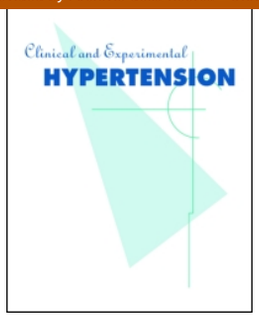

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Effect of statin therapy on pulse wave velocity: A meta-analysis of randomized controlled trials

Lanfranco D'elia [a], Ersilia La Fata[a], Arcangelo Iannuzzi[b], and Paolo O. Rubba[a]

[a]Department of Clinical Medicine and Surgery, "Federico II" University of Naples Medical School, Naples, Italy; [b]Department of Medicine and Medical Specialties, A. Cardarelli Hospital, Naples, Italy

ABSTRACT

Background and Objective: Arterial stiffness (AS) is an independent cardiovascular risk factor. A number of studies have reported a beneficial role of statins on AS albeit with controversial results, in addition to their effects on lipid profile. Therefore, we carried out a meta-analysis of the available randomized controlled trials assessing the effects of statin therapy on AS, in the attempt to reach more definitive conclusions. *Methods:* A systematic search of the on-line databases available up to March 2017 was conducted, including intervention studies reporting AS expressed by carotid-femoral pulse wave velocity (PWV), as difference between the effects of treatment with or without statins. For each study, mean difference (MD) and 95% confidence intervals (CI) were pooled using a random effect model. *Results:* Eleven studies met the pre-defined inclusion criteria, for a total of 573 participants and 2–144 weeks' intervention time. In the pooled analysis, statin therapy was associated with a −6.8% (95% C.I.: −11.7 to −1.8) reduction in PWV. There was significant heterogeneity among studies (I^2 = 96%); none of the study characteristics seems to have influenced the effect of statin use on PWV. *Conclusions:* The results of this meta-analysis suggest that statin therapy reduces AS. This effect appears to be at least in part independent of the changes in blood pressure and lipid profile.

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Pulse wave velocity; Arterial stiffness; Statins; HMG-CoA-reductase inhibitors; Cardiovascular disease prevention; Meta-analysis

Introduction

Carotid-femoral pulse wave velocity (PWV), the gold standard of non-invasive arterial stiffness measurement, is an independent predictor of cardiovascular outcomes in both the general population and patients at high risk of cardiovascular disease (1 –3). A number of studies have reported a beneficial role of statins on arterial stiffness, in addition to their effects on lipid profile (4). In particular, experimental studies have shown a favorable *pleiotropic* effect of statins on cardiovascular risk through their role in enhancing nitric oxide bioavailability (5), their antioxidant effect (6), and their interaction with the renin-angiotensin-aldosterone system (7).

However, some of the intervention studies carried out were flawed by their low statistical power and the heterogeneity of the participants' features (4,8–10). Recently, a meta-analysis also tried to provide definite evidence of the favorable effect of statin therapy on arterial stiffness (11), but this study as well had major limitations, as it included studies using different indices of arterial stiffness, did not report other published randomized controlled trials, and did not assess possible confounders of the relationship.

In the attempt to provide stronger evidence of the role of statins on arterial stiffness, we carried out a meta-analysis of the available randomized clinical trials meeting strictly predefined inclusion criteria to test the hypothesis that statin use reduces PWV—as estimate of arterial stiffness, calculate the extent of this effect and, lastly, evaluate the effect of potential confounders on this relationship.

Methods

Data sources and search strategy

This meta-analysis was planned, conducted, and reported according to the PRISMA statement (12) (Supplementary Table S1). We performed a systematic search of the available publications using MEDLINE, Scopus, and the Cochrane Library, up to March 2017 (updated to 29 March 2017). The search strategy, without restrictions, used the expressions "statin" OR "statins" OR "HMG-coa reductase inhibitor" AND "pulse wave velocity" OR "PWV" OR "arterial stiffness" OR "aortic stiffness" OR "arterial compliance", or combinations thereof, either in medical subject headings or in the title/abstract. Further information was retrieved through a manual search of references from recent reviews and relevant published original studies.

