The article by Cuadrado et al. [3] published in this issue reports on a randomized trial comparing the effect of low-dose aspirin (LDA) vs LDA plus low-intensity warfarin (LDA+W) in the primary prophylaxis of aPL carriers selected from patients with SLE and from women with pure obstetric APS. By following up 166 patients for nearly 4 years, this study is the largest and the most long-lasting controlled trial for the primary prevention in aPL carriers ever published. Despite these strengths, the trial could not reach a definite conclusion. The authors identified some issues that limited the power of the trial. All points are important and need to be discussed as lessons to be learned in designing future studies.

The first problem was the low recruitment rate. The novel and breakthrough combination therapy of LDA+W was unattractive and many patients refused to participate. We presume that aPL carriers did not feel motivated to comply with a drug regimen that carries the risk of bleeding and requires frequent blood sampling and lifestyle modifications. Therefore the first lesson to be learned is that drugs used in primary prophylaxis need to be acceptable to individuals who only carry a risk factor and do not generally perceive themselves as sick.

A second problem was that the inclusion of low-risk patients may explain the lower than expected rate of thrombosis seen in the study. When the trial was designed, the relevance of the serological profile in risk stratification was not as clear as it is today. It is now well accepted that patients should be assessed for a complete aPL profile, including lupus anticoagulant (LA), aCL, and anti-β2-glycoprotein I antibodies [4]. A general consensus exists on the high-risk profile being characterized by positive LA, high IgG titre and triple positivity for aPL tests [5]. There is evidence that this group of aPL carriers are those who are at more risk of developing the first thromboembolic event [6]. Thus the second lesson to be learned is that a trial focusing on the primary thromboprophylaxis is more likely to be informative if only patients with a clinically significant aPL profile are enrolled.

A third problem is the analysis of concomitant risk factors for thrombosis. The authors [3] reported that thrombosis occurred in all but one patient who carried such factors, even though none of these factors could be considered an independent predictor of the event. We are all aware that thrombosis is a multifactorial process, therefore the third lesson to be learned may be that the presence of concomitant vascular risk factors and/or a systemic autoimmune disease should be taken into consideration for risk stratification in any study dealing with the primary prophylaxis [5]. But this is only one aspect of the risk assessment: the other important aspect is the timely recognition of high-risk conditions. It is assumed in clinical practice that situations such as immobilization, puerperium and long-haul flights may trigger the thrombotic process by acting as a second hit [7]. The prophylaxis of these high-risk situations with low molecular weight heparin (LMWH) was demonstrated to be more efficacious than continuous prophylaxis with LDA in reducing thromboembolic events in a large prospective cohort [8]. As clinicians, our feeling is that proper management of high-risk situations may prevent most of these events. Therefore we believe that a study dealing with primary thromboprophylaxis should take this variable into account.

As discussed, a crucial issue is the choice of medication. It must be acceptable to individuals who carry a risk factor. HCQ is a drug of interest [9], being generally well tolerated and not requiring any particular monitoring, with the exception of periodic eye examinations. Experimental data have shown the anti-inflammatory and anti-platelet activity of HCQ, possibly accounting for the protective effect of HCQ against thrombosis that was demonstrated in several studies [5]. Statins are also worth mentioning because they have been shown to be able to reverse the proinflammatory and procoagulant state induced by aPL [9]. Cuadrado et al. [3] did not find any benefit in patients who were taking HCQ or statins in addition to the trial medications. But the study was not focused on these aspects, and the number of patients on HCQ/statins may have been too low to see any difference. Turning to
molecules that are not classical drugs, vitamin D is a novel actor on stage. In vitro studies have shown that vitamin D is capable of reversing aPL-induced thrombogenicity [10]. Epidemiological data are in line with this observation, as it was reported that APS patients frequently have insufficient levels of vitamin D, and those with thrombosis have significantly lower vitamin D levels compared with those with pure obstetric APS [10].

Does any aPL carrier need a chronic pharmacological intervention to prevent thrombosis? Probably not. The low thrombosis rate observed in aPL carriers [7] is similar to that reported by Cuadrado et al. [3] (1.8 events/100 person-years), which makes us ponder whether the risk of bleeding associated with LDA (which is currently the most widely used drug in aPL primary prevention) may be greater than the benefit of thrombosis prevention [7]. The high-risk profile patients may be those who are good candidates for primary prophylaxis with LDA [5], but they are also the right target population for any other drug that may undergo a trial for primary prophylaxis in aPL carriers. This setting would also be the best one to check the efficacy of LMWH in the management of high-risk situations.

In conclusion, the primary prophylaxis of thrombosis in aPL carriers is still an open field and there are possible strategies to improve treatment. In our opinion, the important points are that studies need to be prospectively designed, with a large, multicentre and well-characterized population, the drug or intervention must be acceptable, only individuals with a high-risk aPL profile should be enrolled and concomitant risk factors must be thoroughly analysed, with particular focus on the use of LMWH in high-risk situations.

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