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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.

Contents

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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

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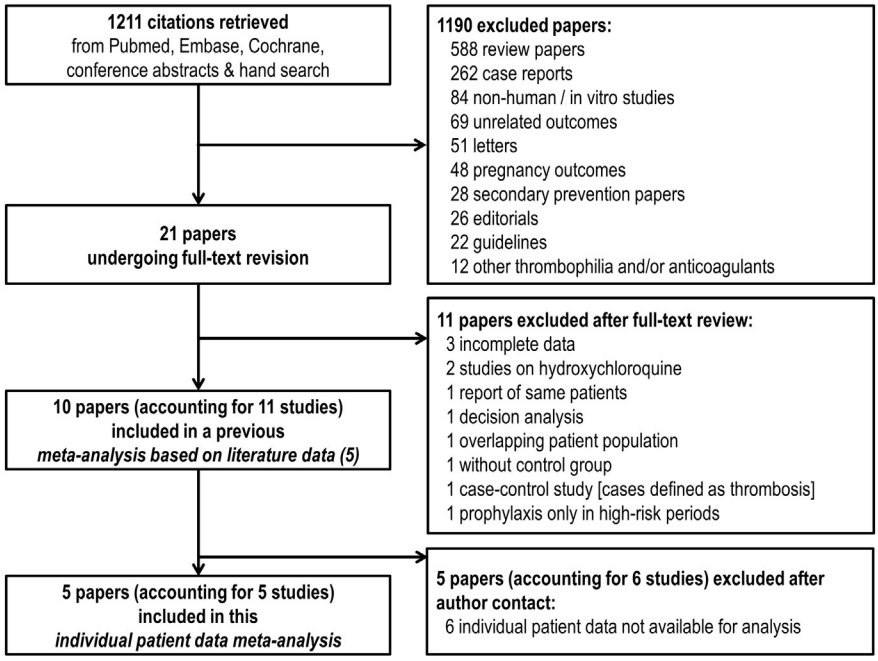

Fig. 1. Flow-chart for study selection and final inclusion in the individual patient data meta-analysis.

index >30). The 5 datasets provided by authors were checked for data consistency, and then pooled into a unique dataset. Unique patient numbers as well as a separate tag for each cohort were added before data analysis, in order to later adjust for the center effect.

2.3. Disease and outcome definitions

SLE was defined according to the 1997 ACR criteria for SLE [18] and presence of aPL according to Sapporo's (before 2006) or Sydney's (after 2006) consensus conference criteria [19,20]. Asymptomatic aPL + carriers were defined as individuals with aPL and no prior history of thrombosis or of any definite autoimmune disease. The main outcome of interest was the occurrence of a first thrombotic event (arterial and/or venous) in patients treated with low-dose aspirin compared to those not treated with low-dose aspirin.

2.4. Statistical analyses

Continuous variables were expressed as medians and ranges or interquartile range (IQR) and categorical variables as numbers and percentages. Differences between groups of patients were tested by the Mann–Whitney test for continuous data, and by Fisher's exact test or the Chi-2 test for categorical data. Adjustment for multiple comparisons of patients characteristics between those treated with and without aspirin was performed using the Bonferroni correction. Using individual-level data, we calculated study-specific hazard ratios (HRs) and 95% Confidence Interval (95%CIs) using frailty model, which is similar to Cox proportional hazards model but is able to take into account model correlations between thrombosis of the same center by using a random component for the hazard function [21]; follow-up time in months was used as the time metric. Baseline age (according to quartiles), gender, underlying disease (SLE, obsAPS and asymptomatic aPL carriers), aPL status (presence or absence of LA, aCL, anti-β2GPI, separately), tobacco use, hypertension or use of anti-hypertensive medication, diabetes mellitus or use of anti-diabetic medication, hyperlipidemia or statin use, and obesity were adjusted for as potential confounding factors in the multivariate analyses. Finally, HRs for SLE patients were adjusted for treatment with hydroxychloroquine. All statistical tests were 2-sided and P values <0.05 were considered to be statistically significant. We used SAS version 9.3 (SAS Institute, USA) for the analyses.

3. Results

3.1. Characteristics of included studies

We pooled data from 2 prospective [11,13] and 3 retrospective [12,13,17] cohort studies. Detailed characteristics of the 5 included studies are presented in Appendix B. These studies were conducted in Argentina, France, Greece, Italy and Spain, between 2005 and 2012. Sample sizes varied from 62 to 129 patients, for a total of 497. The median age at study entry was 37.4 years (range: 6.7–85.4). Two hundred and twenty one patients received continuous prophylaxis with low-dose aspirin and 276 did not. The median length of follow-up was 76.8 months (IQR: 46 to 113 months), accounting for 3469 patient-years of follow-up. Forty-four arterial and 35 venous first thrombotic events occurred during the follow-up. The detailed characteristics of patients treated with aspirin and those not treated with aspirin are shown in Table 1.

3.2. Incidence of first thrombosis during follow-up

The incidence of a first thrombotic event (of any type) in all aPL carriers was 2.45 per 100 patient-years (1.47 per 100 patient-years in those treated with low-dose aspirin and 3.18 per 100 patient-years in those not treated with low-dose aspirin).

