

Statins for Primary Prevention of Cardiovascular and Cerebrovascular Events in Diabetic Patients without Established Cardiovascular Diseases: A Meta-Analysis

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Abstract



Aims: Lipid-lowering medications could lead to a significant reduction in major cardiovascular events in patients with diabetes. However, there was still controversy regarding the use of statins in patients with diabetes for primary prevention. The meta-analysis was performed to evaluate the outcomes of statin-therapy in diabetic patients without established cardiovascular diseases.

Methods: 7 randomized controlled trials of statin- vs. control-therapy in patients with diabetes were included. A total number of 12 711 patients were involved. The outcomes of interest were major adverse cardiovascular and cerebrovascular events (MACCE), including myocardial infarction, stroke, all-cause mortality and coronary revascularization.

Results: A total of 1 376 MACCE occurred during follow-up, with 9.54% (605 patients) in the statin therapy group and 12.10% (771 patients) in control group. Statin therapy was associated with a significant reduction in the incidence of MACCE (0.79, 95%CI 0.66–0.95; $P=0.01$). Meanwhile, the risk of stroke and coronary revascularization were reduced 29 and 26% in statin therapy group. However, there was no statistical difference of all-cause mortality between statin- and control-therapy group (3.73 vs. 4.65%, $P=0.13$).

Conclusions: For primary prevention in patients with diabetes without established cardiovascular disease, statin therapy could reduce the cardiovascular and cerebrovascular events, but not all-cause mortality.

Introduction



Diabetes is one of the major health problems worldwide. According to the results of China National Diabetes and Metabolic Disorders Study, the prevalence of total diabetes in China were 9.7% [1]. In patients with diabetes, cardiovascular and cerebrovascular disease is the major cause of morbidity and mortality. Current medical evidence suggested that lipid-lowering medications could lead to a significant reduction in major cardiovascular events in patients with diabetes. As one of lipid-lowering medications, statin has been considered to play a very important role in reducing the mortality of coronary artery disease [2–5].

However, with regard to the primary prevention, conflicting evidence has resulted in controversy regarding the use of statins in patients with diabetes without established cardiovascular disease [6, 7]. Therefore, the present meta-analysis was designed to clarify the efficacy of statin on primary prevention of cardiovascular and cerebro-

vascular events in patients with diabetes without established cardiovascular diseases.

Patients and Methods



Study objective and search strategy

The primary aim of the present meta-analysis was to evaluate the efficacy of statins in the prevention of cardiovascular and cerebrovascular end points in diabetic patients without established cardiovascular diseases.

Using the following key words: “statin” or “HMG-CoA reductase inhibitor” or “atorvastatin” or “simvastatin” or “pravastatin” or “fluvastatin” or “lovastatin” or “rosuvastatin” and “diabetes” or “diabetes mellitus”, we searched PUBMED, MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials from 1990 to 2011 for all randomized controlled trials and registries reporting outcomes. The search was supplemented by reviews of reference lists for all relevant studies. All relevant reports identified were included without language restriction.

Study identification and extraction

Trials that met the following criteria were included: (1) Randomized controlled trials; (2) patients with diabetes without established cardiovascular disease; (3) there was a direct comparison between statins group and control group for primary prevention of vascular events; (4) outcomes including any of major cardiovascular and cerebrovascular events, such as fatal or non-fatal myocardial infarction, cardiac sudden death, coronary revascularization (percutaneous coronary intervention or coronary artery bypass grafting), angina, all-cause mortality and fatal or non-fatal stroke; (5) follow-up duration at least 12 months.

The following information was collected: (1) first author's names; (2) trial names; (3) the year of publication or presentation; (4) target population of trials (5) total sample size and subgroup sample size; (5) history of hypertension, smoking, body mass index and basic HbA1c (6) baseline cholesterol and triglycerides and changes; (7) the type and daily dosage of the statin therapy; (8) primary and secondary outcomes of the studies; (9) the mean period of follow-up.

Study outcome

The outcomes of interest were major adverse cardiovascular and cerebrovascular events (MACCE), including fatal or non-fatal myocardial infarction (MI), cardiac sudden death, identified coronary heart disease (CHD), coronary revascularization (percutaneous coronary intervention or coronary artery bypass

grafting), angina pectoris and fatal or non-fatal stroke. All-cause mortality was also evaluated across the trials.

Statistical analysis

The meta-analysis was performed according to the recommendations from the Cochrane Collaboration with Review Manager 5.0. The effect of statins on the occurrence of MACCE or each event was presented as odds ratio (OR) with 95% confidence intervals (CI) using a fixed-effects model. Alternatively, random-effects meta-analyses were performed when between-study variability existed. Heterogeneity was quantified using the I^2 statistic (I^2 represents the percentage of variability due to between-study variability.) We regarded I^2 of less than 25%, 25–50%, and greater than 50% as low, moderate and high amounts of heterogeneity, respectively. Publication bias was evaluated using the funnel plot. Results were considered statistically significant if $P < 0.05$.

