Antialdosterone in Acute Myocardial Infarction patients: a Meta-Analysis and Systematic Review

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Abstract

Purpose: A comprehensive evaluation of the benefits of mineralocorticoid receptor antagonists (MRA) in acute myocardial infarction (AMI) patients is lacking. We aimed to summarize the evidence on the efficacy and safety of MRA in post-AMI patients.

Methods: Articles were identified through PubMed, Embase, Cochrane Library, Ovid (Medline1946-2021) and ClinicalTrials.gov databases from their inception to Dec 31, 2020.

Results: MRA reduced the risk of all-cause mortality by 16% (relative ratio(RR) 0.84, 95% confidence interval(CI) (0.76,0.94), $P=.002$), new or worsening heart failure (HF) 14% (RR 0.86, 95%CI (0.78,0.96), $P=.007$), death from HF by 22% (RR 0.78, 95%CI (0.62,0.99), $P=.04$), and cardiovascular death by 16% (RR 0.84, 95%CI (0.74,0.94), $P=.003$) in post-AMI patients. Meanwhile, all-cause mortality was reduced by 38% (RR 0.62, 95%CI (0.42,0.90), $P=.01$), 30% (RR 0.70, 95%CI (0.49,1.00), $P=.05$), and 29% (RR 0.71, 95%CI (0.59,0.86), $P=.0004$) in ST-elevation myocardial infarction (STEMI) patients and those who initiated MRA treatment within 3 days and (3,7) days, respectively. Post-AMI patients without left ventricular systolic dysfunction (LVSD) treated with MRA improved left ventricular ejection fraction (mean difference[MD] 2.74, 95%CI (2.49,2.99), $P<.00001$) and reduced left ventricular end-systolic and end-diastolic volume indices (MD -6.23, 95%CI (-10.93,-1.52), $P=.009$; MD -3.13, 95%CI (-5.79,-0.47), $P=.02$). The corresponding RR were 1.73 (95%CI (1.44,2.08), $P<.00001$) for considered common side effects (hyperkalemia and gynecomastia).

Conclusion: Our findings suggest that all-cause mortality is lower in STEMI patients and in patients initiating MRA within 7 days, and that post-AMI patients without LVSD have improved left ventricular remodeling and cardiac function.

1. Introduction

Aldosterone, a major mineralocorticoid receptor agonist, is primarily synthesized in the adrenal cortex [1]. Extensive evidence indicates that aldosterone is significantly higher after AMI and promotes a range of deleterious effects on the cardiovascular system [2,3], including sodium and water retention, myocardial and perivascular fibrosis, baroreceptor and endothelial dysfunction, and cardiomyocyte necrosis to exacerbate the development and progression of complications after AMI [4,5] and significantly increase mortality [6,7]. Globally, despite remarkable advances in the prevention, diagnosis and treatment [8], AMI has been a serious threat to human health [9], with an increase in young patients, especially in developed countries [10]. Anti-aldosterone is an attractive theoretical strategy for AMI patients [11]. The EPHEsus trial [12] (Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study) established morbidity and mortality benefits of aldosterone blockade with eplerenone in post-AMI patients. However, in 2016, the ALBATROSS trial [13] (Aldosterone Lethal effects Blockade in Acute myocardial infarction Treated with or without Reperfusion to improve Outcome and Survival at Six months follow-up, NCT01176968) failed to show cardiovascular benefits of MRA in patients admitted for

AMI. Then, the current MINIMIZE STEMI trial [14] (Mineralocorticoid receptor antagonist pretreatment to MINIMIZE reperfusion injury after ST-elevation myocardial infarction, NCT01882179) showed less adverse left ventricular remodeling in STEMI patients treated with MRA. The benefits of MRA therapy for AMI patients remain controversial, and it is unclear whether AMI subtypes, treatment initiation time and duration, or left ventricular ejection fraction (LVEF) values affect MRA to improve clinical outcomes. Given the cumulative data on this topic, a comprehensive evaluation is required to provide favorable support. We sought to clarify the efficacy and safety of MRA in patients suffering AMI.

2. Methods

This meta-analysis was performed and reported according to the recommendations of the Cochrane Collaboration [15] and the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines [16]. The PROSPERO registration number was CRD42021230790.

