Received: 5 November 2023 | Accepted: 14 March 2024

DOI: 10.1111/jebm.12601

ARTICLE

WILEY

Thiazide-associated hyponatremia in arterial hypertension patients: A nationwide population-based cohort study

Soie Kwon[1] | Hasung Kim[2] | Jungkuk Lee[2] | Jungho Shin[1,3] | Su Hyun Kim[3,4] | Jin Ho Hwang[1,3]

[1]Department of Internal Medicine, Chung-Ang University Hospital, Seoul, Republic of Korea

[2]Data Science Team, Hanmi Pharm. Co., Ltd, Seoul, Republic of Korea

[3]Department of Internal Medicine, Chung-Ang University College of Medicine, Seoul, Republic of Korea

[4]Department of Internal Medicine, Chung-Ang University Gwangmyeong Hospital, Gyeonggi, Republic of Korea

Correspondence
Jin Ho Hwang, Division of Nephrology, Department of Internal Medicine, Chung-Ang University Hospital, Chung-Ang University College of Medicine, Seoul 06973, Republic of Korea.
Email: dennyjinho@gmail.com

Abstract

Objective: Thiazides are the first-line treatment for hypertension, however, they have been associated with hospitalizations for thiazide-associated hyponatremia (TAH). The aim of this study was to evaluate the risk of TAH and other drug-associated hyponatremia in a Korean population.

Methods: The study used big data from the National Health Insurance Sharing Service of 1,943,345 adults treated for hypertension from January 2014 to December 2016. The participants were divided into two groups based on the use of thiazides. Cox proportional hazard models were used to identify independent risk factors for the occurrence of hyponatremia.

Results: The study found that hyponatremia-related hospitalizations were significantly higher in the thiazide group than the control group (2.19% vs. 1.45%). The risk increased further with concurrent use of other diuretics or desmopressin, and thiazide+spironolactone+desmopressin and hospitalization risk further increased (4.0 and 6.9 times). Multivariate analysis showed that hyponatremia occurrence increased with age, diabetes mellitus, depression, and thiazide use (hazard ratio = 1.436, $p < 0.001$). The thiazide group had better 6-year overall survival than the control group but had more fractures and hyponatremia.

Conclusions: Thiazide use is associated with an increased risk of hyponatremia and related complications. However, the mortality rate decreased in those who received thiazides, suggesting that thiazide use itself is not harmful and may help decrease complications and improve prognosis with proper, cautious use in high-risk patients.

KEYWORDS
desmopressin, diuretics, electrolyte, hyponatremia, thiazides

1 | INTRODUCTION

Hyponatremia is a very commonly encountered electrolyte imbalance, and it is the most common electrolyte imbalance when considering mild hyponatremia in inpatients who frequently undergo fasting and various invasive procedures or operations. Hyponatremia occurred in 5% to 10% of inpatients and 13.7% of outpatients who are prescribed thiazides.[1–4] Hyponatremia is associated with gait disturbance

or mild neurologic symptoms; however, in severe cases, hyponatremia increases the risk of falls and associated fractures and is a poor prognostic factor in hospitalized patients.[5,6] The causes of hyponatremia are highly diverse; however, antidiuretic hormone (ADH) action is essential for the mechanism unless there is excessive water intake, such as primary polydipsia or beer potomania. Following the Joint National Committee 7 guideline recommendation of thiazides as first-line treatment for hypertension, hospitalizations for hyponatremia in patients on thiazides have been frequently encountered in clinical settings, although the actual incidence and risk of hyponatremia have not been ascertained in South Korea.[7,8]

Hyponatremia in patients on thiazides or other electrolyte imbalances were dose-dependent side effects of thiazide use, and thiazide use itself might cause acute hyponatremia; however, occurrence of hyponatremia in patients on thiazides was not common and developed in a minor proportion of susceptible individuals.[1] A diagnosis of thiazide-induced hyponatremia (TIH) was clinically defined by hyponatremia in individuals taking thiazides and manifests as hypovolemia or euvolemia, improved following the cessation of thiazide use, did not improve before cessation of thiazides, and did not recur after recovery in the absence of thiazides.[9] Due to the distinction of TIH could be made with certainty only in retrospect, the cases of euvolemic hyponatremia developing in a patient receiving a thiazide were referred as "thiazide-associated hyponatremia (TAH)." TAH occurred in a heterogeneous group of patients, and thiazides might not be directly responsible in all instances.[9]

The risk and incidence of hyponatremia in patients on thiazides in Korea were unknown and the hyponatremia risk increase conferred by concomitant use of other hyponatremia-inducing agents, such as spironolactone and desmopressin, was undetermined.[10] Through big data analysis of the National Health Insurance Service (NHIS) data in Korea, this study was conducted to determine the risk of hyponatremia in patients on thiazides and the additional risk conferred by concomitant diseases or drug use.

2 | METHODS

2.1 | Study design and database

We conducted a nationwide population-based cohort study. In the Republic of Korea, the Health Insurance Review and Assessment service oversees the assessment of adequacy in drug prescriptions and treatment details, and health check-ups are handled by the NHIS. The NHIS runs the National Health Insurance Sharing Service (NHISS) and supports policies for the use of national health information data and academic research by offering a sample research database, customized research database, and health and disease indicators. The database encompasses a comprehensive record of patient interactions with medical facilities, encompassing diagnostic codes for assorted comorbidities, a log of hospital admissions, and details pertaining to prescribed medications. Upon appraisal of the research proposal, NHIS provides de-identified information on specific variables requested by the researcher. For the risk evaluation of hyponatremia in patients on thiazides and other drug-associated hyponatremia, we used big data from the NHISS.

2.2 | Participants and data collection

Adult patients (age ≥20 years) who were confirmed to have received treatment for hypertension from January 2014 to December 2016 were included in the analysis set. This included individuals diagnosed with hypertension until 2014 (with ongoing tracking) plus new hypertension diagnoses in 2015 and 2016 (without allowing duplicate patients). Owing to a data limit of 500 GB for research samples, a randomly sampled data set that comprised 20% of all patients treated for hypertension between 2014 and 2016 was used. We excluded patients with diagnostic codes of hyponatremia, from both inpatient and outpatient clinics, before the first prescription of thiazides.

Information on the patients' age, sex, and comorbidities, including hypertension, diabetes mellitus (DM), dyslipidemia, osteoporosis, heart failure, chronic kidney disease (CKD), and depression, were collected. Moreover, we collected all the medication data using the Anatomical Therapeutic Chemical Classification System and all the diagnostic data using the International Statistical Classification of Diseases and Related Health Problems (ICD)−10 codes (Table S1).

