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Review Article

Comparison of carvedilol vs. bisoprolol for heart failure with reduced ejection fraction (HFrEF): A systematic review and meta-analysis from the Asian population

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Abstract

China, Indonesia, and Malaysia have the highest age-standardized rates of heart failure in Asia, according to the Global Burden of Disease study. While numerous systematic reviews and meta-analyses have compared bisoprolol and carvedilol in HFrEF, most have focused on Western populations. To address this gap, we conducted a meta-analysis of RCTs and cohort studies involving Asian patients with HFrEF from PubMed and Cochrane databases that reported all-cause mortality, hospital admission, and left ventricular ejection fraction (LVEF) increase. The search result identified five eligible studies, primarily from Taiwan, Japan, and South Korea, with a total of 11,577 participants. The meta-analysis revealed no significant difference between bisoprolol and carvedilol in terms of all-cause mortality (RR 1.04, p 0.62, I^2 = 0%), hospitalization (RR 1.23, p. 0.23, I^2 = 0%), and LVEF increase (RR -1.40, p. 0.50, I^2 = 0%). These findings suggest that both drugs have comparable efficacy in the Asian population.

Keywords

beta blocker, bisoprolol, carvedilol, heart failure with reduced ejection fraction, systematic review, meta-analysis

Introduction

Heart failure with reduced ejection fraction (HFrEF) global prevalence increased by 29% from 2010–2019 (Shahim et al. 2023). The total prevalence of HFrEF globally is estimated to be 1–3% (Shahim et al. 2023). Meanwhile, according to the data on the Global Burden of Disease (GBD) for Asia, China, Indonesia, and Malaysia have the highest age-standardized rates (ASRs) of heart failure in Asia (Feng et al. 2024). The global mortality rates due to all-cause mortality of HFrEF patients reached 16.8 per 100 person-years, and the mortality rates in Southeast Asia exhibited a higher prevalence than other Asian regions that reached 13% per year (MacDonald et al. 2020).

Beta blockers are one of the important drug classes and have the greatest impact to reduce the mortality or morbidity in HFrEF patients via reduction of the heart rate, and the meta-regression exhibited a relative risk reduction of 18% for every five beats/minute heart rate reduction (McAlister et al. 2009). However, results

from systematic reviews and meta-analyses have shown inconsistent and conflicting findings regarding which type of beta blocker is most effective. Dinicolantonio et al. (2013) meta-analysis of 4563 patients showed that carvedilol significantly reduced all-cause mortality by 45% (fixed model ratio) compared to bisoprolol (Dinicolantonio et al. 2013). However, other meta-analyses, such as Chatterjee et al. (2013), found no significant difference in all-cause mortality between bisoprolol and carvedilol (Chatterjee et al. 2013). Additionally, another meta-analysis by Liu et al. (2023) suggested that bisoprolol was superior to carvedilol in reducing all-cause mortality by 25% (Liu et al. 2023).

The existing systematic review and meta-analysis comparing bisoprolol and carvedilol in HFrEF have primarily focused on global data, particularly from populations in America and Europe. However, there is a lack of data from systematic reviews and meta-analyses that specifically focus on Asian populations. The comparison of bisoprolol and carvedilol becomes a focus of this research due to their widespread use as beta-blockers for HFrEF in Asia, including Indonesia (Teng et al. 2018). Therefore, research on the efficacy of these drugs in Asian HFrEF patients is crucial for selecting the most appropriate beta-blockers to reduce mortality and morbidity in this region, especially in Indonesia. Furthermore, the findings of this research are expected to serve as a reference for beta-blocker selection in HFrEF patients across Asia, particularly Indonesia.

Materials and methods

The comparative research of bisoprolol and carvedilol was conducted according to the PRISMA guidelines (Page et al. 2021).

Data source and search

The data source and search for randomized controlled trials (RCTs) and observational cohort studies that examined the efficacy of bisoprolol and carvedilol in Asian patients with HFrEF were conducted in PubMed and Cochrane databases from January 1, 2014, to August 31, 2024. This research was on human studies only. The keywords used for this search were "heart failure," "heart failure with reduced ejection fraction," "bisoprolol," and "carvedilol," as well as supplementary text terms used alongside a proven PubMed and Cochrane search method.

