Should we lower cholesterol as much as possible?

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The campaign still faces several key challenges. It has had limited success in engaging patients and families, payers, and employers. Their involvement would provide hospitals with a more urgent sense of external demand for high quality care. Also, because it was not compulsory for hospitals to submit process and outcome data for the six interventions and because the calculations of lives saved are imprecise at hospital level, the campaign can give only limited information about performance of individual facilities.

The campaign's pluralistic approach has also led to various challenges. The regional nodes participate voluntarily, making it difficult to standardise support to participants. These field offices have different amounts of time and resources for campaign activities, although clear expectations and toolkits have helped limit variation in performance. In addition, the campaign did not enforce a deadline for enrolling hospitals, resulting in a constant stream of new participants. Their forward momentum would have been improved by a robust induction process and a system for ongoing, customised coaching in quality improvement methods.

Finally, the campaign has had to work hard to maintain coalitions of partners, participants, and nodes, given complex relationships and the strong interests of different parties. Regular communication, clear definition of each party's role, and an unambiguous national agenda have all been vital. The institute hopes that the campaign has created a national network for continuous improvement that can be used to generate powerful and sustained efforts for years to come.

DRC, who worked tirelessly for the campaign, died on 7 April 2006. We thank Jane Roessner for her contribution to the preparation and editing of this article.

Contributors and sources: CJM manages all aspects of the 100 000 Lives Campaign at the Institute for Healthcare Improvement; DRC was instrumental in researching the evidence supporting the campaign's six interventions; MWS is a leader in developing and refining the institute's spread model; and AGN oversees the campaign's field operations. CJM is guarantor.

Summary points

The US 100 000 Lives Campaign aims to cut hospital deaths over 18 months

The campaign focuses on six effective, evidence based, clinical interventions

Rapid spread of change is facilitated by a national and regional support network

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Controversy

Should we lower cholesterol as much as possible?

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Statins are portrayed as harmless drugs that almost everyone would benefit from, but little is known about the side effects at the high doses now being suggested

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People at high risk of cardiovascular disease should be treated more aggressively. This is the message from the American National Cholesterol Education Program published last year.[1] By aggressively, it means that low density lipoprotein (LDL) cholesterol concentrations should be lowered to less than 1.81 mmol/l. Recently, Getz et al calculated that in Norway, one of the healthiest nations in the world, about 85% of men and more than 20% of the women over age 40 would be classified as high risk using this criterion.[2] If followed, the new recommendations might therefore put most of the Western world's adult population on statin therapy. As the risk to benefit ratio for a more drastic lowering of low density lipoprotein cholesterol is unknown we question the wisdom of this advice.

Are higher statin doses safe?

To achieve this new goal, people at high risk would have to take higher statin doses than currently suggested. This would increase the risk of adverse side effects. In the treating to new targets (TNT) trial, the only study comparing a low and high dose of the same statin, not even 80 mg atorvastatin was able to lower

mean low density lipoprotein cholesterol below 1.81 mmol/l.[3] Clinical experience has taught us that a dose increase of that size of any drug will inevitably increase both the number and the seriousness of side effects. This apparently did not concern the authors, who concluded, "Intensive lipid lowering therapy with 80 mg of atorvastatin per day in patients with stable CHD [coronary heart disease] provides significant clinical benefit."

However, overall mortality was not reduced because the smaller number of cardiovascular deaths in the 80 mg atorvastatin group was offset by increased deaths from other causes leaving a benefit of 250 (5%) fewer non-fatal cardiovascular events. Because many non-fatal events resolve with little residual damage or discomfort, meticulous recording of all possible adverse side effects is mandatory. However, the authors have not provided adequate information on adverse events.[4 5]

Deficient information about side effects

The authors failed to elaborate on their criteria for determining whether an adverse effect was considered related to treatment. Surprisingly, that decision was not made by the authors but by the investigator with direct responsibility for the patients. Specific information about the symptoms that were designated as side effects was also incomplete. For instance, only the number of patients with aminotransferase concentrations that were persistently over three times the upper limit of normal was listed (51 more cases in the high dose group). Why not give the number of participants showing any persistent rise as is customary in drug trials?

In the recent incremental decrease in end points through aggressive lipid lowering (IDEAL) trial,[6] which compared usual dose simvastatin with 80 mg atorvastatin, no significant difference was seen on the major end points. However, the number of adverse effects were far higher than in any previous statin trial. Almost 90% of participants in both groups had side effects, and in almost half of them they were recorded as serious. The authors of the IDEAL trial did not comment on this alarming finding except by mentioning that "there was no difference between the groups in the frequency of adverse events that were rated as serious"; neither did they inform readers about the nature of these events.

Adverse effects of statins

Many adverse effects are first recognised in the post-marketing surveillance process, and their frequency is likely to be understated because few doctors report them. A request among general practitioners in Rhode Island found that the serious side effects that had been reported from any drug to the Food and Drug Administration included only 1% of those observed.[7] Nevertheless, many hitherto unknown potential side effects from statins have already been reported.

Heart failure

All statins inhibit the synthesis of hydroxymethylglutaryl coenzyme A reductase, an enzyme involved in synthesis of the precursor of cholesterol and other important molecules such as coenzyme Q10, vital for mitochondrial energy production. Thus statins lower plasma Q10 concentrations and worsen cardiac function in patients with heart failure, and oral coenzyme Q10 can improve or prevent this serious complication.[8–10] Heart failure has not been reported with statins, possibly because it has been seen to be the result of the primary disease rather than an adverse effect but also because patients with imminent or manifest congestive failure are routinely excluded from statin trials.

