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Effects of Angiotensin Converting Enzyme Inhibition or Angiotensin Receptor Blockade in Dialysis Patients: A Nationwide Data Survey and Propensity Analysis

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Abstract: Long-term benefit of using a renin–angiotensin–aldosterone system blocker such as an angiotensin-converting enzyme inhibitor (ACEI) or an angiotensin II receptor blocker (ARB) for patients already receiving dialysis remains undetermined. The aim of this study is to assess the efficacy and safety of ACEI or ARB use in dialysis patients. We performed a population-based cohort study with time-to-event analyses to estimate the relation between the use of ACEI/ARB and their outcomes. We used a nationwide database (Registry for Catastrophic Illnesses) for Taiwan, which has data from 1995 to 2008 nearly of all patients who received dialysis therapy. The records of all dialysis patients aged ≥18 with no evidence of cardiovascular (CV) events in 1997 and 1998 (133,564 patients) were examined. Users (n = 50,961) and nonusers (n = 59,913) of an ACEI/ARB were derived. We then used propensity score matching and Cox proportional hazards regression models to estimate adjusted hazard ratios (HRs) for all-cause mortality and CV events in users and nonusers of an ACRI/ARB. The 15,182 patients, who used an ACEI/ARB, and the 15,182 nonusers had comparable baseline characteristics during the 14 years of follow-up. The mortality was significantly greater in patients who did not use an ACEI/ARB (HR = 0.90, 95% confidence interval = 0.86–0.93). Subgroup analysis of 3 tertiles of patients who used different total amounts of ACEI/ARB during the study period indicated that CV events were more common in patients who used an ACEI/ARB for a short duration (tertile 1: HR = 1.63), but less common in those who used an ACEI/ARB for long durations (tertile 2: HR = 1.05; tertile 3: HR = 0.94; trend for declining HR from tertile 1 to 3: $P < 0.001$). The mortality benefit provided by use of an ACEI/ARB was consistent across most patient subgroups, as was the benefit of ARB monotherapy rather than ACEI monotherapy. Independent of traditional risk factors, overall mortality was significantly lower in dialysis patients who used an ACEI/ARB. In addition, subjects who used an ACEI/ARB for longer durations were significantly less likely to experience CV events.

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Abbreviations: ACEI = angiotensin-converting enzyme inhibitor, ACS = acute coronary syndrome, ARB = angiotensin II receptor blocker, CAD = coronary artery disease, CHF = congestive heart failure, CKD = chronic kidney disease, CV = cardiovascular, DM = diabetes mellitus, ESRD = end-stage renal disease, HTN = hypertension, LVH = left ventricular hypertrophy.

INTRODUCTION

Cardiovascular (CV) disease is the leading cause of mortality in patients receiving dialysis, and the incidence of CV disease is >10 times greater in dialysis patients than the general population.[1,2] Dialysis patients experience sodium and water overload, increased activity of the sympathetic nervous system, and abnormal response of the renin–angiotensin system (RAS), leading to a greater incidence of hypertension (HTN), which is a major cause of CV disease and mortality. In addition, dialysis patients with chronic HTN, volume overload, and upregulation of the RAS can experience left ventricular hypertrophy (LVH).[3–5] There is evidence that LVH is significantly and independently associated with mortality and CV morbidity.[6,7] Therefore, there are strong relationships between RAS activation and several major clinical endpoints in dialysis patients.

Randomized controlled trials of general populations reported that angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs) had CV protective effects in subjects with high CV risk[8–10]; however, the effect of these drugs on clinical endpoints, such as mortality or CV events, in dialysis patients remains uncertain.[11] Use of an ACEI or an ARB may lead to electrolyte imbalance, such as hyperkalemia or hypokalemia, and this is especially significant in dialysis patients. In particular, a recent randomized study reported that high or low serum potassium was associated with increased risk of CV and renal disease.[12] On the contrary, RAS blockade may have a positive role in reducing the progression of coronary atheroma, thereby providing protection from CV events.[13] Therefore, the effect of RAS blockade with an ACEI or an ARB in dialysis patients is unknown.