Study selection

For a published study to be included in the meta-analysis, the following criteria had to be met: (a) original article, (b) adult population study, (c) randomized controlled trial, (d)

CONTACT Lanfranco D'Elia lanfranco.delia@unina.it Department of Clinical Medicine and Surgery; "Federico II" University of Naples Medical School, Via S. Pansini, 5, Naples 80131 Italy.

Lanfranco D'Elia and Ersilia La Fata authors contributed equally to this work

Supplemental data for this article can be accessed on the publisher's website.

indication of a difference in PWV between statin use and no statin use in one or more patients' cohorts, (e) indication of the number of participants included in the exposed and control group of each cohort.

Data extraction and quality assessment

Two reviewers (LD, ELF) independently assessed study eligibility and extracted the data. Discrepancies over the inclusion of studies and the interpretation of the data were resolved in conference, and consensus was reached after discussion.

The main characteristics of the studies identified and the respective populations are recorded and reported in Table 1. The risk of bias of the studies included in the meta-analysis was independently assessed by two reviewers (LD, ELF) according to established criteria (16), and reported in Supplementary Table S2.

Statistical analysis

A detailed description of the statistical methods has been reported previously (17,18). Mean differences (MD) and standard error (SE) of the defined outcomes were extracted from the selected publications. In case these were not available, MD and SE were calculated from the comparison of the outcomes during statin therapy against no statin use. Because of the heterogeneity among studies of baseline levels and the subsequent changes, the between-regimen changes in PWV were utilized in the analyses after conversion to percentages. The pooled MD and 95% confidence interval (CI) was estimated using a random-effect model (19). The Cochrane Q test and the I^2 statistic were used to evaluate statistical heterogeneity across the studies. Funnel plots were constructed and visually assessed for possible publication bias (20). Egger's weighted regression test and Begg's rank correlation test were also used to explore potential publication bias. In case of significant funnel plot asymmetry, the pooled MD estimate was recalculated by the "trim and fill" method (21). The influence of the individual cohorts or of a particular study was estimated by sensitivity analysis. Moreover, meta-regression and subgroup analyses were used to identify associations between changes in PWV and relevant study or patient characteristics as possible sources of heterogeneity. Given the substantial difference in treatment duration between the study carried out by Fassett et al (13) and other trials included, separate analyses were also performed excluding this study. All statistical analyses were performed using the Stata Corp. software (version 11.2, College Station, Texas, USA) and the graphic representation was carried out by MIX software (version 1.7, Kitasato Clinical Research Center, Kanagawa, Japan) (22).

Results

Characteristics of the studies included in the meta-analysis

Of a total of 662 publications retrieved (Figure 1), 24 studies were potentially relevant and were reviewed in full-text (8–10,13–15,23–41). Thirteen of them were excluded because

Table 1. Characteristics of the studies included in the meta-analysis.

First Author, year (ref)	Country	Cohort (n. of participants)	Selected features of the study participants	Mean Age (yrs)	Mean BMI (Kg/m^2)	Duration of intervention (wks)	Assessment Method	Comparison (n. of participants)	Study Design
Fassett et al. (13)	Australia	CKD patients (21M,13W)	CKD (serum creatinine >1.36 mg/dL), all levels of serum cholesterol and proteinuria	63.6	28.6	144	Applanation tonometry (Sphygmocor)	Atorvastatin 10 mg (16) vs Placebo (18)	PA-DB
Wallaceet al. (8)	United Kingdom	Healthy participants (24M,26W)	Volunteers without cardiovascular risk factors	26.0	23.2	2	Applanation tonometry (Sphygmocor)	Simvastatin 40 mg (25) vs Placebo (25)	PA-DB
Kanaki et al. (14)	Greece	Hypertensive and Hypercholesterolemic patients (24M,26W)	Hypertension (SBP: 140–160, DBP: 90–100 mm Hg, under antihypertensive treatment - 1 agent or stage 1 hypertension without treatment), Hypercholesterolemia without hypolipidemic treatment (LDL >3.4 mmol/L associated with 1–2 cardiovascular risk factors or LDL > 3.9 mmol/L at low cardiovascular risk)	59.2	29.5.	26	Applanation tonometry (Sphygmocor)	Atorvastatin 10 mg (25) vs Placebo (25)	PA-DB
Joyeux-Faure et al. (9)	France, Switzerland	OSA patients (40M, 11W)	OSA, no CVD, no statin and antihypertensive treatment	54.0	28.5	12	Pressure transducer (Complior)	Atorvastatin 40 mg (25) vs Placebo (26)	PA-DB
Ballard et al. (15)	US	Patients with statin myalgia (67M, 48W)	Myalgia during statin treatment	60.3	28.4	8_a	Applanation tonometry (Sphygmocor)	Simvastatin 20 mg (100) vs Placebo $(100)_b$	CO-DB
John et al. (10)	United Kingdom	COPD patients (50M, 20W)	COPD, hypercholesterolemia <6.5 mmol/L	64.5	-	6	Applanation tonometry (Sphygmocor)	Simvastatin 20 mg (31) vs Placebo $(32)_b$	PA-DB

