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REVIEW

The in-hospital administration of sacubitril/valsartan in acute myocardial infarction: A meta-analysis

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Abstract

There is a need to address the evidence gap regarding the in-hospital administration of sacubitril/valsartan in acute myocardial infarction patients. After searching MEDLINE, Google Scholars and Scopus, a random-effects meta-analysis of randomized controlled trials comparing the in-hospital administration of the angiotensin receptor-neprilysin inhibitors (ARNis) versus the standard therapy in patients with reduced heart failure due to myocardial infarction was performed. The primary outcome was major adverse cardiovascular events. All-cause mortality, cardiac death, rehospitalization for heart failure, non-fatal myocardial infarction (MI), changes in left ventricular ejection fraction, left ventricular volumes, N terminal pro brain natriuretic peptide and adverse events were the secondary endpoints. Nine studies (eight randomized controlled trials and one echo-substudy) with a total 6597 individuals (angiotensin-converting enzyme inhibitor/angiotensin receptor blocker: 3300 patients vs. ARNis: 3297 patients) were included for quantitative analysis. Median follow-up was 6 months. Patients receiving an in-hospital coadministration of ARNi had a lower risk of major cardiovascular event [odds ratio (OR) 0.45, 95% confidence interval (CI) 0.32–0.63, $P < 0.0001$] and lower rate of repeat rehospitalization for heart failure (OR 0.40, 95% CI 0.26–0.62, $P < 0.0001$), compared with a standard regimen. Additionally, left ventricle volumes were significantly lower in the ARNi group [left ventricular end-diastolic volume, mean difference (MD) 11.48 mL, 95% CI 6.10–16.85, $P < 0.0001$; left ventricular end-systolic volume, MD 7.09 mL, 95% CI 2.89–11.29, $P = 0.0009$] with a significant change in left ventricular ejection fraction (MD 3.07, 95% CI 1.61–4.53, $P < 0.0001$), compared with standard therapy. No significant differences were observed in terms of cardiac death, all cause of mortality, non-fatal myocardial infarction and N terminal pro brain natriuretic peptide. Higher rates of iatrogenic hypotensive events were observed in the ARNi group compared with the standard therapy (OR 1.42, 95% CI 1.26–1.60, P value < 0.00001). In patients with acute myocardial infarction related heart failure, the in-hospital administration of ARNis was associated with a reduced risk of major cardiovascular events and re-hospitalization for heart failure, as well as cardiac remodelling, but higher rates of hypotensive events compared with standard therapy.

Keywords acute myocardial infarction; angiotensin receptor-neprylisin Inihibitors; heart failure; medical therapy; sacubitril; valsartan

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Introduction

Over the past two decades, advances in revascularization strategies have progressively improved the outcomes of patients with acute myocardial infarction (AMI). However, heart failure (HF) is a common concern in daily practice as it strongly correlates with future re-hospitalizations and death.[1–4] The Cardiovascular Disease in Norway Project, which included 86 771 patients from 2001 to 2009, found that 18.7% of patients admitted for AMI also presented with signs of decompensated HF.[5]

The pathogenesis of post-AMI HF involves several factors. Firstly, myocyte death with subsequent inflammatory response, microembolization of debris and reactive oxygen species following epicardial revascularization may play a relevant role.[6,7] Furthermore, the development of HF may be exacerbated by co-morbidities such as anaemia, chronic obstructive pulmonary disease (COPD) and chronic kidney disease (CKD).[6] While primary coronary transcatheter angioplasty (PTCA) remains a cornerstone in the treatment of acute coronary syndrome (ACS), adjunctive supportive pharmacologic therapies could also improve the prognosis of these patients.[7] Previous clinical trials have shown that early blockade of the renin-angiotensin system is linked to improved survival rates and lower incidence of major adverse cardiac events (MACEs), particularly in patients with anterior AMI or high-risk characteristics (Killip II/III, heart rate over 100 b.p.m.) upon admission.[8–12] Based on this evidence, international guidelines recommend early administration of angiotensin-converting enzymes inhibitors (ACEi) or angiotensin receptor blockers (ARB) in patients with AMI.[13,14]

The advent of sacubitril/valsartan has revolutionized HF management. Indeed, inhibiting neprilysin further increases circulating vasoactive peptides and counterbalances neurohormonal overactivation, which results in vasoconstriction, sodium retention and negative remodelling.[15] The PARADIGM-HF and PIONEER-HF studies demonstrated the superiority of sacubitril/valsartan over ramipril in patients without AMI. The administration of sacubitril/valsartan was found to significantly reduce all-cause and cardiovascular mortality rates, hospital readmissions, and improve symptoms and functional limitation.[16,17] Currently, there is a need to address the evidence gap regarding the in-hospital use of sacubitril/valsartan in AMI patients. The PARADISE-MI trial did not demonstrate a benefit of angiotensin receptor-neprilysin inhibition in the setting of ACS, although it raised some methodological concerns.[18] To address this issue, this systematic review and meta-analysis aimed to investigate the prognostic impact of the in-hospital administration of sacubitril/valsartan in patients with AMI-related HF.

Methods

The present analysis was conducted in accordance with Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines[19] and was preregistered in the international prospective register of systematic reviews (PROSPERO CRD42024554363). The data that support the findings of this study are available from the corresponding author upon reasonable request. Approval from institutional review board for this study was waived because of the lack of individual patient information. Patient written consent for the publication of the study was not received because of the lack of individual patient information.

Search strategy

We searched MEDLINE, Google Scholar and Scopus until February 2024 to identify randomized trials that compared clinical and echocardiographic outcomes of two different drug regimens in patients with HF and HF reduced ejection fraction (HFrEF) due to AMI. Specifically, we evaluated the effectiveness of an immediate therapeutic strategy based on angiotensin receptor-neprilysin inhibitors (ARNi) compared with the current standard of care, which involves ACE inhibitors or ARBs. A combination of keywords and MeSH terms were used to search for studies related to 'acute myocardial infarction', 'angiotensin receptor antagonists', 'ARNi', 'ACE inhibitors', 'ARBs' and 'reduced heart failure'. Furthermore, relevant studies were identified by manually searching through the reference lists of the articles.

