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ORIGINAL ARTICLE

A Randomized Trial of Targeted Hyponatremia Correction in Hospitalized Patients

Julie Refardt, M.D., Ph.D.,[1,2,3] Laura Potasso, M.D., Ph.D.,[1,2,4] Anissa Pelouto, M.D.,[3] Moritz Trappe, M.D.,[5,6] Claudia Gregoriano, Ph.D.,[7] Markus Koster, M.D.,[8] Ivana Dora Vodanovic, M.D.,[9] Dario Norello, M.D., Ph.D.,[10] Svenja Ravioli, M.D.,[11,12] Sadrija Cukoski, M.D.,[5,6] Maria Boesing, M.D., Ph.D.,[2,4] Basil Ryser, M.D.,[11] Lana Sambula, M.D.,[9] Nikola Rapsch, M.D.,[5,6] Sophie Monnerat, M.D., Ph.D.,[1,2] Julia Beck, M.D.,[1,2] Sven Lustenberger, M.D.,[1,2] Deborah R. Vogt, Ph.D.,[2] Laura Werlen, Ph.D.,[2] Joyce Santos de Jesus, RN,[1,2] Martina Bontognali, M.D.,[8] Philipp Schuetz, M.D.,[7] Adrienne A.M. Zandbergen, M.D., Ph.D.,[3] Alessandro Peri, M.D., Ph.D.,[10,13] Darko Kastelan, M.D., Ph.D.,[9] Gregor Lindner, M.D.,[11,12] Joerg Leuppi, M.D., Ph.D.,[2,4] Stefan Bilz, M.D.,[8] Beat Mueller, M.D.,[7] Volker Burst, M.D.,[5,6] Ewout J. Hoorn, M.D., Ph.D.,[3] and Mirjam Christ-Crain, M.D., Ph.D.,[1,2] for the HIT study investigators*

Abstract

BACKGROUND Chronic hyponatremia is associated with adverse outcomes, including falls, neurocognitive disorders, and mortality, but whether hyponatremia itself increases morbidity and mortality, or is simply an indicator of underlying disease severity, remains unclear. We aimed to evaluate the effects of targeted hyponatremia correction versus routine care on mortality and rehospitalization rates.

METHODS We conducted a randomized, controlled, parallel-group, multicenter trial across nine European centers. Hospitalized participants with plasma sodium lower than 130 mmol/l were assigned to undergo either a multifaceted targeted correction of hyponatremia (intervention) or routine care for hyponatremia (control). The primary outcome was the combined risk of death or rehospitalization within 30 days of trial inclusion.

RESULTS A total of 2173 patients were randomly assigned to intervention (n=1079) or control (n=1094). The median age was 73 years (interquartile range, 63 to 81) and 48% were male. The median baseline sodium levels were 127 mmol/l (interquartile range, 124 to 128) in both groups. The mean (± standard deviation) maximum absolute change in sodium levels during the treatment period was 10.0 mmol/l (±5.6) in the intervention group, compared with 8.7 mmol/l (±5.6) in the control group, resulting in normal sodium levels (defined as 135–145 mmol/l) in 641 (60.4%) and 492 (46.2%) patients in the intervention and control groups, respectively. Within 30 days after inclusion, the primary outcome occurred in 20.5% (218 of 1065 patients) in the intervention group and 21.8% (234 of 1073 patients) in the control group (estimated absolute difference, −1.3 percentage points; 95% confidence interval, −4.9 to 2.2; P=0.45). Death occurred in 86 (8.0%) patients and rehospitalization in 141 (13.2%) patients in the intervention group compared with 88 (8.0%) patients and 151 (14.1%) patients in the control group. Overcorrection occurred in 25 (2.3%) patients in the intervention group and 16 (1.4%) patients in the control group; no cases of osmotic demyelination syndrome were observed.

For details see the Supplementary Appendix.

The author affiliations are listed at the end of the article.

Julie Refardt can be contacted at j.refardt@erasmusmc.nl or at the Department of Internal Medicine, Erasmus Medical Center, Rotterdam, the Netherlands.

CONCLUSIONS In hospitalized patients with chronic hyponatremia, a targeted correction intervention resulted in higher normonatremia rates but did not reduce a composite outcome of 30-day mortality and rehospitalization. (Funded by the Swiss National Science Foundation [grant number, 33 IC30_192979]; ClinicalTrials.gov number, NCT03557957.)

Introduction

Hyponatremia is the most common electrolyte disorder in hospitalized patients, with an estimated prevalence of up to 30%.[1,2] It is classified according to volume status as hypovolemic, hypervolemic, or euvolemic, and according to time of development as acute (present for 48 hours or less) or chronic (present for more than 48 hours).[3-5]

While acute hyponatremia can present with severe symptoms caused by cerebral edema requiring immediate treatment, chronic hyponatremia, especially if mild to moderate, may present with few or no symptoms and may not be considered clinically relevant.[6,7] For instance, one international registry study of adult patients from 225 sites in the United States and European Union showed that among patients with a median sodium level of 125 mmol/l, laboratory tests to evaluate the etiology of hyponatremia were obtained in less than 50% of cases, and up to 75% of patients were still hyponatremic at discharge.[6]

Yet, evidence links chronic hyponatremia with complications such as gait alterations, falls, fractures, and neurocognitive disorders.[8-12] Chronic hyponatremia is also associated with higher overall morbidity and 30-day mortality, specifically in disorders of pneumonia, stroke, heart failure, or liver cirrhosis.[13-17] However, it remains uncertain whether chronic hyponatremia is responsible for the observed increase in morbidity and mortality,[18] or whether it is an indicator of the severity of the underlying disease.[19]

Recent small interventional studies and one small trial have shown that correction of chronic hyponatremia is associated with improvements in neuromuscular and neurocognitive outcomes, bone markers, and quality of life.[8,20-23] Similarly, several retrospective cohort studies and one meta-analysis reported reduced mortality and rehospitalization risks among patients reaching a normal sodium level.[13,24-26] However, whether targeted correction of hyponatremia beyond current practice, as reflected in the Hyponatremia Registry,[6] reduces 30-day mortality and rehospitalization risks has yet to be evaluated in a prospective randomized trial.