3.3. Risk of first thrombosis in aPL carriers treated with aspirin versus without

After pooling the 5 included studies and taking into account the center effect, we found an HR (further referred to as HR_{center}) of 0.50 (95%CI: 0.30 to 0.82) for the risk of a first thrombotic event (of any type) in aPL carriers treated with low-dose aspirin versus without (Fig. 2A). After further adjustment on the gender, age, and presence of cardiovascular risk factors, the HR (further referred to as HR_{CVRF}) was 0.43 (95%CI: 0.25–0.76) (Fig. 2A). Because we could not perform subgroup analyses for each combination of aPL for the reason that such

Table 1
Characteristics of patients treated with versus without aspirin.

Patients characteristics	With aspirin ($n = 221$)	Without aspirin ($n = 276$)	p-value
Demographic data			
Female, *n* (%)	196 (89%)	241 (87%)	0.68
Age, years, median (range)	37.5 (6.7–80.5)	37.2 (8.5–85.1)	0.82
Duration of follow-up, months, median (IQR)	77.8 (53.3–114.5)	75.6 (36.5–110.7)	0.15
Thrombotic events			
All thromboses, *n* (%)	25 (11%)	54 (20%)	0.01
Arterial, *n*	15	29	
Venous, *n*	10	25	
Underlying diseases[c]			
Systemic lupus, *n* (%)	109 (49%)	83 (30%)	<0.0001[a]
Obstetrical APS, *n* (%)	15 (7%)	65 (24%)	<0.0001[a]
Asymptomatic carriers, *n* (%)	66 (30%)	105 (38%)	0.06
Other auto-immune diseases	33 (15%)	24 (9%)	0.04
Other treatments			
Treatment with hydroxychloroquine, *n* (%)	50 (23%)	35 (13%)	0.004
aPL profiles			
LA, *n* (%)	113 (59%)	168 (67%)	0.09
aCL (IgG and/or IgM), *n* (%)	200 (91%)	246 (89%)	0.66
Anti-β2GP1 (IgG and/or IgM), *n* (%)[b]	99 (55%)	124 (61%)	0.25
Cardiovascular risk factors			
Tobacco use (former or current), *n* (%)	38 (17%)	36 (13%)	0.21
Hypertension (or treatment for), *n* (%)	42 (19%)	47 (17%)	0.64
Diabetes mellitus (or treatment for), *n* (%)	12 (5%)	18 (7%)	0.71
Dyslipidemia (or treatment for), *n* (%)	33 (15%)	37 (13%)	0.70
Obesity (BMI >30), *n* (%)	17 (8%)	27 (10%)	0.43

n: number of event; IQR: Interquartile range; APS: antiphospholipid syndrome. LA: lupus anticoagulant; aCL: anticardiolipin antibodies; anti-β2GP1: anti-β2-glycoprotein-1 antibodies.
[a] The Chi-2 test remains significant after Bonferroni correction for multiple testing.
[b] Search for anti-β2GP1 was performed in 378 patients.
[c] Total >497 because some patients had both SLE & obs APS.

multiple testing would have strongly expanded the risk of type I error, we further adjusted the HR for the presence of aCL, anti-β2GPI and LA, separately (further referred to as HR_{aPL}), and found an HR of 0.43 (95%CI: 0.25–0.75) (Fig. 2A). Finally, after adjustment for treatment with hydroxychloroquine (further referred to as HR_{HCQ}), we found an HR of 0.43 (95%CI: 0.25–0.75) (Fig. 2A).

In subgroup analyses for arterial thrombosis, the HR_{center} was 0.57 (95%CI: 0.30–1.09), the HR_{CVRF} was 0.43 (95%CI: 0.20–0.93), the HR_{aPL} was 0.43 (95%CI: 0.20–0.92) and the HR_{HCQ} was 0.43 (95%CI: 0.20–0.93) (Fig. 2B). For venous thrombosis, the HR_{center} was 0.44 (95%CI: 0.21–0.95), the HR_{CVRF} was 0.45 (95%CI: 0.20–1.00), the HR_{aPL} was 0.48 (95%CI: 0.21–1.10) and the HR_{HCQ} was 0.49 (95%CI: 0.22–1.11) (Fig. 2C). A summary of HRs for the effect of aspirin in all aPL carriers is shown in Table 2.

3.4. Risk of first thrombosis in SLE patients with aPL treated with aspirin versus without

For the risk of a first thrombotic event (of any type) in SLE patients treated with low-dose aspirin versus without, pooled data analysis revealed a HR_{center} of 0.42 (95%CI: 0.22 to 0.83), a HR_{CVRF} of 0.33 (95%CI: 0.13–0.84), a HR_{aPL} of 0.32 (95%CI: 0.12–0.84) and a HR_{HCQ} of 0.43 (95%CI: 0.25–0.75) (Appendix C). For arterial thrombosis, the HR_{center} was 0.47 (95%CI: 0.20–1.13), the HR_{CVRF} was 0.26 (95%CI: 0.07–1.04), the HR_{aPL} was 0.24 (95%CI: 0.06–0.98) and the HR_{HCQ} was 0.43 (95%CI: 0.20–0.94) (Appendix C). For venous thrombosis, the HR_{center} was 0.39 (95%CI: 0.13–1.12), the HR_{CVRF} could not be computed due to statistical model instability, the HR_{aPL} was 0.48 (95%CI: 0.11–2.16) and the HR_{HCQ} was 0.49 (95%CI: 0.21–1.10) (Appendix C). Importantly, we found no independent protective effect of hydroxychloroquine (Appendix D). A summary of HRs for the effect of aspirin in SLE patients is shown in Table 2.

