Primary prevention of atrial fibrillation with angiotensin-converting enzyme inhibitors and angiotensin receptor blockers in patients with end-stage renal disease undergoing dialysis

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Current evidence suggests that angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) reduce the incidence of new atrial fibrillation (AF) in a variety of clinical conditions, including the treatment of left ventricular dysfunction or hypertension. Here we assessed whether ACEIs and ARBs could decrease incidence of new-onset AF in patients with end-stage renal disease (ESRD). We identified patients from the Registry for Catastrophic Illness, a nation-wide database encompassing almost all of the patients receiving dialysis therapy in Taiwan from 1995 to 2008. Propensity score matching and Cox proportional hazards regression models were used to estimate hazard ratios for new-onset AF. Among 113,186 patients, 13% received ACEIs, 14% received ARBs therapy, and 9% received ACEIs or ARBs alternatively. After a median follow-up of 1524 days, the incidence of new-onset AF significantly decreased in patients treated with ACEIs (hazard ratio 0.587, 95% confidence interval 0.519–0.663), ARBs (0.542, 0.461–0.637), or ACEIs/ARBs (0.793, 0.657–0.958). The prevention of new-onset AF was significantly better in patients taking longer duration of ACEI or ARB therapy. The effect remained robust in subgroup analyses. Thus both ACEIs and ARBs appear to be effective in the primary prevention of AF in patients with ESRD. Hence, renin–angiotensin system inhibition may be an emerging treatment target for the primary prevention of AF.

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KEYWORDS: ACE inhibitors; chronic kidney disease; hemodialysis

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The prevalence of atrial fibrillation (AF) increases with age and with underlying diseases.[1] Hypertensive heart disease, coronary heart disease, and congestive heart failure (CHF) are the most common underlying disorders in patients with AF.[2–5] Angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) were commonly used in the treatment of hypertension (HTN), acute myocardial infarction, and CHF according to the current guidelines. For primary prevention of AF, *post hoc* analyses of randomized trials and observations from nonrandomized studies have suggested that ACEI and ARBs reduce the incidence of new-onset AF in a variety of conditions, including left ventricular dysfunction,[6–8] HTN,[9–11] and after coronary artery bypass graft surgery.[12] The possible mechanisms proposed to explain the benefit of angiotensin blockade include direct effects such as the improvement of atrial structural and electrical remodeling and indirect effects such as better control of CHF and HTN.[13] In patients with normal renal function, ACEIs and ARBs have been proved to decrease cardiovascular mortality in high-risk patients, including postmyocardial infarction and CHF.[14,15] In patients with end-stage renal disease (ESRD), the presence of myocardial dysfunction, fluid and electrolyte shifts, poor oxygen saturation, and autonomic dysfunction, either alone or in combination, promotes the development of cardiac arrhythmias.[16] However, there is a paucity of evidence concerning the cardiovascular benefits of ACEIs and ARBs in dialysis patients. The present study was undertaken to assess the impact of treatment with ACEIs or ARBs on the development of AF in a large cohort of ESRD patients. We hypothesized that, compared with patients not receiving ACEIs or ARBs, both therapeutic classes would be associated with lower AF risks.

RESULTS

Patient characteristics

There were 113,186 patients who met the study inclusion criteria; 71,480 (64%) did not use ACEIs or ARBs, while

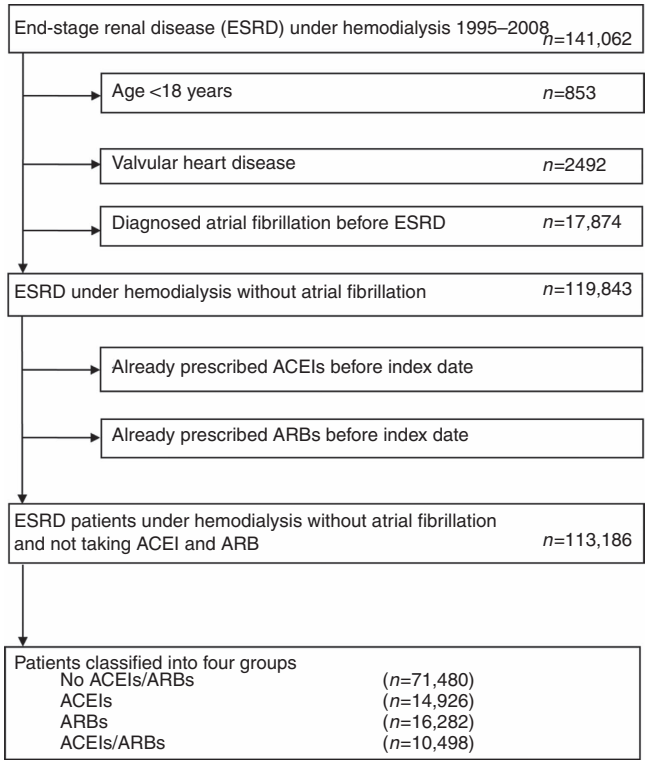

Figure 1 | Patient flow diagram. ACEIs, angiotensin-converting enzyme inhibitors; ARBs, angiotensin receptor blockers.

