Clinical and Applied Thrombosis/Hemostasis
Volume 26: 1-8

DOI: 10.1177/1076029620910808
journals.sagepub.com/home/cat
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Association Between the Change in Total Bilirubin and Risk of Bleeding Among Patients With Nonvalvular Atrial Fibrillation Taking Dabigatran

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Abstract

There is still a lack of effective biomarkers for the prediction of the risk of bleeding events among patients with nonvalvular atrial fibrillation (NVAF) taking dabigatran. This study aimed to investigate the association between change in total bilirubin (CTBIL) and risk of bleeding among patients with NVAF taking dabigatran. The CTBIL was the difference in serum total bilirubin at out of follow-up from baseline serum total bilirubin. A total of 486 patients with NVAF treated with dabigatran (110 mg twice daily) were recruited from 12 centers in China from February 2015 to December 2017. All patients were followed for 3 months. Cox proportional hazards regression analysis was used to evaluate the association between the CTBIL and bleeding. Moreover, a Cox proportional hazards regression with cubic spline functions and smooth curve fitting (the penalized spline method) and 2 piecewise Cox proportional hazards models were used to address the nonlinearity between CTBIL and bleeding. The mean (SD) follow-up duration was 81.2 (20.2) days. In all, 67 patients experienced bleeding events. A U-shaped association was observed between the CTBIL and bleeding, with increased hazard ratios (HRs) in relation to either low or high CTBIL levels. For CTBIL <6.63 μmol/L, the HR (95% confidence interval [CI]) was 0.90 (0.84-0.96), and for CTBIL ≥6.63 μmol/L, the HR (95% CI) was 1.35 (1.14-1.60). Our findings showed a U-shaped relationship between CTBIL and bleeding. Both low and high levels of CTBIL were associated with a higher risk of bleeding.

Keywords

total bilirubin, atrial fibrillation, dabigatran, bleeding, real-world study

Date received: 19 December 2019; revised: 05 February 2020; accepted: 10 February 2020.

Introduction

Atrial fibrillation (AF) has become a significant cause of increased risk of stroke, sudden death, and cardiovascular morbidity worldwide.[1,2] The key in the management of patients with AF is to prevent the occurrence of stroke and thromboembolic events.[3] A large amount of evidence also suggests that new oral anticoagulants (NOACs), such as dabigatran, which is a direct thrombin inhibitor, are convenient and safe alternatives to vitamin K antagonists.[4] However, NOACs substantially reduce the risk of stroke and thromboembolic events with an inherent increased bleeding risk. The RE-LY study showed that the rate of major or minor bleeding was 14.62% per year in patients with nonvalvular atrial fibrillation (NVAF) taking dabigatran (110 mg twice daily).[5] At present, the risk of bleeding during anticoagulation in patients with AF can be assessed by the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation[6] and Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile international normalized ratio, Elderly (>65 years), Drugs/alcohol concomitantly (HAS-BLED)[7] scores, which are mainly

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based on clinical risk factors. However, the risk factors for bleeding and stroke overlap to a large extent. Therefore, it is necessary to find independent risk indicators to evaluate the risk of bleeding events in patients with NVAF.

Serum bilirubin, the catabolic product of the heme catabolic pathway, has long been used as a biomarker for hepatic metabolic and excretory capacity.[8] Elevated serum bilirubin is a biomarker not only for cholestasis but also for hepatocellular liver diseases.[9] However, there is now an increasing number of observational epidemiological studies showing that mildly increased serum bilirubin concentration might act as a powerful chain-breaking antioxidant and anti-inflammatory agent in the biological systems, contributing to plasma, tissue protection, and cellular protection, and thereby contributing to the prevention of the development and progression of cardiovascular disease (CVD) and other diseases associated with enhanced oxidative stress.[10] Experimental evidence has shown that modestly hyperbilirubinemia has beneficial effects on the prevention of CVD, metabolic syndrome, and type 2 diabetes mellitus.[8] To our knowledge, no study has examined the association of both low and high levels of changes in total serum bilirubin with bleeding in patients with NVAF; therefore, we performed a prospective cohort study to investigate the relationship between the changes in total serum bilirubin and bleeding in patients with NVAF treated with dabigatran (110 mg twice daily).

