Clinical Outcomes of Patients with Atrial Fibrillation who Survived from Bleeding Event: The Results from COOL-AF Thailand Registry

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Abstract

Background Bleeding events are often reported among patients with atrial fibrillation (AF), irrespective of antithrombotic use. This study is to determine clinical outcomes of patients with AF who survived from bleeding event.

Methods We analyzed data from COOL-AF (Cohort of Antithrombotic Use and Optimal International Normalized Ratio Levels in Patients with Atrial Fibrillation) Thailand registry. Outcomes of patients who experienced any bleeding were compared with patients who had never bleed. Time updated multivariate Cox-proportional hazard models were used to estimate the risk for clinical outcomes of patients with and without bleeding.

Results Of total 3,405 patients (mean age: 67.8 ± 11.3 years; 41.9% female) in COOL-AF registry, 609 patients (17.9%) reported bleeding event occurs and 568 patients (93.3%) survived though hospital discharge. Patients who survived major bleeding ($n = 126$) were at increased risk for both death (adjusted hazard ratio [HR]: 4.44, 95% confidence interval [CI]: 2.91–6.75, $p < 0.001$) and stroke/systemic embolism (adjusted HR: 4.49, 95% CI: 2.19–9.24, $p < 0.001$). Minor bleeding also increased subsequent death (adjusted HR: 2.13, 95% CI: 1.56–2.90, $p < 0.001$). Up to 30% of patients who survived major bleeding and 6.3% of minor bleedings discontinued oral anticoagulation. Discontinuation was associated with very high death rate (42.1%), whereas patients who resumed oral anticoagulation after bleeding had lower mortality (10%). The most common causes of death in patients who survived a bleeding event were not related to cardiovascular causes nor bleeding.

Conclusion Patients with AF who have bleeding events have an increased risk for subsequent death and stroke and systemic embolism. These patients should be identified as vulnerable clinically complex patients and require a holistic approach to their AF management.

Keywords
- atrial fibrillation
- bleeding
- death
- oral anticoagulants

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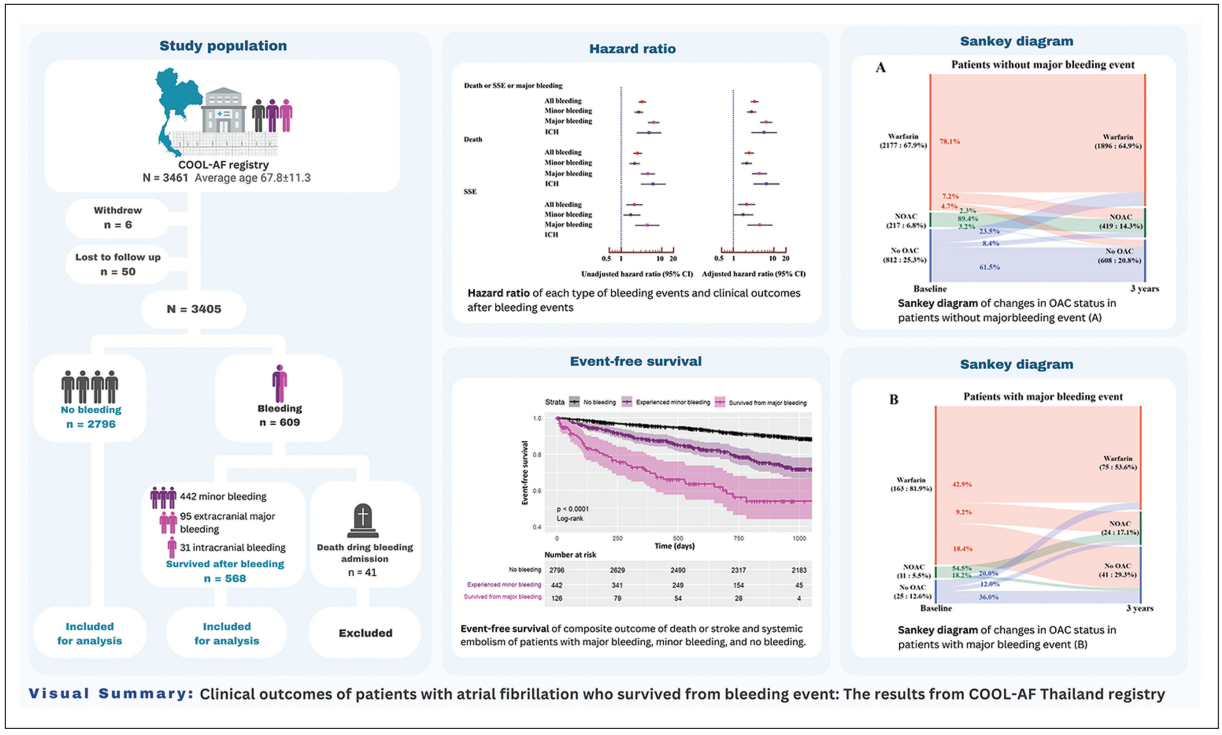

Visual Summary: Clinical outcomes of patients with atrial fibrillation who survived from bleeding event: The results from COOL-AF Thailand registry

Introduction

Patients with atrial fibrillation (AF) are at increased risk of mortality and morbidity from stroke and systemic embolism (SSE) and guidelines recommend oral anticoagulants (OAC) to reduce this risk.[1–3] However, antithrombotic agents confer a bleeding risk, whereby 5.1 to 7.9% of patients in recent clinical trials sustained major bleeding events during treatment.[4] AF patients also appear to be at higher risk of bleeding, even in the absence of OAC use.[5] While many modifiable and nonmodifiable risks impact on bleeding events, a higher propensity to bleeding may be observed among Asian populations.[6]

These bleeding events may be linked to other unfavorable outcomes such as further SSE, mortality, and recurrent bleeding,[7,8] although more limited data are available from large prospective Asian cohorts of patients with AF. Recent systematic reviews and meta-analyses have provided compelling evidence supporting the safety and favorable outcomes associated with resuming anticoagulation therapy following the resolution of correctable bleeding episodes including intracranial hemorrhage (ICH).[9–11] However, a considerable number of patients who experienced serious bleeding may discontinue treatment for stroke prevention indefinitely and further result in more embolic events. While the nonvitamin K antagonist oral anticoagulants (NOACs) are generally safer choices in term of bleeding when compared with vitamin K antagonists (e.g., warfarin), many patients globally (including in Thailand) had limited accessibility to NOACs due to limited health care coverage and reimbursement. Therefore, majority of patients still used only warfarin as their OAC, for stroke prevention.

