Note: This is a two-article spread with a shared commentary. Please scroll down for the second article.

Simvastatin reduced mortality and vascular events in high-risk patients

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.

QUESTION

In patients with a high 5-year risk for death, does simvastatin reduce mortality and vascular events?

DESIGN

Randomized (allocation concealed*), blinded (participants, clinicians, data collectors, and outcome assessors),* placebo-controlled trial with mean follow-up of 5 years.

SETTING

69 U.K. hospitals.

PATIENTS

20 536 patients who were 40 to 80 years of age (28% were ≥ 70 y of age, 75% men); had nonfasting total cholesterol levels ≥ 3.5 mmol/L; and had a substantial 5-year risk for death because of a history of coronary heart disease (CHD), occlusive disease of noncoronary arteries, or diabetes mellitus or a history of treated hypertension (in men ≥ 65 y of age). Exclusion criteria included a clear indication for statin therapy according to the patient's doctor; abnormal liver or renal function; muscle problems; concurrent treatment with cyclosporin, fibrates, or high-dose niacin; potential for pregnancy; and serious medical conditions. Follow-up was 99.7%.

INTERVENTION

Run-in treatment consisted of 4 weeks of placebo and 4 to 6 weeks of simvastatin, 40 mg/d. Compliant patients who did not have serious problems during the run-in phase were allocated to simvastatin, 40 mg/d (n = 10 269), or placebo (n = 10 267). Patients were also randomized in a 2 × 2 factorial design to antioxidant vitamins (vitamin E, 600 mg/d; vitamin C, 250 mg/d; and β-carotene, 20 mg/d) or placebo (see companion report).

MAIN OUTCOME MEASURES

All-cause, vascular, and nonvascular mortality. Secondary outcomes included major coronary events (nonfatal myocardial infarction or death from CHD); stroke; revascularization; and cancer.

MAIN RESULTS

Analysis was by intention to treat. Simvastatin led to a reduction in all-cause and vascular mortality, major coronary events, stroke, and revascularization (Table). Simvastatin and placebo did not differ for nonvascular mortality (Table) or cancer incidence.

CONCLUSION

In patients with a high 5-year risk for death, simvastatin safely reduced all-cause mortality, vascular mortality, and vascular events.

Sources of funding: UK Medical Research Council; British Heart Foundation; Merck & Co; Roche Vitamins.

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*See Glossary.

Simvastatin vs placebo in high-risk patients at mean 5-year follow-up†

Outcomes	Simvastatin	Placebo	RRR (95% CI)	NNT (CI)
All-cause mortality	13%	15%	13% (6 to 19)	58 (37 to 128)
Vascular mortality	7.6%	9.1%	17% (9 to 25)	66 (44 to 134)
Nonvascular mortality	5.3%	5.6%	5% (–7 to 15)	Not significant
Major coronary event‡	8.7%	12%	27% (21 to 33)	33 (26 to 46)
Stroke	4.3%	5.7%	25% (15 to 34)	73 (51 to 131)
Revascularization	9.1%	12%	24% (17 to 30)	39 (29 to 58)

†Abbreviations defined in Glossary; RRR, NNT, and CI calculated from data in article.
‡Nonfatal myocardial infarction or death from coronary disease.

COMMENTARY

The MRC/BHF Heart Protection Study (HPS) of cholesterol lowering and antioxidant supplementation in a wide range of high-risk persons is the largest randomized trial of CHD prevention to date and should profoundly influence how statins and antioxidants are prescribed. In terms of vascular-event prevention, the trial's main message was that risk reductions conferred by long-term statin therapy depended chiefly on a person's overall risk for major vascular events rather than on their initial blood lipid level. Also, such benefit was achieved safely.

Remarkably, the number needed to treat (NNT) with statins for 5 years to prevent the first major vascular event was similar across pretreatment cholesterol levels (NNT range 18 [95% CI 13 to 27] to 19 [CI 14 to 30]) and age categories (NNT range 16 [CI 11 to 26] to 19 [CI 14 to 36]) and in patients with previous CHD only (NNT 18 [CI 13 to 26]) or diabetes only (NNT 21 [CI 14 to 40]). These observations were also consistent with results from previous statin trials (Table available at www.acpjc.org) in which the greatest benefit (smaller NNT per year) occurred among those at greatest risk (1). With increasing age, however, smaller NNTs per year for CHD events may not necessarily yield greater cumulative benefit in terms of life-years and quality of life gained (2). Preventing a CHD event at 50 rather than at 70 years of age may yield much greater potential for cumulative benefit. Thus, contrary to implications of the HPS and the National Cholesterol Education Program (ATP III) guidelines (3), greater CHD risk reduction may not parallel greater overall benefit in the elderly.

