Antiphospholipid syndrome: treatment controversies

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Antiphospholipid syndrome (APS) is a well-recognized cause of thrombosis and adverse obstetric events such as early and late miscarriage and pre-eclampsia. Therapeutic studies focused on APS have important limitations regarding their design and/or the characteristics of the patients included, often obtaining contradictory conclusions. Treatment of patients with APS and thrombosis should be individualized. Patients with stroke and recurrent events are candidates for indefinite, high-intensity anticoagulation (with a target international normalized ratio (INR) of 3.0–4.0). Those with nonlife-threatening venous thrombotic events could receive anticoagulation at the standard level (target INR 2.0–3.0). Likewise, the optimal management of miscarriage in APS is not well established. While the combination of aspirin–low molecular weight heparin is generally recommended, aspirin alone may have a role in treating women with early pregnancy losses only. In all settings, adequate peripartum thromboprophylaxis should be accomplished. Statins and hydroxychloroquine will probably play an important role in the future management of APS.

It is now 23 years since the original description of the antiphospholipid syndrome (APS), also known as Hughes syndrome [1]. The clinical spectrum of APS has now widened beyond thrombosis at the venous and arterial level and early as well as late miscarriage: small vessel thrombosis, pre-eclampsia, thrombocytopenia, valvular heart lesions, pulmonary hypertension, adrenal insufficiency and a large spectrum of neurological manifestations are being increasingly recognized [2,3]. Little has been published on therapy. Most studies have been focused mainly on the secondary prevention of thrombotic events and pregnancy loss. In this article, the authors will critically review the currently available data on the management of APS.

Thrombosis

Long-term prognosis in APS is most influenced by the risk of thrombosis. Unfortunately, the optimal therapy for the prevention of recurrent events is still a matter of debate [4–7]. The main reason for the controversy is the fact that recruiting homogeneous and comparable groups of patients with APS, both from the clinical and laboratory point of view, is difficult. It is likely that not only one, but several different forms of APS exist, and that future identification of subsets of patients would allow more tailored therapies [8]. A summary of the key issues relating to APS and thrombosis is shown in **Box 1**.

Prophylaxis of recurrent thrombosis: the studies

The risk of recurrent thrombosis in patients with APS is high, having been reported in between 22 and 69% of cases [9–15]. It is also known that the location of the first event is predictive: venous thrombosis usually follows venous thrombosis and recurrences of arterial events are mainly arterial [9,10].

Retrospective studies published between 1992 and 1995 by Rosove and colleagues [9], Derksen and colleagues [16] and Khamashta and colleagues [10] showed that the risk of recurrent thrombosis in patients not having, and especially stopping anticoagulation was unacceptably high. More recent, prospective, long-term follow-up studies of patients with venous thromboembolism have confirmed that the risk of recurrence in patients with APS is significantly higher than in patients without antiphospholipid antibodies (aPL) [12,13]. Regarding the arterial bed, recurrent strokes are frequent in untreated patients with moderate-to-high titers of anticardiolipin antibodies (aCL) and lupus anticoagulant (LA) [7,14,15].

Given the increased chance of recurrent events in patients with APS presenting with thrombosis, indefinite anticoagulation is generally accepted as the standard secondary prophylaxis for thrombosis in this group [17,18].

The studies by Rosove and colleagues [9] and Khamashta and colleagues [10] also demonstrated the superiority of oral anticoagulation over aspirin in preventing recurrent thrombosis and a

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future medicine

Box 1. Antiphospholipid syndrome and thrombosis: key points.

- Antiphospholipid syndrome is a major cause of both arterial and venous thromboembolism, especially in younger patients.
- Prevention of recurrent thrombosis in antiphospholipid syndrome (APS) should be tailored according to the severity of the thrombotic events and the estimated risk of recurrence and bleeding.
- Patients with arterial events, particularly stroke and recurrent events, are candidates for high-intensity anticoagulation (target international normalized ratio [INR] 3.0–4.0). Standard-intensity anticoagulation (target INR 2.0–3.0) could be sufficient for patients presenting with nonlife-threatening venous thromboembolism.
- Antimalarials and statins are good candidates for adjuvant therapies in the near future.

significant dose-related effect of anticoagulants: patients aimed for an international normalized ratio (INR) higher than 3.0 had a lower risk of new events as compared with those aimed for a lower intensity.

