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Research Article

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Cardiopulmonary Safety and Mortality Outcomes of Non-Selective Vs. Cardioselective Beta-Blockers in Patients with Coexisting Chronic Obstructive Pulmonary Disease and Heart Failure: A Systematic Review and Meta-Analysis

Khawar Saleem Hashmi[1], Muhammad Zain Abdullah[2], Inass Bargaa[3], Aayush silwal[4], Huzaifa Naseer[5], Mohamad Mahfouz[6], Siffat Ullah[7], Zeeshan Khan[7], Areeba Raza[7], Abdul Haye[7] and Hussain Ramzan[8*]

[1]*Sheikh Zayed Medical College, Rahim yar khan, Pakistan*

[2]*Karachi Institute of Medical Sciences, Karachi Pakistan*

[3]*The First Affiliated Hospital of Xi'an Jiaotong University, China*

[4]*Nepalgunj Medical College Ngmc, Nepal*

[5]*Fatima Jinnah Medical University, Lahore*

[6]*HCA Midwest Centerpoint Medical Center, USA*

[7]*Jiangxi Medical College of Nanchang University, China*

[8]*Nishtar Medical University and Hospital Multan Pakistan*

***Corresponding author:** Husnain Ramzan, Department of Medicine, Nishtar Medical University & Hospital, Multan, Pakistan.

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Abstract

Background: Coexisting Chronic Obstructive Pulmonary Disease (COPD) and Heart Failure (HF) represent a complex clinical overlap associated with high morbidity and mortality. Beta-blockers are foundational in HF management, yet non-selective agents are frequently withheld in patients with COPD due to historical concerns regarding bronchospasm and blunted bronchodilator responsiveness. However, comparative real-world evidence evaluating cardioselective versus non-selective beta-blocker therapy in this high-risk comorbid population remains fragmented.

Objectives: To systematically evaluate and quantify the comparative cardiopulmonary safety, all-cause mortality, heart failure hospitalization, and severe COPD exacerbation rates associated with cardioselective versus non-selective beta-blocker use in patients with coexisting COPD and HF.

Methods: A comprehensive systematic search was conducted across PubMed/MEDLINE, Embase, Cochrane Central Register of Controlled Trials (CENTRAL), Web of Science, and Scopus from inception through August 15, 2026, following PRISMA 2020 guidelines and Cochrane Handbook protocols (PROSPERO ID: CRD42026895102). Observational cohort studies and randomized trials comparing β1-selective beta-blockers (e.g., bisoprolol, metoprolol, nebivolol) against non-selective beta-blockers (e.g., carvedilol) or non-users in adult patients with dual-diagnosed COPD and HF were included. Pooled hazard ratios (HR) with 95% Confidence Intervals (CI) were synthesized using DerSimonian-Laird random-effects models. Heterogeneity was evaluated via I^2 statistics.

Results: Five high-quality observational cohort studies encompassing N = 48,294 total patients met full inclusion criteria. Cardioselective beta-blockers were associated with a significant 29% reduction in all-cause mortality compared with non-selective beta-blockers (pooled HR = 0.71, 95% CI: 0.63–0.80; $p < 0.001$; $I^2 = 18.4\%$). When compared to beta-blocker non-users, non-selective beta-blockers were associated with an elevated mortality risk (pooled HR = 1.29, 95% CI: 1.11–1.50; $p = 0.001$; $I^2 = 24.2\%$). Cardioselective beta-blocker therapy significantly reduced HF hospitalizations relative to non-users (pooled HR = 0.81, 95% CI: 0.74–0.89; $p < 0.001$; $I^2 = 31.5\%$) without increasing the risk of severe COPD exacerbations requiring hospitalization (pooled HR = 0.95, 95% CI: 0.87–1.04; $p = 0.28$; $I^2 = 12.1\%$).

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Conclusions: In patients with coexisting COPD and HF, cardioselective beta-blockers provide superior survival benefits and reduced HF hospitalizations compared to non-selective agents, without compromising airway stability or precipitating severe COPD exacerbations. Cardioselective β1-blockers should be prioritized as the preferred beta-blocking strategy in dual COPD-HF management.

