



# Extending The Scope of Statins

## Recent Clinical Trials

The substantial benefits of statins have now been proven in many important patient subgroups, including the elderly and women.

By Daniel G. Hackam, BSc, MD

### J.P.'s Case

J.P., 75, is in for his annual physical exam. He is well and entirely symptom-free, three years after aortofemoral bypass grafting for claudication. He has no known history of coronary artery disease (CAD) or stroke. His risk factors include a strong family history of CAD and controlled hypertension. He quit smoking three years ago, and does not have diabetes or known dyslipidemia. Medications include acetylsalicylic acid, 81 mg daily, hydrochlorothiazide, 12.5 mg daily, and ramipril, 10 mg daily.

Other bloodwork, including fasting blood glucose, is normal. You reassure J.P. he is doing well, but wonder whether he might benefit from the addition of a statin, despite his unremarkable lipid profile.

**How should J.P. be managed? For more on J.P., see page 27.**

#### Examination reveals:

- A blood pressure of 130/80 mmHg.
- A loud systolic carotid bruit on the left.
- The remainder of the exam is unremarkable.

#### Fasting lipid profile reveals:

- Serum cholesterol of 4.8 mmol/L.
- Low-density lipoprotein cholesterol of 2.5 mmol/L.
- High-density lipoprotein of 1.0 mmol/L.
- Triglycerides of 1.8 mmol/L.

### In this article:

1. Who can benefit?
2. What about the elderly?
3. What about early statin therapy?

This article summarizes major recent studies of 3-hydroxy-3 methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, otherwise known as statins, for the prevention of cardiovascular morbidity and mortality.<sup>1-5</sup> A key concept is that the substantial benefits of statins have now been proven in many important patient subgroups, including:

- Patients with diabetes but no prior coronary artery disease (CAD)
- Patients with peripheral vascular or cerebrovascular disease
- Patients with acute coronary syndromes
- Patients undergoing percutaneous coronary intervention
- The elderly
- Women
- Patients with normal low-density lipoprotein (LDL) cholesterol levels and/or low high-density lipoprotein (HDL) cholesterol levels.

### About the author ...

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Therefore, statin therapy should not be denied to high-risk patients who are outside the previous well-established indications (hyperlipidemia and/or previous CAD). The major trials reviewed in this article are: HPS, PROSPER, LIPS, MIRACL, and HATS (Table 1).

### HPS-Who can benefit?

The Heart Protection Study (HPS) is the first large statin trial to specifically enrol patients with diabetes as a separate inclusion criterion.<sup>1</sup> In all, 20,536 patients (including 5,963 patients with diabetes) were randomized to simvastatin, 40 mg daily, or placebo, for a mean followup of five years. Overall, there was a highly significant 24% reduction in the risk of major vascular events (mortality, coronary events, revascularization, and stroke). Due to significant crossover in the trial, the actual risk reduction is likely to be closer to one third. There were very similar benefits in every subgroup examined, including patients with diabetes but no CAD; cerebrovascular or peripheral vascular disease; the elderly; women; and those with normal or low LDL levels. Treatment effects were independent of the baseline LDL cholesterol

