Editorial

Cardiovascular risk in patients with Sjögren's syndrome: is it time for a new approach?

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The risk of cardiovascular (CV) disease in patients with Sjögren's syndrome (SS) may now be considered an extra-glandular feature of the disease as growing and convincing evidence supports that the disease, like other systemic autoimmune disorders, is characterised by higher prevalence of subclinical atherosclerosis and increased risk of major CV events in comparison to the general population (1-3). In this scenario, the demonstration that, like rheumatoid arthritis, prevalence of subclinical atherosclerosis in SS is comparable to patients with diabetes mellitus, which is managed as a coronary heart disease equivalent, is relevant and suggests the importance of CV screening and prevention procedures in SS patients, as in patients with diabetes mellitus (4). Moreover, there is sound theoretical underpinning that, although more prevalent in SS patients, traditional CV risk factors do not fully account for the increased CV morbidity and that concomitant, interacting immune-mediated and inflammatory mechanisms significantly contribute to the pathogenesis of CV damage in these patients (2, 5, 6).

However, despite the significant improvement in the knowledge of mechanisms associated with CV risk in SS and the availability of international recommendations for its management in patients with systemic connective diseases, including SS (7), the magnitude of the problem is far from being understood and adequately managed. In this setting, a recent analysis of a wide SS cohort included in the Big Data Sjögren Registry showed that the percentage of deaths attributable to CV diseases (27%) was equal to that attributable to infections and double as compared to deaths due to systemic SS itself (8). In a retrospective analysis of 312 SS patients, it is remarkable that

a first cerebrovascular event, not associated to atrial fibrillation, occurred at the age of 55 years (9). Thus, recognizing these challenges raises some key points to be faced.

First of all, there is an urgent need to identify novel biomarkers and autoantibodies potentially associated with CV risk and systemic involvement in these patients (10). Indeed, very few, small sample, studies tested some specific biomarkers of endothelial vascular damage and activation in SS, without a conclusive definition of their pathogenic role (11). Nevertheless, the demonstration that some of these molecules, as anti-endothelial cell antibody, soluble trombomodulin, vascular cell adhesion molecule-1, nytrosine, asymmetric dimethylarginine and endothelial microparticles, were significantly increased in SS patients with atherosclerotic burden in comparison to control subjects suggests the need to validate these biomarkers in larger studies (6, 12). In particular, the next step to be explored will be to investigate the relationship between some specific biomarkers of atherosclerosis and endothelial damage and measures of subclinical atherosclerosis or overt CV manifestations in these patients. In this setting, there is evidence that established biomarkers of atherosclerosis risk and CV disease in the general population may exert a different role in patients with SS, thus confirming the complex and still unexplored mechanism underlying CV damage in these patients. As example, it is intriguing the recent demonstration that although SS patients are characterised by significantly increased levels of proprotein convertase subtilisin/kexin type 9, a key established pro-atherogenic regulator of lipid metabolism contributing to CV risk in the general population, in comparison to control subjects, protein concentration does

not correlate with lipid levels nor with measures of atherosclerosis (13). This implies that some established biomarkers of atherosclerosis may play a different pathogenic mechanism in the context of an inflammatory background or of immune system dysregulation. Probably, a significant research progress in this field can be achieved by the application of bioinformatics analysis of microarray data, which may allow the identification of shared hub genes and genetic susceptibility contributing to the pathogenesis of both atherosclerosis and SS. The AT genotypic alteration of the rs1014569 BAFF variant increased the risk of plaque formation in a Greek cohort of 148 primary SS patients (14). In a recent study, Qi X *et al*. identified four key genes significantly expressed both in SS and in atherosclerosis process which contributed to the pathogenesis of both conditions, thus suggesting that overexpression of these genes could dysregulate immune cells, stimulate pro-atherogenic cytokines and contribute to atherosclerosis progression (15). Indeed, artificial neural network and deep learning analysis techniques have been demonstrated to be useful to elaborate prediction models to investigate the relationship between disease-specific features and CV risk factors and events in cohorts of SS patients, allowing better stratification of CV disease in these patients (16). Undoubtedly, the identification of specific biomarkers, the application of artificial network techniques and the implementation of studies of proteomic analysis will allow the identification of disease specific clusters and phenotypes at higher risk of atherosclerosis and CV events to drive a personalised approach to these patients, as recently demonstrated in different SS cohorts (17, 18).

