# Direct oral anticoagulants in antiphospholipid syndrome: Meta-analysis of randomized controlled trials

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Abstract:

**Background**: The gold standard for secondary thromboprophylaxis in APS is long term anticoagulation with vitamin K antagonists (VKAs). Because of their widespread use and potential advantages of directs oral anticoagulants (DOACs) over VKAs, they have been prescribed in APS without definitive evidence of their safety and efficacy in this context. Recent specific randomized controlled trials (RCT) in APS and results from pivotal RCTs comparing DOACs vs VKAs are now available. Their results are conflicting but these studies have been conducted in different APS populations.

**Purpose of review**: To summarize available data from RCT and determine risks of recurrent thrombosis and bleeding.

**Results**: Four studies were included and 23 and 10 thrombotic events were recorded among 282 and 294 APS patients treated with DOACs and warfarin respectively. Overall recurrent thrombotic events were not significantly increased during DOACs treatment (OR = 2.22 [95% CI, 0.58-8.43]) compared to VKAs. However, when different types of thrombosis were analyzed separately, there was an increased risk of recurrent arterial thrombosis (5.17 [95% CI, 1.57-17.04]) with DOACs compared to warfarin but no significant higher risk of venous thrombosis (OR 0.69 [95% CI, 0.23-2.06). No increased risk of bleeding was found.

**In conclusion**: In APS patients treated with DOACs compared to those treated with warfarin, no evidence of a higher risk of recurrent venous thromboembolism was found however there was a significantly increased risk of recurrent arterial thrombosis. Moreover risk of recurrent arterial thrombosis tended to be more frequent in patients with a history of arterial thrombosis. These results are in line with international guidelines which recommend not to use DOACs in APS patients with a history of arterial thrombosis but raise the question of the efficacy of DOACs to prevent venous thrombosis in a subset of APS patients without a

history of arterial thrombosis.

1.  Introduction

Antiphospholipid syndrome (APS) is an immune disorder characterized by, at least one thrombotic event (arterial, venous or small vessel thrombosis) or obstetrical morbidity with positivity of at least one persistently antiphospholipid antibody (aPL): lupus anticoagulant (LA), IgG or IgM anticardiolipin antibodies (aCL) and IgG or IgM anti-$\beta_2$-glycoprotein-I (a$\beta_2$-GPI) [1]. To date, the gold standard for secondary thromboprophylaxis is long term anticoagulation by warfarin [2].

Due to potential advantages (fewer drug/food interactions, fixed dose, reduced major bleeding) of directs oral anticoagulants (DOACs) over vitamin K antagonists (VKAs), they have been prescribed empirically in APS in last few years while specific RCTs were conducted. Three published controlled randomized trials (RCT) comparing DOACs vs VKAs in APS are now available and one paper analyzing APS patients from pivotal RCT of dabigatran [3–6]. Their results may seem conflicting but these studies included different populations of APS patients.

After the TRAPS trial comparing rivaroxaban vs VKAs in triple positive aPL patients was prematurely stopped due to an increased risk of thrombosis in patients treated with rivaroxaban, the European Medicines Agency (EMA) and the European League Against Rheumatism (EULAR) guidelines recommended against the use of DOACs in APS patients, especially those at high risk with triple positivity (positivity of all three classification laboratory criteria) [7,8]. EULAR guidelines recommended against the use of DOACs also in APS patients with history of arterial thrombosis due to a high number of arterial thrombotic recurrences in the TRAPS trial and one subsequent study [5,9]; whereas the European Society of Cardiology recommended against DOACs use in all APS patients [10]. Data regarding recurrent venous thromboembolism (VTE) during DOAC treatment in APS patients are less

clear-cut. The British Society for Haematology Guidelines on Investigation and Management of APS have recommended against the introduction of DOACs in APS patients with acute venous event but for eventless patients already treated with DOACs, a switch for VKAs should not be systematically considered [11,12]. The objective of this study was to summarize available data from RCTs comparing DOACs to VKAs regarding risks of recurrent thromboses either arterial or venous and the risk of bleeding.

## 2. Materials and Methods

### 2.1 Meta-analysis protocol

Our study protocol was registered on PROSPERO. We conducted this meta-analysis according to the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) guidelines [13].

