Association between body mass index and the risk of bleeding in elderly patients with non-valvular atrial fibrillation taking dabigatran: a cohort study

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Abstract

Background Uncertainty remains regarding the association between body mass index (BMI) and the risk of bleeding in patients with non-valvular atrial fibrillation (NVAF). We aimed to investigate the association between BMI and the risk of bleeding in elderly NVAF patients taking dabigatran.

Methods A total of 509 elderly NVAF patients, who were being treated at twelve centers in China from February 2015 to December 2017 and taking dabigatran, were analyzed. The exposure and outcome variables were BMI at baseline and bleeding events within the subsequent six months, respectively. Cox proportional hazards regression analysis was used to evaluate the association between BMI and the risk of bleeding. Moreover, the Cox proportional hazards regression with cubic spline functions and smooth curve fitting was conducted.

Results During the six-month follow-up, 50 participants experienced bleeding. Every 1 kg/m² increase in BMI was associated with a 12% increased risk of bleeding (P = 0.021). Compared to those with BMI values in Tertile 1 (< 22.5 kg/m²), the adjusted hazard ratio (HR) of bleeding for participants in Tertile 2 (22.5–25.3 kg/m²) and Tertile 3 (> 25.3 kg/m²) were 2.71 (95% CI: 1.02–7.17) and 3.5 (95% CI: 1.21–8.70), respectively. The P-trend-value was significant in all models. The adjusted smooth curve showed a linear association between BMI and bleeding. None of the stratified variables showed significant effect modification on the association between BMI and bleeding (P interaction > 0.05).

Conclusions BMI was significantly and positively associated with the risk of bleeding in elderly NVAF patients treated with dabigatran.

Keywords: Atrial fibrillation; Bleeding; Body mass index; Dabigatran

1 Introduction

Atrial fibrillation (AF) is the most common sustained arrhythmia and is associated with severe complications, including stroke, mortality and hospitalizations.\(^1\) The introduction of oral anticoagulants dramatically reduces the risk of stroke and thromboembolism.\(^2\) Dabigatran, a competitive direct thrombin inhibitor, is the usual direct-acting non-vitamin K antagonist oral anticoagulant (NOAC) applied in patients with non-valvular AF (NVAF) and can reduce the incidence of stroke and thromboembolism.\(^3,4\) However, anticoagulation therapy including dabigatran in NVAF patients is associated with a risk of bleeding, especially among elderly patients.\(^5,6\) The results from the National Registry of Atrial Fibrillation showed that the annual rates of bleeding were 3.74% and 2.99% in patients on dabigatran doses of 150 mg and 110 mg twice daily, respectively.\(^7\) Currently, there are five scoring systems for predicting bleeding risk in NVAF patients, including HAS-BLED, HEMORR2HAGES, ATRIA, ORBIT, and ABC.\(^8-12\) While these bleeding risk scores have been derived and developed mainly in patients who are on vitamin K antagonist oral anticoagulants (VKAs), there remains little knowledge about the risk factors for dabigatran-related bleeding. Therefore, it is necessary to explore the predictive factors of dabigatran-related bleeding in elderly NVAF patients.

Body mass index (BMI), a marker of obesity, is a well-known risk factor for cardiovascular diseases, including diabetes, coronary heart disease (CHD),\(^13\) cardiovascular death,\(^14\) and AF.\(^15,16\) The relationship between BMI and the risk of bleeding events among patients with a high risk

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of atherothrombotic disease has been well established\textsuperscript{[17–19]} However, in NVAF patients, the relationship between BMI and bleeding occurrence has been controversial.\textsuperscript{[20–23]} While some observational studies have confirmed that elevated BMI predicts the development of bleeding,\textsuperscript{[20,23]} several other studies have failed to show a significant contribution of BMI to bleeding risk.\textsuperscript{[21,22]} These conflicting results might be attributed to the differences in cohort characteristics, sample size, racial groups and adjustment of confounders. Additionally, these studies investigated only the linear relationship between BMI and bleeding; they did not discuss the nonlinear relationship. Importantly, to our knowledge, the association between BMI and bleeding in elderly NVAF patients taking dabigatran is still uncertain. Therefore, the objectives of this study were to explore the association between BMI and the risk of bleeding in elderly NVAF patients taking dabigatran.

