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STATIN THERAPY REDUCES PLASMA ENDOTHELIN-1 CONCENTRATIONS: A META-ANALYSIS OF 15 RANDOMIZED CONTROLLED TRIALS

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ABSTRACT:

OBJECTIVE: Raised plasma endothelin-1 (ET-1) levels may be a risk factor for vascular dysfunction and cardiovascular (CV) disease. This meta-analysis assessed the effect of statins on circulating ET-1 concentrations

METHODS AND RESULTS: The search included PUBMED, Cochrane Library, Web of Science, Scopus, and EMBASE up to September 30, 2014 to identify randomized controlled trials (RCTs) with ET-1 measurement during statin therapy. Quantitative data synthesis was performed using a random-effects model, with weighed mean difference (WMD) and 95% confidence interval (CI) as summary statistics. Data from 15 RCTs showed that statin therapy significantly reduces plasma ET-1 concentrations (WMD: -0.30 pg/mL, 95%CI: -0.47, -0.13; p<0.01). This effect was robust in sensitivity analysis, and not largely affected by the duration of statin therapy (<12 weeks – WMD: -0.51 pg/mL, 95%CI: -0.89, -0.14, p<0.01; >12 week – WMD: -0.19 pg/mL, 95%CI: -0.49, -0.05; p=0.01; >40 mg/day – WMD: -0.38 pg/mL, 95%CI: -0.68, -0.08; p=0.01). Lipophilic (atorvastatin, simvastatin, fluvastatin, and cerivastatin – WMD: -0.34 pg/mL, 95%CI: -0.55, -0.13; p<0.01), but not a hydrophilic statin (pravastatin – WMD: -0.18 pg/mL, 95%CI: -0.44 -0.08; p>0.05) had a significant effect in promoting ET-1 reduction.

CONCLUSIONS: Statin therapy significantly reduces circulating ET-1 concentrations, regardless of treatment duration or dose of statins. This effect of statins may be influenced by statin lipophilicity. There is a need to establish whether lowering ET-1 levels has a beneficial effect on CV events.

Keywords: endothelin-1, endothelial dysfunction, lipophilicity, statins, therapy.

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BACKGROUND

Atherosclerosis leads to cardiovascular diseases (CVD), a major cause of morbidity and mortality ^{1, 2}. The endothelium plays a role in atherogenesis, and endothelial dysfunction is considered to be involved in the onset of CVD and its progression ². Endothelial dysfunction results in reduced nitric oxide and prostacyclin bioavailability, vasoconstriction, oxidative stress, inflammation, and platelet activation ^{3, 4}.

Among molecules that may modulate endothelial function, endothelin-1 (ET-1) is a peptide, which is primarily produced by vascular endothelial cells ⁵. ET-1 was first identified as a vasoconstrictor ⁶. The synthesis of ET-1 starts from precursor peptides; endothelin-converting enzyme converts pro-endothelin to ET-1 ⁷. ET-1 is multifunctional, and promotes inflammation and cell proliferation within arterial vessel walls ⁵. The synthesis of ET-1 is mediated by various factors, including oxidized low-density lipoprotein (LDL), platelet activation, and hypoxia ⁸⁻¹⁰. Conversely, ET-1 may also induce LDL oxidation and platelet activation ¹¹. Thus, overproduction of ET-1 may be associated with increased risk for CVD ⁵. The control of ET-1 expression might provide benefits against the development of atherosclerosis and CVD events. Consistent with this is the observation that antagonism of the ET-1 system can modify atherogenesis ¹².

Many clinical trials have reported the beneficial effects of statins in CVD prevention ¹³⁻¹⁶. Recently, attention has been paid to the pleiotropic actions of statins beyond simple cholesterollowering ¹⁷⁻¹⁹. In experimental studies, statins can inhibit ET-1 production ²⁰; however, **findings concerning changes in ET-1 concentrations following statin therapy have been inconsistent.** Therefore, in the present meta-analysis we evaluated the impact of statin therapy on circulating ET-1 concentrations.

METHODS

Search Strategy

This study was designed according to the guidelines of the 2009 preferred reporting items for systematic reviews and meta-analysis (PRISMA) statement ²¹. Our search included SCOPUS (http://www.scopus.com), Medline (http://www.ncbi.nlm.nih.gov/pubmed), Web of Science (http://apps.webofknowledge.com), and Cochrane Library (www.thecochranelibrary.com/) databases. It was limited to randomized controlled trials (RCTs) carried out from January 1, 1970 to September 30, 2014, investigating the potential effects of statin therapy on ET-1 concentrations. The databases were searched using the following search terms in titles and abstracts (also in combination with MESH terms): (rosuvastatin or pravastatin or fluvastatin or simvastatin or atorvastatin or pitavastatin or lovastatin or cerivastatin or "statin therapy" or statins) and (endothelin-1 or endothelin or ET-1). The wild-card term "*" was used to increase the sensitivity of the search strategy. No language restriction was used in the literature search. The search was limited to studies in human. Two reviewers (CS and AS) evaluated each article separately. Disagreements were resolved by discussion with a third party (MB).

Study Selection

Original studies were included if they met the following inclusion criteria: (i) a randomized controlled trial (RCT) in either parallel or cross-over design, (ii) investigating the impact of statin therapy on plasma/serum levels of ET-1, (iii) treatment duration of at least two weeks, and, (iv) presentation of sufficient information on ET-1 concentrations at baseline and at the end of study in both statin and control groups or providing the net changes in each group.

Exclusion criteria were: (i) non-clinical studies, (ii) uncontrolled trials, (iii) lack of sufficient information on baseline or follow-up ET-1 levels, (iv) inability to obtain adequate details of study methodology or results from the article or the investigators, and, (v) the study was ongoing. Exclusion of an article for the latter reason was carried out if no feedback was received after contacting the author(s).

Data extraction

Eligible studies were reviewed and the following data were abstracted: 1) first author's name, 2) year of publication, 3) study location, 4) number of participants in the statin and control groups, 5) age, gender and body mass index (BMI) of study participants, 6) baseline levels of total cholesterol, LDL cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglycerides, high-sensitivity C-reactive protein (hsCRP) and glucose, 7) systolic and diastolic blood pressure, and, 8) data regarding baseline and follow-up concentrations of ET-1. In case the values were only presented as graphs, the GetData Graph Digitizer 2.24 (http://getdata-graph-digitizer.com/) software was used to digitize and extract the data.

Quality assessment

The quality of included studies was assessed using the Jadad scale. This scale encompasses randomization (0-2 points), blinding (0-2 points), and dropouts and withdrawals (0-1 point). The overall score of a study according to this scale ranges between 0-5, with higher scores indicative of a better quality ²². Studies with Jadad scores of ≤ 2 and ≥ 3 were considered as low- and high-quality, respectively ²³.

