Cardiovascular Topics

Improving cardiac function of angiotensin receptor/neprilysin inhibitor in patients with acute myocardial infarction: a systematic review and meta-analysis

Qiuli Niu, Changyuan Wang, Xiurong Xing

Abstract

Aim: As the impact of angiotensin receptor/neprilysin inhibitor (ARNI) on cardiac function in acute myocardial infarction (AMI) patients is unclear in clinical therapy, we conducted this research to investigate the actual effects of improving cardiac function with ARNI in AMI patients.

Methods: Publications were checked up to June 2022. Standardised mean differences (SMD) and 95% confidence intervals (CI) were utilised for assessing the size of the effect of continuous variables. To assess the magnitude of the effect of dichotomous variables, a relative risk (RR) with 95% CI was used.

Results: ARNI could improve left ventricular ejection fraction (SMD = 0.40; 95% CI: 0.23–0.58), while lowering left ventricular end-diastolic volume (SMD = –0.43, 95% CI: –0.78 to –0.08), left ventricular end-systolic volume (SMD = –0.39, 95% CI: –0.66 to –0.11) and left ventricular end-diastolic diameter (SMD = –0.49; 95% CI: –0.65 to –0.33). Besides, it could decrease the rates of major adverse cardiac events (RR = 0.55; 95% CI: 0.43–0.69) and heart failure (RR = 0.42; 95% CI: 0.31–0.58).

Conclusion: ARNI could greatly improve cardiac function in AMI patients.

Keywords: ARNI, AMI, cardiac function, ACEI, ARB

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Myocardial necrosis resulting from coronary artery ischaemia and hypoxia is a life-threatening feature of acute myocardial infarction (AMI).[1] Protecting the function of the heart, preventing necrosis of the myocardium, and reducing the incidence of infarction are the primary goals of the treatment.[2] Percutaneous coronary intervention (PCI) is a successful treatment for AMI because it can eliminate coronary artery stenosis, alleviate chest discomfort and other symptoms, and reduce mortality.[3-5]

Complications after surgery are substantial. Cardiac dysfunction is one of the most prevalent postoperative consequences, affecting patients' physical health and quality of life. Around 25% of AMI patients suffer from cardiac failure.[6]

Despite the fact that a significant amount of evidence suggests that beta-blockers, angiotensin-converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARB) could substantially suppress left ventricular (LV) remodelling and lower the risk of mortality in patients with AMI, these patients still have a high risk of re-hospitalisation for heart failure (HF) and death.[7,8] Considering neuroendocrine hormones, such as the renin–angiotensin–aldosterone system (RAAS), and the sympathetic nervous system (SNS) contribute significantly to the development of LV remodelling and the onset of HF following AMI,[9] controlling neuroendocrine hormone balance is an effective method to improve patients' outcome.

In the past, RAAS inhibition has mostly concentrated on the therapeutic application of ACEI and ARB. More recently, however, angiotensin receptor/neprilysin inhibitor (ARNI) has become the most current weapon to be added to this array.[10] Sacubitril/valsartan is an innovative ARNI that integrates the neprilysin inhibitor sacubitril with valsartan.

In recent clinical trials comparing the advantages of sacubitril/valsartan and ACEI/ARB in AMI patients, it was discovered that sacubitril/valsartan could enhance the LV ejection fraction (LVEF) and significantly lower the risk of major adverse cardiac events (MACE), re-hospitalisation rate for HF, and LV dimension.[8,11-13] However, there is disagreement over how effective it is in actual medical practice in patients with AMI.

Docherty *et al.* discovered that, compared to valsartan, sacubitril/valsartan did not significantly enhance LVEF or reduce NT-proBNP level, LV volume or LV mass index in AMI patients.[14] Consequently, we did a meta-analysis to assess whether the combination of sacubitril and valsartan could provide more therapeutic benefits in improving cardiac function than ACEI/ARB medicines for AMI patients.

Methods

This meta-analysis was performed to investigate the effect of ARNI, compared with ACEI/ARB, in patients with MI. All the protocols were based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.

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The English electronic databases MEDLINE, PubMed, EMBASE (Ovid), Web of Science, Scopus and Cochrane Central Registry of Controlled Trials along with the Chinese electronic databases such as Chinese Biomedical Literature Database, Chinese National Knowledge Infrastructure (CNKI), Wanfang, VIP and Google Scholar were searched for studies assessing the efficacy of ARNI on improving cardiac function in patients with MI up to June 2022.

Medical subject headings (MeSH) terms such as: 'AMI' or 'MI' or 'ST-segment elevation myocardial infarction (NSTEMI)' or 'non-ST-segment elevation myocardial infarction (NSTEMI)' and 'sacubitril/valsartan' or 'angiotensin converting enzyme inhibitor or angiotensin receptor blocker (ACEI/ARB)' were utilised in our search strategy. Review articles, trial reference lists and conference abstracts with potentially relevant information were manually reviewed.

Two reviewers separately conducted the screening process. After carefully reading the articles, two reviewers extracted the basic details and findings from the included studies, as well as the characteristics of the study participants (gender, age, country, sample size and interventions) for both the experimental and control groups. These details included the study title, first author, publication year, author information and document source. Consensus was achieved by double-checking each other's work if there were inconsistencies.

The studies meeting the following criteria based on PICOS criteria were included: (1) patients with MI over 18 years of age; (2) patients undergoing ARNI therapy; (3) patients in the control group receiving standard ACEI/ARB medication; (4) the main result endpoints included at least one item of cardiac reverse remodelling evaluated by echocardiography; (5) secondary outcome indicators included blood pressure, NT-proBNP, MACE, re-admission rate, HF and MI events; (6) follow up for at least one month.

Studies were excluded if they had: (1) incomplete information or data; (2) improper control; (3) unappropriated article types such as letters, reviews, editorials, case reports and protocols; (4) non-human experiments.

Each study was separately reviewed by two investigators and disagreements were settled by a third researcher. The article with the most comprehensive data was collected when several articles reported the same data

The Newcastle–Ottawa scale (NOS) was performed with quality assessments. The total score varied from 0 to 9 points, with 'excellent quality' research receiving a score greater than 6. Two reviewers independently evaluated the quality of the studies, while a third partner resolved any disagreements.

