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Original Article

Could statin reduce fracture risk? Evidence from a systematic review and meta-analysis

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Abstract: Some studies determined that statins could reduce the risk of fractures. However, the other studies did not confirm this result. This study aims to determine whether statins was significantly associated with reduced fracture risk. The Pubmed, Cochrane library, and Embase databases were searched independently by 2 investigators to retrieve relevant studies published to Mar 21, 2015. The strength of the association between statins and fractures risk was calculated with the OR and respective 95% CIs. The significance of the pooled OR was determined by the Z test, and *P*-values of less than 0.05 were considered significant. A total of 17 articles of more than 1800000 individuals were included in the meta-analysis. We observed a statistically significant association between statins and fractures risk. The data showed that statins could decrease the risk of fractures (OR=0.80; 95% CI, 0.73-0.88; *P*<0.00001) in a random-effect model. When only considered the old population (more than 50 years old), our results found that statins was significantly associated with decreased fractures risk (OR=0.72; 95% CI, 0.59-0.87; *P*=0.0006). When only considered the females, we also found that statins was significantly associated with decreased fractures risk (OR=0.76; 95% CI, 0.63-0.92; *P*=0.005). This meta-analysis suggested that statins might decrease fracture risk in the old population and the females.

Keywords: Statin, fracture, association

Introduction

Statins are the 3-hydroxy-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors [1]. Statins could inhibit the conversion of HMG-CoA to mevalonate. This function could limit the synthesis of cholesterol. Statins are often used to prevent cardiovascular diseases. However, due to its pleiotropic effects, statins are also used prevent other diseases, such as fractures [2]. Mundy et al. [3] found that lovastatin and simvastatin increased bone formation when injected subcutaneously over the calvaria of mice and increased cancellous bone volume when orally administered to rats. Thylin et al. also found that simvastatin can stimulate murine cranial bone apposition, particularly when delivered under an occlusive membrane [4]. Sugiyama et al. suggested that simvastatin could activate the bone morphogenetic protein (BMP)-2 promoter [5]. Some studies determined that statins reduced the risk of fractures. However, other studies have shown that statins are unlikely to play crucial roles in fractures in clinical study [6-20]. The reason for these discrepancies may be due to different sample size. Therefore, in order to derive a more comprehensive estimation of the association between statins and fractures risk, we conducted a meta-analysis to investigate this relationship.

Methods

Publication search

The Pubmed, Cochrane library, and Embase databases were searched independently by 2 investigators to retrieve relevant studies published to Mar 21, 2015. The search criteria "statins" and "fracture" were used in text word searches. MeSH terms such as "hydroxymethylglutaryl-CoA reductase inhibitors" and "fractures, bone" were also searched. The "related

