SUPPLEMENTARY APPENDIX FOR THE STUDY:

Empagliflozin increases plasma sodium levels in patients with the syndrome of inappropriate antidiuresis – a randomized, double-blind, placebo-controlled study

Table of Contents

1. ADDITIONAL STATISTICAL INFORMATION

1.1 Sample size estimation

Sample size is estimated to be able to show the superiority of empagliflozin as add-on compared to the standard fluid restriction with regard to the primary endpoint change in the plasma sodium concentration from baseline to day 4. Sample size assumptions were based on the findings of Greenberg et al. (2015) who reported a median daily change in the plasma sodium concentration from baseline of 1.2 mmol/l with and inter-quartile range (IQR) of 0.3–2.5, concentration which indicates a right skewed distribution. Assuming a constant daily change within the first four days, this corresponds to a medium change in plasma sodium concentration of 4.8 (1.2 - 10).

Sample size was calculated using a re-sampling procedure. Each total sample size (n = 50 --150) was evaluated by sampling 999 times n/2 individual samples for each group as follows. In order to come as close as possible without further knowledge to the skewed distribution, we assumed the following distribution for the primary endpoint: half of all values (values larger than the median) in the placebo group were sampled without replacement from 5000 simulated values from a normal distribution with mean = 4.8 and standard-deviation = 7.6 which were > 4.8 (larger than the median).The other half of the values (values smaller than the median) in the placebo group were sampled without replacement from 5000 simulated values from a normal distribution with mean = 4.8 and standard deviation = 5.2 which were < 4.8 (smaller than the median). The same procedure was applied for the empagliflozin group, however assuming mean = 6.8. Superiority of SGLT-2 inhibitor as add-on compared to the standard fluid restriction is declared when a two-sample Wilcoxon rank sum test is statistically significant ($p<0.05$). Sample size was set to ensure at least 90% power at a significance level of 0.05.

Assuming a difference in change in the plasma sodium concentration from baseline to day 4 of 2.0 between empagliflozin and placebo group, a total of 93 patients should be recruited, in order to have a total of 83 evaluable patients, considering a drop-out rate of 10%.

1.2 Multiple imputation

In case of missing plasma sodium values at day 5, the primary endpoint was imputed using multiple imputation by chained equations (MICE). The R package mice van Buuren & Groothuis-Oudshoorn (2011) was used. The primary end-point was imputed using linear regression. In this linear regression, trial arm and all plasma sodium measurements (baseline, 12h, 24h, 36h, 48h, 72h and 96h) and the interaction terms with trial arm were considered as predictors. We thus assumed that plasma sodium values at day 5 are missing at random (MAR), conditionally on trial arm and previous plasma sodium measurements. In order to select the best imputation model, potential associations of the primary endpoint with plasma sodium at each measurement time were inspected visually by means of scatterplots, using the respective complete cases. Based on these, plasma sodium at baseline and at day 4 seemed to show an association with the primary endpoint. We compared three regression models (sodium at baseline plus trial arm; sodium at day 4 plus trial arm; sodium at baseline and day 4 plus trial arm). The regression model including trail arm, sodium at baseline and at day 4 in the two interaction terms with trial arm was best (AIC 355, vs. 456 and 432) and was hence used as imputation model. Missing values in sodium at day 4 were first imputed using linear regression with trial arm, baseline plasma sodium and the interaction term as predictors. We imputed 10 data sets, using 20 iterations each. Convergence of the MICE algorithm was assessed graphically and considered good. Plausibility of imputed values was checked graphically by comparing observed and imputed values and considered good. A total of m = 10 imputed data sets were produced. The primary analysis was performed on each imputed data set and the results were pooled applying Rubin's rule (Rubin, 2004).

1.3 Area under the curve *(AUC)*

AUCs were calculated using linear trapezoidal method. Single missing values were interpolated by averaging the immediately preceding and subsequent value. In case of two or more consecutive missing values, or in case of missing baseline value, no AUC was calculated (set to missing value). In case of missing value at day 5, the value of day 4 was used (LOCF).

