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Original Article

Alkali therapy lessens risks of ischemic heart disease in ckd patients: a nationwide propensity-score-matched cohort study

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Abstract: Purpose: Metabolic acidosis is commonly implicated in ischemic heart disease (IHD) in patients with chronic kidney disease (CKD). Alkali therapy to correct metabolic acidosis in CKD patients appears to preserve kidney function and survival. However, the benefits of alkali therapy on IHD have been unclarified in CKD patients in the literature. Methods: Using the National Health Insurance Research Database between 2000 and 2010, 162 CKD patients with sodium bicarbonate supplementation were enrolled and propensity score-matched with 324 CKD patients without sodium bicarbonate supplementation according to age, sex, index date, diabetes, hypertension, hyperlipidemia, antihypertension drugs, antidiabetic drugs, statin, antiplatelet drug, erythropoietin-stimulating agents, and CKD stages. Main outcomes were IHD events and adverse effects of sodium bicarbonate. Results: The risk of IHD events was significantly lower in CKD patients with bicarbonate supplementation that those without bicarbonate supplementation (adjusted hazard ratio = 0.666, 95% CI = 0.429-0.959, $P < 05$). As stratified to different stages of CKD patients, the lower risk of IHD was significantly associated with bicarbonate supplementation in patients with CKD stage 1-3. However, there were lower but insignificant in IHD events in CKD stage 4-5. The increased cumulative bicarbonate dosages appeared to be associated with the lower IHD events in CKD patients, indicating a protective role of bicarbonate supplementation. Conclusions: Bicarbonate supplementation is associated with a lower IHD risk in CKD patients, especially at CKD stage 1-3. As regards CKD stage 4-5, the benefit of bicarbonate supplementation on IHD risk needs to be clarified in a large cohort study.

Keywords: Chronic kidney disease, ischemic heart disease, alkali therapy

Introduction

Metabolic acidosis is commonly implicated in ischemic heart disease (IHD) in patients with chronic kidney disease (CKD). Metabolic acidosis, one of the most complications in CKD, leads to adverse consequences, such as the deteriorations of glucose intolerance [1], malnutrition [2], bone disorders [3], and IHD [4]. One study of 1,283 patients showed that low serum bicarbonate (≤ 23 mmol/L) is significantly the risk of incident IHD processes in patients with type 2 diabetes [5]. Also, a decreased bicarbonate concentration is an independent risk factor for mortality in patients undergoing peritoneal dialysis [6] and for progression of CKD to end-stage renal disease (ESRD) [7] and heart failure [8-10] in CKD patients. Furthermore, a clinical study of 1,094 CKD patients suggested that higher serum bicarbonate levels (average 28 to 30 mmol/l) within the normal range are associated with better survival and slowing CKD progression to ESRD [11].

Alkali therapy, bicarbonate supplementation, is commonly supplied to correct metabolic acido-

sis in CKD patients [12-17]. For example, in the SoBIC trial of a 2-year, randomized, controlled, open-label clinical study, oral bicarbonate supplementation ameliorated decline of renal function, survival, and change in markers of bone metabolism in CKD patients [13]. A 3-year randomized control trial, enrolled 108 patients, demonstrated that using sodium bicarbonate or base-producing fruits and vegetables in patients with CKD stage 3, lowered dietary acid by 50% could decrease urine excretion of angiotensinogen and preserve glomerular filtration rate [15]. In a prospective randomized study, oral sodium bicarbonate, through correction of metabolic acidosis, improved thyroid function in pre-dialysis CKD patients [16]. In a randomized clinical trial with more than 1 year of follow-up, hydration with sodium bicarbonate reduced the incidence of renal replacement therapy and mortality than hydration with sodium chloride (3% vs 21%, respectively; P = 0.037) in CKD patients with receiving emergent coronary procedures [17]. Bicarbonate supplementation, for alkali therapy of metabolic acidosis in CKD patients, appears to preserve organs function and survival.

The Taiwan National Health Insurance (NHI) program has provided compulsory universal health insurance since 1995, and it covers more than 99% of the population of Taiwan. Hence, claims data obtained from the National Health Insurance Research Database (NHIRD) are ideal for longitudinal cohort studies [18-23]. According to our review of the literature, bicarbonate supplementation seems to preserve organs function and survival; however, a few studies have examined the association between bicarbonate supplementation and IHD events in CKD patients. Thus, using the NHIRD, we investigated the effects of bicarbonate supplementation on IHD events in patients in different stages of CKD.

