Guidelines for the treatment of antiphospholipid syndrome

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ABSTRACT

The antiphospholipid syndrome (APS) is a systemic autoimmune disease characterized by arterial and venous thrombosis, gestational morbidity and presence of elevated and persistently positive serum titers of antiphospholipid antibodies. The treatment of APS is still controversial, because any therapeutic decision potentially faces the risk of an insufficient or excessive antithrombotic coverage associated with anticoagulation and its major adverse effects. This guideline was elaborated from nine relevant clinical questions related to the treatment of APS by the Committee of Vasculopathies of the Brazilian Society of Rheumatology. Thus, this study aimed at establishing a guideline that included the most relevant and controversial questions in APS treatment, based on the best scientific evidence available. The questions were structured by use of the PICO (patient, intervention or indicator, comparison and outcome) process, enabling the generation of search strategies for evidence in the major primary scientific databases (MEDLINE/PubMed, Embase, Lilacs, Scielo, Cochrane Library, Premedline via OVID). A manual search for evidence and theses was also conducted (BDDT and IBICT). The evidence retrieved was selected based on critical assessment by using discriminatory instruments (scores) according to the category of the therapeutic question (JADAD scale for randomized clinical trials and Newcastle-Ottawa scale for non-randomized studies). After defining the potential studies to support the recommendations, they were selected according to level of evidence and grade of recommendation, according to the Oxford classification.

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The antiphospholipid syndrome (APS) is a systemic autoimmune disease characterized by arterial and venous thrombosis, gestational morbidity and presence of elevated and persistently positive serum titers of antiphospholipid antibodies. It is currently recognized as the most frequent cause of acquired thrombophilia associated with venous and arterial thrombosis.

The current classification meant for inclusion in clinical research protocols, but often used in daily practice to establish the diagnosis of APS(D) and indicate a treatment, was reviewed in 2006 and includes clinical and laboratory criteria.

Clinical criteria

- Vascular thrombosis: one or more episodes of arterial or venous thrombosis or thrombosis of small vessels of any organ or tissue, confirmed on Doppler or histopathology, vasculitis excluded;
- Gestational morbidity:
  - One or more deaths of a morphologically normal fetus after the 10th gestational week, confirmed on ultrasound or by examining the fetus;
  - One or more premature births of a morphologically normal fetus before the 34th gestational week due to eclampsia, preeclampsia or causes of placental insufficiency;
  - Three or more spontaneous abortions before the 10th gestational week, with neither maternal hormonal nor anatomical abnormalities, paternal and maternal chromosomal causes excluded.

Laboratory criteria

- Presence of lupus anticoagulant antibody (LA) in the plasma on two or more occasions at a minimum 12-week interval, detected according to the recommendations of the International Society on Thrombosis and Hemostasis (ISTH);
- Moderate (> 40) to high (> 80) titers of IgG or IgM anticardiolipin antibodies (ACL) on two or more occasions at a minimum 12-week interval, detected by using standard ELISA test;
- IgG or IgM anti-beta 2-GPI antibodies in the plasma on two or more occasions at a minimum 12-week interval, detected by using standard ELISA test.

The presence of arterial or venous thrombosis or thrombosis of small vessels is the major characteristic of the disease and the major cause of death in those patients. The disease can affect vessels of any caliber and from any place. The most frequently reported events are deep venous thrombosis, pulmonary embolism, and encephalic vascular accident (EVA). Untreated patients with APS have been reported to be at high risk for recurrence (B).3

The treatment of APS is still controversial, because any therapeutic decision potentially faces the risk of an insufficient or excessive antithrombotic coverage associated with anticoagulation and its major adverse effects. Currently, the indication of lifelong oral anticoagulation in cases of arterial, venous or microcirculatory thrombosis is consensual, but its intensity and possibility of interruption are still discussed. The new anticoaguants (rivaroxaban and dabigatran), indicated to prevent EVA and systemic embolism in patients with non-valvular atrial fibrillation after hip or knee arthroplasty, are still being studied in patients with APS, and the short- and medium-term study results are awaited. New anticoaguants that do not require
monitoring and bearing a lower risk of bleeding are certainly of interest. Once confirmed their efficacy and safety, they will have a solid place in the arsenal of APS treatment. However, the current objective of the research in the area is to improve the therapeutic management of APS, aiming at acting on the pathogenic process triggered by antiphospholipid antibodies. The candidates are as follows: agents potentially used in primary prophylaxis, such as hydroxychloroquine and clopidogrel; agents used in more severe situations, such as intravenous gamma globulin and rituximab; and others more recently introduced that can reduce antibody production, such as tocilizumab and belimumab.

