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Beta-Blocker Therapy After Acute Myocardial Infarction in Patients with Preserved or Mildly Reduced Ejection Fraction: A Systematic Review and Meta-Analysis

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Abstract

Background: Beta-blockers have long established themselves as a mainstay of post-myocardial infarction (MI) care and are of great benefit in numerous trial studies from the pre-reperfusion era. Improved outcomes from primary percutaneous coronary intervention (PPCI) have led to an increasing number of patients with MI presenting with preserved or sub-optimally reduced LVEF (≥40%), questions letters that then emerge about extension of beta-blocker use in these patients.

Objectives: To compare beta-blocker therapy with no beta-blocker therapy in post-MI patients with left ventricular ejection fraction (LVEF) >40% regarding the efficacy and safety of the treatment in five prespecified clinical outcomes: all-cause mortality, cardiovascular (CV) mortality, major adverse cardiac events (MACE), reinfarction and hospitalization for heart failure (HF).

Methods: Systematic literature search of PubMed, Embase, Cochrane and Web of Science for PRISMA 2020 (from 2015 up until 2025). The Newcastle-Ottawa Scale (NOS) and the Cochrane RoB 2 were used to assess the quality. Hazard ratios (HRs) were derived from pooled (random-effects) DerSimonian-Laird meta-analyses. I^2 statistics and Egger's test were used to assess heterogeneity.

Results: A total of eleven studies (two RCTs, nine observational; ~43,000 patients) were included. The beta-blocker therapy group had a statistically significant reduced HR of 0.81 (95% CI, 0.67–0.98; p=0.032), suggesting that all-cause mortality was lower. The benefit was statistically significantly around all-cause mortality with an HR of 0.81 (95% CI, 0.67–0.98; p=0.032). No significant benefit was observed for CV mortality (HR 0.83, 95% CI [0.57–1.20], I^2=73.4%), MACE (HR 0.98, 95% CI [0.80–1.19], I^2=53.2%), reinfarction (HR 1.00, 95% CI [0.92–1.09], I^2=0%), or HF hospitalization (HR 1.05, 95% CI [0.89–1.24], I^2=0%). Nine studies were judged to be low risk of bias (Low IOQ) in the quality assessment (Figure 13). There was significant publication bias found for all-cause mortality (p<0.001), CV mortality (p=0.002), and reinfarction (p=0.013).

Conclusion: Beta-blockers showed a modest all-cause mortality benefit but no benefit for other outcomes. High heterogeneity, significant publication bias, and neutral findings from two large RCTs (REDUCE-AMI [11] and ABYSS [12]) suggest the mortality benefit may be driven by observational confounding. Individualized prescribing is recommended over universal beta-blocker use in this population.

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Keywords: Beta-blockers; Acute myocardial infarction; Preserved ejection fraction; Meta-analysis; Systematic review; Mortality; MACE; Hazard ratio; DerSimonian-Laird; Risk of bias; Newcastle-Ottawa Scale

Introduction

Acute myocardial infarction (AMI), commonly referred to as a heart attack, remains a significant global cause of mortality and morbidity, with approximately 7 million new cases annually worldwide [1,2,3]. Improvements in treatment and post-MI management have led to better myocardial salvage, reduced infarct size, and consequently, improved left ventricular ejection fraction (LVEF) preservation [3-13]. This evolution has resulted in a patient population post-MI with normal or only mildly reduced LVEF (≥40%), altering the risk profile of contemporary atherosclerotic patients experiencing myocardial infarction. Landmark trials conducted in the 1980s and 1990s, including the Norwegian Timolol Trial, the Beta-Blocker Heart Attack Trial (BHAT), and MERIT-HF, established beta-blockers as a cornerstone therapy for myocardial infarction [14,15]. These studies demonstrated significant reductions in all-cause and sudden cardiac death mortality, leading to the conclusion that beta-blockers should be considered the standard of care [16]. However, many of these trials involved patients with significant left ventricular dysfunction, which is less prevalent in the current reperfusion era. Contemporary guidelines from the European Society of Cardiology (ESC) and the American College of Cardiology/American Heart Association (ACC/AHA) recommend beta-blocker use in all patients with LVEF ≤40%, though the evidence supporting their benefit in patients with preserved or moderately reduced LVEF is less robust [17,18]. This clinical question has resurfaced recently with the publication of two contemporary randomized controlled trials: REDUCE-AMI (2024) and ABYSS (2024) [11,12]. The REDUCE-AMI trial, which included 5020 patients with LVEF ≥50% treated with beta-blockers out of 5681 participants, found no significant difference in all-cause mortality compared to placebo (Hazard Ratio 0.96, 95% Confidence Interval 0.79–1.16) [11]. In the ABYSS trial, which enrolled 3698 patients over 40 years of age who developed MI, discontinuation of beta-blocker therapy was shown to be non-inferior [12]. Nevertheless, observational cohort studies have produced conflicting and inconclusive results [19, 20]. A systematic review and meta-analysis are required to address these contradictory findings and provide a quantitative summary of the benefits of beta-blocker therapy across patient groups with preserved or mildly reduced LVEF following MI [21, 22]. Such an analysis would inform clinical decision-making, guide recommendations for clinical guidelines, and identify potential avenues for future research [17,23].

