

**PHARMACOTHERAPY OF HEART FAILURE: A NARRATIVE REVIEW OF
CONTEMPORARY GUIDELINE-DIRECTED DRUG THERAPY**

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Abstract

Heart failure remains one of the most common, costly, and lethal cardiovascular syndromes worldwide, affecting more than 64 million people globally and carrying a prognosis that is often worse than many forms of cancer. Over the past four decades, pharmacological management has evolved from a purely symptomatic, diuretic-centred approach into a sophisticated, evidence-driven strategy that targets the neurohormonal maladaptation underlying the disease. This narrative review summarizes the pharmacotherapy of heart failure with a focus on guideline-directed medical therapy (GDMT) for heart failure with reduced ejection fraction (HFrEF). We discuss the mechanistic rationale, clinical evidence, dosing principles, and safety considerations of the four foundational drug classes — renin–angiotensin system inhibitors (including angiotensin receptor–neprilysin inhibitors), evidence-based beta-blockers, mineralocorticoid receptor antagonists, and sodium–glucose cotransporter-2 inhibitors — followed by symptom-directed agents such as loop diuretics, digoxin, ivabradine, and vericiguat. Special attention is given to heart failure with preserved ejection fraction, comorbidity-driven choices, and the practical challenge of up-titration and adherence. Collectively, modern combination therapy has transformed heart failure from an inexorably fatal condition into a chronic disease in which survival and quality of life can be meaningfully improved.

Keywords: Heart failure; guideline-directed medical therapy; HFrEF; ACE inhibitors; beta-blockers; mineralocorticoid receptor antagonists; SGLT2 inhibitors.

1. Introduction

Ask any cardiologist what has changed most in heart failure care over the last thirty years and the answer rarely concerns a single miracle drug. Instead, the transformation has been cumulative: a steady accumulation of randomized evidence showing that carefully chosen combinations of ordinary medicines, started early and pushed to target doses, can halve the risk of death and hospitalization in selected patients. Heart failure is not a single disease but a clinical syndrome in which the heart is unable to pump or fill sufficiently to meet the body's needs. Its burden is enormous. In the United States alone, more than six million adults live with the condition, and despite declining age-adjusted mortality, the absolute number of cases continues to rise as populations age and more people survive myocardial infarction [1].

The syndrome is conventionally divided by left ventricular ejection fraction (LVEF) into heart failure with reduced ejection fraction (HFrEF, $LVEF \leq 40\%$), mildly reduced ejection fraction (HFmrEF), and preserved ejection fraction (HFpEF, $LVEF \geq 50\%$) [1,2]. This distinction matters therapeutically: nearly all mortality-reducing therapy has been established in HFrEF, whereas treatment of HFpEF remains largely centred on comorbidity management, symptom relief, and — more recently — sodium–glucose cotransporter-2 (SGLT2) inhibition. The purpose of this review is to walk through the pharmacological armamentarium in a clinically grounded way, explaining not only which drugs are recommended but why they work, how they are used in practice, and where their limits lie.

2. The Pathophysiological Rationale for Drug Therapy

A failing ventricle sets in motion a chain of compensatory responses that are initially life-preserving but ultimately self-destructive. Reduced cardiac output lowers renal perfusion, which triggers renin release from the juxtaglomerular apparatus. Renin cleaves angiotensinogen to angiotensin I, which is converted by angiotensin-converting enzyme (ACE), predominantly in the pulmonary circulation, into angiotensin II — a potent vasoconstrictor that also stimulates aldosterone secretion, sodium and water retention, sympathetic activation, and pathological myocardial remodelling (Figure 1). In parallel, baroreceptor unloading drives sympathetic nervous system activation, raising heart rate and contractility at the cost of myocyte calcium overload, apoptosis, and arrhythmogenicity. Natriuretic peptides, released in response to wall stretch, are the body's counter-regulatory signal, promoting natriuresis, vasodilation, and anti-fibrotic effects — but in chronic heart failure this brake is

overwhelmed and, in the case of neprilysin-degraded peptides, metabolically short-lived.

Virtually every drug class that improves survival in HFrEF interrupts one or more arms of this neurohormonal cascade (Figure 2). Understanding this biology explains two otherwise puzzling clinical observations: first, drugs that are negatively inotropic or that lower blood pressure in the short term (beta-blockers, ACE inhibitors) nonetheless prolong life; and second, drugs that acutely relieve congestion (loop diuretics) improve symptoms dramatically but, used alone, do not modify the disease's lethal trajectory.

