**Supplemental text S1**

1. Exclusion criteria for the systematic literature review
2. Search terms for the systematic literature review
3. Quality ratings of the included studies

**1. Exclusion criteria for the systematic literature review**

• Animal studies

• Basic science studies, laboratory definition studies

• Pediatric studies

• Narrative review, editorials, letters

• Case reports

• Conference abstracts

• Non-English language publications

• Not related to PICO questions (unrelated topic)

• Publications on the same cohort (same cohorts)

• Other (other disorder or not related to prevention or management topics in APS)

**2. Search terms for the systematic literature review**

**Search 1: Risk factors**

**Pubmed**

((((((((((((("**Antiphospholipid Syndrome**"[Majr]) AND surgery)) OR (("**Antiphospholipid Syndrome**"[Majr]) AND perioperative)) OR (("**Antiphospholipid Syndrome**"[Majr]) AND immobilization)) OR (("**Antiphospholipid Syndrome**"[Majr]) AND diabetes mellitus)) OR (("**Antiphospholipid Syndrome**"[Majr]) AND estrogens)) OR (("**Antiphospholipid Syndrome**"[Majr]) AND hyperlipidemia)) OR (("**Antiphospholipid Syndrome**"[Majr]) AND smoking)) OR (("**Antiphospholipid Syndrome**"[Majr]) AND "hypertension"[MeSH Terms]))) NOT systemic lupus))

NOT ((((((((((((("**Antiphospholipid Syndrome**"[Majr]) AND surgery)) OR (("**Antiphospholipid Syndrome**"[Majr]) AND perioperative)) OR (("**Antiphospholipid Syndrome**"[Majr]) AND immobilization)) OR (("**Antiphospholipid Syndrome**"[Majr]) AND diabetes mellitus)) OR (("**Antiphospholipid Syndrome**"[Majr]) AND estrogens)) OR (("**Antiphospholipid Syndrome**"[Majr]) AND hyperlipidemia)) OR (("**Antiphospholipid Syndrome**"[Majr]) AND smoking)) OR (("**Antiphospholipid Syndrome**"[Majr]) AND "hypertension"[MeSH Terms]))) NOT systemic lupus) AND Case Reports[ptyp])

**Embase**

**'antiphospholipid syndrome'**/exp/mj AND '**surgery**'/exp/mj OR antiphospholipid AND **('syndrome'**/exp OR syndrome) AND perioperative OR antiphospholipid AND ('**syndrome**'/exp OR syndrome) AND ('**immobilization**'/exp OR immobilization) OR

'antiphospholipid syndrome' AND 'diabetes mellitus':ab,ti OR'antiphospholipid syndrome' AND estrogen OR 'antiphospholipid syndrome' AND 'smoking':ti,ab,kw OR 'antiphospholipid syndrome' AND '**hypertension**'/exp/mj NOT systemic Lupus

**Cochrane**

Antiphospholipid syndrome AND hypertension OR smoking OR hyperlipidemia OR estrogens OR diabetes OR immobilization OR perioperative OR surgery

**Search 2: Patient education**

**Pubmed**

Search (((((((((((antiphospholipid syndrome AND diet)) OR (antiphospholipid syndrome AND physical activity)) OR (antiphospholipid syndrome AND physical activity)) OR (antiphospholipid syndrome AND exercise)) OR (antiphospholipid syndrome AND fatigue)) OR (antiphospholipid syndrome AND rehabilitation)) OR (antiphospholipid syndrome AND physiotherapy)) OR (antiphospholipid syndrome AND physical therapy)) OR (antiphospholipid syndrome AND patient education))) NOT systemic lupus

**Embase**

(Antiphospholipid syndrome AND (‘patient education’ OR ‘Physical therapy’ OR physiotherapy OR rehabilitation OR fatigue OR exercise OR ‘physical activity’ OR ‘nutrition’) NOT ‘systemic lupus erythematosus’

**Cochrane**

antiphospholipid syndrome AND (diet OR patient education OR physical therapy OR physiotherapy OR rehabilitation OR fatigue OR exercise OR physical activity)

