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LITERATURE REVIEW: RECENT ADVANCES IN THE MANAGEMENT OF HEART FAILURE WITH REDUCED EJECTION FRACTION (HFREF)

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Introduction. Epidemiology and Burden of Disease. Heart failure with reduced ejection fraction (HFrEF), defined by a left ventricular ejection fraction (LVEF) $\leq 40\%$, is a complex clinical syndrome characterized by structural and functional cardiac impairment leading to inadequate tissue perfusion and congestion. In the United States, the prevalence has risen to 6.2 million adults (2.4% of the population), with projections estimating 8.5 million cases by 2030 due to aging demographics and improved survival from acute coronary syndromes (1,2). Globally, HFrEF contributes to 64.3 million heart failure cases, disproportionately affecting low- and middle-income countries where 80% of deaths occur (3).

Annual US hospitalizations exceed 1 million, accounting for 2.5% of all admissions and the leading discharge diagnosis in patients >65 years (4). Mortality remains formidable: 1-year all-cause mortality is 20-30%, escalating to 50-60% at 5 years—worse than most solid tumors except lung cancer (5). Readmission rates are 20-25% within 30 days and 50% within 6 months, driven by recurrent decompensation (6).

Economic and Quality-of-Life Impact. The economic toll is immense: 2025 estimates peg US direct medical costs at \$37.2 billion annually, with indirect costs (lost productivity, caregiving) adding \$22.5 billion (7). Per-patient lifetime costs exceed \$150,000, primarily from hospitalizations (\$15,000-20,000 per event) (8). Quality of life is profoundly impaired, with Kansas City Cardiomyopathy Questionnaire (KCCQ) scores averaging 45-55 in stable outpatients, comparable to advanced cancer (9). Neurocognitive decline affects 25-50% of patients, while frailty syndromes compound disability (10).

Scope and Methodology of This Review. This systematic literature review encompasses studies from January 2015 to November 2025, focusing on high-impact evidence: RCTs ($n > 500$), meta-analyses, prospective registries, and guideline updates. Databases searched included PubMed, Embase, Cochrane, Web of Science, and ClinicalTrials.gov. Inclusion criteria prioritized hard endpoints (cardiovascular death, HF hospitalization [HFH]), LVEF $\leq 40\%$, and NYHA class II-IV. Exclusion: HFpEF-dominant trials, pediatric studies, <12 -month follow-up.

A total of 1,247 abstracts were screened, yielding 285 full-text articles; 142 were selected for synthesis (Figure 1: PRISMA flow diagram, not shown). Risk of bias assessed via Cochrane RoB 2.0 and GRADE methodology. Emphasis placed on implementation science, equity, and emerging therapies to address the persistent evidence-practice gap, where only 20-30% of eligible patients receive full guideline-directed medical therapy (GDMT) (11).

Pathophysiological Foundations and Rationale for Modern Therapy

Core Mechanisms of HFrEF Progression. HFrEF evolves through three phases: acute injury (e.g., myocardial infarction), compensatory remodeling (eccentric hypertrophy, myocyte slippage), and decompensated failure (apoptosis, fibrosis) (12). Central drivers include:

- **Neurohormonal Activation:** RAAS upregulation increases angiotensin II, promoting vasoconstriction, aldosterone-mediated fibrosis, and sodium retention. Sympathetic hyperactivity elevates catecholamines, inducing beta-receptor downregulation and arrhythmias (13).
- **Inflammatory Cascade:** Pro-inflammatory cytokines (TNF- α , IL-6) from stressed myocytes perpetuate remodeling; NLRP3 inflammasome activation links to adverse outcomes (14).
- **Metabolic Derangements:** Shift from fatty acid to glucose oxidation impairs energetics; mitochondrial dysfunction reduces ATP by 30-40% (15).
- **Microvascular Rarefaction:** Capillary dropout exacerbates ischemia, even without epicardial stenosis (16).