Materials and methods

Data sources

The Human Ethics Committee of Tri-Service General Hospital approved this study (No. 2-105-05-082) and granted a waiver of informed consent. In this study, we used data from the NHIRD in Taiwan between 2000 and 2010 to investigate the association between bicarbonate supplementation and the incidence of IHD in patients in different stages of CKD. The NHIRD is a population-based claims database provided by the NHI Administration and is managed by the National Health Research Institutes; the data cover more than 99% of all residents of Taiwan.

All data in the NHIRD are encrypted to protect patient privacy. The database provides a patient identification number; birth date; sex; names of medical institutions providing care; International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnostic codes; drug prescriptions; procedure codes; health care costs; dates of admission and discharge; date of death; outpatient and inpatient claims data; and related information. All datasets can be interlinked through the unique identification number assigned to each patient.

Study cohort and patient selection

This study employed all of the registered information and items of the original claims of 1 million individuals between January 1, 2000, and December 31, 2010, from the NHIRD. All enrolled patients were older than 18 years and had been diagnosed as CKD at least 3 consecutive times within intervals of at least 3 months according to ICD-9-CM code 585 (chronic kidney disease) to minimize selection bias. CKD patients were stratified into 4 subgroups (stage 1-2, 3, 4, 5 of CKD) based on the stage of kidney function by ICD-9-CM code. These patients also had no other kidney-related condition, nor had they received renal dialysis or a transplant before the cohort entry date. Thus, these patients all had a primary diagnosis of CKD. The exclusion criteria were as follows: 1) patients who had bicarbonate supplementation prior to CKD diagnosis, 2) patients under hemodialysis or peritoneal dialysis, 3) patients with ischemic heart disease (IHD) prior to the study, 4) patients with cancers or neoplasms of uncertain behavior (ICD-9-CM 235-238), 5) patients with chronic obstructive pulmonary disease (ICD-9-CM 490-492, 494, or 496), and 6) patients with digestive system diseases (ICD-9-CM 570-579) including cirrhosis, hepatitis, hepato-encephalopathy, pancreatitis, choleliths with or without obstruction, hepatorenal syndrome, liver infarction, and liver abscess. Furthermore, we excluded patients who had

