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CLINICAL RESEARCH
Arrhythmias

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

Pascal B. Meyre [1,2], Steffen Blum [1,2], Elisa Hennings[1,2], Stefanie Aeschbacher [1,2], Tobias Reichlin [3], Nicolas Rodondi [4,5], Jürg H. Beer[6], Annina Stauber[7], Andreas Müller [7], Tim Sinnecker[8,9], Elisavet Moutzouri[4,5], Rebecca E. Paladini[1,2], Giorgio Moschovitis [10], Giulio Conte[11], Angelo Auricchio[11], Alexandra Ramadani[1,2], Matthias Schwenkglenks [12,13], Leo H. Bonati[8], Michael Kühne [1,2], Stefan Osswald [1,2], and David Conen[14]*, on behalf of the Swiss-AF and BEAT-AF Investigators

3,277 AF patients

100% on OAC

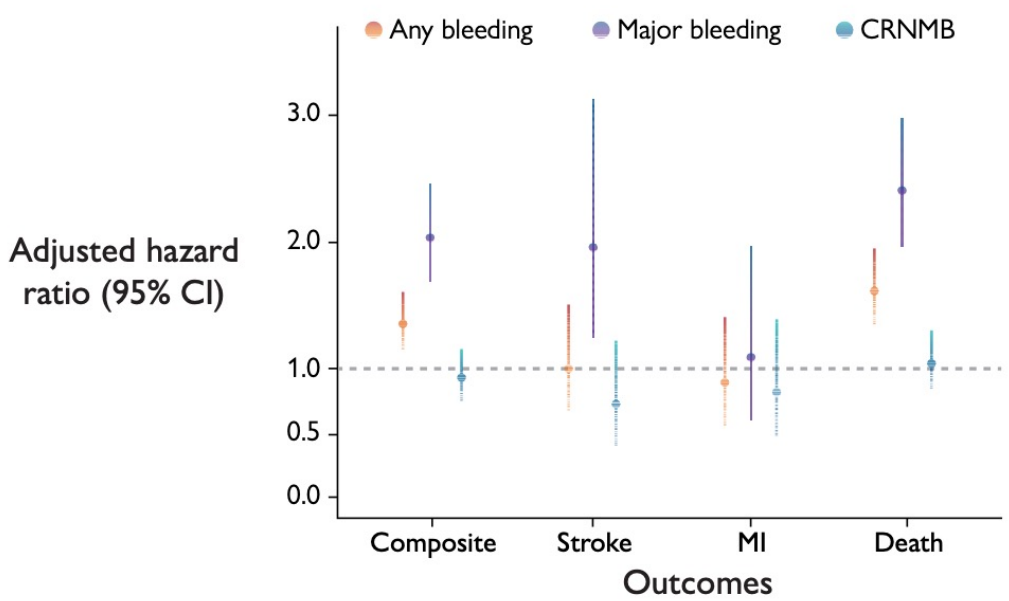
4.1 years Median follow-up

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

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Table 1 Characteristics of patients stratified by incident bleeding

Characteristic	All ($n = 3277$)	Any new bleeding ($n = 646$)[a]	No bleeding ($n = 2631$)	P-value[b]
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	1601 (49.0)	317 (49.1)	1291 (49.2)	
Never	1432 (43.8)	284 (43.9)	1140 (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	1455 (45.1)	254 (39.7)	1188 (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	2377 (72.6)	507 (78.5)	1872 (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	1374 (41.9)	231 (35.8)	1143 (43.5)	
Vitamin K antagonists	1903 (58.1)	415 (64.2)	1488 (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

[a]Variables are time-updated from baseline to the new bleeding event.
[b]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 $\chi 2$ 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 ischaemic attack; PCI = percutaneous coronary intervention.

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

Pascal B. Meyre [1,2], Steffen Blum [1,2], Elisa Hennings[1,2], Stefanie Aeschbacher [1,2], Tobias Reichlin [3], Nicolas Rodondi [4,5], Jürg H. Beer[6], Annina Stauber[7], Andreas Müller [7], Tim Sinnecker[8,9], Elisavet Moutzouri[4,5], Rebecca E. Paladini[1,2], Giorgio Moschovitis [10], Giulio Conte[11], Angelo Auricchio[11], Alexandra Ramadani[1,2], Matthias Schwenkglenks [12,13], Leo H. Bonati[8], Michael Kühne [1,2], Stefan Osswald [1,2], and David Conen[14]*, on behalf of the Swiss-AF and BEAT-AF Investigators

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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)[a]	*P* value
Primary outcome								
Stroke, myocardial infarction, or death from any cause	222/646 (34.4)	7.08	501/2631 (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	109/2631 (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	89/2631 (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	233/2631 (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	363/2631 (13.8)	2.82	2.16 (1.82–2.57)	<0.001	1.62 (1.35–1.95)	<0.001

[a]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.

