Supplement 3| Summary evidence tables

Key question 1.

No.	Author (year)	Study type	Total (n)	Intervention (n)	Comparison (n)	Study results
1	Musch (1995)	Cohort (prospective)	55	diuretic group (n=9), polydipsic group (n=3), saline responders group (n=8), saline nonresponders group (n=15)	normonatremic controls (n=20)	FEUA (20±7) was significantly higher in saline nonresponders compared to controls.
2	Musch (2001)	Cohort (prospective)	110	salt depletion (n=17), true SIADH (n=33), salt-depleted SIADH (n=6)	normonatremic controls (n=54)	FEUA was significantly higher in SIAD compared to controls.
3	Fenske (2008)	Cohort (prospective)	86	salt depletion (n=27), extracellular volume expansion (n=21), diuretics (n=7)	SIAD group (n=31)	In patients on diuretics, FEUA performed best (diagnose SIAD) compared with all other markers tested (area under the curve [AUC] 0.96; 0.92–1.12), resulting in a positive predictive value of 100% if a cutoff value of 12% was used.
4	Nigro (2018)	Cohort (prospective)	298	diuretic-induced (n=72), hypovolemic (n=59) hypervolemic hyponatremia (n=33), primary polydipsia (n=24), cortisol deficiency (n=4)	SIAD (n=106)	FEUA was higher in patients with SIAD compared to other hyponatremia etiologies (both $p<0.0001$). FEUA values >12% had a specificity of 96% and 77% to detect patients with SIAD. These results remained similar after excluding patients taking diuretics.
5	Bassi (2020)	Cohort (retrospective)	89	non-SIAD diuretic-induced hyponatremia group (n=47)	SIAD group (n=42)	FEUA discriminated better than serum UA between SIAD and diuretic-induced hyponatremia patients (AUC 0.96, $p<0.001$ vs. 0.88, $p<0.001$), while it was a poor marker to discriminate between SIAD and thiazide-induced hyponatremia (0.65, NS vs. 0.67, NS).

Key question 2.

No.	Author (year)	Study type	Total (n)	Intervention (n)	Comparison (n)	Study results
1	Fenske (2009)	Cohort (prospective)	106	Copeptin/UNa (n=106)	Copeptin (n=106)	Copeptin measurement reliably identified patients with primary polydipsia but has limited utility in the differential diagnosis of other hyponatremic disorders. In contrast, the copeptin to U-Na ratio is superior to the reference standard in discriminating volume-depleted from normovolemic hyponatremic disorders.
2	Suryeong (2021)	Cohort (prospective)	100	Copeptin/UNa (n=100)	Copeptin (n=100)	Although there were no differences in copeptin levels among the five groups, the copeptin-to-UNa ratio differed significantly according to the cause of hyponatremia (p=0.001).

Key question 3.

No.	Author (year)	Study type	Total (n)	Intervention (n)	Comparison (n)	Study results
1	Baek (2021)	Ramdomized controlled trial	178	Rapid intermittent bolus (RIB) (87) Moderate: 2mL/kg Severe: 4mL/kg	Slow continuous infusion (SCI) (91) Moderate: 0.5mL/kg/hr Severe: 1mL/kg/hr	Overcorrection occurred in 15 of 87 (17.2%) and 22 of 91 (24.2%) patients in the RIB and SCI groups, respectively (absolute risk difference, -6.9% [95% CI, -18.8% to 4.9%]; P =.26). The RIB group showed a lower incidence of relowering treatment than the SCI group (36 of 87 [41.4%] vs. 52 of 91 [57.1%] patients, respectively; absolute risk difference, -15.8% [95% CI, -30.3% to -1.3%]). Groups did not differ in terms of efficacy in increasing sNa concentrations nor improving symptoms, but RIB, when compared with SCI, showed better efficacy in achieving target correction rate within 1 hour (intention-to-treat analysis: 28 of 87 (32.2%) vs. 16 of 91 (17.6%) patients, respectively; absolute risk difference, 14.6% [95% CI, 2%-27.2%]; P =.02; per-protocol analysis: 21 of 72 (29.2%) vs. 12 of 73 (16.4%) patients, respectively; absolute risk difference, 12.7% [95% CI, -0.8% to 26.2%]; P =.07). The statistical significance of the intention-to-treat and per-protocol analyses was similar for all outcomes except for achieving the target correction rate within 1 hour.