Statistical analysis

Stata statistical software (version 13.0; Stata Corp, College Station, TX, USA) was used to conduct the statistical analysis. The effect size of continuous variables was assessed by standardised mean difference (SMD) and 95% confidence intervals (CI). For dichotomous variables, the effect size was estimated by risk ratio (RR) with 95% CI. The heterogeneity between studies was estimated by Q-test and I^2 analysis.

The source of heterogeneity was examined using meta-regression analysis. To check for publication bias, Egger's linear regression test and Begg's funnel plot were utilised. At $p < 0.05$, differences were deemed statistically significant.

Results

In total, the online search yielded 3 775 potentially relevant articles; 3 348 articles were excluded after review; 1 678 literature reviews and other sorts of invalid references were removed: 184 were articles in languages other than English; 257 articles involved trials on non-human species; 419 were duplicates and 273 articles were on patients in heart failure. The details are shown in Fig. 1.

Four hundred and seventy-seven articles remained for more detailed assessment. We further excluded 439 studies due to incomplete trials (n = 170), non-target interventions (n = 148), information that could not be directly extracted (n = 121), inadequate data (n = 10), inappropriate control groups (n = 10), and non-target outcomes (n = 4). In the end, 14 studies were included in the meta-analysis.[8,13,15-26]

Table 1 summarises the features of the 14 included studies. Overall, 2 475 patients were included in this meta-analysis, and the sample size ranged from 24 to 582 patients (median 112). The publication years were from 2020 to 2022. Thirteen studies were conducted in China, two in Egypt and one in the USA. The follow up of the study was between three and 23 months. Ten of the studies were randomised, controlled trials (RCT) and four were cohort studies. Nine of the studies reported the outcomes of ARNI compared with ARB and six reported the outcomes of ARNI compared with ACEI.

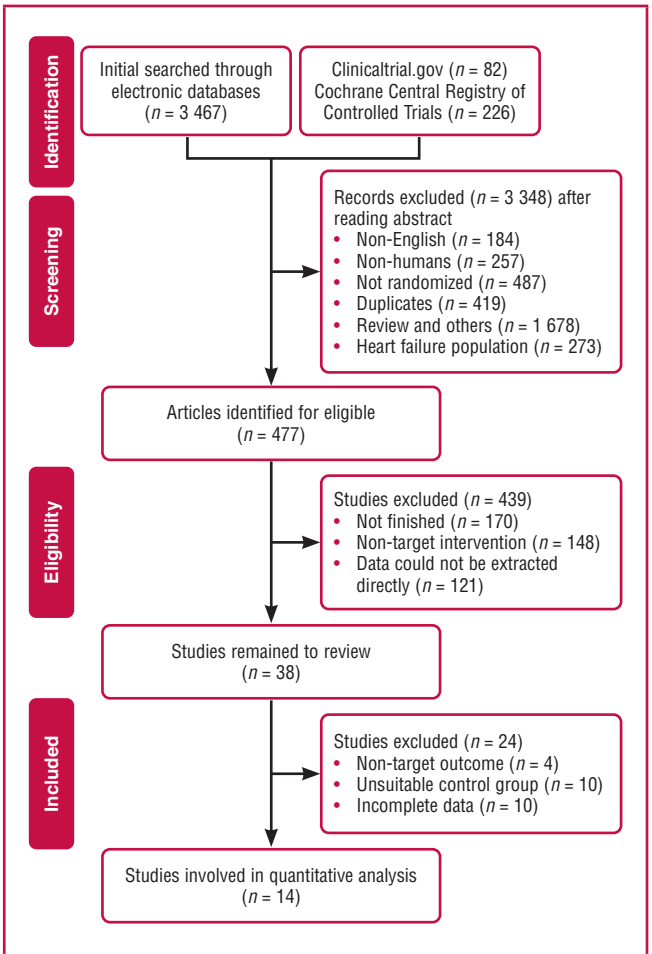

Fig. 1. Diagram of selection procedures of included studies.

Table 1. Characteristics of all studies

Author	Country	Type of disease	No of patients T	No of patients C	Age mean (SD) T	Age mean (SD) C	Gender (M/F) T	Gender (M/F) C	Intervention	NOS scale	Study type	Endpoint	Follow up (months)
Cui, 2020	China	NSTEMI	40	38	62.3 (8.73)	65 (9.40)	23/17	20/18	ARNI vs ARB	7	RCT	1, 2, 6, 9, 12	6
Dong, 2020	China	STEMI	40	40	63.9 (8.2)	62.0 (7.6)	23/17	26/14	ARNI vs ARB	7	RCT	1, 2, 6, 7, 8, 11	6
Wang, 2020	China	STEMI	80	80	59.0 (10.3)	58.0 (10.4)	69/11	67/13	ARNI vs ARB	7	RCT	1, 3, 4, 7, 8, 12, 13, 14, 15	6
Yang, 2020	China	AMI	42	45	67.2 (4.2)	67.6 (3.8)	25/17	26/19	ARNI vs ARB	7	RCT	1, 2, 6, 8, 12, 16	12
Abdelnabi, 2021	Egypt	AMI	45	40	58 (11.6)	59.6 (11.6)	30/15	29/11	ARNI vs ARB	7	RCT	1, 7, 8, 10, 11	6
Shea, 2021	China	AMI	291	291	61.8 (11.9)	62.0 (12.5)	223/68	228/63	ARNI vs ACEI	6	Cohort study	8, 9, 10, 11	6
Sheb, 2021	China	AMI	291	291	61.8 (11.9)	62.1 (12.5)	223/68	226/65	ARNI vs ARB	6	Cohort study	8, 9, 10, 11	6
Yang, 2021	China	AMI	38	38	60 (13)	55 (12)	31/7	35/3	ARNI vs ARB	7	RCT	1, 3, 4, 5, 6, 7, 12, 13, 14, 16	3
Han, 2021	China	AMI	26	48	62.5 (12.2)	58 (12.1)	18/8	32/16	ARNI vs ARB	6	Cohort study	1, 3, 4	6
Ye, 2022	China	AMI	84	86	62.3 (12.8)	63.5 (11.6)	52/28	56/30	ARNI vs ARB	6	Cohort study	1, 2, 9	12
Pfeffer, 2021	USA	AMI	2830	2831	64 (11.6)	63.5 (11.4)	2167/663	2131/700	ARNI vs ACEI	8	RCT	10, 12, 18	23
Reqz, 2021	Egypt	STEMI	100	100	52 (9.2)	57 (11.6)	86/14	88/12	ARNI vs ACEI	8	RCT	1, 2, 7, 8, 11, 17	6
Wang, 2021	China	AMI	68	69	59.1 (7.2)	60.6 (7.6)	52/16	54/15	ARNI vs ACEI	7	RCT	1, 6, 7, 13, 14, 15	6
Zhang, 2021	China	STEMI	79	77	60.3 (11.7)	60 (10.9)	59/20	55/22	ARNI vs ACEI	7	RCT	1, 7, 9	6
Dong, 2022	China	STEMI	14	10	64 (10)	63 (11)	NA	NA	ARNI vs ACEI	7	RCT	1, 3, 4, 6, 8, 12	9

