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*Review Article*

# From Four Pillars to Pharmacist-Led Optimization: A Narrative Review of Contemporary Heart Failure Pharmacotherapy and the Clinical Pharmacist's Role in Bridging the Guideline-to-Practice Gap

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**Background:** Heart failure remains one of the most consequential chronic syndromes in clinical medicine, affecting more than 64 million people worldwide and imposing a rising burden as populations age. The therapeutic landscape has shifted dramatically since 2021, yet the translation of guideline evidence into bedside practice remains strikingly incomplete. **Objective:** This narrative review consolidates the contemporary pharmacotherapy of heart failure across the ejection fraction spectrum and defines the clinical pharmacist's role in closing the persistent guideline-to-practice gap. **Methods:** Peer-reviewed literature, society guidelines, and landmark randomized trials published through early 2026 were identified through structured searches of PubMed, Scopus, and major cardiology society repositories, with emphasis on evidence reshaping practice since the 2021 European and 2022 American guidelines. **Results:** The four pillars of therapy now anchor management of reduced ejection fraction, while non-steroidal mineralocorticoid antagonists and incretin-based agents have extended evidence-based options into mildly reduced and preserved ejection fraction. Despite this, only a minority of eligible patients receive complete therapy within recommended timeframes. Pharmacist-led titration, adherence support, and comorbidity management consistently improve optimization rates. **Conclusion:** Realizing the promise of modern heart failure pharmacotherapy depends less on new molecules than on disciplined implementation. The clinical pharmacist is uniquely positioned to convert guideline knowledge into measurable patient benefit.

**Keywords**: Clinical Pharmacist, Guideline-Directed Medical Therapy, Heart Failure, Pharmaceutical Care, Quadruple Therapy, SGLT2 Inhibitors.

## INTRODUCTION

Few syndromes in contemporary medicine carry the dual burden that heart failure does: relentless prevalence on one hand, and a treatment landscape transformed almost beyond recognition on the other. Heart failure affects more than 64 million people worldwide, and reducing its social and economic toll has become a major global public health priority.[1] The number alone understates the human reality. Behind it lie repeated hospitalizations, eroded quality of life, caregivers stretched thin, and health systems absorbing costs that continue to climb. The trajectory in much of the world points upward as populations age and survivorship after acute cardiac events improves.[1] The epidemiology also carries a sobering signature. Global age-standardized prevalence has risen over recent decades, with ischemic heart disease and hypertensive heart disease together accounting for well over half of all cases.[1] These are, in large measure, the consequences of conditions clinicians see every day, which means heart failure is not a distant specialist concern but a predictable endpoint of the cardiometabolic disease that fills general wards and outpatient clinics alike. What makes the present moment remarkable is the contrast between this

burden and the tools now available to meet it. For decades, the pharmacotherapy of heart failure advanced incrementally. That pattern has broken. Since the publication of the 2021 European Society of Cardiology guidelines and the 2022 American guidelines, the field has witnessed an evidence surge that few areas of medicine can match.[2-3] The management of reduced ejection fraction has consolidated around four foundational drug classes, while entirely new evidence has, for the first time, extended disease-modifying therapy into mildly reduced and preserved ejection fraction, populations that until recently had almost nothing to offer beyond symptom control. And yet the central problem of heart failure care today is not a shortage of effective therapy. It is the failure to deliver therapy that already exists. The evidence on this point is unambiguous and, frankly, uncomfortable. Registry data have revealed sustained patterns of underuse and underdosing of guideline-directed medical therapy among eligible patients, and these gaps have remained largely unchanged over the past decade despite quality improvement initiatives and strong guideline recommendations.[4-5] The shortfall is not marginal; in real-world cohorts, only a small minority of patients receive complete therapy at adequate doses.[4] A therapeutic revolution, in other words, is being squandered at the bedside. This is the gap that the present review addresses, and it is precisely the territory where the clinical pharmacist becomes indispensable. The barriers to optimization are well characterized and largely human rather than scientific: therapeutic inertia, misplaced reassurance from apparent clinical stability, concern over adverse effects such as hypotension and hyperkalemia, fragmented follow-up, and the sheer complexity of titrating four drug classes in patients who are often elderly and burdened by comorbidity.[5] Each of these is a problem of process and vigilance, and each falls squarely within the competencies that define modern pharmaceutical care. Accordingly, this narrative review pursues two linked aims. The first is to consolidate, in a single coherent account, the contemporary pharmacotherapy of heart failure across the full ejection fraction spectrum, integrating the foundational four pillars with the newer agents that have reshaped practice since 2021. The second, and the element that distinguishes this review, is to map that therapeutic knowledge directly onto the role of the clinical pharmacist, articulating where pharmacist-led intervention can convert guideline evidence into measurable patient benefit. The intention is not to add another summary of trials to a crowded literature, but to bridge the space between what the guidelines recommend and what patients actually receive, a space in which the pharmacist is arguably the most underused asset in the heart failure team.

## MATERIALS AND METHODS

This article was conceived as a narrative review rather than a systematic review, a design chosen deliberately to serve its purpose. The aim was not to pool quantitative outcomes across homogeneous studies, but to synthesize a rapidly evolving and heterogeneous body of evidence, ranging from landmark randomized trials to society guidelines and real-world registries, into a coherent clinical account oriented toward pharmacy practice. A narrative approach permits the integration of therapeutic, implementation, and professional-role perspectives that a strictly protocol-driven synthesis would tend to fragment.

