

Central and Brachial Blood Pressures, Statins, and Low-Density Lipoprotein Cholesterol A Mediation Analysis

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Abstract—Central blood pressure may be a better predictor of cardiovascular disease than brachial pressure. Although statins reduce brachial pressure, their impact on central pressure remains unknown. Furthermore, whether this effect is mediated through a decrease in low-density lipoprotein cholesterol (LDL-c) is unknown. This study aims to characterize the association of statins and LDL-c with central and brachial blood pressures and to quantify their respective effects. Of the 20004 CARTaGENE participants, 16507 had available central blood pressure, LDL-c, and Framingham risk score. Multivariate analyses were used to evaluate the association between central pressure and LDL-c in subjects with or without statins. The impact of LDL-c on the association between statin and pressure parameters was determined through mediation analyses. LDL-c was positively associated with systolic and diastolic central pressure in nonusers ($\beta=0.077$ and 0.106 ; $P<0.001$) and in participants with statins for primary ($\beta=0.086$ and 0.114 ; $P<0.001$) and secondary prevention ($\beta=0.120$ and 0.194 ; $P<0.003$). Statins as primary prevention were associated with lower central systolic, diastolic, and pulse pressures (-3.0 , -1.6 , and -1.3 mm Hg; $P<0.001$). Mediation analyses showed that LDL-c reduction contributed to 15% of central systolic and 44% of central diastolic pressure changes associated with statins and attenuated 22% of the effects on central pulse pressure. Similar results were found with brachial pressure components. In conclusion, reduction of LDL-c was associated with only a fraction of the lower blood pressures in statin user and seemed to be mostly associated with improvement of steady (diastolic) pressure, whereas non-LDL-c-mediated pathways were mostly associated with changes in pulsatile pressure components. (*Hypertension*. 2018;71:415-421. DOI: 10.1161/HYPERTENSIONAHA.117.10476.) • **Online Data Supplement**

Key Words: blood pressure ■ cardiovascular disease ■ cholesterol, LDL ■ secondary prevention

Through its lipid-lowering effect, statin therapy is indicated in individuals at risk of cardiovascular disease, both as primary and secondary prevention.¹ Previous studies have shown a linear relationship between reduction in serum LDL cholesterol (LDL-c) and cardiovascular mortality.² However, whether mechanisms other than lipid improvement play a role in the reduction of cardiovascular mortality associated with statin use is still an ongoing discussion.³⁻⁵

Although clinical studies looking into the effects of statin use on brachial blood pressure (BP) have yielded conflicting results, 2 meta-analyses have shown that statin use lowers systolic BP by ≈ 2 to 2.5 mm Hg.^{6,7} Some studies suggest that central BP may potentially be a better predictor of cardiovascular burden than brachial BP.^{8,9} Yet, few studies have looked at the impact of statins on central BP, with inconsistent results.¹⁰⁻¹³ Antihypertensive drugs vary in their ability to decrease cardiovascular events despite similar reduction of brachial BP, which may partly be explained by a greater reduction of central BP by certain drug classes.^{9,14,15} For example, renin-angiotensin

system inhibitors and calcium channel blockers produce greater reductions of central BP than β -blockers, for a similar effect on peripheral BP. Whether statins preferentially reduce central or brachial BP remains to be determined. Furthermore, different mechanisms have been suggested to explain the BP reduction with statins, and it is yet to be determined to what extent it is mediated by the concomitant improvement of LDL-c.

The objectives of this study were to investigate the association of statin therapy and LDL-c with brachial and central BP parameters using data from a large populational study and to quantify the magnitude of the BP-lowering effects of statins attributable to change in serum LDL-c.

Methods

Study Design and Population

The data that support the findings of this study are available from the corresponding author on reasonable request. The CARTaGENE cohort randomly recruited 20004 individuals of 40 to 70 years old

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between July 2009 and October 2010 in major urban regions of the Canadian province of Quebec, with the goal of investigating social, environmental, and medical determinants of chronic diseases. The survey included health and lifestyle questionnaires, medication lists, brachial BP measurements, central pulse-wave analyses, and analysis of blood and urine samples. A detailed description of the method for the selection process, data collection, and sampling results of the CARTaGENE cohort are published elsewhere.^{15–17} All participants provided signed informed consent, and the study adhered to the Declaration of Helsinki. This study has been approved by all appropriate Ethics Committees.