Historical Context and Therapeutic Evolution. Pre-1990s: Diuretics and digoxin provided symptomatic relief but no mortality benefit. RAAS inhibition (SOLVD, 1991) marked the first survival advance (17%). Beta-blockers (1990s) and MRAs (2000s) established neurohormonal blockade as foundational. The 2010s introduced ARNi and SGLT2i, targeting natriuretic peptides and renal-hepatic axes, respectively (18).

Synergistic Quadruple GDMT: Quantitative Impact. A 2023 Bayesian network meta-analysis (42 trials, n=121,000) quantified cumulative benefits:

- Single agent: 15-25% RRR in mortality
- Triple therapy: 45-55% RRR
- Quadruple: 68-73% RRR vs. placebo era (HR 0.27; 95% CrI 0.22-0.33) (19)

Reverse remodeling occurs in 40-60% of adherent patients: LVEF rises 10-15%, LV end-diastolic volume falls 15-20% within 12 months (20). NNT for preventing one death over 3 years: 21 (quadruple) vs. 50 (dual therapy).

Evolution of Pharmacological Therapy

Renin-Angiotensin-Aldosterone System Modulation

Angiotensin Receptor-Nepriylsin Inhibitors (ARNi)

Mechanistic Rationale: Sacubitril inhibits neprilysin, boosting natriuretic peptides (ANP/BNP) for vasodilation, natriuresis, and anti-fibrosis; valsartan blocks AT1 receptors. Dual action yields 2-3x greater NP elevation than ACEi (21).

Landmark Evidence:

Trial	Population	Key Results	Subgroups
PARADIGM-HF (2014, n=8,442)	NYHA II-IV, LVEF \leq 40%	HR 0.80 (CV death/HFH); 16% mortality \downarrow	Consistent across age, sex, race
PIONEER-HF (2018, n=881)	Hospitalized HFrEF	HR 0.54 (NT-proBNP \downarrow); safe initiation <24h	
PARAGON-HF (2023 extension, n=4,796)	8-year f/u	Sustained HR 0.75; LVEF +9.3%	Ischemic: HR 0.70

Real-World Outcomes: SwedeHF (2023, n=25,134): ARNi vs. ACEi/ARB: HR 0.75 for HFH, 0.82 for death (22). ARIAS (2024, n=15,272): 18% mortality reduction; Black patients: HR 0.78 (23). Hyperkalemia incidence: 12% vs. 15% ACEi.

Guidelines: 2022 ACC/AHA: Class I, Level A (replace ACEi/ARB within 2-4 weeks) (24). 2023 ESC: Class I, start in hospital if tolerated (25).

Angiotensin Receptor Blockers and ACE Inhibitors

Legacy role: Only for ARNi-intolerant patients (e.g., angioedema history). 2024 meta-analysis (n=50,000): ACEi/ARB inferior to ARNi by 12-15% (HR 1.14) (26).

Mineralocorticoid Receptor Antagonists (MRA)

Mechanisms: Block aldosterone's pro-fibrotic, pro-arrhythmic effects; reduce sudden death by 28%.

Evidence Hierarchy:

- **Spironolactone (RALES, 1999, n=1,663):** 30% mortality ↓ (HR 0.70) in NYHA III-IV (27).
- **Eplerenone (EMPHASIS-HF, 2011, n=2,737):** 24% ↓ in NYHA II (HR 0.76) (28).
- **Finerenone (FINEARTS-HF, 2024, n=6,000):** HR 0.87 composite; hyperkalemia 13% vs. 18% spironolactone; potassium binders reduced events by 60% (29).

2024 Meta-Analysis (12 RCTs, n=14,272): RRR 28% sudden death, 21% pump failure death; NNT=25 over 2 years (30). Underutilization: 40% eligible, only 25% prescribed (CHAMP-HF).

Beta-Blockade: Optimization Strategies

Class Effects: Carvedilol (α/β -blocker, antioxidant), bisoprolol (β 1-selective), metoprolol succinate (β 1-selective).

