

Recurrent thrombosis in patients with antiphospholipid antibodies treated with vitamin K antagonists or rivaroxaban

Antiphospholipid antibodies (aPL) include lupus anticoagulant (LA), anticardiolipin antibodies (aCL) and anti- β 2 glycoprotein I antibodies (a β 2-GPI). This condition is a severe acquired thrombophilia associated with an increased risk of venous and arterial thrombosis and adverse pregnancy outcome.¹ The presence of aPL and clinical manifestations define the antiphospholipid syndrome (aPS).² Patients with persistent laboratory evidence of aPL require long-term anticoagulant therapy after the first thrombotic episode, particularly those with triple aPL positivity.³ The drugs of choice are the vitamin-K antagonists (VKA) at adjusted doses to maintain an international normalized ratio (INR) between 2.0 and 3.0. Despite VKA therapy, the risk of recurrent thrombosis remains high, varying from 3 to 24%^{4,5} and even increasing the intensity of therapy to an INR of 3.0-4.0 does not reduce the probability of recurrence.^{4,6} Direct oral anticoagulant (DOAC) drugs represent a valid and safe anticoagulant alternative to VKA and their use has been suggested also in patients with aPS,⁷⁻⁹ although several reports raised safety issues.¹⁰ To investigate the recurrent rate of thrombosis in patients with aPS treated with VKA or DOAC we followed our cohort diagnosed from 2013, year of the introduction of the first DOAC (rivaroxaban) on the Italian market for the treatment and secondary prevention of venous thromboembolism.

Patients consecutively referred to our Thrombosis Center for a thrombophilia workup from September 2013 to December 2016 after an episode of objectively documented venous thrombosis formed the initial study population. Those who tested positive for the presence of aPL were followed to investigate the risk of recurrent thrombosis and the risk of bleeding. The latter was classified as major or minor according to the definition of the International Society of Thrombosis and Haemostasis (ISTH).¹¹ Patients on VKA monitoring INR at our Thrombosis Center were interviewed at any blood sampling and those who were monitoring INR at other sites or those on DOAC were interviewed by telephone every three months by one of us (IM, MA) for the occurrence of recurrent thrombosis and bleeding episodes, and invited to come back to the Center with the objective documentation of the events (deep vein thrombosis of the limbs, pulmonary embolism, cerebral or splanchnic vein thrombosis, acute myocardial infarction, transient ischemic attack, ischemic stroke). Patients were followed from the starting date to the end of anticoagulant therapy with VKA or DOAC, or to the date of recurrent thrombosis, major bleeding or May 15, 2017 (administrative censoring). In case of switching therapy from VKA to DOAC or *vice versa*, patients were considered separately for each period of drug intake. The Institutional Review Board of the Hospital approved this study and patients gave their written informed consent to participate. aPL were evaluated as recommended by the Subcommittee on Lupus Anticoagulant/Phospholipid/Dependent Antibodies of the ISTH.¹² Details on laboratory tests and statistical analysis can be found in the *Online Supplementary Appendix*.

In the study period, 672 patients with venous thrombosis were referred to the Center. Twenty-eight of them (4.2%) had confirmed aPS with at least one positivity for LA, aCL or a β 2-GPI. Their general characteristics at index event are shown in Table 1. Fifteen patients took VKA

and 13 took DOAC (rivaroxaban in all cases). The reason for choosing one or the other treatment was based only on physicians' and patients' preference. Nearly half of the patients on both treatment groups had triple positivity for LA, aCL and a β 2-GPI, and the other risk factors for thrombosis were also similarly distributed. Rivaroxaban was the first anticoagulant therapy in 9 patients (15 mg bid for 21 days followed by 20 mg od), whereas 4 switched from VKA to rivaroxaban (20 mg od) at their own request. No patient switched from rivaroxaban to VKA. Four patients ended oral anticoagulant therapy because of pregnancy (switch to LMWH), patient's choice, post-traumatic event and decision of general prac-

Table 1. Baseline characteristics at index event of the 28 patients with antiphospholipid syndrome.