Cardiovascular disease (previous myocardial infarct, angina, stroke, or transient ischemic attack) and smoking status were self-reported. Participants provided their list of medications, which was verified for accuracy and compliance by the nurse performing the questionnaires. Presence of diabetes mellitus was defined as glycosylated hemoglobin A1c $\geq 6.5\%$ or fasting glucose ≥ 7 mmol/L or nonfasting glucose ≥ 11.1 mmol/L or use of a hypoglycemic agent.¹⁸ Estimated glomerular filtration rate was estimated from isotope dilution mass spectrometry-calibrated serum creatinine using the Chronic Kidney Disease Epidemiology Collaboration equation.¹⁹ For the purposes of this study, participants with missing central BP measurements, serum lipid levels, or 10-year Framingham risk score²⁰ were excluded. To minimize the heterogeneity of the study population, participants were separated according to statin indication, with primary and secondary prevention treatment defined as per ACC/AHA guidelines (American College of Cardiology/American Heart Association).¹ Primary prevention included (1) participants with a serum LDL-c level ≥ 4.91 mmol/L and (2) diabetic participants between 40 and 70 years of age with a serum LDL-c between 1.81 and 4.90 mmol/L and (3) nondiabetic participants between 40 and 70 years of age with a serum LDL-c between 1.81 and 4.90 mmol/L and a 10-year Framingham risk score $\geq 7.5\%$. The secondary prevention subgroup included participants with history of clinical cardiovascular disease (acute coronary syndromes, myocardial infarct, stable or unstable angina, arterial or coronary revascularization, stroke or transient ischemic attack, and peripheral arterial disease of likely atherosclerotic origin). See [online-only Data Supplement](#) for description of pulse-wave analysis and BP measurements.

Statistical Analyses

To assess the association between serum LDL-c levels and BP parameters (brachial and central systolic, diastolic, and pulse pressures), multivariate linear regression analyses were performed. Covariates that are known or suspected to have an impact on the outcome or the exposure were included in the multivariate regression analyses: age, sex, body mass index, presence of diabetes mellitus, history of cardiovascular disease, active smoking status, heart rate, estimated glomerular filtration rate, serum uric acid levels, and use of β -blockers, calcium channel blockers, diuretics, renin-angiotensin system blockers, and aspirin. To reduce the confounding impact of LDL-c reduction with statin use, analyses were performed in subgroups defined according to statin treatment allocation: (1) no statins; (2) statin used as primary prevention of cardiovascular disease; and (3) statin used as secondary prevention of cardiovascular disease.

To evaluate the association between statin use and BP parameters, univariate ANOVA were performed, and estimated marginal means (adjusted means) were calculated using general linear models with adjustments for all covariates listed above, with Bonferroni-corrected post hoc comparisons. Analyses were performed in subgroups defined according to statin treatment indication, for example, primary and secondary prevention, regardless of whether participants received statins. To minimize the heterogeneity of the study population, participants who did not meet the criteria for statin therapy as primary or secondary prevention were considered without a clear indication and were excluded from these analyses, in an attempt to reduce the bias associated with lower BPs in these healthier individuals who were not taking statins.

To characterize the BP-lowering effects of statins that could be explained by a concomitant decrease in LDL-c, a mediation analysis was performed. Mediation analyses are used to test how a given mediator (LDL-c) affects the relationship between an independent variable (statin) and an outcome variable (BP parameters). It allows

quantification of the total effect (the association between the independent and outcome variables), the direct effect (the total effect without the influence of the mediator) and the indirect effect (the effect of the independent variable on the outcome variable attributable to the mediator). Percent mediation can be calculated by dividing the indirect effect with the total effect and represents the proportion of the total effect attributable to the mediator. For the purpose of this study, all mediation analyses were performed using the PROCESS Statistical Package for SPSS (release 2.16.3), with bootstrapping with 5000 resamples to calculate indirect effect and confidence intervals.²¹ Because statin users were more likely to be treated for hypertension, a propensity score-matched cohort with forced matching for treated hypertension status was developed as part of the sensitivity analysis (see [online-only Data Supplement](#) for methodology of propensity score matching). A second sensitivity analysis was performed by restricting analysis to the highest quality data acquisition of pulse-wave analysis (operator index > 80). Interactions were tested between LDL-c levels (centered around mean) and statins using multivariable linear regressions for all BP parameters.

Normally distributed continuous data are presented as mean \pm SD and compared with Student *t* tests. Categorical data were compared with Pearson χ^2 test. *P* values < 0.05 were considered significant. Analyses were performed with IBM SPSS Statistics software, version 24.0 (IBM Corp, Armonk, NY).