2.3 | Definitions

Hypertension was defined according to disease codes that were prepared in accordance with the Korean Standard Classification of Diseases (I10, I11, I12, I13, or I15) or by prescription of antihypertensive medications continuously for more than 6 months. Participation in the thiazide group was defined by the prescription of thiazides or thiazide-like diuretics, including hydrochlorothiazide (HCT) alone, various angiotensin receptor blocker (ARB)+HCT combinations, and of chlorthalidone, indapamide, or metolazone. The participants' data were analyzed by dividing these data into groups that either received thiazides for more than 7 days (thiazide group) or had never been prescribed thiazides (control group). Hyponatremia was defined based on hospitalization for the ICD-10 codes of E871 (hypo-osmolality and hyponatremia) or E222 (syndrome of inappropriate secretion of antidiuretic hormone, SIADH). In addition, data on admission with ICD-10 code of E878 (electrolyte imbalance not otherwise specified) were collected separately.

2.4 | Study outcome

The diagnostic codes for hyponatremia (E871, E222), and electrolyte imbalance NOS (E878) were collected until 1 year after the grouping (thiazide vs. nonthiazide). All cases of hyponatremia that occurred within 1 year after the patient was first prescribed thiazides were included, regardless of when they occurred. The diagnostic codes for

osteoporosis with fracture (M80), fractures of various body parts (S12, S22, S32, S89, T02, T08, T10, and T12), acute renal failure (N17), ischemic heart disease (I20-25), and cerebrovascular disease (I60-64) were collected until 3 years after the grouping (Table S1). To evaluate the effect of hyponatremia on the outcomes, the all-cause mortality, and diagnostic codes of fractures (M80, S12, S22, S32, S89, T02, T08, T10, and T12) and pneumonia (J12-18), which likely follows hyponatremia were collected separately (Table S1).

2.5 | Ethical approval

The study protocol was reviewed and approved by the institutional review board of Chung-Ang University Hospital (Registration number 1908-010-16277), and it conformed to the provisions of the Declaration of Helsinki revised in 2013. The requirement of informed consent was waived because this study was based on a national database and given the practical impossibility of obtaining consent from the anonymized subjects.

2.6 | Statistical analysis

The analyses and calculations in this study were performed using SAS® Enterprise guide version 7.1 (SAS Institute, Cary, NC, USA). Continuous variables were expressed as means ± standard deviations (SDs), and categorical variables as frequencies (percentages). The independent *t*-test was used to compare two continuous variables whereas the one-way ANOVA was used to undertake intergroup comparisons with three or more continuous variables based on the normality assumption. The chi-square test was used to analyze categorical variables. Survival analyses were performed using the Kaplan-Meier method, and intergroup comparisons were performed using the log-rank test. The Cox proportional hazard model was used to identify independent risk factors for the occurrence of hyponatremia and to calculate the hazard ratio (HR) and 95% confidence interval (CI). Age (continuous variable), sex, diabetes, heart failure, CKD, spironolactone, and desmopressin were used as basic covariates, and multivariate analysis was performed by adding thiazide and variables found to be significant in univariate analysis one by one. Statistical significance was set at a level of $p < 0.05$.

3 | RESULTS

3.1 | Baseline characteristics

In 2014, 2015, and 2016, a total of 1,623,555, 1,681,577, and 1,753,196 patients with prevalent hypertension, respectively, were included in this study. In 2015 and 2016, those who had previously been diagnosed with hypertension and were prescribed antihypertensive medication were included. Therefore, 1,961,737 patients with hypertension, after excluding overlapping patients, were screened and data from 1,943,345 patients were analyzed after excluding 18,392 patients who were prescribed thiazides for less than 7 days in a year (Figure S1). In this study, 78.7% ($n = 607,069$) of the thiazide group had been prescribed thiazides for more than 6 months, and 94% ($n = 667,323$) had been prescribed thiazides for more than 3 months. Table 1 showed the baseline characteristics of the 1,943,345 patients (mean age 62.6 years, 50.2% men). The thiazide group included more female participants and those who were in their 70s and 80s (54.3% vs. 41.2%, $p < 0.001$), and the mean age was higher (63.9 vs. 61.8 years, $p < 0.001$). Furthermore, the prevalence of DM, dyslipidemia, osteoporosis, heart failure (HF), and depression was significantly high in the thiazide group whereas the prevalence of CKD was low (2.9% vs. 3.8%, $p < 0.0001$). There was no significant difference in the use of β-blockers according to thiazide use although calcium-channel blocker (CCB) and α-blocker use was low and angiotensin-converting enzyme inhibitor (ACEi) or ARB use were significantly higher in the thiazide group. The prevalence of diuretic use, such as spironolactone or loop diuretics, was significantly lower in the thiazide group than that in the no-thiazide group as was the rate of desmopressin use (all $p < 0.0001$).

3.2 | Development of hyponatremia in patients on thiazides

A total of 33,451 patients (0.017%) experienced hyponatremia among a total of 1,943,345 patients. Hospitalization for hyponatremia (E871 or E222; 2.2% vs. 1.5%), for unspecified electrolyte imbalance code (E878; 4.5% vs. 3.9%), and all of them, if any of E871, E222, or E878 was applicable (6.1% vs. 5.1%), increased significantly in the thiazide-use group (Figure 1). In patients who received thiazide monotherapy, hyponatremia occurred more often in those who received metolazone, indapamide, hydrochlorothiazide, and chlorthalidone (3.3%, 2.7%, 2.1%, and 2.1%, respectively); when two or more thiazides were concurrently prescribed, the incidence of hyponatremia increased by 4.0%, which was 2.8 times higher than that of the control group (Figure 2A). The occurrence of hyponatremia (E871, E222) following combination therapy with other diuretics or desmopressin was associated with a 1.4 times higher risk in the thiazide-alone group than in the control group; moreover, when spironolactone or loop diuretics were used concomitantly with thiazide, the risk increased more than 4 times. When thiazide + spironolactone + desmopressin were used simultaneously, the risk reached 6.9 times (Figure 2B). When thiazide and desmopressin were administered together, the likelihood of being hospitalized four or more times increased by 11-fold (Figure 3).

3.3 | Factors affecting hyponatremia occurrence

In the group of patients with hyponatremia, there were more women (58.0% vs. 49.6%), the average age increased by more than 10 years, and there were significantly more underlying diseases, such as DM, HF, and CKD, than in the nonhyponatremia group. Furthermore, thiazide, spironolactone, loop diuretics, and desmopressin were used more often, and CCB or ARB/ACEi prescription rates tended to be low.

