Statins: Evidence for effectiveness

Outhoff K, MBChB, FFPM

Senior Lecturer, Department of Pharmacology, Faculty of Health Sciences, University of Pretoria, Pretoria
Correspondence to: Kim Outhoff, e-mail: kim.outhoff@up.ac.za
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Abstract

Since their introduction in 1987, statins have become the largest-selling prescription drugs worldwide, and have kept both the scientific and lay press captivated. There were reports this year alone that statins may prevent hysterectomies in women with fibroids, are linked to better health outcomes after brain haemorrhage, may protect against the microvascular complications of diabetes, as well as against cerebral reperfusion injuries, may lower the risk of Barrett’s oesophagus, alter the inflammatory response to the common cold, slow the progression of advanced multiple sclerosis, and offer added benefit to men with erectile dysfunction. Amid this hype and against a backdrop of more than a billion people potentially taking statins, the obvious question is whether or not current evidence on the safety and efficacy of statins still overwhelmingly favours these agents for their licensed indication of lowering cholesterol and preventing cardiovascular disease morbidity and mortality.

Introduction

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The principle therapeutic benefits of statins derive from their ability to reduce cholesterol low-density lipoprotein (LDL) by inhibiting 3-hydroxy-3-methyl-glutaryl-CoA (HMG-CoA) reductase enzymes. It appears that the greater the LDL reduction, the greater the risk reduction of CVD events. There is also evidence that statins reduce vascular inflammation, improve endothelial function and diminish thrombus formation. In terms of quantifying their efficacy in reducing CVD mortality, a meta-analysis involving approximately 170,000 patients from 76 randomised trials revealed that patients on statin therapy achieved a 10% risk reduction in all-cause mortality compared to those on control interventions, and that each 10% change in absolute LDL levels was associated with a 1.1% risk reduction. The significant reduction in mortality in patients on statin therapy appeared to be largely attributable to a 20% greater reduction in CVD deaths specifically, compared to control-treated patients. A 10% reduction in LDL in the subset of CV patients was associated with a substantial 5.6% risk reduction in CVD mortality. Regarding major cardiovascular events, this analysis found an 18% risk reduction for fatal myocardial infarction (MI), a highly significant 26% reduction in non-fatal MI and a highly significant effect of statins on the coronary revascularisation status of statin users. A strongly significant effect favouring statins was found when assessing fatal strokes, and somewhat reassuringly, there was no evidence to substantiate concerns that statins may increase the risk of haemorrhagic strokes, in particular. A comparison of different statins found no statistically significant differences with regard to their ability to lower CVD mortality, although lovastatin was found to potentially exert a greater therapeutic effect. Others have shown that the benefits of standard statin therapy, while significant in the first year, are greater in subsequent years, reinforcing the recommendation for prolonged statin therapy in all patients at high risk of any type of major vascular event.

A 1 mmol/l decrease in LDL leads to a 20% reduction in major vascular events, including coronary death, non-fatal MI, coronary revascularisation and strokes. A meta-analysis of more intensive lowering of LDL with statin therapy revealed that further reductions in LDL to approximately 1.2 mmol/l produced definite further reductions in the incidence of heart attacks, revascularisation and ischaemic strokes. In fact, each 1 mmol/l reduction in LDL was associated with an additional 20% reduction in these vascular events.

As the benefits of statin therapy are clear, the risks pertaining to both standard and intensive lowering of LDL warrant further scrutiny. Meta-analysis data of important adverse events from standard LDL lowering clinical trials revealed no differences in first-incident cancer after randomisation between statin and control groups. No differences were found in the incidence of rhabdomyolysis either. However, the data revealed a significant increased rate of new-incident diabetes, as well as elevated serum aspartate (AST) aminotransferase and creatine kinase (CK)
levels in statin versus control groups. The latter is usually found in large quantities in heart and skeletal muscle cells, and raised serum levels are an indication of myopathy.

Adverse event data in more intensive LDL-lowering trials reported definite excesses in the incidence of myopathy of four per 10 000 (compared to one per 10 000 in standard statin therapy trials), and were associated with 80 mg, rather than 20 mg, simvastatin use. The placebo-corrected incidences per 100 000 patient years in otherwise healthy clinical trial participants was found to be 190 for minor muscle pain, five for myopathy (with significant elevations in CK), and 1.6 for rhabdomyolysis. Other real-world estimates of muscle complaints are in excess of 10% in patients on high-dose statins. It appears that myopathy relates more to statin dose and blood levels than to LDL reduction, and may therefore be influenced by important patient characteristics, statin pharmacokinetics and drug-drug interactions. Thus, high doses of statins confer significant additional CVD benefits, but are associated with a higher risk of mild to moderate muscular symptoms, with a median time of onset of one month following the initiation of statin therapy. It has been proposed that higher-potency statins at standard doses could help patients to attain their treatment goals without increasing the risk of myopathy.

Table I details the approximate equipotency of statins, based on clinical trial usage.

