Renal Replacement Therapy

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Assessment of the effect of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers in peritoneal dialysis patients: a systematic review and meta-analysis on clinical trials

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Abstract

Background: Renin-angiotensin system inhibitors (RASIs), either angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, are widely used in patients with non-dialysis chronic kidney disease, as a renin-angiotensin system (RAS) blockade has renoprotective effects. Several studies show that preserving residual renal function is important for a better prognosis in peritoneal dialysis (PD) patients. Here, we systematically reviewed the beneficial or harmful effects of RAS blockade in PD patients.

Methods: PubMed, the Cochrane Library, Embase, the Ichushi web databases, and other resources were selected to search clinical guidelines, systematic reviews, and randomized controlled trials (RCT) published before April 14, 2017, using "peritoneal dialysis," "angiotensin-converting enzyme inhibitors," "angiotensin II type 1 receptor blockers," and "randomized controlled trial" as keywords. Desired results were total mortality, technical survival, urine volume, residual renal function calculated by *glomerular filtration rate* (GFR), cardiovascular events, and anuria progression rate. The study protocol is registered in PROSPERO (International Prospective Register of Systematic Reviews) under the registration number CRD42018104106.

Results: Of a total of 339 studies, eight were identified as suitable for the analysis. Only one study was blinded, whereas the other seven studies were open-label. RASI appeared to preserve residual renal function, GFR (4 studies, 163 participants, mean difference [MD] 0.97 mL/min/1.73 m^2, 95% confidence interval [CI] 0.49–1.44), and urine volume (6 studies, 194 participants, MD 142.56 mL 95% CI 25.42–259.69), although there were no beneficial effects of RASI on total mortality, technical survival, cardiovascular events, and anuria rate.

Conclusions: Our analysis found that RASIs contribute to preserving GFR and urine volume in PD patients. As the number of study participants is small, further studies with a larger sample size are required.

Keywords: Peritoneal dialysis, Renin-angiotensin system inhibitors, Residual renal function, Systematic review

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Background

Residual renal function (RRF) is recognized as a significant factor in improving the prognosis of patients undergoing peritoneal dialysis (PD). Preserving RRF contributes to achieving adequate dialysis targets and improving fluid status. A reanalysis report of the Canada-USA (CANUSA) Peritoneal Dialysis Study Group study showed that an increment in urine volume or preserved glomerular filtration rate (GFR) is associated with better chances of survival [1]. Furthermore, several past studies have reported the benefits of preserving RRF in PD patients [2–6]. For these reasons, a renoprotective strategy is crucial for improving the mortality and technical survival of PD patients.

Renin-angiotensin system inhibitors (RASIs), angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs), have renoprotective and mortality-reducing effects in chronic kidney disease (CKD) patients [7, 8]. These drugs are generally used as first-line therapy for CKD patients with hypertension. The clinical practice guideline of the Japanese Society of Nephrology also recommends RASIs for CKD patients [9]. In view of these facts, the clinical question arose as to whether RASIs preserve the RRF of PD patients. Several clinical studies were performed to estimate the effect of RASIs on RRF of PD patients [10–22], including both randomized controlled trials (RCTs) and non-RCTs, with conflicting results.

This study intended to evaluate the beneficial or harmful effects of RASIs as well as the effect of preserving RRF in patients receiving PD. We systematically reviewed relevant RCTs investigating the effect of RASIs on residual renal function in PD patients. We also examined the differences in impact of ACEIs and ARBs.

Methods

The study is presented following Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) guidelines [23]. The protocol for the systematic review (SR) and meta-analysis was registered with the International Prospective Register of Systematic Reviews (PROSPERO), registration ID CRD42018104106.

Study selection and data management

Initially, with the help of an expert librarian, we searched article records included in previously reported SRs and clinical practice guidelines (CPGs) dealing with the effects of RASIs in PD from 1 January 1988 to 10 April 2017. The searched databases were PubMed, Cochrane Library, Embase, Ichushi web, and other resources. After the search for optimal SRs and CPGs, we identified the articles included in the SRs and CPGs.

We then electronically screened the same databases to identify any articles missed by the initial search (1 January 1988 to 10 April 2017). The keywords for database screening were "peritoneal dialysis," "angiotensin-converting enzyme inhibitors," "angiotensin type II receptor blockers," and "randomized controlled trial." The full strategy is described in Additional file 1. In the case of articles where the required data were not available, we contacted the authors by email.

Four reviewers (MI, YS, YK, and KY) independently screened all the titles and abstracts according to a priori selection criteria. Subsequently, the same reviewers assessed the eligibility of the full texts of all the potentially suitable articles.

Inclusion and exclusion criteria

We included completed RCTs that assessed the effects of RASIs in patients undergoing PD. Our primary outcome was the RRF (change of urine volume or GFR). Other outcomes of interest were all-cause mortality, technical survival, anuria rate, and cardiovascular events.

The comparison patterns were as follows:

1. ACEI or ARB + other drugs versus placebo + other drugs
2. ACEI or ARB + other drugs versus other drugs
3. ACEI + other drugs versus ARB + other drugs.

We also included trials with adult (> 18 years old) end-stage kidney disease (ESKD) patients undergoing PD without restrictions on age, sex, or ESKD as a primary disease.

We excluded studies involving participants with acute kidney injuries, receiving hemodialysis (HD) or PD/HD combined therapy and anuria.

Data extraction

Data extraction was carried out independently by the four review authors (MI, YS, YK, and KY) using standardized methods. Where a comparison of more than two interventional drugs or control drugs existed in a study, the reports were handled as separate studies in one analysis. Studies not written in English were translated before assessment.

Risk of bias assessment

The four review authors (MI, YS, YK, and KY) independently assessed the risk of bias in included studies using the risk of bias tool in the Cochrane handbook [24].

We assessed the random sequence generation, allocation concealment, blinding, incomplete outcome data, selective reporting, and others. Risks in each domain were assessed in the following three categories: high risk, low risk, and unclear. Any discrepancy was identified and resolved through discussion (with a third author where necessary).

Data synthesis and statistical methods

We conducted the analysis comparing the effects of RASIs and other drugs as "SR1.1." regarding ACEIs and

ARBs together as RASIs although ACEIs and ARBs have different mechanisms of action. The market share of ARBs is larger than ACEIs in Japan, suggesting that a separate comparison of the effects of ARBs and ACEIs against other drugs does not reflect reality. Additionally, we conducted a comparison of the independent effects of ACEIs and ARBs as "SR1.2." to address the question of whether either is more favorable for PD patients.

The results were analyzed using Review Manager (RevMan), Version 5.3 software (The Cochrane Collaboration, Oxford, UK). Dichotomous outcome results with a low event rate were expressed as risk difference (RD) with 95% confidence intervals (CI). Where a significant number of events occurred, the risk ratio (RR) was used for analysis. For continuous scale outcomes (residual renal function and urine volume), results were expressed as the mean difference (MD). Heterogeneity across the included studies was assessed statistically by calculating the overall I^2 values. Data were pooled using the random-effect model.

