Title	Factor Xa inhibitors for preventing recurrent thrombosis in patients with antiphospholipid syndrome : a longitudinal cohort study
Author(s)	Sato, T.; Nakamura, H.; Fujieda, Y.; Ohnishi, N.; Abe, N.; Kono, M.; Kato, M.; Oku, K.; Bohgaki, T.; Amengual, O.; Yasuda, S.; Atsumi, T.
Citation	Lupus, 28(13), 1577-1582 https://doi.org/10.1177/0961203319881200
Issue Date	2019-10-21
Doc URL	http://hdl.handle.net/2115/76206
Rights	T Sato , H Nakamura, Y Fujieda , N Ohnishi, N Abe , M Kono, M Kato, K Oku, T Bohgaki, O Amengual, S Yasuda and T Atsumi, Factor Xa inhibitors for preventing recurrent thrombosis in patients with antiphospholipid syndrome: a longitudinal cohort study, Lupus, 28, pp. 1577-1582. Copyright c 2019 The Author(s). DOI: 10.1177/0961203319881200
Type	article (author version)
Additional Information	There are other files related to this item in HUSCAP. Check the above URL.
File Information	Lupus_28_1577.pdf

[Instructions for use](#)

Factor Xa inhibitors for preventing recurrent thrombosis in patients with antiphospholipid syndrome: A longitudinal cohort study.

T. Sato, H. Nakamura, Y. Fujieda, N. Ohnishi, N. Abe, M. Kono, M. Kato, K. Oku, T. Bohgaki, O. Amengual, S. Yasuda and T. Atsumi.

Department of Rheumatology, Endocrinology and Nephrology, Faculty of Medicine and Graduate School of Medicine, Hokkaido University, Sapporo, Japan

Corresponding author: Yuichiro Fujieda, MD., PhD.

Department of Rheumatology, Endocrinology and Nephrology, Faculty of Medicine, Hokkaido University, N15 W7, Kita-ku, 060-8638, Sapporo, Japan

E-mail address: edaichi@med.hokudai.ac.jp

Telephone number: +81-11-706-5913 (Fax number: +81-11-706-7710)

Running title: Factor Xa inhibitors in APS patients

Summary

Objective: To clarify the efficacy and safety of factor Xa inhibitors for APS patients in real world utilization.

Methods: This is a retrospective cohort study comprised of all consecutive patients with APS for 18 years in our department. Patients treated with factor Xa inhibitors were extracted from the cohort. As control groups, patients treated with warfarin were selected with matched age, gender, coexistence of SLE and the presence of antiplatelet therapy, following we used propensity score for each of risk factors as an additional covariate in multivariate Cox proportional hazard regression. Primary endpoint was set as thrombotic and hemorrhagic event-free survival for 5 years.

Results: Among 206 patients with APS, 18 had a history of anti-Xa therapy (5 rivaroxaban, 12 edoxaban, 1 apixaban). In 14 out of 18 patients on anti-Xa therapy, factor Xa inhibitors were switched from warfarin. Event-free survival was significantly shorter during anti-Xa therapy than that during warfarin therapy in these 14 patients (Hazard ratio: 12.1, 95% CI: 1.73-248, $p=0.01$). Similarly, event-free survival in patients treated with factor Xa inhibitors was significantly shorter compared with controls (Hazard ratio: 4.62, 95% CI: 1.54-13.6, $p=0.0075$).

In multivariate Cox proportional hazard model, event-free survival in patients with anti-Xa therapy remained significantly shorter (Hazard ratio: 11.9, 95% CI: 2.93-56.0, $p=0.0005$).

Conclusions: Factor Xa inhibitors for APS may not be recommended.

1 **Key Words:** antiphospholipid syndrome, factor Xa inhibitor, hemorrhage, thrombosis,

2 warfarin

3

1 **Introduction**

2 Antiphospholipid syndrome (APS) is an autoimmune disease characterized by the presence of
3 antiphospholipid antibody (aPL) with clinical manifestations of arterial thrombosis, venous
4 thrombosis and/or pregnancy morbidity. According to the guidelines on the investigation and
5 management of APS published in 2012 [1], the gold standard for the secondary prevention of
6 thrombosis is warfarin. However, the preventive outcome of warfarin therapy has not been
7 satisfactory yet in APS patients [2]. Since warfarin treatment requires maintaining the
8 prothrombin time-international normalized ratio (PT-INR) between the therapeutic and safety
9 ranges, clinicians have to take into account possible drug interactions and educate patients to
10 avoid certain foods high in vitamin K, thus complicating the patient's daily life.

