

Primary prevention of cardiovascular disease events with renin-angiotensin system blockade in autosomal dominant polycystic kidney disease dialysis patients

A nationwide cohort study

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Abstract

Although renin-angiotensin system (RAS) blockade has been shown to reduce cardiovascular disease (CVD) in the general population and high-risk subjects, their protective effect in autosomal dominant polycystic kidney disease (ADPKD) patients under dialysis was still unknown. By using the database from 1995 to 2008 Taiwan National Health Insurance Research Database (Registry for Catastrophic Illnesses), we included 387 ADPKD patients who received dialysis therapy, aged ≥ 18 year-old, and with no evidence of CVD events in 1997 and 1998. We utilized Cox proportional hazards regression analysis and propensity score matching to evaluate adjusted hazard ratios for all-cause mortality and CVD events in users ($n=231$) and nonusers ($n=156$) of an angiotensin-converting enzymes inhibitor (ACEI) / angiotensin II receptor blocker (ARB) during the 12 years of follow-up. All study subjects were followed up for more than 3 months. There was no significant difference between the ACEI/ARB treatment group and the control group in incident CVD events except ischemic stroke and transient ischemic accident (TIA). The results remain similar between groups before and after propensity score matching. Moreover, there was no significant difference in outcomes between ACEI/ARB treatment over 50% of follow-up period and without ACEI/ARB treatment after propensity score matching. This nationwide cohort study failed to prove the protective effects of long-term ACEI or ARB on incident CVD events among APKD dialysis patients. Further larger scale, multicenter and randomized control trials are warranted to show the causal association

Abbreviations: ACEI = angiotensin-converting enzymes inhibitor, ACS = acute coronary syndrome, ADPKD = autosomal dominant polycystic kidney disease, ARB = angiotensin II receptor blocker, BP = blood pressure, CI = coronary intervention, CVD = cardiovascular disease, ESRD = end-stage renal disease, PS = propensity score, RAS = renin-angiotensin system.

Keywords: angiotensin II receptor blocker, angiotensin-converting enzymes inhibitor, autosomal dominant polycystic kidney disease, cardiovascular disease

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All data generated or analyzed during this study are included in this published article [and its supplementary information files].

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1. Introduction

Autosomal dominant polycystic kidney disease (ADPKD) is the most common hereditary cause of end-stage renal disease (ESRD), accounting for 8% to 10% of ESRD patients in western countries.^[1] It occurs 1 of 400 to 1000 individuals^[2,3] and is characterized by development of cystic dilatation of renal tubules with progressive destruction of renal parenchyma.^[4,5] As the cysts grow, 45% of patients will progress to ESRD by the age of 60 and up to 75% by the age of 70.^[6] Hypertension is very common in ADPKD, occurring in 50% to 70% of patients before renal function impairment,^[7,8] and is associated with rapid progression to ESRD and adverse cardiovascular disease (CVD) outcomes.^[9] Left ventricular diastolic dysfunction, endothelial dysfunction, and increased carotid artery intima-media thickness are found in young ADPKD patients who have normal blood pressure (BP) and renal function.^[10] CVD complications have been a major cause of death in patients with ADPKD and the risk of CVD death is estimated to be 1.6 to 3.2-fold higher in these patients.^[9,11]

Several mechanisms of cardiovascular dysfunction have been proposed in ADPKD patients, including activation of renin-angiotensin system (RAS), impaired nitric oxide dependent vasodilatation, increased sympathetic nerve activity and plasma endothelin-1 concentration, and insulin resistance.^[12,13] Among them, RAS activation plays an essential role. When compared with calcium channel blocker, RAS blockade may decrease urinary albumin excretion in subjects with ADPKD.^[14] However, uncertainty remains concerning the optimal choice of antihypertensive therapy in subjects with ADPKD in terms of in slowing progression to renal failure and CVD outcomes in ADPKD.^[14–17]