**Information sources and search strategy.** Relevant literature was identified through structured searches of PubMed/MEDLINE, Scopus, and the Cochrane Library, supplemented by direct retrieval from the online repositories of major cardiovascular societies, including the European Society of Cardiology, the American College of Cardiology, the American Heart Association, and the Heart Failure Society of America. The reference lists of key reviews and guideline documents were hand-searched to capture sources not surfaced by database queries. Search terms were combined using Boolean operators and included variations of heart failure, guideline-directed medical therapy, quadruple therapy, four pillars, ejection fraction, sodium–glucose cotransporter-2 inhibitor, angiotensin receptor–neprilysin inhibitor, mineralocorticoid receptor antagonist, clinical pharmacist, pharmaceutical care, and medication optimization.

**Eligibility and selection.** Priority was given to evidence shaping practice after the 2021 European and 2022 American heart failure guidelines, with particular attention to phase 3 randomized controlled

trials, contemporary society guideline updates and expert consensus pathways, and real-world implementation data published through early 2026. Foundational older trials were retained where they remain the basis of current recommendations, since a review of contemporary therapy cannot be severed from the pivotal studies on which today's guidance still rests. English-language, peer-reviewed publications were included. Conference abstracts without full-text availability, non-peer-reviewed preprints, and sources lacking methodological transparency were excluded. Where multiple reports addressed the same trial or dataset, the most complete and authoritative publication was cited.

**Synthesis.** Selected evidence was organized thematically rather than chronologically, structured around the ejection fraction spectrum, the foundational drug classes, the acute care setting, and the implementation of therapy in routine practice. Throughout, the clinical pharmacist's contribution was treated as an integrating thread rather than a separate appendage, reflecting the central argument of the review. Because no primary patient data were generated or analyzed, ethics committee approval was not applicable to this work.

## Heart Failure Definitions and Classification Across the Ejection Fraction Spectrum

Before therapy can be discussed coherently, the language of heart failure itself must be clear, because in this syndrome the classification is not academic bookkeeping. It dictates which drugs are indicated, how strongly they are recommended, and which patients stand to benefit. For the clinical pharmacist evaluating a prescription or counselling at the bedside, knowing where a patient sits on the ejection fraction spectrum is the first and most consequential piece of information.

Heart failure is best understood not as a single disease but as a clinical syndrome: a constellation of symptoms and signs arising from a structural or functional cardiac abnormality that impairs the heart's ability to fill or eject blood. Breathlessness, fatigue, and fluid retention are its familiar surface features, but beneath them lies a wide variety of underlying causes. The dominant contributors globally are ischemic heart disease and hypertensive heart disease, which together account for well over half of cases,[1] a reminder that heart failure is frequently the downstream consequence of conditions clinicians manage long before the syndrome declares itself. The organizing principle of modern classification is the left ventricular ejection fraction (LVEF). Its prominence is partly historical and partly pragmatic. Over successive decades of clinical trials, LVEF became the enrichment criterion that defined trial populations, and because therapies were proven within those populations, the ejection fraction bands inherited from those trials now determine who is eligible for what.[6] The contemporary framework, harmonized across the major American and European guidelines, defines four categories. Heart failure with reduced ejection fraction (HFrEF) denotes an LVEF of 40% or less; heart failure with mildly reduced ejection fraction (HFmrEF) an LVEF of 41% to 49%; heart failure with preserved ejection fraction (HFpEF) an LVEF of 50% or greater; and heart failure with improved ejection fraction (HFimpEF) a baseline LVEF of 40% or less that has risen by at least 10 points to a value exceeding 40%.[7] Each category carries a distinct clinical personality, and these differences matter for pharmaceutical care. Patients with reduced ejection fraction tend to be younger and more often male, with more pronounced ventricular remodelling and higher natriuretic peptide levels, whereas those with preserved or mildly reduced ejection fraction are more frequently older women, in whom atrial fibrillation and hypertension feature prominently.[7] These are not merely demographic curiosities. They shape comorbidity burden, polypharmacy risk, and tolerance of the very drugs used to treat the syndrome, all of which fall within the pharmacist's domain of vigilance. For the milder and preserved phenotypes, the ejection fraction value alone is insufficient. A diagnosis additionally requires objective evidence of raised left ventricular filling pressures, demonstrated through elevated natriuretic peptides or by noninvasive or invasive haemodynamic measurement.[2] This requirement guards against over-diagnosis in patients whose breathlessness has a non-cardiac explanation, and it underscores why natriuretic peptide interpretation is a competency every pharmacist counselling these patients should possess. The category of improved ejection fraction deserves particular emphasis precisely because it is so easily mishandled. The

definition was constructed deliberately to keep these patients anchored to their original disease.[2] A patient whose ejection fraction recovers from 30% to 45% has improved but has not been cured; the recovery is, in large part, a product of the therapy itself. Withdrawing guideline-directed treatment on the strength of a reassuring echocardiogram risks precipitating relapse, and this is a scenario in which a vigilant pharmacist, recognizing that improvement is contingent rather than permanent, can prevent a damaging deprescribing error. A further refinement has emerged in the most recent consensus thinking. The 2025 clinical consensus statement on the use of LVEF reaffirms its central role while emphasizing that ejection fraction is a dynamic measurement and a trajectory rather than a fixed label, with patients moving between worsening, unchanged, and recovered states over time.[6] This trajectory-based view has direct therapeutic implications, because it reframes the goal of treatment as the active maintenance of an improved state rather than the achievement of a one-time target. It is, in essence, an argument for sustained pharmaceutical care rather than episodic intervention. Taken together, these definitions form the scaffold on which the remainder of this review is built. The four pillars of therapy were established in, and remain anchored to, the reduced ejection fraction population. The genuine novelty of the past two years lies in evidence extending disease-modifying treatment beyond that group, into the mildly reduced and preserved categories that classification once consigned to symptom control alone. Understanding the spectrum is therefore the necessary prelude to understanding why the therapeutic landscape has changed so profoundly, and where the pharmacist's expanding role now reaches.

