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Effect of statins on arterial wall inflammation as assessed by 18F-FDG PET CT: an updated systematic review and meta-analysis

Tannaz Jamialahmadi[1,2*], Željko Reiner[3,4], Luis E. Simental-Mendia[5], Wael Almahmeed[6], Sercan Karav[7], Ali H. Eid[8], Francesco Giammarile[9] and Amirhossein Sahebkar[10,11,12*]

Abstract

Background Pathogenesis of atherosclerosis is largely mediated by inflammatory process. Statins are lipid-lowering drugs which also have anti-inflammatory effects. 18 fluorine radiolabeled fluorodeoxyglucose (18 F-FDG) positron emission tomography-computed tomography (PET-CT) is considered to be a good indicator of arterial wall inflammation. Therefore, in this meta-analysis the role of statins on inflammatory process in the artery wall was evaluated using this method since its actual validity for this purpose is not yet well established.

Methods PubMed, Scopus, Web of Science, ClinicalTrials.gov, and Google Scholar databases were searched using MESH terms and keywords. Funnel plot, Begg's rank correlation, and Egger's weighted regression tests evaluated publication bias in the meta-analysis. In cases where funnel plot asymmetry was observed, the "trim and fill" method was used to check the input of potentially missing studies.

Results Findings of 10 clinical trials involving 373 subjects showed a remarkable reduction of arterial wall 18 F-FDG uptake according to target-to-background ratio (TBR) index after treatment with statins. Subgroup analysis showed a significant decrease in TBR with high-intensity and non-significant reduction of TBR with low-to-moderate-intensity statin therapy.

Conclusion Treatment with statins suppressed arterial wall inflammation as shown by using 18 F-FDG PET-CT.

Keywords Statins, Atherosclerosis, Inflammation, 18F-FDG PET-CT, Cardiovascular disease

*Correspondence:
Tannaz Jamialahmadi
Jamiat931@gmail.com
Amirhossein Sahebkar
amir_saheb2000@yahoo.com
[1]Pharmaceutical Research Center, Pharmaceutical Technology Institute, Mashhad University of Medical Sciences, Mashhad, Iran
[2]Medical Toxicology Research Center, Mashhad University of Medical Sciences, Mashhad, Iran
[3]Department of Internal Medicine, University Hospital Center Zagreb, Zagreb, Croatia
[4]Polish Mother's Memorial Hospital Research Institute, Lodz 93-338, Poland
[5]Biomedical Research Unit, Instituto Mexicano Del Seguro Social, Durango, México
[6]Heart and Vascular Institute, Cleveland Clinic Abu Dhabi, Abu Dhabi, United Arab Emirates
[7]Department of Molecular Biology and Genetics, Canakkale Onsekiz Mart University, Canakkale 17100, Turkey
[8]Department of Basic Medical Sciences, College of Medicine, QU Health, Qatar University, Doha, Qatar
[9]Nuclear Medicine and Diagnostic Imaging Section, International Atomic Energy Agency, Vienna, Austria
[10]Center for Global Health Research, Saveetha Institute of Medical and Technical Sciences, Saveetha Medical College and Hospitals, Saveetha University, Chennai, India
[11]Biotechnology Research Center, Pharmaceutical Technology Institute, Mashhad University of Medical Sciences, Mashhad, Iran
[12]Applied Biomedical Research Center, Mashhad University of Medical Sciences, Mashhad, Iran

Introduction

Statins are among the most widely used medications, which have many beneficial effects on preventing the progression of atherosclerotic cardiovascular disease (ASCVD) [1–3]. The main anti-atherosclerotic mechanism of statins is based on LDL-cholesterol reduction. However, numerous biological and pharmacological effects have also been discovered for these drugs, which are independent of their putative cholesterol-lowering activity [4–14]. Since atherosclerosis is largely driven by inflammatory process, the anti-inflammatory role of statins is also beneficial [15–18]. Atherogenesis is a complex process in which due to binding to adhesion molecules, monocytes migrate into intima where they mature into macrophages which became loaded with cholesterol rich LDL particles and are transformed into foam cells. All these events stimulate inflammatory and immune reactions [19]. Subsequent migration and proliferation of smooth muscle cells lead to deposition of extracellular matrix which contributes to the formation of a fibrous plaque. The clinical manifestations of atherosclerosis occur when vulnerable plaques are ruptured which causes thrombus formation on them which could also be triggered by inflammation [20, 21]. Radionuclide imaging with 18fluorine radiolabeled fluorodeoxyglucose (18 F-FDG) positron emission tomography-computed tomography (PET-CT) is for more than a decade considered to be a possible indicator of arterial wall inflammation. Compared to other cell types, activated inflammatory cells show higher 18 F-FDG uptake because of their increased metabolic activity [22, 23]. It is also a validated method for quantifying atherosclerotic plaque inflammation which might help to quantify plaque vulnerability and thrombus formation on them [24, 25]. There have been a number of studies reporting the impact of statins on arterial wall inflammation using 18 F-FDG PET-CT. Besides, according to some studies these drugs could not reduce arterial wall inflammation in the aorta or carotid arteries of patients with chronic kidney disease [26]. Meta-analysis, as the highest level of evidence, will enable more conclusive evidence from the performed studies and a more accurate estimation of the effect size of statins on arterial wall inflammation. Therefore, a meta-analysis was conducted to find by using 18 F-FDG PET-CT whether statins do have a beneficial effect on reducing vessel wall inflammation.

