Atorvastatin in the treatment of primary hypercholesterolemia and mixed dyslipidemias

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Authors' objectives
To assess the efficacy and safety of atorvastatin in the treatment of dyslipidemias.

Searching
MEDLINE (January 1960 to April 1998) and Current Contents were searched for articles published in the English language. Additional references were sought from bibliographies of identified studies and unpublished data from manufacturers.

Study selection
Study designs of evaluations included in the review
The authors selected open and controlled human and animal clinical trials on the pharmacology, pharmacokinetics, therapeutic use and adverse effects of atorvastatin, limited to information on human clinical trials. Randomised clinical trials (RCTs) and open clinical trials that evaluated atorvastatin in humans were included. Study duration ranged from 8 weeks to 1 year.

Specific interventions included in the review
Treatments included atorvastatin (from 2.5 mg to 80 mg/day); colestipol (20000mg/day); atorvastatin 10mg plus colestipol 2000 mg/day); fluvastatin (20 to 40 mg/day); lovastatin (20 to 80 mg/day); pravastatin (10 to 40 mg/day); simvastatin (10 to 40 mg /day); niacin 3000mg/day; and placebo. Concomitant diet therapy consisting of the NCEP Step 1 Diet (see Other Publications of Related Interest no.1) was used in all patients both as an adjunct or prior to drug therapy. Some patients were also treated with plasmapheresis.

Participants included in the review
Participants included patients with primary hypercholesterolemia defined variably as (LDL-C equal/greater than 160 mg/dL; TG < 400 mg/dL), (LDL-C equal/greater than 160 mg/dL; TG < 350 mg /dL), and (mean TG 603.3 mg/dL); hypercholesterolemia (LDC-C > 145 mg/dL; TG < 400 mg/dL); homozygous or heterozygous familial hypercholesterolemia; combined hyperlipidaemia; isolated hypertriglyceridermia (TC equal/greater than 200mg/dL; TG between 200 mg and 800mg/dL); and non insulin dependent diabetes mellitus and hypercholesterolemia (LDL equal / greater than 159 mg/dL). Abbreviations used above: TG: triglycerides; LDL- (C): low density lipoprotein (cholesterol); TC: total cholesterol.

Outcomes assessed in the review
Outcomes included the following biochemical tests: fasting TC, fasting LDL-C; fasting HDL-C; fasting TG; apolipoprotein B (apo B); apolipoprotein a (Lp- a); and adverse reactions.

How were decisions on the relevance of primary studies made?
The authors do not state how the papers were selected for the review, or how many of the authors performed the selection.

Assessment of study quality
Brief mention was made of some aspects of validity but no formal assessment was undertaken.

Data extraction
The authors do not state how the data were extracted for the review, or how many of the authors performed the data extraction.
Methods of synthesis
How were the studies combined?
The studies were combined in a narrative review.

How were differences between studies investigated?
The authors do not state how differences between the studies were investigated.

Results of the review
Three multicentre, double-blind, placebo-controlled trials (176 patients) compared atorvastatin at various doses with placebo. Seven clinical trials compared atorvastatin in various doses with other lipid-lowering agents: 3 double-blind RCTs (1,531 patients) and 4 open RCTs (761 patients).

Atorvastatin (2.5 mg to 80 mg per day) lowered LDL-C by 35% to 61% and TG by 14% to 45% compared with placebo. 6 different doses of atorvastatin were tested resulting in small numbers of patients per dose. There appeared to be a greater reduction with increasing dose of atorvastatin in fasting TC and fasting LDL-C.

Atorvastatin with other lipid lowering agents: Results were difficult to interpret due to multiple doses of both atorvastatin and the comparison drug. Significance levels were reported variably as 'compared with atorvastatin 10mg' and 'compared to atorvastatin 40 mg' and as 'compared with atorvastatin at milligram equivalent doses'. No information of equivalent doses between atorvastatin and other drugs was given.

Atorvastatin vs niacin (1 open RCT, 108 patients): Atorvastatin 10 mgs/day led to significantly greater reductions in TC, TG, LDL-C and significantly increased HDL-C compared to niacin.

Atorvastatin vs colestipol (1 open RCT, 86 patients): Atorvastatin 10 mg/day led to significantly greater reductions in TC, TG, LDL-C and significantly increased HDL-C compared to colestipol.

Atorvastatin vs lovastatin (1 multicentre RCT with 1049 patients, plus 1 multicentre RCT with 3 different doses of lovastatin given to 43 patients and 4 different doses of atorvastatin given to 195 patients): inconsistent results between trials and across doses for TC, TG and LDL-C. No difference noted between drugs for HDL-C.

Atorvastatin vs pravastatin: (1 multicentre RCT with 593 patients, plus 1 multicentre RCT with 3 different doses of pravastatin given to 80 patients and 4 different doses of atorvastatin given to 195 patients): results from the trial using multiple doses of both drugs were impossible to interpret. The other trial showed atorvastatin 10 to 20 mg/day led to significantly greater reductions in TC, TG, LDL-C compared to pravastatin 20 to 40 mg/day.

