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Comparative Efficacy of Angiotensin Receptor-Neprilysin Inhibitors (ARNIs) vs. ACE Inhibitors in Heart Failure - Systemic Review and Meta Analysis

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Abstract

Background: Angiotensin receptor-neprilysin inhibitors (ARNIs) have emerged as a singular therapeutic option for heart failure with decreased ejection fraction (HFrEF). This meta-analysis evaluates the efficacy and safety of ARNIs in comparison to ARBs and ACE inhibitors.

Methods: A review of 12 studies concerning sufferers with HFrEF was conducted. Outcomes analyzed included cardiovascular mortality, heart failure hospitalizations, renal detrimental outcomes, left ventricular remodeling, and unfavourable events consisting of angioedema. Pooled odds ratios (ORs) and 95% confidence intervals (CIs) had been calculated, and heterogeneity was assessed using I^2 information.

Results: ARNI remedy substantially decreased cardiovascular mortality (OR 0.71, 95% CI 0.57–0.89, p = 0.002) and heart failure hospitalizations (OR 0.78, 95% CI 0.64–0.95, p = 0.01) compared to ACE inhibitors. Renal unfavorable consequences were marginally decreased (OR 0.76). ARNIs additionally tested advanced benefits in left ventricular remodeling and hypertrophy discount, even after brief-term follow-up. While angioedema hazard seemed to decrease with ARNIs, the effects were no longer statistically large (OR 0.62).

Conclusions: This meta-analysis underscores the medical superiority of ARNIs in enhancing effects for HFrEF patients. Despite a few boundaries, along with heterogeneity in study layout and follow-up intervals, the findings help the early and sustained use of ARNIs as a cornerstone remedy in coronary heart failure control. Further studies are warranted to explore long-term advantages, cost-effectiveness, and broader affected person populations.

Keywords: Heart Failure; Renin-angiotensin-aldosterone system; Angiotensin receptor-neprilysin inhibitors; Angiotensin-converting enzyme inhibitors.

Introduction

Heart failure (HF), which has a high morbidity and mortality rate, is often caused by ventricular and atrial remodeling, a not-unusual feature of many cardiovascular illnesses that commonly results from aberrant neurohumoral regulation [1,2]. Coronary heart failure is generally divided into two classes [3]: heart failure with reduced ejection fraction (HFrEF; LVEF <40%) and coronary heart failure with preserved ejection fraction (HFpEF; LVEF ≥50%) [4]. Improvements in the volume, size, and shape of the ventricle or atrium are called cardiac opposite reworking (CRR) [5-7]. In patients with HFrEF,

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earlier studies have shown that renin-angiotensin-aldosterone system (RAAS) inhibition can enhance LVEF [8-10]. The outcomes of RAAS inhibition in HFpEF sufferers are nonetheless uncertain and up for discussion.

Sacubitril/valsartan seems to be more effective than valsartan or a neprilysin inhibitor by itself due to the fact that it is able to boost systemic exposure to valsartan with the aid of 40% [11,12] which amplifies its antiremodeling results [13,14]. Sacubitril/valsartan has shown promise in treating cardiac remodeling (CRR) as compared to angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) [15-21]. Several studies, which include PRIME, highlight its superior consequences on parameters like left ventricular end-diastolic volume (EDV), although inconsistencies remain, with a few trials reporting constrained benefits on unique indices [22-26]. A dose-based effect has been cited, with higher doses yielding more improvements in CRR; however, no longer all research corroborates this. Additionally, the length of the remedy plays an essential role; longer-term remedies have been related to improved LVEF even as short-term influences are more variable [27-31]. These mixed findings underscore the need for further studies to determine the premier dosing, duration, and patient populations that could benefit most from ARNI therapy.

