Supplementary Figure 1 Funnel plot for daily fluid balance (primary outcome). The effect size of the mean difference is plotted against study precision (SE) for the dailay fluid balance, where dotted lines indicate the pooled effect estimate and 95% confidence intervals.

Supplementary Table 1 Literature search.

Supplementary Table 2 List of exclusion reasons for all potential references (excluded).

Supplementary Table 3 Risk of bias assessment.

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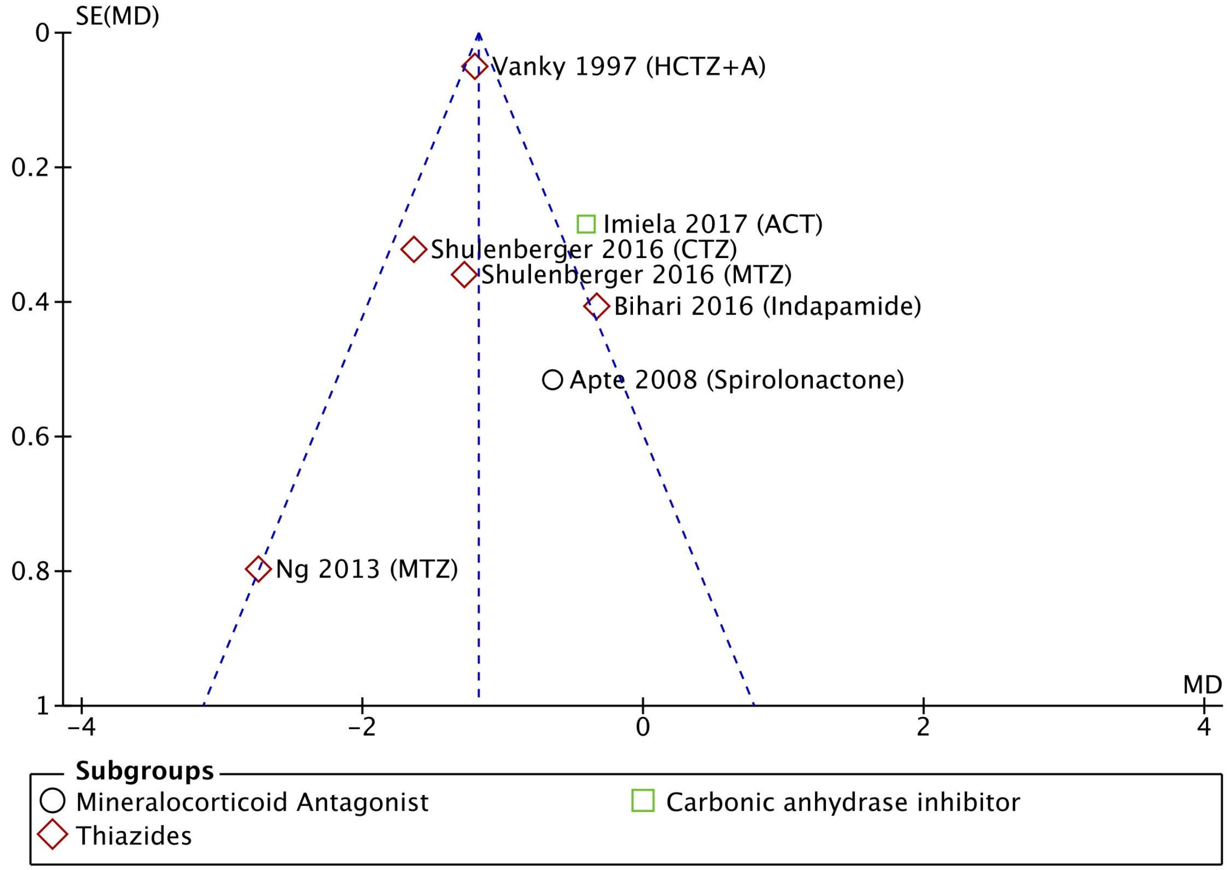
Figure



Supplementary Figure 1 Funnel plot for daily fluid balance (primary outcome). The effect size of the mean difference is plotted against study precision (SE) for the dailay fluid balance, where dotted lines indicate the pooled effect estimate and 95% confidence intervals.