Quantitative Data Synthesis

Meta-analysis was conducted using Review Manager, version 5.2 (Cochrane Collaboration), and Comprehensive Meta-Analysis (CMA) V2 software (Biostat, NJ) ²⁴. Standard deviations (SDs) of the mean difference were calculated using the following formula: SD = square root $[(SD_{pre-treatment})^2 + (SD_{post-treatment})^2 - (2R \times SD_{pre-treatment} \times SD_{post-treatment})]$, assuming a correlation coefficient (R) = 0.5. In case of reporting SEM, 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 end of follow-up in the treatment group – measure at baseline in the treatment group) – (measure at 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 statin type, statin dose, study design, treatment duration, and the characteristics of populations being studied ²⁵. Effect sizes were expressed as weighed mean difference (WMD) and 95% confidence interval (CI). *Post-hoc* subgroup analyses were carried out to explore the impact of dose (<40 mg/day *vs* >40 mg/day), duration (<12 weeks *vs* >12 weeks), and type (lipophilic *vs* hydrophilic) of statin therapy on plasma ET-1 concentrations. In order to evaluate the influence of each study on the overall effect size, sensitivity analysis to detect statistically significant difference between statin and control groups was performed using the PS software ²⁷.

In the absence of trials making head-to-head comparison of hydrophilic versus lipophilic statins, the effect of these two types of statins on plasma ET-1 levels were compared using adjusted indirect comparison according to the method proposed by Song *et al.* 28 and Bucher *et*

al. ²⁹. In this method, treatment effects estimated for each type of statins in the random-effects model could be compared indirectly through common controls.

Meta-regression

Random-effects meta-regression was performed using unrestricted maximum likelihood method to evaluate the association between calculated WMD in plasma ET-1 concentrations with duration and dose of treatment with statins, **as well as age, gender and changes in plasma** LDL-C concentrations as potential moderators of treatment response.

Publication bias

Potential publication bias was explored using visual inspection of Begg's funnel plot asymmetry, and Begg's rank correlation and Egger's weighted regression tests. Duval and Tweedie "trim and fill" and "fail-safe N" methods were used to adjust the analysis for the effects of publication bias ³⁰.

Heterogeneity Analysis

Heterogeneity analysis was performed using the **Cochrane's** Q test and I^2 index. Another attempt to explore heterogeneity was made *via* the Galbraith plot, a scatter plot of WMD divided by its standard error (Z-statistic) against the reciprocal of the standard error in the included studies.

RESULTS

The initial screening for potential relevance removed the articles in whose titles and/or abstracts were obviously irrelevant. Among the 30 full text articles assessed for eligibility, 15 studies were excluded because of: lack of assessment of plasma ET-1 concentrations (n=1), insufficient data on plasma ET-1 levels (n=4), not being an original research study (n=1), not having an appropriate RCT design (n=4), short (<2 weeks) duration of treatment (n=2) and non-English language (n=3) (**Figure 1**).

Characteristics of included studies

After final assessment, 15 RCTs³¹⁻⁴⁵ met the inclusion criteria and were considered for the final meta-analysis. In total, 810 participants were randomized, of whom 421 were allocated to statin intervention and 389 to controls. The number of participants in these trials ranged from 32 to 82. Included studies were published between 1999 and 2013, and were conducted in Egypt, Norway, Russian Federation, Canada, USA (2 trials), Italy, Taiwan (3 trials), Poland, China, Japan, Sweden, and India. The following statin doses were administered in the included trials: 10 to 80 mg atorvastatin/day, 10 to 40 mg pravastatin/day, 40 mg/day simvastatin and fluvastatin, and 0.15 mg/day cerivastatin. Duration of statin intervention ranged between 2 weeks and 12 months. 12 trials were designed as parallel-group studies and 3 as crossover, comprising a total of 16 treatment arms, **The measurements of ET-1 concentrations were based on the included** studies are shown in **Table 1**. The systematic assessment of bias in the included studies is shown in **Supplemental Table 1**.

Quantitative data synthesis

The meta-analysis of data from 15 RCTs (comprising 16 treatment arms) ^{31.45} showed a significant effect of statin therapy in reducing plasma ET-1 concentrations (WMD: -0.30 pg/mL, 95%CI: -0.47, -0.13; p = 0.0004; **power = 100%**) (**Figure 2**). This effect size was robust in sensitivity analysis and omission of a single study did not significantly change the overall estimated effect size (**Supplemental Figure 1**). When the analysis was repeated using the fixed-effects model, significant results were again obtained (WMD: -0.16 pg/mL, 95%CI: -0.23, -0.09; p < 0.00001). In the subgroup analysis, the effect of statins on plasma ET-1 was significant in both subsets of studies with treatment durations >12 weeks (WMD: -0.19 pg/mL, 95%CI: -0.36, -0.02; p = 0.03) and <12 weeks (WMD: -0.51 pg/mL, 95%CI: -0.89, -0.14, p = 0.008) (Figure 3). With respect to statin dose, a significant reduction of plasma ET-1 levels was observed with both statin doses <40 mg/day (WMD: -0.27 pg/mL, 95%CI: -0.49, -0.05; p = 0.01) and >40 mg/day (WMD: -0.38 pg/mL, 95%CI: -0.68, -0.08, p = 0.01) (Figure 4).

Adjusted indirect meta-analysis

In order to compare the effects of hydrophilic versus lipophilic statins on plasma ET-1 levels, a subgroup analysis was first conducted to estimate the effect size. In the subgroup analysis, lipophilic (comprising 7 treatment arms with atorvastatin, 2 arms with simvastatin, 1 arm with fluvastatin and 1 arm with cerivastatin) (WMD: -0.34 pg/mL, 95%CI: -0.55, -0.13; p = 0.001) but not hydrophilic (comprising 5 treatment arms with pravastatin) (WMD: -0.18 pg/mL, 95%CI: -0.44, 0.08, p = 0.17) statins had a significant effect in lowering plasma ET-1 levels (**Figure 5**). A superior effect of lipophilic compared with hydrophilic statins was also

confirmed in the adjusted indirect comparison, where the effect size was estimated to be -0.16 pg/mL (95% CI: -0.20, -0.12, Z = 7.62, p < 0.05; **power = 100%**).

Meta-regression

The meta-regression analysis was conducted to assess the association of changes in plasma ET-1 concentrations with dose and duration of statin therapy as potential moderator variables. Consistent with the results of subgroup analysis, the impact of statins on plasma ET-1 concentrations was found to be independent of administered dose (slope: 0.001; 95%CI: -0.008 to 0.010; p = 0.808) and duration of supplementation (slope: -0.002; 95%CI: -0.030 to 0.026; p = 0.888). In addition, no significant association was found between changes in plasma LDL-C concentrations (slope: 0.004; 95%CI: -0.007 to 0.016; p = 0.439), baseline age (slope: -0.010; 95%CI: -0.039 to 0.019; p = 0.502), and sex (frequency of male subjects in each study) (slope: 0.005; 95%CI: -0.007 to 0.017; p = 0.449) with the changes in plasma ET-1 concentrations (Supplemental Figure 2).

Publication bias

The funnel plot of the study precision (inverse standard error) by effect size (mean difference) was asymmetric and suggested potential publication bias. This observation was further supported by the results of Begg's rank correlation (Kendall's Tau with continuity correction = -0.39, Z = 2.12, two-tailed *p*-value = 0.034) and Egger's linear regression (intercept = -2.49, standard error = 0.83; 95%CI = -4.26, -0.71, t = 3.01, df = 14.00, two-tailed *p* = 0.009) tests. The observed publication bias was imputed using trim-and-fill correction. Two potentially missing studies were imputed leading to a corrected effect size that was still significant -0.25

pg/mL (95%CI: -0.42, -0.09). The "fail safe N" method indicated that 156 theoretically missing studies would be required to make the overall estimated effect size non-significant. Funnel plot of the impact of statins on plasma ET-1 concentrations is illustrated in **Supplemental Figure 3**.