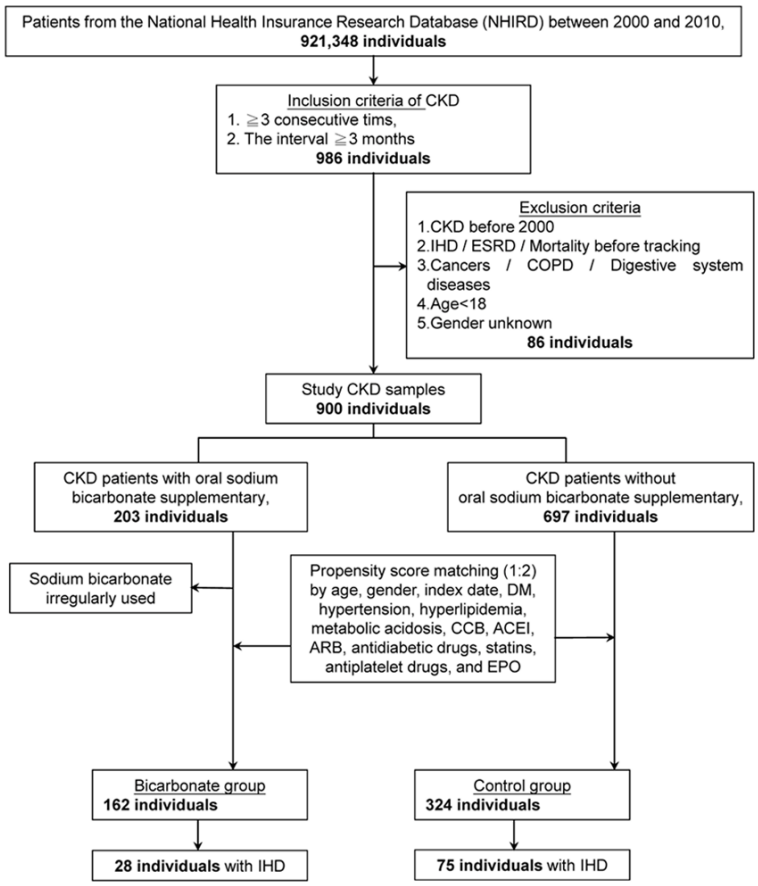

Figure 1. Cohort assembly in this study. ARB, angiotensin II receptor blockers; ACEI, angiotensin-converting enzyme inhibitors; CKD, chronic kidney disease; CCB, calcium-channel blockers; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; ESRD, end-stage renal disease; EPO, erythropoiesis; IHD, ischemic heart disease. The discontinued supplementation of sodium bicarbonate means the duration of bicarbonate supplementation less than 30 days and interval longer than 90 days.

bicarbonate supplementation irregularly (i.e., for a duration of fewer than 30 days and over an interval that was longer than 90 days).

A total of 986 individuals were enrolled. Enrolled patients underwent propensity score matching twice for age, sex, diabetes mellitus, hypertension, hyperlipidemia, and index date. After applying the exclusion criteria, a total of 900 cases were enrolled and analyzed. These enrolled patients with CKD were divided into the case group with sodium bicarbonate supplementation (n = 162) and the control group without sodium bicarbonate supplementation (n = 324), as showed in **Figure 1**. The ATC code for oral sodium bicarbonate is B05XA02. The cumulative dosage of sodium bicarbonate was further analyzed and stratified to different cumulative dosage: < 180, 180-359, 360-539, 540-719, or ≥ 720. Erythropoiesis (EPO)-stimulating agents can be prescribed to maintain hemoglobin at ≥ 10 gm/dL in patients with stage 5 of CKD (a serum creatinine concentration greater than 530 μmol/L) and anemia (hemoglobin level < 9 gm/dL) according to Taiwan NHI Referral Guidelines. The ICD-9-CM codes for the comorbidities are as follows: diabetes mellitus (250-250.3, 250.7, 250.4-250.6), hypertension (401-405), and hyperlipidemia (272.0-272.4).

Finally, the bicarbonate group and the control group were enrolled and propensity-score-matched (1:2) by age, sex, index date, diabetes, hypertension, hyperlipidemia, and baseline usage of calcium-channel blockers (CCB; amlodipine, nifedipine, diltiazem, felodipine, lacidipine, nicardipine, nisoldipine, verapamil), angiotensin-converting enzyme inhibitors (ACEI; benazepril, enalapril, cilazapril, fosinopril, lisinopril, moexipril, quinapril, ramipril) or angiotensin II receptor blockers (ARB; candesartan, eprosartan, irbsartan, losartan, olmesartan, valsartan), antidiabetic drugs (metformin, glimepiride, glyburide, chlorpropamide, glipizide, acarbose, miglitol, pioglitazone, rosiglitazone, repaglinide, nateglinide, sitagliptin, vildagliptin, saxagliptin, alogliptin, linagliptin, empagliflozin, dapagliflozin, canagliflozin, exenatide, liraglutide, insulin), statins (lovastatin, simvastatin, pravastatin, rosuvastatin), antiplatelet drugs (aspirin, clopidogrel, ticagrelor, ticlopidine), and Erythropoiesis (EPO)-stimulating agents. The index date was defined as the onset date of oral sodium bicarbonate supplementation. The study follow-up period started from the onset date of oral sodium bicarbonate supplementation.

Table 1. Clinical characteristics in ckd patients with and without bicarbonate supplementation

