

Original article

Low-dose aspirin vs low-dose aspirin plus low-intensity warfarin in thromboprophylaxis: a prospective, multicentre, randomized, open, controlled trial in patients positive for antiphospholipid antibodies (ALIWAPAS)

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Abstract

Objectives. The objectives of this study are to examine the efficacy and safety of low-dose aspirin (LDA) vs LDA plus low-intensity warfarin (LDA + W) in the primary thrombosis prevention of aPL-positive patients with SLE and/or obstetric morbidity and the role of clinical and serological markers in the development of thrombosis.

Methods. In this 5-year prospective, randomized, open, controlled trial, 166 patients with aPL were randomly assigned using a minimization protocol to receive treatment with LDA ($n = 82$) or LDA + W [international normalized ratio (INR) = 1.5] ($n = 84$). Sixty-six patients who declined randomization were followed up in an observational arm. Clinical and laboratory characteristics and medication side effects were recorded.

Results. There were no differences in the number of thromboses between patients treated with LDA (4/82) or LDA + W (4/84) [hazard ratio (HR) 1.07, 95% CI 0.27, 4.3]. The incidence of thrombosis in the randomized patients was 8/166 (1.8 events/100 person-years) (HR 1.07, 95% CI 0.27, 4.3) and in the observational arm was 7/66 (4.9 events/100 person-years) (HR 2.43, 95% CI 0.87, 6.79). Sixty-five of 66 patients included in the observational arm received LDA. None of the examined clinical or serological factors appeared to predict thrombosis. Medication side effects included mild gastrointestinal symptoms in the LDA group ($n = 2$) and bleeding in the LDA + W group ($n = 11$; 1 nasal and 10 menorrhagia). The risk difference for bleeding was 13% (CI 6, 20).

Conclusion. No differences in the number of thromboses were observed between patients treated with LDA vs those treated with LDA + W. More episodes of bleeding were detected in the LDA + W group. The LDA + W regime was significantly less safe and not as acceptable as LDA alone.

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Introduction

aPLs, namely lupus anticoagulant (LA), aCLs and antibodies to β 2-glycoprotein I (anti- β 2-GPI), have been associated with an increased risk of arterial and venous thrombosis and pregnancy morbidity [1]. The prevalence of aPLs is 2–12% in the normal population [2], 30–50% in SLE patients [2–4], 10–26% for first stroke [5–7] and 10–40% in women with recurrent pregnancy loss [8, 9].

The actual thrombotic risk of untreated individuals with aPLs is not well established. Studies performed in patients with SLE showed an annual prevalence of thrombosis close to 3% [10–14]. On the other hand, data from populations of women with purely obstetric APS or asymptomatic individuals are more heterogeneous, with annual incidence rates ranging from 0 to 7.4% [9, 15–18].

The primary thrombosis prevention in aPL-positive patients remains controversial. In the general population, the options for primary prevention of cardiovascular disease mainly include aspirin and in some cases oral anticoagulation. A recent meta-analysis [19] demonstrated that although aspirin reduces non-fatal myocardial infarction, the rate of all mortality causes (death due to coronary heart disease and stroke) did not differ significantly between the aspirin and the control groups. The role of aspirin in the prevention of venous thromboembolism is also unclear [20]. Many clinical trials have demonstrated the effectiveness of oral anticoagulation for the primary and secondary prevention of venous thromboembolism, myocardial infarction and stroke. Low-intensity warfarin therapy, either alone or in combination with low-dose aspirin (LDA), has also been shown to be effective in the primary prevention of ischaemic heart disease [21], in patients with non-valvular atrial fibrillation [22] and in other prothrombotic situations [23, 24].

The side effects of LDA use include indigestion, nausea and vomiting in ~17% of the reported cases, gastrointestinal bleeding in up to 2.5% and intracranial haemorrhage in 0.4% [25, 26]. Warfarin use has also been associated with an increased risk of bleeding directly related to the international normalized ratio (INR). Estimates range from 2 to 3% for major haemorrhage and 0.6% for fatal bleeding events [27].

