APPENDIX A. Search strategies used in this systematic review.

MEDLINE (via PUBMED)

#1	hyperkalemia[TIAB] OR hyperkalaemia[TIAB] OR hyperpotassemia[TIAB] OR hyperkalemia[MESH]
#2	“calcium gluconate”[TIAB] OR “calcium gluconate”[MESH] OR “calcium chloride”[TIAB] OR “calcium chloride”[MESH] OR “sodium bicarbonate”[TIAB] OR “insulin plus glucose”[TIAB] OR “insulin-glucose”[TIAB] OR “insulin plus dextrose”[TIAB] OR “insulin-dextrose”[TIAB] OR fenoterol[TIAB] OR fenoterol[MESH] OR salbutamol[TIAB] OR albuterol[TIAB] OR albuterol[MESH] OR furosemide[TIAB] OR furosemide[MESH] OR bumetanide[TIAB] OR bumetanide[MESH] OR “potassium binder”[TIAB] OR “potassium-binding”[TIAB] OR “potassium-lowering”[TIAB] OR “Polystyrene Sulfonate”[TIAB] OR Kayexalate[TIAB] OR patiromer[TIAB] OR veltassa[TIAB] OR “sodium zirconium cyclosilicate”[TIAB] OR “ZS-9”[TIAB] OR fludrocortisone[TIAB] OR hydrocortisone[TIAB] OR hydrocortisone[MESH] OR aminophylline[TIAB] OR aminophylline[MESH]
#3	(clinical[TIAB] AND trial[TIAB]) OR (clinical trials as topic[MH] OR clinical trial[PT] OR random*[TIAB] OR random allocation[MH] OR therapeutic use[MESH Subheading] OR ("Observational Study[PT] OR case-control[TIAB] OR "Case-Control Studies"[MESH] OR case-comparison[TIAB] OR case-compeer[TIAB] OR case-base[TIAB] OR retrospective[TIAB] OR cohort[TIAB] OR "Cohort Studies"[MESH] OR concurrent[TIAB] OR longitudinal[TIAB] OR observational[TIAB]) NOT (systematic review*[TIAB] OR review[PT] OR meta-analysis[PT] OR meta-analysis[TIAB] OR letter[PT] OR newspaper article[PT] OR comment[PT])

#1 AND #2 AND #3

THE COCHRANE LIBRARY (Trials)

#1	hyperkalemia:ti,ab,kw or hyperkalaemia:ti,ab,kw or hyperpotassemia:ti,ab,kw or [mh hyperkalemia]
#2	"calcium gluconate":ti,ab,kw or [mh "calcium gluconate"] or "calcium chloride":ti,ab,kw or [mh "calcium chloride"] or "sodium bicarbonate":ti,ab,kw or "insulin plus glucose":ti,ab,kw or "insulin-glucose":ti,ab,kw or "insulin plus dextrose":ti,ab,kw or "insulin-dextrose":ti,ab,kw or fenoterol:ti,ab,kw or [mh fenoterol] or salbutamol:ti,ab,kw or albuterol:ti,ab,kw or [mh albuterol] or furosemide:ti,ab,kw or [mh furosemide] or bumetanide:ti,ab,kw or [mh bumetanide] or "potassium binder":ti,ab,kw or "potassium-binding":ti,ab,kw or "potassium-lowering":ti,ab,kw or "Polystyrene Sulfonate":ti,ab,kw or Kayexalate:ti,ab,kw or patiromer:ti,ab,kw or veltassa:ti,ab,kw or "sodium zirconium cyclosilicate":ti,ab,kw or "ZS-9":ti,ab,kw or fludrocortisone:ti,ab,kw or hydrocortisone:ti,ab,kw or [mh hydrocortisone] or aminophylline:ti,ab,kw or [mh aminophylline]

#1 AND #2

LILACS (via BIREME)