Yet, not all of the studies found similar results. Patients with venous thromboembolism and aPL included in general cohorts did not have an increased risk of recurrent events while they were treated with oral anticoagulants at the standard intensity, with INRs between 2.0 and 3.0 [12,13,19–21]. Moreover, Derksen and colleagues reported on the prospective follow-up of eight women with APS and previous stroke [22], all fulfilling Sapporo criteria [23] and seven of them positive for LA, who were treated with low-dose aspirin only. After a median follow-up of 8.9 years, the frequency of recurrent thrombotic events was similar to that expected in aPL-negative patients with stroke (3.5 events per 100 patients/year, 95% confidence interval [CI]: 0.4–12.5). Thus, all of these studies call into question the need for high-intensity – or even any – anticoagulation in patients with APS with both venous and arterial events.

Randomized clinical trials in APS are essential in establishing the best regime for the secondary prevention of thrombosis associated with APS. Crowther and colleagues in Canada [24] and Finazzi and colleagues in Europe [25], published in 2003 and 2005 respectively, similarly designed trials comparing conventional- (i.e., target INR 2.0–3.0) with high-intensity anticoagulation (i.e., target INR 3.0–4.0) in patients with APS and thrombosis. Of note, patients with noncardioembolic arterial events randomized to standard therapy in the European study received low-dose aspirin instead of warfarin [25]. Results from these trials were also similar; indeed, Finazzi and colleagues included in their paper a combined analysis of both studies, showing a borderline significantly increased frequency of recurrent events among patients in the high-intensity group (odds ratio [OR]:2.49, 95% CI: 0.93–6.67, p = 0.07). On the other hand, major bleeding was more frequent, albeit nonsignificantly, among patients receiving conventional-intensity anticoagulation, while minor bleeding was statistically more likely in patients randomized to an INR of 3.0–4.0.

Additional data on the secondary prevention of thrombosis in patients with APS and stroke came in 2004 from the AntiPhospholipid Antibodies Stroke Study (APASS) [26]. This was a subgroup analysis of a previously published randomized clinical trial, the Warfarin versus Aspirin Recurrent Stroke Study (WARSS), which compared low-intensity anticoagulation with aspirin for the secondary prevention of stroke [27]. The APASS aimed to define the role of aPL in predicting recurrent strokes, as well as in the response to therapy. Blood samples were stored from 1770 patients (80% of WARSS participants) and aCL (including immunoglobulin (Ig)G, IgM and IgA isotypes) and LA were determined once.

After 2 years of follow-up, aPL-positive and negative patients had similar frequencies of primary end points: death from any cause, 3.6 versus 3.3%; stroke 11.3 verus 10.7%; transient ischemic attack 4.0 versus 6.8% and so forth. The response to warfarin or aspirin was uniformly similar among patients with and without aPL.

The two main conclusions of the APASS were assertive: testing for LA or aCL did not confer important knowledge for the prognosis or treatment of patients with recently diagnosed ischemic stroke; and warfarin was not associated with fewer thrombotic events than aspirin among patients with aPL and stroke [26].

Currently, several experts in the field encourage the use of a standard 2.0–3.0 INR target for the secondary prevention of thrombosis, whether

venous or arterial, in all patients with APS [28,29]. Such a recommendation is based on three facts: the limitations of the retrospective studies; the results of clinical trials (including APASS) and the increased risk of bleeding among patients treated with high-intensity warfarin.

Thus, we have different studies, different designs and different results. At this point the key questions are: why are the conclusions not homogeneous? What therapeutic recommendations can be given?

Prophylaxis of recurrent thrombosis: critical review. 'All that glitters is not gold'

The studies by Rosove and colleagues [9] and Khamashta and colleagues [10] have the obvious limitation of being retrospective. This type of design has important intrinsic drawbacks in studies focused on therapy, including the non-randomized assignment of treatment, the potential for an important amount of missing information and patient recall bias. In addition, both studies classified patients according to aimed rather than actually achieved INR and the studies did not analyze arterial and venous events separately.

