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Bleeding and ischemic events after first bleed in anticoagulated atrial fibrillation patients: risk and timing

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Abstract

Aims: To determine the risk of subsequent adverse clinical outcomes in anticoagulated patients with atrial fibrillation (AF) who experienced a new bleeding event.

Methods and results: Anticoagulated AF patients were followed in two prospective cohort studies. Information on incident bleeding was systematically collected during yearly follow-up visits and events were adjudicated as major bleeding or clinically relevant non-major bleeding (CRNMB) according to the International Society on Thrombosis and Haemostasis guidelines. The primary outcome was a composite of stroke, myocardial infarction (MI), or all-cause death. Time-updated multivariable Cox proportional-hazards models were used to compare outcomes in patients with and without incident bleeding. Median follow-up was 4.08 years (interquartile range [IQR], 2.93-5.98). Of the 3,277 patients included (mean age 72 years, 28.5% women), 646 (19.7%) developed a new bleeding, 297 (9.1%) a major bleeding and 418 (12.8%) a CRNMB. The incidence of the primary outcome was 7.08 and 4.04 per 100 patient-years in patients with and without any bleeding, adjusted hazard ratio (aHR), 1.36, 95% confidence interval (CI) 1.16-1.61; P<0.001; median time between a new bleeding and a primary outcome 306 days (IQR, 23-832). Recurrent bleeding occurred in 126 patients (incidence, 8.65 per 100 patient-years [95% CI, 7.26-10.30]). In patients with and without a major bleeding, the incidence of the primary outcome was 11.00 and 4.06 per 100 patient-years, aHR 2.04, 95% CI, 1.69-2.46; P<0.001; median time to a primary outcome 142 days (IQR, 9-518), and 59 had recurrent bleeding (11.61 per 100 patient-years [95% CI, 8.99-14.98]). The incidence of the primary outcome was 5.29 and 4.55 in patients with and without CRNMB, aHR 0.94, 95% CI 0.76-1.15; P=0.53, median time to a composite outcome 505 days (IQR, 153-1079), and 87 had recurrent bleeding (8.43 per 100 patient-years [95% CI, 6.83-10.40]). Patients who had their OAC discontinued after their first bleeding episode

had a higher incidence of the primary composite than those who continued OAC (63/89 vs. 159/557 patients; aHR 4.46, 95% CI, 3.16-6.31; P<0.001).

Conclusions: In anticoagulated AF patients, major bleeding but not CRNMB was associated with a high risk of adverse outcomes, part of which may be explained by the discontinuation of OAC. Most events occurred late after the bleeding episode, emphasizing the importance of long-term follow-up in these patients.

Keywords: Atrial fibrillation, oral anticoagulation, bleeding, outcomes, stroke, death.

Introduction

Oral anticoagulation (OAC) very effectively reduces the risk of stroke in patients with atrial fibrillation (AF) (1, 2), but is associated with a higher risk of bleeding. Large randomized trials showed that patients taking direct oral anticoagulants (DOACs) have a major bleeding risk of approximately 2-3% per year (3-5).

Few studies have investigated the association of incident bleeding events with the subsequent risk of clinical outcomes in anticoagulated patients with AF. A post-hoc analysis from the ARISTOTLE (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation) trial found that major bleeding episodes are associated with a higher risk of death, ischemic stroke, or myocardial infarction (MI) within the first 30 days after the index bleeding event, but the long-term prognosis was not evaluated (6). The incidence of stroke and death was higher in patients who had a major bleeding in a cohort study of Japanese AF patients, but only 55% of included patients took OAC (7). Moreover, information on clinically relevant non-major bleedings (CRNMB) was not available in either study, although it is three times more common than major bleeding in patients taking OAC (8-10). Another study suggested that CRNMB is associated with a higher risk of all-cause death and major bleeding within 30 days of follow-up (8). We are not aware of long-term follow-up data after a bleeding event in anticoagulated AF populations. Such data are of major importance in the discussion of whether patients should continue or discontinue their OAC after stabilization of the initial bleeding episode.

We analyzed two cohorts of AF patients taking OAC to better understand the long-term risk of adverse clinical outcomes in patients with a new documented bleeding episode.

Methods

We included patients with previously diagnosed AF from 2 prospective, multicenter cohort studies in Switzerland that used a very similar methodology. The Basel Atrial Fibrillation (BEAT-AF) study enrolled 1,553 patients from 2010 to 2014 across 7 centers in Switzerland (11), and the Swiss Atrial Fibrillation (Swiss-AF) study enrolled 2,415 patients from 2014 to 2017 across 14 centers in Switzerland (12). Both studies had almost identical inclusion and exclusion criteria, as shown in **Supplementary Table 1**. Eligible patients had to have previously diagnosed AF. Patients were excluded if they had secondary forms of AF or were unable to sign an informed consent. For the purpose of this analysis, we combined the BEAT-AF and Swiss-AF datasets and limited our analysis to patients taking OAC at enrolment. From the combined sample, 67 patients were excluded because they had no follow-up information and 617 patients because they were not taking OAC at enrolment, leaving a total of 3,277 patients (**Supplementary Figure 1**). Both studies comply with the Declaration of Helsinki, the study protocols were approved by the local ethics committees, and written informed consent was obtained from all participants.