Heterogeneity analysis

The meta-analysis indicated a significant heterogeneity based on the calculated I^2 value of 75%, thus supporting the choice of random-effects model. A Galbraith plot was used to identify RCTs that are outside the pooled 95%CI estimate and might serve as potential outliers causing heterogeneity. According to the plot, 4 RCTs ^{39-41, 46} resided outside the limits of the 95%CI. A second analysis excluding these 4 RCTs showed a low inter-study heterogeneity ($I^2 = 10\%$); yet the pooled effect turned out to be marginally significant (WMD: -0.08 pg/mL, 95%CI: -0.16-0.00; p = 0.06) (Supplemental Figure 4). This latter analysis yielded significant results under the fixed-effects model (WMD: -0.08 pg/mL, 95%CI: -0.15-0.00; p = 0.05).

DISCUSSION

The present meta-analysis suggests that statin therapy reduces plasma ET-1 concentrations. The efficacy of statins was independent of therapeutic duration or dose. Since there have been no intervention studies specific for the reduction of ET-1 levels in relation to the CVD outcomes, the relevance of the mean level of the reduction (-0.30 pg/mL) on CVD prevention still remains to be determined. Even if so, these findings are of large interest since ET-1 may be a potential therapeutic target for atheroprotection ⁵.

The robustness of our combined analysis was verified in sensitivity analysis and it was found that the significance of the pooled estimate is the result of all studies rather than a single study. Our analysis included a study with cerivastatin that is a statin withdrawn from the market. However, when the analysis was repeated after excluding the cerivastatin arm, the result remained significant (WMD: -0.26 pg/mL, 95%CI: -0.41, -0.10; p = 0.002). In this analysis, although a greater effect size was calculated for the subset of trials with <12 weeks treatment duration compared with the subset lasting >12 weeks, no association between treatment duration and effect size was found in the meta-regression analysis. It may be hypothesized that the greater effect in the subset of trials with <12 weeks duration might be due to the fact that all studies – except one ³⁴ - in this subset used lipophilic statins, which were found to have a greater effect compared with hydrophilic statins in terms of reducing plasma ET-1 levels. In contrast, there were four trials ³⁵⁻³⁸ with hydrophilic statins in the subset of trials with >12 weeks treatment duration.

The biological mechanisms involved in the reduction of ET-1 by statins are not completely known. Some experimental studies report that statins may inhibit ET-1 expression at the transcriptional level in vascular endothelial cells ²⁰. In addition, ET-1 is synthesized by conditions in which oxidized LDL, platelet activation and oxidative stress exist ^{9, 10, 47}. Statins inhibit these conditions ^{17, 18, 48, 49}. More studies are required.

ET-1 in the circulation mainly stems from vascular cells ⁵, while urinary ET-1 is thought to reflect kidney derived production ⁵⁰. It has been suggested that urinary ET-1 reflects overall endogenous production of this protein ⁵¹. Besides plasma ET-1 measurement, 4 studies included in this meta-analysis measured urinary ET-1 levels; they confirmed a significant reduction of urinary ET-1 during statin therapy ^{36-38, 41}.

In addition to cholesterol-lowering effects, the so-called pleiotropic effects of statins have been the subject of increasing debate ^{17, 18}. These effects may be mainly due to LDL-C reduction

(and in turn, plaque stabilization, reduced inflammation, **and oxidative stress, etc.**)⁵². Variations in these pleiotropic effects might decrease residual CVD risk. While there is a correlation between ET-1 and LDL oxidation ^{8, 11}, ET-1 concentrations are not clearly correlated with LDL-C levels. Future clinical studies are needed to determine to what degree the reduction of ET-1 is independent of an anti-oxidative pleiotropic effect of statins.

We show a possible superior effect of lipophilic compared with hydrophilic statins on the reduction of ET-1. There is also additional evidence (besides data on pravastatin), which shows no significant effect of rosuvastatin on plasma ET-1 concentrations ^{52, 53}. A debate exists about the clinical impact of statin lipophilicity ⁵⁴⁻⁵⁹, as disposition of hydrophilic statins could be mediated via active transporters ⁶⁰. The reasons for the different effects of lipophilic/hydrophilic statins on ET-1 may be due to a wider tissue distribution with lipophilic statins ⁶¹. Unlike the hepatic tissue, uptake of hydrophilic statins by non-hepatic tissues such as vascular cells and myocardial tissue, as the sources of ET-1, is less than lipophilic statins ^{62, 63}. A recent meta-analysis of 13 RCTs indicated that lipophilic statins are better than hydrophilic statins for the treatment of heart failure ⁶⁴. The issue of statin lipophilicity requires further investigation; in our opinion, until that time lipophilicity should not influence the choice of statin.

This meta-analysis has limitations. The studies included had relatively short follow-up durations (2 weeks – 12 months) and most had a small number of participants (32 - 82). Furthermore, in relation to the study durations, they did not assess long-term CVD outcomes. The variations in study durations and statin doses may have not been of sufficient diversity to assess the impact of these factors on the ET-1-lowering effect of statins. Therefore, there is still a need for data from additional trials to identify determinants of ET-1 response to statin therapy, and also the impact of novel LDL-lowering agents ^{65, 66} on plasma ET-1

levels. To address inter-study heterogeneity, a conservative random-effects model was applied. In addition, sensitivity analysis confirmed that the pooled estimate is not significantly deviated by a single study.

CONCLUSIONS

In conclusion, the findings of the present meta-analysis suggest that statin therapy significantly reduces plasma ET-1 concentrations, regardless of treatment duration or statin dose. Statin properties, such as lipophilicity, may affect the level of ET-1 reduction. Larger, well-designed studies with longer follow-up are needed to validate our findings, and to determine the parameters that could determine ET-1 response to statin therapy. Whether reduction of plasma ET-1 concentrations can prevent atherosclerosis and CV events also requires further investigations.

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The authors declare that they have no competing interests. This meta-analysis was written independently; no company or institution supported it financially. Some of the authors have given talks, attended conferences and participated in trials and advisory boards sponsored by various pharmaceutical companies. No professional writer was involved in the preparation of this meta-analysis.

The meta-analysis has been selected for an oral presentation at the 83rd European Atherosclerosis Society (EAS) Congress in Glasgow during the FREE COMMUNICATIONS – CLINICAL STUDIES session (Tuesday, March 24, 2015).

AUTHORS' CONTRIBUTION:

AS - designed the study, made the statistical analysis, corrected the draft of the paper; KK, CS - designed the study, made the literature search, drafted the manuscript; SU - made the statistical analysis, drafted the manuscript; DPM, SRJ, KKR, MJB, JR, PPT, PM, GYHL – discussed the design of the study, corrected the draft of the paper; MB - designed the study, made the literature search, drafted the manuscript, prepared the revised version, submitted the paper.

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 Table 1. Demographic characteristics of the included studies.

