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The effect of statins on cardiovascular outcomes by smoking status: A systematic review and meta-analysis of randomized controlled trials

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ABSTRACT

Smoking is an important risk factor for cardiovascular disease (CVD) morbidity and mortality. The impact of statin therapy on CVD risk by smoking status has not been fully investigated. Therefore we assessed the impact of statin therapy on CVD outcomes by smoking status through a systematic review of the literature and meta-analysis of available randomized controlled trials (RCTs). The literature search included EMBASE, ProQuest, CINAHL and PUBMED databases to 30 January 2016 to identify RCTs that investigated the effect of statin therapy on cumulative incidence of major CVD endpoints (e.g. non-fatal myocardial infarction, revascularization, unstable angina, and stroke). Relative risks (RR) ratios were calculated from the number of events in different treatment groups for both smokers and non-smokers. Finally 11 trials with 89,604 individuals were included. The number of smokers and non-smokers in the statin groups of the analyzed studies was 8826 and 36,090, respectively. The RR for major CV events was 0.73 (95% confidence interval [CI]: 0.67–0.81; $p < 0.001$) in nonsmokers and 0.72 (95%CI: 0.64–0.81; $p < 0.001$) in smokers. Moderate to high heterogeneity was observed both in non-smokers ($I^2 = 77.1\%$, $p < 0.001$) and in smokers ($I^2 = 51.6\%$, $p = 0.024$) groups. Smokers seemed to benefit slightly more from statins than non-smokers according to the number needed to treat (NNT) analysis (23.5 vs 26.8) based on RRs applied to the control event rates. The number of avoided events *per* 1000 individuals was 42.5 (95%CI: 28.9–54.6) in smokers and 37.3 (95%CI: 27.2–46.4) in non-smokers. In conclusion, this meta-analysis suggests that the effect of statins on CVD is similar for smokers and non-smokers, but in terms of NNTs and number of avoided events, smokers seem to benefit more although non-significantly.

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1. Background

Currently, smoking is a cause of 5 million premature deaths globally each year with 50% of smokers being middle age persons [1,2]. According to the World Health Organization (WHO) the deaths caused by smoking will increase to as many as 8 million persons/year [3]. Cigarettes contain >5000 carcinogenic, toxic and mutagenic chemicals, stable and unstable free radicals, and reactive oxygen that substantially increase the morbidity and mortality from pulmonary disease and a wide array of cancers worldwide [4]. Smoking, a preventable public health issue, also represents an important individual risk factor for cardiovascular disease (CVD) morbidity and mortality [5], additional to heritable and environmental risk factors, such as male gender, dyslipidemia, obesity, hypertension, diabetes, lack of physical activity, and inflammation [6]. Transcriptomic studies have shown that smoking is responsible for changing gene expression in whole blood, circulating monocytes and lymphocytes in humans [6–8]. A recent study on young, healthy intermittent smokers showed a rapid increase in the number of circulating endothelial progenitor cells and microparticles of leukocyte, platelet and endothelial origin even after smoking a single cigarette, suggesting a systemic cascade of vascular events that might promote mechanisms important in the development of atherosclerosis [9].

Statins are commonly prescribed drugs [10] that are well tolerated and which effectively reduce the risk of CV events both in primary and secondary prevention [11,12]. They play a critical role in CVD patients, as they significantly lower the risk of acute myocardial infarction (AMI), stroke, cardiovascular revascularization, cardiac mortality and all-cause mortality [13,14]. Importantly, these effects might be observed irrespective of whether low density lipoprotein cholesterol (LDL-C) goals are achieved [13,14]. Cigarette smoking was found, to diminish the beneficial effect of statins in some clinical trials [15], but the role of cigarette smoking in modifying the effects of statin therapy is not well studied. Therefore, we aimed to assess the impact of statin therapy on CV outcomes by smoking status, through systematic reviews of the literature and meta-analysis of prospective controlled studies.

