Autoimmunity Reviews xxx (2011) xxx–xxx

Contents lists available at SciVerse ScienceDirect

Autoimmunity Reviews

journal homepage: www.elsevier.com/locate/autrev

Review

Thromboprophylaxis in carriers of antiphospholipid antibodies (APL) without previous thrombosis: "Pros" and "Cons"

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ARTICLE INFO

Available online xxxx

Keywords:
Anti-phospholipid antibodies
Carriers
Thromboprophylaxis
Risk factors

ABSTRACT

The presence of anti-phospholipid (aPL) is necessary but not sufficient to induce a thrombotic event. The "second hit" hypothesis suggested that an additional trigger may be needed to develop a vascular event in aPL carriers. In this article, pro and con of primary thromboprophylaxis in aPL carriers is deeply discussed, concluding that univocal data are not available, due to conflicting results of available clinical trials. However, in clinical practice the primary thromboprophylaxis is not indicated in all unselected asymptomatic aPL carriers, and the best strategy begin with the assessment of the peculiar risk profile of the subject. Thus, it is mandatory to eliminate modifiable prothrombotic risk factors (i.e. smoking, oral contraceptive), to treat the irreversible risk factors (i.e. hypertension, diabetes) and to introduce an aggressive prophylaxis with subcutaneous LMWH in high-risk situations (i.e. surgical procedures with prolonged immobilization). A different evaluation should be addressed to aPL carriers with a concomitant autoimmune disease that are considered as an additional pro-thrombotic risk factor. Similarly, concomitant positivity for more than one antiphospholipid test confer a stronger risk of developing the thrombotic manifestations. Specific trials with larger cohorts of patients are needed to better clarify this issue.

Contents

1. Introduction

Since its discovery, it has been clear that Anti-phospholipid Syndrome (APS) is characterized by thrombosis; however, anti-phospholipid (aPL) are necessary but not sufficient to induce a thrombotic event. The "second hit" hypothesis has been suggested to explain this apparent paradox: an additional trigger may be needed to develop a vascular event in aPL carriers and up to a third of patients have other thrombotic risk factors at the time of the event. It has been demonstrated that aPL positive patients have a whole risk of thrombosis ranging between 0 and 3.8% [1]. In certain circumstances, primary thromboprophylaxis may be needed also in aPL carriers without any previous thrombotic event. Difference in incidence of thrombotic events between patients and asymptomatic carriers with aPL depends at least partially on the proportion of coincident non-aPL thrombotic risk factors [2]. The elimination of reversible thrombosis risk factors (such as smoking or use of oral contraceptives) and the use of

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1568-9972/$ – see front matter © 2011 Published by Elsevier B.V.
doi:10.1016/j.autrev.2011.10.014

prophylaxis during high-risk periods (such as surgical procedures) are crucial.

A consensus document has been elaborated at the 13th International Congress on Antiphospholipid Antibodies, held in Galveston in April 2010, on the primary and secondary thromboprophylaxis in individuals with aPL, after a systematic and critical review of the literature [3]. When considering thromboprophylaxis in aPL positive subjects variables to take into account are aPL profile (type, levels, persistence), other associated risk factors and underlying autoimmune disease. Thus, the presence of Lupus Anticoagulant (LA), particularly if combined with anti-cardiolipin (aCL) and anti-β2-GPI (a-β2GPI) (the so called "triple positivity"), and the presence of isolated, persistently positive aCL at medium–high levels is considered a high-risk serological aPL profile.

Systemic autoimmune diseases such as Systemic Lupus Eryhtematosus (SLE) are now considered independent cardiovascular risk factor and they have to be considered when evaluating primary thromboprophylaxis.

When approaching aPL positive patients, a balance between individual risk of thrombosis and benefits and risks induced by antithrombotic therapies is mandatory.

