

# Statins in Rheumatic Heart Disease

## Taking the Bite Out?\*

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*"Rheumatic fever licks the joints, . . . but it bites the heart."*

—Ernest-Charles Lasègue (1)

Although infrequent in the developed world, rheumatic heart disease (RHD) remains a major health problem worldwide, and with increasing immigration over the past decades, will continue to be encountered in most cardiology practices. The World Health Organization has estimated that more than 15 million people worldwide are affected, with a half million new cases of acute rheumatic fever (ARF) yearly (2). These estimates are most likely conservative given the inadequate access to medical care in the populations most at risk for streptococcal infections. Moreover, the data on RHD are mostly based on auscultatory evidence of valvular disease in those at risk for the sequelae of ARF, with many patients having occult valvular involvement (3).

See page 1874

Although ARF is theoretically preventable through the use of antibiotic treatment for streptococcal infections, once ARF has occurred, there has been no proven therapy to prevent progression to valvular involvement beyond the prevention of recurrent episodes of ARF (recurrent ARF episodes are thought to contribute to further valve damage). In this issue of the *Journal*, Antonini-Canterin et al. (4) report on a possible new therapy to prevent progression of RHD, namely the use of statins. In a retrospective echocardiography-based study, the investigators report that the progression of rheumatic aortic valve disease, as assessed by peak aortic velocity, was significantly slower in the patients who received statin therapy. Specifically the annual change in peak aortic velocity was  $0.05 \pm 0.07$  m/s/year versus  $0.12 \pm 0.11$  m/s/year ( $p = 0.001$ ) in those on statin therapy versus those not on statin therapy. Moreover, rapid progression (defined as an annual rate of  $\geq 0.1$  m/s) was found in almost one-half of the patients not receiving

statins but only in 10% of the statin-treated patients. Mean follow-up was 8.5 years, thereby providing relatively long-term data.

The study is innovative and important in that it highlights a potentially simple therapy, but also has significant limitations. In assessing the clinical applicability of this data, several key questions need to be addressed. What is the scientific rationale for statin therapy for RHD? What are the possible limitations of this retrospective study? What can we learn from similar retrospective studies with statins in other disease states? Can this data be applied to patients in the absence of a prospective randomized trial?

ARF is characterized by an abnormal immune response to infection with rheumatogenic group A streptococci, and much progress has been made in understanding why certain individuals are susceptible to ARF. Associations with certain human leukocyte antigen types, abnormal T-cell activation and infiltration, and the presence of B-cells with a distinctive alloantigen (d8/17) have been identified in ARF patients, along with genetic variations in tumor necrosis factor alpha (reviewed by Bryant et al. [5]). The inflammation of ARF results in a characteristic histopathological picture, including the presence of Aschoff bodies and leukocyte infiltration. Although the pathognomonic Aschoff bodies are rarely seen in the valves themselves, ARF does lead to an acute valvulitis with inflammation and edema of the leaflets. Fibrin-platelet thrombi occur along the leaflet contact zones (6). Fibrosis of the affected valves leads to deformity, stenosis, and insufficiency. The progression to manifest RHD, particularly the calcification that accompanies RHD, was until recently thought to be a passive process attributable to the abnormal hemodynamics caused by the deformed valves. Recent studies, however, have highlighted the presence of ongoing inflammation (7) (as evidenced by high C-reactive protein levels) and oxidative stress, as well as the participation of T-lymphocytes and inflammatory cytokines (8). Moreover, calcification fronts in explanted valves have been shown to colocalize with vascular endothelial growth factor expression (suggestive of neoangiogenesis) and osteoblast-like bone formation (9). These data suggest that progression of RHD is not a passive process but rather the result of an organized inflammatory process. If indeed RHD is an inflammatory disease, then modulators of

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the immune response may have a role in preventing progression of disease.

Although statins were developed to lower blood cholesterol levels and specifically low-density lipoprotein (LDL) levels, it has been appreciated since the 1990s that statins also possess non-LDL-lowering effects (reviewed by Shaw et al. [10]). Although the term pleiotropism has been applied to these additional effects, most are a direct result of the downstream effect of inhibiting 3-hydroxy-3-methylglutaryl coenzyme A, the rate limiting enzyme in the synthesis of cholesterol. Specifically, by inhibiting mevalonic acid formation, statins also decrease the formation of isoprenoid intermediaries that serve as important intracellular signal molecules for the rho-associated coiled-coil containing protein kinase pathway. Mevalonic acid itself induces cellular growth and differentiation. Recent data suggest that for the same level of LDL reduction, higher-dose statins in comparison with a statin/ezetimibe combination result in a greater reduction in rho-associated coiled-coil containing protein kinase activity and improved endothelial function, with similar effect on high-sensitivity C-reactive protein (11). Statins therefore are thought to possess anti-inflammatory properties. There is thus a rationale for considering statin therapy for the inflammatory aspects of RHD.

The pleiotropic effects of statins have led to their proposed use in various cardiovascular (heart failure, calcific aortic stenosis, atrial fibrillation) and noncardiovascular diseases (osteoporosis, Alzheimer disease). Almost invariably the initial impetus has been retrospective studies similar to the study by Antonini-Canterin et al. (4). Unfortunately, large-scale randomized trials have failed to confirm these preliminary findings in either heart failure (12) or in calcific aortic stenosis (13). The experience with osteoporosis has been similar—a randomized trial (14) has failed to confirm the findings of observational studies (15). The findings from the SEAS (Simvastatin and Ezetimibe in Aortic Stenosis) (13) study of aortic stenosis are particularly relevant. Contrary to the findings of a previous small open-label study (16), there was no efficacy detected with the treatment of simvastatin 40 mg/ezetimibe 10 mg on either clinical end points (need for aortic valve replacement) or echocardiographic progression of disease. Although the pathologic processes in calcific aortic stenosis and RHD are distinct, inflammation is thought to participate in both. In this regard, the disappointing experience in the SEAS trial should at least lead to caution in embracing the results of the present study in RHD.

What is the explanation for the disparate effects between retrospective observational studies and randomized trials? One possibility is the phenomenon of prevention bias, a term coined by Barrett-Connor (17) to highlight the finding that taking certain medications, such as hormone replacement therapy, or in the present study statins, may be a marker for other health-promoting behaviors. That still leaves unanswered how these unmeasured confounders are slowing the progression of disease in the patients receiving statins.

The study by Antonini-Canterin et al. (4) is also limited to disease progression in the aortic valve, with no data on progression in the mitral valve because most of their patients had already had interventions on the mitral valve. The mitral valve is the more frequently involved valve in RHD and is often more severely affected.

Given the retrospective nature of the present study, the results, although potentially very important, can in a strict sense be considered hypothesis generating only and in need for further confirmation in a placebo-controlled trial. Is it reasonable to expect such a study? The SEAS trial required 1,873 patients to be adequately powered for clinical end points. For echocardiographic end points, however, smaller studies would be adequately powered, as illustrated by the findings in this retrospective with only 164 patients. Given the importance of the issue, it would be hoped that a multicenter international effort, perhaps led by the World Health Organization, be instituted to formally test the statin hypothesis in a prospective placebo-controlled manner.

What should clinicians do in the interim? For some patients, the presence of concomitant indications for statin therapy makes the decision easy. For the rest, the decision to initiate treatment is more complex. Women have a higher incidence of progression to valvular RHD than men. Unfortunately, the progression of RHD is likely to occur during childbearing years for women. Statins are contraindicated in pregnancy and in women who are likely to become pregnant. Therefore, this not-fully-proven option is not appropriate for many at risk of RHD.

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