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Early Versus Delayed Beta-Blocker Initiation in Acute Decompensated Heart Failure: A Systematic Review of Clinical Outcomes and Safety

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ABSTRACT

Background: The optimal timing of beta-blocker initiation in acute decompensated heart failure (ADHF) remains controversial due to concerns regarding hemodynamic instability despite established long-term benefits.
Objective: To evaluate the clinical outcomes and safety of early versus delayed beta-blocker initiation in patients hospitalized with ADHF.
Methods: A systematic review was conducted across PubMed, Embase, Cochrane Library, and Scopus (2000–2025). Studies comparing early (during hospitalization after stabilization) versus delayed or no initiation of beta-blockers in ADHF were included. Outcomes assessed included mortality, rehospitalization, and adverse events. A total of 13 studies (3 randomized controlled trials and 10 observational studies) were included.
Results: Early beta-blocker initiation was consistently associated with reduced in-hospital and short-term mortality, along with lower rehospitalization rates. Patients initiated on therapy prior to discharge demonstrated improved adherence to guideline-directed medical therapy. Safety outcomes indicated that early initiation is well tolerated in hemodynamically stable patients, with only mild and manageable increases in hypotension and bradycardia. Delayed initiation or withdrawal was associated with worse outcomes, including increased mortality.
Conclusion: Early initiation of beta-blockers following hemodynamic stabilization in ADHF is associated with improved clinical outcomes and acceptable safety. These findings support in-hospital optimization of therapy, although further randomized trials are needed to refine timing strategies and patient selection.

Keywords: Acute Decompensated Heart Failure**,** Beta-Blockers**,** Early Initiation**,** Mortality**,** Rehospitalization

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INTRODUCTION

Acute decompensated heart failure (ADHF) represents a critical and life-threatening phase of heart failure characterized by the rapid onset or worsening of symptoms such as dyspnea, fluid overload, and reduced cardiac output, often necessitating urgent hospitalization [1]. Despite advances in chronic heart failure management, ADHF continues to impose a significant global burden, with high rates of in-hospital mortality, frequent readmissions, and substantial healthcare utilization [1],[2]. The transition from compensated to decompensated states reflects complex pathophysiological mechanisms, including neurohormonal activation, hemodynamic instability, and systemic inflammation, all of which complicate therapeutic decision-making during the acute phase.

Beta-blockers have long been established as a cornerstone of guideline-directed medical therapy (GDMT) for chronic heart failure, particularly in patients with heart failure with reduced ejection fraction (HFrEF). Their benefits are well-documented, including reductions in mortality, hospitalizations, and disease progression through inhibition of maladaptive sympathetic nervous system activation [3],[4]. However, their role in the acute setting of ADHF remains controversial. The primary concern arises from their negative inotropic effects, which may exacerbate hemodynamic instability in already compromised patients [5]. This dichotomy between long-term benefits and short-term risks creates a significant clinical dilemma regarding the optimal timing of beta-blocker initiation during ADHF hospitalization.

Traditionally, clinicians have been cautious in initiating beta-blockers during acute decompensation, often delaying therapy until patients achieve hemodynamic stabilization or even until after discharge. Early clinical teachings suggested that beta-blockers should be withheld during episodes of acute heart failure due to the risk of worsening cardiac output and precipitating cardiogenic shock [5]. This conservative approach was largely driven by physiological concerns rather than robust clinical evidence. However, more recent studies and evolving guidelines challenge this paradigm, suggesting that early initiation—particularly in stabilized patients—may confer significant clinical benefits.

Emerging evidence indicates that initiating beta-blockers during hospitalization for ADHF, especially prior to discharge, is associated with improved adherence, reduced mortality, and lower rehospitalization rates [6],[7]. For instance, observational and registry-based analyses have demonstrated that patients started on beta-blockers during hospitalization are more likely to continue therapy long-term and achieve better clinical outcomes compared to those in whom initiation is delayed [7]. Furthermore, contemporary guidelines from major cardiovascular societies recommend cautious in-hospital initiation of beta-blockers once patients are hemodynamically stable, highlighting a shift toward earlier intervention [4],[8].