**Search 3: Primary prevention (antiphospholipid antibodies but no event)**

**Pubmed**

Search

(((clotting OR clot OR thrombosis OR bleed OR bleeding OR stroke OR myocardial infarction OR embolism OR accident OR hemorrhage) AND **Humans** [Mesh] AND English[lang])) AND (((("**Antibodies, Antiphospholipid**"[Mesh] AND **Humans**[Mesh] AND English[lang])) NOT ("**Antiphospholipid Syndrome**"[Mesh] AND **Humans**[Mesh] AND English[lang]) NOT assays NOT mouse) AND **Humans**[Mesh] AND English[lang]) AND (prevention) Filters: Humans; English

antiphospholipid antibodies[Title] NOT assays NOT mice NOT APS, NOT Antiphospholipid Syndrome, humans, English

prevent events antiphospholipid antibodies NOT antiphospholipid antibody syndrome humans, English

**Embase**

**'blood clotting'**/exp OR 'blood clotting' OR clot OR '**thrombosis**'/exp OR thrombosis OR '**bleeding**'/exp OR bleeding OR '**stroke**'/exp OR stroke OR **'heart infarction'**/exp OR 'heart infarction' OR **'embolism**'/exp OR embolism OR **'cerebrovascular accident'**/exp OR 'cerebrovascular accident' OR '**hemorrhage**'/exp OR hemorrhage AND 'phospholipid antibody' NOT 'antiphospholipid syndrome' NOT assay NOT mouse AND [english]/lim AND ([young adult]/lim OR [adult]/lim OR [middle aged]/lim OR [aged]/lim OR [very elderly]/lim)

**Cochrane**

antiphospholipid antibody

**Search 4: Management of thrombotic APS**

**PubMed**

(((clotting OR clot OR thrombosis OR bleed OR bleeding OR stroke OR myocardial infarction OR embolism OR accident OR hemorrhage) AND **Humans**[Mesh] AND English[lang])) AND (((((antiphospholipid syndrome) AND (prevention OR treatment OR LDA OR heparin OR hydroxychloroquine OR coumadin OR anticoagulants OR anticoagulation OR VKA OR vitamin K antagonists OR antiplatelet drugs OR clopidogrel OR dabigatran OR rivaroxaban OR apixaban OR rituximab)))

NOT (((antiphospholipid syndrome) AND (prevention OR treatment OR aspirin OR heparin OR hydroxychloroquine OR coumadin OR anticoagulants OR anticoagulation OR VKA OR vitamin K antagonists OR antiplatelet drugs OR clopidogrel OR dabigatran OR rivaroxaban OR apixaban OR rituximab)) AND Case Reports[ptyp])) AND **Humans**[Mesh] AND English[lang]) Filters: Humans; English

Search for SLE and thrombosis and drugs

((((prevention OR treatment OR LDA OR heparin OR hydroxychloroquine OR coumadin OR anticoagulants OR anticoagulation OR VKA OR vitamin k antagonists OR antiplatelet drugs OR clopidogrel OR dabigatran OR rivaroxaban OR apixaban OR rituximab)) AND Humans[Mesh] AND English[lang])) AND (((systemic lupus erythematosus OR SLE) AND thrombosis) AND **Humans**[Mesh] AND English[lang]) NOT Case Reports[ptyp]

**Embase**

'systemic lupus erythematosus' AND ('blood clotting' OR clot OR thrombosis OR bleed OR 'bleeding' OR stroke OR myocardial) AND infarction OR embolism OR accident OR hemorrhage) AND ('prevention and control' OR 'prevention' OR treatment OR LDA OR heparin OR hydroxychloroquine OR coumadin OR anticoagulants OR anticoagulation OR VKA OR antiplatelet) AND drugs OR clopidogrel OR dabigatran OR rivaroxaban OR apixaban OR rituximab)

Search for SLE and thrombosis and drugs

Thrombosis AND (systemic lupus erythematosus OR SLE) AND ('prevention and control' OR 'prevention' OR treatment OR LDA OR heparin OR hydroxychloroquine OR coumadin OR anticoagulants OR anticoagulation OR VKA OR antiplatelet) AND drugs OR clopidogrel OR dabigatran OR rivaroxaban OR apixaban OR rituximab)

**Cochrane Database**

Search “antiphospholipid”