We therefore aimed to determine the effect of a targeted hyponatremia correction as compared with standard care on the combined risk of 30-day mortality and rehospitalization in hospitalized patients with chronic hypotonic hyponatremia.

Methods

TRIAL DESIGN AND PARTICIPANTS

This pragmatic randomized, controlled, parallel-group, international, multicenter superiority trial with blinded outcome assessment was performed at nine centers in Europe between August 2018 and April 2024, including both university and regional hospitals. The local ethics committees of all centers approved the trial protocol, and written informed consent was obtained from all patients. The trial was registered at ClinicalTrials.gov (NCT03557957).

Eligible patients were 18 years of age or older with hypotonic hyponatremia, defined as having a plasma sodium level lower than 130 mmol/l with a plasma osmolality of 300 mOsm/kg or less, at admission or any time during hospitalization on any wards, and in whom hyponatremia was considered to be chronic based on the time course of sodium evolution and absence of severe symptoms. Patients with severe symptomatic hyponatremia, that is, vomiting, confusion, seizures, or decreased levels of consciousness, in need of immediate correction with hypertonic saline, were excluded to avoid delaying treatment, but could be included once symptoms improved and if hyponatremia persisted for more than 48 hours after the initial treatment. Patients were also excluded in cases of end-of-life care, kidney disease requiring renal replacement therapy, acute liver failure, Wernicke's encephalopathy, hepatic encephalopathy occurring within 2 months before inclusion, hepatorenal syndrome, pregnancy or breastfeeding, and strict isolation due to hematological disease.

SCREENING, INCLUSION, AND RANDOMIZATION

Plasma sodium values ordered through routine care were reviewed several times daily in each center by the local trial physician. Patients were invited to participate in the trial as soon as the diagnosis of hypotonic hyponatremia below 130 mmol/l was confirmed. Patients were eligible for trial participation at any time during their hospitalization.

After providing informed consent, participants underwent a standardized initial assessment to document the reason for hospitalization, comorbidities, and relevant clinical and routine laboratory parameters. Neurocognitive assessment was performed using the Trail Making Test,[27] a two-part neuropsychological assessment that measures visual attention, processing speed, and cognitive flexibility (scores reflect time taken to complete the test; range varies by population, with lower scores indicating better performance).

Participants were randomly assigned to either targeted plasma sodium correction (intervention group) or standard treatment (control group) in a 1:1 ratio. Randomization was stratified by trial site, using randomly permuted block sizes.

TARGETED CORRECTION OF HYPONATREMIA

The targeted hyponatremia correction intervention was based on a predefined standardized diagnostic and treatment protocol in accordance with the international hyponatremia treatment guidelines[3,4] and specialty guidelines[28-31] (Fig. S1 in the Supplementary Appendix), implemented by daily input from the trial team (described below).

The predominant cause of hyponatremia was determined by the trial team based on medical history, clinical presentation, clinical assessment of extracellular fluid status, and laboratory tests. Specific instructions were available for every category and subcategory of hyponatremia as a stepwise approach, starting with basic treatment recommendations and escalating according to the severity of the underlying disease and/or treatment response. For example, patients with hyponatremia due to the syndrome of inappropriate antidiuresis received first fluid restriction, followed by the administration of oral urea, and lastly tolvaptan if no sufficient sodium increase was reached. If the etiology of hyponatremia remained unclear or was determined to be of mixed origin by the trial team, treatment was based on the predominant diagnosis.

Treatment response and adherence were evaluated daily by the trial team, and diagnosis and subsequent treatment were adjusted accordingly. Treatment was intensified if the daily increase in plasma sodium was less than 2 mmol/l, maintained if the increase was 2–12 mmol/l, and discontinued if the increase was greater than 12 mmol/l (or greater than 18 mmol/l in 48 hours). An increase of greater than 12 mmol/l in any 24-hour period or greater than 18 mmol/l in any 48-hour period was defined as overcorrection, independent of the time point of its occurrence, and treated with sodium-lowering therapy (hypotonic intravenous fluids with or without desmopressin).[3] Apart from hyponatremia correction, the local trial team did not influence treatment objectives and decisions, which remained at the discretion of the attending physicians. Targeted plasma sodium correction was maintained until a normal sodium level, defined as plasma sodium between 135 and 145 mmol/l, was achieved and maintained for the duration of the index hospitalization, or until the patient was discharged from the hospital. Targeted correction was discontinued if the patient was still hospitalized 30 days after inclusion and a normal sodium level was not yet reached. If the treating physicians transitioned the treatment to end-of-life care, targeted correction was discontinued, but the patient remained in the intervention group.

The decision to discharge a patient was not influenced by the trial team. The local trial team made the final diagnosis of hyponatremia etiology at discharge based on the diagnostic and treatment protocol, all available clinical and laboratory information, and treatment response. After discharge, further management of hyponatremia, if necessary, was left to the treating physician according to the recommendations (if any) by the attending physician during index hospitalization.

STANDARD OF CARE

In the control group, standard of care was based on the European hyponatremia treatment guidelines[3]; however, individual treatment of hyponatremia was solely at the discretion of the attending physicians, who were not involved in the trial. Treatment decisions and the course of plasma sodium levels were only recorded by the trial team after patients were discharged using the medical records and patient charts. Overcorrection and their outcomes were assessed according to the cutoffs described above. Final hyponatremia diagnosis was made by the trial team after discharge based on the diagnostic and treatment protocol, all available clinical and laboratory information, and treatment response.

