Bridging therapy in antiphospholipid syndrome and antiphospholipid antibodies carriers: case series and review of the literature.

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Abstract

Peri-operative management of patients on warfarin involves assessing and balancing individual risks for thromboembolism and bleeding. The timing of warfarin withdrawal and a tailored pre/postoperative management (including the substitution of heparin in place of warfarin, the so-called bridging therapy) is critical in patients with prothrombotic conditions. The antiphospholipid syndrome (APS) is the most common cause of acquired thrombophilia. In this particular subset of patients, as the risk of thrombosis is higher than in general population, bridging therapy can represent a real challenge for treating physicians. Only few studies have been designed to address this topic. We aim to report our experience and to review the available literature in the peri-procedural management of APS and antiphospholipid antibody-positive patients, reporting adverse events and attempting to identify potential risk factor associated with thrombosis or bleeding complications.

Keywords

- Antiphospholipid syndrome;
- Bridging therapy;
- Anticoagulation;
- Warfarin;
- Thrombosis;
- Bleeding

1. Introduction

Peri-operative management of patients on warfarin involves assessing and balancing individual risks for thromboembolism [1] and [2] and bleeding [3]. Indeed, the timing of warfarin withdrawal and a tailored pre/postoperative management (the so-called bridging therapy) are critical elements to avoid thromboembolic complications. Bridging therapy is defined as the temporary peri-operative substitution of low-molecular-weight heparin (LMWH) or unfractionated heparin (UH) in place of warfarin [4]. An effective bridging therapy approach aims to both control the thromboembolic risk that drives the need for an aggressive peri-procedural strategy (bridging therapy), and the procedural bleeding risk determines how and when anticoagulant therapy should be resumed [1] and [5].

Despite several strategies with various clinical indications are nowadays available[5] and [6], data from randomized controlled trials are still limited and the question of whether patients should undergo bridging therapy is not resolved [1] and [7].

Recently, Siegel et al. [6] showed an increased bleeding risk in heparin bridged patients compared with non-bridged, whereas the thrombotic risk seems not to differ between the two groups [6]. Two prospective randomized trials (PERIOP-2 and BRIDGE) attempting to address this uncertainty are ongoing [8].

All together, due to the lack of sound evidence, an individualized approach and involvement of the patient in decision making process is at present advised [7].

The antiphospholipid syndrome (APS) is the most common cause of acquired thrombophilia [7], [9] and [10], characterized by the association of antiphospholipid antibodies (aPL) with thrombosis and/or pregnancy loss [11]. Thrombotic events can affect venous, arterial side or the microvascular district.

In the presence of aPL, the therapeutic approach is influenced by the presence of previous clinical manifestations [2]. For aPL carriers, without history of vascular and/or obstetric events, thromboprophylaxis in acute high-risk situations is highly recommended. Secondary thromboprophylaxis in APS with thrombosis is provided using oral anticoagulant (OAT), normally lifelong. Therapy in pregnant women with APS aims to improve both maternal and fetal outcomes; APS patients with a history of pregnancy morbidity but no vascular thrombosis are usually treated with prophylactic doses of LMWH plus low-dose aspirin (LDA). Patients with a history of thrombotic events should receive full antithrombotic doses of LMWH plus LDA. For all cases anticoagulation for 6 weeks of postpartum is warranted [11] and [12].

Bridging therapy in APS patients has been evaluated in only few studies designed to address this topic [13] and [14]. In this particular subset of patients, as the risk of thrombosis is higher than in general population [15], bridging therapy can represent a real challenge for treating physicians [16].

This case study aimed to report our experience in the peri-procedural management in a cohort of APS and aPL-positive patients attending the Immunology Department, reporting adverse events and attempting to identify potential risk factor associated with thrombosis or bleeding complications.

2. Patients and methods

This study retrospectively included 36 consecutive patients undergoing any invasive procedure who attended Immunology Department at Ospedale Umberto I, Torino from April 2005 to June 20013. All patients tested positive at least twice for aPL and 16 of those fulfilled the current APS classification criteria [17]. Demographic, clinical and laboratory characteristics are summarized in Table 1.

Inclusion criteria for this study were (1) confirmed aPL positivity, (2) antiaggregant or OAT because of clinical history of thrombosis and/or pregnancy morbidity and (3) bridging therapy required for invasive procedure. Included patients met all the above inclusion criteria.

