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

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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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