Search (SLE OR systemic lupus erythematosus) AND thrombosis

**Search 5: Management of obstetric APS**

**Pubmed**

(((((((((((("**Antiphospholipid Syndrome**"[Majr]) AND "obstetric antiphospholipid syndrome")) OR (("**Antiphospholipid Syndrome**"[Majr]) AND "refractory obstetric antiphospholipid syndrome")) OR (("**Antiphospholipid Syndrome**"[Majr]) AND "pregnancy morbidity")) OR (("**Antiphospholipid Syndrome**"[Majr]) AND "**pregnancy complications**"[Majr])) OR (("**Antiphospholipid Syndrome**"[Majr]) AND "fetal loss")) OR (("**Fetal Death**"[Majr]) AND ("**Antiphospholipid Syndrome**"[Majr]))) OR ((("**Antiphospholipid Syndrome**"[Majr])) AND abortions)) OR ((("**Antiphospholipid Syndrome**"[Majr])) AND "**abortion, spontaneous**"[Majr])) OR ((("**Antiphospholipid Syndrome**"[Majr])) AND "**pre-eclampsia**"[Mesh])) OR ((("**Antiphospholipid Syndrome**"[Majr])) AND "**eclampsia**"[Mesh])) OR ((("**Antiphospholipid Syndrome**"[Majr])) AND placental insufficiency) NOT systemic lupus NOT case report

**Embase**

'antiphospholipid syndrome':ti,ab,kw AND **'placenta insufficiency'**/exp OR 'antiphospholipid syndrome':ti,ab,kw AND '**eclampsia**'/exp OR 'antiphospholipid syndrome':ti,ab,kw AND '**preeclampsia**'/exp/mj OR 'antiphospholipid syndrome':ti,ab,kw AND **'spontaneous abortion**'/exp/mj OR 'antiphospholipid syndrome':ti,ab,kw AND 'abortion':ti,ab,kw

OR antiphospholipid syndrome':ab,ti AND **'fetus death'**/mj OR 'antiphospholipid syndrome':ab,ti AND **'fetus wastage'**/mj OR 'antiphospholipid syndrome':ab,ti AND **'pregnancy complication'**/mj OR **'antiphospholipid syndrome'**/mj AND 'pregnancy morbidity':ab,ti OR 'antiphospholipid syndrome' AND peripartum OR **'antiphospholipid syndrome'**/mj AND 'obstetric antiphospholipid syndrome':ti OR 'antiphospholipid syndrome':ti AND 'pregnancy':ti NOT systemic lupus NOT case reports

**Cochrane**

Antiphospholipid AND pregnancy OR obstetric OR peripartum OR fetal OR abortion OR miscarriage OR preeclampsia OR eclampsia OR placental insufficiency

**Search 6: Catastrophic APS**

**Pubmed**

catastrophic antiphospholipid syndrome AND (risk factors OR prevention OR surgery) NOT "systemic lupus"

catastrophic antiphospholipid syndrome AND (rituximab OR eculizumab) NOT "systemic lupus"

catastrophic antiphospholipid syndrome AND treatment NOT "systemic lupus" NOT (catastrophic antiphospholipid syndrome AND treatment NOT "systemic lupus" Filters: Case Reports)

**Embase**

1. (**'catastrophic antiphospholipid syndrome'**/exp OR 'catastrophic antiphospholipid syndrome') AND (**'risk factor'**/exp OR 'risk factor' OR 'prevention'/exp OR prevention OR '**surgery**'/exp OR surgery) NOT ('systemic lupus erythematosus'/exp OR 'systemic lupus erythematosus') NOT 'case report':it
2. (**'catastrophic antiphospholipid syndrome'**/exp OR 'catastrophic antiphospholipid syndrome') AND ('**rituximab**'/exp OR rituximab OR '**eculizumab**'/exp OR eculizumab) NOT (**'systemic lupus erythematosus'**/exp OR 'systemic lupus erythematosus') NOT 'case report':it
3. (**'catastrophic antiphospholipid syndrome'**/exp OR 'catastrophic antiphospholipid syndrome') AND ('**treatment**'/exp OR treatment OR '**therapy**'/exp OR therapy) NOT (**'systemic lupus erythematosus'**/exp OR 'systemic lupus erythematosus') NOT 'case report':it

**Cochrane**

Antiphospholipid AND catastrophic

**3. Quality ratings of the included studies**

Table A. Cochrane risk of bias assessment for randomized controlled trials with direct or indirect treatment comparisons. + low risk of bias; ? unclear risk of bias; - high risk of bias.

