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Primary thromboprophylaxis with low-dose aspirin and antiphospholipid antibodies: Pro's and Con's

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ABSTRACT

Whether primary prophylaxis should be prescribed in individuals with antiphospholipid antibodies (aPL) remains controversial due to the lack of relevant evidence-based data. Indeed, it is unclear whether the benefit of LDA outweighs the risk of major bleeding associated LDA in a low-risk population. On the contrary, stratification of aPL-positive subjects according to their aPL profile (combination, isotype and titer), presence of other concomitant risk factors for thrombosis and coexistence of an underling autoimmune disease is essential to decide whether primary prophylactic therapy should be prescribed. Additionally, the management of modifiable thrombotic risk factors is a necessary strategy, and the use of transient prophylaxis is crucial during high-risk periods. Specifically designed prospective trials are urgently needed to determine the real prophylactic impact of aspirin, as well as of alternative or concomitant therapeutic strategies such as hydroxychloroquine, statins or DOACS in aPL positive patients.

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1. Introduction

Antiphospholipid antibodies (aPL) are a heterogeneous family of autoantibodies directed against phospholipids and/or phospholipid-binding proteins, which include, among others, lupus anticoagulants (LA), anti-cardiolipin antibodies (aCL) and anti-β2GPI antibodies (anti-β2GPI). aPL predispose to pregnancy morbidity and vascular thrombosis such as in the antiphospholipid syndrome (APS) [1]. Significant titers of aPL can be detected in a great variety of situations from the general population, including pre-surgical testing (i.e in case of elevated activated partial thromboplastin time), blood donors (in the presence of a false-positive Venereal Disease Research Laboratory test), during investigations for oral contraceptives prescription or for spontaneous abortion, fetal death or premature birth but also in patients with autoimmune diseases such as systemic lupus erythematosus (SLE). aPL may also be detected during infections but in that case are mostly transient. The exact prevalence of aPL in the general population is currently debated due to issues with aPL assay standardization and thresholds [1, 2]. Cross-sectional studies have reported the presence of aPL in up to 10% of healthy blood donors [3,4], but this does not reflect most centers' experience, and persistently positive aPL has been shown to be a rare situation (<2%) in healthy individuals [4]. Besides, in a large cohort of blood donors, no thrombotic event was observed after 12 months of follow-up among patients found to have aCL [4]. Based on a limited number of studies, the incidence of a first thrombotic event is therefore estimated to range from 0 to 2.8 for 100 patient-years in asymptomatic aPL-positive individuals [5]. A recently published 15-year follow-up study on aPL carriers identified an annual rate of thrombosis of 2.3% per patient-years [6]. When single-positive aPL carriers were considered separately, the risk decreased to 0.65%, comparable to the known risk in the general population [6]. Conversely, aPL positivity is common in SLE, where it is reported in 11–86% of patients [7], and associated with a risk of a first thrombotic event ranging from 1 to 3.8 for 100 patient-years [8]. Another situation is obstetrical APS [9] where the thrombotic risk may be as high as 7 for 100 patient-years in patients with SLE [10].

While there is a general agreement on long-term anticoagulation to prevent recurrences of thrombosis in APS patients, there is only limited evidence regarding the adequate primary prevention of thrombosis in aPL carriers. The use of low-dose aspirin (LDA) for the primary prevention of cardiovascular events remains controversial in the general population [11–14]. However, the use of LDA has been advocated in patients with aPL at high-risk for thrombosis [10], while no univocal evidence-based recommendations have supported this strategy to date. It therefore remains to determine the best strategy to predict and prevent thrombosis at the individual level. Another element is that we should clearly differentiate between transient high-risk situations, where prophylaxis is required for a brief period, and other situations that may require long-term prophylaxis.

2. PRO'S

2.1. Data from observational studies

>10 observational studies examined the potentially protective effect of LDA in asymptomatic aPL+ individuals, patients with SLE and aPL, or patients with obstetrical APS.

