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Comparison of incidence of acute kidney injury, chronic kidney disease and end-stage renal disease between atrial fibrillation and atrial flutter: real-world evidences from a propensity score-matched national cohort analysis

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Abstract

We investigated the adverse renal outcomes in patients affected by either atrial fibrillation (Afib) or atrial flutter (AFL). Using the Taiwan National Health Insurance research database, both cohorts were 1:1 propensity score matched based on age, sex, index year, and comorbidity using logistic regression model. Hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) of acute kidney injury (AKI), chronic kidney disease (CKD), and end-stage renal disease (ESRD) between the two cohorts were obtained using Cox proportional hazard regression models. Competing-risks regression models were applied to calculate the subhazard ratios (SHRs) and corresponding 95% CIs of the adverse renal outcomes. Afib patients were 1.15 and 1.33 times more likely to experience CKD and ESRD, respectively, than AFL patients (incidence rate per 10,000 person-years (IR): CKD, 10.8 vs 9.41; ESRD, 4.44 vs 3.34), with the adjusted HRs of 1.18 and 1.32 (CKD, 95% CI = 1.07–1.30; ESRD, 95% CI = 1.12–1.55). Afib patients were 1.08 times (95% CI = 1.01–1.16) more likely to have AKI than AFL patients after adjusting for confounding covariates. Competing risk analysis showed that Afib patients were 1.08 (95% CI = 1.01–1.15), 1.18 (95% CI = 1.07–1.30) and 1.32 (95% CI = 1.12–1.55) times more likely to experience AKI, CKD and ESRD than AFL subjects. This study showed that Afib conferred worse renal events of AKI, CKD and ESRD than AFL.

Keywords Atrial fibrillation · Atrial flutter · Acute kidney injury · Chronic kidney disease · End-stage renal disease

Introduction

The negative cardiovascular prognostic role of atrial arrhythmia, including atrial flutter (AFL) and atrial fibrillation (Afib) is well known in both general and in specific population [1–4]. In addition to the impact of atrial arrhythmia on adverse cardiovascular events, the renal outcomes attract more attention recently since the therapeutic strategy is largely different between individuals affected by atrial arrhythmia whether comorbid with renal function impairment or not [5–8]. Hence, understanding of the risk for the prediction of adverse renal outcomes in this patient group is an unmet need, not only it can eventually be used for the identification of individuals with atrial arrhythmia more likely to benefit from screening programs but also to identify potential participants for primary prevention trials.

Existing investigations have not explored the differential renal outcomes between patients with AFL and Afib. In addition, research on the comprehensive spectrum of adverse renal outcomes, including acute kidney injury (AKI), chronic kidney disease (CKD) and end-stage renal disease (ESRD), is currently unavailable. Therefore, we performed a propensity score matched analysis of national health insurance data in a very large population of Taiwanese Chinese inhabitants in an effort to explore the incident renal events among subjects with clinically detected AFL/Afib. The impact of adverse renal outcomes on mortality was also addressed in this study.

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Methods

Data source

The National Health Insurance Research Database (NHIRD), implemented in 1995, included nearly all Taiwan population [9]. The National Health Insurance (NHI) program offered comprehensive medical care including outpatient and inpatient care for nearly 99% of 23.74 million Taiwan population. The NHI program has been explained in previous study [10, 11]. The diseases were defined by the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) codes. The Research Ethics Committee of China Medical University and Hospital in Taiwan has consented to the study (CMUH-104-REC2-115).