Thrombotic risks assessment included arterial hypertension (systolic pressure > 140 mm Hg or diastolic pressure > 90 mm Hg), obesity (body mass index > 30 kg/m^2), diabetes mellitus (baseline glycemia > 126 mg/dl in at least two occasions), smoking, active or treated neoplasia, use of oral contraceptives, underlying systemic autoimmune diseases and genetic hypercoagulables states.

The considered bleeding risks factors were previous hemorrhagic events, thrombocytopenia, use of non-steroidal anti-inflammatory drugs (NSAIDs), von Willebrand disease and coagulation factors deficiencies [18].

Preoperative therapy, time of stopping and LMWH doses before and after intervention were retrospectively collected. Adverse events, namely, thrombosis and bleeding, were as previously defined [18].

3. Autoantibodies detection

The aCL and the anti-β2GPI were detected by ELISA as described previously [19]. Plasma samples were tested for the presence of LA according to the recommended criteria from the ISTH Subcommittee on lupus anticoagulant-phospholipid-dependent antibodies [20].

4. Results

We retrospectively described 45 procedures in 36 aPL-positive patients: of those, 20 (55%) were aPL carriers and 16 (44%) were APS. Demographic and immunological characteristics are reported in Table 1. Overall, we described one hemorrhagic and four thrombotic events. Three thrombotic events occurred in the APS group (2 venous and 1 arterial thrombosis), while 1 venous thrombosis occurred in the aPL carrier group.
Table 2 and Table 3 summarized the outcomes in all APS and aPL patients, respectively.
A detailed case analysis is reported in Table 4. A case-by-case analysis of patients who suffered for any adverse outcome has been performed, as follows:
Event 1 (patient 8): a patient with obstetric APS developed deep vein thrombosis (DVT) in the postpartum period because of fixed dose of LMWH (enoxaparin 40 mg, equivalent to 4000 IU; with weight 80 kg corresponding to 50 U/kg/die).

Event 2 (patient 17): an aPL-positive patient with undifferentiated connective tissue disease (UCTD) developed a cerebral venous thrombosis (CVT) after labor, which occurred 66 hours after LMWH was stopped. Concomitant microcytic anemia (Hb 7,8) favored the adverse event.

Event 3 (patient 15): a patient with thrombotic APS (DVT) in SLE (malar rash, photosensivity, arthritis, anti-nuclear antibodies, anti-DNA antibodies), who was on LDA because she stopped OAT few years ago, developed DVT after necrosectomy of necrotic ulcer tissue followed by skin graft. She received LMWH (enoxiparin 40 mg OD) for 8 days. Smoke and bed rest, added to low dosage and short period of heparin prophylaxis could justify the onset of DVT.

Event 4 (patient 14): a patient with thrombotic APS (pulmonary embolism) in SLE (autoimmune hemolytic anemia, arthritis, sierositis and anti-nuclear antibodies), presented hemorrhage (loss of 6 g Hb) followed by thrombotic event (myocardial infarction) after orthopedic procedure. NSAIDs post-surgery prescription and early somministration of LMWH could explain significant bleeding, whereas smoke, post-splenectomy thrombocytosis were highlighted as arterial thrombotic risk factors. Treatment after procedure changed from OAT to OAT + LDA.

5. Discussion

This report describes a cohort of APS and aPL-positive patients requiring bridging therapy for surgery or invasive procedure. To the best of our knowledge, we report the largest study addressing the topic of bridging therapy in aPL-positive patients.

Bridging therapy in APS and aPL carriers represents a challenge for many reasons. Several factors such as stasis, endothelial injury and aPL related hypercoagulability may contribute to the development of postoperative thromboembolic events. APS patients may have increased risk of postoperative thrombosis, making prophylaxis with

heparin or warfarin in patients with APS mandatory [13]. Besides, surgery itself is an established trigger factor for CAPS, severe microvascular form that affects multiple organ systems, and it is fatal in approximately half of patients [21]. SLE, associated to APS (in 50% of cases), provides an increased risk of thrombosis [22] and [23] and immunosuppressive therapy may complicate the management of peri-operative period.
Young people are generally affected, and fertility is not compromised in APS patients: for those reasons, delivery and cesarean section deserve particular attention in these patients. Indeed, labor and cesarean section accounts for a high percentage of total procedures (69%) in our cohort.

