Original Article

Association between platelet count and the risk of bleeding among patients with nonvalvular atrial fibrillation taking dabigatran after radiofrequency ablation: a cohort study

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Background: A reduction in platelet count or function can be a risk factor for bleeding in anticoagulated patients. However, the association between platelet count and the risk of bleeding among nonvalvular atrial fibrillation (NVAF) patients taking dabigatran remains unclear. The aim of this study was to investigate the relationship between platelet count and the risk of bleeding among patients with NVAF taking dabigatran after radiofrequency ablation.

Methods: In this multicenter, prospective and observational study, a total of 576 NVAF patients treated with dabigatran (110 mg bid) after radiofrequency ablation were recruited from 12 centers in China from February 2015 to December 2017. All patients were followed for 3 months. The association between platelet count and the risk of bleeding was evaluated by Cox proportional hazards regression analysis. To explore the nonlinearity between platelet count and bleeding, we used a Cox proportional hazards regression model with cubic spline functions and smooth curve fitting and a two-piecewise Cox proportional hazards model.

Results: During a median follow-up duration of 87 days, 50 patients experienced bleeding events. Overall, there was an inverse relationship between the risk of bleeding and platelet count. Low platelet count ($<100\times10^9$/L) were associated with an increased risk of bleeding [hazard ratio (HR), 4.05; 95% confidence interval (CI): 1.32–12.46] compared to normal counts. The adjusted smooth curve showed a nonlinear relationship between platelet count and bleeding events. The inflection point of the platelet count was 105×10^9/L. For platelet counts $<105\times10^9$/L, the HR (95% CI) was 0.89 (0.84–0.95), and for platelet counts $\geq105\times10^9$/L, the HR (95% CI) was 1.01 (0.95–1.08).

Conclusions: Low platelet counts were associated with an increased risk for bleeding among patients with NVAF taking dabigatran after catheter ablation.

Keywords: Platelet; atrial fibrillation (AF); dabigatran; radiofrequency ablation; bleeding

Submitted Jul 17, 2020. Accepted for publication Aug 14, 2020.
doi: 10.21037/cdt-20-645
View this article at: http://dx.doi.org/10.21037/cdt-20-645

Introduction

Atrial fibrillation (AF) remains an important risk factor for systemic embolism and stroke (1,2). Substantial evidence suggests that anticoagulation with warfarin reduces this risk by two-thirds, whereas antiplatelet therapy decreases the risk of systemic embolism and stroke by only 22% (3). There is a lot of evidence that dabigatran, which is a direct thrombin inhibitor, is convenient and safe alternatives to VKAs based on the results of the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial (4). Although non-vitamin K antagonist (VKA) oral anticoagulants (OACs) (NOACs) can prevent systemic embolism and stroke, they can cause bleeding. The benefits of NOACs in treatment of nonvalvular atrial fibrillation (NVAF) are based on a balance between reducing the risk of stroke and reducing the risk of bleeding. The risk of bleeding in AF patients undergoing OAC therapy can be assessed by hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalized ratio, elderly (>65 years), drugs/alcohol concomitantly (HAS-BLED) (5), older age (>75 years), reduced haemoglobin/haematocrit/ history of anaemia, bleeding history, insufficient kidney function, and treatment with antiplatelet (ORBIT) (6) and Hepatic or Renal Disease, Ethanol Abuse, Malignancy, Older Age, Reduced Platelet Count or Function, Re-Bleeding, Hypertension, Anemia, Genetic Factors, Excessive Fall Risk and Stroke (HEMORR2HAGES) scores (7). However, these scores were mainly obtained and developed mainly among patients taking VKAs. The relationship between the risk factors for bleeding and NOACs is not well understood.

Platelets play a key role by accelerating some steps in the coagulation process. A reduction in platelet count or function is a risk factor for bleeding in anticoagulated patients based on the HEMORR2HAGES scores (7). However, in this trial, all patients receiving OAC therapy were treated with warfarin or aspirin and did not consume a NOAC. To the best of our knowledge, no epidemiological trials have focused on the relationship of platelets with bleeding in NVAF patients taking dabigatran. Therefore, the goal of this paper was to investigate the relationship between platelet count and dabigatran-related bleeding in NVAF patients after catheter ablation. We present the following article in accordance with the STROBE reporting checklist (available at http://dx.doi.org/10.21037/cdt-20-645).