OUTCOMES AND OUTCOME ASSESSMENT

The primary outcome was the combined risk of death or rehospitalization within 30 days of trial inclusion. Secondary outcomes included mortality and rehospitalization within 30 days (analyzed separately) and within 1 year of trial inclusion (analysis not reported herein); change in sodium levels and rate of sodium correction, including maximum change from trial inclusion until discharge from index hospitalization; time to and rate of patients reaching normonatremia; rate of hyponatremia

persistence or recurrence within 30 days; complications due to overcorrection of hyponatremia (e.g., osmotic demyelination according to magnetic resonance imaging scan or neurologic diagnosis[32]); length of index hospital stay; occurrence of falls or fractures within 30 days; quality of life as evaluated by the EuroQol 5-Dimension 5-Level questionnaire[33] (test comprising five dimensions: mobility, self-care, usual activities, pain and discomfort, and anxiety and depression, with each dimension score ranging from 0 to 5; higher scores indicate greater problems) at the day 30 assessment; Trail Making Test A at admission and at discharge; Trail Making Test B at discharge; and 30-day rehospitalization and/or mortality rates according to hyponatremia etiology, age, sex, and main hyponatremia treatment.

If an outcome occurred during the intervention period, it was assessed and recorded by the trial team. An additional 30-day outcome assessment was performed by trial staff who were not involved in the active trial phase and were blinded to treatment assignment. The blinded outcome assessors contacted the patient by phone, or the family physician in the event the patient could not be reached, as well as reviewed medical records.

In a planned interim analysis, a data and safety monitoring board evaluated the trial after the first 1000 patients completed the 30-day follow-up on December 6, 2021, to determine whether or not the trial could proceed and recommended trial continuation. For additional information on this analysis, see Supplementary Appendix, page 7.

SAMPLE SIZE CALCULATION

Sample size determination was based on demonstrating a between-group difference in the primary outcome, assuming an event rate of 23% under standard care and 18% in the intervention group (5-percentage-point absolute risk difference[34,35]; for additional details, see Supplementary Appendix, page 7). To achieve 80% power for a Pearson's chi-square test with an alpha (α) error rate of 5%, we calculated that 2050 patients would need to be evaluated. Accounting for a dropout rate up to 10%, we aimed to recruit 2278 patients.

STATISTICAL ANALYSIS

While designing the trial, we judged that our intervention would require at least 24 hours to show an effect. Patients who were discharged or relocated before this time period may have only partly received the intervention or may have many missing secondary outcomes. The full analysis set was therefore defined as all randomly assigned patients who received the assigned treatment for at least 24 hours, including patients who died within the first 24 hours. Patients in this set were analyzed according to treatment assignment. The per-protocol set was defined as all patients from the full analysis set for whom the primary outcome was available and who received targeted treatment according to protocol at least 75% of the time. To ensure that possible adverse effects of the intervention were documented, the safety analysis was based on all randomly assigned patients.

The analysis of the primary outcome was based on the full analysis set, including all patients with data available (complete case analysis), complemented by best- and worst-case imputations (assuming that of those participants with missing primary outcome, none in the intervention group but all in the control group experienced an event and vice versa[36]) as defined in the statistical analysis plan. Proportions were tested for a difference using Pearson's chi-square test without Yates' correction, with 95% confidence intervals estimated using the Wilson score method with continuity correction.

Predefined subgroup analyses for hyponatremia severity (moderate vs. severe, i.e., plasma sodium 121–129 mmol/l vs. 120 mmol/l or less), hyponatremia etiology, age (70 years or greater vs. less than 70 years), and sex; and with Charlson Comorbidity Index[37] (a weighted index that takes into account both the number and the seriousness of comorbid diseases, assigning them a weight from 1 to 6 according to the relative risk of dying within a year) at baseline as covariate (post hoc analysis) were conducted. Binary end points were analyzed using generalized linear models; continuous end points were analyzed using linear models. Time-to-event end points were analyzed using Cox proportional hazards models, from which we derived the cause-specific hazard ratios, accounting for competing risks (death vs. other events). Patients without an event were censored at their last known follow-up or at 30 days, whichever came first.[38] A possible learning effect in the control group was examined by analyzing the achievement of normal plasma sodium with center-specific time since first patient inclusion as a covariate. Evaluation of secondary outcomes was considered exploratory, and our protocol did not specify a plan to adjust for multiple comparisons; confidence intervals are not adjusted for multiplicity and therefore should not be used in place of hypothesis testing. All analyses were predefined in a statistical report and analysis plan, unless stated otherwise, using R version 4.4.1 (R Core Team, 2024).[39]

Results

PATIENT CHARACTERISTICS

Between August 2018 and April 2024, 5906 hospitalized patients were screened for inclusion in the trial. After applying exclusion criteria, 2212 patients were randomly assigned to receive the targeted hyponatremia intervention (intervention group) or standard of care (control group) (Fig. 1). Thirty-nine patients withdrew consent before the 30-day analysis, leaving 2173 patients in the full analysis set. The per-protocol analysis included 2049 patients (124 patients not treated according to protocol). Of the patients in the full analysis set, 1079 (49.7%) were randomly assigned to the intervention group and 1094 (50.3%) to the control group. The primary outcome was available for 1065 (98.7%) and 1073 (98.1%) patients in the intervention and control groups, respectively.

Baseline and patient characteristics are described in Table 1 and Table S1. The median age was 73 years (interquartile range, 63 to 81) and 48% were male. At inclusion, median plasma sodium levels were 127 mmol/l (interquartile range, 124 to 128) in both groups. Only 6.2% of patients in the entire cohort had severe hyponatremia (plasma sodium less than 120 mmol/l), including 77 patients (7.1%) in the intervention group and 57 patients (5.2%) in the control group. The cohort was generally representative of European patients with hyponatremia (Table S2).

