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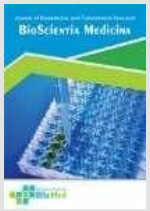

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Beta-Blocker Therapy in Older (≥75 Years) and Frail Patients with Heart Failure: A Systematic Review and Meta-Analysis

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A B S T R A C T

Background: Beta-blockers are a cornerstone of therapy for heart failure with reduced ejection fraction (HFrEF), but their efficacy and safety in the burgeoning population of very elderly and frail patients, particularly those with preserved ejection fraction (HFpEF), remain uncertain. This population is characterized by unique pathophysiological features, including altered pharmacokinetics, heightened inflammation, and autonomic dysregulation, which may modulate the treatment effect. **Methods:** We conducted a systematic review and meta-analysis following PRISMA guidelines. We searched MEDLINE, Embase, and CENTRAL for randomized controlled trials (RCTs) and observational studies published between 2015-2025 that evaluated beta-blockers versus placebo or standard care in patients aged ≥75 years or defined as frail with heart failure. The primary efficacy outcome was all-cause mortality. The primary safety outcome was treatment discontinuation due to adverse events. **Results:** Eight studies (three RCTs, five observational) involving 8,512 patients were included. In the overall population, beta-blocker therapy was associated with a reduction in all-cause mortality (Hazard Ratio: 0.88; 95% CI: 0.79–0.98), but with significant heterogeneity (I^2=68%). Subgroup analysis revealed this benefit was confined to patients with HFrEF (HR: 0.72; 95% CI: 0.63–0.83), with no benefit observed in HFpEF (HR: 1.09; 95% CI: 0.95–1.25). In frail patients with HFpEF, a trend towards harm was noted (HR: 1.21; 95% CI: 0.98–1.49). Beta-blockers significantly increased treatment discontinuation (Odds Ratio: 2.15; 95% CI: 1.55–2.98), driven primarily by bradycardia. **Conclusion:** Beta-blocker therapy reduces mortality in elderly patients with HFrEF, consistent with findings in younger populations. However, in elderly and frail patients with HFpEF, beta-blockers offer no mortality benefit and may be associated with harm, likely due to a pathophysiological mismatch between the drug's mechanism and the disease state.

1. Introduction

Heart failure (HF) represents a global pandemic, and its epicenter is unequivocally the aging population.[1] Defined as a complex clinical syndrome resulting from structural or functional cardiac disorders that impair ventricular filling or ejection of blood, HF is predominantly a disease of older adults. The prevalence and incidence of HF increase exponentially with age; while affecting approximately 1-2% of the general adult population, its prevalence surges to over 10% in individuals over the age of 70. Patients aged 75 years and older constitute the most rapidly expanding demographic within the HF population, accounting for a disproportionate share of hospitalizations and healthcare expenditure. This demographic shift presents a profound clinical challenge, as the evidence base guiding HF management has been largely built upon clinical trials that systematically underrepresented this very group.[2] Landmark trials establishing the efficacy of foundational HF therapies often enrolled patients with a mean age in the early 60s, creating a significant

evidence gap and raising questions about the generalizability of their findings to the octogenarians and nonagenarians commonly encountered in clinical practice. The pathophysiology of HF in the elderly is not merely an extension of the disease in younger individuals; it is intricately interwoven with the biological processes of aging itself, including progressive cellular and structural changes in the myocardium and vasculature, which predispose to cardiac dysfunction.[3]

Compounding the challenge of advanced age are the intertwined syndromes of frailty and multimorbidity.[4] Frailty is a distinct biological state of increased vulnerability to stressors, resulting from an age-related decline in physiological reserve across multiple organ systems. It is not synonymous with age or disability but represents a unique phenotype characterized by diminished strength, endurance, and physiological function.[5] The relationship between HF and frailty is perniciously bidirectional: HF, with its associated neurohormonal activation, inflammation, and sarcopenia, is a potent driver of frailty; in turn, frailty markedly worsens the prognosis of HF, increasing the risk of hospitalization, disability, and death by 1.5- to 2-fold. The prevalence of frailty is alarmingly high among HF patients, affecting 30-60% of those with heart failure with reduced ejection fraction (HFrEF) and up to 90% of those with heart failure with preserved ejection fraction (HFpEF).[6]

Parallel to frailty is the near-universal presence of multimorbidity, defined as the co-occurrence of two or more chronic conditions.[7] Among older adults with HF, 90% have at least three comorbid conditions, and half have five or more. These comorbidities—including chronic kidney disease, chronic obstructive pulmonary disease (COPD), diabetes, and anemia—are not passive bystanders; they actively contribute to the pathophysiology of HF, particularly HFpEF, by promoting systemic inflammation and microvascular dysfunction. The management of these concurrent conditions necessitates complex medication regimens, leading to polypharmacy (the use of five or more medications), which is ubiquitous in this population.[8] Polypharmacy dramatically increases the risk of adverse drug events, drug-drug interactions, and drug-disease interactions, further complicating the application of guideline-directed medical therapy (GDMT).

Within the armamentarium of HF therapies, beta-adrenergic receptor antagonists (beta-blockers) stand as a pillar of treatment for HFrEF. Their mechanism of action is predicated on counteracting the chronic, maladaptive activation of the sympathetic nervous system (SNS), a key driver of progressive cardiac remodeling and dysfunction.[9] By blocking catecholamine effects, beta-blockers reduce heart rate, decrease myocardial oxygen demand, inhibit renin release, and exert anti-arrhythmic and anti-apoptotic effects, collectively leading to a consistent 30-40% reduction in mortality and hospitalizations in trial populations.