Methods

Study Design and Population

The study population was drawn from the Monitor System for the Safety of Dabigatran Treatment (MISSION-AF; ClinicalTrials.gov Identifier: NCT02414035). The MISSION-AF was a multicenter, prospective, and observational study conducted from February 2015 to December 2017. The trial was conducted at 12 study sites in China. The institutional review board of each participating study site approved the study. All the patients provided written informed consent. Data collection utilized an electronic data capture system, and the data were reviewed regularly throughout the trial by an independent data and safety monitoring committee. The inclusion criteria were as follows: (1) the patient was aged $\geq$18 years; (2) the patient was diagnosed with NVAF based on the 2014 American Heart Association/American College of Cardiology/Heart Rhythm Society guidelines for the management of patients with AF[11]; (3) the patient had a CHA_2DS_2-VASc score $\geq$1 or was receiving radiofrequency ablation; and (4) the patient voluntarily signed the written informed consent form. The major exclusion criteria included a history of heart valve disorders or stroke within the previous 14 days; acute coronary syndrome within 1 year in patients with AF; hematuria; severe liver dysfunction; severe renal impairment (estimated glomerular filtration rate [eGFR] <30 mL/min/1.73 m^2); major surgery in the previous month; a history of intracranial, intraocular, spinal, retroperitoneal, or atraumatic intra-articular bleeding; gastrointestinal hemorrhage or hematuria; alcohol abuse or drug addiction; poor compliance; and participation in any other clinical trial for investigational drugs and medical devices.

Study Variables and Definition of Terms

The primary study outcome was the time to first occurrence of all bleeding events at the 3-month follow-up. Major bleeding was defined as (1) fatal bleeding; (2) a reduction in hemoglobin concentration of at least 20 g/L or the transfusion of at least 2 units of blood; and (3) symptomatic bleeding in a critical area or organ such as: retroperitoneal, intracranial, intraocular, intraspinal, intra-articular, pericardial, and intramuscular areas with compartment syndrome. All other bleeding events were regarded as minor.[12,13]

The exposure was the changes in total bilirubin (CTBIL), and the CTBIL was the difference in serum total bilirubin at out of follow-up from baseline serum total bilirubin. The total bilirubin concentrations obtained at baseline and out of follow-up were recorded as a continuous variable and were determined with automated biochemical profiling (Beckman Synchron LX20; Beckman Coulter, Inc, Indianapolis, Indiana) in accordance with consistent standard methods at the laboratories of different centers. Laboratory staff were not aware of the research protocol.

All examinations were conducted at these 12 study sites. Self-administered standardized questionnaires were used to identify general information (age, sex, body mass index [BMI]), lifestyle behaviors (smoking status and alcohol status), AF type, radiofrequency ablation, medical history (such as hypertension, coronary heart disease [CHD], heart failure [HF], peripheral arteriopathy disease [PAD], transient ischemic attack [TIA], stroke, and history of bleeding), and medication use, the related risk factors for the CHA_2DS_2-VASc score and the HAS-BLED score and the Laboratory test (eGFR, TBIL, blood platelet [PLT], alanine aminotransferase [ALT], γ-glutamyl transferase [GGT]). Height and weight were measured by trained nurses. We calculated BMI. Sitting blood pressure was measured twice in the right arm after 10 minutes of rest. The average of 2 measurements was used. Smoking and drinking habits were categorized as never, former, and current based on a questionnaire and the medical records. Estimated glomerular filtration rate was estimated by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.[14] Measurements of PLT, ALT, and GGT; urine analysis; and stool analysis were performed in the laboratory medicine department of the study sites.

Treatment and Follow-Up Procedure

All eligible participants received oral dabigatran (110 mg twice daily) treatment. Participants were scheduled for follow-up at 1 month, 3 months, 6 months, and 12 months. At each follow-up visit, vital signs, study drug adherence, concomitant

medication, laboratory tests, adverse events, and possible outcome events were documented by specialized staff and physicians. The out-of-follow-up time for the last patient occurred in May 2018. Data were stored in an electronic data acquisition system.