Table 1 | Demographic and clinical characteristics of study subjects

	Control	ACEIs	ARBs	ACEIs/ARBs
n (%)	71,480 (64)	14,926 (13)	16,282 (14)	10,498 (9)
Age (mean), years	61	58*	57*,†	56*,†,‡
18–64 (%)	54.1	62.3*	66.8*,†	71.1*,†,‡
65–74 (%)	26.6	25.2*	21.6*,†	20.9*,†
⩾75 (%)	19.3	12.5*	11.6*	8*,†,‡
Gender, female %	51.9	49.0*	51.3†	51.9†
Hemodialysis	85.6	97.4*	98.8*,†	98.5*,†,‡
HTN, %	66.8	88.8*	94.6*,†	96.2*,†,‡
DM, %	39.8	53.6*	55.1*,†	54.2*
Dyslipidemia	29.4	35.6*	49.8*,†	48.1*,†,‡
Ischemic stroke/TIA, %	4.4	9.2*	6.1*,†	10.1*,†,‡
Hemorrhagic stroke, %	4.5	7.0*	5.1*,†	7.0*,‡
CAD, %	31.4	47.3*	46.3*	55.0*,†,‡
PAD, %	22.7	27.7*	27.7*	31.5*,†,‡
CHF hospitalization, %	20.4	31.6*	26.6*,†	33.2*,†,‡
Medications				
Beta-blocker	20.6	53.9*	63.6*,†	81.6*,†,‡
CCBs	34.3	81.4*	84.1*,†	94.5*,†,‡
Diuretics	14.0	30.6*	44.7*,†	50.9*,†,‡
Statin	11.6	21.8*	33.8*,†	38.1*,†,‡
OADs	13.0	27.9*	32.1*,†	35.6*,†,‡
Insulin	7.5	15.5*	2.4*,†	25.3*,†,‡

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CAD, coronary artery disease; CCBs, calcium channel blocker; CHF, congestive heart failure; DM, diabetes mellitus; HD, hemodialysis; HTN, hypertension; OAD, oral antidiabetic drug; PAD, peripheral artery disease; TIA, transient ischemic accident.
*$P<0.05$ compared with the no ACEI/ARB category. †$P<0.05$ compared with ACEI category. ‡$P<0.05$ compared with ARB category.

14,926 (13%) used ACEIs, 16,282 (14%) used ARBs and 10,498 (9%) used ACEIs or ARBs alternatively (ACEIs/ARBs). The majority (>99%) of patients in the ACEIs/ARBs group received both medications alternatively and only <1% patients were prescribed with combination therapy. Patients not receiving ACEIs or ARBs treatment served as the control group. The median follow-up time was 1524 days. The algorithm is listed in Figure 1.

Clinical and demographic characteristics are listed in Table 1. Patients in control group were significantly elder than the other three groups, and there were significantly less female patients in ACEIs group as compared with other three groups. The prevalence of receiving hemodialysis therapy was significantly higher in the other three groups (97.4, 98.8, and 98.5% respectively) than in the control group (85.6%). The prevalence of risk factors was higher in the ACEIs, ARBs, and ACEIs/ARBs groups than in the control group, including HTN (88.8, 94.6, and 96.2% vs. 66.8%), diabetes mellitus (DM) (53.6, 55.1, and 54.2% vs. 39.8%), dyslipidemia (35.6, 49.8, and 48.1% vs. 29.4%). The prevalence of comorbidities, including ischemic stroke/transient ischemic accident (9.2, 6.1, and 10.1% vs. 4.4%), hemorrhagic stroke (7.0, 5.1, and 7.0% vs. 4.5%), coronary artery disease (CAD) (47.3, 46.3, and 55.0% vs. 31.4%), peripheral artery disease (PAD) (27.2, 27.7, and 31.5% vs. 22.7%), and CHF hospitalization (31.6, 26.6, and 33.2% vs. 20.4%), was also higher in the ACEIs and ARBs groups than in the control group. It is worth noting that patients in ACEIs/ARBs group were more likely to have HTN and comorbidities than the other three groups. Among the medication use, as compared with the control group, beta-blockers (53.9, 63.6% vs. 20.6%), calcium channel blockers (81.4, 84.1% vs. 34.3%), diuretics (30.6, 44.7% vs. 14.0%), statin (21.8, 33.8% vs. 11.6%), oral antidiabetic drugs (27.9, 32.1% vs. 13.0%) were more common in the ACEIs and ARBs groups, whereas the insulin (15.5, 2.4% vs. 7.5%) were less common in the ARBs groups. As expected, all the medications use was still more frequent in the ACEIs/ARBs group as compared with that in the other three groups.

Main outcome: AF

The median days of follow-up durations were 1441, 1821, 1245, and 2008 days in the control, ACEIs, ARBs, and ACEIs/ARBs groups, respectively. The absolute incidence of new-onset AF during the entire follow-up period was less in the ACEIs (2.2%), ARBs (1.1%), and ACEIs/ARBs (1.2%) groups as compared with that in the control group (4.4%) (Table 2). After transforming the incidence into patient-years, the incidence was still the highest in the control group (0.80 per 100 patient-years) as compared with that in the ACEIs (0.36 per 100 patient-years), ARBs (0.24 per 100 patient-years), and ACEIs/ARBs groups (0.21 per 100 patient-years).

The results of Cox's regression analyses are demonstrated in Table 3. After adjusting for potential confounders, in comparison with the control group, use of ACEIs