Assessment of Predicted Rate and Associated Factors of Dabigatran-induced Bleeding Events in Malaysian Patients with Non-Valvular Atrial Fibrillation

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ABSTRACT - Purpose: To assess the predicted rate and the factors associated with bleeding events among patients with non-valvular atrial fibrillation (NVAF) receiving dabigatran therapy. **Methods:** This retrospective cohort study includes adult patients of two tertiary hospitals in Malaysia. Potential study subjects were identified using pharmacy supply database or novel oral anticoagulant (NOAC) registry. Demographics, clinical data and laboratory test results were extracted from the medical records of the patients or electronic databases. The main outcome measure is the occurrence of a bleeding event. Bleeding events were classified into major bleeding, clinically relevant non-major bleeding, or minor bleeding, according to the International Society on Thrombosis and Haemostasis criteria. We consider clinically relevant non-major bleeding events or major bleeding events as clinically relevant bleeding events. An occurrence of any bleeding event was recorded from the initiation of NOAC therapy until the death of a patient, or the date of permanent discontinuation of NOAC use, or the last day of data collection. The predicted rate of dabigatran-induced bleeding events per 100 patient-years was estimated. **Results:** During a median follow-up period of 18 months, 73 patients experienced 90 bleeding events. Among these patients, 25 including 4 fatal cases, experienced major bleeding events. The predicted rate per 100 patient-years of follow-up of any bleeding events was 9.0 [95% CI 6.9 to 11.1]; clinically relevant bleeding events 6.0 [95% CI 4.8 to 8.3], and major bleeding events 3.0 [95% CI 1.9 to 4.2]. The independent risk factor for clinically relevant bleeding events is prior bleeding. While prior bleeding or congestive heart failure is linked with major bleeding events. **Conclusions:** The predicted rate for dabigatran-induced major bleeding episodes is low but these adverse events carry a high fatality risk. Preventive measures should target older patients who have prior bleeding or congestive heart failure.

INTRODUCTION

Novel oral anticoagulants (NOACs), such as dabigatran, rivaroxaban, apixaban and edoxaban are approved as an alternative agent to warfarin for the indication of stroke prevention in patients with non-valvular atrial fibrillation (NVAF) (1). NOACs are more likely to be prescribed to younger patients, patients with a lower estimated risk of stroke or a lower risk of bleeding, and those who are not on clopidogrel therapy than warfarin (2). Bleeding events are the most common adverse effect of NOAC therapy (3-6). These NOAC-induced bleeding events can be costly (7), inconvenient or fatal (8; 9). Comparable rates of major bleeding associated with dabigatran and warfarin use are noted (5; 6; 10-13). In some studies, dabigatran may result in a lower (14-16), or a higher event rate of major bleeding than warfarin (17).

Various underlying factors may increase the risk of dabigatran-induced bleeding events. For example, older adults (13; 18; 19), or patients with renal impairment (20; 21) are at an increased risk of developing dabigatran-induced bleeding. Asian dabigatran users, however, seem to have a better safety profile than non-Asian users (22-24).

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Similar to other NOACs, dabigatran is linked with a lower risk of intracranial bleeding events than warfarin (17; 25-28). Dabigatran, however, is associated with an increased (3; 8; 12; 25; 26), or a similar risk of gastrointestinal bleeding events when compared to warfarin (24; 29; 30).

Recent advance in drug development and evidence-based practice have made NOAC use safer. Lately, idaricuzimab was identified as an antidote to dabigatran (31). Practical guideline on NOAC use was published (1). Nonetheless, managing patients receiving dabigataran therapy remains challenging because of potentially fatal bleeding complications, limited availability of antidote and few encounters to reinforce the safe use of the drug (32).

There are limited data on the safety of NOACs in Malaysian population (33). Therefore, we aimed to determine the predicted rate of dabigatran-induced bleeding events, and to identify potential factors associated with these adverse events. We chose to include patients on dabigatran because the drug is the most widely used NOAC for stroke prevention among Malaysian patients.

METHODS

Design and participants

This retrospective cohort study involves patients with NVAF receiving dabigatran for stroke prevention between January 2010 and December 2014 at the University of Malaya Medical Centre (UMMC) and the Institute Jantung Negara (IJN or the National Heart Institute) of Malaysia. Institutional medical ethics approvals were obtained at both sites.