Results

Results of search

The previous SR and CPG search yielded two SRs [25, 26] which contained four [10, 11, 15, 27] and six [10, 15–18, 20] RCTs in each, with two [10, 15] duplicated. We thus identified eight articles from this step. Through a new database search, 329 titles and abstracts were identified, of which, three articles [11, 19, 22] were potentially eligible. We carried out full-text article assessments of 11 studies and excluded three for the following reasons: duplication [11], inconsistent outcomes [27], and a too short observational period [22]. Finally, eight trials were entered into this review. Figure 1 shows the details of the study selection process.

The eight RCTs included in the analysis are summarized in Table 1. One study assessed the efficacies of ACEIs [10]. Two studies compared the effects of ACEIs and ARBs with a cross-over RCT [16], and a parallel RCT [20]. The remaining five studies assessed the effects of ARB [11, 15, 17–19], where one study conducted two intervention groups using different ARBs [19].

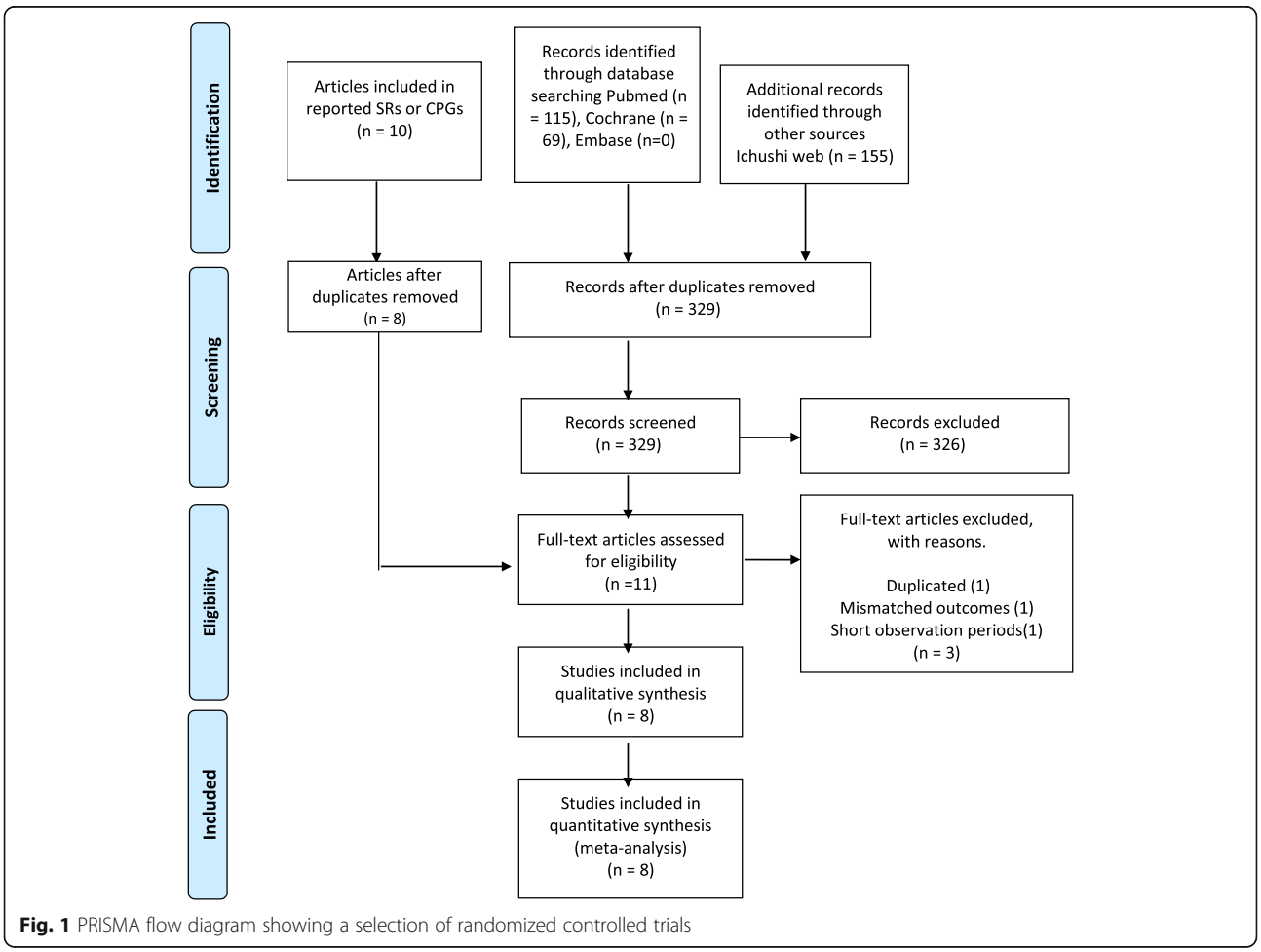

Fig. 1 PRISMA flow diagram showing a selection of randomized controlled trials

Table 1 Characteristics of studies included in this systematic review

Studies	Study design	Location/setting	No. patients (intervention/ control)	Age, years (intervention/ control)	Treatment of intervention group	Treatment of control group	Follow-up, months
Li [10]	Open-label RCT	Hong Kong/single center	30/30	58.0/59.1	Ramipril 5 mg/day	Conventional antihypertensive therapy except for ACEI or ARB or both	12
Phakdeekitcharoen [16]	Open-label cross-over RCT	Thailand/single center	29	44.8	Group 1: Enalapril 10 mg/day Group 2: Candesartan 8 mg/day	Group 1: Candesartan 8 mg/day Group 2: Enalapril 10 mg/day	4
Reyes-Marín [20]	Parallel RCT	Mexico/single center	30/30	42.5/49.2	Group 1: Enalapril 10 mg/day	Group 2: Losartan 50 mg/day	12
Suzuki [11]	Double-blind RCT	Japan/single center	14/10	56/57	Valsartan 40~80 mg/day	Conventional antihypertensive therapy	12
Suzuki [15]	Open-label RCT	Japan/single center	18/16	63.5/63.5	Valsartan 40~80 mg/day	Conventional antihypertensive therapy except for ACEI or ARB or both	24
Shigenaga [19]	Open-label RCT	Japan/single center	15/15	52.9/53.3	Group 1: Candesartan l~4 mg/day Group 2: Valsartan ~ 40 mg/day	Conventional antihypertensive therapy except for ACEI or ARB or both	6
Zhong [18]	Open-label RCT	China/single center	24/20	44	Irbesartan 300 mg/day	Conventional antihypertensive therapy except for ACEI or ARB or both	12
Wang [17]	Open-label RCT	China/single center	19/13	42	Valsartan 80 mg/day	Conventional antihypertensive therapy except for ACEI or ARB or both	28

Abbreviations: *RCT* randomized controlled trial, *ACEI* angiotensin-converting enzyme inhibitor, *ARB* angiotensin receptor blocker

Table 2 Summary of risk of bias assessment

Studies	Cochrane collaboration tool						
	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective outcome reporting	Other sources of bias
Li [10]	Low risk	Low risk	Unclear risk	Low risk	Low risk	Unclear risk	Unclear risk
Phakdeekitcharoen [16]	Unclear risk	Low risk	Unclear risk	Low risk	High risk	Unclear risk	Unclear risk
Reyes-Marin [20]	Unclear risk	Low risk	Unclear risk	Low risk	Unclear risk	Unclear risk	Unclear risk
Suzuki [11]	Unclear risk	Unclear risk	Low risk	Low risk	Unclear risk	Unclear risk	Unclear risk
Suzuki [15]	Low risk	Low risk	Unclear risk	Low risk	Unclear risk	Unclear risk	Unclear risk
Shigenaga [19]	Unclear risk	Unclear risk	Unclear risk	Low risk	Unclear risk	Unclear risk	Unclear risk
Zhong [18]	Low risk	High risk	Unclear risk	Low risk	High risk	Unclear risk	Unclear risk
Wang [17]	Low risk	Unclear risk	Unclear risk	Low risk	High risk	Unclear risk	Unclear risk

Risk of bias in included studies

Table 2 summarizes the details of our assessment of the risk of bias among the included studies. Four studies used computer-generated lists for randomization [10, 15, 17, 18]. Two of these had not detailed the randomization method [17, 18], but the authors of a previous SR confirmed that these studies also used the computer-generated methods [26]. One study provided no information on allocation concealment [18]. Three studies had incomplete outcome data [16–18]. Most of our primary outcomes analyzed in the review were obtained from objective data, and not influenced by the blinding of patients and investigators.

