Antiphospholipid syndrome (APS) is one of the most frequent acquired thrombophilias. Thromboses can be at both the venous and arterial level, are usually recurrent and frequently affect cerebral circulation. Although it is difficult to predict which patients with antiphospholipid antibodies (aPL) will develop thrombosis, once a thrombotic event has taken place, secondary prevention is mandatory. Recommendations for treatment of APS have long been based on studies with a retrospective design. Recently, three prospective studies (two controlled and one uncontrolled small series) have addressed the role of antiaggregant and anticoagulant therapy in patients with stroke and aPL. However, results from prospective and retrospective studies are not in full agreement. In addition to the obvious differences in design, other factors such as the important variability in the study groups account for the discrepancy. While future investigation must better define homogeneous subsets of patients with APS, current secondary prophylaxis of thrombosis in these patients must be tailored according to individual estimated risk of recurrences, risk of haemorrhage and severity of potential recurrent events. Due to the often devastating consequences of stroke, we believe there is a place for prolonged, high-intensity anticoagulation in patients with APS and cerebral arterial thrombosis.

Antiphospholipid syndrome (APS) is defined by the development of thrombosis and/or adverse obstetric events in the presence of antiphospholipid antibodies (aPL) [1]. This syndrome was described in great clinical detail in the early 1980s [2] and is nowadays considered to be one of the most frequent acquired thrombophilias [3]. Patients with aPL have been shown to be at a higher risk of recurrent thrombotic events in prospective studies, both at the venous [4, 5] and arterial level [6, 7].

The cerebral circulation is particularly affected in APS. Cerebrovascular disease carries high mortality and morbidity, with important and often disabling sequelae. Thus, preventing recurrent thrombotic stroke is one of the main therapeutic goals in APS [8]. On the other hand, antiaggregant and anticoagulant therapy are not free from serious side-effects [9]. Thus it is not surprising that an important debate follows the search for the optimal treatment of stroke in APS [10].

Data on the therapeutic approach to stroke in patients with APS are scarce. Until recently, only retrospective studies were available [11–14], with the resulting risk of bias and a high degree of uncertainty. Fortunately, two prospective controlled studies [15, 16] and a small prospective case series [17] have been published in recent months. However, resulting data are conflicting.

Early retrospective studies

While stroke was recognized as a major feature of the syndrome in the earliest descriptions [2], the first therapeutic data to come from retrospective studies were published between 1992 and 1995. Rosove and Brewer [11] studied 70 patients with thrombosis (44% arterial) and aCL and/or lupus anticoagulant (LA). Repeated positivity or medium to high titres of aCL was not a requirement for entering the study; however, only 17% of patients had low-titre aCL. Khamashta et al. [12] analysed 147 patients with venous (54%) or arterial thrombosis (46%). Repeated medium to high titres of aCL and/or LA were needed for inclusion in the study.

These two studies suggested the need for prolonged anticoagulation in APS patients with thrombosis. The risk of recurrent events was higher in those who were untreated or given aspirin alone than in those receiving warfarin. It is notable that the highest risk period for thrombosis was 6 months after stopping anticoagulation [12]. Further, the studies by Rosove and Brewer [11] and Khamashta et al. [12] found a dose-related effect of oral anticoagulation, i.e. patients aimed to a target International Normalized Ratio (INR) ≥3.0 had a significantly lower risk of recurrent thrombosis than those aimed at less intense anticoagulation.

In 1997, Krnic-Barrie et al. [13] published a retrospective review of 61 patients with APS. Thirty eight patients (62%) had presented with arterial events. Medium to high titres of aCL and/or LA were required for the diagnosis of APS. These authors analysed the influence of treatment on the rate of recurrent arterial and venous thrombosis. Aspirin decreased arterial events as compared with untreated patients, although statistical significance was not reached (relative risk 0.43; 95% CI 0.13–1.37). The difference was statistically significant, however, between untreated patients (0.192 events per patient-yr) and those receiving warfarin (0.051 events per patient-yr), with a resulting relative risk of 0.26 (95% CI 0.11–0.64). The intensity of oral anticoagulation was measured in a minority of patients, thus not providing relevant data on their different efficacies.
New data

In 2002, we performed a retrospective analysis during the course of 1 yr for 66 patients with definite APS according to the Sapporo criteria—i.e. all patients having persistently positive aCL at medium to high titres and/or LA who were treated with warfarin to a target INR 3.0-4.0 [14]. Thrombotic and bleeding events were recalled by the patients themselves during personal interviews and also documented from medical records. Seventy-seven per cent of patients had a history of arterial thrombosis, 75% of whom had suffered a previous stroke.

This study showed that, in real clinical practice, INRs were frequently below the desired range, although INRs lower than 2 were infrequent. We observed a low rate of life-threatening bleeding (four episodes of major bleeding or six events per 100 patient-yr; 95% CI 1.6-15), with only one episode of intracranial haemorrhage—probably precipitated by head trauma—and, remarkably, no fatal events. The potential of APS for recurrent thrombosis was shown by the high rate of thrombotic event seen (six cases, or nine episodes per 100 patient-yr; 95% CI 3.3-19.6). Four of these recurrent events took place in the arterial bed. Interestingly, INRs were documented in all but one patient at the time of recurrence and found to be between 2.1 and 2.6, values within the usual therapeutic range of oral anticoagulation.

