

Thiazide and thiazide-like diuretics are associated with improved cardiovascular and renal outcomes in patients with chronic kidney disease

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ABSTRACT

Introduction: Hypervolemia is a prevalent comorbidity of chronic kidney disease (CKD) patients. Thiazide diuretics (THZ) are the most common treatment for volume overload and hypertension (HTN). This study examines the association between THZ usage and clinical outcomes among CKD patients in a nationwide cohort.

Method: The total number of patients in the study was 24,312. After matching with one non-user randomly selected from the CKD population, we identified 8501 patients in the THZ and the comparison cohorts. Cox proportional hazards regression analysis was conducted to estimate the associations of THZ on the incidence of all-cause mortality, end-stage renal disease (ESRD), congestive heart failure (CHF), acute myocardial infarction (AMI), peripheral arterial occlusive disease (PAOD), and stroke.

Results: The all-cause mortality rate was significantly lower in THZ users than in non-users (hazard ratio [HR] = 0.65, 95% confidence interval [CI] = 0.60–0.71). The THZ usage was associated with a lower incidence of ESRD, AMI, PAOD, and stroke ($P < 0.05$). In subgroup analysis, some significant clinical outcomes were related with CKD stages 3 and 4 ($P < 0.05$); however, there were no clinical associations in CKD stage 5. In further THZ subtype analysis, there were clinical associations with fewer deaths, ESRD, AMI, and PAOD accompanying chlorthalidone treatment. Moreover, the indapamide prescription was linked to lower mortality, ESRD, AMI, and PAOD prevalence. However, there were significantly greater incidences of ESRD, CHF, and AMI in the metolazone users.

Conclusion: THZ usage is associated with lower mortality and incidence of ESRD, AMI, PAOD, and stroke s in patients with CKD stages 3 and 4.

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Key words: CKD, ESRD, heart attack, thiazide

CLINICAL IMPACT

What is New

- Thiazide usage is associated with reductions in mortality, end-stage kidney disease (ESKD), acute myocardial infarction (AMI), peripheral artery occlusive disease (PAOD) and stroke in patients with advanced chronic kidney disease (CKD).
- Chlorthalidone was linked to less death, ESRD, AMI and PAOD; and indapamide to a lower prevalence of mortality, ESKD, AMI and PAOD. However, metolazone was not.

Clinical Implications

- Our study provides evidence that thiazides, in particular chlorthalidone and indapamide, are associated with favourable outcomes in CKD patients.

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INTRODUCTION

Chronic kidney disease (CKD) is an increasingly pressing global health issue due to its strong link to serious complications such as end stage renal disease (ESRD), cardiovascular disease (CVD) and mortality.¹ Over the last few decades, its impact has become more severe, moving from 27th to 18th on the list of leading causes of global mortality in 2010.² In the US, the prevalence rate of CKD is estimated to be as high as 15%³ while globally the rate ranges from 11% to 13%.⁴ In Taiwan, where 2.8 million patients suffer from CKD, the prevalence of CKD in adults was 12% in 2018.⁵ Given its global prevalence and its negative impact on health, CKD is a critical public health concern.

CKD is commonly associated with hypervolemia and hypertension (HTN).^{6, 7} The pathophysiology of these conditions varies. Specifically, with the decline in renal function, the filtration of sodium is reduced, leading to inappropriate suppression of tubular reabsorption and subsequent volume expansion.⁸⁻¹⁰ The renin-angiotensin-aldosterone system and the sympathetic nervous system become activated, resulting in elevated blood pressure. Therefore, the management of volume overload and HTN is crucial in treating CKD. The primary treatments for HTN in CKD are angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs). However, with the progression of renal function, the use of renin-angiotensin-aldosterone system blockers may need to be discontinued.¹¹

To treat both volume overload and HTN, diuretics are widely used. Thiazide (THZ) diuretics primarily act on the Na⁺/Cl⁻ cotransporter (NCC) in the distal convoluted tubule of the nephron, which is responsible for 7% of total sodium reabsorption.¹² THZ diuretics include THZ-type diuretics hydrochlorothiazide and THZ-like diuretics, such as indapamide and chlorthalidone. Although distal diuretics are less effective in controlling volume in CKD compared to loop diuretics, a pilot study showed that adding chlorthalidone to the antihypertensive regimen in patients with CKD and HTN could significantly reduce systolic blood pressure.¹³ Similarly, a study by Cirillo et al. demonstrated a significant reduction in systolic blood pressure by 19mmHg from baseline in patients with CKD and HTN compared to patients in the control group.¹⁴ Recently published research shows that distal diuretics are as effective as dietary sodium restriction in reducing blood pressure and extracellular volume in CKD.¹⁵ While THZ-type and THZ-like diuretics have been found to be effective in lowering blood pressure in patients with CKD, their impact on clinical outcomes requires further investigation. Therefore, this study aims to explore

the association between THZ usage and clinical outcomes in patients with CKD in Taiwan, using the Taiwanese National Health Insurance Research Database (NHIRD), one of the world's largest population-based cohorts.¹⁶

