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Recurrent Thrombosis With Direct Oral Anticoagulants in Antiphospholipid Syndrome: A Systematic Literature Review and Meta-analysis

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ABSTRACT

Purpose: The treatment of thrombosis in patients with antiphospholipid syndrome (APS) usually requires long-term anticoagulation with vitamin K antagonists. The effectiveness of direct oral anticoagulants (DOACs) in APS has not been fully addressed. The purpose of this research was to analyze the efficacy (thrombotic event–free time) and tolerability (bleeding events) of DOACs in patients with APS.

Methods: We performed a descriptive analysis of a systematic review of data from patients with APS treated with DOACs reported in the literature, via EMBASE, PubMed, and the European League Against Rheumatism and American College of Rheumatology congresses. After systematic review, a meta-analysis of data from clinical trials was performed.

Findings: A total of 728 patients, accounting for 731 courses of treatment with DOACs, were identified. The majority (48.3%) presented with triple anti-phospholipid antibody positivity. The prevalence of thrombosis during DOAC treatment was 13.9%. Analysis of risk factors for recurrent thrombosis suggested that a higher mean (SD) number of prior thrombotic events (1.80 [0.87] vs 1.67 [1.45]; $P = 0.012$), history of combined arterial and venous thrombosis (27.3% vs 9.2% [$P < 0.0001$]; odds ratio [OR] = 3.72 [95% CI, 1.91–7.25]), use of immunosuppressant treatment (41.7% vs 12.7% [$P = 0.03$]; OR = 4.9 [95% CI, 1.21–19.76]), and no reason to switch anticoagulant treatment other than patient's decision (32% vs 2.8% [$P = 0.001$]; OR = 16.24 [95% CI, 3.16–83.52]) were associated with a high risk for re-thrombosis.

Implications: The findings from this systematic literature review and meta-analysis suggest that DOACs are not effective in patients with APS, especially in high-risk patients, such as those with a history of recurrent thrombosis, a history of combined arterial and venous thrombosis, or a need for immunosuppressant treatment, who may have poorer outcomes. Data suggest avoiding the use of DOACs in these patients. There are limited data to inform decisions on the use of DOACs in non–high-risk patients with APS. (*Clin Ther*. xxxx;xxx:xxx) © 2019 Published by Elsevier Inc.

Key words: antiphospholipid syndrome, direct oral anticoagulants, systematic review.

INTRODUCTION

Antiphospholipid syndrome (APS) is an autoimmune acquired thrombophilia defined as the occurrence of venous and arterial thromboses, and/or recurrent fetal losses, frequently accompanied by a moderate thrombocytopenia, in the presence of circulating anti-phospholipid antibodies (aPL), namely lupus anticoagulant, anticardiolipin, and anti–β_2-glycoprotein I ($_{anti-}\beta_2$-GPI) antibodies.[1] Specific clinical and immunologic criteria were developed to classify patients as having definite APS.[2] The

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cornerstone of secondary thromboprophylaxis in patients with APS is long-term anticoagulation.[3]

Currently, there are 2 main types of oral anticoagulants: vitamin K antagonists (VKAs) and direct oral anticoagulants (DOACs). Compared to DOACs, VKAs have several disadvantages in terms of efficacy and tolerability, such as their narrow therapeutic window, the unpredictable pharmacokinetic and pharmacodynamics due to drug interactions and cytochrome P450–dependent mechanisms, and the influence of dietary vitamin K intake. In addition, patients need to be treated initially with heparin.[5]

Some Phase III, randomized, controlled trials of DOACs have included a low number of patients with APS,[6] but specific analysis in these patients has not been made. The efficacy and tolerability of DOACs in thrombotic conditions other than APS have driven some clinical trials,[7–9] cohort studies, and case reports assessing the use of these agents in patients with APS. In addition, some studies have had important limitations, such as a lack of data on immunologic or clinical profile.[10] In other cases, patients with APS with a recognized high risk for thrombosis were excluded, such as the recently published ASTRO-APS (Apixaban for the Secondary Prevention of Thrombosis Among Patients With Antiphospholipid Syndrome) protocol modification,[11] in which patients with APS and a history of arterial thrombosis were excluded.

The clinical and laboratory heterogeneity of patients with APS raises questions about the efficacy of DOACs in specific subsets, such as those with triple aPL positivity, in whom these agents seemed to be ineffective.[12] To date, data remain controversial, with some case reports and series showing good profiles of efficacy and tolerability,[13,14] while other studies have shown a lack of efficacy in the form of thrombotic relapses.[15–18] The number of studies reporting the use of DOACs in patients with APS has increased over the years, including a broad spectrum of patients with recurrent thrombotic events, comorbidities, and associated autoimmune diseases, who might be otherwise not included in clinical trials. Therefore, a pooled analysis of these data could show the efficacy and tolerability of DOACs in clinical practice.

MATERIALS AND METHODS

A systematic literature review was performed according to the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) 2009 statement (Table I).[19]

We conducted a systematic literature review by searching in 2 databases (PubMed and EMBASE). In addition, we reviewed abstracts from the annual meetings of the European League Against Rheumatism (EULAR) and American College of Rheumatology (ACR). For PubMed and EMBASE database searching, we reviewed all articles published with abstracts written in English, Spanish, French, or Japanese identified using the following terms: *antiphospholipid syndrome, direct oral anticoagulants, rivaroxaban, apixaban, dabigatran,* and *edoxaban.* No date filter was used in the PubMed and EMBASE searches.

For abstract recruitment from the EULAR congresses (http://scientific.sparx-ip.net/archiveeular), we searched the term *antiphospholipid syndrome* from the years 2009–2017 and selected those that mentioned direct anticoagulant use.

For abstract recruitment from the ACR congresses (https://www.rheumatology.org/Learning-Center/Publications-Communications/Abstract-Archives), we followed the same described method but from the year 2012, as there were no previous data available, and an Adobe.pdf search of abstract supplements published from 2010 to 2011 and containing the term *antiphospholipid syndrome* was acquired from the same website. The last review of databases was performed on July 23, 2018.

All available abstracts were reviewed, and those describing patients with APS treated with any DOACs were selected. In addition, we reviewed the citations of selected articles, and any relevant studies that included patients with APS on DOAC treatment were included. We excluded articles with no abstract available and reports in which no clinical follow-up was described. In order to encompass as many reported patients as possible, whenever the abstract was absent, we tried to find it at the journal, and whenever there was no follow-up described, we contacted the corresponding author. If any information about follow-up was provided, the article was selected for analysis. After selection of the articles and abstracts, all duplicates were removed.

From the selected articles and abstracts we conducted an analysis of provided data, including type of cohort/study, age, sex, confirmed or

Table I. PRISMA 2009 Checklist.[19]

Section/Topic	No.	Checklist Item	Page No.
Title	1	We used indicative title identified as systematic review and meta-analysis	1
Abstract			
Structured summary	2	Structured summary provided	2
Introduction			
Rationale	3	Rationale for the review described in the context of what is already known	3–4
Objectives	4	PICO search strategy P = Patients diagnosed with APS I = Treatment with DOACs C = Frequency O = New thrombosis; major or minor bleeding; other causes of discontinuation of treatment	5–6
Methods			
Protocol and registration	5	There is a nonregistered protocol designed for a Master's degree thesis. The protocol was modified to include one Polish report.	x
Eligibility criteria	6	All studies that included patients diagnosed with APS treated with DOACs that reported outcomes and time of follow-up were selected for the systematic review. Studies without abstracts were excluded, as abstract review was the screening method. Only randomized controlled trials were included in meta-analysis.	4–5
Information sources	7	Search was performed on Pubmed, EMBASE, EULAR, and ACR databases, authors of 2 studies were contacted for additional information. Last date searched was July 23, 2018.	4–5
Search terms	8	"Antiphospholipid syndrome AND direct oral anticoagulants," "antiphospholipid syndrome AND rivaroxaban," "antiphospholipid syndrome AND apixaban," "antiphospholipid syndrome AND dabigatran," and "antiphospholipid syndrome AND edoxaban"	4

