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Antiplatelet and anticoagulant agents for primary prevention of thrombosis in individuals with antiphospholipid antibodies (Review)

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[Intervention Review]

Antiplatelet and anticoagulant agents for primary prevention of thrombosis in individuals with antiphospholipid antibodies

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ABSTRACT

Background

Antiphospholipid syndrome (APS) is an autoimmune disease characterised by the presence of antiphospholipid (aPL) antibodies that have prothrombotic activity. Antiphospholipid antibodies are associated with an increased risk of pregnancy complications (recurrent miscarriage, premature birth, intrauterine growth retardation) and thrombotic events (both arterial and venous). The most common thrombotic events include brain ischaemia (stroke or transient ischaemic attack) and deep vein thrombosis. To diagnose APS, the presence of aPL antibodies in two measurements and at least one thrombotic event or pregnancy complication are required. It is unclear if people with positive aPL antibodies but without any previous thrombotic events should receive primary antithrombotic prophylaxis.

Objectives

To assess the effects of antiplatelet or anticoagulant agents versus placebo or no intervention or other intervention on the development of thrombosis in people with aPL antibodies who have not had a thrombotic event. We did not address obstetric outcomes in this review as these have been thoroughly addressed by other Cochrane Reviews.

Search methods

We searched the Cochrane Vascular Specialised Register (4 December 2017), the Cochrane Central Register of Controlled Trials (CENTRAL) (last search 29 November 2017), MEDLINE Ovid, Embase Ovid, CINAHL, and AMED (searched 4 December 2017), and trials registries (searched 29 November 2017). We also checked reference lists of included studies, systematic reviews, and practice guidelines, and contacted experts in the field.

Selection criteria

We included randomised controlled trials (RCTs) that compared any antiplatelet or anticoagulant agents, or their combinations, at any dose and mode of delivery with placebo, no intervention, or other intervention. We also included RCTs that compared antiplatelet or anticoagulant agents with each other or that compared two different doses of the same drug. We included studies performed in people of any age and with no history of thrombosis (as defined by APS Sapporo classification criteria or updated Sydney classification criteria), but with aPL antibodies confirmed on at least two separate measurements. The studies included both pregnant women who tested positive for

aPL antibodies and had a history of recurrent obstetric complications, as well as non-pregnancy related cases with positive screening for antibodies, in accordance with the criteria mentioned above.

Data collection and analysis

Pairs of authors independently selected studies for inclusion, extracted data, and assessed the risk of bias for the included studies and quality of evidence using GRADE. Any discrepancies were resolved through discussion or by consulting a third review author when necessary. In addition, one review author checked all the extracted numerical data.

Main results

We included nine studies involving 1044 randomised participants. The studies took place in several countries and had different funding sources. No study was at low risk of bias in all domains. We classified all included studies as at unclear or high risk of bias in two or more domains. Seven included studies focused mainly on obstetric outcomes. One study included non-pregnancy-related cases, and one study included both pregnancy-related cases and other patients with positive results for aPL antibodies. The remaining studies concerned women with aPL antibodies and a history of pregnancy failure. Four studies compared anticoagulant with or without acetylsalicylic acid (ASA) versus ASA only and observed no clear difference in thrombosis risk (risk ratio (RR) 0.98, 95% confidence interval (CI) 0.25 to 3.77; 4 studies; 493 participants; low-quality evidence). No major bleeding was reported, but minor bleeding risk (nasal bleeding, menorrhagia) was higher in the anticoagulant with ASA group as compared with ASA alone in one study (RR 22.45, 95% CI 1.34 to 374.81; 1 study; 164 participants; low-quality evidence). In one study ASA was compared with placebo, and there were no clear differences in thrombosis (RR 5.21, 95% CI 0.63 to 42.97; 1 study; 98 participants; low-quality evidence) or minor bleeding risk between the groups (RR 3.13, 95% CI 0.34 to 29.01; 1 study; 98 participants; low-quality evidence), and no major bleeding was observed. Two studies compared ASA with low molecular weight heparin (LMWH) versus placebo or intravenous immunoglobulin (IVIG), and no thrombotic events were observed in any of the groups. Moreover, there were no clear differences in the risk of bleeding requiring transfusion (RR 9.0, 95% CI 0.49 to 164.76; 1 study; 180 participants; moderate-quality evidence) or postpartum bleeding (RR 1.30, 95% CI 0.60 to 2.81; 1 study; 180 participants; moderate-quality evidence) between the groups. Two studies compared ASA with high-dose LMWH versus ASA with low-dose LMWH or unfractionated heparin (UFH); no thrombotic events or major bleeding was reported. Mortality and quality of life data were not reported for any of the comparisons.

Authors' conclusions

There is insufficient evidence to demonstrate benefit or harm of using anticoagulants with or without ASA versus ASA alone in people with aPL antibodies and a history of recurrent pregnancy loss and with no such history; ASA versus placebo in people with aPL antibodies; and ASA with LMWH versus placebo or IVIG, and ASA with high-dose LMWH versus ASA with low-dose LMWH or UFH, in women with aPL antibodies and a history of recurrent pregnancy loss, for the primary prevention of thrombotic events. In a mixed population of people with a history of previous pregnancy loss and without such a history treated with anticoagulant combined with ASA, the incidence of minor bleeding (nasal bleeding, menorrhagia) was increased when compared with ASA alone. Studies that are adequately powered and that focus mainly on thrombotic events are needed to draw any firm conclusions on the primary prevention of thrombotic events in people with antiphospholipid antibodies.

PLAIN LANGUAGE SUMMARY

Anticoagulant and antiplatelet drugs, or both, for reducing the risk of blood clots in susceptible individuals

Background

Antiphospholipid (aPL) antibodies are proteins produced by the immune system in some people that are directed against components of their own cells. The presence of such antibodies may increase the risk of developing blood clots (thrombosis) in the blood vessels or pregnancy-related complications (such as recurrent miscarriage, stillbirth, premature birth, or serious illness of a pregnant woman). Blood clots within arteries can cause strokes, resulting in brain damage or reversible neurological symptoms. Blood clots in veins are associated with a buildup of fluid in the limbs (oedema) and pain, and if moved or translocated, may cause a blockage in a major vessel in the lung (pulmonary embolism).

In individuals who have previously had a thrombotic event, two types of drugs are commonly used to prevent recurrent thrombotic events: anticoagulants and antiplatelet agents. Anticoagulants prevent clots (thrombus) formation by interfering with the activity of proteins involved in blood clotting (clotting factors), while antiplatelets, usually aspirin, prevent platelet aggregation and impair clot formation. The most common side effect of anticoagulant or antiplatelet treatment is a tendency to bleed. However, little is known about the benefits and harms of using anticoagulants and antiplatelets in people who have aPL antibodies but have not previously had any thrombotic event.

Review question

This review aimed to establish the potential benefits and harms of using anticoagulants and antiplatelet drugs for preventing thrombotic events, in people who are susceptible but have not as of yet had any thrombotic event.

Study characteristics

The evidence is current as of December 2017. We searched for studies that randomly allocated people with aPL antibodies and without any previous thrombotic event to different treatments, including anticoagulants, antiplatelet drugs, or both. We identified nine studies involving 1044 participants. The studies took place in several different countries. One study was multicentred and had a variety of funding sources. In two studies aspirin was compared with placebo (dummy treatment). Four studies compared an anticoagulant with or without aspirin with aspirin alone. The remaining studies compared combinations of antiplatelet agents, anticoagulants, other treatments, or two different doses of the same drug. The majority of the studies concerned women with aPL antibodies and a history of pregnancy failure. One study included non-pregnancy-related cases, and one study included pregnancy-related cases and other patients with positive results for aPL antibodies.

Key results

We summarised the effects of the treatments using the following comparisons: aspirin only versus placebo, anticoagulant only or with aspirin versus aspirin only, aspirin with anticoagulant versus placebo or other treatment. We found no clear differences in the number of individuals with thrombotic events in the compared groups. One study revealed an increased risk of minor bleeding (such as nasal bleeding or intensified menstruation) in participants receiving aspirin and anticoagulant. All other analyses did not show any meaningful differences in the number of participants with bleeding. None of the studies reported on risk of death or quality of life. We found no clear difference between the groups in any of the comparisons for unwanted effects other than bleeding, where this information was reported; the more common of these effects included mild gastrointestinal symptoms in the aspirin group and allergic reactions in the aspirin with anticoagulant group.

Quality of the evidence

We assessed none of the studies as at low risk of bias because of methodological concerns or reporting of the results. We judged the overall quality of evidence to be low to moderate, it was downgraded due to unclear or high risk of bias, small number of studies and imprecise results.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Anticoagulant with or without ASA versus ASA only

Anticoagulant with or without ASA versus ASA only

Patient or population: people with antiphospholipid antibodies and no history of thrombosis

Settings: specialist centres

Intervention: anticoagulant with or without ASA

Comparison: ASA only

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	ASA	AC or AC + ASA			
Thrombosis Median follow-up reported in 1 study: 37.2 months (ASA group) 32.4 (AC or AC + ASA group), no IQR given	17 per 1000	16 per 1000 (4 to 64)	RR 0.98 (0.25, 3.77)	493 (4 RCTs)	⊕⊕⊕⊖ Low^a
Bleeding - major	No events reported.	No events reported.	Not estimable	493 (4 RCTs)	-
Bleeding - minor (not requiring hospital admission) Median follow-up reported in 1 study: 37.2 months (ASA group) 32.4 (AC or AC + ASA group), no IQR given	0 per 1000	133 per 1000 (8 to 2294)	RR 22.45 (1.34, 374.81)	164 (1 RCT)	⊕⊕⊕⊖ Low^b
Mortality	Not reported	Not reported	Not reported	Not reported	-
Quality of life	Not reported	Not reported	Not reported	Not reported	-
Adverse event other than bleeding	In Cuadrado 2014, 4 cases of mild gastrointestinal symptoms (2 severe constipations and 2 stomach upsets, not clear if the same or different participants) in the ASA group and 1 case of an allergic reaction in the combination therapy group were				

reported. [Farquharson 2002](#) and [Alalaf 2012](#) reported no information about adverse events not related to bleeding or obstetric failure, while [Rai 1997](#) reported that in both groups interventions were well tolerated and that in the heparin group there were no cases of thrombocytopenia or vertebral fractures.

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

AC: anticoagulant; **ASA:** acetylsalicylic acid; **CI:** confidence interval; **IQR:** interquartile range; **RCT:** randomised clinical trial; **RR:** risk ratio

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

^aDowngraded by one level due to unclear or high risk of bias in more than one domain in all studies and one level due to wide 95% CI for both benefit and harm.

^bDowngraded by one level due to wide 95% CI and one level due to the presence of only one study with a small number of participants.

Summary of findings 2. ASA versus placebo

ASA versus placebo

Patient or population: people with antiphospholipid antibodies and no history of thrombosis

Settings: university department and 3 unspecified centres

Intervention: ASA

Comparison: placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	Placebo	ASA			
Thrombosis Mean follow-up 2.3 +/- 0.95 years	20 per 1000	105 per 1000 (13 to 860)	RR 5.21 (0.63, 42.97)	98 (1 RCT)	⊕⊕○○ Low^a
Bleeding - major	No events reported.	No events reported.	Not estimable	98 (1 RCT)	-
Bleeding - minor	20 per 1000	63 per 1000	RR 3.13 (0.34, 29.01)	98	⊕⊕○○

Mean follow-up 2.3 +/- 0.95 years	(7 to 581)		(1 RCT)	Low^a
Mortality	Not reported	Not reported	Not reported	-
Quality of life	Not reported	Not reported	Not reported	-
Adverse event other than bleeding	Minor gastrointestinal disturbances occurred in 5 participants who received ASA compared to 1 participant in the placebo group.			

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

ASA: acetylsalicylic acid; **CI:** confidence interval; **RCT:** randomised clinical trial; **RR:** risk ratio

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

^aDowngraded by one level due to risk of bias (unclear risk of bias for allocation concealment, selective reporting, and incomplete outcome data, and high risk of other bias) and one level because of single study and imprecision (wide 95% CI).

Summary of findings 3. ASA with LMWH versus placebo or IVIG

ASA with LMWH versus placebo or IVIG

Patient or population: people with antiphospholipid antibodies and no history of thrombosis

Settings: university department and women's health hospital

Intervention: ASA with LMWH

Comparison: placebo or IVIG

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	Placebo or IVIG	ASA + LMWH			
Thrombosis Up to 2 months postpartum in Dendrinios 2009 , not specified in Ismail 2016	0 participants developed thrombosis in both studies.		Not estimable	258 (2 RCTs)	-

Bleeding - major (bleeding requiring transfusion) Length of follow-up not specified	0 per 1000	45 per 1000 (3 to 806)	RR 9.00 (0.49, 164.76)	180 (1 RCT)	⊕⊕⊕⊖ Moderate^a
Bleeding - other (bleeding during first trimester) Length of follow-up not specified	212 per 1000	189 per 1000 (106 to 342)	RR 0.89 (0.50, 1.61)	180 (1 RCT)	⊕⊕⊕⊖ Moderate^a
Bleeding - other (postpartum haemorrhage) Length of follow-up not specified	112 per 1000	146 per 1000 (68 to 315)	RR 1.30 (0.60, 2.81)	180 (1 RCT)	⊕⊕⊕⊖ Moderate^a
Mortality	Not reported	Not reported	Not reported	Not reported	-
Quality of life	Not reported	Not reported	Not reported	Not reported	-
Adverse events other than bleeding Follow-up: up to 2 months postpartum	In 1 study examining pregnant women, 3 cases of nausea, hypotension, and tachycardia were reported in the IVIG (control) group, as compared to none in the intervention group.				

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

ASA: acetylsalicylic acid; **CI:** confidence interval; **IVIG:** intravenous immunoglobulin; **LMWH:** low molecular weight heparin; **RCT:** randomised clinical trial; **RR:** risk ratio

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

^aDowngraded by one level because of single study and imprecision (wide 95% CI).

Summary of findings 4. ASA + high-dose LMWH versus ASA + low-dose LMWH or UFH

ASA + high-dose LMWH versus ASA + low-dose LMWH or UFH

Patient or population: people with antiphospholipid antibodies and no history of thrombosis

Settings: specialist centres

Intervention: ASA + high-dose LMWH

Comparison: ASA + low-dose LMWH or UFH

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	ASA + low-dose LMWH or UFH	ASA + high-dose LMWH			
Thrombosis	0 participants developed thrombosis.		Not estimable	120 (2 RCTs)	-
Bleeding - major/excessive	0 participants developed major/excessive bleeding episodes.		Not estimable	120 (2 RCTs)	-
Subcutaneous bruises Follow-up: entire pregnancy	100 per 1000	100 per 1000 (22 to 456)	RR 1.00 (0.34 to 2.93)	120 (2 RCTs)	⊕⊕⊕⊕ Low^a
Mortality	Not reported	Not reported	Not reported	Not reported	-
Quality of life	Not reported	Not reported	Not reported	Not reported	-
Adverse events other than bleeding	1 case of skin allergy was reported in the ASA + UFH group.				

The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

ASA: acetylsalicylic acid; **CI:** confidence interval; **LMWH:** low molecular weight heparin; **RCT:** randomised clinical trial; **RR:** risk ratio; **UFH:** unfractionated heparin

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

^aDowngraded by one level due to risk of bias (unclear risk of bias for blinding and selective reporting, high risk for other bias) and one level due to small selected population (pregnant women) and imprecision (wide 95% CI).

BACKGROUND

Description of the condition

Antiphospholipid syndrome (APS), also known as Hughes syndrome, is an autoimmune condition triggered by antiphospholipid (aPL) antibodies that have prothrombotic activity. The aPL antibodies are a heterogeneous group of antibodies directed against certain proteins in blood, such as protein C (Chen 2010), and on platelet cell membranes (annexin V) (Rand 2008), tissue factor and other (Chen 2010). The risk of prothrombotic activity varies depending on the type of antibodies, which include: anticardiolipin (aCL) antibodies, anti-beta2-glycoprotein I (anti- β_2 GPI) antibodies, and lupus anticoagulant (LA) (Sebastiani 1999). According to the literature, aPL antibodies are found in approximately 1% to 5% of the general population; 6% (interquartile range (IQR) 2% to 13%) of women who present with pregnancy complications; 9% of women with spontaneous abortion; 9.5% (IQR 5.3% to 13.8%) of individuals with deep vein thrombosis; 11% (IQR 4% to 23%) of individuals with myocardial infarction; and 13.5% (IQR 6.8% to 23.3%) of individuals with ischaemic stroke (Amengual 2015; Andreoli 2013; Gomez-Puerta 2014). The aPL antibodies can be detected in people diagnosed with various conditions, such as autoimmune diseases, and most commonly systemic lupus erythematosus (SLE) (Abu-Shakra 1995), or during diagnostic processes that investigate foetal deaths, premature births, and recurrent spontaneous abortions (Miyakis 2006). The isolated presence of aPL antibodies is insufficient to diagnose APS. According to the modified criteria by Miyakis 2006, a person is required to meet at least one clinical criterion related to either vascular thrombosis or an obstetric complication, as well as the presence of one or more specified aPL antibody on two or more occasions, at least 12 weeks apart. It is unclear if individuals who have aPL antibodies present in their circulating blood but who have not experienced any thrombotic clinical events should receive primary antithrombotic prophylaxis. Empson 2005 conducted a Cochrane Review addressing this issue in pregnant women with prior miscarriage and aPL antibodies, and showed that combined unfractionated heparin (UFH) and acetylsalicylic acid (ASA) may reduce pregnancy loss by 54%. More recently, another systematic review, Amengual 2015, assessed the effect of ASA in asymptomatic women who were positive for aPL antibodies and who had no history of recurrent miscarriage or intrauterine foetal death. Amengual 2015 did not find evidence of the superiority of prophylactic treatment with ASA compared to placebo or usual care to prevent obstetric complications in otherwise healthy women with aPL antibodies during their first pregnancy.

Description of the intervention

Antiplatelet drugs inhibit platelet function, mostly platelet aggregation, which reduces the probability of thrombus formation (Depta 2015; Weitz 2012). The most commonly used antiplatelet agent is acetylsalicylic acid (ASA), which is also known as aspirin. Anticoagulants are agents that interfere with blood coagulation and thereby reduce fibrinogen polymerisation and blood clot formation.

In standard practice, antiplatelet agents (ASA, clopidogrel, prasugrel, and ticagrelor) are used in people with coronary artery disease (Montalescot 2013; Roffi 2016; Windecker 2014), or peripheral artery disease (Alonso-Coello 2012), to prevent thrombus formation.

Anticoagulant agents (vitamin K antagonists (VKA): warfarin, acenocoumarol) and non-vitamin K antagonists, which are known as direct oral anticoagulants (DOAC) (dabigatran, rivaroxaban, apixaban, edoxaban) (Ageno 2012; Kearon 2016), are used to prevent thrombus formation in people with atrial fibrillation (Lip 2014). Vitamin K antagonists are also used after implantation of an artificial heart valve (Whitlock 2012), to treat venous thromboembolism (Kearon 2016; Weitz 2016), and in the primary prevention of thromboembolic complications in people with knee or hip replacement surgery (Gomez-Outes 2012).

Low molecular weight heparins (LMWHs) and, less often, UFH are also used to treat and prevent thrombotic events (Garcia 2012; Vandvik 2012), for example in individuals who are immobilised because of a medical condition, Kahn 2012, or surgery, Douketis 2012, in people with cancer (Farge 2016), or in pregnant women with thrombophilia (Bates 2012).