METHOD

In Taiwan, the National Health Insurance Administration, Ministry of Health and Welfare holds a medical insurance programme, called the National Health Insurance (NHI) programme, which was initiated in 1995 by merging three existing health insurance programmes. The Taiwanese NHI system is a compulsory, nationwide insurance system that enrolls 99% of the 23.74 million residents of Taiwan and has contracts with 97% of Taiwanese health providers.¹⁷ The Taiwanese National Health Insurance Research Database (NHIRD), which compiles data from insurance claims by the National Health Insurance Research Institutes, has been made publicly available for research since 2000. The NHIRD comprehensively includes Chinese and Western medicine outpatient visits, hospitalisations, medicine offered by the NHI programme, medication refilled, laboratory and imaging examinations, and medical procedure codes.¹⁸ The diseases diagnosed are coded according to the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM). The Institutional Review Board approved this cohort study of Kaohsiung Medical University (KMUH-IRB-EXEMPT(I)-20160022).

Study participants

We conducted a retrospective cohort study. Patients with CKD were defined when one or more of the following ICD-9-CM diagnostic codes were used (ICD-9-CM codes 095.4, 189, 223, 236.9, 250.4, 271.4, 274.1, 403-404, 440.1, 442.1, 446.21, 447.3, 572.4, 580-589, 590-591, 593, 642.1, 646.2, 753) that were newly diagnosed by physicians from January 1, 2000 to December 31, 2010, according to the NHIRD records of the CKD cohort. The date of the first CKD diagnosis was considered the index date. We excluded patients aged younger than 20 years (n=4662) and older than 100 years (n=13). Also excluded were patients who had missing demographic data records (n=141); diagnosis of renal transplantation (n=15), ESRD (n=2267) before CKD diagnosis; expired within 90 days after the index date (n=809); received renal replacement therapy (RRT) within 90 days after the index date (n=538); suffered from CVD within 90 days after the index date (n=489); or did not receive THZ diuretics for at least 90 days between the index date and the endpoint time of the study (n=8,793). Patients did not receive antihypertensive agents at least 90 days