Study selection

Two independent reviewers (TN and AP) selected studies based on the inclusion criteria. A study was suitable for inclusion if it reported on RCTs and observational cohort studies in HFrEF patients, the patient population was Asian, it compared bisoprolol and carvedilol, and reported all-cause mortality, hospital admission, and LVEF increase.

Data quality assessment

All the data were appraised for validity according to the risk of bias tool recommended by Cochrane.

Data synthesis and analysis

The data was analyzed using RevMan version 5.3 with a 95% confidence interval. The data was considered statistically significant if the p-value was less than 0.05.

Results

A search yielded 142 articles (98 from PubMed and 44 from Cochrane). These 142 articles were screened based on their abstracts. After screening, 128 articles were excluded, and 8 were included. The included articles underwent full-text assessment, resulting in the exclusion of 3 articles due to the non-Asian patient population. Thus, only 5 articles met the inclusion criteria for quantitative analysis or meta-analysis. The patients in these 5 articles were from Taiwan, Japan, and South Korea (n = 11,577 patients) (Fig. 1). Among the included articles, 3 were RCTs (Hori et al. 2014; Toyoda et al. 2017; Tsutsui et al. 2019), and 2 articles were cohort studies (Lin et al. 2017; Choi et al. 2019) (Fig. 1). Based on the Cochrane risk of bias assessment, it was found that one of the five articles exhibited a low risk of bias, two demonstrated a moderate risk of bias, and the remaining two articles displayed a high risk of bias (Fig. 2).

All-cause mortality results

The meta-analysis of four articles (n = 11,510 patients), which combined RCTs and cohort studies, revealed no statistically significant difference in all-cause mortality between carvedilol and bisoprolol when analyzed using a random-effects model (RR 1.04 [0.88, 1.24] CI 95%, p 0.62, I^2 = 0%) or fixed-effect model (RR 1.03 [0.87, 1.23] CI 95%, p 0.70, I^2 = 0%) (Fig. 3A, B). Upon conducting a subgroup analysis restricted to RCTs, the meta-analysis yielded consistent findings (n = 276 patients) (RR 0.79 [0.22, 2.89], CI 95%, p. 0.72, I^2 = 0%), or from the meta-analysis of the 2 cohort studies (n = 11,234 patients) (RR 1.05 [0.88, 1.25], CI 95%, p 0.58, I^2 = 0%) (Fig. 3C, D). Nevertheless, meta-analyses that pooled data from both RCTs and cohort studies, or exclusively from cohort studies, demonstrated a trend towards lower all-cause mortality with bisoprolol. Conversely, meta-analyses solely comprising RCTs indicated a trend favoring carvedilol in terms of all-cause mortality.

Hospital admission results

A meta-analysis of three articles (n = 11,510 patients) combining RCTs and cohort studies showed no significant difference between carvedilol and bisoprolol in terms of hospital admission when using a random-effects model (RR 1.23 [0.88, 1.71]). CI 95%, p. 0.23, I^2 = 0%) or using a fixed effect model (RR 1.21 [0.87, 1.69], CI 95%,