M: men; W: women; CAD: coronary artery disease; CO: crossover; PA: parallel-arm; DB: double-blind; OL: open-label intervention; CVD: cardiovascular disease; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; OSA: obstructive sleep apnea; CKD: chronic kidney disease; COPD: chronic obstructive pulmonary disease; $_a$ the duration of intervention in myalgic patients was comprised between 1 and 3 weeks $_b$ PWV available for a sub-group of participants.

they reported the outcomes as difference from baseline (28–32) or did not report outcomes of interest (33–40). Overall, 11 studies met the inclusion criteria and were used for the meta-analysis (8–10,13–15,23–27). The relevant features of the studies are provided in Table 1. The meta-analysis involved a total of 573 male and female participants from 10 countries six from Europe, 2 from the USA and Australia, and 1 from China. The duration of the interventions ranged from 2 to 144 weeks.

Nine studies recruited patients with hypercholesterolemia —this was the only disease in two studies (23,25)—while in the other studies hypercholesterolemia was associated with hypertension (14,24), mialgia (15), coronary artery disease (26), owerweight/obesity (27), obstructive sleep apnea syndrome (9), or chronic renal failure (13); lastly, only one study included healthy participants (8) or patients with chronic obstructive pulmonary disease (10). All the studies recruited both male and female participants. PWV was assessed by different methods, six studies using applanation tonometry (Sphygmocor device - PWV Medical Pty. Ltd., Sidney, Australia) (8,10,13–15,25) and the other investigations using a pressure transducer (three the Complior device, Colson Medicals, France; one Windaq, and other one generic brand) (9,23,24,26,27). All had a cross-over design (15,23), except for two which had a parallel-arms design. Nine investigations were double blinded for the use of placebo, whereas another one was open-label (25). Blinding was not specified in one study (26). Six studies evaluated the effects of Atorvastatin, four estimated the effects of Simvastatin, and only one assessed the effects of Rosuvastatin (25). External funding sources were declared in all but two studies (25,26); five received pharmaceutical industry funding. The evaluation of the "risk of bias" indicated that all studies were at low-risk (Supplementary Table S2).

Effect of statin use on PWV

Detailed features of the eleven studies (with overall 573 participants) included in this analysis are given in Table 1 and Supplementary Table S2 (8–10,13–15,23–27). In the pooled analysis, the use of statins was associated with a significantly lower average PWV (–6.8%, 95% CI: −11.7 to −1.8; $p < 0.01$) compared with no use. There was significant between-study heterogeneity (Q = 245.5, $p < 0.01$; $I^2 = 96\%$) (Figure 2).

The evaluation of the individual studies showed a trend toward a favorable association between statin use and PWV in eight studies (10,13–15,23,25–27), with a significant reduction in five of them (14,15,25–27). Conversely, a non-significant adverse association was observed in another three investigations (8,9,24). Sensitivity analysis showed that the average change in PWV did not vary substantially when any individual study was excluded (Supplementary Table S3). The funnel plot for the effect of statin use on PWV change indicated an asymmetrical distribution at the visual inspection. Although Egger's and Begg's tests did not detect a significant publication bias (Egger: $p = 0.72$, Begg: $p = 0.62$), the "trim and fill" method, which identified three possibly missing studies, showed a change of the effect from −6.8% to −10.5% in PWV (MD = −10.5%; −15.7% to −5.4%).

