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CLINICAL RESEARCH

Periprocedural anticoagulation in the uninterrupted edoxaban vs. vitamin K antagonists for ablation of atrial fibrillation (ELIMINATE-AF) trial

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Aims This *post hoc* analysis of ELIMINATE-AF evaluated requirements of unfractionated heparin (UFH) and procedure-related bleeding in atrial fibrillation (AF) patients undergoing ablation with uninterrupted edoxaban or vitamin K antagonist (VKA) therapy.

Methods and results Patients were randomized 2:1 to once-daily edoxaban 60 mg (or dose-reduced 30 mg) or dose-adjusted VKA (target international normalized ratio: 2.0–3.0). Uninterrupted anticoagulation was mandated for 21–28 days' pre-ablation and 90 days' post-ablation. During ablation, UFH administration targeted an activated clotting time (ACT) of 300–400 s. Periprocedural bleeding was differentiated between procedure-related (bleeding at puncture side, cardiac tamponade) and unrelated events. Of 614 randomized patients, 553 received study drug and underwent catheter ablation (edoxaban $n = 375$; VKA $n = 178$). The median (Q1–Q3) time from last dose to ablation procedure was 14.8 (13.3–16.5) vs. 16.5 (14.8–19.5) h (edoxaban vs. VKA group, respectively). Mean ACT (SD) ≥300 s was observed in 52% edoxaban- vs. 76% VKA-treated patients, despite a higher mean (SD) UFH dose in the edoxaban vs. VKA group [14 261 (6397) IU vs. 11 473 (4300) IU; exploratory *P*-value < 0.0001]. In the edoxaban group, 13 patients (3.5%) had procedure-related bleeds of whom 9 had received an UFH dose above the median (13 000 IU). In the VKA arm, 7 patients (3.9%) had procedure-related bleeds of whom 3 had received an UFH dose above the median (10 225 IU).

Conclusion The rate of procedure-related major/clinically relevant non-major bleeding did not differ between the treatment arms despite higher doses of UFH used with edoxaban vs. VKA to achieve a target ACT during AF ablation.

Keywords Edoxaban • Non-vitamin K antagonist oral anticoagulants • Anticoagulant • Atrial fibrillation • Ablation • Periprocedural anticoagulation

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What's new?

- This *post hoc* analysis of ELIMINATE-AF showed that patients anticoagulated with edoxaban during atrial fibrillation ablation received a higher dose of unfractionated heparin (UFH) to achieve recommended level of activated clotting time (ACT) than those treated with vitamin K antagonist.
- Despite the higher UFH dose, the mean ACT was lower in patients treated with edoxaban.
- The number of patients with procedure-related major/clinically relevant non-major bleeding did not differ between the treatment arms despite higher doses of UFH used in combination with edoxaban.

Introduction

Catheter ablation of atrial fibrillation (AF) is the most frequently performed ablation procedure world-wide and constitutes an effective treatment modality. However, the procedure can entail serious complications, including stroke, transient ischaemic attack, and cardiac tamponade.[1] To minimize these complications, current guidelines recommend continuation of oral anticoagulation with vitamin K antagonists (VKAs) or non-VKA oral anticoagulants (NOACs) during the procedure, maintaining effective anticoagulation.[2] Four randomized controlled trials compared uninterrupted VKA vs. uninterrupted NOAC therapy in patients undergoing AF ablation.[3–6] Each of these trials demonstrated low rates of ischaemic and bleeding events in patients treated with uninterrupted NOAC therapy. These results have prompted the guideline recommendation to perform AF ablation without interruption of warfarin or NOAC therapy.[2] The guidelines also recommend systemic anticoagulation with unfractionated heparin (UFH) during the ablation procedure to achieve an activated clotting time (ACT) of >300 s to avoid procedure-related thromboembolic events.[1,2] Recent observations indicate that in order to achieve this target, heparin requirements may differ in patients receiving different NOACs compared to VKA.[7–11] While Calkins *et al.*[10] demonstrated that the amount of UFH required in subjects treated with the factor II inhibitor dabigatran or warfarin was similar, mean UFH doses tended to be higher in patients receiving a factor Xa inhibitor.[3,5]

This *post hoc* analysis of the ELIMINATE-AF trial evaluated the correlation between UFH doses and ACT in patients undergoing AF ablation on an uninterrupted edoxaban- or VKA-based anticoagulation regimen. Particularly, the relationship between UFH doses and periprocedural major or clinically relevant non-major (CRNM) bleeding events was evaluated in detail.