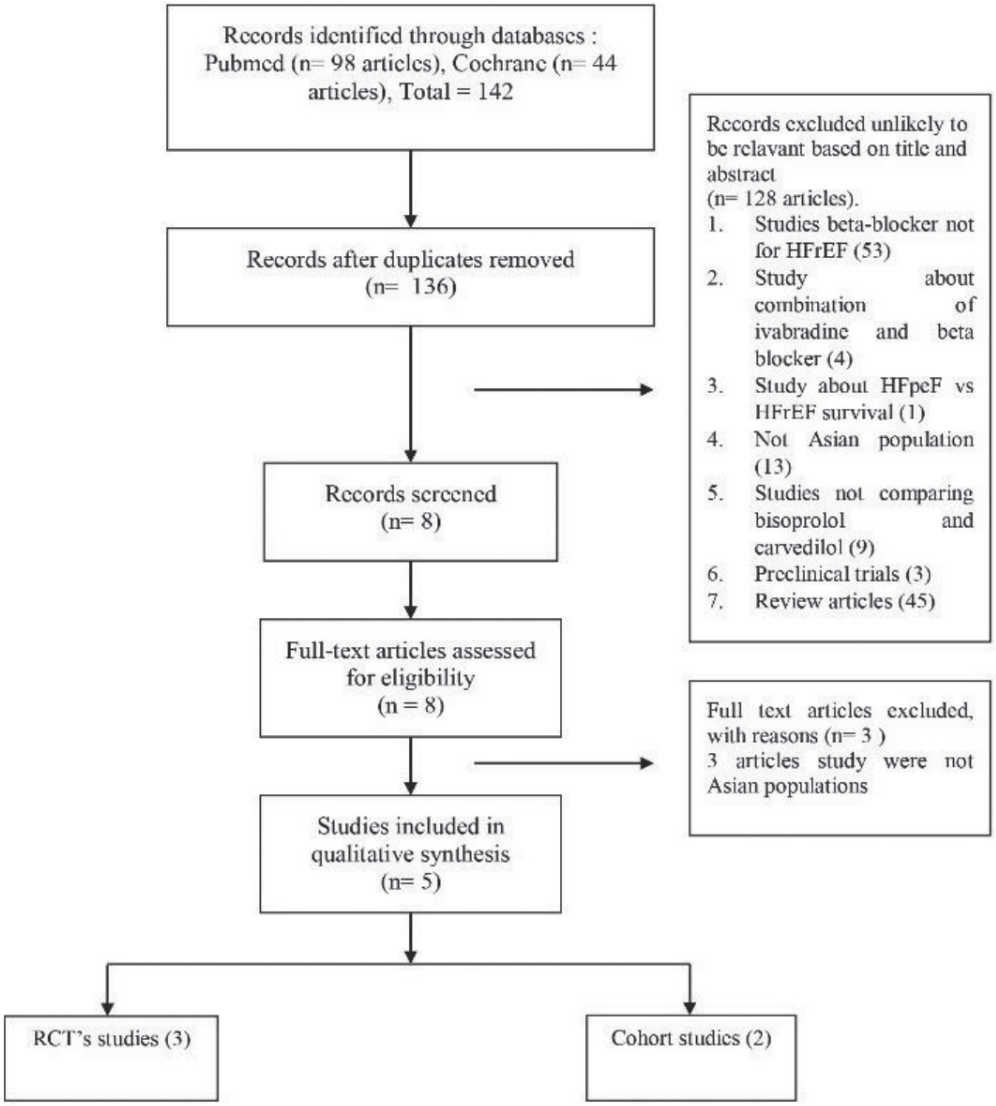


Figure 1. Flowchart of data search.