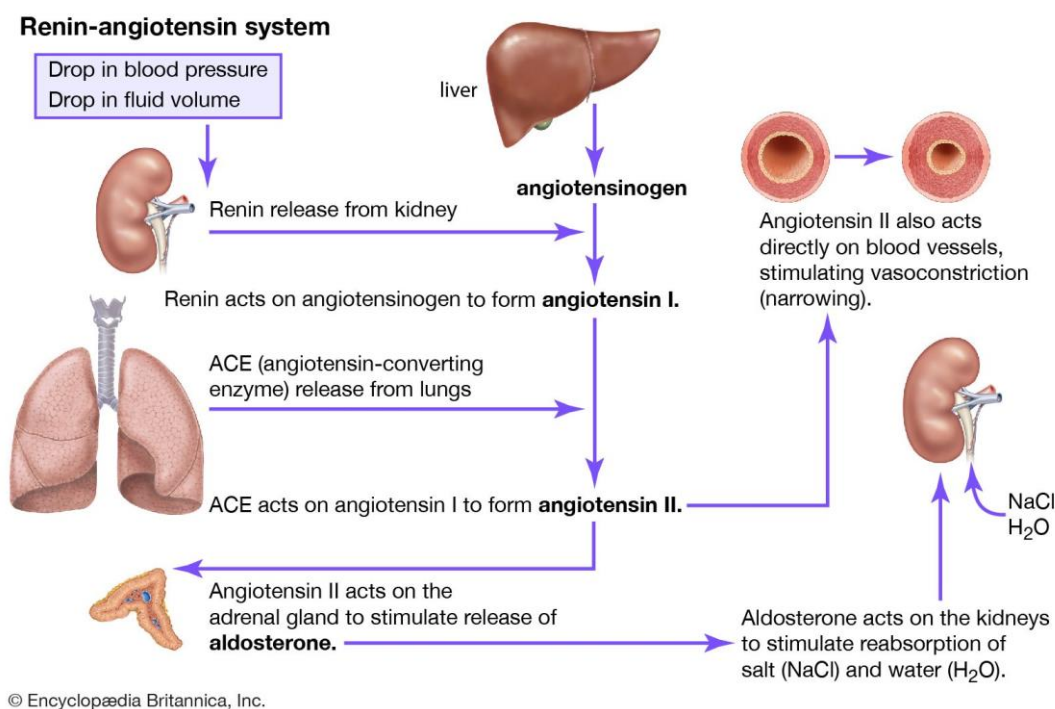


Figure 1. The renin–angiotensin–aldosterone system: the central therapeutic target in heart failure. (Image source: Encyclopaedia Britannica, britannica.com)

Left Heart Failure: Pathophysiology (Neurohormonal Activation)

