Calcific aortic valve disease is the most common acquired valvular disorder in developed countries. Disease involvement of the trileaflet aortic valve spans the spectrum from “aortic sclerosis,” characterized by valve thickening, fibrosis, and microscopic calcification without left ventricular outflow obstruction, to frank “aortic stenosis,” characterized by more severe involvement with limitation of valve opening (1). Aortic sclerosis is present in more than 25% of individuals over the age of 65 years and aortic stenosis in 2%, with the prevalence of both manifestations dramatically increasing with more advanced age (1–3). The dynamic and inflammatory nature of calcific aortic stenosis has been well appreciated in recent years, and many pathobiologic features of calcific aortic valve disease exhibit striking similarity to coronary atherosclerosis. C-reactive protein (CRP), which has been an extremely useful predictive biomarker of the inflammatory nature of calcific aortic valve disease is underscored by studies in the rabbit model, where dietary cholesterol loading led to aortic valve lesions similar to human aortic stenosis (9).

The renin-angiotensin system further contributes to the inflammatory nature of the aortic valve lesion. Angiotensin-converting enzyme (ACE), as well as angiotensin II and the angiotensin II type-1 receptor, have been identified in aortic sclerotic lesions (1,2,10), which stimulate monocyte infiltration and macrophage uptake of modified LDL (2).

Calcification, the hallmark characteristic of aortic valve stenosis, is also clearly a feature of the active inflammatory process, occurring in valve regions of lipid disposition, especially oxidized lipids, with additional stimulus provided by macrophage- and T lymphocyte-produced cytokines (2,6). Early in the disease process, active microscopic areas of calcification are seen colocalizing in areas of lipoprotein accumulation and inflammatory cell infiltration; as the disease progresses, active bone formation is seen (1,2,11,12).

The similarity of the inflammatory, fibrotic, and calcification processes of aortic valve disease and atherosclerosis is reinforced by the concordance of risk factors associated with both disease entities (2,3,13). Furthermore, the incidence of adverse coronary events is significantly higher in patients with calcific aortic stenosis, even after adjustment for cardiac risk factors and known atherosclerotic disease (1,14).

Therapies that are effective in reducing coronary artery disease morbidity and mortality by stabilizing coronary plaque and reducing plaque inflammation may also reduce progression of calcific aortic stenosis. Retrospective studies suggested that statins slow the progression of aortic valve stenosis (15), and treatment of the hypercholesterolemic rabbit model with atorvastatin significantly reduced the progression of aortic valve disease (9). A recent prospective, open-label study found that rosuvastatin significantly reduced the progression of moderate to severe calcific aortic stenosis (baseline mean valve area 1.23 cm²) in hypercholesterolemic patients (16); although a randomized, placebo-controlled trial did not demonstrate a beneficial effect of atorvastatin on the progression of calcific aortic stenosis in patients with more severe aortic stenosis (baseline mean valve area 1.03 cm²) (17). These observations suggested the...
hypothesis that the inflammatory processes of aortic stenosis, amenable to pharmacologic intervention, were earlier stages in the evolution of aortic valve disease and that as the valve calcified there may be a decrease in the inflammatory state and, hence, an inability to alter the disease’s natural history with statins (16).

The ACE inhibitors, which have been effective in reducing cardiovascular events in patients with coronary artery disease, presumably by reducing endothelial inflammation and cholesterol accumulation, have similarly been shown in some (18), but not all (19), retrospective studies to reduce the progression of valve calcification. Studies in which ACE inhibitors did not appear to be beneficial included patients with more severe aortic stenosis (2).

If inflammation is the fundamental process of early aortic valve disease, with calcification predominating in the later stages, one might anticipate that markers of inflammation, such as CRP, would reflect early aortic valve disease activity and perhaps be less useful as a marker in later stages. The available data do not support such a concept. C-reactive protein has been localized in the valve tissue of aortic stenosis in both native valves and bioprosthetic aortic valves, with a positive correlation between serum CRP values and valve CRP expression (20). C-reactive protein values are increased in patients with severe symptomatic aortic stenosis awaiting valve surgery compared with matched controls (21) and decline after aortic valve replacement (22).

The study by Novaro et al. (5) in this issue of the Journal provides new data from a broad-based population cohort that the early inflammatory stages of aortic sclerosis and aortic stenosis are not well predicted by CRP values. C-reactive protein values were obtained at study entry in 5,621 subjects in the Cardiovascular Health Study and were investigated cross-sectionally, to determine association with aortic sclerosis or aortic stenosis, and longitudinally, to determine whether baseline CRP values identified those subjects likely to develop aortic sclerosis or aortic stenosis by echocardiography in 5-year follow-up. They observed that older age, male gender, hypertension, coronary artery disease, and renal insufficiency, but not CRP values, were associated with the presence of increasing calcific aortic valve abnormality and that CRP values were not related to the progression from a normal aortic valve to aortic sclerosis or stenosis, nor progression from aortic sclerosis to aortic stenosis. African-American ethnicity was significantly protective from developing calcific aortic valve disease.

How do we make sense of these apparent discrepancies that CRP appears not to reflect the early inflammation phase of calcific aortic valve disease but does reflect the later calcific stages of the disease? The first methodologic consideration is that the single CRP value at study entry may have been too distant from the time that calcific aortic stenosis was developing during the follow-up period to reflect the inflammatory change that would later occur. It is also possible that the inflammatory process in early calcific aortic valve disease was not substantial enough to lead to an elevated serum value. It is also clear from the previously noted associations between CRP and severe aortic stenosis that CRP may be a more active, direct participant in the later stages of the disease progression (23) and not simply a biomarker passively reflecting the early inflammatory stages of disease. C-reactive protein provides valuable prognostic information concerning adverse cardiovascular events in coronary disease as well (4), but it does not reflect the presence or severity of subclinical anatomic coronary artery disease (24,25).

The study by Novaro et al. (5) does add important new understanding concerning the genetic determinants of calcific aortic valve disease. Genetic characteristics of calcium metabolism may be central to the development of valvular calcification (26), and the observation that African Americans were protected from development of calcific aortic valve disease, as the authors indicate (5), may be related to a genetic predisposition toward less calcification of vascular and valve tissue and lower incidence of osteoporosis.

It would be of enormous value to identify a biomarker to predict patients likely to develop aortic sclerosis and those likely to progress to aortic stenosis. Given the dynamic and relatively slowly progressive inflammatory process of aortic stenosis, pharmacologic therapies could then be directed toward those patients at highest risk to reduce the frequency and severity of valve dysfunction. This paradigm of understanding the development and progression of calcific aortic stenosis, and the associated opportunities for pharmacologic intervention, may still be operative, but the most appropriate biomarker may not be CRP. C-reactive protein is certainly an excellent biomarker of coronary disease risk and also of severe aortic stenosis, but its role to reflect the early stages of calcific aortic valve disease is much less clear. There will need to be many more large-scale population-based studies with serial CRP (and other biomarker) measurements, as well as serial echoes, to identify better tracking tools of disease progression and to guide the nature and timing of potential pharmacologic interventions. Given the widespread incidence of calcific aortic stenosis and the current limitation of surgical intervention as the only therapeutic option, such a search is certainly worth pursuing.

Reprint requests and correspondence: Dr. Peter H. Stone, Cardiovascular Division, Brigham & Women’s Hospital, 75 Francis Street, Boston, Massachusetts 02115. E-mail: pstone@partners.org.

REFERENCES