Serum potassium changes due to concomitant ACEI/ARB and spironolactone therapy: A systematic review and meta-analysis

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Purpose. To provide evidence of serum potassium changes in individuals taking angiotensin-converting enzyme inhibitors (ACEIs) and/or angiotensin receptor blockers (ARBs) concomitantly with spironolactone compared to ACEI/ARB therapy alone.

Methods. PubMed, Embase, Scopus, and Web of Science were searched for studies including exposure to both spironolactone and ACEI/ARB therapy compared to ACEI/ARB therapy alone. The primary outcome was serum potassium change over time. Main effects were calculated to estimate average treatment effect using random effects models. Heterogeneity was assessed using Cochran's Q and I^2. Risk of bias was assessed using the revised Cochrane risk of bias tool.

Results. From the total of 1,225 articles identified, 20 randomized controlled studies were included in the meta-analysis. The spironolactone plus ACEI/ARB group included 570 patients, while the ACEI/ARB group included 547 patients. Treatment with spironolactone and ACEI/ARB combination therapy compared to ACEI/ARB therapy alone increased the mean serum potassium concentration by 0.19 mEq/L (95% CI, 0.12-0.26 mEq/L), with intermediate heterogeneity across studies (Q statistic = 46.5, P = 0.004; I^2 = 59). Sensitivity analyses showed that the direction and magnitude of this outcome did not change with the exclusion of individual studies, indicating a high level of reliability. Reporting risk of bias was low for 16 studies (80%), unclear for 3 studies (15%) and high for 1 study (5%).

Conclusion. Treatment with spironolactone in combination with ACEI/ARB therapy increases the mean serum potassium concentration by less than 0.20 mEq/L compared to ACEI/ARB therapy alone. However, serum potassium and renal function must be monitored in patients starting combination therapy to avoid changes in serum potassium that could lead to hyperkalemia.

Keywords: angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, hyperkalemia, spironolactone

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Inhibition of the renin-angiotensin-aldosterone system (RAAS) is a common approach in the treatment of high blood pressure and cardiovascular and renal diseases. The combination of 2 or more RAAS inhibitors (ie, angiotensin-converting enzyme inhibitors [ACEIs], angiotensin receptor blockers [ARBs], aldosterone receptor antagonists, and direct renin inhibitors) can trigger disturbances in serum potassium levels.[1] Because these medications are often used in combination for clinical benefit, prescribers routinely face the challenge of responding appropriately to clinical decision support (CDS) alerts about potentially life-threatening drug-drug interactions (DDIs). This is particularly true in patients with comorbidities and those taking many medications. Computerized physician order entry in combination with CDS offers an opportunity to detect potential DDIs and alert prescribing physicians.[2] However, current CDS systems lack specificity about which patients should not receive combination therapy, and alert fatigue has been identified as a major limitation of these systems in clinical practice.[3]

One strategy for making a CDS system more reliable in the context of RAAS inhibitor use is to explore evidence that could be incorporated into the system so that clinicians are notified about drug combinations that can potentially cause hyperkalemia. High levels of potassium may cause life-threatening cardiac arrhythmias, muscle weakness, or paralysis. Symptoms usually develop at serum concentrations higher than 6.5 to 7.0 mEq/L, with rate of change being more important than serum level.[4]

Aldosterone is a fundamental mineralocorticoid involved in the maintenance of water and electrolyte balance. Its secretion is primarily controlled by the renin-angiotensin system through angiotensin II.[5] Aldosterone is responsible for cardiac remodeling in heart failure and is a key component of inflammation and fibrosis leading to renal complications.[6] The nonselective aldosterone blocker spironolactone, given in doses of 25 to 50 mg per day alone and concomitantly with ACEIs and/or ARBs, has been investigated in patients with diabetes mellitus, microalbuminuria,

or nephrotic albuminuria to slow chronic kidney disease progression and protect against cardiac fibrosis and left ventricular dysfunction.[7,8] However, all of these agents—whether used separately or concomitantly—have the potential to cause hyperkalemia. The aim of the study described here was to systematically evaluate the evidence concerning changes in serum potassium in individuals taking ACEIs and/or ARBs and spironolactone concomitantly compared to those taking ACEIs and/or ARBs alone.

Methods

We conducted a systematic literature review and meta-analysis of studies evaluating the occurrence of hyperkalemia among individuals exposed to both ACEI/ARB and spironolactone therapy versus ACEI/ARB therapy alone. The null hypothesis of the study was that exposure to the combination of ACEI/ARB therapy and spironolactone does not increase the risk of hyperkalemia relative to ACEI/ARB therapy alone.