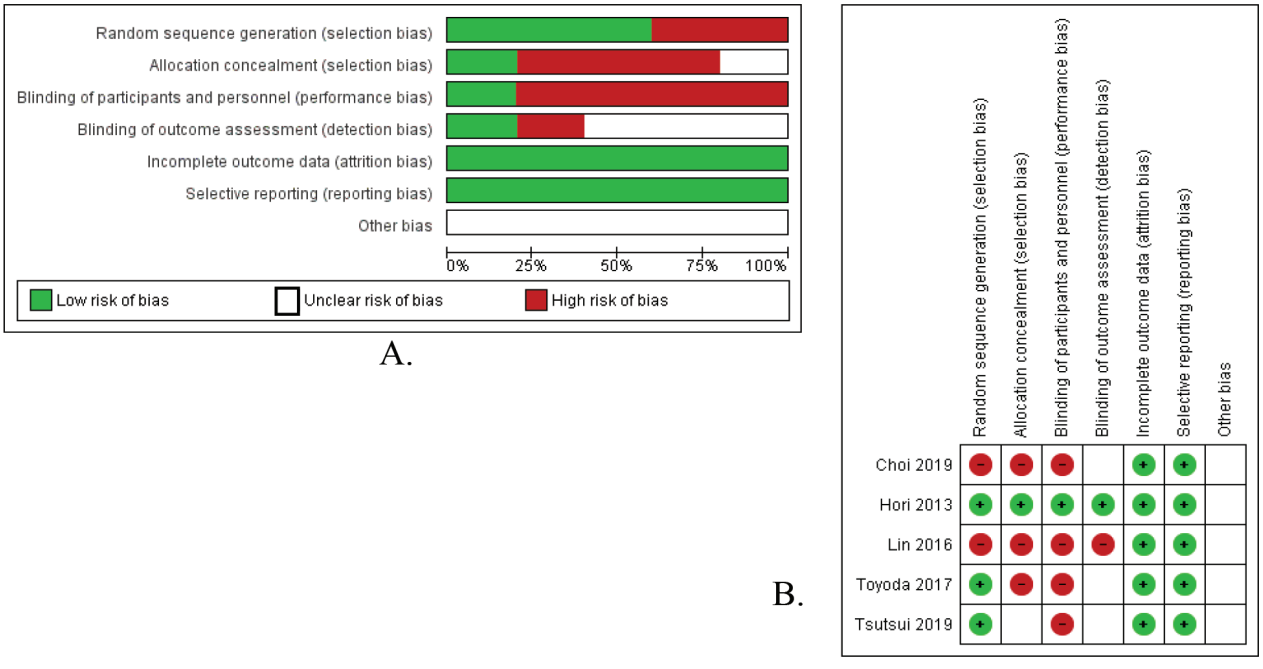
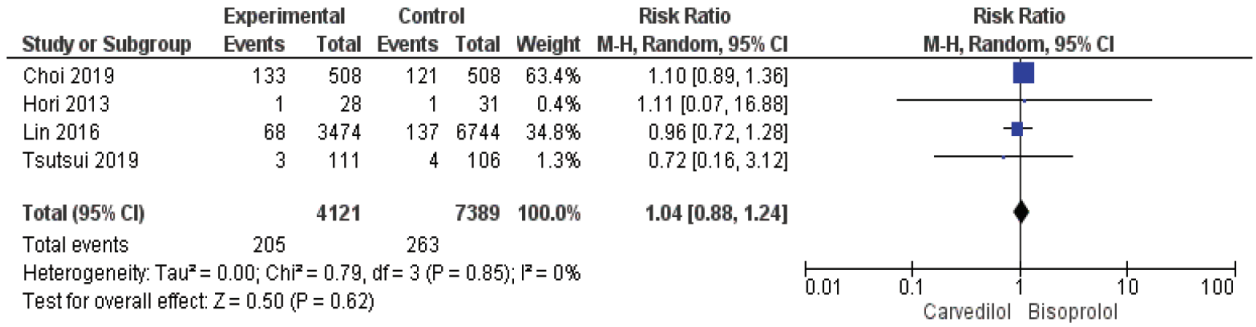
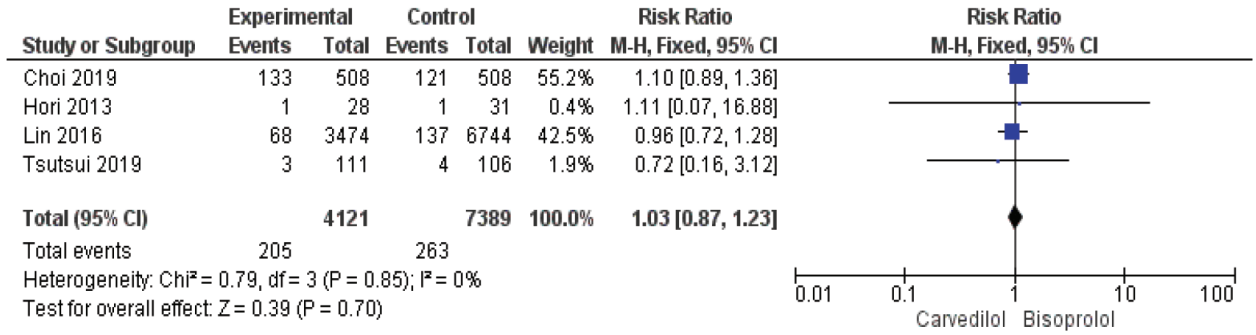


Figure 2. The Cochrane risk of bias of the studies. **A.** Risk of bias graph; **B.** Risk of bias summary.



