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UPMC PARIS UNIVERSITAS

Current View of the Treatment of Antiphospholipid Syndrome

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Antiphospholipid antibodies

- 40 % of SLE patients
→ 40% thrombosis

-Recurrent miscarriages = 1% of the population
→10 % = APS

Anticardiolipin antibodies can be found in 2% to 5% of a normal population

These antibodies increase in prevalence with increasing age, with IgG and IgM aCL being observed in 12% to 52% of an elderly population

Panel 1: Clinical manifestations of antiphospholipid syndrome

Frequent (>20% of cases)

- Venous thromboembolism
- Thrombocytopenia
- Miscarriage or fetal loss
- Stroke or transient ischaemic attack
- Migraine
- Livedo reticularis

Less common (10–20% of cases)

- Heart valve disease
- Pre-eclampsia or eclampsia
- Premature birth
- Haemolytic anaemia
- Coronary artery disease

Unusual (<10% of cases)

- Epilepsy
- Vascular dementia
- Chorea
- Retinal artery or vein thrombosis
- Amaurosis fugax
- Pulmonary hypertension
- Leg ulcers
- Digital gangrene
- Osteonecrosis
- Antiphospholipid syndrome nephropathy
- Mesenteric ischaemia

Rare (<1% of cases)

- Adrenal haemorrhage
- Transverse myelitis
- Budd-Chiari syndrome

Wilson WA, Gharavi AE, Koike T, et al. International consensus statement on preliminary classification criteria for definite antiphospholipid syndrome: report of an international workshop. Arthritis Rheum 1999; 42: 1309–11.

Classification for this syndrome needed at least one clinical manifestation

together with positive tests for circulating antiphospholipid antibodies, including lupus anticoagulant or anticardiolipin, or both, at medium-high values,

detected at least twice in 6 weeks.

SYDNEY REVISION OF SAPPORO CRITERIA (2006)

Miyakis S, Lockshin MD, Atsumi T, et al. International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS). *J Thromb Haemost* 2006; 4: 295–306.

Clinical criteria

Vascular thrombosis

• **One or more clinical episodes of arterial, venous, or small vessel thrombosis, in any tissue or organ.**

• **Thrombosis should be supported** by objective validated criteria—ie, unequivocal findings of appropriate **imaging studies or histopathology**. For histopathological support, thrombosis should be present without substantial evidence of inflammation in the vessel wall.

Pregnancy morbidity, defined by one of the following criteria:

• **One or more unexplained deaths** of a morphologically healthy fetus at or beyond the 10th week of gestation, with healthy fetal morphology documented by ultrasound or by direct examination of the fetus.

• **One or more premature births** of a morphologically healthy newborn baby before the 34th week of gestation because of: eclampsia or severe pre-eclampsia defined according to standard def nitions or recognised features of placental failure.

• **Three or more unexplained consecutive spontaneous abortions** before the 10th week of gestation, with maternal anatomical or hormonal abnormalities and paternal and maternal chromosomal causes excluded.

Laboratory criteria

- **Lupus anticoagulant** present in plasma, on two or more occasions at least 12 weeks apart, detected according to the guidelines of the International Society on Thrombosis and Hemostasis (Scientific Subcommittee on lupus anticoagulant/phospholipid-dependent antibodies).

- **Anticardiolipin antibody of IgG or IgM isotype**, or both, in serum or plasma, present in medium or high titres (**ie, >40 GPL or MPL, or greater than the 99th percentile**) on two or more occasions, at least 12 weeks apart, measured by a standardised ELISA.

- **Anti-β2-gycoprotein 1 antibody of IgG or IgM isotype, or both, in serum or plasma (in titres greater than the 99th percentile**), present on two or more occasions, at least 12 weeks apart, measured by a standardised ELISA, according to recommended procedures.

Main modifications

- Time elapsed between two positive determinations = 12 weeks to assure the detection of persistent antibodies only; and anti-β2-glycoprotein 1,
- Both anti-β2-glycoprotein 1 IgG and IgM,
- Medium titres of anticardiolipin, or anti-β2-glycoprotein 1 > than the 99th percentile.

Non-APS criteria antiphospholipid antibodies

- Anticardiolipin IgA
- Anti-β2GPI IgA
- Antiphosphatidylserine
- Antiphosphatidylethanolamine
- Prothrombin alone (aPT-A)
- Phosphatidylserine-prothrombin (aPS/PT) complex

Preliminary criteria for the classification of catastrophic APS

1.Evidence of involvement **of three** or more organs, systems, or tissues.

2. Development of manifestations **simultaneously or in less than a week.**

3. **Confirmation by histopathology** of small vessel occlusion in at least one organ or tissue.

4. **Laboratory confirmation** of the presence of antiphospholipid antibodies

Management of thrombosis

Management of thrombosis

- **secondary thromboprophylaxis:** patients with APS who have already had a thrombotic event and antiphospholipid Abs

- **primary thromboprophylaxis**: antibody carriers without previous thrombosis, which can be either
  - purely asymptomatic individuals,
  - patients with systemic lupus erythematosus,
  - or women with obstetric APS

Secondary thromboprophylaxis in APS

2 key issues :

- arterial and venous events should be treated differently ?

- APS same treatment as the general population ?

