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Cumulative Incidence of Thiazide-Induced Hyponatremia

A Population-Based Cohort Study

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Background: According to drug labels, the frequency of thiazide-induced hyponatremia is unknown or uncommon to very rare (that is, <1 in 10 000 to <1 in 100), but the exact burden remains unclear.

Objective: To estimate the increase in the cumulative incidence of hyponatremia using thiazide diuretics compared with nonthiazide antihypertensive drugs in routine clinical practice.

Design: Population and register-based cohort study using target trial emulation.

Setting: Denmark, 1 January 2014 to 31 October 2018.

Participants: Two target trials were emulated among persons aged 40 years or older who had no recent prescription for any antihypertensive drug, had no previous hyponatremia, and were eligible for the studied antihypertensive treatments. The first target trial emulation compared new use of bendroflumethiazide (BFZ) versus a calcium-channel blocker (CCB). The second target trial emulation compared new use of hydrochlorothiazide plus a renin–angiotensin system inhibitor (HCTZ–RASi; that is, combination pill) versus a RASi alone.

Measurements: Two-year cumulative incidences of sodium levels less than 130 mmol/L using stabilized inverse probability of treatment–weighted survival curves.

Results: The study compared 37 786 new users of BFZ with 44 963 of a CCB and 11 943 new users of HCTZ–RASi with 85 784 of a RASi. The 2-year cumulative incidences of hyponatremia were 3.83% for BFZ and 3.51% for HCTZ–RASi. The risk differences were 1.35% (95% CI, 1.04% to 1.66%) between BFZ and CCB and 1.38% (CI, 1.01% to 1.75%) between HCTZ–RASi and RASi; risk differences were higher with older age and higher comorbidity burden. The respective hazard ratios were 3.56 (CI, 2.76 to 4.60) and 4.25 (CI, 3.23 to 5.59) during the first 30 days since treatment initiation and 1.26 (CI, 1.09 to 1.46) and 1.29 (CI, 1.05 to 1.58) after 1 year.

Limitation: The study assumed that filled prescriptions equaled drug use, and residual confounding is likely.

Conclusion: Treatment initiation with thiazide diuretics suggests a more substantial excess risk for hyponatremia, particularly during the first months of treatment, than indicated by drug labeling.

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Thiazide diuretics are commonly used to treat uncomplicated hypertension, a key modifiable risk factor for the development and progression of cardiovascular disease (1, 2). Although thiazide diuretics are considered effective, low-cost, and generally well-tolerated and hence a rational choice for first-line treatment of uncomplicated hypertension, they may cause significant adverse effects, such as hyponatremia (thiazide-induced hyponatremia) (3–5). Symptoms of hyponatremia range widely, from no or mild symptoms, such as fatigue or falls, to severe and potentially life-threatening neurologic symptoms, including unconsciousness and seizures (4, 6).

The exact burden of thiazide-induced hyponatremia is unclear. Drug labels report the frequency of this adverse event variably; most classify it as unknown or uncommon to very rare (that is, <1 in 10 000 to <1 in 100) (7–13). In contrast, 1 thiazide trial found a cumulative incidence of hyponatremia of 4.1% over an average follow-up of 4.5 years (14), whereas another recent trial reported an incidence of 5.4% over a median follow-up of 2.4 years (15). In addition, a retrospective cohort study of outpatients found hyponatremia among 3 in 10 patients using thiazides (based on a total of 220 exposed participants) (16). Altogether, observational research evaluating the cumulative incidence of thiazide-induced hyponatremia is limited, is constrained by small sample sizes and inadequate confounder control, and comes with diverging findings highly dependent on the studied population (16–19). Because choices about antihypertensive treatment should balance potential effects and risks, it is important to clarify the actual extent of thiazide-induced hyponatremia to aid rational pharmacotherapy.

We therefore took advantage of the Danish registers, which include information on prescription drug use

See also:

Web-Only
Supplement

and laboratory blood test results, to emulate pragmatic target trials of the cumulative incidence of hyponatremia during new use of thiazide diuretics compared with new use of alternative antihypertensive drugs in routine clinical practice.

METHODS

Specification of the Target Trials

Study Overview

We designed this observational analysis to emulate pragmatic target trials estimating the increase in the cumulative incidence of hyponatremia with new use of thiazides compared with alternative nonthiazide antihypertensive drugs (namely, calcium-channel blockers [CCBs] or renin–angiotensin system inhibitors [RASis]). Supplement Table 1 (available at Annals.org) lists the key protocol components. Two separate target trials were specified, 1 comparing use of bendroflumethiazide (BFZ) versus a CCB and another comparing use of hydrochlorothiazide plus a RASi (HCTZ–RASi) versus a RASi alone. In Denmark, thiazides, CCBs, and RASis are first-line choices for treatment of uncomplicated hypertension (20), and during the study period HCTZ was mainly used as part of combination pills also containing a RASi. Although CCBs are not reported to cause hyponatremia, hyponatremia is a reported adverse effect in some labels for drugs containing a RASi, with a frequency varying among unknown, uncommon, rare, and very rare (that is, <1 in 10 000 to <1 in 100); we therefore specified the aforementioned comparisons to isolate the effect of the respective thiazides on hyponatremia risk (21–25). The target trials are specified as follows.

The study was approved by Statens Serum Institut's Data Protection and Information Security Department; under Danish law, neither informed consent nor ethics committee approval is required for strictly register-based studies.