Methods

Study design

The design, methodology, and primary results of ELIMINATE-AF have been previously reported in detail.[6,12] In brief, ELIMINATE-AF (ClinicalTrials.gov: NCT02942576) was a multinational, multicentre, randomized, open-label, parallel-group, blinded-endpoint evaluation (PROBE) study. The protocol was approved by the institutional review board or independent ethics committee at each participating study centre. All patients provided written informed consent prior to enrolment. Adult patients (≥18 years of age) with documented non-valvular AF (paroxysmal, ≤7 days; persistent, >7 days but ≤12 months; long-standing persistent, >12 months) scheduled for their first or repeated catheter ablation for AF were eligible. Patients were randomized in a 2:1 ratio to receive edoxaban or VKA using a block randomization method. Patients randomized to edoxaban received once-daily edoxaban 60 mg (30 mg if they met 1 or more of the criteria for dose reduction).[12] The preferred VKA varied across countries (phenprocoumon in Germany and Belgium, acenocoumarol in Spain, and warfarin in Belgium and in all other countries). Patients randomized to a VKA were required to maintain an international normalized ratio of 2.0–3.0 at least for the last 10 days prior to ablation.

Uninterrupted anticoagulation was mandated for 21–28 days pre-ablation and continued for 90 days post-ablation. The maximum interval between the last pre-ablation edoxaban dose and the ablation procedure was 18 h in order to maintain sufficient inhibition of endogenous factor Xa. During ablation, UFH was used according to contemporary guideline recommendations[1,2] targeting an ACT of 300–400 s. The first dose of UFH was given after sheath placement before or immediately after the transseptal puncture. For the duration of the ablation when catheters were in the left atrium, investigators were instructed to maintain an ACT ≥300 s by administering repeated boluses of UFH. Activated clotting time was assessed within 15 min after the administration of the bolus dose and regularly thereafter. Study medication was restarted at least 6 h post-sheath removal after achieving adequate haemostasis.

Parameters of coagulation were correlated with major or CRNM bleeding events (ISTH definition). For this purpose, only those events were considered which occurred from start of ablation up to 48 h after the end of the ablation procedure. Periprocedural bleeding was differentiated between procedure-related (bleeding at puncture side and cardiac tamponade) and unrelated events.

Statistical analysis

The administered heparin doses and ACT values in both treatment groups are presented descriptively. All *P*-values for group comparisons are exploratory.

Results

Patient population

A total of 632 patients were enrolled at 58 sites across 11 countries in Europe, Asia, and Canada. Of these, 614 patients were randomized, and 602 received at least one dose of study medication. A total of 553 subjects (375 in the edoxaban group and 178 in the VKA group) received study drug and underwent catheter ablation. The baseline characteristics of the two patient groups were well balanced (*Table 1*) and represented a typical AF ablation population with a male preponderance and a mean age of 60.5 years. The median (Q1–Q3) time interval between the last intake of study medication and start of the ablation procedure was 14.8 (13.3–16.5) h in the edoxaban group vs. 16.5 (14.8–19.5) h in the VKA group.

Heparin dosing and activated clotting time measurements

Data on UFH use on the day of ablation were collected in 552 patients, 374 assigned to edoxaban therapy and 178 assigned to

receive VKA. The median (Q1–Q3) UFH dose administered was higher in the edoxaban group than in the VKA group (*Table 2*). Heparin dosing tended to be lower in patients with a first ACT measurement of ≥300 vs. <300 s for all patients (*Table 2*).