On the other hand, these two studies had the strength of including populations who, probably or definitely, had APS according to currently accepted criteria [23]. In addition, a sizeable number of patients with severe APS, as defined by previous recurrent events and APS secondary to systemic lupus erythematosus (SLE) were included in the analyses. The high rates of recurrent thrombosis among untreated patients confirms this aspect. Finally, results of both studies were consistent in showing fewer recurrent events among patients treated with warfarin than in those treated with aspirin, less thrombosis in patients with high-intensity anticoagulation and a low-to-moderate risk of severe bleeding complications. In addition, patients with INR documented at the time of thrombosis were almost always below 3.0, although frequently above 2.0, which supports the idea of insufficient protection of standard-intensity anticoagulation.

The series by Derksen and colleagues was the first group of patients with definite APS and stroke who were prospectively followed-up for a prolonged period of time [22] . However, the small sample size (number of participants = 8), with the resulting wide CI for the risk of recurrent thrombosis (0.4–12.5 per 100 patients/year), makes this observation almost anecdotal.

The studies by Finazzi and colleagues [25] and Crowther and colleagues [24] had the optimal design of randomized clinical trials, including intention-to-treat analysis. Accordingly, their results should be considered definitive. Unfortunately, this is not the case owing to important limitations. First, patients with venous thrombosis accounted for 68–78% of the patients recruited, in fact, patients with recent strokes were excluded from the Canadian trial [24]. Moreover, exclusion also affected, in both studies, patients with thrombosis under anticoagulant treatment. These facts confer upon the APS populations of both trials the label of 'mild'. As a consequence, the event rates were much lower than expected. The study by Finazzi and colleagues was terminated early, well before achieving the estimated sample size, due to difficulties in enrolling patients [25]. All of the above resulted in a significant increase of β error.

However, the most relevant drawback of both trials was the poor achievement of therapeutic goals in the groups randomized to high-intensity anticoagulation. In the Canadian study, this group was below the 'therapeutic range' 43% of the time [24]. Finazzi and colleagues did not report on this issue [25], but mean INR in the high-intensity group was 3.2, suggesting a significant number of measurements below the threshold of 3.0. Crowther and colleagues reported the INR at the time of all thrombotic recurrences [24] and, not surprisingly, most thrombotic episodes in both groups (6 out of 8) took place when INRs were lower than 3.0. In this setting of not achieving the intended high-intensity anticoagulation in one of the study arms, the intention-to-treat analysis can be misleading. If patients had been analyzed according to actual INR, results would have been likely to show a reduction of events among those kept at INRs higher than 3.0.

The APASS study had the two main advantages of being a prospective design and having a large sample size [26]. However, this study was actually a subgroup analysis of a trial that was designed to compare the efficacy of antiaggregants and oral anticoagulants to prevent recurrences in the general population with stroke. Unfortunately, criteria for classifying a patient as aPL positive were inaccurate: single aPL determination, including aCL of the IgA isotype, admitting low-titers of aCL only and LA tests not performed according to international recommendations. As an expected result, as many as 41% of individuals in an unselected population

of patients with stroke – averaging 63 years of age – were aPL positive. Only 6.7% of patients were positive for both aCL and LA, and just 0.2% had aCL at high titers. It is therefore clear that most patients included in APASS did not have APS. Owing to these limitations, the results of APASS were immediately criticized following their publication [30–32]. In fact, the authors themselves acknowledged that their results could not be generalized to younger patients or those with other manifestations of APS [7,26].

Issue of bleeding

Bleeding is the main adverse effect of oral anticoagulants. The rate of life-threatening bleeding in subjects taking warfarin is variable and dependent upon a number of factors. The average yearly rate of bleeding is 0.25% [33]. This rises rapidly when the INR exceeds 4.0. It is therefore possible that serious bleeding complications occur in APS [34], especially if treated with high-intensity anticoagulation.

A retrospective study of 66 patients with definite APS according to Sapporo criteria and treated with oral anticoagulation to a target INR of 3.5 (range of 3.0 to 4.0) atempted to define the risk of bleeding in this group [35]. Despite frequent lower-than-desired INRs, the annual risk of major hemorrhage was clearly higher than the 'expected' 0.25% (six events per 100 patients, 95% CI: 1.6–15.0). On the other hand, only one case of cerebral bleeding was seen (in a woman who withdrew anticoagulation control during several months) and there were no fatal events. Moreover, recurrent thromboses were of more concern than bleeding, with six thrombotic events (9.1 per 100 patient/years, 95% CI: 3.3–19.6) that occurred with INRs between 2.1 and 2.6 – the standard therapeutic range.

