EPH196

Updated Evidence of Hyperkalemia Occurrence: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

Raduc, Andrea; Villa Zapata, Lorenzo.
Mercer University, College of Pharmacy, Atlanta, GA, USA

MERCER UNIVERSITY
COLLEGE OF PHARMACY

Background

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.

Objective

To provide updated evidence of serum potassium changes in patients treated with angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) taken concomitantly with spironolactone compared to ACEI/ARB therapy alone.

Methods

A search of PubMed, Embase, Scopus, and Web of Science identified studies including patients receiving both spironolactone and ACEI or ARB therapy compared to ACEI/ARB therapy alone.

Mean differences of serum potassium change over time were calculated for each study to estimate an average treatment effect using random effects models.

Heterogeneity was assessed using Cochran's Q and I^2.

Uncertainty was reported using a prediction interval.

Statistical analyses were performed using R, version 4.2.2.

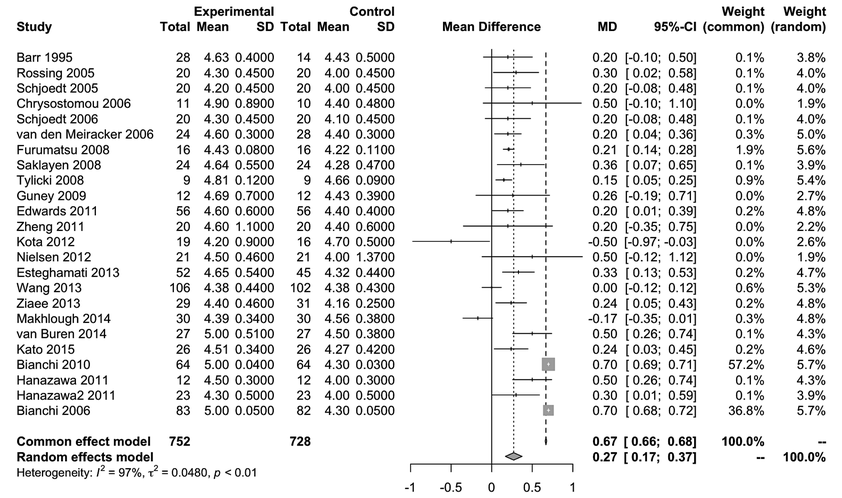
Results

- Of the initial articles identified, 24 randomized controlled studies were included in the meta-analysis, including 752 patients receiving spironolactone (20-50mg) plus ACEI/ARB and 728 patients receiving ACEI/ARB alone.
- Patients receiving spironolactone and ACEI/ARB had a mean serum potassium concentration that was 0.27 mEq/L higher (95% CI: 0.17-0.37 mEq/L) than those receiving ACEI/ARB alone.
- Heterogeneity was high across studies (tau2: 0.0480, [0.0226 to 0.1025]; I2: 96.8% [96.0% to 97.4%]; Q statistic= 719.84, p-value < 0.0001).
- A predicted interval of -0.20 to 0.74 was calculated to help clinicians interpret the value of the treatment effect.

Table 1. Summary of studies reporting serum potassium levels with the use of ACEI/ARB therapy alone or in combination with spironolactone.

Author	Year	SPL-ACEI/ARB	Mean	SD	ACEI/ARB	Mean	SD	Spironolactone Dose
Barr	1995	28	4.63	0.40	14	4.43	0.50	50mg/d
Rossing	2005	20	4.30	0.45	20	4.00	0.45	25mg/d
Schjoedt	2005	20	4.20	0.45	20	4.00	0.45	25mg/d
Bianchi	2006	83	5.00	0.05	82	4.30	0.05	25mg/d
Chrysostomou	2006	11	4.90	0.89	10	4.40	0.48	25mg/d
Schjoedt	2006	20	4.30	0.45	20	4.10	0.45	25mg/d
van den Meiracker	2006	24	4.60	0.30	28	4.40	0.30	25-50mg/d
Furumatsu	2008	16	4.43	0.08	16	4.22	0.11	25mg/d
Saklayen	2008	24	4.64	0.55	24	4.28	0.47	25mg/d
Tylicki	2008	9	4.81	0.12	9	4.66	0.09	25mg/d
Guney	2009	12	4.69	0.70	12	4.43	0.39	25mg/d
Bianchi	2010	64	5.00	0.04	64	4.30	0.03	25mg/d
Edwards	2011	56	4.60	0.60	56	4.40	0.40	25mg/d
Hanazawa	2011	12	4.50	0.30	12	4.00	0.30	25mg/d
Hanazawa2	2011	23	4.30	0.50	23	4.00	0.50	25mg/d
Zheng	2011	20	4.60	1.10	20	4.40	0.60	20mg/d
Kota	2012	19	4.20	0.90	16	4.70	0.50	25mg/d
Nielsen	2012	21	4.50	0.46	21	4.00	1.37	25mg/d
Esteghamati	2013	52	4.65	0.54	45	4.32	0.44	25mg/d
Wang	2013	106	4.38	0.44	102	4.38	0.43	20mg/d
Ziaee	2013	29	4.40	0.46	31	4.16	0.25	25mg/d
Makhlough	2014	30	4.39	0.34	30	4.56	0.38	25mg/d
van Buren	2014	27	5.00	0.51	27	4.50	0.38	25mg/d
Kato	2015	26	4.51	0.34	26	4.27	0.42	25mg/d

Figure 1. Forest plot of randomized controlled trials of combination ACEI/ARB and spironolactone versus ACEI/ARB therapy alone: effect on serum potassium.



- A second meta-analysis of 20 studies including 574 patients receiving 25 mg of spironolactone plus ACEI/ARB and 564 patients receiving ACEI/ARB alone showed a larger mean difference in potassium concentration of 0.30 mEq/L (95% CI, 0.18 to 0.41 mEq/L).
- The heterogeneity was also high (tau2: 0.0521, [0.024 to 0.129]; I2:96.6% [95.6% to 97.3%]), and the prediction interval was -0.20 to 0.79.

Conclusion

Patients treated with spironolactone and ACEI/ARB have higher mean serum potassium concentrations than those receiving ACEI/ARB therapy alone.

We recommend monitoring of serum potassium and renal function in patients starting combination therapy to avoid potential hyperkalemia.

References

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