Data collection, analyses and outcomes

The names and registration numbers of patients who received dabigatran therapy were identified from the pharmacy supply database of UMMC and the NOAC registry of IJN. A list of potential study subjects was sent to the Patient Information Service Centre for the retrieval of their medical records. Patients with NVAF, aged at least 18 years old, and received dabigatran were eligible to be included. Patients with no documented follow-up information, or patients with active liver disease or severe renal impairment (requiring dialysis or kidney transplant) or patients whose medical records are not traceable were excluded.

The demographics and clinical information were gathered retrospectively from medical folders or electronic medical records of the patients. Data collection was carried out between the beginning of June 2014 and the end of September 2016.

An occurrence of a bleeding event is the main outcome measure. We extracted this information from documented patient self-reports during outpatient visits, records of ward admissions, the Department of Accident and Emergency admissions at either hospitals or referral letters from other healthcare centers to the UMMC or IJN.

The stroke risk of the study subjects at the initiation of NOAC therapy was estimated using CHA_2DS_2-VASc risk score (34). In addition, HAS-BLED risk score was used to assess a one-year major bleeding risk of a patient (35). The estimated glomerular filtration rate (eGFR) was calculated using the Modification of Diet in Renal Disease (MDRD) formula (36). Renal impairment is defined as an eGFR of < 60 mL/min/1.73 m^2 for more than three months with or without kidney damage or diagnosed chronic kidney disease (37). Liver impairment is defined as chronic hepatic disease (such as cirrhosis) or significant hepatic derangement as evidenced by serum alanine aminotransferase or aspartate aminotransferase of three times higher than the upper limits, or bilirubin two times more than the upper limit (35).

The main outcome measure of this study is an occurrence of a bleeding event. Bleeding events are defined according to the International Society on Thrombosis and Haemostasis (ISTH) criteria, and are classified into three categories: major, minor and clinically relevant non-major bleeding events (38; 39).

A major bleeding (MB) event is defined as "a fatal bleeding, and/or symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome, and/or bleeding causing a fall in hemoglobin level of 20 g L^{-1} (1.24 mmol L^{-1}) or more, or leading to transfusion of two or more units of whole blood or red cells" (38). Clinically relevant non-major bleeding events is a bleeding event which cannot be categorized as a major bleeding, but requires medical interventions, unscheduled visits to healthcare facility, and leads to a temporary interruption of anticoagulant therapy, or any other discomfort or impairment of activities of daily living (39). On the other hand clinically relevant bleeding event refers to major bleeding

events and clinically relevant non-major bleeding events.

Those patients who experienced a bleeding episode, whether it was a major, minor or clinically relevant non-major bleeding event, were included in the sub-group of "Patients with any bleeding events". An occurrence of a bleeding event was recorded from the initiation of NOAC therapy until the death of a patient, or the date of permanent discontinuation of NOAC use, or the last day of data collection. The secondary outcome is an estimation of a cumulative hazard rate of any dabigatran-induced bleeding event.

STATISTICAL ANALYSIS

Frequency (proportion) was used to summarize categorical variables, while mean and standard deviation or median and range (where applicable) were used to summarize continuous variables related to patient data during the baseline analysis. An odds ratio was estimated using a binary logistic regression to assess each risk factor so as to identify the predictors associated with a first clinically relevant bleeding event. Those variables with a significant association with bleeding events in univariate analyses with a P value < 0.05, were further analyzed using multivariate logistic regression models to determine the adjusted odds ratios, and the 95% confidence intervals for the factors associated with bleeding events (40). Nelson-Aalen cumulative hazard rates of the first episode of bleeding events were generated using package 'Survival' (41) from the R programming language (40). In R, the Nelson-Aalen estimate of cumulative hazard rate is obtained by specifying type="aalen" option in the Survfit() command which gives the estimate of the negative log of survival function. A predicted rate of bleeding events per 100 patient-years was estimated using package 'OpenEpi' (42).

RESULTS

Five hundred and twenty two patients were screen, and 478 patients with NVAF receiving dabigatran were included in this study. A flow chart describing the identification and selection of study subjects according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement guideline (43) is shown in **Figure 1**.