Based on the MISSION-AF, we analyzed the relationship between CTBIL and bleeding events. In this study, we analyzed the data only for the 3-month follow-up period because the study population included some patients with NVAF having CHA_2DS_2-VASc scores of 0 for men and 1 for women. Anticoagulation needs to be maintained only for 8 weeks after ablation for these patients.[15] In addition, the risk of bleeding events with dabigatran was highest during the first 90 days of treatment.[16,17] A total of 929 patients with NVAF treated with dabigatran completed the 3-month follow-up.

Statistical Analysis

Continuous variables are expressed as the mean ± standard deviation (for normal distributions) or the median (minimum, maximum; for skewed distributions). Categorical variables are expressed as numbers and frequencies. Categorical variables were expressed in frequency or as a percentage. To test for differences in characteristics among patients with different CTBIL values, continuous variables were compared using 1-way analysis of variance, and a c^2 test was used for categorical variables. Univariate logistic regression analyses were performed to calculate of the hazard ratio (HR) for bleeding events. To calculate the HR for bleeding, the CTBIL were treated as a continuous variable and were categorized into 4 groups: group 1, <−10 μmol/L; group 2, −10 to 0 μmol/L; group 3, 0 to 10 μmol/L; and group 4, ≥10 μmol/L. The association of CTBIL with bleeding events was estimated using Cox proportional hazards models. Models were incrementally adjusted for the following potential confounders based on theoretical considerations and their availability in this study: model 1, crude model; model 2, adjusted for age, gender, smoking, drinking, and BMI; model 3, additionally accounted for PLT count, eGFR, baseline TBIL, ALT, GGT, comorbidities (hypertension, CHD, HF, previous stroke or TIA, PAD, and history of bleeding) and medications (angiotensin-converting enzyme inhibitors [ACEIs]/angiotensin II receptor blockers [ARBs], β-blockers, proton pump inhibitors [PPIs], amiodarone, anti-PLT agents, and statins). And then nonlinearities were explored with multivariable fractional polynomials. We used fractional polynomial regression models to explore nonlinear associations of the CTBIL with bleeding events, in which the CTBIL was treated as a continuous variable. If nonlinearity was detected, we first calculated the inflection point using a recursive algorithm and then constructed a 2 piecewise Cox proportional hazard model on both sides of the inflection point. We determined the best fit model based on *P* values for the log likelihood ratio test. All the analyses were performed with the statistical software packages in R (http://www.R-project.org; The R Foundation) and Empower Stats (http://www.empowerstats.com, X&Y Solutions, Inc, Boston, Massachusetts). A 2-sided *P* value <.05 was considered statistically significant for all tests.

Results

Baseline Characteristics of Selected Participants

Based on the inclusion and exclusion criteria, a total of 486 patients between February 2015 and December 2017 were selected for the final data analysis (Figure 1). The average age of the 486 selected participants was 64.3 ± 11.4 years old, and approximately 56.7% of the participants were male. Baseline characteristics of the groups of patients with different CTBIL values are described in Table 1. No statistically significant differences were detected in gender, BMI, smoking, CHD, HF, PAD, TIA, stroke, history of bleeding, PLT count, ALT, GGT, eGFR, ACEIs/ARBs, β-blockers, PPIs, amiodarone, digoxin, anti-PLT agents, and statins among different CTBIL groups (*P* values > .05). The patients in the group with the highest CTBIL values group were more likely to be older and receive radiofrequency ablation and had a higher CHA_2DS_2-VASc score, and this group had a lower HAS-BLED score and baseline serum bilirubin and rate of persistent AF, hypertension, and drinking than the others group.

Association Between the CTBIL and the Risk of Bleeding

Bleeding events occurred in 67 participants (29 males and 38 females), and the incidence rate was 13.8% (67/486). The bleeding events included 45 hematuria cases, 5 gingival bleeding cases, 1 gastrointestinal bleeding case, 1 skin ecchymosis case, 8 hemoptysis cases, 6 epistaxis cases, and 1 other bleeding case. Table 2 presents logistic regression results for bleeding associated with the levels of CTBIL divided into 4 groups. In the fully adjusted model (model 3), compared to the lowest level of CTBIL, the multivariate adjusted HRs (95% confidence intervals [CIs]) of bleeding events associated with the group 2, group 3, and group 4 of CTBIL were 0.45 (95% CI: 0.18-1.14), 0.22 (95% CI: 0.08-0.59), and 1.04 (95% CI: 0.25-4.26), respectively. When the CTBIL was applied to the fully adjusted model as a categorical variable, the trend of the effect in different CTBIL groups was not equidistant. These results suggested that the association between the CTBIL and bleeding events was likely to be nonlinear and after adjusting for confounding factors, the multivariate analysis suggested that baseline TBIL, ALT and GGT levels were no independently associated with bleeding (Supplemental Material).