Given the impact of bleeding on outcomes, the limited data from large Asian AF cohorts and increase sensitivity of Asians to bleeding on OAC, this analysis from our multicenter nationwide cohort study aimed to determine the effects of bleeding events on the subsequent management and clinical outcomes.

Methods

We analyzed data from COOL-AF (Cohort of Antithrombotic Use and Optimal International Normalized Ratio Levels in Patients with Atrial Fibrillation) Thailand registry. Briefly, patients in this prospective nationwide study were age of 18 years or older who were diagnosed with nonvalvular AF from 27 public hospitals across the country during 2014 to 2017. All patients were stable and outpatient and had not been hospitalized for at least 1 month prior to enrollment. The study protocol was approved by the Central Research Ethics Committee. Written informed consent was obtained from all included patients prior to participation, and the study was conducted in accordance with the principles set forth in the Declaration of Helsinki and the International Conference on Harmonization for Good Clinical Practice Guidelines. Site investigators were informed to enroll patients consecutively. We followed the International Society on Thrombosis and Haemostasis (ISTH) criteria for bleeding definition.[12] In this particular analysis, we identified patients who experienced any bleeding event (minor and major bleeding) during their 3-year follow-up. We excluded patients who died during the same bleeding event ($n = 41$). Patients who survived bleeding event to hospital discharge were enrolled and compared with other patients in the registry who had never bled.

We also subdivided patients with nonfatal bleeding into three subgroups: patients with minor bleeding, patients survived from major bleeding, and patients survived from

intracranial bleeding (which were also included in major bleeding group). We focused on clinical outcomes after bleeding episode including SSE, recurrent bleeding, and all-cause death. Ischemic stroke was defined as acute onset of focal neurological deficit lasting at least 24 hours, and less than 24 hours for transient ischemic attack (TIA). Imaging data from computed tomography brain scan or magnetic resonance imaging were required to be uploaded into the web-based system but no need to be positive. Major bleeding was defined by the ISTH criteria.[12] We also analyzed rate of continuation or discontinuation of OAC after each bleeding category and clinical outcomes after each choice.

Statistical Analysis

Baseline demographic and clinical data were interpreted using descriptive statistics. Continuous data are presented as mean ± standard deviation, and categorical data are shown as number and percentage. Comparison was made between patients survived from bleeding and patients who had never bleed. Student's *t*-test was used to compare continuous data, and chi-square test was used to compare categorical data. Clinical outcomes including SSE, death, and bleeding are presented in per 100 patient-years. Univariate and multivariate Cox proportional hazard model analyses were performed to assess the risk of clinical outcomes of patients with and without bleeding. Bleeding was used as a time-updated covariate in the Cox models. Adjusted variables were age, sex, time after diagnosis of AF, AF types, symptomatic AF, history of heart failure, history of coronary artery disease (CAD), cardiac implantable electronic device, hypertension, history of ischemic stroke/TIA, diabetes mellitus, smoking, dyslipidemia, renal replacement therapy, dementia, antiplatelet, and anticoagulant. The multivariable Cox models were adjusted for time-updated covariates taking into account the changes over time.

The results of Cox proportional hazard model analyses are shown as unadjusted and adjusted hazard ratio (HR) and 95% confidence interval (CI). All statistical analyses were performed using the R version 3.6.3 (www.r-project.org) and the SPSS statistical software version 18.0 (SPSS, Inc., Chicago, Illinois, United States).

Results

Of all 3,405 patients in COOL-AF registry, 609 patients (17.9%) experienced bleeding during follow-up. Forty-one patients (6.7%) did not survive the bleeding episode; hence, the mortality rate of the first bleeding episode were 6.7% from all patients with bleeding events and up to 24% from patients with major bleeding. There was no significant difference for most of the baseline characteristics in ►**Table 1** between patients with fatal and nonfatal bleeding except for age. Patients with fatal bleeding had an older age compared with those with nonfatal bleeding (75.4 ± 7.9 vs. 70.5 ± 10.0, $p < 0.001$). Patients with fatal bleeding had a greater proportion of ICH compared with those with nonfatal bleeding (29 out of 41 [70.7%] vs. 41 out of 568 [7.2%], $p < 0.001$). Patients with warfarin and fatal bleeding had a lower time in the therapeutic range (TTR) compared with those with nonfatal bleeding (30.5 ± 27.8 vs. 50.0 ± 26.1%, $p = 0.001$). Finally, 568 patients (93.3%, mean age: 70.5 ± 10.0 years; 46.1% female) survived the first bleeding and available for analysis (442 minor bleeding and 126 major bleeding). Flow diagram of study population is shown in ►**Fig. 1**.

►**Table 1** demonstrates baseline characteristics of patients who survived any bleeding events compared with those with no bleeding event. Patients who survived bleeding were older than patients who had never bled (70.5 ± 10 vs. 67.1 ± 11.4 years, $p < 0.001$), had longer duration of AF (3.9 ± 5.3 vs. 3.3 ± 4.1 years, $p < 0.001$), had more several comorbidities including history of CAD, hypertension, diabetes, and kidney disease require renal replacement therapy. As a result, patients who survived bleeding had higher mean CHA_2DS_2-VASc and HAS-BLED scores than patients who had never bled. A greater proportion of patients who survived bleeding used OAC compared with patients who had never bleed (82.2 vs. 65.8%, $p < 0.001$). Patients who survived bleeding also used less NOACs (3.7 vs. 7.3%, $p = 0.002$).

Clinical Outcomes after Bleeding Events

Patients who survived bleeding events had a higher crude risk for clinical outcomes compared with those with no bleeding outcome as shown by incidence rate (►**Fig. 2A–D**) and unadjusted and adjusted HRs and 95% CI (►**Fig. 3**). Patients who sustained major bleeding were at high risk for future all-cause death (16.0 per 100 patient-year) when compared with patients who had never bled (3.48 per 100 patient-year, adjusted HR: 4.49, 95% CI: 2.19–9.24, $p < 0.001$). Mortality risk was highest among patients who suffered intracranial bleeding (21.68 per 100 patient-year, adjusted HR: 6.58, 95% CI: 3.15–13.74, $p < 0.001$). Patients who experienced minor bleeding also at increased risk for all-cause mortality (7.55 per 100 patient-year, adjusted HR: 2.13, 95% CI: 1.56–2.90, $p < 0.001$).

