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Therapy with direct oral anticoagulants for secondary prevention of thromboembolic events in the antiphospholipid syndrome: a systematic review and meta-analysis of randomised trials

Josefine B H Adelhelm,[1] Robin Christensen,[2,3] Gustavo G M Balbi,[4] Anne Voss [1,3]

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For numbered affiliations see end of article.

Correspondence to
Dr Anne Voss; anne.voss@rsyd.dk

ABSTRACT

Objective Antiphospholipid syndrome (APS) is a systemic autoimmune disorder characterised by venous thrombosis (VT) or arterial thrombosis (AT) and/or pregnancy morbidity and the presence of antiphospholipid antibodies. Direct oral anticoagulants (DOACs) hold several advantages to vitamin K antagonists (VKAs) for prevention of thrombosis and we wish to evaluate DOACs compared with VKAs in secondary prevention of thromboembolic events in patients with APS.

Methods We conducted searches of the published literature using relevant data sources (MEDLINE, Embase and Cochrane CENTRAL), and of trial registers for unpublished data and ongoing trials. We included randomised trials examining individuals >18 years with APS classified according to the criteria valid when the trial was carried out. Randomised controlled trials had to examine any DOAC agent compared with any comparable drug. We tabulated all occurrences of events from all eligible randomised trials. Due to few events, ORs and 95% CIs were calculated using the Peto method.

Results 5 randomised trials comprising 624 patients met the predefined eligibility criteria. The primary outcome measure was new thrombotic events, a composite endpoint of any VT or AT, during the VKA-controlled phase of treatment. According to the I^2 inconsistency index, there was evidence of statistical heterogeneity across the studies (I^2=60%). Across trials, 29 and 10 thrombotic events were observed in 305 and 319 patients with APS treated with DOAC and VKA, respectively, corresponding to a combined Peto OR of 3.01 (95% CI 1.56 to 5.78, p=0.001). There was a significantly increased risk of AT while treated with DOACs compared with VKA (OR 5.5 (2.5, 12.1) p<0.0001), but no difference in the risk of VT (p=0.87). We found no significant difference in risk of bleeding.

Conclusions DOACs were associated with a significant increase in the risk of a new thrombotic event, especially AT, favouring standard prophylaxis with warfarin.

PROSPERO registration number CRD42019126720.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Vitamin K antagonists (VKAs) are the only anticoagulants recommended for secondary prevention of thrombosis in antiphospholipid syndrome (APS), and we wish to evaluate direct oral anticoagulants (DOACs) compared with VKAs for this.

WHAT THIS STUDY ADDS

⇒ DOACs were associated with a significant increase in the risk of a new thrombotic event, especially arterial thrombosis, favouring standard prophylaxis with warfarin.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The results of our meta-analysis might suggest that a subset of patients with APS with only venous thrombosis history might benefit from DOAC treatment. Since scientific studies so far report the results heterogeneously, we propose in future to use a core outcome set in this area of research.

INTRODUCTION

Background

Antiphospholipid syndrome (APS) is a systemic autoimmune disorder characterised by venous thrombosis (VT) or arterial thrombosis (AT) and/or pregnancy morbidity in the presence of antiphospholipid antibodies (aPL) on two or more occasions at least 12 weeks apart. The aPL include lupus anticoagulant, anticardiolipin antibody or anti-β2 glycoprotein I IgG or IgM antibodies.[1] APS occurs as a primary condition, or secondary in the presence of, for example, SLE.[2] Evidence suggests that the aPL profile is prognostic, and triple positivity increases the risk of thromboembolic events.[3]

The European Alliance of Associations for Rheumatology recommends for secondary prophylaxis of thrombosis APS 'treatment with VKAs (vitamin K antagonists) with INR (internationalised normalised ratio) 2–3 or INR 3–4' considering the individual's risk of bleeding and recurrent thrombosis.

Treatment with VKA with INR 2–3 plus low-dose aspirin may also be considered.[4]

The pharmacodynamics of direct oral anticoagulants (DOACs) are inhibition of either factor IIa (thrombin; for example, dabigatran etexilate) or factor Xa (eg, rivaroxaban, edoxaban or apixaban). DOACs are easy to use with simple dosing, anticoagulation monitoring is not indicated and drug plasma levels should not be followed. However, dosage should be adjusted in patients with impaired renal or liver function.[5]

Rationale

Lifelong treatment with VKA implies frequent monitoring of INR and may be experienced as a burden by the patient, as indicated by scientific studies demonstrating a decrease in quality of life.[6] Furthermore, the dose–response relationship between coumarins and INR is affected by many factors including dietary habits, genetic interactions, drug interactions, etc, which may increase the risk of bleeding including life-threatening episodes.[7 8]

DOACs are recommended for secondary prophylaxis in patients with deep vein thrombosis and pulmonary embolism not related to APS,[5] and it is relevant to explore the potential of DOACs in secondary prevention of thromboembolic events in APS. If DOACs could replace VKA, partially or completely, we hypothesise that it could potentially reduce the risk of bleeding episodes and change the patient's perception of own illness. In 2016–2017, two authors[9 10] showed positive case reports on 23 and 24 patients with APS, respectively, treated with DOAC for secondary prophylaxis.

In 2021, a meta-analysis of randomised controlled trials (RCTs) by Dufrost *et al*[11] found a significantly higher risk of recurrent AT, but not for VT, when comparing DOACs with VKA for secondary prophylaxis. The same year, Aibar and Schulman published a meta-analysis on RCTs and cohorts comparing any antithrombotic regimen in APS,[12] and found that VKA was more effective than DOAC (relative risk (RR): 0.25; 95% CI: 0.07 to 0.93) to prevent recurrent AT. Both concluded that DOACs should not be used for patients with APS with a history of AT. Khairani *et al* confirmed this including four RCTs and emphasised that patients with thrombotic APS on DOACs compared with VKA have increased risk of AT.[13] Recently, Shah *et al* also found increased risk of stroke among patients with APS treated with DOACs and calculated RRs that may indicate DOACs to be associated with higher risks of thrombotic events.[14] In the present meta-analysis, we included data from all five present RCTs on patients with APS published 2016–2022 as seen below.

Objectives

Our objectives were to examine whether DOACs reduce the incidence of secondary APS-related AT and VT, by reviewing randomised trials that assess the efficacy and safety of these drugs for secondary prophylaxis in patients with APS.

METHODS

Protocol and registration

The review protocol was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols guidelines[15] and registered with the International Prospective Register of Systematic Reviews on 12 April 2019 (CRD42019126720); the original protocol is available as online supplemental appendix 1. The reporting of the systematic review and meta-analysis follows the recommendations from the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.[16]

Information sources and search strategy

Literature search strategies were developed in collaboration with a research librarian (LØ). We searched Cochrane Central Register of Controlled Trials, MEDLINE and Embase in May 2022 (see online supplemental appendix 2 for search strategy). The electronic database search was supplemented by searching ongoing trial registers: https://www.clinicaltrials.gov/; https://www.clinicaltrialsregister.eu/; https://www.who.int/ictrp/en and https://clinicaltrials.bayer.com/. We also scanned the reference lists of included studies and relevant reviews identified through the search. No language limits were imposed on the search.

Study selection and data extraction

Literature search results were uploaded to Covidence. The first review author (JBHA) screened the titles and abstracts yielded by the search against the eligibility criteria. We included RCTs examining individuals >18 years with APS classified according to the criteria valid when the trial was carried out. RCTs had to examine any DOAC agent compared with any comparable drug (ie, both active and placebo comparators). We obtained full reports for all titles that appeared to meet the eligibility criteria. Review authors (JBHA/AV) independently screened full-text reports and decided whether these met the inclusion criteria; we resolved disagreement through discussion (RC). The first review author (JBHA) extracted data from the included trials, using a customised Microsoft Excel spreadsheet database. All analyses were based on data reported on the intention-to-treat (ITT) principle whenever possible. The major efficacy outcome was incident thromboembolic events; other major outcomes were (1) bleeding and (2) death. Major bleeding was defined by the International Society on Thrombosis and Haemostasis as clinically overt bleeding associated with any of the following: (1) fatal outcome; (2) involvement of a critical anatomical site; and (3) fall in haemoglobin concentration of at least 20 g/L or the need for transfusion of ≥2 units of packed red blood cells or whole blood.[17]

Risk of bias in individual studies

We used the Cochrane Collaboration tool[18] to facilitate the assessment of possible risk of bias and evaluated five bias domains: selection bias (random sequence

generation and allocation concealment); performance bias (blinding of participants and personnel); detection bias (blinding of outcome assessment); attrition bias (incomplete outcome data) and reporting bias (selective reporting). Each bias domain was graded low risk, high risk or unclear risk. Then, each RCT was assigned an overall risk of bias in terms of low risk (low for all key domains), high risk (high for ≥1 key domain) and unclear risk (unclear for ≥1 key domain).

Statistical analysis

Anticipating that the major outcomes would correspond to rare outcome events, we followed recommendations of Bradburn *et al*[19] and used Peto ORs and 95% CIs as the primary analysis approach to compare the DOAC and comparator groups.

Because all trials had similar duration of follow-up for all treatment groups, the use of ORs represents a valid approach to assessing the risk associated with the use of DOAC. Trials in which patients had no events in either group were excluded from analyses. P values are two sided. We tested for heterogeneity with the Cochran's Q-test and used the method proposed by Higgins *et al* to measure inconsistency, where I^2 is interpreted as the percentage of total variation across several studies due to heterogeneity.[20] Results in forest plots present Peto OR estimates and 95% confidence for each major outcome, to give a visual suggestion of the amount of study heterogeneity and of the overall combined results of the included studies. While the primary meta-analyses were based on ORs and 95% CIs calculated with the use of the Peto method, we also performed meta-analyses using absolute risk differences as the effect measure, applying both a fixed and random-effects approach. Subgroup analyses and sensitivity analyses using alternative meta-analysis approaches are presented in online supplemental appendices 3–6. Data were analysed with the use of Review Manager V.5.3 (The Cochrane Collaboration).

Outcome Reporting Bias In Trials

Outcome reporting bias (ORB) occurs when variables are selected for publication based on their results.[21] To explore the risk of ORB, an outcome matrix was produced to help identify missing study outcome data. In the outcome matrix, the outcomes of interest in the review and how they were reported in the trial are listed in the columns and the different studies listed in the rows. The Outcome Reporting Bias In Trials (ORBIT) Matrix enabled us to evaluate the risk of ORB in the qualitative evidence synthesis. Further, the following were also done: (1) checking the reasons, when available, for excluding studies to ensure that no studies were excluded because they did not report the outcomes of interest in the review; and (2) assessing the eligible studies as to whether the review outcomes of interest were reported and what other core outcomes were reported in the included trials. If important outcomes were not reported, authors were contacted for information.