**Table 1: Classification of Heart Failure Across the Left Ventricular Ejection Fraction Spectrum**

| Sr. No. | Category | Abbrev. | LVEF | Additional diagnostic requirement |
|---|---|---|---|---|
| 1 | HF with reduced ejection fraction | HFrEF | ≤ 40% | Symptoms and/or signs of HF |
| 2 | HF with mildly reduced ejection fraction | HFmrEF | 41–49% | Symptoms/signs plus evidence of raised LV filling pressures |
| 3 | HF with preserved ejection fraction | HFpEF | ≥ 50% | Symptoms/signs plus evidence of raised LV filling pressures |
| 4 | HF with improved ejection fraction | HFimpEF | Baseline ≤ 40%, ≥ 10-pt rise, second value > 40% | Maintain HFrEF-directed therapy despite improvement |

HF = heart failure; LV = left ventricular; LVEF = left ventricular ejection fraction.

## Pharmacotherapy of Heart Failure with Reduced Ejection Fraction: The Four Pillars

If a single idea has reshaped heart failure care in the past decade, it is the recognition that effective treatment of reduced ejection fraction is not a matter of choosing among drug classes but of combining them. Contemporary guidelines now carry Class 1 recommendations for four foundational therapies in HFrEF: a renin–angiotensin system inhibitor, preferably an angiotensin receptor–neprilysin inhibitor; an evidence-based beta-blocker; a mineralocorticoid receptor antagonist; and a sodium–glucose cotransporter-2 inhibitor.[2] These are the four pillars, and the architectural metaphor is apt. Each bears load independently, but the structure stands only when all four are in place. For the pharmacist, this framework is liberating in its clarity and demanding in its execution. The goal for almost every patient with reduced ejection fraction is the same: all four classes, initiated early and titrated toward target doses, unless a specific contraindication forbids it. The art lies in sequencing, monitoring, and managing the interactions and adverse effects that accompany the simultaneous use of agents that all, in their own way, perturb haemodynamics and electrolytes.

### Renin–angiotensin system inhibition and the ascendancy of ARNI

The first pillar targets the renin–angiotensin–aldosterone system, the neurohormonal axis whose chronic activation drives the remodelling and fluid

retention central to heart failure progression. For years, angiotensin-converting enzyme inhibitors and angiotensin receptor blockers held this role. They remain effective and entirely acceptable, but the field has moved decisively toward the angiotensin receptor–neprilysin inhibitor sacubitril/valsartan, which adds neprilysin inhibition to angiotensin blockade, augmenting beneficial natriuretic peptide signalling while suppressing the maladaptive axis. The pivotal PARADIGM-HF trial established this superiority, demonstrating that sacubitril/valsartan reduced cardiovascular death and heart failure hospitalization compared with enalapril.[8] An ACE inhibitor or ARB remains an acceptable alternative where side effects or cost preclude the ARNI. For the pharmacist, two safety points dominate. A washout period of at least 36 hours must separate an ACE inhibitor from the first dose of sacubitril/valsartan, because their overlap precipitates angioedema. And blood pressure must support initiation, since hypotension is the most common barrier to titration.

**Beta-blockade**

The second pillar, the evidence-based beta-blocker, counters the sympathetic overactivity that, like RAAS activation, is initially compensatory but ultimately corrosive to the failing heart. The benefit is a class-restricted one; only bisoprolol, carvedilol, and sustained-release metoprolol succinate carry the trial evidence, a distinction the pharmacist must guard, since substitution of another beta-blocker forfeits the proven mortality reduction. The governing principle of beta-blocker use is timing. These agents are initiated only when the patient is euvolaemic and haemodynamically stable, never during active decompensation, because their negative inotropy can transiently worsen congestion before long-term benefit accrues. Titration proceeds slowly, in a “start low, go slow” rhythm, with the pharmacist well placed to pace dose increases against heart rate, blood pressure, and symptom tolerance.

**Mineralocorticoid receptor antagonism**

The third pillar, mineralocorticoid receptor antagonism with spironolactone or eplerenone, completes the neurohormonal blockade by opposing aldosterone directly. Its mortality benefit, established in the RALES and EMPHASIS-HF trials, is substantial,[9-10] and yet it is the pillar most consistently neglected in practice, with a large share of eligible patients left untreated despite its well-established benefit and relative affordability.[4] This neglect is, in part, a problem of misplaced caution, and it is precisely where pharmacist vigilance pays dividends. The legitimate concern with MRAs is hyperkalaemia, particularly when renal function is impaired or when the agent is combined, as it usually is, with RAAS inhibition. The answer is not avoidance but surveillance: baseline and serial monitoring of potassium and renal function, attention to interacting drugs, and patient counselling on potassium-rich salt substitutes. A monitorable risk should not be allowed to deny patients a life-prolonging therapy, and the pharmacist is the team member best positioned to make that argument operational.

