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Comparing the efficacy and safety of direct oral anticoagulants versus Vitamin K antagonists in patients with antiphospholipid syndrome: a systematic review and meta-analysis

Xiaoling Wu[a,*], Shaobo Cao[b,*], Bo Yu[a] and Tao He[b]

Thromboprophylaxis is the cornerstone strategy for thrombotic antiphospholipid syndrome (APS). Data comparing direct oral anticoagulants (DOACs) to Vitamin K antagonists (VKAs) in the secondary prevention of thrombosis in APS patients remain contentious.

We aim to review and analyse literature on the efficacy and safety of DOACs compared with VKAs in treating patients with APS. A literature search was performed from inception to 31 December 2021. Subgroups were analysed based on the risk stratification of APS profiles and different DOAC types.

A total of nine studies with 1131 patients were included in the meta-analysis. High-risk APS patients (triple positive APS) who used DOACs displayed an increased risk of recurrent thrombosis [risk ratio = 3.65, 95% confidence interval (95% CI): 1.49–8.93; $I^2 = 29\%$, $P = 0.005$] compared with those taking VKAs. Similar risk of recurrent thrombosis or major bleeding was noted in low-risk APS patients (single or double antibody-positive) upon administering DOACs or VKAs. The utilization of Rivaroxaban was associated with a high risk of recurrent thromboses (RR = 2.63; 95% CI: 1.56–4.42; $I^2 = 0$, $P = 0.0003$), particularly recurrent arterial thromboses (RR = 4.52; 95% CI: 1.99–10.29; $I^2 = 0$, $P = 0.18$) in overall APS patients. Comparisons of the rate of recurrent thrombosis events and major bleeding events when using dabigatran or apixaban versus VKAs yielded no statistical differences.

In the absence of contraindications, this meta-analysis suggests that VKAs remain the first-choice treatment for high-risk APS patients, with DOACs a more appropriate option for low-risk APS patients. Different DOACs may exhibit different levels of efficacy and safety for thromboprophylaxis in APS patients and require further exploration. *Blood Coagul Fibrinolysis* **33:389–401**

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Introduction

Antiphospholipid syndrome (APS) is an acquired autoimmune disorder manifested by the persistent presence of antiphospholipid antibodies (aPL) [including lupus anticoagulant, anticardiolipin antibodies (aCL) and antiβ2 glycoprotein I antibodies (aβ2-GPI)], which can result in recurrent thrombophilia and obstetrical morbidity [1]. It is clinically heterogeneous, with the risk of occurrence and recurrence of thrombosis dependent on the profile of aPL, concomitant diseases and anticoagulation strategies [2]. Thromboprophylaxis is the absolute cornerstone strategy for thrombotic APS; however, controversies exist at the level of anticoagulant drug selection.

Although the use of Vitamin K antagonists (VKAs), notably warfarin (target international normalized ratio [INR], 2 to 3), requires that patients are highly compliant to a healthy lifestyle and that INR is monitored frequently, they remain the recommended standard therapy for long-term thromboprophylaxis in patients with APS after the first thrombotic episode [3]. Compared with VKAs, direct oral anticoagulants (DOACs, such as rivaroxaban, apixaban, edoxaban and dabigatran) have appealing benefits, including no need to monitor anticoagulants' effect, fewer drug-food interactions, fixed-dose prescribing, fewer cases of significant bleeding and many more [3]. To date, data comparing DOACs to VKAs for the secondary prevention of thrombosis in APS patients remain limited and debatable. Of the published cohort studies and randomized clinical trials (RCTs) related to thromboprophylaxis in APS patients, some found that DOACs were not substandard to VKAs [4–7], and the others produced contrasting results [8–13].

Four reviews and meta-analyses evaluating the efficacy and safety of DOACs versus VKAs in APS patients have

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been published. Two of these investigations have limited value currently because cohort studies and RCTs were rarer at the time of their completion than they are now [14,15]; cohort evaluations and RCTs remain incredibly scarce. Two related meta-analyses were published recently: one included four RCTs [16], and the other enrolled three RCTs and four observational studies [17]. Assessment of four RCTs by Dufrost *et al.* [16] concluded that the DOACs used in APS patients were not less effective than VKAs in preventing recurrent venous thromboembolism; however, they significantly increased the risk of recurrent arterial thrombosis. On the contrary, Koval *et al.* [17] demonstrated that DOACs, particularly rivaroxaban, provided poorer efficiency than VKAs when given to patients with APS because they tripled the thromboembolic risk.

Evidence from case series, RCTs and a meta-analysis has indicated that high-risk APS patients with triple positivity or a history of arterial thrombosis are associated with a higher risk of thrombosis [8–10,12,18]. Several international guidelines do not recommend DOACs in place of warfarin (INR goal 2–3) as preferred thromboprophylaxis treatment for high-risk APS patients [1,3,19]. However, whether and which DOACs can be used in low-risk APS patients (presence of one or two antiphospholipid antibody profiles) warrants further exploration given their advantages. Both meta-analyses mentioned above did not perform subgroup evaluations based on different risk stratifications of APS or detailed DOAC drug types [16,17].

Three retrospective cohort studies on the subject were also published recently [6,7,12]. One was performed upon the completion of the Antiphospholipid Syndrome (TRAPS) Trial, with most patients involved in the TRAPS trial switched to warfarin, except for six patients who remained on DOACs [12]. Interestingly, the individuals enrolled in the two latest cohort studies were mostly low-risk APS patients; still, both investigations yielded contradictory results [6,7]. In light of that outcome and existing controversies, we conducted this systematic review and meta-analysis to compare the efficacy and safety of DOACs versus VKAs for thromboprophylaxis in different risk-stratified APS patients. We also sought to establish whether different DOACs display varying levels of efficacy and safety for thromboprophylaxis in APS patients.

Materials and methods

Search strategy and study selection

We systematically searched PubMed, the Cochrane Central Register of Controlled Trials and EMBASE using the following keywords and their Mesh terms: 'antiphospholipid syndrome' and 'direct oral anticoagulants', 'novel oral anticoagulant' or 'apixaban', 'dabigatran', 'edoxaban' and 'rivaroxaban' until 31 December 2021. Search language was restricted to English. References in identified reports and review articles were also mined to identify potentially relevant studies. This research was performed per the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

Inclusion and exclusion criteria

Studies comparing reported clinical outcomes in patients with APS using DOACs or VKAs were included. The following types of articles were excluded: review articles or commentaries, case reports and articles not in the English language. Investigations with insufficient data for estimating the efficacy and safety of DOACs were also excluded. Multiple articles published by the same institution and with overlapping individuals were scrutinized, and that with the most significant number of cases or the most extended follow-up was selected; the others were excluded.

