SPECIAL ARTICLE

Analyses of Cancer Data from Three Ezetimibe Trials

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ABSTRACT

BACKGROUND

Five years of statin therapy lowers low-density lipoprotein (LDL) cholesterol substantially and, over a 5-year period, results in reductions in the incidence of cardiovascular events. The Simvastatin and Ezetimibe in Aortic Stenosis (SEAS) trial (ClinicalTrials.gov number, NCT00092677) has raised the hypothesis that adding ezetimibe to statin therapy for larger LDL cholesterol reductions might increase the incidence of cancer.

METHODS

We compared the results of a hypothesis-generating analysis of the incidence of cancer in the SEAS trial of ezetimibe plus simvastatin in 1873 patients (mean follow-up after ezetimibe or matching placebo was begun, 4.1 years) with a hypothesis-testing analysis of cancer data from the two large ongoing trials of this regimen: the Study of Heart and Renal Protection (SHARP) (NCT00125593) with 9264 patients (mean follow-up, 2.7 years) and the Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) (NCT00202878), currently with 11,353 patients (mean follow-up, 1.0 year).

RESULTS

In the SEAS trial, assignment to ezetimibe was associated with an increase in any new onset of cancer (101 patients in the active-treatment group vs. 65 in the control group) from several cancer sites. In SHARP and IMPROVE-IT combined, there was no overall excess of cancer (313 active-treatment vs. 326 control; risk ratio, 0.96; 95% confidence interval, 0.82 to 1.12; P=0.61) and no significant excess at any particular site. Among patients assigned to ezetimibe, there were more, albeit not significantly more, deaths from cancer (97, vs. 72 in the control group; P=0.07), but there were also fewer, although not significantly fewer, other cases of cancer (216, vs. 254 in the control group; P=0.08). There was no evidence of a trend in the risk ratio for incidence of or death from cancer with increasing duration of follow-up.

CONCLUSIONS

The available results from these three trials do not provide credible evidence of any adverse effect of ezetimibe on rates of cancer. Follow-up of longer duration will permit the balance of risks and benefits to be determined more reliably.

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The Cholesterol Treatment Trialists' meta-analysis of individual data for more than 90,000 patients randomly assigned, in equal proportions, to receive either statin therapy or control treatment in 14 trials[1] showed that use of statin therapy reduces the incidence of heart attack, stroke, and revascularization procedures by about one fifth for each reduction of 40 mg per deciliter (1 mmol per liter) in low-density lipoprotein (LDL) cholesterol. In contrast, on the basis of 5614 patients with onset of cancer after randomization in those trials, there was no evidence that lowering LDL cholesterol by an average of about 40 mg per deciliter by means of approximately 5 years of statin therapy increases the risk of developing a first cancer (which occurred in 2810 patients receiving a statin vs. 2804 controls; risk ratio, 1.00; 95% confidence interval [CI], 0.95 to 1.04) (Fig. 1). Nor was there a trend toward increased risk ratios for cancer among patients with lower levels of cholesterol or with increasing duration of statin treatment. When cancer was analyzed according to site, there was no significant excess of any particular type of cancer.

In these trials, cancer developed and caused death in 2163 patients during the scheduled follow-up period; the relative risk for death from cancer in the statin group as compared with the control group was 1.01 (99% CI, 0.91 to 1.12).

Results of one of the trials had previously raised concern about a possible excess risk of breast cancer (affecting 9 women in the statin group vs. 0 in the placebo group; nominal P=0.004 before appropriate allowance was made for this being the most extreme result for any type of cancer).[2] There was, however, no significant excess of breast cancer among the much larger number of women in other statin trials (96 women in the statin groups vs. 92 controls; risk ratio, 1.01; 99% CI, 0.73 to 1.40; P=0.6).[1] Similarly, although another of the trials reported an apparent excess risk of cancer among people over 69 years of age (245 persons in the statin group vs. 199 in the placebo group, uncorrected P=0.02),[3] there was again no significantly increased risk of cancer among the larger number of such patients in other statin trials (risk ratio vs. controls, 1.03; 99% CI, 0.91 to 1.16; P=0.4).[1]

These examples illustrate that unduly data-dependent emphasis on results that are unexpected and often extreme in particular studies can be misleading. They also reinforce the value of testing such unexpected hypothesis-generating findings independently with the use of a separate database larger than the one that generated the hypothesis in the first place.[4,5]