Materials and methods

Search Strategy.

The study was performed using the preferred reporting items for systematic reviews and meta-analysis (PRISMA) guidelines [27]. PubMed, Google Scholar, Scopus, Web of Science, and ClinicalTrials.gov databases were searched based on the following terms in titles and abstracts: ("statin" OR "lipid lowering agents" OR "HMG-CoA reductase inhibitor" OR "Atorvastatin" OR "Pravastatin" OR "Fluvastatin" OR "Simvastatin" OR "Rosuvastatin" OR "Lovastatin" OR "Pitavastatin") AND (18 F-fluorodeoxyglucose OR FDG OR "18 F-fluorodeoxyglucose" OR "18 F-FDG" OR "18F-FDG" OR "FDG-18 F" OR "FDG-18F" OR fluorodeoxyglucose OR "18F FDG" OR "18 F FDG" OR "18 FDG" OR 18FDG). The wild-card term "*" was used to improve the sensitivity of the search strategy. The search was performed from inception to September 5, 2023.

Study selection

Among the original studies selected, the inclusion criteria were: studies focused on the effect of statins on arterial wall inflammation by FDG PET-CT, studies that presented arterial wall FDG uptake as target-to-background ratio (TBR) values prior to and after statin administration or presented net change values. Exclusion criteria were: non-clinical and non-interventional studies such as observational studies with case-control, cohort designs, cross-sectional as well as studies that did not provide sufficient data on baseline or post treatment TBR values or arterial wall FDG uptake.

Data extraction

Following data from eligible studies were taken into consideration: (1) first author's name, (2) the year of publication, (3) the number of included subjects, (4) study design (5) the type of statin therapy used, (6) the dose of statin, (7) the duration of treatment.

Quality Assessment

Cochrane criteria were used to assess the quality of the studies included in this meta-analysis [28].

Quantitative data synthesis

The meta-analysis was conducted using Comprehensive Meta-Analysis (CMA) V4 software [29]. To estimate the heterogeneity of the included publications, a random-effects model and the generic inverse variance weighting method were used [30]. Standard deviations (SDs) were calculated based on the reported data or estimated using formulas. Cochrane Q and I^2 statistic were used to assess heterogeneity. The study presented effect sizes as weighted mean difference (WMD) and 95% confidence interval (CI). Sensitivity analysis assessed the influence of each single study on the overall effect size [31].

Meta-regression

A meta-regression model was used to investigate the relationship between the estimated effect size on arterial wall inflammation and potential confounders such as baseline TBR, treatment duration, mean changes in

circulating levels of LDL-cholesterol and CRP. The model used random-effects and aimed to assess the impact of these factors on treatment response.

Publication Bias

Funnel plot and Egger's weighted regression tests as well as Begg's rank correlation evaluated publication bias in the meta-analysis. In cases where funnel plot asymmetry was observed, the "trim and fill" method was used to check the input of potentially missing studies [32]. The number of potentially missing studies needed to render the p-value non-significant was estimated using the "fail-safe N" method, which serves as another indicator of publication bias.

Results

Study selection process

Seventy-seven articles were selected following the search in databases, and 65 were excluded after the review of titles and abstracts. Then, 12 full-text articles were checked and two were excluded because one was a non-interventional study and the other had incomplete data. Thus, 10 clinical trials were included in this meta-analysis (presented as Fig. 1).

Study characteristics

Ten clinical trials were included in this analysis involving 373 individuals and 14 different treatment arms. All these publications analyzed the whole vessel TBR of the index vessel. Furthermore, four trials provided data on the TBR of the MDS of the index vessel. Besides the whole vessel TBR four trials also detected TBR of the MDS of the index vessel. The included studies [33–42] used different types and dosages of statins. They were published between 2010 [42] and 2021 [33]. Study designs were open-label [34, 39–42], a prospective randomized trial [33], a prospective interventional study [35] and parallel group studies [36–38]. Selected studies enrolled subjects