CVD is the leading cause of mortality in patients receiving dialysis.^[18,19] In addition to fluid and sodium overload, dialysis patients are found to have increased sympathetic activity and abnormal response to RAS, both of them result in higher incidence of hypertension and left ventricular hypertrophy (LVH). Although angiotensin-converting enzymes inhibitor (ACEI) and angiotensin II receptor blocker (ARB) have been shown to reduce CVD morbidity and mortality in the general population and high risk subjects,^[20–22] their protective effect in ESRD patients under dialysis remained uncertain.^[2,3] Our previous study revealed that the overall mortality was significantly greater in patients who did not use an ACEI/ARB in ESRD patients on dialysis in a nationwide cohort.^[18] In addition, subjects who used an ACEI/ARB for longer durations were significantly less likely to experience CVD events.^[18] However, it remained unclear about the role of ACEI/ARB in primary prevention of CVD events in ADPKD patients with ESRD. To fill this gap, we hypothesize that the use of ACEI or ARB is associated with the reduction of major cardiovascular events in ADPKD patients on dialysis in a nationwide cohort.

2. Materials and methods

2.1. Study population

Using Registry for Catastrophic Illness database from a national health insurance program in Taiwan, we obtained patients' baseline data including sex, birth data, medication history, and diagnostic codes based on the International Classification of Diseases (ICD), Ninth Revision, Clinical Modification (ICD-9-CM; www.icd9-data.com/2007) for the analyses. In the current study, we included 607 ADPKD subjects undergoing

hemodialysis or peritoneal dialysis, and age ≥ 18 years between 1995 and 2008. We excluded 193 subjects with history of acute coronary syndrome (ACS) or previous stroke before dialysis. Twenty seven subjects were excluded due to follow-up < 3 months. All enrolled subjects were followed from 1995 to 2009, with a median follow-up time was 1110 days (interquartile range, 558–2142 days). By reviewing of the pharmacy prescription database, we also gathered information on prescribed drugs, dosage, and duration. Subjects were divided into study group (with ACEI/ARB) and control group (without ACEI/ARB). Patients under ACEI/ARB > 30 consecutive days were included in study group. Ten kinds of ACEIs (about 90 of generic drugs with various dose) and 7 kinds of ARBs (about 60 of generic drugs with various dose) were studied. Finally, there were 387 subjects included in the final analyses. The designed patient flow diagram is shown in Fig. 1. The study was approved by the Research Ethics Committee of the National Taiwan University Hospital, Taipei, Taiwan. All methods were carried out in accordance with relevant guidelines and regulations.

2.2. Comorbidities and outcomes

Comorbidities were identified by diagnoses at hospital discharge or from clinic records, and included hypertension (ICD-9-CM codes: 401.X–405.X), diabetes mellitus (250.X, 249.X), hyperlipidemia (272.X), CVD events including coronary artery disease (411.X– 414.X, V17.3, V81.0), atrial fibrillation (427.31,