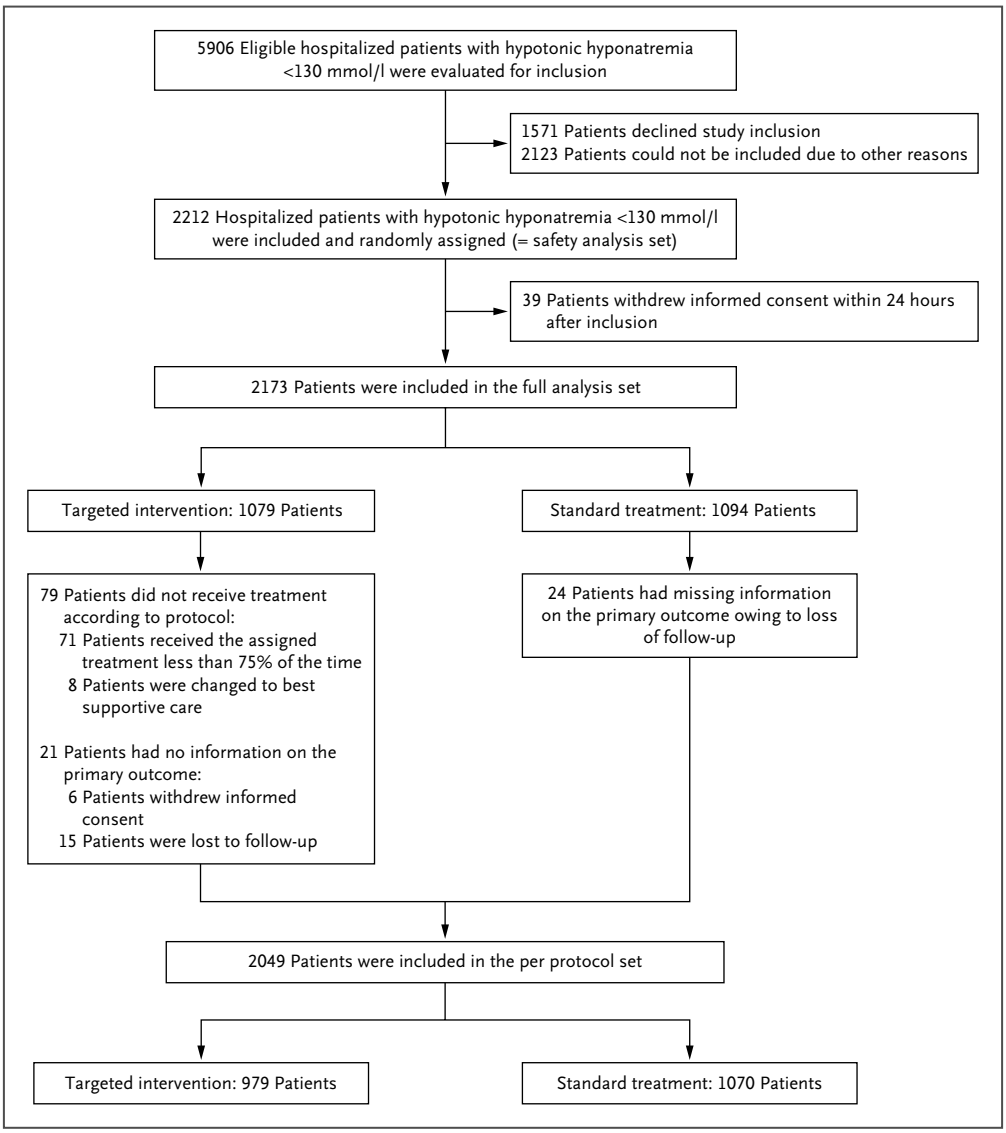

Figure 1. Patient Inclusion Flow Diagram.

Table 1. Patient Characteristics.*

Baseline Characteristic	Overall	Control	Intervention
Patients — n (%)	2173 (100)	1094 (50.3)	1079 (40.6)
Sex, male — n (%)	1038 (47.8)	525 (48.0)	513 (47.5)
Age, years — median (IQR)	73.0 (63.0–81.0)	72.0 (63.0–81.0)	73.0 (62.5–81.0)
BMI — median (IQR)	24.0 (21.3–27.6)	24.2 (21.3–27.7)	23.9 (21.3–27.3)
Systolic blood pressure, mmHg — median (IQR)	125.0 (110.0–144.0)	124.0 (110.0–143.0)	125.0 (111.0–145.0)
Diastolic blood pressure, mmHg — median (IQR)	72.0 (64.5–80.0)	71.0 (64.0–80.0)	72.0 (65.0–80.0)
Heart rate, beats per minute — median (IQR)	80.0 (70.0–90.0)	80.0 (70.0–91.0)	79.0 (69.0–89.0)
Comorbidity			
Charlson Comorbidity Index — median (IQR)	4.0 (3.0–5.0)	4.0 (3.0–6.0)	4.0 (3.0–5.0)
Diabetes mellitus — n (%)	360 (16.6)	180 (16.4)	180 (16.7)
Hypertension — n (%)	1326 (61.0)	662 (60.5)	664 (61.5)
Heart failure — n (%)	309 (14.2)	157 (14.4)	152 (14.1)
Kidney disease — n (%)	561 (25.8)	283 (25.8)	278 (25.8)
Liver disease — n (%)	84 (3.9)	41 (3.7)	43 (4.0)
COPD — n (%)	243 (11.2)	134 (12.2)	109 (10.1)
Cerebrovascular disease — n (%)	202 (9.3)	102 (9.3)	100 (9.3)
Malignant disease — n (%)	748 (34.4)	384 (35.1)	364 (33.7)
Laboratory values			
Plasma sodium, mmol/l — median (IQR)	127.0 (124.0–128.0)	127.0 (125.0–128.0)	127.0 (124.0–128.0)
Severe hyponatremia <120 mmol/l — n (%)	134 (6.2)	57 (5.2)	77 (7.1)
Plasma osmolality, mmol/l — median (IQR)	267.0 (260.0–274.0)	267.0 (260.0–275.0)	267.0 (260.0–274.0)
Type of hyponatremia — n (%)			
Euvolemic	1073 (53.8)	514 (52.3)	559 (55.3)
Hypovolemic	613 (30.8)	305 (31.0)	308 (30.5)
Hypervolemic	306 (15.4)	163 (16.6)	143 (14.2)
Hospital-acquired hyponatremia	534 (24.8)	257 (23.5)	277 (25.7)