11 Factor Xa inhibitors are effective and safe alternatives to warfarin in patients with
12 atrial fibrillation and venous thromboembolism. Factor Xa inhibitors showed equivalent
13 efficacy to warfarin on inhibiting thrombin generation in non-APS patients with venous
14 thromboembolism [3].

15 To clarify whether factor Xa inhibitors would be an effective and safe alternative to
16 warfarin in APS, two randomized controlled trials (RCT) have been conducted. In the
17 Rivaroxaban in APS (RAPS) trial, 54 APS patients treated with rivaroxaban were compared
18 with 56 treated with warfarin. The primary endpoint was set as thrombin generation on day 42,
19 and the secondary endpoints as occurrence of thromboembolism and/or bleeding events up to

1 day 210. Since no thrombotic events were documented during the study period, the authors
2 stated that there was no increased thrombotic risk in patients treated with rivaroxaban compared
3 to warfarin users, even though the patients treated with rivaroxaban had a significant increased
4 thrombin generation as the surrogate marker of thrombotic tendency [4].

5 On the contrary, Trial on Rivaroxaban in Antiphospholipid Syndrome (TRAPS)
6 showed that thrombotic or bleeding events occurred more frequently in the rivaroxaban group
7 than in the warfarin group [5]. The trial was terminated prematurely because of an excess of
8 events among patients in the rivaroxaban arm. TRAPS included only high-risk APS patients
9 with triple positive for criteria aPL (lupus anticoagulant, anti-cardiolipin and anti- β 2-
10 glycoprotein I antibodies of the same isotype), thus the subjects in this trial do not represent
11 the general APS population. Knowing the limitations of these two RCT, real world evidence of
12 factor Xa inhibitors for APS has not been established yet. To explore the clinical relevance of
13 factor Xa inhibitors for APS patients in general clinical setting, we conducted this retrospective
14 cohort study.

Patients and Methods

Study design and approval

This is a single-center retrospective cohort study conducted at Rheumatology department in Hokkaido University Hospital. This study was executed in accordance with ethical principles of the Declaration of Helsinki and Good Clinical Practice guidelines and approved by Hokkaido University Hospital ethics committee (approval number: 018-0136). Participants were provided informed consent verbally.

Patients

The cohort comprised consecutive patients who were diagnosed as APS between April 1990 and March 2018 in our Rheumatology department. The attending physicians and authors verified the diagnosis of APS according to the Sydney-revised Sapporo criteria [6] for definite APS. The coexistence of systemic lupus erythematosus (SLE) was diagnosed according to the American College of Rheumatology (ACR) revised criteria [7].

Patients treated with factor Xa inhibitors were extracted from the cohort. As controls, patients treated with warfarin were selected from the same cohort at 1:2 with matched age, gender, coexistence of SLE and the presence of antiplatelet therapy.

Endpoint and variables

Primary endpoint was set as event-free survival for 5 years. Event was defined as recurrence of arterial/venous thrombosis and severe bleeding requiring hospitalization and/or blood transfusion. Arterial/venous thrombosis and bleeding were diagnosed by angiography, ultrasonography, computed tomography scan and/or magnetic resonance imaging.

All potential confounding factors associated with arterial/venous thrombosis or bleeding events were recorded at the time of treatment exposure. The confounding factors included hypertension, diabetes mellitus, dyslipidemia, smoking, obesity, chronic kidney disease (CKD), initial manifestations of APS (arterial thrombosis and venous thrombosis), aPL profile and use of corticosteroids. Hypertension was defined as the use of any antihypertensive medication or blood pressure higher than 140/90 mmHg on more than two occasions during the follow-up period. Diabetes mellitus was defined as the use of any antidiabetic medication or hemoglobin A1c > 6.5%. Dyslipidemia was defined as the use of any lipid-lowering agents, serum low-density lipoprotein concentration > 140 mg/dL, high-density lipoprotein concentration < 40 mg/dL or triglyceride > 150 mg/dL. Current cigarette smoking was defined as any cigarette or cigar during the follow-up period. Obesity was defined as body mass index > 25, and CKD as estimated glomerular filtration rate < 45 mL/min.

Determination of antiphospholipid antibodies and antiphospholipid score

IgG or IgM anticardiolipin antibodies, IgG or IgM anti-beta2 glycoprotein I antibodies, IgG or

IgM phosphatidylserine-dependent anti-prothrombin antibody were assayed by enzyme-linked immunosorbent assay as described previously.

