Anaesthetic considerations for patients with antiphospholipid syndrome undergoing non-cardiac surgery

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Abstract
Antiphospholipid syndrome (APS) is an acquired thrombotic autoimmune disorder that is clinically characterized by the development of thrombosis and obstetric morbidities in patients with antiphospholipid antibodies. Due to hypercoagulability, the focus of management is anticoagulation for the prevention of thrombosis and its recurrence. When such patients undergo surgery, however, the underlying risk of thrombosis increases as a result of anticoagulant withdrawal, immobilization, and/or intimal injury. Conversely, there is also an increased risk of bleeding due to thrombocytopenia, possible disseminated intravascular coagulation, or progression to catastrophic APS, as a result of excessive anticoagulation, surgery, and infection. Measures for appropriate perioperative anticoagulation are discussed in this review, as well as anaesthetic considerations for preventing perioperative complications in patients with APS undergoing non-cardiac surgery.

Keywords
Antiphospholipid syndrome, anaesthetic management, anticoagulation, hypercoagulability, surgery, catastrophic antiphospholipid syndrome, intraoperative coagulation monitoring

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Introduction
Antiphospholipid syndrome (APS) is an acquired disorder that was first described in 1983 as anticardiolipin syndrome, and is characterized by thrombotic and obstetric...
manifestations associated with the presence of antiphospholipid antibodies (aPLs). Research concerning APS has advanced continuously over the last 35 years, and APS is now considered to have a multifactorial aetiopathogenesis and involves three well established aPLs: lupus anticoagulant (LA), anticardiolipin antibody (aCL), and anti-β2 glycoprotein I antibody (aβ2GPI). Since the discovery of these three main antibodies, the past 10 years have seen extensive research into novel autoantibodies. Although not included in the diagnostic criteria, anti-β2 glycoprotein I domain I antibody (aβ2GPI DI) and antiphosphatidylserine/prothrombin complex antibody (aPS/PT) have recently emerged as antibodies that are strongly associated with APS. In addition to these, probable APS related antibodies, such as immunoglobulin (Ig) A isotype of anticardiolipin antibody (IgA aCL), anti-β2 glycoprotein I antibody (IgA aβ2GPI), antiprothrombin antibody (aPT), and antiphosphatidylethanolamine antibody (aPE), are being studied extensively. Classification of APS depends on the clinical manifestations: thrombotic APS, characterized by venous, arterial, or microvascular thrombosis; obstetric APS, characterized by obstetric complications in pregnant women, such as recurrent miscarriage, intrauterine growth restriction, and severe pre-eclampsia; and catastrophic APS (CAPS), which accounts for less than 1% of all APS cases and is characterized by multiorgan failure resulting from microthrombi. The prevalence of APS is estimated to be 50 patients per 100 000 population, with an incidence of two patients per 100 000 population per year, and a female-to-male ratio of 5:1. Considering the characteristic hypercoagulability seen in patients with APS, management and treatment focus on preventing thrombosis. However, in such patients undergoing surgery, attention should be given to the occurrence of thrombotic complications while also considering the possibility of perioperative bleeding. Anaesthesiologists have the serious challenge of several considerations for the perioperative anticoagulation and anaesthetic management of patients with APS. The first anaesthetic case report of a patient with lupus anticoagulants was published in 1987, followed 6 years later by publication of the first anaesthetic recommendations for patients with APS. Since then, numerous case reports involving patients with APS have been published, however, no report has specifically discussed the anaesthetic management of these patients. In the present review, measures for appropriate perioperative anticoagulation in patients with APS are discussed. Additionally, perioperative anaesthetic considerations are systematically described in each section, by dividing patients with APS into four groups according to thrombotic and bleeding risk, for convenience.

Patients with APS possess an abnormal in vitro coagulation profile, so standard techniques cannot be used to perform anticoagulation for cardiopulmonary bypass (CPB), to monitor the coagulation profile and set the target level for CPB, or to apply anticoagulation reversal strategies for cardiac surgery. Thus, the intraoperative considerations for cardiac surgery are completely different from those for non-cardiac surgery. The present report aims to review overall methods of anticoagulation and anaesthetic management that anaesthesiologists can routinely refer to, rather than to review the specific conditions of cardiac surgery. Therefore, details of cardiac surgery are excluded from the review. Several databases (PubMed, Google Scholar, and Embase) were searched for papers published between October 1980 and September 2019, using the following keywords: antiphospholipid syndrome,
antiphospholipid antibody, anesthesia or anaesthesia, anesthetic management, perioperative management, perioperative anticoagulation, bridging anticoagulation, and catastrophic antiphospholipid syndrome. References from relevant papers were also selectively reviewed for additional information. All relevant randomized clinical trials, case reports and case series, review articles, and letters were included.

**Table 1.** Clinical manifestations of antiphospholipid syndrome.

| Vascular thrombosis                  |
|--------------------------------------|
| Arterial thrombosis                  |
| Stroke                               |
| Transient ischaemic attack           |
| Myocardial infarction                |
| Venous thrombosis                    |
| Deep vein thrombosis                 |
| Pulmonary embolism                    |
| Small vessel thrombosis              |
| Obstetric morbidity                  |
| ≥1 unexplained fetal death at or beyond week 10 of gestation |
| ≥1 premature birth due to severe pre-eclampsia, eclampsia, or consequences of placental insufficiency |
| ≥3 unexplained consecutive spontaneous abortions before week 10 of gestation |
| Cardiac manifestations               |
| Valvular heart disease (vegetations and/or thickening) |
| Cardiomyopathy                       |
| Neurological manifestations          |
| Cognitive dysfunction                |
| Headache or migraine                 |
| Multiple sclerosis                   |
| Transverse myelopathy                |
| Epilepsy                             |
| Dermatologic manifestations          |
| Livedo reticularis                   |
| Skin ulceration                      |
| Pseudo-vasculitic lesion             |
| Distal gangrene                      |
| Superficial phlebitis                |
| Malignant atrophic papulosis-like lesion |
| Subungal splinter haemorrhage         |
| Renal manifestations                 |
| Thrombotic microangiopathy           |
| Chronic vascular damage              |
| Haematologic manifestations          |
| Thrombocytopaenia                    |
| Haemolytic anaemia                   |

Clinical manifestations and diagnosis

The clinical manifestations of APS are extensive (Table 1), with vascular thrombosis and pregnancy morbidities being the two main features. Thrombosis can be divided into arterial thrombosis (including stroke, transient ischaemic attacks [TIA], myocardial infarction [MI]
and rarely, acute thromboembolic events in the aorta or pulmonary artery), venous thrombosis (including deep vein thrombosis [DVT] and pulmonary thromboembolism [PTE]) and microvessel thrombosis. APS related pregnancy morbidities comprise recurrent miscarriages, fetal deaths, and premature births resulting from placental insufficiency such as intrauterine growth restriction and pre-eclampsia. In a 3-year study from June 2010 by the European Registry on Obstetric Antiphospholipid Syndrome (EUROAPS), the most common obstetric complication among 247 obstetric patients with APS was recurrent miscarriages before 10 weeks of gestation.

