Original Article

Whether Warfarin Therapy is Associated with Damage on Renal Function in Chinese Patients with Nonvalvular Atrial Fibrillation

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Abstract

Background: Warfarin is the most common oral anticoagulant to decrease the stroke risk associated with atrial fibrillation (AF). There are very few prospective studies that have explored whether warfarin has an association with damage on renal function in Chinese patients with nonvalvular AF (NVAF). The aim of this study was to evaluate the effects of warfarin on renal function and study the factors associated with kidney dysfunction in Chinese adult NVAF patients without dialysis therapy.

Methods: From January 2011 to December 2013, a total of 951 NVAF patients from 18 hospitals were enrolled. The estimated glomerular filtration rate (eGFR) was calculated from baseline and follow-up serum creatinine levels. Kaplan–Meier survival curves compared the survival of a ≥25% decline in eGFR (hereafter, endpoint), while Cox models estimated hazard ratios (*HR*s) and 95% confidence intervals for this event after adjustment for age, gender, and selected potential risk factors for renal dysfunction. Cox regression analysis of the various clinical potential variables was performed to identify the predictors of a ≥25% decline in eGFR.

Results: After a 58-month follow-up, 951 NVAF patients were divided by observation into warfarin (n = 655) and no anticoagulation groups (n = 296) and 120 (12.6%) patients experienced renal endpoint. Kaplan–Meier survival curves showed that the survival period was not different in the two groups (χ^2 = 0.178, log-rank P = 0.67), but patients with systolic blood pressure (SBP) <140 mmHg have significant difference with patients with SBP ≥140 mmHg (χ^2 = 4.903, log-rank P = 0.03). Multivariate Cox regression analysis revealed baseline eGFR and SBP as independent predictors of the endpoint, with *HR*s of 1.00, and 1.02, respectively.

Conclusion: In patients with NVAF, eGFR and SBP are associated with the deterioration of kidney function while Warfarin is not the risk factor of the ≥25% decline in eGFR.

Trial Registration: Chinese Clinical Trial Registry (No. ChiCTR-OCH-13003729); http://www.chictr.org.cn/showproj.aspx?proj = 5831.

Key words: Anticoagulation; Estimated Glomerular Filtration Rate; Nonvalvular Atrial Fibrillation; Renal Function; Warfarin

Introduction

Atrial fibrillation (AF) is one of the most common cardiac arrhythmias and causes a 5- to 7-fold increased risk of ischemic stroke and mortality.[1,2] The prevention of thromboembolism using warfarin is the cornerstone of AF management. Although warfarin is the most commonly prescribed oral anticoagulant worldwide since 1950,[3] and despite the strong evidence of stroke prevention in patients with nonvalvular atrial fibrillation (NVAF),[4] it remains underused in the real world, particularly China.

The common known reasons for warfarin underuse include a narrow therapeutic window, multiple interactions with a variety of common medicines and foods and inconsistent pharmacokinetics and pharmacodynamics that can cause hemorrhage.[5] In addition, specific warfarin-related renal damage has recently garnered attention[6-8] and has been reported in patients with or without chronic kidney disease,[8] further preventing its use in AF patients.

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On the other hand, a retrospective study[9] revealed that long-term warfarin therapy for as long as 18 months delays the deterioration of kidney function and achieves a longer survival time in older patients with CKD and AF. The effects of warfarin on the kidneys reportedly involve not only renal tubular obstruction by red blood cell, but also other potential mechanisms, such as oxidative stress damage to the renal tubules, inhibition of the activation of growth arrest-specific gene 6 products to protect the kidney.[9,10] Warfarin, a Vitamin K antagonist, has been proven to inhibit glomerular mesangial cells by interfering with the activation of growth arrest-specific gene 6 products,[11,12] which stimulates glomerular mesangial cell proliferation and hypertrophy.[13] However, because of the lack of prospective studies, the effects of warfarin on renal function in NVAF patients remain unclear. Therefore, we conducted this prospective study to evaluate the effects of warfarin on renal function and explore the factors associated with kidney dysfunction in adult patients with electrocardiography-detected NVAF and no dialysis therapy.