For the detection of lupus anticoagulant, the guidelines recommended by the Subcommittee for Standardization of the International Society on Thrombosis and Haemostasis were followed [8].

The antiphospholipid score (aPL-S), a quantitative marker that represents aPL profile, was calculated in each patient as described previously [9]. An aPL-S more than 30 indicates a high risk of developing thrombosis.

Statistical analysis

Categorical variables described as counts and percentages were compared with Fisher's exact test. Continuous variables expressed as the mean $\pm$ standard deviation and were assessed using t test. Event-free survival was estimated by Kaplan-Meier method, and all potential confounding factors were assessed using univariate and multivariate Cox proportional hazard model. Because of the relatively few patients treated with factor Xa inhibitors, propensity score was used for each of risk factors as an additional covariate in multivariate Cox proportional hazard regression. The distribution of propensity scores for determining the probability of taking factor Xa inhibitors and the Concordance statistic are shown in Supplementary Figure 1. The distributions of confounding covariates between the groups were shown in

1 Supplementary Figure 2. In all statistical analyses, $p < 0.05$ was taken to indicate statistical
2 significance. All statistical analyses were performed using JMP® Pro 12.2.0 (SAS Institute Inc.,
3 Cary, North Carolina, USA).

Results

Patients' profile

The cohort comprised 206 patients with APS. The mean age was 42.8 ± 16.3 years old, 178 (86%) were female, 101 (49%) had SLE, 119 (58%) had arterial thrombosis and 66 (32%) had venous thrombosis.

Among the patients, 18 had a history of anti-Xa therapy (5 rivaroxaban, 12 edoxaban, 1 apixaban). 36 patients on warfarin treatment matching in age, gender, coexistence of SLE and use of antiplatelet therapy were selected from the same cohort as control group (warfarin group). Patients' characteristics at the initiation of observation are summarized in Table 1. In anti-Xa therapy group, 8 patients (44.4%) had arterial thrombosis, 13 (72.2%) venous thrombosis, and 3 (16.7%) both arterial/venous thrombosis. Triple positivity of criteria aPL was detected in 6 patients (33.3%), and 8 (44.4%) had high aPL-S more than 30. Whereas in warfarin group, 26 (72.2%) had arterial thrombosis, 19 (52.8%) venous thrombosis and 10 (55.6%) both arterial/venous thrombosis. Triple positivity of criteria aPL was found in 14 patients (38.9%), and 19 (52.8%) had high aPL-S more than 30. Percentage of patients with triple positivity and prevalence of patients with high aPL-S were not significantly different between the two groups. Patients with warfarin had significantly greater proportion of the history of arterial thrombosis (72.2% versus 44.4%, $p=0.0463$).

Comparison between factor Xa inhibitors and warfarin in the same patients

In 14 out of 18 patients on anti-Xa therapy, factor Xa inhibitors were switched from warfarin because the patients wished to avoid food restrictions containing a lot of vitamin K. Thus, first, we compared the endpoint between warfarin therapy period and anti-Xa therapy period in each of the 14 patients using Cox proportional hazard model. Intensity of warfarin level was controlled at a PT-INR between 2.0 to 3.0. Patients' characteristics at the initiation of each drug were summarized in Supplementary Table 1. There was no statistically significant difference between the backgrounds in each group. Event-free survival was significantly shorter during anti-Xa therapy than that during warfarin therapy (Figure 1-A). Considering the fact that the patients are inevitably younger on warfarin therapy period because all initially used warfarin and then switched to anti-Xa therapy, we used multivariate Cox proportional hazard model including age as a covariate and found that anti-Xa therapy was still associated with a hazard ratio of 14.0 (95% CI: 1.76-306, $p=0.0108$). Recurrences of thrombosis were observed in 1 patient (1.92/100 person-years) during warfarin therapy period and in 4 patients (18.5/100 person-years) during anti-Xa therapy, respectively. The details of thrombosis were branch retinal vein occlusion during warfarin therapy, and 2 for each cerebral infarction and deep vein thrombosis during anti-Xa therapy. There were no severe bleeding events during warfarin therapy whereas subarachnoid hemorrhage was observed in 1 patient (4.62/100 person-years) during anti-Xa therapy. The aPL-S was not significantly different between warfarin ($37.5 \pm$

4.96) and anti-Xa (32.5 ± 5.61 , $p = 0.51$) therapy periods.