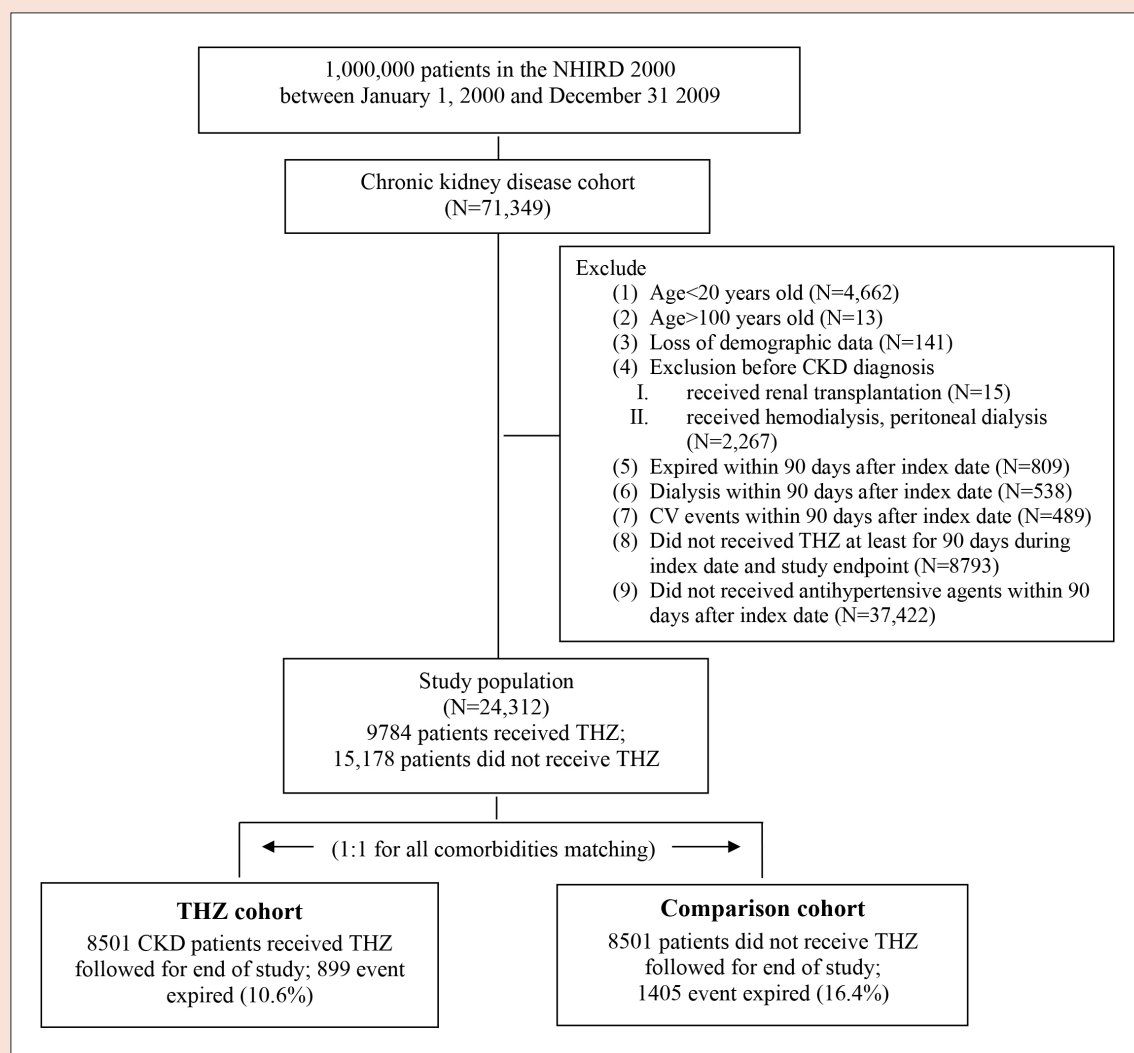
between the index date and the endpoint time of the study were also excluded ($n=37,422$). Then we matched according to sex and age with a one-to-one ratio for the study cohort (THZ cohort) with the definition of THZ diuretics usage for more than 90 days and comparison cohort randomly selected patients with the CKD cohort without taking THZ diuretics. Age was calculated from the date of birth to the date of CKD diagnosis. The follow-up period started from their entry to the study cohort to the date of the CKD event, administrative censoring, or December 31, 2010 (Fig. 1).

Outcome measures

In Taiwan, patients with ESRD requiring RRT can apply for a catastrophic illness card. Cardholders are exempt from the cost-sharing required by the NHI programme. Patients with ESRD were defined as patients who had received a catastrophic illness card for dialysis and claimed for haemodialysis or peritoneal dialysis for at least three months

(ICD-9-CM code 585). The duration of follow-up for the patients were estimated from the index date to the study endpoint date, censoring caused by death during hospitalisation, loss in follow-up, withdrawal from the insurance system, or the end of December 31, 2010. The comorbidities included in our study were hypertension (ICD-9-CM codes 401-405); diabetes mellitus (ICD-9-CM code 250); hyperlipidaemia (ICD-9-CM code 272); CVD (ICD-9-CM codes 410, 412, 428); cerebrovascular diseases (ICD-9-CM codes 430-438); liver disease (ICD-9-CM codes 571-572, 456.0-456.2); gout (ICD-9-CM code 274.x); obesity (ICD-9-CM code 278.x); and depression (ICD-9-CM codes 296.2, 296.3). CKD stage 5 was defined by (ICD-9-CM code 585) CKD patients receiving NHI-covered erythropoiesis-stimulating agent treatment, indicating that their estimated GFR levels of $<15\text{ mL/min/1.73m}^2$ and haemoglobin $<9\text{ gm/dL}$.¹⁹ The outcomes of interest in the study included mortality, ESRD, CHF, AMI, PAOD and stroke.

Fig. 1. Flow diagram of study population.