Results



Eligible studies and baseline characteristics

The electronic database search identified 7 studies, which fulfilled our eligibility criteria. The included studies enrolled a total of 12711 participants (6340 patients in statin-therapy group and 6371 in control-therapy group). The baseline characteristics of each study [6–12] were summarized in **Table 1**. We found

Table 1 Studies and baseline characteristics.

Trial	AFCAPS/TexCAPS [8]	PROSPER [9]	HPS [10]	CARDS [11]	ASCOT-LLA [7]	ASPEN [6]	MEGA [12]
first author and year	Downs JR 1998	Shepherd J 2002	HPS group 2003	Colhoun H 2004	Sever P 2005	Knopp RH 2006	Tajima N 2008
target population	patients with average or below average cholesterol levels	older patients with cardiovascular risk factors	patients with non-fasting cholesterol at least 3.5 mmol/l	patients without high LDL-C level, had one or more of the following: hypertension, retinopathy, smoking, microalbuminuria	patients with hypertension	patients with LDL-C <4.1 mmol/l	patients with hypercholesterolemia
number of patients (statin/control)	155 (84/71)	623 (303/320)	2912 (1428/1410)	2838 (1428/1410)	2532 (1258/1274)	1905 (959/946)	1746 (853/893)
mean age (years)	58.0	75.0	NA(40–80)	61.5	63.1	60.5	58.3
current smoking (%)	12	27	NA	22	20	13	20
hypertension (%)	22	62	NA	84	100	52	42
mean body mass index (Kg/m ²)	27	27	NA	29	30	29	24
HbA1c (%)	NA	NA	NA	7.8	NA	7.6	6.9
statin type	lovastatin	pravastatin	simvastatin	atorvastatin	atorvastatin	atorvastatin	pravastatin
dosage (mg/day)	20–40	40	40	10	10	10	10–20
baseline TC (mmol/L) (% change)	5.7 (–19.3%)	5.7 (NA)	NA	5.4 (–21.8%)	5.5 (–18.3%)	5.0 (–19.8%)	6.3 (–11.0%)
baseline LDL-C (mmol/L) (% change)	3.9 (–26.5%)	3.8 (NA)	NA	3.0 (–33.9%)	3.4 (–27.6%)	3.0 (–30.5%)	4.0 (–18.0%)
baseline HDL-C (mmol/L) (% change)	1.0 (4.8%)	1.3 (NA)	NA	1.4 (4.0%)	1.3 (1.5%)	1.2 (1.9%)	1.5 (5.0%)
baseline TG (mmol/L) (% change)	1.7 (–12.7%)	1.5 (NA)	NA	2.0 (–15.9%)	1.7 (–12.6%)	1.6 (–4.7%)	1.4 (–7.0%)
outcomes	MACCE	MACCE	MACCE	MACCE; CR; death; stroke;	MACCE; CR; stroke	MACCE; CR; death; stroke;	MACCE; death; MI; stroke; CI
follow-up (years)	5.2	3.2	4.8	3.9	3.3	4.0	5.3

CI: cerebral infarction; CR: Coronary revascularization; HDL-C: high density lipoprotein cholesterol; LDL-C: low density lipoprotein cholesterol; MACCE: major adverse cardiovascular and cerebrovascular events; MI: myocardial infarction; NA: not available; TC: total cholesterol; TG: triglycerides

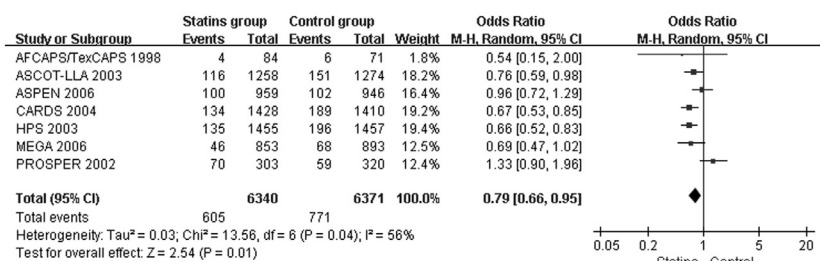


Fig. 1 Odds ratios of major adverse cardiovascular and cerebrovascular events associated with statin vs. control therapy in patients with diabetes.

