The evidence on trial: cholesterol lowering and cancer

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In an ideal world, medical care would be informed by a complete evidence base, implemented through supportive and appropriately funded systems and enacted by patients who, after being fully informed about the overall potential net benefits and any personal costs, complied with their recommended therapies.

The reality is in stark contrast. The evidence is usually incomplete, many governments do not “value” prevention, while the time pressures on professionals hinder their ability to deliver evidence-based care. In addition, the general population may become increasingly sceptical about some aspects of medical treatments, particularly in relation to the ever-growing incidence of adverse events leading to product withdrawals. This is often because of cultural factors and, at times, the sensational reporting by media of any safety concerns, disproportionately to the benefits of a treatment. As a consequence, full compliance of patients with recommended therapies infrequently occurs.

The recently published Simvastatin and Ezetimibe in Aortic Stenosis (SEAS) study has again ignited controversy related to the possibility that cholesterol lowering may be associated with cancer.1 The question is a very important one. Cholesterol-lowering agents, particularly statins, are among the most commonly prescribed drugs, and their initiation may translate to potential exposure for 30 years or more. This article examines the scientific evidence base underlying such discussions and this topic in particular.

SEAS STUDY

Ezetimibe inhibits the intestinal absorption of cholesterol by binding to the Niemann–Pick CI-like 1 protein. The combination of ezetimibe and an HMG-CoA reductase inhibitor (“statin”) is logical. This is because statins lower low-density lipoprotein (LDL) cholesterol by inhibition of cholesterol synthesis and upregulation of the hepatic LDL receptor which clears cholesterol from the vascular compartment, but at the same time, they increase the intestinal absorption of cholesterol.

In the double-blind controlled SEAS trial, 1873 patients with asymptomatic mild-moderate aortic stenosis and no indication for statin therapy were randomised to receive the coformulation of simvastatin 40 mg and ezetimibe 10 mg daily or matching placebo. The study was based on previous observational data relating cholesterol and cholesterol lowering to progression of aortic stenosis and the known associated pathology of the aortic valve in this condition, which resembles atherosclerosis.

Despite a large reduction in LDL cholesterol of 61% to a mean of 53 mg/dl (1.3 mmol/l) at 8 weeks, and a 54% reduction over total follow-up (of a mean of 4.1 years), treatment with simvastatin and ezetimibe failed to reduce the primary end-point, a composite of aortic valve disease events and ischaemic cardiovascular events (hazard ratio 0.96; 95% CI 0.83 to 1.12; p = 0.59). Results concerning secondary endpoints were mixed, with a significant reduction in ischaemic cardiovascular events, but not aortic valve disease events alone.

Why the controversy? In the group assigned simvastatin and ezetimibe, incident cancer was diagnosed in 105 patients (11.1%) compared with 70 patients (7.5%) among those assigned placebo (p = 0.01). The excess cancers in those randomised to simvastatin and ezetimibe were not clustered at any particular site. Further analysis showed that the risk of incident cancer was not associated with the degree of LDL-cholesterol lowering. Fatal cancers occurred in 39 patients (4.1%) of those randomised to simvastatin and ezetimibe, and 23 (2.5%) of those randomised to placebo. The hazard ratio for cancer-related mortality was 1.67; 97% CI 1.00 to 2.79; p = 0.05 using the prespecified Cox proportional hazards model (p = 0.06 with Yates’ logrank continuity correction). Notably, neither cancer incidence nor mortality was designated as a primary or secondary endpoint in SEAS, and these results arose from analyses of possibly a large set of safety endpoints and thereby are at greater risk of being merely a chance finding.

These unexpected results in an unplanned endpoint could only be considered as hypothesis generating, rather than being definitive. Realising this, the pooled interim analysis of cancer data from two ongoing placebo-controlled trials of simvastatin and ezetimibe accompanied the SEAS publication, along with two editorials.2, 3

The two trials in the pooled interim analyses were the Study of Heart and Renal Protection (SHARP) study4 and the Improved Reduction of Outcomes: Vytorin Efficacy Intervention Trial (IMPROVE-IT).5 These trials are ongoing in patients with chronic kidney disease and following acute coronary syndromes, respectively. The SHARP study is a placebo-controlled trial of simvastatin 20 mg and ezetimibe 10 mg, and 9264 patients with a mean follow-up of 2.7 years and IMPROVE-IT (testing simvastatin 40 mg and ezetimibe 10 mg) including 11 353 patients with a mean follow-up of 1.0 year at the time of the pooled analysis of cancer data. In the combined analysis of SHARP and IMPROVE-IT, there was no increase in either all incident cancers (313 on simvastatin and ezetimibe vs 326 on placebo, risk ratio 0.96; 95% CI 0.82 to 1.12; p = 0.61) or cancer at any organ-specific site. There was a non-significant excess in cancer deaths (97 vs 72; p = 0.07) in those randomised to receive simvastatin/ezetimibe but fewer non-fatal cancers (216 vs 254; p = 0.08).

