

Lupus and Thrombosis



You cannot convince people with the facts when they have already made up their minds¹

When a patient with systemic lupus erythematosus (SLE) develops thrombosis, the immediate diagnostic consideration is antiphospholipid syndrome (APS). If the tests for antiphospholipid antibodies (aPL) are positive, the diagnosis of APS is usually confirmed without particular attention to the causal association or confounding factors (i.e., the aPL profile/persistency and the presence or absence of other transient/persistent thrombotic risk factors). If tests for aPL are negative, the diagnosis of “seronegative APS associated with lupus” is sometimes entertained. Because this clinical scenario is not uncommon, it is important to review a couple of “facts,” especially for those who have not yet made up their minds.

The risk of thrombosis for a patient with SLE is significantly higher than for the general population. Independent of aPL, due to the increased incidence of traditional cardiovascular and nontraditional lupus-related thrombosis risk factors (Table 1), SLE patients are at significantly increased risk of premature atherosclerosis and/or thrombosis^{2,3}. The prevalence of vascular events in SLE patients ranges between 10% and 30%^{4,5}, for symptomatic coronary artery disease 6–20%^{6–8}, stroke 2–15%^{7–9}, and subclinical coronary artery disease 30–40%^{6,10}. A Patient Discharge Database analysis has estimated that women with SLE aged 18–44 years are hospitalized with myocardial infarction or stroke almost 9 times more often than the general population⁷.

Risk of thrombosis in the general population rises with age and increasing number of thrombosis risk factors¹¹. Patients with SLE, who are already at increased risk for thrombosis, are also susceptible to thrombosis triggers or the risk associated with genetic hypercoagulable states (Table 1). For instance, an association between homozygous mannose-binding lectin variant alleles and an increased risk

of arterial thrombosis in patients with SLE (after adjustment for age, sex, hypertension, smoking, and aPL) has been suggested¹²; similarly, the presence of factor V Leiden and prothrombin mutations may increase the risk of venous thrombosis in aPL-positive SLE patients¹³.

Not every positive aPL test is diagnostically and clinically significant in SLE patients. Interpretation of a significantly positive aPL test in SLE patients should take into account the following rules: Transient aPL positivity is common in the general population, especially during infections, and thus the documentation of the persistence (at least 12 weeks apart) of autoimmune aPL is crucial¹⁴; a positive lupus anticoagulant test is a more specific but less sensitive predictor of aPL-related events than is anticardiolipin antibodies (aCL)¹⁵; moderate to high titer aCL IgG/M (> 40 U as per the updated APS classification criteria¹⁴) and/or anti- β_2 -glycoprotein I IgG/M antibodies are more strongly associated with aPL-related clinical events than are low titers; and multiple positive aPL tests impart a worse prognosis than does any single type of test. Further, a significant aPL profile may not be clinically relevant (i.e., responsible for the thrombotic event) in every SLE patient; although cross-sectional and prospective cohort studies demonstrate a predictive role of aPL for future vascular events, the strength of association varies among studies (from none to strong) and a confirmed direct causal pathway between aPL and thrombosis in humans does not yet exist^{16,17}.

Thus, the presence of a significant aPL profile is only one of the risk factors for thrombosis, and it is common for patients with SLE to develop thrombosis in the absence of aPL^{2,3,6,18}. Indeed, a recent LUMINA (LUpus in MINorities, NAture versus Nurture) cohort analysis has demonstrated that older age, smoking, longer patient followup time, elevated C-reactive protein levels, and the presence of aPL are independent risk factors for vascular events¹⁹. In addition, a recent Hopkins Lupus Cohort analysis has demonstrated

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Table 1. Factors that contribute to the increased risk of premature atherosclerosis and thrombosis in lupus patients^{2,3}.

• Demographic characteristics
Age, gender, ethnicity
• Increased prevalence of traditional cardiovascular risk factors
Hypertension, diabetes mellitus, proatherogenic lipid profile, elevated homocysteine levels, obesity, sedentary lifestyle, early menopause
• Acquired lupus-specific risk factors
Chronic inflammation, renal disease, corticosteroid use (controversial), vasculitis, Libman-Sacks endocarditis, anti-oxidized LDL antibodies, elevated C-reactive protein and proatherogenic cytokines
• Acquired thrombosis triggers
Smoking, oral contraceptives, hormone replacement therapy, pregnancy, prolonged hospitalization, immobilization, surgical procedures
• Genetic hypercoagulable states
• Persistent antiphospholipid antibodies
Positive lupus anticoagulant test, moderate-to-high titer anticardiolipin and anti- β_2 -glycoprotein-I antibodies

that interethnic differences exist in the incidence of thrombotic events in SLE patients⁸.