A.



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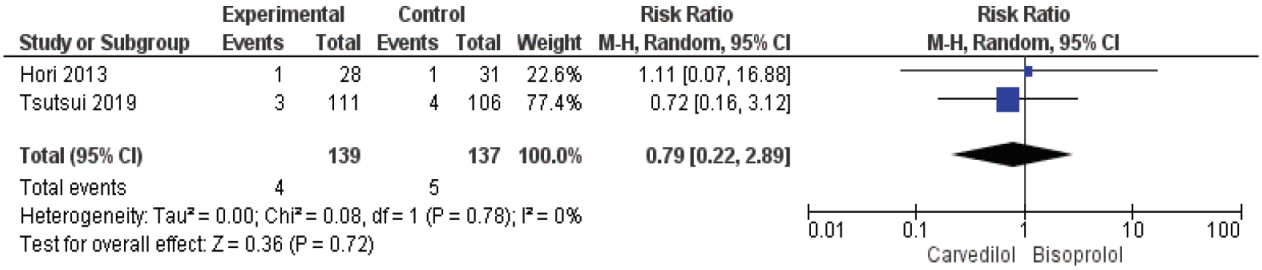
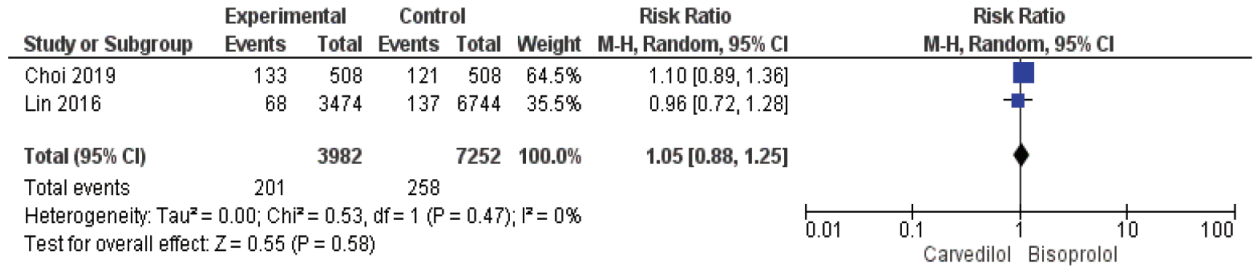


C.



D.

Figure 3. Forest plot all-cause mortality; **A.** All-cause mortality random effect (combination of RCTs and cohort); **B.** All-cause mortality fixed effect (combination of RCTs and cohort); **C.** All-cause mortality (RCTs); **D.** All-cause mortality (cohort).

p 0.25, I^2 = 0%) (Fig. 4A, B). A meta-analysis restricted to RCTs and employing a random-effects model yielded consistent findings (RR 0.94 [0.39, 2.25] CI 95%, p. 0.89, I^2 = 0%), and also for the fixed-effect model (RR 0.88 [0.38, 2.07], CI 95%, p. 0.77, I^2 = 0%) (Fig. 4C, D). However, when looking at the trends in meta-analyses that combined RCTs and cohort studies, there was a tendency towards lower hospital admission rates with bisoprolol. In contrast, meta-analyses that only included RCTs showed a trend towards lower hospital admission rates with carvedilol.

Left ventricular ejection fraction (LVEF) increased as a result

A meta-analysis of two articles (n = 126 patients) from RCTs showed no significant difference between carvedilol and bisoprolol in terms of increased LVEF when using a random-effects model (RR -1.40 [-5.44, 2.64], CI 95%, p. 0.50, I^2 = 0%) or using a fixed-effect model (RR -1.40 [-5.44, 2.64], CI 95%, p. 0.50, I^2 = 0%) (Fig. 5A, B). However, when looking at the trends in meta-analyses of RCTs, there was a tendency for carvedilol to increase LVEF.