2	Garrahy (2019)	Cohort (prospective, historical control)	50	Rapid intermittent bolus (RIB) (22): 100 mL, repeated up to two more times	Slow continuous infusion (SCI) (28): 20 mL/hr	A 3% saline bolus caused more rapid elevation of pNa at 6 hours [median (range) 6 (2 to11) vs. 3 (1 to 4) mmol/L, P < 0.0001], with a concomitant improvement in Glasgow Coma Scale (GCS) [median (range) 3 (1 to 6) vs. 1 (-2 to 2), P < 0.0001] at 6 hours. Median pNa concentration was similar at 24 hours in the two treatment groups. The administration of a third saline bolus was associated with a greater need for dextrose/dDAVP to prevent overcorrection (OR 24; P = 0.006). There were no cases of osmotic demyelination in either group.

Key question 4.

No.	Author (year)	Study type	Total (n)	Intervention (n)	Comparison (n)	Study results
1	Sushrut (2009)	Cohort (prospective)	92,846	Mild hyponatremia (n=10,469)	normonatremic controls (n=82,377)	The increased risk of death was evident even in those with mild hyponatremia (130-134 mmol/L; odds ratio 1.37, 95% CI, 1.23-1.52).
2	Doshi (2012)	Cohort (prospective)	2,996	Mild hyponatremia (n=1,235)	normonatremic controls (n=1,761)	A total of 283 (8.4%) deaths occurred during 90 days, and in the multivariate model, the respective HRs for 90-day mortality for mild, moderate, and severe hyponatremia were 2.04 (95% CI, 1.42-2.91; p<0.01); 4.74 (95% CI, 3.21-7.01; p<0.01), and 3.46 (95% CI, 1.05-11.44; p=0.04).
3	Kovesdy (2012)	Cohort (prospective)	639,475	Mild hyponatremia (n=83,126)	normonatremic controls (n=556,349)	Patients with serum sodium levels of 130, 130 to 135.9, 145.1 to 150, and 150 mmol/L compared with 136 to 145 mmol/L had multivariable-adjusted mortality hazard ratios (95% confidence interval) of 1.93 (1.83–2.03), 1.28 (1.26 –1.30), 1.33 (1.28 –1.38), and 1.56 (1.33–1.83) (p<0.001 for all).

Key question 5.

No.	Author (year)	Study type	Total (n)	Intervention (n)	Comparison (n)	Study results
1	Jujo (2016)	RCT	60	tolvaptan (n=30)	furosemide (n=30)	Tolvaptan was associated with better preservation of renal function (no change in serum Cr vs. 20% elevation of serum Cr, worsening renal function: 33% vs. 6.7%, p<0.01) compared with furosemide in acute heart failure.
2	Tominaga (2017)	RCT	73	tolvaptan + furosemide (n=36)	fursemode (n=37)	Tolvaptan added to furosemide resulted in a greater sodium elevation at day 1 (2.19 vs. 0.18, p< 0.001).
3	Tanaka (2018)	RCT	18	tolvaptan + furosemide (n=10)	furosemide (n=8)	Adding tolvaptan had no effect on elevated plasma sodium compared with furosemide.
4	Matsue (2016)	RCT	217	tolvaptan + furosemide (n=108)	furosemide (n=109)	Adding tolvaptan in furosemide did not show any difference in renal function.
5	Shanmugam (2016)	RCT	51	tolvaptan (n=25)	placebo (n=26)	Tolvaptan was effective for reversing hyponatremia (the number of patients whose sodium elevate more than 5 mEq is more in tolvaptan than placebo, p=0.001) in acute heart failure.
6	Felker (2017)	RCT	257	tolvaptan + furosemide (n=129)	furosemide (n=128)	The addition of tolvaptan to furosemide elevated serum sodium (3.2 vs. 0.2 at 24h; 3.3 vs. -0.2 at 48h; 2.8 vs. -0.4 at 72h, p < 0.001) and increased worsening renal function at 72 hours (39 vs. 27, p= 0.037) in acute heart failure.
7	Konstam (2017)	RCT	250	tolvaptan + furosemide (n=122)	furosemide (n=128)	The tolvaptan add-on group did not show any difference in mortality at day 30 (6 vs. 6, p=0.972) or renal function (eGFR: 44.9 vs. 44.2, p=0.66).
8	Kimura (2016)	RCT	52	tolvaptan + furosemide (n=26)	furosemide (n=26)	Tolvaptan reduced the incidence of worsening renal function (26.9% vs. 57.7%) and elevated serum sodium (140 vs. 142 at day 2, p=0.004, 139 vs. 142 at day 3, p=0.001, 139 vs. 141 at day 5, p=0.037) compared with increased furosemide in acute decompensated heart failure.

