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

Qiao Chen (13088138035@163.com)
Tianjin Medical University https://orcid.org/0000-0001-5767-9315
Die Zhao
Tianjin Medical University
Jie Sun
Tianjin Medical University
Chengzhi Lu (hzmhvski198040244@126.com)
Tianjin Medical University

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Abstract

We aimed to summarize the evidence on the efficacy and safety of mineralocorticoid receptor antagonists (MRA) in post acute myocardial infarction (AMI) patients. Articles were identified through PubMed, Embase, Cochrane Library, Ovid (Medline1946-2021) and ClinicalTrials.gov databases from their inception to December 31, 2020. MRA reduced the risk of all-cause mortality by 16% (relative ratio (RR) 0.84, 95% confidence interval (CI) (0.76, 0.94), P = 0.002). Meanwhile, all-cause mortality was reduced by 38% (RR 0.62, 95% CI (0.42, 0.90), P = 0.01), 30% (RR 0.70, 95% CI (0.49, 1.00), P = 0.05), and 29% (RR 0.71, 95% CI (0.59, 0.86), P = 0.0004) 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 < 0.00001) and reduced left ventricular end-systolic and end-diastolic volume indices (MD -6.23, 95% CI (-10.93, -1.52), P = 0.009; MD -3.13, 95% CI (-5.79, -0.47), P = 0.02). The corresponding RR were 1.73 (95% CI (1.44, 2.08), P < 0.00001) for considered common side effects (hyperkalemia and gynecomastia). 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 MINIMISE 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) affect the clinical efficacy of MRA. Given the cumulative data on this topic, a comprehensive evaluation is required to provide favorable support.

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] (Supplementary material 1).

2.1. Search strategy

Articles were searched through electronic databases. Details of full search strategy were provided in Supplemental material 2. The inclusion criteria were as follows: (1) included post-AMI patients; (2) were clinical prospective randomized controlled trials (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.

2.2. Trials selection

Two investigators (Qiao Chen and Die Zhao) independently obtained eligible articles. Discrepancies were discussed with a third reviewer (Jie Sun) 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.

2.3. 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 ≤ 40%. If a given trial could be divided into ≥ 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 ≥ 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. Baseline characteristics of trials included in the meta analysis.

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. Baseline characteristics of patients included in the meta analysis.

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, 6 h[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, (3-14 d) / 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, 24 h/ 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, 4 h/ 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, 6-12 h/ 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, 12 h/ 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, (1-14 d)/ 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, 24 h/ 327	≤ 2.5 ≤ 5.0	≥ 40 I	ND
Wu. [26] (2013)	ST + SP (20) vs. ST	STEMI, 24 h/ 616	≤ 2.5 ≤ 5.0	NR I-III	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, 24 h/ 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,72 h/ 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, 12 h/ 70	NA < 5.0	> 40 NR	62.0(10.0)/ 60.0(13.0) 33(5)/ 27(5)

[a] time from disease onset to trial entry; [b] mean (standard deviation); [c] male/ 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.

2.6. Statistical analysis

Heterogeneity was assessed by CochranQ test and $P < 0.1$ was considered significant [31]. 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 $P < 0.05$ was considered statistically significant. Subgroup analyses were conducted according to LVEF, 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 $P < 0.1$ 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 0.83 (95% CI: 0.52 to 1.14) showed a good agreement between reviewers (Supplemental material 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 = 0.002, 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 = 0.01, I^2 = 0%; RR 0.70, 95% CI (0.49, 1.00), P = 0.05, I^2 = 0%; RR 0.71, 95% CI (0.59, 0.86), P = 0.0004, I^2 = 0%, Fig. 4). Early administration of MRA within 7 days resulted in a significant reduction in death after randomization (RR 0.71, 95% CI (0.60, 0.84), P < 0.0001, I^2 = 0%, Fig. 3).

The Begg's test (P = 0.64) and the Egger's test (P = 0.63) were observed, and funnel plot was symmetrical distribution, which represented a low publication bias (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

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). The EPHESUS trial [12] provided weights of 81.1% for new or worsening HF. RR excluding it resulted in no statistical significance: from (0.86, p = 0.007) to (0.86, p = 0.23).

3.4. Cardiovascular and all-cause hospitalizations

MRA groups (n = 452/5294; n = 1493/3384) had a greater reduction than control arms (n = 537/5193; n = 1531/3376), but pooled data showed that MRA treatment was not associated with a reduced risk of cardiovascular or all-cause hospitalizations, respectively (Table 3).

Table 3. Other statistical results of mineralocorticord receptor antagonists use in post-AMI patients.

Outcomes	Trials	N	RR/ MD	95% CI	P value	Heterogeneity	
						I^2 (%)	P value
Left ventricular ejection fraction	8	1707	2.96	(0.96, 4.96)	0.004	92	< 0.000
Left ventricula end-systolic daimeter (cm)	3	748	-0.19	(-0.53, 0.15)	0.26	94	< 0.000
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	< 0.000
E/A ratio	3	907	0.12	(0.10, 0.14)	< 0.000	0	0.80
New or worsening HF	8	10515	0.86	(0.78, 0.96)	0.007	0	0.74
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
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; I^2 = inconsistency index.