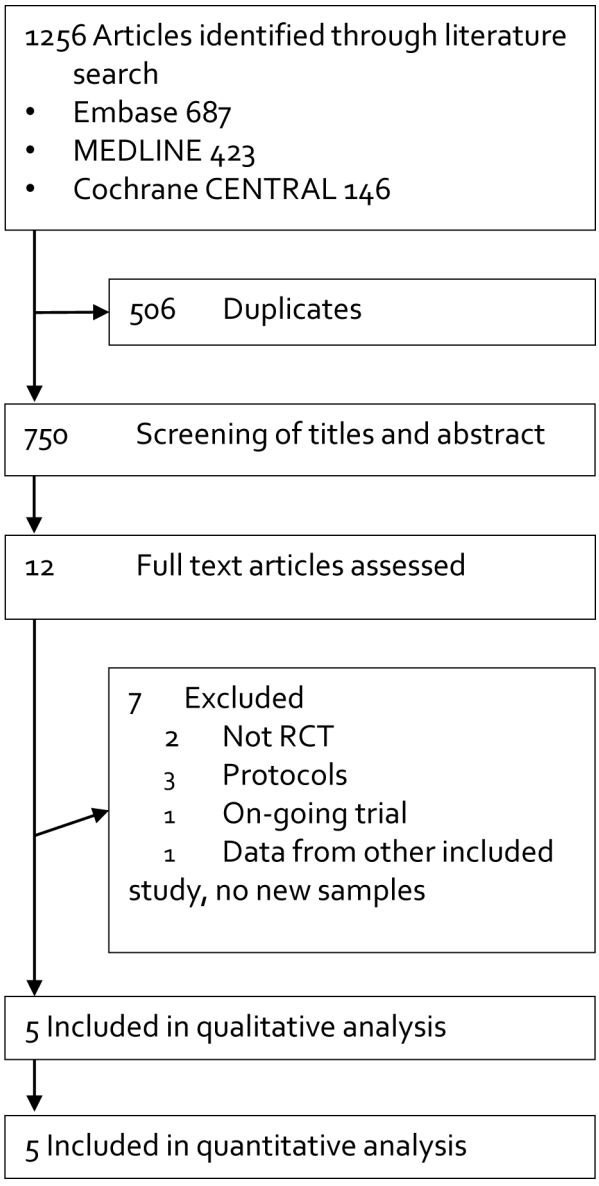

Figure 1 PRISMA flow chart of studies included. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RCT, randomised controlled trial.

Patient and public involvement

The present research questions were conceived from patients' inquiries in the outpatient clinic. Patient partners were involved when the review protocol was prepared. The results will be presented in national patient partner groups.

RESULTS

Results of the search

As illustrated in figure 1, 750 studies were identified from the databases after de-duplication. After title and abstract screening by JBHA, 738 articles were excluded, leaving 12 articles for full-text scrutiny by JBHA and AV. Searching trial registries, we found one ongoing trial (ClinicalTrials.gov no. NCT03684564, RISAPS). Six publications met the inclusion criteria[22–27] for qualitative analysis, but just five

studies were included in the review, since Arachchillage *et al*[23] analysed data from the RAPS trial.[24] Goldhaber *et al*[26] performed post-hoc subgroup analysis based on data from RE-COVER I+II[28 29] and RE-MEDY.[30]

Qualitative evidence synthesis

Description of included studies

Study and patient characteristics of the five eligible randomised trials[22 24–27] are listed in table 1. The included studies comprised 305 patients with APS treated with rivaroxaban 20 mg/day or dabigatran etexilate 150 mg two times per day and 320 comparators treated with VKA (warfarin, target INR 2.0–3.0). The patients included in Goldhaber *et al*[26] and the RAPS trial[24] had a history of VT only, whereas patients in the other studies had histories of both venous and arterial events. The pooled mean age for the DOAC group was 47.2 years (SD 13.8) and 47.7 years (SD 15.5) for the VKA group. The pooled body mass index (BMI) for the DOAC group was 28 kg/m^2 (SD 6) and 28.8 kg/m^2 (SD 6) for the VKA group. Overall, the groups were comparable in terms of age, BMI and sex. However, the percentage of patients with APS with SLE varies noticeably, from 9% in the Woller *et al*[22] DOAC group to 33% in the Ordi-Ros *et al*[27] DOAC group; only the RAPS was stratified for SLE. Woller *et al*, Ordi-Ros *et al* and TRAPS[25] have collected data on cardiovascular risk factors; 36% of the DOAC group and 40% in the VKA group were smokers; 32% of the DOAC group and 29% of the VKA group had known hyperlipidaemia; 32% of the DOAC group and 35% of the VKA group had hypertension. Less than 10% in each group had diabetes.

Description of ongoing studies

Still underway, the RISAPS trial (ClinicalTrials.gov ID: NCT03684564) will compare higher-intensity rivaroxaban 15 mg two times per day versus higher-intensity warfarin (INR 3.0–4.0) for 24 months, in patients with APS, with or without SLE, after experiencing a stroke, a transient ischaemic attack or other ischaemic brain damage caused by blood clots in the brain arteries or smaller blood vessels. Planned completion is end of 2024, and the trial manager has been contacted for an update in June 2022.

Thromboembolic events

As seen in figure 2A, the pooled number of thromboembolic events was 29 in the DOAC group and 10 in the warfarin group. The summary OR for thromboembolic events was statistically significant (3.01 (95% CI 1.56 to 5.78)) with a moderate-to-large degree of inconsistency (I^2=60%), also visualised by individual OR values ranging from 0.84 (95% CI 0.18 to 3.82) to 10.33 (95% CI 1.9 to 56.3).

Bleeding and death

Bleeding events are shown as overall events in figure 2B and the subgroup of major bleeding events is shown in figure 2C. For overall bleeding events, there were a total of 63 events in the DOAC group(s) and 70 in the warfarin group, corresponding to a summary OR for bleeding events of 0.92 (95% CI 0.62 to 1.37) which was not significant. All trials further subgrouped for major bleeding events, as seen in figure 2C. With 11 major bleeding events in the DOAC group and 12 in the warfarin group and an OR 0.94 (95% CI 0.41 to 2.17, p=0.88), there was also no significant difference between treatment groups for major bleeding events. Figure 2D shows that there were no deaths related to treatment, but only three studies report this outcome. One cardiovascular death was observed in the TRAPS trial[25] in a patient from the DOAC group with known heart failure; the death occurred 433 days after suspension of DOAC while the patient was back on warfarin. Unfortunately, due to the outcome reporting method of Goldhaber *et al*,[26] it is unclear whether Goldhaber *et al* observed any deaths related to VT in the study period or only non-fatal VTs.

Subgroup analyses

Risk of thrombosis in subgroups of the trial population was analysed based on type of thrombosis, thrombosis history prior to trial inclusion and triple aPL positivity (forest plots of ORs in online supplemental appendix 6). There was a significantly increased risk of AT while treated with DOACs compared with VKA (OR 5.5, 95% CI 2.5 to 12.1, p<0.0001), whereas there was no difference in the risk of VT (p=0.87).

DOACs were significantly worse than VKA for secondary prophylaxis, especially among patients with a history of AT (OR 5.5 (95% CI 2.1 to 14.7) p=0.0006). Although less harmful, DOACs were also inferior to VKA in patients with a history of VT (OR 2.7 (95% CI 1.2 to 6.1) p=0.01). The risk of thrombosis for the subgroup of aPL triple-positive patients was higher with DOACs than VKA (OR 3.8 (95% CI 1.66 to 8.65) p=0.002). Unfortunately, not all trials characterised how many patients had a history of both AT and VT or described the patients' aPL profiles.

Other outcomes

Due to three strokes in the DOAC arm, Woller *et al*[22] doubled the daily dose of DOAC, after inclusion of 25 patients. Nevertheless, three more events occurred and subsequently all patients with a history of AT were excluded. Ordi-Ros *et al*[27] registered catastrophic APS in one patient receiving DOAC. The RAPS trial[24] measured thrombin generation as a primary efficacy endpoint and the endogenous thrombin potential was significantly higher in the DOAC group as compared with the warfarin group at day 42, but it did not reach the prespecified non-inferiority threshold of less than 20% difference in mean percentage change. RAPS trial also measured quality of life and found no difference between treatment groups in terms of health utility, but a small difference in the visual analogue score favoured the DOAC group (mean difference 6.5 (95% CI 1.4 to 11.5) p=0.013). Patient satisfaction with DOAC was significantly higher than with warfarin, assessed by Woller *et al*.[22]

Table 1 Characteristics of included randomised trials

Study	Country	DOAC	Duration of follow-up	Sample size	Age, years	BMI, kg/m^2, mean (SD)	Female sex, %	Triple positive, %	Previous thrombotic event, %	
									Arterial	Venous
Woller *et al*[22] ASTRO-APS	USA	Apixaban 2.5 mg (5 mg) two times per day	365 days	Apixaban n=23 VKA n=25	Apixaban mean 46 (SD 12) VKA mean 49 (SD 14)	Apixaban 31 (8) VKA 32 (6)	Apixaban 83 VKA 84	Apixaban 30 VKA 28	Apixaban 26 VKA 44	Apixaban 87 VKA 72
Ordi-Ros *et al* [27] EUDRA-2010-019764-36	Spain	Rivaroxaban 20 mg once daily	35.4 months	Rivaroxaban n=95 VKA n=95	Rivaroxaban median 47 (IQR 40–55) VKA median 51 (IQR 38–63)	Rivaroxaban 28 (5.1) VKA 29 (6.0)	Rivaroxaban 64 VKA 63	Rivaroxaban 17.2 VKA 8.8	Rivaroxaban 39 VKA 36	Rivaroxaban 73 VKA 74
Pengo *et al*[25] TRAPS	Italy	Rivaroxaban 20 mg once daily	611 days	Rivaroxaban n=59 VKA n=61	Rivaroxaban mean 46.5 (SD 10) VKA mean 46.1 (SD 13)	Rivaroxaban 26.1 (6) VKA 25.5 (6)	Rivaroxaban 66 VKA 62	Rivaroxaban 100 VKA 100	Rivaroxaban 19 VKA 23	Rivaroxaban 64 VKA 64
Cohen *et al*[24] RAPS	UK	Rivaroxaban 20 mg once daily	210 days	Rivaroxaban n=57 VKA n=59	Rivaroxaban mean 47 (SD 17) VKA mean 50 (SD 14)	Rivaroxaban 28 (6) VKA 30 (6)	Rivaroxaban 74 VKA 71	Rivaroxaban 12 VKA 20	Rivaroxaban 0 VKA 0	Rivaroxaban 100 VKA 100
Goldhaber *et al*[26] RE-COVER, RE-COVER II and RE-MEDY	USA	Dabigatran etexilate 150 mg two times per day	210 days	Dabigatran etexilate n=71 VKA n=80	Dabigatran etexilate mean 48 (SD 15) VKA mean 47 (SD 19)	Dabigatran etexilate 29 (7) VKA 29 (6)	Dabigatran etexilate 34 VKA 39	N/A	Dabigatran etexilate 0 VKA 0	Dabigatran etexilate 100 VKA 100

BMI, body mass index; DOAC, direct oral anticoagulant; N/A, not available; VKA, vitamin K antagonist.

