and overall co-morbid disease state management lends to complex care for patients with heart failure. Therefore, it is recommended not only to optimize heart failure therapies, but also the reconciliation of non-cardiac medications to reduce side effects, interactions, and cost, as well as allow for the potential up-titration of heart failure therapies.

Access to several multidisciplinary resources is readily available while patients are admitted. For example, many hospitals have social workers to help with discharge planning, pharmacists to review medications, and nurses for heart failure patient assessment. There is clinical inertia around optimizing heart failure GDMT while a patient is hospitalized. A recent pilot study (IMPLEMENT-HF) utilized cardiologists and pharmacists to virtually optimize heart failure therapies for patients who had a diagnosis of HFrEF but were hospitalized for other reasons [44]. Eighty-nine of the 118 total patients were included in the GDMT intervention group. Within this group, 46% experienced intensification of their GDMT during their hospitalization (compared to 31% in the usual care arm) and increased 30-day follow-up. Capitalizing on medical optimization during admission was first explored in a study from Gattis et al. which established that patients are more likely to continue therapies when they are prescribed on discharge from heart failure hospitalization [49]. IMPLEMENT-HF built on this concept and demonstrated the impact of a multidisciplinary team in the optimization of heart failure therapies during hospitalization. Furthermore, the utilization of a pharmacist to perform medication histories, assessment of drug interactions, and potential cost barriers can reduce challenges to the incorporation of GDMT. The beneficial impact of virtual consultation for inpatients with HFrEF that are hospitalized for non-cardiovascular cause was demonstrated in a pilot randomized study that was recently published, furthering the evidence to support multi-disciplinary virtual care for inpatients [50].

IMPLEMENT-HF authors postulate that a similar virtual model could be utilized in an outpatient setting with non-cardiology visits. In a recent quality study by Desai et al. patient navigators identified ambulatory heart failure patients through the EMR [32, 51]. Pharmacists performed symptom assessment and medication adjustments according to guidelines remotely to optimize GDMT over a 3-month period. In comparison to the usual care group, the remote titration group demonstrated a significant increase in the utilization of ARNI/ACEi/ARB and guideline-directed beta-blockers [32]. This study demonstrates the significance of utilizing non-physician team members in optimizing medications in ambulatory patients with heart failure.

Given the unpredictable effect out-of-pocket expense may have on clinician hesitation to prescribe as well as patient adherence, multidisciplinary approaches to streamline cost barriers may provide an important avenue to improving GDMT uptake [52]. A recent study by Faridi et al. characterized costs among all Medicare prescription drug plans, 36.7% did not provide any coverage for dapagliflozin, and 5.1% did not provide any coverage for empagliflozin. Furthermore, 99.1% and 98.5% of these plans provided restrictive coverage (due to ≥ tier 3 cost sharing) for ARNI and SGLT2 inhibitors, respectively. Prior authorization for ARNI and SGLT2i remains necessary with many insurance providers [53]. The average out-of-pocket cost for quadruple therapy with ARNI + beta-blocker + MRA + SGLT2 inhibitor was $94 for a 30-day supply. This resulted in $2217 in annual out-of-pocket costs. In comparison, the median out-of-pocket cost for a beta-blocker, ACEi/ARB, and spironolactone was all under $10 (median $3) per month [53]. While updated societal guidelines have included value statements, with agents like ARNI and SGLT2 inhibitors (dapagliflozin and empagliflozin) meeting traditional cost-effectiveness thresholds, they may still be unaffordable for many patients [1, 53–57].

When a patient has been identified as not having insurance, a case worker or social worker may provide applications for federal insurance programs. Other options for uninsured patient populations include applying for drug manufacturer assistance for branded drugs and utilizing generic medications when able. For those patients with Medicare who are unable to afford their out-of-pocket costs, there may be additional funds available through disease-specific grant foundations. Patients with commercial insurance may have the ability to apply for coupon cards. Some centers may also have institution-specific medication assistance programs for uninsured or under-insured patients. Institutions have also utilized their outpatient retail pharmacies to help reduce medication barriers through finding financial assistance and delivering medications free of cost. Recommendations to streamline the prior authorization process and enhance payment assistance programs have been proposed. However, at present, financial toxicity related to out-of-pocket expenses from HFrEF therapies remains a significant barrier to therapy initiation and adherence [55].

Though prescription data is often used as a proxy for appropriate implementation of GDMT and used to populate EHR-based and traditional patient registries, adherence data would suggest an even more dire problem, with > 25% of patients never filling their prescription for ARNI therapy in a recent analysis [58]. Beyond prescription data, adherence to medical therapy

will also be an important metric to track and build evidence for how and why implementation efforts can fall short and/or why "real-world" data may not replicate benefits seen in seminal clinical trials. As many active clinicians observe, EHR-based prescription lists and actual patient adherence to pharmacotherapy are not always concordant.

Real-time evidence generation and EHR-based heart failure registries

As evident in Table 1, EHR-based HF patient registries have grown in size and capabilities in recent years and are becoming a powerful source for quality improvement, clinical operations, and implementation research [59]. Robust evidence to guide the appropriate strategies in using remote monitoring technology, multidisciplinary teams, and EHR-based alerts is needed given limitations in resources and the personnel/costs associated with implementation efforts. While national registries, such as CHAMP-HF, are useful for understanding broader and generalizable trends in the use of GDMT, they lack the timeliness needed to create rapid change locally and fail to capture institution-specific variation in, and barriers to, the implementation of optimal HF care [18•]. In order to facilitate a movement from a reactive care model that is reliant on timely and/or appropriate referrals, to a proactive care delivery paradigm where patients are systematically identified and engaged in appropriate care, there is a need for local HF disease management data to support population health efforts and enable real-time, patient-specific interventions.