Our meta-analysis [15] including a total of 1208 patients and 139 thrombotic events showed that patients treated with LDA had approximately a 2-fold reduction in the risk of a first thrombotic event compared to those not treated with LDA, and that such protective effect could be demonstrated for asymptomatic aPL individuals, as well as among patients with SLE or obstetrical APS. Importantly, the risk reduction did not maintain statistical significance when only prospective studies or those with the best methodological quality were considered. Another limitation inherent to literature-based meta-analyses is that we were unable to take into account additional cardiovascular risk factors to adjust the analysis. In order to overcome this caveat, we performed a patient-level meta-analysis [16] of 5 international cohort studies including 497 subjects and 79 first thrombotic events for a total of 3469 patient-years of follow-up. After adjustment at the patient-level on CVRD, aPL profiles, and treatment with hydroxychloroquine, the HR for the risk of a first thrombosis of any type in aPL carriers treated with LDA versus those not treated with aspirin was 0.43 (95%CI 0.25–0.75). Subgroup analysis revealed a protective effect of LDA against arterial (HR: 0.43 [95%CI: 0.20–0.93]) but not venous (HR: 0.49 [95%CI: 0.22–1.11]) thrombosis. Subgroup analyses according to underlying disease revealed a protective effect of aspirin against arterial thrombosis for systemic lupus erythematosus (SLE) (HR: 0.43 [95%CI: 0.20–0.94]) but also for asymptomatic aPL carriers (HR: 0.43 [95%CI 0.20–0.93]). This individual patient data meta-analysis therefore shows that the risk of first thrombotic event, as well of first arterial thrombotic event, is significantly decreased among SLE patients and asymptomatic aPL individuals treated by low-dose aspirin after adjustment for aPL profiles and additional cardiovascular risk factors.

2.2. Current recommendations for thromboprophylaxis

The consensus document elaborated by one of the task Force at the 13th International Congress on aPL [10] recommends that patients with SLE and positive LA or isolated persistent aCL at medium-high titers receive primary thromboprophylaxis with hydroxychloroquine (HCQ) (grade 1B) and low-dose aspirin (grade 2B). In non-SLE individuals with aPL and no previous thrombosis, the task force suggests long-term thromboprophylaxis with low-dose aspirin in those with a high-risk aPL profile, especially in the presence of other thrombotic risk factors (Grade 2C). The high risk profiles outlined by the task force are LA positivity, triple positivity, isolated persistently positive aCL at medium–high titers, while patients with isolated, intermittently positive aCL or anti-β2GPI at low-medium titers are considered to be at low risk. A key question is whether the potentially protective effect of low-dose aspirin outweighs the risk of bleeding (0.5–1 for 100 patient-years) induced by the prophylaxis. Given the estimated thrombotic rate, primary prophylaxis with LDA appears more relevant among patients with aPL and associated autoimmune diseases (thrombosis rate: 2 to 5 per 100 patient-years) than in asymptomatic low-risk carriers in which the risk is about 1% patient-years (range 0–2.8). Regarding the specific issue of the benefit/risk ratio, Wahl et al. [17] used a Markov decision analysis to compare prophylactic aspirin, oral anticoagulant therapy and observation in asymptomatic aPL-positive patients with SLE. This study demonstrates that the prophylactic role of LDA generally outweighs the treatment-associated risk of major bleeding in SLE patients with aCL or LA.

2.3. Transient prophylaxis during high risk periods

An effective thromboprophylaxis with subcutaneous low molecular weight heparin (LMWH) should be recommended in patients with persistently positive aPL during high risk situations such as prolonged immobilization, recent surgery, pregnancy pre- and peri-partum, ovarian stimulation, thalidomide therapy and SLE patients with nephritic syndrome and low albumin levels. In these situations, thromboprophylaxis with low molecular weight heparin or aspirin have been shown to be effective in reducing thrombotic complications [18,19].

3. CON'S

3.1. Data from randomized controls trials

Unfortunately, the task force recommendation [10] is not supported by high-quality studies. Currently, the Antiphospholipid Antibody Acetylsalicylic Acid (APLASA) study [20] is the sole randomized

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