The worldwide number of patients with end-stage renal disease (ESRD) who are undergoing dialysis has significantly

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grown in the recent decades. In particular, the current incidence and prevalence of ESRD are extremely high in Taiwan.[14] Thus, we performed a nationwide, population-based study of a large cohort of dialysis patients from Taiwan, with the use of propensity score (PS) matching to reduce selection bias and confounding effects, to examine the effect of use of an ACEI/ARB on major clinical endpoints.

METHODS

Study Population and Outcomes

A universal National Health Insurance program was implemented in Taiwan in March 1995, and 96% of the total population of Taiwan are currently enrolled in this program.[15] Data for gender, birth date, use of medications, and diagnostic codes based on the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM; www.icd9data.com/2007) were retrieved for the analyses performed in this study. We used the Registry for Catastrophic Illness database from the National Health Research Institute. This database encompasses almost 100% of all patients who received renal replacement therapy from 1995 to 2008 in Taiwan (about 23 million people). Following review of ambulatory and inpatient claims data, we included ESRD subjects undergoing hemodialysis or peritoneal dialysis, >18 years, and with no history of CV events in 1997 and 1998. All included subjects were followed from 1997 to 2009, with a medium follow-up time of 1428 days. Subjects with histories of acute coronary syndrome (ACS; including unstable angina, Q-wave or non-Q wave myocardial infarction; ICD-9-CM codes: 410.X, 411.1) or previous stroke (eg, transient ischemic accident, ischemic stroke, or hemorrhagic stroke; 430.X–432.X, 435.X, 434.X) were excluded. The designed patient flow diagram is shown in Figure 1. The main variables of interest were use of an ACEI or an ARB, which were identified from prescription claims data. We collected information on prescribed drugs, dosage and dates of prescriptions, supply days, and total number of dispensed pills by review of the outpatient pharmacy prescription database, which is part of the claims database. A total of 110,874 subjects were included in the final analyses. The clinical outcomes were death, new-onset ACS (including unstable angina, Q-wave or non-Q wave myocardial infarction), and stroke. The study was approved by the Institutional Review Board of the National Taiwan University Hospital, Taipei, Taiwan.

Comorbidities

The presence of a comorbidity was defined by diagnosis at hospital discharge or review of the clinical record, after the index use of an ACEI or an ARB. We searched the database for the presence of HTN (ICD-9-CM codes: 401.X–405.X), diabetes mellitus (250.X, 249.X), hyperlipidemia (272.X), CV disease including coronary artery disease (CAD) (411.X–414.X, V17.3, V81.0) and peripheral arterial disease (250.7, 443.X, 444.2), congestive heart failure (CHF) (428.0–428.3, 428.9), atrial fibrillation (427.31, 427.3), and chronic kidney disease (CKD) (585.X–588.X).

Propensity Score-Based Matching

PS matching is a statistical method used to account for observed covariates in the comparison of 2 treatment groups. In the present study, the PS was the conditional probability for use of an ACEI/ARB (binary dependent variable) under a set of measurements.[16] Clinical risk factors, such as sex, age, HTN, diabetes, heart failure, comorbidities, and use of a medication other than an ACEI/ARB were added into a nonparsimonious multivariable logistic regression model to predict the preference for use of an ACEI/ARB. The predicted probability derived from the logistic equation was used as the PS for each individual. Subjects using and not using an ACEI/ARB were pooled together and sorted according to their PS in an ascending order. These 2 groups were then matched by the PS. Subjects without appropriate matches within the acceptable rank range were excluded from further analysis. The remaining patients constituted a well-matched 1:1 prospective cohort.