	Patients on vitamin K antagonists	Patients on rivaroxaban*
N.	15	13
Men/Women	10/5	9/4
BMI, kg/m ² , mean (SD)	26.8 (3.9)	28.3 (3.2)
Age at thrombosis, years, mean (SD)	43.1 (15.8)	46.2 (16.4)
Index event, n (%)		
Deep vein thrombosis	11 (80)	8 (61.5)
Pulmonary embolism	2 (13.3)	1 (7.7)
Both	2 (13.3)	4 (30.8)
Antiphospholipid profile, n (%)		
Lupus anticoagulant	3 (20)	7 (53.8)
Anticardiolipin antibodies [†]	2 (13.3)	–
Anti-2 glycoprotein I antibodies [‡]	1 (6.7)	–
Double positivity [§]	2 (13.3)	–
Triple positivity	7 (46.7)	6 (46.2)
Risk factors for venous thrombosis, n (%)		
None	3 (20)	5 (38.5)
Cancer	1 (6.7)	–
Immobilization	1 (6.7)	1 (7.7)
Trauma	3 (20)	2 (15.4)
Infection	2 (13.3)	1 (7.7)
Oral contraceptive use	2 (13.3)	2 (15.4)
Pregnancy/puerperium	–	1 (7.7)
Autoimmune disease	2 (13.3)	3 (23.1)
Cardiovascular risk factors, n (%)		
None	11 (73.3)	9 (69.2)
Diabetes	–	1 (7.7)
Hypertension	4 (26.7)	2 (15.4)
Dyslipidemia	1 (6.7)	–
Smoking	1 (6.7)	1 (7.7)
Inherited thrombophilia abnormalities, n (%)		
None	14 (93.3)	13 (100)
AT, PC or PS deficiency	1 (6.7)	–
Factor V Leiden	1 (6.7)	–
G20210A prothrombin mutation	–	–

N, n: number; SD: Standard Deviation; BMI: body mass index; AT: antithrombin; PC: protein C; PS: protein S; aCL: anticardiolipin antibodies. *Nine patients received only rivaroxaban and 4 shifted from vitamin K antagonists to rivaroxaban. [†]IgM (both patients). [‡]IgG: [§]Lupus anticoagulant and anti- β 2 glycoprotein I (a β 2-GPI) antibodies IgG and IgM; anticardiolipin IgG and anti- β 2 glycoprotein I antibodies IgG, all at medium-high titer (>40 GPL or MPL for aCL and >10 U/mL for a β 2-GPI).

itioner. Patients who took both drugs were counted in the two treatment groups for the respective periods of treatment, for a total of 20 periods for VKA and 13 periods for rivaroxaban. Mean follow up was 21.9 [Standard Deviation (SD) 12.9] months for all aPS patients, 23.6 (SD 13.2) months in VKA (41.3 patient years) and 19.0 (SD 12.3) months in rivaroxaban (20.6 patient years).

Five patients experienced recurrent thrombosis, one on VKA for an incidence rate of 2.4 (95%CI: 0.2-11.3) per 100 patient years and 4 on rivaroxaban for an incidence rate of 19.4 (95%CI: 6.5-46.2) per 100 patient years. The INR of the patient on VKA in the week before recurrence was 3.8. Figure 1 shows the Kaplan-Meier curves of recurrent thrombosis according to the type of anticoagulant therapy. The cumulative incidence at 24 months of follow up was 42% (95%CI: 8.3-75.7) in patients on rivaroxaban and 7.1% (95%CI: 1-41) in those on VKA and the HR for recurrent thrombosis in patients on rivaroxaban *versus* those on VKA was 7.53 (95%CI: 0.84-67.6). After 24 months of follow up no recurrence was observed for the entire observational period of 48 months for patients on VKA and 43 months for patients on rivaroxaban. Table 2 shows the detailed characteristics of patients with recurrent thrombosis. Recurrent events were arterial in 4 patients (3 acute myocardial infarction and one cerebral ischemic stroke of non-cardioembolic origin) and venous in one (cerebral vein thrombosis). All patients with recurrent thrombosis had triple positivity for LA, aCL and β 2-GPI and none was taking antiplatelet together with oral anticoagulant therapy. Other than aPS, no other thrombophilia markers nor additional risk factors for thrombosis (cancer, immobilization, trauma, infection, oral contraceptive use, autoimmune disease, diabetes, hypertension, dyslipidemia, smoking) were recorded, apart from type 2 diabetes poorly controlled by non-insulin glucose-lowering drugs in the patient with recurrent stroke. All patients were overweight or had class 1 obesity. No patient had major or clinically relevant non-major bleeding during follow up.

To date, data on efficacy and safety of DOAC in patients with aPS are limited and controversial. The only randomized controlled trial of 116 patients with aPS observed a higher endogenous thrombin potential in those receiving rivaroxaban than VKA, although there was no recurrent VTE during six months of follow up. However, the proportion of triple positivity aPS was low

(12% in rivaroxaban and 20% in the VKA arm).¹³ A recent review of studies in patients with aPS and recurrent thrombosis while on DOAC reported 19 recurrent arterial or venous thrombosis out of 122 patients (15.6%) during a mean observation time of 12.6 months.¹⁰ The aPL profile was not available for all patients, but apparently half of recurrent thrombosis occurred in aPS patients with triple positivity. A low frequency of recurrence was observed in a cohort study of patients at low risk for single or double positivity aPS.¹⁴ In our study, nearly half the patients in both treatment groups, VKA or rivaroxaban, had triple positivity and all recurrent events were observed in such patients. In addition, the similar characteristics of patients in the two treatment groups make the risk of confounding by indication unlikely. Apart from overweight or class 1 obesity, no systemic risk factors for thrombosis other than triple positivity aPS were observed in patients with recurrent events.