Study	Abou Raya et	Asberg et al. ³²	Barsuk et al. ³³	Dupuis <i>et</i> <i>al</i> ³⁴	Economides <i>et</i> <i>al.</i> ⁴⁵	Glorioso et al. ³⁵	Lee <i>et</i> <i>al</i> . ³⁶	Lee <i>et</i> <i>al.</i> ³⁸	Lee et al. ³⁷	Lewandow ski <i>et al.</i> ³⁹	Li & Hui <i>et al.</i> ⁴⁰	Mozaffaria n <i>et al.</i> ⁴²	Nakamura <i>et al.</i> ⁴¹	Tehrani et al ⁴³	Usharani et al. ⁴⁴
Year	2007	2003	2013	1999	2004	1999	2002	2005	2009	2010	2005	2005	2001	2013	2008
Jadad	3	4	3	3	4	4	5	5	5	3	3	5	4	3	3
Locatio n	Egypt	Norway	Russian Federati	Canada	USA	Italy	Taiwan	Taiwan	Taiwan	Poland	China	USA	Japan	Sweden	India
Design	Random ized, placebo- controll ed parallel group trial	Random ized double- blind placebo- controlle d parallel group	on Random ized placebo- controlle d parallel group trial	Randomiz ed double- blind placebo- controlled parallel group trial	Randomized double-blind placebo- controlled parallel group trial	Randomiz ed double- blind placebo- controlled crossover group trial	Randomi zed double- blind placebo- controlle d parallel- group	Randomi zed double- blind placebo- controlle d parallel- group	Randomi zed double- blind placebo- controlle d parallel- group	Randomize d double- blind placebo- controlled parallel- group trial	Randomize d double- blind placebo- controlled parallel- group trial	Randomize d double- blind placebo- controlled crossover group trial	Randomize d double- blind placebo- controlled parallel- group trial	Randomize d double- blind placebo- controlled crossover group trial	Randomized placebo- controlled parallel- group trial
Duratio	6 months	trial 12	30 days	6 weeks	12 weeks	32 weeks	trial 6 months	trial 12	trial 6 months	8 weeks	2 weeks	16 weeks	6 months	2 months	8 weeks
Inclusio n criteria	Patients fulfillin g the ACR prelimin ary classific ation criteria for Systemi c Sclerosi s	Kidney transpla nt recipient s over 18 yr of age with a total cholester ol of 4.0–9.0 mmol/L	Patients with terminal chronic renal failure, included in hemodia lysis program not less than 6 months, with dyslipid emia, aged 35-70 yrs, hemoglo bin level ≥ 100 g/L, urea reductio n rate (URR) $\geq 65\%$	Patients admitted to the coronary care unit of the Montreal Heart Institute with a diagnosis of acute myocardia 1 infarction or unstable angina if they had admission total serum cholestero $l \ge 5.2$ mmol/L cholestero	Patients aged 21- 80 years and at risk for type 2 diabetes (either having a first- degree relative with type 2 diabetes and normal glucose tolerance or impaired glucose tolerance defined as a 2-h blood glucose value between 140–199 mg/dl during a 75-g oral glucose tolerance test) or had type 1 or type 2 diabetes	Patients aged 40 to 70 years who had diastolic hypertensi on and primary hyperchol esterolemi a and who were not taking any lipid- lowering or antihypert ensive drugs	Patients with proteinuri a and stable, well- controlle d hypertens ion with a seated diastolic blood pressure of 90 mm Hg and systolic blood pressure of 140 mm Hg at a 3- month screening period	Consecut ive proteinuri c patients with stable, well- controlle d hypertens ion with a seated diastolic blood pressure of 90 mm Hg and systolic blood pressure of 140 mm Hg at a 3- month screening period	Patients with chronic obstructi ve pulmonar y disease in whom a routine echocardi ogram showed pulmonar y hypertens ion, stable for at least 3 months and between 40 and 80 yrs of age	Men with hypercholes terolemia (total and LDL cholesterol levels ≥90 and ≥115mg/dl, respectively), and mild- to moderate essential hypertensio n (blood pressures: 140– 179/90– 109mmHg)	Patients with angiographi cally- documente d coronary artery disease	Patients with heart failure and at least New York Heart Association class II symptoms and left ventricular ejection fraction <40%	Normotensi ve type 2 diabetic patients with microalbum inuria (20– 200µg/min) and dyslipidemi a (total cholesterol >200 mg/dl, LDL cholesterol <35 mg/dl, HDL cholesterol <35 mg/dl, and triglyceride >150 mg/dl)	Patients aged between30 and 70 yrs with type 1 diabetes and elevated levels of low-density lipoprotein (LDL) (>2.5 mmol/L) and/or total cholesterol (>4.5 mmol/L)	Patients with type 2 diabetes, 21–80 yrs, with fasting plasma glucose of ≥130 mg/dL, a glycosylated haemoglobi n (HbA1c) range of between 7% and 11%, and taking stable antihypergly caemic medications for a 2- month period