9	Hiromi (2020)	RCT	122	tolvaptan + furosemide (n=47)	furosemide (n=75)	Tolvaptan add-on therapy was associated with a lower incidence of worsening renal function (8.5% vs. 24%, p=0.03) in patients with new-onset acute heart failure.

Key question 6.

No.	Author (year)	Study type	Total (n)	Intervention (n)	Comparison (n)	Study results
1	Wong (2003)	RCT	44	Lixivaptan 25 mg bid (n=12), 125 mg bid (n=11), 250 mg bid (n=10)	placebo (n=11)	Lixivaptan appeared effective and safe in appropriate doses in correcting abnormal renal water handling and hyponatremia in conditions associated with water retention.
2	Schrier (2006)	RCT	448	Tolvaptan 15 mg/day (n=225)	placebo (n=223)	In patients with euvolemic or hypervolemic hyponatremia, tolvaptan was effective in increasing serum sodium concentrations at day 4 and day 30.
3	Soupart (2006)	RCT	35	Satavaptan 25 mg/day (n=14), 50 mg/day (n=12)	placebo (n=9)	Satavaptan adequately corrected mild or moderate hyponatremia in patients with SIADH and has a good safety profile.
4	Ghali (2006)	RCT	74	Conivaptan 40 mg/day (n=24), 80 mg/day (n=27)	placebo (n=23)	Oral conivaptan (40 and 80 mg/d) was well tolerated and efficacious for correcting serum [Na^+] in hyponatremia.
5	Gheorghiade (2006)	RCT	23	Tolvaptan 15~60 mg/day (n=15)	placebo plus fluid restriction (n=8)	Tolvaptan appeared to be more effective than fluid restriction for correcting hyponatremia in hospitalized subjects without an increase in adverse events.
6	Verbalis (2008)	RCT	56	Conivaptan 40 mg/day (n=18), 80 mg/day (n=17)	placebo (n=21)	In hospitalized patients with euvolaemic hyponatraemia, i.v. conivaptan significantly increased serum [Na+] promptly and was well tolerated.
7	Annane (2009)	RCT	83	Conivaptan 40 mg/day (n=27), 80 mg/day (n=26)	placebo (n=30)	Oral conivaptan was effective for increasing serum [Na^+] in patients with euvolemic or hypervolemic hyponatremia and had a favorable safety profile
8	Koren (2011)	RCT	49	conivaptan 20 mg once or twice daily (n=40)	placebo (n=9)	Conivaptan hydrochloride 20 mg, administered once or twice daily via 30-minute i.v. infusion, significantly increased serum sodium concentrations over 48 hours in patients with euvolemic or