2 Methods

2.1 Study population

Data from a cohort study conducted between February 2015 and December 2017 in twelve hospitals in China, which was a subset of the Monitor System for the Safety of Dabigatran Treatment study (MISSION-AF, Clinical Trial Number: NCT02414035). The study was supported by the Major New Drug Creation Program from National Science and Technology Major Project (2014ZX09303305) of China. Details regarding the method and design of the study have been introduced in previous publications.\textsuperscript{[24]} Briefly, participants with NVAF who initiated dabigatran (110 mg twice daily) orally after diagnosis were nonselectively and consecutively enrolled and were followed up at one month, three months and six months. At each follow-up, vital signs, study drug adherence, concomitant medication use, laboratory tests and outcomes were documented by trained research staff and physicians. The cut-off date for participant follow-up was May 2018. The project was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of the Second Affiliated Hospital of Nanchang University, Jiangxi, China. Informed written consent was obtained from all patients before their enrollment in this study.

Finally, a total of 942 participants completed the follow-up and outpatient reviews at six months. Participants meeting any of the following criteria were excluded: (1) patients aged < 60 years (n = 261); (2) participants with missing BMI values (n = 99); and (3) participants with missing laboratory test data (n = 73). The final sample size included in the analysis was 509 participants (Figure 1).

2.2 Outcome and exposure variables

The exposure and outcome variables were BMI at baseline and bleeding events within the subsequent six months. According to published guidelines and studies, we obtained the final outcome variable (bleeding events). Major bleeding was defined as: (1) fatal bleeding; (2) a reduction in hemoglobin concentration by at least 20 g/L, transfusion of at least two units of blood; or (3) symptomatic bleeding in a crucial area or organ that required hospitalization. Minor bleeds were defined as bleeds that did not fulfill the criteria for major bleeds.\textsuperscript{[25,26]}

2.3 Covariates and term definitions

The present study included demographic data, general information, and variables that affect BMI or bleeding events according to previous study reports and our clinical experiences. Therefore, the following variables were used to construct the fully adjusted model: (1) continuous variables included age; CHA\textsubscript{2}-DS\textsubscript{2}-VASc score [congestive heart failure (HF), hypertension, aged 75 years or over, diabetes mellitus, previous stroke or transient ischemic attack (TIA), vascular disease, 65–74 years of age, female]; the HAS-BLED score (hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalized ratio, elderly, drugs/alcohol concomitantly), obtained at baseline; systolic blood pressure (mmHg); leukocyte count (10\textsuperscript{9}/L); platelet count (10\textsuperscript{12}/L) and the estimated glomerular filtration rate (eGFR, mL/min per 1.73 m\textsuperscript{2}) obtained at baseline and follow-up; and (2) categorical variables included gender; smoking; drinking; AF type; radiofrequency ablation; self-reported medical history, including hypertension, HF, CHD, peripheral arterial disease (PAD),
TIA, stroke, diabetes mellitus; and concomitant drugs, such as amiodarone, other antiarrhythmic drugs, antiplatelet drugs, angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), proton pump inhibitors (PPIs) and statins, obtained at baseline. CHA2DS2-VASc (stroke or TIA, age ≥ 75 years: 2 points; and congestive HF, hypertension, 65–74 years of age, diabetes, female sex, vascular disease including peripheral vascular disease, aortic and coronary disease: 1 point). The eGFR was estimated by the Chronic Kidney Disease Epidemiology Collaboration equation. Blood pressure was measured twice in the right arm after 10 minutes of rest; the average of the two measurements was used. Hypertension was defined as systolic blood pressure ≥ 140 mmHg, diastolic blood pressure ≥ 90 mmHg or a self-reported physician diagnosis of hypertension. Information about current smoking and drinking habits, previous medical history, and the use of concomitant drugs was based on a questionnaire and medical records. Participants were categorized in terms of smoking/drinking as never smokers/drinkers, former smokers/drinkers (i.e., nonsmokers/drinkers who previously smoked/drank daily for at least one year) and current smokers/drinkers (i.e., daily smoking/drinking).