1: LVEF; 2: LVEDD; 3: LVEDV; 4: LVESV; 5: LAD; 6: NT-proBNP; 7: MACE; 8: HF; 9: re-admission; 10: cardiac death; 11: MI; 12: adverse side effects; 13: SBP; 14: DBP; 15: HR; 16: 6MWT; 17: LVESD; 18: mortality.
ACEI, angiotensin converting enzyme inhibitors; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor/neprilysin inhibitor; C, control; DBP, diastolic blood pressure; HF, heart failure; LAD, left atrial diameter; LVEDD, left ventricular end-diastolic diameter; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic diameter; LVESV, left ventricular end-systolic volume; MACE, major adverse cardiovascular events; MI, myocardial infarction; NA, not applicable; NOS, Newcastle–Ottawa Scale; NSTEMI, non-ST-elevation myocardial infarction; RCT, randomised controlled trial; SBP, systolic blood pressure; STEMI, ST-elevation myocardial infarction; T, treatment: 6MWT, six-minute walk time.

LVEF data were studied in 11 articles. The forest plot illustrates that the LVEF of five studies was markedly higher in the ARNI group compared with the control group. The overall outcomes showed that there was a significantly higher LEVF when the ARNI group was compared with the control group (SMD = 0.40; 95% CI: 0.23–0.58; $p < 0.01$) (Fig. 2).

Four articles reported the data of LVEDV, and two of the studies showed a significantly lower LVEDV in the ARNI group. The complete results showed that LVEDV had statistically significantly decreased in the ARNI group compared to the control group (SMD = –0.43, 95% CI: –0.78 to –0.08; $p = 0.02$) (Fig. 3).

Four articles reported the data of LVESV, and two of the studies showed a significantly lower LVESV in the ARNI group. The overall results showed that the LVSEV level was significantly reduced in the ARNI group compared to the control group (SMD = –0.39, 95% CI: –0.66 to –0.11; $p < 0.01$) (Fig. 4).

Five articles reported the data of LVEDD, and four of the studies showed a significantly lower LVEDD in the ARNI group. The overall outcomes showed that the LVEDD level was significantly reduced in the ARNI group when compared with the control group (SMD = –0.49, 95% CI: –0.65 to –0.33; $p < 0.01$) (Fig. 5).

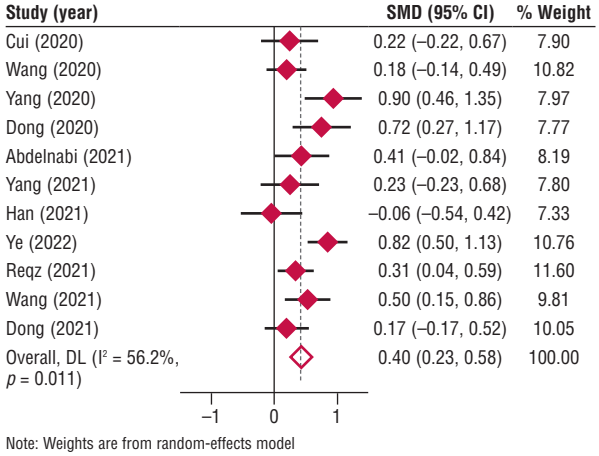

Fig. 2. Forest plot of LVEF levels after ARNI treatment.

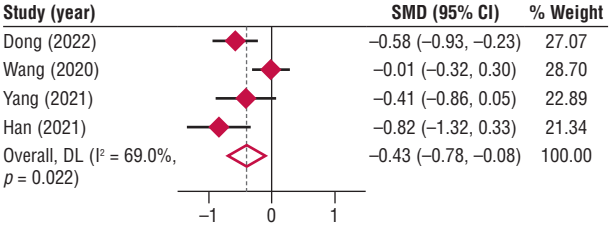

Fig. 3. Forest plot of LVEDV levels after ARNI treatment.

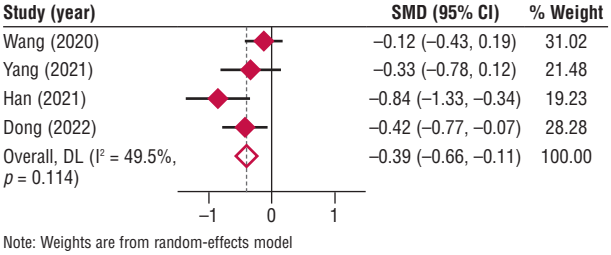

Fig. 4. Forest plot of LVESV levels after ARNI treatment.

Eight articles reported the data of MACE, and three of the studies showed a significantly lower incidence of MACE in the ARNI group. The complete results showed a lower incidence of MACE in the ARNI group compared to the control group (RR = 0.55, 95% CI: 0.43–0.69; $p < 0.01$) (Fig. 6).

Seven articles reported the data of HF, and four of the studies showed a significantly lower rate of HF in the ARNI group. In the overall results, a lower HF incidence was found in the ARNI group compared to the control group (RR = 0.42, 95% CI: 0.31–0.58; $p = 0.82$) (Fig. 7).

Four articles reported the data of adverse events, and the results showed that there were no significant differences between the ARNI group and control group (RR = 1.01, 95% CI: 0.99–1.04; $p = 0.32$) (Fig. 8).