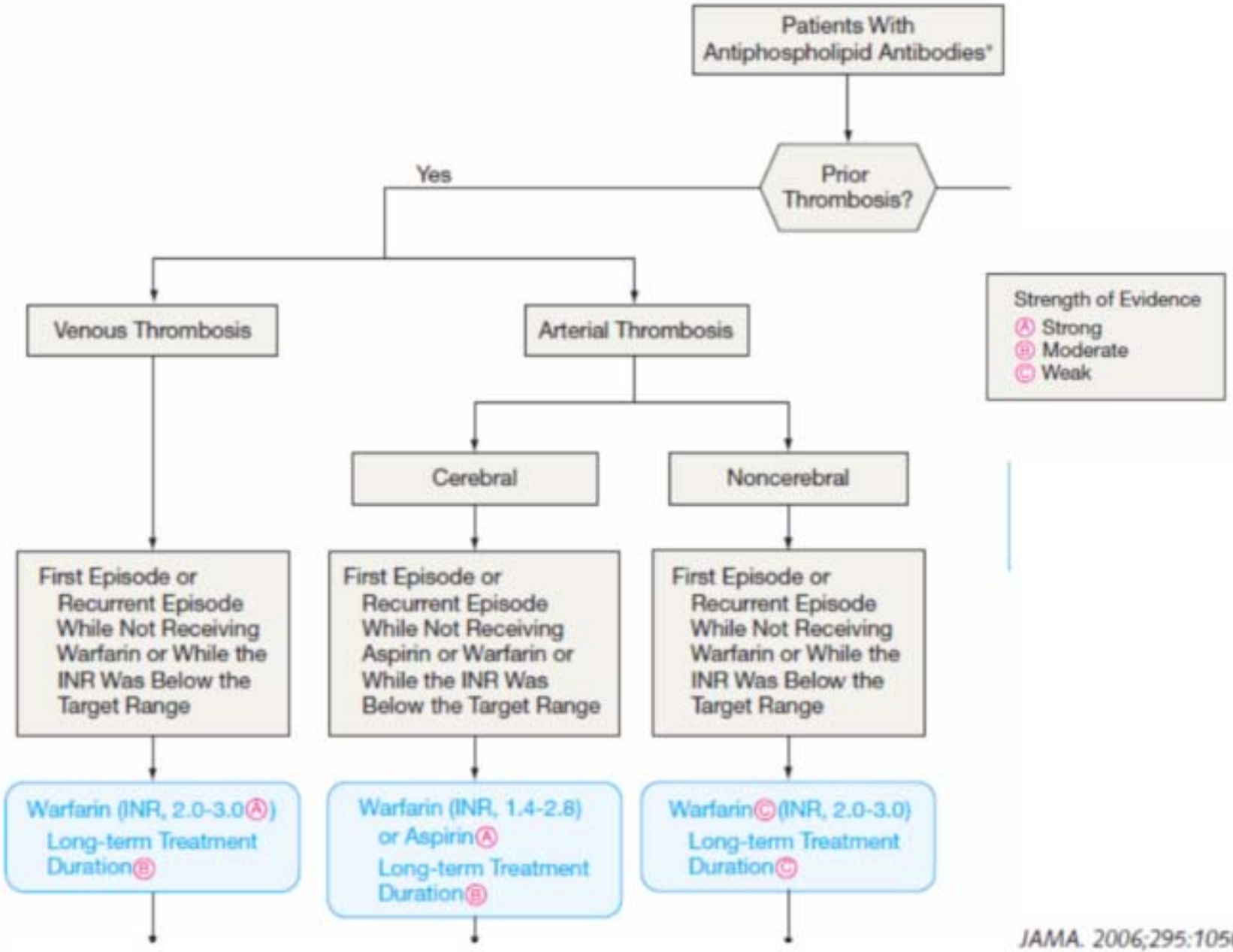
Secondary thromboprophylaxis in APS

Management of Antiphospholipid Antibody Syndrome

A Systematic Review

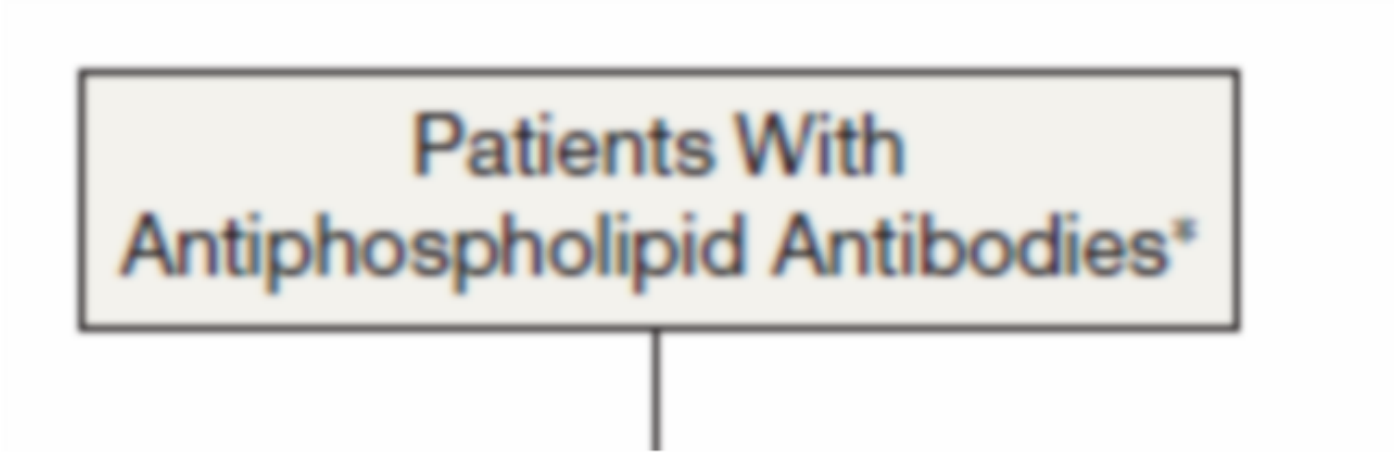
Wendy Lim, MD
Mark A. Crowther, MD
John W. Eikelboom, MBBS

JAMA. 2006;295:1050-1057



JAMA. 2006;295:1050-1057

Secondary thromboprophylaxis in APS



*Importance of transient antiphospholipid antibodies is uncertain.