### 2.2 Search strategy

We conducted a systematic literature search in MEDLINE, EMBASE and Cochrane including all articles published until March 24, 2020 reporting the use of DOACs in APS patients. Search terms (including MeSH terms) were: *antiphospholipid antibodies*, *antiphospholipid syndrome*, *lupus coagulation inhibitor*, *antibodies anticardiolipin*, *familial antiphospholipid syndrome*, *anti-β2-glycoprotein-I* and *lupus erythematosus systemic* and *direct oral anticoagulant*, *DOAC*, *novel oral anticoagulant*, *NOAC*, *rivaroxaban*, *apixaban*, *edoxaban*, *dabigatran*. The search was done without restrictions regarding study design, publication date or language.

### 2.3 Eligibility

Eligible articles were randomized controlled trials about APS patients according to Sapporo-Sydney criteria treated with any DOACs (dabigatran etexilate, rivaroxaban, apixaban, edoxaban). We excluded case series, cases reports, cross sectional studies, abstracts, reviews and editorials.

### 2.4 Search and Extraction

All available abstract were reviewed according to PRISMA guidelines. We used a systematic review management software (Covidence systematic review software, Veritas Health Innovation, Melbourne, Australia. www.covidence.org) to screen all selected article, extract data and evaluate quality assessment of study.

We deleted duplicates, excluded publications which were not eligible. All titles and abstracts were screened. Then we reviewed full text articles and extracted data independently by two investigators (V.D., S.Z.). Results were compared and conflicts were resolved by consensus.

### 2.5 Statistical analyses

The primary outcome was recurrent thrombosis (either arterial, venous, small vessel thrombosis) during anticoagulant treatment. We analyzed results from each study using the intention-to-treat method when available as well as the per protocol method. We obtained pooled risk estimates of recurrent thrombosis with DOACs vs VKAs (OR) by using random-effects models, according to DerSimonian and Laird method.

Analyzes were performed with the use of Review Manager 5 Software (RevMan [Computer program]. Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014).

2.6 Risk of bias assessment

We assessed the risk of bias of included randomized controlled trials using the Revised Cochrane risk-of-bias tool for randomized trials (RoB 2) (available at https://methods.cochrane.org/risk-bias-2) [14]. Two reviewers (V.D. and D.W.) evaluated all studies independently. The tool allows to evaluate 5 areas: randomization process, deviation from the intended interventions, missing outcome data, measurement of the outcome and selection of the reported results. We added a 6$^{th}$ item for the overall risk of bias in the study. For each primary study, risk of bias was assessed as low, high or unclear. If necessary, discrepancies were resolved by consensus.

3. Results

3.1 Literature flow chart

Literature search identified 1005 publications with the use of MEDLINE (n=230), EMBASE (n=837) and Cochrane Library (n=11) from 1989 to March, 24$^{st}$ 2020. Finally, 4 RCTs were included in the analysis (Figure 1).

3.2 Study characteristics

The four RCTs included were published between 2016 and 2019. Their main characteristics are summarized in Table 1. The RAPS, TRAPS and EUDRA-2010-019764-36 studies were open-label and non-inferiority trials.

The RAPS study was the first randomized controlled trial comparing rivaroxaban with warfarin in 110 APS patients without previous arterial thrombosis [3]. The primary outcome was the mean percentage change of endogenous thrombin potential which was increased two-

fold during DOACs treatment. There was no thrombotic event during the follow up of 210 days.

The TRAPS trial compared rivaroxaban with warfarin in triple positive APS patients [4]. This study was prematurely stopped after the enrollment of less than a third of the expected number of patients because of an excess of thrombotic events in the group of patients treated with rivaroxaban. There were 8 (13.5%) thrombotic events (7 arterial and 1 venous) in the group treated with rivaroxaban while no thrombotic event was recorded in the group treated with warfarin.

The EUDRA-2010-019764-36 study compared rivaroxaban with acenocoumarol in 190 APS patients [5]. There were 12 (12.6%) events (11 arterial and 2 venous with one catastrophic APS syndrome in one patient) in the group treated with rivaroxaban and 6 (6.3%) (3 arterial and 3 venous) in the group treated with acenocoumarol.

Post-hoc analysis of patients with thrombophilia including APS were performed in RE-COVER®, RE-COVER II™ and RE-MEDY™ studies which were double-blind randomized controlled trials comparing dabigatran etexilate with warfarin in APS patients with previous VTE were published in a single paper [6,15,16]. Among patients with thrombophilia; 71 and 80 APS patients were treated either with dabigatan etexilate or warfarin respectively. However, in this study, APS was defined using at least one positive test for lupus anticoagulant and/or for anticardiolipin antibodies combined with symptomatic VTE and thus did not completely fulfill all Sapporo-Sydney criteria. Primary efficacy outcome was recurrent, symptomatic, objectively confirmed VTE/VTE-related death from randomization to the end of the prespecified treatment period (6 months). There were respectively 3 (4.2%) and 4 (5%) events in the group treated with dabigatran etexilate and warfarin respectively.