In the Simvastatin and Ezetimibe in Aortic Stenosis (SEAS) trial (ClinicalTrials.gov number, NCT00092677),[6] which is reported on in this issue of the *Journal*, an apparent excess of about one half in the incidence of any new cancer was observed during mean follow-up of approximately 4 years among the 944 patients randomly assigned to ezetimibe plus simvastatin as compared with the 929 randomly assigned to placebo. This excess, however, is based on only 101 people and 65 people with cancer, respectively (Table 1), so the range of uncertainty around the relative risk is wide (95% CI, 1.13 to 2.12; 99% CI, 1.02 to 2.33; uncorrected P=0.006 before any allowance is made for this being the hypothesis-generating result). If there were an adverse effect of ezetimibe plus simvastatin on the incidence of cancer, then given previous epidemiologic studies of cancer in humans[7-9] and studies of chemical carcinogenesis in animals,[10,11] the excess observed in the SEAS trial should be dominated by a few particular types of cancer and the relative risk should

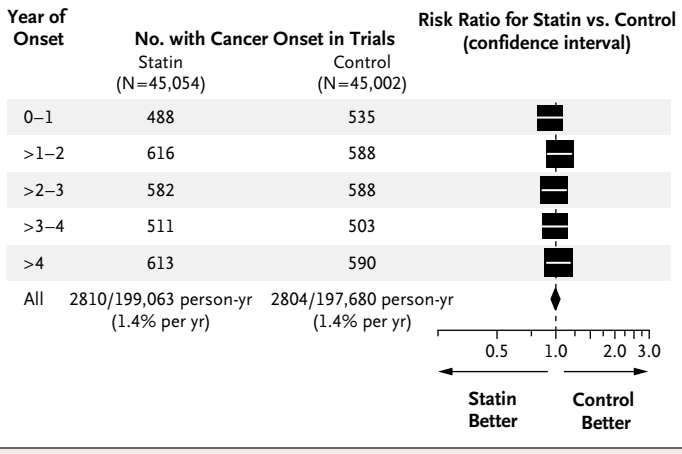

Figure 1. Relative Risk of Onset of Cancer from the Cholesterol Treatment Trialists' (CTT) Meta-Analysis of Statin Trials, According to Year of Onset.

Risk ratios are reported for participants at risk for a first cancer after randomization. Squares with horizontal lines are risk ratios and the corresponding 99% confidence intervals, with the sizes of the squares proportional to the amount of statistical information. The overall risk ratio (diamond) was 1.00 (95% confidence interval, 0.95 to 1.04). The chi-square statistic for trend in the risk ratio for all trials combined was 0.69 (P=0.40). The data include published data from 13 trials and unpublished data from the 14th trial in the CTT meta-analysis.

Table 1. Numbers of Persons with Onset of Fatal or Nonfatal Cancer in the SEAS Trial and in SHARP and IMPROVE-IT.

Value	SEAS Trial				SHARP and IMPROVE-IT			
	Active Treatment (N=944)	Control (N=929)	Uncorrected P Value	Corrected P Value*	Active Treatment (N=10,319)	Control (N=10,298)	Uncorrected P Value	Corrected P Value*
Total follow-up for cancer (person-yr)	3810	3826			18,246	18,255		
Any cancer								
No.	101	65	0.006†	—	313	326	0.61	—
Percent per yr	2.7	1.7			1.7	1.8		
Site of cancer (no. of persons)‡								
Lip, mouth, pharynx, or esophagus	1	1	1.00	1.00	16	14	0.86	1.00
Stomach	5	1	0.23	1.00	6	9	0.60	1.00
Large bowel or intestine	9	8	1.00	1.00	36	39	0.81	1.00
Pancreas	3	1	0.63	1.00	5	7	0.77	1.00
Liver, gallbladder, or bile ducts	2	3	1.00	1.00	10	11	1.00	1.00
Lung	7	10	0.60	1.00	33	28	0.61	1.00
Other respiratory site	1	0	1.00	1.00	4	2	0.68	1.00
Skin	18	8	0.08	0.80	74	89	0.27	1.00
Breast	8	5	0.60	1.00	21	19	0.88	1.00
Prostate	21	13	0.24	1.00	25	36	0.20	1.00
Kidney	2	2	1.00	1.00	25	11	0.03	0.48
Bladder	7	7	1.00	1.00	18	20	0.87	1.00
Genital site	4	4	1.00	1.00	6	5	1.00	1.00
Hematologic site	7	5	0.79	1.00	19	19	1.00	1.00
Other known site	3	1	0.63	1.00	11	11	1.00	1.00
Unspecified	9	6	0.63	1.00	20	18	0.88	1.00

* Multiple uncorrected P values are reported; any value that is based on data from more than five patients could have yielded a value less than 0.05 by chance. Uncorrected P values that are less than the inverse of the number of such tests were therefore corrected by multiplying by the number of such tests to correct for this multiplicity of comparisons; other corrected P values are 1.00.