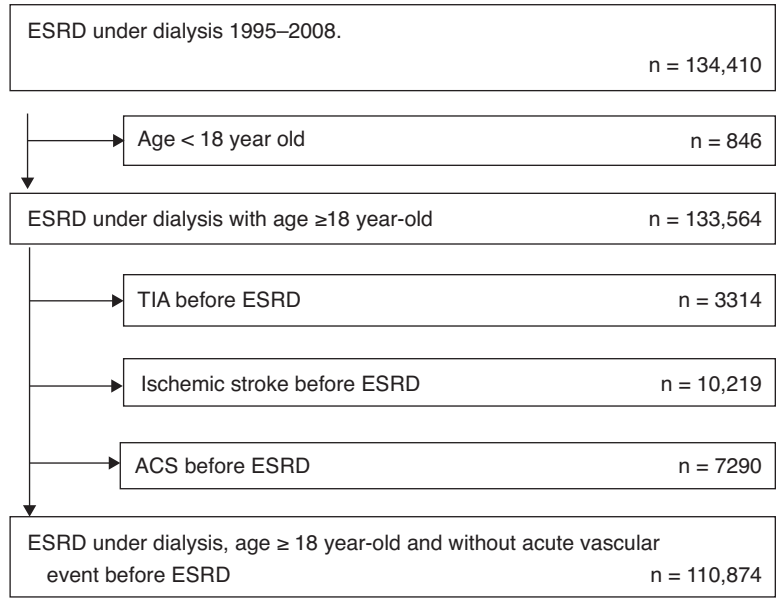

FIGURE 1. Designed patient flow diagram. ACS = acute coronary syndrome, ESRD = end-stage renal disease.

Statistical Analysis

For analysis of the baseline characteristics of users and nonusers of an ACEI/ARB, categorical covariates were compared with the χ^2 test. For estimation of the risk associated with the duration of ACEI/ARB use and development of CV events and mortality, Cox proportional hazard models (with adjustment for age, gender, risk factors [HTN, diabetes, hyperlipidemia] in Model 1; with adjustment for all Model 1 factors in addition to CAD, peripheral artery disease, CHF, atrial fibrillation, and use of other drugs in Model 2) were used. Subjects who did not use an ACEI/ARB were the reference group, and were compared with patients who used an ACEI/ARB for different durations. The study subjects were divided into tertiles according to the total duration of ACEI/ARB use. The event-free survival time was defined as the time from the day of the enrollment to the occurrence of an event (cardiovascular event or mortality). If an event did not occur, the case was classified as censored at the end of the study, the time of death, withdrawal of insurance, loss of contact, or receipt of kidney transplantation, whichever occurred first.

Subgroup analyses were used to determine if the results remained for subgroups with different age, gender, CV disease incidence, or use of concomitant medications. Kaplan–Meier curves were plotted to show the event-free survival of users and nonusers of an ACEI/ARB. To compare the effects between use of an ACEI and an ARB, we used Cox proportional hazard models to adjust for possible confounding factors. Subjects who did not use ACEI/ARB served as the reference group, and were compared with patients who used an ACEI/ARB after PS matching by use of a logistic regression model. All analyses were performed with SPSS 15.0 for Windows 7 (SPSS Inc, Chicago, IL). For all analyses, a 2-tailed P value <0.05 was considered statistically significant.

RESULTS

Demographic and Clinical Characteristics of Enrolled Patients

Table 1 summarizes the basic demographic and clinical characteristics of the patient population. A total of 110,874 subjects (57,635 women [52.0%] and 53,239 men [48.0%]) were included in the final analyses. The median follow-up period was 1428 days. An ACEI or an ARB was prescribed to 50,961 subjects (46.0%). Compared with the control group, subjects receiving an ACEI or an ARB were younger (57.4 ± 14.2 vs 61.5 ± 14.8 years, $P < 0.001$) and more likely to be male (52.4% vs 51.5%, $P = 0.003$), receive hemodialysis rather than peritoneal dialysis (98.4% vs 83.7%, $P < 0.001$), and have a comorbid CV condition including HTN (90.3% vs 63.6%, $P < 0.001$), diabetes (50.8% vs 38.0%, $P < 0.001$),

TABLE 1. Basic Characteristics of the Study Subjects Before and After Propensity Adjustment