Eligibility Criteria

For both target trials, eligibility criteria included age 40 years or older between 1 January 2014 and 31 October 2018, no use of any antihypertensive drug within the past year, at least 2 years with a known address in Denmark, and not living in the Central Denmark Region (because laboratory data were unavailable to us from this region during the study period). We did not include a requirement for a diagnosis of hypertension because we had access to only diagnoses assigned in secondary health care. However, we expect that the indication for most new use of antihypertensive therapy would be (uncomplicated) hypertension and that therapy would be initiated by general practitioners in the primary care setting. Antihypertensive treatment due to other conditions (for example, in relation to kidney disease, heart failure, prevention of kidney stone recurrence, or diabetes insipidus) would typically require secondary health care services (for example, by hospital referral as part of the diagnostic process or treatment), on which we have information from the Danish National Patient Register (26). Accordingly, exclusion criteria (see Supplement Table 2, available at Annals.org, for further specification of sources and definitions) included a history of secondary hypertension, end-stage illness, hyponatremia, or a contraindication to the studied drugs or a condition where 1 treatment strategy would be preferred over the other (defined for both target trials as severe renal or hepatic impairment, adrenal insufficiency disorder, gout, hypo- or hyperkalemia [potassium level ≤3.0 or ≥5.5 mmol/L], ischemic heart disease [including use of nitrates], or heart failure; for the comparison of BFZ vs. CCB, also defined as diabetes insipidus, ulcerative or obstructive gastrointestinal disorder, kidney stone, aortic stenosis, pulmonary hypertension, Raynaud syndrome, or edema; for the comparison of HCTZ–RASi vs. RASi, also defined as aliskiren or sacubitril use, diabetes or use of antidiabetic drugs, renal disorder or estimated glomerular filtration rate <60 mL/min/1.73 m^2, or cholestasis or biliary obstruction disorder).

Treatment Strategies

The treatment strategies compared for the first target trial were initiation of BFZ use at baseline versus initiation of CCB use at baseline. Those for the second target trial were initiation of HCTZ–RASi use at baseline versus initiation of RASi use at baseline. All treatment strategies included not initiating more than 1 of the studied treatment strategies at baseline. For all treatment strategies, initiation of use is defined as filling a first prescription for the drug, consistent with an intention-to-treat design. That is, treatment strategy is assigned at baseline and cannot be changed thereafter regardless of actual use of the drug or switching to or adding on another antihypertensive drug.

Study Outcomes

The outcomes of interest are hyponatremia (a laboratory blood test result with a sodium level <130 mmol/L; primary outcome), severe hyponatremia (sodium level <125 mmol/L), hospitalization with hyponatremia (sodium level <130 mmol/L), any hyponatremia (sodium level <135 mmol/L), hypernatremia (sodium level >145 mmol/L; negative control outcome), and all-cause mortality. Each outcome was analyzed separately.

Each eligible individual was followed from assignment of a treatment strategy for outcome events until 2 years had passed (to capture both possible short- and longer-term effects and given the intention-to-treat design), death, emigration, moving to the Central Denmark Region, or the end of the study period, whichever occurred first.

Analysis Approach

The causal estimands of interest represent the intention-to-treat effect of being assigned to the treatment strategies, which mitigates concerns about overestimating the potential risk increase.

Cumulative incidences were estimated using the Kaplan–Meier estimator, which also includes baseline covariates by stabilized inverse probability of treatment weights (IPTWs). For individuals assigned to a thiazide treatment strategy, the weights were set to 1. For those assigned to the treatment strategy using a nonthiazide antihypertensive comparator drug, the weights were $[(1 - p_0) / (1 - p_c)] / (p_0 / p_c)$, with p_0 equal to the crude probability of assignment to the specific thiazide drug and p_c equal to the same probability given covariates. Probabilities were computed by logistic regression.

Absolute risk differences (RDs) and risk ratios were calculated from the cumulative incidences at the end of the 2-year follow-up, and the corresponding 95% CIs were calculated using the SEs from the Kaplan–Meier estimates. Changes in the relative risk during follow-up were assessed by hazard ratios (HRs) estimated using an adjusted Cox regression that similarly adjusted for covariates by stabilized IPTWs, with time since treatment initiation included as the underlying time scale and parameterized as a 5-knot restricted cubic spline. Basic subgroup analyses were done according to sex, age (10-year bins), and number of comorbid conditions (0, 1 to 2, or ≥3) to identify potential subgroups for whom treatment strategies may be most harmful.

Emulation of the Target Trials

We explicitly emulated the target trials described above by linkage of individual-level information from various Danish registers of health care and demography (see **Supplement Tables 1** to **4**, available at Annals.org, for definitions and **Supplement Figure 1**, available at Annals.org, for study design) (26–33). These registers are updated as part of routine administration, including reimbursement of clinical care (28).

We obtained information about filled prescriptions from the Register of Medicinal Product Statistics, which holds individual-level data on all prescriptions filled at Danish pharmacies since 1995, including the Anatomical Therapeutic Chemical classification code, date of filled prescription, strength, and pack size (27). Inclusion and exclusion criteria and information about potential confounders were extracted from the Register of Medicinal Product Statistics, the Danish Civil Registration System, Statistics Denmark, the Register of Laboratory Results for Research, and the National Patient Register. The Danish Civil Registration System contains complete historical information on addresses, migration, vital status, sex, and birth date on all Danish residents (29). Statistics Denmark holds near-complete information on income and educational level (values were missing for 5.5% and 1.9%, respectively, of the study cohort and were imputed using the mode value) (30, 31). The Register of Laboratory Results for Research contains data on laboratory blood test results (requested by primary and secondary health care providers) that are coded by use of the Nomenclature for Properties and Units terminology and performed by all clinical biochemical laboratories in 4 of 5 Danish regions since 2014, including information on Nomenclature for Properties and Units codes and sampling date (32). From this register, we also obtained information about the study outcome of hyponatremia. The National Patient Register holds information on all secondary health care services during hospital contacts (that is, inpatient admissions and outpatient and emergency department visits), including diagnoses and procedure codes (assigned using International Classification of Diseases, 10th Revision [since 1994], and Nordic Medico-Statistical Committee codes, respectively) (26). In addition, the Danish National Health Service Register contains information on services delivered by all independent health care professionals (primarily general practitioners) working under contract with the public health insurance (that is, codes for reimbursement). Specific codes assigned in relation to diagnoses in this register are limited, but it provides an opportunity to take into account health care–seeking behavior in the primary sector at a more general level (33).