Patients survived major bleeding had stroke/systemic embolism for 5.57 per 100 patient-year compared with 1.26 per 100 patient-year in patients who had never bleed during follow-up (adjusted HR: 4.49, 95% CI: 2.19–9.24, $p < 0.001$, ►**Figs. 2** and **3**). Patients who experienced minor bleeding had marginally increased risk for future stroke/systemic embolism (2.13 per 100 patient-year; adjusted HR: 1.74, 95% CI: 0.98–3.09, $p = 0.058$).

►**Fig. 4** demonstrates cumulative event rate of composite outcomes of all-cause death, SSE and major bleeding in patients with major bleeding, minor bleeding, and no bleeding. Patients with major bleeding were the highest risk group. Patients with minor bleeding had a lower risk than those with major bleeding but higher risk than patients with no bleeding.

Among 568 patients who survived first bleeding event, the incidence rate of having major bleeding following the first bleeding was 3.75 per 100 person-years. The incidence rate of major bleeding after major bleeding, ICH, and minor bleeding were 10.88 (6.35–17.45), 10.86 (2.96–27.82), and 2.81 (1.93–3.94), respectively. The predictors for major bleeding after the first bleeding event were age (HR: 1.048 [1.015–1.082], $p = 0.004$), male sex (HR: 4.237 [1.992–9.009], $p < 0.001$), and diabetes (HR: 1.866 [1.018–3.423], $p = 0.044$).

Table 1 Baseline characteristics

Variables	All ($n = 3,364$)	All bleeding ($n = 568$)	No bleeding ($n = 2,796$)	p-Value
Age (y)	67.7 ± 11.3	70.5 ± 10.0	67.1 ± 11.4	<0.001
Female gender	1,409 (41.9%)	262 (46.1%)	1,147 (41%)	0.025
Time after diagnosis of AF (y)	3.4 ± 4.3	3.9 ± 5.3	3.3 ± 4.1	0.006
Atrial fibrillation				
Paroxysmal	1,140 (33.9%)	188 (33.1%)	952 (34%)	0.854
Persistent	639 (19.0%)	112 (19.7%)	527 (18.8%)	
Permanent	1,585 (47.1%)	268 (47.2%)	1,317 (47.1%)	
Symptomatic AF	2,591 (77.0%)	420 (73.9%)	2,171 (77.6%)	0.056
History of heart failure	898 (26.7%)	153 (26.9%)	745 (26.6%)	0.886
History of coronary artery disease	536 (15.9%)	119 (21.0%)	417 (14.9%)	<0.001
Cardiac implantable electronic device	339 (10.1%)	60 (10.6%)	279 (10.0%)	0.673
Hypertension	2,299 (68.3%)	450 (79.2%)	1,849 (66.1%)	<0.001
History of ischemic stroke/TIA	585 (17.4%)	108 (19%)	477 (17.1%)	0.263
Diabetes mellitus	825 (24.5%)	175 (30.8%)	650 (23.2%)	<0.001
Smoking	670 (19.9%)	126 (22.2%)	544 (19.5%)	0.138
Dyslipidemia	1,892 (56.2%)	347 (61.1%)	1,545 (55.3%)	0.011
Renal replacement therapy	38 (1.1%)	12 (2.1%)	26 (0.9%)	0.015
Dementia	29 (0.9%)	5 (0.9%)	24 (0.9%)	0.959
CHA_2DS_2-VASc score				
Low risk	287 (8.5%)	19 (3.3%)	268 (9.6%)	<0.001
Intermediate risk	548 (16.3%)	60 (10.6%)	488 (17.5%)	
High risk	2,529 (75.2%)	489 (86.1%)	2,040 (73.0%)	
HAS-BLED score	1.5 ± 1.0	1.8 ± 1.1	1.5 ± 1.0	<0.001
0	489 (14.5%)	51 (9.0%)	438 (15.7%)	
1–2	2,350 (69.9%)	388 (68.3%)	1,962 (70.2%)	
≥3	525 (15.6%)	129 (22.7%)	396 (14.2%)	
Antiplatelet	881 (26.2%)	154 (27.1%)	727 (26.0%)	0.583
Anticoagulant	2,534 (75.3%)	488 (85.9%)	2,046 (73.2%)	<0.001
Warfarin	2,308 (68.6%)	467 (82.2%)	1,841 (65.8%)	<0.001
NOACs	226 (6.7%)	21 (3.7%)	205 (7.3%)	0.002

Abbreviations: AF, atrial fibrillation; NOACs, nonvitamin K antagonist oral anticoagulants; TIA, transient ischemic attack.

Anticoagulant Strategy after Surviving Bleeding

Among patients who survived bleeding, 488 patients (85.9%) received OAC before their bleeding event; of these, 467 (95.7%) received warfarin and 21 (4.3%) received NOACs. According to this study, 85.9% (488 out of 568) was the percentage of patients who received OAC at the time of nonfatal bleeding. Among 488 patients, 414 (84.8%) resumed OAC, 15 (3.1%) changed OAC, and 57 (11.7%) discontinued OAC. Majority of patients who discontinued warfarin received no treatment for stroke prevention in AF. Left Atrial Appendage Occluder (LAAO) was implanted in two cases or 3.5% of patients with discontinued OAC. We rarely implant LAAO due to financial limitation. For patients with survived major bleeding (102 patients with warfarin before bleeding), 67 (65.7%) resumed warfarin, 31 (30.4%) discontinued OAC, and 4 (3.9%) switched to NOACs after their bleeding event. In patients who had intracranial bleeding as a cause of major bleeding (27 taking warfarin), 9 (33.3%) continued warfarin, 19 (63.3%) discontinued OAC, and 1 (3.3%) switched to NOACs. Of patients who had major gastrointestinal bleeding (81 taking warfarin), 63 (77.8%) continued warfarin, 15 (18.5%) discontinued OAC, and 3 (3.7%) switched to NOACs (►**Table 2**). Among 488 patients with bleeding with OAC, 57 (11.7%) discontinued OAC after bleeding. Among 2,046 patients with baseline OAC without bleeding event, 131 (6.4%) discontinued OAC ($p < 0.001$ for rate of OAC discontinuation between patients with and without bleeding). OAC discontinuation was associated with the increased risk of composite outcome (49.1 vs. 17.9%, $p < 0.001$). ►**Fig. 5** shows Sankey diagram of changes in OAC status in patients without