	Control (N = 59,913)	ACEI/ARB (N = 50,961)	*P*	Control (N = 15,182)	ACEI/ARB (N = 15,182)	*P*
Baseline characteristics						
Age	61.5 ± 14.8	57.4 ± 14.2	<0.001	59.8 ± 14.7	59.9 ± 14.4	0.506
Gender, F	52.4	51.5	0.003	52.8	52.6	0.765
Hemodialysis	83.7	98.4	<0.001	97.6	96.4	<0.001
Risk factors						
HTN	63.6	90.3	<0.001	84.4	83.8	0.132
DM	38.0	50.8	<0.001	51.9	51.5	0.442
Hyperlipidemia	28.0	41.2	<0.001	41.1	40.9	0.735
Comorbidities						
CAD	28.7	46.4	<0.001	43.5	43.9	0.495
PAD	22.1	27.7	<0.001	29.3	30.0	0.163
CHF	18.4	29.3	<0.001	28.6	28.6	0.949
AF	4.8	6.7	<0.001	6.9	7.4	0.071
Medications						
Antiplatelet	11.0	31.4	<0.001	23.7	24.9	0.019
Warfarin	3.4	6.6	<0.001	6.0	6.0	0.904
Beta-blocker	17.6	56.0	<0.001	39.2	40.4	0.022
CCB	29.4	77.2	<0.001	61.2	61.2	0.962
OHA	9.2	30.9	<0.001	21.2	22.3	0.021
Insulin	6.0	16.2	<0.001	13.0	13.0	0.959
Statin	10.2	26.2	<0.001	20.6	21.2	0.230
Outcomes						
CV events	10.7	18.4	<0.001	13.5	18.3	<0.001
Acute coronary syndrome	2.4	8.7	<0.001	4.1	7.1	<0.001
Ischemic stroke	5.4	5.0	0.003	6.6	5.6	<0.001
Hemorrhagic stroke	2.9	4.7	<0.001	2.8	5.6	<0.001
Mortality	34.6	30.0	<0.001	33.5	33.3	0.780

ACEI = angiotensin-converting enzyme inhibitor, AF = atrial fibrillation, ARB = angiotensin II receptor blocker, CAD = coronary artery disease, CCB = calcium channel blocker, CHF = congestive heart failure, DM = diabetes mellitus, HTN = hypertension, OHA = oral hypoglycemia agent, PAD = peripheral artery disease.

hyperlipidemia (41.2% vs 28.0%, $P < 0.001$), CAD (46.4% vs 28.7%, $P < 0.001$), peripheral artery disease (27.7% vs 22.1%, $P < 0.001$), CHF (29.3% vs 18.4%, $P < 0.001$), or atrial fibrillation (6.7% vs 4.8%, $P < 0.001$). Patients using an ACEI/ARB were also more likely to receive a concomitant medication, including an antiplatelet drug (31.4% vs 11.0%, $P < 0.001$), warfarin (6.6% vs 3.4%, $P < 0.001$), a β-blocker (56.0% vs 17.6%, $P < 0.001$), a calcium channel blocker (77.2% vs 29.4%, $P < 0.001$), an oral hypoglycemic agent (30.9% vs 9.2%, $P < 0.001$), insulin (16.2% vs 6.0%, $P < 0.001$), or a statin (26.2% vs 10.2%, $P < 0.001$). During the study period, there were more CV events in the group, especially ACS (8.7% vs 2.4%, $P < 0.001$) and hemorrhagic stroke (4.7% vs 2.9%, $P < 0.001$), but the overall mortality was higher in the control group (30.03% vs 34.6%, $P < 0.001$).

The propensity-based matching process identified 15,182 patients who used an ACEI or an ARB and 15,182 patients who used neither drug (Table 1). As expected, due to the matching, these 2 groups had smaller differences in age, sex, comorbidities, use of other medications, and other clinical variables (Table 1). No subjects were lost to follow-up in either group. After PS matching, the ACEI/ARB group still had more CV events, including ACS (7.1% vs 4.1%, $P < 0.001$) and hemorrhagic stroke (5.6% vs 2.8%, $P < 0.001$), although overall mortality was similar (33.3% vs 33.5%, $P = 0.780$).

