

Lack of efficacy of direct oral anticoagulants compared to warfarin in antiphospholipid antibody syndrome

Direct oral anticoagulants (DOAC) have a predictable anticoagulant effect, a rapid onset and offset of action, and fewer drug-drug interactions than vitamin K antagonists (VKA). These compounds have demonstrated similar efficacy and a better safety profile compared to VKA for the treatment of venous thromboembolism (VTE)¹ and for stroke prevention in patients with non-valvular atrial fibrillation (FANV)² in large randomized controlled trials and meta-analyses.

Patients with antiphospholipid antibody syndrome (APS) require long-term anticoagulation for the secondary prevention of thrombotic events.^{3,4} In this setting, VKA were shown to be more effective than DOAC⁵⁻⁷ and are therefore recommended by international guidelines.⁴ However, the risk of recurrent thrombosis remains high even with VKA treatment, varying from 3% to 24%,^{8,9} and even increasing the intensity of VKA therapy does not reduce the probability of recurrence.^{8,10}

It is clear that adequate anticoagulation therapy still represents a clinical challenge in patients with APS and further investigation is needed before declaring DOAC ineffective. It has been reported that patients with previous arterial or venous manifestation recur with the same type of thromboses and that the risk of recurrence on DOAC is higher in patients with a history of arterial events.¹¹ Two randomized clinical trials (RCT) comparing DOAC and warfarin in APS have been prematurely interrupted due to the evidence of increased incidence of thrombotic events in the DOAC group,^{6,7} especially strokes. However, it remains unclear whether VKA are more effective than DOAC also in patients with VTE history and no arterial events. The aim of our study was to provide the best evidence from RCT on the risk of major vascular events and bleeding in patients with APS treated with DOAC *versus* warfarin and to evaluate if patients with no history of arterial thrombosis may be candidate to treatment with DOAC.

We performed a systematic review and meta-analysis of the literature including RCT that investigated the role of DOAC in patients with APS. For this purpose, PubMed, Medline, Embase and Cochrane databases were searched (from inception to 25/05/2022), according to the PRISMA guidelines. A combination of the following titles was used: "antiphospholipid syndrome" and "direct oral anticoagulants" or "apixaban", "dabigatran", "edoxaban", "rivaroxaban". Two physicians (IG and FD) independently reviewed titles and abstracts of manuscripts detected through database searches to identify poten-

tially suitable studies for further evaluation. The number of arterial and venous thrombotic events and of major bleedings, according to the International Society on Thrombosis and Hemostasis definition, by treatment group was collected. A composite outcome of arterial and venous events plus major hemorrhagic events was compared between patients in treatment with DOAC or warfarin. Efficacy and safety were individually calculated and a sub-group analysis of separate arterial and venous events was also performed. Finally, a comparison of efficacy was done in patients without previous history of arterial events. We calculated relative risk and corresponding 95% confidence interval (CI) for each outcome. Outcomes across the studies were combined using the restricted maximum-likelihood method and compared with the DerSimonian and Laird random-effects model. We assessed and quantified statistical heterogeneity across the studies using the Cochran Q statistic and I² test. All analyses were performed by STATA version 17.0 software for Mac (StataCorp. 2019. Stata Statistical Software: Release 17. StataCorp Ltd, College Station, TX, USA).

Four RCT comparing DOAC and warfarin in patients with APS were selected, three with rivaroxaban and one with apixaban. A total of 468 patients were included in this meta-analysis, 231 randomized to DOAC and 237 to warfarin. The weighted mean age was 48.1 years with a higher prevalence of women (68.8%). Treatment assignment was open label in each study.

In total, 51 major events (10.9%, 95% CI: 8.08-13.72) were recorded in the entire study population: 26 arterial thromboses (51.0%), five venous thromboses (9.8%) and 20 major bleedings (39.2%). The number of events was greater in the DOAC group (15.1%) than in the warfarin group (6.7%) with a risk ratio (RR) of 2.61 (95% CI: 0.95-7.19), that was close to statistical significance ($P=0.06$) (Figure 1).

Treatment with DOAC was associated with a more than 3-fold increased risk of thrombotic events (RR 3.50, 95% CI: 1.04-11.84) as compared to warfarin (Figure 2A). There was no difference in the number of major bleedings between patients treated with DOAC and warfarin (Figure 2B).

