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A Systematic Review

Comparative Effectiveness of Early Versus Delayed Optimization in Acute Decompensated Heart Failure: A Systematic Review

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Abstract:

Aim: Acute decompensated heart failure (ADHF) is followed by a vulnerable period in which recurrent congestion, rehospitalization and death are common. This systematic review evaluated whether early initiation and optimization of guideline-directed medical therapy (GDMT), compared with delayed or usual-care optimization, improves clinical outcomes after an ADHF hospitalization. Early optimization was defined prospectively as initiation or meaningful dose escalation during hospitalization or within 14 days after discharge, with a planned reassessment pathway. Delayed optimization was defined as usual care, discharge without a structured rapid-titration plan, or initiation more than 14 days after stabilization.

Materials and methods: A protocol-informed review was structured according to PRISMA 2020 and a PICO framework. Eligible studies were randomized trials and comparative observational studies of adults hospitalized with ADHF or acute heart failure that compared an early strategy with delayed/usual care. MEDLINE/PubMed, Embase, CENTRAL, Web of Science, Scopus, CINAHL, ClinicalTrials.gov, WHO ICTRP and reference lists were prespecified. The primary outcome was all-cause death or heart-failure readmission; secondary outcomes included individual mortality, readmission, length of stay, quality of life, renal dysfunction, hyperkalemia, hypotension and treatment attainment. Risk of bias was planned with RoB 2 for randomized trials and ROBINS-I for nonrandomized studies. A random-effects meta-analysis was planned when at least three sufficiently homogeneous estimates were available; otherwise, findings were synthesized narratively.

Results: The most direct randomized evidence was the multinational STRONG-HF trial, which enrolled 1,078 patients recently hospitalized for acute heart failure and compared high-intensity care with rapid up-titration and close follow-up against usual care. The composite of all-cause death or heart-failure readmission at 180 days occurred in approximately 15.2% versus 23.3%, favoring early optimization, with an adjusted risk ratio of about 0.66. Adverse events, particularly hypotension, hyperkalemia and renal impairment, were more frequent, although serious adverse events were similar. Supporting evidence from hospitalization-initiation trials of sacubitril/valsartan and sodium-glucose cotransporter-2 inhibitors, together with observational cohorts, generally supports earlier treatment, but indirectness, open-label designs, selection of clinically stable patients and variable definitions limit certainty.

Conclusion: Early, structured GDMT optimization after stabilization from ADHF probably reduces the combined risk of death or heart-failure readmission compared with delayed optimization. Benefit appears to depend on clinical stability, residual congestion assessment, renal and electrolyte surveillance, and early outpatient contact rather than medication escalation alone. The evidence is strongest for a bundled strategy involving rapid initiation, dose escalation and frequent monitoring; it is less certain whether one drug class should universally precede another or whether the same approach applies to severe shock, marked renal dysfunction, active ischemia or predominantly HFpEF. Future trials should compare operational definitions of early care, include under-represented populations, report patient-important safety outcomes, and evaluate implementation in resource-limited settings.

Keywords: Acute Decompensated Heart Failure; Guideline-Directed Medical Therapy; Early Optimization; Rehospitalization; Mortality.

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Introduction

Acute decompensated heart failure is a clinical syndrome characterized by new or worsening symptoms and signs of congestion, impaired perfusion, or both, requiring urgent evaluation and frequently hospital admission. Although inpatient diuresis relieves symptoms, the period immediately after discharge remains high risk. Patients may leave hospital with persistent hemodynamic vulnerability, incomplete decongestion, renal or electrolyte abnormalities, and little opportunity for medication review. At the same time, contemporary heart-failure therapy has changed from a sequential model centered on an angiotensin-converting enzyme inhibitor and beta-blocker to a four-pillar approach incorporating renin–angiotensin system inhibition or angiotensin receptor–neprilysin inhibition, evidence-based beta-blockade, mineralocorticoid-receptor antagonism and sodium-glucose cotransporter-2 inhibition.

The therapeutic dilemma is familiar. Clinicians may hesitate to initiate or increase disease-modifying treatment during an acute admission because blood pressure is low, creatinine has risen, potassium is abnormal, or the patient appears clinically fragile. Conversely, postponement can become therapeutic inertia: a planned outpatient adjustment is not completed, follow-up is missed, and the patient remains exposed to recurrent congestion without the full protective effect of GDMT. The question is therefore not whether unstable shock should receive routine up-titration, but whether clinically stabilized patients with ADHF benefit from a deliberate early strategy rather than waiting several weeks.

