CME CREDIT

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The Heart Protection Study: High-risk patients benefit from statins, regardless of LDL-C level

ABSTRACT

The landmark Heart Protection Study (*Lancet* 2002; 360:7–22) found benefit in treating subjects at high risk of a coronary event with simvastatin 40 mg daily, regardless of baseline low-density lipoprotein cholesterol level and in all subgroups, including women and the elderly. The study found no benefit of simvastatin therapy in preventing noncardiac events (eg, dementia, osteoporotic fractures), and no negative effects, such as an increase in cancer, respiratory disease, or suicide.

NEARLY ALL PATIENTS at high risk of a coronary event should be taking a statin drug, regardless of their low-density lipoprotein cholesterol (LDL-C) level. This is the major implication of the results of the recently published Heart Protection Study.[1]

The study found a significant reduction in mortality, myocardial infarction, stroke, and the need for coronary and noncoronary revascularization procedures in treated patients, making a strong argument for widespread adoption of statin therapy in eligible patients. The widespread identification and treatment of high-risk patients would significantly reduce the immense worldwide burden of cardiovascular disease.

We explain the rationale, design, findings, and implications of this important study.

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BACKGROUND

Before the Heart Protection Study, clinical trials had demonstrated the following issues:

- The higher the cholesterol level, the greater the risk of cardiovascular event and of dying of cardiovascular causes[2,3]
- The risk of coronary events can be lowered with the use of the lipid-lowering drugs niacin,[4] cholestyramine (a bile-acid sequestrant),[5] or gemfibrozil (a fibrate)[6]
- Drugs that inhibit 3-hydroxy-3-methylglutaryl-coenzyme A reductase (commonly called "statins") can reduce both the incidence of events and the mortality rate. Moreover, these drugs are beneficial in populations at varying risks of coronary events,[7–11] including patients with:
  - Hyperlipidemia and recent myocardial infarction[8]
  - Elevated cholesterol and no history of myocardial infarction[7]
  - Average levels of total cholesterol and LDL-C, low levels of high-density lipoprotein cholesterol (HDL-C), and no coronary artery disease[10]
  - Prior coronary artery bypass grafting[12] and prior percutaneous coronary artery intervention.[13]

Statins are grossly underused, even in patients who would clearly benefit

The 2001 guidelines from the National Cholesterol Education Program (NCEP III)[14] were based on this information. These guidelines call for lower goal levels of LDL-C for patients at higher risk (**TABLE 1**). Patients in the highest risk category have a goal LDL-C level of less than 100 mg/dL; these patients include those with a prior coronary event, diabetes,[15]

TABLE 1

National Cholesterol Education Program guidelines

RISK CATEGORY	LOW-DENSITY LIPOPROTEIN CHOLESTEROL (LDL-C), MG/DL		
	GOAL LEVEL	LEVEL AT WHICH TO INITIATE THERAPEUTIC LIFESTYLE CHANGES	LEVEL AT WHICH TO CONSIDER DRUG THERAPY
Coronary heart disease (CHD) or CHD risk equivalent* (10-year risk > 20%)	< 100	≥ 100	≥ 130 (if 100–129, drug optional)
2 or more risk factors† (10-year risk ≤ 20%)	< 130	≥ 130	10-year risk 10%–20%: ≥ 130 10-year risk < 10%: ≥ 160
0 or 1 risk factor	< 160	≥ 160	≥ 190 (if 160–189, drug optional)

*CHD risk equivalents: diabetes mellitus, peripheral vascular disease, carotid artery disease, abdominal aortic aneurysm
†Risk factors: cigarette smoking, hypertension (blood pressure > 140/90 mm Hg or on antihypertensive medication), low high-density lipoprotein (HDL) level (< 40 mg/dL), family history of premature CHD (CHD in a male first-degree relative younger than age 55 or in a female first-degree relative younger than 65 years), age ≥ 45 years (men) or ≥ 55 years (women); HDL cholesterol ≥ 60 mg/dL counts as a "negative" risk factor—its presence removes one risk factor from the total count

ADAPTED FROM EXECUTIVE SUMMARY OF THE THIRD REPORT OF THE NATIONAL CHOLESTEROL EDUCATION PROGRAM (NCEP) EXPERT PANEL ON DETECTION, EVALUATION, AND TREATMENT OF HIGH BLOOD CHOLESTEROL IN ADULTS (ADULT TREATMENT PANEL III). JAMA 2001; 285:2486–2497.

