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Letter to the Editor

Cor homini lupus? Identification of risk factors implicated in cardiovascular events in patients with Systemic Lupus Erythematosus in Romania

Cardiovascular disease (CVD) accounts for up to 35% of mortality in patients with systemic lupus erythematosus (SLE) [1]. Emerging evidence supports that SLE disease activity is associated with up to two times higher cardiovascular (CV) risk than traditional risk factors [2]. According to an interesting recent study of Salvetti et al. left ventricular function in premenopausal women suffering from SLE was inferior compared to control subjects matched for sex, age, body mass index (BMI), blood pressure and antihypertensive therapy. Moreover, the femoral and carotid pulse wave velocity were affected by the treatment of SLE with steroids [3]. These findings suggest that younger SLE patients are not spared from cardiovascular disease [1]. Hence, identifying further risk factors associated with CV events in SLE is essential, in order to improve CV care and decrease CV morbidity and mortality among these patients.

Although, CVD mortality in SLE has been investigated since 1995 [4], there is a decline in relevant studies emphasizing on European populations. Particularly in Eastern Europe, there have been less than ten relevant publications in Pubmed-indexed journals since 2013. Taking into account the recent efforts to create an SLE cardiovascular risk equation across the globe [5], it is important to pay attention to risk factors implicated in CVD among SLE patients at a regional or national level. In this letter, the authors report early findings of a relevant prospective follow-up/observational study in a major university hospital in Bucharest, Romania.

This analysis is based on data from 170 SLE patients from the Dr. Ion Cantacuzino Hospital in Bucharest, Romania, enrolled in our non-interventional cohort study between January 2015 and July 2019. The Pearson chi-square test was performed for the analysis of categorical variables, whereas continuous ones were compared utilizing the Student's t-test. SPSS Statistics for Windows, Version 26.0 (Armonk, NY: IBM Corp) was employed, in order to identify statistically significant (p value <0.05) risk factors for the development of CVD in the medical history of SLE patients.

The mean age of the patients was 48.4 $\pm$ 13.2 years. The vast majority of them (96%) were women and the mean disease duration was 11.1 $\pm$ 8.1 years. Participants were diagnosed with SLE at a mean age of 37.2 $\pm$ 12.6 years. Every study participant had at least one comorbidity and almost half of them suffered from dyslipidemia or hypertension (49% and 41%, respectively). Obesity (BMI>30) was encountered in every 5th patient, whereas diabetes mellitus and smoking history were equally present in 11% of the patients. Regarding CVD, 27% of participants suffered from coronary artery disease and 15% of them had heart failure. Additionally, valvular disease and vasculitis were equally observed in 11% of study population, whereas anemia and lymphopenia were present in every 4th participant. 1 out of 3 patients was under rate-control (b-blockers) and aspirin or statin were both prescribed in 25% of study participants. As for SLE management, most of the study participants were under medium or low dose of corticosteroids (35% and 38%, respectively), while hydroxychloroquine, vitamin D and azathioprine were commonly used (68%, 62% and 31%, respectively).

CVD was significantly more frequently encountered in older patients with SLE (aged older than 50 years; $p<0.001$). Participants with comorbid dyslipidemia, as well as those with hypertension suffered significantly more often from CVD ($p=0.028$ and 0.008, respectively). Regarding the non-traditional risk factors associated with CVD in SLE patients, none of them was significantly associated with CVD development in our cohort, even if there was a trend towards greater incidence of CVD in patients under non-steroid anti-inflammatory drugs (NSAIDs; $p=0.074$).

The analysis of patients' history also yielded that antiphospholipid syndrome was significantly associated with higher stroke incidence ($p=0.010$). Moreover, patients with duration of SLE greater than 5 years suffered more frequently from CVD, compared with those with SLE for less than 5 years ($p=0.049$). Pulmonary embolism was observed more often in patients receiving high dose of corticosteroid treatment ($p=0.001$), while a higher incidence of deep venous thrombosis occurred in patients with anemia and nephritic syndrome ($p=0.022$ and 0.031, respectively). Finally, patients with diabetes mellitus suffered significantly more often from arrhythmias, heart failure and coronary artery disease (0.011, 0.048 and 0.049, respectively).