Each component of the target trial protocols was emulated using these observational data. We classified participants into the drug treatment groups—thiazide or nonthiazide antihypertensive comparator—on the basis of the first filled prescription in the study period. This date is the baseline (index date); eligibility criteria and baseline covariates were evaluated at the index date only. The compared treatment groups were considered exchangeable on this index date conditional on the covariates (**Supplement Table 4**). The observational analytic analogues for the estimation of intention-to-treat effects were equivalent to those in the target trials, and we adjusted for these baseline covariates to emulate randomization.

We used SAS, version 9.4 (SAS Institute), and R, version 4.0.2 (34) (R Foundation), for data management and statistical analyses.

Additional Analyses

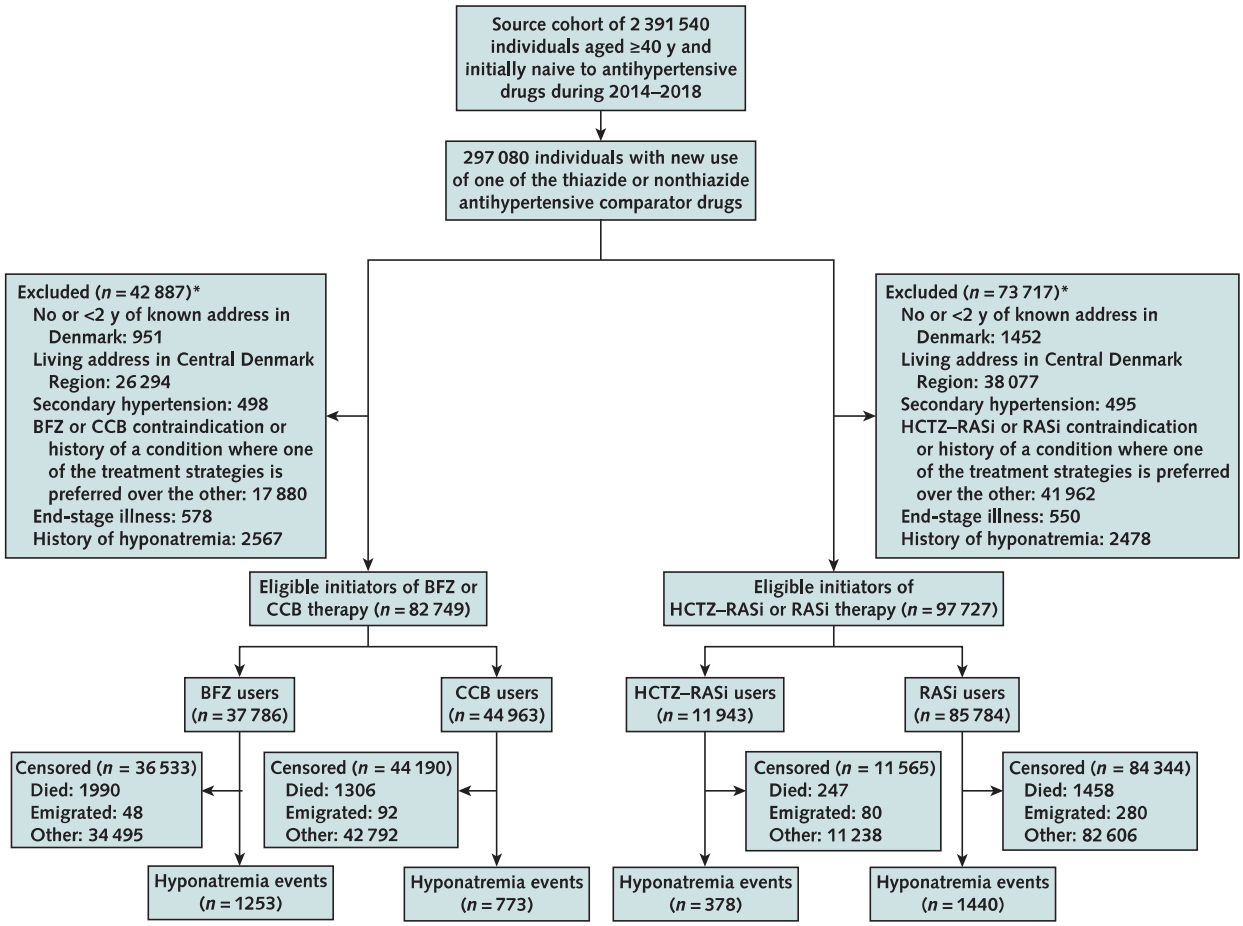
In additional analyses, we used different sets of exclusion criteria, made additional adjustment for covariates, and stratified by thiazide dose at treatment initiation.

On examining findings from the primary set of analyses, we compared the risk for hyponatremia (sodium level <130 mmol/L) and all-cause mortality in an analysis restricted to individuals who had been equipped with a blood pressure monitoring device by their primary health care provider before treatment initiation (that is, a cohort where the treatment indication—hypertension—is highly specific). In addition, we included inverse probability of censoring weight adjustment in the primary analysis and used an IPTW-adjusted Aalen–Johansen estimator with death as the competing risk.

Role of the Funding Source

The funders had no role in the design or conduct of the study; collection, management, analysis, or interpretation of the data; preparation, review, or approval of

Figure 1. Study flow diagram.



See Supplement Figure 1 (available at Annals.org) for a graphical illustration of the study design and Supplement Table 1 (available at Annals.org) for an overview of key components of the target trial protocol. BFZ = bendroflumethiazide; CCB = calcium-channel blocker; HCTZ–RASi = hydrochlorothiazide plus RASi combination pill; RASi = renin–angiotensin system inhibitor.