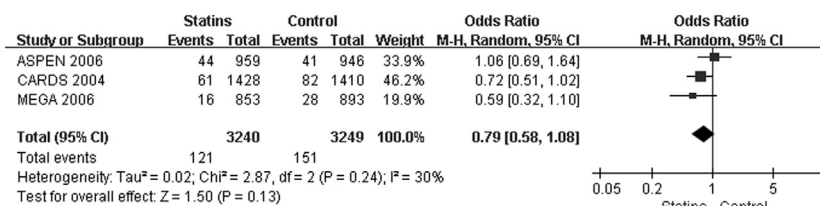


Fig. 2 Odds ratios of all-cause mortality associated with statin vs. control therapy in patients with diabetes.

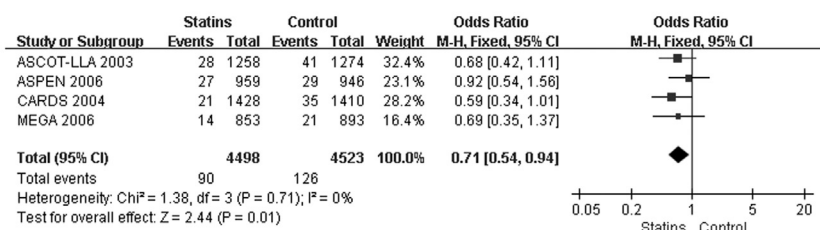


Fig. 3 Odds ratios of stroke associated with statin vs. control therapy in patients with diabetes.

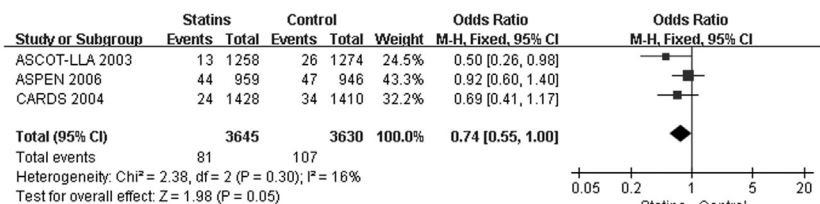


Fig. 4 Odds ratios of coronary revascularization associated with statin vs. control therapy in patients with diabetes.

that basic cholesterol levels were mildly elevated in the target patients, while basic triglycerides levels were normal.

Effect of statin therapy on MACCE

There were 7 studies reported the MACCE data after at least 3.2 years follow-up. A total of 12 711 patients were enrolled, including 6340 patients in statin-therapy group and 6371 in control-therapy group. A total of 1 376 MACCE occurred during follow-up, with 9.54% (605 patients) in the statin therapy group and 12.10% (771 patients) in control group. Statin therapy was associated with a significant reduction in the incidence of MACCE (0.79, 95%CI 0.66–0.95; $P=0.01$; **Fig. 1**).

Effect of statin therapy on all-cause mortality

With regard to the effect of statin on the all-cause mortality, there were 272 events among 6489 patients in 3 trials. The all-cause mortality was 3.73% among statin therapy group, which was similar to the rate (4.65%) among control group ($P=0.13$, **Fig. 2**).

Effect of statin therapy on stroke

A total of 216 stroke events occurred in 4 studies, including fatal and non-fatal stroke. There were 90 cases (2.0%) of stroke among statin therapy patients and 126 cases (2.79%) among control-therapy patients (**Fig. 3**). The risk of stroke was reduced 29% in statin therapy group (0.71, 95%CI 0.54–0.94; $P=0.01$) by the fixed effects model, with no significant heterogeneity ($P=0.71$).

Effect of statin therapy on coronary revascularization

Patients with diabetes, treated with statin or placebo, differed significantly with respect to the risk of coronary revascularization (including percutaneous coronary intervention or coronary artery bypass grafting) in 3 trials. There were 81 cases (2.22%) of coronary revascularization in statin group and 107 cases (2.95%) in control group (0.74, 95%CI 0.55–1.00; $P=0.05$ and $P=0.30$ for heterogeneity), shown in **Fig. 4**.

Publication bias

Funnel plots were performed for all outcomes, including the incidence of MACCE, mortality, stroke and coronary revascularization were symmetrically displayed.

Discussion

The present meta-analysis suggests that for primary prevention in patients with diabetes without established cardiovascular disease, statin therapy could reduce the cardiovascular and cerebrovascular events, but not all-cause mortality.

As one of confirmed risk factors, diabetes mellitus is not only associated with a 2- to 4-fold increase in the risk of coronary artery disease (CAD), but also related to its severity [13,14]. In 2001, the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) report elevated diabetes from a CHD risk factor to a CHD risk equivalent. Meanwhile, ATP III also recommended the initiation of pharmacotherapy for patients with a CHD risk equivalent (the presence of diabetes, peripheral arterial disease, abdominal aortic aneurysm, carotid artery disease or multiple risk factors with a 10-year Framingham risk of CHD of >20%) and an LDL-C concentration of ≥ 130 mg/dl [15]. Current medical evidence [2,3] suggested that lipid-lowering medications could lead to a significant reduction in major cardiovascular events in patients with diabetes. As one of lipid-lowering medications, statin has been considered to play a very important role in reducing the mortality of coronary artery disease [4,16,17].