3.5. Risk of first thrombosis in asymptomatic individuals with aPL with aspirin versus without

For the risk of a first thrombotic event (of any type) in asymptomatic individuals treated with low-dose aspirin versus without, pooled data analysis revealed a HR_{center} of 0.46 (95%CI: 0.17 to 1.20), a HR_{CVRF} of 0.38 (95%CI: 0.15–1.00), a HR_{aPL} of 0.43 (95%CI: 0.25–0.76) and a HR_{HCQ} of 0.43 (95%CI: 0.25–0.75) (Appendix E). For arterial thrombosis, the HR_{center} was 0.28 (95%CI: 0.06–1.33), the HR_{CVRF} was 0.21 (95%CI: 0.04–0.98), the HR_{aPL} could not be computed due to statistical model instability and the HR_{HCQ} was 0.43 (95%CI: 0.20–0.93) (Appendix E). For venous thrombosis, the HR_{center} was 0.63 (95%CI: 0.19–2.13), the HR_{CVRF} was 0.57 (95%CI: 0.17–1.95), the HR_{aPL} was 0.49 (95%CI: 0.21–1.10) and the HR_{HCQ} was 0.49 (95%CI: 0.22–1.11) (Appendix E). A summary of HRs for the effect of aspirin in asymptomatic individuals with aPL is shown in Table 2.

4. Discussion

The adequate strategy for the primary prophylaxis of thrombosis in patients with aPL is an important and controversial issue [3]. We have herein performed a pooled patient-level data analysis of a large number of patients from five international cohorts to examine the effect of low-dose aspirin on the risk of a first thrombotic event in patients with aPL. We found that the use of low dose aspirin was associated with a significant decrease in the risk of a first thrombotic event of any type and of a first arterial thrombotic event specifically, after adjustment for several potential cofactors.

Up to now, a single randomized, double-blind, placebo-controlled clinical trial, namely the Antiphospholipid Antibody Acetylsalicylic Acid (APLASA) study [3] addressed our question of interest. This study, which showed no protective effect of aspirin, was terminated early

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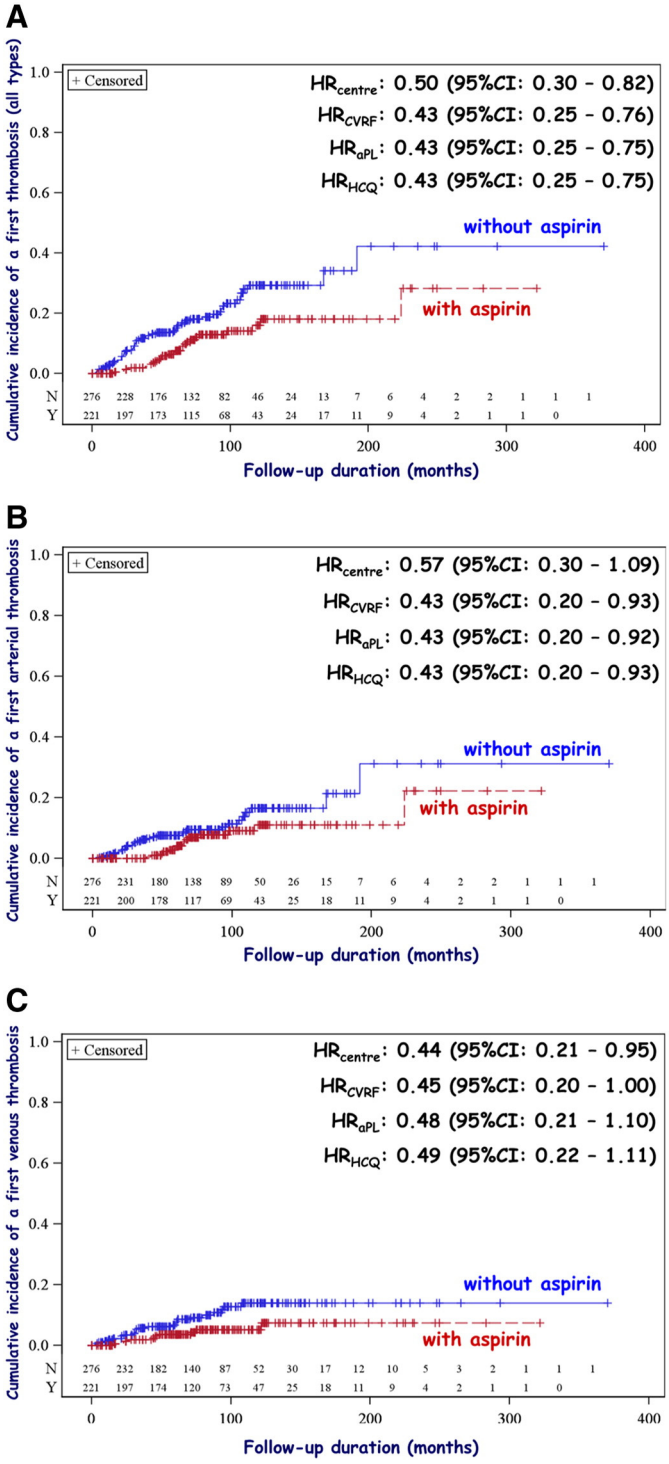

