

# Use of Direct Oral Anticoagulants in Patients with Antiphospholipid Syndrome

Lupus Anticoagulant (LA)/Antiphospholipid Antibodies (aPL) Subcommittee

Person responsible (Chair / Principal Investigator): Katrien Devreese, Stéphane Zuiluy and Hannah Cohen

### Description Abstract

Clarity and guidance is required with regard to direct oral anticoagulants (DOACs) use in antiphospholipid syndrome (APS) patients, within the confines of the recent European Medicines Agency (EMA) recommendations and the limited evidence base. To address this, the Lupus Anticoagulant (LA)/Antiphospholipid Antibodies (aPL) Scientific and Standardization Committee (SSC) chair and co-chairs propose that they write guidance for physicians to help them manage APS patients. This guidance will also serve as a call and focus for research.

Despite conflicting data (EMA recommendations, EULAR guidelines), the document provided by the SSC LA/aPL of the ISTH will give clarity and guidance to physicians based on all available evidence. Uncertainty in this field will be addressed.

Furthermore, this guidance document will also serve as a call and focus for research: Of note, no one has ever looked at the use of high-intensity DOACs to determine whether the thrombotic recurrence rate is lower than that seen with VKAs. In this regard, the RISAPS trial is investigating the use of high-intensity rivaroxaban 15mg twice daily vs warfarin, target INR 3.5 in APS patients with stroke or other ischaemic brain damage. <https://doi.org/10.1186/ISRCTN10280992>. Furthermore, physicians will be asked to follow up prospectively, within a Registry (separate ISTH project) all patients on DOACs as this could help to identify those that could benefit from DOACs; and to consider the potential for other DOAC studies.

Design and methodology (Data expected to collect, sample size and statistical analysis): The Subcommittee will work with the Control of Anticoagulation Subcommittee on a joint guidance document.

Study population (Inclusion, exclusion, eligibility) (patient population; recruitment of participating institutions/physicians and subjects; minimum number needed; expected number): Not applicable.

Expected timeline:

Project was approved by the Guidance and Guidelines Committee in August 2019

# SSC Subcommittee Project/Collaborative Project

Submission of the manuscript is expected by November 2019

Expected outcomes (ie. publications): Guidance statement

Publication type (SSC Communication, Guidance document or original article): Guidance document

Description of project set/up and management, needed infrastructure and resources (summary):  
Not applicable.

Possible references:

1. Pengo V, Denas G, Zoppellaro G, Jose SP, Hoxha A, Ruffatti A, et al. Rivaroxaban vs warfarin in high-risk patients with antiphospholipid syndrome. *Blood*. 2018; **132**: 1365–71.

2. MA/PRAC/219985/2019. Pharmacovigilance Risk Assessment Committee (PRAC).

[https://www.ema.europa.eu/en/documents/other/new-product-information-wording-extracts-prac-recommendations-signals-adopted-8-11-april-2019-prac\\_en.pdf](https://www.ema.europa.eu/en/documents/other/new-product-information-wording-extracts-prac-recommendations-signals-adopted-8-11-april-2019-prac_en.pdf)

3. Pengo V, Ruffatti A, Legnani C, Gresele P, Barcellona D, Erba N, Testa S, Marongiu F, Bison E, Denas G. Clinical course of high-risk patients diagnosed with antiphospholipid syndrome. *J Thromb Haemost*. 2010; **8**: 237-42.

4. Cohen H, Hunt BJ, Efthymiou M, Arachchilage DRJ, Mackie IJ, Clawson S, 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**: e426-436.

5. K. Legault, M. Blostein, M. Carrier, S. Khan, S. Shulman, S. Shivakumar, C. Wu, M. Crowther. Single-arm Pilot Feasibility Cohort Study of Rivaroxaban in Antiphospholipid Syndrome. Poster presented (PB424) at *International Society on Thrombosis and Haemostasis*. 18-21<sup>st</sup> July 2018. Dublin, Ireland.

6. Crowther MA, Ginsberg JS, Julian J, Denburg J, Hirsh J, Douketis J, Laskin C, Fortin P, Anderson D, Kearon C. A comparison of two intensities of warfarin for the prevention of recurrent thrombosis in patients with the antiphospholipid antibody syndrome. *N Engl J Med*. 5. 2003; **349**: 1133-8.

7. Finazzi G, Marchioli R, Brancaccio V, Schinco P, Wisloff F, Musial J, Baudo F, Berrettini M, Testa S, D'angelo A. 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**: 848-53.

## SSC Subcommittee Project/Collaborative Project

8. Dufrost V, Risse J, Reshetnyak T, Satybaldyeva M, Du Y, Yan X-X, et al. Increased risk of thrombosis in antiphospholipid syndrome patients treated with direct oral anticoagulants. Results from an international patient-level data meta-analysis. *Autoimmun Rev.* 2018; **17**: 1011–21.
9. van Es N, Coppens M, Schulman S, Middeldorp S, Buller HR. Direct oral anticoagulants compared with vitamin K antagonists for acute venous thromboembolism: Evidence from phase 3 trials. *Blood.* 2014; **124**: 1968-75.
10. Woller SC, Stevens SM, Kaplan DA, Branch DW, Aston VT, Wilson EL, Gallo HM, Johnson EG, Rondina MT, Lloyd JF, Evans RS, Elliott CG. Apixaban for the Secondary Prevention of Thrombosis Among Patients With Antiphospholipid Syndrome: Study Rationale and Design (ASTRO-APS). *Clin Appl Thromb Hemost.* 2016; **22**: 239-47.
11. Woller SC, Stevens SM, Kaplan DA, T Rondina M. Protocol Modification of Apixaban for the Secondary Prevention of Thrombosis Among Patients With Antiphospholipid Syndrome Study. *Clin Appl Thromb Haemost.* 2018; **24**: 192.
12. Andreoli L, Chighizola CB, Banzato A, et al. Estimated frequency of antiphospholipid antibodies in patients with pregnancy morbidity, stroke, myocardial infarction and deep vein thrombosis: a critical review of the literature. *Arthritis Care Res (Hoboken).* 2013; **65**: 1869–73.
13. Tektonidou MG, et al. *Ann Rheum Dis.* 2019; **0**: 1–9. doi:10.1136/annrheumdis-2019-215213