Supplement 6| Clinical evidence profiles (GRADE tables)

Key question 1.

FEUA in SIAD compared to FEUA in diuretics for hyponatremia

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	FEUA in SIAD	FEUA in diuretics	Relative (95% CI)	Absolute (95% CI)		
FEUA												
5	observational studies	not serious	not serious	not serious	not serious	none	233	154	-	MD 5.73 higher (4.56 higher to 6.9 higher)	⊕⊕◯◯ Low	CRITICAL
FENa												
5	observational studies	not serious	serious[a]	not serious	serious[b]	none	233	154	-	MD 0.07 higher (0.06 lower to 0.21 higher)	⊕◯◯◯ Very low	IMPORTANT

CI: confidence interval; MD: mean difference

a. Significant heterogeneity within studies
b. Confidence interval exceeded the minimally important difference (MID)

Key question 2.

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Copeptin / urine sodium in the differential diagnosis of hyponatremia									
2	observational studies	not serious	not serious	not serious	not serious	none	Copeptin measurement reliably identifies 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 secondary AVP release from primary AVP release.	⊕◯◯◯ Very low	CRITICAL

Key question 3.

Rapid intermittent bolus compared with slow continuous infusion for symptomatic severe hyponatremia (sNa ≤ 125 mmol/L)

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Increased delta Sodium									
At 1HR: (RCT)									
1	randomized trials	serious[a]	not serious	not serious	serious[b]	none	At 1 hour, delta serum sodium was significantly higher in the RIB group than in the SCI group (3.84 mmol/L vs. 1.97 mmol/L, P =0.010)	⊕⊕◯◯ Low	IMPORTANT
At 6 HR: (RCT)									
1	randomized trials	serious[a]	not serious	not serious	serious[b]	none	No significant differences between the groups were observed in delta serum sodium at 6 hours.	⊕⊕◯◯ Low	IMPORTANT
At 6 HR: (non RCT)									
1	observational studies	not serious	not serious	serious[c]	serious[b]	none	At 6 hours, delta serum sodium was significantly higher in the RIB group than in the SCI group (6 mmol/L vs. 3 mmol/L, P <0.0001)	⊕◯◯◯ Very low	IMPORTANT
At 12 HR: (RCT)									
1	randomized trials	serious[a]	not serious	not serious	serious[b]	none	At 12 hours, delta serum sodium was significantly higher in the SCI group than in the RIB group (6.79 mmol/L vs. 8.41 mmol/L, P =0.029)	⊕⊕◯◯ Low	NOT IMPORTANT

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
At 12 HR: (non RCT)									
1	observational studies	not serious	not serious	serious[c]	serious[b]	none	At 12 hours, delta serum sodium was significantly higher in the RIB group than in the SCI group (8 mmol/L vs. 5 mmol/L, P =0.0001)	⊕◯◯◯ Very low	NOT IMPORTANT
At 24 HR: (RCT)									
1	randomized trials	serious[a]	not serious	not serious	serious[b]	none	At 24 hours, delta serum sodium was significantly higher in the SCI group than in the RIB group (7.76 mmol/L vs. 9.38 mmol/L, P =0.023)	⊕⊕◯◯ Low	NOT IMPORTANT
At 24 HR: (non RCT)									
1	observational studies	not serious	not serious	serious[c]	serious[b]	none	No significant differences between the groups were observed in the delta sodium at 24 hours.	⊕◯◯◯ Very low	NOT IMPORTANT
Changing GCS									
At 6 HR (non RCT)									
1	observational studies	not serious	not serious	serious[c]	serious[b]	none	More rapid elevation in GCS at 6 hours occurred in the RIB group compared to SCI groups (3 vs. 1, P <0.0001).	⊕◯◯◯ Very low	IMPORTANT
At 24 HR (RCT)									
1	randomized trials	serious[a]	not serious	not serious	serious[b]	none	No significant differences between the groups were observed in the GCS at 24 hours.	⊕⊕◯◯ Low	NOT IMPORTANT
At 24 HR (non RCT)									
1	observational studies	not serious	not serious	Serious[c]	serious[b]	none	The improvement in GCS was similar in the two groups at 24 hours.	⊕◯◯◯ Very low	NOT IMPORTANT
Target Correction rate									
Within 1 HR (RCT)									
1	randomized trials	serious[a]	not serious	not serious	serious[d]	none	The proportion of patients achieving target correction rate within 1 hour was higher in the RIB group (32.2% [28/87] vs. 17.6% [16/91]; absolute risk difference, 14.6% [95% CI 2% to 27.2%], p=0.02)	⊕⊕◯◯ Low	IMPORTANT
Within 24 HR (RCT)									
1	randomized trials	serious[a]	not serious	not serious	serious[d]	none	No significant differences between the groups were observed in the incidence of target correction rate in 24 hours.	⊕⊕◯◯ Low	NOT IMPORTANT
Within 24 HR (non RCT)									

