The effectiveness and safety of angiotensin-converting enzyme inhibition or receptor blockade in vascular diseases in patients with hemodialysis

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Abstract

Patients with end-stage renal disease (ESRD) who are on hemodialysis have high risk of vascular diseases. Our study sought to examine whether angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin type 1 receptor blockers (ARBs) could reduce the frequencies of cardiovascular and cerebrovascular events in patients receiving hemodialysis using the medication possession ratio (MPR) method of analysis.

This retrospective cohort study identified cases of ESRD with dialysis from the National Health Insurance Research Database between 1999 and 2006, and used Cox-regression methods to evaluate risk of poor outcomes. Primary outcomes, including death from any cause, and secondary outcomes, including admission for stroke, myocardial infarction, and heart failure, were examined.

Compared to the nonuser group, the adjusted HRs for mortality of the nonadherence group and the adherence group were 0.81 (95% CI: 0.76–0.86) and 0.98 (95% CI: 0.86–1.13), respectively. Cardiovascular events were more frequent in patients with ESRD receiving ACEIs /ARBs than in nonusers. Compared with nonusers, the hazard of secondary outcome significantly increased in the nonadherence group or adherence group in 10 years follow-up.

Compared with patients with diabetes or chronic kidney disease, patients on hemodialysis may not experience the same cardiovascular and cerebrovascular benefits from ACEIs/ARBs use.

Abbreviations: ACEIs = angiotensin-converting enzyme inhibitors, AF = atrial fibrillation, ARBs = angiotensin type 1 receptor blockers, CI = confidence interval, CCB = calcium channel blockers, cDDDs = cumulative DDDs, CKD = chronic kidney disease, COPD = chronic obstructive pulmonary disease, DDD = definite daily dose, ESRD = end-stage renal disease, HMG-CoA = 3-hydroxy-3-methylglutaryl-coenzyme A, HRs = hazard ratios, ICD-9 = International Classification of Disease, ninth revision, MPR = medication possession ratio, NHI = National Health Insurance, NHIRD = National Health Insurance Research Database, PPI = proton pump inhibitors, PVD = peripheral vascular diseases, SDs = standard deviations.

Keywords: angiotensin-converting enzyme inhibition, angiotensin-receptor blockade, hemodialysis

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1. Introduction

Chronic kidney disease (CKD) and end-stage renal disease (ESRD) are global public health problems with increasing numbers of patients and poor prognoses in terms of morbidity and mortality.[1,2] Taiwan has the highest incidence and prevalence rates of ESRD in the world, and the number of patients with ESRD increased rapidly following the launch of National Health Insurance in Taiwan.[3,4]

Patients with ESRD are at high risk of cardiovascular and cerebrovascular diseases, which are the leading causes of mortality among patients with ESRD.[5,6] Independent of their effects on blood pressure, angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin type 1 receptor blockers (ARBs) improve outcomes and survival in patients with diabetes, congestive heart failure, and prior myocardial infarction and provide protection for patients with diabetic nephropathy against progression to ESRD.[7–14]

A previous observational study analyzed outcomes in patients with ESRD who were receiving hemodialysis and were started on therapy with an ACEIs, ARBs, or both, and compared the effects of ACEIs and ARBs on cardiovascular events. The method of analysis for this study was intention to treat, regardless of whether patients completed or changed their antihypertensive medication regimen.[15] The purpose of the present study was to

examine whether ACEIs or ARBs could reduce the frequency of cardiovascular events in Asian patients with ESRD who were receiving hemodialysis, using the medication possession ratio (MPR) method to assess patient medication adherence.

2. Methods

2.1. Data sources

This was a retrospective cohort study, and that was using database from the National Health Insurance Research Database (NHIRD) in Taiwan population. NHIRD included information of ambulatory, outpatient, and hospital inpatient care. NHIRD also have dose, drug type, quantity, and dispensing date of prescription drugs, which was used in this study.

In this study, we extracted ESRD cases with dialysis were according to the International Classification of Disease, ninth revision (ICD-9) and catastrophic illness certificates. The certificate of ESRD on a catastrophic illness published by Ministry of Health and Welfare in Taiwan, which is evaluated by 2 nephrologists from the applying hospital, and rechecked documents according to administration of dialysis treatments routinely, and laboratory data indicating stage V or IV CKD. All applying information are checked by the other physician in Ministry of Health and Welfare before the certificate can be issued. The NHIRD data consisted of reidentified secondary data released to the public for research purposes in our study. This study was approved by the Institutional Review Board of Kaohsiung Medical University Hospital (KMUHIRB-EXEMPT (I)-20170009).

2.2. Study sample

We selected ESRD patients with dialysis from catastrophic illness certificates given from 1997 to 2009. For catastrophic illness certificates, the cases of ESRD with dialysis were defined according to the ICD-9: 585 (CKD); 403.01, 403.11, and 403.91 (hypertensive heart and renal disease with renal failure); and 404.02, 404.03, 404.12, 404.13, 404.92, and 404.93 (hypertensive renal disease with renal failure). The date of first-time dialysis was assigned as the index date. Among patients who had received dialysis after ESRD, we only included patients who had received dialysis for over 3 months. To avoid selection bias due to time limitation of database in this study, the last follow up time was December 31, 2009, in which can provide sufficient information through 2006. We extracted adult ESRD patients with dialysis between 1999 and 2006, with 3 years of available records in our database.