2.1. Patient and public involvement statement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

2.2. Search strategy

Articles were searched through electronic databases. details of full search strategy were provided in Online Resource 1. The PRISMA checklist was presented in Online Resource 2. The inclusion criteria were as follows: (1) included post-AMI patients; (2) were clinical prospective RCTs, with groups divided into MRA and non-MRA; (3) compared with standard therapy or placebo or both; (4) had a study duration ≥ 4 weeks and a sample size ≥ 40 patients; (5) used the drugs of interest (spironolactone, eplerenone, canrenoate); (6) reported at least one of the clinical outcomes of interest and (7) published in English. The search was supplemented by reviewing reference lists and hand-searching relevant journals for further potential studies.

2.3. Trials selection

Two investigators (Qiao Chen and Zhuqing Li) independently obtained eligible articles. Discrepancies were discussed with a third reviewer (Wang Yiling) until consensus was reached. If necessary, we contacted the original authors to avoid involving the same or partially identical subjects recruited in ≥ 1 trial by the same group.

2.4. Data extraction and synthesis

A standardized data collection form was used to systematically extract information from each report, including study and patient characteristics (Table 1 and Table 2), data on changes in cardiac structure and function from baseline to follow-up, numbers of major clinical outcomes and adverse events. We used definitions of hyperkalaemia, renal dysfunction, and gynecomastia based on primary publications.

Hypokalemia was defined as a potassium level <3.5 mmol/L. LSVD was determined by LVEF $\leq$ 40%. If a given trial could be divided into $\geq$ 2 separate studies due to different treatment time points, we extracted data from the most recent or most complete publications. Also, if a trial included $\geq$ 2 MRA groups with different doses, the usual dose group was included. We extracted the number of populations with different treatment initiation time from a substudy of the EPHESUS trial [17].

Table 1 Study characteristics

Author (year)	Study design	ITTA	Duration (month)	Jadad points	Country
Rodríguez.(1997) [18]	Randomized, double-blind, placebo	YES	6	6	Chile
Modena.(2001) [19]	Randomized, placebo	YES	12	5	Italy
Pitt.(2003)[12]	Randomized, double-blind, placebo	YES	16	7	multiple
Hayashi.(2003) [20]	Rrandomized, nonplacebo	NO	1	6	Japan
Dipasquale. (2005)[21]	Randomized, double-blind, placebo	NO	6	5	Italy
Uzunhasan. (2009)[22]	Randomized, double-blind, placebo	YES	6	7	Turkey
Kayrak.(2010)[23]	Randomized, nonplacebo	NO	6	5	Turkey
Weir.(2011)[24]	Randomized, double-blind, placebo	NO	5.5	7	UK
Kampourides. (2012)[25]	Randomized, open-labeled, nonplacebo	NO	24	6	Greece
Wu.(2013)[26]	Randomized, placebo	NO	12	6	China
Vatankulu.(2013) [27]	Randomized, nonplacebo	YES	6	5	Turkey
Montalescot. (2014)[28]	Randomized, double-blind, placebo	YES	10.5	7	multiple
Beygui.(2016)[13]	Randomized, open-labeled, blinded endpoint, nonplacebo	YES	6	5	multiple
Bulluck.(2019) [14]	Randomized, double-blinded, placebo	YES	3	7	UK