Guidelines call for lower LDL-C goals for patients at higher risk

peripheral vascular disease, carotid artery disease, abdominal aortic aneurysm, or a calculated 10-year risk of a coronary event of 20% or greater. (Risk can be calculated on the basis of the patient's age, sex, total cholesterol level, smoking status, HDL-C level, and systolic blood pressure using a program derived from Framingham data, available online at **www.nhlbi.nih.gov/guidelines/cholesterol/profmats.htm.**)

UNRESOLVED DILEMMAS

However, unresolved dilemmas remained, eg:

- Are statins beneficial in patients with known coronary artery disease and an optimal or low LDL-C level? Post hoc analyses of data from previous studies showed mixed results, with some showing minimal benefit of lowering LDL-C beyond 125 mg/dL but others suggesting accretive benefit with further reduction.[16,17]
- Are statins beneficial in women and elderly people? Statin therapy was generally accepted to be effective in women and elderly persons on the basis of post hoc analyses of other randomized clinical trials, but this had not been clearly proved.
- Do statins confer other benefits besides reducing coronary events? Data from observational studies and meta-analysis of previous statin trials suggested a beneficial effect on the risk of stroke,[18] neurocognitive decline,[19,20] osteoporosis, and fractures.[21,22]

DESIGN OF THE HEART PROTECTION STUDY

The MRC/BHF (Medical Research Council/British Heart Foundation) Heart Protection Study assessed the long-term benefits of simvastatin in a large number of patients at high risk of adverse vascular events.

Study population

The study enrolled 20,536 men and women aged 40 to 80 years who had hypercholesterolemia and were considered at increased risk of death from coronary artery disease within 5 years.

Inclusion criteria: All patients had to have a nonfasting blood cholesterol concentration of 135 mg/dL or greater (no upper limit) and at least one of the following conditions:

- Coronary artery disease (prior myocardial infarction, unstable or stable angina, coronary artery bypass graft, or percutaneous coronary intervention)

- Evidence of cerebrovascular disease (nondisabling nonhemorrhagic stroke, transient cerebral ischemia, carotid endarterectomy or angioplasty)
- Peripheral vascular disease (lower extremity arterial stenosis manifested as intermittent claudication or the need for arterial surgery or angioplasty)
- Type 1 or type 2 diabetes
- Treated hypertension (only in men older than 65 years).

Exclusion criteria. Patients were ineligible if their physicians felt that statin therapy was indicated or if they had any of the following conditions:

- Chronic liver disease or evidence of abnormal liver function (eg, an alanine aminotransferase [ALT] level > 1.5 times the upper limit of normal)
- Impaired renal function (creatinine level > 2.3 mg/dL)
- Inflammatory muscle disease (polymyositis or dermatomyositis) or creatine kinase level greater than three times the upper limit of normal
- Concurrent therapy with cyclosporin, fibrates, or high-dose niacin
- Childbearing potential (ie, premenopausal women not surgically sterilized or using reliable contraception)
- Severe heart failure
- Severe noncardiac illness expected to affect long-term survival (eg, severe chronic pulmonary disease or any malignancy other than nonmelanoma skin cancer)
- A neuropsychiatric disorder expected to limit compliance with treatment and follow-up (eg, severely disabling stroke, dementia, or psychiatric illness).