Variables	Total (N = 486)		Bicarbonate (N = 162)		Bicarbonate (N = 162)		*P*
	n	n/N, %	n	n/N, %	n	n/N, %	
Age (years)	59.10 ± 17.88		58.45 ± 17.41		58.45 ± 17.41		0.573
Age groups (years)							0.999
18-29	21	4.32	7	4.32	14	4.32	
30-39	48	9.88	16	9.88	32	9.88	
40-49	84	17.28	28	17.28	56	17.28	
50-59	105	21.6	35	21.6	70	21.6	
60-69	102	20.99	34	20.99	68	20.99	
70-79	90	18.52	30	18.52	60	18.52	
≥ 80	36	7.41	12	7.41	24	7.41	
Sex							0.999
Male	267	54.94	89	54.94	178	54.94	
Female	219	45.06	73	45.06	146	45.06	
Comorbidities							
DM	148	30.45	48	29.63	100	30.86	0.835
Hypertension	117	24.07	40	24.69	77	23.77	0.823
Hyperlipidemia	17	3.5	5	3.09	12	3.7	0.8
Medicine							
CCB	109	22.43	38	23.46	71	21.91	0.73
Antidiabetic drugs	131	26.95	41	25.31	90	27.78	0.589
ACEI/ARB	38	7.82	13	8.02	25	7.72	0.905
Statins	13	2.67	4	2.47	9	2.78	0.842
Antiplatelet drugs	80	16.46	28	17.28	52	16.05	0.729
EPO-stimulating agents	98	20.16	30	18.52	68	20.99	0.522
CKD stage							0.859
1-2	156	32.1	56	34.57	100	30.86	
3	145	29.84	48	29.63	97	29.94	
4	115	23.66	36	22.22	79	24.38	
5	70	14.4	22	13.58	48	14.81	
Cumulative dosage							
< 180			16	9.88			
180-359			37	22.84			
360-539			49	30.24			
540-719			44	27.16			
≥ 720			16	9.88			

ARB, angiotensin II receptor blockers; ACEI, angiotensin-converting enzyme inhibitors; CKD, chronic kidney disease; CCB, calcium-channel blockers; DM, diabetes mellitus; EPO, erythropoiesis.

Outcome measures

The primary outcome measure was IHD (ICD-9-CM codes: 410-414) assessed between January 1, 2000, and December 31, 2010, after the supplementation of oral sodium bicarbonate. All the study participants were followed up from the index date until the onset of IHD (ICD-9-CM codes: 410-414), withdrawal from the NHI program, death, or the end of 2010. We also analyzed the relationship between $NaHCO_3$ cumulative dose and IHD incidence rate. Finally, we assessed the outcome measures with hazard ratios (HRs) of IHD in each group.

Statistical analysis

Baseline distributions of demographic characteristics and comorbidities were compared between sodium bicarbonate supplementation and the control group using the x^2 test for categorical variables and the t-test for continuous variables. Through propensity score matching, the two groups were balanced with respect to known confounders to ensure comparability during an-alyses [24]. Multivariate models were simultaneously adjusted for age, sex, diabetes mellitus, hypertension, hyperlipidemia, calciumchannel blockers, antidiabetic drugs, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, statins, antiplatelet drugs, erythropoiesis stimulating agents and chronic kidney disease stage. After stratifying by age, sex, comorbidities, and medication, the relative risk for IHD in sodium bicarbonate supplementation group was compared with that in control group using the Cox model. Cumulative incidence curves of IHD for the two cohorts were assessed using the Kaplan-Meier analysis, and differences between cohorts were evaluated using the log-rank test. Univariable and multivariable Cox

Table 2. Risky comparison of Ischemic Heart Disease in CKD Patients With and Without Bicarbonate Supplementation

	Bicarbonate		Control		Adjusted HR (95% CI)
	Event	Total	Event	Total	
Overall	28	162	75	324	0.666 (0.429-0.959)
Age (years)					
18-29	0	7	0	14	NA
30-39	0	16	0	32	NA
40-49	1	28	7	56	0.551 (0.318-0.796)*
50-59	9	35	10	70	0.524 (0.342-0.752)*
60-69	8	34	12	68	0.616 (0.401-0.970)*
70-79	6	30	33	60	0.864 (0.598-1.302)
≥ 80	4	12	13	24	0.971 (0.699-1.548)
Sex					
Male	15	89	47	178	0.561 (0.312-1.010)
Female	13	73	28	146	0.968 (0.562-1.773)
DM					
Yes	10	48	30	100	0.803 (0.425-1.496)
No	18	114	45	224	0.604 (0.402-1.348)
Hypertension					
Yes	11	40	27	77	0.768 (0.510-1.562)
No	17	122	48	247	0.651 (0.312-1.270)
Hyperlipidemia					
Yes	0	5	1	12	0
No	28	157	74	312	0.666 (0.429-0.959)*
CCB					
Yes	2	38	5	71	0.513 (0.284-0.897)*
No	26	124	70	253	0.736 (0.548-1.104)
Antidiabetic drugs					
Yes	1	41	6	90	0.612 (0.329-1.201)
No	27	121	69	234	0.848 (0.598-1.498)
ACEI/ARB					
Yes	1	13	3	25	0.524 (0.267-0.801)*
No	27	149	72	299	0.698 (0.422-0.991)*
Statins					
Yes	0	4	4	9	0
No	28	158	71	315	0.666 (0.429-0.959)*
Antiplatelet drugs					
Yes	2	28	2	52	0.602 (0.345-0.913)*
No	26	134	73	272	0.713 (0.501-1.134)
EPO-stimulating agents					
Yes	7	30	10	68	0.689 (0.423-1.096)
No	21	132	65	256	0.651 (0.329-0.907)*
CKD stage					
1-2	5	56	20	100	0.301 (0.192-0.428)*
3	8	48	25	97	0.434 (0.277-0.620)*
4	10	36	21	79	0.696 (0.421-1.001)
5	5	22	9	48	0.797 (0.520-1.162)