3.3 Risk of recurrent thrombosis in APS while on DOACs compared to VKAs

Overall, 23 and 10 thrombotic events were recorded among 282 and 294 APS patients treated with DOACs and warfarin respectively. One patient had two thrombotic events (one arterial and one venous) during a catastrophic APS event.

Odds ratio (OR) for all recurrent thromboses (arterial and venous) during DOACs treatment was 2.22 [95% CI, 0.58-8.43]. It tends toward a highest thrombotic risk during DOACs treatment without reaching significance. Results are detailed in Figure 2A. Only the TRAPS study reported the mean time to thrombosis event which was 9.3 months. In patients treated with DOACs, most of thromboses were arterial (18/24, 75%): 14 strokes, 3 myocardial infarctions, 1 peripheral thrombosis. The OR for the occurrence of an arterial recurrent thrombosis during DOACs treatment was 5.17 [95% CI, 1.57-17.04] (Figure 2B). Among them, 11 (61%) patients had history of arterial thrombosis. However, the OR for the occurrence of a thrombotic event in patient with previous arterial thrombosis was 3.81 [95% CI 0.78-18.68] (Figure 3A). At the opposite, there was no increased risk of recurrent VTE when patients treated with DOACs were compared to those treated with VKAs: OR 0.69 [95% CI, 0.23-2.06] (Figure 2C); furthermore, patients with a history of venous thrombosis only did no have a higher risk of recurrent thrombosis: 1.58 [95% CI 0.56-4.42] (Figure 3B). When the subgroup of patients with triple positivity was analyzed separately, a trend towards a non-significant higher risk of recurrent thrombosis during DOACs treatment compared to VKAs was found. These results are shown in Figure 3C.

Similar analysis using the per-protocol method yielded similar results (data not shown, available as needed).

3.4 Risk of bleeding in APS patients treated with DOACs vs VKAs

Major bleeding was considered as defined in each study according to the ISTH criteria. There was no major bleeding reported in RAPS study. Risk of bleeding was 1.02 [95% CI 0.42-2.45]. Results are shown in Figure 4A. Due to different definitions of clinically relevant non major bleeding in included studies, we didn't analyze this criterion.

Regarding the occurrence of any bleeding, there no difference between patients treated with DOACs or VKAs (OR 0.85 [95% CI, 0.37-1.97]). Results are show in Figure 4B.


### 3.5 Risk-of bias assessment

Risk of bias assessment and summary of the risk for bias are reported in the Figures 5A and 5B.

Study by Goldhaber et al. was a *post-hoc* analysis of data from RE-COVER®, RE-COVER II$^{TM}$ and RE-MEDY$^{TM}$ studies which were double blind, double dummy randomized controlled trials [6]. The three other studies, RAPS, TRAPS and EUDRA-2010-019764-36 were open-label non inferiority trials [3–5]. Randomization was performed by web randomization service in RAPS and TRAPS trials and by computer in EUDRA-2010-019764-36 [3,4]. Randomization was stratified by center and presence of systemic lupus erythematosus (SLE) in RAPS and EUDRA-2010-019764-36 trials and by sex and presence or absence of an autoimmune disease in TRAPS [3–5]. In TRAPS and EUDRA-2010-019764-36 study, randomization was performed after written informed consent was obtained, so risk of bias about allocation concealment was low [4,5]. In the RAPS study, it was not explicitly mentioned [3]. RAPS, TRAPS and EUDRA-2010-019764-36 studies were open label trials, so the risk of performance bias wass unclear; however, there were no event recorded in RAPS study in the both groups, so we considered that this risk was low in this study. However, because of the absence of VTE event, we considered that the risk of bias concerning blinding of outcome assessment and reported outcomes was unclear. In TRAPS

and EUDRA-2010-019764-36 studies, diagnoses of arterial and VTE were confirmed by objective imaging techniques and were validated by an independent blinded safety and event-adjudication committee [4,5]. Regarding the risk about presence of incomplete outcome data, in EUDRA-2010-019764-36 study, the number of outcome was similar in per protocol and intention-to-treat methods, therefore we considered that the risk of bias was low [5]. In the TRAPS study, more patients modified or stopped their assigned therapy and we considered that risk of bias was unclear [4]. Regarding reported results, reported data agreed with prespecified protocol however in the TRAPS trial clinically relevant non major bleeding and any bleeding were no reported [4]. For the global risk of bias assessment, we classified all studies as unclear because of different reasons: RAPS was not designed to identify a clinical endpoint, the study by Goldhaber et al. was a post hoc analysis of three previous published RCT, TRAPS study was prematurely stopped before reaching the planned needed number of subjects and was an open label study as were RAPS and EUDRA-2010-019764-36 studies [3–6].