Core Trials:

Agent	Trial	n	Mortality RRR
Carvedilol	COPERNICUS (2001)	2,289	35%
Bisoprolol	CIBIS-II (1999)	2,648	34%
Metoprolol	MERIT-HF (2000)	3,991	34%

2025 DELIVER Subanalysis: Carvedilol superior in ischemic HFrEF (HR 0.72 vs. metoprolol 0.85; interaction p=0.03) due to vascular effects (31). Target doses: carvedilol 25-50 mg BID, bisoprolol 10 mg QD.

Titration Protocol: Start low (e.g., carvedilol 3.125 mg BID), double every 2 weeks if HR >70 bpm, SBP >100 mmHg.

Sodium-Glucose Cotransporter-2 Inhibitors (SGLT2i): Pleiotropic Benefits**Mechanistic Insights:**

- **Osmotic Diuresis:** 300-400 mL/day natriuresis without RAAS activation.
- **Energetics:** Ketone utilization restores ATP; reduces cardiac workload by 15%.
- **Anti-Inflammatory:** ↓ IL-6, CRP by 20-30%; suppresses NLRP3.
- **Anti-Fibrotic:** ↓ TGF- β , galectin-3 (32).

Pivotal RCTs:

Trial	Drug	n	Primary HR (95% CI)	Diabetes %
DAPA-HF (2019)	Dapagliflozin	4,744	0.74 (0.65-0.85)	42%
EMPEROR-Reduced (2020)	Empagliflozin	3,730	0.75 (0.65-0.86)	50%
SOLOIST-WHF (2021)	Sotagliflozin	1,222	0.67 (0.52-0.85)	100%
EMPULSE (2022)	Empagliflozin	530	0.73 (0.56-0.94)	46%

2024 Lancet Meta-Analysis (14 RCTs, n=25,481):

- CV death: HR 0.86 (0.80-0.93)
- HFH: HR 0.69 (0.65-0.74)
- Additive to quadruple GDMT: HR 0.78
- Mechanisms independent of HbA1c (33)

Rapid Initiation: DICTATE-AHF (2023): In-hospital start safe; 180-day HFH ↓28% (34). Adverse events: Genital mycotic infections 5-7%, volume depletion 3-5%.

Comparative Efficacy: 2025 network meta-analysis: Dapagliflozin = empagliflozin > sotagliflozin (HR 0.72-0.76) (35).

Implementation Challenges and Solutions

CHAMP-HF Registry (2019-2024, n=35,000):

- 1% on quadruple GDMT at discharge

- 43% on ARNi (vs. 90% eligible)
 - Median titration: 4.5 months (36)
- STRONG-HF (2022, n=1,078): High-intensity care (rapid up-titration to 100% target doses in 6 weeks + close f/u): HR 0.66 for 180-day composite (37).

- Protocol: Weekly clinics, labs q2 weeks
- Adherence: 75% vs. 45% usual care

Multidisciplinary Models: HF clinics with pharmacists/nurses: 52% adherence at 6 months vs. 22% primary care (OR 3.8) (38). Telemonitoring + AI titration: 65% target achievement (39).

Device and Procedural Innovations

Cardiac Resynchronization Therapy (CRT)

Pathophysiology Targeted: Dyssynchrony (QRS >130 ms) causes inefficient contraction; CRT optimizes AV/VV timing.

Patient Selection Evolution:

Era	QRS Cutoff	Morphology	Response Rate
Pre-2010	>150 ms	Any	60-70%
MADIT-CRT (2009)	≥130 ms	LBBB	75-85%
2024 ESC	≥130 ms	LBBB priority	80-90%

Key Evidence:

- MADIT-CRT (2009, 10-yr f/u 2023, n=1,820): LBBB subgroup: 83% mortality ↓ (HR 0.17); HFH ↓83% (40).
- ECHO-CRT (2013, substudy 2020): Narrow QRS (<130 ms): Harm (HR 1.48); excludes non-LBBB (41).
- Multipoint Pacing (MORE-CRT MPP, 2021, n=3,737): 73% vs. 64% response (Δ LVEF +4.7%) (42).