The above clinical manifestations of APS are common in individuals without any underlying disease, or with an autoimmune disease besides APS. Therefore, a positive aPL test is essential to diagnose APS. The Sapporo diagnostic criteria were first officially published in 1999, then a newly revised version was published in 2006. According to the revised Sapporo criteria, APS can only be diagnosed when patients show at least one clinical manifestation of vascular thrombosis or pregnancy morbidity and satisfy the laboratory criteria for at least one of the following three aPLs: LA, aCL, or αβ2GPI. Although aPLs are present in approximately 5% of the general population, they are mostly temporary and present in low titres. Moreover, the laboratory criteria for APS are relatively strict, so not all of these individuals are diagnosed with APS. The aPLs included in the laboratory criteria must show a positive test result when measured over an interval of at least 12 weeks. Useful LA detection guidelines were updated in 2009 by the Scientific and Standardization Subcommittee of the International Society of Thrombosis and Haemostasis (SSC-ISTH) for standardization of the LA detection assay. Likewise, for aCL and αβ2GPI, recommendations for optimal laboratory detection by solid assays were presented in 2014 by the SSC-ISTH. As per this recommendation, a greater than 99th percentile titre of IgG or IgM is needed in enzyme linked immunosorbent assay of serum or plasma. These aPLs not only serve as a criterion for diagnosis, but also as risk factors for the clinical events of thrombosis and obstetric complications in patients with APS, and are also included in the Global APS Score (GAPSS), which is a scoring system for risk stratification in patients with APS. Efforts to agree and standardize aPL testing remain an ongoing process. Recently, Sciascia et al. assessed the agreement between local laboratories and APS core laboratories for aCL and αβ2GPI in blood samples from 497 patients with APS, obtained between 2013 and 2016 and stored in core laboratory facilities. The authors demonstrated categorical agreement of over 80% for moderate to high titres of antibodies, ascertaining that the use of local laboratories in APS inclusion criteria is both reliable and reproducible.

Management

Despite ongoing investigation and much debate regarding the management of APS, repeated advances have been made over the last 30 years. APS is characterised by hypercoagulability; thus, the main objective of APS management is anticoagulation for the prevention of thrombosis and obstetric complications. Anticoagulation can be divided into primary thromboprophylaxis for aPL carriers with no prior history of vascular thrombosis and/or obstetric events, and secondary thromboprophylaxis for the prevention of recurrence after thrombotic and/or obstetric events in patients with a prior history. The management of obstetric APS and CAPS is slightly different.
In primary thromboprophylaxis, it is unclear whether prescribing low-dose aspirin in all aPL carriers is beneficial due to an increased risk of major bleeding. Therefore, lifestyle changes to modulate cardiovascular risk factors are key; including smoking cessation, weight loss, and control of hypertension and hyperlipidaemia. However, patients with APS who have a high-risk profile, as shown in Table 2, are recommended to take low-dose aspirin (75–100 mg/d). In addition, a prophylactic dose of low-molecular-weight heparin (LMWH) is considered in high-risk situations such as surgery, prolonged immobilization, and the puerperium.

Secondary thromboprophylaxis is used for patients with a history of venous or arterial thrombosis. In cases of previous venous thrombosis, anticoagulation is performed with a target international normalized ratio (INR) of 2.0–3.0. In patients with a history of arterial thrombosis, management remains controversial. According to the report of a Task Force at the 13th International Congress on Antiphospholipid Antibodies, patients with APS having arterial thrombosis require high-intensity anticoagulation with a target INR of 3.0–4.0, or a target INR of 2.0–3.0 combined with low-dose aspirin; however, this recommendation was non-graded due to lack of consensus. A later retrospective trial of 139 patients with APS and history of arterial thrombosis found that, compared with antiplatelet agents or anticoagulants alone, combined therapy could reduce the rate of thrombosis recurrence. A more recent retrospective trial of 90 patients with APS showed that, unlike the above-mentioned treatment methods, therapy with dual antiplatelet agents may be a safe and effective modality. However, there remains a lack of evidence to support this assertion, and prospective randomized controlled trials are needed to fully understand how best to manage patients with APS and a history of arterial thrombosis.

Catastrophic APS is rare and accounts for approximately 1% of APS cases, however, the mortality rate is 50%. In a systematic review of 500 patients registered in the CAPS Registry between 1992 and 2014, the mortality rate was found to be 37%, despite aggressive treatment. According to recently published clinical practice guidelines for CAPS, despite weak evidence due to the rarity of CAPS, combination therapy with glucocorticoid, heparin, and plasmapheresis or intravenous immunoglobulin is recommended over single agent therapy for first-line treatment. In refractory cases, the use of rituximab may increase survival.

### Table 2. Factors for high risk of thrombosis in asymptomatic antiphospholipid antibody carriers.

| High risk factors                          |
|-------------------------------------------|
| aPL related factors                       |
| LA positivity                             |
| Double aPL positivity (any combination of LA, aCL, or aβ2GPI) |
| Triple aPL positivity (simultaneous positivity for LA, aCL, and aβ2GPI) |
| Presence of persistently high aPL titres  |
| Traditional cardiovascular risk factors   |
| Hypertension                               |
| Hyperlipidaemia                            |
| Smoking                                   |
| Diabetes                                  |
| Obesity                                   |
| Concomitant of systemic autoimmune disease|
| Systemic lupus erythematosus               |
| Rheumatoid arthritis                      |
| Inherited thrombophilia                    |
| Antithrombin defects                       |
| Protein C defects                          |
| Protein S defects                          |
| Factor V Leiden mutation                   |
| Prothrombin variant G20210A mutation       |
| Hyperhomocystinaemia                       |
| Elevated factor VIII levels                |

