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Author: Maciej Banach Madalina Dinca Sorin Ursoniu Maria-Corina Serban George Howard Dimitri P. Mikhailidis Stephen Nicholls Gregory Y.H. Lip Stephen Glasser Seth S. Martin Paul Muntner Jacek Rysz Peter P. Toth Amirhossein Sahebkar

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A PRISMA-compliant Systematic Review and Meta-Analysis of Randomized Controlled Trials Investigating the Effects of Statin Therapy on Plasma Lipid Concentrations in HIV-Infected Patients

Maciej Banach[1-3*#], Madalina Dinca[4*], Sorin Ursoniu[5], Maria-Corina Serban[6,7], George Howard[8], Dimitri P. Mikhailidis[9], Stephen Nicholls[10], Gregory Y.H. Lip[11], Stephen Glasser[12], Seth S. Martin[13], Paul Muntner[6], Jacek Rysz[1,2], Peter P. Toth[13,14] Amirhossein Sahebkar[15,16] for the *Lipid and Blood Pressure Meta-analysis Collaboration (LBPMC) Group*

** Drs Banach and Dinca contributed equally to this work.*

[1]Chair of Nephrology and Hypertension, Medical University of Lodz, Lodz, Poland; [2]Healthy Aging Research Centre (HARC), Medical University of Lodz, Lodz, Poland; [3]Polish Mother's Memorial Hospital Research Institute, Lodz, Poland. [4]Independent Pharmacist Researcher, Leuven, Belgium; [5]Department of Functional Sciences, Discipline of Public Health, "Victor Babes" University of Medicine and Pharmacy, Timisoara, Romania; [6]Department of Epidemiology, University of Alabama at Birmingham, Birmingham, AL, USA; [7]Department of Functional Sciences, Discipline of Pathophysiology, "Victor Babes" University of Medicine and Pharmacy, Timisoara, Romania; [8]Departments of Biostatistics, UAB School of Medicine, Birmingham, AL, USA; [9]Department of Clinical Biochemistry, Royal Free Campus, University College London Medical School, University College London (UCL), London, UK; [10]South Australian Health and Medical Research Institute, University of Adelaide, Australia; [11]University of Birmingham Centre for Cardiovascular Sciences, City Hospital, Birmingham, UK; [12]Department of Preventive Medicine, University of Alabama at Birmingham, Birmingham, AL, USA; [13]The Johns Hopkins Ciccarone Center for the Prevention of Heart Disease, Baltimore, MD, USA; [14]Preventive Cardiology, CGH Medical Center, Sterling, Illinois, USA; [15]Biotechnology Research Center, Mashhad University of Medical Sciences, Mashhad, Iran; [16]Metabolic Research Centre, Royal Perth Hospital, School of Medicine and Pharmacology, University of Western Australia, Perth, Australia

***Correspondence to:** Prof. Maciej Banach, MD, PhD, FNLA, FAHA, FESC; FASA, Head, Department of Hypertension, WAM University Hospital in Lodz, Medical University of Lodz, Zeromskiego 113; 90-549 Lodz, Poland. **Phone:** +48 42 639 37 71; **Fax:** +48 42 639 37 71; **E-mail:** maciejbanach77@gmail.com

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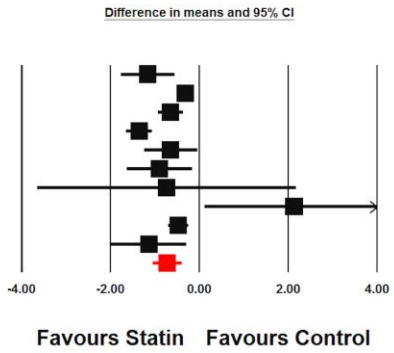
Graphical abstract

Forest plot displaying WMD and 95%CI for the impact of statin therapy on plasma concentrations of LDL-C in HIV-infected patients.

LDL-C

Study name	Difference in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Bonnet et al., 2007	-1.160	0.306	0.094	-1.760	-0.560	-3.788	0.000
Calmy et al., 2010	-0.300	0.057	0.003	-0.412	-0.188	-5.238	0.000
Eckard et al., 2014	-0.650	0.140	0.020	-0.925	-0.375	-4.638	0.000
Ganesa et al., 2011	-1.350	0.144	0.021	-1.632	-1.068	-9.391	0.000
Hurlimann et al., 2006	-0.640	0.300	0.090	-1.229	-0.051	-2.131	0.033
Lo et al., 2015	-0.890	0.373	0.139	-1.620	-0.160	-2.388	0.017
Stein et al., 2014	-0.730	1.481	2.194	-3.633	2.173	-0.493	0.622
Nakanjako et al., 2015	2.140	1.028	1.056	0.126	4.154	2.082	0.037
Montoya et al., 2012	-0.470	0.111	0.012	-0.688	-0.252	-4.234	0.000
Moyle et al., 2001	-1.130	0.429	0.184	-1.972	-0.288	-2.631	0.009
	-0.717	0.165	0.027	-1.040	-0.394	-4.352	0.000



ABSTRACT:

Statin therapy may lower plasma lipid concentrations, but the evidence in HIV-infected patients is still unclear. Therefore, we aimed to investigate the impact of statin therapy on plasma lipid concentrations through a systematic review of the literature and meta-analysis of available randomized controlled trials (RCTs). The literature search included PUBMED, SCOPUS, Web of Science and Google Scholar up to October 30, 2015. The meta-analysis was performed using either a fixed-effects or random-effect model according to I^2 statistic. Effect sizes were expressed as weighted mean difference (WMD) and 95% confidence interval (CI). Two investigators independently reviewed the title or abstract, further reviewed the full-texts and extracted information on study characteristics and study outcomes. Meta-analysis of 12 RCTs with 697 participants suggested significant reductions in plasma concentrations of low density lipoprotein (LDL) cholesterol (WMD: -0.72 mmol/L [-27.8 mg/dL], 95%CI: -1.04, -0.39, p<0.001; I^2=85.7%), total cholesterol (WMD: -1.03 mmol/L [-39.8 mg/dL], 95%CI: -1.42, -0.64, p<0.001; I^2=94.7%) and non-high density lipoprotein cholesterol (non-HDL-C) (WMD: -0.81 mmol/L [-31.3 mg/dl], 95%CI: -1.32, -0.30, p=0.002; I^2=76.5%), and elevations in HDL-C (WMD: 0.072 mmol/L [2.8 mg/dL], 95%CI: 0.053, 0.092, p<0.001; I^2=0%) following treatment with statins (mostly of moderate-intensity). No significant alteration in plasma triglycerides (TG) concentrations was found (WMD: -0.16 mmol/L [-14.2 mg/dL], 95%CI: -0.61, 0.29, p=0.475; I^2=90.2%). All these effects were robust in sensitivity analysis, suggesting that the computed effect is not driven by any single study. In subgroup analysis, no significant difference was found among different statins in terms of changing plasma concentrations of LDL-C, HDL-C and TG. However, atorvastatin was found to be more efficacious in reducing plasma total cholesterol concentrations (p < 0.001). In conclusion, the meta-analysis suggested significant reductions in plasma concentrations of LDL-C, total cholesterol and non-HDL-C, and elevations in HDL-C, but no significant alteration in plasma TG following treatment with statins.

Key words: HIV, efficacy, lipids, safety, statin therapy.

No. of words: 300

ABBREVIATIONS:

ART = antiretroviral therapy

AUC24 = 24h area under the concentration-time curve

BMI = body mass index

CI = confidence interval

CYP = cytochrome

HDL-C = high density lipoprotein cholesterol

HIV = human immunodeficiency virus

HMG-CoA = 3-hydroxy-3-methylglutaryl-CoA

ICAM-1 = intracellular adhesion molecule-1

LDL = low density lipoprotein

LFA_1 = lymphocyte function antigen-1

non-HDL-C = non-high density lipoprotein cholesterol

RCT = randomized controlled trial

SD = standard deviation

TG = triglycerides

WMD = weighted mean difference

INTRODUCTION

In comparison with the general population, patients infected with human immunodeficiency virus (HIV) are 50-100% more likely to develop cardiovascular disease, despite controlling for major risk factors such as hypertension, cholesterol, and smoking (1). The Veterans Aging Cohort Study on 82,459 patients (HIV positive: n=27 350) found a 1.5-times higher risk of acute myocardial infarction in HIV infected patients than normal population (2).