Study selection and data extraction

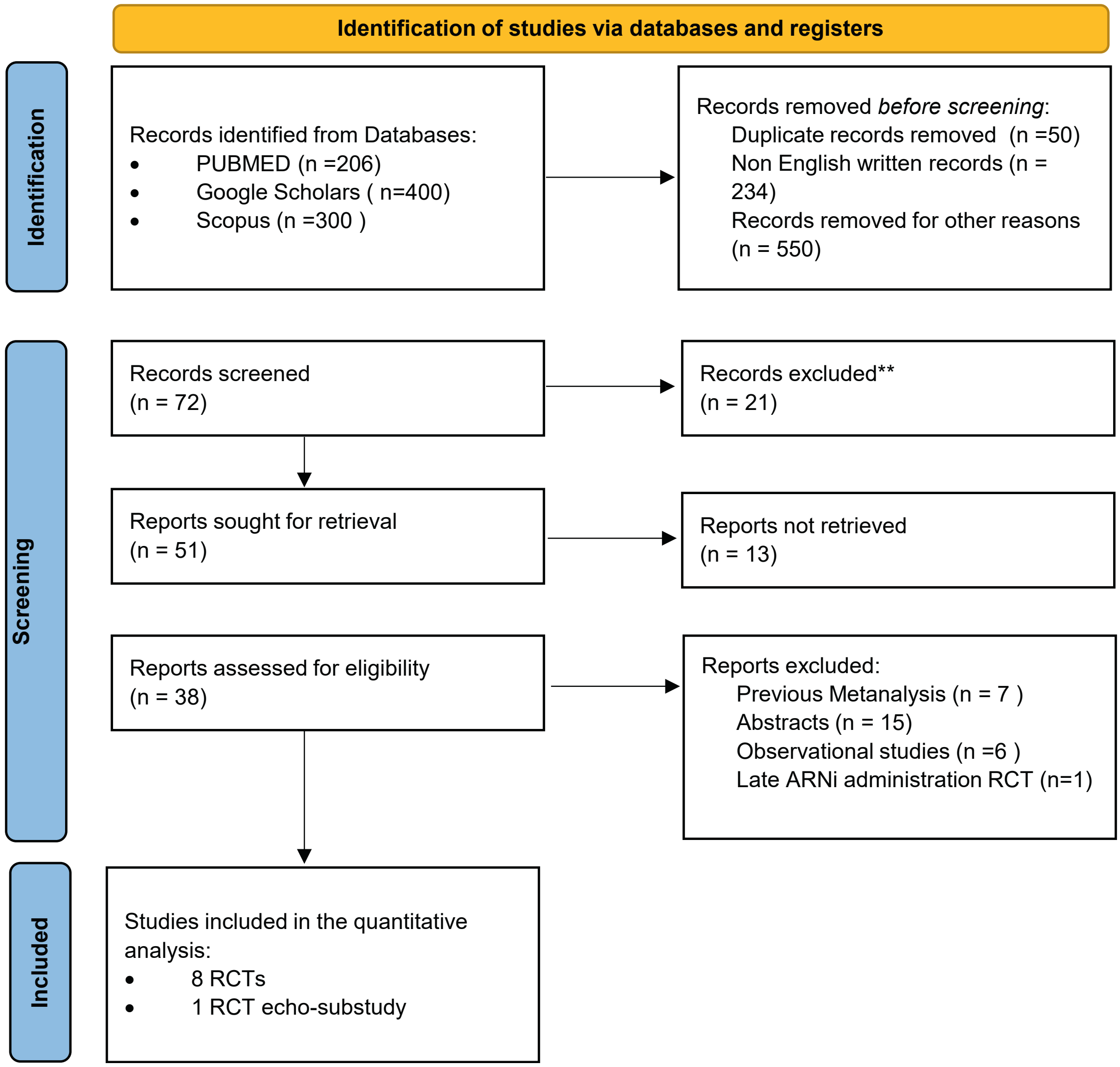
Two independent physicians (A.L. and R.D.C.) screened the literature for duplicate results, and disagreements were resolved by a third author (G.D.P.). For studies with overlapping samples, the publication with the largest cohort was selected. Animal or in vitro studies, case reports, conference presentations, editorials, reviews and expert opinions were excluded.

Eight English-language studies comparing clinical and/or echocardiographic outcomes in patients with AMI-related HFrEF after a clinical and laboratory evaluation receiving in-hospital standard medical therapy and ARNi were included in the quantitative analysis.[20–28] Studies that focused on out-hospital administration of ARNi were excluded from the quantitative analysis. The PRISMA flowcharts of the study selection process are shown in *Figure* 1. Data on investigators, year, journal, design, study period, follow-up period, procedural approach, sample size, patient characteristics and outcomes were extracted independently by two authors (A.L. and R.D.C.) and checked by a third author (G.D.P.). The Cochrane Risk of Bias ROB2.0 tool was used to assess the quality of randomized trials, while ROBINS1 tool for the quality of non-randomized trials.[29,30] Publication bias was assessed by means of funnel plots.

Outcomes

Major adverse cardiovascular events were the primary outcome, while rehospitalization for HF, all-cause mortality, non-fatal MI and cardiac death were the secondary ones.

Figure 1 PRISMA 2020 flow diagram of the searching strategy.



Other secondary outcomes included changes in N terminal pro brain natriuretic peptide (NT-proBNP), left ventricular end systolic volume (LVESV), left ventricular end diastolic volume (LVEDV), left ventricular ejection fraction (LVEF) and adverse events (hypotension and renal impairment) from baseline to study endpoint as measured by echocardiography.

Statistical analysis

Continuous variables are presented as mean (standard deviation) or median (first and third quartile), while categorical variables are expressed as *n* (%). Statistical pooling for incidence estimates was performed using a random-effect model with generic inverse-variance weighting. Risk estimates with 95% confidence intervals (CIs) were computed using RevMan 5.2 (The Cochrane Collaboration, The Nordic Cochrane Centre, Copenhagen, Denmark). Hypothesis testing for superiority was conducted at the two-tailed 0.05 level. The I^2 statistic was used to assess heterogeneity, with low heterogeneity defined as 0%–25%, moderate heterogeneity defined as 25%–50%, and substantial heterogeneity defined as greater than 50%. A sensitivity analysis was performed when significant heterogeneity resulted from the primary analysis. A subgroup meta-analysis of trials including patients who received only ACE inhibitors and ARBs was also performed.

The level of evidence for the meta-analysis results was assessed using the GRADE approach.[31] Evidence was graded as high, moderate, low or very low. For assessments of the overall quality of evidence for each outcome, including pooled data from randomized controlled trials (RCTs) only, we lowered the evidence from 'high quality' by one level for serious (or two levels for very serious) study limitations (risk of bias), indirectness of evidence, serious inconsistency, imprecision of effect estimates or potential publication bias.

Results

After conducting a thorough search for studies comparing the two medical regimens, a total of nine studies (eight RCTs and one echo-substudy) were identified globally. These trials involved a significant number of patients, with a total of 6597 individuals included for quantitative analysis. Out of these patients, 3300 received an ACEi/ARBi-based regimen, while the remaining 3297 patients were administered an ARNi-based regimen. The 554 patients in the echo-substudy are participants in the PARADISE-MI trial. Therefore, numbers and baseline characteristics were not considered separately. Median follow-up was 6 months. Characteristics of the included studies are summarized in *Table* 1. The two cohorts did not differ in terms of age [60, interquartile range (IQR) 58–64 vs. 60, IQR 58–63.5], gender (77% of males, IQR 72%–86% vs. 80% of males, IQR 71%–88%) and cardiovascular risk factors (arterial hypertension: 55%, IQR 42%–66% vs. 54%, IQR 47%–67%; dyslipidaemia: 55%, IQR 19%–86% vs. 53%, IQR 16%–94%; diabetes: 34%, IQR 22%–44% vs. 33%, IQR 27%–42%) (*Table* 2).