(*continued on next page*)

Table I. (*Continued*)

Section/Topic	No.	Checklist Item	Page No.
		were searched on both Pubmed and EMBASE databases.	
Study selection	9	Screening of studies was done by reviewing abstracts of search results; all studies with an abstract describing Patients with APS receiving DOACs were eligible for systematic review and with data described in the PICO (see topic 4 above) with any information about follow-up (time or outcome) were included in the systematic review.	4–5
Data collection process	10	Data from reports were collected in an Excel spreadsheet (Microsoft Corp, Redmond, Washington). Depending on the type of study and report, data were collected directly from tables or from case-report body text.	x
Data items	11	Variables included in the Excel spreadsheet of the systematic review were: Type of report, patient age, patient sex, status of confirmed APS before DOAC treatment, APS type (primary or secondary), name of DOAC used, DOAC dose, previous anticoagulant treatment, Time on previous anticoagulant treatment, Initial event (venous, arterial, microvascular or any combination of previously noted), number of thrombotic events before use of DOAC, reason for change anticoagulant treatment, number of thrombotic events while DOAC treatment, type of event while DOAC treatment (venous, arterial, microvascular or any combination of previously noted), time from DOAC start to thrombotic event, steroid dose, type of antiaggregant treatment if used, type of immunosuppressant if used, use of hydroxychloroquine, history of bleeding prior to DOAC treatment, number of bleeding events after DOAC treatment, type of bleeding event (major or minor), patient death, patient comorbidities, patient smoking status, APS immune profile (lupus anticoagulant, anticardiolipin and anti–β-$_2$ microglobulin), non criteria APS–associated event before use of DOAC, non criteria	5–6

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Table I. (*Continued*)

Section/Topic	No.	Checklist Item	Page No.
		APS—associated event while on DOAC treatment, confounders described in the report (possible associated factor for thrombosis).	
Risk for bias in individual studies	12	Assessment of biases was done for randomized controlled trials	4—5
Summary measures	13	Principal summary measures are means with SDs and percentages	x
Synthesis of results	14	Data were combined through the addition of data from each individual patient when possible or by using means when only pooled data were given. $I^2 = 0\%$ for thrombosis at 6 months, major bleeding at 6 months and deaths; $I^2 = 29\%$ for relevant bleeding at 6 months, $I^2 = 66\%$ for any bleeding at 6 months.	5—6
Risk for bias across studies	12	Assessment for biases in randomized controlled trials was done.	12—14
Summary measures	13	Principal summary measures are means with SDs and percentages	6
Synthesis of results	14	Data were combined through the addition of data from each individual patient when possible or by using means when only pooled data were given. $I^2 = 0\%$ for thrombosis at 6 months, major bleeding at 6 months and deaths; $I^2 = 29\%$ for relevant bleeding at 6 months, $I^2 = 66\%$ for any bleeding at 6 months.	7—15
Risk for bias across studies	15	Assessment for biases in randomized controlled trials was done. Limited data recorded and disparity of outcomes and report designed was noted in this systematic review. Also, the possibility of publication bias was noted.	12—14
Additional analyses	16	Comparative analysis between subgroups with and without thrombosis during DOAC treatment was done, Pearson χ^2 test and Fisher exact test were performed according to systematic review protocol.	6
Results			
Study selection		Prism flow chart included in the study	Figure 1

(*continued on next page*)

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Table I. (*Continued*)

Section/Topic	No.	Checklist Item	Page No.
Study characteristics		Noted in Table 2	Table 2
Risk for bias within studies		There was no systematic assessment for studies included in systematic review	x
Results of individual studies		Meta-analysis was performed with bias assessment. Outcomes data are reported in Table 2 and meta-analysis on pages 12-14	Table 3, pages 12-14
Synthesis of results		Thrombosis risk (odds ratio) at 6 months with warfarin compared to DOACs: 0.15 (0.02−1.36); bleeding risk (odds ratio) at 6 months with warfarin compared to DOACs: 1.14 (0.33−3.95); death risk (odds ratio) at 6 months with warfarin compared to DOACs: 0.89 (0.22−3.55)	Figures 4-10
Risk for bias across studies		There was low risk for bias in 33% of items assessed, with a high risk rate of 24%. Remaining 43% had unclear risk for bias.	Figure 2
Additional analysis		There were no additional analyses.	x
Discussion			
Summary of evidence	24	Findings suggest, with low-strength evidence, that DOAC treatment is ineffective as secondary treatment of APS. Nonetheless, high-risk patients may have worse outcomes, suggesting that in this subset of patients DOAC use should be avoided, resulting in a selection bias in the overall analysis.	7−15
Limitations	25	The major limitation of this study was the incomplete data reported and heterogeneity of studies included. Other limitations included that this study was not a peer-reviewed systematic analysis, risk for publication bias of Patients with APS treated with DOACs, and reporting bias with pooled data.	16−19
Conclusions	26	Present evidence suggests inferiority of DOACs compared to warfarin in high-risk Patients with APS, although the level of evidence is low. Meta-analysis conducted with 3 biased clinical trials showed a trend toward inferiority	20

Table I. (*Continued*)

Section/Topic	No.	Checklist Item	Page No.
		of DOACs compared to warfarin, without statistical significance. The overall rate of relapse that the systematic review of the literature was similar to the rate described in international registries of patients given the standard-of-care treatment. Decisions on using them should be made cautiously, especially in high-risk patients, namely, those with recurrent events, arterial and venous thrombosis, or in need of immunosuppressant treatment. More data are needed in order to have strong evidence of effectiveness of DOACs in low-risk Patients with APS. There is an undue difference between reported cases and the data compiled. A more systematic way of reporting cases and sharing datasets would address the problem; there is still room to define a series of recommendations when reporting cases of APS syndrome.	
Funding	27	This systematic review and meta-analysis received no public or private funding. J.S.-R. participated in the protocol design, data collection, data analysis, and manuscript writing and review; G.E. participated in the initial idea of systematic review, protocol design, and manuscript writing and review; R.C. participated in manuscript writing and review; and D.V. conducted data analysis for meta-analysis. All authors approved the final version of the manuscript submitted to the journal.	x

ACR = American College of Rheumatology; APS = antiphospholipid syndrome; DOACs = direct oral anticoagulants; D.V. = David Varillas; EULAR = European League Against Rheumatism; G.E. = Gerard Espinosa; J.S.-R. = Jorge Sanchez-Redondo; PICO = Participants-Intervention-Comparison/Comparator-Outcome search strategy; PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses; R.C. = Ricard Cervera.

nonconfirmed APS (seronegative APS, seropositive with nonclinical criteria APS features), previous treatment if any, immunologic profile, APS type (primary or associated with other diseases), relevant comorbidities, prior APS-associated events (venous and arterial thrombosis, obstetric manifestation), number of prior events, time on VKA treatment prior to switch to DOAC, reasons for treatment switch, type and dose of DOAC used, duration of follow-up, outcomes (thrombosis and type, any APS-associated nonthrombotic outcomes, mortality, no thrombotic recurrence), time to outcome, associated drugs (eg, antiaggregants, glucocorticoids, or immunosuppressant agents), bleeding events (major or minor) previous to and during DOAC use, smoking status, noncriteria APS-related events prior to DOAC use, and factors associated with specific outcomes (comorbidities, treatment withdrawal). Data from all recruited patients were taken from the literature. We conducted both a descriptive analysis of available data and a comparative analysis between patients with and without recurrent thrombosis.