Subject selection

The cohort study focused on inpatient insurant aged ≥ 20 years with a diagnosis of either Afib (ICD-9-CM 427.31) or AFL (ICD-9-CM 427.32) during 2000–2012. The index date for Afib/AFL patient was the date with a first diagnosis of Afib or AFL. Those diagnosed with AKI (ICD-9-CM 584.5, 584.6, 584.7, 584.8, 584.9), CKD (ICD-9-CM 585) (extracted from inpatients datasets of NHIRD), or ESRD (ICD-9-CM 585) (extracted from Registry for Catastrophic Illness Patient Database of NHIRD) prior to the index date were excluded. The follow-up would not end until the occurrence of one of the followings, individuals diagnosed with AKI, CKD or ESRD, censored for death, withdrew from the insurance, or at the end of 2013. All CKD events were recorded, but follow-up was not turned down and subsequent events such as CKD or deaths were recorded as well. Both cohorts were 1:1 propensity score matched based on age, sex, index year, and comorbidity using logistic regression model. Comorbidity contained diabetes mellitus, abnormal liver function, hypertension, hyperlipidemia, coronary artery disease (CAD), congestive heart failure (CHF), chronic obstructive pulmonary disease (COPD), autoimmune disease, gout, and peripheral artery disease (PAD).

Statistical analysis

We applied standardized mean difference on mean age and strata of age, sex, and comorbidity. The difference between the two cohorts was negligible if standardized mean difference was ≤ 0.1. We defined incidence as the number of events (including AKI, CKD, and ESRD) divided by person-years. Respective calculated crude and adjusted hazard ratios (HRs) with corresponding 95% confidence intervals (CIs) of AKI, CKD, and ESRD between the two cohorts were obtained via univariable and multivariable Cox proportional hazard regression models. We obtained crude and adjusted subhazard ratios (SHRs) and corresponding 95% CIs of AKI, CKD, and ESRD through univariable and multivariable competing-risks regression models in which death was considered as the competing risk. Variables in the multivariable model were those which were found to be significant in the univariable Cox model. Cumulative incidences of AKI, CKD, and ESRD of patients with AFL or Afib were obtained through Kaplan–Meier method and the difference was evaluated through the log-rank test. The analyses were operated via SAS 9.4 software (SAS Institute, Cary, NC, USA). The significance was not turned down if $P < 0.05$.

Results

Both cohorts were 17450 patients. Table 1 shows that the mean age (SD) of Afib and AFL patients was 69.3 (14.2) and 69.4 (14.8) years, respectively. The distribution of Afib and AFL patients did not differ on mean age and strata of age, sex, and comorbidity after propensity score matching.

Table 2 shows that Afib patients were 1.15 and 1.33 times more likely to experience CKD and ESRD, respectively, than AFL patients (incidence rate per 10,000 person-years (IR): CKD, 10.8 vs 9.41; ESRD, 4.44 vs 3.34), with the adjusted HRs of 1.18 and 1.32 (CKD, 95% CI = 1.07–1.30; ESRD, 95% CI = 1.12–1.55). Afib patients were also 1.08 times (95% CI = 1.01–1.16) more likely to have AKI than AFL patients after adjusting for the confounding covariates.

After adjustment for the associated confounding factors and consideration of the competing risk of death, Afib patients were 1.14 and 1.32 times more likely to experience CKD and ESRD than AFL subjects, with the adjusted SHRs of 1.18 (95% CI = 1.07–1.30) and 1.32 (95% CI = 1.12–1.55), respectively (Table 3). Afib patients were 1.08 times (95% CI = 1.01–1.15) more likely to have AKI than AFL individuals after adjusting for the covariates and consideration of the competing risk of death. Table 4 demonstrates that Afib patients were not more likely to die after AKI, CKD, or ESRD than AFL ones. Figure 1 shows that cumulative incidences of CKD and ESRD for Afib and AFL patients were significantly different (log-rank test: CKD, $P = 0.007$; ESRD, $P < 0.001$). However, cumulative incidences of AKI of Afib and AFL were not significantly different (log-rank test: AKI, $P = 0.1$).