Effects of interventions

The summaries of the findings for all the outcomes in SR1.1. and SR1.2. are summarized in Additional files 2 and 3, respectively. SR1.1. is a comparison of RASIs including ARBs or ACEIs versus conventional therapy for preserving RRF in PD patients. SR1.2. is a comparison of ARBs versus ACEIs for preserving RRF in PD patients.

Residual renal function (GFR)

SR1.1.

Four studies (ARB, 3; ACEI, 1) reported the effects of RASIs versus other antihypertensive drugs on RRF after follow-up periods of over 12 months. The comparison of RASIs and other drugs indicated a small but significant benefit in preserving RRF (mean difference [MD] 0.97 mL/min/1.73 m^2, 95% confidence interval [CI] 0.49–1.44, $I^2 = 79\%$), suggesting that RASIs have renoprotective effects compared to other antihypertensive drugs (Fig. 2). However, significant heterogeneity was identified. In subgroup analysis, ARBs significantly reduced the decline of RRF (MD 1.11 mL/min/1.73 m^2, 95% CI 0.38–1.83, $I^2 = 76\%$), and ACEIs also preserved RRF (MD 0.72 mL/min/1.73 m^2, 95% CI 0.54–0.90) compared to other antihypertensive drugs. There was significant heterogeneity for the effects of ARBs.

SR1.2.

One study found no significant differences in RRF preservation between ARBs and ACEIs over 12 months (MD 0.18 mL/min/1.73 m^2, 95% CI − 0.04 to 0.40) (Fig. 2).

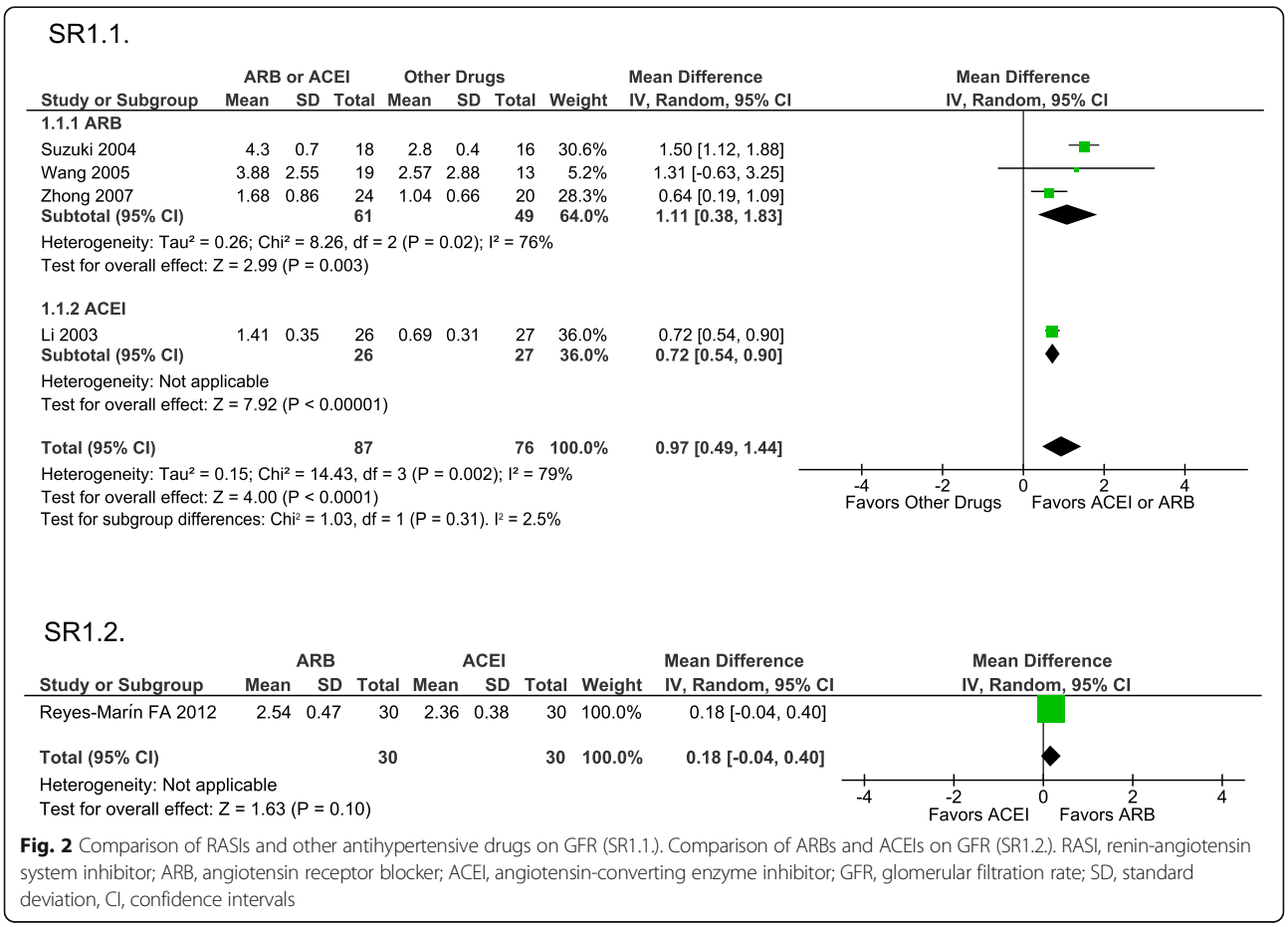

Fig. 2 Comparison of RASIs and other antihypertensive drugs on GFR (SR1.1.). Comparison of ARBs and ACEIs on GFR (SR1.2.). RASI, renin-angiotensin system inhibitor; ARB, angiotensin receptor blocker; ACEI, angiotensin-converting enzyme inhibitor; GFR, glomerular filtration rate; SD, standard deviation, CI, confidence intervals

Urine volume

SR1.1.

Five studies reported the efficacies of ARBs versus other antihypertensive drugs on urine volume change after follow-up periods of over 6 months. One study compared two ARBs (Candesartan and Valsartan) and controls [19]. Therefore, we deemed that the study involved two comparisons (Shigenaga 2009 and Shigenaga 2009b) and included the data as two independent studies. ARBs significantly prevented the reduction in urine volume with extensive heterogeneity (MD 142 mL, 95% CI 25.42–259.69, $I^2 = 80\%$) (Fig. 3). There were no data about the urine volume change in the study comparing ACEIs and other drugs.