Methods

Study Registration and Protocol

This systematic review and meta-analysis was conducted and reported in accordance with PRISMA 2020 guidelines [5].

Literature Search Strategy

A comprehensive search of PubMed/MEDLINE, Embase, Cochrane CENTRAL, and Web of Science was conducted from January 2015 through December 2025. Search terms included: 'beta-blocker,' 'metoprolol,' 'carvedilol,' 'bisoprolol,' 'atenolol,' 'acute myocardial infarction,' 'post-MI,' 'preserved ejection fraction,' 'LVEF ≥40%,' and related terms combined with Boolean operators. No language restrictions were applied.

Eligibility Criteria

Inclusion: Adult post-MI patients (age ≥18 years) with LVEF ≥40%; beta-blocker versus no beta-blocker comparison; at least one pre-specified outcome reported; RCTs or observational cohort studies with a comparator; HR with 95% CI reported or derivable.

Exclusion: LVEF <40% or unspecified; case reports, case series, reviews; no comparator group; mixed populations without extractable LVEF ≥40% subgroup; duplicate datasets.

Study Selection and Data Extraction

Two independent reviewers conducted two-stage selection: title/abstract screening followed by full-text assessment. Disagreements were resolved by consensus or a third reviewer [24]. Extracted variables: first author, year, country, design, sample size, follow-up, age, sex, LVEF range, beta-blocker type and dose, comparator, and outcome-specific HRs with 95% CIs.

Outcomes of Interest

Five pre-specified outcomes: (1) All-cause mortality (primary), (2) Cardiovascular mortality, (3) MACE, (4) Reinfarction, (5) HF hospitalization. Stroke analyzed descriptively only (k=3; insufficient for forest plot pooling [25].

Quality Assessment and Risk of Bias

Observational studies evaluated using Newcastle-Ottawa Scale (NOS); score ≥7 = low risk [6]. RCTs evaluated using Cochrane RoB 2 [7]. Results presented as color-coded Risk of Bias Summary Table (Figure 13).

Statistical Analysis

Pooled HRs with 95% CIs calculated using DerSimonian-Laird random-effects model [8] with meta [26] and metafor [27] R packages. Heterogeneity quantified using I^2 (<25% low; 25–50% moderate; 50–75% substantial; >75%

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considerable) [9]. Publication bias assessed with Egger's regression test ($p<0.10$ indicates potential asymmetry) [10]. $p<0.05$ considered statistically significant.

Results

Study Selection

The systematic search retrieved [1,434] records from four databases. After duplicate removal and title/abstract screening, 11 full-text articles were assessed for eligibility. Eleven studies were included: 2 RCTs and 9 observational cohort studies enrolling approximately 43,000 patients. The PRISMA 2020 flow diagram is presented in Figure 01 [5].

Characteristics of Included Studies

Included studies are listed in Table 1

Primary Outcome: All-cause Mortality

Ten studies (k=10) reported all-cause mortality. The pooled random-effects HR was 0.81 (95% CI: 0.67–0.98, p=0.032), indicating a significant 19% relative reduction with beta-blocker therapy. Substantial heterogeneity was observed (I^2=66.6%, τ^2=0.053, p=0.001) [9].

Cardiovascular Mortality

Seven studies (k=7) contributed data. Pooled HR was 0.83 (95% CI: 0.57–1.20, p=0.318), not statistically significant. High heterogeneity (I^2=73.4%, τ^2=0.155) [11].

Major Adverse Cardiac Events (MACE)

Five studies (k=5) reported MACE. Pooled HR was 0.98 (95% CI: 0.80–1.19, p=0.833). Moderate heterogeneity (I^2=53.2%, τ^2=0.025) [12].