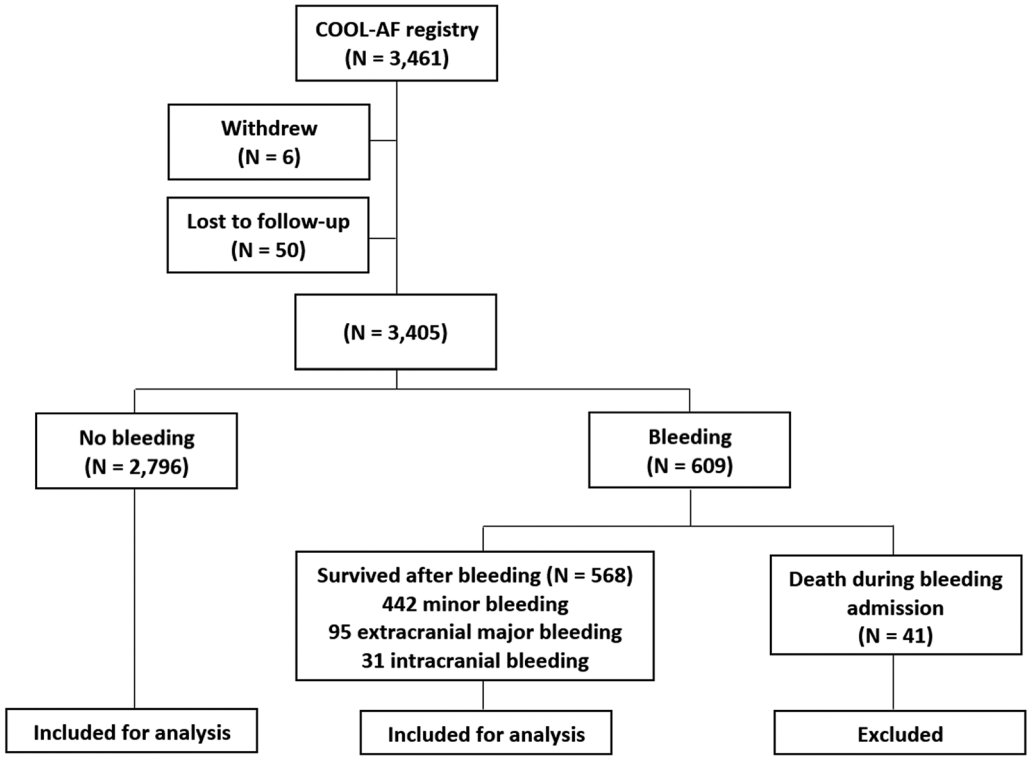

Fig. 1 Diagram of study population. COOL-AF, Cohort of Antithrombotic Use and Optimal International Normalized Ratio Levels in Patients with Atrial Fibrillation.

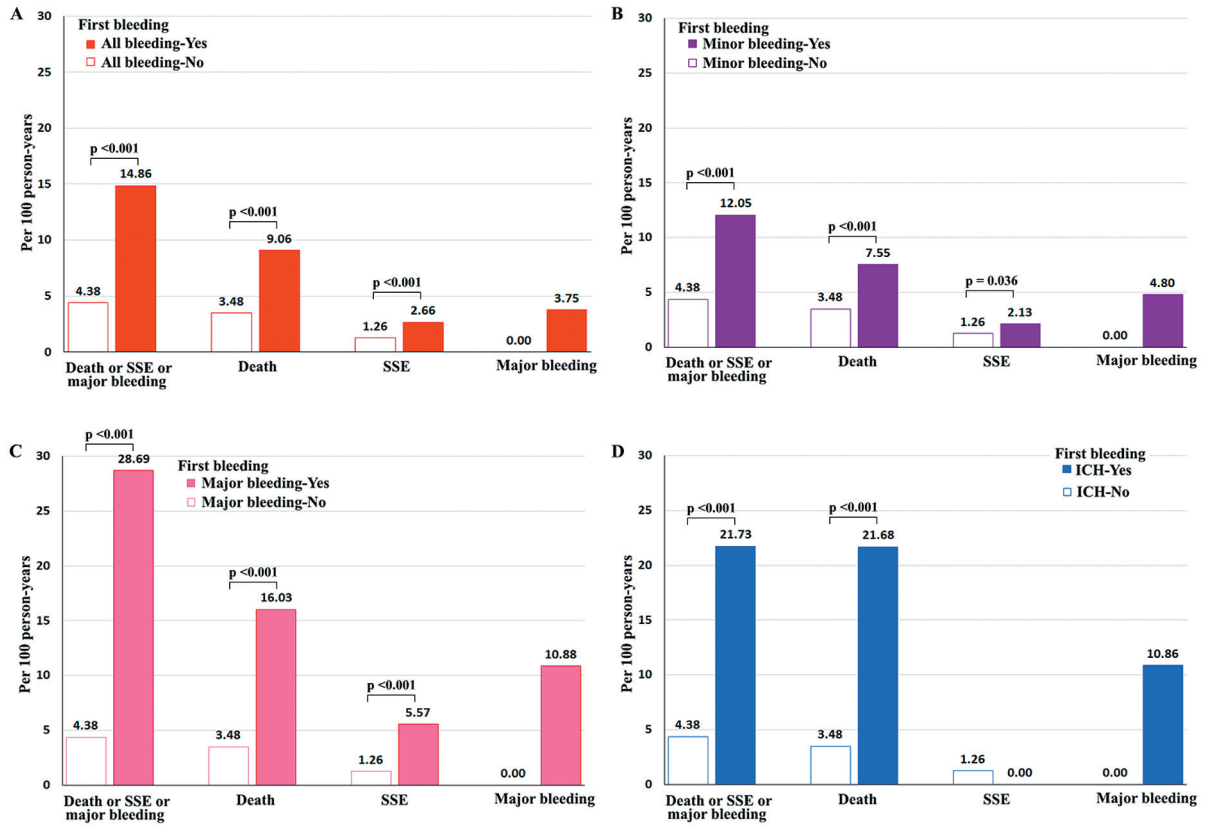

Fig. 2 Incidence rate of clinical outcomes of patients with each type of bleeding event compared with those no bleeding. (**A**) All bleeding; (**B**) minor bleeding; (**C**) major bleeding; and (**D**) intracranial hemorrhage. SSE, ischemic stroke/systemic embolism.

