Cardiovascular Innovations and Applications

Vol. 11 (2026) 8
ISSN 2009-8618
DOI 10.15212/CVIA.2025.0042

EDITORIAL

Guideline-Directed Medical Therapy in Heart Failure: The Need for Speed

Alvina Karam[1] and Juan M. Aranda[1]

[1]*Division of Cardiovascular Medicine, University of Florida College of Medicine, Gainesville, FL, USA*

Heart failure (HF) represents one of the most pressing health challenges globally, affecting more than 64 million people worldwide. Despite therapeutic progress, HF remains a leading cause of hospitalization and mortality, particularly in patients with reduced ejection fraction (HFrEF), with annual costs, including hospitalizations, pharmacotherapy, and productivity losses, measured in the hundreds of billions of dollars [1, 2]. Readmissions remain common: roughly one in four patients is rehospitalized within 30 days in many healthcare systems, and one in two within 6 months, reflecting not only the complexity of patients with HF but also the challenges of post-discharge care [3]. Despite decades of advances, 5-year mortality in HF approximates that of many cancers, thereby underscoring the urgency for better care delivery [2, 3].

Currently, multiple therapies unequivocally reduce death and hospitalization in HFrEF. Yet, these therapies are initiated late, under-titrated, or discontinued in routine practice, hence diluting the benefits seen in trials [4, 5]. Guideline-directed medical therapy (GDMT) refers to the evidence-based "four pillars" that form the pharmacologic backbone of HFrEF care: angiotensin receptor–neprilysin inhibitor (ARNI) or, where unavailable, angiotensin-converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB); evidence-based beta-blockers; mineralocorticoid receptor antagonists (MRAs); and sodium–glucose cotransporter-2 inhibitors (SGLT2i) [1, 6].

However, real-world implementation lags behind clinical evidence. Studies indicate that fewer than half of eligible patients receive all four classes, and even fewer reach target doses. This persistent gap in clinical implementation undermines the full potential of these life-saving therapies and represents the next frontier of HF care.

This editorial argues that the promise of GDMT can only be realized through a system-wide reorientation toward rapid initiation, optimization, and sustained adherence.

Four Pillars: From Evidence to Everyday Practice

The evidence base for each pillar is robust and complementary.

1. ARNI: In PARADIGM-HF, sacubitril/valsartan (ARNI) reduced the risk of cardiovascular death or HF hospitalization compared with enalapril, with early separation of event curves and consistent benefits across key subgroups [7]. It demonstrated a 20% reduction in the composite endpoint of cardiovascular death or HF hospitalization and a 16% reduction in all-cause mortality.
2. Beta-blockers: Previously, beta-blocker trials, including MERIT-HF, CIBIS-II, and COPERNICUS, demonstrated substantial reductions in mortality, sudden death, and worsening HF when combined with standard therapy, with benefits

Correspondence: **Juan M. Aranda Jr**, **MD**, 1329 SW 16th St., P.O. Box 100288, Gainesville, FL, 32608, USA, E-mail: ARANDJM@medicine.ufl.edu

