Diastolic blood pressure achieved at target systolic blood pressure (120–140 mm Hg) and dabigatran-related bleeding in patients with nonvalvular atrial fibrillation: A real-world study

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Abstract

Objective: Elevated systolic blood pressure (SBP) can significantly increase the bleeding risk in patients with atrial fibrillation (AF). However, it is unclear whether elevated diastolic blood pressure (DBP), in the presence of well-controlled SBP is also associated with bleeding. Therefore, we aimed to examine the specific relationship between DBP and bleeding in patients with AF treated with anticoagulants and had well-controlled SBP.

Methods: We analyzed data from 542 of 929 patients with nonvalvular AF (NVAF) treated with dabigatran from the Monitor System for the Safety of Dabigatran Treatment study (MISSION-AF) who had a SBP of 120–140 mm Hg at the time of enrollment. The association between DBP and bleeding was analyzed using multivariate logistic regression and smooth curve fitting (penalized spline method). Threshold saturation effect analysis was used to show the nonlinear relationship between DBP and bleeding.

Results: After 3 months of follow-up, 49 bleeding events occurred. Compared with participants with DBP <80 mm Hg, those with DBP ≥80 mm Hg had a 118% higher bleeding risk [hazard ratio (HR): 2.18; 95% confidence interval (CI): 1.19, 3.98; p<0.05]. The smooth curve showed a nonlinear relationship between DBP and bleeding risk, and the inflection point of DBP was 80 mm Hg. When DBP was ≥80 mm Hg, the bleeding risk increased by 59% (HR: 1.59; 95% CI: 1.16, 2.19; p<0.05) for every 5 mm Hg increase in DBP.

Conclusion: Upon achieving an optimal SBP (120–140 mm Hg), a higher DBP might be associated with a higher bleeding risk in patients with NVAF treated with dabigatran. *(Anatol J Cardiol 2020; 24: 267-73)*

Keywords: atrial fibrillation, bleeding, blood pressure, dabigatran, hypertension

Introduction

Epidemiological surveys have shown that approximately 33.59 million patients have atrial fibrillation (AF) worldwide, with a prevalence of approximately 3%; most patients with AF have nonvalvular AF (NVAF) (1, 2). Stroke is the most important complication in patients with AF, and oral anticoagulants (OACs) can effectively prevent stroke (3). However, taking OACs was often associated with a high bleeding risk among patients with AF (4).

Previous studies have suggested that higher systolic blood pressure (SBP) significantly increases the bleeding risk in patients with AF (5, 6). It should be noted that higher SBP often coexists with abnormal diastolic blood pressure (DBP) (7, 8). However, to the best of our knowledge, few previous studies have examined the specific relationship between DBP and bleeding risk in the population with AF. Therefore, the association between abnormal DBP and bleeding risk in patients with AF is unclear. In addition, previous studies have suggested that the bleeding risk is the lowest when SBP is controlled at 120–140 mm Hg (9).

Hence, our study aimed to examine the association between DBP and bleeding risk in the presence of optimal SBP (120–140 mm Hg) among patients with NVAF treated with dabigatran.

Methods

Subject population and design

Our current study was a subgroup analysis of the Monitor System for the Safety of Dabigatran Treatment (MISSION-AF)

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Accepted Date: 21.05.2020 **Available Online Date:** 21.07.2020

DOI:10.14744/AnatolJCardiol.2020.11823

Anatol J Cardiol 2020; 24: 267-73
DOI:10.14744/AnatolJCardiol.2020.11823

study. More details can be found on the related website (ClinicalTrials.gov Identifier: NCT02414035). Briefly, the MISSION-AF is a large, observational, multicenter, double-blind study. From February 2015 to December 2017, 929 participants were recruited from 12 hospitals throughout China. Details regarding the research population definition, inclusion, and exclusion criteria were discussed in detail in a previously published article (10).

The study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of the Second Affiliated Hospital of Nanchang University. Informed written consent was obtained from all patients before they were enrolled in this study.

Data collection

The exposure variable was mean DBP, defined as the mean value of DBP measured before the bleeding event. Both DBP and SBP were measured thrice using an electronic sphygmomanometer (OMRON; Japan), with a 5-min rest between each measurement. Three consecutive measurements were obtained on the right arm, with 1-min intervals between each measurement. Subsequently, SBP and DBP were calculated as the mean of three independent measurements. The outcome variable was bleeding events that occurred at 3 months of follow-up. In the present study, bleeding events were confirmed based on clinical symptoms, imaging examinations, and laboratory tests, including major and minor bleeding. Major bleeding was defined as (1) fatal bleeding; (2) routine blood tests indicating that hemoglobin is reduced by >20 g/L in a short period of time, or requirement of red blood cell infusion; and (3) symptomatic bleeding in a critical area or organ. Other bleeding events not mentioned previously were defined as minor bleeding (11, 12).

