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Sequential changes in renal function and the risk of stroke and death in patients with atrial fibrillation

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ABSTRACT

Background: Renal dysfunction has been proposed for the risk factor for stroke and bleeding in atrial fibrillation (AF). The impact of changes in renal dysfunction over time and the relationship to stroke and bleeding risk in these patients remain unknown. We investigated sequential change in renal function (estimated glomerular filtration rate, eGFR) and the risk for clinical events (ischaemic stroke, death and major bleeding) over time in a cohort of 617 AF patients followed up for 2 years.

Methods: eGFR was estimated at baseline, 6 months and 12 months using three formulas (Modification of Diet in Renal Disease equation, MDRD, Chronic Kidney Disease Epidemiology Collaboration, CKD-EPI, and Cockcroft–Gault equation). Changes in eGFR and the risk for clinical events were analysed by Cox models, receiver operating curves (ROC), and Kaplan–Meier survival curves.

Results: When patients with eGFR ≤ 60 ml/min/1.73 m^2 were compared to patients with eGFR > 60 ml/min/1.73 m^2, there was an increase over time in stroke or death, or death, with impaired renal function (all $p < 0.05$). An *absolute decrease* in eGFR ≥ 15 ml/min/1.73 m^2 on Cockcroft–Gault and CKD-EPI and ≥25 ml/min/1.73 m^2 on MDRD were associated with an increased risk for stroke or death, death, and ischaemic stroke at 6 months (all $p < 0.05$), but not major bleeding. A *relative reduction* (decline of ≥25%) in eGFR was also an independent risk. ROC analysis showed that a relative reduction in eGFR ≥25% at 6 months and 12 months modestly predicted the occurrence of stroke or death in patients with AF (c-indexes: 0.57 to 0.61, $p < 0.05$).

Conclusion: In patients with AF, an absolute decrease in eGFR ≥ 15 ml/min/1.73 m^2 on Cockcroft–Gault and CKD-EPI, and ≥25 ml/min/1.73 m^2 on MDRD, or a relative reduction (≥25%) in eGFR, independently predicted the risk for the endpoints 'stroke or death', 'death' or (at 6 months) ischaemic stroke. Deteriorating renal function increases the risk of death in AF patients.

1. Introduction

Patients with renal dysfunction are at increased cardiovascular risk and mortality, including stroke [1,2]. Patients with chronic kidney disease and chronic dialysis are also at risk of developing atrial fibrillation (AF) and in such patients, the risk of ischemic stroke is particularly high, especially in the elderly [3–5].

Approximately 6–17% of patients with AF have chronic renal disease [6–8]. In the AnTicoagulation and Risk Factors in Atrial Fibrillation (ATRIA) study, 43% of patients had an estimated glomerular filtration rate (eGFR) <60 ml/min/1.73 m^2 [9]. In randomized clinical trials, AF patients with moderate renal impairment ranged from 15% to 21% [10–12]. With other comorbidities, such as heart failure, the rate of moderately or severely impaired renal function (eGFR ≤60 ml/min/1.73 m^2) could be much higher, rising to 47% [13]. Thus, the impact of renal dysfunction on the risk of AF and its complications (e.g. stroke, death, and bleeding) is of great concern.

In the ATRIA cohort, reduced eGFR at *baseline* was associated with a graded, increased risk for stroke and thromboembolism in patients with AF, even after adjustment for known risk factors for stroke [9]. AF patients with decreased eGFR also have significantly greater mortality and cardiovascular event rates [14]. In AF patients undergoing catheter ablation, renal dysfunction not only independently predicted the risk for the recurrence of AF [15], but also increased the risk for stroke and thromboembolism [16]. Based on one analysis from an anticoagulated clinical trial cohort, renal dysfunction has been proposed to provide additive predictive value to stroke risk stratification scores [16,17].

On the other hand, anticoagulant-related bleeding risk significantly increases with severe renal dysfunction [18]. Indeed, the risk of hemorrhagic stroke was twofold greater on warfarin therapy amongst AF patients on hemodialysis, compared to those without warfarin [19]. Frequent monitoring of renal function is recommended in AF patients, especially in those on novel oral anticoagulants [20]. However, prior

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studies investigating renal dysfunction and AF were based on using eGFR at baseline and its impact on the risk of future stroke.