Some limitations of our study need to be discussed. First, the small sample size does not allow us to draw firm conclusions or to speculate on the excess of arterial over venous recurrent thrombosis, despite the fact that all index events were venous. Second, since all our patients on DOAC took rivaroxaban, which remains the most widely prescribed given that it first came on the Italian market as treatment of venous thromboembolism,

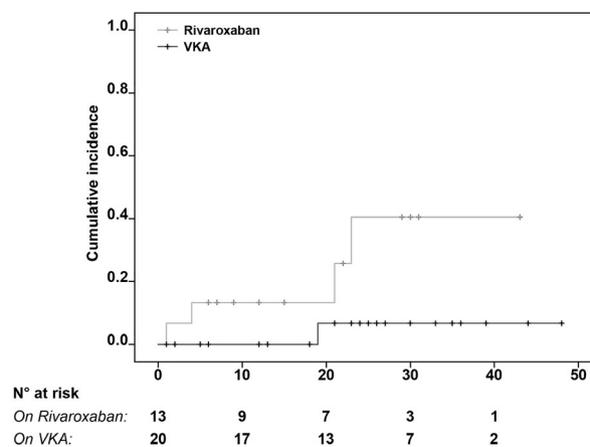


Figure 1. Cumulative incidence of recurrent thrombosis according to anticoagulant therapy. VKA: vitamin K antagonists.

Table 2. Characteristics of patients with recurrent thrombosis during anticoagulant treatment.

	#1	#2	#3	#4	#5
Type of anticoagulant therapy	Rivaroxaban	Rivaroxaban	Rivaroxaban	Rivaroxaban	VKA
Sex	M	M	M	F	M
Antiphospholipid profile	Triple positivity				
Age at index event, years	67	47	28	37	35
Type of index event	DVT	DVT	DVT+PE	DVT	DVT
Switch from VKA to rivaroxaban	No	No	Yes	No	No
Time on anticoagulant treatment until recurrence	23 months	1 month	21 months	4 months	22 months
Age at recurrent thrombosis, years	69	47	37	37	39
BMI, kg/m ²	27.4	30.2	30.7	27.5	26.7
Type of recurrent thrombosis	Stroke	AMI	AMI	CVT	AMI

VKA: vitamin K antagonists; M: male; F: female; BMI: body mass index; DVT: deep vein thrombosis; PE: pulmonary embolism; AMI: acute myocardial infarction; CVT: cerebral vein thrombosis.

our results cannot be generalized to other DOAC. Third, diagnosis of LA is sometimes critical in patients on DOAC because of their influence on the diluted Russel viper venom test. We are confident that we did not have false positive aPS diagnosis because the 7 patients with LA and without aCL or β 2-GPI antibodies also had positive silica clotting time. Finally, since our study was not designed as a randomized trial, no surrogate marker for recurrent thrombosis was considered. We do not have information on time in therapeutic INR range, anti-Xa activity nor real drug intake of our patients, and therefore the possibility of scarce compliance in patients with recurrent thrombosis cannot be ruled out.

In conclusion, the limited experience on the use of DOAC in clinical practice and data from real-life clinical practice are not sufficient to establish whether they are equally effective as VKA in treatment and secondary prevention of thrombosis in patients at very high thrombotic risk, such as those with aPS. We observed an increased risk of recurrent thrombosis in patients with triple positivity aPS treated with rivaroxaban compared to those treated with VKA and this provides further insights into the post-market surveillance of DOAC. Although the combination of low-dose rivaroxaban and acetylsalicylic acid reduces morbidity and mortality of coronary artery disease in non-aPS patients,¹⁵ there is no evidence of the efficacy of rivaroxaban alone in preventing arterial thrombosis. While awaiting the results of an ongoing randomized controlled trial ([clinicaltrials.gov identifier: 02157272](https://clinicaltrials.gov/ct2/show/study?term=02157272)), we suggest caution in prescribing rivaroxaban to patients with triple positivity aPS.