Unavailable, inaccurate, and unreliable data were excluded from analysis, as described: if there were no available data in any field, they were not included in the analysis despite the inclusion of the remainder of data; if treatment was described as *oral anticoagulation* with no concretion of DOAC or VKA, data from the specific patient was not included in the analysis; if treatment was described as *direct oral anticoagulant* or *new (oral) anticoagulant,* data were included with blank space in the type and dose of DOAC fields; whenever there were reasonable doubts about any patient included in 2 or more different publications, all except 1 were excluded from the analysis; if a series of patients was reported as an aggregate, whenever the data were given with mean (SD), the mean (age, follow-up) of the group of patients in the series was used; if any other data were provided but were unrelated to a specific patient outcome, given in a 1-to-1 relationship, the patient's data were excluded from the comparative analysis but were taken into account for descriptive analysis. Patient entry was duplicated if a patient received 2 or more courses of DOACs.

Among retrieved articles, we selected clinical trials the data from which we conducted a meta-analysis.

Statistical Analysis

A descriptive analysis of the whole sample was made. Results from continuous variables are presented as means (SD) and categorical data as number (%). In cases in which information was available, we categorized patients according to the presence of thrombosis recurrence with DOAC treatment to determine associated factors. For statistical evaluation, a contingency table test was used (the Fisher exact test for 2 variables or the Pearson χ^2 test for >2 variables) to identify significant differences or associations among the groups for qualitative variables and the Wilcoxon test was used for the quantitative ones. Differences in which $P < 0.05$ were considered significant. Significant differences on univariate comparisons were then retested by forward multivariate logistic regression, with calculation of odds ratio (OR) estimates and 95% CI. The data were collected in an Excel database (Microsoft Corp, Redmond, Washington), and all statistical analysis was performed with R software version 3.5, powered by RStudio version 1.1.453, in association with R commander 2.4-4. The dataset created for this study is available at figshare and datadryad. Meta-analysis was performed using Review Manager version 5.3 from the Cochrane Collaboration.[20]

RESULTS

Literature Search

We found 1503 articles and abstracts fulfilling the described search criteria, of which 138 were selected. After a check for duplicates, the final number of articles included in the present review was 65 (5 were excluded due to insufficient data provided [3 with no data of APS diagnosis and 2 with no outcome provided]) (Figure 1).[13–18,20–72] Although there were 3 articles from Sciascia et al[13,32,35] that suggested redundant information, patients were included just once (from the larger study[13]), and the other 2 papers[32,35] were reviewed in order to fulfill as much data as possible.

The main characteristics of included studies are described in Table II. There was great variability in the data reported in the different studies, with a general lack of information in the majority of the variables (with 14,856 empty entries from a total of 21,960, representing 67.7% of them). Most of the

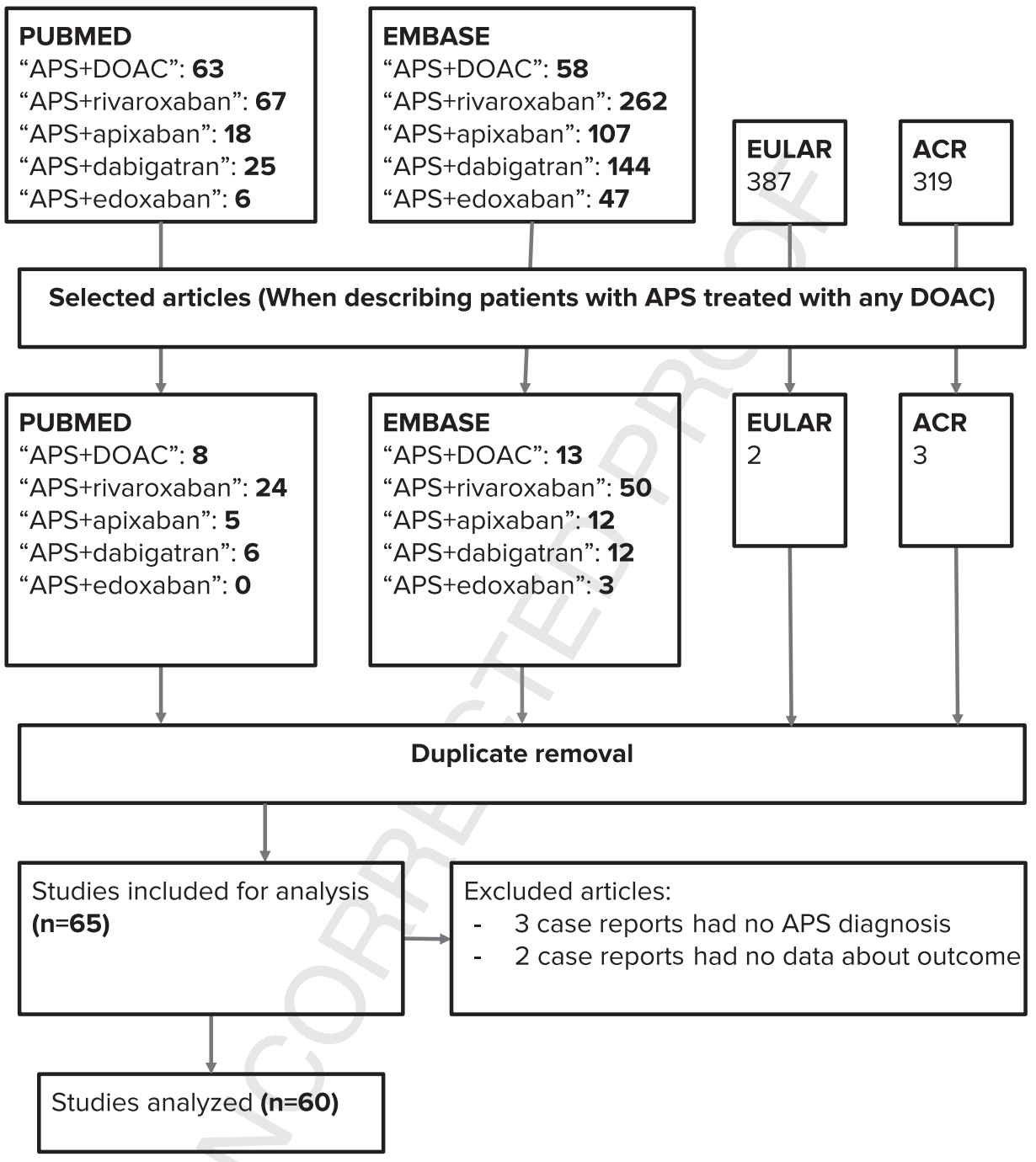

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[19] flow chart of article research results and selection process. ACR = American College of Rheumatology; APS = antiphospholipid syndrome; DOAC = Direct oral anticoagulant; EULAR = European League Against Rheumatism.

Table II. Main characteristics of studies finally included in the systematic review of the literature.

Study	Type of Study	No. of Patients	Type of DOAC	Type of Event	Duplicates	Comments
Sciascia and Hunt[13]	Prospective	18	R	Venous	Refs 31 and 34	
Noel et al[14]	Retrospective	26	R, D	V&A		
Satybaldyeva et al[24]	Prospective	28	D	ND		Pooled data
Unlu et al[26]	Retrospective	19	R, D	V&A		Pooled data if no relapse
Sciascia et al[32]	Prospective	11*	R	Venous	Refs 13 and 34	
Gerotziafas et al[34]	Prospective	28	R	Venous		
Sciascia et al[35]	Prospective	6*	R	Venous	Refs 13 and 31	
Garret[45]	Retrospective	139	R, D	Venous		Pooled data
Restrepo Correa[47]	Retrospective	7	R	V&A		
Abu-Zeinah and Oromendia[49]	Retrospective	9	ND	ND		Pooled data no time to event data
Leblebjian[50]	Retrospective	41	ND	ND		Pooled data no time to event data
Gundabolu et al[53]	Retrospective	14	ND	V&A		Pooled data no time to event data
Haładyj and Olesińska[58]	Prospective	23	R	V&A		†
Cohen et al[9]	Clinical trial	57	R	Venous		Pooled data
Goldhaber et al[6]	Clinical trial	71	D	ND		Pooled data
Resseguier et al[64]	Retrospective	21	R	V&A		Discordant data between table and text
Betancur et al[66]	Retrospective	8	R	V&A		
Kunk et al[67]	Retrospective	11	R, A	V&A		No demographic data
Malec et al[68]	Prospective	56	R, D, A	V&A		
Pengo et al[71]	Clinical trial	59	R	V&A		
Refs 15–18, 21–23, 25, 27–31, 33, 36–44, 46, 48, 51–52, 54–57, 59–63, 65, 69, and 70	Case report	68	R, D, A	V&A		Variable information reported