Supplementary Table 1 Literature search (using MeSH)

Literature search	
Ovid Medline Search (May 5, 2021)	Respiratory insufficiency.sh
	Respiration, artificial.sh
	Acute lung injury.sh
	Respiratory depression.af
	Mechanical ventilation.af
	Ventilatory depressin.af
	Hypoxemia.af
	ARDS.af
	'Acute respiratory distress syndrome'.af
	'Acute lung injury'.af
	Intubation.af
	(#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11) /limit to humans
	Diuretics.sh
	Thiazides.sh
	Sodium chloride symporter inhibitors.sh
	Hydrochlorothiazide.sh
	Metolazone.sh
	Chlorthalidone.sh
	Acetazolamide.sh
	Carbonic anhydrase inhibitors.sh
	Eplerenone.sh
	Triamterene.sh
	Epithelial sodium channel blockers.sh
	Amiloride.sh
	Diuretics combination.af
	Diuretic combination.af

	Thiazide.af
	Hydrochlorothiazide.af
	HCTZ.af
	Hydrodiuril.af
	Metolazonde.af
	Zaroxolyn.af
	Chlorthalidone.af
	Acetazolamide.af
	Diamox.af
	Spironolactone.af
	Aldactone.af
	Eplerenone.af
	Inspra.af
	Triamterene.af
	Amiloride.af
	Midamor.af
	#13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42
	Furosemide.sh
	Bumetanide.sh
	Torsemide.sh
	Sodium potassium chloride symporter inhibitors.sh
	Loop diuretic.af
	Loop diuretics.af
	Furosemide.af

	Bumetanide.af
	Bumex.af
	Lasix.af
	Frusemide.af
	Torsemide.af
	#44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55
	Intensive care units.sh
	Intensive care unit.af
	#57 OR #58
	Fluid balance.af
	Fluid management.af
	Acute heart failure.af
	Water-electrolyte balance.sh
	#60 OR #61 OR #62 OR #63
	#12 AND #43. (23 and 56). (ventilation + diuretics)
	#12 AND #56 (23 and 69). (ventilation + Lasix)
	#12 AND #64 (23 and 77). (ventilation + fluid management)
	#43 AND #56 AND #59. (56 – 69 and 72). (Lasix + autre diuretics + ICU)
	#43 AND #59. (autre diuretics + ICU)
	#56 AND #59. (Lasix + ICU)
	#65 OR #66 OR #67 OR #68 OR #69 OR #70
	Total 2498 results (before deduplication)
EMBASE Search (May 5, 2021)	'Respiratory failure'*/exp AND [humans]/lim
	'Artificial ventilation'/exp AND [humans]/lim
	'Adult respiratory distress syndrome'/exp AND

	[humans]/lim 'Acute lung injury'/exp AND [humans]/lim #1 OR #2 OR #3 OR #4 'Diuretic agent'/exp 'Thiazide diuretic agent'/exp 'Hydrochlorothiazide'/exp 'metolazone'/exp 'acetazolamide'/exp 'carbonate dehydratase inhibitor'/exp 'spironolactone'/exp 'mineralocorticoid antagonist'/exp 'triamterene'/exp 'amiloride'/exp 'epithelial sodium channel blocking agent'/exp #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 'Furosemide'/exp 'loop diuretic agent'/exp 'bumetanide'/exp 'torasemide'/exp #18 OR #19 OR #20 OR #21 'intensive care unit'/exp 'fluid balance'/exp or 'fluid balance' #5 AND #17 AND #22 #17 AND #22 AND #23 AND #24 #25 OR #26 Total: 3254 results (before deduplication)
Cochrane Library (May 5, 2021)	Diuretics combination Intensive care

	#1 AND #2
	Diuretics
	Mechanical ventilation
	#4 AND #5
	Loop diuretic
	Thiazide diuretic
	#2 AND #7 AND #8
	Acetazolamide
	#2 AND #7 AND #10
	#3 OR #6 OR #9 OR 11
	Total: 59 (before deduplication)
Prospero–(May 5, 2021)	Diuretics combination
	Intensive care
	Diuretics
	Mechanical ventilation
	Loop diuretic
	Thiazide diuretic
	Acetazolamide
	#1 OR #1 AND #2 OR #3 AND #4 OR #2 AND #6 OR #4 and #7 OR #2 AND #7
	Total: 0
Research of Annual meeting's Abstracts Database (May 5, 2021)	American Society of Nephrology: 0 Abstract
	European Society of Intensive Care Medicine: 0 Abstract
	Society of Critical Care Medicine: 2 Abstracts