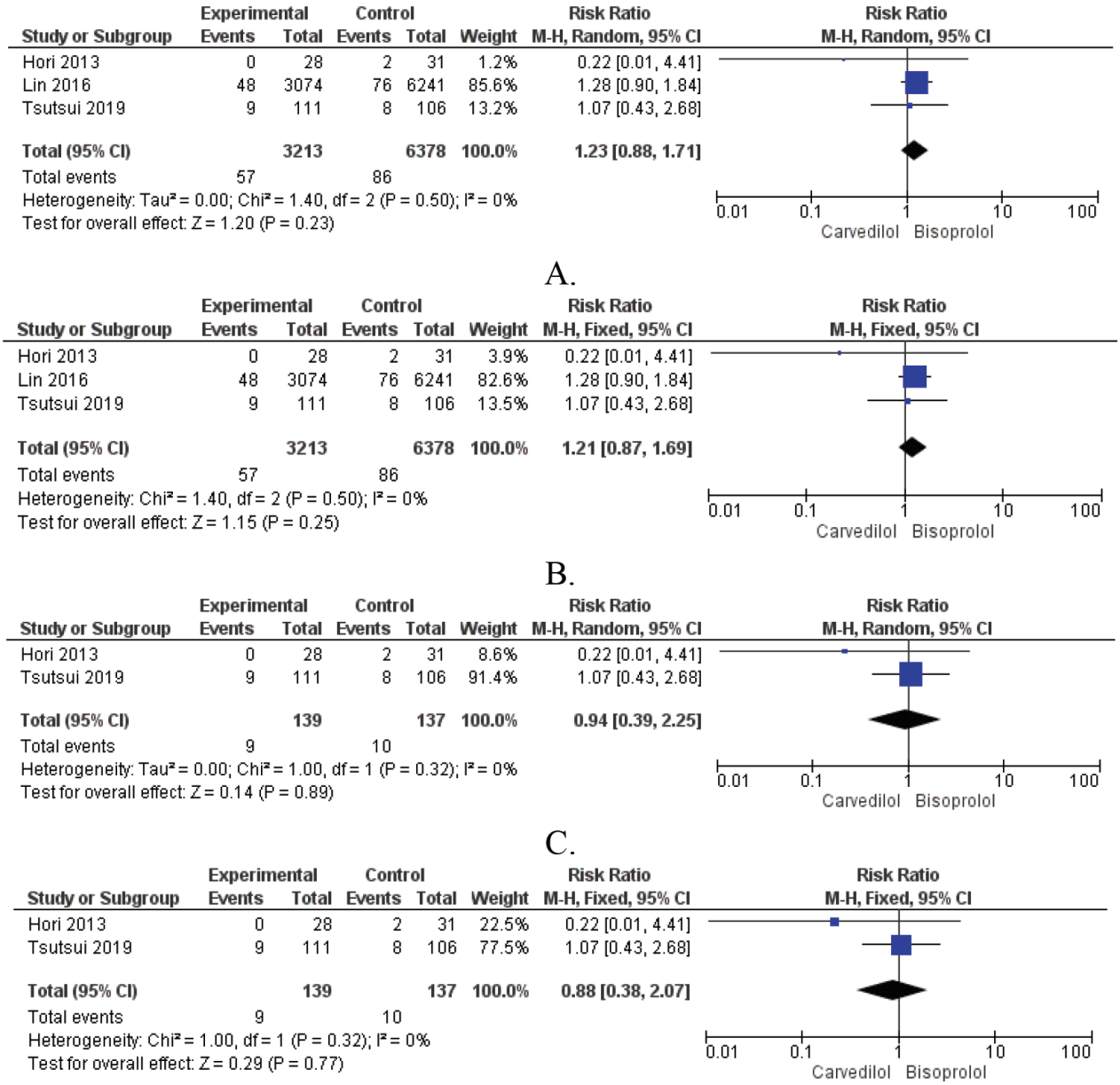


Figure 4. Forest plot hospital admission; **A.** Hospital admission random effect (combination of RCTs and cohort); **B.** Hospital admission fixed effect (combination of RCTs and cohort); **C.** Hospital admission random effect (RCTs); **D.** Hospital admission fixed effect (RCTs).

