Efficacy and Safety of Direct Oral Anticoagulants in Patients With Antiphospholipid Syndrome: A Systematic Review and Meta-Analysis

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Abstract

Due to a high risk of recurrent thromboembolism in patients with antiphospholipid syndrome (APS), long-term anticoagulation is recommended. For decades, vitamin K antagonists (VKAs) have been the gold standard for thromboprophylaxis in these patients. Due to the widespread use of direct oral anticoagulants (DOACs) in various thromboembolic conditions and their potential advantages compared to VKAs, several studies have been conducted to evaluate their safety and efficacy in APS.

We performed a literature search using PubMed, Embase, and Cochrane databases for studies comparing DOACs to VKAs in patients with APS. Relative risk (RR) and the corresponding 95% confidence intervals (95% CI) were estimated for recurrent thromboembolic events, bleeding, and mortality.

A total of 1437 patients pooled from 12 studies were analyzed. The risk of recurrent thrombosis, especially arterial thrombosis, doubled with DOACs compared to VKAs (RR 2.61, 95% CI 1.44-4.71; p=0.001). The risk further increased in patients with a triple-positive antiphospholipid antibody profile (RR 4.50, 95% CI 1.91-10.63; p=0.006) and with the use of rivaroxaban (RR 3.95, 95% CI 1.10-13.44; p=0.02). The risk of major bleeding and mortality were not significantly different between the two arms. A trend favoring DOACs compared to VKAs was observed for all bleeding events.

This meta-analysis comes in agreement with previous studies and supports the use of VKAs in APS. Our study revealed that VKAs remain the gold standard for the management of APS, especially triple-positive APS. DOACs, particularly rivaroxaban, are not as effective in preventing recurrent thromboembolism in high-risk APS patients. Further studies are needed to evaluate the role of DOACs apart from rivaroxaban with a focus on their efficacy in the management of isolated or double-positive APS.

Introduction And Background

Antiphospholipid syndrome (APS) is an autoimmune disorder characterized by at least one thromboembolic (TE) event (venous, arterial, or small vessel) and/or pregnancy morbidity (one or more unexplained fetal deaths, one or more premature births, and three or more unexplained consecutive spontaneous abortions) in the presence of at least one persistent (12 weeks) antiphospholipid antibody (aPL): lupus anticoagulant (LA), IgG or IgM anticardiolipin antibodies (aCL), IgG or IgM anti-β2-glycoprotein antibodies (anti-β2GPI) (Sapporo criteria) [1]. Patients who exhibit positive testing for all three antibodies (triple-positivity) appear to have a worse prognosis due to their high risk for recurrent thrombosis and pregnancy complications [1,2]. The estimated incidence of APS is approximately five per 100,000 persons per year, with a prevalence of around 40-50 cases per 100,000 persons, and is seen more commonly in women (1:3.5, male-female ratio) between 15-50 years of age [3]. Catastrophic APS, the most severe form of APS, which accounts for approximately 1% of all APS cases, is associated with an overall mortality rate of 37% [4].

After a first thrombotic event, the risk of recurrent thromboembolism increases by 10-67% in APS, and long-term anticoagulation is indicated [5,6]. For decades, vitamin K antagonists (VKAs) have been recommended as the gold standard agents for the treatment and prevention of recurrent TE events in APS. However, long-term treatment with VKAs is a great clinical challenge due to the need for close international normalized ratio (INR) monitoring, inconsistent quality of anticoagulation, lack of adherence, and the risk of major bleeding [5,6]. Direct oral anticoagulants (DOACs) emerged over the last decade as a practicable alternative to VKAs and have been widely used to treat and prevent several TE conditions; thanks to their capability to evade most obstacles that are seen with the use of VKAs as mentioned above [7].