3.5. 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 ventricula end-diastolic daimeter but not in left ventricula end-systolic daimeter under MRA treatment (Table 3). The ratio of mitral diaslotic early flow velocity E to mitral late flow velocity A (E/A) 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 < 0.00001, I^2 = 0%; MD −6.23, 95% CI (−10.93, −1.52), P = 0.009, I^2 = 98%; MD −3.13, 95% CI (−5.79, −0.47), P = 0.02, I^2 = 29%, Fig. 6), treated ≤ 6 months (MD 3.86, 95% CI (1.43, 6.29), P = 0.002, I^2 = 93%; MD −5.39, 95% CI (−9.73, −1.04), P = 0.02, I^2 = 97%; MD −3.41, 95% CI (−5.50, −1.32), P = 0.001, I^2 = 0%, Fig. 7) subgroups, the statistical results were significant, respectively.

3.6. 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 < 0.00001, 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 = 0.004, I^2 = 74%; MD 0.02 (mg/dl), 95% CI (−0.00, 0.04), P = 0.05, I^2 = 73%, Fig. 8), but no corresponding increase in

the incidence of renal dysfunction was found (Table 3). In contrast, hypokalemia occured less frequently in MRA groups (Table 3). Eplerenone (RR 1.48, 95% CI (1.21, 1.82), P = 0.0002, I^2 = 0%), canrenate (RR 3.47, 95% CI (1.43, 8.42), P = 0.006, I^2 = 29%), spironolactone (RR 10.33, 95% CI (2.85, 37.41), P = 0.0004, I^2 = 0%) respectively increased the incidence of hyperkalemia.

4. Discussion

The current 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.

Post-AMI patients without LVSD were observed to have statistically significant improvements in cardiac ultrasound parameters. 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]. 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 [32] based on benefits seen in three landmark trials: RALES (Randomized Aldactone Evaluation Study) [33], EPHESUS [12] and EMPHASIS-HF (Eplerenone in Mild Patients Hospitalization And SurvIval Study in Heart Failure, NCT00232180) [34]. MAR are not currently recommended as a standard of care for post-AMI patients without LVSD. Our findings provide possible evidence for the use of MRA in these patients. E/A ratio is an echocardiographic index to assess left ventricular diastolic dysfunction. Increased E/A ratio resulted in improved diastolic function [35]. 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, 36, 37]. Therefore, we call for further investigation on noninvasive indicators in response to MRA to prove its predictive value in cardiac remodeling.

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. We found that the earlier the treatment, the lower the all-cause mortality. Early administration of MRA within 7 days resulted in a 29% reduction in death after randomization. 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 [38]. 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. 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, but may instead have deleterious effects [13], and whether it was applicable to NSTEMI patients required further investigation.

The present study shows that hyperkalemia was higher in AMI patients treated with MRA (4.8%) than in 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 [39].

Coadministration of MRA and angiotension converting enzyme inhibitors (ACEI) has been considered relatively contraindicated owing to potential hyperkalemia. However, the RALES pilot study [40] and the subsequent RALES trial [33] 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 [41] 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 [42], 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 [43]. 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. [44] had highlighted that eplerenone was effective in patients after AMI whether treated with or without percutaneous coronary intervention (PCI). Ongoing Clear-Synergy trial (**NCT03048825**) is a multicenter, international SYNERGY stent registry that is embedded within a randomized, blinded, double-dummy, 2x2 factorial design trial of colchicine versus placebo and spironolactone versus placebo in patients with myocardial infarction who have undergone primary 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

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No funding was received for conducting this study.

Conflicts of interest

The authors declare that there is no conflict of interest regarding the publication of this article.

Data availability

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

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Conceptualization: Qiao Chen