TABLE 1 Baseline characteristics of the participants.

Characteristics		No thiazide ($n = 1,233,269$, %)	Thiazide ($n = 710,076$, %)	p Value
Male		651,531 (52.83)	324,671 (45.72)	<0.001
Age, decade	20s	10,293 (0.83)	2,256 (0.32)	<0.001
	30s	44,856 (3.64)	16,424 (2.31)	
	40s	160,818 (13.04)	76,534 (10.78)	
	50s	332,290 (26.94)	177,030 (24.93)	
	60s	315,659 (25.60)	180,548 (25.43)	
	70s	255,653 (20.73)	178,352 (25.12)	
	80s	100,103 (8.12)	71,076 (10.01)	
	≥90s	13,597 (1.10)	7,856 (1.11)	
Age, years[a]		61.8 ± 13.2	63.9 ± 12.7	<0.001
Diabetes mellitus		687,092 (55.71)	426,586 (60.08)	<0.001
Dyslipidemia		929,269 (75.35)	565,571 (79.65)	<0.001
Osteoporosis		400,023 (32.44)	271,972 (38.30)	<0.001
Heart failure		127,727 (10.36)	85,235 (12.00)	<0.001
Chronic kidney disease		46,240 (3.75)	20,911 (2.94)	<0.001
Depression		320,578 (25.99)	199,607 (28.11)	<0.001
Coprescribed antihypertensive medications	CCB	735,175 (59.61)	322,066 (45.36)	<0.001
	ARB or ACEi	700,092 (56.77)	573,075 (80.71)	<0.001
	β-Blocker	204,329 (16.57)	118,234 (16.65)	0.135
	α-Blocker	19,184 (1.56)	10,156 (1.43)	<0.001
Coprescribed diuretics/desmopressin	Spironolactone	28,938 (2.35)	11,425 (1.61)	<0.001
	Furosemide	57,224 (4.64)	17,732 (2.50)	<0.001
	Torsemide	16,746 (1.36)	4280 (0.60)	<0.001
	Desmopressin	3761 (0.30)	1689 (0.24)	<0.001

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium-channel blocker.
[a]Data are expressed as the mean ± standard deviation.

In patients with hyponatremia, the frequency of combination diuretic therapy, including the rate of use of two or more thiazide drugs, was significantly high (Table 2).

In multivariate analysis, the occurrence of hyponatremia increased with age (HR = 1.069, 95% CI 1.068 to 1.070, $p < 0.001$ per 1-year increase), DM (HR = 1.453, 95% CI 1.415 to 1.492, $p < 0.001$), and depression (HR = 1.530, 95% CI 1.496 to 1.565, $p < 0.001$). Among antihypertensive medications, thiazide use was associated with an increased risk of hyponatremia (HR = 1.436, 95% CI 1.404 to 1.469, $p < 0.001$). Desmopressin was the agent that was most associated with the risk of hyponatremia (HR = 2.144, 95% CI 1.915 to 2.400), followed by loop diuretics (HR = 2.126, 95% CI 2.046 to 2.208) and spironolactone (HR = 1.506, 95% CI 1.430 to 1.586) (Table 3).

3.4 | Outcomes depending on thiazide use

In the survival analysis, the thiazide group had a better 6-year overall survival than the control group (HR = 0.922, 95% CI 0.913 to 0.930, $p < 0.001$) despite more osteoporotic fractures (HR = 1.252, 95% CI 1.223 to 1.282, $p < 0.001$), other traumatic fractures (HR = 1.212, 95% CI 1.198 to 1.227, $p < 0.001$), and hospitalization for hyponatremia ($p < 0.001$, Figure 4).

3.5 | Outcomes based on the occurrence of hyponatremia

Patients with hyponatremia had significantly higher mortality rates (HR = 7.008, 95% CI 6.854 to 7.165), hospitalizations for osteoporosis with pathological fractures (HR = 1.923, 95% CI 1.799 to 2.056), traumatic fractures (HR = 1.474, 95% CI 1.417 to 1.533), and pneumonia (HR = 3.290, 95% CI 3.208 to 3.374) than those without hyponatremia (all $p < 0.001$; Figure S2). When examining the outcome by combining thiazide use with the occurrence of hyponatremia, the populations with hyponatremia showed a poorer outcome than those without hyponatremia for all-cause mortality, various fractures, and pneumonia. In terms of all-cause mortality and pneumonia, thiazide use was associated with a more favorable outcome than thiazide nonuse but was associated with a poor outcome in terms of various fractures (Figure 5).

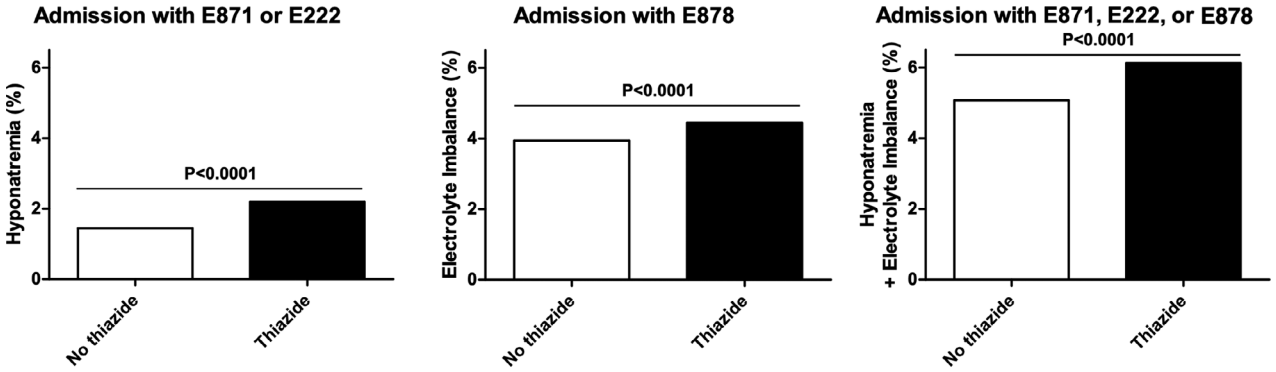

FIGURE 1 The percentage of hospitalizations for hyponatremia between thiazide users and nonusers. **ICD**-10 codes: E871, Hypo-osmolality and hyponatremia; E222, Syndrome of inappropriate secretion of antidiuretic hormone; E878, Other disorder of electrolyte and fluid balance, not elsewhere classified.