Early optimization may work through several mechanisms. Initiating low doses before discharge converts intention into an actual prescription, while repeated visits create opportunities to adjust diuretics, assess congestion, and monitor renal function and potassium. Early use of drugs with rapid clinical benefit may reduce recurrent hospitalization during the vulnerable post-discharge phase. A bundled intervention may also improve adherence and coordination between inpatient and outpatient teams. However, early treatment can cause symptomatic hypotension, worsening renal function, hyperkalemia, bradycardia or intolerance if applied without individual assessment.

The STRONG-HF trial provided the clearest direct test of this implementation question. It compared high-intensity care, including rapid escalation of several oral therapies and close follow-up, with usual care after an acute heart-failure admission. The trial reported a clinically important reduction in 180-day death or heart-failure readmission, but its open-label design, selection of patients considered suitable for rapid escalation and bundled intervention make it difficult to isolate the contribution of any single medication. Other trials, including PIONEER-HF, EMPULSE and SOLOIST-WHF, evaluated initiation of specific therapies during or shortly after hospitalization and provide complementary, though not identical, evidence.

This review was designed to synthesize the comparative effectiveness and safety of early versus delayed optimization after ADHF. It explicitly separates direct comparisons of a timing strategy from indirect evidence concerning initiation of individual GDMT classes. The review also establishes a reproducible protocol, eligibility criteria, search strategy, extraction plan, risk-of-bias approach and analysis framework so that the manuscript can be updated after the final database searches.

Materials and Method

Protocol and reporting framework: The review question was formulated before finalizing the evidence synthesis and follows the PICO structure. The planned report follows PRISMA 2020. The protocol should be registered prospectively in PROSPERO or OSF before submission; no registration number is assigned in this draft. Any post-protocol changes should be dated and justified in the final report. The PRISMA flow diagram should be completed from the exported search files rather than estimated retrospectively.

Review question and PICO: Population: adults aged 18 years or older hospitalized with ADHF or acute heart failure, including HFrEF, HFmrEF and HFpEF, who are clinically stabilized before discharge or early outpatient titration.

Intervention: early initiation or optimization of one or more GDMT classes during hospitalization or within 14 days after discharge, preferably accompanied by a structured reassessment pathway.

Comparator: delayed initiation, delayed dose escalation, discharge with usual care, or optimization beginning more than 14 days after stabilization.

Primary outcome: composite all-cause mortality or heart-failure hospitalization/readmission by 90 or 180 days, prioritizing the longest prespecified follow-up within 6 months.

Secondary outcomes: all-cause mortality, heart-failure hospitalization, cardiovascular mortality, emergency visits, length of stay, health-related quality of life, proportion at target dose, renal dysfunction, hyperkalemia, hypotension, bradycardia and treatment discontinuation.

Eligibility Criteria: Randomized controlled trials, quasi-randomized trials and comparative cohort studies were eligible. Single-arm studies, case series, case reports, cross-sectional surveys, pharmacokinetic studies, pediatric studies and studies limited to cardiogenic shock without a separable stabilized subgroup were excluded. Studies were required to report at least one prespecified clinical or safety outcome. Studies of acute heart failure

therapies were included only when timing of initiation or optimization was a central comparison; trials comparing two drugs without a timing contrast were used as indirect contextual evidence and not pooled with direct timing studies.

No language restriction was planned at the search stage. Non-English reports were translated where feasible. Conference abstracts were eligible for the primary search but were included in quantitative synthesis only when sufficient numerical data and a defined comparator were available. Duplicate publications from the same cohort were linked, with the longest or most complete follow-up retained for each outcome.

Information Sources and Search Strategy: The planned search covers MEDLINE/PubMed, Embase, Cochrane CENTRAL, Web of Science Core Collection, Scopus and CINAHL from database inception to 12 August 2026. ClinicalTrials.gov and the WHO International Clinical Trials Registry Platform will be searched for ongoing, completed and unpublished studies. Reference lists of eligible studies and relevant reviews will be screened, and forward citation searching will be performed for pivotal trials. The core PubMed concept is: ((heart failure[MeSH Terms] OR heart failure[Title/Abstract] OR acute decompensated[Title/Abstract] OR acute heart failure[Title/Abstract]) AND (optimization[Title/Abstract] OR up-titration[Title/Abstract] OR initiation[Title/Abstract] OR intensification[Title/Abstract] OR guideline-directed[Title/Abstract] OR quadruple therapy[Title/Abstract]) AND (early[Title/Abstract] OR rapid[Title/Abstract] OR inpatient[Title/Abstract] OR discharge[Title/Abstract] OR delayed[Title/Abstract] OR usual care[Title/Abstract])). Database-specific subject headings and spelling variants will be added. The complete executed strings, dates, filters and record counts should be placed in an appendix.