Effect of Duration of ACEI/ARB Use

Table 2 shows the hazard ratios (HRs) for different clinical outcomes in PS-matched patients who took an ACEI/ARB for different durations (≤37, 38–180, and ≥181 days). The results show that subjects who used an ACEI/ARB for shorter durations (T1) had significantly greater risk for a CV event, even after adjustment for possible confounding factors (Model 1: HR = 1.73, 95% confidence interval [CI] = 1.61–1.86, $P < 0.001$; Model 2: HR = 1.64, 95% CI = 1.52–1.76, $P < 0.001$ and Figure 2B), and especially for development of hemorrhagic strokes (Model 1: HR = 4.44, 95% CI = 3.93–5.03, $P < 0.001$; Model 2: HR = 3.30, 95% CI = 2.91–3.74, $P < 0.001$). Also, the results show that subjects who took an ACEI/ARB had a greater risk for ACS (Model 2: HR = 1.55, 95% CI = 1.40–1.71, $P < 0.001$) while had a lower risk for ischemic stroke (Model 2: HR = 0.75, 95% CI = 0.68–0.82). Overall mortality rate was lower in patients who used an ACEI/ARB (Model 1: HR = 0.90, 95% CI = 0.86–0.93, $P < 0.001$; Model 2: HR = 0.90, 95% CI = 0.86–0.93, $P < 0.001$ and Figure 2A). In addition, the protective effects seemed to be greatest for patients who used an ACEI/ARB for the longest time (T3 for Model 1: HR = 0.74, 95% CI = 0.70–0.79, $P < 0.001$; T3 for Model 2: HR = 0.79, 95% CI = 0.74–0.84, $P < 0.001$).

Comparison of ACEI and ARB

Finally, we compared use of an ACEI and an ARB with controls after PS matching (Table 3). Cox regression models were applied for adjustment of baseline characteristics (Model 1), comorbidities, and concomitant medications (Model 2) for assessment of between-group differences. After complete adjustment, ACEI use still had protective effects for ischemic stroke (Model 2: HR = 0.78, 95% CI = 0.70–0.87, $P < 0.001$), but was associated with increased risk for ACS (Model 2: HR = 1.64, 95% CI = 1.45–1.85, $P < 0.001$) and hemorrhagic stroke (Model 2: HR = 1.66, 95% CI = 1.45–1.91, $P < 0.001$). ARB use improved overall mortality (Model 2: HR = 0.82, 95% CI = 0.77–0.88, $P < 0.001$), but was associated with a trend for increasing hemorrhagic stroke. Direct comparison indicated that use of an ARB had a stronger protective effect on overall mortality ($P < 0.001$ for Models 1 and 2).

DISCUSSION

To the best of our knowledge, this is the first large-scale, nationwide study to examine the effect of ACEI or ARB usage on clinical endpoints in a dialysis population. Our results showed that after adjustment for various potential risk factors, patients who received RAS blockade therapy with an ACEI or an ARB had about 10% lower overall mortality. Furthermore, the benefit of ACEI/ARB usage was greater for patients who used drugs for longer durations. In particular, analysis of all CV events indicated increased risk for dialysis patients who used an ACEI/ARB for ≤37 days, but lower risk for patients who could tolerate RAS blockade and used medication for >38 days. However, even with control of various confounding factors by propensity matching and Cox regression methods, use of ACEI/ARB was associated with an ∼80% greater risk of hemorrhagic stroke. Further comparison of the effects of ACEI and ARB usage in our dialysis population indicated that ARB usage was associated with better overall survival.