There was also no evidence of a trend in the risk of incident or fatal cancer with increasing duration of follow-up in this pooled analyses of the SHARP study and IMPROVE-IT.6 This might be expected if the treatment were related to cancer risk. Together, these point towards the increased cancer incidence and mortality in SEAS being merely a chance finding. The authors concluded that “the available results … do not provide credible evidence of any adverse effect of ezetimibe on rates of cancer.”7

SCIENTIFIC EVIDENCE BASE

In general, the evidence related to benefit or harm of specific interventions is derived from multiple sources. These include:
Carcinogenicity in rodents is generally assumed to indicate risk for humans, particularly when compounds are genotoxic in both rats and mice, and several sites are involved. In the case of statins, it was accepted that the hepatic carcinogenicity observed in rodents was related to a non-genotoxic mechanism which involved the induction of peroxisomal proliferation. Fibrates (including nafenopin), and substances such as phthalate plasticisers used in medical devices, produce similar effects. However, human hepatic cells are quite resistant to drug-induced peroxisomal proliferation. What has not been clear is why statin administration can lead to the development of tumours in rodents at other sites where peroxisomal proliferation has not been observed. In addition, although there has been a substantial margin of safety when clinical doses are compared on a mg/kg body weight to the lowest statin doses producing tumours in rodents, the margins are less when statin blood concentration areas under the curve (AUC) data are compared.

Other basic science: potential for protective effects of statins and adverse effects of ezetimibe

Experimental data have also suggested that statins may protect against cancer by stimulation of apoptosis,10–12 modulation of the inhibitory effects of vascular endothelium-derived growth factor (VEGF) on apoptosis, promotion of cell cycle arrest and reduction in tumour cell adhesion and migration.13–14 Inhibition of enzymatic processes for signalling proteins such as Ras may also prevent further growth of existing cancers and tumour metastases, possibly by effects on angiogenesis.15 16

In the case of ezetimibe, the editorials9 4 accompanying the publication of SEAS (1) and the pooled analysis of the SHARP study and IMPROVE-IT (2) suggested a note of caution. This is because ezetimibe blocks not only the absorption of cholesterol but also phytosterols and other molecular substances that have been linked to protection against cancer.9 4 17 However, animal studies have not shown that low phytosterol levels are associated with development of tumours.

Epidemiological studies

Data from epidemiological studies are also conflicting, and some studies suggest that statins may protect against cancer. Representative among these analyses:

- A case-control study from the USA reported an overall relative risk for any cancer among statin users of 1.0 (95% CI 0.9 to 1.2) compared with the reference exposure group.20 Analysis was restricted to subjects followed for at least 3 years (median 6.4 years). Marginally significantly increased risks of colon cancer and rectal cancer were reported among current statin users of 5 years or longer, with a relative risk of 3.5 (95% CI 1.1 to 10.9) and 4.2 (95% CI 1.0 to 16.6), respectively.

- A prospective cohort of 2781 patients with definite or possible familial hypercholesterolaemia was compared with the expected mortalities in the general population. A standardised mortality ratio for the cohort of 0.6 (95% CI 0.4 to 0.8) was observed (32 cancer deaths in total) over an 18-year period.21 In this study, widespread statin usage did not occur until halfway through the study recruitment period.

- A large ongoing prospective cohort study of male health professionals in the USA reported a relative risk for prostate cancer of 0.41 (95% CI 0.19 to 0.77) among participants reporting the use of “cholesterol lowering agents”16 (which were predominantly statins but without direct identification of brand, type or dose of agent used), compared with never users, monitored over a 12-year period to the beginning of 2002.22 It is most likely that widespread statin usage did not occur in this study until about half-way through follow-up, and results could possibly be influenced by selection bias induced by 22% of eligible participants being excluded from analysis due to not reporting baseline medication use.

- A case-control study in Massachusetts with a follow-up of just under 4 years estimated an odds ratio of 0.92 (95% CI 0.78 to 1.09) of developing colorectal cancer among participants who had utilised statins regularly for at least 3 months.23

- A Danish population-based cohort study reported adjusted rate ratios for cancer among statin users of 0.86 (95% CI 0.78 to 0.95) compared with 0.73 (95% CI 0.55 to 0.98) for non-statin users.24 The mean follow-up period was 3.3 years for the statin cohort and 5.1 years for non-statin users. This possible protective effect of statins was observed despite the older age of those on statins.