2. SUPPLEMENTARY FIGURES AND TABLES

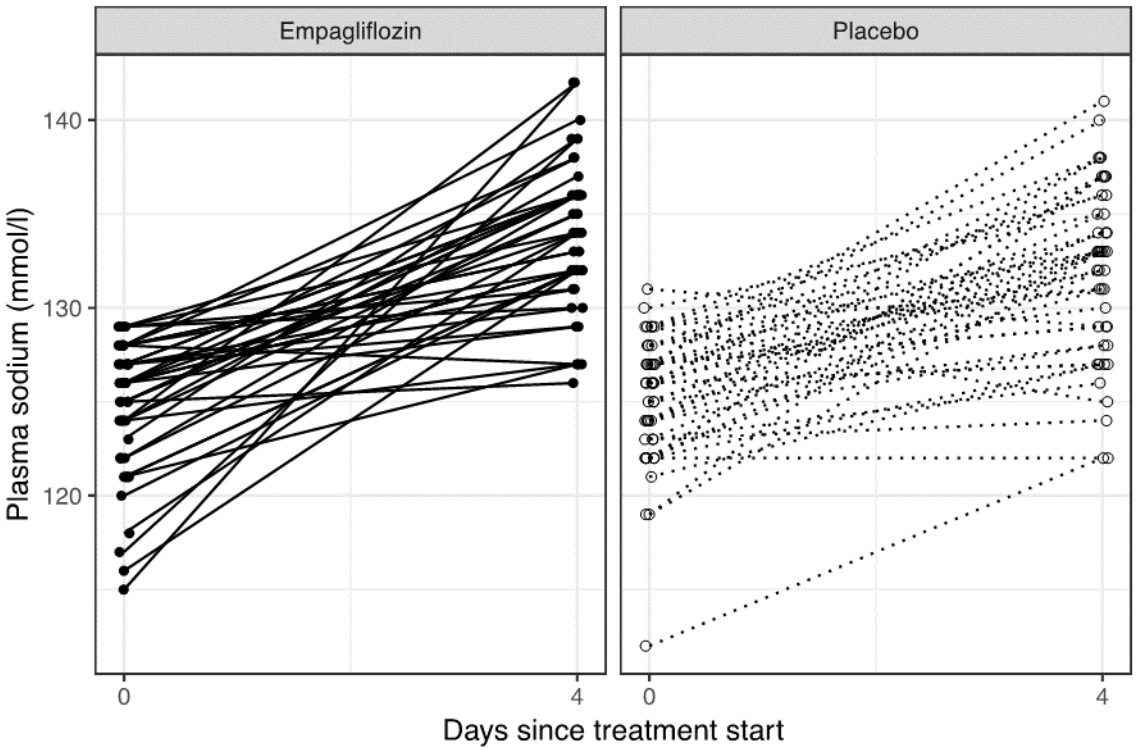
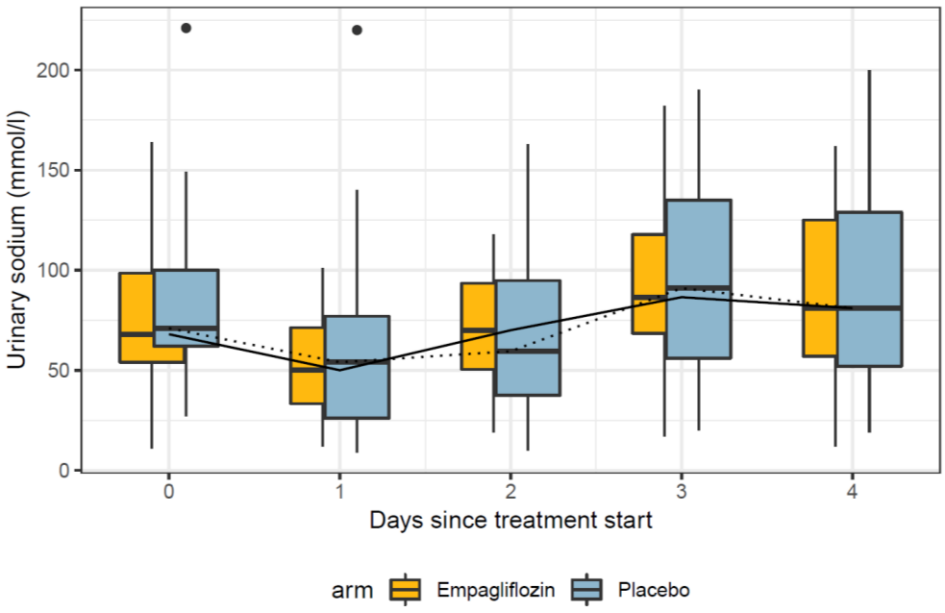
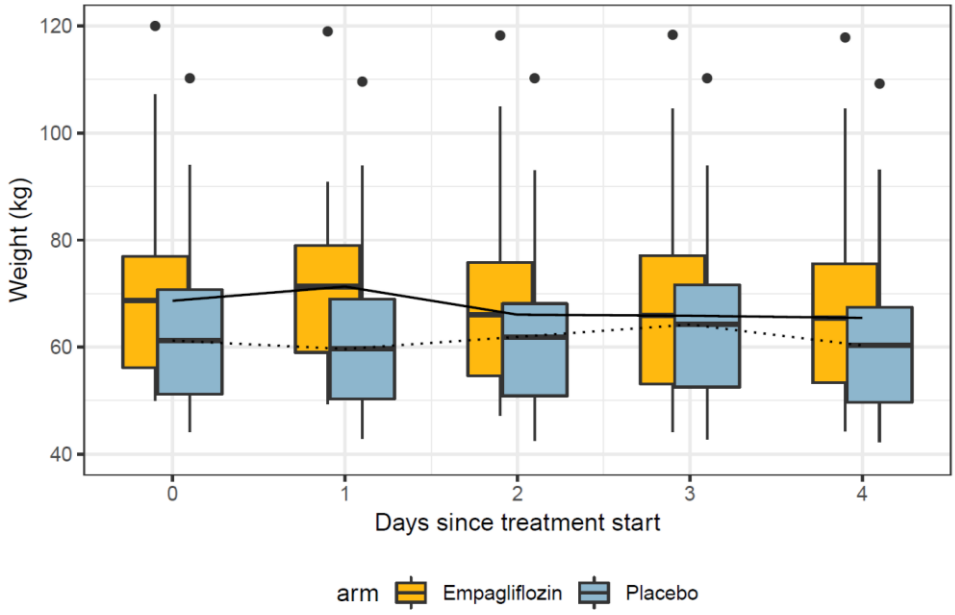


Figure S1 Plasma sodium levels at baseline and after 4 days of treatment according to trial arm. Measures of each patient are connected by a separate line.