The median (Q1–Q3) ACT over the course of the ablation was lower in the edoxaban group than in the VKA group (*Table 3*; exploratory *P*-value <0.0001). An individual mean ACT of ≥300 s over the course of the procedure was achieved in 52% of patients in the edoxaban group vs. 76% in the VKA group. Median (Q1–Q3) heparin dosing was similar in patients with mean ACT measurement of <300 vs. ≥300 s (*Table 3*). In the edoxaban treatment group, the first ACT was ≥300 s for 47% and in the VKA group for 66% of patients (exploratory *P* < 0.0001; *Table 4*).

Table 1 Patient characteristics

ITT analysis set	Total *N* = 614	Edoxaban *N* = 411	VKA *N* = 203
Age (years)	60.5 (53–67)	60.0 (53–67)	61.0 (52–67)
Male, *n* (%)	439 (71.5)	290 (70.6)	149 (73.4)
CHA_2DS_2-VASc score			
Mean (SD)	1.7 (1.5)	1.8 (1.6)	1.7 (1.4)
Median (Q1–Q3)	2.0 (1.0–3.0)	2.0 (1.0–3.0)	2.0 (1.0–2.0)
Medical history, *n* (%)			
Congestive heart failure	110 (17.9)	71 (17.3)	39 (19.2)
Previous CAD (prior MI, prior PCI, or prior CABG)	117 (19.2)	76 (18.6)	41 (20.3)
Previous MI	24 (3.9)	19 (4.6)	5 (2.5)
Previous stroke/TIA[a]	30 (4.9)	22 (5.4)	8 (3.9)
Peripheral artery disease	10 (1.6)	7 (1.7)	3 (1.5)
Diabetes mellitus	87 (14.2)	55 (13.4)	32 (15.8)
Hypertension	371 (60.4)	250 (60.8)	121 (59.6)
Mild valvular heart disease	52 (8.5)	32 (7.8)	20 (9.9)
AF type, *n* (%)			
Paroxysmal	415 (67.6)	284 (69.1)	131 (64.5)
Persistent	166 (27.0)	105 (25.5)	61 (30.0)
Long-standing persistent	33 (5.4)	22 (5.4)	11 (5.4)
Ablation population, mITT with ablation analysis set	*N* = 553	*N* = 375	*N* = 178
Last dose of IP to start of CA procedure (h)			
Median (Q1–Q3)	15.4 (13.5–17.1)	14.8 (13.3–16.5)	16.5 (14.8–19.5)
Sheath removal to next dose of IP (h)			
Median (Q1–Q3)	6.7 (6.1–8.0)	6.7 (6.1–8.0)	6.6 (6.1–7.9)
Type of CA performed, *n* (%)			
De novo CA	460 (83.2)	315 (84.0)	145 (81.5)
Re-do CA	93 (16.8)	60 (16.0)	33 (18.5)
CA technique used, *n* (%)			
Radiofrequency	368 (66.7)	247 (65.9)	121 (68.4)
Cryoballoon	181 (32.8)	127 (33.9)	54 (30.5)
Other	3 (0.5)	1 (0.3)	2 (1.1)
Percentage time in TTR (2.0–3.0) with VKA			
N			178
Mean (SD)			64.1 (21.1)
Median			64.8
Q1–Q3			48.3–82.1
Percentage time in TTR (1.8–3.2) with VKA			
N			178
Mean (SD)			80.9 (17.0)
Median			84.7
Q1–Q3			70.8–95.2

CA, catheter ablation; CABG, coronary artery bypass grafting; CAD, coronary artery disease; IP, investigational product; ITT, intent to treat; mITT, modified intent to treat; PCI, percutaneous coronary intention; TIA, transient ischaemic attack; TTR, time in therapeutic range; VKA, vitamin K antagonist.
[a]Includes ischaemic, embolic, and undetermined; haemorrhagic stroke prohibited.