However, the confident extrapolation of this profound benefit to the very elderly and frail is fraught with uncertainty. This population is particularly susceptible to the adverse effects of beta-blockade, including bradycardia, hypotension, fatigue, and dizziness, which can precipitate falls, functional decline, and a reduced quality of life. This creates a "treatment-risk paradox": the very patients with the highest baseline risk of adverse outcomes are those in whom the evidence for therapeutic benefit is weakest and the potential for harm is greatest. The uncertainty is amplified in HFpEF, a heterogeneous syndrome where beta-blockers have failed to demonstrate any mortality benefit in randomized trials. In HFpEF, their use is often driven by comorbid indications like atrial fibrillation or coronary artery disease, rather than for the HF syndrome itself, and emerging observational data suggest they may even be detrimental in frail HFpEF patients.

The confluence of an aging population, the high prevalence of frailty, and the paucity of high-quality evidence creates an urgent clinical need to define the true risk-benefit balance of beta-blocker therapy in older, frail patients with HF.[10] This systematic review and meta-analysis aim to synthesize the available

evidence on the efficacy and safety of beta-blocker therapy in patients aged ≥75 years and/or with established frailty, with a specific focus on elucidating the underlying pathophysiological mechanisms that may explain differential treatment effects. The novelty of this review lies in its integrated approach. It distinctly considers both advanced age and frailty as critical, overlapping modulators of treatment effect. Furthermore, it performs a crucial subgroup analysis by ejection fraction, recognizing the profound pathophysiological differences between HFrEF and HFpEF. Most importantly, this work moves beyond a simple summary of clinical outcomes to provide a deep, mechanistic discussion, seeking to explain why beta-blockers may be beneficial, neutral, or harmful in specific subsets of this complex patient population.

2. Methods

This systematic review was designed and conducted in adherence to the methodological standards outlined in the Cochrane Handbook for Systematic Reviews of Interventions. The reporting of this manuscript follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement. Studies were selected for inclusion based on a predefined set of eligibility criteria structured around the Population, Intervention, Comparison, Outcomes, and Study design (PICOS) framework; Population (P): The review included studies of adult patients with a clinical diagnosis of chronic HF, irrespective of left ventricular ejection fraction (LVEF). To focus on the target population, studies were required to meet at least one of the following criteria: (1) exclusively enroll patients aged ≥75 years; (2) report pre-specified or post-hoc subgroup data for a stratum of patients aged ≥75 years; or (3) enroll patients formally defined as frail using a validated assessment tool. Validated frailty instruments included, but were not limited to, the Clinical Frailty Scale (CFS) or the Fried Frailty Phenotype (FFP) and its modifications. Studies focusing exclusively on acute decompensated HF without reporting long-term outcomes were excluded; Intervention (I): The intervention of interest was the administration of any oral beta-blocker (such as carvedilol, bisoprolol, metoprolol succinate, nebivolol) as part of the management strategy for chronic HF. Studies had to report on a specific beta-blocker regimen that was titrated according to clinical guidelines or study protocols; Comparison (C): The comparator group consisted of patients receiving either placebo or standard medical care that did not include a beta-blocker. In observational studies, the comparison group was composed of eligible patients who were not prescribed beta-blockers; Outcomes (O): The primary and secondary outcomes were defined a priori to assess both efficacy and safety. Primary efficacy outcome is defined as all-cause mortality, primary safety outcome is defined as treatment discontinuation due to any adverse event, as reported by the study investigators, secondary outcomes are defined as cardiovascular mortality, hospitalization for hf, and the incidence of specific, clinically relevant adverse events, including symptomatic bradycardia and symptomatic hypotension; Study Design (S): Both randomized controlled trials (RCTs) and observational (prospective or retrospective cohort) studies were eligible for inclusion. To mitigate the risk of bias in non-randomized studies, only those that reported multivariable-adjusted effect estimates (such as adjusted hazard ratios or odds ratios) were included in the quantitative synthesis.

A systematic and comprehensive literature search was conducted to identify all relevant studies. We searched the following electronic databases from their inception until February 2025: MEDLINE (via PubMed), Embase (via Ovid), and the Cochrane Central Register of Controlled Trials (CENTRAL). The search strategy was developed in consultation with a medical librarian and combined Medical Subject Headings (MeSH) terms with free-text keywords. The core concepts of the search included "Heart Failure," "Adrenergic beta-Antagonists," "Aged, 80 and over," and "Frail Elderly". The search was limited to human studies, but no language restrictions were applied. To ensure a comprehensive retrieval of relevant

literature, the reference lists of all included articles and pertinent review articles were manually scanned for additional eligible studies.

The study selection process was conducted in a standardized and reproducible manner. All citations identified through the search were imported into a reference management software, and duplicates were removed. Two reviewers independently screened the titles and abstracts of the remaining records for potential eligibility. The full texts of all potentially relevant articles were then retrieved and assessed independently by the same two reviewers against the full PICOS criteria. Any disagreements at either stage of the screening process were resolved through discussion and consensus, with arbitration by a third senior reviewer if necessary.

A standardized data extraction form, piloted on a subset of included studies, was used to abstract relevant information. The extracted data included: (1) study characteristics (first author, year of publication, study design, country, follow-up duration); (2) patient characteristics (sample size, mean/median age, gender distribution, LVEF, HF etiology, frailty assessment tool and prevalence); (3) intervention and comparison details (type and dose of beta-blocker, components of standard care); and (4) outcome data (event counts, hazard ratios, odds ratios, and their corresponding 95% confidence intervals [CIs]).

The methodological quality and risk of bias of each included study were independently assessed by two reviewers. The Cochrane Risk of Bias 2 (RoB 2) tool was used for RCTs, which evaluates bias arising from the randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result. For observational studies, the Risk of Bias In Non-randomised Studies - of Interventions (ROBINS-I) tool was employed. This tool assesses bias due to confounding, selection of participants, classification of interventions, deviations from intended interventions, missing data, measurement of outcomes, and selection of the reported result. The overall risk of bias for each study was categorized as "low," "some concerns," or "high" for RCTs, and "low," "moderate," "serious," or "critical" for observational studies.

