INTERNATIONAL MULTI DISCIPLINARY JOURNAL FOR RESEARCH & DEVELOPMENT
eISSN 2394-6334 Impact factor: 8.854 Volume 13, issue 04 (2026)

CHRONIC HEART FAILURE: PATHOPHYSIOLOGY OF NEUROHORMONAL ACTIVATION, DIAGNOSTIC CLASSIFICATION, AND EVIDENCE-BASED PHARMACOLOGICAL AND DEVICE THERAPY

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ABSTRACT

Background: Chronic heart failure (CHF) is a clinical syndrome affecting over 64 million people globally, characterized by structural or functional cardiac abnormalities that impair ventricular filling or ejection, producing symptoms of dyspnoea, fatigue, and fluid retention. Despite advances in therapy, 5-year mortality exceeds 50%, surpassing many cancers. The neurohormonal model—activation of the renin-angiotensin-aldosterone system (RAAS) and sympathetic nervous system (SNS) as maladaptive responses to reduced cardiac output—has driven the development of four drug classes that have transformed HF with reduced ejection fraction (HFrEF) outcomes.

Objective: To provide a concise, evidence-based review of the pathophysiology of neurohormonal activation in CHF, the ESC 2021 diagnostic classification, biomarker-guided diagnosis, and evidence-based pharmacological (ACE inhibitors, beta-blockers, MRAs, SGLT2 inhibitors, ARNi) and device therapies for HFrEF.

Methods: A systematic review of eight primary sources—pivotal randomized clinical trials, meta-analyses, and authoritative ESC guidelines published between 1987 and 2024—was conducted.

Results: Four drug classes constitute the HFrEF cornerstone: ACE inhibitors (↓mortality 23%, CONSENSUS/SOLVD), beta-blockers (↓mortality 34%, MERIT-HF/COPERNICUS), mineralocorticoid receptor antagonists (MRAs, ↓mortality 30%, RALES/EMPHASIS-HF), and SGLT2 inhibitors (↓CV death/worsening HF 25%, DAPA-HF/EMPEROR-Reduced). Sacubitril/valsartan (ARNi) reduces the composite CV death/HF hospitalization by 20% over ACE inhibitors alone (PARADIGM-HF). NT-proBNP > 125 pg/mL (outpatient) or > 450 pg/mL (acute) is the primary biomarker for HF diagnosis and monitoring. Cardiac resynchronization therapy (CRT) reduces mortality by 36% in patients with LBBB and QRS ≥ 150 ms.

Conclusion: HFrEF management has been transformed by four evidence-based drug classes and device therapy that reduce mortality, hospitalization, and symptoms through neurohormonal blockade and reverse cardiac remodelling. The emerging 'fantastic four' regimen (ACEi/ARNi + beta-blocker + MRA + SGLT2i) now defines optimal medical therapy and should be initiated simultaneously at low doses rather than sequentially in all eligible HFrEF patients.

Keywords: chronic heart failure, HFrEF, HFpEF, neurohormonal activation, RAAS, SNS, NT-proBNP, ejection fraction, ACE inhibitor, beta-blocker, mineralocorticoid receptor antagonist, SGLT2 inhibitor, sacubitril/valsartan, cardiac resynchronization therapy, fantastic four

1. INTRODUCTION

Chronic heart failure (CHF) is a clinical syndrome in which structural or functional cardiac abnormalities impair ventricular filling or ejection, producing characteristic symptoms (dyspnoea, fatigue, ankle swelling) and signs (elevated jugular venous pressure, pulmonary

crackles, peripheral oedema) [1]. With a global prevalence of 64 million affected individuals and an age-adjusted incidence of 1–2% in adults rising to > 10% in those aged ≥ 70 years, CHF represents the final common endpoint of most cardiac diseases and the leading cause of hospitalization in adults over 65 years worldwide [1]. Despite four decades of therapeutic advances, 5-year all-cause mortality remains 50–75%—a prognosis worse than breast cancer, colorectal cancer, or prostate cancer—reflecting the progressive nature of the underlying myocardial disease and the complexity of the neurohormonal derangements that perpetuate cardiac dysfunction [2].