Discussion

In this study from the Taiwan National Health Insurance research database, we included 17450 patients with either AFL or Afib, 1:1 propensity matched by age, sex,

Table 1 Baseline characteristics of hospitalized patients, by the presence of atrial fibrillation or atrial flutter, and after matching for propensity score

Variables	Atrial fibrillation (*N* = 17450)	Atrial flutter (*N* = 17450)	Standardized mean difference[a]
Age, year			
≤ 49	1822 (10.4)	1985 (11.4)	0.03
50–64	3838 (22.0)	3623 (20.8)	0.03
≥ 65	11790 (67.6)	11842 (67.9)	0.03
Mean ± SD	69.3 ± 14.2	69.4 ± 14.8	0.001
Sex			
Female	6298 (36.1)	6365 (36.5)	0.01
Male	11152 (63.9)	11085 (63.5)	0.01
Comorbidity			
Diabetes	4590 (26.3)	4466 (25.6)	0.02
Abnormal liver function	2747 (15.7)	2721 (15.6)	0.004
Hypertension	9588 (55.0)	9541 (54.7)	0.005
Hyperlipidemia	2206 (12.6)	2253 (12.9)	0.008
CAD	7084 (40.6)	7134 (40.9)	0.006
CHF	3669 (21.0)	3779 (21.7)	0.02
COPD	3290 (18.9)	3336 (19.1)	0.007
Autoimmune disease	1000 (5.73)	1028 (5.89)	0.007
Gout	1301 (7.46)	1361 (7.80)	0.01
PAD	746 (4.28)	767 (4.40)	0.006

[a] A standardized mean difference of ≤ 0.10 indicates a negligible difference between the two cohorts

CAD coronary artery disease, *CHF* congestive heart failure, *COPD* chronic obstructive pulmonary disease, *PAD* peripheral artery disease

comorbidity and index year. Compared to AFL patients, those with Afib had higher risks of AKI, CKD and ESRD.

The potential strength of this study is the large patient population that is identified and the high rate of national enrollment in this national registry. Moreover, the statistical method with propensity matching approach from this well-validated dataset makes the result highly reliable.

Atrial arrhythmia is associated with adverse renal outcomes in the general population and is one of the commonest conditions in patients at risk of renal function impairment [5–8]. However, comparison of the differential impact of AFL and Afib on renal outcomes is currently unavailable. In this respect, the present study is timely and addresses the important topic. The findings of this study are novel not only to compare the AFL and Afib with regard to the incidence of adverse renal outcomes, but also to explore the differential influence of AFL/Afib on the spectrum of kidney function deterioration; that is, AKI, CKD and ESRD. Afib was found to confer an increased risk of the above renal adverse outcomes as compared to AFL, even controlled for the competing risk of death. As a consequence, it does seem that the findings of this current work would translate in significant changes of the process of risk stratification currently suggested in the setting of renal management in patients with AFL/Afib.

In this study, while cumulative incidence of CKD and ESRD was significantly higher among Afib patients than among AFL patients, the cumulative incidence of AKI did not reach statistical significance. AKI could be more related to acute/subacute haemodynamic modifications that may be considered similar among the AFib/AFL. On the contrary, chronic renal impairment of any degree could be more affected by factors that need longer time to cause harm. Previous studies have found that Afib and CKD share potential mediators contributing to both conditions, such as a pro-oxidant state, increased activation of renin–angiotensin–aldosterone system, increased inflammatory markers [12–14]. Moreover, Afib promotes myocardial fibrosis and similar modifications could involve the kidney too [12–15]. The hypothesis of pathogenic mechanisms should still be verified by further studies.

The link between atrial arrhythmia and renal outcomes is clear [16–20]. Previous reports showed that age and medical comorbidity were associated with adverse outcomes in patients with AFL/Afib [1–4]. In this propensity score matched study, the underlying mechanism connecting atrial arrhythmia and renal adverse outcomes might beyond the medical comorbid diseases. Either structural or electrical remodeling is a possible factor for this observation [16–20]. The potential for higher incidence of adverse renal outcomes

Table 2 Incidence and hazard ratios (HRs) of acute kidney injury, chronic kidney disease, and end-stage renal disease in the atrial fibrillation cohort compared with the propensity score-matched atrial flutter cohort