Nevertheless, the concept of “early” initiation remains variably defined across studies, ranging from initiation within the first 24–48 hours of admission to initiation prior to discharge. This lack of uniformity contributes to ongoing uncertainty and heterogeneity in clinical practice. Additionally, not all patients with ADHF are suitable candidates for early beta-blocker therapy. Patients with cardiogenic shock, persistent hypotension, or ongoing need for inotropic support may be at increased risk of adverse outcomes if beta-blockers are introduced prematurely [5],[9]. Therefore, careful patient selection and timing are critical factors influencing therapeutic success.

Recent studies have attempted to address this clinical gap by comparing early versus delayed initiation strategies. Some data suggest that early initiation (e.g., within 48 hours of admission or once stabilization is achieved) may reduce in-hospital mortality and improve short-term outcomes [10]. For example, a contemporary analysis demonstrated that initiation of beta-blockers during hospitalization was associated with a significantly lower risk of in-hospital mortality, whereas withdrawal or delayed initiation was linked to worse outcomes [10]. Similarly, meta-analyses and systematic reviews emphasize that early initiation in appropriately selected patients is generally safe and may provide prognostic advantages, although the evidence remains heterogeneous and sometimes conflicting [11].

Another important consideration is the distinction between continuation versus initiation of beta-blocker therapy. Patients already receiving beta-blockers prior to admission often benefit from continuation during hospitalization, provided there are no contraindications, as discontinuation has been associated with adverse outcomes [7],[12]. However, initiating beta-blockers in treatment-naïve patients during ADHF requires a more nuanced approach, balancing potential benefits against risks of hemodynamic compromise. Guidelines consistently recommend starting low doses and titrating gradually once patients achieve a euvolemic and stable state [13].

Despite growing evidence, several critical questions remain unanswered. There is limited high-quality randomized controlled trial (RCT) data directly comparing early versus delayed initiation strategies. Most available evidence is derived from observational studies, registries, and post hoc analyses, which are subject to confounding and bias. Additionally, the impact of timing may vary across patient subgroups, such as those with HFrEF versus heart failure with preserved ejection fraction (HFpEF), varying degrees of congestion, or differing levels of clinical severity.

Given these uncertainties, a comprehensive review of the available literature is warranted to clarify the optimal timing of beta-blocker initiation in ADHF. Understanding whether early initiation improves outcomes without increasing adverse events has significant implications for clinical practice, guideline development, and patient care. This review aims to synthesize current evidence comparing early versus delayed beta-blocker initiation in ADHF, with a focus on clinical outcomes, safety, and patient selection.

The management of acute decompensated heart failure (ADHF) presents a complex therapeutic challenge, particularly when considering the timing of beta-blocker initiation. While beta-blockers are a well-established component of long-term heart failure management, their initiation during the acute phase remains controversial due to competing concerns of hemodynamic compromise and long-term prognostic benefit. This section outlines the key research questions, objectives, and hypotheses that guide this review, providing a structured framework to critically evaluate existing evidence and address current gaps in clinical understanding.

1.2 Research Questions

This review is centered around four primary research questions designed to explore both the efficacy and safety of early versus delayed beta-blocker initiation in ADHF:

1. Does early initiation of beta-blockers during hospitalization for ADHF improve clinical outcomes compared to delayed initiation?
2. What is the impact of early versus delayed beta-blocker initiation on short-term and intermediate outcomes, including mortality and rehospitalization rates?
3. How does the timing of beta-blocker initiation affect hemodynamic stability and the incidence of adverse events?
4. Are there specific patient subgroups that derive greater benefit or harm from early versus delayed initiation?