2.4 Statistical analyses

The continuous variables are presented as the mean ± SD or median ± interquartile range (IQR), and categorical variables are expressed as a frequency or percentage. We used the Pearson’s chi-squared test (categorical variables), one-way ANOVA or Kruskal-Wallis H tests (continuous variables) to test for differences among the different BMI groups (Tertile 1: < 22.5 kg/m²; Tertile 2: 22.5–25.3 kg/m²; Tertile 3: > 25.3 kg/m²). Multivariate Cox proportional hazards models were carried out to estimate the hazard ratio (HR) and 95% confidence interval (CI) between BMI and bleeding. We constructed three models based on clinical experiences and literature: Model 1, with no adjustment for covariates; Model 2, with adjustment only for sociodemographic data; and Model 3, which included Model 2 plus the other covariates presented in Table 1. To address the exact shape association between BMI and bleeding events in NVAF patients, Cox proportional hazards regression models with cubic spline functions and smooth curve fitting (penalized spline method) were conducted. Subgroup analyses were performed using stratified Cox proportional hazards regression analyses. In addition, to ensure the robustness of the data analysis, we performed a sensitivity analysis. We converted BMI into a categorical variable and calculated the P_{resid}-value. The purpose was to verify the results of BMI as a continuous variable and to observe the possibility of non-linearity.

All analyses were performed with statistical software packages in R software (version 3.3.1; http://www.R-project.org) and EmpowerStats (http://www.empowerstats.com, X & Y Solutions, Inc, Boston, MA, USA). All statistical tests were two-sided, and P-value < 0.05 was considered to be statistically significant.

3 Results

3.1 Baseline characteristics of the selected participants

Based on the inclusion and exclusion criteria, a total of 509 elderly NVAF patients (mean age: 70.01 ± 6.67 years; 48.13% were females) were selected for the final analysis. The baseline characteristics of participants are presented as BMI tertiles in Table 1. No statistically significant differences were detected for the following factors among the different BMI groups: age, gender, smoking, drinking, AF type, radiofrequency ablation, HF, PAD, TIA, stroke, CHA2DS2-VASc score, HAS-BLED score, drug combination, systolic blood pressure, eGFR, heart rate and platelet count (all P > 0.05). Participants with the highest tertile of BMI had higher leukocyte count values and a higher proportion of hypertension and diabetes mellitus than those in the other groups.

3.2 Association between BMI and the risk of bleeding

In this study, bleeding events occurred in 50 participants (48 minor bleeding events and 2 major bleeding events), including 30 hematuria cases, 5 gastrointestinal bleeding cases, 7 gingival bleeding cases, 7 skin ecchymosis cases and 1 epistaxis case. We constructed three models to analyze the independent role of BMI in bleeding. The HR and 95% CI for these three equations are listed in Table 2. In the Model 1, for every 1 kg/m² increase in BMI, the risk of bleeding increased by 9% (HR = 1.09, 95% CI: 1.01–1.18). After adjustment for different confounders, a positive association between BMI and bleeding was still found in the Model 2 & Model 3. Similarly, in the fully adjusted model (Model 3), for every 1 kg/m² increase in BMI, the risk of bleeding increased by 12% (HR = 1.12, 95% CI: 1.02–1.24). Compared to participants in Tertile 1, the adjusted HR of bleeding for participants in Tertile 2 and Tertile 3 were 2.71 (95% CI: 1.02–7.17) and 3.25 (95% CI: 1.21–8.70), respectively. The P_{resid}-value was significant in all the models. We also converted BMI to a categorical variable as clinical cutoffs (< 25 kg/m², 25–30 kg/m², and ≥ 30 kg/m²). Compared to participants with BMI < 25 kg/m², there was a significantly
### Table 1. Baseline characteristics of all patients stratified by BMI.