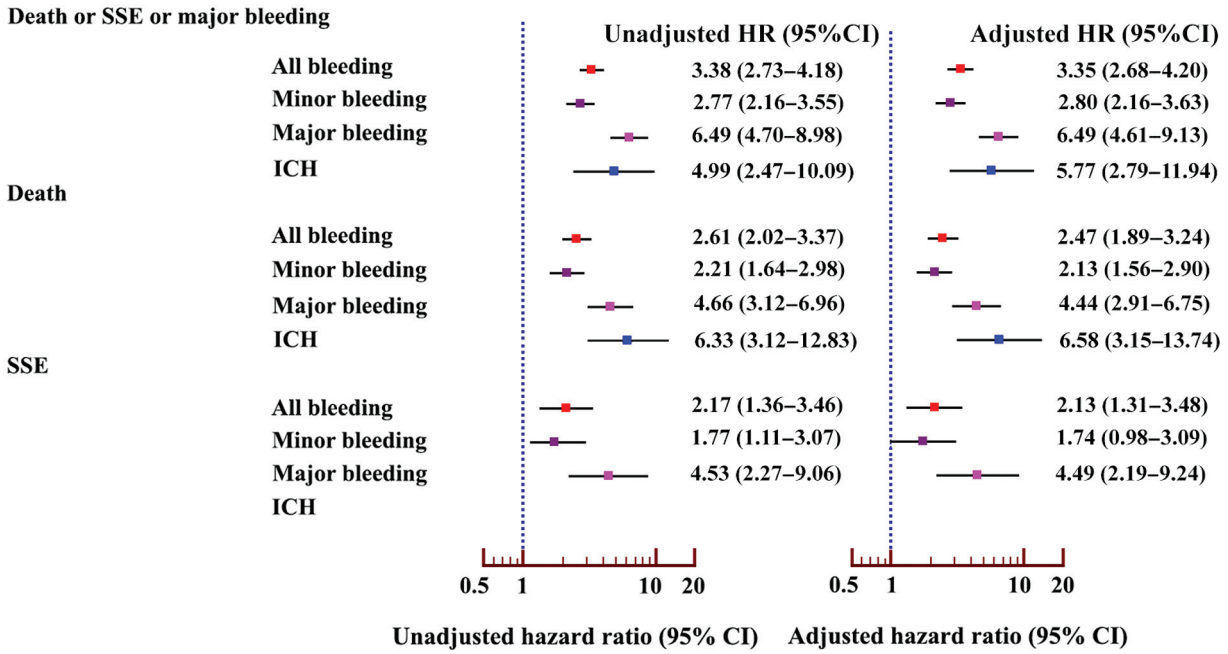

Fig. 3 Hazard ratio of each type of bleeding events and clinical outcomes after bleeding events. CI, confidence interval; HR, hazard ratio; ICH, intracranial hemorrhage; SSE, ischemic stroke/systemic embolism.

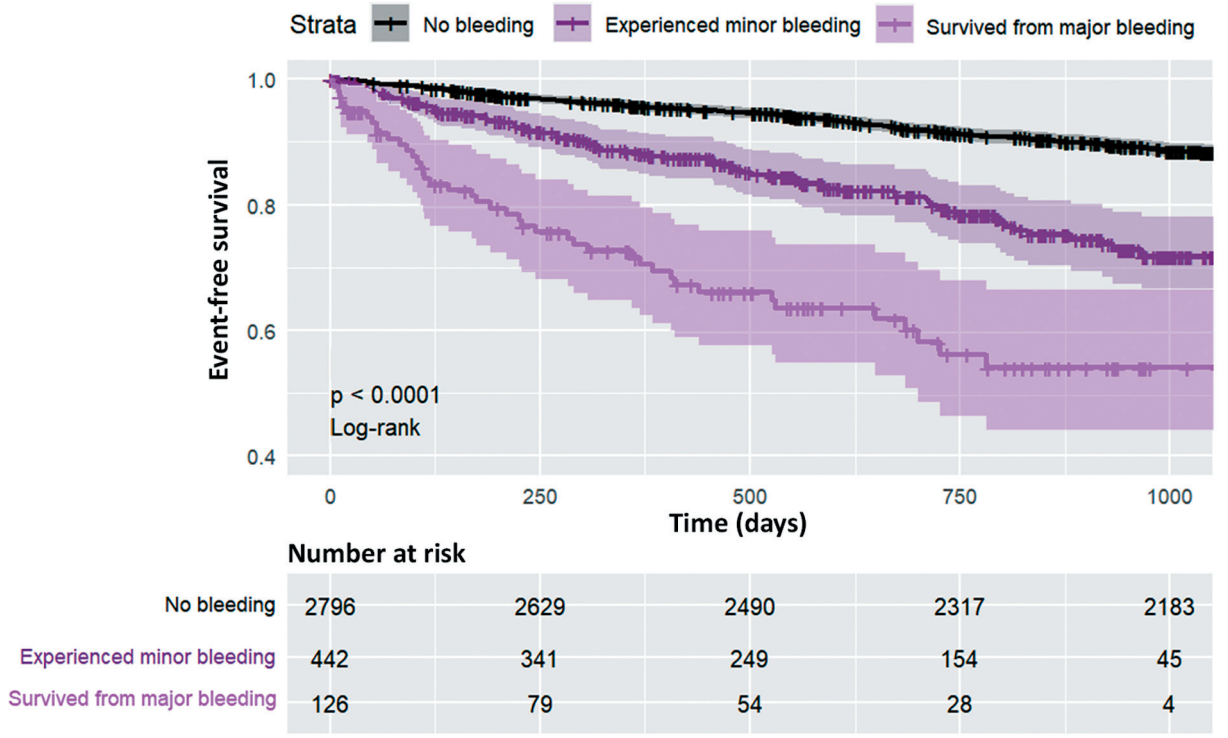

Fig. 4 Event-free survival of composite outcome of death or stroke and systemic embolism of patients with major bleeding, minor bleeding, and no bleeding.

and with major bleeding event. Comparing to patients without major bleeding event, proportion of warfarin use decreased in those with major bleeding event, whereas proportion of NOACs and no OAC increased.

For patients who experienced minor bleeding while receiving warfarin (363 patients), 329 (90.6%) continued warfarin, 23 (6.3%) discontinued OAC, and 11 (3.0%) switched to NOACs after bleeding. There was no case with NOAC bleeding switching to warfarin after events.

