Original Article
Relationship between statin adherence and long-term clinical consequences in patients with cardiovascular disease: a systematic review and meta-analysis

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Abstract: Prior studies suggest that good statin adherence correlated with reduced risk of all-cause mortality and cardiovascular disease (CVD) events in the general population. However, the relationship between statin adherence and long-term clinical consequences in CVD patients is still unknown. We searched PubMed, EMBASE, and the Cochrane Library databases from 1965 to September 2015, using the search terms "adherence", "discontinuation", "persistence", and "statins". The outcome measures were risk ratios (RRs) with 95% confidence intervals (CI) assessing the relationship between statin adherence and clinical consequences in CVD patients. The primary end point was all-cause mortality, and the secondary end points were hospitalization for recurrence of CVD and revascularization. A total of 6 studies, including 38,301 patients, were included in this meta-analysis. The pooled RR favoring good statin adherence was 0.64 for all-cause mortality (95% CI: 0.52-0.80), 0.79 for hospitalization for recurrence of CVD (95% CI: 0.65-0.97), and 1.00 for revascularization (95% CI: 0.72-1.39). Thus, good statin adherence reduced the risk of all-cause mortality by 36% and the risk of hospitalization for recurrence of CVD by 21%, but had no impact on the risk of revascularization. CVD patients with good statin adherence have improved clinical consequences such as all-cause mortality and hospitalization for recurrence of CVD, but not revascularization. Statin medication adherence should be considered a real-world treatment problem among CVD patients. Measures to improve statin adherence to achieve better clinical consequences are urgently required.

Keywords: Statin adherence, cardiovascular disease, meta-analysis
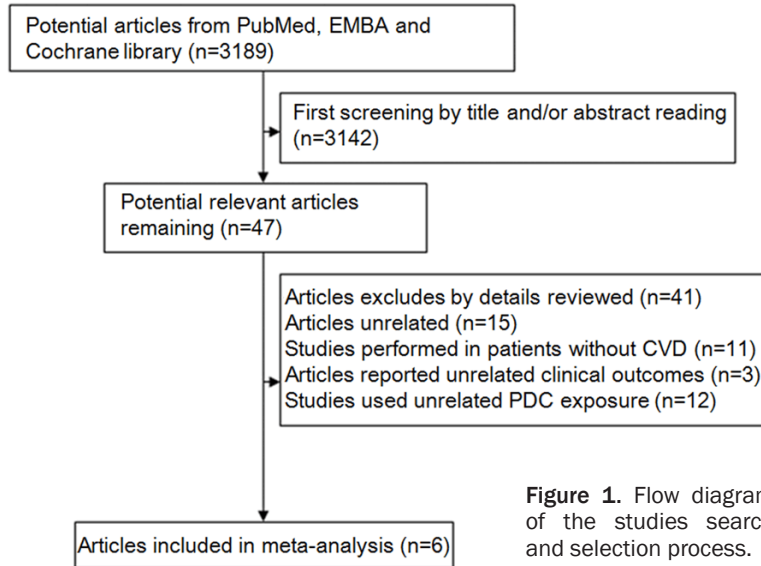
Introduction

Statins are hydroxy-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors that inhibit the rate-limiting step of cholesterol synthesis. Their lifesaving effects in reducing morbidity and mortality in patients with cardiovascular disease (CVD) have been proven by numerous clinical trials [1-7]. However, in real-world settings, the effectiveness of statin therapy is different from that seen in clinical trials, and is mostly inferior to trial results. This is mainly caused by poor statin medication adherence.

Medication adherence can be defined as the extent to which a patient takes medications as prescribed and instructed by their doctors [8].

The effectiveness of essential medication cannot be achieved with poor patient adherence. Several prior studies have assessed the impact of poor statin adherence, such as nonfatal myocardial infarction and mortality, in CVD patients [9-14], but a single study with a relatively small study population does not have sufficient power to verify the precise effect. Two meta-analyses performed by Chowdhury and Vera [15, 16] pooled data on the impact of poor statin adherence on adverse outcomes but did not focus on the impact in a CVD patient population. Thus, we performed this meta-analysis to obtain a better understanding of the relationship between statin adherence and clinical consequences in patients with CVD.