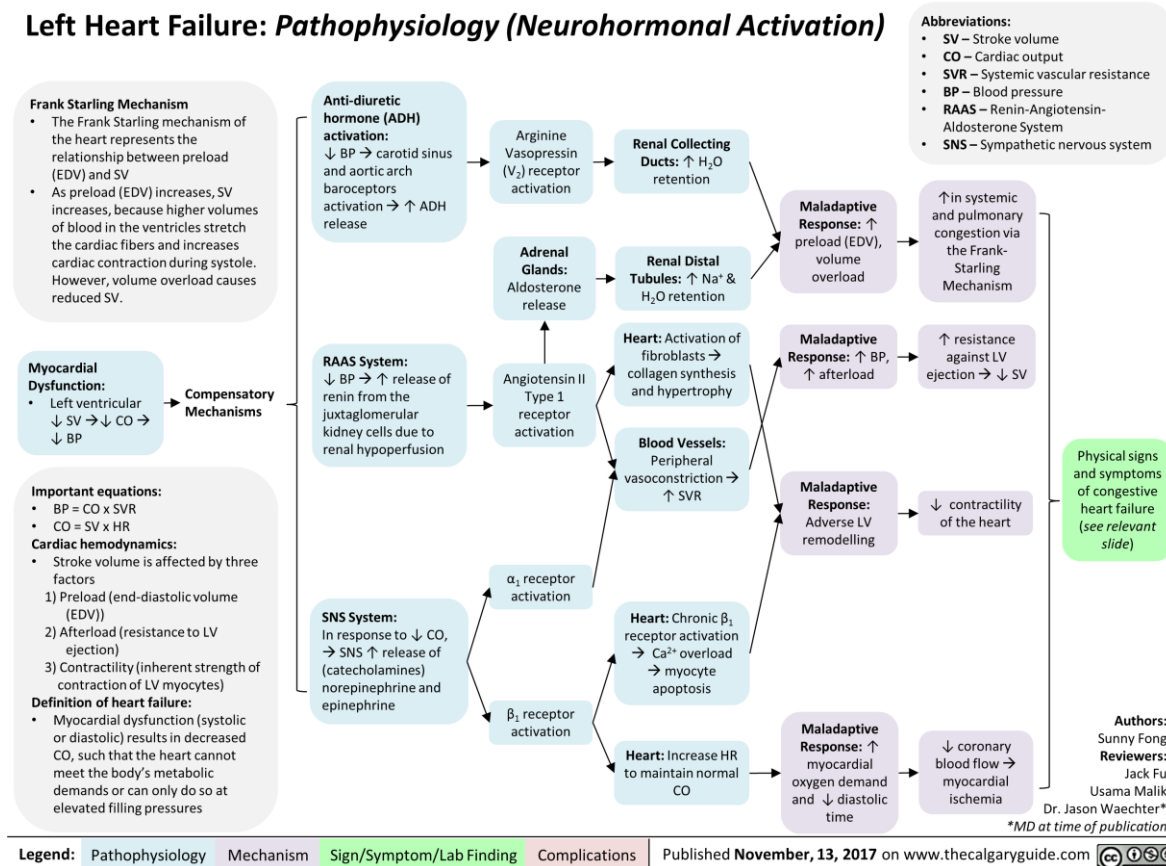


Figure 2. Neurohormonal activation and maladaptive responses in left heart failure. (Image source: Calgary Guide, University of Calgary)

3. Inhibition of the Renin–Angiotensin–Aldosterone Axis

3.1 ACE inhibitors and ARBs

ACE inhibitors were the first drug class to prove that heart failure mortality could be reduced by neurohormonal blockade. In the landmark CONSENSUS trial, enalapril reduced one-year mortality from 52% to 36% in patients with severe heart failure [3]; the SOLVD treatment trial extended this benefit to mild-to-moderate disease, demonstrating a 16% relative reduction in mortality alongside fewer hospitalizations [4]. Angiotensin receptor blockers (ARBs) such as losartan and valsartan offer an alternative for patients who develop intolerable cough or angioedema on ACE inhibitors, with valsartan shown to be non-inferior in the Val-HeFT and CHARM-Alternative populations [1]. Because both classes cause vasodilation of the efferent arteriole, clinicians must anticipate an expected rise in serum creatinine at initiation;

an increase of up to 30% from baseline is generally acceptable, provided potassium remains below 5.5 mmol/L.

3.2 Angiotensin receptor–neprilysin inhibition (ARNI)

Sacubitril/valsartan, the first-in-class ARNI, pairs valsartan with a neprilysin inhibitor that slows the degradation of natriuretic peptides, bradykinin, and other vasoactive peptides. In PARADIGM-HF, sacubitril/valsartan reduced the composite of cardiovascular death or heart failure hospitalization by 20% relative to enalapril and cut cardiovascular mortality by 20% — arguably the single most important drug trial in modern heart failure care [10]. Current guidelines therefore recommend substitution of an ARNI for an ACE inhibitor or ARB in symptomatic HFrEF patients who remain stable, with a mandatory 36-hour washout after ACE inhibitor use to avoid angioedema from bradykinin accumulation [1].

4. Beta-Adrenergic Receptor Blockade

Blocking the sympathetic nervous system in a failing heart seemed counterintuitive when first proposed. Yet three landmark trials — CIBIS-II (bisoprolol), MERIT-HF (metoprolol succinate), and the carvedilol program — established that beta-blockers reduce all-cause mortality by roughly one third in stable HFrEF [5–7]. Only three agents carry this evidence base: carvedilol, metoprolol succinate (the extended-release formulation, not tartrate), and bisoprolol. The practical art lies in initiation: start low, go slow. Patients are typically begun on one-eighth to one-quarter of the target dose and up-titrated at two-week intervals as tolerated, with transient fatigue and fluid retention being the most common obstacles. Crucially, beta-blockers should not be started — or dose-escalated — during frank decompensation; a common mistake is discontinuing the drug during a flare, when in fact it should merely be held or reduced and then re-established once euvolemia returns.