©2026 The Authors. Creative Commons Attribution 4.0 International License

compuscript

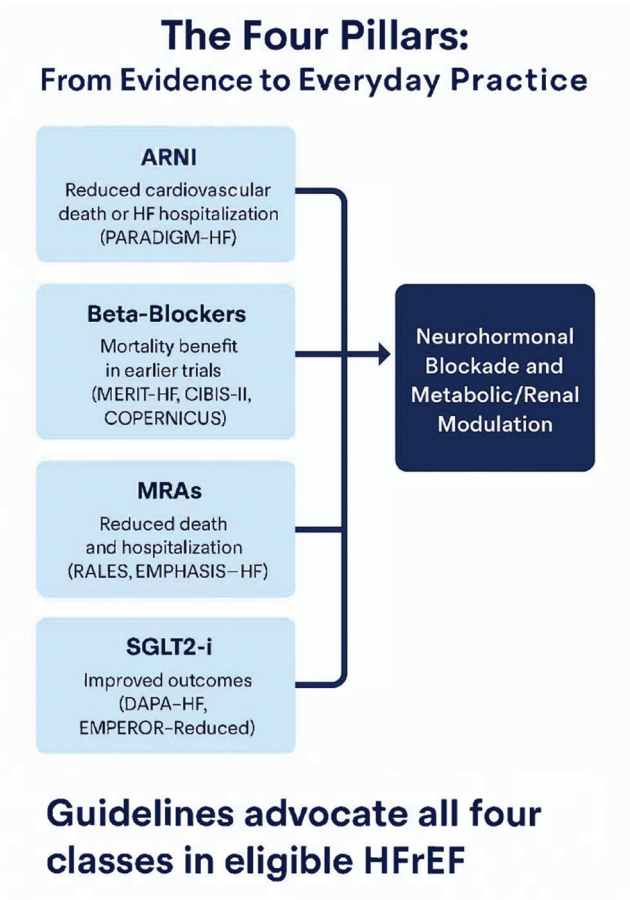

Figure 1 Four Pillars of Guideline-Directed Medical Therapy (GDMT). ARNI, Angiotensin receptor–neprilysin inhibition; MRAs, mineralocorticoid receptor antagonists; SGLT2i, sodium–glucose cotransporter-2 inhibitors.

extending to patients with advanced symptoms provided careful up-titration was undertaken [8–10]. For example, in MERIT-HF, metoprolol resulted in about 34% mortality reduction versus placebo in HFrEF.

3. MRAs: They cemented their role with RALES (spironolactone in advanced HFrEF) and EMPHASIS-HF (eplerenone in milder HFrEF), each showing marked reductions in death and hospitalization, mediated in part by antifibrotic and antiarrhythmic effects [11, 12].
4. SGLT2i: The newest pillar, SGLT2 inhibitors, conferred meaningful reductions in cardiovascular death and HF hospitalization in DAPA-HF (dapagliflozin) and EMPEROR-Reduced (empagliflozin) trials, irrespective of diabetes status and on top of background therapy [13, 14].

These classes act on partially distinct axes – neurohormonal blockade (ACEi/ARB/ARNI, beta-blocker, and MRA) and metabolic/renal modulation (SGLT2i) – and their benefits are at least additive (Figure 1). Modeling suggests that the simultaneous use of these classes can yield large absolute risk reductions within months, not years [6]. Reflecting this totality of evidence, the 2021 ESC and 2022 AHA/ACC/HFSA guidelines advocate that eligible patients with HFrEF receive all four classes, with an increasing preference for early or even near-simultaneous initiation rather than prolonged sequential layering [1, 6].

Bridging the Gap: Where We Fall Short

Implementation lags far behind evidence. The CHAMP-HF registry of US outpatients with HFrEF documented that large proportions of eligible patients were not prescribed ARNI, MRA, or SGLT2i, and that only a small minority reached target doses of renin–angiotensin system inhibitors and beta-blockers [4]. Among those treated, dose up-titration proceeded slowly or not at all, and discontinuations were common. Hospital-based programs paint a similar picture: data from the Get With The Guidelines-Heart Failure program highlight the under-use of foundational therapies at discharge and limited post-discharge intensification [5].

Barriers exist at multiple levels:

- Patient level: Polypharmacy, out-of-pocket costs (especially for ARNI and SGLT2i), hypotension, hyperkalemia, and perceived side-effect burden complicate adherence.
- Provider level: Clinical inertia, fears of renal function decline, and simple scarcity of time during short visits impede initiation and up-titration.
- System level: Fragmented transitions of care, limited pharmacist or nurse-titration support, and misaligned incentives perpetuate suboptimal delivery [3–6]. The net effect is that many patients never experience the full benefits documented in trials, and the earliest, highest-yield window after hospitalization is often missed.

The 2022 AHA/ACC/HFSA guidelines emphasize early and simultaneous initiation, ideally within the first 4 weeks after diagnosis, to maximize survival benefits. The TRANSITION and STRONG-HF

trials demonstrated that accelerated, in-hospital initiation and up-titration were both safe and effective, challenging the traditional sequential approach.

Accelerating GDMT: Rethinking Timing and Sequencing

A key paradigm shift in HF care is moving away from the traditional step-wise, sequential build-up of therapy, toward early simultaneous initiation of the four foundational agents, ideally within weeks rather than months. The STRONG-HF randomized trial operationalized an intensive strategy that initiated and up-titrated GDMT to high doses within 2 weeks, coupled with close follow-up and biomarker guidance. This approach reduced the composite of all-cause death or HF readmission in 180 days compared with usual care, with acceptable safety [15]. Importantly, benefits emerged early, during the period of highest vulnerability after discharge [3, 15]. Complementary inpatient trials such as PIONEER-HF showed that ARNI could be started safely during hospitalization for acute decompensated HF, resulting in early reductions in natriuretic peptides and clinical events [16].