Five articles reported the data of incidence of MI, and the findings demonstrated that there were no significant differences between the ARNI group and control group (RR = 0.94, 95% CI: 0.50–1.76; $p = 0.85$) (Fig. 9).

Six articles reported the data of NT-proBNP level, and the outcomes illustrated that there were no significant differences between the ARNI group and the control group (SMD = 0.00, 95% CI: –0.23–0.24; $p = 0.98$) (Fig. 10).

Three articles reported the data of systolic (SBP) and diastolic blood pressure (DBP), and no statistically significances were observed between two groups (SMD = –0.12, 95% CI: –0.33–0.08; $p = 0.25$) (Fig. 11) SMD = –0.11, 95% CI: –0.31–0.10; $p = 0.31$) (Fig. 12).

Five articles reported the data of re-admission to hospital, and the results showed that there were no significant differences between the ARNI group and control group (RR = 0.77, 95%

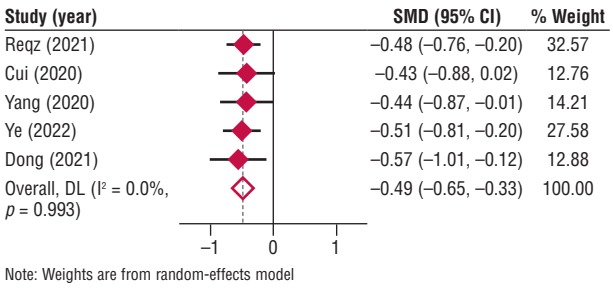

Fig. 5. Forest plot of LVEDD levels after ARNI treatment.

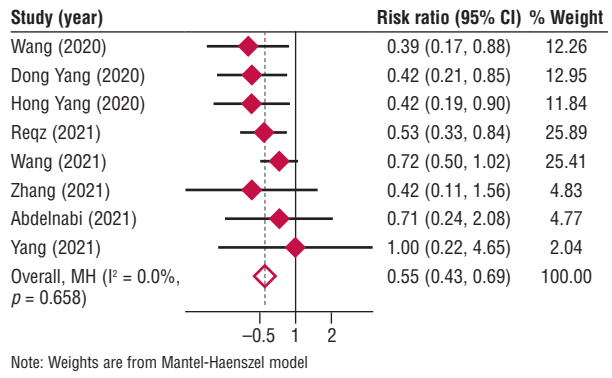

Fig. 6. Forest plot of MACE levels after ARNI treatment.

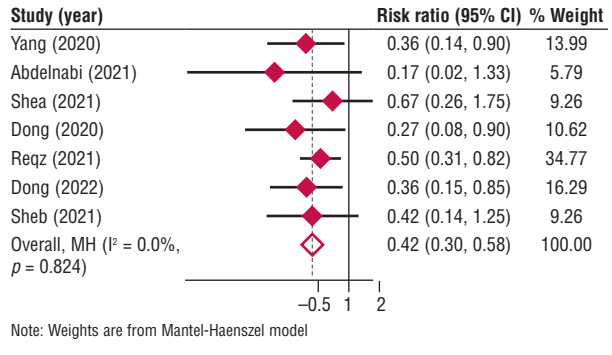

Fig. 7. Forest plot of HF levels after ARNI treatment.

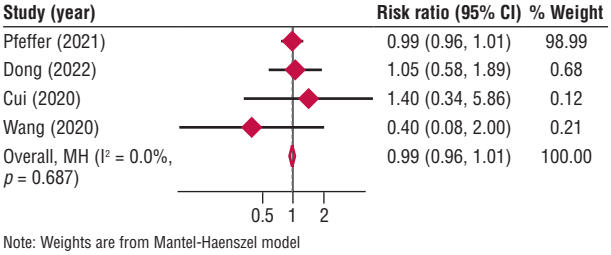

Fig. 8. Forest plot of incidence of adverse events after ARNI treatment.

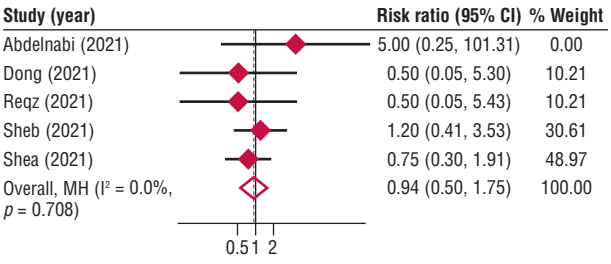

Fig. 9. Forest plot of MI levels after ARNI treatment.

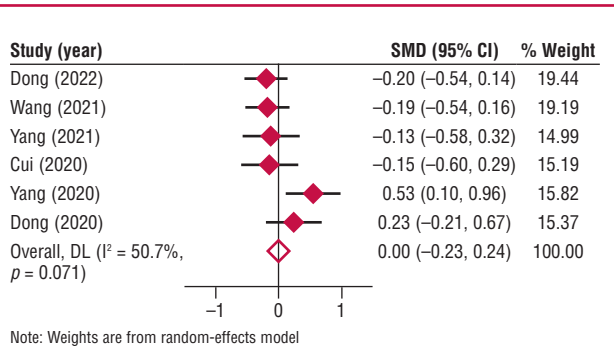

Fig. 10. Forest plot of NT-proBNP levels after ARNI treatment.

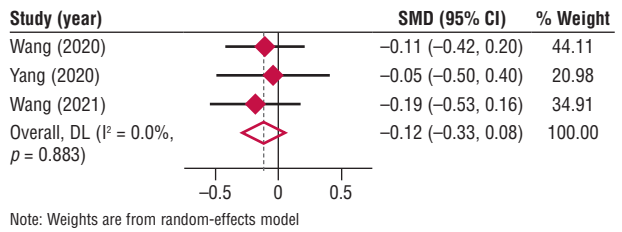

Fig. 11. Forest plot of SBP levels after ARNI treatment.

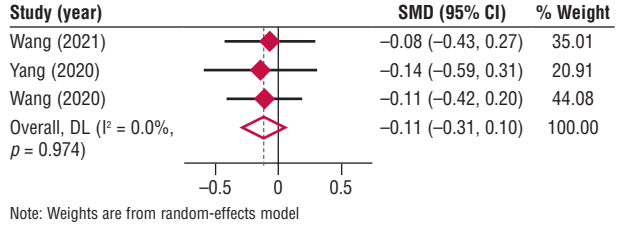

Fig. 12. Forest plot of DBP levels after ARNI treatment.