SR1.2.

One study reported no significant difference in urine volume change between ARBs and ACEIs over 12 months (MD 145.0 mL, 95% CI − 8.35 to 298.35) (Fig. 3).

Anuria

SR1.1.

Three studies (ARB, 2; ACEI, 1) indicated no significant difference in the risk ratio of the complete anuria progression rate between patients treated with RASIs and those treated with other antihypertensive drugs after follow-up periods greater than 12 months (RR 0.70, 95% CI 0.48–1.02, $I^2 = 0\%$) (Fig. 4). In subgroup analysis, there was no significant difference in the risk ratio of the anuria progression rate in the studies comparing ARBs and other antihypertensive drugs (RR 0.91, 95% CI 0.43–1.94, $I^2 = 0\%$), though ACEIs showed a significant reduction of the anuria progression rate (RR 0.64, 95% CI 0.41–0.99).

SR1.2.

The comparison between ARBs and ACEIs in one study showed no significant difference in the risk ratio of the anuria progression rate over twelve months (RR 1.09, 95% CI 0.57–2.07) (Fig. 4).

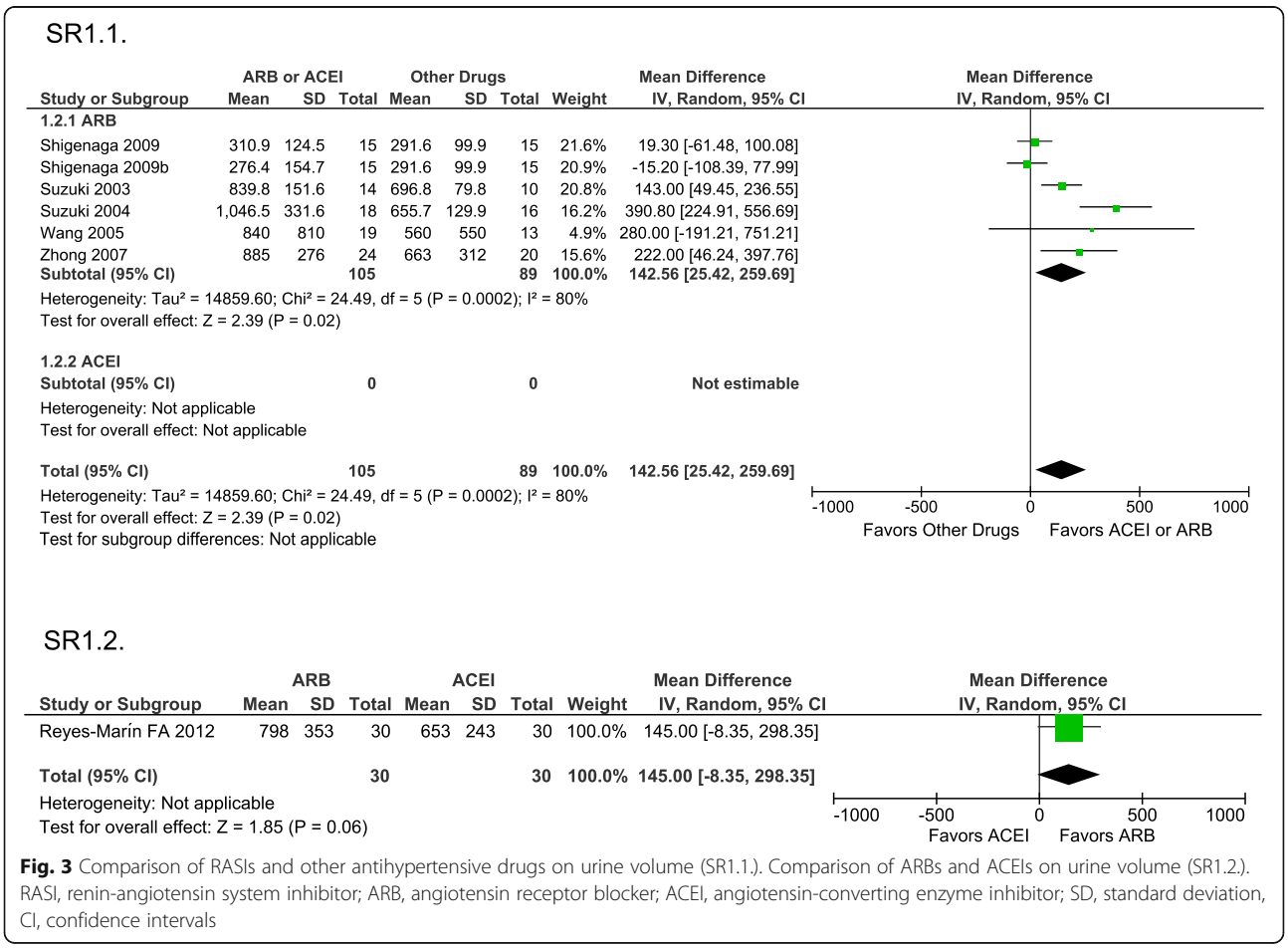

Fig. 3 Comparison of RASIs and other antihypertensive drugs on urine volume (SR1.1.). Comparison of ARBs and ACEIs on urine volume (SR1.2.). RASI, renin-angiotensin system inhibitor; ARB, angiotensin receptor blocker; ACEI, angiotensin-converting enzyme inhibitor; SD, standard deviation, CI, confidence intervals