How the intervention might work

The presence of aPL antibodies is associated with an increased risk of thrombus formation with all its consequences (Giannakopoulos 2007; Giannakopoulos 2013). People who have had a thrombotic event and who meet APS criteria are recommended to receive anticoagulation (Ruiz-Irastorza 2011). The benefits of antiplatelet (ASA) use in the context of primary prevention of cardiovascular events have been shown (Guirguis-Blake 2016), and anticoagulants have been examined in the primary prevention of several prothrombotic conditions (MRCGPRF 1998; Rasmussen 2012). It is therefore assumed that antiplatelet and anticoagulant agents may decrease the incidence of thrombus formation based on their mechanism of action (Cuadrado 2014; Erkan 2007). Acetylsalicylic acid, a commonly used antiplatelet agent, acts through inhibition of platelet cyclooxygenase 1 (COX-1), which leads to blockage of the production of thromboxane A2 (TXA2) (Warner 2011), while clopidogrel, another commonly used antiplatelet agent, acts through the blockage of P2Y receptors on platelets, thus impairing their function (Wijeyeratne 2011). Unfractionated heparin and LMWHs are administered intravenously or subcutaneously and form complexes with antithrombin molecules, which leads to the neutralisation of factor Xa and deactivation of thrombin (Garcia 2012). Additionally, UFH directly inhibits thrombin activity. Vitamin K antagonists are oral antagonists of vitamin K. They reduce the production of coagulation factors II, VII, IX, and X and proteins C and S (Ageno 2012). Among DOAC, there are direct thrombin inhibitors (dabigatran), which block the catalytic site or the substrate recognition site in the thrombin molecule, and factor Xa inhibitors (rivaroxaban, apixaban, edoxaban), which cause factor Xa inhibition that is not mediated by antithrombin (Ageno 2012).

The administration of all anticoagulants is generally associated with a high risk of bleeding. Vitamin K antagonists are potentially teratogenic and require regular international normalised ratio (INR) monitoring (Torbicki 2008). Important UFH side effects are heparin-induced thrombocytopenia (HIT) and osteopenia (Linkins 2012; Rajgopal 2008). Low molecular weight heparins, for which the most common complications are bleeding, allergic reactions, and injection site reactions, are associated with a lower risk of HIT (Junqueira 2012; Martel 2005), and some studies also indicate a lower risk of major bleeding compared to UFH (Ali Khan 2014).

Why it is important to do this review

The issue of secondary prevention of thrombosis in people with APS has been or will be addressed by other Cochrane Reviews. Two Cochrane Reviews have thoroughly addressed obstetric outcomes: one review included people with aPL antibodies or lupus anticoagulant (Empson 2005), while the other included people with unexplained recurrent miscarriage with or without inherited thrombophilia (de Jong 2014). One Cochrane Review protocol considers using antiplatelets or anticoagulants to prevent recurrent peripheral vascular thrombosis (Islam 2016). We have also published a Cochrane Review on secondary prevention of recurrent thrombosis, particularly ischaemic stroke, in people with APS (Bala 2017a). However, we have not identified any Cochrane Review that addresses the issue of primary prevention of thrombosis in individuals with aPL antibodies, while at least one randomised controlled trial (RCT) has investigated this issue (Erkan 2007). Two recently published systematic reviews addressed this issue in part (Arnaud 2014; Qushmaq 2014). Arnaud 2014 assessed the effect of ASA and included all types of study designs (RCTs and observational studies, both prospective and retrospective), and Qushmaq 2014 considered all primary prophylactic interventions but included all types of study designs and excluded studies published in languages other than English. This Cochrane Review presents a broader scope of studies, including those that assess antiplatelet agents other than acetylsalicylic acid, as well as anticoagulants.

OBJECTIVES

To assess the effects of antiplatelet and anticoagulant agents versus placebo or no intervention or other intervention on the development of thrombosis in people with aPL antibodies who have not had a thrombotic event.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs).

Types of participants

People of any age with no history of thrombosis (as defined by APS Sapporo classification criteria (Wilson 1999), or updated Sydney classification criteria (Miyakis 2006)), but with aPL antibodies confirmed on at least two separate measurements (time period between measurement as defined in the criteria current when the study was done), including LA, anti- β_2 GPI antibodies, and aCL antibodies (all detected using the assays recommended at the time when the study was conducted). We also included studies that addressed pregnant women with a history of recurrent pregnancy loss and positive aPL antibodies.

Types of interventions

We included studies that compared any antiplatelet or anticoagulant agents, or their combinations, at any dose and administered using any mode of delivery with placebo, no intervention, or other intervention (such as hydroxychloroquine). We also included studies that compared antiplatelet or anticoagulant agents with each other or that compared two different doses of the same drug.

Types of outcome measures

Primary outcomes

1. Any acute arterial or venous thrombosis diagnosed based on the APS Sapporo classification criteria (Wilson 1999), or updated Sydney classification criteria (Miyakis 2006), which would be confirmed by objectively validated methods, including (but not limited to) deep vein thrombosis, pulmonary embolism, myocardial infarction, ischaemic stroke, transient ischaemic attack, peripheral thromboembolism.
2. Bleeding based on definitions of minor or major bleeding (Schulman 2005).
3. Total mortality.

We planned to analyse any acute arterial and venous thrombosis events combined and separately by the type of event (such as myocardial infarction, deep vein thrombosis, etc.). However, the numbers of each type of events were very low per study, and one study did not report the type of events by participant randomised. We therefore decided not to perform analyses by the type of event.

In our protocol we planned to analyse obstetric failure among thrombotic events, however as this outcome was thoroughly addressed by other Cochrane Reviews (de Jong 2014; Empson 2005), we did not analyse this outcome.

Secondary outcomes

1. Quality of life as measured by a validated questionnaire.
2. Adverse event other than bleeding, e.g. gastrointestinal disturbances, urticaria, other allergic reactions, dizziness, peptic ulcers, insomnia, or headache.

Search methods for identification of studies

Electronic searches

The Cochrane Vascular Information Specialist (CIS) first searched the following databases for relevant trials (15 February 2017):

- the Cochrane Vascular Specialised Register (15 February 2017);
- the Cochrane Central Register of Controlled Trials (CENTRAL; 2017, Issue 1) via the Cochrane Register of Studies Online.

See Appendix 1 for details of the search strategy used to search CENTRAL.

The Cochrane Vascular Specialised Register is maintained by the CIS and is constructed from weekly electronic searches of MEDLINE Ovid, Embase Ovid, CINAHL (Cumulative Index to Nursing and Allied Health Literature), AMED (Allied and Complementary Medicine Database), and through handsearching of relevant journals. The full list of databases, journals, and conference proceedings searched, as well as the search strategies used, are described in the Specialised Register section of the Cochrane Vascular module in the Cochrane Library (www.cochranelibrary.com).

The CIS also searched the following trial registries for details of ongoing and unpublished studies (15 February 2017):

- ClinicalTrials.gov (www.clinicaltrials.gov);
- World Health Organization International Clinical Trials Registry Platform (www.who.int/trialsearch);
- ISRCTN Register (www.isrctn.com/).

See [Appendix 2](#) for details of the search strategy used.

The CIS subsequently performed a follow-up search of the Cochrane Vascular Specialised Register (4 December 2017), the Cochrane Central Register of Controlled Trials (CENTRAL) (last search 29 November 2017), MEDLINE Ovid, Embase Ovid, CINAHL, and AMED (searched 4 December 2017), and trials registries (searched 29 November 2017). See [Appendix 3](#) for details of the search strategies used.

Searching other resources

We checked the references of included studies, systematic reviews, health technology assessments, and practice guidelines relevant to the topic of this review. We contacted experts in the field, including PL Meroni (Milan), MA Khamashta (London), PG de Groot (Utrecht), P de Moerloose (Geneva), and V Pengo (Padova), and manufacturers of the brand-name drugs (mainly direct oral anticoagulants (DOAC)) for additional studies (Bristol-Myers Squibb-Pfizer, Pfizer Europe, Boehringer Ingelheim International, Aspen Pharma, Eli Lilly, Bayer Pharma AG, Alfasigma).

Data collection and analysis

Selection of studies

We used Covidence software for abstract and full-text screening ([Covidence 2017](#)). We eliminated duplicate records of the same study using appropriate software. We divided work between two pairs of review authors (EP, KJ, DWK and MMB or WL). In each group, one of the review authors is a medical student involved in research work and trained in methodology or an active clinician and the other is an experienced review author (it is not possible to identify specific pairs when using Covidence software). The review authors in the above-mentioned pairs independently screened the titles and abstracts of the search results against the eligibility criteria. Any discrepancies were resolved by discussion between the review author pair, with a third review author (MMB, WL, AU) acting as an arbiter when necessary. We retrieved the full-text articles of studies that appeared to fulfil the inclusion criteria and selected studies for inclusion. Any discrepancies were resolved by discussion between the review author pair, with a third review author (MMB, WL, AU) acting as an arbiter when necessary. We screened the gathered reports for multiple publications of the results of the same study. We assessed the following aspects: time, location, the study authors, the number of participants, the baseline data, the doses and frequencies of drug administration. If necessary, we contacted the authors of the reports or studies, or both, to clarify or add any important information. We included studies based on the data we collected in the described process. We listed all studies excluded after full-text assessment in a 'Characteristics of excluded studies' table. We displayed the study selection process in a PRISMA study flow diagram.

Data extraction and management

We collected data on study design and methods, population intervention, outcomes, and results of the included studies. We planned to use and prepare the Cochrane Vascular data extraction template in Covidence if sufficient form adjustment options were available ([Covidence 2017](#)), however as the adjustment in Covidence was insufficient, we prepared a data extraction form on the basis of the Cochrane Vascular data extraction template in Microsoft Excel and used Covidence for the 'Risk of bias'

assessment. We first pilot-tested a data collection form to check if we needed to add, erase, or rephrase some additional fields or options. In the case of multiple reports being available for the same study, we extracted data from all of the reports into a single data collection form.

Two pairs of review authors independently extracted the data as outlined above. Any disagreements were discussed between the review author pair, and when necessary by asking a third review author (MMB, WL, AU) for their opinion. If we were unable to resolve a disagreement, we planned to describe this in the review.

Assessment of risk of bias in included studies

We used the Cochrane 'Risk of bias' assessment tool, as outlined in Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2011](#)). Pairs of review authors (formed from EP, KJ, MMB, DWK, and WL) independently applied the tool to each included study. Any disagreements were resolved by discussion or by consulting a third review author (AU) when necessary. In addition, one review author checked all numeric results against the original reports (MMB).

We assessed risk of bias for the following domains ([Higgins 2011](#)).

1. Random sequence generation.
2. Allocation concealment.
3. Blinding of participants and personnel.
4. Blinding of outcome assessment.
5. Incomplete outcome data.
6. Selective outcome reporting.
7. Other bias.

We graded the risk of bias as high, low, or unclear for each domain and included a justification for our judgement in the 'Risk of bias' tables. We judged a trial as at low risk of bias if it was at low risk of bias in each of the 'Risk of bias' domains; we judged all other trials as at high risk of bias. We took the 'Risk of bias' assessment into account in our interpretation of the data.

Measures of treatment effect

We calculated the risk ratio (RR) and 95% confidence interval (CI) for all the primary endpoints available (any thrombosis, bleeding), and planned to do this for the secondary endpoints described as adverse events other than bleeding (e.g. gastrointestinal disturbances or allergic reactions). However, adverse events other than bleeding were reported in such a way that prevented pooling, and therefore were summarised narratively. For the quality of life indicators, we planned to determine the mean difference (MD) or standardised mean difference (SMD) values and 95% CIs, depending on whether the same or different scales were used in the included studies.

Unit of analysis issues

The participants were the unit of analysis. If an included study had a mixture of units of analysis, we planned to adjust them to one common unit. We discussed any unusual issues within the review author team and planned to adjust the methods outlined in the published protocol accordingly. If any cross-over studies met the inclusion criteria of the review, we planned to include only the first period of such studies in our analyses.

Dealing with missing data

For one study with missing data, we contacted the authors of the original report for the missing data or for the reasons for exclusion of the data. For data missing at random, we analysed only the available data. We analysed the potential impact of missing data on the results using sensitivity analyses, and discussed this in the review.

Assessment of heterogeneity

Since we assessed the effects of the introduction of several different drugs, we expected clinical diversity. We planned to estimate statistical heterogeneity visually (overlap of CIs derived from single studies) and by using the χ^2 test, with a significance level of $P = 0.10$. We also planned to calculate the percentage of variability that stemmed from heterogeneity (I^2 statistic).

Assessment of reporting biases

In order to minimise reporting bias, we planned to search multiple sources (see the [Search methods for identification of studies](#) section). We planned to visually assess funnel plots to screen for small-study effects if at least 10 studies were included in a meta-analysis ([Higgins 2011](#)).

Data synthesis

As mentioned in the [Assessment of heterogeneity](#) section, we expected heterogeneity to be significant. We therefore planned to perform meta-analyses using a random-effects model. If we were unable to pool the data due to considerable heterogeneity, as defined in the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2011](#)), we planned to summarise the findings in the form of tables, figures, and text. We used Review Manager 5 to perform the analyses ([RevMan 2014](#)).

Subgroup analysis and investigation of heterogeneity

We planned to analyse the effect of the antiplatelet and anticoagulant agents separately. Provided the number of studies included in the analysis was sufficient (at least 10 included studies), we planned to analyse the effects of the interventions in relation to different subgroups of antiplatelet agents and anticoagulants and, if the information was available, the presence of additional risk factors of thrombosis (e.g. smoking, the use of contraception/hormone replacement therapy, obesity, neoplasms, and heart failure). If possible, we planned to analyse the effects in subgroups according to the type of antibodies present as well as the number of types of antibodies present (i.e. one, two, or three types of antibodies). We did not have a sufficient number of studies per comparison to perform subgroup analyses.

Sensitivity analysis

We planned to assess the following.

1. The impact of risk of bias on study results: we planned to analyse the results of studies at low risk of bias versus studies at high risk of bias (see the [Assessment of risk of bias in included studies](#) section). However, as none of the studies was assessed as at low risk of bias, we could not perform this analysis.
2. The impact of missing data: we performed analyses by 'best-case scenario' (when all participants with missing data in the intervention group were assumed to have had a good outcome, and all participants with missing data in the control group were assumed to have had a poor outcome) and by 'worst-case scenario' (when all participants with missing data in the intervention group were assumed to have had a poor outcome, and all participants with missing data in the control group were assumed to have had a good outcome) and compared the results of trials that had no missing data with trials that had missing data.

'Summary of findings' tables

Two review authors independently assessed the quality of the evidence using the GRADE approach, as specified by the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2011](#)), and by [Atkins 2004](#). We summarised the quality of the evidence in 'Summary of findings' tables (separately for anticoagulants and antiplatelets) using GRADEpro Guideline Development Tool (GDT) ([GRADEpro GDT 2015](#)). In the 'Summary of findings' tables we included all of the prespecified outcomes (primary and secondary, see the [Types of outcome measures](#) section). In case of composite outcomes, we planned to present results for the composite and also for the individual components of the composite.

RESULTS

Description of studies

Results of the search

We performed our last searches on 4 December 2017 and identified 418 records after the removal of duplicates ([Figure 1](#)). Of these, 79 were retrieved and their full texts checked. We excluded 66 records due to: wrong study design (33 records of reviews, guidelines, comments, etc. and 5 records not an RCT); wrong population (18 records); wrong intervention (2 records); and wrong outcomes (i.e. obstetric failure only or coagulation activation only) (8 records). The reasons for exclusion are reported in the [Characteristics of excluded studies](#) table. We finally included nine studies that fulfilled our inclusion criteria, reported in 12 references ([Alalaf 2012](#); [Cuadrado 2014](#); [Dendrinis 2009](#); [Erkan 2007](#); [Farquharson 2002](#); [Fouda 2010](#); [Fouda 2011](#); [Ismail 2016](#); [Rai 1997](#)). In addition, we identified one ongoing trial reported as a record in ClinicalTrials.gov ([NCT03100123](#)).

Figure 1. Study flow diagram.

Included studies

The nine included studies were all randomised clinical trials that were performed between 1993 and 2013. One study was described as double-blind ([Erkan 2007](#)); in one study there was no information about blinding ([Ismail 2016](#)); and the remaining studies were not blinded.

Detailed information on each study is presented in the [Characteristics of included studies](#) table.

Participants

The studies included 1044 randomised individuals with no history of thrombosis as defined by APS Sapporo classification criteria ([Wilson 1999](#)), or updated Sydney classification criteria ([Miyakis 2006](#)), but who were tested positive for aPL antibodies on at least two separate measurements (time period between measurement as defined in the criteria current when the study was done), including LA, anti- β_2 GPI antibodies, and aCL antibodies. Additionally, in eight studies with 714 individuals recurrent pregnancy losses was the main inclusion criterion or one of the inclusion criteria ([Alalaf 2012](#); [Cuadrado 2014](#); [Dendrinis 2009](#); [Farquharson 2002](#); [Fouda 2010](#); [Fouda 2011](#); [Ismail 2016](#); [Rai 1997](#)).

Location

Three of the studies were performed in Egypt ([Fouda 2010](#); [Fouda 2011](#); [Ismail 2016](#)), [Farquharson 2002](#) and [Rai 1997](#) were performed in the UK, [Alalaf 2012](#) in Iraq, and [Dendrinis 2009](#) in Greece. [Cuadrado 2014](#) was a multicentre study performed in several European countries and in Mexico. In [Erkan 2007](#) the country where the study was performed and where follow-up took place was not specified; only a co-ordinating centre in the USA was mentioned.

Setting

[Farquharson 2002](#) and [Rai 1997](#) were based in miscarriage clinics. [Dendrinis 2009](#), [Fouda 2010](#), and [Fouda 2011](#) took place at university hospitals. [Alalaf 2012](#) and [Ismail 2016](#) were performed at a maternity teaching hospital and a women's health hospital, respectively. [Cuadrado 2014](#) was based in 14 tertiary hospitals and one district hospital. In [Erkan 2007](#) the type of medical units where the study was performed was not specified.

Interventions

In two studies an intervention was compared with a placebo ([Erkan 2007](#); [Ismail 2016](#)); in [Erkan 2007](#) the intervention was 81 mg ASA, and in [Ismail 2016](#) it was 81 mg ASA combined with 40 mg enoxaparin. [Alalaf 2012](#) compared 100 mg ASA with 2500 IU bemiparin. In [Dendrinis 2009](#) the intervention group was given 75 mg ASA and 4500 IU heparin, whereas the control group received 400 mg/kg intravenous immunoglobulin (IVIG). In three studies all participants received ASA (75 mg), and the intervention group additionally received anticoagulant (in [Farquharson 2002](#) this was 5000 IU of LMWH subcutaneously, in [Rai 1997](#) 5000 IU of UFH subcutaneously, in [Cuadrado 2014](#) warfarin with the target international normalised ratio (INR) 1.5 with a range of 1.3 to 1.7). In [Fouda 2010](#) two doses of enoxaparin were compared (20 mg versus 40 mg), with both groups additionally given 75 mg of ASA. In [Fouda 2011](#) 40 mg enoxaparin was compared with UFH 5000 IU subcutaneously, twice daily; all participants were given 75 mg ASA.

In some of the studies concomitant treatment was used: folic acid in [Alalaf 2012](#); prenatal vitamins, oral calcium, and vitamin D in [Fouda 2010](#) and [Fouda 2011](#); and hydroxychloroquine, steroids, and non-steroidal anti-inflammatory drugs (NSAIDs) in 57%, 33%, and 40% of participants, respectively in [Erkan 2007](#).

