Nutrition, Metabolism & Cardiovascular Diseases (2017) 27, 396–406

Available online at www.sciencedirect.com

Nutrition, Metabolism & Cardiovascular Diseases

journal homepage: www.elsevier.com/locate/nmcd

SYSTEMATIC REVIEWS AND META-ANALYSES

Statin use and risk of new-onset diabetes: A meta-analysis of observational studies

M. Casula [a,*], F. Mozzanica [a], L. Scotti [b], E. Tragni [a], A. Pirillo [c], G. Corrao [b], A.L. Catapano [a,d]

[a] Epidemiology and Preventive Pharmacology Centre (SEFAP), Department of Pharmacological and Biomolecular Sciences, University of Milan, Via Balzaretti 9, 20133, Milan, Italy
[b] Department of Statistics and Quantitative Methods, Division of Biostatistics, Epidemiology and Public Health, University of Milano-Bicocca, Via Bicocca degli Arcimboldi 8, 20126, Milan, Italy
[c] Center for the Study of Atherosclerosis, E. Bassini Hospital, Via M. Gorki 50, Cinisello Balsamo, 20092, Milan, Italy
[d] IRCCS MultiMedica, Via Milanese 300, 20099, Sesto S. Giovanni (MI), Italy

Received 8 November 2016; received in revised form 11 January 2017; accepted 2 March 2017
Available online 10 March 2017

KEYWORDS
Statins;
Incident diabetes;
Meta-analysis;
Observational studies

Abstract *Background and aims:* Meta-analyses of randomized control trials investigating the association between incident diabetes and statin use showed an increased risk of new-onset diabetes (NOD) from 9% to 13% associated with statins. However, short follow-up period, unpowered sample size, and lack of pre-specified diagnostic criteria for diabetes detection could be responsible of an underestimation of this risk. We conducted a meta-analysis of published observational studies to evaluate the association between statins use and risk of NOD.
Methods and results: PubMed, EMBASE and MEDLINE databases were searched from inception to June 30, 2016 for cohort and case–control studies with risk of NOD in users vs nonusers, on ≥1000 subjects followed-up for ≥1 year. Two review authors assessed study eligibility and risk of bias and undertook data extraction independently. Pooled estimates were calculated by a random-effects model and between-study heterogeneity was tested and measured by I^2 index. Furthermore, stratified analyses and the evaluation of publication bias were performed. Finally, the meta-analysis included 20 studies, 18 cohort and 2 case–control studies. Overall, NOD risk was higher in statin users than nonusers (RR 1.44; 95% CI 1.31–1.58). High between-study heterogeneity (I^2 = 97%) was found. Estimates for all single statins showed a class effect, from rosuvastatin (RR 1.61; 1.30–1.98) to simvastatin (RR 1.38; 1.19–1.61).
Conclusions: The present meta-analysis confirms and reinforces the evidence of a diabetogenic effect by statins utilization. These observations confirm the need of a rigorous monitoring of patients taking statins, in particular pre-diabetic patients or patients presenting with established risk factors for diabetes.

* Corresponding author. Fax: +39 02 503 18386.
E-mail address: sefap@unimi.it (M. Casula).

http://dx.doi.org/10.1016/j.numecd.2017.03.001

Introduction

Statin therapy represents the basis for the management of hypercholesterolemia and prevention of cardiovascular disease [1,2]. Statins are generally safe and well tolerated. However, some studies have reported an association between statin therapy and the risk of new-onset diabetes.

The first trial that evaluated the relationship between statin therapy and incident type 2 diabetes was the West of Scotland Coronary Prevention Study (WOSCOPS), which observed that pravastatin 40 mg/day was associated with a 30% risk reduction for incident diabetes in a high-risk population of men with severe hypercholesterolemia [3]. Since then, several other studies have investigated this relationship, reporting controversial results. In fact, while some studies did not show any apparent effect of statins on the development of new diabetes [3–6], other investigations suggested an increased risk. Among these, the JUPITER (Justification for the Use of Statin in Prevention: an Intervention Trial Evaluating Rosuvastatin) trial, in which statin treatment was associated with small but significantly higher levels of glycated hemoglobin and incidence rates of diabetes [7], and an analysis of the WHI (Women's Health Initiative), which reported an increased risk of diabetes mellitus in postmenopausal women taking statins [8]. These findings, together with observations from other clinical trials [9], led to hypothesize that statin therapy might trigger mechanisms leading to the development of diabetes. Several meta-analyses have thus evaluated data from available trials to define whether statin therapy may have a role in the development of type 2 diabetes, and observed an excess risk ranging from 9% up to 13% [10–14]. In particular, the increased risk of incident diabetes seems to be associated with high-intensity statin therapy [13]. A recent meta-analysis [15] showed that statins, as a class, significantly increase the risk of new-onset diabetes by 12% and that atorvastatin 80 mg was associated with the highest risk, followed by rosuvastatin, and simvastatin 80 mg; high dose atorvastatin increased the risk of diabetes even when compared with other statins such as pravastatin, simvastatin or low-dose atorvastatin, in agreement with previous findings.

Despite the risk of incident diabetes is low both in absolute and when compared with the significant reduction of cardiovascular events, the real weight of this risk is still undetermined. In addition, randomized clinical trials (RCTs) have several limitations that might reduce the actual relevance of such increased risk [16]. RCTs in fact, did not include diabetes risk as a primary outcome; as a consequence, they could not reach adequate statistical power and sample size to find an association between statin use and diabetes risk. In addition, the absence of pre-specified criteria for diabetes diagnosis and detection, together with selection bias and dropout from studies, may lead to an underestimation of adverse cases. Finally, the relatively short follow-up period typical of RCTs or the possibility to prematurely terminate the trial once benefits are documented may preclude the detection of a chronic condition such as diabetes [16]. On the other hands, observational studies can be very large and have unlimited duration and follow-up, thus increasing the chance to detect adverse events with low incidence. Aim of the present study was thus to investigate the relationship between statin therapy and risk of incident diabetes by undertaking a meta-analysis of all available observational studies.

Methods

This study was designed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines [17,18].

Study selection criteria

We evaluated observational studies that reported or allowed to calculate risk of new-onset diabetes (NOD) with statin use.

Studies were included if they met the following criteria: (1) the study examined risk of NOD for statin use *vs* non-use; (2) the study recruited 1000 participants or more; (3) follow-up was at least 1 year; (4) the risk estimate was reported as an odds ratio (OR), hazard ratio (HR) or relative risk (RR); (5) the 95% CI for the risk estimate was included.

Search strategy

PubMed, MEDLINE, and EMBASE were searched from inception to 30 June 2016. The search strategy included keywords and MeSH terms relating to statins and type 2 diabetes.

The keywords included: *"hydroxymethylglutaryl-CoA reductase inhibitors"* or *"statins"*, *"diabetes"*, *"cohort study"* or *"case–control study"*. One of the complete search strings is presented in Supplementals.

We excluded studies published as abstracts. The review was restricted to original articles published in English. We also manually searched bibliographies of included studies as well as existing systematic reviews for any other articles that may be potentially suitable.

Data extraction and evaluation

Two authors independently scanned all titles and abstracts and excluded articles that clearly were not observational studies on the topic. We proceeded to assess full-text versions of potentially relevant articles and conducted more detailed checks against our eligibility criteria. Disagreements were resolved by discussion.

We used preformatted tables (Table 1) to record study design and participant characteristics. Data extracted from observational studies were first author, year of publication, mean age range of participants, median follow-up time, drug exposure, and definition of NOD. We also extracted full adjusted estimates of risk along with 95% confidence intervals.