aPL, antiphospholipid antibody; LA, lupus anticoagulant; aCL, antcardiolipin antibody; aβ2GPI, anti-β2 glycoprotein I.
In pregnant women, combination therapy with low-dose aspirin and unfractionated heparin or LMWH is effective in the prevention of obstetric complications. Any oral anticoagulants should be withdrawn as soon as pregnancy is confirmed in order to prevent teratogenicity.\textsuperscript{37} Irrespective of the pregnancy history, in patients with no history of thrombosis, low-dose aspirin and a prophylactic dose of unfractionated heparin or LMWH are used for primary prevention, whereas in patients with a history of thrombotic events, low-dose aspirin and a therapeutic dose of unfractionated heparin or LMWH are used for secondary prevention.\textsuperscript{9} After delivery, the former patients are recommended to receive a prophylactic dose of LMWH for at least 6 weeks, and the latter patients are recommended to start warfarin as soon as possible after bleeding is adequately controlled. However, patients with APS who have not received any thromboprophylaxis before delivery and do not carry any risk factors for thrombosis generally require LMWH for only 7 days following delivery.\textsuperscript{37,38}

Direct oral anticoagulants (DOACs) include the direct thrombin inhibitors, e.g. dabigatran etexilate, and the direct anti-factor Xa inhibitors, e.g. rivaroxaban, apixaban, and edoxaban. Unlike warfarin, DOACs have the advantages of predictable anticoagulant effects at a fixed dose without the need for blood level monitoring, and few drug-drug interactions and drug-food interactions, making them attractive for patients with APS. Therefore, a study of DOACs for secondary prevention of thrombosis in APS is currently underway, and the use of DOACs remains under debate. In a randomized controlled trial of patients with APS and a previous episode of venous thromboembolism, conducted in 2016, Cohen et al.\textsuperscript{39} demonstrated the efficacy and safety of rivaroxaban for venous thrombosis in patients with APS without clinically significant bleeding. Thereafter, the 15th International Congress on aPL Task Force on Treatment Trends report stated that more research was required to assess the usefulness of rivaroxaban, and that evidence remained insufficient for the use of DOACs in patients with APS.\textsuperscript{40} Interestingly, in a recent multicentre randomized controlled trial on patients with APS and a high risk for thromboembolic recurrence, Pengo et al.\textsuperscript{41} reported that incidences of thromboembolic and major bleeding events were 12\% and 7\%, respectively, in patients treated with rivaroxaban, and 0\% and 3\%, respectively, in those treated with warfarin. The authors emphasized that use of DOACs in patients with APS showed no benefit or excessive risk.

As mechanisms for the pathogenesis of APS are increasingly identified, new targeted therapies are emerging, in addition to anti-thrombotic therapy. These potential APS treatments include statins, hydroxychloroquine, rituximab, eculizumab, sirolimus, defibrotide, and peptide therapies, which are not yet recognized as standard treatments for APS due to a lack of large controlled trials.\textsuperscript{42} Statins and hydroxychloroquine have anti-inflammatory and anti-thrombotic effects that can be considered in refractory APS as potentially reducing APS related manifestations.\textsuperscript{43,44} Rituximab is favourable in the treatment of non-criteria APS manifestations, and several case reports have shown recovery in refractory CAPS, thus it may be considered in refractory APS and CAPS.\textsuperscript{13,45,46} Eculizumab is an anti-complement monoclonal antibody that plays a critical role in APS pathogenesis, and may be a therapeutic option in critically ill and refractory CAPS patients who fail standard therapy.\textsuperscript{47} Sirolimus, defibrotide, and peptide
therapies are not currently available for APS treatments due to limited clinical data.

**Perioperative anticoagulation**

**Preoperative anticoagulation**

Patients with APS not only exhibit a high risk of perioperative thrombosis due to withdrawal of chronic anticoagulation treatment, but may also exhibit a high risk of bleeding due to excessive anticoagulation. Therefore, the decision to discontinue anticoagulation treatment in the perioperative period requires careful risk–benefit assessments. The appropriate period of withdrawal should be carefully determined and appropriate bridging anticoagulation should be provided.48

Preoperative interruption periods for aspirin and warfarin are 7 and 5 days, respectively. However, there is no universally accepted withdrawal regimen, and there can be debate in cases with both perioperative thrombotic and bleeding risks.49 Procedures associated with low risk of bleeding, as shown in Table 3,50,51 can usually be performed without interrupting anticoagulation, and the limited blood loss in these procedures can be controlled with local haemostatic pressure.50 Although aspirin increases the risk of major bleeding, Saunders et al.52 recommended that, even in surgery with high risk of bleeding, aspirin intake should be continued perioperatively because the thrombotic risk in patients with APS is too high. In addition, it has been reported that the preoperative warfarin cessation period should be extended from 5 days to 7 days in patients receiving high-intensity anticoagulation therapy with a target INR of ≥3.0.52

Typically, in patients with high risk of thromboembolism, such as those with mechanical heart valves, atrial fibrillation, and/or venous thromboembolism, bridging anticoagulation with unfractionated heparin or LMWH is recommended during the perioperative period.50 Because APS is also an underlying disease with high risk of thrombosis, bridging anticoagulation with unfractionated heparin or LMWH during the warfarin interruption period is also recommended for patients with APS.52

Table 3. Non-cardiac surgeries categorised according to high or low risk of bleeding.

| Surgery type                              | High bleeding risk                                                                 | Low bleeding risk                                                                 |
|-------------------------------------------|----------------------------------------------------------------------------------|----------------------------------------------------------------------------------|
| Surgery involving highly vascularised organs (kidney, liver, and spleen) | Minor dental procedure                                                          | tooth extraction                                                                 |
| Intracranial surgery                      |                                                                                 | endodontic procedure                                                             |
| Spinal surgery                            |                                                                                 | Minor dermatologic procedure                                                     |
| Bowel resection surgery                   |                                                                                 | excision of BCC or SCC in skin                                                   |
| Urologic surgery                          |                                                                                 | excision of actinic keratoses                                                     |
| Cancer surgery                            |                                                                                 | excision of skin nevi                                                             |
| Major orthopaedic surgery                 |                                                                                 | Minor ophthalmologic procedure                                                   |
| Reconstructive plastic surgery            |                                                                                 | cataract extraction                                                              |
| Major surgery with extensive tissue injury|                                                                                 | phacoemulsification                                                              |
| Any major operation (procedure duration > 45 min) |                                                                                 | Pacemaker implantation or ICD implantation                                      |

BCC, basal cell carcinoma; SCC, squamous cell carcinoma; ICD, implantable cardioverter defibrillator.
A high (therapeutic) dose is the anticoagulation dose used for treating acute venous thromboembolism or acute coronary syndrome: equivalent to 1 mg/kg (twice per day) or 1.5 mg/kg (once per day) enoxaparin, with unfractionated heparin administered to achieve activated partial-thromboplastin time (aPTT) of approximately 1.5–2.0 times the control value. A low (prophylactic) dose is the anticoagulation dose used for preventing postoperative venous thromboembolism: equivalent to 30 mg (twice per day) or 40 mg (once per day) enoxaparin, with unfractionated heparin administered at a dose of 5000–7500 international units (IU) twice per day. Low (prophylactic)-dose regimens are effective in the prevention of postoperative venous thromboembolic events, such as stroke, is limited.

