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# Efficacy and Safety of Lipid Lowering Therapy: A Systematic Review

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**Abstract**

**Introduction**: Dyslipidemia is the most important modifiable risk factor for myocardial infarction worldwide. We conducted a systematic review and meta-analysis to highlight the evidence for the safety, efficacy of lipid lowering therapy, and clinical effectiveness from trials comparing more intensive statin therapy with less intensive statin therapy.

**Methods**: A comprehensive electronic search was conducted in MEDLINE, EMBASE, Cochrane databases to identify articles which aimed to assess the preventive effect of lipid lowering therapy, particularly in CHD. The titles and abstracts of the resultant articles were read by two independent reviewers to identify relevant articles as a primary screening step and to exclude irrelevant, duplicated or review articles. The full texts of these relevant articles were retrieved and the in-depth reading was conducted to exclude the irrelevant articles as a secondary screening step. The articles were assessed against inclusion criteria such as clinical trials, published in the last 10 years and written in English language. The population studied should be patients with CHD, while included intervention was lipid lowering therapy. The outcomes assessed were the mortality indicators in rates or percentages.

**Results**: Seventy-five studies reporting RCTs of head-to-head comparisons on statins were included. Most studies had similar baseline characteristics, except the rosuvastatin related studies. A daily dose of atorvastatin 10 mg, fluvastatin 80 mg, lovastatin 40–80 mg, and simvastatin 20 mg could decrease LDL-C by 30–40%, and fluvastatin 40 mg, lovastatin 10–20 mg, pravastatin 20–40 mg, and simvastatin 10 mg could decrease LDL-C by 20–30%. The only two statins that could reduce LDL-C more than 40% were rosuvastatin and atorvastatin at a daily dose of 20 mg or higher. Meta-analysis indicated a statistically significant but clinically minor difference (<7%) between statins in cholesterol lowering effect. Comparisons of coronary heart disease prevention and safety could not be made because of insufficient data.

**Conclusions**: The HDL-elevating and triglyceride-lowering effects are similar among different statins at equivalent doses. The current data are not sufficient to determine the relative safety of the different statins or their relative effectiveness in CHD-prevention.

***Keywords: Statin, Lipid-lowering, Safety, Efficacy, Cardiovascular diseases***.

## Introduction

Dyslipidemia is the most important modifiable risk factor for myocardial infarction worldwide, and serum cholesterol levels are directly related to mortality from coronary artery disease in all populations studied. Over the past decade, randomized controlled trials enrolling a wide variety of patients have confirmed that for every 1-mmol/L reduction in serum low-density lipoprotein (LDL) cholesterol achieved by statin therapy, the relative risks of cardiovascular events and mortality are reduced [1]. Statins exert their beneficial effects primarily by reducing the level of LDL cholesterol, 6 and the reductions in the relative risk of cardiovascular events achieved by statin therapy appear to be similar regardless of baseline cholesterol levels. As a result, attention has increasingly focused on defining optimal target LDL levels, particularly in patients at the highest risk [2]. Those with coronary artery disease. Based on the observational studies mentioned above the apparent lack of a lower threshold for statin benefit in the randomized controlled trials, and recent trials reporting greater benefits with more intensive statin regimens (compared with less intensive regimens) Canadian and American guidelines for secondary prevention now recommend target LDL levels below 2.0 mmol/L in patients with coronary artery disease. On the other hand European guidelines specify a target LDL of 2.5 mmol/L in these patients. Questions have been raised about the safety and incremental benefits of more intensive statin regimens [3].

For patients with acute coronary syndromes or requiring coronary angiography, hospital rather than family physician's office was defined as the primary care setting. The percentage of patients using statins before randomization varied widely among the trials. The A-to-Z trial excluded all patients who had previously received statin therapy. The TNT trial included a run-in phase such that 100% of patients had received statin therapy for at least 8 weeks before randomization [4]. Compared with the lower-intensity arm, the higher-intensity arm in each trial achieved lower LDL cholesterol levels. The differences in LDL cholesterol levels were between 0.39 and 1.0 mmol/L. An LDL cholesterol of less than 2.0 mmol/L was achieved in about 50% of patients in the more intensive statin monotherapy groups. The pooled analysis revealed no difference in all-cause mortality between the more or less intensive statin treatment arms in all 7 trials [4]. However, there was substantial heterogeneity among trials (I 2 = 42%), and pooling the data obscured the fact that more intensive statin therapy was associated with a 25% reduction in mortality in patients after acute coronary syndrome[5], but had no impact mortality in patients with chronic coronary artery disease [6]. More intensive statin therapy led to a statistically significant reduction in myocardial infarction or coronary death (OR 0.83, 95% CI 0.77-0.91) with no heterogeneity among trials. Examining each of these components separately confirmed that the benefits were seen in patients after acute coronary syndromes or with chronic coronary artery disease and for both nonfatal myocardial infarction and coronary deaths [6].