## 4. Discussion

This meta-analysis clearly shows an increased risk of arterial recurrent thrombosis during DOACs treatment, in studies comparing Xa inhibitors and VKAs. There was no increased risk of VTE over time.  Regarding the risk of recurrent thrombosis on DOACs according to the history of thrombotic event, no higher risk was detected in patients with a history of VTE only, but patients with history of arterial events tended to develop new thrombotic events while on DOACs (without reaching statistical significance however).  No increased risk of major or any bleeding was shown in either treatment group.

 Among patients with arterial recurrent thrombosis, most of them had history of arterial thrombotic APS related events.  However, in this meta-analysis, the higher risk of recurrent

thrombosis restricted to patients with a history of arterial events didn't reach statistical significance. In a previous meta-analysis of Cerdà et al. this risk was statistically different. This may be explained by the use of a different statistical test: risk difference with fixed effects model due to a low population's heterogeneity ($I^2$ 49%, p= 0.16). In our meta-analysis, we used odds ratios and random effects models analyzing all events in patients with history of arterial events (arterial thrombosis and history of both venous and arterial event) from intention to treat study reports; with the use of a fixed effect, the result would also have been significantly different, but would reflect a less conservative approach (results of fixed effects models are not shown, but available as needed). In the same way, we didn't show a statistical higher risk of thrombosis in patients with triple positivity whereas Cerdà et al. did. With fixed effects models, the risk of thrombosis was statistically higher during DOACs treatment also (results are not shown, available as needed). We chose to use random effects models for all statistical tests in this meta-analysis to have comparable conservative results. These results are in line with the existence of a higher thrombotic risk with DOACs in APS patients with history of arterial thrombosis and triple positivity and suggest a lack of statistical power [4,5,17,18].

Regarding the higher risk of arterial event during DOACs treatment, the assumption has been made that while DOACs target only one coagulation factor VKAs inhibit both classical pathways of coagulation. A better inhibition of coagulation pathways during VKAs treatment may explain these results. A insufficient drug concentration is an alternative hypothesis because of it has been shown in animal models that a stronger inhibition of Xa and an higher dose of rivaroxaban were necessary to prevent arterial thrombosis than venous thrombosis [19]. Another explanation of insufficient drug concentration and treatment failure may be poor treatment adherence. However, the adherence rates in TRAPS and EUDRA-2010-019764-36 studies was regarded as satisfactory [4,5]. Additional therapy with

hydroxychloroquine (HCQ) could prevent recurrent thrombosis lowering aPL titers [20–22]. In their study, Goldhaber et al. didn't report if APS patients were treated with HCQ. In TRAPS and EUDRA-2010-019764-36 studies, HCQ was used in a small proportion of patients however its use in patients with recurrent thrombosis wasn't reported and this small proportion of patients doesn't allow a firm conclusion. Nevertheless, the proportion of patients treated with HCQ was balanced in the two arms in both studies [4,5].

Finally, in APS patients with history of arterial thrombosis, the use of low dose aspirin with VKAs are often considered. In these studies, only a small proportion of patients took aspirin. It is well known that the control of cardiovascular risk factors is crucial to avoid arterial thrombotic event during APS, whether these risk factors were strictly controlled has not been reported in detail in the primary studies. Moderate thrombocytopenia is frequently reported in primary APS and SLE associated APS. It seems to be associated with high-risk aPL profile, lupus flare and recurrent thrombosis [23,24]. Moderate thrombocytopenia could promote the occurrence of thrombosis reflecting a high-risk thrombotic profile with platelet consumption. Moreover marked or profound thrombocytopenia may warrant to stop antithrombotic agents and favor subsequent thrombosis. In studies included in this meta-analysis, association of recurrent thromboses with thrombocytopenia or the occurrence of a lupus flare wasn't described.

In this meta-analysis, no higher risk of recurrent VTE over time was shown. In the RAPS study, in which patients with history of arterial thrombosis were excluded, there was no recurrent thrombotic event during 6 months of follow-up [3]. The study of Goldhaber et al. analyzed patients with an acute VTE. Even if history of arterial thrombosis was not an exclusion criterion, the incidence of arterial thrombotic events was not reported [6].