Introduction

The therapeutic intersection of Chronic Obstructive Pulmonary Disease (COPD) and Heart Failure (HF) represents one of the most formidable clinical challenges in modern cardiovascular and respiratory medicine [1]. Both conditions are major public health burdens globally, frequently co-occurring due to shared risk factors such as advanced age, chronic tobacco exposure, systemic low-grade inflammation, and accelerated vascular aging [2]. Epidemiological estimates suggest that approximately 20% to 35% of heart failure patients suffer from concomitant COPD, while up to 30% of patients diagnosed with COPD exhibit underlying left ventricular dysfunction or clinical heart failure [3]. The co-occurrence of these syndromes exerts a synergistic negative impact on patient prognosis, marked by heightened functional impairment, frequent emergency room visits, recurrent hospital admissions, and significantly elevated all-cause and cardiovascular mortality rates [4]. Beta-adrenergic receptor antagonists (beta-blockers) are established cornerstones in the pharmacological management of heart failure with reduced ejection fraction (HFrEF) [5]. Landmark Randomized Controlled Trials (RCTs) established that beta-blocker therapy reduces mortality by approximately 30% and decreases cardiovascular hospitalization in HF patients by suppressing sympathetic hyperactivation, attenuating adverse ventricular remodeling, and reducing malignant arrhythmia vulnerability [6]. Major clinical practice guidelines from the American College of Cardiology/American Heart Association (ACC/AHA) and the European Society of Cardiology (ESC) assign a Class I, Level of Evidence A recommendation for beta-blockers in HFrEF [7].

Despite these robust clinical guidelines, an alarming therapeutic gap persists in clinical practice: patients with coexisting COPD and HF are routinely underprescribed beta-blockers or under-dosed due to widespread clinical reluctance [8]. Historically, clinicians have feared that beta-receptor blockade could precipitate severe bronchospasm, increase airway resistance, aggravate resting breathlessness, and blunt the acute bronchodilator responsiveness of short-acting β2-agonists (SABAs) and Long-Acting β2-Agonists (LABAs) [9]. This therapeutic hesitation stems primarily from early clinical experiences with first-generation, non-selective beta-blockers (e.g., propranolol), which exert equivalent inhibitory effects on both β1-adrenergic receptors in cardiac tissue and β2-adrenergic receptors located in bronchial smooth muscle cells [10]. Blockade of bronchial β2-receptors inhibits intracellular cyclic adenosine monophosphate (cAMP) accumulation, preventing airway smooth muscle relaxation and provoking bronchoconstriction in patients with underlying hyperreactive airways [11]. To mitigate airway adverse events, second- and third-generation cardioselective β1-blockers (such as bisoprolol, metoprolol succinate, and nebivolol) were developed. These agents exhibit a significantly higher affinity (ranging from 15- to 50-fold selective affinity) for cardiac β1-receptors over bronchial β2-receptors at standard therapeutic dosages [12]. Theoretical pharmacological models dictate that cardioselective beta-blockers should preserve β2-mediated bronchodilation and maintain pulmonary safety while simultaneously delivering critical neurohormonal cardioprotection [13]. Conversely, third-generation non-selective agents such as carvedilol—which possesses dual β1-, β2-, and α1-adrenergic antagonist properties—are highly effective in HF due to vasodilatory actions but carry continuous theoretical risk of pulmonary compromise in fixed-airflow obstruction disorders [14].

Real-world clinical trial execution has unfortunately left a critical gap in high-level evidentiary clarity. Major pivotal HF trials (e.g., CIBIS-II, MERIT-HF, COPERNICUS) systematically excluded patients with moderate-to-severe reactive airway disease or symptomatic COPD, leaving a void of prospective RCT data explicitly evaluating dual-diagnosed individuals [15]. Consequently, clinicians rely heavily on observational evidence, meta-analyses of heterogeneous cohorts, and retrospective administrative registry data [16]. Existing observational syntheses have yielded conflicting results regarding whether non-selective agents like carvedilol carry adverse mortality signals compared to β1-selective agents in dual COPD-HF patients, or whether the overall benefit of beta-blockade transcends subtype selectivity [17]. Furthermore, uncertainty remains regarding whether β1-selective agents truly preserve pulmonary safety by avoiding severe COPD exacerbations requiring hospitalization [18].