Nonlinearity and the Threshold Effect Between the CTBIL and the Risk of Bleeding

In multivariable-adjusted spline regression models, a U-shaped association between the CTBIL and bleeding was observed at ~6 μmol/L as an inflection point (Figure 2). The result of the smooth curve fitting showed that the relationship between the CTBIL and bleeding events was nonlinear (after adjusting for

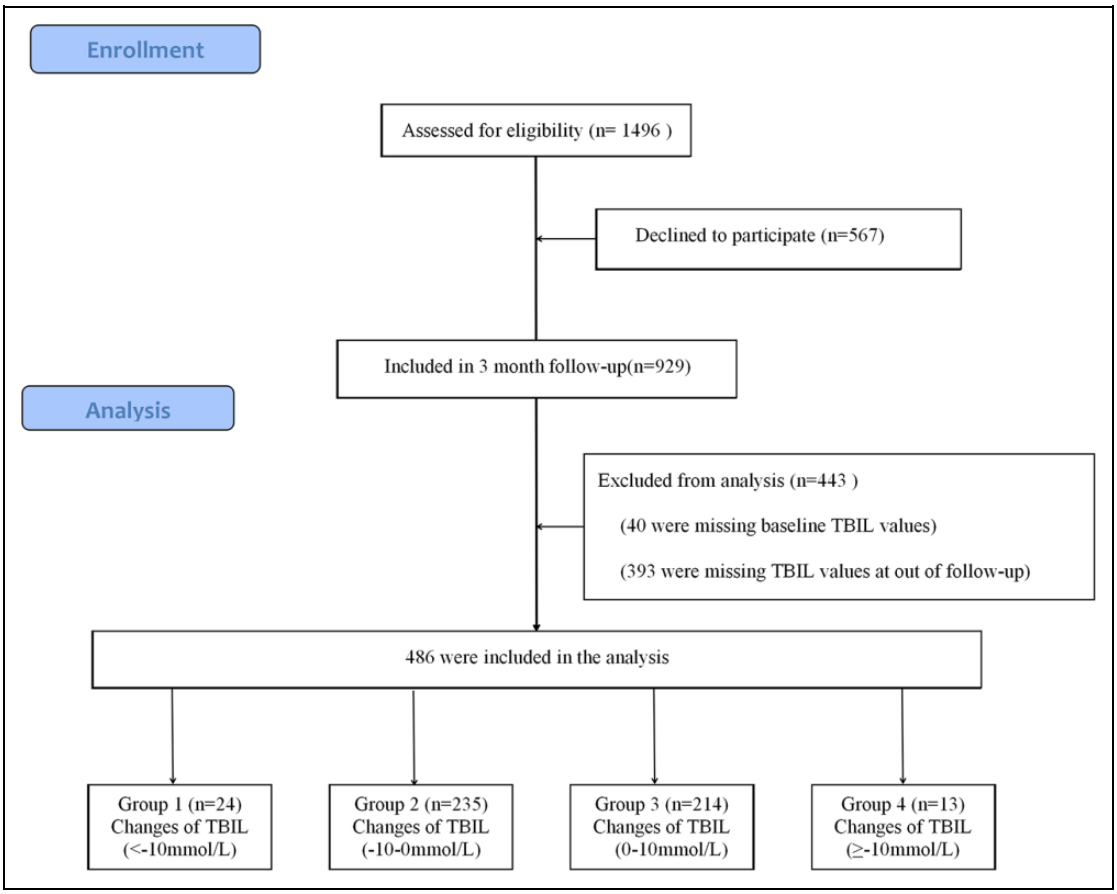

Figure 1. Study flow diagram.