The risk of bias assessment for randomized and not randomized controlled studies is shown in Figure S1A and Figure S1B, respectively. *Table* 1 provides definitions of MACEs for the trials. The main analysis results are presented in *Table*s 3. Funnel plots for visual inspection of publication is reported as Figures S2 and S3. Lastly, *Table* 4 reported the grading of evidence using the GRADE approach.

Major adverse cardiac event

Among 6597 patients (3297 receiving ARNi and 3300 receiving standard therapy), an ARNi-based regimen was associated with a lower risk of MACE compared with the standard therapy (OR 0.51, 95% CI 0.34–0.76, P = 0.0009, I^2 57%). Substantial heterogeneity was documented for cohorts. See *Figure* 2A. Results were not affected after removal of the PARADISE-MI trial, which introduced moderate heterogeneity (OR 0.43, 95% CI 0.31–0.61, $P < 0.00001$, I^2 = 0%) (*Figure* 2B).

All-cause of mortality and cardiac death

Pooled results from four studies comparing ARNi versus ACEi/ARBi among 6176 patients showed a similar risk of all-cause mortality (OR 0.88, 95% CI 0.73–1.06, P = 0.18, I^2 = 0%) as of cardiac death (OR 0.89, 95% CI 0.72–1.10, P = 0.28) See *Figure*s 3A and 4A. These results were not affected after the removal of PARADISE-MI (all-cause mortality: OR 1.49, 95% CI 0.45–5, P value = 0.52; cardiac death: OR 3.29, 95% CI 0.51–21.22, P value = 0.21). See *Figure*s 3B and 4B.

Rehospitalization for heart failure

ARNi-based regimen was associated with lower rate of repeat rehospitalization for HF compared with a standard regimen (OR 0.49, 95% CI 0.29–0.82, P = 0.007) (*Figure* 5A). Substantial heterogeneity was documented for both cohorts. Results were not affected after removal of the PARADISE-MI trial, which introduced moderate heterogeneity (OR 0.39, 95% CI 0.25–0.61, $P < 0.0001$, I^2 = 0%). See *Figure* 5B.

Non-fatal myocardial infarction

The analysis showed no significant differences between the two regimens in terms of non-fatal myocardial infarction for AMI related HF (OR 0.90, 95% CI 0.33–2.46, P = 0.84). Studies included were characterized by strong homogeneity (I^2 = 0%). See *Figure* 6.

Echocardiographic data

Pooled data from eight studies involving 1302 patients showed a significant increase in left ventricular ejection fraction (LVEF) scores after treatment with ARNi compared with baseline [mean difference (MD) 2.65%, 95% CI 1.20–4.10, P = 0.0003]. See *Figure*s 7A. Results were not affected after removal of the PARADISE-MI echo sub-study, which introduced moderate heterogeneity (MD 3.07, 95% CI 1.61–4.53, $P < 0.0001$, I^2 = 42%) (*Figure* 7B).

Summary data from four studies with a total of 590 patients showed a significant decrease in left ventricular end-diastolic volume after receiving ARNi compared with baseline (MD 11.48 mL, 95% CI 6.10–16.85, $P < 0.0001$, I^2 = 12%) and in left ventricular end-systolic volume after treatment with ARNi (MD 7.09 mL, 95% CI 2.89–11.29, P = 0.0009, I^2 = 0%). See *Figure* 8A,B.

Effects of angiotensin-receptor neprilysin inhibitor on brain natriuretic peptides

Pooled data of three studies, globally encompassing 340 patients, did not show a significant difference in BNP reduced after taking ARNi compared with baseline (MD 132.36, 95% CI 177.96–442.68, P = 0.40) (Figure S4) A significant difference in BNP was registered after the removal of the study by Yang et al., which introduced high heterogeneity (MD

Table 1 Included studies

Authors	Year	Characteristics of included studies	Sample size	Control group	Time of ARNi administration	Concomitant drugs	Follow-up	MACE/MACCE definition and major findings
Rezq et al.[21] SAVE-STEMI	2021	Egypt Double-blind randomized multicentre	200	Ramipril	Not specified but before discharge	Aspirin, P2Y12 inhibitors, beta-blockers statins	6 months	MACE: Composite endpoint of cardiac death, myocardial infarction (MI) and HF hospitalization. Major findings: Early initiation of sacubitril/valsartan was associated with clinical benefit and improvement in myocardial remodelling in post-STEMI patients.
Yang et al.[22]	2023	China Not blinded Randomized Single centre	148	Valsartan	Not specifief but early administration	Aspirin, clopidogrel/ticagrelor, beta-blockers, furosemide, spironolactone, Statins	6 months	MACE: Death from coronary heart disease, myocardial infarction, heart failure, severe arrhythmia and recurrent angina pectoris. Major findings: Sacubitril/valsartan inhibited ventricular remodelling and prevented heart failure after PCI in patients with AMI;
Dong et al.[23]	2022	China Double-blind Randomized Single centre	131	Enalapril	Within 24 hours after PCI	Antiplatelet, statins, beta-blockers, mineralocorticoid receptor antagonists diuretics, and inotropes were used according to the patient's condition	6 months	MACCE: Death, reinfarction, outpatient HF or HF hospitalization, malignant arrhythmia or stroke Major findings: Early initiation of ARNi provided significant clinical benefits.
Fan et al.[24]	2023	China Not blinded Randomized Single centre	78	Irbsesartan	Not specified, but before discharge	Aspirin, ticagrelor	3 months	MACE: Rehospitalization due to heart failure, recurrent AMI, recurrent UA, malignant arrhythmia, repeat revascularization and cardiac death Major findings: Sacubitril/valsartan improved the cardiac function, prevented ventricular remodelling and further optimized the clinical efficacy of PCI in AMI patients.
Zang et al.[26]	2021	China Not blinded Randomized Single centre	186	Perindopril	Within 24 hours	NA	6 months	Not specified Major findings: Patients with ST-elevation myocardial infarction after primary percutaneous coronary intervention could benefit from early administration of sacubitril/valsartan
Wang et al.[27]	2021	China Not blinded Randomized Single centre	137	Enalapril	After hemodynamic stabilization	NA	6 months	MACCE: Death, MI, stoke and repeat revascularization Major findings: Sacubitril/valsartan attenuated LV remodelling and dysfunction and was effective in LV systolic dysfunction patients post AAMI
Abdelnabi et al.[25]	2023	USA Not blinded Randomized Single centre	192	Valsartan	Not specified, but before discharge	NA	6 months	MACCE: Heart failure, myocardial infarction, cerebrovascular stroke, target vessel revascularization and death Major findings: Sacubitril/valsartan was associated with significantly lower heart failure incidence and total MACCE at 6 months follow-up

(*Continues*)

Table 1 (continued)

Authors	Year	Characteristics of included studies	Sample size	Control group	Time of ARNi administration	Concomitant drugs	Follow-up	MACE/MACCE definition and major findings
Pfeffer et al. PARADISE-MI[20]	2021	UK Double-blinded Multicentre	5661	Ramipril	Not specified, but before discharge	DAPT, mineralcorticoid, diuretic, statin, beta-blockers	23 months	MACE: death from cardiovascular causes, hospitalization for heart failure and outpatient episode of heart failure Major findings: Sacubitril-valsartan was not associated with a significantly lower incidence of death from cardiovascular causes or incident heart failure than ramipril among patients with acute myocardial infarction
Shah et al.[28]	2022	Echo-substudy of PARADISE MI	544	Ramipril	Not specified, but before discharge	-	8 months	The primary endpoint was not a clinical outcome but an echocardiographic endpoint (change in LVEF and LAVI) Major findings: Treatment with sacubitril/valsartan compared with ramipril after AMI did not result in changes in ejection fraction and atrial volume at 8 months

MACE, major adverse cardiovascular events; MACCE, major adverse cardiovascular and cerebrovascular events; NA, not available; PCI, percutaneous coronary intervention.