Despite virological suppression with antiretroviral therapy, HIV related immune activation and increased inflammation are associated with mortality related to cardiovascular disease (3). Immune activation may mediate various comorbidities, such as vascular disease, diabetes mellitus or high risk of arterial and venous thrombosis (4, 5). HIV infection is accompanied by various disturbances of plasma lipids; moreover HIV protease inhibitors, which have been shown to reduce hepatic clearance and increase biosynthesis of serum cholesterol, increase insulin resistance, centrally obesity, lipodystrophy and coronary artery calcification (6-8). As such, hyperlipidemia and hypertriglyceridemia are common metabolic effects of protease inhibitors (9, 10).

Disruption of lipid rafts due to 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) reductase inhibitors reduces HIV-1 particle production (11) but also inhibit lymphocyte function antigen-1 (LFA_1), down-regulate *Rho* activity (12), and have effects on intracellular adhesion molecule-1 (ICAM-1), essential for viral entry and exit (13). The best choice of a pharmacologic agent for HIV patients taking protease inhibitors drugs might be pravastatin, which is not substantially metabolized by cytochrome (CYP) $3A_4$, decreasing the risk of hypothetic drug-drug interactions (14).

Statins could be particularly advantageous in HIV-infected individuals because of the pleiotropic effects of reducing inflammation and immune activation, but the findings concerning changes in plasma lipid parameters concentrations following statin therapy have been inconsistent. Therefore, in the present meta-analysis we evaluated in HIV patients, the impact of statin therapy on plasma lipid concentrations.

METHODS

This study was designed according to the guidelines of the 2009 preferred reporting items for systematic reviews and meta-analysis (PRISMA) statement (15). Due to the study design (meta-analysis of randomized controlled trials) no Institutional Review Board (IRB) approval, as well as no patients' informed consents were obtained.

Search Strategy

PubMed/Medline, SCOPUS, Web of Science and Google Scholar databases were searched using the following search terms in titles and abstracts: (Hydroxymethylglutaryl-CoA Reductase Inhibitors OR statin OR statins OR HMG-CoA Reductase Inhibitors OR Hydroxymethylglutaryl-Coenzyme A Inhibitors OR Hydroxymethylglutaryl-CoA Inhibitors OR atorvastatin OR simvastatin OR rosuvastatin OR fluvastatin OR pravastatin OR pitavastatin OR lovastatin OR cerivastatin OR "statin therapy" OR statins) AND ("AIDS" OR "HIV" OR "HIV infection") AND (randomized). The wild-card term ''*'' was used to increase the sensitivity of the search strategy. The search was limited to articles published in English language. The literature was searched from inception to October 30, 2015. Two reviewers (MD and MCS) evaluated each article independently. Disagreements were resolved by discussion with a third party (MB).

Study Selection

Original studies were included if they met the following criteria: (i) randomized placebo-controlled trial (RCT) with either parallel or cross-over design, (ii) investigated the impact of statin therapy, either as monotherapy or combination therapy, on plasma/serum lipid concentrations, (iii) providing sufficient information on baseline and end-trial plasma/serum lipid concentrations in both statin and control groups at baseline and at the end of follow-up in each group or providing the net change values.

Exclusion criteria were: (i) non-interventional trials, (ii) lack of a placebo control group for statin therapy, (iii) observational studies with case-control, cross-sectional or cohort design, and, (iv) lack of sufficient information on baseline or follow-up plasma/serum lipid concentrations.

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 the statin and control groups; 6) type and dose of statin; 7) treatment duration; 9) age, sex and body mass index (BMI) of study participants; 9) systolic and diastolic blood pressures; and 10) serum/plasma concentrations of lipid parameters including total cholesterol, low density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL-C) and triglycerides (TG). Data extraction was performed independently by 2 reviewers; disagreements were resolved by a third reviewer.

Quality assessment

A systematic assessment of bias in the included studies was performed using the Cochrane criteria (16). This involves evaluating the risk of bias as ‘low risk’, ‘high risk or ‘unclear risk’.

The final category implies either lack of information or doubt over the potential for bias. There are seven analyzed domains comprising: 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.

Risk-of-bias assessment was performed independently by 2 reviewers; disagreements were resolved by a third reviewer.

Quantitative Data Synthesis

Meta-analysis was conducted using Comprehensive Meta-Analysis (CMA) V2 software (Biostat, NJ) (17). Net changes in measurements (change scores) were calculated as follows: measure at end of follow-up − measure at baseline. For single-arm cross-over trials, net changes in plasma concentrations of lipids were calculated by subtracting the value after control intervention from that reported after treatment. All values were collated as percent change from baseline in each group. Standard deviations (SDs) of the mean difference were calculated using the following formula: SD = square root $[(SD_{pre\text{-}treatment})^2 + (SD_{post\text{-}treatment})^2 - (2R \times SD_{pre\text{-}treatment} \times SD_{post\text{-}treatment})]$, assuming a correlation coefficient (R) = 0.5. If the outcome measures were reported in median and interquartile range (or 95% confidence interval [CI]), mean and standard SD values were estimated using the method described by Wan *et al.*(18). Conversion of 95% CI to SD was performed using the instructions of the Cochrane Handbook(16). Where standard error of the mean (SEM) was only reported, standard deviation (SD) was estimated using the following formula: SD = SEM × sqrt (*n*), where *n* is the number of subjects.

Net changes in measurements (change scores) were calculated for parallel and cross-over trials, as follows: (measure at the end of follow-up in the treatment group − measure at baseline in the treatment group) − (measure at the end of follow-up in the control group − measure at baseline in the control group). A random-effects model (using DerSimonian-Laird method) and the generic inverse variance method were used to compensate for the heterogeneity of studies in terms of study design, treatment duration, and the characteristics of populations being studied (19). Inter-study heterogeneity was assessed using Cochran Q test and I^2 index. In order to evaluate the influence of each study on the overall effect size, sensitivity analysis was conducted using leave-one-out method, i.e. iteratively removing one study each time and repeating the analysis.

Meta-regression

A weighted random-effects meta-regression using an unrestricted maximum likelihood model was performed to assess the association between the overall estimates of effect size with duration of treatment and baseline lipid values as potential confounders.

Publication bias

Potential publication bias was explored using visual inspection of Begg's funnel plot asymmetry, Egger's weighted regression, and "fail safe N" tests. The Duval & Tweedie "trim and fill" methodwas used to adjust the analysis for the effects of publication bias (20).

RESULTS

Flow and characteristics of included studies

The initial screening for potential relevance removed articles when titles and/or abstracts were obviously irrelevant and did not refer to the main aim of the analysis. Among the 32 full text articles assessed for eligibility, 20 studies were excluded due to the lack of a control group (n=14), the lack of plasma lipid concentrations data (n=5) and the lack of statins (n=1) (**Figure 1**). After final assessment, 12 trials achieved the inclusion criteria and were analyzed for the final meta-analysis (21-32).

Characteristics of included studies

In total, 697 patients in the 12 selected studies were included; 343 participants were allocated to statin therapy groups, and 354 served as controls. The number of participants in these trials ranged between 21 and 147. Included studies were published between 2001 and 2015, and were conducted in the USA (n=5), United Kingdom, France, Australia, Switzerland, Uganda and Colombia. One study was multicenter and was carried out in Australia and Switzerland.

The following statin doses were administered in the included trials: 40 mg/day of pravastatin, 10 mg/day of rosuvastatin, 20 to 80 mg/day of atorvastatin and 40 mg/day of lovastatin. Duration of statin intervention ranged between 8 and 48 weeks. Among the 12 included trials, 8 were designed as parallel group and 4 as crossover studies. Demographic and baseline parameters of the included studies are shown in **Table 1.**

Risk of bias assessment

An unclear risk of bias with respect to sequence generation, allocation concealment and blinding of outcome assessment was observed in some studies. Two trials were not blind, but

studies were low-risk in terms of other sources of bias. The systematic assessment of bias in the included studies is presented in **Table 2.**

Effect of statin therapy on plasma lipid concentrations

Overall, the impact of statins on plasma concentrations of total cholesterol, LDL-C, HDL-C, triglycerides and non-HDL-C was assessed in 10, 9, 8, 8 and 2 studies, respectively. Meta-analysis suggested significant reductions in plasma concentrations of LDL-C (WMD: -0.72 mmol/L [-27.8 mg/dL], 95%CI: -1.04, -0.39, $p < 0.001$; $I^2 = 85.7\%$; **Figure 2**), total cholesterol (WMD: -1.03 mmol/L [-39.8 mg/dL], 95% CI: -1.42, -0.64, $p < 0.001$; $I^2 = 94.7\%$; **Figure 2**) and non-HDL-C (WMD: -0.81 mmol/L [-31.3 mg/dl], 95% CI: -1.32, -0.30, $p = 0.002$; $I^2 = 76.5\%$; **Figure 2**), and elevations in HDL-C (WMD: 0.072 mmol/L [2.8 mg/dL], 95% CI: 0.053, 0.092, $p < 0.001$; $I^2 = 0\%$; **Figure 2**) following treatment with statins. No significant alteration in plasma TG concentrations was found (WMD: -0.16 mmol/L [-14.2 mg/dL], 95% CI: -0.61, 0.29, $p = 0.475$; $I^2 = 90.2\%$; **Figure 2**). All these effects were robust in sensitivity analysis, suggesting that the computed effect is not driven by any single study (**Supplemental Figure 1**).