The management of individuals with antiphospholipid antibodies and no previous thrombotic events, such as primary thromboprophylaxis, is still a matter of concern and debate. Thus, this study aimed at establishing a guideline that included the most relevant and controversial questions in APS treatment, based on the best scientific evidence available.

Material and methods

This guideline was elaborated from nine relevant clinical questions related to the treatment of APS by the Committee of Vasculopathies of the Brazilian Society of Rheumatology. The questions were structured by use of the PICO (patient, intervention or indicator, comparison and outcome) process, enabling the generation of search strategies (Appendix 1) for evidence in the major primary scientific databases (MEDLINE/PubMed, Embase, Lilacs, Scielo, Cochrane Library, Premedline via OVID). A manual search for evidence and theses was also conducted (BDTD and IBICT). The evidence retrieved was selected based on critical assessment by using discriminatory instruments (scores) according to the category of the therapeutic question (JADAD scale for randomized clinical trials and Newcastle-Ottawa scale for non-randomized studies). After defining the potential studies to support the recommendations, they were selected according to level of evidence and grade of recommendation, based on the Oxford classification.

Grade of recommendation and level of evidence:
A: data derived from more consistent experimental and observational studies.
B: data derived from less consistent experimental and observational studies.
C: case reports (uncontrolled studies).
D: expert opinion without explicit critical appraisal, or based on consensus, physiological studies or animal models.

Results

1. Do asymptomatic individuals positive for antiphospholipid antibodies (moderate or high IgG or IgM LA+ or ACL or anti-beta 2-GP) and with no history of thrombosis benefit from anticoagulation? And from antiplatelet agents?

Adult patients with antiphospholipid antibodies on a mean 36-month follow-up and undergoing continuous thromboprophylaxis (aspirin) show no difference in the risk of thromboembolic events. However, patients undergoing thromboprophylaxis and at risky situations (surgery/immobilization, pregnancy/puerperal period) show a 31% reduction in the risk of thrombotic events (NNT:3) (B).3

The primary prevention of thrombosis in patients positive for antiphospholipid antibodies either with low doses of aspirin (75 mg/day) or with aspirin associated with warfarin shows 5% of thrombotic events for both forms of prophylaxis, and, in one to five years, there is an incidence of 4.9 events per 100 patient-years in both groups (B).7 A 5% reduction in the risk of thrombotic events (NNT:20) is observed in patients with antiphospholipid antibodies on primary prevention with aspirin and/or coumarins (B).5

Thrombosis prophylaxis (low dose of aspirin, long-term warfarin or heparin) in patients with antiphospholipid antibodies (medium/high titers of ACL) and arterial hypertension can reduce the risk of events by 51.2% (NNT:2) (B).6 In populations positive for antiphospholipid antibody, the prophylactic use of aspirin can reduce the risk of thrombotic events in 17% of the cases over 120 months (NNT:6) (B).7

However, there is evidence of no difference between using aspirin or not to prevent thrombotic events in those patients; in addition, there is even a 6% increase in the risk of thrombotic events (NNH:16) in patients on aspirin (B).8

The benefit of thromboprophylaxis (primary prevention) is controversial in patients with antiphospholipid antibodies and no clinical symptoms (B).9

In pregnant women with consecutive spontaneous abortions, with neither antiphospholipid antibodies nor any apparent cause, the use of aspirin or enoxaparin does not reduce the risk of new events (A).10

Recommendation

Because of the controversial results of thromboprophylaxis (primary prevention) in patients positive for antiphospholipid antibodies, the continuous administration of aspirin and/or coumarins cannot be recommended to those patients, their use being reserved to situations with an elevated risk of thrombosis.

2. Is anticoagulation for undetermined time indicated to patients positive for antiphospholipid antibodies and with a history of venous thrombosis? What should the target INR be?