Therefore, a high (therapeutic) dose of unfractionated heparin or LMWH is recommended for bridging anticoagulation in patients with APS.

In patients receiving bridging anticoagulation with a therapeutic dose of unfractionated heparin or LMWH, the last dose of unfractionated heparin and LMWH is generally administered 4–6 h and 24 h before surgery, respectively. The last dose of LMWH involves half the total daily dose for minimizing residual anticoagulant effects during surgery.

A study of appropriate perioperative anticoagulation in 43 patients with APS undergoing elective surgery between 2006 and 2012, showed that patients provided with optimal management according to guidelines, such as anticoagulant withdrawal and high-dose bridging therapy, had significantly lower incidence of thrombotic and haemorrhagic complications. Thus, the present authors recommend high-dose bridging anticoagulation before surgery in patients with APS, as current research shows no significant increase in perioperative bleeding complications, even if high doses are used. Larger studies in patients with APS are required to investigate differences in the incidence of bleeding and thrombotic complications between low- and high-dose bridging anticoagulation therapy administered in the perioperative period.

When emergency surgery is required for patients with APS who are receiving chronic warfarin therapy, preoperative anticoagulation management becomes more difficult due to the lack of time for correcting the coagulation status. In particular, the half-life of warfarin is 2–4 days; thus, further measures may be required for reversal of the anticoagulation effects before surgery. This can be achieved by administering vitamin K, fresh frozen plasma, prothrombin complex concentrate, or activated recombinant factor VII; preoperative INR is generally corrected to ≤1.5.

The incidence of haemorrhagic events is reported to be significantly lower in patients with a preoperative corrected INR of <1.5 than in those with a corrected INR of >1.5. Importantly, rapid correction and overcorrection should be avoided, with the former causing immediate thrombosis and the latter complicating the restoration of anticoagulation to a therapeutic range following surgery, and increasing the risk of postoperative thrombotic complications.

Generally, a low dose of oral vitamin K (1–2 mg) is recommended. Even if INR is ≥3.0, slow correction with low dose vitamin K or slow infusion of fresh frozen plasma is preferred over rapid correction for emergency surgery.

Appropriate management of anticoagulation is also necessary in pregnant women who will receive epidural analgesia or neuraxial anaesthesia. With regard to needle/catheter placement for neuraxial block, according to the 2018 American Society of Regional Anesthesia and Pain Medicine
(ASRA) guidelines, there is no requirement for holding in case of low-dose aspirin with single agent therapy. Needle/catheter placement should be performed at least 4–5 h after administration of unfractionated heparin, and 12 and 24 h after administration of the last dose for low- and high-dose LMWH, respectively. Combined use of low-dose aspirin with heparin, or another antiplatelet agent that affects clotting mechanisms, warrants caution due to risk of bleeding complications, such as spinal haematoma.

Postoperative anticoagulation

In patients who have received preoperative bridging anticoagulation, postoperative bridging anticoagulation is needed until the anticoagulation effects of warfarin are within the therapeutic range for at least 24 h. For patients undergoing non-high bleeding risk surgeries, bridging anticoagulation with a therapeutic dose can be restarted at 24 h after surgery. In contrast, for patients undergoing major surgeries with a high risk of bleeding, as shown in Table 3, bridging anticoagulation can be delayed up to 48–72 h following surgery. However, if bleeding persists even 72 h after surgery, options such as low-dose bridging anticoagulation or restarting warfarin without bridging anticoagulation, can be considered. The timing of resumption of antithrombotic therapy is based on an appropriate assessment of the patient’s clinical relative risks of bleeding and risks of thrombosis. If an epidural catheter has been placed after epidural analgesia or neuraxial anaesthesia, removal of the catheter is recommended 1 h before restarting unfractionated heparin or 4 h before restarting LMWH, according to ASRA guidelines. The whole process of perioperative anticoagulation management is summarized in Table 4.

Anaesthetic considerations

Background

In this review, patients with APS are divided into four groups according to thrombotic and bleeding risk, as shown in Table 5, in order to systematically describe anaesthetic considerations in the perioperative period. During surgery itself, patients with APS are divided into only two groups (all patients and those undergoing surgery with a high bleeding risk), as all patients should receive maximal thrombosis prevention. Patients were divided into high and low thrombosis risk using adjusted GAPSS (aGAPSS), and high or low bleeding risk according to type of surgery. Further details on the criteria that were applied for each risk stratification are provided below.

In 2013, the GAPSS was suggested as a quantitative scoring system to predict the risk of clinical manifestations in APS. Risk factors in the GAPSS include aPLs and also the cardiovascular thrombotic risk factors of hyperlipidaemia and arterial hypertension. The score was calculated for each patient by adding points corresponding to risk factors. However, in routine clinical settings, because aPS/PT, one factor of the GAPSS scale, is not included in the laboratory criteria for APS, the aGAPSS is used, which excludes aPS/PT. The aGAPSS comprises 3 points for hyperlipidaemia, 1 point for arterial hypertension, 5 points for aCL IgG/IgM, 4 points for aβ2GPI IgG/IgM, and 4 points for LA; with a total score range from 0 to 17 points. A high aGAPSS value is not only associated with initial thrombotic events, particularly arterial thrombotic events, but also recurrent thrombotic events, and has also been reported as a valid guide for planning treatment decisions in clinical practice. The predictable cut-off aGAPSS value with the highest sensitivity and specificity for high risk of recurrent thrombosis is
reported to be \( \geq 7 \) points.\(^{60}\) The present review used this aGAPSS value to define patients at high-risk for perioperative thrombosis recurrence.