Data curation: Qiao Chen, Die Zhao

Methodology: Jie Sun

Formal analysis: Qiao Chen, Die Zhao

Supervision: Chengzhi Lu

Writing – original draft: Qiao Chen

Writing – review and editing: Die Zhao, Jie Sun

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Figures

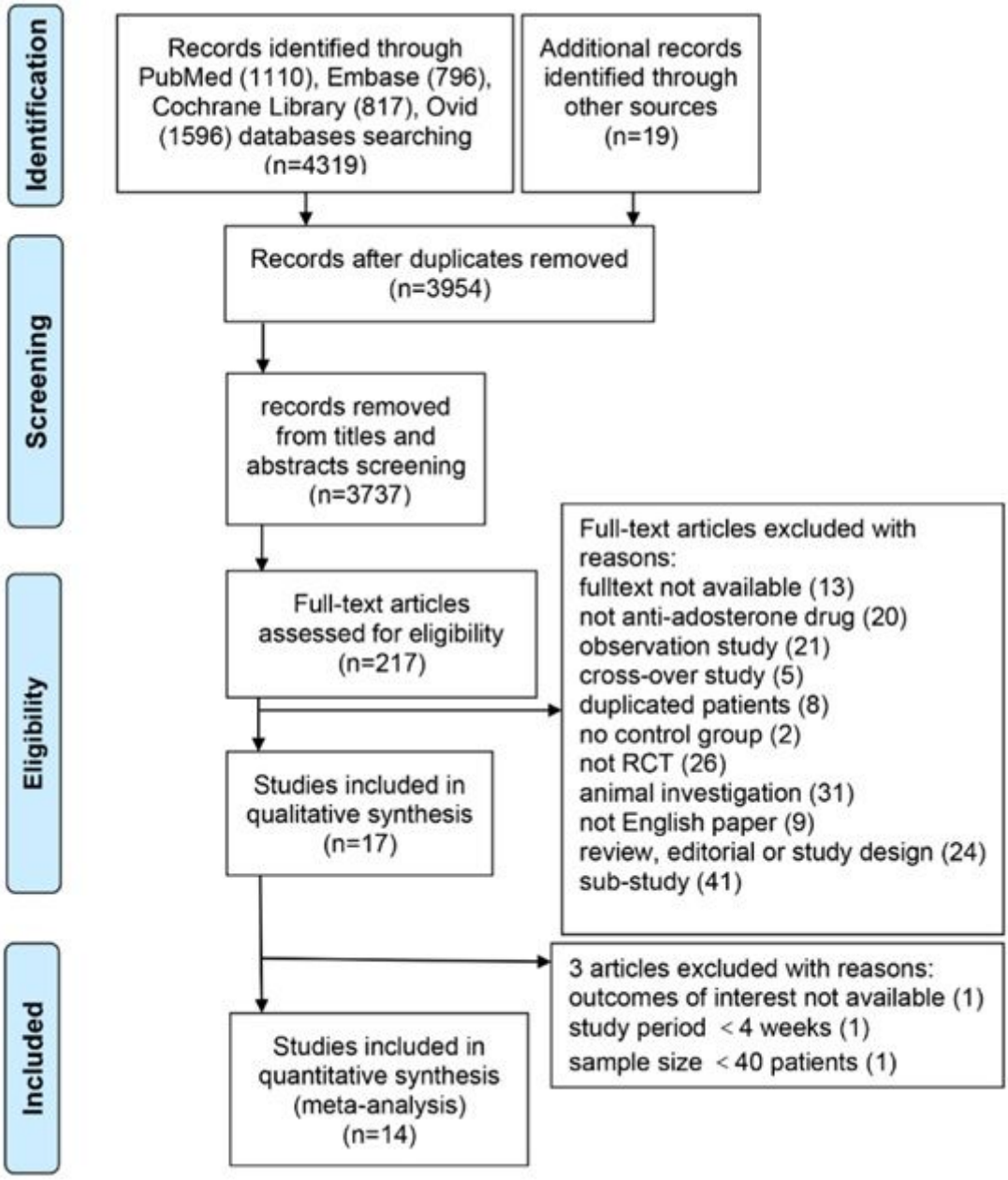

Figure 1

Preferred reporting items for systematic reviews and meta-analyses flow diagram. This flow chart records the process of literature screening and the reasons for exclusion.

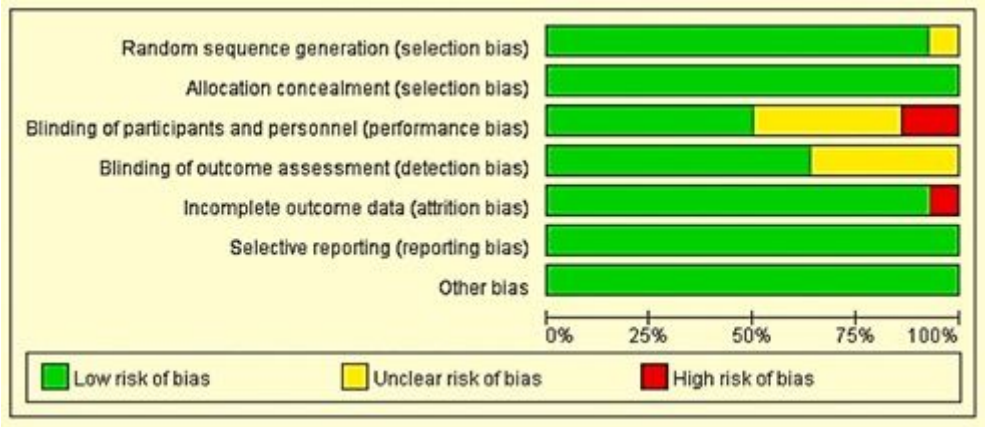

Figure 2

The risk of bias graph of the included trials. Green represents low risk, yellow unclear risk, and red high risk.