Patients who discontinued OAC after bleeding events have very high mortality rate (41.7% of those with minor bleeding and 42.4% of major bleeding discontinued OAC) (►**Table 3**). This is compared with patients who resumed OAC with either warfarin or NOACs, where mortality was 9.7% and

Table 2 Decision on anticoagulant regimen after bleeding events

	Overall ($n = 2,534$)	Discontinue before ($n = 2$)	Using warfarin before bleeding ($n = 2,306$)	Using NOAC before bleeding ($n = 226$)
All bleeding				
Number of patients	488	2	465	21
Same	414/488 (84.8%)		396/465 (85.2%)	18/21 (85.7%)
Change OAC category	15/488 (3.1%)		15/465 (3.2%)	0/21 (0.0%)
OAC discontinuation	57/488 (11.%)		54/465 (11.6%)	3/21 (14.3%)
Major bleeding				
Number of patients	110	0	102	8
Same	73/110 (66.4%)		67/102 (65.7%)	6/8 (75.0%)
Change OAC category	4/110 (3.6%)		4/102 (3.9%)	0/8 (0.0%)
OAC discontinuation	33/110 (30.0%)		31/102 (30.4%)	2/8 (25.0%)
Site of bleeding—ICH				
Number of patients	30	0	27	3
Same	10/30 (33.3%)		9/27 (33.3%)	1/3 (33.3%)
Change OAC category	1/30 (3.3%)		1/27 (3.7%)	0 (0.0%)
OAC discontinuation	19/30 (63.3%)		17/27 (63.0%)	2/3 (66.7%)
Site of bleeding—extracranial bleeding				
Number of patients	86	0	81	5
Same	53/86 (61.6%)		63/81 (77.8%)	5/5 (100.0%)
Change OAC category	3/86 (3.5%)		3/81 (3.7%)	0 (0.0%)
OAC discontinuation	29/86 (33.7%)		15/81 (18.5%)	0 (0.0%)
Minor bleeding				
Number of patients	378	2	363	13
Same	341/378 (90.7%)		329/363 (90.6%)	12/13 (92.3%)
Change OAC category	11/378 (2.9%)		11/363 (3.0%)	0/13 (0.0%)
OAC discontinuation	24/378 (6.3%)		23/363 (6.3%)	1/13 (7.7%)

Abbreviations: ICH, intracranial hemorrhage; NOACs, nonvitamin K antagonist oral anticoagulants; OAC, oral anticoagulants.

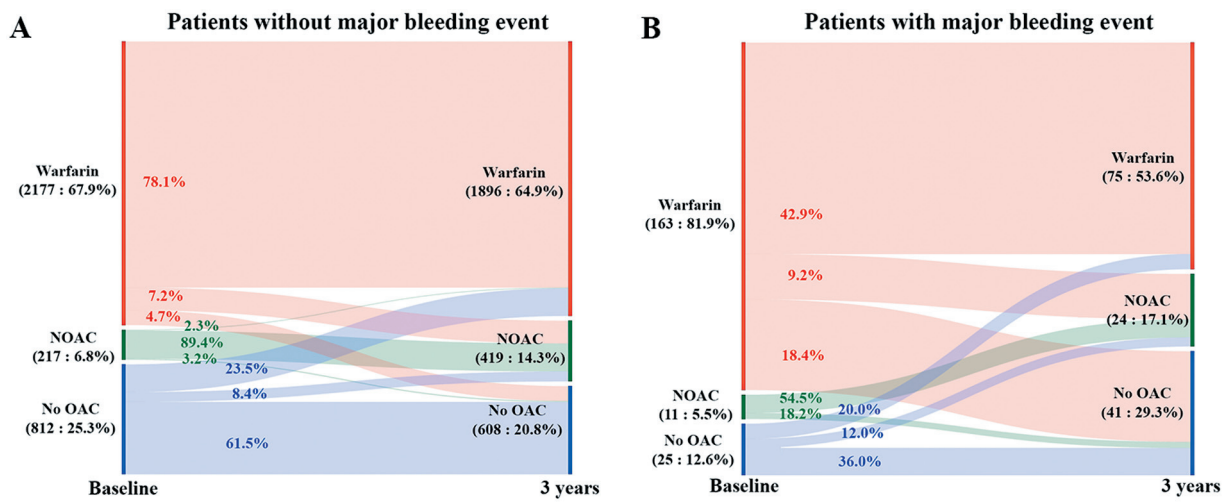

Fig. 5 Sankey diagram of changes in OAC status in patients without (**A**) and with major bleeding event (**B**). NOAC, nonvitamin K antagonist oral anticoagulant; OAC, oral anticoagulant.

Table 3 Clinical events after bleeding stratified by anticoagulant strategy after bleeding

	Overall ($n = 2,534$)	Death or SSE or major bleeding	Death	Major bleeding	SSE	ICH
All bleeding						
Patients with all bleeding	488	105/488 (21.5%)	68/488 (13.9%)	45/488 (9.2%)	17/488 (3.5%)	15/488 (3.1%)
Continue warfarin	414/488 (84.8%)	74/414 (17.9%)	43/414 (10.4%)	35/414 (8.5%)	14/414 (3.4%)	9/414 (2.2%)
Change to NOAC	15/488 (3.1%)	2/15 (13.3%)	0/15 (0.0%)	0/15 (0.0%)	2/15 (13.3%)	0/15 (0.0%)
Discontinue OAC	57/488 (11.%)	28/57 (49.1%)	24/57 (42.1%)	9/57 (15.8%)	1/57 (1.8%)	6/57 (10.5%)
Major bleeding						
All patients with major bleeding	110	34/110 (30.9%)	23/110 (20.9%)	14/110 (9.1%)	4/110 (3.6%)	4/110 (3.6%)
Continue warfarin	73/110 (66.4%)	18/73 (24.7%)	9/73 (12.3%)	9/73 (12.3%)	3/73 (4.1%)	0/73 (0.0%)
Change to NOAC	4/110 (3.6%)	1/4 (25.0%)	0/4 (0.0%)	0/4 (0.0%)	1/4 (25.0%)	0/4 (0.0%)
Discontinue OAC	33/110 (30.0%)	15/33 (45.5%)	14/33 (42.4%)	5/33 (3.0%)	0/33 (0.0%)	4/33 (12.1%)
Site of bleeding—ICH	30	8/30 (26.7%)	8/30 (26.7%)	4/30 (13.3%)	0/30 (0.0%)	4/30 (13.3%)
Continue warfarin	10/30 (33.3%)	0/10 (0.0%)	0/10 (0.0%)	0/10 (0.0%)	0/10 (0.0%)	0/10 (0.0%)
Change to NOAC	1/30 (3.3%)	0/1 (0.0%)	0/1 (0.0%)	0/1 (0.0%)	0/1 (0.0%)	0/1 (0.0%)
Discontinue OAC	19/30 (63.3%)	8/19 (42.1%)	8/19 (42.1%)	4/19 (21.1%)	0/19 (0.0%)	4/19 (21.1%)
Site of bleeding—extracranial bleeding	86	26/86 (30.2%)	15/86 (17.4%)	10/86 (11.6%)	4/86 (4.7%)	0 (0.0%)
Continue warfarin	68/86 (79.1%)	18/68 (26.5%)	9/68 (13.2%)	9/68 (13.2%)	3/68 (4.4%)	0 (0.0%)
Change to NOAC	3/86 (3.5%)	1/3 (33.3%)	0/3 (0%)		1/3 (33.0%)	
Discontinue OAC	15/86 (17.4%)	7/15 (46.7%)	6/15 (40.0%)	1/15 (6.7%)	0/15 (0.0%)	0 (0.0%)
Minor bleeding						
Patients with minor bleeding	378	72/378 (19.0%)	45/378 (11.9%)	31/378 (8.2%)	14/378 (3.7%)	11/378 (2.9%)
Continue warfarin	341/378 (90.7%)	57/341 (16.7%)	34/341 (10.0%)	26/341 (7.6%)	12/341 (3.5%)	9/341 (2.6%)
Change to NOAC	11/378 (2.9%)	1/11 (9.1%)	0/11 (0.0%)	0/11 (0.0%)	1/11 (9.1%)	0/11 (0.0%)
Discontinue OAC	24/378 (6.3%)	13/24 (54.2%)	10/24 (41.7%)	4/24 (16.7%)	1/24 (4.2%)	2/24 (8.3%)