5. Mineralocorticoid Receptor Antagonists

Aldosterone escapes chronic ACE inhibition and drives sodium retention, myocardial fibrosis, and potassium wasting. Spironolactone proved its lethality in RALES, where it reduced mortality by 30% in patients with severe HFrEF already on standard therapy [8]; eplerenone extended the benefit to post-infarction and mildly symptomatic patients in EPHESUS and EMPHASIS-HF respectively [9]. The price of this protection is hyperkalemia, which is common enough that contemporary practice increasingly uses potassium binders such as patiromer to keep patients on therapy. Gynecomastia, a class

nuisance of spironolactone, usually resolves on switching to the more selective eplerenone. Renal function and electrolytes should be checked within one to two weeks of initiation or dose change, then periodically thereafter.

6. Sodium–Glucose Cotransporter-2 Inhibitors: From Diabetes to Heart Failure

Few chapters in cardiovascular medicine are as remarkable as the repurposing of SGLT2 inhibitors. Developed as oral hypoglycemics, dapagliflozin and empagliflozin were found to reduce heart failure hospitalizations in diabetic populations, prompting dedicated heart failure trials. DAPA-HF showed that dapagliflozin reduced cardiovascular death or worsening heart failure by 26% in HFrEF patients regardless of diabetes status [11]; EMPEROR-Reduced confirmed the class effect with empagliflozin [12]. The mechanism appears multifactorial — osmotic diuresis, improved tubuloglomerular feedback, reduced preload and afterload, and possibly favourable metabolic and anti-inflammatory effects — rather than simply glucose lowering. Two observations cemented their place in therapy: benefit is consistent across the ejection fraction spectrum (including HFpEF, as shown in DELIVER [17]), and side effects are comparatively benign, limited mainly to genital mycotic infections and rare euglycemic ketoacidosis [2,11,12]. Guidelines now position SGLT2 inhibitors as a core component of the 'four pillars' of HFrEF therapy, safe to start even in patients with relatively low blood pressure [1].

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HEART FAILURE GUIDELINE-DIRECTED MEDICAL THERAPY (GDMT)

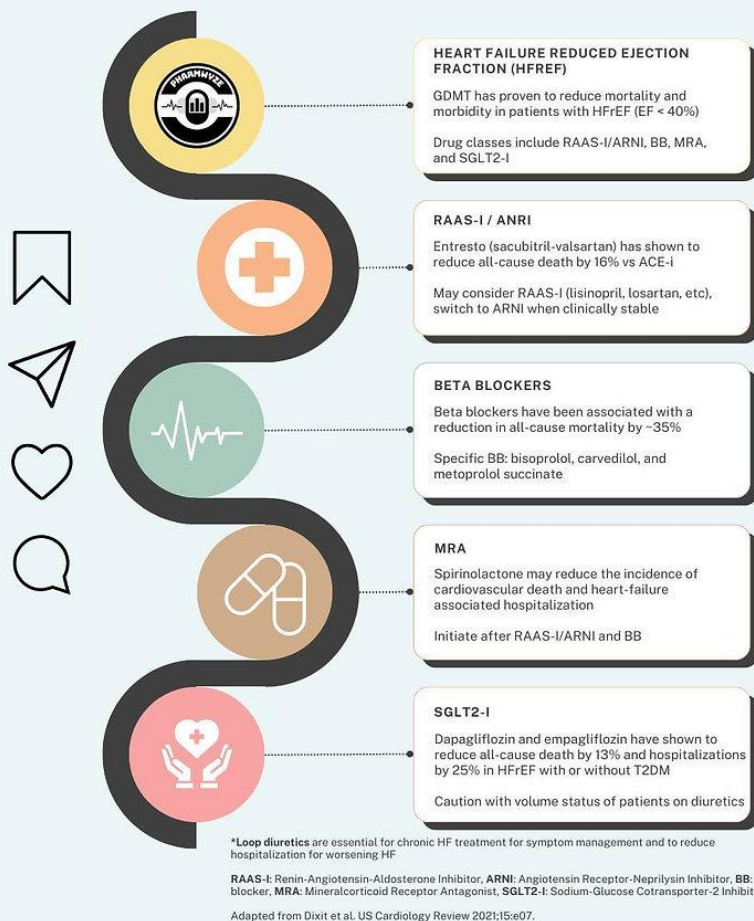


Figure 3. Summary of guideline-directed medical therapy for heart failure with reduced ejection fraction. (Image source: pharmwyz.com, adapted from US Cardiology Review)