As Ahmad and Desai have highlighted, the rapid expansion of large integrated health system with unified medical record systems has allowed for large-scale, relatively low-cost, evidence generation through the EHR. The Yale EHR-based HF registry has been used to evaluate the impact of clinical alerts that highlight patient prognosis and tailored clinical alerts in the prescribing of GDMT. The evaluation and publication of "neutral" implementation studies, like REVEAL-HF, can prevent duplicative ineffectual use of limited IT resources by other centers [18•, 25]. Furthermore, PROMPT-HF demonstrated that tailored clinical alerts geared toward GDMT optimization can make an impact [4, 22•]. However, the primary improvement was seen with prescribing patterns of beta-blockers, and alerts did not lead to a significant change in prescribing of ARNI, MRA, or SGLT2i. At our center, the use of EHR-based registries has enabled a collaborative effort between our Cardiovascular Medicine Department and Accountable Care Organization (ACO) to facilitate proactive outreach aimed at improving access to cardiovascular care for those on suboptimal therapy and high-risk features of advanced heart failure. In our experience, multidisciplinary resourcing of high-yield navigators, pharmacists, nursing, and investment in EHR infrastructure can be augmented through partnerships aimed at reducing acute utilization through novel care paradigms. The aforementioned STRONG-HF trial which showed a clear reduction in re-hospitalization with rapid GDMT titration post-acute heart failure discharge could strengthen the argument for payers and health systems to more heavily resource-intensive HF management programs [12].

Further implementation studies may evaluate strategies for early initiation and faster titration of any given therapy and determine optimal and

tailored combinations of HFrEF therapies [60]. The effectiveness of optimal titration algorithms, clinician education, centralized prior authorization, cost-reduction efforts, and different care settings (i.e., remote monitoring technologies, patient messaging, and patient outreach through navigators) can and should be evaluated through the use of EHR-based registries. As PROMPT-HF has demonstrated, provider randomization for "low-risk" interventions can allow for rapid enrollment and execution of clinical trials at relatively low cost [18•, 22•]. Investigators from the recently published "all virtual" study on Impact of Canagliflozin on Health Status, Quality of Life, and Functional Status in Heart Failure (CHIEF-HF) examined the impact of canagliflozin on patient-reported outcomes by enrolling patients, executing the study protocol, and reporting their findings without the costly and time-intensive requirements for in-person research visits and screening [61, 62]. Evidence generation in the implementation of proven heart failure therapy is an area with significant potential to reduce patient morbidity and mortality outside of the traditional large-scale clinical trial aimed at FDA approval. EHR-based registries that enable implementation trials around chronic disease management can help to address this ongoing public health need.

Though the focus of our review was GDMT implementation in HFrEF, the rapidly growing evidence for clinical benefit of SGLT2i in the HFpEF and HFmrEF patients necessitates translating lessons learned from prior efforts into a large population with significant co-morbidities and unique challenges [63, 64]. Avoiding the "natural history" of implementation observed in the HFrEF population will require rapid dissemination of effective implementation strategies.

Lastly, incorporation of machine learning (ML) algorithms into care delivery may provide further nuance with regard to patient selection and titration schema in patients with HF [65]. Such algorithms and data may help us move from expert guidance on titration to data-driven information that incorporates patient factors (vital signs, laboratory studies, allergies, current medications, drug-drug interactions, and comorbid conditions) to generate therapy recommendations to the clinicians. However, the impact of learning algorithms on providing clinical benefit in HF care remains unproven [66].

Conclusions

A large therapeutic gap between guideline-directed recommendations and real-world practice exists in the contemporary management of patients with HFrEF. Many strategies are being developed in an attempt to close this gap, as outlined in this review. The integration of multidisciplinary team-based approaches, auto-populating HF registries that can measure integrated health system performance, remote monitoring technologies including wearables,

non-traditional visits, and EHR-embedded tools including clinical alerts have tremendous potential to reduce implementation gaps and improve HF outcomes. Who will receive, interpret, and act on growing amounts of patient data remains an unanswered question that will continue to limit the scalability of studies that do not incorporate and disseminate the appropriate resourcing (i.e., nursing, physician, pharmacist, and APPs) to effectively deploy novel technologies or strategies of HF care. Simple alerting or prompting may have a limited impact but is easily scalable, while intensive HF management with dedicated experts is effective but requires intensive resources and a visit structure that is difficult to replicate in contemporary US health systems. Additional studies are needed to refine populations for intervention and calibrate appropriate resourcing of effective strategies for optimizing HF care. A multifaceted approach to improving HF therapy that incorporates iterative evidence generation to confirm effectiveness and efficacy is within reach for many contemporary health systems. With time, we may prove that the multidisciplinary, technology-enabled whole is greater than the sum of its parts in modern HF care.

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Compliancewith Ethical Standards

Conflict of Interest

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Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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•• Of major importance

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