† This uncorrected P value of 0.006 requires substantial correction for the fact that it was the SEAS result for any cancer that unexpectedly generated the hypothesis being studied. (Uncorrected P values of 0.01, or even 0.001, that generate an unexpected hypothesis cannot be used directly to test it.)

‡ Since cancer could develop at more than one site in a patient, the sum of the site-specific numbers exceeds the number of persons with any cancer in the active-treatment and control groups (by 6 and 10, respectively, in the SEAS trial and by 16 and 12, respectively, in SHARP and IMPROVE-IT).

increase significantly with increasing duration of follow-up; neither of these is the case (Table 1 and Fig. 2, respectively).

To test this hypothesis of an increase in the overall incidence of cancer, the principal investigators of two larger clinical trials of ezetimibe plus simvastatin that are currently in progress — the Study of Heart and Renal Protection (SHARP)[12] (NCT00125593) and the Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT)[13] (NCT00202878) — obtained the agreement of their independent data and safety monitoring committees to unblind the interim data on cancer (but not on any other outcomes) among more than 20,000 randomized patients for the analysis reported here.

METHODS

CONTRIBUTING TRIALS AND DATA

In the hypothesis-generating SEAS trial, 1873 patients with aortic stenosis were randomly assigned to receive 10 mg of ezetimibe plus 40 mg of simvastatin daily in a single pill or to receive placebo.[6] The first 196 of these patients were initially assigned to simvastatin alone or to placebo but were

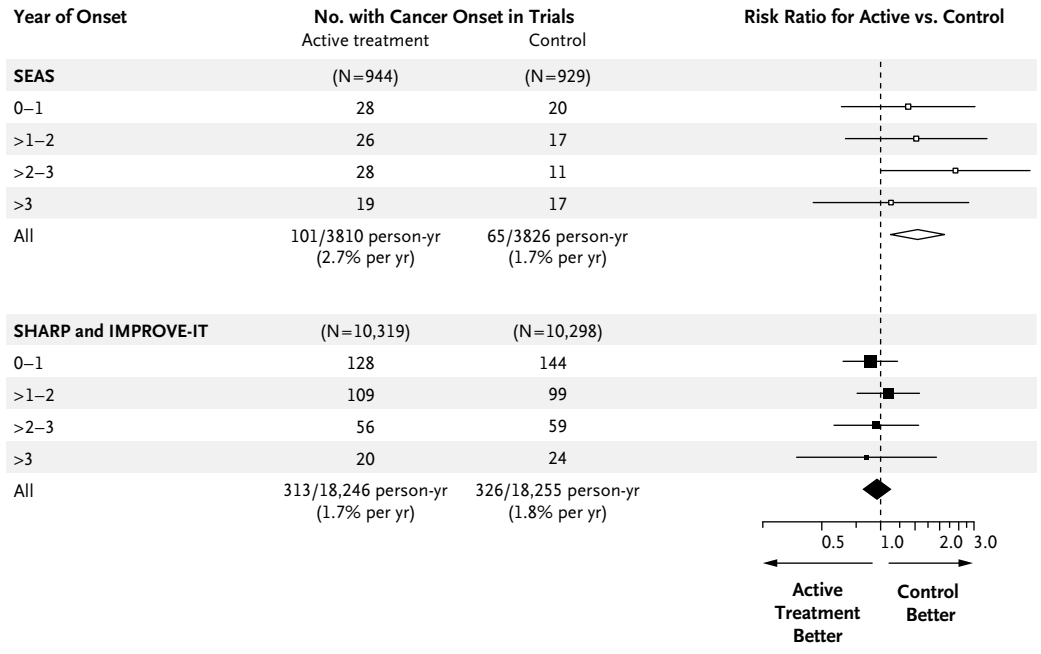

Figure 2. Relative Risk of Onset of Cancer in the SEAS Trial and in SHARP and IMPROVE-IT, According to Year of Onset.