In 2003, Derksen et al. [17] reported on the clinical course of eight women with APS presenting with a stroke (all positive for aPL on at least two occasions and seven of them positive for LA) who were prospectively followed up after starting treatment with low-dose aspirin only. They found that after a median follow-up of 8.9 yr, the frequency of recurrent thrombotic events was similar to that expected in aPL-negative patients with stroke (3.5 events per 100 patient-yr; 95% CI 0.4-12.5). This study raised the possibility that antiaggregation may be enough for patients with APS presenting with arterial ischaemic cerebrovascular events.

Also in 2003, Crowther et al. [15] published the only randomized clinical trial comparing the efficacy of different intensities of anticoagulation in the secondary prophylaxis of thrombosis in patients with APS. The study enrolled 114 patients with APS and previous confirmed thrombosis who were randomized to either moderate-intensity (INR 2.0-3.0) or high-intensity (INR 3.1-4.0) oral anticoagulation. Repeated positivity for aCL at medium to high titres and/or LA was a requirement for entering the study. This trial had a double-blind design and included an intention-to-treat analysis.

Recurrent thrombotic events were seen at a lower than expected rate (7% of the whole population after a mean follow-up of 2.6 yr). Patients randomized to high-intensity anticoagulation had a higher, though non-significant, rate of thrombosis than those in the moderate-intensity group (10.7 vs 3.4%; hazard ratio 3.1; 95% CI 0.6-15). Neither minor nor major bleeding events were different between both groups. The main conclusion of this study was that a usual INR range of 2.0-3.0 is enough for preventing re-thrombosis in patients with APS.

The most recent prospective data on APS and stroke came in early 2004 with the publication of the Antiphospholipid Antibodies and Stroke Study, or APASS [16]. The authors aimed to define the role of aPL in predicting recurrent strokes and response to therapy. They took advantage of the Warfarin vs Aspirin Recurrent Stroke Study (WARRS), a randomized clinical trial started in 1993 comparing aspirin with low-intensity anticoagulation (INR 1.4-2.8) for secondary prevention of stroke. Blood samples were stored from 1770 patients (80% of WARRS participants), and aCL (including IgG, IgM and IgA isotypes) and LA were determined. Seven hundred and twenty patients (41% of WARRS participants included) tested positive for aPL. However, many of them did so at a low titre of aCL (190 IgG, 58 IgM and 134 IgA). Only 120 patients (6.7%) were positive for both aCL and LA and only four patients (0.2%) had IgG aCL at high titres.

The results of APASS showed similar frequencies of the primary end points (death, recurrent ischaemic stroke, transient ischaemic attack, myocardial infarction, peripheral or visceral artery thrombosis and venous thromboembolism) among aPL-positive and aPL-negative patients after 2 yr of follow-up: death from any cause, 3.6 vs 3.3%; stroke 11.3 vs 10.7%; transient ischaemic attack 4.0 vs 6.8%; and so forth. However, the subgroup of patients positive for both aCL and LA were more likely to suffer recurrent thrombotic events as compared with aPL-negative patients (hazard ratio 1.36; 95% CI 0.97-1.92). Response to warfarin or aspirin was uniformly similar among patients with and without aPL.

Accordingly, the two main conclusions of the authors of the APASS study were: (1) testing for LA or aCL did not confer important knowledge for prognosis or treatment of patients with recently diagnosed ischaemic stroke; (2) warfarin was not associated with fewer thrombotic events than aspirin among patients with aPL and stroke [16].

Critical review

Retrospective design has important intrinsic limitations in studies focused on therapy, including the non-randomized assignment of treatment, the potential for an important amount of missing information and patient recall bias.

All retrospective studies presented above are subject to these serious limitations. In addition, only the study by Kmiec-Barrie et al. [13] separately analysed arterial and venous events. This is an important point, as remarked on by Derksen et al. [17], since aspirin is less useful in prophylaxis of venous thromboembolism and this form of analysis may underestimate its effect on preventing recurrent arterial events. Regarding the intensity of anticoagulation, the studies by Rosove and Brewer [11] and Khamashta et al. [12] classified patients according to target, not actually achieved, INRs.

However, and despite these and other potential flaws, all the retrospective studies had the strength of including populations who, probably or definitely, had APS according to currently accepted criteria [1]. Medium to high titres of aCL and/or LA were required in all but Rosove and Brewer’s study [11], but even in this study, patients with low-titre aCL were remarkably few. Repeated positivity for aPL was expressly needed in the studies by Khamashta et al. [12] and Ruiz-Irastorza et al. [14]. Moreover, patients with previous recurrent events and those with APS secondary to systemic lupus erythematosus were included in the analyses, thus accounting for populations of patients with a particularly high-risk APS, as shown by the high rates of recurrent thrombosis among untreated patients.