The adjusted covariables were as follows: age (years); sex (male, female); body mass index (BMI, kg/m^2); heart rate (HR, bpm); estimated glomerular filtration rate (eGFR, ml/min/1.73 m^2); smoking status (never, former, or current); alcohol consumption status (never, former, or current); AF type (paroxysmal, persistent); radiofrequency ablation; CHA_2DS_2-VASc score (congestive heart failure, hypertension, age≥75 years or between 65 and 74 years, previous stroke or transient ischemic attack, vascular disease, diabetes mellitus, and female sex); HAS-BLED score (hypertension, abnormal renal function, abnormal liver function, age ≥65 years, history of stroke, bleeding, labile INRs, use of other drugs, and concurrent alcohol intake); and past medical history, including hypertension, heart failure (HF), stroke, systemic embolism, and history of medication, such as angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), calcium channel blockers (CCBs), diuretics, β-blockers, aspirin, clopidogrel, and warfarin. All of the above covariates were obtained from baseline data.

Follow-up

Our study data were obtained 1 and 3 months after the patients started taking dabigatran. Information, including routine blood, liver function, and renal function tests, BP measurements, and occurrence of adverse events during the follow-up period, was collected.

Statistical analysis

Continuous and categorical variables were presented as mean±SD and percentage (%), respectively. We divided the patients into three groups based on a DBP of 70 and 80 mm Hg, and the baseline characteristics of the study populations were described. First, DBP and bleeding events were used as independent and dependent variables, respectively, in a multivariate logistic regression analysis to assess the relationship between DBP and bleeding. Subsequently, we visually demonstrated the nonlinear relationship between DBP and bleeding through smooth curve fitting (penalized spline method). Furthermore, we accurately identified the curve inflection point by the threshold saturation effect and analyzed the nonlinear relationship between DBP and bleeding in patients with NVAF treated with dabigatran.

All data analyses and form production were performed using the statistical package R (http://www.R-project.org, The R Foundation) and Empower (R) (www.empowerstats.com; X&Y Solutions, Inc., Boston, MA, USA). When two-tailed p was <0.05, the analysis results were considered statistically significant.

Results

Baseline characteristics of all patients

The 3-month follow-up period was completed by 929 patients, and this analysis included 542 elderly patients with NVAF (mean age: 65.12±10.79 years; 58.49% men) after excluding patients with SBP <120 and >140 mm Hg (n=387). Figure 1 shows the inclusion process of the study population. The total number of bleeding events was 49 (including 32 hematuria, 6 gingival bleeding, 6 skin ecchymosis, 3 gastrointestinal bleeding, 1 hemoptysis, and 1 other bleeding case). All bleeding events were minor, and the incidence rate was 9.04% (49/542). Table 1 shows the baseline

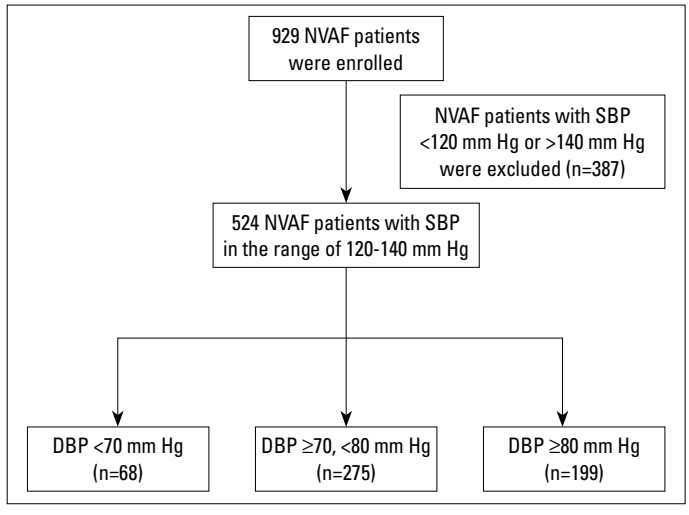

Figure 1. Flow chart of the study patients

Table 1. Baseline characteristics of all patients stratified by diastolic blood pressure categories