**Sodium–glucose cotransporter-2 inhibition**

The fourth and newest pillar arrived from an unexpected direction. SGLT2 inhibitors, developed as glucose-lowering agents, proved to reduce cardiovascular death and heart failure hospitalization in patients with reduced ejection fraction regardless of diabetes status. The DAPA-HF and EMPEROR-Reduced trials delivered remarkably concordant results, each demonstrating a reduction of roughly one-quarter in the composite of cardiovascular death or heart failure hospitalization.[11-12] For the pharmacist, this pillar is in one respect refreshingly simple. Because the starting dose equals the target dose used in the trials, SGLT2 inhibitors require no titration.[11] Dapagliflozin or empagliflozin is begun at its fixed dose and left there. The counselling points are correspondingly specific: an expected, benign early dip in eGFR that should not prompt discontinuation; genital mycotic infections, modestly more common on therapy and manageable with hygiene advice; volume status, since the diuretic effect may necessitate loop diuretic adjustment; and the rare but serious risk of euglycaemic ketoacidosis, with its attendant sick-day guidance.

**From four drugs to one strategy: the case for early, rapid optimization**

Naming the pillars is the easy part. The decisive shift in contemporary thinking concerns how quickly they are assembled. The older, cautious model introduced

one agent at a time over many months, often leaving patients on partial therapy indefinitely. That model has been abandoned. Current guidance favours initiating all four classes promptly in newly diagnosed patients, because in combination they provide the greatest reduction in symptoms, hospitalizations, and death.[2-3] This rapid-sequencing philosophy rests on sound logic. The drugs act through complementary mechanisms, their benefits are largely additive, and much of the excess mortality in heart failure clusters in the early period after diagnosis or hospitalization, precisely when therapy is too often still being assembled piecemeal. The 2023 European focused update reinforced this with a recommendation for rapid in-hospital sequencing and frequent review during the first weeks after discharge.[3] The reordering is not arbitrary: agents may be introduced in whatever sequence a given patient's blood pressure, heart rate, renal function, and potassium will best tolerate, which is itself an argument for pharmacist involvement, since optimizing that sequence is a quintessentially pharmaceutical judgement. The uncomfortable counterpoint, developed in the sections that follow, is how rarely this ideal is achieved. In a contemporary registry of patients hospitalized for HFrEF, only a minority were discharged on triple therapy and fewer still on quadruple therapy including an SGLT2 inhibitor.[5] Four pillars exist; the building, too often, does not get built. That gap is the review's central concern, and the pharmacist its most promising remedy.

**Table 2: The Four Pillars Of Guideline-Directed Medical Therapy In Heart Failure With Reduced Ejection Fraction**

| Sr. No. | Pillar | Representative agents | Principal mechanism | Key trial(s) | Pharmacist monitoring priority |
|---|---|---|---|---|---|
| 1 | RAAS inhibition (ARNI preferred) | Sacubitril/valsartan; enalapril; candesartan | Suppresses maladaptive RAAS; ARNI augments natriuretic peptide signalling | PARADIGM-HF | BP; renal function; ≥ 36-h washout from ACEi before ARNI |
| 2 | Beta-blockade (class-restricted) | Bisoprolol; carvedilol; metoprolol succinate | Counters chronic sympathetic overactivation | MERIT-HF; CIBIS-II | Initiate when euvolaemic; HR; BP; titrate slowly |
| 3 | MRA | Spironolactone; eplerenone | Blocks aldosterone-driven remodelling/fibrosis | RALES; EMPHASIS-HF | Serum potassium; renal function; interacting drugs |
| 4 | SGLT2 inhibition | Dapagliflozin; empagliflozin | Cardiorenal protection independent of glycaemia | DAPA-HF; EMPEROR-Reduced | No titration; volume status; genital infection; rare euglycaemic ketoacidosis |

ACEi = angiotensin-converting enzyme inhibitor; ARNI = angiotensin receptor–neprilysin inhibitor; BP = blood pressure; HR = heart rate; MRA = mineralocorticoid receptor antagonist; RAAS = renin–angiotensin–aldosterone system; SGLT2 = sodium–glucose cotransporter-2.

## Extending Disease-Modifying Therapy into Mildly Reduced and Preserved Ejection Fraction

For most of the history of heart failure pharmacotherapy, a hard line ran through the ejection fraction spectrum. Below the line, in reduced ejection fraction, lay an expanding arsenal of disease-modifying drugs. Above it, in mildly reduced and preserved ejection fraction, lay therapeutic emptiness. Trial after trial of the agents that transformed HFrEF, the RAAS inhibitors and beta-blockers, failed to show convincing benefit when ejection fraction was preserved. For the substantial population with these phenotypes, many of them older women burdened by hypertension, obesity, and atrial fibrillation, the message was bleak: little could be offered beyond symptom relief. That line has now been crossed, and its crossing is the most consequential development in heart failure care since the consolidation of the four pillars. It is also the element that makes a

contemporary review genuinely contemporary, because the evidence rewriting this territory has emerged almost entirely within the past three years.