Some studies have found that the risk for thrombosis in aPL-positive patients was increased in patients with conventional risk factors for cardiovascular disease such as hypertension [10, 15, 28, 29]. Persistently positive aPL levels and the combination of aCL, anti- β 2-GPI and LA (triple positivity) could also significantly increase the risk of thrombosis [10, 30]. This study was designed to compare the efficacy and safety of LDA with LDA plus warfarin (LDA + W) in the primary prevention of thrombosis

in aPL-positive patients with SLE and/or obstetric criteria for APS.

Patients and methods

This study was conducted from February 2001 until June 2006. Fourteen centres across the UK and other parts of Europe (five tertiary referral centres in the UK, eight tertiary referral centres and one district hospital in Europe) included patients in the study. In the last year of the study, due to recruitment problems, one tertiary referral centre from Mexico was also invited to participate. Approval from the Multicentre Research Ethics Committee was obtained (MREC 00/01/39) and each participating centre applied locally and obtained ethical approval. All patients signed a written informed consent and the study was conducted according to the Declaration of Helsinki (2000 amendment) and the International Conference on Harmonization Guidelines for Good Clinical Practice, as adopted by the European Union in 2001 (trial registration number ISRCTN81818945).

Study population

Inclusion criteria were (i) the presence of aPLs (medium or high titres of aCL defined as IgG > 20 GPL and/or IgM > 20 MPL and/or LA positive) on at least two occasions, with an interval of 6 weeks, during the year previous to inclusion in the study; (ii) SLE patients meeting four or more ACR criteria for the classification of SLE [31] and/or patients with a history of pregnancy morbidity as defined in the classification criteria for APS (Sapporo 1998) [32] and (iii) age between 18 and 65 years.

Exclusion criteria were positive for aPLs but without SLE or obstetric APS, previous thrombotic events, uncontrolled hypertension, active gastric or duodenal ulcer, severe thrombocytopenia (platelets < 50 000 mm³), hepatic failure, severe illness (i.e. cancer), allergy to aspirin, allergy to warfarin or current pregnancy. Those patients who fulfilled criteria to be included but were not willing to be randomized were followed up in the observational arm.

Study design

Since it was planned to recruit all patients during the first year of the study and follow them up for the next 4 years, the total duration of the trial was designed to be 5 years. However, due to a low recruitment rate, the inclusion period was extended for the entire 5 years.

Randomization

Due to the large number of factors that might affect thrombosis rates, allocation was carried out by minimization in order to achieve closely balanced treatment

groups [33]. Factors included in the minimization protocol were (i) age, (ii) conventional risk factors for thrombosis (smoking, hypertension, hyperlipidaemia, diabetes, oral contraceptives), (iii) the presence or absence of SLE, (iv) the presence or absence of an adverse pregnancy history and (v) treatment including no treatment, corticosteroids, antimalarials and immunosuppressive agents. An independent individual not involved in the trial carried out the randomization under the supervision of the statistician. Treatment allocation was concealed from both the patient and researcher before trial entry, and was revealed only after the patient details had been collected and the patient entered the study.

Sample size

The power of the study and subsequently the required sample size was calculated based on the number of events expected in the aspirin group. At the time of the study design (1999), three relevant studies were available. Ginsburg *et al.* [34] showed that among men in the Physicians Health cohort, the risk ratio for thrombosis associated with medium levels of aCL was 5.3. The incidence of thrombosis in patients who were found to have aPL but no history of thrombosis was ~4–5%/year [14, 16].

We assumed that LDA would reduce the thrombosis event rate to 3 cases/100 subjects/year. For the comparison of LDA and LDA + W, 95 events should be observed in the study interval in order to detect a halving of the risk with 90% power at a nominal significance level of $\alpha = 0.05$. It was calculated that over a 5-year period 443 patients in each arm of the study would be needed. Recruiting a sample size of 1000 patients would allow for a dropout rate of approximately 10%.