Outcomes

The primary outcome in [Alalaf 2012](#), [Farquharson 2002](#), [Dendrinis 2009](#), [Fouda 2010](#), [Fouda 2011](#), [Ismail 2016](#), and [Rai 1997](#) was live birth, whereas in [Cuadrado 2014](#) it was a documented thrombosis (which included deep vein thrombosis in venography or ultrasonography, pulmonary embolism in a computed tomography (CT) scan, radionuclide lung scan, or angiography, thrombosis in intracerebral vessels on magnetic resonance imaging (MRI), retinal thrombosis in ophthalmological examination and angiography, peripheral or mesenteric arterial thrombosis in arteriography; myocardial infarction, amaurosis fugax, and transient ischaemic attack as per standard definitions), and in [Erkan 2007](#) the primary outcome was acute thrombosis (defined as a stroke confirmed by neuroimaging, deep vein thrombosis by Doppler ultrasonography, pulmonary embolism in CT scan, myocardial infarction).

In [Alalaf 2012](#) the secondary outcomes included maternal and foetal complications (specified as embolic events, pre-eclampsia, ecchymosis, and preterm labour). In [Cuadrado 2014](#) secondary outcomes were defined as clinical and serological risk factors for thrombosis, medication side effects, and death of any cause. In [Dendrinis 2009](#) secondary outcomes included haemorrhages, pregnancy-associated hypertension, fractures during pregnancy or up to two months postpartum, reduced maternal bone mineral density, and death.

[Fouda 2010](#) and [Fouda 2011](#) included the following secondary outcomes: bleeding/haemorrhages, neonatal bleeding, thrombocytopenia, intrauterine growth restriction, intrauterine foetal death, preterm delivery, congenital anomalies, pre-eclampsia, spontaneous osteoporotic fractures, and thrombotic events.

In [Ismail 2016](#) the secondary outcomes were first- and second-trimester spontaneous abortion, vaginal bleeding during pregnancy, pre-eclampsia and pregnancy-induced hypertension, intrauterine growth restriction, abruptio placentae, and preterm delivery. The last was the only secondary outcome mentioned in [Rai 1997](#). In [Erkan 2007](#) transient ischaemic attack was classified as a secondary outcome; gastrointestinal disturbances and minor and major bleeding episodes were reported as "other outcomes".

Excluded studies

Reasons for exclusion are provided in the [Characteristics of excluded studies](#) table.

Risk of bias in included studies

Details for each included study are presented in the [Characteristics of included studies](#) table. The overall risk of bias in each domain for the included studies is shown in [Figure 2](#). Risk of bias by trial is presented in [Figure 3](#).

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

	Random sequence generation	Allocation concealment	Blinding of participants and personnel: All outcomes	Blinding of participants and personnel: Death	Blinding of participants and personnel: Bleeding	Blinding of participants and personnel: Thromboembolic events	Blinding of participants and personnel: Adverse events	Blinding of outcome assessment: All outcomes	Blinding of outcome assessment: Thromboembolic events	Blinding of outcome assessment: Death	Blinding of outcome assessment: Bleeding	Blinding of outcome assessment: Adverse events	Incomplete outcome data	Selective reporting	Other sources of bias
Alalaf 2012	⊖	⊖	?					?					+	⊖	⊖
Cuadrado 2014	+	+		+	?	+	⊖		+	+	?	⊖	⊖	+	⊖
Dendrinios 2009	+	?		+		?	?		?	+		?	⊖	?	+
Erkan 2007	+	?	+					+					?	?	⊖
Farquharson 2002	+	+				?			?				+	?	⊖
Fouda 2010	+	+			?	?	?		?		?	?	+	?	⊖
Fouda 2011	+	+		+	?	?		?		+	?	+	+	?	⊖
Ismail 2016	+	+	+						?		+	+	+	?	+
Rai 1997	+	+	?					?					+	?	+

All of the included studies were published as full articles, and no single study was at low risk of bias in all domains.

Allocation

For one study we judged the risk of bias for the random sequence generation and allocation concealment domains as high, since the explanation of random allocation of the procedure suggested an alternate allocation with changed ratios of allocation (Alalaf 2012).

The other eight studies presented clear information about sequence generation and were judged as at low risk of bias (Cuadrado 2014; Dendrinios 2009; Erkan 2007; Farquharson 2002; Fouda 2010; Fouda 2011; Ismail 2016; Rai 1997). In six studies computer-generated randomisation was used (Erkan 2007; Farquharson 2002; Fouda 2010; Fouda 2011; Ismail 2016; Rai 1997), in one study a random number table (Dendrinios 2009), and in one study minimisation protocol (Cuadrado 2014).

The risk of bias for the allocation concealment domain was unclear in two studies because no detailed information was provided ([Dendrinios 2009](#); [Erkan 2007](#)). We judged the risk of bias for allocation concealment as low for the other six studies because they used opaque, sealed envelopes ([Fouda 2010](#); [Fouda 2011](#); [Ismail 2016](#)), allocation was by an independent individual not involved in the trial ([Cuadrado 2014](#); [Rai 1997](#)), or a telephone randomisation ([Farquharson 2002](#)).

Blinding

In the analysed studies outcomes were reported and measured in different ways. We therefore assessed blinding either for all outcomes together (if the influence was the same) or for main groups/types of outcomes separately.

We assessed the blinding of participants, personnel, and outcome assessors in three studies for all outcomes together ([Alalaf 2012](#); [Erkan 2007](#); [Rai 1997](#)). For one study we judged the blinding of participants, personnel, and outcome assessors for thromboembolic events, adverse events, and death ([Dendrinios 2009](#)); for one study we judged the blinding of participants, personnel, and outcome assessors for thromboembolic events, bleeding, adverse events, and death ([Cuadrado 2014](#)), and one study reported only information about thromboembolic events, so we judged blinding only for this outcome ([Farquharson 2002](#)). In two studies the blinding of participants, personnel, and outcome assessors was reported for thromboembolic events, adverse events, and bleeding ([Fouda 2010](#); [Fouda 2011](#)). In one study we assessed the blinding of participants and personnel for all outcomes together, but analysed the blinding of outcome assessors for thromboembolic events, adverse events, and bleeding separately ([Ismail 2016](#)).

For one study we judged the risk of bias related to the blinding of participants, personnel, and outcome assessors as low for all outcomes ([Erkan 2007](#)). We assessed the study by [Ismail 2016](#) to be at low risk of bias for blinding of participants and personnel for bleeding and adverse events, but not for thromboembolic events, which we judged to be at unclear risk of bias because no clear information about this outcome definition or verification was provided.

In two studies participants and personnel were not blinded and clear definitions of outcomes were not provided, so it was not possible to assess if the lack of blinding could have influenced the outcomes ([Alalaf 2012](#); [Rai 1997](#)). We therefore assessed the risk of bias for these studies as unclear for all outcomes.

In [Cuadrado 2014](#) participants and personnel were not blinded, but thromboembolic events were verified by objective methods, and in our judgement the lack of blinding did not influence this outcome and the outcome of death. We therefore judged the risk of bias for these two outcomes as low. However, adverse events were not objectively verified in this study, and as the lack of blinding was likely to influence this outcome, we judged the risk of bias for adverse events as high. For the outcome bleeding the definition was unclear, therefore we judged the risk of bias for bleeding as unclear.

[Dendrinios 2009](#) did not provide any information about blinding, so we judged the risk of bias for thromboembolic events and adverse events as unclear, and the risk of bias for death as low because the lack of blinding probably did not influence this outcome.

[Farquharson 2002](#) did not provide any information about blinding, so the risk of bias was unclear for this study.

In [Fouda 2010](#) participants and personnel were not blinded, and clear definitions of the analysed outcomes were not provided. The risk of bias for this study was unclear for every outcome because it was not possible to assess whether the lack of blinding could have influenced the outcome assessment.

In [Fouda 2011](#) participants and personnel were not blinded, but we judged the risk of bias for bleeding as low because this outcome was clearly defined and objectively verified and the lack of blinding was unlikely to influence this outcome assessment. Definitions were not provided for thromboembolic events and adverse events, and we could not judge if the lack of blinding could have influenced outcome assessment, therefore we judged the risk of bias for these two outcomes as unclear.

Incomplete outcome data

We assessed six studies as at low risk of bias for incomplete outcome data because there were either no missing outcome data or there was a low and similar number of missing participants ([Alalaf 2012](#); [Farquharson 2002](#); [Fouda 2010](#); [Fouda 2011](#); [Ismail 2016](#); [Rai 1997](#)).

We judged [Cuadrado 2014](#) as at high risk of bias due to the difference in the number of participants followed up between the experimental and control groups.

We assessed [Dendrinios 2009](#) as at high risk of bias because participants were excluded from the analysis after randomisation. The trial described an analysis of a primary outcome (live births) as intention-to-treat, but in our judgement what was meant by that was not clearly explained or if it was applied to other outcomes as well.

We assessed [Erkan 2007](#) as at unclear risk of bias for incomplete outcome data because insufficient information about the analysis of lost to follow-up data of participants was provided.

Selective reporting

We assessed the risk of selective reporting in [Cuadrado 2014](#) as low because we could access the protocol, and all prespecified outcomes were reported and well described.

We judged the risk of bias for selective reporting in [Alalaf 2012](#) as high because the protocol was not available, and the side effects described in the methods section were not completely reported.

We assessed the risk of bias for selective reporting for the remaining seven studies as unclear as protocols for these studies were not available ([Dendrinios 2009](#); [Erkan 2007](#); [Farquharson 2002](#); [Fouda 2010](#); [Fouda 2011](#); [Ismail 2016](#); [Rai 1997](#)). [Dendrinios 2009](#) and [Fouda 2011](#) did report all outcomes prespecified in the methods section.

Other potential sources of bias

We did not identify any other potential sources of bias in three studies ([Dendrinios 2009](#); [Ismail 2016](#); [Rai 1997](#)). [Erkan 2007](#) was sponsored by Bayer, which we identified as a potential risk for favouring the ASA group.

Five studies were underpowered and recruited fewer participants than had been calculated as their sample size: the estimated sample size in [Fouda 2011](#) was 1447, and only 60 were recruited; the estimated sample size in [Fouda 2010](#) was 410 participants, but the analysed number of participants was only 60; the planned sample size in [Cuadrado 2014](#) was 443 participants in each arm, and the analysed number of participants was a total of 166; the planned sample size in [Farquharson 2002](#) was 220, and the study included 98 participants; the initially planned sample size in [Erkan 2007](#) was 110 per group; after interim analysis it was estimated that 30,363 participants in each arm would be needed to test the original hypothesis that ASA had a beneficial effect; the study included a total of 98 participants. Due to this low recruitment rate, we judged all five studies as at high risk of bias.

We assessed [Alalaf 2012](#) as at high risk of bias because the intervention in one of the groups was introduced before pregnancy, while in the other group it was introduced after the confirmation of pregnancy. In addition, no details on the structure of the groups in terms of diabetes and no sample size calculation were provided.

Effects of interventions

See: **Summary of findings for the main comparison** Anticoagulant with or without ASA versus ASA only; **Summary of findings 2** ASA versus placebo; **Summary of findings 3** ASA with LMWH versus placebo or IVIG; **Summary of findings 4** ASA + high-dose LMWH versus ASA + low-dose LMWH or UFH

We summarised the effects of interventions in four comparison groups, as follows.

1. Anticoagulant with or without acetylsalicylic acid (ASA) versus ASA only in women with a history of recurrent pregnancy loss and in people with no such history ([Alalaf 2012](#); [Cuadrado 2014](#); [Farquharson 2002](#); [Rai 1997](#)).
2. ASA only versus placebo in people with positive aPL antibodies ([Erkan 2007](#)).
3. ASA with low molecular weight heparin (LMWH) versus placebo or IVIG in women with recurrent pregnancy loss ([Dendrinis 2009](#); [Ismail 2016](#)).
4. ASA with high-dose LMWH versus ASA with low-dose LMWH or unfractionated heparin (UFH) in women with recurrent pregnancy loss ([Fouda 2010](#); [Fouda 2011](#)).

We reported the results for these comparisons for each outcome.

We planned to conduct a sensitivity analysis regarding risk of bias. However, there were almost no differences in the risk of bias between the studies, and none of the studies was considered to be at low risk of bias.

To assess the impact of missing data we performed an analysis of the worst-best and best-worst case scenarios for [Cuadrado 2014](#) and [Dendrinis 2009](#).

Outcome: any arterial or venous thrombosis

Comparison: anticoagulant with or without ASA versus ASA only

All studies in this group assessed this outcome. However, only [Cuadrado 2014](#), which included a mixed population of women with a history of recurrent pregnancy loss and people with no such history, reported thrombotic events: four cases in both the

intervention and the control groups. In the meta-analysis there was no clear difference in risk of this outcome (risk ratio (RR) 0.98, 95% confidence interval (CI) 0.25 to 3.77; 4 studies; 493 participants; low-quality evidence; [Analysis 1.1](#)).

Since the dropout rate was quite high in [Cuadrado 2014](#) (at least one year of follow-up was completed only in 69 out of 83 participants in the intervention group and 75 out of 81 participants in the control group), we performed a sensitivity analysis. The results of the best-worst case scenario analysis did not differ from the main analysis (RR 0.39, 95% CI 0.13 to 1.19; 4 studies; 493 participants; [Analysis 5.1](#)).

In the simulation where all missing participants in the intervention group were assumed to develop thrombosis and none in the control group (worst-best case scenario), ASA with anticoagulant was associated with a higher risk of any thrombosis (RR 4.39, 95% CI 1.55 to 12.42; 4 studies; 493 participants; [Analysis 5.2](#)).

Comparison: ASA only versus placebo

In [Erkan 2007](#), which included people with positive aPL antibodies, one case of thrombosis in the control group versus five cases in the intervention group (cases of transient ischaemic attack included) were reported. There was no clear difference between the groups, with an RR of 5.21 and a considerably wide 95% CI from 0.63 to 42.97 (1 study; 98 participants; low-quality evidence; [Analysis 2.1](#)).

Comparison: ASA + LMWH versus placebo or IVIG

In [Dendrinis 2009](#) and [Ismail 2016](#), which included women with a history of recurrent pregnancy loss, no thrombotic events were observed in either the intervention or the control group, therefore the effect was not estimable ([Analysis 3.1](#)). There were no significant differences in the results of the sensitivity analysis performed to assess the impact of missing data ([Analysis 6.1](#); [Analysis 6.2](#)).

Comparison: ASA + high-dose LMWH versus ASA + low-dose LMWH or UFH

In both [Fouda 2011](#) and [Fouda 2010](#), which included women with a history of recurrent pregnancy loss, no thrombotic events occurred, so the effect of the intervention was not estimable ([Analysis 4.1](#)).

Outcome: bleeding

Comparison: anticoagulant with or without ASA versus ASA only

In this comparison only [Cuadrado 2014](#), which included a mixed population, explicitly reported bleeding episodes, as 11 minor bleeding episodes defined as not requiring hospital admission (one nasal and 10 menorrhagia) in the intervention group (ASA + warfarin) compared to none in the control group, indicating a higher risk of minor bleeding (RR 22.45, 95% CI 1.34 to 374.8; 1 study; 164 participants; low-quality evidence; [Analysis 1.2](#)) for treating with two drugs as compared with ASA only. [Cuadrado 2014](#) reported no cases of major bleeding. Among other studies, which included women with a history of recurrent pregnancy loss, [Farquharson 2002](#) reported no data on any type of bleeding, while [Alalaf 2012](#) reported five cases of ecchymosis at the injection site in the bemiparin group, and [Rai 1997](#) reported mild bruising at the injection site in participants receiving heparin without providing any details.

Comparison: ASA only versus placebo

In [Erkan 2007](#), which included participants with positive aPL antibodies, no major bleeding events and three minor bleeding episodes in the intervention group and one in the control group were reported. However, the difference between the groups was not significant (RR 3.13, 95% CI 0.34 to 29.01; 1 study; 98 participants; low-quality evidence; [Analysis 2.2](#)). In addition, two cases of easy bruising were reported in the intervention group and one case in the control group.

Comparison: ASA + LMWH versus placebo or IVIG

Both studies reported on women with a history of recurrent pregnancy loss. [Dendrinios 2009](#) did not report on bleeding episodes.

In [Ismail 2016](#), four major bleeding episodes (defined as requiring blood transfusion) in the treatment group and none in the placebo group were noted, with no clear difference between the groups (RR 9.0, 95% CI 0.49 to 164.76; 1 study; 180 participants; moderate-quality evidence; [Analysis 3.2](#)). Additionally, there were 17 (19%) participants with bleeding in the first trimester of pregnancy in the intervention group and 19 (21%) such cases in the control group ([Analysis 3.2](#)), and 13 (14%) cases of postpartum haemorrhage in the intervention group and 10 (11%) in the control group ([Analysis 3.2](#)), however no significant differences between the groups were reported for these outcomes.

Since there was no information on whether the cases of major bleeding, first-trimester bleeding, and postpartum haemorrhages concerned the same or different participants, we did not pool all of the above for the total bleeding event risk in any of the groups.

Comparison: ASA + high-dose LMWH versus ASA + low-dose LMWH or UFH

Both studies reported on women with a history of recurrent pregnancy loss. In [Fouda 2010](#), no postpartum bleeding episodes were reported, and in [Fouda 2011](#), no excessive bleeding episodes were reported ([Analysis 4.2](#)). In both studies three cases of subcutaneous bruising in each group were reported (RR 1.00, 95% CI 0.34 to 2.93; 2 studies; 120 participants; low-quality evidence; [Analysis 4.3](#)).

Outcome: total mortality

None of the included studies assessed this outcome.

Outcome: quality of life

None of the included studies assessed this outcome.

Outcome: adverse event other than bleeding

Comparison: anticoagulant with or without ASA versus ASA only

In [Cuadrado 2014](#), which included a mixed population, four cases of mild gastrointestinal symptoms were reported in the group of participants who received ASA (two severe constipations and two stomach complaints; it is not clear if these were the same or different participants). Moreover, one case of an allergic reaction in the group receiving the combination of drugs was reported. Among studies that reported on women with a history of recurrent pregnancy loss, there were no reports of adverse events other than bleeding or obstetric failure in [Farquharson 2002](#) and [Alalaf 2012](#). [Rai 1997](#) reported that in both groups the interventions were

well tolerated, and there were no cases of thrombocytopenia or vertebral fractures in the heparin group.

Comparison: ASA only versus placebo

In [Erkan 2007](#), which reported on individuals with positive aPL antibodies, minor gastrointestinal disturbances occurred in five participants who received ASA compared to one participant in the placebo group.

Comparison: ASA + LMWH versus placebo or IVIG

Both studies reported on women with a history of recurrent pregnancy loss. [Dendrinios 2009](#) reported nausea, hypotension, and tachycardia in three participants in the control (IVIG) group as compared to none in the intervention group.

In [Ismail 2016](#), no cases of heparin-induced thrombocytopenia and no cases of allergies were reported.

Comparison: ASA + high-dose LMWH versus ASA + low-dose LMWH or UFH

Both studies reported on women with a history of recurrent pregnancy loss. [Fouda 2010](#) and [Fouda 2011](#) reported no osteoporotic fractures or thrombocytopenia. [Fouda 2011](#) reported one case of skin allergy in the ASA + UFH group.