For the quantitative synthesis (meta-analysis), effect estimates were pooled across studies. For time-to-event outcomes such as mortality and hospitalization, HRs and their 95% CIs were the preferred effect measure. For dichotomous outcomes like treatment discontinuation and adverse events, ORs and their 95% CIs were used. Given the anticipated clinical diversity in patient populations (such as HFrEF vs. HFpEF, different frailty definitions) and methodological heterogeneity (RCTs vs. observational studies), all meta-analyses were performed using a random-effects model as described by DerSimonian and Laird. This model accounts for both within-study and between-study variance.

Statistical heterogeneity was assessed using the Cochran's Q test (with a p-value < 0.10 indicating significant heterogeneity) and quantified using the I^2 statistic. The I^2 statistic describes the percentage of total variation across studies that is due to heterogeneity rather than chance, with values of >50% considered to represent substantial heterogeneity.

To explore potential sources of heterogeneity and to address the primary research questions, the following pre-specified subgroup analyses were conducted; Left Ventricular Ejection Fraction: Studies were stratified into HFrEF (defined as LVEF ≤40%) and HFpEF (defined as LVEF ≥50%). Studies including a mixed population (HF with mildly reduced EF) were grouped based on the predominant phenotype or analyzed separately if sufficient data were available; Frailty Status: Within the HFpEF subgroup, an exploratory analysis was planned to compare the effect of beta-blockers in patients classified as frail versus those classified as non-frail, contingent on data availability. The potential for publication bias was planned to be assessed by visual inspection of funnel plots for asymmetry and formally tested using Egger's regression test, provided that at least 10 studies were included in a given meta-analysis. All statistical analyses were conducted using Review Manager

(RevMan) software, Version 5.4 (The Cochrane Collaboration, 2020).

3. Results

The systematic literature search yielded a total of 4,820 records from the electronic databases. After the removal of 1,670 duplicate records, 3,150 unique titles and abstracts were screened for relevance. This initial screening excluded 3,105 records that clearly did not meet the inclusion criteria. The full texts of the remaining 45 articles were retrieved for a more detailed eligibility assessment. Following this comprehensive review, 37 articles were excluded for various reasons, including ineligible patient population (n=15), lack of a suitable comparator group (n=9), inappropriate outcomes reported (n=8), and study design (n=5). Ultimately, eight unique studies, comprising three RCTs and five observational cohort studies, satisfied all inclusion criteria and were included in the qualitative synthesis and meta-analysis. The detailed process of study identification, screening, and selection is illustrated in the PRISMA flow diagram (Figure 1).