		DBP, mm Hg			
Characteristics[a]	**Total**	**<70**	**70–80**	**≥80**	***P*-value**
Number	542	68	275	199	
Age, years	65.12±10.79	65.78±11.22	65.92±10.20	63.79±11.33	0.092
Male, n (%)	317 (58.49)	34 (50.00)	160 (58.18)	123 (61.81)	0.231
BMI, kg/m^2	24.56±3.56	24.29±3.76	24.55±3.51	24.68±3.57	0.765
HR, bpm	81.57±19.25	78.71±15.31	79.82±18.25	84.94±21.28	0.036
eGFR, ml/min/1.73 m^2	81.42±16.89	80.64±17.25	81.49±16.26	81.57±17.70	0.588
Smoking, n (%)					0.584
Never	394 (72.83)	53 (77.94)	200 (72.73)	141 (71.21)	
Former	73 (13.49)	10 (14.71)	35 (12.73)	28 (14.14)	
Current	74 (13.68)	5 (7.35)	40 (14.55)	29 (14.65)	
Drinking, n (%)					0.786
Never	417 (77.08)	55 (80.88)	207 (75.27)	155 (78.28)	
Former	69 (12.75)	6 (8.82)	38 (13.82)	25 (12.63)	
Current	55 (10.17)	7 (10.29)	30 (10.91)	18 (9.09)	
AF type, n (%)					0.813
Paroxysmal	298 (55.08)	35 (51.47)	152 (55.47)	111 (55.78)	
Persistent	243 (44.92)	33 (48.53)	122 (44.53)	88 (44.22)	
Radiofrequency, n (%)	357 (65.87)	40 (58.82)	184 (66.91)	133 (66.83)	0.424
CHA_2DS_2-VASc score					0.572
<2	197 (36.35)	24 (35.29)	95 (34.55)	78 (39.20)	
≥2	345 (63.65)	44 (64.71)	180 (65.45)	121 (60.80)	
HAS-BLED score					0.326
<3	527 (97.23)	68 (100.00)	266 (96.73)	193 (96.98)	
≥3	15 (2.77)	0 (0.00)	9 (3.27)	6 (3.02)	
Comorbidities, n (%)					
Hypertension	281 (51.85)	36 (52.94)	137 (49.82)	108 (54.27)	0.62
HF	125 (23.06)	23 (33.82)	60 (21.82)	42 (21.11)	0.078
Stroke	64 (11.81)	7 (10.29)	28 (10.18)	29 (14.57)	0.315
Systemic embolism	2 (0.37)	0 (0.00)	2 (0.73)	0 (0.00)	0.377
Diabetes mellitus	61 (12.30)	7 (10.45)	35 (13.78)	19 (10.86)	0.587
Medication use, n (%)					
ACEIs/ARBs	181 (33.39)	36 (52.94)	80 (29.09)	65 (32.66)	<0.001
CCBs	105 (19.37)	20 (29.41)	41 (14.91)	44 (22.11)	0.012
Diuretic	81 (14.94)	9 (13.24)	38 (13.82)	34 (17.09)	0.563
β-blockers	217 (40.04)	30 (44.12)	92 (33.45)	95 (47.74)	0.006
Aspirin	12 (2.21)	2 (2.94)	4 (1.45)	6 (3.02)	0.475
Clopidogrel	6 (1.11)	0 (0.00)	3 (1.09)	3 (1.51)	0.591
Warfarin	7 (1.29)	0 (0.00)	5 (1.82)	2 (1.01)	0.446

[a]Data are presented as number (%) or mean±standard deviation.
BMI - body mass index; HR - heart rate; eGFR - estimate glomerular filtration rate; AF - atrial fibrillation; DBP - diastolic blood pressure; CHA_2DS_2-VASc - congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, previous stroke or diastolic blood pressure; transient ischemic attack, vascular disease, 65–74 years of age, female sex; HAS-BLED - hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalized ratio, elderly, drugs/alcohol concomitantly; HF - heart failure; ACEIs - angiotensin-converting enzyme inhibitors; ARBs - angiotensin receptor blockers; CCBs - calcium channel blockers.

Anatol J Cardiol 2020; 24: 267-73
DOI:10.14744/AnatolJCardiol.2020.11823

characteristics of patients based on the DBP groups (<70 mm Hg, 70–80 mm Hg, ≥80 mm Hg). The following variables were not significantly different between the DBP groups: age, sex, BMI, eGFR, smoking, alcohol consumption, AF type, radiofrequency ablation, CHA_2DS_2-VASc score, HAS-BLED score, hypertension, HF, stroke, systemic embolism, diabetes mellitus, and diuretic, aspirin, clopidogrel, and warfarin use (all p>0.05). The high DBP group (≥80 mm Hg) had higher HR and β-blocker medication rates and lower ACEI/ARB and CCB medication rates (all p<0.05).