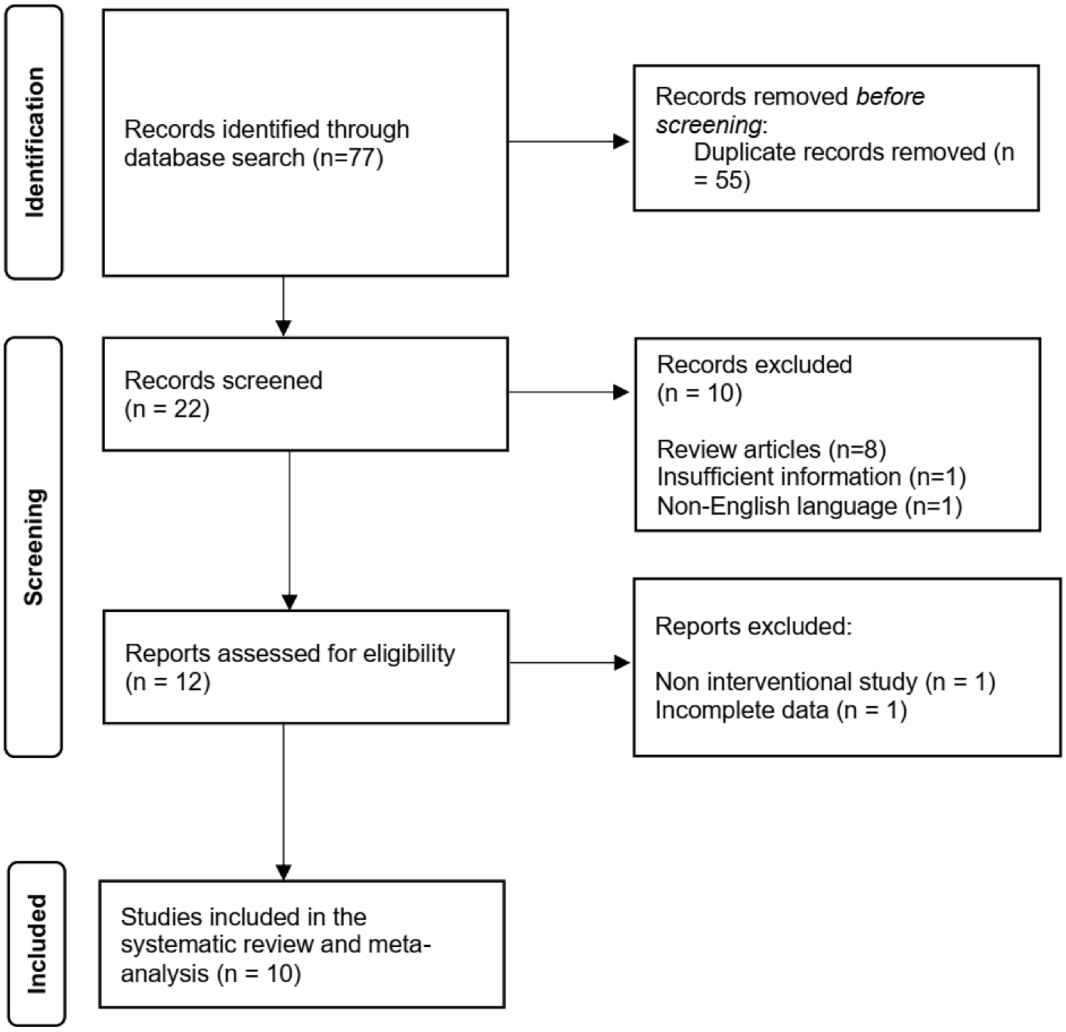


Fig. 1 Flow chart of the number of studies selected for meta-analysis

who had ASCVD risk factors or who had proven atherosclerosis [34, 37–40], stable angina pectoris [42], HIV-infection [33, 36], acute coronary syndrome [35], and ankylosing spondylitis [41]. Table 1 presents the clinical and biochemical characteristics of the included clinical trials.

18 F-FDG PET CT procedure

Different studies used 18 F-FDG PET with contrast-enhanced CT imaging to evaluate arterial wall inflammation in different vessels. Ishii et al. [42] measured 18 F-FDG uptake in the ascending aorta and right and left femoral arteries, while Lo et al. [36] assessed 18 F-FDG uptake in the aorta. Emami et al. [34] evaluated the arterial FDG in the left and right carotid and aorta while Boczar et al. assessed 18 F-FDG uptake in the aorta, bone marrow as well as spleen [33]. Two studies [38, 39] performed FDG PET-CT imaging of the thoracic aorta and carotid arteries, while two studies [35, 41] assessed arterial wall inflammation in carotid arteries. Subramanian et al. assessed 18 F-FDG uptake in the periodontium [37]. Wu et al. [40] evaluated FDG uptake in various arterial segments, including the aortic arch, ascending aorta, abdominal aorta, thoracic descending aorta, and both iliofemoral arteries.

Risk of Bias Assessment

In terms of random sequence generation and allocation concealment, three trials which were included had a high risk of bias [35, 40, 41]. Additionally, three studies were found to have a risk of bias in terms of blinding of participants, outcome assessors and personnel [33, 34, 42]. However, all of the selected studies demonstrated a low risk of bias for incomplete outcome data and selective outcome reporting. More information regarding the assessment of bias can be found in Table 2.

Quantitative data synthesis

Meta-analysis of data from ten studies including 373 participants and 14 treatment arms showed a significant decrease in 18 F-FDG uptake according to TBR index after treatment with statins (WMD: −0.100, 95% CI: −0.159, −0.042, $p=0.001$; I^2: 84.90%) (Fig. 2A). Sensitivity analysis was also performed (Fig. 2B).

Four studies with five treatment arms showed a significant reduction in arterial MDS TBR after statin administration (WMD: −0.194, 95% CI: −0.272, −0.126, $p<0.001$; I2: 61.71%) (Fig. 3A). Sensitivity analysis was also performed (Fig. 3B).