Effect of individual statins on plasma lipids and lipoproteins concentrations

In subgroup analysis, no significant difference was found among different statins, each generally of moderate intensity, in terms of changing plasma concentrations of LDL-C, HDL-C and TG (**Figure 3**). However, atorvastatin was found to be more efficacious in reducing plasma total cholesterol concentrations ($p < 0.001$) (**Figure 3**).

Meta-regression

Meta-regression analysis was conducted to evaluate the association between changes in plasma lipid concentrations and duration of treatment and baseline lipid values as potential confounders of treatment response. None of the changes in the assessed lipid parameters were found to be significantly associated with treatment duration (**Figure 4**). With respect to baseline values, a significant association was found for total cholesterol (slope: 0.27, 95% CI: 0.05, 0.50, $p = 0.018$), but not LDL-C, HDL-C and triglycerides (**Figure 5**).

Publication bias

Visual inspection of funnel plots suggested an asymmetry in the effects on plasma HDL-C and TG concentrations, but not LDL-C and total cholesterol. Using the "trim and fill" method, 4 and 1 potentially missing studies were imputed for the meta-analyses of HDL-C and TG, respectively (**Figure 6**). These imputations did not change the statistical significance of the effect size (WMD: 0.08 mmol/L [3 mg/dL], 95% CI: 0.05, 0.10 [HDL-C] and WMD: -0.26 mmol/L [23 mg/dL], 95% CI: -0.70, 0.19 [TG]).

In addition to visual inspection of funnel plots, presence of publication bias was explored using Begg's rank correlation test, Egger's linear regression test, and the "fail safe N" test. Results of these tests are shown in **Supplemental Table 1**.

Safety of statin therapy

Adverse events reported in the included trials are summarized in **Supplemental Table 2**. Since the exact number of subjects experiencing adverse events was not provided in most of the

included studies, meta-analysis comparing the safety of statin therapy versus control was not performed.

DISCUSSIONS

To our knowledge, this meta-analysis of RCTs is the first to assess the effect of statins on plasma lipid concentrations in HIV infected individuals. Data from 12 trials following treatment with statins suggested significant reductions in plasma concentrations of LDL-C, total cholesterol and non-HDL-C, and elevations in HDL-C. No significant alteration in plasma TG concentration was found. All these effects were robust in sensitivity analysis, suggesting that the computed effect is not driven by any single study.

In the recent meta-analysis on this issue by Gili *et al.* (33) the efficacy and safety of different statins in the group of HIV-positive patients was evaluated. However, the authors included all available studies (both RCTs and observational), limiting the inferential strength of their data. Having all their available studies included, there were only 736 patients, whereas we included 697 patients in 12 RCTs. They noticed that rosuvastatin 10 mg/day and atorvastatin 10 mg/day provided the largest reduction in total cholesterol levels (mean -1.67 mmol/L [-64.68 mg/dL] and mean -1.44 mmol/L [-55.68 mg/dL], respectively], and atorvastatin 80 mg/day and simvastatin 20 mg/day provided the largest reduction in LDL-C [mean -2.10 mmol/L [-81.21 mg/dL] and -1.57 mmol/L [-60.71 mg/dL], respectively]. The mean discontinuation rate observed in their study was 0.12 per 100 person-years and was the highest with atorvastatin 10 mg/day (26.5 per 100 person-years) (33).

Due to drug-drug interactions through the cytochrome enzymes, concomitant use of statins in the context of previous therapy with protease inhibitors needs caution (34). Indeed, most of

the statins interfere with metabolism of anti-retroviral drugs due to the fact that they are metabolized *via* the cytochrome P450 3A4 isoform, inducing increased toxicity (13). These safety warnings have limited statin therapy in HIV-infected individuals receiving simultaneous antiretroviral therapy (35). Since pravastatin is a cytochrome P450 independent and water-soluble statin it seems it might be the most advantageous on plasma lipids in HIV-infected individuals (36). However, Fichtenbaum *et al.*, analyzing drug-to-drug interactions, demonstrated a significantly larger the median 24h area under the concentration-time curve (AUC_{24}) for simvastatin and atorvastatin, while pravastatin had a decreased AUC_{24} when given concomitantly with ritonavir and saquinavir (37).

The mechanism underlying the interactions between pravastatin and anti-retroviral drugs may be due to a competition at the cytochrome level that transports protein P-glycoprotein and may also be caused by genetic polymorphism (13). However, in HIV-infected patients on statin therapy, it has been recommended that plasma concentrations of protease inhibitors be evaluated to avoid drug-drug interaction (38). Current guidelines suggest that in HIV patients receiving protease inhibitors, fluvastatin and pravastatin are most safe to use, atorvastatin can be used at submaximal efficacy doses and administrated only with caution and monitoring, while lovastatin and simvastatin should not be used (35).

In HIV patients, rosuvastatin, pravastatin, and pitavastatin have been reported in clinical trials to have satisfactory safety profiles (39). Due to the safe pharmacokinetic profile of pitavastatin, the Evaluating the Use of Pitavastatin to Reduce the Risk of Cardiovascular Disease in HIV-Infected Adults (REPRIEVE) trial is an ongoing large randomized double-blind trial of 6,500 HIV-infected patients that will evaluate the efficacy of pitavastatin 4 mg versus placebo for primary CVD prevention (40). The REPRIEVE trial is currently funded by the National

Institutes of Health's National Heart, Lung, and Blood Institute (NHLBI), National Institute of Allergy and Infectious Diseases (NIAID) and AIDS Clinical Trials Group (40-42).

The present meta-analysis has several limitations. Most importantly, there were only several eligible RCTs, and most had relatively small numbers of patients. Furthermore, the included studies were heterogeneous: different statin preparations, doses, duration of treatment, study design, and duration of follow-up.

*In conclusion***,** in HIV patients, this meta-analysis suggested significant reductions in plasma concentrations of LDL-C, total cholesterol and non-HDL-C, and elevations in HDL-C, but no significant alteration in plasma TG following treatment with statins. Further large-scale, well-designed trials are required to fully address the differential effects on statins on lipid parameters in the context of HIV infection.

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Contributors: Maciej Banach 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. M.D., and S.U. contributed to the data acquisition, data analysis and interpretation, and drafting of the manuscript; A.S. contributed to the statistical analysis and the writing and revising of the manuscript; M.C-S. contributed to the data acquisition, drafting and critical revision of the manuscript; H.G., D.P.M., S.N., G.Y.H.L., S.G., S.S.M., P.M., J.R., P.P.T. 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.

Conflict of interest: This meta-analysis was written independently; no company or institution supported it financially. No authors have any conflict of interest concerning the preparation of this analysis. No professional writer was involved in the preparation of this meta-analysis. The meta-analysis will be presented during the European Society of Cardiology Annual Congress in Rome in August 2016 (abstract No. 302).

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TABLES LEGENDS:

Table 1. Demographic characteristics of the included studies.

Table 2. Risk of bias assessment in the studies included in this meta-analysis.

FIGURE LEGENDS:

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

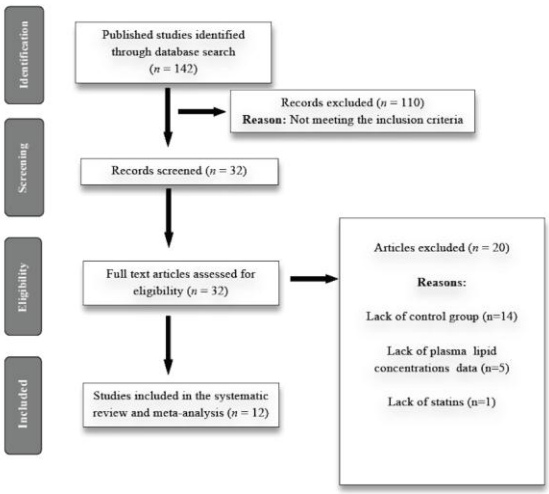
Figure 2. Forest plot displaying weighted mean difference and 95% confidence intervals for the impact of statin therapy on plasma concentrations of LDL-C, total cholesterol, HDL-C, triglycerides and non-HDL-C.

