ORIGINAL ARTICLE

Electrocardiographic Findings of Atrial Abnormality as a Predictor of Major Adverse Cardiovascular Events in Non-Dialysis Chronic Kidney Disease

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Background: Electrocardiographic (ECG) evidence of atrial abnormality indicated by the abnormal P wave indices have been shown to be associated with an increased mortality in various cohorts. However, data in chronic kidney disease (CKD) patients are scarce.

Objective: To examine whether ECG findings of atrial abnormality can predict all-cause mortality in non-dialysis CKD patients.

Materials and Methods: The authors analyzed data from CORE-CKD (Thailand) Registry that enrolled patients with pre-dialysis CKD. All baseline ECG were reviewed to determine the pertinent ECG parameters such as atrial flutter or atrial fibrillation, P wave terminal force in lead V1 (PTFV1), maximal P wave duration, complete interatrial block, P wave axis, and PR interval. Cox regression analysis was utilized to estimate the prognostic value of all relevant ECG parameters for long-term survival.

Results: There were 253 patients who had interpretable baseline ECG and completed long-term outcome data. Median age was 65 years old and 60.8% were male. Median estimated glomerular filtration rate (eGFR) was 36.35 mL/minute/1.73 m^2, mostly were in CKD stage 3 or 4, and the major cause of CKD was diabetic nephropathy in 46.2%. During median follow-up of 58.4 months, 13 patients, or 5.1%, died. Cox regression analysis demonstrated that atrial arrhythmias or P wave indices such as PTFV1, maximal P wave duration, complete interatrial block, P wave axis, and PR interval, were not associated with increased risk of all-cause mortality.

Conclusion: The authors demonstrated that the ECG parameters indicating atrial abnormalities were not associated with increased risk of mortality in pre-dialysis CKD patients.

Keywords: Atrial abnormality; Chronic kidney disease; Electrocardiogram; P wave indices

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Chronic kidney disease (CKD) is acknowledged as one of the significant risk factors for the development of cardiovascular diseases through the process of systemic chronically proinflammatory state that contributes to vascular and cardiac remodeling processes, atherosclerotic lesions, aberrant calcification, and myocardial fibrosis[1]. Approximately, half of all fatalities in individuals with moderate to severe CKD are due to cardiovascular causes, compared to 26% of the normal kidney function group[2]. Leading cause of cardiovascular death in CKD results from atherosclerosis-related complications such as myocardial infarction, stroke, and heart failure[2,3]. Many therapeutic options for cardiovascular diseases are limited and less effective in advanced CKD stages. Developing user-friendly predictive tools could optimize early management of cardiovascular risk factors and enhance outcomes for CKD patients.

The 12-lead electrocardiography (ECG) is a commonly used, non-invasive, and inexpensive technology available in variety of healthcare settings, and it is suggested for the initial evaluation of every CKD patient according to current standard guidelines[4,5]. P wave indices, such as P wave duration, P wave terminal force in lead V1 or PTFV1, P wave axis, and PR interval, and atrial arrhythmia

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were ECG parameters that directly reflects atrial structure and electrical activity[6,7]. In fact, left ventricular (LV) dysfunction in CKD necessitates a higher left atrial (LA) pressure to maintain LV filling and is accompanied by LA remodeling[8]. In other words, atrial remodeling is a marker of more advanced cardiovascular disease, and evidence of atrial abnormality on an ECG may be associated with a poor prognosis.

Recent large cohort studies of middle-aged participants suggest some anomalous P waves may be linked to mortality, though the findings are inconclusive. However, PTFV1 values higher than 6,000 microvolt (μV) * milliseconds (ms) (μV*ms) are associated with increased risks of atrial fibrillation, heart failure, and death in the Finnish middle-aged population[9]. The National Health and Nutrition Examination Survey (NHANES) showed that a higher P wave duration in lead II, a negative P wave in V1, and an abnormal P wave axis, out of the range 0° to 75°, are associated with cardiovascular and all-cause mortality[10-12]. The Atherosclerosis Risk in Communities (ARIC) study found that a negative P wave in V1 can predict the risk of sudden cardiac death[13]. Additionally, the Framingham Heart Study reported that a PR interval longer than 200 ms is associated with higher risks of atrial fibrillation, pacemaker installation, and all-cause death, with a hazard ratio of 1.44 in 7,454 individuals[14]. However, several studies in this field had yielded negative results[15,16].