Validation

We validated the ICD-9-CM codes for the identification of CKD by analysing the medical records (charts) of 200 patients who had CKD ICD-9-CM codes 095.4, 189, 223, 236.9, 250.4, 271.4, 274.1, 403-404, 440.1, 442.1, 446.21, 447.3, 572.4, 580-589, 590-591, 593, 642.1, 646.2, 753 from the inpatient and outpatient claims database from January 2008 to December 2010 in Kaohsiung Municipal Ta-Tung Hospital, a regional teaching hospital in Taiwan. The contents of this database were similar to those of the NHIRD. Nephrologists ascertained the clinical diagnosis of CKD. Clinical diagnosis of CKD was determined according to the estimated GFR levels of $<60\text{mL/min/1.73m}^2$ for more than three months. Positive predictive values (PPV) of both diseases were estimated. There were 193 cases confirmed the diagnosis with CKD. The positive PPV of CKD is 0.96.

Statistical analysis

An independent t-test, chi-square test, or Fisher's exact test was employed to compare the distribution of risk factors between the THZ and control cohorts. Cox proportional hazard regression analyses were conducted to calculate the crude and adjusted hazard ratios (HRs) for the risk of clinical outcomes. Multiple Cox proportional hazard regression analyses were performed after adjustment for sex, age and any history of HTN, DM, hyperlipidaemia, cerebrovascular disease, CVD, liver disease, gout and cancer. Statistical analyses were performed using SAS 9.3 software (SAS Institute, Inc., Cary, NC, USA). Statistical significance was set at $P<0.05$.

RESULTS

Baseline characteristics of the THZ cohort and comparison cohort

The study enrolled 24,312 patients with chronic kidney disease (CKD) from 2000 to 2010. After matching with a one-to-one ratio, 8501 patients had a prescription for THZ diuretics for 90 days. Among them, 44.1% had been treated with THZ-type (bendroflumethiazide and hydrochlorothiazide), 48.8% with indapamide, 2.2% with chlorthalidone, and 4.9% with metolazone. The mean age was 64.11 ± 12.67 years, and 52.4% of the patients were female. The distributions of age, sex, index year, visiting a nephrologist within three years before the index date, region of residence, comorbidities, and anti-hypertensive medications were similar between the THZ cohort and the comparison cohort (Table 1). The baseline characteristics between THZ-type and THZ-like diuretics were presented as in Supplementary Table S1.

Clinical outcomes of THZ diuretics in patients with CKD

During the follow-up period, 10.5% of patients died, 16.7% suffered from CHF, 14.6% suffered from AMI, 11.4% suffered from PAOD, 17.0% suffered from stroke, and 15.4% required long-term RRT. The incidence rate ratios of total mortality, AMI, PAOD, stroke and ESRD were significantly lower in the THZ cohort than the comparison cohort ($P<0.001$). In CKD stages 3 and 4, THZ diuretic usage reduced mortality (52%), AMI (21%), stroke (12%) and ESRD (52%) (Table 2). There was no significant clinical protection for CHF with THZ diuretics usage in patients with CKD stages 3 and 4. However, in patients with CKD stage 5, THZ diuretics users experienced neutral effects on clinical outcomes compared with THZ diuretics non-users (Table 3).

The associations of THZ-type and THZ-like diuretics subtypes and clinical outcomes

In the THZ diuretics subtype analysis, there were no significant differences in clinical outcome benefits in the THZ cohort compared to the comparison cohort among THZ-type diuretics users. With indapamide usage, the risks of mortality, AMI, PAOD, and ESRD were significantly lower in the THZ cohort than the comparison cohort ($P<0.05$). With chlorthalidone usage, the risks of total mortality, AMI and ESRD were significantly lower in the THZ cohort than the comparison cohort ($P<0.05$). However, there were significant higher risks of clinical outcomes, including ESRD, CHF and PAOD, between the THZ cohort and the comparison cohort with metolazone usage ($P<0.05$) (Table 4).

DISCUSSION

Our study examined the association of using THZ diuretics in patients with CKD. Our results revealed that patients who used THZ diuretics associated with reduced incidences of mortality, AMI, stroke, PAOD and ESRD compared to those who did not. In the subgroup analysis of patients with CKD stage 3 and 4, THZ diuretics usage was associated with the same clinical outcomes. However, in patients with CKD stage 5, we did not observe any beneficial clinical relations with THZ diuretics usage. Further analysis by subtype revealed that chlorthalidone users were related to lower incidences of mortality, PAOD and ESRD. Indapamide users were also linked to lower incidences of mortality, AMI, PAOD and ESRD. Conversely, THZ-type diuretics including bendroflumethiazide and hydrochlorothiazide did not show any significant difference in clinical outcomes. Interestingly, metolazone users were associated with higher incidences of CHF, AMI and ESRD than non-users.