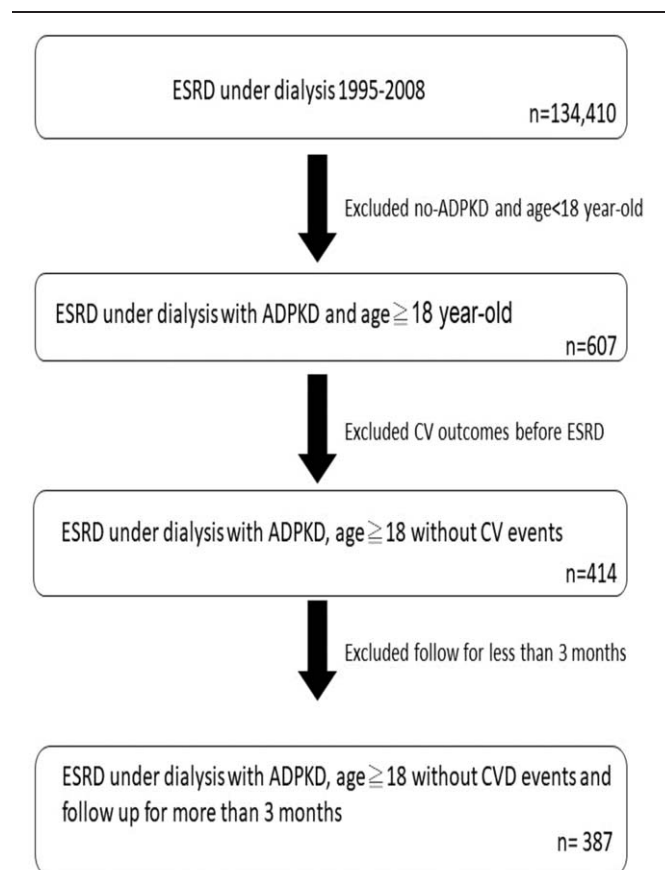


Figure 1. Designed patient flow diagram. ADPKD=autosomal dominant polycystic kidney disease, CVD events=cardiovascular disease events, ESRD=end-stage renal disease.

427.3), valvular heart disease (394.X-396.X), and liver cirrhosis (571.X, 572.X). The endpoints of the present study were new onset ACS (410.X, A270, 411.1), coronary intervention (CI): percutaneous coronary intervention (00.66, 36.0X), transient ischemic accident (433.X), ischemic stroke: (434.X, A293, A292), hemorrhagic stroke: (430.X, 431.X, 432.X), peripheral arterial disease (250.7, 443.X, 444.2), heart failure (428.0-428.3, 428.9), and death. The event-free survival time was defined as the time from the day of dialysis therapy to an endpoint. If an event did not occur, the case was regarded as censorship at the end of the study, withdraws from the insurance, loss contact, and receiving kidney transplantation.

2.3. Propensity score-based matching

Propensity score (PS) matching is a statistical technique used to control the covariates to make 2 groups more comparable in observation study. In the current study, the PS dependent variable was receiving ACEI/ARB treatment or not. Other covariates, such as age, sex, hypertension, diabetes mellitus, dyslipidemia, comorbidities, and medications (antiplatelet, warfarin, beta-blocker, Statin), were put into a non-parsimonious logistic regression model. Participants were excluded from further analysis if an appropriate PS match could not be found. In the final analysis, the remaining subjects composed a matched 1:1 or 1:2 according to the original case number in each group.

2.4. Statistical analysis

All analyses were performed with SPSS 15.0 for WINDOWS 7 (SPSS Inc., Chicago, IL). Student *t* test was performed to compare

continuous variables while chi-squared test was used to test categorical covariates. Fisher exact test was used instead for categorical variable if any expected value within a 2×2 table was below 5. Multivariate Cox proportional hazard models were used to derive the adjusted HRs for developing incidents CV events in both groups. All the confounder factors (age, sex, risk profiles, comorbidity, and medication usage) was adjusted in this model. To adjust the potential selection bias, the propensity score was added in the final model. Moreover, we performed a subgroup analysis by including patients with more aggressive ACEI/ARB treatment (defined as ACEI/ARB treatment over 50% of the follow-up period) to test the consistency. Kaplan-Meier curves were performed to show the event-free survival trend between subjects with and without taking ACEI/ARB and tested by log-rank test. *P* value <.05 was considered statistically significant in all analyses.

3. Results

3.1. Demographic and clinical characteristic of enrolled patients

The demographic and characteristic of the patients was shown in Table 1. Subjects treated with ACEI/ARB for >30 consecutive days served as the study group, and those treated with <30 consecutive days or no medication served as the control group. An ACEI or ARB was prescribed to 231 subjects (59.7%). Subjects taking an ACEI or ARB were at higher prevalence of hypertension (94.8% vs 73.7%, *P*<.001) and more likely to receive a concomitant medication, including beta-blocker (72.7% vs 37.8%, *P*<.01) and statin (28.1% vs 13.5%,

Table 1

Characteristics of patients with and without ACEI/ARB treatment before and after propensity score matching.