Concerns about bleeding risk in patients with APS have recently emerged, with no universal stratification system for bleeding risk that is specifically applicable to these patients. Inherent characteristics, such as renal or liver failure, older age, and uncontrolled hypertension, can be associated with an increased risk of bleeding in patients with APS.\(^{48}\) Factors such as previous haemorrhagic events, thrombocytopenia, use of non-steroidal anti-inflammatory drugs, von Willebrand disease, and coagulation factor deficiencies have been used to assess bleeding risk in patients with APS,\(^{61}\) but these factors have not been universally proven as bleeding risk factors in APS. Therefore, the present review categorised bleeding risk using surgery type alone, which is an essential consideration for anaesthesiologists in the perioperative setting and one of the major factors in perioperative anticoagulation. Surgery type was classified as high or low risk using American College of Chest Physicians guidelines,\(^{50}\) and with reference to Spyropoulos et al.,\(^{51}\) as shown in Table 3. There may also be patients undergoing surgeries with intermediate (non-high, non-low) bleeding risk, that don’t belong to any category in Table 3; non-high bleeding risk surgeries refer to a combination of intermediate and low bleeding risk surgeries.

Perioperative considerations are summarised in Table 5, listed ‘A’, ‘B’, ‘C’, and ‘D’. Since patients with APS are fundamentally at high risk of thrombosis, ‘A’ considerations should be applied in all patients.

### Table 4. Perioperative anticoagulation for non-cardiac surgery in patients with APS receiving long-term warfarin.

| Recommendation |
|----------------|
| **Preoperative anticoagulation** |
| 5–7 DBS | Warfarin hold (Do not interrupt anticoagulation for low bleeding risk surgery)\(^a\) |
| 3–5 DBS | Start bridging anticoagulation with high-dose UFH or LMWH |
| <1 DBS | UFH: administer last dose 4–6 h before surgery |
| | LMWH: administer last dose 24 h before surgery, half of total daily dose |
| | INR > 1.5 consider low-dose oral vitamin K (1–2 mg) |
| | consider delaying surgery |
| **Operation** |
| **Postoperative anticoagulation** |
| POD < 1 | Consider starting anticoagulation as soon as possible by assessing postoperative haemostasis |
| POD 1–3 | Start bridging with high-dose UFH or LMWH non-high bleeding risk surgery:\(^a\) start 24 h after surgery high bleeding risk surgery:\(^a\) can be delayed until 48–72 h after surgery |
| POD >4–5 | When INR reaches therapeutic range, discontinue bridging anticoagulation |

\(^a\)See Table 3 for summary of high bleeding risk and low bleeding risk surgeries.

DBS, day before surgery; UFH, unfractionated heparin; LMWH, low-molecular-weight heparin; INR, international normalised ratio; POD, postoperative day.
| Preoperative management | Non-high bleeding risk surgery (low or intermediate risk surgery) | High bleeding risk surgery |
|------------------------|------------------------------------------------------------------|---------------------------|
| aGAPSS < 7<sup>a</sup>  | A                                                                | A + C                     |
| aGAPSS ≥ 7<sup>a</sup> | A + B                                                            | A + B + C + D            |
| A                      | Apply physical prophylactic methods until the morning of surgery  |                           |
|                        | Take patient's history (previous thrombosis or pregnancy history)|                           |
|                        | Chest X-ray, ECG, standard laboratory tests including coagulation |                           |
|                        | profile                                                             |                           |
|                        | Consider following further evaluations                              |                           |
|                        | Further laboratory tests: anti-factor Xa assay, platelet function  |                           |
|                        | test, fibrinogen, D-dimer, antithrombin III, aPT, TEG or ROTEM     |                           |
|                        | Further imaging studies: echocardiography, doppler US, CT (CT    |                           |
|                        | angiography) MRI (MRA)                                              |                           |
| B                      | Consider correcting the patient's coagulation function preoperatively|                           |
| C                      | Correct preoperative anaemia                                        |                           |
| D                      | Prepare cross-matched blood products                                |                           |
| Postoperative          | A                                                                  |                           |
| management              | Apply physical prophylactic methods continuously                    |                           |
|                        | Maintain normothermia with temperature monitoring                   |                           |
|                        | Adequate hydration                                                   |                           |
|                        | Prophylactic broad-spectrum antibiotics                             |                           |
|                        | Utilize blood products rather than whole bloods                     |                           |
|                        | Consider invasive monitoring (continuous arterial BP, CVP, PAP, TEE)|                           |
|                        | Consider periodic blood gas analysis or coagulation laboratory test  |                           |
|                        | Consider point-of-care coagulation monitoring (ACT, TEG or ROTEM)   |                           |
| A                      | Optimal analgesia                                                   |                           |
|                        | Early mobilization as possible                                       |                           |
|                        | Apply physical prophylactic methods until full mobilization         |                           |
|                        | Chest X-ray, ECG, standard laboratory tests including coagulation   | Consider for differential |
|                        | profile                                                             | diagnosis                  |
|                        | Cerebral infarction or TIA                                          | Brain CT or MRI           |
|                        | MI or ischaemic heart disease                                        | ECG, troponin-T           |
|                        | Deep vein thrombosis                                                | Doppler US, lower limb    |
|                        | Pulmonary thromboembolism                                           | CT angiography             |
|                        | Other vascular thromboembolism                                       | Chest CT or CT angiography,|
|                        | Cardiac manifestations                                              | D-dimer                    |
|                        | Renal manifestations                                                | CT angiography, doppler US|
|                        | Neurological manifestations                                          | Echocardiography, BNP      |
|                        |                                                                    | Doppler US, abdominal CT, |
|                        |                                                                    | urinalysis, renal function |
|                        | B                                                                  | Carotid US, brain MRI,    |
|                        | Periodic vital sign monitoring plus physical examination             | neuropsychological test    |
|                        | Strongly suspect vascular thrombosis if postoperative signs do not   |                           |
|                        | follow a normal course                                               |                           |
|                        | C                                                                  |                           |
|                        | Periodic vital sign monitoring plus physical examination             |                           |
|                        | Ensure that anticoagulation is not excessive                         |                           |

(continued)
with APS to prevent perioperative thromboembolism. ‘B’ considerations are additional for prevention of thrombotic complications in patients with APS who have proven high recurrence rate of thrombosis. ‘C’ considerations prepare for the possibility of perioperative haemorrhage in addition to thrombotic risk in patients with APS, and ‘D’ considerations are for complex situations where patients are at high risk of both thrombosis and bleeding.