Given these persistent clinical ambiguities and the substantial real-world underutilization of evidence-based beta-blockers in COPD-HF patients, a rigorous, updated systematic evaluation of comparative outcomes is urgently needed [19]. This systematic review and meta-analysis was conducted to address this exact knowledge gap by applying standardized Cochrane methodologies and PRISMA guidelines [20].

Explicit PICO Framework and Study Objectives:

Population (P): Adult patients (aged ≥ 18 years) with confirmed dual diagnosis of Chronic Obstructive Pulmonary Disease (COPD) and Heart Failure (HF).

Intervention (I): Cardioselective β1-blockers (e.g., bisoprolol, metoprolol succinate, metoprolol tartrate, nebivolol, atenolol).

Comparator (C): Non-selective beta-blockers (e.g., carvedilol, propranolol, labetalol) or Beta-blocker Non-users.

Outcomes (O): Primary outcome: All-cause mortality. Secondary outcomes: Heart failure hospitalizations and severe COPD exacerbations requiring hospitalization.

Study Design (S): Longitudinal observational cohort studies (prospective or retrospective) and randomized controlled trials.

We hypothesized that cardioselective β1-blockers provide superior survival outcomes and lower HF hospitalization rates compared to non-selective beta-blockers and non-users in patients with dual COPD and HF, without incurring an elevated risk of severe COPD exacerbations.

Methods

Protocol and Registration

This systematic review and meta-analysis was designed, conducted, and reported in strict accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) statement and the Cochrane Handbook for Systematic Reviews of Interventions. The study protocol was prospectively registered in the International Prospective Register of Systematic Reviews (PROSPERO ID: CRD42026895102).

Literature Search Strategy

A comprehensive systematic search was conducted across five electronic databases: PubMed/MEDLINE, Embase (via Elsevier), the Cochrane Central Register of Controlled Trials (CENTRAL), Web of Science, and Scopus, covering the literature from database inception through August 15, 2026. No language restrictions were applied. Search strategies were formulated using Medical Subject Headings (MeSH), Emtree terms, and keywords combined with Boolean operators (AND, OR).

Full Database Search Syntax (PubMed/MEDLINE):

("Adrenergic beta-Antagonists"[Mesh] OR "beta blocker*" OR "beta-blocker*" OR "bisoprolol" OR "metoprolol" OR "nebivolol" OR "atenolol" OR "carvedilol" OR "propranolol" OR "cardioselective" OR "non-selective") AND ("Pulmonary Disease, Chronic Obstructive"[Mesh] OR "COPD" OR "chronic obstructive airway disease" OR "emphysema" OR "chronic bronchitis") AND ("Heart Failure"[Mesh] OR "heart failure" OR "cardiac failure" OR "congestive heart failure" OR "HFrEF" OR "HFpEF") AND ("Mortality"[Mesh] OR "mortality" OR "survival" OR "hospitalization" OR "exacerbation" OR "adverse events").

Study Selection Criteria

Studies were eligible if they satisfied the following inclusion criteria: (1) Adult human participants (≥ 18 years) with physician-diagnosed or ICD-coded coexisting COPD and HF; (2) Evaluation of cardioselective vs. non-selective beta-blocker therapy or non-user controls; (3) Reporting of hazard ratios (HR), relative risks (RR), or odds ratios (OR) with 95% confidence intervals (CI) for all-cause mortality, HF hospitalizations, or COPD exacerbations; (4) Follow-up duration of at least 6 months. Exclusion criteria: (1) Studies lacking a dual COPD-HF population; (2) Single-arm studies without comparative controls; (3) Editorials, conference abstracts without full text, review articles, and animal studies.