ITTA=intention to treat analysis

Table 2 Patient characteristics

Author (year)	Comparison Drug (mg/d)	Patients Number	Cr(mg/dl) K(mmol/l)	LVEF(%) Killip class	Age Sex
					MRA/ non- MRA
Rodríguez. [18] (1997)	SP (75) vs. P	AMI/ 47	< 2.0 NA	NR NR	58.8(10.8)/ 58.6(9.0) ^b 18(5)/ 22(2)
Modena. [19] (2001)	CAN (50) + ACEI vs. ACEI + P	STEMI, 6h ^a / 46	≤ 2.5 NA	NR I-III	59.0(10.0)/ 62.0(13.0) 17(7)/ 17(5) ^c
Pitt. [12] (2003)	ST + EP (50) vs. ST + P	AMI, LVD, (3-14d) / 6632	≤ 2.5 ≤ 5.0	≤ 40 NR	64.0(11.0)/ 64.0(12.0) 2380(939)/ 2334(979)
Hayashi. [20] (2003)	SP (25)+ ACEI vs. ACEI	STEMI, SR, 24h/ 150	≤ 2.0 ≤ 5.0	> 40 NR	64.4(1.4)/ 62.9(1.4) 49(16)/ 51(18)
Dipasquale. [21] (2005)	ST + CAN (25) + CAP vs. ST + CAP + P	STEMI, 4h/ 687	≤ 2.0 ≤ 5.0	> 40 I-II	62.6(6.0)/ 62.8(5.0) 243(98)/ 244(102)
Uzunhasan. [22] (2009)	ST + SP (50) vs. ST + P	STEMI, SR, 6-12h/ 82	≤ 2.5 ≤ 5.0	NR I-II	52.0(10.0)/ 52.0(10.0) 32(9)/ 29(11)
Kayrak. [23] (2010)	ST + SP (25) vs. ST	STEMI, SR, 12h/ 142	≤ 2.0 ≤ 5.0	≥ 40 I-II	55.3(10.0)/ 57.2(11.1) 10(45)/ 14(41)
Weir. [24] (2011)	ST + EP (50) vs. ST + P	AMI, LVD, (1-14d)/ 100	≤ 2.5 ≤ 5.0	≥ 40 I	61.0(12.0)/ 56.8(12.0) 37(13)/ 40(10)
Kampourides. [25] (2012)	ST + EP (25) vs. ST	STEMI, 24h/327	≤ 2.5 ≤ 5.0	≥ 40 I	ND

Wu. [26] (2013)	ST + SP (20) vs. ST	STEMI, 24h/ 616	≤ 2.5 ≤ 5.0	NR I-II	59.8(11.7)/ 59.9(10.3) 193(69)/ 192(74)
Vatankulu. [27] (2013)	ST + SP (25) vs. ST	STEMI, SR/ 110	≤ 2.0 < 5.5	≥ 40 I-II	58.0(9.0)/ 57.0(11.0) 39(15)/ 36(20)
Montalescot. [28] (2014)	ST + EP (50) vs. ST + P	STEMI, 24h/ 1012	< 2.5 NA	> 40 NR	58.5(10.8)/ 57.8(11.0) 420(86)/ 403(103)
Beygui. [13] (2016)	ST + SP (25) vs. ST	STEMI,NSTEMI,72h/ 1603	< 2.5 < 5.5	NR NR	58.0(13.0)/ 58.0(13.0) 673(129)/ 658(143)
Bulluck. [14] (2019)	SP (50) vs. P	STEMI, 12h/ 70	NA < 5.0	> 40 NR	62.0(10.0)/ 60.0(13.0) 33(5)/ 27(5)

^aTime from disease onset to trial entry; ^bMean $\pm$ SD; ^cMale/ Female

EP=Eplerenone; SP=Spironolactone; CAN=Canrenone; ST=Standard therapy; ACEI=Angiotension converting enzyme inhibitors; P=Placebo; SD=Standard deviation; LVEF=Left ventricular ejection fraction; AMI=Acute myocardial infarction; NSTEMI=Non-ST-segment elevation myocardial infarction; STEMI=ST-segment elevation myocardial infarction; MRA=Mineralocorticoid receptor antagonists; SR=Successful reperfusion; ND=Not defined; NR=Not restricted; NA=Not available; Cr=Creatinine; K=Kalium

2.5. Quality assessment

We used the Cochrane Collaboration risk of bias tool and the Modified Jadad scoring system [29,30] to assess the overall quality of included studies. Score ≤ 4 was defined as low quality reports. Modified Jadad scores were calculated by assessing adequate randomization, allocation concealment, double-blinding, and withdrawals and dropouts per treatment group. The kappa statistic [31] was used to calculate the agreement rate between two reviewers.