* The combined total of excluded individuals is not a sum of the individual exclusion criteria because individuals could be excluded for >1 of the stated reasons.

the manuscript; or decision to submit the manuscript for publication.

RESULTS

Study Population

Figure 1 is a flow chart of the cohort construction, and the Table shows the baseline characteristics of participants in each emulated trial: 82 749 participants for the comparison of BFZ versus a CCB and 97 727 for HCTZ–RASi versus a RASi (see Supplement Table 5, available at Annals.org, for an extended version and Supplement Figure 2, available at Annals.org, for baseline sodium distributions). Thiazide and nonthiazide initiators were, on average, of similar age in each emulated trial. A higher proportion of BFZ users were female, and BFZ users had a slightly higher baseline prevalence of comorbid conditions and use of comedications than users of a CCB. Baseline characteristics were generally similar in the emulation comparing HCTZ–RASi with RASi users. After IPTWs were applied, baseline characteristics were more similar for both target trial emulations, with standardized differences below 10% (Supplement Table 6 and Supplement Figures 3 and 4, available at Annals.org).

Among BFZ initiators, 69.5% received a first prescription with a dose of 2.5 mg and 30.5% with a dose of 1.25 mg; corresponding numbers for 25-mg and 12.5-mg doses of HCTZ were 21.2% and 78.8%, respectively, which did not differ materially across subgroups (Supplement Table 7, available at Annals.org). Adherence to assigned treatment was initially lower for BFZ than CCB users but similar for HCTZ–RASi and RASi users (Supplement Figure 5, available at Annals.org). In both emulations, blood sodium level ascertainment was similar among thiazide and nonthiazide users in terms of timing, frequency, and proportion of individuals with any sodium measurement during follow-up (Supplement Figures 6 to 9, available at Annals.org).

A total of 2026 participants in the emulated trial among BFZ and CCB users and 1818 in the emulated trial among HCTZ–RASi and RASi users developed hyponatremia (sodium level <130 mmol/L) during the 2-year follow-up.

Cumulative Incidence of Hyponatremia

Figure 2 shows the 2-year cumulative incidences of hyponatremia (sodium level <130 mmol/L) comparing users of thiazides versus nonthiazide antihypertensive comparator drugs. For BFZ versus CCB use, the 2-year cumulative incidence of hyponatremia (sodium level <130 mmol/L) was 3.83%, with an estimated observational analogue 2-year RD of 1.35% (95% CI, 1.04% to 1.66%). The corresponding values for HCTZ–RASi versus RASi use were 3.51% and 1.38% (CI, 1.01% to 1.75%), respectively.

Figure 3 shows the 2-year RDs overall and by subgroup. In the emulated trial among BFZ and CCB users, the cumulative incidence and RD estimates were higher among men than women (Figure 3), but no differences were found for the comparisons of HCTZ–RASi versus RASi or BFZ versus CCB when restricting to individuals who had been supplied with a blood pressure measuring

Table. Baseline Characteristics of Individuals Aged 40 Years or Older for the 2 Target Trial Emulations of Users of Thiazides Compared With Nonthiazide Antihypertensive Comparator Drugs and Risk for Hyponatremia*

Characteristic	BFZ Versus CCB Use		HCTZ–RASi Versus RASi Use	
	BFZ (*n* = 37 786)	CCB (*n* = 44 963)	HCTZ–RASi (*n* = 11 943)	RASi (*n* = 85 784)
Demographics				
Female sex	27 962 (74.0)	22 328 (49.7)	5609 (47.0)	41 162 (48.0)
Mean age (SD), *y*	63.0 (13.5)	63.0 (12.0)	60.7 (11.0)	60.6 (11.2)
Educational level				
≤9 y	12 074 (32.0)	13 178 (29.3)	3382 (28.3)	22 375 (26.1)
10–12 y	16 367 (43.3)	20 322 (45.2)	5518 (46.2)	39 367 (45.9)
13–15 y	7316 (19.4)	8567 (19.1)	2254 (18.9)	17 644 (20.6)
≥16 y	2029 (5.4)	2896 (6.4)	789 (6.6)	6398 (7.5)
Baseline laboratory blood test results				
Has baseline sodium measurement†	23 180 (61.3)	30 215 (67.2)	7251 (60.7)	59 982 (69.9)
Mean sodium level (SD), *mmol/L*†	140 (2.4)	140 (2.4)	140 (2.4)	140 (2.3)
Mean potassium level (SD), *mmol/L*†	4.1 (0.36)	4.0 (0.36)	4.0 (0.37)	4.0 (0.35)
eGFR 30–<60 mL/min/1.73 m^2	1551 (4.1)	2112 (4.7)	NA‡	NA‡
Medical history in past 5 y				
Diabetes	700 (1.9)	655 (1.5)	NA‡	NA‡
Cancer	2878 (7.6)	2587 (5.8)	458 (3.8)	3625 (4.2)
Liver disease or peritonitis	250 (0.7)	239 (0.5)	60 (0.5)	358 (0.4)
Pancreatitis	132 (0.3)	168 (0.4)	34 (0.3)	223 (0.3)
Cerebrovascular disease	1097 (2.9)	2587 (5.8)	449 (3.8)	4739 (5.0)
Alcohol or drug abuse	761 (2.0)	867 (1.9)	241 (2.0)	1509 (1.8)
Inflammatory bowel disease	308 (0.8)	286 (0.6)	58 (0.5)	515 (0.6)
Drug use in past year				
Drugs for acid-related disorders	8332 (22.1)	7580 (16.9)	1703 (14.3)	13 189 (15.4)
NSAIDs	10 537 (27.9)	10 021 (22.3)	2747 (23.0)	19 714 (23.0)
Antiepileptics	2655 (7.0)	1761 (3.9)	410 (3.4)	3287 (3.8)
Opioids	6766 (17.9)	5332 (11.9)	1331 (11.1)	9440 (11.0)
Antidepressants	5444 (14.4)	4792 (10.7)	1122 (9.4)	8708 (10.2)
Antipsychotics	1664 (4.4)	1384 (3.1)	298 (2.5)	2126 (2.5)
Agents for COPD	5263 (13.9)	4400 (9.8)	1062 (8.9)	8218 (9.6)
Number of drugs used in past year				
1–3	13 343 (35.3)	19 002 (42.3)	5111 (42.8)	37 664 (43.9)
4–6	10 006 (26.5)	10 584 (23.5)	2556 (21.4)	19 883 (23.2)
7–9	5676 (15.0)	4427 (9.8)	986 (8.3)	7873 (9.2)
≥10	4868 (12.9)	2847 (6.3)	509 (4.3)	4299 (5.0)
Days hospitalized in past year				
1–7	4306 (11.4)	5641 (12.5)	995 (8.3)	8607 (10.0)
8–14	882 (2.3)	1151 (2.6)	144 (1.2)	1356 (1.6)
≥15	894 (2.4)	1289 (2.9)	124 (1.0)	1193 (1.4)