However, in terms of their diabetogenic potential, a recent study has shown that compared with pravastatin, treatment with higher-potency statins, especially atorvastatin and simvastatin, may be associated with an increased risk of new-onset diabetes. Although different types and doses of statins appear to have different potentials to increase the incidence of diabetes, the diabetogenic tendencies of this class have led to the US Food and Drug Administration (FDA) requirement that this information is added to all statin safety labels.

Other recent significant changes to FDA labelling concern lovastatin dose limitations (lovastatin is structurally related to simvastatin) because of its potential for clinically important drug-drug interactions. Lovastatin is a cytochrome P450 3A4 (CYP3A4) substrate and strong CYP3A4 inhibitors, such as itraconazole, may significantly increase lovastatin exposure up to 20-fold, resulting in possible rhabdomyolysis. Other CYP3A4 inhibitors, including ketoconazole, posaconazole, erythromycin, clarithromycin and telithromycin; as well as human immunodeficiency virus protease inhibitors, boceprevir, telaprevir, and nefazodone; are also contraindicated withlovastatin use. In addition, dose limitations are imposed on patients taking danazol, diltiazem, verapamil and amiodarone.

Considerations for the safe use of statins also include the risk of hepatic injury, which occurs rarely and unpredictably in approximately 1% of patients. Although the FDA has removed the need for routine periodic monitoring of liver enzymes in patients taking statins, it has recommended that liver enzyme tests are performed before statin therapy is started, and as clinically indicated thereafter. Patients with transaminase levels of no more than three times the upper limit of normal can continue taking statins as the elevations often resolve spontaneously. The coexisting elevation of transaminase levels from non-alcoholic fatty liver disease and stable hepatitis B and C viral infections is not a contraindication to statin use.

Taken together, the extensive efficacy and safety data have informed current guidelines. The 2013 American Heart Association blood cholesterol guideline reiterates that the initiation of moderate-intensity or high-intensity statin therapy is critical in reducing atherosclerotic cardiovascular disease (ASCVD) events, and further specifies that statin therapy reduces these events across the spectrum of baseline LDL levels > 70 mg/dL. The experts note that the relative reduction in ASCVD risk is consistent for both primary and secondary prevention, as well as for various patient subgroups, and the absolute reduction in ASCVD events is proportional to absolute baseline ASCVD risk.

The guideline identifies four major groups of adults in whom the benefits of statin therapy clearly outweigh the potential risks of serious side-effects:

- Individuals with clinical ASCVD.
- Individuals with primary elevations of LDL ≥ 190 mg/dL.
- Individuals aged 40-75 years with diabetes, with LDL 70-189 mg/dL.
- Individuals without clinical ASCVD or diabetes aged 40-75 years, with LDL 70-189 mg/dL and an estimated 10-year ASCVD risk of 7.5% or higher.

### Table I: Approximate equipotency of statins, based on clinical trial usage

<table>
<thead>
<tr>
<th>High-intensity statin therapy</th>
<th>Moderate-intensity statin therapy</th>
<th>Low-intensity statin therapy</th>
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<tbody>
<tr>
<td>On average, a daily dose lowers LDL by ≥ 50%</td>
<td>On average, a daily dose lowers LDL by 30% to &lt; 50%</td>
<td>On average, a daily dose lowers LDL by &lt; 30%</td>
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<tr>
<td>Atorvastatin 40-80 mg</td>
<td>Atorvastatin 10-20 mg</td>
<td>Simvastatin 10 mg</td>
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<tr>
<td>Rosuvastatin 20-40 mg</td>
<td>Rosuvastatin 5-10 mg</td>
<td>Lovastatin 40 mg</td>
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<td></td>
<td>Simvastatin 20-40 mg</td>
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<td></td>
<td>Lovastatin 40 mg</td>
<td>Pravastatin 10-20 mg</td>
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<td></td>
<td>Pravastatin 40-80 mg</td>
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<td>Fluvastatin XL 80 mg</td>
<td>Fluvastatin 20-40 mg</td>
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<tr>
<td></td>
<td>Fluvastatin 40 mg bid</td>
<td>Fluvasatin 20-40 mg</td>
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<td></td>
<td>Pitavastatin 2-4 mg</td>
<td>Pitavastatin 1 mg</td>
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bid: twice daily, LDL: low-density lipoprotein
The 2014 National Institute for Clinical Excellence (NICE) guidelines for lipid modifications recommend that patients are started on high-intensity statin treatment if they have a 10% or more risk of CVD in the next 10 years, rather than the previous target of 20%, and recommend that atorvastatin 20 mg, rather than simvastatin, is used as the preferred initial treatment option in patients identified as high risk.22

Inter-individual variability in response to statins may be partially due to genetic variations, and in future, the selection of the most effective statin for individuals may potentially be informed by pharmacogenetic data.23 Despite this current limitation, the effectiveness of statins for the primary and secondary prevention of CVD is undisputed. At least 450 deaths are prevented for every 10 000 patients treated if patients with a 20% risk or more of suffering such a cardiovascular event over a 10-year period take statins for at least five years.24 The use of statins in these eligible patients is deemed to be relatively safe, particularly if the risks of serious adverse effects are moderated by good scientific evidence and clinical judgement.

References