Fig. 2. Cumulative incidence of all type (panel A), arterial (panel B) and venous (panel C) thrombosis in all aPL carriers treated with low-dose aspirin versus without. HR: hazard ratio by frailty models; 95%CI: 95% Confidence Interval; HR_{center}: Hazard Ratio taking into account the center effect. HR_{CVRF}: Hazard Ratio taking into account the center effect, and adjusted for gender, age, and presence of cardiovascular risk factors; HR_{aPL}: Hazard Ratio taking into account the center effect, and adjusted for gender, age, presence of cardiovascular risk factors, and presence of aCL, anti-β2GPI and LA, separately. HR_{HCQ}: Hazard Ratio taking into account the center effect, and adjusted for gender, age, presence of cardiovascular risk factors, presence of aCL, anti-β2GPI and LA (separately), and treatment with hydroxychloroquine. The cross-marks show censored individuals. The numbers at the bottom of the figure show the number of patients at risk treated with (Y) aspirin and without (N).

because no thrombotic event occurred in the placebo group. This was attributed to the relatively short follow-up duration, the good control of additional vascular risk factors and the inclusion of a significant proportion of individuals with at low thrombotic risk [5]. Conversely, patients included in our pooled data analysis had a high thrombotic risk (3.18 per 100 patient-years in those not treated with low-dose aspirin). Therefore, both the larger sample size and higher thrombotic risk of patients included in our study may explain the discrepancies with the previous APLASA study.

In SLE patients, the use of low-dose aspirin was associated with a significant decrease in the risk of a first thrombotic event (of any type) and of a first arterial thrombosis, after adjustment for center effect, gender, age, cardiovascular risk factors, aPL profiles and treatment with hydroxychloroquine. We observed no independent protective effect of hydroxychloroquine, while both in vitro and observational data suggest that the latter may have an anti-thrombotic effect [22–24]. This finding should be interpreted with caution as only 44% of SLE patients were treated with hydroxychloroquine across the 5 included cohorts. This may account for a lack of statistical power and limit the detection of an anti-thrombotic effect of hydroxychloroquine, if any. Of note, a recent systematic review of the literature concluded that the evidence for the antithrombotic effect of antimalarials were moderate [25].

A major strength of this study, besides the use of individual patient data, is that we were able to adjust our analyses on individual traditional cardiovascular risk factors [6]. This is crucial because cardiovascular risk factors may have a strong impact on the thrombotic risk in aPL patients. For instance, hypertension was found to be an independent predictor of thrombosis in the retrospective study by Ruffatti [14], and arterial events have been associated with the coexistence of metabolic syndrome in primary APS [26]. Urbanus et al. have also shown that smoking increases the risk of arterial thrombosis in patients with positive lupus anticoagulant test [27]. Lack of adjustment for cardiovascular risk factors was therefore a major pitfall of previous studies.

An additional strength of this work is that we were able to assess not only the number of thrombotic events but also their cumulative incidence in the same manner as in a survival analysis. For this we used frailty models, which are random effect models for time-to-event data similar to Cox proportional hazard model, but that are able to take into account more adequately the center effect [21]. Taking into account this variability in the models allowed us to account at the same time for both known and unknown confounders. The former include the prospective or retrospective study designs, the heterogeneous laboratory methods used for the measurement of aPL, and differences in the modalities of patient follow-up between included studies. Altogether, we were able to successfully take into account the confounding factors that were not satisfactorily addressed in previous studies.

Our results should nevertheless be interpreted with some limitations in mind. First, only 5 of the 11 studies included in our previous meta-analysis based on literature data were included in this individual patient data analysis. This is due to the fact that other authors could not share or did not wish to share individual patient data, which is obviously a common problem in this kind of analyses. Importantly, included studies were ranked as having high and low methodological quality in our previous meta-analysis and are therefore representative of a broad range of study quality. Of the 3 studies with significant effect estimates in the original meta-analysis, two have been included in the current study. We were therefore able to retain most original studies with significant estimates. While we certainly do not claim that the inclusion of 5 studies has no impact on the generalizability of study estimates, we believe that being able to report on individual patient data of 5 international studies with nearly 500 patients included and adjustment on cardiovascular risk factors offers new perspectives in an important field in which evidence-based medicine is scarce and no further trial is currently being planned.