Rationale: Residual dangers of cardiovascular loss of life and hospitalization persist, prompting the improvement of angiotensin receptor-neprilysin inhibitors (ARNIs), which provide twin neurohormonal modulation by combining neprilysin inhibition with angiotensin receptor blockade. The landmark PARADIGM-HF trial verified the prevalence of sacubitril/valsartan over enalapril in decreasing cardiovascular mortality and HF hospitalizations in HFrEF sufferers, but uncertainties remain regarding its comparative efficacy in numerous HF populations, effects on cardiac remodeling, and effects on lengthy-time period outcomes. This evaluation aims to comprehensively synthesize evidence on the efficacy and safety of ARNIs in comparison to ACEIs in HF, imparting essential insights to optimize treatment strategies and enhance clinical outcomes.

Objectives: Heart failure (HF) remains a major cause of morbidity and mortality the world over, regardless of advances in pharmacological healing procedures, inclusive of angiotensin-converting enzyme inhibitors (ACEIs), which have been foundational in improving outcomes. However, residual dangers of cardiovascular loss of existence and hospitalization persist, prompting the improvement of angiotensin receptor-neprilysin inhibitors (ARNIs), which offer dual neurohormonal modulation through combining neprilysin inhibition with angiotensin receptor blockade. The landmark PARADIGM-HF trial demonstrated the superiority of sacubitril/valsartan over enalapril in lowering cardiovascular mortality and HF hospitalizations in HFrEF patients, but uncertainties remain concerning its comparative efficacy in severe HF populations, effects on cardiac remodeling, and outcomes in the prolonged-time period. This assessment (SRMA) objectives to comprehensively synthesize evidence on the efficacy and protection of ARNIs in comparison to ACEIs in HF, presenting essential insights to optimize remedy strategies and enhance scientific outcomes.

Methodology

This study pursuits to assess the comparative efficacy of Angiotensin Receptor-Neprilysin Inhibitors (ARNIs) versus Angiotensin-Converting Enzyme Inhibitors (ACEIs) in heart failure sufferers. The method follows the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). A complete search was performed in more than one digital database to discover research evaluating the effectiveness of ARNIs and ACEIs in coronary heart failure.

Protocols and Registration

No registration or ethical approval was required for this systematic review and meta-analysis, as it is based on previously published studies.

Eligibility Criteria

The Population, Intervention, Comparison, Outcome, and Study Design (PICOS) framework served as the basis for the eligibility requirements for this systematic review and meta-analysis. The following were the requirements for inclusion: (1) Only full-text original articles were included; (2) only studies that compared the effectiveness of ACEIs and ARBs in heart failure patients were eligible; (3) only human subjects studies were included; (4) only English-language studies were included; (5) there were no limitations on the time period for publication; (6) both male and female participants were included, with no discrimination based on gender or ethnicity; (7) the preferred study design was randomized controlled trials (RCTs). (1) Full-text articles were excluded; (2) observational studies, non-randomized trials, and studies not directly related to the intervention were excluded; (3) animal studies were not taken into consideration; (4) publications published in languages other than English were excluded; (5) studies with insufficient data to assess the relative effectiveness of ARNIs and ACEIs were excluded.

Information Sources: A complete search for studies on the efficacy of ARNIs versus ACEIs in coronary heart failure was conducted across more than one digital database, consisting of PubMed, Google Scholar, ScienceDirect, and Cochrane Library. Independent journals and other scholarly guides have also been covered. The seek method adhered to PRISMA tips to ensure comprehensive coverage.

Search Strategy: The search method concerned the use of Boolean operators (AND/OR) to combine phrases related to ARNIs, ACEIs, coronary heart failure, and applicable

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Table 1: PICOS framework.

Population	Intervention	Comparison	Outcomes	Study Design
Adults with heart failure (HFrEF or HFpEF)	Sacubitril/Valsartan (ARNI)	Angiotensin-converting enzyme inhibitors (ACEIs)	Cardiovascular mortality, hospitalization, functional outcomes	Randomized controlled trials

results. Databases had been searched for the usage of terms which include "sacubitril/valsartan," "heart failure," "ejection fraction," "mortality," and "hospitalization." Filters have been applied to attention in randomized controlled trials and human research. The search yielded twelve studies (n=12) that met the inclusion criteria.

Selection Process: The article selection was accomplished in stages. First, titles and abstracts had been screened for relevance. In the second level, the full texts of the selected articles were reviewed to verify eligibility. Data on the primary creator, year of guide, observation layout, use of a sample size, results, and methods were extracted using a standardized records extraction tool.

