

Statins and Mortality in Connective Tissue Diseases: Should We Resume the Cardio-rheumatology Spirit in Our Clinics?

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# Statins and Mortality in Connective Tissue Diseases: Should We Resume the Cardio-rheumatology Spirit in Our Clinics?



In 1912, Windaus reported that atherosclerotic plaques from aortas of human subjects contained over 30-fold higher concentrations of cholesterol than did normal aortas<sup>1</sup>, and in 1913 the Russian pathologist Nikolai Anitschkow<sup>2</sup>, feeding pure cholesterol to rabbits, produced marked hypercholesterolemia and severe atherosclerosis of the aorta. In 1974, Brown and Goldstein discovered the low-density lipoprotein (LDL) receptor and the regulation of cholesterol metabolism in the cells<sup>3</sup>, and in 1976 Akira Endo<sup>4</sup> discovered a fungal metabolite that could block cholesterol synthesis by inhibiting the enzyme hydroxymethylglutaryl CoA. These key steps paved the way to the understanding of LDL cholesterol (LDL-C) levels as one of the primary targets in prevention of ischemic heart attacks and to the discovery of statins as the therapeutic drug capable of reducing the cardiovascular (CV) risk. Since they were first approved in 1987, statins have represented substantial potential for safe, effective, and inexpensive primary prevention of ASCVD (atherosclerotic CV diseases). Among the several risk factors defined in the last 20 years, inflammation and inflammatory biomarkers such as high-sensitivity C-reactive protein (hsCRP) and interleukin 6 have arisen as predictors of future CV events, along with conventional LDL-C or high-density lipoprotein cholesterol (HDL-C). Randomized trial data have also shown that statins reduce not only hsCRP but also CV event rates independently of their effect on LDL-C level. This led to a focus on a further effect of statins: their antiinflammatory effect<sup>5,6,7</sup>, which appears particularly important in all rheumatic diseases [the chronic arthritides as well as the connective tissue diseases (CTD)], because all are characterized by an increased risk of major CV events (MACE)<sup>8,9</sup>.

This premise is key to understanding why the prophylaxis of MACE in rheumatology certainly should focus on the control of classical risk factors<sup>10</sup> as well as (most importantly) on the control of the underlying immune inflammation — disease activity that *per se* produces deleterious effects on

the endothelium. This rationale led to the development of the European League Against Rheumatism (EULAR) recommendation that strongly emphasizes that in rheumatoid arthritis (RA), psoriatic arthritis (PsA), and ankylosing spondylitis (AS), the CV disease risk score (CVD-RS) should be multiplied by 1.5, to reinforce the concept of the effect of inflammation in determining a higher overall risk<sup>11,12,13</sup>.

In this issue of *The Journal*, Jorge, *et al*<sup>14</sup> evaluated the effect on mortality of statin use and non-use among patients with systemic lupus erythematosus (SLE), systemic sclerosis (SSc), primary Sjögren syndrome (pSS), dermatomyositis (DM), polymyositis (PM), mixed CTD, Behçet disease (BD), or antineutrophil cytoplasmic antibody-associated vasculitis (AAV). Unfortunately, no recommendations exist on how to deal with CVD risk in these conditions. The authors provided strong data by examining matched cohorts of 2305 statin users and 2305 non-users in a UK general population database (The Health Improvement Network<sup>15</sup>). The data suggest that statin initiation is associated with reduced all-cause mortality (HR 0.84, 95% CI 0.72–0.98). Importantly, the HR was 0.83 for SLE, 0.87 for pSS, and 0.63 for SSc. The numbers of patients with DM, PM, BD, and AAV were too small to define the relative risk of each category. Prescribing statins in patients with immunological-inflammatory myositis presents a real challenge<sup>16</sup>, because musculoskeletal symptoms are a well-known complication of statin use and range from myalgias and cramps (which occur in 9–20% of statin users) to life-threatening rhabdomyolysis, a rare event occurring at a rate of ~0.4 per 10,000 patient-years. Therefore, these data should be strongly internalized by the rheumatological community because they certainly support the recommendations already provided by EULAR for RA, PsA, and AS. One principle of those recommendations is that the rheumatologist should take care of the CV risk, and in keeping with this, the

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CVD-RS should be adopted and used in SLE, pSS, SSc, and all CTD. This means resuming the cardio-rheumatology spirit, thus offering a treat-to-target algorithm for the CVD risk in each of these conditions.

