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Pravastatin, simvastatin, and atorvastatin appear equally effective for preventing cardiovascular events

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Background

People with high blood pressure are at increased risk of cardiovascular events. Statins have been found to reduce risks, but the relative efficacy of different statins remains uncertain.

Objective

Zhou and colleagues compared the effectiveness of different statins for preventing cardiovascular events.

Method

This meta-analysis included eight placebo-controlled trials with 63,695 participants.

The authors searched for randomised trials published between 1980 and 2004. To be eligible for inclusion, studies had to compare placebo or usual care with either pravastatin (5 trials), simvastatin (2 trials), or atorvastatin (3 trials) for long-term prevention of cardiovascular events; include cardiovascular diseases or death as an outcome; include at least 1000 participants; and have at least one year of follow up.

The authors used a random effects model to calculate pooled relative risks for each type of statin and then made indirect comparisons.

Main results

There was no significant difference between statins in reducing fatal coronary heart disease and nonfatal myocardial infarctions (simvastatin vs pravastatin relative risk 0.93, 95% CI 0.84 to 1.03; atorvastatin vs simvastatin relative risk 0.84, 95% CI 0.66 to 1.08; atorvastatin vs pravastatin relative risk 0.79, 95% CI 0.61 to 1.02). Nor was there any significant difference in fatal and nonfatal strokes, all cardiovascular deaths, or all-cause mortality.

Authors’ conclusions

The authors concluded that, when used at standard doses, pravastatin, simvastatin, and atorvastatin appear equally effective for preventing cardiovascular events.

Overall quality

Commentary

There is good evidence that statins lower cardiovascular mortality and morbidity in both primary and secondary prevention and across a wide range of LDL cholesterol levels and risk profiles at treatment initiation. Most trials compare statins with placebo. Until recently, no data permitted comparison of these drugs with each other in terms of cardiovascular mortality and morbidity.

The PROVE-IT/TIMI-22 study found better outcomes with aggressive LDL lowering to median levels of 62 mg/dl using 80 mg atorvastatin compared to more moderate therapy using 40 mg pravastatin, which lowered LDL to 95 mg/dl.1 However, since these treatments yielded different levels of LDL reduction, PROVE-IT left open the question of whether statins differ in a clinically important way for the same degree of LDL lowering.

Despite similar mechanisms of cholesterol lowering, the various statin drugs differ in many of their other properties. In particular, the anti-inflammatory properties of statins may have effects beyond LDL lowering. In vitro studies suggest differences in these non-lipid lowering effects between the statins. However, we lack direct comparative clinical studies of different statins with the same degree of LDL reduction. Such a study would be useful not only in terms of guiding therapy, but also could provide insights into the underlying pathophysiology of atherosclerosis and the mechanisms of benefit of the statins.

This study’s contribution

In the absence of such direct studies in the literature, Zhou and colleagues collated comparative data using a form of meta-analysis — adjusted indirect comparison. This method attempts to estimate the relative effect of competing interventions in a way that respects the randomisation assigned in each trial and tries to take into account the different clinical characteristics across studies.

Caveats

This study requires cautious interpretation for a number of reasons. Firstly, the trials included in this study involved very different populations ranging widely in event rates and other characteristics, despite similar relative risk reduction across different patient populations. Despite the best attempts of any statistical technique to account for this heterogeneity, pooling these groups presents challenges to interpretation. For instance, primary prevention populations with low event rates may require observation periods beyond those of the traditional clinical trial to establish differences between active therapies.

The authors state that the degree of LDL lowering in all the trials was similar. In fact this varied from as little as 17% in ALLHAT-LLT to as much as 46% in GREACE. These two most heterogeneous trials were included only in the secondary analysis, but it is important to note the differences.

Some recent trials such as IDEAL and TNT have not been included in the analysis because they were published after the review was completed.2–4

Implications

Although each statin is associated with clinical benefits, there is increasing evidence that ‘lower is better’ when it comes to achieved LDL levels. The PROVE-IT/TIMI-22 trial established this principle in the setting of acute coronary syndromes.1 The increased atheroma regression seen by intravascular ultrasound with aggressive lipid-lowering in the REVERSAL study provides further insights into this ‘lower is better’ notion.5 Given that statins have fairly flat dose-response curves, the most potent lipid lowering statins may therefore produce the most benefit for many individuals. However, factors such as lipid solubility, protein binding, half-life, generation of active metabolites, and other drug-specific characteristics may also have clinically important consequences beyond LDL-lowering potency.

Unfortunately, outside the context of acute coronary syndromes we currently lack randomised studies with clinical endpoints to establish the relevance of these drug-specific differences. In the meantime, data syntheses such as those presented by Zhou and colleagues, while far from conclusive, provide food for thought.

The authors reported no study sponsorship.

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