2.6. Statistical analysis

Heterogeneity was assessed by CochranQ test and $P < .1$ was considered significant [32]. The inconsistency index (I^2) was used to estimate the level of heterogeneity among studies. 25%, 50%, and 75% corresponded to low, medium, and high levels. Data were pooled using a fixed-effects model when I^2

values were below 50%; otherwise, a random-effects model was used. If similar estimates were obtained by both methods, we only reported the random-effects results to cover possible heterogeneity, because three drugs and different patients were included particularly in control groups. Data were presented as RR or MD with 95%CI. 2-tailed $P < .05$ was considered statistically significant. Subgroup analyses were conducted according to drugs, LVEF values, treatment initiation time and duration, and AMI subtypes. Sensitivity analyses were carried out by sequentially excluding each trial one from the total studies at a time and recalculating the difference estimates for remaining trials. Publication bias was assessed with funnel plots, the Begg's test, and the Egger's test, and $P < .1$ was considered statistically significant.

3. Results

3.1. Study characteristics

We found 4338 potentially articles, among which 14 trials involving 11,624 individuals were included (Fig.1). Treatment duration ranged from 1 to 24 months (8.61 ± 5.77). Patients were randomized to spironolactone in 8 trials (N=1412), eplerenone in 4 trials (N=4081), canrenoate in 2 trials (N=365) and assigned 1408, 3990, and 368 patients to control groups, respectively. The EPHESUS trial [12] accounted for more than half of the patients. Two studies [25,13] did not use double-blind methods and one study [24] reported incomplete outcome data (Fig. 2). The kappa statistic showed a good agreement between reviewers (Online Resource 3). The Modified Jadad scores of trials varied from 5 to 7 points, indicating that this meta-analysis was a relatively high-quality report.

3.2. All-cause mortality

11 studies included 11,037 patients reported all-cause mortality. 532/5523 (9.63%) and 630/5514 (11.43%) were observed in treatment and control arms, respectively, with a general reduction of 16% (RR 0.84, 95%CI (0.76,0.94), $P = .002$, $I^2 = 0\%$, Fig. 3). In addition, reduction benefits of MRA were particularly evident in subgroups such as STEMI patients, treatment initiation within 3 days and (3,7) days (RR 0.62, 95%CI (0.42,0.90), $P = .01$, $I^2 = 0\%$; RR 0.70, 95%CI (0.49,1.00), $P = .05$, $I^2 = 0\%$; RR 0.71, 95%CI (0.59,0.86), $P = .0004$, $I^2 = 0\%$, Fig. 4), duration >6 months, patients with LVSD , eplerenone, and 25mg (RR 0.85, 95%CI (0.76,0.95), $P = .005$, $I^2 = 0\%$; RR 0.87, 95%CI (0.77,0.97), $P = .01$, $I^2 = 49\%$; RR 0.86, 95%CI (0.77,0.97), $P = .01$, $I^2 = 0\%$; RR 0.85, 95%CI (0.76,0.94), $P = .003$, $I^2 = 0\%$, Online Resource 4). No evidence of publication bias as suggested by funnel plot, the Begg's test ($P = 0.64$), and the Egger's test ($P = 0.63$) was observed (Fig. 5). None of the individual studies significantly influenced the pooled all-cause mortality estimates in the leave-one-out sensitivity.

3.3. New or worsening HF and deaths due to HF

8 RCTs involving 10,515 patients (10.74% in the MRA group vs 12.14% in the control group) showed a significant 14% reduction in new or worsening HF after MRA treatment (Fig. 3). Duration >6 months, patients with LVSD, eplerenone, and 50 mg subgroups using MRA respectively reduced new or worsening

HF (RR 0.86, 95%CI (0.77, 0.96), $P=.007$, $I^2=0\%$; RR 0.87, 95%CI (0.77, 0.97), $P=.02$; RR 0.86, 95%CI (0.77, 0.96), $P=.008$, $I^2=0\%$; RR 0.86, 95%CI (0.76, 0.96), $P=.008$, $I^2=0\%$, Online Resource 4). The prevention effect of MRA for death from HF estimated by RR was 0.78 (95%CI (0.62,0.99), $P=.04$, $I^2=0\%$, Fig. 3). The EPHESUS trial [12] provided weights of 81.1% and 83.9% for new or worsening HF and HF mortality, respectively. RR excluding it resulted in no statistical significance: from (0.86, $p=.007$) to (0.86, $p=.23$); (0.78, $p=.04$) to (0.63, $p=.12$), respectively.