Overall, SLE constitutes a complex syndrome, associated with increased risk for accelerated atherosclerosis and CV events, including coronary heart disease [1]. In this cohort of Romanian patients, we showed that some traditional risk factors were significantly associated with higher prevalence of CVD, although these initial results should be interpreted in the context of the absence of multivariable adjustment and the nature of this study. To our knowledge, this is the first study to investigate the significance of traditional and non-traditional risk factors for CVD in Romanian patients with SLE. These data could facilitate the development of a population-based SLE cardiovascular risk equation in conjunction with similar studies, enabling personalized medicine approaches in these patients. Incorporating imaging in this effort should be considered with an eye on a recent meta-analysis by Di Minno et al. indicating the efficacy of speckle tracing echocardiography in the detection of right and left ventricular dysfunction in SLE patients [9]. The study of Salvetti et al. has been alarming in this regard, given that

Paraphrasing the popular latin proverb "homo homini lupus (a man is a wolf to another man)". "Cor (heart in latin) homini lupus" refers to the cardiovascular implications of SLE indicating that cardiovascular disease adds up to SLE morbidity and mortality

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imaging highlighted significant CV disparities between patients with SLE and matched controls. On the contrary, the clinical components of the Framingham risk score or the 24-hour blood pressure monitoring failed to do so [3]. Treat-to-target approaches to SLE have recently questioned the efficacy of the Framingham score in predicting CVD mortality in these patients [10]. Therefore, further investigation of CVD risk factors in SLE at the level of specific populations is necessary.

The well-known traditional risk factors – dyslipidemia, diabetes mellitus, hypertension, history of coronary artery disease, metabolic syndrome, increased age – fail to totally account for the increased prevalence of adverse CV events (due to accelerated atherosclerosis) in these patients. Underlying autoimmune mechanisms, disease-specific factors, such as antiphospholipid antibodies and lupus nephritis, and drug treatment effects (e.g high prevalence of hypertension, dyslipidemia and insulin resistance in the use of corticosteroids) are the three principal etiologic factors explaining the increased CV risk in the absence of traditional risk factors. The definition of the relative weight of each of these factors in patients with SLE still remains elusive, but challenging. In addition, the issue gets even more complicated taking into account the different genetic background and the heterogeneity of genetic expression among studied populations.

Heretofore, several, but relatively few, previous studies have attempted to both identify the incidence of traditional and non-traditional risk factors in a cohort of lupus patients, and evaluate their importance in developing CVD. In a 3-year follow-up cohort in Brazil, C. Monção et al. [6] concluded to results similar to ours, indicating that dyslipidaemia is the most strong predictor of CVD in these patients. Additionally, in a multi-ethnic cohort, Sergio Toloza et al. [7] supported that a combination of traditional and non-traditional baseline risk factors should be blamed for the significant occurrence of CV events in SLE. Smoking, elevated serum levels of C-reactive protein and antiphospholipid antibodies (indicating high levels of inflammation) were among the strongest. At the same time, a retrospective, cross-sectional analysis in China showed that increased age, higher diastolic blood pressure, higher serum creatinine levels, long-term use of glucocorticoids, and lower high density lipoprotein levels are independent risk factors for the development of CVD [8].

The reported observational analysis was performed to feature baseline predictors of hazard for CV events, being simply a snapshot of CVD risk assessment in our study. These early findings are expected to be complemented by the results of the follow-up process in our patients, which is going to provide evidence about the significance of the association between these CVD risk factors with the outcomes of this Romanian population suffering from SLE. Hence, the risk factors that will be strongly correlated with higher rates of adverse clinical events can be correlated with imaging studies taking into account the emerging relevant evidence [2,9]. In the long run, it is possible to incorporate translational research to this approach in an effort to trace genetic traits increasing the CV risk of these patients.

In conclusion, tracing ethnic differences in cardiovascular risk factors of SLE has lately become quite relevant. With an eye on precise medicine, it is pivotal to increase awareness towards this research trend globally and particularly in the Eastern Europe region.

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