Antioxidant intervention had no effect on CHD outcomes (or the incidence of cancer) but was associated with minor increases in low-density lipoprotein cholesterol and triglyceride levels. These negative findings were in accord with several randomized controlled trials, including the large Heart Outcomes Prevention Evaluation Study (4).

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Antioxidant vitamins did not reduce death, vascular events, or cancer in high-risk patients

MRC/BHF Heart Protection Study of antioxidant vitamin supplementation in 20 536 high-risk individuals: a randomised placebo-controlled trial. Lancet. 2002;360:23-33.

QUESTION

In patients with a high 5-year risk for death, does antioxidant supplementation reduce death, vascular events, and cancer?

DESIGN

Randomized (allocation concealed*), blinded (participants, clinicians, data collectors, and outcome assessors),* placebo-controlled trial with mean follow-up of 5 years.

SETTING

69 U.K. hospitals.

PATIENTS

20 536 patients who were 40 to 80 years of age (28% were ≥ 70 y of age, 75% men); had nonfasting total cholesterol levels ≥ 3.5 mmol/L; and had a substantial 5-year risk for death because of a history of coronary heart disease (CHD), occlusive disease of noncoronary arteries, or diabetes mellitus or a history of treated hypertension (in men ≥ 65 y of age). Exclusion criteria included a clear indication for statin therapy according to the patient's doctor, abnormal liver or renal function, severe heart failure, severe chronic airway disease, cancer, and indication for high-dose vitamin E supplements. Follow-up was 99.7%.

INTERVENTION

Patients received 2 months of active vitamins during a run-in phase. Compliant patients without serious problems during the run-in phase were allocated to antioxidant vitamins (synthetic vitamin E, 600 mg/d, plus vitamin C, 250 mg/d, plus β-carotene, 20 mg/d) (n = 10 269) or placebo (n = 10 267). Patients were also randomized in a 2 × 2 factorial design to simvastatin, 40 mg/d, or placebo.

MAIN OUTCOME MEASURES

All-cause, vascular, and nonvascular mortality. Secondary outcome measures included major coronary events (nonfatal myocardial infarction or death from CHD); stroke; revascularization; and cancer.

MAIN RESULTS

Analysis was by intention to treat. Antioxidants did not differ from placebo for any outcome (Table).

CONCLUSION

In patients with a high 5-year risk for death, antioxidant vitamins did not reduce mortality, coronary events, stroke, revascularization, or cancer.

Sources of funding: UK Medical Research Council; British Heart Foundation; Merck & Co; Roche Vitamins.

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*See Glossary.

Antioxidant vitamins vs placebo for high-risk patients at mean 5-year follow-up†

Outcomes	Antioxidant vitamins	Placebo	RRI (95% CI)	NNH
All-cause mortality	14.1%	13.5%	4% (–3 to 12)	Not significant
Vascular mortality	8.6%	8.2%	5% (–5 to 15)	Not significant
Nonvascular mortality	5.5%	5.3%	4% (–8 to 17)	Not significant
Major coronary event‡	10.4%	10.2%	2% (–6 to 11)	Not significant
			RRR (CI)	NNT
Stroke	5.0%	5.0%	1% (–12 to 13)	Not significant
Revascularization	10.3%	10.6%	2% (–6 to 10)	Not significant
Cancer (except nonmelanoma skin cancer)	7.8%	8.0%	2% (–8 to 11)	Not significant

†Antioxidant vitamins were vitamin E, vitamin C, and β-carotene. Abbreviations defined in Glossary; RRI, RRR, NNT, NNH, and CI calculated from data in article.
‡Nonfatal myocardial infarction or death from coronary disease.

COMMENTARY

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Thus, the unreal expectations aroused by observational studies and the Cambridge Heart Antioxidant Study (CHAOS) have been put to rest (5). Observational studies can mislead owing to unidentified confounding factors, and CHAOS was small, was done in the prestatin era, and had incomplete follow-up.

In conclusion, given that benefits conferred by statins are mainly determined by premorbid CHD risk rather than the lipid level, identifying persons with "abnormal" lipid profiles and dosage titration to preset target lipid levels become questionable. It may nevertheless be appropriate to monitor lipid levels during treatment to verify that cholesterol has been lowered to the degree expected. Antioxidants cannot be recommended for CHD prevention. Instead, greater efforts should be directed at implementing appropriate, proven preventive measures (use of aspirin, β-blockers, angiotensin-converting enzyme inhibitors, and statins) in high-risk persons.

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