CI: 0.55–1.09; $p = 0.14$) (Fig. 13).

The subgroup analysis was completed according to the following factors: control type (ACEI or ARB), sample size (< 100 or ≥ 100) and study quality (score < 7 or score ≥ 7). We performed a subgroup analysis according to control type, and the included studies were categorised into two groups: ACEI as the control group or ARB as the control group.

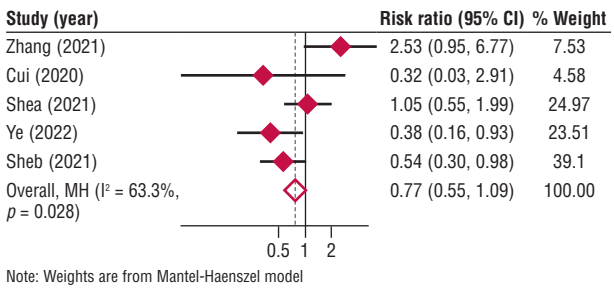

Fig. 13. Forest plot of re-admission levels after ARNI treatment.

ARNI could substantially increase the LVEF in two subgroups (Table 2). Meanwhile, ARNI significantly decreased the LVEDD (Table 3), LVEDV (Table 4), LVESV (Table 5), and the risk ratio of HF (Table 6) and MACE in both subgroups (Table 7). We also found in the ACEI subgroup that NT-proBNP level was reduced by ANRI (SMD: –0.20; 95% CI: –0.44 to –0.05) (Table 8).

Stratification group analysis was carried out in accordance with the sample size and the studies were split into two subgroups: those with a NOS scale < 7 and those with a NOS scale ≥ 7. The findings indicated that LVEDD (Table 3), LVEDV (Table 4) and LVESV (Table 5) were decreased by ARNI in both subgroups.

In the subgroup with a score ≥ 7, LVEF was significantly improved after ARNI (SMD: 0.38; 95% CI: 0.23–0.54), (Table 2). The risk ratio of HF (RR: 0.39; 95% CI: 0.27–0.57) (Table 6) and MACE (RR: 0.55; 95% CI: 0.43–0.69) (Table 7) was decreased after ARNI. In the subgroup with a score < 7,

Table 2. Subgroup analysis of LVEF

Category	*No of studies*	*Heterogeneity statistic*	p-*value*	I² *(%)*	*SMD*	*95% CI*
Control type						
0 (ACEI)	3	1.75	0.42	0.0	0.33	0.14–0.51
1 (ARB)	8	20.04	0.01	65.1	0.43	0.19–0.68
Quality of studies						
0 (score < 7)	2	9.06	0.03	89.0	0.40	–0.46–1.25
1 (score ≥7)	9	12.23	0.14	34.6	0.38	0.23–0.54
Sample size						
0 (< 100)	6	11.66	0.40	57.1	0.41	0.13–0.69
1 (≥ 100)	5	11.14	0.03	64.1	0.40	0.16–0.63

ACEI, angiotensin converting enzyme inhibitors; ARB, angiotensin receptor blocker; LVEF, left ventricular ejection fraction.

Table 3. Subgroup analysis of LVEDD

Category	*No of studies*	*Heterogeneity statistic*	p-*value*	I² *(%)*	*SMD*	*95% CI*
Control type						
0 (ACEI)	1	0.00	NA	NA	–0.48	–0.76 to –0.20
1 (ARB)	4	0.25	0.00	0.0	–0.49	–0.69 to –0.30
Quality of studies						
0 (score < 7)	1	0.00	NA	NA	–0.48	–0.76 to –0.20
1 (score ≥7)	4	0.22	0.97	0.0	–0.49	–0.69 to –0.30
Sample size						
0 (<100)	3	0.22	0.90	0.0	–0.48	–0.73 to –0.22
1 (≥100)	2	0.02	0.90	0.0	–0.49	–0.65 to –0.33

ACEI, angiotensin converting enzyme inhibitors; ARB, angiotensin receptor blocker; LVEDD, left ventricular end-diastolic diameter.

Table 4. Subgroup analysis of LVEDV

Category	*No of studies*	*Heterogeneity statistic*	p-*value*	I² *(%)*	*SMD*	*95% CI*
Control type						
0 (ACEI)	1	0.00	NA	NA	–0.58	–0.93 to –0.23
1 (ARB)	3	7.76	0.02	74.2	–0.38	–0.86 to –0.09
Quality of studies						
0 (score < 7)	1	0.00	NA	NA	–0.82	–1.32 to –0.33
1 (score ≥ 7)	3	5.88	0.05	66.0	–0.32	–0.69 to –0.04
Sample size						
0 (< 100)	2	1.49	0.22	32.9	–0.60	–1.01 to –0.19
1 (≥ 100)	2	5.57	0.02	82.0	–0.29	–0.84–2.62

ACEI, angiotensin converting enzyme inhibitors; ARB, angiotensin receptor blocker; LVEDV, left ventricular end-diastolic volume.

Table 5. Subgroup analysis of LVESV

Category	*No of studies*	*Heterogeneity statistic*	p-*value*	I² *(%)*	*SMD*	*95% CI*
Control type						
0 (ACEI)	1	0.00	NA	NA	–0.42	–0.77 to –0.07
1 (ARB)	3	5.74	0.06	65.2	–0.40	–0.80 to –0.01
Quality of studies						
0 (score < 7)	1	0.00	NA	NA	–0.84	–1.33 to –0.34
1 (score ≥ 7)	3	1.67	0.44	0.0	–0.27	–0.48 to –0.06
Sample size						
0 (< 100)	2	2.18	0.90	54.2	–0.57	–1.07 to –0.08
1 (≥ 100)	2	0.02	0.90	36.7	–0.26	–0.55 to –0.03

ACEI, angiotensin converting enzyme inhibitors; ARB, angiotensin receptor blocker; LVESV, left ventricular end-systolic volume.