Study identification. A systematic review was conducted using university-affiliated access to PubMed, Embase, Scopus, and Web of Science databases. The following search terms (and combinations thereof) were used: *spironolactone, angiotensin-converting inhibitors, ACE inhibitor, ACEI, angiotensin receptor blocker, angiotensin II receptor blockers, ARB, potassium, serum potassium,* and *hyperkalemia*. Articles from repository outlines of previous reviews and protocols were also accessed. We used text words and health-related word variants of "potassium" and combined them with generic drug names for ACEIs and ARBs. These terms were additionally screened in the database to include word variants and generic drug names of either "ACE Inhibitor" or "angiotensin receptor blocker." We additionally searched the reference lists for studies not initially found in the search. No restrictions on publication date or language were applied, in accordance with best practices for conducting thorough meta-analyses.[9]

Study selection and outcomes measures. Two researchers identified potential studies and a third researcher acted as referee in cases of disagreement. A study was included if all of the following criteria were met: (1) it was a randomized controlled trial providing data of individuals exposed to ACEI/ARB therapy alone and those receiving combination ACEI/ARB and spironolactone therapy; (2) it reported the duration of concomitant use of combination therapy; (3) it reported the number of patients experiencing hyperkalemia (as defined by International Classification of Diseases [ICD-9 or ICD-10] codes) as an outcome; and (4) the authors reported a serum potassium level in both groups at the beginning of the study, during concomitant use, and at the end of the study, allowing for a calculation of mean difference between treatment arms.

A study was excluded if it did not report original findings (eg, a review article) or if it did not provide data on changes in serum potassium. For each study, year and country of publication, number of patients by treatment arm, age range of participants, duration of drug therapy, and serum potassium outcomes were extracted. For each study, the authors examined characteristics of exposed and unexposed subjects to identify potential confounding variables.

Risk of bias. Risk of Bias 2 (the RoB 2 tool), a revised Cochrane risk of bias tool for randomized trials, was utilized to assess risk of bias.[10] A good-quality study addresses risk of bias by comparing results to a control group and has low attrition rates and a large sample size. A fair-quality study meets a majority, but not all, of the good-quality criteria while maintaining resistance to significant bias.

Statistical analysis. Summary effects were calculated as an estimate of the mean difference in serum potassium concentration and its corresponding 95% confidence interval (CI). Two-sided *P* values of < 0.05 were considered statistically significant. In addition, a random-effects model that assumes different underlying true effects was used. Statistical heterogeneity was evaluated using the I^2 statistic, with values of 25%, 50%, and 75% representing low, intermediate, and high heterogeneity, respectively. Cochran's *Q* statistic was reported, with significant heterogeneity assumed when the *P* value of the statistic is less than 0.1 and I^2 is greater than 50%. Publication bias

was assessed by creating a funnel plot for the serum potassium mean difference using Egger's test. A lack of publication bias was defined by a symmetric funnel-shaped distribution and by a 2-tailed significance level of $P > 0.05$ in Egger's test. In many meta-analyses, there is large variation in the strength of the effect. To reflect this uncertainty, here we report the prediction interval to help with the clinical interpretation of the heterogeneity by valuing what true treatment effects could be anticipated in future studies.

To evaluate robustness of findings, sensitivity analyses were performed using the leave-one-out approach, through which one study at a time is iteratively removed and serum potassium mean differences recalculated; combined serum potassium mean differences that remained stable with study removal suggested that results were not driven by any single study and that similar results could be obtained after excluding that study. The meta-analysis and the corresponding graphical visualization through a forest plot were performed using R, version 3.6.1 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Study characteristics. A total of 1,225 articles were initially identified using the systematic review search criteria. A total of 527 articles were excluded due to duplication or nonhuman subjects. Six hundred ninety-eight studies were screened by title and abstract, leading to exclusion of 600 articles for reasons outlined in Figure 1. A full-text review was conducted on the remaining 98 articles; from among these, 20 reports on randomized controlled studies (1.6% of the articles initially considered) were selected to be included in the meta-analysis.[11-30] Two of the included studies were conducted in North America, 9 in Europe, 8 in Asia, and 1 in Oceania. In the intervention arms of 16 studies including a total of 392 patients, ACEI/ARB therapy in combination with 25 mg of spironolactone was used; in 2 studies with a total of 126 patients, ACEI/ARB therapy along with 20 mg of spironolactone was used; and in 2 additional studies with a total of 52 patients, a combination of ACEI/ARB therapy with 50 mg of spironolactone was used.