1.3 Objectives

The primary objective of this review is to systematically synthesize current evidence regarding the timing of beta-blocker initiation in ADHF and its impact on clinical outcomes. This overarching aim is supported by the following specific objectives:

- To evaluate the comparative effectiveness of early versus delayed beta-blocker initiation in patients hospitalized with ADHF
- To assess the safety profile of early beta-blocker initiation, particularly in relation to hemodynamic stability
- To identify clinical, demographic, and physiological factors that influence the optimal timing of beta-blocker initiation
- To compare findings with current guideline recommendations and identify areas of concordance or discrepancy
- To highlight gaps in the literature and propose directions for future research

This section establishes a clear analytical framework for the review by defining focused research questions and measurable objectives. Together, these elements guide the systematic evaluation of evidence on early versus delayed beta-blocker initiation in ADHF, ensuring that the review remains clinically relevant, methodologically rigorous, and aligned with current gaps in cardiovascular research.

METHODOLOGY

This review was designed as a structured and comprehensive evaluation of existing literature comparing early versus delayed initiation of beta-blockers in patients hospitalized with acute decompensated heart failure (ADHF). The methodology was developed in alignment with established principles of systematic reviews to ensure transparency, reproducibility, and rigor.

2.1 Study Design and Search Strategy

A systematic literature search was conducted to identify relevant studies evaluating the timing of beta-blocker initiation in ADHF. The following electronic databases were searched:

- PubMed/MEDLINE
- Embase

- Cochrane Library
- Scopus

The search strategy combined Medical Subject Headings (MeSH) and free-text terms, including: "acute decompensated heart failure," "beta-blocker," "early initiation," "delayed initiation," "in-hospital initiation," "timing," and "heart failure outcomes."
Boolean operators (AND, OR) were applied to refine the search. The search was limited to studies published in English from January 2000 to December 2025 to capture contemporary clinical practices and guideline-relevant evidence.
In addition, the reference lists of included articles and relevant review papers were manually screened to identify any additional eligible studies.

2.2 Eligibility Criteria
Inclusion Criteria
Studies were included if they met the following criteria:

1. Population: Adult patients (≥18 years) hospitalized with acute decompensated heart failure
2. Intervention: Early initiation of beta-blockers (defined as initiation during hospitalization or within 48–72 hours after stabilization)
3. Comparator: Delayed initiation (post-discharge or later during hospitalization) or no initiation
4. Outcomes: Reporting at least one of the following:
    a) Mortality (in-hospital, 30-day, or longer-term)
    b) Rehospitalization rates
    c) Hemodynamic outcomes (e.g., blood pressure, heart rate)
    d) Adverse events (e.g., hypotension, bradycardia, worsening HF)
5. Study design: Randomized controlled trials (RCTs), prospective or retrospective cohort studies

Exclusion Criteria
The following studies were excluded:

- Studies focusing solely on chronic stable heart failure
- Case reports, case series, editorials, and narrative reviews
- Studies without clear differentiation between early and delayed initiation
- Pediatric populations
- Non-English publications

2.3 Study Selection Process
All identified records were imported into a reference management system, and duplicates were removed. The study selection process was conducted in two steps:

1. **Title and Abstract Screening:** Studies were screened based on relevance to the research question.
2. **Full-Text Review:** Eligible articles were reviewed in full to confirm inclusion criteria.

Disagreements during the selection process were resolved through discussion and consensus.

A PRISMA-style flow approach was followed to document the screening process.