*The table shows characteristics and demographics of all included patients from the full analysis set. Data are presented as frequency (percentage) and median (interquartile range). The Charlson Comorbidity Index is a weighted index that takes into account both the number and the seriousness of comorbid diseases, assigning them a weight from 1 to 6 according to the relative risk of dying within a year. BMI denotes body-mass index (the weight in kilograms divided by the square of the height in meters); COPD, chronic obstructive pulmonary disease; and IQR, interquartile range.

The most common treatment in the intervention group was fluid restriction (40%), followed by administration of isotonic fluids (25%) and urea (15%), compared with no treatment (35%), fluid restriction (26%), and isotonic fluids (23%) in the control group. In the intervention group, 56% (608 patients) received combined treatments versus 31% (334 patients) in the control group. Additional details on hyponatremia treatment are reported in Table 2 and Table S3.

During the intervention period, patients in the intervention group experienced a maximum absolute change (mean ± standard deviation) in plasma sodium of 10.0±5.6 mmol/l compared with 8.7±5.6 mmol/l in the control group. Additional details on the course of the plasma sodium levels are shown in Figure S2. A normal sodium level was reached by 60.4% (641 of 1061) of patients in the intervention group compared with 46.2% (492 of 1065) of patients in the control group (absolute difference, 14.3 percentage points; 95% confidence interval [CI], 10.0 to 18.6) resulting in a cause-specific hazard ratio of 1.54 (95% CI, 1.37 to 1.74; Fig. 2A). In addition, 55.9% (572 of 1023) of patients had a normal sodium level at discharge in the intervention group versus 36.8% (382 of 1038) of patients in the control group (absolute difference, 19 percentage points; 95% CI, 14.7 to 23.3). Hyponatremia recurrence or

Table 2. Hyponatremia Treatment.*

	Overall (N=2173)	Control (N=1094)	Intervention (N=1079)
Main treatment of hyponatremia† — n (%)			
No treatment	411 (19)	384 (35)	27 (2.5)
Isotonic fluids	526 (24)	253 (23)	273 (25)
Fluid restriction	711 (33)	280 (26)	431 (40)
Oral urea	182 (8)	25 (2.3)	157 (15)
Vaptans	66 (3)	16 (1.5)	50 (4.1)
Other	238 (11)	123 (11)	115 (11)
Specific information missing	39 (2)	13 (1.2)	26 (2.4)
Number of different treatments used — n (%)			
0/missing information	450 (21)	397 (36)	53 (5)
1	781 (36)	363 (33)	418 (39)
2	537 (25)	207 (19)	330 (31)
3	259 (12)	87 (8)	172 (16)
≥4	146 (7)	40 (4)	106 (10)

* The table provides an overview of hyponatremia treatment used during the observation period.
† If patients received several treatments, only the final effective treatment was counted (i.e., only fluid restriction=fluid restriction; fluid restriction and/or only urea=urea; fluid restriction and/or only vaptans=vaptans).

persistence rates within 30 days were similar between the intervention and the control groups: 41.7% (250 of 600) and 40.9% (246 of 602) of patients, respectively.

PRIMARY OUTCOME

Within 30 days after inclusion, the primary outcome of death or rehospitalization occurred in 20.5% (218 of 1065 patients) in the intervention group and 21.8% (234 of 1073 patients) in the control group (estimated absolute difference, −1.3 percentage points; 95% CI, −4.9 to 2.2; P=0.45). The finding for the primary outcome was consistent when accounting for potential center effects (estimated absolute difference, 1.2 percentage points; 95% CI, −4.6 to 2.5) in the per-protocol analysis (estimated absolute difference, −2.2 percentage points; 95% CI, −5.8 to 1.5) as well as in the best- and worst-case scenarios (Table 3).

SECONDARY OUTCOMES

Separately, death occurred in 8.0% (86 of 1079) of patients in the intervention group (4.9% in hospital and 3.1% after discharge), compared with 8.0% (88 of 1094 patients) of patients in the control group (4.9% in hospital and 3.1% after discharge). During the same time period, 13.2% (141 of 1065 patients) were rehospitalized in the intervention group compared with 14.1% (151 of 1073 patients) in the control group. The intervention was not associated with a difference in time to primary outcome (hazard ratio, 0.93; 95% CI, 0.78 to 1.12), time to death (hazard ratio, 0.99; 95% CI, 0.74 to 1.34), or rehospitalization (hazard ratio, 0.98; 95% CI, 0.73 to 1.32; Fig. 2B–2D).

The median length of hospital stay was similar in the intervention and control groups: 7 (interquartile range, 7 to 7) and 7 (interquartile range, 7 to 8) days, respectively (cause-specific hazard ratio, 0.95; 95% CI, 0.88 to 1.04). The median length of intervention was 6 days (interquartile range, 3 to 12) for patients in the intervention group compared with 3 days (interquartile range, 0 to 8) for patients in the control group.

There were no apparent differences between the intervention and control groups in neurocognitive assessment, quality of life, or rates of falls or fractures at discharge or 30-day follow-up (Table S4).