In patients with a history of venous thrombosis and moderate to high titers of ACL and/or LA, anticoagulation with a target range for INR of 2.0 to 3.0 reduces the risk of recurrence similarly to anticoagulation with a target range for INR of 3.0 to 4.0, as compared to no anticoagulation (B).2

In patients with antiphospholipid antibodies, the use of moderate intensity anticoagulation with warfarin (target range for INR of 2.0 to 3.0) as compared to no treatment reduces the risk of venous thrombosis by 80% to 90% (B).8

Intensive regimens of anticoagulation (INR between 3.5 and 4.5) as compared to conventional regimens (INR between 2.0 and 3.0) for the treatment of patients with APS reduce the risk of thrombosis recurrence at similar rates, but intensive anticoagulation increases the risk of mild bleeding (B).11,12
In the treatment of patients with APS and a history of venous thrombosis with warfarin, the following target ranges for INR yielded similar recurrence indices: INR between 3.0 and 4.0, 7.1%; and INR between 2.0 and 3.0, 2.2% (A). The recurrence risk of thrombosis in patients with APS and no treatment for one year is 29%. Anticoagulation with warfarin (INR between 2.0 and 3.0) reduces the risk by 19% (NNT:5), and when the goal is an INR > 3.0, either associated or not with aspirin, the risk is reduced by 27.5% (NNT:4). After six months of treatment cessation, the risk is increased by 100% (NNH:1) (B). In patients with a history of venous or arterial thrombosis and positive for antiphospholipid antibody, treatment with warfarin (INR between 2.0 and 2.9) and aspirin (75 mg/day) leads to a 21% increase in the risk of recurrence within 24 months as compared to warfarin (INR > 2.9) and aspirin (75 mg/day) (B).

Patients positive for antiphospholipid antibodies and previous venous thrombosis, when treated with anticoagulation, have an increase in the likelihood of thrombosis-free survival of 50% and 78% within two and eight years, respectively (B). The thromboprophylaxis of patients with APS and previous venous thrombosis recommends maintaining long-term anticoagulation with oral anticoagulants, aiming at an INR between 2.0 and 3.0 (B).

**Recommendation**

Patients with APS and previous venous thrombosis should remain on anticoagulants for undetermined time, aiming at an INR between 2.0 and 3.0.

3. **Is anticoagulation for undetermined time indicated for patients with APS and previous arterial thrombosis? Which should the target INR be?**

The recurrence rate of thrombotic events in patients with APS and previous arterial thrombosis is greater in untreated patients and lower in those on warfarin and INR between 3.0 and 4.0, as compared to low-intensity warfarin (INR between 2.0 and 3.0) or aspirin alone. Patients with arterial events are at a greater risk of recurrence than those with venous events (B).

Warfarin and aspirin seem to be equivalent in preventing thromboembolic complications in patients with their first ischemic EVA and positive for antiphospholipid antibodies. The use of warfarin (INR 1.4–2.8) or aspirin (325 mg/day) does not differ regarding the risk for cerebral arterial thrombotic events (recurrence) (A). The number of arterial events (transient cerebral ischemia, EVA or death due to EVA) occurring in patients with antiphospholipid antibodies and history of arterial thrombotic events during thromboprophylaxis with high-intensity warfarin (INR between 3.5 and 4.5) or standard warfarin (INR between 2.0 and 3.0) is similar (B).

The risk of recurrence of thrombotic events in patients with antiphospholipid antibody and history of arterial thrombosis in a three-year follow-up on warfarin (target INR between 3.1 and 4.0) or aspirin (target INR between 2.0 and 3.0) is 21.4% and 7.6%, respectively (A). There is a 56% reduction in the risk of recurrence of arterial events in anticoagulated patients with antiphospholipid antibody as compared to untreated ones. Patients on high-intensity warfarin (INR > 3.0) either with or without aspirin have a 90% probability of not experiencing a new thrombotic event within five years (B).

Regarding the thromboprophylaxis of arterial events in patients with antiphospholipid antibodies, treatment with warfarin (INR > 2.9) and aspirin (75 mg/day) reduces the risk of events by 50% as compared to aspirin alone at the same dosage. The recurrence risk of thrombotic events does not differ between warfarin with an INR greater than or lower than 2.9 (B).

Triple-positive APS patients (with three positive antiphospholipid tests) have a high recurrence rate, more frequently arterial. Warfarin with a target INR between 2.0 and 3.0 is more effective than low-dose aspirin or no therapy; however, in patients on warfarin (target INR between 2.0 and 3.0) for six years, the recurrence rate is 30% (B).

Over a five-year treatment with oral anticoagulants, patients with APS have an 11% reduction in the recurrence risk of arterial events as compared to untreated patients (B).