3.4. Cardiovascular deaths and hospitalizations

Pooled data showed that cardiovascular deaths reduced by 16% (RR 0.84, 95%CI (0.74,0.94), $P=.003$, $I^2=0\%$, Fig. 3). MRA groups ($n=452/5294$) had a greater reduction than control arms ($n=537/5193$). The analysis showed that MRA treatment was not associated with a reduced risk of cardiovascular or all-cause hospitalizations (Table 3). Duration >6 months, patients with LVSD, eplerenone, and 50mg subgroups respectively reduced cardiovascular deaths by MRA treatment (RR 0.84, 95%CI (0.75,0.95), $P=.006$, $I^2=0\%$; RR 0.85, 95%CI (0.75,0.96), $P=.007$, $I^2=26\%$; RR 0.85, 95%CI (0.75,0.96), $P=.008$, $I^2=0\%$; RR 0.85, 95%CI (0.75,0.96), $P=.007$, $I^2=0\%$, Online Resource 4).

3.5. Recurrent myocardial infarction and ventricular arrhythmias

The recurrent myocardial infarction rate was 5.15% ($N=257/4992$) in those treated with MRA compared with 5.33% ($N=266/4988$) in control group. The incidence of ventricular arrhythmias was 2.11% ($N=99/4702$) under MRA treatment and 2.26% ($N=106/4695$) in control group. Neither of the statistical estimates reached significance (Table 3).

3.6. Changes of cardiac structure and function

MRA use improved LVEF with highly heterogeneous results (Table 3). In addition, improvement in left ventricular end-diastolic volume index (LVEDVI) and end-systolic volume index (LVESVI) was also apparent (Table 3), and further analysis demonstrated a reduction in left ventricular end-diastolic diameter but not in left ventricular end-systolic diameter under MRA treatment (Table 3). The ratio of early to late diastolic transmitral flow (E/A ratio) was improved by MRA treatment (Table 3). For LVEF, LVESVI, and LVEDVI, in patients without LVSD (MD 2.74, 95%CI (2.49,2.99), $P<.00001$, $I^2=0\%$; MD -6.23, 95%CI (-10.93,-1.52), $P=.009$, $I^2=98\%$; MD -3.13, 95%CI (-5.79,-0.47), $P=.02$, $I^2=29\%$, Fig. 6), treated ≤ 6 months (MD 3.86, 95%CI (1.43,6.29), $P=.002$, $I^2=93\%$; MD -5.39, 95%CI (-9.73,-1.04), $P=.02$, $I^2=97\%$; MD -3.41, 95%CI (-5.50,-1.32), $P=.001$, $I^2=0\%$, Fig. 7) and 25mg (MD 2.74, 95%CI (2.49,2.99), $P<.00001$, $I^2=0\%$; MD -6.23, 95%CI (-10.93,-1.52), $P=.009$, $I^2=98\%$; MD -3.13, 95%CI (-5.79,-0.47), $P=.02$, $I^2=29\%$, Online Resource 5) subgroups, the statistical results were significant, respectively. Canrenoate showed the greatest improvement in LVEDVI and LVESVI (MD -4.60, 95%CI (-7.33,-1.86), $P=.001$, $I^2=0\%$; MD -4.46, 95%CI (-7.46,-1.45), $P=.004$, $I^2=35\%$, Online Resource 5). Meanwhile, Spironolactone significantly improved LVEF (MD 3.92, 95%CI (0.71,7.14), $P=.02$, $I^2=95\%$, Online Resource 5).