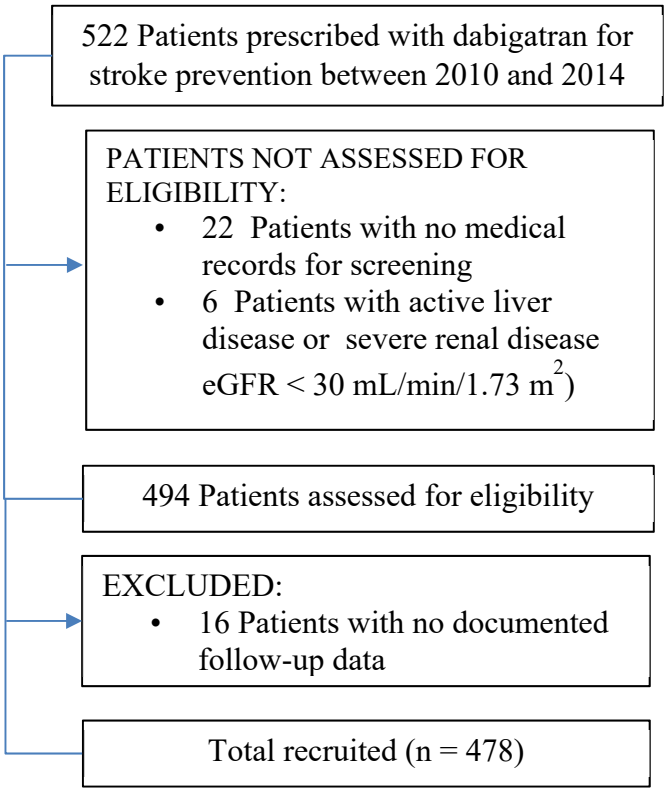

Figure 1. A flow chart describing the identification and selection of study subjects according to the STROBE statement guideline.

Most of the study subjects were naive dabigatran users. Majority were male patients of Chinese descent. Most of the patients had a high calculated stroke risk at baseline. Hypertension was the most common stroke risk factor. The baseline characteristics of all patients and subgroups of patients without any bleeding event, patients with a first bleeding event, or major bleeding event or clinically relevant bleeding event are summarized in **Table 1**.

Table 1. Baseline characteristics of all patients

Patient characteristics	All patients	Bleeding			
	n= 478	None n = 405	Any n = 73	Major n = 25	Clinically relevant n = 53
†Age in years, median (Range)	70 (30 - 91)	69 (30 - 91)	73 (42 - 90)	70 (42 - 90)	72 (42 - 90)
< 65	144 (30)	121 (30)	23 (32)	8 (32)	20 (38)
≥ 65 to < 75	185 (39)	166 (41)	19 (26)	7 (28)	12 (23)
≥ 75	149 (31)	118 (29)	31 (43)	10 (40)	21 (40)
Sex					
Male	251 (53)	208 (51)	43 (59)	15 (60)	32 (60)
Female	227 (48)	197 (49)	30 (41)	10 (40)	21 (40)
Race					
Chinese	247 (52)	207 (51)	40 (55)	15 (60)	31 (58)
Malay	179 (37)	152 (38)	27 (37)	9 (36)	18 (34)
Indian	52 (11)	46 (11)	6 (8)	1 (4)	4 (8)
Smoking status					
Non-smokers	426 (89)	362 (89)	64 (88)	20 (80)	46 (87)
Smokers	37 (8)	33 (8)	4 (6)	2 (8)	3 (6)
Ex-smokers	15 (3)	10 (3)	5 (7)	3 (12)	4 (8)
Alcohol drinkers	12 (3)	11 (3)	1 (1)	1 (4)	1 (2)
Medical history					
Hypertension	377 (79)	317 (78)	60 (82)	21 (84)	45 (85)
Diabetes mellitus	184 (38)	154 (38)	30 (41)	10 (40)	25 (47)
CCF	100 (21)	79 (20)	21 (29)	11 (44)	17 (32)
Prior stroke/TIA	107 (22)	85 (21)	22 (30)	8 (32)	17 (32)
Liver disease	67 (14)	57 (14	10 (14)	5 (20)	8 (15)
Renal impairment	178 (38)	136 (34)	32 (44)	10 (40)	28 (53)
†eGFR (mL/min/1.73 m^2)	67 (30 - 210)	67 (30 - 210)	65 (30 - 156)	67 (36 - 116)	65 (30 - 116)
Missing SCR	7 (2)	7 (2)	0 (0)	0 (0)	0 (0)
Malignancy	25 (5)	20 (5)	5 (7)	2 (8)	4 (8)
Prior bleeding	19 (4)	11 (3)	8 (11)	6 (24)	8 (15)
Anemia (Hgb < 130 g/L in men, < 120 g/L in women)	141 (70)	113 (28)	28 (38)	11 (44)	23 (42)
Missing Hgb data	27 (5)	23 (32)	4 (6)	1 (4)	1 (2)
Peptic ulcer disease	43 (9)	32 (8)	11 (15)	4 (16)	8 (15)
High fall risk	24 (5)	18 (4)	6 (8)	3 (12)	4 (8)
Stroke and bleeding risk					
†CHA_2DS_2-VASc score	3 (0 - 8)	3 (0 - 8)	4 (1 - 8)	4 (1 - 8)	4 (1 - 8)
†HAS-BLED score	2 (0 - 5)	2 (0 - 5)	2 (0 - 5)	2 (0 - 4)	2 (0 - 4)
Medication					
Concomitant aspirin use	156 (33)	129 (32)	27 (37)	11 (44)	19 (36)
Concomitant clopidogrel use	102 (21)	83 (21)	19 (26)	7 (28)	14 (26)