Table 6. Subgroup analysis of HF

Category	No of studies	Heterogeneity statistic	p-value	I^2 (%)	RR	95% CI
Control type						
0 (ACEI)	3	0.46	0.79	0.0	0.45	0.30–0.67
1 (ARB)	4	2.24	0.52	0.0	0.38	0.22–0.66
Quality of studies						
0 (score < 7)	2	0.40	0.53	0.0	0.54	0.26–1.11
1 (score ≥ 7)	5	2.01	0.73	0.0	0.39	0.27–0.57
Sample size						
0 (< 100)	3	0.48	0.79	0.0	0.29	0.15–0.58
1 (≥ 100)	4	0.98	0.81	0.0	0.42	0.31–0.58

ACEI, angiotensin converting enzyme inhibitors; ARB, angiotensin receptor blocker; HF, heart failure.

Table 7. Subgroup analysis of MACE

Category	No of studies	Heterogeneity statistic	p-value	I^2 (%)	RR	95% CI
Control type						
0 (ACEI)	3	1.56	0.46	0.0	0.60	0.46–0.80
1 (ARB)	5	1.91	0.75	0.0	0.47	0.32–0.69
Quality of studies						
1 (score ≥ 7)	8	5.02	0.66	0.0	0.55	0.43–0.69
Sample size						
0 (< 100)	4	1.66	0.65	0.0	0.50	0.32–0.78
1 (≥ 100)	4	2.86	0.41	0.0	0.57	0.43–0.74

ACEI, angiotensin converting enzyme inhibitors; ARB, angiotensin receptor blocker; MACE, major adverse cardiovascular events.

Table 8. Subgroup analysis of NT-proBNP

Category	No of studies	Heterogeneity statistic	p-value	I^2 (%)	SMD	95% CI
Control type						
0 (ACEI)	2	0.00	0.96	0.0	–0.20	–0.44 to –0.05
1 (ARB)	4	6.42	0.09	53.3	0.13	–0.20–0.45
Quality of studies						
1 (score ≥ 7)	6	10.15	0.07	50.7	0.00	–0.23–0.24
Sample size						
0 (< 100)	4	6.42	0.09	53.3	0.13	–0.20–0.45
1 (≥ 100)	2	0.00	0.96	0.0	–0.20	–0.44–0.05

ACEI, angiotensin converting enzyme inhibitors; ARB, angiotensin receptor blocker.

Table 9. Subgroup analysis of re-admission

Category	No of studies	Heterogeneity statistic	p-value	I^2 (%)	RR	95% CI
Control type						
0 (ACEI)	2	7.02	0.00	85.7	0.86	0.72–1.88
1 (ARB)	3	3.78	0.15	47.1	1.45	0.89–2.36
Quality of studies						
0 (score < 7)	3	3.87	0.15	48.3	0.64	0.44–0.94
1 (score ≥ 7)	2	2.84	0.09	64.8	1.70	0.74–3.90
Sample size						
0 (< 100)	1	0.00	NA	NA	0.32	0.03–2.91
1 (≥ 100)	4	10.28	0.02	70.8	0.79	0.56–1.21

ACEI, angiotensin converting enzyme inhibitors; ARB, angiotensin receptor blocker.

Table 10. Subgroup analysis of SBP

Category	No of studies	Heterogeneity statistic	p-value	I^2 (%)	SMD	95% CI
Control type						
0 (ACEI)	1	0.00	NA	NA	–0.19	–0.54–0.16
1 (ARB)	2	0.05	0.83	0.0	–0.09	–0.34–0.17
Quality of studies						
1 (score ≥ 7)	3	0.25	0.88	0.0	–0.12	–0.33–0.09
Sample size						
0 (< 100)	1	0.00	NA	NA	–0.05	–0.50–0.40
1 (≥ 100)	2	0.11	0.74	0.0	–0.14	–0.37 to –0.09

ACEI, angiotensin converting enzyme inhibitors; ARB, angiotensin receptor blocker; SBP, systolic blood pressure.

Table 11. Subgroup analysis of DBP

Category	No of studies	Heterogeneity statistic	p-value	I^2 (%)	SMD	95% CI
Control type						
0 (ACEI)	1	0.00	NA	NA	–0.08	–0.43–0.27
1 (ARB)	2	0.01	0.91	0.0	–0.12	–0.38–0.13
Quality of studies						
1 (score ≥ 7)	3	0.05	0.97	0.0	–0.11	–0.31–0.10
Sample size						
0 (< 100)	1	0.00	NA	NA	–0.14	–0.60–0.31
1 (≥ 100)	2	0.02	0.90	0.0	–0.10	–0.33 to –0.32

ACEI, angiotensin converting enzyme inhibitors; ARB, angiotensin receptor blocker; DBP, diastolic blood pressure.

re-admission to hospital (RR: 0.64; 95% CI: 0.44–0.94), (Table 9) was considerably reduced after ARNI.

We performed a subgroup analysis based on sample size, and the studies were split into two subgroups: those with fewer than 100 patients and those with 100 or more patients. We found that LVEF (Table 2) was significantly improved in both subgroups, but LVEDD (Table 3), LVEDV (Table 4), LVESV (Table 5), SBP (Table 10) and DBP (Table 11) were reduced in both subgroups. The risk ratio of HF (Table 6) and MACE (Table 7) were significantly decreased in both subgroups.

Neither Egger's test nor Begg's funnel plots revealed any evidence of publication bias among LVEF, LVEDD, LVEDV, LVESV, adverse events, MACE, MI events, HF events, re-admission events, SBP, DBP and NT-proBNP levels (Figs 14, 15, Table 12)

Table 12. Metabias of all studies

Variables	Begg's p-value	Egger's p-value (95% CI)
LVEDV	0.31	0.26 (–23.28–11.03)
LVEDD	0.81	0.83 (–1.85–2.13)
LVEF	0.88	1.00 (–5.95–5.95)
LVESV	0.46	0.38 (–26.8–13.7)
SBP	1.00	0.68 (–20.76–22.65)
DBP	1.00	0.63 (–9.90–8.93)
NT-proBNP	0.45	0.31 (–7.67–18.74)
AEs	NA	NA
HF	1.00	0.01 (0.46–1.59)
MI	0.30	0.02 (0.58–1.32)
Re-admission	0.30	0.25 (–1.43–2.09)
MACE	0.26	0.49 (–0.89–1.56)

AE, adverse events; DBP, diastolic blood pressure; HF, heart failure; LVEDD, left ventricular end-diastolic diameter; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic diameter; LVESV, left ventricular end-systolic volume; MACE, major adverse cardiovascular events; MI, myocardial infarction; SBP, systolic blood pressure.