**Recommendation**

The treatment of patients with antiphospholipid antibody and history of arterial thrombosis should be long and performed with warfarin (INR between 2.0 and 3.0 or INR > 3.0) either associated or not with antiplatelet agents. The prospective studies that found no difference between high-intensity warfarin and standard INR included a small group of patients with arterial thrombosis, hindering, thus, definitive conclusions. The authors suggest long-term anticoagulation with high-intensity warfarin.

4. **Is anticoagulation for undetermined time indicated for patients with APS who have only obstetric events? And antiplatelet therapy?**

In patients with obstetric APS on aspirin (75,100 mg/day) having used low-weight heparin during pregnancy and six weeks after delivery, the number of thrombotic events in 36 months can be 3.3/100 patient-years. The determinant factor for events, independently of anticoagulation or antiplatelet therapy, is the presence of at least two antibodies, when the rate of events is 4.6/100 patient-years (C).

The five-year incidence of thrombotic events in pregnant patients with obstetric manifestations of APS can be 2.5%, being even reported in one patient on aspirin. Approximately 7.4% of the patients on anticoagulants can have hemorrhagic manifestations (B).

Treating women with APS and obstetric manifestations by using low-dose aspirin reduces the risk of thrombotic event by 49% over an eight-year follow-up (B).

The nine-year follow-up of patients with obstetric APS (obstetric events) treated with low-dose aspirin (100 mg/day), as compared to patients with no antiphospholipid antibody, shows an increased risk for pulmonary embolism of 31%, for deep venous thrombosis of 103%, and for EVA of 13% (B).
Recommendation

Patients diagnosed with APS and exclusive presence of obstetric events should undergo long-term thromboprophylaxis with low-dose aspirin, aiming at reducing thrombotic events, especially the arterial ones.

5. Should a primipara positive for antiphospholipid antibodies with no history of thrombosis undergo any intervention?

In female patients positive for antiphospholipid antibodies, considered at low-risk due to the lack of associated morbidities (none or one spontaneous abortion or no previous thrombosis), low-dose aspirin reduces the risk of neither events nor complications (B).

The risk of venous thromboembolism in pregnant patients positive for antiphospholipid antibody and with no history of thrombotic events is similar to that of pregnant patients with no antiphospholipid antibody (B). The risk of thrombotic events in patients with antiphospholipid antibodies and history of obstetric events is 19% in 12 months, but the risk of patients with antiphospholipid antibody and no history of obstetric events is 0% (zero) (B); thus, pharmacological treatment (thromboprophylaxis) is not justified in those patients (B).

Recommendation

 Patients with antiphospholipid antibodies and no history of thrombotic events should not receive pharmacological treatment during pregnancy.

6. Is oral anticoagulation indicated for pregnant women (between 14 and 35 weeks) with APS and previous thrombosis? Which should the target INR be?

Oral anticoagulants are recommended during pregnancy (16th to 36th week), or even for six weeks after delivery (D), to patients with antiphospholipid antibody and history of thrombosis, mainly arterial thrombosis, based on extrapolation of the use of oral anticoagulants in similar, but not pregnant, patients and on the fact of the lower teratogenic risk of those medications at that phase of pregnancy (D).

Events can recur in 20% of patients with APS, even when on oral anticoagulants (80% with INR between 2.0 and 3.0, and 20% with INR > 3.0) (B). The use of oral anticoagulants (INR between 2.0 and 3.0) in 80% of patients with APS reduces the recurrence risk of thromboembolism within five years by 22% (NNT: 5) (B). However, their specific use in pregnant women has not been properly studied.

Recommendation

Pregnant patients with APS and history of thromboembolic events should not receive oral anticoagulants, because their use in that population has not been properly studied.

7. Is heparin indicated to pregnant women with APS and previous thrombosis? Which dosing should be used for unfractionated and low molecular weight heparin?

Treating pregnant women with APS and history of thromboembolic events (venous or arterial) with dalteparin (5,000 IU/day, subcutaneously, once a day, increasing to twice a day between the 16th and 20th gestational week) can cause a 100% reduction in thrombotic events over a 35-week follow-up (B).

In pregnant women with APS and history of thromboembolic events, treatment with full dose low molecular weight heparin associated with aspirin during pregnancy and for six weeks after delivery can reduce the recurrence risk of thrombotic events by 100% (NNT: 1) (B).

Comparing the use of low molecular weight heparin (enoxaparin, 1 mg/kg/day) associated with 100 mg of aspirin and warfarin (INR between 2 and 2.5) from the 14th to the 34th gestational week to patients with APS and one previous thrombotic episode shows a 28.5% increase in the risk of thrombosis in those receiving warfarin (NNH: 4) (B).