Study intervention

Patients had an initial visit to obtain the necessary data for randomization. After being allocated to one of the treatment groups, they had a baseline assessment, followed by six monthly visits. Data regarding conventional risk factors for thrombosis were collected at all visits. All clinical events (notably thrombotic or haemorrhagic events) were particularly scrutinized with standard methods to objectively document them.

Study medications

Aspirin 75–125 mg (depending on the preparation available in the participant country) was administered in both groups. Low-intensity oral anticoagulation (target INR = 1.5, range 1.3–1.7) was added in the LDA + W group.

Outcome measures

The primary outcome measure was thrombosis. As only objectively verified thrombotic events were considered as an end point, the following investigations were performed in order to document the event: ultrasonography or venography for deep vein thrombosis, spiral CT scan or radionuclide lung scan or angiography for pulmonary embolism, MRI or angiography for thrombosis in intracerebral

vessels, ophthalmological examination and fluorescein angiography (where possible) for retinal thrombosis and arteriography for peripheral or mesenteric arterial thrombosis. For the diagnosis of myocardial infarction we followed the World Health Organization (WHO) classification where two-thirds of the following criteria were required: (i) ECG characteristic changes (2 mm ST increase in V4–V6 or 1 mm in I, II and aVF); (ii) ischaemic chest pain lasting >30 min; and (iii) increase in cardiac enzymes (at least twice their normal value). Amaurosis fugax was defined as sudden monocular blindness lasting <24 h and transient ischaemic attack as neurological symptoms or signs lasting <24 h [35]. Secondary outcomes were the identification of clinical and serological risk factors for thrombosis, side effects of medications and death of any cause. Side effects of medications were ascertained by questionnaire at the follow-up visits or from patients' general physician/local hospital reports.

aPL detection

aPLs were tested every year in all patients and every 6 months in some patients. Once the patient was recruited, a local laboratory stored the samples, which were sent and analysed later in the core laboratory. Final analysis was performed with the aPL results of the core laboratory. LA was measured according to the guidelines recommended by the Subcommittee on Lupus Anticoagulant/Phospholipid-dependent Antibodies [36]. The aCL ELISA was performed according to the standardized technique [37]. Anti- β 2-GPI was detected by ELISA as described previously [38]. Antiprothrombin antibodies were detected using the phosphatidylserine/prothrombin complex as an antigen, as previously described [39].

Statistical analysis

Analysis was conducted according to the intention-to-treat principle, i.e. each patient was analysed according to their original randomized treatment irrespective of later changes that might occur. Patients with incomplete follow-up were regarded as censored after the last occasion on which data were collected.

Quantitative and qualitative data were described by using mean (s.d.), n (%) or median (quartiles) as appropriate. The total follow-up time for the patients receiving each treatment was calculated and treatment-specific rates of thrombosis were obtained. Thrombosis-free survival rates were calculated by the Kaplan–Meier method for different treatments and were compared by the log-rank test. Proportional hazards regression analysis with the Wald significance test was then used to examine the effect of the treatments and patient characteristics on the risk of developing thrombosis. The results were presented as hazard ratios (HRs) with their 95% CIs and P -values. For adverse events, risk differences (RDs), 95% CIs and exact P -values were found using standard methods. The number to be treated to cause harm (NNH) was calculated as $1/\text{RD}$ when event rates were significantly higher in the active treatment arm.

Results

A total of 232 patients were included in the trial. Eighty-two patients were randomized to LDA and 84 to LDA + W. Sixty-six patients who declined randomization were included in the observational arm (Fig. 1); in this group, all patients but one (with no treatment) were taking LDA. Demographic data, conventional risk factors for thrombosis, treatments with HCQ, corticosteroids and immunosuppressive drugs were similar in both randomized groups. All these variables were included in the minimization programme so that the distribution was balanced. aPL distribution at study entry is also shown in Table 1.

