ANTIPHOSPHOLIPID SYNDROME

CHI Formulary Indication Review

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Abbreviations

aCL	Anticardiolipin
anti β-2GPI	Antibeta-2 Glycoprotein
APD	Antiplatelet Drug
aPL	Antiphospholipid Antibodies
APS	Antiphospholipid Syndrome
CADTH	Canadian Agency for Drugs and Technologies in Health
CAPS	Catastrophic APS
DOAC	Direct Oral Anticoagulant
ELISA	Enzyme-Linked Immunosorbent Assay
EULAR	European League Against Rheumatism
GPL	IgG Antiphospholipid Units/mL
HAS	Haute Autorité de Santé
IgG	Immunoglobulin G
INR	International Normalized Ratio
IQWIG	Institute for Quality and Efficiency in Healthcare
LA	Lupus Anticoagulant
LDA	Low-Dose Aspirin
LMWH	Low-Molecular-Weight Heparin
MPL	IgM Antiphospholipid Units/mL
NICE	National Institute for Health and Care Excellence
NVAF	Non-valvular Atrial Fibrillation
OAPS	Obstetric APS
PAPS	Primary APS
PBAC	Pharmaceutical Benefits Advisory Committee
SLE	Systemic Lupus Erythematous
VKA	Oral Vitamin K Antagonist
VTE	Venous Thromboembolism

Executive Summary

Antiphospholipid syndrome (APS) is a systemic autoimmune disorder characterized by recurrent venous or arterial thrombosis with or without pregnancy morbidity in the presence of persistent antiphospholipid antibodies (aPL). aPL are autoantibodies that are directed against phospholipid-binding proteins[1]. These include the lupus anticoagulant (LA), anticardiolipin (aCL) and antibeta-2 glycoprotein (antiβ-2GPI) autoantibodies, which should be present in moderate-to-high titer on two occasions at least 12 weeks apart. The condition was first described in association with systemic lupus erythematous (SLE) but in 53% of patients, it exists alone as primary APS (PAPS). APS is also less commonly associated with other autoimmune rheumatic diseases such as rheumatoid arthritis, dermatomyositis, systemic sclerosis and Sjögren's syndrome. Catastrophic APS (CAPS) is a rare, life-threatening variant of APS. It is characterized by the acute development of widespread thrombosis resulting in the failure of three or more organs in less than 1 week. It can occur as the presenting event or in those with known APS. The mortality rate is high, 30–50% despite treatment[2].

While not all patients with aPL develop APS, there is a strong association between the presence of aPL and venous thrombosis, myocardial infarction, and ischemic stroke. Antibody profile, including type, titer, and underlying comorbidities, may determine the likelihood of developing clinical APS. Triple positivity with positive lupus anticoagulant and high titers of anticardiolipin and anti-beta-2-glycoprotein I antibodies pose a high risk for the development of APS. In contrast, isolated or intermittent positivity or low titers of anticardiolipin or anti-beta-2-glycoprotein I antibodies pose a low risk. aPL are considered pathogenic as they play an important role in thrombosis, and they are not just a serological marker of APLS[1].

As per Dabit et al., there have been few population-based studies that estimated the prevalence and incidence of APS. The estimated incidence and prevalence among most of these studies ranged between 1 and 2 cases per 100,000 and 40 and 50 cases per 100,000 respectively. The prevalence of antiphospholipid antibodies in patients with obstetric morbidity was 6–9%, while in arterial events and venous thromboembolism was 9–10%[3]. However, this data remains limited. The mortality of patients with APS is 50– 80% higher than the general population. In Saudi Arabia, as of 2020, the prevalence of APS is 1–5% among asymptomatic subjects, however it goes up to 16–44% among people with thrombosis or pregnancy morbidities[4].

APS may more commonly manifest as chest pain, shortness of breath, nausea, pain, redness, warmth and swelling of the limbs, speech alterations and upper body discomfort specifically at the level of the arms, back, neck and jaw. To a lesser extent, APS may be characterized by rashes, chronic headaches, memory loss and heart valve impairment[5].

Classification criteria for APS have been developed to select patients for clinical and laboratory research purposes. Although classification criteria should not be used for diagnostic purposes, the principles on which they are based can be useful to guide clinicians in diagnosing patients and documenting key disease features. In 2006, an international consensus statement was published to update the classification criteria for definite APS, also called the Sapporo classification criteria (table 1)[6].

Table 1. Revised Sapporo Classification Criteria for Antiphospholipid Syndrome (APS)

Antiphospholipid syndrome is present if at least 1 of the clinical criteria and 1 of the laboratory criteria that follow are met*
Clinical criteria
1. Vascular thrombosis[¶] 1 or more clinical episodes[Δ] of arterial, venous, or small vessel thrombosis[◊], in any tissue or organ. Thrombosis must be confirmed by objective validated criteria (ie, unequivocal findings of appropriate imaging studies or histopathology). For histopathologic confirmation, thrombosis should be present without significant evidence of inflammation in the vessel wall.
2. Pregnancy morbidity a. 1 or more unexplained deaths of a morphologically normal fetus at or beyond the 10th week of gestation, with normal fetal morphology documented by ultrasound or by direct examination of the fetus; or b. 1 or more premature births of a morphologically normal neonate before the 34th week of gestation because of: (i) eclampsia or severe preeclampsia defined according to standard definitions, or (ii) recognized features of placental insufficiency[§]; or c. 3 or more unexplained consecutive spontaneous abortions before the 10th week of gestation, without maternal or hormonal abnormalities, and paternal and maternal chromosomal causes excluded. In studies of populations of patients who have more than 1 type of pregnancy morbidity, investigators are strongly encouraged to stratify groups of subjects according to a, b, or c above.
Laboratory criteria[¥]
1. LA present in plasma, on 2 or more occasions at least 12 weeks apart, detected according to the guidelines of the International Society on Thrombosis and Hemostasis (Scientific Subcommittee on LAs/phospholipid-dependent antibodies).
2. aCL of IgG and/or IgM isotype in serum or plasma, present in medium or high titer (i.e., >40 GPL or MPL, or >the 99th percentile), on 2 or more occasions, at least 12 weeks apart, measured by a standardized ELISA.

3. Anti-beta2 glycoprotein I antibody of IgG and/or IgM isotype in serum or plasma (in titer >the 99th percentile), present on 2 or more occasions, at least 12 weeks apart, measured by a standardized ELISA, according to recommended procedures.

*** Classification of APS should be avoided if less than 12 weeks or more than 5 years separate the positive aPL test and the clinical manifestation.**

¶ Coexisting inherited or acquired factors for thrombosis are not reasons for excluding patients from APS trials. However, 2 subgroups of APS patients should be recognized, according to: (a) the presence; and (b) the absence of additional risk factors for thrombosis. Indicative (but not exhaustive) cases include: age (>55 in men and >65 in women) and the presence of any of the established risk factors for cardiovascular disease (hypertension, diabetes mellitus, elevated LDL or low HDL cholesterol, cigarette smoking, family history of premature cardiovascular disease, body mass index ≥ 30 kg/m^2, microalbuminuria, estimated GFR <60 mL $minute^{-1}$), inherited thrombophilias, oral contraceptives, nephrotic syndrome, malignancy, immobilization, and surgery. Thus, patients who fulfill criteria should be stratified according to contributing causes of thrombosis.

Δ A thrombotic episode in the past could be considered as a clinical criterion, provided that thrombosis is proved by appropriate diagnostic means and that no alternative diagnosis or cause of thrombosis is found.

◊ Superficial venous thrombosis is not included in the clinical criteria.

§ Generally accepted features of placental insufficiency include: (i) abnormal or non-reassuring fetal surveillance test(s), e.g., a non-reactive non-stress test, suggestive of fetal hypoxemia; (ii) abnormal Doppler flow velocimetry waveform analysis suggestive of fetal hypoxemia, e.g., absent end-diastolic flow in the umbilical artery; (iii) oligohydramnios, e.g., an amniotic fluid index of 5 cm or less; or (iv) a postnatal birth weight less than the 10th percentile for the gestational age.

¥ Investigators are strongly advised to classify APS patients in studies into one of the following categories: I, more than 1 laboratory criteria present (any combination); IIa, LA present alone; IIb, aCL antibody present alone; IIc, anti-beta2 glycoprotein I antibody present alone.

LA: lupus anticoagulant; aCL: anticardiolipin antibody; Ig: immunoglobulin; ELISA: enzyme-linked immunosorbent assay; APS: antiphospholipid syndrome; aPL: antiphospholipid antibodies; LDL: low-density lipoprotein; HDL: high-density lipoprotein; GFR: glomerular filtration rate.

Although catastrophic APS patients represent less than 1% of all patients with APS, they are usually in a life-threatening medical situation that requires high clinical awareness. The careful and open discussion of several proposals by all participants in the presymposium workshop on APS consensus, held in Taormina in September 2002, has allowed the acceptance of a preliminary set of classification criteria (table 2)[7].

Table 2. Preliminary Criteria for the Classification of Catastrophic Antiphospholipid Syndrome (CAPS)

Preliminary Criteria for the Classification of Catastrophic Antiphospholipid Syndrome
Diagnostic Criteria 1. Evidence of the involvement of three or more organs, systems, or tissues 2. Development of manifestations simultaneously or in less than one week 3. Histopathological confirmation of small vessel occlusion in at least one organ or tissue 4. 4. Analytical confirmation of the presence of antiphospholipid antibodies (lupus anticoagulant and/or anticardiolipin and/or antiβ2 glycoprotein I antibodies)
Definitive Catastrophic APS All four criteria
Probable Catastrophic APS a. All four criteria, except for only two organs, systems, and/or tissues involved b. All four criteria, except for the absence of laboratory confirmation (within at least 6 weeks) owing to the early death of a patient never tested for aPL before the catastrophic APS c. Criteria (1), (2), and (4) d. Criteria (1), (3), and (4) and the development of a third event between one week and one month after presentation, despite anticoagulation

If left untreated, APS may cause life threatening blood clots subsequently leading to stroke or heart attacks[5]. The main treatment goals are the management of acute thrombosis and prevention of thrombosis recurrence and pregnancy morbidity[8].

This report compiles all clinical and economic evidence related to antiphospholipid syndrome according to the relevant sources. The ultimate objective of issuing APS guidelines by the Council of Health Insurance (CHI) is to update the IDF (CHI Drug Formulary) with **the best available clinical and economic evidence related to drug therapies, ensuring timely and safe access to APS patients in Saudi Arabia**. The main focus of the review was on North American, European and other international guidelines issued within the last five years. To elaborate, North American guidelines discussed the classification criteria for definite APS, primary and secondary antithrombotic prophylaxis, pregnancy morbidity, obstetric APS and proposed future treatments. Furthermore, European guidelines drew focus on diagnosis, patient risk stratification, and pharmacological management of the different forms of APS. International guidelines delved into the risk factors for thrombosis in pregnant women and management of APS with and without SLE. In addition, recent

systematic reviews and meta-analyses were tackled; thereby providing an in-depth understanding of the different APS drug therapies and their placement in pharmacological management.

Main recommendations issued by different Health Technology Assessment (HTA) bodies on the use of the current medications in APS were reviewed and summarized under each drug therapy table in Section 2.0. These include the National Institute for Health and Care Excellence (NICE), the Canadian Agency for Drugs and Technologies in Health (CADTH), Haute Autorité de Santé (HAS), the Institute for Quality and Efficiency in Healthcare (IQWIG), and the Pharmaceutical Benefits Advisory Committee (PBAC).

The management of APS involves a **multidisciplinary approach**. **Drug therapy is an integral component for the management of antiphospholipid syndrome.** Distinct from other autoimmune conditions, APS is treated with anticoagulation rather than immunosuppression. The mainstay of treatment is heparin, followed by warfarin. Current consensus is for lifelong anticoagulation as the recurrence risk is high. Newer oral anticoagulants (direct oral anticoagulants or DOACs) initially held the hope of escaping the intense monitoring required with warfarin; however, they have fallen out of practice. Immune modulating drugs, including hydroxychloroquine, azathioprine, steroids, IVIg, rituximab and belimumab, have been used in APS, especially in those with recurrent thrombosis despite anticoagulation, with currently little evidence to support their use[9]. In cases of CAPS that have been associated with SLE, published case reports have demonstrated a possible role of cyclophosphamide as part of the management, although it is not yet recommended by the clinical guidelines detailed in section 1.0[10–12].

Section 2.0 provides a full description of each pharmacological agent with final statements on the placement of therapy. All recommendations are well supported by reference guidelines, Grade of Recommendation (GoR), Level of Evidence (LoE) and Strength of Agreement (SoA) reflecting specific drug class role in the management of antiphospholipid syndrome.

Major recommendations for suggested drug therapies are summarized in the table below:

Table 3. SFDA-Registered Drugs for the Management of Antiphospholipid Syndrome (APS)

Medication	Indication	Line of Therapy	Level of Evidence/ Recommendation	HTA Recommendations
Warfarin	Antiphospholipid Syndrome patients who have suffered from thrombosis	1st	Strong Recommendation[2]	Positive Recommendation from HAS[13]
Unfractionated Heparin	Antiphospholipid Syndrome	1st	Strong Recommendation[2,9,14–18]	N/A
Enoxaparin	Antiphospholipid Syndrome	1st	Strong Recommendation[2,9,14–18]	N/A
Tinzaparin	Antiphospholipid Syndrome	1st	Strong Recommendation[2,9,14–18]	N/A
Bemiparin	Antiphospholipid Syndrome	1st	Strong Recommendation[2,9,14–18]	N/A
Aspirin	Antiphospholipid Syndrome – Prophylaxis (Low Dose)	1st	Strong Recommendation[14,18]	N/A
Methyl-prednisolone	Catastrophic Antiphospholipid Syndrome	1st in combination with heparin	Strong Recommendation[14]	Positive Recommendation form HAS[19]

The report concludes with the addition of a key recommendation synthesis section, which emphasizes the utilization of each drug class for specific patient groups.

Section 1.0 Summary of Reviewed Clinical Guidelines & Evidence

1.1 KSA Guidelines

To date, no clinical guidelines have been issued by Saudi bodies for the management of antiphospholipid syndrome.

1.2 European Guidelines

1.2.1 A Review on Management of Antiphospholipid Syndrome in Clinical Practice [*Italian Journal of Medicine*, 2023]

The following review does not provide a specified grade of evidence or level of recommendation.

The purpose of this review, published in the Italian Journal of Medicine 2023, is to aid both general practitioners and specialists recognize, accurately diagnose, and manage APS; the recommendations are detailed below[14]:

Diagnosis

- In addition to the classification criteria detailed in table 1 above, patients who are positive for aPL may present with no related symptoms. Such patients are usually identified during evaluation for other problems, such as early miscarriages, systemic autoimmune diseases, and an elevated activated partial-thromboplastin time.

Patient Risk Stratification: "Antiphospholipid Profile"

- The aPL profile spectrum is defined by the aPL type, the titer of the antibody, the persistence of aPL positivity in repeated measurements, and the single or multiple antibody positivity.
- It is possible to recognize and correlate some spectrum with increasing risk of clinical potential vascular events and consequently to justify the choice of the intensity of treatment.
- It is generally accepted as:
    - High-risk aPL profile: Four different conditions are considered in this profile if the presence of positive titers is demonstrated on two or more occasions at least 12 weeks apart.

        - Lupus anticoagulant (LA)
        - Double positive (any combination of aCL, anti-β2GPI)
        - Triple positive
        - Presence of persistently high titer of aPL.
    - Medium-high aPL titers:
        - aCL antibody IgG/IgM isotype in titers >40 IGG phospholipid (GPL) units or >40 IgM phospholipid (MPL) units or >99th percentiles, measured by ELISA.
        - anti-β2GPI antibody of IgG/ IgM isotype in titer >99th percentiles, measured by ELISA.
    - Low-risk aPL profile: single positive antibody of aCL or anti-β2GPI at low-medium titers, especially if the positive titer is transient.
- Asymptomatic patients with confirmed positive aPL are not considered for the diagnosis of APS, however, clinicians should assess aPL antibody risk and subsequent evaluation for treatment if required.

Pharmacological Management

- Long-term anticoagulation with a vitamin K antagonist (VKA) is the standard of care for patients who develop thrombosis, considering the high rate of recurrent thrombosis in patients with APS.
- A primary prevention treatment with low-dose aspirin (LDA) 75-100 mg daily is recommended in asymptomatic patients with a high-aPL risk profile.
- In patients with low-risk aPL profile, LDA as primary thromboprophylaxis may be considered.
- Other non-anticoagulant drugs have been proposed in aPL-positive subjects for primary thromboprophylaxis.
- The 16th International Congress on Antiphospholipid Antibodies and EULAR recommendations have suggested the use of statins in patients with additional cardiovascular risk factors, although their role remains unclear.
- **Management of Venous Thrombosis in Antiphospholipid Syndrome**
    - The standard treatment for patients with venous thrombosis in APS is initial anticoagulation with unfractionated heparin or low molecular weight heparin transitioned to a VKA, commonly warfarin, which is continued indefinitely.

- A target INR of 2.5 (2.0-3.0) is recommended.
- The type of venous thromboembolism (VTE), whether provoked or unprovoked, and the aPL profile are important elements to consider for the duration of anticoagulant treatment.
- In patients with provoked first venous thrombosis, the therapy should be continued as for patients without APS, according to international guidelines.
- In this subgroup of patients, prolonged treatment should be considered only in high-risk aPL profile patients or in the presence of additional risk factors for recurrence (VTE).
- Long-term anticoagulation in first-provoked VTE patients remains unclear.

- **Management of Arterial Thrombosis in Antiphospholipid Syndrome**
  - The 2011 report by a task force of the 13th International Congress on APLA suggested that patients with definite APS and arterial thrombosis should be treated with warfarin at an INR >3.0 or combined antiplatelet and anticoagulant (INR 2.0-3.0) therapy.
  - High-intensity anticoagulation should be used very judiciously, if at all in APS patients, and reserved for those with a high-risk APLA profile and additional cardiovascular risk factors in whom the potential benefit outweighs the risk of bleeding.
- **Use of Direct Oral Anticoagulants (DOACs)**
  - The use of DOACs should be limited to use in patients who are refractory or intolerant to VKA or low molecular weight heparin.
  - DOACs could be considered in patients with a clear contraindication to VKA (intolerance or allergy) or those not able to achieve a target INR despite good adherence to VKA.
  - The current international guidelines are not in favor of recommending DOACs for secondary prevention of thrombotic APS, especially in the context of arterial thrombosis and triple-positive aPL patients.
- **Management of Refractory Thrombotic Antiphospholipid Syndrome**
  - It is suggested to verify that the patient is adequately anticoagulated with a target INR in the therapeutic range, as well as a therapeutic factor X level and to consider higher intensity anticoagulation.

- For still refractory patients, adjunctive non-anticoagulant therapies such as statins, hydroxychloroquine, and rituximab may be an option, but no well-designed clinical studies support their use.

- **Management of Catastrophic Antiphospholipid Syndrome (CAPS)**
  - Early diagnosis of CAPS is essential due to its rapid, progressive, and fatal nature.
  - The optimal treatment of CAPS is unknown and prospective trials for treatments of CAPS have not been conducted.
  - Based on observational data and expert opinion, anticoagulation with heparin and high-dose steroids (methylprednisolone 1000 mg daily for 3 days or longer) are the mainstay of therapy.
  - Additional recommendations include searching for and treating any precipitating factor such as infection and debriding/amputating any necrotic tissues to limit inflammation.
  - Plasma exchange has been shown to improve mortality in the CAPS registry.
  - Intravenous immunoglobulin alone does not appear to be beneficial in patients with CAPS.
  - Eculizumab has been reported to successfully treat patients with refractory CAPS.
  - The pathogenesis of APS supports the use of biologic agents as a targeted treatment approach and new drugs are investigated for patients with refractory APS or CAPS.
  - New evidence underlines the potential efficacy of biologics such as anti-CD38 monoclonal antibody (Daratumumab), BAFF/Blys inhibitor (Belimumab), BTK inhibitor (Zanubrutinib), Anti-TNF-a monoclonal antibody (adalimumab, certolizumab).

- **Management of Obstetric Antiphospholipid Syndrome**
  - The most common approach for management is the combination of heparin (unfractionated or low molecular weight; prophylactic or intermediate dose) and low-dose aspirin (75-100 mg) daily for women who fulfill the clinical and serologic criteria for obstetric APS.
  - In women with APS and prior thrombosis, aspirin, and therapeutic dose LMWH should be employed.
  - Women who are anticoagulated with VKA should be switched to LMWH since warfarin has been linked to fetal malformations.