**Preoperative considerations**

Evaluation of thrombosis is the most important preoperative surgical assessment in patients with APS. A medical history of thrombosis, identification of underlying disease and thrombotic risk factors, and screening for hidden thrombosis by imaging studies, such as computed tomography (CT) angiography, echocardiography, and venous ultrasound (US) for DVT, should be considered preoperatively for all patients with APS. If the patient with APS has recently experienced a thrombotic event, elective surgery should be delayed by at least 3 months due to potential risk of rethrombosis or progression to CAPS.62

In female patients with APS, current pregnancy and gravida and para status should be identified, in addition to the presence of obstetric complications in any previous pregnancies.

A complete blood count including platelet count, and coagulation tests including
INR, prothrombin time (PT) and aPTT, are routinely used to check for coagulation status, which is important for the evaluation of patients with APS. However, interpretation of aPTT requires careful attention in such patients. LA, which is one of the aPLs, targets the epitopes of the negatively charged phospholipid binding protein, so prolongs phospholipid-dependent in vitro coagulations tests, such as aPTT.\textsuperscript{17} In contrast, LA itself increases the risk of thrombosis and pregnancy complications in vivo, thus, a hypercoagulable state should be considered despite prolonged or normal aPTT.\textsuperscript{63} The anti-factor Xa assay, which directly measures factor Xa activity, may be used for patients with APS when baseline aPTT is increased due to lupus anticoagulants.\textsuperscript{52} In addition, around 30\% of patients with APS may have thrombocytopenia, but most exhibit no clinical symptoms and have a platelet count $\geq 50,000/\mu l.\textsuperscript{64}$ Nevertheless, in patients with abnormal platelet function, even mild thrombocytopenia can be problematic, and therefore, further platelet function tests can be performed.\textsuperscript{48,52}

Laboratory tests, such as liver function and kidney function, are used to check if APS is accompanied by liver failure or renal insufficiency. In addition, if an electrocardiogram (ECG) or chest radiograph show abnormal findings, further echocardiography or CT angiography can be performed to check for preoperative cardiac and pulmonary comorbidities. In planning a major surgery, with the expectation of perioperative bleeding, it is important to correct preoperative anaemia in order to reduce the transfusion rate and postoperative mortality, and prepare cross-matched blood products to utilize in an emergency.\textsuperscript{65} In patients at high risk of recurrent thrombosis (aGAPSS $\geq 7$) who are scheduled to undergo a major surgery, a requirement of continuous monitoring in the intensive care unit (ICU) should be expected, for close follow-up.

A preoperative inferior vena cava (IVC) filter may be used preoperatively to prevent thromboembolism in patients with APS; however, this procedure itself may cause thrombosis and should be avoided if possible. IVC filter placement may be considered when patients with lower extremity DVT show active bleeding or recurrent DVT.\textsuperscript{52,66}

\textbf{Intraoperative considerations}

\textbf{Intraoperative management.} A general anaesthesia or neuraxial anaesthesia, such as spinal, epidural, or combined spinal epidural anaesthesia, can be performed. Most patients diagnosed with APS receive a therapeutic dose of anticoagulation; therefore, this raises valid concerns of complications that can occur after neuraxial anaesthesia, such as spinal haematoma. Nevertheless, in pregnant women, neuraxial anaesthesia offers numerous maternal and fetal benefits compared with general anaesthesia, and is known to be relatively safe, and therefore, studies have investigated neuraxial anaesthesia in patients with APS.\textsuperscript{54,67} As long as a deranged coagulation profile is not observed after holding preoperative anticoagulation for an appropriate duration, neuraxial anaesthesia can be safely performed to patients with APS, except in those scheduled to receive massive transfusion, or patients scheduled to undergo emergency surgery immediately after heparin administration.\textsuperscript{57,67} If there is no problem with platelet function, data have shown that neuraxial anaesthesia may be safely performed on pregnant women with a platelet count of 80,000–100,000/\mu l.\textsuperscript{68,69} One case of safe and successful administration of combined spinal-epidural anaesthesia for caesarean section in a patient with APS having mild thrombocytopenia (platelet count 85,000/\mu l) has been reported.\textsuperscript{67} Thus, even for patients other than pregnant women, if
the benefits of neuraxial anaesthesia outweigh the risks relative to general anaesthesia, anaesthesiologists should be aware that neuraxial anaesthesia can be performed safely in patients with APS having appropriate perioperative anticoagulation and acceptable laboratory profiles.

The anaesthetic agent of choice for patients with APS has not been studied or established. Generally, inhalation and intravenous (IV) anaesthetics are demonstrated to show no differences in their effects on blood coagulation status, such as platelet function, clot firmness, and fibrinolytic capacity. Therefore, the choice of anaesthetic agent in patients with APS does not differ greatly from other patients.

Intraoperative prevention of thrombotic complications in patients with APS should be aggressive, regardless of whether the recurrent thrombotic risk (aGAPSS level) is low or high. Physical prophylactic methods are necessary for preventing perioperative thromboembolism, including use of simple antithrombotic compression stockings, gradual compression stockings, and intermittent pneumatic compression devices. These devices may prevent perioperative thromboembolism by reducing venous stasis and increasing venous return and should be continuously worn from the morning of surgery until complete mobilization of the patient.

During surgery, particularly in patients under general anaesthesia, hypothermia readily occurs due to impaired thermoregulation and exposure to the cold operating room. Hypothermia directly damages enzymes in the coagulation cascade and causes defects in platelet function, which in turn affects coagulation function. Indeed, in clinical practice, patients with hypothermia show more blood loss and higher transfusion requirements than those with normothermia. Thus, maintenance of normothermia along with intraoperative temperature monitoring is essential for patients with APS. Methods to avoid hypothermia include using a humidifier and heating circuit for humidification and airway heating, respectively; cutaneous warming insulators, such as cotton blankets or surgical drapes; and forced-air warming devices. Cold IV fluids may also contribute to hypothermia by causing heat loss; therefore, fluid warmers should be used during large volume fluid resuscitation or massive blood transfusion.

Adequate intraoperative hydration is also necessary for the prevention of dehydration. In patients with obstetric APS in particular, dehydration and hypotension should be avoided because they not only increase the maternal blood viscosity but also decrease fetal blood flow. On the other hand, intraoperative fluid overload, which may cause progressive respiratory failure in patients with CAPS, should also be avoided.