2.3. Drug use

Patients who were prescribed a standard dose of ACEI as one definite daily dose (DDD) or ARB once daily as one DDD, as determined by the number of claimed prescriptions within the follow-up time, were included. To decrease immortal-time bias and to include the same patients in our study, we only included patients whose first dose of ACEIs or ARBs was prescribed within 90 days before or after the index date. Moreover, we also excluded patients with <90 cumulative DDDs (cDDDs) within 90 days before and after the index date. All patients survived for at least 1 month after the index date. Patients were categorized as ACEIs/ARBs users and nonusers in our study. Patients with ACEIs/ARBs MPRs >80% during follow-up were categorized as

ACEIs/ARBs adherence users. Furthermore, ACEIs/ARBs MPRs <80% during follow-up were classified as ACEIs/ARBs non-adherence in this study.

Patients diagnosed with stroke (ICD-9: 430–438), heart failure (ICD-9: 428) or myocardial infarction (ICD-9: 410) before the index date were excluded. Furthermore, we also excluded patients with missing information. The comorbidities were evaluated depend on 1 inpatient diagnosis code and 1 outpatient diagnosis code 2 years before the index date. Comorbidities included hyperlipidemia, hypertension, diabetes mellitus, malignancy, atrial fibrillation (AF), liver cirrhosis, chronic obstructive pulmonary disease (COPD), sleep apnea, thyroid disease, asthma, and peripheral vascular diseases (PVD). Hypertension was physician-diagnosed as a systolic blood pressure ≥140 mm Hg or treatment with antihypertensive medication. Dyslipidemia was defined as physician-diagnosed or treatment for elevated blood lipids. Diabetes was defined as physician-diagnosed or ongoing treatment of diabetes.[16,17] The age, gender, geographical region, income, and urbanicity of study population were also evaluated at baseline. Patients were divided into low and high income groups according to annual income. Use of concomitant drugs was identified according to claimed prescriptions for 1 year before the index date These drugs included diuretics, beta-blockers, alpha-blockers, calcium channel blockers (CCBs), 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitor (statin), antiplatelet drugs, proton pump inhibitors (PPI), vitamin K antagonists, and diabetes medication.

2.4. Outcomes

Primary outcomes and mortality were evaluated. Information about primary outcomes was coded on catastrophic illness certificates. Secondary outcomes included a composite endpoint of admission to hospital for IS (hemorrhagic stroke and ischemic stroke), acute myocardial infarction, and heart failure. Admission to hospital for secondary outcomes was depended on the primary or secondary diagnoses (ICD-9). These outcomes were estimated separately over time. The methods for determining stroke, the protocols regarding drug administration, and the diagnostic procedures related to complications utilized in this study were validated in a previous study.[18]

2.5. Statistics

The hazard of vascular disease (primary and secondary outcome) of ACEIs/ARBs was examined in ESRD patients who underwent dialysis during a 10-year follow-up. We characterized ACEIs/ARBs nonusers and ACEIs/ARBs users as ACEIs/ARBs-adherent and ACEIs/ARBs-nonadherent, and these groups were stratified according to MPR ≥80% and by age, gender, demographic characteristics, comorbidities, and medication use at baseline. Each case was followed-up until the first occurrence of one of the outcome measures or until the end of the follow-up period. All cases in which none of the outcomes had occurred by the end of follow-up (December 31, 2009) were defined as censored. All data are expressed as frequencies (percentages) and the means ± standard deviations (SDs). The P-value <0.05 was defined as statistical significance in this study.

A Cox proportional hazards model was used to evaluate the association of outcomes with ACEI/ARB use during follow-up. Univariate and multivariate models were used to estimate hazard ratios (HRs) in the Cox proportional hazards model to assess the differences in primary and secondary outcomes between ACEIs/
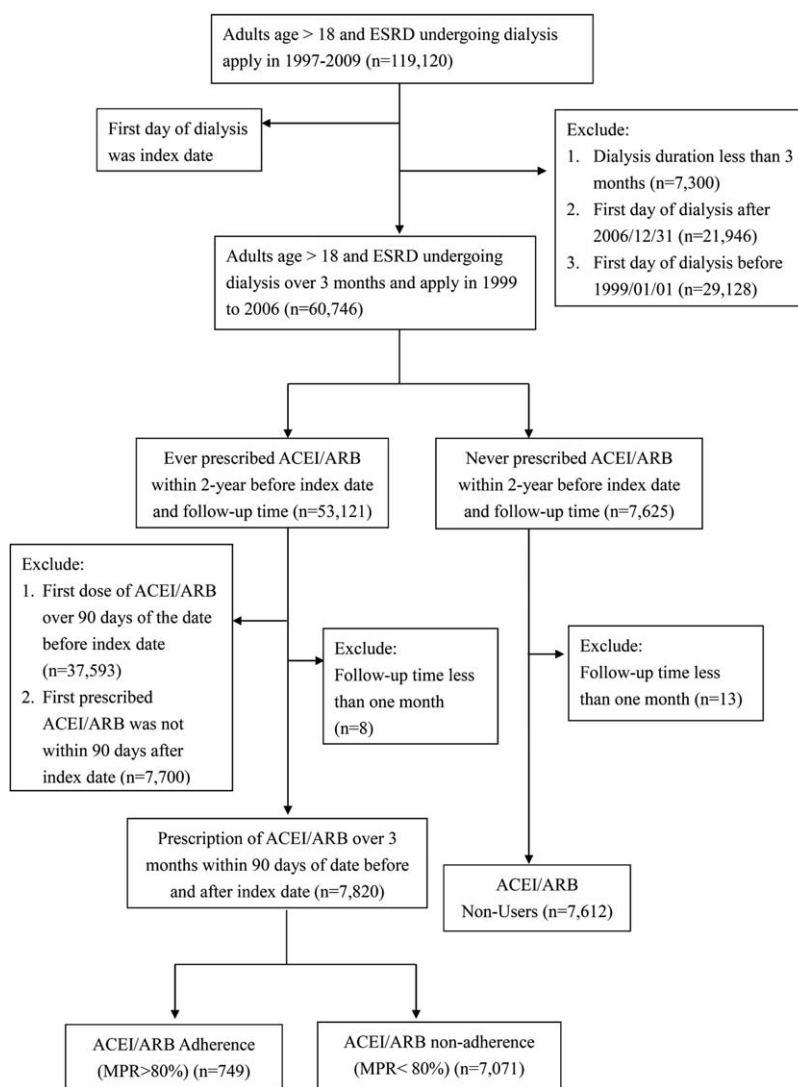
Figure 1. Study inclusion flowchart.

