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The Association of Losartan and Ramipril Therapy With Kidney and Cardiovascular Outcomes in Patients With Chronic Kidney Disease

A Chinese Nation-Wide Cohort Study in Taiwan

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Abstract: The aim of this nation-wide cohort study was to assess the association of using an angiotensin-converting enzyme inhibitor (ACEi) or angiotensin II receptor blocker (ARB) therapy on the prognosis of hypertensive patients with chronic kidney disease (CKD).

We used Cox's proportional hazard regression model to estimate hazard ratios (HRs) for the risk of end-stage renal disease (ESRD), all-cause mortality, cardiovascular mortality, and first hospitalization for cardiovascular disease (CVD) for losartan and ramipril versus conventional antihypertensive agents.

In total, 136,266 hypertensive patients with CKD in Taiwan were followed up from 2001 to 2008. In an average follow-up of 5.9 years, 7364 (5.40%) patients reached ESRD, 4165 (3.06%) patients died, and 6163 (4.52%) patients had their first hospitalization for CVD. Use of losartan or ramipril was associated with a lower risk of the endpoints compared with the conventional group. In the losartan group, the risks of ESRD, all- and cardiovascular-cause mortality, and first hospitalization for CVD were decreased by 9.2% ($P = 0.01$), 24.6% ($P < 0.001$), 12.4% ($P = 0.03$), and 36.0% ($P = 0.01$), respectively. In the ramipril group, these risks decreased by 7.6% ($P = 0.02$) for ESRD, 56.9% ($P < 0.001$) for all-cause mortality, 7.5% ($P = 0.04$) for cardiovascular mortality, and 24.7% ($P < 0.001$) for first hospitalization.

This study indicated that losartan and ramipril had distinct association on the prognosis of hypertensive patients with CKD, and was first to disclose that the mean time to reach each endpoint for patients in the losartan, ramipril, and conventional group was not significantly different. However, further study is needed to confirm results of the present study.

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Abbreviations: ACEi = angiotensin-converting enzyme inhibitor, ARB = angiotensin II receptor blocker, CHD = coronary heart disease, CI = confidence interval, CKD = chronic kidney disease, CVD = cardiovascular disease, DM = diabetes mellitus, ESRD = end-stage renal disease, HR = hazard ratio, ICD-9-CM = the International Classification of Disease Ninth Revision Clinical Modification.

INTRODUCTION

The incidence and prevalence of end-stage renal disease (ESRD) has been constantly rising and costing many medical resources in dialysis and kidney transplantations. ESRD has become a global healthcare issue and a financial burden to many governments.[1,2] The number of ESRD patients worldwide has increased at a rate of 7%.[3] During the past 10 years, Taiwan has also confronted a serious challenge because the incidence and prevalence of ESRD have increased 2.6 and 3.7 times, respectively.[2] Taiwan has had the greatest incidence and the second greatest prevalence of ESRD since 2000 in an international comparison based on data from the US Renal Data System.[4]

ESRD is primarily caused by chronic kidney disease (CKD). Many studies have confirmed that hypertension is 1 of the factors leading to the deterioration of kidney function. In addition, CKD is a common disease that tremendously affects the quality of life of individuals and significantly increases morbidity and mortality.[5] Use of an angiotensin-converting enzyme inhibitor (ACEi) or angiotensin II receptor blocker (ARB) to block the rennin–angiotensin system is suggested to slow the progression of ESRD from CKD. However, even

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with the application of ACEi or ARB, many patients with CKD still progress to ESRD.[6–14] This study provides an opportunity to reverse the persistent increase of ESRD incidence in Taiwan.