**SGLT2 inhibitors: the first breach**

The breakthrough came, once again, from the SGLT2 inhibitors. The EMPEROR-Preserved trial with empagliflozin and the DELIVER trial with dapagliflozin demonstrated, for the first time with convincing consistency, that a disease-modifying therapy could reduce heart failure events in patients across the mildly reduced and preserved range.[13-14] The effect was driven principally by fewer hospitalizations rather than a dramatic reduction in death, but for a population that had nothing, it was a watershed. The guidelines responded, and United States heart failure guidance now carries a Class 2a recommendation for SGLT2 inhibitor therapy in both HFmrEF and HFpEF.[2] In practical terms, this made the SGLT2 inhibitor the first and, for a time, the only agent with a strong recommendation across the upper ejection fraction spectrum, a remarkable trajectory for a drug class that began as a diabetes treatment. For the pharmacist, the counselling and monitoring points carry over intact from the HFrEF setting: fixed dosing without titration, attention to volume status, and the familiar vigilance around genital infection and, rarely, euglycaemic ketoacidosis.

**Finerenone: a genuine second pillar emerges**

If the SGLT2 inhibitors breached the line, the FINEARTS-HF trial began to build a second structure behind it. Steroidal mineralocorticoid antagonists had long disappointed in preserved ejection fraction. The nonsteroidal MRA finerenone changed that picture. FINEARTS-HF provided the first definitive evidence that a mineralocorticoid receptor antagonist is beneficial in HFmrEF and HFpEF, reducing a composite of cardiovascular death and total worsening heart failure events, and because the benefit held in patients already taking an SGLT2 inhibitor, finerenone emerged as a candidate second pillar for this population.[15] The mechanistic rationale is instructive and worth the pharmacist's understanding. Unlike the steroidal agents spironolactone and eplerenone, which act as partial agonists, finerenone engages the receptor differently, a difference thought to underlie its distinct anti-inflammatory and antifibrotic profile in the heart, kidney, and vasculature.[15] The pharmacist should appreciate that guideline status here is a moving target; the evidence has in several respects outpaced the formal recommendations, and formulary and cost-effectiveness assessments are still catching up. Counselling on finerenone mirrors MRA vigilance generally, with hyperkalaemia the principal monitorable risk, though its potassium effect is generally more modest than that of the steroidal agents.

**Incretin-based therapy: treating the phenotype, not just the heart**

A third and conceptually distinct avenue has opened through the incretin-based therapies, and it reframes how the preserved-ejection-fraction patient might be approached. A large proportion of HFpEF is intimately bound up with obesity, and the STEP-HFpEF programme tested whether treating the obesity could treat the heart failure. In that programme, weekly subcutaneous semaglutide significantly reduced heart-failure-related symptoms and physical limitation while improving exercise capacity in obese patients with HFpEF.[16] This is a different kind of benefit from the others in this section. Rather than blocking a neurohormonal axis, it addresses the cardiometabolic substrate of the disease itself, and the improvement in symptoms and function speaks directly to what these patients most want: to breathe and move with less difficulty. These findings provide a strong rationale for dedicated morbidity and mortality trials of incretin-based therapies in patients with obesity-related HFmrEF and HFpEF.[16] For the pharmacist, this signals an expanding role in a class already familiar from diabetes and obesity practice, with its established counselling around gastrointestinal tolerability, dose escalation, and injection technique now extending into cardiovascular care.

**A spectrum-wide framework takes shape**

Taken together, these developments dissolve the old binary. Where once the question was simply "reduced or not," the contemporary framework recognizes a continuum along which therapeutic options now exist at every point. The SGLT2 inhibitor functions, in effect, as a unifying agent with benefit across nearly

the entire spectrum. Finerenone extends meaningful neurohormonal modification into the preserved range for the first time. Incretin-based therapy offers a route to treat the obese phenotype that dominates HFpEF. For pharmacy practice, the implication is direct and significant. The patient with preserved ejection fraction can no longer be regarded as a patient for whom little can be done. Such patients now warrant active, evidence-based pharmacotherapy and the same disciplined attention to optimization, monitoring, and adherence that reduced ejection fraction has long received. Recognizing eligibility, initiating appropriate agents, and surveilling their safety across this expanded landscape is precisely the kind of contribution the clinical pharmacist is positioned to make, and it is a contribution that the literature, until very recently, had no occasion to describe.

**Table 3: Emerging Disease-Modifying Therapies for Heart Failure with Mildly Reduced and Preserved Ejection Fraction**

| Sr. No. | Drug class / agent | Pivotal trial(s) | Key finding | Recommendation / status |
|---|---|---|---|---|
| 1 | SGLT2 inhibitors (empagliflozin, dapagliflozin) | EMPEROR-Preserved; DELIVER | Reduced HF events across mildly reduced and preserved range; driven mainly by fewer hospitalisations | Class 2a recommendation in HFmrEF and HFpEF (US guidance) |
| 2 | Non-steroidal MRA (finerenone) | FINEARTS-HF | First definitive evidence of MRA benefit in HFmrEF/HFpEF; reduced composite of CV death and total worsening-HF events | Approved for HF with LVEF ≥ 40%; guideline adoption evolving |
| 3 | Incretin-based therapy (semaglutide; tirzepatide) | STEP-HFpEF; STEP-HFpEF DM | Reduced HF-related symptoms and physical limitation; improved exercise capacity in obesity-related HFpEF | Outcome trials anticipated; not yet a formal HF guideline recommendation |

CV = cardiovascular; HF = heart failure; HFmrEF/HFpEF = HF with mildly reduced/preserved ejection fraction; LVEF = left ventricular ejection fraction; MRA = mineralocorticoid receptor antagonist; SGLT2 = sodium–glucose cotransporter-2.

