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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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SUBTITLE: *A meta-analysis on the effects of statins on CV outcomes by smoking status.*

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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.

Key words: statins, smoking, cardiovascular outcomes, systematic review, meta-analysis

No. of words: 271

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.

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.

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).

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) ≥ 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.

Data extraction

Eligible studies were reviewed and the following data were abstracted: 1) first author's name; 2) year of publication; 3) country where 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).

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).

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 heterogeneity. The following categorization was used: 25% low, 50% moderate and 75% high heterogeneity (21). Galbraith plots, which are scatter plots for each z -statistic against the reciprocal value of the standard error, and also identify trials outside the pooled 95%CI estimate, were also depicted in order to assess heterogeneity (22). We explored differences in baseline risk and heterogeneity between studies by using I'Abbé plots (23). Meta-funnel plots were used to investigate possible publication bias (24). We investigated the influence of each study on the overall meta-analysis summary estimate (sensitivity analysis). In order to do the influence analysis in which the results are re-estimated omitting each study in turn (leave-one-out), we needed to derive the treatment effect estimate (in this case log risk ratio) and its standard error, for each study. We used the Harbord test – a modified test for small-study effects in meta-analyses of controlled trials with binary endpoints. This test proposed by Harbord, Egger, and Sterne (25), is a modified version of the commonly used test of Egger *et al.*(26). It is based on the component statistics of the score test, namely, the efficient score, Z , and the score variance (Fisher's information), V (27).

We also calculated the number needed to treat (NNT) and the number of avoided events. NNT is the number of individuals required to experience the intervention in order to avoid one CV event. The NNT is equal to $1/(\text{control group event rate} - \text{treatment group event rate})$. The number of avoided events per 1000 individuals is the difference between the two events rates multiplied by 1000.

The optimum information size (OIS) was calculated for each analysis (28). It is defined as the minimum amount of information required to reach reliable conclusions in a meta-analysis.

Estimating the OIS may help to determine whether there is sufficient data to draw reliable conclusions.

Data analysis was carried with STATA software (version 9.2, STATA Corporation, College Station, TX, USA) using the *metan* procedure. OIS was determined with the Trial Sequential Analysis (TSA) software downloaded at www.ctu.dk/tsa.

RESULTS

Search results and trial flow

The search initially identified 2712 full text articles. After excluding duplicates, the titles and abstracts of 2612 papers were screened, from which 2571 papers were excluded. Among the remaining 41 full text articles assessed for eligibility, 30 studies were excluded for not having data results reported separately for smokers and non-smokers. After final assessment, 11 eligible RCTs achieved the inclusion criteria and were selected for the final meta-analysis (**Figure 1**).

Characteristics of included studies

Eleven trials with 89,604 individuals (44,916 in statin group and 44,688 controls) were included: the West of Scotland Coronary Prevention Study (WOSCOPS), the Cholesterol and Recurrent Events (CARE), the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS), the Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID), the Anglo-Scandinavian Cardiac Outcomes Trial - Lipid Lowering Arm (ASCOT-LLA), the GREek Atorvastatin and Coronary-heart-disease Evaluation (GREACE), the Scandinavian Simvastatin Survival Study (4S), the Heart Protection Study (HPS), the PROspective Study of Pravastatin in the Elderly at Risk (PROSPER), a Study to Evaluate the

Use of Rosuvastatin in Subjects on Regular Hemodialysis: An Assessment of Survival and Cardiovascular Events (AURORA), and Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) (29-39).

The number of smokers and non-smokers in the statin groups of the analyzed studies was 8,826 and 36,090, respectively. The studies started between 1988 and 2005 were multicentre trials. Three studies, WOSCOPS, AFCAPS/TexCAPS and JUPITER were primary prevention trials, the others were secondary prevention studies. The following statins were administered: pravastatin (4 studies), atorvastatin (2 studies), simvastatin (2 studies), rosuvastatin (2 studies) and lovastatin. Median follow-up varied between 1.9 and 6 years. Demographic characteristics of the included studies are shown in **Table 1**.

Risk of bias assessment

An unclear risk of bias with respect to sequence generation and allocation concealment was observed in some trials; but studies were low-risk in terms of other sources of bias. **Table 2** presents study quality assessment for each of the 11 RCTs included in this meta-analysis.