BFZ = bendroflumethiazide; CCB = calcium-channel blocker; COPD = chronic obstructive pulmonary disease; eGFR = estimated glomerular filtration rate; HCTZ–RASi = hydrochlorothiazide plus RASi combination pill; NA = not applicable; NSAID = nonsteroidal anti-inflammatory drug; RASi = renin–angiotensin system inhibitor.

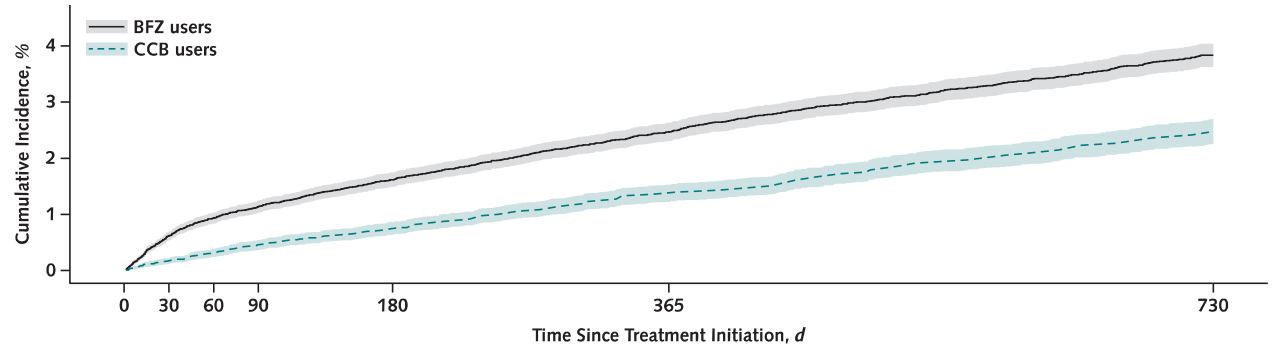
* Values are numbers (percentages) unless otherwise specified.

† Not included in the stabilized inverse probability of treatment weights. See Supplement Table 5 (available at Annals.org) for the full baseline characteristics.

‡ The variable was an exclusion criterion for this comparison.

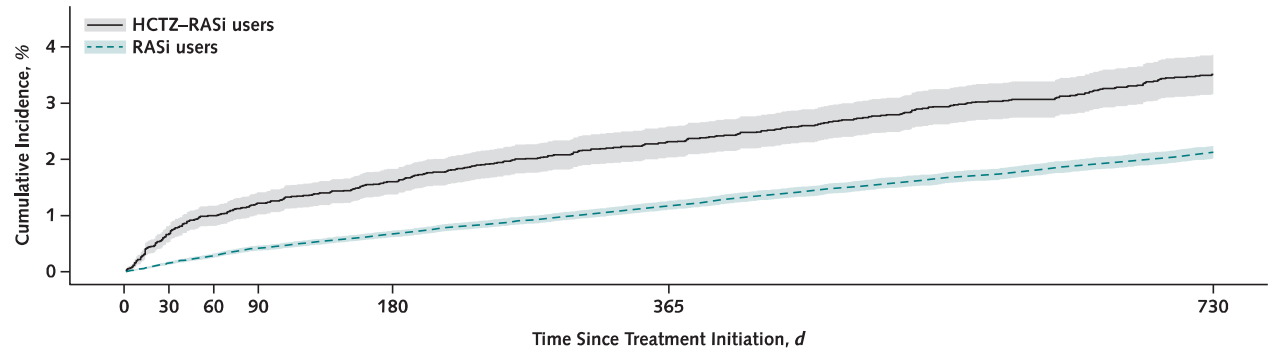
Figure 2. Cumulative incidences of hyponatremia (sodium level <130 mmol/L) for the 2 target trial emulations of users of thiazides compared with nonthiazide antihypertensive comparator drugs during 2 y of follow-up.