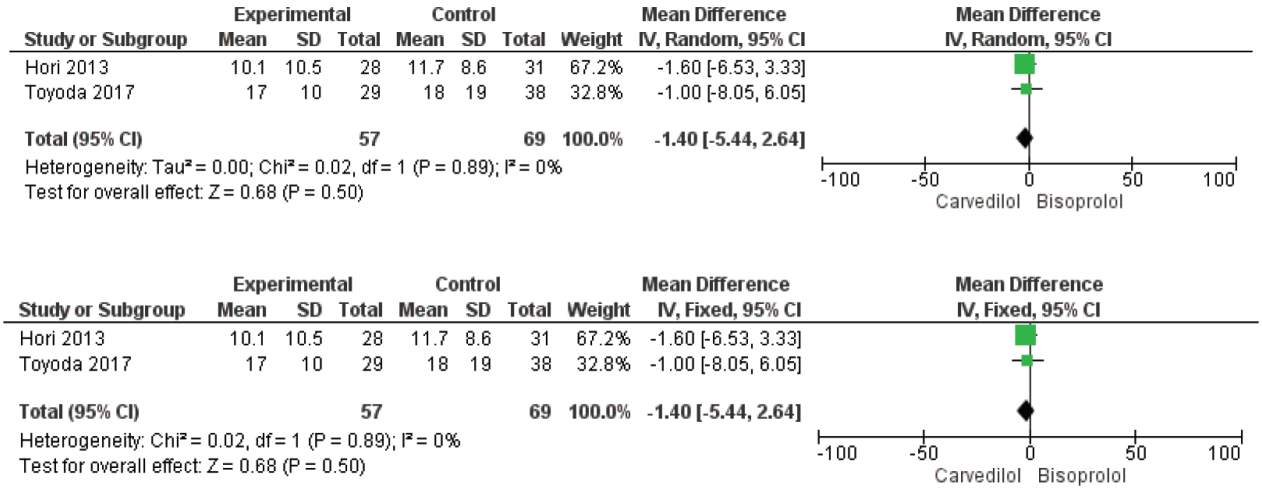


Figure 5. Forest plot LVEF increased; **A.** LVEF increased random effect (RCTs); **B.** LVEF increased fixed effect (RCTs).

Discussion

Bisoprolol and carvedilol are commonly used beta-blockers in Asia for the treatment of heart failure with reduced ejection fraction (HFrEF), especially in Indonesia. Both drugs are considered first-line beta-blocker options for HFrEF according to guidelines from the American Heart Association/American College of Cardiology (AHA/ACC) and the Indonesia Cardiovascular Association (Heidenreich et al. 2022; PERKI 2023). Our meta-analysis did not find a statistically significant difference between bisoprolol and carvedilol in terms of all-cause mortality, hospital admission, and increased LVEF, with low heterogeneity. These findings indicate that both drugs have comparable efficacy in the Asian population. Thus, drug selection should consider individual patient clinical factors, including comorbidities, patient preferences, contraindications, adverse effects, pharmacoeconomics, and patient adherence to therapy.

HFrEF is a progressive disease with complex pathological processes that cause heart function to decline over time (González-Juanatey et al. 2022). The pathophysiology of this condition involves myocardial injury, reduced cardiac output, neurohumoral activation, ventricular remodeling, diastolic dysfunction, and valve regurgitation (Narayan et al. 2023). Moreover, other studies have shown that the immune system is involved in HFrEF as a result of myocardial damage that generates damage-associated molecular patterns (DAMPs), leading to immune system activation (innate and adaptive immunity), cytokine production, and autoantibody generation against cardiac antigens (Castillo et al. 2020). These factors are associated with disease severity, poor prognosis, and increased risk of rehospitalizations (Castillo et al. 2020). All of these pathological processes lead to a lack of oxygen, which can potentiate further damage in the myocardium and other organs or tissues. Beta blockers (carvedilol and bisoprolol) are crucial for HFrEF due to improvement to all of these pathological processes and also enhance the effects of other medications.

