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Long-term efficacy and safety of statin treatment beyond six years: A meta-analysis of randomized controlled trials with extended follow-up

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ABSTRACT

Large-scale randomized controlled trials (RCTs) have well demonstrated the beneficial effects of cholesterol-lowering treatment with statins in patients at high risk of vascular disease. However, large statin RCTs were usually restricted to the typical 5–6 years. Moreover, non-cardiovascular events, especially the risk of cancer, probably failed to emerge within a restricted period of 6 years. The aim of this study was to evaluate the long-term efficacy and safety of statin treatment by performing a meta-analysis of statin RCTs with extended follow-up beyond 6 years. Six RCTs with post-trial follow-up were eligible for inclusion, involving 47,296 patients with total follow-up ranging from 6.7 to 14.7 years. During the post-trial period, all the surviving participants were advised to take a statin and the cholesterol level were almost identical between the original statin group and the original placebo group. Over the entire 6.7–14.7 years of follow-up, a significant reduction in the rates of all-cause mortality (relative risk 0.90, 95% confidence interval 0.85–0.96; $P = 0.0009$), cardiovascular mortality (0.87, 0.81–0.93; $P < 0.0001$) and major coronary events (0.79, 0.72–0.86; $P < 0.00001$) was observed in favour of the original statin group. During 2-year post-trial period, further reduction in all-cause mortality (0.83, 0.74–0.93; $P = 0.001$), cardiovascular mortality (0.81, 0.69–0.95; $P = 0.01$) and major coronary events (0.77, 0.63–0.95; $P = 0.01$) was observed among initially statin-treated patients. Over the entire follow-up period, statin treatment did not increase the incidence of cancers (0.99, 0.95–1.04; $P = 0.79$), deaths from cancers (1.00, 0.93–1.07; $P = 0.98$) and non-cardiovascular mortality (0.95, 0.90–1.00; $P = 0.07$). In conclusion, statin treatment beyond 6 years is effective and safe in patients at high risk of vascular events. Moreover, earlier treatment with statin may not only preserve the initial benefit but also have further survival benefit for additional 2 years. Further studies are called for to explore the underlying mechanisms.

1. Introduction

Large-scale randomized controlled trials (RCTs) have demonstrated that treatment with 3-hydroxy-3-methylglutaryl-coenzyme A inhibitors (statins) to lower cholesterol reduces the risk of cardiac events in populations at increased risk of cardiovascular disease [1–4]. Recently, a meta-analysis of data from 170,000 participants has revealed that lowering LDL cholesterol by about 1 mmol/L reduces vascular mortality and morbidity by about a quarter in a wide range of patients, consisting of non-fatal myocardial infarction (MI) by 27%, coronary heart disease (CHD) death by 20%, coronary revascularization by 25%, and strokes by 16%, without increasing the risk of non-vascular mortality or morbidity [5]. Randomized controlled trials are considered the gold standard in the hierarchy of research designs for evaluating the efficacy and safety of a treatment intervention. Confounding factors cannot be completely controlled in an observational study due to unobserved covariates. However, RCTs are generally considered more costly and time consuming than other studies. To date, large statin RCTs and meta-analyses have been usually restricted to the typical 5–6 years. Limited evidence is available about

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longer-term efficacy and safety of continuous statin treatment. Moreover, non-cardiovascular events, especially the risk of cancer, probably failed to emerge within a restricted period of 6 years. There is still some concern that cholesterol-lowering treatment for longer periods may increase the risk of non-cardiovascular mortality including cancer and thereby offset the beneficial effects on vascular events [6,7].

After termination of the randomized in-trial phase, prolonged follow-up of surviving trial participants has been performed in several statin trials during the post-trial period, yielding an entire duration of more than 6 years. The aim of this study was to conduct a meta-analysis to assess the efficacy and safety of long-term (>6 years) LDL cholesterol lowering treatment with statins.

2. Methods

The study was performed according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement [8].

2.1. Search strategy

Electronic databases including PubMed, EMBASE, BIOSIS Previews, Cochrane central register of controlled trials, Web of Science and SCOPUS were searched up to 1 January 2013 to identify relevant studies reported in English, using the MeSH terms "HMG-CoA reductase inhibitor", "statin", "atorvastatin", "rosuvastatin", "simvastatin", "fluvastatin", "pravastatin" "lovastatin" and "pivastatin". Reference lists of identified studies were scrutinized to reveal additional citations. Conference proceedings from American College of Cardiology (2003–2013), American Heart Association (2003–2013), European Society of Cardiology Congress (2003–2013), European Atherosclerosis Society (2010–2013) and National Lipid Association (2011–2013) were also searched.