The median follow-up time was 3.1 years [interquartile range (IQR) 2.0–4.1] for the LDA group patients, 2.7 (IQR 1.5–3.7) for the LDA + W group and 2.2 years (IQR 1.5–2.6) for the observational arm.

A total of 22 patients were lost to follow-up before the planned end of the study (3 from the observational arm, 10 randomized to LDA and 9 randomized to LDA + W) and therefore had incomplete survival data. In addition, 2 patients from the LDA group stopped taking the study medication because of severe constipation and 19 patients from the LDA + W group were switched to LDA alone because of side effects (11 with minor bleeding and 1 allergic reaction), failing to keep their INR on target or being unwilling to take the study medication. Non-compliance varied substantially between the randomized groups [risk difference 21% (95% CI 12%, 30%, $P < 0.001$)].

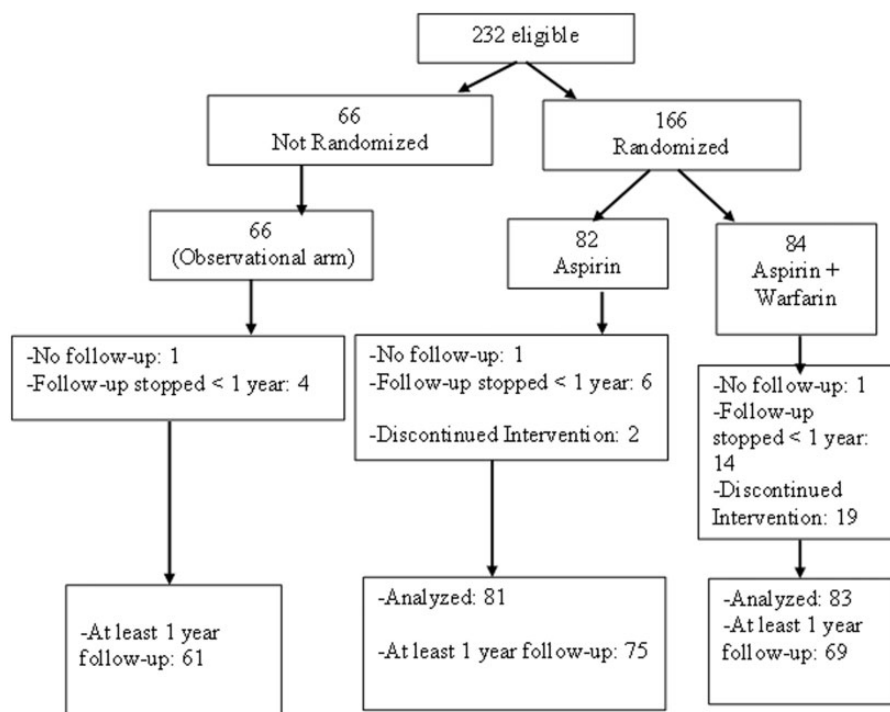
There were eight thrombotic events (four in each group) among the randomized subjects, followed for an average of 2.77 years (Fig. 2). The HR for the additional effect of warfarin was 1.07 (95% CI 0.27, 4.29, $P = 0.92$).

The incidence of thrombotic events in the randomized patients was 1.8 events/100 person-years at risk (1.7 for LDA, 1.8 for LDA + W). The number of thrombotic events in the observational arm was double that in the randomized group [7/66, 4.9 events/100 person-years at risk vs 8/166, 1.8 events/100 person-years at risk, respectively (HR 2.43, 95% CI 0.87, 6.79)]. There were no demographic, clinical or serological differences between randomized and observational arm patients with the exception of smoking, which was more frequent in randomized patient (28.3% vs 12%, $P = 0.003$) and hypertension, which was more frequent in the observational arm (11.5% vs 30%, $P = 0.001$). The type of thrombosis and characteristics of patients who developed thrombosis are summarized in supplementary Table S1, available at *Rheumatology* Online.