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
1	observational studies	not serious	not serious	serious[c]	serious[d]	none	No significant differences between the groups were observed in the incidence of target correction rate within 24 hours.	⊕◯◯◯ Very low	NOT IMPORTANT
Overcorrection within 48HR (RCT)									
1	randomized trials	serious[a]	not serious	not serious	serious[d]	none	Overcorrection occurred in 17.2% (15/87) in the RIB group and 24.2% (22/91) in SCI group (absolute risk difference,-6.9% [95% CI -18.8% to 4.9%], p=0.26)	⊕⊕◯◯ Low	CRITICAL
Overcorrection within 24HR (non RCT)									
1	observational studies	not serious	not serious	serious[c]	serious[d]	none	No significant differences between the groups were observed in the overcorrection rate within 28 hours.	⊕◯◯◯ Very low	CRITICAL
Relowering Treatment within 48HR (RCT)									
1	randomized trials	serious[a]	not serious	not serious	serious[d]	none	The RIB group showed a lower incidence of re-lowering treatment than the SCI group (41.4% [36/87] vs. 57.1% [52/91]; absolute risk difference, -15.8% [95% CI -30.3% to -1.3%], p=0.04)	⊕⊕◯◯ Low	CRITICAL
Relowering Treatment within 24HR (non RCT)									
1	observational studies	not serious	not serious	serious[c]	serious[d]	none	No significant differences between the groups were observed in the incidence of relowering treatment in 24 hours.	⊕◯◯◯ Very low	CRITICAL
Osmotic demyelination Syndrome within 48HR (RCT)									
1	randomized trials	serious[a]	not serious	not serious	very serious[d,f]	none	There were no events of ODS in either group.	⊕◯◯◯ Very low	IMPORTANT
Osmotic demyelination Syndrome within 24HR (non RCT)									
1	observational studies	not serious	not serious	serious[c]	very serious[d,f]	none	There were no events of ODS in either group.	⊕◯◯◯ Very low	IMPORTANT
Mortality during admission within (RCT)									
1	randomized trials	serious[a]	not serious	not serious	very serious[d,f]	none	No significant differences between the groups were observed in the incidence of mortality rate during admission.	⊕⊕◯◯ Low	NOT IMPORTANT
Mortality during admission (non RCT)									

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
1	observational studies	not serious	not serious	Serious[c]	very serious[d,f]	none	No significant differences between the groups were observed in mortality rate.	⊕◯◯◯ Very low	NOT IMPORTANT

CI: confidence interval; OR: odds ratio

a. Assignment order not concealed
b. Total number of subjects < 400 patients
c. RIB in prospective cohort vs. SCI in historical control

Key question 4.

Mild hyponatremia versus normonatremia in terms of mortality

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Long term	placebo	Relative (95% CI)	Absolute (95% CI)		
Long-term mortality												
2	observational studies	not serious	not serious	not serious	not serious	none	35860/93595 (38.3%)	192948/638726 (30.2%)	OR 1.46 (1.44 to 1.48)	85 more per 1,000 (from 82 more to 88 more)	⊕⊕◯◯ Low	CRITICAL
Short-term mortality												
2	observational studies	not serious	not serious	not serious	not serious	none	624/11704 (5.3%)	2068/84138 (2.5%)	OR 2.09 (1.90 to 2.30)	25 more per 1,000 (from 21 more to 30 more)	⊕⊕◯◯ Low	CRITICAL

CI: confidence interval; OR: odds ratio

Key question 5.