1.2.2 Recommendations of the Spanish Rheumatology Society for Primary Antiphospholipid Syndrome. Part I: Diagnosis, Evaluation and Treatment [2020]

The Spanish Rheumatology Society has issued a two-part guideline on the management of antiphospholipid syndrome. The part detailed below tackles the diagnosis, evaluation, and treatment of APS; the following levels of evidence/grades of recommendation were opted[20]:

Table 4. Spanish Rheumatology Society Levels of Evidence/Grades of Recommendation

Levels of Evidence	
1++	High-quality meta-analyses, systematic reviews of clinical trials, or high-quality clinical trials with very low risk of bias.
1+	Well-conducted meta-analyses, systematic reviews of clinical trials, or well-conducted clinical trials with very low risk of bias.
1-	Meta-analyses, systematic reviews of clinical trials or clinical trials with high risk of bias.
2++	High-quality systematic reviews of cohort or case-control studies. Cohort or case-control studies with very low risk of bias and high probability of establishing a causal relationship.
2+	Well-conducted cohort or case-control studies with low risk of bias and moderate probability of establishing a causal relationship.
2-	Cohort or case-control studies with high risk of bias and significant risk that the relationship is not causal.
3	Non-analytical studies, such as case reports and case series.
4	Expert opinion.
Grades of Recommendation	
A	At least one meta-analysis, systematic review or clinical trial classified as 1++ and directly applicable to the guideline's target population; or a volume or scientific evidence composed of studies classified as 1+ and with high concordance between them.
B	A volume of scientific evidence composed of studies classified as 2++, directly applicable to the guideline's target population and demonstrating high concordance between them; or scientific evidence extrapolated from studies classified as 1++ or 1+.
C	A volume of scientific evidence composed of studies classified as 2+ directly applicable to the guideline's target population and that

	demonstrate high consistency among them; or scientific evidence extrapolated from studies classified as 2+.
D	Level 3 or 4 scientific evidence; or scientific evidence extrapolated from studies classified as 2+.
√	Good clinical practice: Recommended practice based on clinical experience and the consensus of the writing team.
Studies classified as 1- and 2- should not be used for the elaboration of recommendations because of their high possibility of bias.	

Diagnosis and Evaluation

- In patients with APS the simultaneous detection of the three antiphospholipid antibodies included in the classification criteria is recommended (LA, aCL and aβ2GPI) to establish the risk of thrombosis or obstetric complications. (Grade C)
- There is a higher risk of clinical manifestations of APS when lupus anticoagulant or more than one antiphospholipid antibody is detected (double and most particularly triple positivity) in the same patient. (Grade B)
- In habitual clinical practice, in the general population with the suspicion of APS or in patients already diagnosed with the disease, the detection of antiphospholipid antibodies not included in the classification criteria is not recommended. (Grade D)
- The detection of antiphospholipid antibodies is not recommended if the patient is anticoagulated and diagnosed. (√)
- In patients with induced thrombosis, a low profile of thrombotic risk and without conventional cardiovascular risk factors, the repetition of antibody determination may be considered to evaluate the need for indefinite anticoagulation. (√)
- A repeat of the determination of the antiphospholipid antibodies included in the classification criteria is recommended (except for lupus anticoagulant), at least at 12 weeks. (√)

Primary Thromboprophylaxis

Table 5 details the clinical and serological risk factors for the development of clinical manifestations in patients who are carriers of antiphospholipid antibodies:

Table 5. Risk Factors for the Development of Clinical Manifestations in Patients Who Are Carriers of Antiphospholipid Antibodies

Clinical and Serological Risk Factors for the Development of Clinical Manifestations in Patients Who Are Carriers of Antiphospholipid Antibodies
Clinical Risk Factors
Classical cardiovascular risk factors
Smoking
AHT
Dyslipidemia
Associated autoimmune disease
SLE
Manifestations associated with APS
Thrombocytopenia
Serological Risk Factors
High risk profile
Positive LA
Triple positivity (LA+ aCL + aβ2GPI)
Persistent positive aCL at medium-high titer
Low risk profile
Intermittently positive aCL or aβ2GPI at medium-low titers

- In patients who are antiphospholipid antibody carriers, without clinical signs associated with APS, specific prophylactic treatment is recommended with low molecular weight heparin in situations of high thrombotic risk (prolonged immobilization, recent surgery, puerperium, or ovary stimulation, etc.) (Grade C)
- In patients with a low risk profile prophylactic treatment is only recommended when associated cardiovascular risk factors are present; low doses of acetylsalicylic acid should be used, while treating or correcting the cardiovascular risk factors. (Grade C)
- In patients who are carriers of antiphospholipid antibodies and associated thrombocytopenia, prophylactic treatment with low doses of acetylsalicylic acid is recommended. (Grade C)

- In patients with a medium/high risk, prophylactic treatment during an indefinite time is recommended with low doses of acetylsalicylic acid. (Grade C)
- In patients who are carriers of antiphospholipid antibodies and without clinical signs associated with APS and who wish to conceive, it is recommended to evaluate prophylactic treatment with low doses of acetylsalicylic acid, according to their risk profile. (Grade C)

Treatment of Primary Antiphospholipid Syndrome – Secondary Thromboprophylaxis

- Patients with antiphospholipid antibodies and with a first episode of venous thrombosis should be treated with unfractionated heparin or low molecular weight heparin followed by vitamin K antagonists. (Grade D)
- In the secondary prevention of venous thrombosis, anticoagulation in a therapeutic range for an INR of 2–3 is recommended. (Grade D)
- In the secondary prevention of venous thrombosis, anticoagulation during an indefinite time is recommended. (Grade D)
- Patients with primary APS and previous arterial thrombotic events should be treated with standard anticoagulation (INR 2–3) to prevent the recurrence of arterial thrombosis. (Grade B)
- In thrombotic APS that is refractory to conventional treatment it is recommended to associate antiaggregant doses of acetylsalicylic acid, hydroxychloroquine, or statins to the conventional therapy. (Grade D)
- When there is a formal contraindication against oral anticoagulants, low molecular weight heparin is recommended as the alternative therapy. (Grade D)
- If recurring arterial thromboses occur while receiving standard anticoagulation, the treatment may be optimized by adding anti-aggregation or increasing the anticoagulation dose (INR 3–4). (Grade D)
- In refractory thrombotic APS, it is recommended that cardiovascular risk factors be strictly controlled, while avoiding situations that predispose to new thrombotic events. (Grade D)
- DOACs may be a good alternative in patients with venous thrombosis who are allergic to dicumarinics and/or who have difficulty in maintaining their INR within a therapeutic range with vitamin K antagonists (√)

Figure 1 describes the Spanish Rheumatology Society comprehensive approach for the management of patients with APS:

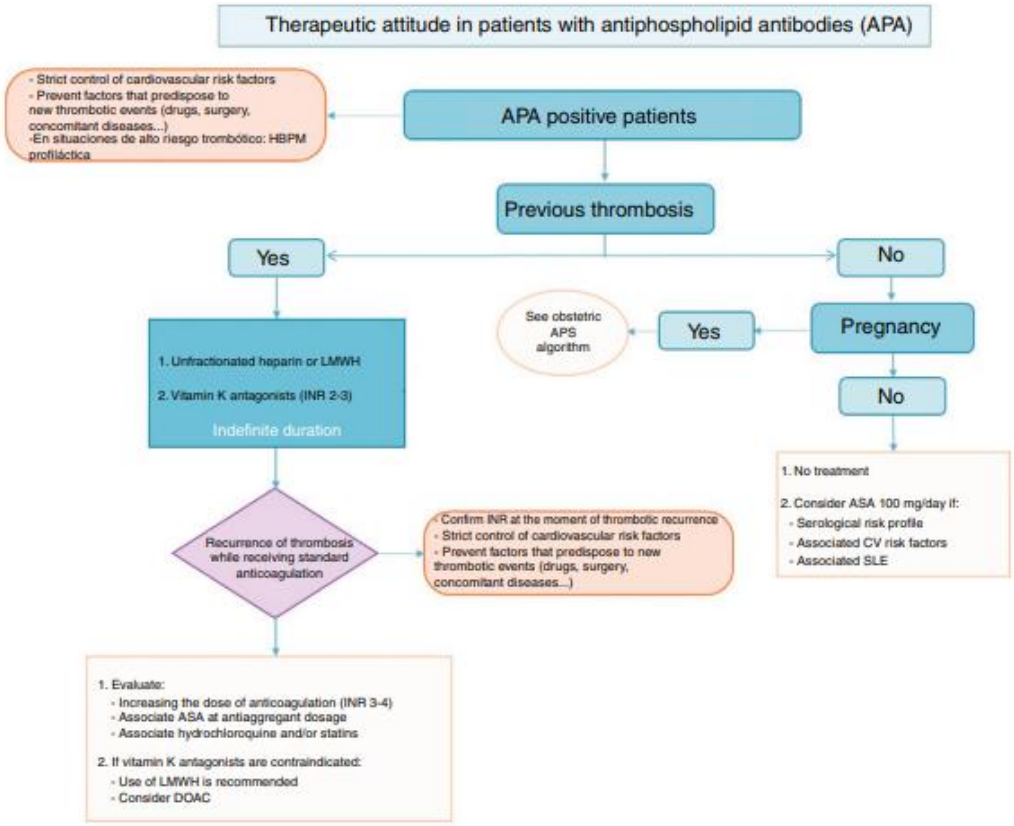

Figure 1. *Therapeutic Approach for the Management of Antiphospholipid Syndrome. Retrieved from the Spanish Rheumatology Society 2020 Guideline.*

1.2.3 Recommendations of the Spanish Rheumatology Society for Primary Antiphospholipid Syndrome. Part II: Obstetric Antiphospholipid Syndrome and Special Situations [2020]

The Spanish Rheumatology Society has issued a two-part guideline on the management of antiphospholipid syndrome. The part detailed below tackles Obstetric APS and Special Situations; the recommendations are detailed below[15]:

Treatment of Obstetric APS

- The use of acetylsalicylic acid at a dose of 100 mg/day prior to conception is suggested for all patients with obstetric APS who wish to become pregnant, maintaining this dose throughout pregnancy. (Grade C)
- In patients with obstetric APS, as a secondary prophylactic treatment, it is recommended to add low molecular weight heparin to acetylsalicylic acid when pregnancy is confirmed, maintaining this throughout gestation. The dose of heparin should be individualized according to the risk of each patient. (Grade C)

- In refractory obstetric APS, conventional treatment consists of hydrochloroquine before pregnancy, maintained throughout gestation, alone or combined with prednisone or an equivalent from the start of pregnancy. (≤10 mg/day during the first three months) (Grade D)
- In patients who develop complications associated with placental insufficiency (pre-eclampsia or delayed intrauterine growth) despite the conventional treatment, the recommendation is to add pravastatin (20 mg/day) from the start of the complication. (Grade C)
- It is not recommended to use intravenous immunoglobulin and plasmapheresis at first, although they may be considered upon lack of response to other treatment options. (√)
- In previously anticoagulated patients with thrombotic APS, vitamin K antagonists should be re-introduced immediately after birth. (√)
- In women with obstetric APS, it is recommended that after birth thromboprophylaxis should be administered using low molecular weight heparin at a prophylactic dose during at least 6 weeks. (√)
- Table 6 details the prophylactic doses of low molecular weight heparin:

Table 6. Prophylactic Doses of Low Molecular Weight Heparin

Weight (kg)	Enoxaparin (mg/day)	Bemiparin (U/day)	Tinzaparin (U/day)
< 50	20	2500	3500
50-90	40	3500	4500
91-130	60		7000
131-170	80		9000
> 170	0.6 mg/kg/day		75 U/kg/day
High prophylaxis	40 mg/12 h		4500 U/12 h

- In patients with thrombotic APS who for any reason are not receiving long-term anticoagulation, thromboprophylaxis with low molecular weight heparin is recommended at intermediate doses, individualizing the dose according to risk during at least 6–12 weeks after giving birth. (Grade D)
- Table 7 details the intermediate doses of low molecular weight heparin:

Table 7. Intermediate Doses of Low Molecular Weight Heparin

Drug	Dose[a]
Bemiparin	5000 U/day
Enoxaparin	1 mg/kg/day
Tinzaparin	8000 UI/day

[a] Estimated and not specified in the technical data sheet.

- In patients with APS who are going to undergo assisted reproduction techniques, individualization according to risk is recommended, associating low molecular weight heparin as the anticoagulant of choice at prophylactic or therapeutic doses. (Grade D)
- Patients with APS who are taking oral anticoagulation should switch to a therapeutic dose of low molecular weight heparin before ovary stimulation and continue the regimen during the pregnancy. (Grade D)
- Patients with APS without chronic anticoagulation are advised to receive treatment with acetylsalicylic acid at an antiaggregant dose and low molecular weight heparin, at an individualized dose, from the start of ovary stimulation to be maintained throughout gestation. (Grade D)
- In women with aPL and triple positivity or high levels of aPL, due to the risk of thrombosis as well as the appearance of obstetric complications, the use of low molecular weight heparin plus acetylsalicylic acid is recommended. (Grade D)
- In situations with a high risk of venous thrombosis, subcutaneous low molecular weight is recommended to be used. (√)

Special Situations

- Rigorous control of anticoagulation is recommended before and after the transplant of a solid organ, especially in the case of kidney transplant. (√)
- Routine screening is recommended for aPL before the transplant of a solid organ in all patients with a history of thromboembolic events. (√)
- Thromboprophylaxis with low molecular weight heparin is recommended in patients with a high-risk serological profile and neoplasia, especially in situations with increased thromboembolic risk (surgery, catheter implantation or the start of chemotherapy) (√)
- Anticoagulation is recommended to be suspended in case of moderate to high-risk invasive procedures or a high risk of hemorrhage, bridging therapy is to be performed. (Grade D)

- It is recommended to use low molecular weight heparin as bridging therapy, at an individualized dose adjusted for weight and kidney function, suspending it at least 24 hours prior to the invasive procedure. (Grade D)
- In pregnant patients with APS who use low molecular weight heparin at a therapeutic or intermediate dose, the recommendation is for the suspension to take place at least 24 hours before giving birth or other procedures.

  During birth, it is not necessary to suspend the treatment in patients who are using acetylsalicylic acid at a dose of 100 mg. (Grade D)
- In a patient with catastrophic APS, the initial treatment must include what is known at triple therapy, which includes: anticoagulation, preferably with intravenous unfractionated heparin, associated with high doses of glucocorticoids, plasmapheresis and/or intravenous immunoglobulin. (Grade D)
- In cases that are refractory to triple therapy, adding rituximab or eculizumab may be considered. (Grade D)
- The algorithm in figure 2 describes the approach to the management of Obstetric APS:

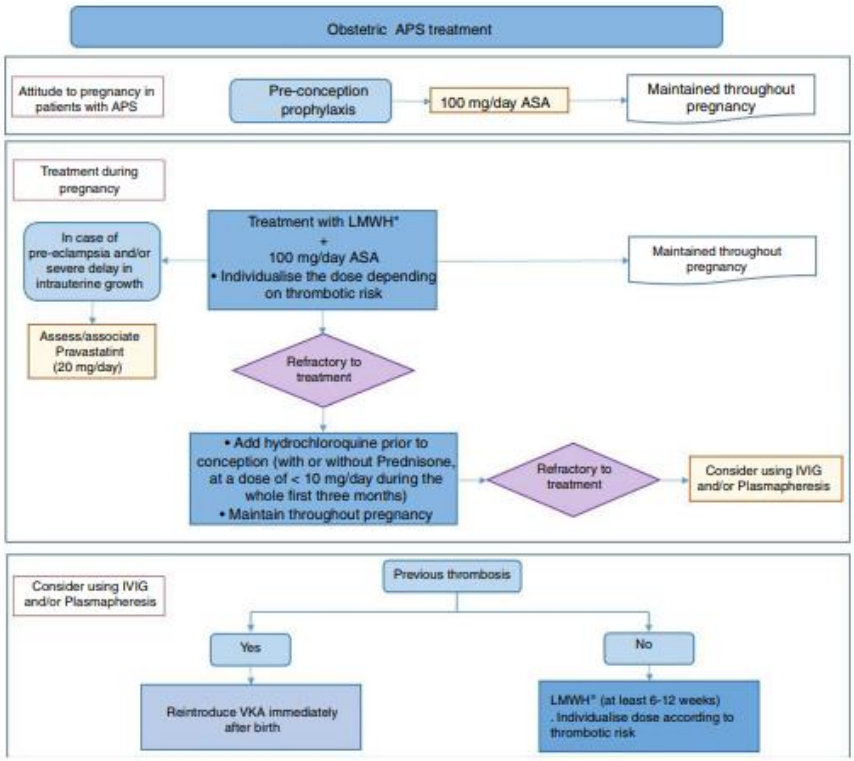

Figure 2. *Treatment Algorithm for Obstetric APS. Retrieved from the Spanish Rheumatology Society 2020 Guideline.*

- The algorithm in figure 3 describes the approach to the management of Catastrophic APS (CAPS):

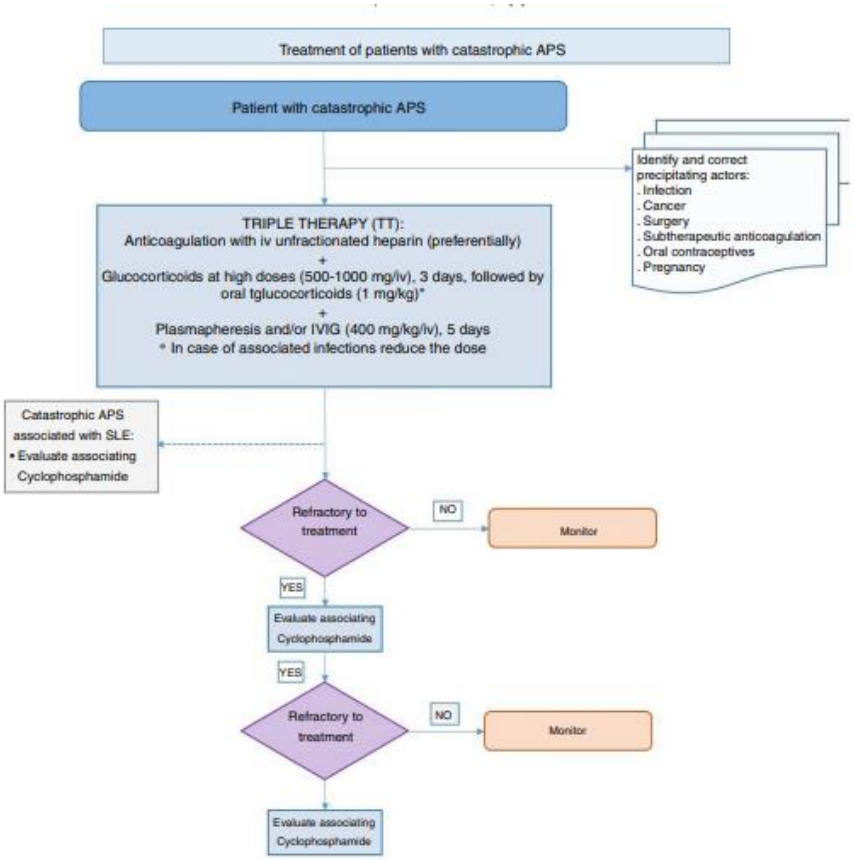

Figure 3. *Treatment Algorithm for Catastrophic APS. Retrieved from the Spanish Rheumatology Society 2020 Guideline.*

1.2.4 EULAR Recommendations for the Management of Antiphospholipid Syndrome in Adults [2019]

The European League Against Rheumatism (EULAR) issued guidelines for the management of antiphospholipid syndrome; the following levels of evidence/grades of recommendation were opted:

"For recommendations with B GoR, we used the statement 'is recommended'. For C and D grades, we mostly used the terms 'may be considered' or 'could be considered', with some exceptions according to experts' judgement about the importance of the intervention. Recommendations that are phrased as 'is recommended' are those that the task force meant, based on the evidence and their experience, should be followed in almost all cases."

