Review

Patient-level analysis of five international cohorts further confirms the efficacy of aspirin for the primary prevention of thrombosis in patients with antiphospholipid antibodies

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ABSTRACT

We performed an individual patient meta-analysis to determine whether aspirin has a significant protective effect on the risk of first thrombosis among patients with antiphospholipid antibodies (aPL). Five international cohort studies with available individual patient-level data, reporting on primary prophylaxis with continuous treatment with low-dose aspirin in patients with aPL were included. The main outcome was the occurrence of a first thrombotic in patients with aPL treated with low-dose aspirin compared to those not treated with low-dose aspirin. Pooled Hazard Ratios (HRs) and 95%CIs were calculated using frailty models. We pooled data from 497 subjects and 79 first thrombotic events (3469 patient-years of follow-up). After adjustment on cardiovascular risk factors, aPL profiles, and treatment with hydroxychloroquine, the HR for the risk of a first thrombosis of any type in aPL carriers treated with low-dose aspirin versus those not treated with aspirin was 0.43 (95%CI 0.25–0.75). Subgroup analysis showed a protective effect of aspirin 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 analysis 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]) and asymptomatic aPL carriers (HR: 0.43 [95%CI 0.20–0.93]). We found no independent protective effect of hydroxychloroquine. This individual patient data meta-analysis 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.

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1. Introduction

The adequate strategy for the primary prophylaxis of thrombosis in patients with antiphospholipid antibodies (aPL) remains very controversial [1–4]. However, experts at the 13th International Congress on antiphospholipid antibodies have advocated the use of low-dose aspirin for primary prophylaxis of thrombosis in aPL carriers with high risk profiles such as lupus anticoagulant (LA) positivity or triple positivity (positivity of LA, anticardiolipin [aCL] and of anti-β2-glycoprotein-I [β2GPI] antibodies) or isolated persistently positive anticardiolipin antibodies aCL at medium-high titers [5]. Recently, we published a meta-analysis based on the literature [6], which revealed that patients treated with low-dose aspirin had an overall 2-fold reduction in the risk of a first thrombotic event compared to those not treated with aspirin. However, this finding was limited by the lack of adjustment on additional cardiovascular risk factors and the various proportions of patients with asymptomatic aPL, systemic lupus erythematosus (SLE) and obstetrical antiphospholipid syndrome (obsAPS) [7,8] in each included study.

In the present study, we were able to further refine our previous findings. We performed an analysis of patient-level data from five international cohorts, to examine the effect of low-dose aspirin on the risk of first thrombotic event in patients with aPL, after adjustment on individual cardiovascular risk factors. Individual patient data meta-analysis is widely regarded as the gold standard, as it uses the 'raw' database obtained from each study to estimate an overall effect and not solely the global data extracted from each paper. In particular, a powerful and detailed analysis of treatment effect can be undertaken, including time-to-event analyses, in-depth data consistency checking, and more importantly adjustment on known confounding factors at the patient-level, to estimate how the characteristics of these patients modify treatment benefit. This study based on patient-level data therefore represents an important advance compared to our previous meta-analysis based on literature data.

2. Methods

2.1. Study population

For our initial meta-analysis based on literature data [6] two main investigators (L.A. & A.M.) searched EMBASE (1974–July 2012), MEDLINE (1966–July 2012) and the Cochrane Database of Systematic Reviews (The Cochrane Library, 2012, issue 7) for original articles without language restrictions. Search strategy combined free text search, exploded MESH/EMTREE terms and all synonyms of the following Medical Subject Headings terms: antiphospholipid antibodies, systemic lupus erythematosus, obstetrical antiphospholipid syndrome, lupus-like syndrome, lupus coagulation inhibitor, anticardiolipin antibodies, beta 2-Glycoprotein I, aspirin, and thrombosis (see the detailed search strategy in Appendix A). We also searched for additional articles from the reference list of relevant papers obtained from the electronic search. In addition, the gray literature was explored by hand searching the conference abstracts of the American College of Rheumatology (ACR) and the European League Against Rheumatism from January 1999 to July 2012.

For the present study, the principal investigators of the 11 studies included in our previous meta-analysis [3,9–17] were contacted to request individual patient-level data. The flow-chart for study selection is shown in Fig. 1. We successfully obtained data from 5 cohort studies yielding a large group of 497 subjects with aPL (further referred to as aPL carriers) reporting on primary prophylaxis (no prior thrombosis) with continuous treatment with low-dose aspirin [11,13,15–17]. Patients treated with clopidogrel or oral anticoagulant or intermittent prophylaxis (i.e., only in high risk periods) were excluded. Ethics approval for these studies was obtained in accordance with the legislation in each country. For the pooled cohort analysis of anonymized data, ethics approval was obtained from the local ethic committee of Île-De-France VI (Paris, France). This research has been conducted in accordance with the Declaration of Helsinki and its subsequent amendments.

2.2. Data collection

Main authors from the five cohort studies were contacted by email and asked to provide the following data for each patient included in their study: a unique patient number, gender, date of birth, individual study dates (date of study entry and end of follow-up), occurrence of a first thrombotic event during the follow-up, if any (date and type of event [arterial or venous]), use of aspirin (yes/no), of hydroxychloroquine (yes/no) [no patient was treated with chloroquine], underlying disease (i.e., asymptomatic aPL carrier, SLE or obsAPS), aPL status (positive search [yes/no, according to local lab] for lupus anticoagulant, anticardiolipin antibodies [IgG and/or IgM], and anti-β2GPI antibodies [IgG and/or IgM], separately), and presence (yes/no) of each of the following cardiovascular risk factors at study entry: tobacco use (defined as current smoking at study entry), arterial hypertension (defined by a physician's diagnosis of hypertension) or use of anti-hypertensive medication, diabetes mellitus (defined by a physician's diagnosis of diabetes mellitus) or use of anti-diabetic medication, hyperlipidemia (defined by a physician's diagnosis of hyperlipidemia) or statin use, and obesity (defined as a body mass