When blood transfusion is required, blood component agents rather than whole blood are recommended. For patients with accompanying severe underlying disease or undergoing high bleeding risk surgery, standard monitoring, and also invasive monitoring, such as central venous pressure and pulmonary artery pressure measurements, or even transoesophageal echocardiography for detecting severe intracardiac thrombosis, may be required.

Anaesthesiologists should be aware that patients with APS can develop severe complications if CAPS is triggered during surgery. The most common triggering factor is infection, which can subsequently progress to septic shock. Infection during surgery should be prevented using prophylactic antibiotics. Because a wide range of common pathogenic microorganisms can aggravate APS, such as *Escherichia coli*, *Streptococcus pyogenes*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Candida species*, and *Herpes virus*, empirical
broad-spectrum antibiotics should be administered. The surgery itself is the second most common triggering factor for CAPS, with several underlying mechanisms: First, the change in hormone, cytokine, and chemokine levels due to stress; secondly, exposure to tissue factors; thirdly, excessive hypercoagulability associated with malignancy (the reason for surgery); and fourthly, withdrawal of chronic anticoagulation therapy. CAPS is associated with a high mortality rate and should be aggressively treated as soon as it is suspected, because it can result in microthrombi in multiple organs and increase the bleeding risk due to haemolysis or disseminated intravascular coagulation (DIC). Indeed, 15% patients with CAPS also exhibit features of DIC, because CAPS and DIC share similar triggering factors and pathogenic mechanisms. Therefore, clinicians should be aware that patients with CAPS commonly exhibit features of DIC and systematically screen for DIC when CAPS is suspected.

Patients with obstetric APS have generally experienced obstetric complications, and are inevitably fearful of fetal loss and other complications due to repeated abortions. Therefore, when these patients undergo caesarean section or other surgeries, the anaesthesiologist plays a crucial role. Pregnancy or puerperium itself can trigger CAPS in approximately 4% patients with APS. These patients also exhibit a high risk of peripartum haemorrhage and PTE. Accordingly, clinicians should be aware of and prepare for possible emergency situations during the perioperative period.

Several case reports of haemorrhagic complications during the peripartum period in patients with APS have been published, including the case of a 39-year-old patient with APS who developed massive hemorrhage due to uterine atony during cesarean section, and a case involving a patient with hypovolemic shock due to a ruptured ectopic pregnancy who required emergency surgery. Additionally, in a large cohort trial of 264 pregnant women with APS, Yelnik et al. suggested that only an emergency caesarean section, not perioperative anticoagulation nor any other factors, was a significant risk factor for haemorrhagic events. In view of both thrombosis and haemorrhage, these studies highlighted the need for detailed anaesthetic management protocols for patients with APS, and the possibility of hemorrhagic events in the context of an emergency cesarean section, should be recognised and prepared for.

Intraoperative coagulation monitoring. Commonly used intraoperative methods for point-of-care coagulation monitoring include the activated clotting time test, heparin concentration measurement using protamine titration, and viscoelastic measurements using thromboelastography (TEG) or rotatory thromboelastometry (ROTEM). Currently, point-of-care coagulation monitoring is mostly implemented to ensure the administration of appropriate doses of heparin and protamine, and to minimize complications by reducing plasma and platelet transfusion during trauma surgery requiring massive transfusion, cardiovascular surgery involving CPB, organ transplantation, or peripartum haemorrhage.

For cardiac surgery in patients with APS, point-of-care coagulation monitoring is frequently used, with many published case reports, but this method is rarely implemented for other types of surgery. As previously mentioned, APS is a paradoxical disease that often shows prolonged aPTT, thrombocytopaenia, and hypoprothrombinaemia in vitro, but is characterized by a clinical presentation of hypercoagulability in vivo. In this context, since conventional coagulation tests only show one part of the coagulation process, they may not correlate
well with the clinical presentation. However, by using TEG or ROTEM, the entire coagulation process can be inspected in real-time, from clot formation to fibrinolysis, and therefore, these methods can be useful in patients with APS. This is supported by a case report by Rezoagli et al.\(^8^4\) in which a patient with APS was admitted to the ICU with septic shock. Although the patient’s vital signs were stable, heparin was stopped because of gradual prolongation of INR and aPTT during hospitalization. However, the patient showed cyanosis and progressive peripheral ischemia of all four limbs, suggesting thrombotic manifestation due to progression to CAPS. TEG was performed and showed a slightly reduced reaction time, and therefore, administration of heparin was immediately resumed, with improvement in the patient’s clinical presentation. With such a paradoxical situation, TEG or ROTEM is useful for the real-time monitoring of the whole coagulation process. The results can be used to provide appropriate treatment to reduce bleeding and thrombotic complications. Further research to determine TEG and ROTEM reference values for patients with APS is necessary to promote the more effective use of viscoelastic haemostatic tests for coagulation monitoring in this patient population.

**Postoperative considerations**

Early mobilization is required to prevent thrombosis following surgery, with a necessity for optimal analgesia to achieve this.\(^9^1,^9^9\) Even if optimal anticoagulation is restarted as soon as possible and early mobilization is achieved, patients with APS should be closely followed with routine tests such as chest X-ray, ECG, and laboratory tests, to check for thrombosis or bleeding complications during the first 2 weeks after surgery.\(^4^9\)

Common thrombotic complications in patients with APS include brain infarction, TIA, DVT, PTE, and MI.\(^1^0^0\) Among these, brain infarction is the most common clinical feature of arterial thrombosis in APS.\(^1^0^0–1^0^2\) Suspected brain infarction should be diagnosed through brain images and treated appropriately.\(^1^0^3\) If acute postoperative hypoxaemia develops, PTE should be suspected.\(^8^2\) In a report of 20 cases involving pregnant women with APS, two patients were observed to experience postpartum PTE,\(^1^0^4\) and postoperative hypoxaemia was stated to be an early sign of PTE that requires immediate intervention. In a case involving a patient with APS who developed PTE after elective hepaticojejunostomy, the patient was reported to have a history of DVT on two occasions and acute cyanosis 3 days following surgery.\(^8^2\) Consequently, the authors suggested that aggressive anticoagulation, to achieve an INR of 3.0–3.5 for the prevention of embolic complications, is needed in patients with APS who have a history of DVT.\(^8^2\) Cases of fatal postoperative arterial thromboembolism in patients with APS have been reported.\(^1^5,^1^0^5\) These cases suggest that postoperative MI can be predicted through changes in the ST segment of the ECG and elevated troponin-T, and can progress to secondary right or left ventricular heart failure. Additionally, if a patient’s postoperative conditions do not follow a normal course, the possibility of vascular thrombosis, as described above, should be strongly suspected, particularly in patients with APS who have high risk of recurrent thrombosis (aGAPSS \(\geq 7\)).\(^1^0^6\)