	Before PS			After PS		
	No ACEI/ARB (N=156)	ACEI/ARB (N=231)	<i>P</i>	No ACEI/ARB (N=80)	ACEI/ARB (N=160)	<i>P</i>
Risk profile, %						
Age	53.1±14.4	52.9±12.9	.881	53.1±12.3	53.1±13.3	.997
Gender	49.4	53.7	.404	51.3	55.6	.521
Hypertension	73.7	94.8	<.001	96.3	93.1	.396
Diabetes mellitus	13.5	10.4	.355	12.5	13.8	.788
Dyslipidemia	32.1	41.1	.070	36.3	41.3	.455
Comorbidity, %						
Coronary artery disease	27.6	26.0	.728	23.8	29.4	.443
Atrial fibrillation	1.9	1.7	.890	1.3	1.9	1.000
Valvular heart disease	1.3	1.7	.725	2.5	2.5	1.000
Liver cirrhosis	19.2	16.0	.412	15.0	17.5	.624
Medication, %						
Antiplatelet	10.9	21.2	.008	13.8	17.5	.458
Warfarin	3.2	3.0	1.000	5.0	3.8	.735
Beta-blocker	37.8	72.7	<.001	62.5	63.8	.850
CCB	59.6	82.7	<.001	72.5	78.8	.179
Alpha-Blocker	19.9	38.1	<.001	30.0	36.9	.181
Statin	13.5	28.1	<.001	21.3	25.0	.520
Outcome, %						
ACS/CI	6.4	4.3	.364	5.0	5.6	1.000
Ischemic stroke/TIA	5.8	1.3	.017	5.0	0.6	.044
Hemorrhagic stroke	5.8	4.8	.661	3.8	5.0	.756
Peripheral artery disease	8.3	3.0	.021	5.0	3.8	.735
Heart failure	8.3	4.3	.102	6.3	5.6	1.000
Mortality	21.8	13.0	.022	18.8	14.4	.381

ACS=acute coronary syndrome, CCB=calcium channel blocker, CI=coronary intervention, PS=propensity score, TIA=transient ischemic accident.

$P < .001$). Otherwise, there was no significant difference in age, sex, risk profile of atherosclerosis and cardiovascular comorbidities, including coronary artery disease, atrial fibrillation, and valvular heart disease between groups. During the study period, there were less ischemic stroke/TIA (1.3% vs 5.8%, $P = .017$) and peripheral artery disease (3.0% vs 8.3%, $P = .021$) in the ACEI/ARB treatment group. In addition, the overall mortality was lower in the treatment group (13.0% vs 21.8%, $P = .022$).

The PS matching enrolled 160 patients in the ACEI/ARB treatment group and 80 patients without taking ACEI/ARB (Table 1). After PS matching, there were smaller differences in age, sex, comorbidities, use of other medication, and other clinical variables between 2 groups. After PS matching, the incidence of ischemic stroke/TIA was significantly lower in ACEI/ARB treatment group than control group (0.6% vs 5.0%, $P = .044$). By contrast, there was no significant difference between groups in incidence of ACS or CI (5.6% vs 5.0%, $P = 1.0$), hemorrhagic stroke (5.0% vs 3.8%, $P = .756$), peripheral artery disease (3.8% vs 5.0%, $P = .735$), and hospitalization due to heart failure (5.6% vs 6.3%, $P = 1.0$). In addition, the overall mortality was similar in both group (14.4% vs 18.8%, $P = .381$). No patients were lost to follow-up in these 2 groups. Additionally, the usages of CCB and alpha-blocker were significantly higher in ACEI/ARB group but after the original propensity matching processes, the significance disappeared.

3.2. Effect of duration of ACEI/ARB use

The hazard ratios for different clinical outcomes in study subjects were analyzed by Cox regression model and shown in Table 2. Compared with the control group, the ACEI/ARB treatment group did not have favorable outcome including ACS, receiving CI, cerebral vascular events, peripheral artery disease, and hospitalization due to heart failure and overall mortality. The results remain similar between groups before and after PS matching.