Data extraction and quality of study assessment

Two reviewers independently extracted data from each article into a prespecified data collection form. Materials were mined from the main text and tables of the published reports and online supplementary materials (if available). If available, the following items were retrieved from each publication: the first author's name, publication year, design and setting, number of individuals, anticoagulation treatment regimen, patient characteristics, follow-up period and clinical outcomes. The outcome of interest was thromboembolic events, including venous and arterial thromboembolism, major bleeding and all-cause mortality. Major bleeding was diagnosed in each study using guidelines from the International Society on Thrombosis and Haemostasis [20].

The risk of biased assessments of RCTs was conducted in line with the criteria in the Cochrane Handbook for Systematic Reviews of Interventions [21]. This methodology explores the adequacy of sequestration, allocation sequence concealment, blinding of participants and study personnel, blinding for outcome assessment, incomplete outcome or selective outcome reporting, and other potential biases. The quality of the included cohort studies was modified evaluated using the Newcastle-Ottawa scale (NOS) [22]. The two reviewers independently analysed the selection, comparability and exposure of each publication and allocated a score of between 0 and 9 to each included cohort. Studies with scores at least 7 were considered suitable for analysis. Any disagreement between the authors was resolved via dialog with a senior reviewer.

Statistics

Data were managed and analysed using Review Manager Software (version 5.4; the Cochrane Collaboration) and STATA software (version 12.0; STATA Corporation, College Station). The Mantel-Haenszel method for dichotomous data was used to calculate aggregated risk ratios and corresponding 95% confidence intervals (95% CIs). Results were considered statistically significant at

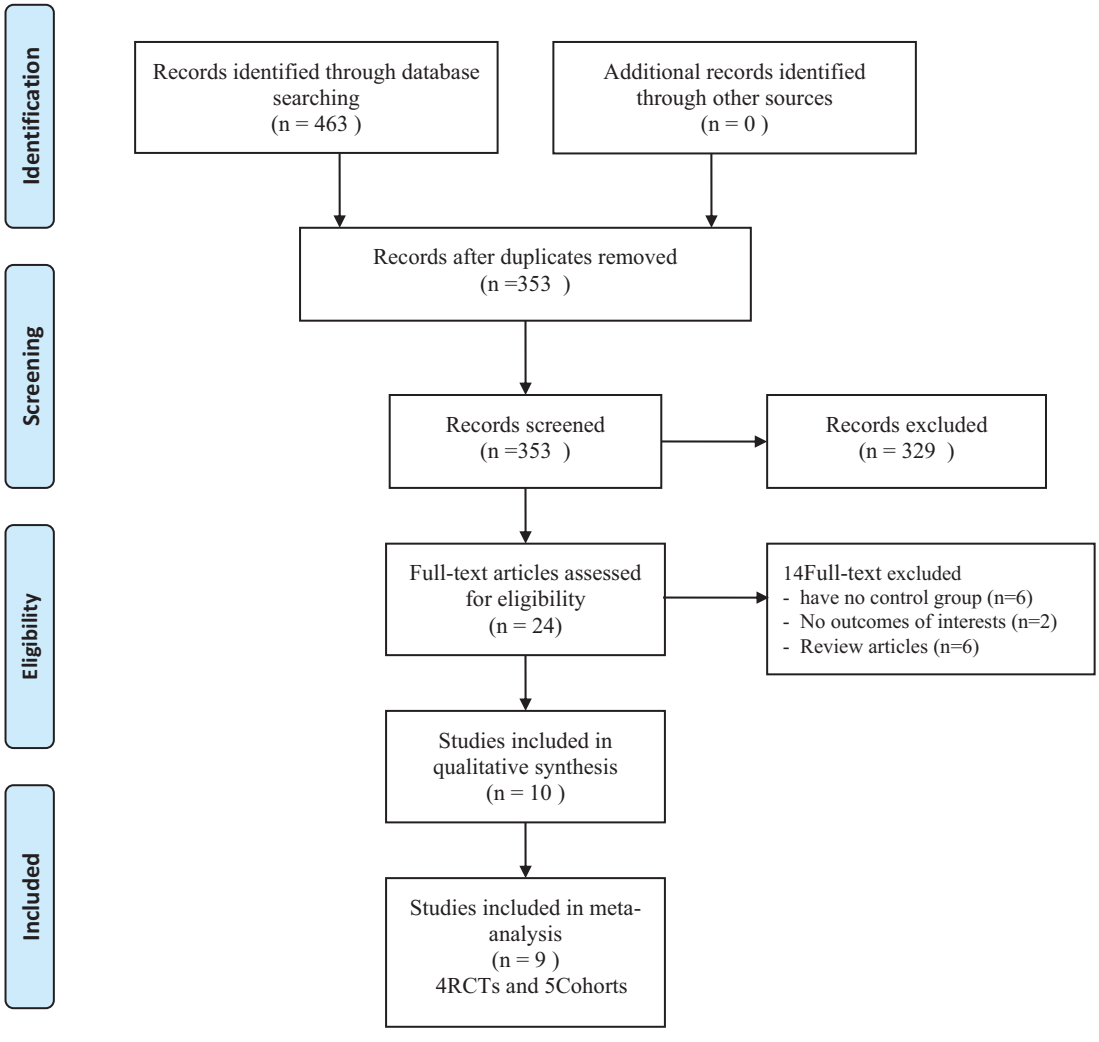
P values less than 0.05. Unexplained statistical heterogeneity between studies was assessed with the aid of the I^2 statistic. A fixed-effects model was used at I^2 of 50% or less and Cochran Q statistic *P* value more than 0.1, and a random-effects model was applied at I^2 more than 50% and Q statistic *P* of 0.1 or less. Subgroup analyses were conducted based on the study designs (RCT and cohort study), DOAC types (rivaroxaban, apixaban, dabigatran) and different risk stratifications of APS (triple antibody-positive, single or double antibody-positive) to avoid method heterogeneity. APS patients with triple-antibody positivity or a history of arterial thrombosis are generally defined as high-risk, while those with single or double-antibody positivity are low-risk. Sensitivity was analysed by excluding one study after the other and re-analysing data. Publication bias was evaluated using Begg's test and Egger's test, with significant publication bias considered existent at *P* values less than 0.05 [23,24].

Results

Search results and the characteristics of included trials

Figure 1 shows the PRISMA flow chart summarizing the search strategy. A total of nine articles, including four RCTs and five cohort studies, with 1131 patients from the literature search were included in this meta-analysis. The RAPS [4], TRAPS [9] and EUDRA [10] were open-label and noninferiority trials. The inquiry by Goldhaber *et al.* [5] examined APS patients with previous VTE in RE-COVER, RE-COVER II and RE-MEDY double-blind, randomized controlled trials comparing dabigatran with warfarin. Four of the five cohort studies we selected were retrospective, and one was prospective in design. The retrospective cohort research by Pengo *et al.* [12], which switched the treatment regimen of most individuals in the DOACs group from the TRAPS trial to warfarin, was excluded because of its association to that trial that ended just before its run. The characteristics of the RCTs and cohort studies are described in full in Table 1.