Similar to these results, serious bleeding has been infrequent in most series of patients with APS [9,10,24,25], whatever target INR was chosen. The crucial point is that APS involves mostly young patients with no other additional risk factors for bleeding. Age has been demonstrated to be a risk factor for severe hemorrhagic episodes in patients placed on long-term anti-coagulation [33] and Piette and Cacoub have recently reported similar experience in their elderly patients with APS [36]. The presence of leukoaraiosis has been regarded as a major risk factor for cerebral hemorrhage in patients taking oral anticoagulants [37]. All these facts must be borne in mind when targeting INR in a individual patient with APS.

Recommendations

The authors advocate prolonged oral anticoagulation as the standard secondary prophylaxis of thrombosis in patients with APS. The intensity of anticoagulation should be individually targeted according to the risk of thrombosis, thrombosis-related damage and bleeding: patients with arterial events (especially stroke and recurrent events) and life-threatening pulmonary embolism should be maintained at INRs higher than 3.0; the standard 2.0–3.0 target INR could be adequate for patients with nonsevere venous thromboembolism. Special caution must be paid to patients with leukoaraiosis and/or previous serious bleeding. Other risk factors for thrombosis, such as smoking, hypertension, hyperlipidemia, diabetes and estrogen use must be strictly corrected.

Pregnancy

APS often becomes apparent during pregnancy, usually in the form of maternal thrombosis, hypertensive disorders and/or miscarriage [2]. Placental thromboses are considered the substratum for the obstetric manifestations of APS [38]; however, they do not explain the whole picture, including, for instance, early pregnancy losses. Recently, complement activation by aPL has been included among the putative pathogenetic mechanisms not only for miscarriage, but also for thrombosis itself [39,40].

In this complex setting, clinical management is often challenging. Little prospective data are available and they are often contradictory. In addition, antithrombotic drugs have an important potential for fetal and maternal toxicity. Therefore, specific therapeutic recommendations differ from center to center. A summary of the key issues relating to APS and pregnancy is shown in **Box 2**.

General measures

All pregnancies in women with APS must be considered high risk and managed, ideally, by a combined team of physicians–obstetricians. All women should be seen more frequently as pregnancy advances. Blood pressure and the presence of protein in the urine must be closely monitored at each visit. Uterine artery Doppler blood flow analyses at 20 and 24 weeks may predict the development of pre-eclampsia and placental insufficiency. Due to the high frequency of prematurity among babies born to mothers with APS, fully equipped neonatal units should be

Box 2. Antiphospholipid syndrome in pregnancy: key points.

- Antiphospholipid syndrome is a major cause of pregnancy complications, not only miscarriage (early and late) but also prematurity, low weight at birth, pre-eclampsia and maternal thromboembolism.
- Aspirin and heparin are the main drugs used to treat miscarriage in antiphospholipid syndrome. Combined treatment is recommended in women with late fetal losses. Treatment of women with recurrent early miscarriage is more open to question and may include low-dose aspirin alone.
- Correct peripartum thromboprophylaxis must be accomplished in all women with antiphospholipid antibodies.
- Doppler studies of the uterine arteries may help predict pre-eclampsia and placental insufficiency.
- Women treated with heparin should receive calcium plus vitamin D during pregnancy and early puerperium.

available in the hospital where delivery is taking place. Close postpartum maternal surveillance is mandatory [41].

Pharmacological management of pregnancy losses in APS

Prednisone, usually in combination with aspirin, was initially considered the drug of choice for the obstetric manifestations of APS. However, case series [42] and two small, randomized clinical trials [43,44] showed that the actual effect of corticosteroids on pregnant women with APS represented more harm than good, with no superiority over regimes containing aspirin with or without heparin and an increased rate of complications such as prematurity and hypertension.

Currently, aspirin and heparin are the recommended drugs for the treatment of miscarriage in women with APS. However, the precise combination of both drugs in different clinical scenarios is still debated.

Two randomized studies have investigated this question [45,46]. It must be noted that an additional study by Kutteh [47], frequently referred to as a randomized clinical trial, was a therapeutic study performed in a 'special' population (i.e., women with LA were excluded), in which treatment was assigned on a consecutive basis, a fact that represents a major bias.