Serum potassium. When considering all 20 studies, we found that serum potassium increased with use of combination therapy versus ACEI/ARB therapy alone (a mean difference of 0.19 mEq/L [95% confidence interval [CI], 0.12-0.26 mEq/L]). The study had an intermediate degree of heterogeneity (Q = 46.48, P = 0.004; I^2 = 59), see Figure 2. In a second analysis, performed after the addition of an outlier study (conducted by Bianchi et al[31] and published in 2006), treatment with spironolactone in combination with ACEI/ARB therapy versus ACEI/ARB therapy alone increased the mean serum potassium concentration by 0.23 mEq/L (95% CI, 0.07-0.39 mEq/L), but the degree of heterogeneity was high (Q = 548.69, P < 0.0001; I^2 = 96).

Due to the large variation in strength of effect, a prediction interval was calculated to help with the clinical interpretation of the heterogeneity by estimating a true treatment effect that can be expected in future studies. Considering all 20 studies, the prediction interval was –0.06 to 0.44 mEq/L of serum potassium. Excluding the aforementioned study of Bianchi et al,[31] the prediction interval was –0.53 to 0.98 mEq/L of serum potassium.

In some studies, changes in serum potassium levels in the intervention and control groups, as well as the number of patients removed from different studies due to hyperkalemia (defined as serum potassium of >5.5 mEq/L), were reported. For patients in the intervention groups, the increases in serum potassium ranged from 0.02 to 0.5 mEq/L. In the control groups in 2 studies, decreases in serum potassium concentration (mean decreases of 0.02 and 0.15 mEq/L, respectively) were reported; see Table 1.

Sensitivity analysis. Results of the sensitivity analysis conducted using the leave-one-out approach are shown in Table 2. Each row displays the summary values computed when the listed study was removed from the meta-analysis. For instance, the values in the first row of data represent the summary computations of mean serum potassium change with use of spironolactone and ACEI/ARB combination therapy for 19 studies, with the study by Barr et al[11] excluded. Results show that the direction and magnitude of the combined studies did not change with the exclusion of individual studies, indicating the results have a high level of reliability.

Publication bias. A visual inspection of the funnel plots (Figure 3) shows that studies exploring the combination of spironolactone and ACEI/ARB therapy are not symmetrical, and Egger's test was significant (P = 0.008).

Risk of bias. The results of the risk of bias assessment evaluating 7 factors that can influence study results are shown in Figure 4. In general, reporting risk of bias was low for 16 studies (80%), unclear for 3 studies (15%) and high for 1 study (5%). When random sequence generation was evaluated, 16 studies (80%) had low risk of bias and 4 (20%) showed unclear risk. When allocation concealment was assessed, 12 studies (60%) were evaluated as having low risk of bias, while 7 studies (35%) had unclear risk of bias and 1 (5%) was classified as high risk. When blinding of participant and personnel and blinding for outcome assessment were assessed, 11 (55%) and 7 (35%) studies were categorized as involving low risk of those respective types of bias, and 5 studies (25%) were categorized as involving high risk of both bias types. When bias related to incomplete outcome data was evaluated, 19 studies (95%) showed low risk and 1 study (5%) showed unclear risk. For selective reporting risk, 17 studies (85%) showed low risk and 3 studies (15%) showed unclear risk. For other sources of bias, 10 studies (50%) showed low risk and 8 (40%) showed unclear risk; in 2 studies (10%), there was not enough information to assess risk.

Discussion

This study sought to evaluate changes in serum potassium in patients receiving a combination of ACEI and/or ARB therapy and spironolactone compared to ACEI/ARB therapy alone. The principal findings were that the addition of spironolactone increased serum potassium levels by a mean of 0.19 mEq/L compared to ACEI/ARB therapy alone. This is a modest amount, but patients taking this combination should be monitored for the potential for hyperkalemia because serum potassium can change over time. In our meta-analysis, half of the included studies reported that patients were withdrawn from study participation due to the occurrence of an acute hyperkalemia event (defined as serum potassium of >5.5 mEq/L). In total, 27 patients were withdrawn for this

reason and were therefore excluded from the included studies. Data for these patients did not contribute to findings for specific studies and therefore to the findings from the meta-analysis. Despite this limitation, the overall findings of this study are that minimal changes in serum potassium occur in the vast majority of patients when exposed to the combination of these medications.

Hyperkalemia is usually defined as having a serum potassium level greater than 5 mEq/L (some definitions specify a threshold of 5.5 mEq/L). Hyperkalemia can result from many underlying conditions, especially chronic kidney disease. Potassium levels greater than 6.5 mEq/L (or lower levels in association with electrocardiogram changes) are considered severe and require urgent treatment.[32,33] Additionally, in patients receiving concomitant ACEI/ARB and spironolactone therapy (even those with normal renal function), it is highly recommended to measure potassium levels before initiating treatment, after 1 week of therapy, and after dose increases.[34] Some landmark studies have reported a risk of hyperkalemia with the combined use of spironolactone and ACEI/ARB therapy. In the RALES study,[35] the incidence of hyperkalemia was associated with higher doses of spironolactone, but the study did not report renal function for those patients. However, the RALES study was not included in our analysis because the results from that study were not reported at the level required by the meta-analysis, meaning that serum potassium levels were not reported.