ARBs-adherent and nonuser groups, and between ACEIs/ARBs-nonadherent and nonuser groups, in follow-up time. We adjusted for demographic characteristics, comorbidities, and other medications in Cox proportional hazards model. Because outcomes may have been influenced by interactions between diseases (diabetes mellitus and hyperlipidemia) and use of treatment medications (statins and diabetes medication), the interactions also were examined in Cox proportional hazards model. Kaplan–Meier method was used to present event rates and time-to-event curves for the primary and secondary outcomes in each group. We used SAS ver. 9.4 (SAS Institute, Inc., Cary, NC) to analysis and process in this study.

3. Results

In this study, a total of 119,120 patients with ESRD, aged more than 18 years, who received hemodialysis therapy from 1997 to 2009 were analyzed; we excluded patients with a dialysis duration less than 3 months. Figure 1 presents the flowchart of study inclusion. The first day of hemodialysis is listed as the index date; index dates after December 31, 2006 and before January 1, 1999 were excluded. Of the remaining subjects, 7625 patients were never prescribed ACEIs/ARBs within 2 years before the date

of hemodialysis and during the follow-up period. There are 7820 patients who used ACEIs/ARBs for more than 3 months in a period ranging from 3 months before to 3 months after the index date. During the study period, only 9.58% of patients (749 of the 7820 cases) qualified as adherent, with a MPR greater than 0.80, and 7071 patients were ACEIs/ARBs nonadherent.

The basic demographics of patients with ESRD who underwent hemodialysis stratified by use of and adherence to ACEIs/ARBs regimens are summarized in Table 1. As illustrated in Table 1, compared to the adherent group, the nonuser group was older, with a mean age of 60.9; predominantly female; and exhibited greater incidence of malignancy, COPD, liver cirrhosis and asthma. Compared to nonusers, the adherent group exhibited greater incidence of diabetes, hyperlipidemia, and hypertension. The rates of diuretics, beta-blockers, CCBs, alpha-blockers, statins, antiplatelet drugs, and warfarin use were also higher in the adherent group. For the patients in the nonadherent group, the incidence of diabetes, hyperlipidemia, and hypertension were greater than those of the patients in the nonuser group, but lower than those in the adherent group.

The outcomes of patients with ESRD who underwent hemodialysis are summarized in Table 2. The primary outcome

Table 1

Characteristics of ESRD undergoing dialysis patients at inclusion, stratified by nonuser, nonadherence, and adherence of ACEI/ARB use in 10 years follow-up.

Variable	ACEI/ARB exposure group			
	Nonuser (n = 7,612)	Nonadherence (n = 7,071)	Adherence (n = 749)	*P*
Age				
Mean (±SD), y	60.9 (15.80).	57.3 (16.10)	52.5 (17.12)	<0.001
Gender				<0.001
Male	3476 (45.6)	3458 (48.9)	433 (57.8)	
Female	4138 (54.4)	3613 (51.1)	316 (42.2)	
Income				0.019
High	2149 (28.22)	2119 (29.97)	238 (31.78)	
Low	5465 (71.78)	4952 (70.03)	511 (68.22)	
Geographical region				0.007
North	3087 (40.54)	2955 (41.79)	408 (54.47)	<0.001
Central	1492 (19.6)	1612 (22.8)	148 (19.76)	
South	2665 (35)	2208 (31.23)	160 (21.36)	
East	370 (4.86)	296 (4.19)	33 (4.41)	
Urbanicity				
Urban	2313 (30.38)	2044 (28.91)	140 (18.69)	<0.001
Rural	5301 (69.62)	5027 (71.09)	609 (81.31)	
Comorbidity				
Diabetes	1668 (21.91)	2356 (33.32)	268 (35.78)	<0.001
Hyperlipidemia	1199 (15.75)	1577 (22.3)	190 (25.37)	<0.001
Hypertension	5005 (65.73)	6322 (89.41)	699 (93.32)	<0.001
Malignancy	1204 (15.81)	727 (10.28)	60 (8.01)	<0.001
Atrial fibrillation	307 (4.03)	358 (5.06)	23 (3.07)	0.002
COPD	1136 (14.92)	1055 (14.92)	79 (10.55)	0.004
Sleep apnea	776 (10.19)	731 (10.34)	73 (9.75)	0.864
PVD	98 (1.29)	106 (1.5)	7 (0.93)	0.314
Liver cirrhosis	1731 (22.73)	1359 (19.22)	119 (15.89)	<.0001
Thyroid disease	349 (4.58)	325 (4.6)	35 (4.67)	0.994
Asthma	884 (11.61)	837 (11.84)	59 (7.88)	0.005
Prescribed drugs				
Diuretics	2119 (27.83)	2942 (41.61)	313 (41.79)	<0.001
β-blockers	1348 (17.7)	1589 (22.47)	151 (20.16)	<0.001
CCB	1167 (15.33)	1561 (22.08)	155 (20.69)	<0.001
Alpha-blocker	1667 (21.89)	2217 (31.35)	274 (36.58)	<0.001
Statin	746 (9.8)	1103 (15.6)	172 (22.96)	<0.001
Antiplatelet drugs	1705 (22.39)	2313 (32.71)	240 (32.04)	<0.001
Diabetes drug	223 (2.93)	209 (2.96)	21 (2.8)	<0.001
Warfarin	1958 (25.72)	2773 (39.22)	303 (40.45)	0972
PPI	1490 (19.57)	1474 (20.85)	138 (18.42)	0.078