A = apixaban; D = dabigatran;
ND = not defined; R = rivaroxaban; Ref = reference number; V&A = venous and arterial.
* After removing duplicates.
† Description of 1 patient with thrombotic recurrence, but the study does not indicate which patient this was.

studies presented pooled data that interfered with the analysis, resulting in a loss of information regarding the specific characteristics of the patients who relapse. With this kind of pooled data, there was a risk that those characteristics could have gotten mixed with those of the rest of the patients. Some data were not collected, because of a lack of confidence (differences in time to relapse described in the text compared to 2 different tables provided in the article[35]). In addition, the data from 1 case with thrombotic relapse were not included because it was impossible to identify the patient from the information in the article.[48] Finally, in 3 cases, authors were contacted in order to retrieve lacking data, with successful responses from 2 of them.

Regarding the small amount of data available, an additional search was performed in clinical collaborative platforms, searching for datasets, figshare (searched with the *dataset only* filter: 55 results for *dabigatran,* 48 results for *rivaroxaban,* 44 results for *apixaban,* and 15 for *edoxaban*) and datadryad (search in "all fields," ie, all search terms retrieved the same only dataset), with no findings relevant to the purpose of this review.

Systematic Review

General Characteristics of Patients

Overall, 728 patients, accounting for 731 courses of treatment with DOACs, were identified (Table III). Of those, 66.8% were female and the mean age was 42.8 (11.9) years (range, 17−81 years). Most of the patients (103/180 [57.2%]) had primary APS, whereas 68/180 (37.8%) had APS associated with systemic lupus erythematosus (SLE), 3 (1.7%) with systemic vasculitis, and 3 (1.7%) with systemic sclerosis. The remaining 3 patients had Sjögren syndrome, mixed connective tissue disease, and/or inflammatory bowel disease. With regard to the history of thrombotic events, the majority of patients (78.2%) presented with venous thrombosis, 9.4% with arterial thrombosis, and 12.4% of patients had both arterial and venous events prior to initiating DOAC treatment. Information on the number of previous thrombotic events was available in 113 cases, 15 (13%) of whom had had 3 or more previous thromboses.

The distribution of patients' aPL profiles is also described in Table III. Of note, nearly half (48.3%) presented with triple aPL positivity. Anti-phosphatidylethanolamine and anti-phosphatidylserine antibody testing was positive in 2 patients each, 1 of whom did not show any other aPL positivity, which did not fulfill the laboratory criteria for APS. Other causes of thrombophilia were described in 8 patients (4 with factor V Leyden, 2 with prothrombin G20210A mutation, and 1 with C-reactive protein deficiency). In 1 additional case, Q15 thrombophilia was not otherwise specified.

Rivaroxaban was the DOAC most frequently used in 76.6% of the cases, followed by dabigatran in 20.8%, and apixaban in 2.6% (Table III). None of the reported patients were using edoxaban. In the majority of patients, the dose of dabigatran was not well established (ie, not reported or pooled data from different doses). From the 134 patients on whom information about previous anticoagulant treatment was given, 112 (83.6%) had previously been treated with VKA with or without low-molecular-weight heparin (LMWH), 5 (3.7%) had received only LMWH, 2 (1.5%) had received fondaparinux, and 15 (11.2%) did not receive any thromboprophylaxis prior to the use of DOACs. In fact, of these 15 patients, 5 (33.3%) received a DOAC as first-line APS therapy.

The mean time from the previous thrombotic event to the use of DOAC was 28.0 (39.9) months (range, 0−153 months), and the mean duration of DOAC treatment (follow-up) was 14.9 (10.5) months (range, 0.3−76 months) (data not shown). Q16

Reasons for Switching Between Anticoagulant Therapies

The main reasons for therapy switching (data available from 96 patients) were international normalized ratio lability or poor adherence to international normalized ratio monitoring (52 [54.1%]), recurrent thrombosis during VKA treatment (12 [12.5%]), physician's choice (10 [10.4%]), patient's choice (10 [10.4%]), bleeding event during VKA (8 [8.3%]), and other reasons (4 [4.2%]) (Table III). In 1 patient, DOAC was prescribed due to arterial cardioembolism associated with atrial fibrillation; APS diagnosis was made while the patient was treated with a DOAC, and treatment remained unchanged.

Table III. Main characteristic of patients with antiphospholipid syndrome treated with direct oral anticoagulants according to the presence of recurrent thrombosis.

Characteristic	No Thrombosis (n = 629)	Thrombosis (n = 102)	Total (N = 731)	P
Age, mean (SD), y	42.0 (12.7) (n = 182)	41.9 (14.5) (n = 69)	42.8 (11.9) (n = 251)	NS
Sex, n/N (%)				
Female	168/239 (70.3)	39/71 (54.9)	207/310 (66.8)	NS
Male	71/239 (29.7)	32/71 (45.1)	103/310 (33.2)	NS
APS type, n/N (%)				
Primary	68/130 (52.3)	35/50 (70)	103/180 (57.2)	NS
Associated with SLE	53/130 (40.8)	15/50 (30)	68/180 (37.8)	NS
Associated with other autoimmune diseases	9/130 (6.9)	0/50 (0)	9/180 (5.0)	NS
Comorbidities, n/N (%)				
None	18/22 (81.8)	4/22 (18.9)	22/47 (46.8)	NS
Proteinuria (excluding active lupus nephritis)	5/6 (83.3)	1/6 (16.7)	6/47 (12.8)	NS
Thrombophilia	5/8 (62.5)	3/8 (37.5)	8/47 (17.0)	NS
Chronic kidney disease	4/7 (57.1)	3/7 (42.9)	7/47 (14.9)	NS
Active SLE	0/2 (0)	2/2 (100)	2/47 (4.3)	NS
DOAC agent n/N (%)				
Rivaroxaban	435/565 (79.4)	70/94 (79.2)	505/659 (76.6)	NS
Dabigatran	117/565 (17.9)	20/94 (16.9)	137/659 (20.8)	NS
Apixaban	13/565 (2.7)	4/94 (3.9)	17/659 (2.6)	NS
Prior treatment, n/N (%)				
VKA	81/93 (87.1)	31/41 (75.6)	112/134 (83.6)	NS
None	10/93 (10.8)	5/41 (12.2)	15/134 (11.2)	NS
LMWH	1/93 (1.1)	4/41 (9.8)	5/134 (3.7)	0.04
Fondaparinux	1/93 (1.1)	1/41 (2.4)	2/134 (1.5)	NS
Time on previous treatment, mean (SD), mo	25.4 (40.4) (n = 49)	33.8 (39.1) (n = 22)	28.0 (39.9) (N = 71)	NS
Previous clinical manifestations, n/N (%)				
Venous	253/306 (82.7)	38/66 (57.5)	291/372 (78.2)	NS
Venous and arterial	28/306 (9.2)	18/66 (27.3)	46/372 (12.4)	<0.0001
Obstetric morbidity	26/306 (8.5)	5/66 (7.58)	31/372 (8.3)	NS
Arterial	25/306 (8.2)	10/66 (15.2)	35/372 (9.4)	NS
No. of previous thromboses, mean (SD)	1.67 (1.45) (n = 72)	1.8 (0.87) (n = 42)	1.72 (1.27) (N = 114)	0.012
Reason for switching, n/N (%)				
INR control	46/71 (64.8)	6/25 (24)	52/96 (54.1)	NS
Recurrent thrombosis on VKA	10/71 (14.1)	2/25 (8)	12/96 (12.5)	NS
Patient's choice	2/71 (2.8)	8/25 (32)	10/96 (10.4)	0.001
Physician's choice	6/71 (8.5)	4/25 (16)	10/96 (10.4)	NS
Hemorrhage on VKA	4/71 (5.6)	4/25 (16)	8/96 (8.3)	NS