Pregnant patients with APS and previous episodes of thrombosis have a high recurrence rate of thrombosis, and the antithrombotic treatment should be maintained during pregnancy and post-partum. The standard regimen combines low-dose aspirin and heparin (unfractionated or low molecular weight). Warfarin, except between the 6th and 12th week, might be an alternative to heparin, and should be reinitiated after delivery (D).

Recommendation

The use of low molecular weight heparin subcutaneously (dalteparin, 5,000 IU/day or enoxaparins, 1 mg/kg/day, doubling one or the other after the 16th week) associated with aspirin (100 mg/day) during pregnancy and after delivery reduces the occurrence of maternal thrombosis and fetal loss. Warfarin is the option after the 13th gestational week. Despite the lack of good quality scientific evidence, the authors recommend, based on case series, case reports and personal experience, that pregnant patients with APS and previous thrombosis maintain full dose and nonprophylactic low molecular weight heparin associated with aspirin during pregnancy due to the high risk of new thromboembolic events in that period.

8. Is there any difference in the management of pregnant women with history of late fetal loss or early abortions? Are there advantages in using aspirin?

Pregnant patients with APS and history of either early abortions or late fetal loss can be managed with low-dose aspirin and low molecular weight heparin.

However, under the same treatment, the outcomes of patients with history of early abortions as compared to those of patients with history of late fetal loss differ, a higher number of premature deliveries and small for gestational age newborns being observed in patients with history of late fetal loss (B).
Comparison of low molecular weight heparin and aspirin in isolation for the treatment of pregnant women with APS and history of repeated abortions shows a 14% increase (NNT:7) in fetal survival and in newborn weight in patients medicated with heparin \((B)\).36

The use of aspirin to treat pregnant patients with APS and repeated abortions has no benefits regarding prenatal complications (for example, premature delivery) and neonatal outcomes (for example, weight) \((B)\).57

Neonatal and obstetric outcomes occur at similar numbers in pregnant patients with antiphospholipid antibody and history of repeated abortions treated with aspirin and low molecular weight heparin as compared to those treated only with aspirin \((A)\).38,39 However, when aspirin is associated with unfractionated heparin, a 29% increase (NNT:3) in newborn survival is observed \((A)\).40

**Recommendation**

Pregnant patients with antiphospholipid antibody and history of early or late abortions should be treated with heparin (unfractionated or low molecular weight) and aspirin.

**9. Is the association of other medications (corticosteroid, immune globulin, rituximab) with anticoagulants in the catastrophic antiphospholipid syndrome (CAPS) advantageous?**

Considering the presence or absence of one single treatment, improvement occurs in 63.1% of the episodes of CAPS treated with anticoagulants versus 22.2% of episodes not treated with anticoagulants (NNT:2). In addition, there is no difference in improvement between presence and absence of individual treatment with other agents, such as corticosteroids, plasmapheresis, immune globulin or antiplatelet agents. The individual use of corticosteroids produces the poorest recovery \((B)\).41,42

When treatments are associated, the most common combination is anticoagulants and corticosteroids, followed by anticoagulants, corticosteroids, plasmapheresis and/or immune globulin. The recovery rate showed no difference between the several combinations, and no difference between combining with anticoagulants or not \((B)\).41,42

**Recommendation**

There are no good quality studies confirming the benefit of the association of other medications with anticoagulants in the treatment of patients with CAPS. Despite the limited good quality scientific evidence, the authors recommend, based on case series, case reports and personal experience, the association of corticosteroid, plasmapheresis and/or rituximab with anticoagulant therapy, because of the high mortality of that condition.

**Conflicts of interest**

The authors declare no conflicts of interest.

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**Appendix 1: Search strategies and words used in the search for the clinical questions.**

**PICO 1**

Do asymptomatic individuals positive for antiphospholipid antibodies (moderate or high IgG or IgM LA+ or ACL or anti-beta 2-GP) and with no history of thrombosis benefit from anticoagulation? And from antiplatelet agents?

**PICO 2**

Is anticoagulation for undetermined time indicated for patients positive for antiphospholipid antibodies and with a history of venous thrombosis? What should the target INR be?

**PICO 3**

Is anticoagulation for undetermined time indicated for patients with APS and previous arterial thrombosis? Which should the target INR be?
PICO 4

Is anticoagulation for undetermined time indicated for patients with APS who have only obstetric events? And anti-platelet therapy?