Study Selection and Data Extraction: Two reviewers should independently screen titles and abstracts, retrieve potentially relevant full texts, and record exclusion reasons. Disagreements should be resolved by discussion or a third reviewer. A standardized extraction form should capture publication details, country, setting, design, sample size, eligibility criteria, baseline ejection fraction, congestion and renal status, intervention timing, drug classes, target doses, follow-up intensity, comparator care, outcomes, effect estimates and funding. Authors should be contacted for missing data when feasible. The unit of analysis will be the participant, not the hospitalization, unless recurrent admissions are explicitly modeled.

Risk of Bias and Certainty: RoB 2 will assess randomized trials across randomization, deviations from intended intervention, missing outcome data, outcome measurement and selective reporting. ROBINS-I will assess nonrandomized studies across confounding, participant selection, classification of intervention, deviations, missing data, outcome measurement and selective reporting. Two reviewers should judge each domain independently. The certainty of evidence for the primary outcome and major safety outcomes should be graded using GRADE, considering risk of bias, inconsistency, indirectness, imprecision and publication bias.

Synthesis Plan: Direct early-versus-delayed comparisons will be synthesized separately from indirect initiation trials. Risk ratios or hazard ratios will be used for dichotomous time-to-event outcomes, mean differences for continuous outcomes measured on the same scale, and standardized mean differences when scales differ. Random-effects models will be used when at least three clinically comparable estimates are available. Heterogeneity will be assessed with I^2 and τ^2, interpreted alongside clinical differences rather than thresholds alone. Prespecified subgroup analyses include HFrEF versus HFpEF/HFmrEF, randomized versus observational design, early inpatient initiation versus early post-discharge titration, and follow-up intensity. Sensitivity analyses will exclude high-risk-of-bias studies, abstract-only reports and studies with an early definition exceeding 14 days. When pooling is inappropriate, a structured narrative synthesis will report direction, magnitude, precision and applicability.

Observation Tables

Table 1: PICO and Operational Definitions

Domain	Prespecified definition
Population	Adults hospitalized for ADHF/acute HF; clinically stabilized before discharge or early titration.
Early optimization	Initiation or meaningful escalation during admission or within 14 days after discharge, with planned reassessment.
Delayed optimization	Usual care, discharge without rapid-titration pathway, or initiation after day 14.
Primary endpoint	All-cause death or HF hospitalization/readmission by 90–180 days.
Safety endpoints	Hypotension, renal impairment, hyperkalemia, bradycardia, drug discontinuation.
Core confounders	Age, sex, EF phenotype, baseline GDMT, systolic BP, eGFR, potassium, congestion, diabetes and prior HF admission.

Table 2: Key Comparative Evidence Identified from the Literature

Study	Design/population	Early strategy	Comparator	Main finding
Mebazaa et al., STRONG-HF (2022)	Open-label RCT; 1,078 recent AHF admissions	Rapid escalation of ACEi/ARB/ARNI, beta-blocker and MRA with frequent visits	Usual care	180-day death or HF re-admission about 15.2% vs 23.3%; adjusted RR about 0.66.
Velazquez et al., PIONEER-HF (2019)	In-hospital stabilized acute HF with reduced EF	Sacubitril/valsartan started before discharge	Enalapril	Greater NT-proBNP reduction; clinical-event analysis supported safety, but not a pure timing trial.
Voors et al., EMPULSE (2022)	Acute HF, irrespective of EF, after stabilization	Empagliflozin initiated during hospitalization	Placebo	Clinical benefit at 90 days across a composite of death, HF events and quality of life; indirect timing evidence.
Bhatt et al., SOLOIST-WHF (2021)	Type 2 diabetes with worsening HF	Sotagliflozin initiated before or shortly after discharge	Placebo	Fewer CV death and HF hospitalization events; treatment was stopped early, limiting precision.
Real-world cohorts (2024–2025)	Comparative observational HFrEF populations	Predischarge or early quadruple therapy	Stepwise/usual care	Generally lower early readmission or mortality; residual confounding likely.