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Table 2
Hazard ratios for the risk of first thrombosis in all patients, SLE patients and asymptomatic individuals.

Pathogenic background	Type of event	HR_{center} (95%CI)	HR_{CVRF} (95%CI)	HR_{aPL} (95%CI)	HR_{HCQ} (95%CI)
All patients ($n = 497$)	Any type	0.50 (0.30–0.82)	0.43 (0.25–0.76)	0.43 (0.25–0.75)	0.43 (0.25–0.75)
	Arterial	0.57 (0.30–1.09)	0.43 (0.20–0.93)	0.43 (0.20–0.92)	0.43 (0.20–0.93)
	Venous	0.44 (0.21–0.95)	0.45 (0.20–1.00)	0.48 (0.21–1.10)	0.49 (0.22–1.11)
SLE patients ($n = 192$)	Any type	0.42 (0.22–0.83)	0.33 (0.13–0.84)	0.32 (0.12–0.84)	0.32 (0.12–0.84)
	Arterial	0.47 (0.20–1.13)	0.26 (0.07–1.04)	0.24 (0.06–0.98)	0.43 (0.20–0.94)
	Venous	0.39 (0.13–1.12)	Model instability*	0.48 (0.11–2.16)	0.49 (0.21–1.10)
Asymptomatic individuals ($n = 171$)	Any type	0.46 (0.17–1.20)	0.38 (0.15–1.00)	0.43 (0.25–0.76)	0.43 (0.25–0.75)
	Arterial	0.28 (0.06–1.33)	0.21 (0.04–0.98)	Model instability*	0.43 (0.20–0.93)
	Venous	0.63 (0.19–2.13)	0.57 (0.17–1.95)	0.49 (0.21–1.10)	0.49 (0.22–1.11)

HR: hazard ratio by frailty models; 95%CI: 95% Confidence Interval; HR_{center}: Hazard Ratio taking into account the center effect. HR_{CVRF}: Hazard Ratio taking into account the center effect and adjusted on the gender, age, and presence of cardiovascular risk factors; HR_{aPL}: Hazard Ratio taking into account the center effect and adjusted on the gender, age, presence of cardiovascular risk factors, and presence of aCL, anti-β2GPI and LA, separately. HR_{HCQ}: Hazard Ratio taking into account the center effect and adjusted on the gender, age, presence of cardiovascular risk factors, presence of aCL, anti-β2GPI and LA (separately), and treatment with hydroxychloroquine. *No result is provided due to lack of convergence of statistical model leading to unstable estimates in this specific group.

Other limitations of the study include the facts that as in any observational analysis, and although we used frailty models, confounding by unmeasured factors remains a possibility. For instance, we were not able to take in account the use of oral contraceptives and inherited thrombophilia, which have been linked to an increased risk of arterial events due to lupus anticoagulant [14]. Also, we were not able to determine the effect of aspirin in patients with obsAPS, due to the limited number of patients or unstable statistical modeling in this subset. Additionally, data on bleeding were not collected and analyzed. Therefore we could not formally assess the benefit/risk ratio of aspirin in this individual patient data meta-analysis. Finally, the 13th aPL task force recommends prophylaxis with low-dose aspirin in SLE patients with LA positivity or isolated persistently positive aCL at medium-high titers, and in non-SLE patients with LA positivity or triple positivity or isolated persistently positive aCL at medium-high titers [5]. Because we could not perform subgroup analyses for each combination of aPL within each pathogenic background, for the reason that such multiple testing would have strongly expanded the risk of type I error, we have rather decided to adjust our analyses for the presence of lupus anticoagulant, aCL and anti-β2GPI antibodies separately (Table 2). This was performed as a manner to take into account differences in the thrombotic risk that may arise from each aPL profile.

Altogether, this individual patient data analysis confirmed the protective effect of low dose aspirin in SLE patients and asymptomatic aPL carriers, after adjustment for individual traditional cardiovascular risk factors. Because the role of these traditional cardiovascular risk factors has been largely overlooked in previous studies, both the use of individual patient data and adjustment for these major confounders are among the major strengths of this study. We believe these results based on currently available patient-level data have direct impact on the management of patients with aPL until further evidence can be gathered from a future randomized controlled trial that remains to be set.

Take-home messages

- The adequate strategy for the primary prophylaxis of thrombosis in patients with antiphospholipid antibodies (aPL) remains controversial.
- Our previous meta-analysis based on literature data 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, with several limitations.
- Here, we performed a patient-level analysis of five international cohorts (i.e, we used the "raw" databases from the studies and not solely the data extracted from the papers), to study the risk of first thrombosis in patients with aPL treated with low-dose aspirin versus without, after adjustment on individual cardiovascular risk factors.
- We observed a strong decrease in the risk of first thrombosis in aPL carriers treated with low-dose aspirin (HR: 0.43 [95%CI 0.25–0.75]).
- Subgroup analysis revealed a protective effect of aspirin against arterial thrombosis for systemic lupus erythematosus (HR: 0.43 [95%CI: 0.20–0.94]) and asymptomatic aPL carriers (HR: 0.43 [95%CI 0.20–0.93]).
- Although limited by the number of included cohorts ($n = 5$), this study based on patient-level data therefore represents an important advance compared to our previous meta-analysis based on literature data.