Due to the potential racial differences in drug effects, current available evidence alone might not ensure the clinical efficacy of drug application.[15] Multiple studies have verified that ACEi and ARB demonstrate excellent kidney-protection effects regardless of whether these patients have type II diabetes mellitus (DM).[6–14] A few clinical studies have shown that ACEi and ARB exhibit cardiovascular benefits in patients with kidney disease. However, these studies combined several endpoints to evaluate the ACEi and ARB therapeutic effects.[9–12,14,15] Therefore, their findings were neither affirmative nor interpreted as final clinical results. It is necessary to conduct a large-scale study to confirm the association of ACEi and ARB therapy on reducing risks of mortality, reaching ESRD, or first hospitalization due to cardiovascular diseases (CVDs).

The National Health Insurance (NHI) program has been implemented in Taiwan for 20 years, and 99.8% of the total population (23.5 million people) is enrolled in the program.[16] In addition, 93.4% of medical facilities signed contracts with the Bureau of NHI. This study used NHI Research Database (NHIRD) data to evaluate the association of losartan, ramipril, and conventional antihypertensive agents on the prognosis of hypertensive patients with CKD. Specifically, the first objective was to study whether losartan and ramipril could lower the incidence of ESRD progression from CKD regardless of whether the patients had DM or not; the second objective was to confirm whether losartan and ramipril could reduce the mortality of CKD patients; and the third objective was to determine whether losartan and ramipril could prolong the progression from CKD to ESRD or death.

METHODS

Data Source

The National Health Research Institute randomly selected a representative database from the NHI Database (NHID) to build NHIRD, which contains healthcare utilization data including sex, date of birth, diagnostic code, drug prescriptions, and medical procedures. The database of inpatient expenditures by admissions and ambulatory care expenditures by visits accounted for 5% and 0.2%, respectively, across the entire database. Ultimately, 1,000,000 insured subjects were randomly selected from NHID and accounted for 4.3% of the total population.[16] This study was approved by the Institutional Review Board of the National Defense Medical Center, and informed consent was waived due to the personal information having been de-identified in the NHIRD.

Design and Participants

The study was designed as a population-based cohort study. Participants in this study were 18- to 70-year-old patients with CKD between 2001 and 2008. Participants were excluded due to missing sex or age information. The conventional group included patients who were only taking conventional antihypertensive medicines such as diuretics, beta-blockers, calcium channel blockers, alpha-blockers, and direct vasodilators without using ARB or ACEi. The losartan group included patients who were taking losartan alone or combined with conventional antihypertensive drugs as needed but without using other ARB or ACEi medicines. The ramipril group included patients who used ramipril alone or combined with conventional antihypertensive drugs as needed but without using other ACEi or ARB medicines.

Definition of CKD

The disease condition was defined according to the diagnostic code constructed by the Bureau of NHI based on the International Classification of Disease, Ninth Revision, Clinical Modification (ICD-9-CM).[17] We defined CKD cases as those with at least 1 CKD diagnostic code (ICD-9 codes 250.4*, 274.1*, 403.1*, 404.2*, 404.3*, 440.1, 442.1, 447.3, 572.4, 580–588, 642.1*, 646.2*) present in the service claim and those who had not reached the stage of ESRD.

Outcome Variables

The outcome variables included time to the first endpoint, incidence, and risk for the patients who were diagnosed with CKD. Endpoints were referred to as the following: ESRD (ICD-9 codes 39.95, 54.98, 55.69), all- and cardiovascular-cause mortality referred to as coronary heart disease (CHD) (ICD-9 codes 410**–414**), heart failure (ICD-9 codes 428*), and stroke (ICD-9 codes 430–438**) in this study, as well as hospitalization for the first time due to CVD. An incident case was defined as when the subject had hypertension and was not diagnosed with CKD in 2000 but was diagnosed with CKD between January 1, 2001 and December 31, 2008 and then was diagnosed with ESRD, died, or was first hospitalized due to CVD. Person-years of the participants indicated the period between the diagnosis of CKD using antihypertensive drugs and occurrence of an endpoint. ESRD was defined as the requirement for long-term dialysis or kidney transplantation.