Unfortunately, the results of the two randomized clinical trials are opposing. Rai and colleagues found the combination low-dose aspirin plus calcium, heparin 5000 IU/12 h better than aspirin alone in achieving a live baby (71 versus 42% successful pregnancies, respectively) [45]. By contrast, the study by Farquharson and colleagues obtained similar results with low-dose aspirin alone or in combination with dalteparin 5000 IU/day (72 vs 78% live births, respectively) [46].

In general, practitioners are more willing to believe the significance of the study when probability <0.05. Unless studies are designed specifically to find equivalence, studies with the final result of 'no difference' may be subject to β error; due to the low number of adverse events, this may have been the case in Farquharson and colleagues study [46]. Therefore, the conclusions of Rai and colleagues are usually accepted by most groups, suggesting that aspirin plus heparin should be the treatment of choice in patients with obstetric APS [17,48,49].

However, the study by Rai and colleagues has a major limitation with regard to the population included in the trial [45]. A total of 63% of the women had a history of early miscarriage only, versus just 4.4% with fetal losses only. Moreover, 83% were positive for LA alone versus 9% positive for both aCL plus LA. This is a very unusual distribution of aPL. In large series of patients with definite APS, aCL are present in over 80% of patients, while LA alone is below 15% [3]. These features raised concerns regarding the use of an over-sensitive test for LA, which could have labeled women with otherwise idiopathic recurrent early miscarriage as having APS. This fact could explain the atypical behavior of the aspirin-only arm, in open contrast with the results of a number of published series showing that a subset of women with APS and poor obstetric history do well with low-dose aspirin in monotherapy, with a 79–100% success rate [50–53]. Indeed, a multivariant analysis of 77 pregnancies with APS from Barcelona has found preconceptional aspirin to be a significant predictor of a successful outcome [54].

Therefore, although routine use of heparin plus aspirin is generally advocated for pregnant women with APS and adverse obstetric history, this approach is not supported by unquestionable data. While combination treatment could be the first option for women with previous fetal losses, which are more typical of APS and with a greater impact on the mother, aspirin in monotherapy still has a role to play in women with recurrent early miscarriages. It is important that every option, with its pros and cons, be discussed in detail with women considering pregnancy in order to achieve a joint decision. In addition, aspirin should be part of any treatment of pregnant women with APS and should be best started before conception [55].

Thromboprophylaxis in APS during pregnancy

Although this group has been systematically excluded from clinical trials, good clinical sense indicates that all women with APS and previous thrombosis should maintain antithrombotic treatment throughout their whole pregnancy and, more importantly, during the postpartum period [55,56]. The same principle applies to those women with aPL whose first thrombotic event occurs during pregnancy. Therefore, combined treatment with low-dose aspirin and full antithrombotic doses of low molecular weight heparin (LMWH) should be given to these patients. Moreover, LMWH is also mandatory in all women with purely obstetric APS during the postpartum period – it is also recommended in asymptomatic women with aPL, especially in those with SLE [55,56].

Thromboprophylaxis may represent a risk during labor and, particularly, with the use of epidural anesthesia. Stopping heparin within 12 h prior to and 12 h after any interventional procedure is generally considered safe. Many anesthesiologists also require a minimum of 3–7 days without aspirin to perform a spinal tap [57]. Even under these circumstances, some still feel more comfortable using general anesthesia in this group of patients.

Despite 'optimal' thromboprophylaxis, recurrent thrombotic events do occur in some patients with APS. Pregnant women are not an exception. In fact, the protection against arterial thrombosis given by heparin may not be enough for some patients. Women with previous arterial events, particularly stroke, must be considered as high risk, both in terms of recurrent thrombosis and pregnancy complications [58]. Warfarin may be needed in cases where recurrent thrombosis has occurred despite therapeutic doses of heparin [59]. However, it must be strictly avoided during organogenesis (6–12th weeks gestation) due to the high risk for fetal malformations. INR must be closely controlled and kept between 2.0–2.5 in order to minimize the probabilities of serious fetal bleeding.

Finally, all women receiving any form of heparin during pregnancy should be given prophylaxis of osteoporosis with daily calcium (1000 mg) plus vitamin D (800 IU/day) [60,61].