2.2. Criteria for study selection

Studies were eligible for inclusion if they met the following criteria: (1) type of original study design was randomized placebo-controlled trial; (2) reporting data about all-cause mortality, cardiovascular mortality, non-cardiovascular mortality and the risk of cancer; (3) entire follow-up duration (in-trial and post-trial period) > 6 years; and (4) the minimal number of included participants was 1000.

2.3. Data extraction and prespecified outcomes

Data were abstracted independently by two investigators (H.L. Lv and D.M. Jin). Inconsistencies were resolved by consensus or a third author arbitration (D.F. Geng). The following data were extracted from each article: details of participant characteristics (age, gender, region, cholesterol level and comorbidity), interventions in each group (categories and doses of statins), prespecified endpoints and duration of follow-up. Prespecified outcomes include all-cause mortality, cardiovascular mortality, major coronary events, non-cardiovascular mortality, cancer morbidity and cancer mortality.

2.4. Statistical analysis

We referred to the guidelines of the Cochrane Handbook for Systematic Reviews of Interventions 4.2.5 in this meta-analysis [9]. Results were expressed as relative risk (RR) with 95% confidence intervals (CIs) for dichotomous outcomes. Heterogeneity across trials was assessed via a standard Chi square test with significance being set at $P < 0.10$ and also assessed by means of I^2 statistic with significance being set at $I^2 > 50\%$. Random effects model was used for statistical analysis due to wide clinical and methodological variability across the trials. Publication bias was evaluated using funnel plots, Begg's test and Egger's test. Sensitivity analysis was performed by eliminating one trial in turn. Statistical analysis was performed using Review Manager 5.1 (The Cochrane Collaboration, Oxford, England), and publication bias was evaluated by Stata version 12.0 (Stata Corp, College Station, TX, USA). A value of $P < 0.05$ was considered statistically significant.

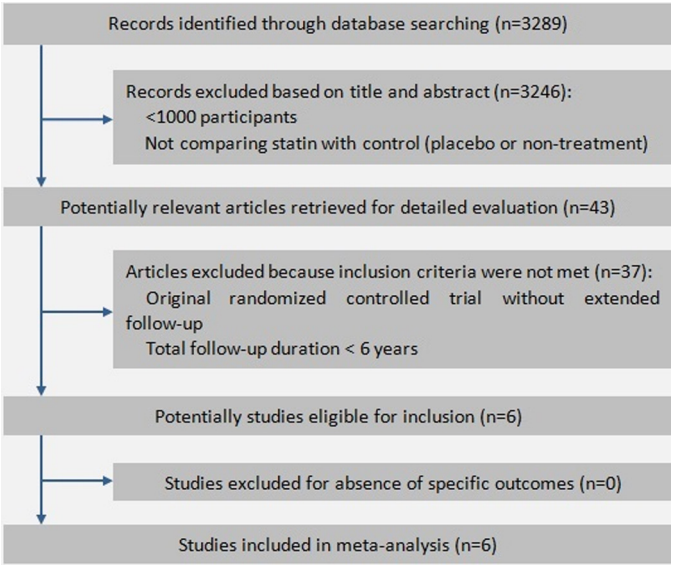

Fig. 1. Meta-analysis flow chart. Flow of article selection in trial.

3. Results

3.1. Study selection

Among 3289 initially retrieved articles, six trials [10–15] with extended follow-up involving 47,296 intention-to-treat patients were eligible for inclusion (Fig. 1): 3 trials of statin vs placebo for primary prevention [12,14,15], and the other three for secondary prevention [10,11,13]. The entire follow-up periods range from 6.7 years in the ALERT trial [15] to 14.7 years in the WOSCOPS trial [12]. Four of the six included trials reported the outcomes of 2-year post-trial follow-up [13,15–17]. Besides 5-year post-trial study, the 4S trial also reported the data about 2-year post-trial follow-up [16]. In the ASCOT-LLA study, data about 8-year extended study [14] was restricted to the UK patients, while data on 2-year post-trial study [17] included patients from the UK, Ireland and the Nordic countries.

3.2. Baseline characteristics

Table 1 summarizes the study characteristics of the included trials during both the in-trial [1,2,4,18–20] and post-trial [10–17] period. In the randomized phase, the WOSCOPS trial [12] performed in 6595 hypercholesterolemic patients with no history of MI, the ASCOT-LLA trial [14] in 4605 hypertensive patients without CHD, the ALERT trial [15] in 2102 renal transplant recipients, the HPS trial [11] in 20,536 patients with coronary disease or at increased risk of vascular events, the 4S [10] and the LIPID [13] trials in 13,458 patients with history of MI or angina pectoris. A total of 41,643 participants were involved in the extended follow-up. During the post-trial period, all surviving participants were advised to take a statin and the cholesterol level was almost identical between the