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Reference | Random sequence generation | Allocation concealment | Blinding of patients/  personnel | Blinding of outcome assessment | Incomplete outcome data | Selective reporting | Other | Overall Rating Risk of Bias |
| Crowther 2003 | + | + | + | + | + | + | + | Low |
| Finazzi 2005 | + | + | - | + | ? | ? | ? | High |
| Rai 1997 | + | + | - | + | + | + | ? | High |
| Laskin 2009 | ? | + | - | + | + | + | ? | High |
| Goldhaber 2016 | + | + | + | + | ? | + | + | Low |
| Cohen 2016 | + | + | - | - | + | + | + | High |
| Pengo 2018 | + | + | - | + | + | + | + | Unclear |
| Schulman 1998 | - | - | - | - | + | ? | + | High |
| Kaaja 1993 | + | - | + | - | + | ? | + | High |
| Cowchock 1997 | - | - | - | - | + | ? | + | High |
| Kahwa 2006 | + | + | + | ? | + | + | + | Unclear |
| van Hoorn 2016 | + | + | - | - | + | + | + | High |

Table B. Ratings of methodological quality by the Newcastle-Ottawa scale of observational studies with direct or indirect treatment comparisons.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Reference | Representativeness | Selection of unexposed | Ascertainment of exposure | Outcome not present at start |
| Mustonen 2014 | b; somewhat representative \* | a; same cohort \* | c; self report | a; true \* |
| Tarr 2007 | b; somewhat representative \* | a; same cohort \* | a; secure record \* | a; true \* |
| Tektonidou 2009 | b; somewhat representative \* | a; same cohort \* | a; secure record \* | a; true \* |
| Erkan 2001 | b; somewhat representative \* | a; same cohort \* | a; secure record \* | a; true \* |
| Ruffatti 2009 | b; somewhat representative \* | a; same cohort \* | a; secure record \* | a; true \* |
| Rosove 1992 | b; somewhat representative \* | a; same cohort \* | a; secure record \* | a; true \* |
| Khamashta 1995 | b; somewhat representative \* | a; same cohort \* | a; secure record \* | a; true \* |
| Ames 2005 | b; somewhat representative \* | a; same cohort \* | a; secure record \* | a; true \* |
| Lima 1996 | d; no description | a; same cohort \* | a; secure record \* | a; true \* |
| Munoz-Rodriguez 1999 | b; somewhat representative \* | a; same cohort \* | a; secure record \* | a; true \* |
| Franklin 2002 | b; somewhat representative \* | a; same cohort \* | a; secure record \* | a; true \* |
| Naru 2010 | c; selected group | a; same cohort \* | a; secure record \* | a; true \* |
| Cohn 2010 | b; somewhat representative \* | a; same cohort \* | a; secure record \* | a; true \* |
| Mohamed 2014 | d; no description | a; same cohort \* | a; secure record \* | a; true \* |
| Ruffatti 2014 | b; somewhat representative \* | a; same cohort \* | a; secure record \* | a; true \* |
| Ginsberg 1995 | b; somewhat representative \* | a; same cohort \* | c; self report | a; true \* |
| Pengo 2010 | b; somewhat representative \* | a; same cohort \* | a; secure record \* | a; true \* |
| Hernandez-Molina 2013 | b; somewhat representative \* | a; same cohort \* | a; secure record \* | a; true \* |
| Taraborelli 2017 | b; somewhat representative \* | a; same cohort \* | a; secure record \* | a; true \* |
| Verro 1998 | b; somewhat representative \* | a; same cohort \* | a; secure record \* | a; true \* |
| Wang 2016 | b; somewhat representative \* | a; same cohort \* | a; secure record \* | a; true \* |
| Del Ross 2013 | b; somewhat representative \* | a; same cohort \* | a; secure record \* | a; true \* |
| Munoz-Rodriguez 1999 | b; somewhat representative \* | a; same cohort \* | a; secure record \* | a; true \* |
| Mekinian 2015 | c; select group | b; different source | a; secure record \* | a; true \* |
| Bramham 2011 | c; select group | a; same cohort \* | a; secure record \* | a; true \* |
| Diejomaoh 2002 | c; select group | a; same cohort \* | a; secure record \* | a; true \* |
| Jeremic 2005 | c; select group | a; same cohort \* | a; secure record \* | a; true \* |
| Heilman 2008 | c; select group | c; no description | a; secure record \* | a; true \* |