Squares with horizontal lines are risk ratios and the corresponding 99% confidence intervals, with the sizes of the squares proportional to the amount of statistical information. The overall risk ratio (diamond) for the SEAS study was 1.55 (95% confidence interval [CI], 1.13 to 2.12) and for SHARP and IMPROVE-IT combined was 0.96 (95% CI, 0.82 to 1.12). The numbers of patients (in either treatment group) with a first cancer recorded during each year (0 to 1, >1 to 2, >2 to 3, and >3) are 201, 194, 115, and 44, respectively, for SHARP and 71, 14, 0, and 0, respectively, for IMPROVE-IT. The chi-square statistic for heterogeneity between risk ratios in SHARP and IMPROVE-IT was 0.01 (P=0.91). The chi-square statistic for trend over time in the risk ratio for SEAS was 0.00 (P=1.00), for SHARP and IMPROVE-IT combined was 0.04 (P=0.84), and for all three trials combined was 0.52 (P=0.47).

soon switched to simvastatin plus ezetimibe or placebo.[6] For these 196 patients, our analyses are from the time of this switch. Recruitment was conducted between 2001 and 2004 and, as planned, follow-up was completed in March 2008 (yielding a mean follow-up of 4.1 years [7636 person-years] for the ezetimibe comparison). Patients were 45 to 85 years of age (mean, 68) at baseline, and 61% were men.

The SHARP trial is comparing 10 mg of ezetimibe plus 20 mg of simvastatin daily as a single pill and placebo in patients with chronic kidney disease.[12] Randomization of 9264 patients took place from 2003 through 2007, with unblinded data available in July 2008, for a mean follow-up period of 2.7 years (24,937 person-years). Patients were at least 40 years of age (mean, 61) at baseline, and 63% were men.

The IMPROVE-IT trial is comparing 10 mg of ezetimibe plus 40 mg of simvastatin daily as a single pill and, as a control, 40 mg of simvastatin daily in patients with acute coronary syndrome.[13] Recruitment started late in 2005 and is ongoing, with unblinded data available in July 2008 for 11,353 (of a planned total of up to 18,000) randomized patients during a mean follow-up period of 1.0 year (11,564 person-years). Patients were at least 50 years of age (median, 62) at baseline, and 77% were men.

After the preliminary results from the SEAS trial became known in July 2008, the principal investigators of SHARP and IMPROVE-IT made the decision to ask the data and safety monitoring committees of those trials to make the interim cancer data available for analysis, without knowledge of the unblinded results of either trial. Given the robust evidence from the Cholesterol Treatment Trialists' meta-analysis that prolonged statin therapy does not materially affect rates of cancer,[1] both SHARP and IMPROVE-IT permit a

relevant test of the effect of ezetimibe on the incidence of cancer.

The current analyses are of the numbers of patients in the three studies who were recorded as having onset of cancer after the treatment period began. As in the prospectively planned Cholesterol Treatment Trialists' meta-analysis,[1] any cancers that were known to be recurrences of preexisting cancers were to be excluded. Of the 169 patients (102 in the active-treatment group and 67 in the control group) with cancer included in the preliminary SEAS analysis that was reported to the Food and Drug Administration in July, subsequent inquiry found that 9 had received the diagnosis of this cancer before the randomized comparison of ezetimibe started (with 2 in the active-treatment group and 3 in the control group having died and 2 in each group still alive), and these patients were excluded. Six additional survivors were found, since the preliminary analyses, to have had onset of cancer during the study period (three in the active-treatment group and three in the control group). This left 166 patients for the current analysis of onset of cancer (101 in the active-treatment group and 65 in the control group).

Information was sought about the primary site of each cancer (coded according to the *International Classification of Diseases, 10th Revision*) and about how long after randomization the first diagnosis occurred. For the few patients known to have died of cancer who were not recorded as having the disease on the date when last seen, the time of onset was estimated to be halfway between the date when last seen and the date of death.

STATISTICAL ANALYSIS

We compared the number of patients observed to have cancer (O) among patients randomly assigned to ezetimibe in each trial with the number that would have been expected (E) if all randomized patients in that trial had been at equal risk, using standard formulas for 2-by-2 tables[14-16] to calculate the variance (V) of (O−E). For the analyses of the incidence of cancer in the ezetimibe trials, the values of (O−E) and V were calculated separately for each year (year 0 to 1, 1 to 2, 2 to 3, and >3), relating onset of cancer in that year to the numbers of patients without cancer who were still being followed at the start of that year, and were then summed over all the study years (yielding a log-rank analysis[16] with respect to year of cancer onset). Analyses of death from cancer by year relate the number of deaths in each year from a cancer with onset during the study to the number of patients who were still alive and being followed at the start of that year.