We previously conducted an IPD meta-analysis in which the global thrombotic risk during DOACs treatment was 16% [17] and then we conducted a sub-group analysis excluding high-

risk APS patients (history of arterial/small vessels thrombosis and triple positivity) and we found a lower thrombotic risk (8.6%) equivalent to an annual thrombotic risk recurrence of 8.4% [25]. These previous published results could suggest a good safety of DOACs in patients without history of arterial thrombosis or triple positivity. However, the lack of dedicated RCT with only non-high-risk APS patients does not allow a definitive conclusion about the safety of DOACs in all of these patients. Importantly, in another meta-analysis of observational data, the annual proportion for recurrent thrombotic event in APS patients with previous VTE who were taking mainly vitamin K antagonists therapy was much lower: 2.7% [26]. This suggest that overall reports of DOACs in APS are subject to a publication bias selecting a significant proportion of high risk patients.

We did not show a higher bleeding risk during DOACs treatment. However, bleeding risks in RCTs do not reflect those in general population due to selection of low bleeding risk patients and a better monitoring during studies.

Differently from our previously published meta-analysis on individual patient data (IPD) [17], we focused here on RCTs and and we included additional RCTs compared to Sanchez-Redondo et al. and Cerdà et al. However, even the present meta-analysis has some limitations. The first is the small number and the significant clinical heterogeneity of included studies. However, we included all data available and we have significant results. For the definition of outcomes, we used the definition of recurrent thrombosis in each study which was the occurrence of arterial or venous thrombosis based on objective imaging techniques. Thus limitations are those of each study. In two studies included in this meta-analysis, TRAPS and EUDRA-2010-019764-36 studies, there was a higher thrombotic risk during DOACs treatment but also a higher number of patients with an high risk thrombotic profile:

100% of triple positivity in TRAPS and more than 50% of patients in EUDRA-2010-019764-36 had an history of arterial thrombosis [4,5]. One the contrary RAPS study included a sub-group of lower risk APS patients but had a very short clinical endpoint (6 months follow-up without any clinical event) [3]. Of note, the prespecified necessary number of subjects wasn't reached in the TRAPs study (overall planned sample size was more than 500 subjects) because the study was prematurely stopped. The study by Goldhaber et al. was a post-hoc analysis of data from RE-COVER®, RE-COVER II™ and RE-MEDY™ studies and wasn't performed specifically to study APS patients and did not report arterial or small vessels thromboses. Furthermore in these studies, not all patients were tested for thrombophilia, the diagnosis of thrombophilia wasn't centralized and for aPL, it didn't follow the Sydney criteria with a confirmation test at 12 weeks [6].


The present meta-analysis showed an increased risk of arterial thrombosis during DOACs treatment and tended towards a higher thrombotic risk in patients with history of arterial thrombosis and triple positivity. These results support the international guidelines which recommend against the use of DOACs in patients with history of arterial thrombosis and triple positivity [7,8,27].

We found no increased risk of venous thrombosis nor a significantly increased thrombotic risk in patient with a history of venous thrombosis only. However, we can't give a definitive conclusion about the safety of DOACs based on these sole data. EULAR guidelines and the Guidance from the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis (ISTH) have proposed that DOACs could be considered in patients not able to achieve a target INR despite good adherence to VKAs or those with contraindications to VKAs or those treated with DOACs for several months with good adherence and without recurrent thrombosis which wouldn't change their treatment despite

appropriate information [8,27]. Nevertheless, if these patients are treated with DOACs, it seems crucial to follow them in order to prospectively record the occurrence of recurrent thrombosis in a large registry [28]. In this context, we are setting up an international registry of thrombotic APS patients treated with DOACs: the OBSTINATE registry (https://apsnancy.com/Research-Projects.php). If the registry confirms a low rate of thrombotic events during DOACs in APS patients without history of arterial and/or small vessels thrombosis and/or triple positivity, their safety could be confirmed in a dedicated RCT.

5. Conclusion

This meta-analysis summarizes all existing RCT of DOACs in APS patients compared to VKAs. Our results do not show a higher risk of recurrent VTE or bleeding during DOACs compared to VKA in APS patients. However, we confirm a high and significant risk of arterial recurrent thrombosis, which seems to be more frequent in patients with a history of arterial thrombosis. In order to confirm the safety of DOACs in an APS patients sub- group, additional studies are warranted.