Supplementary Table 2 List of exclusion reasons for all potential references

List of exclusion reasons for all potential references	
Protocol only (no data) (n = 1)	Nct. Stop Hypernatremia, Use Metolazone, for Aggressive, Controlled, Effective Diuresis. https://clinicaltrialsgov/show/NCT01617798
Case report (< 5 cases) or Editorial (n = 3)	Cochrane GM, Clark TJ. Ventilatory response to spironolactone in respiratory failure. British journal of diseases of the chest. 1972;66(1):67-70.
	Contou D, de Prost N, Mekontso Dessap A. Acetazolamide and Invasive Mechanical Ventilation for Patients With COPD. JAMA. 2016;316(1):99-100.
	Girerd N, Aubry M, Lantelme P, Huttin O, Rossignol P. Intravenous Mineralocorticoid Receptor Antagonist Use in Acutely Decompensated Heart Failure with Diuretic Resistance. Int Heart J. 2021 Jan 30;62(1):193-196. doi: 10.1536/ihj.20-442. Epub 2021 Jan 16. PMID: 33455988
Pediatric studies (n = 2)	Kouyoumjian S, Lieu P, Epstein D, Moromisato D. Addition of chlorothiazide to overcome furosemide-resistant fluid retention following cardiac surgery. Pediatric Critical Care Medicine. 2012;13(6):713.
	Kouyoumjian S, Moromisato D, Lieu P, Epstein D, Amirnovin R. Addition of chlorothiazide as an effective adjunct to furosemide for fluid retention following cardiac surgery. Critical Care Medicine. 2012;40(12):68.
No respiratory failure patients nor lung fluid overload (n = 2)	Alsuhebany N, Aqel R, Alballa H, Al-Ayoubi F, Bawazeer G, Alhabib K, et al. Differential effects of intravenous bolus furosemide and continuous furosemide infusion on in-

	hospital management and outcomes among patients admitted with acute decompensated heart failure. Journal of the Saudi Heart Association. 2016;28(3):199-200. Pendexter J, Polly D, Nguyen V, Chen Z, Cole R, Tang K. Comparison of oral metolazone versus oral chlorothiazide in patients with acute decompensated heart failure with loop diuretic resistance 2020 ACCP Annual Meeting (Virtual) October 19 - 30, 2020. J Am Coll Clin Pharm, 3: 1525-1689. https://doi.org/10.1002/jac5.1351
No individual data for participants receiving diuretics combination as opposed to diuretic monotherapy (n = 13)[1]	Bahloul M, Chaari A, Tounsi A, Turki O, Chtara K, Hamida CB, et al. Impact of acetazolamide use in severe exacerbation of chronic obstructive pulmonary disease requiring invasive mechanical ventilation. International journal of critical illness and injury science. 2015;5(1):3-8. Bissell BD, Laine ME, Thompson Bastin ML, Flannery AH, Kelly A, Riser J, et al. Impact of protocolized diuresis for de-resuscitation in the intensive care unit. Critical Care. 2020;24(1). Brown AJ, Cutuli SL, Eastwood GM, Bitker L, Marsh P, Bellomo R. A pilot randomised controlled trial evaluating the pharmacodynamic effects of furosemide versus acetazolamide in critically ill patients. Critical care and resuscitation : journal of the Australasian Academy of Critical Care Medicine. 2019;21(4):258-64. Dieso, Patricia; Kiracofe, Brittany; Fay, Lauren; Parker, Jessica; Ice, Calvin. Furosemide-Induced Contraction Alkalosis: Diuretic Effect of Acetazolamide vs. Continued Furosemide, Critical Care Medicine: January 2021 -

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Faisy C, Mokline A, Sanchez O, Tadie J-M, Fagon J-Y. Effectiveness of acetazolamide for reversal of metabolic alkalosis in weaning COPD patients from mechanical ventilation. Intensive care medicine. 2010;36(5):859-63.

Gulsvik R, Skjorten I, Undhjem K, Holo L, Frostad A, Saure EW, et al. Acetazolamide improves oxygenation in patients with respiratory failure and metabolic alkalosis. The clinical respiratory journal. 2013;7(4):390-6.

Heming N, Urien S, Fulda V, Meziani F, Gacouin A, Clavel M, et al. Population pharmacodynamic modeling and simulation of the respiratory effect of acetazolamide in decompensated COPD patients. PloS one. 2014;9(1):e86313.

Mazur JE, Devlin JW, Peters MJ, Jankowski MA, Iannuzzi MC, Zarowitz BJ. Single versus multiple doses of acetazolamide for metabolic alkalosis in critically ill medical patients: a randomized, double-blind trial. Critical care medicine. 1999;27(7):1257-61.