Association between DBP achieved at target SBP (120–140 mm Hg) and bleeding risk

In this study, we constructed three models for analyzing the independent association between DBP and bleeding in Table 2. In the fully adjusted model (model 3), the bleeding risk increased by 13% for every 5 mm Hg increase in DBP (HR: 1.13; 95% CI, 0.93–1.38). Subsequently, DBP was converted from a continuous variable to a categorical variable (<80 mm Hg, 70–80 mm Hg, ≥80 mm Hg) according to clinical experience and literature (13). When the intermediate group (70–80 mm Hg) was used as the reference group, the bleeding risk of the lower DBP and higher DBP groups increased by 137% and 169%, respectively (<70 mm Hg; HR: 2.37; 95% CI, 1.17; 4.14; ≥80 mm Hg; HR,: 2.69; 95% CI: 1.38; 5.28). Because the number of patients with DBP <70 mm Hg was relatively small, we combined the low (<70 mm Hg) and medium DBP groups (70–80 mm Hg) into a reference group (<80 mm Hg). Compared with the reference group (<80 mm Hg), the bleeding risk in the high DBP group (≥80 mm Hg) increased by 118% (HR: 2.18; 95% CI: 1.19; 3.98, p<0.05).

Nonlinear relationship between DBP and bleeding risk

Adjusted smooth curve fitting showed that the relationship between DBP and bleeding was nonlinear (Fig. 2). On the left side of the inflection point, the bleeding risk decreased as DBP increased. The bleeding risk increased in individuals with DBP levels on the right side of the inflection point, and the right side of the curve was steeper. We fit the association between DBP and bleeding using the two piecewise binary logistic regression model (Table 3). The p for the log likelihood ratio test was <0.05, indicating that the two piecewise binary logistic regression was more suitable for fitting the association between DBP and bleed-

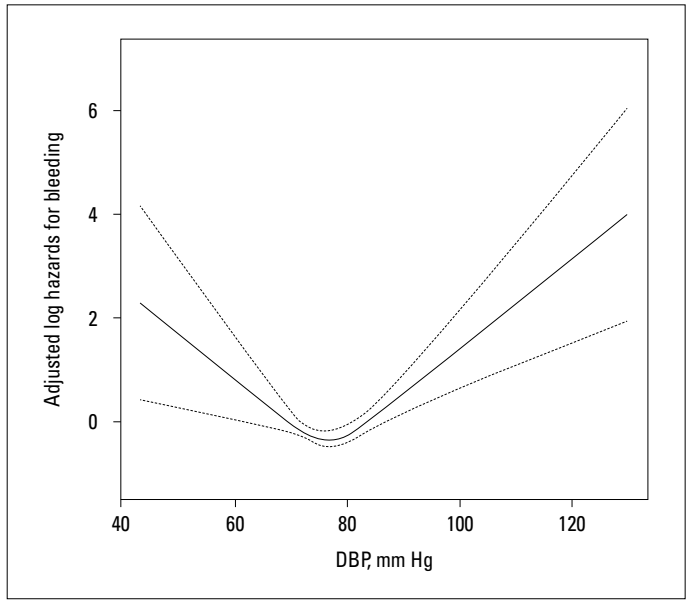

Figure 2. The smooth curve fitting shows a nonlinear association between diastolic blood pressure and bleeding among patients with NVAF treated with dabigatran. Adjusted factors include age, sex, BMI, HR, eGFR, smoking, drinking, AF type, radiofrequency ablation, CHA_2DS_2-VASc score, HAS-BLED score, hypertension, HF, stroke, systemic embolism, ACEIs/ARBs, CCBs, diuretic, β-blockers, aspirin, clopidogrel, and warfarin

Table 2. Unadjusted and adjusted association between diastolic blood pressure and bleeding