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					≥1.2	e≥4.5 mmol/L												
$ \begin{array}{ c c c c c c c c c c c c c c c c c c c$	Statin		atorvast	fluvastat	atorvast	pravastati	atorv	astatin	pravastati	pravastati	pravastati	pravastati	simvastatin	simvastatin	atorvastatin	cerivastatin	atorvastatin	atorvastatin
Shim in thin in thing in the thing in thing in thing in the thing in thing in the the thin the thing in the the the thing in the thin the thin t			40	10 /1	auii	11	20	/1	11	10	10	11	40 /1	40 /1	10 /1	0.15	00 /1	10 /1
$ \begin{array}{ c c c c c c c c c c c c c c c c c c c$	Statin interven tion		40 mg/day	40mg/da y	20 mg/day	40 mg/day	20 m	ig/day	20 to 40 mg/day**	ng/day	ng/day	40 mg/day	40 mg/day	40 mg/day	10 mg/day	0.15 mg/day	80 mg/day	10 mg/day
$ \begin{array}{c c c c c c c c c c c c c c c c c c c $	Particip	Case	20	37	28	28	15#	19##	25	31	42	27	15	16	22	30	20	23 [§] 23 ^{§§}
$ \begin{array}{c c c c c c c c c c c c c c c c c c c $		Cont rol	20	35	26	27	15#	18##	25	32	40	26	16	16	22	30	20	23
$ \begin{array}{ c $	Age	Case	59.9±10	52±13	NS	55±2.1	48±13 [#]	51±	53±2	50±9	50±9	71±8	39.0±10.2	NS	51±11	58±10	44 (39–61)	50.47±
$ \begin{array}{ c c c c c c c c c c c c c c c c c c c$	(years)		.1					14##				(10.35 [§]
$ \begin{array}{ c c c c c c c c c c c c c c c c c c c$																		$55.52\pm 10.76^{\$\$}$
$ \begin{array}{ c c c c c c c c c c c c c c c c c c c$		Cont rol	58.7±9. 2	51±17	NS	56±2.3	49±11#	55± 11 ^{##}		47±8	48±8	72±6	38.3±10.1	NS		55±9		49.75±8.18
$ \begin{array}{c c c c c c c c c c c c c c c c c c c $	Male	Case	22.5	81.1	70.59	81.48.0	54.05#	57.5##	43.0	58.06	69.05	74.07	100.0	NS	86.36	60.0	50.0	52.17 [§]
$ \begin{array}{ c c c c c c c c c c c c c c c c c c c$	(%)														-			52.17 ^{§§}
$ \begin{array}{ c c c c c c c c c c c c c c c c c c c$		Cont rol	12.5	71.4	76.47	92.85				65.62	67.5	73.08	100.0	NS		66.6		52.38
$ \begin{array}{ c c c c c c c c c c c c c c c c c c c$	BMI	Case	NS	NS	NS	NS	29.5±5	29.8±	25.8±4.2	24.7±1.1	24.8±1.4	22±2	28.7±4.5	NS	31.8±6.4	NS	25±3	25.03±1.83 [§]
$ \begin{array}{ c c c c c c c c c c c c c c c c c c c$	(kg/m²)	Cont	NC	NC	NC	NC	.8*	9.4**		245.12	24 (112	22+1	27.2 4 1	NC	-	NC	-	24.66±2.42 ⁸⁸
$ \begin{array}{ c c c c c c c c c c c c c c c c c c c$		rol	IND	INS	INS	IND				24.5±1.2	24.0±1.5	25±1	27.3±4.1	IND		IND		23.98±2.33
$ \begin{array}{ c c c c c c c c c c c c c c c c c c c$	hs-CRP	Case	3.79	NS	NS	NS	0.24	0.30	NS	NS	NS	NS	NS	NS	3.2±0.9 ^{\$}	NS	NS	NS [§]
$ \begin{array}{ c c c c c c c c c c c c c c c c c c c$	(mg/L)		(1.8)				$(0.07 - 0.07)^{\#}$	(0.11-										
$ \begin{array}{ c c c c c c c c c c c c c c c c c c c$							0.35)"	0.62)**							~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~			NS ^{§§}
$ \begin{array}{ c c c c c c c c c c c c c c c c c c c$		Cont rol	3.85 (1.4)	NS	NS	NS	0.20 (0.06–	0.41 (0.17–		NS	NS	NS	NS	NS	4.8±1.3**	NS		NS
$ \begin{array}{ c c c c c c c c c c c c c c c c c c c$		0	100.2.2	201.40	NG	246.65.5	0.53)#	0.76)##	0.40.70.00	210.00	200 22	2.40	2.10	NG	202.27	2.62, 12	105 20 10	106.70
$ \begin{array}{ c c c c c c c c c c c c c c c c c c c$	Total choleste	Case	198.3±2	201.49± 46.32	NS	246.65±7.	193±4 2 [#]	$205\pm 40^{\#}$	242.79±20 07	7210±23	208±23	240± 43	249± 30.6	NS	202±37	262±42	$185.28\pm19.$	196.78± 35.28 [§]
$ \begin{array}{ c c c c c c c c c c c c c c c c c c c$	rol		5.5	10.52		55	-	10				15	50.0				5	195.0±
$ \begin{array}{ c c c c c c c c c c c c c c c c c c c$	(mg/dL)																	41.16 ^{§§}
$ \begin{array}{ c c c c c c c c c c c c c c c c c c c$		Cont rol	189.4±2 5.9	201.11± 52.49	NS	247.43±5. 4	216±3 2 [#]	208± 47 ^{##}		205±23	202±23	245 ± 39	232± 22.1	NS		258±42		196.95± 35.72
$ \begin{array}{ c c c c c c c c c c c c c c c c c c c$	LDL-C	Case	112.6±2	132.4±3	NS	160.19±5.	115±3	124±	166.37±	125±23	121±24	145±	169±	NS	129±28	208±46	119.66±19.	123.50±
$ \begin{array}{ c c c c c c c c c c c c c c c c c c c$	(mg/dL)		1.4	9.76		4	1#	36***	18.91			46	32.5				3	38.73 ⁸
$ \begin{array}{ c c c c c c c c c c c c c c c c c c c$																		$120.35\pm$ $42.13^{\$\$}$
$ \begin{array}{ c c c c c c c c c c c c c c c c c c c$		Cont	111.8±2	132.4±4	NS	167.52±6.	129±2	125±		123±25	123±25	148±	157±	NS		210±40		125.29±
$ \begin{array}{ c c c c c c c c c c c c c c c c c c c$		rol	0.9	5.55		95	8 [#]	X 37 ^{##}			26.5	50	29.1		25.0	22.12	46.00	34.94
$\begin{array}{ c c c c c c c c c c c c c c c c c c c$	HDL-C	Case	59.9±19	38.6±11.	NS	39.76±2.3	53±9"	63±14#	56.36±	36±4	38±5	65±15	44±	NS	35±8	22±12	46.32	36.82±5.45 [®]
$ \begin{array}{ c c c c c c c c c c c c c c c c c c c$	(ing/uL)	Cont	.0	25.51.1	NC	42.02.2.0	(()) (#	50.	11.77	27.4	29.5	(1) 12	1.0	NC	-	24+14	54.04)	38.78±7.69 ^{§§}
		rol	.5	55.51±1 0.42	NS	43.23±3.0 9	06±24"	59± 14 ^{##}		3/±4	38±3	61±13	43 ± 12.0	INS		24±14		36.38± 7.67

Triglyce	Case	NS	173.46±	NS	193.81±1	132±9	101± 79##	116.82±	241±42	249±42	146±70	156±	NS	218±226	202±38	61.95±26.5	182.26±
(mg/dI)			11/./		5.95	0	/0	30.28				52.1				5	43.63
(ing/uL)																	$176.39\pm$ 27.61 ^{§§}
	Cont	NS	147.79±	NS	193.81±1	116±7	106±		226±52	237±56	180±66	159±	NS		198±32		170.14±
	rol		80.53		7.7	1"	79**					52.0					47.54
Glucose (mg/dL)	Case	NS	NS	NS	NS	92±12#	163± 72 ^{##}	81.9± 5.94	NS	NS	NS	NS	NS	NS	NS	NS	161.21± 19.74 [§]
																	155.04± 17.94 ^{§§}
	Cont rol	NS	NS	NS	NS	89±10 [#]	182± 79 ^{##}		NS	NS	NS	NS	NS		NS		161.19± 19.97
SBP (mmHg)	Case	NS	148±19	NS	116±3.4	126±1 2 [#]	128± 14 ^{##}	149± 6	117±10	118±10	133±16	142± 11.8	NS	107±16	122±14	130±15	127.73± 11.96 [§]
																	$130.43 \pm 18.59^{\$\$}$
	Cont rol	NS	142±17	NS	122±3.6	123±2 1 [#]	125±13 ##		123±10	124±10	134±15	136± 9.5	NS		124±12		126.38± 15.43
DBP	Case	NS	89±7	NS	74±4.3	$80{\pm}7^{\#}$	80±9##	97±2	72±5	72±6	76±10	91±	NS	NS	78±10	74±8	80.95±7.93 [§]
(mmHg)										4		10.8					81.82±10.02
	Cont rol	NS	90±9	NS	72±2.5	79±10 [#]	78±9##		74±5	74±5	75±9	86± 11.0	NS		76±12	-	80.71±7.48
Endothe	Case	3.2±1.7	1.19±1.0	2.24±0.3	1.46±0.7	0.82±0	1.19±0.	4.5±2.1	1.80±0.6	1.87±0.5	2.03±1.1	1.38±1.56	3.2±1.4	1.7±0.2 ^{\$}	1.9±1.0	1.28±0.38	1.31±0.33 [§]
lin-1 (pg/mL)			2*	2		.25#	42##		0	5	8						1.38±0.51 ^{§§}
	Cont rol	2.98±1. 9	1.19±0.8 7*	2.24±0.3 2	1.48±0.8	0.89±0 .40 [#]	1.02±0. 29 ^{##}		1.84±0.6 0	1.84±0.5 6	2.15±0.9 4	0.57±0.44	3.0±1.2	1.7±0.1 ^{\$\$}	NS	1.17±0.33	1.21±0.49