Pooled analysis excluding the study by Fassett and collaborators (13) (including ten studies and 539 total participants) showed that statin use was associated with a significant and favorable effect on PWV (MD = −7.2%, 95% CI: −12.4 to −1.9; $p < 0.01$) compared with no use. The sensitivity analysis did not

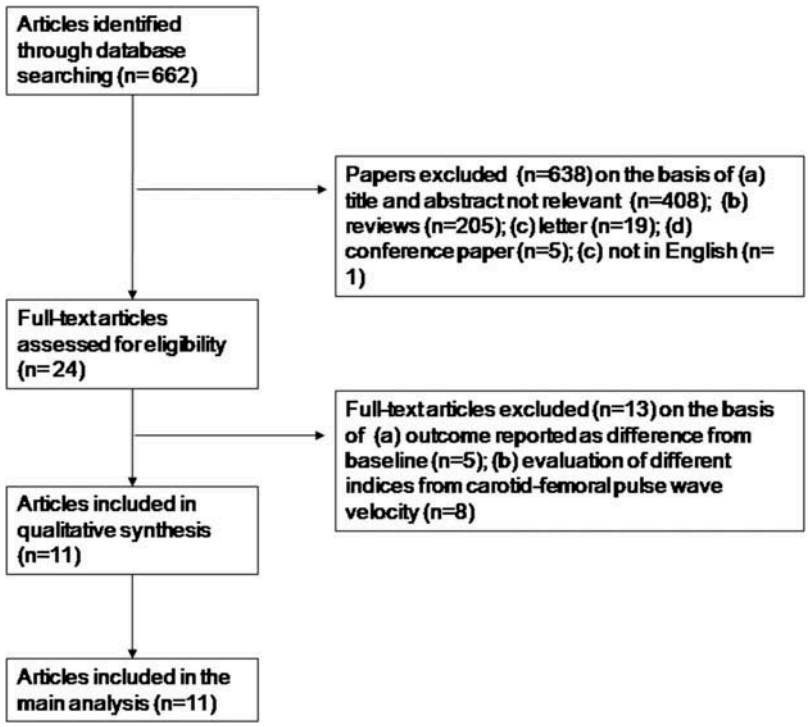

Figure 1. Stepwise procedure for selection of the studies.
Flowchart indicating the results of the systematic review with inclusions and exclusions.

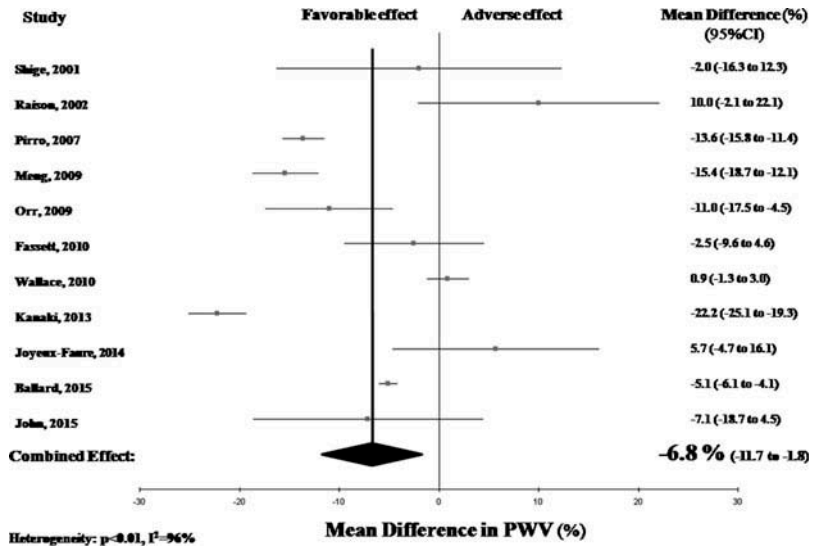

Figure 2. Effect of statin use on carotid-femoral pulse wave velocity (PWV).
Forest plot of the effect of statin use on PWV in 11 published studies. Results are expressed as Mean Difference (MD) (%) and 95% confidence intervals (95% CI).

show substantially changes in the effect of statin use (Supplementary Table S4). There was a significant heterogeneity among studies (Q = 244.0, p < 0.01; I^2 = 96%), and there was no evidence of publication bias (Egger's test: p = 0.67, Begg's test: p = 0.59). However, the "trim and fill" method once again identified two possibly missing studies, modifying the pooled estimate to a MD of −9.9% (95% CI: −15.0% to −4.9%).