Atorvastatin vs simvastatin (2 RCT with 226 patients plus 1 multicentre RCT with 3 different doses of simvastatin given to 80 patients and 4 different doses of atorvastatin given to 195 patients): results from the trial using multiple doses of drugs were impossible to interpret. The other 2 trials showed Atorvastatin 10 to 20 mg/day led to significantly greater reductions in TC, TG, and LDL-C compared to simvastatin 10 to 20 mg/day.

Atorvastatin vs fluvastatin (1 multicentre RCT with 2 different doses of simvastatin given to 24 patients and 4 different doses of atorvastatin given to 195 patients): results from this trial using multiple doses of both drugs were impossible to interpret and were based on a very small sample size.

Safety data is reported based on pooled data from 21 completed and 23 ongoing clinical trials with 4271 patients on atorvastatin for a total of more than 3000 patient years (see Other Publications of Related Interest no.2). No details of this study were presented. The most frequent adverse effects of atorvastatin were constipation, flatulence, dyspepsia, abdominal pain, and myalgia (in 1% to 3% of patients). These adverse effects occurred in 2% to 5% of patients on other HMG-CoA reductase inhibitors. The 4271 patients on atorvastatin experienced: elevated serum transaminases in 0.7%; no rhabdomyolysis; and myalgia and muscle pain in 21% on atorvastatin compared to 23% of 742 patients on other HMG-CoA reductase inhibitors.

Cost information
The overall direct cost in 1995 of simvastatin treatment for secondary prevention of coronary heart disease ranged from $3800 to $27400 per year of life saved (see Other Publications of Related Interest no.3). Yearly acquisition costs were reported as: atorvastatin (10 to 80 mg) = $666 to $4116; cerivastatin (0.2 to 0.3 mg) = $403; fluvastatin (20 to 80 mg) = $444 to $994; lovastatin (10 to 80 mg) = $466 to $2956; pravastatin (10 to 40 mg) = $666 to $1213; simvastatin (5 to 40 mg) = $650 to $1342. Costs based on average wholesale price.

Authors' conclusions
Atorvastatin appears to reduce TC, LDL-C, TG and apo B to a greater extent than do currently available hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors. Adverse effects of atorvastatin appear to be similar to those of other HMG-CoA reductase inhibitors and should be routinely monitored. Long term safety data is required.

CRD commentary
The aims and inclusion criteria were defined. Unpublished data were sought. Some relevant details of primary studies were either tabulated or described, but information in general was very scant. Some aspects of validity were mentioned. The following omissions in reporting of included studies were mentioned: exclusion criteria; number of patients who met the NCEP goals; reasons for withdrawal of patients; and number of patients with underlying coronary heart disease. Clinical and research implications of the review were included.

No details were given of keywords used in the literature search which was restricted to English language literature or of methods used to select primary studies or extract data. No formal assessment of study validity was undertaken. Several of the primary studies included many treatment arms with small numbers of patients per arm, thus making interpretation of results difficult. Equivalent doses of drugs were not discussed. Some comparison of results from different studies would have been helpful. No mention was made of whether the analysis of individual multicentre trials included assessment of study centre effect or comment on between site heterogeneity. No assessment of heterogeneity was performed. No mention was made of the potential for producing significant results when multiple comparisons are undertaken. Results on adverse reactions were based on studies which were not included in the review. Costs of monitoring patients need to be take into account when costs of therapy are being considered.

It is not possible to comment on the comparative efficacy of atorovastatin given the information presented.

Implications of the review for practice and research
Practice: The authors consider that liver function results should be monitored prior to and during initial therapy with atorvastatin, at 6 and 12 weeks of therapy, or at increasing dosage titration and semiannually thereafter; that atorvastatin should be used cautiously in patients with a history of hypersensitivity reaction to other statins; atorovastatin is contraindicated in patients with active liver disease, unexplained persistent elevations of transaminases or a hypersensitivity reaction and during pregnancy or in nursing mothers; potential risks and benefits should be evaluated when using atorvastatin in conjunction with immunosuppressive agents, fibric acid derivatives, niacin, erythromycin, or azole antifungals; that symptoms of unexplained muscle pain, tenderness or weakness should be continually monitored especially if accompanied by malaise or fever; atorvastatin should be withheld/discontinued in an acute serious condition suggestive of myopathy or where there is a risk for developing renal failure secondary to rhabdomyolysis.

Research: The authors consider that the following areas require research: long term safety data on atorvastatin; cost-effectiveness studies comparing atorvastatin with other HMG-CoA reductase inhibitors; studies evaluating the impact of atorvastatin on cardiovascular morbidity and mortality; and studies evaluating the impact of lipid-lowering therapy in a larger number of women, the elderly (> 70 years), and patients with diabetes for treatment of primary and secondary prevention of coronary heart disease.

Bibliographic details
Other publications of related interest

Indexing Status
Subject indexing assigned by NLM

MeSH
Animals; Anticholesteremic Agents /adverse effects /chemistry /therapeutic use; Atorvastatin Calcium; Clinical Trials as Topic; Heptanoic Acids /adverse effects /chemistry /therapeutic use; Humans; Hypercholesterolemia /drug therapy; Hyperlipidemias /drug therapy; Pyrroles /adverse effects /chemistry /therapeutic use; Treatment Outcome

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Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.