Methods

Study design and population

Details of the trial design, outcome definitions and patients have been published (8). Patients were recruited from 12 study sites in China between February 2015 and December 2017. In brief, a total of 576 patients with NVAF after radiofrequency ablation received oral dabigatran (110 mg bid) treatment (9). An electronic data collection system was used for the data collection process and the data were reviewed regularly throughout the trial by an independent data and safety monitoring committee. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Second Affiliated Hospital of Nanchang University research committee (MISSION-AF, ClinicalTrials.gov Identifier: NCT02414035) and informed consent was taken from all the patients.

Study variables and definitions of terms

The primary study outcome was the first occurrence of all bleeding events during the 3-month follow-up period. Major bleeding was defined as (I) fatal bleeding; (II) a reduction in the hemoglobin concentration of at least 20 g/L with the transfusion of at least two units of blood; and (III) symptomatic bleeding in a critical area or organ. All other bleeding events were classified as minor (10,11).

The platelet counts obtained at baseline were treated as a continuous variable and measured by automatic blood analysis equipment in accordance with the standard methods that were consistent across the laboratories at the different centers. Laboratory staff members were not aware of the research protocol.

Treatment and follow-up procedure

Based on the MISSION-AF database, we analyzed the effect of platelet count on frequencies of bleeding events in NVAF patients. In present study, we only analyzed the 3-month follow-up date, because the study population included some NVAF patients with CHA2DS2-VASc scores of 0 for men and 1 for women. Anticoagulation only needs to be maintained for only 8 weeks after ablation for these patients (12). Any decisions to continue anticoagulation with dabigatran after the 3-month follow-up period were based on the guidelines (12) and at the professional

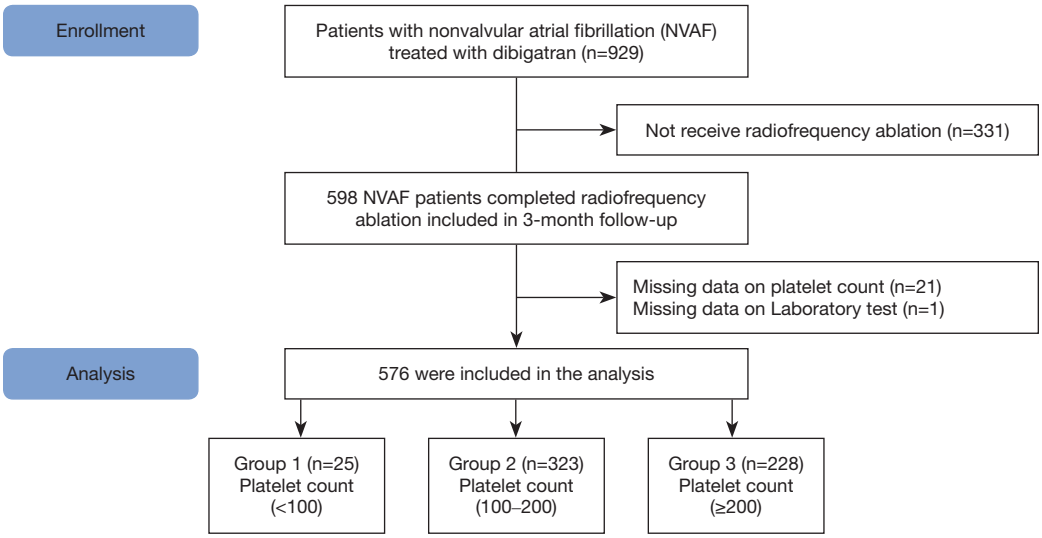

Figure 1 Study flow diagram.

physician's discretion. In addition, the risk for bleeding events with dabigatran was highest during the first 90 days of treatment (13,14). A total of 576 NVAF patients treated with dabigatran completed the 3 months of follow-ups.