The number of arterial events was significantly higher in the DOAC group (9.9%) compared with the warfarin group (1.3%) with a RR of 4.55 (95% CI: 1.63-12.72) (Figure 2C). The majority of arterial events were strokes (86.3%) with an increased risk of cerebral ischemic events of 13.6 times

(95% CI: 2.63-70.68) with DOAC. There was no difference in the risk of VTE between the groups (Figure 2D). The number of patients with no prior history of arterial thrombotic events was 355 (75.8%) with 177 patients assigned to DOAC and 178 to warfarin. The number of events recorded was greater in DOAC-treated patients (5.6%) than in warfarin-treated patients (1.1%) with a RR

of thrombosis recurrence of 3.05 (95% CI: 0.91-10.21), which was close to statistical significance ($P=0.07$) (Figure 3). All recorded events were arterial events in the DOAC group while events in the warfarin group were two deep vein thromboses. Heterogeneity among the studies was moderate ($I^2=40.7%$), but not significant for the principal analysis

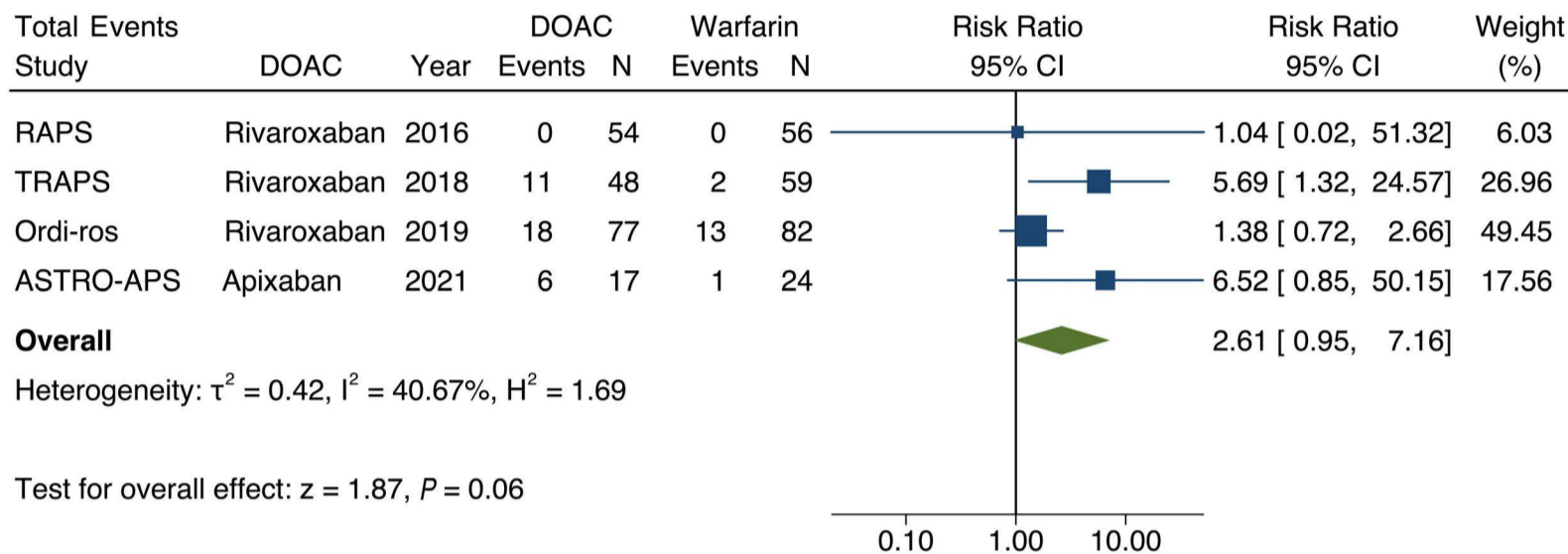
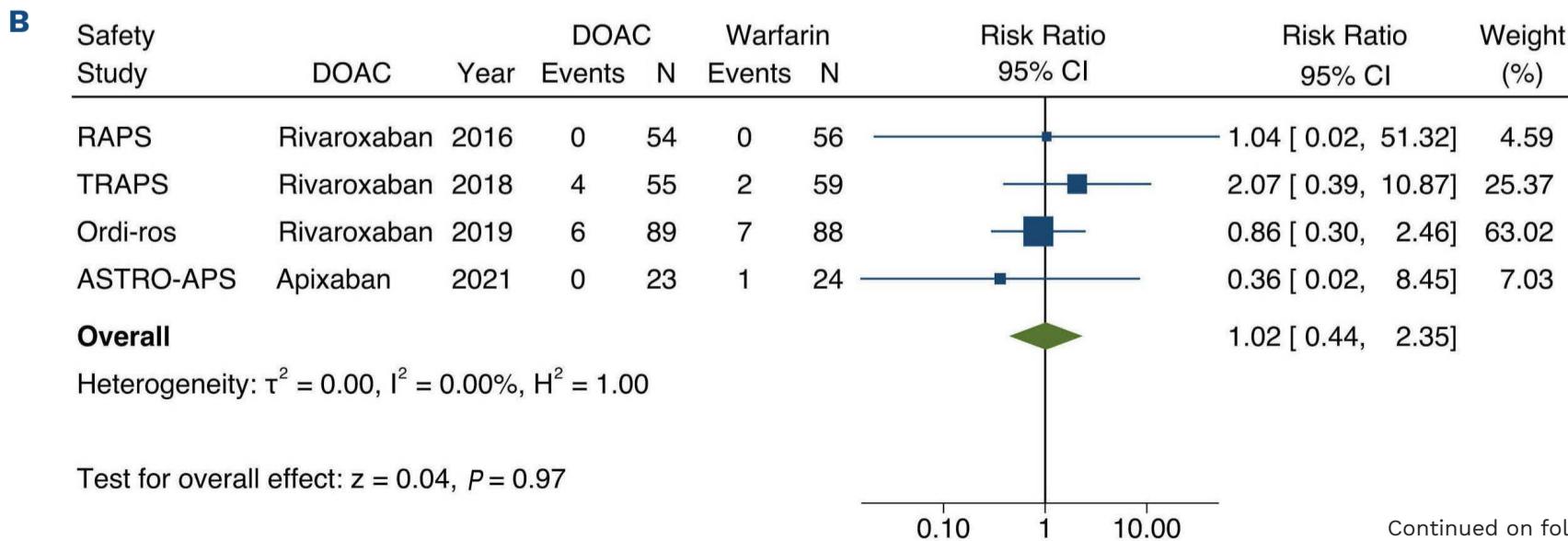
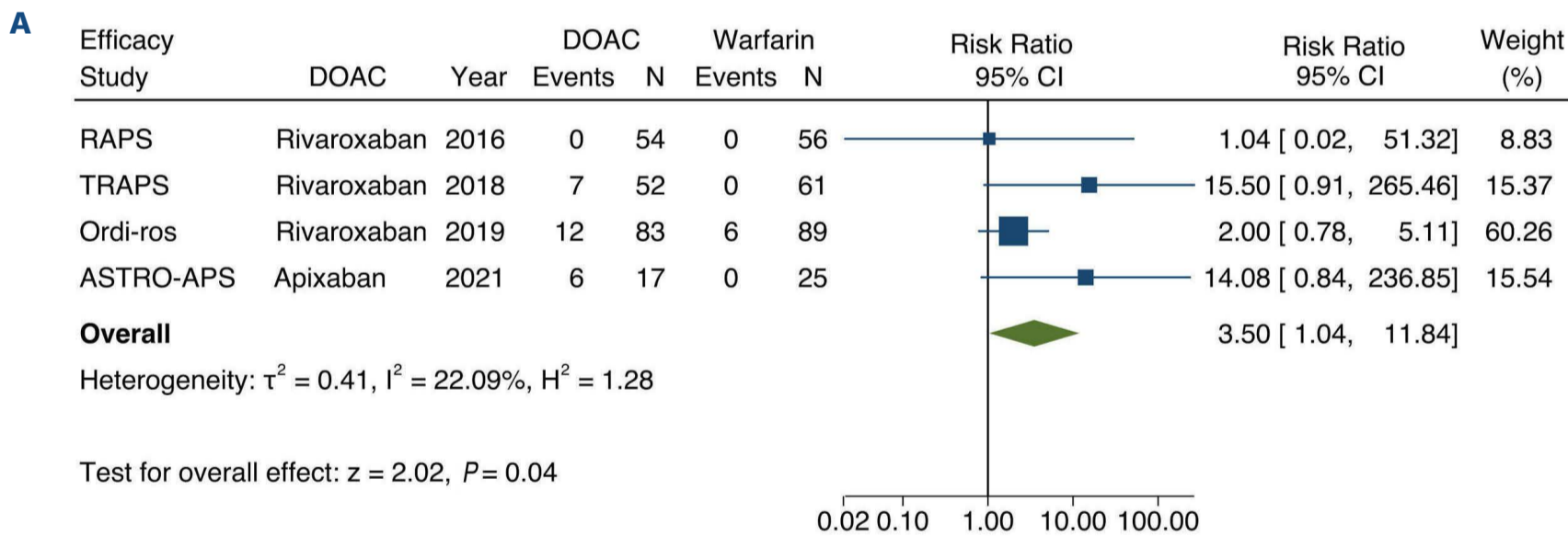


Figure 1. Incidence of events in patients treated with direct oral anticoagulants compared with warfarin. DOAC: direct oral anti-coagulants; N: number; CI: confidence interval.