However, with regard to the primary prevention, conflicting evidence has resulted in controversy regarding the use of statins in patients with diabetes without established cardiovascular disease. A significant 37% reduction in risk of cardiovascular events was observed with atorvastatin in CARDS, and a significant 33% reduction in risk of cardiovascular events was observed in HPS. However, in the study of ASCOT-LLA [7], a nonsignificant 16% reduction in coronary heart disease death and nonfatal myocardial infarction was observed with 10mg of atorvastatin in patients with diabetes. Moreover, in the study of ASPEN [6], 10.4% of atorvastatin-treated patients without prior MI or interventional procedure experienced a primary cardiovascular end point, which was similar to the incidence in placebo-treated subjects (10.8%, $P>0.05$). Researchers did not find a significant reduction in the primary composite end point comparing 10 mg of atorvastatin with placebo (13.7 and 15.0%, $P>0.05$). When compared with CARDS, primary prevention patients in ASPEN were younger and less hypertensive and included less smokers and men. The low risk of CHD in primary prevention patients with diabetes may account for the unpromising result. Therefore, we designed this meta-analysis to clarify the efficacy of statin on primary prevention of cardiovascular and cerebrovascular events in patients with diabetes without established cardiovascular diseases.

A total of 7 trials were ultimately included in this meta-analysis, involving 12711 patients with diabetes without established cardiovascular diseases (6340 randomized to the statin-therapy group and 6371 randomized to the control-therapy group). After analysis the incidence of total MACCE, we found that statin therapy reduced 21% incidence of MACCE, which benefited the patients with diabetes for the primary prevention. In addition, statin therapy also reduced the risk of stroke (29%) and coronary revascularization (26%) in patients with diabetes, although the

change of all-cause mortality did not reach the statistical difference. The results indicated that statin therapy in low risk patients, even without established coronary heart disease, myocardial infarction and stroke, did benefit for the primary prevention.

As regards with primary prevention, it should be taken into account for cost performance. It had been confirmed in previous studies that different type and different dosage of statin had different efficacy on the level of cholesterol and risk reduction of cardiovascular events [18,19]. 10 mg atorvastatin could decrease the serum level of LDL-C by 30–40%. In order to achieve the similar effects, lovastatin should increase to 40–80 mg, while simvastatin was 20 mg [20]. However, it was interesting that we did not find more benefit from the usage of higher dosage or stronger efficacy of statins in our meta-analysis. For example, although the reduced ratio of MACCE was similar between the study of MEAG [31%, (OR 0.69, 95%CI 0.47–1.02)] and CARDS [33%, (OR 0.67, 95%CI 0.53–0.85)], the dosage and types of statin were quite different. In the study of MEGA, the statin usage was 10–20 mg pravastatin daily, which reduced the level of LDL-C by 18%, while 10 mg atorvastatin reduced the serum level of LDL-C by 33% in the study of CARDS. These data implied us that higher dosage of statin or greater reduction of LDL-C should not be the sole consideration of various factors in primary prevention for patients with diabetes. The benefit might be offset by the side effects of large dosage of different statins. In the present meta-analysis, we also investigated whether different type of statin had different efficacy on reduction in the incidence of MACCE. We conduct a sub-analysis by including 3 trials (CARDS, ASCOT-LLA and ASPEN), which atorvastatin was assigned in the studies, and found that the MACCE (0.78, 95%CI 0.63–0.95; $P=0.01$) was similar to the MACCE (0.79, 95%CI 0.66–0.95; $P=0.01$) when all the statin trials were included. These data implied that for the primary prevention, the benefits of statin therapy are likely to be similar.

Our study had several limitations. First, this meta-analysis was limited by the lack of complete availability of relevant data. Data of all-cause mortality, cardiac mortality, stroke and myocardial infarction were not available in some included studies. Therefore, there may be reporting bias in these outcomes. Especially, all-cause mortality was only reported in 3 trials which suggested this analysis might be underpowered on all-cause mortality. Second, the usage of other medicine, such as ACEI/ARB, beta-blocker and aspirin, were not unclear. It has been clearly demonstrated that these medicine might influence the incidence of cardiovascular events. Third, longer follow-up period was needed for the primary prevention, which would be more meaningful for guiding further therapeutic plan.

Conclusions

For primary prevention in patients with diabetes without established cardiovascular disease, statin therapy could reduce the cardiovascular and cerebrovascular events, but not all-cause mortality.

Acknowledgments

None.

Conflict of Interest: None.

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