Values are expressed as mean \pm SD or median (25–75 percentiles). ABBREVIATIONS: 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; BMI: body mass index; *the value was provided following 12 week treatment, # denotes at risk of type 2 diabetes arm; ## denotes diabetic patients arm; **If total plasma cholesterol was >5.46 mmol/L 8 weeks after randomization or 8 weeks after crossover, the drug dose was doubled to 40 mg/day; \$ denotes value after statin; \$\$ denotes value after placebo; \$ denotes statin group \$\$ denotes NCB-02 group (two capsules containing curcumin 150 mg twice daily).

Study	Ref	SEQUENCE GENERATION	ALLOCATION CONCEALMENT	BLINDING OF PARTICIPANTS AND PERSONNEL	BLINDING OF OUTCOME ASSESSMENT	INCOMPLETE OUTCOME DATA	SELECTIVE OUTCOME REPORTING	OTHER POTENTIAL THREATS TO VALIDITY
Abou Raya <i>et al.</i> 2007	31	U	U	Н	Н	L	L	L
Asberg <i>et al.</i> 2003	32	L	L	L	L	L	L	н
Barsuk <i>et al.</i> 2013	33	U	U	н	н	L	L	Н
Dupuis <i>et al.</i> 1999	34	U	U	L	L	L	L	L
Economides et al. 2004	45	U	L	L	L	L	L	L
Glorioso <i>et al.</i> 1999	35	U	L	L	L	L	L	L
Lee et al. 2002	36	L	L	L	L	L	L	L
Lee et al. 2005	38	L	L	L	L	L	L	L
Lee et al. 2009	37	L	L	L	L L	L	L	L
Lewandowski et al. 2010	39	U	U	U	U	L	L	L
Li & Hui <i>et al.</i> 2005	40	U	U	L	L	U	U	U
Mozaffarian <i>et</i> <i>al</i> . 2005	39	L	L	Ĺ	L	L	L	L
Nakamura <i>et al.</i> 2001	41	U	U	U	U	L	L	L
Tehrani <i>et al.</i> 2013	43	U	U	U	U	L	L	L
Usharani <i>et al.</i> 2008	44	U	U	н	U	L	L	L

Supplemental Table 1. Assessment of risk of bias in the included studies using Cochrane criteria.

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

FIGURE LEGENDS:

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

Figure 2. Forest plot detailing weighted mean difference and 95% confidence intervals for the impact of statin therapy on plasma endothelin-1 concentrations. Meta-analysis was performed using a random-effect model with inverse variance weighting.

Figure 3. Forest plot detailing weighted mean difference and 95% confidence intervals for the impact of statin therapy on plasma endothelin-1 concentrations in trials with treatment durations of <12 weeks (above) and > 12 weeks (below). Meta-analysis was performed using a random-effect model with inverse variance weighting.

Figure 4. Forest plot detailing weighted mean difference and 95% confidence intervals for the impact of statin therapy on plasma endothelin-1 concentrations in trials with statin doses of <40 mg/day (above) and >40 mg/day (below). Meta-analysis was performed using a random-effect model with inverse variance weighting.

Figure 5. Forest plot detailing weighted mean difference and 95% confidence intervals for the impact of statin therapy on plasma endothelin-1 concentrations in trials **with hydrophilic** (above) and hydrophobic (below) statins. Meta-analysis was performed using a random-effect model with inverse variance weighting.

Supplemental Figure 1. Leave-one-out sensitivity analysis of the impact of statin therapy on plasma endothelin-1 concentrations

Supplemental Figure 2. Meta-regression plots of the association between mean changes in plasma endothelin-1 concentrations and potential moderator variables. The size of each circle is inversely proportional to the variance of change.

Supplemental Figure 3. Funnel plot detailing publication bias in the studies reporting the impact of statin therapy on plasma endothelin-1 concentrations. Open circles represent observed published studies; closed circles represent imputed unpublished studies.

Supplemental Figure 4. Galbraith plot of the weighted mean difference divided by its standard error (*Z*-score) versus the reciprocal standard error (precision)

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	5	Statin		C	ontrol			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% Cl	IV, Random, 95% Cl
Abou-Raya et al., 2007	-0.8	1.51	20	0.02	1.73	20	2.2%	-0.82 [-1.83, 0.19]	
Asberg et al., 2003	0.48	0.31	37	0.48	0.35	35	9.8%	0.00 [-0.15, 0.15]	+
Barsuk et al., 2013	1.06	0.41	28	1.12	0.32	26	9.3%	-0.06 [-0.26, 0.14]	
Dupuis et al., 1999	-0.16	3.47	28	-0.02	3.93	27	0.7%	-0.14 [-2.10, 1.82]	
Economides et al., 2004a	-0.01	0.25	15	-0.06	0.36	15	9.0%	0.05 [-0.17, 0.27]	-
Economides et al., 2004b	-0.22	0.37	19	-0.04	0.3	18	9.0%	-0.18 [-0.40, 0.04]	
Glorioso et al., 1999	2.96	1.4	25	4.06	1.8	25	2.6%	-1.10 [-1.99, -0.21]	
Lee et al., 2002	-0.1	0.56	31	-0.09	0.59	32	8.1%	-0.01 [-0.29, 0.27]	
Lee et al., 2005	-0.18	0.53	42	-0.11	0.57	40	8.7%	-0.07 [-0.31, 0.17]	
Lee et al., 2009	-0.31	1.04	27	0.08	0.93	26	5.1%	-0.39 [-0.92, 0.14]	
Lewandowski et al., 2010	-0.64	1.36	15	0.41	0.81	16	3.1%	-1.05 [-1.84, -0.26]	
Li & Hui, 2005	-1.4	1.23	16	-0.2	1.11	16	3.0%	-1.20 [-2.01, -0.39]	
Mozaffarian et al., 2005	1.6	0.94	22	1.7	0.47	22	6.1%	-0.10 [-0.54, 0.34]	
Nakamura et al., 2001	-0.8	0.87	30	0.08	0.84	30	6.2%	-0.88 [-1.31, -0.45]	_
Tehrani et al., 2013	-0.09	0.34	17	0.06	0.32	17	9.0%	-0.15 [-0.37, 0.07]	
Usharani et al., 2008	-0.66	0.29	23	0.14	0.59	21	8.2%	-0.80 [-1.08, -0.52]	
Total (95% CI)			395			386	100.0%	-0.30 [-0.47, -0.13]	•

Heterogeneity: Tau² = 0.07; Chi² = 59.00, df = 15 (P < 0.00001); l² = 75% Test for overall effect: Z = 3.54 (P = 0.0004)