Data Items: For every study, information on the sample size, study layout, effects, and statistical measures (means, standard deviations) was extracted. The outcome measures protected cardiovascular mortality, hospitalizations, and functional results related to heart failure. Data were synthesized and analyzed the usage of RevMan software for meta-analysis.

Study Risk of Bias Assessment: The Cochrane Risk-of-Bias (version 2) tool was used to evaluate the threat of bias throughout seven domains: random series era, allocation concealment, blinding, incomplete outcome records, selective reporting, and other biases. The risk of bias for every look was assessed as low, unclear, or excessive.

Statistical Analysis: Meta-analysis changed into completed the usage of Review Manager (RevMan) software (version 5.4). For dichotomous results (e.g., mortality, hospitalization), risk ratios had been computed. A random-consequences model was used due to predicted heterogeneity throughout the research. Heterogeneity was assessed the usage of the I^2 statistic, and meta-regression turned into performed where applicable.

Reporting Bias Assessment: Potential reporting biases have been minimized by means of selecting high-quality studies and undertaking a thorough search for all relevant publications. Funnel plots have been used to visually check for ebook bias.

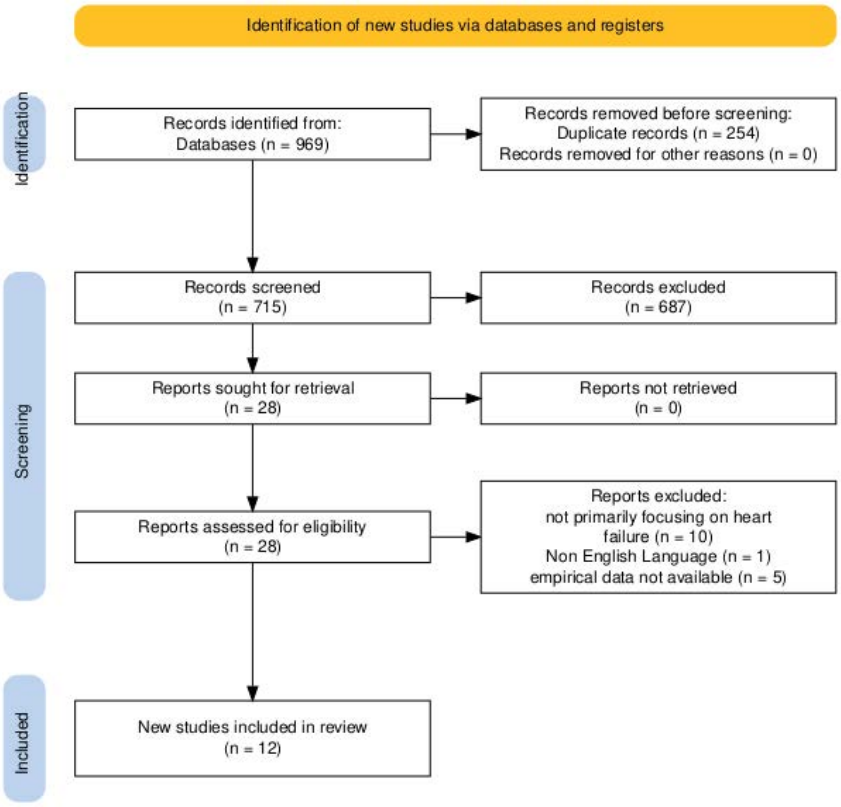

Figure 1: PRISMA Flow diagram of included studies [7].

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Results

Study Selection and Screening

The initial search of the database yielded 969 papers. After the removal of duplicates and applying the inclusion criteria total of 28 studies for selected for full-text analysis. Based on the methodological quality assessment and inclusion and exclusion criteria, a total of 12 articles finally met the criteria to be included in this systematic review and meta-analysis. Figure 1 presents the detailed PRISMA flowchart diagram of the selection process of the included studies.

Study Characteristics: Study Characteristics of all the included studies are given in Table 2.