(tw:(hyperkalemia or hyperkalaemia or hyperpotassemia)) AND (tw:("calcium gluconate" or "calcium chloride" or "sodium bicarbonate" or "insulin plus glucose" or "insulin-glucose" or "insulin plus dextrose" or "insulin-dextrose" or fenoterol or salbutamol or albuterol or furosemide or bumetanide or "potassium binder" or "potassium-binding" or "potassium-lowering" or "Polystyrene Sulfonate" or Kayexalate or patiromer or veltassa or "sodium zirconium cyclosilicate" or "ZS-9" or fludrocortisone or hydrocortisone or aminophylline))

APPENDIX B. Excluded studies.

They did not assess patients with hyperkalemia (n = 8)
1. Allon M, Takeshian A, Shanklin N. Effect of insulin-plus-glucose infusion with or without epinephrine on fasting hyperkalemia. Kidney Int. 1993/01/01. 1993;43(1):212–7.
2. Allon M, Shanklin N. Effect of albuterol treatment on subsequent dialytic potassium removal. Am J Kidney Dis. 1995/10/01. 1995 Oct;26(4):607–13.
3. Allon M, Shanklin N. Effect of bicarbonate administration on plasma potassium in dialysis patients: interactions with insulin and albuterol. Am J Kidney Dis. 1996/10/01. 1996 Oct;28(4):508–14.
4. Anker SD, Kosiborod M, Zannad F, Pina IL, McCullough PA, Filippatos G, et al. Maintenance of serum potassium with sodium zirconium cyclosilicate (ZS-9) in heart failure patients: results from a phase 3 randomized, double-blind, placebo-controlled trial. Eur J Hear Fail. 2015/05/27. 2015;17(10):1050–6.
5. Batterink J, Lin J, Au-Yeung SH, Cessford T. Effectiveness of Sodium Polystyrene Sulfonate for Short-Term Treatment of Hyperkalemia. Can J Hosp Pharm. 2015/09/04. 2015;68(4):296–303.
6. Pancu D, LaFlamme M, Evans E, Reed J. Levalbuterol is as effective as racemic albuterol in lowering serum potassium. J Emerg Med. 2003/07/17. 2003;25(1):13–6.
7. Pitt B, Anker SD, Bushinsky DA, Kitzman DW, Zannad F, Huang IZ. Evaluation of the efficacy and safety of RLY5016, a polymeric potassium binder, in a double-blind, placebo-controlled study in patients with chronic heart failure (the PEARL-HF) trial. Eur Hear J. 2011/01/07. 2011;32(7):820–8.
8. Pitt B, Bakris GL, Weir MR, Freeman MW, Lainscak M, Mayo MR, Garza D, Zawadzki R, Berman L, Bushinsky DA. Long-term effects of patiromer for hyperkalaemia treatment in patients with mild heart failure and diabetic nephropathy on angiotensin-converting enzymes/angiotensin receptor blockers: results from AMETHYST-DN. ESC Heart Fail. 2018;5(4):592-

602.

They did not compare different interventions during all the study or during some phase of it (n = 14)