VRA compared to loop diuretic treatment in hypervolemic hyponatremia for the patients with heart failure

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with loop diuretics treatment in hypervolemic hyponatremia	Risk with VRA				
Mortality: overall studies	53 per 1,000	45 per 1,000 (25 to 83)	RR 0.85 (0.47 to 1.56)	835 (5 RCTs)	⊕⊕⊕◯ Moderate[1,a]	
Worsening Renal Function	280 per 1,000	252 per 1,000 (193 to 330)	RR 0.90 (0.69 to 1.18)	586 (4 RCTs)	⊕⊕⊕⊕ High	
Mortality: VRA add-on studies	49 per 1,000	46 per 1,000 (24 to 86)	OR 0.93 (0.48 to 1.81)	775 (4 RCTs)	⊕⊕⊕⊕ High	
Sodium correction		MD 3.21 higher (3.12 higher to 3.29 higher)	-	382 (3 RCTs)	⊕⊕⊕⊕ High	

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI: confidence interval; MD: mean difference; OR: odds ratio; RR: risk ratio

a. wide range of CI

Key question 6.

Vaptans compared to placebo for all-cause mortality

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with vaptans				
All-cause mortality	70 per 1,000	59 per 1,000 (36 to 94)	OR 0.83 (0.50 to 1.38)	1087 (9 RCTs)	⊕⊕⊕◯ Moderate[a]	
All-cause mortality-euvolemia	65 per 1,000	29 per 1,000 (10 to 81)	OR 0.43 (0.14 to 1.27)	363 (3 RCTs)	⊕⊕⊕◯ Moderate[b]	
All-cause mortality-euvolemia or hypervolemia	72 per 1,000	71 per 1,000 (42 to 122)	OR 0.99 (0.56 to 1.78)	724 (6 RCTs)	⊕⊕⊕◯ Moderate[a]	

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
CI: confidence interval; OR: odds ratio

a. wide confidential interval
b. low incidence, wide confidential interval

Vaptans compared to placebo for normalization of serum sodium

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with vaptans				
serum sodium normalization	165 per 1,000	564 per 1,000 (487 to 638)	OR 6.53 (4.80 to 8.89)	1117 (11 RCTs)	⊕⊕⊕⊕ High	
serum sodium normalization - euvolemia	194 per 1,000	499 per 1,000 (365 to 633)	OR 4.15 (2.40 to 7.20)	363 (3 RCTs)	⊕⊕⊕⊕ High	
serum sodium normalization - euvolemia or hypervolemia	154 per 1,000	597 per 1,000 (505 to 682)	OR 8.12 (5.59 to 11.80)	754 (8 RCTs)	⊕⊕⊕⊕ High	

Vaptans compared to placebo for overcorrection of serum sodium

Outcomes	Anticipated absolute effects* (95% CI)	Relative effect	№ of participants	Certainty of the evidence	Comments

	Risk with placebo	Risk with vaptans	(95% CI)	(studies)	(GRADE)	
overcorrection	26 per 1,000	52 per 1,000 (19 to 137)	OR 2.06 (0.71 to 5.94)	324 (5 RCTs)	⨁⨁◯◯ Low[a,b]	
overcorrection - euvolemia	42 per 1,000	36 per 1,000 (8 to 151)	OR 0.87 (0.19 to 4.09)	157 (2 RCTs)	⨁⨁⨁◯ Moderate[b]	
overcorrection - euvolemia or hypervolemia	0 per 1,000	0 per 1,000 (0 to 0)	OR 4.16 (0.76 to 22.73)	167 (3 RCTs)	⨁⨁◯◯ Low[a,b]	

Key question 7.

DDAVP (proactive, reactive) vs. no DDAVP

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	DDAVP (proactive, reactive)	No DDAVP	Relative (95% CI)	Absolute (95% CI)		
overcorrection												
2	observational studies	not serious	not serious	not serious	not serious	none	35/216 (16.2%)	0.0%	RR 0.88 (0.63 to 1.23)	0 fewer per 1,000 (from 0 fewer to 0 fewer)	⨁◯◯◯ Very low	IMPORTANT
osmotic demyelination syndrome												
2	observational studies	not serious	not serious	not serious	not serious	none	1/216 (0.5%)	0.0%	RR 5.92 (0.37 to 94.28)	0 fewer per 1,000 (from 0 fewer to 0 fewer)	⨁◯◯◯ Very low	CRITICAL

CI: confidence interval; RR: risk ratio

DDAVP (proactive, reactive) vs. DDAVP (rescue)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	DDAVP (proactive, reactive)	DDAVP (rescue)	Relative (95% CI)	Absolute (95% CI)		
osmotic demyelination syndrome												
2	observational studies	not serious	not serious	not serious	not serious	none	1/216 (0.5%)	1/48 (2.1%)	RR 0.23 (0.01 to 3.57)	16 fewer per 1,000 (from 21 fewer to 54 more)	⨁◯◯◯ Very low	CRITICAL
survival												
2	observational studies	not serious	not serious	not serious	not serious	none	206/216 (95.4%)	51/52 (98.1%)	RR 0.98 (0.92 to 1.03)	20 fewer per 1,000 (from 78 fewer to 29 more)	⨁◯◯◯ Very low	IMPORTANT