**Figures**

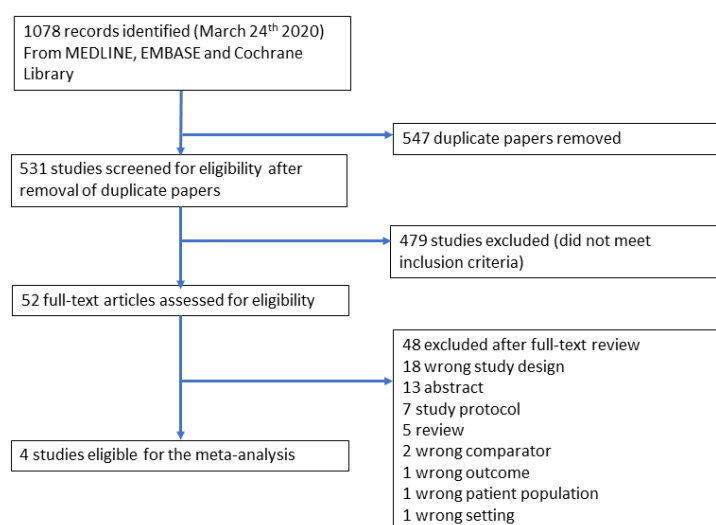Figure 1: Flow chart of study identification for meta-analysis



Figure 2: Occurrence of any (A), arterial (B) and venous (C) recurrent thrombosis during VKAs and DOACs treatment and (intention-to-treat method)
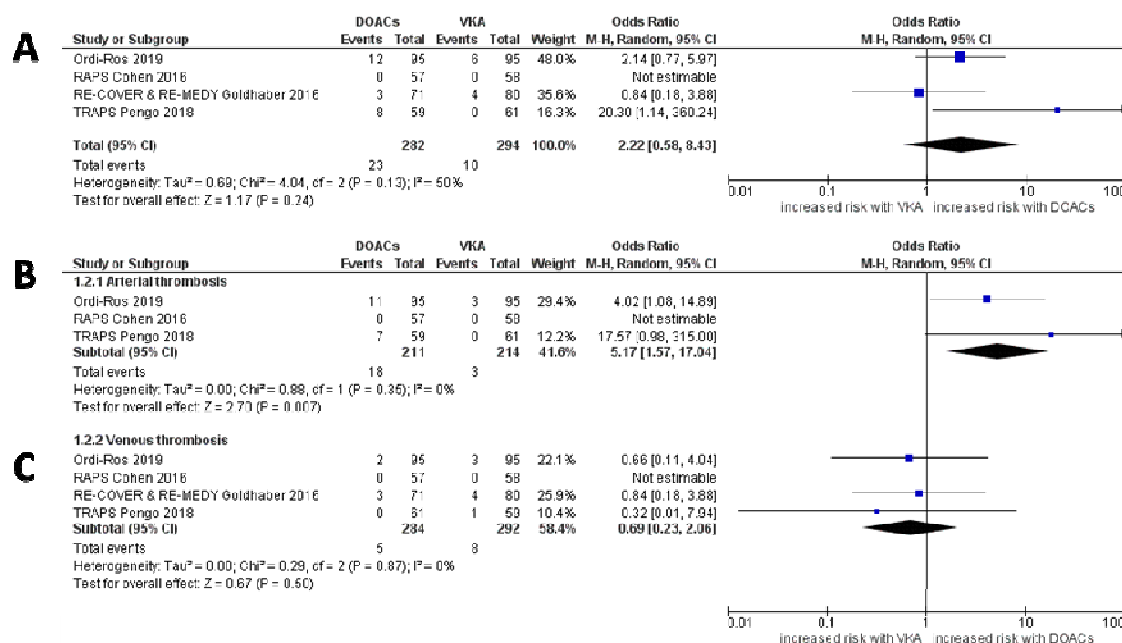
Figure 3: occurrence of thrombosis during DOACs and VKAs treatment in patients with previous arterial thrombosis (A), previous VTE only (B) or triple positivity (C)
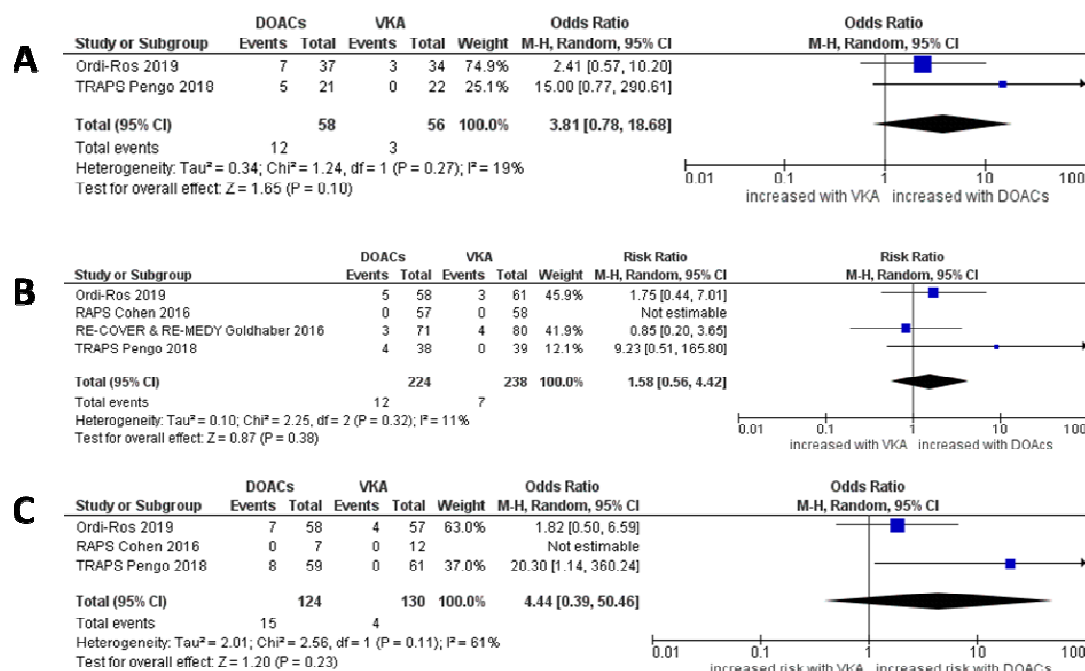