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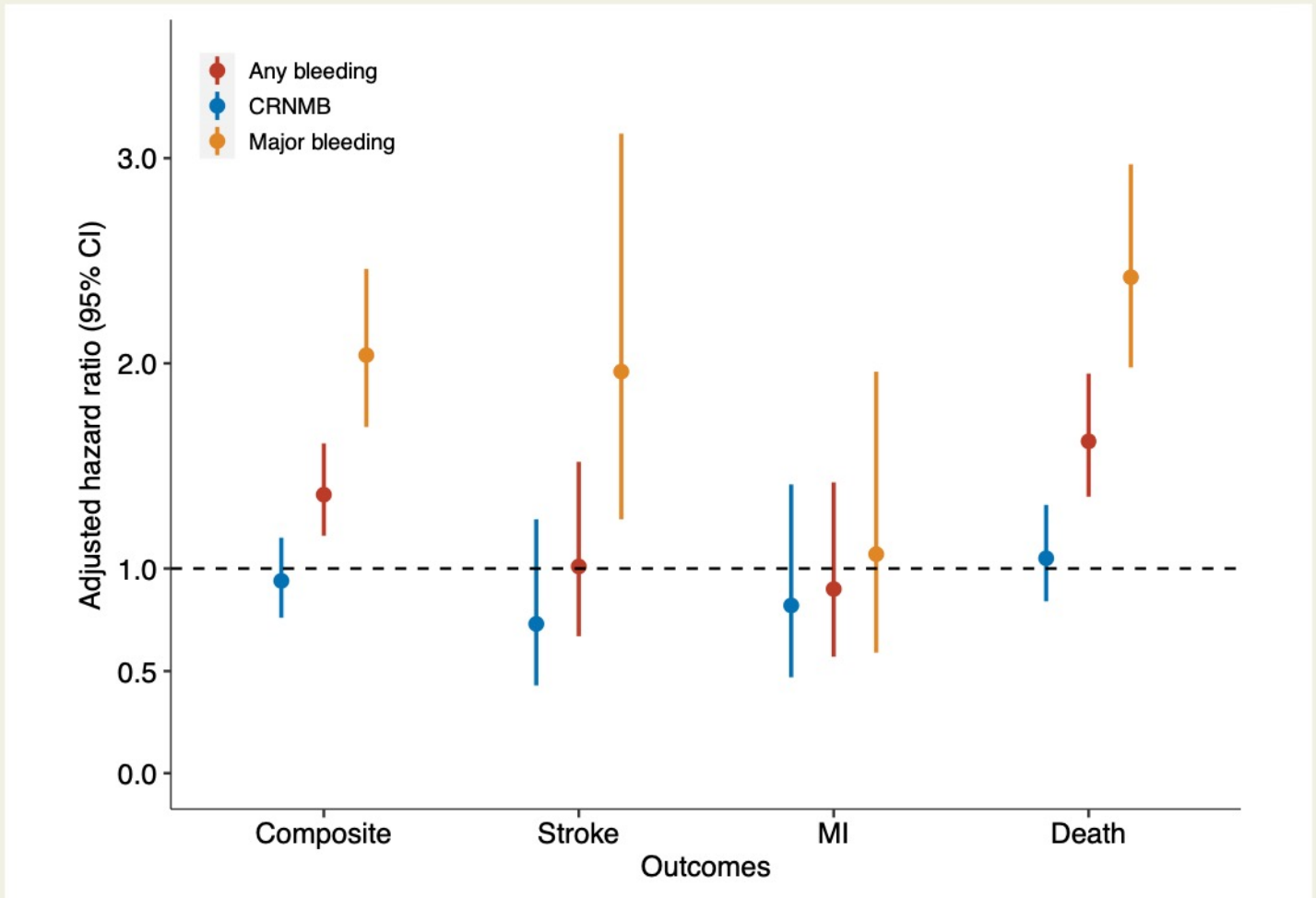

Figure 1 Risk of adverse outcomes according to new bleeding events. Shown are adjusted hazard ratios with 95% confidence intervals for adverse outcomes according to new bleeding events. CRNMB = clinically relevant non-major bleeding; composite = composite outcome of stroke, MI and death; MI = myocardial infarction.