Figure 3. Subgroup meta-analysis for the impact of different statins on plasma concentrations of lipids.

Figure 4. Random-effects meta-regression plots of the association between mean changes in plasma concentrations of lipids and duration of statin treatment.

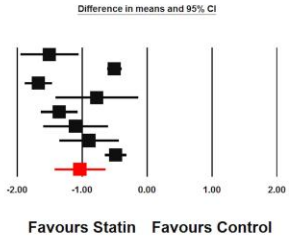
Figure 5. Random-effects meta-regression plots of the association between mean changes in plasma concentrations of lipids and baseline lipid values.

Figure 6. Funnel plot displaying publication bias in the studies reporting the impact of statin therapy on plasma concentrations of lipids.



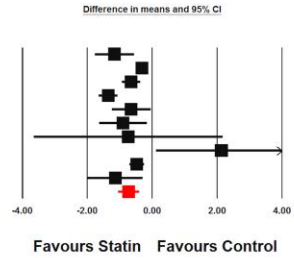
Total cholesterol

Study name	Difference in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Bonnet et al., 2007	-1.500	0.226	0.051	-1.943	-1.057	-6.629	0.000
Calmy et al., 2010	-0.500	0.056	0.003	-0.610	-0.390	-8.909	0.000
Ganesa et al., 2011	-1.670	0.108	0.012	-1.881	-1.459	-15.527	0.000
Hurlimann et al., 2006	-0.770	0.324	0.105	-1.405	-0.135	-2.375	0.018
Lo et al., 2015	-1.350	0.145	0.021	-1.634	-1.066	-9.331	0.000
Stein et al., 2014	-1.100	0.253	0.064	-1.596	-0.604	-4.348	0.000
Moyle et al., 2001	-0.890	0.232	0.054	-1.345	-0.435	-3.831	0.000
Mallon et al., 2006	-0.480	0.085	0.007	-0.647	-0.313	-5.623	0.000
	-1.030	0.199	0.039	-1.419	-0.641	-5.187	0.000



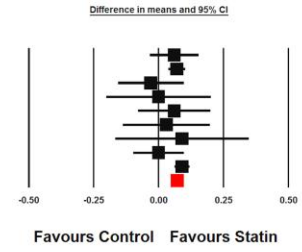
LDL-C

Study name	Difference in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Bonnet et al., 2007	-1.160	0.306	0.094	-1.760	-0.560	-3.788	0.000
Calmy et al., 2010	-0.300	0.057	0.003	-0.412	-0.188	-5.238	0.000
Eckard et al., 2014	-0.650	0.140	0.020	-0.925	-0.375	-4.638	0.000
Ganesa et al., 2011	-1.350	0.144	0.021	-1.632	-1.068	-9.391	0.000
Hurlimann et al., 2006	-0.640	0.300	0.090	-1.229	-0.051	-2.131	0.033
Lo et al., 2015	-0.890	0.373	0.139	-1.620	-0.160	-2.388	0.017
Stein et al., 2014	-0.730	1.481	2.194	-3.633	2.173	-0.493	0.622
Nakanjako et al., 2015	2.140	1.028	1.056	0.126	4.154	2.082	0.037
Montoya et al., 2012	-0.470	0.111	0.012	-0.688	-0.252	-4.234	0.000
Moyle et al., 2001	-1.130	0.429	0.184	-1.972	-0.288	-2.631	0.009
	-0.717	0.165	0.027	-1.040	-0.394	-4.352	0.000



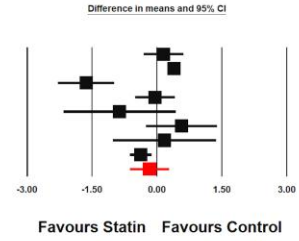
HDL-C

Study name	Difference in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Bonnet et al., 2007	0.060	0.048	0.002	-0.034	0.154	1.258	0.209
Calmy et al., 2010	0.070	0.016	0.000	0.039	0.101	4.412	0.000
Funerburg et al., 2015	-0.030	0.064	0.004	-0.156	0.096	-0.466	0.641
Hurlimann et al., 2006	0.000	0.103	0.011	-0.201	0.201	0.000	1.000
Lo et al., 2015	0.060	0.071	0.005	-0.079	0.199	0.847	0.397
Stein et al., 2014	0.030	0.085	0.007	-0.137	0.197	0.353	0.724
Nakanjako et al., 2015	0.090	0.131	0.017	-0.166	0.346	0.689	0.491
Moyle et al., 2001	0.000	0.049	0.002	-0.096	0.096	0.000	1.000
Mallon et al., 2006	0.090	0.015	0.000	0.061	0.119	6.122	0.000
	0.072	0.010	0.000	0.053	0.092	7.283	0.000



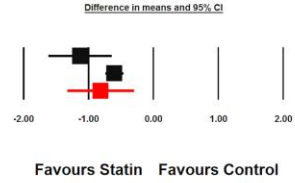
Triglycerides

Study name	Difference in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Bonnet et al., 2007	0.160	0.231	0.053	-0.292	0.612	0.694	0.488
Calmy et al., 2010	0.400	0.048	0.002	0.306	0.494	8.379	0.000
Hurlimann et al., 2006	-1.630	0.330	0.109	-2.277	-0.983	-4.937	0.000
Lo et al., 2015	-0.040	0.230	0.053	-0.491	0.411	-0.174	0.862
Stein et al., 2014	-0.860	0.659	0.435	-2.152	0.432	-1.304	0.192
Nakanjako et al., 2015	0.570	0.416	0.173	-0.246	1.386	1.369	0.171
Moyle et al., 2001	0.180	0.608	0.369	-1.011	1.371	0.296	0.767
Mallon et al., 2006	-0.370	0.126	0.016	-0.616	-0.124	-2.942	0.003
	-0.164	0.230	0.053	-0.615	0.286	-0.714	0.475



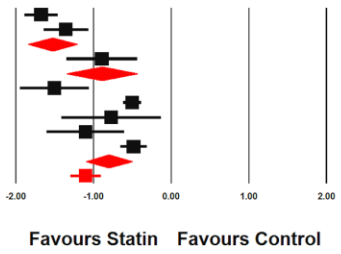
Non-HDL-C

Study name	Difference in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Stein et al., 2014	-1.130	0.247	0.061	-1.614	-0.646	-4.580	0.000
Mallon et al., 2006	-0.600	0.072	0.005	-0.741	-0.459	-8.355	0.000
	-0.812	0.260	0.067	-1.321	-0.303	-3.128	0.002



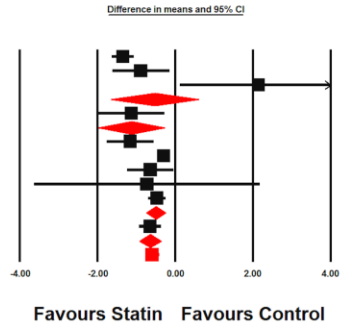
Total cholesterol

Group by Statin type	Study name	Difference in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Atorvastatin	Ganesa et al., 2011	-1.670	0.108	0.012	-1.881	-1.459	-15.527	0.000
Atorvastatin	Lo et al., 2015	-1.350	0.145	0.021	-1.634	-1.066	-9.331	0.000
Atorvastatin		-1.525	0.159	0.025	-1.837	-1.212	-9.569	0.000
Lovastatin	Moyle et al., 2001	-0.890	0.232	0.054	-1.345	-0.435	-3.831	0.000
Lovastatin		-0.890	0.232	0.054	-1.345	-0.435	-3.831	0.000
Pravastatin	Bonnet et al., 2007	-1.500	0.226	0.051	-1.943	-1.057	-6.629	0.000
Pravastatin	Calmy et al., 2010	-0.500	0.056	0.003	-0.610	-0.390	-8.909	0.000
Pravastatin	Hurlimann et al., 2006	-0.770	0.324	0.105	-1.405	-0.135	-2.375	0.018
Pravastatin	Stein et al., 2014	-1.100	0.253	0.064	-1.596	-0.604	-4.348	0.000
Pravastatin	Mallon et al., 2006	-0.480	0.085	0.007	-0.647	-0.313	-5.623	0.000
Pravastatin		-0.798	0.151	0.023	-1.093	-0.503	-5.304	0.000
Overall		-1.095	0.099	0.010	-1.289	-0.901	-11.065	0.000