265.78, 95% CI 200.78–330.79, P value < 0.00001, $I^2 = 0\%$) (Figure S5).

Safety outcomes

Pooled results from three studies with a total of 5937 patients (ARNi: 2979 patients; ACEi/ARBs: 2346 patients) showed no significant differences between the study groups in terms of overall adverse events (OR 1.07, 95% CI 0.93–1.22, P value = 0.35) with strong homogeneity ($I^2 = 0\%$). See *Figure* 9A. Specifically, patients treated with ARNis had a higher risk of iatrogenic hypotension compared with the control group (OR 1.42, 95% CI 1.26–1.60, P value < 0.00001) with a strong homogeneity ($I^2 = 0\%$), although this result was mainly driven by PARADISE-MI (*Figure* 9B). Finally, there were no significant differences between the two study groups in terms of renal impairment (OR 1, 95% CI 0.85–1.17, P value = 0.99). See *Figure* 9C.

Subgroup analysis

We also performed a subgroup analysis for MACE and rehospitalizations for HF according to the drugs in the control arm. Patients receiving ARNis had lower rates of MACE (OR 0.60, 95% CI 0.39–0.90, P value = 0.01) and rehospitalizations for HF (OR 0.57, 95% CI 0.34–0.96, P value = 0.03) compared with those receiving ACE inhibitors. See Figures S10–S11. Similarly, patients who received ARNis had lower rates of MACE (OR 0.38, 95% CI 0.19–0.35, P value = 0.005) and a trend towards significance for HF rehospitalizations (OR 0.30, 95% CI 0.08–1.08, P value = 0.07) compared with those who received ARBs. See Figures S12–S13.

Discussion

In this meta-analysis, we sought to compare outcomes among patients treated with ARNi or ACEi/ARB after AMI before the discharge. The main findings can be summarized as follows (Central Illustration):

- The ARNi group had a lower probability of experiencing MACE and HF rehospitalizations compared with patients treated with angiotensin-converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARBs).
- All-cause death and re-infarction rates did not differ significantly between the two groups, and a non-significant trend towards reduced cardiovascular death rates was observed for the ARNi population.
- Left ventricular volumes were significantly lower in the ARNi group and there was a strong trend towards an increase in left ventricular ejection fraction (LVEF) in this group.
- NT-proBNP concentrations were not significantly different between the two cohorts.
- A higher rate of hypotensive events has been reported in the ARNi group compared with those who have received ACEi/ARBs.

Table 2 Clinical characteristics of patients enrolled

	Sex (male), %	Age (years), years old (±SD)	Previous MI (%)	Anterior AMI (%)	LVEF (%)	NT-pro-BNP (mcg/L)
ARNi (*n* = 3362)	76 (IQR 72–86)	60 (IQR 58–64)	8.2 (IQR 0–16)	71 (IQR 68–93)	42 (IQR 36–47)	1168 (IQR 869–1569)
ACEi/ARB (*n* = 3341)	79 (IQR 71–88)	60 (IQR 58–63)	4.8 (IQR 0–16)	74 (IQR 68–94)	43 (IQR 36–48)	1033 (IQR 700–1289)
P value	0.59	0.6	0.41	1	1	0.41

AMI, anterior myocardial infarction; HTN, hypertension; IQR, interquartile ratio; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NT-proBNP, N terminal pro brain natriuretic peptide.

Table 3 Summary of the outcomes of the meta-analysis

	In-hospital administration ARNi versus standard therapy (ACEi/ARBs)
	OR [95% CI]
MACEs	0.45 [0.32–0.63]
All-cause death	0.88 [0.73–1.06]
Cardiac death	0.89 [0.72–1.10]
Rehospitalization for heart failure	0.40 [0.26–0.62]
Non-fatal MI	0.90 [0.33–2.46]
	MD [95% CI]
LVEF, %	3.07 [1.61–4.53]
LVEDV, mL	11.48 [6.10–16.85]
LVESV, mL	7.09 [2.89–11.29]
NT-pro-BNP, mcg/L	132.36 [177.96–442.68]

ACEi, angiotensin-converting enzymes inhibitors; ARBs, angiotensin receptor blockers; ARNi, angiotensin receptor-neprylisin inhibitors; CI, confidence interval; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, Left ventricular end-systolic volume; MACE, major cardiovascular events; MD, mean difference; MI, myocardial infarction; OR, odds ratio; NT-proBNP, N-terminal pro-brain natriuretic peptide.

Recent international guidelines on ACS do not provide specific recommendations for the early introduction of ARNi in patients with reduced LVEF, despite its established use in the treatment of HF patients with reduced LVEF of various aetiologies.[13,14] Also, the recent 2023 update guidelines of HF proposed by the ESC underlines the importance of early introduction and rapid up-titration of the four pillars for HFrEF, but without a clear differentiation among ACEi and ARNi.[32] There is increasing evidence[33,34] supporting the early initiation and up-titration of ARNi therapy in patients with reduced LVEF. Consistent with previous findings,[35,36] our study confirmed the efficacy of ARNi, even in the AMI subgroup, particularly in preventing HF rehospitalizations, which appears to drive the difference in major cardiovascular events.

The reverse remodelling resulting from ARNi treatment has already been linked to improved outcomes in HFrEF patients.[37] The PARADISE-MI results sparked a lively debate among the scientific community regarding ARNi therapy in AMI patients due to the lack of benefit on hard endpoints in such a large RCT and the higher rates of symptomatic hypotension.[21] However, there is a strong pathophysiological rationale for the beneficial effects of ARNi in cardiac remodelling after myocardial infarction.[38] It is widely acknowledged that adverse remodelling begins soon after ischaemic injury due to a complex interplay between mechanical and neuro-hormonal pathways, ultimately resulting in ventricular thinning and dilation.[39] Natriuretic peptides, which are secreted by the atrial and ventricular cardiomyocytes in response to increased wall stress and stretching of the peri-MI tissue, promote apoptosis inhibition and collagen synthesis.[40] Furthermore, inhibiting the renin-angiotensin system leads to favourable cardiac remodelling due to the harmful effects of angiotensin II.[41] This includes the release of growth factors and mediators that promote the deposition of extracellular matrix, vasoconstriction and water retention, which increase wall stress and contribute to chamber dilation and fibrosis. It is important to note that this is an objective evaluation based on scientific evidence.[42] The VALIANT trial and its echography sub-study demonstrated that valsartan and captopril are not inferior to ACE inhibitors in preventing adverse atrial and ventricular remodelling and HF events after AMI.[43] The synergistic mechanism of ARNi, particularly in the early period after AMI, may be of great interest in preventing definite and irreversible adverse remodelling.[44]