Statistical analysis

Continuous variables are expressed as the mean ± standard deviation or the median (minimum, maximum). Categorical variables are expressed as numbers and frequencies. To test for differences among patients with different platelet count groups (group 1, $<100\times10^9$/L; group 2, $100–200\times10^9$/L; and group 3, $\geq200\times10^9$/L), we compared continuous variables using one-way analysis of variance (ANOVA). and categorical variables using the chi-squared test or Fisher's exact test. The hazard ratio (HR) and 95% confidence interval (CI) between platelet count and bleeding events were evaluated using Cox proportional hazards models. The 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 habits, drinking habits, BMI and the type of AF; and model 3, additionally accounted for eGFR, comorbidities (hypertension, CHD, HF, previous stroke or TIA, PAD, and a history of bleeding), medications (ACE inhibitors (ACEIs)/ angiotensin II receptor blockers (ARBs), beta-blockers, proton-pump inhibitors (PPIs), amiodarone, digoxin, antiplatelet agents, and statins). Then, we used fractional polynomial regression models to explore nonlinear associations of platelet counts and bleeding events, in which platelet counts were treated as continuous variables. If nonlinearity was detected, we first calculated the inflection point using a recursive algorithm and then constructed a two-piecewise Cox proportional hazard model on both sides of the inflection point. We determined the best-fit model based on the P values from the log likelihood ratio test. We also examined if the association between PLT count and bleeding varied by sex, age, type of AF, smoking, drinking and SBP. A sensitive analysis restricting the sample only to the patients without treatment of Antiplatelet agents was performed. 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, MA). A two-sided P value <0.05 was considered statistically significant for all tests.

Results

Patient characteristics

Based on the inclusion and exclusion criteria, a total of 576 patients were included for the final data analysis (mean age: 61.9±10.2 years; 61.4% were male) (*Figure 1*). *Table 1* shows the baseline characteristics in three groups of patients with platelet counts. The patients in the group with the highest platelet count were more likely to be younger

Table 1 Baseline characteristics of participants

Characteristics	Platelet count, $\times 10^9$/L			P value
	<100 (N=25)	100–200 (N=323)	≥200 (N=228)	
Patients characteristic				
Age, years	63.8±6.6	62.8±9.9	60.4±10.8	0.014
Male, n (%)	18 (72.0)	216 (66.9)	120 (52.6)	0.002
BMI (kg/m^2)	23.4±3.8	24.3±3.4	24.9±3.5	0.045
SBP (mmHg)	126.7±13.1	126.0±14.9	124.7±16.5	0.575
Current smoker	11 (44.0)	58 (18.2)	41 (18.0)	0.012
Current drinker	7 (28.0)	73 (22.8)	44 (19.4)	0.504
Type of AF, persistent	7 (28.0)	114 (35.3)	58 (25.6)	0.049
Risk factors, n (%)				
Hypertension	12 (48.0)	135 (41.8)	115 (50.4)	0.129
Coronary heart	0 (0.0)	25 (7.7)	10 (4.4)	0.115
Heart failure	5 (20.0)	36 (11.1)	24 (10.5)	0.362
PAD	0 (0.0)	7 (2.2)	3 (1.3)	0.598
Stroke or TIA	2 (8.0)	24 (7.4)	12 (5.3)	0.576
Prior bleeding	0 (0.0)	2 (0.6)	3 (1.3)	0.612
Diabetes mellitus	3 (12.0)	31 (9.6)	40 (17.5)	0.023
Laboratory test				
eGFR, L/min	79.7±16.7	85.2±15.0	87.5±15.4	0.026
ALT, U/L	27.1±13.7	25.5±18.8	24.1±17.3	0.584
CHA_2DS_2-VASc Score, n (%)				0.618
0	5 (20.0)	73 (22.6)	40 (17.5)	
1	8 (32.0)	84 (26.0)	68 (29.8)	
≥2	12 (48.0)	166 (51.4)	120 (52.6)	
HAS-BLED Score, n (%)				0.547
<3	25 (100.0)	319 (98.8)	223 (97.8)	
≥3	0 (0.0)	4 (1.2)	5 (2.2)	
Drugs at start of study, n (%)				
ACEIs/ARBs	5 (20.0)	77 (23.8)	70 (30.7)	0.150
CCB	5 (20.0)	48 (14.9)	39 (17.1)	0.664
Beta-blockers	4 (16.0)	72 (22.3)	63 (27.6)	0.220
PPIs	4 (16.0)	72 (22.3)	63 (27.6)	0.132
Amiodarone	15 (60.0)	191 (59.1)	134 (58.8)	0.991
Digoxin	0 (0.0)	3 (0.9)	3 (1.3)	0.791
Antiplatelet agents	0 (0.0)	8 (2.5)	9 (3.9)	0.406
Statins	35 (18.2)	50 (26.0)	47 (24.5)	0.156

BMI, body mass index; SBP, systolic blood pressure; AF, atrial fibrillation; HF, heart failure; PAD, peripheral arteriopathy disease; TIA, transient ischemc attack; eGFR, estimated glomerular filtration rate; ALT, alanine aminotransferase; ACEI, angiotensin converting enzyme inhibitors; ARB, angiotensin receptor blocker; CCB, calcium channel block; PPI, proton pump inhibitor. 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.

