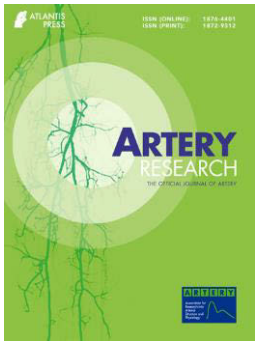

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Review

Should a statin be given to all hypertensive patients?

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Abstract Statins have become an essential treatment for primary and secondary prevention of cardiovascular risk. This has been firmly established for patients with a relatively high risk for cardiovascular complications. Recent studies, in particular the HOPE trial, has extended this observation to patients with intermediate cardiovascular risk, including hypertensive patients. On the other hand, statin use has been associated with side effects in a small percentage of patients. The decision to add a statin to the drug treatment of a hypertensive patient should be based on an assessment of the individual's potential risk reduction and the perceived side effects of the treatment.

Contents

Statins are pivotal drugs in the control of cardiovascular risk. The original trials in the 1990's that showed the effectiveness of statins in reducing cardiovascular risk in coronary heart disease[1,2] have been followed-up by long term safety and efficacy trials.[3–6] These extended follow-up studies showed a legacy effect, with improved survival and a substantial reduction in cardiovascular outcomes over periods up to 20 years.[3–6] Furthermore, long-term statin treatment does not influence cancer or death from non-cardiovascular causes during long-term follow-up.[5,6] In a recently published large-scale review about the efficacy

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and safety of statin therapy Collins et al.[7] concluded that statin therapy reduces the risk of major vascular events (i.e., coronary deaths or myocardial infarctions, strokes, and coronary revascularization procedures) by about one-quarter for each mmol/L reduction in LDL cholesterol during each year (after the first) that it continues to be taken. The absolute benefits of statin therapy depend on an individual's absolute risk of occlusive vascular events.[7] Statin therapy has been shown to reduce vascular disease risk during each year it continues to be taken, so larger absolute benefits would accrue with more prolonged therapy.[7]

A systematic review and meta-analysis on the therapeutic equivalence of statins has shown that standard daily doses of statins can decrease LDL-cholesterol by 20—50%.[7,8] However, it has become clear that the favorable effect of statins on cardiovascular risk cannot be exclusively explained on the basis of LDL-cholesterol lowering. Statins have pleiotropic pharmacological actions, which include improvement of endothelial function, reduced vascular inflammation and fibrosis, reduced platelet aggregability and stabilization of the atherosclerotic plaque.[9,10]

These studies support the wider adoption of statins in primary and secondary prevention strategies. Further evidence for such a role of statins in primary prevention strategies has come from the recently published Heart Outcomes Prevention Evaluation (HOPE)-3 trial.[11—14] The primary results of this trial have been published in 3 articles in the New England Journal of Medicine[11—13] in conjunction with an editorial that puts the results into the perspective of primary prevention of cardiovascular risk.[14] In brief, HOPE-3 was a double-blind randomized, placebo-controlled trial. It had a 2-by-2 factorial design, in which 12,705 intermediate risk men (≥55 years of age) and women (≥60 years of age) were randomly assigned to receive rosuvastatin at a dose of 10 mg per day or placebo and were also randomly assigned to receive antihypertensive treatment with candesartan at a dose of 16 mg per day plus hydrochlorothiazide at a dose of 12.5 mg per day or placebo for a median treatment period of 5.6 years. Treatment with rosuvastatin resulted in a 24% lower risk of cardiovascular events than with placebo. In the rosuvastatin group there was no excess of diabetes or cancers, but there was an excess of muscle symptoms.[11] The antihypertensive therapy did not result in a significantly lower risk of cardiovascular events, although in one of the three prespecified hypothesis-based subgroups, participants in the subgroup for the upper third of systolic blood pressure (>143.5 mm Hg) who were in the active-treatment group had a significantly lower cardiovascular risk.[12] Finally, the combination of rosuvastatin, candesartan and hypochlorothiazide was associated with a significantly lower rate of cardiovascular events than dual placebo among persons of intermediate risk who did not have cardiovascular disease.[13]

The relative risk reduction (RRR) of rosuvastatin in this primary intervention trial was 24%. In absolute terms it was a reduction in the rate of cardiovascular events from 4.8% (over a period of 5.6 years) in the placebo treated group to 3.7% in the rosuvastatin group. These data are in agreement with those of a meta-analysis of randomized trials of statin therapy which led to a RRR of 25% of cardiovascular events in a primary-prevention population.[15] Taken together these data make a strong case for statin treatment in patients with an intermediate risk who do not yet have cardiovascular disease.

Several aspects of these results need further attention. First of all, the potential gain in cardiovascular risk reduction should in individual patients be weighed against the discomfort, in particular due to muscle symptoms.[7,8] In the HOPE-3 trial more participants in the rosuvastatin group than in the placebo group had muscle pain or weakness (5.8% versus 4.7%), although there was no significant difference between 2 groups in the number of participants in whom the assigned treatment was permanently discontinued because of muscle symptoms (1.3% versus 1.2%).[11] The recent large-scale review by Collins et al.[7] gives detailed data on statin-related adverse effects. They state that the only serious adverse effects of statin therapy are myopathy, new-onset diabetes mellitus, and, probably, hemorrhagic stroke. Typically, treatment of 10.000 patients for 5 years with an effective regimen of a statin would cause about 5 cases of myopathy, 50—100 new cases of diabetes, and 5—10 hemorrhagic strokes.[7] Statin therapy may cause symptomatic adverse events, in particular muscle pain or weakness, in up to about 50—100 patients.[7] Collins eta al[7] make the point that placebo-controlled randomized trials have shown that almost all of the symptomatic adverse events that are attributed to statin therapy in routine practice are not actually caused by it. They express their concern that exaggerated claims about side-effect rates with statin therapy may be responsible for its under-use among individuals at increased risk of cardiovascular events.

Another issue is the question whether the amount of LDL reduction is decisive for the degree of cardiovascular reduction. The HOPE-3 trial was not designed to answer this question. In contrast, the statin was given independently of the pre-treatment cholesterol or LDL level. Still the statin treatment was associated with 26.5% reduction in LDL cholesterol level. Recent guidelines[16,17] recommend a risk based approach to statin use rather than an approach that is based primarily on LDL cholesterol levels. The recently published IMPROVE-IT trial[18] aimed at studying the impact of further reducing the LDL-cholesterol level in patients with acute coronary syndrome by adding ezetimibe to a standard treatment with 40 mg simvastatin. The combined ezetimibe/simvastatin treatment led to a 22% lower LDL cholesterol concentration than the placebo/simvastatin treatment. However, the RRR in cardiovascular events was only 6%. The results of these trials suggest that LDL reduction may not be the only mechanism whereby statins reduce cardiovascular risk. Pharmacological research in the past two decades has suggested pleiotropic effects of statins beyond LDL cholesterol reduction.[9,10]

In conclusion, new insights from pharmacological studies as well as clinical trials suggest new paradigms for statin use in primary cardiovascular prevention. Even in patients with intermediate cardiovascular risk without overt cardiovascular disease statin use may offer benefits, partly independent of LDL cholesterol reduction. Since hypertension contributes importantly to overall cardiovascular risk, the use of a statin should be considered in hypertensive patients. However, the individual decision to use a statin should be based upon individualized estimates of risk reduction and adverse effects.[19,20]

Conflict of interest statement

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