Myalgia and rhabdomyolysis

Muscle complaints are claimed to occur in less than 1% of patients taking statins, but this is almost certainly an underestimate. In a study of 22 professional athletes with familial hypercholesterolaemia who were treated with various statins, sixteen discontinued the treatment because of muscle side effects.[11] Competitive athletes may be more sensitive to muscle pain and weakness, but even mild symptoms may have a deleterious effect on elderly people and others who already have muscular weakness.

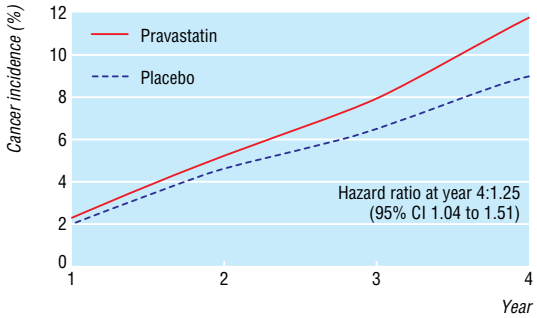
In rare cases, myopathy has led to rhabdomyolysis and death from renal failure. In the TNT trial,[3] five non-fatal cases of rhabdomyolysis were reported, four of them during the treatment period. To consider them unrelated to the treatment because they were not dose-dependent, as did the authors, seems premature. In a recent review of statin side effects the authors had found 4.2 cases of rhabdomyolysis per 100 000 patient years after atorvastatin treatment.[12] If true, and if the five cases observed in the TNT trial (50 000 patient years) were not due to treatment it means that rhabdomyolysis should be twice as common in untreated people than in those treated with statins.

Mental and neurological symptoms

Cholesterol is vital for the development and function of the brain. It is therefore unsurprising that reduced concentrations may produce mental and neurological complaints such as severe irritability, aggressive behaviour, suicidal impulses, cognitive impairment, memory loss, global amnesia, polyneuropathy, and erectile dysfunction.[13–19] In many cases the symptoms were reversible and re-occurred after re-challenge. None of these side effects are mentioned on the product labels or information inserts for statins.

Cancer

At least five animal experiments have found that the statins are carcinogenic in amounts that produce blood concentrations similar to those achieved by doses



Cancer incidence after statin treatment of elderly people at risk of vascular disease[23]

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commonly administered to patients.[20] Nevertheless, the FDA approved them because cell experiments did not convincingly prove that statins were either mutagenic or genotoxic. But carcinogenicity may be due to the effects of statins on cholesterol because numerous cohort studies have found low cholesterol to be a risk factor for cancer. This may take a long time to surface. No increase of cancer was seen in a 10 year follow-up of participants in the Scandinavian simvastatin survival study, and the authors therefore concluded that 10 years of statin treatment does not induce cancer.[21] Neither does 10 years' smoking tobacco.

A significant increase in breast cancer was seen in the cholesterol and recurrent events trial (CARE), with most cases being recurrences.[22] Since then patients with a history of cancer have been excluded from statin trials. If statin treatment is carcinogenic it should be seen first in people at high risk such as smokers and old people. As far as we know, no trial has analysed cancer incidence separately for smokers and non-smokers. In the trial of pravastatin in elderly individuals at risk of vascular disease (PROSPER), the only statin trial exclusively in elderly people, the significant increase in cancer mortality neutralised the benefit from fewer cardiovascular deaths (figure).[23] This finding was dismissed by referring to a meta-analysis of all statin trials that failed to find an association with cancer, but the authors ignored mentioning that the mean age of participants in these trials was about 25 years lower than in PROSPER.

Selection bias

The low frequency of side effects in the TNT trial compared with the IDEAL trial may be explained by the way patients were selected for treatment. In the TNT trial more than 3000 people were excluded because they did not fulfil the criteria, already had raised aminotransferase concentrations, cancer, or another disease associated with a limited lifespan, or for "other reasons." After one to eight weeks' treatment with low dose atorvastatin, an additional 5429 patients were rejected, including 197 with non-fatal clinical endpoints, 193 with adverse events, 69 who did not comply with the treatment, 195 who had ischaemic events, 15 with fatal clinical endpoints, and 373 for other reasons. No information was provided on the nature of the side effects or the causes of death. Similarly, it is not clear which side effects later caused 7.2% to stop the treatment.[3] Finally, of the 18 468 patients originally screened for the TNT trial, only 10 003 (54%) were selected, whereas for the IDEAL trial the number was 91.7%, meaning that the patients studied in the TNT trial were much healthier than those included in the IDEAL trial and also than those seen in the doctor's office.

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Competing interests: UR, PJR, and MCS have argued in the scientific press and elsewhere that high cholesterol is not the cause of atherosclerosis and coronary heart disease.

Summary points

US recommendations for low density lipoprotein cholesterol concentrations could put most of the Western world's adult population on statins

Doses of statins would have to be more than eight times higher than currently used

Increasing the dose of atorvastatin by eight times does not lower total mortality

Adverse side effects in clinical trials are under-reported

Any reduction in non-fatal events may be outweighed by more numerous and more severe adverse effects

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