We reviewed the INR at the time of the event. Eight patients were within the target range for this study (1.3–1.7). Three patients had an INR < 1.3 . We do not know the INR at the time of the event for three patients.

Different dosages of LDA (75 and 100 mg) were analysed separately and no statistically significant difference was found in the two subgroups (data not shown). The impact of all other medications known to potentially reduce the risk of thrombosis (e.g. HCQ, statins and

Fig. 1 Number of patients eligible and randomized in the ALIWAPAS study.

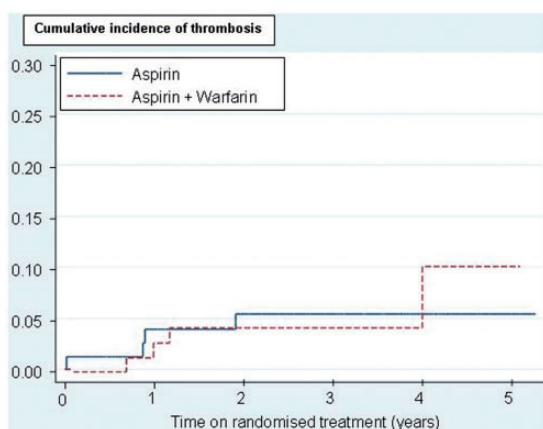


Patients who refused randomization were included in the observational arm.

TABLE 1 Clinical and laboratory characteristics of patients at study entry

| | LDA (n = 82) | LDA + W (n = 84) | Observational arm (n = 66) |
|----------------------------|--------------|------------------|----------------------------|
| Age, mean (s.d.), years | 37.8 (10.7) | 37.8 (10.6) | 41.2 (11.4) |
| Female | 80 (96) | 80 (95) | 66 (100) |
| Race (White, Black, other) | 72, 3, 7 | 76, 4, 4 | 61, 4, 1 |
| SLE | 62 (75) | 62 (73) | 44 (67) |
| Obstetric APS | 28 (35) | 29 (36) | 26 (41) |
| Hypertension | 9 (11) | 10 (12) | 20 (30) |
| Hypercholesterolaemia | 8 (10) | 12 (14) | 11 (17) |
| Hypertriglyceridaemia | 0 | 4 (5) | 5 (7) |
| Smoking | 23 (29) | 24 (31) | 8 (12) |
| Obesity | 6 (7) | 12 (14) | 9 (14) |
| Diabetes | 0 | 1 (1.2) | 2 (3) |
| Nephrotic syndrome | 0 | 1 (1.2) | 2 (3) |
| Oral contraceptives | 6 (7) | 5 (6) | 4 (6) |
| LA | 47/68 (69) | 53/64 (83) | 28/39 (71.7) |
| aCL IgG | 31/67 (46) | 23/62 (37) | 17/41 (41.4) |
| aCL IgM | 11/66 (16.6) | 13/61 (21) | 8/41 (19.5) |
| Anti- β 2-GPI IgG | 10/57 (17.5) | 13/58 (22.4) | 6/27 (22.2) |
| Anti- β 2-GPI IgM | 4/57 (7) | 6/58 (10) | 4/27 (6.8) |
| Anti-prothrombin IgG | 8/57 (14) | 4/58 (7) | 2/24 (8.3) |
| Antiprothrombin IgM | 16/57 (28) | 20/58 (34) | 7/24 (29) |

Values are n (%) unless stated otherwise.

Fig. 2 Kaplan–Meier survival analysis of primary outcome in the ALIWAPAS study (follow-up in years).

antioxidant agents) was analysed and we did not find any difference stratifying patients for the use of these medications.