other covariates presented in Table 1). We fitted the association between the CTBIL and bleeding events using the Cox proportional hazards regression model and the 2 piecewise Cox proportional hazards regression model, respectively. The *P* for the log likelihood ratio test was .001. This result indicated that the piecewise Cox proportional hazards regression model was more suitable for fitting the association between the CTBIL and bleeding events. Using a 2 piecewise Cox proportional hazards regression and recursive algorithm, we calculated the inflection point to be 6.63 μmol/L. For CTBIL <6.63 μmol/L, the HR and 95% CI were 0.91 and 0.87-0.96, respectively. For a CTBIL ≥6.63 μmol/L, the HR and 95% CI were 1.30 and 1.10-1.55, respectively (Table 3).

Discussion

To our knowledge, this was the first prospective cohort study showing that the association between the CTBIL and bleeding events followed a U-shaped curve. A slight increase in serum total bilirubin concentration can reduce the risk of bleeding events, but decreased or excessively elevated levels of serum total bilirubin were significantly associated with higher HR of bleeding events. Findings of this study are important for decision-making while choosing dabigatran as an anticoagulant in patients with disturbed liver functions. In case if the bilirubin is slightly increased along with disturbed liver functions, we can assume it as nature's protective mechanism to prevent liver disease associated bleeding tendency which is not available to the patients of hepatic disease with decreased or excessively increased serum bilirubin.

Although the mechanism underlying the association between the risk of bleeding events and the CTBIL is not fully understood, there are some possible explanations. Impaired liver function is a risk factor for bleeding in anticoagulated patients with NVAF.[7] Bilirubin is a marker of impaired liver function. Elevated bilirubin concentration is an indicator not only for cholestasis but also for hepatocellular liver disease, and serum bilirubin serves as a biomarker for the severity of liver disease and is a component of almost all liver prognosis scores, including the Model for End-stage Liver Disease (MELD) and Child-Turcotte-Pugh (CTP) scores.[18] When the serum bilirubin is excessively elevated in patients taking dabigatran, it represents the impairment of liver function in the patient, and the majority of the blood coagulation factors are synthesized by hepatocytes in human. Impaired liver function means a decrease in the production of coagulation factors that will increase the risk of bleeding events. Although renal excretion is the dominant elimination pathway of dabigatran and accounts for 80% of its total clearance, the rest of the drug is conjugated with glucuronic acid to form acyl glucuronides,

Table 1. Baseline Characteristics of the Participants.[a]