Table B continued.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Reference | Comparability of cohorts | Outcome assessment | Followup long enough for outcomes to occur | Adequacy of followup |
| Mustonen 2014 | none | c; self report | a; yes \* | d; no statement |
| Tarr 2007 | none | b: record linkage \* | a; yes \* | d; no statement |
| Tektonidou 2009 | a; comparable on aPL, thrombotic risk factors \*\* | b: record linkage \* | a; yes \* | d; no statement |
| Erkan 2001 | a; comparable on aPL \* | b: record linkage \* | a; yes \* | d; no statement |
| Ruffatti 2009 | none | b: record linkage \* | a; yes \* | d; no statement |
| Rosove 1992 | none | b: record linkage \* | a; yes \* | d; no statement |
| Khamashta 1995 | none | b: record linkage \* | a; yes \* | b; small number unlikely to alter \* |
| Ames 2005 | none | b: record linkage \* | a; yes \* | d; no statement |
| Lima 1996 | none | b: record linkage \* | a; yes \* | a; complete followup \* |
| Munoz-Rodriguez 1999 | none | b: record linkage \* | a; yes \* | a; complete followup \* |
| Franklin 2002 | none | b: record linkage \* | a; yes \* | a; complete followup \* |
| Naru 2010 | a; comparable on maternal risk factors | b: record linkage \* | a; yes \* | a; complete followup \* |
| Cohn 2010 | none | b: record linkage \* | a; yes \* | a; complete followup \* |
| Mohamed 2014 | none | b: record linkage \* | a; yes \* | a; complete followup \* |
| Ruffatti 2014 | a; stratified results on major risk factors | b: record linkage \* | a; yes \* | a; complete followup \* |
| Ginsberg 1995 | none | c; self report | a; yes \* | b; small number unlikely to alter \* |
| Pengo 2010 | none | b; record linkage \* | a; yes \* | c; 19% with < 1 year followup |
| Hernandez-Molina 2013 | none | b; record linkage \* | a; yes \* | d; no statement |
| Taraborelli 2017 | none | b; record linkage \* | a; yes \* | d; no statement |
| Verro 1998 | none | b; record linkage \* | b; no | d; no statement |
| Wang 2016 | none | b; record linkage \* | b; no | d; no statement |
| Del Ross 2013 | a; comparable on maternal risk factors \* | b; record linkage \* | a; yes \* | a; complete followup \* |
| Munoz-Rodriguez 1999 | none | b: record linkage \* | a; yes \* | a; complete followup \* |
| Mekinian 2015 | a; comparable on aPL \* | b; record linkage \* | a; yes \* | a; complete followup \* |
| Bramham 2011 | a; pre-post comparison \* | b; record linkage \* | a; yes \* | a; complete followup \* |
| Diejomaoh 2002 | none | b; record linkage \* | a; yes \* | a; complete followup \* |
| Jeremic 2005 | none | b; record linkage \* | a; yes \* | c; exclusion of 15% |
| Heilman 2008 | none | b; record linkage \* | a; yes \* | a; complete followup \* |

Table B continued.

|  |  |  |
| --- | --- | --- |
| Reference | Stars | Rating |
| Mustonen 2014 | 4 | Intermediate |
| Tarr 2007 | 6 | Intermediate |
| Tektonidou 2009 | 7 | High |
| Erkan 2001 | 7 | High |
| Ruffatti 2009 | 6 | Intermediate |
| Rosove 1992 | 6 | Intermediate |
| Khamashta 1995 | 7 | High |
| Ames 2005 | 6 | Intermediate |
| Lima 1996 | 6 | Intermediate |
| Munoz-Rodriguez 1999 | 7 | High |
| Franklin 2002 | 7 | High |
| Naru 2010 | 7 | High |
| Cohn 2010 | 7 | High |
| Mohamed 2014 | 6 | Intermediate |
| Ruffatti 2014 | 8 | High |
| Ginsberg 1995 | 5 | Intermediate |
| Pengo 2010 | 6 | Intermediate |
| Hernandez-Molina 2013 | 6 | Intermediate |
| Taraborelli 2017 | 6 | Intermediate |
| Verro 1998 | 5 | Intermediate |
| Wang 2016 | 5 | Intermediate |
| Del Ross 2013 | 8 | High |
| Munoz-Rodriguez 1999 | 7 | High |
| Mekinian 2015 | 6 | Intermediate |
| Bramham 2011 | 7 | High |
| Diejomaoh 2002 | 6 | Intermediate |
| Jeremic 2005 | 5 | Intermediate |
| Heilman 2008 | 5 | Intermediate |