CI: confidence interval; RR: risk ratio

DDAVP (rescue) vs. no DDAVP

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	DDAVP (rescue)	No DDAVP	Relative (95% CI)	Absolute (95% CI)		
osmotic demyelination syndrome												
2	observational studies	not serious	not serious	not serious	not serious	none	1/48 (2.1%)	0.0%	RR 13.00 (1.20 to 140.79)	0 fewer per 1,000 (from 0 fewer to 0 fewer)	⊕◯◯◯ Very low	CRITICAL

CI: confidence interval; RR: risk ratio

DDAVP (all) vs. no DDAVP

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	DDAVP (all)	No DDAVP	Relative (95% CI)	Absolute (95% CI)		
osmotic demyelination syndrome												
2	observational studies	not serious	not serious	not serious	not serious	none	2/270 (0.7%)	0.0%	RR 4.71 (0.67 to 33.27)	0 fewer per 1,000 (from 0 fewer to 0 fewer)	⊕◯◯◯ Very low	CRITICAL
Survival to discharge												
2	observational studies	not serious	not serious	not serious	not serious	none	258/270 (95.6%)	1095/1208 (90.6%)	RR 1.06 (1.02 to 1.09)	54 more per 1,000 (from 18 more to 82 more)	⊕◯◯◯ Very low	IMPORTANT

DDAVP: desmopressin, CI: confidence interval; RR: risk ratio

Key question 8.

Not applicable

Key question 9.

Children (≥1 month) RCT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Isotonic	Hypotonic	Relative (95% CI)	Absolute (95% CI)		
Risk of hypernatremia												
16	randomized trials	not serious	not serious	not serious	serious[a]	none	60/1607 (3.7%)	36/1623 (2.2%)	OR 1.67 (0.92 to 3.04)	14 more per 1,000 (from 2 fewer to 42 more)	⨁⨁⨁◯ Moderate	CRITICAL
Risk of hyponatremia												
16	randomized trials	not serious	not serious	not serious	not serious	none	117/1608 (7.3%)	301/1623 (18.5%)	OR 0.32 (0.24 to 0.43)	118 fewer per 1,000 (from 134 fewer to 96 fewer)	⨁⨁⨁⨁ High	CRITICAL

Children (non-RCT)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Isotonic	Hypotonic	Relative (95% CI)	Absolute (95% CI)		
Hyponatremia (<135 mmol/L)												
2	observational studies	not serious	not serious	not serious	not serious	none	183/850 (21.5%)	218/714 (30.5%)	OR 0.54 (0.28 to 1.02)	114 fewer per 1,000 (from 196 fewer to 4 more)	⨁⨁◯◯ Low	CRITICAL
Moderate hyponatremia (<130 mmol/L)												
2	observational studies	not serious	not serious	not serious	not serious	strong association	22/850 (2.6%)	51/714 (7.1%)	RR 0.38 (0.22 to 0.62)	44 fewer per 1,000 (from 56 fewer to 27 fewer)	⨁⨁⨁◯ Moderate	CRITICAL
Hypernatremia												
2	observational studies	not serious	not serious	not serious	serious[a]	none	35/850 (4.1%)	23/714 (3.2%)	OR 1.25 (0.73 to 2.13)	8 more per 1,000 (from 8 fewer to 34 more)	⨁◯◯◯ Very low	CRITICAL

Neonate (RCT)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Isotonic	Hypotonic	Relative (95% CI)	Absolute (95% CI)		
Risk of hyponatremia												
2	randomized trials	not serious	not serious	not serious	serious[a]	none	3/73 (4.1%)	21/71 (29.6%)	OR 0.11 (0.03 to 0.35)	252 fewer per 1,000 (from 283 fewer to 168 fewer)	⨁⨁⨁◯ Moderate	CRITICAL
risk of hypernatremia												
2	randomized trials	not serious	not serious	not serious	serious[b]	none	28/73 (38.4%)	5/71 (7.0%)	OR 8.24 (1.84 to 36.91)	314 more per 1,000 (from 52 more to 666 more)	⨁⨁⨁◯ Moderate	CRITICAL