Treatment

The Heart Protection Study used a 2 × 2 factorial design in which patients were randomized to receive either simvastatin 40 mg daily or placebo and either antioxidant vitamin supplements or placebo. This review covers only the simvastatin arm. In brief, antioxidant therapy appeared to confer no benefit and had no effect on the benefit of statin therapy.[23]

Before being randomized, all patients underwent a "placebo run-in" for 4 weeks to allow the investigators to review their baseline levels of liver enzymes, creatinine, and creatine kinase. Then, all patients received simvastatin 40 mg daily for 4 to 6 weeks to assess the response of each patient's levels of LDL-C to the drug.

Each patient's primary physician used the laboratory values from this phase of the study to determine if the patient should be excluded from the study, ie, if he or she had a clear indication for or contraindication to statin therapy. All eligible, consenting patients were then randomly assigned to receive either simvastatin 40 mg daily or placebo plus either antioxidant vitamins or placebo.

Follow-up

Patients were evaluated every 4 months for 1 year and every 6 months for the remainder of the study, which lasted about 5 years.

Patients who could not or would not come to their follow-up appointments were contacted by telephone at their scheduled follow-up time, and they were asked to stop their treatment. Patients' primary care physicians were encouraged to start statins if they thought they were indicated clinically. If this occurred before 1998, the study drug was stopped. If this occurred after 1998, the study drug was continued and the statin was added in a dose equivalent to 40 mg of simvastatin (LDL-C-lowering capacity), because simvastatin had been approved for clinical use in a dosage of up to 80 mg daily.

ALT levels were measured in all patients; creatinine kinase concentrations were measured only in patients who developed muscle symptoms.

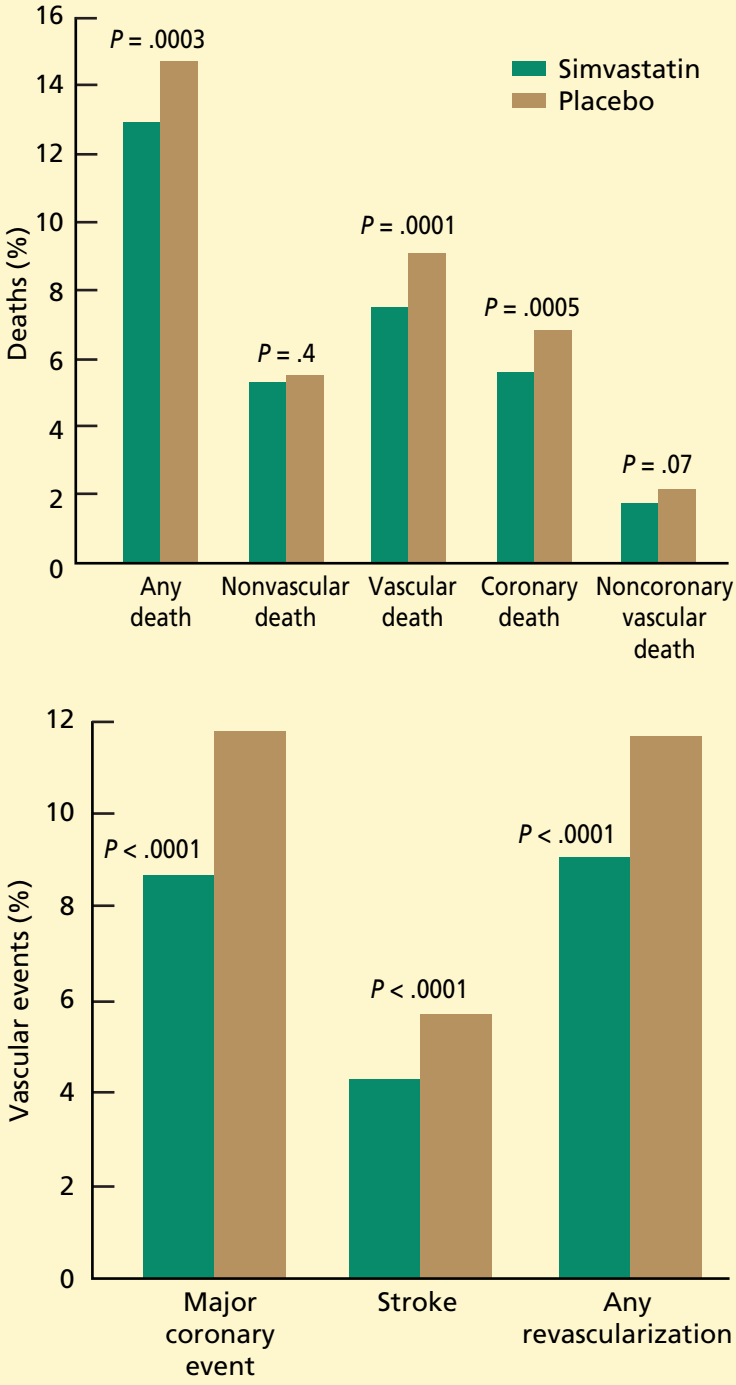
Side effects were not increased in the simvastatin group