SUBGROUP ANALYSES

Exploratory examinations of the predefined subgroups of hyponatremia etiology and severity and sex did not suggest an association with the primary outcome (Fig. 3). However, we note that among patients 70 years of age or over, the intervention was associated with a lower risk of the primary outcome (odds ratio, 0.76; 95% CI, 0.57 to 1.00).

Our data did not suggest substantial center-specific differences in the rates of the primary outcome (Fig. S3) or learning effects for achieving normonatremia (accounting for time since center-specific first patient enrolled; Table S5).

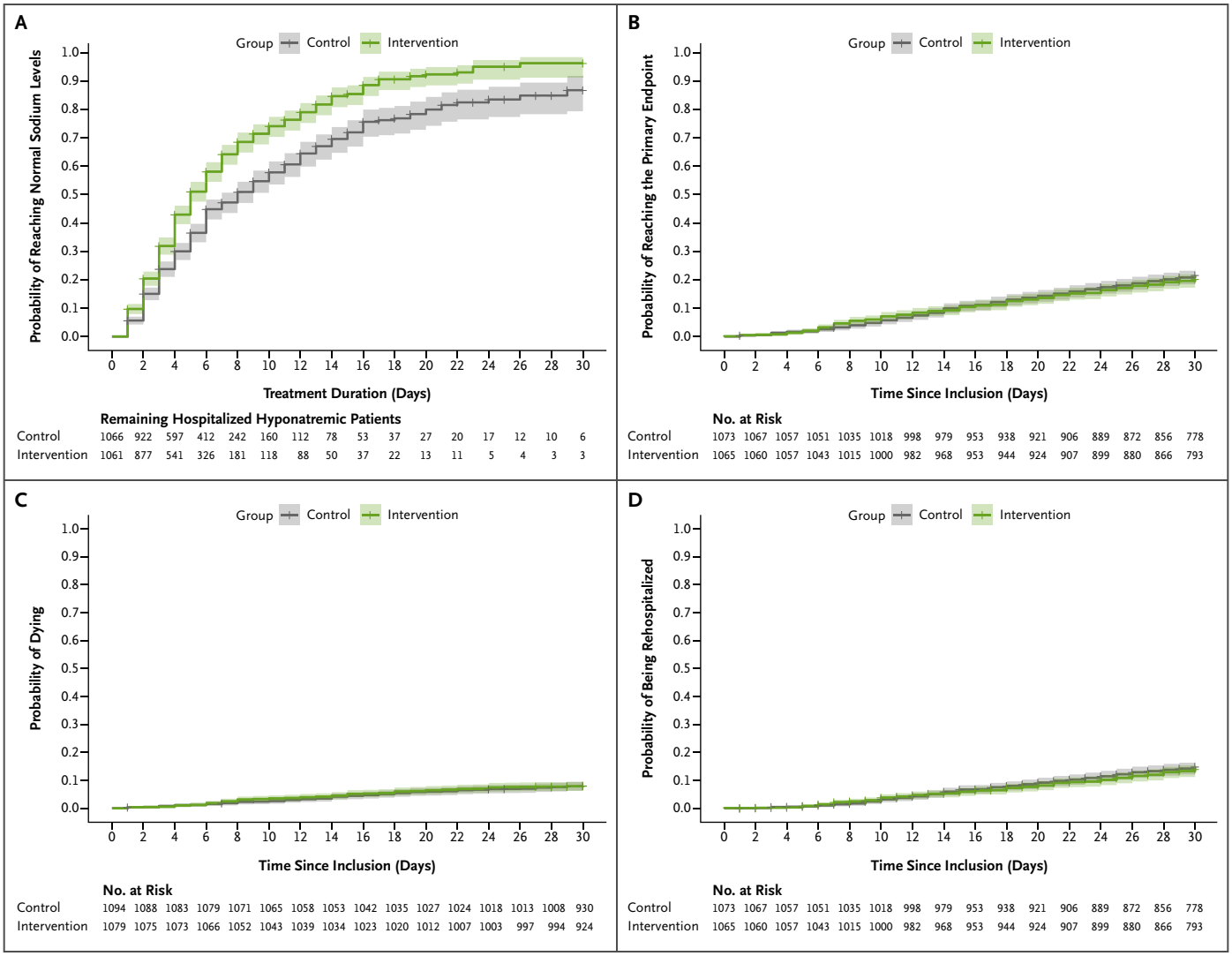

Figure 2. Time-to-Event Analyses.

This figure shows Kaplan–Meier curves illustrating probability by treatment group of reaching normal sodium levels during treatment (Panel A), death or rehospitalization within 30 days (Panel B), death within 30 days (Panel C), and rehospitalization within 30 days (Panel D), with patients who died before rehospitalization censored at the time of death.

In addition, our data provide no evidence for a correlation between center-specific rates for reaching normonatremia and the primary outcome (Fig. S4).

POST HOC ANALYSES

No differences in the primary outcome were observed between the main hyponatremia treatments (descriptive evaluation; Table S6). We note a possible association of the effect of the intervention with the Charlson Comorbidity Index (odds ratio, 0.9; 95% CI, 0.81 to 1.00). Reaching a normal plasma sodium level at discharge, regardless of the treatment group, was associated with decreased odds of the primary outcome of death or rehospitalization within 30 days (odds ratio, 0.74; 95% CI, 0.60 to 0.91).