Additional analyses

The meta-regression analysis indicates that the lipid profile, that is, total cholesterol, LDL-cholesterol, triglycerides and HDL-cholesterol, did not affect the effect of statin on PWV, either at baseline or after treatment (p > 0.05) (Table 2, Supplementary Table S5). Likewise, baseline blood pressure (BP) values and their changes after treatment (i.e. systolic and diastolic BP, and mean arterial pressure) did not affect the relationship between statin use and PWV changes (p > 0.05) (Table 2, Supplementary Table S5).

A separate analysis including the studies with hypercholesterolemic participants (9,13–15,23–27) found a favorable effect of statin use on PWV (MD = −7.7%, −13.3 to −2.1; p < 0.01), also when the study by Fassett and collaborators was excluded (MD = −8.3%, −14.3 to −2.3; p < 0.01). The analysis stratified by countries of study development suggested a stronger association between statin use and changes in PWV in studies performed in the USA compared to those carried out in Europe, Australia and China, but the comparison did not achieve statistically significant difference (Table 3, Supplementary Table S6).

Likewise, the studies that utilized applanation tonometry as instrumental method for measurement of PWV tended to provide a stronger effect of statin use than those utilizing pressure transducer, but the comparison did not achieve statistically significant difference (Table 3, Supplementary Table S6). In addition, subgroup analysis in relation to the type of statin utilized did not detect significant differences in the effect produced (Table 3, Supplementary Table S6).

Age, BMI, year of publication, total number of participants, gender, and length of the intervention and PWV at baseline were no significant sources of heterogeneity by meta-regression analyses (Table 2, Supplementary Tables S5).

Discussion

The results of this meta-analysis indicate a direct association between statin use and decreased arterial stiffness in the controlled randomized intervention trial of statin use having PWV changes as the main endpoint. This effect appears to be at least in part independent of the changes in BP and lipid profile.

This finding was strengthened by the detection of a favorable effect in as many as 8 of the 11 individual cohorts included in the analysis and by the observation that a (not significant) opposite trend was reported in only three studies (8,9,24). However, one of them included a sample of healthy young participants with low PWV at baseline, and short length of intervention (8). Another study involved patients with obstructive sleep apnea syndrome, without comorbidities, and that exhibited low stiffening at baseline (9). Finally, the unfavorable effect was found in a small study with participants on stable antihypertensive therapy, in whom the vascular benefit of statin use may have been concealed (24). Although PWV is known to be strongly associated with age (41,42), we failed to find significant differences in the effect of statin use on PWV as a function of the mean age of the various study cohorts. It is worth noting that a reduction in BP was observed in eight of the 11 studies; two did not report any information on BP (15,26), while only one detected an increase in BP after treatment (24). The greater reduction in BP was observed in participants without antihypertensive treatment (9), while the inverse effect of statin on BP was described in a small trial with patients on stable antihypertensive therapy (24). Despite the strong association between BP and PWV (41,42), and also the evidence of a favorable effect

Table 2. Meta-regression analysis of the effect of statin treatment on pulse wave velocity.

