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Review

Statintherapy in the primary and the secondary prevention of ischaemic cerebrovascular diseases

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ABSTRACT

Introduction: Stroke is a major public health problem. It is the third leading cause of death worldwide and results in hospital admissions, morbidity, and long-term disability. Despite the inconsistent or weak association between cholesterol and stroke, statins can reduce the incidence of stroke in high-risk populations and in patients with a stroke or transient ischaemic attack.
Methods: The aim of our study was to review the efficacy of statin therapy in both primary and secondary stroke prevention. We also reviewed the effectiveness and cost-effectiveness among different statins and we also reviewed the possible effect of treatment added to statin monotherapy.
Results: There is evidence that statin therapy in both primary and secondary prevention significantly reduces subsequent major coronary events but only marginally reduces the risk of stroke recurrence. There is no clear evidence of beneficial effect from statins in those with previous haemorrhagic stroke and it is unclear whether statins should be started immediately post stroke or later. There is a pressing need for direct evidence, from head-to-head trials, to determine whether individual statins provide differing protection from clinically important events in stroke prevention. It is possible that combinations of lipid-lowering agents did not improve clinical outcomes more than high-dose statin monotherapy, although clinical trials are still ongoing.

1. Introduction

A close association between serum lipid levels and the incidence of coronary heart disease (CHD) has been well proven in middle-aged and elderly people [1]. However, the relation between plasma cholesterol and cholesterol subfractions with cerebrovascular disease is much more controversial. Despite the inconsistent or weak association between cholesterol and stroke, statins can reduce the incidence of stroke in high-risk populations and in patients with a stroke or transient ischaemic attack [2]. Taken together, these data suggest a role for statins in stroke prevention independent of coronary artery disease risk reduction or serum lipid levels. Statins have been associated with a variety of pleiotropic effects, including atherosclerotic plaque stabilization, decreased inflammation, improvement in endothelial function, and altered thrombogenicity [3,4]. The aim of our study was to review the efficacy of statin therapy in both primary and secondary stroke prevention. We also reviewed the effectiveness and cost-effectiveness among different statins, and we also collected articles based on treatment added to statin therapy.

2. Primary prevention

Several important systematic reviews currently exist showing the clinical effectiveness of statins across cardiovascular diseases (CVD) outcomes in secondary prevention populations [5,6]. Three systematic reviews have examined specifically primary prevention populations and come to discordant conclusions about the role of statins in clinical events and mortality [7–9]. To clarify the disconcordat results a recent meta-analysis (using strict inclusion–exclusion criteria) including 19 trials (63899 patients) represented a comprehensive meta-analysis of statin therapy for primary prevention. 11 trials (n = 31,035) examined the effect of statin therapy on stroke mortality and this meta-analysis found a pooled RR of 1.05 (95% CI: 0.79 to 1.39, p = 0.72 [I2 = 0%, 95% CI: 0% to 43%, heterogeneity p = 0.53]) [3]. This was in concordance with a recent meta-analysis based on statin therapy in same prevention [10]. They also evaluated statin effects on all-stroke incidence in 18 trials (n = 57,430) and found an RR of 0.88 (95% CI: 0.78 to 1.00, p = 0.05 [I2 = 15%, 95% CI: 0% to 53%, heterogeneity p = 0.27]). Using

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meta-regression, they were unable to identify within-class differences among the differing statins [3,10]. As an important result, the incidence of cancer was not elevated nor was rhabdomyolysis.

A very recent review and updated meta-analysis of statins for stroke prevention identified statin trials that included 165 792 individuals at high risk of stroke. Incidence of all strokes was reduced by 18% (95% CI 13–23%, p<0.0001); incidence of fatal stroke was reduced by 13% (−3 to 27, p = 0.10), although this did not reach statistical significance, and incidence of haemorrhagic stroke did not increase (RR 1.03, 95% CI 0.75–1.41, p = 0.88;), without evidence of heterogeneity across the trials. In a meta-regression analysis of all major statin trials, each 1 mmol/L (39 mg/dL) decrease in concentration of LDL cholesterol equated to a relative risk reduction for stroke of 21·1% (6.3–33.5, p = 0.009) [4].

3. Secondary prevention

Secondary prevention of stroke not only includes prevention of recurrent stroke but also other vascular events. In the Heart Protection Study, 10.3% of patients in the simvastatin group and 10.4% in the placebo group had a recurrent stroke, with a signifi cant heterogeneity (p = 0.002) between relative risks in groups with and without cerebrovascular disease before randomisation. This neutral effect is probably because the study was not powered for this comparison [11].

The SPARCL trial was the only trial that evaluated statins in secondary prevention of non-cardioembolic stroke and transient ischaemic attack and included patients within 6 months of their qualifying event [12]. In this study, 11.2% (265/2365) of patients receiving atorvastatin and 13.1% (311/2366) of patients receiving placebo had a recurrent stroke, which was a signifi cant diff erence after prespecifi ed adjustment for age and sex (HR 0.84, 95% CI 0.71–0.99, p = 0.03). A significant decrease in major cardiovascular events was also seen (0·80, 0.69–0.92, p = 0.002).

The treatment effect did not differ in men versus women, in individuals aged less than 65 years versus those aged more than 65 years, in those with carotid stenosis at entry versus no carotid stenosis, in patients with diabetes versus without diabetes, and across ischaemic stroke subtype at entry. In all these subgroups, statins seem to decrease the risk of major coronary events with equal efficacy. In the SPARCL trial, the size of the reduction in stroke risk was greater in patients who had carotid stenosis, in those who had an atherothrombotic stroke at entry or diabetes, and in patients who were younger than 65 years. The treatment effect did not significantly differ among any of these subgroups [13–17]. A recent analysis of this trial suggested that the outcome of recurrent ischaemic cerebrovascular events might be improved among statin users as compared with nonusers [18].

