Systematic Review

- Traditional, narrative reviews, usually written by experts in the field, are qualitative, narrative summaries of evidence on a given topic. Typically, they involve informal and subjective methods to collect and interpret information.
- "A systematic review is a review in which there is a comprehensive search for relevant studies on a specific topic, and those identified are then appraised and synthesized according to a predetermined and explicit method."*

เกณฑ์แพทยสภาเรื่อง systematic reviews

1.2.5.1 identifying and selecting studies

1.2.5.2 quality of evidence assessments

1.2.5.3 combining the findings of independent studies

1.2.5.4 variation between study findings

1.2.5.5 summarizing and interpreting results

เกณฑ์ 5 ข้อของแพทยสภาเป็นวิธีทำ systematic reviews

1.2.5.1 identifying and selecting studies
ค้นหาบทความและคัดเลือก

1.2.5.2 quality of evidence assessments
ประเมินคุณภาพของแต่ละบทความ

1.2.5.3 combining the findings of independent studies
รวมข้อค้นพบจากแต่ละบทความ

1.2.5.4 variation between study findings
ความแตกต่างของข้อค้นพบระหว่างบทความ

1.2.5.5 summarizing and interpreting results
สรุปและแปลผลภาพรวม

Key-words of Systematic Review

- Systematic review VS Meta-analysis
- Cochrane database of systematic reviews
- Risk of bias in primary studies
- Random effect VS Fixed effect models
- Heterogeneity (variation among studies)
- Forest plot VS Funnel plot

1.2.5.1 identifying and selecting studies
ค้นหาบทความและคัดเลือก

ค้นหาบทความในฐานข้อมูลต่างๆ เช่น

- MEDLINE : PUBMED
- COCHRANE : reviews and database
- EMBASE : Excerpta Medica Database
- Grey literature : thesis, dissertation, unpublished

ค้นหาอย่างน้อย 2 คนโดยเป็นอิสระต่อกัน นำมาคัดเลือกร่วมกันหรืออาจต้องมีบุคคลที่สามช่วยตัดสินในกรณีที่ความเห็นไม่ตรงกัน

1.2.5.2 quality of evidence assessments
ประเมินคุณภาพของแต่ละบทความ

ตัวอย่างแนวทางการประเมินคุณภาพบทความ RCT
The Cochrane Risk of Bias Tool

- Selection bias : allocation concealment
- Performance bias : blinding participants
- Detection bias : blinding assessors
- Attrition bias : incomplete data
- Reporting bias : selective outcome reporting
- Other bias: bias in other domains

1.2.5.3 combining the findings of independent studies
รวมข้อค้นพบจากแต่ละบทความ

Meta-analysis : การประมวลผลรวมของการศึกษาต่างๆ เข้าด้วยกันด้วยวิธีการทางสถิติ มี 2 models

1. Fixed effects model
   -assumes that the true effect of treatment is the same for every study
2. Random effects model
   -assumes that the true effect estimate for each study vary

1.2.5.4 variation between study findings
ศึกษาความแตกต่างของข้อค้นพบระหว่างบทความ

Concepts and sources of heterogeneity

- Clinical heterogeneity : differences in patients characteristics or treatment regimen
- Methodological heterogeneity : variation in study design, outcome or duration of follow-up
- Statistical heterogeneity : multiple “true” treatment effects across the studies
- The play of chance : uncontrollable factors