As combination of LDA and heparin is considered the standard of care to minimize the risk of maternal thromboembolism and it has been proven to improve fetal-maternal outcome in aPL pregnancy [24], optimal timing for stopping them is essential for a correct management and to plan intervention such as epidural procedures. It is generally accepted that aspirin could be stopped at least 10 days before delivery (normally at 34° weeks of gestation), despite the possibility of using of aspirin during the delivery is still under debate [25] and [26]. LMWH should be suspended 12–24 hours before neuraxial anesthesia (depending on dosage of heparin) and resumed 12 hours after catheter removal [24]. In APS and aPL-positive patients, LMWH should be continued for 6–8 weeks after delivery [26]. It is usually suggested to induce the delivery as an effective strategy to optimize the timing for stopping heparin, aiming to reduce the risks for both thrombotic and hemorrhagic complications related to the puerperium. This can also reduce the need for cesarean section, which may require general anesthesia, known as a potential cause of complication and increased risk of death [26].
In this study, despite the heterogeneity of the study population, when analyzing the patients who suffered for adverse events, it is possible draw to some general considerations. First, all patients with adverse events were LA positive (aPL profile including triple positivity, Miyakis I or IIa [19]). LA is considered the strongest risk factor among aPL for thrombosis [27], and a special attention is required when a thrombo-prophylaxis is planned in patients with LA, especially when associated with multiple positivity. However, we think that the presence of LA might have had a role in inducing thrombosis, while the association with the hemorrhagic event is more difficult to be interpreted.
Second, the co-existence of anemia and thromboembolism seems to be evident in cases 17 and 14. An association between anemia (defined as < 9 g/dl) and CVT has been recognized by Stolz et al. [28]. In our cohort, case 17 presented with a severe microcytic anemia (Hb 7,8 g/dl at the time of CVT). However, it worth noting that this happened in the absence of thrombocytosis, which is frequently seen in iron deficiency anemia and could justify an hypercoagulability.
In case 14, several risk factors coexisted, for both bleeding or thrombotic complication. SLE itself is strong risk for thromboembolic event, while an early re-introduction of LMWH and the use of NSAIDs in analgesic therapy enabled bleeding. In the same patients, a severe blood loss occurred, and this has been linked with the occurrence of myocardial infarction [29] and [30]. This case highlights the concept that major attention should be paid in aPL-positive patients also when assessing the bleeding risk. Indeed, the major bleeding indirectly influenced damage in patient 14 (triggering the onset of a thrombotic event) and, after all, it resulted in a change of treatment (fromOAT to OAT + LDA).
Moreover, the index event reported in this study impact on the diagnosis and consequently on the treatment of patient 8 (OAPS to O-T APS) and 17 (from UCTD with aPL positivity to UCTD associated to APS).

No CAPS, the most dangerous complication of APS, was observed in our cohort. One can speculate that this can be due to a sufficiently intensive thrombo-prophylactic management; however, it is not possible to rule out that the our cohort was not wide enough to observe the occurrence of this rare condition (less than 1% of all APS patients).

We acknowledge that this study suffers for some limitations. Our cohort appears to be very heterogeneous, showing additional risk factors such SLE, corticosteroid therapy, thrombocytopenia and renal diseases, or cancer. Besides, different types of surgical procedures have been taken into account: renal biopsy, orthopedic, cardiovascular, abdominal, cutaneous and gynecologic surgery. Unlike other patient population studies for BT, it should be remembered that thrombotic risk may involve both venous and arterial side in aPL patients.

In conclusion, the heterogeneity and the complexity of the cases make difficult to outline management recommendations. However, on the basis of our experience, we suggest that a multidisciplinary evaluation of the single case before procedure, aiming to tailor the tromboprophylaxis management can be an effective strategy to reduce adverse events.

Probably in some patients conventional doses of heparin may result in a "under-coagulation" (patients 8 and 15); for that reason, a weight adjusted prophylactic dose of 100 U/kg can be suggested [4].
Larger, prospective studies are warranted to further evaluate the correlation between hemorrhagic adverse events and subsequent damage accrual in APS patients.