Methods

Study population

From January 2011 to December 2013, 951 NVAF patients from 18 hospitals led by Beijing Anzhen Hospital were enrolled. All patients in the study were screened according to the following criteria: diagnosis of NVAF, no history of anticoagulant therapy before enrolment and available baseline, and multiple follow-up serum creatinine (SCr) levels. Patients with consumption of warfarin or no anticoagulant for <3 months, metastatic cancer, dementia, cirrhosis, renal failure caused by end-stage renal disease or requiring dialysis, previous hemorrhagic disease, and/or peptic ulcers were excluded.

This prospective observational cohort study was approved by the Ethics Committee of Beijing Anzhen Hospital, constituted in accordance with the National Health and Medical Research Council guidelines.

The risk of stroke was estimated using the $CHADS_2$ (C - cardiac failure, H - hypertension, A - age ≥75 years, D - diabetes mellitus, and S - stroke) score[14] derived as follows: congestive heart failure (CHF) (1 point), hypertension (1 point), age ≥75 years (1 point), diabetes mellitus (1 point), and previous stroke or TIA (2 points).

Measurements of kidney function

To assess the estimated glomerular filtration rate (eGFR), SCr levels of all eligible patients were measured at baseline and at 3, 6, 12, 18, and 24 months, up to the end of the observation period. All eGFR values available from enrollment to the end of the observation period were included in our calculations. At least two SCr values were required to estimate a decline in eGFR. eGFR was calculated using the modified glomerular filtration rate estimating equation for Chinese patients:[15] $eGFR\ (ml \cdot min^{-1} \cdot 1.73\ m^{-2}) = 186 \times (SCr\ [\mu mol/L] \times 0.0113)^{-1.154} \times age^{-0.203} \times 0.742$ (if female) × 1.233 (if Chinese). The decrease ratio was calculated as follows: (first eGFR − last eGFR)/(first eGFR) × 100%.

Follow-up

The study endpoint was a ≥25% decline in eGFR from baseline during the follow-up period, which suggested the deterioration of renal function according to The National Kidney Foundation's KDIGO guidelines of 2012.[16] The patients having taken warfarin were monitored for their international normalized ratio (INR) values at least every 2 weeks for the first 3 months and at least monthly thereafter, with an INR target of 2–3. All patients were followed every 3–6 months at the cardiology clinic or by telephone, and their data were recorded under strict surveillance. All outcomes were reviewed and classified by a committee.

Statistical analyses

All analyses were conducted using SAS 9.2 version (SAS Institute, Cary, NC, USA). Data are expressed as mean ± standard deviations (SDs) for normally distributed continuous variables and as proportions for categorical variables. Baseline values and time-independent outcomes were compared between the two groups using Chi-square tests (for categorical data) or two-sample independent *t*-tests (for continuous data). Kaplan–Meier survival curves were plotted to compare a ≥25% decline in eGFR. Log-rank tests were used to determine statistical significance (set at $P < 0.05$). Univariate and multivariate Cox regression analyses of the various clinical variables were performed to identify the predictors of a ≥25% decline in eGFR. Stepwise models of the candidate variables were used to determine the final variables for inclusion in the multivariate models; these included variables with a $P < 0.2$ in univariate analysis and clinically relevant variables such as age, gender, hazard ratio (*HR*), systolic blood pressure (SBP) ≥140 mmHg (1 mmHg = 0.133 kPa), $CHADS_2$ score and history of AF ablation, stroke/transient ischemic attack (TIA), hypertension, diabetes, CHF, coronary heart disease (CHD), hypertrophic cardiomyopathy, dilated cardiomyopathy, smoking, β-blocker use, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker use, and statin use. A value of $P < 0.05$ was considered statistically significant.

Results

Baseline characteristics

By the end of December 2013, a total of 951 AF subjects were enrolled in the study. The eligible patients were then divided by observation into a warfarin group with 655 (68.9%) patients and a no anticoagulation group with 296 (31.1%) patients.