In Fig. 2, we demonstrated the probability of incident CV event-free survival in subjects receiving ACEI/ARB before and after PS-matching by the Kaplan–Meier curve and log rank test to provide a statistical comparison of 2 groups. The results showed that there was no significant difference in composite endpoints between groups before and after PS matching (Fig. 2A and B).

3.3. Characteristics of patients with ACEI/ARB treatment over 50% of follow-up period

Table 3 analyses the demographic and clinical characteristic in ADPKD subjects on dialysis treated with ACEI/ARB for >50% of

follow-up period. The results showed the patients who used ACEI/ARB had higher prevalence of hypertension (95.5% vs 73.7%, $P < .001$) and more likely to receive a concomitant medication, including beta-blocker (74.5% vs 37.8%, $P < .01$) and statin (27.3% vs 13.5%, $P < .001$). During the study period, there were less event of heart failure (1.83% vs 8.3%, $P = .023$) in the ACEI/ARB treatment group. There was no significant difference in overall mortality between ACEI/ARB treatment group and control group (12.7% vs 21.8%, $P = .058$). After PS matching, the ACEI/ARB group had similar heart failure event (0.0% vs 6.5%, $P = .058$), and the overall mortality was similar in both group (13.0% vs 19.5%, $P = .275$).

4. Discussion

To the best of our knowledge, this is the first study to investigate the impact of RAS blockade on incident CVD events in ADPKD subjects on dialysis. This nationwide cohort study failed to support the protective role of long-term RAS blockade treatment in reducing incident CVD events among ADPKD dialysis patients. In order to test the consistency and influence of RAS blockade duration of on incident CVD events, we compared subjects with ACEI/ARB treatment for >50% of follow-up period. The result was similar and also failed to support such protective role of RAS blockade in reducing incident CVD events.

Higher left ventricular mass index can be found since early stage of ADPKD and is significantly associated with ambulatory systolic BP in normotensive and hypertensive ADPKD patients.^[24] LVH is at the prevalence of around 48% among hypertensive and 23% among normotensive ADPKD patients. Hypertension is known to occur frequently and early in ADPKD and considered as a contributing factor for LVH in part due to earlier onset and inadequate treatment.^[25] The HALT PKD study using cardiac magnetic resonance to assess LVH and reported ADPKD patients with <50 years of age and prior use of RAS blockade have lower prevalence of LVH, and therefore early BP intervention can decrease LVH progression and might potentially decrease CVD mortality.^[26] In UK General Practice Research Database provide further evidence that early and aggressive BP control in ADPKD through increasing coverage and intensity of antihypertensive therapy can effectively lower all-cause mortality in ADPKD patients.^[27] However, the above study results did not provide evidence to suggest preferential benefit from ACEI/ARB treatment. Currently, there was no prospective randomized controlled trial investigating the effects of ACEI/ARB treatment on mortality and CVD events in ADPKD subjects on dialysis.

Table 2
Hazard ratios (95% CI) of different outcomes by using patients without ACEI/ARB treatment as reference group before and after propensity score matching.

	Before PS		After PS	
	HR (95% CI)	P	HR (95% CI)	P
ACS/CI	0.468 (0.167–1.315)	.150	0.862 (0.228–3.262)	.862
Ischemic stroke/TIA	0.257 (0.061–1.079)	.063	0.165 (0.018–1.528)	.165
Hemorrhagic stroke	1.000 (0.337–2.964)	1.000	1.297 (0.321–5.233)	.715
Peripheral artery disease	0.558 (0.197–1.583)	.273	0.902 (0.218–3.730)	.887
Heart failure	0.470 (0.183–1.208)	.117	0.952 (0.287–3.153)	.936
Mortality	0.748 (0.428–1.308)	.309	0.786 (0.404–1.530)	.478

Model adjusted for age, sex, risk profile, comorbidity and medications.