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	Expe	rimen	tal	C	ontrol			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% Cl	IV, Random, 95% Cl
Barsuk et al., 2013	1.06	0.41	28	1.12	0.32	26	24.8%	-0.06 [-0.26, 0.14]	
Dupuis et al., 1999	-0.16	3.47	28	-0.02	3.93	27	3.3%	-0.14 [-2.10, 1.82]	
Lewandowski et al., 2010	-0.64	1.36	15	0.41	0.81	16	12.3%	-1.05 [-1.84, -0.26]	
Li & Hui, 2005	-1.4	1.23	16	-0.2	1.11	16	12.0%	-1.20 [-2.01, -0.39]	
Tehrani et al., 2013	-0.09	0.34	17	0.06	0.32	17	24.4%	-0.15 [-0.37, 0.07]	
Usharani et al., 2008	-0.66	0.29	23	0.14	0.59	21	23.2%	-0.80 [-1.08, -0.52]	
Total (95% CI)			127			123	100.0%	-0.51 [-0.89, -0.14]	•
Heterogeneity: Tau ² = 0.14;	Chi ^z = 2	8.07, d	f= 5 (P	< 0.000	01); I² =	= 82%			-2 -1 0 1 2
Test for overall effect: $Z = 2$.	66 (P = l	1.008)							Favours Statin Favours Control

	Expe	erimen	tal	C	ontrol			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% Cl	IV, Random, 95% Cl
Abou-Raya et al., 2007	-0.8	1.51	20	0.02	1.73	20	2.4%	-0.82 [-1.83, 0.19]	
Asberg et al., 2003	0.48	0.31	37	0.48	0.35	35	16.4%	0.00 [-0.15, 0.15]	+
Economides et al., 2004a	-0.01	0.25	15	-0.06	0.36	15	14.3%	0.05 [-0.17, 0.27]	
Economides et al., 2004b	-0.22	0.37	19	-0.04	0.3	18	14.5%	-0.18 [-0.40, 0.04]	
Glorioso et al., 1999	2.96	1.4	25	4.06	1.8	25	3.0%	-1.10 [-1.99, -0.21]	
Lee et al., 2002	-0.1	0.56	31	-0.09	0.59	32	12.3%	-0.01 [-0.29, 0.27]	-+-
Lee et al., 2005	-0.18	0.53	42	-0.11	0.57	40	13.8%	-0.07 [-0.31, 0.17]	
Lee et al., 2009	-0.31	1.04	27	0.08	0.93	26	6.6%	-0.39 [-0.92, 0.14]	
Mozaffarian et al., 2005	1.6	0.94	22	1.7	0.47	22	8.3%	-0.10 [-0.54, 0.34]	
Nakamura et al., 2001	-0.8	0.87	30	0.08	0.84	30	8.4%	-0.88 [-1.31, -0.45]	_ _
Total (95% CI)			268			263	100.0%	-0.19 [-0.36, -0.02]	◆
Heterogeneity: Tau ² = 0.04;	Chi² = 2	4.77, d	f= 9 (P	= 0.003	3); ² =	64%			
Test for overall effect: Z = 2.	22 (P = 0	1.03)							Eavours Statin Eavours Control

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	Expe	rimen	tal	С	ontrol			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% Cl	IV, Random, 95% Cl
Barsuk et al., 2013	1.06	0.41	28	1.12	0.32	26	13.5%	-0.06 [-0.26, 0.14]	-+
Economides et al., 2004a	-0.01	0.25	15	-0.06	0.36	15	13.1%	0.05 [-0.17, 0.27]	+
Economides et al., 2004b	-0.22	0.37	19	-0.04	0.3	18	13.2%	-0.18 [-0.40, 0.04]	
Glorioso et al., 1999	2.96	1.4	25	4.06	1.8	25	4.3%	-1.10 [-1.99, -0.21]	
Lee et al., 2002	-0.1	0.56	31	-0.09	0.59	32	12.1%	-0.01 [-0.29, 0.27]	-+-
Lee et al., 2005	-0.18	0.53	42	-0.11	0.57	40	12.8%	-0.07 [-0.31, 0.17]	
Mozaffarian et al., 2005	1.6	0.94	22	1.7	0.47	22	9.4%	-0.10 [-0.54, 0.34]	
Nakamura et al., 2001	-0.8	0.87	30	0.08	0.84	30	9.5%	-0.88 [-1.31, -0.45]	_ -
Usharani et al., 2008	-0.66	0.29	23	0.14	0.59	21	12.1%	-0.80 [-1.08, -0.52]	
Total (95% CI)			235			229	100.0%	-0.27 [-0.49, -0.05]	•
Heterogeneity: Tau ^z = 0.08;	Chi ² = 4	1.01, d	f= 8 (P	< 0.000	001); I ^z	= 80%			
Test for overall effect: $Z = 2$.	44 (P = 0	.01)							-Z -1 U 1 Z
	,								Favours Statin Favours Control

	Expe	erimen	tal	C	ontrol			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% Cl	IV, Random, 95% Cl
Abou-Raya et al., 2007	-0.8	1.51	20	0.02	1.73	20	7.0%	-0.82 [-1.83, 0.19]	
Asberg et al., 2003	0.48	0.31	37	0.48	0.35	35	28.9%	0.00 [-0.15, 0.15]	+
Dupuis et al., 1999	-0.16	3.47	28	-0.02	3.93	27	2.2%	-0.14 [-2.10, 1.82]	
Lee et al., 2009	-0.31	1.04	27	0.08	0.93	26	15.9%	-0.39 [-0.92, 0.14]	
Lewandowski et al., 201	0 -0.64	1.36	15	0.41	0.81	16	9.8%	-1.05 [-1.84, -0.26]	_
Li & Hui, 2005	-1.4	1.23	16	-0.2	1.11	16	9.5%	-1.20 [-2.01, -0.39]	(
Tehrani et al., 2013	-0.09	0.34	17	0.06	0.32	17	26.7%	-0.15 [-0.37, 0.07]	-=+
Total (95% CI)			160			157	100.0%	-0.38 [-0.68, -0.08]	•

Total (95% CI)	160	157	100.0%	-0.38 [-0.68, -0.
Heterogeneity: Tau ² = 0.08; Chi ² = 1	17.34, df = 6 (P = 0.008); l ² =	65%		
Test for overall effect: Z = 2.47 (P =	0.01)			