DISCUSSION

Summary of main results

We identified four studies comparing anticoagulants (with or without ASA) versus ASA. In one of these studies that included a mixed population of women with a history of recurrent pregnancy loss and people with no such history, thrombotic events were reported in similar numbers in both treatment groups. However, the incidence rate of thrombosis was low, and therefore conclusions from this comparison are limited, especially given that the calculated sample size was not reached (low-quality evidence). The risk of minor bleeding episodes, which was explicitly reported in only one of the four studies, was higher in the group treated with anticoagulant and ASA as compared with ASA only (low-quality evidence). Three studies that included women with a history of recurrent pregnancy loss did not report any cases of thrombosis.

We identified one study comparing ASA with placebo in people with positive aPL antibodies, which showed no clear difference in the risk of both thrombotic and bleeding events. As the study was small and underpowered, we judged the quality of evidence to be low, and therefore were not able to draw any meaningful conclusions.

In two studies comparing ASA combined with LMWH versus placebo or IVIG in women with a history of recurrent pregnancy loss, no thrombotic events were reported, preventing us from drawing any conclusions about this outcome. However, in those studies, which focused mainly on obstetric outcomes, several episodes of major and minor bleeding were reported, with no clear differences between the groups (moderate-quality evidence).

We found two small studies comparing ASA combined with high-dose LMWH versus ASA combined with low-dose LMWH or UFH, in women with a history of recurrent pregnancy loss, which also focused mainly on obstetric outcomes. No thrombotic events or major bleeding was reported, so any conclusions were not possible.

Overall completeness and applicability of evidence

In studies comparing ASA combined with LMWH versus IVIG or placebo and ASA combined with high-dose LMWH versus ASA combined with low-dose LMWH or UFH that were performed in women with a history of recurrent pregnancy loss, no thrombotic events were reported. In one study comparing warfarin combined with ASA versus ASA alone in a mixed population, the number of thrombotic events was low, and the study was seriously underpowered (originally planned sample size 1000, included 232), with a higher dropout rate in the combined-treatment group (Cuadrado 2014). An increased number of minor bleeding episodes was reported in the warfarin group, but due to the above-mentioned reasons, the evidence was of low quality (Cuadrado 2014). In the other study that reported thrombotic events, which compared ASA with placebo in people with positive aPL antibodies, the incidence of the events was also low, and the study was also underpowered (originally planned sample size 220, included 98) (Erkan 2007).

Most of the analysed studies recruited pregnant women (or women planning a pregnancy) and were focused on obstetric outcomes. In fact, only one study involved exclusively non-pregnancy-related cases (Erkan 2007). Cuadrado 2014 studied a mixed population of pregnancy-related and non-pregnancy-related cases. The remaining studies included pregnant women with a history of obstetric complications. Most authors agree that in the case of women with aPL antibodies and recurrent miscarriage, the underlying cause is not solely thrombosis-related (Marchetti 2013; Meroni 2011; Sebire 2002; Shamonki 2007; Skrzypczak 2011), therefore these studies were eligible for inclusion. Still, it seems intuitive that the results of such studies cannot be applied to the general population. Clearly there is a need for further investigation in this field with respect to a broader population of people with aPL antibodies.

The proportion of participants with each type of antibody differed between studies, but due to the low number of studies and their heterogeneity we could not examine the influence of this issue on the effects of the studied interventions.

Quality of the evidence

We analysed data from nine studies involving 1044 participants with aPL antibodies. The studies were published between 1997 and 2016. We judged none of the included studies to be at low risk of bias in all domains. The most common problems included blinding of participants and personnel, which was at unclear or high risk of bias for at least one outcome in seven studies; blinding of outcome assessors, which was at unclear or high risk of bias for at least one outcome in eight studies; and selective outcome reporting, which was at unclear or high risk of bias in eight studies. We judged randomisation to be at high risk of bias in one study and allocation concealment to be at unclear or high risk of bias in three studies. We judged dealing with missing data to be at high risk of bias in two studies and unclear risk of bias in one study. Also, in many of the included studies the calculated sample size was not achieved. For most comparisons, either single studies provided results or single studies were included, therefore we did not assess heterogeneity. In meta-analyses where more than one study was included, we did not detect any heterogeneity between the results of the studies. However, all of the analyses provided imprecise results with wide

confidence intervals. We could not assess publication bias due to the small number of studies.

We judged the quality of the evidence to be low for the following comparisons: anticoagulant with or without ASA compared to ASA; ASA compared with placebo; and ASA with high-dose LMWH compared with ASA with low-dose LMWH or UFH. We downgraded the quality of the evidence due to concerns regarding risk of bias and imprecision. We judged the quality of the evidence for the comparison ASA with LMWH versus placebo or IVIG to be moderate, downgrading by one level due to imprecision.

For further details, please see [Summary of findings for the main comparison](#); [Summary of findings 2](#); [Summary of findings 3](#); [Summary of findings 4](#).

Potential biases in the review process

Our searches, conducted by the Cochrane Vascular Group, were comprehensive and performed without any restrictions. We supplemented the searches by seeking additional systematic reviews and practice guidelines to check references. In addition, we checked included and excluded studies in three other Cochrane Reviews covering similar topics (Bala 2017a; de Jong 2014; Empson 2005). We sought additional information from experts and manufacturers. Our review identified more trials than the other two reviews addressing primary prevention in people with aPL antibodies (Arnaud 2014; Qushmaq 2014).

Since the number of studies included in each comparison was low, we did not produce funnel plots.

Agreements and disagreements with other studies or reviews

We identified seven recent reviews, meta-analyses, or practice guidelines that covered the topic of primary prevention of thrombosis in people with aPL antibodies.

Arnaud 2014 assessed the effect of ASA and included all types of study designs (RCTs and observational studies, both prospective and retrospective). It included only one RCT on ASA, which was also included in our review. The authors concluded that the risk of the first thrombotic event was reduced in people taking ASA (low-dose), but the effect was not significant in the analyses that included studies with the best methodological quality, therefore additional properly designed, high-quality RCTs are needed. The same authors requested individual patient data from 11 included cohort studies and obtained data from five of those studies (Arnaud 2015; two prospective and three retrospective studies). They aimed to assess the effect of ASA (low-dose) on the risk of first thrombotic event in people with aPL antibodies using individual patient-level data. After adjustment on several confounders, Arnaud 2015 concluded that risk of first thrombosis is significantly lower in aPL-positive patients treated with low-dose ASA.

Qushmaq 2014 addressed all primary prophylactic interventions but included all types of study designs and excluded studies published in languages other than English. It included only one RCT on ASA, which was also included in our review. The authors concluded that ASA and hydroxychloroquine reduced the frequency of thrombotic events in people with aPL antibodies and systemic lupus erythematosus (SLE), but this was mainly based on the results of observational studies. Four documents were practice

guidelines (Andreoli 2017; Bates 2012; Erkan 2014; Ruiz-Irastorza 2011). Andreoli 2017 recommended, based on limited evidence, anticoagulation or antiplatelet therapy or both in family planning for women with SLE and/or antiphospholipid syndrome. Bates 2012 recommended the use of heparin (UFH in a prophylactic or intermediate dose or LMWH in a prophylactic dose) in combination with low-dose ASA in women with a history of recurrent pregnancy loss and who met laboratory criteria for aPL antibodies. Ruiz-Irastorza 2011 recommended the use of hydroxychloroquine and low-dose ASA in people with SLE and lupus anticoagulant (LA) or anticardiolipin (aCL) antibodies at medium and high titres, while they recommended long-term use of low-dose ASA in people without SLE with a high-risk aPL profile, and especially in the presence of other risk factors for thrombosis. Erkan 2014 reviewed the evidence on treatments other than traditional anticoagulants or antiplatelet agents and did not identify any completed studies of oral direct thrombin or anti-factor Xa inhibitors for primary prevention in people with aPL antibodies.

AUTHORS' CONCLUSIONS

Implications for practice

The evidence identified in this Cochrane Review was insufficient to draw any conclusions on the benefit of using anticoagulant with or without acetylsalicylic acid (ASA) versus ASA alone; ASA versus placebo; ASA with low molecular weight heparin (LMWH) versus placebo or intravenous immunoglobulin; and ASA with high-dose LMWH versus ASA with low-dose LMWH or unfractionated heparin, for the primary prevention of thrombotic events in people with antiphospholipid antibodies, without previous thrombotic

events. In people treated with anticoagulant combined with ASA, the incidence of minor bleeding (nasal bleeding, menorrhagia) was increased compared with treatment using ASA alone. Given the insufficient evidence for reduced thromboembolism and concomitant higher bleeding rates in the analysed clinical setting, the use of anticoagulant agents combined with ASA is generally unadvised. Introducing such a therapy may be considered in patients with additional thrombotic risk factors accompanied by a regular assessment of the balance of thrombosis against bleeding.

Implications for research

Studies that are adequately powered and focused mainly on thrombotic events, as well as that include participants other than women with a history of obstetric complications, are needed to enable the drawing of any meaningful conclusions on the primary prevention of thrombotic events in people with antiphospholipid antibodies, in particular those with persistently high levels of these antibodies.

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Antiplatelet and anticoagulant agents for primary prevention
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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Alalaf 2012

Methods	<p>Study type: RCT</p> <p>Location: Iraq</p> <p>Time frame: September 2007 to July 2010</p> <p>Setting: maternity teaching hospital, Erbil city, Kurdistan region, North of Iraq</p> <p>Number of centres: 1</p> <p>Follow-up: NR</p>
Participants	<p>Total number of participants: 141</p> <p>Recruitment method: maternity teaching hospital patients</p> <p>Informed consent: yes</p> <p>Inclusion criteria: aged 18 to 42 years at the time of interview; a history of at least 2 unexplained consecutive pregnancy losses before 20 weeks gestation; persistent presence of aCL antibodies or LA or both on 2 occasions 8 weeks apart</p> <p>Exclusion criteria: SLE, known peptic ulcer disease, sensitivity to ASA or heparin depending on patient's history report, previous venous thromboembolic disease requiring ongoing anticoagulant therapy, and failure to consent to participate</p> <p>Age mean (SD): control: 30.61 (6.325), intervention: 31.44 (5.8)</p> <p>Female: control 61 (100%), intervention 80 (100%)</p> <p>SLE: NR</p> <p>Cardiovascular risk factors: NR</p> <p>Antibodies present: LA, aCL, anti-β_2GPI (details NR)</p>
Interventions	<p>Treatment groups: control: ASA 100 mg coated tablets, intervention: bempiparin 2500 IU anti-Xa/0.2 mL solution for injection in prefilled syringes</p> <p>Duration of interventions: up to 36 weeks of gestation</p> <p>Concomitant treatment: yes - folic acid</p>
Outcomes	<p>Primary outcomes: live birth rate</p> <p>Secondary outcomes: obstetric complications, foetal and maternal adverse events</p> <p>Other outcomes: side effects</p>
Notes	<p>Funding: NR</p>

Alalaf 2012 (Continued)

Originally planned sample size: NR

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation	High risk	Quote: "1st case attained the hospital complaining from RM and proved to have APS, was randomized to LDA group, the second case attained the hospital and filled the inclusion criteria; LMWH was prescribed to her, sometimes two cases of Heparin followed one case of LDA. All the cases received the drug randomly." Comment: women referred to the hospital were consecutively given LDA, then LMWH, sometimes in a 2:1 ratio.
Allocation concealment	High risk	Quote: "the 1st case attained the hospital complaining from RM and proved to have APS, was randomized to LDA group, the second case attained the hospital and filled the inclusion criteria" Comment: no information about concealment
Blinding of participants and personnel All outcomes	Unclear risk	Comment: no blinding, no clear definitions or methods of measurements of outcomes, not possible to assess if lack of blinding could have influenced the outcome
Blinding of outcome assessment All outcomes	Unclear risk	Comment: no blinding, no clear definitions or methods of measurements of outcomes, not possible to assess if lack of blinding could have influenced the outcome
Incomplete outcome data	Low risk	Comment: no missing outcome data
Selective reporting	High risk	Comment: no protocol available, side effects described in methods section not completely reported
Other sources of bias	High risk	Comment: 1. Low-dose aspirin given before pregnancy in the LDA group. Bemiparin group received treatment after pregnancy was diagnosed. No details on the structure of the groups in terms of diabetes. 2. No sample size calculation.

Cuadrado 2014

Methods	Study type: RCT, minimisation Location: UK, other countries in Europe, Mexico Time frame: February 2001 to June 2006 Setting: 5 tertiary referral centres in the UK, 8 tertiary referral centres and 1 district hospital in other European countries, 1 tertiary referral centre in Mexico Number of centres: 15 Follow-up: control group: 37.2 months (median); intervention group: 32.4 months (median)
Participants	Total number of participants: 232

Cuadrado 2014 (Continued)

Recruitment method: locally in 14 centres

Informed consent: yes

Inclusion criteria: (i) presence of aPLs (medium or high titres of aCL defined as IgG > 20 GPL and/or IgM > 20 MPL and/or LA positive) on at least 2 occasions, with an interval of 6 weeks, during the year previous to inclusion in the study; (ii) SLE patients meeting 4 or more ACR criteria for the classification of SLE and/or patients with a history of pregnancy morbidity as defined in the APS Sapporo classification criteria; and (iii) age between 18 and 65 years

Exclusion criteria: positive for aPLs but without SLE or obstetric APS, previous thrombotic events, uncontrolled hypertension, active gastric or duodenal ulceration, platelets < 50,000/mm³, hepatic failure, severe illness, allergy to ASA, warfarin, current pregnancy

Age mean (SD): control: 37.8 (10.7), intervention 37.8 (106)

Female: control 80 (96%), intervention 80 (95%)

SLE: control 62 (75%), intervention 62 (73%)

Cardiovascular risk factors:

Control: hypertension 9 (11%), hypercholesterolaemia 8 (10%), hypertriglyceridaemia 0 (0%), smoking 23 (29%), obesity 6 (7%)

Intervention: hypertension 10 (12%), hypercholesterolaemia 12 (14%), hypertriglyceridaemia 4 (5%), smoking 24 (31%), obesity 12 (14%)

Antibodies present:

Control: LA 47/68 (69%), aCL IgG 31/67 (46%) IgM 11/66 (16%), anti-β₂GPI: IgG 10/57 (17.5%) IgM 4/57 (7%)

Intervention: LA 53/64 (83%), aCL IgG 23/62 (37%) IgM 13/61 (21%), anti-β₂GPI: IgG 13/58 (22.4%) IgM 6/58 (10%)

Interventions

Treatment groups: control: ASA 75 to 125 mg, intervention: ASA 75 to 125 mg and warfarin (target INR = 1.5, range 1.3 to 1.7) (ASA dose depending on the preparation available in the participant country)

Duration of interventions: 37.2 (median months)

Concomitant treatment: no

Outcomes

Primary outcomes: thrombosis (objectively verified thrombotic events; the following investigations were performed in order to document the event: ultrasonography or venography for deep vein thrombosis, spiral CT scan or radionuclide lung scan or angiography for pulmonary embolism, MRI or angiography for thrombosis in intracerebral vessels, ophthalmological examination and fluorescein angiography (where possible) for retinal thrombosis, and arteriography for peripheral or mesenteric arterial thrombosis; for the diagnosis of myocardial infarction the World Health Organization (WHO) classification was followed, where two-thirds of the following criteria were required: (i) ECG characteristic changes (2 mm ST increase in ECG leads V4-V6 or 1 mm in I, II and aVF); (ii) ischaemic chest pain lasting > 30 min; and (iii) increase in cardiac enzymes (at least twice their normal value), amaurosis fugax was defined as sudden monocular blindness lasting < 24 h and transient ischaemic attack as neurological symptoms or signs lasting < 24 h)

Secondary outcomes: clinical and serological risk factors for thrombosis, side effects of medications, death of any cause

Other outcomes: NR

Notes

Funding: Arthritis Research UK (clinical trial grant 15600)

Originally planned sample size: 1000

Cuadrado 2014 (Continued)

We attempted to contact Dr Cuadrado for results clarification but were unsuccessful.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation	Low risk	Comment: randomisation carried out using minimisation protocol
Allocation concealment	Low risk	Comment: allocation by independent individual, explicit statement that treatment allocation was concealed
Blinding of participants and personnel Death	Low risk	Comment: no blinding, outcome not likely to be influenced
Blinding of participants and personnel Bleeding	Unclear risk	Comment: no blinding, unclear outcome definition
Blinding of participants and personnel Thromboembolic events	Low risk	Comment: no blinding, however outcome verified by objective methods, not likely to be influenced
Blinding of participants and personnel Adverse events	High risk	Comment: no blinding, outcome is not objectively verified and likely to be influenced
Blinding of outcome assessment Thromboembolic events	Low risk	Comment: no blinding, however outcome verified by objective methods, not likely to be influenced
Blinding of outcome assessment Death	Low risk	Comment: no blinding, outcome not likely to be influenced
Blinding of outcome assessment Bleeding	Unclear risk	Comment: no blinding, unclear outcome definition
Blinding of outcome assessment Adverse events	High risk	Comment: no blinding, outcome is not objectively verified and likely to be influenced
Incomplete outcome data	High risk	Comment: approximately 10% more participants in the experimental group than in the control group have follow-up shorter than 1 year
Selective reporting	Low risk	Comment: all outcomes reported
Other sources of bias	High risk	Comment: low recruitment rate, sample size not achieved

Dendrinios 2009

Methods

Study type: RCT

Location: Greece

Dendrinos 2009 (Continued)

Time frame: March 2002 to March 2006

Setting: university department

Number of centres: 1

Follow-up: up to 2 months postpartum

Participants	<p>Total number of participants: 85</p> <p>Recruitment method: patients referred to the authors' department</p> <p>Informed consent: yes</p> <p>Inclusion criteria: age 18 to 39 years; ≥ 3 consecutive spontaneous abortions before 10 weeks of gestation, and positive aPL antibodies (aCL antibody of IgG and/or IgM isotype in blood, present in medium or high titres, or on 2 or more occasions at least 6 weeks apart; and LA present in plasma, on 2 or more occasions at least 6 weeks apart)</p> <p>Exclusion criteria: SLE; ASA allergy or sensitivity to ASA; a chromosomal or anatomic abnormality or a luteal phase defect; confirmed peptic ulcer; previous thromboembolism, hypertension, or current treatment with antihypertensive drugs; previous prednisone therapy; an abnormal chest radiograph result; or a positive result of a tuberculin skin test</p> <p>Age mean (SD): intervention 31.1 (1), control 32 (0.8)</p> <p>Female: intervention 40 (100%), control 38 (100%)</p> <p>SLE: NR</p> <p>Cardiovascular risk factors: NR</p> <p>Antibodies present: LA, aPL, anti-β_2GPI (details NR)</p>
Interventions	<p>Treatment groups:</p> <p>Control: IVIG 400 mg/kg as soon as positive pregnancy test every 28 days until 32 weeks of gestation</p> <p>Intervention: ASA 75 mg/d and 4500 IU of heparin (Innohep) as soon as woman had a positive pregnancy test result (LMWH dose adapted so that factor Xa levels were within the recommended prophylactic range); ASA was discontinued at 32 weeks of gestation or at the time of an abortion, and heparin at 38 weeks of gestation or at the time of an abortion</p> <p>Duration of interventions: until 32/38 weeks of gestation or abortion</p> <p>Concomitant treatment: control group: calcium 500 mg/day</p>
Outcomes	<p>Primary outcomes: live birth</p> <p>Secondary outcomes: maternal adverse effects during pregnancy and postdelivery (haemorrhages, pregnancy-associated hypertension, fractures during pregnancy or up to 2 months postpartum, reduced maternal bone mineral density, and death)</p> <p>Other outcomes: NR</p>
Notes	<p>Funding: NR</p> <p>Originally planned sample size: NR</p>
Risk of bias	
Bias	<p>Authors' judgement Support for judgement</p>