The recommendations are detailed below[18]:

General Recommendations

- Risk stratification in aPL-positive individuals should include determination of the presence of a high-risk aPL profile (defined as any of the following: multiple aPL positivity, lupus anticoagulant or persistently high aPL titers), history of thrombotic and/or obstetric APS, coexistence of other systemic autoimmune diseases such as systemic lupus erythematous (SLE), and the presence of traditional cardiovascular risk factors.
- General measures for aPL-positive individuals should include screening for and strict control of cardiovascular risk factors (smoking cessation; management of hypertension, dyslipidemia, and diabetes; and regular physical activity) in all individuals and particularly those with a high-risk aPL profile, screening for and management of venous thrombosis risk factors, and use of LMWH in high-risk situations such as surgery, hospitalization, prolonged immobilization, and the puerperium.
- Patient education and counselling on treatment adherence, INR monitoring in patients treated with VKA, use of perioperative bridging therapy with LMWH for patients on oral anticoagulants, oral contraceptive use, pregnancy and postpartum period, postmenopausal hormone therapy, and lifestyle recommendations (diet, exercise) are important in the management of APS.

Pharmacological Management

Primary Thromboprophylaxis in aPL-Positive Subjects:

1. In asymptomatic aPL carriers (not fulfilling any vascular or obstetric APS classification criteria) with a high-risk aPL profile with or without traditional risk factors, prophylactic treatment with LDA (75–100 mg daily) is recommended (2a/B).
2. In patients with SLE and no history of thrombosis or pregnancy complications:
    a. With high-risk aPL profile, prophylactic treatment with low-dose aspirin (LDA) is recommended (2a/B).
    b. With low-risk aPL profile, prophylactic treatment with LDA may be considered (2b/C).
3. In non-pregnant women with a history of obstetric APS only (with or without SLE), prophylactic treatment with LDA after adequate risk/benefit evaluation is recommended (2b/B).

Secondary Thromboprophylaxis in APS

4. In patients with definite APS and first venous thrombosis:
    a. Treatment with VKA with a target INR 2–3 is recommended (1b/B).

b. Rivaroxaban should not be used in patients with triple aPL positivity due to the high risk of recurrent events (1b/B).

   DOACs could be considered in patients not able to achieve a target INR despite good adherence to VKA or those with contraindications to VKA (eg, allergy or intolerance to VKA) (5/D).

c. In patients with unprovoked first venous thrombosis, anticoagulation should be continued long term (2b/B).

d. In patients with provoked first venous thrombosis, therapy should be continued for a duration recommended for patients without APS according to international guidelines (5/D).

   Longer anticoagulation could be considered in patients with high-risk aPL profile in repeated measurements or other risk factors for recurrence (5/D).

5. In patients with definite APS and recurrent venous thrombosis despite treatment with VKA with target INR of 2–3:

   a. Investigation of, and education on, adherence to VKA treatment, along with frequent INR testing, should be considered (5/D).

   b. If the target INR of 2–3 had been achieved, the addition of LDA, the increase of INR target to 3–4 or the change to LMWH may be considered (4–5/D).

6. In patients with definite APS and first arterial thrombosis:

   a. Treatment with VKA is recommended over treatment with LDA only (2b/C).

   b. Treatment with VKA with INR 2–3 or INR 3–4 is recommended, considering the individual's risk of bleeding and recurrent thrombosis (1b/B).

      Treatment with VKA with INR 2–3 plus LDA may also be considered (4/C).

   c. Rivaroxaban should not be used in patients with triple aPL positivity and arterial events (1b/B).

      Based on the current evidence, it is not recommended to use DOACs in patients with definite APS and arterial events due to the high risk of recurrent thrombosis (5/D).

7. In patients with recurrent arterial thrombosis despite adequate treatment with VKA, after evaluating for other potential causes, an increase of INR target to 3–4, addition of LDA or switch to LMWH can be considered (4–5/D).

Obstetric APS

8. In women with a high-risk aPL profile but no history of thrombosis or pregnancy complications (with or without SLE), treatment with LDA (75–100 mg daily) during pregnancy should be considered (5/D).
9. In women with a history of obstetric APS only (no prior thrombotic events), with or without SLE:
    a. With a history of ≥ 3 recurrent spontaneous miscarriages <10th week of gestation and in those with a history of fetal loss (≥10th week of gestation), combination treatment with LDA and heparin at prophylactic dosage during pregnancy is recommended (2b/B).
    b. With a history of delivery < 34 weeks of gestation due to eclampsia or severe pre-eclampsia or due to recognized features of placental insufficiency, treatment with LDA or LDA and heparin at prophylactic dosage is recommended considering the individual's risk profile (2b/B).
    c. With clinical 'non-criteria' obstetric APS such as the presence of two recurrent spontaneous miscarriages <10th week of gestation, or delivery ≥ 34 weeks of gestation due to severe pre-eclampsia or eclampsia, treatment with LDA alone or in combination with heparin might be considered based on the individual's risk profile (4/D).
    d. With obstetric APS treated with prophylactic dose heparin during pregnancy, continuation of heparin at prophylactic dose for 6 weeks after delivery should be considered to reduce the risk of maternal thrombosis (4/C).
10. In women with 'criteria' obstetric APS with recurrent pregnancy complications despite combination treatment with LDA and heparin at prophylactic dosage, increasing heparin dose to therapeutic dose (5/D) or addition of HCQ (4/D) or low-dose prednisolone in the first trimester (4/D) may be considered.

    Use of intravenous immunoglobulin might be considered in highly selected cases (5/D).
11. In women with a history of thrombotic APS, combination treatment of LDA and heparin at therapeutic dosage during pregnancy is recommended (4/C).

Catastrophic APS (CAPS)

12. Prompt treatment of infections by early use of anti-infective medications in all aPL-positive individuals and minimization of interruptions in anticoagulation or low INR level in patients with thrombotic APS are recommended to help prevent the development of CAPS (4/D).

13. For first-line treatment of patients with CAPS, combination therapy with glucocorticoids, heparin and plasma exchange or intravenous immunoglobulins is recommended over single agents or other combinations of therapies.

    Additionally, any triggering factor (e.g., infections, gangrene, or malignancy) should be treated accordingly (5/D).

14. In patients with refractory CAPS, B cell depletion (e.g., rituximab) or complement inhibition (e.g., eculizumab) therapies may be considered (4/D).

1.3 North American Guidelines

1.3.1 An Update on the Management of Antiphospholipid Syndrome [2020]

The following review does not provide a specified grade of evidence or level of recommendation.

Rodziewics and D'Cruz issued an updated review on the management of antiphospholipid syndrome with the aim to summarize the current recommended and emerging treatment for thrombotic, obstetric and noncriteria manifestations of APS; the recommendations are detailed below[2]:

Primary Antithrombotic Prophylaxis

Antiplatelet Agents

- Low-dose aspirin (LDA) is used in the general population for the secondary prevention of arterial thrombosis.
- The role of aspirin for primary prevention in asymptomatic patients with persistent aPL is less clear.
- Recently published European League Against Rheumatism (EULAR) guidance recommends prophylactic LDA in asymptomatic aPL carriers with a high-risk profile; those with persistently high aPL titers, 'double' or 'triple positivity' (a combination of LA and one of aCL or β2GPI, or all three).

Secondary Antithrombotic Prophylaxis

Anticoagulant Treatment

- **Vitamin K Antagonists**
    - The gold standard treatment for APS patients who have suffered thrombosis is treatment with an oral vitamin K antagonist (VKA) to achieve a target international normalized ratio (INR) of 2.0–3.0.

- Recurrence rates without anticoagulation are high; therefore, it is generally accepted that anticoagulation should be continued lifelong.
- The 13th International Congress on Antiphospholipid Antibodies task force, as well as current EULAR guidance recommend that patients with definite APS and a first venous event receive lifelong oral anticoagulation to a target INR of 2.0–3.0.
- EULAR also tackles patients with unprovoked first venous thrombosis and recommends that anticoagulation in this group be continued for a duration for patients without APS, unless a high-risk aPL profile or other risk factors for recurrence are present.
- Lifelong high- or standard-intensity anticoagulation plus an antiplatelet drug (APD) are advised for those with arterial thrombosis or recurrent venous thromboembolism (VTE) on standard intensity treatment.

- **Direct Oral Anticoagulants**
  - Direct oral anticoagulants (DOACs) such as rivaroxaban, apixaban and dabigatran are licensed for use in the general population for the secondary prevention of VTE and the prevention of arterial thrombosis in nonvalvular atrial fibrillation.
  - DOACs are favorable alternative agents to VKAs because they do not require blood monitoring, have fewer dietary and drug interactions and have a rapid and predictable onset of action which precludes the need for heparinization in the acute setting.
  - Of note, several commonly prescribed drugs can potentiate or inhibit DOAC activity and include diltiazem, ketoconazole and carbamazepine.
  - DOACs might be considered for the prevention of VTE in patients with low-risk aPL profiles who are intolerant of, or poorly compliant with, VKAs.
  - The European Medicines Agency recently issued a special warning that DOACs are not recommended for APS patients with a history of thrombosis, especially in those that are triple positive.

Pregnancy Morbidity

- Pre-pregnancy counselling in patients with known APS is vital to ensure conventional cardiovascular and APS-specific risk factors can be identified and managed.
- Previous pregnancy outcomes and triple-antibody positivity are the best predictors of adverse pregnancy outcomes in APS, but other factors include SLE-APS and previous history of thrombosis.

- Of the three diagnostic aPLs, LA is the most predictive of adverse pregnancy outcome.
- VKAs are teratogenic; therefore, in APS patients with prior thrombosis or pregnancy morbidity, therapeutic dose low-molecular-weight heparin (LMWH) and LDA is accepted treatment.
- For those patients with purely obstetric APS (OAPS) and no prior thrombosis, prophylactic dose LMWH and LDA until 6 weeks postpartum is recommended.
- In addition to routine fetal monitoring scans, monthly ultrasound scans with power Doppler imaging are recommended during the third trimester of pregnancy to assess for signs of placental insufficiency.

Obstetric APS (OAPS) and Thrombosis

- There is no real consensus on whether patients with OAPS should continue long-term antithrombotic or anticoagulant treatment.
- These patients are at increased risk of thrombotic manifestations compared to the general population.
- EULAR recommends that individuals with a history of OAPS be offered prophylactic dose LDA and pending further studies, it seems appropriate to consider LDA ± anticoagulant treatment in patients with OAPS and other risk factors for thrombosis.

Immune-Modulating Therapies in Thrombotic and Pure Obstetric APS

- **Hydroxychloroquine**
    - In SLE-APS, and also those without aPL, HCQ use is associated with a reduction in the rates of arterial and venous thromboses. It has been suggested to also have a similar effect in PAPS.
    - A recent study titled HIBISCUS plans to examine the effect of HCQ on secondary thrombosis and APS related pregnancy morbidity in PAPS. Pending these results and given the long-term relative safety of HCQ, it seems reasonable to consider the addition of HCQ to VKA in the treatment of PAPS patients with previous arterial or recurrent thrombosis especially in high-risk patients[21].
    - The HYPATIA trial, is a currently ongoing multicenter trial examining the use of HCQ versus placebo in aPL-positive women planning to conceive. Pending the results, it seems reasonable to consider the addition of HCQ to those patients with obstetric PAPS refractory to

conventional treatment and before any consideration of low-dose prednisolone given its more favorable safety profile in pregnancy[22].

- **Rituximab:**
    - Rituximab appears to be a promising treatment for SLE-APS patients with thrombotic disease refractory to conventional anticoagulant treatment, particularly if they have evidence of active SLE; however, further studies are needed for confirmation.

Proposed Future Treatments

- Potential future treatments in the pipeline include Eculizumab (Humanized monoclonal antibody against the C5 complement component), Sirolimus (Inhibits neointimal proliferation after endovascular injury through inhibition of mammalian target of rapamycin complex (mTORC) signaling), Defibrotide (A mixture of single (90%) and double-stranded (10%) phosphodiester oligo-nucleotides which has antithrombotic, anti-inflammatory and anti-ischemic properties), and Statins; specifically Fluvastatin and Pravastatin.
- It seems appropriate to initiate statins in APS patients with hypercholesterolemia, other cardiovascular risk factors or thrombotic disease resistant to conventional anticoagulation.

1.3.2 American College of Obstetricians and Gynecologists (ACOG) Practice Bulletin 132: Antiphospholipid Syndrome Clinical Management Guidelines for Obstetrician–Gynecologists [2012]

The American College of Obstetricians and Gynecologists has issued clinical practice guidelines for the management of APS; the following grades of recommendation/levels of evidence were opted[23]:

Table 8. ACOG Grades of Evidence/Levels of Recommendation

ACOG Grades of Evidence/Levels of Recommendation
I Evidence obtained from at least one properly designed randomized controlled trial.
II-1 Evidence obtained from well-designed controlled trials without randomization.
II-2 Evidence obtained from well-designed cohort or case–control analytic studies, preferably from more than one center or research group.
II-3 Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments also could be regarded as this type of evidence.

III Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.
Based on the highest level of evidence found in the data, recommendations are provided and graded according to the following categories:
Level A—Recommendations are based on good and consistent scientific evidence. Level B—Recommendations are based on limited or consistent scientific evidence. Level C—Recommendations are based primarily on consensus and expert opinion.

The laboratory criteria for the diagnosis of APS are:

1. Lupus anticoagulant present in plasma, on two or more occasions at least 12 weeks apart. It is interpreted as either present or absent. Testing for lupus anticoagulant is ideally performed before the patient is treated with anticoagulants, **or**
2. Anticardiolipin antibody of immunoglobulin G (IgG) and/or immunoglobulin M isotype in serum or plasma, present in medium or high titer (ie, greater than 40 GPL or MPL, or greater than the 99th percentile), on two or more occasions, at least 12 weeks apart, **or**
3. Anti-β2-glycoprotein I of immunoglobulin G (IgG) and/or immunoglobulin M isotype in serum or plasma (in titer greater than 99th percentile for a normal population as defined by the laboratory performing the test), present on two or more occasions, at least 12 weeks apart.

The clinical criteria for the diagnosis of APS are:

1. Vascular thrombosis

   One or more clinical episodes of arterial, venous, or small vessel thrombosis, in any tissue or organ, **or**
2. Pregnancy morbidity
   a. One or more unexplained deaths of a morphologically normal fetus at or beyond the 10th week of gestation, with normal fetal morphology documented by ultrasound or by direct examination of the fetus, **or**
   b. One or more premature births of a morphologically normal neonate before the 34th week of gestation because of eclampsia or severe preeclampsia, or features consistent with placental insufficiency, **or**
   c. Three or more unexplained consecutive spontaneous pregnancy losses before the 10th week of pregnancy, with maternal anatomic or hormonal abnormalities and paternal and maternal chromosomal causes excluded.

General recommendations

- The goals of treatment for APS during pregnancy are to improve maternal and fetal–neonatal outcome.
- Obstetric indications for antiphospholipid antibody testing should be limited to a history of one fetal loss or three or more recurrent embryonic or fetal losses. **(Level B)**
- Testing for antiphospholipid antibodies should be performed in women with a prior unexplained venous thromboembolism, a new venous thromboembolism during pregnancy, or in those with a history of venous thromboembolism but not tested previously. **(Level B)**
- In women with APS and a history of stillbirth or recurrent fetal loss but no prior thrombotic history, prophylactic doses of heparin and low-dose aspirin during pregnancy and 6 weeks of postpartum should be considered. **(Level B)**
- For women with APS who have had a thrombotic event, most experts recommend prophylactic anticoagulation with heparin throughout pregnancy and 6 weeks postpartum. **(Level C)**
- For women with APS who have not had a thrombotic event, expert consensus suggests that clinical surveillance or prophylactic heparin use antepartum in addition to 6 weeks of postpartum anticoagulation may be warranted. **(Level C)**
- For long-term management postpartum, patients with APS should be referred to a physician with expertise in treatment of the syndrome, such as an internist, hematologist, or rheumatologist. **(Level C)**
- Women with APS should not use estrogen-containing contraceptives. **(Level C)**

1.4 International Guidelines

1.4.1 Management of Women with Antiphospholipid Antibodies or Antiphospholipid Syndrome During Pregnancy [2021]

The following review article does not provide a specified grade of evidence or level of recommendation.

The recommendations of the following review, published by Seoul National University in the Journal of Korean Medical Science, are mainly based on the report of the International Congress on aPL Task Force of the American College of Chest Physicians (ACCP) Evidence-Based Clinical Practice Guidelines and The American

College of Obstetricians and Gynecologists practice bulletin (detailed in section 1.3.2 above); the recommendations are detailed below[17]:

Risk Factors for Thrombosis in Pregnant Women

- The risk of thrombosis increases during pregnancy due to profound hormonal changes and decreased mobility during the period of pregnancy.
- The risk of thrombosis depends on the stages of pregnancy and delivery methods, being higher during the third than during the first trimester and even higher during the early postpartum period.
- Delivery by cesarean section is associated with a higher risk of thrombosis than vaginal delivery.
- Other major risk factors include personal history of thrombosis, thrombophilia, systemic lupus erythematosus, APS, heart disease, obesity, diabetes, smoking, sickle cell disease, immobility during the antepartum period, postpartum hemorrhage ≥ 1,000 mL with surgery, preeclampsia with fetal growth restriction, blood transfusion, and postpartum infection.

Management

Table 9 summarizes the recommendations for the treatment of aPL-positive women and women with APS:

Table 9. Recommendations for the Treatment of aPL-Positive Women and Women with APS

Variables	aPL-positive women	Obstetric APS[c]	Vascular APS[d]
Primary prophylaxis for thrombosis	· Not recommended · LDA for patients with other cardiovascular risk factors, systemic lupus erythematosus, or high-risk aPL profile[a] · LMWH in high-risk situations[b]	· Generally not recommended	· Warfarin to target INR 2.0–3.0 for secondary prophylaxis for thrombosis
Antepartum	· Options include - No treatment, LDA alone and LDA plus LMWH · LDA is generally recommended, especially in patients at high risk of preeclampsia	· Preconceptional LDA · LDA plus a prophylactic dose of LMWH after confirmation of intrauterine pregnancy · LDA alone is acceptable in patients with a history of premature birth due to uteroplacental insufficiency and no history of fetal death	· LDA plus a therapeutic dose of LMWH when pregnancy is confirmed · Frequent pregnancy test and switch to heparin from warfarin
Postpartum	· LDA for 6 weeks after vaginal delivery and a prophylactic dose of LMWH and LDA for 6 weeks after cesarean delivery in selected patients	· LDA and a prophylactic dose of LMWH for 6 weeks · LDA alone for 6 weeks in women with preterm vaginal deliveries due to placental insufficiency	· Restart warfarin 4–6 hr after vaginal delivery and 6–12 hr after cesarean delivery

aPL = anti-phospholipid antibody, APS = anti-phospholipid syndrome, LDA = low dose aspirin, LMWH = low molecular weight heparin, INR = international normalized ratio, aCL = anti-cardiolipin.
[a]Positive lupus anticoagulant (LA), triple positivity (LA, aCL antibody, anti-β2 glycoprotein I antibody), and isolated persistently positive aCL at medium to high titers; [b]Surgery, prolonged immobilization, and puerperium; [c]Anti-phospholipid syndrome with obstetric complications only and without vascular complications; [d]APS with history of thromboembolism.

Table 10 details the dosing regimens of anticoagulation regimens:

Table 10. Dosages of Anticoagulation Regimens

Anticoagulation regimen	Anticoagulation dosage
Prophylactic LMWH	- Enoxaparin, 40 mg SC once daily - Dalteparin, 5,000 units SC once daily - Tinzaparin, 4,500 units SC once daily - Nadroparin, 2,850 units SC once daily
Therapeutic LMWH	- Enoxaparin, 1 mg/kg SC every 12 hr - Daleparin, 200 units/kg SC once daily - Dalteparin, 100 units/kg every 12 hours - Tinzaparin, 175 units/kg once daily (target anti-Xa level in a therapeutic range of 0.6–1.0 units/mL 4 hr after last injection for twice-daily regimen)
Prophylactic UFH	- 5,000–7,000 units SC every 12 hr in the first trimester - 7,500–10,000 units SC every 12 hr in the second trimester - 10,000 units SC every 12 hr in the second trimester unless aPTT is elevated
Therapeutic UFH	- 10,000 units or more SC every 12 hr in doses adjusted to target aPTT in the therapeutic range (1.5–2.5 × controls) 6 hr after injection

LMWH = low molecular weight heparin, SC = subcutaneous, UFH = unfractionated heparin, aPTT = activated partial thromboplastin time.