Results

Overall Characteristics of the Cohort

Of the 20004 participants of CARTaGENE, 3497 were excluded because of missing pulse-wave analysis, LDL-c levels, or Framingham risk score (Figure). The remaining 16507 participants were included in study cohort, with subgroups defined according to either treatment allocation (LDL-c analyses) or treatment indication (statin analyses).

The overall characteristics of statin users ($n=3068$) and nonusers ($n=13439$) are presented in Table S1 in the [online-only Data Supplement](#), which shows a difference in almost all baseline characteristics between both groups. Among the 8966 participants with an ACC/AHA indication of statin use for primary prevention, only 2368 received statins (26%), which may reflect different practice guideline during enrollment. In participants with an indication of statin use for secondary prevention (participants with previous clinical cardiovascular disease),

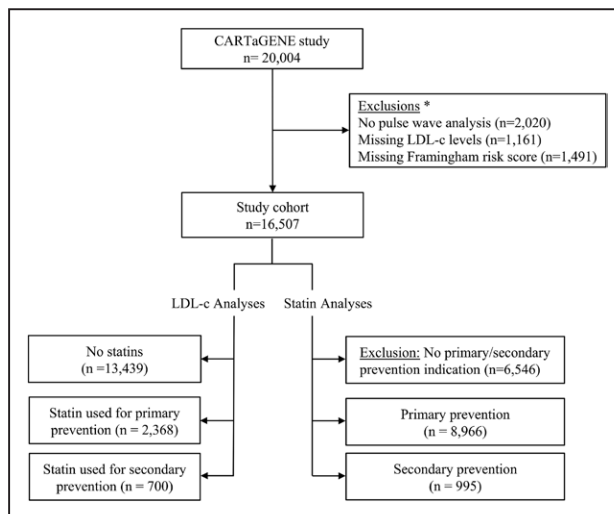


Figure. Study design, inclusions, and exclusions. *Participants can have more than one exclusion criteria. LDL-c indicates low-density lipoprotein cholesterol.

700 of 995 (70%) received a statin. As above, most baseline characteristics were different in statin users compared with nonusers in both primary and secondary prevention subgroups (Table 1). Both brachial and central systolic and diastolic BPs were lower in statin users of the primary prevention subgroup, whereas pulse pressures were similar. In opposition, brachial/central pulse pressures were higher in statin users of the secondary prevention subgroup but not the other BP parameters.

Association Between Serum LDL-c and BP Parameters

Given the impact of statin use on LDL-c levels, participants with and without statins were analyzed separately. In the group without statins, higher levels of serum LDL-c were associated with increased brachial systolic and diastolic BP (Table 2). Serum LDL-c levels were also positively associated with central systolic BP, diastolic BP, and pulse pressure. In the primary and secondary prevention statin groups, results

were similar to those without statin use, apart from an absence of association with central pulse pressure.

Association Between Statin Use and BP

The association between statin use and BP parameters was analyzed using general linear models with calculation of adjusted means in all individuals with indication of statin use for primary prevention and for secondary prevention (Table 3). Within the primary prevention group, individuals receiving statins (n=2368) had lower central systolic BP (−3.0 mm Hg; 95% confidence interval, −3.8 to −2.3 mm Hg), diastolic BP (−1.7 mm Hg; 95% confidence interval, −2.2 to −1.2), and pulse pressure (−1.3; 95% confidence interval, −1.8 to −0.9) compared with nonusers (n=6598). All brachial BP parameters were similarly decreased with statin use. Within the secondary prevention group, a trend toward lower brachial and central BP parameters was observed.

Table 1. Characteristics of the Primary and Secondary Prevention Groups According to Statin Use