Dendrinos 2009 (Continued)

Random sequence generation	Low risk	Comment: randomisation was performed in blocks of 8 and 6 using random number tables
Allocation concealment	Unclear risk	Comment: no information about concealment
Blinding of participants and personnel Death	Low risk	Comment: no information, outcome not likely to be influenced by lack of blinding
Blinding of participants and personnel Thromboembolic events	Unclear risk	Comment: no information about blinding, not clear how the outcome was assessed
Blinding of participants and personnel Adverse events	Unclear risk	Comment: no information about blinding, not clear how the outcomes were assessed, therefore not possible to assess the influence of lack of blinding
Blinding of outcome assessment Thromboembolic events	Unclear risk	Comment: no information about blinding, not clear how the outcome was assessed
Blinding of outcome assessment Death	Low risk	Comment: no blinding, but lack of blinding probably did not influence the outcome
Blinding of outcome assessment Adverse events	Unclear risk	Comment: no information about blinding, no information about the assessment of outcomes or their definition, therefore not possible to assess if lack of blinding could have influenced outcome
Incomplete outcome data	High risk	Comment: participants excluded from the analysis after randomisation due to non-compliance or discontinuations. Intention-to-treat analysis cited for primary outcome, but not explained.
Selective reporting	Unclear risk	Comment: no protocol available, all outcomes described in methods section were reported
Other sources of bias	Low risk	Comment: no other bias identified

Erkan 2007

Methods	Study type: RCT, double-blind Location: NR Time frame: June 2001 to April 2005 Setting: NR Number of centres: 3 Follow-up: 2.30 +/- 0.95 years
Participants	Total number of participants: 98 Recruitment method: patients from clinic and collaborative centres Informed consent: yes

Erkan 2007 (Continued)

Inclusion criteria: individuals who were ≥ 18 years of age, with or without systemic autoimmune diseases, who fulfilled at least 1 of the following criteria: a positive LA test result, as defined by the International Society on Thrombosis and Haemostasis on ≥ 2 occasions, at least 6 weeks apart, and/or positive aCL antibodies (IgG/IgM/IgA) ≥ 20 units on ≥ 2 occasions at least 6 weeks apart

Exclusion criteria: diagnosis of APS based on the original Sapporo classification criteria; a history of thrombosis, pulmonary embolism, or transient ischaemic attack; use of regular-dose warfarin or an antiplatelet agent (including ASA); ASA allergy; history of bleeding within the last 5 years that required hospitalisation or blood transfusion or both; severe thrombocytopenia, active gastric/duodenal ulcer; active malignancy, chronic viral infection with HIV or hepatitis C; pregnancy

Age mean (SD): intervention 43.1 (12.8), control 42.7 (14)

Female: intervention 44 (92%), control 44 (88%)

SLE: intervention 30 (63%), control 34 (68%)

Cardiovascular risk factors:

Intervention: hypertension 12 (25%), diabetes 4 (8%), hyperlipidaemia/dyslipidaemia 3 (6%), smoking 10 (21%)

Control: hypertension 10 (20%), diabetes 2 (4%), hyperlipidaemia/dyslipidaemia 2 (4%), smoking 4 (8%)

Antibodies present: information on high risk/low-risk antibodies only (the low-risk aPL profile was defined as IgG, IgM, or IgA 20 to 39 units; the high-risk aPL profile was defined as IgG, IgM, or IgA 40 units and/or positive LA test results)

Interventions	<p>Treatment groups: intervention: ASA 81 mg daily, control: placebo</p> <p>Duration of interventions: 2.27 $\pm$ 0.91 (ASA) vs 2.33 $\pm$ 0.99 (control)</p> <p>Concomitant treatment: HCQ, steroids, NSAID (57%, 33%, 40% respectively)</p>
Outcomes	<p>Primary outcomes: acute thrombosis (stroke confirmed by neuroimaging, deep vein thrombosis by Doppler ultrasonography, pulmonary embolism by CT scan (ventilation/perfusion or spiral)), acute MI confirmed by ECG and increased cardiac enzymes</p> <p>Secondary outcomes: TIA (transient focal neurologic abnormalities with negative neuroimaging study)</p> <p>Other outcomes: ASA-related adverse events (abdominal pain, nausea, vomiting, anorexia, heartburn, dyspepsia, any bleeding)</p>
Notes	<p>Funding: New York Chapter of the Arthritis Foundation and New York Community Trust (Bayer Pharmaceutical provided ASA and placebo)</p> <p>Originally planned sample size: 220</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation	Low risk	Comment: computer-generated stratified randomisation
Allocation concealment	Unclear risk	Comment: details not provided
Blinding of participants and personnel All outcomes	Low risk	Comment: investigators, co-ordinators, participants blinded

Erkan 2007 (Continued)

Blinding of outcome assessment All outcomes	Low risk	Comment: outcomes clearly defined and confirmed objectively or assessors blinded (participants)
Incomplete outcome data	Unclear risk	Comment: insufficient information about analysis of data for participants lost to follow-up
Selective reporting	Unclear risk	Comment: no protocol available
Other sources of bias	High risk	Comment: Bayer was the sponsor of the study - potential risk of favouring the ASA group. Initially planned sample size was 110 per group, after interim analysis it was estimated as 30,363 in each arm; the study included a total of 98 participants.

Farquharson 2002

Methods	Study type: RCT Location: UK Time frame: January 1997 to January 2000 Setting: miscarriage clinic Number of centres: 1 Follow-up: NR
Participants	Total number of participants: 98 Recruitment method: miscarriage clinic patients Informed consent: NR Inclusion criteria: women, 18 to 41 years, at least 3 consecutive pregnancy losses or 2 consecutive losses with proven foetal death after 10 weeks' gestation; 2 positive tests for aPL antibody more than 6 weeks apart (with positive levels defined as > 9 U/mL for IgG and > 5 U/mL for IgM) Exclusion criteria: parental chromosomal abnormality, uterine anomaly, previous arterial or venous thrombosis, use of steroids during pregnancy, systemic lupus erythematosus requiring medication or complicated by nephritis, and other thrombophilia such as activated protein C resistance or protein C/S deficiency Age mean (SD): control 33 (4.9), intervention 33 (4.8) Female: control 47 (100), intervention 51 (100) SLE: NR Cardiovascular risk factors: NR Antibodies present: Control: LA 18 (38%), aCL 7 (15%) Intervention: LA 23 (45%), aCL 9 (18%)
Interventions	Treatment groups: control: ASA 75 mg/d, intervention: ASA 75 mg/d + LMWH 5000 U sc Duration of interventions: from before 12 weeks' gestation until delivery

Farquharson 2002 (Continued)

Concomitant treatment: NR

Outcomes	<p>Primary outcomes: live birth</p> <p>Secondary outcomes: other pregnancy-related outcomes</p> <p>Other outcomes: maternal thrombosis</p>
Notes	<p>Funding: LUPUS UK and NHS R&D (NWEST)</p> <p>Originally planned sample size: 220</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation	Low risk	Comment: computer-generated randomisation, blocks of 20
Allocation concealment	Low risk	Comment: telephone randomisation to the Trials Unit at the Centre for Cancer Epidemiology at the University of Manchester
Blinding of participants and personnel Thromboembolic events	Unclear risk	Comment: no information about blinding, not clear how the outcome was assessed
Blinding of outcome assessment Thromboembolic events	Unclear risk	Comment: no information about blinding, not clear how the outcome was assessed
Incomplete outcome data	Low risk	Comment: no missing data, ITT analysis, 24 not adherent but included in the analysis
Selective reporting	Unclear risk	Comment: no protocol available
Other sources of bias	High risk	Comment: sample size calculated by the authors (n = 220) not achieved; interim analysis mentioned as planned, but not reported

Fouda 2010

Methods	<p>Study type: RCT</p> <p>Location: Egypt</p> <p>Time frame: December 2008 to May 2010</p> <p>Setting: Obstetrics and Gynecology Department, Cairo University Hospital, Egypt</p> <p>Number of centres: 1</p> <p>Follow-up: NR</p>
Participants	<p>Total number of participants: 60</p> <p>Recruitment method: clinic patients</p> <p>Informed consent: yes</p>

Fouda 2010 (Continued)

Inclusion criteria: minimum of 3 consecutive pregnancy losses before 10 weeks' gestation and positive LA and/or aCL antibodies (IgG and IgM) on at least 2 occasions at least 12 weeks apart

Exclusion criteria: paternal chromosomal abnormalities or uterine abnormalities (detected by hysterosalpingography, saline infusion sonography or office hysteroscopy), luteal phase defect, abnormal thyroid function tests, hyperprolactinaemia, polycystic ovary syndrome, SLE, previous thromboembolism, peptic ulcer, age < 19 years or > 37 years, BMI < 19 or > 30, or sensitivity to ASA or heparin

Age mean (SD): intervention 27.13 (3.67), control 28.93 (4.18)

Female: intervention 30 (100%), control 30 (100%)

SLE: NR

Cardiovascular risk factors: NR

Antibodies present:

Intervention: LA 10 (33%), aCL IgG 8 (27%) IgM 4 (20%)

Control: LA 9 (30%), aCL IgG 6 (20%) IgM 5 (17%)

Interventions	<p>Treatment groups: intervention: enoxaparin 40 mg/day + ASA 75 mg/day, control: enoxaparin 20 mg/day + ASA 75 mg/day</p> <p>Duration of interventions: whole pregnancy</p> <p>Concomitant treatment: prenatal vitamins, oral calcium (600 mg twice daily), vitamin D</p>
Outcomes	<p>Primary outcomes: live birth rate</p> <p>Secondary outcomes: excessive bleeding, thrombocytopenia, IUGR; spontaneous osteoporotic fractures; preterm delivery, pre-eclampsia; intrauterine foetal death; neonatal bleeding; congenital anomalies, thrombotic event</p> <p>Other outcomes: NR</p>
Notes	<p>Funding: NR</p> <p>Originally planned sample size: calculated 410, reduced to 60 due to time constraints</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation	Low risk	Comment: computer-generated random numbers
Allocation concealment	Low risk	Comment: concealed in opaque envelopes
Blinding of participants and personnel Bleeding	Unclear risk	Comment: no blinding, insufficient definition
Blinding of participants and personnel Thromboembolic events	Unclear risk	Comment: no blinding, no definition of thrombotic event is given
Blinding of participants and personnel Adverse events	Unclear risk	Comment: no blinding, insufficient definition

Fouda 2010 (Continued)

Blinding of outcome assessment Thromboembolic events	Unclear risk	Comment: insufficient information to judge (no information about outcome assessment)
Blinding of outcome assessment Bleeding	Unclear risk	Comment: no blinding, insufficient definition
Blinding of outcome assessment Adverse events	Unclear risk	Comment: no blinding, insufficient definition
Incomplete outcome data	Low risk	Comment: no missing outcome data
Selective reporting	Unclear risk	Comment: no protocol available, most of the prespecified outcomes were reported
Other sources of bias	High risk	Comment: low recruitment rate, sample size not achieved

Fouda 2011

Methods	Study type: RCT Location: Egypt Time frame: June 2006 to December 2009 Setting: Cairo University Number of centres: 2 Follow-up: NR
Participants	Total number of participants: 60 Recruitment method: hospital patients Informed consent: yes Inclusion criteria: a history of 3 or more consecutive spontaneous abortions before 10 weeks of gestation, and positive LA and/or aCL antibodies (IgG and IgM) on 2 or more occasions at least 12 weeks apart; age between 18 and 37 years; and BMI between 19 and 29 Exclusion criteria: paternal chromosomal abnormalities; uterine malformation detected by hysterosalpingography or office hysteroscopy; cervical incompetence; luteal phase defect; abnormal thyroid function tests; hyperprolactinaemia; polycystic ovary syndrome; hereditary thrombophilia; SLE; previous venous or arterial thrombotic episodes; diabetes mellitus; kidney or liver disease; gastric ulcer; and sensitivity to ASA, UFH, or enoxaparin Age mean (SD): intervention 27.47 (SD 3.2), control 28.57 (SD 3.48) Female: intervention 30 (100%), control 30 (100%) SLE: NR Cardiovascular risk factors: NR Antibodies present: Intervention: LA 12 (40%), aCL IgG 7 (23%) IgM 5 (17%)

Fouda 2011 (Continued)

Control: LA 10 (33%), aCL IgG 5 (17%) IgM 8 (27%)

Interventions	<p>Treatment groups: intervention: enoxaparin 40 mg/day sc + ASA 75 mg/day, control: heparin calcium 5000 IU sc, twice daily + ASA 75 mg/day</p> <p>Duration of interventions: whole pregnancy</p> <p>Concomitant treatment: prenatal vitamins, 600 mg oral calcium twice daily, and 400 IU vitamin D₃ twice daily</p>
Outcomes	<p>Primary outcomes: live birth rate</p> <p>Secondary outcomes: excessive haemorrhage, thrombocytopenia, IUGR, intrauterine foetal death, preterm delivery, neonatal bleeding, congenital anomalies, pre-eclampsia, spontaneous osteoporotic fractures</p> <p>Other outcomes: NR</p>
Notes	<p>Funding: NR</p> <p>Originally planned sample size: calculated 1447, reduced to 60</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation	Low risk	Comment: computer-generated randomisation list
Allocation concealment	Low risk	Comment: opaque, sealed envelopes
Blinding of participants and personnel Bleeding	Low risk	Comment: open-label study, but outcome clearly defined and objectively confirmed, so not likely to be influenced by lack of blinding
Blinding of participants and personnel Thromboembolic events	Unclear risk	Comment: open-label study, no clear definition of the outcome and assessment
Blinding of participants and personnel Adverse events	Unclear risk	Comment: open-label study, no clear definition of the outcome and assessment
Blinding of outcome assessment Thromboembolic events	Unclear risk	Comment: open-label study, no clear definition of the outcome and assessment
Blinding of outcome assessment Bleeding	Low risk	Comment: open-label study, but outcome clearly defined and objectively confirmed, so not likely to be influenced by lack of blinding
Blinding of outcome assessment Adverse events	Unclear risk	Comment: open-label study, no clear definition of the outcome and assessment
Incomplete outcome data	Low risk	Comment: no missing outcome data
Selective reporting	Unclear risk	Comment: no protocol, all outcomes reported

Fouda 2011 (Continued)

Other sources of bias	High risk	Comment: low recruitment rate (estimated: 1447; recruited: 60)
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Ismail 2016

Methods	<p>Study type: RCT</p> <p>Location: Egypt</p> <p>Time frame: January 2011 to June 2013</p> <p>Setting: Women's Health Hospital, Assiut University, Egypt</p> <p>Number of centres: 1</p> <p>Follow-up: to 6 weeks after delivery</p>
Participants	<p>Total number of participants: 180</p> <p>Recruitment method: gynaecology outpatient clinic patients</p> <p>Informed consent: yes</p> <p>Inclusion criteria: diagnosis of APS was made on the basis of 2 positive test results, at least 12 weeks apart, for the presence of either LA or aCL antibodies and a history of 3 or more consecutive first-trimester (≤ 13 weeks) spontaneous abortions, or 2 or more second-trimester spontaneous abortions (13 to 24 weeks) with the same partner</p> <p>Exclusion criteria: history of thromboembolic events, bleeding tendencies, hypersensitivity to ASA or enoxaparin, congenital anomalies of the uterus, cervical insufficiency, uncontrolled diabetes mellitus, or chromosomal anomalies affecting either participants or their partners, pregnancy at study enrolment following the use of assisted reproductive techniques</p> <p>Age mean (SD): intervention 25.5 (4.7), control 27.6 (4.8)</p> <p>Female: intervention 90 (100%), control 90 (100%)</p> <p>SLE: NR</p> <p>Cardiovascular risk factors: NR</p> <p>Antibodies present: NR</p>
Interventions	<p>Treatment groups: intervention: 40 mg of enoxaparin sc daily + 81 mg of ASA daily, control: placebo</p> <p>Duration of interventions: from preconception to 6 weeks after delivery</p> <p>Concomitant treatment: folic acid, calcium</p>
Outcomes	<p>Primary outcomes: rate of live birth after 24 weeks of pregnancy, clinical pregnancy rate at 0 to 6 months, clinical pregnancy rate at 6 to 12 months</p> <p>Secondary outcomes: rate of first- and second-trimester spontaneous abortion, vaginal bleeding during pregnancy, pre-eclampsia, pregnancy-induced hypertension, abruptio placentae, preterm delivery, IUGR</p> <p>Other outcomes: complications of enoxaparin use (maternal or neonatal bleeding or both, heparin-induced thrombocytopenia, pain and bruising at injection sites, hypersensitivity to heparin, teratogenicity), and thromboembolic events</p>
Notes	<p>Funding: NR</p>

Ismail 2016 (Continued)

Originally planned sample size: 180

We obtained additional information and clarification of results from Dr Ismail.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation	Low risk	Quote: "Using a computer-generated sequence, participants were randomly allocated in a 1:1 ratio to receive enoxaparin plus aspirin or placebo.(...) A minimization procedure employing a computer-based algorithm was applied to avoid chance imbalances in important stratification variables"
Allocation concealment	Low risk	Quote: "To ensure allocation concealment, an independent secretary stored all the sealed envelopes containing each participant's group assignment; all envelopes were kept closed until data analysis was completed. Additionally, a central telephone system was used whereby an independent secretary spoke with patients to arrange all follow-up visits." Comment: allocation concealment properly implemented
Blinding of participants and personnel All outcomes	Low risk	Quote: "Study drugs and placebo were prepared by the pharmacy department of the study institution, with all placebo treatments manufactured to be identical to study medications. Study drugs and placebo were stored in identical ampoules and as tablets of identical size, shape, and colour; study treatments were distributed to participants by study institution staff without informing them of their treatment assignment. Clinicians, investigators, and data analysts were masked to the group assignments." Comment: blinding implemented appropriately
Blinding of outcome assessment Thromboembolic events	Unclear risk	Comment: no clear definition of outcome and assessment, no information about blinding of outcome assessors
Blinding of outcome assessment Bleeding	Low risk	Comment: no blinding but lack of blinding would not have influenced the outcome, as clear definition of outcome provided
Blinding of outcome assessment Adverse events	Low risk	Comment: participants, clinicians, and investigators were reported to be blinded
Incomplete outcome data	Low risk	Comment: similar percentage of participants lost to follow up, ITT analysis
Selective reporting	Unclear risk	Comment: no protocol, no information about thrombotic events
Other sources of bias	Low risk	Comment: no other sources of bias

Rai 1997

Methods

Study type: RCT

Location: UK

Time frame: April 1993 to July 1995

Setting: recurrent miscarriage clinic at St Mary's Hospital in London

Rai 1997 (Continued)

	Number of centres: 1 Follow-up: NR
Participants	Total number of participants: 90 Recruitment method: recurrent miscarriage clinic patients Informed consent: yes Inclusion criteria: a history of 3 or more consecutive miscarriages and positive results for aPL antibodies on at least 2 occasions more than 8 weeks apart before becoming pregnant Exclusion criteria: previous thromboembolism, SLE, a uterine abnormality, hypersecretion of luteinising hormone, and multiple pregnancy, abnormal karyotype Age mean (range): control 34 (22 to 44), intervention 32 (23 to 40) Female: control 45 (100%), intervention 45 (100%) SLE: NR Cardiovascular risk factors: NR Antibodies present: Control: LA 34 (76%), aCL 5 (11%) Intervention: LA 40 (89%), aCL 3 (7%)
Interventions	Treatment groups: control: ASA 75 mg/day, intervention: ASA 75 mg/day + calcium heparin 5000 IU sc daily Duration of interventions: up to 34 weeks gestation Concomitant treatment: NR
Outcomes	Primary outcomes: live births Secondary outcomes: premature delivery (before 37 weeks of gestation) Other outcomes: safety, adverse events
Notes	Funding: Arthritis and Rheumatism Council Originally planned sample size: 80 to 90