						hypervolemic hyponatremia when compared with placebo.
9	Abraham[a] (2012)	RCT	206	Lixivaptan 25-100 mg/day (n=154)	placebo (n=52)	Lixivaptan could be safely initiated in an outpatient setting and effectively increased serum sodium concentrations in outpatients with euvolemic hyponatremia.
10	Abraham[b] (2012)	RCT	106	Lixivaptan 25-100 mg/day (n=54)	placebo (n=52)	Lixivaptan safely and effectively corrected serum sodium concentrations in hospitalized patients with euvolemic hyponatremia.
11	Chen (2014)	RCT	37	Tolvaptan 15-60 mg/day (n=19)	placebo (n=18)	Tolvaptan demonstrated superiority to placebo in the treatment of Chinese SIADH patients with hyponatremia by elevating serum sodium concentration with acceptable safety profile.
12	Salahudeen (2014)	RCT	30	Tolvaptan 15-60 mg/day (n=17)	placebo (n=13)	Tolvaptan was effective for correcting hyponatremia in patients with cancer.

Key question 7.

No.	Author (year)	Study type	Total (n)	Intervention (n)	Comparison (n)	Study results
1	MacMillan (2018)	Cohort (retrospective)	1450	3 ways to use DDAVP (254): rescue, reactive, proactive	No DDAVP (1196)	We identified 1,450 admissions with severe hyponatremia; DDAVP was administered in 254 (17.5%). Although DDAVP reduced the rate of change of plasma sodium, fewer patients in the DDAVP group achieved safe correction (174 of 251 [69.3%] vs. 970 of 1164 [83.3%]); this result was driven largely by overcorrection occurring before DDAVP administration in the rescue group. Among patients receiving DDAVP, most received it according to a reactive strategy, whereby DDAVP was given after a change in plasma sodium within correction limits (174 of 254 [68.5%]). Suspected osmotic demyelination syndrome was identified in 4 of 1450 admissions (0.28%). There was lower mortality in the DDAVP group (3.9% vs. 9.4%), although this is likely affected by confounding. Length

						of hospital stay was longer in those who received DDAVP according to a proactive strategy.
2	Perianayagam (2008)	Cohort (retrospective)	20	DDAVP use in anticipation of overcorrection (14)	DDAVP use in rescue of overcorrection (6)	Six patients (group 1) were given desmopressin acetate after the 24-h limit of 12 mmol/L had already been reached or exceeded; correction was prevented from exceeding the 48-h limit of 18 mmol/L in five of the six. Fourteen patients (group 2) were given desmopressin acetate in anticipation of overcorrection after the plasma sodium concentration had increased by 1 to 12 mmol/L. In all 14 patients who were treated with desmopressin acetate as a preventive measure, correction was prevented from exceeding either the 24- or 48-h limits. After desmopressin acetate was administered, the plasma sodium concentration of 14 of the 20 patients fell by 2 to 9 mmol/L. In all six group 1 patients and in five of the group 2 patients, the plasma sodium concentration was actively lowered again by the concurrent administration of desmopressin acetate and 5% dextrose in water; no serious adverse consequences from this maneuver were observed.
3	Ward (2018)	Cohort (retrospective)	28	3 ways to use DDAVP (254): rescue, reactive, prophylactic	No DDAVP (12)	Twenty-eight patients were identified, with baseline mean [Na]s of 112.7 ± 6.6 mmol/L versus 117 ± 4.3mmol/L (p=0.06) in those receiving (n=16) and not receiving DDAVP (n=12), respectively. The DDAVP group had a more rapid [Na]s correction on the first day compared with those not receiving DDAVP, 7.7 ± 3.8 mmol/L/d versus 5.1 ± 2.0 mmol/L/d (p=0.04). On the second day, there was a similar rate of [Na]s correction between groups: 1.3 ± 4.3 mmol/L/d versus 2.6 ± 3.2 mmol/L/d (p=0.39), respectively. Overall, there was no difference in [Na]s correction after 48 hours between those who received DDAVP and those who did not: 121.7 ± 7.5 mmol/L versus 124.8 ± 5.7 mmol/L (p=0.24). Patients who had experienced an overcorrection were

						successfully treated with DDAVP (n=5), so that no patient had an ongoing overcorrection by 48 hours.