ACS=acute coronary syndrome, CI=coronary intervention, PS=propensity score, TIA=transient ischemic accident.

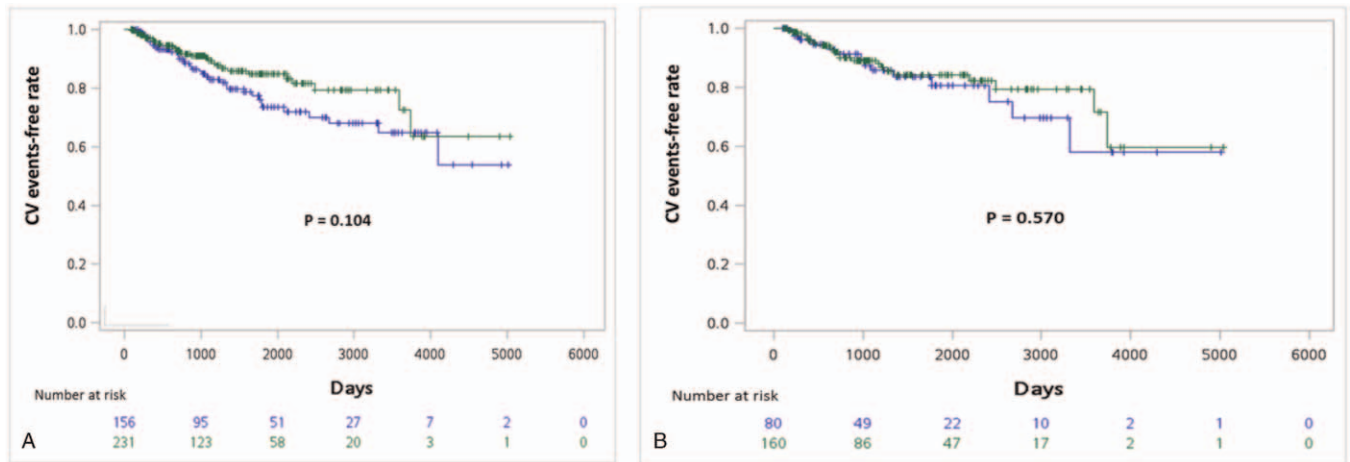


Figure 2. The Kaplan–Meier curve of cardiovascular events-free rate between patients treated with (green) and without (blue) ACEI/ARB (A). The Kaplan–Meier curves of cardiovascular event-free rate after PS matching were also illustrated (B). The cardiovascular events were defined as composite outcome, including acute coronary syndrome, coronary intervention, ischemic stroke, transient ischemic accident, hemorrhagic stroke, peripheral artery disease, and hospitalization due to heart failure and overall mortality. ACEI=angiotensin-converting enzymes inhibitor, ARB=angiotensin II receptor blockade, PS=propensity score.

In general, ADPKD patients had better survival on dialysis than non-ADPKD patients.^[28] There is a trend of the increase in the number of ADPKD patients being dependent on renal replacement therapy from 1990s to 2000s and is thought to be related to greatly improvement on dialysis survival rather than incidence of dialysis increase.^[29] CVD, coronary artery disease, and infection are the leading causes of death in ADPKD patient

on dialysis.^[30,31] Although several evidences have demonstrated that ACEI and ARB can effectively reduce the BP and offer cardioprotective effects on dialysis patients,^[18,32] there is no available literature discussing the effects of RAS blockade on reducing the occurrence of CVD events and survival benefit on ADPKD patients on dialysis. In the current study, we found that long-term ACEIs and ARBs failed to reduce the risk of ACS or CI,

Table 3

Characteristics of patients with ACEI/ARB treatment over 50% of follow-up period and without ACEI/ARB treatment before and after propensity score matching.