Table 3: Outcome Framework for Final Extraction

Outcome	Time point	Preferred measure	Interpretive priority
Death or HF readmission	90 and 180 days	HR or RR with 95% CI	Primary patient-important outcome
All-cause mortality	In-hospital, 90, 180 days	RR/HR	Critical outcome
HF hospitalization	90, 180 days	RR/HR	Critical outcome
Treatment attainment	Discharge, 30, 90 days	Proportion at target/half-target dose	Implementation outcome
Renal impairment	During titration	Study-defined or creatinine rise ≥0.3 mg/dL	Safety; distinguish transient change from severe AKI
Hyperkalemia/hypotension	During titration	Events and discontinuation	Safety and feasibility
Quality of life	30–180 days	KCCQ or validated scale	Patient-reported benefit

Table 4: Risk-Of-Bias and Applicability Assessment

Evidence domain	Likely judgment for direct evidence	Reason	Impact on interpretation
Randomization	Low risk in STRONG-HF	Central randomized allocation reported	Supports causal inference
Blinding	Some concerns	Open-label intervention and follow-up	Could influence admission, reporting and treatment decisions
Intervention deviations	Some concerns	Bundled high-intensity care; adherence varies	Cannot isolate drug timing effect
Missing outcomes	Low to some concerns	Follow-up was structured but event ascertainment may vary	Usually modest impact if balanced
Outcome measurement	Some concerns	Hospitalization adjudication and open-label care	Potential detection bias
Observational confounding	Serious to critical concern	Clinicians select patients fit for early therapy	Associations should not be treated as causal
Applicability	Moderate	Stable patients represented better than shock or severe renal dysfunction	Do not generalize to all ADHF

Results

The evidence base supports a distinction between early optimization as a coordinated care strategy and early initiation of an individual drug. The direct randomized evidence is dominated by STRONG-HF, a multinational open-label trial of patients admitted with acute heart failure who were not receiving full doses of recommended therapy. The high-intensity group received systematic clinical assessment, rapid escalation toward recommended doses and repeated early follow-up, whereas the usual-care group reflected local practice. At 180 days, the composite of all-cause death or heart-failure readmission was lower with high-intensity care, approximately 15.2% compared with 23.3%, corresponding to an adjusted risk ratio near 0.66 and an absolute difference of roughly 8 percentage points. These figures imply a number needed to treat of approximately 12 over six months, although the estimate belongs to the complete bundled strategy rather than to a single medication.

The benefit was accompanied by more treatment-related adverse events. Hypotension, hyperkalemia and renal impairment were reported more often in the intensive-care arm, especially during the early titration period. Importantly, serious adverse events were not materially increased, suggesting that monitoring and dose adjustment can make rapid optimization feasible in selected patients. The trial nevertheless excluded or under-represented people with profound instability, severe renal dysfunction, marked hyperkalemia or other contraindications. Thus, the findings support early treatment after stabilization, not indiscriminate escalation during shock or unresolved hypoperfusion.

PIONEER-HF provides complementary evidence for beginning sacubitril/valsartan during hospitalization after hemodynamic stabilization rather than waiting for a later outpatient visit. It demonstrated a greater reduction in NT-proBNP than enalapril and no major excess in worsening renal function, symptomatic hypotension or hyperkalemia in the trial population. EMPULSE similarly supports in-hospital initiation of empagliflozin in stabilized acute heart failure across ejection-fraction categories, with improvement in a hierarchical clinical-benefit endpoint. SOLOIST-WHF supports early initiation of sotagliflozin in patients with diabetes and worsening heart failure, but early discontinuation and the combined pre- and post-discharge initiation window limit certainty.

Observational studies generally report that predischarge or early quadruple therapy is associated with fewer short-term readmissions, shorter hospitalization and lower mortality than conventional stepwise care. However, patients selected for early therapy may have better blood pressure, renal function, social support, clinician access and adherence potential. Confounding by indication can operate in both directions: unstable patients are less likely to receive early drugs, while high-risk patients may receive more intensive follow-up. For this reason, observational estimates should reinforce feasibility and implementation signals but should not replace randomized evidence.

Statistical Analysis: Analyses should be performed in R using metafor or a validated equivalent, with the complete code archived alongside the extraction dataset. Missing standard errors will be obtained from confidence intervals, p values or authors when possible. Sensitivity analyses will exclude studies at high or critical risk of bias, studies defining early treatment as more than 14 days, and studies with substantial crossover. The certainty of evidence will be rated for the primary endpoint, mortality, heart-failure hospitalization and serious adverse events. A clinically important effect should be interpreted alongside absolute risks and treatment burden, not only relative measures.

Discussion

This review indicates that early, structured optimization is more effective than delayed or unstructured care for selected patients recovering from ADHF. The strongest direct evidence evaluates a care pathway rather than an isolated prescription: therapy is started or intensified before discharge, doses are advanced rapidly, and the patient is reviewed repeatedly with laboratory and clinical surveillance. The consistency of supportive evidence from in-hospital initiation trials strengthens biological and practical plausibility, even though those trials were not designed as direct early-versus-delayed comparisons.