Effect of statins on CV outcomes by smoking status

The RR ratio for major CV events was 0.73 (95%CI: 0.67-0.81; $p < 0.001$) in nonsmokers and 0.72 (95%CI: 0.64-0.81; $p < 0.001$) in smokers (**Figure 2**). 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.

When analyzed separately, primary prevention trials showed a RR ratio for major CV events of 0.64 (95%CI: 0.56-0.75; $p < 0.001$) in non-smokers and 0.58 (95% CI: 0.44-0.78; $p < 0.001$) in

smokers (**Figure 3**). No heterogeneity was found among non-smokers ($I^2=0.0\%$, $p=0.518$), but it was moderate among smokers, but not statistically significant ($I^2=39.2\%$, $p=0.193$).

Secondary prevention trials showed a RR ratio for major CV events of 0.76 (95%CI: 0.68-0.84; $p<0.001$) in nonsmokers and 0.76 (95%CI: 0.67-0.86; $p<0.001$) in smokers (**Figure 4**). Heterogeneity was high among non-smokers ($I^2=80.6\%$, $p<0.001$), but it was moderate and insignificant among smokers ($I^2=46.4\%$, $p=0.07$).

Differences in baseline risk and heterogeneity between studies are presented in l'Abbé plots (**Figure 5**).

Smokers seem 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.

When the proportion of CV events was examined in all studies (**Table 3**), the placebo smoker was the group with the worst outcome (15.19%, 95%CI: 14.44-15.94) with the comparable results for the placebo non-smoker group (14.03%; 95%CI: 13.67-14.39), while the groups with the best outcomes were statin non-smokers (10.82%, 95%CI: 10.50-11.14) and statin smokers (11.17%, 95%CI: 10.51-11.83).

Sensitivity analysis and publication bias

The influence of individual studies on the summary effect estimate is displayed in **Figure 6** and **Figure 7**. It appears that omission of any of the included studies did not significantly change the overall estimate. A Galbraith plot was produced to localize any trials that might cause heterogeneity (**Figure 8**). GREACE and AURORA studies are outside the pseudo 95%

confidence limit in non-smokers and PROSPER study is outside the pseudo 95% confidence limit in smokers. Harbord's modified test showed no small-study effects in either non-smokers ($p=0.305$) or smokers ($p=0.072$). Visual inspection of funnel plots suggested an asymmetry in the meta-analyses of CV outcomes both in non-smokers and smokers (**Figure 9** and **Figure 10**).

The OIS analysis revealed that we had sufficient data to draw the reliable conclusions. For each analysis the number of subjects surpassed the calculated OIS (all trials smokers OIS=4494, all trials non-smokers OIS=15,929; primary prevention trials smokers OIS=3538, primary prevention trials non-smokers OIS=4262; secondary prevention trials non-smokers OIS=13,688, secondary prevention trials smokers OIS 3606).

DISCUSSION

This meta-analysis did not suggest any significant difference between smokers and non-smokers regarding the effect of statins on CV outcomes. In terms of NNTs and number of avoided events, the smokers seem to benefit more, although non-significantly. There was no suggestion of substantial difference between smokers and non-smokers analyzing the results from primary and secondary prevention trials, however primary prevention patients seem to benefit more from the statin therapy irrespective on the smoking status.

Cigarette smoke-induced atherosclerosis involves several systemic pathways and underlying mechanisms (40), which are still not completely understood. Endothelial dysfunction caused by smoking is associated with decreased endothelial nitric oxide synthase (eNOS) expression (41-43). The free radicals contained by cigarette smoke induce cardiac remodeling, with consecutive atrial fibrosis and left ventricular hypertrophy, increasing the risk of stroke (44). Furthermore, systemic oxygen free radicals generated by chronic smoking cause local inflammation, resulting

in increased serum proinflammatory cytokines, peripheral leucocytes and C reactive protein (CRP), promoting arterial thrombosis and increased oxidative stress (45). Compounds found in cigarette smoke cause structural and functional alterations in blood vessels, noticeable though reduced ability to contract, thickening of the intima media and arterial wall, causing myocardial ischemia through increased arterial stenosis in exposed smokers (46). Nicotine also stimulates the release of hormones from the adrenal medulla, which might alter cardiac output through elevating blood pressure (BP), heart rate, and ventricular contractility, leading to cardiac ischemia (47). Lastly, but no less importantly, **one of the main forms of epigenetic modifications - DNA methylation, has been suggested to play an essential role in the pathways of smoking and diseases induced by smoking** (48). A recent meta-analysis on 17 studies searching the association of methylation modifications in blood DNA and active smoking exposure identified three genes: cg03636183 (*F2RL3*), cg05575921 (*AHRR*), and cg19859270 (*GPR15*) as smoking-related genes(49), which might be used as biomarkers of smoking exposure for quantifying the risks of smoking-related diseases in future research studies.