Management of APS with SLE

- Management of APS in SLE should be in line with the treatment of primary APS.
- All patients with rheumatic and musculoskeletal disease including SLE should be screened for aPL at diagnosis or before or early in pregnancy.
- For SLE patients who are aPL positive, LDA is recommended especially in patients with high-risk aPL profile (persistently positive medium/high titers or multiple positivity) and/or with other atherosclerotic/thrombophilic factors.

1.4.2 16th International Congress on Antiphospholipid Antibodies Task Force Report on Antiphospholipid Syndrome Treatment Trends [2020]

The following report does not provide a specified grade of evidence or level of recommendation.

The 16th International Congress on Antiphospholipid Antibodies Task Force on APS Treatment Trends reviewed the current status with regard to existing and novel treatment trends for APS, which is the focus of this Task Force report. It reviews and updates “APS Treatment Trends” that have been discussed during the 16th International Congress on aPL, convened in Manchester, United Kingdom, in September 2019. It represents a continuation of the work of the 14th and 15th International Congress on aPL Task Force Reports The recommendations are detailed below[24]:

General recommendations

- DOACs should be avoided in APS patients with arterial thrombosis. For these patients, first line therapy should be a VKA.
- DOACs should be avoided in thrombotic APS patients with small vessel thrombosis or aPL-related cardiac valvular disease. The first line anticoagulant option should be a VKA.
- For patients found to have single- or double-positive aPL following a first episode of VTE (in the acute setting or later in their course), continuation of the DOAC may be considered, while awaiting confirmation of persistence of aPL, based on testing after at least 12 weeks, and thereafter.

  Testing for β2GPI, to distinguish patients with double- rather than triple aPL positivity should be performed if a DOAC is considered.
- For triple aPL-positive APS patients, if started on a DOAC upon initial presentation with a first episode of VTE, and upon considering limitations of testing (especially as it pertains to assessment for the presence of LA), it is recommended that therapy be switched to warfarin or an alternative VKA.
- DOACs should not be used in APS patients with recurrent thrombosis while on standard-intensity VKA. Other treatment options may include an increased target INR range, standard treatment dose low-molecular-weight heparin (LMWH), fondaparinux if VKA/LMWH are not suitable, or the addition of antiplatelet therapy.
- In asymptomatic aPL carriers, with or without SLE, or in individuals with prior obstetric APS, with persistent LA, double- or triple-aPL positivity, or persistently high aPL titer, LDA should be considered for primary prevention of thrombosis on a case-by case basis.
- In asymptomatic aPL carriers, with or without SLE, or in individuals with prior obstetric APS who have any other aPL laboratory phenotypes, LDA may be considered for primary prevention of thrombosis on a case-by-case basis.
- The risk-benefit analysis should include patient related factors for arterial thrombosis and VTE. Risk factors for bleeding and upper gastrointestinal reflux disease should also be taken into account.
- There is insufficient evidence to make strong recommendations about the use of LDA for secondary prevention following a first APS-associated arterial thrombosis. LDA may be considered, in combination with standard-intensity VKA (target INR 2.5, range 2.0–3.0), in APS patients with a first arterial thrombosis, with an alternative option high-intensity VKA.

- LDA may be considered, in combination with anticoagulation, in APS patients who develop recurrent arterial or venous thrombosis while on standard intensity VKA.
- The addition of HCQ may be considered as adjunctive to antithrombotic treatment, for anticoagulant refractory thrombotic APS.
- The addition of HCQ to standard treatment may be considered in patients with obstetric APS refractory to standard treatment with LDA and LMWH.
- Statins may be beneficial in the primary and secondary prevention of arterial thrombosis in patients with aPL/APS. However, based on available data, statins cannot be recommended in patients with aPL/APS in the absence of hyperlipidemia.
- Statins may be considered as adjunctive to antithrombotic treatment in anticoagulant-refractory thrombotic APS patients.
- Vitamin D deficiency and insufficiency should be corrected in all aPL-positive patients.
- Rituximab may have a role in the treatment of some aPL-related non-criteria manifestations, such as thrombocytopenia, diffuse alveolar hemorrhage, aPL-related nephropathy and microvascular skin ulcers. Rituximab may also have a role in refractory CAPS. There is a paucity of evidence to inform the use of rituximab for anticoagulant-refractory thrombotic APS.
- Anti-complement therapy should be considered in cases of CAPS and refractory microangiopathic disease.

1.4.3 International Society on Thrombosis and Haemostasis (ISTH) Guidance of the Use of Direct Oral Anticoagulants in Patients with Thrombotic Antiphospholipid Syndrome [2020]

The Lupus Anticoagulant/Antiphospholipid Antibodies Scientific and Standardization Committee (SSC) of the International Society on Thrombosis and Haemostasis (ISTH), in collaboration with the SSC on Control of Anticoagulation, has produced guidance herein to help healthcare professionals manage thrombotic APS patients. Definitive studies have not been done to establish with certainty the place of DOACs in the treatment of APS in all clinical situations. The purpose of this guidance is to provide advice to clinicians while there is limited evidence[25]. The guidance statements on the use of DOACs in APS patients are listed below:

1. We recommend that for the treatment of thrombotic APS among patients with any of the following (termed “high-risk” APS patients):
    a. Triple positivity
    b. Arterial thrombosis
    c. Small vessel thrombosis or organ involvement
    d. Heart valve disease according to Sydney criteria

    VKA should be used instead of DOACs.
2. We recommend that DOACs should not be used in patients with recurrent thrombosis while on therapeutic intensity VKA. In this circumstance, other therapeutic options may include an increased target INR range, treatment dose LMWH, or the addition of antiplatelet therapy.
3. We recommend that DOACs should not be used in APS patients who are non-adherent to VKA. In this circumstance, other options may include education on adherence to VKA treatment along with frequent INR testing.
4. In single or double positive non-“high risk” APS patients who have been on DOACs with good adherence for several months for a first episode of VTE, we recommend a discussion with the patient of options including perceived risks and uncertainties, in the spirit of shared decision-making and review of whether continued treatment with a DOAC is appropriate.
5. In single- or double-positive non-“high risk” APS patients with a single prior VTE requiring standard-intensity VKA, with allergy or intolerance to VKA or erratic INRs despite patient adherence, we suggest that alternative VKAs, if available, should be considered prior to consideration of a DOAC.

1.5 Systematic Reviews & Meta Analyses

Table 11 below tackles a systematic review and meta-analyses issued in 2023 for antiphospholipid syndrome.

Table 11. Systematic Reviews and Meta-Analyses in Antiphospholipid Syndrome

Study	Author (year)	Study Title	Primary Objective	Outcomes	Results
1	Khairani et al. (2023)[26]	***"Direct Oral Anticoagulants vs Vitamin K Antagonists in Patients With Antiphospholipid Syndromes"***	To compare the efficacy and safety of DOACs with VKAs for the prevention of subsequent venous and/or arterial thrombosis in patients with thrombotic APS.	The 2 main efficacy outcomes were as follows: 1) composite of arterial thrombotic events; and 2) venous thromboembolic events. Other efficacy outcomes included acute myocardial infarction, ischemic stroke or transient ischemic attack, acute major limb events, pulmonary embolism (PE), deep vein thrombosis (DVT), all-cause death, and a composite of any arterial or venous	Overall, the use of DOACs compared with VKAs was associated with increased odds of subsequent arterial thrombotic events (OR: 5.43; 95% CI: 1.87-15.75; P < 0.001, I^2 = 0%), especially stroke, and the composite of arterial thrombotic events or VTE (OR: 4.46; 95% CI: 1.12-17.84; P = 0.03, I^2 = 0%). The odds of subsequent VTE (OR: 1.20; 95% CI: 0.31-4.55; P = 0.79, I^2 = 0%), or major bleeding (OR: 1.02; 95% CI: 0.42-2.47; P = 0.97; I^2 = 0%) were not significantly different between the 2 groups. Most findings were consistent within subgroups. Patients with thrombotic antiphospholipid syndrome randomized to DOACs compared with VKAs appear to have increased risk for arterial thrombosis. No significant differences were observed between patients randomized to DOACs vs VKAs in the risk of subsequent VTE or major bleeding.

				thromboembolic events. The main safety outcome was major bleeding. Clinically relevant nonmajor bleeding was also assessed.	
2	Adelhelm et al. (2023)[27]	***"Therapy with direct oral anticoagulants for secondary prevention of thromboembolic events in the antiphospholipid syndrome: a systematic review and meta-analysis of randomized trials"***	To evaluate DOACs compared with VKAs in secondary prevention of thromboembolic events in patients with APS.	The major efficacy outcome was incident thromboembolic events; other major outcomes were (1) bleeding and (2) death.	Across trials, 29 and 10 thrombotic events were observed in 305 and 319 patients with APS treated with DOAC and VKA, respectively, corresponding to a combined Peto OR of 3.01 (95% CI 1.56 to 5.78, p=0.001). There was a significantly increased risk of AT while treated with DOACs compared with VKA (OR 5.5 (2.5, 12.1) p<0.0001), but no difference in the risk of VT (p=0.87). There was no significant difference in risk of bleeding. DOACs were associated with a significant increase in the risk of a new thrombotic event, especially AT, favoring standard prophylaxis with warfarin.
3	Hooper et al. (2023)[28]	***"Does adding hydroxychloroquine to empiric treatment improve***	To evaluate the risk of pregnancy loss upon treatment with HCQ among	The primary outcomes of interests were live	The findings suggest a significant benefit of HCQ in addition to aspirin and heparin for patients with APS to mitigate the risk of antiphospholipid

		the live birth rate in refractory obstetrical antiphospholipid syndrome? A systematic review"	women with refractory obstetrical APS.	birth (LB) and pregnancy loss (PL). Secondary outcomes were adverse obstetrical complications, including both maternal and neonatal complications, and gestational age of delivery.	antibody mediated obstetrical complications. Randomized controlled trials with standardized patient selection criteria need to be conducted to corroborate these findings.

Section 2.0 Drug Therapy

2.1 Anticoagulant Agents

2.1.1 Warfarin

Information on Warfarin is detailed in the table below[29,30]:

Table 12. Drug Therapy with Warfarin

<table>
<tr><th colspan="2">SCIENTIFIC NAME
WARFARIN</th></tr>
<tr><td>SFDA Classification</td><td>Prescription</td></tr>
<tr><td>SFDA</td><td>Yes</td></tr>
<tr><td>US FDA</td><td>Yes</td></tr>
<tr><td>EMA</td><td>Yes</td></tr>
<tr><td>MHRA</td><td>Yes</td></tr>
<tr><td>PMDA</td><td>Yes</td></tr>
<tr><td>Indication (ICD-10)</td><td>D68.61</td></tr>
<tr><td>Drug Class</td><td>Antithrombotic Agents</td></tr>
<tr><td>Drug Sub-class</td><td>Vitamin K Antagonists</td></tr>
<tr><td>ATC Code</td><td>B01AA03</td></tr>
<tr><td>Pharmacological Class (ASHP)</td><td>Anticoagulant - Vitamin K Antagonist</td></tr>
<tr><th colspan="2">DRUG INFORMATION</th></tr>
<tr><td>Dosage Form</td><td>Tablet</td></tr>
<tr><td>Route of Administration</td><td>Oral use</td></tr>
<tr><td>Dose (Adult) [DDD]*</td><td>Initial: 5mg orally once daily.
<table>
<tr><th></th><th>Standard dosing for patients who are not expected to be sensitive to warfarin</th><th>Reduced dosing for patients expected to be more sensitive to warfarin</th></tr>
<tr><td>Initial dose</td><td>5 mg daily for 3 days</td><td>2.5 mg daily for 3 days</td></tr>
<tr><td colspan="3">Check INR the morning of day 4</td></tr>
</table></td></tr>
</table>

	<1.5	7.5 to 10 mg daily for 2 to 3 days	5 to 7.5 mg daily for 2 to 3 days
	1.5 to 1.9	5 mg daily for 2 to 3 days	2.5 mg daily for 2 to 3 days
	2 to 3	2.5 mg daily for 2 to 3 days	1.25 mg daily for 2 to 3 days
	3.1 to 4	1.25 mg daily for 2 to 3 days	0.5 mg daily for 2 to 3 days
	>4	Hold until INR <3	Hold until INR <3
Maximum Daily Dose Adults*	N/A		
Dose (pediatrics)	Target INR between 2 to 3: Day 1: Initial loading dose (if baseline INR is 1 to 1.3): Oral: 0.2 mg/kg/day once daily; maximum dose: 10 mg/dose; use a reduced initial loading dose of 0.1 mg/kg if patient has undergone a Fontan procedure or has liver dysfunction. Days 2 to 4: Additional loading doses are dependent upon patient's INR: Oral: INR 1.1 to 1.3: Repeat the initial loading dose. INR 1.4 to 1.9: Dose is 50% of the initial loading dose. INR 2 to 3: Dose is 50% of the initial loading dose. INR 3.1 to 3.5: Dose is 25% of the initial loading dose.		

	INR >3.5: Hold the drug until INR <3.5, then restart at 50% of previous dose. Days ≥5: Maintenance doses are dependent upon patient's INR (Ref): Oral: INR 1.1 to 1.4: Increase previous dose by 20%. INR 1.5 to 1.9: Increase previous dose by 10%. INR 2 to 3: No change in dose. INR 3.1 to 3.5: Decrease previous dose by 10%. INR >3.5: Hold the drug until INR <3.5, then restart at 20% less than the previous dose.
Maximum Daily Dose Pediatrics*	N/A
Adjustment	**Altered Kidney Function:** There are no specific dosage adjustments recommended for any degree of kidney impairment. **Hemodialysis, intermittent (thrice weekly):** Unlikely to be dialyzed (highly protein bound): Patients with end-stage kidney disease (ESKD) tend to require ~20% lower doses compared to patients with normal kidney function and have a significant risk of bleeding. Use lower initial doses and monitor INR frequently. **Peritoneal dialysis:** Unlikely to be dialyzed (highly protein bound): Patients with ESKD tend to require ~20% lower doses compared to patients with normal kidney function and have a

	significant risk of bleeding. Use lower initial doses and monitor INR frequently. **CRRT:** Avoid use. **PIRRT (eg, sustained, low-efficiency diafiltration):** Avoid use. **Dosing: Hepatic Impairment: Adult** There are no dosage adjustments provided in the manufacturer's labeling. However, the response to oral anticoagulants may be markedly enhanced in obstructive jaundice, hepatitis, and cirrhosis. INR should be closely monitored.
Prescribing edits*	N/A
AGE (Age Edit)	N/A
CU (Concurrent Use Edit)	N/A
G (Gender Edit)	N/A
MD (Physician Specialty Edit)	N/A
PA (Prior Authorization)	N/A
QL (Quantity Limit)	N/A
ST (Step Therapy)	N/A
EU (Emergency Use Only)	N/A
PE (Protocol Edit)	N/A
SAFETY	
Main Adverse Drug Reactions (Most common and most serious)	**Most serious:** Atheroemboli/cholesterol micro emboli, calciphylaxis, decreased bone mineral density, hemorrhage, skin necrosis/gangrene. **Most common:** Hemorrhage from any tissue or organ.
Drug Interactions*	**Category X:** • Defibrotide • Hemin • MiFEPRIStone • Omacetaxine • Oxatomide • Streptokinase • Tamoxifen

	• Urokinase • Vorapaxar
Special Population	**Older adults:** The elderly may be more sensitive to anticoagulant therapy. **Patients with genomic variants in CYP2C9 and/or VKORC1:** Presence of the CYP2C9*2 or *3 allele and/or polymorphism of the vitamin K oxidoreductase (VKORC1) gene may have increased sensitivity to warfarin (eg, lower doses needed to achieve therapeutic anticoagulation). The *2 allele is reported to occur with a frequency of 4% to 11% in African Americans and Caucasians, respectively, while the *3 allele frequencies are 2% to 7% respectively. Other variant 2C9 alleles (eg, *5, *6, *9, and *11) are also associated with reduced warfarin metabolism and thus may increase sensitivity to warfarin but are much less common. Lower doses may be required in these patients. Genetic testing may help determine appropriate dosing.
Pregnancy	Use is contraindicated during pregnancy except in patients with mechanical heart valves who are at high risk for thromboembolism; use is also contraindicated in patients with threatened abortion, eclampsia, or preeclampsia.
Lactation	Warfarin is considered compatible with breastfeeding. The manufacturer recommends monitoring of breastfeeding infants for bruising or bleeding.
Contraindications	Hypersensitivity to warfarin or any component of the formulation; hemorrhagic tendencies (eg, active GI ulceration, patients bleeding from the GI, respiratory, or GU tract; cerebral

	aneurysm; CNS hemorrhage; dissecting aortic aneurysm; spinal puncture and other diagnostic or therapeutic procedures with potential for significant bleeding); recent or potential surgery of the eye or CNS; major regional lumbar block anesthesia or traumatic surgery resulting in large, open surfaces; blood dyscrasias; malignant hypertension; pericarditis or pericardial effusion; bacterial endocarditis; unsupervised patients with conditions associated with a high potential for noncompliance; eclampsia/preeclampsia, threatened abortion, pregnancy (except in women with mechanical heart valves at high risk for thromboembolism).
Monitoring Requirements	**Adults:** Prothrombin time, INR; hematocrit; may consider genotyping of CYP2C9 and VKORC1 prior to initiation of therapy; however, routine genetic testing is not recommended. **Frequency of INR monitoring:** During warfarin initiation, monitor INR daily for hospitalized patients and every 1 to 3 days for non-hospitalized patients. After initiating warfarin therapy, INR should be monitored every 2 to 3 days during the first week of therapy. Once a stable response to therapy is achieved, INR monitoring may be performed less frequently: once a week for the first 1 to 2 weeks, then every 2 weeks, and eventually monthly thereafter. Very stable and reliable patients may have their monitoring extended up to every 12 weeks.
Precautions	**Bariatric surgery:** High risk for hemorrhage post-surgery: Avoid warfarin if possible immediately after

	gastric bypass and sleeve gastrectomy; significant risk for hemorrhage, readmission, and mortality. Several studies have observed warfarin dose reduction postoperatively with a subsequent return to preoperative doses 6 to 12 months after surgery. The change in dose requirement may be multifactorial but is most likely due to attributable variation in the time to resuming full solid intake and the consequent alteration in the intake of vitamin K-containing foods. Monitor INR closely in the early postoperative period and up to 1 year after surgery or when significant nutritional or supplementation changes occur. **Dietary insufficiency:** Use with caution in patients with prolonged dietary insufficiencies (vitamin K deficiency). **Heparin-induced thrombocytopenia:** Use with caution in patients with heparin-induced thrombocytopenia and venous thromboembolism; limb ischemia, necrosis, and gangrene have occurred when warfarin was started or continued after heparin was stopped. Warfarin monotherapy is contraindicated in the initial treatment of heparin-induced thrombocytopenia; warfarin initially inhibits the synthesis of protein C, potentially accelerating the underlying active thrombotic process. **Hepatic impairment:** Reduced liver function, regardless of etiology, may impair synthesis of coagulation factors leading to increased warfarin sensitivity. **Infection:** Use with caution in patients with acute infection or active TB or any disruption of normal GI flora; antibiotics

	and fever may alter response to warfarin. **Renal impairment:** Use with caution in patients with renal impairment. Patients with renal impairment are at increased risk for bleeding diathesis; frequent INR monitoring is recommended. **Thyroid disease:** Use with caution in patients with thyroid disease; warfarin responsiveness may increase.
Black Box Warning	**Bleeding risk:** Warfarin can cause major or fatal bleeding. Perform regular monitoring of international normalized ratio (INR) on all treated patients. Drugs, dietary changes, and other factors affect INR levels achieved with warfarin therapy. Instruct patients about prevention measures to minimize the risk of bleeding and to report immediately to their health care provider signs and symptoms of bleeding.
REMS*	N/A

HEALTH TECHNOLOGY ASSESSMENT (HTA)

The table below lists the HTA reviews and recommendations of antiphospholipid syndrome treatment options by the following agencies/institutes/authorities: National Institute for Health and Care Excellence (NICE), Canadian Agency for Drugs and Technologies in Health (CADTH), Haute Autorité de Santé (HAS), Institute for Quality and Efficiency in Health Care (IQWIG), and Pharmaceutical Benefits Advisory Committee (PBAC) as applicable. **The recommendations below are for Warfarin.**

Table 13. HTA Analysis for Warfarin

MEDICATION	AGENCY	DATE – HTA RECOMMENDATION
Warfarin	NICE	Not available
	CADTH	Not applicable
	HAS[13]	**Positive Recommendation** – February 9, 2018

		The medical benefit provided by Warfarin remains significant: To prevent thromboembolic complications related to non-valvular atrial fibrillation (NVAF). In the treatment of DVT and PE and the prevention of their recurrence, replacing heparin.
	IQWIG	Not available
	PBAC	Not applicable

CONCLUSION STATEMENT – Warfarin

The gold standard treatment for APS patients who have suffered thrombosis is treatment with an oral vitamin K antagonist (VKA) to achieve a target international normalized ratio (INR) of 2.0–3.0. VKAs are teratogenic; therefore, in APS patients with prior thrombosis or pregnancy morbidity, therapeutic dose low-molecular-weight heparin (LMWH) and LDA is accepted treatment. Warfarin is given as 5mg orally once daily; dosing is adjusted based on INR readings. Some HTA bodies such as HAS have backed its use. Warfarin use is limited by its heightened risk of developing atheroemboli/cholesterol micro emboli, calciphylaxis, decreased bone mineral density, hemorrhage, and skin necrosis/gangrene.