Abbreviations: ICH, intracranial hemorrhage; NOACs, nonvitamin K antagonist oral anticoagulants; OAC, oral anticoagulants; SSE, ischemic stroke/systemic embolism.

11.7% in patients after minor and major bleeding, respectively. Risk for stroke after first bleeding was 3.5, numerically more commonly in patients who resumed OAC (3.7%) compared with patients who discontinued (1.8%). Conversely, subsequent bleeding occurred more commonly in patients who discontinued OAC (15.8%) compared with those who resumed OAC (8.2%).

The rate of temporary discontinuation of OAC was 125 out of 488 patients with bleeding (25.6%) and 483 out of 2046 patients without bleeding (23.6%), $p = 0.351$. OAC temporary discontinuation had no significant effect on the impact of bleeding event on the composite outcome (interaction test; $p = 0.124$). There were 886 episodes of OAC temporary discontinuation in 608 patients. Bridging therapy was used in 128 out of 886 OAC temporary discontinuation episodes (14.4%).

For patients with warfarin, mean TTR was $53.7 \pm 26.3\%$. TTR was $50.0 \pm 26.1\%$ in patients with bleeding and $54.7 \pm 26.3\%$ for those without bleeding ($p = 0.001$). Proportion of TTR $\geq 65\%$ was 137 (29.5%) in patients with bleeding and 660 (37.8%) for those without bleeding ($p = 0.001$).

Causes of Death among Patients who Survived Bleeding Episode

Death was the most common clinical outcomes during follow-up. We divided causes of death into three main categories: cardiovascular (CV) death, death due to hemorrhage, and deaths with no association with CV cause or hemorrhage (non-CV/nonbleeding death).

After bleeding during treatment with OAC, 68 of 488 patients (13.9%) died during follow-up. Of these, 12 (17.6%) were CV deaths, 12 (17.6%) were deaths due to hemorrhage, and 44 (64.7%) were non-CV/nonhemorrhage deaths (►**Table 4**). These proportions were similar with all bleeding severity categories and sites. In 23 deaths after survived major bleeding, 5 (21.7%) were CV deaths, 4 (17.4%) were deaths due to hemorrhage, and 14 (60.9%) were non-CV/nonhemorrhage death. In 45 deaths after minor bleeding, 7 (15.6%) were CV death, 8 (17.8%) were death due to hemorrhage, and 30 (66.7%) were non-CV/nonhemorrhage death. The most common non-CV/nonbleeding cause of death overall was infection (45.5%).

Table 4 Causes of subsequent death after bleeding events stratified by antithrombotic strategy after bleeding

	All patients with bleeding ($n = 488$)	Patients who continue VKA after bleeding ($n = 414$)	Patients who change to NOAC after bleeding ($n = 15$)	Patients who discontinue OAC after bleeding ($n = 57$)
All-cause death	68/488 (13.9%)	43/414 (10.4%)	0/15	24/57 (42.1%)
CV death	12 (2.5%)	10 (2.4%)		2 (3.5%)
Sudden cardiac death	4	3		1
Fatal myocardial infarction	2	2		
Heart Failure death	4	3		1
Fatal stroke	2	2		
Fatal bleeding	12 (2.5%)	6 (1.4%)		5 (8.8%)
Intracerebral hemorrhage	7	3		4
Hemorrhage that neither CV bleeding nor stroke	5	3		1
Non-CV, nonbleeding death	44 (9.0%)	27 (6.5%)		17 (29.8%)
Pulmonary	1			1
Renal	2	1		1
Infection/sepsis	20	15		5
Trauma	2	1		1
Neurological	3	1		2
Malignancy	1	1		
Senile	2	2		
Other non-CV dead	2	1		1
Undetermined	11	5		6

Abbreviations: CV, cardiovascular; NOACs, nonvitamin K antagonist oral anticoagulants; OAC, oral anticoagulants; VKA, vitamin K antagonist.

Discussion

The principal findings of our analysis from the COOL-AF Thailand registry are as follows: (1) patients with AF who have bleeding events have an increased risk for subsequent death and SSE; (2) up to 30% of patients who survived major bleeding and 6.3% of minor bleedings discontinued oral anticoagulation. Discontinuation was associated with very high death rate (42.1%), whereas patients who resumed oral anticoagulation after bleeding had lower mortality (10%); and (3) causes of death were mostly nonrelated to CV causes nor bleeding (most commonly, infection: 45.5%).

COOL-AF is a prospective multicenter registry that enrolled AF patients from 2014 to 2017 to identify optimal international normalized ratio (INR) for Thai patients. During timing of the study, access to NOACs was restricted in the most AF patients. These data, therefore, partly represent bleeding outcomes related to warfarin use. Our data showed that bleeding is very common outcome during treatment with warfarin, where up to 17.9% experienced bleeding during follow-up. Patients who had bleeding event had a higher risk of clinical outcomes compared with those with no bleeding event.