The predictability of survival outcomes based on atrial abnormality ECG findings is mostly derived from populations with normal kidney function, and data in CKD patients is scarce. The present study aimed to examine ECG findings of atrial abnormalities that can predict survival outcomes in non-dialysis CKD patients, to better understand the predictability of P wave indices in this population.

Materials and Methods

Data were extracted from the CORE-CKD Thailand Registry, a multicenter, non-interventional prospective cohort of CKD patients at high risk for cardiovascular events or renal disease progression. Informed consent was obtained from all enrolled patients at the start of the study. The registry was approved by the Central Research Ethics Committee (CREC: COA-CRE 004/2014) and the Institutional Review Board of Faculty of Medicine, Chiang Mai University (approval number 189/2022).

Inclusion criteria included non-dialysis CKD patients with an estimated glomerular filtration rate (eGFR) of less than 60 mL/minute/1.73 m², calculated by the Modification of Diet in Renal Disease (MDRD) equation, age over 18 years, and available and interpretable baseline 12-lead ECG. Exclusion criteria were patients with an eGFR of less than 15 mL/minute/1.73 m² or those undergoing renal replacement therapy, evidence of atrial fibrillation from baseline ECG, those with atrial pacing rhythm without intrinsic P waves on the baseline 12-lead ECG, and those with incomplete or unavailable follow-up data.

Definition

P wave terminal force in lead V1 (PTFV1):

PTFV1 is a product of depth in microvolt (μV) and duration in milliseconds (ms) of negative deflection of P wave in lead V1. Abnormal PTFV1 is defined as 4000 μV*ms or more[17,18].

Complete interatrial block:

Complete interatrial block or third-degree interatrial block is evidence of electrical impulse blocking in the upper and middle part of interatrial septum, in the Bachmann bundle zone, and/or in the upper part of LA, so that LA activation occurs from caudal to cranial direction via fibers in vicinity of coronary sinus. ECG criteria of complete interatrial block shows that (a) P-wave duration of 120 ms or more and (b) the morphology of P wave are usually bimodal in lead I and VL and biphasic (±) in leads II, III, and VF[19].

Maximal P wave duration:

To determine the maximal P wave duration, the authors assessed the P wave duration in each lead from the onset to offset of the P wave deflection using EP Caliber software, selecting the highest value. A total P wave duration of 120 ms or more, indicates prolonged atrial activation time[17].

P wave axis:

It is a measure of the net positive or negative P-wave deflection based on six limb leads, derived from ECG machine calculations. Abnormal P-wave axis is defines as any value outside 0° to 75°[19].

PR interval:

PR duration is the time from the beginning of the P wave to the onset of the QRS complex. The PR interval value was obtained from the ECG machine's computation. Abnormal PR interval is defined as 200 ms or more[20].

Data collection

Data were collected from the CORE-CKD

Thailand Registry between August 2014 and March 2019. Baseline demographic and clinical data were recorded, including CKD etiology such as diabetic nephropathy, hypertensive nephropathy, and glomerulonephritis, age, gender, body mass index, smoking and alcohol history, and history of various medical conditions such as diabetes, hypertension, coronary artery disease, atrial fibrillation, and chronic heart failure. Information on CHA_2DS_2-VASc scores[21] for congestive heart failure, hypertension, age of 75 years or older, diabetes mellitus with one point for each factor, and stroke/transient ischemic attack (TIA) with two points for each factor, for a scores range between 0 and 6, history of cardiac interventions, malignancy, and medications was also reviewed. Baseline laboratory results were recorded, including serum creatinine, eGFR, serum electrolytes, and low-density lipoprotein cholesterol (LDL-C).