Ida Martinelli,¹ Maria Abbattista,¹ Paolo Bucciarelli,¹ Armando Tripodi,^{1,2} Andrea Artoni,¹ Francesca Gianniello,¹ Cristina Novembrino^{1,2,3} and Flora Peyvand^{1,2,3,4}

¹A. Bianchi Bonomi Hemophilia and Thrombosis Center, Fondazione IRCCS Ca' Granda - Ospedale Maggiore Policlinico, Milano; ²Department of Clinical Sciences and Community Health; ³Laboratory of Clinical Chemistry and Microbiology and ⁴Department of Pathophysiology and Transplantation, University of Milan, Italy

Correspondence: ida.martinelli@policlinico.mi.it
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References

1. Pengo V, Ruffatti A, Legnani C, et al. Clinical course of high-risk patients diagnosed with antiphospholipid syndrome. *J Thromb*

2. Haemost. 2010;8(2):237-242.
2. Cervera R, Piette J, Font J, et al. Antiphospholipid syndrome: clinical and immunologic manifestations and patterns of disease expression in a cohort of 1,000 patients. *Arthritis Rheum.* 2002;46(4):1019-1027.
3. Ruiz-Irastorza, G Cuadrado M, Ruiz-Arruza I, Brey R, et al. Evidence-based recommendations for the prevention and long-term management of thrombosis in antiphospholipid antibody-positive patients: Report of a Task Force at the 13th International Congress on Antiphospholipid Antibodies. *Lupus.* 2011;20(2):206-218.
4. Crowther M, Ginsberg JS, Julian J, et al. A comparison of two intensities of warfarin for the prevention of recurrent thrombosis in patients with the antiphospholipid antibody syndrome. *N Engl J Med.* 2003;349(12):1133-1138.
5. Prandoni P, Simioni P, Girolami A. Antiphospholipid antibodies, recurrent thromboembolism, and intensity of warfarin anticoagulation. *Thromb Haemost.* 1996;75(5):859.
6. Finazzi G, Marchioli R, Brancaccio V, et al. A randomized clinical trial of high-intensity warfarin vs. conventional antithrombotic therapy for the prevention of recurrent thrombosis in patients with the antiphospholipid syndrome (WAPS). *J Thromb Haemost.* 2005; 3(5):848-853.
7. Haładaj E, Olesińska M. Rivaroxaban - A safe therapeutic option in patients with antiphospholipid syndrome? Our experience in 23 cases. *Reumatologia.* 2016;54(3):146-149.
8. Noel N, Dutasta E, Costedoat-Chalumeau N, et al. Safety and efficacy of oral direct inhibitors of thrombin and factor Xa in antiphospholipid syndrome. *Autoimmun Rev.* 2015;14(8):680-685.
9. Malec K, Goralczyk T, Undas A. The use of direct oral anticoagulants in 56 patients with antiphospholipid syndrome. *Thromb Res.* 2017; 152:93-97.
10. Dufrost V, Risse J, Zuily S, Wahl D. Direct Oral Anticoagulants Use in Antiphospholipid Syndrome: Are These Drugs an Effective and Safe Alternative to Warfarin? A Systematic Review of the Literature. *Curr Rheumatol Rep.* 2016;18(12):74.
11. Kaatz S, Ahmad D, Spyropoulos A, Schulman SS; Subcommittee on Control of Anticoagulation. Definition of clinically relevant non-major bleeding in studies of anticoagulants in atrial fibrillation and venous thromboembolic disease in non-surgical patients: communication from the SSC of the ISTH. *J Thromb Haemost.* 2015; 13(11):2119-2126.
12. Devreese KMJ, Pierangeli SS, de Laat B, Tripodi A, Atsumi T, Ortel TL. Testing for Antiphospholipid antibodies with Solid Phase Assays: Guidance from the SSC of the ISTH. *J Thromb Haemost.* 2014; 12(5):792-795.
13. Cohen H, Hunt BJ, Efthymiou M, et al. Rivaroxaban versus warfarin to treat patients with thrombotic antiphospholipid syndrome, with or without systemic lupus erythematosus (RAPSS): a randomised, controlled, open-label, phase 2/3, non-inferiority trial. *Lancet Haematol.* 2016;3(9):e426-e436.
14. Resseguiere AS, Pereira B, Rieu V, Le Guenno G, Grobost V, Ruivard M. Direct oral anticoagulants: an alternative treatment for thrombotic antiphospholipid syndrome? *Lupus.* 2017;26(12):1297-1303.
15. Anand SS, Bosch J, Eikelboom JW, et al. Rivaroxaban with or without aspirin in patients with stable peripheral or carotid artery disease: an international, randomised, double-blind, placebo-controlled trial. *Lancet.* 2017 Nov 10. [Epub ahead of print].