BFZ vs. CCB users



	Day 30	Day 60	Day 90	Day 180	Day 365	Day 730
BFZ users: events/PY, *n/years*	234/3077	350/6098	425/9067	593/17 615	871/33 792	1253/60 795
BFZ users: incidence (95% CI), %	0.62 (0.54–0.70)	0.94 (0.84–1.03)	1.14 (1.03–1.25)	1.62 (1.49–1.75)	2.47 (2.31–2.63)	3.83 (3.62–4.04)
CCB users: events/PY, *n/years*	64/3658	117/7241	176/10 759	279/21 013	488/40 059	773/70 380
CCB users: incidence (95% CI), %	0.17 (0.12–0.23)	0.32 (0.24–0.39)	0.46 (0.37–0.54)	0.75 (0.64–0.87)	1.38 (1.22–1.53)	2.48 (2.26–2.70)
Risk difference (95% CI), %	0.45 (0.35–0.55)	0.62 (0.50–0.74)	0.69 (0.55–0.83)	0.86 (0.69–1.03)	1.09 (0.87–1.31)	1.35 (1.04–1.66)

HCTZ–RASi vs. RASi users



	Day 30	Day 60	Day 90	Day 180	Day 365	Day 730
HCTZ–RASi users: events/PY, *n/years*	81/974	118/1932	144/2878	188/5668	266/11 088	378/20 198
HCTZ–RASi users: incidence (95% CI), %	0.68 (0.53–0.83)	0.99 (0.82–1.17)	1.22 (1.02–1.42)	1.60 (1.37–1.83)	2.31 (2.04–2.59)	3.51 (3.16–3.86)
RASi users: events/PY, *n/years*	137/6975	239/13 797	344/20 483	545/39 952	905/75 859	1440/132 497
RASi users: incidence (95% CI), %	0.16 (0.13–0.19)	0.29 (0.25–0.33)	0.42 (0.37–0.47)	0.68 (0.62–0.73)	1.18 (1.11–1.26)	2.12 (2.01–2.24)
Risk difference (95% CI), %	0.52 (0.37–0.67)	0.71 (0.53–0.89)	0.80 (0.6–1.00)	0.93 (0.70–1.16)	1.13 (0.84–1.42)	1.38 (1.01–1.75)

The cumulative incidences among comparator groups were adjusted using stabilized inverse probability of treatment weighting, weighted to the respective analyzed thiazide users. BFZ = bendroflumethiazide; CCB = calcium-channel blocker; HCTZ–RASi = hydrochlorothiazide plus RASi combination pill; PY = person-years; RASi = renin–angiotensin system inhibitor.

device before treatment initiation (constituting 11.7% of BFZ, 22.5% of CCB, 20.4% of HCTZ–RASi, and 26.3% of RASi users) (**Supplement Figures 10** to **12**, available at Annals.org). In both emulated trials, the cumulative incidence and RD estimates increased with older age as well as number of comorbid conditions (**Supplement Figures 13** and **14**, available at Annals.org) but the risk ratios remained mostly similar (**Supplement Figure 15**, available at Annals.org).

The HR for hyponatremia was highest during the first months since treatment initiation but remained elevated throughout the 2-year follow-up period for both emulated trials (for example, from a more than 3-fold increased relative risk estimate during the first month to an approximately 30% increased relative risk estimate after 1 year) (**Figure 4** and **Supplement Table 8**, available at Annals.org). Subgroup analyses in both emulations showed similar patterns of higher

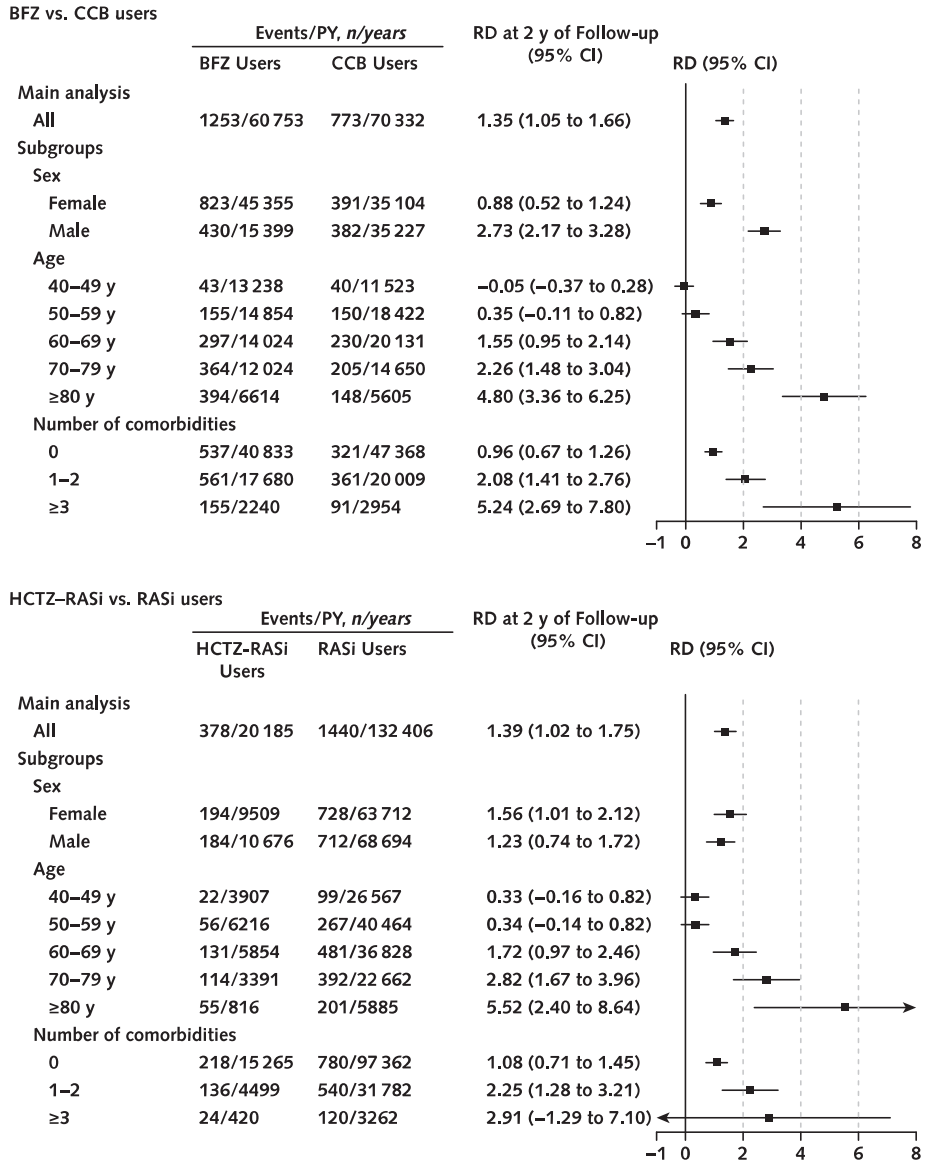
HRs in the short-term period after treatment initiation than in later periods (Supplement Figures 16 to 18, available at Annals.org).