Secondary thromboprophylaxis in APS

Table 1. Summary of selected studies*

Author, year (ref.)	No.	Type of study	Sapporo criteria for aPL
Rosove, 1992 (12)	70	Retrospective cohort	No
Derksen, 1993 (24)	19	Retrospective cohort	Yes
Khamashta, 1995 (13)	147	Retrospective cohort	Yes
Krnic-Barrie, 1997 (25)	61	Retrospective cohort	No
Muñoz-Rodriguez, 1999 (14)	47	Retrospective cohort	Yes
Ruiz-Irastorza, 2002 (15)	66	Retrospective cohort	Yes
Wittkowsky, 2006 (27)	36	Retrospective cohort	Yes
Girón-Gonzàlez, 2004 (23)	158	Prospective cohort	Yes
Ames, 2005 (17)	67	Prospective cohort	Yes
Ginsberg, 1995 (19)	16	Prospective cohort subgroup analysis	No
Prandoni, 1996 (20)	15	Retrospective cohort subgroup analysis	Yes
Rance, 1997 (26)	27	Retrospective cohort subgroup analysis	No
Schulman, 1998 (21)	68	RCT subgroup analysis	No
Levine, 2004 (22)	720	RCT subgroup analysis	No
Crowther, 2003 (16)	114	RCT	Yes
Finazzi, 2005 (18)	109	RCT	Yes

* aPL = antiphospholipid antibodies; RCT = randomized controlled trial.
† Six unspecified events.
‡ Eighteen patients died at the time of the presenting event and were not subject to followup.

Secondary thromboprophylaxis in APS

Table 1. Summary of selected studies*

Author, year (ref.)	No.	Type of study	Sapporo criteria for aPL	Thrombotic events at diagnosis, arterial/venous
Rosove, 1992 (12)	70	Retrospective cohort	No	31/39
Derksen, 1993 (24)	19	Retrospective cohort	Yes	0/19
Khamashta, 1995 (13)	147	Retrospective cohort	Yes	67/80
Krnic-Barrie, 1997 (25)	61	Retrospective cohort	No	38/23
Muñoz-Rodriguez, 1999 (14)	47	Retrospective cohort	Yes	19/28
Ruiz-Irastorza, 2002 (15)	66	Retrospective cohort	Yes	51/32
Wittkowsky, 2006 (27)	36	Retrospective cohort	Yes	14/16†
Girón-Gonzàlez, 2004 (23)	158	Prospective cohort	Yes	70/106‡
Ames, 2005 (17)	67	Prospective cohort	Yes	17/50
Ginsberg, 1995 (19)	16	Prospective cohort subgroup analysis	No	0/16
Prandoni, 1996 (20)	15	Retrospective cohort subgroup analysis	Yes	0/15
Rance, 1997 (26)	27	Retrospective cohort subgroup analysis	No	0/27
Schulman, 1998 (21)	68	RCT subgroup analysis	No	0/68
Levine, 2004 (22)	720	RCT subgroup analysis	No	720/0
Crowther, 2003 (16)	114	RCT	Yes	27/87
Finazzi, 2005 (18)	109	RCT	Yes	44/75

* aPL = antiphospholipid antibodies; RCT = randomized controlled trial.
† Six unspecified events.
‡ Eighteen patients died at the time of the presenting event and were not subject to followup.

Arthritis & Rheumatism (Arthritis Care & Research)
Vol. 57, No. 8, December 15, 2007, pp 1487–1495
DOI 10.1002/art.23109

ORIGINAL ARTICLE

A Systematic Review of Secondary Thromboprophylaxis in Patients With Antiphospholipid Antibodies

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Antiphospholipid syndrome

Guillermo Ruiz-Irastorza, Mark Crowther, Ware Branch, Munther A Khamashta

www.thelancet.com **Published online September 6, 2010**

Secondary thromboprophylaxis in APS recommendations

	Secondary prophylaxis
Patients with definite antiphospholipid syndrome and first venous event*	Indefinite anticoagulation to a target INR 2·0–3·0
Patients with definite antiphospholipid syndrome and arterial event*	Indefinite anticoagulation to a target INR 3·0–4·0 or combined antithrombotic treatment
Patients with definite antiphospholipid syndrome and recurrent events despite warfarin with a target intensity of 2·0–3·0	Indefinite anticoagulation to a target INR 3·0–4·0 or alternative therapies such as extended therapeutic dose low-molecular-weight heparin
Patients with venous thromboembolism with single positive or low-titre antiphospholipid antibodies	As per usual recommendations for deep vein thrombosis treatment
Patients with arterial thrombosis with single positive or low-titre antiphospholipid antibodies	As per usual recommendations for arterial thrombosis

INR=international normalised ratio. *Less aggressive or long-lasting antithrombotic treatments might be appropriate in low-risk patients.

Table 1: **Recommendations for secondary prophylaxis in patients with antiphospholipid antibodies and thrombosis**

Primary thromboprophylaxis in AP(S)

- The risk of thrombosis among healthy patients with antiphospholipid antibody (1% per year).

Finazzi G,, et al. Natural history and risk factors for thrombosis in 360 patients with antiphospholipid antibodies: a four-year prospective study from the Italian registry. Am J Med 1996; ***100:*** *530–36*.

Giron-Gonzalez JA,. Antiphospholipid syndrome and asymptomatic carriers of antiphospholipid antibody: prospective analysis of 404 individuals. J Rheumatol 2004; 31: 1560–67.

- Among 552 randomly selected blood donors, no thrombotic events were observed after 12 months of follow-up among patients found to have aCL.

Vila P, Hernandez MC, Lopez-Fernandez MF, Batlle J. Prevalence, follow-up and clinical significance of the anticardiolipin antibodies in normal subjects. Thromb Haemost. 1994;72:209-213.