Natriuretic peptides have been suggested to slow the progression of coronary atherosclerosis and to positively regulate coronary arterial tone and blood flow.[45–47]

The lack of differences between ARNi and standard therapy on coronary endpoints may be attributed to the marginal effect of these molecules on coronary atherosclerotic mechanisms. In both the PARADIGM-HF and PARADISE-MI substudies,[48,49] ARNi therapy reduced the coronary composite endpoint, which includes cardiovascular death and angina re-hospitalizations. Adverse myocardial remodelling and improvement in LVEF could have reduced cardiovascular death. Additionally, the lower rates of angina re-hospitalizations could have been due to the improved hemodynamic profile resulting from increased diuresis and cardiac function, ultimately leading to a reduced imbalance between myocardial perfusion and oxygen demand. It would be of great interest to test ANRI in coronary endpoints exclusively, even though such a study would require a large population to detect small differences in event rates.

Table 4 GRADE evidence profile

Certainty assessment							No. of patients		Effect			
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ARNi	ACEi/ARBs	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
MACE												
8	Randomized trials	Serious	Not serious	Serious	Not serious	All plausible residual confounding would reduce the demonstrated effect	392/3361 (11.7%)	487/3337 (14.6%)	OR 0.51 (0.34–0.76)	66 fewer per 1000 (from 91 fewer to 31 fewer)	⊕⊕⊕◯ Moderate	
All cause of mortality												
4	Randomized trials	Serious	Not serious	Serious	Not serious	All plausible residual confounding would reduce the demonstrated effect	217/3090 (7.0%)	245/3089 (7.9%)	OR 0.88 (0.73–1.06)	9 fewer per 1000 (from 20 fewer to 4 more)	⊕⊕⊕◯ Moderate	
Cardiac death												
4	Randomized trials	Serious	Not serious	Serious	Not serious	All plausible residual confounding would reduce the demonstrated effect	171/3016 (5.7%)	191/3020 (6.3%)	OR 0.89 (0.72–1.10)	7 fewer per 1000 (from 17 fewer to 6 more)	⊕⊕⊕◯ Moderate	
Rehospitalization for heart failure												
7	Randomized trials	Serious	Not serious	Serious	Not serious	All plausible residual confounding would reduce the demonstrated effect	202/3293 (6.1%)	269/3268 (8.2%)	OR 0.49 (0.29–0.82)	40 fewer per 1000 (from 57 fewer to 14 fewer)	⊕⊕⊕◯ Moderate	
Non-fatal MI												
5	Randomized trials	Serious	Not serious	Serious	Not serious	All plausible residual confounding would reduce the demonstrated effect	8/320 (2.5%)	9/323 (2.8%)	OR 0.92 (0.36–2.36)	2 fewer per 1000 (from 18 fewer to 35 more)	⊕⊕⊕◯ Moderate	
LVEF												
6	Randomized trials	Serious	Serious	Serious	Not serious	All plausible residual confounding would reduce the demonstrated effect	399	400	-	MD 3.07 higher (1.61 higher to 4.53 higher)	⊕⊕◯◯ Low	
Adverse events												
3	Randomized trials	Serious	Not serious	Serious	Not serious	All plausible residual confounding would reduce the demonstrated effect	2374/2979 (79.7%)	2346/2958 (79.3%)	OR 1.07 (0.93–1.22)	11 more per 1000 (from 12 fewer to 31 more)	⊕⊕⊕◯ Moderate	

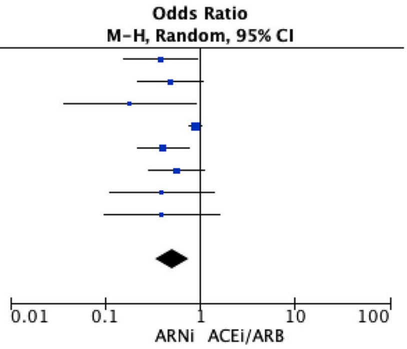
ACEi, angiotensin-converting enzymes inhibitors; ARBs, angiotensin receptor blockers; ARNi, angiotensin receptor-neprylisin inhibitors; CI, confidence interval; LVEF, left ventricular ejection fraction; MACE, major cardiovascular events; MD, mean difference; MI, myocardial infarction; OR, odds ratio.

Figure 2 MACE. Primary (A) and sensitivity (B) analysis. ACEi, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; ARNi, angiotensin receptor-neprilysin inhibitor; CI, confidence interval; M-H, Mantel–Haensel.

(A)

Study or Subgroup	ARNi Events	ARNi Total	ACEi/ARB Events	ACEi/ARB Total	Weight	Odds Ratio M-H, Random, 95% CI
Abdelnabi 2023	8	96	18	94	11.5%	0.38 [0.16, 0.93]
Dong 2022	13	64	22	64	13.0%	0.49 [0.22, 1.08]
Fan 2023 et al.	2	39	9	39	5.0%	0.18 [0.04, 0.90]
M.A. Pfeffer 2021	315	2830	349	2831	25.8%	0.89 [0.76, 1.05]
Rezq 2021	20	100	38	100	16.0%	0.41 [0.22, 0.77]
Wang 2021	27	68	37	69	15.2%	0.57 [0.29, 1.12]
Yang 2023	4	85	7	63	7.2%	0.40 [0.11, 1.41]
Zhang 2021	3	79	7	77	6.3%	0.39 [0.10, 1.59]
Total (95% CI)		**3361**		**3337**	**100.0%**	**0.51 [0.34, 0.76]**
Total events	392		487			

Heterogeneity: $Tau^2 = 0.15$; $Chi^2 = 16.42$, df = 7 (P = 0.02); $I^2 = 57\%$
Test for overall effect: Z = 3.31 (P = 0.0009)



(B)

Study or Subgroup	ARNi Events	ARNi Total	ACEi/ARB Events	ACEi/ARB Total	Weight	Odds Ratio M-H, Random, 95% CI
Abdelnabi 2023	8	96	18	94	14.1%	0.38 [0.16, 0.93]
Dong 2022	13	64	22	64	17.4%	0.49 [0.22, 1.08]
Fan 2023 et al.	2	39	9	39	4.3%	0.18 [0.04, 0.90]
M.A. Pfeffer 2021	315	2830	349	2831	0.0%	0.89 [0.76, 1.05]
Rezq 2021	20	100	38	100	27.5%	0.41 [0.22, 0.77]
Wang 2021	27	68	37	69	24.1%	0.57 [0.29, 1.12]
Yang 2023	4	85	7	63	6.8%	0.40 [0.11, 1.41]
Zhang 2021	3	79	7	77	5.7%	0.39 [0.10, 1.59]
Total (95% CI)		**531**		**506**	**100.0%**	**0.43 [0.31, 0.61]**
Total events	77		138			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 2.00$, df = 6 (P = 0.92); $I^2 = 0\%$
Test for overall effect: Z = 4.90 (P < 0.00001)

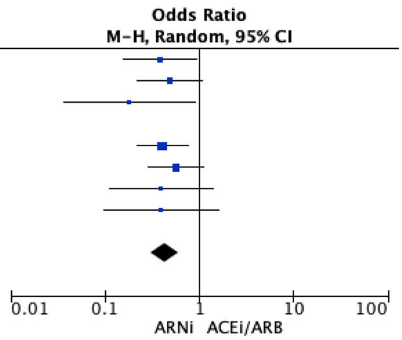
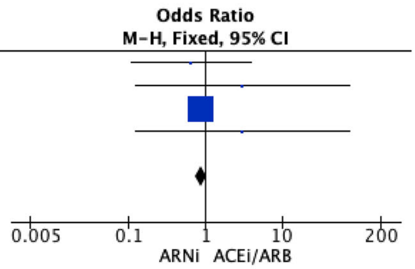


Figure 3 All cause of mortality. Primary (A) and sensitivity (B) analysis. ACEi, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; ARNi, angiotensin receptor-neprilysin inhibitor; CI, confidence interval; M-H, Mantel–Haensel.