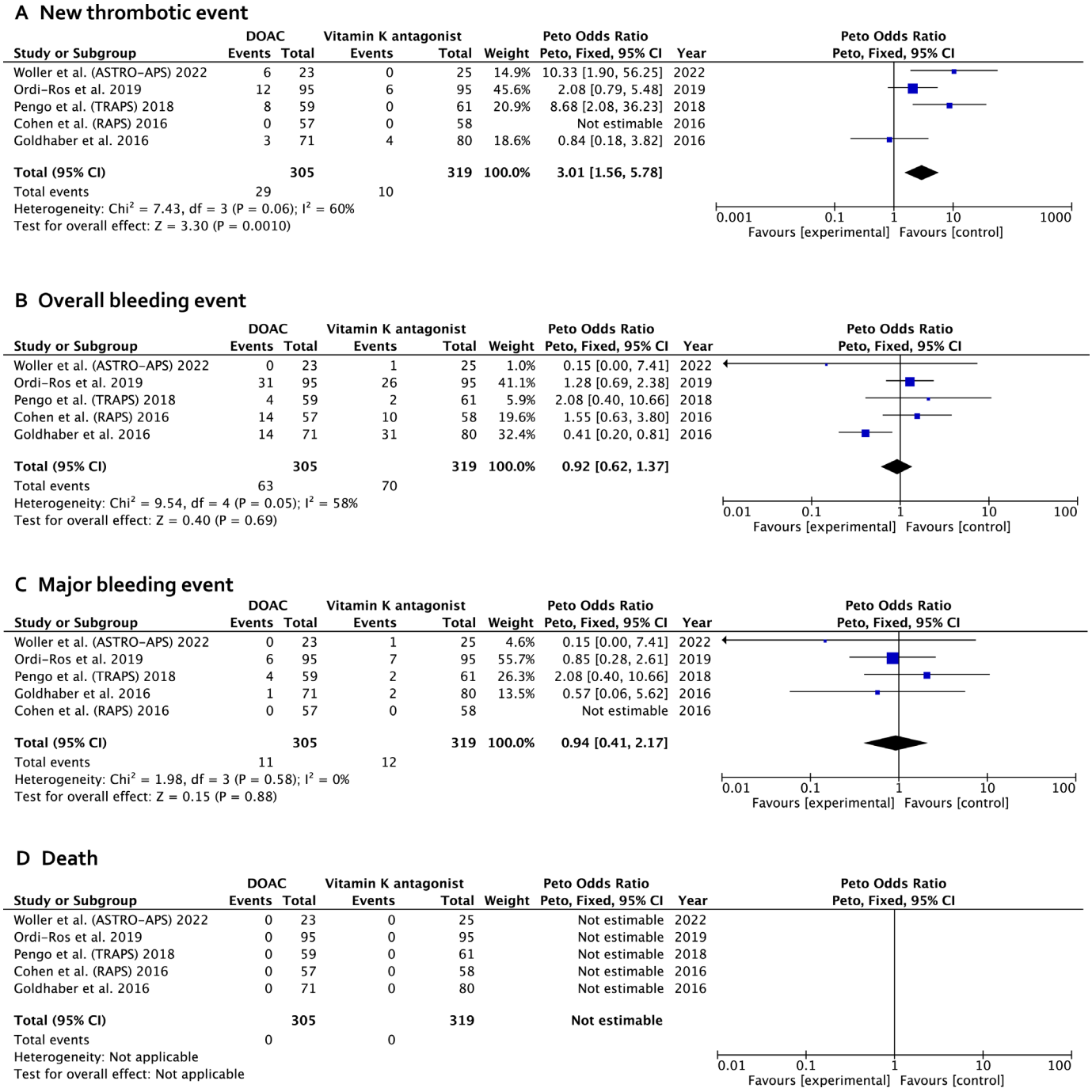

Figure 2 Forest plots of outcomes (A–D) for comparison of DOACs versus warfarin (Peto OR). DOAC, direct oral anticoagulant.

Risk of bias in included studies

Figure 3A presents our risk of bias assessments for each of the eligible studies, supported by figure 3B illustrating each risk of bias item presented as percentages across all included studies.

All of the included trials used correct methods of randomisation and correct allocation concealment, minimising risk of selection bias on the included individuals. Only Goldhaber *et al*[26] used double-blinding, the other trials found the need to do open-label studies. For outcomes such as thrombosis and bleeding, we estimate that they have been objectively evaluated and most trials had blinded committees assess potential outcomes as prespecified in the protocols. However, because of a lack of blinding of participants reporting on their perceived change in quality of life and satisfaction with anticoagulant treatment, we judge a high risk of performance bias, due to the subjective nature of the outcome measures. There are no available data on the reason for 6.3% attrition in each treatment group in Ordi-Ros *et al*,[27] and Goldhaber *et al*[26] do not comment on the reason for a large proportion of loss to follow-up in RE-MEDY (20%) or the proportion of patients with APS lost to follow-up. Hence, risk of attrition bias is high in these studies. Selective

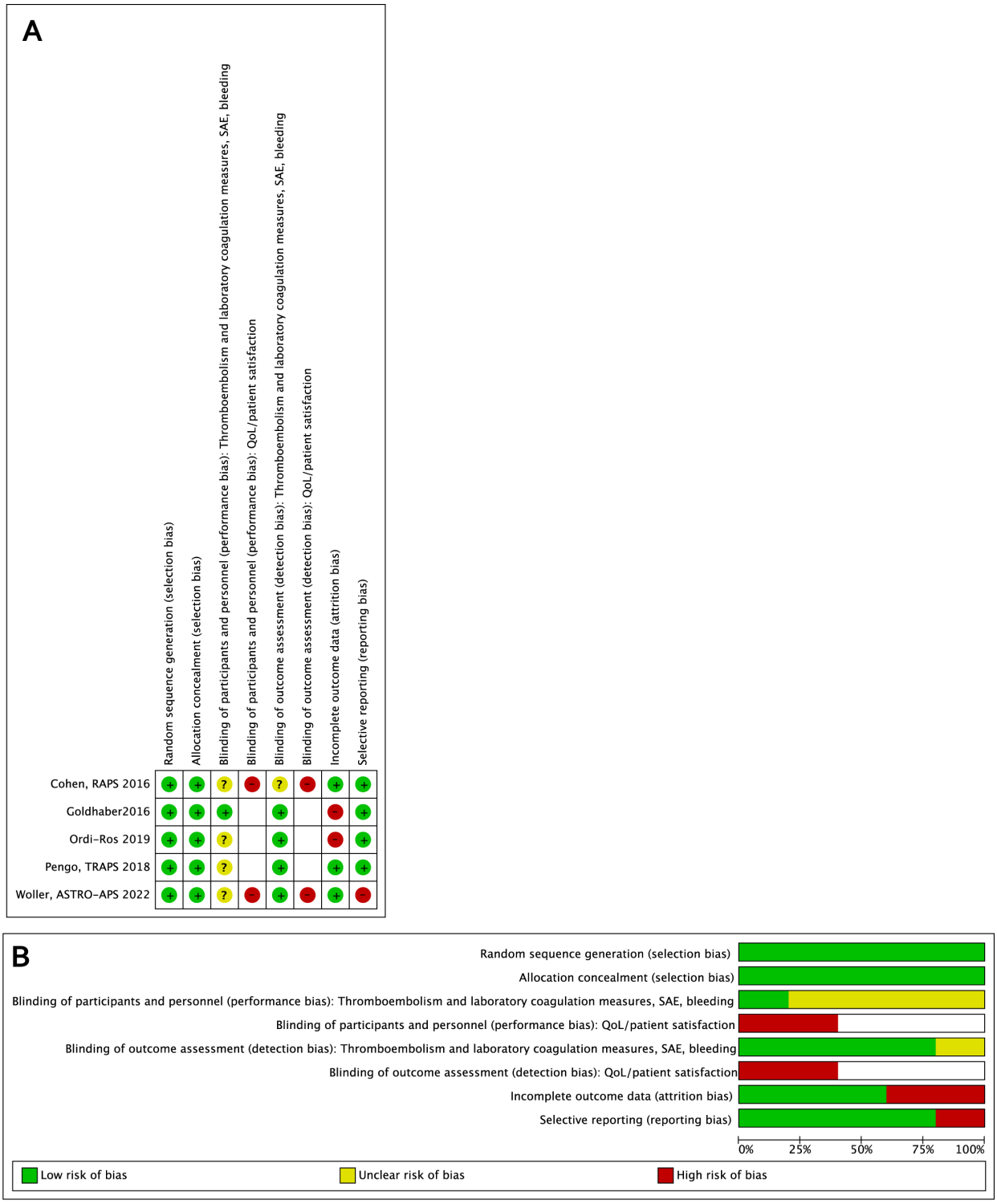

Figure 3 (A) Risk of bias summary and (B) risk of bias graph. QoL, quality of life; SAE, serious adverse event.

reporting bias is generally low, but when compared with the study protocol, Woller *et al*'s study[22] lacks outcome data on metrics of ability to include patients, compliance and nuisance bleeding.