Primary thromboprophylaxis in AP(S)

Erkan D, Harrison MJ, Levy R, et al. Aspirin for primary thrombosis prevention in the antiphospholipid syndrome: a randomized, doubleblind, placebo-controlled trial in asymptomatic antiphospholipid antibody-positive individuals. *Arthritis Rheum* 2007; 56: 2382–91.

- no difference between asymptomatic antiphospholipid antibody carriers given low-dose aspirin and those given placebo

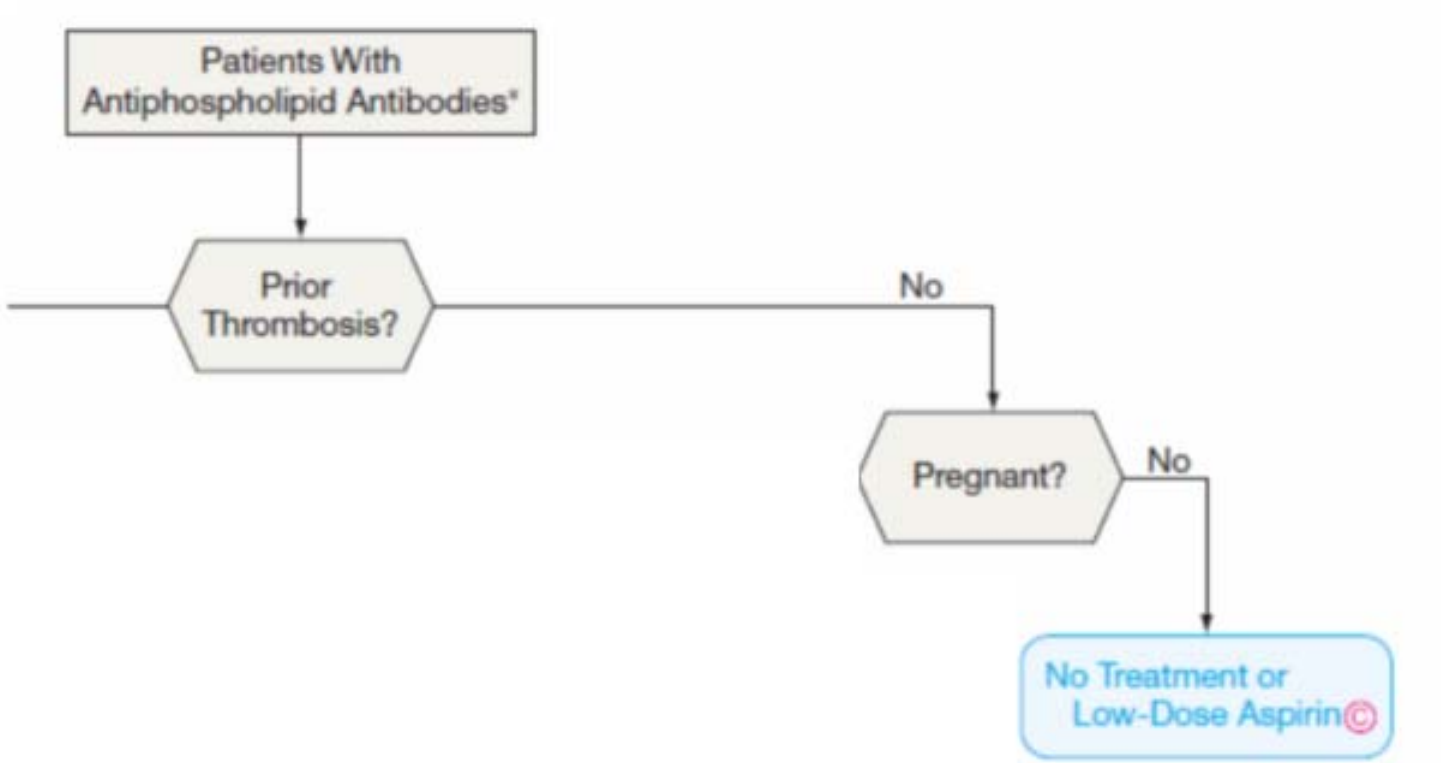
- rate of thrombosis in patients given placebo was zero,
- study was underpowered to detect a beneficial effect of aspirin.

Primary thromboprophylaxis in APS

- Observational studies have consistently shown a protective effect of aspirin in asymptomatic antiphospholipid antibody carriers with systemic lupus erythematosus

- Risk of severe hemorrhages under aspirin ~1%

Primary thromboprophylaxis in APS



Primary thromboprophylaxis in AP(S)

- In patients with SLE, the incidence of thrombosis was 2 per 100 personyears in a prospective cohort of 551 patients of whom 49% had either LA or aCL.

Petri M. Thrombosis and systemic lupus erythematosus: the Hopkins Lupus Cohort perspective. *Scand J Rheumatol.* 1996;25:191-193.

Primary thromboprophylaxis in APS

	Primary thromboprophylaxis
Patients with systemic lupus erythematosus and lupus anticoagulant and/or persistently positive anticardiolipin	Hydroxychloroquine and consider low-dose aspirin
Patients with obstetric antiphospholipid syndrome	Low-dose aspirin or no therapy
Asymptomatic carriers of antiphospholipid antibodies	No therapy or low-dose aspirin
All patients with antiphospholipid antibodies	Strict control of vascular risk factors
High-risk situations (surgery, post partum, long-lasting immobilisation)	Adequate thrombophylaxis

Table 2: **Primary thromboprophylaxis in patients with antiphospholipid antibodies**

Primary thromboprophylaxis in APS

- Stratification according to the immunological profile ?