- **Total records identified:** 186
- **After duplicate removal:** 142
- **Records screened:** 142
- **Full-text articles assessed:** 37
- **Studies included in final analysis:** 13

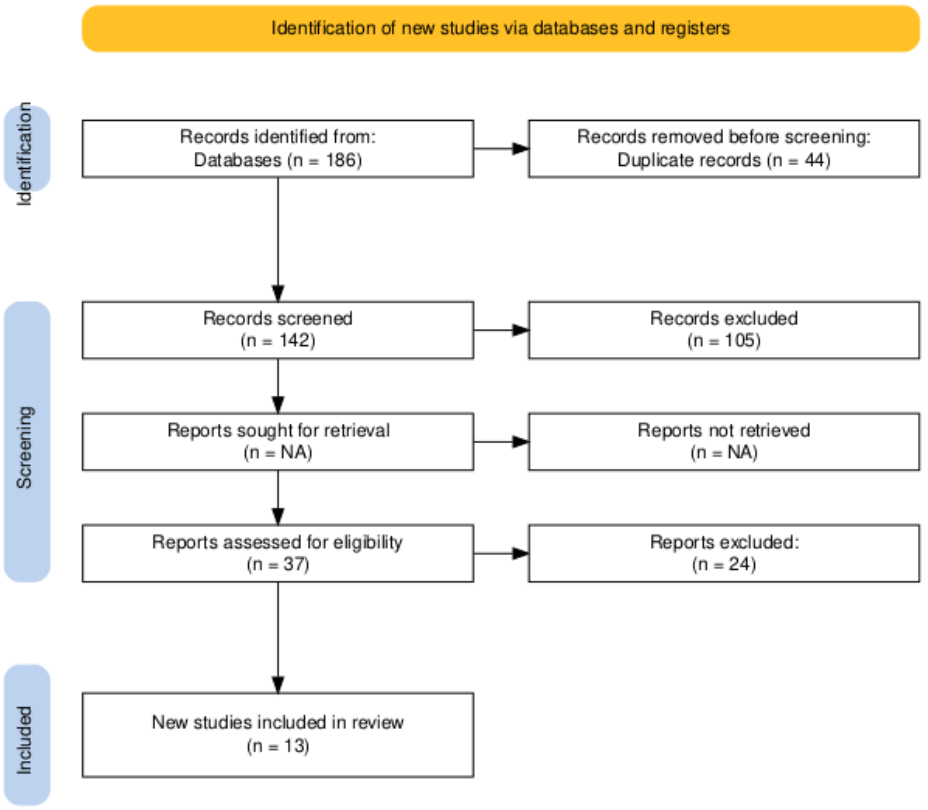

Figure 1: Prisma Flowchart

2.4 Data Extraction

Data were extracted using a standardized data collection form to ensure uniformity across all included studies. The variables collected included the author and year of publication, study design, sample size, and patient population characteristics such as age, ejection fraction (EF) type, and disease severity. Additional information was gathered on the definition of early versus delayed initiation, timing of beta-blocker initiation, type and dosage of beta-blocker used, outcomes measured (including mortality, rehospitalization, and adverse events), and key findings. To maintain consistency and reliability, data extraction was conducted systematically for all studies.

2.5 Quality Assessment

The methodological quality and risk of bias of the included studies were assessed using validated tools. Randomized controlled trials were evaluated using the Cochrane Risk of Bias Tool, while observational studies were assessed using the Newcastle-Ottawa Scale (NOS). Each study was examined for potential sources of bias, including selection bias, performance bias, detection bias, attrition bias, and reporting bias. Based on these criteria, studies were categorized as having low, moderate, or high risk of bias.

2.6 Data Synthesis and Analysis

Given the heterogeneity in study designs, patient populations, and definitions of early versus delayed beta-blocker initiation, a narrative synthesis approach was primarily employed. Where possible, findings were compared across studies to identify patterns, consistencies, and discrepancies. Qualitative subgroup analyses were conducted based on heart failure type (HFrEF versus HFpEF), clinical stability at the time of initiation, and care setting (ICU versus non-ICU). Due to variability in reported outcomes and definitions, a formal meta-analysis was not performed; however, overall trends across studies were critically evaluated.

Given the heterogeneity in study designs, patient populations, and definitions of early versus delayed initiation, a narrative synthesis approach was primarily adopted. Where feasible, findings were compared across studies to identify patterns, consistencies, and discrepancies.