How should the CVD-RS be evaluated? If there are national guidelines, these should be strictly followed, and a baseline CVD-RS should be calculated for every patient. Yet the scientific cardiologic community in Europe suggests that unless known familial or specific risk factors are present, the CV assessment may be considered in men > 40 years of age and in women > 50 years of age or postmenopausal with no known CV risk factors. In addition, the risk assessment is not a one-time event but should be repeated, for example every 5 years<sup>17</sup>. Yet women with SLE may be younger than 40 and many have thrombophilia and renal disease. How should we move in these cases with the CVD-RS? Certainly we treat hypertension, high cholesterol, and thrombophilia, in addition to the underlying systemic illness. Is this enough? The US National Lipid Association (NLA) 2015 guidelines recommend a stepwise approach to risk management: first identifying the highest ASCVD risk category, then treating to specific non-HDL-C and LDL-C goals based on the risk category. Per the NLA approach, all patients with renal failure stage 3B [estimated glomerular filtration rate (eGFR) –30 to 44 ml/min/1.73 m<sup>2</sup>] or stage 4 chronic kidney disease are considered at high risk and should be treated to a goal non-HDL-C < 130 mg/dl and LDL-C < 100 mg/dl<sup>18</sup>. In addition, given the risk of toxicity with high-dose statins, the Kidney Disease: Improving Global Outcomes working group recommends statin dosing regimens that have been shown to be beneficial in randomized trials performed in patients with eGFR < 60 ml/min/1.73 m<sup>2</sup>. This includes moderate-intensity statins such as daily atorvastatin 20 mg, rosuvastatin 10 mg, simvastatin 40 mg, pravastatin 40 mg, fluvastatin 80 mg, or pitavastatin 2 mg<sup>19</sup>. But in patients with normal GFR, what is the threshold to consider for treatment with statins? The European Society of Cardiology/European Atherosclerosis Society suggests a threshold of > 10% 10-yr risk and LDL-C < 70 mg/dl; OR 5%–10% 10-yr risk and LDL-C > 70 mg/dl; OR 1%–5% 10-yr risk and LDL-C > 100 mg/dl for age 40–65 yrs<sup>20</sup>. Is this correct for patients with CTD or chronic inflammatory arthritis, or should we push to control more fully the inflammatory-immunologic burden? While waiting for recommendations for the therapeutic approach with statins in all the above conditions, the cardio-rheumatology spirit should lead all rheumatologists to carry in their coat pocket an app able to calculate the CVD-RS, so that they can give the patient the most appropriate therapeutic strategy to reduce the risk of MACE with statins.

The demonstration that statins can reduce MACE in CTD encourages adoption of therapeutic strategies in those patients, as well as in chronic arthritides. Yet the adoption of key rules to define the CVD risk and the level of risk at which statins and other drugs should be initiated is a critical issue

that needs to be addressed. The research agenda should define:

- the risk level of MACE according to the various disease activity levels and disease duration;
- the most suitable CVD-RS to be assessed and when and how often it should be evaluated;
- the multiplication factor (of the CVD-RS) that should be adopted in each condition according to the level of disease activity and severity;
- the LDL-C level at which statins should be initiated in the different illnesses and what the target level should be;
- which statin should be preferred according to the data available in the various rheumatic inflammatory diseases and their organ involvement (i.e., renal SLE); and
- how to assess, longitudinally, including with imaging techniques, the risk of MACE in the various arthritides and CTD.

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