Expe	rimen	tal	C	ontrol			Mean Difference	Mean Difference
Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% Cl	IV, Random, 95% Cl
-0.16	3.47	28	-0.02	3.93	27	1.7%	-0.14 [-2.10, 1.82]	
2.96	1.4	25	4.06	1.8	25	7.3%	-1.10 [-1.99, -0.21]	
-0.1	0.56	31	-0.09	0.59	32	34.6%	-0.01 [-0.29, 0.27]	-
-0.18	0.53	42	-0.11	0.57	40	39.6%	-0.07 [-0.31, 0.17]	-
-0.31	1.04	27	0.08	0.93	26	16.9%	-0.39 [-0.92, 0.14]	
		153			150	100.0%	-0.18 [-0.44, 0.08]	•
0.03; Ch Z = 1.37	i ² = 6.0 (P = 0.	36, df = 17)	4 (P = 0	0.17); P	²= 37%			
	Expe Mean -0.16 2.96 -0.1 -0.18 -0.31 0.03; Ch Z = 1.37	Experiment Mean SD -0.16 3.47 2.96 1.4 -0.1 0.56 -0.18 0.53 -0.31 1.04 0.03; Chi² = 6.3 Z = 1.37 (P = 0.37)	Experimental Mean SD Total -0.16 3.47 28 2.96 1.4 25 -0.1 0.56 31 -0.18 0.53 42 -0.31 1.04 27 IS3 0.03; Chi ^P = 6.36, df = 21.37 (P = 0.17) 1.01	Experimental Coll Mean SD Total Mean -0.16 3.47 28 -0.02 2.96 1.4 25 4.06 -0.11 0.56 31 -0.09 -0.18 0.53 42 -0.11 -0.31 1.04 27 0.08 ISS 0.03; Chi² = 6.36, df = 4 (P = 0) 2 = 1.37 (P = 0.17) -0.17)	Experimental Control Mean SD Total Mean SD -0.16 3.47 28 -0.02 3.93 2.96 1.4 26 4.06 1.8 -0.1 0.56 31 -0.09 0.59 -0.18 0.53 42 -0.11 0.57 -0.31 1.04 27 0.08 0.93 ISS 0.03; Chi ² = 6.36, df = 4 (P = 0.17); P 2 = 1.37 (P = 0.17) 2 3 3	Experimental Control Mean SD Total Mean SD Total -0.16 3.47 28 -0.02 3.93 27 2.96 1.4 25 4.06 1.8 25 -0.1 0.56 31 -0.09 0.59 32 -0.18 0.53 42 -0.11 0.57 40 -0.31 1.04 27 0.08 0.93 26 ISS 150 0.03; Chi ² = 6.36, df = 4 (P = 0.17); I ² = 37% 21.37 (P = 0.17) 150	Experimental Control SD Total Mean SD Total Weight -0.16 3.47 2.8 -0.02 3.93 2.7 1.7% 2.96 1.4 2.5 4.06 1.8 2.5 7.3% -0.11 0.56 3.1 -0.09 0.59 3.2 34.6% -0.18 0.53 4.2 -0.11 0.57 4.0 39.6% -0.31 1.04 2.7 0.08 0.93 2.6 16.9% 0.03; Chi² = 6.36, df = 4 (P = 0.17); l² = 37% 150 100.0% 12.37 (P = 0.17); l² = 37% 10.0%	Experimental Total Rom SD Fotal Rean Mean Mean

Study or Subgroup	Expe Mean	erimen SD	tal Total	C Mean	ontrol SD	Total	Weight	Mean Difference IV, Random, 95% Cl	Mean Difference IV, Random, 95% Cl
Abou-Raya et al., 2007	-0.8	1.51	20	0.02	1.73	20	3.2%	-0.82 [-1.83, 0.19]	
Asberg et al., 2003	0.48	0.31	37	0.48	0.35	35	12.6%	0.00 [-0.15, 0.15]	-+-
Barsuk et al., 2013	1.06	0.41	28	1.12	0.32	26	12.1%	-0.06 [-0.26, 0.14]	
Economides et al., 2004a	-0.01	0.25	15	-0.06	0.36	15	11.7%	0.05 [-0.17, 0.27]	+
Economides et al., 2004b	-0.22	0.37	19	-0.04	0.3	18	11.8%	-0.18 [-0.40, 0.04]	
Lewandowski et al., 2010	-0.64	1.36	15	0.41	0.81	16	4.5%	-1.05 [-1.84, -0.26]	
Li & Hui, 2005	-1.4	1.23	16	-0.2	1.11	16	4.4%	-1.20 [-2.01, -0.39]	
Mozaffarian et al., 2005	1.6	0.94	22	1.7	0.47	22	8.4%	-0.10 [-0.54, 0.34]	
Nakamura et al., 2001	-0.8	0.87	30	0.08	0.84	30	8.5%	-0.88 [-1.31, -0.45]	_ -
Tehrani et al., 2013	-0.09	0.34	17	0.06	0.32	17	11.7%	-0.15 [-0.37, 0.07]	
Usharani et al., 2008	-0.66	0.29	23	0.14	0.59	21	10.9%	-0.80 [-1.08, -0.52]	
Total (95% CI)			242			236	100.0%	-0.34 [-0.55, -0.13]	•
Hotorogonoity: Tou? - 0.09	Chiž – St	5 2 2 A	f = 107		10043	IZ = 01 (×.		

Heterogeneity: Tau² = 0.08; Chi² = 52.33, d Test for overall effect: Z = 3.19 (P = 0.001) 10 (F : 0.00001); I² = 81 %

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HIGHLIGHTS:

- Raised ET-1 levels may be a risk factor for vascular dysfunction and CVD.
- We showed that statin therapy significantly reduces ET-1 (-0.30 pg/mL).
- Lipophilic, but not a hydrophilic statin had a significant effect on ET-1 reduction
- We need to establish whether lowering ET-1 has a beneficial effect on CV events.

Study name		Statistics with study removed							Difference in means (95% CI) with study removed			
	Point	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value					
Abou-Raya et al., 2007	-0.293	0.086	0.007	-0.461	-0.126	-3.430	0.001	1		- 1	1	
Asberg et al., 2003	-0.346	0.094	0.009	-0.530	-0.162	-3.691	0.000			-		
Barsuk et al., 2013	-0.339	0.094	0.009	-0.524	-0.155	-3.612	0.000		⊢∔∎	-		
Dupuis et al., 1999	-0.308	0.086	0.007	-0.476	-0.140	-3.591	0.000			-		
Economides et al., 2004a	-0.344	0.091	0.008	-0.522	-0.166	-3.786	0.000		⊢	-		
Economides et al., 2004b	-0.328	0.094	0.009	-0.512	-0.143	-3.487	0.000			-		
Glorioso et al., 1999	-0.280	0.084	0.007	-0.445	-0.116	-3.340	0.001			-		
Lee et al., 2002	-0.337	0.091	0.008	-0.515	-0.158	-3.699	0.000			_		
Lee et al., 2005	-0.335	0.093	0.009	-0.516	-0.154	-3.620	0.000			-		
Lee et al., 2009	-0.303	0.088	0.008	-0.475	-0.130	-3.439	0.001			-		
Lewandowski et al., 2010	-0.276	0.084	0.007	-0.440	-0.112	-3.302	0.001		_	⊢ I		
Li & Hui, 2005	-0.271	0.082	0.007	-0.432	-0.109	-3.281	0.001			⊢ I		
Mozaffarian et al., 2005	-0.323	0.089	0.008	-0.498	-0.148	-3.612	0.000			_		
Nakamura et al., 2001	-0.256	0.081	0.007	-0.415	-0.097	-3.149	0.002					
Tehrani et al., 2013	-0.331	0.094	0.009	-0.515	-0.146	-3.516	0.000		┝╼╋	_		
Usharani et al., 2008	-0.229	0.074	0.005	-0.373	-0.084	-3.090	0.002		_			
	-0.306	0.085	0.007	-0.472	-0.139	-3.603	0.000					
								-1.00	-0.50	0.00	0.50	

Favours Statins Favours Placebo

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Chillin Nr