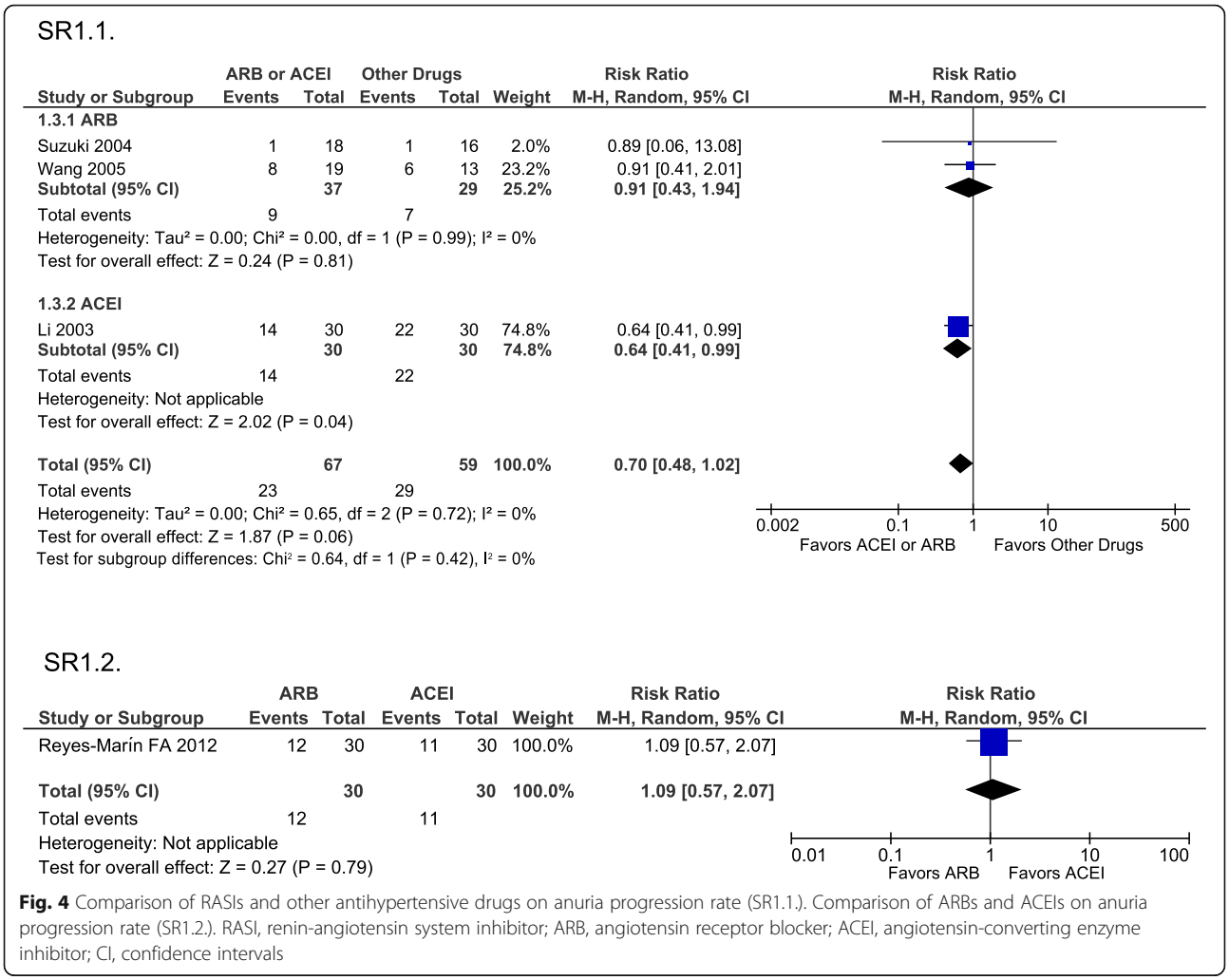

Fig. 4 Comparison of RASIs and other antihypertensive drugs on anuria progression rate (SR1.1.). Comparison of ARBs and ACEIs on anuria progression rate (SR1.2.). RASI, renin-angiotensin system inhibitor; ARB, angiotensin receptor blocker; ACEI, angiotensin-converting enzyme inhibitor; CI, confidence intervals

All-cause mortality

SR1.1.

We identified the outcome data of all-cause mortality from all six studies (ARB, 5; ACEI, 1). The comparison indicated no significant difference in the risk difference of all-cause mortality between RASIs and other antihypertensive drugs after follow-up periods of over 6 months (RD 0.00, 95% CI − 0.04 to 0.05, $I^2 = 0\%$) (Fig. 5). The subgroup analysis also showed no significant differences when comparing ARBs and other drugs (RD 0.00, 95% CI − 0.05 to 0.05, $I^2 = 0\%$), and ACEIs and other drugs (RD 0.03, 95% CI − 0.11 to 0.17).

SR1.2.

The comparison between ARBs and ACEIs in one study showed no significant difference in the risk difference of all-cause mortality over 12 months (RD 0.00, 95% CI − 0.06 to 0.06) (Fig. 5).

Technical survivals

SR1.1.

All six studies (ARB, 5; ACEI, 1) were included in the analysis, indicating no significant difference in the risk difference of technical survival between RASIs and other antihypertensive drugs after follow-up periods of over 6 months (RD − 0.00, 95% CI − 0.05 to 0.04, $I^2 = 0\%$) (Fig. 6). In one study of ARBs [18], the authors mentioned that one participant in the control group transferred to hemodialysis because of ultrafiltration failure; however, the participant was not counted in the final data. Thus, we considered the participant as having a technical failure and added one to the analysis. In another study of ACEIs [10], two participants received kidney transplants and dropped out of the study. We considered them not to be technical failure patients and removed them from the participant tally. The subgroup analysis also showed no significant differences in both comparisons of ARBs and other drugs (RD − 0.01, 95% CI − 0.06 to 0.04, $I^2 = 0\%$), nor

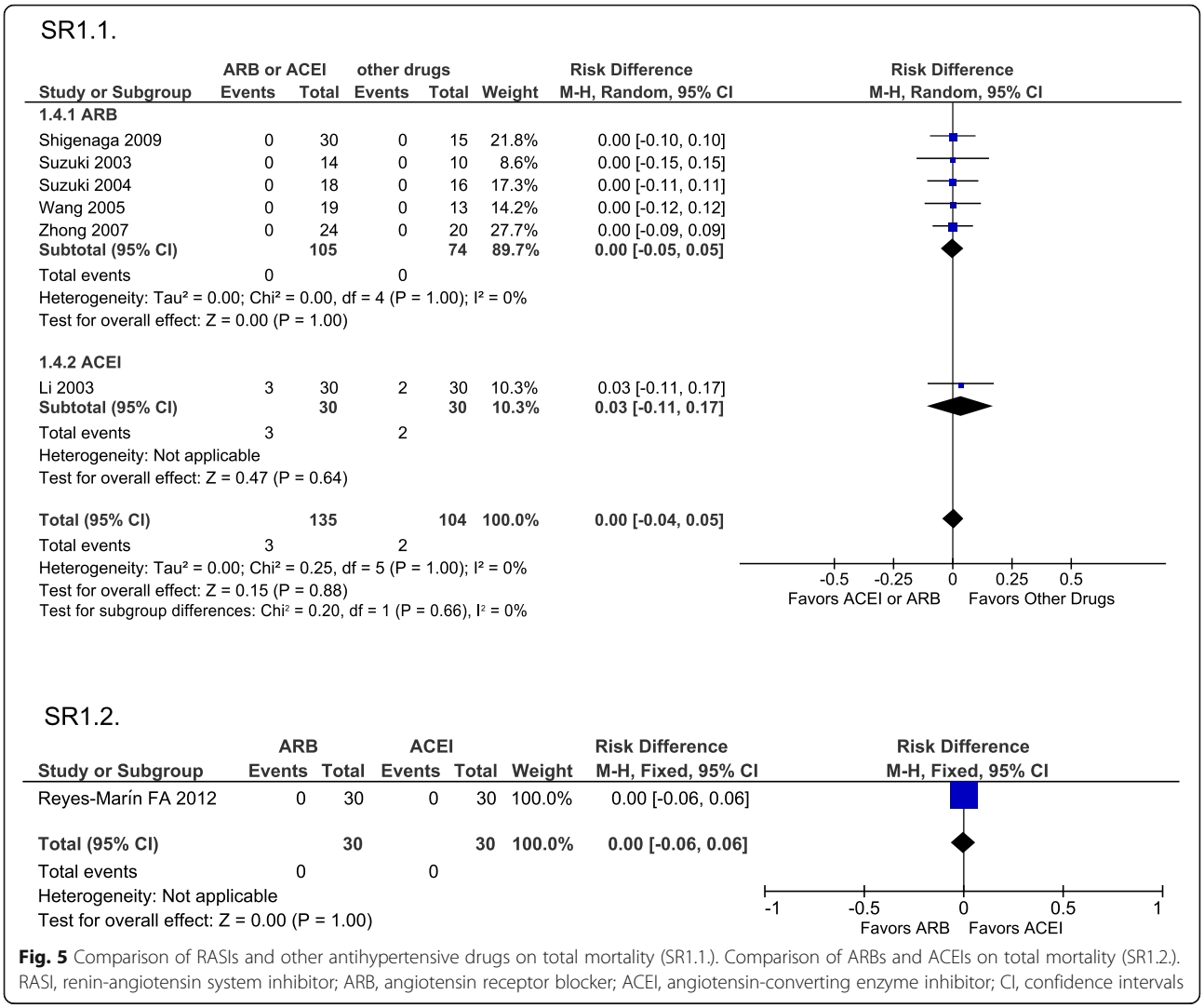

Fig. 5 Comparison of RASIs and other antihypertensive drugs on total mortality (SR1.1.). Comparison of ARBs and ACEIs on total mortality (SR1.2.). RASI, renin-angiotensin system inhibitor; ARB, angiotensin receptor blocker; ACEI, angiotensin-converting enzyme inhibitor; CI, confidence intervals

in the comparison of ACEIs and other drugs (RD 0.03, 95% CI − 0.11 to 0.18).