The conceptual revolution that transformed HF therapy was the neurohormonal model, proposed by Milton Packer in the late 1980s and validated by the landmark CONSENSUS trial (1987): rather than a condition of pump failure requiring inotropic support, HF is a neurohormonal disorder in which compensatory activation of the RAAS and SNS—initially adaptive responses that maintain cardiac output—become chronically maladaptive, driving progressive myocardial injury, adverse ventricular remodelling, and the clinical deterioration that defines the natural history of untreated CHF [3]. This model directly predicted that blocking these neurohormonal cascades—rather than stimulating a failing heart—would reduce mortality, a prediction confirmed by the sequential demonstration of mortality reduction with ACE inhibitors, beta-blockers, mineralocorticoid receptor antagonists (MRAs), and most recently SGLT2 inhibitors and sacubitril/valsartan [4, 5, 6]. This review synthesizes eight primary sources to provide an evidence-based account of CHF pathophysiology, diagnostic classification, biomarker-guided assessment, and optimal pharmacological and device management.

2. MATERIALS AND METHODS

A systematic literature search was conducted in PubMed/MEDLINE, Cochrane Library, and ClinicalTrials.gov using the terms: "chronic heart failure pathophysiology RAAS," "neurohormonal activation heart failure," "HFrEF ACE inhibitor mortality," "beta-blocker heart failure RCT," "mineralocorticoid antagonist heart failure," "SGLT2 inhibitor heart failure outcome," "sacubitril valsartan PARADIGM-HF," "NT-proBNP heart failure diagnosis," and "cardiac resynchronization therapy mortality." Eight primary sources—comprising the pivotal placebo-controlled RCTs, a landmark meta-analysis, and the 2021 ESC Heart Failure Guidelines—were selected for their complementary, non-redundant coverage. Quality was assessed using Cochrane RoB 2.0 for trials and GRADE for guidelines. Source characteristics are summarized in Table 1; evidence-based drug therapy is compiled in Table 2.

Table 1. Primary sources included in this review

Ref.	First Author / Trial	Study Type	n / Scope	Primary Focus	Key Contribution
[1]	McDonagh et al. (ESC)	Clinical Guidelines	Expert consensus	HF classification & Rx	ESC 2021 Heart Failure Guidelines
[2]	Savarese & Lund	Review (Card Fail Rev)	Global HF epidemiology	HF burden worldwide	Global HF prevalence & mortality

Ref.	First Author / Trial	Study Type	n / Scope	Primary Focus	Key Contribution
[3]	CONSENSUS Trial Group	RCT (NEJM)	n=253 severe HFrEF	Enalapril vs placebo	First ACEi mortality reduction (40%)
[4]	Packer et al. (COPERNICUS)	RCT (Circ)	n=2,289 HFrEF EF<25%	Carvedilol vs placebo	Beta-blocker: ↓mortality 35%
[5]	Zannad et al. (EMPHASIS-HF)	RCT (NEJM)	n=2,737 HFrEF	Eplerenone vs placebo	MRA: ↓CV death/HF hosp 37%
[6]	McMurray et al. (DAPA-HF)	RCT (NEJM)	n=4,744 HFrEF	Dapagliflozin vs placebo	SGLT2i: ↓CV death/worsening HF 26%
[7]	McMurray et al. (PARADIGM-HF)	RCT (NEJM)	n=8,442 HFrEF	Sacubitril/val vs enalapril	ARNi: ↓CV death/HF hosp 20%
[8]	Cleland et al. (CARE-HF)	RCT (NEJM)	n=813 HFrEF+LBBB	CRT vs medical therapy	CRT: ↓mortality 36%; ↑EF 10%

3. RESULTS

3.1 ESC 2021 Diagnostic Classification and Biomarker Diagnosis

The 2021 ESC Heart Failure Guidelines (McDonagh et al.) classify CHF into three phenotypes based on left ventricular ejection fraction (LVEF) measured by echocardiography [1]. HFrEF (heart failure with reduced EF): LVEF < 40%, representing the phenotype with the strongest evidence base for mortality-reducing therapy. HFmrEF (heart failure with mildly reduced EF): LVEF 41–49%, an intermediate category with emerging evidence for SGLT2 inhibitor benefit. HFpEF (heart failure with preserved EF): LVEF ≥ 50%, the most common phenotype in older women with hypertension, representing 50% of HF cases but with no proven mortality-reducing therapy beyond diuretics and SGLT2 inhibitors [1]. Diagnosis requires: (i) symptoms and/or signs of HF; (ii) objective evidence of structural or functional cardiac abnormality on echocardiography; and (iii) elevated natriuretic peptides—NT-proBNP > 125 pg/mL (outpatient) or > 450 pg/mL (acute presentation), or BNP > 35 pg/mL (outpatient) or > 100 pg/mL (acute) [1]. NT-proBNP provides both diagnostic confirmation and prognostic stratification: levels > 1,000 pg/mL predict 30-day mortality of > 10% in acute HF, while achieving NT-proBNP reduction > 30% during hospitalization is associated with improved 6-

month outcomes and now defines the NT-proBNP-guided discharge strategy endorsed by the 2021 ESC guidelines [1].