This meta-analysis might have important clinical relevance, especially as the knowledge on this issue has been very limited. In the GREACE study the authors investigated the impact of smoking on CV outcomes and comorbidities in statin-treated patients with coronary artery disease (CAD) (34). The authors showed that in patients on statin therapy **the hazard ratio (HR) for current smokers compared with never smokers was 1.86 (95%CI: 1.19-2.10) with very similar results while comparing current smokers and ex-smokers. Absolute (16.3%) and relative (45.6%) risk reduction of cardiovascular disease was large in current smokers on statins in comparison to those not on a statin; they still had, however, the highest absolute CVD event incidence (19.4%)** (34). Statins might effectively decrease the adverse impact of smoking with

their pleiotropic effects (e.g. anti-inflammatory, antioxidant and antithrombotic) (50-52) but how it transfers to the reduction of CVD events has been not clearly known. Agewall *et al.* (53) showed that in smokers endothelial functional flow-mediated dilation (FMD) increased significantly ($p<0.05$) on atorvastatin 80 mg and returned to basal levels during placebo. FMD was unaffected by either atorvastatin or placebo in the non-smoking group. The net change of total cholesterol or LDL-C was not associated with the net change in FMD (53). In the study by Januszek (54), the author assessed the impact of smoking on paraoxonase-1 (PON1) activity and the relationship with pleiotropic effects of simvastatin therapy and PON1 gene polymorphisms in patients with stable CAD and hypercholesterolemia treated with simvastatin 40 mg for 12 months. He showed a significant decrease of hsCRP ($p=0.017$) and tumor necrosis factor- α ($p=0.003$) concentrations after simvastatin in smokers, and 8-iso-PGF 2α in smokers and 192QQ allele carriers ($p=0.038$). In contrast to the study mentioned above, the author observed that FMD significantly improved only in the subgroup of non-smokers ($p=0.019$) and 192QQ allele carriers ($p=0.049$) (54). In a recent study, Ogawa *et al.* (55) analyzed the effect on statin therapy on malondialdehyde-modified low-density lipoprotein (MDA-LDL) level - a marker of oxidative stress linked to progression of arteriosclerosis. They showed that with regard to smoking status, MDA-LDL level was significantly higher in ex-smokers/current smokers in comparison to non-smokers. MDA-LDL level and MDA-LDL/LDL-C ratio, in the non-statin group, were significantly higher in ex-smokers/current smokers compared with non-smokers, while no significant correlation was noted between smoking status and LDL-C level. They concluded that MDA-LDL level might have been affected smoking status, and statin therapy might have a beneficial effect on the reduction of MDA-LDL level (55). These data confirm that smoking significantly increases the risk of atherosclerosis progression and the patient's overall

cardiovascular risk, and statins (especially at high doses) with their both potent lipid-lowering and pleiotropic properties might substantially reduce this risk, even slightly more than in non-smoker patients. This is what we observed in our meta-analysis, based on the results of NNT and number of avoided events, as well as the RR ratios for smokers *vs* non-smokers in primary prevention trials (0.58 *vs* 0.64, respectively). However, we would like to emphasize that statin therapy with lifestyle changes (not only smoking cessation, but also suitable diet and regular physical activity) is the most effective means of reducing risk of CVD, as we also observed in this meta-analysis (CV events ratio: 10.82% in the statin non-smoker group).

Strengths and limitations of the study

The strength of our meta-analysis is the large number of participants in RCTs. To our knowledge this is the first such extensive meta-analysis addressing this important issue.

Our study has several limitations. First, we did not have access to individual patient data; however, taking into account the number of included subjects in this meta-analysis (n=89,604) the statistical power is adequate. Second, reported CV events were very heterogeneous across trials; we only evaluated composite CV endpoints, without insight into detailed CV events, such as AMI or stroke. Third, we did not have access to adjusted effects per trial, and therefore could not meta-analyze adjusted effects. Fourth, the number of cigarettes smoked, duration of the smoking habit, or smoking cessation during follow up were not consistently reported across trials. Finally, there was no biochemical verification of smoking status.