	Model 1		Model 2		Model 3	
DBP, mm Hg†	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Continuous, 5 mm Hg	1.09 (0.91, 1.32)	0.353	1.11 (0.92, 1.33)	0.272	1.13 (0.93, 1.38)	0.222
Categories						
<70	2.09 (0.90, 4.89)	0.088	1.90 (0.81, 4.45)	0.141	2.37 (0.92, 6.09)	0.073
70–80	Reference		Reference		Reference	
≥80	2.14 (1.14, 4.00)	0.018	2.20 (1.17, 4.14)	0.014	2.69 (1.38, 5.28)	0.004
Categories						
<80	Reference		Reference		Reference	
≥80	1.76 (1.01, 3.09)	0.047	1.86 (1.06, 3.27)	0.031	2.18 (1.19, 3.98)	0.012

†Cox proportional hazards models were used to estimate HR and 95% CI.
Model 1: adjusted for none.
Model 2: adjusted for age and sex.
Model 3: adjusted for age, sex, BMI, HR, eGFR, smoking, drinking, AF type, radiofrequency ablation, CHA_2DS_2-VASc score, HAS-BLED score, hypertension, HF, stroke, systemic embolism, ACEIs/ARBs, CCBs, diuretic, β-blockers, aspirin, clopidogrel, and warfarin.
BMI - body mass index; HR - heart rate; eGFR - estimate glomerular filtration rate; AF - atrial fibrillation; DBP - diastolic blood pressure; HR - hazard ratio; CI - confidence interval; HF - heart failure; ACEIs - angiotensin-converting enzyme inhibitors; ARBs - angiotensin receptor blockers; CCBs - calcium channel blockers

Table 3. Threshold effect analysis of diastolic blood pressure on bleeding

	Number (%)	Model 1		Model 2		Model 3	
		HR (95%CI)	*P*-value	HR (95%CI)	*P*-value	HR (95%CI)	*P*-value
DBP, 5 mm Hg*	49 (9.04)	1.09 (0.91, 1.32)	0.353	1.11 (0.92, 1.33)	0.272	1.13 (0.93, 1.38)	0.222
Inflection point							
<80 mm Hg	24 (7.00)	0.78 (0.58, 1.03)	0.083	0.80 (0.59, 1.08)	0.141	0.81 (0.58, 1.12)	0.197
≥80 mm Hg	25 (12.56)	1.58 (1.19, 2.08)	0.001	1.55 (1.16, 2.07)	0.003	1.59 (1.16, 2.19)	0.004
P for log likelihood ratio test		0.007		0.014		0.017	

*Cox proportional hazards models were used to estimate HR and 95% CI.
Model 1: adjusted for none.
Model 2: adjusted for age and sex.
Model 3: adjusted for age, sex, BMI, HR, eGFR, smoking, drinking, AF type, radiofrequency ablation, CHA_2DS_2-VASc score, HAS-BLED score, hypertension, HF, stroke, systemic embolism, ACEIs/ARBs, CCBs, diuretic, β-blockers, aspirin, clopidogrel, and warfarin.
BMI - body mass index; HR - heart rate; eGFR - estimate glomerular filtration rate; AF - atrial fibrillation; DBP - diastolic blood pressure; HR - hazard ratio; CI - confidence interval; HF - heart failure; ACEIs - angiotensin-converting enzyme inhibitors; ARBs - angiotensin receptor blockers; CCBs - calcium channel blockers

ing. The inflection point of DBP was 80 mm Hg. The HRs (95% CIs) were 0.81 (0.58–1.12) and 1.59 (1.16–2.19) on the left and right sides of the inflection point, respectively. The results suggested that bleeding risk increased only with DBP levels on the right of the inflection point (DBP ≥80 mm Hg).

Discussion

This is the first report on the relationship between DBP and bleeding when SBP was controlled within the ideal range (120–140 mm Hg) in patients with NVAF treated with dabigatran. In our study, when the DBP was 80 mm Hg, it was associated with the lowest bleeding risk. In patients with DBP <80 mm Hg, a negative relationship was found between DBP and bleeding risk [HR: 0.81; 95% (CI): 0.58–1.12]. In contrast, when DBP was ≥80 mm Hg, DBP was positively associated with bleeding risk [HR: 1.59; 95% (CI): 1.16–2.19]. Our findings suggested a nonlinear relationship between DBP and bleeding risk when SBP was controlled at 120–140 mm Hg in patients with NVAF treated with dabigatran.