ACEI therapy provides an important benefit for patients with increased risk of CV disease. In patients with known CV disease, ACEIs reduce mortality, myocardial infarction, stroke, and new-onset CHF independent of cardiac function.[10] Therefore, the American College of Cardiology guidelines recommend use of an ACEI as standard therapy for patients with established vascular disease, independent of left ventricular function or concomitant HTN.[17] However, there is less evidence supporting the use of ARBs for prevention of myocardial infarction and CV deaths. In addition, some studies have identified an ''ARB–myocardial infarction paradox,'' in which ARB-induced increase of angiotensin II leads to unopposed stimulation of angiotensin II receptors, growth promotion, fibrosis, and hypertrophy, and also has proatherogenic and proinflammatory effects.[18] CKD and ESRD are related to various vascular pathologies, and are thus strongly associated with CV morbidity.[19] Our current findings from a large dialysis cohort clarify the possible short and long-term effects of the use of an ACEI or an ARB on CV events. Although the overall CV events seemed to significantly increase after the use of an ACEI/ARB, most of the morbidity was in patients who received short-duration therapy (≤37 days). As the duration ACEI/ARB use increased, the risks diminished. In other words, if dialysis subjects can tolerate the initial adverse effects of RAS blockade, they will ultimately experience long-term benefits. In particular, some dialysis cases probably suffer from hyperkalemia or other serious side effects following initial use of an ACEI/ARB, and this may lead to arrhythmia or another serious CV event. Thus, clinicians should more carefully follow dialysis subjects in the first few months of treatment with an ACEI/ARB to decide whether continued use can be justified. This recommendation is supported by our results, which indicate that short-term use of an ACEI/ARB increased CV risks, even after PS matching and multivariable regression adjustment.

The current study indicates that dialysis patients on an ARB without concomitant use of ACEI had ∼20% reduced risk of overall death relative to those only using an ACEI. The mechanisms by which use of an ARB is more effective than an ACEI in lowering mortality in patients with ESRD has not been

TABLE 2. Hazard Ratios of ACEI/ARB vs Control and Tertiles of ACEI/ARB Treatment Period vs Control for Different Outcomes After Propensity Adjustment

	Overall ACEI/ARB vs Control (N = 30,364)	T1 vs Control ≤ 37 d (N = 5094)	T2 vs Control 38–180 d (N = 5051)	T3 vs Control ≤ 81 d (N = 5037)	*P*
CV event					
Model 1	1.24 (1.17–1.31) $P < 0.004$	1.73 (1.61–1.86) $P < 0.001$	1.06 (0.97–1.15) $P = 0.177$	0.97 (0.90–1.06) $P = 0.504$	<0.001
Model 2	1.23 (1.16–1.31) $P < 0.001$	1.64 (1.52–1.76) $P < 0.001$	1.05 (0.96–1.14) $P = 0.268$	0.94 (0.94–1.11) $P = 0.692$	<0.001
ACS					
Model 1	1.57 (1.42–1.73) $P < 0.001$	1.23 (1.07–1.42) $P = 0.003$	1.51 (1.32–1.73) $P < 0.001$	1.94 (1.72–2.19) $P < 0.001$	<0.001
Model 2	1.55 (1.40–1.71) $P < 0.001$	1.62 (1.40–1.87) $P < 0.001$	1.49 (1.30–1.70) $P < 0.001$	1.55 (1.37–1.75) $P < 0.001$	<0.001
Ischemic stroke					
Model 1	0.75 (0.68–0.82) $P < 0.001$	0.83 (0.73–0.94) $P = 0.004$	0.84 (0.74–0.96) $P = 0.009$	0.59 (0.52–0.68) $P < 0.001$	<0.001
Model 2	0.75 (0.68–0.82) $P < 0.001$	0.73 (0.64–0.83) $P < 0.001$	0.83 (0.73–0.95) $P = 0.006$	0.67 (0.58–0.78) $P < 0.001$	<0.001
Hemorrhagic stroke					
Model 1	1.85 (1.65–2.08) $P < 0.001$	4.44 (3.93–5.03) $P < 0.001$	0.92 (0.76–1.12) $P = 0.414$	0.56 (0.45–0.70) $P < 0.001$	<0.001
Model 2	1.96 (1.75–2.21) $P < 0.001$	3.30 (2.91–3.74) $P < 0.001$	1.00 (0.82–1.21) $P = 0.987$	0.84 (0.67–1.05) $P = 0.130$	<0.001
Mortality					
Model 1	0.90 (0.86–0.93) $P < 0.001$	0.93 (0.89–0.99) $P = 0.012$	1.01 (0.96–1.07) $P = 0.639$	0.74 (0.70–0.79) $P < 0.001$	<0.001
Model 2	0.90 (0.86–0.93) $P < 0.001$	0.89 (0.85–0.94) $P < 0.001$	1.00 (0.95–1.06) $P = 0.923$	0.79 (0.74–0.84) $P < 0.001$	<0.001

Model 1 adjusted for age, gender, and risk factors (HTN, DM, and hyperlipidemia). Model 2 adjusted for Model 1 along with comorbidities (CAD, PAD, CHF, and AF) and medications.