ARB, angiotensin II receptor blockers; ACEI, angiotensin-converting enzyme inhibitors; CKD, chronic kidney disease; CCB, calcium-channel blockers; DM, diabetes mellitus; EPO, erythropoiesis; HR, hazards ratio; NA, not applicable. Adjusted for all covariates after propensity score matching (**Table 1**). *Denotes P < 0.05 and was considered statistically significant.

regression analyses were used to estimate hazard ratios (HRs) HRs and 95% confidence intervals (95% CIs) for all outcomes. All variants with a significant difference ($P < 0.05$) in univariable analysis were entered into the multivariable model, Kaplan-Meier curves, and a log-rank test. In the outcomes analysis, *P* values lower than 0.05 were statistically significant. All data analyses were conducted using SPSS software version 22 (SPSS Inc., Chicago, IL, USA).

Results

In this study, 203 patients with oral sodium bicarbonate supplementation were identified from the NHIRD between January 2000 and December 2010, as showed in **Figure 1**. Furthermore, patients and controls were propensity-score-matched (1:2) by age, sex, index date, and all covariates and divided into bicarbonate group (n = 162) and control group (n = 324). The two groups did not exhibit significant differences in age, sex, diabetes, hypertension, hyperlipidemia, and baseline usage of antihypertensive and antidiabetic drugs, statins, EPO, and antiplatelet drugs (**Table 1**).

Table 2 and **Figure 2** showed the significantly negative association between bicarbonate supplementation and the risk of IHD based on the timing of bicarbonate supplementation. Also, our data showed that compared with controls, there were the lower IHD events in bicarbonate group with younger age

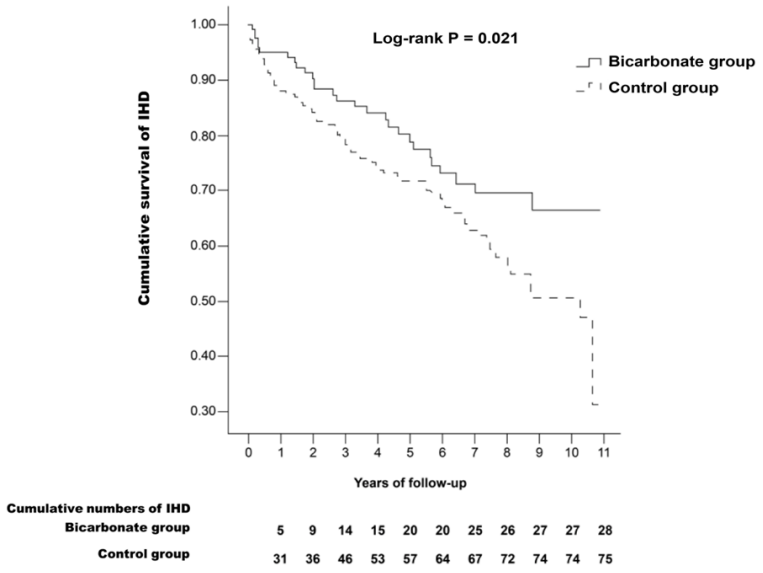

Figure 2. Cumulative hazards in bicarbonate and control groups in a cox proportional hazards regression model: Ischemic heart disease (IHD) in CKD patients with and without bicarbonate supplementation.

