Arterial endothelial function and wall thickness in familial hypercholesterolemia and familial combined hyperlipidemia and the effect of statins: a systematic review and meta-analysis

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CRD summary
The authors concluded that, in patients with familial hypercholesterolaemia, statin treatment was associated with a significant reduction in carotid artery wall thickness and improvements in brachial artery endothelial function. The high variability and unclear quality of the included studies means that the extent to which the authors’ conclusions are reliable is uncertain.

Authors’ objectives
To evaluate the effect of statins on arterial properties in patients with familial hypercholesterolaemia and familial combined hyperlipidaemia.

Searching
PubMed and the Cochrane Library were searched up to March 2010 for full-length published English language articles in peer-reviewed journals. Search terms were reported. Reference lists of articles were scanned for further studies.

Study selection
Randomised placebo-controlled trials, or non-controlled longitudinal studies that evaluated the effect of statins on changes in carotid or femoral artery intima-media thickness (subclinical atherosclerosis) or brachial artery flow-mediated dilation in patients with familial hypercholesterolemia or familial combined hyperlipidaemia were eligible for inclusion. Acute intervention studies (statin treatment lasting less than two weeks) were excluded.

All included studies were published since 1995. Drug doses varied, as did the receipt of additional therapies (where reported, these included resin, dietary, and physical activity interventions), the percentage of males (28% to 63%), participant age (12 to 60 years), and patient risk factor profiles. The active (statin) treatments included atorvastatin, fluvastatin, pravastatin, rosuvastatin, simvastatin, cholestyramine, torcetrapide, ezetimibe, and pactimibe. Duration of treatment ranged from three to 36 months in studies measuring intima-media thickness, and eight weeks to nine months in studies measuring brachial artery flow-mediated dilation. The definition of treatment intensity in this review was based on findings from recent literature.

Two reviewers independently selected the studies for inclusion. Disagreements were resolved by consensus.

Assessment of study quality
The authors did not report performing any quality assessment of the included studies.

Data extraction
Means and standard deviations were extracted to enable the presentation of mean differences (MDs) and 95% confidence intervals (CIs).

Two reviewers independently extracted the data. Disagreements were resolved by consensus.

Methods of synthesis
Where three or more studies were available for each type of dyslipidaemia (familial hypercholesterolaemia or familial combined hyperlipidaemia) and per marker of arterial structure/function, a meta-analysis was carried out using a fixed-effect model. A random-effects model was used where substantial heterogeneity was indicated (assessed by $I^2$). Pooled mean differences were calculated using unstandardised data.
Sensitivity analysis was conducted to explore the influence of different study characteristics. Meta-regression analysis was used to investigate the moderating role of duration and intensity of treatment.

Publication bias was assessed using a funnel plot. Further analysis was carried out using Duvel and Tweedie’s trim-and-fill method, and by the fail-safe N test.

**Results of the review**

It appeared that 23 studies (sample size range: 16 to 454) were included in the review of intervention studies, but not all of these were included in the meta-analysis. Seven studies were described as randomised double-blind controlled trials.

In familial hypercholesterolaemia patients, Statins were associated with significant improvements in arterial properties, shown by increased brachial artery flow-mediated dilation (MD 5.39%, 95% CI 2.86 to 7.92; I²=92.5%; six studies). In familial hypercholesterolaemia patients that had previously received no treatment or below optimum statin therapy, statins decreased carotid artery intima-media thickness (MD -0.025 mm, 95% CI -0.042 to 0.009 mm; I²= 78.9%; five studies)

In familial combined hyperlipidaemia patients, limited data (three studies) showed that statins were associated with significantly increased brachial artery flow-mediated dilation (MD 2.06%, 95% CI 0.43 to 3.69).

In meta-regression analyses, changes in brachial artery flow-mediated dilation were significantly related to the product of duration and intensity. In addition to these moderators, age, and the reduction of total and low-density lipoprotein-cholesterol levels were significant influences on changes in carotid artery intima-media thickness.

There were no other statistically significant differences. Sensitivity analysis did not materially alter the finding for brachial artery flow-mediated dilation in familial hypercholesterolaemia patients.

There was no evidence of publication bias.

**Authors’ conclusions**

In patients with familial hypercholesterolaemia, treatment with statins was associated with significant improvements in carotid artery intima-media thickness and brachial artery flow-mediated dilation. There were limited data suggesting improvements in brachial artery flow-mediated dilation in patients with familial combined hyperlipidaemia.

**CRD commentary**

The review question was clear. Inclusion criteria were potentially reproducible, albeit in a broad sense for study design and intervention. The search strategy appeared limited in its reliance on two electronic databases; the restriction to published English language articles may mean that studies were missed. Associated language and publication biases were possible, although the latter was assessed and found not to be a significant threat in the review. The processes for selection of studies and data extraction were conducted with efforts to minimise error and bias.

The absence of any reported quality assessment of the included studies made it difficult to assess their reliability and subsequent impact on the review findings. Study details were presented, although it was difficult to interpret the overall number of studies included in the review. The details provided suggested substantial clinical heterogeneity. Statistical heterogeneity was high in the analyses that reported significant findings, so a meta-analysis might not have been the most appropriate method of synthesis.

The authors’ conclusions reflect the evidence presented but, given the potential methodological limitations above, the extent to which these conclusions are reliable is unclear.

**Implications of the review for practice and research**

**Practice:** The authors stated that the correlation between duration and intensity of statin treatment and significant improvement in arterial properties reinforces the importance of aggressive long-term therapy in patients with familial hypercholesterolaemia. The evaluation of arterial thickness and endothelial function may be a useful risk stratification
tool to detect atherosclerotic disease in patients with familial hypercholesterolaemia and familial combined hyperlipidaemia.

**Research:** The authors did not state any implications for research.

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