Simvastatin reduced mortality and vascular events


**QUESTION:** In patients with a high 5-year risk of death, does simvastatin reduce mortality and vascular events?

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

**Setting**
69 UK hospitals.

**Patients**
20,536 patients who were 40–80 years of age (28% were ≥ 70 y of age, 75% men); had nonfasting total cholesterol levels ≥ 5.5 mmol/l; and had a substantial 5-year risk of 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 4–6 weeks of simvastatin, 40 mg/day. Compliant patients who did not have serious problems during the run in phase were allocated to simvastatin, 40 mg/day (n = 10,269), or placebo (n = 10,267). Patients were also randomised 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; revascularisation; 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 1). Simvastatin and placebo did not differ for nonvascular mortality (table) or cancer incidence.

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

*See glossary.

**COMMENTARY**

The MRC/BHF Heart Protection Study (HPS) of cholesterol lowering and antioxidant supplementation in a wide range of high-risk patients is the largest randomised 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 of 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 the statin 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 2 on opposite page) in which the greatest benefit (smaller NNT per year) occurred among those at greatest risk. With increasing age, however, smaller NNTs per year for CHD events may not necessarily yield greater cumulative benefit. Preventing a CHD event at 50 rather than 70 years of age may yield much greater potential for cumulative benefit (life years and quality of life gained), thus, contrary to implications of the HPS and the National Cholesterol Education Program (ATP III) guidelines, 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 randomised controlled trials, including the large Heart Outcomes Prevention Evaluation Study. Thus, the unreal expectations aroused by observational studies and the Cambridge Heart Antioxidant Study (CHAOS) have been put to rest. 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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Antioxidant vitamins did not reduce death, vascular events, or cancer in high risk patients


QUESTION: In patients with a high 5 year risk of death, does antioxidant supplementation reduce death, vascular events, and cancer?

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

Setting
69 UK hospitals.

Patients
20 536 patients who were 40–80 years of age (28% were ≥ 70 y of age, 75% men); had nonfasting total cholesterol levels ≥ 5.5 mmol/l; and had a substantial 5 year risk of 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. Patients were also randomised in a 2 × 2 factorial design to simvastatin, 40 mg/day, or placebo.

Main results
Analysis was by intention to treat. Antioxidants did not differ from placebo for any outcome (table 1).

Conclusion
In patients with a high 5 year risk of death, antioxidant vitamins did not reduce mortality, coronary events, stroke, revascularisation, or cancer.

**See glossary.

Table 1. Antioxidant vitamins v placebo for high risk patients at mean 5 year follow up†

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Antioxidant vitamins</th>
<th>Placebo</th>
<th>RRI (95% CI)</th>
<th>NNH (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All cause mortality</td>
<td>14.1%</td>
<td>13.5%</td>
<td>4% (3 to 12)</td>
<td>Not significant</td>
</tr>
<tr>
<td>Vascular mortality</td>
<td>8.6%</td>
<td>8.2%</td>
<td>5% (5 to 15)</td>
<td>Not significant</td>
</tr>
<tr>
<td>Nonvascular mortality</td>
<td>5.5%</td>
<td>5.3%</td>
<td>4% (8 to 17)</td>
<td>Not significant</td>
</tr>
<tr>
<td>Major coronary event‡</td>
<td>10.4%</td>
<td>10.2%</td>
<td>2% (6 to 11)</td>
<td>Not significant</td>
</tr>
<tr>
<td>Stroke</td>
<td>5.0%</td>
<td>5.0%</td>
<td>1% (12 to 13)</td>
<td>Not significant</td>
</tr>
<tr>
<td>Revascularisation</td>
<td>10.3%</td>
<td>10.6%</td>
<td>2% (6 to 10)</td>
<td>Not significant</td>
</tr>
<tr>
<td>Cancer (except nonmelanoma skin cancer)</td>
<td>7.8%</td>
<td>8.0%</td>
<td>2% (8 to 11)</td>
<td>Not significant</td>
</tr>
</tbody>
</table>

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

Table 2. Coronary heart disease (CHD) event prevention for statins v placebo

<table>
<thead>
<tr>
<th>Individual trials (combined trials)†‡</th>
<th>Patient group</th>
<th>Mean or median follow up</th>
<th>RRR (95% CI)</th>
<th>NNH (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>a) AFCAPS/TexCAPS</td>
<td>No CHD, normal cholesterol</td>
<td>5.4 years</td>
<td>37% (21 to 50)</td>
<td>49 (33 to 99)</td>
</tr>
<tr>
<td>b) WOSCOPS</td>
<td>No CHD, high cholesterol</td>
<td>4.9 years</td>
<td>31% (17 to 43)</td>
<td>44 (29 to 95)</td>
</tr>
<tr>
<td>c) CARE</td>
<td>CHD, normal cholesterol</td>
<td>5.0 years</td>
<td>24% (9 to 36)</td>
<td>33 (20 to 99)</td>
</tr>
<tr>
<td>d) LIPID</td>
<td>CHD, normal cholesterol</td>
<td>6.1 years</td>
<td>24% (12 to 35)</td>
<td>28 (20 to 48)</td>
</tr>
<tr>
<td>e) 4S</td>
<td>CHD, high cholesterol</td>
<td>5.2 years</td>
<td>34% (25 to 41)</td>
<td>12 (9 to 17)</td>
</tr>
<tr>
<td>(a + b)</td>
<td>No CHD</td>
<td>5.2 years</td>
<td>33% (22 to 42)</td>
<td>47 (34 to 74)</td>
</tr>
<tr>
<td>(c + d + e)</td>
<td>CHD</td>
<td>5.4 years</td>
<td>26% (20 to 31)</td>
<td>23 (19 to 31)</td>
</tr>
<tr>
<td>(a + c + d)</td>
<td>Normal cholesterol</td>
<td>5.5 years</td>
<td>25% (18 to 31)</td>
<td>39 (30 to 55)</td>
</tr>
<tr>
<td>(b + e)</td>
<td>High cholesterol</td>
<td>5.2 years</td>
<td>30% (23 to 37)</td>
<td>29 (22 to 43)</td>
</tr>
</tbody>
</table>

*Funding sources:
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