2.1.2 Unfractionated Heparin

Information on Unfractionated Heparin is detailed in the table below[29,30]:

Table 14. Drug Therapy with Unfractionated Heparin

SCIENTIFIC NAME UNFRACTIONATED HEPARIN	
SFDA Classification	Prescription
SFDA Approval	Yes
US FDA	Yes
EMA	Yes
MHRA	Yes
PMDA	Yes
Indication (ICD-10)	D68.61
Drug Class	Antithrombotic Agent
Drug Sub-class	Heparin Group

ATC Code	B01AB01
Pharmacological Class (ASHP)	Anticoagulant Agent
DRUG INFORMATION	
Dosage Form	Solution, Intravenous
Route of Administration	Intravenous Use / Subcutaneous Use
Dose (Adult) [DDD]*	**In pregnancy**[17]**:** **Prophylactic UFH:** 5,000–7,000 units SC every 12 hours in the first trimester 7,500–10,000 units SC every 12 hours in the second trimester 10,000 units SC every 12 hours in the second trimester unless aPTT is elevated **Therapeutic UFH:** 10,000 units or more SC every 12 hours. Doses adjusted to target aPTT in the therapeutic range (1.5–2.5 × controls) 6 hours after injection
Maximum Daily Dose Adults*	N/A
Dose (pediatrics)	**Initial Dose:** 75 to 100 units/kg (intravenous bolus over 10 minutes) **Maintenance Dose:** Infants: 25 to 30 units/kg/hour; Infants < 2 months have the highest requirements (average 28 units/kg/hour) Children > 1 year of age: 18 to 20 units/kg/hour; Older children may require less heparin, similar to weight-adjusted adult dosage.
Maximum Daily Dose Pediatrics*	N/A
Adjustment	**For Adults:** **Altered Kidney Function:** IV, SUBQ: Mild to severe impairment: No initial dosage adjustment necessary. Renal replacement therapies: Poorly dialyzed: IV, SUBQ: No supplemental dose or initial dosage adjustment

	necessary in patients receiving renal replacement therapies (eg, hemodialysis, peritoneal dialysis, CRRT, PIRRT). **Hepatic Impairment:** No dosage adjustment required; adjust therapeutic heparin according to aPTT or anti-Factor Xa activity. **For Pediatrics:** All patients: No dosage adjustment required; adjust therapeutic heparin according to aPTT or anti-Xa activity.
Prescribing edits*	N/A
AGE (Age Edit)	N/A
CU (Concurrent Use Edit)	N/A
G (Gender Edit)	N/A
MD (Physician Specialty Edit)	N/A
PA (Prior Authorization)	N/A
QL (Quantity Limit)	N/A
ST (Step Therapy)	N/A
EU (Emergency Use Only)	N/A
PE (Protocol Edit)	N/A
SAFETY	
Main Adverse Drug Reactions (most common and most serious)	**Most common:** Hemorrhage, thrombocytopenia, HIT and HITT, hypersensitivity reactions, and elevations of aminotransferase levels. **Most serious:** Vasospasm, acute adrenocortical insufficiency, anaphylactic shock, and skin ulcerations at the injection site.
Drug Interactions*	**Category X:** • Andexanet Alfa (Coagulation Factor Xa [Recombinant], Inactivated) • Apixaban • Corticorelin • Dabigatran Etexilate

	• Defibrotide • Edoxaban • Hemin • MiFEPRIStone • Omacetaxine • Oritavancin • Rivaroxaban • Streptokinase • Telavancin • Urokinase • Vorapaxar
Special Population	Older adult: Use with caution in patients >60 years of age, particularly women; older adults can be more sensitive to heparin and a higher incidence of bleeding has been reported in these patients. May require lower doses.
Pregnancy	Heparin may be used for anticoagulation in pregnancy. Due to a better safety profile and ease of administration, the use of low molecular weight heparin (LMWH) is generally preferred over heparin (unfractionated heparin [UFH]) in pregnancy. Anticoagulant therapy for the prevention and treatment of thromboembolism in pregnant patients can be discontinued prior to induction of labor or a planned cesarean delivery or LMWH can be converted to UFH in higher risk patients. Patients with mechanical heart valves have an increased risk of adverse maternal and fetal outcomes and these risks are greater without appropriate anticoagulation. UFH or LMWH may be used in pregnant patients with mechanical heart valves. Increased monitoring is required to maintain

	adequate therapeutic concentrations during pregnancy. Some products contain benzyl alcohol as a preservative; their use in pregnant patients is contraindicated by some manufacturers; use of a preservative-free formulation is recommended.
Lactation	Heparin is considered acceptable for use in patients who are breastfeeding. However, some products contain benzyl alcohol as a preservative; their use in breastfeeding patients is contraindicated by some manufacturers due to the association of gasping syndrome in premature infants.
Contraindications	Hypersensitivity to heparin or any component of the formulation (unless a life-threatening situation necessitates use and use of an alternative anticoagulant is not possible); severe thrombocytopenia; history of heparin-induced thrombocytopenia; history of heparin-induced thrombocytopenia with thrombosis; uncontrolled active bleeding (except when this is due to disseminated intravascular coagulation); not for use when appropriate blood coagulation tests cannot be obtained at appropriate intervals (applies to full-dose heparin only). **Note:** Some products contain benzyl alcohol as a preservative; their use in neonates, infants, or pregnant or breastfeeding women is contraindicated by some manufacturers.
Monitoring Requirements	Hemoglobin, hematocrit, platelet count, PT, aPTT, signs/symptoms of bleeding, risk factors for bleeding, fecal occult

	blood test (if clinically indicated); potassium. Level of anticoagulation can be monitored by anti-Factor Xa activity **or** aPTT (calibrated by anti-Factor Xa activity or by protamine titration assay) **or** activated clotting time depending upon the indication. Patients with antiphospholipid syndrome may have a prolonged aPTT at baseline due to effects of the antiphospholipid antibodies. In order to prevent a prolonged value from being mistaken for therapeutic anticoagulation, aPTT should be measured at baseline. In this situation, anti-Factor Xa monitoring may be preferred. Platelet count should be routinely monitored when the risk of heparin-induced thrombocytopenia (HIT) is >1%. If the patient experienced HIT within the past 100 days after receiving heparin or low-molecular-weight heparin, risk of recurrence is higher. Monitor closely if pre-exposure history is uncertain. When the risk of HIT is <1%, routine platelet count monitoring is not necessary.
Precautions	**Bleeding:** May occur, including fatal events. Caution should be exercised in patients with an increased risk of bleeding, including subacute bacterial endocarditis; congenital or acquired bleeding disorders; active ulcerative or angiodysplastic GI diseases; continuous GI tube drainage; severe uncontrolled hypertension; history of hemorrhagic stroke; use shortly after brain, spinal, or ophthalmologic surgery or other invasive procedures including spinal tap or spinal anesthesia; concomitant

	treatment with platelet inhibitors; recent GI bleeding; impaired hemostasis; thrombocytopenia or platelet defects; patients with hereditary antithrombin deficiency receiving concurrent antithrombin replacement therapy; severe liver disease; hypertensive or diabetic retinopathy; renal failure; or in patients (especially women) >60 years of age. Discontinue if bleeding occurs; severe hemorrhage or overdosage may require protamine. **Heparin resistance:** Dose requirements >35,000 units/24 hours to maintain a therapeutic aPTT may occur in patients with antithrombin deficiency, increased heparin clearance, elevations in heparin-binding proteins, and elevations in factor VIII and/or fibrinogen; frequently encountered in patients with fever, thrombosis, thrombophlebitis, infections with thrombosing tendencies, myocardial infarction, cancer, and in postsurgical patients; measurement of anticoagulant effects using anti-Factor Xa levels may be of benefit. **Hepatic effects:** Elevations in serum aminotransferases have been observed during therapy. These elevations should be evaluated with caution as they may occur and resolve in the setting of the underlying condition for which heparin is being used. **Hyperkalemia:** Hyperkalemia may occur, especially in patients with diabetes, renal impairment, history of metabolic acidosis, history of hyperkalemia, or taking concomitant

	potassium-sparing medication; may suppress aldosterone production. **Hypersensitivity reactions:** Hypersensitivity reactions, including fever, chills, urticaria, asthma, rhinitis, lacrimation, and anaphylaxis, have been reported. In patients with a documented hypersensitivity reaction, heparin should only be considered in life-threatening situations when use of an alternative anticoagulant is not possible. Some products are derived from animal tissue and may be contraindicated in patients with animal allergies (ie, pork). **Osteoporosis:** May occur with prolonged use (>6 months) due to a reduction in bone mineral density. **Thrombocytopenia:** Mild thrombocytopenia (platelet count >100,000/m3) may occur during therapy. Heparin-induced thrombocytopenia (HIT), a serious antibody-mediated reaction resulting from irreversible aggregation of platelets, may occur. Patients who develop HIT may be at risk of developing a new thrombus (heparin-induced thrombocytopenia with thrombosis [HITT]). Discontinue therapy and consider alternatives if platelet count falls below 100,000/mm3, there is a >50% reduction in platelet count from baseline, and/or thrombosis develops while on heparin therapy. Onset of HIT or HITT is usually delayed (5 to 10 days after exposure in heparin-naive individuals) and can occur up to several weeks after discontinuation of heparin. "Rapid onset" HIT can occur within 24 hours of heparin initiation, especially in

	patients with recent heparin exposure within the previous 100 days. Use with extreme caution (for a limited duration) or avoid use in patients with history of HIT, especially if administered within 100 days of a HIT episode.
Black Box Warning	N/A
REMS*	N/A

HEALTH TECHNOLOGY ASSESSMENT (HTA)

The table below lists the HTA reviews and recommendations of antiphospholipid syndrome treatment options by the following agencies/institutes/authorities: National Institute for Health and Care Excellence (NICE), Canadian Agency for Drugs and Technologies in Health (CADTH), Haute Autorité de Santé (HAS), Institute for Quality and Efficiency in Health Care (IQWIG), and Pharmaceutical Benefits Advisory Committee (PBAC) as applicable. **The recommendations below are for Unfractionated Heparin.**

Table 15. HTA Analysis for Unfractionated Heparin

MEDICATION	AGENCY	DATE – HTA RECOMMENDATION
Unfractionated Heparin	NICE	Not available
	CADTH	Not applicable
	HAS	N/A
	IQWIG	Not available
	PBAC	Not applicable

CONCLUSION STATEMENT – Unfractionated Heparin

The standard treatment for patients with venous thrombosis in APS is initial anticoagulation with unfractionated heparin or low molecular weight heparin transitioned to a VKA, commonly warfarin, which is continued indefinitely. In CAPS, based on observational data and expert opinion, anticoagulation with heparin and high-dose steroids (methylprednisolone 1000 mg daily for 3 days or longer) are the mainstay of therapy. In OAPS, the most common approach for management is the combination of heparin (unfractionated or low molecular weight; prophylactic or intermediate dose) and low-dose aspirin (75-100 mg) daily for women who fulfill the clinical and serologic criteria for obstetric APS. UFH is given as 10,000 units or more SC every 12 hours in doses adjusted to target aPTT in the therapeutic range (1.5–2.5 × controls) 6 hours after injection. When given as prophylaxis, it is dosed as 5,000–

7,000 units SC every 12 hours in the first trimester, 7,500–10,000 units SC every 12 hours in the second trimester and 10,000 units SC every 12 hours in the second trimester unless aPTT is elevated[17]. The use of UFH is limited by the heightened risk of developing vasospasm, acute adrenocortical insufficiency, anaphylactic shock, and skin ulcerations at the injection site.

2.1.3 Low Molecular Weight Heparins

2.1.3.1 Enoxaparin

Information on Enoxaparin is detailed in the table below[29,30]:

Table 16. Drug Therapy with Enoxaparin

SCIENTIFIC NAME ENOXAPARIN	
SFDA Classification	Prescription
SFDA Approval	Yes
US FDA	Yes
EMA	Yes
MHRA	Yes
PMDA	Yes
Indication (ICD-10)	D68.61
Drug Class	Antithrombotic Agent
Drug Sub-class	Heparin Group
ATC Code	B01AB05
Pharmacological Class (ASHP)	Low Molecular Weight Heparin
DRUG INFORMATION	
Dosage Form	Injection, for Subcutaneous and Intravenous Use
Route of Administration	Intravenous Use and Subcutaneous Use
Dose (Adult) [DDD]*	**Prophylactic Dosing[15]:** For those who weigh < 50 kg: 20 mg/day 50-90 kg: 40 mg/day 91-130 kg: 60 mg/day 131-170 kg: 80 mg/day > 170 kg: 0.6 mg/kg/day High prophylaxis: 40 mg/12h

	Intermediate Doses of LMWH[15]: 1 mg/kg/day
Maximum Daily Dose Adults*	N/A
Dose (pediatrics)	**In case of thrombosis, prophylaxis:** Infants 1 to <2 months: SUBQ: 0.75 mg/kg/dose every 12 hours. Infants ≥ 2 months, Children, and Adolescents: SUBQ: 0.5 mg/kg/dose every 12 hours. **Thrombosis, treatment:** Initial: Infants 1 to <2 months: SUBQ: 1.5 mg/kg/dose every 12 hours. Infants ≥2 months, Children, and Adolescents: SUBQ: 1 mg/kg/dose every 12 hours. **Alternate dosing:** 1 to <3 months: SUBQ: 1.8 mg/kg/dose every 12 hours. 3 to 12 months: SUBQ: 1.5 mg/kg/dose every 12 hours. 1 to 5 years: SUBQ: 1.2 mg/kg/dose every 12 hours 6 to 18 years: SUBQ: 1.1 mg/kg/dose every 12 hours.
Maximum Daily Dose Pediatrics*	N/A
Adjustment	**Altered Kidney Function:** CrCl >50 mL/minute: No dose adjustment necessary for most indications. CrCl 30 to 50 mL/minute: No dose adjustment necessary for most indications. CrCl <30 mL/minute: Venous thromboembolism prophylaxis (except in trauma patients): SUBQ: 30 mg once daily. Venous thromboembolism treatment: SUBQ: 1 mg/kg once daily.

	Hemodialysis, intermittent (thrice weekly) (systemic anticoagulation): SUBQ: Not dialyzable: Avoid use if possible, as there may be accumulation of active heparin metabolites that are undetected by anti-factor Xa assays. Serious bleeding complications have been reported with use in patients who are dialysis dependent or have severe kidney failure **Peritoneal dialysis:** SUBQ: Not dialyzable. Avoid use if possible. **CRRT or PIRRT (systemic anticoagulation):** SUBQ: Avoid use if possible. Significant clearance unlikely. If used, monitor closely for bleeding and utilize anti-factor Xa monitoring. **Hepatic Impairment:** There are no dosage adjustments provided in the manufacturer's labeling (has not been studied); use with caution.
Prescribing edits*	N/A
AGE (Age Edit)	N/A
CU (Concurrent Use Edit)	N/A
G (Gender Edit)	N/A
MD (Physician Specialty Edit)	N/A
PA (Prior Authorization)	N/A
QL (Quantity Limit)	N/A
ST (Step Therapy)	N/A
EU (Emergency Use Only)	N/A
PE (Protocol Edit)	N/A
SAFETY	
Main Adverse Drug Reactions (most common and most serious)	**Most common:** Anemia, hematoma at injection site, nausea, fever. **Most serious:** Major bleeding, spinal or epidural hematomas, thrombocytopenia.
Drug Interactions*	**Category X:**

	• Apixaban • Dabigatran Etexilate • Defibrotide • Edoxaban • Hemin • MiFEPRIStone • Omacetaxine • Rivaroxaban • Urokinase • Vorapaxar
Special Population	**Older adult:** Use with caution in older patients; delayed elimination may occur. Dosage alteration/adjustment may be required (eg, omission of IV bolus and reduced treatment dose in acute STEMI in patients ≥75 years of age). **Low weight patients:** Risk of bleeding may be increased in women <45 kg and in men <57 kg. **Elective surgery/procedure:** In patients receiving bridging anticoagulation with therapeutic dose enoxaparin, the last dose should be administered ~24 hours prior to the surgery/procedure. For patients on a twice-daily regimen, administer 1 dose in the morning the day before surgery. For patients on a once-daily regimen, administer 50% of the dose in the morning the day before surgery. Reinitiate therapy ≥24 hours after the surgery/procedure when bleeding risk is acceptable.
Pregnancy	Low-molecular-weight heparin (LMWH) does not cross the placenta. Due to pregnancy-induced physiologic changes, some pharmacokinetic properties of LMWH may be altered; dosing adjustment may be required. Prophylactic doses of LMWH may also

	need modifying in pregnant patients at extremes of body weight. The risk of venous thromboembolism (VTE) is increased in pregnant patients especially during the third trimester and first week postpartum. LMWH is recommended over unfractionated heparin for the treatment of acute VTE in pregnant patients. LMWH is also recommended over unfractionated heparin for VTE prophylaxis in pregnant patients with certain risk factors (eg, homozygous factor V Leiden, antiphospholipid antibody syndrome with ≥3 previous pregnancy losses). LMWH may also be considered for VTE prophylaxis in pregnant patients with COVID-19. LMWH may be used prior to cesarean delivery in patients with additional risk factors for developing VTE. Risk factors may include a personal history of DVT or PE, inherited thrombophilia, or patients with class III obesity. LMWH may also be used in pregnant patients with mechanical heart valves. When choosing therapy, fetal outcomes (ie, pregnancy loss, malformations), maternal outcomes (ie, VTE, hemorrhage), burden of therapy, and maternal preference should be considered. Patients with mechanical heart valves have an increased risk of adverse fetal and maternal outcomes (including valve thrombosis) and these risks are greater without appropriate anticoagulation. Increased monitoring of anti-factor Xa levels is required; frequent dose titration may be needed to maintain adequate therapeutic anti-factor Xa concentrations during

	pregnancy. Multiple-dose vials contain benzyl alcohol (avoid in pregnant patients due to association with gasping syndrome in premature infants); use of preservative-free formulations is recommended.
Lactation	It is not known if enoxaparin is present in breast milk. Small amounts of another low-molecular-weight heparin (LMWH) have been detected in breast milk; however, because they have a low oral bioavailability, LMWHs are unlikely to cause adverse events in a breastfeeding infant. According to the manufacturer, the decision to breastfeed during therapy should consider the risk of infant exposure, the benefits of breastfeeding to the infant, and the benefits of treatment to the mother. LMWH is considered compatible with breastfeeding.
Contraindications	Known hypersensitivity to enoxaparin (eg, pruritus, urticaria, anaphylactic/anaphylactoid reactions), heparin, pork products, or any component of the formulation (including benzyl alcohol in multiple-dose vials); history of immune mediated heparin-induced thrombocytopenia (HIT) in the past 100 days or in the presence of circulating antibodies; active major bleeding. Additional contraindications (not in US labeling): Use of multiple-dose vials in newborns or premature neonates; acute or subacute bacterial endocarditis; major blood clotting disorders; active gastric or duodenal ulcer; hemorrhagic cerebrovascular accident (except if there are systemic emboli); severe