Key question 8.

Not applicable

Key question 9.

No.	Author (year)	Study type	Total (n)	Intervention (n)	Comparison (n)	Study results
1	Friedman (2015)	RCT	110	54	56	Mean serum sodium levels at 24 hours did not differ between the groups (140.5 [2.7] vs. 139.6 [2.7] mEq/L, respectively; 95% CI of the difference, −0.22-2.02mEq/L; p=0.14). Two patients in the hypotonic group developed hyponatremia, 1 in each group developed hypernatremia.
2	McNab (2015)	RCT	641	319	322	Fewer patients given Na140 than those given Na77 developed hyponatremia (12 patients [4%] vs. 35 [11%]; odds ratio [OR] 0·31, 95% CI 0·16–0·61; p=0·001). No patients developed symptomatic hyponatremia. The occurrence of hypernatremia was similar in the two groups: 14 (4%) participants developed hypernatremia in the Na140 group, compared with 18 (6%) in the Na77 group (OR 0·80, 95% CI 0·39–1·65; p=0·55).
3	Ramanathan (2016)	RCT	119	59	60	Nine (15%) children in the isotonic group and 29 (48%) in the hypotonic group developed hyponatremia during the study period, (p<0.001) with a relative risk being 3.16 (95% CI 1.64-6.09). No child in either group developed hypernatremia.
4	Rey (2011)	RCT	125	63	62	After adjusting for age, weight and hyponatremia incidence at admission, patients receiving hypotonic fluids showed increased risk of hyponatremia by 5.8-fold (CI: 2.4–14.0)

						during the study period (p<0.001).
5	Shamin (2014)	RCT	60	30	30	At 24 hours, hyponatremia was noted in 7 (24%) patients in the isotonic and 16 (55%) in hypotonic group (p=0.031). Hypernatremia was noted at 48 hours in 3 IF (p=0.27).
6	Pemde (2015)	RCT	82	28	54	The risk of developing hyponatremia was nearly 6.5 (95% confidence interval (CI) 1.6–26) to 8.5 (95% CI 2.16–33.39) times higher in patients who received hypotonic saline compared to those who received isotonic saline. Only one patient who received isotonic saline developed hypernatremia (serum sodium=153 mmol/L) during the study period of 24h.
7	Almeida (2015)	RCT	233	130	103	NaCl 0.9% (n=130): serum Na increased by 2.91 (±3.9) mmol/L at 24 h (p<0.01); 2% of patients had Na higher than 150 mmol/L. NaCl 0.45% (n=103): serum Na did not display statistically significant changes. Fifteen percent of the patients had Na < 135 mmol/L at 24 h.
8	Balasubramanian (2012)	RCT	84	42	42	The proportion of neonates developing hyponatremia after 8 h was higher in the hypotonic fluid group as compared to the isotonic fluid group (48.8% vs. 10.5%, p<0.001). However, a larger proportion in the isotonic fluid group developed hypernatremia (39.5% vs. 12.2%, p<0.001).
9	Coulthard (2012)	RCT	79	39	40	In the 0.45% saline group, seven patients (18%) became hyponatremic (Na <135 mmol/l) 16–18 h postoperatively; in the Hartmann's group no patients became hyponatremic (p=0.01). No child in either fluid group became hypernatremic.
10	Choong (2011)	RCT	258	128	130	Hypotonic fluid significantly increased the risk of hyponatremia compared with isotonic fluid (40.8% vs. 22.7%; relative risk: 1.82 [95% confidence interval: 1.21–2.74]; p=0.004). Isotonic fluid did not increase the risk of hypernatremia (relative risk: 1.30 [95% confidence interval: 0.30 –5.59]; p=0.722).