2. Thromboprophylaxis in aPL carriers without previous thrombosis: "pro" view

APS is characterized by vascular thrombosis and/or fetal morbidity, in the presence of aPL. aPL are a heterogeneous group of antibodies directed against phospholipid-binding proteins, currently detectable by anti-cardiolipin (anti-CL), anti-β_2 glycoprotein I (anti-β_2GPI) and lupus anticoagulanlt (LA) assays. aPL are not only diagnostic markers of APS, but are also considered to exert a pathogenetic role. Experimental data suggest aPL are necessary but not sufficient to trigger a thrombotic event: a "second hit" would be required to induce a vascular manifestation. Among the three assays, LA has been shown to best correlate with the occurrence of both arterial and venous thromboses, while anti-β_2GPI and anti-CL are apparently less strongly associated. It has been demonstrated that the concomitant positivity for more than one test, particularly LA positivity, the IgG isotype and medium-high titers confer a stronger risk of developing the clinical manifestations of the syndrome. There is extensive evidence that patients with APS, being at high-risk of recurrence of thrombotic events, benefit from long-term anticoagulation. Much more debated is the management of asymptomatic patients with aPL positivity confirmed 12 weeks apart, without a clinical history of venous or arterial thrombosis. To date, few clinical trials have addressed the role of primary prophylaxis in asymptomatic aPL subjects, and not univocal results have been reported [2,4–6]. Moreover, the limited number of patients enrolled and the low incidence of outcome events make even more difficult to draw definitive conclusions. In fact, aPL carriers present a rather low rate of vascular manifestations: a 3-year prospective observational cohort-study on 178 asymptomatic aPL carriers without underlying autoimmune diseases reported no thrombotic events in those not receiving primary prophylaxis [2]. The only randomized, double-blind, placebo-controlled trial (the APLASA study) investigating the efficacy of low-dose aspirin (LDA) as primary prevention of thrombotic events suggested aPL-positive individuals do not benefit from primary thrombosis prophylaxis: among 98 asymptomatic aPL carriers, LDA was not more effective than placebo for primary prophylaxis of thrombotic events. aPL-positive individuals were found to develop a first vascular event when additional procoagulant risk factors were present [4]. Concordingly, retrospective cohort studies reported that 46–76% of APS patients have other thrombotic risk factors at the time of vascular events. Among these, conventional cardiovascular risk factors as hypertension, diabetes, hypercholesterolemia, smoking and obesity play a pivotal role [5,2,7–10]. In particular, an Italian collaborative study group prospectively identified hypertension and LA as independent risk factors for a first thrombotic event among asymptomatic aPL carriers [11]. Inherited cause of thrombophilia must also be taken into account: activated protein C resistance, protein C, protein S and factor II deficiency, homozygous mutation in methylenetetrahydrofolate reductase gene leading to plasmatic hyperhomocysteinemia. Puerperium, trauma, infection, surgery and prolonged immobilization should also be regarded as transient high-risk conditions for venous thrombosis. There is a growing body of evidence showing that a proper management of modifiable prothrombotic risk factors may abate the actual risk of a major vascular event. Therefore, it is strongly advisable to promptly correct modifiable risk factors, while an aggressive thromboprophylasxis with subcutaneous low molecular weight heparin (LMWH) should be administered to cover high-risk situations.

However, the scenario could be different when considering solely aPL carriers with an underlying autoimmune conditions: a 1998 study on anti-CL positive patients with SLE reported an annual event rate of 3.8% [12]. Wahl and colleagues used a Markov decision analysis model to evaluate the prophylactic role of LDA in aPL-positive SLE patients, suggesting that it was effective in reducing the number of thrombotic events. In particular, LDA induced a benefit that outweighed the treatment-associated risk of major bleeding [13]. Hence, there is emerging evidence in support of LDA role in patients with underlying autoimmune diseases. Systemic autoimmune conditions as SLE and Rheumatoid Arthritis are now regarded as independent cardiovascular risk factor, with systemic inflammation strongly contributing to the accelerated atherosclerosis and overall cardiovascular burden. In particular, thrombosis accounts for more than 1/3 of deaths related to SLE, aPL status being the strongest predictor of thrombotic event.

Another group of patients at higher thrombosis risk that may benefit from LDA as primary prophylaxis is represented by aPL-positive women with pregnancy morbidity not fulfilling the Sydney Criteria for a formal diagnosis of APS. A retrospective study in aPL-positive women who only experienced a fetal loss showed that LDA significantly reduced the incidence of vascular thrombosis after pregnancy: the event incidence was 10% in those receiving LDA and 59% in the untreated group [14]. In addition, an experts survey strongly suggests therapy with LDA in women with a strong aPL positivity even during the first pregnancy owing to the high-risk of fetal loss.

Alternative therapeutic strategies have been recently proposed in the management of aPL carriers: some studies have pointed out that hydroxychloroquine (HCQ) may be useful to prevent the development of thrombosis among lupus patients [15–17]. Certainly a better knowledge of APS pathogenesis might help identifying new therapeutic targets. Nowadays there is little evidence of the benefits of novel treatment options, as rituximab or alternative antiplatelet drugs.

In conclusion, aPL carriers should be risk-stratified according to the aPL status, the presence of cardiovascular risk factors, either inherited or acquired. Modifiable risk factors should be promptly corrected; estrogen-containing oral contraceptives should be avoided, LMWH should be given in high-risk situations for venous thrombosis. The best treatment strategy should be tailored according to the peculiar risk profile: primary thromboprophylaxis is not indicated in all unselected asymptomatic aPL carriers. On the other hand, the coexistence of an underlying systemic autoimmune disease, the concomitance of non-modifiable procoagulant risk factors, a high-risk aPL profile, a history of foetal loss should be counted as key-elements in favor of primary thromboprophylaxis. It is important to avoid concomitant prescription of LDA and anti-inflammatory drugs, as the latter can lead to actual resistance to aspirin.