DISCUSSION

In our comprehensive literature search, five clinical trials were identified, two had to modify the study protocol and both terminated early, due to excess of events in the intervention drug arm and due to low patient accrual, respectively.[22 25] The results of the meta-analysis have some limitations: only five RCTs are available, with a total study population of just 625 patients. Additionally, each individual study has several limitations. For instance, the study by Goldhaber *et al*[26] was a post-hoc analysis of three RCTs, which were not designed to examine patients with

APS, as they did not test all patients for thrombophilia and positivity for aPL was not confirmed after a minimum of 12 weeks, as required by classification criteria.[1]

Besides APS history and type of anticoagulant treatment, other risk factors such as age and smoking should be considered, when evaluating a person's cardiovascular risk. A 2013 cross-sectional study[31] found that the combination of smoking and aPL antibodies was strongly associated with vascular events. Hence, 35–40% of the trial population in this meta-analysis are smokers and none of the included RCTs took this confounder into account. Previously, a 'two-hit hypothesis' has been suggested for APS. In addition to persistent positivity for aPL, a 'second hit' is required to 'trigger' events. Factors such as inflammation, infection, genetic predispositions, age, smoking and traditional cardiovascular risk factors (hypertension, diabetes mellitus, hyperlipidaemia, obesity, etc) are all suggested as 'second hits' and should be controlled for when trying to understand the real impact of DOACs in patients with APS.[32 33]

The results might partly be biased by the heterogeneity regarding thrombosis history and autoantibody profile in the trial populations, for example, patients in Goldhaber *et al* and RAPS[24] had a history of only VT and unknown antibody profile, whereas patients in the TRAPS trial[25] had previous VT or AT and were triple aPL positive. In the as-treated analysis of thrombotic events in Woller *et al*,[22] after excluding patients with a history of AT, the rate of events in the DOAC arm was one-third of the ITT analysis. Through subgroup analyses, we found the risk of thrombosis in patients with a history of AT to be twice as high as those with a history of VT, but with reservations that some patients had a history of both AT and VT. In short, this might indicate a potential role of DOACs in selected populations with APS, and the choice of treatment may be stratified according to aPL profile and/or whether the thromboembolic history included venous or arterial events.

The follow-up time in the included studies varies from 7 months in RAPS and Goldhaber *et al* to 36 months in Ordi-Ros *et al*, the latter reporting the highest number of thromboembolic events and bleeding events. Indeed, the APS ACTION registry showed that even though higher than the general population, incident thrombotic events in APS are rare, 2.09 events per 100 patient-years based on almost 4000 patient-years of follow-up.[34] Hence, more events might potentially have been observed in the other trials, if patients had been followed for a longer period of time.

Due to the limited number of available publications in this area, it is not surprising that a core outcome set has not yet been developed. Nevertheless, the major core outcomes were measured in all five included studies. Inspired by table 2, we suggest the following three tiers of outcome measurements for future trials: *tier 1* core outcomes: new thrombotic event (venous/arterial/microvascular), bleeding (clinically relevant, major/minor), all-cause death and cardiovascular death. *Tier 2* consideration for most trials: quality of life/patient satisfaction, anatomical location of thrombotic event, anatomical location of bleeding event, compliance, catastrophic APS. *Tier 3* consideration for some trials: time in therapeutic range for VKA, significant decrease in haemoglobin level, need for blood transfusion.

All three major review outcomes regarding benefit and harm were reported in all of the included trials as shown in the ORBIT Matrix in table 2.

Differences between protocol and review: we prespecified bleeding as a review outcome of interest, but did not distinguish between major, minor, clinically relevant, etc. In the meta-analysis, we chose to arrange the analysis into overall bleeding and major bleeding, to make results more accurate and clinically relevant.

CONCLUSION

After a comprehensive literature search, this systematic review and meta-analysis summarises all available RCTs for the use of secondary prophylaxis with DOACs versus VKA in patients with APS, including the latest ASTRO-APS Study. We found no clinical value in choosing DOACs over VKA for secondary thrombosis prophylaxis in patients

Table 2 ORBIT Matrix for assessment of outcome reporting bias in included trials

	Outcomes in review			Other relevant core outcomes							
Study	New TE	Bleeding	Death	QoL/PS	TE: venous	TE: arterial	CRB	MBE	Adverse events	Compliance	CAPS
Woller *et al*[22]	✔	✔	✔	✔	✔	✔	✔	✔			
Ordi-Ros *et al*[27]	✔	✔	✔		✔	✔	✔	✔		✔	✔
TRAPS 2018[25]	✔	✔	✔		✔	✔		✔			
Goldhaber *et al*[26]	✔	✔			✔		✔	✔			
RAPS[24]	✔	✔	✔	✔	✔	✔	✔	✔	✔		

✔: full reporting of outcome.
CAPS, catastrophic antiphospholipid syndrome; CRB, clinically relevant bleeding; MBE, major bleeding event; ORBIT, Outcome Reporting Bias In Trials; PS, patient satisfaction; QoL, quality of life; TE, thromboembolism.

with APS. In fact, DOACs seem to be less effective, especially to those experiencing incident AT. A change from VKA to DOAC does not occur to be beneficial for the patients with APS in terms of risk of bleeding.

However, a subset of patients with APS with only VT history might benefit from DOAC treatment, but this should be addressed by well-designed trials. We suggest the trial outcomes mentioned above as the core outcome set in this area of research and encourage the Outcome Measures in Rheumatology Initiative to further define a core domain set for trials in patients with APS.

Author affiliations
[1]Department of Rheumatology, Odense University Hospital, Odense, Denmark
[2]Section for Biostatistics and Evidence-Based Research, the Parker Institute, Copenhagen University Hospital, Copenhagen, Denmark
[3]Department of Clinical Research, University of Southern Denmark Faculty of Health Sciences, Odense, Denmark
[4]Department of Clinical Medicine, Federal University of Juiz de Fora, Juiz de Fora, Brazil

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Contributors JBHA—guarantor, conceptualisation, methodology, formal analysis, investigation, writing and visualisation. RC—methodology, formal analysis and writing. GGMB—validation, writing, reviewing and editing. AV—conceptualisation, validation, investigation, writing and supervision.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Not required.

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Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as supplemental information.

ORCID iD
Anne Voss http://orcid.org/0000-0001-6582-2636

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Effectiveness of Anticoagulant Therapy for Antiphospholipid Syndrome: *Protocol for a systematic review of randomised trials with focus on outcome reporting*

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Authors/Collaborators

Josefine Bak Højer Christensen, BScMed[1], Professor Robin Christensen, MSc, PhD[1,2,], Lasse Østengaard[3], Gustavo Guimarães Moreira Balbi, MD[4] and Anne Voss, MD, PhD[1]

Affiliations

1: Research Unit of Rheumatology, Department of Clinical Research, University of Southern Denmark, Odense University Hospital, Denmark.

2: Musculoskeletal Statistics Unit, The Parker Institute, Bispebjerg and Frederiksberg Hospital, Denmark & Department of Rheumatology, Odense University Hospital, Denmark.

3: Research Department of Evidence Based Medicine, University Library of Southern Denmark, Denmark.

4: Department of Rheumatology, Hospital Universitário, Universidade Federal de Juiz de Fora, Juiz de Fora, MG, Brazil.

Corresponding Author

Associate Professor & Consultant Anne Voss, MD, PhD (ORCID iD: 0000-0001-6582-2636)

Department of Rheumatology, Odense University Hospital

Sdr. Boulevard 29, Building 2, Entrance 96, 130 or 132, 1st floor, 5000 Odense C

E-mail: Anne.Voss@rsyd.dk / +45 2917 7041

ABSTRACT

Background: Antiphospholipid Syndrome (APS) is defined as a systemic autoimmune disorder characterised by venous or arterial thrombosis and/or pregnancy morbidity in the presence of persistent laboratory evidence of antiphospholipid antibodies (aPL) (1). The currently recommended thrombosis prophylaxis therapy in APS patients is lifelong vitamin K antagonist with a target Internationalised Normalised Ratio of 2-3 (2). Frequent monitoring is required when patients are prescribed Vitamin K Antagonists (VKA), meaning an economic and personal burden (3). The dose-response relationship between INR and coumarins is affected by many factors including nutritional status incl. vitamin K intake, genetic interactions, drug interactions, smoking and alcohol use, renal, hepatic and cardiac function etc. (3). The aim of this systematic review is to evaluate the effectiveness and harms associated with use of Direct Oral Anticoagulants (DOACs) in patients with APS compared with VKA or other comparators, for the potential benefit of patient safety and increased life quality.

Methods and Analysis: We will include randomised controlled trials examining individuals (>18 years) with APS that compare any DOAC agents with any comparable drug class. We will search for eligible studies in Embase, Medline and Cochrane Central Register of Controlled Trials (CENTRAL) and grey literature (e.g. trial registers and reference lists of included studies. We will screen the titles and abstracts yielded by the search against the inclusion criteria. We will obtain full reports for all titles that appear to meet the inclusion criteria or where there is any uncertainty and we will then independently screen the full text reports. To facilitate the assessment of possible risk of bias for each study, we will collect information using the Cochrane Collaboration tool (4). We will examine heterogeneity between trials with a standard Q-test statistic (testing the hypothesis of homogeneity) (5) and present the I^2 value. Primary outcome of interest is: Secondary thromboembolic events. Among the secondary outcomes are *(i)* catastrophic APS (secondary thrombosis in >3 organs in less than a week), *(ii)* bleeding; and *(iii)* death, as well as other minor outcomes.

Discussion: The findings of this review will provide evidence for decision-making with regards to therapy of choice for patients with APS, possibly determining whether DOACs should be considered an equal therapy to VKA or other prophylactic therapy. Furthermore, we will focus on outcome reporting/mapping from the eligible RCTs.

Systematic review registration: Registered with the International Prospective Register of Systematic Reviews (PROSPERO) on 2019-04-12. Registration number: CRD42019126720.

INTRODUCTION

Background

Antiphospholipid Syndrome (APS) is defined as a systemic autoimmune disorder characterised by venous or arterial thrombosis and/or pregnancy morbidity in the presence of persistent laboratory evidence of antiphospholipid antibodies (aPL). APS occurs as a primary condition, or it can occur in the presence of Systemic Lupus Erythematosus (SLE) or another systemic autoimmune disease (1).

The currently recommended thrombosis prophylaxis therapy in APS patients is lifelong vitamin K antagonist (e.g. warfarin) with a target internationalised normalised ratio (INR) of 2-3 (2). The evidence for primary prophylaxis (patients with positive aPL without a history of thrombosis) is sparse - hence anticoagulant treatment is aimed at secondary prophylaxis (1).

Various terms have been used to describe a therapeutic class of oral anticoagulants - the DOACs. Terms in the medical literature include: Direct Oral Anticoagulants (DOAC), Novel or New or Non-Vitamin K Oral Anticoagulants (NOAC) and target-specific oral anticoagulants (TSOAC) (6). In this protocol we will use the term DOAC.

The pharmacodynamics of DOACs are inhibition of either factor IIa (thrombin; e.g. dabigatran) or factor Xa (e.g. rivaroxaban, edoxaban or apixaban). Normally, there is no indication for anticoagulation monitoring for the DOACs, and drug plasma levels should not be followed or used for dose adjustments (6).