McCoy IE, Chertow GM, Chang TIH. Patterns of diuretic use in the intensive care unit. PloS one. 2019;14(5):e0217911.

Mekontso Dessap A, Roche-Campo F, Kouatchet A, Tomicic V, Beduneau G, Sonneville R, et al. Natriuretic

	peptide-driven fluid management during ventilator weaning: a randomized controlled trial. American journal of respiratory and critical care medicine. 2012;186(12):1256‐63.
	Moviat M, Pickkers P, van der Voort PHJ, van der Hoeven JG. Acetazolamide-mediated decrease in strong ion difference accounts for the correction of metabolic alkalosis in critically ill patients. Critical care (London, England). 2006;10(1):R14.
	Rialp Cervera G, Raurich Puigdevall JM, Moran Chorro I, Martin Delgado MC, Heras la Calle G, Mas Serra A, et al. Effects of early administration of acetazolamide on the duration of mechanical ventilation in patients with chronic obstructive pulmonary disease or obesity-hypoventilation syndrome with metabolic alkalosis. A randomized trial. Pulmonary pharmacology & therapeutics. 2017;44:30-7.
Repeated abstract - Completed reference is already included (*n* = 3)	Apte YV, Bellomo R, Warrillow S, Goldsmith D, Gillies M, McGain F. A pilot study of the effects of combined therapy with frusemide and spironolactone on serum sodium and natriuresis in critically ill patients. Intensive Care Medicine. 2009;35:S152.
	Michaud C, Mintus K. Intravenous chlorothiazide versus enteral metolazone for sequential nephron blockade in the ICU. Critical care medicine. 2016;44(12):291‐.
	Velagapudi C, Bansal S, Munoz K, Brune S, Prasad A. Safety and efficacy of high dose spironolactone in loop diuretic resistant acute decompensated heart failure. Circulation. 2018; 138.

[1]Corresponding authors of these studies were contacted to obtain additional information.

Supplementary Table 3 Risk of bias assessment (based on the primary outcome measurement: Daily Fluid balance)

Ref.	Selection bias		Performance bias	Detection bias	Attrition bias	Reporting bias	Overall bias
	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	
Randomised controlled trials (RoB2 tool)							
Apte *et al*[1]	Unclear	Low	Low	Low	Low	Low	Low
Bihari *et al*[2]	Low	Low	Unclear	Low	Low	Low	Low
Imiela *et al*[3]	Low	Low	Unclear	Low	Low	Low	Low

Ref.	Confounding	Selection bias	Intervention classification	Deviation from intervention	Missing data	Measure of outcomes	Selection of reporting results	Overall bias
Non-randomised trials (ROBINS-I tool)								
Vánky *et al*[4]	Unclear	High	Low	Low	High	Low	Low	Unclear

Ref.	Selection	Comparability	Outcome

	Representativeness of exposed cohort	Selection of non-exposed cohort	Ascertainment of exposure	Outcome not present at start	Most important factor	Additional factor	Assessment of outcome	Duration of follow-up	Adequacy of follow-up
Observational studies (Newcastle-Ottawa scale tool)									
Bohn *et al*[5]1	-	-	-	-	-	-	-	-	-
Heming *et al*[6]1	-	-	-	-	-	-	-	-	-
Michaud *et al*[7]1	-	-	-	-	-	-	-	-	-
Ng *et al*[8]	Yes	N/A2	Yes	N/A	Yes	Yes	Yes	Yes	Yes
Shulenberger *et al*[9]	Yes	N/A2	Yes	N/A	No3	Yes	Yes	Yes	Yes

Low: Low risk of bias; High: High risk of bias; Unclear: Data availability does not allow to determine the risk of bias; Yes: Adequate to minimise risk of bias; No: Inadequate to minimise risk of bias.

1The studies by Bohn *et al*[5], Heming *et al*[6], and Michaud *et al*[7]. did not report the primary outcome of interest (fluid balance) on which the current risk of bias assessment is based.

2These studies used a paired comparison, where patients were compared to themselves before and after the exposure.

3These studies did not control for the most important confounding factor affecting the daily fluid balance: the furosemide dose received.