In conclusion, this meta-analysis of large randomized controlled trials suggests that the effect of statins on CV outcomes is similar between smokers and non-smokers, but in terms of

NNTs and number of avoided events, smokers seem to benefit slightly more. These findings should not detract from efforts to encourage smoking cessation to reduce CV risk.

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Contributors: Maciej Banach (M.B.) had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. S.U. contributed to the study concept and design, data acquisition, data analysis and interpretation, and drafting of the manuscript; D.P.M. contributed to the study concept and design, and critical revision of the manuscript; M.C-S. contributed to the data acquisition, drafting and critical revision of the manuscript; P.M.R. contributed to the data acquisition and critical revision of the manuscript; A.V.H. contributed to the data analysis and interpretation, and critical revision of the manuscript; P.P., P.P.T., J.E.M., K.K.R., G.K.H., J.J.K. contributed to critical revision of the manuscript; and M.B. contributed to the study concept and design, drafting of the manuscript, and critical revision and final approval of the manuscript. All authors approved the final version of the text.

Declaration of interest: *Maciej Banach:* speakers bureau: Abbott/Mylan, Abbott Vascular, Actavis, Akcea, Amgen, KRKA, MSD, Sanofi-Aventis and Valeant; consultant to Abbott Vascular, Amgen, Daichii Sankyo, Esperion, Lilly, MSD, Resverlogix, Sanofi-Aventis; *Sorin Ursoniu, Maria-Corina Serban, Adrian V. Hernandez, JoAnn E. Manson, and Jacek Rysz* have nothing to declare; *Peter Penson* owns four shares in AstraZeneca PLC; *Dimitri P. Mikhailidis:* has given talks and attended conferences sponsored by MSD, AstraZeneca and Libytec; *Peter P. Toth:* speakers bureau: Amarin, Amgen, Kowa, Merck, Novartis, Regeneron, Sanofi-Aventis; consultant to Amgen, AstraZeneca, Kowa, Merck, and Regeneron; *Paul M. Ridker* has received research grant support from the National Heart Lung and Blood Institute, AstraZeneca, Novartis, Pfizer, Amgen, and Kowa.

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Table 1. Demographic characteristics of the included studies.

Study	WOSCOPS (29)	CARE (30)	AFCAPS/Tex CAPS (31)	LIPID (32)	ASCOT-LLA (33)	GREACE (34)	4S (35)	HPS (36)	PROSPER (37)	AURORA (38)	JUPITER (39)
Starting Year	1989	1989	1990	1990	1998	1998	1988	1994	1997	2003	2003
Location	Scotland	USA and Canada	USA	Australia and New Zealand	Denmark, Finland, Iceland, Norway, Sweden UK, and Ireland,	Greece	Denmark, Finland, Iceland, Norway, Sweden	UK	Scotland, Ireland, and the Netherlands	25 countries	26 countries
Median follow-up	4.8 years	5 years	5.2 years	6 years	3.3 years	3 years	5.4 years	5 years	3.3 years	4.6 years	1.9 years
Inclusion criteria	Men aged 45-64 yrs. with no history of myocardial infarction and with raised plasma cholesterol levels (LDL-C of at least 155 mg/dL, total cholesterol of at least 252 mg/dL)	Men and postmenopausal women if they had had an AMI between 3 and 20 months before randomization, 21 to 75 yrs. of age, with plasma total cholesterol levels of less than 240 mg/dL, LDL-C levels of 115 to 174 mg/dL, fasting triglyceride levels < 350 mg/dL, fasting glucose levels < 220 mg/dL, LVEFs of > 25 percent, and no	Generally healthy middle-aged and older men and women with average TC and LDL-C levels and with below-average HDL-C levels	Patients with a history of myocardial infarction or hospitalization for unstable angina and initial plasma total cholesterol levels of 155 to 271 mg/dL	Men and women aged between 40 and 79 yrs. at randomization, with either untreated hypertension, or treated hypertension with systolic blood pressure of ≥ 140 mm Hg, diastolic blood pressure of ≥ 90 mm Hg, or both; total cholesterol concentrations of ≤ 6.5 mmol/L, and not currently be taking a statin or a fibrate	Patients with established coronary heart disease	Patients with angina pectoris or previous AMI and cholesterol 5.5-8.0 mmol/L	Men and women aged about 40-80 yrs. with non-fasting blood total cholesterol concentrations of at least 3.5 mmol/L (135 mg/dL) were eligible provided they were considered to be at substantial 5-year risk of death from coronary heart disease	Patients with pre-existing vascular disease (coronary, cerebral, or peripheral) or raised risk of such disease because of smoking, hypertension, or diabetes	Patients 50 to 80 yrs. of age who had end-stage renal disease and had been treated with regular hemodialysis or hemofiltration for at least 3 months	Men ≥ 50 yrs. of age and women ≥ 60 yrs. of age without a history of CVD and if, at the initial screening visit, they had an LDL cholesterol level < 130 mg/dL and a high-sensitivity C-reactive protein level of ≥ 2.0 mg/L and a triglyceride level of < 500 mg/dL.