With respect to clinical benefit, the RALES study[35] assessed the use of the combination of spironolactone and ACEI therapy to decrease the risk of mortality in patients with severe heart failure. This study showed a positive impact on patient outcomes, specifically because spironolactone acts as a cardioprotective agent due to its mechanism of action of blocking aldosterone, which has been associated with myocardial and vascular fibrosis, direct vascular injury, and baroreceptor dysfunction.[35]

Using spironolactone in combination with ACEI/ARB therapy should not be contraindicated. A retrospective observational study found that adding spironolactone to ACEI or ARB therapy may

produce a benefit in patients with persisting proteinuria who have an estimated glomerular filtration rate (eGFR) of ≥60 mL/min/1.73 m^2, a ratio of urine albumin to creatinine of ≥1 (g/g Cr), or plasma aldosterone of >80 pg/mL.[36] Hyperkalemia (defined as a potassium concentration of ≥5.5 mEq/L) occurred in 51 of 304 patients(16.7%) who were treated using gastrointestinal ion exchange, and 9 of the 137 patients with an eGFR of <60 mL/min/1.73 m^2 (6.5%) developed severe hyperkalemia.

In addition to being used in patients with heart failure, spironolactone has also been used in patients with resistant hypertension; however, its use must be closely monitored in patients with chronic kidney disease due to the possibility of hyperkalemia. A phase 2 multicenter clinical trial[37] suggested the use of the potassium binder patiromer in patients using spironolactone who have chronic kidney disease; however, the cost and risk of other DDIs with patiromer may make less-expensive initial approaches to control chronic hyperkalemia (eg, close patient follow-up) preferable.

Hyperkalemia is uncommon but not necessarily rare. Renal function is a key component of potassium homeostasis. A study in a large integrated rural healthcare system in central and northeastern Pennsylvania sought to evaluate the frequency and patterns of hyperkalemia and its management, including frequency of potassium monitoring and risk of hyperkalemia associated with certain medication classes. The main findings of this study were that hyperkalemia is a transient phenomenon that increases with lower eGFR (ie, <30 mL/min per 1.73 m^2); among antihypertensive medications, ACEIs were the most strongly associated with serum potassium levels of >5.5 mEq/L (hazard ratio [HR], 1.58 [95% CI, 1.45-1.71]; $P < 0.001$). Potassium-sparing diuretics and ARBs were weakly associated with serum potassium levels of >5.5 mEq/L but not to a statistically significant degree (HRs of 1.13 [95% CI, 0.96-1.34; $P = 0.141$] and 1.10 [95% CI, 0.97-1.25; $P = 0.131$], respectively). Use of a combination of ACEI/ARB therapy and potassium-sparing diuretic medications increased the risk of hyperkalemia, which was controlled by dose reduction of either or both medications.[38]

Other studies have found that the risk of hyperkalemia is increased with the combination of spironolactone and ACEI/ARB therapy. A meta-analysis of 16 studies exploring the effect of a mineralocorticoid receptor antagonist and ACEI/ARB therapy found a significant increase in the relative risk (RR) of developing hyperkalemia between patients receiving the combination and monotherapy (RR, 4.02; 95% CI, 2.48-6.52). When the influence of the individual mineralocorticoid antagonist was explored, the RR of hyperkalemia increased by over 4-fold among patients taking spironolactone (RR, 4.58; 95% CI, 2.60-8.08), while there was no difference in RR in patients treated with finerenone (RR, 2.22; 95% CI, 0.13-38.13) compared with ACEI/ARB therapy alone.[39]

While patients taking the combination of potassium-sparing diuretics and ACEIs or ARBs are at risk for hyperkalemia, the risk is not consistent across all patients. Computerized CDS can be utilized to link patient data and pharmacy data and provide warnings to clinicians about this and other potential DDIs in situations where patients are at risk for hyperkalemia.[40] In particular, the CDS system can be programmed to provide warnings to clinicians when the patient has a potassium level that puts them at risk of developing hyperkalemia. For example, an investigation conducted at a University of Illinois hospital alerted clinicians about anomalous serum potassium levels at the time of prescribing ACEIs or ARBs, potassium supplementation, or potassium-sparing diuretics, with asynchronous CDS alerts notifying clinicians when abnormal potassium results were found in patients still on the medications.[41] The main results showed that clinicians agreed with synchronous CDS alerts in managing hyperkalemia in inpatient settings. On the other hand, asynchronous alerts were not demonstrated to have an impact on clinicians' actions. The system also offered a daily report that was effective in detecting potentially risky situations that had not been corrected after the real-time asynchronous alert; however, the report's impact on changing clinicians' practices and improving patient outcomes was difficult to establish.[41]