Characteristics	Primary Prevention			Secondary Prevention		
	No Statin (n=6598)	Statin (n=2368)	P Value	No Statin (n=295)	Statin (n=700)	P Value
Age, y	55.5 (50.3–62.5)	59.2 (53.0–64.8)	<0.001	57.8 (51.5–64.8)	62.3 (56.1–66.3)	<0.001
Sex, %	68.8	62.1	<0.001	52.2	74.1	<0.001
Body mass index, kg/m ²	27.9±4.9	29.7±5.3	<0.001	28.8±6.1	29.9±5.5	0.01
Diabetes mellitus, %	7.6	28.5	<0.001	16.4	31.4	<0.001
Smoking (active), %	25.6	17.6	<0.001	25.3	22.2	0.3
eGFR, mL/min per 1.73 m ²	86.7±14.1	84.4±15.3	<0.001	84.2±15.7	81.8±15.9	0.03
Uric acid, μmol/L	323.1±76.4	321.6±76.8	0.4	316.4±89.7	336.4±82.9	0.001
Fasting glucose, mmol/L	5.75±1.57	6.39±2.40	<0.001	6.21±2.59	6.53±2.40	0.06
Total cholesterol, mmol/L	5.56±0.94	4.32±0.92	<0.001	5.17±1.08	3.86±0.81	<0.001
LDL cholesterol, mmol/L	3.50±0.81	2.31±0.77	<0.001	3.10±0.96	1.96±0.70	<0.001
HDL cholesterol, mmol/L	1.16±0.37	1.11±0.34	<0.001	1.19±0.41	1.03±0.31	<0.001
Aspirin, %	8.3	42.5	<0.001	41.7	79.7	<0.001
Treated hypertension, %	22.8	49.8	<0.001	49.7	83.8	<0.001
Antihypertensive drugs, n	0 (0–0)	0 (0–1)	<0.001	0 (0–1)	2 (1–2)	<0.001
Renin–angiotensin blockers, %	15.5	38.8	<0.001	30.8	59.1	<0.001
Diuretics, %	6.7	15.5	<0.001	15.3	20.0	0.08
Calcium channel blockers, %	5.1	13.3	<0.001	17.6	23.9	0.03
β-Blockers, %	4.0	10.8	<0.001	20.7	51.9	<0.001
Controlled BP, %	74.3	79.3	<0.001	80.5	83.2	0.3
Systolic BP, mm Hg	130.6±14.7	128.1±14.9	<0.001	125.2±17.0	126.3±15.6	0.3
Diastolic BP, mm Hg	77.0±10.1	74.9±9.8	<0.001	71.9±10.4	70.6±10.0	0.08
Pulse pressure, mm Hg	53.7±10.7	53.2±11.5	0.07	53.3±12.7	55.6±11.9	0.006
Heart rate, bpm	68.4±11.1	69.5±11.3	<0.001	67.3±11.7	65.0±12.2	0.06
Central systolic BP, mm Hg	119.9±14.6	117.5±14.3	<0.001	115.6±16.5	116.4±15.3	0.5
Central diastolic BP, mm Hg	78.1±10.2	76.0±10.0	<0.001	72.9±10.6	71.6±10.1	0.06
Central pulse pressure, mm Hg	41.8±10.5	41.5±10.8	0.3	42.7±12.2	44.8±11.5	0.009

Values are expressed as median (interquartile range) or mean±SD accordingly. P value is for comparison between statin use and no statin use in the primary and secondary prevention groups. Controlled BP is defined as BP <140/90 mm Hg. BP indicates blood pressure; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; and LDL, low-density lipoprotein.

Table 2. Association Between LDL-c and BP Parameters in Individuals Without Statins and With Statin Use in the Primary Prevention Group and in the Secondary Prevention Group

Parameters	No Statins (n=13 439)		Primary Prevention Statin Users (n=2368)		Secondary Prevention Statin Users (n=700)	
	β	P Value	β	P Value	β	P Value
Systolic BP, mmHg	0.077	<0.001	0.086	<0.001	0.120	0.003
Diastolic BP, mmHg	0.106	<0.001	0.114	<0.001	0.194	<0.001
Pulse pressure, mmHg	0.011	0.2	0.013	0.5	-0.004	0.9
Central systolic BP, mmHg	0.089	<0.001	0.089	<0.001	0.130	0.001
Central diastolic BP, mmHg	0.105	<0.001	0.111	<0.001	0.184	<0.001
Central pulse pressure, mmHg	0.025	0.001	0.016	0.4	0.012	0.7

Adjusted for age; sex; body mass index; presence of diabetes mellitus; history of cardiovascular disease; active smoking status; heart rate; eGFR; serum uric acid levels; and use of β -blockers, calcium channel blockers, diuretics, renin-angiotensin system blockers, and aspirin. BP indicates blood pressure; eGFR, estimated glomerular filtration rate; and LDL-c, low-density lipoprotein cholesterol.