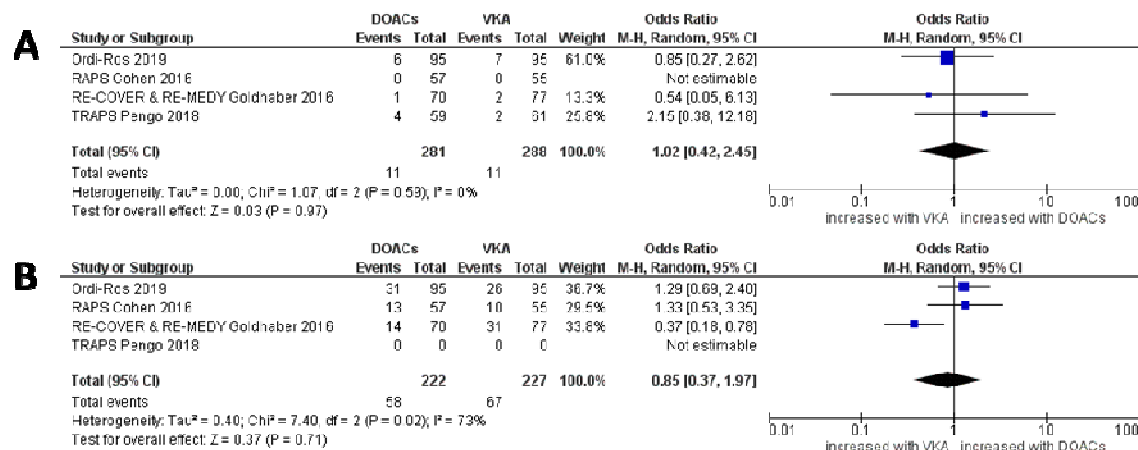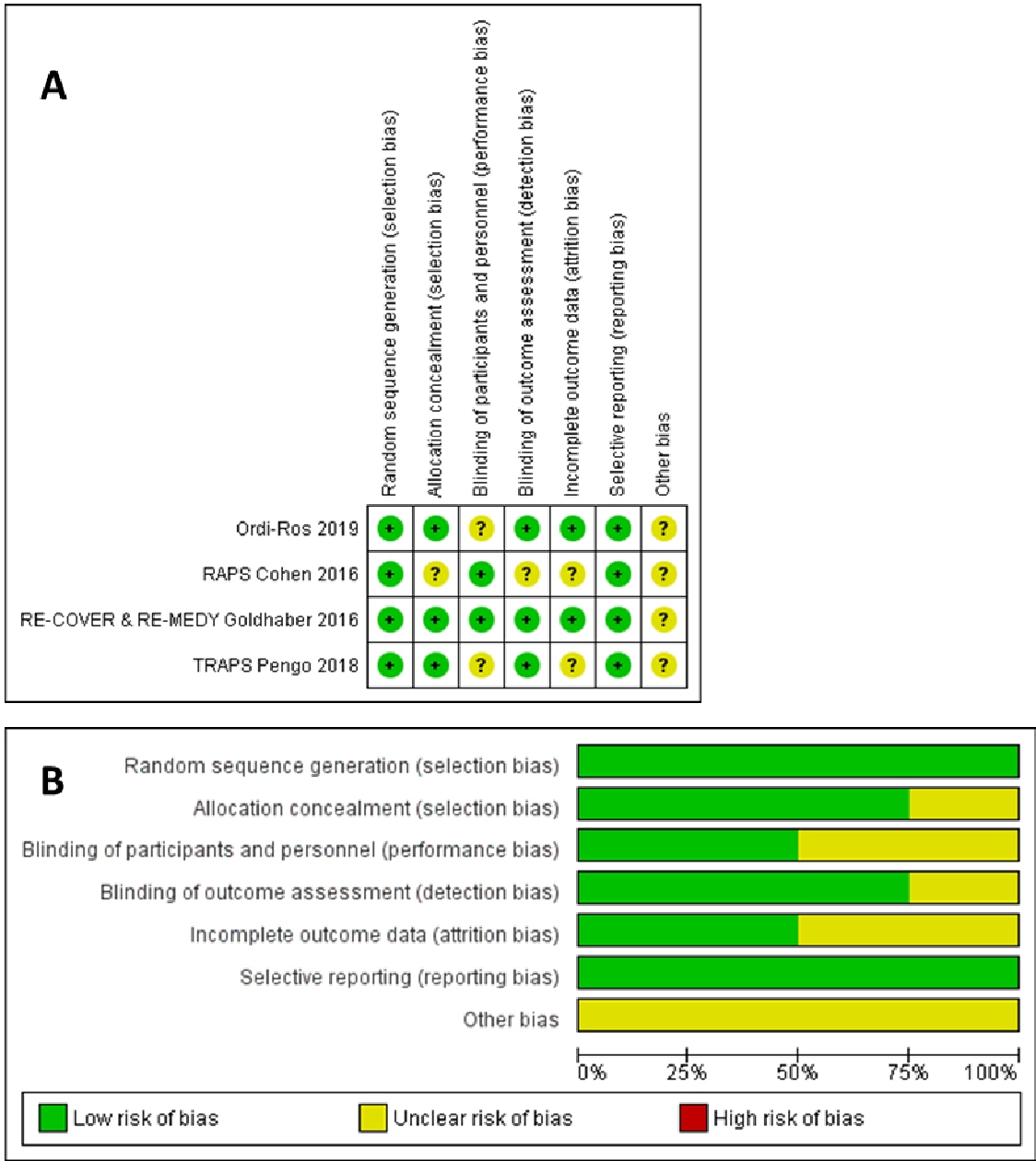Figure 4: Occurrence of major bleeding (A) and any bleeding (B) during DOACs and VKAs