Rationale

Frequent monitoring is required when patients are prescribed Vitamin K Antagonists (VKA), meaning an economic and personal burden (3). The dose-response relationship between INR and coumarins is affected by many factors including nutritional status incl. vitamin K intake, genetic interactions, drug interactions, smoking and alcohol use, renal, hepatic and cardiac function etc. (3). A recent literature review by Signorelli et al. (7) reviewed the therapeutic trends and potential future treatments of APS and concluded that the results of on going trials, in particular those examining DOACs and the efficacy and safety of new immunomodulatory therapies in APS, are needed to inform future treatment recommendations in this area of high unmet need (7).

Knowing that DOACs holds advantageous properties of prophylactic treatment in other diseases, such as prevention of stroke in patients with atrial fibrillation (8), systematic reviews indicate that the evidence may be less in trials of medical and surgical prophylaxis (9).

Aim and Objectives

The aim of the systematic review is to evaluate the effectiveness and harms associated with use of DOAC in patients with APS compared with vitamin K antagonists or other comparators. Our objectives are to examine whether DOACs reduce the incidence of APS-related arterial and venous thromboembolism, by reviewing randomised, controlled trials that assessed the efficacy (or safety) of these drugs for secondary prophylaxis. Additionally, other manifestations related to APS will be registered (see *Data items*). As a secondary objective we will systematically explore the outcome domains and measurement instruments reported across the available trials and evaluate how likely it is that these trials are subject to selective reporting bias.

The systematic review will address the following questions:

1. When compared with vitamin K antagonists or other comparators, what are the comparative effectiveness and harms of DOACs in the prevention of thromboembolic events of patients with APS?

2. Is there an advantage of DOACs or are the treatments comparable in terms of benefit and harm?

3. Which outcome measurements are used in the available literature? Explicit focus on outcome reporting/mapping from the eligible RCTs.

METHODS

Protocol and registration

This protocol was conducted in accordance with the PRISMA-P guidelines and registered with the International Prospective Register of Systematic Reviews (PROSPERO) on 2019-04-12. Registration number CRD42019126720.

Eligibility criteria

Studies will be considered potentially eligible based on the following criteria.

Study designs: We will include randomised controlled trials (RCTs) including cluster RCTs, excluding cross-over designs.

Participants: We will include studies examining individuals (>18 years) with APS diagnosed according to the criteria valid when the study was carried out.

Interventions and comparators: We will include studies that compare any DOAC agents, or their combinations, at any dose and administered using any mode of delivery, with any comparable drug class.

Information sources and Search strategy

Literature search strategies will be developed using subject headings and free text search related to our research question. We will search Cochrane Central Register of Controlled Trials (CENTRAL), Medline and Embase. The electronic database search will be supplemented by searching on-going trials registers: US National Institutes of Health Ongoing Trials Register (www.ClinicalTrials.gov); European Trials Register (www.clinicaltrialsregister.eu); The World Health Organization (WHO) International Trials Registry Platform (www.who.int/ictrp/en). To ensure literature saturation, we will scan the reference lists of included studies or relevant reviews identified through the search. If there is time, we will search databases of pharmaceutical companies and contact experts on the topic.

No language limits will be imposed on the search, although only studies in languages other than English that can be translated adequately using Google translate will be included, due to resource limits. The specific search strategies will be created in collaboration with a Research Librarian (LØ) from the University of Southern Denmark with expertise in systematic review searching. A draft search strategy is included in appendix 1.

Study selection

Literature search results will be uploaded to Covidence. The first review author (JBHC) will screen the titles and abstracts yielded by the search against the inclusion criteria. We will obtain full reports for all titles that appear to meet the inclusion criteria or where there is any uncertainty. Review authors (JBHC/AV) will then independently screen the full text reports and decide whether these meet the inclusion criteria. We will resolve disagreement through discussion. We will record the reasons for

excluding trials. Neither of the review authors will be blind to the journal titles or to the study authors or institutions.

Data collection process

We will to the best of our abilities use Covidence for data extraction. If difficulties occur, we will also apply a customised Microsoft Excel spread sheet database. The first review author (JBHC) will extract data from the included trials, supervised by AV. One review author (RC) will additionally perform random check across all the data extracted.

Data items

We will extract data on study settings, duration of intervention, population inclusion and exclusion criteria as well as population characteristics, details of interventions and co-interventions, as well as details of outcomes and their definitions. We will extract the generic and trade name of the experimental intervention, the type of comparator used, dosage, patient characteristics (average age, gender, mean duration of symptoms), trial design, trial size, duration of follow-up, type and source of financial support and publication status from trial reports.

Major outcomes:

Primary: Secondary thromboembolic events. Among the secondary outcomes are *(i)* catastrophic APS (secondary thrombosis in >3 organs in less than a week), *(ii)* bleeding; and *(iii)* death.

Minor outcomes: Osteonecrosis, indicent organ dysfunction due to infarctions, e.g. Adrenal Insufficiency, pulmonary hypertension, proteinuria etc., haemolytic anaemia, transverse myelitis, superficial thrombophlebitis, Libman-Sacks endocarditis, Budd-Chiari syndrome, first case of epilepsy, psychosis or migraine.

Risk of bias in individual studies

To facilitate the assessment of possible risk of bias for each study, we will collect information using

the Cochrane Collaboration tool (4).

Table 1: Risk of bias domains

Bias domain	**Bias item**	**Support for judgment**	**Review authors' judgment (assess as *low, unclear* or *high* risk of bias)**
Selection bias	Random sequence generation	Describe the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups.	Selection bias (biased allocation to interventions) due to inadequate generation of a randomised sequence.
	Allocation concealment	Describe the method used to conceal the allocation sequence in sufficient detail to determine whether intervention allocations could have been foreseen before or during enrolment.	Selection bias (biased allocation to interventions) due to inadequate concealment of allocations before assignment.
Performance bias	Blinding of participants and personnel*	Describe all measures used, if any, to blind trial participants and researchers from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective.	Performance bias due to knowledge of the allocated interventions by participants and personnel during the study.
Detection bias	Blinding of outcome assessment*	Describe all measures used, if any, to blind outcome assessment from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective.	Detection bias due to knowledge of the allocated interventions by outcome assessment.
Attrition bias	Incomplete outcome data*	Describe the completeness of outcome data for each main outcome, including attrition and exclusions from the analysis. State whether attrition and exclusions were reported, the numbers in each intervention group (compared with total randomised participants), reasons for attrition or exclusions where reported, and any reinclusions in analyses for the review.	Attrition bias due to amount, nature, or handling of incomplete outcome data.
Reporting bias	Selective reporting	State how selective outcome reporting was examined and what was found.	Reporting bias due to selective outcome reporting.

Summary measures

We will describe study characteristics according to sample size, characteristics of study participants, study duration, duration of treatment and source of funding. Because our outcomes of interest are rare, we will follow recommendations of Bradburn and colleagues (10) and use Peto Odds Ratios to compare the DOAC and comparator groups. We report results including 95% confidence intervals and forest plots for both measures so that findings can be compared. We will estimate a relative risk for each trial, computed from summary statistics. Results in forest plots will be reported as Peto's Odds Ratio estimates and 95% confidence intervals; with the extent of inconsistency measured using I^2 statistics and between study heterogeneity represented in prediction intervals (11).

Synthesis of results

Evidence synthesis will be provided based on the information presented in the text and tables to summarise and explain the characteristics and findings of the included studies. We will explore the relationship and findings both within and between the included studies, in line with the guidance from the Centre for Reviews and Dissemination (12). If possible (i.e. two or more trials reporting on the same PICO question) we will perform as described above; the statistical heterogeneity and inconsistency will be assessed with the I^2 statistic (13). For sensitivity analyses, we will also use inverse variance methods under fixed and random effects models for the outcomes with the largest number of treatment events; random effects models can be problematic for meta-analyses of rare events.

Anticipating rare event rates (14) we will combine the individual study results by performing meta-analyses using SAS software (version 9.4), applying a restricted maximum likelihood (REML) method to estimate the between study variance and the outcome data (15, 16). We will examine heterogeneity between trials with a standard *Q*-test statistic (testing the hypothesis of homogeneity) (5) and present the I^2 value, which can be interpreted as the percentage of total variation across several studies due to heterogeneity (13). On the basis of combined estimates, we will estimate the number needed to treat and the number needed to harm, with 95% confidence intervals, since this method enables direct translation into clinical practice; these data will be calculated on the basis of the combined relative measure, applying the overall event rate in the placebo group as a proxy for baseline risk (17). To investigate potential sources of clinical heterogeneity, we will assess the extent to which study-level variables are associated with safety by fitting REML-based meta-regression

models (18).

We are interested in the following subgroup analyses for the primary outcomes by age (<40 v ≥40), sex (<50% male v ≥50% male), ethnicity (<50% white v ≥50% white), smoking status (smokers v majority non-smokers) and whether or not the study was sponsored by a pharmaceutical company. Studies will not be categorised as sponsored by a pharmaceutical company if the drug was provided at no cost by the manufacturer and/or if the research was investigator initiated—that is, the drug and some funding was provided by the manufacturer although there was no other involvement in study conduct or publication and data were independently held by the researchers. Whenever possible, tests for subgroup differences will be performed.

Outcome Reporting Bias In Trials (ORBIT) Matrix

Outcome reporting bias (ORB) occurs when variables are selected for publication based on their results. This can impact upon the results of a meta-analysis, biasing the pooled treatment effect estimate (19). The review will be assessed for ORB by 1) checking the reasons, when available, for excluding studies to ensure that no studies were excluded because they did not report the outcomes of interest in the review; 2) assessing the eligible studies as to whether the review outcomes of interest were reported. Each study will be classified using a system developed in the ORBIT (Outcome Reporting Bias In Trials) project to indicate whether ORB is suspected and we will provide the reason for the suspicion. Authors of trials that do not report the outcomes of interest will be contacted for information. Thus our review will not exclude trial per default if they have not reported the outcomes of interest; rather we will consider the potential for outcome reporting bias in all eligible trials.

Risk of bias across studies

We will perform stratified analyses according to methodological characteristics of the trials accompanied by appropriate tests for interaction between trial characteristic and effect estimates. In order to determine whether reporting bias is present, we will determine whether the protocol of the RCT was published before recruitment of patients of the study was started. For studies published after May 2004 we will screen the Clinical Trial Register at the International Clinical Trials Registry Platform of the World Health Organisation (https://www.who.int/ictrp/en/). We will evaluate whether selective reporting of outcomes is present (outcome reporting bias). We will compare the fixed effect estimate against the random effects model to assess the possible presence of small sample bias in the published literature (i.e. in which the intervention effect is more beneficial in smaller studies). In the presence of small sample bias, the random effects estimate of the intervention is more beneficial than the fixed effect estimate. The potential for reporting bias will be further explored by funnel plots if ≥10 studies are available.