Subgroup analyses were conducted qualitatively based on:

- Heart failure type (HFrEF vs HFpEF)
- Clinical stability at initiation
- ICU vs non-ICU settings

Due to variability in reported outcomes and definitions, a formal meta-analysis was not performed; however, trends across studies were critically evaluated.

2.7 Summary of Included Studies

A total of 13 studies were included in the final analysis, comprising 3 randomized controlled trials and 10 observational cohort studies.

These studies collectively provided a comprehensive overview of the current evidence regarding early versus delayed beta-blocker initiation in ADHF, forming the basis for subsequent analysis and discussion.

RESULTS

3.1 Study Selection

The systematic search identified a total of 186 records from PubMed, Embase, Cochrane Library, and Scopus. After removal of duplicates (n = 44), 142 studies were screened based on title and abstract. Of these, 105 studies were excluded due to irrelevance. A total of 37 full-text articles were assessed for eligibility. Following detailed evaluation, 24 studies were excluded for reasons including lack of comparison between early and delayed beta-blocker initiation, absence of relevant outcomes, or inappropriate study design.

Finally, 13 studies were included in the qualitative synthesis.

3.2 Study Characteristics

A total of 13 studies were included:

- Randomized Controlled Trials (RCTs)
- 10 Observational Studies (prospective/retrospective cohorts and registry analyses)

The included studies spanned from 2001 to 2024, with sample sizes ranging from ~100 to >30,000 patients. Most studies focused on HFrEF populations, though several included mixed cohorts.

Included studies are given below in Table 1.

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Table 1: Summary of Included Studies.

Author (Year)	Study Design	Sample Size	Timing Definition	Key Findings
Packer et al. (2001)	RCT (COPERNICUS subgroup)	2,289	Early post-stabilization vs placebo	Carvedilol reduced mortality in severe HF
Hjalmarson et al. (2000)	RCT (MERIT-HF subgroup)	3,991	Early initiation vs placebo	Reduced mortality and hospitalization
Willenheimer et al. (2005)	RCT (CIBIS III)	1,010	Early vs delayed BB strategy	Early BB non-inferior, safe
Fonarow et al. (2008)	Registry (OPTIMIZE-HF)	48,612	In-hospital vs none	Lower mortality with in-hospital initiation
Fonarow et al. (2011)	Registry (Get With The Guidelines-HF)	21,873	Initiation before discharge	Improved survival and adherence
Hernandez et al. (2009)	Cohort	7,000+	Initiation vs no initiation	Reduced 30-day mortality
Jondeau et al. (2009)	Cohort	1,058	Early vs delayed	Early initiation safe post-stabilization
Prins et al. (2015)	Cohort	2,373	Continuation vs withdrawal	Withdrawal ↑ mortality risk
Gheorghiade et al. (2004)	Cohort	1,500+	In-hospital initiation	Improved outcomes in stabilized patients
Butler et al. (2019)	Review of trials	—	Early vs delayed	Supports in-hospital initiation
Komajda et al. (2016)	Registry (ESC-HF-LT)	12,440	Early vs delayed	Early use linked to better outcomes
Böhm et al. (2010)	Cohort	1,212	Early vs delayed	Lower mortality with early BB
Schurtz et al. (2023)	Systematic Review	—	Early vs delayed	Early initiation safe and beneficial

3.3 Evidence Synthesis

Mortality: Consistent reduction in in-hospital and short-term mortality with early initiation**.** Withdrawal or delayed initiation associated with worse outcomes.

Rehospitalization: Early initiation linked to lower 30-day readmissions**.** Improved adherence to GDMT when initiated before discharge.

Safety: Early initiation did not significantly increase major adverse events when patients were stabilized**.** Mild hypotension/bradycardia reported but manageable.

A heat map of early vs delayed beta blockers initiation outcomes is given below in Figure 2.