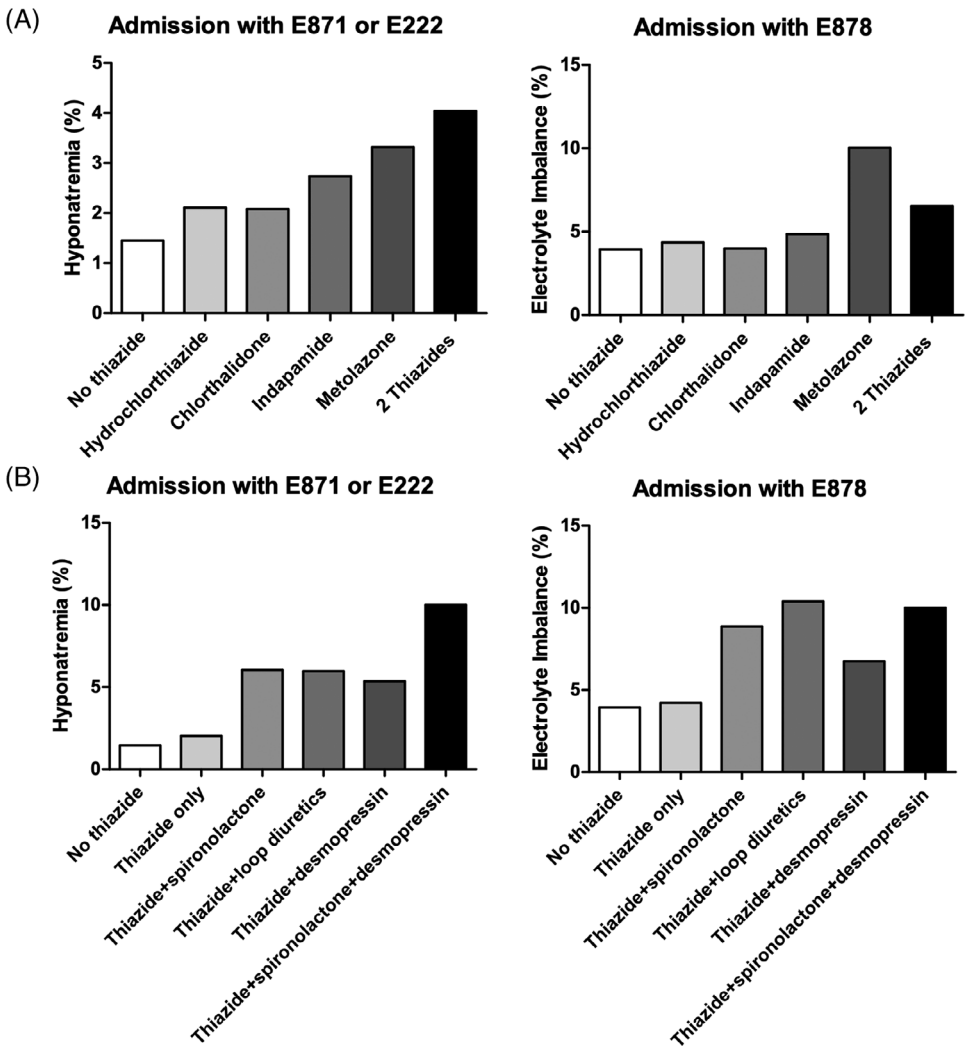

FIGURE 2 The percentage of hospitalizations for hyponatremia in the different diuretic groups. (A) Hyponatremia-related hospitalizations by specific thiazides and thiazide-like diuretics; (B) hyponatremia-related hospitalizations among the different diuretic groups or desmopressin. ICD-10 codes: E871, Hypo-osmolality and hyponatremia; E222, Syndrome of inappropriate secretion of antidiuretic hormone; E878, Other disorder of electrolyte and fluid balance.

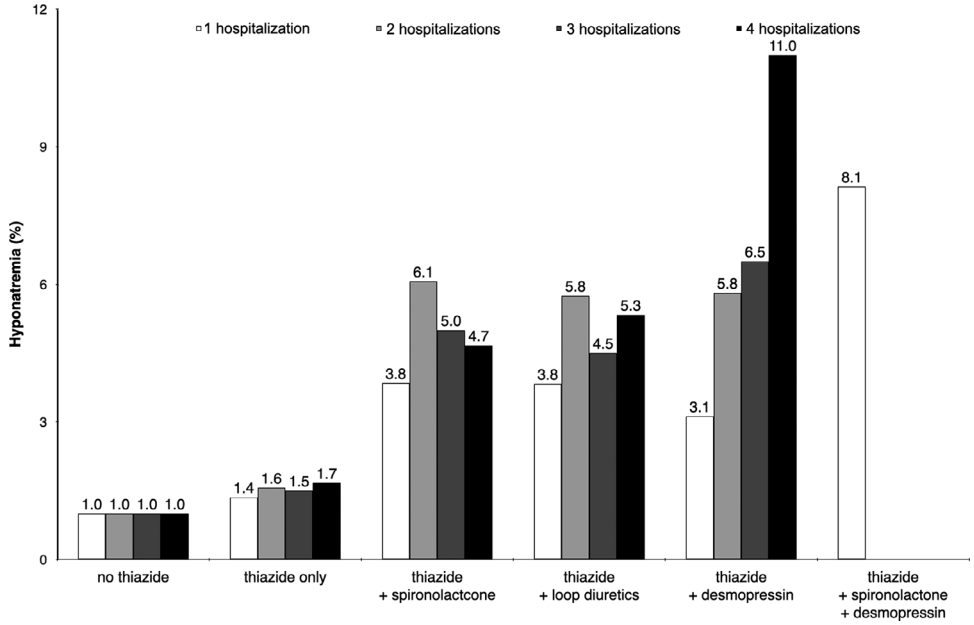

FIGURE 3 Frequency distribution of hospitalizations for hyponatremia among the different diuretic groups.

4 | DISCUSSION

In this study, thiazide use in antihypertensive treatment increased the hyponatremia-related hospitalization rate and the risk further increased when two or more drugs were used concomitantly or in combination with another diuretics or desmopressin. Thiazide use decreased all-cause mortality, but increased hospitalizations due to hyponatremia and fractures. Nonetheless, regardless of thiazide use, hyponatremia significantly increased the risks of mortality and hospitalizations due to fractures or pneumonia.