Continued on following page.

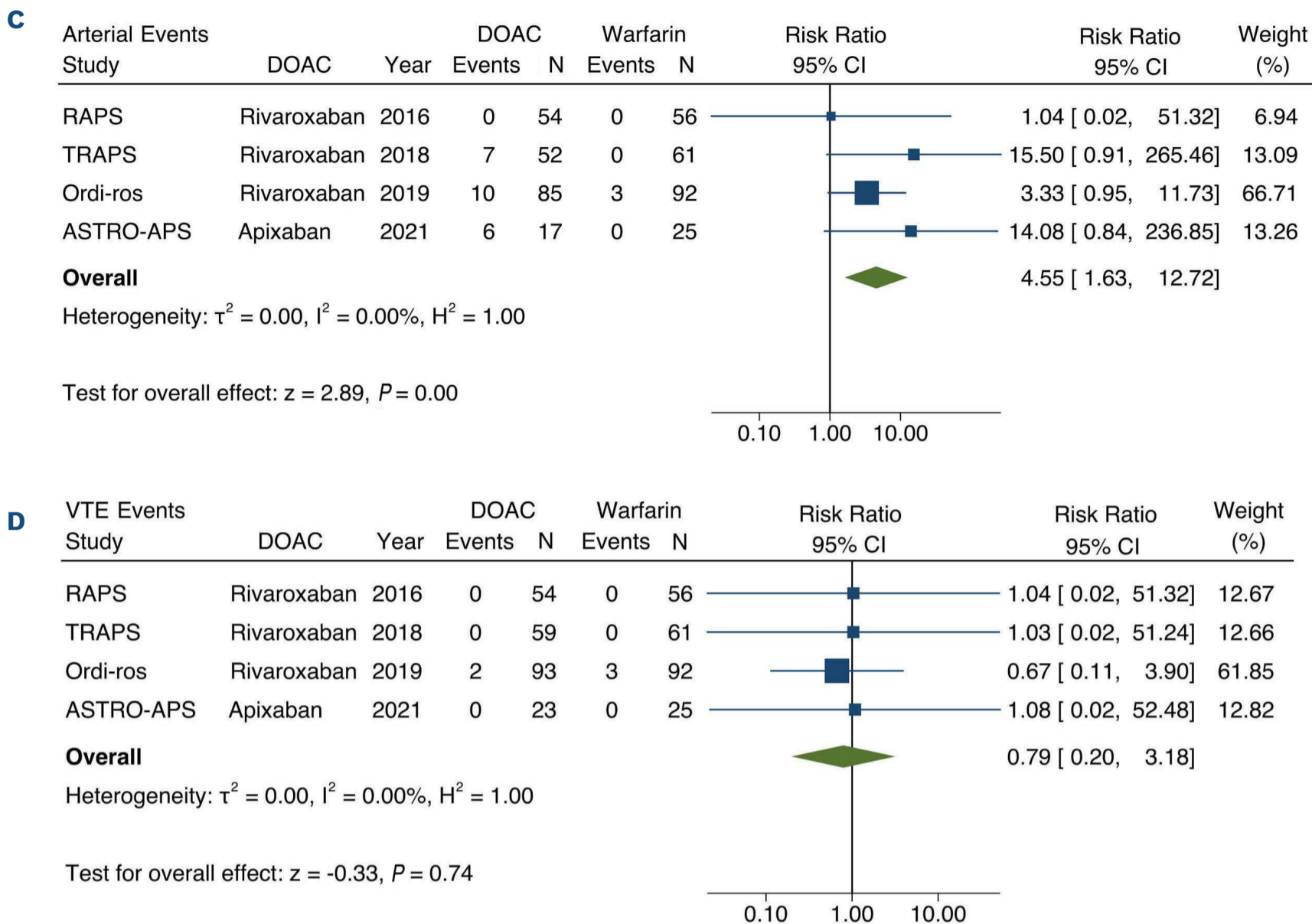


Figure 2. Comparison between patients treated with direct oral anticoagulants or warfarin. (A) Incidence of thrombotic events, (B) major bleedings, (C) arterial events and (D) venous events. DOAC: direct oral anticoagulants; N: number; CI: confidence interval; VTE: venous thromboembolism.

