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1. Roberts WC, Ko JM. Frequency by decades of unicuspid, bicuspid, and tricuspid aortic valves in adults having isolated aortic valve replacement for aortic stenosis, with or without associated aortic regurgitation. *Circulation* 2005;111:920-5.
2. Katz R, Wong ND, Kronmal R, et al. Features of the metabolic syndrome and diabetes mellitus as predictors of aortic valve calcification in the Multi-Ethnic Study of Atherosclerosis. *Circulation* 2006;113:2113-9.
3. Garg V, Muth AN, Ransom JF, et al. Mutations in NOTCH1 cause aortic valve disease. *Nature* 2005;437:270-4.
4. Helse S, Oksjoki R, Lindstedt KA, et al. Complement system is activated in stenotic aortic valves. *Atherosclerosis* 2008;196:190-200.
5. Akat K, Borggreffe M, Kaden JJ. Aortic valve calcification — basic science to clinical practice. *Heart* 2008 July 16 (Epub ahead of print).
6. Weiss RM, Ohashi M, Miller JD, Young SG, Heistad DD. Calcific aortic valve stenosis in old hypercholesterolemic mice. *Circulation* 2006;114:2065-9.
7. Rajamannan NM, Subramaniam M, Caira F, Stock SR, Spelsberg TC. Atorvastatin inhibits hypercholesterolemia-induced calcification in the aortic valves via the Lrp5 receptor pathway. *Circulation* 2005;112:Suppl:1229-1234.
8. Rossebø AB, Pedersen TR, Boman K, et al. Intensive lipid lowering with simvastatin and ezetimibe in aortic stenosis. *N Engl J Med* 2008;359:1343-56.
9. Anger T, Pohle FK, Kandler L, et al. VAP-1, Eotaxin3 and MIG as potential atherosclerotic triggers of severe calcified and stenotic human aortic valves: effects of statins. *Exp Mol Pathol* 2007;83:435-42.
10. Aikawa E, Nahrendorf M, Sosnovik D, et al. Multimodality molecular imaging identifies proteolytic and osteogenic activities in early aortic valve disease. *Circulation* 2007;115:377-86.

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Ezetimibe and Cancer — An Uncertain Association

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The randomized clinical trial is considered to be the most reliable tool to assess the efficacy and safety of new drugs. At times, however, randomized trials detect adverse events that are unanticipated and not easily explained on the basis of current knowledge. An unexpected finding of this kind may ultimately prove to be due to chance, but follow-up studies sometimes confirm the adverse drug effect. Particularly when an unexpected finding raises a safety concern with regard to a drug, physicians face uncertainty about how to act on the information.

In this issue of the *Journal*, we publish the results of the Simvastatin and Ezetimibe in Aortic Stenosis (SEAS) trial (ClinicalTrials.gov number, NCT00092677),¹ a clinical trial of lipid-lowering therapy that, even before its publication, has generated considerable public attention. In the trial, a combination of simvastatin and ezetimibe was compared with placebo with respect to the incidence of cardiovascular events in older people with aortic-valve stenosis. The treatment had no impact on the progression of aortic stenosis or on cardiovascular clinical events in general, with the exception of coronary-artery bypass surgery, which was performed (usually at the time of aortic-valve replacement) less frequently in the active-treat-

ment group than in the placebo group. There was little uncertainty, however, that the primary end point was null, since the hazard ratio for treatment relative to placebo was 0.96, with a 95% confidence interval (CI) of 0.83 to 1.12.

There was, however, an unexpected finding in the trial. An excess of incident cancers was observed in the simvastatin–ezetimibe group, with 105 in that group as compared with 70 in the placebo group ($P=0.01$). There was an increase in the incidence of a variety of cancers, including prostate, gastrointestinal, and skin cancers. Also, deaths from cancer were more frequent in the active-treatment group (39 deaths, vs. 23 in the placebo group), although the difference achieved only borderline statistical significance ($P=0.05$).

The SEAS investigators suggested that the difference in incident cancers could have occurred by chance but acknowledged that the unanticipated findings should be pursued through additional studies. Using existing data, the Clinical Trial Service Unit and Epidemiological Studies Unit at Oxford University were able to undertake such a study. The researchers had access to interim cancer data in two large ongoing clinical trials, the Study of Heart and Renal Protection (SHARP) (NCT00125593) and the Improved Reduction of

Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) (NCT00202878), which were unblinded only for cancer outcomes but provided relatively short follow-up (a mean of 2.7 years and 1.0 year, respectively, as compared with 4.1 years in the SEAS trial). Because of the large size of these trials, however, they provided more cancer data than the SEAS trial, even in patients with 3 or more years of follow-up. The Oxford researchers examined the data to determine whether the imbalance in incident cancers and cancer deaths observed in the SEAS trial was replicated in the ongoing trials. They asked whether the increased risk of cancer in the SEAS trial reflected a previously unobserved true signal or was simply the play of chance. It should be noted that the Oxford group is also conducting the SHARP trial and received research funding from Merck and Schering-Plough for the work. The authors note, however, that their analyses were performed independently of the companies.

The analysis by the Oxford group, reported in this issue of the *Journal*,² failed to confirm the increase in cancer incidence noted in the SEAS trial ($P=0.61$ for the incidence of all cancers in the combined IMPROVE-IT and SHARP active-treatment groups as compared with the placebo groups). However, as in the SEAS trial, a nonsignificant increase in cancer mortality was observed ($P=0.07$). It is important to note that none of the three trials were designed primarily to address cancer risk. However, cancer mortality is an end point that would be expected to be reliable.

When the cancer mortality data from the SEAS, SHARP, and IMPROVE-IT trials were combined, there was an increase in cancer mortality risk in the combined ezetimibe groups (134 deaths, as compared with 92 deaths in controls; risk ratio, 1.45; 95% CI, 1.02 to 2.05; uncorrected $P=0.007$). Because this P value was obtained from one of several data-driven analyses rather than from a test of a single prespecified hypothesis, it should be interpreted cautiously. The Ox-

ford researchers believe that this finding is due entirely to the play of chance rather than to a true increase in cancer mortality. They argue that an increase in the risk of cancer death, if real, should be paralleled by an increase in the risk of cancer incidence, which was not found in the combined analysis, and that there is no plausible mechanism for such an effect.

Although the Oxford group may ultimately prove to be correct, it is appropriate to raise a note of caution. Whether the increased mortality risk is due solely to the play of chance is uncertain. Ezetimibe interferes with the gastrointestinal absorption not only of cholesterol, but also of other molecular entities that could conceivably affect the growth of cancer cells. The fact that the combined data from all three trials showed an increase in cancer mortality with ezetimibe should not be assumed to be a chance finding until further data are in. It is appropriate that SHARP and IMPROVE-IT continue. Careful follow-up of the patients in these trials will be essential, and other existing data sets on ezetimibe-treated patients should be analyzed for cancer end points. The Food and Drug Administration has already announced that during the next few months it will conduct its own analysis of the potential cancer hazard of ezetimibe.

We will continue to follow the matter, and we are prepared to promptly publish in the *Journal* new information that sheds further light on this unexpected finding. Physicians and patients are unfortunately left for now with uncertainty about the efficacy and safety of the drug.

Dr. Ware reports serving on a data and safety monitoring board for Schering-Plough.

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1. Rossebø AB, Pedersen TR, Boman K, et al. Intensive lipid lowering with simvastatin and ezetimibe in aortic stenosis. *N Engl J Med* 2008;359:1343-56.

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

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