	uncontrolled hypertension; diabetic or hemorrhagic retinopathy; other conditions or diseases involving an increased risk of hemorrhage; injuries to and operations on the brain, spinal cord, eyes, and ears; spinal/epidural anesthesia when repeated dosing of enoxaparin (1 mg/kg every 12 hours or 1.5 mg/kg daily) is required, due to increased risk of bleeding.
Monitoring Requirements	Platelet count, hemoglobin, hematocrit, fecal occult blood, signs and symptoms of bleeding, anti-factor Xa levels (as appropriate), and serum creatinine at baseline and during therapy; monitoring of PT and/or aPTT is not necessary. Routine monitoring of anti-factor Xa activity is not required but has been utilized in patients with obesity and/or kidney insufficiency. For patients >144 kg, if anti-factor Xa monitoring is available, adjusting dose based on anti-factor Xa activity is recommended; if anti-factor Xa monitoring is unavailable, reduce dose if bleeding occurs. Monitor obese patients closely for signs/symptoms of thromboembolism. Monitoring anti-factor Xa activity is recommended in pregnant women receiving therapeutic doses of enoxaparin or when receiving enoxaparin for the prevention of thromboembolism with mechanical heart valves. Lumbar puncture/neuraxial anesthesia: In patients who are anticoagulated during or immediately following a lumbar puncture or neuraxial anesthesia (eg, epidural anesthesia/analgesia or spinal

	anesthesia/analgesia), monitor frequently for signs and symptoms of neurological impairment (midline back pain, sensory and motor deficits, bowel and/or bladder dysfunction).
Precautions	**Bleeding:** To minimize risk of bleeding following PCI, achieve hemostasis at the puncture site after PCI. If a closure device is used, sheath can be removed immediately. If manual compression is used, remove sheath 6 hours after the last IV/SubQ dose of enoxaparin. Do not administer further doses until 6 to 8 hours after sheath removal; observe for signs of bleeding/hematoma formation. **Hyperkalemia:** May rarely cause hyperkalemia possibly by suppressing aldosterone production. Most commonly occurs in patients with risk factors for the development of hyperkalemia (eg, kidney dysfunction, concomitant use of potassium-sparing diuretics or potassium supplements, hematoma in body tissues). **Thrombocytopenia:** Use with extreme caution or avoid in patients with history of HIT. In patients with a history of HIT, use only if >100 days have elapsed since the prior HIT episode and no circulating antibodies are present (HIT may still occur in these patients; assess risk vs benefit and use only after non-heparin alternative treatments are considered). Discontinue therapy and consider alternative treatment if platelets are <100,000/mm3 and/or thrombosis develops. **Kidney impairment:** Use with caution in patients with kidney impairment; dosage adjustment may be required. In pediatric patients with kidney

	impairment, more frequent monitoring is recommended.
Black Box Warning	**Spinal/Epidural Hematoma:** Epidural or spinal hematomas may occur in patients who are anticoagulated with LMWHs or heparinoids and are receiving neuraxial anesthesia or undergoing spinal puncture. These hematomas may result in long-term or permanent paralysis. Consider these risks when scheduling patients for spinal procedures. Factors that can increase the risk of developing epidural or spinal hematomas in these patients include use of indwelling epidural catheters; concomitant use of other drugs that affect hemostasis, such as nonsteroidal anti-inflammatory drugs (NSAIDs), platelet inhibitors, and other anticoagulants; a history of traumatic or repeated epidural or spinal punctures; and a history of spinal deformity or spinal surgery. Optimal timing between the administration of enoxaparin and neuraxial procedures is not known. Monitor patients frequently for signs and symptoms of neurological impairment. If neurological compromise is noted, urgent treatment is necessary. Consider the benefits and risks before neuraxial intervention in patients anticoagulated or to be anticoagulated for thromboprophylaxis.
REMS*	N/A

HEALTH TECHNOLOGY ASSESSMENT (HTA)

The table below lists the HTA reviews and recommendations of antiphospholipid syndrome treatment options by the following agencies/institutes/authorities: National Institute for Health and Care Excellence (NICE), Canadian Agency for Drugs and Technologies in Health (CADTH), Haute Autorité de Santé (HAS), Institute for Quality and Efficiency in Health Care (IQWIG), and Pharmaceutical Benefits Advisory Committee (PBAC) as applicable. **The recommendations below are for Enoxaparin.**

Table 17. HTA Analysis for Enoxaparin

MEDICATION	AGENCY	DATE – HTA RECOMMENDATION
Enoxaparin	NICE	Not available
	CADTH	Not available
	HAS	Not applicable
	IQWIG	Not available
	PBAC	Not applicable

CONCLUSION STATEMENT – Enoxaparin

The standard treatment for patients with venous thrombosis in APS is initial anticoagulation with unfractionated heparin or low molecular weight heparin transitioned to a VKA, commonly warfarin, which is continued indefinitely. For obstetric APS, the most common approach for management is the combination of heparin (unfractionated or low molecular weight; prophylactic or intermediate dose) and low-dose aspirin (75-100 mg) daily. In patients who are antiphospholipid antibody carriers, without clinical signs associated with APS, specific prophylactic treatment is recommended with low molecular weight heparin in situations of high thrombotic risk. Thromboprophylaxis with low molecular weight heparin is recommended in patients with a high-risk serological profile and neoplasia, especially in situations with increased thromboembolic risk. Enoxaparin is to be given as follows: Prophylactic Dosing: For those who weigh < 50 kg: 20 mg/day, 50-90 kg: 40 mg/day, 91-130 kg: 60 mg/day, 131-170 kg: 80 mg/day, > 170 kg: 0.6 mg/kg/day, High prophylaxis: 40 mg/12h. Intermediate Doses of LMWH: 1 mg/kg/day. Its use is limited by the heightened risk of developing major bleeding, spinal or epidural hematomas and thrombocytopenia.

2.1.3.2 Tinzaparin

Information on Tinzaparin is detailed in the table below[29,30]:

Table 18. Drug Therapy with Tinzaparin

SCIENTIFIC NAME TINZAPARIN	
SFDA Classification	Prescription
SFDA Approval	Yes
US FDA	No
EMA	No
MHRA	Yes
PMDA	Yes
Indication (ICD-10)	D68.61
Drug Class	Antithrombotic Agent
Drug Sub-class	Heparin Group
ATC Code	B01AB10
Pharmacological Class (ASHP)	Low Molecular Weight Heparin
DRUG INFORMATION	
Dosage Form	Injectable, Subcutaneous Solution Prefilled Syringe, Subcutaneous
Route of Administration	Subcutaneous Use
Dose (Adult) [DDD]*	**Prophylactic Dosing[15]:** For those who weigh < 50 kg: 3500 U/Day 50-90 kg: 4500 U/Day 91-130 kg: 7000 U/Day 131-170 kg: 9000 U/Day > 170 kg: 75 U/Kg/Day High prophylaxis: 4500 IU/12h
Maximum Daily Dose Adults*	Maximum dose in prophylaxis: 14,000 anti-Xa units once daily
Dose (pediatrics)	N/A
Maximum Daily Dose Pediatrics*	N/A
Adjustment	**Altered Kidney Function:** CrCl ≥30 mL/minute: No dosage adjustment necessary.

	CrCl 20 to <30 mL/minute: No dosage adjustment necessary; however, use with caution. CrCl <20 mL/minute: Use of alternative agents should be considered. Hemodialysis, intermittent (thrice weekly): Unlikely to be significantly dialyzable (large molecular weight): For most indications (eg, thrombosis treatment/prophylaxis), use of alternative agents should be considered. If use of tinzaparin is deemed necessary, no initial dosage adjustment is necessary; however, risk of bleeding is increased. Peritoneal dialysis: Unlikely to be significantly dialyzable (large molecular weight): Use of alternative agents should be considered. If use of tinzaparin is deemed necessary, no initial dosage adjustment is necessary. CRRT or PIRRT (eg, sustained, low-efficiency diafiltration): SUBQ: Use of alternative agents should be considered. **Hepatic Impairment:** There are no dosage adjustments provided in the manufacturer's labeling. Does not undergo hepatic metabolism; however, has been associated with transient increases in transaminase levels; use with caution.
Prescribing edits*	N/A
AGE (Age Edit)	N/A
CU (Concurrent Use Edit)	N/A
G (Gender Edit)	N/A
MD (Physician Specialty Edit)	N/A
PA (Prior Authorization)	N/A
QL (Quantity Limit)	N/A
ST (Step Therapy)	N/A

EU (Emergency Use Only)	N/A
PE (Protocol Edit)	N/A
SAFETY	
Main Adverse Drug Reactions (most common and most serious)	**Most common:** Headache, nausea, vomiting, diarrhea, constipation. **Most serious:** Hematuria, urinary tract infections, chest pain, hemorrhage.
Drug Interactions*	**Category X:** • Apixaban • Dabigatran Etexilate • Defibrotide • Edoxaban • Hemin • MiFEPRIStone • Omacetaxine • Rivaroxaban • Urokinase • Vorapaxar
Special Population	**Older adult:** Use with caution due to increased bleeding risks. **Elective surgery/procedure:** In patients receiving bridging anticoagulation with therapeutic dose tinzaparin, the last dose should be administered ~24 hours prior to the surgery/procedure; reinitiate therapy ≥24 hours after the surgery/procedure when bleeding risk is acceptable. **Extreme body weights:** Use with caution in patients <45 kg or >120 kg; limited experience in these patients. Individualized clinical and laboratory monitoring are recommended.
Pregnancy	Tinzaparin does not cross the placenta. An increased risk of fetal bleeding or teratogenic effects has not been reported. Due to pregnancy-induced physiologic changes, some pharmacokinetic

	properties of low-molecular-weight heparin (LMWH) may be altered; dosing adjustment may be required. Prophylactic doses of LMWH may also need modified in pregnant patients at extremes of body weight. Use is contraindicated in conditions involving increased risks of hemorrhage, including patients with imminent abortion. The risk of venous thromboembolism (VTE) is increased in pregnant patients, especially during the third trimester and first week postpartum. LMWH is recommended over unfractionated heparin for the treatment of acute VTE in pregnant patients. LMWH is also recommended over unfractionated heparin for VTE prophylaxis in pregnant patients with certain risk factors (eg, homozygous factor V Leiden, antiphospholipid antibody syndrome with ≥3 previous pregnancy losses). LMWH may also be considered for VTE prophylaxis in pregnant patients with COVID-19. LMWH may be used prior to cesarean delivery in patients with additional risk factors for developing VTE. Risk factors may include a personal history of deep vein thrombosis or pulmonary embolism, inherited thrombophilia, or patients with class III obesity. LMWH may also be used in pregnant patients with mechanical heart valves. When choosing therapy, fetal outcomes (ie, pregnancy loss, malformations), maternal outcomes (ie, VTE, hemorrhage), burden of therapy, and maternal preference should be considered. Patients with mechanical

	heart valves have an increased risk of adverse fetal and maternal outcomes (including valve thrombosis), and these risks are greater without appropriate anticoagulation. Increased monitoring of anti-factor Xa levels is required; frequent dose titration may be needed to maintain adequate therapeutic anti-factor Xa concentrations during pregnancy. Multiple-dose vials contain benzyl alcohol (avoid use in pregnant patients due to association with gasping syndrome in premature infants); use of preservative-free formulation is recommended.
Lactation	It is not known if tinzaparin is present in breast milk. Small amounts of another low-molecular-weight heparin (LMWH) have been detected in breast milk; however, because they have a low oral bioavailability, LMWHs are unlikely to cause adverse events in a breastfeeding infant. According to the manufacturer, caution should be used if administered to a breastfeeding patient. LMWH is considered compatible with breastfeeding.
Contraindications	Hypersensitivity to tinzaparin, heparin, or other low molecular weight heparins (LMWH), or any component of the formulation; active bleeding from a local lesion such as an acute ulcer (eg, gastric, duodenal) or ulcerating carcinoma; history of confirmed or suspected immunologically mediated heparin-induced thrombocytopenia (HIT) or positive in vitro platelet-aggregation test in the presence of tinzaparin; acute or subacute septic

	endocarditis; active major hemorrhage or conditions/diseases involving increased risk of hemorrhage (eg, severe hepatic insufficiency, imminent abortion); hemophilia or major blood clotting disorders; acute cerebral insult or hemorrhagic cerebrovascular accidents without systemic emboli; uncontrolled severe hypertension; diabetic or hemorrhagic retinopathy; injury or surgery involving the brain, spinal cord, eyes or ears; spinal/epidural anesthesia in patients requiring treatment dosages of tinzaparin; use of multi-dose vials containing benzyl alcohol in children <3 years of age, premature infants, and neonates.
Monitoring Requirements	CBC with platelet count (at baseline then periodically throughout therapy); renal function (use Cockcroft-Gault formula); hepatic function; potassium (baseline and regularly thereafter in patients at risk for hyperkalemia); stool for occult blood. Routine monitoring of anti-Xa levels is generally not recommended; however, anti-Xa levels may be beneficial in certain patients (eg, children, obese patients, patients with severe renal insufficiency receiving therapeutic doses, and possibly pregnant women receiving therapeutic doses). Peak anti-Xa levels are measured 4 to 6 hours after administration. Monitoring of PT and/or aPTT is not recommended.
Precautions	**Bleeding:** Monitor patient closely for signs or symptoms of bleeding, which may occur at any site. Certain patients are at increased risk of bleeding. Risk factors include bacterial endocarditis; congenital or acquired bleeding

	disorders; active ulcerative or angiodysplastic GI diseases; severe uncontrolled hypertension; history of hemorrhagic stroke; or use shortly after brain, spinal, or ophthalmology surgery; those concomitantly treated with drugs that increase the risk of bleeding (eg, antiplatelet agents, anticoagulants); recent GI bleeding; thrombocytopenia or platelet defects; severe liver disease; hypertensive or diabetic retinopathy; or in patients undergoing invasive procedures. Withhold or discontinue for minor bleeding. Protamine infusion may be necessary for serious bleeding. **Hyperkalemia:** Monitor for hyperkalemia. Heparin can cause hyperkalemia by suppressing aldosterone production; similar reactions could occur with LMWHs. Most commonly occurs in patients with risk factors for the development of hyperkalemia (eg, diabetes, renal dysfunction, preexisting metabolic acidosis, concomitant use of potassium-sparing diuretics or potassium supplements, long-term use of tinzaparin, and hematoma in body tissues). **Thrombocytopenia:** Cases of thrombocytopenia including thrombocytopenia with thrombosis have occurred. Use with caution in patients with history of thrombocytopenia (drug-induced or congenital) or platelet defects; monitor platelet count closely. Use is contraindicated in patients with history of confirmed or suspected heparin-induced thrombocytopenia (HIT) or positive in vitro test for antiplatelet

	antibodies in the presence of tinzaparin. Discontinue therapy and consider alternative treatment if platelets are <100,000/mm3 and/or thrombosis develops. **Thrombocytosis:** Asymptomatic thrombocytosis has been observed with use, particularly in patients undergoing orthopedic surgery or with concurrent inflammatory process; discontinue use with increased platelet counts and evaluate the risks/necessity of further therapy.
Black Box Warning	N/A – No longer available in the US.
REMS*	N/A

HEALTH TECHNOLOGY ASSESSMENT (HTA)

The table below lists the HTA reviews and recommendations of antiphospholipid syndrome treatment options by the following agencies/institutes/authorities: National Institute for Health and Care Excellence (NICE), Canadian Agency for Drugs and Technologies in Health (CADTH), Haute Autorité de Santé (HAS), Institute for Quality and Efficiency in Health Care (IQWIG), and Pharmaceutical Benefits Advisory Committee (PBAC) as applicable. **The recommendations below are for Tinzaparin.**

Table 19. HTA Analysis for Tinzaparin

MEDICATION	AGENCY	DATE – HTA RECOMMENDATION
Tinzaparin	NICE	Not available
	CADTH	Not available
	HAS	**Positive Recommendation** – January 20, 2010 The actual benefit provided by Tinzaparin specialties remains significant in the MA indications.
	IQWIG	Not available
	PBAC	Not applicable

CONCLUSION STATEMENT – Tinzaparin

The standard treatment for patients with venous thrombosis in APS is initial anticoagulation with unfractionated heparin or low molecular weight heparin transitioned to a VKA, commonly warfarin, which is continued indefinitely. For obstetric APS, the most common approach for management is the combination of heparin (unfractionated or low molecular weight; prophylactic or intermediate dose) and low-dose aspirin (75-100 mg) daily. In patients who are antiphospholipid antibody carriers, without clinical signs associated with APS, specific prophylactic treatment is recommended with low molecular weight heparin in situations of high thrombotic risk. Thromboprophylaxis with low molecular weight heparin is recommended in patients with a high-risk serological profile and neoplasia, especially in situations with increased thromboembolic risk. Tinzaparin is to be given as follows: Prophylactic Dosing: For those who weigh < 50 kg: 3500 U/Day, 50-90 kg: 4500 U/Day, 91-130 kg: 7000 U/Day, 131-170 kg: 9000 U/Day, > 170 kg: 75U/Kg/Day, High prophylaxis: 4500 IU/12h. Intermediate Doses of LMWH: 8000 UI/d SC. The use of Tinzaparin is limited by its heightened risk of developing hematuria, urinary tract infections, chest pain, and hemorrhage.

2.1.3.3 Bemiparin

Information on Bemiparin is detailed in the table below[29,30]:

Table 20. Drug Therapy with Bemiparin

SCIENTIFIC NAME BEMIPARIN	
SFDA Classification	Prescription
SFDA Approval	Yes
US FDA	No
EMA	Yes
MHRA	Yes
PMDA	No
Indication (ICD-10)	D68.61
Drug Class	Antithrombotic Agent
Drug Sub-class	Heparin Group
ATC Code	B01AB12
Pharmacological Class (ASHP)	Low Molecular Weight Heparin
DRUG INFORMATION	
Dosage Form	Solution, Subcutaneous

Route of Administration	Subcutaneous Use
Dose (Adult) [DDD]*	**Prophylactic Dosing:** For those who weigh < 50 kg: 2500 U/Day 50-90 kg: 3500 U/Day **Intermediate Doses of LMWH:** 5000 U/d SC (75 UI/d SC approx.)
Maximum Daily Dose Adults*	N/A
Dose (pediatrics)	N/A
Maximum Daily Dose Pediatrics*	N/A
Adjustment	**Altered Kidney Function: Adult** CrCl ≥30 mL/minute: No dosage adjustment necessary; however, close monitoring is recommended if CrCl <80 mL/minute. CrCl <30 mL/minute: Consider monitoring anti-Xa levels ~4 hours post-dose. **Hepatic Impairment: Adult** Mild to moderate impairment: There are no dosage adjustments provided in the manufacturer's labeling (insufficient data); use with caution. Severe impairment: Use is contraindicated.
Prescribing edits*	AGE
AGE (Age Edit)	Safety and effectiveness of Bemiparin in pediatric patients have not been established.
CU (Concurrent Use Edit)	N/A
G (Gender Edit)	N/A
MD (Physician Specialty Edit)	N/A
PA (Prior Authorization)	N/A
QL (Quantity Limit)	N/A
ST (Step Therapy)	N/A
EU (Emergency Use Only)	N/A
PE (Protocol Edit)	N/A
SAFETY	