Figure 5: Risk for bias assessment (A) and summary of the risk for bias (B)

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Table 1: Main characteristics of included RCT

| First author | Name of study | Year | Country | Number of randomized patients | DOACs and dose, n (%) | Triple positivity, % | Duration of follow up | Thrombosis (DOACs vs VKA ) |
|---|---|---|---|---|---|---|---|---|
| H. Cohen [3] | RAPS | 2016 | United Kingdom | Rivaroxaban n=57 Warfarin n=59 | Rivaroxaban 20mg OD: 55 (96%) Rivaroxaban 15mg OD: 2 (4%) | 25% | 210 days | 0% vs 0% |
| V. Pengo [4] | TRAPS | 2018 | Italy | Rivaroxaban n=59 Warfarin n= 61 | Rivaroxaban 20mg OD: 57 (97%) Rivaroxaban15mg OD: 2 (3%) | 100% | 611 days | 22% vs 3% |
| J. Ordi-Ros [5] | EUDRA-2010-019764-36 | 2019 | Spain | Rivaroxaban n=95 Acenocoumarol n=95 | Rivaroxaban 20mg OD: 90 (95%) Rivaroxaban15mg OD: 5 (5%) | 61.1% | 35.4 months | 12.6% vs 6.3% |
| S.Z. Goldhaber [6] | RE-COVER®, RE-COVER II™, and RE-MEDY™ | 2016 | International | Dabigatran etexilate n=71 Warfarin n=80 | Dabigatran etexilate 150mg BID : 71 (100%) | NR | NR | 4.2% vs 5% |

BID: Twice daily; NR: not reported; OD: Once daily; VKA: Vitamin K antagonist