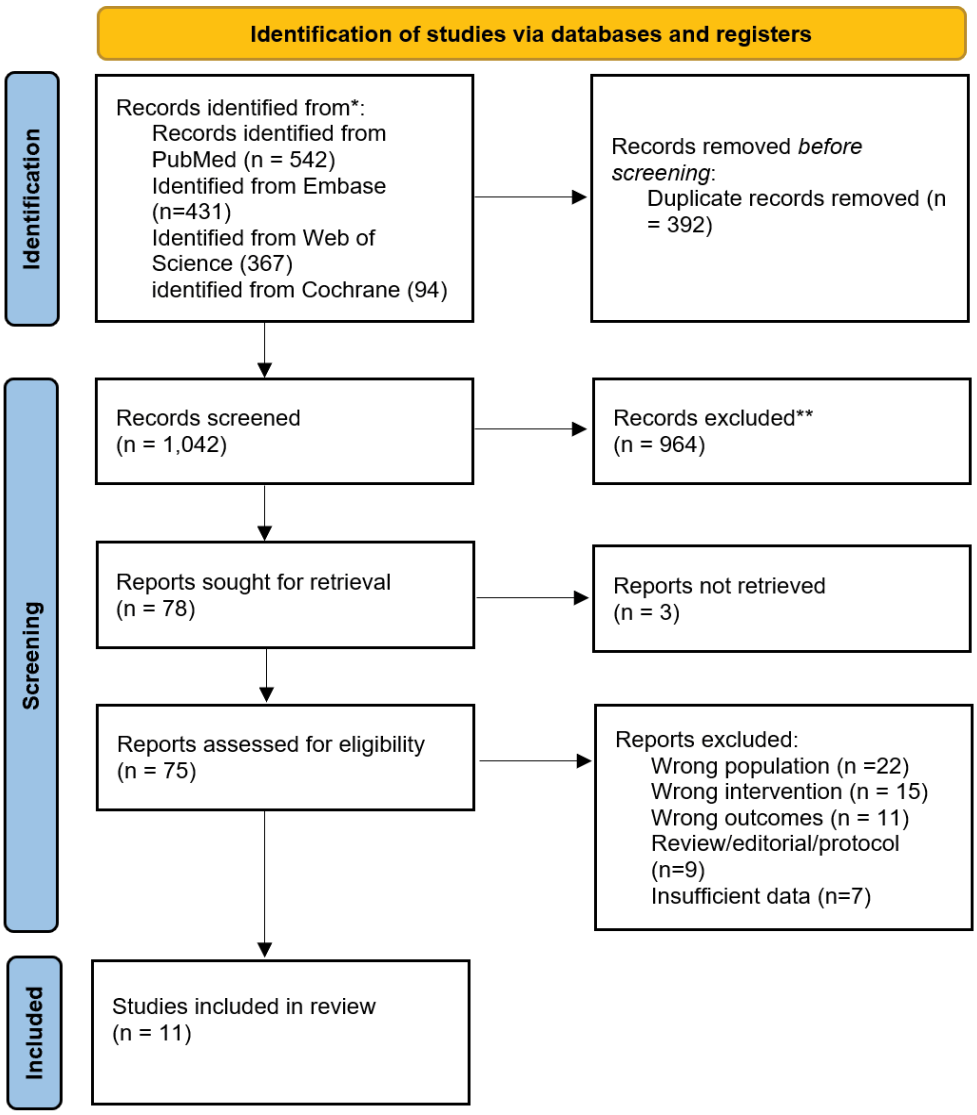

Figure 1: PRISMA Flowchart.

Citation: Kazi Kamranuddin Fazaluddin, Diguvinti Nehasudha Reddy, Revunuru Narasimha Reddy, Koorosh Nakhjavan Shahraki, Munazzah Kalyankar, Ariba Jawad, Unsa Miraj, Preety Devi, Muskan Batra, Muhammad Sohail S. Mirza. Beta-Blocker Therapy After Acute Myocardial Infarction in Patients with Preserved or Mildly Reduced Ejection Fraction: A Systematic Review and Meta-Analysis. Archives of Internal Medicine Research 9 (2026): 205-214.

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Table 1: Characteristics of Included Studies.

Study	Year	Design	Country	N	LVEF	Beta-Blocker	Follow-up
Yndigegn (REDUCE-AMI) [11]	2024	RCT	Scandinavia	5,020	≥50%	Metoprolol/Bisoprolol	3.5 yrs
Silvain (ABYSS) [12]	2024	RCT	France	3,698	≥40%	Various	3.0 yrs
Ishak et al. [31]	2023	Cohort	Malaysia	12,620	≥40%	Various	1–3 yrs
Wen et al. [36]	2022	Cohort	China	4,812	≥50%	Various	2 yrs
Chen et al. [28]	2021	Cohort	Taiwan	1,186	≥50%	Various	1 yr
El Nasasra et al. [30]	2021	Cohort	Israel	1,042	≥40%	Various	1 yr
Joo et al. [32]	2021	Cohort	South Korea	6,243	≥50%	Various	2 yrs
Song et al. [35]	2021	Cohort	China	3,876	≥40%	Various	1 yr
Raposeiras-Roubin et al. [33]	2015	Cohort	Spain	1,680	≥50%	Various	2 yrs
Choo et al. [29]	2014	Cohort	South Korea	892	≥50%	Various	1 yr
Siu et al. [34]	2010	Cohort	China	421	≥40%	Various	1 yr