ACE = angiotensin converting enzyme, ARB = angiotensin receptor blocker, CCB = calcium channel blocker, CCB = calcium channel blockers, COPD = chronic obstructive pulmonary disease, ESRD = end-stage renal disease, PPI = proton pump inhibitors, PVD = peripheral vascular diseases, SD = standard deviation.

was all-cause mortality, and secondary outcomes included myocardial infarction, ischemic stroke, hemorrhage stroke, and congestive heart failure. As shown in Table 2, the mortality rate was 37.2% in the nonuser group, 34.0% in the nonadherent group, and 30.8% in the adherent group. The unadjusted HRs revealed that the nonadherent group and the adherent group exhibited lower mortality rates than nonusers, with HRs of 0.83 (95% CI: 0.79–0.88) and 0.79 (95% CI: 0.69–0.91), respectively. Compared to the nonuser group, the adjusted HRs for mortality in the nonadherent and adherent groups were 0.81 (95% CI: 0.76–0.86) and 0.98 (95% CI: 0.86–1.13), respectively. Cardiovascular events were more frequent in patients with ESRD receiving ACEIs/ARBs compared to nonusers. Compared to nonusers, the adjusted HRs in the nonadherent group for myocardial infarction, ischemic stroke, hemorrhage stroke, and congestive heart failure were 1.75 (95% CI: 1.54–1.98), 1.62 (95% CI: 1.40–1.88), 1.28 (95% CI: 1.04–1.56), and 2.69 (95% CI: 2.30–3.14), respectively. Compared to nonusers, the adjusted

HRs in the adherent group for myocardial infarction, ischemic stroke, hemorrhage stroke, and congestive heart failure were 2.69 (95% CI: 2.18–3.31), 1.76 (95% CI: 1.31–2.38), 2.61 (95% CI: 1.86–3.65), and 4.64 (95% CI: 3.66–5.87), respectively.

Table 3 illustrates the Cox proportional-hazard model that was used to adjust for potential confounders in predictions of all-cause mortality, ischemic stroke, and myocardial infarction. Compared to nonusers, the HRs for all-cause mortality in the nonadherent and adherent groups were 0.815 (95% CI: 0.768–0.864) and 0.988 (0.861–1.134), respectively. As illustrated in Table 3, both nonadherence and adherence to ACEIs/ARBs treatment were associated with increased risk of ischemic stroke or myocardial infarction. Compared with nonusers, the nonadherent group exhibited a 62% increase in the risk of ischemic stroke, and the adherent group exhibited a 78% increase in the risk of ischemic stroke. Furthermore, ACEIs/ARBs users among the hemodialysis patients also exhibited increased risk of myocardial infarction (HRs of 1.747 in the nonadherent group and 2.685 in the adherent group).

Table 2

Association between ESRD undergoing dialysis patients treated with ACEI/ARB in follow-up period and risk of stroke, MI, CHF, and death.

Outcome	Nonuser (n = 7612)	Nonadherence (n = 7071)	Adherence (n = 749)	Nonadherence vs nonuser unadjusted HR	P	Adherence vs nonuser unadjusted HR	P	Nonadherence vs nonuser adjusted HR*	P	Adherence vs nonuser adjusted HR*	P
						Events after discharge					
Primary outcome											
All-cause death	2829 (37.2%)	2406 (34.0%)	231 (30.8%)	0.83 (0.79–0.88)	<0.001	0.79 (0.69–0.91)	<0.001	0.81 (0.76–0.86)	<0.001	0.98 (0.86–1.13)	0.801
Secondary outcome											
MI	391 (5.1%)	1034 (14.6%)	132 (17.6%)	2.48 (2.21–2.79)	<0.001	3.40 (2.80–4.14)	<0.001	1.75 (1.54–1.98)	<0.001	2.69 (2.18–3.31)	<0.001
Ischemic stroke	302 (4.0%)	587 (8.3%)	54 (7.2%)	1.90 (1.66–2.19)	<0.001	1.75 (1.31–2.34)	<0.001	1.62 (1.40–1.88)	<0.001	1.76 (1.31–2.38)	<0.001
Hemorrhagic stroke	176 (2.3%)	243 (3.4%)	78 (10.4%)	1.48 (1.22–1.79)	<0.001	2.71 (1.97–3.73)	<0.001	1.28 (1.04–1.56)	0.021	2.61 (1.86–3.65)	<0.001
CHF	226 (3.0%)	887 (12.5%)	117 (15.6%)	3.71 (3.21–4.29)	<0.001	5.16 (4.12–6.44)	<0.001	2.69 (2.30–3.14)	<0.001	4.64 (3.66–5.87)	<0.001

ACEI = angiotensin converting enzyme inhibitor, ARB = angiotensin receptor blocker, CCB = calcium channel blocker, CHF = congenial heart failure, ESRD = end-stage renal disease, HR = hazard ratio, MI = myocardial infarction.
* Adjusted for age, gender, comorbidity, and prescribed drugs.