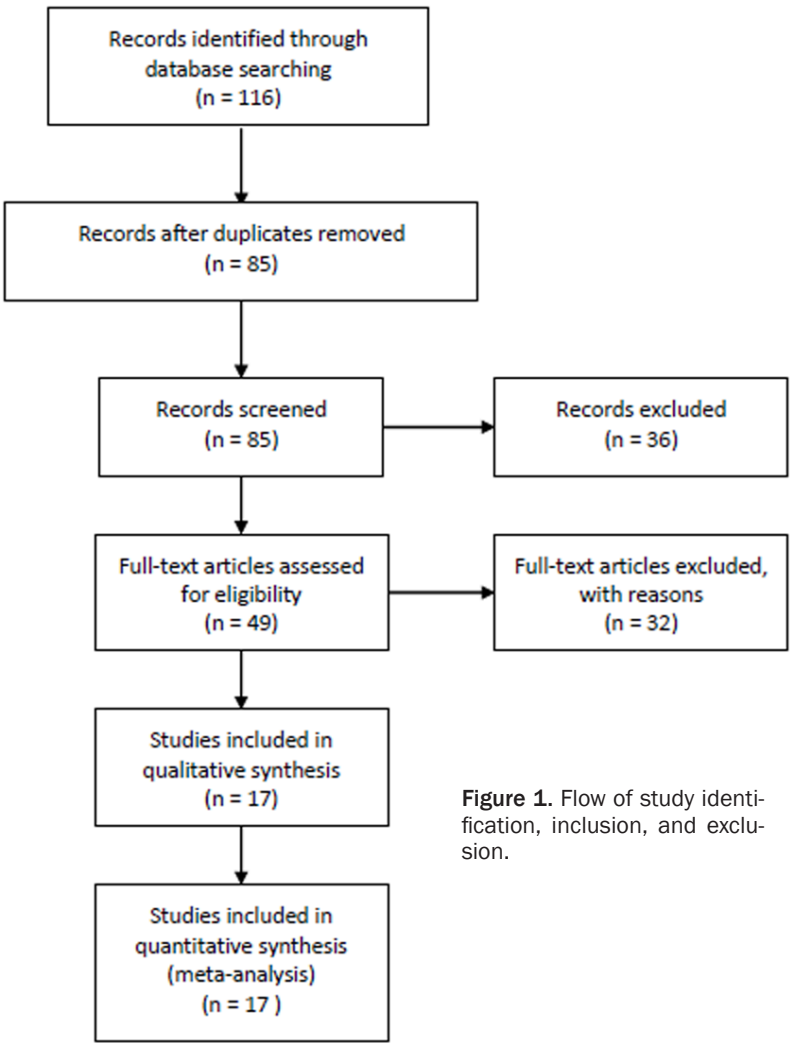

Figure 1. Flow of study identification, inclusion, and exclusion.

articles" function was used to broaden the search. The reference lists of the selected articles were also manually examined to find relevant studies that were not discovered during the database searches. There was no language restriction.

Exclusion criteria

The following exclusion criteria were defined as follows: A) incomplete raw data, B) repetitive reports, and C) material and methods used were not well described or reliable. Fractures were confirmed by the site principal investigator using radiographs, computed tomography, bone scan, or other methods. We used reliability of the methods for patient selection and statistical analysis as quality variables to accurately assess the quality measures of interest. All titles, abstracts and full papers of potentially relevant studies were assessed for eligibility. When several reports from the same study were published, only the most recent or informative one was included in this meta-analysis.

Data extraction

Two investigators extracted all variables and outcomes of interest independently. Disagreements were resolved through discussion and consensus. Data on first author and year of publication, study design, age, gender, numbers of sample size were extracted.

Quality assessment

The included studies were assessed independently by the two reviewers using the Newcastle-Ottawa Scale (NOS). The NOS employs a star rating system to assess quality from 3 broad perspectives of the study: (1) selection of the study groups, (2) comparability of the groups, and (3) identification of the exposure (for case-control studies) or outcome of interest (for cohort studies). Scores ranged from 0 to 9 stars. We considered a study awarded 0-3, 4-6, or 7-9 as a low-, moderate-, or high-quality study, respectively.

Statistical analysis

The strength of the association between statins and fractures risk was calculated with the OR and respective 95% CIs. The significance of the pooled OR was determined by the Z test, and *P*-values of less than 0.05 were considered significant. Statistical heterogeneity among studies was assessed with the I^2 statistics. This value ranges from 0% (complete consistency) to 100% (complete inconsistency). If the I^2-value was more than 50%, the random-effects model was chosen to calculate the pooled OR; otherwise the fixed-effects model was used. The statistical heterogeneity was investigated by Galbraith plot. In the sensitivity analysis, we did

Table 1. Characteristics of the included studies

First author/Year	Study design	Age	Gender	No. of participants	Adjusted	Quality score
Chan 2000	Case-control	≥ 60	Female	3675	Yes	7
Meier 2000	Case-control	50 to 89	Mixed	27319	Yes	8
Wang 2000	Case-control	≥ 50	Mixed	6110	Yes	7
van Staa 2001	Case-control	≥ 50	Mixed	163760	Yes	7
Pasco 2002	Case-control	50 to 95	Female	1375	Yes	8
Ray 2002	Retrospective cohort	≥ 50	Mixed	34584	Yes	8
LaCroix 2003	Prospective cohort	50 to 95	Female	93934	Yes	9
Rejnmark 2004	Case-control	≥ 18	Mixed	39934	Yes	6
Schoofs 2004	Prospective cohort	≥ 55	Mixed	3469	Yes	7
Bauer (FIT) 2004	Prospective cohort	55 to 80	Female	6459	Yes	7
Bauer (Rotterdam) 2004	Prospective cohort	≥ 55	Female	4878	Yes	7
Bauer (SOF) 2004	Prospective cohort	≥ 65	Female	2763	Yes	7
Bauer (HERS) 2004	Prospective cohort	44 to 79	Female	8422	Yes	7
Scranton 2005	Retrospective cohort	None	Mixed	91052	Yes	7
Rejnmark 2006	Case-control	None	Mixed	498617	Yes	8
Smeeth 2008	Retrospective cohort	35 to 85	Mixed	729529	Yes	7
Bakhireva 2010	Case-control	≥ 50	Female	3608	Yes	8
Helin-Salmivaara 2012	Retrospective cohort	45 to 75	Female	102839	Yes	8
Peña 2014	Prospective cohort	≥ 50	Mixed	17802	Yes	9
Ward (PSM) 2014	Retrospective cohort	None	Mixed	13934	Yes	9
Ward W 2014	Retrospective cohort	None	Female	23062	Yes	9
Ward M 2014	Retrospective cohort	None	Male	21411	Yes	9