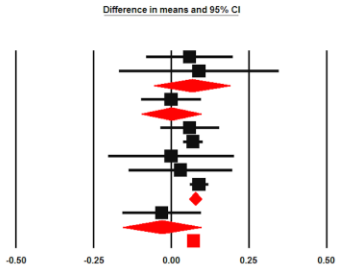
LDL-C

Group by Statin type	Study name	Difference in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Atorvastatin	Ganesa et al., 2011	-1.350	0.144	0.021	-1.632	-1.068	-9.391	0.000
Atorvastatin	Lo et al., 2015	-0.890	0.373	0.139	-1.620	-0.160	-2.388	0.017
Atorvastatin	Nakanjako et al., 2015	2.140	1.028	1.056	0.126	4.154	2.082	0.037
Atorvastatin		-0.536	0.572	0.327	-1.656	0.584	-0.938	0.348
Lovastatin	Moyle et al., 2001	-1.130	0.429	0.184	-1.972	-0.288	-2.631	0.009
Lovastatin		-1.130	0.429	0.184	-1.972	-0.288	-2.631	0.009
Pravastatin	Bonnet et al., 2007	-1.160	0.306	0.094	-1.760	-0.560	-3.788	0.000
Pravastatin	Calmy et al., 2010	-0.300	0.057	0.003	-0.412	-0.188	-5.238	0.000
Pravastatin	Hurlimann et al., 2006	-0.640	0.300	0.090	-1.229	-0.051	-2.131	0.033
Pravastatin	Stein et al., 2014	-0.730	1.481	2.194	-3.633	2.173	-0.493	0.622
Pravastatin	Montoya et al., 2012	-0.470	0.111	0.012	-0.688	-0.252	-4.234	0.000
Pravastatin		-0.509	0.126	0.016	-0.756	-0.261	-4.031	0.000
Rosuvastatin	Eckard et al., 2014	-0.650	0.140	0.020	-0.925	-0.375	-4.638	0.000
Rosuvastatin		-0.650	0.140	0.020	-0.925	-0.375	-4.638	0.000
Overall		-0.596	0.090	0.008	-0.773	-0.418	-6.586	0.000



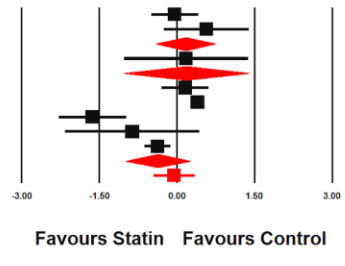
HDL-C

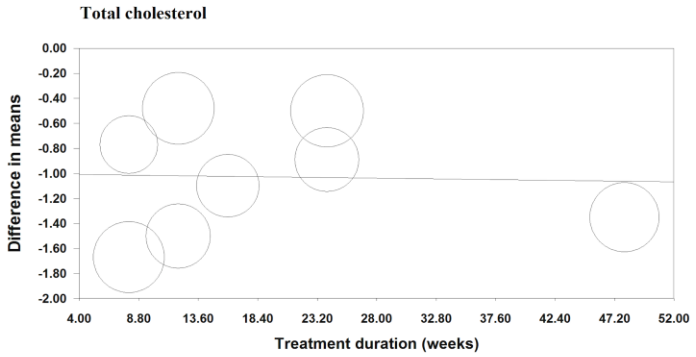
Group by Statin type	Study name	Difference in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Atorvastatin	Lo et al., 2015	0.060	0.071	0.005	-0.079	0.199	0.847	0.397
Atorvastatin	Nakanjako et al., 2015	0.090	0.131	0.017	-0.166	0.346	0.689	0.491
Atorvastatin		0.067	0.062	0.004	-0.055	0.189	1.073	0.283
Lovastatin	Moyle et al., 2001	0.000	0.049	0.002	-0.096	0.096	0.000	1.000
Lovastatin		0.000	0.049	0.002	-0.096	0.096	0.000	1.000
Pravastatin	Bonnet et al., 2007	0.060	0.048	0.002	-0.034	0.154	1.258	0.209
Pravastatin	Calmy et al., 2010	0.070	0.016	0.000	0.039	0.101	4.412	0.000
Pravastatin	Hurlimann et al., 2006	0.000	0.103	0.011	-0.201	0.201	0.000	1.000
Pravastatin	Stein et al., 2014	0.030	0.085	0.007	-0.137	0.197	0.353	0.724
Pravastatin	Mallon et al., 2006	0.090	0.015	0.000	0.061	0.119	6.122	0.000
Pravastatin		0.078	0.010	0.000	0.058	0.099	7.529	0.000
Rosuvastatin	Funerburg et al., 2015	-0.030	0.064	0.004	-0.156	0.096	-0.466	0.641
Rosuvastatin		-0.030	0.064	0.004	-0.156	0.096	-0.466	0.641
Overall		0.072	0.010	0.000	0.053	0.092	7.283	0.000

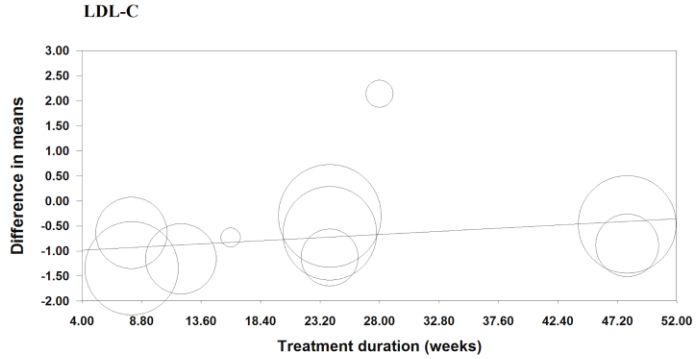


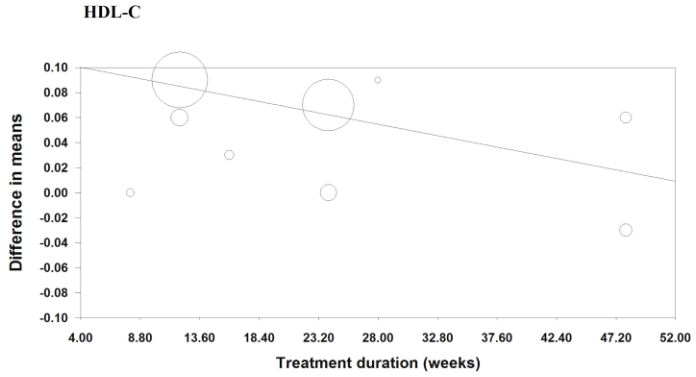
Triglycerides

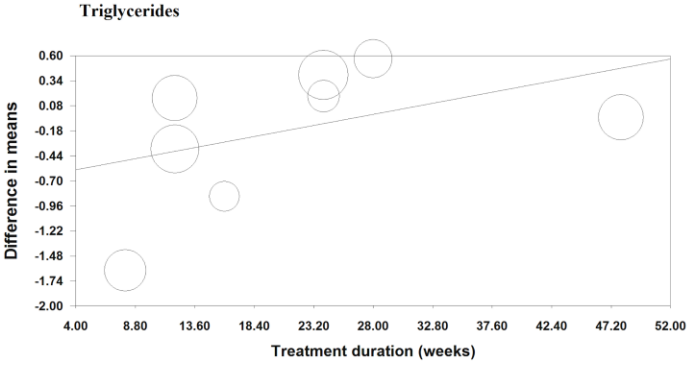
Group by Statin type	Study name	Difference in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Atorvastatin	Lo et al., 2015	-0.040	0.230	0.053	-0.491	0.411	-0.174	0.862
Atorvastatin	Nakanjako et al., 2015	0.570	0.416	0.173	-0.246	1.386	1.369	0.171
Atorvastatin		0.166	0.289	0.083	-0.399	0.732	0.576	0.564
Lovastatin	Moyle et al., 2001	0.180	0.608	0.369	-1.011	1.371	0.296	0.767
Lovastatin		0.180	0.608	0.369	-1.011	1.371	0.296	0.767
Pravastatin	Bonnet et al., 2007	0.160	0.231	0.053	-0.292	0.612	0.694	0.488
Pravastatin	Calmy et al., 2010	0.400	0.048	0.002	0.306	0.494	8.379	0.000
Pravastatin	Hurlimann et al., 2006	-1.630	0.330	0.109	-2.277	-0.983	-4.937	0.000
Pravastatin	Stein et al., 2014	-0.860	0.659	0.435	-2.152	0.432	-1.304	0.192
Pravastatin	Mallon et al., 2006	-0.370	0.126	0.016	-0.616	-0.124	-2.942	0.003
Pravastatin		-0.369	0.313	0.098	-0.983	0.246	-1.176	0.240
Overall		-0.051	0.200	0.040	-0.444	0.342	-0.254	0.800