Kaplan–Meier analysis in Fig. 2 showed a significant difference in survival rates between nonadherent ($P < 0.0001$) with nonusers and adherent groups ($P = 0.007$) with nonusers. However, there is no significant difference in survival rates between nonadherent and adherent groups ($P = 0.5485$). Furthermore, from Fig. 3, Kaplan–Meier analysis showed there were lower survival rate in ischemic stroke between nonadherence ($P < 0.0001$) with nonusers and adherence ($P < 0.0001$) with nonusers. It did not show similar result of lower survival rate in ischemic stroke between nonadherent and adherent groups ($P = 0.7423$).

4. Discussion

In this nationwide cohort study involving retrospective analysis of a claims database, we showed that the incidence of myocardial infarction, ischemic stroke, hemorrhagic stroke, and congestive heart failure was higher in patients with ESRD who received hemodialysis and had ever used ACEIs/ARBs compared with a group of patients who had never used these drugs. ACEIs/ARBs were associated with reduced all-cause mortality compared with nonusers who received hemodialysis, but the same pattern was not observed for cardiovascular events. Our analyses showed that ACEIs/ARBs may increase the incidence of cerebral vascular accidents and cardiovascular disease in ESRD patients receiving hemodialysis.

The major strength of our study is that the data were from a real-world setting in an Asian population. This is the first study that was designed to include information about adherence to ACEIs/ARBs in hemodialysis patients via the use of MPRs, and it revealed a low rate of adherence to the use of ACEIs among patients with hemodialysis. The low adherence rates to ACEIs/ARBs in hemodialysis patients in Taiwan, which has a high incidence and prevalence of ESRD, may be a problem for effective treatment of cardiovascular disease.

Nonadherence in patients taking medication is a major concern. Many direct and indirect methods are available to assess medication adherence. MPR is a noninvasive, pharmacy-based measure of medication adherence that allows for the examination of large amounts of data. MPR evaluates the percentage of time that a patient has access to medication.[19] MPR is a useful and easy to use tool for detecting adherence, and it can identify patients' needs and improve medication adherence.[20] Despite proportion of days covered (PDC) provides more current estimate of medication adherence than MPR, when multiple medications are intended to be used concomitantly. However, in our study, patients are not intended to use ACEI and ARB concomitantly and there is no difference of results between MPR and PDC in each outcome.

Only a limited number of studies have investigated MPR in patients with CKD, and no studies have investigated MPR for hemodialysis patients. A previous study assessed the efficacy and safety of ACEI or ARB use in dialysis patients from similar population. From this study, despite of the mortality was lower in patients who did not use an ACEI/ARB than users, the other CV events still were inconsistent. Furthermore, the authors compare different exposure time to no-users, they did not consider dose or MPR as factor in their study.[15] Otherwise, a previous study evaluated whether adherence to hypertension therapy among patients newly treated for hypertension reduces the risk of ESRD. This study revealed that an MPR $\geq 80\%$ in a newly diagnosed hypertensive population is associated with a 33% reduction in risk of ESRD onset.[21] A previous study revealed that ACE

Table 3

Adjusted hazard ratios for factors associated with the risk of ischemic stroke, myocardial infarction, and primary outcome in follow-up period.

Variable	Primary outcome		Ischemic stroke		Myocardial infarction	
	HR (95% CI)[*]	P	HR (95% CI)[*]	P	HR (95% CI)[*]	P
ACEI/ARB exposure						
Nonuser	1		1		1	
Nonadherence	0.815 (0.768–0.864)	<0.001	1.618 (1.394–1.878)	<0.001	1.747 (1.542–1.979)	<0.001
Adherence	0.988 (0.861–1.134)	0.862	1.779 (1.319–2.399)	<0.001	2.685 (2.181–3.306)	<0.001
Age	1.047 (1.044–1.049)	<0.001	1.038 (1.032–1.043)	<0.001	1.04 (1.036–1.045)	<0.001
Male	0.778 (0.736–0.824)	<0.001	0.978 (0.854–1.12)	0.746	0.672 (0.604–0.746)	<0.001
Comorbidity						
Diabetes	1.232 (1.098–1.383)	<0.001	1.142 (0.845–1.544)	0.388	1.132 (0.91–1.407)	0.267
Hyperlipidemia	0.88 (0.807–0.96)	0.004	1.123 (0.924–1.365)	0.245	1.152 (0.987–1.346)	0.073
Hypertension	0.877 (0.816–0.942)	<0.001	1.124 (0.91–1.388)	0.279	1.136 (0.953–1.354)	0.156
COPD	1.182 (1.103–1.268)	<0.001	1.074 (0.904–1.276)	0.417	1.006 (0.874–1.157)	0.937
Asthma	1.017 (0.94–1.101)	0.669	1.205 (1.004–1.445)	0.045	1.003 (0.867–1.16)	0.969
PVD	1.083 (0.892–1.315)	0.418	1.224 (0.772–1.939)	0.39	1.371 (0.995–1.888)	0.054
Atrial fibrillation	1.129 (1.008–1.264)	0.036	1.056 (0.805–1.386)	0.693	1.022 (0.84–1.243)	0.83
Malignancy	1.391 (1.295–1.494)	<0.001	1.035 (0.846–1.266)	0.74	0.89 (0.754–1.05)	0.168
Sleep apnea	0.946 (0.868–1.03)	0.200	0.804 (0.647–0.998)	0.048	1.106 (0.943–1.298)	0.214
Liver cirrhosis	1.262 (1.184–1.344)	<0.001	1.064 (0.903–1.253)	0.458	0.941 (0.825–1.072)	0.359
Prescribed drugs						
Diuretics	1.141 (1.077–1.208)	<0.001	1.027 (0.896–1.177)	0.704	1.078 (0.969–1.198)	0.167
β-blockers	1.065 (0.996–1.138)	0.065	0.949 (0.808–1.116)	0.528	1.147 (1.021–1.29)	0.021
CCB	1.01 (0.944–1.08)	0.778	0.991 (0.848–1.159)	0.912	1.153 (1.028–1.293)	0.015
Alpha-blocker	0.95 (0.893–1.011)	0.107	1.082 (0.937–1.249)	0.282	1.004 (0.898–1.122)	0.948
Antiplatelet drugs	1.093 (1.027–1.164)	0.005	1.278 (1.104–1.481)	0.001	1.763 (1.573–1.975)	<0.001
Warfarin	1.074 (0.932–1.238)	0.321	1.091 (0.78–1.524)	0.611	0.978 (0.746–1.283)	0.875
Statin	0.835 (0.726–0.959)	0.011	1.4 (1.082–1.812)	0.011	2.128 (1.758–2.576)	<0.001
Diabetes drug	1.329 (1.215–1.454)	<0.001	1.029 (0.799–1.325)	0.826	1.27 (1.058–1.524)	0.010
PPI	1.25 (1.173–1.332)	<0.001	1.081 (0.922–1.269)	0.336	1.315 (1.159–1.493)	<0.001