Fig. 1



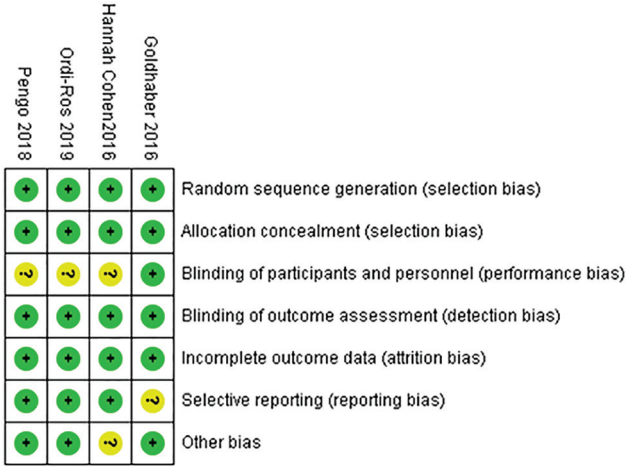
Flow chart on the selection of eligible studies.

Table 1 Characteristics of included studies

					Relevant patients (*n*)		Age, mean ± SD or median quartile		Triple positive (%)		Intervention		Follow-up	
Year	Design	Criteria	Exclusion	Country	DOAC	VKA	DOAC	VKA	DOAC	VKA	DOAC(*n*)	VKA	DOAC	VKA
2020	Retrospective cohort	High risk and low risk	NR	Germany	119	81	55 (21–81)	51 (21–76)	7%	4.2%	Rivaroxaban 20mg/d (92), apxiaban 5 mg twice daily (42), dabigatran 150 mg twice daily (3)and edoxaban 60 mg/day (4)	INR 2.0–3.0	16 months	32months
2021	Retrospective cohort	Low risk	Triple positive, history of arterial thrombosis	USA	39	57	56 (39–66)	54 (36–69)	0	0	Rivaroxaban(35), dabigatran(3), apixaban(1)	INR 2.0–3.0	NR	NR
2016	RCT	High risk and low risk	NR	International	71	80	47.8 (14.9)	47.4 (16.8)	NR	NR	Dabigatran 150 mg twice daily (71)	INR 2.0–3.0	NR	NR
2016	RCT	High risk and low risk	history of arterial thrombosis, recurrent venous thromboembolism when taking VKA, pregnancy, severe renal impairment, thrombocytopenia	UK	57	59	47 (17)	50(14)	12%	20%	Rivaroxaban 20 mg/day (or 15mg/day for patients with a creatinine clearance of 30to49 ml/min/ 1.73 m^2) (57)	INR 2.0–3.0	210 days	210 days
2018	Retrospective cohort	High risk and low risk	NR	Italy	13	15	46.2 (16.4)	43.1(15.8)	46.2%	46.7%	Rivaroxaban (15 mg twice daily for 21 days followed by 20 mg/ day) (13)	INR 2.0–3.0	43 months	48 months
2020	Prospective cohort	High risk and low risk	Stroke within the previous 3 months, pregnancy, severe renal impairment, thrombocytopenia	Poland	82	94	44±11	45 ± 13	40%	21%	Rivaroxaban 20 mg/day (36), apxiaban 5 mg twice daily (42), dabigatran 150 mg twice daily (4)	INR 2.0–3.0	45 months	62 months
2019	RCT	High risk and low risk	Had intracranial haemorrhage, stroke, or gastrointestinal bleeding within the previous 3 months, significant bleeding diathesis, pregnancy, severe renal impairment, thrombocytopenia	Spain	95	95	47 (40–55)	51 (38–63)	61%	60%	Rivaroxaban 20 mg/day (or 15mg/d for patients with a creatinine clearance of 30 to 49 ml/min/ 1.73 m^2) (95)	INR 2–3 (or 3.1–4.0 if history of recurrent thrombosis)	34.1 months	33.1 months
2018	RCT	High risk	Significant bleeding diathesis, current pregnancy or breast feeding, severe renal impairment, concomitant treatment with other anticoagulants	Italy	59	61	46.5 ± 10.2	46.1 ± 13.2	100%	100%	Rivaroxaban 20 mg/day (or 15 mg/day for patients with a creatinine clearance of 30 to 49 ml/min/ 1.73 m^2) (59)	INR 2.0–3.0	611 days	611 days
2019	Retrospective cohort	High risk and low risk	NR	Japan	18	39	47.7 ± 17.1	42.6 ± 13.4	33.3%	38.9%	Rivaroxaban (5), edoxaban (12), apixaban (1)	INR 2.0–3.0	60 months	60 months

DOAC, direct oral anticoagulant; NR, not reported; VKA, Vitamin K antagonist.

Fig. 2



Risk of bias assessment for randomized controlled trials.

Quality of study assessment

The risk of bias assessment for the included RCTs is presented in Fig. 2. The performance biases for three trials with open-label study designs [4,9,10] were ambiguous, as were the selective reporting bias for investigation by Goldhaber *et al.* [5] because it was a post-hoc analysis of three previous published RCTs and the follow-up duration time bias in the RAPS trial due to the relatively short follow-up time. The selection, detection and attrition biases were deemed low risk for all trials. In summary, all the RCTs were considered high-quality.

The risk of bias assessment for the cohort studies was assessed with NOS (Supplementary Table 1, http://links.lww.com/BCF/A135). All selected studies scored at least 7 and were deemed fit for inclusion in the meta-analysis.

Clinical outcomes

Comparing the efficacy and safety of direct oral anticoagulants versus Vitamin K antagonists in overall antiphospholipid syndrome patients

First, we determined the pooled risk ratio of DOACs relative to VKAs for thromboprophylaxis in overall APS patients (Fig. 3). There was no significantly increased risk of recurrent thrombosis (risk ratio = 1.53, 95% CI: 0.92–2.55; $I^2 = 24\%$, $P = 0.10$) (Fig. 3a) and recurrent venous thromboembolism (risk ratio = 1.22, 95% CI: 0.68–2.17; $I^2 = 0\%$, $P = 0.51$) in the DOAC group (Fig. 3b) compared with the VKA group in both RCTs and cohort studies, as determined by subgroup analyses (Fig. 3a,b). Disappointingly, DOACs showed a markedly considerable aptitude for risk of recurrent arterial thrombosis (risk ratio = 2.27, 95% CI: 1.28–4.00; $I^2 = 29\%$, $P = 0.005$) in APS patients (Fig. 3c). The RCT subgroup displayed a substantially more inflated risk of recurrent arterial thrombosis (risk ratio = 5.33, 95% CI: 1.74–16.32; $I^2 = 0\%$, $P = 0.003$), while the subgroup of cohort studies exhibited no noteworthy differences (risk ratio = 1.36, 95% CI: 0.68–2.71; $I^2 = 9\%$, $P = 0.38$) (Fig. 3c).

