

THERAPEUTICS

Simvastatin reduced mortality and vascular events in diabetes mellitus

Collins R, Armitage J, Parish S, et al. MRC/BHF Heart Protection Study of cholesterol-lowering with simvastatin in 5963 people with diabetes: a randomised placebo-controlled trial. *Lancet*. 2003;361:2005-16.

QUESTION

In patients with diabetes mellitus, does simvastatin reduce vascular events?

DESIGN

Randomized {allocation concealed*}†, blinded {participants, clinicians, data collectors, and outcome assessors}‡, placebo-controlled trial with mean 4.8-year follow-up.

SETTING

{69 U.K. hospitals}‡.

PATIENTS

5963 patients who were 40 to 80 years of age (mean age 62 y, 70% men); had nonfasting blood total cholesterol levels ≥ 3.5 mmol/L; and had a medical history of diabetes mellitus, coronary heart disease, occlusive disease of noncoronary arteries, or treated hypertension (if also male and ≥ 65 y of age). Exclusion criteria included indications or contraindications for statin therapy; myocardial infarction, stroke, or admission for angina in the previous 6 months; chronic liver disease; severe renal disease; and life-threatening conditions other than vascular disease or diabetes. $>99.5\%$ of patients had complete follow-up.}‡

INTERVENTION

After a run-in phase, compliant patients were allocated to simvastatin, 40 mg/d ($n = 2978$), or placebo ($n = 2985$). Patients in each group were also allocated to antioxidants or placebo.

MAIN OUTCOME MEASURES

Coronary events (myocardial infarction or coronary death), stroke, revascularization, and major vascular events (major coronary events, strokes, and revascularizations).

MAIN RESULTS

{Analysis was by intention to treat.}† Patients in the simvastatin group had fewer coronary events, strokes, revascularization procedures, and major vascular events (Table).

CONCLUSION

In adults with diabetes mellitus, simvastatin therapy at 40 mg daily reduced vascular events.

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*See Glossary.

†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.

‡Information provided by author.

Simvastatin vs placebo in diabetes mellitus at mean 4.8-year follow-up[§]

Outcomes	Simvastatin	Placebo	RRR (95% CI)	NNT (CI)
Major coronary event	9.4%	13%	26% (14 to 36)	31 (21 to 60)
Stroke	5.0%	6.5%	23% (4.8 to 37)	69 (38 to 353)
Revascularization	8.7%	10%	16% (1.3 to 28)	62 (32 to 770)
Major vascular event¶	20%	25%	19% (11 to 27)	21 (15 to 37)

[§]Abbreviations defined in Glossary; RRR, NNT, and CI calculated from data in article.

||Myocardial infarction or coronary death.

¶Major coronary events, strokes, and revascularizations.

COMMENTARY

Heart Protection Study (HPS) participants were selected for having a high risk for cardiovascular disease, not for having high low-density lipoprotein (LDL) cholesterol levels. 2463 of the 5963 participants who had diabetes also had a history of vascular disease at baseline; 2426 had pretreatment LDL levels < 3.0 mmol/L. The most important result was that a standard 40 mg daily of simvastatin (not treatment to target cholesterol levels) reduced LDL levels by about 1 mmol/L on average, and reduced major cardiovascular events by 22% in all diabetic participants. In an extensive subgroup analysis, treatment benefit differed little across age, sex, type of diabetes, duration of diabetes, degree of glucose control, baseline cholesterol level, or presence of known vascular disease.

The study by Collins and colleagues adds weight to the mounting evidence that treating diabetes with a statin can reduce the risk for major cardiovascular events, even though the most common lipid abnormality in diabetes is a combination of low high-density lipoprotein (HDL) and high triglyceride levels (a marker for small dense LDL levels often observed without high cholesterol levels). The results for cholesterol lowering are more impressive and more consistent than the results for treating hyperglycemia and highlight the need to do both when managing patients with diabetes.

This landmark study provides abundant evidence that diabetes is a heart disease equivalent in terms of future cardiovascular risk. It is now clear that any lowering of total cholesterol or LDL cholesterol levels should be attempted in all patients with diabetes. In fact, one could question the need to measure cholesterol at all, although most physicians will feel more comfortable knowing where they started, and many patients will be motivated to continue medication if they can see their cholesterol levels fall. Another reason to measure lipid levels (including nonfasting triglyceride levels) is to identify patients with particularly high triglyceride or low HDL levels for special therapy. Total, LDL, and HDL cholesterol levels do not need to be measured in fasting patients, which makes test results easier to monitor.

This well-done, well-analyzed trial solidifies the evidence for treating almost all diabetic patients with statins and has already sparked considerable discussion about the need for cholesterol measurement, treatment targets, and combination therapies. The HPS results do not address whether additional lipid-lowering treatment for the common combination of high triglyceride and low HDL levels provides additional cardiovascular benefit relative to costs and risks.

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