→ *AP patients with triple positivity for lupus anticoagulant, anticardiolipin, and anti-β2-glycoprotein 1 are at the highest risk for venous and arterial thrombosis and for obstetric complications.*

Pregnancy management

- preconception counselling
- complete profile of antiphospholipid antibodies
- frequent prenatal visits
- uterine and umbilical artery Doppler assessments

Pregnancy management

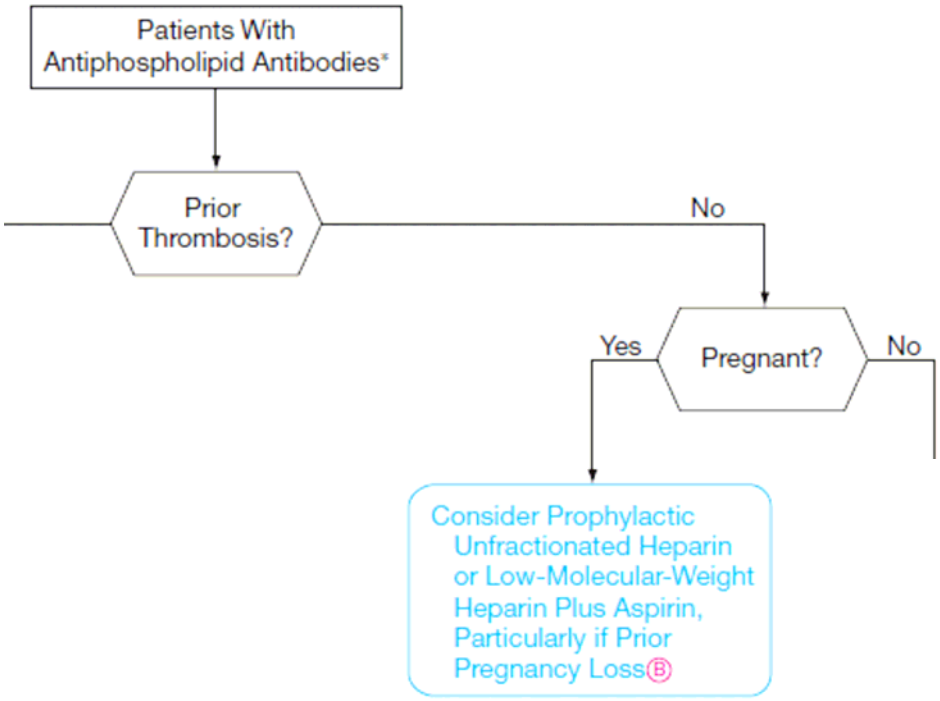
Classify pregnant women in one of the following groups:

1. **recurrent early miscarriage** and no other features of APS,

2. **one or more previous fetal deaths** (at more than 10 weeks' gestation) or previous early delivery (at less than 34 weeks' gestation) because of severe pre-eclampsia or placental insufficiency.

3. **history of thrombosis**, irrespective of pregnancy history.