The baseline characteristics of patients in the two groups were shown in Table 1. The patients in the no anticoagulation group were older than those in the warfarin group. The level of SBP, number of SBP ≥140 mmHg, and $CHADS_2$ scores were lower in the warfarin group than those in no anticoagulation group. Moreover, the number in a history of CHF, hypertension, diabetes, stoke/TIA, and CHD were

Table 1: Baseline characteristics of NVAF patients receiving warfarin therapy and those without any anticoagulation therapy

Variables	Warfarin (n = 655)	No anticoagulants (n = 296)	Statistical values	P
Age (years)	63.0 ± 11.4	71.8 ± 12.8	–10.16*	<0.0001
Female, n (%)	254 (38.8)	107 (36.2)	0.60†	0.4390
Current/ex-smoker, n (%)	224 (34.4)	100 (33.9)	0.02†	0.8780
BMI (kg/m^2)	25.8 ± 3.7	25.1 ± 3.7	2.71*	0.0070
Scr (μmol/L)	80.0 ± 21.2	86.5 ± 28.1	5.34*	0.0010
eGFR (ml·min^{-1}·1.73 m^{-2})	107.7 ± 49.0	102.2 ± 63.7	–3.51*	0.1870
Hypercholesteremia, n (%)	312 (47.6)	148 (50.0)	0.46†	0.4990
Heart rate (beats/min)	83.3 ± 22.9	84.7 ± 26.2	–0.75*	0.4530
SBP (mmHg)	126.7 ± 16.4	131.3 ± 18.0	–3.93*	<0.0001
DBP (mmHg)	77.2 ± 10.3	77.3 ± 12.1	–0.08*	0.9360
SBP ≥140 mmHg, n (%)	142 (21.7)	101 (34.2)	16.85†	<0.0001
Comorbidities, n (%)				
CHF	147 (22.4)	129 (43.6)	44.22†	<0.0001
Hypertension	367 (56.0)	221 (74.7)	29.99†	<0.0001
Diabetes	145 (22.1)	100 (33.8)	14.46†	0.0001
Stoke/TIA	98 (15.0)	71 (24.0)	11.36†	0.0007
CHD	83 (12.7)	87 (29.4)	38.82†	<0.0001
Respiratory disease	59 (9.0)	53 (18.0)	15.56†	<0.0001
HCM	12 (1.8)	2 (0.7)	1.90†	0.2470
DCM	8 (1.2)	1 (0.3)	1.70†	0.2880
$CHADS_2$	1.4 ± 1.2	2.4 ± 1.4	–7.95*	<0.0001
History of AF ablation, n (%)	40 (6.1)	7 (2.4)	6.05†	0.0140
Medications, n (%)				
Asprin/clopidogrel	43 (6.6)	220 (74.3)	467.85†	<0.0001
ACEI/ARBs	259 (39.5)	142 (48.0)	5.94†	0.0150
β-blocker	298 (45.5)	158 (53.4)	5.08†	0.0240
Statin	218 (33.3)	143 (48.3)	19.55†	<0.0001
Antiarrhythmics	327 (49.9)	65 (22.0)	65.80†	<0.0001

Data are presented as mean ± SDs or n (%). *: t values; †: χ^2 values; NVAF: Nonvalvular atrial fibrillation; BMI: Body mass index; eGFR: Estimated modified glomerular filtration rate; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; AF: Atrial fibrillation; SCr: Serum creatinine; CHF: Congestive heart failure; TIA: Transient ischemic attack; CHD: Coronary heart disease; HCM: Hypertrophic cardiomyopathy; DCM: Dilated cardiomyopathy; $CHADS_2$: C - Cardiac failure, H - hypertension, A - Age ≥75 years, D - Diabetes mellitus, S - Stroke; ACEI: Angiotensin-converting enzyme inhibitor; ARBs: Angiotensin receptor blockers; SDs: Standard deviations.

less in the warfarin group than those in no anticoagulation group. There were no significant differences in gender, eGFR and diastolic blood pressure values, a history of hypercholesterolemia, and β-blocker use between the two groups. The use of statins and renin–angiotensin system inhibitors was more frequent in the no anticoagulation group, while the use of antiarrhythmics was more frequent in the warfarin group.

Renal endpoint

After an average of 19.8 ± 10.8 months' follow-up, 120 (12.6%) patients experienced renal endpoint. There was no significant difference of ≥25% decline in eGFR between the warfarin group and the anticoagulation group [11.9% vs. 14.2%, log-rank P = 0.673, Figure 1]. But a Kaplan–Meier curve showed a significant difference in renal endpoint between patients with SBP <140 mmHg and SBP ≥140 mmHg [χ^2 = 4.903, log-rank P = 0.027, Figure 2].