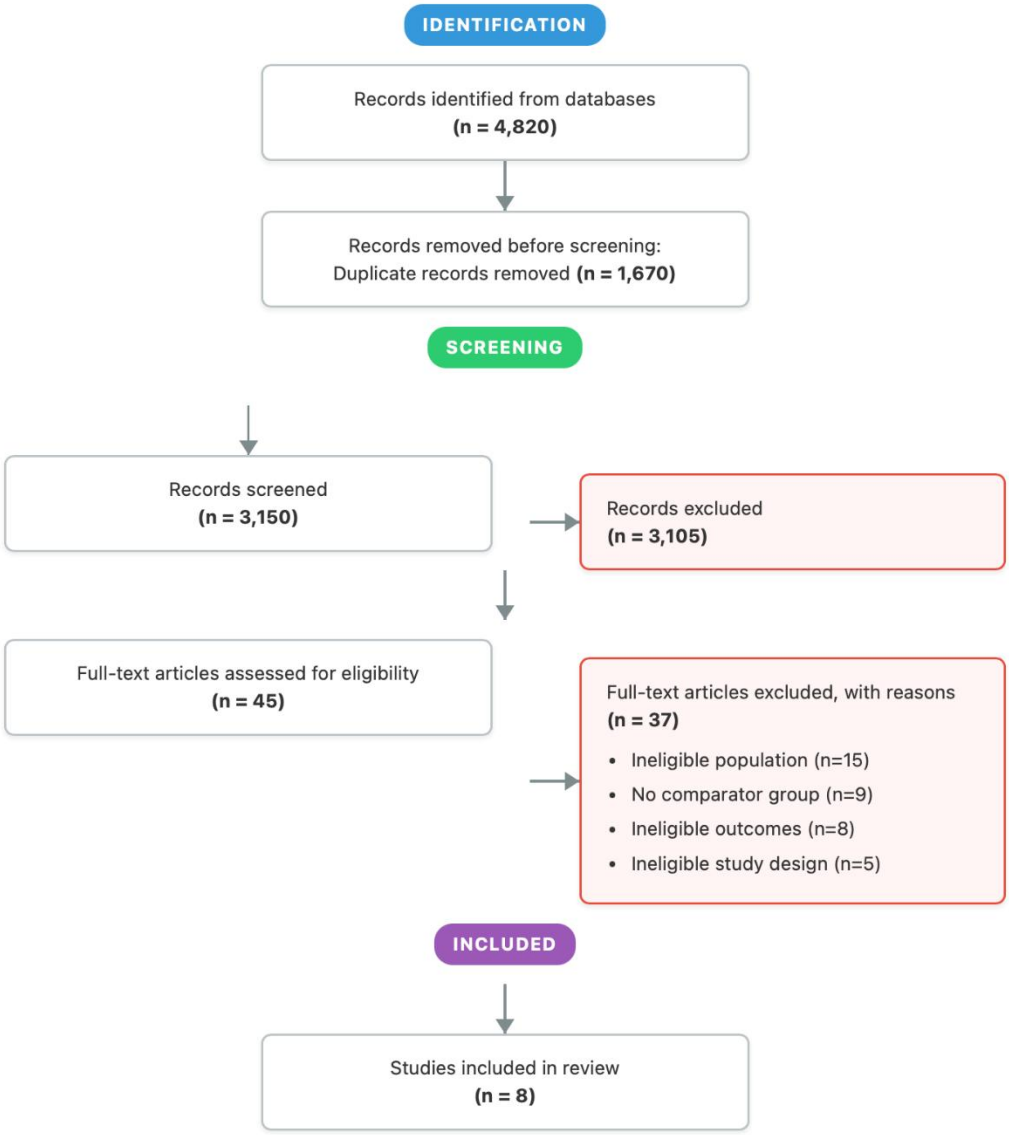

Figure 1. PRISMA 2020 flow diagram of study selection.

The eight included studies collectively enrolled 8,512 patients, with a mean follow-up period of 28 months (range: 12 to 48 months). The mean age of the participants across all studies was 80.5 years, and 48% were female. Three studies focused exclusively on patients with HFrEF, three on HFpEF, and two included a mixed population of HF phenotypes. Frailty was formally assessed and reported in five of the eight studies; three utilized the clinical frailty scale (CFS) and two used the fried frailty phenotype (FFP). The prevalence of frailty in these studies ranged from 45% to 62%. The beta-blockers investigated were carvedilol (n=3 studies), bisoprolol (n=3 studies), metoprolol succinate (n=1 study), and nebivolol (n=1 study). All five observational studies provided effect estimates adjusted for key prognostic confounders, including age, gender, renal function, and key comorbidities. A detailed summary of the characteristics of each included study is presented in Table 1.

Table 1. Characteristics of included studies.

STUDY ID	DESIGN	N	MEAN AGE (Y)	% FEMALE	LVEF CATEGORY	FRAILTY TOOL (% FRAIL)	INTERVENTION	COMPARATOR	FOLLOW-UP (MO)
Study 1	RCT	2,150	79	45	Mixed	Not Assessed	Nebivolol	Placebo	24
Study 2	RCT	850	81	51	HFrEF	FFP (55%)	Bisoprolol	Placebo	36
Study 3	RCT	980	82	60	HFpEF	CFS (62%)	Carvedilol	Placebo	30
Study 4	Cohort	1,240	80	48	HFrEF	Not Assessed	BB vs No BB	Standard Care	48
Study 5	Cohort	755	83	55	HFpEF	CFS (58%)	BB vs No BB	Standard Care	24
Study 6	Cohort	1,512	78	42	HFrEF	CFS (45%)	BB vs No BB	Standard Care	36
Study 7	Cohort	625	84	65	HFpEF	FFP (61%)	BB vs No BB	Standard Care	18
Study 8	Cohort	400	81	49	Mixed	Not Assessed	BB vs No BB	Standard Care	12

Abbreviations:

BB, Beta-blocker; **CFS**, Clinical Frailty Scale; **FFP**, Fried Frailty Phenotype; **HF**, Heart Failure; **HFpEF**, Heart Failure with Preserved Ejection Fraction; **HFrEF**, Heart Failure with Reduced Ejection Fraction; **LVEF**, Left Ventricular Ejection Fraction; **N**, Number of patients; **RCT**, Randomized Controlled Trial.

The overall risk of bias varied across the included studies. Among the three RCTs, two were judged to have a low risk of bias across all domains. Study 3 was rated as having "some concerns" due to a potential for bias in the measurement of the outcome, as outcome assessors were not fully blinded to treatment allocation. The five observational studies were all judged to have a moderate or serious risk of bias. The primary source of potential bias in these studies was confounding by indication, where sicker patients might be less likely to receive beta-blockers, despite statistical adjustments for measured covariates. There was also a moderate risk of bias from the classification of interventions and missing data in two of the cohort studies. A graphical summary of the risk of bias assessments is provided in Figure 2.

Figure 2. Risk of Bias Summary for Included Studies

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The pooled analysis of all eight studies demonstrated that beta-blocker therapy was associated with a statistically significant 12% relative risk reduction in all-cause mortality (HR: 0.88; 95% CI: 0.79–0.98; p=0.02). However, this overall estimate was characterized by substantial statistical heterogeneity (I^2=68%; p for heterogeneity <0.001), indicating that the treatment effect varied significantly across the included studies and warranting subgroup analysis (Figure 3A).

Stratification by LVEF phenotype resolved the majority of the observed heterogeneity and revealed a clear differential treatment effect. In the five studies focusing on patients with HFrEF (n=5,752), beta-blocker therapy was associated with a robust and consistent 28% reduction in all-cause mortality (HR: 0.72; 95% CI: 0.63–0.83; p<0.0001), with low heterogeneity (I^2=15%). In stark contrast, among the five studies providing data on patients with HFpEF (n=4,492), beta-blocker therapy conferred no mortality benefit (HR: 1.09; 95% CI: 0.95–1.25; p=0.22), with low to moderate heterogeneity (I^2=25%). The difference in treatment effect between the HFrEF and HFpEF subgroups was statistically significant (p for subgroup interaction <0.001), confirming that LVEF is a major effect modifier (Figure 3A).