Statistical Analysis

Endpoints were analyzed according to the intention-to-treat principle. We used Cox's proportional hazard regression model to assess the incidence and risk of each endpoint. Hazard ratios (HRs) were calculated and adjusted for sex, age, CHD, stroke, heart failure, DM (ICD-9 code 250), dyslipidemia (ICD-9 code 272), obesity (ICD-9 code 278), and concomitant antihypertensive treatment. The degree of risk reduction was calculated as $(1\text{-HR}) \times 100\%$. We compared categorical and quantitative data between groups with the χ^2 test and ANOVA, respectively. All statistics involved a 2-tailed test. A P value < 0.05 indicated statistical significance. Data were analyzed in SPSS (version 20; IBM., Armonk, NY, USA).

RESULTS

In total, 136,445 patients were assessed for eligibility, and 179 subjects were excluded due to missing sex (135 subjects) or age (44 subjects) information. The study cohort consisted of 136,266 individuals. The average and total follow-up time was 5.9 years (range: 0.1–7.8 years) and 803,006 person-years, respectively (Fig. 1); 7364 (5.40%) patients reached ESRD, 4165 (3.06%) patients died, and 6163 (4.52%) patients were first hospitalized due to CVD.

In total, 6377 patients were in the losartan group, among whom 335 (5.25%) patients reached ESRD, 185 (2.90%) patients died (89 patients died of CVD), and 281 (4.41%) patients were first hospitalized due to CVD; 2597 patients were included in the ramipril group, among whom 133 (5.12%) patients reached ESRD, 73 (2.81%) patients died (38 patient died of CVD), and 110 (4.24%) patients were first hospitalized due to CVD. In the conventional group, there were 127,292

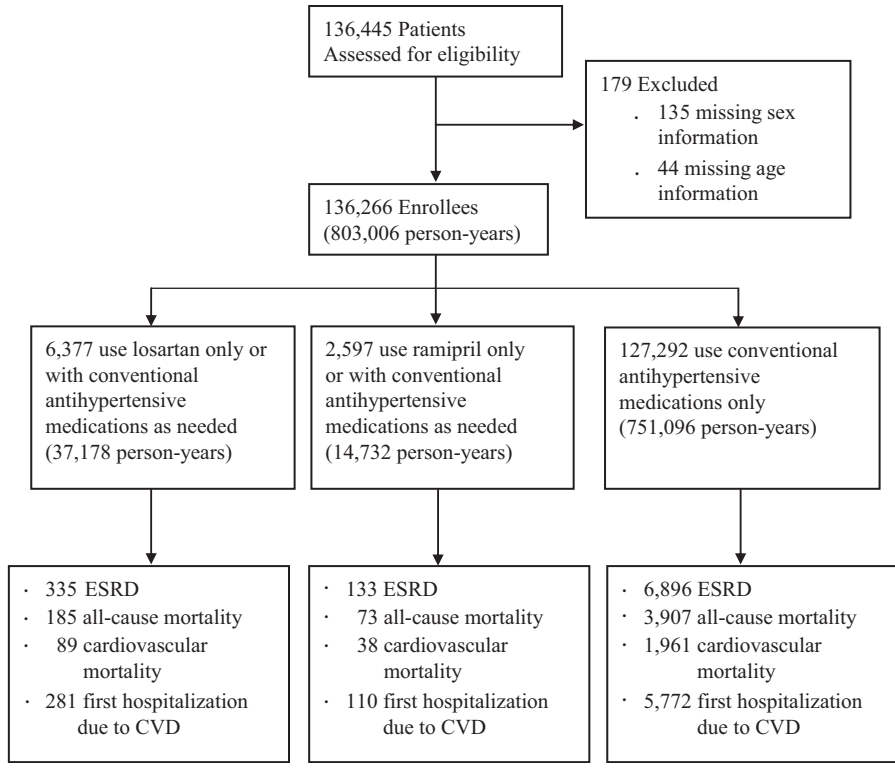

FIGURE 1. Study cohort, follow-up diagram, and outcomes during the study period of 2001 to 2008.

patients. Of these patients, 6896 (5.42%) reached ESRD, 3907 (3.07%) died (1961 patients died of CVD), and 5772 (4.53%) were first hospitalized for CVD.