Other randomized controlled trials have sought to use CDS to improve management of serum potassium changes due to DDIs; however, a highly patient-specific CDS alert was shown to have little impact on the management of potentially serum potassium–increasing DDIs.[42]

Nevertheless, these results showed it is necessary to contextualize and improve the performance of CDS to ensure safety in hospitalized patients at risk for changes in serum potassium due to DDIs. Some electronic health record (EHR) systems have implemented decision rules to reduce alerts for this combination based on the presence of a recent serum potassium level. The alert triggered only when the serum potassium concentration exceeded a preset value. Our findings suggest this might be reasonable for many patients and avoid inappropriate alerting by evaluating the patient record in the EHR for a recent serum potassium level. On the other hand, in patients with decreased renal function or with other comorbidities associated with increased serum potassium concentrations, the potential for hyperkalemia should be of concern and patients monitored appropriately.

Our study had several limitations that should be considered when interpreting the results. Due to a lack of subject-level data, our study could not adjust results for other covariates that could potentially affect serum potassium, such as patient adherence to therapy, demographics, comorbidities, and renal function.

Eleven studies reported that a total of 27 patients were excluded from trials because they showed different levels of hyperkalemia that were not possible to control with the use of corrective measures (eg, adjusting the spironolactone dose); this could have led us to underrate our estimation of serum potassium values. Also, pooled data from trials with varying durations, doses and combinations of drugs, and patient characteristics are subject to bias. Our analysis of serum potassium concentration was also susceptible to several biases because the methods for collecting data varied across the studies. When we conducted the study search, we were focused on reports of concomitant use of spironolactone with ACE/ARB therapy and the effect of this combination on serum potassium levels. Seventeen studies reported the use of 25 mg of spironolactone, 2 studies used 50 mg of spironolactone, and 2 used 20 mg of spironolactone. These differences in doses could have an impact on changes in serum potassium levels and would be necessary to investigate in future studies.

Despite these limitations, our study provides a comprehensive analysis evaluating changes in serum potassium due to the utilization of a combination of potential serum potassium modifiers. Sensitivity analyses using the leave-one-out approach showed that estimates of changes in serum potassium in patients receiving spironolactone and ACEI/ARB combination therapy do not appear to be driven by a single study. Publication bias was observed through Egger's test and the visual funnel plot assessment. Risk of bias assessment showed that, in general, studies included in this meta-analysis had a low risk of bias.

Conclusion

Our analysis suggests that treatment with spironolactone combined with ACEI/ARB therapy produces a modest but significant increase in serum potassium compared to ACEI/ARB therapy alone. Serum potassium and renal function must be monitored in patients starting combination therapy to avoid the occurrence of hyperkalemia.

Disclosures

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Figure 1. Flow chart of study selection according to PRISMA guidelines.

Figure 2. Forest plot of randomized controlled trials of combination ACEI/ARB and spironolactone versus ACEI/ARB therapy alone: effect on serum potassium.

Figure 3. Serum potassium mean differences for the combination of spironolactone and ACEI/ARB therapy.

Figure 4. Assessment of risk of bias of included studies.

Key Points

- Changes in serum potassium levels need to be assessed in patients taking angiotensin-converting enzyme inhibitors (ACEIs) and/or angiotensin receptor blockers (ARBs) concomitantly with spironolactone, especially in those starting combination therapy.
- The lowest effective doses of spironolactone and ACEIs and/or ARBs should be used if combination therapy is necessary.
- Serum potassium and renal function should be frequently monitored and treatment reconsidered if hyperkalemia occurs.