Table 2 Relationship between platelet count and dabigatran-related bleeding in different models

	N	Model 1		Model 2		Model 3	
		HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
PLT ($\times10^9$)	576 [50]	1.00 (1.00, 1.01)	0.768	0.95 (0.91, 1.00)	0.557	1.00 (0.99, 1.00)	0.357
PLT count, $\times10^9$/L							
<100	25 [4]	Reference		Reference		Reference	
100–200	323 [24]	0.44 (0.15, 1.27)	0.131	0.34 (0.11, 1.01)	0.053	0.24 (0.08, 0.75)	0.014
≥200	228 [22]	0.59 (0.20, 1.70)	0.328	0.38 (0.13, 1.16)	0.106	0.26 (0.08, 0.86)	0.028
P for trend			0.892		0.650		0.395
Dichotomous							
<100	25 [4]	1.99 (0.72, 5.54)	0.185	2.81 (0.98, 8.01)	0.054	4.05 (1.32, 12.46)	0.014
≥100	551 [46]	Reference		Reference		Reference	

Model 1: crude model. Model 2: adjusted for age, gender smoking, drinking, BMI, type of AF. Model 3: as model 2, and additionally adjusted for eGFR, hypertension, CHD, HF, previous stroke or TIA, PAD, history of bleeding, ACEIs/ARBs, beta-blockers, PPIs, amiodarone, digoxin, antiplatelet agents and statins.

and have a higher BMI and eGFR, and this group had a higher proportion of females than the other groups. No statistically significant differences were detected in the SBP, drinking habits, CHA2DS2-VASc score, HAS-BLED score, hypertension, CHD, HF, PAD, TIA, the history of stroke, history of bleeding, ACEIs/ARBs, beta-blockers, PPIs, amiodarone, digoxin, antiplatelet agent, and statins among the different platelet count groups (P values >0.05).

Association between platelet count and the risk of bleeding

The median follow-up period was 87 days. The number of bleeding events was 50 participants (21 males and 29 females), and the incidence rate was 8.7% (50/576). The bleeding events included 33 hematuria cases, 4 gingival bleeding cases, 1 skin ecchymosis case, 5 hemoptysis cases, 6 epistaxis cases and 1 other bleeding case. *Table 2* presents the relationship between platelet count and bleeding events. In the fully adjusted model (model 3), the multivariate-adjusted HRs (95% CIs) of the bleeding events associated with the middle platelet count group and the group with the highest platelet count, compared with the group with the lowest platelet count, were 0.24 (95% CI: 0.08–0.75; P=0.014) and 0.26 (95% CI: 0.08–0.86; P=0.028), respectively. Compared with the normal platelet count group (≥100×10^9/L), the low platelet count group (<100×10^9/L) was associated with a higher prevalence of bleeding (4.05 95% CI, 1.32–12.46; P=0.014). When platelet count was included in the final regression model as a categorical variable, the magnitudes of the effects on the different platelet count groups were not equal. The results suggest that the relationship between platelet count and bleeding events may be nonlinear.

Nonlinearity between platelet count and the risk of bleeding

The adjusted smooth curve showed that the association between platelet count and bleeding events was nonlinear (*Figure 2*). There was a nonlinear relationship, with a significantly higher risk for bleeding observed in patients with lower platelet counts. We fitted the association between platelet count and bleeding events using the Cox proportional hazards regression model and two-piecewise Cox proportional hazards regression model (*Table 3*). The P value for the log likelihood ratio test was less than 0.05. This result indicates that the two-piecewise Cox proportional hazards regression model is more suitable for fitting the association between platelet count and bleeding events. Using a two-piecewise Cox proportional hazards regression and recursive algorithm, we calculated the inflection point to be 105×10^9/L. In model 3, for platelet counts <105×10^9/L, each 1×10^9 increase in platelet count was associated with an 11% decreased in the risk of bleeding events (P<0.001). For platelet counts ≥105×10^9/L, the relationship between platelet count and the risk of bleeding events was not significant. Details of the subgroup analyses

are presented in *Figure S1*. The association between platelet count and bleeding events was consistent in the following subgroups: sex, age, BMI, type of AF, smoking, drinking and SBP (all P for interaction >0.05). Sensitivity analysis showed that the association between platelet count and bleeding events remained statistically significant in patients without treatment of antiplatelet agents (*Table S1*).