How to cite this article

Gullapalli K, Prasad R M, Al-Abcha A, et al. (September 22, 2022) Efficacy and Safety of Direct Oral Anticoagulants in Patients With Antiphospholipid Syndrome: A Systematic Review and Meta-Analysis. Cureus 14(9): e29449. DOI 10.7759/cureus.29449
Several clinical studies have previously evaluated the use of DOACs, predominantly rivaroxaban, in patients with APS, but the data on their safety and efficacy are conflicting [8-14]. A meta-analysis of these studies by Koval et al. [15] revealed an increased TE risk with DOACs compared with VKAs. More recently, multiple randomized and non-randomized studies have been conducted. Apixaban for secondary prevention of thromboembolism among patients with antiphospholipid syndrome (ASTRO-APS) is a randomized clinical trial (RCT) by Woller et al. that compared apixaban with warfarin in the treatment of APS [16]. The results revealed an increased number of recurrent thrombotic events in the DOACs arm (6 of 23) compared to warfarin (0 of 25). Pengo et al. [9] conducted the trial of rivaroxaban in antiphospholipid syndrome (TRAPS), an RCT that terminated prematurely on January 28, 2018, after finding a high incidence of arterial thrombosis in the rivaroxaban group. Following termination of the trial, most patients (n=109) were switched to warfarin, whereas six patients remained on DOACs. A two-year follow-up study describing the events between January 28, 2018, and January 28, 2020, was recently published, the results of which further support the use of warfarin in high-risk patients with APS [17].

More recently, multiple randomized and non-randomized studies have been conducted. Apixaban for secondary prevention of thromboembolism among patients with antiphospholipid syndrome (ASTRO-APS) is a randomized clinical trial (RCT) by Woller et al. that compared apixaban with warfarin in the treatment of APS [16]. The results revealed an increased number of recurrent thrombotic events in the DOACs arm (6 of 23) compared to warfarin (0 of 25). Pengo et al. [9] conducted the trial of rivaroxaban in antiphospholipid syndrome (TRAPS), an RCT that terminated prematurely on January 28, 2018, after finding a high incidence of arterial thrombosis in the rivaroxaban group. Following termination of the trial, most patients (n=109) were switched to warfarin, whereas six patients remained on DOACs. A two-year follow-up study describing the events between January 28, 2018, and January 28, 2020, was recently published, the results of which further support the use of warfarin in high-risk patients with APS [17].

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In contrast, contrary data from Franke et al. [19] and Liu et al. [20] indicate that DOACs may be safe in this group. Due to contrasting results from different studies and the availability of several more recent RCTs and observational studies, we performed a systematic review and meta-analysis to compare the safety and efficacy of DOACs to VKAs in APS.

**Review**

**Materials and methods**

**Information Sources, Search Strategies, and Data Extraction**

We performed a comprehensive literature search using multiple electronic databases: PubMed, Embase, and Cochrane, from inception to June 14, 2022. The search included the following keywords: “direct oral anticoagulants,” “apixaban,” “rivaroxaban,” “dabigatran,” “edoxaban,” and “vitamin K antagonists,” “warfarin,” and “antiphospholipid syndrome.” After removing duplicates, two reviewers (KG and RP) independently reviewed the search results and screened the articles against the inclusion and exclusion criteria to assess their eligibility.

**Inclusion/Exclusion Criteria**

The inclusion criteria consisted of (1) double-arm longitudinal studies; RCTs, and observational studies (prospective or retrospective), (2) comparison of DOACs versus VKAs or warfarin, (3) DOACs were either rivaroxaban, apixaban, dabigatran, or edoxaban, (4) reported either efficacy or safety outcomes; recurrent thromboembolic events, major bleeding, any bleeding, and mortality, (5) human subjects, and (6) adults diagnosed with APS. Exclusion criteria consisted of (1) ongoing or irretrievable data, (2) single-arm studies, (3) animal studies, (4) case reports, case series, reviews, abstracts, protocols, letters to the editor, comments, or summaries for patients, (5) studies with an unclear outcome or conclusion, and (6) articles published in a language other than English.

**Outcome**

The primary outcome of this meta-analysis was recurrent TE events, which may include a composite of arterial and venous events. Arterial events include stroke, transient ischemic attack (TIA), myocardial infarction (MI), or peripheral artery disease (PAD). Venous events include deep vein thrombosis (DVT), pulmonary embolism (PE), cerebral venous thrombosis (CVT), or recurrent thrombosis in an inferior vena cava (IVC) filter. Secondary outcomes included major bleeding (as defined by the International Society on Thrombosis and Hemostasis criteria), all bleeding events (including major bleeding, clinically relevant non-major bleeding, and minor bleeding), and mortality.