7. Symptom-Directed and Adjunctive Pharmacotherapy

7.1 Loop diuretics

Furosemide, bumetanide, and torsemide remain the workhorses for congestion. They relieve dyspnoea and oedema rapidly and remain essential during decompensation, but no trial has shown they improve survival when used alone. The therapeutic targets are clinical — resolution of jugular venous pressure, orthopnoea, and peripheral oedema — rather than a fixed dose. Over-diuresis provokes prerenal azotemia and electrolyte derangements; under-diuresis leaves the patient in a vicious cycle of recurrent

admission. Torsemide's reliable bioavailability makes it attractive when furosemide response is erratic, a strategy formally compared in the TRANSFORM-HF trial.

7.2 Digoxin and ivabradine

Digoxin, the oldest cardiac drug still in use, reduces heart failure hospitalization without affecting mortality, as the Digitalis Investigation Group showed [15]. Its narrow therapeutic index demands vigilance for toxicity — nausea, visual changes, and arrhythmia — particularly in renal impairment and hypokalemia. Ivabradine offers a more modern, mechanistically elegant option: selective inhibition of the sinoatrial If current slows heart rate without negative inotropy. In SHIFT, ivabradine reduced cardiovascular death or hospitalization in patients in sinus rhythm with a resting rate ≥ 70 beats per minute despite maximally tolerated beta-blockade [14].

7.3 Vericiguat and vasodilators

Vericiguat, an oral soluble guanylate cyclase stimulator, reduced the composite of cardiovascular death or hospitalization by 10% in the high-risk, recently decompensated VICTORIA population [13], filling a niche for patients who deteriorate despite the four pillars. Hydralazine–isosorbide dinitrate retains a specific evidence base in self-identified Black patients with symptomatic HFrEF (A-HeFT) and in those intolerant of RAAS blockade. Intravenous inotropes — milrinone, dobutamine, levosimendan — are reserved for cardiogenic shock or palliation, since they worsen long-term outcomes when used chronically.

8. Comparative Overview of Major Drug Classes

Table 1 summarizes the principal pharmacological classes used in chronic heart failure, their mechanisms, evidence of outcome benefit, and key monitoring requirements.

Drug class	Representative agents	Principal mechanism	Outcome evidence	Key adverse effects / monitoring
ACE inhibitors	Enalapril, lisinopril, ramipril	Block conversion of angiotensin I to II; reduce vasoconstriction	Reduced mortality and hospitalization (CONSENSUS, SOLVD)	Cough, angioedema, hyperkalemia, creatinine rise

		n and aldosterone		
ARBs	Losartan, valsartan, candesartan	Block angiotensin II type-1 receptor	Mortality/morbidity benefit; alternative to ACEi (CHARM-Alternative)	Hyperkalemia, hypotension, renal dysfunction
ARNI	Sacubitril/valsartan	AT1 blockade plus neprilysin inhibition, raising natriuretic peptides	Superior to enalapril; 20% CV death reduction (PARADIGM-HF)	Angioedema (washout after ACEi), hypotension
Beta-blockers	Carvedilol, metoprolol succinate, bisoprolol	Antagonize chronic sympathetic activation; anti-arrhythmic, anti-remodelling	~35% mortality reduction (CIBIS-II, MERIT-HF, COPERNICUS)	Bradycardia, fatigue, fluid retention; start low, go slow
MRA	Spironolactone, eplerenone	Aldosterone blockade; antifibrotic, potassium-sparing	30% mortality reduction in severe HFrEF (RALES); benefit across severity (EMPHASIS-HF)	Hyperkalemia, renal impairment; gynecomastia (spironolactone)
SGLT2 inhibitors	Dapagliflozin, empagliflozin	Glucosuric diuresis, improved tubuloglomerular feedback, metabolic effects	26% reduction CV death/HF hosp. (DAPA-HF); class effect (EMPEROR-Reduced); benefit in HFpEF (DELIVER)	Genital mycotic infection, rare euglycemic ketoacidosis; minimal BP effect