Research is currently aiming at identifying new aPL subsets, with different pathogenetic potential: this would be helpful to further categorize patients.

3. Thromboprophylaxis in aPL carriers without previous thrombosis: "con" view

Asymptomatic patients carrying only the laboratory criteria for the APS [18] are at low risk of vascular complications and whether

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they need a primary prophylaxis with low-dose aspirin is a matter of debate. To tackle this issue, the expected benefit/risk of aspirin in the prevention of thrombosis and the results of clinical studies in this setting should be considered.

3.1. Lessons from primary prevention trials with aspirin outside APS

The use of aspirin in six "primary" prevention trials enrolling approximately 58,000 persons who were at variable cardiovascular risk has been reviewed [19]. If one compares the absolute benefits of aspirin prophylaxis in these trials, it becomes apparent that the level of cardiovascular risk in the control population (i.e., those receiving placebo) is a major determinant of the absolute benefit of antiplatelet therapy. As a result, the first step in deciding whether to consider aspirin for primary prophylaxis is an assessment of the annual risk for that individual of developing a cardiovascular event. In other words, the balance between preventing vascular occlusion and causing excess bleeding with aspirin depends critically on the absolute thrombotic risk vs hemorrhagic risk of the patient. In individuals who are at low risk for vascular occlusion (e.g., less than 1% per year), a very small absolute benefit is offset by exposure of a large number of healthy subjects to undue bleeding complications. In contrast, in patients who are at high risk of cardiovascular or cerebrovascular complications (e.g., >3% per year), the substantial absolute benefit of aspirin prophylaxis clearly outweighs the risk.

3.2. Estimating the risk of thrombosis in asymptomatic carriers of antiphospholipid antibodies (aPL)

Based on a limited number of studies [reviewed in 20], unselected asymptomatic aPL carriers have a 0–2.8% annual thrombosis risk. In a 3-year prospective observational cohort study of 178 asymptomatic, persistently aPL-positive individuals without systemic autoimmune diseases, Giron-Gonzalez et al. reported no thromboses in participants receiving no prophylaxis (except during high-risk periods such as surgeries) [2]. The Italian Registry of APS carried out a multicenter, prospective cohort investigation of 360 unselected patients, mostly with LA (>90%), prospectively observed for a median of 3.9 years (range 0.5 to 5) [10]. Overt LES or LES-like syndrome was diagnosed in 135 patients (37%). Thirty-four patients developed a thrombotic complication, with a total incidence of 2.5% patient-years. The incidence of thrombosis in 243 asymptomatic patients (67%) was 0.95% per year. In patients with systemic autoimmune diseases, the incidence of thrombosis was found to be slightly higher. A recent prospective study of 258 aPL carriers (69% with an associated systemic autoimmune diseases) followed for a mean of 35 months (range 1–48) reported a first thrombotic event in 14 subjects with an annual incidence rate of 1.86%. In this study, thromboembolic events were significantly reduced only when antithrombotic prophylaxis was administered in high-risk situations and not continuously [11].

3.3. The role of associated thrombotic risk factors

The thrombosis risk in the general population rises with the increasing number of thrombosis risk factors and age. Well-established thrombosis risk factors such as hypertension or smoking can coexist in aPL-positive individuals at the time of an event and may even be responsible for triggering acute thrombosis [9,21]. The results obtained in aspirin trials that have recruited high-risk men and women demonstrate that proper management of modifiable risk factors by current multifactorial strategies can reduce the actual risk of experiencing a major vascular event to a level at which the additional benefit of aspirin does not clearly outweigh the risk of major bleeding complications [19].

3.4. Clinical studies of aspirin in asymptomatic patients with aPL

Primary thrombosis prophylaxis strategies in asymptomatic aPL-positive individuals are poorly studied [20]. The Antiphospholipid Antibody Acetylsalicylic Acid (APLASA) study was a multicenter, randomized, double-blind, placebo-controlled clinical trial in which asymptomatic, persistently aPL-positive individuals were randomized to receive a daily dose of 81 mg of aspirin or placebo [4]. In this study, 98 individuals were randomized to receive aspirin (n = 48) or placebo (n = 50) (mean ± SD follow up period 2.30 ± 0.95 years). The thrombosis incidence rate was 2.75% patient-years for aspirin-treated subjects and 0% patient-years for the placebo-treated subjects (hazard ratio 1.04, 95% CI 0.69–1.56) ($P = 0.83$). In a parallel observational study, the thrombosis incidence rates were 2.70% patient-years for aspirin-treated subjects and 0% patient-years for those not treated with aspirin. All but 1 patient with thrombosis in either study had concomitant thrombosis risk factors and/or systemic autoimmune disease at the time of thrombosis. These results suggest that asymptomatic, persistently aPL-positive individuals do not benefit from low-dose aspirin for primary thrombosis prophylaxis, have a low overall annual incidence rate of acute thrombosis, and develop vascular events when additional thrombosis risk factors are present. There are some limitations of this study, including the small sample size and insufficient power resulting from the rarity of aPL and the difficulty in identifying asymptomatic aPL-positive patients. Despite these drawbacks, the APLASA study is the first randomized clinical trial of asymptomatic, persistently aPL-positive individuals and its results are consistent with the bulk of epidemiological and clinical data reviewed above.