Table 2 Heparin dose requirements in patients with ACT <300 s vs. ≥300 s

Heparin dose (IU)	Total (*N* = 553)	Edoxaban (*N* = 375)	VKA (*N* = 178)
N	552	374	178
Mean (SD)	13 361.8 (5945.3)	14 260.9 (6397.2)	11 472.6 (4300.4)
Median	12 301	13 000	10 225
Q1–Q3	10 000–16 000	10 000–17 500	8541–14 000
First ACT			
<300 s			
N	256	195	61
Mean (SD)	14 679.6 (6510.8)	15 423.0 (6766.6)	12 303.2 (4957.6)
Median	14 000	14 250	12 000
Q1–Q3	10 000–18 000	11 000–18 000	9000–15 500
≥300 s			
N	292	176	116
Mean (SD)	12 264.4 (5136.7)	13 051.0 (5697.9)	11 070.0 (3869.7)
Median	11 000	12 500	10 000
Q1–Q3	9000–15 000	10 000–15 875	8520–13 000
Minimum ACT			
<300 s			
N	417	301	116
Mean (SD)	13 737.5 (6138.9)	14 515.9 (6445.5)	11 717.8 (4716.6)
Median	12 500	13 000	10 500
Q1–Q3	10 000–17 000	10 000–18 000	8400–15 000
≥300 s			
N	131	70	61
Mean (SD)	12 295.1 (5113.1)	13 361.5 (6073.5)	11 071.4 (3372.7)
Median	12 000	12 500	10 250
Q1–Q3	9000–14 500	10 000–15 750	9000–13 000
Maximum ACT			
<300 s			
N	50	43	7
Mean (SD)	12 265.2 (5131.7)	12 889.8 (5184.4)	8428.6 (2636.7)
Median	11 000	11 720	8000
Q1–Q3	10 000–15 000	10 000–16 000	8000–9000
≥300 s			
N	498	328	170
Mean (SD)	13 505.9 (6005.2)	14 482.7 (6510.2)	11 621.3 (4315.4)
Median	12 500	13 000	10 800
Q1–Q3	10 000–16 000	10 000–18 000	9000–14 000
Mean ACT			
<300 s			
N	219	177	42
Mean (SD)	13 833.8 (6432.1)	14 427.3 (6689.9)	11 332.7 (4463.9)
Median	12 500	13 000	10 000
Q1–Q3	10 000–16 331	10 000–17 000	8000–13 000
≥300 s			
N	329	194	135
Mean (SD)	13 099.0 (5574.7)	14 180.1 (6108.6)	11 545.5 (4266.4)
Median	12 000	13 000	10 600
Q1–Q3	10 000–16 000	10 000–17 500	9000–14 000

ACT, activated clotting time; IU, international units; SD, standard deviation.

Table 3 Overview of ACT

	Total (*N* = 553)	Edoxaban (*N* = 375)	VKA (*N* = 178)
Individual mean ACT (s)			
N	548	371	177
Mean (SD)	314.2 (51.4)	302.8 (41.6)	338.0 (61.2)
Median	307.7	301.4	332.6
Q1–Q3	281.6–341.5	277.0–330.4	300.5–371.0
Mean ACT categories, *n* (%)			
<300 s	219 (40.0)	177 (47.7)	42 (23.7)
≥300 s	329 (60.0)	194 (52.3)	135 (76.3)
Individual first ACT (s)			
N	548	371	177
Mean (SD)	307.3 (89.5)	293.9 (76.7)	335.2 (106.7)
Median	304.0	293.0	348.0
Q1–Q3	250.0–365.0	246.0–350.0	256.0–400.0
First ACT categories, *n* (%)			
<300 s	256 (46.7)	195 (52.6)	61 (34.5)
≥300 s	292 (53.3)	176 (47.4)	116 (65.5)
Individual minimum ACT (s)			
N	548	371	177
Mean (SD)	246.3 (75.8)	240.3 (65.3)	258.8 (93.0)
Median	240.0	240.0	246.0
Q1–Q3	182.0–296.5	187.0–284.0	179.0–320.0
Minimum ACT categories, *n* (%)			
<300 s	417 (76.1)	301 (81.1)	116 (65.5)
≥300 s	131 (23.9)	70 (18.9)	61 (34.5)
Individual maximum ACT (s)			
N	548	371	177
Mean (SD)	365.8 (65.2)	350.7 (53.7)	397.5 (75.2)
Median	361.0	351.0	390.0
Q1–Q3	328.5–395.0	317.0–376.0	357.0–426.0
Maximum ACT categories, *n* (%)			
<300 s	50 (9.1)	43 (11.6)	7 (4.0)
≥300 s	498 (90.9)	328 (88.4)	170 (96.0)

ACT, activated clotting time; SD, standard deviation.