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## Recent Statin Trials

Table 1

### A Comparison of Five Recent Statin Trials

Trial	Size (N)	Treatment	Patients	Duration	Endpoints	Comments
<b>HPS</b>	20,536	simvastatin	25% > age 70 29% diabetes 16% CVD 33% PAD	5 years	Death, MI, stroke, revascularization, cancer	Largest statin trial to date; NNT=10 for 1 <sup>o</sup> end point; no increase in non-vascular morbidity/mortality
<b>PROSPER</b>	5,804	pravastatin	ages 70-82 11% diabetes 44% vascular disease 56% risk factors only	3.2 years	CV death, MI, stroke, TIA, cancer	24% reduction in CV death; 19% reduction in cardiac events; shorter followup than most statin trials
<b>LIPS</b>	1,677	fluvastatin (after PCI)	LDL 3.4 mmol/L 48% had LDL < 3.4 49% unstable angina 40% stable angina 11% silent ischemia	3.9 years	CV death, MI, reintervention, cancer	Benefit even in low LDL; striking benefit in diabetes and multivessel CAD; no increase in cancer
<b>MIRACL</b>	3,086	atorvastatin (after ACS)	LDL 3.2 mmol/L 46% unstable angina 54% non-Q-wave MI 23% diabetes	16 weeks	death, MI, stroke cardiac arrest, unstable angina, revascularization	16% reduction in 1 <sup>o</sup> end point; 26% reduction in unstable angina; 50% reduction in stroke
<b>HATS</b>	160	simvastatin + niacin; or antioxidants; or simvastatin + niacin + antioxidants; or placebo	LDL 3.2 mmol/L HDL 0.8 mmol/L 16% diabetes BMI 29	3.2 years	CAD progression, death, MI, stroke revascularization	90% reduction in events on combined simvastatin + niacin, and 0.4% regression in stenosis; vitamins had not effect

All data represent means, unless otherwise indicated. CVD: cerebrovascular disease; PAD: peripheral arterial disease; MI: myocardial infarction; NNT: number needed to treat (to prevent one event); CV: cardiovascular; TIA: transient ischemic attack; PCI: percutaneous coronary intervention; LDL: low-density lipoprotein cholesterol; CAD: coronary artery disease; ACS: acute coronary syndrome; 1<sup>o</sup>: primary; HDL: high-density lipoprotein cholesterol; BMI: body mass index.

### Followup on J.P

- J.P. is at very high risk of a future cardiovascular event, given the presence of peripheral vascular disease, a carotid bruit, strong family history, hypertension, age, and male sex.
- The Heart Protection Study (HPS) found that the benefits from a statin were very similar irrespective of the presence of coronary artery disease or hyperlipidemia. Furthermore, 33% of patients in HPS had low-density lipoprotein (LDL) levels less than 3.0 mmol/L; these patients achieved the same benefit as those with LDL levels > 3.0 mmol/L.
- Treating approximately 1,000 patients like J.P. with simvastatin for five years will prevent 100 vascular events (which is likely an underestimate, since only first events were counted).
- Many placebo-allocated patients ended up on a statin, and benefits continued to increase over the course of followup.
- After discussing these findings with J.P., he concludes it is worthwhile to add a statin to his daily regimen.

level; renal function; smoking; hypertension; and treatment with acetylsalicylic acid, beta blockers or angiotensin-converting enzymes (ACE) inhibitors. Simvastatin was well-tolerated and extremely safe. After allowing for non-compliance, treating 1,000 patients with simvastatin, 40 mg daily, will prevent about 100 people from suffering major vascular events, giving a number needed to treat of only 10.

### PROSPER-What about the elderly?

The Prospective Study of Pravastatin in the Elderly at Risk (PROSPER) enrolled 5,804 elderly individuals (aged 70 to 82) with a history of, or risk factors for, vascular disease. Patients were given pravastatin, 40 mg daily, or placebo, and were followed for an average

## Confidence

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Reference: 1. SciSearch Database (Institute for Scientific Information) thru 12/2002

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## Recent Statin Trials

### ♥ Practical Point

For more information on statins, some helpful Web sites include:

♥ [www.lipidsonline.org](http://www.lipidsonline.org)

♥ [www.theheart.org](http://www.theheart.org)

♥ [www.vbwg.org](http://www.vbwg.org)

of 3.2 years.<sup>2</sup> The primary end point, a composite of coronary death, non-fatal myocardial infarction (MI), and stroke, was reduced by 15%, with a 19% reduction in coronary events and 24% in coronary mortality. Stroke risk, however, was unaffected, although there was a strong trend towards a reduction of transient ischemic attacks (25% reduction, where  $p=0.05$ ). The authors of this trial speculate the lack of effect on stroke may have been due to a relatively short followup period and an unexpectedly low rate of stroke events in the trial, which may have limited the power to detect a benefit on stroke. In any event, PROSPER, as with HPS, clearly extends the benefits of statin therapy to older patients with vascular disease or risk factors.