(A)

Study or Subgroup	ARNi Events	ARNi Total	ACEi/ARB Events	ACEi/ARB Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Abdelnabi 2023	2	96	3	94	1.3%	0.65 [0.11, 3.95]
Dong 2022	1	64	0	64	0.2%	3.05 [0.12, 76.21]
M.A. Pfeffer 2021	213	2830	242	2831	98.3%	0.87 [0.72, 1.06]
Rezq 2021	1	100	0	100	0.2%	3.03 [0.12, 75.28]
Total (95% CI)		**3090**		**3089**	**100.0%**	**0.88 [0.73, 1.06]**
Total events	217		245			

Heterogeneity: $Chi^2 = 1.26$, df = 3 (P = 0.74); $I^2 = 0\%$
Test for overall effect: Z = 1.35 (P = 0.18)



(B)

Study or Subgroup	ARNi Events	ARNi Total	ACEi/ARB Events	ACEi/ARB Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Abdelnabi 2023	2	96	3	94	75.2%	0.65 [0.11, 3.95]
Dong 2022	1	64	0	64	12.4%	3.05 [0.12, 76.21]
M.A. Pfeffer 2021	213	2830	242	2831	0.0%	0.87 [0.72, 1.06]
Rezq 2021	1	100	0	100	12.5%	3.03 [0.12, 75.28]
Total (95% CI)		**260**		**258**	**100.0%**	**1.24 [0.33, 4.67]**
Total events	4		3			

Heterogeneity: $Chi^2 = 1.10$, df = 2 (P = 0.58); $I^2 = 0\%$
Test for overall effect: Z = 0.32 (P = 0.75)

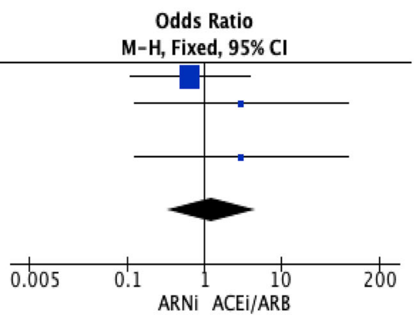


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Figure 4 Cardiac death. Primary (A) and sensitivity (B) analysis. ACEi, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; ARNi, angiotensin receptor-neprilysin inhibitor; CI, confidence interval; M-H, Mantel–Haensel.

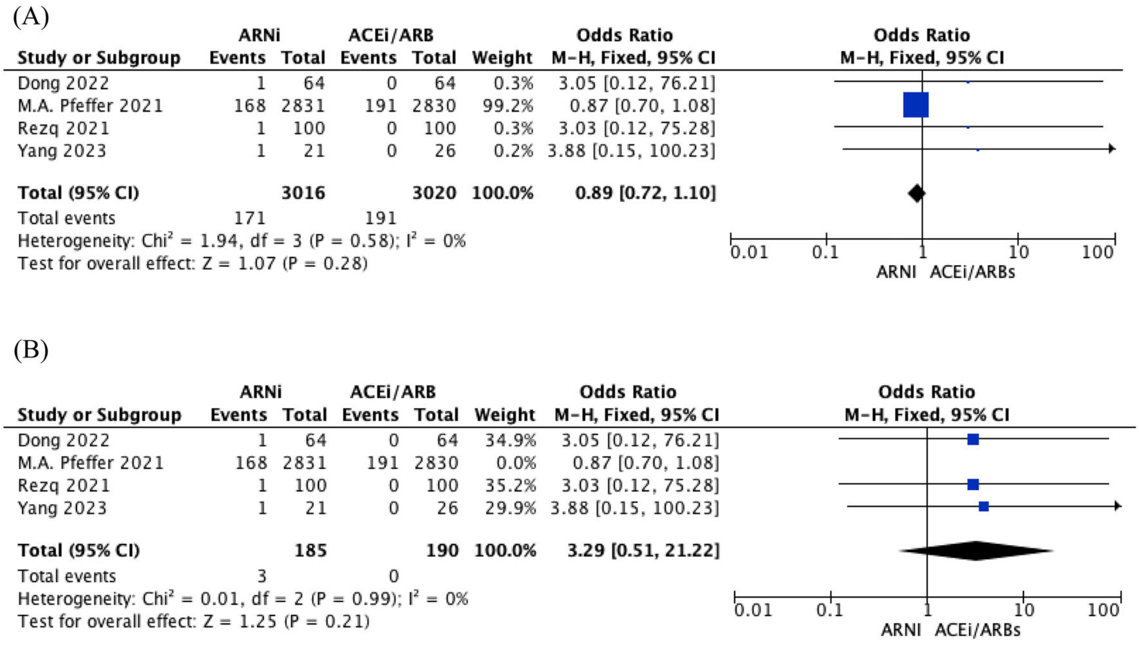
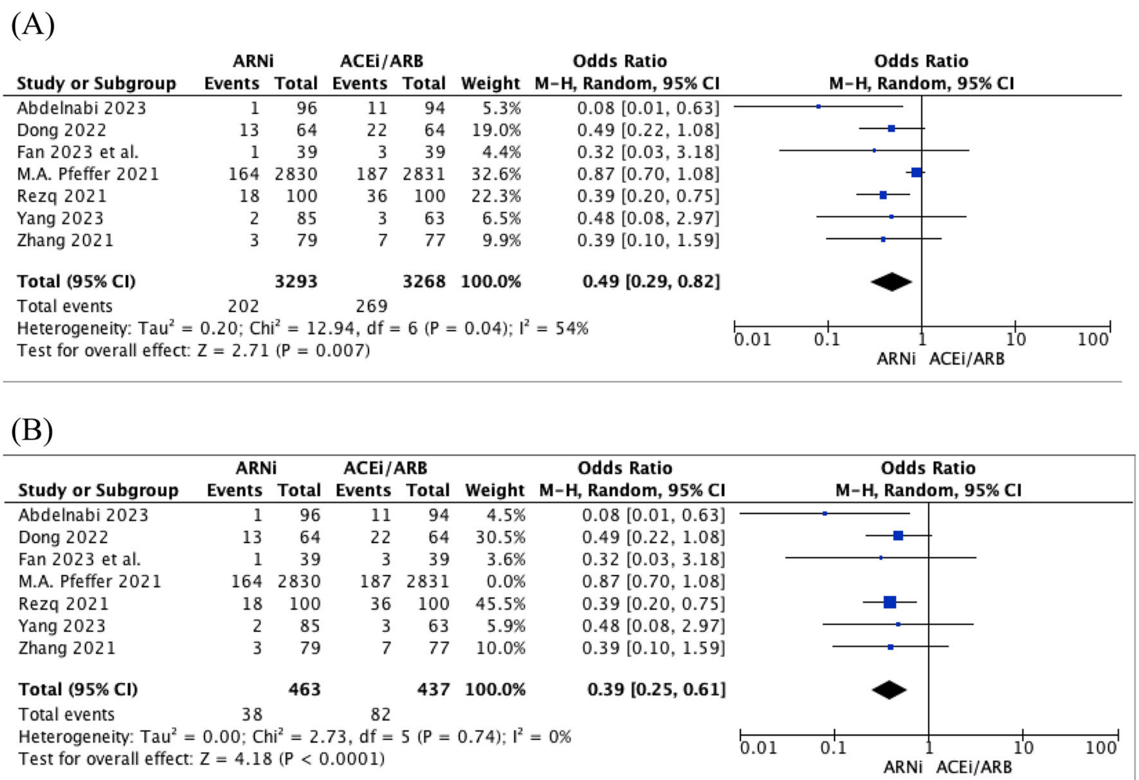