Table 1. Demographic characteristics between THZ and comparison cohort in CKD population.

	Before matching (n=24,312)		P value	After matching (n=17,002)		P value
	THZ cohort (n=9784)	Comparison cohort (n=14,528)		THZ cohort (n=8501)	Comparison cohort (n=8501)	
Age(Mean±SD)	64.67 (±12.43)	59.74 (±16.03)	<0.001	64.11 (±12.67)	64.30 (±13.24)	0.340
20-44	970 (6.8)	2786 (19.2)		656 (7.7)	575 (6.8)	
45-64	3911 (40.0)	5731 (39.4)		3506 (41.2)	3491 (41.1)	
65-74	3008 (30.7)	3217 (22.1)		2497 (29.4)	2533 (29.8)	
75-100	2195 (22.4)	2794 (19.2)		1842 (21.7)	1902 (22.4)	
Gender (%)						
Female	5294 (54.1)	7036 (48.4)	<0.001	4456 (52.4)	4350 (51.2)	0.104
Male	4490 (45.9)	7492 (51.6)		4045 (47.6)	4151 (48.8)	
Region						
Northern	4094 (41.8)	6588 (45.3)	<0.001	3674 (43.2)	3750 (44.1)	0.563
Central	2886 (29.5)	3869 (26.6)		2427 (28.5)	2338 (27.5)	
Southern and eastern	2804 (28.7)	4071 (28.0)		2400 (28.2)	2413 (28.4)	
Visit nephrologist within 3 year before index date						
0	7674 (78.4)	11745 (80.8)	<0.001	6727 (79.1)	6651 (78.2)	0.133
1-6	1560 (15.9)	2030 (14.0)		1293 (15.2)	1335 (15.7)	
>6	550 (5.6)	753 (5.2)		481 (5.7)	515 (6.1)	
Comorbidities(%)						
Diabetes	4399 (45.0)	4834 (33.3)	<0.001	3636 (42.8)	3706 (43.6)	0.278
Coronary artery disease	634 (6.5)	843 (5.8)	0.196	526 (6.3)	604 (7.1)	0.051
Congestive heart failure	441 (4.5)	598 (4.1)	0.567	377 (4.4)	401 (4.7)	0.378
Acute myocardial fraction	295 (3.0)	493 (3.4)	0.025	270 (3.2)	298 (3.5)	0.232
Peripheral vascular disease	147 (1.5)	234 (1.6)	0.372	129 (1.5)	135 (1.6)	0.710
Peripheral vascular disease	147 (1.5)	234 (1.6)	0.372	129 (1.5)	135 (1.6)	0.710

Table 1. Demographic characteristics between THZ and comparison cohort in CKD population. (Cont'd)

	Before matching (n=24,312)		P value	After matching (n=17,002)		P value
	THZ cohort (n=9784)	Comparison cohort (n=14528)		THZ cohort (n=8501)	Comparison cohort (n=8501)	
Cerebral vascular disease	342 (3.5)	528 (3.6)	0.251	313 (3.7)	331 (3.9)	0.495
Cancer	140 (1.4)	289 (2.0)	<0.001	130 (1.5)	119 (1.4)	0.483
Charlson comorbidity index						
0	8023 (82.0)	11814 (81.3)	0.007	6940 (81.6)	6862 (80.7)	0.219
1	1353 (13.8)	2182 (15.0)		1224 (14.4)	1265 (14.9)	
≥2	408 (4.2)	532 (3.7)		337 (4.0)	374 (4.4)	
Medication						
ACEI	3480 (35.6)	3027 (20.8)	<0.001	2684 (31.6)	2686 (31.6)	0.974
ARB	2551 (26.1)	2222 (15.3)	<0.001	1966 (23.1)	1965 (23.1)	0.985
α-Blockers	1362 (13.9)	1498 (10.3)	<0.001	1081 (12.7)	1105 (13.0)	0.582
β-Blockers	4358 (44.5)	4331 (29.8)	<0.001	3483 (41.0)	3485 (41.0)	0.975
Calcium channel blockers						
Nondihydropyridine	1145 (11.7)	1064 (7.3)	<0.001	883 (10.4)	891 (10.5)	0.841
Dihydropyridine	5002 (51.1)	4493 (30.9)	<0.001	3929 (46.2)	4006 (47.1)	0.237
Other antihypertensives	721 (7.4)	292 (2.0)	<0.001	287 (3.4)	335 (3.9)	0.051
Loop diuretics	982 (10.0)	1307 (8.9)	<0.001	803 (9.4)	765 (8.9)	0.063
THZ-type and THZ-like						
THZ-type	4301 (44.0)			3747 (44.1)		
Metolazone	491 (5.0)			419 (4.9)		
Chlorthalidone	219 (2.2)			189 (2.2)		
Indapamide	4773 (48.8)			4146 (48.8)		

Abbreviation: SD=standard deviation.