## Acute Heart Failure and the Vulnerable Phase: Rapid Optimization as a Therapeutic Imperative

The chronic, ambulatory management discussed so far is only half the story. Most patients meet the health system not in a stable clinic but in the throes of an acute decompensation, breathless and congested, admitted to hospital. This acute episode is far more than an exacerbation to be relieved and discharged. It is a pivotal moment whose handling shapes the patient's trajectory for months afterward, and it is a setting in which the clinical pharmacist's reach is unusually direct.

### Stabilizing the acute episode

The immediate priority in acute heart failure is the relief of congestion. Intravenous loop diuretics remain the cornerstone of decongestion, titrated against urine output, body weight, and symptoms. It is essential, however, to keep diuretics in perspective. They are indispensable for comfort and safety, yet they modify the syndrome's natural history not at all; the agents that prolong life are the foundational disease-modifying classes, not the diuretic that relieves the breathlessness. The pharmacist's role during stabilization includes rational diuretic dosing, vigilance for the electrolyte disturbances that aggressive diuresis provokes, and attention to renal function as volume is removed.

### The vulnerable phase: a window that closes quickly

What gives the acute admission its lasting significance is what follows it. The weeks immediately after discharge constitute what the literature now terms the vulnerable phase, a period of elevated risk in which patients are disproportionately

likely to deteriorate, to be readmitted, or to die.[17] The patient who leaves hospital feeling improved is, paradoxically, at one of the most dangerous junctures of their illness. Historically, this window was poorly used. Guidance recommended early follow-up, but the evidence underpinning it was weak and the target doses to which medications should be advanced were never clearly specified.[17] Patients were discharged on partial therapy, reviewed weeks later if at all, and left under-treated through precisely the interval when intervention mattered most.

**STRONG-HF and the rapid up-titration paradigm**

The trial that transformed thinking about this window was STRONG-HF, and its result was decisive enough to halt the study early. After enrolling more than 1,000 patients, the data and safety monitoring board recommended early termination because the between-group differences were greater than expected, indicating that intensive follow-up with rapid up-titration of guideline-directed therapy is clinically significant after admission for acute heart failure.[17] The strategy tested was straightforward in concept and demanding in execution: initiate the foundational therapies before discharge and advance them swiftly to full doses within the first weeks afterward, guided by frequent visits and biomarker-led safety checks. The outcome justified the intensity. Rapid up-titration of renin–angiotensin inhibition, a beta-blocker, and a mineralocorticoid receptor antagonist to full optimal doses within weeks of discharge, using frequent safety assessments, significantly reduced the 180-day risk of heart failure readmission or death and improved quality of life, regardless of ejection fraction.[17] Crucially, this benefit was achieved safely: although the high-intensity arm recorded slightly more treatment-emergent adverse events, there was no difference in serious adverse events between the groups. The guidelines absorbed the lesson quickly, and the 2023 European focused update now recommends initiation and rapid up-titration of guideline-directed therapy after a heart failure hospitalization as a Class I recommendation.[3]

**Where the pharmacist becomes indispensable**

The STRONG-HF model is, in essence, a protocol of structured, frequent, parameter-guided medication titration. It is difficult to imagine a clinical activity more squarely within the pharmacist's competence. Up-titration in the trial was guided by specific safety indicators, including thresholds for estimated glomerular filtration rate, serum potassium, systolic blood pressure, heart rate, and natriuretic peptide trajectory.[17] Each of these is a number a pharmacist reads, interprets, and acts upon as a matter of routine. The handling of hyperkalaemia in the trial is especially instructive for pharmacy practice. Hyperkalaemia was a frequent cause of discontinuation of therapy, particularly the MRA, yet the strategy of frequent follow-up allowed slower titration and lower doses while maintaining MRA treatment in most patients, without any adverse relationship to the risk of death or readmission.[17] This is the difference between blunt discontinuation and skilled management. A rising potassium need not mean abandoning a life-prolonging drug; with vigilant monitoring, dose adjustment, attention to interacting medications, and where appropriate the use of potassium-binding agents, therapy can be preserved. That nuanced, surveillance-intensive judgement is the essence of pharmaceutical care, and it converts a STRONG-HF protocol from an aspiration into a deliverable reality. The acute admission and its aftermath, then, represent the sharpest illustration of this review's central argument. The evidence is unambiguous that rapid, monitored optimization during the vulnerable phase saves lives, and the activity it requires, frequent and disciplined titration against clinical and laboratory parameters, is one the pharmacist is trained and positioned to lead.

**The Clinical Pharmacist at the Centre: From Guideline Knowledge to Patient Benefit**

Everything in this review has pointed toward a single conclusion. The pharmacotherapy of heart failure is now powerful, evidence-rich, and spread across the entire ejection fraction spectrum, yet its benefits are squandered with dismaying regularity at the point of delivery. The four pillars exist but are rarely all built. Rapid optimization saves lives but is seldom executed. New agents extend hope into territory once barren, but eligibility goes unrecognized. The decisive problem of modern heart failure care is not pharmacological but operational, and operational problems of medication use are the native habitat of the clinical pharmacist.