Table III. (*Continued*)

Characteristic	No Thrombosis (n = 629)	Thrombosis (n = 102)	Total (N = 731)	P
Other	6/71 (8.4)	5/25 (20)	4/96 (4.2)	NS
aPL profile, n/N (%)				
Triple aPL positivity	85/185 (45.9)	34/61 (55.7)	119/246 (48.3)	NS
Isolated aCL	36/185 (19.5)	7/61 (11.5)	43/246 (17.4)	NS
Isolated LAC	17/185 (9.2)	5/61 (8.2)	22/246 (8.9)	NS
LAC plus aCL	17/185 (9.2)	5/61 (8.2)	22/246 (8.9)	NS
aCL plus anti−α_2-GPI	14/185 (7.6)	8/61 (13.1)	22/246 (8.9)	NS
Isolated anti−α_2-GPI	11/185 (5.9)	1/61 (1.6)	12/246 (4.9)	NS
LAC plus anti−α_2-GPI	5/185 (2.7)	1/61 (1.6)	6/246 (2.4)	NS
Corticosteroids dosing, n/N (%)				
None	17/30 (56.7)	7/9 (77.8)	24/39 (61.5)	NS
<7.5 mg/d	11/30 (36.7)	0/9 (0)	11/39 (28.2)	NS
7.5−30 mg/d	1/30 (3.3)	2/9 (22.2)	3/39 (7.7)	NS
>30 mg/d	1/30 (3.3)	0/9 (0)	1/39 (3.5)	NS
Hydroxychloroquine use, n/N (%)	39/55 (70.9)	5/10(50)	44/65 (67.7)	NS
Immunosuppressant use, n/N (%)	7/55 (12.7)	5/12 (41.7)	12/67 (17.9)	0.03
Antiaggregant use, n/N (%)				
None	21/27 (77.8)	6/12 (50)	27/39 (69.2)	NS
Aspirin	5/27 (18.5)	4/12 (33.3)	9/39 (23.1)	NS
Clopidogrel	1/27 (3.7)	0/12 (0)	1/39 (2.6)	NS
Aspirin + clopidogrel	0/27 (0)	2/12 (16.7)	2/39 (5.1)	NS
Bleeding on DOACs therapy	37/272 (13.6)	6/37 (16.2)	43/309 (13.9)	NS

anti−α_2-GPI = anti-α_2-glycoprotein I antibody; aCL = anticardiolipin antibody; aPL = antiphospholipid antibodies; DOACs = direct oral anticoagulants; INR = International Normalized Ratio; LAC = lupus anticoagulant; LMWH = low molecular weight heparin; NS = not statistically significant; SLE = systemic lupus erythematosus; VKA = vitamin K antagonist.

Outcomes

Q17 Overall, the prevalence of thrombosis recurrence was 102 in 731 (13.9%) courses of DOAC treatment. Five patients had >1 thrombotic episode during DOAC treatment. The majority of events took place in the first year of treatment, with 9 of 53 patients (17%) having a reported time to re-thrombosis of >12 months of treatment with DOAC (range, 15−34 months). The mean duration of DOAC treatment at the time of re-thrombosis was 7.5 (8.1) months (range, 0.2−34 months). Of note, confounding factors were described in 11 cases: therapeutic noncompliance (4 cases), Libman-Sacks endocarditis (3 cases), catastrophic APS (2 cases), and SLE flare requiring immunosuppression (2 cases). Recurrent thromboses took place in venous vessels in 43 cases (42.2%), in arterial vessels in 42 (41.2%), both in venous and arterial vessels in 2 (2%), and microthrombus in 5 (4.9%). In 10 cases (9.8%), the type of relapse was not reported (data not shown). Q18

Comparative Analysis Among Patients With APS on DOAC Treatment, According to the Presence of Thrombotic Recurrence

A stratified analysis of patients with APS who presented with thrombotic recurrence versus those who did not present with thrombosis recurrence during DOAC therapy is depicted in Table III. Information about variables is reported in 37% of patients with recurrent thrombosis. However,

key variables such as the DOAC agent (84%) and the aPL profile (57%) were more frequently reported. Duration of follow-up was reported in 58% of cases.

Of note, the independent factors for the risk of thrombosis with DOAC treatment were the number of previous thromboses (1.80 [0.87] vs 1.67 [1.45]; $P = 0.012$), previous arterial and venous thrombosis (27.3% vs 9.2% [$P < 0.0001$]; OR = 3.72 [95% CI, 1.91−7.25]), previous treatment with LMWH (9.8% vs 1.1% [$P = 0.04$]; OR = 9.95 [95% CI, 1.08−91.97]), patient's choice as the mean reason for switching anticoagulant treatment (32% vs 2.8% [$P = 0.001$]; OR = 16.24 [95% CI, 3.16−83.52]), and the use of immunosuppressant treatment (42% vs 13% [$P = 0.03$], OR = 4.9 [95% CI, 1.21−19.76]). In the last case, 4 patients developed thrombosis on rituximab treatment, representing the 100% of reported patients with rituximab, and it was not possible to calculate OR, $P < 0.001$ (Fisher exact test). Given the lack of data regarding immunosuppressant treatment in patients with APS, we were not able to properly analyze each treatment separately. The rate of recurrent thrombosis was higher in patients with SLE activity (15% of cases of active SLE and 0 of those with inactive SLE).

The aPL profile did not seem to modify the risk for recurrent thrombosis in patients with APS treated with DOACs (Table III). Unfortunately, the lack of data on aPL levels precluded any analysis about their role in thrombosis risk.

Safety Profile

Unfortunately, some studies[71] reported only major and not minor bleeding. Overall, 43 of 309 patients (13.9%) developed bleeding during DOAC treatment. There were 11 cases (25.6%) of major bleeding reported: 8 patients were on rivaroxaban, 1 was on apixaban, and 2 were on a nonspecified DOAC. One patient presented disseminated intravascular coagulation and catastrophic APS while on rivaroxaban.

Six of 7 patients with major bleeding and immunologic profile had triple aPL positivity. There were no reports of death due to bleeding. One of 43 patients had bleeding prior to treatment switch to DOAC.

Meta-Analysis

Selected Clinical Trials and Risk-for-bias Assessment

Among selected articles, there were only 3 randomized controlled trials (Cohen et al,[9] Goldhaber et al,[6] and the TRAPS [Rivaroxaban Versus Warfarin in High-Risk Patients With Antiphospholipid Syndrome] study[71]). Outcomes analyzed were: thrombosis after 6 months, overall bleeding after 6 months, and reported death of any cause after 6 months. Subgroups of arterial thrombosis after 6 months, venous thrombosis after 6 months, major bleeding after 6 months, and clinically relevant bleeding after 6 months were included in the meta-analysis. We considered bleeding *clinically relevant* if a clinical trial reported bleeding as clinically relevant according to their own criteria and protocol.

We assessed the risk for bias in included studies using details provided in Chapter 8.7a of the Cochrane Handbook for Systematic Reviews of Interventions (https://training.cochrane.org/handbook).

We include a summary of the risks for bias in Table II, a methodologic quality graph in Figure 2, and a methodologic quality summary in Figure 3.