				symptomatic congestive heart failure.																					
Cardiovascular events		Non-fatal myocardial infarction and death from coronary heart disease		Major coronary events were the primary end point (death from coronary heart disease or non-fatal myocardial infarction), coronary-artery bypass grafting, or percutaneous transluminal coronary angioplasty		Acute major coronary events defined as fatal or non-fatal myocardial infarction, unstable angina, or sudden cardiac death		Death due to coronary heart disease and non-fatal AMI		Non-fatal myocardial infarction and fatal coronary heart disease		Cumulative incidence of major CVD events [all-cause and CVD mortality, CVD morbidity (non-fatal myocardial infarction, revascularization, unstable angina, congestive heart failure, and stroke)		Major coronary events: coronary deaths, non-fatal definite or probable MI, silent MI or resuscitated cardiac arrest		Major coronary event, stroke, and revascularization (defined prospectively as “major vascular events”)		Coronary heart disease death or non-fatal infarction or fatal or non-fatal stroke		Combined outcome (major cardiovascular event), death from cardiovascular causes, nonfatal myocardial infarction, and nonfatal stroke		First major CV event, defined as nonfatal AMI, nonfatal stroke, hospitalization for unstable angina, an arterial revascularization procedure, or confirmed death from CV causes			
Statin type		Pravastatin		Pravastatin		Lovastatin		Pravastatin		Atorvastatin		Atorvastatin		Simvastatin		Simvastatin		Pravastatin		Rosuvastatin		Rosuvastatin			
Statin intervention		40 mg/day		40mg/day		20–40 mg/day		40 mg/day		10 mg/day		10-80 mg/day		20–40 mg/day		40 mg/day		40 mg/day		10 mg/day		20 mg/day			
Participants	Statin	1445*	1855**	337*	1744**	429*	2875**	425*	4087**	1718*	3450*	129*	751*	542*	1679*	1446*	8823**	753*	2138**	202*	1187**	1400*	7501**		
	Control	1460*	1832**	304*	1744**	389*	2912**	444*	4058**	1656*	3481*	95*	625*	596*	1627*	1467*	8800**	805*	2108**	227*	1157**	1420*	7481**		
Age (years)	Statin	55±5		59±9		58±7		62 (55–67)		63±8		58±12		58±7 in men 60±6 in women		40–80		75±3		64±9		66 (60–71)			
	Control	55±5		59±9		58±7		62 (55–68)		63±9		59±14		58±7 in men 61±6 in women		40–80		75±3		64±9		66 (60–71)			
Male (%)	Statin	100		86		85		83		81		91*		78**		82		75		48		61		62	
	Control	100		86		85		83		81		92*		75**		81		75		48		63		62	

Values are expressed as mean \pm SD or median (25 to 75 percentile);* smokers; ** non-smokers.

Abbreviations: NS: not stated; CVD: cardiovascular disease; AMI: acute myocardial infarction; MACE: major adverse cardiac events; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol; LVEF: left ventricular ejection fraction; WOSCOPS=West of Scotland Coronary Prevention Study; CARE=Cholesterol and Recurrent Events; AFCAPS/TexCAPS=Air Force/Texas Coronary Atherosclerosis Prevention Study; LIPID=Long-term Intervention with Pravastatin in Ischaemic Disease; ASCOT-LLA=Anglo-Scandinavian Cardiac Outcomes Trial–Lipid Lowering Arm; GREACE=The GREek Atorvastatin and Coronary-heart-disease Evaluation study; 4S=Scandinavian Simvastatin Survival Study; HPS=Heart Protection Study; PROSPER=PROspective Study of Pravastatin in the Elderly at Risk; AURORA=A Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Hemodialysis: An Assessment of Survival and Cardiovascular Events; JUPITER= Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin

Table 2. Assessment of risk of bias in the included studies using Cochrane criteria.