At study enrolment and during yearly follow-up visits, trained study personnel collected information about patient demographics, risk factors, medical history, and current medical therapy (including OAC) using standardized case report forms. AF type was categorized according to guideline recommendations at the time of protocol development into paroxysmal, persistent, or permanent (13). Body mass index was calculated as weight in kilogram divided by height in meters squared. Three consecutive blood pressure measurements were obtained at study enrolment and the mean was used for all analyses.

Bleeding and other clinical outcomes

In accordance with the International Society on Thrombosis and Haemostasis (ISTH) guidelines, major bleeding was defined as either fatal bleeding, clinically overt bleeding that reduced the hemoglobin level by ≥20 g/L or required transfusion, or symptomatic bleeding in a critical area (14). CRNMB was defined as bleeding not fulfilling the major bleeding criteria, but that was clinically overt and necessitated either hospitalization, change of antithrombotic therapy, or medical or surgical intervention (15). Further details about bleeding definitions are provided in **Supplementary Table 2**. Information on bleeding events was routinely collected by standardized case report forms during yearly follow-up visits. Visits were performed either in person or by phone call. If a bleeding event was reported by the patient or detected in the medical records, detailed information was collected from the corresponding hospitals and/or treating physicians about this event. All bleeding events were adjudicated by a clinical event committee that was unaware of other study-specific information.

The primary outcome of this analysis was a composite of ischaemic stroke, MI, and death from any cause. Additional outcomes for this study were the individual components of the composite outcome, as well as cardiovascular death. Definitions of all outcomes were identical in both cohorts and are provided in **Supplementary Table 2**. All clinical outcomes were adjudicated by a clinical endpoint committee.

Statistical analysis

Baseline characteristics were stratified by the presence or absence of a new bleeding event during follow-up. We also compared patients on OAC (included in the current analysis) with those not on OAC but having a guideline-based indication for OAC (excluded from the current analysis). Characteristics were compared using two sample t-test for normally distributed continuous variables or Wilcoxon rank-sum tests for non-normally distributed

variables. Categorical variables were compared using χ^2 tests or Fisher's exact tests depending on the cell counts (Fisher's exact test was used if cell count was <5 in any cell). In patients with an incident bleeding event, baseline characteristics reflect those obtained during the last follow-up visit prior to the bleeding. We calculated incidence rates per 100 patient-years for any bleeding, major bleeding and CRNMB, considering first events only. Patients who did not or not yet develop a bleeding event represented the comparator group. Bleeding was used as a time-updated covariate in univariable and multivariable Cox proportional-hazards models to estimate the risk of clinical outcomes in patients with compared to those without a bleeding event. All multivariable models were adjusted for time-updated covariates taking into account changes over time. These variables included age, smoking status (active, past, and never), alcohol consumption (non-drinkers, >0 to <1 drink/day, 1 to <2 drinks/day, and ≥2 drinks/day), AF type (paroxysmal, persistent, and permanent), type of OAC (none, DOAC, and vitamin K antagonist [VKA]), antiplatelet use, and history of MI, heart failure, stroke/transient ischemic attack (TIA), diabetes, hypertension, or chronic kidney disease. Non-modifiable covariates included in the models were sex, history of bleeding prior to study enrollment, and study cohort (BEAT-AF or Swiss-AF). Results were presented as adjusted hazard ratios (aHR) with 95% confidence intervals (CI). Separate models were constructed for any bleeding, major bleeding, and CRNMB. The proportional hazards assumption was checked and satisfied.

To better determine the long-term risks of clinical outcomes independent of short-term complications directly related to the initial bleeding episode, we performed a sensitivity analysis where we excluded outcome events that occurred within 30 days after the bleeding event. The same time-updated covariates indicated above were used in these

models. Patients who died within 30 days after the bleeding event were excluded from these analyses.

In a next step, we assessed the frequency of switching from one OAC drug to another and discontinuation of OAC therapy after a major bleeding or CRNMB. These analyses were restricted to patients with a bleeding event during follow-up, and only the first bleeding event was considered. Changes and discontinuation in OAC therapy before and after bleeding were plotted using Sankey diagrams (SankeyMATIC) and are presented separately for any bleeding, major bleeding, and CRNMB. The association of OAC discontinuation with the composite outcome and its components was evaluated in the same subgroup of patients. Incidence rates were compared using incidence ratios, and adjusted HR were obtained from multivariable Cox models as described above. We assessed the incidence of recurrent bleeding events again in all patients who had a first episode of bleeding. Incidence rates for any recurrent bleeding, recurrent major bleeding and recurrent CRNMB were calculated per 100 patient-years. Finally, we performed an analysis where we assessed the association of OAC plus antiplatelet with the risk of bleeding events using the same multivariable Cox models as described above.

For all analyses, we considered a 2-sided $P < 0.05$ to indicate statistical significance. All statistical analyses were performed using STATA, version 17.0 (StataCorp LLC) and R statistical software, version 4.1.2.

Results

Table 1 shows baseline characteristics stratified by the presence or absence of an incident bleeding event. Patients with an incident bleed were older, had more often a history of prior bleeding or chronic kidney disease, and were more often taking VKA than patients without an incident bleed (all P<0.001). The characteristics of patients not on OAC despite a guideline-based indication are provided in **Supplementary Table 3**. These patients more often had a history of bleeding and more often were on single or dual antiplatelet therapy (all p<0.001).