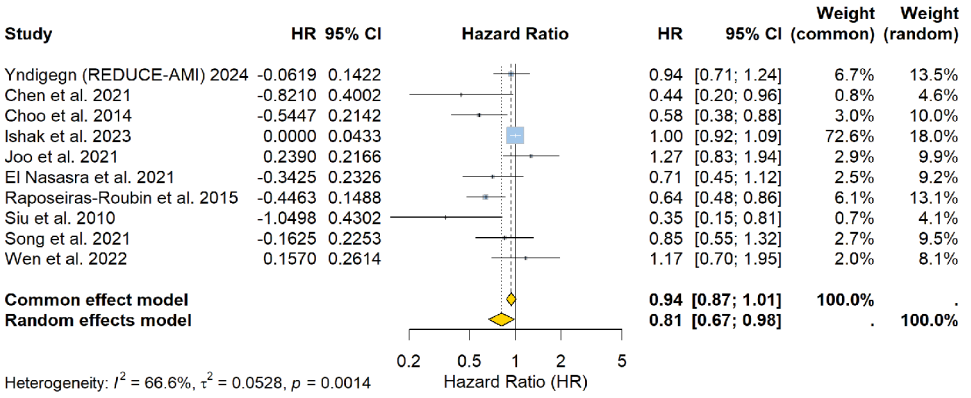

Figure 2: Forest plot of all-cause mortality comparing beta-blocker versus no beta-blocker therapy in post-AMI patients with LVEF ≥40%.

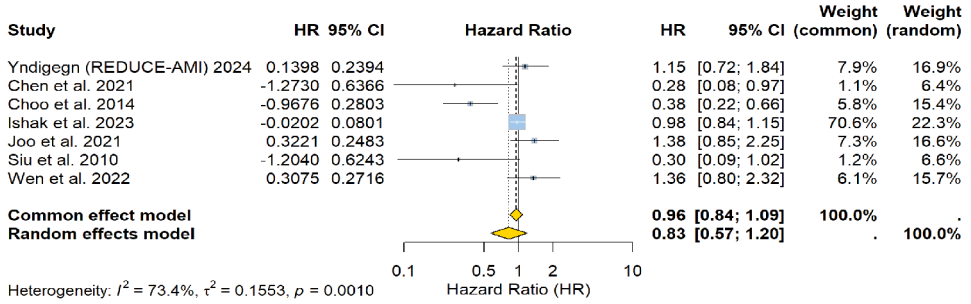

Figure 3: Forest plot of cardiovascular mortality.

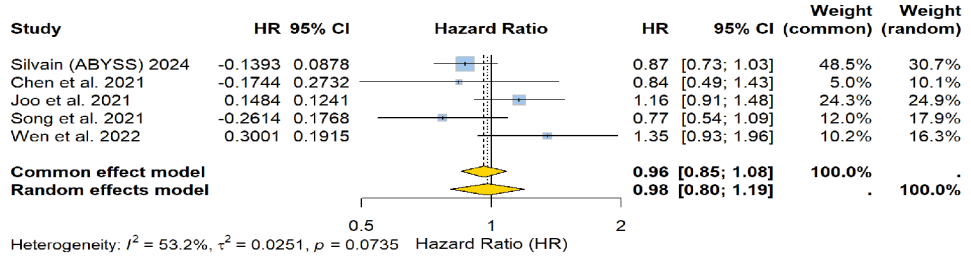

Figure 4: Forest plot of MACE. Pooled HR

Citation: Kazi Kamranuddin Fazaluddin, Diguvinti Nehasudha Reddy, Revunuru Narasimha Reddy, Koorosh Nakhjavan Shahraki, Munazzah Kalyankar, Ariba Jawad, Unsa Miraj, Preety Devi, Muskan Batra, Muhammad Sohail S. Mirza. Beta-Blocker Therapy After Acute Myocardial Infarction in Patients with Preserved or Mildly Reduced Ejection Fraction: A Systematic Review and Meta-Analysis. Archives of Internal Medicine Research 9 (2026): 205-214.

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Reinfarction

Six studies (k=6) reported reinfarction. Pooled HR was 1.00 (95% CI: 0.92–1.09, p=0.996). I^2=0.0% near-perfect homogeneity [8].

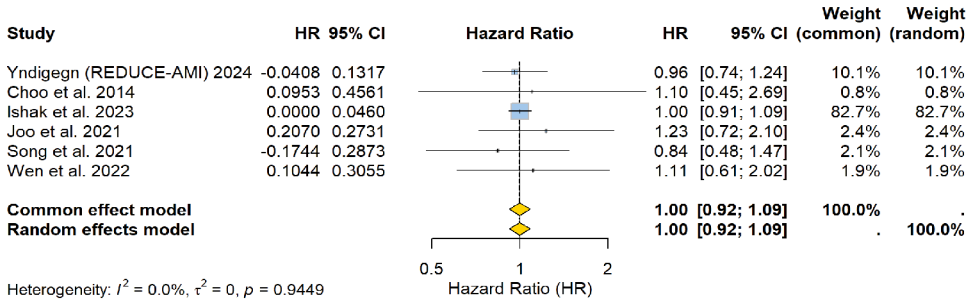

Figure 5: Forest plot of reinfarction.