Supplementary Table 4 Efficacy endpoints for all included studies

Ref.	Treatment group	Efficacy/physiological endpoints		
		Urine output, L/24 h	Fluid balance, L/24 h	Natriuresis, mmol/24 h
Mineralocortocoid-antagonist				
Apte *et al*[1]	Spironolactone + Furosemide (*n* = 10)	1.34 (1.15-2.35)	-1.2 (-2.2; -0.8)	119 (-49-195)[1]
	Furosemide (*n* = 10)	1.58 (1.26-1.96)	-0.8 (-1.4; -0.2)	49 (-129-114)[1]
Thiazides				
Bihari *et al*[2]	Indapamide + Furosemide (*n* = 20)	2.83 (2.04-3.28)	-0.8 (-2.1; -0.5)	210 (123-292)
	Furosemide (*n* = 20) (baseline)	2.48 (1.98-3.58)	-0.7 (-1.7; -0.1)	119 (92-159)
Bohn *et al*[5]	CTZ + Furosemide (*n* = 34)	3.88 (0.55-7.21)	-	-
	Furosemide (*n* = 34) (baseline)	1.81 (0.17-3.79)	-	-
	MTZ + Furosemide (*n* = 16)	3.96 (2.07-5.85)	-	-
	Furosemide (*n* = 16) (baseline)	2.10 (0.94-3.26)	-	-
Michaud *et al*[7]	CTZ + Furosemide (*n* = 58)	4.66 (0.50-8.20)	-	-
	Furosemide (*n* = 58) (baseline)	2.26 (0.30-6.00)	-	-
	MTZ + Furosemide (*n* = 64)	3.29 (0.40-9.00)	-	-

	Furosemide (*n* = 64) (baseline)	1.64 (0.40-4.50)	-	-
Ng *et al*[8]	MTZ + Furosemide (*n* = 42)	3.79 ± 2.01	-3.4 ± 4.9	-
	Furosemide (*n* = 42) (baseline)	2.30 ± 1.25	-0.7 ± 1,7	-
Shulenberger *et al*[9]	CTZ + Furosemide (*n* = 40)	3.98 ± 2.00	-2.1 ± 1.8	-
	Furosemide (*n* = 40) (baseline)	2.12 ± 0.83	-0.5 ± 0.9	-
	MTZ + Furosemide (*n* = 38)	3.71 ± 1.75	-1.8 ± 1.8	-
	Furosemide (*n* = 38) (baseline)	2.44 ± 1.27	-0.6 ± 1.3	-
Vánky *et al*[4]	HCTZ + Amiloride + Furosemide (*n* = 20)	2.95 ± 0.16	-2.3 ± 0.2	-
	Furosemide (*n* = 57)	2.25 ± 0.12	-1.1 ± 0.2	-
Carbonic anhydrase inhibitor				
Heming *et al*[6]	Acetazolamide + Furosemide (*n* = 29)	-	-	-
	N/A[2]	-	-	-
Imiela *et al*[3]	Acetazolamide + Furosemide (*n* = 10)	2.60 ± 0.63	-0.3 ± 0.6	258 ± 130
	Furosemide (*n* = 10)	2.56 ± 1.07	+0.1 ± 0.7	213 ± 112

CTZ: Chlorothiazide; MTZ: Metolazone; HCTZ: Hydrochlorothiazide.

[1]Was reported as the change in the 24-h urine sodium from baseline.

[2]No comparison group reported.

Supplementary Table 5 Clinical endpoints for all included studies

Ref.	Treatment group	Efficacy/clinical endpoints		
		ICU LOS, d	Hospital LOS, d	In-hospital mortality, *n* (%)
Mineralocortocoid-antagonist				
Apte *et al*[1]	Spironolactone + Furosemide (*n* = 10)	3 (2-3)	-	-
	Furosemide (*n* = 10)	4 (3-5)	-	-
Thiazides				
Bihari *et al*[2]	Indapamide + Furosemide (*n* = 20)	5.8 (3.9-13.1)	14.2 (7.4-29.2)	5 (25)
	Furosemide (*n* = 20)	5.4 (2.8-9.0)	15.0 (7.0-22.5)	5 (25)
Bohn *et al*[5]	CTZ + Furosemide (*n* = 34)	-[1]	-[1]	-[1]
	MTZ + Furosemide (*n* = 16)	-[1]	-[1]	-[1]
Michaud *et al*[7]	CTZ + Furosemide (*n* = 58)	10.0 (2.4-90.8)	22.7 (3.6-108.9)	11 (19)
	MTZ + Furosemide (*n* = 64)	8.3 (2.8-184.4)	16.5 (2.0-184.4)	17 (27)
Ng *et al*[8]	MTZ + Furosemide (*n* = 42)	-	-	0 (0)
Shulenberger *et al*[9]	CTZ + Furosemide (*n* = 40)	-	36.2 ± 38.2	3 (7.5)
	MTZ + Furosemide (*n* = 38)	-	31.0 ± 31.7	9 (24)
Vánky *et al*[4]	HCTZ + Amiloride + Furosemide (*n* = 20)	-	12.2 ± 1.1	-
	Furosemide (*n* = 57)	-	9.8 ± 0.3	-
Carbonic anhydrase inhibitor				
Heming *et al*[6]	ACT + Furosemide (*n* = 29)	21 (6-123)	-	10 (34)