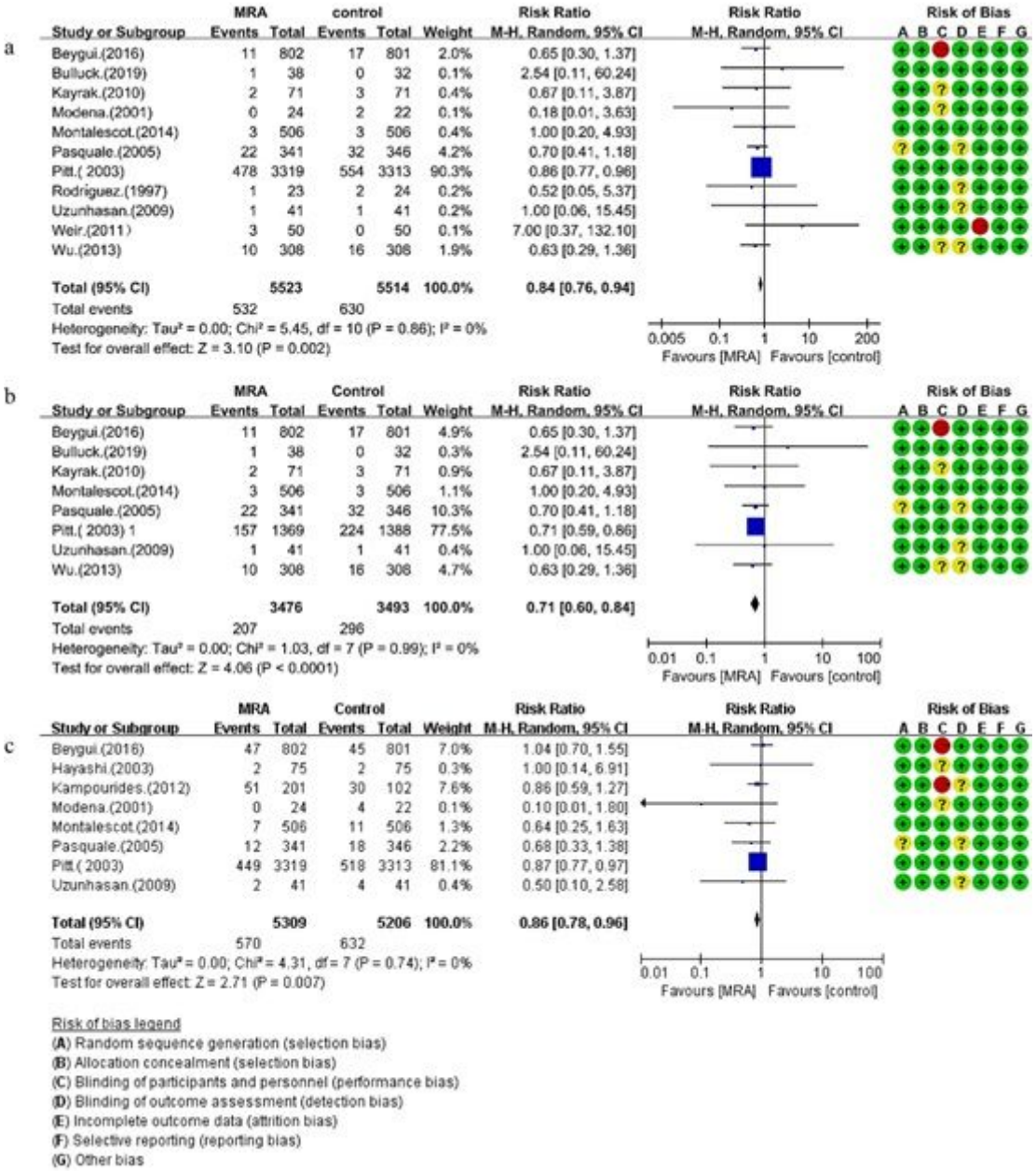

Figure 3

Forest plots of clinical outcomes. (a) all-cause mortality; (b) all-cause mortality in patients administrated MRA within 7 days after AMI ; (c) new or worsening HF.