Additional analyses using alternative eligibility criteria or adjustment for additional covariates provided results similar to those of the primary analyses (Supplement Figure 19, available at Annals.org). Effect estimates were larger for participants initiating thiazide treatment with a higher dose at baseline (Supplement Table 9, available at Annals.org).

Cumulative Incidence of Alternative Outcomes

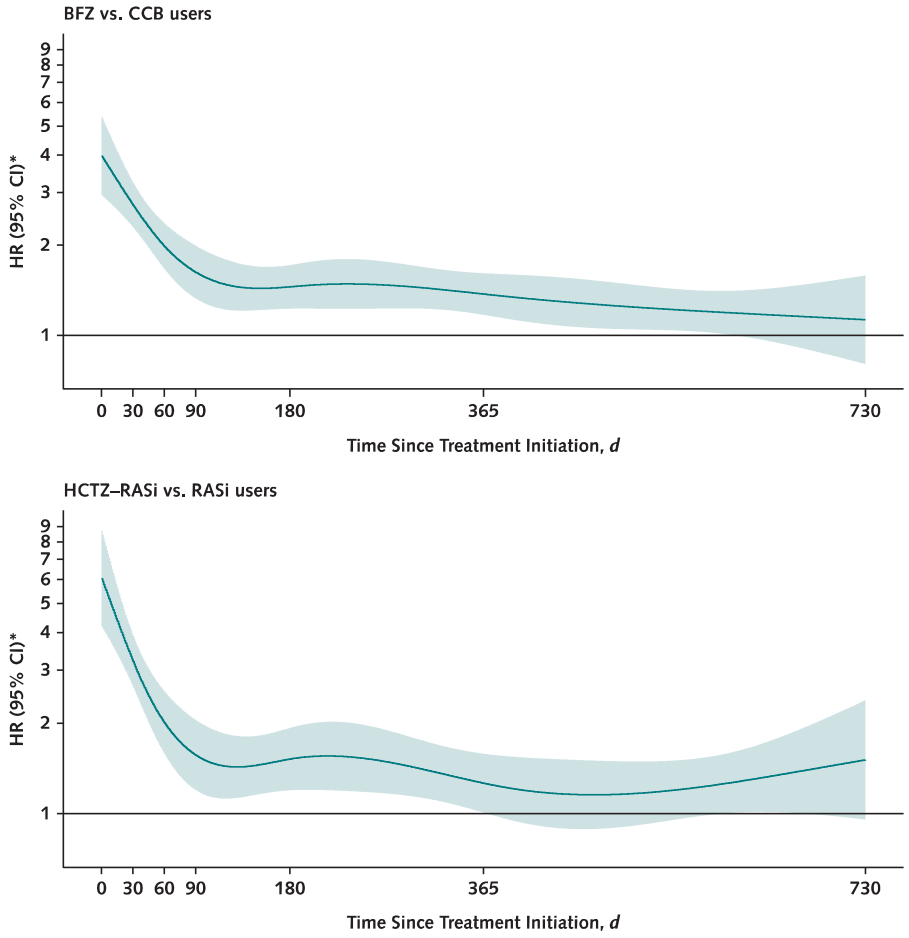
In both emulations, thiazide users had higher 2-year cumulative incidences of the alternative outcomes severe hyponatremia (sodium level <125 mmol/L) and hospitalization with hyponatremia (sodium level <130 mmol/L) than users of nonthiazide antihypertensive comparator drugs (Supplement Figures 20 and 21, available at Annals.org). The risk pattern for severe hyponatremia was consistent with the primary outcome analysis across subgroups (Supplement Figure 22, available at Annals.org) and with similar

Figure 3. Risk differences of hyponatremia (sodium level <130 mmol/L) for the 2 target trial emulations of users of thiazides compared with nonthiazide antihypertensive comparator drugs after 2 y of follow-up, overall and by subgroups.



BFZ = bendroflumethiazide; CCB = calcium-channel blocker; HCTZ–RASi = hydrochlorothiazide plus RASi combination pill; PY = person-years; RASi = renin–angiotensin system inhibitor; RD = risk difference.

Figure 4. Hazard ratios of hyponatremia (sodium level <130 mmol/L) for the 2 target trial emulations of users of thiazides compared with nonthiazide antihypertensive comparator drugs, by time since treatment initiation.



BFZ = bendroflumethiazide; CCB = calcium-channel blocker; HCTZ–RASi = hydrochlorothiazide plus RASi combination pill; HR = hazard ratio; RASi = renin–angiotensin system inhibitor.
* Log scale.

changes in HRs during follow-up (**Supplement Figure 23**, available at Annals.org).

The risk for any hyponatremia (sodium level <135 mmol/L) was higher for thiazide than nonthiazide antihypertensive comparator drugs but similar for the negative control outcome of hypernatremia (sodium level >145 mmol/L) in both emulations (**Supplement Figures 24** and **25**, available at Annals.org).