Table 1 Continued…

Concomitant ACEIs use	139 (29)	118 (29)	21 (29)	8 (32)	15 (28)
Concomitant ARB use	120 (25)	103 (25)	17 (23)	5 (20)	11 (21)
Prior warfarin use	120 (25)	105 (26)	15 (21)	6 (24)	11 (21)
Dabigatran dosage regimen					
Dabdigatran 75 mg bd	15 (3)	11 (3)	4 (6)	2 (8)	3 (6)
Dabigatran 110 mg bd	226 (47)	189 (47)	37 (51)	13 (52)	28 (53)
Dabigatran 150 mg bd	237 (50)	205 (51)	32 (44)	10 (40)	22 (42)

Abbreviations: †data presented as median and range, CCF, congestive cardiac failure; TIA, transient ischemic attack; eGFR, estimated Glomerular Filtration Rate; Hgb, hemoglobin; CHA_2DS_2-VAS_C, Congestive heart failure, Hypertension, Age ≥75 years, Diabetes, previous Stroke, Vascular disease, Age 65-74 years, Sex category; HAS-BLED, Hypertension, Abnormal renal or liver function, Stroke, Bleeding, Labile INR, Elderly, Drugs or alcohol abuse; ACEIs, Angiotensin-Converting Enzyme Inhibitors; ARB, Angiotensin II Receptor Blockers; bd, twice daily. Note: Clinically relevant bleeding event includes both major bleeding and clinically relevant non-major bleeding event.

During a median follow-up period of 18 months (ranged from 3 days to 65 months), 73 patients experienced 90 bleeding events. Most of the patients had bleeding events which were considered to be directly related to dabigatran therapy. Nineteen patients had other possible causes of the bleeding events such as peptic ulcer disease, fall, respiratory infections, hemorrhoids, enlarged prostate surgery, other medical procedures and high blood pressure. Of the 25 major bleeding events, 4 led to deaths within 30 days after the bleeding episode (**Table 2**).

Of the 73 patients who experienced a first bleeding event, 55 restarted dabigatran therapy. Eighteen patients, including four who died, stopped dabigatran permanently. Among those who discontinued dabigatran, seventeen had a CHA_2DS_2-VASc ≥ 2; five received antiplatelet therapy and one received apixaban.

Using time-to-event analysis with package OpenEpi (44), the predicted first bleeding event rate per 100 patient-years of follow-up of any bleeding events was 9 [95% CI 6.9 to 11.1]; clinically relevant bleeding events, 6.0 [95% CI 4.8 to 8.3], and major bleeding events, 3 [95% CI 1.9 to 4.2] **(Table 3)**.

As shown in **Table 4**, factors such as CHA_2DS_2-VASc score ≥ 2, prior bleeding, congestive heart failure, renal impairment and a HAS-BLED score ≥ 3 is linked with the occurrence of a first clinically relevant bleeding event. After adjusting for all factors which are associated with clinically relevant bleeding events in the univariate analysis, only prior bleeding emerged as an independent risk factor.