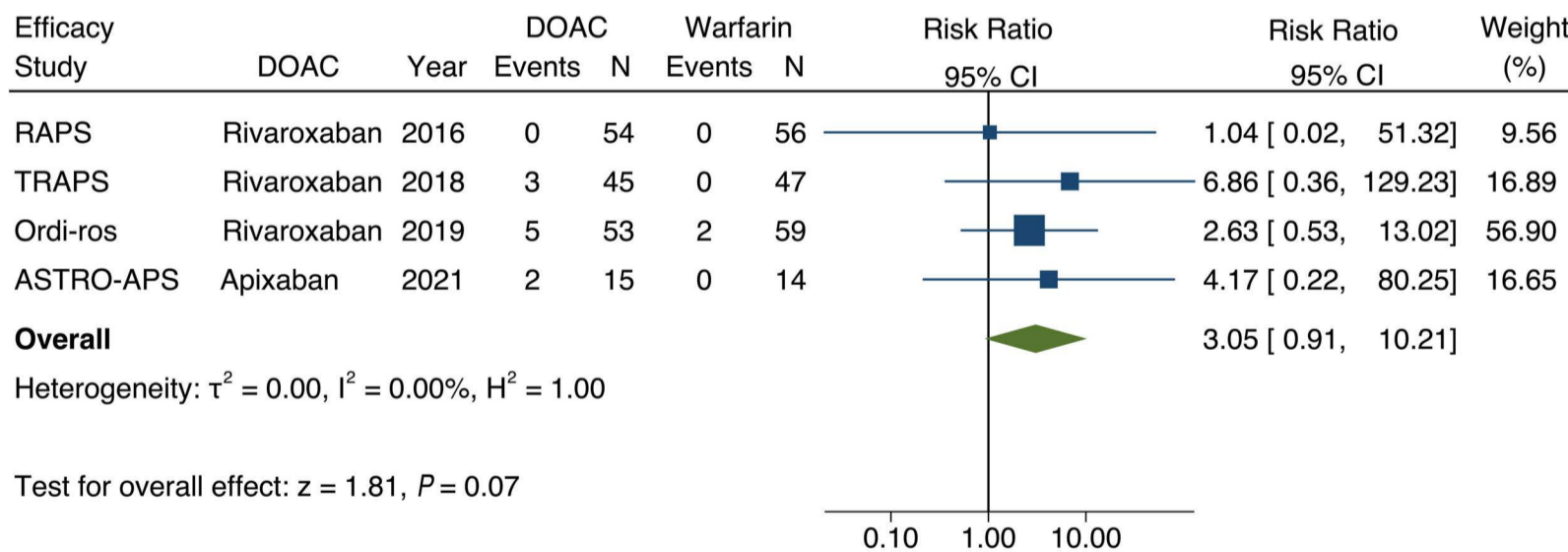


Figure 3. Incidence of thrombotic events in patients without history of arterial events treated with direct oral anticoagulants compared with warfarin. DOAC: direct oral anticoagulants; N: number; CI: confidence interval.

(Figure 1) and low or absent for all the other analyses. In this meta-analysis we confirmed that DOAC are less effective than warfarin in preventing recurrence of thrombotic events in APS patients. The excess of thrombosis in patients treated with DOAC was due to arterial events, while we found no difference in the occurrence

of VTE between the two treatment groups. It has been suggested that the use of DOAC may be considered in some selected cases of APS, such as individuals with a history of a single venous thrombosis or with a low-risk APL antibody profile, but, until now, no studies are available to support this hypothesis.

We found that DOAC therapy is associated with an increased risk of arterial events, particularly stroke, also in “high-risk” APS patients treated for prior venous thrombotic events or miscarriages. Arterial events were also reported in patients with “low-risk” APL antibody profile, but only few patients with these characteristics were included in the studies selected for our meta-analysis, and, thus, no conclusions can be drawn.