SAFETY ANALYSES

Overcorrection, defined as an increase in plasma sodium level of greater than 12 mmol/l in any 24-hour period or greater than 18 mmol/l in any 48-hour period, occurred in 25 of 1098 patients (2.3%) randomly assigned to the intervention and 16 of 1114 patients (1.4%) randomly assigned to the control group (P=0.14). Among these, 8 of

Table 3. Mortality and Rehospitalization Rates.*

Events	Control	Intervention	Estimated Absolute Difference, Percentage Points (95% CI)
Full analysis set — n	1094	1079	
Death or rehospitalization within 30 days — n (%)†	234/1073 (21.8)	218/1065 (20.5)	−1.3 (−4.9 to 2.2)‡
Death within 30 days — n (%)	88/1094 (8.0)	86/1079 (8.0)	−0.1 (−2.4 to 2.3)
Rehospitalization within 30 days — n (%)†	151/1073 (14.1)	141/1065 (13.2)	−0.8 (−3.8 to 2.2)
Per-protocol analysis set			
Death or rehospitalization within 30 days — n (%)	234/1070 (21.9)	193/979 (19.7)	−2.2 (−5.8 to 1.5)
Best/worst-case scenario — n (%)			
Best-case scenario	255/1094 (23.3)	218/1079 (20.2)	−3.1 (−6.7 to 0.5)
Worst-case scenario	234/1094 (21.4)	232/1079 (21.5)	0.1 (−3.4 to 3.7)

* Event rates shown as numbers (n) and percentages (%) and 95% confidence intervals. Confidence intervals are not adjusted for multiplicity and should not be used in place of hypothesis testing. Best- and worst-case scenarios are based on the assumption that of those participants with a missing primary outcome, none in the intervention group but all in the control group experienced an event, and vice versa.
† Data for 30-day rehospitalization were missing for 35 patients.
‡ P value=0.45.

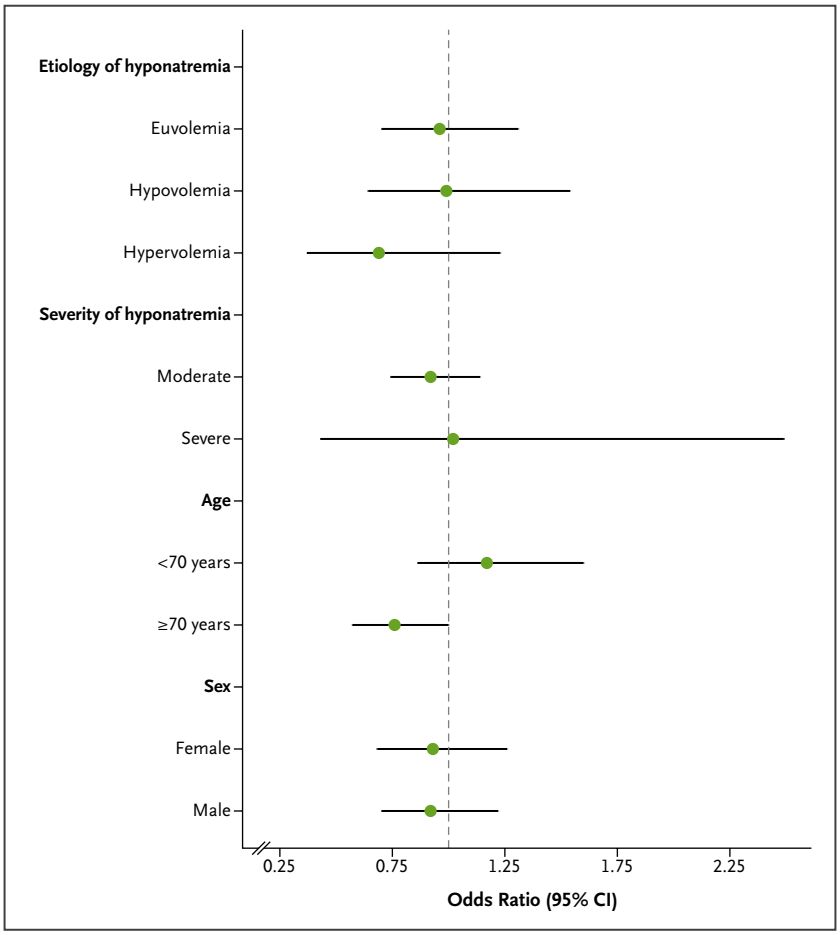

Figure 3. Subgroup Analyses.

This figure shows the effects of the randomly assigned treatment group (intervention vs. control) on the primary outcome estimated within each subgroup using separate logistic regression models. The dashed vertical line indicates an odds ratio of 1, meaning equal probability for the primary outcome in the intervention group as compared with standard care. Correspondingly, odds ratios below 1 and greater than 1 indicate lower and higher probability, respectively. Error bars represent 95% confidence intervals. Confidence intervals are not adjusted for multiplicity and should not be used in place of hypothesis testing. CI denotes confidence interval.

25 patients (32%) and 4 of 16 patients (25%) in the intervention and control groups, respectively, had severe hyponatremia. When applying the more conservative threshold of correcting by 8 mmol/l in 24 hours to all patients with severe hyponatremia, overcorrection occurred in 29 of 77 patients (38%) in the intervention group and 21 of 57 patients (37%) in the control group. An adverse event (e.g., prolongation of hospitalization) due to overcorrection was recorded in 13 of 1079 patients (1.2%) in the intervention group and 9 of 1095 patients (0.8%) in the control group. No cases of osmotic demyelination syndrome and no association with hyponatremia treatment were observed.

Worsening hyponatremia led to acute symptoms despite treatment in 5 of 1098 patients (0.5%) in the intervention group and 1 of 1114 patients (0.1%) in the control group (P=0.10). Treatment intensification led to the resolution of symptoms and an increase in plasma sodium levels in all affected patients.

Discussion

In this large, pragmatic, multicenter, randomized trial evaluating treatment of chronic hyponatremia, targeted correction of plasma sodium levels did not reduce a composite of 30-day mortality or readmission rates as compared with standard care. The results were consistent in the per-protocol and subgroup analyses. In this population with moderate hyponatremia, the intervention resulted in a mean maximum sodium change of 10.0 mmol/l and a normal plasma sodium level by the time of discharge in 60.4%, compared with 8.7 mmol/l and 46% in the control group.