Finally aspirin is *not* indicated in *all* asymptomatic patients with confirmed aPL positivity because: a) the estimated prevalence of thrombosis in unselected cases is about 1% patient-years (range 0–2.8); b) this level of thrombotic risk is equivalent to that of major bleeding associated with the use of aspirin and therefore the expected benefit does not outweigh the risk; c) these expectations have been confirmed by at least one randomized clinical trial, although with methodological limits [9]. The management of modifiable thrombotic risk factors can be an alternative and safer strategy, considering that many vascular events occur in the presence of concomitant non-aPL triggering conditions. Whether primary prophylaxis with aspirin may be useful for some subsets of aPL patients at particularly high thrombotic risk, such as those with overt SLE or with special patterns of antibodies [22], remains to be established in appropriate clinical studies.

4. Conclusion

In conclusion, the topic is quite controversial; in fact only few clinical trials have evaluated the role of primary prophylaxis in this specific group of subjects. The contrasting results observed were probably determined by the different study design, the small number of cohort analyzed and the low incidence of events [2,4–6]. In particular, the APLASA study, the first multicenter double-blind placebo-controlled RCT in the area, compared a dose of 81 mg of aspirin daily with placebo in asymptomatic aPL-positive individuals concluding that aspirin was not beneficial in preventing thrombosis. This trial showed some limitations, including a low incidence of events in both groups, resulting perhaps by the exclusion of higher-risk patients (those with obstetric APS) and inclusion of lower risk patients (those with IgA aCL). Notably, all but one of the thrombotic events occurred in patients with additional thrombotic risk factors, or autoimmune diseases. Another important limitation of APLASA study was the small simple size included, due to recruitment difficulties, leaving the study underpowered [4]. Prospective RCTs specifically designed to evaluate the use of aspirin and other non-aspirin antithrombotic therapies are required, considering larger cohorts, including also patients with high prothrombotic risk. In a commentary following the

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APLASA it has been estimated that 30,000 patients may be required for each treatment arm to achieve conclusive results. In clinical practice it is mandatory to eliminate modifiable prothrombotic risk factors, such as smoking or use of oral contraceptive. The irreversible risk factors, such as hypertension and diabetes, should be treated with specific and appropriate therapies. An aggressive prophylaxis with subcutaneous LMWH should be administered to cover high-risk situations, such as surgical procedures with prolonged immobilization. A different evaluation should be addressed to aPL carriers affected by a concomitant autoimmune diseases, such as SLE, that are considered as an additional pro-thrombotic risk factor. Data today available suggested that LDA in aPL-positive SLE patients could be effective to prevent thrombotic events, without significant increase of bleeding risk [13]. Moreover, in aPL-positive women with pregnancy morbidity, LDA administration is suggested during the pregnancy, to reduce the risk of fetal loss and after pregnancy to reduce the incidence of vascular thrombosis after pregnancy [14]. Similarly, concomitant positivity for more than one test, particularly LA positivity, the IgG isotype and medium-high titers confer a stronger risk of developing the clinical manifestations of the syndrome.

Recently the administration of HCQ is proposed as primary prophylactic treatment, due to its anti-aggregant properties, particularly in patients with SLE [15–17]. We can conclude that the primary thromboprophylaxis is not indicated in all unselected asymptomatic aPL carriers, and the best strategy in the treatment of aPL carriers begin with the assessment of the peculiar risk profile of the single subject.

Take-home messages

- aPL are able to exert a pathogenetic role in APS.
- An additional trigger may be needed to develop a vascular event in aPL carriers (second hit hypothesis).
- Few clinical trials, with no univocal results addressed the role of primary prophylaxis in aPL carriers.
- aPL carriers should be risk-stratified according to aPL status and presence of cardiovascular risk factors (inherited or acquired).
- It is mandatory to eliminate modifiable prothrombotic risk factors, and treat the irreversible risk factors with an aggressive prophylaxis (subcutaneous LMWH) in high-risk situations.
- A concomitant autoimmune diseases, such as SLE, in aPL carriers should be considered as an additional pro-thrombotic risk factor.

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