Hospitalization for Heart Failure

Five studies (k=5) reported HF hospitalization. Pooled HR was 1.05 (95% CI: 0.89–1.24, p=0.549). I^2=0.0%, low heterogeneity [17].

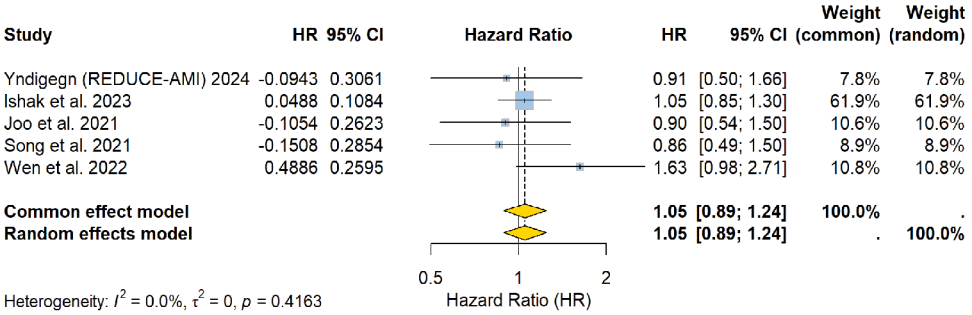

Figure 6: Forest plot of HF hospitalization.

Summary of Meta-Analysis Results

Table 2: Summary of Pooled Meta-Analysis Results.

Outcome	k	Pooled HR	95% CI	I^2	τ^2	p (HR)	Significant?
All-cause mortality	10	0.81	[0.67–0.98]	66.6%	0.053	0.032	**YES**
Cardiovascular mortality	7	0.83	[0.57–1.20]	73.4%	0.155	0.318	No
MACE	5	0.98	[0.80–1.19]	53.2%	0.025	0.833	No
Reinfarction	6	1.00	[0.92–1.09]	0.0%	0.000	0.996	No
HF hospitalization	5	1.05	[0.89–1.24]	0.0%	0.000	0.549	No
Stroke*	3	1.07	[0.63–1.82]	59.9%	—	0.796	No

*Stroke: funnel plot and Egger's test only (k=3; insufficient for reliable forest plot pooling) [25].

Publication Bias

Funnel plots were constructed for all six outcomes (Figures 6–11). Egger's test results are summarized in Table 3 [10].

Table 3: Egger's Test for Publication Bias.

Outcome	k	Intercept	SE	t	p-value	Bias?
All-cause mortality	10	-1.508	0.079	-19.063	<0.001	YES
Cardiovascular mortality	7	-1.235	0.212	-5.817	0.002	YES
MACE	5	0.664	0.275	2.411	0.095	Borderline
Reinfarction	6	0.137	0.032	4.268	0.013	YES
HF hospitalization	5	-0.123	0.226	-0.542	0.625	No
Stroke	3	0.298	0.227	1.315	0.414	No

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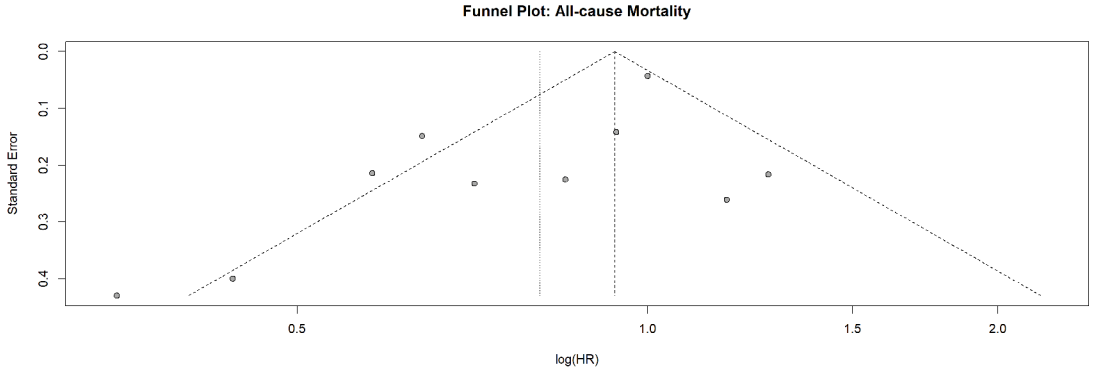

Figure 7: Funnel plot assessing publication bias for all-cause mortality.