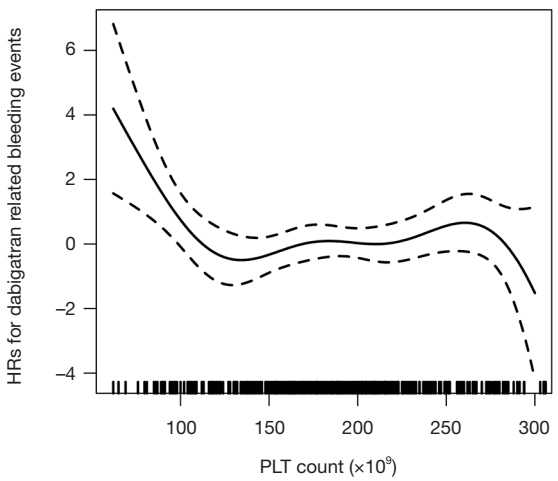

Figure 2 Platelet count and risk of dabigatran-related bleeding. Adjusted Hazard ratios (HRs; solid line) and 95% CI (dashed line) for dabigatran-related bleeding events by platelet count. All adjusted for adjusted for age, gender, smoking, drinking, BMI, type of AF, eGFR, hypertension, CHD, HF, previous stroke or TIA, PAD, history of bleeding, ACEIs/ARBs, beta-blockers, PPIs, amiodarone, digoxin, antiplatelet agents and stains.

Discussion

In the present study, our purpose was to determine the relationship between platelet count and bleeding events among NVAF patients receiving radiofrequency ablation in China. A nonlinear association was found, which suggests that patients with platelet counts <105×10^9/L are associated with a high incidence of bleeding events. This association remained after a multivariate adjustment for other confounding factors was performed.

The association between platelet count and the risk of bleeding is likely not complex because platelets play a central role in the coagulation process. A number of previous studies have reported conflicting conclusions regarding the association between platelet count and the risk of bleeding events. A recent study showed a U-shaped association between platelet count and major bleeding events among patients with acute venous thromboembolism (VTE) receiving VKAs (15). In that study, patients were categorized into five groups (<100,000/mL, 100,000–150,000/mL, 150,000–300,000/mL, 300,000–450,000/mL, and >450,000/mL). Patients with the lowest or highest platelet counts had a remarkably increased risk of major bleeding compared with the other patients. However, patients enrolled in this study were diagnosed with acute deep vein thrombosis and pulmonary embolism. The IMPROVE study, which involved 15,156 patients, showed an increased risk of bleeding events was associated with reduced platelet count (16), and a low platelet count was defined as <50×10^9/L in medical patients. However, in that study, platelet count was simply categorized into two

Table 3 Threshold effect analysis of platelet count on bleeding events

	Number	Model 1		Model 2		Model 3	
		HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
Total	576 [50]	1.00 (1.00, 1.01)	0.768	0.95 (0.91, 1.00)	0.557	1.00 (0.99, 1.00)	0.357
Inflection point							
<105×10^9/L	546 [46]	0.95 (0.91, 0.99)	0.028	0.93 (0.88, 0.98)	0.004	0.89 (0.84, 0.95)	<0.001
≥105×10^9/L	30 [4]	1.00 (1.00, 1.01)	0.316	1.00 (0.99, 1.01)	0.794	1.01 (0.95, 1.08)	0.771
P for log likelihood ratio test			0.060		0.016		0.002

Model 1: crude model. Model 2: adjusted for age, gender smoking, drinking, BMI, type of AF. Model 3: as model 2, and additionally adjusted for eGFR, hypertension, CHD, HF, previous stroke or TIA, PAD, history of bleeding, ACEIs/ARBs, beta-blockers, PPIs, amiodarone, digoxin, antiplatelet agents and statins.

groups, so the effect of mildly reduced platelet count levels on the risk of bleeding events could not be examined. HEMORR2HAGES scores showed that a reduction in platelet count or function was a independent predictor for bleeding among anticoagulated patients (7). However, that study was mainly focused on the risk factors of bleeding events in patients taking warfarin or aspirin, and they chose 75 years as the age threshold.