A practical approach is to prioritize mortality-reducing therapies and achieve pharmacological breadth early in the course of the disease. Many physicians now follow an approach that includes the following:

(1) Start low doses of ARNI (or ACEi/ARB), evidence-based beta-blocker, MRA, and SGLT2i before discharge or in the first post-discharge visit;
(2) schedule follow-up within 7–14 days for labs and titration;
(3) empower pharmacists and nurse practitioners to adjust doses under protocol; and
(4) use standardized order sets and electronic medical record (EMR) prompts to reduce omission errors [6, 15, 17].

The historical fear that simultaneous initiation is hemodynamically intolerable is not substantiated when doses are modest and monitoring is structured. Indeed, the greater risk is therapeutic nihilism: delaying life-saving drugs until a hypothetical "stable" state that never arrives.

Integration of Multidisciplinary Teams

HF is a team sport. Multidisciplinary HF clinics integrating cardiologists, HF nurses, pharmacists, dietitians, social workers, and primary care improve the rates of GDMT initiation, titration, and persistence, thereby translating to fewer hospitalizations and better quality of life [17–19]. Pharmacist-led up-titration programs accelerate reaching target doses while ensuring monitoring of electrolytes and renal function, and nurse navigators close gaps in transitions of care.

The advent of digital health further enables this transformation. Telemedicine visits, remote hemodynamic/volume monitoring (e.g., via implantable pulmonary artery sensors), and artificial intelligence-driven decision support tools allow for closer patient follow-up, earlier detection of adverse effects, and timelier titration. Pilot projects in large healthcare systems show that remote monitoring plus guided titration may be associated with improved GDMT adherence and fewer readmissions (data emerging) [18]. Embedding EMR-driven alerts for initiation/titration of GDMT, integrated pharmacist workflow, and home monitoring may close the implementation gap.

Combining a multidisciplinary model with digital integration is imperative if we are to move from "prescribe and hope" to "prescribe, monitor, titrate, sustain" (Figure 2).

GDMT Beyond HFrEF: Expanding the Frontiers

The SGLT2i story has broadened the horizon beyond HFrEF. In EMPEROR-Preserved and DELIVER trials, empagliflozin and dapagliflozin, respectively, reduced the risk of worsening HF or cardiovascular death across the spectrum from mildly reduced to preserved EF, thus establishing an outcome-modifying therapy for HFpEF long considered a therapeutic desert [13, 20]. Importantly, benefits accrued irrespective of diabetes and were seen early, paralleling HFrEF experience [13, 20].

Other frontiers include the acute decompensated HF (initiating therapy in hospital) and cardiorenal syndrome (cross-talk between HF and renal