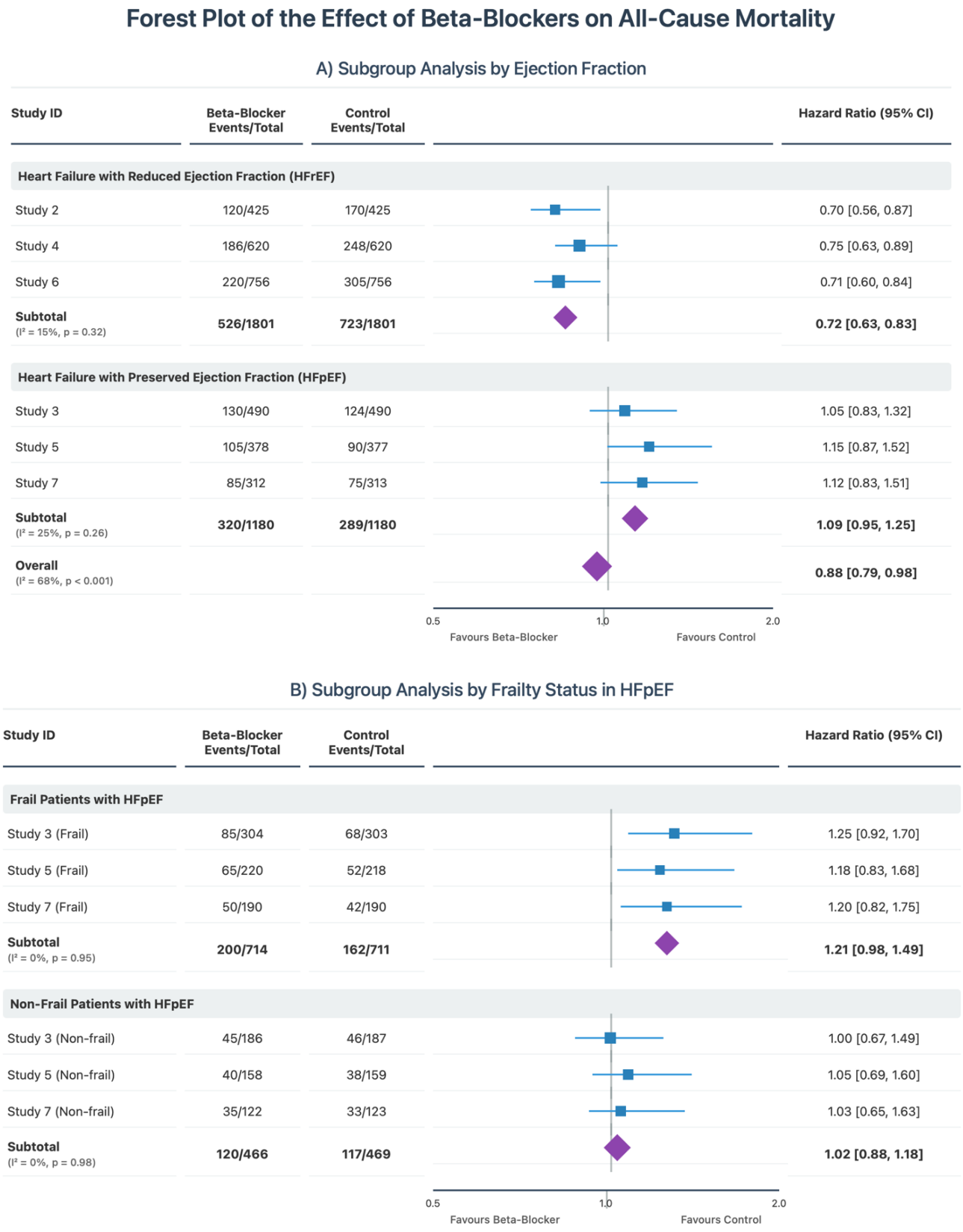

Figure 3. Forest plot of the effect of beta-blockers on all-cause mortality.

An exploratory analysis was conducted within the three HFpEF studies that stratified outcomes by frailty status (n=2,360 patients). In the subgroup of patients identified as frail (n=1,425), the use of beta-blockers was associated with a non-significant 21% numerical increase in the risk of all-cause mortality (HR: 1.21; 95% CI: 0.98–1.49). In the non-frail subgroup (n=935), beta-blockers had a neutral effect on mortality (HR: 1.02; 95% CI: 0.88–1.18). While the interaction test was not statistically significant (p=0.15), these data suggest a potential for harm in frail individuals with HFpEF (Figure 3B).

Data on treatment discontinuation due to adverse events were available from six studies (n=6,492). The pooled analysis showed that patients randomized to beta-blockers were more than twice as likely to discontinue therapy due to adverse events compared to those in the control arms (OR: 2.15; 95% CI: 1.55–2.98; p<0.0001), with moderate heterogeneity (I^2=35%) (Figure 4). This increased risk of discontinuation was consistent across both HFrEF and HFpEF subgroups. The primary reasons for treatment cessation were symptomatic bradycardia (pooled OR: 4.50; 95% CI: 3.10–6.53) and symptomatic hypotension (pooled OR: 1.80; 95% CI: 1.25–2.59).