On the other hand, prior bleeding, congestive heart failure, CHA_2DS_2-VASc score ≥ 2, and HAS-BLED score ≥ 3 were linked with an increased risk of a first major bleeding event. Among these factors, only prior bleeding and congestive heart failure show a significant association with major bleeding events in multivariate analysis **(Table 5)**.

Table 2. Frequency, severity, and origins of bleeding events in all patients

Severity and origin of bleeding events	All patients (n = 478)
	Frequency of bleeding events
Major bleeding events	25 (4 deaths)
Intracranial bleeding	8
Gastrointestinal bleeding	17
Clinically relevant non-major bleeding events	33
Minor bleeding events	32
All bleeding events	90

Note: Among the 73 patients with bleeding events, 57 patients experienced a single bleeding event, while 16 patients had recurrent bleeding events (15 experienced 2 bleeding events, while 1 patient experienced 3 bleeding events).

Table 3. The predicted event rate per 100 patient-years for any bleeding events, clinically relevant bleeding events, and major bleeding events

	All patients (N = 478)		
	No. of events	**Patient-years under risk**	**Predicted event rate* per 100 patient-years [95 % Confidence interval]**
Any bleeding events	73	825	8.9 [6.9 - 11.1]
Clinically relevant bleeding	53	832	6.4 [4.8 - 8.3]
Major bleeding events	25	857	2.9 [1.9 - 4.2]

*Event rate = Number of events ÷ total patient-time under risk. The total patient-time under risk is the sum of all days from the date of initiation of dabigatran therapy until the date of the first bleeding event or the date of discontinuation of dabigatran or the date of death or the last date of follow-up if no bleeding event occurred during the follow-up period. The event rate is scaled to a unit of 'number of bleeding events per 100 patients-years' by dividing the event rate by 365 (to convert days to years) and multiplying by 100 (to convert per patient-year to per 100 patient-years). Note: Clinically relevant bleeding event includes both major bleeding and clinically relevant non-major bleeding event.

Table 4. Predictors of clinically relevant bleeding events

Risk factors	**Unadjusted OR**	**95 % CI**	**P value**	**Adjusted OR**	**95% CI**	**P value**
Prior bleeding	6.86	2.54 - 17.87	0.001*	6.86	2.54 - 17.87	0.001*
CHA_2DS_2-VASc ≥ 2	2.93	1.46 - 6.57	0.004*	2.93	1.46 - 6.57	0.004*
HAS-BLED ≥ 3	1.96	1.06 - 3.55	0.028*	1.96	1.06 - 3.55	0.028*
Congestive heart failure	2.01	1.05 - 3.71	0.029*	2.01	1.05 - 3.71	0.029*
Renal Impairment	1.92	1.07 - 3.44	0.027*	1.92	1.07 - 3.44	0.027*
Age ≥ 75 years	1.47	0.80 - 2.65	0.204	1.47	0.80 - 2.65	0.204
Anemia	1.73	0.94 - 3.12	0.072	1.73	0.94 - 3.12	0.072
Peptic ulcer disease	1.69	0.66 - 3.81	0.238	1.69	0.66 - 3.81	0.238
Female sex	0.79	0.44 - 1.41	0.429	0.79	0.44 - 1.41	0.429
Liver disease	1.11	0.46 - 2.36	0.800	1.11	0.46 - 2.36	0.800
Prior warfarin use	0.88	0.43 - 1.70	0.721	0.88	0.43 - 1.70	0.721
Concomitant aspirin use	1.10	0.59 - 2.00	0.747	1.10	0.59 - 2.00	0.747
Concomitant clopidogrel use	1.12	0.54 - 2.16	0.746	1.12	0.54 - 2.16	0.746
Concomitant ACEI use	0.99	0.51 - 1.83	0.969	0.99	0.51 - 1.83	0.969
Concomitant ARB use	0.78	0.37 - 1.52	0.487	0.78	0.37 - 1.52	0.487
Dabigatran 150 mg bd vs. dabigatran 110 mg bd	0.69	0.37 - 1.25	0.687	0.69	0.37 - 1.25	0.687
Stroke or TIA	1.81	0.95 - 3.34	0.061	1.81	0.95 - 3.34	0.061
Malignancy	1.61	0.45 - 4.44	0.402	1.61	0.45 - 4.44	0.402
Hypertension	1.54	0.73 - 3.62	0.285	1.54	0.73 - 3.62	0.285
Diabetes	1.42	0.79 - 2.54	0.231	1.42	0.79 - 2.54	0.231
High fall risk	1.69	0.48 - 4.70	0.355	1.69	0.48 - 4.70	0.355