	Before PS			After PS		
	No ACEI/ARB (N=156)	ACEI/ARB (N=110)	P	No ACEI/ARB (N=77)	ACEI/ARB (N=77)	P
Risk profile, %						
Age	53.1 ± 14.4	54.1 ± 11.5	.566	53.1 ± 12.3	53.1 ± 13.3	
Gender	49.4	53.6	.492	55.8	51.9	.628
Hypertension	73.7	95.5	<.001	94.8	93.5	1.000
Diabetes mellitus	13.5	11.8	.693	15.6	11.7	.481
Dyslipidemia	32.1	40.9	.138	40.3	37.7	.741
Comorbidity, %						
Coronary artery disease	27.6	21.8	.288	24.7	23.4	.850
Atrial fibrillation	1.9	0.9	.645	0.0	1.3	.620
Valvular heart disease	1.3	2.7	.407	1.3	3.9	.657
Liver cirrhosis	19.2	16.4	.549	18.2	18.2	1.000
Medication, %						
Antiplatelet	10.9	15.5	.273	14.3	16.9	.657
Warfarin	3.2	1.8	.703	1.3	2.6	1.000
Beta-blocker	37.8	74.5	<.001	67.5	66.2	.864
CCB	59.6	82.7	<.001	75.3	83.1	.160
Alpha-Blocker	19.9	41.8	<.001	29.9	37.7	.197
Statin	13.5	27.3	<.001	22.1	24.7	.703
Outcome, %						
ACS/CI	6.4	4.5	.516	2.6	3.9	1.000
Ischemic stroke/TIA	5.8	0.9	.050	5.2	1.3	.620
Hemorrhagic stroke	5.8	6.4	.841	1.3	7.8	.116
Peripheral artery disease	8.3	2.7	.058	3.9	3.9	1.000
Heart failure	8.3	1.8	.023	6.5	0.0	.058
Mortality	21.8	12.7	.058	19.5	13.0	.275

ACS=acute coronary syndrome, CCB=calcium channel blocker, CI=coronary intervention, PS=propensity score, TIA=transient ischemic accident.

hemorrhagic stroke, peripheral artery disease (PAD), hospitalization due to heart failure, and all-cause mortality in ADPKD dialysis patients. ACEIs and ARBs treatment seemed to lower the risk of ischemic stroke and TIA, although this might be attributed to the higher percentage of patients who were on anti-platelet therapy in the ACEI group. It is worth to mention that in a recent nationwide population-based cohort study, both statin and RAS blockade significantly reduced both hemorrhagic and ischemic strokes in ADPKD subjects without ESRD or cerebrovascular accident (CVA).^[33] It is possible that RAS blockade should be given earlier during the course of progressive vascular damage. Further study is warranted to elucidate the effect of RAS blockade in ADPKD patients under dialysis.

The main strengths of this present study are 2-fold. First, our present study was a population-based, nationwide study that recruited all validated dialysis patients in Taiwan and followed them for a 12-year period. Second, all medications and comorbidities were recorded under the national health insurance policy. Our study also had several imitations. First, we exclusively relied on claim data, so there may be a bias in disease classification. Second, the reliance on registry data did not enable to adjust the analyses for key risk factors of CVD, such as the lipid profile and smoking habit. Third, we didn't have a control group who received neither ACRI nor ARB and therefore it is hard to conclude that ACEI/ARBs were not significantly associated with the differences observed in these analyzed outcomes. These issues might undermine the reliability of the study findings. Other possible confounding factors, including electrolyte imbalance, inflammation parameters, and nutritional status and vascular calcification data were not available in the registry data to adjust the risk of cardiovascular events and mortality. Fourth, a limitation of PS matching was that it dealt with known confounding factors. Some unknown confounding factors, which might be unequally distributed in both treatment and control groups, might have affected the observed difference in our study.

5. Conclusions

In summary, in our nationwide cohort study of ADPKD patient on dialysis from Taiwan, we failed to show the protective role of RAS blockade treatment for longer durations in primary prevention of CVD events in ADPKD patients on dialysis. RAS blockade treatment might reduce the risk of ischemic stroke and TIA. However, further larger scale, multicenter, and randomized control trials are warranted to show the causal association.

Author contributions

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