Pregnancy management



Strength of Evidence
- Ⓐ Strong
- Ⓑ Moderate
- Ⓒ Weak

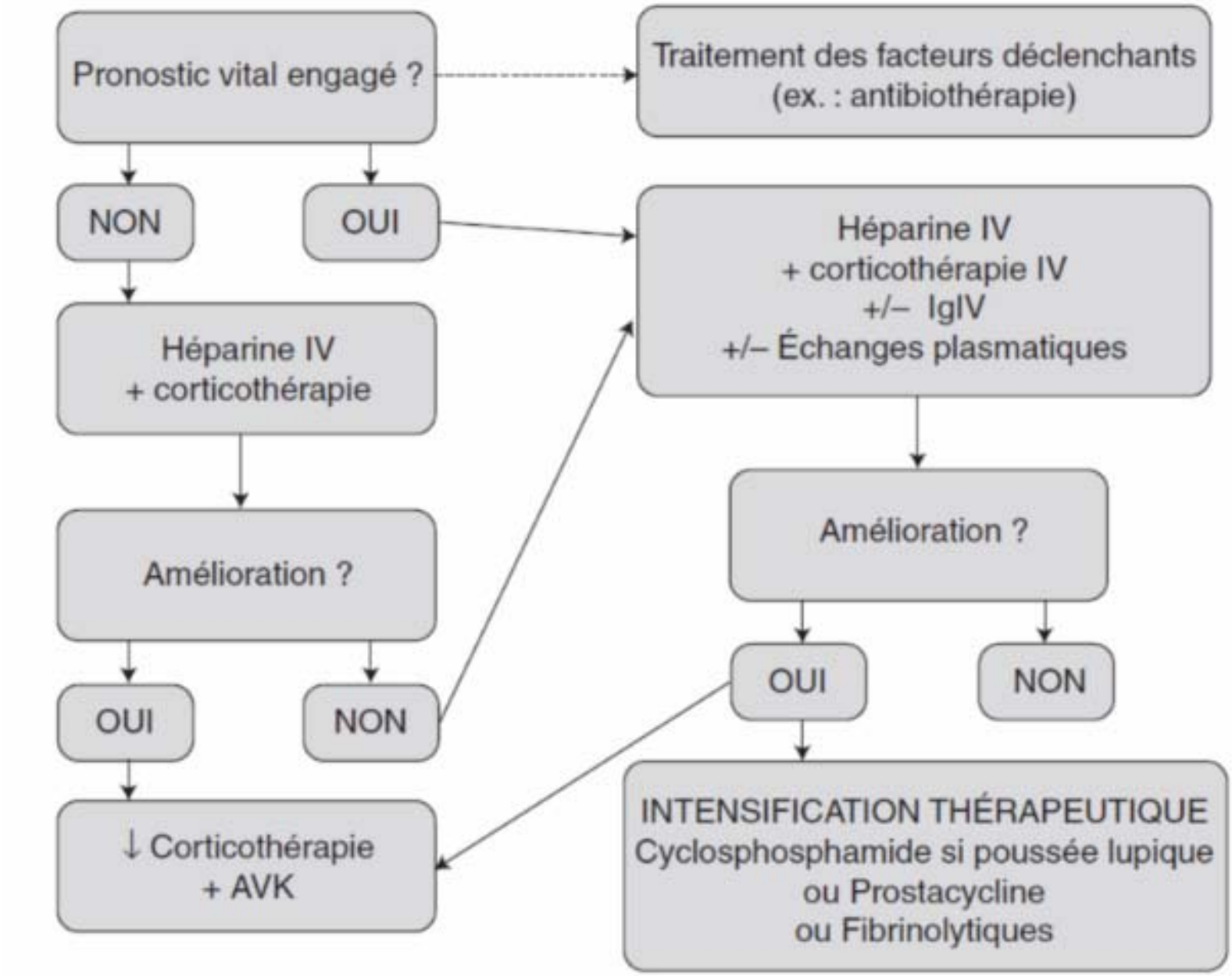
Pregnancy management

	Regimen
Antiphospholipid syndrome without previous thrombosis and recurrent early (pre-embryonic or embryonic) miscarriage	Low-dose aspirin alone or together with either unfractionated heparin (5000–7500 IU subcutaneously every 12 h) or LMWH (usual prophylactic doses)
Antiphospholipid syndrome without previous thrombosis and fetal death (more than 10 weeks' gestation) or previous early delivery (<34 weeks gestation) due to severe pre-eclampsia or placental insufficiency	Low-dose aspirin plus: • Unfractionated heparin (7500–10 000 IU subcutaneoulsy every 12 h in the first trimester; 10 000 U subcutaneously every 12 h in the second and third trimesters, or every 8–12 h adjusted to maintain the mid-interval aPTT* 1·5 times the control mean) • LMWH (usual prophylactic doses)
Antiphospholipid syndrome with thrombosis	Low-dose aspirin plus: • Unfractionated heparin (subcutaneously every 8–12 h adjusted to maintain the mid-interval aPTT* or heparin concentration (anti-Xa activity)* in the therapeutic range) • LMWH (usual therapeutic dose—eg, enoxaparin 1 mg/kg subcutaneously, or dalteparin 100 U/kg subcutaneously every 12 h, or enoxaparin 1·5 mg/kg/day subcutanously, or dalteparin 200 U/kg/day subcutaneously)†

aPTT= activated partial thromboplastin time. LMWH=low-molecular-weight heparin. *Women without a lupus anticoagulant in whom the aPTT is normal can be monitored with the aPTT. Women with lupus anticoagulant should be monitored with antifactor Xa activity. †Need for dose adjustments over the course of pregnancy remains controversial.[91] Some experts argue that in the absence of better evidence, it is prudent to monitor anti-factor Xa LMWH concentrations 4–6 h after injection with dose adjustment to maintain a therapeutic antifactor Xa concentration (0·6 to 1·0 U/mL if a twice-daily regimen is used; slightly higher if a once-daily regimen is chosen).

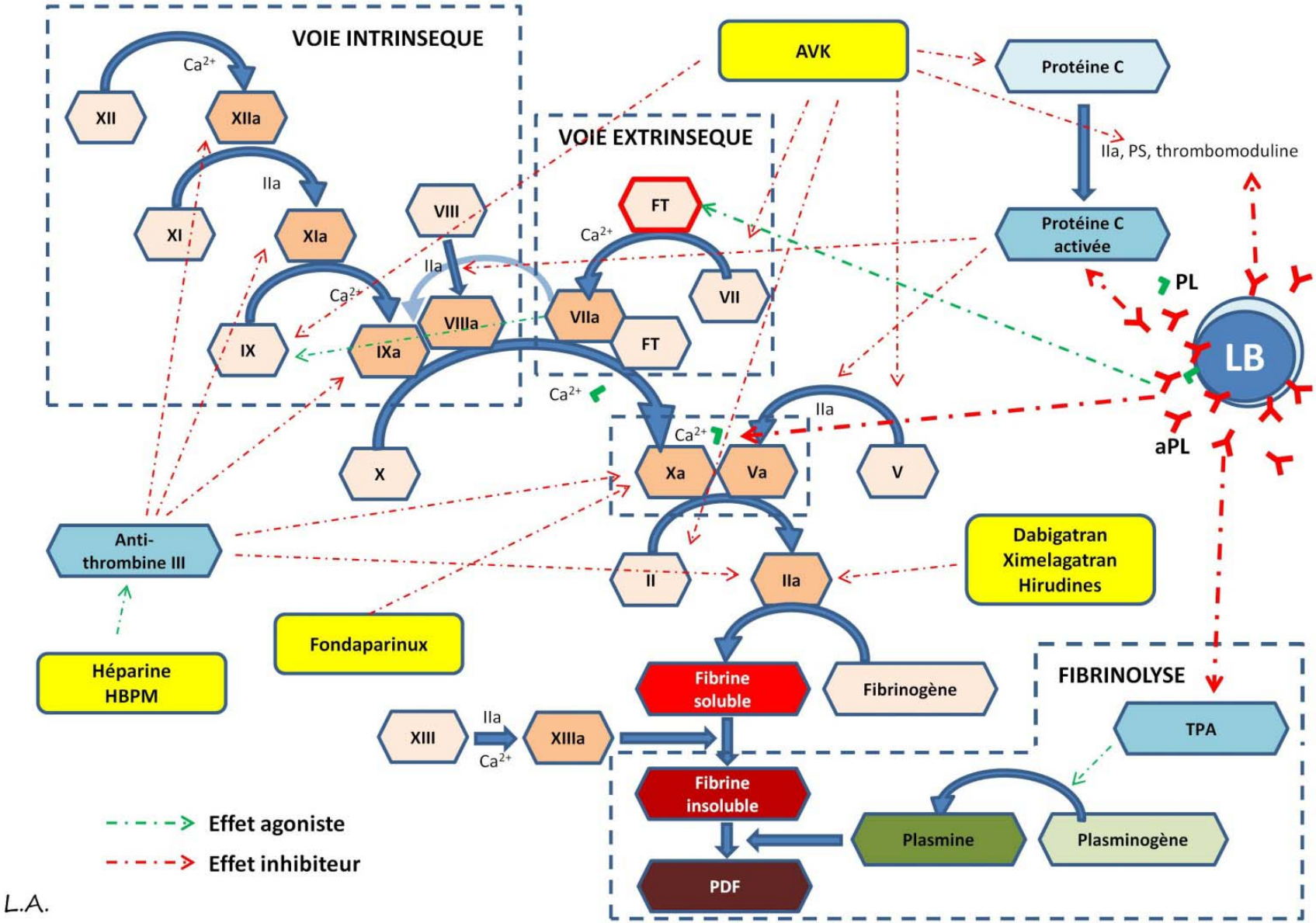
Table 3: **Suggested regimens for the treatment of antiphospholipid syndrome in pregnancy**