Abbreviations: OR, Odds Ratio; CI, Confidence Interval; CHA_2DS_2-VASc; Congestive heart failure, Hypertension, Age ≥ 75 years, Diabetes and previous Stroke, Vascular disease, Age 65-74 years, Sex category; HAS-BLED, Hypertension, Abnormal renal or liver function, Stroke, Bleeding, Labile INR; ACEIs, Angiotensin-Converting Enzyme Inhibitor; vs. versus; ARB, Angiotensin II Receptor Blocker; TIA, Transient Ischemic Attack; bd, twice daily. *P value < 0.05 (statistically significant).

No significant difference in the odds ratios of having any first bleeding events or clinically relevant bleeding events or major bleeding events was observed with 150 mg bd or 110 mg bd dosing regimens of dabigatran in our study.

The estimated cumulative hazard rate of any first bleeding event is moderate at 40%; while that of clinically relevant bleeding events is 37%, and for major bleeding events is low at 10%. As displayed in **Figure 2**, a plot for any bleeding events over time exhibits a steeply rising curve during the early phase of dabigatran use. The curve plateaus out after about 45 months. The estimated cumulative hazard rate for clinically relevant bleeding events shows a similar

trend of higher hazard rate during the early phase of dabigatran therapy; while that of major bleeding events show a gentler rise until about 15 months after the initiation of dabigatran therapy.

DISCUSSION

Asians have a high burden of stroke secondary to atrial fibrillation that necessitates the use of anticoagulants such as dabigatran (23; 24). We predicted a first bleeding event rate per 100 patient-years of dabigatran-associated bleeding among Malaysian patients with NVAF, and add to the evidence of real-world dabigatran safety. A previous single center study involving Malaysian patients with NVAF receiving dabigatran with a median follow-up period of 10 months at the National Heart Institute are descriptive in nature (33). The bleeding event rate and the predictors of dabigatran-induced bleeding were not estimated nor determined. On the other hand, the current study, involves patients with NVAF from 2 referral centers (University of Malaya and the National Heart Institute), with a longer median follow-up period of 18 months. As a result, more major and clinically relevant bleeding events were observed in our study. Furthermore, more information on the dates of bleeding event occurrence were extracted to allow the "time-to-event" analysis.

The estimated rate of any first bleeding event is lower than that reported in the RE-LY trial (13). Asians have been shown to have less risk of bleeding with dabigatran than non-Asians (22; 23). The estimated rate of a first dabigatran-induced clinically relevant bleeding event in this study is lower than that reported for rivaroxaban (14.9 % per year) and warfarin (14.5 % per year) in ROCKET-AF trial (19). The rate of a first major bleeding, however, is comparable to those reported in previous studies (5; 10; 11; 45; 46).

Table 5. Predictors of major bleeding events

Risk factors	Unadjusted OR	95% CI	P value	Adjusted OR	95% CI	P value
Prior bleeding	10.69	3.45 - 30.40	0.0001*	9.03	2.81 - 26.75	0.0001*
Congestive heart failure	3.21	1.38 - 7.30	0.005*	2.84	1.18 - 6.74	0.017*
HAS-BLED ≥ 3	2.39	1.03 - 5.41	0.036*	1.95	0.80 - 4.62	0.131
CHA_2DS_2-VASc ≥ 2	3.06	1.21 - 10.31	0.035*	2.20	0.41 - 40.66	0.457
Age ≥ 75 years	1.54	0.65 - 3.47	0.307			
Age ≥ 65 years	1.10	0.47 - 2.89	0.830			
Female sex	0.73	0.31 - 1.63	0.443			
Liver disease	1.55	0.50 - 3.99	0.399			
Anemia	2.04	0.87 - 4.67	0.092			
Concomitant ACEI use	1.16	0.46 - 2.67	0.741			
Concomitant ARB use	0.73	0.24 - 1.86	0.547			
Renal Impairment	1.31	0.57 - 2.95	0.512			
Prior warfarin use	0.94	0.34 - 2.28	0.896			
Concomitant aspirin use	1.69	0.72 - 3.76	0.217			
Concomitant clopidogrel use	1.47	0.56 - 3.47	0.406			
Dabigatran 150 mg bd vs. dabigatran 110 mg bd	0.72	0.30 - 1.68	0.450			
Peptic ulcer disease	2.02	0.57 - 5.64	0.217			
Stroke or TIA	1.68	0.67 - 3.90	0.241			
Malignancy	1.42	0.46 - 3.63	0.502			
Hypertension	1.43	0.53 - 4.99	0.521			
Diabetes	1.07	0.46 - 2.41	0.874			
High fall risk	2.86	0.63 - 8.96	0.115			