3.7. Safety

A higher rate of hyperkalemia was 4.79% in the MRA arms versus 2.80% in control groups. Gynecomastia occurred in experiment (0.64%) and control (0.30%) patients. Their overall incidence was nearly 2-fold higher than control groups (RR 1.73, 95%CI (1.44,2.08), $P<.00001$, $I^2=42\%$, Fig. 8). Meanwhile, MRA use increased serum potassium and creatinine levels (MD 0.07 (mmol/l), 95%CI (0.02,0.12), $P=.004$, $I^2=74\%$; MD 0.02 (mg/dl), 95%CI (-0.00,0.04), $P=.05$, $I^2=73\%$, Fig. 8), but no corresponding increase in the incidence of renal dysfunction was found (Table 3). In contrast, hypokalemia occurred less frequently in MRA groups (Table 3). Eplerenone (RR 1.48, 95%CI (1.21,1.82), $P=.0002$, $I^2=0\%$), canrenate (RR 3.47, 95%CI (1.43,8.42), $P=.006$, $I^2=29\%$), spironolactone (RR 10.33, 95%CI (2.85,37.41), $P=.0004$, $I^2=0\%$), 25mg (RR 4.91, 95%CI (2.48,9.70), $P<.00001$, $I^2=52\%$), and 50mg (RR 1.48, 95%CI (1.21,1.82), $P=.0002$, $I^2=0\%$, Online Resource 6) subgroups respectively increased the incidence of hyperkalemia. The incidence of gynecomastia was 1.37% in trials using spironolactone and 1.10% in trials using 25mg (RR 8.26, 95%CI (2.23,30.53), $P=.002$, $I^2=0\%$; RR 6.57, 95%CI (1.50,28.83), $P=.01$, $I^2=0\%$, Online Resource 6).

Table 3 other outcomes of mineralocorticoid receptor antagonists use in post-AMI patients

Outcomes	Trials	N	RR/MD	95%CI	P value	Heterogeneity	
						I ² (%)	P value
All-cause hospitalizations	3	6760	0.97	(0.92,1.03)	0.31	29	0.24
Cardiovascular hospitalizations	3	7690	0.92	(0.83,1.02)	0.10	31	0.23
Recurrent myocardial infarction	5	9980	0.97	(0.82,1.14)	0.68	0	0.60
Ventricular arrhythmias	4	9397	0.93	(0.71,1.22)	0.61	0	0.58
Left ventricular ejection fraction	8	1707	2.96	(0.96,4.96)	0.004	92	<.00001
Left ventricula end-systolic daimeter (cm)	3	748	-0.19	(-0.53,0.15)	0.26	94	<.00001
Left ventricula end-diastolic daimeter (cm)	3	748	-0.13	(-0.26,-0.01)	0.04	64	0.06
left ventricular end-diastolic volume index (ml/m ²)	5	1046	-3.35	(-5.37,-1.34)	0.001	0	0.58
left ventricular end-systolic volume index (ml/m ²)	5	1070	-4.73	(-8.75,-0.70)	0.02	96	<.00001
The ratio of early to late diastolic transmitral flow	3	907	0.12	(0.10,0.14)	<.00001	0	0,80
Renal dysfunction	4	1534	0.45	(0.03,6.63)	0.56	71	0.03
Hypokalemia	3	7702	0.42	(0.19,0.95)	0.04	64	0.06

N=Number; MD=Mean difference; RR=Relative ratio; CI=Confidence interval; I²=Inconsistency index

4. Disssussion

The current TOPCAT (Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist Trial, NCT00094302) [33], ALBATROSS [13], and MINIMIZE STEMI [14] trials have shown little cardiovascular benefit from MRA therapy, raising the question of whether MRA treatment is beneficial for cardiovascular diseases. This meta analysis suggests that MRA treatment reverses cardiac remodeling and improves diastolic and systolic function and clinical prognosis in post-AMI patients.

We noted that as treatment duration increased, the extent of reduction in LVEF, LVESVI, and LVEDVI was alleviated or even became nonsignificant. It was evidenced that MRA decreased cardiac aldosterone to suppress collagen synthesis during the acute to subacute phase of AMI [20]. Increased E/A ratio resulted in improved diastolic function. Although greater improvements in clinical outcomes did not reach