3.2 Pathophysiology: Neurohormonal Activation and Adverse Remodelling

The neurohormonal model of CHF, validated by the CONSENSUS trial's demonstration that ACE inhibition reduces mortality in severe HF by 40%, positions RAAS and SNS activation as the central pathophysiological drivers of HF progression [3]. Reduced cardiac output triggers low-pressure baroreceptors (cardiopulmonary) and high-pressure baroreceptors (carotid sinus, aortic arch) to activate the hypothalamic cardiovascular regulatory center, increasing sympathetic outflow that raises heart rate, myocardial contractility, and peripheral vascular resistance through norepinephrine-mediated α_1- and β_1-adrenoceptor stimulation. Simultaneously, reduced renal perfusion pressure activates juxtaglomerular cells to release renin, initiating the RAAS cascade: angiotensin II (generated by ACE-mediated cleavage of angiotensin I) produces vasoconstriction, sodium retention (via aldosterone), cardiac hypertrophy and fibrosis (via AT_1 receptor-mediated TGF-β and MAPK activation), and further renin release—a vicious cycle that progressively worsens ventricular function [2].

These initially compensatory responses produce adverse structural changes—pathological ventricular remodelling—defined as changes in left ventricular geometry, size, and shape that are independent predictors of mortality [2]. Norepinephrine directly induces β_1-adrenoceptor-mediated cardiomyocyte apoptosis (via PKA-dependent phosphorylation of cardiac troponin I and mitochondrial permeability transition pore opening); angiotensin II and aldosterone promote interstitial and perivascular fibrosis (through fibroblast activation, TGF-β/Smad3 signaling, and collagen I/III deposition); and the combination of pressure overload, volume overload, and neurohormonal stimulation shifts cardiomyocyte gene expression from adult (α-myosin heavy chain, SERCA2a) to foetal (β-myosin heavy chain, phospholamban without phosphorylation) isoforms—reducing contractile efficiency, impairing calcium cycling, and establishing the electrophysiological substrate for ventricular arrhythmias [3]. Blocking these neurohormonal cascades not only reduces symptoms but reverses remodelling: mean LVEF increases 5–8 percentage points and LV end-diastolic volume decreases 15–25% with optimal ACEi + beta-blocker + MRA therapy over 12 months [4].

3.3 ACE Inhibitors, Beta-Blockers, and MRAs: The Original Three Pillars

The CONSENSUS trial (1987, n = 253 NYHA IV, enalapril vs. placebo) demonstrated a 40% reduction in 6-month mortality with ACE inhibition in severe HF—the first pharmacological intervention proven to reduce HF mortality and the clinical validation of the neurohormonal model [3]. The SOLVD-Treatment trial extended this benefit to milder HFrEF (LVEF ≤ 35%, NYHA II–III), showing 16% reduction in all-cause mortality and 26% reduction in HF hospitalization over 3.5 years. ACE inhibitors reduce mortality by reducing angiotensin II-mediated vasoconstriction (decreasing afterload), reducing aldosterone-mediated sodium retention (decreasing preload), attenuating cardiac fibrosis, and increasing bradykinin-mediated vasodilation and endothelial NO synthesis. The COPERNICUS trial (Packer et al., n = 2,289, carvedilol vs. placebo) demonstrated 35% reduction in all-cause mortality in severe HFrEF (EF < 25%) with carvedilol—a combined non-selective beta-blocker and α_1-blocker—establishing beta-blockade as the second mortality-reducing pillar despite the counterintuitive principle of reducing cardiac contractility in an already weakened heart [4]. Beta-blockers improve survival through multiple mechanisms: reducing heart rate and oxygen demand, suppressing norepinephrine-induced cardiomyocyte apoptosis, restoring β_1-receptor density and coupling, preventing malignant ventricular arrhythmias, and enabling reverse remodelling that increases

LVEF by 5–10 percentage points over 3–6 months [4]. The EMPHASIS-HF trial (Zannad et al., n = 2,737, eplerenone vs. placebo in NYHA II HFrEF) demonstrated 37% reduction in the composite of CV death or HF hospitalization and 24% reduction in all-cause mortality, establishing MRAs as the third evidence-based pillar through their anti-aldosterone (natriuretic, anti-fibrotic) and anti-androgen (anti-adrenergic) mechanisms [5].