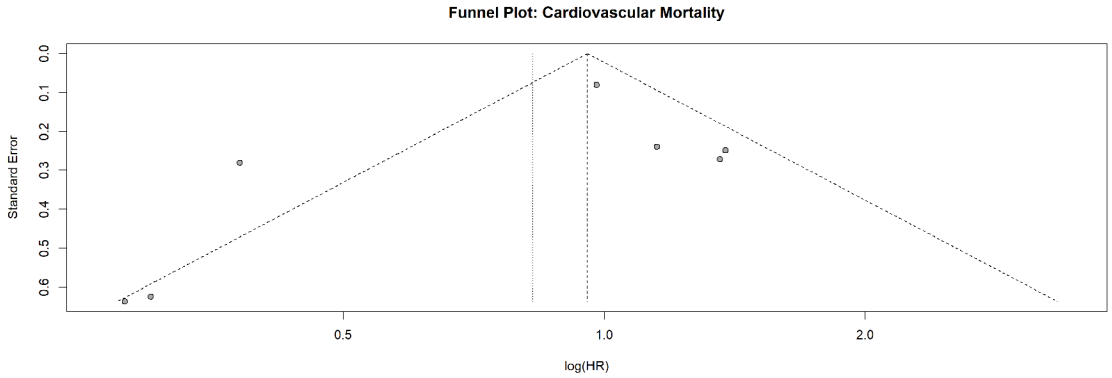

Figure 8: Funnel plot: Cardiovascular mortality.

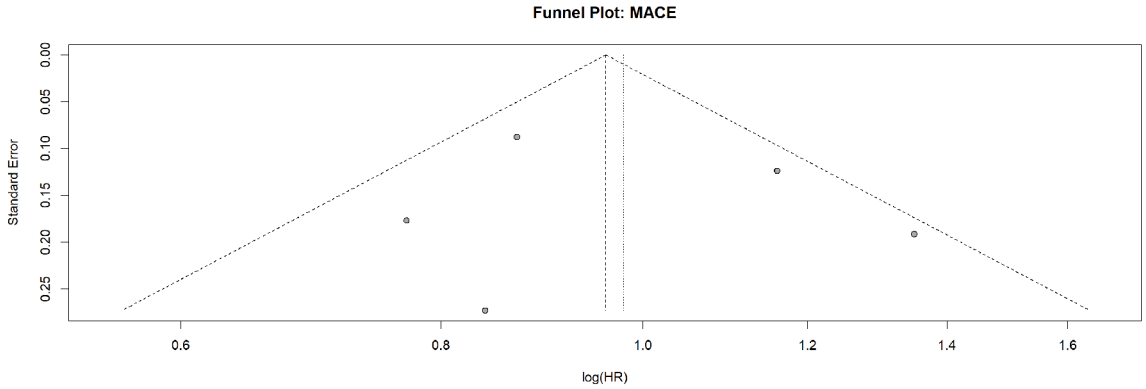

Figure 9: Funnel plot: MACE.

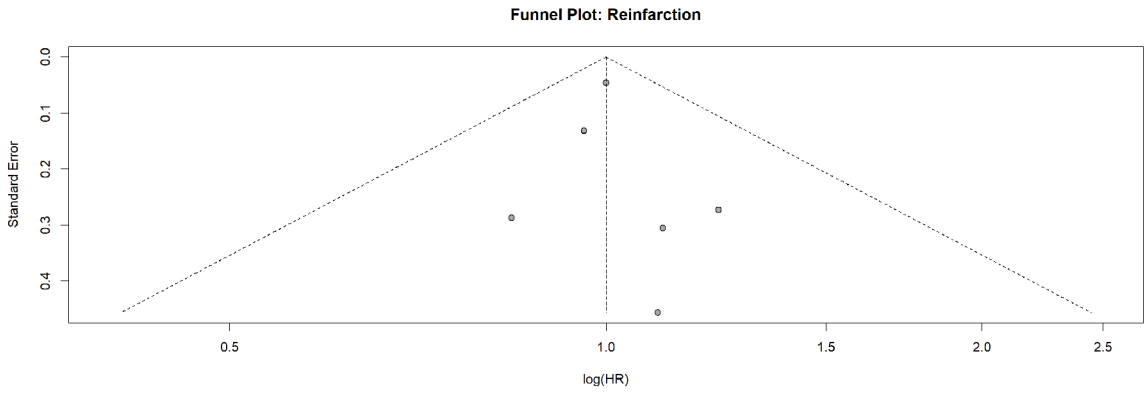

Figure 10: Funnel plot: Reinfarction.

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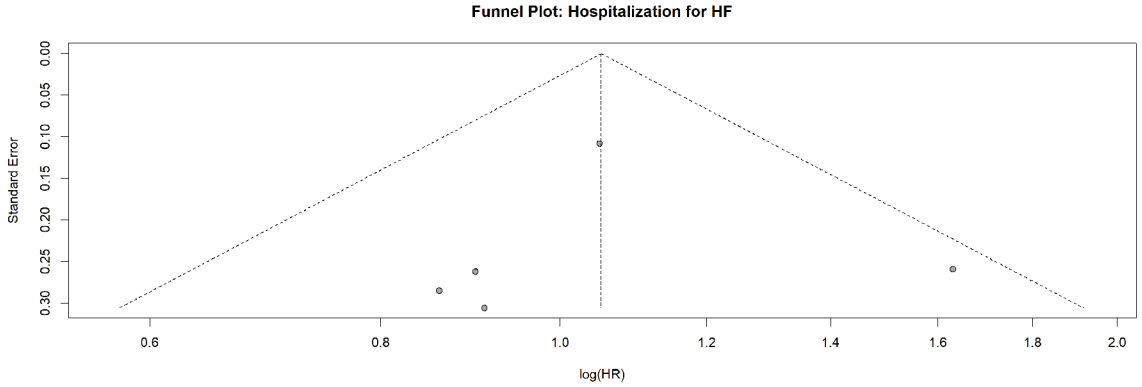