Baseline Characteristics

Table 1 shows the participants baseline characteristics. The average ages of the losartan, ramipril, and conventional groups were 54.1, 54.2, and 53.9 years, of whom 49.8%, 49.7%, and 50.2% were women, respectively. The numbers of patients who used antihypertensive drugs among the 3 groups were 78.7%, 75.4%, and 79.0%, respectively. The number of patients who used antihypertensive drugs in the ramipril group was significant lower than those of the conventional and losartan groups ($P = 0.01$). The numbers of patients who had a medical history

TABLE 1. Baseline Characteristics of the Patients

Characteristics	Losartan Group (n = 6377)	Ramipril Group (n = 2597)	Conventional Group (n = 127,292)	*P* Value
Age, y (mean ± SD)	54.1 ± 11.7	54.2 ± 11.4	53.9 ± 11.5	0.2
Age, y (min–max)	39–68	40–68	39–70	
Sex, n (%)				0.45
Female	3176 (49.8)	1291 (49.7)	63,901 (50.2)	
Male	3201 (50.2)	1306 (50.3)	63,391 (49.8)	
No. of antihypertensive drugs				
Median	2	2	2	
Interquartile range	0–3	0–3	0–3	
Medical history, n (%)				
Use of antihypertensive drugs	5019 (78.7)	1958 (75.4)	100,561 (79.0)	0.01
Stroke	166 (2.6)	65 (2.5)	2546 (2.0)	0.04
CHD	332 (5.2)	130 (5.0)	6492 (5.1)	0.74
Heart failure	38 (0.6)	13 (0.5)	636 (0.5)	0.66
DM	134 (2.1)	55 (2.1)	2291 (1.8)	0.2
Dyslipidemia	64 (1.0)	23 (0.9)	1273 (1.0)	0.89
Obesity	51 (0.8)	18 (0.7)	764 (0.6)	0.79

CHD = coronary heart disease, DM = diabetes mellitus, SD = standard deviation.

of stroke among the 3 groups were 2.6%, 2.5%, and 2.0%, respectively, and were ranked as losartan group = ramipril group > conventional group ($P = 0.04$). There was no significant difference between the numbers of patients with CHD ($P = 0.74$), heart failure ($P = 0.66$), DM ($P = 0.2$), dyslipidemia ($P = 0.89$), and those with obesity ($P = 0.79$) among the 3 groups.

Incidence and Risk of ESRD

The incidence of ESRD in the losartan, ramipril, and conventional groups was 9.01, 9.03, and 9.18 per 1000 person-years, respectively. The risk of reaching ESRD for patients in the former 2 groups was significantly lower than that in the conventional group. In the losartan (HR: 0.908; 95% confidence interval [CI]: 0.802–0.975; $P = 0.01$) and ramipril (HR: 0.924; 95% CI: 0.811–0.964; $P = 0.02$) groups, the risk of reaching ESRD were reduced 9.2% and 7.6% (Table 2), respectively.

All-Cause and Cardiovascular-Cause Mortality

In the losartan, ramipril, and conventional groups, the all-cause mortalities were 4.98, 4.96, and 5.20 per 1000 person-years, respectively. The risks of death in the losartan (HR: 0.754; 95% CI: 0.579–0.901; $P < 0.001$) and ramipril (HR: 0.431; 95% CI: 0.312–0.655; $P < 0.001$) groups were significantly lower than that in the conventional group. Losartan and ramipril reduced the risk of all-cause mortality by 24.6% and 56.9%, respectively. The cardiovascular mortalities in the above 3 groups were 2.39, 2.58, and 2.61 per 1000 person-years, respectively. The cardiovascular mortality in the losartan group was significantly lower than that in the conventional group (HR: 0.876; 95% CI: 0.614–0.972, $P = 0.03$). However, there were slightly different in the risks of cardiovascular mortality between the ramipril and conventional groups was observed (HR: 0.925; 95% CI: 0.801–0.998; $P = 0.04$).