Of 4731 patients, 67% had ischemic strokes, 31% TIAs, and 2% hemorrhagic strokes as entry events. In addition to atorvastatin treatment (HR 1.68, 95% CI 1.09 to 2.59, p = 0.02), Cox multivariable regression including baseline variables significant in univariable analyses showed that hemorrhagic stroke risk was higher in those having a hemorrhagic stroke as the entry event (HR 5.65, 95% CI 2.82 to 11.30, p<0.001), in men (HR 1.79, 95% CI 1.13 to 2.84, p = 0.01), and with age (10 y increments, HR 1.42, 95% CI 1.16 to 1.74, p = 0.001). There were no statistical interactions between these factors and treatment. Multivariable analyses also found that having Stage 2 (JNC-7) hypertension at the last study visit before a hemorrhagic stroke increased risk (HR 6.19, 95% CI 1.47 to 26.11, p = 0.01), but there was no effect of most recent LDL-cholesterol level in those treated with atorvastatin.

A recent meta-analysis showed that in secondary prevention of non-cardioembolic stroke, statin therapy also significantly reduced the risk of recurrent stroke (relative risk 0.84, 0.71–0·99, p = 0.03) and major cardiovascular events (0.80, 0.69–0.92, p = 0.002) [4].

A Cochrane meta-analysis based on the management of serum lipids for preventing stroke recurrence was very recently published including eight studies involving approximately 10,000 participants. The active interventions were pravastatin, atorvastatin, simvastatin, clofibrate, and conjugated oestrogen. Fixed-effect analysis showed no overall effect on stroke recurrence but statin therapy alone had a marginal benefit in reducing subsequent cerebrovascular events in those with a previous history of stroke or TIA (odds ratio (OR) 0.88, 95% confidence interval (CI) 0.77 to 1.00). There was no evidence that such intervention reduced all-cause mortality or sudden death (OR 1.00, 95% CI 0.83 to 1.20). Three statin trials showed a reduction in subsequent serious vascular events (OR 0.74, 95% CI 0.67 to 0.82). In view of this and the evidence of the benefit of statin therapy in those with a history of CHD, patients with ischaemic stroke or TIA, with or without a history of established CHD, should receive statins [19].

In SPARCL, the risk of stroke decreased as risk-factor control increased (on-treatment LDL concentration <1.8 mmol/L [70 mg/dL], triglyceride concentration <1.7 mmol/L [150 mg/dL], blood pressure <120/80 mm Hg, and baseline HDL concentration >1.3 mmol/L [50 mg/dL]); the risk of stroke decreased for patients with the optimum control of one (HR 0.98, 95% CI 0.76–1.27), two (0.78, 0.61–0.99), three (0.62, 0.46–0.84), and four (0.35, 0.13–0.96) of these factors compared with those with control of none. Results were similar for major cardiovascular events [20].

4. Optimal lipid target levels

The major recommendations for modifications to footnote the ATP III treatment algorithm are the following: in high-risk persons, the recommended LDL-C goal is <100 mg/dL, but when risk is very high, an LDL-C goal of <70 mg/dL is a therapeutic option, i.e., a reasonable clinical strategy, on the basis of available clinical trial evidence. This therapeutic option extends also to patients at very high risk who have a baseline LDL-C<100 mg/dL. Moreover, when a high-risk patient has high triglycerides or low high-density lipoprotein cholesterol (HDL-C), consideration can be given to combining a fibrate or nicotinic acid with an LDL-lowering drug. For moderately high-risk persons (2<risk factors and 10-year risk 10% to 20%), the recommended LDL-C goal is <130 mg/dL, but an LDL-C goal <100 mg/dL is a therapeutic option on the basis of recent trial evidence. The latter option extends also to moderately high-risk persons with a baseline LDL-C of 100 to 129 mg/dL. When LDL-lowering drug therapy is employed in high-risk or moderately high-risk persons, it is advised that intensity of therapy be sufficient to achieve at least a 30% to 40% reduction in LDL-C levels [3,4,20].

It had been hypothesized that high-intensity statin therapy, designed to reach very low levels of LDL-C, particularly if achieved in conjunction with substantial elevation of HDL-C, might be resulted in regression of coronary atherosclerosis. Accordingly, the ASTEROID trial had been designed (A Study to Evaluate the Effect of Rosuvastatin on Intravascular Ultrasound-Derived CoronaryAtheroma Burden) to examine the effects of high-intensity statin therapy on IVUS-derived measures of coronary disease progression. Rosuvastatin is the most recently introduced statin and typically produces greater reductions in LDL-C and larger increases in HDL-C than previously available agents [21]. Between November 2002 and October 2003, 507 patients had a baseline intravascular ultrasound (IVUS) examination and received at least 1 dose of study drug (it was used to assess coronary atheroma burden). After 24 months, 349 patients had evaluable serial IVUS examinations. Very high-intensity statin therapy using rosuvastatin 40 mg/d achieved an average LDL-C of 60.8 mg/dL and increased HDL-C by 14.7%, resulting in significant regression of atherosclerosis; the mean (SD) change in PAV for the entire vessel was −0.98% (3.15%), with a median of −0.79% (97.5% CI, −1.21% to −0.53%) (p<.001 vs baseline). The mean (SD) change in atheroma volume in the most diseased 10-mm subsegment was −6.1 (10.1) mm^3, with a median of −5.6 mm^3 (97.5% CI, −6.8 to −4.0 mm^3) (p<.001 vs