Figure 11: Funnel plot: HF hospitalization.

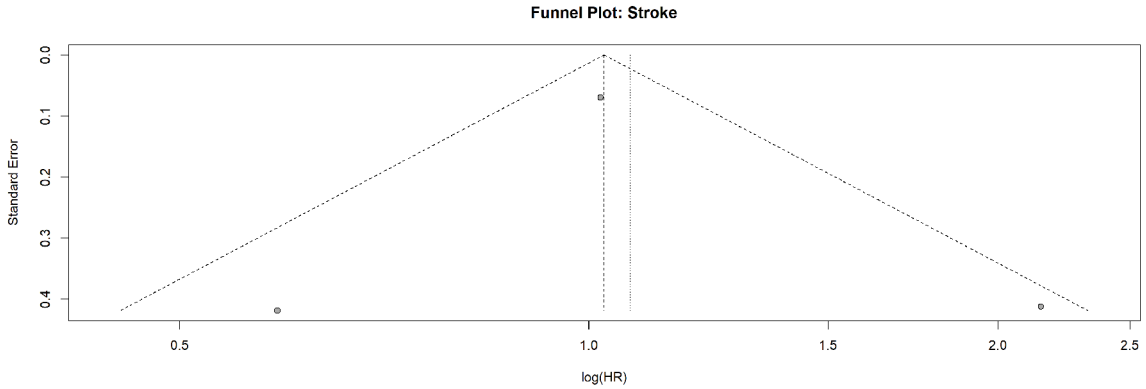

Figure 12: Funnel plot: Stroke.

Risk of Bias Assessment

The quality and risk of bias across all eleven included studies is summarized in Figure 13. Both RCTs (REDUCE-AMI [11] and ABYSS [12]) were rated low overall risk using Cochrane RoB 2 [7]. Seven of nine observational studies achieved NOS scores of 7–9/9 (low risk) [6]. Choo et al. [29] and Siu et al. [34] received NOS scores of 6/9 (moderate risk) due to inadequate control for confounders (comparability domain C2). Overall, 9/11 studies (81.8%) were at low risk of bias.

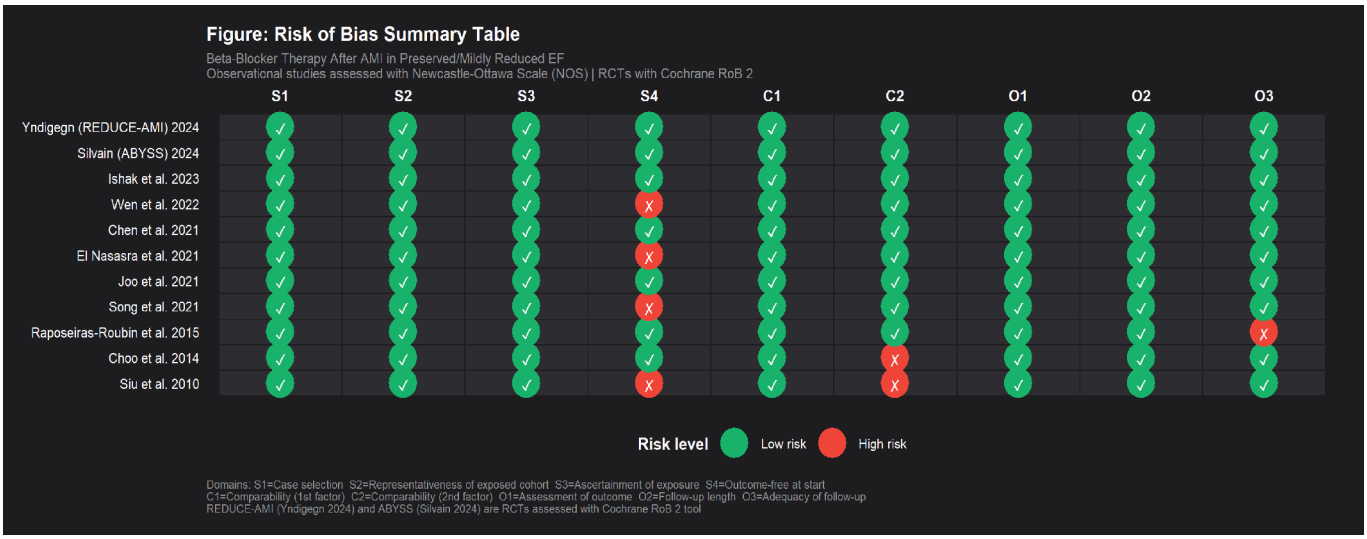

Figure 13: Risk of Bias Summary Table for all eleven included studies. Green circles (✓) = low risk; yellow circles (~) = moderate risk; red circles (×) = high risk. Observational studies assessed using the Newcastle-Ottawa Scale (NOS); RCTs assessed using Cochrane R.