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No author has any conflict of interest to disclose.

Contributions:

Laurent Arnaud, Hervé Devilliers & Alexis Mathian designed research. Amelia Ruffatti, Maria Tektonidou, Ricardo Forastiero, Vittorio Pengo, Marc Lambert, Guillaume Lefevre, Maria Angeles Martinez-Zamora, Juan Balasch, Laurent Arnaud, Alexis Mathian, Denis WAHL & Zahir Amoura performed research. Hervé Devilliers & Laurent Arnaud performed statistical analysis. Laurent Arnaud, Hervé Devilliers, Alexis Mathian & Zahir Amoura analyzed data. Laurent Arnaud, Hervé Devilliers, Alexis Mathian & Zahir Amoura wrote the paper. All authors approved the final manuscript.

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Appendix A. Search strategy

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. The specific search strategy for PubMed was: ((“Lupus Erythematosus, Systemic”[Mesh]) OR (“Lupus”[All Fields]) OR (“Antiphospholipid Syndrome”[Mesh]) OR (“Antiphospholipid Syndrome”[All Fields]) OR (“lupus-like”[All Fields]) OR (“beta 2-Glycoprotein I”[Mesh]) OR (“Antibodies, Antiphospholipid”[Mesh]) OR (“Antiphospholipid”[All Fields])) AND ((“thrombosis”[All Fields]) OR (“thrombosis”[Mesh])) AND ((“aspirin”[Mesh]) OR (“aspirin”[All Fields])). The specific search strategy for Embase was: (((‘systemic lupus erythematosus’/exp OR ‘systemic lupus erythematosus’) OR (‘antiphospholipid syndrome’/exp OR ‘antiphospholipid syndrome’) OR (‘lupus like syndrome’/exp OR ‘lupus like syndrome’) OR (‘beta2 glycoprotein 1 antibody’/exp OR ‘beta2 glycoprotein 1 antibody’) OR (‘phospholipid antibody’/exp OR ‘phospholipid antibody’)) AND (‘thrombosis’/exp OR ‘thrombosis’) AND ((‘aspirin’/exp OR ‘aspirin’) OR (‘acetylsalicylic acid’/exp OR ‘acetylsalicylic acid’)))

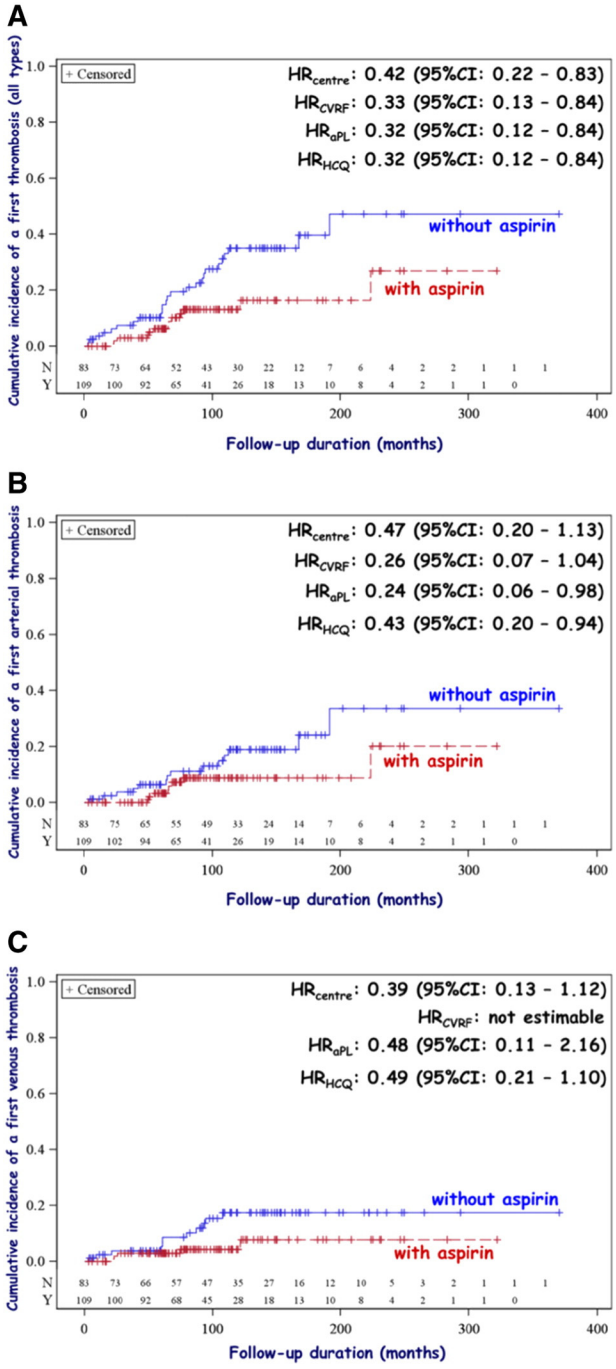
Appendix B. Characteristics of the five cohort studies included in the pooled analysis