Predictors of the renal endpoint

In univariate Cox regression analysis, variates of female, eGFR, SBP, SBP ≥140 mmHg, and hypertension,

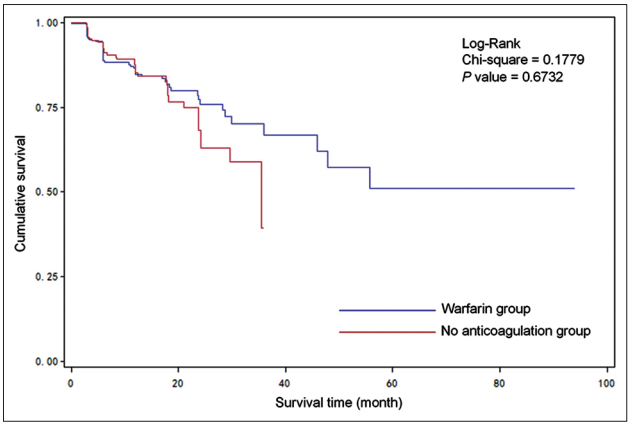

Figure 1: Kaplan–Meier survival curve for time to a ≥25% decline in estimated glomerular filtration rate in nonvalvular atrial fibrillation patients receiving warfarin therapy and those without any anticoagulant therapy.

respectively, predicted the incidence of ≥25% decrease in eGFR in NVAF patients. Multivariate Cox regression analyses [Table 2] revealed eGFR and SBP as independent predictors of a ≥25% decline in eGFR, with warfarin

therapy found not to be a risk factor for this renal endpoint in NVAF patients.

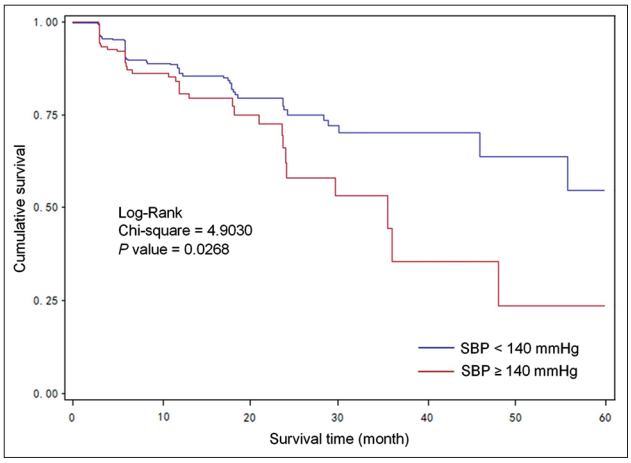

Figure 2: Kaplan–Meier survival curve for time to a ≥25% decline in estimated glomerular filtration rate in nonvalvular atrial fibrillation patients' systolic blood pressure <140 mmHg and those systolic blood pressure ≥140 mmHg ($P < 0.05$).

Table 2: Univariate and multivariate Cox proportional hazard regression analyses for a ≥25% decline in eGFR

Covariates	Hazard ratio (95% *CI*)	*P*
Univariate analysis		
Warfarin	0.92 (0.63–1.35)	0.6754
Age	1.01 (1.00–1.03)	0.0850
Female	1.50 (1.05–2.14)	0.0275
BMI	0.97 (0.92–1.02)	0.2659
Current/ex–smoker	0.72 (0.48–1.10)	0.1261
eGFR	1.00 (1.00–1.01)	<0.0001
Heart rate	1.01 (1.00–1.01)	0.0680
SBP	1.02 (1.01–1.02)	0.0028
SBP ≥140 mmHg	1.55 (1.00–2.41)	0.0485
CHF	1.32 (0.91–1.91)	0.1457
Hypertension	1.57 (1.03–2.41)	0.0366
Diabetes	1.35 (0.92–1.99)	0.1243
Stroke/TIA	0.77 (0.48–1.24)	0.2845
CHD	0.96 (0.60–1.53)	0.8702
HCM	0.95 (0.55–1.64)	0.8609
DCM	2.67 (0.98–7.27)	0.0539
$CHADS_2$	1.08 (0.94–1.25)	0.2668
History of AF ablation	1.38 (0.60–3.13)	0.4484
ACEI/ARBs	1.29 (0.90–1.84)	0.1670
Statin	1.10 (0.76–1.59)	0.6017
Antiarrhythmics	1.00 (0.69–1.45)	0.9961
Multivariable analysis		
eGFR	1.00 (1.00–1.01)	<0.0001
SBP	1.02 (1.01–1.03)	0.0007