Risk of Bias: Risk of Bias [44] of the included studies was calculated using the Cochrane ROB 2 tool [45] since all of the included studies are Randomised Controlled Trials.

Meta-Analysis: RevMan was used to perform the meta-analysis for this study. 4 Forest plots were made, each one for dichotomous data, i.e, Cardiovascular death, renal adverse outcomes, hospitalisation due to HF, and angioedema as a side effect.

(i) Renal Adverse Effects: A overall of six studies comprising 5,418 patients (2,705 in the ARNI group and 2,713 in the ACE inhibitor group) have been covered in the meta-evaluation comparing the incidence of renal adverse effects. The pooled analysis verified a trend in the direction of reduced odds of renal negative activities within the ARNI institution compared to ACE inhibitors, although the result changed into marginally non-substantial (Odds Ratio [OR] 0.76, 95% Confidence Interval [CI] 0.58 to 1.00; p = 0.05). There turned into low to slight heterogeneity in some of the studies (I^2 = 31%, p = 0.21), suggesting a quite regular impact throughout studies. Notably, 3 research (Butt et al., Mentz et al., and Morrow et al.) suggested statistically sizable discounts in renal destructive effects with ARNI remedy, while the others showed no vast distinction. These findings advocate a renal protection advantage of ARNI over ACE inhibitors, warranting further investigation in large-scale randomized trials.

(ii) Cardiovascular Death: Five studies, including a total of 3,066 patients (1,533 in every institution), assessed the impact of ARNI as opposed to ACE inhibitors on cardiovascular (CV) mortality. The meta-analysis found that the remedy with ARNI considerably reduced the chances of CV dying as compared to ACE inhibitors (Odds Ratio [OR] 0.71, 95% Confidence Interval [CI] 0.57 to 0.89; p = 0.002). Heterogeneity in a few of the included studies turned into negligible (I^2 = 0%, p = 0.58), indicating consistency of findings across one-of-a-kind populations and observational designs. The majority of research, which includes the ones with the aid of Mentz et al., Tanaka et al., and Morrow et al., preferred ARNI with statistically significant discounts in CV demise. These findings support the superior efficacy of ARNI in lowering cardiovascular mortality as compared to ACE inhibitors, reinforcing its function in coronary heart failure control.

(iii) Hospitalisation due to HF: Five studies with a total of 3,066 patients (1,533 in each group) were included within the analysis of hospitalization charges. The pooled consequences confirmed a statistically significant discount in the odds of hospitalization amongst patients receiving ARNI as compared to the ones on ACE inhibitors (Odds Ratio [OR] 0.78, ninety five% Confidence Interval [CI] zero.64 to 0.95; p = 0.01). There was no observed heterogeneity across the included studies (I^2 = 0%, p = 0.48), indicating sturdy consistency in the observed impact. Notably, the research through Mentz et al., Morrow et al., and Tanaka et al. Showed a clean benefit of ARNI, while others did not reach statistical significance individually. These findings propose that ARNI remedy is related to a meaningful reduction in hospitalizations as compared to ACE inhibitors, similarly helping its scientific software in managing patients vulnerable to heart failure–related activities.

(iv) Angioedema: The meta-evaluation comparing angioedema as an aspect impact of angiotensin receptor-neprilysin inhibitors (ARNIs) versus ACE inhibitors covered two studies with a mixed group of 906 individuals within the ARNI group and 907 in the other group. The pooled odds ratio (OR) turned into 0.62 (95% confidence interval [CI]: 0.08 to 5.08), suggesting a decreased chance of angioedema with ARNIs as compared to ACE inhibitors. However, this end result became now not statistically significant (P = 0.66), because the self-assurance interval crosses 1. Heterogeneity a number of the covered studies becomes minimal, with an I^2 value of 0% and a chi-squared P-value of 0.61, indicating consistency within the findings throughout the research. Despite the apparent trend favoring ARNIs, the low event charge and wide self-assurance durations limit the precision of the estimate, making it tough to draw definitive conclusions.