Figure 5 Rehospitalization for heart failure. Primary (A) and sensitivity (B) analysis. ACEi, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; ARNi, angiotensin receptor-neprilysin inhibitor; CI, confidence interval; M-H, Mantel–Haensel.



DOI: 10.1002/ehf2.15082

Figure 6 Non-fatal MI. ACEi, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; ARNi, angiotensin receptor-neprilysin inhibitor; CI, confidence interval; M-H, Mantel–Haensel.

Study or Subgroup	ARNi Events	ARNi Total	ACEi/ARB Events	ACEi/ARB Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Abdelnabi 2023	3	96	1	94	10.9%	3.00 [0.31, 29.37]
Dong 2022	3	64	3	64	31.8%	1.00 [0.19, 5.15]
Fan 2023 et al.	0	39	1	39	16.5%	0.32 [0.01, 8.22]
Rezq 2021	1	100	2	100	22.0%	0.49 [0.04, 5.55]
Yang 2023	1	21	2	26	18.9%	0.60 [0.05, 7.11]
Total (95% CI)		**320**		**323**	**100.0%**	**0.92 [0.36, 2.36]**
Total events	8		9			

Heterogeneity: $Chi^2 = 1.81$, df = 4 (P = 0.77); $I^2 = 0\%$
Test for overall effect: Z = 0.17 (P = 0.86)

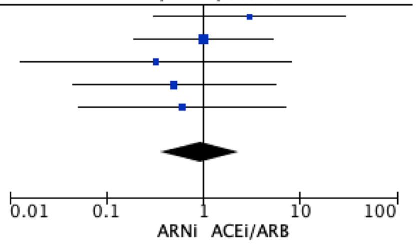
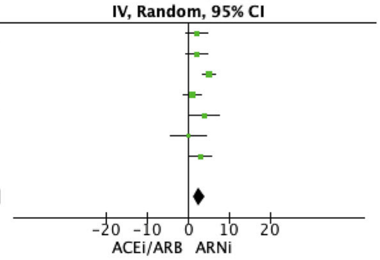


Figure 7 Left ventricular ejection fraction. Primary (A) and sensitivity (B) analysis. ACEi, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; ARNi, angiotensin receptor-neprilysin inhibitor; CI, confidence interval; M-H, Mantel–Haensel.

(A)

Study or Subgroup	ARNi Mean	ARNi SD	ARNi Total	ACEi/ARB Mean	ACEi/ARB SD	ACEi/ARB Total	Weight	Mean Difference IV, Random, 95% CI
Abdelnabi 2023	48	11	96	46	8	94	14.2%	2.00 [−0.73, 4.73]
Dong 2022	52	8	64	50	8	64	14.0%	2.00 [−0.77, 4.77]
Fan 2023 et al.	55	3	39	50	4	39	21.3%	5.00 [3.43, 6.57]
PARADISE-MI Echosubstudy	48	11	206	47	11	209	17.7%	1.00 [−1.12, 3.12]
Rezq 2021	46	12	100	42	14	100	10.3%	4.00 [0.39, 7.61]
Yang 2023	55	7	21	55	8	26	8.2%	0.00 [−4.29, 4.29]
Zhang 2021	46	12	79	43	2	77	14.4%	3.00 [0.32, 5.68]
Total (95% CI)			**605**			**609**	**100.0%**	**2.65 [1.20, 4.10]**

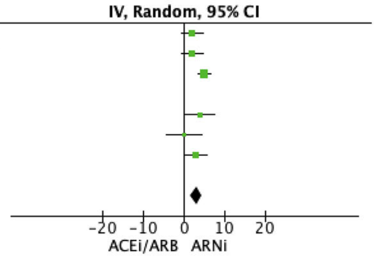
Heterogeneity: $Tau^2 = 1.93$; $Chi^2 = 12.86$, df = 6 (P = 0.05); $I^2 = 53\%$
Test for overall effect: Z = 3.58 (P = 0.0003)



(B)

Study or Subgroup	ARNi Mean	ARNi SD	ARNi Total	ACEi/ARB Mean	ACEi/ARB SD	ACEi/ARB Total	Weight	Mean Difference IV, Random, 95% CI
Abdelnabi 2023	48	11	96	46	8	94	17.0%	2.00 [−0.73, 4.73]
Dong 2022	52	8	64	50	8	64	16.7%	2.00 [−0.77, 4.77]
Fan 2023 et al.	55	3	39	50	4	39	28.2%	5.00 [3.43, 6.57]
PARADISE-MI Echosubstudy	48	11	206	47	11	209	0.0%	1.00 [−1.12, 3.12]
Rezq 2021	46	12	100	42	14	100	11.7%	4.00 [0.39, 7.61]
Yang 2023	55	7	21	55	8	26	9.1%	0.00 [−4.29, 4.29]
Zhang 2021	46	12	79	43	2	77	17.3%	3.00 [0.32, 5.68]
Total (95% CI)			**399**			**400**	**100.0%**	**3.07 [1.61, 4.53]**

Heterogeneity: $Tau^2 = 1.33$; $Chi^2 = 8.56$, df = 5 (P = 0.13); $I^2 = 42\%$
Test for overall effect: Z = 4.13 (P < 0.0001)



This meta-analysis presents several limitations that should be taken into consideration. Firstly, it is worth noting that the majority of the RCTs included in this analysis were not blinded. This lack of blinding may introduce potential bias and affect the reliability of the results. Secondly, it is important to acknowledge that the majority of these trials were conducted in China. While these findings provide valuable insights, it is essential to consider the potential limitations in generalizing the conclusions to other populations or regions. Further research from diverse geographical locations would be beneficial to enhance the generalizability of the conclusions. Thirdly, there are no data on the dose of ARNi or ACEi/ARBs, and the use of ACEi/ARBs in the control group varied between the included trials. This variation may introduce bias and affect the accuracy of the results. Standardizing the use of these drugs in the control group would have strengthened the validity of the analysis. Furthermore, significant heterogeneity was observed in the analysis of some outcomes, and subgroup analysis failed to explain the main sources of heterogeneity. This suggests that there may be other factors contributing to the observed differences in outcomes among the included trials. In addition, the heterogeneity of MACE definitions in the included studies, as shown in *Table* 1, may also have an impact on the results of our

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Figure 8 Left ventricular end-diastolic volume (A) and left ventricular end-systolic volume (B). ACEi, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; ARNi, angiotensin receptor-neprilysin inhibitor; CI, confidence interval; M-H, Mantel–Haensel.