ACEI = angiotensin converting enzyme inhibitor, ARB = angiotensin receptor blocker, CCB = calcium channel blocker, CI = confidence interval, COPD = chronic obstructive pulmonary disease, ESRD = end-stage renal disease, HR = hazard ratio, PPI = proton pump inhibitors, PVD = peripheral vascular disease.
[*] Adjusted for age, gender, comorbidity, and prescribed drugs.

inhibitor use was lower (50% MPR) in patients with CKD and coronary heart disease events, and CCB use was higher (47% MPR) compared with non-CKD populations (58% MPR for ACEIs and 38% MPRs for CCBs).[22] In our study, hemodialysis patients exhibited a low level of adherence to treatment with ACEIs/ARBs, and less than 10% of patients met criteria for good adherence (MPR ≥80%). In our population, diuretics and alpha-blockers were prescribed more frequently than CCB and beta-blockers. Diuretics are frequently used in patients with CKD to control extracellular fluid volume expansion and blood pressure. Alpha-blockers are usually prescribed after other medicines have been tried because of their uncommon side effects and relief from prostatic hyperplasia symptoms. CCBs also have few side effects and were broadly used in patients with ESRD in our study population.
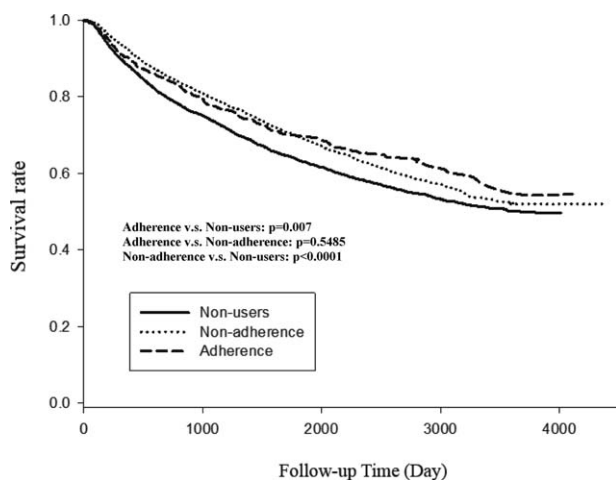
Figure 2. Kaplan–Meier curves of survival rates of nonuser, nonadherent, and adherent groups.
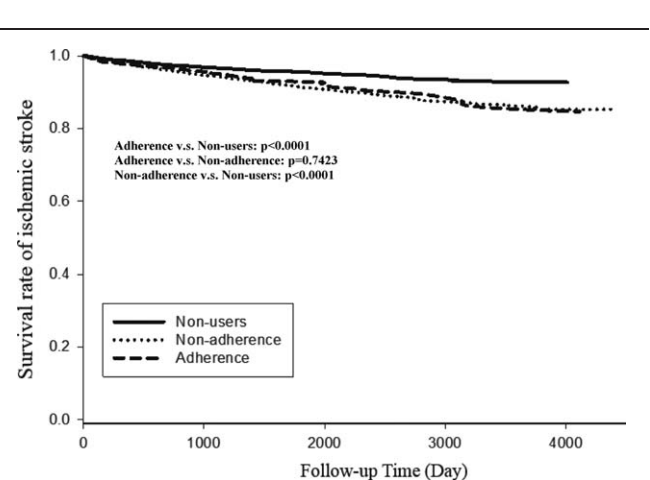
Figure 3. Kaplan–Meier curves of ischemic stroke between nonuser, nonadherent, and adherent groups.