The nonlinear association between platelet count and bleeding events is biologically plausible. Hemostasis can be viewed as four separate but interrelated events: compression and vasoconstriction; the formation of a platelet plug; blood coagulation; and clot retraction. In addition, platelets regulate bleeding in three stages. First, they form multicellular aggregates linked by protein strands at openings in blood vessels. The aggregates form a physical barrier that begins to limit blood loss soon after the opening occurs. Second, phospholipids on the platelet plasma membrane activate the enzyme thrombin, which initiates a cascade of events ending in clot formation. Finally, platelets possess multiple storage granules, which they discharge (secrete) to enhance coagulation. A reduction in platelet count or function can increase coagulation time, which can increase the risk of bleeding events.

The current findings suggest that a reduction in platelet count or function is linked with a high risk of bleeding. In a prospective double-blind study of 194 patients with acute VTE, patients with platelet counts $<150\times10^9$ /L had an increased risk of bleeding (17). Beyth *et al*. (18) reported that a reduced platelet count was an independent risk factor for bleeding events in patients taking coumarins. A previous observational study also indicated that platelet count or function was associated with bleeding in AF patients taking on warfarin or aspirin (7). The existing bleeding risk scores are mainly focused on patients taking VKAs, and there are few studies examining the risk of bleeding events associated with NOCAs. In the present study, we expanded these observations in a multicenter, prospective and observational study among NVAF patients taking dabigatran and, for the first time, explored the associations of platelet count with bleeding events in NVAF patients who underwent catheter ablation.

This study has several limitations. First, the findings in this study were based on a 110 mg dabigatran dose instead of a 150 mg dabigatran dose, so the conclusions cannot be applied to patients taking 150 mg of dabigatran. Some previous studies showed that a 110 mg dose of dabigatran in Asian populations yields pharmacokinetics and clinical outcomes in Asian populations that are similar to those in Western populations taking a 150 mg dabigatran dose (19,20). Additionally, Asians have a relatively small body size and lower renal clearance, as well as genetic differences in metabolic or pharmacodynamic features, and lower doses of dabigatran may enhance the safety (21,22). Second, all patients enrolled in this study were NVAF patients who underwent catheter ablation, and additional large studies are needed to confirm our findings in all NVAF patients. In order to reduce the risk of operation, the platelet count of all patients was greater than 50×10^9/L, but we still observed that the risk of bleeding events of group T1 was higher than other groups. *Table S2* shows that the average mean, median and range of platelet counts in all groups. Third, the sample size was small, and the mean HAS-BLED score was 0.69 in all patients; thus, the incidence of major bleeding events was very low. Therefore, all bleeding events were minor bleeding events, we can only perform a statistical analysis of the relationship between platelet count and minor bleeding. However, prior studies showed that the occurrence of minor bleeding may predict major bleeding events and may lead to a decrease in the effectiveness of OAC therapy (23). Finally, the group of patients where majority bleeding is expected (PLT counts $<100\times10^9$/L) is the smallest (25 patients only out of 576), hence the conclusions can not be easily deducted.

Despite these limitations, this study may have several clinical implications. First, to our knowledge, it is the first time to assess the association of platelet count with the risk of bleeding events in NVAF patients taking dabigatran in a prospective study. We carefully controlled for confounders by using standardized clinical and laboratory procedures. These strengths enabled the researchers to investigate the association between platelet count and bleeding independent of possible confounders. Second, to avoid bias caused by differences in treatment of antiplatelet agents, we carried out a sensitivity analysis focused on the patients without treatment of antiplatelet agents, the association between platelet count and bleeding events remained statistically significant (*Table S1*). Third, physicians should be conscious of the significant risk for bleeding associated with reduced platelet count among NVAF patients taking dabigatran.

Conclusions

In this multicenter, prospective and observational study, we found that a reduced platelet count was independently associated with an increased risk of bleeding events in

NVAF patients who underwent catheter ablation and were taking dabigatran. Our study supports a nonlinear relationship between platelet count and the risk of bleeding events. Additional randomized studies may be warranted to confirm the causality of these observational results.

Acknowledgments

Funding: 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).