The second strength of retrospective series is the consistency across the different studies in showing fewer recurrent events among patients treated with warfarin than in those treated with aspirin [11–13], less thrombosis in patients with high-intensity anticoagulation [11, 12] and a low to moderate risk of severe bleeding complications [12–14]. In addition, patients with INR documented at the time of thrombosis were almost exclusively below 3.0, though in many cases above 2.0 [11, 12, 14].

The series by Derksen et al. [17] was the first group of patients with APS and stroke who were prospectively followed up for a prolonged period of time. The authors applied stringent criteria for the diagnosis of APS. The main weakness of this study is the very small sample size, with the resulting wide confidence interval for the risk of recurrent thrombosis (0.4 to 12.5 events per 100 patient-yr). This notably overlaps with that obtained by
Ruiz-Irastorza et al. [14] in patients treated with high-intensity oral anticoagulation (3.3 to 19.6 events per 100 patient-yr), reflecting the great variability of APS in terms of risk of recurrence.

The study by Crowther et al. [15] had, on paper, an optimal design, including double-blindness and intention-to-treat analysis. However, there were some important issues. First, patients having recent strokes were excluded; as an expected consequence, 76% of patients had venous thrombosis only. Patients with thrombosis under anticoagulant treatment were also excluded and those with SLE were few (16 patients). Thus, and despite the stringent criteria regarding aPL positivity, the population chosen by Crowther et al. was certainly at a lower risk of recurrent events than those included in retrospective series, a fact that is illustrated by the lower rates of thrombotic recurrences they found.

Another important limitation of this trial is that patients in the high-intensity group were below the ‘therapeutic range’ 43% of the time, therefore high-intensity anticoagulation was only partially achieved. Not surprisingly, most thrombotic episodes in both groups (six out of eight) took place when INRs were lower than 3.0, a fact that is actually in agreement with data from retrospective studies.

Apart from the prospective design, the APASS study [16] has the main advantage of its large sample size. However, this study is actually a subgroup analysis of a trial that was designed to compare the efficacy of antiaggregants and oral anticoagulants to prevent recurrences in the general population with stroke. In fact, the huge proportion of aPL-positive patients in an unselected population of patients with stroke averaging 63 yr of age can only be explained by the few stringent entry criteria: single aPL determination, including aCL of the IgA isotype, admitting low-titre aCL only and LA not performed according to international recommendations [1]. Thus, as opposed to retrospective series [11–14] and the studies by Dørksen et al. [17] and Crowther et al. [15], most patients included in APASS did not have APS. It is noteworthy that the minority of patients positive for both aCL and LA—maybe some of them with ‘real’ APS—had a worse outcome. Moreover, the lack of different outcome between aPL-positive patients treated with aspirin or warfarin may actually support the idea that oral anticoagulation to an INR below 3.0 (the range in the study was 1.4 to 2.8) is not enough for patients with APS and arterial events.

Due to these limitations, the results of APASS were immediately criticized after their publication [18–20]. In fact, the authors themselves acknowledged that their results could not be generalizable to younger patients or those with other manifestations of APS [16].

What can be concluded from current data?

Patients presenting with stroke who fulfil criteria for definite APS should be considered at high risk for recurrent events. This may be particularly true in those with already recurrent disease and in patients with SLE, in whom APS has been shown a major determinant of long-term outcome [21]. Other populations with stroke, such as those with transient, low-titre aCL, should not be considered different from the general population with cerebrovascular disease [10].

Published data suggest a marked variability of risk for recurrences among patients who fulfil criteria for APS. Thus, a standard therapeutic approach would certainly not be applicable to all patients.

Published data show, however, that the frequency and severity of bleeding complications is not high in patients with APS treated with oral anticoagulation, even at target INRs >3.0 [14, 15, 22], maybe due in part to the lower age of this population as compared with, for example, patients with chronic atrial fibrillation [14]. In addition, while recurrent thromboses are exceptional with INRs >3.0, many cases have been documented within the ‘usual’ therapeutic range of 2.0–3.0 [14, 15].

Thus, the assumption that intermediate-intensity anticoagulation (i.e. target INR 2.0–3.0), or even antiaggregant drugs only, can be safely indicated in all patients with definite APS and stroke seems unjustified on the basis of currently available evidence. Therefore, specific therapy must be determined on an individual basis, taking into account the severity of the initial thrombotic event, the concurrent presence of other vascular risk factors or additional thromboses and the estimated bleeding risk according to age, bleeding history and polypharmacy [23]. The presence of LA [24] and, probably, very high-titre aCL should be also borne in mind when deciding the optimal treatment for a given patient. Accordingly, high-intensity oral anticoagulation would be justified in a sizeable number of patients with APS and stroke.

Future well-designed trials will hopefully help us stratify risks in populations with APS. They should also better define the role of current and future drugs, such as statins, hydroxychloroquine and ximelagatran [25], in the management of this condition.

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References