Imiela *et al*[3]	ACT + Furosemide (n = 10)	-	-	-
	Furosemide (n = 10)	-	-	-

Results are presented in median (IQR), or mean ± SD.

[1]Data were not presented individually for ICU patients included in the primary analysis (n = 34, n = 16).

Supplementary Table 6 Risk of safety events for all included studies

Ref.	Treatment group	Safety events			
		AKI, *n* (%)	KRT, *n* (%)	Hypernatremia, *n* (%)	Hypotensive event, *n* (%)
Mineralocortocoid-antagonist					
Apte *et al*[1]	Spironolactone + Furosemide (*n* = 10)	-	-	-	-
	Furosemide (*n* = 10)	-	-	-	-
Thiazides					
Bihari *et al*[2]	Indapamide + Furosemide (*n* = 20)	0 (0)	0 (0)	0 (0)	-
	Furosemide (*n* = 20)	0 (0)	0 (0)	0 (0)	-
Bohn *et al*[5]	CTZ + Furosemide (*n* = 34)	-[1]	-[1]	-[1]	-[1]
	MTZ + Furosemide (*n* = 16)	-[1]	-[1]	-[1]	-[1]
Michaud *et al*[7]	CTZ + Furosemide (*n* = 58)	-	6 (10)	-	30 (52)[2]
	MTZ + Furosemide (*n* = 64)	-	6 (9)	-	40 (63)[2]
Ng *et al*[8]	MTZ + Furosemide (*n* = 42)	-	-	-	19 (45)[3]
Shulenberger *et al*[9]	CTZ + Furosemide (*n* = 40)	6 (15)	-	-	-
	MTZ + Furosemide (*n* = 38)	10 (26)	-	-	-
Vánky *et*	HCTZ + Amiloride + Furosemide (*n* = 20)	3 (15)	-	-	-

al[4]	Furosemide (*n* = 57)	4 (7)	-	-	-
Carbonic anhydrase inhibitor					
Heming *et al*[6]	Acetazolamide + Furosemide (*n* = 29)	0 (0)	0 (0)	-	-
Imiela *et al*[3]	Acetazolamide + Furosemide (*n* = 10)	-	-	-	-
	Furosemide (*n* = 10)	-	-	-	-

AKI: Acute kidney injury; KRT: Kidney replacement therapy; CTZ: Chlorothiazide; MTZ: Metolazone; HCTZ: Hydrochlorothiazide.

[1]Data were not presented individually for ICU patients included in the primary analysis (*n* = 34, *n* = 16).

[2]Defined as a mean arterial pressure < 65 mmHg or systolic arterial pressure < 90 mmHg.

[3]Defined as systolic arterial pressure < 90 mmHg.

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1 **Apte Y**, Bellomo R, Warrillow S, Goldsmith D, Gillies M, McGain F. Pilot randomised double-blind controlled trial of high-dose spironolactone in critically ill patients receiving a frusemide infusion. *Crit Care Resusc* 2008; **10**: 306-311 [PMID: 19049481]

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8 **Ng TM**, Konopka E, Hyderi AF, Hshieh S, Tsuji Y, Kim BJ, Han SY, Phan DH, Jeng AI, Lou M, Elkayam U. Comparison of bumetanide- and metolazone-based diuretic regimens to furosemide in acute heart failure. *J Cardiovasc Pharmacol Ther* 2013; **18**: 345-353 [PMID: 23538300 DOI: 10.1177/1074248413482755]

9 **Shulenberger CE**, Jiang A, Devabhakthuni S, Ivaturi V, Liu T, Reed BN. Efficacy and Safety of Intravenous Chlorothiazide versus Oral Metolazone in Patients with Acute

Decompensated Heart Failure and Loop Diuretic Resistance. *Pharmacotherapy* 2016; **36**: 852-860 [PMID: 27393709 DOI: 10.1002/phar.1798]