From this study, 6.7% of patients who experienced bleeding did not survive the episode. The risk of death directly from bleeding might rise to 24% in patients with major bleeding and as high as 48.3% in patients with ICH. Moreover, patients who survived their bleeding episode to hospital discharge also sustains a high risk of subsequent death, stroke, and systemic embolism. The risk of subsequent death was 2-fold higher in patients with minor bleeding and 4.4-fold higher with major bleeding when compared with patients who had never bleed. These risks for clinical outcomes of our Asian patients with bleeding compared with those with no bleeding were higher than the report from combined European cohort data of the BEAT-AF and SWISS-AF registry.[8] Nevertheless, the results from BEAT-AF and SWISS-AF registry reported only patients who were on OAC, whereas our study were based on an AF population. While the definitions of major bleeding were the ISTH criteria similar in both reports, the increased risk of clinical outcomes from our study may be related to a greater use of warfarin in our study. Another explanation may be related to the increased risk of clinical outcomes in Asian AF patients[13–15] compared with non-Asians,[16,17] including for bleeding. We previously reported that AF patients with a history of major bleeding had an increased risk death, SSE, and major bleeding compared with patients without history of major bleeding.[18] The results of the current study compared outcomes of patients with and without bleeding event during the follow-up with the time-updated multivariate Cox model emphasizing the need for the better management of bleeding events in AF patients.

Nearly one-third of patients who experienced major bleeding episodes during follow-up discontinued OAC. Minor bleeding events result in discontinuation only for 6.3%. Nevertheless, discontinuation of OAC after bleeding was

more likely related to poor outcomes, with subsequent death in up to 42.1%. Also, up to 70.8% of death after OAC discontinuation were neither CV nor bleeding, suggesting clinically complex or fragile phenotypes.[19] The majority of patients in our study who re-initiated OAC after their bleeding event remained to be on warfarin, partly related to the government reimbursement policy to limited the use of NOACs, which were considered to be more expensive medications. The rate of OAC discontinuation after the bleeding episode was 13.8% from a previous study,[8] which is comparable to 14.8% in our study. The median from bleeding event to primary outcome was 306 days (interquartile range [IQR]: 23–832) for the previous study[8] compared with 245 days (IQR: 110–543) in our study. A long-term follow-up is required to monitor and start appropriate treatment for these patients.

Around two-third of subsequent death were non-CV, non-bleeding related, broadly similar to the report from the Fushimi AF registry.[20] We have also reported similar causes of death in the COOL-AF population.[21] The Fushimi AF study showed that as high as 85% died from non-CV deaths, which is probably includes bleeding-related death. Hence, patients who experienced bleeding episode during treatment for stroke prevention are vulnerable clinically complex patients who require a more holistic approach to their AF management. We observed a paradoxical data from stroke and bleeding after the first bleed. Risk for stroke after first bleeding was more commonly in patients who resumed OAC and subsequent bleeding occurred more commonly in patients who discontinued OAC after the bleeding event. We believed that paradoxical outcomes observed in this study are result from patient character that prone to bleed tend to discontinue use of OAC. Therefore, even after OAC discontinuation, they still had bleeding tendency. Likewise, patients who prone to have thrombotic events tend to continue OAC. Physicians often opt to discontinue anticoagulation therapy for stroke prevention in patients deemed too ill to derive benefit from treatment. They fear of rebleeding, so they tend to keep a low INR. Patients also fear of rebleeding, so they may intend to skip the dose of OAC. Therefore, the thrombotic risk still remained. As we can see from the TTR data of our study that patients with warfarin after the bleeding event had a TTR of $50.0 \pm 26.1\%$, whereas patients who never bled had a TTR of $54.7 \pm 26.3\%$ ($p = 0.001$). Consequently, the cessation of anticoagulants may not directly precipitate non-CV mortality but rather signifies susceptibility to various medical conditions.[22] Among 10 comorbidities (hypertension, heart failure, CAD, stroke, peripheral arterial disease, diabetes, hypo- or hyperthyroidism, anemia, renal disease, and liver disease), the number of comorbidities in our studies was greater in patients with bleeding (3.0 ± 1.5) compared with those without bleeding (2.5 ± 1.5) ($p < 0.001$). Indeed, the holistic approach has been associated with improved clinical outcomes, including lower mortality, stroke, and major bleeding.[23,24]

A systematic review of 21 observational studies involved 96,448 patients showed that AF patients not OAC represent population at higher risk of bleeding.[5] Previous studies in AF patients with gastrointestinal bleeding who resume OAC had better subsequent ischemic outcomes.[25,26] In our study, we found that patients who continued OAC suffered from SSE more than patients who discontinued OAC. This might be due to the fact that 42.1% who discontinued OAC died during follow-up, compared with only 10.0% who continued with OAC. Thus, death might have been a competing event, attenuating the occurrence of stroke after OAC discontinuation. Moreover, patients who experienced bleeding might restart OAC with a more cautious approach (e.g., lower or suboptimal range of target INR) leading to more embolic events.[27]

Limitations

This study is limited by its observational design, but was a prospective nationwide cohort designed to be fairly inclusive of study sites. Excluding patients who died at during the same hospital admission as the index bleeding events probably mask ischemic or bleeding events occur within the admission. At the time of data collection (2014–2017), most of the AF patients in Thailand were using warfarin for SSE prevention, and thus, we have too small numbers of patients on NOACs due to limitation of health care cost coverage. A large proportion of patients with bleeding in our study died of non-CV causes, and the death event may mask both ischemic and bleeding outcomes which might followed the bleeding episodes.

Conclusion

Patients with AF who have bleeding events have an increased risk for subsequent death and SSE. Cause of death were mostly nonrelated to CV causes nor bleeding. These patients should be identified as vulnerable clinically complex patients and require a holistic approach to their AF management.

What is known about this topic?

- Oral anticoagulants, which is recommended in most patients with atrial fibrillation, had an increased risk of bleeding.
- The decision to restart or discontinue anticoagulation after bleeding episodes based on a thorough assessment of thrombotic and rebleeding risks.

What does this paper add?

- Patients who survived major bleeding ($n = 126$) were at increased risk for both death (adjusted HR: 4.44, 95% CI: 2.91–6.75, $p < 0.001$) and stroke/systemic embolism (adjusted HR: 4.49, 95% CI: 2.19–9.24, $p < 0.001$).
- Discontinuation was associated with very high death rate (42.1%), whereas patients who resumed oral anticoagulation after bleeding had lower mortality (10%).

Data Availability Statement

The dataset that was used to support the results and conclusion of this study are included within the manuscript. The data underlying this article will be shared on reasonable request to the corresponding author.

Authors' Contribution

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

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Conflict of Interest

G.Y.H.L.: Consultant and speaker for BMS/Pfizer, Boehringer Ingelheim, Anthos, and Daiichi-Sankyo. No fees are directly received personally. He is a National Institute for Health and Care Research (NIHR) Senior Investigator and co-principal investigator of the AFFIRMO project on multimorbidity in AF, which has received funding from the European Union's Horizon 2020 research and innovation program under grant agreement no. 899871. All other authors hereby declare no personal or professional conflicts of interest relating to any aspect of this particular study.

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