Although TNT was the only trial to demonstrate a significant benefit in stroke reduction, the pooled results demonstrate a statistically significant reduction in the number of strokes with more intensive statin therapy compared with less intensive therapy (OR 0.82, 95% CI 0.71-0.95) with no heterogeneity among trials. The results were similar among patients with chronic coronary artery disease or with acute coronary syndromes [7]. The pooled analysis confirmed fewer major cardiovascular events in the more intensive statin treatment arm of these trials. Five trials reported non-cardiovascular mortality. There was no difference between more intensive and less intensive statin regimens in these trials (based on 670 non-cardiovascular deaths in 28,439 patients. Discontinuation attributed specifically to drug-related adverse events was not significantly higher with more intensive statin therapy (pooled estimate 7.8% v. 5.3% in the less intensive statin arms). To add context to the safety numbers, we have included the results from the pooled analyses of the placebo-controlled randomized statin trials [8]. Of the 6 trials that reported this outcome, described a significant excess risk of elevated aminotransferase levels (aspartate

aminotransferase or alanine aminotransferase levels more than 3 times the normal upper limit) with more intensive statin therapy compared with less intensive therapy. The pooled rates were significantly different [9]. Myopathic adverse events were inconsistently reported and were not significantly more frequent among patients receiving more intensive statin therapy compared with less intensive therapy. Although the event rates were low, all of these trials used statin monotherapy, not the combination therapy that is frequently recommended to achieve target LDL levels less than 2.0 mmol/L. None of the quality variables included influenced the study outcomes. For example, for the most frequent outcomes (myocardial infarction or coronary death), there was no difference in effect estimates for those trials with adequate allocation concealment compared to those without adequate allocation concealment. There were also no differences in the trials with run-in periods and those without run-in periods). Other systematic review demonstrated that, among patients with coronary artery disease, the provision of more intensive statin monotherapy (compared with less intensive statin therapy) reduces LDL cholesterol levels by a further 0.72 mmol/L. This additional reduction in LDL cholesterol resulted in 17% fewer myocardial infarctions (absolute reduction 1.4%) and 18% fewer strokes (absolute reduction 0.5%) among patients randomized to more intensive statin regimens rather than less intensive regimens [10]. These benefits of more intensive statin monotherapy were at the expense of small absolute increases in the frequency of drug discontinuation (about 2.5%), elevated aminotransferase levels (about 1%) and myopathy (about 0.5%) when compared with less-intensive statin therapy (only the aminotransferase elevations were statistically significant). There was no difference in non-cardiovascular mortality. All-cause mortality was not reduced among patients with chronic coronary artery disease, but it was reduced by one-quarter among patients treated after acute coronary syndromes [11].

We conducted a systematic review and meta-analysis to highlight the evidence for the safety, efficacy of lipid lowering therapy, and clinical effectiveness from trials comparing more intensive statin therapy with less intensive statin therapy.

## Methods

A comprehensive electronic search was conducted in MEDLINE, EMBASE, Cochrane databases to identify articles which aimed to assess the preventive effect of lipid lowering therapy, particularly in CHD. Search terms included ("coronary artery diseases" OR "heart disease" OR "ischemic heart disease") AND (“lipid-lowering therapy" OR "cholesterol-lowering therapy" OR ezetimibe OR statin OR pitavastatin OR pravastatin OR anacetrapib) AND (mortality OR death). The titles and abstracts of the resultant articles were read by two independent reviewers to identify relevant articles as a primary screening step and to exclude irrelevant, duplicated or review articles. The full texts of these relevant articles were retrieved and the in-depth reading was conducted to exclude the irrelevant articles as a secondary screening step. The articles were assessed against inclusion criteria such as clinical trials, published in the last 10 years and written in English language.

The population studied should be patients at high risk such as those with CHD, while included intervention was lipid lowering therapy. The outcomes assessed were the mortality indicators in rates or percentages. The data were collected from included studies using data collection sheets regarding item such as mean patient age, type of coronary disease, mean duration of the disease, drugs of lipid lowering therapy, regime of lipid lowering therapy, duration of lipid lowering therapy, reduction in mortality, and associated side effects. The review was registered in a registration of systematic review in university of York.