Traitement du CAPS



Future therapies

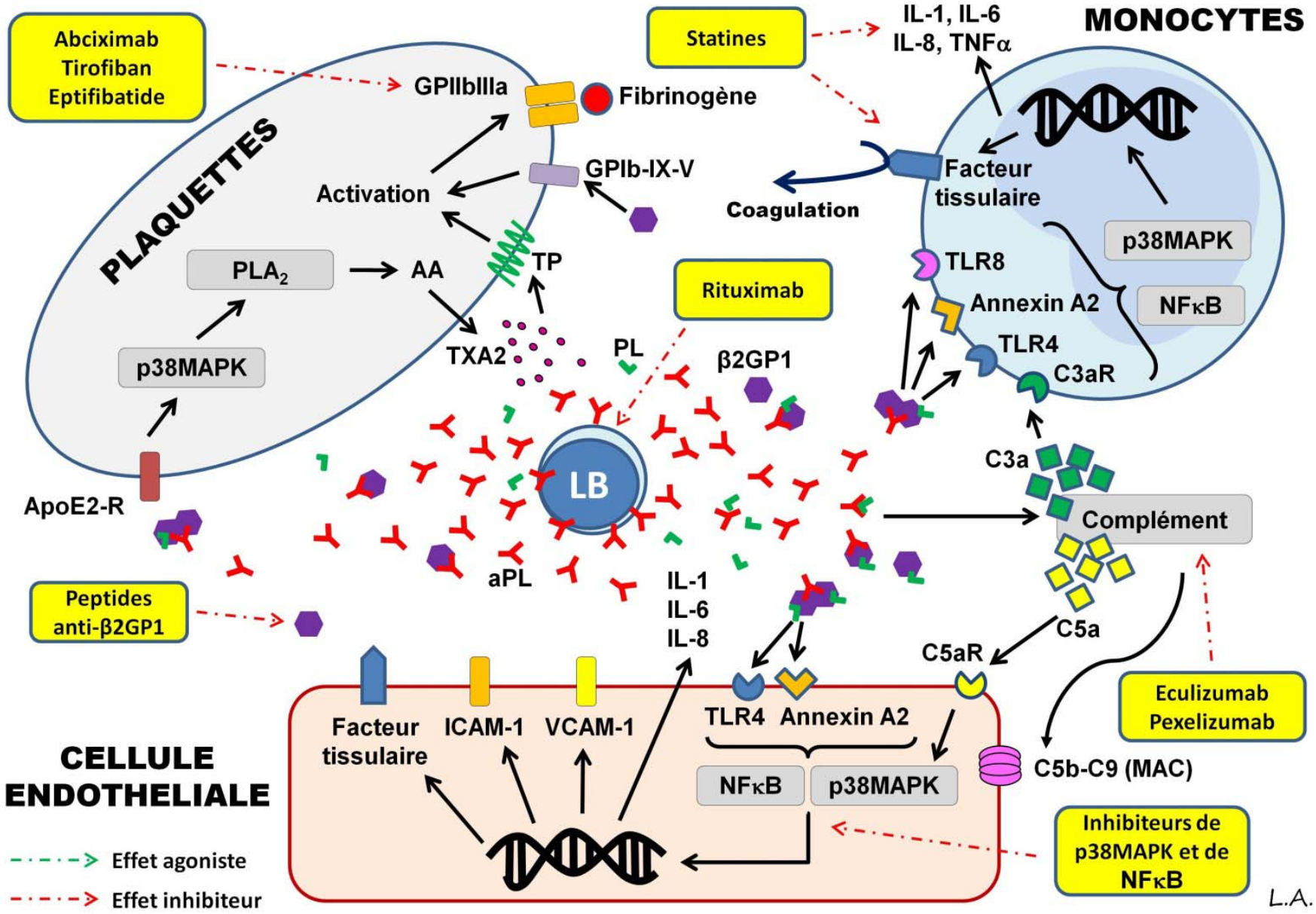
Future therapies



Panel 3: Potential future therapies for antiphospholipid syndrome

- Combination antiaggregant therapy (low-dose aspirin plus clopidogrel or dipyridamole)
- Oral antifactor Xa drugs (rivaroxaban, apixaban)
- Direct thrombin inhibitors (dabigatran)

Future therapies



Future therapies

Inhibition of Complement

- **Circulating levels of C' components are lower in APS.**

Oku K . Complement activation in patients with primary antiphospholipid syndrome. Ann Rheum Dis 2009;68:1030-5

- **Reduced expression of DAF + greater deposition of C3 and C4 components in endometrial tissue from aPL-positive women with recurrent miscarriage.**