Take-home messages

• Bridging therapy in APS can represent a challenge as the risk of thrombosis is higher than in general population.

• A multidisciplinary evaluation of the single case before any invasive procedure, aiming to tailor the tromboprophylaxis management can be an effective strategy to reduce adverse events in APS.

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Table 1. Demographic and immunological characteristics of the 36 patients treated with bridging therapy.

	APS n. 16	APL n. 20
F/M	13/3	20/0
Age at procedure (years)	49 (31–73)	36 (21–53)
Time of APS/aPL diagnosis	1992–2002	1995–2011
aPL profile		
M I*	12 (triple positivity in 9)	13 (triple positivity in 8)
M IIa	2	3
Other autoimmune diseases associated	68% (56% patients with SLE)	70% (25% patients with SLE)
Procedures time frame	1/2006–1/2013	4/2005–6/2013
Obstetrical intervention	47%	84,6%
Thrombotic adverse events	2 venous, 1 arterial	1 venous
Hemorragic adverse events	1	0

* M I, aPL profile according to Myiakis I [17]: more than one laboratory criteria present (any combination); M IIa, profile according to Myiakis Iia [17]: LA present alone; Triple positivity: LA, aCL, anti-b2glycoprotein-I antibodies.

Table 2. Clinical characteristics, peri-procedural management and outcome of APS patients.

Patient no.	Age (procedure)	Sex	Diagnosis and treatment before procedure	aPL profile (closer to procedure)	Procedure	LMWH interruption before and after procedure	LMWH doses before and after intervention	Thrombosis risk factors	Bleeding risk factors	Thrombotic and hemorrhagic event	Diagnosis treatment after procedure
1	46	F	O-APS on LDA	ACLM +	CS	1/1	< 100 UI/kg × 1/100 UI/kg × 1	–	–	–	O-APS on LDA
2	33	F	O-APS + UCTD on LDA	LAC+ACL-G+B2GPI-G +	SL	1/0	< 100 UI/kg × 1/100 UI/kg × 1	Steroid Treatment/thrombotic events familiarity HTA	–	–	O-APS + UCTD on LD
3	34	F	O-APS + SLE on LDA	LAC + ACLG + ACLM+B2GPI-G+B2GPI-M +	CS	1/2	100 UI/kg × 1/100 UI/kg × 1	Smoke	Thrombocytopenia	–	O-APS + SLE on LDA
4	41	F	T-APS + S.SJOGREN	ACLG + B2GPI-M +	SL	2/0	< 100 UI/kg × 1/100 UI/kg × 1	Protein S Deficiency	–	–	T-APS + S.SJOGREN in OAE
5	39	F	T-APS + SLE on LDA	LAC+ACL-GB2GPI-G	SL	1/1	100 UI/kg × 2/100 UI/kg × 2	Smoke	–	–	T-APS + SLE on OAT
6	35	F	T-APS + UCTD on LDA	LAC+ACL-G + B2GPI-G +	CS	1/1	< 100 UI/kg × 1/100 UI/kg × 1	Smoke – Thrombotic events familiarity	–	–	T-APS + UCTD on LDA
7	35	F	T-O-APS + SLEon LDA	LAC+ACL-G + B2GPI-G +	CS	1/1	100 UI/kg × 2/100 UI/kg × 2	HTA – obesity-steroid therapy	–	–	T-O-APS + SLEon LD