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation	Low risk	Quote: "Patients were randomly assigned in equal proportion to the two treatment groups by means of a computer generated random number list (Systat 5.2.1; Macintosh)." Comment: computer-generated random number list
Allocation concealment	Low risk	Quote: "The randomisation list was kept by an independent member of staff not involved in the trial." Comment: only a person outside the study had access
Blinding of participants and personnel	Unclear risk	Comment: lack of blinding, definition of outcome unclear, therefore not possible to judge if lack of blinding could have influenced the outcomes

Rai 1997 (Continued)

All outcomes

Blinding of outcome assessment All outcomes	Unclear risk	Comment: lack of blinding, definition of outcome unclear, therefore not possible to judge if lack of blinding could have influenced the outcomes
Incomplete outcome data	Low risk	Comment: no missing data
Selective reporting	Unclear risk	Comment: no protocol available
Other sources of bias	Low risk	Comment: no other sources of bias

aCL: anticardiolipin

ACR: American College of Rheumatology

anti- β_2 GPI: anti-beta2-glycoprotein I

aPL: antiphospholipid

APS: antiphospholipid syndrome

ASA: acetylsalicylic acid

BMI: body mass index

CT: computed tomography

ECG: electrocardiography

GPI: glycoprotein I

GPL: G phospholipids

HCQ: hydroxychloroquine

IgA: immunoglobulin A

IgG: immunoglobulin G

IgM: immunoglobulin M

INR: international normalised ratio

ITT: intention-to-treat

IUGR: intrauterine growth restriction

LA: lupus anticoagulant

LDA: low-dose aspirin

LMWH: low molecular weight heparin

MI: myocardial infarction

MPL: M phospholipids

MRI: magnetic resonance imaging

NR: not reported

NSAID: non-steroidal anti-inflammatory drugs

RCT: randomised controlled trial

RM: recurrent miscarriage

sc: subcutaneously

SD: standard deviation

SLE: systemic lupus erythematosus

TIA: transient ischaemic attack

UFH: unfractionated heparin

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Anonymous 2010	Wrong patient population: aPL antibodies not confirmed
Arachchilage 2016	Wrong patient population: secondary prevention
Cohen 1996	Wrong outcomes: obstetric failure only
Cohen 2016	Wrong patient population: secondary prevention

Study	Reason for exclusion
Cowchock 1992	Wrong outcomes: only obstetric outcomes, thromboembolism not assessed
Cowchock 1997	Wrong outcomes: obstetric failure only
Crowther 2003	Wrong patient population: secondary prevention
Douketis 1999	Wrong outcomes: prothrombin fragment 1 + 2 level (F1 + 2); thromboembolic events/bleeding not assessed
Finazzi 2005	Wrong patient population: secondary prevention
Goel 2006	Wrong study design: non-RCT
Kondrat'eva 2010	Wrong patient population: secondary prevention
Kutteh 1996	Wrong study design: non-RCT
Lopez-Pedrerá 2015	Wrong intervention: no anticoagulant/antiplatelet intervention
Mohamed 2014	Wrong study design: non-randomised comparative study
Moreira da Costa 2015	Wrong study design: non-RCT
NCT02295475	Wrong patient population: secondary prevention
NCT02926170	Wrong patient population: secondary prevention
Noble 2005	Wrong study design: non-randomised trial
O'Neil 2007	Wrong patient population: secondary prevention
Pattison 2000	Wrong outcomes: obstetric failure only
Pengo 2016	Wrong patient population: secondary prevention
Roubey 2010	Wrong patient population: study group consisted of aPL-positive patients or people with other thrombophilia
Scarpellini 2009	Wrong outcomes: only obstetric outcomes, thromboembolism not assessed
Stephenson 2004	Wrong outcomes: obstetric failure only
Stern 2001	Wrong outcomes: only effectiveness of implantation assessed
Villamil 2016	Wrong intervention: no antiplatelet/anticoagulant intervention
Woller 2016	Wrong patient population: secondary prevention
Yamazaki 2009	Wrong patient population: not primary prevention

aPL: antiphospholipid

RCT: randomised controlled trial

Characteristics of ongoing studies [ordered by study ID]

NCT03100123

Trial name or title	A pilot study assessing the feasibility of a randomized controlled trial evaluating aspirin versus low-molecular-weight heparin (LMWH) and aspirin in women with antiphospholipid syndrome and pregnancy loss
Methods	Study type: multicentre, open-label, randomised controlled trial Location: Canada Number of centres: 2 Time frame of the study: November 2017 to November 2019
Participants	Inclusion criteria: <ul style="list-style-type: none"> confirmed pregnancy 18 years or older 2 or more unexplained pregnancy loss before the 10th week of gestation and/or 1 or more unexplained pregnancy loss at or beyond the 10th week of gestation 1 or more APS laboratory criteria present, according to revised Sapporo criteria Exclusion criteria: <ul style="list-style-type: none"> greater than 11 weeks + 6 days gestational age at time of randomisation indication(s) for prophylactic or therapeutic-dose anticoagulation contraindication to heparin or ASA received 7 or more doses of LMWH previous participation in the trial geographic inaccessibility refused consent
Interventions	<ul style="list-style-type: none"> Experimental arm: ASA 81 mg orally daily in tablet form Standard care arm: low molecular weight heparin: tinzaparin 4500 IU sc daily until 20 weeks gestation, and then 4500 IU sc twice daily until 37 weeks gestation
Outcomes	Primary outcome: the primary feasibility outcome of the pilot trial is the mean recruitment rate per centre per month. Secondary outcomes: <ul style="list-style-type: none"> proportion of sites requiring more than 18 months to obtain all required approvals/contracts from time of delivery of all study documents proportion of screened patients who meet eligibility criteria (i.e. patients who meet inclusion criteria and are also eligible based on exclusion criteria) proportion of eligible participants who provide consent proportion of withdrawals/loss to follow-up among randomised participants cross-over rate between standard care and experimental study arms level of compliance with study drug through participant recall and participant medication diary reasons for physician and patient non-consent
Starting date	6 November 2017
Contact information	Contact: Leslie Skeith, MD, Veronica Whitham, BSc 613-737-8899 ext 71068 Ottawa Hospital Research Institute
Notes	Funding: Ottawa Hospital Research Institute

NCT03100123 (Continued)

NCT03100123

APS: antiphospholipid syndrome
ASA: acetylsalicylic acid
LMWH: low molecular weight heparin
sc: subcutaneously

DATA AND ANALYSES

Comparison 1. Anticoagulant with or without ASA versus ASA only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Thrombosis	4	493	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.25, 3.77]
2 Minor bleeding	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Analysis 1.1. Comparison 1 Anticoagulant with or without ASA versus ASA only, Outcome 1 Thrombosis.

Analysis 1.2. Comparison 1 Anticoagulant with or without ASA versus ASA only, Outcome 2 Minor bleeding.

Comparison 2. ASA only versus placebo

Outcome or sub-group title	No. of studies	No. of participants	Statistical method	Effect size
1 Thrombosis	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2 Bleeding	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Analysis 2.1. Comparison 2 ASA only versus placebo, Outcome 1 Thrombosis.

Study or subgroup	ASA n/N	placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Erkan 2007	5/48	1/50		5.21[0.63,42.97]
			Favours ASA Favours placebo	

Analysis 2.2. Comparison 2 ASA only versus placebo, Outcome 2 Bleeding.

Study or subgroup	ASA n/N	placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Erkan 2007	3/48	1/50		3.13[0.34,29.01]
			Favours ASA Favours placebo	

Comparison 3. ASA with LMWH versus placebo or IVIG

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Thrombosis	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2 Bleeding	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 Bleeding requiring transfusion	1	180	Risk Ratio (M-H, Fixed, 95% CI)	9.0 [0.49, 164.76]
2.2 Bleeding during first trimester	1	180	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.50, 1.61]
2.3 Postpartum haemorrhage	1	180	Risk Ratio (M-H, Fixed, 95% CI)	1.3 [0.60, 2.81]

Analysis 3.1. Comparison 3 ASA with LMWH versus placebo or IVIG, Outcome 1 Thrombosis.

Study or subgroup	ASA+LMWH n/N	placebo or IVIG n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Dendrinos 2009	0/40	0/38			Not estimable
Ismail 2016	0/90	0/90			Not estimable

Analysis 3.2. Comparison 3 ASA with LMWH versus placebo or IVIG, Outcome 2 Bleeding.

Study or subgroup	ASA+LMWH n/N	placebo or IVIG n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
3.2.1 Bleeding requiring transfusion					
Ismail 2016	4/90	0/90		100%	9[0.49,164.76]
Subtotal (95% CI)	90	90		100%	9[0.49,164.76]
Total events: 4 (ASA+LMWH), 0 (placebo or IVIG)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.48(P=0.14)					
3.2.2 Bleeding during first trimester					
Ismail 2016	17/90	19/90		100%	0.89[0.5,1.61]
Subtotal (95% CI)	90	90		100%	0.89[0.5,1.61]
Total events: 17 (ASA+LMWH), 19 (placebo or IVIG)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.37(P=0.71)					
3.2.3 Postpartum haemorrhage					
Ismail 2016	13/90	10/90		100%	1.3[0.6,2.81]
Subtotal (95% CI)	90	90		100%	1.3[0.6,2.81]
Total events: 13 (ASA+LMWH), 10 (placebo or IVIG)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.67(P=0.5)					
Test for subgroup differences: Chi²=2.66, df=1 (P=0.26), I²=24.87%

Comparison 4. ASA + high-dose LMWH versus ASA + low-dose LMWH or UFH

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Thrombosis	2	120	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Major/excessive bleeding	2	120	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3 Subcutaneous bruises	2	120	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.34, 2.93]

Analysis 4.1. Comparison 4 ASA + high-dose LMWH versus ASA + low-dose LMWH or UFH, Outcome 1 Thrombosis.

Analysis 4.2. Comparison 4 ASA + high-dose LMWH versus ASA + low-dose LMWH or UFH, Outcome 2 Major/excessive bleeding.

Analysis 4.3. Comparison 4 ASA + high-dose LMWH versus ASA + low-dose LMWH or UFH, Outcome 3 Subcutaneous bruises.

Comparison 5. Sensitivity analyses anticoagulant with or without ASA versus ASA only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Thrombosis best-worst scenario	4	493	Risk Ratio (M-H, Fixed, 95% CI)	0.39 [0.13, 1.19]
2 Thrombosis worst-best scenario	4	493	Risk Ratio (M-H, Fixed, 95% CI)	4.39 [1.55, 12.42]

Analysis 5.1. Comparison 5 Sensitivity analyses anticoagulant with or without ASA versus ASA only, Outcome 1 Thrombosis best-worst scenario.

Analysis 5.2. Comparison 5 Sensitivity analyses anticoagulant with or without ASA versus ASA only, Outcome 2 Thrombosis worst-best scenario.

Comparison 6. Sensitivity analyses ASA with LMWH versus placebo or IVIG

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Thrombosis best-worst scenario	2	265	Risk Ratio (M-H, Fixed, 95% CI)	0.13 [0.01, 2.51]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2 Thrombosis worst-best scenario	2	265	Risk Ratio (M-H, Fixed, 95% CI)	8.4 [0.47, 151.34]

Analysis 6.1. Comparison 6 Sensitivity analyses ASA with LMWH versus placebo or IVIG, Outcome 1 Thrombosis best-worst scenario.

Analysis 6.2. Comparison 6 Sensitivity analyses ASA with LMWH versus placebo or IVIG, Outcome 2 Thrombosis worst-best scenario.

APPENDICES

Appendix 1. CENTRAL search strategy 15 February 2017

Search run on Wed Feb 15 2017			Hits retrieved
#1	MESH DESCRIPTOR Antiphospholipid Syndrome		52
#2	MESH DESCRIPTOR Antibodies, Antiphospholipid EXPLODE ALL TREES		90

(Continued)

#3	(aPL antibodies):TI,AB,KY	3
#4	APS :TI,AB,KY	191
#5	(Hughes syndrome):TI,AB,KY	0
#6	(antiphospholipid near2 syndrome):TI,AB,KY	135
#7	#1 OR #2 OR #3 OR #4 OR #5 OR #6	341
#8	MESH DESCRIPTOR Thrombosis	1238
#9	MESH DESCRIPTOR Thromboembolism	899
#10	MESH DESCRIPTOR Venous Thromboembolism	242
#11	MESH DESCRIPTOR Venous Thrombosis EXPLODE ALL TREES	2005
#12	(thrombus* or thrombopro* or thrombotic* or thrombolic* or thromboemboli* or thrombos* or embol* or microembol*):TI,AB,KY	17951
#13	MESH DESCRIPTOR Pulmonary Embolism EXPLODE ALL TREES	735
#14	(PE or DVT or VTE):TI,AB,KY	4704
#15	((vein* or ven*) near thromb*):TI,AB,KY	6380
#16	(blood near3 clot*):TI,AB,KY	2761
#17	(pulmonary near3 clot*):TI,AB,KY	5
#18	(lung near3 clot*):TI,AB,KY	4
#19	#8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18	23298
#20	MESH DESCRIPTOR Anticoagulants EXPLODE ALL TREES	8078
#21	(anticoagul* or anti-coagu*):TI,AB,KY	7680
#22	MESH DESCRIPTOR Heparin EXPLODE ALL TREES	3826
#23	*parin*:TI,AB,KY	54717
#24	UFH:TI,AB,KY	447
#25	LMWH:TI,AB,KY	809
#26	LMH:TI,AB,KY	6
#27	(Ariven or Arteven or Calcilean or Hepalean or Hepathrom or Leparan or Lipo-Hepin or Liquaemin or Liquemin or Pabyrin or Pularin or Thromboliquine or Vetren):TI,AB,KY	9
#28	(Clexane or klexane or lovenox):TI,AB,KY	42
#29	(Fragmin):TI,AB,KY	178

(Continued)

#30	(Innohep):TI,AB,KY	11
#31	clivarin* :TI,AB,KY	20
#32	(danaproid or danaparoid):TI,AB,KY	37
#33	(antixarin):TI,AB,KY	2
#34	(Zibor or cy 222 or embolex or monoembolex):TI,AB,KY	38
#35	(rd 11885 or RD1185):TI,AB,KY	0
#36	(Kabi-2165 or Kabi 2165):TI,AB,KY	39
#37	(emt-966 or emt966 or emt-967 or emt977 or pk-10169 or pk10169):TI,AB,KY	8
#38	(fr-860 or fr860 or cy-216 or cy216):TI,AB,KY	51
#39	(kb101 or lomoparan or orgaran):TI,AB,KY	28
#40	(fluxum or lohepa or lowhepa):TI,AB,KY	11
#41	(op 2123 or op2123):TI,AB,KY	1
#42	(ave 5026 or ave5026):TI,AB,KY	2
#43	(M118 or RO-1):TI,AB,KY	9
#44	*coumar*:TI,AB,KY	616
#45	(*warfarin or (vitamin near/3 antagonist*)):TI,AB,KY	2855
#46	(VKA or phenindione or Sinthrome or nicoumalone or phenprocoumon or Marcumar or Marcumar or Falithrom or AVK or phenprocoumon* or aldocumar or carfin or jantoven or kumatox or lawarin or marevan or prothromadin or sofarin or tedicumar or tintorane or waran or warfant or warfilone or warner-in):TI,AB,KY	389
#47	MESH DESCRIPTOR Antithrombins EXPLODE ALL TREES	1235
#48	MESH DESCRIPTOR Hirudin Therapy	75
#49	(thrombin near3 inhib*):TI,AB,KY	506
#50	hirudin*:TI,AB,KY	364
#51	(dabigatran or Pradaxa or Rendix):TI,AB,KY	393
#52	(BIBR-953* or BIBR953* or BIBR-1048 or BIBR1048):TI,AB,KY	9
#53	(ximelagatran or Exanta or Exarta or melagatran):TI,AB,KY	150
#54	(AZD0837 or AZD-0837):TI,AB,KY	14
#55	(S35972 or S-35972):TI,AB,KY	0

(Continued)

#56	MESH DESCRIPTOR Factor Xa Inhibitors	295
#57	(Factor X* near4 (antag* or inhib* or block*)):TI,AB,KY	584
#58	(FX* near4 (antag* or inhib* or block*)):TI,AB,KY	48
#59	(10* near4 (antag* or inhib* or block*)):TI,AB,KY	1073
#60	(rivaroxaban or Xarelto):TI,AB,KY	526
#61	(Bay-597939 or Bay597939):TI,AB,KY	0
#62	(betrixaban or PRT054021):TI,AB,KY	19
#63	apixaban:TI,AB,KY	300
#64	(BMS-562247 or BMS-562247 or ELIQUIS):TI,AB,KY	0
#65	(DU-176b or DU176b):TI,AB,KY	11
#66	(PRT-054021 or PRT054021):TI,AB,KY	1
#67	(YM150 or YM-150 or LY517717 or LY-517717 or DU-176b or DU176*):TI,AB,KY	39
#68	(GW813893 or "Tak 442" or TAK442 or PD0348292 or GSK-813893 or GSK813893):TI,AB,KY	3
#69	edoxaban or lixiana:TI,AB,KY	157
#70	*ixaban:TI,AB,KY	326
#71	*axaban:TI,AB,KY	6
#72	*exaban:TI,AB,KY	11
#73	etexilate:TI,AB,KY	126
#74	agatroban:TI,AB,KY	1
#75	*parinux:TI,AB,KY	303
#76	MESH DESCRIPTOR Platelet Aggregation Inhibitors EXPLODE ALL TREES	8396
#77	MESH DESCRIPTOR Phosphodiesterase Inhibitors EXPLODE ALL TREES	5495
#78	MESH DESCRIPTOR Tetrazoles	1823
#79	(antiplatelet* or anti-platelet* or antiaggreg* or anti-aggreg*):TI,AB,KY	3253
#80	((platelet or thromboxane or thrombocyte or cyclooxygenase or cyclo-oxygenase or phosphodiesterase or fibrinogen or PAR-1) near3 (antagonist or inhibitor)):TI,AB,KY	2349
#81	((gp* or glycoprotein* or protease or P2Y12 or TXA2) near3 inhibit*):TI,AB,KY	3199
#82	thienopyridine:TI,AB,KY	266

(Continued)

#83	(ticlopidine or Ticlid):TI,AB,KY	1748
#84	(clopidogrel or Plavix):TI,AB,KY	3014
#85	(Prasugrel or Effient or Efient or Prasita):TI,AB,KY	501
#86	(ticagrelor or AZD6140 or Brilinta):TI,AB,KY	436
#87	(elinogrel or PRT060128 or PRT-060128):TI,AB,KY	8
#88	(cangrelor or AR-C6993* or ARC6993*):TI,AB,KY	50
#89	(SCH530348 or SCH-530348):TI,AB,KY	19
#90	E5555:TI,AB,KY	5
#91	(terutroban or Triplion):TI,AB,KY	14
#92	(aspirin* or nitroaspirin or ASA):TI,AB,KY	17036
#93	(acetylsalicylic acid):TI,AB,KY	4935
#94	(acetyl salicylic acid*):TI,AB,KY	109
#95	(triflusal or disgren):TI,AB,KY	97
#96	(Cilostazol or Pletal or Pletaal):TI,AB,KY	464
#97	(dipyridamol* or Persantine):TI,AB,KY	1129
#98	(OPC-13013 or OPC13013):TI,AB,KY	5
#99	(picotamide or picotinamide):TI,AB,KY	41
#100	satigrel:TI,AB,KY	3
#101	vorapaxar:TI,AB,KY	84
#102	indobufen:TI,AB,KY	82
#103	#20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55 OR #56 OR #57 OR #58 OR #59 OR #60 OR #61 OR #62 OR #63 OR #64 OR #65 OR #66 OR #67 OR #68 OR #69 OR #70 OR #71 OR #72 OR #73 OR #74 OR #75 OR #76 OR #77 OR #78 OR #79 OR #80 OR #81 OR #82 OR #83 OR #84 OR #85 OR #86 OR #87 OR #88 OR #89 OR #90 OR #91 OR #92 OR #93 OR #94 OR #95 OR #96 OR #97 OR #98 OR #99 OR #100 OR #101 OR #102	92582
#104	#7 AND #19 AND #103	72