Periprocedural anticoagulation and bleeding events

Between sheath insertion and up to 48 h after sheath removal, major, or CRNM bleeding events occurred in 17 (4.5%) edoxaban- compared with 7 (3.9%) VKA-treated patients (*Table 5*). In the edoxaban group, 11 of the 17 patients (65%) with bleeding events had received an UFH dose above the median (13 000 IU) while in the VKA arm, 3 of 7 patients (43%) with bleeding events had received an UFH dose above the median (10 225 IU) (*Table 5*). Procedure-related (bleeding at puncture site and cardiac tamponade) major or CRNM bleeding events occurred in 13 (3.5%) edoxaban- vs. 7 (3.9%) VKA-treated patients (*Table 6*). In the edoxaban group, 9 of 13 patients with procedure-related bleeds had received an UFH dose above the median (13 000 IU) while in the VKA arm, 3 of 7 patients with procedure-related bleedings received an UFH dose above the median (10 225 IU) (*Figure 1*).

Discussion

The present *post hoc* analysis of the ELIMINATE-AF trial shows that patients assigned to edoxaban during AF ablation procedure received a higher dose of UFH than those treated with VKA. Despite the higher administered UFH dose, the mean ACT was lower in the group of subjects treated with edoxaban. The number of patients with major or CRNM bleeding events related to the ablation procedure did not differ between the treatment arms despite higher doses of UFH used in combination with edoxaban. Of note, in the edoxaban group, 9 of 13 major or CRNM bleeding events occurred in patients who received an UFH dose above the median.

Our observations confirm those reported from other studies using uninterrupted factor Xa therapy around the time of AF ablation and extend these findings specifically to patients anticoagulated with edoxaban. For instance, in the VENTURE-AF study, the average total heparin dose used to manage ACT in patients undergoing catheter

Table 4 ACT and heparin dose according to the time from the last dose of study medication edoxaban/VKA to start of the ablation procedure (for sheath insertion and trans-septal puncture)

CA procedure performed, *n* (%)	Time from edoxaban dose to septal puncture (*N* = 375, 100%)				
	0 to <8 h	8 to <16 h	16 to <24 h	≥24 h	Total
N (%)	3 (0.8)	248 (66.1)	118 (31.5)	6 (1.6)	375 (100.0)
Heparin dose (IU)					
N	3	248	117	6	374
Mean (SD)	14 300.0 (2696.3)	14 280.8 (6428.4)	14 262.4 (6477.0)	13 388.8 (5865.7)	14 260.9 (6397.2)
Median	13 000.0	13 000.0	12 500.0	12 750.0	13 000.0
Q1–Q3	12 500.0–17 400.0	10 000.0–17 750.0	10 000.0–17 000.0	8000.0–19 000.0	10 000.0–17 500.0
First ACT, *n* (%)					
0 to <100 s	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
100 to <200 s	0 (0.0)	32 (12.9)	7 (6.1)	1 (20.0)	40 (10.8)
200 to <300 s	0 (0.0)	104 (41.9)	49 (42.6)	2 (40.0)	155 (41.8)
≥300 s	3 (100.0)	112 (45.2)	59 (51.30)	2 (40.0)	176 (47.4)
Total	3 (100.0)	248 (100.0)	115 (100.0)	5 (100.0)	371 (100.0)
Mean ACT, *n* (%)					
0 to <100 s	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
100 to <200 s	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
200 to <300 s	1 (33.3)	127 (51.2)	46 (40.0)	3 (60.0)	177 (47.7)
≥300 s	2 (66.7)	121 (48.8)	69 (60.0)	2 (40.0)	194 (52.3)
Total	3 (100.0)	248 (100.0)	115 (100.0)	5 (100.0)	371 (100.0)