A retrospective study using a database from a medical center[23] revealed that one-third of CKD patients exhibit poor medical adherence (MPR <80%) to antihypertensive agents. This study focused on patients with CKD and not ESRD. Moreover, medication adherence in this study included all types of antihypertension medications, whereas our report provides detailed insight into adherence to ACEIs/ARBs, cardiovascular events and some of the important factors that may affect medication adherence. Low adherence rates to medication among patients with cardiovascular diseases are common. The magnitude of drug nonadherence varies according to the method of measurement, the population studied and the specific medications assessed.[24] There are many reasons, both intentional and unintentional, for poor medication adherence. There are 5 reasons of for nonadherence, including health system, disease condition, patient factors, reasons for therapy (i.e., complexity of regimen and medication side effects), and socioeconomic reasons.[24] In our study group, patients with multiple comorbidities needed to take more than one type of medication to control underlying disease. Otherwise, most nephrologists prescribed a B-complex vitamin along with folic acid and phosphorus binders for hemodialysis. The use of ACEIs and ARBs may result in adverse effects, which are more common in CKD and ESRD and including a decrease in glomerular filtration rate, hypotension, and hyperkalemia. These side effects can typically be managed by discontinuation of the agent and also result in poor adherence.

In a recent study, Kevin et al[15] found that there was no significant difference in the risk of cardiovascular, all-cause, or cerebrovascular mortality in patients receiving hemodialysis who were begun on an ARBs or ACEIs regimen, after adjusting for baseline covariates; they also found that there were no statistical interaction effects of patient characteristics on mortality. In their unadjusted models, initiation of an ARBs (vs an ACEIs) was associated with lower risk of cardiovascular death and death due to any cause but not with cerebrovascular mortality. Similar to their studies, our study revealed that all-cause mortality was decreased in hemodialysis patients following adherent and nonadherent use of ACEIs/ARBs before adjusting for baseline covariates. However, the protective effect was not observed in the adherent group following adjustment for baseline covariates. In our analysis, the risk of myocardial infarction, ischemic or hemorrhagic stroke and congestive heart failure were higher in patients using ACEIs/ARBs, and these results were also noted after the adjustment. Kevin et al reported the risk of cardiovascular death, death from any cause and cerebrovascular death in chronic hemodialysis patient using ACEIs/ARBs, but these authors did not mention the risk of cardiovascular events or cerebrovascular accidents in this population. In a prospective, randomized clinical trial, 469 patients with hemodialysis received ARBs to control blood pressure.[25] This study found no significant difference in cardiovascular events or death between hemodialysis patients with hypertension who used ARBs and other antihypertensive medications. Although no significant difference was identified, the risk of ischemic stroke, hemorrhagic stroke, and myocardial infarction were slightly higher in the ARB group than the control group. One meta-analysis[26] revealed that ACEI treatment reduced stroke, nonfatal myocardial infarction, cardiovascular and total mortality in high-risk patients, whereas ARBs use only mildly reduced the risk of stroke. Another meta-analysis reported that ACEIs reduced all-cause mortality, cardiovascular mortality, and major cardiovascular

events in patients with diabetes, whereas ARBs had no benefits on these outcomes.[27] These 2 studies revealed that ACEIs can reduce all-cause mortality and cardiovascular events in high-risk patients and patients with diabetes. Another study focused on hemodialysis patients[28] and used multivariable analysis to demonstrate that ACEIs and ARBs were not independently associated with a reduction in all-cause mortality or hospitalization for myocardial infarction, stroke, or heart failure. That study used an intention-to-treat approach to analyze a database and did not examine medication adherence. Our results were based on a "real-world" database, and we used MPRs to examine adherence. We found that ACEIs/ARBs may increase the risk of cardiovascular events and cerebrovascular accidents in patients on hemodialysis. These increases may have contributed to the high prevalence of comorbidities in the ACEIs/ARBs group, including diabetes, hyperlipidemia, and hypertension; these underlying diseases cause poor circulation.

There are several limitations to our study. As a retrospective observational analysis, this study only provides associative information. The exact temporal relationships between ACEIs/ARBs use and cardiovascular events are difficult to ascertain with this retrospective design. However, we attempted to control for major known confounders and found an association between ACEIs/ARBs use and cardiovascular events in hemodialysis patients. Second, our data may carry the risk of potential disease misclassification bias, but the validity of diagnostic coding in the NHIRD has been proven.[29] Third, no laboratory data, such as blood pressure, serum cholesterol levels, blood glucose, or glycosylated hemoglobin fraction, were available to assess disease severity. However, we selected a nationwide database with clearly defined criteria, and our findings are generalizable to other Asian populations.

Finally, a large, definitive, randomized, double-blind trial of ACEIs or ARBs with increased numbers of hemodialysis patients is warranted to better define the associations of this population with substantial cardiovascular morbidity and mortality.

5. Conclusions

In summary, from a large national population database, using Cox-regression analysis, and patients were divided into nonuser, nonadherence, and adherence in our survey, we found that ACEI or ARB therapy in patients on hemodialysis may not benefit cardiovascular and cerebrovascular outcomes. However, this was not true for mortality. The results of this study are limited by the lack of available data on creatinine clearance and smoking status of the participants. Future studies are recommended to elucidate the exact mechanisms underlying the associations between ESRD, comorbidities, and prescribed drugs, including ACEI/ARB enabling more specific interpretation of our findings.

References

[1] El Nahas AM, Bello AK. Chronic kidney disease: the global challenge. Lancet 2005;365:331–40.
[2] Levey AS, Atkins R, Coresh J, et al. Chronic kidney disease as a global public health problem: approaches and initiatives—a position statement from Kidney Disease Improving Global Outcomes. Kidney Int 2007;72:247–59.
[3] Hwang SJ, Tsai JC, Chen HC. Epidemiology, impact and preventive care of chronic kidney disease in Taiwan. Nephrology (Carlton) 2010;15:3–9.
[4] Yang WC, Hwang SJ. Taiwan Society of NephrologyIncidence, prevalence and mortality trends of dialysis end-stage renal disease in Taiwan from 1990 to 2001: the impact of national health insurance. Nephrol Dial Transplant 2008;23:3977–82.