Patient no.	Age (procedure)	Sex	Diagnosis and treatment before procedure	aPL profile (closer to procedure)	Procedure	LMWH interruption before and after procedure	LMWH doses before and after intervention	Thrombosis risk factors	Bleeding risk factors	Thrombotic and hemorrhagic event	Diagnosis treatment after procedure
8	32	F	O-APS on LDA	LAC+ACL-G + B2GPI-G +	IL	2/0	< 100 UI/kg × 1/100 UI/kg × 1	PreviousDVT	–	DVT	O-APS on OAT
9	39	F	O-APS on LDA	B2GPI-G +	CS	1/0	100 UI/kg × 1/100 UI/kg × 2	Smoke, Overweight	–	–	O-APS on LDA
10	31	M	T-APS + SLE on OAT	LAC+ACL-GB2GPI-G	Surgery	1/0	100 UI/kg × 1/100 UI/kg × 1	HTA, Obesity	–	–	T-APS on OAT
11/1st procedure	57	F	T-APS + SLE on LDA	LAC +	Surgery	0/0	100 UI/kg × 1/100 UI/kg × 1	HTA, Obesity	–	–	T-APS + SLE on LDA
11/2nd procedure	60	F	T-APS + SLE on LDA	LAC +	Surgery	0/0	100 UI/kg × 1/100 UI/kg × 1	HTA, Obesity	–	–	T-APS + SLE on LDA
12	60	F	T-APS + SLE on LDA	LAC+ACL-M + B2GPI-M +	Surgery	1/0	< 100 UI/kg × 1/100 UI/kg × 1	Obesity/Steroid treatment	–	–	T-APS + SLE on LDA
13	39	F	OT-APS on LDA	LAC+ACL-G +	Voluntary Interruption of pregnancy	1/0	100 UI/kg × 2/100 UI/kg × 2	–	–	–	OT-APS on LDA
14/1st procedure	64	M	T-APS + SLE on OAT	LAC + ACLG + ACLM +	Surgery	1/1	100 UI/kg × 2/100 UI/kg × 1	Smoke, steroid therapy, (anemia post	NSAD	ACS/Local bleeding	T-APS + SLE on OAT + Clopid

Patient no.	Age (procedure)	Sex	Diagnosis and treatment before procedure	aPL profile (closer to procedure)	Procedure	LMWH interruption before and after procedure	LMWH doses before and after intervention	Thrombosis risk factors	Bleeding risk factors	Thrombotic and hemorrhagic event	Diagnosis treatment after procedure
								bleeding)		, loss of 6 g Hb	ogrel
14/2nd procedure	68	M	T-APS + SLE on OAT	LAC + ACLG + ACLM +	Surgery	0/1	100 UI/kg × 1/100 UI/kg × 1	Smoke, steroid therapy	–	–	T-APS + SLE on OAT
15/1st procedure	75	F	T-APS + SLE on LDA	LAC + ACLG + B2GPIG +	Surgery	0/1	−/< 100 UI/kg × 1	Smoke			T-APS + SLE on LDA
15/2nd procedure	76	F	T-APS + SLE on LDA	LAC + ACLG + B2GPIG +	Surgery	1/1	−/< 100 UI/kg × 1	Smoke	–	DVT	T-APS + SLE on LDA
16	64	M	T-APS + SLE on LDA	LAC +	Surgery	3/1	100 UI/kg × 1/100 UI/kg × 1	HTA,Overweight, Steroid therapy	–	–	T-APS + SLE on LDA

Table 3. Clinical Characteristics, peri-procedural management and outcome of antiphsopholipid antibody-positive patients.

Patient no.	Age (procedure)	sex	Diagnosis and Treatment before procedure	aPL Profile (closer to procedure)	Procedure	LMWH interruption before and after procedure	LMWH doses before and after intervention	Thrombosis risk factors	Bleeding Risk Factors	Thrombotic and Hemorrhagic event	Diagnosis Treatment after Procedure
17	39	F	APL + UCTD	LAC +	IL	2/1	100 UI/kg × 1/100 UI/kg × 1	–	–	CVST	T-APS + UCTD on OAT
18/1st procedure	32	F	APL + SLE on LDA	ACLG +	CS	1/1	< 100 UI/kg × 1/< 100 UI/kg × 1	Overweight	–	–	APL + SLE on LDA
18/2nd procedure	37	F	APL + SLE	ACLG +	CS	0/3	−/< 100 UI/kg × 1	Overweight	–	–	APL + SLE
19	41	F	APL on LDA	ACLM+B2GPIM +	SL	1/1	< 100 UI/kg × 1/< 100 UI/kg × 1	–	–	Bleeding	APL on LDA
20	38	F	APL on LDA	ACLM+B2GPIM +	CS	1/1	< 100 UI/kg × 1/< 100 UI/kg × 1	Overweight	–	–	APL
21	37	F	APL + UCTD on LDA	LAC+B2GPIM +	CS	1/1	< 100 UI/kg × 1/< 100 UI/kg × 1	–	–	–	APL + UCTD
22/1st procedure	53	F	APL + UCTD on LDA	LAC + ACLG + B2GPIG +	Surgery	2/2	−/100 UI/kg × 1	Obesity, Smoke, HTA, (cancer)	Thrombocytopenia	–	APL + UCTD on LDA
22/2nd	39	F	APL on	LAC + B2GPIG +	CS	1/1	< 100 UI/kg × 1/< 100	Steroid	–	–	APL