Main Adverse Drug Reactions (most common and most serious)	**Most common:** Hematoma and/or ecchymosis at the injection site, pain at the injection site. **Most serious:** Osteoporosis, hyperkalemia, bleeding complications, anaphylaxis, thrombocytopenia.
Drug Interactions*	**Category X:** • Apixaban • Dabigatran Etexilate • Defibrotide • Edoxaban • Hemin • MiFEPRIStone • Omacetaxine • Rivaroxaban • Urokinase • Vorapaxar
Special Population	N/A
Pregnancy	Adverse events were not observed in animal reproduction studies. Information related to the use of Bemiparin is limited.
Lactation	It is not known if Bemiparin is excreted into breast milk; breast-feeding is not recommended by the manufacturer.
Contraindications	Hypersensitivity to Bemiparin, any component of the formulation, other low molecular weight heparins and/or heparin, or substances of porcine origin; history of confirmed or suspected immunologically mediated heparin-induced thrombocytopenia (HIT); disseminated intravascular coagulation (DIC) due to HIT; active hemorrhage or increased risk of bleeding due to impairment of hemostasis; severe hepatic or pancreatic impairment; injuries to and operations on the brain, spinal cord, eyes, and ears within the last 2 months; acute infective

	endocarditis and slow endocarditis; organic lesions likely to bleed (active peptic ulceration, hemorrhagic stroke, cerebral aneurysm, cerebral neoplasms); spinal/epidural anesthesia in patients requiring treatment dosages of Bemiparin.
Monitoring Requirements	Antifactor Xa levels (recommended to obtain levels 4 hours post dose in patients with severe renal insufficiency); renal function; serum electrolytes (prior to therapy in patients at risk of hyperkalemia and regularly if treatment is prolonged >7 days); platelet counts (baseline, on the first day of therapy, routinely every 3 to 4 days, and at the end of therapy).
Precautions	**Bleeding:** Monitor patient closely for signs or symptoms of bleeding. Certain patients are at increased risk of bleeding. Risk factors include severe liver disease, uncontrolled arterial hypertension, history or GI disease, thrombocytopenia, nephrolithiasis and/or urethrolithiasis, choroid and retinal vascular disease, any other organic lesions with increased bleeding risk, patients undergoing lumbar puncture and/or spinal or epidural anesthesia, and patients treated concomitantly with platelet inhibitors. **Cutaneous necrosis:** Cutaneous necrosis preceded by purpura or infiltrated or painful erythematous blotches has been reported rarely; discontinue treatment immediately if suspected. **Hyperkalemia:** May cause hyperkalemia due to suppressing aldosterone production. Most commonly occurs in patients with risk

	factors for the development of hyperkalemia (eg, renal dysfunction, diabetes mellitus, concomitant use of potassium-sparing diuretics or potassium supplements). Monitor for hyperkalemia, especially in patients on prolonged therapy (>7 days). **Thrombocytopenia:** Rare cases of severe thrombocytopenia have occurred. This generally occurs within 5 to 21 days of treatment initiation or may occur earlier in patients with a history of heparin-induced thrombocytopenia (HIT). Monitor platelet counts closely. Use is contraindicated in patients with history of confirmed or suspected HIT. Discontinue therapy and consider alternative treatment if platelets are significantly reduced (30% to 50% reduction) or if results of in vitro antiplatelet antibody tests are positive in the presence of Bemiparin or other LMWH.
Black Box Warning	N/A – No longer available in the US.
REMS*	N/A

HEALTH TECHNOLOGY ASSESSMENT (HTA)

The table below lists the HTA reviews and recommendations of antiphospholipid syndrome treatment options by the following agencies/institutes/authorities: National Institute for Health and Care Excellence (NICE), Canadian Agency for Drugs and Technologies in Health (CADTH), Haute Autorité de Santé (HAS), Institute for Quality and Efficiency in Health Care (IQWIG), and Pharmaceutical Benefits Advisory Committee (PBAC) as applicable. **The recommendations below are for Bemiparin.**

Table 21. HTA Analysis for Bemiparin

MEDICATION	AGENCY	DATE – HTA RECOMMENDATION
Bemiparin	NICE	Not available
	CADTH	Not available
	HAS	Not available

	IQWIG	Not available
	PBAC	Not applicable

CONCLUSION STATEMENT – Bemiparin

The standard treatment for patients with venous thrombosis in APS is initial anticoagulation with unfractionated heparin or low molecular weight heparin transitioned to a VKA, commonly warfarin, which is continued indefinitely. For obstetric APS, the most common approach for management is the combination of heparin (unfractionated or low molecular weight; prophylactic or intermediate dose) and low-dose aspirin (75-100 mg) daily. In patients who are antiphospholipid antibody carriers, without clinical signs associated with APS, specific prophylactic treatment is recommended with low molecular weight heparin in situations of high thrombotic risk. Thromboprophylaxis with low molecular weight heparin is recommended in patients with a high-risk serological profile and neoplasia, especially in situations with increased thromboembolic risk. Bemiparin is to be given as follows: Prophylactic Dosing: Prophylactic Dosing: For those who weigh < 50 kg: 2500 U/Day, 50-90 kg: 3500 U/Day. Intermediate Doses of LMWH: 5000 U/d SC (75 UI/d SC approx.) The use of Bemiparin is limited by the heightened risk of developing osteoporosis, hyperkalemia, bleeding complications, anaphylaxis, and thrombocytopenia.

2.2 Antiplatelet Agents

2.2.1 Aspirin

Information on Aspirin are detailed in the table below[29,30]:

Table 22. Drug Therapy with Aspirin

SCIENTIFIC NAME ACETYL SALICYLIC ACID	
SFDA Classification	Over the counter (OTC)
SFDA	Yes
US FDA	Yes
EMA	Yes
MHRA	Yes
PMDA	Yes
Indication (ICD-10)	D68.61
Drug Class	Other analgesics and antipyretics
Drug Sub-class	Salicylic acid and derivatives

ATC Code	N02BA01
Pharmacological Class (ASHP)	Antiplatelet, Non-opioid analgesic - Irreversible COX1/COX2 Inhibitor
DRUG INFORMATION	
Dosage Form	Enteric-coated tablets
Route of Administration	Oral
Dose (Adult) [DDD]*	Low Dose Aspirin: 75-100 mg
Maximum Daily Dose Adults*	325 mg
Dose (pediatrics)	N/A
Maximum Daily Dose Pediatrics*	N/A
Adjustment	**Altered Kidney Function:** No dose adjustment required **Hepatic Impairment:** Avoid use in severe liver disease
Prescribing edits*	AGE
AGE (Age Edit)	Aspirin should not be given to children aged under 16 unless on the advice of a physician.
CU (Concurrent Use Edit)	N/A
G (Gender Edit)	N/A
MD (Physician Specialty Edit)	N/A
PA (Prior Authorization)	N/A
QL (Quantity Limit)	N/A
ST (Step Therapy)	N/A
EU (Emergency Use Only)	N/A
PE (Protocol Edit)	N/A
SAFETY	
Main Adverse Drug Reactions (most common and most serious)	**Most common:** Nausea, diarrhea, abdominal pain. **Most serious:** Bleeding, thrombocytopenia, anaphylaxis and melena.
Drug Interactions*	**Category X:** Dexibuprofen Dexketoprofen Influenza Virus Vaccine (Live/Attenuated) Ketorolac (Nasal)

	Ketorolac (Systemic) Macimorelin Measles, Mumps, Rubella, and Varicella Virus Vaccine Omacetaxine Probenecid Sulfinpyrazone Urokinase Varicella Virus Vaccine
Special Population	**GI Bleed Patients:** An individualized and multidisciplinary approach should be used to manage patients with an acute GI bleed who are on antiplatelet medications. Aspirin for primary prevention of cardiovascular events should be avoided in most patients with GI bleed who do not have high risk factors for cardiovascular events. However, aspirin for secondary cardiovascular prevention should not be discontinued in patients with established cardiovascular disease, even in the setting of a GI bleed. If held in the setting of a GI bleed, aspirin for secondary cardiovascular prevention should be resumed on the day hemostasis is confirmed by endoscopy. **Pediatrics:** When used for self-medication (OTC labeling): Children and teenagers who have or are recovering from chickenpox or flu-like symptoms should not use this product. Changes in behavior (along with nausea and vomiting) may be an early sign of Reye syndrome; patients should be instructed to contact their healthcare provider if these occur. **Surgical Patients:** Patients who have recently undergone percutaneous coronary intervention with stenting or balloon angioplasty should continue

	antiplatelet therapy until it is safe to temporarily hold treatment. In patients undergoing CABG, aspirin may be continued until the time of surgery. Elective surgery for these patients should be delayed. Aspirin can typically be continued perioperatively in patients who undergo elective non-cardiac surgery. If aspirin interruption is necessary, discontinue therapy ≤7 days before surgery, and resume as soon as possible (eg, ≤24 hours) after surgery based on bleeding and thrombotic risks.
Pregnancy	Fetal outcomes are influenced by maternal dose; low dose aspirin (≤150 mg/day) is not associated with the same risks as higher doses and has a positive effect on some pregnancy outcomes. Adverse effects reported in the fetus following maternal use of high dose aspirin include mortality, intrauterine growth restriction, salicylate intoxication, bleeding abnormalities, and neonatal acidosis. Use of aspirin close to delivery may cause premature closure of the ductus arteriosus. Adverse effects reported in the mother include anemia, hemorrhage, prolonged gestation, and prolonged labor. Except when used in lower doses for pregnancy-related conditions, maternal use of aspirin should be avoided beginning 20 weeks gestation. The American College of Obstetricians and Gynecologists and United States Preventive Services Task Force recommend the use of low-dose aspirin for patients with ≥1 of the following high-risk factors: history of preeclampsia, multifetal gestation, chronic hypertension, type 1 or type 2

	diabetes mellitus, renal disease, autoimmune disease (eg, systemic lupus erythematosus, antiphospholipid syndrome), or combinations of multiple moderate risk factors. Low-dose aspirin is also recommended for patients with ≥2 of the following moderate risk factors: nulliparity, BMI >30, family history of preeclampsia, Black race (due to social, rather than biological, factors), lower income, age ≥35 years, personal history factors (eg, low birth weight or small for GA, previous adverse pregnancy outcome, >10-year pregnancy interval), or in vitro conception. Low-dose aspirin may also be considered in patients with ≥1 of the following moderate risk factors: Black race (due to social, rather than biological, factors), lower income. In addition to preventing preeclampsia, low-dose aspirin is also recommended to improve other pregnancy outcomes and decrease the risk of thrombosis in patients with a positive antiphospholipid antibody (aPL) test. The addition of heparin or low-molecular-weight heparin may also be needed in patients with obstetric or thrombotic antiphospholipid syndrome (APS). Low-dose aspirin is also recommended for pregnant patients with systemic lupus erythematosus (SLE).
Lactation	Low-dose aspirin may be used in breastfeeding patients; however, standard doses of aspirin should be avoided due to the possible risk of neonatal metabolic acidosis, hemolysis, and the theoretical risk of Reye syndrome Low doses of aspirin (75 to 162

	mg/day) may be used; however, other agents are preferred if higher doses are needed. When used for vascular indications, breastfeeding may be continued during low-dose aspirin therapy.
Contraindications	Hypersensitivity to NSAIDs; patients with asthma, rhinitis, and nasal polyps; use in children or teenagers for viral infections, with or without fever.
Monitoring Requirements	Monitor for signs and symptoms of drug reaction with eosinophilia and systemic symptoms (eg, fever, rash, lymphadenopathy, eosinophilia in association with other organ system involvement such as hepatitis, nephritis, hematological abnormalities, myocarditis, myositis; early symptoms of hypersensitivity reaction may occur without rash).
Precautions	• **Bariatric surgery:** - Altered absorption and efficacy: Altered absorption and efficacy may occur. - Gastric ulceration: Evaluate the risk vs benefit of aspirin after surgery; if aspirin therapy is continued (eg, cardiovascular indications), use the lowest possible dose with concurrent administration of proton pump inhibitor (PPI); risk of gastric ulceration after gastric bypass and sleeve gastrectomy may be increased. • **Bleeding disorders:** Use with caution in patients with platelet and bleeding disorders. • **Dehydration:** Use with caution in patients with dehydration.

	• **Ethanol use:** Heavy ethanol use (>3 drinks/day) can increase bleeding risks. • **Gastrointestinal disease:** Use with caution in patients with erosive gastritis. Avoid use in patients with active peptic ulcer disease. • **Hepatic impairment:** Avoid use in severe hepatic failure. • **Renal impairment:** Low-dose aspirin (eg, 75 to 162 mg daily) may be safely used in patients with any degree of renal impairment.
Black Box Warning	N/A
REMS*	N/A

HEALTH TECHONOLOGY ASSESSMENT (HTA)

The table below lists the HTA reviews and recommendations of antiphospholipid syndrome treatment options by the following agencies/institutes/authorities: National Institute for Health and Care Excellence (NICE), Canadian Agency for Drugs and Technologies in Health (CADTH), Haute Autorité de Santé (HAS), Institute for Quality and Efficiency in Health Care (IQWIG), and Pharmaceutical Benefits Advisory Committee (PBAC) as applicable. **The recommendations below are for Aspirin.**

Table 23. HTA Analysis for Aspirin

Medication	Agency	Date – HTA Recommendation
Aspirin	NICE	Not available
	CADTH	Not applicable
	HAS	Not available
	IQWIG	Not applicable
	PBAC	Not applicable

CONCLUSION STATEMENT- ASPIRIN

In asymptomatic aPL carriers with a high-risk aPL profile with or without traditional risk factors, prophylactic treatment with LDA is recommended. In patients with SLE and no history of thrombosis or pregnancy complications: With high-risk aPL profile, prophylactic treatment with LDA is recommended, and with low-risk aPL profile, prophylactic treatment with LDA may be considered. In non-pregnant women with a history of obstetric APS only (with or without SLE), prophylactic treatment with LDA after adequate risk/benefit evaluation is recommended. In women with a high-risk aPL profile but no history of thrombosis or pregnancy complications (with or without SLE), treatment with LDA during pregnancy should be considered. LDA is given as 75-100mg once daily. It also may be given in combination with heparin groups in certain cases. The use of Aspirin is limited by its heightened risks of developing bleeding, thrombocytopenia, anaphylaxis, and melena; however, since it is given at a low dose, the risk of adverse events is minimal compared to higher doses.

2.3 Corticosteroids

2.3.1 Methylprednisolone

Information on Methylprednisolone is detailed in the table below[29,30]:

Table 24. Drug Therapy with Methylprednisolone

SCIENTIFIC NAME METHYLPREDNISOLONE	
SFDA Classification	Prescription
SFDA Approval	Yes
US FDA	Yes
EMA	Yes
MHRA	Yes
PMDA	Yes
Indication (ICD-10)	D68.61
Drug Class	Anti-inflammatory Agent
Drug Sub-class	Corticosteroids
ATC Code	H02AB02
Pharmacological Class (ASHP)	Systemic Corticosteroids
DRUG INFORMATION	
Dosage Form	Oral solution, solution for injection
Route of Administration	Oral and intravenous use

Dose (Adult) [DDD]	1000 mg per day for 3-5 days
Maximum Daily Dose Adults	N/A
Dose (pediatrics)	N/A
Maximum Daily Dose Pediatrics	N/A
Adjustment	There are no dosage adjustments provided in the manufacturer's labeling.
Prescribing edits	CU, QL
AGE (Age Edit)	N/A
CU (Concurrent Use Edit)	In CAPS, based on observational data and expert opinion, anticoagulation with heparin and high-dose steroids (methylprednisolone 1000 mg daily for 3 days or longer) are the mainstay of therapy.
G (Gender Edit)	N/A
MD (Physician Specialty Edit)	N/A
PA (Prior Authorization)	N/A
QL (Quantity Limit)	The duration of treatment is a few days. A longer duration of steroids may be needed, and this can usually be given orally but this will be decided following discussion with the consultant physician.
ST (Step Therapy)	N/A
EU (Emergency Use Only)	N/A
PE (Protocol Edit)	N/A
SAFETY	
Main Adverse Drug Reactions (most common and most serious)	**Most common:** Hypertension, tachycardia, nausea. **Most serious:** Adrenal suppression (tertiary adrenal insufficiency), Cushing syndrome, hyperglycemia, apathy/depression, peptic ulcers, infections, osteoporosis, glaucoma, and cataracts.
Drug Interactions*	**Category X:** Aldesleukin BCG (Intravesical) Brivudine

	Cladribine Desmopressin Disulfiram Fexinidazole Fusidic Acid (Systemic) Indium 111 Capromab Pendetide Lapatinib Macimorelin Methotrimeprazine Mifamurtide MiFEPRIStone Nadofaragene Firadenovec Natalizumab Ornidazole Pimecrolimus Rilpivirine Ritlecitinib Ruxolitinib (Topical) Secnidazole Simeprevir Tacrolimus (Topical) Talimogene Laherparepvec Tertomotide
Special Population	**Older adults:** Use with caution in elderly patients with the smallest possible effective dose for the shortest duration. **Pediatrics:** May affect growth velocity; growth should be routinely monitored in pediatric patients.
Pregnancy	Teratogenic effects: Pregnancy Category C Corticosteroids should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.
Lactation	Systemically administered corticosteroids appear in human milk and could suppress growth, interfere with endogenous corticosteroid production, or cause other untoward

	effects. Because of the potential for serious adverse reactions in nursing infants from corticosteroids, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.
Contraindications	Hypersensitivity to methylprednisolone or any component of the formulation; systemic fungal infection (except intra-articular injection for localized joint conditions); intrathecal administration; live or attenuated virus vaccines (with immunosuppressive doses of corticosteroids); immune thrombocytopenia (formerly known as idiopathic thrombocytopenic purpura). Significant drug interactions exist, requiring dose/frequency adjustment or avoidance.
Monitoring Requirements	Blood pressure, blood glucose, electrolytes; weight; intraocular pressure (use >6 weeks); consider routine eye exams with chronic use; creatine kinase; bone mineral density; growth and development in children; HPA axis suppression.
Precautions	**Adrenal suppression:** May cause hypercortisolism or suppression of hypothalamic-pituitary-adrenal (HPA) axis, particularly in younger children. **Hepatic effects:** High doses of methylprednisolone IV (usually doses of 1 g/day in adults) may induce a toxic form of acute hepatitis (rare); serious hepatic injury may occur, resulting in acute liver failure and death. Time to onset can be several weeks or longer; resolution has been observed after discontinuation of therapy. Discontinue methylprednisolone if toxic hepatitis

	occurs. Avoid use of high doses in patients with a history of methylprednisolone-induced toxic hepatitis. **Septic arthritis:** May occur as a complication to parenteral therapy; institute appropriate antimicrobial therapy as required. **Cardiovascular disease:** Use with caution in patients with heart failure (HF) and/or hypertension; use has been associated with fluid retention, electrolyte disturbances, and hypertension. Use with caution following acute myocardial infarction (MI); corticosteroids have been associated with myocardial rupture. **Gastrointestinal disease:** Use with caution in patients with GI diseases (diverticulitis, fresh intestinal anastomoses, active or latent peptic ulcer, ulcerative colitis, abscess or other pyogenic infection) due to perforation risk. **Head injury:** Increased mortality was observed in patients receiving high-dose IV methylprednisolone; high-dose corticosteroids should not be used for the management of head injury. **Hepatic impairment:** Use with caution in patients with hepatic impairment, including cirrhosis; long-term use has been associated with fluid retention. **Ocular disease:** Not recommended for the treatment of optic neuritis; may increase frequency of new episodes. Use with caution in patients with a history of ocular herpes simplex; corneal perforation has occurred; do not use in active ocular herpes simplex.

	Renal impairment: Use with caution in patients with renal impairment; fluid retention may occur. **Seizure disorders:** Use corticosteroids with caution in patients with a history of seizure disorder; seizures have been reported with adrenal crisis. **Septic shock or sepsis syndrome:** Corticosteroids should not be administered for the treatment of sepsis in the absence of shock. **Systemic sclerosis (scleroderma):** Use of higher dose corticosteroid therapy (in adults, ≥15 mg/day of prednisone or equivalent) in patients with systemic sclerosis may increase the risk of scleroderma renal crisis; avoid use when possible. **Thyroid disease:** Changes in thyroid status may necessitate dosage adjustments; metabolic clearance of corticosteroids increases in hyperthyroid patients and decreases in hypothyroid ones.
Black Box Warning	N/A
REMS*	N/A

HEALTH TECHNOLOGY ASSESSMENT (HTA)

The table below lists the HTA reviews and recommendations of antiphospholipid syndrome treatment options by the following agencies/institutes/authorities: National Institute for Health and Care Excellence (NICE), Canadian Agency for Drugs and Technologies in Health (CADTH), Haute Autorité de Santé (HAS), Institute for Quality and Efficiency in Health Care (IQWIG), and Pharmaceutical Benefits Advisory Committee (PBAC) as applicable. **The recommendations below are for Methylprednisolone.**

Table 25. HTA Analysis for Methylprednisolone

MEDICATION	AGENCY	DATE – HTA RECOMMENDATION
Methylprednisolone	NICE	Not available
	CADTH	Not available
	HAS[19]	**Positive Recommendation** – April 30, 2021 Favorable opinion for reimbursement in all MA indications for general corticosteroid therapy, when high doses are necessary.
	IQWIG	Not available
	PBAC	Not applicable

CONCLUSION STATEMENT- Methylprednisolone

Based on observational data and expert opinion, anticoagulation with heparin and high-dose steroids (methylprednisolone 1000 mg daily for 3 days or longer) are the mainstay of therapy. Methylprednisolone is backed by HAS as an HTA body; however, its use if limited by its heightened risk of developing adrenal suppression (tertiary adrenal insufficiency), Cushing syndrome, hyperglycemia, apathy/depression, peptic ulcers, infections, osteoporosis, glaucoma, and cataracts.