As is conventional for testing hypotheses, two-sided P values are used: the nominal P value is calculated as the probability of the chi-square statistic with 1 degree of freedom exceeding $(|O-E|-0.5)^2 \div V$. (Use of this continuity correction of 0.5 for P value and confidence-interval calculations is appropriate, although it makes the P values slightly less extreme than those calculated by more approximate methods such as the Cox regressions used in the SEAS article.[6]) To correct for the multiplicity of tests in the analyses of site-specific cancer, the nominal P value was corrected by multiplying it (where appropriate) by the number of comparisons being made.[17] The one-step estimate of the event rate ratio (i.e., the risk ratio) for cancer is provided by the formula $\exp[(O-E) \div V]$. Since $(O-E) \div V$ has a variance of $1 \div V$, the continuity-corrected 95% confidence interval for the risk ratio is $\exp\{[O-E] \div V \pm [0.5 \div V + 1.96 \div \sqrt{V}]\}$. Risk ratios are given with 95% confidence intervals for the overall results and, to make some allowance for multiplicity of comparisons, with 99% confidence intervals (replacing 1.96 in the formula above by 2.576) for subgroup results. Any trend in the log risk ratio between the time periods considered was assessed by means of a standard multigroup chi-square test for trend.

RESULTS

HYPOTHESIS-TESTING ANALYSES OF THE INCIDENCE OF CANCER

The SHARP and IMPROVE-IT trials, with a total of 20,617 randomized patients, include about four times the number of patients for whom development of a new cancer was recorded as does the SEAS trial with 1873 patients and involve more than four times the person-years of follow-up (36,501 vs. 7636) (Table 1). If ezetimibe did increase the incidence of cancer by about 50%, then an increase should have been clearly apparent in the aggregate data from these two hypothesis-testing trials. Instead, 313 cancer cases were recorded among the patients who had been assigned to receive ezetimibe, as compared with 326 among those who had not (P=0.61), yielding

a risk ratio of 0.96, with a comparatively narrow 95% confidence interval of 0.82 to 1.12 that robustly excludes a 50% increase (Fig. 2).

When an unexpected hypothesis generated by one study is being tested by other studies, an uncorrected test of the combined results from the hypothesis-generating and hypothesis-testing studies is not statistically appropriate.[4,5] It is only the results from the hypothesis-testing studies on their own that provide an unbiased test of the new hypothesis. Even so, when newly diagnosed (i.e., incident) cancers in all three trials were considered together, there was still no significant excess: 414 in the active-treatment groups as compared with 391 in the control groups (risk ratio, 1.06; 95% CI, 0.92 to 1.22; P=0.46).

SITE-SPECIFIC CANCERS

In the SEAS trial, there were no significant increases of any particular types of cancer: the largest absolute excesses were of skin cancer (affecting 18 patients [2 with melanoma] in the active-treatment group vs. 8 [3 with melanoma] in the control group; uncorrected P=0.08) and prostate cancer (21 vs. 13 patients, uncorrected P=0.24). Table 1 shows the sites in 16 broad groups; finer subdivision yielded smaller numbers of cases per site but revealed no excesses greater than those of skin and prostate cancer. In contrast, in SHARP and IMPROVE-IT, these patterns were reversed: during the follow-up period, there were fewer, albeit not significantly fewer, patients receiving a diagnosis of skin cancer (74 patients in the active-treatment group [13 with melanoma], vs. 89 in the control group [16 with melanoma]) or a diagnosis of prostate cancer (25 vs. 36, respectively). As would be expected if active treatment has no real effect on the incidence of any type of cancer, about half the 16 site-specific results in SHARP and IMPROVE-IT favor ezetimibe and about half do not, with only 1 of these 16 comparisons (that for kidney cancer, which occurred in 25 patients in the active-treatment group vs. 11 in the control group) reaching nominal significance (uncorrected P=0.03 [before being multiplied by 16 to correct for the multiplicity of tests], corrected P=0.48).

TIME TRENDS IN THE RISK RATIO

Previous experience with the epidemiologic characteristics of the incidence of cancer in humans[7-9] and with chemical carcinogenesis in laboratory animals[10,11] shows that a causative factor that substantially increases the incidence of cancer would be expected to produce an increasing relative risk over time. But there was no evidence of a trend in the relative risk of cancer with increasing duration of follow-up in SHARP and IMPROVE-IT (P=0.84) (Fig. 2) or in all three trials together (P=0.47). The cancers in IMPROVE-IT all occurred within less than 2 years; in SHARP, however, 3894 patients and 1022 patients have been followed for at least 3 years and 4 years, respectively. About half the apparent excess incidence of cancer in the SEAS trial was observed within 2 years after treatment was started, during which period there were more than five times the number of patients with cancer in SHARP and IMPROVE-IT as in the SEAS study, without any apparent excess (Fig. 2). Moreover, more than 3 years after randomization, there was little apparent difference in incidence of cancer in the SEAS trial (19 patients with cancer in the active-treatment group vs. 17 in the control group), in SHARP and IMPROVE-IT (20 vs. 24), or in all three together (39 vs. 41).