Most importantly, renal (dys)function is not a static parameter, and changes over time [21]. The impact of changes in renal dysfunction over time and the relationship to stroke and bleeding risk in these patients remains unknown.

The objective of present study is to investigate the association between *sequential changes* in renal function (estimated glomerular filtration rate, eGFR) and the risk for clinical events (ischaemic stroke, death and major bleeding) over time in a cohort of 617 AF patients followed up for 2 years.

2. Methods

There were 1034 patients who were entered into this study at baseline, and complete renal function data (baseline, 6 months and 12 months—the specific focus of this substudy) were available for 617 patients with AF admitted to the PLA General Hospital between 1 November 2007 and 31 July 2010, a large teaching hospital with 4000 beds in Beijing, China. These 617 patients were eligible for this prospective study, and there were no significant differences compared to non-included patients (data not shown). Inclusion criteria were a pre-existing diagnosis of permanent, persistent, or paroxysmal AF, development of new-onset AF during their current admission (defined on having an ECG or Holter recording). Renal function was evaluated at baseline, 6 months, and 12 months. Two-year follow-up was performed to ascertain major clinical events (ischaemic stroke, all-cause death, and major bleeding).

Exclusion criteria were patients without complete clinical data, including clinical follow up and renal function, for example, patients who only had renal function on one or two of three time points (except missing values for death). Patients with rheumatic or infective valvular heart disease were excluded. Patients presenting with AF due to a transient cause (e.g. perioperative, electrocution disturbance, infection, etc.) were also excluded.

Patients were admitted with a primary diagnosis of AF or a major comorbid diagnosis (secondary diagnosis) of AF (International Classification of Disease, 9th Revision [ICD-9]/ International Classification of Disease, 10th Revision [ICD-10] codes 427.3, 427.31/I48). ICD-10 codes have been used since 2008 in the PLA General Hospital. We used our established hospital electronic databases to identify the clinical events during follow-up. Information on comorbidities and events were based on ICD-10 codes which defined comorbidities as summarized in the Webonly Supplement. The study was approved by the PLA General hospital Ethical Committee.

Stroke risk of the patients was assessed using the $CHADS_2$ score (one point each for the presence of congestive heart failure, hypertension, age 75 years or older, and diabetes mellitus; two points for history of stroke or transient ischaemic attack, TIA) and the CHA_2DS_2-VASc score (two points each for age 75 years or older and previous stroke/TIA; one point each for systolic heart failure, hypertension, diabetes mellitus, age 65–74 years, vascular disease and female gender) [22,23]. The HAS-BLED (one point each for the presence of uncontrolled hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile INR, age ≥ 65 years, and concomitant drugs (e.g. aspirin, non-steroidal anti-inflammatory drugs (NSAIDs) and alcohol use) was used to calculate bleeding risk [24].

2.1. Definitions of end points and risk factors

Given the nature of our 'real world' dataset, some deaths could have been due to (undiagnosed) stroke, since not all subjects had cerebral imaging or post-mortem studies. Thus, the primary outcome was defined as the composite of "stroke or death" during follow-up, especially since oral anticoagulation in AF reduces stroke (by 64%) and all cause mortality by 26% [25]. Secondary outcomes were as follows: death, ischaemic stroke, and major bleeding.

Ischaemic stroke was defined as a focal neurologic deficit of sudden onset diagnosed clinically by a neurologist and confirmed by CT or MRI imaging. Major bleeding was defined as an intracranial or extracranial haemorrhage or a decrease in the blood haemoglobin level of more than 2.0 g/dl, the need for a transfusion of 2 or more units of blood, the need for corrective surgery, or any combination of these events. A transient ischaemic attack (TIA) was defined as a focal neurologic deficit of sudden onset, lasting 24 h or less. Vascular disease was defined as coronary artery disease, peripheral vascular disease, or a previous thromboembolism other than stroke/TIA.