Random Sequence Generation

We considered the study by Cohen et al[9] as having a low risk for bias as that study explicitly reported the randomization process. Goldhaber et al[6] did not explicitly report the randomization process but gave data from other randomized, controlled trials in which the randomization sequence generation was described. TRAPS[71] assigned patients to the randomization process according to sex and the presence of underlying autoimmune disease; thus, we considered the study as having a high risk for randomization bias.

Allocation Concealment

In Cohen et al,[9] randomization was performed by a Web-based independent randomization service (sealed envelope, London, UK) to ensure allocation concealment. There was insufficient information about the process of generating the sequence to allow for a "low-risk" or "high-risk" assessment in Goldhaber et al.[6] In TRAPS,[71] participants or

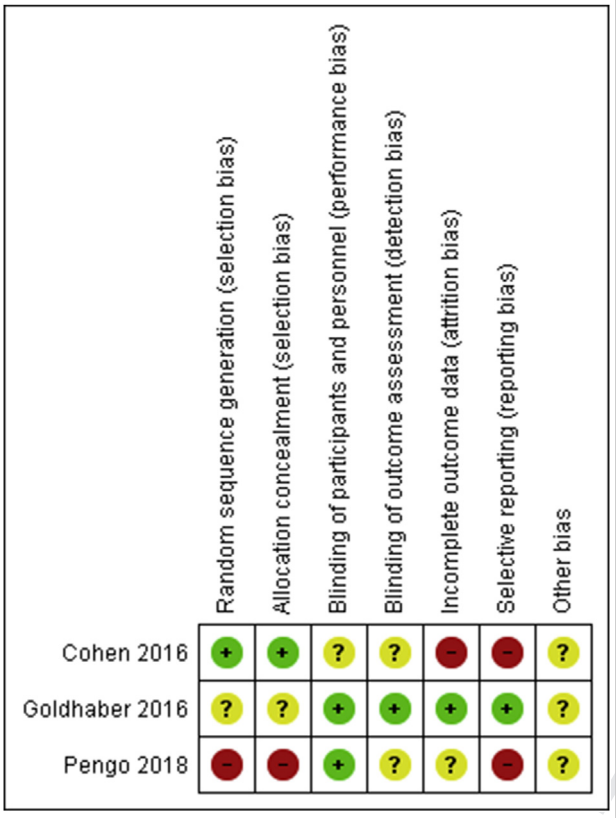

Figure 2. Summary of risk for bias. Review of each author's opinions about each risk-for-bias item included in the study.

investigators who recruited participants could anticipate assignments and therefore introduce selection bias, such as assignment according to any other explicitly unconcealed procedure.

Blinding of Participants and Personnel

No blinding of personnel or participants was described in the protocol of Cohen et al[9]; thus, we considered the study as having an unclear risk for bias. The blinding of participants and key staff was ensured in the Goldhaber et al[6] and TRAPS[71] studies.

Blinding of Outcomes Assessments

No outcomes assessments were described as blinded in the study by Cohen et al.[9] In the study by Goldhaber et al,[6] an evaluation of blinding was performed, but it is possible that the blinding was broken and that the measurement of the results was influenced by the lack of blinding. This outcome was not tackled in the TRAPS[71] study.

Incomplete Outcomes Data

We considered the study by Cohen et al[9] at high risk for bias due to the lack of data on thrombosis outcomes reported. Goldhaber et al[6] had no missing data on results. We classified as unclear the risk for bias in the TRAPS[71] study due to the absence of data on thrombosis and death outcomes reported.

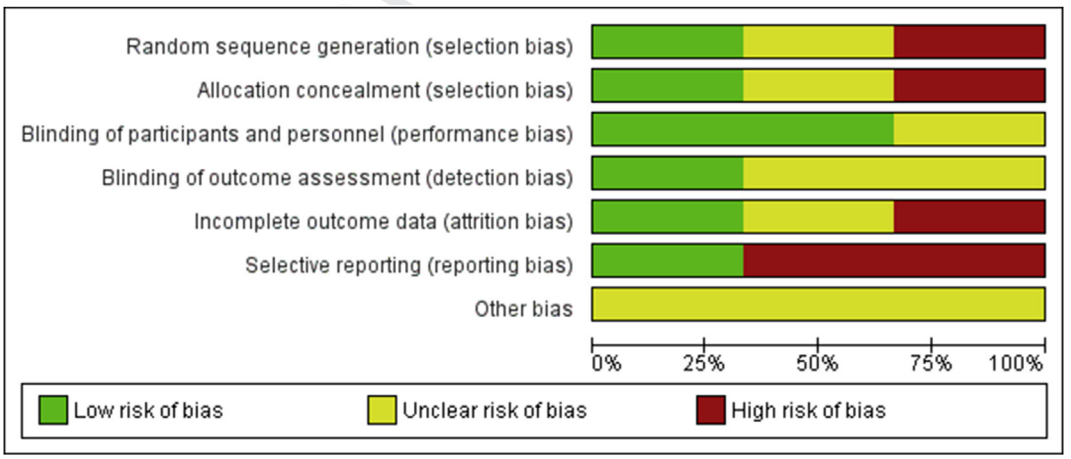

Figure 3. Risk for bias. Review of each author's opinions about each risk-for-bias item presented as percentages across all subjects.

Selective Reporting

The Cohen et al[9] and TRAPS[71] studies contained 1 or more unspecified primary outcomes. The study protocol of Goldhaber et al[6] was available, and all results (primary and secondary) that were of interest for review were described and prespecified.

Other Bias

There was insufficient information to assess whether there was a significant risk for bias in any of the randomized controlled trials.

Meta-analysis Results

Graphic representation of the findings is shown in Figures 4–6.

Major Bleeding at 6 Months

All 3 randomized controlled trials, with a total of 366 participants, measured major bleeding.[6,9,71] Researchers reported data as a categorical outcome (presence or absence of major bleeding). The risk ratio (RR) for major bleeding at 6-month follow-up of treatment with warfarin was 0.94 (95% CI, 0.14 to 6.30; $P = 0.93$; Figure 4A). The quality of the evidence was low due to concerns about attrition bias, selection bias, selective reporting, and absence of events in one of the studies. Q19

Clinically Relevant Bleeding at 6 Months

Two studies with a total of 258 participants measured clinically relevant bleeding (Cohen et al,[9] Goldhaber et al[6]). Researchers reported data as a categorical outcome (presence or absence of clinically relevant bleeding). The RR for clinically relevant bleeding at 6-month follow-up of treatment with warfarin was 1.55 (95% CI, 0.57–4.20; $P = 0.18$; Figure 4B). The quality of the evidence was low due to concerns about attrition bias, selection bias, and selective reporting. Q20

Thrombosis at 6 Months

Two studies with a total of 219 participants measured thrombosis (Cohen et al,[9] TRAPS[71]). Researchers reported data as a categorical outcome (presence or absence of thrombosis). The RR for thrombosis at 6-month follow-up of treatment with