- Linkage of a community pharmacy-based database to hospital discharge studies (malignant lymphomas (pravastatin), and substances such as phthalate plasticisers used in medical devices, produce similar effects. However, human hepatic cells are quite resistant to drug-induced peroxisomal proliferation. What has not been clear is why statin administration can lead to the development of tumours in rodents at other sites where peroxisomal proliferation has not been observed. In addition, although there has been a substantial margin of safety when clinical doses are compared on a mg/kg body weight to the lowest statin doses producing tumours in rodents, the margins are less when statin blood concentrations areas under the curve (AUC) data are compared.

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records for residents of eight Dutch cities concluded that statins were protective against cancer when used for longer than 4 years (adjusted odds ratio 0.50; 95% CI 0.40 to 0.63).25 Self-report of statin use was confirmed by examining prescription records in 95.6% of a subgroup. The use of fibric-acid derivatives was not associated with reduced risk (adjusted odds ratio 1.08; 95% CI 0.59 to 2.01).26

A US case-control study showed that after adjustment for other potential risk factors, statin use was associated with a significant reduction in prostate cancer risk (odds ratio 0.38; 95% CI 0.21 to 0.69) and specifically more aggressive prostate cancer (Gleason score ≥7).27

The methodology differed in these studies examining possible associations of cholesterol lowering and cancer. Confounding also remains a potential problem, even after attempts were made to minimise this using approaches such as propensity analysis.

**Clinical trials**

Large-scale clinical trials have established beyond any reasonable doubt that cholesterol lowering, particularly with statins, reduces atherothrombotic events.27 28

Two individual statin trials had previously raised concern about a possible association of statin treatment with cancer. In the Cholesterol and Recurrent Events (CARE) trial, with a mean follow-up of 4.9 years, breast cancer occurred in nine patients who were randomised to pravastatin 40 mg daily and none assigned placebo.29 However, this result was not replicated in the larger Long-Term Intervention Pravastatin in Ischaemic Disease (LIPID) study which tested the same dose of pravastatin;29 nor was there an excess of breast cancer in those randomised to placebo in the analysis by the Cholesterol Treatment Trials' Collaboration (risk ratio 1.01; 95% CI 0.73 to 1.40; p = 0.76).

In FROSPER, another trial of pravastatin in individuals aged 70 years and over at baseline, over a mean of 5.2 years' follow-up, there was an excess of cancers in those randomised to active treatment (245 vs 199 persons; uncorrected p = 0.02).30 Again, this was also not replicated in similar patients in the Cholesterol Treatment Trials Collaboration (risk ratio 1.03; 95% CI 0.91 to 1.16; p = 0.47).

Longer-term data concerning clinical trial patients exposed to statin therapy come from extended follow-up in the Scandinavian Simvastatin Survival Study (4S),31 the Long-term Intervention with Pravastatin in Ischaemic Disease (LIPID) study32 and the West of Scotland Coronary Prevention Study (WOSCOPS).33–36 These have not shown any association of statin treatment with either incident cancer or cancer death (table 1).

**Meta-analyses**

Contemporary meta-analyses of the association between statins and all malignancies have typically produced overall neutral results for all cancers.37 34–36 There were also no significant associations for organ-specific malignancies such as breast cancer37 and melanoma,36 nor for pravastatin38 and atorvastatin39 as individual agents, although one recent meta-analysis reported an increased risk of cancer among elderly patients treated with pravastatin.40

The Cholesterol Treatment Trials Collaboration44 is noteworthy because of the availability of individual patient data from 14 statin trials involving more than 90 000 patients in whom total cholesterol was lowered by about 1 mmol/l (40 mmol/l). The CTTC analysis showed no evidence of increased cancer risk among a total of 5614 patients who had incident cancer after randomisation to the particular trial (risk ratio 1.00; 95% CI 0.95 to 1.04); nor were there any differences in cancer deaths (in 2163 patients, relative risk 1.01; 95% CI 0.91 to 1.12) or signal that cancer incidence was increased in those with lower cholesterol levels or with a longer duration of treatment.

A more recent meta-analysis included 15 randomised controlled statin trials with more than 100 person years of follow-up (average follow-up 4.5 years) and 5752 new cases of cancer.41 A higher incidence of cancer was found among patients achieving lower low-density lipoprotein cholesterol (LDL-C) levels. This is consistent with observations in previous epidemiological studies but confounding factors related to cancer and LDL-C, as well as the context of the trials involved, may have influenced the results observed.42

To support this, subjects randomised to treatment with a placebo rather than a statin demonstrated the same association between low LDL-C and cancer risk.43 Of most interest, though, the cancer incidence was higher among patients utilising lower doses of statins (p = 0.003 and p = 0.007 for comparisons between low and high dose, and intermediate and high dose, respectively). This may represent a chance finding, but one possible explanation could be potentially biphasic effects of statins on angiogenesis, in which they may enhance and inhibit angiogenesis at low and high doses, respectively.44

The duration of treatment in the randomised trials was only approximately 4–6 years, much less than the length of potential exposure to drug therapy. In addition, these neutral results would be expected for any solid tumour carcinoma where the duration of exposure was substantially less than the latency period.