**Data Analysis**

We scrutinized results from each study using the intention-to-treat (ITT) method when available. Data were pooled using Review Manager (RevMan) Version 5.4.1 (The Cochrane Collaboration, Denmark, 2014). The outcomes were treated as dichotomous variables. The Mantel-Haenszel random-effects models were used to estimate the risk ratios (RR) and the corresponding 95% confidence intervals (95% CI). Two-sided p values <0.05 were considered statistically significant. Heterogeneity was assessed using I². Statistical heterogeneity was considered substantial if I² >50%. The meta-analysis was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines [21]. Each study was evaluated independently by KG and RP to evaluate the risk of bias.

**Results**

**Included Studies**
Our literature search identified 1816 publications. Finally, a total of 12 studies were included in the analysis after assessing eligibility. These include four RCTs, one post hoc subgroup analysis, one follow-up study of an RCT, and six cohort studies (two prospective and four retrospective studies) [8-14,16-20]. Figure 1 shows the PRISMA flow diagram.

### Table 1: Characteristics of the included studies

| S. no. | Study name/author name (reference) | Pub. year | Study design | Study population | Patients (n) | Intervention | Outcomes | Follow-up (months) |
|--------|-----------------------------------|-----------|--------------|------------------|--------------|--------------|----------|-------------------|
| 1      | EUDRA-2010-018784-36/Ord-Ros et al. [9] | 2019      | Phase II RCT, multicenter | Adult APS patients with arterial or venous thrombosis receiving acenocoumarol | 190          | Rivaroxaban versus VKA | Primary: New thrombotic events and major bleeding. Secondary: Time to thrombosis, type of thrombosis, change in quantitative synthesis | 36 |

PRISMA: preferred reporting items for systematic reviews and meta-analysis. Reference [21].
| Study | Design | Year | Population Characteristics | Interventions | Primary Outcomes | Secondary Outcomes |
|-------|--------|------|----------------------------|---------------|------------------|-------------------|
| 1. TRAPS/Pengo et al. [9] | Phase II RCT, multicenter | 2018 | Adult triple-positive (high-risk) APS patients with a history of thrombosis | Rivaroxaban versus warfarin | Biomarker levels, cardiovascular death, and non-major bleeding | | |
| 2. RE-COVER I/RE-COVER II/RE-MEDY/Goldhaber et al. [10] | Post hoc subgroup analysis of the three Phase III RCTs (RE-COVER I, RE-COVER II, RE-MEDY) | 2016 | Adults with objectively confirmed, symptomatic proximal DVT or PE (RE-COVER, RE-COVER II), Adults with objectively confirmed, symptomatic DVT or PE treated with approved anticoagulant for 3-12 months or with dabigatran in RE-COVER I or RE-COVER II (RE-MEDY) | Dabigatran versus warfarin | Primary: Recurrent objectively confirmed, symptomatic VTE; death associated with VTE. Secondary: Major bleeding, clinically relevant non-major bleeding, all bleeding events | | |
| 3. RAPS/Cohen et al. [11] | Phase II/III RCT, multicenter | 2016 | Adult thrombotic APS patients with previous venous TE on standard intensity warfarin for at least three months | Rivaroxaban versus warfarin | Primary: Percentage change in ETP from randomization to day 42. Secondary: Occurrence of TE up to 210 days after randomization, thrombin generation, serious adverse events, and bleeding events | | |
| 4. Sato et al. [12] | Retrospective cohort | 2019 | Adult APS with prior history of thrombosis | Rivaroxaban/edoxaban/apixaban versus warfarin | Primary: Event-free survival for five years (resurgence of arterial/venous thrombosis and severe bleeding requiring hospitalization and/or transfusion). | | |
| 5. Martinelli et al. [13] | Prospective cohort, single center | 2018 | Adult APS patients with a history of venous thrombosis | Rivaroxaban versus VKA | Primary: Recurrence of thrombosis. Secondary: Major bleeding and clinically relevant non-major bleeding. | | |
| 6. Malec et al. [14] | Prospective cohort, single center | 2019 | Adult patients with APS | Rivaroxaban/apixaban/dabigatran versus warfarin | Primary: Symptomatic TE events (venous or arterial), PE, SVT, stroke, TIA, MI. Secondary: Major bleeding, clinically relevant non-major bleeding. | | |
| 7. ASTRO-APS/Weiler et al. [16] | Phase IV RCT, multicenter | 2021 | Adult thrombotic APS patients receiving some form of anticoagulation | Apixaban versus warfarin | Primary: Rate of thrombosis and vascular death. Rate of major and clinically relevant non-major bleeding. Secondary: Net clinical benefit | | |
| 8. TRAPS (two-year follow-up)/Pengo et al. [17] | Phase II RCT, multicenter | 2020 | Adult triple-positive APS patients with a history of thrombosis | Rivaroxaban/dabigatran versus warfarin | Recurrent thromboembolic events | | |
A total of 1437 adults with APS followed over a mean weighted period of 28.5 months (ranging between 6 and 72 months) were included in this meta-analysis. Of these, 634 constituted the DOACs arm (44%), and 803 constituted the VKAs group (56%). The mean age was similar in both groups (48.4 years for DOACs and 48.5 years for VKAs; p=0.95). Females constituted 61.3% of the DOACs group and 56.2% of the VKAs arm. The mean body mass index (BMI) was also comparable between the groups (28.6 versus 28.4, respectively; p=0.88).