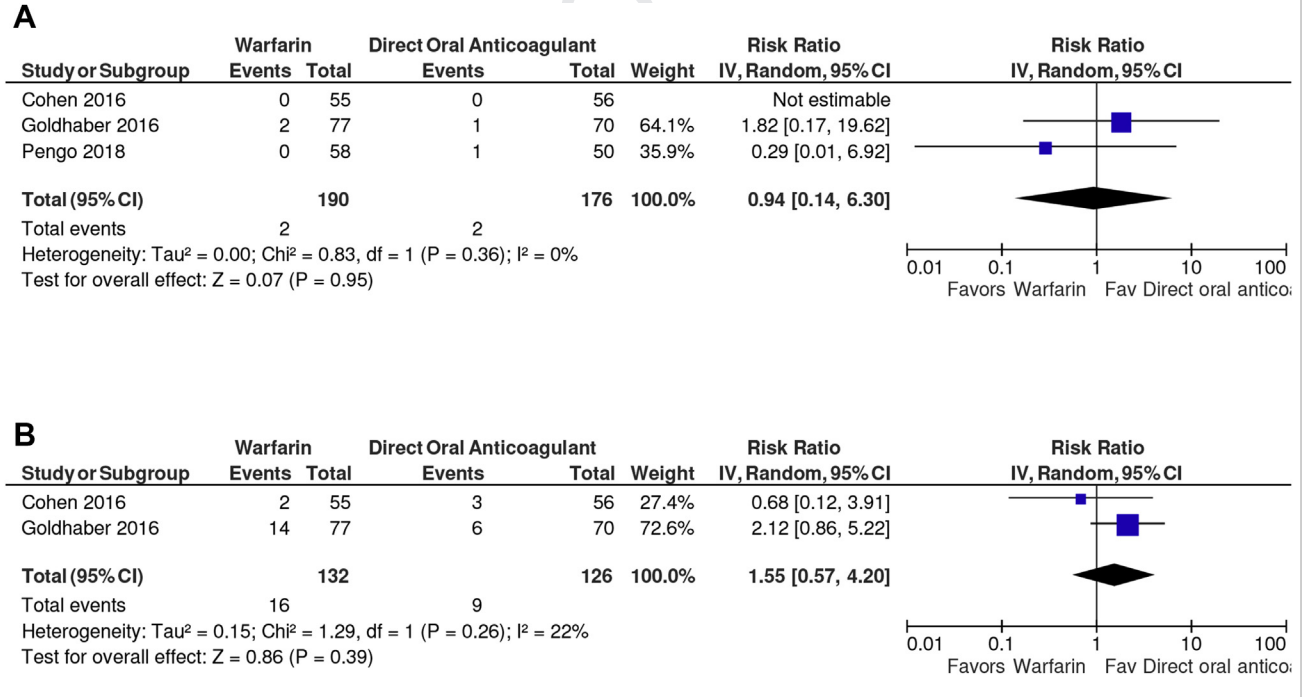

Figure 4. Major (A) and clinically relevant (B) bleeding at 6 months.

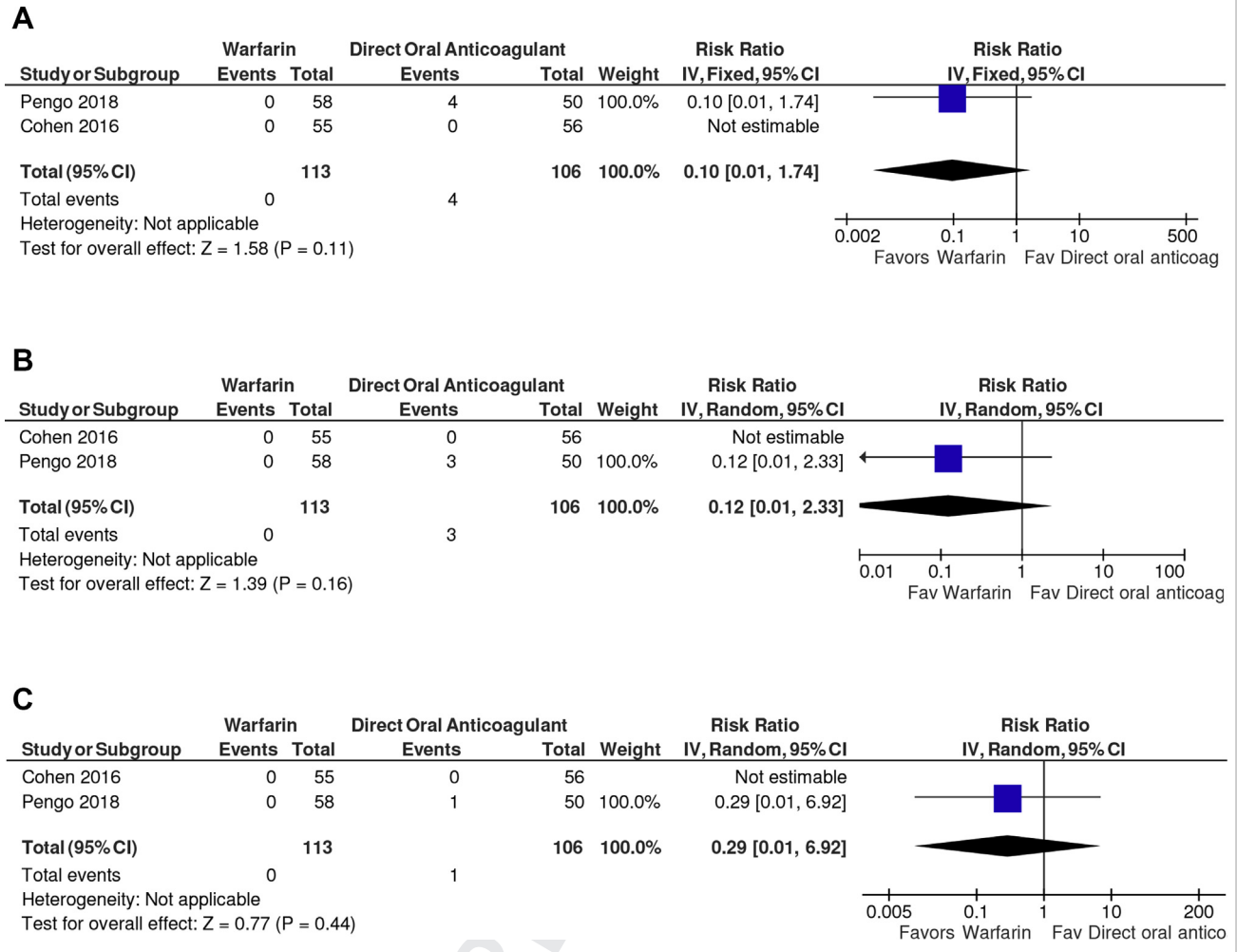

Figure 5. Any (A), arterial (B), and venous (C) thrombosis at 6 months.

warfarin was 0.10 (95% CI, 0.01−1.74; $P = 0.13$; Figure 5A). The quality of evidence was low due to a high risk for biases in selection, randomization, attrition, and absence of events in one of the studies.

Arterial Thrombosis at 6 Months

Two studies with a total of 219 participants measured arterial thrombosis (Cohen et al,[9] TRAPS[71]). Researchers reported data as a categorical outcome (presence or absence of arterial thrombosis). The RR for arterial thrombosis at 6-month follow-up of treatment with warfarin was 0.12 (95% CI, 0.01−2.33; $P = 0.18$; Figure 5B). The quality of the evidence was low due to concerns about attrition bias, selection bias, selective reporting, and absence of events in one of the studies.

Venous Thrombosis at 6 Months

Two studies with a total of 219 participants measured venous thrombosis (Cohen et al,[9] TRAPS[71]). Researchers reported data as a categorical outcome (presence or absence of venous thrombosis). The RR for venous thrombosis at 6-month follow-up of treatment with warfarin was 0.29 (95% CI, 0.01−6.92; $P = 0.48$; Figure 5C). The quality of the evidence was low due to concerns about attrition bias, selection bias, selective reporting, and absence of events in one of the studies.

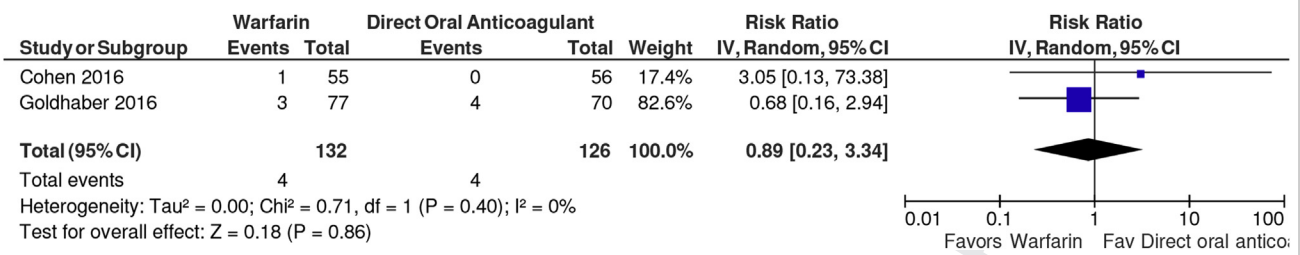

Figure 6. Death at 6 months.