The occurrence of major bleeding events and all-cause mortality was used to evaluate the safety of DOACs relative to VKAs in the treatment of APS. No significantly increased risk of major bleeding events (risk ratio = 1.04, 95% CI: 0.53–2.04; $I^2 = 0\%$, $P = 0.91$) was noted in the DOAC group compared with the VKA group. Both the RCT subgroup (risk ratio = 1.03, 95% CI: 0.45–2.31; $I^2 = 0\%$, $P = 0.95$) and the cohort subgroup (risk ratio = 1.07, 95% CI: 0.31–3.64; $I^2 = 0\%$, $P = 0.92$) demonstrated similar outcomes (Fig. 3d). Pooled analyses (risk ratio = 1.14, 95% CI: 0.47–2.79; $I^2 = 0$, $P = 0.77$) found no amplified risk of all-cause mortality by DOACs in APS patients compared with VKAs (Fig. 3e).

Comparing the efficacy and safety of direct oral anticoagulant s versus Vitamin K antagonists for thromboprophylaxis in antiphospholipid syndrome patients with different risk stratifications

We explored the effectiveness and safety of DOACs versus VKAs in (Fig. 4) preventing thrombosis in APS patients with specified risk stratifications. The use of DOACs resulted in an increased risk of recurrent thrombosis (risk ratio = 3.65, 95% CI: 1.49–8.93; $I^2 = 29\%$, $P = 0.005$) in high-risk APS patients compared with VKAs; however, no substantial risk of recurrent thrombosis was found in the use of DOACs versus VKAs in the low-risk group (risk ratio = 1.65, 95% CI: 0.72–3.81; $I^2 = 20\%$, $P = 0.24$) (Fig. 4a).

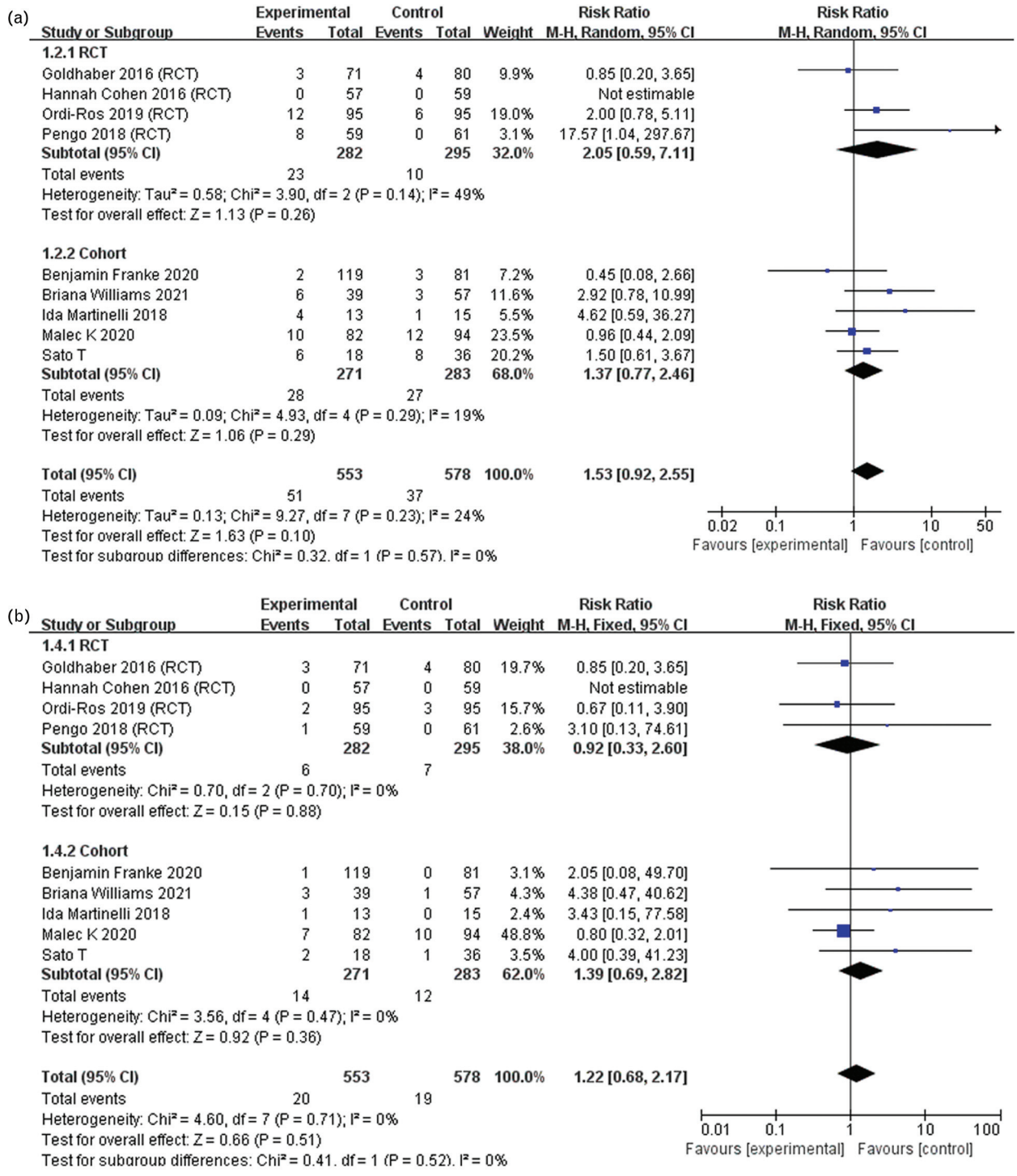
There was no significantly augmented risk of major bleeding events in the high-risk subgroup when using DOACs compared with the application of VKAs (risk ratio = 2.07, 95% CI: 0.39–10.87; $P = 0.39$). This outcome was true for the low-risk subgroup too (risk ratio = 1.10, 95% CI: 0.26–4.63; $P = 0.90$) (Fig. 4b).

The efficacy and safety of different DOACs could not be explored in APS patients with various stratifications due to the limited number of articles.

Comparing different direct oral anticoagulant s to Vitamin K antagonists for thromboprophylaxis in overall antiphospholipid syndrome patients

In order to ascertain the efficacy and safety of various DOACs in the treatment of APS, we further examined the risk ratios for rivaroxaban, apixaban and dabigatran-relayed recurrent thrombosis. Interestingly, only rivaroxaban correlated with a high risk of recurrent thromboses (risk ratio = 2.63; 95% CI, 1.56–4.42; $I^2 = 0$, $P = 0.0003$) (Fig. 5a) and a high risk of recurrent arterial thromboses (risk ratio = 4.52; 95% CI, 1.99–10.29; $I^2 = 0$, $P = 0.18$)