A



B

Figure S2: A) Course of urinary sodium levels during intervention, **B)** Course of body weight during intervention

Boxes contain the 25 through 75% quantiles (spanning the interquartile range), the thick horizontal line is the median. Whiskers indicate the most extreme values lying within the box-edge and 1.5 times the interquartile range. All eventual further values are plotted as individual points (outliers).

Table S1 Changes of plasma sodium

A	Trial group	Timepoint	Median (IQR)	n
	Empagliflozin	24h	4 (2-6)	41
	Placebo	24h	3 (0-4.3)	44
	Empagliflozin	48h	8 (3-10)	41
	Placebo	48h	5 (2-7.8)	42
	Empagliflozin	Discharge	10 (5-13.8)	42
	Placebo	Discharge	7 (2.8-13)	44
B	**Effect**	**Timepoint**	**Estimate (95% CI)**	**p-value**
	Baseline P-sodium	24h	-0.3 (-0.5,-0.1)	0.008
	Trial group: Placebo - Empagliflozin	24h	-1.8 (-3.2, -0.3)	0.017
	Baseline P-sodium	48h	-0.5 (-0.8, -0.3)	<0.001
	Trial group: Placebo - Empagliflozin	48h	-1.7 (-3.5, 0.1)	0.064
	Baseline P-sodium	Discharge	-1.1 (-1.3, -0.8)	<0.001
	Trial group: Placebo - Empagliflozin	Discharge	-1.3 (-3.0, 0.4)	0.137

Table S1

A) Summary statistics for changes in plasma sodium from baseline to different timepoints.

IQR = inter-quartile range

B) Associations of changes in plasma sodium from baseline to 24h, 48h and discharge with baseline plasma sodium values and trial group. Each time point was analyzed in a separate linear regression model.

CI = confidence interval. P = plasma

Table S2 Effects of covariates on main effect

Covariate	Effect	Estimate (95% CI)	p-Value
Plasma sodium	Main effect	-1.17 (-1.54,-0.81)	<0.001
	Interaction term	0.54 (0.02,1.05)	0.045
Urinary sodium	Main effect	-0.04 (-0.09,0.02)	0.177
	Interaction term	-0.01 (-0.08,0.06)	0.787
Plasma urea	Main effect	-0.19 (-1.08,0.7)	0.680
	Interaction term	-0.68 (-1.98,0.63)	0.314
Urinary urea	Main effect	-0.01 (-0.03,0.01)	0.230
	Interaction term	0.01 (-0.02,0.04)	0.478
Plasma uric acid	Main effect	0 (-0.02,0.02)	0.975
	Interaction term	0.01 (-0.01,0.04)	0.341
Urinary uric acid	Main effect	-2.18 (-3.98,-0.38)	0.021
	Interaction term	1.23 (-1.84,4.29)	0.437
Plasma glucose	Main effect	-0.76 (-2.11,0.58)	0.270
	Interaction term	1.05 (-0.66,2.76)	0.234
Urinary glucose	Main effect	57.37 (-59.32,174.06)	0.341
	Interaction term	-48.16 (-171.13,74.81)	0.447
Plasma osmolality	Main effect	-0.37 (-0.5,-0.24)	<0.001
	Interaction term	0.21 (0.04,0.38)	0.018
Urinary osmolality	Main effect	-0.01 (-0.02,0)	0.109
	Interaction term	0 (-0.01,0.02)	0.809
Plasma sodium <125mmol/l	Main effect	7.37 (4.36,10.38)	<0.001
	Interaction term	-3.68 (-7.79,0.44)	0.084
Age (years)	Main effect	-0.01 (-0.14,0.11)	0.827
	Interaction term	0.03 (-0.15,0.21)	0.763

Sex (male)	Main effect Interaction term	-1.95 (-5.45,1.55) 2.25 (-2.58,7.09)	0.279 0.364
Etiology	Main effect Interaction term	1.2 1.1	0.298 0.362

Table S2 Estimated main effects of covariates and their interaction term with trial group for the primary endpoint, absolute change in plasma sodium from baseline to end of treatment.
All covariates refer to baseline measurements. The main effect indicates how the primary endpoint depends on the covariate, and the interaction term indicates how this effect differs between trial arms. For etiology, the estimate represents the F-value of the ANOVA (global test). For all other covariates, the estimates are given as absolute effects with 95% confidence intervals (CI). Each covariate was analyzed in a separate linear regression model. For urinary uric acid, estimates are indicated per 1000 ml/l.