CANCER OUTCOME

Among the patients in the active-treatment groups in SHARP and IMPROVE-IT, there was an excess, albeit not significant, of deaths from cancer with onset during the studies (97 deaths, vs. 72 in the control groups; P=0.07), but there was a shortfall, also not significant, in the number of other patients with onset of cancer during the studies (216 patients, vs. 254 in the control group; P=0.08) (Fig. 3), a proportion of whom will eventually also die of it. No significant excesses of death from any particular type of cancer were observed in SHARP and IMPROVE-IT (or in the SEAS trial [Table 2]). The largest absolute excess in SHARP and IMPROVE-IT was of death from lung cancer (21 patients in the active-treatment group, vs. 12 in the control group), but this finding was not reinforced by the patients with lung cancer recorded who were not, at least not yet, known to have died of it (12 and 16 patients, respectively) or by the results for onset of lung cancer in the SEAS trial (7 and 10 patients, respectively) (Tables 1 and 2).

When all three trials were considered together, there was a nominally significant excess of death from cancer among the patients assigned to receive ezetimibe as compared with the controls (134 vs. 92; risk ratio, 1.45; 99% CI, 1.02 to 2.05;

Recorded Cancer Outcome	No. with Cancer Onset in Trials		Risk Ratio for Active vs. Control (confidence interval)
	Active treatment	Control	
SEAS			
Already died of cancer	37	20	
Not yet dead from cancer	64	45	
Total	101 (2.7% per yr)	65 (1.7% per yr)	
SHARP and IMPROVE-IT			
Already died of cancer	97	72	
Not yet dead from cancer	216	254	
Total	313 (1.7% per yr)	326 (1.8% per yr)	

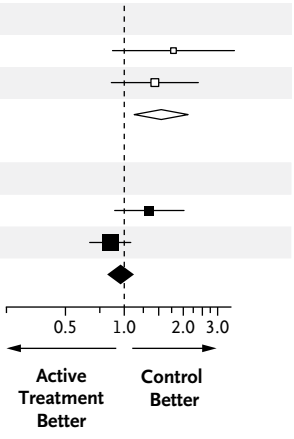

Figure 3. Relative Risk of Onset of Cancer in the SEAS Trial and in SHARP and IMPROVE-IT, According to Recorded Outcome.

Squares with horizontal lines are risk ratios and the corresponding 99% confidence intervals, with the sizes of the squares proportional to the amount of statistical information; the diamonds indicate the overall risk ratios and 95% confidence interval. The overall risk ratio (diamond) for the SEAS study was 1.55 (95% confidence interval [CI], 1.13 to 2.12) and for SHARP and IMPROVE-IT combined was 0.96 (95% CI, 0.82 to 1.12). The chi-square statistic for the difference between the risk ratios from the SEAS study and from SHARP and IMPROVE-IT combined was 7.5 (P=0.006).

uncorrected P=0.007). This P value for all three studies together does not, however, provide an unbiased test of the hypothesis generated by the SEAS trial. Moreover, this apparent excess of deaths from cancer is not reinforced by the shortfall in the numbers, in the three active-treatment groups, with onset of cancer that has not, at least not yet, been recorded as causing death (280 patients, vs. 299 controls). Nor was there any evidence of a trend in the relative risk of death from cancer over time in SHARP and IMPROVE-IT alone (P=0.25) (Fig. 4) or in all three trials together (P=0.54).

DISCUSSION

Many clinical trials of new drugs for a variety of conditions are in progress at any given time, and these trials routinely monitor not only the outcomes that are expected to be affected by the trial treatments but also many outcomes that are completely unrelated to the trial treatments. Each year, this monitoring may generate many thousands of analyses of associations between a treatment and an unrelated outcome. On the basis of chance alone, many conventionally significant associations (e.g., those with P<0.01 or even P<0.001) of particular drugs with particular outcomes will arise that misleadingly suggest an unexpected benefit or hazard (as happened with statin therapy[2,3]). Against this background, trial results with such P values that indicate an unexpected hazard should generally be treated not as good evidence of a hazard but merely as a finding that generates a hypothesis that should be tested by means of statistically independent evidence, preferably based on much larger numbers of relevant outcomes.[4,5]

Previous large-scale randomized trials have shown that substantial lowering of LDL cholesterol through various statin regimens is not itself associated with any significant effects on the rates of cancer during approximately 5 years of treatment and follow-up (Fig. 1).[1] For the addition of ezetimibe to statin therapy, the unexpected hypothesis raised by the SEAS results was that the overall incidence of cancer might be increased by about 50% (with about half of this excess being seen within less than 2 years after the start of the study treatment). This hypothesis came from a subsidiary analysis; the overall incidence of cancer was not prespecified as a primary

Table 2. Numbers of Deaths from Cancer in the SEAS Trial and in SHARP and IMPROVE-IT.