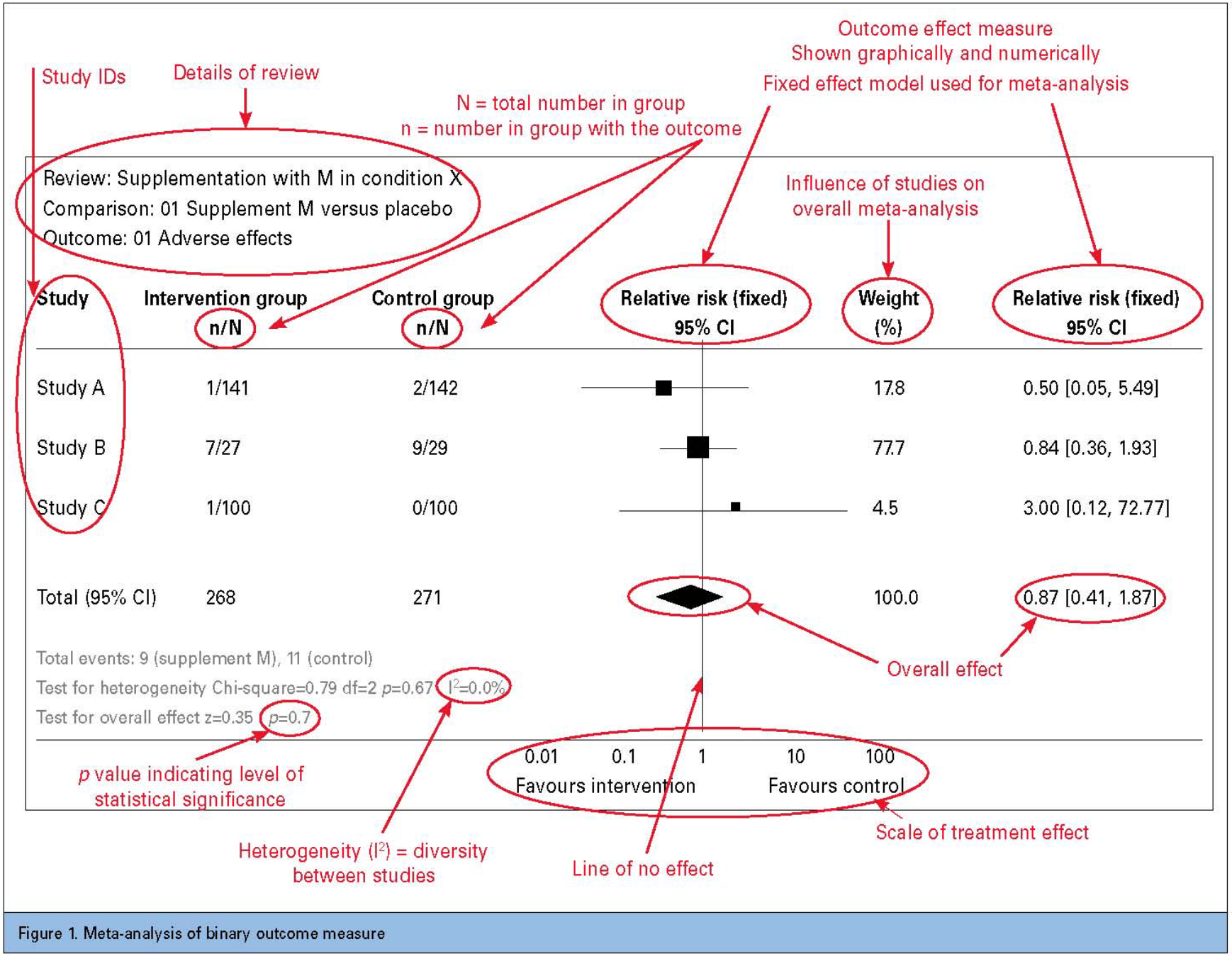
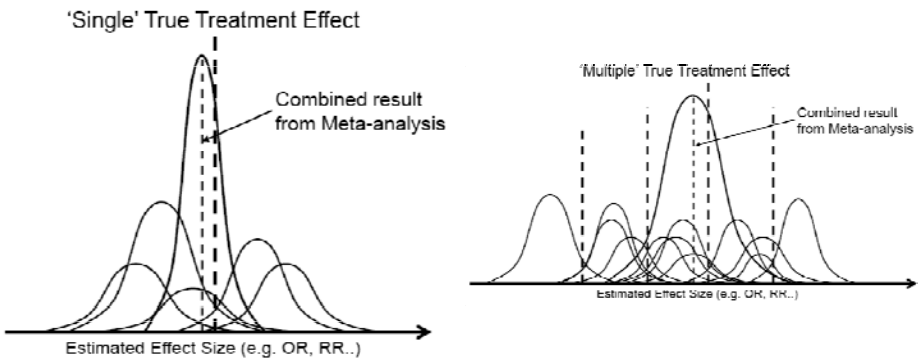