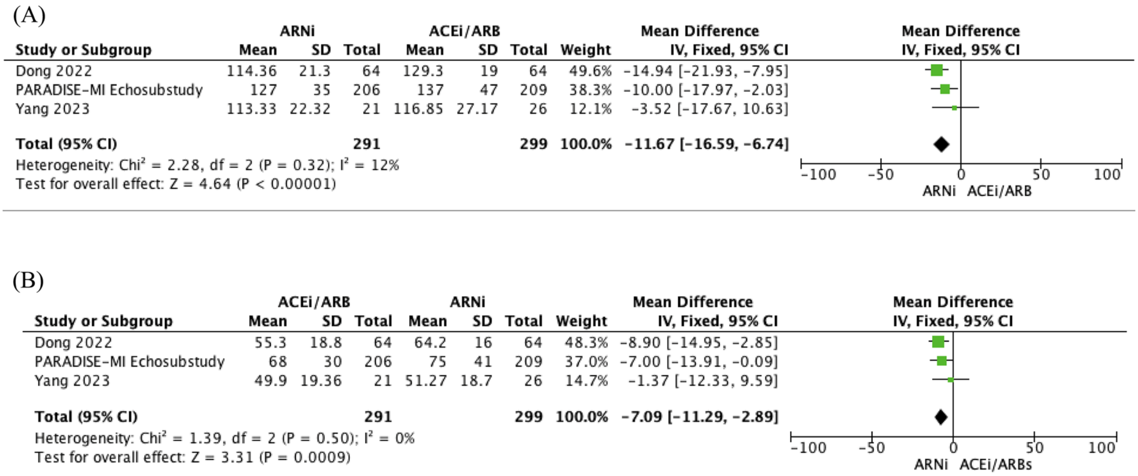
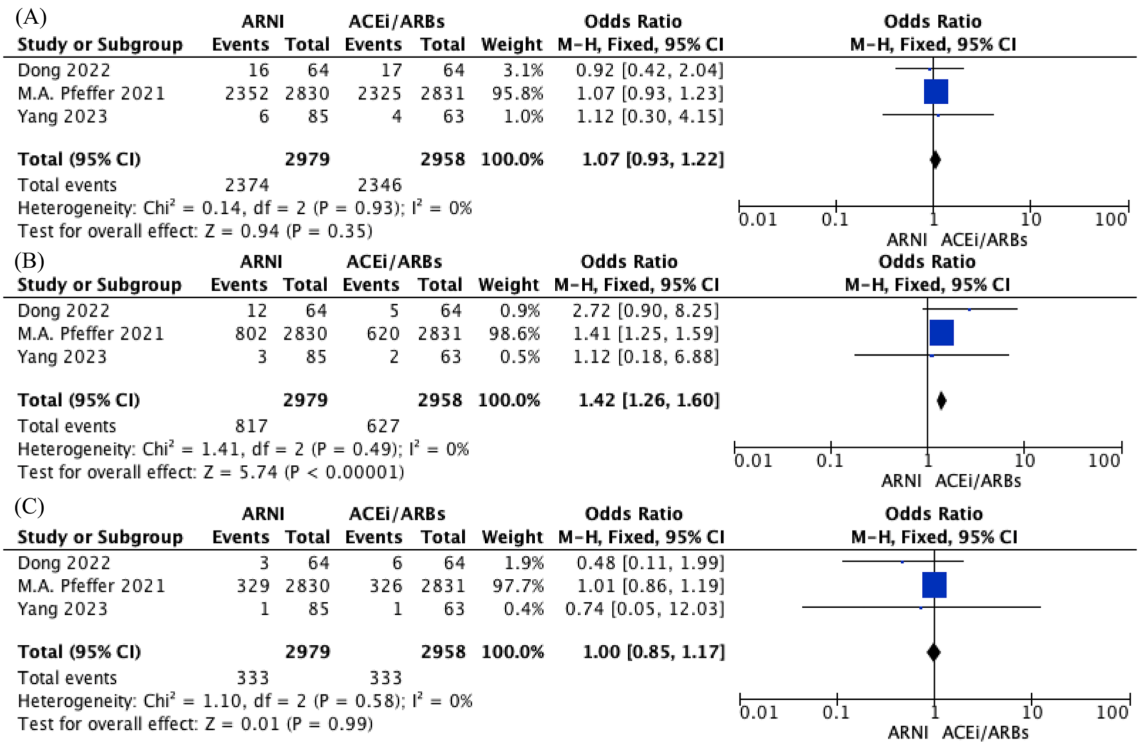


Figure 9 Overall adverse events (A), hypotension (B) and renal impairment (C). ACEi, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; ARNi, angiotensin receptor-neprilysin inhibitor; CI, confidence interval; M-H, Mantel–Haensel.



meta-analysis. Lastly, due to the absence of original data, the authors were unable to conduct further subgroup analysis based on other important parameters, such as age, dose and course of SV. These parameters could potentially influence the outcomes and their absence limits the ability to draw more specific conclusions.

Conclusions

In patients with AMI related HF, the in-hospital administration of ARNis was associated with a reduced risk of MACEs and re-hospitalizations for heart failure, as well as cardiac remodelling, compared with standard therapy.

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Conflict of interest

None declared.

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None.

Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Baseline characteristics of patients.
Figure S1. Risk bias assessment.
Figure S2. Funnel plots for publication bias of clinical outcomes.
Figure S3. Funnel plots for publication bias of echocardiographic outcomes.
Figure S4. NT-pro-BNP.
Figure S5. NT-pro-BNP (sensitivity analysis).
Figures S6. Sensitivity analysis for All-cause of death.
Figure S7. Sensitivity analysis for MACE.
Figure S8. Sensitivity analysis for Cardiac Death.
Figure S9. Sensitivity analysis for Rehospitalization for heart failure.
Figure S10. Subgroup analysis for MACE (ARNIs vs ACE-inihibitors).
Figure S11. Subgroup analysis for Rehospitalizations for heart failure (ARNIs vs ACE-inihibitors).
Figure S12. Subgroup analysis for MACE (ARNIs vs ARBs).
Figure S13. Subgroup analysis for Rehospitalizations for heart failure (ARNIs vs ARBs).
Supplemental List – Studies included.

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