Hyponatremia increased socioeconomic costs related to cognitive dysfunction and an increased risk of falls.[11] If the serum electrolyte levels were not tested following thiazide diuretic use, hyponatremia might not be recognized due to the asymptomatic nature of the disorder.[12] The median time to hyponatremia in patients taking thiazides had been reported in various studies and ranges from less than 2 weeks to 19 days, and from several months to several years after thiazide initiation.[2,10,13–15] Clinically, hyponatremia in patients on thiazides often occurred when solute intake decreased or when an event that could cause volume depletion occurred in patients who had been stably taking thiazide for a long period of time. Therefore, even patients who had been stably maintained with thiazide use for several years could not be considered free from a risk for hyponatremia.[16]

In general, if hyponatremia occurred in patients on thiazides, resumption of thiazide use was not recommended.[17] In the clinic, some patients would immediately discontinue the drug when hyponatremia occurred, and some patients in whom blood pressure could not be adequately controlled without thiazides might decide to maintain thiazide use while paying attention to the patients' oral intake. The limitation of studies that used big data was that it was not possible to undertake a detailed evaluation of the characteristics and circumstances of each individual patient. In this study, patients who were prescribed thiazide for more than 7 days were grouped into the thiazide group for analysis as there was no significant difference in the occurrence of hyponatremia according to the prescription period when the thiazide prescription period was subdivided into 1, 3, 6, and 12 months. Among those with thiazide use for less than 7 days, there might be those who discontinued treatment due to drug-related acute hyponatremia. However, the incidence of hyponatremia in this group was not higher than that of patients who used the drug for more than 7 days. Thus, it was judged that it was difficult to ascertain whether the drug was prescribed for a sufficient period. In addition, the reason for the lack of an increased risk for hyponatremia that was proportional to the duration of thiazide use might reflect a consequential aspect in that thiazides might have been used for a long time because hyponatremia did not occur. Therefore, to minimize the limitations of these factors, this study analyzed the hyponatremia risk itself as related to thiazide use and whether the risk for hyponatremia increases when thiazides were prescribed together with other drugs.

In this study, only data on the occurrence of hyponatremia for up to 1 year after taking thiazide were collected/analyzed for the clarification of the study outcome. Therefore, it was possible that the incidence of hyponatremia was lower than the actual incidence of thiazide-related hyponatremia that had been experienced in the clinic. Even patients who had been taking thiazide with a stable condition for a long time could develop severe hyponatremia when they were in a situation that requires them to be *nil per os* or if they had poor oral intake while continuing thiazide use.[9,16] Also, we incorporated the diagnostic code E222 (SIADH) to identify instances of hyponatremia. In clinical practice, the diagnosis of SIADH should be made ideally after excluding hyponatremia caused by thiazide use. However, many cases in clinical settings might not reveal the precise cause of hyponatremia, and since SIADH diagnosis was considered a "diagnosis of exclusion," there were instances where the provisional diagnosis included the possibility

TABLE 2 Participant characteristics stratified according to the occurrence of hyponatremia.

Characteristics		Hyponatremia (-) (n = 1,909,894, %)	Hyponatremia (+) (n = 33,451, %)	p Value
Male		962,158 (50.38)	14,044 (41.98)	<0.001
Age, decade	20s	12,491 (0.65)	58 (0.17)	<0.001
	30s	61,050 (3.20)	230 (0.69)	
	40s	236,316 (12.37)	1036 (3.1)	
	50s	506,083 (26.50)	3237 (9.68)	
	60s	490,590 (25.69)	5617 (16.79)	
	70s	421,091 (22.05)	12,914 (38.61)	
	80s	161,964 (8.48)	9215 (27.55)	
	≥90s	20,309 (1.06)	1144 (3.42)	
Age, years[a]		62.4 ± 13.0	73.1 ± 11.4	<0.001
Diabetes mellitus		1,088,405 (56.99)	25,273 (75.55)	<0.001
Dyslipidemia		1,467,019 (76.81)	27,821 (83.17)	<0.001
Osteoporosis		652,856 (34.18)	19,139 (57.22)	<0.001
Heart failure		205,298 (10.75)	7664 (22.91)	<0.001
Chronic kidney disease		64,942 (3.40)	2209 (6.60)	<0.001
Depression		505,420 (26.46)	14,765 (44.14)	<0.001
Prescribed antihypertensive medications	Thiazide	694,530 (36.36)	15,546 (46.47)	
	CCB	1,039,534 (54.43)	17,707 (52.93)	<0.001
	ARB or ACEi	1,252,236 (65.57)	20,931 (62.57)	<0.001
	β-Blocker	315,742 (16.53)	6821 (20.39)	<0.001
	α-Blocker	28,349 (1.48)	991 (2.96)	<0.001
Coprescribed diuretics/desmopressin	Spironolactone	38,358 (2.01)	2005 (5.99)	<0.001
	Loop diuretics	88,980 (4.66)	4330 (12.94)	<0.001
	Desmopressin	5139 (0.27)	311 (0.93)	<0.001
Thiazides ≥2 kinds		27,578 (1.44)	1751 (5.23)	<0.001
Thiazide + spironolactone		10,682 (0.56)	687 (2.05)	<0.001
Thiazide + loop diuretics		15,440 (0.81)	980 (2.93)	<0.001
Thiazide + desmopressin		1429 (0.07)	81 (0.24)	<0.001
Thiazide + spironolactone + desmopressin		27 (0.00)	3 (0.01)	<0.001

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium-channel blocker.
[a]Data are expressed as the mean ± standard deviation.

of SIADH, even if only slight. Additionally, a study suggested that fractional excretion of uric acid was the sole method to determine if SIADH was present in patients using diuretics.[18] Given that this test was not conducted for all hyponatremia patients and considering the practical difficulty in identifying a clear cause for all hyponatremia patients, our primary aim in this study was to detect cases with a potential for hyponatremia in patients on thiazides through diagnostic codes without missing any relevant instances, hence this diagnosis was included as well.

In the baseline characteristics, the prevalence of CKD in the thiazide group was low, which might be a result that reflected the tendency to limit thiazide prescription in advanced CKD with hyperuricemia because hyperuricemic exacerbation was unavoidable with thiazide use.[19] The distribution trend of concurrently prescribed antihypertensive drugs indicated a significantly higher prescription of ACEi or ARB in the thiazide-use group and might be related to the high prescription rate of ACEi or ARB in Korean patients with hypertension. Furthermore, this might be related to the fact that many combination pill forms of thiazide and RAAS inhibitors were available and could be based on the recommendation of a single-pill combination treatment to improve drug compliance.[20,21]

Although patients using thiazide + spironolactone + desmopressin were at a higher risk of hyponatremia than other patients, the reason for only one occurrence of hyponatremia in these patients was likely attributable to the fact that after one episode of hyponatremia, medications that could increase the hyponatremia risk were excluded as

TABLE 3 Results of the multivariate analysis for the occurrence of hyponatremia.