Appendix 2. Trials registries searches 15 February 2017

ClinicalTrials.gov

73 studies found for: antiphospholipid

World Health Organization International Clinical Trials Registry Platform

65 records for 57 trials found for: antiphospholipid

ISRCTN Register

21 results for: antiphospholipid

Appendix 3. Follow-up search strategies November/December 2017

Source	Search strategy	Hits retrieved
1. MEDLINE In-process and other non-indexed citations and MEDLINE 1950-present (Ovid SP) (2017 ONLY)	1 Antiphospholipid Syndrome/ 8228	62
Searched 4 December 2017	2 exp Antibodies, Antiphospholipid/ 9033	
	3 aPL antibodies.ti,ab. 321	
	4 APS.ti,ab. 10942	
	5 "Hughes syndrome".ti,ab. 180	
	6 "antiphospholipid adj2 syndrome".ti,ab. 0	
	7 or/1-6 21671	
	8 Thrombosis/ 69315	
	9 Thromboembolism/ 23814	
	10 Venous Thromboembolism/ 8453	
	11 exp Venous Thrombosis/ 54084	
	12 (thrombus* or thrombopro* or thrombotic* or thrombolic* or thromboemboli* or thrombos* or embol* or microembol*).ti,ab. 316286	
	13 exp Pulmonary Embolism/ 38164	
	14 (PE or DVT or VTE).ti,ab. 47775	
	15 ((vein* or ven*) adj3 thromb*).ti,ab. 72239	
	16 (blood adj3 clot*).ti,ab. 10458	
	17 (pulmonary adj3 clot*).ti,ab. 198	
	18 (lung adj3 clot*).ti,ab. 48	
	19 or/8-18 408490	
	20 exp Anticoagulants/ 214555	
	21 (anticoagul* or anti-coagu*).ti,ab. 86806	
	22 exp Heparin/ 65466	
	23 heparin*.ti,ab. 85147	
	24 UFH.ti,ab. 2032	
	25 LMWH.ti,ab. 4479	
	26 LMH.ti,ab. 434	

(Continued)

- 27 (Ariven or Arteven or Calcilean or Hepalean or Hepathrom or Leparan or Lipo-Hepin or Liquaemin or Liquemin or Pabyrin or Pularin or Thromboliquine or Vetren).ti,ab. 55
- 28 (Clexane or klexane or lovenox).ti,ab. 241
- 29 Fragmin.ti,ab. 384
- 30 Innohep.ti,ab. 21
- 31 clivarin*.ti,ab. 28
- 32 (danaproid or danaparoid).ti,ab. 449
- 33 antixarin.ti,ab. 1
- 34 (Zibor or cy 222 or embolex or monoembolex).ti,ab. 59
- 35 (rd 11885 or RD1185).ti,ab. 1
- 36 (Kabi-2165 or Kabi 2165).ti,ab. 41
- 37 (emt-966 or emt966 or emt-967 or emt977 or pk-10169 or pk10169).ti,ab. 43
- 38 (fr-860 or fr860 or cy-216 or cy216).ti,ab. 99
- 39 (kb101 or lomoparan or orgaran).ti,ab. 113
- 40 (fluxum or lohepa or lowhepa).ti,ab. 12
- 41 (op 2123 or op2123).ti,ab. 3
- 42 (ave 5026 or ave5026).ti,ab. 8
- 43 (M118 or RO-1).ti,ab. 140
- 44 coumar*.ti,ab. 16405
- 45 (warfarin or (vitamin adj3 antagonist*)).ti,ab. 26213
- 46 (VKA or phenindione or Sinthrome or nicoumalone or phenprocoumon or Marcoumar or Marcumar or Falithrom or AVK or phenprocoumon* or aldocumar or carfin or jantoven or kumatox or lawarin or marevan or prothromadin or sofarin or tedicumar or tintorane or waran or warfant or warfilone or warnerin).ti,ab. 2709
- 47 exp Antithrombins/ 20598
- 48 Hirudin Therapy/ 684
- 49 (thrombin adj3 inhib*).ti,ab. 10229
- 50 hirudin*.ti,ab. 3471
- 51 (dabigatran or Pradaxa or Rendix).ti,ab. 3811
- 52 (BIBR-953* or BIBR953* or BIBR-1048 or BIBR1048).ti,ab. 14
- 53 (ximelagatran or Exanta or Exarta or melagatran).ti,ab. 652
- 54 (AZD0837 or AZD-0837).ti,ab. 31
- 55 (S35972 or S-35972).ti,ab. 2
- 56 Factor Xa Inhibitors.ti,ab. 1086
- 57 (Factor X* adj4 (antag* or inhib* or block*)).ti,ab. 4546

(Continued)

- 58 (FX* adj4 (antag* or inhib* or block*)).ti,ab. 1654
- 59 (10* adj4 (antag* or inhib* or block*)).ti,ab. 81139
- 60 (rivaroxaban or Xarelto).ti,ab. 3487
- 61 (Bay-597939 or Bay597939).ti,ab. 2
- 62 apixaban.ti,ab. 2183
- 63 (BMS-562247 or BMS-562247 or ELIQUIS).ti,ab. 47
- 64 (DU-176b or DU176b).ti,ab. 26
- 65 (PRT-054021 or PRT054021).ti,ab. 4
- 66 (YM150 or YM-150 or LY517717 or LY-517717 or DU-176b or DU176*).ti,ab. 67
- 67 (GW813893 or "Tak 442" or TAK442 or PD0348292 or GSK-813893 or GSK813893).ti,ab. 16
- 68 (edoxaban or lixiana).ti,ab. 892
- 69 etexilate.ti,ab. 723
- 70 agatroban.ti,ab. 1
- 71 exp Platelet Aggregation Inhibitors/ 107579
- 72 exp Phosphodiesterase Inhibitors/ 85845
- 73 Tetrazoles/ 11647
- 74 (antiplatelet* or anti-platelet* or antiaggreg* or anti-aggreg*).ti,ab. 31484
- 75 ((platelet or thromboxane or thrombocyte or cyclooxygenase or cyclo-oxygenase or phosphodiesterase or fibrinogen or PAR-1) adj3 (antagonist or inhibitor)).ti,ab. 20364
- 76 ((gp* or glycoprotein* or protease or P2Y12 or TXA2) adj3 inhibit*).ti,ab. 49431
- 77 thienopyridine.ti,ab. 983
- 78 (ticlopidine or Ticlid).ti,ab. 2653
- 79 (clopidogrel or Plavix).ti,ab. 11473
- 80 (Prasugrel or Effient or Efient or Prasita).ti,ab. 1828
- 81 (ticagrelor or AZD6140 or Brilinta).ti,ab. 1801
- 82 (elinogrel or PRT060128 or PRT-060128).ti,ab. 52
- 83 (cangrelor or AR-C6993* or ARC6993*).ti,ab. 456
- 84 (SCH530348 or SCH-530348).ti,ab. 68
- 85 E5555.ti,ab. 20
- 86 (terutroban or Triplion).ti,ab. 59
- 87 (aspirin* or nitroaspirin or ASA).ti,ab. 70039
- 88 acetylsalicylic acid.ti,ab. 8940
- 89 acetyl salicylic acid*.ti,ab. 802

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90 (triflusal or disgren).ti,ab. 183

91 (Cilostazol or Pletal or Pletaal).ti,ab. 1589

92 (dipyridamol* or Persantine).ti,ab. 8584

93 (OPC-13013 or OPC13013).ti,ab. 31

94 (picotamide or picotinamide).ti,ab. 111

95 satigrel.ti,ab. 4

96 vorapaxar.ti,ab. 230

97 indobufen.ti,ab. 174

98 or/20-97 654251

99 7 and 19 and 98 4435

100 randomized controlled trial.pt. 505457

101 controlled clinical trial.pt. 100426

102 randomized.ab. 442085

103 placebo.ab. 205331

104 drug therapy.fs. 2147127

105 randomly.ab. 305213

106 trial.ab. 465590

107 groups.ab. 1884917

108 or/100-107 4448119

109 exp animals/ not humans.sh. 4743197

110 108 not 109 3846919

111 99 and 110 1424

112 2017*.ed. 954730

113 111 and 112 62

114 from 113 keep 1-62 62

2. EMBASE	1 Antiphospholipid Syndrome/ 13340	63
1974 to (2017 ONLY)	2 exp Antibodies, Antiphospholipid/ 10672	
Searched 4 December 2017	3 aPL antibodies.ti,ab. 450	
	4 APS.ti,ab. 13550	
	5 "Hughes syndrome".ti,ab. 174	
	6 "antiphospholipid adj2 syndrome".ti,ab. 0	
	7 or/1-6 27751	
	8 Thrombosis/ 92570	
	9 Thromboembolism/ 48884	

(Continued)

- 10 Venous Thromboembolism/ 29859
- 11 exp Venous Thrombosis/ 93279
- 12 (thrombus* or thrombopro* or thrombotic* or thrombolic* or thromboem-
boli* or thrombos* or embol* or microembol*).ti,ab. 334991
- 13 exp Pulmonary Embolism/ 66110
- 14 (PE or DVT or VTE).ti,ab. 65140
- 15 ((vein* or ven*) adj3 thromb*).ti,ab. 82886
- 16 (blood adj3 clot*).ti,ab. 9074
- 17 (pulmonary adj3 clot*).ti,ab. 218
- 18 (lung adj3 clot*).ti,ab. 55
- 19 or/8-18 474200
- 20 exp Anticoagulants/ 457874
- 21 (anticoagul* or anti-coagu*).ti,ab. 99680
- 22 exp Heparin/ 92647
- 23 heparin*.ti,ab. 70674
- 24 UFH.ti,ab. 3144
- 25 LMWH.ti,ab. 7352
- 26 LMH.ti,ab. 505
- 27 (Ariven or Arteven or Calcilean or Hepalean or Hepathrom or Leparan or
Lipo-Hepin or Liquaemin or Liquemin or Pabyrin or Pularin or Thromboliquine
or Vetren).ti,ab. 27
- 28 (Clexane or klexane or lovenox).ti,ab. 542
- 29 Fragmin.ti,ab. 279
- 30 Innohep.ti,ab. 38
- 31 clivarin*.ti,ab. 24
- 32 (danaproid or danaparoid).ti,ab. 616
- 33 antixarin.ti,ab. 0
- 34 (Zibor or cy 222 or embolex or monoembolex).ti,ab. 12
- 35 (rd 11885 or RD1185).ti,ab. 0
- 36 (Kabi-2165 or Kabi 2165).ti,ab. 0
- 37 (emt-966 or emt966 or emt-967 or emt977 or pk-10169 or pk10169).ti,ab. 0
- 38 (fr-860 or fr860 or cy-216 or cy216).ti,ab. 4
- 39 (kb101 or lomoparan or orgaran).ti,ab. 107
- 40 (fluxum or lohepa or lowhepa).ti,ab. 11
- 41 (op 2123 or op2123).ti,ab. 2
- 42 (ave 5026 or ave5026).ti,ab. 13

(Continued)

- 43 (M118 or RO-1).ti,ab. 95
- 44 coumar*.ti,ab. 16168
- 45 (warfarin or (vitamin adj3 antagonist*).ti,ab. 34403
- 46 (VKA or phenindione or Sinthrome or nicoumalone or phenprocoumon or Marcoumar or Marcumar or Falithrom or AVK or phenprocoumon* or aldocumar or carfin or jantoven or kumatox or lawarin or marevan or prothromadin or sofarin or tedicumar or tintorane or waran or warfant or warfilone or warnerin).ti,ab. 3830
- 47 exp Antithrombins/ 7897
- 48 Hirudin Therapy/ 42908
- 49 (thrombin adj3 inhib*).ti,ab. 10057
- 50 hirudin*.ti,ab. 2574
- 51 (dabigatran or Pradaxa or Rendix).ti,ab. 6972
- 52 (BIBR-953* or BIBR953* or BIBR-1048 or BIBR1048).ti,ab. 18
- 53 (ximelagatran or Exanta or Exarta or melagatran).ti,ab. 804
- 54 (AZD0837 or AZD-0837).ti,ab. 43
- 55 (S35972 or S-35972).ti,ab. 6
- 56 Factor Xa Inhibitors.ti,ab. 1374
- 57 (Factor X* adj4 (antag* or inhib* or block*).ti,ab. 5202
- 58 (FX* adj4 (antag* or inhib* or block*).ti,ab. 2626
- 59 (10* adj4 (antag* or inhib* or block*).ti,ab. 67594
- 60 (rivaroxaban or Xarelto).ti,ab. 6586
- 61 (Bay-597939 or Bay597939).ti,ab. 1
- 62 apixaban.ti,ab. 3945
- 63 (BMS-562247 or BMS-562247 or ELIQUIS).ti,ab. 90
- 64 (DU-176b or DU176b).ti,ab. 54
- 65 (PRT-054021 or PRT054021).ti,ab. 4
- 66 (YM150 or YM-150 or LY517717 or LY-517717 or DU-176b or DU176*).ti,ab. 119
- 67 (GW813893 or "Tak 442" or TAK442 or PD0348292 or GSK-813893 or GSK813893).ti,ab. 34
- 68 (edoxaban or lixiana).ti,ab. 1313
- 69 etexilate.ti,ab. 1267
- 70 agatroban.ti,ab. 1
- 71 exp Platelet Aggregation Inhibitors/ 239121
- 72 exp Phosphodiesterase Inhibitors/ 53488
- 73 Tetrazoles/ 2414

(Continued)

- 74 (antiplatelet* or anti-platelet* or antiaggreg* or anti-aggreg*).ti,ab. 41493
- 75 ((platelet or thromboxane or thrombocyte or cyclooxygenase or cyclo-oxy-
genase or phosphodiesterase or fibrinogen or PAR-1) adj3 (antagonist or in-
hibitor)).ti,ab. 15191
- 76 ((gp* or glycoprotein* or protease or P2Y12 or TXA2) adj3 inhibit*).ti,ab.
50010
- 77 thienopyridine.ti,ab. 1504
- 78 (ticlopidine or Ticlid).ti,ab. 2396
- 79 (clopidogrel or Plavix).ti,ab. 20219
- 80 (Prasugrel or Effient or Efient or Prasita).ti,ab. 3255
- 81 (ticagrelor or AZD6140 or Brilinta).ti,ab. 3110
- 82 (elinogrel or PRT060128 or PRT-060128).ti,ab. 86
- 83 (cangrelor or AR-C6993* or ARC6993*).ti,ab. 643
- 84 (SCH530348 or SCH-530348).ti,ab. 94
- 85 E5555.ti,ab. 28
- 86 (terutroban or Triplion).ti,ab. 81
- 87 (aspirin* or nitroaspirin or ASA).ti,ab. 83196
- 88 acetylsalicylic acid.ti,ab. 6791
- 89 acetyl salicylic acid*.ti,ab. 771
- 90 (triflusal or disgren).ti,ab. 175
- 91 (Cilostazol or Pletal or Pletaal).ti,ab. 2322
- 92 (dipyridamol* or Persantine).ti,ab. 5207
- 93 (OPC-13013 or OPC13013).ti,ab. 5
- 94 (picotamide or picotinamide).ti,ab. 74
- 95 satigrel.ti,ab. 20
- 96 vorapaxar.ti,ab. 333
- 97 indobufen.ti,ab. 59
- 98 or/20-97 710273
- 99 7 and 19 and 98 7447
- 100 randomized controlled trial/ 437650
- 101 controlled clinical trial/ 408481
- 102 random\$.ti,ab. 1132164
- 103 randomization/ 68186
- 104 intermethod comparison/ 223714
- 105 placebo.ti,ab. 215213
- 106 (compare or compared or comparison).ti. 326736

(Continued)

- 107 ((evaluated or evaluate or evaluating or assessed or assess) and (compare or compared or comparing or comparison)).ab. 1562487
- 108 (open adj label).ti,ab. 60147
- 109 ((double or single or doubly or singly) adj (blind or blinded or blind-ly)).ti,ab. 153458
- 110 double blind procedure/ 119366
- 111 parallel group\$1.ti,ab. 18989
- 112 (crossover or cross over).ti,ab. 70151
- 113 ((assign\$ or match or matched or allocation) adj5 (alternate or group\$1 or intervention\$1 or patient\$1 or subject\$1 or participant\$1)).ti,ab. 241228
- 114 (assigned or allocated).ti,ab. 282341
- 115 (controlled adj7 (study or design or trial)).ti,ab. 252973
- 116 (volunteer or volunteers).ti,ab. 168202
- 117 trial.ti. 206175
- 118 or/100-117 3373917
- 119 2017*.dc. 1694109
- 120 99 and 118 and 119 63

3. CINAHL (EBSCOhost)
(2017 ONLY)

Searched 4 December
2017

- S107 S98 AND S105 AND S106 6
- S106 EM 2017 182,744
- S105 S99 OR S100 OR S101 OR S102 OR S103 OR S104 952,284
- S104 TX randomly 41,763
- S103 TX "treatment as usual" 709
- S102 TX "double-blind*" 755,656
- S101 TX "single-blind*" 8,678
- S100 TX trial 236,802
- S99 MH "Clinical Trials" 90,899
- S98 S7 AND S19 AND S97 231
- S97 S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30 OR S31 OR S32 OR S33 OR S34 OR S35 OR S36 OR S37 OR S38 OR S39 OR S40 OR S41 OR S42 OR S43 OR S44 OR S45 OR S46 OR S47 OR S48 OR S49 OR S50 OR S51 OR S52 OR S53 OR S54 OR S55 OR S56 OR S57 OR S58 OR S59 OR S60 OR S61 OR S62 OR S63 OR S64 OR S65 OR S66 OR S67 OR S68 OR S69 OR S70 OR S71 OR S72 OR S73 OR S74 OR S75 OR S76 OR S77 OR S78 OR S79 OR S80 OR S81 OR S82 OR S83 OR S84 OR S85 OR S86 OR S87 OR S88 OR S89 OR S90 OR S91 ... 51,427
- S96 TX indobufen 6
- S95 TX vorapaxar 48
- S94 TX satigrel 0

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(Continued)

S93 TX picotamide or picotinamide 8

S92 TX OPC-13013 or OPC13013 0

S91 TX Cilostazol or Pletal or Pletaal 204

S90 TX triflusal or disgren 23

S89 TX acetylsalicylic acid 408

S88 TX terutroban or Triplion 12

S87 TX E5555 4

S86 TX SCH530348 or SCH-530348 12

S85 TX cangrelor or AR-C6993* or ARC6993* 60

S84 TX elinogrel or PRT060128 or PRT-060128 2

S83 TX ticagrelor or AZD6140 or Brilinta 391

S82 TX Prasugrel or Effient or Efient or Prasita 360

S81 TX clopidogrel or Plavix 2,595

S80 TX ticlopidine or Ticlid 1,020

S79 TX thienopyridine 193

S78 TX gp* or glycoprotein* or protease or P2Y12 or TXA2) n3 inhibit*); 4,288

S77 TX platelet or thromboxane or thrombocyte or cyclooxygenase or cyclo-oxygenase or phosphodiesterase or fibrinogen or PAR-1) n3 (antagonist or inhibitor 6,893