Subgroup analysis showed that arterial wall TBR was significantly reduced in those patients who were treated with high-intensity statins (WMD: −0.154, 95% CI: −0.258, −0.051, $p=0.004$) and there was a non-significant reduction of TBR in those treated with low-to-moderate-intensity (WMD: −0.059, 95% CI: −0.120, 0.001, $p=0.053$) statin therapy (Fig. 4).

Meta-regression

To evaluate the impact of potential confounding factors on the effects of statin treatment on arterial wall inflammation, a random-effects meta-regression was performed. The results suggested a significant association between the effect of statins on TBR and LDL-cholesterol change (slope: 0.006; 95% CI: 0.001, 0.010;

Table 1 Clinical and biochemical characteristics of the included clinical trials

Author	Study design	Target Population	Treatment duration	*n*	Study groups
Boczar et al. 2022 [33]	Prospective randomized trial	HIV infection	6 months	17 18	Rosuvastatin 10 mg/day Control
Emami et al. 2015 [34]	Open-label trial	History of atherosclerosis	3 months	24 24	Atorvastatin 80 mg/day Placebo
Ishii et al. 2010 [42]	Randomized, open-label trial	Adults with stable angina pectoris	6 months	15 15	Atorvastatin 5 mg/day Atorvastatin 20 mg/day
Kim et al. 2020 [35]	Prospective interventional study	Acute coronary syndrome	1 month	13	Atorvastatin 20 mg/day
Lo et al. 2015 [36]	Randomized, double-blind, placebo-controlled	HIV-infected patients	1 year	17 20	Atorvastatin 40 mg/day Placebo
Subramanian et al. 2013 [37]	Randomized, double-blind, active-controlled	Adults with risk factors or with established atherosclerosis	3 months	29 29	Atorvastatin 10 mg/day Atorvastatin 80 mg/day
Tawakol et al. 2013 [38]	Randomized, double-blind trial	Individuals with arterial inflammation	3 months	34 34	Atorvastatin 10 mg/day Atorvastatin 80 mg/day
van der Valk et al. 2016 [41]	Open-label trial	Patients with ankylosing spondylitis	3 months	18	Atorvastatin 40 mg/day
Watanabe et al. 2015 [39]	Randomized, open-label trial	Patients with hyperlipidemia	6 months	10 10	Pitavastatin 2 mg/day Pravastatin 10 mg/day
Wu et al. 2012 [40]	Open-label trial	Patients with atherosclerosis	3 months	43 34	Atorvastatin 40 mg/day Control

Table 2 Quality of bias assessment of the included studies according to the Cochrane guidelines

Study	Sequence generation	Allocation concealment	Blinding of participants, personnel and outcome assessors	Incomplete outcome data	Selective outcome reporting	Other sources of bias
Boczar et al. 2022 [33]	U	U	H	L	L	U
Emami et al. 2015 [34]	U	U	H	L	L	U
Ishii et al. 2010 [42]	U	L	H	L	L	U
Kim et al. 2020 [35]	H	H	H	L	L	U
Lo et al. 2015 [36]	L	L	L	L	L	L
Subramanian et al. 2013 [37]	U	U	L	L	L	L
Tawakol et al. 2013 [38]	U	U	U	L	L	U
van der Valk et al. 2016 [41]	H	H	H	L	L	U
Watanabe et al. 2015 [39]	U	U	H	L	L	U
Wu et al. 2012 [40]	H	H	H	L	L	U

L, low risk of bias; H, high risk of bias; U, unclear risk of bias

$p=0.011$), but there were no significant association with treatment duration (slope: 0.006; 95% CI: –0.001, 0.014; $p=0.119$), CRP change (slope: 0.062; 95% CI: -0.021, 0.146; $p=0.145$), and baseline TBR (slope: -0.031; 95% CI: –0.368, 0.306; $p=0.856$) (Fig. 5).

Publication Bias

After applying the "trim and fill" method to account for potentially missing studies the corrected effect size was found to be -0.121 (95% CI: -0.18, -0.06) (Fig. 6). Begg's rank correlation (tau = -0.04, z=0.21, $p=0.826$) and Egger's regression test (t=0.52, df=12, $p=0.609$) did not indicate any publication bias. The "fail-safe N" test results suggested that 282 additional publications would be needed to reduce to zero the observed significant result. Since we were able to identify only ten eligible publications (with 14 treatment arms) for this meta-analysis, it is highly unlikely that 282 studies were missed, indicating the absence of any significant publication bias.

Discussion

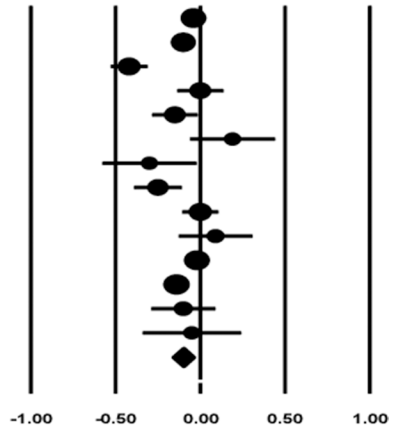
This is the second meta-analysis ever made on this topic. It was performed to find whether statins have a beneficial effect on arterial wall inflammation using a 18 F-FDG PET-CT method. Findings from ten studies including 373 participants and 14 treatment arms demonstrated a notable decrease in arterial wall 18 F-FDG uptake according to TBR index following administration of statins. A large effect size was reported in the leave-one-out sensitivity analysis which was not mainly driven by any single study. A significant association between the effect of statins on TBR and LDL-cholesterol change was found, but there were no significant associations with treatment duration, CRP change and baseline TBR.