9. Bakris GL, Pitt B, Weir MR, Freeman MW, Mayo MR, Garza D, et al. Effect of Patiromer on Serum Potassium Level in Patients With Hyperkalemia and Diabetic Kidney Disease: The AMETHYST-DN Randomized Clinical Trial. Jama. 2015/07/15. 2015;314(2):151–61.
10. Hagan AE, Farrington CA, Wall GC, Belz MM. Sodium polystyrene sulfonate for the treatment of acute hyperkalemia: a retrospective study. Clin Nephrol. 2015/11/21. 2016;85(1):38–43.
11. Janjua HS, Mahan JD, Patel HP, Mentser M, Schwaderer AL. Continuous infusion of a standard combination solution in the management of hyperkalemia. Nephrol Dial Transpl. 2011/01/12. 2011;26(8):2503–8.
12. Kosiborod M, Rasmussen HS, Lavin P, Qunibi WY, Spinowitz B, Packham D, et al. Effect of sodium zirconium cyclosilicate on potassium lowering for 28 days among outpatients with hyperkalemia: the HARMONIZE randomized clinical trial. Jama. 2014/11/18. 2014;312(21):2223–33.
13. McGowan CE, Saha S, Chu G, Resnick MB, Moss SF. Intestinal necrosis due to sodium polystyrene sulfonate (Kayexalate) in sorbitol. South Med J. 2009/04/18. 2009;102(5):493–7.
14. Weir M, Bushinsky D, Mayo M, Garza D, Stasiv Y, Arthur S, et al. Patiromer lowers serum potassium in patients with elevated potassium and diabetes and advanced CKD on RAAS inhibitors: Results from OPAL-HK and AMETHYST-DN. Vol. 58, Diabetologia. 2015. p. S533-s534.
15. Weir MR, Bakris GL, Gross C, Mayo MR, Garza D, Stasiv Y, et al. Treatment with patiromer decreases aldosterone in patients with chronic kidney disease and hyperkalemia on renin-angiotensin system inhibitors. Kidney Int. 2016/06/29. 2016 Sep;90(3):696–704.
16. Pitt B, Bakris GL, Bushinsky DA, Garza D, Mayo MR, Stasiv Y, et al. Effect of patiromer on reducing serum potassium and preventing recurrent

hyperkalaemia in patients with heart failure and chronic kidney disease on RAAS inhibitors. Eur J Hear Fail. 2015/10/16. 2015;17(10):1057–65.

17. Mandelberg A, Krupnik Z, Houri S, Smetana S, Gilad E, Matas Z, et al. Salbutamol metered-dose inhaler with spacer for hyperkalemia: how fast? How safe? Chest. 1999/03/20. 1999;115(3):617–22.
18. McClure RJ, Prasad VK, Brocklebank JT. Treatment of hyperkalaemia using intravenous and nebulised salbutamol. Arch Dis Child. 1994/02/01. 1994;70(2):126–8.
19. Pergola PE, Spiegel DM, Warren S, Yuan J, Weir MR. Patiromer Lowers serum potassium when taken without food: comparison to dosing with food from an open label, randomized, parallel group hyperkalemia study. Am J Nephrol. 2017; 46 (4): 323-332.
20. Weir MR, Mayo MR, Garza D, Arthur SA, Berman L, Burshinsky D, Wilson DJ, Epstein M. Effectiveness of patiromer in the treatment of hyperkalemia in chronic kidney disease patients with hypertension on diuretics. J Hupertens. 2017, 35 Suppl 1: S57-S63.
21. Weir MR, Bunshinsky DA, Benton WW, Woods SD, Mauo MR, Arthur SP, Pitt B, Bakris GL. Effect of Patiromer on hyperkalemia recurrence in older chronic kidney disease patients taking RAAS inhibitors. Am J Med 2018, 131 (5): 555-564.
22. Georgianos PI, Liampas I, Kyriakou A, Vaios V, Raptis V, Savvidis N, Sioulis A, Liakopoulos V, Balaskas EV, Zebekakis PE. Evaluation of the tolerability and efficacy of sodium polystyrene sulfonate for long-term management of hyperkalemia in patients with chronic kidney disease. Int Urol Nephrol 2017; 49 (12): 2217-2221.

They did not assess efficacy and/or safety outcomes (n = 5)

23. Buck ML. Clinical experience with spironolactone in pediatrics. Ann Pharmacother. 2005/04/07. 2005;39(5):823–8.
24. Hoste EA, Colpaert K, Vanholder RC, Lameire NH, De Waele JJ, Blot SI, et al. Sodium bicarbonate versus THAM in ICU patients with mild metabolic acidosis. J Nephrol. 2005/07/14. 2005;18(3):303–7.
25. Jadoul M, Karaboyas A, Goodkin DA, Tentori F, Li Y, Labriola L, et al. Potassium-binding resins: Associations with serum chemistries and

interdialytic weight gain in hemodialysis patients. Am J Nephrol. 2014/03/20. 2014;39(3):252–9.