SR1.2.

The comparison between ARBs and ACEIs in one study [20] showed no significant difference in the risk difference of technical survival over 12 months (RD 0.00, 95% CI − 0.06 to 0.06) (Fig. 6).

Cardiovascular events

SR1.1.

Cardiovascular events were reported in two studies (ARB, 1; ACEI, 1). The comparison showed no significant difference in the risk difference of cardiovascular events between RASIs and other antihypertensive drugs after follow-up periods of over 12 months (RD 0.00, 95% CI − 0.09 to 0.09, $I^2 = 0\%$) (Fig. 7). The subgroup analysis also showed no significant differences in both comparisons of ARBs versus other drugs (RD 0.00, 95% CI − 0.11 to 0.11, $I^2 = 0\%$), nor in the comparison of ACEIs versus other drugs (RD 0.00, 95% CI − 0.09 to 0.09).

SR1.2.

The comparison between ARBs and ACEIs in one study showed no significant difference in the risk ratio of a cardiovascular event (RR 1.33, 95% CI − 0.33 to 5.45) (Fig. 7).

Hyperkalemia

SR1.1.

Hyperkalemia was reported in one study comparing two ARBs and other antihypertensive drugs and showed no significant difference in the risk of hyperkalemia over 6 months (RD 0.00, 95% CI − 0.10 to 0.10) (Fig. 8).

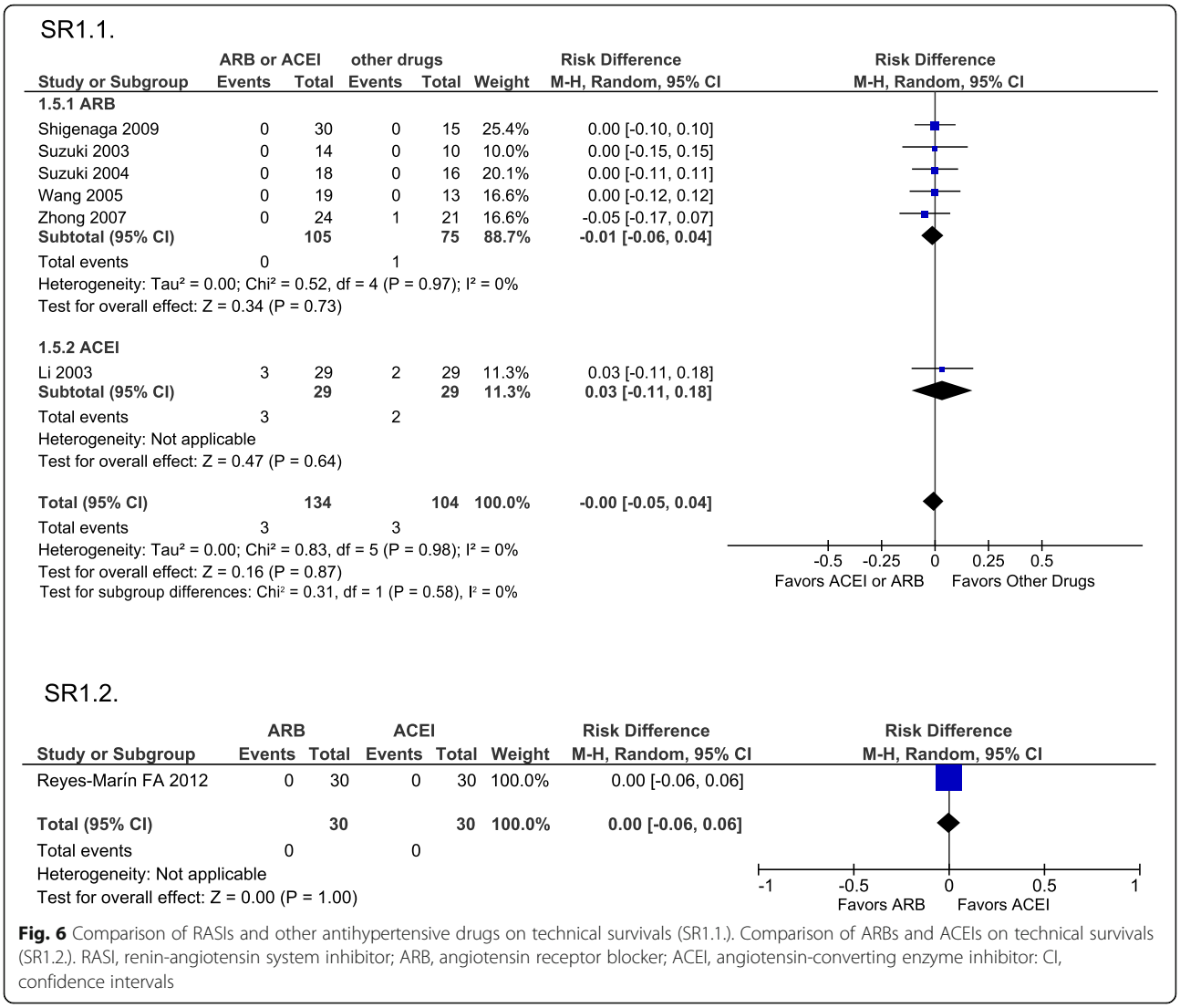

Fig. 6 Comparison of RASIs and other antihypertensive drugs on technical survivals (SR1.1.). Comparison of ARBs and ACEIs on technical survivals (SR1.2.). RASI, renin-angiotensin system inhibitor; ARB, angiotensin receptor blocker; ACEI, angiotensin-converting enzyme inhibitor: CI, confidence intervals

SR1.2.

The comparison between ARBs and ACEIs in two studies showed no significant difference in the risk difference of hyperkalemia after follow-up periods of over 4 months (RD 0.00, 95% CI − 0.06 to 0.06, $I^2 = 0\%$) (Fig. 8).

Discussion

In this systematic review, we evaluated eight RCTs and 320 participants. Five studies compared ARBs with other antihypertensive drugs [11, 15, 17–19], and one assessed two ARBs and control drugs [19]. One study compared ACEIs with other antihypertensive drugs [10]. Two studies, one of which was a cross-over RCT [16], compared ARBs with ACEIs [16, 20]. Some meta-analysis in this report was performed combining studies with different follow-up periods, although we considered these variations to be clinically acceptable.