Resting 12-lead ECG at baseline was performed and calibrated at voltage of 10 mm/mV and paper speed of 25 mm/second. The ECG parameters assessed in the present study included P wave indices in sinus rhythm for duration and voltage of negative part of P wave in V1 and PTFV1, maximal P wave duration, evidence of complete interatrial block, and P wave axis, PR interval, and evidence of atrial arrhythmia for atrial tachycardia and atrial fibrillation, which indicate atrial abnormalities. All quantitative parameters were manually measured by EP Calipers software, version 2.4.1 (EP Studios, Inc.) (41) and all ECG device measurement results were reviewed. To avoid inter-observer variation, there was only one ECG interpreter and recorder in the present study. The medical records of all enrolled patients were reviewed for long-term survival outcomes.

Statistical analysis

Categorical variables were presented as frequency and percentage. They were compared by using chi-square test. Continuous variables with normal distribution were presented as mean ± standard deviation (SD) and compared by using unpaired t-test. The non-normally distributed data were reported as median, interquartile range (IQR) and p-value. The data were compared by using Mann-Whitney U test. The univariable and multivariable analysis were analyzed by Cox regression analysis with pre-specified risk factors as age, history of smoking, history of alcohol consumption, coronary artery disease, cerebrovascular disease, diabetes mellitus, eGFR, and LDL-C. The multivariable analysis was analyzed by including the statistically significant variable at p value of less than 0.05 from the univariate analysis. A p-value of less than 0.05 was considered statistically significant. All statistical analyses were performed by IBM SPSS Statistics, version 29.0 (IBM Corp., Armonk, NY, USA) (241).

Results

Initially, the authors included 517 patients with interpretable ECG from the CORE-CKD Thailand Registry. After excluding individuals with incomplete long-term data, the final analysis consisted of 253 patients.

Baseline characteristics of the studied population

Baseline characteristics of the studied population are shown in Table 1. Median age was 65 years old, 88.9% of the study patients had underlying hypertension, 71.1% had dyslipidemia, about half (48.6%) had diabetes mellitus, and mean hemoglobin A1c (HbA1c) at baseline was 6.0%. Median serum creatinine was 1.78 mg/dL, median eGFR 36.35 mL/minute/1.73 m^2 and the majority were in stage 3 to 4 CKD. The most common cause of CKD among the study population was diabetic nephropathy in 46.2%, followed by hypertensive nephropathy at 32%. Glomerular diseases were the rarest cause.

Comparison of each characteristic between survivor and non-survivor group is demonstrated in Table 1. Majorities of baseline characteristics were not different between both groups. Non-survivors were likely to have higher prevalence of cerebrovascular diseases at 23% compared to 6.2% (p=0.05) and history of smoking at 61.5% compared to 33.8% (p=0.041) more than survivors. Low-density lipoprotein (LDL) levels were higher in non-survivor group than survivor group with median level of 123.0 compared to 95.0 mg/dL, respectively (p=0.023).

Median follow-up time was 58.4 months, with a range of 29.6 to 61.1 months. Eighteen patients (7.1%) were lost to follow-up. Additionally, 13 (5.1%) of the patients died during the follow up period with mean time to death of 33.02 months (range of 20.40 to 46.33 months).

ECG parameters of atrial activity

Table 2 demonstrated baseline ECG parameters in the study population and comparison between the survivor and non-survivor groups. The median heart rate was 72 beats per minute and RR interval was 833.33 ms. Most patients (96.8%) had normal sinus rhythm. There were only eight patients (3.2%) with history of atrial flutter or atrial fibrillation. There