Appendix 1 Draft for Search Strategy in Embase

Database(s): **Embase Classic+Embase** 1947 to 2019 March 14
Search Strategy: 15-03-2019 kl. 10.15

#	Searches	Results
1	antiphospholipid syndrome/	15303
2	(Antiphospholipid Antibody Syndrome or Anti-Phospholipid Antibody Syndrome).mp.	2124
3	ashersons.mp.	50
4	exp Antibodies, Antiphospholipid/	12683
5	((antiphospholipid or anti-phospholipid or phospholipid or anti-cardiolipin or anticardiolipin or cardiolipin or beta 2-glycoprotein I) adj5 (auto$ or antibod$ or syndrome or inhibit$)).mp.	32767
6	1 or 2 or 3 or 4 or 5	32771
7	Anticoagulant$.mp. or anticoagulant agent/	179703
8	((anticoagula* or anti-coagula* or antithrombotic or anti thrombotic or anti-thrombotic) adj2 (agent$ or drug$ or therapy)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]	152669
9	anticoagulation.mp. or anticoagulation/	84179
10	(direct oral anticoagulant$ or DOAC$ or direct-acting oral anticoagulant$).mp.	3973
11	(new oral anticoagulant$ or Novel Oral Anticoagulant$ or non-vitamin K antagonist$ oral anticoagulant$ or NOAC$).mp.	7375
12	(target-specific oral anticoagulant$ or TSOAC).mp.	191
13	betrixaban.mp. or betrixaban/ or bevyxxa.mp.	528
14	factor Xa inhibitor.mp. or blood clotting factor 10a inhibitor/ or factor 10a inhibitor.mp.	4953
15	xarelto.mp. or rivaroxaban/	14092
16	apixaban.mp. or apixaban/ or (eliquis or eliques).mp.	9706
17	dabigatran etexilate/ or dabigatran/ or dabigatran.mp. or (pradaxa or pradax).mp.	13911
18	edoxaban.mp. or edoxaban/ or savaysa.mp.	3533
19	thrombin inhibitor$.mp. or thrombin inhibitor/ or antithrombin/ or direct thrombin inhibitor$.mp.	19316
20	(factor 2a inhibitor or factor IIa inhibitor).mp.	51
21	7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20	238670
22	(random$ or factorial$ or assign$ or allocat$).mp.	1936816
23	randomized controlled trial/	539212
24	(Randomized controlled trial or randomised controlled trial or randomzed controlled study or randomised controlled study).mp.	710748
25	22 or 23 or 24	1936816

26	6 and 21 and 25	561
27	6 and 21	11790

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Appendix B Search Strategies for *Therapy with Direct Oral Anticoagulants for Antiphospholipid Syndrome: A Systematic Review and Meta-Analysis of Randomized Trials*

PROSPERO CRD42019126720

Medline Search Strategy Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily

#1 Antiphospholipid Syndrome/
#2 (Antiphospholipid Antibody Syndrome or anti-phospholipid antibody syndrome).mp.
#3 ashersons.mp.
#4 exp Antibodies, Antiphospholipid/
#5 ((antiphospholipid or anti-phospholipid or phospholipid or anti-cardiolipin or anticardiolipin or cardiolipin or beta 2-glycoprotein) adj5 (auto$ or antibod$ or syndrome or inhibit$)).mp.
#6 1 or 2 or 3 or 4 or 5
#7 Anticoagulant$.mp. or Anticoagulants/
#8 ((anticoagula* or anti-coagula* or antithrombot* or anti thrombot* or anti-thrombot*) adj2 (agent$ or drug$ or therapy)).mp.
#9 (direct oral anticoagulant$ or DOAC$ or direct-acting oral anticoagulant$).mp.
#10 (new oral anticoagulant$ or Novel Oral Anticoagulant$ or non-vitamin K anticoagulant$ or NOAC$).mp.
#11 (target-specific oral anticoagulant$ or TSOAC).mp.
#12 (betrixaban or bevyxxa).mp.
#13 factor Xa inhibitor$.mp. or Factor Xa Inhibitors/ or factor 10a inhibitor$.mp.
#14 xarelto.mp. or Rivaroxaban/ or Rivaroxaban.mp.
#15 (apixaban or eliquis or eliques).mp.
#16 dabigatran.mp. or Dabigatran/ or dabigatran etexilate.mp. or pradaxa.mp. or pradax.mp.
#17 (edoxaban or Savaysa or Lixiana).mp.
#18 (thrombin inhibitor$ or antithrombin or direct thrombin inhibitor$).mp. or antithrombin

#19 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18
#20 ((randomized controlled trial or controlled clinical trial).pt. or randomized.ab. or randomised.ab. or clinical trials as topic.sh. or randomly.ab. or trial.ti.) not (exp animals/ not humans.sh.)
#21 6 and 19 and 20

Embase Search Strategy ***Classic+Embase***

#1 antiphospholipid syndrome/
#2 (Antiphospholipid Antibody Syndrome or Anti-Phospholipid Antibody Syndrome).mp.
#3 ashersons.mp.
#4 exp Antibodies, Antiphospholipid/
#5 ((antiphospholipid or anti-phospholipid or phospholipid or anti-cardiolipin or anticardiolipin or cardiolipin or beta 2-glycoprotein) adj5 (auto$ or antibod$ or syndrome or inhibit$)).mp.
#6 1 or 2 or 3 or 4 or 5
#7 Anticoagulant$.mp. or anticoagulant agent/
#8 ((anticoagula* or anti-coagula* or antithrombotic or anti thrombotic or anti-thrombotic) adj2 (agent$ or drug$ or therapy)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
#9 anticoagulation.mp. or anticoagulation/
#10 (direct oral anticoagulant$ or DOAC$ or direct-acting oral anticoagulant$).mp.
#11 (new oral anticoagulant$ or Novel Oral Anticoagulant$ or non-vitamin K antagonist$ oral anticoagulant$ or NOAC$).mp.
#12 (target-specific oral anticoagulant$ or TSOAC).mp.
#13 betrixaban.mp. or betrixaban/ or bevyxxa.mp.
#14 factor Xa inhibitor.mp. or blood clotting factor 10a inhibitor/ or factor 10a inhibitor.mp.
#15 xarelto.mp. or rivaroxaban/ or rivaroxaban.mp.
#16 apixaban.mp. or apixaban/ or (eliquis or eliques).mp.
#17 dabigatran etexilate/ or dabigatran/ or dabigatran.mp. or (pradaxa or pradax).mp.
#18 edoxaban.mp. or edoxaban/ or savaysa.mp. or Lixiana.mp.
#19 thrombin inhibitor$.mp. or thrombin inhibitor/ or antithrombin/ or direct thrombin inhibitor$.mp.
#20 (factor 2a inhibitor or factor IIa inhibitor).mp.
#21 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20
#22 double-blind procedure/ or randomized controlled trial/ or single-blind procedure/ or (random* or factorial* or placebo* or (doubl* adj blind*) or (singl* adj blind*) or assign* or allocat* or volunteer*).tw.
#23 6 and 21 and 22

CENTRAL Search Strategy *Cochrane Library – Central Register of Controlled Trials*

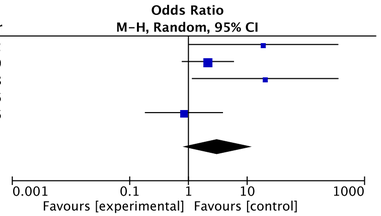
#1 MeSH descriptor: [Anticoagulants] explode all trees
#2 (anticoagulants or anticoagulation):ti,ab,kw (Word variations have been searched)
#3 (anticoagulation agent):ti,ab,kw (Word variations have been searched)
#4 (anticoagulation drugs):ti,ab,kw (Word variations have been searched)
#5 (anticoagulation therapy):ti,ab,kw (Word variations have been searched)
#6 (new oral anticoagulants or NOAC or novel oral anticoagulants or non-vitamin k antagonist oral anticoagulant):ti,ab,kw (Word variations have been searched)
#7 (direct oral anticoagulants or direct-acting oral anticoagulants or DOAC):ti,ab,kw (Word variations have been searched)
#8 (target specific anticoagulants or TSOAC):ti,ab,kw (Word variations have been searched)
#9 (betrixaban or bevyxxa):ti,ab,kw (Word variations have been searched)
#10 (factor xa inhibitor or factor 10a inhibitor):ti,ab,kw (Word variations have been searched)
#11 (xarelto or rivaroxaban):ti,ab,kw (Word variations have been searched)
#12 (apixaban or eliquis or eliques):ti,ab,kw (Word variations have been searched)
#13 (dabigatran or dabigatran etexilate or pradaxa or pradax):ti,ab,kw (Word variations have been searched)
#14 (edoxaban or savaysa or lixiana):ti,ab,kw
#15 (thrombin inhibitor or antithrombin or direct thrombin inhibitor):ti,ab,kw (Word variations have been searched)
#16 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 #15
#17 ("antiphospholipid syndrome"):ti,ab,kw (Word variations have been searched)
#18 MeSH descriptor: [Antiphospholipid Syndrome] explode all trees
#19 ("antiphospholipid antibody syndrome"):ti,ab,kw (Word variations have been searched)
#20 ("antiphospholipid antibodies"):ti,ab,kw (Word variations have been searched)
#21 ("antiphospholipid antibody"):ti,ab,kw (Word variations have been searched)
#22 ("anticardiolipin antibodies"):ti,ab,kw (Word variations have been searched)
#23 (anticardiolipin antibody):ti,ab,kw (Word variations have been searched)
#24 (beta 2 glycoprotein):ti,ab,kw (Word variations have been searched)
#25 #17 or #18 or #19 or #20 or #21 #22 #23 or #24
#26 #16 and #25

Appendix figure 1. Forest plots of review outcomes Odds Ratio Random

A: New thrombotic event

	DOAC		Vitamin K antagonist			Odds Ratio	
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Random, 95% CI**	**Year**
Woller et al. (ASTRO-APS) 2022	6	23	0	25	14.9%	18.94 [1.00, 358.35]	2022
Ordi-Ros et al. 2019	12	95	6	95	39.1%	2.14 [0.77, 5.97]	2019
Pengo et al. (TRAPS) 2018	8	59	0	61	15.4%	20.30 [1.14, 360.24]	2018
Cohen et al. (RAPS) 2016	0	57	0	58		Not estimable	2016
Goldhaber et al. 2016	3	71	4	80	30.6%	0.84 [0.18, 3.88]	2016
Total (95% CI)		**305**		**319**	**100.0%**	**3.14 [0.81, 12.16]**	
Total events	29		10				