Outcome	Atrial fibrillation ($N=17450$)	Atrial flutter ($N=17450$)
Acute kidney injury		
Follow-up time (year, Mean ± SD)	4.26 ± 3.69	4.39 ± 3.66
Event	1708	1660
Person-years	74365	76584
Rate[a]	23.0	21.7
Crude HR (95% CI)	1.06 (0.99, 1.13)	1 (Reference)
Adjusted HR[b] (95% CI)	1.08 (1.01, 1.16)*	1 (Reference)
Chronic kidney disease		
Follow-up time (year, Mean ± SD)	4.30 ± 3.69	4.44 ± 3.67
Event	812	729
Person-years	75154	77461
Rate[a]	10.8	9.41
Crude HR (95% CI)	1.15 (1.04, 1.27)**	1 (Reference)
Adjusted HR[b] (95% CI)	1.18 (1.07, 1.30)**	1 (Reference)
End-stage renal disease		
Follow-up time (year, Mean ± SD)	4.35 ± 3.70	4.48 ± 3.68
Event	337	261
Person-years	75,955	78,259
Rate[a]	4.44	3.34
Crude HR (95% CI)	1.33 (1.13, 1.56)***	1 (Reference)
Adjusted HR[b] (95% CI)	1.32 (1.12, 1.55)***	1 (Reference)

*$p<0.05$; **$p<0.01$; ***$p<0.001$

[a]Rate, incidence rate, per 10,000 person-years; crude HR, crude hazard ratio

[b]Covariables found significantly associated with acute kidney injury, chronic kidney disease, and end-stage renal disease in the univariable Cox proportional regression model were further examined by the multivariable Cox proportional regression model

Table 3 Incidence and subhazard ratios (SHRs) of acute kidney injury, chronic kidney disease, and end-stage renal disease in propensity score (PS)-matched cohorts, using the univariable and multivariable competing-risks regression models

Outcome	Competing-risks regression models	
	Atrial fibrillation ($N=17450$)	Atrial flutter ($N=17450$)
Acute kidney injury		
Crude SHR (95% CI)	1.05 (0.99, 1.13)	1 (Reference)
Adjusted SHR[a] (95% CI)	1.08 (1.01, 1.15)*	1 (Reference)
Chronic kidney disease		
Crude SHR (95% CI)	1.14 (1.03, 1.26)**	1 (Reference)
Adjusted SHR[a] (95% CI)	1.18 (1.07, 1.30)**	1 (Reference)
End-stage renal disease		
Crude SHR (95% CI)	1.32 (1.13, 1.56)***	1 (Reference)
Adjusted SHR[a] (95% CI)	1.32 (1.12, 1.55)***	1 (Reference)

Crude SHR, crude subhazard ratio

*$p<0.05$, **$p<0.01$, ***$p<0.001$

[a]Covariables found significantly associated with acute kidney injury, chronic kidney disease, and end-stage renal disease in the univariable competing-risks regression model were further examined by the multivariable competing-risks regression model

in patients that suffered from Afib is possibly related to many variables not considered in the present study. With the nature of observational retrospective study, the firm conclusion of any pathophysiological relation is difficult to draw. The link between atrial arrhythmia and kidney dysfunction could be further investigated, e.g., by analyzing features of patients who develop adverse renal outcomes, including confounding factors not considered in this study, to identify the group of

Table 4 Incidence and hazard ratios (HRs) of mortality after developing acute kidney injury, chronic kidney disease, or end-stage renal disease in the atrial fibrillation cohort compared with the propensity score-matched atrial flutter cohort

Outcome	Atrial fibrillation	Atrial flutter
After acute kidney injury		
Death	772	811
Rate[a]	35.4	38.3
Crude HR (95% CI)	0.92 (0.84, 1.02)	1 (Reference)
Adjusted HR (95% CI)[b]	0.95 (0.86, 1.05)	1 (Reference)
After chronic kidney disease		
Death	404	393
Rate[a]	29.1	31.8
Crude HR (95% CI)	0.93 (0.81, 1.06)	1 (Reference)
Adjusted HR (95% CI)[b]	0.96 (0.83, 1.10)	1 (Reference)
After end-stage renal disease		
Death	203	162
Rate[a]	34.4	36.8
Crude HR (95% CI)	0.96 (0.78, 1.19)	1 (Reference)
Adjusted HR (95% CI)[b]	1.05 (0.85, 1.29)	1 (Reference)