Outcomes measured

At each follow-up visit, information was recorded for any suspected myocardial infarction, stroke, vascular procedures (including amputations), cancer or other serious adverse events, and reasons for any hospital admissions. If the patient had died, the death was classified as a coronary death if it was attributed to myocardial infarction or other coronary disease (including heart failure due to coronary disease) or if it was sudden or unexpected without autopsy evidence of another cause.

The primary outcome measures were:

- All-cause mortality



DATA FROM HEART PROTECTION STUDY COLLABORATIVE GROUP. 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.

FIGURE 1

- Coronary mortality
- Noncoronary mortality.

The secondary outcome measures were:

- Death due to specific noncoronary cause
- Major coronary event (defined as a composite of coronary death or nonfatal myocardial infarction)
- Major vascular event (a composite of major coronary event, stroke, or noncoronary revascularization procedure)
- Fatal or nonfatal stroke.

RESULTS

A total of 10,269 patients were randomized to receive simvastatin, and 10,267 to placebo. The compliance rate (defined as intake of more than 80% of pills since the prior follow-up visit) was 85% among the simvastatin users; 17% of patients receiving placebo started nonstudy statin therapy during the study. Since the analysis was by intention to treat, the use of statins in the placebo group and the noncompliance in 15% of the simvastatin group diluted the magnitude of observed differences between the groups.

Reduction in mortality

At 5 years, 1,328 (12.9%) of the patients in the simvastatin group had died, compared with 1,507 (14.7%) of the patients in the placebo group—an absolute difference of 1.8 percentage points or a 12% relative risk reduction (P = .0003). Put another way, one death could be prevented by treating 55 patients for 5 years. Most of the reduction in death was due to a 16% relative risk reduction in vascular deaths; no difference was noted in the incidence of nonvascular deaths (FIGURE 1).

Reduction in vascular events

Therapy with simvastatin was beneficial with respect to all vascular end points (FIGURE 1). The relative risk reductions were:

- Nonfatal myocardial infarctions 38%
- First strokes (any degree of severity) 25%
- Coronary revascularization procedures 30%
- Noncoronary revascularization procedures 15%.

A nonsignificant difference in the incidence of vascular events was evident at 1 year of treatment, and a significant reduction of

about one fourth was noted in subsequent years of follow-up.

The reduction in events was similar in multiple subgroups, including women and the elderly, and was largely uninfluenced by pretreatment lipoprotein values (FIGURE 2). Notably, treatment was beneficial even if the patient's baseline LDL-C level was lower than 100 mg/dL: in this subgroup the incidence of first major vascular events was 16.4% in the simvastatin group vs 21.0% in the placebo group (P = .0001). Benefit was also evident in patients receiving other cardioprotective drugs such as angiotensin-converting enzyme inhibitors, beta-blockers, and aspirin.