| Characteristics | Total (n = 509) | Tertile 1 (< 22.5 kg/m²) | Tertile 2 (22.5–25.3 kg/m²) | Tertile 3 (> 25.3 kg/m²) | Statistical values |
|----------------|-----------------|--------------------------|-----------------------------|--------------------------|-------------------|
|                |                 | (n = 161)                | (n = 172)                   | (n = 176)                | (F value*/H value†/χ² value#) P-value |
| Age, yrs       | 70.01 ± 6.67    | 70.33 ± 6.71             | 70.42 ± 6.69                | 69.32 ± 6.59             | 1.442 * 0.237  |
| Female         | 245 (48.13%)    | 242 (75.47%)             | 15 (8.72%)                 | 18 (10.55%)              | 2.441 # 0.295  |
| SBP, mmHg      | 127.42 ± 15.97  | 126.83 ± 18.62           | 126.66 ± 13.91             | 128.72 ± 15.22           | 2.267 * 0.413  |
| Leukocyte count, 10⁹/L | 6.14 ± 1.70 | 5.73 ± 1.55              | 6.18 ± 1.74                | 6.47 ± 1.72              | 8.294 * < 0.001 |
| Platelet count, 10⁹/L  | 176.56 ± 54.80 | 173.47 ± 56.83           | 178.11 ± 55.62             | 177.91 ± 52.22           | 0.372 * 0.689  |
| Heart rate, beats/min | 80.31 ± 18.33 | 79.75 ± 18.78            | 82.19 ± 19.47              | 78.99 ± 16.61            | 1.456 * 0.239  |
| Smoking        |                 |                          |                            |                          | 6.738 * 0.150  |
| Never          | 387 (76.18%)    | 124 (77.50%)             | 131 (76.16%)               | 132 (75.00%)             | 0.466 * 0.977  |
| Former         | 53 (10.43%)     | 15 (9.38%)               | 19 (11.05%)                | 19 (10.80%)              | 1.871 * 0.176  |
| Current        | 68 (13.39%)     | 21 (13.12%)              | 22 (12.79%)                | 25 (14.20%)              | 0.372 † 0.689  |
| Drinking       |                 |                          |                            |                          | 3.393 * 0.183  |
| Never          | 450 (88.58%)    | 137 (85.09%)             | 158 (91.86%)               | 155 (88.57%)             | 2.370 * 0.306  |
| Former         | 18 (3.54%)      | 10 (6.21%)               | 2 (1.16%)                  | 6 (3.43%)                | 3.866 * 0.145  |
| Current        | 40 (7.87%)      | 14 (8.70%)               | 12 (6.98%)                 | 14 (8.00%)               | 1.609 * 0.447  |
| AF type        |                 |                          |                            |                          | 3.393 * 0.183  |
| Paroxysmal     | 277 (54.42%)    | 78 (48.45%)              | 98 (56.98%)                | 101 (57.39%)             | 0.164 # 0.921  |
| Persistent     | 232 (45.58%)    | 83 (51.55%)              | 74 (43.02%)                | 75 (42.61%)              | 0.365 # 0.833  |
| Radiofrequency ablation | 319 (62.67%) | 95 (59.01%)              | 113 (65.70%)               | 111 (63.07%)             | 1.609 * 0.447  |
| Medical history |                 |                          |                            |                          | 3.393 * 0.183  |
| Hypertension   | 299 (58.74%)    | 76 (47.20%)              | 102 (59.30%)               | 121 (68.75%)             | 16.138 # < 0.001 |
| HF             | 139 (27.31%)    | 43 (26.71%)              | 46 (26.74%)                | 50 (28.41%)              | 0.164 # 0.921  |
| CHD            | 48 (9.43%)      | 17 (10.56%)              | 15 (8.72%)                 | 16 (9.09%)               | 0.365 * 0.833  |
| PAD            | 14 (2.75%)      | 2 (1.24%)                | 5 (2.91%)                  | 7 (3.98%)                | 2.375 * 0.305  |
| TIA            | 4 (0.79%)       | 3 (1.86%)                | 0                          | 1 (0.57%)                | 3.866 * 0.145  |
| Stroke         | 53 (10.41%)     | 20 (12.42%)              | 13 (7.56%)                 | 20 (11.36%)              | 2.370 * 0.306  |
| Diabetes mellitus | 69 (14.71%) | 16 (10.67%)              | 15 (9.43%)                 | 38 (23.75%)              | 15.902 * 0.012 |
| Drug combination |                 |                          |                            |                          | 3.209 * 0.201  |
| Amiodarone     | 212 (41.65%)    | 64 (39.75%)              | 82 (47.67%)                | 66 (37.50%)              | 4.054 * 0.132  |
| Other antiarrhythmic drug | 42 (8.25%) | 17 (10.56%) | 11 (6.40%) | 14 (7.95%) | 1.935 * 0.380 |
| Antiplatelet drugs | 15 (2.95%) | 2 (1.24%) | 5 (2.91%) | 8 (4.55%) | 3.260 * 0.201 |
| PPIs           | 229 (44.99%)    | 74 (45.96%)              | 83 (48.26%)                | 72 (40.91%)              | 1.987 * 0.370  |
| ACEIs/ARBs     | 199 (39.10%)    | 54 (33.54%)              | 66 (38.37%)                | 79 (44.89%)              | 4.603 * 0.100  |
| Statins        | 159 (31.24%)    | 47 (29.19%)              | 49 (28.49%)                | 63 (35.80%)              | 2.620 * 0.270  |
| CHA₂DS₂-VASc score | 505 (99.46%) | 111 (21.81%) | 38 (23.60%) | 35 (20.35%) | 0.523 * 0.770 |
| < 2            | 111 (21.81%)    | 38 (23.60%)              | 35 (20.35%)                | 38 (21.59%)              | 0.523 * 0.770  |
| ≥ 2            | 398 (78.19%)    | 123 (76.40%)             | 137 (79.65%)               | 138 (78.41%)             | 0.523 * 0.770  |
| HAS-BLED score | 488 (95.87%)    | 151 (93.79%)             | 165 (95.93%)               | 172 (97.73%)             | 3.299 * 0.192  |
| < 3            | 488 (95.87%)    | 151 (93.79%)             | 165 (95.93%)               | 172 (97.73%)             | 3.299 * 0.192  |
| ≥ 3            | 2 (4.13%)       | 10 (6.21%)               | 7 (4.07%)                  | 4 (2.27%)                | 3.299 * 0.192  |