Potential articles from PubMed, EMBA and Cochrane library (n=3189)

First screening by title and/or abstract reading (n=3142)

Potential relevant articles remaining (n=47)

Articles excludes by details reviewed (n=41)
Articles unrelated (n=15)
Studies performed in patients without CVD (n=11)
Articles reported unrelated clinical outcomes (n=3)
Studies used unrelated PDC exposure (n=12)

Articles included in meta-analysis (n=6)

Figure 1. Flow diagram of the studies search and selection process.

plete articles were included. This study was conducted in accordance with the declaration of Helsinki. This study was conducted with approval from the Ethics Committee of Chinese PLA General Hospital. Written informed consent was obtained from all participants.

Data extraction and quality assessment

Two reviewers (XWH and MLL) performed the data extraction independently. The following information was extracted from each included study: first author's name; publication year; geographic location; design of study; patient population; patient numbers; exposure definition; categories of variables and reference group; and covariates adjusted in the statistical analysis. Information was examined and adjudicated by an additional reviewer (ZXJ), and discrepancies were resolved by consensus with another reviewer (FB), who referred to the original articles.

The Newcastle-Ottawa Scale (NOS) [17] was used to assess the quality of each eligible study. In an NOS form, a "star-system" was used to assess study quality with a range from 0 to 9 stars. We considered a study that was awarded ≥7 stars as a high-quality study, as standard grading criteria have not been defined.

End points of the study

The primary endpoint was long-term all-cause mortality. All-cause mortality included both cardiac and noncardiac death. Secondary endpoints included hospitalization for recurrence of CVD and revascularization.

Statistical analysis

The adjusted HR, RR, OR, and corresponding 95% CI were extracted from each included study and used to assess the impact of statin adherence on the clinical consequences in CVD patients. Overall combined RRs and corresponding 95% CI were pooled using a random-effects model because of the existence of

Material and methods

Search strategy and selection criteria

Observational studies (case-control and cohort studies) assessing the impact of statin adherence on CVD patients were eligible for inclusion in our meta-analysis, without any restriction on language of publication. A literature search was performed for relevant articles in PubMed (from 1965 to September 2015), EMBASE (from 1965 to September 2015), and the Cochrane Library databases using the search terms "adherence", "discontinuation", "persistence", and "statins". Manual searching of reference lists from relevant original and review articles was also performed to avoid missing relevant studies.

To be included in our meta-analysis, studies had to meet the following criteria: (1) case-control, nested case-control, or cohort study design; (2) performed in CVD patients; (3) performed in an adult population (≥18 years old); (4) relative risk (RR), odds ratio (OR), or hazard ratio(HR) was reported to assess the impact of statin adherence on clinical consequences in CVD patients; and (5) proportion of days covered (PDC) was used to quantify statin adherence; PDC≥80% was considered to be good adherence and PDC<80% was considered to be poor adherence. Studies performed among the general population or population without CVD were excluded. If more than one article reported data from a study, the most recent and com-