During a median follow-up of 4.08 years (IQR, 2.93-5.98), 646 patients (19.7%) developed a bleeding event, with an incidence of 4.62 per 100 patient-years (95% CI, 4.28-4.99). The primary composite outcome occurred in 34.4% of patients with and in 19.0% of patients without a new bleeding (P<0.001) (**Table 2**). In univariable and multivariable analyses, bleeding was associated with a higher risk of the composite outcome (**Table 2, Figure 1**). Similar results were observed for cardiovascular and all-cause death, but not for stroke and MI. The median time from a new bleeding to a composite outcome was 306 days (IQR, 23-832) (**Figure 2A**). Among 646 patients with a new bleeding event, 126 developed recurrent bleeding with an incidence of 8.65 per 100 patient-years (95% CI, 7.26-10.30), 64 recurrent major bleeding (4.10 per 100 patient-years; 95% CI, 3.21-5.23) and 83 recurrent CRNMB (5.61 per 100 patient-years; 95% CI, 4.52-6.96) (**Supplementary Figure 2**).

A new major bleeding event was observed in 297 patients (9.1%), with an incidence of 1.98 per 100 patient-years (95% CI, 1.77-2.22), and 84.5% of patients were hospitalized due to major bleeding. The composite outcome occurred in 48.8% of patients with and in 19.4% of patients without a new major bleeding (P<0.001). The median time from major bleeding to a composite outcome event was 142 days (IQR, 9-518) (**Figure 2A**). The

unadjusted and adjusted relative risk for the composite outcome was higher in patients with compared to those without a major bleeding (**Table 3, Figure 1**). We observed similar results for all other outcomes, except for MI. Among the 297 patients with a new major bleeding, 59 patients had recurrent bleeding with an incidence of 11.61 per 100 patient-years (95% CI, 8.99-14.98), 29 recurrent major bleeding with an incidence of 5.22 per 100 patents-years (95% CI, 3.63-7.51), and 43 recurrent CRNMB with an incidence of 7.42 per 100 patents-years (95% CI, 5.51-10.01) (**Supplementary Figure 2**).

A total of 418 patients (12.8%) had a new CRNMB, with an incidence of 2.90 per 100 patient-years (95% CI, 2.63-3.19), and 42.3% were hospitalized due to the CRNMB. Patients with a new CRNMB did not have a higher rate of the composite outcome compared to those without a CRNMB (**Table 4, Figure 1**). The median time from CRNMB to the occurrence of a composite outcome was 505 days (IQR, 153-1079) (**Figure 2A**). In univariable and multivariable analyses, CRNMB was not significantly associated with the primary or any of the secondary outcomes (**Table 4**). Among 418 patients who had a new CRNMB, 87 patients had recurrent bleeding (8.43 per 100 patient-years [95% CI, 6.83-10.40]), 45 a recurrent major bleeding (4.09 per 100 patient-years [95% CI, 3.05-5.48]) and 54 recurrent CRNMB (5.09 per 100 patient-years [95% CI, 3.90-6.65]) (**Supplementary Figure 2**).

In analyses excluding events within the first 30 days after a bleeding event, the results for the composite outcome in patients with any new bleeding, new major bleeding, and new CRNMB remained largely unchanged (**Supplementary Tables 4-6**).

Table 5 and **Supplementary Figure 3A-C** report the change in OAC at the first follow-up visit after the bleeding event. Among patients with any new bleeding, 13.8% discontinued their OAC therapy and 10.8% switched to a different OAC. After a major bleeding episode, 21.2% had their OAC discontinued, and this proportion was similar whether patients were on

VKA or DOAC before the bleeding event. In these patients, 17.5% had their OAC therapy switched, and switches occurred more often from VKA to DOAC than from DOAC to VKA. In patients who had a new CRNMB, 10.0% had their OAC therapy discontinued. OAC was discontinued more often in patients on a VKA than those on a DOAC. Changes in OAC occurred in 8.6% of patients, and they more often involved switches from VKA to DOAC than from DOAC to VKA. In subgroup analyses including only patients with a new bleeding during follow-up, the incidence of the composite outcome was higher among patients who after the bleeding episode discontinued OAC than among those who continued OAC (63/89 vs. 159/557 patients; aHR 4.46, 95% CI, 3.16-6.31; P<0.001) (**Supplementary Table 7, Supplementary Figure 4**). No difference was observed for incident stroke, but the number of strokes in this subgroup was small (**Supplementary Table 7, Supplementary Figure 5**). In additional analyses, a combination of OAC and antiplatelets was not significantly associated with a higher risk of bleeding events in multivariable models (**Supplementary Table 8**).

Discussion

With 4.6 adjudicated bleeding events per 100 patient-years, this prospective study confirmed a significant bleeding risk in anticoagulated AF patients. Patients with an incident major bleeding had a higher risk of subsequent adverse outcomes, including stroke and death (**Structured Graphical Abstract**). When events that occurred within 30 days were excluded, major bleeding remained significantly associated with a higher risk of adverse outcomes during long-term follow-up. By contrast, CRNMB was not associated with any of the assessed outcomes in time-updated multivariable models. Importantly, OAC was discontinued in a significant number of patients after a new bleeding event, more often among those with a major bleeding, and these patients had a higher incidence of the composite outcome than those who continued OAC.