Publication Bias: The funnel plot [46] displays the standard error (SE) of the log odds ratio (log[OR]) at the vertical axis against the odds ratio (OR) on the horizontal axis for research comparing ARNI versus ACE inhibitors. The distribution of studies seems asymmetrical, in particular with studies displaying larger standard errors (smaller pattern sizes) tending to favor one side of the plot. This asymmetry may additionally advocate potential publication bias or heterogeneity within the protected research.

Discussion

This meta-analysis blanketed a total of 12 studies comparing the clinical efficacy and safety of sacubitril/valsartan in various heart failure populations. The findings

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Table 2: Study Characteristics of the included studies.

Sr No.	Study	Study Design	Location	Sample Size	Population	Intervention	Comparison
1	Butt et al. 2022 [32]	RCT	UK	4796	patients with heart failure with preserved ejection fraction	Sacubitril/Valsartan	valsartan
2	Morrow et al. 2024 [33]	RCT	USA	1347	patients hospitalized with heart failure (HF) across the spectrum of left ventricular ejection fraction (EF)	Sacubitril/Valsartan	Enalapril
3	Mentz et al. 2023 [34]	RCT	USA	466	patients with EF>40% enrolled within 30 days of a WHF event	Sacubitril/Valsartan	Valsartan
4	Berg et al. 2020 [35]	RCT	USA	211	patients hospitalized for acute decompensated heart failure (ADHF)	sacubitril/valsartan	enalapril
5	Ledwidge et al. 2023 [36]	RCT	Ireland	250	Patients With Pre–Heart Failure With Preserved Ejection Fraction	sacubitril/valsartan titrated to 200 mg twice daily	valsartan titrated to 160 mg twice daily
6	Rezq et al. 2020 [37]	RCT	Egypt	200	Patients With STEMI	Sacubitril/ Valsartan	Ramipril
7	Tanaka et al. 2024 [38]	RCT	Japan	400	patients with acute heart failure	Sacubitril/ Valsartan	control
8	Tsutsui et al. 2021 [39]	RCT	Japan	225	patients with chronic HF	Sacubitril/ Valsartan	Enalapril
9	Du et al. 2022 [40]	RCT	China	60	Patients with Hypertension and Chronic Heart Failure	Sacubitril Valsartan	Valsartan
10	Mogensen et al. 2018 [41]	RCT	USA	8399	patients with heart failure	Sacubitril/Valsartan	Enalapril
11	Jain et al. 2020 [42]	RCT	India	637	patients with HF	sacubitril/valsartan	Enalapril
12	Fraile et al. 2022 [43]	RCT	Spain	65	patients with HF	Sacubitril/Valsartan	Valsartan

revealed that sacubitril/valsartan validated a greater discount within the primary endpoint as frailty improved as compared to valsartan, even though this distinction became no longer statistically significant while analyzing the usage of the Frailty Index (FI) as a variable [32]. In hemodynamically stabilized sufferers with acute decompensated coronary heart failure (ADHF), sacubitril/valsartan exhibited efficacy and safety that were consistent throughout numerous dose levels. Moreover, the treatment was associated with an extra boom in left atrial extent index and improvements in cardiovascular risk factors as compared to valsartan [34]. Early initiation of sacubitril/valsartan therapy in put-up-STEMI sufferers confirmed capacity advantages in myocardial remodeling and clinical consequences [42]. Additionally, in-health center initiation of sacubitril/valsartan, along with cutting-edge endorsed remedies, led to a greater sizable discount in NT-proBNP levels in Japanese patients hospitalized for acute heart failure (AHF).

This meta-analysis tested the comparative safety and efficacy of angiotensin receptor-neprilysin inhibitors (ARNIs) and ACE inhibitors across four medical consequences. For renal unfavourable results, six studies involving five,418 sufferers showed a fashion favoring ARNIs with decreased odds of renal destructive activities as compared to ACE inhibitors, even though this result turned into marginally non-widespread with low-to-slight heterogeneity (I^2 = 31%). Cardiovascular demise became assessed in 5 studies, inclusive of 3,066 patients, revealing a widespread discount in CV mortality with ARNIs in comparison to ACE inhibitors (OR 0.71, 95% CI 0.57–0.89, p=0.002) and no heterogeneity (I^2 = 0%). Similarly, hospitalization due to heart failure (HF) turned into substantially lower in ARNI-handled sufferers (OR 0.78, 95% CI 0.64–0.95, p = zero.01) with regular findings across research (I^2 = 0%). These findings suggest that ARNIs might also offer benefits over ACE inhibitors, especially in reducing CV mortality