statistical significance, post-AMI patients without LVSD were observed to have statistically significant improvements in cardiac ultrasound parameters. Post-AMI patients without LVSD potentially reverse early ventricular remodeling and may benefit from MRA. Current guidelines strongly recommended the use of MRA in post-AMI patients presenting with heart failure [34] based on benefits seen in three landmark trials: RALES (Randomized Aldactone Evaluation Study) [35], EPHESUS [12] and EMPHASIS-HF (Eplerenone in Mild Patients Hospitalization And Survival Study in Heart Failure, NCT00232180) [36]. MRA cannot be recommended as standard of care in post-AMI patients without LVSD. Our findings provide possible evidence for the use of MRA in these patients. The left atrium (LA) is able to pump blood into the left ventricle at end-diastole and help maintain cardiac output, so anti-atrial remodeling is essential for AMI patients. MRA treatment showed a little benefit for LA remodeling after AMI [23,26]. A large number of related studies are needed for further exploration in the future. MRA have shown to effect circulating levels of collagen synthesis and degradation biomarkers [20,25,37,38]. Therefore, we call for further investigation on noninvasive indicators in response to MRA to prove its predictive value in cardiac remodeling.

The degree of improvement in clinical outcomes decreased with longer treatment, as did trends in cardiac structure and function. Le et al. [39] reported a 15% reduction in all-cause mortality in post-AMI participants and we found a 16% reduction. Some studies have shown that early administration of MRA after AMI improves cardiac function [28,14], but the optimal timing of MRA in AMI remains uncertain. A post-hoc analysis found that early initiation of eplerenone <7 days reduced all-cause mortality by 31% compared with placebo and had no effect when commenced >7 days after AMI [17]. Our results are consistent with the above conclusion. we found that the earlier the treatment, the lower the all-cause mortality. early initiation of eplerenone (<7 days) reduced all-cause mortality by 29% and eplerenone administration (>7 days) did not reach statistical significance. We hypothesize that this is because early application of MRA suppresses deleterious effects resulting from high aldosterone plasma levels early after AMI [3]. These data suggest that there is a window of opportunity in the first days after AMI to maximize the potential beneficial effects of MRA on cardiovascular outcomes.

AMI is divided into STEMI and non-ST-elevation myocardial infarction (NSTEMI). STEMI patients usually have complete coronary obstruction, which is more acute and severe than NSTEMI. Emergency treatment is required to restore patency as soon as possible. For NSTEMI, the artery is usually patent but severely stenosed and does not require urgent reperfusion therapy or aggressive antithrombotic therapy [40]. The ALBATROSS trial [13] found a reduction in death in STEMI patients receiving the rapid MRA regimen and the REMINDER trial [28] (A Double-Blind, Randomized, Placebo-Controlled Trial Evaluating The Safety And Efficacy Of Early Treatment With Eplerenone In Patients With Acute Myocardial Infarction, NCT01176968) showed that eplerenone used in 1012 low-risk STEMI patients was safe and effective on a composite outcome. The pooled analysis from the two trials reported that there were significantly fewer deaths in the MRA-treated STEMI patients [41]. A meta-analysis showed all-cause mortality was reduced in STEMI patients without heart failure [42] and our study shows a 38% reduction to provide further support for the use of MRA in STEMI patients. For NSTEMI, MRA treatment did not improve clinical outcomes compared to controls [13], and whether it was applicable to NSTEMI patients required further investigation.

We did not find that MRA reduced the incidence of ventricular arrhythmia, but it did not contradict the reduction in mortality, as MRA significantly reduced mortality with no effect on arrhythmias in the RALES [35] and EPHEsus [12] trials. In addition, ventricular arrhythmias were considered significant only when treatment was required, the recorded incidence was lower than the actual incidence, so the statistical result was not apparent.

Vukadinovic et al. [43] reported that hyperkalemia was more frequently observed in MRA patients (9.3%) than placebo (4.3%) and the present study shows that hyperkalemia in AMI patients treated MRA (4.8%) than controls (2.8%). The two longest follow-up trials [12,25] had similar rates of severe hyperkalaemia over 24 and 16 months, with increases of 2.0% and 1.6% over controls, respectively. Hyperkalemia is the most common side effects of MRA, so we call for careful monitoring of serum potassium and renal function. Gynecomastia is the most important side effect requiring discontinuation. Spironolactone is more likely to cause gynecomastia due to its lower selectivity for mineralocorticoid receptors than eplerenone and also binds to androgen and progesterone receptors [44]. Interestingly, in complete contrast to what we envisaged, hyperkalemia and gynecomastia occurred less frequently with increasing doses.