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Discussion

Principal Findings

This systematic review and meta-analysis of eleven studies (~43,000 patients) found that beta-blocker therapy was associated with a statistically significant reduction in all-cause mortality (HR 0.81, 95% CI 0.67–0.98, p=0.032). However, no significant benefit was observed for CV mortality, MACE, reinfarction, or HF hospitalization [8,10].

All-cause Mortality

The 19% reduction in all-cause mortality must be interpreted cautiously given the high heterogeneity (I^2=66.6%) and significant publication bias (p<0.001) [9,10]. Both REDUCE-AMI [11] and ABYSS [12] individually found no significant mortality benefit, and prior meta-analyses similarly found borderline or no benefit when RCT data were isolated [21,22]. The pooled mortality benefit is likely driven by observational confounding [23].

Cardiovascular Mortality

The non-significant HR for CV mortality (0.83, I^2=73.4%) suggests insufficient evidence to conclude that beta-blockers reduce CV-specific mortality in preserved LVEF post-MI patients [3]. Future analyses should separate sudden cardiac death from HF-related death [13].

MACE

The null MACE finding (HR 0.98) aligns with ABYSS, which reported HR 0.89 (0.77–1.02) [12]. Moderate heterogeneity (I^2=53.2%) likely reflects MACE definition differences [4].

Reinfarction

The pooled HR of exactly 1.00 with I^2=0.0% provides compelling homogeneous evidence that beta-blockers do not reduce reinfarction risk in this population [18,10].

Risk of Bias and Study Quality

The overall methodological quality was satisfactory: 9/11 studies (81.8%) rated low risk of bias (Figure 13). Both RCTs had low risk under Cochrane RoB 2 [7]. Choo et al. [29] and Siu et al. [34] had moderate NOS scores (6/9) due to insufficient comparability domain control [6]. Confounding by indication remains an inherent limitation of observational studies in this domain [23,37].

Hospitalization for Heart Failure

The null HF hospitalization finding (HR 1.05, I^2=0.0%) is consistent with the absence of the mechanistic substrate (LV remodeling, systolic dysfunction) that underpins beta-blocker benefit in HFrEF [38,35].

Publication Bias

Significant Egger's test results for all-cause mortality (p<0.001), CV mortality (p=0.002), and reinfarction (p=0.013) represent an important limitation [10]. The two large contemporary RCTs should be weighted most heavily in clinical interpretation [11,12].

Comparison with Existing Literature

Our analysis extends prior meta-analyses [21,22] by including eleven studies (vs. 5–7 previously), incorporating ABYSS, and analyzing five distinct outcomes. A large Swedish registry also found no benefit of beta-blockers on HF outcomes in post-MI patients with preserved LVEF [39].

Clinical Implications

These findings challenge universal beta-blocker prescribing post-MI regardless of LVEF. Patients with LVEF <40%, ongoing anginal symptoms, arrhythmias, or high adrenergic state may still benefit; those with well-preserved LVEF after successful PPCI may be candidates for beta-blocker avoidance or early discontinuation [17,18]. ESC and ACC/AHA guidelines should be updated to address this patient subgroup explicitly [40].

Limitations

We examined predominantly observational study designs, with publication bias evident for multiple outcomes and high heterogeneity for mortality outcomes (I2>65%), and found that only three of the studies provided forest plot poolable data; beta-blocker type and dose, length and adherence, and reporting of beta-blockers were inconsistent among studies.

Conclusion

A total of 11 studies with 43,000 patients included who had post-MI with preserved or mildly reduced LVEF were included in this systematic review and meta-analysis, which revealed that beta-blocker therapy led to a statistically significant reduction in all-cause mortality (HR 0.81, 95% CI 0.67-0.98). But there was no obvious effect on cardiovascular mortality, MACE, reinfarction or hospitalisation for HF. The large variation in results across the studies, combined with the 2 recent large contemporary RCTs (REDUCE-AMI [11] and ABYSS [12]) with no apparent difference in results, supports the conclusion that the perceived all-cause mortality benefit may be due to observational confounding. This represents a departure from the sustained use of beta-blockers in all post-MI patients with LVEF in the preserved range and the need for an individualized approach to treatment based on evidence [21,22]. There is an urgent need for larger, well-powered, prospective RCTs with standardised definitions of outcome.

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