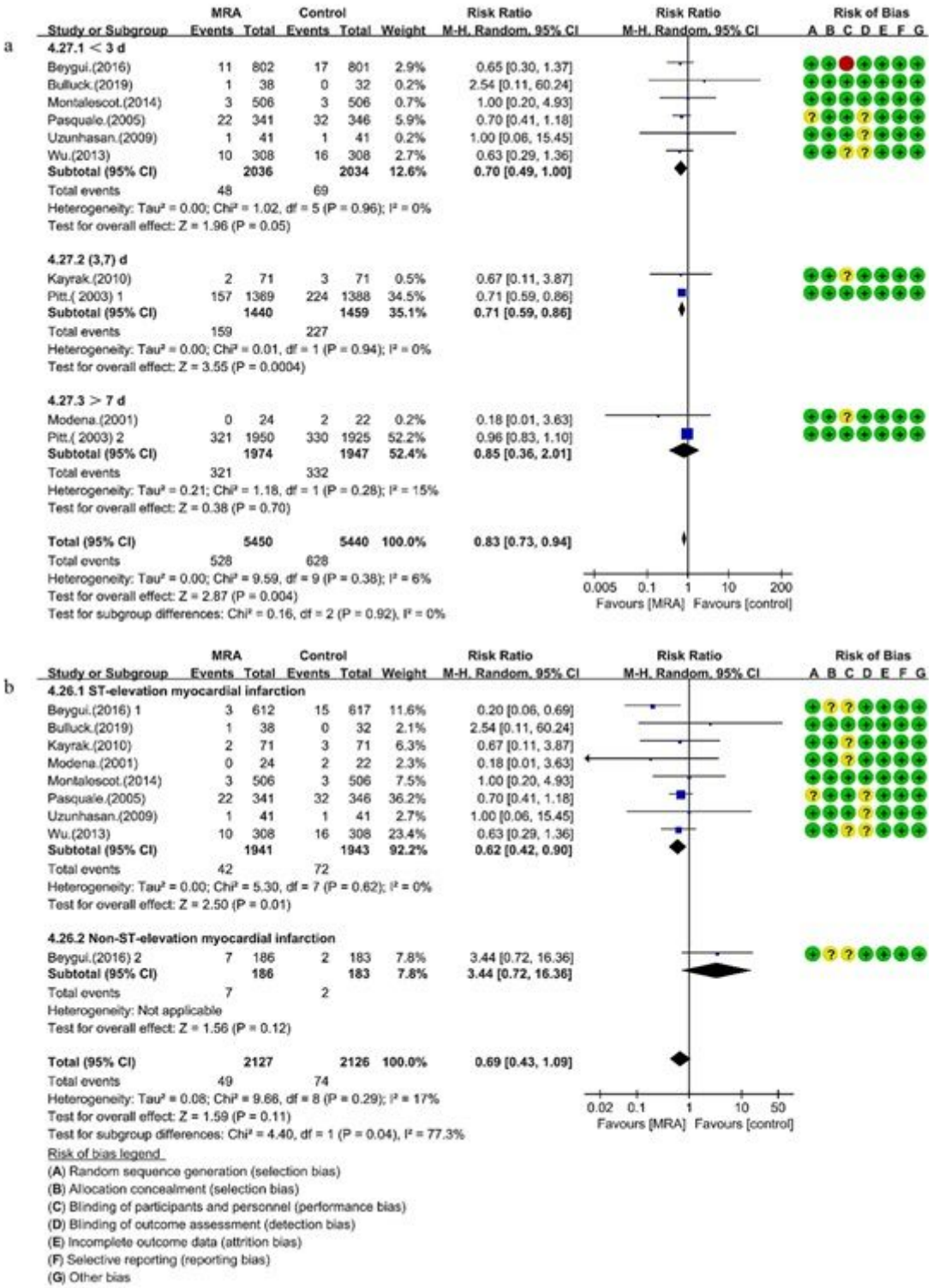

Figure 4

Subgroup analysis of all-cause mortality based on treatment initiation time and AMI subtypes. (a) treatment initiation time; (b) AMI subtypes.