Future perspective

The relationship between complement activation and clinical expression of APS is currently the subject of major research in this field, with possible therapeutic implications. In fact, data from Girardi and colleagues in a mouse model demonstrated that low-dose heparin, without anti-factor X activity but retaining the capacity of complement inactivation, prevented miscarriage, while full antithrombotic doses of fondaparinux and hirudin, neither of which have any effect on complement activation, were ineffective [39]. Although data in humans are still lacking, this line of research may help us to understand the complex and wide range of APS manifestations and design more targeted therapies. It is possible that women with recurrent early miscarriage, fetal losses or thrombosis belong to different pathogenetic subgroups of APS, thus, treatment may differ for these different manifestations of APS.

The role of drugs other than antiaggregants, antithrombotics and anticoagulants in APS is just emerging. One firm candidate for the near future is the well-known hydroxychloroquine. The antithrombotic and lipid-lowering properties of this drug have been suggested in SLE patients [62,63]. Moreover, increased survival of lupus patients receiving hydroxychloroquine has been shown [64]. Protection against cardiovascular events seems to be the main mechanism for this long-term beneficial effect. Accordingly, hydroxychloroquine, a drug with an excellent safety profile, could be used as an adjuvant therapy in patients with APS at high risk of thrombosis and/or bleeding.

Finally, the antithrombotic properties of statins – beyond their cholesterol-lowering effects – have been shown in animal models of APS and herald its widespread use in APS patients, irrespective of lipid levels [65].

It should be borne in mind that APS is not a minor condition, but rather a syndrome with a potentially grim prognosis, in fact, it is a major adverse predictor in patients with SLE [66]. Therefore, every effort must be made to its early detection and treatment, taking into account the different subgroups. In addition, the correction of vascular risk factors is of primary importance in the management of patients with APS.

Executive summary

Antiphospholipid syndrome & thrombosis

- Antiphospholipid syndrome (APS) is the cause of recurrent thrombosis at the venous, arterial and small vessel level.
- Long-term anticoagulation treatment is generally accepted as first-line therapy.
- High-intensity anticoagulation (i.e., a target international normalized ratio of 3.0–4.0) was suggested by retrospective studies as the treatment of choice for patients with APS and thrombosis.
- Recent, prospective data (case series, randomized clinical trials and subgroup analysis) support the use of standard therapy (i.e., target international normalized ratio (INR) 2.0–3.0 or low-dose aspirin) for this group. However, important limitations regarding the groups of patients included in the studies and accomplishment of therapeutic objectives preclude generalization of the conclusions of the studies.
- In summary, treatment of patients with APS and thrombosis should be individualized. Patients with stroke and recurrent events are candidates for indefinite high-intensity anticoagulation (target INR 3.0–4.0). Those with nonlife-threatening venous thromboembolism could receive anticoagulation at the standard level (target INR 2.0–3.0).

Obstetric antiphospholipid syndrome

- Recurrent miscarriage – most typically late fetal death – is the main obstetric manifestation of APS. In addition, other complications, such as severe pre-eclampsia, prematurity and low weight at birth, are frequently seen.
- The mother is also at an increased risk for thromboembolic complications during pregnancy. Those with a past history of stroke, especially if recent, are particularly prone to recurrent thrombosis.
- The optimal management of miscarriage in APS is not well established. Randomized controlled trials are few, small and contradictory in their results. While the combination of aspirin–low molecular weight heparin is generally recommended, aspirin alone may have a role in women with early pregnancy losses only.
- In all settings, adequate peripartum thromboprophylaxis should be accomplished. In women receiving heparin throughout the whole pregnancy, calcium plus vitamin D should be administered to prevent the development of osteoporosis.
- General obstetric care includes Doppler surveillance of uterine and umbilical flow in order to predict the occurrence of pre-eclampsia and placental insufficiency.

Future perspective

- Future therapeutic approaches of APS must be based on specific clinical profiles of the different subgroups of this syndrome, which should enable tthe prediction of thrombosis, bleeding and pregnancy complications. Among putative new drugs for APS, hydroxychloroquine is a firm candidate due to its excellent safety profile and antithrombotic properties, which have already shown important clinical consequences in patients with systemic lupus erythematosus. Statins have also shown antithrombotic effects in animal models of APS and are thus other potential therapeutic agents for the near future.

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