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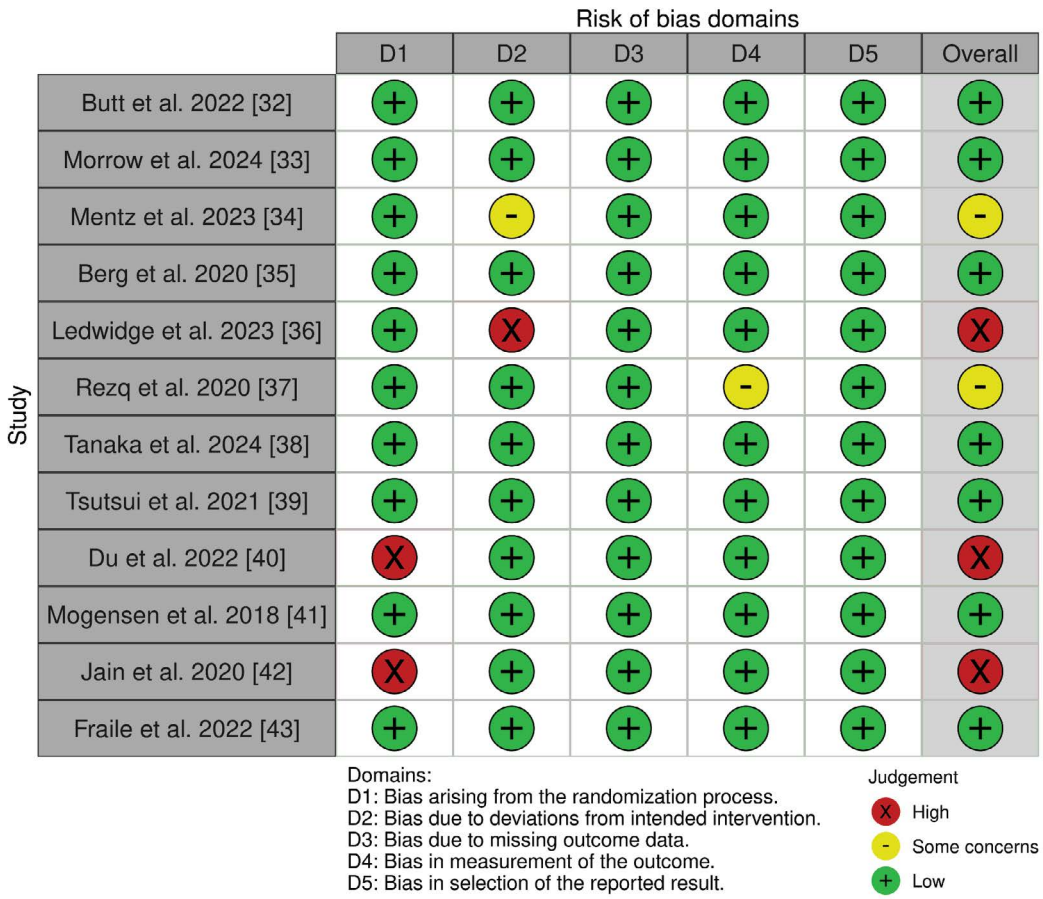

Figure 2: Risk of Bias of the included studies.