Francis J. Impaired expression of endometrial differentiation markers and complement regulatory proteins in patients with recurrent pregnancy loss associated with antiphospholipid syndrome. Mol Hum Reprod 2006;12:435-438

Shamonki JM. Excessive complement activation is associated with placental injury in patients with antiphospholipid antibodies. Am J Obstet Gynecol 2007;196:167.e1-e5

Holers VM,et al. Complement C3 activation is required for antiphospholipid antibody- induced fetal loss. J Exp Med 2002;195:211-20

Inhibition of Complement

- **C3 and C9 colocalisation with aPL in the mesenteric vessels of a rat model of thrombosis** . Fischetti F. Thrombus formation induced by antibodies to beta2-glycoprotein I is complement dependent and requires a priming factor. Blood 2005;106:2340-6

- **Blocking C3, C4 or C5 by molecular inhibitors or gene knockout prevens fetal loss driven by aPL in vivo** . Girardi G Complement C5a receptors and neutrophils mediate fetal injury in the antiphospholipid syndrome. J Clin Invest 2003;112:1644-54

- **Anti-C5 monoclonal antibodies inhibit aPL-mediated thrombosis in mouse** Pierangeli SS, Requirement of activation of complement C3 and C5 for antiphospholipid antibody-mediated thrombophilia. Arthritis Rheum 2005;52:2120-4

- **C5a receptor antagonist peptide inhibits aPL-driven in vivo thrombosis and ex vivo TF expression and activity in mice.** Pierangeli SS, Antiphospholipid syndrome treatment beyond anticoagulation: are we there yet? Lupus 2010;19:475-85

Future therapies

Rituximab

- **Decrease of ApL**

Ramos-Casals M, Brito-Zeron P, Munoz S, et al, BIOGEAS STUDY Group. A systematic review of the off -label use of biological therapies in systemic autoimmune diseases. *Medicine (Baltimore)* 2008; **87**: 345–64.

Ioanou Y,. B cell depletion therapy for patients with systemic lupus erythematosus results in a significant drop in anticardiolipin antibody titres. Ann Rheum Dis 2008;67:425-6

Future therapies

- **Inhibition of ApL binding through beta(2)-glycoprotein I**

Ostertag MV,. A peptide that mimics the Vth region of beta-2- glycoprotein I reverses antiphospholipid-mediated thrombosis in mice. Lupus, 2006, *15* : 358-365.

Ionnou Y. Binding of antiphospholipid antibodies to discontinuous epitopes on domain I of human beta(2)-glycoprotein I : mutation studies including residues R39 to R43. Arthritis Rheum, 2007, *56* : 280-290

Ioannou Y. In vivo inhibition of antiphospholipid antibody induced pathogenicity utilizing the antigenic target peptide domain I of beta2-glycoprotein I : proof of concept. J Thromb Haemost, 2009, *7*: 833-842

Future therapies

Inhibition of GPIIb/IIIa receptor

aPL promote upregulation of the glycoprotein IIb/IIIa (GPIIb/IIIa) receptor on activated platelets exposing negative phospholipids

GPIIb/IIIa receptor antagonist prevents aPL-induced thrombosis in a well-characterised mouse microcirculation model of thrombotic APS,

GPIIb/IIIa-knockout mice were protected from aPLrelated pathogenesis

Pierangeli SS. Intracellular signaling triggered by antiphospholipid antibodies in platelets and endothelial cells: a pathway to targeted therapies. Thromb Res 2004;114:467-76

Future therapies

- **in vitro evidence that aPL drive activation of both NF-kB and p38MAPK**

Dunoyer-Geindre S, NFkappaB is an essential intermediate in the activation of endothelial cells by anti-beta2-glycoprotein I antibodies. Thromb Haemost 2002;88:851-7

Espinola RG, . E-Selectin mediates pathogenice ffects of antiphospholipid antibodies. J Thromb Haemost 2003;1:843-8

Bohgaki M. The p38 mitogen-activated proteinkinase (MAPK) pathway mediates induction of the tissue factor gene in monocytes stimulated with human monoclonal anti-beta2 glycoprotein I antibodies. Int Immunol 2004;16:1633-41

Vega-Ostertag M. Involvement of p38 MAPK in the up-regulation of tissue factor onendothelial cells by antiphospholipid antibodies. Arthritis Rheum 2005;52:1545-54

Future therapies

Statins

- **In vitro, fluvastatin and to a lesser extent simvastatin inhibit aPL-induced endothelial cell activation**

Meroni PL. Statins prevent endothelial cell activation induced by antiphospholipid (anti-beta2-glycoprotein I) antibodies: effect on the proadhesive and proinflammatory phenotype. Arthritis Rheum 2001;44:2870-8

Ferrara DE, Fluvastatin inhibits up-regulation of tissue factor expression by antiphospholipid antibodies on endothelial cells. J Thromb Haemost 2004;2:1558-63

- **In vivo fluvastatin and pravastatin prevent aPL-mediated thrombosis and inflammation and pregnancy loss.**

Ferrara DE. Inhibition of the thrombogenic and inflammatory properties of antiphospholipid antibodies by fluvastatin in an in vivo animal model. Arthritis Rheum 2003;48:3272-9

Girardi G. Pravastatin prevents miscarriages in antiphospholipid antibody-treated mice. J Reprod Immunol 2009;82:126-31

Redecha P, Pravastatin prevents miscarriages in mice: role of tissue factor in placental and fetal injury. Blood 2009;113:4101-9

Future therapies

Statins

- **Fluvastatin reduces inflammatory proteins in monocytes from patients with the APS and aPL-positive asymptomatic patients.** Pierangeli SS, Lupus 2010;19:475-85

Conclusions

- Better definition of the disease
- Better indications of the treatment
- Stratification of the risk
- Lack of RCT
- Future therapies ?