Previous studies found that major bleeding increases the risk of subsequent death, stroke, and MI in anticoagulated patients in the first 30 days after the bleeding event (5, 6). However, much less was known about the long-term risks. This is one of the first studies to inform the associations between new-onset bleeding and subsequent risk of outcomes during long-term follow-up in anticoagulated AF patients. Our findings provide several novel insights. First, the median time to an adverse outcome event after a major bleed was 142 days (**Figure 2A**) indicating that most adverse events occur a long time after the acute bleeding episode has resolved. Second, 49% of patients with a major bleeding event had a stroke, MI or death over the course of the study, emphasizing the high risk of adverse events and the importance of long-term risk assessment in this population. Third, discontinuation of OAC after a bleeding episode was associated with a higher risk of adverse outcomes. Excluding events within the first 30 days after the initial bleeding confirmed our findings. While previous studies suggested a very high risk of stroke in the first 30 days after a

bleeding episode, our study did not assess this period, because of the small number of events during this period. Finally, CRNMBs were more common but were not independently associated with clinical outcomes. However, it is important to emphasize that 1 in 10 patients had their OAC discontinued after a CRNMB, and these discontinuations may be associated with a higher risk of subsequent adverse events (16).

Several reasons may explain the high long-term risk of adverse outcomes after major bleeding. First, the occurrence of a major bleeding usually requires therapeutic action, such as OAC discontinuation, transfusions of pack red cells, surgery, or OAC reversal. These interventions may induce a prothrombotic state which helps to explain the short-term risk of adverse events (17, 18). Second, more than 20% of patients who had a major bleeding had their OAC discontinued during long term follow-up (**Table 5**). It is likely that OAC discontinuations after a bleed have contributed to the higher long-term risk of adverse outcomes (**Supplementary Table 7, Supplementary Figure 4**). Third, major bleeding and stroke share common risk factors, increasing both the risk of bleeding and thromboembolic events, and this significant overlap can't be entirely addressed by multivariable adjustment (19, 20).

In our study, incident CRNMB was not associated with a higher risk of death or other adverse events. By contrast, data from GARFIELD-AF previously suggested that CRNMB was associated with a higher risk of death in AF patients (21). However, 33% of patients were not on OAC in GARFIELD-AF, and the incidence of CRNMB was only 1.1 per 100 patient-years compared with 2.9 per 100 patient-years in our study. These data suggest that the previous study looked at a lower bleeding risk population who did not get systematically anticoagulated, and who had a shorter follow-up, such that the two studies may not be directly comparable. Nevertheless, the 95% CIs around the risk estimates in our study

suggest that we can't exclude a slightly higher risk of death and other adverse outcomes after CRNMB. Independent of this prognostic issue, CRNMBs remain an important outcome as they are associated with an increased consumption of health care resources. A small retrospective study estimated a total cost of CRNMBs of 36'214 € per 1,000 AF patients (22). CRNMBs are a nuisance for patients and may led to unwillingness to continue OAC (23, 24). Indeed, 10% of patients with CRNMB discontinued their OAC in our study and 42% were admitted to the hospital, underscoring the importance of CRNMB, even if they were not significantly associated with adverse events in our study.

The high risk of adverse outcomes suggests that OAC resumption should be considered in patients after a bleeding event. Observational studies found a lower rate of stroke and death among patients who had their OAC resumed (25-28). However, recurrent bleeding was common in our study (**Supplementary Figure 2**), suggesting that OAC resumption may lead to a high rebleeding risk. Although the benefit of OAC resumption after a bleeding event seems favorable in observational studies (29), randomized trials are needed to determine the optimal treatment strategy in these high-risk patients. Recent research has also suggested that factor XI (FXIa) inhibitors may be promising in this area, because their bleeding risk may be lower than that of a DOAC (30, 31).

Given all these issues associated with bleeding, bleeding prevention remains a crucial issue. DOACs reduce the risk of major bleeding by 14% as compared to VKAs (2), and FXIa may be even safer (32). Clinicians should also address potentially modifiable bleeding risk factors such avoiding concomitant antiplatelet therapy, initiating proton pump inhibitors in patients who are at high risk of gastrointestinal bleeding, or reducing alcohol consumption (33). Because of the small number of patients and the resulting wide 95% CIs, we could not

confirm a significantly higher bleeding risk among patients using a combination of OAC and antiplatelets.

Strengths of our study include the prospective design and the long-term follow-up with regularly updated covariates. Nonetheless, there are some potential limitations that deserve discussion. First, although we controlled for multiple confounders in our time-updated models, there may be residual confounding that could have influenced the observed associations, as in any observational study. Second, data on OAC prescription was collected on a yearly basis. We do not have information about shorter OAC interruptions directly after the bleeding events. However, our medication data provide an accurate picture in the analysis of long-term clinical events after a bleeding episode. Third, we only included patients on OAC at study entry. Patients who previously had to discontinue OAC because of a prior bleeding episode were therefore not included, which may have led to an underestimation of the true bleeding risk in patients taking OAC. Forth, information on study outcomes and medication use was collected yearly, and it is possible that some less severe outcomes and short OAC interruptions may have been missed. Fifth, our study was underpowered to detect small effect sizes. Finally, our study included AF patients from mostly European descent, and the generalizability of our findings to other populations remains to be determined.