The difference of two cohort was estimated by independent t test or chi-square test.

*THZ: bendroflumethiazide, and hydrochlorothiazide

Table 2. The risk of clinical outcomes between THZ cohort and comparison cohort.

	Before matching						After matching					
	THZ cohort			Comparison cohort			THZ cohort			Comparison cohort		
	No. cases	Per PY	No. cases	Per PY	SHR (95%CI)	P value	No. cases	Per PY	No. cases	Per PY	SHR (95%CI)	P value
Mortality	1065	17.25	1683	22.05	0.66 (0.61-0.72)	<0.001	889	16.46	1140	26.79	0.65 (0.60-0.71)	<0.001
ESRD	1743	29.51	2329	32.09	0.73 (0.69-0.78)	<0.001	1305	25.07	1516	37.48	0.71 (0.66-0.77)	<0.001
CHF	1710	30.44	1858	25.76	0.96 (0.90-1.03)	0.246	1421	28.83	1280	32.23	0.95 (0.88-1.02)	0.170
AMI	1493	25.64	1820	24.86	0.84 (0.79-0.91)	<0.001	1238	24.28	1248	30.74	0.82 (0.76-0.89)	<0.001
PAOD	1153	19.08	1723	23.05	0.69 (0.64-0.75)	<0.001	973	18.42	1188	28.60	0.68 (0.63-0.74)	<0.001
Stroke	1721	30.32	1930	26.64	0.92 (0.86-0.99)	0.020	1442	28.99	1329	33.29	0.91 (0.84-0.98)	0.011

Adjusted all comorbidities. AMI: acute myocardial infarction, CHF: congestive heart failure, ESRD: end stage renal disease, PAOD: peripheral arterial occlusive disease
PY: patient year

Table 3. The risk of clinical outcomes between THZ cohort and comparison cohort in different CKD stages.

	Before matching					After matching				
	THZ cohort		Comparison cohort			THZ cohort		Comparison cohort		
	No. cases	Per PY	No. cases	Per PY	SHR (95%CI)	P value	No. cases	Per PY	No. cases	SHR (95%CI)
CKD stage 3-4										
Mortality	1063	17.23	2313	30.76	0.65 (0.60-0.70)	<0.001	892	16.42	1392	33.94 (0.58-0.69)
ESRD	1641	27.80	2271	31.33	0.73 (0.68-0.78)	<0.001	1374	26.40	1519	38.82 (0.65-0.75)
CHF	1708	30.44	1840	25.60	0.96 (0.90-1.03)	0.254	1444	29.13	1238	31.86 (0.88-1.03)
AMI	1458	25.06	1802	24.70	0.84 (0.78-0.90)	<0.001	1248	24.33	1221	30.84 (0.75-0.88)
PAOD	1151	19.06	1706	22.90	0.69 (0.64-0.75)	<0.001	975	18.34	1150	28.42 (0.31-0.73)
Stroke	1717	30.28	1911	26.47	0.92 (0.86-0.99)	0.017	1452	29.05	1281	32.93 (0.84-0.98)
CKD stage 5										
Mortality	2	31.29	20	76.13	1.37 (0.20-9.57)	0.751	2	31.90	13	62.87 (0.34-23.19)
ESRD	12	540.30	58	562.67	1.66 (0.77-3.61)	0.200	12	540.29	45	575.45 (0.93-4.66)
CHF	2	31.90	18	72.34	1.00 (0.18-5.52)	0.997	2	31.90	13	67.39 (0.18-7.24)
AMI	5	92.13	18	72.05	2.58 (0.53-12.49)	0.239	5	92.13	11	56.82 NA
PAOD	2	31.90	17	66.16	NA		2	31.90	12	58.83 (0.28-15.50)
Stroke	4	66.13	19	75.24	NA		4	66.13	14	71.66 (0.69-19.87)

Adjusted all comorbidities. AMI: acute myocardial infarction, CHF: congestive heart failure, ESRD: end stage renal disease, PAOD: peripheral arterial occlusive disease
PY: patient year

Table 4. Subtype THZ diuretics analysis of risks of clinical outcomes between THZ cohort and comparison cohort.