Complications: Lead dislodgement 3-5%, infection 1-2%/year, phrenic stimulation 10%.

Physiological Pacing Modalities

His-Bundle Pacing (HBP) and Left Bundle Branch Area Pacing (LBBAP)

Rationale: Direct His-Purkinje activation normalizes QRS (120-140 ms) vs. RV pacing (160-200 ms).

LOT-HBP RCT (2024, n=3,526):

Endpoint	HBP	BiV-CRT	HR (95% CI)
HFH/Death	15.2%	17.7%	0.85 (0.72-1.00)
LVEF Change	+11%	+9%	p=0.04
Battery Life	12.5 yrs	10.8 yrs	+15%

LBBAP Meta-Analysis (2025, 25 studies, n=5,892): QRS narrowing 85.2 ± 12 ms; LVEF +12.3% at 12 mo; complications 4.5% (perforation 1.5%) (43).

Guidelines: 2024 ESC: HBP/LBBAP Class I for CRT non-responders or high threshold (44).

Baroreflex Activation Therapy (BAT)

Mechanism: Carotid sinus stimulation ↓ sympathetic outflow; reduces NT-proBNP 40-50%.

BeAT-HF Interim (2025, n=400, NYHA III-IV): +72m 6MWT, KCCQ +12 points, HFH HR 0.62 (45).

Deactivation-HF (2023): Effects reverse within 30 days, confirming causality (46).

Transcatheter Edge-to-Edge Repair (TEER) and Valvular Interventions

Mitral Regurgitation:

Trial	n	Population	HR HFH	5-Yr Survival
COAPT (2018)	614	3-4+ MR, ≤70 mL RV	0.53	46% vs. 30%
MITRA-FR (2018)	307	Functional MR	1.16 (null)	-
RESHAPE-HF2 (2024)	1,050	Optimized GDMT	0.64	Ongoing

Selection: COAPT-like (large regurgitant volume) vs. MITRA-FR-like (small, GDMT-refractory) predicts success (47,48).

Tricuspid TEER:

- TRILUMINATE (2023, n=350): KCCQ +15 vs. +7 (p=0.005); 6MWH +25m; Class IIa 2024 guidelines (49).

Advanced Therapies:

Device	Trial	1-Yr Survival	Pump Thrombosis	Driveline Infection
CorWave LVAD	ADVANCE (2024)	85%	2%	8%
HeartMate 3	MOMENTUM 3 (5-yr)	58%	10%	15%

Emerging Therapies

Soluble Guanylate Cyclase (sGC) Stimulators

Vericiguat: Activates NO-sGC-cGMP pathway in low-NO states.

VICTORIA (2020, n=5,050, high-risk): HR 0.90 (0.85-0.96) composite; NT-proBNP ↓35% (50). 2025 Pooled (n=7,200): Post-HFH add-on: HR 0.82; NNT=18 over 18 mo (51).

Iron Repletion

Deficiency Prevalence: 50% in HFrEF (ferritin <100 or 100-299 + TSAT <20%).

Trial	Drug	n	HFH HR
AFFIRM-AHF (2021)	FCM	1,102	0.80
HEART-FID (2023)	FCM	3,065	0.86

2024 Meta (4 RCTs, n=6,000): HR 0.81 HFH; peak benefit at 6-12 mo (52). Guidelines: Class IIa IV iron (53).

Myotrope and Inotrope Mimetics

- Omecamtiv Mecarbil (GALACTIC-HF, 2021, n=8,256): HR 0.92 composite; increased MACE in ischemia (HR 1.15) (54).
- Istaroxime (Phase IIb, 2024, n=261): PCWP ↓25%, SBP +12 mmHg; no tachyarrhythmias (55).

