

CORRESPONDENCE



Calcific Aortic Stenosis

TO THE EDITOR: In their article on intensive lipid lowering, Rossebø et al. (Sept. 25 issue)¹ report that therapy with simvastatin and ezetimibe did not reduce aortic-valve disease and calcifications in patients with mild-to-moderate asymptomatic aortic stenosis. In an accompanying editorial, Otto² accurately states that “calcific aortic stenosis is not atherosclerosis.” However, she does not take advantage of this opportunity to develop the conclusion further. Indeed, in a variety of murine models, vascular calcification develops in the absence of overt atherosclerosis.³ Furthermore, osteoprotegerin has been reported to inhibit vascular calcification without affecting atherosclerosis,³ and therapy with bone morphogenetic protein 7 (BMP-7) has also shown similar results.⁴ Therefore, it might be the right time to look more closely at the calcific aortic valve in other models and conditions, including chronic renal disease, in which the incidence of calcification is increased⁵ and the cellular basis of calcification has been clarified.

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THE AUTHORS REPLY: In our study, we reported that clinical end points and echocardiographic hemodynamic measures of the progression of aortic stenosis were not influenced by combined lipid-lowering therapy. For clinical purposes, our findings resolved the role of lipid lowering in patients with mild-to-moderate aortic stenosis. The influence on the degree of calcification of the valve is the subject of an ongoing substudy. We agree with Pazianas that future research should focus on basic cellular pathophysiology. Since renal insufficiency was an exclusion criterion in our study, we were unable to study its effect on the progression of valve disease. In addition to the mechanisms mentioned by Pazianas, the factors that activate and regulate the alpha-smooth-muscle actin-positive valve interstitial cells (myofibroblasts), which also induce biomineralization, are strong candidates.¹ Other mechanisms include possible up-regulation of osteogenic genes and

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numerous regulatory processes, possibly resembling vascular processes.² The role of Ca-phosphate product, calcification of matrix vesicles, fetuin-A,³ the osteoprotegerin–RANKL–RANK axis,⁴ BMP-7, and the renin–angiotensin system⁵ must be clarified in valvular tissue and in human aortic valves *in vivo*.

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THE EDITORIALIST REPLIES: As Pazianas notes, recent studies highlight the differences between calcific aortic stenosis and atherosclerosis. Unlike atherosclerosis, increased oxidative stress in calcific aortic valves is associated with increased lev-

els of superoxide and hydrogen peroxide, possibly mediated by the uncoupling of nitric oxide synthase activity.¹ The association between increased oxidative stress and leaflet calcification suggests a possible causal relationship, perhaps potentiated by genetic and clinical factors.² Decreased activity of normal tissue inhibitors appears to be a factor in both pathologic angiogenesis and in dystrophic calcification of valve leaflets.³ For example, reduced expression of chondromodulin-I, an antiangiogenic factor, has been shown in aged mice with calcific valve disease.⁴ In addition, studies of human valves with a range of disease from normal to severe stenosis showed progressive increases in gene expression of osteopontin, osteoprotegerin, and bone sialoprotein II, along with decreased expression of other noncollagenous matrix proteins. The complexity of this active disease process is a challenge for researchers but also suggests there are many potential targets for intervention to prevent disease progression.

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Analyses of Cancer Data from Three Ezetimibe Trials

TO THE EDITOR: The article by Peto et al. (Sept. 25 issue),¹ which reports cancer incidence and mortality in three clinical trials of ezetimibe, raises disturbing scientific and ethical questions. Premature unblinding of ongoing trials is not a reliable approach to the evaluation of drug safety. In their discussion of one of the trials, the Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT), the authors report that the mean exposure to ezetimibe was only 12 months,

which is insufficient time for any hazard to emerge. Analysis of short-term trials dilutes any evidence of an excess risk. The most relevant statistical analysis is the upper 95% confidence interval for the observed relative risk. For cancer mortality in the two confirmatory trials, the Study of Heart and Renal Protection (SHARP) and IMPROVE-IT, the relative risk was 1.35 (approximate 95% confidence interval, 0.98 to 1.84), which was not reported by Peto et al. Thus, these two trials can only