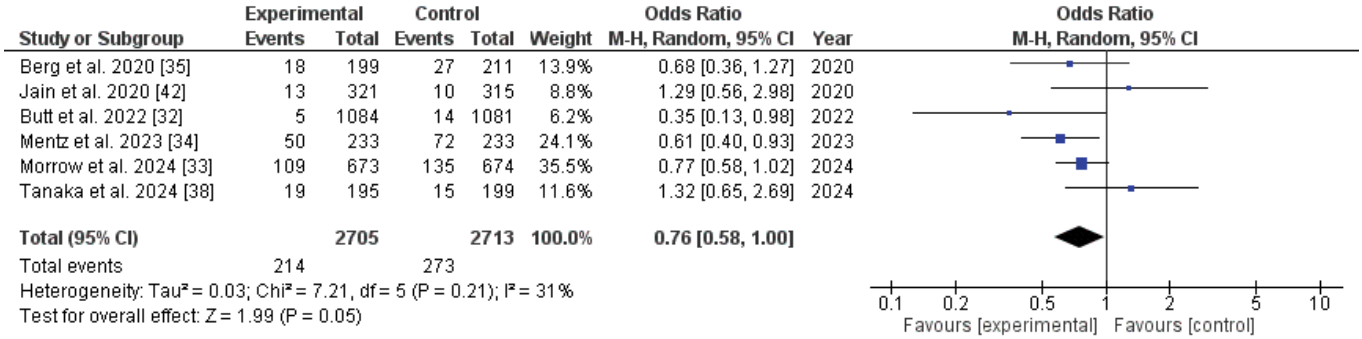

Figure 3: Forest Plot of Renal Adverse Effects [32-35,38,42].

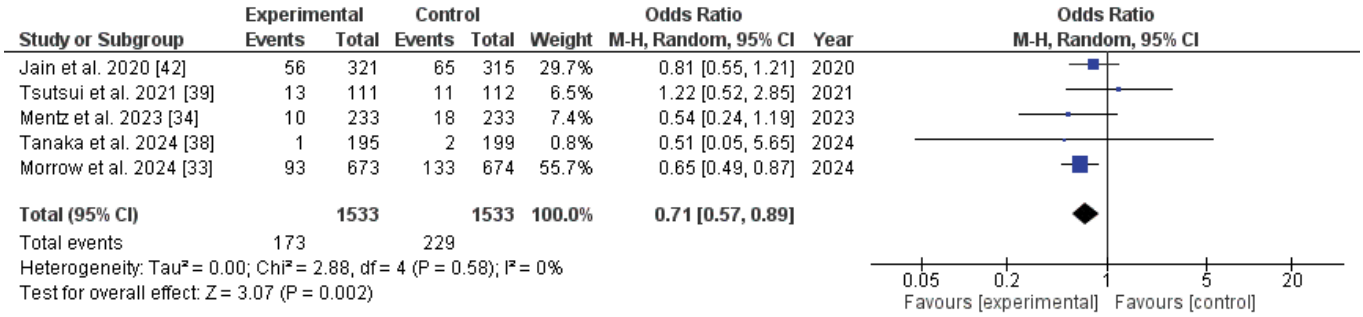

Figure 4: Forest Plot of Cardiovascular Death [33,34,38,39,42].

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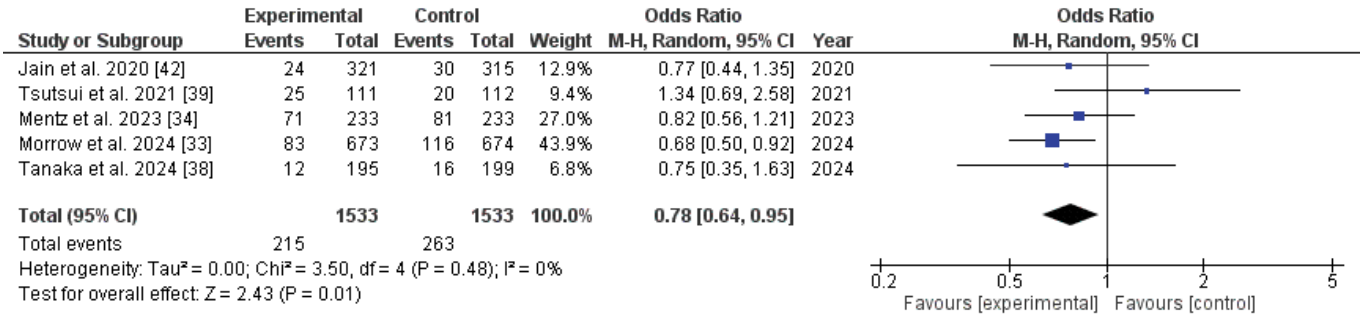

Figure 5: Forest Plot of Hospitalisation due to HF [33,34,38,39,42].