Abbreviations: OR, Odds Ratio; CI, Confidence Interval; HAS-BLED, Hypertension, Abnormal renal or liver function, Stroke, Bleeding, Labile INR; CHA_2DS_2-VASc, Congestive heart failure, Hypertension, Age ≥75 years, Diabetes and previous Stroke, Vascular disease, Age 65-74 years, Sex category; ACEI, Angiotensin-Converting Enzyme Inhibitor; ARB, Angiotensin II Receptor Blocker; vs. versus; bd, twice daily; TIA, transient ischemic attack; Vs., Versus. *P value < 0.05 (statistically significant).

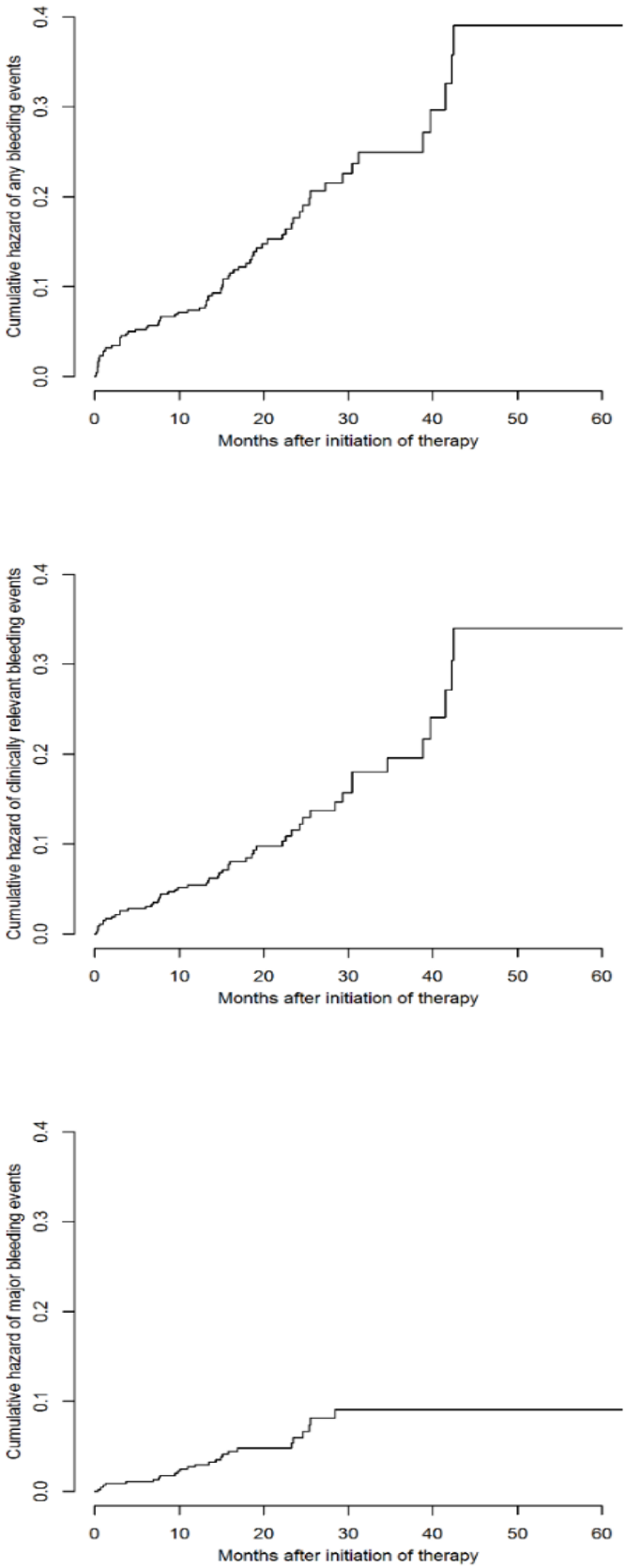

Figure 2. Estimated cumulative hazard rate function for any bleeding event (top panel), clinically relevant bleeding events (middle panel) and major bleeding events (lower panel) for all study subjects.