A summary of the risk of bias for each individual study is depicted in Figure 2.
Outcomes

The risk of all recurrent TE events in APS patients while on DOACs compared to VKAs: A total of 108 patients (7.51%) developed recurrent TE events. Of these, 55 were arterial events (50.9%), and 53 were venous (49.0%). In the DOACs group, 62 out of 634 patients (9.7%) developed recurrent thrombosis; 38 (61.2%) were arterial and 24 (38.7%) venous. In the VKAs group, out of 803 patients, 46 (5.72%) suffered recurrent thromboembolism with a predominance of venous events (63%). The primary outcome of recurrent TE events was significantly higher in the DOACs arm compared to the VKAs (RR 1.91, 95% CI 1.08-3.37; p=0.03; I²=46%; 12 studies). Though no statistically significant differences were observed between
RCTs, and retrospective and prospective studies, the magnitude of the risk was superior in RCTs (RR 3.94 95% CI 1.24-12.55; p=0.02; I²-57%) (Figure 3).

| Study or Subgroup | DOACs Events | VKA Events | Risk Ratio M-H, Random, 95% CI Year |
|-------------------|-------------|------------|-----------------------------------|
| 1.3.1 RCTs        |             |            |                                   |
| Cohen 2016        | 0           | 57         | Not estimable 2016                |
| Distlhabler 2016  | 3           | 71         | 0.95 (0.90, 3.60) 2016            |
| Pengo 2018        | 6           | 59         | 17.57 (9.84, 29.67) 2018          |
| Oni-Rex 2019      | 12          | 95         | 3.00 (0.78, 11.1) 2019            |
| Pengo 2021        | 2           | 6          | 12.11 (2.47, 69.39) 2021          |
| Winter 2021       | 6           | 23         | 14.69 (3.84, 53.85) 2021          |
| Subtotal (65% CI) | 311         | 429        | 3.94 (1.24, 12.55)              |
| Total events      | 31          | 13         |                                   |
| Heterogeneity: Tau²= 0.81; Chi²= 9.25, df = 4 (P = 0.06); P= 57% |
| Test for overall effect: Z = 2.32 (P = 0.02) |

1.3.2 Retrospective studies

| Study or Subgroup | DOACs Events | VKA Events | Risk Ratio M-H, Random, 95% CI Year |
|-------------------|-------------|------------|-----------------------------------|
| Sato 2019         | 6           | 10         | 1.50 (0.61, 3.67) 2019            |
| Williams 2021     | 6           | 39         | 2.92 (0.78, 10.88) 2021           |
| Franklin 2021     | 2           | 159        | 0.45 (0.06, 3.46) 2021            |
| Liu 2022          | 3           | 52         | 0.88 (0.23, 3.35) 2022            |
| Subtotal (65% CI) | 238         | 265        | 1.33 (0.70, 2.52)               |
| Total events      | 17          | 20         |                                   |
| Heterogeneity: Tau²= 0.03; Chi²= 3.23, df = 3 (P = 0.36); P= 7% |
| Test for overall effect: Z = 0.97 (P = 0.33) |