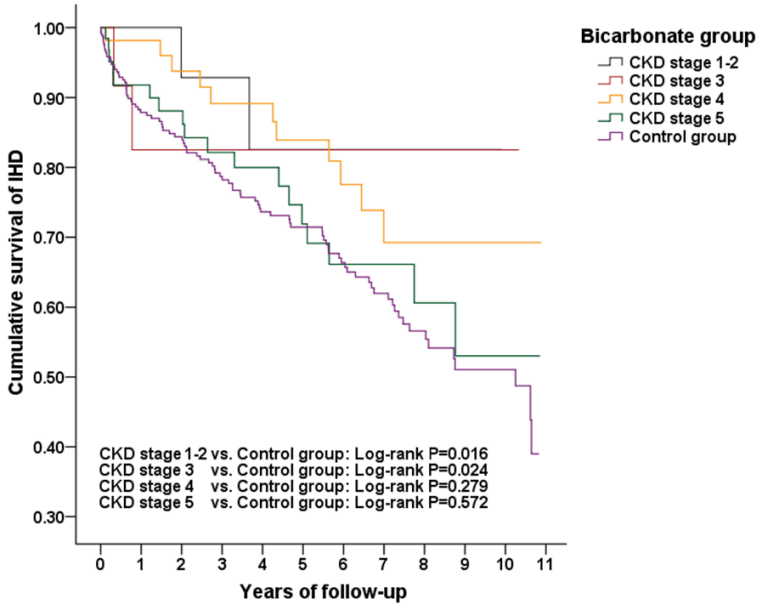

Figure 3. Cumulative hazards in bicarbonate and control groups in a cox proportional hazards regression model: Comparisons of IHD risk in different stages of CKD.

of below 69 years old. The bicarbonate group without hyperlipidemia and with taking CCB, ACEI/ARB, statin and anti-platelet drugs were associated with the lower IHD events than those in the control group. As depicted in **Table 2** and **Figure 3**, furthermore, when we focused on the different stages of CKD patients who received bicarbonate, the lower risk of IHD was associated with bicarbonate supplementation in patients with CKD stage 1-3. However, there were lower but insignificant in IHD events in CKD stage 4-5.

We further analyzed and compared the effects of different cumulative dosages of sodium bicarbonate supplementation that the increased cumulative bicarbonate dosages were gradually associated with the lower IHD events, especially significant at greater than 360 g, as shown in **Table 3**.

Concerning major adverse effects of bicarbonate supplementation, there were insignificantly few evens of hypopotassemia, hypocalcemia, and hypernatremia observed in this study, as showed in Supplementary Table 1.

Discussion

The present study was the first to examine the risk of IHD events in CKD patients with sodium bicarbonate supplementation. After multivariate adjustment and subgroup analysis, the major findings of our study are outlined as follows: (1) bicarbonate supplementation was associated with a decreased risk of IHD in CKD patients; (2) as stratified to different stages of CKD patients, the lower risk of IHD was significantly associated with bicarbonate supplementation in patients with CKD stage 1-3. However, there were lower but insignificant in IHD events in CKD stage 4-5; and (3) the increased cumulative bicarbonate dosages were significantly associated with the lowered IHD risks, indicating that long-term bicarbonate supplementation appeared to be a protective effect against IHD events in CKD patients.

Table 3. Association between cumulative bicarbonate dosage and risk of ischemic heart disease in CKD patients

	Bicarbonate		Control		Adjusted HR (95% CI)
	Event	Total	Event	Total	
Overall	28	162	75	324	0.666 (0.429-0.959)
Cumulative dose					
< 180	6	16			0.725 (0.498-1.101)
180-359	10	37			0.833 (0.553-1.145)
360-539	7	49			0.639 (0.391-0.911)*
540-719	4	44			0.452 (0.272-0.735)*
≥ 720	1	16			0.351 (0.124-0.549)*

Adjusted for all covariates after propensity score matching (**Table 1**). *Denotes P < 0.05 and was considered statistically significant.

Bicarbonate supplementation is commonly supplied to preserve organs function and survival in CKD patients [12-17]. A systematic review of short- and long-term effects of alkali therapy in CKD patients demonstrated that bicarbonate may afford a long-term benefit in slowing the progression of CKD and is not associated with adverse effects, such as hypertension [25]. Also, our study showed a benefit of long-term bicarbonate supplementation on protecting against IHD events in CKD patients. Further, we found that there were few adverse events (hypernatremia, hypocalcemia, hypopotassemia) observed in the whole course of this cohort study. Therefore, these studies support a long-term bicarbonate supplementation may be safe and beneficial to protect against organs dysfunction in CKD patients.