Value	SEAS Trial				SHARP and IMPROVE-IT			
	Active Treatment (N=944)	Control (N=929)	Uncorrected P Value	Corrected P Value*	Active Treatment (N=10,319)	Control (N=10,298)	Uncorrected P Value	Corrected P Value*
Total follow-up for death (person-yr)	4001	3933			18,604	18,644		
Death from any cancer								
No.	37	20	0.04†	—	97	72	0.07	—
Percent per yr	0.9	0.5			0.5	0.4		
Site of fatal cancer								
Lip, mouth, pharynx, or esophagus	1	0	1.00	1.00	7	8	1.00	1.00
Stomach	4	1	0.38	1.00	3	5	0.72	1.00
Large bowel or intestine	3	1	0.63	1.00	5	10	0.30	1.00
Pancreas	2	0	0.49	1.00	4	5	1.00	1.00
Liver, gallbladder, or bile ducts	2	3	1.00	1.00	6	5	1.00	1.00
Lung	6	8	0.77	1.00	21	12	0.17	1.00
Other respiratory site	1	0	1.00	1.00	3	1	0.62	1.00
Skin	0	0	—	1.00	1	1	1.00	1.00
Breast	1	0	1.00	1.00	2	0	0.48	1.00
Prostate	2	0	0.49	1.00	4	1	0.37	1.00
Kidney	1	0	1.00	1.00	7	1	0.08	0.88
Bladder	4	1	0.38	1.00	4	2	0.68	1.00
Genital site	3	2	1.00	1.00	1	0	1.00	1.00
Hematologic site	3	2	1.00	1.00	6	10	0.45	1.00
Other known site	1	0	1.00	1.00	7	1	0.08	0.88
Unspecified	3	2	1.00	1.00	16	10	0.33	1.00

* Multiple uncorrected P values are reported; any value that is based on data from more than five patients could have yielded a value less than 0.05 by chance. Uncorrected P values that are less than the inverse of the number of such tests were therefore corrected by multiplying by the number of such tests to correct for this multiplicity of comparisons; other corrected P values are 1.00.

† This uncorrected P value of 0.04 requires substantial correction for the fact that it was the SEAS result for any cancer that unexpectedly generated the hypothesis being studied. (Uncorrected P values of 0.01, or even 0.001, that generate an unexpected hypothesis cannot be used directly to test it.)

outcome or even a secondary outcome in the SEAS trial. In aggregate, the hypothesis-testing SHARP and IMPROVE-IT trials involve about four times as much information about the incidence of cancer as does the hypothesis-generating SEAS trial. In the analysis of SHARP and IMPROVE-IT (or of all three trials together), there was no significant excess incidence of cancer, either overall or at any particular site, and there was no suggestion of an emerging trend with longer treatment and follow-up periods. Epidemiologic knowledge about chemical causes of cancer in humans[7-9] suggests that a large proportional increase in the incidence of several types of solid tumor over a small fraction of the human life span is implausible.

Considered in isolation, the observation that there were more deaths, albeit not significantly more, from cancer among patients receiving ezetimibe in SHARP and IMPROVE-IT might be cause for concern. But, as was the case for newly diagnosed cancers, there were no significant excesses of death from any particular type of cancer. Moreover, the number of other cases of cancer was lower, though not significantly so, in the active-treatment groups as compared with the control groups. A factor that truly increased the risk of death from cancer substantially and rapidly (as compared with the usual induction time of, e.g., lung cancer by smoking[8,9]) would also be likely to increase the incidence of cancer substantially over the same timescale. Hence, the tendency seen in SHARP and IMPROVE-IT for

Year of Death	No. with Onset and Death from Cancer in Trials		Risk Ratio for Active vs. Control (confidence interval)
	Active treatment	Control	
SEAS	(N=944)	(N=929)	
0–1	5	3	
>1–2	1	8	
>2–3	10	3	
>3	21	6	
All	37/4001 person-yr (0.9% per yr)	20/3933 person-yr (0.5% per yr)	
SHARP and IMPROVE-IT	(N=10,319)	(N=10,298)	
0–1	31	21	
>1–2	38	25	
>2–3	24	18	
>3	4	8	
All	97/18,604 person-yr (0.5% per yr)	72/18,644 person-yr (0.4% per yr)	

