

numerous regulatory processes, possibly resembling vascular processes.<sup>2</sup> The role of Ca-phosphate product, calcification of matrix vesicles, fetuin-A,<sup>3</sup> the osteoprotegerin–RANKL–RANK axis,<sup>4</sup> BMP-7, and the renin–angiotensin system<sup>5</sup> 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.<sup>1</sup> The association between increased oxidative stress and leaflet calcification suggests a possible causal relationship, perhaps potentiated by genetic and clinical factors.<sup>2</sup> Decreased activity of normal tissue inhibitors appears to be a factor in both pathologic angiogenesis and in dystrophic calcification of valve leaflets.<sup>3</sup> For example, reduced expression of chondromodulin-I, an antiangiogenic factor, has been shown in aged mice with calcific valve disease.<sup>4</sup> 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),<sup>1</sup> 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

rule out a risk of death from cancer of 84% or more. The conclusion that there is no “credible evidence” for a cancer risk associated with ezetimibe is simply not supported by the data. The use of incomplete studies to rule out a safety hazard represents a dangerous precedent. If such a standard were widely applied, risky therapies would be routinely misclassified as safe, with potentially catastrophic public health consequences.

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1. Peto R, Emberson J, Landray M, et al. Analyses of cancer data from three ezetimibe trials. *N Engl J Med* 2008;359:1357-66.

**THE AUTHORS REPLY:** It is not in the interest of public health to label potentially useful drugs as unsafe if there is no credible evidence that they are — or, of course, to overlook reliable evidence of hazard if it does emerge. To help avoid both these serious errors, unexpected findings, such as those regarding the risk of cancer in the Simvastatin and Ezetimibe in Aortic Stenosis (SEAS) trial, that generate but do not prove the hypothesis of a new hazard should be tested independently in a separate, substantial data set.

For ezetimibe, the only large, randomized data set is that from interim results of the SHARP and IMPROVE-IT trials. It already involves four times as many cancers as SEAS did but does not suggest

any increase in cancer incidence, either overall (313 in the ezetimibe group vs. 326 in the control group) or more than 3 years after randomization (20 in the ezetimibe group vs. 24 in the control group, all in the SHARP trial; with 19 vs. 17 after year 3 in the SEAS trial). In the SHARP and IMPROVE-IT trials, a nonsignificant difference in the number of cancers that had already caused deaths (97 in the ezetimibe group vs. 72 in the control group) was counterbalanced by a nonsignificant difference in the number of cancers (216 vs. 254) that had not yet caused death. (Fig. 4 of our article gives the confidence interval that Nissen mistakenly thought we had omitted.)

Provided an appropriate distinction is made between hypothesis-generating and hypothesis-testing findings (as in our article), the trial results provide no credible evidence of an adverse effect of ezetimibe. Continuation of the SHARP and IMPROVE-IT trials will provide further evidence about the effects of a statin plus ezetimibe (which reduces the level of low-density lipoprotein cholesterol more than monotherapy can), not only on safety but also on the major vascular outcomes this treatment may prevent.

Concerns about possible conflicts of interest were raised by the Congressional Committee on Oversight and Investigations; the response from the Clinical Trial Service Unit to the U.S. Congress is available on the unit's Web site.<sup>1</sup>

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1. Clinical Trial Service Unit. CTSU response to U.S. Congress. (Accessed December 10, 2008, at <http://www.ctsu.ox.ac.uk/news/ctsu-response>.)

## Lung Cancer

**TO THE EDITOR:** In the introductory remarks of their article, Herbst et al. (Sept. 25 issue)<sup>1</sup> note, “Smoking causes all types of lung cancer but is most strongly linked with small-cell lung cancer and squamous-cell carcinoma.” In the legend to Figure 1, they also note, “Most tumors that are not related to smoking are adenocarcinomas and develop in the peripheral airways.” This statement almost echoes Kreyberg's observation<sup>2</sup> in 1962

regarding the “slight, if any” relationship between cigarette smoking and adenocarcinoma of the lung.

In the past 47 years, adenocarcinoma has become the predominant type of cancer cell in male smokers as well as female smokers. In the period from 1959 to 1991, the incidence of adenocarcinoma increased dramatically, by a factor of 10 in men and by a factor of 17 in women.<sup>3</sup>