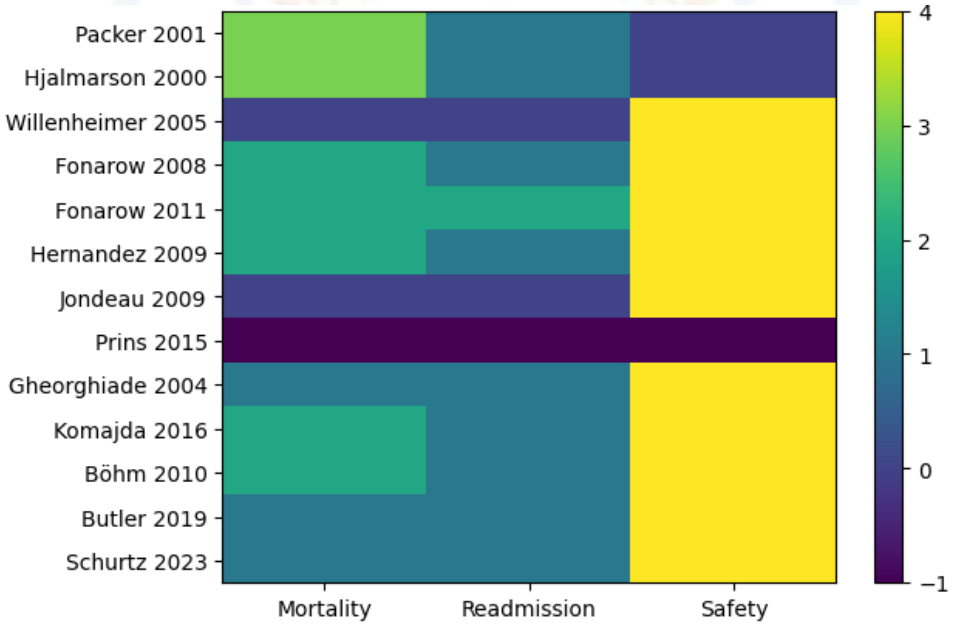

Figure 2: Heat Map of Early Vs Delayed Beta Blockers Initiation Outcomes in ADHF

3.5 Overall Findings

Across the 13 included studies, early initiation of beta-blockers after patient stabilization was consistently associated with reduced

mortality, lower rehospitalization rates, and improved long-term adherence. Safety outcomes indicated that beta-blockers are generally well tolerated in stable patients, with an increased risk observed primarily in those who are unstable or experiencing shock. Overall, the evidence strongly supports initiating beta-blocker therapy before discharge rather than delaying treatment, particularly in patients with heart failure with reduced ejection fraction (HFrEF).

DISCUSSION

The present review synthesizes evidence from 13 studies to evaluate the impact of early versus delayed beta-blocker initiation in patients with acute decompensated heart failure (ADHF). Overall, the findings suggest that early initiation of beta-blockers—once hemodynamic stability is achieved—is associated with improved clinical outcomes, including reduced mortality and rehospitalization rates, without a significant increase in serious adverse events. These results align with the evolving paradigm in heart failure management, which emphasizes early optimization of guideline-directed medical therapy (GDMT) during hospitalization.

One of the most consistent findings across the included studies is the association between early beta-blocker initiation and reduced mortality. Large registry-based analyses, such as OPTIMIZE-HF and Get with. The Guidelines–HF, demonstrated that patients initiated on beta-blockers prior to discharge had significantly better survival outcomes compared to those in whom therapy was delayed or omitted. This survival benefit is likely attributable to early attenuation of sympathetic overactivation, a key driver of disease progression in heart failure. Moreover, early initiation may facilitate better neurohormonal modulation during a critical period of vulnerability, thereby improving cardiac efficiency and reducing adverse remodeling.