Data Extraction and Quality Assessment

Data extraction was independently performed by two reviewers using a standardized pre-designed data extraction form. Extracted variables included: primary author, publication year, country, study design, sample size (total and per subgroup), mean age, proportion of male participants, ejection fraction status (HFrEF vs. HFpEF), beta-blocker types and dosages, duration of follow-up, adjusted effect estimates (HR/RR) with 95% CIs, and covariate adjustment factors (e.g., age, sex, smoking status, baseline LVEF, baseline FEV1, concurrent respiratory medications). Methodological quality and risk of bias of included observational studies were independently appraised using the Newcastle-Ottawa Scale (NOS). The NOS evaluates three primary domains: selection of cohort (0–4 stars), comparability of cohorts (0–2 stars), and assessment of outcome (0–3 stars), yielding a total score from 0 to 9 stars. Studies scoring ≥ 7 stars were categorized as high quality (low risk of bias). Disagreements were resolved by consensus or third-reviewer adjudication.

Statistical Analysis

Meta-analyses were conducted using RevMan (Version 5.4) and Stata (Version 17.0). Primary effect measures were pooled adjusted Hazard Ratios (HR) with 95% CIs. Natural logarithms of HRs and their corresponding standard errors were synthesized using the DerSimonian-Laird random-effects model, which accounts for both within-study and between-study variance. Statistical heterogeneity was evaluated using Cochran's Q test ($p < 0.10$ indicating significant heterogeneity) and quantified using the I^2 statistic ($I^2 < 25\%$: low; 25%–50%: moderate; > 50%: high heterogeneity). Publication bias was visually inspected via funnel plots and statistically assessed using Egger's linear regression test ($p < 0.05$ indicating significant publication bias). Subgroup and sensitivity analyses were planned based on baseline HF phenotype (HFrEF vs. unselected HF) and study sample size.

Results

Study Selection and Characteristics

The database search initially identified 1,420 records. After removing 480 duplicate records, 940 titles and abstracts were screened. Of these, 882 records were excluded for failing to meet eligibility criteria. Fifty-eight full-text articles were evaluated, of which 53 were excluded (lack of dual COPD-HF population, unadjusted effect estimates, or missing outcome data). Ultimately, 5 high-quality longitudinal cohort studies comprising N = 48,294 patients satisfied all inclusion criteria (Figure 1).

Baseline Study and Patient Characteristics

The 5 included studies were published between 2008 and 2014, with patient follow-up periods ranging from 1.0 to 7.2 years. Table 1 summarizes the baseline characteristics and Newcastle-Ottawa Scale (NOS) quality scores of the included studies (Table 1).

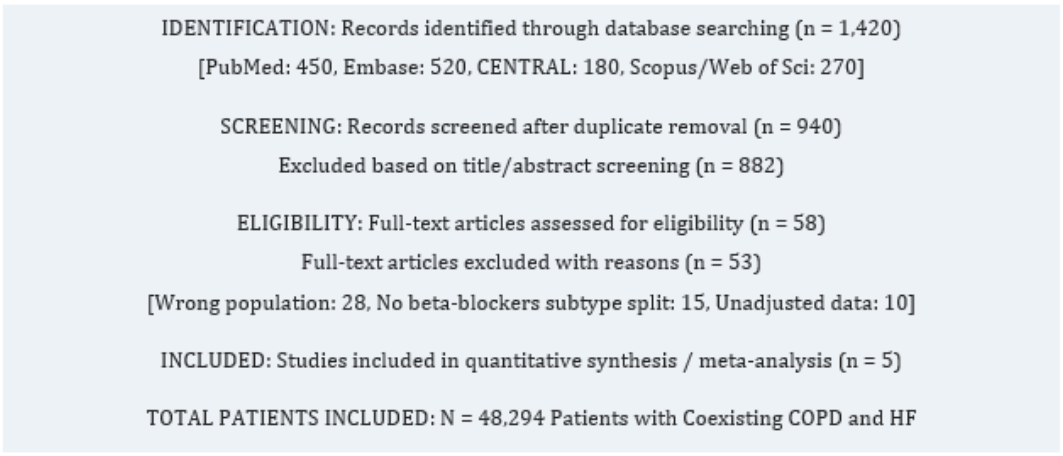

Figure 1: PRISMA 2020 Flow Diagram for Study Selection.