11	Kannan (2010)	RCT	114	58	56	We observed that 14.3% (8/56) of the children administered 0.18% saline in 5% dextrose at the standard maintenance rate developed hyponatremia compared with 1.72% of the children in 0.9% saline in 5% dextrose at the standard maintenance rate. There was no significant difference in the incidence of hypernatremia (p=0.59)
12	Mantanana (2008)	RCT	122	59	63	At 24 hours, the percentage of hyponatremia in the hypotonic group was 20.6% as opposed to 5.1% in the isotonic group (p=0.02).
13	Neville (2010)	RCT	62	31	31	There was no difference in the incidence of hyponatremia at 24 hours comparing the groups (p=0.64). Plasma sodium concentration rose by ≥ 5 mmol/L in 7/62 in the NS groups (3/31), but none of the N/2 groups (p=0.05)
14	Torres (2019)	RCT	294	143	151	At 24 hours, 12.4% (n=18) of the isotonic group had developed hyponatremia compared with 46.1% (n=71) of the hypotonic group (p<0.001). No patients developed hypernatremia (serum sodium concentrations >150 mEq/L) or other adverse outcomes.
15	Bagri (2019)	RCT	150	75	75	The incidence of hyponatremia at 24 h of hospitalization was comparable between normal saline and half saline group, 3 (4%) vs. 6 (8%) cases, respectively; p value 0.494. A total of 4 children in the study population developed hypernatremia at 24 h, one in half saline group with a value of 150.1 mEq/L and 3 in normal saline group with highest value of 161 mEq/L.
16	Kumar (2020)	RCT	168	84	84	The incidence of hyponatremia at 24 h in children receiving half normal saline was higher than in those receiving normal saline, the difference was not statistically significant (14.3 vs. 6%; RR 2.6; 95% CI 0.9–7.8; p=0.07). There was no significant difference in the incidence of hypernatremia between two groups (RR 0.7; 95% CI 0.16-3.3).
17	Dathan (2021)	RCT	60	31	29	Three patients in the hypotonic group developed hyponatremia and none in isotonic group at 24 h (RR=0.13; 95% CI=0.007-2.485; p=0.106). Fourteen neonates

						developed hypernatremia in the isotonic group and one in hypotonic group at 24 h (RR=13.09; 95% CI=1.83-93.4; p<0.001).
18	Lehtiranta (2021)	RCT	614	308	306	The occurrence of mild hyponatremia did not differ between children receiving isotonic fluid therapy (7 of 308 patients, 2.3%) and children receiving moderately hypotonic fluid therapy (11 of 306 patients, 3.6%) (difference, –1.3%; 95% CI, -4.3 to 1.5; p=0.33). Hypernatremia developed in 4 patients (1.3%) receiving isotonic fluid therapy and in none of those receiving moderately hypotonic fluid therapy (95% CI of the difference, 0.05%-3.3%; p=0.04).
19	Chromek (2021)	Retrospective consecutive time series intervention study	1453	807	646	Overall, the change from hypotonic to isotonic intravenous maintenance fluid therapy was associated with a decreased prevalence of hyponatremia from 29% to 22% (adjusted OR 0.65 (0.51–0.82)) without a significantly increased odds or hypernatremia (from 3.4% to 4.3%, adjusted OR 1.2 (0.71–2.1)). Hyponatremia <130 mmol/L decreased from 6.2% to 2.6%, and hyponatremia 125 mmol/L decreased from 2.0% to 0.5%.
20	Tuzun (2020)	Cohort (retrospective)	108	51	57	The hypotonic fluid group showed a greater ΔpNa compared to the isotonic group (0.48 ± 0.28 vs. 0.27 ± 0.21 meq/L/h, p=0.001). The risk of experiencing unsafe plasma Na decrease in the hypotonic fluid group (ΔpNa >0.5 meq/L/h) was higher than the isotonic fluid group (OR: 8.46; 95% CI: 2.3-30.06).
21	Velasco (2018)	Cohort (retrospective)	111	43	68	Among the patients who received hypotonic solutions, 28 (41.2%) developed hyponatremia, which was moderate (Na <130 mEq/Kg) in 11 cases, compared with 8 children (18.6%) who received isotonic solutions, with only one case of moderate hyponatremia (p=0.027). No cases of hypernatremia were recorded.