Loop diuretics	Furosemide, torsemide, bumetanide	Inhibit Na-K-2Cl cotransporter in ascending limb; reduce preload	Symptom relief only; no proven mortality benefit	Electrolyte loss, prerenal azotemia, ototoxicity at high dose
Ivabradine	Ivabradine	Selective If channel inhibition; slows sinus rate	Reduced CV death/HF hosp. in sinus rhythm ≥ 70 bpm (SHIFT)	Bradycardia, visual phosphenes; only if sinus rhythm
Digoxin	Digoxin	Na/K-ATPase inhibition; positive inotropy; AV nodal slowing	Fewer HF hospitalizations, neutral mortality (DIG)	Narrow therapeutic index; toxicity worsened by hypokalemia, renal impairment
Vericiguat	Vericiguat	Soluble guanylate cyclase stimulator; cGMP-mediated vasodilation	10% reduction in CV death/HF hosp. after decompensation (VICTORIA)	Hypotension, anaemia; add-on for worsening HFrEF

Table 1. Overview of major pharmacological classes in chronic heart failure.

9. Heart Failure with Preserved Ejection Fraction and Special Populations

Pharmacotherapy for HFpEF tells a humbler story. Aldosterone antagonism showed benefit in a pooled, older analysis (TOPCAT) in selected subgroups, and ARNI and ARB trials yielded neutral composite endpoints. The genuine breakthrough came with SGLT2 inhibitors: DELIVER demonstrated that dapagliflozin reduced cardiovascular death or worsening heart failure across the full LVEF spectrum, including patients above 60% [17]. Otherwise, treatment centres on blood pressure control, rhythm management of atrial fibrillation, diuretics for congestion, and treatment of diabetes, obesity, and sleep apnoea. In right-sided failure and pulmonary hypertension, vasodilator therapy requires caution; in advanced renal disease, RAAS blockers and

MRAs must be dosed judiciously; and in pregnancy, ACE inhibitors, ARBs, and ARNIs are strictly contraindicated. Iron deficiency deserves mention as a therapeutic target in its own right — intravenous ferric carboxymaltose improved symptoms and reduced hospitalizations in AFFIRM-AHF [16] — and is now routinely screened for in guideline follow-up.

10. Landmark Randomized Trials in Heart Failure Pharmacotherapy

Trial (year)	Agent / class	Population	Principal result
CONSENSUS (1987)	Enalapril (ACEi)	Severe HFrEF	40% reduction in 6-month mortality; established neurohormonal blockade
SOLVD-Treatment (1991)	Enalapril (ACEi)	Mild–moderate HFrEF	16% reduction in mortality; fewer HF hospitalizations
RALES (1999)	Spironolactone (MRA)	Severe HFrEF	30% reduction in mortality on background therapy
CIBIS-II (1999)	Bisoprolol (BB)	Moderate–severe HFrEF	34% reduction in mortality; trial stopped early for benefit
MERIT-HF (1999)	Metoprolol succinate (BB)	Mild–severe HFrEF	34% reduction in mortality
PARADIGM-HF (2014)	Sacubitril/valsartan (ARNI)	Symptomatic HFrEF	20% reduction in CV death or HF hospitalization vs. enalapril
DAPA-HF (2019)	Dapagliflozin (SGLT2i)	HFrEF, ± diabetes	26% reduction in CV death or worsening HF

			regardless of diabetes
EMPEROR-Reduced (2020)	Empagliflozin (SGLT2i)	HFrEF	25% reduction in CV death or HF hospitalization
VICTORIA (2020)	Vericiguat (sGC stimulator)	Recently decompensated HFrEF	10% reduction in CV death or HF hospitalization
DELIVER (2022)	Dapagliflozin (SGLT2i)	HF with LVEF > 40%	18% reduction in CV death or worsening HF

Table 2. Selected randomized controlled trials that shaped guideline-directed medical therapy.

11. Putting It Together: Sequencing, Monitoring, and Adherence

Guidelines now frame HFrEF treatment around the four pillars initiated rapidly and concurrently — or in quick sequence — rather than the older, leisurely 'one drug at a time' escalation. SGLT2 inhibitors are particularly attractive first-line agents because they are well tolerated and require little up-titration, while ARNI, beta-blockers, and MRAs are titrated toward target doses derived from the trials that proved their benefit. Real-world data remain sobering: in many registries, fewer than a quarter of eligible patients receive all four pillars at any meaningful dose, and even fewer reach target doses. Blood pressure, renal function, electrolytes, and clinical congestion should be reassessed at every step. Patient education matters as much as prescription — daily weights, salt moderation, and recognition of early congestion empower patients to avert admissions. Multidisciplinary heart failure clinics, telemonitoring, and pharmacist-led titration programs consistently demonstrate improved GDMT uptake and outcomes.