Data are presented as means ± SD or n (%). ACEIs: angiotensin-converting enzyme inhibitors; AF: atrial fibrillation; ARBs: angiotensin receptor blockers; BMI: body mass index; CHD: coronary heart disease; eGFR: glomerular filtration rate; HF: heart failure; PAD: peripheral arteriopathy; PPIs: proton pump inhibitors; SBP: systolic blood pressure; TIA: transient ischemic attack.

Increased risk of bleeding for the participants with BMI values of 25–30 kg/m² and ≥ 30 kg/m² (all P < 0.05). The F value was significant in all the models, suggesting that the association between BMI and bleeding was likely to be linear.
Table 2. Relationship between BMI and bleeding in different models.

| BMI Category | n     | Model 1                              | Model 2                              | Model 3                              |
|--------------|-------|--------------------------------------|--------------------------------------|--------------------------------------|
|              |       | HR (95% CI)                          | HR (95% CI)                          | HR (95% CI)                          |
| Continuous   | 509   | 1.09 (1.01–1.18)                     | 1.10 (1.02–1.19)                     | 1.12 (1.02–1.24)                     |
| Tertiles     |       |                                       |                                       |                                       |
| < 22.5 kg/m² | 161   | Reference                            | Reference                            | Reference                            |
| 22.5–25.3 kg/m² | 172  | 2.08 (0.94–4.61)                     | 2.23 (1.00–5.01)                     | 2.71 (1.02–7.17)                     |
| > 25.3 kg/m² | 176   | 2.26 (1.04–4.90)                     | 2.40 (1.10–5.24)                     | 3.25 (1.21–8.70)                     |
| Post-trend-value |     |                                       |                                       |                                       |
| BMI category |       |                                       |                                       |                                       |
| < 25 kg/m²   | 315   | Reference                            | Reference                            | Reference                            |
| 25–30 kg/m²  | 168   | 1.73 (0.96–3.13)                     | 1.79 (0.99–3.25)                     | 2.12 (1.04–4.31)                     |
| ≥ 30 kg/m²   | 26    | 3.20 (1.30–7.87)                     | 3.53 (1.42–8.82)                     | 3.67 (1.20–11.26)                    |
| Post-trend-value |     |                                       |                                       |                                       |

Model 1: adjusted for none. Model 2: adjusted for age, gender, smoking, and drinking. Model 3: adjusted for variables in Model 2 plus AF type, therapeutic strategy, hypertension, HF, CHD, PAD, TIA, stroke, diabetes mellitus, amiodarone, other antiarrhythmic drug, antiplatelet drugs, ACEIs/ARBs, stain, PPIs, CHA2DS2-VASc score, HAS-BLED score, SBP, leukocyte count, platelet count, and eGFR. Refer to Cox proportional hazards models were used to estimate HR and 95% CI. ACEIs: angiotensin-converting enzyme inhibitors; AF: atrial fibrillation; ARBs: angiotensin receptor blockers; BMI: body mass index; CI: confidence interval; CHD: coronary heart disease; eGFR: glomerular filtration rate; HF: heart failure; HR: hazard ratio; PAD: peripheral arteriopathy; PPIs: proton pump inhibitors; SBP: systolic blood pressure; TIA: transient ischemic attack.