Comparison between patients treated with factor Xa inhibitors and those treated with warfarin

Next, we compared the endpoint between 18 patients treated with factor Xa inhibitors and 36 patients treated with warfarin. There were 6 (21.4/100 person-years) and 8 (5.50/100 person-years) cases of recurrences of thrombosis in the factor Xa inhibitors and warfarin groups, respectively. For detailed information about the thrombosis, 4 patients had cerebral infarction and 2 patients developed deep vein thrombosis in the factor Xa inhibitors group. In the warfarin group, 5 cases of cerebral infarction, 1 case of deep vein thrombosis, 1 case of amaurosis fugax and 1 case of transient ischemic attack were observed. On the other hand, severe bleeding event were observed in 1 patient (3.56/100 person-years) in the factor Xa inhibitors group and in 2 patients (1.32/100 person-years) in the warfarin group. The former was subarachnoid hemorrhage and the latter being cerebellar hemorrhage and diverticular bleeding.

Event-free survival of the patients treated with factor Xa inhibitors was significantly shorter than that of patients in the warfarin group (Figure 1-B). All potential confounding factors were assessed using univariate and multivariate Cox proportional hazard model (Table 2). In univariate Cox proportional hazard model, factor Xa inhibitors was significantly associated with the events. In multivariate Cox proportional hazard model, factor Xa inhibitors was still significantly associated with the events. It turned out that the patients with a history of venous

1 thrombosis have lower risks of the events.

2

3

Discussion

We firstly assessed the clinical efficacy of factor Xa inhibitors for APS patients in real world utilization and showed that event-free survival was significantly shorter during anti-Xa therapy than that during warfarin therapy in our cohort. This study provided further additional information as follows: 1) longitudinal efficacy and safety up to 5 years, 2) data of heterogeneous APS patients, and 3) the use of rivaroxaban, edoxaban and apixaban.

Factor Xa inhibitors have been proposed as a potential alternative treatment for APS patients unless the patients are at high risk of thrombosis such as triple aPL positivity or high aPL-S [4, 10, 11]. TRAPS study showed that rivaroxaban led to more frequent thrombotic or bleeding events only in APS patients with triple positivity of criteria aPL [5]. However, in our study including all APS patients other than triple positivity, anti-Xa therapy showed poor event-free survival as well. Some case reports and case series reported the use of factor Xa inhibitors in APS patients [10, 11], and several authors have documented thrombosis recurrence after switching from warfarin to factor Xa inhibitors [12, 13]. *Signorelli et al.* reported a case series of 8 APS patients with failure of thrombotic prevention during rivaroxaban use (5 were switched from warfarin), remarkably they all developed thrombotic events within a year [14]. Similarly, *Dufrost V et al.* reported failure of anti-Xa therapy in 4 patients with APS [15]. These studies, even considering the limitation of lacking a comparator arm, suggest that switching from warfarin to factor Xa inhibitors might lead to increase in relapse of thrombosis. Consistent

1 with those case reports, our study showed a significant lower event-free survival during anti-
2 Xa therapy compared with warfarin therapy in real world utilization.

3 Our patients in warfarin group had significantly greater proportion of history of
4 arterial thrombosis than those in anti-Xa therapy group, suggesting that our patients treated
5 with warfarin might be at a higher risk of thrombosis. In other words, anti-Xa therapy still had
6 a poor event-free survival in the patients with lower risk of thrombosis. Hazard ratio increased
7 after adjustment of confounding factors which could contribute to the risk of thrombosis.

8 We acknowledge some limitations in our study. First, number of patients treated with
9 factor Xa inhibitors was small. Second, the study was conducted in a single center. Third, our
10 study was performed as a retrospective design, although the patients were regularly followed-
11 up. Due to these limitations, it will be difficult to reach a strong conclusion regarding the
12 efficacy and safety of factor Xa inhibitors for APS patients in real world utilization.

13 In conclusion, our findings could suggest that factor Xa inhibitors for heterogenous
14 APS may not be recommended. Prospective large-scale and long-term studies are required to
15 evaluate efficacy and safety of factor Xa inhibitors in APS patients.

Acknowledgment

We especially thank the patients, who made this study possible. No specific funding was received to carry out the work described in this manuscript.