	Time from VKA dose to septal puncture (*N* = 178, 100%)				
	0 to <8 h	8 to <16 h	16 to <24 h	≥24 h	Total
N (%)	2 (1.1)	77 (43.3)	70 (39.3)	29 (16.3)	178 (100.0)
Heparin dose (IU)					
N	2	77	70	29	178
Mean (SD)	11 197.5 (5377.6)	11 000.5 (4468.9)	10 767.6 (3517.2)	14 446.6 (4490.0)	11 472.6 (4300.4)
Median	11 197.5	10 000.0	10 000.0	14 000.0	10 225.0
Q1–Q3	7395.0–15 000.0	8000.0–12 500.0	8500.0–12 500.0	12 000.0–16 000.0	8541.0–14 000.0
First ACT, *n* (%)					
0 to <100 s	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
100 to <200 s	0 (0.0)	13 (16.9)	7 (10.0)	4 (14.3)	24 (13.6)
200 to <300 s	0 (0.0)	13 (16.9)	15 (21.4)	9 (32.1)	37 (20.9)
≥300 s	2 (100.0)	51 (66.2)	48 (68.6)	15 (53.6)	116 (65.5)
Total	2 (100.0)	77 (100.0)	70 (100.0)	28 (100.0)	177 (100.0)
Mean ACT, *n* (%)					
0 to <100 s	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
100 to <200 s	0 (0.0)	1 (1.3)	0 (0.0)	0 (0.0)	1 (0.5)
200 to <300 s	0 (0.0)	18 (23.4)	14 (20.0)	9 (32.1)	41 (23.2)
≥300 s	2 (100.0)	58 (75.3)	56 (80.0)	19 (67.9)	135 (76.3)
Total	2 (100.0)	77 (100.0)	70 (100.0)	28 (100.0)	177 (100.0)

ACT, activated clotting time; IU, international units; SD, standard deviation; VKA, vitamin K antagonist.

ablation for AF was higher in patients receiving rivaroxaban vs. those receiving VKA (13.871 vs. 10.964 units; $P < 0.001$).[3] Similarly, a larger dose of UFH was required with uninterrupted apixaban compared with VKA to achieve the target ACT ≥300 s, and the ACT during the procedure was lower (342.1 ± 23.1 vs. 363 ± 26.5 s, $P < 0.001$) with apixaban.[13] The comparable observation was made in the AXAFA-AFNET 5 trial.[5] In contrast, a sub-analysis of the RE-CIRCUIT trial has recently shown that a similar amount of UFH was needed in patients anticoagulated with dabigatran vs. those treated with warfarin to achieve an ACT of >300 s during ablation.[10] These studies, however, did not report on bleeding events in relation to UFH dose or ACT.

Table 5 Major or CRNM bleeding events (ISTH) occurring from start of ablation up to 48 h after the end of the ablation procedure

	Total (*N* = 553), *n* (%)	Edoxaban (*N* = 375), *n* (%)	VKA (*N* = 178), *n* (%)
Major or CRNM bleeding (ISTH)	24 (4.3)	17 (4.5)	7 (3.9)
Heparin dose < median of treatment arm[a]		6	4
Heparin dose ≥ median of treatment arm[a]		11	3
Major bleeding (ISTH)	10 (1.8)	7 (1.9)	3 (1.7)
Heparin dose < median of treatment arm[a]		2	1
Heparin dose ≥ median of treatment arm[a]		5	2

CRNM, clinically relevant non-major bleeding; ISTH, International Society on Thrombosis and Haemostasis.
[a]Median heparin dose was 13 000 IU in edoxaban arm and 10 225 IU in VKA arm.

Table 6 Procedure-related major or CRNM bleeding events (ISTH) occurring from start of ablation up to 48 h after the end of the ablation procedure

	Total (*N* = 553), *n* (%)	Edoxaban (*N* = 375), *n* (%)	VKA (*N* = 178), *n* (%)
Major or CRNM bleeding (ISTH)	20 (3.6)	13 (3.5)	7 (3.9)
Heparin dose < median of treatment arm[a]		4	4
Heparin dose ≥ median of treatment arm[a]		9	3
Major bleeding (ISTH)	9 (1.6)	6 (1.6)	3 (1.7)
Heparin dose < median of treatment arm[a]		1	1
Heparin dose ≥ median of treatment arm[a]		5	2

CRNM, clinically relevant non-major bleeding; ISTH, International Society on Thrombosis and Haemostasis; IU, international units.
[a]Median heparin dose was 13 000 IU in edoxaban arm and 10 225 IU in VKA arm.