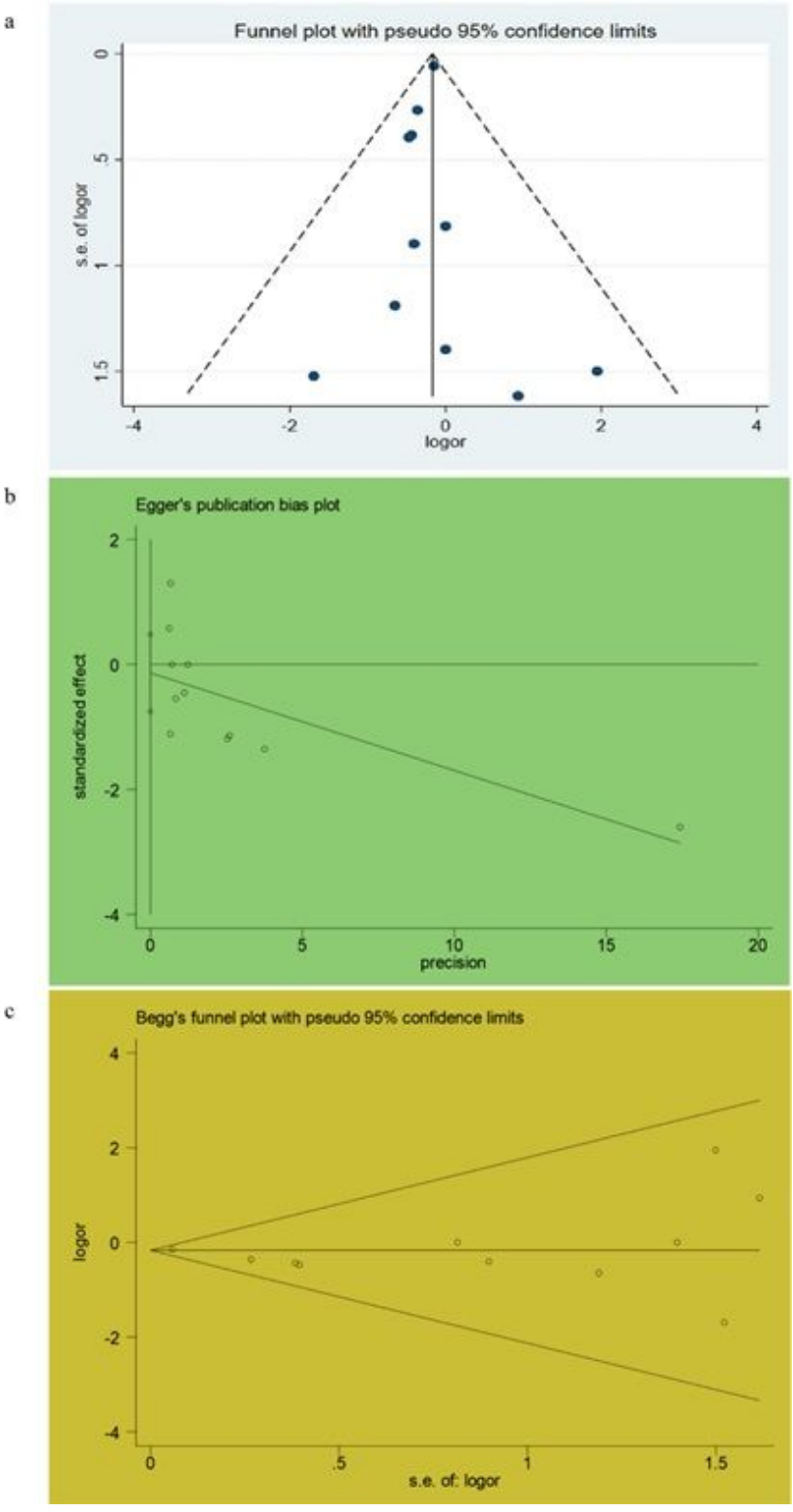

Figure 5

Funnel plots of all-cause mortality depicting the publication bias.

