

# The treatment of cholesterol: safety and efficacy of statin therapy

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## Introduction

Statins are the most widely prescribed class of drugs worldwide, and also the most powerful cholesterol-lowering drugs currently available. Statins inhibit 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG CoA) reductase, which leads to reduced cholesterol synthesis. In addition, low-density cholesterol receptors on the hepatocyte surface are upregulated, leading to increased clearance of cholesterol. Cholesterol levels are reduced, which leads to a significant reduction in cardiovascular events, of 25-45%.

Statins are well tolerated and are believed to have minimal side-effects. Recent large meta-analyses and systematic reviews have shown no convincing evidence for changes in cognitive function or risk of cancer after statin use.<sup>1</sup> However, there is a slight risk of myopathy, liver enzyme elevation and, very rarely, rhabdomyolysis. There is also a small increased risk of incident type 2 diabetes mellitus. The overwhelming benefit of statins far outweighs the small increase in relative risk for the development of these side-effects.

## How effective are statins?

The following findings were made in a meta-analysis, conducted in 2005, of 14 randomised, controlled trials with > 90 000 participants treated for five years:<sup>2</sup>

- For every 1 mmol/l that low-density lipoprotein (LDL) cholesterol is reduced, mortality is reduced by 12% [95% confidence interval (CI): 9-16%] over five years, and one person's life is saved for every 83 persons treated over five years [number needed to treat (NNT): 83].
- For every 1 mmol/l that LDL cholesterol is reduced, coronary heart disease is reduced by 19% (95% CI: 15-24%) over five years. This translates into 14 (95% CI: 9-19) fewer deaths per 1 000 treated patients without pre-existing coronary heart disease.

This meta-analysis demonstrated that larger reductions in LDL cholesterol produced larger reductions in vascular disease events. For example, reducing LDL cholesterol by 1.5 mmol/l may reduce vascular events by one third. Also, continued treatment over time increased the absolute benefit.

In 2010, a meta-analysis of data on 129 526 participants in 26 trials demonstrated that more intense treatment with statins versus standard treatment with statins produced a significant reductions of 15% (95% CI: 11-18%) in major vascular events.<sup>3</sup> Total mortality was reduced by a significant 10% (95% CI: 7-13%) per 1 mmol/l reduction in LDL cholesterol. The conclusions that could be drawn from this meta-analysis were that further reductions in LDL cholesterol with more intense statin therapy safely reduced further cardiovascular events, and that reducing LDL cholesterol by 2-3 mmol/l may reduce cardiovascular events by 40-50%.

This year, a meta-analysis attempted to address the remaining uncertainty about whether statin therapy is of overall benefit in primary prevention. Data from 27 trials were scrutinised.<sup>4</sup> The use of statins reduced the risk of major vascular events by 21% (95% CI: 19-23%). This reduction was irrespective of age, sex, baseline level of LDL cholesterol or the presence of previous vascular events. The risk reductions were also similar in all the risk categories, as measured by the Framingham risk score. These highly significant risk reductions were achieved without significant increase of side-effects, including cancer. The use of statins in primary prevention is therefore significantly effective and safe.

## What are the lipid targets?

Currently, an LDL cholesterol target of < 3 mmol/l seems to be the ideal in normal people without an elevated risk. For high-risk people, an LDL level < 2.6 mmol/l should be aimed for and, in very high-risk people, the LDL level should probably be < 1.8 mmol/l. The question remains: how low should LDL levels be reduced for maximal cardiovascular protection?

## Is it dangerous to reduce LDL cholesterol?

There are no intrinsic dangers associated with lowering cholesterol, and no hard evidence to the contrary exists. Levels of cholesterol are controlled by the LDL receptor, which acts as a homeostatic mechanism, so that lowering serum cholesterol does not decrease intracellular cholesterol levels.<sup>5</sup>

There are no convincing data from randomised clinical trials proving increases of cancer or cognitive decline.<sup>1</sup> All other side-effects are small in number, and are completely overshadowed by the significant benefit of statin treatment.

### Are there groups that may not benefit?

Patients with heart failure with reduced ejection fraction may not benefit if statin therapy is only initiated with the onset of heart failure. This does not imply that statin therapy, if started long before, should now be stopped when heart failure occurs.

There is also some doubt if patients with end-stage renal failure could benefit from statin therapy, as there are currently not enough data.

### What about women?

There has been a suggestion that women may not benefit as much as men from statin therapy. A meta-analysis of 18 randomised trials which included 141 235 participants, of which 40 275 were women, and describing 21 468 cardiovascular events was published recently. The odds to develop a cardiovascular event were reduced to the same extent in men and women. This was also observed in mortality.<sup>6</sup> The conclusion was that statin therapy should be used in appropriate patients, without regard to sex.

### Should we be treating earlier?

Fatty streaks are already extensive at the age of 30 years in many, and these will probably develop into fibrous atherosclerotic

plaques later. So, the question remains: should we not start treatment earlier if we want to change the natural history of this disease?

### Conclusion

Statin therapy benefits many people, whether used as secondary or primary prevention, by reducing cardiovascular events and mortality. The benefit varies with baseline risk. This protective role of statins applies to many categories of patients, including the old and women, and, in many cases, in children as well.

We also need to establish the role of statins in combination with other lipid-modifying drugs, such as ezetimibe, niacin, fibrates and omega-3 fatty acids.

How aggressively should cholesterol be reduced, and how early should we start? These are questions which may be answered soon.

### References

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Depression is common, affecting approximately 121 million people worldwide. It is among the leading causes of disability and can lead to substantial impairments in a person's ability to take care of their everyday responsibilities. At its worst, depression can lead to suicide, a tragic outcome that is associated with the loss of roughly 850 000 lives every year.

As many as two thirds of people with depression either do not realise, or do not accept, that they have a treatable illness. Therefore, they do not seek professional help. When patients first seek treatment in the primary care setting, the presenting symptoms can often be somatic, such as fatigue, headaches, abdominal complaints or sleep problems. This results in the underlying diagnosis of depression being missed. In addition, because many people misperceive the illness to be a

personal weakness or failing, they do not seek professional help and avoid being diagnosed.

Although depression can be diagnosed reliably in primary care and although many effective treatments are available, including psychotherapy used either alone or in combination with medication, it is estimated that fewer than 25% of people who are affected by depression have access to or undergo treatment.

Most patients with bipolar disorder present with depression and are commonly misdiagnosed as having unipolar depression. However, recognition of bipolar disorder is important because it is associated with substantial morbidity and mortality if untreated, and because the treatment differs from that of unipolar depression.

This module provides an update on unipolar depression in order for the pharmacist to play a role in improving the quality of care, patient satisfaction with care and patient health outcomes and functioning.

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