Pregnancy Complications AND (Antiphospholipid Syndrome OR Anti-Phospholipid Antibody Syndrome OR Antiphospholipid Antibody Syndrome OR Anti-Phospholipid Syndrome OR Antibodies, Antiphospholipid ) AND (Platelet Aggregation Inhibitors OR Anticoagulants OR Coumarins OR Heparin OR Aspirin) AND ((clinical[Title/Abstract] AND trial[Title/Abstract]) OR clinical trials[MeSH Terms] OR clinical trial[Publication Type] OR random*[Title/Abstract] OR random allocation[MeSH Terms] OR therapeutic use[MeSH Subheading] OR Comparative study OR Epidemiologic methods)

PICO 5

Should a primipara positive for antiphospholipid antibodies with no history of thrombosis undergo any intervention?

Pregnancy AND (Antiphospholipid Syndrome OR Anti-Phospholipid Antibody Syndrome OR Antiphospholipid Antibody Syndrome OR Anti-Phospholipid Syndrome OR Antibodies, Antiphospholipid ) AND ((clinical[Title/Abstract] AND trial[Title/Abstract]) OR clinical trials[MeSH Terms] OR clinical trial[Publication Type] OR random*[Title/Abstract] OR random allocation[MeSH Terms] OR therapeutic use[MeSH Subheading] OR Comparative study OR Epidemiologic methods)

PICO 6

Is oral anticoagulation indicated for pregnant women (between 14 and 35 weeks) with APS and previous thrombosis? Which should the target INR be?

Pregnancy AND (Antiphospholipid Syndrome OR Anti-Phospholipid Antibody Syndrome OR Antiphospholipid Antibody Syndrome OR Anti-Phospholipid Syndrome OR Antibodies, Antiphospholipid ) AND ((clinical[Title/Abstract] AND trial[Title/Abstract]) OR clinical trials[MeSH Terms] OR clinical trial[Publication Type] OR random*[Title/Abstract] OR random allocation[MeSH Terms] OR therapeutic use[MeSH Subheading] OR Comparative study OR Epidemiologic methods)

PICO 7

Is heparin indicated to pregnant women with APS and previous thrombosis? Which dosing should be used for unfractionated and low molecular weight heparin?

Pregnancy AND (Antiphospholipid Syndrome OR Anti-Phospholipid Antibody Syndrome OR Antiphospholipid Antibody Syndrome OR Anti-Phospholipid Syndrome OR Antibodies, Antiphospholipid) AND heparin AND (Embolism and Thrombosis OR Arterial Occlusive Diseases) AND ((clinical[Title/Abstract] AND trial[Title/Abstract]) OR clinical trials[MeSH Terms] OR clinical trial[Publication Type] OR random*[Title/Abstract] OR random allocation[MeSH Terms] OR therapeutic use[MeSH Subheading] OR Comparative study OR Epidemiologic methods)

PICO 8

Is there any difference in the management of pregnant women with history of late fetal loss or early abortions? Are there advantages in using aspirin?

Pregnancy AND (Antiphospholipid Syndrome OR Anti-Phospholipid Antibody Syndrome OR Antiphospholipid Antibody Syndrome OR Anti-Phospholipid Syndrome OR Antibodies, Antiphospholipid) AND heparin AND ((clinical[Title/Abstract] AND trial[Title/Abstract]) OR clinical trials[MeSH Terms] OR clinical trial[Publication Type] OR random*[Title/Abstract] OR random allocation[MeSH Terms] OR therapeutic use[MeSH Subheading] OR Comparative study OR Epidemiologic methods)

PICO 9

Is the association of other medications (corticosteroid, immune globulin, rituximab) with anticoagulants in the catastrophic antiphospholipid syndrome (CAPS) advantageous?

Antiphospholipid Syndrome OR Anti-Phospholipid Antibody Syndrome OR Antiphospholipid Antibody Syndrome OR Anti-Phospholipid Syndrome OR Antibodies, Antiphospholipid) AND Catastrophic AND ((clinical[Title/Abstract] AND trial[Title/Abstract]) OR clinical trials[MeSH Terms] OR clinical trial[Publication Type] OR random*[Title/Abstract] OR random allocation[MeSH Terms] OR therapeutic use[MeSH Subheading] OR Comparative study OR Epidemiologic methods)

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