In addition to the APS-related thrombotic events described above, there may also be non-criteria APS manifestations, such as cardiac, neurological, dermatological, renal, and haematological manifestations, as shown in Table 1. First, valvular heart disease, which is the most common cardiac manifestation, represents a risk
factor for postoperative arterial thromboembolism, such as peripheral arterial thrombosis and ischaemic stroke. Thus, screening of valve lesions through transthoracic echocardiography (TTE) is necessary perioperatively, and detection or follow up of valve lesions through TTE or transesophageal echocardiography will be necessary for patients with APS. Secondly, if patients complain of acute back pain, haematuria, or uncontrolled hypertension, then acute nephropathy due to renal artery thrombosis or thrombotic microangiopathy may be suspected; in these cases, doppler US or abdominal CT may be helpful for differential diagnosis, with the addition of urinalysis, renal function tests, and biopsies. Treatments include anticoagulation therapy, percutaneous angioplasty, and occasionally nephrectomy, and plasma exchange with anticoagulation is a first-line therapy in the case of thrombotic microangiopathy. Thirdly, livedo reticularis (reticular- or mottled-patterned skin lesions that appear as persistent, non-reversible, and purplish discoloration of the skin), is the most frequent dermatologic manifestation of APS, and there are several case reports of livedo reticularis following surgery. Since livedo reticularis is also associated with a high risk for arterial thrombosis and cerebrovascular events in APS, patients with APS and livedo reticularis may require close follow-up. Lastly, cognitive dysfunction and headache or migraine are frequently described as APS-related non-stroke central neurologic manifestations. There is evidence of improvement of these manifestations with anticoagulation, however, in cases of persistent neurological symptoms despite anticoagulation therapy, the use of glucocorticoids is recommended.

Postoperative bleeding is difficult to manage in patients with APS undergoing anticoagulation due to the underlying high risk of thrombosis. In particular, holding anticoagulation requires careful risk-benefit assessment. If postoperative anticoagulation has been initiated, it should be maintained unless there is an active bleed, and low-dose unfractionated heparin or LMWH should be considered, even if there is active bleeding. If anticoagulation is inevitably stopped, it should be restarted as soon as possible once active bleeding is controlled. Additionally, when bleeding is present in patients with APS, the clinician should be aware of possible common causes, such as excessive anticoagulation, adrenal haemorrhage, lupus anticoagulant-hypoprothrombinaemia syndrome (LA-HPS), diffuse alveolar haemorrhage (DAH), and CAPS, and the need of appropriate differential diagnosis and treatment following surgery.

If patients with APS develop sudden hypotension, fever, or back pain in the postoperative period, adrenal infarction or haemorrhage should be suspected. Because these conditions are usually accompanied by adrenal insufficiency, IV hydrocortisone should be administered immediately on suspicion. The gold standard of adrenal haemorrhage diagnosis is adrenal biopsy, but abdominal CT may be used to visualize the adrenal gland and confirm haemorrhage. Even in cases of adrenal haemorrhage, antithrombotic therapy should be maintained as far as possible, due to the risk of thrombosis as an underlying problem. Adrenal insufficiency due to adrenal haemorrhage is particularly common in patients with CAPS, who additionally require intravenous immunoglobulin or plasma exchange.

Lupus anticoagulant-hypoprothrombinaemia syndrome has a heterogenous clinical manifestation that can show either minimal haemorrhagic manifestation, such as epistaxis or ecchymosis, or major haemorrhagic manifestation such as gastrointestinal, gynaecologic and urologic bleeding. In LA-positive
patients with APS and prolonged PT, if unexplained bleeding persists, LA-HPS should be suspected, and the prothrombin level and aPT should be ascertained for differential diagnosis. First-line therapy for LA-HPS is corticosteroids and, similar to adrenal haemorrhage, antithrombotic therapy should be maintained due to the high risk of thrombosis.

In patients with APS presenting with postoperative symptoms, such as dyspnoea, haemoptysis, hypoxic respiratory failure, and the laboratory finding of anaemia, DAH should be suspected, and chest CT and bronchoalveolar lavage (BAL) using bronchoscopy may aid the differential diagnosis. In most patients with DAH, ground glass opacities in chest CT and hemosiderin-laden macrophages in BAL can be detected. Caution is required due to frequent progression to CAPS. Corticosteroids and cyclophosphamide may be used as first line therapy, but there remains a lack of evidence.

Catastrophic APS, the most severe variant of APS, is characterized by thrombotic microangiopathy and multiorgan failure, and is associated with thrombotic complications, together with DAH and adrenal haemorrhage, as described previously. Saranteas et al. reported the case of a 30-year-old woman who progressed to CAPS in the postpartum period after caesarean section and developed a central vein thrombus due to the chronic in-dwelling central vein catheter. If CAPS is suspected, aggressive treatment is required immediately, but also close monitoring for further thrombotic or bleeding complications. In patients with suspected CAPS, in addition to the platelet count, INR, PT, and aPTT, it is also necessary to accurately ascertain the coagulation status using viscoelastic tests (TEG or ROTEM), and to be aware of the possibility of sepsis or even DIC, showing both elevated coagulation and fibrinolysis.

**Conclusion**

Antiphospholipid syndrome is an autoimmune disease with various clinical manifestations, and its main features are thrombosis and obstetric complications. APS is characterized by hypercoagulability, so the focus of management and treatment is the prevention of thrombosis. The risk of not only thrombosis but also bleeding increases in the perioperative period, therefore, among perioperative considerations, appropriate anticoagulant withdrawal and bridging anticoagulation are essential for preventing bleeding complications while reducing the thrombotic risk. The continuous use of physical prophylactic methods in addition to pharmacological interventions during surgery is important, and optimal anaesthetic management and coagulation monitoring should be implemented according to the patient’s coagulation state. Finally, awareness regarding potential postoperative thrombotic and bleeding complications is necessary. In particular, early diagnosis and treatment are essential in the event of stroke, PTE, MI, and adrenal insufficiency, which are potentially fatal and frequently reported complications.

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