Further analyses using restricted cubic splines confirmed the dose-relationship between BMI and bleeding (Figure 2). The fully adjusted smooth curve indicated that the association of BMI with bleeding was also linear.

3.3 Subgroup analysis

We further explored the role of other covariates between BMI and bleeding. As shown in Figure 3, the association between BMI and risk of bleeding was consistent in the following subgroups: gender, AF type, therapeutic strategy, hypertension, CHD, HF, diabetes mellitus, eGFR, CHA2DS2-VASc score and HAS-BLED score (all \( P_{interaction} > 0.05 \)).

4 Discussion

In the present study, we found that, after adjusting for other covariates, BMI was positively associated with the risk of bleeding in elderly NVAF patients who take dabigatran (110 mg twice daily). Each 1 kg/m² increase in BMI was associated with a 12% increase in risk of bleeding. Additionally, the subgroup analyses showed that none of the stratification variables showed significant effect modification on the association between BMI and bleeding \( P_{interaction} > 0.05 \).

The association between BMI and the risk of bleeding has been examined in several previous studies. Boriani, et al.\(^20\) used data from 21028 AF participants who was...
| Characteristic                | Number of participants | HR (95% CI)       | P_{value} |
|-----------------------------|------------------------|-------------------|-----------|
| Gender                      |                        |                   |           |
| Male                        | 264                    | 1.13 (0.98–1.30)  | 0.472     |
| Female                      | 245                    | 1.06 (0.94–1.18)  |           |
| AF type                     |                        |                   |           |
| Paroxysmal                  | 277                    | 1.13 (1.00–1.29)  | 0.326     |
| Persistent                  | 232                    | 1.03 (0.91–1.18)  |           |
| Therapeutic strategy        |                        |                   |           |
| Others                      | 190                    | 1.02 (0.90–1.16)  | 0.193     |
| Radiofrequency ablation     | 319                    | 1.15 (1.01–1.31)  |           |
| Hypertension                |                        |                   |           |
| No                          | 210                    | 1.24 (1.04–1.48)  | 0.075     |
| Yes                         | 299                    | 1.03 (0.92–1.15)  |           |
| CHD                         |                        |                   |           |
| No                          | 461                    | 1.07 (0.97–1.18)  | 0.418     |
| Yes                         | 48                     | 1.23 (0.89–1.70)  |           |
| HF                          |                        |                   |           |
| No                          | 370                    | 1.10 (0.99–1.22)  | 0.486     |
| Yes                         | 139                    | 1.02 (0.84–1.23)  |           |
| Diabetes mellitus           |                        |                   | 0.96      |
| No                          | 400                    | 1.08 (0.97–1.20)  |           |
| Yes                         | 69                     | 1.09 (0.90–1.31)  |           |
| eGFR, mL/min per 1.73 m²    |                        |                   | 0.96      |
| < 60                        | 79                     | 1.08 (0.90–1.29)  |           |
| ≥ 60                        | 425                    | 1.08 (0.98–1.21)  |           |
| CHA2DS2-VASc score          |                        |                   | 0.185     |
| < 2                         | 111                    | 1.31 (0.97–1.78)  |           |
| ≥ 2                         | 398                    | 1.07 (0.97–1.17)  |           |
| HAS-BLED score              |                        |                   | 0.411     |
| < 3                         | 488                    | 1.07 (0.97–1.18)  |           |
| ≥ 3                         | 21                     | 1.24 (0.88–1.74)  |           |

Figure 3. The association between BMI and the risk of bleeding in various subgroups. The HR of bleeding in relation to BMI were calculated using the Cox proportional hazards regression models. Each subgroup analysis adjusted, if not stratified, for age, gender, smoking, drinking, AF type, therapeutic strategy, hypertension, CHD, PAD, TIA, stroke, diabetes mellitus, amiodarone, other antiarrhythmic drug, antiplatelet drugs, ACEIs/ARBs, statin, PPIs, CHA2DS2-VASc score, HAS-BLED score, SBP, leukocyte count, platelet count, eGFR. ACEIs: angiotensin-converting enzyme inhibitors; AF: atrial fibrillation; ARBs: angiotensin receptor blockers; BMI: body mass index; CI: confidence interval; CHD: coronary heart disease; eGFR: glomerular filtration rate; HF: heart failure; HR: hazard ratio; PAD: peripheral arterialopathy; PPIs: proton pump inhibitors; SBP: systolic blood pressure; TIA: transient ischemic attack.