2. Methods

We followed the guidelines of the 2009 preferred reporting items for systematic reviews and meta-analysis (PRISMA) statement [16]. Due to the study design (meta-analysis) neither Institutional Review Board (IRB) approval, nor patient informed consent were needed or obtained.

2.1. Search strategy

The literature search included EMBASE, ProQuest, CINAHL and PUBMED databases to 30 January 2016 to identify primary or secondary prevention RCTs investigating the effect of statin therapy on cumulative incidence of major CVD endpoints (e.g. non-fatal myocardial infarction, CV revascularization, unstable angina, and stroke). Databases were searched using the following terms in titles and abstracts: ("atorvastatin" OR "simvastatin" OR "rosuvastatin" OR "fluvastatin" OR "pravastatin" OR "pitavastatin" OR "lovastatin" OR "cerivastatin" OR "statin therapy" OR "statins" OR "hydroxymethylglutaryl-CoA reductase inhibitors") AND "smoking" AND "randomized controlled trial". Additional searches for potential trials included the references of review articles on that issue, and the abstracts from selected congresses: scientific sessions of the European Society of Cardiology (ESC), the American Heart Association (AHA), American College of Cardiology (ACC), European Society of Atherosclerosis (EAS) and National Lipid Association (NLA). The wild-card term "*" was used to increase the sensitivity of the search strategy. The literature search was limited to articles published in English and to studies in humans.

All paper abstracts were screened by two reviewers (SU and MCS) in an initial process to remove ineligible articles. The remaining articles were obtained in full-text and assessed again by the same two researchers who evaluated each article independently, carried out data extraction and quality assessment. Disagreements were resolved by discussion with a third party (MB).

2.2. Study selection

The criteria for inclusion in this meta-analysis were: (i) randomized treatment allocation, (ii) a placebo arm, (iii) follow-up of at least 1 year, (iv) CV event as the primary or secondary endpoint, (v) $\geq$100 participants in the intervention group, (vi) results reported separately for smokers and non-smokers.

Exclusion criteria were: (i) non-clinical studies, (ii) lack of a statin-free control group in the study design, and, (iii) lack of sufficient information on smoking status on baseline or during follow-up.

2.3. Data extraction

Eligible studies were reviewed and the following data were abstracted: 1) first author's name; 2) year of publication; 3) country were the study was performed; 4) study design; 5) number of participants in statin and control groups; 6) statin type; 7) statin intervention; 8) median follow-up; 9) age and gender of study participants; 10) data regarding CV events. If data were presented separately for never-smokers and ex-smokers, these two categories were collapsed into a non-smoker category.

Data extraction was performed independently by 2 reviewers (SU and MCS); disagreements were resolved by a third reviewer (MB).

2.4. Quality assessment

Assessment of risk of bias in the studies included in the analysis was performed systematically using the Cochrane quality assessment tool for RCTs [17]. The Cochrane tool has 7 criteria for quality assessment: random sequence generation (selection bias), allocation sequence concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective outcome reporting (reporting bias) and other potential sources of bias. The risk of bias in each study was judged to be low, high or unclear.

Risk-of-bias assessment was performed independently by 2 reviewers (SU and MCS); disagreements were resolved by a third reviewer (MB).

2.5. Statistical analyses

Relative risks (RR) were calculated from the number of events in different treatment groups for smokers and for non-smokers in the included RCTs. We used the DerSimonian and Laird [18] random effects models as a primary method and the Mantel-Haenszel (MH) [19,20] method as an alternative approach to calculate the pooled RR and 95% confidence intervals (CIs). DerSimonian and Laird method uses a simple random effects model allowing for treatment effects to vary across studies. It uses a simple non-iterative method to estimate the inter-study treatment effect variance. The MH method uses a fixed-effect approach to meta-analysis. Heterogeneity among RRs was evaluated with the Higgins' I^2 statistic that describes the percentage of total variation among studies due to