Characteristics	Change in Total Bilirubin, μmol/L				*P* Value
	<−10	−10 to 0	0 to 10	≥10	
N	24	235	214	13	
Patients characteristic					
Age, years	58.1 ± 12.8	63.9 ± 11.6	64.96 ± 10.9	71.25 ± 8.0	.005
Male, %	18 (75.0)	130 (55.3)	119 (55.6)	8 (66.7)	.257
BMI, kg/m^2	24.2 ± 3.0	24.7 ± 3.6	24.1 ± 3.5	23.6 ± 3.1	.287
SBP, mm Hg	125.5 ± 13.5	126.3 ± 16.1	126.5 ± 15.8	128.1 ± 15.9	.972
Type of AF, persistent	6 (25.0)	125 (53.2)	131 (61.5)	6 (50.0)	.005
Radiofrequency ablation	14 (58.3)	166 (70.6)	150 (70.1)	4 (33.3)	.032
Risk factors, n (%)					
Hypertension	7 (29.2)	108 (46.0)	124 (57.9)	7 (58.3)	.010
Diabetes mellitus	3 (12.5)	29 (12.3)	28 (13.1)	1 (8.3)	.968
Coronary heart disease	1 (4.2)	11 (4.7)	14 (6.5)	0 (0.0)	.671
HF	6 (25.0)	43 (18.3)	40 (18.7)	4 (33.3)	.527
PAD	0 (0.0)	4 (1.7)	7 (3.3)	1 (8.3)	.326
Previous stroke or TIA	3 (12.5)	28 (11.9)	26 (12.2)	1 (8.3)	.983
Prior bleeding	0 (0.0)	2 (0.9)	3 (1.4)	0 (0.0)	.864
Current smoker	8 (33.3)	43 (18.3)	43 (20.2)	3 (25.0)	.527
Current drinker	10 (41.7)	46 (19.7)	40 (18.7)	0 (0.0)	<.001
Laboratory test					
PLT count, 10^9/L	164.2 ± 42.4	185.7 ± 57.0	180.3 ± 49.0	182.9 ± 54.4	.255
TBIL, umol/L	29.3 ± 7.3	16.0 ± 5.3	12.5 ± 4.8	14.2 ± 5.5	<.001
ALT, U/L	33.8 ± 30.9	25.3 ± 19.9	25.1 ± 18.6	39.7 ± 31.5	.138
GGT, U/L	62.57 ± 78.35	42.30 ± 38.07	39.35 ± 33.40	52.12 ± 38.18	.274
eGFR, L/min	84.9 ± 18.5	83.6 ± 18.1	83.7 ± 15.9	79.0 ± 12.8	.693
CHA_2DS_2-VASc Score, n (%)		0.026			
0	7 (29.2)	40 (17.0)	24 (11.2)	0 (0.0)	
1	6 (25.0)	61 (26.0)	47 (22.0)	1 (8.3)	
≥2	11 (45.8)	134 (57.0)	143 (66.8)	11 (91.7)	
HAS-BLED Score, n (%)		0.020			
<3	21 (87.5)	225 (95.7)	211 (98.6)	12 (100.0)	
≥3	3 (12.5)	10 (4.3)	3 (1.4)	0 (0.0)	
Drugs at start of study, n (%)					
ACEIs/ARBs	6 (25.0)	72 (30.6)	78 (36.5)	5 (41.7)	.419
β-blockers	12 (50.0)	89 (37.9)	77 (36.0)	6 (50.0)	.462
PPIs	8 (33.3)	103 (43.8)	89 (41.6)	4 (33.3)	.695
Amiodarone	9 (37.5)	101 (43.0)	87 (40.7)	5 (41.7)	.934
Digoxin	3 (12.5)	6 (2.6)	8 (3.7)	1 (8.3)	.079
Antiplatelet agents	2 (8.3)	3 (1.3)	7 (3.3)	0 (0.0)	.128
Statins	6 (25.0)	60 (25.5)	63 (29.4)	4 (33.3)	.767

Abbreviations: ACEI, angiotensin-converting enzyme inhibitors; AF, atrial fibrillation; ALT, alanine aminotransferase; ARB, angiotensin receptor blocker; BMI, body mass index; eGFR, estimated glomerular filtration rate; GGT, γ-glutamyl transferase; HF, heart failure; PAD, peripheral arteriopathy disease; PLT, platelet; PPI, proton pump inhibitor; SBP, systolic blood pressure; TBIL, total bilirubin; TIA, transient ischemic attack.

[a] CHA_2DS_2-VASc score awards 1 point each for congestive heart failure, hypertension, diabetes mellitus, vascular disease, age 65 to 74 years, and female (sex category) and 2 points each for age ≥75 years and previous stroke or TIA. HAS-BLED score awards 1 point each for hypertension, abnormal renal or liver function, stroke, bleeding history, labile INR, age 65 years or older, and antiplatelet drug or alcohol use.

which are predominantly excreted via the bile. Impaired liver function will increase dabigatran exposure and prolong its half-life, which also increases the rate of occurrence of bleeding events.[19] Similarly, our study found that patients in the group with the lowest CTBIL had higher baseline serum bilirubin than other groups, which means these patients had worse liver function. And disturbed liver function was associated with increased risk of bleeding.

Reduced PLT count or function is also a risk factor for bleeding in anticoagulated patients derived from the $HEMORR_2HAGES$ score.[20] Suvansri and her colleagues suggested that elevated levels of serum bilirubin can affect PLT function and clot formation.[21] Increased serum bilirubin levels inhibited ADP-induced PLT factor 3 (PF3) activation, PLT-derived thromboplastin, and clot retraction in PLTs obtained from hyperbilirubinemic neonates.[22] The inhibition of PLT-derived thromboplastin and PF3 in hyperbilirubinemic conditions demonstrated that serum bilirubin at greater concentrations can significantly reduce the quality of clot formation by affecting PLTs.[23] Therefore, excessively elevated levels of

Table 2. Relationship Between the Change in Total Bilirubin and Dabigatran-Related Bleeding in Different Models.