Author, *year*	Study type	Number enrolled	Population studied		Age[a] *Years median (range)*	Patients treated with aspirin *nb. (%)*	Follow-up duration *Months, median (IQR)*	Thrombotic events, *nb.*		
			Obstetrical APS *nb. (%)*	SLE *nb. (%)*				Total	Arterial[b]	Venous[c]
Forastiero (2005)	Pros	109	34 (31.2)	20 (18.3)	41.3 (15–85)	31 (28.4)	43.9 (15.1–68.1)	12	6	6
Hereng (2008)	Retro	99	4 (4.0)	39 (39.4)	39.5 (15–80)	73 (73.7)	88.7 (67.2–119.7)	14	7	7
Tektonidou (2009)	Retro	129	0 (0.0)	129 (100)	26.8 (7–62)	72 (55.8)	106.5 (67.9–151.7)	26	16	10
Pengo/Ruffatti (2011)	Pros	98	4 (4.1)	4 (4.1)	43.4 (13–77)	31 (31.6)	48.7 (24.3–85.2)	23	12	11
Martinez-Zamora (2012)	Retro	62	38 (61)	0 (0)	35.6 (19.2–57.2)	14 (22.6)	90.0 (77.0–111.1)	4	3	1

APS, antiphospholipid syndrome; SLE, Systemic Lupus Erythematosus; Retro, retrospective cohort study; Pros, prospective cohort study; IQR, Interquartile range; [a]At study entry; [b]Including transient ischemic attack and catastrophic antiphospholipid syndrome; [c]Including pulmonary embolism.

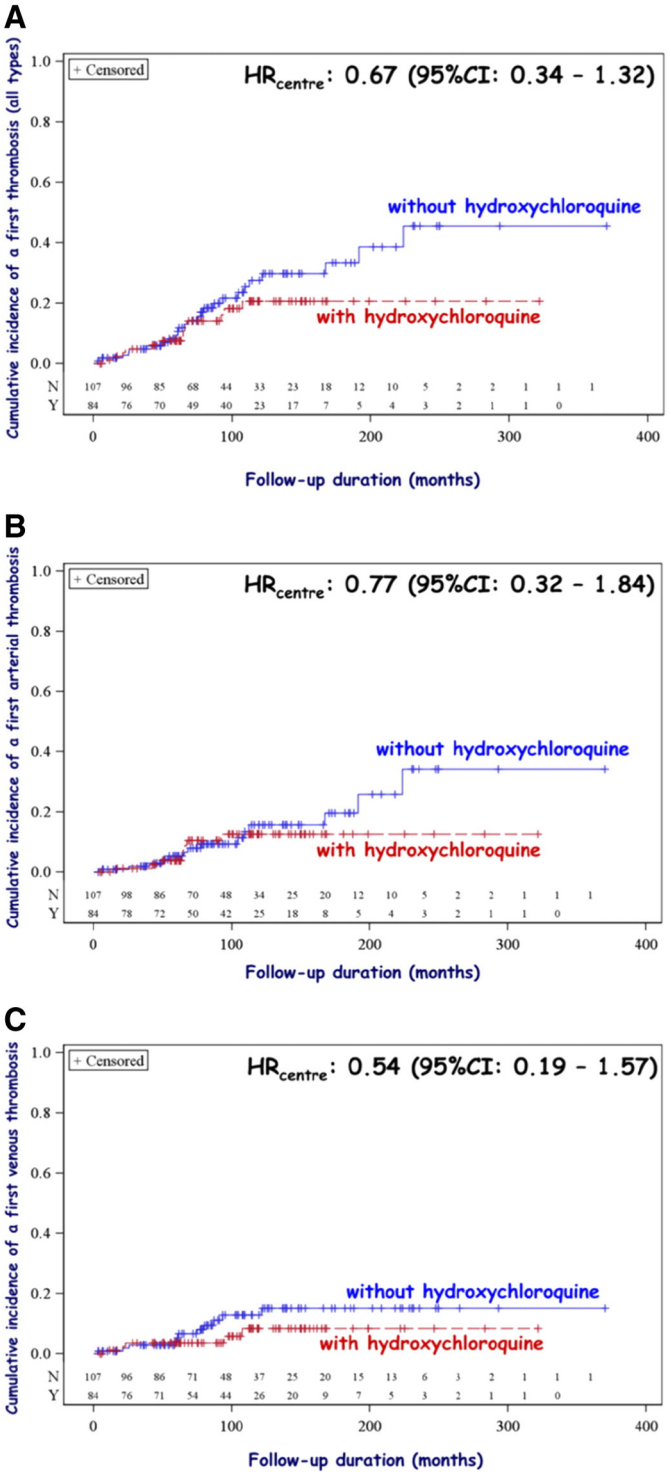
Appendix C. Cumulative incidence of all type (panel A), arterial (panel B) and venous thrombosis in SLE patients treated with versus without low-dose aspirin

HR: hazard ratio by frailty models; 95%CI: 95% Confidence Interval; HR_{center}: Hazard Ratio taking into account the center effect. HR_{CVRF}: Hazard Ratio taking into account the center effect, and adjusted for gender, age, and presence of cardiovascular risk factors; HR_{aPL}: Hazard Ratio taking into account the center effect, and adjusted for gender, age, presence of cardiovascular risk factors, and presence of aCL, anti-β2GPI and LA, separately. HR_{HCQ}: Hazard Ratio taking into account the center effect, and adjusted for gender, age, presence of cardiovascular risk factors, presence of aCL, anti-β2GPI and LA (separately), and treatment with hydroxychloroquine. The cross-marks show censored individuals. The numbers at the bottom of the figure show the number of patients at risk treated with (Y) aspirin and without (N).