The first and only similar meta-analysis was published by our group several years ago and it was based on only seven studies that had 287 participants and 10 treatment arms. Following treatment with low to moderate doses of statins, TBR was significantly reduced. TBR values after treatment with statins were not influenced by duration and dosage of drugs, variation in plasma cholesterol and CRP level neither by initial TBR values [31].

Arterial wall inflammation in patients with coronary heart disease who were treated with statins was found to be lower than in those who were not treated [43]. However, most of these studies were estimating the inflammation of the coronary arteries and other arteries wall based upon inflammatory markers in blood such as IL-1β, IL-6 and particularly hsCRP concentration [44, 45]. The 18 F-FDG PET-CT technique was only used in some studies to evaluate the severity of inflammation in atheroma plaques [46]. 18 F-FDG PET-CT has been mostly used for identifying increased tracer uptake in symptomatic carotid plaques, and the tracer uptake has been shown to correlate with plaque inflammation and vulnerability [47]. Therefore, 18 F-FDG PET CT is considered to be a promising method for noninvasive characterization of high-risk atherosclerotic plaques. However, it has been shown already several years ago that 18 F-FDG uptake also predicts major atherosclerotic events (MACE) in a stable population after adjusting for cardiovascular risk factors [48] but as well that 18 F-FDG uptake is higher in plaque-free arterial segments suggesting an arterial inflammatory state even at early stages of aterosclerosis [49]. Neverheless, it has to be stressed again that there are not many studies analyzing the effects of statins on arterial wall inflammation in humans using 18 F-FDG PET CT. Apart from those included in this meta-analysis, it is worth while to mention the results of another study which also used 18 F-FDG PET CT. This study has shown that anti-inflammatory effect of a statin continues throughout its use up to one year, even though yielding stable below-target plasma LDL-cholesterol levels at 3 months [50]. Important are the results of the first study which evaluated the effects of statins on the inflammation of the coronary arteries by using 18 F-FDG PET

A.

Study name	Difference in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Ishii , 2010, A 5mg	-0.040	0.024	0.001	-0.086	0.006	-1.690	0.091
Ishii , 2010, A 20mg	-0.100	0.034	0.001	-0.166	-0.034	-2.953	0.003
Wu, 2012	-0.420	0.055	0.003	-0.528	-0.312	-7.651	0.000
Tawakol, 2013, A 10mg	0.000	0.069	0.005	-0.134	0.134	0.000	1.000
Tawakol, 2013, A 80mg	-0.150	0.068	0.005	-0.283	-0.017	-2.208	0.027
Subramanian, 2013, A 10mg	0.190	0.128	0.016	-0.060	0.440	1.489	0.137
Subramanian, 2013, A 80mg	-0.300	0.141	0.020	-0.576	-0.024	-2.128	0.033
Watanabe, 2015, PI	-0.250	0.071	0.005	-0.390	-0.110	-3.511	0.000
Watanabe, 2015, PR	0.000	0.054	0.003	-0.106	0.106	0.000	1.000
Lo 2015	0.090	0.111	0.012	-0.127	0.307	0.814	0.415
Emami, 2015	-0.020	0.023	0.001	-0.065	0.025	-0.866	0.386
Van der Valk, 2016	-0.140	0.010	0.000	-0.160	-0.120	-13.627	0.000
Kim, 2020	-0.100	0.096	0.009	-0.288	0.088	-1.041	0.298
Boczar, 2022	-0.050	0.148	0.022	-0.340	0.240	-0.338	0.735
Pooled	-0.100	0.030	0.001	-0.159	-0.042	-3.363	0.001
Prediction Interval	-0.100			-0.303	0.102		



B.

Study name	Point	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Ishii , 2010, A 5mg	-0.107	0.033	0.001	-0.172	-0.042	-3.214	0.001
Ishii , 2010, A 20mg	-0.100	0.033	0.001	-0.165	-0.035	-3.019	0.003
Wu, 2012	-0.073	0.026	0.001	-0.124	-0.021	-2.781	0.005
Tawakol, 2013, A 10mg	-0.108	0.031	0.001	-0.169	-0.047	-3.479	0.001
Tawakol, 2013, A 80mg	-0.096	0.031	0.001	-0.158	-0.035	-3.065	0.002
Subramanian, 2013, A 10mg	-0.111	0.030	0.001	-0.170	-0.053	-3.738	0.000
Subramanian, 2013, A 80mg	-0.094	0.030	0.001	-0.153	-0.034	-3.094	0.002
Watanabe, 2015, PI	-0.089	0.031	0.001	-0.149	-0.029	-2.895	0.004
Watanabe, 2015, PR	-0.109	0.031	0.001	-0.170	-0.048	-3.507	0.000
Lo 2015	-0.109	0.030	0.001	-0.168	-0.050	-3.604	0.000
Emami, 2015	-0.110	0.032	0.001	-0.172	-0.047	-3.431	0.001
Van der Valk, 2016	-0.095	0.036	0.001	-0.165	-0.024	-2.622	0.009
Kim, 2020	-0.100	0.031	0.001	-0.161	-0.040	-3.237	0.001
Boczar, 2022	-0.102	0.030	0.001	-0.161	-0.042	-3.341	0.001
Pooled	-0.100	0.030	0.001	-0.159	-0.042	-3.363	0.001
Prediction Interval	-0.100	0.000	0.000	-0.303	0.102	0.000	0.000