		Model 1		Model 2		Model 3	
Changes of TBIL, μmol/L	N	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Continuous	486 (67)	0.95 (0.91-0.99)	.024	0.95 (0.91-1.00)	.028	0.95 (0.90-0.99)	.018
Categories							
<-10	24 (6)	Reference		Reference		Reference	
-10-0	235 (39)	0.62 (0.26-1.47)	.281	0.53 (0.22-1.30)	0.168	0.45 (0.18-1.14)	.093
0-10	214 (17)	0.29 (0.11-0.73)	.009	0.26 (0.10, 0.68)	0.006	0.22 (0.08, 0.59)	.003
≥10	13 (4)	1.38 (0.39-4.90)	.616	1.19 (0.31, 4.61)	0.804	1.04 (0.25-4.26)	.958
P for trend			.034		0.035		.033

Abbreviations: ACEI, angiotensin-converting enzyme Inhibitors; ALT, alanine aminotransferase; ARB, angiotensin receptor blocker; BMI, body mass index; CI, confidence interval; eGFR, estimated glomerular filtration rate; GGT, γ-glutamyl transferase; HR, hazard ratio; PAD, peripheral arteriopathy disease; PLT, platelet; PPI, proton pump inhibitor; TBIL, total bilirubin; TIA, transient ischemic attack.

[a]Model 1: crude model. Model 2: adjusted for age, gender, smoking, drinking, BMI. Model 3: as model 2, and additionally adjusted for PLT count, eGFR, baseline TBIL, ALT, GGT, hypertension, CHD, heart failure, previous stroke or TIA, PAD, history of bleeding, ACEIs/ARBs, β-blockers, PPIs, amiodarone, antiplatelet agents, statins.

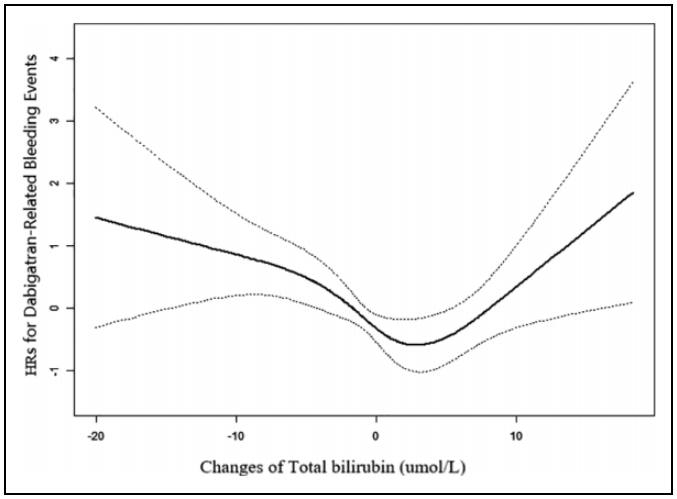

Figure 2. The Change in total bilirubin (TBIL) and risk of dabigatran-related bleeding. Adjusted hazard ratios (HRs; solid line) and 95% confidence interval (CIs; dashed line) for dabigatran-related bleeding events by the change in TBIL. All were adjusted for age, gender, smoking, drinking, body mass index (BMI), platelet (PLT) count, estimated glomerular filtration rate (eGFR), baseline TBIL, alanine aminotransferase (ALT), γ-glutamyl transferase (GGT), hypertension, coronary heart disease (CHD), heart failure, previous stroke or transient ischemic attack (TIA), peripheral arteriopathy disease (PAD), history of bleeding, angiotensin-converting enzyme inhibitors (ACEIs)/angiotensin II receptor blockers (ARBs), proton pump inhibitors (PPIs), amiodarone, antiplatelet agents, and statins.

total bilirubin can inhibit PLT function to increase the risk of bleeding events.

The association between decreased level of total bilirubin and increased risk of bleeding events is undiscovered. There are some possible mechanisms to explain it. In humans, serum bilirubin has been demonstrated to be protective against an array of diseases associated with increased oxidative stress, and low serum total bilirubin concentration has been demonstrated to be a risk factor for systemic diseases associated with increased oxidative stress, such as CVD and diabetes.[10] Undoubtedly, all these diseases will increase the risk of bleeding events in patients taking dabigatran. However, further study is warranted to elucidate the mechanism underlying the role of the CTBIL in bleeding events.