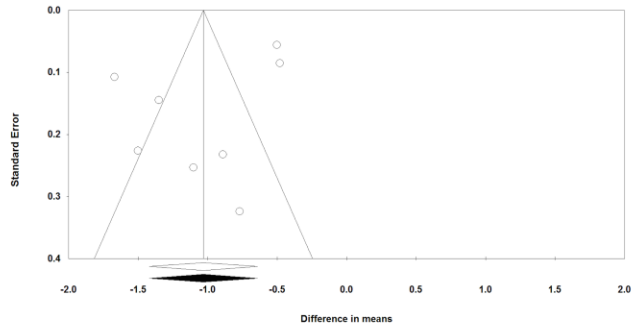




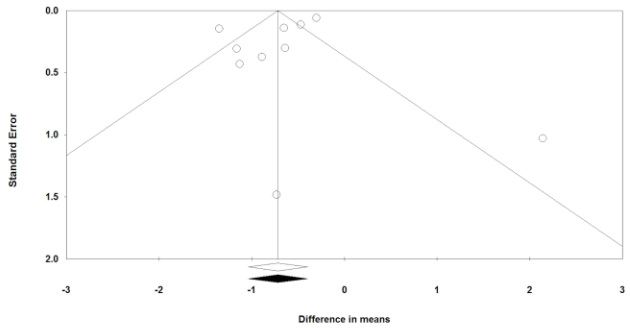




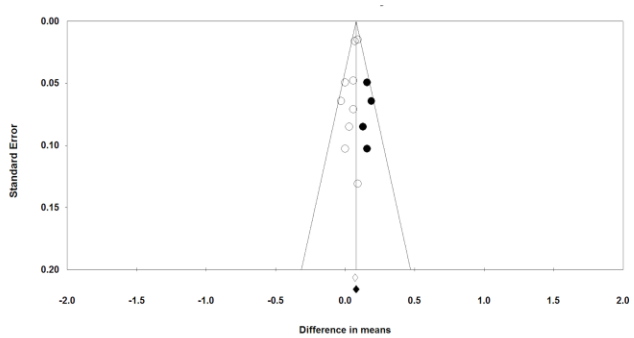
Total cholesterol



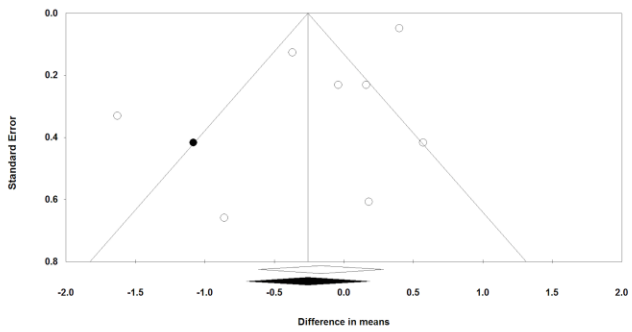
LDL-C



HDL-C

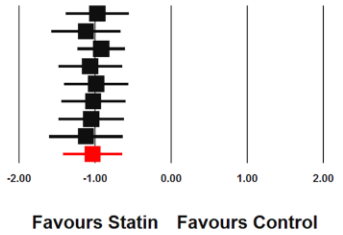


Triglycerides



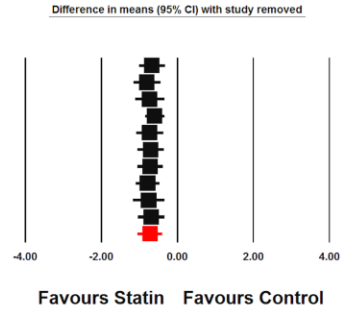
Total cholesterol

Study name	Point	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Bonnet et al., 2007	-0.966	0.209	0.044	-1.377	-0.556	-4.613	0.000
Calmy et al., 2010	-1.115	0.231	0.053	-1.567	-0.663	-4.836	0.000
Ganesa et al., 2011	-0.916	0.157	0.025	-1.224	-0.609	-5.842	0.000
Hurlimann et al., 2006	-1.060	0.213	0.045	-1.478	-0.643	-4.976	0.000
Lo et al., 2015	-0.982	0.213	0.046	-1.400	-0.563	-4.598	0.000
Stein et al., 2014	-1.021	0.215	0.046	-1.442	-0.600	-4.751	0.000
Moyle et al., 2001	-1.049	0.217	0.047	-1.475	-0.623	-4.828	0.000
Mallon et al., 2006	-1.117	0.244	0.060	-1.596	-0.638	-4.568	0.000
	-1.030	0.199	0.039	-1.419	-0.641	-5.187	0.000



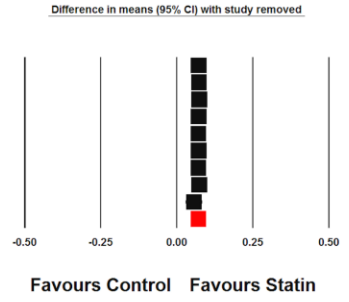
LDL-C

Study name	Point	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Bonnet et al., 2007	-0.666	0.172	0.030	-1.004	-0.329	-3.871	0.000
Calmy et al., 2010	-0.795	0.179	0.032	-1.145	-0.445	-4.453	0.000
Eckard et al., 2014	-0.723	0.194	0.038	-1.104	-0.342	-3.722	0.000
Ganesa et al., 2011	-0.590	0.125	0.016	-0.836	-0.345	-4.707	0.000
Hurlimann et al., 2006	-0.725	0.178	0.032	-1.075	-0.375	-4.063	0.000
Lo et al., 2015	-0.700	0.174	0.030	-1.041	-0.358	-4.009	0.000
Stein et al., 2014	-0.716	0.167	0.028	-1.044	-0.389	-4.291	0.000
Nakanjako et al., 2015	-0.778	0.160	0.026	-1.092	-0.465	-4.869	0.000
Montoya et al., 2012	-0.747	0.209	0.044	-1.156	-0.338	-3.582	0.000
Moyle et al., 2001	-0.682	0.171	0.029	-1.019	-0.346	-3.980	0.000
	-0.717	0.165	0.027	-1.040	-0.394	-4.352	0.000



HDL-C

Study name	Point	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Bonnet et al., 2007	0.073	0.010	0.000	0.053	0.093	7.178	0.000
Calmy et al., 2010	0.074	0.013	0.000	0.049	0.098	5.797	0.000
Funerburg et al., 2015	0.075	0.010	0.000	0.055	0.094	7.443	0.000
Hurlimann et al., 2006	0.073	0.010	0.000	0.053	0.092	7.317	0.000
Lo et al., 2015	0.072	0.010	0.000	0.053	0.092	7.235	0.000
Stein et al., 2014	0.073	0.010	0.000	0.053	0.092	7.291	0.000
Nakanjako et al., 2015	0.072	0.010	0.000	0.053	0.092	7.251	0.000
Moyle et al., 2001	0.075	0.010	0.000	0.055	0.095	7.435	0.000
Mallon et al., 2006	0.057	0.013	0.000	0.031	0.084	4.273	0.000
	0.072	0.010	0.000	0.053	0.092	7.283	0.000



Triglycerides

Study name	Point	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Bonnet et al., 2007	-0.223	0.266	0.071	-0.745	0.299	-0.838	0.402
Calmy et al., 2010	-0.278	0.237	0.056	-0.742	0.187	-1.170	0.242
Hurlimann et al., 2006	0.054	0.194	0.038	-0.326	0.435	0.279	0.780
Lo et al., 2015	-0.189	0.264	0.070	-0.706	0.328	-0.717	0.473
Stein et al., 2014	-0.111	0.238	0.056	-0.577	0.354	-0.468	0.639
Nakanjako et al., 2015	-0.256	0.249	0.062	-0.744	0.232	-1.029	0.304
Moyle et al., 2001	-0.195	0.243	0.059	-0.671	0.282	-0.800	0.423
Mallon et al., 2006	-0.129	0.264	0.070	-0.647	0.388	-0.490	0.624
	-0.164	0.230	0.053	-0.615	0.286	-0.714	0.475

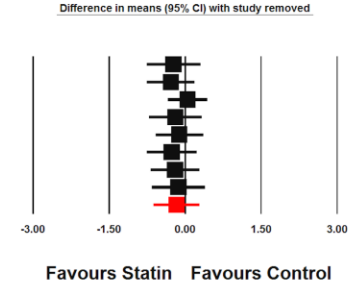


Table 1. Demographic characteristics of the included studies.