**The activities that close the gap**

The barriers to optimization share a common character. Therapeutic inertia, the failure to advance a dose that could be advanced. Misplaced reassurance, the mistaking of stability for adequacy. Fear of adverse effects, the abandonment of a drug over a manageable risk. Fragmented follow-up, the loss of the patient through the cracks of the vulnerable phase. Each of these is a failure of vigilance, continuity, or judgement about medications, and each maps onto a defined pharmacist activity. Medication reconciliation at every transition guards against the omissions and duplications that fragmented care produces. Structured, protocol-guided titration converts the rapid-optimization ideal into routine, advancing each pillar against the patient's blood pressure, heart rate, renal function, and potassium. Proactive monitoring of electrolytes and renal function transforms the feared adverse effect from a reason to stop therapy into a parameter to be managed. Patient education and adherence support address the substantial share of treatment failure that originates not with the prescription but with the patient's understanding of it. And comorbidity management, the diabetes, chronic kidney disease, and atrial fibrillation that travel with heart failure, draws on the breadth of pharmaceutical knowledge that few other team members possess.

**The evidence that pharmacists deliver**

These claims would be hollow without outcome data, and the data are encouraging. A systematic review and meta-analysis of non-physician-led optimization furnishes the clearest evidence: pharmacist- and nurse-led interventions for the initiation and up-titration of guideline-directed therapy improved guideline concordance compared with usual physician care.[18] The magnitude is not trivial; in that analysis, the likelihood of up-titration roughly doubled for both renin–angiotensin system inhibitors and beta-blockers under non-physician-led care, although no significant association was found for mineralocorticoid antagonist initiation.[18] For two of the four pillars, in other words, pharmacist or nurse involvement was associated with a doubling of the chance that therapy was advanced toward its effective dose. The direction of evidence is consistent across settings: where pharmacists are embedded in heart failure care, more patients receive more of the therapy that prolongs their lives. This matter because the cost of inaction is measurable, since delayed or deferred therapy exposes patients to excess, avoidable risk during the very period when treatment confers the greatest benefit.[4-5] Optimization is not a bureaucratic nicety; the delay the pharmacist prevents is, in aggregate, a survival difference.

**New models, new reach**

The pharmacist's contribution is also evolving in form, not merely expanding in volume. Remote optimization supported by telemonitoring has emerged as a particularly promising model, extending the reach of structured optimization beyond the clinic walls and offering a way to optimize more patients faster while consuming fewer in-person resources.[18] For health systems strained by the sheer prevalence of heart failure, this is precisely what is needed, and the pharmacist is well suited to lead it. In this account, the pharmacist is not an add-on to an already crowded team but a force multiplier, freeing physician time, widening access, and improving the very outcomes that define quality in heart failure care.

**The argument in sum**

The case assembled here is straightforward. Heart failure pharmacotherapy has become extraordinarily effective, yet its translation into practice fails at predictable, well-characterized points. Those points are, almost without exception, problems of medication management, and the activities that resolve them, reconciliation, titration, monitoring, education, and comorbidity care, are the established competencies of the clinical pharmacist. The evidence consistently shows that pharmacist involvement raises the proportion of patients who receive optimal therapy. The clinical pharmacist is therefore not a peripheral contributor to heart failure care but, on the evidence, one of the most underused instruments available for closing the gap between what the guidelines promise and what patients receive.

**Table 4: Implementation Barriers Mapped To Clinical Pharmacist Interventions**

| Sr. No. | Level | Representative barrier | Corresponding pharmacist intervention |
|---|---|---|---|
| 1 | Clinician | Therapeutic inertia; failure to initiate or up-titrate | Protocol-driven, parameter-guided titration toward target doses |
| 2 | Clinician | Fear of adverse events (hypotension, hyperkalaemia, renal decline) | Proactive electrolyte and renal monitoring; dose adjustment rather than discontinuation |
| 3 | Clinician | Workload of monitoring and approvals | Pharmacist assumption of monitoring/optimization workload, relieving prescriber time |
| 4 | Patient | Limited health literacy; non-adherence; side effects | Structured counselling; adherence support; side-effect management |
| 5 | Patient | Comorbidity burden (diabetes, CKD, atrial fibrillation) | Comorbidity-aware medication management |
| 6 | System | Fragmented care across transitions | Medication reconciliation at every care transition |
| 7 | System | Limited specialist/clinic capacity; rural distance | Pharmacist-led and telemonitoring-supported remote titration models |

CKD = chronic kidney disease.

**Why the Gap Persists: Barriers to Implementation**

A review that argued only for the pharmacist's promise, without confronting the full anatomy of the problem, would be incomplete and unconvincing. The implementation gap in heart failure has proven stubborn precisely because it is not the product of any single failing. It is woven from barriers operating at three distinct levels, the patient, the clinician, and the health system, and these reinforce one another.[5] Understanding each level honestly is the precondition for situating the pharmacist's role within a realistic solution, rather than overstating it as a cure-all.