The strengths of this study were that we addressed the nonlinearity between the CTBIL and the risk of bleeding events and further explained the nonlinearity. Physicians can use changes in serum total bilirubin levels to assess the risk of bleeding in patients with NVAF taking dabigatran.

Our study also has several limitations. First, this research had a small sample size, because this study is a real-world study, so the sample size was not controlled. And the sample size is too small to be analyzed hierarchically. Second, the sample size is small, so the number of major bleeding events is small, and we were unable to perform statistical analysis of the relationship between the CTBIL and major bleeding. Although this study only shows the relationship between the CTBIL and only minor bleeding events in patients with NVAF taking dabigatran, prior studies have shown that the occurrence of minor bleeding may predict major bleeding events and may lead to the stoppage of effective OAC therapy.[24] Third, total bilirubin consists of unconjugated bilirubin and conjugated bilirubin, and this study did not further discover which form is more relevant to bleeding events. In our study, only ALT and GGT were taken as hepatic enzymatic markers, other liver function tests were not taken because ALT is considered more liver-specific than aspartate aminotransferase. Moreover, GGT is a reliable indicator for biliary disease.[25] Finally, the findings in this study were based on 110 mg instead of 150 mg dabigatran doses, so conclusions cannot be applied to patients taking 150 mg of dabigatran. Some previous studies showed that 110 mg doses of dabigatran in Asian populations yield similar pharmacokinetics and comparable clinical outcomes to those of the 150 mg doses of dabigatran dose in Western populations.[26,27] Additionally, Asians have a relatively small body size and lower renal clearance than Western populations, as well as genetic

Table 3. Threshold Effect Analysis of the Change in TBIL on Dabigatran-Related Bleeding Events.[a]

		Model 1		Model 2		Model 3	
	N	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR(95% CI)	*P* Value
Total	486(67)	0.95 (0.91-0.99)	.024	0.95 (0.91-1.00)	.028	0.95 (0.90-0.99)	.018
Inflection point							
<6.63 μmol/L	442(60)	0.93 (0.89-0.97)	<.001	0.92 (0.88-0.96)	<.001	0.91 (0.87-0.96)	<.001
≥6.63 μmol/L	44(6)	1.33 (1.15-1.54)	.001	1.27 (1.09-1.48)	.002	1.30 (1.10-1.55)	.003
P for log likelihood ratio test			.001		.002		.001

Abbreviations: ACEI, angiotensin-converting enzyme Inhibitors; ALT, alanine aminotransferase; ARB, angiotensin receptor blocker; BMI, body mass index; CI, confidence interval; eGFR, estimated glomerular filtration rate; GGT, γ-glutamyl transferase; HR, hazard ratio; PAD, peripheral arteriopathy disease; PLT, platelet; PPI, proton pump inhibitor; TBIL, total bilirubin; TIA, transient ischemic attack.

[a]Model 1: crude model. Model 2: adjusted for age, gender, smoking, drinking, BMI. Model 3: as model 2, and additionally adjusted for PLT count, eGFR, baseline TBIL, ALT, GGT, hypertension, CHD, heart failure, previous stroke or TIA, PAD, history of bleeding, ACEIs/ARBs, β-blockers, PPIs, amiodarone, antiplatelet agents, statins.

differences in metabolic or pharmacodynamic features, and lower doses of dabigatran may can improve safety.[28,29]

Conclusion

Our study revealed a U-shaped association between the CTBIL and dabigatran-related bleeding events in a Chinese population. Additional studies are warranted to confirm our findings in large sample prospective cohorts and to provide basic medical research to elucidate the potential mechanisms underlying the relationship between CTBIL and dabigatran-related bleeding events.

Authors' Note

All procedures performed in studies involving human participants were in accordance with the ethical standards of the Second Affiliated Hospital of Nanchang University research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This study was supported by the Major New Drug Creation Program from National Science and Technology Major Project (NO.2014ZX09303305) and the Science and Technology Planning Project of Jiangxi Province (NO.20161ACG70012).

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Supplemental Material

Supplemental material for this article is available online.

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