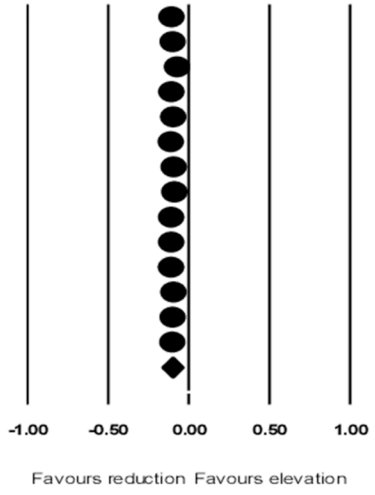


Fig. 2 Quantitative Data Synthesis (arterial wall uptake). **A** Effect of statin therapy on arterial wall FDG uptake. Forest plot shows weighted mean difference (WMD) and 95% confidence intervals for the effect of statin administration on arterial wall FDG uptake based on whole vessel TBR index. 2 **B** leave-one-out sensitivity analysis

CT which showed that the anti-inflammatory effect of statins was substantially greater within unstable coronary plaques improving their internal composition and architecture [51].

Since the results of all these studies were to a certain degree controversial, this meta-analysis was performed hoping that it can give some clear answers to the still open questions concerning the effect of statins on inflammation of the artery wall by using the 18 F-FDG PET CT tenique.

This study has some limitations. One of them is that the clinical outcomes were not assessed since none of the included studies had this data. However, our findings suggest that statins had a beneficial effect decreasing inflammation in the arteries' wall and most probably are even beneficial for the plaque composition because they suppress the intraplaque inflammation. Therefore, there

A.

Study name	Difference in means	Standard error	Statistics for each study: Variance	Lower limit	Upper limit	Z-Value	p-Value
Tawakol, 2013 A10mg	-0.100	0.146	0.021	-0.385	0.185	-0.687	0.492
Tawakol, 2013 A 80mg	-0.360	0.099	0.010	-0.553	-0.167	-3.654	0.000
Lo, 2015	-0.030	0.085	0.007	-0.197	0.137	-0.352	0.725
Emami, 2015	-0.170	0.016	0.000	-0.202	-0.138	-10.410	0.000
Van der Valk, 2016	-0.240	0.017	0.000	-0.273	-0.207	-14.120	0.000
Pooled	-0.194	0.035	0.001	-0.262	-0.126	-5.594	0.000
Prediction Interval	-0.194			-0.400	0.012		

B.

Study name	Point	Standard error	Statistics with study removed: Variance	Lower limit	Upper limit	Z-Value	p-Value
Tawakol, 2013 A10mg	-0.199	0.036	0.001	-0.270	-0.127	-5.463	0.000
Tawakol, 2013 A 80mg	-0.178	0.035	0.001	-0.247	-0.110	-5.098	0.000
Lo, 2015	-0.214	0.033	0.001	-0.280	-0.149	-6.423	0.000
Emami, 2015	-0.196	0.064	0.004	-0.322	-0.070	-3.043	0.002
Van der Valk, 2016	-0.167	0.057	0.003	-0.278	-0.056	-2.955	0.003
Pooled	-0.194	0.035	0.001	-0.262	-0.126	-5.594	0.000
Prediction Interval	-0.194	0.000	0.000	-0.400	0.012	0.000	0.000

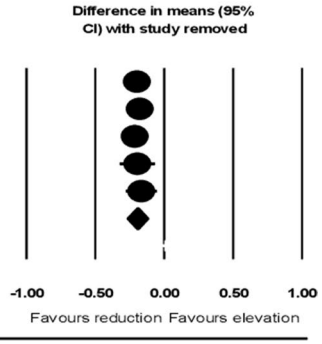


Fig. 3 Effect of statin therapy on FDG uptake of the most diseased arterial segment (MDS). Forest plot displays weighted mean difference (WMD) and 95% confidence intervals for the effect of statin administration on arterial wall FDG uptake based on the MDS of vessel TBR