**Clinician-level barriers**

At the clinician level, the dominant obstacle is therapeutic inertia, the quiet failure to start or advance a therapy that should be started or advanced. Its causes are several and overlapping: misperceptions about a patient's clinically stable status, potential biases against older, female, or comorbid patients, and concerns over therapy-related adverse events such as hypotension, impaired renal function, and hyperkalaemia.[5] A particularly damaging pattern attaches to the sickest patients, in whom guideline-directed therapy is underused most, even though these patients potentially benefit the most and the very signs that prompt caution may reflect disease progression that the therapy itself could stabilize.[5] The paradox is cruel: caution is exercised most heavily where boldness would help most. Layered onto these clinical judgements is the simple matter of workload. The burden associated with obtaining approvals and monitoring patients through optimization is substantial, and in a busy practice it competes with every other demand on a clinician's time.[5]

**Patient-level barriers**

Patients bring their own, often formidable, obstacles, including limited health literacy, drug affordability, intolerable side effects, and mistrust related to marginalization.[5] Cost looms especially large for the newer agents that this review has shown to be transformative, and access to SGLT2 inhibitors and ARNI can remain prohibitive on grounds of cost alone.[5] The cruelty here is structural: the drugs with the strongest modern evidence are frequently the least affordable, so the therapeutic advance and the access barrier rise together. These burdens, moreover, are not distributed evenly, with amplified gaps appearing among minoritized groups, women, and those of lower socioeconomic status.[5] The implementation gap is thus also an equity gap.

**System-level barriers**

The health system itself frequently lacks the architecture to deliver optimal therapy, with disparities in access to specialist care, restrictive drug policy and pricing, and inadequate funding for integrated-care programmes all contributing.[5] The logistical demands of optimization collide directly

with the realities of service capacity, since the in-office up-titration that optimization requires is genuinely difficult to sustain, and gaps widen further for patients who cannot easily reach specialist care because of work, transportation, or rural distance. This dimension carries a global weight that a review oriented toward broad pharmacy practice must not overlook, since a large share of those living with heart failure reside in low- and middle-income countries, where specialist cardiologists are scarcest and systems most strained.[5]

**Situating the pharmacist honestly**

Set against this anatomy, the pharmacist's role must be claimed with appropriate modesty. No pharmacist can legislate drug prices, redraw insurance formularies, or abolish the socioeconomic disparities that shape access. Those are problems for policy, and to pretend otherwise would be to overstate the case. Yet within this sobering landscape, the pharmacist addresses a remarkable share of what remains tractable. Therapeutic inertia yields to protocol-driven titration. The workload of monitoring and approvals is precisely the burden a pharmacist can assume, relieving the overstretched clinician. Limited health literacy is the daily target of pharmacist counselling. The fear of adverse events, the single most pervasive clinical barrier, is answered by the surveillance and dose-management expertise that defines the profession. And in resource-limited and rural settings, the pharmacist offers exactly what the system-level analysis demands: a way to extend safe, structured optimization beyond the narrow bottleneck of specialist availability. The barriers are real, but they are not destiny, and the pharmacist is positioned to dismantle a meaningful portion of them.

## CONCLUSION

The story of heart failure pharmacotherapy in the present era is, at its core, a story of two velocities. The science has moved with breathtaking speed, while its delivery to patients has scarcely moved at all. This review has traced both, and the gap between them is the single most important fact in contemporary heart failure care. The therapeutic transformation is genuine and profound. For reduced ejection fraction, the four pillars have consolidated into a coherent, mortality-reducing foundation, no longer assembled cautiously over months but initiated early and advanced rapidly toward target doses. For the mildly reduced and preserved phenotypes, the therapeutic emptiness that defined them for decades has, within just the past few years, given way to a growing menu: SGLT2 inhibitors spanning nearly the entire ejection fraction spectrum, finerenone establishing the first credible neurohormonal option above the old dividing line, and incretin-based therapies treating the obese phenotype that drives so much preserved-ejection-fraction disease. In the acute setting, the vulnerable phase after discharge has been redefined from a period of passive recovery into a window of decisive, life-saving intervention. And yet, as this review has documented at every turn, that armoury sits largely unused. Only a small minority of eligible patients receive complete therapy at adequate doses. The reasons are not mysterious; they are the well-characterized barriers of inertia, fear, fragmentation, cost, and constrained capacity, operating across patient, clinician, and system. The decisive challenge of modern heart failure care, in short, is no longer discovery. It is delivery. This reframing is what gives the clinical pharmacist's role its weight. The activities that close the gap, medication reconciliation, structured titration, proactive monitoring, adherence-focused education, and comorbidity management, are the established competencies of pharmaceutical care, and the evidence consistently shows that pharmacist involvement raises the proportion of patients who receive the therapy that prolongs their lives. Several directions deserve emphasis as the field looks forward. First, the integration of pharmacists into heart failure teams should move from local initiative to structural norm, supported by formal scopes of practice that permit the independent titration the evidence rewards. Second, the newer agents and the rapid-sequencing strategies that have reshaped the landscape demand dedicated study of how pharmacist-led models perform with them specifically, since much of the existing evidence predates the full four-pillar and spectrum-wide era. Third, digital and remote optimization models hold particular promise for extending the pharmacist's reach into precisely the rural and resource-limited settings where specialist access is thinnest. Finally, the equity dimension must remain in view; any implementation strategy that improves average performance while leaving disparities untouched has

only partly succeeded. A concluding reflection is warranted. The history of heart failure has, for fifty years, been written largely as a history of molecules. The next chapter may be written differently, not as a history of what we discover but of how faithfully we deliver what we already possess. In that chapter, the clinical pharmacist stands to be not a footnote but a protagonist. Realizing the full promise of the therapeutic revolution this review has described will depend, in large measure, on recognizing that promise is kept at the bedside, in the disciplined, vigilant work of optimization, and on empowering the professionals best equipped to do it. The drugs are ready. The task now is to ensure the patients receive them.

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**Conflicts of Interest**

The author declares no conflicts of interest with respect to the publication of this manuscript.

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