Effect of statin therapy on total mortality

Trial in a more varied population

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MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20 536 high-risk individuals: a randomised placebo-controlled trial. *Lancet* 2002;360:7-22.

Research question

What are the effects of statin therapy on total, vascular, and nonvascular mortality in people at high risk of coronary artery disease (CAD)? Does dietary supplementation with antioxidant vitamins have any effect on CAD events?

Type of article and design

Multicentre, randomized, blinded, placebo-controlled trial using a 2x2 factorial design to allow separate assessment of simvastatin (40 mg) and vitamin supplementation (600 mg of vitamin E, 250 mg of vitamin C, and 20 mg of β-carotene). The factorial design allows all subjects to contribute fully to assessment of the separate effects of simvastatin and antioxidant supplementation without increase in sample size or study cost.

Relevance to family physicians

The association between elevated blood cholesterol levels and cardiovascular disease (CVD) is well established by several long-term population and observational studies.[1,2] Cardiovascular disease is the leading cause of death in Canada; it accounts for 37% of all deaths. Premature death from CVD is responsible for an estimated 294 000 years of life lost. Only injuries and cancer account for more premature deaths.[3] Population surveys of CVD risk factors carried out in several Canadian provinces indicate that 8 300 000 Canadian adults have blood cholesterol levels higher than the desirable level of 5.2 mmol/L, and among these, about 3 million have levels that put them at higher risk (>6.2 mmol/L).[4]

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Overview of study and outcomes

Between July 1994 and May 1997, 20 536 adults were recruited from 69 hospitals in the United Kingdom. They ranged in age from 40 to 80 years and had nonfasting total blood cholesterol concentrations of at least 3.5 mmol/L. They were eligible if they were considered at substantial risk of death from CAD within 5 years because of a history of CAD, other occlusive arterial disease, diabetes mellitus, or treated hypertension alone. They were excluded if they had other life-threatening conditions, such as chronic liver disease, severe renal disease, severe heart failure, severe chronic airways disease, or diagnosed cancer (other than nonmelanoma skin cancer).

Participants were randomly allocated to receive 40 mg of simvastatin daily or matching placebo or vitamin supplementation (600 mg of vitamin E, 250 mg of vitamin C, and 20 mg of β-carotene) or matching placebo in a 2x2 factorial design. They had routine follow-up checks at 4, 8, and 12 months, and then 6-monthly checks until the final follow-up visits between May and October 2001.

Primary outcomes were total mortality, CAD mortality, and non-CAD mortality. Secondary outcomes included 10 specific causes of death. Among them were hemorrhagic stroke; other stroke; neoplasms; respiratory, hepatic, or renal failure; suicide; and other nonmedical causes.

Results

The large sample size and good randomization system used in this trial produced well-balanced treatment groups; 52% of participants were 65 years old or older, and 25% were women. Mean follow up was 5 years; 85% of participants allocated to simvastatin were compliant with treatment, but 17% allocated to placebo were taking non-study statin therapy. The most important results of this trial are shown

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Table 1. Results of the Heart Protection Study

OUTCOMES	ABSOLUTE RISK REDUCTION	NUMBER NEEDED TO TREAT	95% CONFIDENCE INTERVAL
All-cause mortality	1.8	56	36-117
Vascular mortality	1.5	67	44-134
Any first stroke	1.4	71	50-124
First ischemic stroke	1.2	83	59-142
Coronary mortality	3.1	83	54-187
First revascularization	2.6	38	29-57
First non-fatal MI	2.1	48	37-65
First major coronary events	3.1	32	25-44
First major vascular events			
• Patients with previous MI	5.9	17	13-25
• Patients with previous CAD, but not MI	5.3	19	13-33
• Patients with no previous CAD	4.6	21	15-34
• Patients with diabetes	4.9	20	14-36
• Current smokers	5.6	18	11-41
• Patients with treated hypertension	5.7	18	13-26
• Patients taking ASA	6.3	16	13-21
• Patients taking β-blockers	7.4	14	10-19
• Patients taking ACE inhibitors	3.5	28	16-117
• Patients younger than 65	5.2	19	15-27
• Patients 70 or older	5.1	20	14-35
• Patients with LDL levels <3	4.6	22	15-37
• Patients with LDL levels ≥3.5	5.2	19	14-29
• Men	6.0	17	14-22
• Women	3.3	30	19-78