RASIs appeared to preserve RRF in GFR (MD 0.97 mL/min/1.73 m^2, 95% CI 0.49–1.44) and urine volume (MD 142.56 ml, 95% CI 25.42–259.69), while there were no beneficial effects of RASIs on total mortality, technical survival, cardiovascular events, and anuria progression rate. RASIs did not increase the risk of hyperkalemia as a harmful effect of intervention for PD patients, although hyperkalemia is the decisive reason for which physicians decide to stop RASIs for CKD patients. However, the meta-analysis of urine volume included the RCTs comparing only ARBs and other drugs, without RCTs comparing ACEIs and other drugs. Only ACEIs showed a beneficial effect (RR 0.64, 95% CI 0.41–0.99) in a subgroup analysis of the anuria progression rate, indirectly suggesting a difference in drug effects between ARBs and ACEIs. However, the direct comparison of ACEIs with ARBs revealed no superiority in either RASI drug in any outcome. In the analysis of GFR and

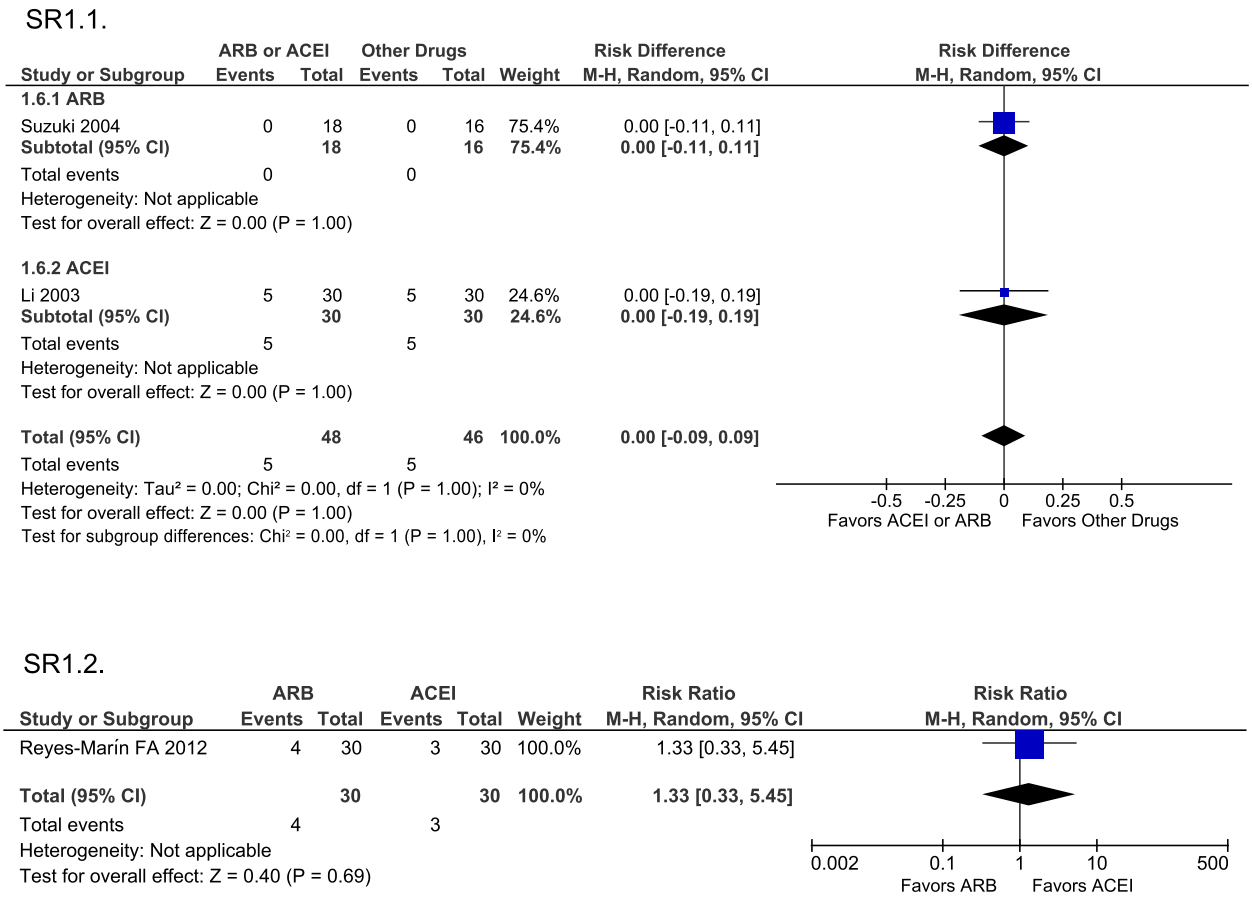

Fig. 7 Comparison of RASIs and other antihypertensive drugs on cardiovascular events (SR1.1.). Comparison of ARBs and ACEIs on cardiovascular events (SR1.2.). RASI, renin-angiotensin system inhibitor; ARB, angiotensin receptor blocker; ACEI, angiotensin-converting enzyme inhibitor; CI, confidence intervals

urine volume, we identified a substantial heterogeneity ($I^2 = 79\%$, $p = 0.002$ and $I^2 = 80\%$, $p = 0.02$, respectively). However, the point estimates in both analyses overlapped or indicated the same tendency in treatment effects (Figs. 2 and 3). Therefore, we considered that the heterogeneities were not clinical. Further detailed subgroup analysis was not possible due to the small number of studies identified.

Most nephrologists prescribe ACEIs and ARBs to preserve renal function in early-stage CKD patients [28]. Several meta-analyses [8, 29] and RCTs [7, 30–35] have reported that ACEIs and ARBs have beneficial effects on the total mortality and the progression to ESKD regardless of the CKD stage and the presence of diabetes. However, recent studies [36, 37] revealed that increased creatinine or decreased GFR after the initiation of RASIs correlated with worse renal outcome in predialysis CKD patients. Another study reported that discontinuation of RASIs delayed the progression to ESKD in advanced CKD patients [38]. These opposing effects of RASIs on predialysis patients make it difficult to determine whether RASIs have renoprotective effects in patients undergoing PD. Nevertheless, we identified a clear renoprotective effect of RASIs in PD patients. The mechanisms underlying the renoprotective impact of RASIs for PD patients are multiple and complex and could involve renal hemodynamic factors [39] and histochemical factors [40–42]. The two studies [11, 19] included in this SR showed cardioprotective effects of RASI in PD patients, which might contribute to the mechanism protecting renal function. Furthermore, these results might be due to the synergistic effects of RASI together with PD.