Fig. 3

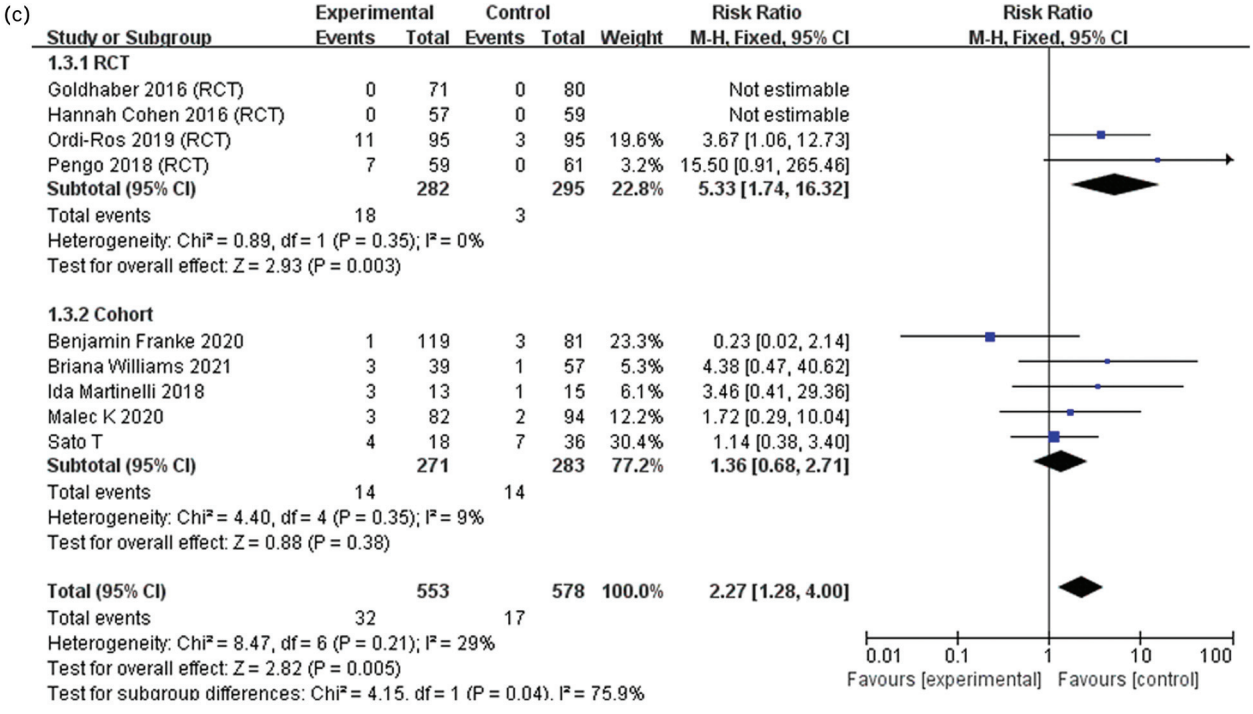


Forest plot for the efficacy and safety of direct oral anticoagulant s in overall antiphospholipid syndrome patients. (a) Occurrence of thromboembolic events. (b) Occurrence of venous thromboembolism. (c) Occurrence of arterial thromboembolism. (d) Major bleeding. (e) All-cause mortality.

(Fig. 5b) in patients with APS. The use of rivaroxaban incurred no heightened risk of recurrent venous thromboembolism relative to VKA utilization (risk ratio = 1.59, 95% CI: 0.79–3.18; $I^2 = 0$, $P = 0.19$) (Fig. 5c). Patients treated with apixaban and dabigatran were not at a higher risk of recurrent thrombosis, recurrent arterial thromboses and venous thromboembolism than those given VKAs.

Fig. 3

(c)



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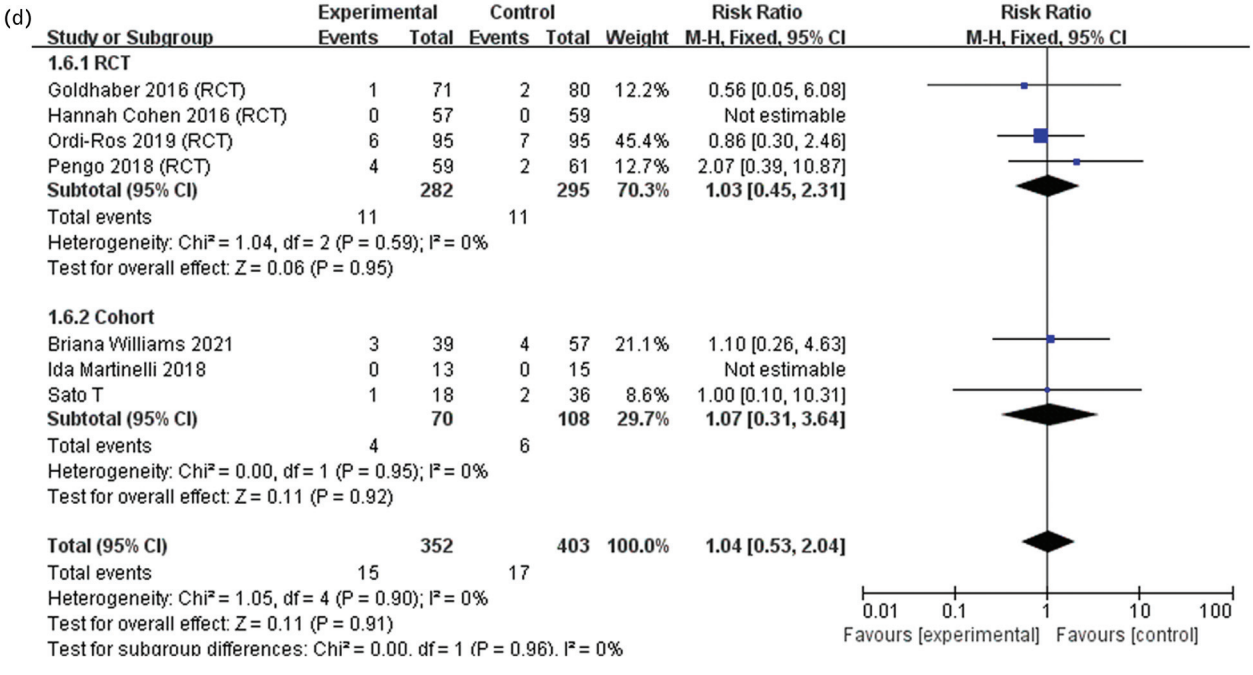

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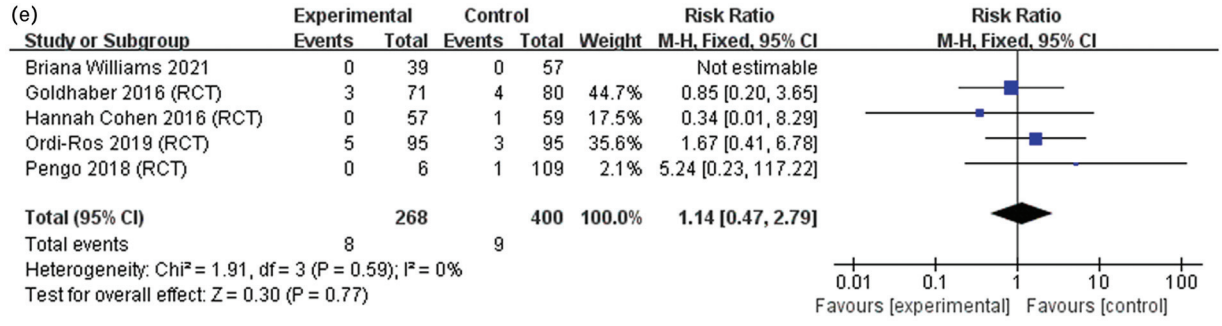
In addition, rivaroxaban and dabigatran prompted no significantly amplified risk of major bleeding than the use of VKAs (Fig. 5d).