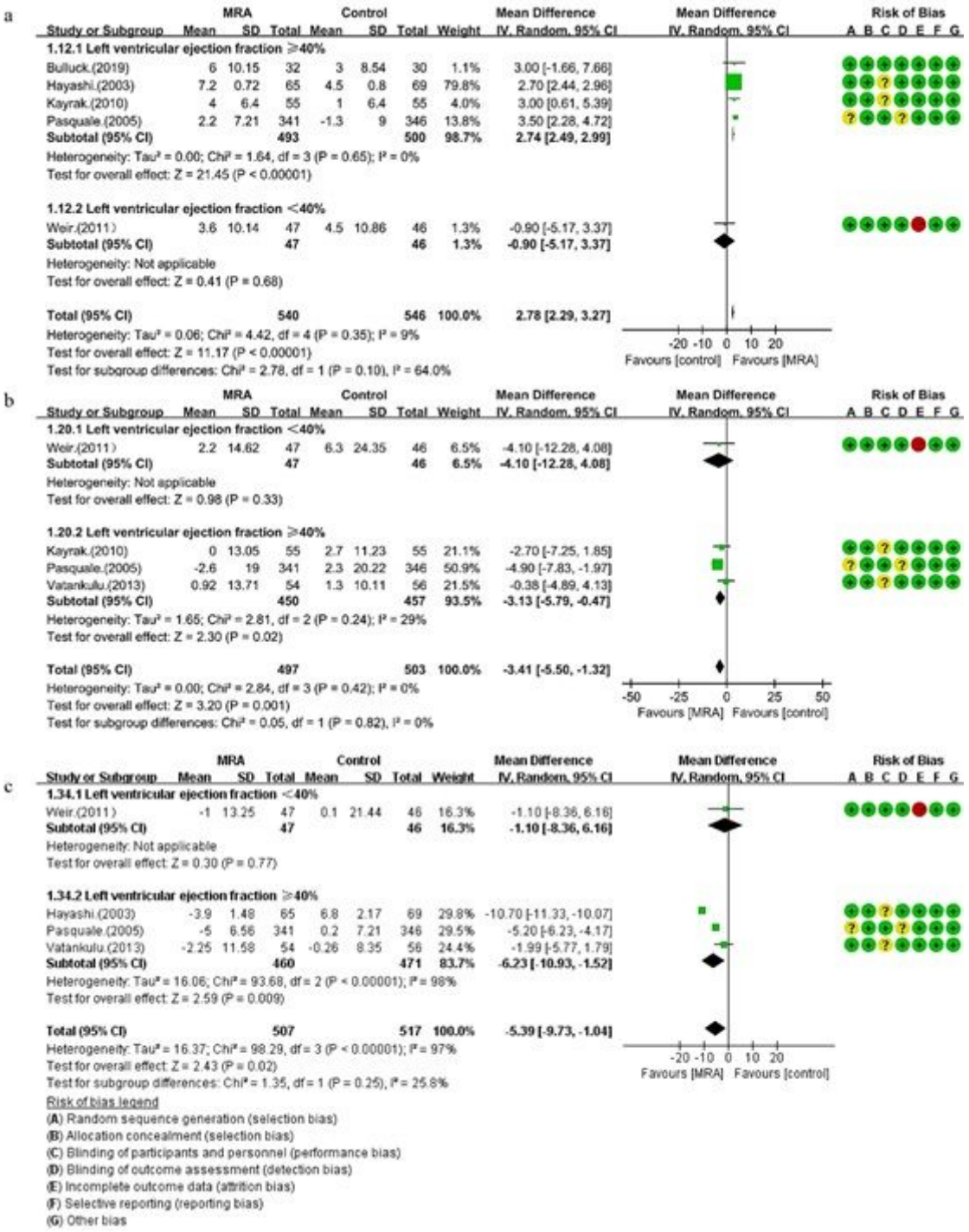

Figure 6

Subgroup analyses of cardiac ultrasound parameters based on LVEF. (a) LVEF; (b) LVEDVI; (c) LVESVI.