Table 1. Summary of Studies Reporting Serum Potassium Levels With Use of ACEI/ARB Therapy Alone or in Combination With Spironolactone

Author	Spironolactone Dose, mg	ACEI/ARB Dose (mg)	Disease Focus	Study Duration, wk	eGFR, mean (SD), mL/min/1.73m^2	Serum Potassium Concentration, Mean (SD), mEq/L		First Reported Change in Serum Potassium, Mean, mEq/L		Exclusions Due to Hyperkalemia in Intervention Group[a]
						Intervention Group	Control Group	Intervention Group	Control Group	
Barr[11]	50	NR	CHF	8	Intervention: 74 (2) Control: 75 (15)	4.63 (0.4 *n* = 28	4.43 (0.50) *n* = 14	+0.45	0.02	4 patients (K+ >5.5 mEq/L)
Rossing[12]	25	1. ENL (40) 2. TRAN (4) 3. IRB (300) + RAM (10) 4. IRB (300) + ENL (40) 5. LST (100) + ENL (40)	DNP	8	Intervention: 71 (6) Control: 74 (6)	4.30 (0.40 *n* = 20	4.00 (0.45) *n* = 20	NR	NR	1 patient (K+ of 7.1 mEq/L)
Schjoedt[13]	25	1. ENL (40, 20, 15) 2. RAM (10) 3. LIS (40) 4. CAP (100) 5. LST (100)	DNP	8	Intervention: 81 (6)[b] Control: 85 (6)[b]	4.20 (0.45 *n* = 20	4.00 (0.45) *n* = 20	NR	NR	2 patients (K+ of 5.7 mEq/L)

Chrysostomou[14]	25	1. RAM (5) 2. IRB (150)	DNP	26	Intervention: 60 (8) Control: 82 (20)	4.90 (0.89 *n* = 11	4.4 (0.48) *n* = 10	+0.4	+0.2	NR
Schjoedt[15]	25	1. ENL (40, 20) 2. TRAN (4) 3. LST (100, 150) 4. IRB (300) 5. VAL (160) 6. LIS (20) + IRB (300)	DNP	8	Intervention: 62(2)[b]; Control: 64(2)[b]	4.30 (0.40 *n* = 20	4.10 (0.45) *n* = 20	NR	NR	NR
van den Meiracker[16]	25	NR	DNP	52	Intervention:74 (9) Control: 59 (8)	4.60 (0.30 *n* = 24	4.40 (0.30) *n* = 28	+0.5	+0.2	5 patients
Furumatsu[17]	25	ENL (5) + LST (50)	DNP	52	Intervention: 79 (10) Control: 69(8)	4.43 (0.08 *n* = 16	4.22 (0.11) *n* = 16	+0.29	+0.16	NR
Saklayen[18]	50	LIS (40) LST (50)	DNP	30	Intervention: 54 (20) Control: 55 (23)	4.64 (0.55 *n* = 24	4.28 (0.47) *n* = 24	+0.35	NR	NR
Tylicki[19]	25	NR	CKD	8	Intervention: 107 (14)[c] Control: 104 (16)[c]	4.81 (0.12 *n* = 9	4.66 (0.09) *n* = 9	+0.31	NR	NR
Guney[20]	25	NR	CKD	26	Intervention: 58 (24) Control: 59 (39)	4.69 (0.70 *n* = 12	4.43 (0.39) *n* = 12	+0.39	–0.02	NR
Edwards[21]	25	NR	CKD	40	NR	4.60 (0.60 *n* = 56	4.40 (0.40) *n* = 56	NR	NR	1 patient (K+ of 6.8 mEq/L)
Zheng[22]	20	BEN (10)	DNP	12	NR	4.60 (1.10 *n* = 20	4.40 (0.60) *n* = 20	NR	NR	NR
Kota[23]	25	NR	DNP	12	NR	4.20 (0.90 *n* = 19	4.70 (0.50) *n* = 16	NR	NR	1 patient (K+ >5.5mEq/L)

Nielsen[24]	25	NR	DNP	8	Intervention: 78[c] Control: 72[c]	4.50 (0.46 *n* = 21	4.00 (1.37) *n* = 21	NR	NR	NR
Esteghamati[25]	25	ENL (30, 40) LST (50, 100)	DNP	78	Intervention: 67 (19) Control: 63 (21)	4.65 (0.54 *n* = 52	4.32 (0.44) *n* = 45	+0.2	NR	3 patients
Wang[26]	20	BEN (20)	CKD	16	Intervention: 66 (22) Control: 66 (24)	4.38 (0.44 *n* = 106	4.38 (0.43) *n* = 102	NR	NR	3 patients (K+ >5.8 mEq/L)
Ziaee[27]	25	ENL (25)	DNP	12	Intervention: 80 (18) Control: 83 (19)	4.40 (0.46 *n* = 29	4.16 (0.25) *n* = 31	+0.29	+0.12	NR
Makhlough[28]	25	LST (12.5)	DNP	12	Intervention: 116 (24) Control: 113 (26)	4.39 (0.34 *n* = 30	4.56 (0.38) *n* = 30	+0.07	+0.07	1 patient (K+ >5.5mEq/L at end of study)
van Buren[29]	25	LST (50, 100)	DNP	48	NR	5.00 (0.51 *n* = 27	4.50 (0.38) *n* = 27	+0.5	+0.2	2 patients
Kato[30]	25	NR	DNP	8	NR	4.51 (0.34 *n* = 26	4.27 (0.42) *n* = 26	+0.21	–0.15	NR
Bianchi[31]	25	NR	CKD	12	Intervention: 59 (3) Control: 56 (2)	5.10 (0.09 *n* = 83	4.40 (0.07) *n* = 82	+0.90	+0.10	4 patients (K+ >5.5 mEq/L)