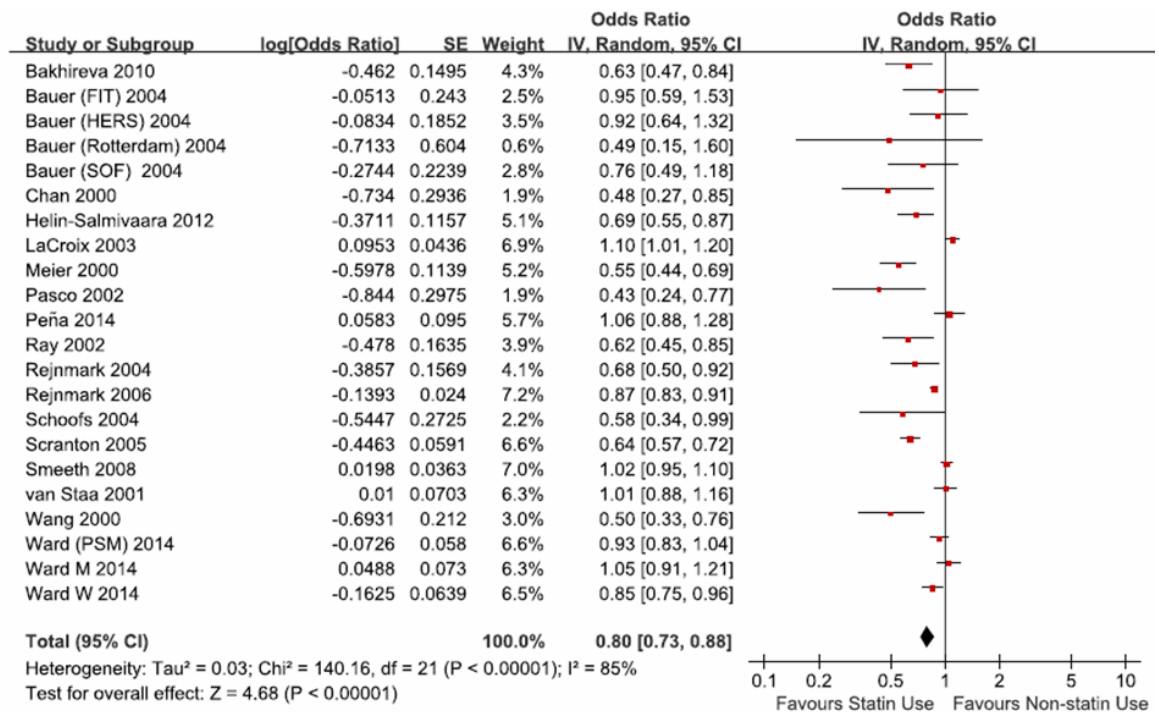

Figure 2. Effect of statins on fracture risk reduction.

the meta-analysis in different study design to assess how conclusions might be affected. The presence of publication bias was assessed by a visual inspection of a funnel plot. Bonferroni

Table 2. Meta-analysis results of the meta-analysis

	OR (95% CI)	*P* Value	I^2 (%)
Overall	0.80 (0.73-0.88)	< 0.00001	85
Age > 50	0.72 (0.59-0.87)	0.0006	85
Female	0.76 (0.63-0.92)	0.005	80

Table 3. Sensitivity analysis of the meta-analysis

	OR (95% CI)	*P* Value	I^2 (%)
Case-control	0.67 (0.55-0.81)	< 0.0001	84
Retrospective cohort	0.83 (0.71-0.97)	0.02	90
Prospective cohort	0.97 (0.83-1.12)	0.65	41

method was used. All statistical tests were used by the Revman 5.1 software (Nordic Cochrane Center, Copenhagen, Denmark) and STATA 11.0 software (Stata Corporation, College Station, TX).