Regarding the secondary outcome measures, predictive factors for thrombosis were evaluated in all 232 patients (15 events). No clinical or biological markers appeared to predict thrombosis (supplementary Table S2, available at *Rheumatology* Online). Looking individually at the patients with thrombotic events, we found that all but one had SLE and/or traditional risk factors for thrombosis (14/15 had SLE, 4 were smokers and 2 ex-smokers, 4 had significant family history of arterial thrombosis, 3

had a BMI > 32, 1 had hypertension, 1 had hypercholesterolemia and 1 had nephrotic syndrome).

Side effects in the LDA group were gastrointestinal symptoms [severe constipation ($n=2$) and stomach upset ($n=2$)]. In the LDA + W group, 11 patients had bleeding episodes (1 nasal and 10 menorrhagia). One patient had an allergic reaction to warfarin. Bleeding episodes were minor, with no patient needing admission to hospital. The risk difference for bleeding episodes was 13% (CI 5.9, 20) and NNH = 7.6 (CI 4.9, 17.0) ($P=0.0007$) by Fisher's exact test. NNH here refers to the number of patients to be treated with LDA + W rather than LDA for 3 years (the median length of follow-up) in order to cause one extra case of bleeding. There were no deaths during the study.

Discussion

In this study the incidence of thrombosis among the randomized patients was 1.76 events/100 persons-years at risk. Different studies have described an increased risk of thrombosis associated with aPLs [9, 10, 15, 17, 18, 28, 40]. This risk varied depending on the population included (obstetric APS, aPL-positive patients with connective tissue disease, mainly SLE, or isolated aPL), the design of the study and the treatment received. Table 2 summarizes the thrombosis rate in different populations coming from some relevant studies. Recently a case-control study reported an increased thrombotic risk in the long term in patients with a previous history of aPLs and recurrent spontaneous abortions [41]. Furthermore, other observational studies confirmed that women with purely

TABLE 2 Thrombosis rate and intervention results from studies on aPL-positive patients

| Author/year [reference] | Study/number | Thrombosis rate/100 patient-years | Intervention | Results |
|---|---|--|--|--|
| SLE Tektonidou <i>et al.</i> 2009 [10] | Ambispective/144 Cohorts | 2.09 | Aspirin HCQ | HR per month: ASA 0.98 (95% CI 0.96, 0.99) HCQ 0.99 (95% CI 0.98, 1.00) Duration of ASA and HCQ use associated with decreased thrombosis Lower incidence of thrombosis in aspirin vs observation group 1/52 (1.9) vs 2/29 (6.9) |
| Tarr <i>et al.</i> 2007 [3] | Prospective/81 | | Aspirin 52 Observation 29 | |
| APS obstetric Ruffatti <i>et al.</i> 2006 [18] Quenby <i>et al.</i> 2005 [17] | Ambispective/37 Retrospective/141 Case-control | 0 0.6 | Heparin during pregnancy | 0 thrombotic events |
| APS obstetric ± SLE Erkan <i>et al.</i> 2001 [9] | Retrospective/65 | Aspirin: 1.3 Observation: 7.4 | Aspirin 31 Observation 34 | Lower incidence with aspirin 1.3/100pts/year vs 7.4/100pts/year |
| Mixed SLE/aPL/APS Obs Ruffatti <i>et al.</i> 2009 [56] Erkan <i>et al.</i> 2007 [28] | Retrospective/370 RCT = APLASA/98 | 1.64 overall 1.33 overall: Aspirin 2.75 Observation 0 | Aspirin 48 Placebo 50 | HR 1.04 (95% CI 0.69, 1.56) Aspirin is not effective to prevent thrombosis |
| Forastiero <i>et al.</i> 2005 [29] Finazzi <i>et al.</i> 1996 [57] Giron-Gonzalez <i>et al.</i> 2004 [15] | Observational/74 Prospective Prospective/97 Prospective/360 Retrospective/178 | 2.2 overall: Aspirin 2.7 Observation 0 2.8 0.95 0 | Aspirin 61 Placebo 13 ASA 325 mg/day (pregnancy) Enoxaparin in high-risk situations | Aspirin is not effective in preventing thrombosis 0 thrombotic events |

obstetric APS are at higher risk for thrombotic complications [42, 43].