Publication bias and heterogeneity analysis

Begg's and Egger's tests determined no significant publication bias ($P = 0.216$) (Supplementary Figure 1, http://links.lww.com/BCF/A135). Sensitivity analyses to evaluate the robustness of the results by excluding one study after another and re-analysing the data identified no influence by a particular publication. However, subgroup analyses indicated that study designs (RCT and cohort study), DOACs types and risk stratification could cause heterogeneity.

Fig. 3



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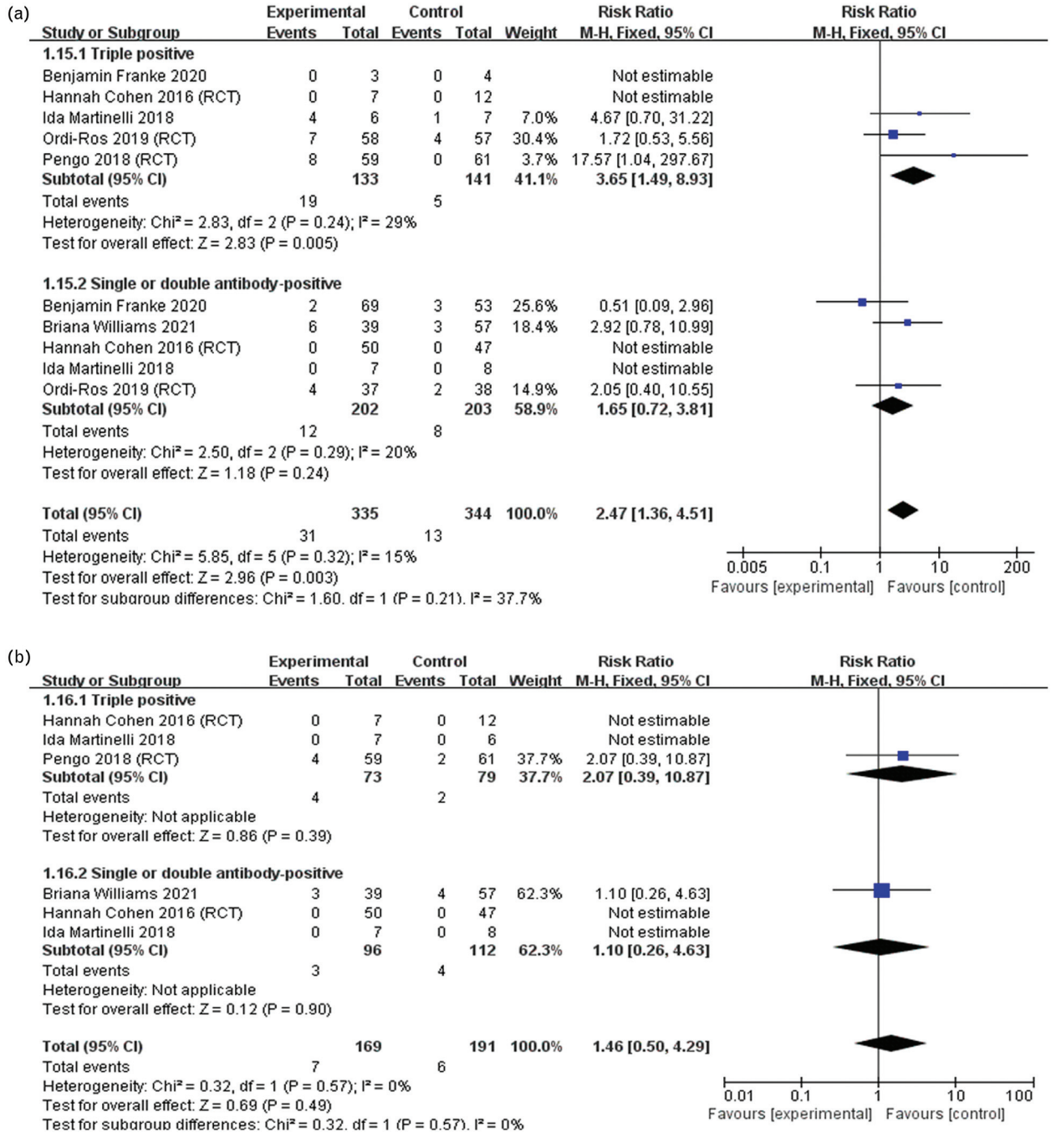
Discussion

Per our meta-analysis, the effectiveness of DOACs for thromboprophylaxis in high-risk APS patients is poorer the impact of VKAs; however, DOACs were comparable to VKAs in their efficiency in low-risk patients. Taking into account different APS patient types, rivaroxaban, which was the most representative drug in all included studies, statistically increased the incidence of arterial thromboembolism, but not venous thromboembolism, compared with VKAs; the other two DOACs (apixaban and dabigatran) displayed a similar tendency, but it was not statistically significant. In terms of safety, there was no statistical difference in the risk of significant bleeding and all-cause mortality in overall APS patients when using DOACs versus when taking VKAs.

Our meta-analysis innovatively explored the effectiveness and safety of DOACs versus VKAs in preventing thrombosis in APS patients with specified risk stratifications. We found that the incidence of thromboembolic events in patients with high-risk APS profiles in the DOAC group was nearly four-fold that in the VKA group, with statistical significance, which was inconsistent with the conclusion derived by a recent meta-analysis [16]. A meta-analysis by Dufrost *et al.* [16] showed a trend towards a nonsignificant higher risk of recurrent thrombosis during treatment with DOACs compared with VKA use in APS patients with triple positivity. Perhaps our addition of two recently published retrospective cohort studies [6,8] to our meta-analysis is responsible for this discrepancy. One of the two recent retrospective investigations found no thromboembolic events in the small minority of patients with triple positivity during follow-up [6]. The other inquiry, on the contrary, identified five of 13 rivaroxaban users with recurrent thrombosis and one of 15 patients in the VKA group with recurrent thrombosis; all the patients with recurrent thrombosis had triple positivity [8]. These findings provide a certain amount of evidence for guidelines recommending the use of warfarin but not DOACs to treat high-risk APS patients [1,13,19]. Given that our meta-analysis found no statistical significance in the difference in impact between DOACs and VKAs on the incidence of thromboembolic events in low-risk APS patients, DOACs could be an appealing therapeutic alternative thanks to its convenience and stability in this specified subgroup. More prospective studies or RCT trials must be scrutinized further to establish the viability of this conclusion.