Results

Literature search

The initial literature search retrieved 116 relevant articles. However, 99 articles were excluded for not investigating the topic or insufficient data after carefully screening the titles and abstracts (**Figure 1**). All studies included were in accordance with NOS scale and only one study defined as moderate-quality study. A total of 17 articles of more than 1800000 individuals were included in the meta-analysis. The characteristics of the included studies are summarized in **Table 1**. A review of the data extraction revealed 100% agreement between the 2 reviewers.

Meta-analysis

As shown in **Figure 2**, we observed a statistically significant association between statins and fractures risk. The data showed that statins could decrease the risk of fractures (OR=0.80; 95% CI, 0.73-0.88; *P*<0.00001) in a random-effect model. When only considered the old population (more than 50 years old), our results found that statins was significantly associated with decreased fractures risk (OR=0.72; 95% CI, 0.59-0.87; *P*=0.0006). When only considered the females, we also found that statins was significantly associated with decreased fractures risk (OR=0.76; 95% CI, 0.63-0.92; *P*=0.005). All the results are summarized in **Table 2**. In the sensitivity analysis (**Table 3**), the results were not altered in case-control studies (OR=0.67; 95% CI, 0.55-0.81; *P*<0.0001) and retrospective cohort studies (OR=0.83; 95% CI, 0.71-0.97; *P*=0.02). However, no significant result was observed in the prospective cohort studies (OR=0.97; 95% CI, 0.83-1.12; *P*=0.65). When the study with moderate-quality was excluded, the result was not changed. The statistical heterogeneity was assessed by Galbraith plot. As shown in **Figure 3**, eleven studies were the outliners. When the 11 studies were deleted, the statistical heterogeneity was disappeared in the meta-analysis (I^2=0). Publication bias was not found in **Figure 4**.

Discussion

This meta-analysis suggested that statins were protective factor of fractures. Besides, results of our study indicated that statins could reduce the risk of fractures in females and old population.

The advantages of this study were, first, our meta-analysis included all the clinical studies with this topic. The sample size was more than 1800000. Thus, the statistical power was enough. Second, the results of our meta-analysis can help clinicians to prescribe statins to target population, such as females and old population. However, some potential limitations were existed in this meta-analysis. First, the observed association was substantially based on observational studies. Possible confounding factors might influence the results. Thus, randomized controlled trial are needed to be conducted to confirm our results. Second, due to insufficient data, we cannot determine if every statin could decrease the risk of fractures. Third, the inconsistency of the base line characteristics between the studies, such as age and gender, might increase the selection bias. Finally, the publication biases cannot be completely excluded due to that all of the included studies were mainly relying on observation.

Statins could also prevent other diseases. Chyou et al. suggested that statins had anti-inflammatory and anti-apoptotic properties with few side effects, making it an attractive therapeutic option for prevention of contrast-induced nephropathy (CIN) [21]. Patti et al. indicated that short-term statin pretreatment may reduce the risk of postoperative atrial fibrilla-