2.2. Definition of change in renal function

Renal function (eGFR) was estimated based on serum creatinine at baseline, 6 month, and 12 month. Three formulas to calculate eGFR were used, as follows:

i. Cockcroft–Gault equation [26], that is: (140-age) × weight (kg) × constant/serum creatinine in μmol/l, constant = 1.04 if female and 1.23 if male.
ii. Modification of diet in renal disease (MDRD) equation [27], that is: eGFR = 186 × [serum creatinine in μmol/l × 0.011]$^{(-1.154)}$ × age$^{(-0.203)}$ × [0.742 if female] × 1.233, 1.233 is the adjusting coefficient for Chinese.
iii. CKD Epidemiology Collaboration (CKD-EPI) equation [28], as follows: Female: 141 × min (serum creatinine in mg/dl/0.7)$^{(-0.329)}$ × max (serum creatinine in mg/dl/0.7)$^{(-1.209)}$ × 0.993^{Age} × 1.018. Male: 141 × min (serum creatinine in mg/dl/0.9)$^{(-0.411)}$ × max (serum creatinine in mg/dl/0.9)$^{(-1.209)}$ × 0.993^{Age}.

The sequential changes in eGFR at 6 months and at 12 months were calculated as the absolute difference and the relative difference. The '*absolute difference*' was defined as the (eGFR at 6 months − eGFR at baseline), or the (eGFR at 12 months − eGFR at baseline). The '*relative difference*' was (eGFR at 6 months − eGFR at baseline)/eGFR at baseline, or (eGFR at 12 months − eGFR at baseline)/eGFR at baseline.

2.3. Statistical analysis

Means and standard deviations (SD) or medians and interquartile ranges (IQR) were calculated for continuous variables as appropriate. Frequencies and percentages were calculated for categorical variables. *T*-test was used for continuous variables with normal distribution or, for log transformed variables with a non-normal distribution. Categorical variables were analysed using chi-square tests. A detailed description of our statistical analysis is provided in Webonly Supplement A. p value of <0.05 was considered as statistically significant. All analyses were performed using IBM SPSS Statistics version 19.0 (SPSS, Inc., Chicago, Illinois).

3. Results

Among the 617 patients with AF who had the indices of renal function documented at baseline, 6 months and 12 months, 12% had renal dysfunction (eGFR ≤ 60 ml/min/1.73 m^2) at baseline using the MDRD formula. There were 67 (11%) on warfarin, who were younger and had less heart failure, coronary artery disease, chronic obstructive pulmonary disease, and prior major bleeding, compared to those without warfarin (n = 550, all $p < 0.05$) (Table 1). Overall, serum creatinine levels increased over time, as shown in Webonly Table w4.

In patients at low risk with a CHA_2DS_2-VASc score = 0, there were no patients with eGFR ≤60 ml/min/1.73 m^2 based on the three formulas (Cockcroft–Gault, MDRD, and CKD-EPI). With the increasing $CHADS_2$, CHA_2DS_2-VASc and HAS-BLED risk scores, the proportion of patients with eGFR ≤60 ml/min/1.73 m^2 increased (Webonly Figure w1).

3.1. Correlates of changes in eGFR over time and subsequent events stratified by decline in eGFR/stable eGFR

There were significant differences in mean absolute difference and mean relative change in eGFR in AF patients at 6 months and 12 months, showing that overall renal function in our AF patient cohort progressively reduced over time (Table 2). Multivariate analysis demonstrated that female gender, hypertension and diuretic use were independently associated with a decrease in eGFR, whilst statin use was marginally protective (Table 3, all data not shown). Low baseline eGFR was strongly related to mean absolute difference and relative change in eGFR on all three formulas (Table 3). Age and BMI were not independent risk factors for change in eGFR.

The incidence rates of clinical adverse events (stroke or death, death, ischaemic stroke, and major bleeding) in AF patients with a decline in eGFR, and those with relatively stable eGFR at 6 months are shown in Fig. 1 and Webonly Figure w2. Additional details of the numbers of events related to the relative or absolute decline in renal function are shown in Webonly Table w5. Those patients with a decline in eGFR at 6 month had higher incidence rates of the composite endpoint of stroke or death and all-cause death (Fig. 1, Webonly Figure w2).

When patients with eGFR ≤60 ml/min/1.73 m^2 were compared to patients with eGFR > 60 ml/min/1.73 m^2, there was an increase over time in stroke or death, or death (but not ischaemic stroke or major bleeding) with impaired renal function even after adjustment for the influencing factors on the change in eGFR (Table 4, Webonly Table w1, Fig. 2).

3.2. Adjusted hazard ratios for stroke or death related to change in eGFR

An absolute decrease in eGFR ≥15 ml/min/1.73 m^2 on Cockcroft–Gault and CKD-EPI (Webonly Table w2) and ≥25 ml/min/1.73 m^2 on MDRD (Table 5) were associated with an increased risk for stroke or