Conclusions

In this prospective long-term study of anticoagulated AF patients, 49% of the patients with an incident major bleeding had a primary outcome event during long-term follow-up. Major bleeding remained significantly associated with subsequent clinical outcomes after comprehensive multivariable adjustment. While CRNMB was more common, it was not associated with a higher risk of adverse outcomes, but a significant number of patients

discontinued OAC, and these patients had a higher risk of adverse events. Controlled studies on optimal management strategies in these high-risk patients are needed.

Abbreviations

aHR	Adjusted hazard ratio
AF	Atrial fibrillation
CI	Confidence interval
CRNMB	Clinically relevant non-major bleeding
DOAC	Direct oral anticoagulants
IQR	Interquartile range
ISTH	International Society on Thrombosis and Haemostasis
MI	Myocardial infarction
OAC	Oral anticoagulation
VKA	Vitamin K antagonist

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Data availability statement

All data will be shared upon reasonable request to the corresponding author.

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Figure legends

Figure 1. Risk of adverse outcomes according to new bleeding events

Shown are adjusted hazard ratios with 95% confidence intervals for adverse outcomes according to new bleeding events.

CRNMB=clinically relevant non-major bleeding; composite= composite outcome of stroke, MI and death; MI=myocardial infarction

Figure 2. Time from bleeding to adverse outcomes according to bleeding type

Panels show the median time (interquartile range) between the new bleeding and an event. Shown are patients who experienced a new bleeding and a clinical event during follow-up. Panel A shows median time between bleeding and composite outcome. Panel B shows median time between bleeding and stroke. Panel C shows median time between bleeding and myocardial infarction. Panel D shows median time between bleeding and cardiovascular death. Panel E shows median time between bleeding and death from any cause.

Structured Graphical Abstract

Relationships between bleeding events and the risk of subsequent adverse outcomes in anticoagulated patients with atrial fibrillation.

Composite consisted of stroke, MI or death; AF=Atrial fibrillation, OAC=Oral anticoagulation, F-up=Follow-up, CRNMB=Clinically relevant non-major bleeding, MI=Myocardial infarction.

Table 1. Characteristics of patients stratified by incident bleeding

Characteristic	All (N=3,277)	Any new bleeding (N=646)*	No bleeding (N=2,631)	P value[a]
Age, years	72±9	77±8	72±9	<0.001
Female sex, no. (%)	934 (28.5)	177 (27.4)	757 (28.8)	0.49
Body-mass index, kg/m^2	27.7±4.8	27.3±4.8	27.7±4.8	0.09
Smoking status, no. (%)				0.93
Active	236 (7.2)	45 (7.0)	193 (7.4)	
Past	1,601 (49.0)	317 (49.1)	1,291 (49.2)	
Never	1,432 (43.8)	284 (43.9)	1,140 (43.5)	
Blood pressure, mmHg	134±19/78±12	134±20/76±12	134±19/78±12	0.97/0.002
Heart rate, bpm	71±17	71±16	70±17	0.13
Type of atrial fibrillation, no. (%)				<0.001
Paroxysmal	1,455 (45.1)	254 (39.7)	1,188 (45.9)	
Persistent	940 (29.2)	155 (24.3)	777 (30.0)	
Permanent	829 (25.7)	230 (36.0)	622 (24.1)	
CHA_2DS_2-VASc score	3.4±1.7	4.0±1.6	3.3±1.7	<0.001
Medical history, no. (%)				
Hypertension	2,377 (72.6)	507 (78.5)	1,872 (71.2)	<0.001
Diabetes mellitus	560 (17.1)	121 (18.7)	452 (17.2)	0.35
Stroke or TIA	612 (18.7)	148 (22.9)	472 (18.0)	0.004
Myocardial infarction	519 (15.8)	117 (18.1)	402 (15.3)	0.08

Prior PCI	685 (20.9)	161 (24.9)	532 (20.2)	0.009
Heart failure	852 (26.0)	232 (35.9)	648 (24.7)	<0.001
Any bleeding	427 (13.0)	118 (18.3)	309 (11.8)	<0.001
Chronic kidney disease	648 (19.8)	183 (28.3)	488 (18.6)	<0.001
Oral anticoagulation type, no. (%)				<0.001
Direct oral anticoagulants	1,374 (41.9)	231 (35.8)	1,143 (43.5)	
Vitamin K antagonists	1,903 (58.1)	415 (64.2)	1,488 (56.6)	
Antiplatelet therapy, no. (%)	481 (14.8)	90 (13.9)	368 (14.1)	0.93
Dual antiplatelet therapy, no (%)	54 (1.7)	8 (1.2)	42 (1.6)	0.59

* Variables are time-updated from baseline to the new bleeding event.

[a] P-values compare patients with and without a new bleeding and are from two-sample t-tests or Wilcoxon rank-sum tests for continuous variables, and from χ^2 tests or Fisher's exact tests for categorical variables.