Variables (n. of studies)	ΔPWV (%) (coefficient)	95% CI	p-value
Age (years) (11)	−0.29	−0.98 to 0.31	0.30
BMI (Kg/m^2) (10)	−0.70	−3.99 to 2.57	0.63
Year of publication (year) (11)	−0.53	−2.11 to 1.04	0.46
Length of intervention (week) (11)	0.01	−0.17 to 0.18	0.93
Number of participants (n) (11)	−0.08	−0.33 to 0.17	0.51
Gender (% men) (11)	0.52	−0.01 to 1.05	0.05
PWV at baseline—statin group (10)	−1.72	−5.03 to 1.58	0.26
PWV at baseline—not statin group (10)	−1.61	−4.91 to 1.68	0.29
Total Cholesterol at baseline (mmol/L) (11)	0.03	−8.31 to 8.38	0.99
LDL-cholesterol at baseline (mmol/L) (11)	−2.23	−11.39 to 6.92	0.59
Triglycerides at baseline (mmol/L) (9)	−0.15	−7.47 to 7.17	0.96
HDL-cholesterol at baseline (mmol/L) (11)	23.62	−2.65 to 49.89	0.07
Total cholesterol difference (mmol/L) (11)	−1.47	−16.92 to 13.98	0.83
LDL-cholesterol difference (mmol/L) (10)	1.40	−6.14 to 8.94	0.68
Triglycerides difference (mmol/L) (8)	5.77	−10.63 to 22.17	0.42
HDL-cholesterol difference (mmol/L) (10)	14.00	−17.94 to 45.95	0.34
Systolic blood pressure at baseline (mm Hg) (11)	−0.09	−0.69 to 0.50	0.73
Diastolic blood pressure at baseline (mm Hg) (11)	0.04	−1.23 to 1.30	0.95
Mean arterial pressure at baseline (mm Hg) (11)	−0.07	−1.06 to 0.92	0.88
Systolic blood pressure difference (mm Hg) (8)	0.62	−2.47 to 3.71	0.64
Diastolic blood pressure difference (mm Hg) (8)	1.58	−2.94 to 6.10	0.42
Mean arterial pressure difference (mm Hg) (8)	0.94	−3.58 to 5.47	0.63

PWV: pulse wave velocity, CI: confidence interval.

Table 3. Subgroup analysis of the effect of statin treatment on pulse wave velocity.

	Variables (n. of cohorts)	Pooled mean (%) reduction PWV	95% CI	*p* for heterogeneity
Country of origin	Europe (6)	−5.2	−14.8 to 4.4	0.9
	US (2)	−7.1	−12.6 to −1.6	
	AUS - China (3)	−7.6	−18.2 to 2.9	
PWV assessment device	Pressure transducer (5)	−3.6	−13.2 to 5.9	0.4
	Applanation tonometry (6)	−8.5	−15.0 to −1.9	
Type of statin	Atorvastatin (6)	−7.2	−15.4 to 1.0	0.4
	Simvastatin (4)	−2.8	−7.7 to 2.1	

PWV: pulse wave velocity, CI: confidence interval

of statin use on BP (43), the results of our meta-regression analysis suggest that the effect of statin use on PWV changes may be independent of the BP changes that occurred during the trials. Likewise, also baseline BP values of the individual studies were not a significant source of heterogeneity.

In all the studies included, there was a significant reduction in total cholesterol during statin therapy, ranging from 0.8 mmol/L in healthy participants (8) to 2.3 mmol/L in patients with sleep apnoea (9). In addition, three of these studies found a positive association between changes in total and LDL cholesterol, and PWV changes (15,25,27). Despite the favorable effect of statin use on cholesterol levels, the changes observed did not affect the relationship between statin use and the reduction in PWV by meta-regression analysis. Similar results were also found for all other lipid parameters evaluated.

Subgroup analysis by type of statin only explored the comparison between atorvastatin and simvastatin—the two most representative classes. Despite the data showing different power between statin classes in terms of cholesterol reduction (44), the comparison did not detect significant difference in the effect of statin treatment on PWV. Analysis stratified by different geographical location suggested a better (but not statistically different) effect in the US than in Europe, Australia or China. However, this result may be affected by the small number of studies included in the subgroup. Similarly to what reported by *Salvi and collaborators* (45), our analysis shows a trend towards differing results in relation to the instrumental method used for PWV measurement, although the difference was not confirmed by subgroup analysis. Noteworthy, there was a large difference between duration of the trials included, from 2 to 144 weeks, but the meta-regression analysis did not show this difference as source of heterogeneity. Other meta-regression analyses failed to find any significant influence for number of participants, gender, BMI and PWV at baseline.

According to the meta-analysis by Upala et al., statin use was associated with reduced arterial stiffness (11). That study was also characterized by severe limitations: the number of randomized controlled trials included was smaller, the indices of arterial stiffness adopted in the studies were different (four studies evaluated carotid-femoral PWV (8,14,25,27), one brachial-ankle PWV (40) and other one carotid PWV (39)), and no potential confounders were explored. Conversely, our meta-analysis included a larger number of randomized controlled trials reporting only the values of carotid-femoral PWV, and took into account a large number of potential confounders.