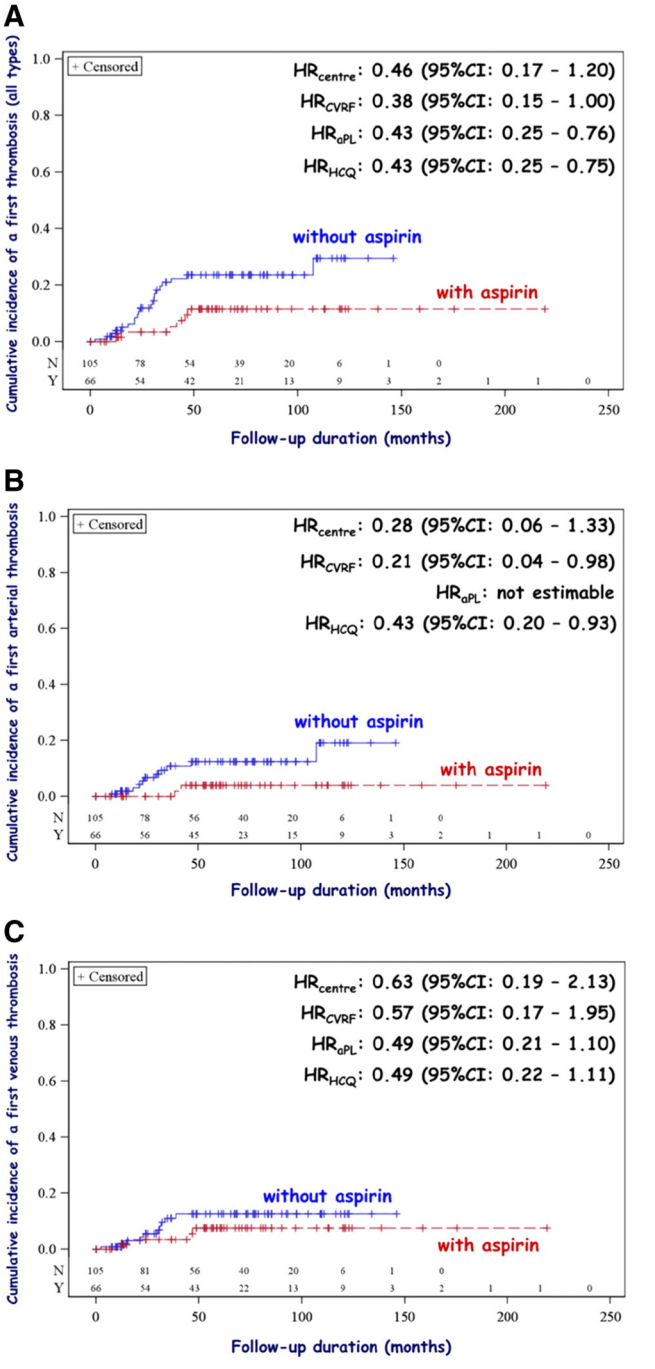
Appendix D. Cumulative incidence of all type (panel A), arterial (panel B) and venous (panel C) thrombosis in SLE patients treated with versus without hydroxychloroquine

HR: hazard ratio by frailty models; 95%CI: 95% Confidence Interval; HR_{center}: Hazard Ratio taking into account the center effect. The cross-marks show censored individuals. The numbers at the bottom of the figure show the number of patients at risk treated with (Y) aspirin and without (N).



Appendix E. Cumulative incidence of all type (panel A), arterial (panel B) and venous (panel C) thrombosis in asymptomatic aPL carriers treated with versus without low-dose aspirin

HR: hazard ratio by frailty models; 95%CI: 95% Confidence Interval; HR_{center}: Hazard Ratio taking into account the center effect. HR_{CVRF}: Hazard Ratio taking into account the center effect, and adjusted for gender, age, and presence of cardiovascular risk factors; HR_{aPL}: Hazard Ratio taking into account the center effect, and adjusted for gender, age, presence of cardiovascular risk factors, and presence of aCL, anti-β2GPI and LA, separately. HR_{HCQ}: Hazard Ratio taking into account the center effect, and adjusted for gender, age, presence of cardiovascular risk factors, presence of aCL, anti-β2GPI and LA (separately), and treatment with hydroxychloroquine. The cross-marks show censored individuals. The numbers at the bottom of the figure show the number of patients at risk treated with (Y) aspirin and without (N).



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