Study		Bonnet *et al.*(21)	Calmy *et al.*(22)	Eckard *et al.*(23)	Funderburg *et al.*(24)	Ganesan *et al.*(25)	Hürlimann*et al.*(26)	Lo *et al.* (27)	Stein *et al.*(28)	Nakanjakoet *al.*(29)	Montoya *et al.*(30)	Moyle *et al.*(31)	Mallon *et al.*(32)
Year		2007	2010	2014	2015	2011	2006	2015	2004	2015	2012	2001	2006
Location		France	Australia & Switzerland	USA	USA	USA	Switzerland	USA	USA	Uganda	Colombia	UK	Australia
Design		Randomized, double-blind placebo-controlled, trial	Randomized, placebo controlled clinical trial	Randomized, double-blind, placebo-controlled trial	Randomized, double-blind placebo-controlled trial	Randomized, double-blind, placebo-controlled crossover trial	Randomized, double blind, placebo controlled crossover, trial	Randomized, double-blind, placebo-controlled trial	Placebo-controlled, double-blind, crossover trial	Randomized double-blind placebo-controlled crossover trial	Randomized, double-blinded, placebo-controlled trial	Randomized, open-label comparative trial	Randomized, double-blind, placebo-controlled trial
Duration of trial		12 weeks	24 weeks	24 weeks	48 weeks	8 weeks	8 weeks	48 weeks	16 weeks	12 weeks	48 weeks	24 weeks	12 weeks
Inclusion criteria		Patients were tested positive for anti-HIV antibodies, had been receiving stable antiretroviral therapy including at least one PI for ≥3 months, had a plasma HIV RNA level of <50 copies/mL for ≥3 months before randomization, a TC ≥5.5 mmol/L with LDL-C ≥ 3.4 mmol/L on fasting	Subcutaneous lipoatrophy in at least two body sites (of moderate or greater severity in at least one site) according to both the patient and their enrolling physician; stable antiretroviral therapy (ART) and plasma HIV viral load <50 HIV-1 RNA copies/mL for at least the preceding 3 months	HIV-infected adults ≥18 years old who had a fasting LDL cholesterol level of ≤130 mg/dL and either a hsCRP level of ≥2 mg/L and/or expression of CD38 and HLA-DR antigens on ≥19% of CD8+ T cells at screening, which occurred≤30 days before enrollment	Patients aged 18 years or older, without known coronary disease or diabetes, and on stable ART for at least 3months and cumulative ART duration of at least 6 months, with HIV-1 RNA <1000 copies per milliliter and fasting LDL-C ≤130 mg/dL and fasting triglycerides ≤500 mg/dL	HIV-infected adults not receiving antiretroviral therapy (ART) with a CD4+ cell count >350 cells/µL, HIV-1 RNA >1000copies/mL, serum low-density lipoprotein (LDL) cholesterol level <130 mg/dL, and serum alanine aminotransferase and aspartate aminotransferase levels, <1.5 times the upper limit of normal	HIV infection, and protease inhibitor-containing anti-retroviral combination therapy for at least four months, which was unchanged for two months	Patients with HIV disease, no history of cardiovascular disease or cardiac symptoms, and evidence of subclinical coronary atherosclerosis, defined by presence of one or more plaques on CCTA but without clinically significant stenosis, defined as greater than 50% left main stenosis or greater than 70% stenosis in any major vessel	Patients with HIV infection of≥6-month duration, undergoing a stable antiretroviral regimen that included a PI for at least 3 months, LDL cholesterol levels >3.36 mmol/L and either triglyceride levels >3.88 mmol/L or high-density lipoprotein (HDL) cholesterol	Individuals with CD4 increase <295 cells/µL after seven years of suppressive cART	Asymptomatic HIV-infected adults who were HAART naive, with a peripheral blood CD4+ T cell count ≥350 cells/mL and detectable viral load yet lower than 100,000 copies/mL	Patients with viral load < 500 copies/ml and cholesterol > 6.5 mmol/l (240 mg/dl)	HIV-infected men (age> 18 years) stable current PI therapy (beginning not less than12 weeks prior to screening with little likelihood of change to the ART regimen expected during the study)and fasting serum total cholesterol > 6.5 mmol/l

		status after at least 12 hours and after 3 months of standardized dietary advice							levels <1.07 mmol/L.				
Statin form		Pravastatin	Pravastatin	Rosuvastatin	Rosuvastatin	Atorvastatin	Pravastatin	Atorvastatin	Pravastatin	Pravastatin	Lovastatin	Pravastatin	Pravastatin
Statin intervention		40 mg/ day	40mg/day	10 mg/day	10 mg/day	80 mg/day	40 mg/day	20/40 mg/day	40 mg/day	40 mg/day	40 mg/day	40mg/day	40 mg/day
Participants	Case	12	10	67	72	22	29	17	20	15	51	14	14
	Control	9	12	69	75			20			53	13	17
Safety		Myalgias (grade 2) were recorded in three patients of the pravastatin group (including one with a two-fold increase of creatine phosphokinase	Five participants (11%) developed sustained grade 3 or 4 hypertriglyceridaemia (four of whom had initiated LPV/r at screening), three patients developed a grade 3 or 4 elevation in creatine kinase and one patient developed grade 3 thrombocytopenia. Two serious adverse events were reported; one participant with known cardiomyopathy was hospitalized for third-degree heart block at week 1 (uridine	One subject withdrew because of a potential adverse event (on day 4 of study, grade 2 myalgias caused the subject to refuse to continue in the study). One additional subject in the statin group stopped treatment at week 5 because of hospitalization for hydration secondary to grade 3 myalgias without rhabdomyol	Two subjects withdrew due to grade 2 myalgias with normal CPK levels; both were on placebo. One additional subject in the statin group stopped treatment at week 5 because of hospitalization for hydration to treat grade 3 myalgias without rhabdomyolysis or renal compromise, but continued to be followed on study,	No grade 3 or 4 elevations in liver-associated enzymes were observed during the study. Three participants had grade 3 elevations in creatinine phosphokinase (CPK) levels. All 3 participants reported myalgias and noted a temporal increase in their physical exercise regimens. Cessation of their altered exercise schedule, without	Values for plasma creatinine, creatinine kinase, aspartate aminotransferase, alanine aminotransferase, and glucose were within normal limits at baseline and did not change during the study.	Myalgias and liver-function-test abnormalities occurred in both treatment and placebo groups at similar rates without any differences in the timing of adverse events. No adverse event led to discontinuation from the study. One participant had myalgias and was reduced to 10 mg, which was tolerated for the duration of the trial. After unblinding at	One subject had an asymptomatic increase in CK >2-times ULN, and another subject had an asymptomatic increase in CK >3-times ULN. mild myalgia developed in 1 subject, and muscle aches characterized as “severe” developed in 2	Myalgias as the commonest in six individuals (three in atorvastatin and three in placebo arms), followed by chest pain in four individuals (three in atorvastatin and one in placebo arms), headache in four individuals (one in atorvastatin and three in placebo arms) and arthralgia	Only two patients suspended the medication due to effects related to lovastatin: one due to an erythematous maculopapular rash during the first week, and the second one due to the serum aminotransferase concentration higher than those allowed by the study protocol	No episodes of myalgia or myositis occurred and creatinine kinase remained stable in both groups throughout 24 weeks of follow-up. Additionally, hepatic transaminase values did not significantly change, although values were significantly higher at baseline in the pravastatin group	No significant changes in serum creatinine, bilirubin, alanine aminotransferase or alkaline phosphatase