ACEI = angiotensin-converting enzyme inhibitor, ACS = acute coronary syndrome, AF = atrial fibrillation, ARB = angiotensin II receptor blocker, CAD = coronary artery disease, CHF = congestive heart failure, DM = diabetes mellitus, HTN = hypertension, PAD = peripheral artery disease.

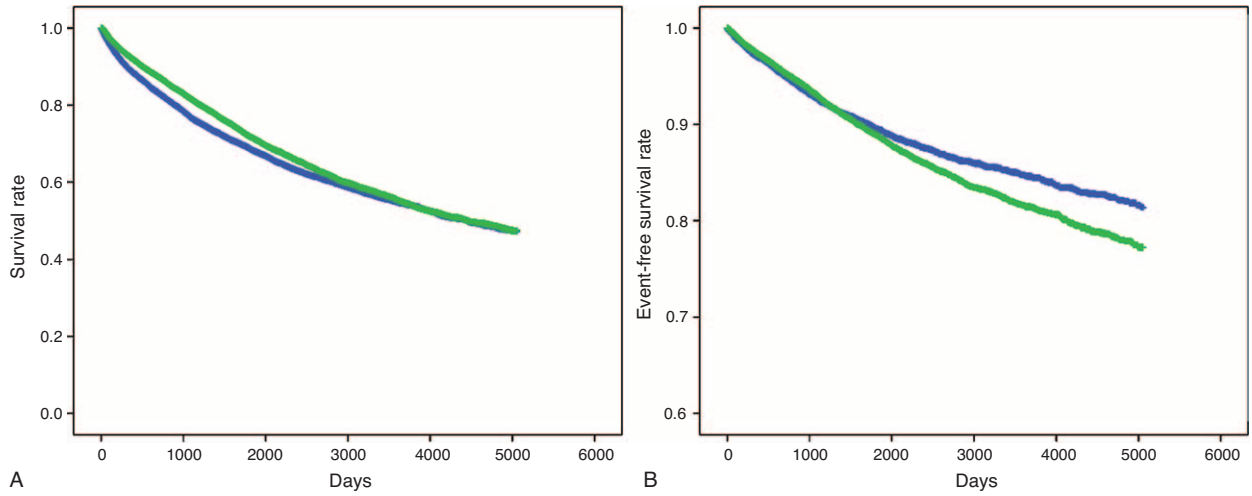

FIGURE 2. (A) Kaplan–Meier curves of dialysis patients for the risk of all-cause mortality, according to prescription of ACEIs and/or ARBs after propensity matching methods. Blue indicates patients not taking ACEI/ARB. Green indicates patients taking ACEIs/ARBs. (B) Kaplan–Meier curves of dialysis patients for the occurrence of cardiovascular events, according to prescription of ACEIs and/or ARBs after propensity matching methods. Blue indicates patients not taking ACEI/ARB. Green indicates patients taking ACEIs/ARBs. ACEI = angiotensin-converting enzyme inhibitor, ARB = angiotensin II receptor blocker.

well elucidated. Nevertheless, Chan et al[20] compared the relative effectiveness of ACEIs and ARBs in reducing mortality in maintenance hemodialysis patients by conducting a 6-year observational analysis of a large dialysis population from the United States. Similar to our results, they found that ARB and non-ACEI antihypertensive therapy was associated with a lower risk of death after adjusting for potential risk factors by PS matching. It is possible that ACEIs potentiate the actions of bradykinin (a vasodilator) by inhibiting its degradation.[21] Bradykinin can induce fibrinolysis and stimulate inflammation under certain conditions.[22,23] The proinflammatory effects of bradykinin could therefore negate the beneficial effects of RAS blockade and lead to worse prognosis.[24–26] Regardless of the underlying mechanism, the findings that ARBs have superior in the treatment of dialysis patients in different dialysis populations (Taiwan and the United States) validate their use for such patients.