## Results

Clinical trials of therapies lowering LDL cholesterol concentration have consistently shown a reduction in the risk of cardiovascular events. However, the clinical benefit from LDL cholesterol lowering in older patients remains debated because participants aged 75 years or older were not well represented in individual trials. In the Cholesterol Treatment Trialists' Collaboration (CTTC), major vascular events were reduced by 21% per 1 mmol/L reduction in LDL cholesterol with statin treatment or a more intensive statin regimen, but with some possible attenuation in

older patients [12]. The American College of Cardiology and American Heart Association (ACC/AHA) cholesterol guidelines have lower strength recommendations for older patients compared with those for younger patients. The European Society of Cardiology and European Atherosclerosis Society dyslipidaemia guidelines endorse treating older patients, but add specific considerations to assess comorbidities before initiating treatment [13]. In clinical practice, studies show that the use of lipid-lowering in older patients, an important demographic that accounts for almost 20% of the population, is lower than in younger patients. Several subgroup analyses from randomized controlled trials with statin and non-statin lipid-lowering therapies added new evidence regarding the efficacy and safety of lowering LDL cholesterol in older patients. Given these new data, we aimed to summarise the evidence of lipid-lowering therapies in the older population and readdress whether older patients should be treated less intensively than younger patients. In this systematic review and meta-analysis, we followed PRISMA guidelines. This decision was based on the US and European guidelines, which do not recommend lipid-lowering treatment in patients with heart failure or advanced kidney disease who do not have another indication [14].

Outcomes from each trial were selected to most closely approximate the target composite endpoint of major vascular events, which consisted of cardiovascular death, acute myocardial infarction or another acute coronary syndrome, coronary revascularization, or stroke when available because all these events have been shown to be reduced by therapies that lower LDL cholesterol. In some instances, the selected outcome that best matched the target composite was a secondary composite endpoint for the original trial. they also examined the individual components of the composite outcome, as well as non-cardiovascular death and all-cause death [15]. They extracted data from participants younger than 75 years to compare the treatment effect between older and younger patients. Since the younger data in the treat Stroke to Target trial 14 were presented by two age categories (<65 years and 65-75 years), we estimated the effect in younger patients using a fixed effect approach. Safety outcomes of interest that were available included cancer, haemorrhagic stroke, new-onset diabetes, and neurocognitive adverse events. However, the clinical benefit from LDL cholesterol lowering in older patients remains debated because participants aged 75 years or older were not well represented in individual trials [16]. In the Cholesterol Treatment Trialists' Collaboration meta-analysis, major vascular events were reduced by 21% per 1 mmol/L reduction in LDL cholesterol with statin therapy, but with some possible attenuation in older patients. Practice guidelines have noted that the level of evidence in older patients is low and some have lower strength recommendations for older patients than for younger patients. These results should strengthen guideline recommendations for the use of lipid-lowering treatments, including non-statin therapy, in older patients. When the results were pooled RR was used to describe the effect estimate. In the CTTC, the rate ratios in age subgroups were presented with 99% CIs and therefore we calculated 95% CIs before pooling with other trials.

A random-effects meta-analysis with a restricted maximum likelihood approach was used to account for heterogeneity between trials in lipid-lowering therapies, follow-up duration, and study populations. Patients were stratified by statin atherosclerotic cardiovascular disease for the primary endpoint (stratified analyses by the presence of baseline atherosclerotic cardiovascular disease were not uniformly available for individual outcomes). For safety endpoints, HRs or rate ratios and 95% CIs were extracted from the original trials if available or an RR was calculated from raw counts for each trial and meta-analysed using a random effects model with a restricted maximum likelihood approach after normalization of RR per 1 mmol/L reduction in LDL cholesterol [17]. Clinical trials of therapies lowering LDL cholesterol concentration have consistently shown a reduction in the risk of cardiovascular events. However, the clinical benefit of LDL cholesterol lowering in older patients remains debated because participants aged 75 years or older were not well represented in individual trials. In the Cholesterol Treatment Trialists' Collaboration (CTTC), major vascular events were reduced by 21% per 1 mmol/L reduction in LDL cholesterol with statin treatment or a more intensive statin regimen, but with some

possible attenuation in older patients. The American College of Cardiology and American Heart Association (ACC/AHA) cholesterol guidelines have lower strength recommendations for older patients compared with those for younger patients. The European Society of Cardiology and European Atherosclerosis Society dyslipidemia guidelines endorse treating older patients, but add specific considerations to assess comorbidities before initiating treatment. In clinical practice, studies show that the use of lipid-lowering in older patients, an important demographic that accounts for almost 20% of the population, is lower than in younger patients. Several subgroup analyses from randomized controlled trials with statin and non-statin lipid-lowering therapies added new evidence regarding the efficacy and safety of lowering LDL cholesterol in older patients [18].