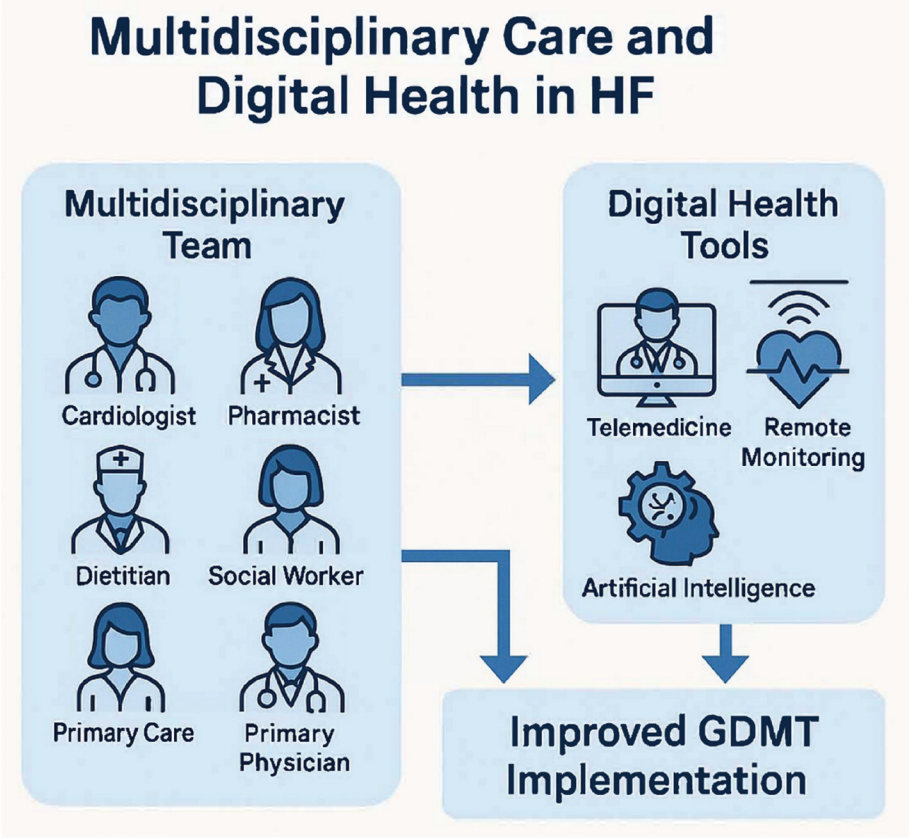

Figure 2 Multidisciplinary Care for Improved Guideline-Directed Medical Therapy (GDMT) Implementation.

failure), and the post–myocardial infarction ventricular remodeling space. Rapid in-hospital initiation of GDMT, particularly ARNI and SGLT2i, appears feasible and safe in many patients once stabilized, with the hospital stay serving as a springboard for post-discharge titration [16, 17]. In advanced HF, including patients bridged with a left ventricular assist device or evaluated for transplant, neurohormonal blockade remains foundational where tolerated, although dosing must be individualized given hemodynamic complexity. Finally, the post–myocardial infarction period represents a window to attenuate adverse remodeling; while not all agents are formally indicated after myocardial infarction for patients without HF, careful attention to EF trajectory and early GDMT in those with new HFrEF is prudent and guideline concordant [1, 6].

Health Equity and Global Implementation

The benefits of GDMT must not be gated by geography or income. Profound disparities in access and persistence exist by race, ethnicity, socioeconomic status, and geography [5]. Novel agents (ARNI and SGLT2i) carry higher acquisition costs in many markets, leading to their under-use among populations with the highest HF burden. Availability and affordability remain major hurdles in low- and middle-income countries.

Addressing inequity requires policy and program solutions:

(1) Cost mitigation through value-based formularies, patient-assistance programs, and equitable copay caps;
(2) task sharing models, which means training nurses and pharmacists to titrate under protocol to expand capacity where cardiologists are scarce;
(3) localized guidelines adaptation, harmonizing with ESC and AHA/ACC/HFSA recommendations while recognizing resource constraints; and
(4) community partnership and health-literacy interventions tailored to language and culture. As generic or lower-cost options emerge, rapid formulary adoption should be prioritized to

accelerate diffusion without sacrificing quality [1, 5, 6, 17].

The Way Forward

We have the evidence; the challenge lies in implementation. Real-world outcomes remain suboptimal not because treatments do not work, but because we fail to deliver them optimally, broadly, and sustainably.

To close this gap, we argue for several actionable items:

- **Policy changes**: Healthcare systems should adopt bundled payment models or performance metrics tied to GDMT initiation and up-titration. A good example would include the percentage of eligible patients with HFrEF on all four pillars by hospital discharge plus 90 days for bundled payment models.
- **Education initiatives**: Training programs for cardiologists, general internists, pharmacists, and nurse practitioners on rapid initiation protocols; integrating EMR prompts and clinical decision support tools.
- **Patient empowerment**: Shared decision-making to align therapy goals (survival, quality of life, and reduced hospitalization) with patient values; home-based monitoring and dosing adjustment under supervised protocols; adherence support and cost transparency.
- **Implementation science trials**: We must shift focus from purely efficacy-based trials to implementation trials. More pragmatic research is needed.
- **Global advocacy**: Encourage global HF consortia to disseminate the "four-pillar" paradigm, adapt guidelines for resource-limited settings, and push for equitable drug access worldwide.

If we commit to rapid initiation, optimization, and sustained adherence supported by teams, technology, and policy, we can convert the HF paradox into progress. Patients with HF lose ground every day that optimal therapy is delayed or underutilized.

Conflict of Interest

Juan M. Aranda is a Deputy-Editor-in-Chief of Cardiovascular Innovations and Applications. He was not involved in the peer-review or handling of the manuscript. Alvina Karam declares that there is no conflict of interest.