**BROADER IMPLICATIONS AND THE NEED FOR PHARMACOVIGILANCE STUDIES**

Conclusions regarding these aspects may be informed in a variety of ways, but ultimately, infrequent events such as cancer require preplanned longer periods of data collection. Randomised controlled trials are the most reliable way to minimise confounding and bias, and to estimate treatment effects. However, as mentioned earlier, they are much less effective in establishing whether or not an intervention is associated with a serious adverse event.

The placebo-controlled trials of statins and published longer-term follow-up of such trials provide some reassurance regarding the safety of statins with respect to any association with cancer. However, the placebo-controlled data are limited by the relatively short period of exposure and also because analysis is made on an intention-to-treat basis. For example, the usual time for induction of lung cancer by smoking is many years longer.45 Longer-term follow-up of trial cohorts is also somewhat flawed because subjects were/must be offered proven therapies (such as statins) at the end of the controlled trials phase, minimising the differential in exposure to the treatment. For example, in the WOSCOPS, during extended follow-up of the cohort, the percentages of participants being treated with a statin among those initially...
assigned to pravastatin and placebo were, respectively, 28.6% and 24.3% at 1 year, 53.6% and 29.4% at 3 years, and 38.7% and 35.2% at 5 years.\(^5\)

New analytical approaches are needed to address problems such as this. Progress has been made recently with statistical methods to assess efficacy associated with full compliance to treatment\(^6\) and assessment of dynamic treatment regimens;\(^6\) however, these methods are necessarily based on strong assumptions.

Many countries have cancer registries and the potential for linkage of administrative datasets utilised in extended follow-up of patients in clinical trials.\(^5\) It is prudent to establish and enhance systems that can link large databases. In the case of statins, one example is provided by the VISN16 database in the USA. Interrogation and case-control analysis in 40 421 women in this database, which contains clinical and demographic information about all veterans (>1.4 million patients) cared for in the fourth Central VA Health Care Network between 1998 and 2004, showed that after appropriate adjustment for age, smoking, alcohol use and diabetes, which were all significant covariates, women using statins were less likely to develop breast cancer (odds ratio 0.49, 95% CI 0.38 to 0.62).\(^5\) Internal consistency was suggested by the fact that increased breast cancer risk was also shown for documented risk factors.

Specifically, pharmacovigilance data during malignancy in patients on long-term cholesterol lowering therapy could be compared with national age-specific incidence and mortality data. Such monitoring could also help ascertain whether any drug-class effect or organ-specific effects exist (deleterious or beneficial). These data-linkage systems should include a variety of stakeholders, including regulatory authorities from different countries and the pharmaceutical industry, all cooperating in the provision of more robust information in this and other important areas of pharmacovigilance. Recent issues surrounding the long-term uncertainty of rosiglitazone, cyclo-oxynase-2 inhibitors and hormone replacement therapy have further highlighted that medication safety must be proven rather than assumed, especially for very widely used medications utilised for long-term therapy.

At this time, it is considered unlikely that cholesterol-lowering generally is associated with cancer. Since the excess cancer mortality in the SEAS trials was not replicated in the interim data in the SHARP and IMPROVE-IT trials, this conclusion will probably extend to simvastatin/ezetimibe as further data are obtained in the ongoing trials.\(^5\)\(^6\)

### WHAT SHOULD WE NOW DO WITH PATIENTS TAKING SIMVASTATIN AND EZETIMIBE (“VTORIN”)?

The Data and Safety Monitoring Committees of both IMPROVE-IT and SHARP have reviewed the cancer data, and have discussed and recommended that both trials continue as planned, with particular surveillance concerning future data in this area. Similarly, the Food and Drug Administration in the USA decided that no action was necessary after SEAS was published.\(^5\) Ezetimibe and its coformulation with a statin are important additions to cholesterol-lowering therapies. It appears inappropriate to withdraw them from patients in whom their indication is clear and to await the results of ongoing clinical trials\(^5\)\(^6\) and further information concerning cancer which should be derived from these trials and other sources, including long-term surveillance data, which are required because of the typically very long latency period before cancer is diagnosed.

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### REFERENCES

Controversies in cardiovascular medicine


44. Steinberg D. Statin treatment does not cause cancer. J Am Coll Cardiol 2008;52.