Our findings show a higher hazard rate of a first bleeding event during the first 40 months of dabigatran therapy. This indicates the importance of close monitoring during the first three years of dabigatran use. As reported previously, bleeding events could lead to permanent discontinuation of dabigatran (47-49). Previous studies reported about 50% of the patients discontinued the drug because of minor or clinically relevant non-major bleeding events. Furthermore, most of those who discontinued dabigatran use are at a high risk of stroke. It is therefore crucial for those who discontinued dabigatran use to receive an alternative oral anticoagulant therapy. Nonetheless, the use of antiplatelet as an alternative to oral anticoagulant in patients with NVAF is not recommended (50).

Similar to a study by Katoh et al., (51) gastrointestinal bleeding is the most common type of major bleeding events in our cohorts. The topical activity of unabsorbed dabigatran at the gastrointestinal mucosa may be related to an increased risk of gastrointestinal bleeding (52).

Gastrointestinal or intracranial bleeding events may also be the cause of four fatal bleeding events in this study. Three of those four affected patients started on NOACs at an older age of 75 years or above. Moreover, two fatal cases had a comorbid congestive heart failure or chronic kidney disease. These risk factors may have contributed to having a major bleeding event, and subsequent death.

Unlike the findings in our study, a study by Reilly et al. involving 9,183 patients (mainly Caucasians) with 35% of them aged 75 years or above, and 3.8% major bleeding events, has identified age as an independent risk factor for a bleeding event (53). In our cohort of 478 patients (mainly Asians), only 31% aged 75 years or older, but 25 patients (5.2%) reported to have major bleeding events. A different racial groups and a smaller sample size may made the association between age and bleeding events less apparent. Age was also not a significant predictor of bleeding events in a similar Asian study conducted among 184 Japanese dabigatran users with atrial fibrillation (51).

Congestive heart failure is also found to be associated with major bleeding events in our cohorts. This risk factor may be related to the prevalent use of nephrotoxic drugs such as angiotensin-converting enzyme inhibitors (ACEIs), or diuretics that worsen renal function in heart failure (18). Moreover, the coexistence of atrial fibrillation with congestive heart failure is associated with a poor clinical outcome and death (54).

Although a higher dose of dabigatran was reported to be linked with a higher risk of major bleeding (13; 46), our study fails to show such linkage. Nonetheless, patients with a high risk of stroke (with a CHA_2DS_2-VASc $\geq$ 2) or bleeding events (with a HAS-BLED score $\geq$ 3), were more likely to experience major bleeding events. An increased risk of major bleeding with increasing CHA_2DS_2-VASc or HAS-BLED scores has been previously described (55-58).

Renal or hepatic dysfunction may escalate the risk of bleeding (21). Nonetheless, neither of these factors shows a link with bleeding events in our study. The precautionary practice of using a lower dose of dabigatran in patients with renal dysfunction, or the avoidance of co-administration of interacting drugs during dabigatran therapy may be the reason for the lack of this association in our patients.

Due to the nature of an observational study design used, this study has some limitations and certain assumptions were made. The exposure to dabigatran is assumed as long as patients filled their prescriptions. The impact of co-administration of over-the-counter products, including non-steroidal anti-inflammatory drugs (NSAIDs) and traditional medicines on the bleeding risk of a patient could not be assessed. Finally, due to a relatively low bleeding event rate, the association between other factors and bleeding events may have become less apparent.

Despite the above-mentioned limitations, this study has highlighted the predicted rate and risk factors associated with dabigatran-induced bleeding among Malaysian patients. The findings of this study have some important implications for planning preventive measures for adverse drug events. As bleeding risk factors are dynamic, periodic assessments of the stroke risk and bleeding risk are important, especially among older adults. Tailored patient education and updating healthcare providers on the emerging data on dabigatran-associated bleeding risk factors can be useful.

CONCLUSIONS

The rate of dabigatran-associated major bleeding events is low, but these adverse events may carry a high fatality risk. Therefore, interventional programs for bleeding prevention should target older patients with congestive heart failure, prior bleeding events, CHA_2DS_2-VASc score $\geq$ 2, and HAS-BLED score $\geq$

3, especially during the first three years of NOAC therapy.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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