No reduction in noncardiovascular events, such as dementia or osteoporotic fractures

With its large sample size and prespecified analysis, the Heart Protection Study provides the most robust data to date on the noncardiac effects of statins. No difference was seen between the two groups in the incidence of:

- **Cancer** (new cancers or cancer-specific mortality)
- **Neuropsychiatric disorders** (cognitive impairment, development of dementia, suicide attempts, or new psychiatric disorders)
- **Respiratory disease** (changes in forced vital capacity or forced expiratory volume in 1 second or hospitalizations for chronic obstructive pulmonary disease, asthma, or other respiratory causes; pulmonary function tests were prospectively studied because low cholesterol levels have been associated with increased mortality from chronic obstructive pulmonary disease)
- **Osteoporotic fractures** (any fracture or fracture of the spine, wrist, or hip).

Safety of simvastatin

Liver function. Elevations in ALT levels greater than two times the upper limit of normal were seen in only a small number of patients, with no significant differences between the two groups (FIGURE 3). About 0.5% of patients stopped treatment due to increases in ALT.

Muscle symptoms. Six percent of patients reported muscle symptoms at each follow-up visit, and one third of the patients reported them at least once. These symptoms were equally common in both groups.

Creatine kinase was measured in patients who reported muscle symptoms; elevations of 4 to 10 times the upper limit of normal were found in 19 patients (0.19%) in the simvastatin group vs 13 (0.13%) in the placebo group; elevations greater than 10 times the upper limit of normal were found in 11 (0.11%) vs 6 (0.06%). The differences were not significant. About 0.5% of patients in each group stopped treatment because of muscle symptoms.

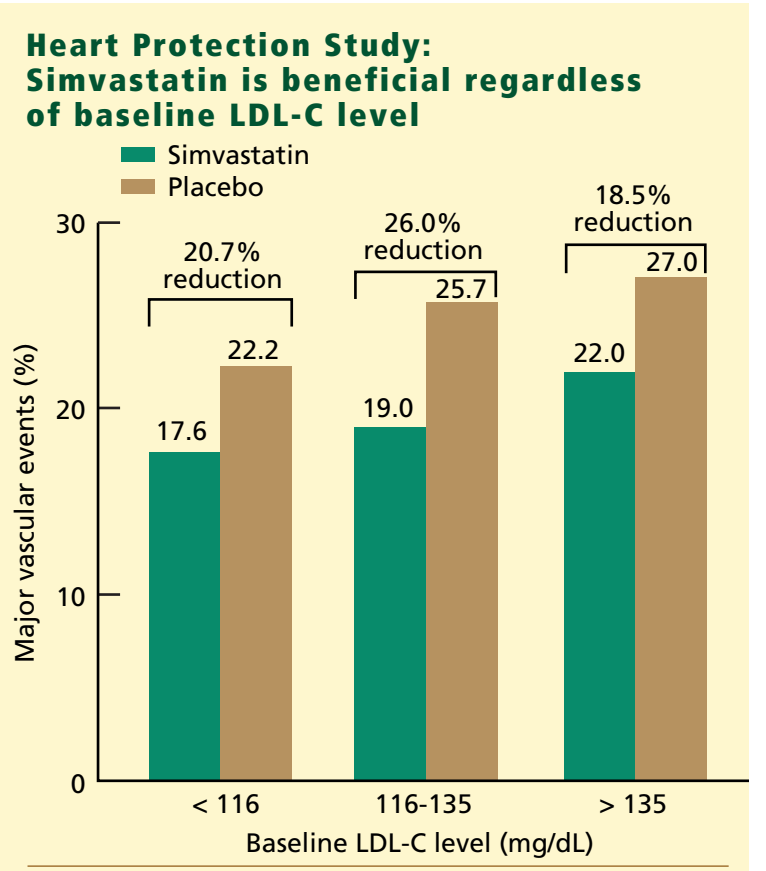


FIGURE 2

INTERPRETING THE HEART PROTECTION STUDY

The landmark Heart Protection Study clearly establishes that statins are safe and effective as cardioprotective therapy. It also provides fur-