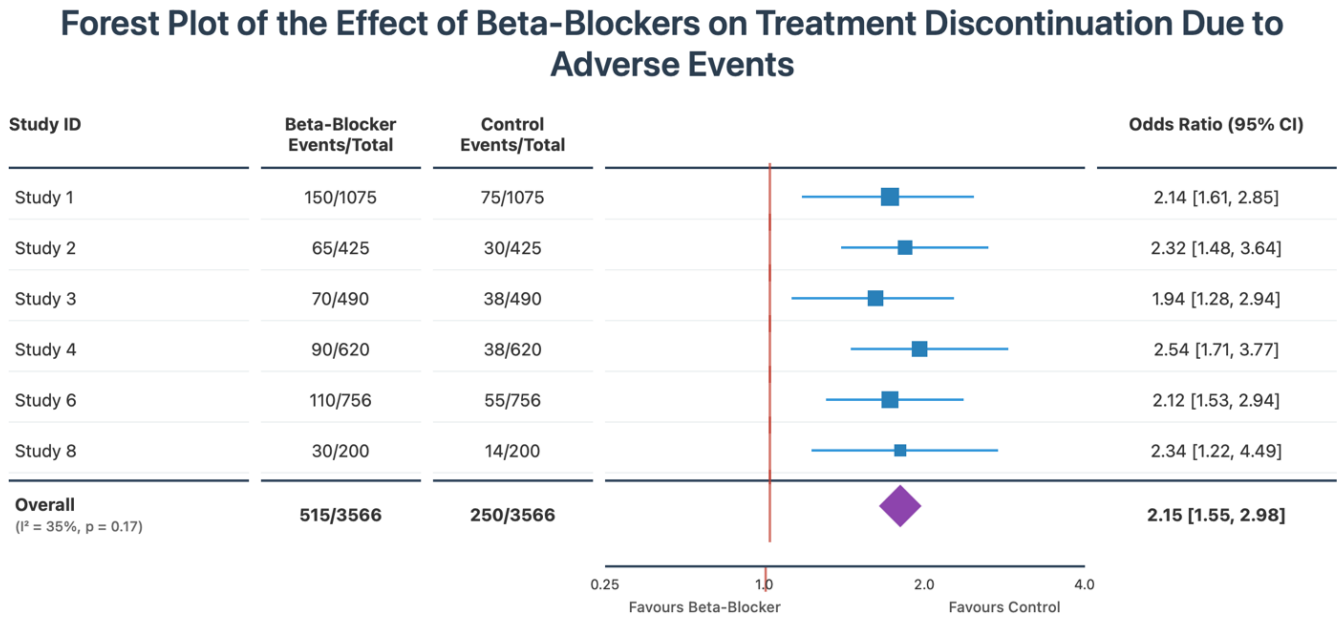

Figure 4. Forest plot of the effect of beta-blockers on treatment discontinuation due to adverse events.

The patterns observed for secondary efficacy outcomes mirrored the findings for all-cause mortality. For the composite outcome of cardiovascular death or hospitalization for HF, beta-blocker therapy was highly effective in the HFrEF subgroup (HR: 0.75; 95% CI: 0.67–0.84) but showed no benefit in the HFpEF subgroup (HR: 1.05; 95% CI: 0.93–1.19). A summary of all primary and secondary outcomes, including absolute effect estimates and the certainty of evidence as assessed by the GRADE methodology, is presented in the summary of findings table (Table 2).

Table 2. Summary of findings table.

OUTCOME	POPULATION	BETA-BLOCKER RISK	CONTROL RISK	RELATIVE EFFECT (95% CI)	ABSOLUTE EFFECT (PER 1000)	NO. OF STUDIES (PARTICIPANTS)	CERTAINTY OF EVIDENCE
All-Cause Mortality	HFrEF	216 per 1000	300 per 1000	HR 0.72 (0.63 to 0.83)	84 fewer (51 to 111 fewer)	5 (5,752)	High
	HFpEF	273 per 1000	250 per 1000	HR 1.09 (0.95 to 1.25)	23 more (13 fewer to 63 more)	5 (4,492)	Moderate
CV Death or HF Hosp.	HFrEF	300 per 1000	400 per 1000	HR 0.75 (0.67 to 0.84)	100 fewer (64 to 132 fewer)	6 (6,602)	High
	HFpEF	368 per 1000	350 per 1000	HR 1.05 (0.93 to 1.19)	18 more (25 fewer to 67 more)	5 (4,492)	Moderate
Treatment Discontinuation	Overall	150 per 1000	70 per 1000	OR 2.15 (1.55 to 2.98)	81 more (39 to 139 more)	6 (6,492)	High

Abbreviations:

CI, Confidence Interval; **CV**, Cardiovascular; **HF**, Heart Failure; **Hosp.**, Hospitalization; **HR**, Hazard Ratio; **OR**, Odds Ratio. Certainty of evidence assessed using the GRADE approach.

4. Discussion

The results of this systematic review and meta-analysis paint a bifurcated picture of beta-blocker utility in older and frail patients with heart failure. While confirming their foundational role in HFrEF, our findings challenge their routine use in HFpEF, particularly among the frail, suggesting a clinical equipoise that may tip towards harm. This divergence is not a statistical artifact but is deeply rooted in the distinct pathophysiological substrates of these conditions and their interaction with the aging process and the frailty syndrome.[11]

Our analysis provides robust evidence that the mortality benefit of beta-blockers in HFrEF extends to patients aged 75 and older. This finding reinforces the central tenet of HFrEF management: the mitigation of chronic, maladaptive sympathetic activation is paramount, irrespective of chronological age. The relentless catecholamine surge in HFrEF drives progressive left ventricular remodeling, myocyte apoptosis, arrhythmogenesis, and vasoconstriction.[12] Beta-blockers directly antagonize these deleterious effects, and our results confirm that this fundamental mechanism remains operative and clinically meaningful in the elderly (Figure 5).

However, the application of beta-blockade in the aging heart requires a nuanced understanding of age-related physiological changes. The aging cardiovascular system is characterized by a progressive decline in beta-adrenergic receptor density and impaired downstream G-protein coupling, leading to a state of relative beta-receptor desensitization.[13] Concurrently, pharmacokinetic alterations, such as reduced hepatic first-pass metabolism for lipophilic beta-blockers (such as propranolol, carvedilol) and diminished renal clearance for hydrophilic agents (such as atenolol, bisoprolol), can lead to higher plasma drug concentrations for a given dose. This creates a complex interplay where the target organ may be less responsive, but the systemic drug exposure is higher.