26. Schafers S, Naunheim R, Vijayan A, Tobin G. Incidence of hypoglycemia following insulin-based acute stabilization of hyperkalemia treatment. J Hosp Med. 2012/04/11. 2012;7(3):239–42.

27. Wang C-H, Huang C-H, Chang W-T, Tsai M-S, Yu P-H, Wu Y-W, et al. The effects of calcium and sodium bicarbonate on severe hyperkalaemia during cardiopulmonary resuscitation: A retrospective cohort study of adult in-hospital cardiac arrest. Resuscitation. 2015/09/28. 2016 Jan;98:105–11.

Study design was not clinical trial, comparative cohort, or case-control (n = 4)

28. Allon M, Copkney C. Albuterol and insulin for treatment of hyperkalemia in hemodialysis patients. Kidney Int. 1990/11/01. 1990;38(5):869–72.

29. Kim HJ. Combined effect of bicarbonate and insulin with glucose in acute therapy of hyperkalemia in end-stage renal disease patients. Nephron. 1996/01/01. 1996;72(3):476–82.

30. Liou HH, Chiang SS, Wu SC, Huang TP, Campese VM, Smogorzewski M, et al. Hypokalemic effects of intravenous infusion or nebulization of salbutamol in patients with chronic renal failure: comparative study. Am J Kidney Dis. 1994/02/01. 1994;23(2):266–71.

31. Yaseen H, Khalaf M, Dana A, Yaseen N, Darwich M. Salbutamol versus cation-exchange resin (kayexalate) for the treatment of nonoliguric hyperkalemia in preterm infants. Am J Perinatol. 2008/04/22. 2008;25(3):193–7.

They do not specify the treatment, just present monoterapy or polypharmacy treatment (n=1)

32. Peacock WF, Rafique Z, Clark CL, Singer AJ, Turner S, Miller J, Char D, Lagina A, Smith LM, Blomkalns AL, Caterino JM, Kosiborod M; REVEAL-ED Study Investigators. Real World Evidence for Treatment of Hyperkalemia in the Emergency Department (REVEAL-ED): A Multicenter, Prospective, Observational Study. J Emerg Med. 2018 Oct 31. pii: S0736-4679(18)30923-5.

APPENDIX C. Summary of risk assessment of bias in different outcomes using RoB v2.0 tool.

Author, year	Randomization process	Deviations from intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported result	Global
Potassium concentration at baseline and at the final time point of intervention						
Lepage, 2015	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Chothia, 2014	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Kaisar,2006	Low risk	Low risk	Low risk	Some concerns	Low risk	Some concerns
Packham, 2015	Some concerns	Low risk	Low risk	Low risk	Some concerns	Some concerns
Singh, 2002	Low risk	Low risk	Low risk	Low risk	Some concerns	Some concerns
Kim, 2007	High risk	High risk	Some concerns	Low risk	Some concerns	High risk
Lens, 1989	High risk	Some concerns	Some concerns	Low risk	Some concerns	High risk
Mushtaq, 2006	High risk	Some concerns	Some concerns	Low risk	Some concerns	High risk
Ramos-Peñafiel, 2015	Some concerns	High risk	Some concerns	Low risk	Some concerns	High risk
Nasir, 2014	Some concerns	Some concerns	Some concerns	Low risk	Low risk	High risk
Potassium mean difference in different groups						
Chothia, 2014	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Packham, 2015	Some concerns	Low risk	Low risk	Low risk	Some concerns	Some concerns
Singh, 2002	Low risk	Low risk	Low risk	Low risk	Some concerns	Some concerns
Ash, 2015	High risk	Some concerns	Low risk	Low risk	Some concerns	High risk
Ngugi, 1997	Some concerns	High risk	Low risk	Low risk	Some concerns	High risk
Lepage, 2015	Some concerns	Low risk	High risk	Low risk	Low risk	High risk
Lens, 1989	Some concerns	Some concerns	Some concerns	Low risk	Some concerns	High risk
Mushtaq, 2006	Some concerns	Some concerns	Some concerns	Low risk	Some concerns	High risk
Saw, 2018.	High risk	Some concerns	Some concerns	Low risk	Low risk	High risk
Wang, 2018	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Nakayama, 2017	High risk	High risk	Low risk	Low risk	Some concerns	High risk
Lost to follow up due to side effects						
Chothia, 2014	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Lepage, 2015	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk

APPENDIX D. Summary of risk assessment of bias using ROBINS-I tool.

Study	Confounding	Selection of participants into the study	Classification of interventions	Deviations from intended interventions	Missing data	Measurement of outcomes	Selections of the reported result
Oschman, 2011	Moderate risk	Moderate risk	Serious risk	Serious risk	No information	Low risk	Serious risk

APPENDIX E. Confidence in evidence of hyperkalemia pharmacotherapy, considering GRADE system.

Comparison	Better alternative	# Studies (# Participants)	Confidence in evidence
Efficacy (serum potassium difference in the final time and difference between the means)			
Fludrocortisone vs. No treatment	No difference	2 (58)	Low [1, 2]
Insulin + glucose vs. Glucose	Insulin + glucose	1 (10)	Moderate [2]
SPS vs. Placebo	SPS	1 (31)	Moderate [2]
CPS vs. SPS	No difference	2 (117)	Low [1, 2]
Salbutamol vs. Placebo	No difference	1 (24)	Low [1, 2]
ZS-9 0.3 g vs. Placebo	No difference	1 (42)	Low [1, 2]
ZS-9 1.25 g vs. Placebo	No difference	1 (312)	Low [1, 2]
ZS-9 2.5 g vs. Placebo	ZS-9 2.5 g	1 (299)	Moderate [2]
ZS-9 3.0 g vs. Placebo	No difference	1 (54)	Low [1, 2]
ZS-9 5 g vs. Placebo	ZS-9 5 g	1 (316)	Moderate [2]
ZS-9 10 g vs. Placebo	ZS-9 10 g	2 (355)	Moderate [2]
Dextrose 50% + insulin vs. Dextrose 10% + sodium bicarbonate + insulin	No difference	1 (50)	Low [1, 2]
Salbutamol IV + dextrose vs. Insulin + glucose	No difference	1 (34)	Low [1, 2]
Salbutamol IV + dextrose vs. Salbutamol IV + insulin + glucose	No difference	1 (34)	Low [1, 2]
Insulin + glucose vs. Salbutamol IV + insulin + glucose	No difference	1 (20)	Low [1, 2]
Salbutamol IV vs. Glucose + insulin	No difference	2 (50)	Low [1, 2]
Salbutamol IV vs. Salbutamol IV + glucose + insulin	No difference	1 (10)	Low [1, 2]
Glucose + insulin vs. Salbutamol IV + glucose + insulin	No difference	1 (10)	Low [1, 2]
Insulin + glucose vs. sodium bicarbonate vs. Salbutamol vs. Insulin + glucose + salbutamol vs. Insulin + glucose + sodium bicarbonate vs. Sodium bicarbonate + salbutamol vs. Sodium bicarbonate	No difference	1 (70)	Low [1, 2]
CPS vs no treatment	CPS	1 (58)	Moderate [2]
Discontinuation due to adverse events			
SPS vs. Placebo	No difference	1 (31)	Moderate [2]
Insulin + glucose vs. Glucose	No difference	1 (10)	Moderate [2]

IV: intravenous, ZS-9: sodium zirconium cyclosilicate; CPS: calcium polystyrene sulfonate, SPS: sodium polystyrene sulfonate; 1 - High risk of bias; 2 – Imprecision.