Discussion

This study aimed at assessing what the effects of ARNI were on cardiac function. Based on our study, LVEF, LVEDD,

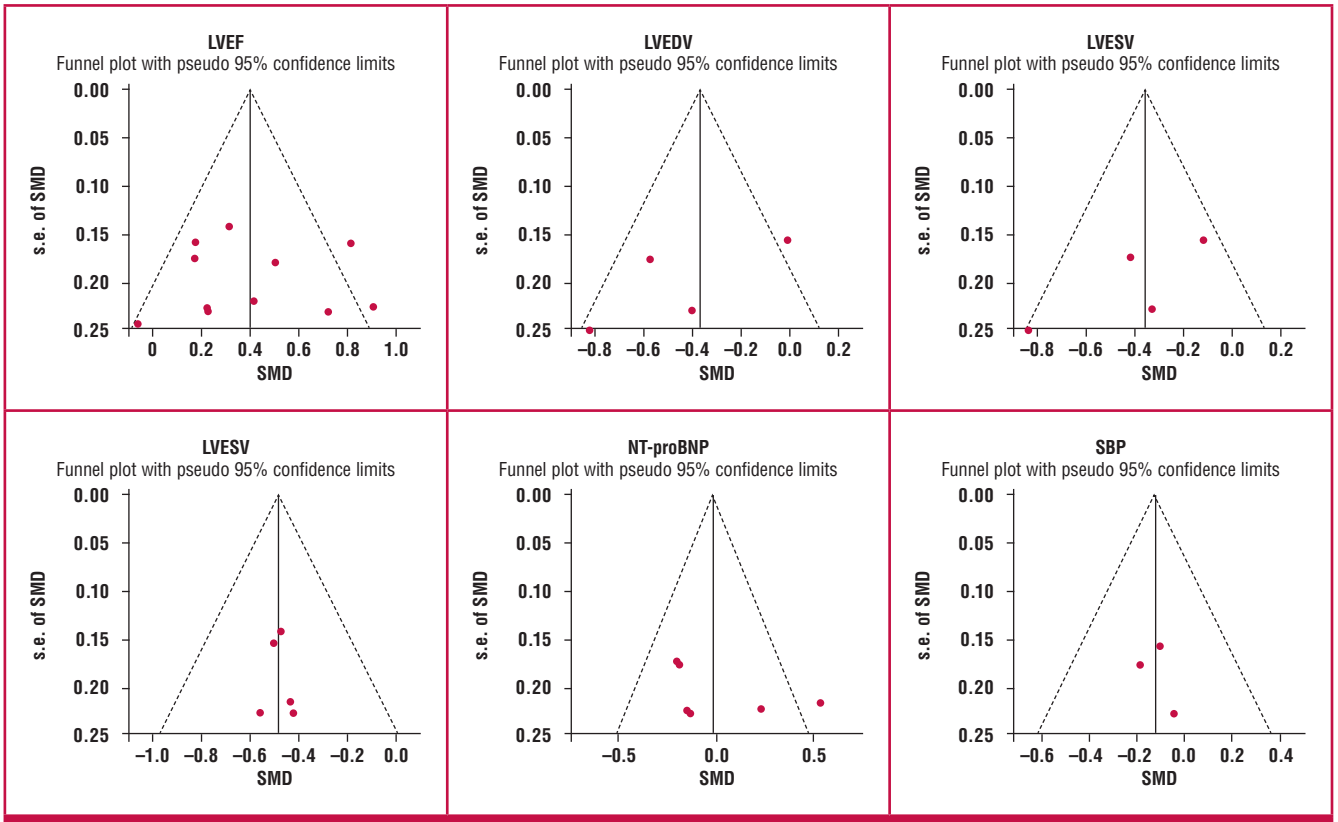

Fig. 14. Metafunnel of LVEF, LVEDV, LVESV, LVEDD, NT-proBNP and SBP.