CHA_2DS_2-VASc=congestive heart failure, hypertension, age ≥75 years (2 points), diabetes, prior stroke or TIA or thromboembolism (2 points), vascular disease, age 65 to 74 years, female sex; TIA= transient ischemic attack; PCI=percutaneous coronary intervention

Table 2. Risk of adverse outcomes after any bleeding

Outcome	Patients with any bleeding		Patients without any bleeding					
	No. of patients/ total no. (%)	Rate per 100 patient-years	No. of patients/ total no. (%)	Rate per 100 patient-years	Unadjusted HR (95% CI)	P value	Adjusted HR (95% CI)*	P value
Primary outcome								
Stroke, myocardial infarction, or death from any cause	222/646 (34.4)	7.08	501/2,631 (19.0)	4.04	1.75 (1.49-2.05)	<0.001	1.36 (1.16-1.61)	<0.001
Secondary outcomes								
Stroke	31/646 (4.8)	0.98	109/2,631 (4.1)	0.86	1.13 (0.76-1.69)	0.55	1.01 (0.67-1.52)	0.95
Myocardial infarction	24/646 (3.7)	0.76	89/2,631 (3.4)	0.70	1.08 (0.69-1.70)	0.74	0.90 (0.57-1.42)	0.66
Cardiovascular death	122/646 (18.9)	3.81	233/2,631 (8.9)	1.81	2.10 (1.69-2.62)	<0.001	1.52 (1.20-1.91)	<0.001
Death from any cause	196/646 (30.3)	6.12	363/2,631 (13.8)	2.82	2.16 (1.82-2.57)	<0.001	1.62 (1.35-1.95)	<0.001

*Multivariable adjustment for age, sex, smoking status, alcohol consumption, type of AF, history of myocardial infarction, heart failure, stroke/TIA, diabetes, hypertension, history of any bleeding, chronic kidney disease, type of OAC (VKA or DOAC), study cohort (BEAT-AF or Swiss-AF), and antiplatelet use.

Table 3. Risk of adverse outcomes after major bleeding

Outcome	Patients with major bleeding		Patients without major bleeding					
	No. of patients/ total no. (%)	Rate per 100 patient-years	No. of patients/ total no. (%)	Rate per 100 patient-years	Unadjusted HR (95% CI)	P value	Adjusted HR (95% CI)*	P value
Primary outcome								
Stroke, myocardial infarction, or death from any cause	145/297 (48.8)	11.00	578/2,980 (19.4)	4.06	2.71 (2.26-3.25)	<0.001	2.04 (1.69-2.46)	<0.001
Secondary outcomes								
Stroke	23/297 (7.7)	1.72	117/2,980 (3.9)	0.81	2.11 (1.35-3.30)	0.001	1.96 (1.24-3.12)	0.004
Myocardial infarction	12/297 (4.0)	0.90	101/2,980 (3.4)	0.70	1.30 (0.71-2.36)	0.40	1.07 (0.59-1.96)	0.82
Cardiovascular death	84/297 (28.3)	6.19	271/2,980 (9.1)	1.84	3.39 (2.65-4.33)	<0.001	2.41 (1.86-3.11)	<0.001
Death from any cause	132/297 (44.4)	9.72	427/2,980 (14.3)	2.90	3.37 (2.77-4.10)	<0.001	2.42 (1.98-2.97)	<0.001

*Multivariable adjustment for age, sex, smoking status, alcohol consumption, type of AF, history of myocardial infarction, heart failure, stroke/TIA, diabetes, hypertension, history of any bleeding, chronic kidney disease, type of OAC (VKA or DOAC), study cohort (BEAT-AF or Swiss-AF), and antiplatelet use.

Table 4. Risk of adverse outcomes after clinically relevant non-major bleeding

Outcome	Patients with clinically relevant non-major bleeding		Patients without clinically relevant non-major bleeding					
	No. of patients/ total no. (%)	Rate per 100 patient-years	No. of patients/ total no. (%)	Rate per 100 patient-years	Unadjusted HR (95% CI)	P value	Adjusted HR (95% CI)*	P value
Primary outcome								
Stroke, myocardial infarction, or death from any cause	114/418 (27.3)	5.29	609/2,859 (21.3)	4.55	1.16 (0.95-1.42)	0.15	0.94 (0.76-1.15)	0.53
Secondary outcomes								
Stroke	16/418 (3.8)	0.74	124/2,859 (4.3)	0.91	0.81 (0.48-1.36)	0.43	0.73 (0.43-1.24)	0.25
Myocardial infarction	15/418 (3.6)	0.69	98/2,859 (3.4)	0.72	0.97 (0.56-1.66)	0.90	0.82 (0.47-1.41)	0.47
Cardiovascular death	58/418 (13.9)	2.65	297/2,859 (10.4)	2.14	1.23 (0.93-1.63)	0.14	0.92 (0.69-1.23)	0.57
Death from any cause	98/418 (23.4)	4.48	461/2,859 (16.1)	3.32	1.34 (1.08-1.67)	0.009	1.05 (0.84-1.31)	0.68

*Multivariable adjustment for age, sex, smoking status, alcohol consumption, type of AF, history of myocardial infarction, heart failure, stroke/TIA, diabetes, hypertension, history of any bleeding, chronic kidney disease, type of OAC (VKA or DOAC), study cohort (BEAT-AF or Swiss-AF), and antiplatelet use.