The estimates of all-cause mortality were initially higher for BFZ than CCB users but similar for HCTZ–RASi and RASi users (**Supplement Figure 26**, available at Annals.org). However, the difference between BFZ and CCB users dissipated when we restricted the analysis to individuals who had been equipped with a blood pressure monitoring device (where therapeutic indication being hypertension was further assured), but the sample size for this analysis was substantially smaller and estimates were imprecise (**Supplement Figure 27**, available at Annals.org). **Supplement Table 10** (available at Annals.org) shows analyses using different analytic approaches, taking death into account as a competing risk by using the Aalen–Johansen estimator and/or adding inverse probability of censoring weights; results of these analyses were consistent with our main findings.

Discussion

In this population-based cohort study that used observational data to emulate target trials, we found a substantial excess risk for hyponatremia with initiation of treatment with thiazide diuretics compared with other first-line antihypertensive drugs. Specifically, the cumulative incidences of moderate to severe hyponatremia (sodium level <130 mmol/L) were approximately 3.5% for the thiazides we studied (BFZ and combination HCTZ–RASi)—about 1.4 percentage points higher than the cumulative incidences with a CCB and a RASi alone, respectively, during the first 2 years of treatment. The RDs of hyponatremia were higher with older age and greater comorbidity burden. In addition, the hazard

rate of hyponatremia was larger in thiazide users than nonthiazide antihypertensive comparator drug users throughout follow-up, with the largest difference in the first months of treatment.

Our results are in remarkable contrast to the frequencies of hyponatremia provided in the product labels for thiazide diuretics. Thiazide-induced hyponatremia is currently reported with inconsistent frequency across existing drug labels; the frequency of this adverse event is most often recognized as unknown or uncommon to very rare (that is, <1 in 10 000 to <1 in 100; time periods not reported) (7–13). According to the European Medicines Agency guideline on summaries of product characteristics, data sources for frequencies reported in drug labels should include clinical trials, postauthorization safety studies, and spontaneous reporting for which, after thorough assessment, a causal relationship between the medicinal product and the adverse event is at least a reasonable possibility (35). Due to the inclusion of participants with prevalent use of antihypertensive drugs before study enrollment, trial data may provide only limited insights into the cumulative incidence of thiazide-induced hyponatremia (14, 15).

Previous observational data on the cumulative incidence of thiazide-induced hyponatremia not only are sparse but also are characterized by methodological inconsistencies (3). Our finding of the highest rate of hyponatremia in the first months after thiazide treatment initiation is in line with previous case reports and observational studies (3, 16, 36). The underlying mechanisms behind thiazide-induced hyponatremia are poorly understood but are considered to involve some combination of excessive fluid intake, cation depletion, osmotic inactivation of sodium, and decreased ability to excrete excess free water (4). The reported incidences in studies vary and are highly dependent on the studied population, setting, and hyponatremia case definition—for example, from a cumulative incidence of 6.5% of any hyponatremia (sodium level <135 mmol/L) within 9 months in 1060 thiazide-using veterans aged 65 years or older to a 10-year cumulative incidence of approximately 30% of hyponatremia (sodium level ≤130 mmol/L) in 220 outpatients receiving thiazides (16–19). Similarly, our reported cumulative incidences of hyponatremia should be interpreted in the context of our study population and setting of Danish adults aged 40 years or older, initially naive to antihypertensive therapy, fulfilling a set of eligibility criteria, and treated during routine clinical care without contraindications to any studied drug. Our study expands on existing evidence, suggesting that the risk for hyponatremia among thiazide users varies greatly across age and comorbidity burden. Although some previous results have associated female sex with thiazide-induced hyponatremia, others have not, and data are limited, in particular for BFZ (3, 16–18, 37–40). We observed no differences by sex when restricting the analyses to a population where the indication for treatment (hypertension) was highly specific, although the sample size was much smaller and estimates were imprecise.

Our study has limitations. First, we used an intention-to-treat design and assumed that a first filled prescription equaled drug use, which may lead to conservative cumulative incidences and relative risk estimates. Second, our study was based on new users. Therefore, our results may not be applicable to use of these drugs as add-on therapy. Likewise, use of thiazide-like diuretics (metolazone, indapamide, and chlorthalidone) has been limited in Denmark, and the generalizability of our results to such drugs is unclear. Third, we had no information on measures of blood pressure, and our new user design implies that treatments were predominantly initiated by general practitioners (that is, primary care) for which no direct registry information on disease diagnoses exists. Because our ascertainment of disease history relied mainly on diagnoses recorded at the time of hospital contacts and that of medication use on prescriptions filled at pharmacies, milder conditions diagnosed and managed by general practitioners only are not captured except if treated with a disease-specific medication. Of note, we expected that other known indications for antihypertensive therapy would require secondary health care services in the form of hospital contacts (particularly if complex or severe) or use of disease-specific medication. Thiazide users and comparator groups had different baseline characteristics of the measures we did have access to. To mitigate this, we considered a wide range of potential confounders using IPTWs. Nevertheless, residual confounding is likely. Fourth, ascertainment bias is a concern. To mitigate this, we defined hyponatremia as having a sodium measurement lower than 130 mmol/L, because we considered moderate to severe hyponatremia to be more likely to manifest with clinical symptoms that would lead to case identification. However, plasma sodium is recommended to be routinely measured in Denmark when a patient is treated with antihypertensive drugs (41), and in both of our emulated target trials, measurement of sodium blood levels was similar in thiazide and nonthiazide antihypertensive drug users. In addition, we found no difference in the incidence of the negative control outcome of hypernatremia, an outcome that is also susceptible to such ascertainment bias.

In conclusion, our findings show that new use of thiazide diuretics suggests a substantial excess risk for hyponatremia that is higher than indicated by drug labeling. The risk is particularly pronounced during the first months of treatment and in persons who are older or have comorbidities. These findings suggest that hyponatremia is a common adverse drug reaction to thiazide treatment and highlight the continued need for clinical awareness as well as monitoring of this adverse drug reaction.

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Note: Dr. Andersson had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analyses.

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