Characteristics		Univariate			Multivariate[a,b]		
		HR	95% CI	*p* Value	HR	95% CI	*p* Value
Male		0.727	0.712-0.743	<0.001	1.304	1.271-1.339	<0.001
Age (risk per 1-year increase)		1.080	1.079-1.081	<0.001	1.069	1.068-1.070	<0.001
Diabetes mellitus		2.302	2.246-2.360	<0.001	1.453	1.415-1.492	<0.001
Dyslipidemia		1.419	1.379-1.461	<0.001	0.926	0.899-0.955	<0.001
Osteoporosis		2.581	2.526-2.638	<0.001	1.245	1.212-1.279	<0.001
Heart failure		2.598	2.532-2.665	<0.001	1.198	1.165-1.232	<0.001
Chronic kidney disease		2.162	2.071-2.258	<0.001	1.300	1.243-1.359	<0.001
Depression		2.249	2.201-2.298	<0.001	1.530	1.496-1.565	<0.001
Antihypertensive medications	Thiazide	1.514	1.482-1.547	<0.001	1.436	1.403-1.468	<0.001
	CCB	0.914	0.894-0.934	<0.001	0.956	0.935-0.977	<0.001
	ARB or ACEi	0.847	0.828-0.866	<0.001	0.941	0.919-0.963	<0.001
	β-Blocker	1.287	1.253-1.321	<0.001	1.024	0.996-1.052	0.090
	α-Blocker	2.108	1.979-2.246	<0.001	1.157	1.084-1.234	<0.001
Other medications	Spironolactone	3.797	3.629-3.973	<0.001	1.506	1.430-1.586	<0.001
	Loop diuretics	3.892	3.770-4.018	<0.001	2.126	2.046-2.208	<0.001
	Desmopressin	3.677	3.289-4.111	<0.001	2.144	1.915-2.400	<0.001

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium-channel blocker; HR, hazard ratio.

[a]Data were analyzed using Cox regression with the Enter method in multivariate analysis.

[b]Age (as a continuous variable), sex, diabetes mellitus, heart failure, chronic kidney disease, spironolactone, and desmopressin were used as covariates together with thiazide use for multivariate analysis.

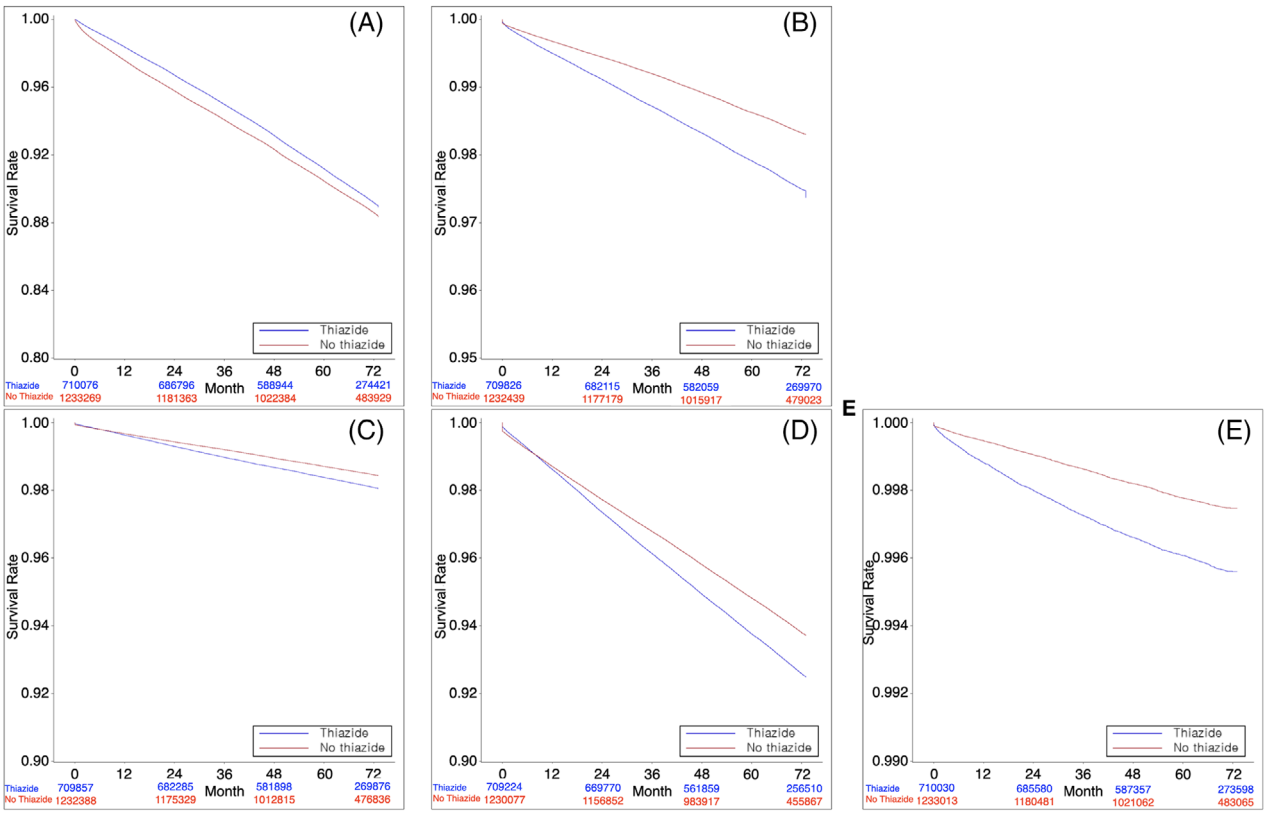

FIGURE 4 Outcomes stratified by thiazide use. (A) All-cause mortality; (B) hospitalization for hyponatremia; (C) osteoporotic fractures; (D) other traumatic fractures; (E) hospitalization more than 2 times for hyponatremia.