DOACs differ in various ways, such as mechanisms and pharmacokinetics [25]. Rivaroxaban and apixaban are factor Xa inhibitors, while dabigatran is a thrombin (IIa) inhibitor. Rivaroxaban only needs to be taken orally once a day, whereas apixaban and dabigatran are taken twice a day. By comparing the efficacy and safety of different DOACs versus VKAs, this meta-analysis identified only rivaroxaban as displaying an unfavourable profile in the recurrence of thromboembolic events, especially arterial thrombosis, possibly because of the differences in anticoagulation strength required for arteriovenous thrombosis prevention. Investigations with animal models have shown that preventing arterial thrombosis requires a more potent inhibition of Xa and a higher dose of rivaroxaban than does venous thrombosis [26]. Because the use of DOACs does not need monitoring and their doses were not regularly adjusted, the therapeutic concentration in the rivaroxaban group may have been insufficient, particularly among patients with poor compliance who tended to skip medication periodically. However, individuals in the VKA group who failed to reach treatment goals (INR, 2–3) were excluded, with such a situation an uncommon occurrence. Moreover, the presence of a different VKA mechanism that inhibits the synthesis of coagulation factors II, VII, IX and X involved in vitamin K could also possibly explain the inferiority of rivaroxaban. The pooled results in our meta-analysis demonstrating apixaban and dabigatran's noninferior profiles compared with VKAs must be verified further with more RCTs because the current sample sizes from the limited articles are too small.

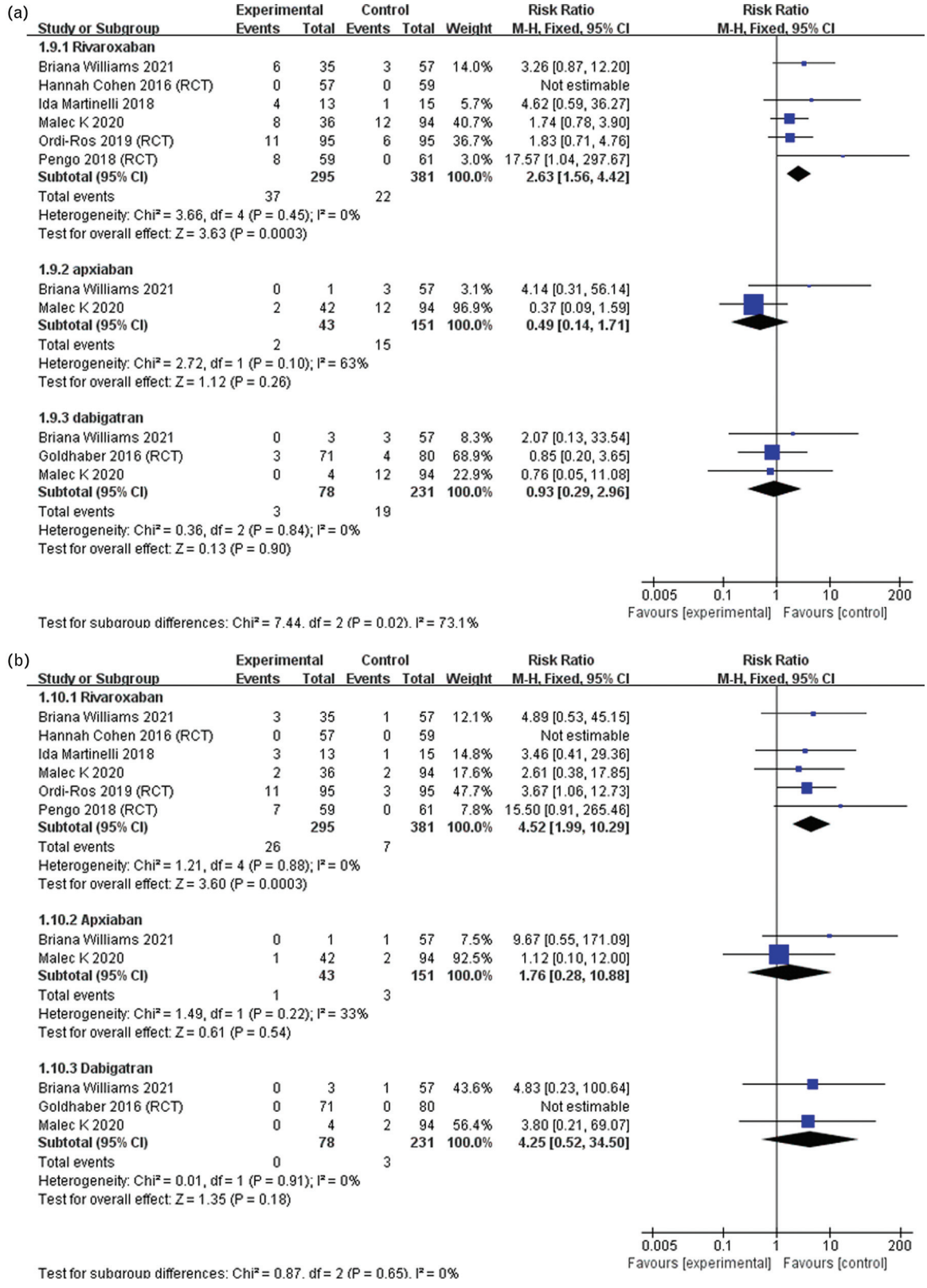
Fig. 4



Subgroup analyses of the risk ratios of direct oral anticoagulant s in treating triple-positive antiphospholipid syndrome patients and nontriple-positive antiphospholipid syndrome patients. (a) Occurrence of thromboembolic events. (b) Major bleeding.

In several diseases that require anticoagulation, such as venous thromboembolic event (VTE) and nonvalvular atrial fibrillation, DOACs have displayed a favourable risk-benefit profile against haemorrhage events compared with VKAs [27–29]. In this meta-analysis, unexpectedly, the risk of major bleeding increased, but without statistical significance, in overall APS patients in the DOACs (particularly rivaroxaban) group compared with the VKA group, matching findings by the two recently published meta-analyses [16,17]. However, this phenomenon should be interpreted cautiously because APS patients with a warfarin INR goal range other than 2.0–3.0 were left entirely out of the RCTs and observative studies included in our meta-analysis. A previous meta-analysis