Carvedilol is a third-generation beta-blocker with multiple mechanisms of action, including inhibition of beta-1, beta-2, and alpha-1 receptors. This multifaceted action results in peripheral vasodilation and maintained cardiac output. Additionally, carvedilol offers the benefit of apoptotic inhibition (Singh and Preuss 2024). In contrast, bisoprolol, a second-generation beta-1 selective blocker, primarily exerts its effects by reducing heart rate and contractility. By selectively targeting beta-1 receptors, bisoprolol directly decreases myocardial oxygen demand. Furthermore, it inhibits renin release from the juxtaglomerular cells in the kidneys (Bazroon and Alrashidi 2024). The pharmacodynamic profile of bisoprolol suggests that it may be a more suitable choice than carvedilol for heart failure patients with concomitant chronic obstructive pulmonary disease (COPD). This assertion is corroborated by the findings of Su et al. (2016), which demonstrated superior survival outcomes with bisoprolol compared to carvedilol (HR=0.40, $P<0.001$) (Su et al. 2016). Conversely, carvedilol exhibited superior efficacy in reducing arterial blood pressure when compared to bisoprolol (Leonetti and Egan 2012). In patients with heart failure and comorbidities who are undergoing hemodialysis or have impaired renal function, both medications have demonstrated equivalent efficacy in enhancing patient survival (Tang et al. 2016).

The pharmacokinetic profile of carvedilol is characterized by rapid absorption, with peak plasma concentrations attained within 1–2 hours post-administration. It exhibits low bioavailability (approximately 25%), a volume of distribution of 1.5 L/kg, and a half-life of 6–7 hours. Carvedilol is primarily metabolized via oxidative pathways followed by glucuronidation, with subsequent elimination primarily through the fecal route (Singh and Preuss 2024). In contrast to carvedilol, bisoprolol exhibits a slower absorption profile, reaching peak plasma concentrations within 2–4 hours. It demonstrates high bioavailability of approximately 80%. Bisoprolol has a volume of distribution of 3.5 L/kg and a half-life ranging from 9 to 12 hours. The primary metabolic pathway for bisoprolol involves CYP3A4-mediated oxidation, and the drug is primarily eliminated via renal excretion, with approximately 50% excreted unchanged (Bazroon and Alrashidi 2024). Pharmacokinetic comparisons between carvedilol and bisoprolol reveal that bisoprolol possesses a more extended half-life. Consequently, bisoprolol can be administered once daily, enhancing patient convenience and adherence. While carvedilol can be administered once daily in extended-release formulations, this option is associated with a higher cost compared to standard carvedilol dosing. Nevertheless, carvedilol exhibits a lower propensity for drug interactions relative to bisoprolol. This is attributed to the fact that bisoprolol is metabolized by CYP3A4, an enzyme with a broad substrate spectrum, leading to interactions with numerous other compounds (Teo et al. 2015).

The dearth of RCTs examining the efficacy of beta-blockers in Asian populations underscores the necessity for additional research with larger patients.

Conclusion

The meta-analysis did not reveal a statistically significant difference between bisoprolol and carvedilol in terms of all-cause mortality, hospital admission, or increased LVEF. These findings suggest that both drugs have comparable efficacy in the Asian population. Therefore, drug selection should be individualized based on patient factors such as comorbidities, preferences, contraindications, adverse effects, cost-effectiveness, and adherence to therapy.

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Additional information

Conflict of interest

The authors have declared that no competing interests exist.

Ethical statements

The authors declared that no clinical trials were used in the present study.
The authors declared that no experiments on humans or human tissues were performed for the present study.
The authors declared that no informed consent was obtained from the humans, donors or donors' representatives participating in the study.
The authors declared that no experiments on animals were performed for the present study.
The authors declared that no commercially available immortalised human and animal cell lines were used in the present study.

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Author contributions

All authors have contributed equally.

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Data availability

All of the data that support the findings of this study are available in the main text.

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