Footnote

Reporting Checklist: The authors present the study in accordance with the STROBE reporting checklist. Available at http://dx.doi.org/10.21037/cdt-20-645

Data Sharing Statement: Available at http://dx.doi.org/10.21037/cdt-20-645

Peer Review File: Available at http://dx.doi.org/10.21037/cdt-20-645

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/cdt-20-645). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are 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. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Second Affiliated Hospital of Nanchang University research committee (MISSION-AF, ClinicalTrials.gov Identifier: NCT02414035) and informed consent was taken from all the patients.

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Cite this article as: Xiong Y, Zhou W, Li M, Wang T, Huang X, Bao H, Cheng X. Association between platelet count and the risk of bleeding among patients with nonvalvular atrial fibrillation taking dabigatran after radiofrequency ablation: a cohort study. Cardiovasc Diagn Ther 2020;10(5):1175-1183. doi: 10.21037/cdt-20-645

Supplementary

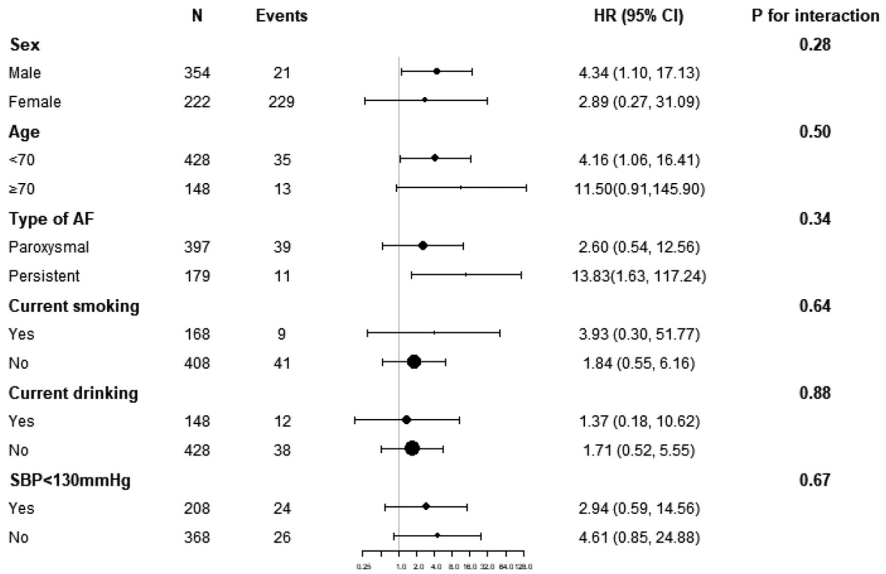

Figure S1 Effect size of platelet count on bleeding in each subgroup. Adjusted, if not stratified, for Adjusted for age, gender, smoking, drinking, BMI, type of AF, eGFR, hypertension, CHD, HF, previous stroke or TIA, PAD, history of bleeding, ACEIs/ARBs, beta-blockers, PPIs, amiodarone, digoxin, antiplatelet agents and stains.

Table S1 Sensitive analysis

	N	Model 1		Model 2		Model 3	
		HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
PLT ($\times 10^9$)	559	1.00 (1.00, 1.01)	0.789	1.00 (0.99, 1.00)	0.570	1.00 (0.99, 1.00)	0.372
PLT count, $\times 10^9$/L							
<100	25 [4]	Reference		Reference		Reference	
100–200	315 [24]	0.44 (0.16, 1.30)	0.141	0.34 (0.11, 0.99)	0.049	0.24 (0.07, 0.76)	0.016
≥200	219 [21]	0.58 (0.20, 1.68)	0.314	0.37 (0.12, 1.14)	0.084	0.25 (0.07, 0.84	0.025
P for trend			0.993		0.519		0.317
Dichotomous							
<100	25 [4]	1.99 (0.71, 5.53)	0.188	2.87 (1.00, 8.27)	0.051	4.13 (1.33, 12.88)	0.015
≥100	534 [45]	Reference		Reference		Reference	

Model 1: crude model. Model 2: adjusted for age, gender smoking, drinking, BMI, type of AF. Model 3: as model 2, and additionally adjusted for eGFR, hypertension, CHD, HF, previous stroke or TIA, PAD, history of bleeding, ACEIs/ARBs, beta-blockers, PPIs, amiodarone, digoxin and statins.

Table S2 The detail of platelet count of three gruops

Platelet count, $\times 10^9$/L	N	Average mean	Median	Range
T1 (<100)	25	86.1	90	62.0–99.4
T2 (100–200)	323	159.4	163	100.0–199.3
T3 (>200)	228	235.9	229	200.0–300.0