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Review

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

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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.

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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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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