Given the high risk of arterial events in APS patients, alternative approaches may be considered in future studies. One of these includes the association of DOAC and low dose aspirin (LDA), for which there are currently insufficient data to provide any recommendation. LDA, in combination with prophylactic dose low molecular weight heparin (LMWH), is the standard of treatment during pregnancy for obstetric APS¹² and the use of LDA has been associated with the same risk of first event compared with LDA plus warfarin in primary prevention of patients positive for antiphospholipid antibodies.¹³ Few data exist on the association of LDA and warfarin for the secondary prevention of thrombotic events in APS. In a small cohort of patients, this drug combination was associated with increased risk of bleeding and no effect on thrombosis recurrence.¹⁴ Yet, this strategy is recommended by the European Alliance Of Association For Rheumatology guidelines as an option following a first arterial thrombosis or recurrent arterial or venous thrombosis in APS patients.¹⁵

In conclusion, the use of DOAC as a single therapeutic approach appears to be insufficiently effective in high risk patients with APS, even without a history of arterial thrombosis. Since in patients treated with VKA the risk of thrombosis remains non-negligible,⁸⁻¹⁰ further studies are needed to assess alternative approaches in this setting.

References

1. 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(12):1968-1975.
2. Ruff CT, Giugliano RP, Braunwald E, et al. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. *Lancet*. 2014;383(9921):955-962.
3. Ruiz-Irastorza G, Cuadrado MJ, Ruiz-Arruza I, 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. Keeling D, Mackie I, Moore GW, Greer IA, Greaves M, British Committee for Standards in H. Guidelines on the investigation and management of antiphospholipid syndrome. *Br J Haematol*. 2012;157(1):47-58.
5. Ordi-Ros J, Saez-Comet L, Perez-Conesa M, et al. Rivaroxaban versus vitamin K antagonist in antiphospholipid syndrome: a randomized noninferiority trial. *Ann Intern Med*. 2019;171(10):685-694.
6. Pengo V, Denas G, Zoppellaro G, et al. Rivaroxaban vs warfarin in high-risk patients with antiphospholipid syndrome. *Blood*. 2018;132(13):1365-1371.
7. Woller SC, Stevens SM, Kaplan D, et al. Apixaban compared with warfarin to prevent thrombosis in thrombotic antiphospholipid syndrome: a randomized trial. *Blood Adv*. 2022;6(6):1661-1670.
8. Crowther MA, 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.
9. Prandoni P, Simioni P, Girolami A. Antiphospholipid antibodies,

Authors

Igor Giarretta,¹ Walter Ageno² and Francesco Dentali^{1,2}

¹Department of Emergency of High-Specialty and Medical Center, ASST-Settelaghi and ²Department of Medicine and Surgery, University of Insubria, Varese, Italy

Correspondence:

F. DENTALI - francesco.dentali@asst-settelaghi.it

<https://doi.org/10.3324/haematol.2022.281586>

Received: June 14, 2022.

Accepted: July 12, 2022.

Prepublished: July 21, 2022.

©2022 Ferrata Storti Foundation

Published under a CC BY-NC license 

Disclosures

No conflicts of interest to disclose.

Contributions

IG, WA and FD conceptualized the study. IG designed and performed the statistical analyses. IG and FD wrote the first draft of the manuscript. FD and WA revised the final version of the paper. All authors participated in data collection, revised and approved the final manuscript. The corresponding author attests that all listed authors meet authorship criteria.

Data-sharing statement

The data presented in this study are available upon request addressed to the corresponding author.

- recurrent thromboembolism, and intensity of warfarin anticoagulation. *Thromb Haemost.* 1996;75(5):859.
10. 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.
11. 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.
12. 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(9):e426-436.
13. Cuadrado MJ, Bertolaccini ML, Seed PT, et al. Low-dose aspirin vs low-dose aspirin plus low-intensity warfarin in thromboprophylaxis: a prospective, multicentre, randomized, open, controlled trial in patients positive for antiphospholipid antibodies (ALIWAPAS). *Rheumatology (Oxford).* 2014;53(2):275-284.
14. Bala MM, Celinska-Lowenhoff M, Szot W, et al. Antiplatelet and anticoagulant agents for secondary prevention of stroke and other thromboembolic events in people with antiphospholipid syndrome. *Cochrane Database Syst Rev.* 2020;10(10):CD012169.
15. Cohen H, Cuadrado MJ, Erkan D, et al. 16th International Congress on Antiphospholipid Antibodies task force report on antiphospholipid syndrome treatment Trends. *Lupus.* 2020;29(12):1571-1593.