STUDY STRENGTHS AND LIMITATIONS

The main strengths of this study are that it was a population-based, nationwide study that captured all validated dialysis cases in Taiwan and followed them for a 12-year period. All comorbidities and medical interventions were carefully recorded under the national health insurance policy. A prospective trial with randomization is the best way to account for unknown confounders. However, the results of our propensity analysis, in which known confounding factors were matched, clearly indicate a long-term benefit of long-term RAS blockade in protecting dialysis patients from mortality and CV events. Nonetheless, our study had several limitations. First, we exclusively relied on claims data, so there may have been a bias in disease classification. Detailed blood test data were not available, so some uncorrected possible confounding factors, such as electrolyte imbalance, could not be considered. Although ARBs seemed to be superior to ACEIs in reducing mortality, patients' lipid profiles and inflammation parameters were not available, so the underlying mechanisms of this effect remain unknown. Second, although we controlled for the most important risk factors in analyzing the benefit of ACEI/ARB usage (age, HTN, and comorbid conditions), a limitation of the PS matching was that it only dealt with known variables. Some unknown factors that were unequally distributed in the ACEI/ARB group and the control group (obesity, smoking, alcohol consumption, family history, lifestyle, and diet) might have affected the observed differences in long-term outcome.

CONCLUSIONS

In summary, this study of dialysis patients from Taiwan showed that overall mortality was lower in subjects who received RAS blockade with an ACEI/ARB, and that this result remained significant in subgroup analyses that accounted for age, sex, concomitant conditions, use of an antiplatelet drug, and use of a statin. Although CV events were more likely during

TABLE 3. Hazard Ratios of ACEI vs Control and ARB vs Control for Different Outcomes After Propensity Adjustment

	ACEI vs Control (N = 6778/15,182)	ARB vs Control (N = 4685/15,182)	*P* for ACEI vs ARB
CV event			
Model 1	1.16 (1.07–1.27) $P = 0.001$	1.11 (1.00–1.24) $P = 0.060$	0.468
Model 2	1.21 (1.13–1.30) $P < 0.001$	1.12 (1.03–1.23) $P = 0.012$	<0.001
ACS			
Model 1	1.50 (1.33–1.69) $P < 0.001$	1.11 (0.94–1.30) $P = 0.222$	<0.001
Model 2	1.64 (1.45–1.85) $P < 0.001$	1.15 (0.98–1.35) $P = 0.099$	<0.001
Ischemic stroke			
Model 1	0.83 (0.74–0.93) $P = 0.001$	0.87 (0.75–1.00) $P = 0.044$	0.002
Model 2	0.78 (0.70–0.87) $P < 0.001$	0.89 (0.77–1.03) $P = 0.106$	<0.001
Hemorrhagic stroke			
Model 1	1.86 (1.62–2.14) $P < 0.001$	1.60 (1.35–1.91) $P < 0.001$	<0.001
Model 2	1.70 (1.48–1.95) $P < 0.001$	1.68 (1.41–2.00) $P < 0.001$	<0.001
Mortality			
Model 1	1.03 (0.98–1.08) $P = 0.228$	0.80 (0.75–0.85) $P < 0.001$	<0.001
Model 2	1.00 (0.95–1.05) $P = 0.970$	0.82 (0.77–0.88) $P < 0.001$	<0.001

Model 1 adjusted for age, gender, and risk factors (HTN, DM, and hyperlipidemia). Model 2 adjusted for Model 1 along with comorbidities (CAD, PAD, CHF, and AF) and medications.

ACEI = angiotensin-converting enzyme inhibitor, ACS = acute coronary syndrome, AF = atrial fibrillation, ARB = angiotensin II receptor blocker, CAD = coronary artery disease, CHF = congestive heart failure, DM = diabetes mellitus, HTN = hypertension, PAD = peripheral artery disease.

initial use of an ACEI/ARB, long-term use provided significant benefits, suggesting a dose-dependent effect. In addition, ARBs provided a significantly greater benefit than ACEIs in protecting dialysis patients from mortality.

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