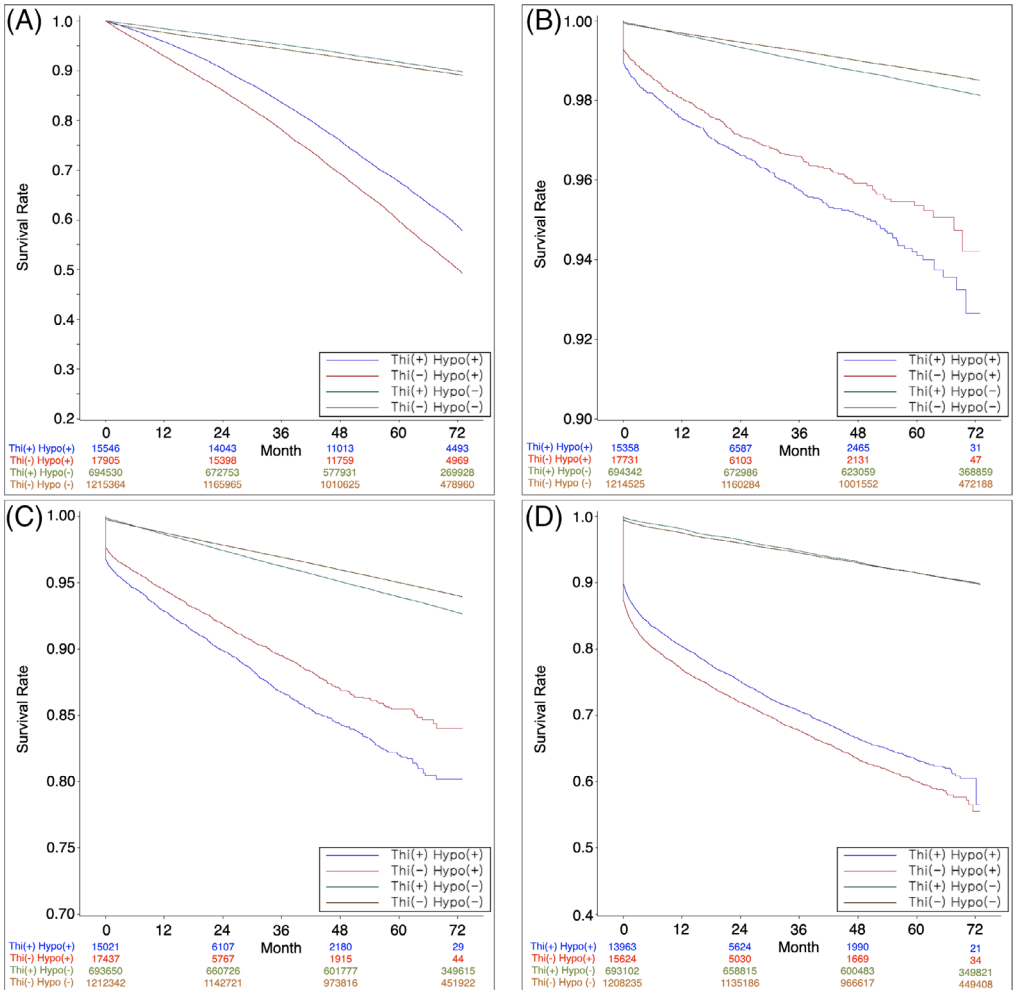

FIGURE 5 Outcomes stratified by thiazide use and the occurrence of hyponatremia. (A) All-cause mortality; (B) hospitalization for osteoporotic fractures; (C) hospitalization for other traumatic fractures; (D) hospitalization for pneumonia.

much as possible on suspicion of a drug-related complication. The reason for the higher risk of hyponatremia with thiazide + spironolactone or loop diuretic use than desmopressin use alone might be because there were many patients with heart failure in the group with concurrent prescription of these drugs. Patients with heart failure often had hypervolemic hyponatremia due to increased ADH secretion and action.[22] Although loop diuretics were the only diuretics that could be used to improve euvolemic or hypervolemic hyponatremia, these drugs increased the risk of hyponatremia in this study.[23] When interpreting the results of this study, it should be noted that the prescription rate of loop diuretics was significantly higher in patients with heart failure.[22] Thus, it was difficult to evaluate the effect of each individual factor on the risk of hyponatremia in a situation wherein multiple comorbidities and polypharmacy exists.

Furthermore, this study showed an increase in several adverse outcomes with thiazide use, in concordance with several previous studies that reported an association of hyponatremia with poor clinical outcomes.[24–27] The in-depth analyzes such as multivariate analysis were not performed about other outcomes other than the occurrence of hyponatremia, so that a causal relationship could not be claimed. However, the correlation shown through this study could be investigated through further study in the future. Although the incidence of hyponatremia increased in the thiazide group and was associated with an adverse outcome and poor prognosis in patients with hyponatremia, the all-cause mortality was lower in the thiazide group. When examining the outcome by combining thiazide use with hyponatremia, the populations with hyponatremia showed higher all-cause mortality rate. Based on the results of the 4-group analysis, it was clear that thiazide use itself was not harmful and could improve survival by increasing sodium excretion and ensuring adequate blood pressure control.[28] By properly monitoring the occurrence of hyponatremia in patients prescribed thiazides, safer and more effective thiazide use can be ensured by minimizing the occurrence of hyponatremia-induced complications.

There were several limitations of this study. First, as this study was based on big data that, by its very nature, precluded access to information on the drug dosage, a dose-dependent effect could not be evaluated. Second, the evaluation of the severity or cause of hyponatremia in individual cases could not be undertaken. Patients who were hospitalized for mild to moderate hyponatremia or for other main illnesses and had concomitant hyponatremia might have been

excluded because the hyponatremia diagnosis code was not entered. Thus, the hyponatremia incidence might have been underestimated. Finally, while data on thiazide prescription itself were collected, the actual medication compliance could not be verified. Additionally, it remained unclear whether the medication was discontinued because of hyponatremia. Despite these limitations, this study was valuable as the first study using big data analysis to examine the occurrence of hyponatremia in patients on thiazides and the hyponatremia risk with concurrent use with other drugs in many patients.

In conclusion, there is an increased risk of hyponatremia in patients on thiazides and related complications in those who were prescribed thiazides. However, the mortality rate decrease in those who received thiazides, suggesting that thiazide itself is not harmful, but that it would be more helpful in reducing complications and improving the prognosis if properly and cautiously used in groups that are at high risk for hyponatremia.