Although the underlying mechanisms to protect against IHD events in bicarbonate supplementation remain unclear, there were reportedly adverse effects of metabolic acidosis on IHD events. Low serum bicarbonate levels are associated with bone mineral loss, increased protein catabolism, and increased mortality in CKD patients [26]. Metabolic acidosis provokes the harmful effects of blood free fatty acids, which are fully protonated and form an oil phase leading to the high risk of IHD [27]. Metabolic acidosis in CKD substantially decreases cardiac functional performance that the reasons are because intracellular acidosis causes directly cardiac dysfunction, impairs cardiac oxidative stress, leading to free radical injury in heart [28, 29]. Metabolic acidosis declines heparin potency in-vitro study, which predisposes to cause thrombus formation and aggravate myocardial ischemia [30]. Thus, bicarbonate supplementation, for alkali therapy of metabolic acidosis in CKD patients, seems to have one of benefit role to reduce IHD events.

Metabolic acidosis, higher serum anion gap, can be present in patients with early CKD stages [31]. There are found serum accumulations of organic solutes in early CKD, even when the GFR is relatively preserved, which leads to lower serum bicarbonate levels. Thus, in our data, bicarbonate users had the lower risks of IHD events than the nonusers in CKD patients, especially CKD stage 1-3. As regards the insignificant bicarbonate benefit in CKD stage 4-5, there are some reasons to be elucidated that advanced CKD has uremic and metabolic complexities in dyslipidemia, calcium and phosphate homeostasis, and chronic systemic inflammation. Uremic toxin and calcium phosphate deposition in vascular walls increase elastic artery stiffness and reduce perfusion of coronary arteries, leading to cause vessel calcification, myocardial infarction, and heart failure, which maybe reduces the efficacy of bicarbonate supplementation in advanced CKD. In our study, there were lower but insignificant in IHD events in CKD stage 4-5. Thus, the benefit of bicarbonate in CKD stage 4-5 on IHD needs to be clarified in large cohort studies.

In this study, bicarbonate supplementation in young age and the users of CCB, ACEI/ARB, statin, and anti-platelet drugs, had the lower IHD events in CKD patients. The users of CCB and ACEI/ARB reduces the risk of major adverse cardiovascular events and the hospitalization of heart failure [32]. A meta-analysis demonstrated that ACEI/ARB users in patients with coronary artery disease have a significant improvement in non-fatal myocardial infarction, stroke, and mortality [33]. Statins have a protective effect on IHD in CKD patients, regardless of serum cholesterol values [34]. Antiplatelet medications, such as aspirin, thienopyridines, and glycoprotein IIb/IIIa receptor blockers, ameliorate IHD risk through platelet aggregation inhibitors [35].

The present study had some strength, such as the usage of a nationwide database and pro-

pensity score matching analysis. This population-based cohort study adjusted for all potential risk factors to minimize the study errors. However, despite its strengths and novelty, the present study had some limitations. First, the Taiwan NHIRD protects the privacy of patients; therefore, we could not obtain information regarding the educational level, occupation, and family history of patients. Second, data on the causes of IHD were not available from the NHIRD; therefore, we could not compare the causes of IHD between the bicarbonate and control groups. Finally, although this population-based observational study adjusted for all potential risk factors, the unmeasured factors may have introduced bias in our results, which thus must be interpreted with caution.

Conclusion

In this nationwide long-term cohort study, bicarbonate supplementation appears to have the lower risks of IHD events than the propensity-score-matched control group in CKD patients, especially at CKD stage 1-3. So far as CKD stage 4-5 is concerned, the benefit of bicarbonate supplementation on IHD events needs to be clarified in a large cohort study in the future.

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Disclosure of conflict of interest

None.

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Supplementary Table 1. Kaplan-Meier cumulative risk of adverse effects in bicarbonate supplementation

$NaHCO_3$ therapy side effects	Individual number	Years of follow-up
Total	3	
Hypopotassemia	1	6.05
Hypocalcemia	1	4.01
Hypernatremia	1	8.82