1.3.3 Prospective studies

| Study or Subgroup | DOACs Events | VKA Events | Risk Ratio M-H, Random, 95% CI Year |
|-------------------|-------------|------------|-----------------------------------|
| Martini 2018      | 4           | 13         | 4.62 (0.58, 36.27) 2018           |
| Malec 2019        | 10          | 82         | 0.36 (0.44, 2.06) 2019            |
| Subtotal (65% CI) | 99          | 169        | 1.54 (0.37, 6.59)               |
| Total events      | 14          | 13         |                                   |
| Heterogeneity: Tau²= 0.62; Chi²= 1.99, df = 1 (P = 0.16); P= 50% |
| Test for overall effect: Z = 0.81 (P = 0.41) |
| Total (65% CI)    | 634         | 803        | 1.91 (0.86, 3.37)               |
| Total events      | 62          | 46         |                                   |
| Heterogeneity: Tau²= 0.30; Chi²= 18.55, df = 10 (P = 0.00); P= 49% |
| Test for overall effect: Z = 2.21 (P = 0.03) |

When the subgroup of patients with triple-positive (high-risk) APS were analyzed separately, a higher magnitude of risk for recurrent thrombosis was observed in the DOACs arm (RR 4.50, 95% CI 1.91-10.63; p=0.0006; I²-18%; seven studies) (Figure 4A). The subgroup with double or isolated aPL also tended to develop increased risk; however, they did not reach statistical significance (RR 1.70, 95% CI 0.73-3.99; p=0.22; I²-0%; six studies) (Figure 4B).
In patients with previous arterial thrombosis, the RR of recurrent TE with DOACs was 2.30 (95% CI 0.78-6.81; p=0.13; I^2=52%) (Figure 5A). In patients with previous venous thrombosis only, RR was 1.67 (95% CI 0.77-3.64; p=0.19; I^2=0%). (Figure 5B).

In the subgroup of patients treated with DOACs other than rivaroxaban, a slight decrease in risk was observed compared to VKAs but was not statistically significant (RR 0.85, 95% CI 0.36-2.02; p=0.72; I^2=14%) (Figure 6A). However, the risk doubled in the subgroup that was treated exclusively with rivaroxaban compared to VKAs (RR 1.95, 95% CI 1.10-3.45; p=0.02; I^2=18%) (Figure 6B).
FIGURE 6: Forest plot of recurrent thromboembolic events with (A) DOACs other than rivaroxaban (apixaban, dabigatran, or edoxaban) versus VKAs and (B) rivaroxaban versus VKAs.

Risk of arterial events in APS patients while on DOACs compared to VKAs: As previously indicated, the outcome of all TE events is a composite of arterial and venous outcomes. The DOACs arm had an increased risk of developing arterial events compared to VKAs (RR 2.61, 95% CI 1.44-4.71; p=0.001; I²=0%; 12 studies) (Figure 7). The risk of recurrent arterial thrombosis among the subgroup of patients receiving concomitant antiplatelet therapy was also analyzed. Two events were reported in the DOACs group (n=50) versus one in the VKAs arm (n=45). Although a trend for increased risk was observed in the DOACs arm, statistical significance was not achieved.

FIGURE 7: Forest plot of recurrent arterial events with DOACs versus VKAs.

Risk of venous events in APS patients while on DOACs compared to VKAs: there was no statistically significant increase in risk was observed in the DOACs group compared to VKAs (RR 1.17, 95% CI 0.66-2.07; p=0.60; I²=8%; 12 studies) (Figure 8).
FIGURE 8: Forest plot of recurrent venous events with DOACs versus VKAs.

DOACs: direct oral anticoagulants; VKA: vitamin K antagonists; CI: confidence interval. References: [8-14,16-20].

The risk of major bleeding, all bleeding, and all-cause mortality in APS patients while on DOACs is compared to VKA: 30 of 515 patients (5.8%) had major bleeding events in the DOACs arm compared to 34 of 722 (4.7%) in the VKAs arm (RR 1.17, 95% CI 0.75-1.89; p=0.52; I²=0%; 11 studies) (Figure 9).