S76 TX antiplatelet* or anti-platelet* or antiaggreg* or anti-aggreg* 3,535

S75 (MH "Phosphodiesterase Inhibitors+") 1,834

S74 (MH "Platelet Aggregation Inhibitors+") 11,567

S73 *parinux 0

S72 argatroban 195

S71 etexilate 325

S70 *exaban 0

S69 *axaban 0

S68 *ixaban 0

S67 edoxaban or lixiana 136

S66 GW813893 or "Tak 442" or TAK442 or PD0348292 or GSK-813893 or GSK813893 24

S65 GW813893 or "Tak 442" or TAK442 or PD0348292 or GSK-813893 or GSK813893 0

S64 YM150 or YM-150 or LY517717 or LY-517717 or DU-176b or DU176* 5

S63 PRT-054021 or PRT054021 0

S62 DU-176b or DU176b 3

(Continued)

S61 BMS-562247 or BMS-562247 or ELIQUIS 15

S60 apixaban 387

S59 betrixaban or PRT054021 15

S58 Bay-597939 or Bay597939 0

S57 rivaroxaban or Xarelto 693

S56 (10* n4 (antag* or inhib* or block*)) 1,798

S55 (FX* n4 (antag* or inhib* or block*)) 43

S54 (Factor X* n4 (antag* or inhib* or block*)) 9,042

S53 TX S35972 or S-35972 0

S52 TX AZD0837 or AZD-0837 0

S51 TX ximelagatran or Exanta or Exarta or melagatran 89

S50 TX BIBR-953* or BIBR953* or BIBR-1048 or BIBR1048 2

S49 TX dabigatran or Pradaxa or Rendix 883

S48 TX hirudin* 283

S47 TX thrombin n3 inhib* 656

S46 (MH "Hirudin") 237

S45 TX VKA or phenindione or Sinthrome or nicoumalone or phenprocoumon or Marcoumar or Marcumar or Falithrom or AVK or phenprocoumon* or aldocumar or carfin or jantoven or kumatox or lawarin or marevan or prothromadin or sofarin or tedicumar or tintorane or waran or warfant or warfilone or warnerin 233

S44 TX (*warfarin or (vitamin n3 antagonist*)) 6,298

S43 TX M118 or RO-1 4,530

S42 TX ave 5026 or ave5026 0

S41 TX op 2123 or op2123 0

S40 TX fluxum or lohepa or lowhepa 1

S39 TX kb101 or lomoparan or organan 2

S38 TX fr-860 or fr860 or cy-216 or cy216 0

S37 TX emt-966 or emt966 or emt-967 or emt977 or pk-10169 or pk10169 0

S36 TX Kabi-2165 or Kabi 2165 0

S35 TX rd 11885 or RD1185 0

S34 TX Zibor or cy 222 or embolex or monoembolex 3

S33 TX antixarin 0

S32 TX danaproid or danaparoid 34

S31 TX clivarin* 1

S30 TX Innohep 3

(Continued)

S29 TX Fragmin 19

S28 TX Clexane or klexane or lovenox 28

S27 TX Ariven or Arteven or Calcilean or Hepalean or Hepathrom or Leparan or Lipo-Hepin or Liquaemin or Liquemin or Pabyrin or Pularin or Thromboliquine or Vetren 1

S26 TX LMH 55

S25 TX LMWH 463

S24 TX UFH 235

S23 TX *parin* 270

S22 (MH "Heparin+") 5,527

S21 TX anticoagul* or anti-coagu* 13,627

S20 (MH "Anticoagulants+") 15,828

S19 S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 44,186

S18 lung n3 clot* 11

S17 pulmonary n3 clot* 19

S16 (blood n3 clot*) 699

S15 TX ((vein* or ven*) n thromb*) 140

S14 TX PE or DVT or VTE 11,499

S13 (MH "Pulmonary Embolism") 4,591

S12 TX thrombus* or thrombopro* or thrombotic* or thrombolic* or thromboemboli* or thrombos* or embol* or microembol*); 35,081

S11 (MH "Venous Thrombosis+") 6,154

S10 (MH "Venous Thromboembolism") 2,904

S9 (MH "Thromboembolism") 3,174

S8 (MH "Thrombosis") 4,493

S7 S1 OR S2 OR S3 OR S4 OR S5 OR S6 2,647

S6 TX antiphospholipid n2 syndrome 865

S5 TX "Hughes syndrome" 11

S4 TX APS 1,946

S3 TX aPL antibodies 105

S2 (MH "Antiphospholipid Syndrome") 699

S1 (MH "Antiphospholipid Syndrome") 699

4. AMED (2017 ONLY)	1 APS.ti,ab. 31	0
Searched 4 December 2017	2 Thrombosis/ 195	
	3 Thromboembolism/ 71	

(Continued)

- 4 (thrombus* or thrombopro* or thrombotic* or thrombolic* or thromboem-boli* or thrombos* or embol* or microembol*).ti,ab. 640
- 5 exp Pulmonary Embolism/ 53
- 6 (PE or DVT or VTE).ti,ab. 242
- 7 ((vein* or ven*) adj3 thromb*).ti,ab. 318
- 8 (blood adj3 clot*).ti,ab. 34
- 9 exp Anticoagulants/ 148
- 10 (anticoagul* or anti-coagu*).ti,ab. 189
- 11 exp Heparin/ 26
- 12 heparin*.ti,ab. 93
- 13 UFH.ti,ab. 1
- 14 LMWH.ti,ab. 12
- 15 LMH.ti,ab. 1
- 16 coumar*.ti,ab. 347
- 17 (warfarin or (vitamin adj3 antagonist*).ti,ab. 84
- 18 (VKA or phenindione or Sinthrome or nicoumalone or phenprocoumon or Marcoumar or Marcumar or Falithrom or AVK or phenprocoumon* or al-documar or carfin or jantoven or kumatox or lawarin or marevan or prothro-madin or sofarin or tedicumar or tintorane or waran or warfant or warfilone or warnerin).ti,ab. 1
- 19 (thrombin adj3 inhib*).ti,ab. 14
- 20 hirudin*.ti,ab. 4
- 21 (dabigatran or Pradaxa or Rendix).ti,ab. 1
- 22 (ximelagatran or Exanta or Exarta or melagatran).ti,ab. 4
- 23 (Factor X* adj4 (antag* or inhib* or block*).ti,ab. 2
- 24 (FX* adj4 (antag* or inhib* or block*).ti,ab. 3
- 25 (10* adj4 (antag* or inhib* or block*).ti,ab. 574
- 26 (rivaroxaban or Xarelto).ti,ab. 1
- 27 exp Platelet Aggregation Inhibitors/ 8
- 28 Tetrazoles/ 0
- 29 (antiplatelet* or anti-platelet* or antiaggreg* or anti-aggreg*).ti,ab. 150
- 30 ((platelet or thromboxane or thrombocyte or cyclooxygenase or cyclo-oxy-genase or phosphodiesterase or fibrinogen or PAR-1) adj3 (antagonist or in-hibitor)).ti,ab. 55
- 31 ((gp* or glycoprotein* or protease or P2Y12 or TXA2) adj3 inhibit*).ti,ab. 107
- 32 (ticlopidine or Ticlid).ti,ab. 4
- 33 (clopidogrel or Plavix).ti,ab. 11

(Continued)

34 (aspirin* or nitroaspirin or ASA).ti,ab. 261

35 acetylsalicylic acid.ti,ab. 39

36 acetyl salicylic acid*.ti,ab. 5

37 (Cilostazol or Pletal or Pletaal).ti,ab. 4

38 (dipyridamol* or Persantine).ti,ab. 12

39 Antiphospholipid.mp. [mp=abstract, heading words, title] 9

40 1 or 39 40

41 or/2-8 862

42 or/9-38 1758

43 40 and 41 and 42 2

44 2017*.up. 6951

45 43 and 44 0

46 39 and 44 0

5. VASCULAR
SPECIALISED REGISTER

Searched 4 December
2017

#1 thrombosis AND INREGISTER

2 2017 AND INREGISTER

#3 1 AND 2

6

6. CENTRAL

Searched 29 November
2017

#1 MESH DESCRIPTOR Antiphospholipid Syndrome 54

#2 MESH DESCRIPTOR Antibodies, Antiphospholipid EXPLODE ALL TREES 90

#3 (aPL antibodies):TI,AB,KY 5

#4 APS :TI,AB,KY 258

#5 (Hughes syndrome):TI,AB,KY 0

#6 (antiphospholipid near2 syndrome):TI,AB,KY 193

#7 #1 OR #2 OR #3 OR #4 OR #5 OR #6 443

#8 MESH DESCRIPTOR Thrombosis 1303

#9 MESH DESCRIPTOR Thromboembolism 943

#10 MESH DESCRIPTOR Venous Thromboembolism 294

#11 MESH DESCRIPTOR Venous Thrombosis EXPLODE ALL TREES 2085

#12 ((thrombus* or thrombopro* or thrombotic* or thrombolic* or thromboemboli* or thrombos* or embol* or microembol*)):TI,AB,KY 21115

#13 MESH DESCRIPTOR Pulmonary Embolism EXPLODE ALL TREES 769

#14 (PE or DVT or VTE):TI,AB,KY 5562

#15 (((vein* or ven*) near thromb*)):TI,AB,KY 7332

#16 ((blood near3 clot*)):TI,AB,KY 3497

#17 (pulmonary near3 clot*):TI,AB,KY 6

28

(Continued)

- #18 (lung near3 clot*):TI,AB,KY 5
- #19 #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 27424
- #20 MESH DESCRIPTOR Anticoagulants EXPLODE ALL TREES 8429
- #21 (anticoagul* or anti-coagu*):TI,AB,KY 8976
- #22 MESH DESCRIPTOR Heparin EXPLODE ALL TREES 3943
- #23 *parin*:TI,AB,KY 62652
- #24 UFH:TI,AB,KY 487
- #25 LMWH:TI,AB,KY 902
- #26 LMH:TI,AB,KY 8
- #27 (Ariven or Arteven or Calcilean or Hepalean or Hepathrom or Leparan or Lipo-Hepin or Liqueamin or Liquemin or Pabyrin or Pularin or Thromboliquine or Vetren):TI,AB,KY 9
- #28 (Clexane or klexane or lovenox):TI,AB,KY 46
- #29 Fragmin:TI,AB,KY 182
- #30 Innohep:TI,AB,KY 12
- #31 clivarin*:TI,AB,KY 20
- #32 (danaproid or danaparoid):TI,AB,KY 46
- #33 antixarin:TI,AB,KY 2
- #34 (Zibor or cy 222 or embolex or monoembolex):TI,AB,KY 38
- #35 (rd 11885 or RD1185):TI,AB,KY 0
- #36 (Kabi-2165 or Kabi 2165):TI,AB,KY 39
- #37 (emt-966 or emt966 or emt-967 or emt977 or pk-10169 or pk10169):TI,AB,KY 8
- #38 (fr-860 or fr860 or cy-216 or cy216):TI,AB,KY 51
- #39 (kb101 or lomoparan or orgaran):TI,AB,KY 28
- #40 (fluxum or lohepa or lowhepa):TI,AB,KY 11
- #41 (op 2123 or op2123):TI,AB,KY 1
- #42 (ave 5026 or ave5026):TI,AB,KY 2
- #43 (M118 or RO-1):TI,AB,KY 9
- #44 *coumar*:TI,AB,KY 664
- #45 (*warfarin or (vitamin near/3 antagonist*)):TI,AB,KY 3285
- #46 (VKA or phenindione or Sinthrome or nicoumalone or phenprocoumon or Marcoumar or Marcumar or Falithrom or AVK or phenprocoumon* or aldocumar or carfin or jantoven or kumatox or lawarin or marevan or prothro-madin or sofarin or tedicumar or tintorane or waran or warfant or warfilone or warnerin):TI,AB,KY 476
- #47 MESH DESCRIPTOR Antithrombins 277

(Continued)

- #48 MESH DESCRIPTOR Antithrombins EXPLODE ALL TREES 1354
- #49 MESH DESCRIPTOR Hirudin Therapy 75
- #50 (thrombin near3 inhib*):TI,AB,KY 559
- #51 hirudin*:TI,AB,KY 383
- #52 (BIBR-953* or BIBR953* or BIBR-1048 or BIBR1048):TI,AB,KY 9
- #53 (ximelagatran or Exanta or Exarta or melagatran):TI,AB,KY 154
- #54 (AZD0837 or AZD-0837):TI,AB,KY 14
- #55 (S35972 or S-35972):TI,AB,KY 0
- #56 MESH DESCRIPTOR Factor Xa Inhibitors 358
- #57 (Factor X* near4 (antag* or inhib* or block*)):TI,AB,KY 708
- #58 (FX* near4 (antag* or inhib* or block*)):TI,AB,KY 56
- #59 (10* near4 (antag* or inhib* or block*)):TI,AB,KY 1226
- #60 (rivaroxaban or Xarelto):TI,AB,KY 767
- #61 (Bay-597939 or Bay597939):TI,AB,KY 0
- #62 (betrixaban or PRT054021):TI,AB,KY 38
- #63 apixaban:TI,AB,KY 457
- #64 (BMS-562247 or BMS-562247 or ELIQUIS):TI,AB,KY 0
- #65 (DU-176b or DU176b):TI,AB,KY 12
- #66 (PRT-054021 or PRT054021):TI,AB,KY 1
- #67 (YM150 or YM-150 or LY517717 or LY-517717 or DU-176b or DU176*):TI,AB,KY 44
- #68 (GW813893 or "Tak 442" or TAK442 or PD0348292 or GSK-813893 or GSK813893):TI,AB,KY 3
- #69 (edoxaban or lixiana):TI,AB,KY 254
- #70 *ixaban:TI,AB,KY 495
- #71 *axaban:TI,AB,KY 8
- #72 *exaban:TI,AB,KY 17
- #73 etexilate:TI,AB,KY 162
- #74 agatroban:TI,AB,KY 1
- #75 *parinux:TI,AB,KY 340
- #76 MESH DESCRIPTOR Platelet Aggregation Inhibitors EXPLODE ALL TREES 8757
- #77 MESH DESCRIPTOR Phosphodiesterase Inhibitors EXPLODE ALL TREES 5673
- #78 MESH DESCRIPTOR Tetrazoles EXPLODE ALL TREES 2866

(Continued)

- #79 (antiplatelet* or anti-platelet* or antiaggreg* or anti-aggreg*):TI,AB,KY 3916
- #80 (((platelet or thromboxane or thrombocyte or cyclooxygenase or cyclo-oxygenase or phosphodiesterase or fibrinogen or PAR-1) near3 (antagonist or inhibitor))):TI,AB,KY 2589
- #81 (((gp* or glycoprotein* or protease or P2Y12 or TXA2) near3 inhibit*)):TI,AB,KY 3512
- #82 thienopyridine:TI,AB,KY 309
- #83 (ticlopidine or Ticlid):TI,AB,KY 1909
- #84 (clopidogrel or Plavix):TI,AB,KY 3552
- #85 (Prasugrel or Effient or Efient or Prasita):TI,AB,KY 648
- #86 (ticagrelor or AZD6140 or Brilinta):TI,AB,KY 647
- #87 (elinogrel or PRT060128 or PRT-060128):TI,AB,KY 8
- #88 (cangrelor or AR-C6993* or ARC6993*):TI,AB,KY 66
- #89 (SCH530348 or SCH-530348):TI,AB,KY 24
- #90 E5555:TI,AB,KY 6
- #91 (terutroban or Triplion):TI,AB,KY 17
- #92 (aspirin* or nitroaspirin or ASA):TI,AB,KY 18368
- #93 (acetylsalicylic acid):TI,AB,KY 5734
- #94 (acetyl salicylic acid*):TI,AB,KY 117
- #95 (triflusal or disgren):TI,AB,KY 103
- #96 (Cilostazol or Pletal or Pletaal):TI,AB,KY 520
- #97 (dipyridamol* or Persantine):TI,AB,KY 1165
- #98 (OPC-13013 or OPC13013):TI,AB,KY 5
- #99 (picotamide or picotinamide):TI,AB,KY 41
- #100 satigrel:TI,AB,KY 3
- #101 vorapaxar:TI,AB,KY 103
- #102 indobufen:TI,AB,KY 82
- #103 #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55 OR #56 OR #57 OR #58 OR #59 OR #60 OR #61 OR #62 OR #63 OR #64 OR #65 OR #66 OR #67 OR #68 OR #69 OR #70 OR #71 OR #72 OR #73 OR #74 OR #75 OR #76 OR #77 OR #78 OR #79 OR #80 OR #81 OR #82 OR #83 OR #84 OR #85 OR #86 OR #87 OR #88 OR #89 OR #90 OR #91 OR #92 OR #93 OR #94 OR #95 OR #96 OR #97 OR #98 OR #99 OR #100 OR #101 OR #102 104894
- #104 #7 AND #19 AND #103 100
- #105 01/01/2017 TO 29/11/2017:CD 109501

(Continued)

#106 #104 AND #105 28

7. ClinicalTrials.gov	antiphospholipid	10
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(www.clinicaltrials.gov)

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2017

8. ICTRP	antiphospholipid	1
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Searched 29 November
2017

CONTRIBUTIONS OF AUTHORS

MMB developed the concept of the study, contributed to the preparation of this review and agreed upon this final version.

EP developed the concept of the study, contributed to the preparation of this review and agreed upon this final version.

WL contributed to the preparation of this review and agreed upon this final version.

DWK contributed to the preparation of this review and agreed upon this final version.

KJ contributed to the preparation of this review and agreed upon this final version.

AU developed the concept of the study, contributed to the preparation of this review and agreed upon this final version.

DECLARATIONS OF INTEREST

MMB receives honoraria as freelancer from a systematic review company that also works for pharmaceutical companies (Kleijnen Systematic Reviews Ltd). I am not aware of any direct conflict of interest.

EP: Abbott Vascular paid for her registration fee for the 20th International Congress of the Polish Cardiac Society.

WL has no known conflicts of interest.

DWK is an investigator in a clinical trial on drug-resistant epilepsy conducted by UCB Pharma.

KJ has no known conflicts of interest.

AU received honoraria for lectures relating to anticoagulant therapy in Poland and had travel expenses covered by Bayer, Boehringer Ingelheim, Pfizer, and Sanofi-Aventis.

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- Chief Scientist Office, Scottish Government Health Directorates, The Scottish Government, UK.

The Cochrane Vascular editorial base is supported by the Chief Scientist Office.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

In our protocol we planned to analyse obstetric failure among thrombotic events, but as this outcome was thoroughly addressed by other Cochrane Reviews, [de Jong 2014](#); [Empson 2005](#), we did not analyse it in this review.

NOTES

We have based parts of the [Methods](#) section on a standard template established by Cochrane Vascular.

INDEX TERMS

Medical Subject Headings (MeSH)

*Antibodies, Antiphospholipid; *Primary Prevention; Anticoagulants [*therapeutic use]; Antiphospholipid Syndrome [*complications]; Platelet Aggregation Inhibitors [*therapeutic use]; Randomized Controlled Trials as Topic; Thrombosis [*prevention & control]

MeSH check words

Humans