Table 1. Baseline characteristics between survivors and non-survivors

	Total (n=253)	Survivors (n=240)	Non-survivors (n=13)	p-value
Age (years); median (IQR)	65.00 (59.00, 70.00)	65.00 (59.00, 70.00)	69.00 (60.00, 73.00)	0.167
Male sex; n (%)	154 (60.8)	145 (60.4)	9 (69.2)	0.772
Cause of CKD; n (%)				
ADPKD	16 (6.3)	16 (6.7)	0 (0)	1.000
Diabetic nephropathy	117 (46.2)	111 (46.3)	6 (46.2)	0.995
Hypertensive nephropathy	81 (32.0)	77 (32.1)	4 (30.8)	0.921
Glomerulonephritis	12 (4.7)	12 (5)	0 (0)	1.000
IgA nephropathy	8 (3.1)	8 (3.3)	0 (0)	1.000
FSGS	4 (1.5)	4 (1.7)	0 (0)	1.000
Renal stone disease	15 (5.9)	14 (5.8)	1 (7.7)	0.557
Tubulointerstitial disease	5 (1.9)	4 (1.7)	1 (7.7)	0.233
Hyperuricemia	67 (26.4)	64 (26.9)	3 (23.1)	0.759
Other causes	10 (3.9)	10 (4.2)	0 (0)	1.000
Underlying conditions; n (%)				
Diabetes mellitus	123 (48.6)	116 (48.3)	7 (53.8)	0.699
Hypertension	225 (88.9)	213 (88.8)	12 (92.3)	0.676
Dyslipidemia	180 (71.1)	172 (71.7)	8 (61.5)	0.530
Malignancy	16 (6.3)	16 (6.7)	0 (0)	1.000
Coronary artery disease	4 (1.6)	3 (1.2)	1 (7.6)	0.191
Cerebrovascular disease	18 (7.1)	15 (6.2)	3 (23.1)	0.05
Chronic heart failure	4 (1.6)	4 (1.7)	0 (0)	1.000
Atrial fibrillation	8 (3.2)	8 (3.3)	0 (0)	1.000
History of smoking; n (%)	89 (35.2)	81 (33.8)	8 (61.5)	0.041
History of alcohol consumption; n (%)	87 (34.4)	80 (33.3)	7 (53.8)	0.129
Body weight (kg); median (IQR)	67.00 (60.20, 77.00)	67.00 (60.50, 77.00)	71.35(55.25, 84.72)	0.947
Laboratory investigations; median (IQR)				
Serum creatinine (mg/dL)	1.78 (1.48, 2.22)	1.75 (1.47, 2.21)	1.79 (1.58, 2.85)	0.373
eGFR (mL/minute/1.73 m^2)	36.35 (28.00, 46.30)	37.00 (28.50, 46.80)	39.55 (22.46, 47.53)	0.609
LDL-C (mg/dL)	96.00 (80.50, 123.00)	95.00 (78.00, 121.50)	123.00 (102.50, 142.00)	0.023
HbA1c (mg/dL)	6.10 (5.50,7.30)	6.10 (5.50,7.25)	6.05 (5.30,7.68)	0.982
Medications; n (%)				
Aspirin	91 (35.9)	88 (36.7)	3 (23.1)	0.388
Beta blocker	85 (33.6)	78 (32.5)	7 (53.8)	0.112
ACEI	47 (18.6)	45 (18.8)	2 (15.4)	0.756
ARB	88 (34.8)	86 (35.8)	2 (15.4)	0.230
Statin	181 (71.5)	175 (72.9)	6 (46.2)	0.037

ACEI=angiotensin-converting enzyme inhibitors; ADPKD=autosomal dominant polycystic kidney disease; ARB=angiotensin receptor blockers; CKD=chronic kidney disease; eGFR=estimated glomerular filtration rate; FSGS=focal segmental glomerulosclerosis; HbA1c=hemoglobin A1c; IgA=immunoglobulin A; LDL-C=low-density lipoprotein cholesterol; IQR=interquartile range

was no statistically significant difference in ECG parameters between the survivor and non-survivor groups.

All P wave indices in patients with baseline sinus rhythm were shown and they were indistinguishable between both groups. Median PTFV1 was 3,262.70 μV*ms, median maximal P wave duration among the study population was 112 ms. Complete interatrial block was found in 24 (9.8%) patients. Median P wave axis was 54° and median PR interval was prolonged as 169 ms. The occurrence of predetermined abnormal P wave index values did not differ between the two groups.

Predictors of all-cause mortality

Table 3 presented the results of both univariable and multivariable Cox regression analyses, including predefined risk factors and ECG parameters of interest. In the univariable analysis, none of the ECG parameters, such as history of atrial arrhythmia for