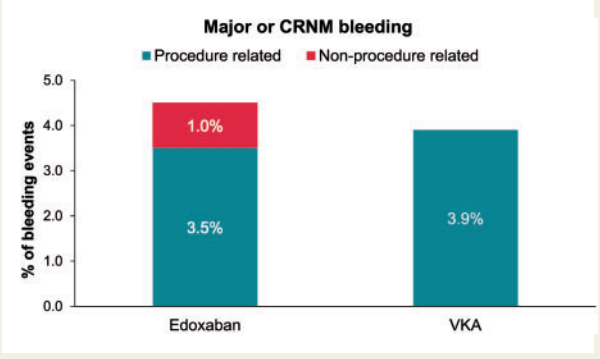

Figure 1 Procedure- and non-procedure-related major or CRNM bleeding events (ISTH) occurring from start of ablation up to 48 h after the end of the ablation procedure. CRNM, clinically relevant non-major; ISTH, International Society on Thrombosis and Haemostasis; VKA, vitamin K antagonist.

The reason for this difference in UFH requirements in patients' anticoagulated with different NOACs is not entirely clear.[11] A likely explanation could be that dabigatran, as a direct thrombin inhibitor, can prolong activated partial thromboplastin time (aPTT) and ACT in a dose-dependent manner, similar to VKAs.[14] Factor Xa inhibitors, on the other hand, may affect ACT or aPTT to a lesser degree.[11] Our observations are in line with other reports which also found shorter baseline ACT in patients on edoxaban therapy.[15] This suggests that patients treated with edoxaban, rivaroxaban, or apixaban are expected to need higher doses of UFH to maintain ACT. It has therefore been speculated that use of ACT to reflect global intraprocedural anticoagulation is limited in the presence of uninterrupted NOAC therapy, particularly when using factor Xa inhibitors.[11]

In almost all patients in the edoxaban arm, the time interval between the last edoxaban dose to septal puncture was <24 h, hence anticoagulation was truly uninterrupted (*Table 4*). The findings from this analysis attest to the safety of an uninterrupted NOAC strategy in patients undergoing AF ablation. Specifically, the low incidence of major or CRNM bleeding endpoints in the edoxaban group despite higher doses of UFH used, is reassuring.

The present analysis has some limitations. Among those is the relatively small sample size, residual bias due to the non-blinded nature of the study, and other inherent inadequacies of *post hoc* analyses. In addition, it is important to emphasize that the occurrence of vascular access bleeding after the ablation procedure may not depend only on anticoagulation drugs but also on multiple other factors such as the mode of puncture (e.g. ultrasound-guided vs. landmark-guided), sheath management after the procedure (e.g. immediate removal with Z stitch vs. delayed removal with compression) or the use of protamine.

Conclusions

The present analysis of the ELIMINATE-AF trial shows that considerably higher doses of UFH were needed with edoxaban vs. VKA to achieve a target ACT during AF ablation. Nevertheless, the number of patients with major or CRNM bleeding events related to the ablation procedure did not differ between treatments despite higher doses of UFH used in combination with edoxaban. However, in the edoxaban group, 9/13 major or CRNM bleeding events occurred in patients who received an UFH dose above the median. Careful postoperative surveillance appears to be indicated in patients in whom higher UFH doses had been administered during ablation.

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Data availability

De-identified individual participant data and applicable supporting clinical study documents are available on request, depending on circumstances, at https://vivli.org. In cases in which clinical study data and supporting documents are provided pursuant to the sponsor's policies and procedures, the sponsor will continue to protect the privacy of the clinical study participants. Details on data sharing criteria and the procedure for requesting access can be found at https://vivli.org/ourmember/daiichi-sankyo/.

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