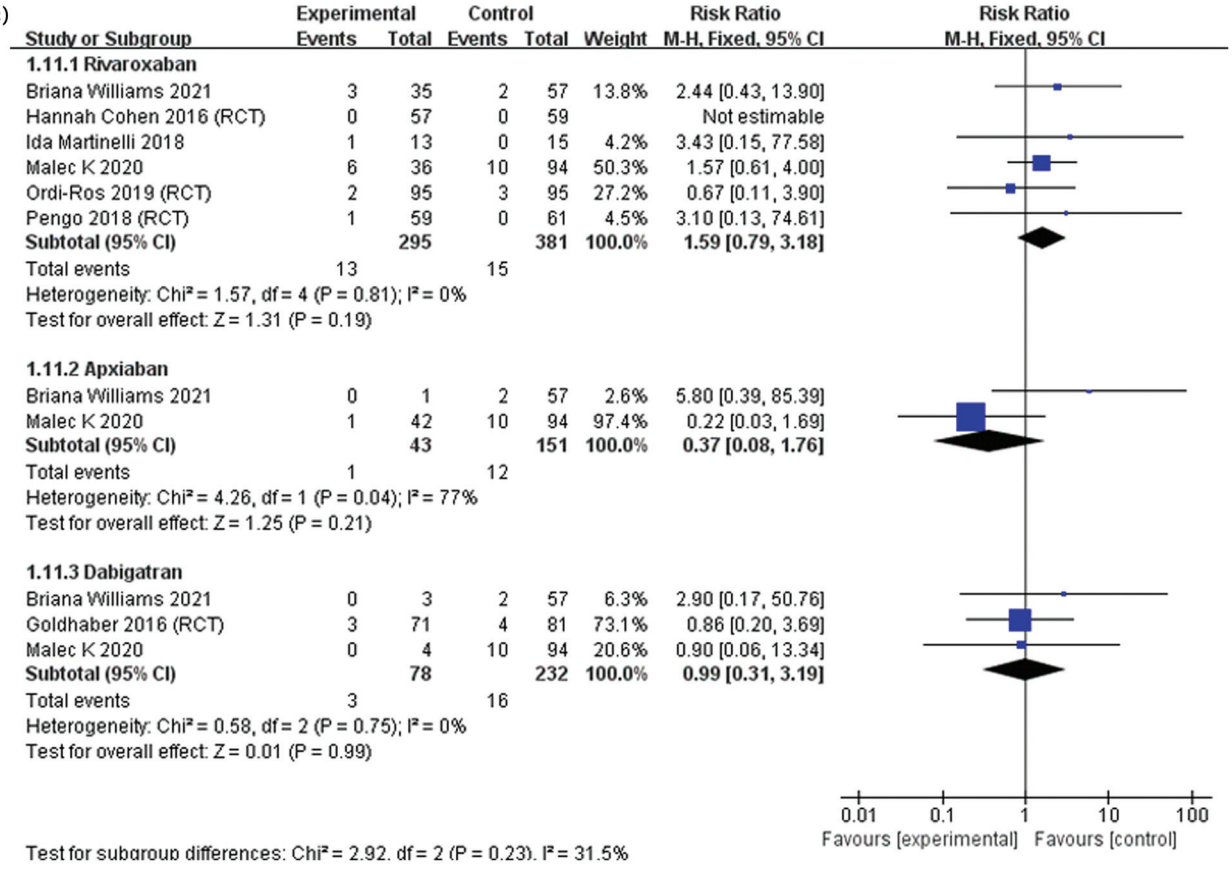
Fig. 5



Subgroup analyses of the risk ratios for the efficacy and safety of different direct oral anticoagulant s in treating patients with antiphospholipid syndrome. (a) Occurrence of thromboembolic events. (b) Occurrence of arterial thromboembolism. (c) Occurrence of venous thromboembolism. (d) Major bleeding.

Fig. 5

(c)



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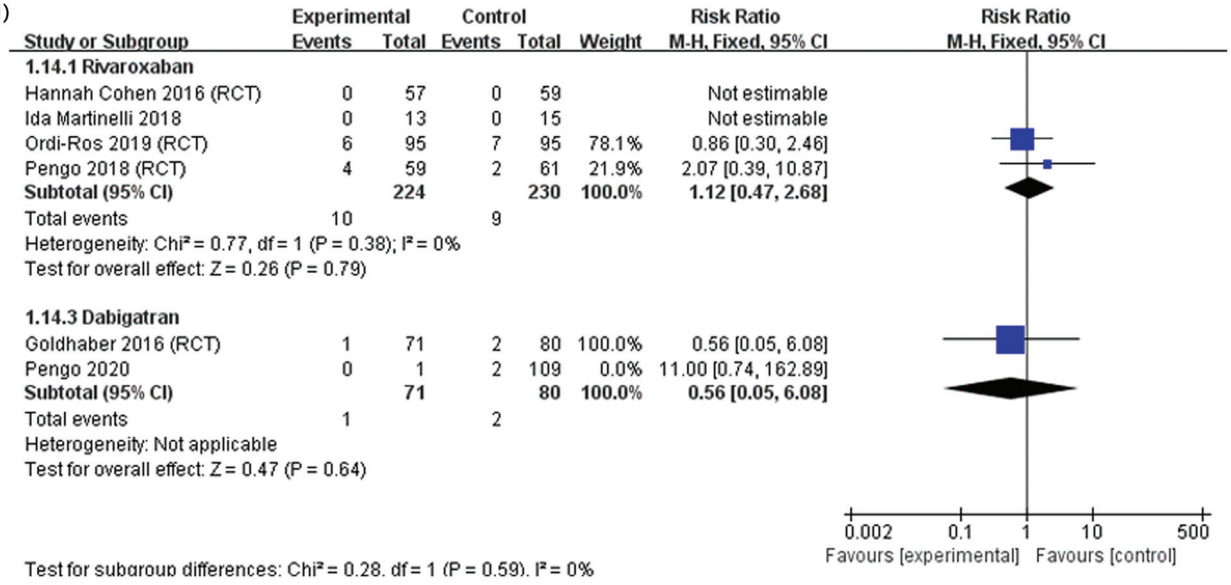

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proved that the risk of bleeding events in atrial fibrillation patients with excessive anticoagulation (INR > 3) was significantly higher relative to the situation in patients who maintained the recommended INR of 2–3 [30]. Therefore, in a real-world experience, DOACs may still represent an attractive alternative treatment option for APS patients looking to mitigate the risk of bleeding, especially those with low-risk; however, this theory must be further examined.

Our study has several limitations. First, the pooled sample sizes are small. Second, three of the included four RCTs trials were open-label designed trials with risks of performance and selection biases because they had no blinded participants and personnel to intervene. This very bias possibly also exists in the six included cohort studies. Third, in order to expand the pooled sample sizes, we jointly analysed RCTs and observational studies; however, these two investigation types differ in methodology, which may have affected the pooled results, as determined by the subgroup analyses based on the experimental design procedures of included articles (Fig. 3c). Fourth, the number of studies included in the meta-analysis, especially in some subgroup analyses, was limited; therefore, publication biases may not have been detected because of the relatively lower power. Hence, our conclusions are not robust; further attempts to establish certainties on the touched-on issues are recommended.

In conclusion, different intensities of anticoagulation strategies must be specified for APS patients with different risk stratifications. This meta-analysis favours the use of VKAs to treat high-risk APS patients and DOACs for patients with lower-risk forms of APS. Furthermore, although rivaroxaban did not perform well versus VKAs, research on the application of DOACs for anticoagulation in APS patients must continue.

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Conflicts of interest

The authors declare that they have no conflict of interest.

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