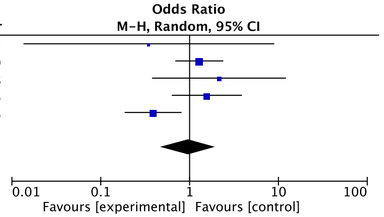
Heterogeneity: Tau² = 0.94; Chi² = 6.35, df = 3 (P = 0.10); I² = 53%
Test for overall effect: Z = 1.66 (P = 0.10)



B: Overall bleeding event

	DOAC		Vitamin K antagonist			Odds Ratio	
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Random, 95% CI**	**Year**
Woller et al. (ASTRO-APS) 2022	0	23	1	25	4.2%	0.35 [0.01, 8.96]	2022
Ordi-Ros et al. 2019	31	95	26	95	31.2%	1.29 [0.69, 2.40]	2019
Pengo et al. (TRAPS) 2018	4	59	2	61	11.7%	2.15 [0.38, 12.18]	2018
Cohen et al. (RAPS) 2016	14	57	10	58	24.4%	1.56 [0.63, 3.88]	2016
Goldhaber et al. 2016	14	71	31	80	28.4%	0.39 [0.19, 0.81]	2016
Total (95% CI)		**305**		**319**	**100.0%**	**0.96 [0.48, 1.95]**	
Total events	63		70				

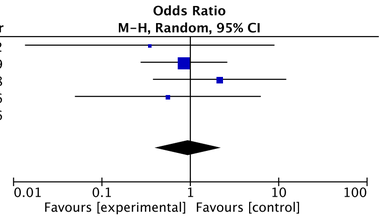
Heterogeneity: Tau² = 0.31; Chi² = 8.92, df = 4 (P = 0.06); I² = 55%
Test for overall effect: Z = 0.10 (P = 0.92)



C: Major bleeding event

	DOAC		Vitamin K antagonist			Odds Ratio	
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Random, 95% CI**	**Year**
Woller et al. (ASTRO-APS) 2022	0	23	1	25	6.9%	0.35 [0.01, 8.96]	2022
Ordi-Ros et al. 2019	6	95	7	95	56.8%	0.85 [0.27, 2.62]	2019
Pengo et al. (TRAPS) 2018	4	59	2	61	24.0%	2.15 [0.38, 12.18]	2018
Goldhaber et al. 2016	1	71	2	80	12.3%	0.56 [0.05, 6.28]	2016
Cohen et al. (RAPS) 2016	0	57	0	58		Not estimable	2016
Total (95% CI)		**305**		**319**	**100.0%**	**0.95 [0.40, 2.22]**	
Total events	11		12				

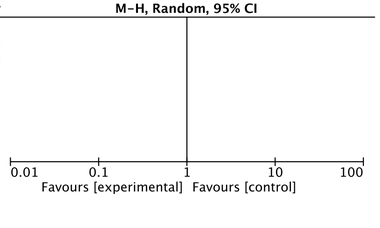
Heterogeneity: Tau² = 0.00; Chi² = 1.44, df = 3 (P = 0.70); I² = 0%
Test for overall effect: Z = 0.13 (P = 0.90)



D: Death

	DOAC		Vitamin K antagonist			Odds Ratio	
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Random, 95% CI**	**Year**
Woller et al. (ASTRO-APS) 2022	0	0	0	0		Not estimable	2022
Ordi-Ros et al. 2019	0	95	0	95		Not estimable	2019
Pengo et al. (TRAPS) 2018	0	59	0	61		Not estimable	2018
Cohen et al. (RAPS) 2016	0	57	0	58		Not estimable	2016
Goldhaber et al. 2016	0	0	0	0		Not estimable	2016
Total (95% CI)		**211**		**214**		**Not estimable**	
Total events	0		0				

Heterogeneity: Not applicable
Test for overall effect: Not applicable

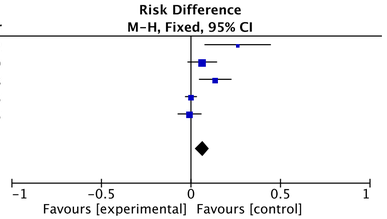


Appendix figure 2. Forest plots of review outcomes Risk Difference, Fixed

A: New thrombotic event

Study or Subgroup	DOAC Events	DOAC Total	Vitamin K antagonist Events	Vitamin K antagonist Total	Weight	Risk Difference M-H, Fixed, 95% CI	Year
Woller et al. (ASTRO-APS) 2022	6	23	0	25	7.7%	0.26 [0.08, 0.45]	2022
Ordi-Ros et al. 2019	12	95	6	95	30.5%	0.06 [-0.02, 0.15]	2019
Pengo et al. (TRAPS) 2018	8	59	0	61	19.2%	0.14 [0.04, 0.23]	2018
Cohen et al. (RAPS) 2016	0	57	0	58	18.4%	0.00 [-0.03, 0.03]	2016
Goldhaber et al. 2016	3	71	4	80	24.1%	-0.01 [-0.07, 0.06]	2016
Total (95% CI)		**305**		**319**	**100.0%**	**0.06 [0.03, 0.10]**	
Total events	29		10				

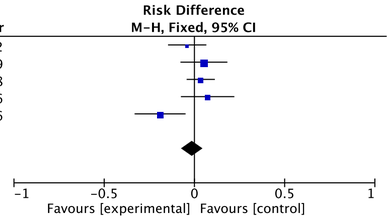
Heterogeneity: Chi² = 25.05, df = 4 (P < 0.0001); I² = 84%
Test for overall effect: Z = 3.24 (P = 0.001)



B: Overall bleeding event

Study or Subgroup	DOAC Events	DOAC Total	Vitamin K antagonist Events	Vitamin K antagonist Total	Weight	Risk Difference M-H, Fixed, 95% CI	Year
Woller et al. (ASTRO-APS) 2022	0	23	1	25	7.7%	-0.04 [-0.15, 0.07]	2022
Ordi-Ros et al. 2019	31	95	26	95	30.5%	0.05 [-0.08, 0.18]	2019
Pengo et al. (TRAPS) 2018	4	59	2	61	19.2%	0.04 [-0.04, 0.11]	2018
Cohen et al. (RAPS) 2016	14	57	10	58	18.4%	0.07 [-0.07, 0.22]	2016
Goldhaber et al. 2016	14	71	31	80	24.1%	-0.19 [-0.33, -0.05]	2016
Total (95% CI)		**305**		**319**	**100.0%**	**-0.01 [-0.07, 0.05]**	
Total events	63		70				

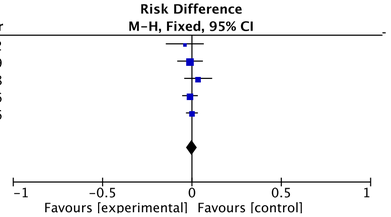
Heterogeneity: Chi² = 10.02, df = 4 (P = 0.04); I² = 60%
Test for overall effect: Z = 0.41 (P = 0.68)



C: Major bleeding event

Study or Subgroup	DOAC Events	DOAC Total	Vitamin K antagonist Events	Vitamin K antagonist Total	Weight	Risk Difference M-H, Fixed, 95% CI	Year
Woller et al. (ASTRO-APS) 2022	0	23	1	25	7.7%	-0.04 [-0.15, 0.07]	2022
Ordi-Ros et al. 2019	6	95	7	95	30.5%	-0.01 [-0.08, 0.06]	2019
Pengo et al. (TRAPS) 2018	4	59	2	61	19.2%	0.04 [-0.04, 0.11]	2018
Goldhaber et al. 2016	1	71	2	80	24.1%	-0.01 [-0.05, 0.03]	2016
Cohen et al. (RAPS) 2016	0	57	0	58	18.4%	0.00 [-0.03, 0.03]	2016
Total (95% CI)		**305**		**319**	**100.0%**	**-0.00 [-0.03, 0.03]**	
Total events	11		12				

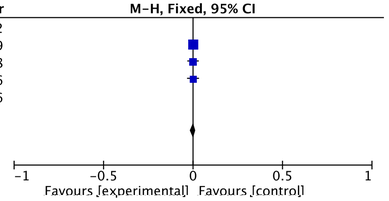
Heterogeneity: Chi² = 1.58, df = 4 (P = 0.81); I² = 0%
Test for overall effect: Z = 0.14 (P = 0.89)



D: Death

Study or Subgroup	DOAC Events	DOAC Total	Vitamin K antagonist Events	Vitamin K antagonist Total	Weight	Risk Difference M-H, Fixed, 95% CI	Year
Woller et al. (ASTRO-APS) 2022	0	0	0	0		Not estimable	2022
Ordi-Ros et al. 2019	0	95	0	95	44.7%	0.00 [-0.02, 0.02]	2019
Pengo et al. (TRAPS) 2018	0	59	0	61	28.2%	0.00 [-0.03, 0.03]	2018
Cohen et al. (RAPS) 2016	0	57	0	58	27.1%	0.00 [-0.03, 0.03]	2016
Goldhaber et al. 2016	0	0	0	0		Not estimable	2016
Total (95% CI)		**211**		**214**	**100.0%**	**0.00 [-0.02, 0.02]**	
Total events	0		0				

Heterogeneity: Chi² = 0.00, df = 2 (P = 1.00); I² = 0%
Test for overall effect: Z = 0.00 (P = 1.00)

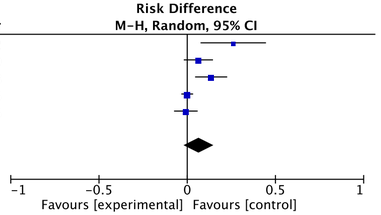


Appendix figure 3. Forest plots of review outcomes Risk Difference Random

A: New thrombotic event

Study or Subgroup	DOAC Events	DOAC Total	Vitamin K antagonist Events	Vitamin K antagonist Total	Weight	Risk Difference M-H, Random, 95% CI	Year
Woller et al. (ASTRO-APS) 2022	6	23	0	25	11.5%	0.26 [0.08, 0.45]	2022
Ordi-Ros et al. 2019	12	95	6	95	20.9%	0.06 [-0.02, 0.15]	2019
Pengo et al. (TRAPS) 2018	8	59	0	61	20.0%	0.14 [0.04, 0.23]	2018
Cohen et al. (RAPS) 2016	0	57	0	58	25.2%	0.00 [-0.03, 0.03]	2016
Goldhaber et al. 2016	3	71	4	80	22.5%	-0.01 [-0.07, 0.06]	2016
Total (95% CI)		**305**		**319**	**100.0%**	**0.07 [-0.02, 0.15]**	
Total events	29		10				