			and pravastatin arm) and another participant was hospitalized for gastroenteritis at baseline (uridine arm).	ysis or renal compromise but continued to be followed during the study but without receiving the study drug.	off study drug, and myalgia resolved soon after study drug was discontinued.	discontinuing treatment assignments, resulted in resolution of the CPK elevations and symptoms.		the conclusion of the study, this participant had received atorvastatin. A second participant had a dose reduction from 40 mg back to 20 mg because of a rise in alanin aminotransferase	subjects.	in three individuals (two in atorvastatin and one in placebo arm). Other expected adverse events included backache (1), neck pain (1), left forearm pain (1); only reported in the atorvastatin arm)			
Age (years)	Case	42 (39–47)	46 (42-57)	45.6 (41.1–51.4)	45.6 (41.1–51.4)	30 (25–38)	43*	52.2±3.8	44.1±1.6	41 (40–50)	32 (26-39)	NS	52±12
	Control	41 (38-50)	47 (44-52)	46.9 (39.2–53.6)	46.9 (39.2–53.6)	30 (25–38)		50.0±5.6		47 (43–51)	31 (27-38)	NS	43±9
Male (%)	Case	92	100	81	81	100	79	79	90	53.3	87	100	100
	Control	78	100	76	76	100	79	81	90	33.3	84	100	100
BMI (kg/m^2)	Case	NS	24 (24-25)	26.6 (23.4–30.0)	26.6 (23.4–30.0)	NS	22.9 (21.4–25.1)	25.6±2.9	NS	20.8 (19.5–21.6)	NS	23.1 (21.7-24.4)	24±1.0
	Control	NS	24 (21-26)	27.2 (23.5–30.5)	27.2 (23.5–30.5)	NS	22.9 (21.4–25.1)	25.8±4.8	NS	24.0 (21.1–26.4)	NS	23.6 (21.9-25.3)	25±3.5
SBP (mmHg)	Case	NS	NS	122 (112–136)	122 (112–136)	NS	120 (114–128)	117±13	125.4±3.2	110 (100–149)	NS	NS	130±14
	Control	NS	NS	120 (110–132)	120 (110–132)	NS	120 (114–128)	119±16	125.4±3.2	140 (112–163)	NS	NS	120±12
DBP (mmHg)	Case	NS	NS	79 (73–85)	79 (73–85)	NS	77 (71–83)	73±8	NS	74 (65–82)	NS	NS	70±15

	Control	NS	NS	80 (72–83)	80 (72–83)	NS	77 (71–83)	76±10	NS	74 (65–82)	NS	NS	80±14
Total Cholesterol (mmol/L)/ mg/dl	Case	6.1 (5.8–6.3) / 235,52 (223,94-243,24)	5.6 (4.5-6.4) / 216,21 (173,74-247,10)	NS	NS	4.34 (3.72–4.45) / 167,57 (143,62-171,81)	6.4 (6.0–7.4) / 247,10 (231,66-285,71)	5.14±0.98 / 198,45±37,83	5.58±0.40 / 215,44±15,44	NS	NS	7.5 (6.7±8.3) / 289,58 (258,69±320,46)	7.6±1.7 / 293,44±65,64
	Control	6.4 (6.1–7.7) / 247,10 (235,58-297,29)	5.6 (4.6-6.2) / 216,21 (177,60-239,38)	NS	NS	4.34 (3.72–4.45) / 167,57 (143,63-171,81)	6.4 (6.0–7.4) / 247,10 (231,66-285,71)	4.97±0.70 / 191,89±27,02)	5.58±0.40 / 215,44±15,44	NS	NS	7.4 (6.8±7.9) / 285,71 (262,55±305,02)	7.6±1.4 / 293,44±54,05
LDL-C (mmol/L) /mg/dl	Case	4.1 (3.7–4.6) / 158,30 (142,86-177,60)	2.8 (2.4-3.3) / 108,10 (92,66-127,41)	2.48 (1.96-2.77) / 95,75 (75,67-106,95)	NS	2.50 (2.25–2.82) / 96,52 (86,87-108,88)	3.7 (2.8–4.2) / 142,86 (108,10-162,16)	3.20±0.95 / 123,55±36,68)	3.47±0.32 / 133,97±12,35	3.1 (2.2-4.9) / 119,69 (84,94-189,19)	2.63(2.20-3.28) 101,54(84,94-126,64)	4.65 (4.1±5.2) / 179,53 (158,30±200,77)	NS
	Control	3.9 (3.7–4.8) / 150,58 (142,85-185,33)	3.5 (2.5-4.1) / 135,13 (96,52-158,30)	2.50 (1.99-3.13) / 96,52 (76,83-120,84)	NS	2.50 (2.25–2.82) / 96,52 (86,87-108,88)	3.7 (2.8–4.2) / 142,85 (108,10-162,16)	3.23±0.83 / 124,71±32,04	3.47±0.32 / 133,97±12.35	4.9 (2.4-6.7) / 189,19 (92,66-258,68)	2.53 (2.30-3.10) / 97,68 (88,80-119,69)	4.68 (3.89±5.47) / 180,69 (150,19±211,19)	NS
HDL-C (mmol/L) /mg/dl	Case	0.9 (0.8–1.1) / 34,74 (30,88-42,47)	1 (0.9-1.3) / 38,61 (34,74-50,19)	NS	1.21 (0.98-1.49) / 46,71 (37,84-57,53)	NS	1.2 (1.1–1.6) / 46,33 (42,47-61,77)	1.34±0.50 / 51,74±19,30	0.94±0.07 / 36,29±2,70	1.7 (1.6-1.8) / 65,63 (61,77-69,49)	NS	0.94 (0.79±1.08) / 36,29 (30,50±41,69)	1.1±0.4 / 42,47±15,44
	Control	1.0 (0.8–1.1) / 38,61 (30,88-42,47)	1.1 (0.81-1.2) / 42,47 (31,27-46,33)	NS	1.19 (0.96-1.47) / 45,94 (37,06-56,75)	NS	1.2 (1.1–1.6) 46,33 / (42,47-61,77)	1.31±0.39 / 50,57±15,058)	0.94±0.07 / 36,29±2,70	1.7 (1.5-2.0) / 65,63 (57,91-77,22)	NS	0.87 (0.72±1.02) / 33,59 (27,79±39,38)	1.1±0.4 / 42,47±15.44)
Triglycerides (mmol/L) /mg/dl	Case	2.0 (1.1–3.3) / 177 (97,35-292,05)	3.9 (2.0-6.2) / 345,15 (177-548,7)	NS	NS	NS	3.0 (2.1–4.0) / 265,5 (185,85-354)	1.36 (1.10-2.31) / 120,36 (97,35-204,43)	3.78±0.67 / 334,53±59,29	1.6 (1.1-2.4) / 141,6 (97,35-212,4)	NS	3.96 (2.84±6.52) / 350,46 (251,34±577,02)	3.8±4.1 / 336,3±362,85
	Control	3.2 (2.1–4.4) / 283,2 (185,85-389,4)	2.3 (1.5-3.5) / 203,55 (132,75-309,75)	NS	NS	NS	3.0 (2.1–4.0) / 265,5 (185,85-354)	1.28 (1.04-1.53) / 113,28 (92,04-135,40)	3.78±0.67 / 334,53±59,29	2.0 (1.4-3.2) / 177 (123,9-283,2)	NS	4.06 (2.20±5.97) / 359,31 (194,7±528,34)	4.9±7.8 / 433,65±690,3
Non-HDL-C (mmol/L) /mg/dl	Case	NS	NS	NS	NS	NS	NS	NS	4.64±0.37 / 179,15±14,28	NS	NS	NS	6.3±1.8 / 243,24±69,49

	Control	NS	NS	NS	NS	NS	NS	NS	4.64±0.37 / 179,15±14,28	NS	NS	NS	6.5±1.9 / 251.35±73.47

Values are expressed as mean ± SD or median (interquartile range);*only median.

ABBREVIATIONS: SD: standard deviation; BMI: body mass index; NS: not stated; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol; SBP: systolic blood pressure; DBP: diastolic blood pressure; hs-CRP: high-sensitivity C-reactive protein; cART: combination antiretroviral therapy; HAART: highly active antiretroviral therapy; PI: protease inhibitors; CCTA: CT angiography

Table 2. Risk of bias assessment in the studies included in this meta-analysis.

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
Bonnet *et al.* 2007(21)	L	L	L	U	L	L	L
Calmy *et al.* 2010(22)	L	L	H	U	L	L	L
Eckard *et al.* 2014(23)	U	U	L	L	L	L	L
Funderburg *et al.* 2015(24)	L	L	L	U	L	L	L
Ganesan *et al.* 2011(25)	U	U	L	L	L	L	L
Hürlimann *et al.* 2006(26)	U	U	L	U	L	L	L
Lo *et al.* 2015(27)	L	L	L	L	L	L	L
Stein *et al.* 2004(28)	U	U	L	U	L	L	L
Nakanjako *et al.* 2015(29)	L	L	L	L	L	L	L
Montoya *et al.* 2012(30)	L	L	L	L	L	L	L
Moyle *et al.* 2001(31)	L	L	H	H	L	L	L
Mallon *et al.* 2006(32)	U	L	L	U	L	L	L

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