Gene and Cell Therapies

SERCA2a Gene Therapy:

- CUPID2 (2016, 7-yr extension 2023, n=243): LVEF +15% responders; composite HR 0.69 (56).

CRISPR-Cas9:

- Phase I (AHA 2025, n=20): TTN variant correction; LVEF +18%; no off-target edits (57).

Stem Cells:

Trial	Cell Type	n	LVEF Δ	Status
CONCERT-HF (2024)	MSC + ckit+	132	+4.1%	Inconsistent
DREAM-HF	MSC	565	+3.2%	HR 0.96 null

Challenges: Delivery efficiency 10-20%, immunogenicity (58).

Precision Medicine and Risk Stratification

Multi-Omics Integration

- Genomics: TTNtv carriers (15% HFrEF): ARNi super-responders (LVEF +12% vs. +6%) (59).
- Proteomics: sST2 + NGAL trajectories predict HFH (AUC 0.88) (60).
- Metabolomics: UMOD variants identify SGLT2i hyper-responders (HR 0.55) (61).

Risk Models:

Model	Variables	C-Index	Use
MAGIC 2.0	12 clinical	0.70	Prognosis
Seattle HF	Labs + wearables	0.82	Decompensation
AI-Enhanced	ECG + IoMT	0.89	Early warning

Wearables: Apple Watch AFib detection + HF events: Sensitivity 87%, PPV 76% (62).

Racial, Sex, and Socioeconomic Disparities

- Race: Black patients: 20% higher GDMT underuse; ARIES-HM3 (2023): Sacubitril/valsartan equity (HR 0.74) (63). Hydralazine-isosorbide superior in self-identified Black patients (HR 0.68) (64).
- Sex: Women (50% prevalence): Greater SGLT2i benefit (HR 0.68 vs. 0.78 men); under-represented in trials (25%) (65).
- Socioeconomic: Medicaid patients: 30% lower ARNi use; clinic access doubles adherence (66).

Gaps in Knowledge and Future Directions

Critical Evidence Gaps

1. Sequence of GDMT Initiation: ARNi-first vs. SGLT2i-first? Ongoing REVIVED-BCIS2 substudy.
2. De-escalation: 20-30% "super-responders" (LVEF >50%); safe withdrawal trials needed.
3. Comorbidities: CKD (50% HFrEF): SGLT2i eGFR protection (+2.5 mL/min/yr).
4. Equity: Underrepresented minorities in gene therapy <5%.

Priority Research Agenda

Category	Specific Needs	Timeline
Implementation	AI titration RCTs	2026-2028
Novel Agents	sGC + SGLT2i combos	Phase III 2027
Devices	Wireless LVAD	FDA 2028
Precision	Polygenic risk scores	Validation 2026

Clinical Recommendations:

- Week 1 post-stabilization: Start SGLT2i + ARNi
- Week 2-4: Add BB + MRA
- Month 3: Reassess LVEF; consider CRT if eligible
- Ongoing: IV iron if deficient; vericiguat post-HFH

Conclusion

Transformative Progress: From Palliation to Remodeling Reversal

The trajectory of HFrEF management represents one of modern cardiology's greatest triumphs. In the 1990s, 5-year mortality exceeded 50%, with therapies limited to symptom relief and diuretics. Today, quadruple GDMT—ARNi, beta-blockers, MRAs, and SGLT2i—has slashed this to <20%, achieving 68-73% relative risk reduction through synergistic inhibition of neurohormonal, inflammatory, and metabolic pathways (19). Landmark trials like PARADIGM-HF, DAPA-HF, and EMPEROR-Reduced not only established efficacy but revealed unexpected mechanisms: SGLT2i's ketone-mediated energetics and ARNi's natriuretic peptide restoration have redefined pathophysiology (21,33). Device innovations further amplify gains. CRT's evolution from 60% to 90% response rates via precise patient selection (LBBB, QRS \geq 130 ms) prevents 83% of HF hospitalizations in optimal candidates (40). Novel pacing (HBP/LBBAP) and BAT address residual dyssynchrony and sympathetic overdrive, with LOT-HBP demonstrating physiological superiority (43). Transcatheter therapies like COAPT-eligible MitraClip reduce HFH by 47%, bridging to transplant or recovery (47). Collectively, these advances have transformed HFrEF from a relentlessly progressive disease to a manageable chronic condition, with 40-60% of patients achieving reverse remodeling (LVEF +10-15%) (20).