Incidence of First Hospitalization Due to CVD

The incidences of first hospitalization due to CVD were 7.56/1000 person-years in the losartan group and 7.47/1000 person-years in the ramipril group and were significantly lower than that in the conventional group (7.68/1000 person-years) (losartan group: HR: 0.640, 95% CI: 0.375–0.899, $P = 0.01$; ramipril group: HR: 0.753, 95% CI: 0.652–0.971, $P < 0.001$). The risk reduction of first hospitalization due to CVD for patients in the losartan and ramipril groups was 36.0% and 24.7%, respectively.

Average Time to Reach Endpoints

The average times for the patients in the losartan, ramipril, and conventional groups to reach each endpoint are listed in Table 3. The average years to reach ESRD, all-cause mortality, and cardiovascular mortality were 4.9 ± 3.5, 5.0 ± 3.7, and 4.9 ± 3.0 years, respectively, in the losartan group, and 4.9 ± 3.1, 5.1 ± 3.0, and 5.0 ± 3.1 years, respectively, in the ramipril group. No significant difference was observed when the former 2 groups were compared with the conventional group with 4.9 ± 3.2, 5.0 ± 3.6, and 4.9 ± 3.4 years, respectively, for each endpoint.

DISCUSSION

During the 5.9-year average follow-up period, we discovered the significant association of losartan and ramipril therapy yielded better kidney protection for patients with CKD,

TABLE 2. Incidence of Each Endpoint

Outcome		RAAS Inhibitors Group		Conventional Group		Adjusted Hazard Ratio (95% CI)	*P* Value
		Number of Events	Rate per 1000 Person-Years	Number of Events	Rate per 1000 Person-Years		
ESRD	Losartan	335	9.01	6896	9.18	0.908 (0.802–0.975)	0.01
	Ramipril	133	9.03			0.924 (0.811–0.964)	0.02
All-cause mortality	Losartan	185	4.98	3907	5.20	0.754 (0.579–0.901)	<0.001
	Ramipril	73	4.96			0.431 (0.312–0.655)	<0.001
Cardiovascular mortality	Losartan	89	2.39	1961	2.61	0.876 (0.614–0.972)	0.03
	Ramipril	38	2.58			0.925 (0.801–0.998)	0.04
First hospitalization due to CVD	Losartan	281	7.56	5772	7.68	0.640 (0.375–0.899)	0.01
	Ramipril	110	7.47			0.753 (0.652–0.971)	<0.001

Adjusted hazard ratios were calculated and adjusted for sex, age, CHD, stroke, heart failure, DM, dyslipidemia, obesity, and concomitant antihypertensive treatment.
CI = confidence interval, CHD = coronary heart disease, CVD = cardiovascular disease, DM = diabetes mellitus, ESRD = end-stage renal disease, RAAS = renin–angiotensin–aldosterone system.

TABLE 3. Comparison Average Time to Endpoint Between RASS Inhibitors and Conventional Group

Outcome		RAAS Inhibitors Group		Conventional Group		*P* Value
		Number of Events	Average Time, Mean ± SD	Number of Events	Average Time, Mean ± SD	
ESRD	Losartan	335	4.9 ± 3.5	6896	4.9 ± 3.2	0.2
	Ramipril	133	4.9 ± 3.1			0.49
All-cause mortality	Losartan	185	5.0 ± 3.7	3907	5.0 ± 3.6	0.7
	Ramipril	73	5.1 ± 3.0			0.48
Cardiovascular mortality	Losartan	89	4.9 ± 3.0	1961	4.9 ± 3.4	0.39
	Ramipril	38	5.0 ± 3.1			0.9