Table 1. Characteristic of studies included in the meta-analysis

Author	Year	Country	Study design	Patient population	Patient number	All-cause mortality events	Follow-up years and median	Variables categories and reference group	Covariates adjusted	Adherence measure	Quality score
Ho et al. [9]	2006	USA	Cohort	CVD and diabetes	2833	NA	3 years follow-up NA	PDC≥0.80 PDC<0.80#	Sex, age co-morbidities baseline A1C, BP and LDL levels	Yes	80.3%
Rasmussen et al. [10]	2007	Canada	Cohort	CVD with prior AMI	14345	3043	4 years follow-up median 2.4 years	PDC≥0.80# PDC 0.40-0.80 PDC<0.40	Sex, age, socioeconomic status year of admission, specialty of attending physician, severity of illness, inter-current hospitalizations during the 1-year and 3-month adherence assessment period, use of respective drug within 6 months prior to admission, concomitant use of angiotensin converting enzyme inhibitors, and, where applicable, statins, β-blockers, and calcium channel antagonists	Yes	High: 24% Intermediate: 20% Low: 16%
Ho et al. [11]	2008	USA	Cohort	CAD with prior MI, PCI or CABG	13596	NA	8 years follow-up median 4.1 years	PDC≥0.80# PDC<0.80	patient demographics, and cardiac and non-cardiac comorbidity variables	Yes	74%
Wei et al. [12]	2008	Scotland	Cohort	CVD	671	61	10 years follow-up median 4.7 years	PDC≥0.80 PDC<0.80#	age, sex, socioeconomic deprivation, calendar year of entry to the study, presence of diabetes mellitus at baseline (defined as on anti-diabetic treatment), other cardiovascular drug prescriptions during the follow-up including angiotensin converting enzyme inhibitors, β-blockers, calcium channel blockers, anticoagulant, cardiac glycosides, diuretics and nitrates, and amount of co-prescribing of cardiovascular drugs	Yes	≥80%
Mcginnis et al. [13]	2009	USA	Cohort	CVD with prior IE	2201	122	7 years follow-up median 3 years	PDC≥0.80 PDC<0.80#	age, sex, CDS, IE type, year of IE, purchases of an anti-platelet agent and β-blocker, and diagnoses of chronic heart failure and diabetes mellitus	Yes	75.4%
Hamood et al. [14]	2015	Israel	Cohort	CVD with prior AMI	4655	864	8 years follow-up median 4.5 years	PDC≥0.80# PDC<0.80	age, gender, ethnicity, district, comorbidity conditions, revascularization, prior use of drug, severity of disease, and health services utilization	Yes	≥80%

NA: data not available; #: reference group in original article; IE: incident cardiac event, defined as an AMI, CABG surgery, or PCI; CDS: chronic disease score.

substantial heterogeneity. Heterogeneity between the studies was evaluated using the chi-square (χ^2) test and I-squared (I^2) statistic [18]. Statistical heterogeneity was considered significant when $P<0.10$ for the χ^2 test or $I^2>50\%$. Potential publication bias was checked by visual inspection of a funnel plot, and Egger's regression test [19] and Begg's test [20] were also used to statistically assess the publication bias. If publication bias was detected, a trim and fill method would be performed to estimate the missing studies and recalculate the pooled RRs [21]. We also conducted a sensitivity analysis by excluding one study each time, and rerunning the analysis to further verify the robustness of the overall results. To assess whether the association between adherence and outcomes was due in part to a healthy adherer effect, we assessed the association between nonadherence with proton pump inhibitors or H2 antagonists and outcomes in the subgroup of patients prescribed these medications in the high heterogeneity presented in Ho's research [11]. All statistical tests were two-sided and used a significance level of $P<0.05$. All analyses were performed using Stata release 11 (Stata Corp, College Station, TX, USA).

Results

Literature search

A total of 3,189 articles were identified from the electronic literature search (**Figure 1**). After initial screening based on titles and abstract reading, 47 articles remained. Then, a full-text assessment was performed for the remaining articles. Finally, 6 articles met our inclusion criteria. Of the 41 articles excluded by full-text evaluation, 15 were unrelated, 11 were carried out among the general population or a population without CVD, 3 reported outcomes other than all-cause mortality, and 12 were based on unrelated PDC exposure.

Study characteristics

Six studies involving 38,301 patients were included in this meta-analysis. The main characteristics of the included studies are shown in **Table 1**. Four studies were based in North America [9-11, 13], one in Asia [14] and one in Europe [12]. All were designed as cohort studies, 4 reported HRs [10, 11, 13, 14], one report-

ed OR [9], and one reported RR [12] of good adherence to statin medication. All studies used PDC to assess statin adherence; PDC≥ 80% was defined as good adherence and PDC<80% was defined as poor adherence. In Rasmussen's study, the author subdivided patient adherence into 3 categories: high (PDC≥80%), intermediate (PDC 40%-79%), and low (PDC<40%). We used a fixed-effect model to pool the intermediate adherence group and low adherence group to generate an HR of PDC<80% group when compared to the reference group. Three studies reported HRs for the good adherence arm rather than the poor adherence arms, and the HRs were recalculated by the exponential of negative ln (HR). Among the studies identified, 6 reported all-cause mortality, 3 reported hospitalization for recurrence of CVD outcome, and 2 reported coronary revascularization outcomes. The subgroup analysis in Ho's research [11] showed that a significant association between nonadherence with these medications and cardiac-specific outcomes would demonstrate the presence of a health adherer effect, because neither proton pump inhibitors nor H2 antagonists have an impact on cardiac outcomes when high heterogeneity is present.