REFERENCES

1. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J 2021;42(36):3599–726.
2. Heidenreich PA, Bozkurt B, Aguilar D, Allen LA, Byun JJ, Colvin MM, et al. 2022 AHA/ACC/HFSA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. J Am Coll Cardiol 2022;79(17): e263–e421.
3. Greene SJ, Fonarow GC, Vaduganathan M, Khan SS, Butler J, Gheorghiade M. The vulnerable phase after hospitalization for heart failure. Nat Rev Cardiol 2015; 12(4):220–9.
4. Greene SJ, Fonarow GC, DeVore AD, Sharma PP, Vaduganathan M, Albert NM, et al. Titration of medical therapy for heart failure with reduced ejection fraction. J Am Coll Cardiol 2019;73(19):2365–83.
5. Lewis WR, Peterson ED, Cannon CP, Super DM, LaBresh KA, Quealy K, et al. An organized approach to improvement in guideline adherence for acute myocardial infarction: results with the Get With The Guidelines quality improvement program. Arch Intern Med 2008;168(16):1813–9.
6. Writing Committee; Maddox TM, Januzzi JL Jr, Allen LA, Breathett K, Butler J, Davis LL, et al. 2021 Update to the 2017 ACC expert consensus decision pathway for optimization of heart failure treatment: answers to 10 pivotal issues about heart failure with reduced ejection fraction: a report of the American College of Cardiology Solution Set Oversight Committee. J Am Coll Cardiol 2021;77(6): 772–810.
7. McMurray JJ, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, et al. Angiotensin–neprilysin inhibition versus enalapril in heart failure. N Engl J Med 2014;371(11):993–1004.
8. MERIT-HF Study Group. Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomised Intervention Trial in-Congestive Heart Failure (MERIT-HF). Lancet 1999;353(9169): 2001–7.
9. CIBIS-II Investigators and Committees. The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II):

a randomised trial. Lancet 1999;353(9146):9–13.
10. Packer M, Coats AJ, Fowler MB, Katus HA, Krum H, Mohacsi P, et al. Effect of carvedilol on survival in severe chronic heart failure. N Engl J Med 2001;344(22): 1651–8.
11. Pitt B, Zannad F, Remme WJ, Cody R, Castaigne A, Perez A, et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. N Engl J Med 1999;341(10):709–17.
12. Zannad F, McMurray JJ, Krum H, van Veldhuisen DJ, Swedberg K, Shi H, et al. Eplerenone in patients with systolic heart failure and mild symptoms. N Engl J Med 2011;364(1):11–21.
13. McMurray JJV, Solomon SD, Inzucchi SE, Køber L, Kosiborod MN, Martinez FA, et al. Dapagliflozin in patients with heart failure and reduced ejection fraction. N Engl J Med 2019;381(21):1995–2008.
14. Packer M, Anker SD, Butler J, Filippatos G, Pocock SJ, Carson P, et al. Cardiovascular and renal outcomes with empagliflozin in heart failure. N Engl J Med 2020; 383(15):1413–24.
15. Mebazaa A, Davison B, Chioncel O, Cohen-Solal A, Diaz R, Filippatos G, et al. Safety, tolerability and efficacy of up-titration of guideline-directed medical therapies for acute heart failure (STRONG-HF): a multinational, open-label, randomised, trial. Lancet 2022;400(10367):1938–52.
16. Velazquez EJ, Morrow DA, DeVore AD, Duffy CI, Ambrosy AP, McCague K, et al. Angiotensin–neprilysin inhibition in acute decompensated heart failure. N Engl J Med 2019;380(6):539–48.
17. Patolia H, Khan MS, Fonarow GC, Butler J, Greene SJ. Implementing guideline-directed medical therapy for heart failure: JACC focus seminar 1/3. J Am Coll Cardiol 2023;82(6):529–43.
18. Abraham WT, Adamson PB, Bourge RC, Aaron MF, Costanzo MR, Stevenson LW, et al. Wireless pulmonary artery haemodynamic monitoring in chronic heart failure: a randomised controlled trial. Lancet 2011;377(9766):658–66.
19. Sokos G, Kido K, Panjrath G, Benton E, Page R 2nd, Patel J, et al. Multidisciplinary care in heart failure services. J Card Fail 2023;29(6):943–58.
20. Anker SD, Butler J, Filippatos G, Ferreira JP, Bocchi E, Böhm M, et al. Empagliflozin in heart failure with a preserved ejection fraction. N Engl J Med 2021;385(16): 1451–61.