Declaration of conflicting interests

T. Atsumi reports grants and personal fees from Astellas, grants and personal fees from Takeda, grants and personal fees from Mitsubishi Tanabe, grants and personal fees from Chugai, grants and personal fees from Pfizer, grants from Daiichi Sankyo, grants from Otsuka, personal fees from Eisai, personal fees from AbbVie, outside the submitted work. S. Yasuda reports grants and speaker's fee from Bristol-Myers Squibb Co., speaker's fee from Chugai, Mitsubishi Tanabe, outside the submitted work. M. Kato reports grants from GSK, grants from Actelion, outside the submitted work. M. Kono reports grants from GSK outside the submitted work. The other authors state that they have no conflict of interest.

Funding

No specific funding was received to carry out the work described in this manuscript.

References

- 1 Keeling D, Mackie I, Moore GW, Greer IA, Greaves M. Guidelines on the investigation and management of antiphospholipid syndrome. *Br J Haematol* 2012;157:47-58.
- 2 Erkan D, Aguiar CL, Andrade D, et al. 14th International Congress on Antiphospholipid Antibodies: task force report on antiphospholipid syndrome treatment trends. *Autoimmun Rev* 2014;13:685-96.
- 3 Arachchillage DR, Efthymiou M, Mackie IJ, Lawrie AS, Machin SJ, Cohen H. Rivaroxaban and warfarin achieve effective anticoagulation, as assessed by inhibition of TG and in-vivo markers of coagulation activation, in patients with venous thromboembolism. *Thromb Res* 2015;135:388-93.
- 4 Cohen H, Hunt BJ, Efthymiou M, et al. Rivaroxaban versus warfarin to treat patients with thrombotic antiphospholipid syndrome, with or without systemic lupus erythematosus (RAPS): a randomised, controlled, open-label, phase 2/3, non-inferiority trial. *Lancet Haematol* 2016;3:e426-36.
- 5 Pengo V, Denas G, Zoppellaro G, et al. Rivaroxaban vs warfarin in high-risk patients with antiphospholipid syndrome. *Blood* 2018;132:1365-71
- 6 Miyakis S, Lockshin MD, Atsumi T, et al. International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS). *J*

1 Thromb Haemost 2006;4:295-306.

2 7 Hochberg MC. Updating the American College of Rheumatology revised criteria for
3 the classification of systemic lupus erythematosus. Arthritis Rheum 1997;40:1725.

4 8 Pengo V, Tripodi A, Reber G, Rand JH, Ortel TL, Galli M, et al. Update of the
5 guidelines for lupus anticoagulant detection. Subcommittee on Lupus
6 Anticoagulant/Antiphospholipid Antibody of the Scientific and Standardisation
7 Committee of the International Society on Thrombosis and Haemostasis. J Thromb
8 Haemost 2009;7:1737-40.

9 9 Otomo K, Atsumi T, Amengual O, et al. Efficacy of the antiphospholipid score for the
10 diagnosis of antiphospholipid syndrome and its predictive value for thrombotic events.
11 Arthritis Rheum 2012;64:504-12.

12 10 Son M, Wypasek E, Celinska-Lowenhoff M, Undas A. The use of rivaroxaban in
13 patients with antiphospholipid syndrome: A series of 12 cases. Thromb Res
14 2015;135:1035-6.

15 11 Betancur JF, Bonilla-Abadia F, Hormaza AA, Jaramillo FJ, Canas CA, Tobon GJ.
16 Direct oral anticoagulants in antiphospholipid syndrome: a real life case series. Lupus
17 2016;25:658-62.

18 12 Win K, Rodgers GM. New oral anticoagulants may not be effective to prevent venous
19 thromboembolism in patients with antiphospholipid syndrome. Am J Hematol

2014;89:1017.

13 Schaefer JK, McBane RD, Black DF, Williams LN, Moder KG, Wysokinski WE.

Failure of dabigatran and rivaroxaban to prevent thromboembolism in

antiphospholipid syndrome: a case series of three patients. *Thromb Haemost*

2014;112:947-50.

14 Signorelli F, Nogueira F, Domingues V, Mariz HA, Levy RA. Thrombotic events in

patients with antiphospholipid syndrome treated with rivaroxaban: a series of eight

cases. *Clin Rheumatol* 2016;35:801-5.

15 Dufrost V, Risse J, Kirchner S, Zuily S, Wahl D. Failure of rivaroxaban to prevent

thrombosis in four patients with anti-phospholipid syndrome. *Rheumatology (Oxford)*

2017;56:1433-4.

1 **Figure legend**

2 **Fig. 1.** Event-free survival curve. **(A)** Comparison between anti-Xa therapy period and warfarin
3 therapy period in the same patients. **(B)** Comparison between patients treated with factor Xa
4 inhibitors and control subjects treated with warfarin.