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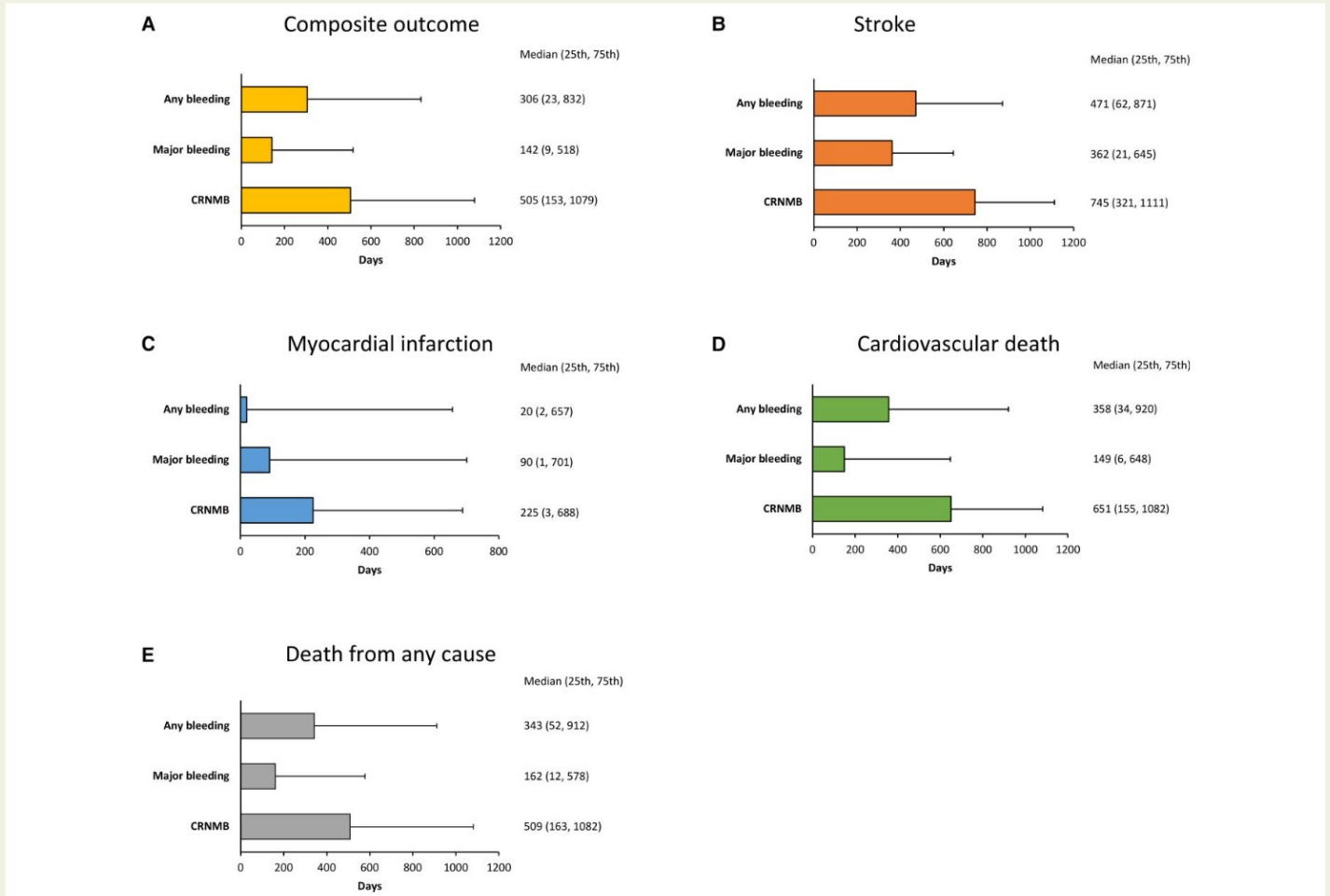

Figure 2 Time from bleeding to adverse outcomes according to bleeding type. Panels show the median time (interquartile range) between the new bleeding and an event. Shown are patients who experienced a new bleeding and a clinical event during follow-up. *Panel A* shows median time between bleeding and 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.

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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)[a]	*P* value
Primary outcome								
Stroke, myocardial infarction, or death from any cause	145/297 (48.8)	11.00	578/2980 (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	117/2980 (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	101/2980 (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	271/2980 (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	427/2980 (14.3)	2.90	3.37 (2.77–4.10)	<0.001	2.42 (1.98–2.97)	<0.001

[a]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.

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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)[a]	*P* value
Primary outcome								
Stroke, myocardial infarction, or death from any cause	114/418 (27.3)	5.29	609/2859 (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	124/2859 (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	98/2859 (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	297/2859 (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	461/2859 (16.1)	3.32	1.34 (1.08–1.67)	0.009	1.05 (0.84–1.31)	0.68

[a]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.

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Table 5 Change and discontinuation of OAC therapy after bleeding

	Overall ($n = 3277$)	Taking VKA before bleeding ($n = 1903$)	Taking DOAC before bleeding ($n = 1374$)	*P* value[a]
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

[a]P value compares patients taking VKA and those taking DOACs before bleeding and are from $\chi 2$ tests or Fisher's exact tests.
OAC = oral anticoagulation, DOAC = direct oral anticoagulant, VKA = vitamin K antagonist.

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Key Question

What is the risk of adverse outcomes in atrial fibrillation (AF) patients on oral anticoagulation (OAC) after a new bleeding event?

Key Finding

Bleeding, especially major bleeding, was associated with a higher risk of the composite of stroke, myocardial infarction (MI) or all-cause death.

Take Home Message

In patients with AF, major bleeding is associated with a very high risk of adverse events, most of them occurring a long time after the initial bleed. Part of the risk can be explained by OAC discontinuation.