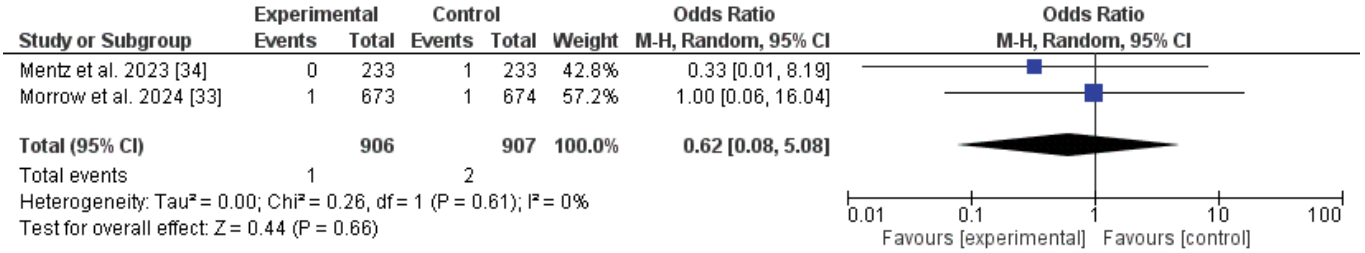

Figure 6: Forest Plot of Angioedema [33,34].

and HF-associated hospitalizations, with a potential trend in the direction of renal protection and decreased angioedema threat, warranting similar research.

Previous meta-analyses, by and large, tested ARNI on blood pressure and the mixed outcome of mortality and coronary heart failure hospitalization. Studies have proven reductions in left ventricular mass index (LVMI) in patients with coronary heart failure with reduced ejection fraction (HFrEF) and those with essential high blood pressure, highlighting ARNI's ability to address cardiac hypertrophy [47,48]. While a few studies have diagnosed sturdy institutions among mortality in sufferers handled with ACEIs or ARBs, not all medicines that induce short-term cardiac remodeling (CRR) have shown improvements in long-term outcomes [49,50]. Further research is required to clarify the link between CRR and reduced mortality following ARNI therapy.

Another observe tested that ARNIs considerably improved left ventricular size and hypertrophy in patients with coronary heart failure with reduced ejection fraction (HFrEF), even within a short-term period comply with-up period. Patients showed more advantages in terms of cardiac reverse remodelling (CRR) whilst treated with ARNIs as early as possible and for a minimum length of three months [51].

This meta-analysis has several obstacles that warrant consideration. While heterogeneity changed into typically low to mild, variations in study designs, patient populations, and treatment protocols may have influenced the results. The brief follow-up intervals of many included research constrained the potential to evaluate long-term outcomes and protection of ARNI therapy. Some vital results, together with quality of lifestyles and cost-effectiveness, had been underrepresented or not assessed. Additionally, the low occurrence of charges for rare negative consequences, consisting of angioedema, decreased the statistical strength to draw definitive conclusions. Although no widespread guide bias changed into detected, the capacity for unpublished poor consequences can't be excluded.

Conclusion

In the end, this meta-evaluation highlights the clinical benefits of angiotensin receptor-neprilysin inhibitors (ARNIs) in patients with heart failure with decreased ejection fraction (HFrEF). ARNI remedy turned into associated with tremendous discounts in cardiovascular mortality, heart failure hospitalizations, and renal negative consequences, along with improvements in left ventricular remodeling and functional effects. Despite a few barriers, along with the variety in take a look at designs and underrepresentation of certain outcomes, these findings strengthen the efficacy and protection of ARNIs in the control of heart failure. Future research with extended follow-up, numerous affected person populations, and a broader assessment of effects, along with pleasant of lifestyles and cost-effectiveness, is warranted to similarly establish the function of ARNIs in coronary heart failure control. This evidence helps the recommendation for early and sustained ARNI initiation as a cornerstone in coronary heart failure treatment to improve patient outcomes.

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