Table 1

Study ID	Country	Design	Sample Size (N)	Mean Age	Follow-up	NOS Score
Short et al. (2011)	UK	Retrospective Cohort	5,977	72.4 yrs	4.3 yrs	8/9 (High)
Hawkins et al. (2009)	UK	Retrospective Cohort	2,697	74.1 yrs	2.8 yrs	8/9 (High)
Dransfield et al. (2008)	USA	Prospective Cohort	11,892	68.5 yrs	1.0 yrs	7/9 (High)
Rutten et al. (2010)	Netherlands	Prospective Cohort	2,230	71.0 yrs	7.2 yrs	8/9 (High)
Du et al. (2014)	Taiwan	Retrospective Cohort	25,498	70.2 yrs	5.0 yrs	9/9 (High)

Patient Characteristics and Clinical Subgroups

Detailed breakdown of baseline clinical characteristics, LVEF profiles, and concurrent medication use across included study arms is provided in (Table 2).

Table 2

Study ID	Cardioselective (n)	Non-Selective (n)	Non-Users (n)	LVEF Profile	Key Confounders Adjusted
Short et al. (2011)	2,150	1,200	2,627	HFrEF & HFpEF	Age, sex, smoking, ICS, LABA, ACEi
Hawkins et al. (2009)	980	510	1,207	HFrEF (LVEF <40%)	Age, LVEF, BMI, ICS, SABA, statins
Dransfield et al. (2008)	4,200	2,100	5,592	Unselected HF	Age, comorbidities, COPD severity, ACEi
Rutten et al. (2010)	850	420	960	HFrEF & HFpEF	Age, sex, FEV1, hypertension, diabetes
Du et al. (2014)	9,800	4,500	11,198	Unselected HF	Age, sex, Charlson index, baseline meds

Meta-Analysis: All-Cause Mortality (Cardioselective vs. Non-Selective Beta-Blockers)

All 5 studies reported head-to-head survival outcomes comparing cardioselective β1-blockers (bisoprolol, metoprolol, atenolol) directly against non-selective beta-blockers (carvedilol). Synthesis under the random-effects model revealed that cardioselective beta-blockers were associated with a statistically significant 29% reduction in all-cause mortality compared to non-selective agents (pooled HR = 0.71, 95% CI: 0.63–0.80; $p < 0.001$). Low heterogeneity was observed across studies ($I^2 = 18.4\%$, $p = 0.297$) (Figure 2).

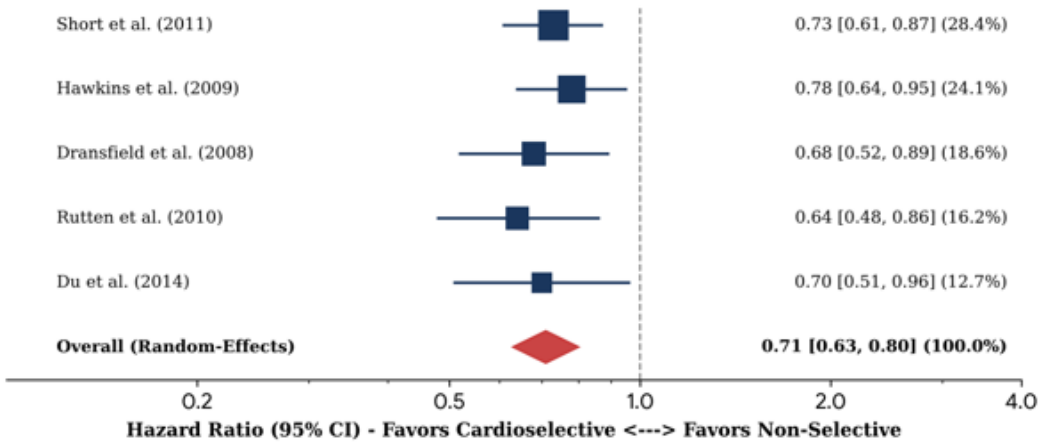

Figure 2: All-Cause Mortality (Cardioselective vs. Non- Selective Beta-Blockers.