Group by intensity	Study name	Difference in means	Standard error	Statistics for each study: Variance	Lower limit	Upper limit	Z-Value	p-Value
High	Wu, 2012	-0.420	0.055	0.003	-0.528	-0.312	-7.651	0.000
High	Tawakol, 2013, A 80mg	-0.150	0.068	0.005	-0.283	-0.017	-2.208	0.027
High	Subramanian, 2013, A 80mg	-0.300	0.141	0.020	-0.576	-0.024	-2.128	0.033
High	Lo 2015	0.090	0.111	0.012	-0.127	0.307	0.814	0.415
High	Emami, 2015	-0.020	0.023	0.001	-0.065	0.025	-0.866	0.386
High	Van der Valk, 2016	-0.140	0.010	0.000	-0.160	-0.120	-13.627	0.000
High	Pooled	-0.154	0.053	0.003	-0.258	-0.051	-2.918	0.004
High	Prediction Interval	-0.154			-0.494	0.186		
Low to Moderate	Ishii , 2010, A 5mg	-0.040	0.024	0.001	-0.086	0.006	-1.690	0.091
Low to Moderate	Ishii , 2010, A 20mg	-0.100	0.034	0.001	-0.166	-0.034	-2.953	0.003
Low to Moderate	Tawakol, 2013, A 10mg	0.000	0.069	0.005	-0.134	0.134	0.000	1.000
Low to Moderate	Subramanian, 2013, A 10mg	0.190	0.128	0.016	-0.060	0.440	1.489	0.137
Low to Moderate	Watanabe, 2015, PI	-0.250	0.071	0.005	-0.390	-0.110	-3.511	0.000
Low to Moderate	Watanabe, 2015, PR	0.000	0.054	0.003	-0.106	0.106	0.000	1.000
Low to Moderate	Kim, 2020	-0.100	0.096	0.009	-0.288	0.088	-1.041	0.298
Low to Moderate	Boczar, 2022	-0.050	0.148	0.022	-0.340	0.240	-0.338	0.735
Low to Moderate	Pooled	-0.059	0.031	0.001	-0.120	0.001	-1.931	0.053
Low to Moderate	Prediction Interval	-0.059			-0.219	0.100		
Overall	Pooled	-0.083	0.027	0.001	-0.136	-0.031	-3.136	0.002
Overall	Prediction Interval	-0.083			-0.284	0.117		