 treated with oral anticoagulants, and found that an elevated BMI was associated with the risk of bleeding. Tittl, et al.\cite{23} prospectively collected data from a noninterventional registry study of 3432 subjects in Germany and found that the risk of bleeding increased with rising BMI in patients receiving fixed-dose NOAC anticoagulation. However, several reports have also yielded conflicting results. Lee, et al.\cite{21} reported that a lower BMI is associated with a higher incidence of major bleeding in patients with AF who have been treated with dabigatran. A meta-analysis of 13 large NOAC trials demonstrated that obese patients were at lower risk of bleeding than normal weight patients (OR = 0.84, 95% CI: 0.72–0.98).\cite{23} Nonetheless, within the Asian populations in the meta-analysis, BMI categories have no effect on the occurrence of bleeding events. These conflicting results might be attributed to the differences in cohort characteristics, sample size, racial groups and adjustment of confounders.

Although, in the present study, the majority of bleeding events were minor bleeding events, our study also carries important clinical implications. Previous studies have investigated whether minor bleeding may predict major bleeding,\cite{26} and may lead to the interruption or discontinuation of anticoagulant treatment, especially for elderly patients.\cite{29} In addition, there was no obvious advantage of 150 mg over 110 mg dabigatran in further reducing the risk of ischemic stroke and all-cause mortality in Asian patients,\cite{30,31} and low-dose dabigatran (110 mg twice daily) has been associated with fewer bleeding events.\cite{32,33} Therefore, physicians...
may conservatively prefer to prescribe low doses of dabigatran (110 mg twice daily) in China. In our study, we provide novel findings regarding the relationship between BMI and the prevalence of minor bleeding in elderly NVAF patients who took 110 mg dabigatran twice daily. These findings may provide important clues to management prognosis and possibly therapeutic approaches of elderly obesity patients with NVAF in China.

The mechanism driving this association is still unclear. However, several possible reasons could account for the association between BMI and bleeding. Obesity was associated with hyperexpression of tumor necrosis factor-α (TNF-α) and plasminogen activator inhibitor-1 (PAI-1), which leads to a chronic pro-inflammatory state and impaired endothelial function. Additionally, a previous study suggested that leukocyte count was an independent predictor of bleeding. The capillary plugging, the production of pro-inflammatory and vasculotoxic factors, like reactive oxygen species, proteases, eicosanoids, and myeloperoxidase-injured microvasculature maybe the potential mechanisms. The increased risk of bleeding at higher BMI values was also confirmed in the analysis adjusted by leukocyte count levels at baseline. Furthermore, the negative effects of diabetes mellitus and hypertension on the cardiovascular system also contribute to bleeding risk in those with AF. Considering the observations that hypertension and diabetes mellitus affected nearly 68.75% and 23.75% of our study population in the high tertile of BMI and the prevalence of bleeding was substantial, we also found an independent effect of BMI and bleeding after adjusting for hypertension and diabetes as covariates.

4.1 Strengths and limitations

Our study has several strengths. Firstly, this study was the first to explore the independent association between BMI and the risk of bleeding in elderly patients with NVAF patients who taking dabigatran (110 mg twice daily) in China. Secondly, we used strict statistical adjustment to minimize residual confounders. Thirdly, we handled target independent variables as both continuous variables and categorical variables. Such approach can reduce the contingency in the data analysis and enhance the robustness of the results. Last but not least, the effect modifier factor analysis made better use of the data and yielded stable conclusions in different subgroups in this study. Further evidence from large prospective studies may further clarify this relationship. However, there are some limitations in the present study. Firstly, the main limitations of this study were its observational nature and the selection bias that may have occurred because the participants without complete data were excluded. Secondly, although we adjusted for a range of confounding variables, the effects of some influential confounders could not be excluded. Thirdly, the population had relatively few underweight patients, which limits the generalizability of these results. Last but not least, the relatively short follow-up period was a shortcoming of our study; however, a previous study observed that the risk of bleeding was significantly elevated during the early phase of anticoagulant therapy initiation.

4.2 Conclusions

BMI was significantly and positively associated with the risk of bleeding in elderly NVAF patients treated with dabigatran. Further evidence from large prospective studies may further clarify this relationship.

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