Abbreviations: BEN, benazepril; CAP, captopril; CHF, congestive heart failure; CKD, chronic kidney disease; DNP, diabetic nephropathy; ENL, enalapril; IRB, irbesartan; K+, potassium; LIS, lisinopril; LST, losartan; NR, not reported; RAM, ramipril; TRAN, trandopril; VAL, valsartan.

[a]Individual K+ level or threshold value for exclusion reported as available.

[b]Expressed as mean and standard error.

[c]Crossover trial.

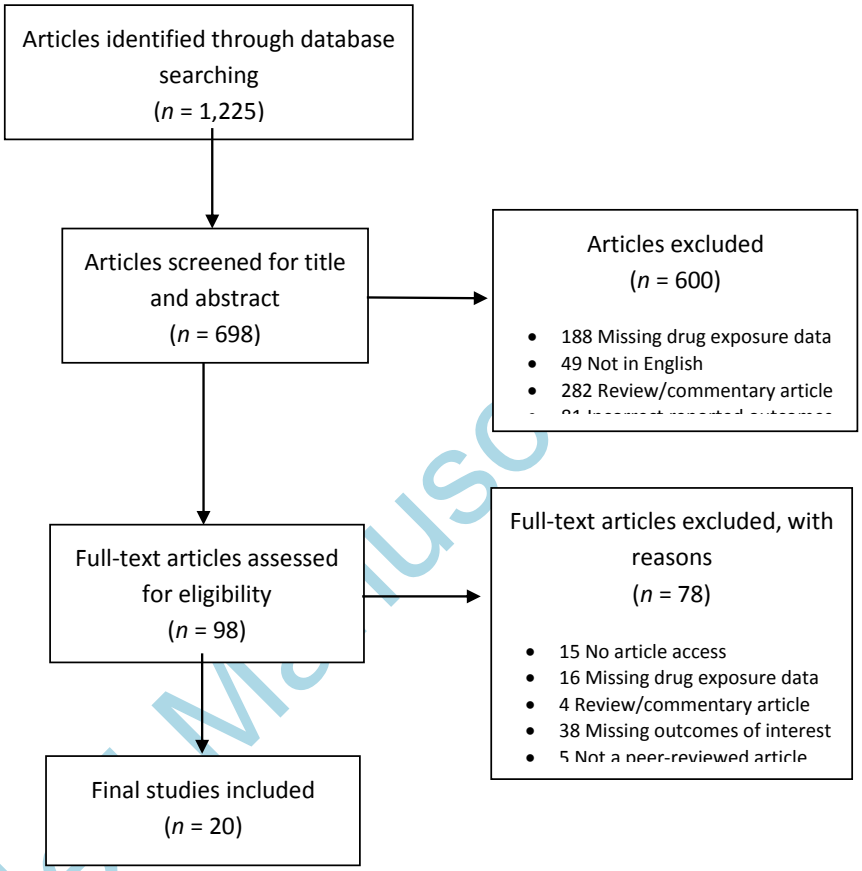
Table 2. Results of Sensitivity Analysis

Study Omitted	Effect (95% CI)[a]
Barr[11]	0.18 (0.14-0.22)
Rossing[12]	0.17 (0.14-0.21)
Schjoedt[13]	0.18 (0.14-0.22)
Chrysostomou[14]	0.18 (0.14-0.21)
Schjoedt[15]	0.18 (0.14-0.22)
van den Meiracker[16]	0.18 (0.14-0.21)
Furumatsu[17]	0.16 (0.11-0.21)
Saklayen[18]	0.17 (0.13-0.21)
Tylicki[19]	0.18 (0.14-0.22)
Guney[20]	0.18 (0.14-0.21)
Edwards[21]	0.18 (0.14-0.21)
Zheng[22]	0.18 (0.14-0.22)
Kota[23]	0.18 (0.14-0.22)
Nielsen[24]	0.18 (0.14-0.21)
Esteghamati[25]	0.17 (0.13-0.21)
Wang[26]	0.20 (0.16-0.24)
Ziaee[27]	0.17 (0.13-0.21)
Makhlough[28]	0.19 (0.15-0.23)
van Buren[29]	0.17 (0.13-0.21)
Kato[30]	0.17 (0.13-0.21)