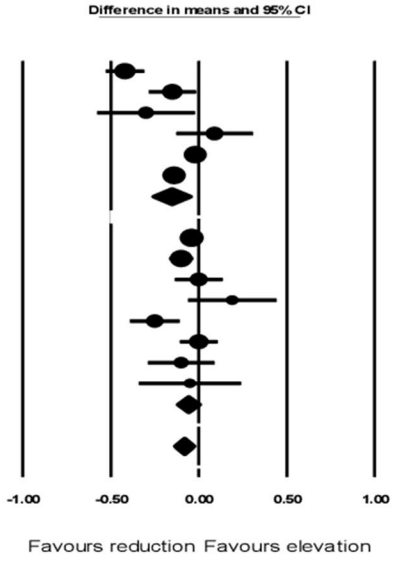


Fig. 4 Forest plot stratified according to the intensity of statin therapy

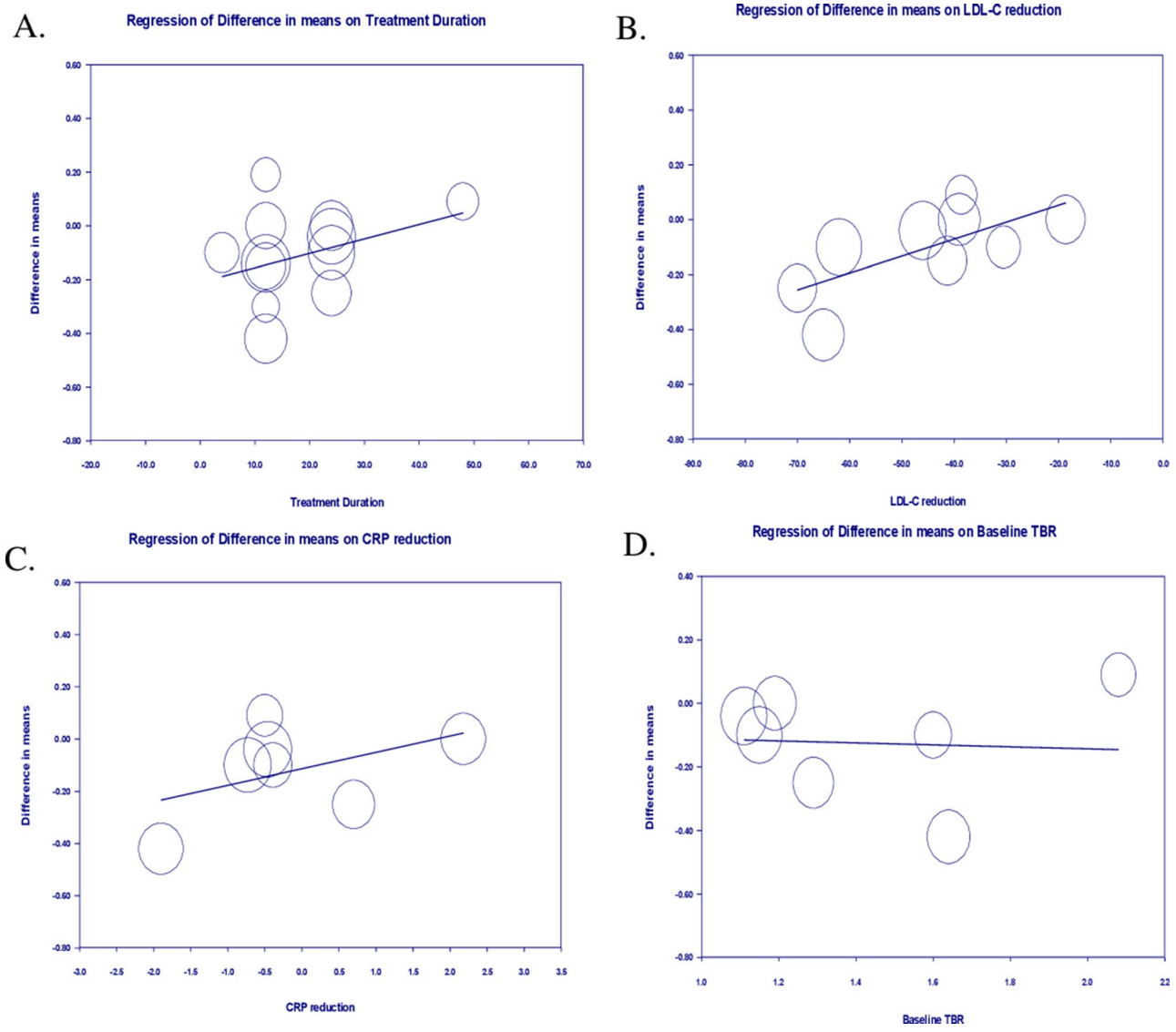


Fig. 5 The results of meta-regression analyses examining the associations between different potential confounders and changes in arterial wall TBR. The analysis investigated the relationship between (**A**) treatment duration, (**B**) alteration in circulating LDL-cholesterol, (**C**) plasma levels of C-reactive protein, (**D**) baseline TBR, and mean changes in arterial wall TBR index

is a possibility that this might be a part of the explanation why is the treatment with statins beneficial preventing ASCVD and decreases clinical outcomes. Another limitation is that we could not explain why the duration of statin therapy, variations in circulating levels of LDL-cholesterol and CRP or initial values of TBR had no impact on TBR values following treatment with statins. Finally, considering the introduction of new cholesterol-lowering agent that can be used on top of statin therapy [52–56], it remains unclear if combination of statins with newer medications in high-risk patients could affect the attenuating impact of statins on arterial wall inflammation.

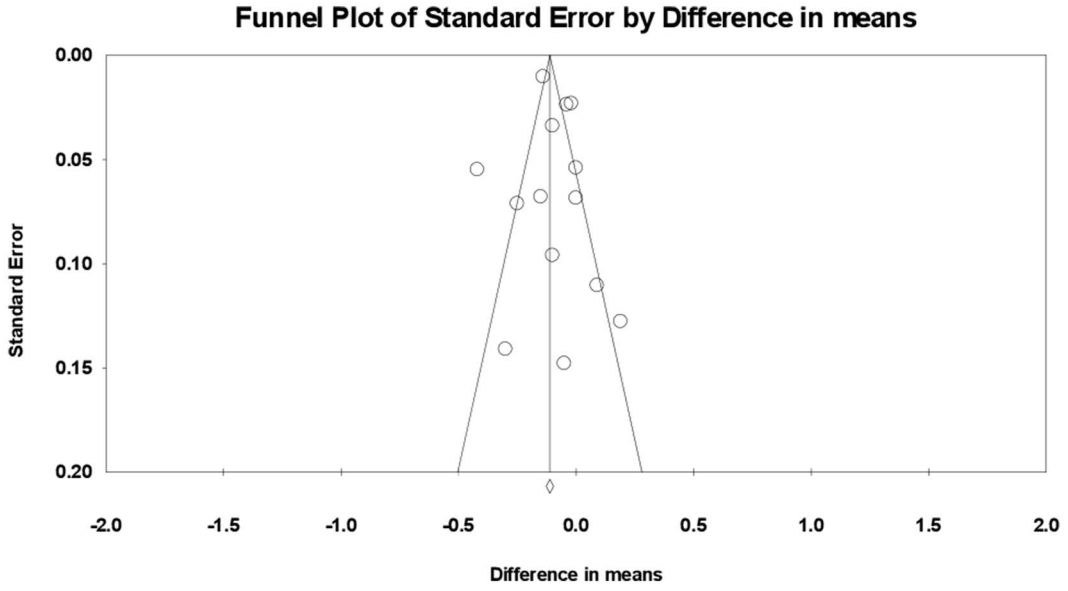


Fig. 6 Funnel plot showing publication bias in the studies

Conclusion

This meta-analysis clearly showed a decrease of arterial wall inflammation after treatment with statins based on a significant reduction of arterial wall 18 F-FDG uptake according to TBR index using 18 F-FDG PET-CT. It has been also shown that 18 F-FDG PET-CT might be a useful noninvasive method to evaluate the degree of arterial wall inflammation.

Author contributions

Conceptualization: AS Writing-original draft: TJ Writing-review and editing: ZR, LES, WA, SK, AHE, FG, AS Approval of the final version: All authors.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethical approval

Not applicable.

Consent to participate

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Consent for publication

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Competing interests

The authors declare no competing interests.

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