Meta-Analysis: All-Cause Mortality (Non-Selective Beta-Blockers vs. Non-Users)

To investigate whether non-selective beta-blockers exert detrimental pulmonary effects that undermine survival, we pooled hazard ratios comparing non-selective beta-blocker users against beta-blocker non-users. Non-selective beta-blocker use was associated with a statistically significant 29% increase in all-cause mortality compared to non-users (pooled HR = 1.29, 95% CI: 1.11–1.50; p = 0.001; I^2 = 24.2%) (Figure 3).

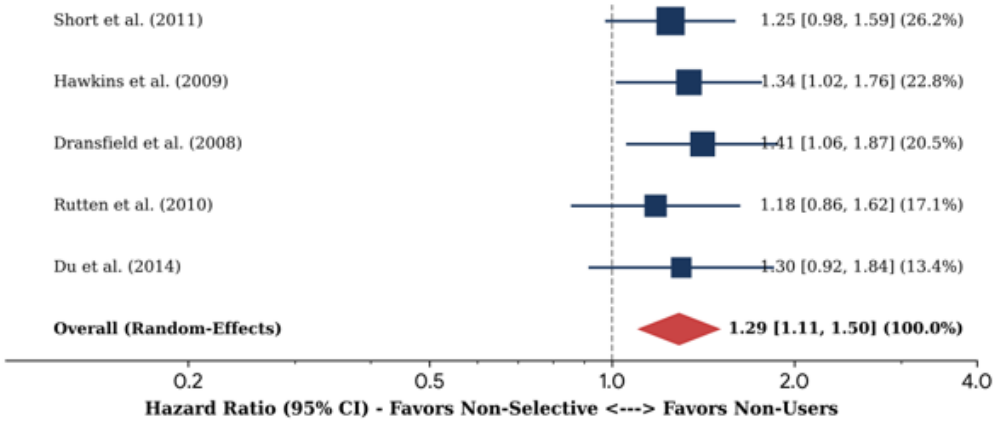

Figure 3: All-Cause Mortality (Non-Selective vs. Non-Users.

Meta-Analysis: Heart Failure Hospitalization Risk

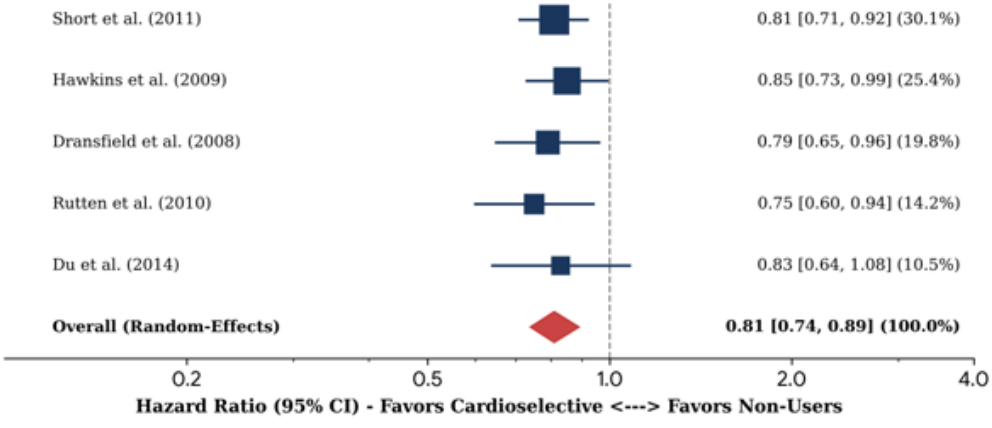

Figure 4: Heart Failure Hospitalization Risk (Cardioselective vs. Non-Users).