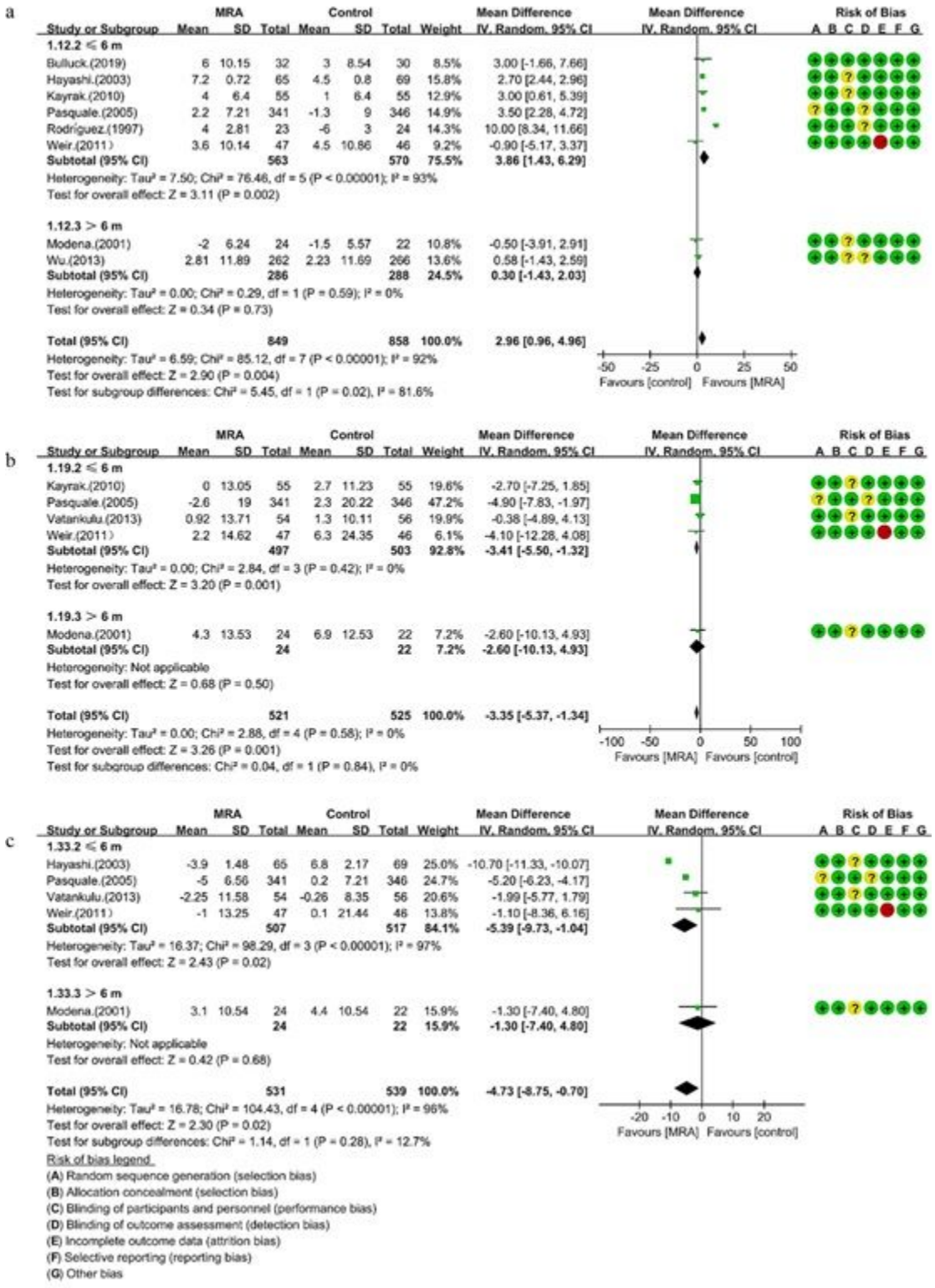

Figure 7

Subgroup analyses of cardiac ultrasound parameters based on treatment duration. (a) LVEF; (b) LVEDVI; (c) LVESVI.

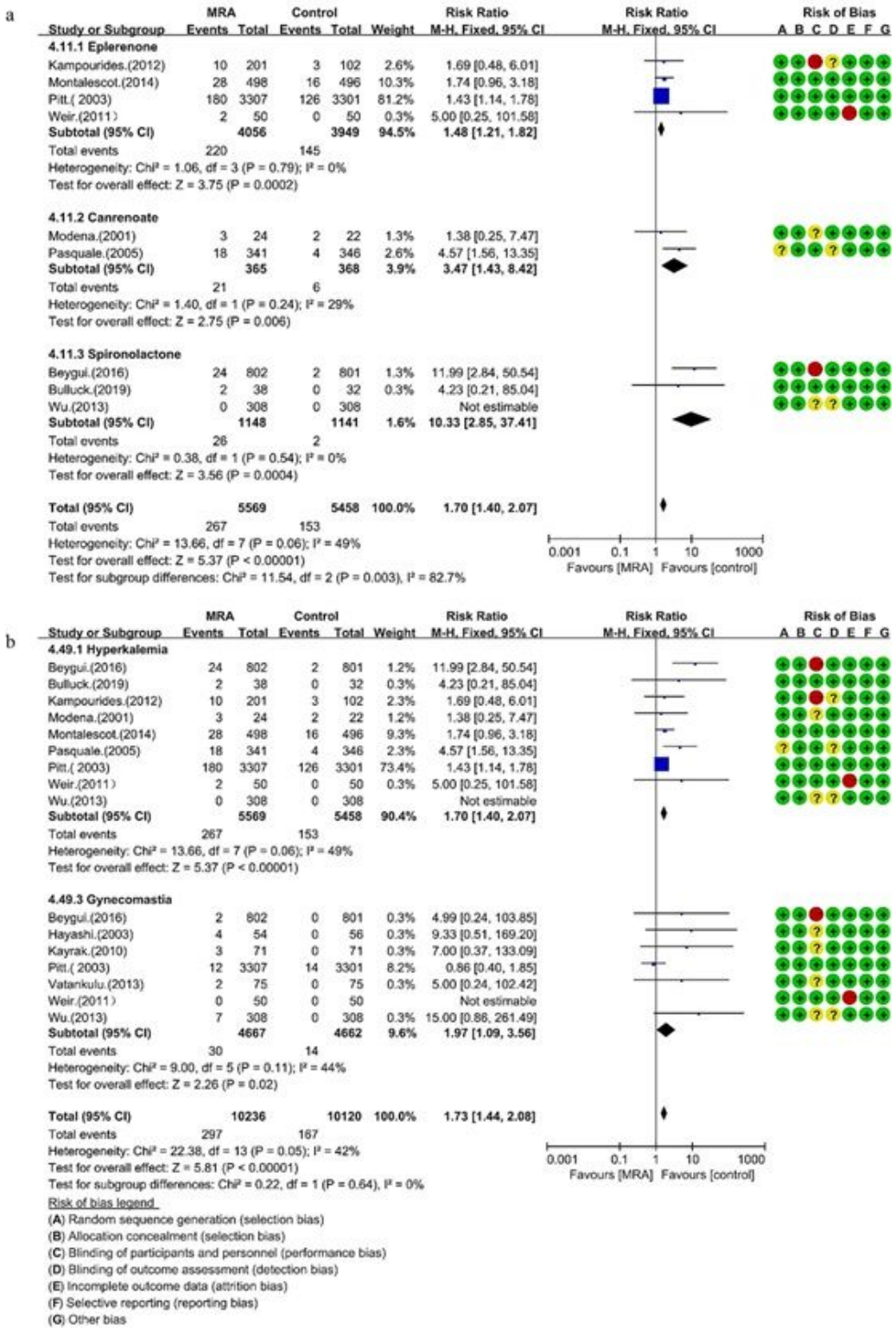

Figure 8

Forest plots of adverse events. (a) subgroup analysis of hyperkalemia based on drug types; (b) hyperkalemia and gynecomastia.

Supplementary Files

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- Supplementalmaterial1.pdf
- Supplementalmaterial2.pdf
- Supplementalmaterial3.pdf