CI: Confidence interval; BMI: Body mass index; eGFR: Estimated modified glomerular filtration rate; SBP: Systolic blood pressure; SCr: Serum creatinine; CHF: Congestive heart failure; TIA: Transient ischemic attack; CHD: Coronary heart disease; HCM: Hypertrophic cardiomyopathy; DCM: Dilated cardiomyopathy; $CHADS_2$: C - Cardiac failure, H - Hypertension, A - Age ≥75 years, D - Diabetes mellitus, S - Stroke; ACEI: Angiotensin-converting enzyme inhibitor; ARBs: Angiotensin receptor blockers.

Discussion

The long-term follow-up of NVAF patients without dialysis therapy revealed that warfarin therapy had no relation to increase the risk of a ≥25% decline in eGFR compared with no anticoagulation. Furthermore, after adjustment for potential clinical risk factors for renal dysfunction, baseline eGFR and SBP were found to be the risk factors associated with the deterioration of kidney function in Chinese NVAF patients.

Despite its relatively unpredictable response, narrow therapeutic range and drug interactions, warfarin is the most widely prescribed oral anticoagulant for patients with AF, deep vein thrombosis or thrombi in other vascular beds, and antiphospholipid syndrome or a cardiac valve replacement. Bleeding is the major adverse effect of warfarin therapy, but other nonhemorrhagic adverse reactions such as warfarin-induced allergic interstitial nephritis and warfarin-related nephropathy are also being reported.[6,11] Though there are many reports of renal damage caused by anticoagulation with warfarin,[6-9] Chang *et al*.[9] conducted a retrospective study and found that after controlling for INR (1.95 ± 1.01; goal, 2–3) and adjusting for potential confounders, warfarin therapy over 18 months could decrease the rate of deterioration of kidney function in older patients with CKD and AF.

To our knowledge, there is no prospective study demonstrating whether or not warfarin therapy is associated with damage of renal function in Chinese NVAF patients. After following a large number of patients and adjusting all potential risk factors for renal dysfunction in Cox regression model, we discovered that warfarin was not associated with the deterioration of renal survival duration of NVAF patients. In this respect, the results of our prospective study were different from known previous studies.

Even though our study was a prospective observational study, it was difficult to control factors at baseline and after treatment initiation in the two groups. The patients in the no anticoagulation group exhibited more severe clinical features compared with those in the warfarin group, such as an older age, higher SBP values and more comorbidities, all of which may confuse the possible effects of warfarin on kidney function. Therefore, appropriate statistical analyses methods for long-term follow-up data were indispensable to evaluate the renal outcomes and treatment effectiveness,[17] and an effective multivariate Cox model was considered essential for our study. After adjusting for all confounding factors in multivariate Cox regression analyses, we observed that baseline eGFR and SBP were risk factors associated with kidney dysfunction and/or aggravated its deterioration in NVAF patients. In a prospective cohort study of type 2 diabetic mellitus, SBP is one of the most powerful independent risk factors for a rapid renal function decline.[18] In our prospective study, warfarin was not associated with the risk of a ≥25% decline in eGFR. Warfarin effect on kidney function is underlying and to be studied further.

This study has several limitations. First, the number of patients in the current study was not large enough with inevitable confounding factors; therefore, the association between warfarin therapy and exacerbation in renal function may not be causal. Second, the follow-up period and number of patients with renal dysfunction were limited. Renal function deterioration may take decades in patients with earlier stages of kidney disease.[19] The long follow-up period and large number of patients with renal dysfunction may influence the significance of our results in future. Third, as an important risk factor for cardiovascular disease and impaired renal function, proteinuria values were missing and not included for the study. Further studies are necessary to discover the effects of warfarin therapy and no anticoagulant therapy with regard to different degrees of renal function deterioration in NVAF patients.

In conclusion, the results of our study of a Chinese cohort suggest that baseline eGFR and SBP are associated with the deterioration of kidney function while Warfarin is not the risk factor associated with kidney function deterioration in NVAF patients without dialysis therapy.

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Conflicts of interest

There are no conflicts of interest.

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