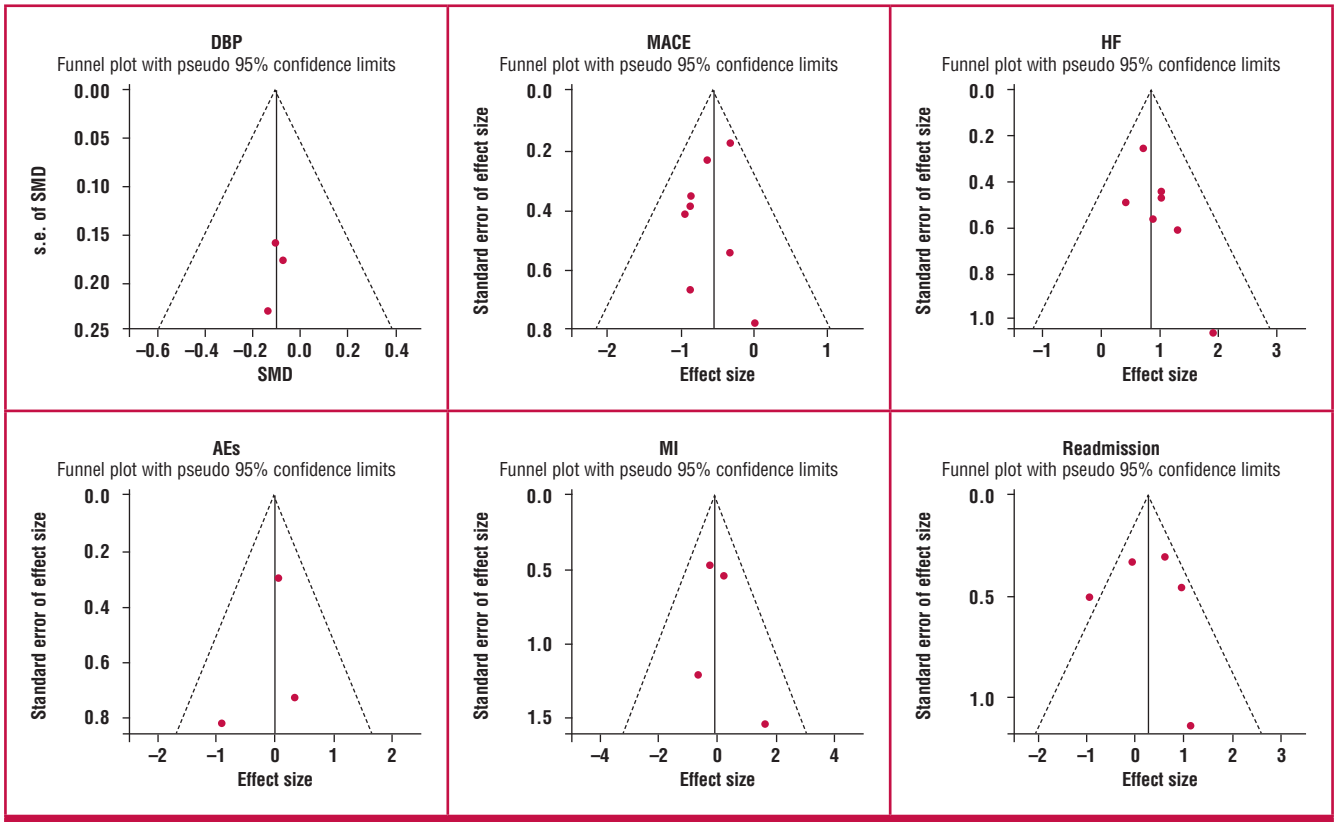

Fig. 15. Metafunnel of DBP, MACE, HF, adverse events, MI and re-admission rates.

LVEDV and LVESV, which serve as clinical indicators of cardiac function, were substantially improved by sacubitril/valsartan. This conclusion was supported by a number of recent investigations,[27,28] but not by Docherty *et al*.,[14] whose findings indicated that there were no significant between-group variations in LVEF and LVEDV.

The different results are most likely due to the timing of ARNI administration. In the trial by Docherty *et al*.,[14] ARNI administration began three months after AMI. Given the fact that myocardial fibrosis and cardiac remodelling always begins at an early stage of AMI, the timing of the initial therapy may result in different levels of improvement in cardiac function.

As we know, after an AMI, abnormal ventricular contraction results in ventricular remodelling and postoperative cardiac dysfunction. In extreme circumstances, pump failure might limit coronary perfusion and worsen underlying myocardial ischaemia. Considerable myocardial cell necrosis may lower contractility and cardiac output, while compensatory activation of neurohormonal pathways such the RAAS and SNS may increase heart volume, pressure load, oxygen consumption, cardiomyocyte hypertrophy and LV remodelling. Hence, inhibiting the RAAS and SNS pathways and boosting the natriuretic peptide system is of benefit for AMI patients with LV dysfunction or high risk of HF.[29]

ARNI is similar to ACEI/ARB, which inhibit the RAAS and neprilysin in order to limit the breakdown of atrial natriuretic peptide and brain natriuretic peptide and to increase the activity of the natriuretic peptide system.[30] Sacubitril/valsartan also increases the haemodynamics by enhancing salt and water elimination from the kidneys and vasodilation, and reduces blood flow. It boosts ventricular preload and afterload, assisting in cardiac remodelling. It reduces blood pressure, more notably SBP, and has been shown to improve the outcome in all SBP groups, including those with persistently low SBP.[31]

In clinical situations, ARNI had been proven since 2016 to contribute positively to the clinical therapy of chronic HF according to the European Chronic Cardiac Failure Guide, the American Cardiac Failure Management Guide and the Chinese Cardiac Failure Guide.[32] However, there is no consensus on the effects of using ARNI to treat HF after an AMI.

One study pointed out that sacubitril/valsartan did not seem to be better than ACEI with regard to cardiac death and the incidence of HF, MI and side effects.[33] However, according to our research, fewer MACE and HF events were found in the ARNI group, which was different from the previous study. We believed that the inclusion of more trials in our study was the primary reason for this result.

In subgroup analysis, we observed that compared with the ACEI or ARB subgroups, ARNI could significantly raise LVEF, and decrease the levels of LVEDD, LVEDV, LVESV, and the risk ratio of HF and MACE. ANRI similarly decreased NT-proBNP level in the ACEI subgroup. Additionally, we discovered that in the subgroup with ≥ 7 score, there was an improvement in LVEF and a reduction in the risk ratio for HF and MACE following ARNI. Meanwhile, in the subgroup with < 7 score, the rate of re-admission was considerably lower after ARNI treatment, which means the quality of the included trials might be a factor that could influence the overall results. As far as sample size subgroup analysis is concerned, LVEF showed a substantial improvement in both subgroups (sample size ≥ 100 and sample size < 100), but LVEDD, LVEDV, LVESV, SBP, DBP, and risk ratios for both MACE and HF showed significant declines in both subgroups.

Our research investigated major indexes of cardiac function such as LVEF, LVEDD, LVEDV and LVESV. Compared with previous studies, we made a full summary of the effect of ARNI on improving cardiac function. Besides, in most previous studies, the researchers investigated only one type of comparison, such as ACEI or ARB. We compared them all, which made our study more comprehensive.

However, there are still several limitations in our research. First, although subgroup analysis was conducted, the source of heterogeneity was not found due to a shortage of data evaluating ARNI function by gender, nationality and age. Therefore, further subgroup analysis was not carried out. Second, the included trials were not all RCTs, therefore trial quality may be a factor influencing the outcomes. Third, more indices could have been discussed in detail, such as stroke volume index and haemodynamic effects, which may have affected prognosis, as summarised by Lutfu *et al*.[34]

Given those facts, the overall results should be interpreted cautiously. We look forward to more high-quality research to investigate the effects of ARNI on cardiac function in patients with AMI, which will provide more detailed evidence for clinical therapy.

Conclusion

From our research, we show that ARNI could significantly improve LVEF while significantly lowering LVEDV, LVESV and LVEDD. It also substantially decreased the incidence of MACE and HF. Considering the benefits, it should be widely used for improving cardiac function in patients with AMI.

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