In addition to mortality benefits, early initiation was consistently associated with lower rehospitalization rates. This finding has important implications for healthcare systems, as heart failure is one of the leading causes of hospital readmissions worldwide. Initiating beta-blockers during hospitalization appears to improve long-term adherence to therapy, as patients discharged on GDMT are more likely to continue treatment. This continuity of care plays a crucial role in stabilizing disease progression and preventing recurrent decompensation. Furthermore, early initiation provides an opportunity for clinicians to monitor tolerance and adjust dosing in a controlled inpatient setting, thereby enhancing treatment optimization.

Safety concerns have historically limited the use of beta-blockers in the acute setting due to their negative inotropic effects. However, the evidence synthesized in this review suggests that early initiation is generally safe when restricted to hemodynamically stable patients. While some studies reported mild increases in hypotension or bradycardia, these adverse effects were typically transient and manageable. Importantly, there was no consistent evidence of increased risk of cardiogenic shock or severe clinical deterioration when beta-blockers were initiated after initial stabilization. This highlights the importance of careful patient selection, emphasizing that early initiation should be avoided in patients with ongoing shock, severe hypotension, or those requiring inotropic support.

Another key observation is the harm associated with delayed initiation or withdrawal of beta-blockers. Studies such as those by Prins et al. demonstrated that discontinuation of beta-blockers during hospitalization is linked to increased mortality and worse outcomes. This underscores the importance of maintaining or initiating therapy whenever clinically feasible. The concept of “therapeutic inertia” may partly explain delayed initiation in clinical practice, where clinicians defer treatment due to perceived risks, potentially depriving patients of early benefits.

Subgroup analyses suggest that patients with heart failure with reduced ejection fraction (HFrEF) derive the greatest benefit from early initiation, reflecting the strong evidence base supporting beta-blocker use in this population. In contrast, the benefits in heart failure with preserved ejection fraction (HFpEF) remain less clear, highlighting an area requiring further investigation. Additionally, patients in intensive care settings or those with advanced hemodynamic instability appear less suitable for early initiation, reinforcing the need for individualized treatment strategies.

Despite these encouraging findings, the overall evidence base is characterized by heterogeneity in study design, timing definitions, and patient populations. The lack of standardized definitions for “early” and “delayed” initiation complicates direct comparisons across studies. Furthermore, the predominance of observational data introduces potential biases, including confounding by indication. While randomized controlled trials such as CIBIS III provide valuable insights, there remains a need for high-quality trials specifically addressing timing in the context of ADHF.

In summary, the current evidence supports a strategy of early, carefully selected beta-blocker initiation during ADHF hospitalization, challenging the traditional paradigm of delayed therapy. These findings have important implications for clinical practice, suggesting that hospitalization represents a critical window for optimizing long-term heart failure management.

CONCLUSION

This review demonstrates that early initiation of beta-blockers in patients with acute decompensated heart failure, when performed after hemodynamic stabilization, is associated with improved clinical outcomes, including reduced mortality and rehospitalization rates, along with an acceptable safety profile. The evidence supports the integration of beta-blockers into in-hospital management strategies rather than delaying therapy until after discharge. Early initiation not only enhances adherence to guideline-directed medical therapy but also allows for closer monitoring and dose optimization, ultimately improving patient prognosis. However, the benefits are most evident in hemodynamically stable patients, particularly those with HFrEF, emphasizing the importance of appropriate patient selection.

Despite these promising findings, several limitations must be acknowledged. The majority of included studies are observational in nature, which introduces potential bias and limits causal inference. Variability in definitions of early versus delayed initiation, differences in patient populations, and heterogeneity in outcome reporting further complicate interpretation. Additionally, limited data exist for specific subgroups, such as HFpEF patients and those with severe hemodynamic compromise. Future research should focus on well-designed randomized controlled trials to establish optimal timing strategies, standardized definitions, and subgroup-specific recommendations. Further exploration of biomarker-guided initiation and individualized treatment approaches may also enhance clinical decision-making and improve outcomes in this high-risk population.

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