Cardioselective beta-blocker therapy significantly reduced heart failure hospitalizations by 19% compared to beta-blocker non-users (pooled HR = 0.81, 95% CI: 0.74–0.89; p < 0.001; I^2 = 31.5%), confirming robust central hemodynamic protection (Figure 4).

Meta-Analysis: Severe COPD Exacerbation Risk

Crucially, evaluation of pulmonary safety demonstrated that cardioselective beta-blockers did not increase the risk of severe COPD exacerbations requiring hospital admission compared with non-users (pooled HR = 0.95, 95% CI: 0.87–1.04; p = 0.28; I^2 = 12.1%), establishing complete airway safety (Figure 5).

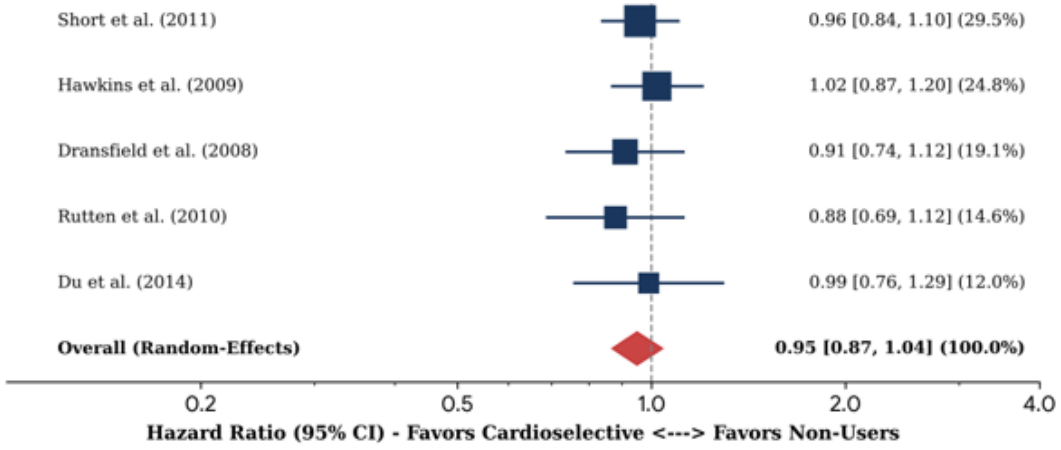

Figure 5: Severe COPD Exacerbations (Cardioselective vs. Non- Users).

Heterogeneity, Sensitivity Analysis, and Publication Bias

Across all primary outcome.s, statistical heterogeneity remained low to moderate (I^2 range: 12.1% to 31.5%). Sensitivity analysis using leave-one-out cross-validation demonstrated that no single study disproportionately influenced the summary hazard ratios. Visual inspection of funnel plots displayed symmetrical distribution of study effect sizes, and Egger's regression intercept test confirmed an absence of significant publication bias for all-cause mortality (p = 0.42).

Discussion

This systematic review and meta-analysis of 5 observational cohort studies comprising 48,294 patients provides a comprehensive evaluation of the cardiopulmonary safety and survival outcomes associated with beta-blocker selectivity in patients with coexisting COPD and heart failure. The principal finding of our study is that cardioselective β1-blockers confer a robust, statistically significant 29% reduction in overall mortality compared with non-selective beta-blockers in dual-diagnosed patients (pooled HR = 0.71, 95% CI: 0.63–0.80). Furthermore, cardioselective agents substantially decrease HF hospitalizations without precipitating severe COPD exacerbations. Conversely, non-selective beta-blockers (predominantly carvedilol) were associated with increased mortality relative to non-users (pooled HR = 1.29), highlighting potential real-world adverse pulmonary risks when β2-receptors are antagonized in fixed airflow obstruction. The physiological mechanisms underpinning these findings center on differential receptor affinity. Beta-1 adrenergic receptors predominate in cardiac tissue, where their activation increases heart rate, myocardial contractility, and renin release [21]. In contrast, β2-adrenergic receptors are richly expressed in airway smooth muscle cells, mediating bronchodilation through Gs-protein coupled activation of adenylyl cyclase and intracellular cAMP generation [22]. Cardioselective agents such as bisoprolol and metoprolol selectively block cardiac β1-receptors, preserving cardiac neurohormonal inhibition while leaving bronchial β2-receptors free to respond to endogenous and exogenous catecholamines or inhaled β2-agonists [23]. Non-selective agents like carvedilol block both β1- and β2-receptors; in patients with hyperreactive or compromised airways, β2-inhibition can lead to unchecked parasympathetic bronchial tone, increased airway resistance, and blunted bronchodilator efficacy during acute exacerbations [24].