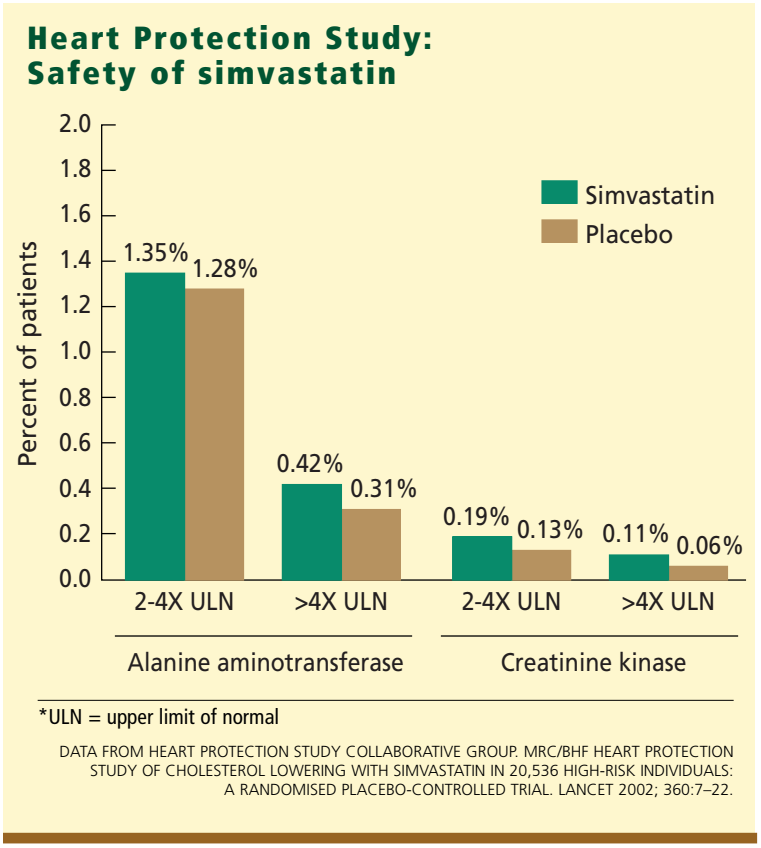


FIGURE 3

ther evidence to support the use of statins in patients at high risk to reduce the risk of cardiovascular events and improve the survival rate. Further, it establishes a role for treating patients on the basis of risk, regardless of their LDL-C levels.

The statins have multiple effects in addition to lipid-lowering, and the reduction in mortality from these agents may be at least in part due to some of these effects.[24] Further, the statins have been shown to confer additional benefit when used in conjunction with a heart-healthy diet.[25] Thus, physicians need to consider both statin therapy and diet when planning treatment for patients who require primary or secondary intervention.

Questions and challenges

The results from the Heart Protection Study may conflict with the strategy of LDL-C targets suggested by the NCEP III guidelines, but both the study and the guidelines share the strategy of targeting risk. By demonstrating benefits in patients with any clinical evidence of atherosclerosis (coronary, cerebrovascular, or peripheral), diabetes, or hypertension (in men older than 65 years), the Heart Protection Study makes it much easier to identify high-risk patients and provides busy physicians with an easy tool to prevent cardiovascular morbidity and mortality.

Despite the proven benefits of statin therapy, data continue to accumulate that suggest that statins are grossly underused even in patients who would clearly benefit from their use.[26,27] Compliance is also a major issue, with recent studies suggesting that adherence to statin therapy at 2 years may be as low as 25%.[28,29] It is incumbent on the medical community, then, to identify, educate, and engage appropriate patients so that the promise of prevention can be realized.

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