The second point to consider is that the approach to the assessment of CV comorbidity in SS patients cannot ignore the risk estimation by the application of validated algorithms that can realistically be integrated into routine clinical practice to optimise effective prevention strategies, as commonly performed in the general population. The development and validation of CV risk algorithms in patients with inflammatory and systemic autoimmune diseases is challenging as several variables, including traditional CV risk factors and disease-specific immune and inflammatory parameters, contribute differently to increase CV morbidity. Thus, the definite contribution of inflammation and immune deregulation to the atherosclerotic damage is quite difficult to quantify. This has been well demonstrated in rheumatoid arthritis, where the application of the different CV risk algorithms commonly employed in the general population resulted in under or over-estimation of CV risk, even after correcting for the 1.5 multiplier, as suggested by the European League Against Rheumatism recommendations (19, 20). Surely, the complex pathogenesis of CV risk in SS, far from being understood and different from that of rheumatoid arthritis, may hinder the correct application and of available CV risk algorithm in this population. Moreover, the knowledge of disease-related parameters significantly contributing as independent variables to CV score in these patients is of paramount importance. In this scenario, the demonstration that systemic inflammation and disease activity contribute as significant independent variables to CV risk score assessed by validated CV algorithms reinforces the hypothesis that algorithms including these variables may perform better in the estimation of 10-year risk of fatal and non-fatal CV events in patients with systemic autoimmune and chronic inflammatory diseases (21). Surely, further prospective studies are needed to identify which CV algorithm has the best predictive performance in these patients and which variables should be included in score calculation.

Finally, a potential research field to be implemented in the pathogenesis of CV damage in SS patients may be the investigation of concomitant mechanisms, other than atherosclerosis, which may contribute to increase CV comorbidity in these patients. Systemic inflammation, indeed, has been recognised as a pivotal factor contributing to left ventricular diastolic dysfunction and consequent heart failure with preserved ejection fraction (22). In this setting, the increasing development of more sensitive imaging techniques, as cardiac magnetic resonance imaging, myocardial perfusion scans and stress contrast echocardiography, allowed the detection of cardiac structural abnormalities even in subclinical stages (23). Interestingly, subclinical left ventricular dysfunction correlated with disease activity and the degree of salivary gland inflammatory infiltrate in a small SS cohort, suggesting that immune and inflammatory mechanisms may exert a possible role in myocardial non-ischaemic dysfunction (24). Similarly, evidence is emerging for a role of inflammatory mechanisms in cardiac autonomic dysfunction in patients with SS (23).

Considering the growing availability of drugs targeting the different inflammatory pathways which contribute to rheumatic disease and atherosclerosis pathogenesis (25), the final step of the convergence of these common pathways will be the identification of targeted therapies guided by patient disease phenotype and CV comorbidity. Surely, utilisation of novel technologies, such as artificial intelligence, would facilitate these objectives. In this setting, artificial neural network analysis allowed, for the first time, the identification of two well distinct patterns of distribution of CV risk in SS by the integration of serologic, epidemiologic and clinical features of different SS cohorts (16). In details, a pattern, centred on non-ischaemic CV events and heart failure, was mainly characterised by the presence of traditional CV risk factors and a closer link with disease glandular features. The second pattern included mainly ischaemic events and appeared to be strictly associated with extra-glandular disease activity and longer disease duration. Intriguingly, the results of the study may further support the co-existence of a non-ischemic mechanism underlying the risk of cardiac dysfunction in these patients (16). However, only growing collaboration of interested experts and scientific societies may ensure improvement and correct applicability of these results.

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