Despite being the largest prospective study attempting to address the primary thromboprophylaxis in aPL-positive patients, our main problem was the low recruitment rate. A substantial number of patients refused to participate given the possibility of being randomized to warfarin and the subsequent need for monitoring the INR, the risk of bleeding and possible interactions with other drugs. These also accounted for a large number of withdrawals in the LDA + W group.

The low recruitment rate led to a low statistical power that is seen in the size of the CIs for the primary effects: HR 1.07 (95% CI 0.27, 4.3). Specifically, these intervals are wide enough to include substantial benefit or harm due to treatment with warfarin rather than aspirin.

In addition, some issues, such as the inclusion of some low-risk patients, may explain the lower than expected rate of thrombosis seen in our study. Some patients that were positive on two separate occasions in the previous year became negative at the time of the study.

The optimal treatment to prevent the first thrombotic event in aPL-positive patients has not yet been elucidated. Data from randomized trials on LDA therapy in the general population have been recently analysed in a meta-analysis [19] showing that LDA use reduces vascular events by ~0.07%/year. This reduction is at the expense of a non-fatal myocardial infarction. However, rates of overall mortality, death due to coronary heart disease and stroke did not differ significantly between the LDA and the control groups.

Some studies suggested that the use of LDA is protective for thrombosis in aPL-positive patients [9, 10]. A retrospective study [10] including 144 SLE patients positive for aPLs and 144 SLE patients negative for aPLs found that the duration of LDA treatment played a protective role against thrombosis in aPL-positive patients, as did the duration of HCQ in both aPL-positive and aPL-negative patients. Ruffatti *et al.* [44] studied 370 patients followed up for a mean period of 5 years. The authors found that long-term thromboprophylaxis with LDA prevented the first thrombotic event in aPL-positive patients. In contrast to these observational studies, the only available randomized, double-blind, placebo-controlled study [28] did not find any difference in the rate of thrombosis between patients randomized to LDA or to placebo. The authors concluded that asymptomatic, persistently aPL-positive individuals do not benefit from LDA for primary thromboprophylaxis. In our view, this conclusion has to be viewed with caution since the sample size was small (98 patients: 48 on aspirin and 50 on placebo), the follow-up period was short (2.3 ± 0.95 years). Moreover, 42% of patients were negative for LA and had low titres for aCL. In addition, some of them were positive only for IgA aCL isotype, suggesting that this was a low-risk population [45].

The most frequent side effect of warfarin is bleeding related to the intensity of anticoagulation and other factors such as age. However, the use of warfarin for secondary

prevention of thrombosis in APS patients has not been associated with a high risk of bleeding [46]. Nine patients in the LDA + W group developed menorrhagia in our study. None of the patients needed admission to the hospital and/or blood transfusion. A meta-analysis reviewing 24 randomized trials [47], showed a 2-fold increase in the risk of gastrointestinal haemorrhage in patients on LDA vs those on placebo. Thus decisions about therapy should consider the use of LDA when the potential benefit of a reduction in the thrombotic risk outweighs the potential harm of an increase in gastrointestinal haemorrhage according to the recommendations of recently published clinical guidelines [48]. In our study only two patients (2.4%) from the LDA group discontinued the medication. We did not observe any episode of severe bleeding, although four patients suffered minor gastrointestinal side effects.

Although this study did not have the power to detect a clinically important difference in efficacy between the treatment groups, we observed a clear difference in tolerability in favour of LDA alone. Thus LDA + W appears to be a poor, unattractive therapeutic approach for primary prevention of thrombosis in this population.