FIGURE 9: Forest plot of major bleeding events with DOACs versus VKAs.

DOACs: direct oral anticoagulants; VKA: vitamin K antagonists; CI: confidence interval. References: [8-14,16-20].

Though a decreased risk for all bleeding events was observed in the DOACs arm compared to VKAs, the results were statistically non-significant (RR 0.86, 95% CI 0.59-1.27; p=0.46; I²=46%; six studies) (Figure 10).

FIGURE 10: Forest plot of all bleeding events with DOACs versus VKAs.

DOACs: direct oral anticoagulants; VKA: vitamin K antagonists; CI: confidence interval. References: [8-14,16-20].

Likewise, with regards to the risk of all-cause mortality, no statistically significant increase was observed in DOACs compared to VKAs. (RR 1.32, 95% CI 0.55-3.21; p=0.53; I²=0%; eight studies) (Figure 11).
antiphospholipid syndrome (RISAPS) is an ongoing phase 2/3 RCT that aims to assess the efficacy of high-
necessary to determine the risks or benefits of dose intensification. Rivaroxaban for stroke patients with
intensity anticoagulation
doses of DOACs may not provide sufficient protection against thrombosis in patients who require high-
efficacy with DOACs
Suboptimal dosing, insufficient drug concentrations, or a short half-life might also contribute to the lack of
fibrinolysis impairment
found to increase the lag time and time to peak thrombin generation, leading to platelet activation and
lag time and the time to peak thrombin generation with DOACs
propagation phases. This leads to a delay in the formation of the prothrombinase complex, lengthening the
phases of thrombin generation are equally affected by warfarin, while DOACs mainly affect the initiation and
dependent clotting factors, DOACs control thrombogenesis by selectively inhibiting factors Xa or IIa
Although not completely understood, several hypotheses have been made regarding the rationale behind
higher thrombotic risk with DOACs. Unlike warfarin, which reduces functional levels of all vitamin K-
commonly used agent in the DOACs arm; very few studies had patients treated with apixaban, dabigatran, or
edoxaban. In our subgroup analysis, DOACs other than rivaroxaban showed a slight decrease in the risk of
recurrent thromboembolism when compared to VKAs. More specifically, we observed a significant increase
in risk for arterial events (stroke/TIA and MI) but not venous thromboembolism (DVT, PE). Several studies
reported recurrent arterial events in patients with previous arterial thrombosis [16,19]. We hence sought to
analyze the risk of recurrent thrombosis according to the index thrombotic event. In our subgroup analysis
of patients with prior arterial thrombosis, the risk of recurrent thrombosis was higher in the DOACs arm
compared to VKAs, but the results were not statistically significant. A similar pattern was observed in the
subgroup with prior venous thromboembolism. Triple-positivity is indicative of a major risk factor for
thrombosis and obstetric complications [22]. In the TRAPS RCT, where only patients with triple-positivity
were included, recurrent arterial thrombotic events were higher in the rivaroxaban arm (7 of 59) compared
to the warfarin (0 of 61) [9]. In addition, in a retrospective cohort study by Williams et al. which excluded
 triple-positive patients, the proportion of patients with recurrent TE was three times higher in the DOACs
group (6 of 39) compared to the warfarin group (3 of 57); however, this was not statistically significant
(p=0.15) [18]. In our subgroup analysis of triple-positive (high-risk) APS patients, the risk of recurrent
thrombosis was four times higher with DOACs compared to VKAs. The increased risk did not reach statistical
significance in patients with isolated or double-positivity. In animal models of APS, platelets were shown to
play a major role in thrombus formation within the arterial circulation [23]. The use of low-dose aspirin is
hence considered in APS patients with a history of arterial thrombosis [6]. In our subgroup analysis, we
attempted to determine if the risk of recurrent arterial thrombosis in the DOACs group changed with the
concomitant use of antiplatelet therapy. However, no conclusions could be drawn due to the small sample
size of patients who took aspirin or other antiplatelet therapies in these studies.