Table 5. Change and discontinuation of OAC therapy after bleeding

	Overall (N=3,277)	Taking VKA before bleeding (N=1,903)	Taking DOAC before bleeding (N=1,374)	P value*
Any bleeding				
Patients with bleeding, n (%)	646 (19.7)	415 (21.8)	231 (16.8)	
Change in OAC category, n (%)	70/646 (10.8)	57/415 (13.7)	13/231 (5.6)	0.001
Discontinuation of OAC therapy, n (%)	89/646 (13.8)	65/415 (15.7)	24/231 (10.4)	0.06
Major bleeding				
Patients with bleeding, n (%)	297 (9.1)	202 (10.6)	95 (6.9)	
Change in OAC therapy, n (%)	52/297 (17.5)	44/202 (21.8)	8/95 (8.4)	0.005
Discontinuation of OAC therapy, n (%)	63/297 (21.2)	45/202 (22.3)	18/95 (19.0)	0.55
Clinically relevant non-major bleeding				
Patients with bleeding, n (%)	418 (12.8)	257 (13.5)	161 (11.7)	
Change in OAC therapy, n (%)	36/418 (8.6)	30/257 (11.7)	6/161 (3.7)	0.005
Discontinuation of OAC therapy, n (%)	42/418 (10.0)	32/257 (12.5)	10/161 (6.2)	<0.001

*P value compares patients taking VKA and those taking DOACs before bleeding and are from χ^2 tests or Fisher's exact tests.
OAC=oral anticoagulation, DOAC=direct oral anticoagulant, VKA=vitamin K antagonist.

Figure 1. Risk of adverse outcomes according to new bleeding events

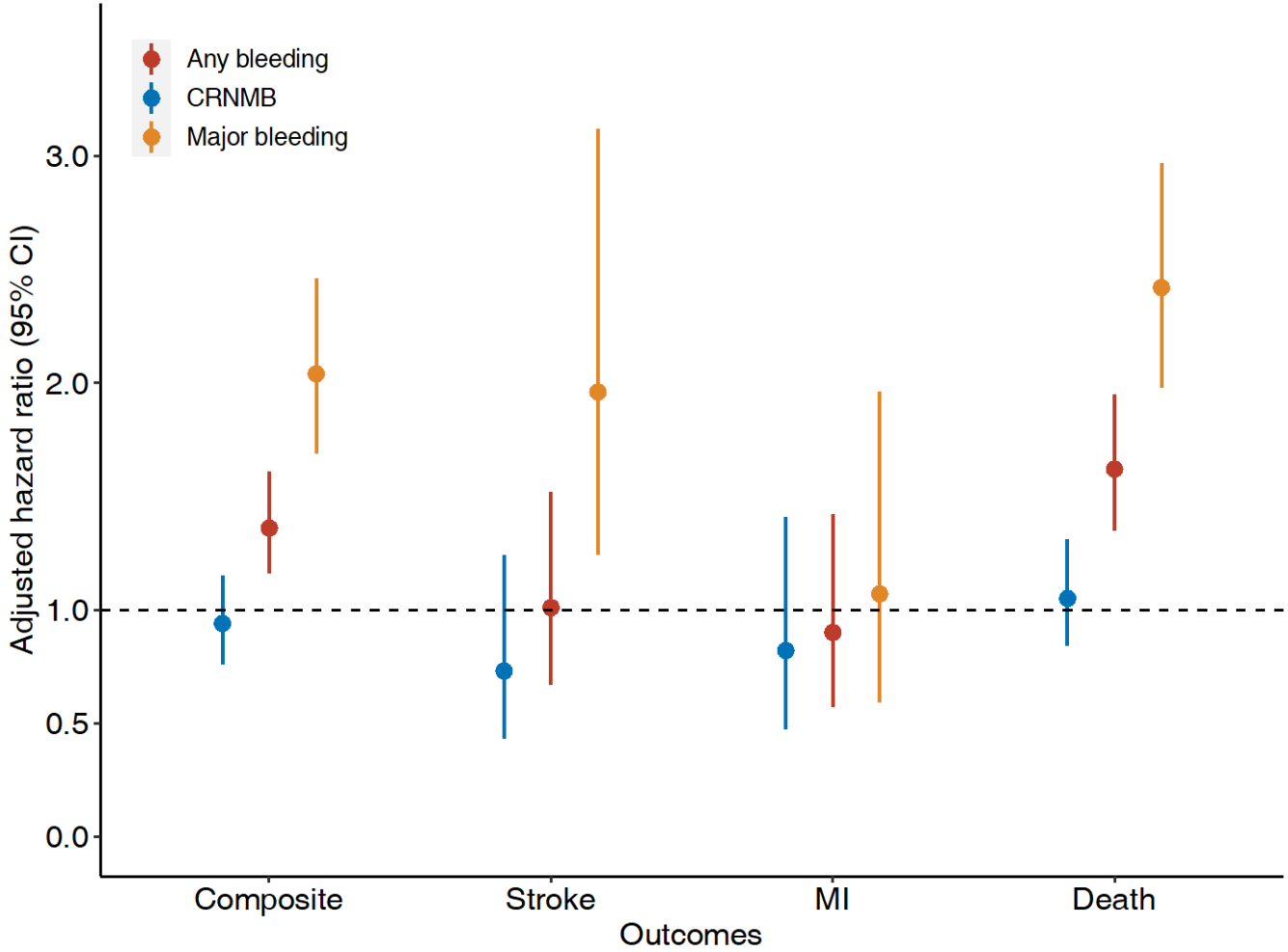
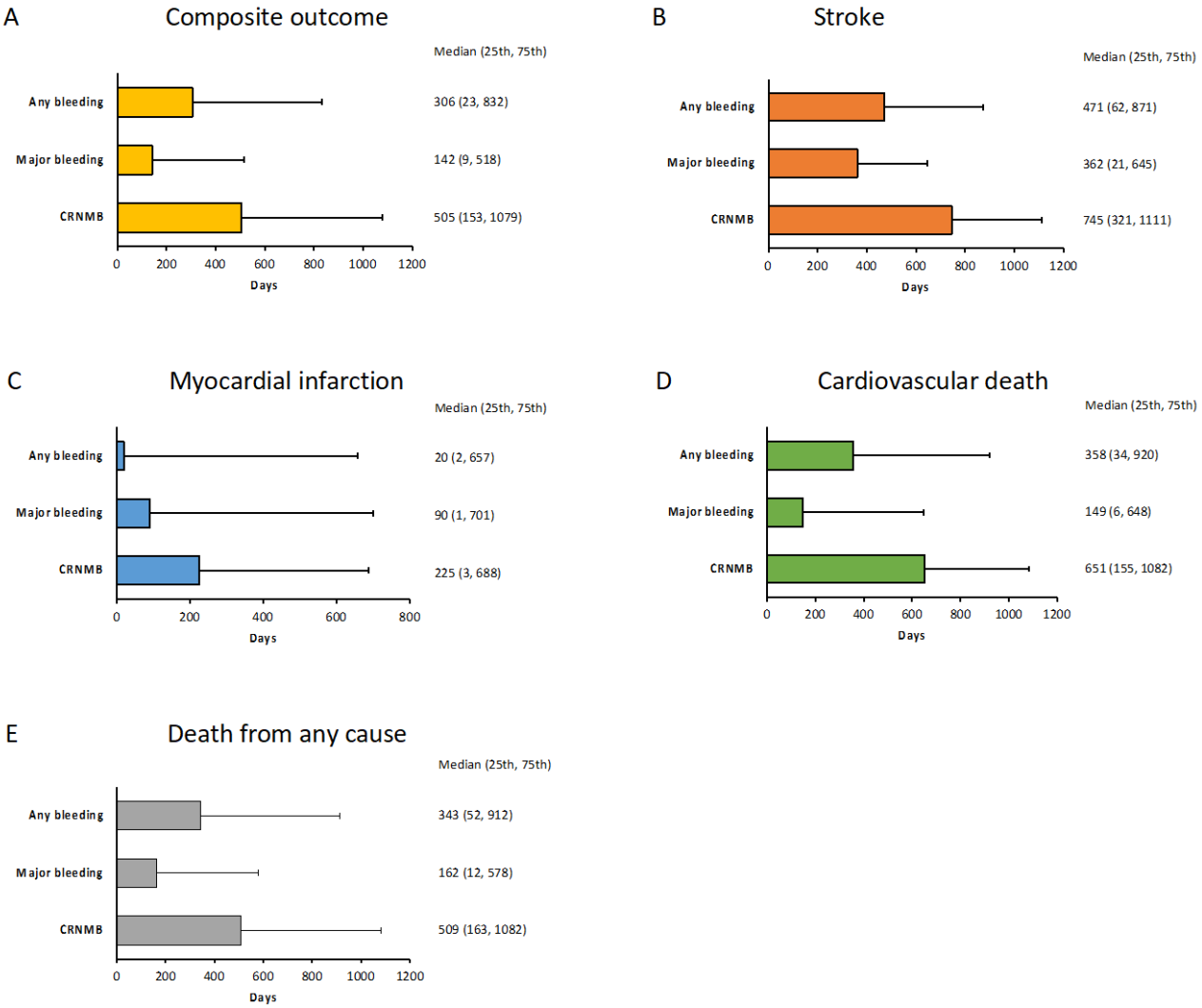