We provide data from a randomized trial about whether the adverse outcomes of hyponatremia can be mitigated through targeted treatment.[40,41] A previous meta-analysis of 15 observational studies including 13,816 patients showed that any improvement of hyponatremia was associated with a reduced risk of overall mortality.[26] More recently, a meta-analysis showed higher survival rates in patients with faster hyponatremia correction.[42] In contrast, the results of the SALT trials (Study of Ascending Levels of Tolvaptan in Hyponatremia),[43] where tolvaptan increased plasma sodium levels in 448 patients with euvolemic or hypervolemic hyponatremia, showed no difference in 30-day mortality between tolvaptan and placebo (5.9% vs. 6.3%). While our post hoc analyses were consistent with previous observations[13,26] that reaching a normal plasma sodium level is associated with lower odds of experiencing the primary outcome independent of the treatment group, targeted treatment did not further reduce this risk. Also in line with previous findings,[26] our subgroup analysis pointed toward a potential positive effect of targeted treatment in older adults, though this trial was not powered to evaluate this subgroup. It is possible that the vulnerability of this patient group to hyponatremia-induced comorbidities plays a role. No associated benefit of the intervention on 30-day mortality and rehospitalization risk was seen according to hyponatremia etiology or severity.

Our findings showed no benefit of intensified hyponatremia treatment on 30-day mortality and rehospitalization rates. This is reminiscent of hyperglycemia, hypertension, or low T3 syndrome in hospitalized patients, where overly strict blood glucose control,[44] antihypertensive treatment,[45] or administration of thyroid hormones[46] were not beneficial. It is, however, important to emphasize that, owing to ethical reasons, the comparator to our intervention was the standard of care and not the absence of treatment. In the hyponatremia registry,[6] 25% of patients were not treated in comparison with 35.1% in the control group of our trial. Our data should therefore not be interpreted as a reason not to treat chronic hyponatremia. Rather, these data suggest that, compared with the currently used standard treatment of chronic hyponatremia in hospitalized patients in the clinical setting evaluated in this trial, a more intensified treatment was not associated with improvement in 30-day mortality, rehospitalization, or other outcomes such as neurocognitive function, quality of life, and rate of falls and fractures.

The intervention was associated with a greater rate of achieving a normal plasma sodium level than the control (60.4% vs. 46%). This rate is similar to that achieved in the SALT trials with tolvaptan (60% after 4 days).[47] However, a normal plasma sodium level was not achieved in all intervention patients. Possible reasons for not reaching higher sodium correction rates were the limited intervention time, as the decision for discharge was made independently of the trial team. In addition, consistent with previous data,[34,48] the included patients were older adults with several comorbidities in whom hyponatremia is often more resistant to treatment.

Our trial has some limitations. First, it was not possible to blind the intervention; possible contamination of the control group — that is, improved hyponatremia awareness — cannot be excluded, but is not supported by our data, as no learning effect for achieving a normal plasma sodium level was seen. To minimize possible bias, assessment of the primary outcome after discharge was blinded. Second, we mainly included patients with moderate hyponatremia. However, according to the hyponatremia registry study,[5]

this cohort is the group in which hyponatremia treatment is most controversial and in which up to 25% of patients did not receive any treatment. Finally, our intervention lasted only as long as the patient was hospitalized, and we cannot draw conclusions about hyponatremia correction in the outpatient setting. Strengths of our trial are its prospective, randomized, pragmatic design; the large sample size; and the inclusion of both regional and university medical centers in five different European countries. This provided data that reflect the current management of hyponatremia.

In summary, in this large randomized controlled trial among hospitalized patients with moderate hyponatremia, targeted correction of hyponatremia as compared with standard of care did not result in a lower 30-day mortality and rehospitalization rate.

Disclosures

Author disclosures and other supplementary materials are available at evidence.nejm.org.

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Deidentified individual participant data that underlie the results reported in this article will be shared upon publication to researchers who provide a methodologically sound proposal to achieve the aims in the approved proposal. Proposals should be directed to the corresponding author. To gain access, data requestors will need to sign a data access agreement.

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Author Affiliations

[1] Departments of Endocrinology, Diabetology, and Metabolism, University Hospital Basel, University of Basel, Basel, Switzerland

[2] Department of Clinical Research, University Hospital Basel, University of Basel, Basel, Switzerland

[3] Department of Internal Medicine, Erasmus Medical Center, Rotterdam, the Netherlands

[4] University Institute of Internal Medicine, Cantonal Hospital Baselland, Liestal, Switzerland

[5] Emergency Department, Faculty of Medicine and University Hospital Cologne, University of Cologne, Cologne, Germany

[6] Department II of Internal Medicine and Center for Molecular Medicine Cologne, Faculty of Medicine and University Hospital Cologne, University of Cologne, Cologne, Germany

[7] Division of Endocrinology, Diabetes, and Metabolism and Division of General Internal Medicine, Medical University Clinic, Medical Faculty, University of Basel, Cantonal Hospital Aarau, Aarau, Switzerland

[8] Department of Endocrinology, Cantonal Hospital St. Gallen, St. Gallen, Switzerland

[9] Department of Endocrinology, University Hospital Centre Zagreb, Zagreb, Croatia

[10] Pituitary Diseases and Sodium Alterations Unit, Department of Endocrinology, Careggi University Hospital, Florence, Italy

[11] Department of Internal and Emergency Medicine, Public Hospital Solothurn, Solothurn, Switzerland

[12] Department of Emergency Medicine, Kepler University Hospital, Johannes Kepler University, Linz, Austria

[13] Department of Experimental and Clinical Biomedical Sciences "Mario Serio", University of Florence, Florence, Italy

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