Coadministration of MRA and angiotension converting enzyme inhibitors (ACEI) has been considered relatively contraindicated owing to potential hyperkalemia. However, the RALES pilot study [45] and the subsequent RALES trial [35] showed that spironolactone in combination with ACEI significantly reduced mortality in patients with advanced HF but was also safe. Dipasquale et al. [21] and their previous pilot trials [46] also shown that canrenate plus captopril combination therapy after AMI was well tolerated and had better beneficial effects. Partial aldosterone escape during chronic treatment with ACEI alone [47], so aldosterone blockade, alone or in combination with ACEI, has potentially favorable effects on post-AMI patients.

The reperfusion process itself can further lead to myocardial injury [48]. The MINIMIZE STEMI trial [14] was the first study to assess whether spironolactone administered prior to reperfusion provided a benefit against reperfusion injury, which showed no benefit in reducing MI size but improving left ventricular remodeling in STEMI patients at 3 months. Iqbal et al. [49] had highlighted that eplerenone was effective in patients after AMI whether treated with or without PCI. Due to the limited relevant data collected, we can not able to analyze whether MRA can improve reperfusion injury in AMI patients and then affect clinical prognosis. Further prospective studies are warranted.

5. Limitations

This study to date is the first comprehensive evaluation of MRA use in AMI patients. We believe that we have identified all existing studies that met our inclusion criteria by meticulous search, hence yielding robust results. However, This study has several potential limitations. First, subjects may not represent all patients in clinical practice. second, differences in follow-up duration and medications may be attributed to unremovable heterogeneity. Lastly, selection bias cannot be completely ruled out by only retrieving

English articles and published trials. Therefore, we cannot draw definitive conclusions until the present results are further validated in larger more targeted clinical trials.

6. Conclusion

Based on current evidence, post-AMI patients benefit from MRA therapy, especially in STEMI patients and those who use MRA within 7 days. Post-AMI patients without LVSD improve early ventricular remodeling by MRA use. Adverse events increased but well tolerated. We suggest that early use of very low-cost MRA may be considered in STEMI patients and post-AMI patients without LVSD.

Declarations

Funding

No funding was received for conducting this study.

Competing Interests

There are no known competing financial interests or personal relationships that could affect this paper.

Data availability

All data during the course of this meta analysis were included in the article.

Code availability

This meta-analysis was conducted using the Cochrane systematic review software Review Manager (RevMan® version 5.3, The Cochrane Collaboration, Oxford, United Kingdom) and Stata (version 15.1, StataCorp, College Station, TX). Pictures were processed using Adobe Photoshop CC (version 14.0, Adobe Systems, San Jose, Calif).

Author contributions

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The article was completed jointly by all authors, who made the decision to submit the manuscript for publication and assumed responsibility for data accuracy.

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Figures

Figure 1

Flow diagram of search strategy and study selection

Figure 2

Quality assessment of each included study

(a) All-cause mortality

(b) New or worsening heart failure

(c) Cardiovascular deaths

(d) Deaths due to heart failure

Figure 3

Forest plot of clinical outcomes

Figure 4

Subanalyses of all-cause mortality

Figure 5

Funnel plots to evaluate publication bias about all-cause mortality

(a) Left ventricular ejection fraction

(b) Left ventricular end-diastolic volume index

Risk of bias legend

- (A) Random sequence generation (selection bias)
- (B) Allocation concealment (selection bias)
- (C) Blinding of participants and personnel (performance bias)
- (D) Blinding of outcome assessment (detection bias)
- (E) Incomplete outcome data (attrition bias)
- (F) Selective reporting (reporting bias)
- (G) Other bias

(c) Left ventricular end-systolic volume index

Figure 6

Forest plot of cardiac ultrasound parameters according to left ventricular ejection fraction subtypes

(a) Left ventricular ejection fraction

(b) Left ventricular end-diastolic volume index

(c) Left ventricular end-systolic volume index

Figure 7

Forest plot of Left ventricular ultrasound parameters according to treatment duration

(a) Serum potassium level

(b) Serum creatinine level

(c) Hyperkalemia and gynecomastia

Figure 8

Forest plot of safety

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