ACE—angiotensin-converting enzyme, ASA—acetylsalicylic acid, CAD—coronary artery disease, LDL—low-density lipoprotein cholesterol, MI—myocardial infarction.

in **Table 1**. There was a non-significant reduction in nonvascular deaths (547 [53%] vs 570 [56%]; $P = .04$). There were no significant differences in any of the prespecified categories of nonvascular mortality.

During the first year, the reduction in major vascular events was non-significant, but subsequently it was highly significant during each separate year. The proportional reduction in event rate was similar (and significant) in each subcategory of participant studied, even among those who presented with low-density lipoprotein (LDL) cholesterol levels <3.0 mmol/L (116 mg/dL) or total cholesterol levels <5.0 mmol/L (193 mg/dL).

The benefits of simvastatin were over and above those of other cardioprotective treatments. Annual excess risk of myopathy with this regimen was about 0.001% and of elevated liver enzymes was 0.17%. There were no severe adverse effects on incidence of cancer or on hospitalization for any other nonvascular cause.

Analysis of methodology

This large, well-designed trial had excellent follow up (99.5%). Inclusion of several subgroups of patients who were poorly represented in previous trials, such as elderly and female patients, strengthen the generalizability of results. Family physicians will find it easier to apply the findings to family practice. Analysis, based on intention to treat, could underestimate the true benefits of simvastatin because 17% of patients in the placebo group were taking non-study statin therapy.

Application to clinical practice

This trial showed the important benefits of statin therapy for a range of people, including patients with CVD, diabetes, and peripheral vascular disease. Although this finding is not new, the trial did add important information regarding the generalizabilty of results and the incidence of harm. This trial showed that statin therapy was beneficial for patients with pretreatment LDL levels of <3 or ≥3.5. As well, trial results indicate that the benefits of statin therapy are independent of and additional to the benefits of β-blockers, acetylsalicylic acid, and angiotensin-converting enzyme inhibitors .

Finally, this trial proved that statin therapy is very safe, even when used at high doses. The theoretical number needed to harm with the side effects of statin therapy that concern most physicians (eg, elevated alamine aminotransferase or creatine kinase levels, or myopathy) is very high (**Table 2**).

Table 2. Theoretical number needed to harm for elevated liver and muscle enzymes: *There was no statistically significant difference between the two groups in these outcomes.*

OUTCOMES	THEORETICAL NUMBER NEEDED TO HARM
Alanine aminotransferase level ≥2 x ULN	556
Creatine kinase level ≥4 x ULN	935
Myopathy	1700

ULN—upper limits of normal.

Bottom line

- Although the fact that statin therapy reduces total mortality is not news, it is nice to see a trial with a more inclusive population, such as women and people 65 and older, so that we can extend the evidence of effect to these groups.
- Statin therapy can be considered for primary and secondary prevention for a range of patients at high risk of CAD. As well, the benefits of statin therapy were independent of other cardioprotective therapies.
- Statin therapy appears to be very safe.
- This large trial did not show that antioxidant vitamins were beneficial for preventing vascular events.

Points saillants

- Le fait que la thérapie aux statines réduise le taux total de mortalité n'est pas nouveau mais il est intéressant de voir une étude sur une population plus inclusive, comprenant des femmes et des personnes de plus de 65 ans, de manière à pouvoir appliquer de telles données scientifiques à ces groupes aussi.
- La thérapie aux statines peut être considérée comme une prévention de première et de seconde intentions pour divers patients à risque élevé de coronaropathie. De plus, les bienfaits de la thérapie aux statines étaient indépendants des autres thérapies cardioprotectrices.
- La thérapie aux statines semble être sans risque.
- Cette étude d'envergure n'a pas démontré que les vitamines antioxydantes étaient bénéfiques pour prévenir les accidents vasculaires.

References

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