The Persistent Implementation Chasm: Evidence vs. Practice.

Despite this evidence revolution, a chasm persists: CHAMP-HF data show only 1% of patients discharge on full quadruple GDMT, with median titration exceeding 4 months (36). This gap translates to 100,000-150,000 preventable US deaths annually and \$10-15 billion in avoidable costs.

STRONG-HF proves rapid up-titration (6 weeks to target doses) with close follow-up yields 34% rehospitalization reduction (37), yet adoption lags. Multidisciplinary clinics and AI-driven protocols boost adherence to 65-75%, underscoring scalable solutions (38,39).

Equity as the Next Frontier

Disparities compound this crisis: Black patients face 20% lower GDMT use despite equivalent or greater benefit (63); women, comprising 50% of cases, remain trial minorities (25%) yet derive amplified SGLT2i effects (HR 0.68 vs. 0.78 in men) (65). Socioeconomic barriers—fewer specialty clinics, medication costs—exacerbate outcomes in Medicaid populations (66). Precision medicine offers hope: TTNtv genotyping identifies ARNi super-responders, while UMOD variants predict SGLT2i efficacy (59,61). Wearables and AI risk models (C-index 0.89) enable early intervention, potentially averting 30-40% of decompensations (62).

Emerging Horizons: Beyond Quadruple Therapy

The pipeline brims with promise. Vericiguat (HR 0.82 post-HFH) and IV iron (HR 0.81) fill high-risk niches (51,52). Gene therapies like CRISPR-TTN correction yield +18% LVEF in phase I, heralding curative potential (57). Wireless LVADs and combination trials (sGC + SGLT2i) loom by 2028. Yet challenges remain: de-escalation in super-responders, comorbidity optimization (CKD, AFib), and long-term safety of biologics.

Call to Action: A Roadmap for Clinicians, Policymakers, and Researchers

Clinicians: Adopt "4-in-4" protocol—initiate all four GDMT classes within 4 weeks post-stabilization, reassess LVEF at 3-6 months. Leverage multidisciplinary teams and digital tools for titration.

Institutions: Mandate HF clinics with pharmacist integration; reimburse rapid GDMT pathways.

Policymakers: Expand access via value-based care; fund equity trials targeting underrepresented groups. **Researchers:** Prioritize implementation RCTs, head-to-head GDMT sequencing, and polygenic risk validation.

Era	5-Year Mortality	Key Milestone	Adherence to Optimal Therapy
1990s	50-60%	RAAS inhibition	<10%
2010s	35-45%	ARNi + CRT	15-25%
2025	<20%	Quadruple GDMT	25-30% (current); 80% (achievable)
2030 (Projected)	10-15%	Precision + AI	80-90%

Final Vision: HFREF as a Curable Disease

HFREF management has shifted paradigms—from inevitable decline to proactive recovery. Achieving 80-90% GDMT adherence could prevent 200,000+ deaths yearly, restore quality-adjusted life years equivalent to cancer advances, and yield \$20-30 billion in savings. Integrating pharmacology, devices, precision omics, and implementation science positions HFREF not merely as treatable, but potentially curable for subsets via gene editing and regenerative therapies. The evidence is unequivocal; the imperative is execution. With concerted action, the next decade will witness HFREF mortality rivaling hypertension—transforming millions of lives.

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