Our results agree with those of previous reported SRs [25, 26] that demonstrated the renoprotective effects of RASIs in PD patients. RCTs included in previous SRs overlapped with those in our SR. The previous SRs used GFR and anuria progression rates to assess the renoprotective effects of RASIs, though our study evaluated RRF using urine volume in addition to the above. We therefore included two RCTs into our SR, which assessed

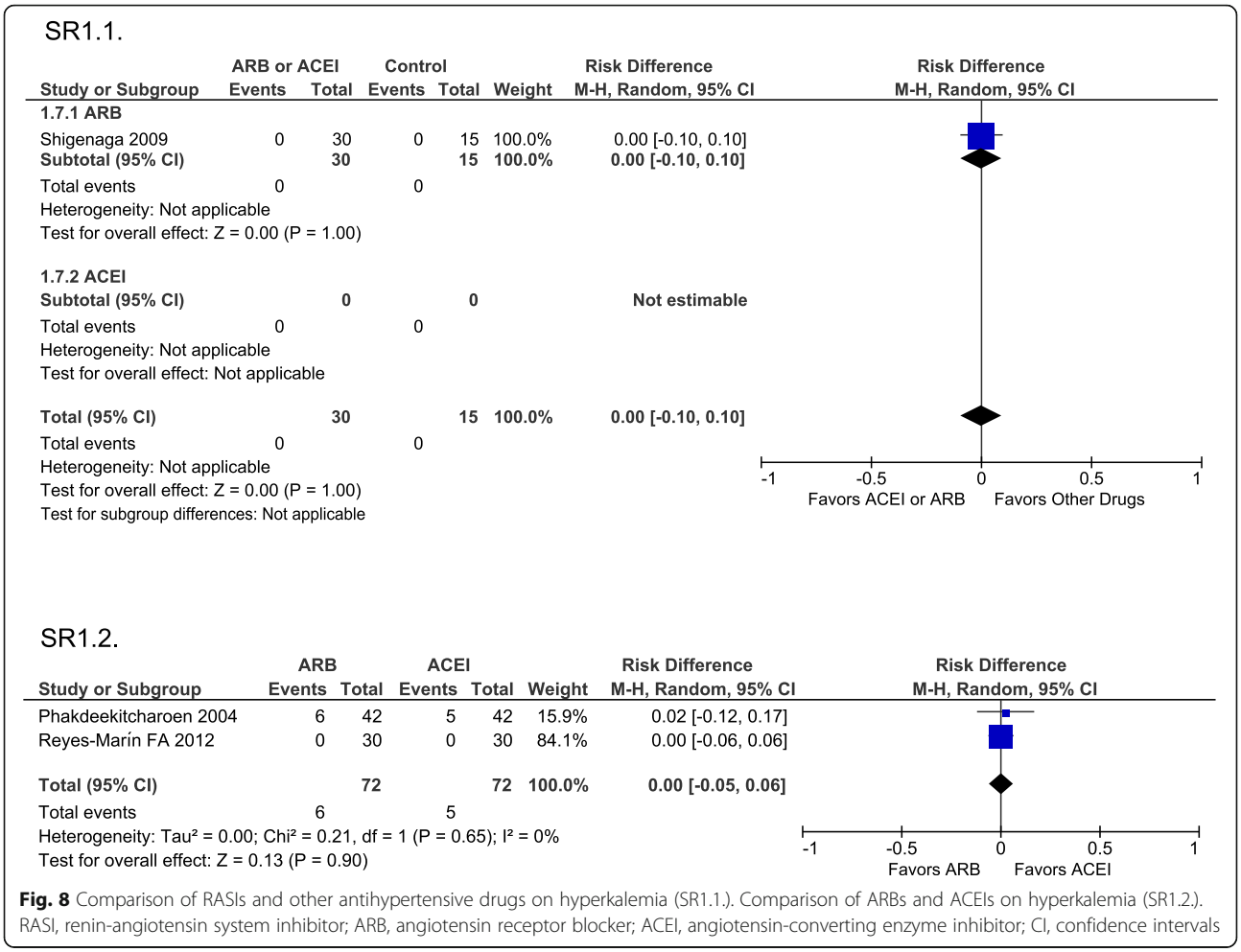

Fig. 8 Comparison of RASIs and other antihypertensive drugs on hyperkalemia (SR1.1.). Comparison of ARBs and ACEIs on hyperkalemia (SR1.2.). RASI, renin-angiotensin system inhibitor; ARB, angiotensin receptor blocker; ACEI, angiotensin-converting enzyme inhibitor; CI, confidence intervals

urine volume as an outcome representing RRF. Urine volume is one of the vital parameters by which patients can be aware of maintaining their renal function.

Several observational studies evaluated the renoprotective effects of RASIs for PD patients which, other than the RCTs included in our SR, showed contradictory results. A retrospective study from Hong Kong reported that the rate of decline of residual GFR was slower in patients who received ACEIs or ARBs [12]. However, three sizeable cohort studies from the US A and the Netherlands concluded that RASIs had no renoprotective benefits for PD patients [13, 14, 21]. The reason for the discrepancy between our findings and the trials showing no benefits of RASIs is complicated. The RCTs included in our SR had stricter patient selection criteria than the observational studies, meaning that patients' background characteristics in the RCTs and the observational studies were considerably different. Therefore, the beneficial effects of RASIs on PD patients might vary according to the patients' individual conditions.

This study has several limitations. First, the number of eligible studies investigating the effect of RASIs in PD patients was very small as we limited them to RCTs. Second, most of the outcomes were not assessed in a blinded manner. Consequently, outcomes such as mortality and technical survival might be affected by performance and detection bias, although residual renal function and urine volume might not be affected. Several past studies [2–6] indicated that preserved residual renal function or urine volume were surrogate markers of hard outcomes such as mortality or technical survival. However, the extent by which residual renal function or urine volume improves these outcomes is unclear. Third, heterogeneity of observation period, type of medicine, and patient background exist between each RCT. Finally, ACEI has different pharmacologic actions than ARB. Although this study showed no difference in primary outcomes between ACEIs and ARBs, only one RCT was eligible for most of the outcomes. Therefore, the possibility of there being different conclusions cannot be excluded. To resolve the abovementioned limitations, more extensive studies, including cohort studies, are warranted.

Conclusion

Our analysis revealed that RASIs contribute to preserving GFR and urine volume in PD patients. As the number of study participants was small, further studies with a larger sample size are required.

Supplementary information

Supplementary information accompanies this paper at (https://doi.org/10.1186/s41100-019-0238-3).

Additional file 1: Search strategy.

Additional file 2: Summary of findings for ARB or ACEI versus conventional therapy (SR1.1.) in PD patients.

Additional file 3: Summary of findings for ARB versus ACEI (SR1.2.) in PD patients.

Abbreviations

ACEI: Angiotensin-converting enzyme inhibitor; ARB: Angiotensin receptor blocker; CI: Confidence interval; CKD: Chronic kidney disease; CPGs: Clinical practice guidelines; ESKD: End-stage kidney disease; GFR: Glomerular filtration rate; HD: Hemodialysis; MD: Mean difference; PD: Peritoneal dialysis; PRISMA: Preferred Reporting Items for Systematic Review and Meta-Analyses; PROSPERO: International Prospective Register of Systematic Reviews; RAS: Renin-angiotensin system; RASI: Renin-angiotensin system inhibitor; RCT: Randomized controlled trials; RD: Risk difference; RR: Risk ratio; RRF: Residual renal function; SR: Systematic review

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Authors' contributions

MI, YS, YK, KY, MR, YI, and HY contributed to the research idea and study design. MI, YS, YK, and KY contributed to the data acquisition and the quality assessment of the risk of bias. MI, YS, and HY contributed to the data analysis/interpretation. HT, YT, and HY contributed to the supervision in all steps of the systematic review. MI and YS wrote the first draft of the manuscript. All authors interpreted the data analysis and critically revised the manuscript.

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Availability of data and materials

All datasets analyzed in this systematic review are referenced in the manuscript.

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable

Competing interests

The authors declare that they have no competing interests.

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