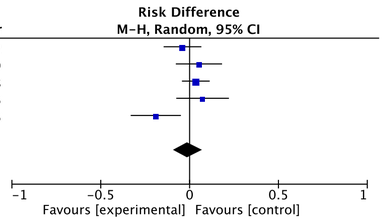
Heterogeneity: Tau² = 0.01; Chi² = 25.05, df = 4 (P < 0.0001); I² = 84%
Test for overall effect: Z = 1.60 (P = 0.11)



B: Overall bleeding event

Study or Subgroup	DOAC Events	DOAC Total	Vitamin K antagonist Events	Vitamin K antagonist Total	Weight	Risk Difference M-H, Random, 95% CI	Year
Woller et al. (ASTRO-APS) 2022	0	23	1	25	21.9%	-0.04 [-0.15, 0.07]	2022
Ordi-Ros et al. 2019	31	95	26	95	18.5%	0.05 [-0.08, 0.18]	2019
Pengo et al. (TRAPS) 2018	4	59	2	61	26.2%	0.04 [-0.04, 0.11]	2018
Cohen et al. (RAPS) 2016	14	57	10	58	16.3%	0.07 [-0.07, 0.22]	2016
Goldhaber et al. 2016	14	71	31	80	17.1%	-0.19 [-0.33, -0.05]	2016
Total (95% CI)		**305**		**319**	**100.0%**	**-0.01 [-0.09, 0.07]**	
Total events	63		70				

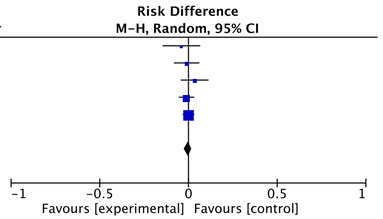
Heterogeneity: Tau² = 0.01; Chi² = 10.02, df = 4 (P = 0.04); I² = 60%
Test for overall effect: Z = 0.25 (P = 0.80)



C: Major bleeding event

Study or Subgroup	DOAC Events	DOAC Total	Vitamin K antagonist Events	Vitamin K antagonist Total	Weight	Risk Difference M-H, Random, 95% CI	Year
Woller et al. (ASTRO-APS) 2022	0	23	1	25	4.7%	-0.04 [-0.15, 0.07]	2022
Ordi-Ros et al. 2019	6	95	7	95	10.4%	-0.01 [-0.08, 0.06]	2019
Pengo et al. (TRAPS) 2018	4	59	2	61	8.8%	0.04 [-0.04, 0.11]	2018
Goldhaber et al. 2016	1	71	2	80	27.9%	-0.01 [-0.05, 0.03]	2016
Cohen et al. (RAPS) 2016	0	57	0	58	48.2%	0.00 [-0.03, 0.03]	2016
Total (95% CI)		**305**		**319**	**100.0%**	**-0.00 [-0.03, 0.02]**	
Total events	11		12				

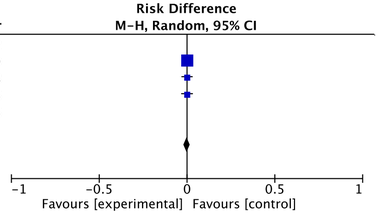
Heterogeneity: Tau² = 0.00; Chi² = 1.58, df = 4 (P = 0.81); I² = 0%
Test for overall effect: Z = 0.25 (P = 0.80)



D: Death

Study or Subgroup	DOAC Events	DOAC Total	Vitamin K antagonist Events	Vitamin K antagonist Total	Weight	Risk Difference M-H, Random, 95% CI	Year
Woller et al. (ASTRO-APS) 2022	0	0	0	0		Not estimable	2022
Ordi-Ros et al. 2019	0	95	0	95	56.3%	0.00 [-0.02, 0.02]	2019
Pengo et al. (TRAPS) 2018	0	59	0	61	22.8%	0.00 [-0.03, 0.03]	2018
Cohen et al. (RAPS) 2016	0	57	0	58	21.0%	0.00 [-0.03, 0.03]	2016
Goldhaber et al. 2016	0	0	0	0		Not estimable	2016
Total (95% CI)		**211**		**214**	**100.0%**	**0.00 [-0.02, 0.02]**	
Total events	0		0				

Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 2 (P = 1.00); I² = 0%
Test for overall effect: Z = 0.00 (P = 1.00)

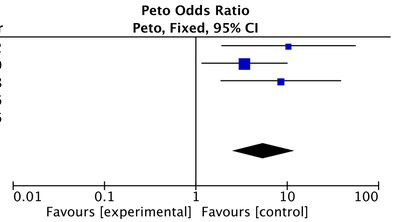


Appendix figure 1. Subgroup analyses

A. Occurrence of arterial thrombosis during treatment with DOACs and VKA

Study or Subgroup	DOAC Events	DOAC Total	Vitamin K antagonist Events	Vitamin K antagonist Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI	Year
Woller et al. (ASTRO-APS) 2022	6	23	0	25	21.4%	10.33 [1.90, 56.25]	2022
Ordi-Ros et al. 2019	11	95	3	95	52.1%	3.41 [1.15, 10.10]	2019
Pengo et al. (TRAPS) 2018	7	59	0	61	26.5%	8.52 [1.86, 38.96]	2018
Goldhaber et al. 2016	0	71	0	80		Not estimable	2016
Cohen et al. (RAPS) 2016	0	57	0	58		Not estimable	2016
Total (95% CI)		**305**		**319**	**100.0%**	**5.51 [2.52, 12.07]**	
Total events	24		3				

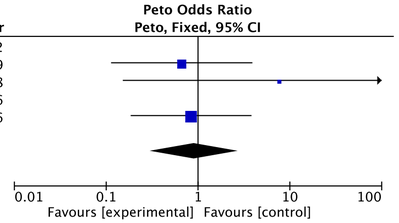
Heterogeneity: Chi^2 = 1.59, df = 2 (P = 0.45); I^2 = 0%
Test for overall effect: Z = 4.27 (P < 0.0001)



B. Occurrence of venous thrombosis during treatment with DOACs and VKA

Study or Subgroup	DOAC Events	DOAC Total	Vitamin K antagonist Events	Vitamin K antagonist Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI	Year
Woller et al. (ASTRO-APS) 2022	0	23	0	25		Not estimable	2022
Ordi-Ros et al. 2019	2	95	3	95	38.9%	0.66 [0.11, 3.91]	2019
Pengo et al. (TRAPS) 2018	1	59	0	61	7.9%	7.64 [0.15, 385.43]	2018
Cohen et al. (RAPS) 2016	0	57	0	58		Not estimable	2016
Goldhaber et al. 2016	3	71	4	80	53.2%	0.84 [0.18, 3.82]	2016
Total (95% CI)		**305**		**319**	**100.0%**	**0.91 [0.30, 2.76]**	
Total events	6		7				

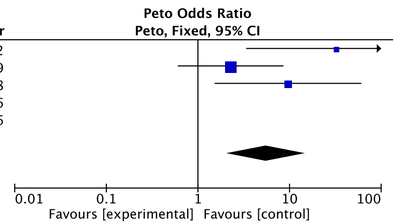
Heterogeneity: Chi^2 = 1.26, df = 2 (P = 0.53); I^2 = 0%
Test for overall effect: Z = 0.16 (P = 0.87)



C. Occurrence of thrombosis during treatment with DOACs and VKA in patients with previous arterial thrombosis

Study or Subgroup	DOAC Events	DOAC Total	Vitamin K antagonist Events	Vitamin K antagonist Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI	Year
Woller et al. (ASTRO-APS) 2022	4	6	0	11	18.3%	32.69 [3.36, 318.04]	2022
Ordi-Ros et al. 2019	7	37	3	34	53.7%	2.28 [0.60, 8.60]	2019
Pengo et al. (TRAPS) 2018	5	21	0	22	27.9%	9.61 [1.52, 60.74]	2018
Cohen et al. (RAPS) 2016	0	0	0	0		Not estimable	2016
Goldhaber et al. 2016	0	0	0	0		Not estimable	2016
Total (95% CI)		**64**		**67**	**100.0%**	**5.55 [2.09, 14.70]**	
Total events	16		3				

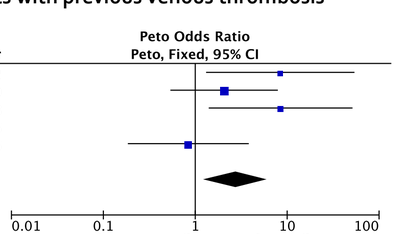
Heterogeneity: Chi^2 = 4.40, df = 2 (P = 0.11); I^2 = 55%
Test for overall effect: Z = 3.45 (P = 0.0006)



D. Occurrence of thrombosis during treatment with DOACs and VKA in patients with previous venous thrombosis

Study or Subgroup	DOAC Events	DOAC Total	Vitamin K antagonist Events	Vitamin K antagonist Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI	Year
Woller et al. (ASTRO-APS) 2022	5	20	0	18	18.3%	8.42 [1.31, 54.01]	2022
Ordi-Ros et al. 2019	6	69	3	70	34.8%	2.06 [0.54, 7.92]	2019
Pengo et al. (TRAPS) 2018	5	38	0	39	19.4%	8.49 [1.40, 51.42]	2018
Cohen et al. (RAPS) 2016	0	57	0	58		Not estimable	2016
Goldhaber et al. 2016	3	71	4	80	27.5%	0.84 [0.18, 3.82]	2016
Total (95% CI)		**255**		**265**	**100.0%**	**2.74 [1.24, 6.07]**	
Total events	19		7				

Heterogeneity: Chi^2 = 5.43, df = 3 (P = 0.14); I^2 = 45%
Test for overall effect: Z = 2.49 (P = 0.01)



E. Occurrence of thrombosis during treatment with DOACs and VKA in patients with triple positivity

Study or Subgroup	DOAC Events	DOAC Total	Vitamin K antagonist Events	Vitamin K antagonist Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI	Year
Woller et al. (ASTRO-APS) 2022	2	7	0	7	8.2%	8.73 [0.49, 156.28]	2022
Ordi-Ros et al. 2019	10	58	5	57	58.4%	2.10 [0.71, 6.18]	2019
Pengo et al. (TRAPS) 2018	8	59	0	61	33.4%	8.68 [2.08, 36.23]	2018
Cohen et al. (RAPS) 2016	0	7	0	12		Not estimable	2016
Goldhaber et al. 2016	0	0	0	0		Not estimable	2016
Total (95% CI)		**131**		**137**	**100.0%**	**3.79 [1.66, 8.65]**	
Total events	20		5				

Heterogeneity: Chi^2 = 2.77, df = 2 (P = 0.25); I^2 = 28%
Test for overall effect: Z = 3.16 (P = 0.002)