

The treatment of cholesterol: issues, effects and targets

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Statins: what are they?

Statins are the most powerful cholesterol lowering drugs currently available. Statins inhibit 3-hydroxy-3-methylglutaryl-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. The end result is a significant reduction in cholesterol levels, and a consequent significant reduction in mortality and cardiovascular events in the appropriate individual.

How effective are statins?

In a meta-analysis of 14 randomised controlled trials with >90 000 participants treated for 5 years:¹

- For every 1 mmol/L that low-density lipoprotein (LDL) cholesterol is reduced, mortality is reduced by 12% [95% CI: 9-16%] over five years, and one person's life is saved for every 83 treated over five years [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 with pre-existing coronary heart disease over five years, compared to four [95% CI: 1-7] fewer deaths per 1 000 treated patients without pre-existing coronary heart disease.

The meta-analysis demonstrated a proximately linear relationship between absolute reductions in LDL cholesterol achieved and the proportional reductions in the incidence of coronary and other major vascular events. Larger LDL reductions produce larger reductions in vascular disease, e.g. a reduction in LDL cholesterol of 1.5 mmol/L may be

expected to reduce the incidence of major vascular events by about one-third.

The meta-analysis also demonstrated that the absolute benefit of statins increased with continuing treatment. On the other hand, one should bear in mind that the absolute benefit of treatment depends on the absolute risk of the patient being treated.

What are the lipid targets to aim for?

Currently, in normal people with a low-estimated global cardiovascular risk, an LDL cholesterol level below 3 mmol/L seems adequate. For high-risk individuals (i.e. risk factors are present), an LDL cholesterol level below 2.6 mmol/L should be the aim (primary prevention). For very high-risk individuals, such as in the case of secondary prevention, after an event, an LDL cholesterol level below 1.8 mmol/L should be the aim.²

In high-risk people who also have low HDL cholesterol and/or elevated triglyceride levels, a statin should be prescribed and a fibrate or niacin (nicotinic acid) added. A triglyceride level greater than 1.7 mmol/L is abnormal, and an HDL cholesterol level below 1.02 mmol/L in men and 1.29 mmol/L in women is considered by many as abnormal.

Is it dangerous to reduce LDL cholesterol?³

There are no intrinsic dangers to lowering LDL cholesterol, and no hard evidence to the contrary exists. Large randomised trials demonstrated a reduction in total mortality. There is no convincing evidence that cancer incidence will rise with statin use. There is some indication that statin use, per se, may increase the development of diabetes mellitus.

Should we be initiating preventive measures earlier?³

Fatty streaks can already be demonstrated in adolescents and can be extensive by 30 years of age. We do treat high-risk children, e.g. familial hypercholesterolemia. So this is a good question: Should we not start to treat people earlier if we want to change the natural history of atherosclerosis? There is some doubt as to whether statins or fibrates will reduce total mortality in primary prevention, i.e. in individuals without cardiovascular disease.

What about the elderly?

With increasing age, risk prediction tools, such as Framingham, become less accurate, clinical data are sparse, and decreasing life expectancy versus time to medication benefit shifts constantly. Yet, at least two pieces of evidence suggest that older age people, including these 80 years and older, will also benefit from statins.^{4,5} In fact, the elderly may benefit by risk reduction in a short follow-up time after initiating treatment.

This does not imply that a low-risk individual should be treated with a statin because of age alone.

Are there patient groups that may not benefit?

It seems that patients with heart failure may not benefit if statins are only then initiated. This does not imply that, in a high-risk individual that has been on a statin for a long period before developing heart failure, the statin now has to be stopped. There is also still some uncertainty if patients with chronic renal failure will benefit from statin therapy. More data are, however, necessary to determine the effects of statin therapy in other subgroups that may or may not benefit.

Can we stop atherosclerosis with statins?

Statin treatment diminishes the progression of coronary atherosclerosis, but regression has only been observed occasionally. Newer studies with intravascular ultrasound will probably clarify this issue in future. The ultimate expectation will be whether the process of atherosclerosis could undergo regression.

Conclusion

Statin treatment benefits people when used as primary and, definitely, secondary prevention, by reducing cardiovascular events and mortality. The benefit varies with the baseline risk of the patient.

This protective role of statins applies to many categories of patients and populations, including the elderly. Two real questions now dominate our thinking: How aggressive should we be with treatment, and how early should we start with treatment to get the maximum benefit in the long term?

Safety concerns with the use of statins have mainly been addressed, and very few unfortunate individuals will experience serious side-effects. The side-effects that may accrue with life-long therapy must be established.

References

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