Of note, previous studies have shown that the risk of adverse events was the lowest when SBP was controlled between 120 and 140 mm Hg (13). Therefore, when SBP was within this range, an independent effect of DBP on bleeding risk was observed. Consistent with our results, the 2017 ACC/AHA Clinical Practice Guideline for High Blood Pressure indicated that DBP ≥80 mm Hg was associated with a higher bleeding risk (14). In addition, the HAS-BLED score is widely used to assess the bleeding risk of patients with AF, and elevated SBP (≥160 mm Hg) was one of the risk factors (15-17). Previous studies have also reported that higher SBP increased the bleeding risk of patients with NVAF treated with anticoagulants (5). However, the HAS-BLED score only included elevated SBP as a risk factor and does not consider uncontrolled DBP as a risk factor. Our study suggested that even if SBP was optimal, elevated DBP (≥80 mm Hg) was associated with a higher bleeding risk in patients with NVAF treated with dabigatran.

Some mechanisms may explain this relationship between DBP and bleeding risk in the DBP ≥80 mm Hg group. A study suggested that DBP increased the bleeding risk possibly through the pathway in which higher DBP impaired endothelial function (18). Another study reported that hypertension increased platelet aggregation and activity, thereby activating the fibrinolytic system, which led to increased bleeding risk (19). A study also found that hypertension was directly related to vascular endothelial lesions, microcirculatory disorders, and modification of the blood coagulation processes (20). In addition, 24 patients had adverse bleeding events in the DBP <80 mm Hg group. However, the association between DBP and bleeding risk was not statistically significant. The negative association between DBP and bleeding risk in the DBP <80 mm Hg group may be because patients with AF treated with anticoagulants inherently had a higher bleeding risk, even if they had a lower BP (21). Therefore, future basic research is needed to explore the mechanism of the relationship between lower DBP and hemorrhage under the effect of anticoagulants.

Of note, most of the bleeding events in our study were minor. Despite this, there are still important clinical implications. First, minor bleeding events are often closely related to major bleeding events (22). In addition, the occurrence of minor bleeding events often interferes with clinical anticoagulant treatment (23). In addition, we used 110 mg dabigatran instead of 150 mg for anticoagulant therapy in our study. The reasons are as follows: first, a previous RE-LY trial confirmed that 110 mg dabigatran was not inferior to 150 mg dabigatran for antithrombotic effects in Asian populations (24). Second, 110 mg dabigatran was selected as the study treatment, considering that 150 mg dabigatran was associated with a higher bleeding risk.

Study limitations

Some limitations should be noted. First, our study was an observational study; hence, evidence may be insufficient to determine a causal relationship between DBP and bleeding. Second, the study participants were Chinese patients with NVAF, and the

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DOI:10.14744/AnatolJCardiol.2020.11823

number of patients was relatively small; thus, the generalizability of the results to other patients with NVAF remained to be verified, and the power calculations were not adequate. Third, our study protocol only included 110 mg dabigatran as an anticoagulant; hence, the study results may not be suitable for patients with NVAF treated with 150 mg dabigatran. Fourth, we did not use 24-h BP monitors to measure BP. In the future, we will combine 24-h BP monitors with the Omron BP monitors. Finally, in the lower DBP group (<80 mm Hg), we observed a "strange phenomenon" in which the bleeding risk was reduced with increasing DBP, but the significant difference was not obvious because our sample size was relatively small. Further research is needed to explain the "strange phenomenon" in the future.

Despite these limitations, our study also had advantages. First, we used the mean DBP to reduce the measurement error caused by the inaccurate measurement of BP in patients with NVAF. Second, this "real-world" study was the first to explore the independent association between DBP and the bleeding risk in patients with NVAF treated with dabigatran. In addition, we provided sufficient statistical power to analyze the relationship between DBP and bleeding. Finally, the findings of the study should be helpful for future research enhancing the predictive models of bleeding.

Conclusion

Our study suggested that even if optimal SBP is achieved (120–140 mm Hg), a higher bleeding risk might be associated with elevated DBP in patients with NVAF treated with dabigatran. The DBP–bleeding risk association was more significant in the DBP ≥80 mm Hg group.

Acknowledgment: This study was supported by the Major New Drug Creation Program from the National Science and Technology Major Project (NO.2014ZX09303305) and the Natural Science Foundation of Jiangxi Province (20192BAB205033).

Conflict of interest: None declared.

Peer-review: Externally peer-reviewed.

Authorship contributions: Concept – Y.Y.; Design – Y.Y.; Supervision – H.B., X.C.; Fundings – X.C.; Materials – H.B., X.C.; Data collection and/or processing – Y.Y., M.L., W.Z., T.W., L.Z., L.H.; Analysis and/or interpretation – Y.Y.; Literature search – H.B., X.C.; Writing – Y.Y.; Critical review – H.B., X.C.

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