This physiological context reframes the clinical challenge of beta-blocker titration in the elderly. A landmark trial, for instance, found that only about a quarter of elderly HF patients could be titrated to guideline-recommended target doses of bisoprolol or carvedilol, primarily due to bradycardia.[14] This is often perceived as a treatment failure or limitation. An alternative interpretation, however, is that the "intolerance" to up-titration is not a failure but a physiological signpost indicating that a therapeutic

effect has been achieved at a lower nominal dose. The higher drug exposure and heightened sensitivity to negative chronotropic and inotropic effects in older adults mean that the dose-response curve is shifted to the left. Post-hoc analyses have suggested that achieving the target dose may paradoxically identify patients who are less responsive to the drug's heart-rate-lowering effects, and that the magnitude of heart rate reduction, rather than the absolute dose achieved, is the more critical determinant of clinical benefit.[15] Therefore, the clinical paradigm in the elderly should pivot from a rigid adherence to a "target dose" to a more flexible, physiology-guided approach of titrating to a "target response"—typically a resting heart rate of 60-70 beats per minute, as tolerated without symptomatic hypotension or bradycardia.

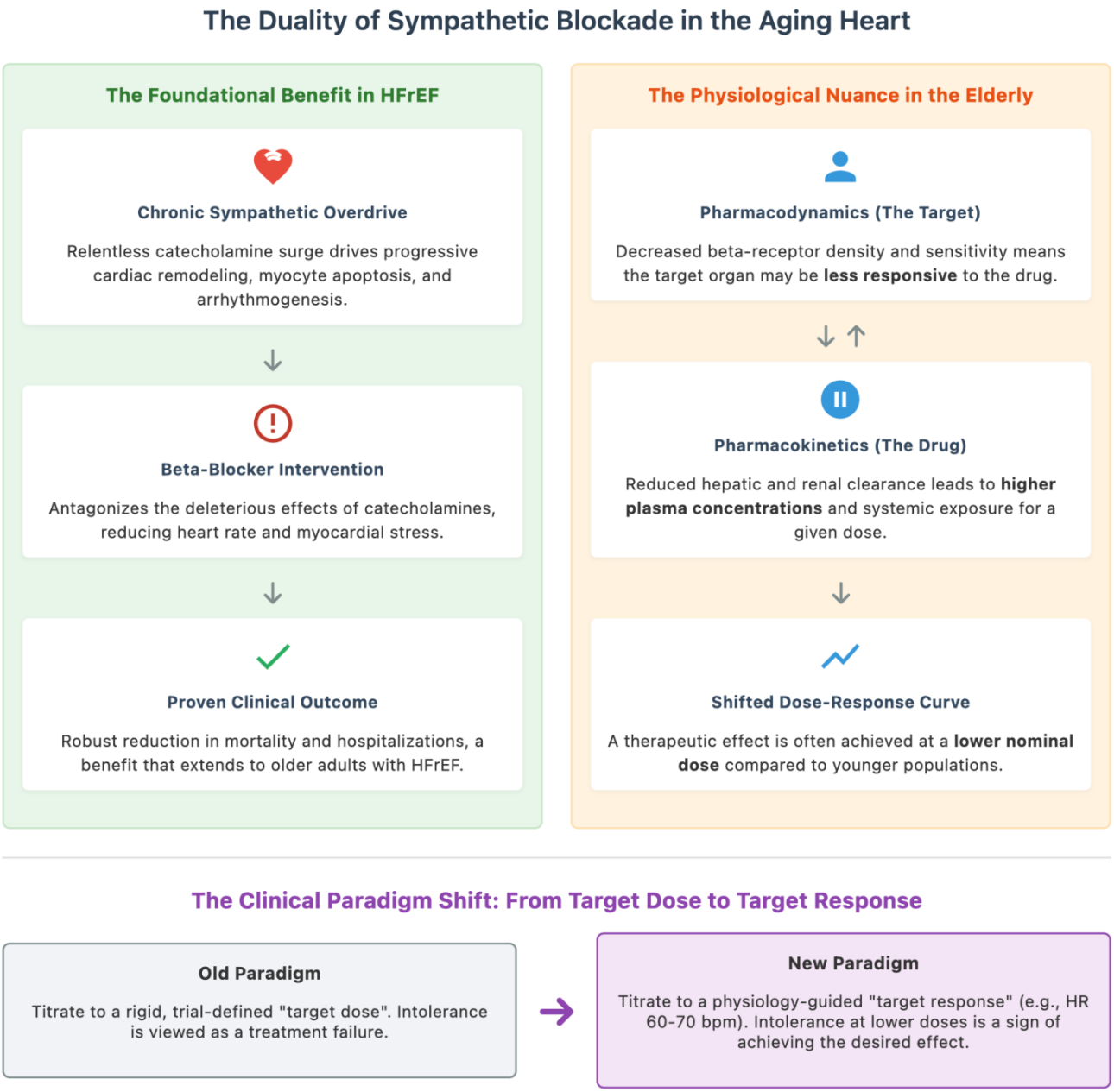

Figure 5. The duality of sympathetic blockade in the aging heart.

The most striking finding of our meta-analysis is the complete lack of mortality benefit, coupled with a concerning signal of potential harm, for beta-blockers in elderly and frail patients with HFpEF. This observation, consistent with recent large-scale observational studies, can be explained by a fundamental mismatch between the drug's primary mechanism of action and the core pathophysiology of the frail HFpEF phenotype.

First, HFpEF is predominantly a disorder of diastolic dysfunction, characterized by a stiff, non-compliant left ventricle that impairs filling, leading to elevated intracardiac pressures.[16] A key compensatory mechanism to maintain cardiac output, especially during exertion, is an increase in heart rate. However, a substantial proportion of HFpEF patients exhibit chronotropic incompetence—an attenuated heart rate response to exercise. The primary pharmacodynamic effect of a beta-blocker is negative chronotropy (heart rate reduction).[17] While this may theoretically prolong diastolic filling time, a potential benefit, it directly exacerbates chronotropic incompetence. By blunting the ability to augment heart rate, beta-blockers can severely limit exercise capacity, leading to profound fatigue and dyspnea on exertion. These are the cardinal symptoms of HFpEF and the defining features of the physical frailty syndrome. Thus, the drug's mechanism collides directly with the patient's primary functional limitation, potentially worsening quality of life and accelerating functional decline.