The risk of major bleeding and mortality was increased in patients treated with DOACs. However, statistical
significance was not achieved for these outcomes. The risk of all bleeding events showed a trend favoring
DOACs but failed to reach statistical significance. Finally, in a majority of studies, rivaroxaban was the most
commonly used agent in the DOACs arm; very few studies had patients treated with apixaban, dabigatran, or
edoxaban. In our subgroup analysis, DOACs other than rivaroxaban showed a slight decrease in the risk of
recurrent thrombosis compared to VKAs, but statistical significance was not achieved, likely due to the small
sample size. However, in patients on rivaroxaban, the thromboembolic risk doubled compared to VKAs. This

Discussion

Our meta-analysis clearly shows that the use of DOACs in APS patients is associated with double the risk of
recurrent thromboembolism when compared to VKAs. More specifically, we observed a significant increase
in risk for arterial events (stroke/TIA and MI) but not venous thromboembolism (DVT, PE). Several studies
reported recurrent arterial events in patients with previous arterial thrombosis [16,19]. We hence sought to
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Although not completely understood, several hypotheses have been made regarding the rationale behind
higher thrombotic risk with DOACs. Unlike warfarin, which reduces functional levels of all vitamin K-
derpendent clotting factors, DOACs control thrombogenesis by selectively inhibiting factors Xa or Ila [11]. All
phases of thrombin generation are equally affected by warfarin, while DOACs mainly affect the initiation and
propagation phases. This leads to a delay in the formation of the prothrombinase complex, lengthening the
lag time and the time to peak thrombin generation with DOACs [11]. Additionally, aPL antibodies were also
found to increase the lag time and time to peak thrombin generation, leading to platelet activation and
fibrinolysis impairment [31,15,23]. Moreover, DOACs exert their effect in a dose-dependent manner.
Suboptimal dosing, insufficient drug concentrations, or a short half-life might also contribute to the lack of
efficacy with DOACs [24]. Most of the available studies had patients on 15-20 mg rivaroxaban/day. These
doses of DOACs may not provide sufficient protection against thrombosis in patients who require high-
intensity anticoagulation [25]. However, further testing in adequately powered clinical trials would be
necessary to determine the risks or benefits of dose intensification. Rivaroxaban for stroke patients with
antiphospholipid syndrome (RISAPS) is an ongoing phase 2/3 RCT that aims to assess the efficacy of high-

FIGURE 11: Forest plot of mortality events with DOACs versus VKAs.

DOACs: direct oral anticoagulants; VKA: vitamin K antagonists; CI: confidence interval. References: [8-14,16-20].
intensity rivaroxaban (15 mg twice daily) versus high-intensity warfarin (INR 3.5) in APS patients with a history of stroke or other ischemic brain manifestations (NCT03684564).

There are, however, certain limitations to the studies included in our analysis. Not all studies were clear about whether patients were recruited based on the Sapporo criteria [1]. Positive lupus anticoagulant is associated with a higher risk of thrombosis [26]. Most of the studies lacked identification of associated antiphospholipid antibodies in patients with higher thrombosis risk. Studies also had variable follow-up times ranging from 6 to 72 months. It can be presumed that in studies with shorter follow-up, the number of thromboembolic events would be much higher if the patients were followed for a longer duration resulting in a higher risk for recurrent TE events than reported. Moreover, several confounding factors such as cardiovascular risk factors (smoking, hypertension, diabetes mellitus, dyslipidemia), coexisting hereditary thrombophilia, concomitant autoimmune conditions such as systemic lupus erythematosus, and other hypercoagulable states might play a role in increasing the thrombosis risk. Very few studies looked for these characteristics in patients with recurrent thromboembolic events. Thus, further studies without these limitations would be noteworthy.

Conclusions
To conclude, our updated meta-analysis reaffirms that the use of DOACs, particularly rivaroxaban poses an increased risk of arterial thrombosis in high-risk (triple-positive) APS patients and is thus not effective in preventing recurrent TE events in these patients. Further studies are warranted to confirm the safety and efficacy of DOACs other than rivaroxaban in the prevention of venous thromboembolism in low-risk APS patients. As such, until further evidence is available, warfarin should remain the drug of choice.

Additional Information
Disclosures
Conflicts of interest: In compliance with the ICMJE uniform disclosure form, all authors declare the following: Payment/services info: All authors have declared that no financial support was received from any organization for the submitted work. Financial relationships: All authors declare that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. Other relationships: All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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