Our secondary outcome measure was to investigate the role of clinical and serological risk factors for thrombosis, including demographic characteristics, conventional risk factors for thrombosis and autoantibody profile. Other studies showed that male sex, hypertension, LA positive, persistently positive aCL, cumulative presence of aPLs and medium to high titres of IgG aCL were independent risk factors for thrombosis [10, 11, 18]. None of the clinical or biological markers analysed appeared to predict thrombosis in our study.

Although the predominant antibody positivity in patients who developed thrombosis was LA (13/15), we did not find any of the measured aPLs, alone or in combination, persistently or intermittently positive, to be predictors of thrombosis. This apparent discrepancy with other studies could be due to the small number of patients recruited, different populations studied, different methods used to measure aPLs and to the fact that some of our patients had a low titre or negative aPL levels at the time of the study. Although several attempts have been made to standardize the aPL assays, a considerable degree of variation still exists [49–54].

Although we could not identify any predictive factors for thrombosis, looking individually at the patients who suffered any thrombotic events, we found that all but one had SLE and/or one of the traditional risk factors for thrombosis. In the study by Erkan *et al.* [28], all but one patient had a systemic autoimmune disease at the time of thrombosis. Giron-Gonzalez *et al.* [15] reported that 50% of patients with APS had concomitant risk factors for thrombosis at the time of the first thrombotic event. A recent prospective study [44] including 258 aPL carriers identified hypertension and LA as independent risk factors for the first thrombotic events in these patients.

Our study has some limitations. As in the majority of investigator-initiated studies, the recruitment of patients

was slower than planned. Although this study took about 6 years to complete, it was still underpowered for showing an effect of LDA + W on the incidence of thrombotic events. Similar limitations have been reported in a recent non-commercial clinical trial [55]. Our study also has several strengths. Mainly, it is the largest randomized trial exploring the primary thromboprophylaxis in aPL-positive patients.

In conclusion, no differences in the number of thrombotic events were observed between patients treated with LDA vs those treated with LDA + W. LDA alone was significantly better accepted and/or tolerated by patients than the LDA + W treatment.

Rheumatology key messages

- Primary thrombosis prevention in aPL-positive patients remains controversial.
- No differences in thrombosis rate were observed between LDA vs LDA plus low-intensity warfarin in aPL-positive patient groups.
- LDA alone was significantly better accepted and/or tolerated by aPL-positive patients than LDA plus low-intensity warfarin treatment.

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Supplementary data

Supplementary data are available at *Rheumatology* Online.

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Clinical vignette

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Cerebral toxoplasmosis following adalimumab treatment in rheumatoid arthritis

A 67-year-old man with a 24-year history of RA underwent anti-TNF- α treatment with adalimumab (s.c. application 40 mg every 2 weeks) due to failure of prior standard treatments. The clinical response was satisfactory. However, 3 months later the patient developed headaches as well as gait and speech disturbances. At admission, neurological examination showed a normal level of consciousness, bilateral peripheral facial palsy and mild left hemiparesis. Brain MRI revealed a round-shaped rim-enhancing lesion centred in the right thalamus (Fig. 1) disclosing increased water diffusivity on an apparent diffusion coefficient map (not shown).

Diagnostic stereotactic brain biopsy revealed perivascular lymphocytic infiltrate with areas of necrosis; PCR amplification for *Toxoplasma gondii* was positive. The patient had no risk factors for toxoplasmosis. Adalimumab treatment was discontinued and treatment with pyrimethamine, sulphadiazine and folinic acid was given for 8 weeks. At that time, clinical examination revealed only bilateral facial palsy. The IFN- γ adalimumab-related inhibitory effect may favour *T. gondii* replication and reactivation [1]. Together with the report of two patients who developed toxoplasmic chorioretinitis [2], our case report illustrates the increased risk of toxoplasmosis in RA patients treated with anti-TNF- α therapy.

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FIG. 1 T2-weighted image demonstrates a large mixed-intensity right thalamic protozoan lesion (arrow).