Patient no.	Age (procedure)	sex	Diagnosis and Treatment before procedure	aPL Profile (closer to procedure)	Procedure	LMWH interruption before and after procedure	LMWH doses before and after intervention	Thrombosis risk factors	Bleeding Risk Factors	Thrombotic and Hemorrhagic event	Diagnosis Treatment after Procedure
procedure			LDA				UI/kg × 1	Therapy			
23/1st procedure	34	F	APL + SLE on LDA	LAC + ACLG + B2GPIG+ B2GPIM +	SL	1/2	< 100 UI/kg × 1/100 UI/kg × 1	Steroid Therapy	–	–	APL + SLE on LDA
23/2nd procedure	36	F	APL + SLE on LDA	LAC + B2GPIG +	CS	1/1	< 100 UI/kg × 1/< 100 UI/kg × 1	Steroid Therapy	–	–	APL + SLE on LDA
24	32	F	APL + SLE on LDA	LAC + ACLG + B2GPIG+ B2GPIM +	Surgery	1/2	< 100 UI/kg × 1/100 UI/kg × 1	Obesity, HTA	Thrombocytopenia	–	APL + SLE on LDA
25	36	F	APL + UCTD on LDA	LAC + ACLG + B2GPIG +	CS	0/2	100 UI/kg × 1/100 UI/kg × 1	–	–	–	APL + UCTD
26	30	F	APL + on LDA	LAC + ACLM +	CS	2/1	< 100 UI/kg × 1/100 UI/kg × 1	–	–	–	APL + on LDA
27	28	F	APL + SLE on LDA	LAC + B2GPIG +	IL	3/1	100 UI/kg × 1/100 UI/kg × 1	Steroid Therapy, Smoke	–	–	APL + SLE on LDA
28/1st procedur	36	F	APL + UCTD on LDA	LAC + ACLG + B2GPIG +	IL	2/1	100 UI/kg × 1/100 UI/kg × 1	Smoke,Protein S Deficiency	–	–	APL + UCTD on LDA
28/2nd	40	F	APL + U	LAC + ACLG + B2GPIG +	CS	0/1	100 UI/kg × 1/100 UI/k	Smoke,Pr	–	–	APL + U

Patient no.	Age (procedure)	sex	Diagnosis and Treatment before procedure	aPL Profile (closer to procedure)	Procedure	LMWH interruption before and after procedure	LMWH doses before and after intervention	Thrombosis risk factors	Bleeding Risk Factors	Thrombotic and Hemorrhagic event	Diagnosis Treatment after Procedure
procedure			CTD on LDA				g × 1	otein S Deficiency			CTD on LDA
29	33	F	APL + on LDA	ACLG +	CS	1/1	100 UI/kg × 1/100 UI/kg × 1	–	–	–	APL + on LDA
30/1st procedure	38	F	APL + on LDA	ACLM+B2GPIM +	CS	2/1	100 UI/kg × 1/100 UI/kg × 2	–	–	–	APL + on LDA
30/2nd procedure	40	F	APL + on LDA	LAC+ACLM+B2GPIM +	CS	1/1	100 UI/kg × 1/100 UI/kg × 1	–	–	–	APL +
31/1st procedure	32	F	APL + U CTD on LDA	LAC + ACLG + ACLM+B2GPI-G+B2GPI-M +	SL	2/1	100 UI/kg × 1/< 100 UI/kg × 1	–	–	–	APL + U CTD on LDA
31/2nd procedure	35	F	APL + U CTD on LDA	LAC + ACLG + ACLM+B2GPI-G+B2GPI-M +	IL	1/1	< 100 UI/kg × 1/< 100 UI/kg × 1	Steroid Therapy	–	–	
32	36	F	APL + on LDA	ACLM +	CS	1/1	100 UI/kg × 1/100 UI/kg × 1	–	–	–	APL +
33	47	F	APL + on LDA	ACLG +	CS	1/1	100 UI/kg × 1/100 UI/kg × 1	Smoke	–	–	APL + R
34/1st procedure	21	F	APL + SLE on LDA	LAC +	CS	1/1	100 UI/kg × 1/100 UI/kg × 1	–	–	–	APL + SLE on LDA