	THZ cohort		Comparison cohort		SHR (95%CI)	P value
	No. cases	Per PY	No. cases	Per PY		
THZ-type						
Mortality	354	28.24	1140	26.79	1.05(0.93-1.14)	0.874
ESRD	493	38.76	1516	37.48	1.03(0.97-1.04)	0.837
CHF	507	34.23	1280	32.23	1.06(0.89-1.12)	0.761
AMI	426	31.65	1248	30.74	1.02(0.89-1.08)	0.653
PAOD	371	30.76	1188	28.60	1.07(0.92-1.12)	0.743
Stroke	549	32.76	1329	33.29	0.98(0.91-1.03)	0.887
Indapamide						
Mortality	437	17.24	1140	26.79	0.64(0.57-0.71)	<0.001
ESRD	665	25.19	1516	37.48	0.72(0.65-0.79)	<0.001
CHF	751	30.26	1280	32.23	1.01(0.92-1.10)	0.898
AMI	670	26.02	1248	30.74	0.89(0.81-0.98)	0.018
PAOD	495	18.50	1188	28.60	0.69(0.62-0.78)	<0.001
Stroke	750	29.77	1329	33.29	0.94(0.86-1.03)	0.177
Chlorthalidone						
Mortality	20	13.73	1140	26.79	0.62(0.40-0.97)	0.037
ESRD	23	16.22	1516	37.48	0.54(0.36-0.82)	0.004
CHF	32	23.37	1280	32.23	0.84(0.59-1.20)	0.335
AMI	31	22.56	1248	30.74	0.83(0.58-1.19)	0.314
PAOD	20	14.00	1188	28.60	0.60(0.39-0.94)	0.026
Stroke	37	27.35	1329	33.29	0.94(0.68-1.31)	0.728
Metolazone						
Mortality	78	27.91	1140	26.79	0.98(0.78-1.24)	0.862
ESRD	124	47.67	1516	37.48	1.28(1.06-1.54)	0.009
CHF	131	54.97	1280	32.23	1.60(1.33-1.92)	<0.001
AMI	111	43.32	1248	30.74	1.41(1.08-1.59)	0.007
PAOD	87	32.37	1188	28.60	1.06(0.85-1.32)	0.606
Stroke	106	41.67	1329	33.29	1.16(0.95-1.41)	0.147

Adjusted all comorbidities. AMI: acute myocardial infarction, CHF: congestive heart failure, ESRD: end stage renal disease, PAOD: peripheral arterial occlusive disease
PY: patient year

Thiazide diuretics in chronic kidney disease

The diuretic effect of THZ medications leads to natriuresis and volume reductio.^{20, 21} In the study of applying THZ-like diuretics in patients with CKD stage 4 and a poorly controlled HTN, chlorthalidone therapy improved blood-pressure control at 12

weeks as compared with a placebo.²² Nevertheless, the precise role of THZ-based therapy and long-term effects in managing CKD patients require further investigation. CKD patients often experience extracellular fluid volume expansion concomitant with a decline in renal function. This

phenomenon results in volume overload, which in turn elevates the risk of CV morbidity and mortality.²³ Furthermore, patients with fluid overload exhibit a higher incidence of progressing to end-stage renal disease and experience a more rapid decline in eGFR.²³

Contemporary guidelines for treating HTN in CKD patients recommend a systolic blood pressure target of less than 120mmHg, based on large randomised controlled trials such as ACCORD and SPRINT.²⁴⁻²⁶ However, this recommendation only pertains to specific stages of CKD. The National Institute for Health and Care Excellence (NICE) CKD guideline proposes that ACEIs or ARBs are the preferred antihypertensive agents.²⁷ For patients who experience adverse effects or uncontrolled HTN with ACEIs or ARBs, alternative or add-on medications are often insufficient. Our study provides additional evidence for the potential clinical utility of THZ and THZ-like diuretics in managing patients with CKD.

Association of THZ usage with clinical outcomes

More and more studies demonstrate the superior mortality reduction of THZ users against THZ non-users.²⁸ Further analysis showed that the observed benefits were mainly confined to chlorthalidone and indapamide diuretic therapy rather than chlorothiazide and hydrochlorothiazide, with a significant reduction in the risk of CV events, CHF and stroke. In our nationwide cohort study, which mainly studied patients with CKD, the THZ treatment was associated with reduced incidence of AMI, PAOD, stroke and total mortality, but not CHF.