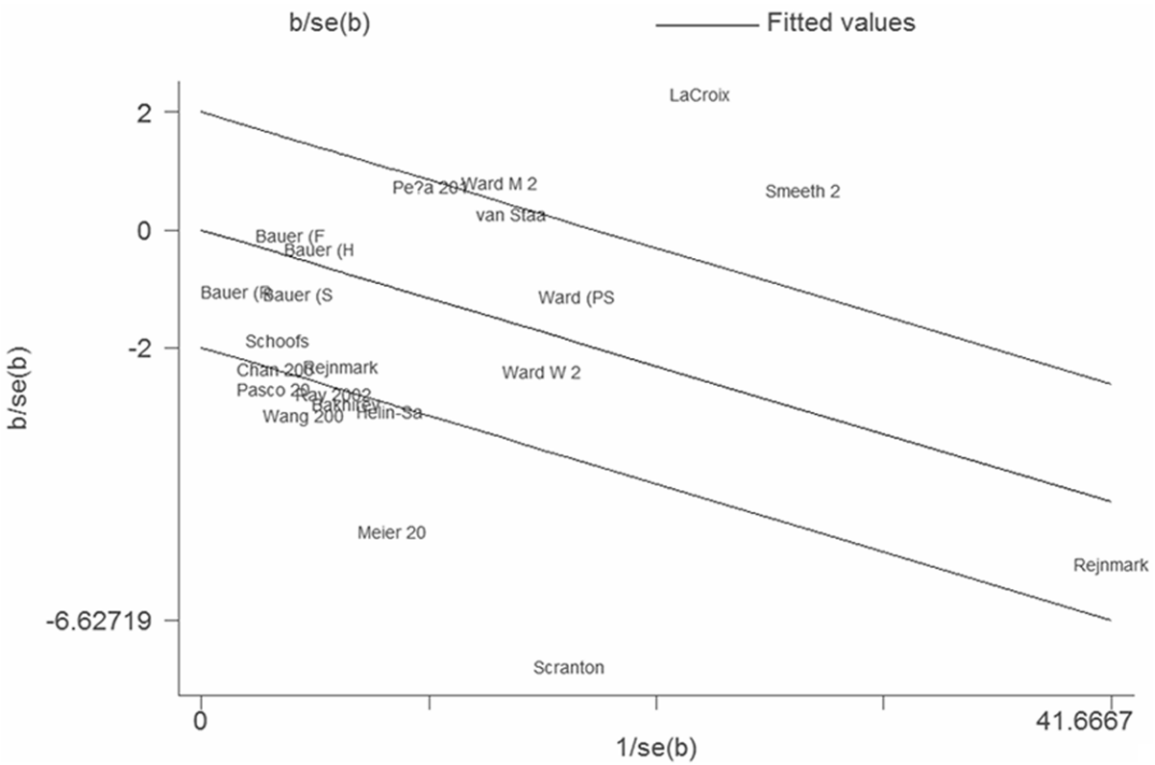

Figure 3. Galbraith plot of statins on fracture risk reduction.

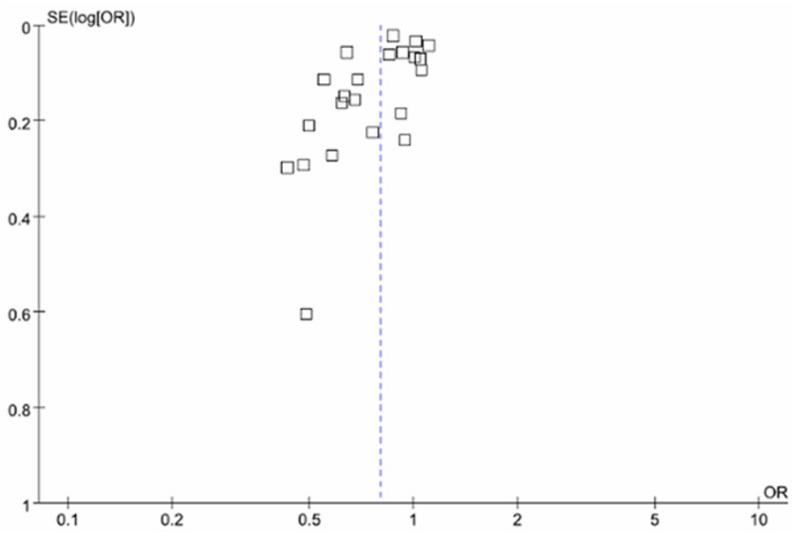

Figure 4. Funnel plot to assess publication bias.

tion among patients undergoing cardiac surgery [22]. Christie and colleagues found that statin treatment after cancer diagnosis is associated with enhanced survival in patients with low-grade, resectable pancreatic ductal adenocarcinoma [23]. What is more, Redlich et al. found that use of any statin was associated with a reduction in risk of depression in individuals over the age of 40 [24].

Pleiotropic effects of statin in prevention in fractures are not very clear. Yamaguchi and colleagues suggested that plasma lipids might be related to bone mass and bone fragility [25]. Ahmed et al. indicated that lower non-fasting serum levels of HDL protect against fractures in women and obese men [26]. Sivas et al. also indicated that serum lipids have impact on vertebrae fracture in Turkish postmenopausal women [27]. Statins could limit cholesterol synthesis, which could increase the expression of LDL receptors in liver cells. Finally, this procedure can enhance clearance of LDL-particles from blood. Thus, statins might have the role in the prevention of fractures [28].

In conclusion, our meta-analysis suggested that statin use was found to significantly associate with decreased fractures risk.

Disclosure of conflict of interest

None.

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