ACKNOWLEDGMENTS

This work was presented as an abstract at the Kidney Week 2022 in Orlando, FL, USA.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

Data generated and/or analyzed during the current study cannot be shared publicly due to the data sharing policy of the National Health Insurance Service (NHIS) of Korea, governed by Article 18 of the Personal Information Protection Act ("Limitation to Out-of-Purpose Use and Provision of Personal Information" available at https://elaw.klri.re.kr/kor_service/lawView.do?hseq=53044&lang=ENG). However, the data are available from the NHIS (study identifier: NHIS-2021-1-557) on reasonable request for researchers who meet the criteria for access to confidential data (https://www.data.go.kr/en/tcs/eds/selectCoreDataView.do?coreDataInsttCode=B551182&coreDataSn=1&searchCondition2=coreDataNmEn&searchKeyword2=).

ORCID

Jin Ho Hwang https://orcid.org/0000-0003-0829-0922

REFERENCES

1. Clayton JA, Rodgers S, Blakey J, Avery A, Hall IP. Thiazide diuretic prescription and electrolyte abnormalities in primary care. *Br J Clin Pharmacol*. 2006;61(1), 87–95.
2. Leung AA, Wright A, Pazo V, Karson A, Bates DW. Risk of thiazide-induced hyponatremia in patients with hypertension. *Am J Med*. 2011;124(11), 1064–1072.
3. Adrogué HJ, Tucker BM, Madias NE. Diagnosis and management of hyponatremia: a review. *JAMA*. 2022;328(3), 280–291.
4. Lee Y, Yoo KD, Baek SHa, et al. Korean Society of Nephrology 2022 Recommendations on controversial issues in diagnosis and management of hyponatremia. *Kidney Res Clin Pract*. 2022;41(4), 393–411.
5. Yang L-J, Wu P-H, Huang T-H, Lin M-Y, Tsai J-C. Thiazide-associated hyponatremia attenuates the fracture-protective effect of thiazide: a population-based study. *PLoS One*. 2018;13(12), e0208712.
6. Barsony J, Kleess L, Verbalis JG. Hyponatremia is linked to bone loss, osteoporosis, fragility and bone fractures. *Front Horm Res*. 2019;52:49–60.
7. Chobanian AV, Bakris GL, Black HR, et al. Seventh report of the joint national committee on prevention, detection, evaluation, and treatment of high blood pressure. *Hypertension*. 2003;42:1206–1252.
8. Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Hypertension*. 2018;71(6), e13–e115.
9. Filippone EJ, Ruzieh M, Foy A. Thiazide-associated hyponatremia: clinical manifestations and pathophysiology. *Am J Kidney Dis*. 2020;75(2), 256–264.
10. Burst V, Grundmann F, Kubacki T, et al. Thiazide-associated hyponatremia, report of the hyponatremia registry: an observational multicenter international study. *Am J Nephrol*. 2017;45(5), 420–430.
11. Hwang KS, Kim G-Ho. Thiazide-induced hyponatremia. *Electrolyte Blood Press*. 2010;8(1), 51–57.
12. Mann SJ. The silent epidemic of thiazide-induced hyponatremia. *J Clin Hypertens (Greenwich)*. 2008;10(6), 477–484.
13. Sharabi Y, Illan R, Kamari Y, et al. Diuretic induced hyponatraemia in elderly hypertensive women. *J Hum Hypertens*. 2002;16(9), 631–635.
14. Fuisz RE, Lauler DP, Cohen P. Diuretic-induced hyponatremia and sustained antidiuresis. *Am J Med*. 1962;33:783–791.
15. Ashraf N, Locksley R, Arieff AI. Thiazide-induced hyponatremia associated with death or neurologic damage in outpatients. *Am J Med*. 1981;70(6), 1163–1168.
16. Rodenburg EM, Hoorn EJ, Ruiter R, et al. Thiazide-associated hyponatremia: a population-based study. *Am J Kidney Dis*. 2013;62(1), 67–72.
17. Liamis G, Filippatos TD, Elisaf MS. Thiazide-associated hyponatremia in the elderly: what the clinician needs to know. *J Geriatr Cardiol*. 2016;13(2), 175–182.
18. Fenske W, StöRk S, Koschker A-C, et al. Value of fractional uric acid excretion in differential diagnosis of hyponatremic patients on diuretics. *J Clin Endocrinol Metab*. 2008;93(8), 2991–2997.
19. Agarwal R, Sinha AD. Thiazide diuretics in advanced chronic kidney disease. *J Am Soc Hypertens*. 2012;6(5), 299–308.
20. Kim HC, Lee H, Lee H-H, et al. Korea hypertension fact sheet 2021: analysis of nationwide population-based data with special focus on hypertension in women. *Clin Hypertens*. 2022;28(1), 1.
21. Unger T, Borghi C, Charchar F, et al. 2020 International Society of Hypertension Global Hypertension Practice Guidelines. *Hypertension*. 2020;75(6), 1334–1357.
22. Rodriguez M, Hernandez M, Cheungpasitporn W, et al. Hyponatremia in heart failure: pathogenesis and management. *Curr Cardiol Rev*. 2019;15(4), 252–261.
23. Szatalowicz VL, Miller PD, Lacher JW, Gordon JA, Schrier RW. Comparative effect of diuretics on renal water excretion in hyponatraemic oedematous disorders. *Clin Sci (Lond)*. 1982;62(2), 235–238.
24. Al Mawed S, Pankratz VS, Chong K, Sandoval M, Roumelioti ME, Unruh M. Low serum sodium levels at hospital admission: outcomes among 2.3 million hospitalized patients. *PLoS One*. 2018;13(3), e0194379.
25. Teo CB, Gan MYi, Tay RYK, Loh WJ, Loh Ne-HW. Association of preoperative hyponatremia with surgical outcomes: a systematic review and meta-analysis of 32 observational studies. *J Clin Endocrinol Metab*. 2023;108(5), 1254–1271.
26. Wald R. Impact of hospital-associated hyponatremia on selected outcomes. *Arch Intern Med*. 2010;170(3), 294–302.
27. Zilberberg MD, Exuzides A, Spalding J, et al. Hyponatremia and hospital outcomes among patients with pneumonia: a retrospective cohort study. *BMC Pulm Med*. 2008;8:16.
28. Wong MCS, Tam WWS, Wang HHX, et al. Predictors of the incidence of all-cause mortality and deaths due to diabetes and renal diseases

among patients newly prescribed antihypertensive agents: a cohort study. *Int J Cardiol*. 2013;168(5), 4705–4710.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Kwon S, Kim H, Lee J, Shin J, Kim SH, Hwang JH. Thiazide-associated hyponatremia in arterial hypertension patients: A nationwide population-based cohort study. *J Evid Based Med*. 2024;1-11. https://doi.org/10.1111/jebm.12601