Death Risk at 6 Months

Two studies with a total of 258 participants measured the risk for death (Cohen et al,[9] Goldhaber et al[6]). Researchers reported data as a categorical outcome (presence or absence of death). The RR for death at 6-month follow-up of treatment with warfarin was 0.89 (95% CI, 0.23−3.34; $P = 0.95$; Figure 6). The quality of the evidence was low due to concerns about attrition bias, selection bias, and selective reporting.

We conducted no planned subgroup or sensitivity analyses due to the lack of data.

DISCUSSION

Results from this meta-analysis suggest a trend toward a lack of efficacy of DOACs in the secondary prevention of thrombosis in patients with APS. However, the quality of evidence was markedly low and there were no statistically significant differences. Due to the lack of data, we did not conduct subgroup analyses, which could have highlighted a difference according to clinical or immunologic risk status of APS. According to the results of the present systematic literature review, the overall frequency of developing new thrombosis while on DOACs was slightly lower than those reported in the literature in the largest cohort of patients with APS taking VKA and/or antiaggregants (14.8% vs 24.8%).[73] This finding suggests the general efficacy of DOACs in this clinical context, in contrast with results from the meta-analysis. This difference can be explained by several hypotheses. On one hand, the analysis of the systematic review is a simple comparison of the descriptive results in larger cohorts of patients with APS, regardless of treatment. Therefore, the evidence to support this hypothesis is lacking. On the other hand, almost half of patients included in the meta-analysis were selected high-risk patients with APS, and the other half showed no events in any arm of the randomized controlled trial, resulting in the possibility of a selection bias and a high risk for assuming a lack of efficacy in all patients with APS due to a lack of efficacy in high-risk patients with APS.

Although we already have evidence of a poorer prognosis in patients with high-risk APS (namely, those with triple aPL positivity),[71] the analysis of overall series suggests that some low-risk patients may benefit from the use of DOACs. Nonetheless, meta-analysis of available clinical trials shows a trend toward a higher risk for thrombosis in patients with APS on DOAC treatment.

The majority of events occur in the first year of treatment, and after 15 months the RR for thrombosis decreases dramatically.

These results suggest that there is still a subset of patients who seem not to benefit from the use of DOACs. In an interim analysis of data from the TRAPS study,[71] the subgroup of triple aPL−positive patients had a significantly greater prevalence of thrombosis on DOACs than the group that had 1 or 2 positive aPL antibody results. Nonetheless, the final result of the present review failed to detect this difference. In the TRAPS study,[71] the authors described 9 thromboses in 59 patients (15%), whereas in the rest of the studies and case reports of triple aPL−positive patients, the prevalence of thrombosis on DOAC treatment was 42% (25 thromboses in 60 patients). It is unclear whether the different thrombosis rate in the TRAPS study compared with the other studies was due to a

publication bias. The TRAPS study required standardized treatment and strict follow-up, which may have led to a better outcome. In addition, as only triple aPL−positive patients were included in the TRAPS study, it remains unclear whether a different response to treatment may exist between triple aPL−positive patients and those who have a different aPL profile. More data are needed in order to assess whether the subtype of antibodies and their serum levels may modulate thrombotic recurrence in patients with APS treated with DOACs. There were insufficient data available to determine the influence of other noncriteria APS-related antibodies in the outcomes of these patients. In patients with recurrent events, sometimes in combination despite anticoagulant treatment, thromboses are more likely to recur with DOAC treatment than in patients with few previous thromboses, suggesting that these drugs may have been of efficacy similar to that of VKA in this subset of patients. Personal history of a combination of arterial and venous events is another risk factor for thrombosis on DOACs.

A careful selection of patients is needed when considering switching therapy from LMWH or VKA to a DOAC. The finding of patient's decision to change therapy as a risk factor for thrombosis reinforces the importance of indications and contraindications of a switch in treatment and the necessity of expertise in the field.

It is essential to know not only which patients may benefit from switching therapy, but also when to do it. Although results show a difference in thrombotic events between patients treated with immunosuppressant agents and those who are not, suggesting the role of immunosuppressant agents in the rate of thrombosis in patients treated with DOACs, an active inflammation that requires treatment with these drugs may be a confounding factor. In fact, the rate of recurrent thrombosis was higher in patients with reported active SLE. The data suggest that DOACs should be avoided also in patients with active inflammatory disease or in need of immunosuppressant treatment.

The great heterogeneity of studies results in an overall high risk for bias, including publication bias and confirmation bias, as pulmonary thromboembolism can be overlooked as the cause of death in patients treated with thrombolytic drugs, as reported in one study.[73] According to those findings, the rate of death related to pulmonary thromboembolism may be higher than reported.

The major limitations of this study were the incomplete data reported and the heterogeneity of studies included. Key factors such as treatment compliance were reported in only a few cases. The shorter half-life of DOACs compared to VKA makes the assessment of compliance vital in order to avoid misestimation of effect. With regard to the treatment regimen, frequency of dosing was not properly reported. This is especially important in patients Q26 treated with LMWH as an adequate dose, and correct anticoagulation measured by anti-Xa activity may change the effect on venous thromboembolism.[74] More frequently reported but yet not enough was the duration of follow-up. Not having enough follow-up time could overestimate the efficacy of DOACs. The use of poster-type reports from congress supplements broadened the number of patients included. However, the type of data presentation may have interfered with further analysis, making the data useful only for calculation of thrombosis ratio, but did not allow for a subanalysis of variables. We tried ambitiously to collect published data on every patient receiving DOACs for APS. Notwithstanding, there were several treated patients included in non-APS selective trials and registries from whom available data were on composite end points, and therefore related information on patients with APS was impossible to acquire.

Cardiovascular risk factors such as smoking status, dyslipidemia, arterial hypertension, or type 2 diabetes mellitus were not reported, all of which may modulate thrombotic risk profile.[75,76]

Although the limitations are diverse, this is the largest review of DOACs used in patients with APS to date. Being systematic in the collection of data from case reports on patients with APS, and sharing datasets not only from large-scale clinical trials but also from congress communications, especially case series in which there are no tables of variables patient by patient, would improve, even in the scenario of weak-quality evidence, future research and analysis of what we know about this topic.

The quality of accumulated evidence on DOACs for secondary thrombosis prevention in patients with APS Q27 in the United States has recently been improving, but it is still low. Further studies designed to determine the

effectiveness of DOACs, some of them ongoing, and more complete subgroup analysis, may shed light on which patients with APS could be treated with DOACs, when to use DOACs, and which DOACs would be optimal.

CONCLUSIONS

The present evidence suggests inferiority of DOACs compared to warfarin in high-risk patients with APS, although the quality of evidence was low and differences were not statistically significant. Meta-analysis of data from 3 biased clinical trials showed a trend toward DOAC inferiority compared to warfarin, but without statistical significance. The overall rate of thrombotic relapse found in this systematic review of the literature was similar to that described in international registries of patients given the standard-of-care treatment. Decisions on using them should be carefully made, especially in high-risk patients, namely, those with recurrent events, arterial and venous thrombosis, or in need of immunosuppressant treatment. More data are needed in order to have strong evidence of the effectiveness of DOACs in low-risk patients with APS. There is an undue difference between reported cases and the data compiled. A more systematic way of reporting cases and sharing datasets would address the problem. New randomized controlled trials avoiding selection bias or targeting a different subgroup of patients with APS are needed to better understand the effects of DOACs in APS.

UNCITED REFERENCE

[4].

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CONFLICTS OF INTEREST

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