The clinical implication is a change in the default question. Instead of asking whether all therapy should wait until the outpatient setting, clinicians should ask whether the patient is sufficiently stable for a low-dose start and what monitoring is needed to make that start safe. Stability should include improving congestion, adequate perfusion, acceptable blood pressure, a manageable potassium concentration and a renal trajectory that can be monitored. Beta-blocker escalation generally requires particular caution when congestion or low output persists, whereas SGLT2 inhibitors have a relatively simple dose regimen but still require assessment of volume status and renal function. RAAS inhibition, ARNI and MRA therapy require electrolyte and renal surveillance.

The evidence does not justify a rigid one-size-fits-all sequence. The choice and order of therapies should reflect blood pressure, heart rate, potassium, eGFR, diabetes, rhythm, congestion and access to follow-up. A simultaneous low-dose approach may shorten time to complete foundational therapy,

while a sequential approach may be preferable when tolerability is uncertain. What appears most important is avoiding indefinite delay, documenting the reason for a temporary hold, and assigning responsibility for the next review.

The main limitation is evidence architecture. STRONG-HF was open label and bundled medication escalation with high-intensity follow-up, so its effect may reflect monitoring, education, adherence and early diuretic adjustment as well as pharmacology. The trial population was selected for rapid optimization and may not represent patients with cardiogenic shock, severe hypotension, advanced kidney disease, active infection or major frailty. Indirect initiation trials often compare a drug with placebo or another drug rather than with delayed initiation, and observational studies are vulnerable to confounding and immortal-time bias.

Implementation may be especially important in health systems with limited specialist access. A feasible pathway can use a discharge checklist, medication reconciliation, laboratory testing at defined intervals, telephone review, early clinic appointments and clear sick-day instructions. In regions where frequent visits are difficult, telemedicine and shared-care protocols may help, but their safety should be evaluated rather than assumed. Equity also matters: early optimization can widen disparities if it depends on transportation, laboratory affordability or continuous access to medicines.

Future research should compare explicit timing windows and identify the minimum safe monitoring package. Trials should report outcomes by ejection-fraction phenotype, sex, age, ethnicity, kidney function and baseline blood pressure, and should include patient-reported outcomes. Pragmatic studies should test pharmacist-led, nurse-led and digitally supported pathways. Economic evaluations should include medication costs, laboratory monitoring, travel, readmissions and productivity. Until such evidence is available, the most defensible interpretation is that early optimization is beneficial when delivered as monitored, individualized care after stabilization.

Conclusion

In adults recovering from acute decompensated heart failure, early initiation and optimization of GDMT is associated with better short-term clinical outcomes than delayed or usual-care optimization. The clearest randomized evidence shows a meaningful reduction in the combined risk of all-cause death or heart-failure readmission at six months when patients receive rapid medication up-titration and frequent early follow-up. Supporting trials of sacubitril/valsartan, empagliflozin and sotagliflozin indicate that selected therapies can be started safely during or soon after hospitalization once the patient is clinically stable.

The intervention should be understood as a care pathway, not simply an instruction to prescribe more drugs. Effective early optimization requires confirmation of improving congestion and perfusion, review of blood pressure and heart rate, assessment of renal function and potassium, medication reconciliation, patient education, and a scheduled reassessment. Dose escalation should be paused or modified when safety signals emerge, with a documented plan for re-initiation. Patients with shock, persistent hypoperfusion, severe uncontrolled congestion, marked hypotension, significant hyperkalemia or rapidly worsening kidney function require individualized management and were not adequately represented in the pivotal evidence.

The available evidence is encouraging but not definitive for every timing question. It is strongest for a bundled rapid-titration strategy in selected post-ADHF patients and weaker for determining the universally optimal sequence of individual drug classes. Open-label design, indirect comparisons, variable definitions of early treatment and confounding in observational cohorts reduce certainty. The final registered review should therefore present the primary randomized estimate separately, avoid double-counting overlapping cohorts, and grade the evidence rather than portraying all studies as equivalent.

A practical conclusion for clinical services is to make delayed optimization the exception that requires a reason. Before discharge, the team should identify eligible therapy, start tolerated low doses, arrange monitoring and specify who will review the patient within one to two weeks. Such a process aligns treatment with the high-risk period after hospitalization while preserving safety. Further randomized and pragmatic studies are needed to establish the most efficient monitoring model, extend evidence to under-represented populations, and determine how early optimization can be delivered equitably across different health systems.

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