Patient no.	Age (procedure)	sex	Diagnosis and Treatment before procedure	aPL Profile (closer to procedure)	Procedure	LMWH interruption before and after procedure	LMWH doses before and after intervention	Thrombosis risk factors	Bleeding Risk Factors	Thrombotic and Hemorrhagic event	Diagnosis Treatment after Procedure
34/2nd procedure	22	F	APL + SLE on LDA	LAC +	Surgery	1/1	100 UI/kg × 1/100 UI/kg × 1	–	–	–	APL + SLE on LDA
35	57	F	APL + UCTD on LDA	LAC +	Surgery	1/1	100 UI/kg × 1/100 UI/kg × 1	Protein S Deficiency	–	–	APL + UCTD on LDA
36	38	F	APL + on LDA	LAC + ACLG + B2GPIG +	IL	1/1	< 100 UI/kg × 1/< 100 UI/kg × 1	–	–	–	APL + on LDA

O-APS, obstetric antiphospholipid syndrome
T-APS, thrombotic antiphospholipid syndrome
SLE, systemic lupus erythematosus
UCTD, undifferentiated connective tissue disease
HTA, arterial hypertension
ACS, acute coronary syndrome
NSAD, non-steroid anti-inflammatory drugs
LDA, low dose aspirin
OAT, oral anticoagulant therapy
LDA, low dose aspirin
OAT, oral anticoagulant therapy
LAC, lupus anticoagulant
ACLG, IgG anti-cardiolipina
ACLM, IgM anti-cardiolipina
B2GPI-G, IgG anti-B2GPI
B2GPI-M, IgM anti-B2GPI
TRIPLE
CS, cesarean section
SL, spontaneous labor
IL, induced labor

DVT, deep venous thrombosis
CVST, cerebral venous sinus thrombosis
LMWH, interruption before and after procedure
0 < 12H
(1) 12–24H
(2) 25–48H
(3) > 48H

Table 4. Clinical Characteristics, peri-procedural management and outcome of patients who experienced adverse events.

Patient no.	Diagnosis and treatment before procedure	aPL profile	Procedures	Adverse events	LMWH interruption before and after intervention (hours)	LMWH doses before and after intervention (UI/kg/die)	Thrombotic risk factors	Bleeding risk factors	Diagnosis and treatment after procedure
8	O-APS on LDA	Triple positivity	Labor	DVT	31/11	< 100 × 1/100 × 1	Pregnancy	No	O/T-APS on OAT
14	T-APS with SLE on OAT	Myiakis I	Orthopedic surgery	Local bleeding, loss of 6 g Hb/MI	12/4	100 × 2/100 × 2	Smoke, bed rest, post-splenectomy thrombocytosis, previous PE, steroid therapy	NSAID post surgery	T-APS with SLE on OAT + LDA + Clopidogrel
15	T-APS with SLE on LDA	Triple positivity	Skin graft after necrosectomy of necrotic tissue	DVT	−/12	−/< 100 × 1	Smoke, bed rest, previous DVT	No	T-APS with SLE on OAT
17	aPL with UCTD on LDA	Myiakis IIa	Labor	CVT	46/20	100 × 1/100 × 1	Microcytic anemia Hb 7,8 g, pregnancy	No	T-APS with UCTD on OAT

SLE, systemic lupus erythematosus
O-APS, obstetric APS
T -APS, thrombotic APS
LDA, low-dose aspirin

OAT, oral anticoagulation therapy
MI, myocardial infarction
DVT, deep venous thrombosis
CVT, cerebral venous thrombosis
NSAID, non-steroidal anti-inflammatory drugs
PE, pulmonary thromboembolism
Myiakis I: more than one laboratory criteria present (any combination); IIa: LA present alone; IIb: aCL antibody present alone; IIc: anti-b2glycoprotein-I antibody present alone. Triple positivity: LA, aCL, anti-b2glycoprotein-I antibodies