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 fasting 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 revascularisation (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.

**Table 1.** Simvastatin v placebo in high risk patients at mean 5 year follow up†

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Simvastatin</th>
<th>Placebo</th>
<th>RRR (95% CI)</th>
<th>NNT (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All cause mortality</td>
<td>13%</td>
<td>15%</td>
<td>13% (6 to 19)</td>
<td>58 (37 to 128)</td>
</tr>
<tr>
<td>Vascular mortality</td>
<td>7.6%</td>
<td>9.1%</td>
<td>17% (9 to 25)</td>
<td>66 (44 to 134)</td>
</tr>
<tr>
<td>Nonvascular mortality</td>
<td>5.3%</td>
<td>6.6%</td>
<td>5% (–7 to 15)</td>
<td>Not significant</td>
</tr>
<tr>
<td>Major coronary event</td>
<td>8.7%</td>
<td>12%</td>
<td>27% (21 to 33)</td>
<td>33 (26 to 46)</td>
</tr>
<tr>
<td>Stroke</td>
<td>4.3%</td>
<td>5.7%</td>
<td>25% (15 to 34)</td>
<td>73 (51 to 131)</td>
</tr>
<tr>
<td>Revascularisation</td>
<td>9.1%</td>
<td>12%</td>
<td>24% (17 to 30)</td>
<td>39 (29 to 58)</td>
</tr>
</tbody>
</table>

†Abbreviations defined in glossary; RRR, NNT, and CI calculated from data in article.

**Sources of funding:**
UK Medical Research Council; British Heart Foundation; Cochrane Collaboration; Merck & Co, Roche Vitamins. For correspondence: Heart Protection Study, Clinical Trial Service Unit, Radcliffe Infirmary, Oxford, UK. hps@ctsu.ox.ac.uk

**Abstract and commentary also published in MCP Journal Club**

**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 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 [14 to 40]). These observations were 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 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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University of Hong Kong, Hong Kong, China

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 ≥ 5.3 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 antioxidants. 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 antioxidants. Patients also received 10 mg of clopidogrel and 100 mg of aspirin daily. All patients were followed up for a mean of 5 years.

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

**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</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>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>RRR (CI)</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke</td>
<td>5.0%</td>
<td>2% (12 to 13)</td>
</tr>
<tr>
<td>Revascularisation</td>
<td>10.3%</td>
<td>2% (6 to 10)</td>
</tr>
<tr>
<td>Cancer (except nonmelanoma skin cancer)</td>
<td>7.8%</td>
<td>8.0%</td>
</tr>
</tbody>
</table>

*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.

**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>NNT (CI)</th>
<th>NNT/year (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>
<td>256 (170 to 514)</td>
</tr>
<tr>
<td>b) WOSCOPS</td>
<td>No CHD, high cholesterol</td>
<td>4.8 years</td>
<td>31% (17 to 43)</td>
<td>44 (29 to 95)</td>
<td>217 (141 to 463)</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>
<td>167 (100 to 496)</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>
<td>172 (122 to 294)</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>
<td>63 (49 to 89)</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>
<td>237 (177 to 382)</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>
<td>129 (103 to 172)</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>
<td>209 (163 to 398)</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>
<td>151 (114 to 221)</td>
</tr>
</tbody>
</table>

*AFPACS/TexCAPS = AirForce/Texas Coronary Atherosclerosis Prevention Study; WOSCOPS = West of Scotland Coronary Prevention Study; CARE = Cholesterol and Recurrent Events; LIPID = Long-term Intervention with Pravastatin in Ischaemic Disease trial; 4S = Scandinavian Simvastatin Survival Study. Abbreviations defined in glossary. For references for these trials, see glossary. For references for these trials, see glossary. For references for these trials, see glossary.
†Results are weighted for combined trials.
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_Evid Based Med_ 2003 8: 11
doi: 10.1136/ebm.8.1.11

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