Figure 2. Time from bleeding to adverse outcomes according to bleeding type



Structured Graphical Abstract

3277 AF patients

100% on OAC

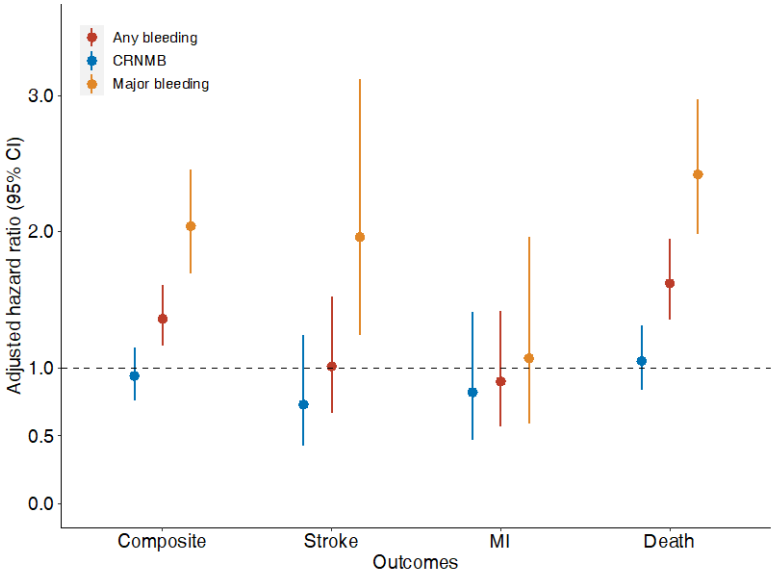
Median f-up 4.1 years

19.7% New bleeding

9.1% New major bleeding

12.8% New CRNMB

Subsequent risk of stroke, MI and death



Median time from:

- New bleeding to composite outcome: 306 days
- New major bleeding to composite outcome: 142 days
- New CRNMB to composite outcome: 505 days