ESRD = end-stage renal disease, RAAS = renin-angiotensin-aldosterone system, SD = standard deviation.

compared with conventional antihypertensive drugs. The reductions in ESRD risk by losartan and ramipril were 9.2% and 7.6%, respectively. The reductions of all-cause mortalities for patients in the losartan and ramipril groups were 24.6% and 56.9%, respectively. The risk of first hospitalization due to CVD was also reduced by 36.0% and 24.7%, respectively. The decreased risk of these endpoints for CKD patients provided further evidence for the better prognosis yielded by losartan and ramipril treatments compared with conventional antihypertensive medicines. The risk of cardiovascular mortality decreased by 12.4% in the losartan group-a value that was significantly lower than that in the conventional group. However, there were slightly significant difference was observed between the ramipril and conventional groups. In addition, the average periods for patients to reach the endpoints among the 3 groups did not significantly differ.

Multiple kidney and cardiovascular clinical trials have been limited by a lack of Asian patient enrollment,[7,10,18] the under-representation of Asian patients,[19–22] a combination of multiple endpoints,[9–12,14,15] or a short follow-up period.[15] For example, Asians in the VALUE trial,[20] Val-HeFT trial,[21] and LIFE trial[22] were made up of only 3.5%, 2.8%, and 0.9%, respectively, of the total subjects. In addition, none of these trials included Taiwanese subjects. Although some recent studies have included Taiwanese patients as study subjects, the subjects were patients with stage 5 CKD[23] or patients receiving kidney replacement therapy.[24,25] The follow-up periods in these studies were too short as well. By contrast, the present investigation included nationally representative samples and covered CKD patients at all stages; moreover, this study, with an average follow-up of 5.9 years, was long enough to evaluate the association of losartan and ramipril therapy with kidney and cardiovascular outcomes in hypertensive patients with CKD.

The risk of each endpoint was analyzed using Cox's proportional hazard regression model. The all-cause mortality in the ramipril group was significantly lower than that in the conventional group-a result that differed from that in the Left Ventricular Dysfunction Prevention study.[26] However, in our study, the risk of cardiovascular mortality was shown to be slightly lower than that in conventional group, which was consistent with the results from the Heart Outcomes Prevention Evaluation (HOPE) study[18] and the ADVANCE trial.[27] Significantly reduced risks in endpoints such as ESRD, all-cause mortality, and first hospitalization due to CVD were observed in this study, indicating the explicit association of ramipril therapy on the prognosis of CKD patients.

In this investigation, the risk of all-cause mortality in the ramipril group differed from that in the Left Ventricular Dysfunction Prevention study.[26] This difference might be due to the exclusion of patients with impaired kidney function, the inclusion of patients with advanced ages (54.2 vs 59.1 years), and more patients with severe clinical conditions in the latter study. Although the risk of cardiovascular death in patients was consistent with the results from that in the HOPE study[18] and the ADVANCE trial,[27] the slightly lower risk of cardiovascular mortality ($P = 0.04$) than that in conventional group might be due to the older age (54.2 vs 66.0 years) of the subjects and more patients with coronary artery disease and stroke in their studies. The ESRD risk reduction in the ramipril group was consistent with the findings by Wright et al,[10] Hou et al,[14] and Hsu et al.[23] However, our records revealed a relatively lower risk than in previous studies,[23] possibly because those studies included CKD patients at stage 3 or more advanced stages.