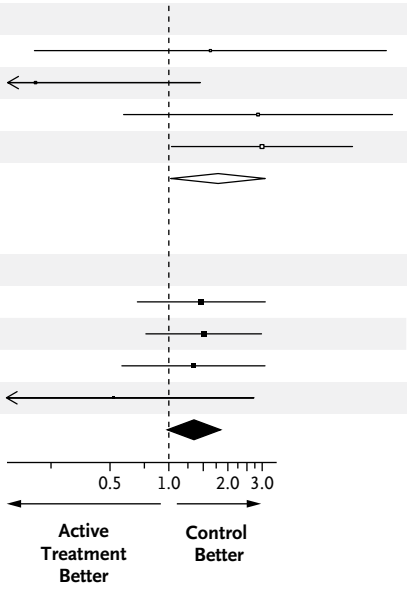

Figure 4. Relative Risk of Death from Cancer in the SEAS Trial and in SHARP and IMPROVE-IT, According to Year of Onset.

Squares with horizontal lines are risk ratios and the corresponding 99% confidence intervals, with the sizes of the squares proportional to the amount of statistical information. The overall risk ratio (diamond) for the SEAS study was 1.78 (95% confidence interval [CI], 1.03 to 3.11) and for SHARP and IMPROVE-IT combined was 1.34 (95% CI, 0.98 to 1.84). The chi-square statistic for heterogeneity between risk ratios in SHARP and IMPROVE-IT was 0.53 (P=0.47). The chi-square statistic for trend in the risk ratio for SEAS was 4.45 (P=0.03), for SHARP and IMPROVE-IT combined was 1.35 (P=0.25), and for all three trials combined was 0.38 (P=0.54). Unlike the 99% confidence intervals in Figure 3, the 95% confidence intervals in this figure do not make any correction for the data-dependent decision to present data on death from cancer separately.

the relative risks of death from cancer and of cancers that have not yet caused death to be opposite in direction from one another is not good evidence for the implausible hypothesis that the tested treatment rapidly affects the risk of death from cancer but not the incidence of cancer. This is a wholly new hypothesis and is not the hypothesis that was generated by the SEAS trial (indeed, the SEAS trial does not support it), and strong, independent evidence would be required before it ceased to be implausible.

Consequently, the currently available results do not provide credible evidence of any adverse effect on cancer of the addition of ezetimibe to statin therapy. In light of these findings and a review of interim data on the other outcomes that were available to them (but that remain unavailable to the investigators and all others), the independent data and safety monitoring committees of both SHARP and IMPROVE-IT have recommended that those trials continue to their scheduled end dates early in the next decade. Continuation of these trials, with regular interim analyses of unblinded data (including increased surveillance for safety) by their data and safety monitoring committees, will permit even more reliable evidence to emerge about the effects of combined ezetimibe and statin therapy (which produces a larger reduction in LDL cholesterol than can be achieved by monotherapy), not only on cancer but also — and, perhaps, most important — on the heart attacks, strokes, and other major vascular outcomes that this treatment may be found to prevent.[18]

The publication of these interim cancer results is a sign of an important and growing problem in the conduct of major clinical trials. Previously, established methods for monitoring interim safety and efficacy data in trials have generally

worked well to help ensure that patients are appropriately protected and that treatments are reliably evaluated,[19,20] and interim results have been made public only if clear evidence of benefit or harm emerged before the scheduled end of the study. Recently, as in the present case, the unusual levels of public discussion of the safety of drugs have led to public disclosure of interim results to reassure patients and their doctors. The need for such premature disclosure of interim findings could be lessened in the future by the initiation of larger, more definitive outcome trials earlier in the life cycle of potentially important new drugs and devices.[21]

These analyses were initiated, conducted, interpreted, and reported (here and, in preliminary form, to the Food and Drug Administration in July) by the authors, independently of any pharmaceutical company. Although the Clinical Trial Service Unit & Epidemiological Studies Unit (CTSU) are conducting SHARP and the Duke Clinical Research Institute is conducting IMPROVE-IT (in collaboration with the Thrombolysis in Myocardial Infarction Study Group), they are doing so independently of the study funders (Merck and Schering-Plough).

The CTSU has a policy of not accepting any honoraria or consultancy fees that directly or indirectly come from industry, although costs of taking part in scientific meetings can be paid. Oxford University is applying for a patent on a genetic test to predict statin-induced myopathy.

Dr. Clare reports having a salaried role as statistician in the IMPROVE-IT trial and Dr. Califf reports receiving consulting fees from Merck and Schering-Plough that are donated to his university and to not-for-profit charities. No other potential conflict of interest relevant to this article was reported.

We thank the patients who have agreed to take part in these trials, the collaborating institutions and investigators, and the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) investigators for unpublished cancer-incidence data.

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