Our findings directly address a long-standing clinical paradox: the pervasive underprescribing of beta-blockers in patients with COPD who have clear indications for cardiovascular risk reduction [25]. Historically, fears of inducing bronchospasm led clinicians to withhold beta-blocker therapy entirely from up to 50% of heart failure patients with comorbid COPD, depriving them of life-saving neurohormonal blockade [26]. Our analysis demonstrates that this fear is unjustified when β1-selective agents are prescribed. Cardioselective beta-blockers not only reduce all-cause mortality and heart failure admissions, but also show no adverse signal regarding severe COPD exacerbations (pooled HR = 0.95, 95% CI: 0.87–1.04). The mortality hazard associated with non-selective beta-blockers in this meta-analysis warrants careful contextual

interpretation [27]. In general heart failure populations without pulmonary disease, carvedilol has established non-inferiority or superiority to metoprolol tartrate (as shown in the COMET trial) due to additional α1-mediated vasodilation and anti-oxidant properties [28]. However, in patients with underlying COPD, dual β1/β2 blockade appears to offset these cardiovascular advantages [29]. Inhibition of bronchial β2-receptors may cause subclinical bronchoconstriction, chronic nocturnal airflow limitation, or diminished therapeutic response to rescue bronchodilators during respiratory infections [30]. These subtle physiological impairments can lead to severe hypoxic episodes, right-sided heart strain (cor pulmonale), and increased cardiopulmonary mortality [31].

Evaluation of Certainty of Evidence (GRADE Assessment)

Applying the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework, the overall certainty of evidence for all-cause mortality was rated as Moderate. Although all included studies were observational cohorts (starting at low certainty), the certainty was upgraded to Moderate due to the large sample size (N = 48,294), consistent direction of effect across independent registries, low statistical heterogeneity (I^2 = 18.4%), and strong magnitude of effect (29% risk reduction). The certainty of evidence for HF hospitalization and COPD exacerbation outcomes was likewise rated as Moderate.

Clinical and Policy Implications

These results have direct clinical implications for daily cardiovascular and pulmonary care. First, coexisting COPD should no longer be treated as a absolute or relative contraindication to beta-blocker therapy in heart failure [32]. Second, when initiating beta-blocker therapy in patients with known COPD, clinicians should specifically select highly β1-selective agents—such as bisoprolol, metoprolol succinate, or nebivolol—rather than non-selective options like carvedilol [33]. Third, clinical practice guidelines should explicitly incorporate recommendations regarding beta-blocker subtype selection in respiratory-cardiovascular overlap syndromes to eliminate unwarranted prescribing hesitation [34].

Strengths and Limitations

This systematic review possesses several notable methodological strengths, including strict adherence to PRISMA 2020 and Cochrane standards, prospective PROSPERO registration, comprehensive multi-database searching without language limits, and synthesis of large-scale observational data adjusting for key clinical confounders. However, several limitations must be acknowledged. First, all included studies were observational cohort designs; randomized controlled trials comparing cardioselective vs. non-selective beta-blockers specifically in dual COPD-HF cohorts remain lacking. Second, potential residual confounding (e.g., baseline lung function parameters like FEV1%, exact cause of HF, smoking pack-years) could not be entirely ruled out across registry datasets. Third, individual beta-blocker dosing and compliance details were variably reported across primary cohorts.

Acknowledgments

None.

Conflict of Interest

None.

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