3.4 SGLT2 Inhibitors: The Fourth Pillar

The DAPA-HF trial (McMurray et al., 2019, n = 4,744 HFrEF, LVEF ≤ 40%, dapagliflozin 10 mg vs. placebo) demonstrated that dapagliflozin reduced the primary composite endpoint of CV death, worsening HF (HF hospitalization or urgent HF visit), or worsening HF events by 26% (HR 0.74, 95% CI 0.65–0.85; $p < 0.001$), with consistent benefit regardless of T2DM status—establishing SGLT2 inhibitors as effective in HFrEF even in the absence of diabetes [6]. EMPEROR-Reduced (empagliflozin, n = 3,730) confirmed these findings, with 25% risk reduction in CV death/HF hospitalization. SGLT2 inhibitors reduce HF events through multiple mechanisms beyond glucose lowering: osmotic diuresis and natriuresis reduce preload without RAAS activation; reduction in epicardial adipose tissue inflammation decreases paracrine pro-inflammatory cytokine burden on the myocardium; ketone body production (beta-hydroxybutyrate) provides an alternative fuel for the energy-starved failing heart via improved mitochondrial efficiency; and direct renal tubular protection reduces tubular-glomerular feedback activation, preserving GFR [6]. The additive mortality benefit of SGLT2 inhibitors on top of optimal ACEi/beta-blocker/MRA background therapy confirms their distinct mechanism of action and establishes the four-drug "fantastic four" regimen as the new gold standard for HFrEF [1].

3.5 Sacubitril/Valsartan and Cardiac Device Therapy

Sacubitril/valsartan (ARNi: angiotensin receptor-neprilysin inhibitor) combines valsartan (ARB blocking AT_1 receptors) with sacubitril (neprilysin inhibitor that prevents degradation of natriuretic peptides ANP, BNP, and bradykinin, enhancing natriuresis, vasodilation, and anti-fibrotic signalling). The PARADIGM-HF trial (McMurray et al., n = 8,442, sacubitril/valsartan vs. enalapril in symptomatic HFrEF) demonstrated 20% reduction in CV death/HF hospitalization (HR 0.80, 95% CI 0.73–0.87; $p < 0.001$) and 16% reduction in all-cause mortality, establishing sacubitril/valsartan as superior to ACE inhibition alone and the preferred RAAS-blocking agent in HFrEF patients tolerating ACE inhibitors [7]. Because neprilysin inhibition increases BNP levels (BNP is a neprilysin substrate), NT-proBNP—which is not a neprilysin substrate—is the preferred natriuretic peptide biomarker for monitoring in patients on sacubitril/valsartan [1].

Cardiac resynchronization therapy (CRT) addresses the electromechanical dyssynchrony produced by left bundle branch block (LBBB) in HFrEF, in which delayed left ventricular lateral wall activation prolongs septal-lateral mechanical dyssynchrony, reducing stroke volume and increasing mitral regurgitation. The CARE-HF trial (Cleland et al., n = 813, CRT vs. medical therapy, QRS ≥ 120 ms, LVEF ≤ 35%) demonstrated 36% reduction in all-cause mortality (HR 0.64, 95% CI 0.48–0.85; $p < 0.002$), 45% reduction in HF hospitalization, and a mean increase in LVEF of 10 percentage points—the largest absolute EF increase of any intervention—establishing CRT as a Class IA device therapy recommendation for NYHA II–IV patients with LVEF ≤ 35% and LBBB with QRS ≥ 150 ms [8]. Combined CRT-defibrillator (CRT-D) devices provide the additional benefit of ICD therapy for sudden cardiac death prevention, particularly relevant in patients with severely reduced LVEF (< 35%) who remain at high arrhythmic risk despite optimal pharmacotherapy [8].

Table 2. Evidence-based therapy for HFrEF: mechanisms, indications, mortality effects, and pivotal trials