Statin adherence and primary endpoint

The pooled RRs for association between statin adherence and all-cause mortality are shown in **Figure 2A**. The combined result revealed lower all-cause mortality rate for good statin adherence patients compared with poor statin adherence patients (RR, 0.64; 95% CI: 0.52-0.80), with an I^2 estimate of 86.8%. Because of the obvious heterogeneity, a sensitivity analysis was performed by excluding one study each time, and recalculating the combined RR for the remaining studies; the result showed that RR and 95% CI did not change substantially (**Figure 3**). We did not detect publication bias based on Begg's test ($P=0.707$) and Egger's regression test ($P=0.487$). However, potential risk of publication bias was observed in the funnel plot. Therefore, we used the trim and fill method to find the missing studies, and further estimated the effect of potential publication bias. The result of the trim and fill method showed that no trimming was performed and the combined result had not been changed; this also proved the robustness of our pooled result (**Figure 4**).
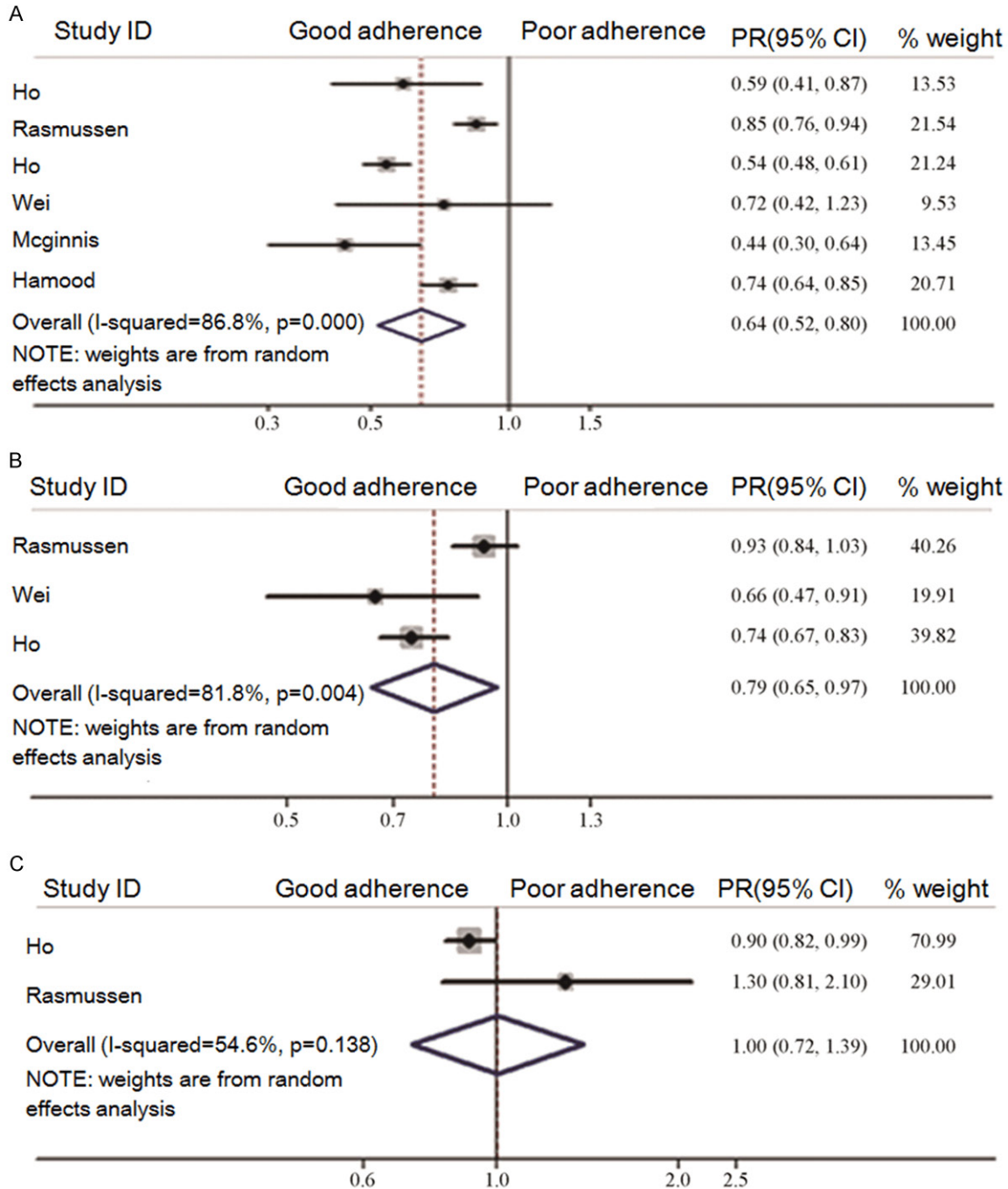
Figure 2. Forest plot of statin adherence associates with clinical consequences. A. Forest plot for all-cause mortality; B. Forest plot for hospitalization for recurrence of CVD; C. Forest plot for revascularization.