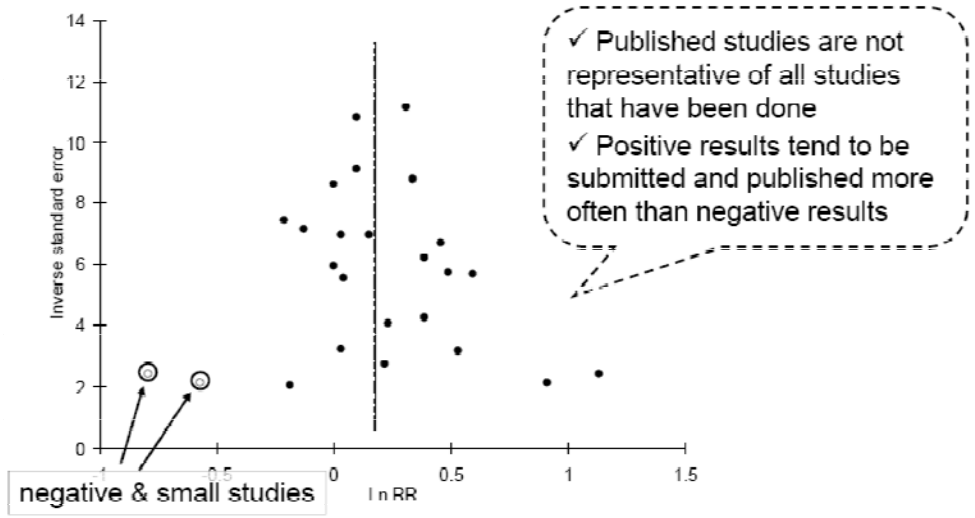
Figure 1. Meta-analysis of binary outcome measure

Ried K. Aus Fam Phys 2006

Fixed effect model **Random effect model**



Funnel plot to detect publication bias



ผู้ป่วยชายไทยอายุ 50 ปี เป็นเบาหวาน เพื่อนแนะนำให้กินยาลดไขมันป้องกันโรคเส้นเลือดหัวใจและสมองอุดตัน จึงมาถามแพทย์ว่าควรกินหรือไม่

- P Patients with diabetes
- I statin
- C placebo
- O cardiovascular and cerebrovascular risks

พิมพ์ search terms ใน PUBMED Clinical Queries ดังนี้

statin risk cardiovascular cerebrovascular diabetes

พบ 12 บทความ ในคอลัมน์ Systematic Reviews

เลือกบทความชื่อ Statins for Primary Prevention of Cardiovascular and Cerebrovascular Events in Diabetic Patients without Established Cardiovascular Diseases: A Meta-Analysis. Exp Clin Endocrinol Diabetes 2012; 120: 116–120

Critical appraisal checklists for systematic review

- What question (PICO) did the systematic review address?
- Is it unlikely that important, relevant studies were missed?
- Were the criteria used to select articles for inclusion appropriate?
- Were the included studies sufficiently valid for the type of question asked?
- Were the results similar from study to study?
- What were the results?
- Will the results help locally?

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

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Key words
- statin
- primary prevention
- diabetes
- coronary heart disease

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.

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Bibliography
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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 cerebrovascular 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, indentified 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

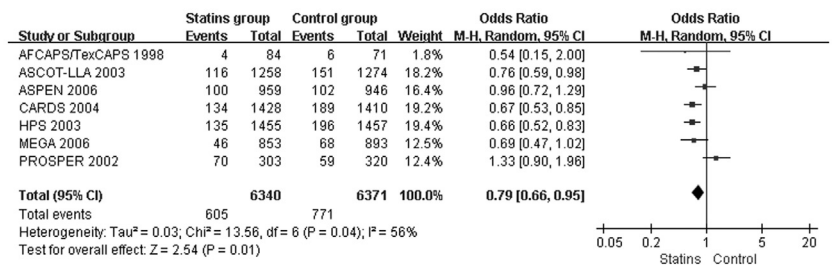

Fig. 1 Odds ratios of major adverse cardiovascular and cerebrovascular events associated with statin vs. control therapy in patients with diabetes.