5

6

Table 1. Patient characteristics

	Factor Xa inhibitors (n = 18)	Warfarin (n = 36)	P value
Age	47.7±17.1	42.6±13.4	0.2791
Female	15(83.3%)	30(83.3%)	1.0000
SLE	13(72.2%)	24(66.7%)	0.6786
SLEDAI	2.92±1.55	5.59±5.59	0.0764
Antiplatelet	11(61.1%)	19(52.8%)	0.5613
Symptom			
Arterial thrombosis	8(44.4%)	26(72.2%)	0.0463
Venous thrombosis	13(72.2%)	19(52.8%)	0.1704
Pregnancy complication	4(22.2%)	7(19.4%)	0.8112
aPL profile			
aCL IgM/IgG	10(55.6%)	17(47.2%)	0.5637
aβ2GPI IgM/IgG	7(50.0%)	23(63.9%)	0.3681
Lupus anticogulant	14(77.8%)	33(91.7%)	0.1520
aPS/PT IgM/IgG	15(83.3%)	25(69.4%)	0.2723
Triple criteria aPL positivity	6(33.3%)	14(38.9%)	0.6902
aPL score	32.5±23.8	37.5±29.8	0.5058
aPL score > 30	8(44.4%)	19(52.8%)	0.5637
Comorbidity			
Hypertension	8(44.4%)	17(47.2%)	0.8470
Diabetes	0(0%)	5(13.9%)	0.0969
Dyslipidaemia	5(27.8%)	16(44.4%)	0.2363
Use of statin	5(27.8%)	15(41.7%)	0.3191
Smoking	7(38.9%)	8(22.2%)	0.1974
Obesity	3(16.7%)	10(27.8%)	0.3680
CKD	2(11.1%)	7(19.4%)	0.4386
Use of corticosteroids	14(77.8%)	27(75.0%)	0.8219
Use of immunosuppressant	1(5.6%) [¶]	7(19.4%) [§]	0.1756

SLEDAI, SLE disease activity index; aPL, antiphospholipid antibodies; aCL,

anticardiolipin antibodies; $\alpha\beta 2$ GPI, anti-beta2 glycoprotein I antibodies; aPS/PT,

phosphatidylserine-dependent anti-prothrombin antibody; CKD, chronic kidney disease

¶, tacrolimus; §, 2 tacrolimus, 2 azathioprine, 2 cyclophosphamide, 1 mizoribine

Table 2. Factors contributing the recurrence of thrombosis

	Univariate analysis			Multivariate analysis		
	Unadjusted HR	(95% CI)	P value	Adjusted HR	(95% CI)	P value
Hypertension	1.13	(0.433-3.03)	0.7952	1.26	(0.446-3.63)	0.6592
Diabetes mellitus	0.960	(0.151-3.42)	0.9568	1.00	(0.0245-40.8)	1.0000
Dyslipidaemia	0.560	(0.178-1.51)	0.2615	1.04	(0.270-3.61)	0.9571
Smoking	1.28	(0.403-3.52)	0.6527	0.781	(0.209-2.38)	0.6786
Obesity	1.37	(0.434-3.70)	0.5657	3.16	(0.801-10.6)	0.0963
CKD	0.838	(0.193-2.58)	0.7772	0.762	(0.130-3.96)	0.7485
Arterial thrombosis	1.44	(0.510-5.13)	0.5082	1.18	(0.296-5.60)	0.8243
Venous thrombosis	0.492	(0.178-1.28)	0.1458	0.191	(0.0340-0.953)	0.0432*
aPL score > 30	0.711	(0.266-1.86)	0.4833	0.817	(0.277-2.31)	0.7044
Use of corticosteroids	0.519	(0.196-1.51)	0.2157	0.485	(0.167-1.517)	0.2039
Factor Xa inhibitors	4.62	(1.54-13.6)	0.0075*	11.9	(2.93-56.0)	0.0005*

* P-values <0.05. P-values were estimated using Cox proportional hazard model. HR, hazard ratio; CKD, chronic kidney disease; aPL, antiphospholipid antibodies.

A

Number at risk

Warfarin	14	14	13	13	13	10	10	9	9	9	8	8	8
Factor Xa inhibitors	14	10	7	6	5	5	5	4	3	1	1	1	0

B

Number at risk

Warfarin	36	34	34	32	32	32	31	29	28	25	23	22	19
Factor Xa inhibitors	18	14	11	9	6	6	6	4	3	1	1	1	0