Statin adherence and secondary endpoints

Among the 6 selected studies, 3 also reported hospitalization for recurrence of CVD. The pooled RR (95% CI) for good adherence compared with poor adherence for hospitalization for recurrence of CVD was 0.79 (95% CI: 0.65-

0.97) (**Figure 2B**), with an I^2 estimate of 81.8%. Two studies reported revascularization outcome; the combined result showed no difference in risk of revascularization between good statin adherence patients and poor statin adherence patients (RR, 1.00; 95% CI: 0.72-1.39), with an I^2 estimate of 54.6% (**Figure 2C**).
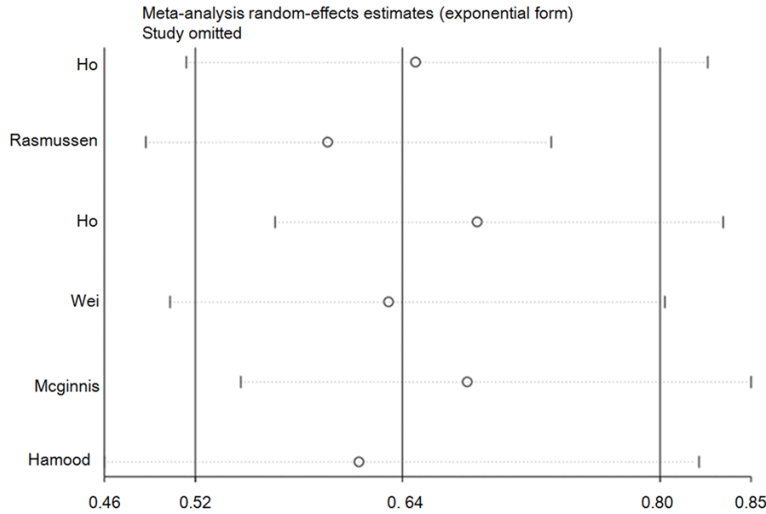
Figure 3. Plot of sensitivity analysis by excluding one study each time and the pooling estimate for the rest of the studies.
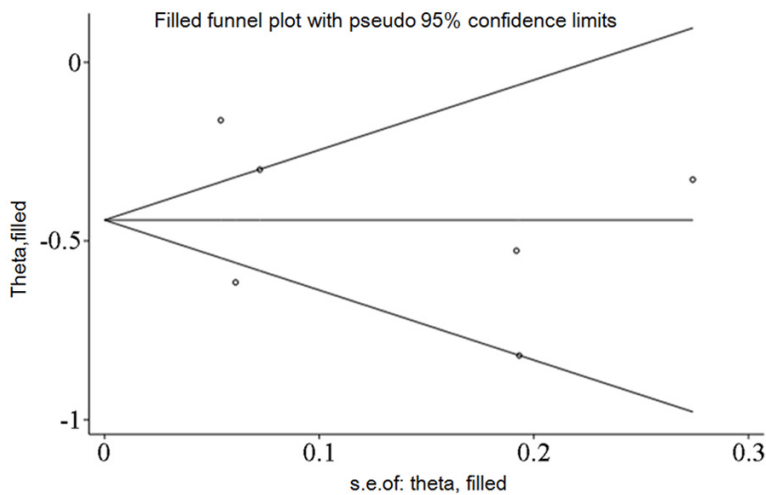
Figure 4. Funnel plot with trim and fill.