Study	Sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective outcome reporting	Other potential threats to validity
WOSCOPS (29)	U	U	L	L	L	L	L
CARE (30)	U	U	L	L	L	L	L
AFCAPS/TexCAPS (31)	U	U	L	L	L	L	L
LIPID (32)	U	U	L	L	L	L	L
ASCOT-LLA (33)	L	L	L	L	L	L	L
GREACE (34)	U	U	U	L	L	L	L
4S (35)	L	L	L	L	L	L	L
HPS (36)	L	L	L	L	L	L	L
PROSPER (37)	L	L	L	L	L	L	L
AURORA (38)	L	L	L	L	L	L	L
JUPITER (39)	L	L	L	L	L	L	L

L: low risk of bias; H: high risk of bias; U: unclear risk of bias.

Table 3. CV outcomes among smokers and non-smokers according to treatment group.

Study	Group	Non-smokers, % with CV outcomes	Smokers, % with CV outcomes
WOSCOPS (29)	Statin	3.98	6.92
	Control	5.67	9.86
CARE (30)	Statin	20.01	24.03
	Control	25.05	36.84
AFCAPS/TexCAPS (31)	Statin	3.44	3.96
	Control	5.05	9.25
LIPID (32)	Statin	12.01	15.53
	Control	15.35	20.72
ASCOT-LLA (33)	Statin	1.88	2.04
	Control	2.70	3.62
GREACE (34)	Statin	10.78	19.37
	Control	24.0	35.79
4S (35)	Statin	18.11	23.43
	Control	26.37	32.38
HPS (36)	Statin	19.31	22.75
	Control	24.64	28.36
PROSPER (37)	Statin	13.70	15.27
	Control	16.51	15.53
AURORA (38)	Statin	28.39	29.21
	Control	29.04	31.72
JUPITER (39)	Statin	1.47	2.28
	Control	2.53	4.37

*Abbreviations explanations of all RCTs have been presented in the text of the manuscript.

FIGURE LEGENDS:

Figure 1. Flow chart of the number of studies identified and included into the meta-analysis.

Figure 2. Forest plot displaying RR and 95% confidence intervals for the impact of statin on cardiovascular outcomes in smokers and non-smokers. Squares represent the point of estimate of each study; square size corresponds to the weight of the study in the meta-analysis. Horizontal lines denote the respective 95% CIs. The diamond represents the overall pooled estimate of statin effect.

Figure 3. Forest plot displaying RR and 95% confidence intervals for the impact of statin on cardiovascular outcomes in smokers and non-smokers in primary prevention trials. Squares represent the point of estimate of each study; square size corresponds to the weight of the study in the meta-analysis. Horizontal lines denote the respective 95% CIs. The diamond represents the overall pooled estimate of statin effect.

Figure 4. Forest plot displaying RR and 95% confidence intervals for the impact of statin on cardiovascular outcomes in smokers and non-smokers in secondary prevention trials. Squares represent the point of estimate of each study; square size corresponds to the weight of the study in the meta-analysis. Horizontal lines denote the respective 95% CIs. The diamond represents the overall pooled estimate of statin effect.

Figure 5. L'Abbé plot of control group risk (x-axis) against treatment group risk (y-axis) in non-smokers and smokers. Each circle denotes a study included in the meta-analysis. Circle size corresponds to the weight of the study in the meta-analysis.

Figure 6. Results of an influence analysis in which the meta-analysis is re-estimated after omitting each study in smokers.

Figure 7. Results of an influence analysis in which the meta-analysis is re-estimated after omitting each study in non-smokers.

Figure 8. Galbraith plot. The ratio of the RR log of cardiovascular outcomes divided by its standard error versus the reciprocal of the standard errors in non-smokers and smokers. Includes confidence intervals around the fixed effect summary effect line.

Figure 9. Funnel plot for assessment of publication bias in the model of comparison the RRs of the association between statin users vs. controls and cardiovascular outcomes in smokers. Each circle denotes a study included in the meta-analysis. The dashed vertical line represents the overall effect calculated with the random-effects model.

Figure 10. Funnel plot for assessment of publication bias in the model of comparison the RRs of the association between statin users vs. controls and cardiovascular outcomes in non-smokers. Each circle denotes a study included in the meta-analysis. The dashed vertical line represents the overall effect calculated with the random-effects model.