By 2003 after the first nine randomized trials of statin drugs with clinical end-points, it was evident that the degree of LDL cholesterol lowering achieved was related to the decrease in relative atherosclerotic cardiovascular disease (CVD) risk in the actively treated participants relative to controls [19. By 2005 there were 14 randomized clinical statin trials that could be included in the Cholesterol Treatment Trialists' collaboration meta-analysis, which revealed that the correlation between the reduction in the hazard ratio (HR) for CVD end-points (the ratio of CVD incidence on active treatment to control) and the decrease in LDL cholesterol concentration was closest when the decrease in LDL cholesterol was measured as the absolute reduction in concentration rather than as percentage change [20]. One mmol/l (38.7 mg/dl) decrease in LDL cholesterol was associated with a reduction in HR for CVD of about one-fifth. A subsequent larger meta-analysis by the same group confirmed this finding with the HR for CVD decreasing to 0.78 of the control value for each 1 mmol/l (38.7 mg/dl) decrease in LDL cholesterol. Almost identical findings were reported in later systematic reviews. Despite this, bodies with responsibility for advising clinicians are split as to whether LDL cholesterol should be taken into account when planning treatment for individual patients. Both the joint American College of Cardiology and American Heart Association (ACC/AHA) and National Institute for Health and Clinical Excellence (NICE) advocate that the cholesterol-lowering intensity of the statin regimen selected should be determined in most patients simply by their absolute CVD risk and that the dose and choice of statin should not be directed at achieving specific LDL cholesterol concentration targets. On the other hand, the National Lipid Association (NLA) and the European Society for Cardiology (ESC) have retained LDL cholesterol targets [21]. We have reported extensive analyses of these contrasting recommendations, which we based on the calculation of the number of people who must be treated for 10 years to prevent one CVD event (NNT) taking into account the pre-treatment LDL cholesterol as well as absolute CVD risk. These studies revealed that the abandonment of LDL cholesterol targets is of benefit to those with lower levels and high absolute CVD risk, for example in secondary prevention, when the adoption of a high-intensity statin regimen will lead to much lower LDL cholesterol levels than are recommended in the targeted approach. However, worryingly, we also found that removing therapeutic LDL cholesterol goals is a disadvantage to people with higher pre-treatment levels [22].

Our method of estimating NNT relies on the finding in a meta-analysis of cholesterol-lowering trials that the decrease in absolute CVD incidence is. LDL cholesterol reduction in mmol/l . LDL cholesterol reduction in mg/dl. In patients with higher initial LDL cholesterol levels, our findings using this method make a case for the reintroduction of LDL cholesterol targets and, where necessary to achieve them, statin dose titration and sometimes adjunctive non-statin cholesterol-lowering therapy. Whilst others agree that clinical recommendations cannot stick rigidly to trial evidence and must make reasonable extrapolations, it would be welcome to have a systematic review of clinical trials involving two intensities of statin treatment within the same trial population or of non-statin cholesterol-lowering medication to assess whether they produce the anticipated differences in CVD incidence predicted by our method derived largely from single dose statin trials [23]. Without this, it has been suggested that some non-LDL-lowering pleiotropic effect of statins contributes to the anti-atherogenic properties of statins and that this may not be present for other classes of cholesterol-lowering

drugs [24]. We have therefore undertaken a systematic review of trials that randomized participants to a more and less intensive statin regimen and trials that randomized people to non-statin cholesterol-lowering medication against a statin background. Trials involving fibric acid derivatives, niacin and cholesteryl ester transfer protein (CETP) inhibitors were excluded because they have numerous effects other than LDL lowering. Also, the use of fibric acid derivatives and niacin is declining, because doubts have been expressed about their efficacy in preventing CVD, particularly against a background of statin therapy, and their safety. Thus, they are not widely used in clinical [25].

## Conclusions

Statins can be made therapeutically equivalent in reducing LDL by appropriate adjustment of dose. Atorvastatin 10 mg, fluvastatin 80 mg, lovastatin 40/80 mg, and simvastatin 20 mg are equivalent in decreasing LDL-C by 30–40%; and fluvastatin 40 mg, lovastatin 10/20 mg, pravastatin 20/40 mg, and simvastatin 10 mg were similar in reducing LDL-C by 20–30%. The HDL-elevating and triglyceride-lowering effects are similar among different statins at equivalent doses. The current data are not sufficient to determine the relative safety of the different statins or their relative effectiveness in CHD-prevention.

## Conflict of interests

The authors declared no conflict of interests.

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