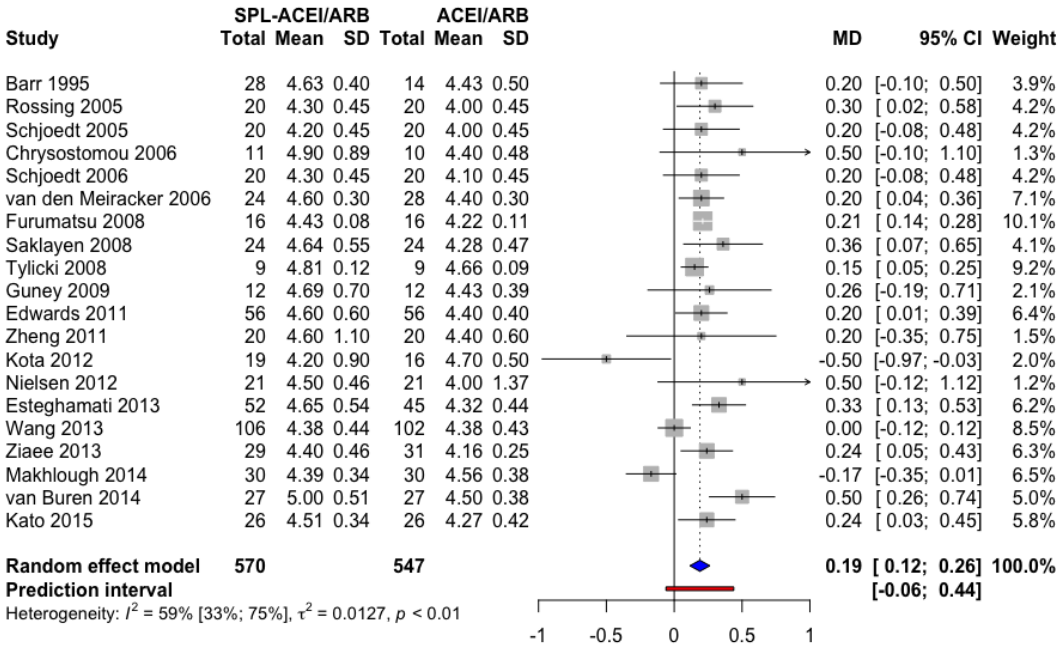
Abbreviation: CI, confidence interval.

[a]Estimated change (mEq/L) in mean serum potassium concentration.

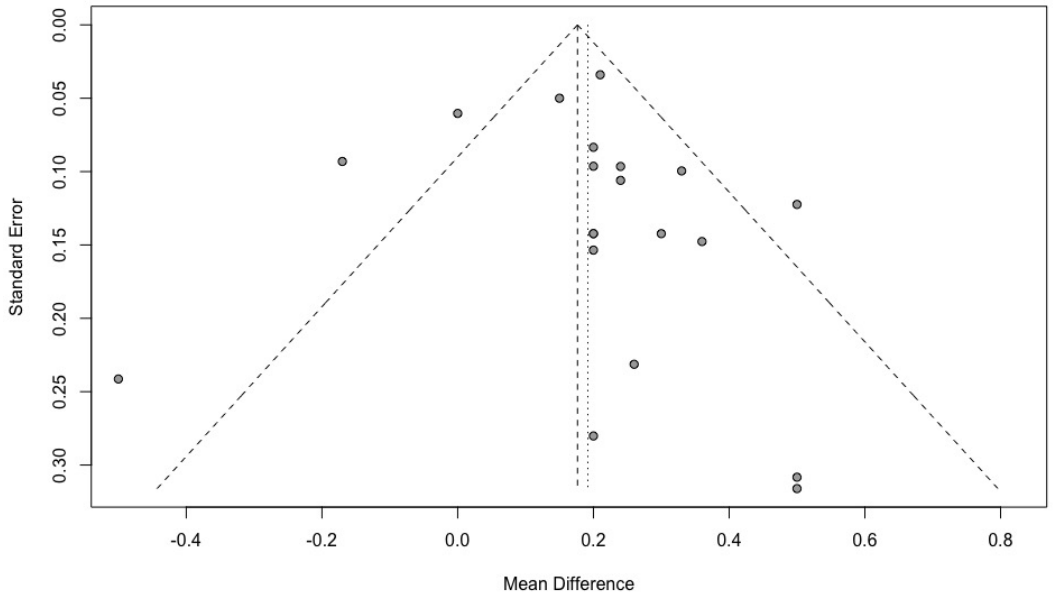
[fig 1]



[fig 2]



[fig 3]



[fig 4]