Discussion

To our knowledge, no meta-analysis has examined the relationship between statin adherence and clinical consequences among patients with CVD. Our study, based on 6 available prospective cohort studies, provided a qualitative and precise estimate of the association between statin adherence and clinical consequences in CVD patients. We found that patients with good statin adherence (PDC≥80%) had a reduced risk of all-cause mortality and hospitalization for recurrence of CVD when compared to patients with poor statin adher-

ence (PDC<80%), and there was no association between statin adherence and risk of revascularization and a non-fatal cardiac event.

Of the 6 studies included in our meta-analysis, all were performed in CVD patients, and the majority indicated that patients with good statin adherence (PDC≥80%) had reduced risk of all-cause mortality. However, Wei's study found no association between statin adherence and all-cause mortality (RR, 0.72; 95% CI: 0.42-1.24) [12]. The pooled results of our meta-analysis were consistent with most of the studies analyzed, and evidence of an association between good statin adherence and all-cause mortality was noted. Other studies which were not included in our analysis also found evidence that good statin adherence was correlated with improved clinical outcome. One study of 1,056 patients with prior myocardial infarction (MI), unstable angina (UA), percutaneous transluminal coronary angioplasty (PTCA), or coronary artery bypass grafting (CABG) evaluated adherence to statin therapy and found that patients with a fill frequency of 80% or greater were half as likely to experience a subsequent MI as the patients with a fill frequency of 60% or less [22]. Additionally, another study found that patients with prior acute myocardial infarction (AMI) and statin PDC<80% were associated with increased occurrence of mortality or acute coronary syndrome (ACS,) compared with patients with PDC≥80% [23]. Overall, the results of these studies indicated that good statin adherence correlated with better but not all clinical consequences. In our analysis, good statin adherence had no association with the risk of revascularization (RR, 1.00; 95% CI: 0.72-1.39).

Statin therapy is essential for CVD patients, but the status of statin adherence is far from satisfactory. Many prior studies had evaluated statin adherence among different patient populations. Benner and his colleagues evaluated statin adherence rates in 34,501 patients, and found that PDC decreased over time with discontinuation rates between 40% and 60% at 1 year after statin therapy initiation [24]. They also found that PDC decreased over time with a mean PDC of 79% in the first month, 56% in the second quarter of the first year, and only 42% at 10 years [24]. One study performed by Newby et al. found that "consistent" use of lipid-lowering therapy was only 44% over a 7-year period [25]. A meta-analysis by Chowdhury demonstrated that prevalence of good adherence for statins was 54% (95% CI: 41%-67%) after combining the results of 12 relevant studies [15]. All these findings indicate that statin adherence becomes suboptimal relatively quickly after initiation, and continues to decrease with time.

The strengths and limitations of our study should be carefully considered. We have reported a comprehensive meta-analysis based on 6 long-term prospective cohort studies among CVD patients. We have used PDC to evaluate statin adherence and assessed the association between statin adherence and clinical consequences, including all-cause mortality, hospitalization for recurrence of CVD, and revascularization. However, our study was limited by the small number of studies available on the analysis of secondary end points of hospitalization for recurrence of CVD and revascularization. Additionally, the patient population was not exactly the same in each of the included studies; for example, the patient population of some studies had AMI or received PTCA or CABG treatment, while others did not. There was heterogeneity among the included studies that could not be explained well, and the dissymmetry of the funnel plot indicated potential publication bias. This publication bias indicated a potential lack of studies with null or negative association between statin adherence and all-cause mortality, which could have resulted in a slight overestimation of the reduction credited here to good adherence to statins.

Conclusions

Our study suggested that good statin adherence correlated with improved clinical outcomes such as all-cause mortality and hospitalization for recurrence of CVD, but not revascularization. Clinicians and patients, especially CVD patients, should have a clear understanding of the impact of poor statin adherence. Developing cost-effective measures to increase adherence should be preferentially considered, and systems to monitor medication adherence over the long term are also needed.

Disclosure of conflict of interest

None.

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