Our study had no specific potential to address the mechanisms of the effect of statin use on arterial stiffness. It is possible that statins exert direct effects on the arterial wall and its components, above and beyond those produced by the changes in lipid parameters (*pleiotropic* effect). Statin treatment may reduce vascular tone by enhancing the nitric oxide availability through the increased expression of endothelial nitric oxide synthase (5,46). Statin therapy may also decrease oxidative stress, by inhibiting reactive oxygen species production (6). Several experimental studies point to the renin-angiotensin-aldosterone system as possible target. Indeed, statin treatment has been shown to down-regulate the expression of angiotensin II type 1 (AT1) receptor in the vascular smooth muscle cells (7,47), and to counteract the effect of concomitant structural alteration in arterial wall mediated by angiotensin II (48). In addition, statins may inhibit endothelin-1 production in vascular smooth muscle cells (49,50), thus reducing the sympathetic activity (51).

In addition to the *pleiotropic* effect, the heterogeneity among participants included could at least in part explain the (BP and lipid profile) independent effect of statins on PWV. Indeed, the trials included were carried out on cohorts both at high cardiovascular risk (e.g. patients with coronary artery disease or chronic kidney disease) and at low risk (e.g. healthy participants). Also the different on-going therapy and duration of the treatment (e.g. use of antihypertensive therapy), as well as the different age or weight among participants, could affect the relationship. In addition, the lifestyle of the participants, such as physical activity or dietary

habits—not evaluated at baseline and during intervention—may potentially affect the results. However, the process of meta-analysis, with the calculation of a pooled estimate of the effect, is functional to overcome at least in part this problem.

The following are the major strengths of our meta-analysis: i) the inclusion of randomized controlled trials only; ii) the inclusion only of studies reporting carotid-femoral PWV—the gold standard of non-invasive measurement of arterial stiffness; iii) all the studies provided cohorts at "low" risk of bias; iv) the finding of a trend to reduction of arterial stiffness during statin use in most cohorts; v) the evaluation of a large number of possible sources of heterogeneity.

On the other hand, the value of our findings is limited by the relatively small number of study cohorts available, by the small number of participants enrolled in the individual trials, and by the large number of features of the participants included. Nevertheless, the effect of statins was significantly favorable in a separate analysis including only the studies with hypercholesterolemic participants.

Furthermore, given the large difference in the duration of the observation between Fassett's investigation and the other studies, the analyses were conducted also without the former (13), yielding similar results. Another limitation is the detectable publication bias, although the "trim and fill" method identified a number of possibly missing studies and indicated an underestimation of the effect of statin. Given the heterogeneity of the type of statin utilized and the limited data for individual class, we were unable to examine a possible dose-response relationship. Finally, a weakness of our study is the fact that no definitive conclusions can be drawn on the long-term effects of statin use on arterial stiffness, since only three of the trials included in the meta-analysis had an intervention period longer than 12 weeks.

In conclusion, the results of this meta-analysis show that use of statin reduces arterial stiffness, at least in part independently of concomitant changes in BP and lipid levels. Given the importance of arterial stiffness as predictor of cardiovascular and all-cause mortality (1–3,52), the effect of statin significantly adds to its already recognized value in cardiovascular disease prevention. Indeed, based on previous studies indicating increments in cardiovascular events and mortality for each 1 m/s increase in PWV (3), a 7% decrease in PWV with statin use is expected to translate into a substantial reduction in cardiovascular risk. In consideration of our results, statin use may be beneficial for hypercholesterolemic patients but also for patients affected by other conditions (28,32).

On research grounds, our systematic review underlines the lack of properly powered randomized controlled trial of the effect of long-term statin use on arterial stiffness; therefore, an effort in this direction is warranted to further support the conclusions of our meta-analysis and expand current knowledge in this field.

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Declaration of interest

The authors declare no conflicts of interest. The authors are responsible for the content and writing of the paper.

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Notes on contributor

Research idea and study design: LD, ELF; data acquisition: LD,ELF; data analysis/interpretation: LD,ELF,AI; statistical analysis: LD,ELF; supervision or mentorship: PR. Each author contributed important intellectual content during manuscript drafting or revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved. All authors read and approved the final manuscript.

ORCID

Lanfranco D'elia http://orcid.org/0000-0002-1782-0211

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