[5] Dirks JH, de Zeeuw D, Agarwal SK, et al. Prevention of chronic kidney and vascular disease: toward global health equity-the Bellagio 2004 Declaration. Kidney Int Suppl 2005;98:S1–6.

[6] Collins AJ, Li S, Ma JZ, et al. Cardiovascular disease in end-stage renal disease patients. Am J Kidney Dis 2001;38:S26–9.

[7] Pfeffer MA, Swedberg K, Granger CB, et al. Effects of candesartan on mortality and morbidity in patients with chronic heart failure: the CHARM-Overall programme. Lancet 2003;362:759–66.

[8] McMurray JJ, Ostergren J, Swedberg K, et al. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function taking angiotensin-converting-enzyme inhibitors: the CHARM-Added trial. Lancet 2003;362:767–71.

[9] Granger CB, McMurray JJ, Yusuf S, et al. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function intolerant to angiotensin-converting-enzyme inhibitors: the CHARM-Alternative trial. Lancet 2003;362:772–6.

[10] Yusuf S, Pfeffer MA, Swedberg K, et al. Effects of candesartan in patients with chronic heart failure and preserved left-ventricular ejection fraction: the CHARM-Preserved Trial. Lancet 2003;362:777–81.

[11] Pfeffer MA, McMurray JJ, Velazquez EJ, et al. Valsartan, captopril, or both in myocardial infarction complicated by heart failure, left ventricular dysfunction, or both. N Engl J Med 2003;349:1893–906.

[12] Lewis EJ, Hunsicker LG, Clarke WR, et al. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. N Engl J Med 2001;345:851–60.

[13] Brenner BM, Cooper ME, De Zeeuw D, et al. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. N Engl J Med 2001;345:861–9.

[14] Parving H-H, Lehnert H, Bröchner-Mortensen J, et al. The effect of irbesartan on the development of diabetic nephropathy in patients with type 2 diabetes. N Engl J Med 2001;345:870–8.

[15] Chan KE, Ikizler TA, Gamboa JL, et al. Combined angiotensin-converting enzyme inhibition and receptor blockade associate with increased risk of cardiovascular death in hemodialysis patients. Kidney Int 2011;80:978–85.

[16] Liu O, Li JR, Gong M, et al. Genetic analysis of six SNPs in candidate genes associated with high cross-race risk of development of thoracic aortic aneurysms and dissections in Chinese Han population. Acta Pharmacol Sin 2010;31:1376–80.

[17] Wang XL, Liu O, Qin YW, et al. Association of the polymorphisms of MMP-9 and TIMP-3 genes with thoracic aortic dissection in Chinese Han population. Acta Pharmacol Sin 2014;35:351–5.

[18] Cheng CL, Kao YH, Lin SJ, et al. Validation of the National Health Insurance Research Database with ischemic stroke cases in Taiwan. Pharmacoepidemiol Drug Saf 2011;20:236–42.

[19] Farmer KC. Methods for measuring and monitoring medication regimen adherence in clinical trials and clinical practice. Clin Ther 1999;21: 1074–90.

[20] Woltmann EM, Valenstein M, Welsh DE, et al. Using pharmacy data on partial adherence to inform clinical care of patients with serious mental illness. Psychiatr Serv 2007;58:864–7.

[21] Roy L, White-Guay B, Dorais M, et al. Adherence to antihypertensive agents improves risk reduction of end-stage renal disease. Kidney Int 2013;84:570–7.

[22] Bansal N, Hsu CY, Chandra M, et al. Potential role of differential medication use in explaining excess risk of cardiovascular events and death associated with chronic kidney disease: a cohort study. BMC Nephrol 2011;12:44.

[23] Schmitt KE, Edie CF, Laflam P. Adherence to antihypertensive agents and blood pressure control in chronic kidney disease. Am J Nephrol 2010;32:541–8.

[24] Ho PM, Bryson CL, Rumsfeld JS. Medication adherence: its importance in cardiovascular outcomes. Circulation 2009;119: 3028–35.

[25] Iseki K, Arima H, Kohagura K, et al. Effects of angiotensin receptor blockade (ARB) on mortality and cardiovascular outcomes in patients with long-term haemodialysis: a randomized controlled trial. Nephrol Dial Transplant 2013;28:1579–89.

[26] Ong HT, Ong LM, Ho JJ. Angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin-receptor blockers (ARBs) in patients at high risk of cardiovascular events: a meta-analysis of 10 randomised placebo-controlled trials. ISRN Cardiol 2013;2013:478597.

[27] Cheng J, Zhang W, Zhang X, et al. Effect of angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers on all-cause mortality, cardiovascular deaths, and cardiovascular events in patients with diabetes mellitus: a meta-analysis. JAMA Intern Med 2014;174: 773–85.

[28] Bajaj RR, Wald R, Hackam DG. Use of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers and cardiovascular outcomes in chronic dialysis patients: a population-based cohort study. Arch Intern Med 2012;172:591–3.

[29] Cheng CL, Lee CH, Chen PS, et al. Validation of acute myocardial infarction cases in the national health insurance research database in Taiwan. J Epidemiol 2014;24:500–7.