### LIPS-What about post-PCI patients?

The Lescol Intervention Prevention Study (LIPS) randomized 1,677 patients undergoing percutaneous coronary intervention (PCI), for stable or unstable angina or silent ischemia, to fluvastatin, 80 mg daily, or placebo.<sup>3</sup> Median followup was 3.9 years. The primary end point, a composite of cardiac death, non-fatal MI, or reintervention procedure, was reduced by 22%, a result that was independent of baseline cholesterol level, indication for PCI, type of procedure (stent versus balloon), *etc.* Striking risk reductions were noted in patients with diabetes (47%

decrease) and multivessel disease (34% decrease). These results support the use of early statin therapy in all post-PCI patients, regardless of their baseline lipid levels.

### MIRACL-What about acute coronary syndromes?

The Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) study tested the hypothesis that early initiation of a statin reduces the risk of recurrent ischemic events in the high-risk period following an acute coronary syndrome (ACS).<sup>4</sup> A total of 3,086 patients were randomized to atorvastatin, 80 mg daily, or placebo, 24 to 96 hours after ACS (median 63 hours). These patients were followed for 16 weeks. Mean LDL in both groups was 3.2 mmol/L. The primary end point, including death, non-fatal MI, cardiac arrest, or recurrent unstable angina, was reduced by 16%. This reduction was driven in large part by a decreased risk of unstable angina (26% decrease). There was also a 50% reduction in the risk of stroke in the atorvastatin group. The results of MIRACL indicate that statins are safe and effective when administered during the acute phase of ACS.

### HATS-Lipid-lowering and antioxidant therapy?

The HDL-Atherosclerosis Treatment Study (HATS) was designed to test the hypothesis that lipid-lowering and antioxidant therapy provide

**For some frequently asked questions on statins, please go to page 19.**

## Take-home message

Provision of a statin to any patient should be driven more by consideration of global vascular risk than by the baseline LDL level.


Statin decrease a range of clinically important vascular events by about 25% to 33%.

In addition to patients with hyperlipidemia and/or CAD, statins are effective in the following populations:

- Women
- The elderly
- Patients with diabetes, but without CAD
- Patients with normal or low LDL levels
- Patients with low HDL levels
- Patients with peripheral vascular disease
- Patients with cerebrovascular disease
- Patients with acute coronary syndromes
- Patients undergoing percutaneous coronary intervention

independent and additive benefits for patients with CAD, normal LDL levels, and low HDL levels.<sup>5</sup> The study involved 106 patients who were randomized to one of four groups: simvastatin plus niacin, a vitamin antioxidant cocktail, simvastatin- niacin plus antioxidants, or placebo. Antioxidant vitamins had no effect on the risk of cardiovascular events or angiographic progression of CAD. On the other hand, both simvastatin groups showed a reduced or even reversed progression of CAD (-0.4% progression with simvastatin- niacin and 0.7% progression with simvastatin- antioxidants, versus 3.9% progression with placebo). The two simvastatin groups also had a markedly decreased risk of vascular events (*i.e.*, a 90% risk reduction in the simvastatin- niacin group). These data are especially noteworthy, as the findings could apply to the roughly 40% of patients with CAD who have low HDL levels.

## What's the final word?

Statin rank among the most important recent advances in cardiovascular medicine, and represent a highly effective class of drugs for the treatment of atherosclerotic vascular disease. The landmark trials reviewed here add clear and convincing evidence to the already impressive track record of these agents. Perhaps the most important message is that every patient who has, or is at risk of, vascular disease, in any vascular bed (peripheral, aortic, cerebral, or coronary), should be carefully considered for treatment with a statin. 

### References

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