Keeping these “facts” in mind, in this issue of *The Journal*, Chang, *et al* describe the incidence pattern of the first occurrence of thrombosis in a cohort of 426 SLE patients in which one-fourth of patients had at least one thrombotic event²⁰. The majority of patients are Caucasian and female. The authors conclude that: (1) The incidence rate (IR) of arterial or venous thrombosis is highest during the first year of SLE diagnosis (IR 4.0, 95% CI 2.2–6.6), with a remarkable increase within the first month of SLE diagnosis (IR 24.8, 95% CI 10.7–48.9); and (2) the incidence rate of arterial thrombosis, but not venous, increases over the course of the disease. Interestingly, these results are consistent with another Canadian Lupus Cohort that has demonstrated that patients with SLE have a relatively higher incidence rate of thrombosis during the first year of diagnosis²¹.

The limitations of Chang’s descriptive, but hypothesis-generating, retrospective study are obvious. First, neither the above-mentioned thrombosis risk factors (including aPL or possible SLE flare-related hospitalizations/immobilizations) nor the effect of age have been incorporated into the analysis. Second, as the authors also note, selection bias is a major consideration, since patients with SLE might have sought medical care for the first time as a consequence of an acute thrombosis; another factor affecting the generalizability may be referral bias, since patients with more severe SLE might have been referred to the tertiary academic center sooner than less severe patients (the shorter time to the first clinic visit from the initial SLE diagnosis in patients who had early thrombosis can be interpreted as evidence of this referral bias). Third, there was no attempt to stratify patients by disease activity or severity at the time of diagnosis:

patients with severe lupus disease activity likely have a different thrombosis risk profile than patients with mild to moderate disease activity. Fourth, methods for outcome measure ascertainment might have resulted in information bias, especially for softer outcomes such as “transient ischemic attack” or “angina.” Finally, even if the authors investigate the incidence pattern of the first thrombosis, patients with history of arterial events were not excluded from the analysis of “first venous thrombosis” and patients with history of venous events were not excluded from the analysis of “first arterial thrombosis.”

Despite these internal and external validity limitations of the study, Chang, *et al* take a “bird’s eye view” approach to describe the thrombosis incidence rate in patients with lupus. In their cohort, the prevalence of arterial events is 3 times more common than venous events, which supports the atherosclerotic nature of SLE. Moreover, their findings further support the positive association between systemic inflammation and thrombosis²², and generate an interesting question: Do active lupus flares, compared to subclinical or no lupus activity, put SLE patients at a higher risk for acute thromboses?

Although their study cannot answer the question above, based on our current knowledge it is fair to say that the presence of SLE (i.e., chronic systemic inflammation) is (1) an independent risk factor for development of atherothrombotic disease over the long term^{22–25}; and (2) a risk factor for the development of thrombosis in persistently aPL-positive patients²⁶. Of note, thrombotic events occur more often in aPL-positive patients with lupus compared to aPL-positive patients without lupus or with other systemic autoimmune diseases²⁶; and there is a higher mortality risk in patients with catastrophic APS with lupus, compared to those without lupus, after adjusting for age, sex, organ involvement, and treatment (Bayraktar D, *et al*, unpublished data).

While the cardiovascular risks associated with SLE have been increasingly recognized, the routine screening of cardiovascular risk factors has not been fully incorporated in the management of patients with SLE^{25,27}. Thus, it is essential that thrombosis risk factors be investigated extensively and regularly in every patient with SLE (i.e., in addition to investigating aPL) and treated rigorously when possible. While the evidence-based effectiveness of aspirin, hydroxychloroquine, statins, or any combination of these medications in primary thrombosis prevention of patients with SLE remains to be determined, aggressive management of clinical and subclinical SLE disease activity seems to play an important role in the prevention of atherothrombotic disease.

In summary, lupus patients are at significantly increased risk for premature atherosclerosis and thrombosis, which is a multifactorial process. A risk-stratified approach to thrombosis risk assessment (i.e., lupus disease activity/severity, traditional and lupus-related as well as acquired and genetic thrombotic risk factors, and aPL profile) is important in the

management of lupus patients; however, there are no evidence-based recommendations yet for the primary thrombosis prevention. Current and future clinical lupus trials²⁸ hopefully will further advance primary thrombosis prevention strategies.

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