Table 2. ECG parameters of atrial activity and survival outcome

	Total (n=253)	Survivors (n=240)	Non-survivors (n=13)	p-value
Heart rate (bpm); mean (IQR)	72.00 (65.00, 82.00)	72.00 (64.00, 81.25)	76.00 (70.50, 89.50)	0.083
RR interval (ms); mean (IQR)	833.33 (731.70, 923.08)	833.33 (738.48, 937.50)	789.47 (670.58, 852.14)	0.060
P wave indices (after excluding atrial flutter and atrial fibrillation)				
PTFV1 (μV*ms); mean (IQR)	3262.70 (2393.60, 4304.66)	3250.27 (2394.60, 4349.91)	3473.20 (1964.46, 4013.60)	0.941
PTFV1 >4,000 μV*ms; n (%)	70 (28.6)	67 (28.8)	3 (25)	0.823
Maximal P wave duration (ms); mean (IQR)	112.00 (103.00, 121.00)	112.00 (103.00, 128.00)	112.00 (103.00, 128.00)	0.978
Maximal P wave duration >120 ms; n (%)	74 (30.2)	69 (29.6)	5 (41.7)	0.466
Complete interatrial block; n (%)	24 (9.8)	23 (9.9)	1 (8.3)	0.924
P wave axis (°); mean (IQR)	54.00 (41.00, 67.00)	54.00 (41.00, 66.00)	56.00 (44.00, 72.00)	0.516
P wave axis out of 0° to 75°; n (%)	46 (18.8)	43 (18.5)	3 (25.0)	0.711
PR interval (ms); mean (IQR)	169.00 (155.00, 187.00)	169.00 (155.00, 187.00)	163.00 (146.00, 194.00)	0.735
PR interval >200 ms; n (%)	49 (20.0)	45 (19.3)	4 (33.3)	0.289

IQR=interquartile range; PTFV1=P wave terminal force in V1

Table 3. Predictors of all-cause mortality

Characteristics	Univariable analysis			Multivariable analysis		
	HR	95% CI	p-value	HR	95% CI	p-value
Age	1.05	0.97 to 1.14	0.213			
Sex	0.70	0.22 to 2.28	0.557			
CAD	4.03	0.52 to 31.02	0.181			
CVA	4.07	1.12 to 14.80	0.033*	2.83	0.53 to 15.14	0.224
Diabetes mellitus	1.35	0.45 to 4.01	0.593			
History of smoking	3.62	1.18 to 11.08	0.024*	3.10	0.73 to 13.10	0.124
History of alcohol consumption	2.57	0.86 to 7.67	0.090			
eGFR	0.99	0.94 to 1.04	0.743			
UPCI	1.17	0.98 to 1.39	0.079			
LDL	1.02	1.00 to 1.03	0.020*	1.02	1.02 to 1.30	0.026
ECG parameters						
Heart rate	1.05	1.01 to 1.09	0.022*	1.04	0.99 to 1.10	0.086
MRAT/AF	3.20	0.41 to 24.64	0.263			
PTFV1	1.00	1.00 to 1.00	0.739			
PTFV1 >4,000 μV*ms	1.19	0.39 to 3.64	0.751			
Maximal P wave duration	1.00	0.96 to 1.05	0.938			
Maximal P wave duration >120 ms	1.60	0.52 to 4.89	0.411			
Complete interatrial block	1.01	0.13 to 7.23	0.99			
P wave axis	1.01	0.98 to 1.04	0.455			
P wave axis out of 0° to 75°	1.31	0.36 to 4.78	0.678			
PR interval	1.00	0.98 to 1.02	0.803			
PR interval >200 ms	1.96	0.60 to 6.37	0.262			

AF=atrial fibrillation; CAD=coronary artery disease; CI=confidence interval; CVA=cerebrovascular disease; eGFR=estimated glomerular filtration rate; HR=hazard ratio; LDL=low-density lipoprotein cholesterol; MRAT=macro-reentrant atrial tachycardia; PTFV1=P wave terminal force in V1; UPCI=urine protein to creatinine index

* Factors which has p-value less than 0.05 in univariable analysis and include in multivariable analysis.

atrial flutter or atrial fibrillation, PTFV1, maximal P wave duration, evidence of complete interatrial block, P wave axis, and PR interval, were associated with survival outcomes in the study population, except for heart rate, which had a hazard ratio of 1.05 and a significant p-value of 0.022 (Table 3). Predefined risk factors associated with survival outcomes, with p-values less than 0.05, included cerebrovascular disease, history of smoking, and LDL-C levels.