12. Emerging Directions

The pipeline remains active. Omecamtiv mecarbil, a selective cardiac myosin activator, increased systolic ejection time and reduced hospitalizations in GALACTIC-HF without a mortality signal, and may yet find a role in highly selected patients. Gene and cell therapies targeting the cardiac cytoskeleton, novel non-steroidal MRAs with a kinder potassium profile (finerenone is under study in heart failure), and RNA-targeted approaches to transthyretin amyloidosis are reshaping what 'heart failure pharmacotherapy' will mean in the coming decade. Perhaps the greatest unrealized

gain, however, is not molecular but logistical: closing the implementation gap between what trials have proven and what patients actually receive.

13. Conclusion

Pharmacotherapy has turned heart failure into a condition in which evidence-based combination treatment can transform prognosis. The modern paradigm — ARNI (or ACE inhibitor/ARB), an evidence-based beta-blocker, a mineralocorticoid receptor antagonist, and an SGLT2 inhibitor, layered on symptom-directed diuretics and individualized adjuncts — attacks the neurohormonal vicious cycle at several levels simultaneously. Success depends less on novelty than on execution: early initiation, courageous up-titration, vigilant monitoring of renal function and potassium, and relentless attention to adherence. For clinicians willing to apply the evidence fully, and for health systems willing to support them, the tools to change the natural history of heart failure already exist.

References

1. Heidenreich PA, Bozkurt B, Aguilar D, et al. 2022 AHA/ACC/HFSA guideline for the management of heart failure. *Circulation*. 2022;145(18):e895–e1032.
2. McDonagh TA, Metra M, Adamo M, et al. 2021 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J*. 2021;42(36):3599–3726.
3. The CONSENSUS Trial Study Group. Effects of enalapril on mortality in severe congestive heart failure: results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). *N Engl J Med*. 1987;316(23):1429–1435.
4. The SOLVD Investigators. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. *N Engl J Med*. 1991;325(5):293–302.
5. The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II) Investigators. The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): a randomised trial. *Lancet*. 1999;353(9146):9–13.
6. Packer M, Bristow MR, Cohn JN, et al. The effect of carvedilol on morbidity and mortality in patients with chronic heart failure. *N Engl J Med*. 1996;334(21):1349–1355.

7. 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):2001–2007.
8. Pitt B, Zannad F, Remme WJ, et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. *N Engl J Med*. 1999;341(10):709–717.
9. Zannad F, McMurray JJV, Krum H, et al. Eplerenone in patients with systolic heart failure and mild symptoms. *N Engl J Med*. 2011;364(1):11–21.
10. McMurray JJV, Packer M, Desai AS, et al. Angiotensin–neprilysin inhibition versus enalapril in heart failure. *N Engl J Med*. 2014;371(11):993–1004.
11. McMurray JJV, Solomon SD, Inzucchi SE, et al. Dapagliflozin in patients with heart failure and reduced ejection fraction. *N Engl J Med*. 2019;381(21):1995–2008.
12. Packer M, Anker SD, Butler J, et al. Cardiovascular and renal outcomes with empagliflozin in heart failure. *N Engl J Med*. 2020;383(15):1413–1424.
13. Armstrong PW, Pieske B, Anstrom KJ, et al. Vericiguat in patients with heart failure and reduced ejection fraction. *N Engl J Med*. 2020;382(20):1883–1893.
14. Swedberg K, Komajda M, Böhm M, et al. Ivabradine and outcomes in chronic heart failure (SHIFT): a randomised placebo-controlled study. *Lancet*. 2010;376(9744):875–885.
15. Digitalis Investigation Group. The effect of digoxin on mortality and morbidity in patients with heart failure. *N Engl J Med*. 1997;336(8):525–533.
16. Anker SD, Comin Colet J, Filippatos G, et al. Ferric carboxymaltose for iron deficiency after acute heart failure: the AFFIRM-AHF randomised clinical trial. *Lancet*. 2021;396(10266):1895–1904.
17. Solomon SD, McMurray JJV, Claggett B, et al. Dapagliflozin in heart failure with mildly reduced or preserved ejection fraction. *N Engl J Med*. 2022;387(12):1089–1098.