Our study confirmed that losartan treatment in combination with conventional antihypertensive drugs as needed for patients with CKD achieves remarkable cardiovascular and kidney protective functions. The risks of endpoints, including ESRD, all-cause mortality, cardiovascular mortality, and first hospitalization due to CVD, were significantly reduced compared with those of the conventional group. The significant association of losartan therapy on patient prognoses was observed in our study. However, many of these patients had already received medications such as diuretics, direct vasodilators, and beta-blockers. Likewise, patients who received calcium channel antagonists did not show an altered losartan effect, although a few studies suggested otherwise in terms of the effect of calcium channel antagonists in protecting cardiovascular and kidney functions.[28,29] From the analysis of endpoint risks, patients in the losartan group showed a significantly lower ESRD risk than did the conventional group, which was in agreement with several previous studies.[6–14] The all-cause mortality of patients in this group was significantly lower than that of the conventional group but different from the results in the Jikei Heart study,[15] VALUE trial,[20] Val-HeFT trial,[21] LIFE trial,[22] and Barry study.[9] The cause might be the older research subjects included in their studies (54.1 vs over 60.0 years). The risk of cardiovascular mortality in this study also differed from the results of the Jikei Heart study, VALUE trial, and LIFE trial. All of these results suggest that although observable prognosis association were observed for losartan and ramipril in patients with hypertension and CKD, these outcomes should not be overinterpreted.

The periods for the patients to reach various endpoints showed no differences among the 3 groups, possibly due to the application of clinical outcomes instead of biochemical laboratory data as evaluation criteria. The clinical outcomes of patients (including ESRD, mortality, and first hospitalization due to CVD) usually required a relatively long period after receiving medication to be observable. By contrast, biochemical laboratory data could reveal variations within a relatively short time. In addition, the results from this study suggested that losartan and ramipril exhibit distinct association on the prognosis of CKD patients. However, several investigations have also suggested that ACEi/ARB administration increases the risk of hyperkalemia in some patients,[8,10,12,14,23] resulting in the switching to other drugs and affecting the endpoint of these patients. Therefore, the periods for the patients to reach various endpoints did not differ among the 3 groups.

This study has several strengths. First, it includes a nationally representative sample. The large sample size allowed us to evaluate the association of losartan and ramipril therapy for the specific endpoint. Second, in contrast with previous studies that did not cover CKD patients at all stages,[7,8,10–12,14,23] we not only included the complete profile of various clinical conditions but also tracked the changes in potential comorbidities developed with time. Third, this study could confirm the results of all study subjects. By contrast, previous studies have included subjects who withdrew or were lost to follow-up, thus failing to follow their endpoints.[7,8,10,12,14] However, this study also exhibited a few limitations. First, because coding of disease and prescription for medical conditions are related to physician practice patterns (eg, perhaps the physicians' prescription of ACEi or ARB were more competent, conscientious, and global in their management of patients' health issues), which are known to vary substantially, and data on physician practice patterns were unavailable for analysis in this study, we cannot rule out that patterns.[30] Second, the database analysis in this study was claim based, and the definition of kidney disease used diagnostic codes rather than a systemic check for kidney impairment. Because laboratory data (such as serum creatinine, urine protein, etc.) and physical examination information (such as blood pressure, etc.) were not available in the NHIRD, we could not confirm the CKD stage in these patients or further analyze the different prognostic effects of losartan and ramipril on patients with different severities of CKD. However, this limitation did not prevent us from confirming the study subjects because, in Taiwan, the diagnosis of kidney disease was based on the estimated glomerular filtration rate. Third, clinical conditions were defined based on diagnostic codes, and misclassification was possible. However, the misclassification might have been random; thus, it would be more likely to underestimate rather than over-estimate the association. Fourth, we could confirm the time when different diseases were diagnosed but not the time of onset. This issue can be minimized as much as possible by optimizing the research design.

In summary, the results from this study indicated that losartan and ramipril exhibit significant association with the prognosis of patients with hypertension and CKD, and was first to disclose that the mean time to reach each endpoint for patients in the losartan, ramipril, or conventional group was not significantly different. Therefore, the association of losartan and ramipril therapy with the prognosis of CKD patients should not be over interpreted. In addition, we held reservation on the approach to combine multiple endpoints in evaluating the clinical effect of ACEi and ARB.

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