Several recent guidelines underscore the importance of treating patients with a history of stroke or transient ischemic attack with a diuretic and possibly with a diuretic/ACEI combination.^{28,29} The proposed mechanism was that greater stimulation of these non-AT1 rescue mechanisms by diuretics—which increase the activity of the renin-angiotensin system, angiotensin receptor blockers, and CCB compared with β -blockers or ACE inhibitors would account for better protection against strokes in patients without CVD.^{30,31} In our study, we recognised a 9% reduction of stroke that was related to THZ usage of CKD.

THZ diuretics decrease extracellular volume, characterised in patients with CKD with natriuresis. In a recent study, distal diuretics could exert a more substantial antihypertensive effect than dietary sodium restriction.¹⁵ Moreover, the BP response was independent of eGFR decline, which is the main contributing factor for ESRD.¹⁵ Beyond the diuretic effect, THZ can activate the calcium-activated potassium (BK) channel in vascular smooth muscles,

resulting in vasorelaxation.^{32,33} These vasodilatory mechanisms are more prominent in CKD.³⁴ In the study of Bank et al. there was an initial eGFR decrease with THZ usage, but eGFR subsequently remained constant or recovered to pretreatment levels.³⁵ With renin-angiotensin inhibitors, THZ and THZ-like diuretics have a renoprotective effect with BP and albuminuria reduction in patients with CKD.³⁶⁻³⁹ Our study supports these results that both chlorthalidone and indapamide use were associated with significantly lower incidences of ESRD.

Differences between THZ and THZ-like diuretics

We observed the different clinical outcomes effects between THZ-type and THZ-like diuretics. Although there is a structural variation among the heterogeneous group of agents, including the THZ-type as well as THZ-like diuretics, the term “THZ diuretic” incorporates all diuretics believed to have a direct action in the distal tubule. Chlorthalidone has a longer half-life compared to THZ-type diuretics at almost 42 hours (range, 29–55 hours). In the SHEP study⁴⁰ only chlorthalidone can significantly lower rates of stroke as well as some other fatal or non-fatal cardiovascular events. In the ALLHAT study, chlorthalidone was beneficial in reducing new-onset heart failure compared with the other treatment used in the trial.²⁸ Indapamide could reduce left-ventricular mass index in hypertensive patients, remarkably improve renal function, and protect elderly patients from stroke, CHF and mortality.^{41,42} Our study endorsed that THZ-like diuretics are associated with significantly lower incidences of mortality, ESRD and PAOD in chlorthalidone usage; and lower incidences of mortality, ESRD, AMI and PAOD with indapamide usage. However, there was no significant clinically beneficial outcomes for bendroflumethiazide and hydrochlorothiazide users than in non-users.

Limitations

This study has several limitations. First, diseases may be misclassified when an administrative database is used. To mitigate this problem, we identified CKD diagnoses according to ICD-9-CM codes for over three months. Moreover, the NHI Administration of Taiwan reviews and charts audits of medical charges and imposes heavy penalties for inappropriate charges or malpractice to ensure the accuracy of claims. Second, the NHIRD lacks information on variables that may contribute to the risk of mortality development—namely, family history of kidney disease, blood pressure, lifestyle, body weight and laboratory data. Thus, we could not adjust for and include these variables in the

propensity analysis, leading to a difference in the propensity score between cohorts. Therefore, we added the Charlson comorbidity index score to the propensity score in multivariable and stratified analyses to control for confounders. Third, there may be confounding factors that could influence the choice of a thiazide over other diuretic medications in patients with CKD. Fourth, CKD stage 5 is identified based on assumption that they will be prescribed EPO, this assumption risk missing patients if they are not prescribed EPO. Finally, the NHIRD is a disconnected research database. The unknown symptom period of CVDs may cause an underestimation of the incidence of CVD in patients with CKD. Despite these limitations, this nationwide population-based longitudinal cohort study clarifies the relationship between THZ usage and the risk of subsequent CVD in an Asian population.

Conclusion

In a Taiwanese nationwide population cohort, THZ diuretics usage were significantly associated with a decreased risk of mortality and CV events in patients with CKD. Further larger RCTs are necessary for confirmation of clinical outcomes.

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Conflict of interest

There was no conflict of interest for all authors.

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