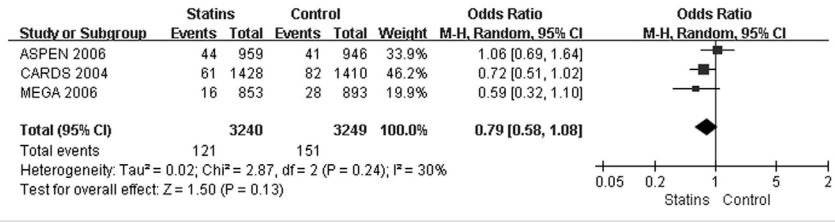

Fig. 2 Odds ratios of all-cause mortality associated with statin vs. control therapy in patients with diabetes.

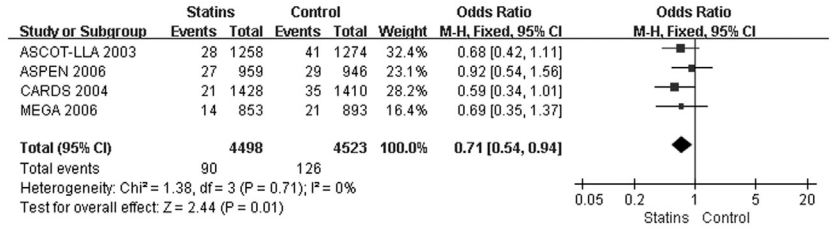

Fig. 3 Odds ratios of stroke associated with statin vs. control therapy in patients with diabetes.

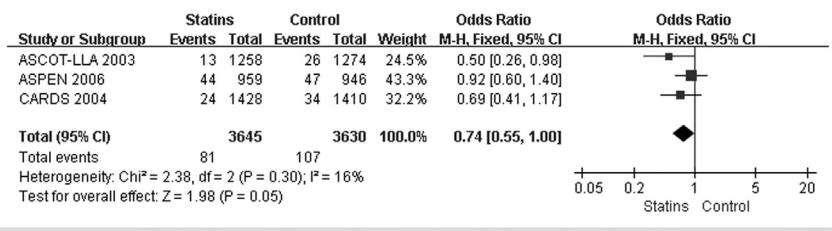

Fig. 4 Odds ratios of coronary revascularization associated with statin vs. control therapy in patients with diabetes.

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 6 340 patients in statin-therapy group and 6 371 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 10 mg 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 12 711 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.

DOES THIS REVIEW ADDRESS A CLEAR QUESTION?

1. Did the review address a clearly focussed issue? Was there enough information on: • The population studied • The intervention given • The outcomes considered	**Yes**	**Can't tell**	**No**
2. Did the authors look for the appropriate sort of papers? The 'best sort of studies' would • Address the review's question • Have an appropriate study design			

ARE THE RESULTS OF THIS REVIEW VALID?

3. Do you think the important, relevant studies were included? Look for • Which bibliographic databases were used • Follow up from reference lists • Personal contact with experts • Search for unpublished as well as published studies • Search for non-English language studies	**Yes**	**Can't tell**	**No**
4. Did the review's authors do enough to assess the quality of the included studies? The authors need to consider the rigour of the studies they have identified. Lack of rigour may affect the studies results.			
5. If the results of the review have been combined, was it reasonable to do so? Consider whether • The results were similar from study to study • The results of all the included studies are clearly displayed • The results of the different studies are similar • The reasons for any variations are discussed			

WHAT ARE THE RESULTS?

6. What is the overall result of the review? Consider • If you are clear about the reviews 'bottom line' results • What these are (numerically if appropriate) • How were the results expressed (NNT, odds ratio, etc)	
7. How precise are the results? Are the results presented with confidence intervals?	

WILL THE RESULTS HELP LOCALLY?

8. Can the results be applied to the local population? Consider whether • The patients covered by the review could be sufficiently different from your population to cause concern • Your local setting is likely to differ much from that of the review	**Yes**	**Can't tell**	**No**
9. Were all important outcomes considered?			
10. Are the benefits worth the harms and costs? Even if this is not addressed by the review, what do you think?			