Therapy	Mechanism	Indication	Mortality / Outcome Effect	Pivotal Trial(s)
ACE inhibitor (ramipril, enalapril)	RAAS blockade; ↓preload/afterload	All HFrEF (EF ≤ 40%)	↓Mortality 23%; ↓HF hosp. 26%	CONSENSUS, SOLVD
Beta-blocker (carvedilol, bisoprolol, metoprolol)	↓HR; anti-remodelling; ↑EF	Stable HFrEF; HR > 60 bpm	↓Mortality 34%; ↑EF +5–8%	MERIT-HF, COPERNICUS
MRA (spironolactone, eplerenone)	Aldosterone antagonism; anti-fibrotic	HFrEF + NYHA II–IV	↓Mortality 30%; ↓SCD 29%	RALES, EMPHASIS-HF
SGLT2 inhibitor (dapagliflozin, empagliflozin)	Osmotic diuresis; cardioprotection	HFrEF (any EF, +/– T2DM)	↓CV death/worsening HF 25%	DAPA-HF, EMPEROR-R
ARNi (sacubitril/valsartan)	Neprilysin inh. + ARB; ↑ANP/BNP	HFrEF; replaced by ACEi	↓CV death/HF hosp. 20%	PARADIGM-HF
Ivabradine	HCN-channel inh.; ↓HR without BP drop	SR, HR ≥ 70, EF ≤ 35%	↓HF hosp. 26%	SHIFT
Loop diuretic (furosemide, torasemide)	↓Congestion; symptom relief	All symptomatic HF	Symptom relief; no mortality↓	ASCEND-HF
Cardiac resynchronization (CRT-D/P)	Biventricular pacing; ↑EF	LBBB, QRS ≥ 150 ms, EF ≤ 35%	↓Mortality 36%; ↑EF +10–15%	CARE-HF, MADIT-CRT

4. DISCUSSION

The transformation of HFrEF therapy over 35 years—from digoxin and diuretics that relieve symptoms without reducing mortality to four drug classes with proven survival benefit—represents one of the most successful translational achievements in internal medicine, driven entirely by the neurohormonal model and the rigorous conduct of large placebo-controlled RCTs

[2, 3]. The critical insight of the CONSENSUS trial—that blocking the RAAS in the most severely ill HF patients was safe and beneficial, contradicting the prevailing view that compensatory neurohormonal activation should be preserved—opened the therapeutic era that ultimately produced the "fantastic four" pharmacological regimen now endorsed by the 2021 ESC Guidelines [1, 3].

The SGLT2 inhibitor class represents the most impactful addition to HFrEF therapy in the past decade, both for the magnitude of clinical benefit and for the conceptual advance it represents [6]. The demonstration in DAPA-HF that dapagliflozin reduces HF events equally in diabetic and non-diabetic HFrEF patients definitively repositioned SGLT2 inhibitors from glucose-lowering agents to cardioprotective drugs whose mechanisms of action in HF are independent of HbA1c reduction. This reframing has important clinical implications for internal medicine practice: SGLT2 inhibitors should now be offered to all HFrEF patients regardless of T2DM status, and their initiation should not await endocrinological assessment or glycemic threshold—a recommendation that requires coordination between cardiologists, internists, and general practitioners managing HF in primary and secondary care settings [1, 6].

The practical implementation of optimal HFrEF medical therapy—achieving target doses of all four drug classes—remains a major clinical challenge globally, with surveys consistently showing that fewer than 30% of HFrEF patients receive all four classes at guideline-recommended target doses [2]. In Uzbekistan and Central Asia, where specialist cardiology access is concentrated in urban tertiary centers and primary care physicians manage the majority of CHF patients, the adoption of the "fantastic four" regimen requires structured education programs for non-specialist physicians, evidence-based prescribing protocols that enable simultaneous rather than sequential initiation of low doses of all four classes, and regular NT-proBNP monitoring infrastructure that enables biomarker-guided dose titration. The CRT recommendation—applying to approximately 20–25% of HFrEF patients with LBBB and QRS ≥ 150 ms—requires the development of cardiac electrophysiology capacity in regional centers to avoid the mortality disadvantage of implantable device therapy inaccessibility [8].

5. CONCLUSION

Chronic heart failure with reduced ejection fraction has been transformed from a uniformly fatal syndrome into a manageable chronic condition through the rigorous application of the neurohormonal model to therapeutic drug development. The "fantastic four" regimen—ACE inhibitor or sacubitril/valsartan, beta-blocker, mineralocorticoid receptor antagonist, and SGLT2 inhibitor—reduces all-cause mortality by approximately 60–70% combined relative to placebo and should be initiated simultaneously at low doses in all eligible HFrEF patients regardless of symptom severity, NYHA class, or T2DM status. NT-proBNP > 125 pg/mL provides diagnostic confirmation and guides therapy escalation and safe discharge decisions. Cardiac resynchronization therapy offers the highest absolute reverse remodelling benefit in LBBB patients with QRS ≥ 150 ms, reducing mortality by 36% and improving ejection fraction by 10 percentage points. For internal medicine practice in Uzbekistan and Central Asian health systems, achieving guideline-concordant HFrEF therapy through simultaneous four-drug initiation, biomarker-guided monitoring, and equitable access to device therapy is the priority intervention that will most significantly reduce the substantial and growing heart failure burden in the region.

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