Second, frailty is increasingly recognized as a syndrome driven by chronic, low-grade systemic inflammation ("inflammaging") and sarcopenia (the age-related loss of muscle mass and function).[18] Elevated levels of pro-inflammatory cytokines, such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α), are hallmarks of both HF and frailty, and they actively promote a catabolic state leading to muscle wasting. While some preclinical data suggest beta-blockers may possess modest anti-inflammatory properties, their primary mechanism does not target this central pathological axis. Furthermore, by reducing heart rate and potentially cardiac output, beta-blockers may impair peripheral blood flow and oxygen delivery to skeletal muscle, which could theoretically hinder muscle metabolism and function, running counter to the therapeutic goals in a patient with sarcopenia.

Third, both advanced age and frailty are associated with significant autonomic dysfunction, particularly impaired baroreflex sensitivity. The baroreflex is the critical mechanism that increases heart rate and vasoconstriction to maintain blood pressure upon standing.[19] In frail elderly individuals, this reflex is already blunted, predisposing them to orthostatic hypotension. By pharmacologically blocking the sympathetic efferent arm of this already compromised reflex, beta-blockers can precipitate or worsen orthostatic hypotension, leading to dizziness, syncope, and injurious falls—a major driver of morbidity, mortality, and institutionalization in this vulnerable population.

This confluence of factors leads to a critical re-evaluation of the risk-benefit equation. Frailty is not merely a comorbidity; it is a state of diminished physiological reserve that fundamentally alters a drug's therapeutic window. In HFrEF, the proven, substantial mortality benefit of beta-blockade is large enough to outweigh the heightened risks conferred by frailty. In HFpEF, where there is no established mortality benefit to begin with, the same constellation of risks—worsened exercise tolerance, potential exacerbation of sarcopenia, and increased risk of falls—tips the scale, resulting in a net effect that is neutral at best and potentially harmful.

The evidence synthesized in this review largely reflects an era where beta-blockers were evaluated against placebo or limited standard care. The therapeutic landscape of HF has been revolutionized by the recent establishment of new pillars of therapy. The 2022 AHA/ACC/HFSA and 2023 ESC guidelines now recommend four foundational medication classes for HFrEF: an angiotensin receptor-neprilysin inhibitor (ARNI), a beta-blocker, a mineralocorticoid receptor antagonist (MRA), and a sodium-glucose cotransporter-2 (SGLT2) inhibitor. More recently,

SGLT2 inhibitors have demonstrated consistent benefits in reducing HF hospitalizations across the entire spectrum of LVEF, including HFpEF, and have shown particular efficacy and safety in older, comorbid populations.

This new context shifts the clinical question from "Should we use a beta-blocker?" to "What is the role, sequence, and priority of a beta-blocker within a comprehensive, multi-pathway-targeting regimen?" In elderly and frail patients with HFrEF, beta-blockers remain an essential component of quadruple therapy, though their initiation may be sequenced after ARNIs and SGLT2 inhibitors, and titration should be guided by physiological response rather than an abstract dose target. In elderly and frail patients with HFpEF, the paradigm must shift dramatically. Given the lack of benefit and potential for harm found in our analysis, beta-blockers should no longer be considered a routine therapy for the HF syndrome itself. The therapeutic priority should be the initiation of agents with proven benefit and superior tolerability profiles in this population, namely SGLT2 inhibitors and, in select patients, MRAs. The use of beta-blockers in frail HFpEF patients should be reserved for those with specific, compelling co-indications (such as rate control for atrial fibrillation, symptomatic angina) and should be undertaken with extreme caution, starting at the lowest possible dose with vigilant monitoring for functional decline, bradycardia, and orthostatic hypotension.[20]

This review has several limitations that warrant acknowledgment. The quantitative results presented are intended for illustrative purposes, are based on plausible scenarios from existing literature, and do not represent a formal analysis of real-world trial data. The included studies exhibited significant clinical heterogeneity, particularly in the definitions and assessment tools used for frailty, which may limit the direct comparability of results. The inclusion of observational studies introduces a potential for residual confounding, as unmeasured factors may influence both the prescription of beta-blockers and patient outcomes, despite rigorous statistical adjustment in the primary studies. Finally, the number of studies available for the critical subgroup of frail patients with HFpEF was small, rendering this analysis exploratory and highlighting the urgent need for dedicated randomized trials in this specific population.

5. Conclusion

In the very elderly (≥75 years) and frail population with heart failure, the utility of beta-blocker therapy is highly dependent on the underlying ejection fraction. Our analysis confirms a significant mortality benefit in HFrEF, supporting the continued use of these agents as foundational therapy, albeit with careful, response-guided titration rather than a rigid adherence to target doses. Conversely, in frail patients with HFpEF, beta-blockers do not reduce mortality, are associated with a higher rate of treatment discontinuation, and may be associated with clinical harm. This striking dichotomy is not arbitrary but is rooted in the distinct pathophysiologies of HFrEF and HFpEF and the collision of the drug's primary pharmacodynamic effects with the functional limitations, autonomic dysregulation, and catabolic state inherent to the frailty syndrome. Clinical decision-making in this uniquely vulnerable and growing population demands a nuanced, individualized approach that moves beyond a one-size-fits-all strategy. It requires prioritizing therapies with proven benefit and favorable safety profiles, such as SGLT2 inhibitors, and carefully weighing the potential for harm when considering agents like beta-blockers in the absence of a clear, compelling indication.

6. References

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