In the multivariable analysis, heart rate, cerebrovascular disease, and history of smoking were no longer associated with survival outcomes. Only the LDL-C level emerged as an independent predictor of long-term mortality in the present study population, with an adjusted hazard ratio of 1.02 and a p-value of 0.026.

Discussion

The authors examined ECG findings of atrial abnormalities such as evidence of atrial arrhythmia and abnormal P wave indices, and long-term survival outcome among 253 CKD patients in CORE-CKD Thailand Registry. There was a comparable incidence of atrial arrhythmia and P wave index values between the survival and non-survival groups. Consequently, evidence of atrial arrhythmia and P wave indices could not predict survival outcomes in the study cohort.

Several cohort studies demonstrated that LA size from imaging studies in CKD patients were much higher than the normal population[22] and may predict all-cause mortality in patients with CKD of varying severity, independent from LV function[23-25]. However, the low sensitivity of the P wave index to detect LA enlargement, as demonstrated in several studies, may limit its clinical utility and applicability[26-29]. A misplaced ECG lead might compromise the precision of P wave indices such as PTFV1[30,31]. Intra-observer and inter-observer variation in measurement of any P wave index could also affect the accuracy.

In addition, CKD is a well-known systemic disease with several competing risks of death, such as metabolic derangements, endocrinopathies, anemia, bleeding tendencies, infections, and neurological complications[1,2,32]. These may attenuate predictivity effect of the authors interested in ECG parameters.

Nevertheless, the present study results contrast with those from other studies. Data from CADKID study[33], a prospective study of 165 consecutive non-dialysis CKD stage 4 and 5 patients, showed a higher prevalence of abnormal P wave indices compared to the present study, with an abnormal P wave duration of 55.7% versus 30.2% in the present study. Data from Deo et al.[34] demonstrated that a PR interval greater than 200 ms is associated with cardiovascular mortality. They enrolled 3,939 CKD participants from the Chronic Renal Insufficiency Cohort (CRIC) study, with a median follow-up of 90 months, during which 750 participants (19%) died. The discrepancy of the results may be due to the differences in CKD stages among the studies.

The present study had limitations. About half of the patients with baseline interpretable ECGs were excluded from the study analysis due to incomplete long-term data. The authors acknowledged that the small number of non-survivors, 13 patients, limited the statistical power to detect associations between ECG parameters and survival outcomes. A larger population and longer follow-up are warranted to elucidate the prognostic effect of ECG findings related to atrial abnormality. In addition, the authors did not exclude patients with cardiac diseases in the study. However, there were only a few patients with significant structural heart disease, including coronary artery disease, chronic heart failure, and paroxysmal atrial fibrillation in the studied population. Due to the fact that these cardiac conditions can influence atrial abnormalities, the authors adjusted for these confounding factors in the multivariate analysis, which revealed that none of the P wave indices could predict mortality in non-dialytic CKD patients. Furthermore, several other outcomes, including new-onset atrial fibrillation, heart failure, and stroke, are more directly linked to atrial abnormalities[35-38]. To elucidate the link between ECG parameters of atrial remodeling and these outcomes in CKD patients, more research is required. Additionally, the present study did not specify whether deaths were cardiac or non-cardiac, which may limit the ability to assess the true association of atrial abnormalities and their impact on survival.

Conclusion

The present study demonstrated that ECG parameters of atrial abnormalities were not associated with an increased risk of all-cause mortality in pre-dialysis CKD patients. Given the limited data in this field, the present study demonstrates the lack of association between ECG markers of atrial remodeling and survival outcomes.

What is already known about this topic?

Atrial abnormality was associated with higher cardiovascular outcome and cardiac death. However, there is still limited data in CKD patients.

What does this study add?

Detection of atrial abnormality by using ECG parameters in CKD patients may not be sensitive enough to predict future major adverse cardiovascular events.

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Authors' contributions

AP, KN performed statistical analysis, wrote the manuscript and tables. PG, PD, WW performed statistical analysis, the data analysis, and data interpretation. PG, TN collected and re-checked the data prior to the analysis. KN, WW designed the cohort, conception of the data analysis, data interpretation and critically revised the manuscript. All authors agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Data availability

The data that support the findings of the present study are available from the corresponding author upon reasonable request.

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Conflicts of interest

All authors have no conflict of interest to declare.

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