[a]Rate, incidence rate, per 100 person-years; crude HR, crude hazard ratio

[b]Covariables found significantly associated with mortality in the univariable Cox proportional regression model were further examined by the multivariable Cox proportional regression model

patients at highest risk of renal complications. The clinical relevance and importance are clear; that is, those with Afib had higher risks of AKI, CKD and ESRD. Physicians should be aware of this issue while caring for patients suffering from atrial arrhythmia, especially those with Afib. A tighter monitoring in patients with Afib and/or an early use of nephroprotective therapy might be a reasonable approach.

Limitations

First, AFL/Afib is a wide spectrum of conditions (i.e., persistent, paroxysmal, permanent AFL/Afib). Neither information with regard to the type of AFL/Afib nor the treatment options required was included in this investigation which might be a significant issue. Although it would be interesting to show any difference among them; based on the limitations of this dataset, it is not possible to show the results by these different conditions. Second, there were no data on AFL/Afib control or AFL/Afib duration. In addition, the study did not offer any data on oral anticoagulation in AFL/Afib patients, nor did the choice of rate control versus rhythm control among study groups. Third, since disease diagnosis was based on ICD coding, the quality of codification may affect the results of the study. Finally, residual confounding is possible because of the restriction of the database.

Conclusions

Afib conferred worse renal events of AKI, CKD and ESRD than AFL.

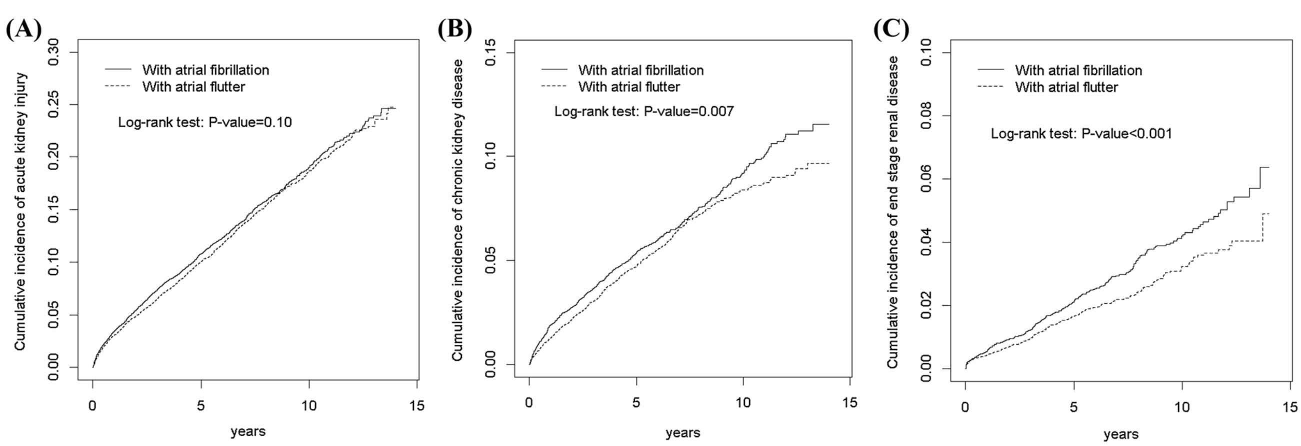

Fig. 1 Cumulative incidence curves of acute kidney injury (**a**), chronic kidney disease (**b**) and end-stage renal disease (**c**) for patients with atrial flutter (dashed line) or with atrial fibrillation (solid line)

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Statement of human and animal rights This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent None.

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