2.4 Aminoquinolines

2.4.1 Hydroxychloroquine

Information on Hydroxychloroquine is detailed in the table below[29,30]:

Table 26. Drug Therapy with Hydroxychloroquine

SCIENTIFIC NAME HYDROXYCHLOROQUINE	
SFDA Classification	Prescription
SFDA Approval	Yes
US FDA	Yes
EMA	Yes
MHRA	Yes
PMDA	Yes
Indication (ICD-10)	D68.61
Drug Class	Antimalarial, Antirheumatic

Drug Sub-class	Aminoquinoline, disease-modifying antirheumatic
ATC Code	P01BA02
Pharmacological Class (ASHP)	Aminoquinoline, disease-modifying antirheumatic
DRUG INFORMATION	
Dosage Form	Tablet
Route of Administration	Oral use
Dose (Adult) [DDD]	The dosage of HCQ that was used was based on the clinical medication for autoimmune diseases (the minimum effective dose should be used for maintenance and should not exceed 6.5 mg/kg/day or 0.4 g/day)[31].
Maximum Daily Dose Adults	Not > 6.5 mg/kg/day using actual body weight or 400 mg, whichever is lower
Dose (pediatrics)	N/A
Maximum Daily Dose Pediatrics	Maximum daily dose: 400 mg/day or 6.5 mg/kg/day
Adjustment	There are no dosage adjustments provided in the manufacturer's labeling; use with caution.
Prescribing edits	CU, ST
AGE (Age Edit)	N/A
CU (Concurrent Use Edit)	HCQ is to be used in combination with VKA.
G (Gender Edit)	N/A
MD (Physician Specialty Edit)	N/A
PA (Prior Authorization)	N/A
QL (Quantity Limit)	N/A
ST (Step Therapy)	The addition of HCQ seems reasonable in patients with obstetric PAPS refractory to conventional treatment or in PAPS patients with previous arterial or recurrent thrombosis. (Especially those of high-risk)
EU (Emergency Use Only)	N/A
PE (Protocol Edit)	N/A

SAFETY	
Main Adverse Drug Reactions (most common and most serious)	**Most common**: Retinopathy, reversible early changes **Most serious**: Cardiomyopathy, G6PD deficiency, delayed hypersensitivity reactions, Hypoglycemia, Neuromuscular effects, Neuropsychiatric effects, QT prolongation, Retinal toxicity
Drug Interactions*	**Category X**: Cimetidine, Mefloquine, Remdesivir
Special Population	No specific recommendations for dosing in older adults. Pediatric patients may have increased sensitivity.
Pregnancy	Hydroxychloroquine can be detected in the cord blood at delivery in concentrations like those in the maternal serum. Adverse perinatal outcomes have not been associated with daily maternal doses of hydroxychloroquine ≤400 mg. Retinal toxicity is a known risk following long-term use or high doses of hydroxychloroquine. Hydroxychloroquine may be beneficial for some pregnant patients with antiphospholipid syndrome.
Lactation	Hydroxychloroquine and the Desethylchloroquine metabolite are present in breast milk. In general, breastfeeding is considered acceptable when the relative infant dose is <10%. According to the manufacturer, the decision to breastfeed during therapy should consider the risk of infant exposure, the benefits of breastfeeding to the infant, and the benefits of treatment to the mother.
Contraindications	Known hypersensitivity to hydroxychloroquine, 4-aminoquinoline

	derivatives, or any component of the formulation. Additional contraindications (not in the US labeling): Preexisting retinopathy; use in children <6 years or weighing <35 kg
Monitoring Requirements	CBC (baseline and periodically), renal function tests, and liver function tests. Obtain ophthalmologic exam at baseline and annually after 5 years of use. Assess muscle strength during prolonged therapy. Assess for signs of cardiomyopathy, bone marrow suppression, neuromuscular effects, and retinal toxicity.
Precautions	Use with caution in patients with myasthenia gravis, avoid use in patients with porphyria and/or psoriasis unless benefits outweigh risks. Use with caution in renal or hepatic impairment. Use with caution in patients with G6PD deficiency due to a potential for hemolytic anemia.
Black Box Warning	N/A
REMS*	N/A

HEALTH TECHNOLOGY ASSESSMENT (HTA)

The table below lists the HTA reviews and recommendations of antiphospholipid syndrome treatment options by the following agencies/institutes/authorities: National Institute for Health and Care Excellence (NICE), Canadian Agency for Drugs and Technologies in Health (CADTH), Haute Autorité de Santé (HAS), Institute for Quality and Efficiency in Health Care (IQWIG), and Pharmaceutical Benefits Advisory Committee (PBAC) as applicable. **The recommendations below are for Hydroxychloroquine.**

Table 27. HTA Analysis for Hydroxychloroquine

MEDICATION	AGENCY	DATE – HTA RECOMMENDATION

Hydroxychloroquine	NICE	Not applicable
	CADTH	Not applicable
	HAS	Not applicable
	IQWIG	Not available
	PBAC	Not applicable

CONCLUSION STATEMENT- Hydroxychloroquine

In thrombotic APS that is refractory to conventional treatment, it is recommended to associate antiaggregant doses of acetylsalicylic acid, hydroxychloroquine, or statins to the conventional therapy. It seems reasonable to consider the addition of HCQ to VKA in the treatment of PAPS patients with previous arterial or recurrent thrombosis especially in high-risk patients and it seems reasonable to consider the addition of HCQ to those patients with obstetric PAPS refractory to conventional treatment and before any consideration of low-dose prednisolone given its more favorable safety profile in pregnancy. HCQ is given at a dose of 6.5 mg/kg/day. Its use is limited by the heightened risk of developing cardiomyopathy, G6PD deficiency, delayed hypersensitivity reactions, hypoglycemia, neuromuscular effects, neuropsychiatric effects, QT prolongation, and retinal toxicity.

Section 3.0 Key Recommendations Synthesis

Classification Criteria for Definite APS

- The APS classification criteria incorporate heterogenous aPL-related clinical and laboratory manifestations into a hierarchically clustered, weighted, and risk-stratified criteria reflecting current thinking about APS, providing high specificity and an improved foundation for APS research[32].
- The revised Sapporo criteria is typically used for the classification of APS.

Diagnosis

- In addition to the classification criteria mentioned above, patients who are positive for APLA may present with no related symptoms. Such patients are usually identified during evaluation for other problems, such as early miscarriages, systemic autoimmune diseases, and an elevated activated partial-thromboplastin time.

Patient Risk Stratification: "Antiphospholipid Profile"

- The aPL profile spectrum is defined by the aPL type, the titer of the antibody, the persistence of aPL positivity in repeated measurements, and the single or multiple antibody positivity.
- It is possible to recognize and correlate some spectrum with increasing risk of clinical potential vascular events and consequently to justify the choice of the intensity of treatment.
- It is generally accepted as:
    - High-risk aPL profile: Four different conditions are considered in this profile if the presence of positive titers is demonstrated in two or more occasions at least 12 weeks apart.
        - LA
        - Double positive (any combination of aCL, anti-β2GPI)
        - Triple positive
        - Presence of persistently high titer of aPL.
    - Medium-high aPL titers:
        - aCL antibody IgG/IgM isotype in titers >40 IGG phospholipid (GPL) units or >40 IgM phospholipid (MPL) units or >99th percentiles, measured by ELISA.
        - anti-β2GPI antibody of IgG/ IgM isotype in titer >99th percentiles, measured by ELISA.

    - Low-risk aPL profile: single positive antibody of aCL or anti-β2GPI at low-medium titers, especially if the positive titer is transient.
- Asymptomatic patients with confirmed positive aPL are not considered for the diagnosis of APS, however, clinicians should assess aPL antibody risk and subsequent evaluation for treatment if required.

<u>Pharmacological Management</u>

Primary Thromboprophylaxis in aPL-Positive Subjects:

- In asymptomatic aPL carriers (not fulfilling any vascular or obstetric APS classification criteria) with a high-risk aPL profile with or without traditional risk factors, prophylactic treatment with LDA (75–100 mg daily) is recommended (2a/B).
- In patients with SLE and no history of thrombosis or pregnancy complications:
    - With high-risk aPL profile, prophylactic treatment with LDA is recommended (2a/B).
    - With low-risk aPL profile, prophylactic treatment with LDA may be considered (2b/C).
- In non-pregnant women with a history of obstetric APS only (with or without SLE), prophylactic treatment with LDA after adequate risk/benefit evaluation is recommended (2b/B).

Secondary Thromboprophylaxis in APS:

- In patients with definite APS and first venous thrombosis:
    - Treatment with VKA with a target INR 2–3 is recommended (1b/B).
    - Rivaroxaban should not be used in patients with triple aPL positivity due to the high risk of recurrent events (1b/B). DOACs could be considered in patients not able to achieve a target INR despite good adherence to VKA or those with contraindications to VKA (eg, allergy or intolerance to VKA) (5/D).
    - In patients with unprovoked first venous thrombosis, anticoagulation should be continued long term (2b/B).
    - In patients with provoked first venous thrombosis, therapy should be continued for a duration recommended for patients without APS according to international guidelines (5/D). Longer anticoagulation could be considered in patients with high-risk aPL profile in repeated measurements or other risk factors for recurrence (5/D).

- In patients with definite APS and recurrent venous thrombosis despite treatment with VKA with target INR of 2–3:
    - Investigation of, and education on, adherence to VKA treatment, along with frequent INR testing, should be considered (5/D).
    - If the target INR of 2–3 had been achieved, addition of LDA, increase of INR target to 3–4 or change to LMWH may be considered (4–5/D).
- In patients with definite APS and first arterial thrombosis:
    - Treatment with VKA is recommended over treatment with LDA only (2b/C).
    - Treatment with VKA with INR 2–3 or INR 3–4 is recommended, considering the individual's risk of bleeding and recurrent thrombosis (1b/B).
    - Treatment with VKA with INR 2–3 plus LDA may also be considered (4/C).
    - Rivaroxaban should not be used in patients with triple aPL positivity and arterial events (1b/B).
    - Based on the current evidence, it is not recommended to use DOACs in patients with definite APS and arterial events due to the high risk of recurrent thrombosis (5/D).
- In patients with recurrent arterial thrombosis despite adequate treatment with VKA, after evaluating for other potential causes, an increase of INR target to 3–4, addition of LDA or switch to LMWH can be considered (4–5/D).

Obstetric APS:

- In women with a high-risk aPL profile but no history of thrombosis or pregnancy complications (with or without SLE), treatment with LDA (75–100 mg daily) during pregnancy should be considered (5/D).
- In women with a history of obstetric APS only (no prior thrombotic events), with or without SLE:
    - With a history of ≥ 3 recurrent spontaneous miscarriages <10th week of gestation and in those with a history of fetal loss (≥10th week of gestation), combination treatment with LDA and heparin at prophylactic dosage during pregnancy is recommended (2b/B).
    - With a history of delivery <34 weeks of gestation due to eclampsia or severe pre-eclampsia or due to recognized features of placental insufficiency, treatment with LDA or LDA and heparin at prophylactic dosage is recommended considering the individual's risk profile (2b/B).

- With clinical ‘non-criteria’ obstetric APS such as the presence of two recurrent spontaneous miscarriages <10th week of gestation, or delivery ≥34 weeks of gestation due to severe pre-eclampsia or eclampsia, treatment with LDA alone or in combination with heparin might be considered based on the individual’s risk profile (4/D).
- With obstetric APS treated with prophylactic dose heparin during pregnancy, continuation of heparin at prophylactic dose for 6 weeks after delivery should be considered to reduce the risk of maternal thrombosis (4/C).

- In women with ‘criteria’ obstetric APS with recurrent pregnancy complications despite combination treatment with LDA and heparin at prophylactic dosage, increasing heparin dose to therapeutic dose (5/D) or addition of HCQ (4/D) or low-dose prednisolone in the first trimester (4/D) may be considered.

  Use of intravenous immunoglobulin might be considered in highly selected cases (5/D).
- In women with a history of thrombotic APS, combination treatment of LDA and heparin at therapeutic dosage during pregnancy is recommended (4/C).

CAPS:

- Prompt treatment of infections by early use of anti-infective medications in all aPL-positive individuals and minimization of interruptions in anticoagulation or low INR level in patients with thrombotic APS are recommended to help prevent the development of CAPS (4/D).
- For first-line treatment of patients with CAPS, combination therapy with glucocorticoids, heparin and plasma exchange or intravenous immunoglobulins is recommended over single agents or other combinations of therapies.

  Additionally, any triggering factor (eg, infections, gangrene or malignancy) should be treated accordingly (5/D).
- In patients with refractory CAPS, B cell depletion (eg, rituximab) or complement inhibition (eg, eculizumab) therapies may be considered (4/D).

Section 4.0 Conclusion

The recommendations provided in this report are intended to assist in the management of antiphospholipid syndrome.

These recommendations should be used to support and not supplant decisions in individual patient management.

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Section 6.0 Appendices

Appendix A. Prescribing Edits Definition

Some covered drugs may have additional requirements, rules, or limits on coverage. These requirements and limits may include:

Prescribing edits Tools	Description
AGE (Age):	Coverage may depend on patient age
CU (Concurrent Use):	Coverage may depend upon concurrent use of another drug
G (Gender):	Coverage may depend on patient gender
MD (Physician Specialty):	Coverage may depend on prescribing physician's specialty or board certification
PA (Prior Authorization):	Requires specific physician request process
QL (Quantity Limits):	Coverage may be limited to specific quantities per prescription and/or time period
ST (Step Therapy):	Coverage may depend on previous use of another drug
EU (Emergency Use only):	This drug status on Formulary is only for emergency use
PE (Protocol Edit):	Use of drug is dependent on protocol combination, doses and sequence of therapy

Appendix B. PubMed Search Methodology Terms

The following PubMed Search Methodology was opted:

Query	Sort By	Filters	Search Details	Results
((((((((((((Antiphospholipid Syndrome[MeSH Terms]) OR (Syndrome, Antiphospholipid[Title/Abstract])) OR (Hughes Syndrome[Title/Abstract])) OR (Syndrome, Hughes[Title/Abstract])) OR (Antiphospholipid Antibody Syndrome[Title/Abstract])) OR (Antibody Syndrome, Antiphospholipid[Title/Abstract])) OR (Antiphospholipid Antibody Syndromes[Title/Abstract])) OR (Syndrome, Antiphospholipid Antibody[Title/Abstract])) OR (Anti-Phospholipid Antibody Syndrome[Title/Abstract])) OR (Anti Phospholipid Antibody Syndrome[Title/Abstract])) OR (Antibody Syndrome, Anti-Phospholipid[Title/Abstract])) OR (Syndrome, Anti-Phospholipid Antibody[Title/Abstract])) OR (Anti-Phospholipid Syndrome[Title/Abstract])) OR (Anti Phospholipid Syndrome[Title/Abstract]))		Guideline, in the last 5 years	("antiphospholipid syndrome"[MeSH Terms] OR "syndrome antiphospholipid"[Title/Abstract] OR "hughes syndrome"[Title/Abstract] OR "syndrome hughes"[Title/Abstract] OR "antiphospholipid antibody syndrome"[Title/Abstract] OR (("antibodie"[All Fields] OR "antibodies"[MeSH Terms] OR "antibodies"[All Fields] OR "antibody s"[All Fields] OR "antibodys"[All Fields] OR "immunoglobulins"[MeSH Terms] OR "immunoglobulins"[All Fields] OR "Antibody"[All Fields]) AND "syndrome antiphospholipid"[Title/Abstract]) OR "antiphospholipid antibody syndromes"[Title/Abstract] OR "syndrome antiphospholipid antibody"[Title/Abstract] OR "anti phospholipid antibody syndrome"[Title/Abstract] OR "anti phospholipid antibody syndrome"[Title/Abstract]	6

OR (Syndrome, Anti-Phospholipid[Title/Abstract])			OR (("antibodie"[All Fields] OR "antibodies"[MeSH Terms] OR "antibodies"[All Fields] OR "antibody s"[All Fields] OR "antibodys"[All Fields] OR "immunoglobulins"[MeSH Terms] OR "immunoglobulins"[All Fields] OR "Antibody"[All Fields]) AND "syndrome anti phospholipid"[Title/Abstract]) OR (("syndrom"[All Fields] OR "syndromal"[All Fields] OR "syndromally"[All Fields] OR "Syndrome"[MeSH Terms] OR "Syndrome"[All Fields] OR "Syndromes"[All Fields] OR "syndrome s"[All Fields] OR "syndromic"[All Fields] OR "syndroms"[All Fields]) AND "anti phospholipid antibody"[Title/Abstract]) OR "anti phospholipid syndrome"[Title/Abstract] OR "anti phospholipid syndrome"[Title/Abstract] OR "syndrome anti phospholipid"[Title/Abstract]) AND ((y_5[Filter]) AND (guideline[Filter]))	

Appendix C. Treatment Algorithm

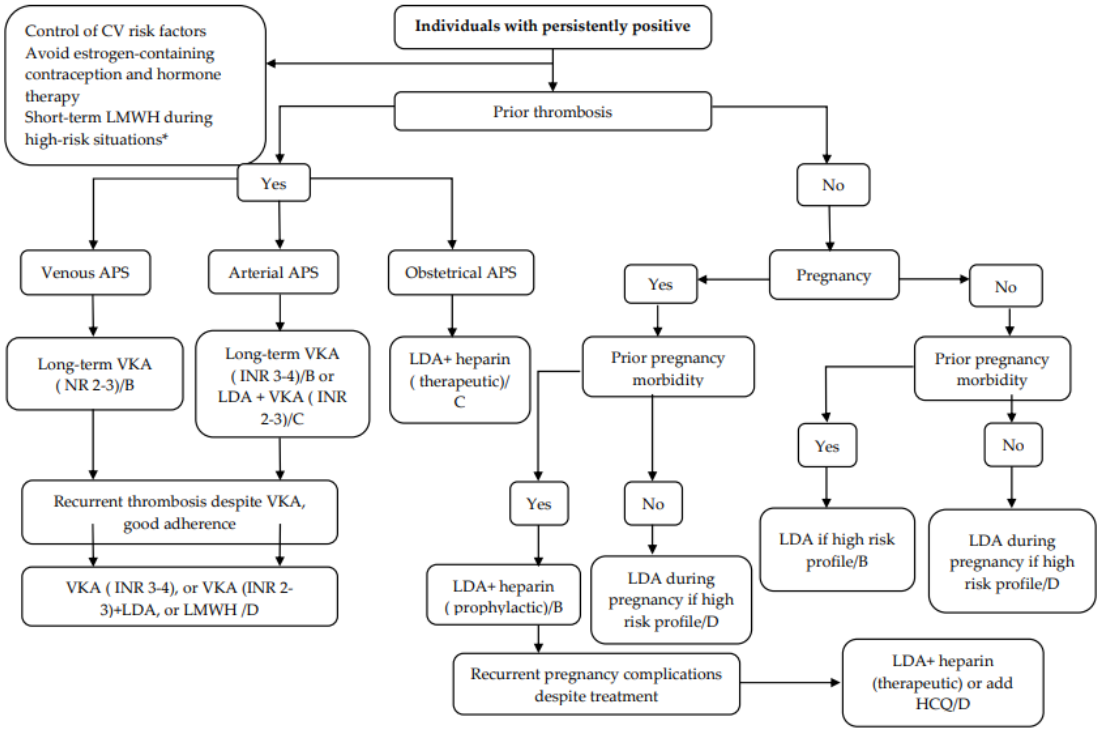

Figure 4. *Treatment Algorithm for the Management of Antiphospholipid Syndrome*

aPL = antiphospholipid antibodies; CV = cardiovascular; DOAC = direct oral anticoagulant; INR = international normalized ratio; LDA = low dose aspirin; LMWH = low molecular weight heparin; VKA = vitamin k antagonist. Recommendation grade: B: consistent level 2 or 3 studies, or extrapolations from level 1 studies; C: level 4 studies or extrapolations from level 2 or 3 studies; D: level 5 evidence or troublingly inconsistent or inconclusive studies of any level.

* Surgery, pregnancy/post-partum, and immobilization[33]