Mediation Analysis

Given the association between BP parameters and both serum LDL-c levels and statin use in the primary prevention subgroup, a mediation analysis was performed to better understand the extent of the interactions. This analysis was performed only in the primary prevention subgroup, as both LDL-c and statin analyses yielded statistically significant results, in contrast to the secondary prevention subgroup. As seen in Table 4, only a fraction of the brachial and central systolic BP changes induced by statins was explained by concomitant decrease of LDL-c (percent mediation 5% and 15%, respectively), when almost half the changes of brachial and central diastolic BP were mediated by LDL-c (46% and 44%, respectively). In contrast, concomitant changes of LDL-c attenuated the reduction of brachial/central pulse pressures by statins (-35% and -22%, respectively). Because LDL-c levels are associated with proportionally lower diastolic BP compared with systolic BP (brachial indirect path effect -0.77 compared with -0.18), the increased difference between these 2 parameters results in an inverse association between LDL-c and pulse pressure (indirect path effect 0.59). In opposition, statin use is associated with proportionally lower systolic BP compared with diastolic BP (direct path effect -3.19 compared with -0.89), which results in lower pulse pressure (direct path effect -2.30). Taken together, the

total effect of statins on pulse pressure is attenuated by their effect on LDL-c change, which explains the negative percent mediation values.

As part of the sensitivity analysis, using propensity score matching of patients for treated hypertension status showed consistent findings (Tables S2 and S3). Furthermore, restricting the analysis to the highest quality of pulse-wave analysis data acquisition showed similar results (Table S4). No interactions were present between LDL-c and statin use for all models.

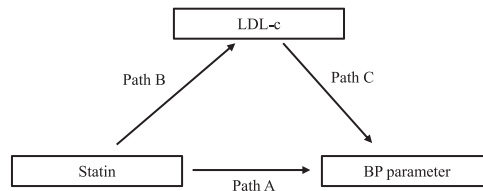
Discussion

This study of 16 507 participants of CARTaGENE shows that both statin use and lower serum LDL-c are associated with lower brachial and central BP. In patients without statins and patients with statins for both primary and secondary prevention of cardiovascular disease, LDL-c levels were positively associated with brachial and central BPs, with a predominant effect on diastolic BPs. In contrast, statin use was associated with lower brachial and central BPs only in individuals fulfilling treatment indication for primary prevention. This remained true in the mediation analysis, which took into consideration the impact of the concomitant reduction of LDL-c with statin use, which in itself influences BP levels. This analysis suggests that mechanisms independent of LDL-c improvement explain a high proportion of the association between lower BPs and

Table 3. Adjusted BP Parameters According to Statin Use in the Primary Prevention and Secondary Prevention Groups

Parameters	Primary Prevention			Secondary Prevention		
	No Statin (n=6598)	Statin (n=2368)	P Value	No Statin (n=295)	Statin (n=700)	P Value
Systolic BP, mmHg	129.5 (128.5–130.5)	126.1 (125.1–127.1)	<0.001	127.5 (125.1–130.0)	125.8 (123.8–127.7)	0.2
Diastolic BP, mmHg	74.2 (73.5–74.8)	72.5 (71.9–73.2)	<0.001	69.6 (68.2–71.1)	69.3 (68.1–70.5)	0.7
Pulse pressure, mmHg	55.3 (54.6–56.0)	53.6 (52.9–54.3)	<0.001	57.9 (56.2–59.6)	56.5 (55.1–57.8)	0.1
Central systolic BP, mmHg	119.1 (118.2–120.1)	116.1 (115.1–117.1)	<0.001	117.9 (115.5–120.3)	116.3 (114.3–118.2)	0.2
Central diastolic BP, mmHg	75.2 (74.6–75.9)	73.6 (72.9–74.2)	<0.001	70.6 (69.1–72.1)	70.3 (69.1–71.5)	0.7
Central pulse pressure, mmHg	43.9 (43.3–44.5)	42.6 (42.0–43.2)	<0.001	47.3 (45.7–48.8)	46.0 (44.7–47.2)	0.1

Estimated marginal means (95% confidence interval) adjusted for age; sex; body mass index; presence of diabetes mellitus; active smoking status; heart rate; eGFR; serum uric acid levels; and use of β -blockers, calcium channel blockers, diuretics, renin-angiotensin system blockers, and aspirin. BP indicates blood pressure; and eGFR, estimated glomerular filtration rate.

Table 4. Mediation Effect by LDL-c in the Association Between Statin Use and BP Parameters in the Primary Prevention Group

BP Parameter	Total Effect	Direct Effect (Path A)	Indirect Effect (Path BC)	Percent Mediation
Systolic BP	-3.37 (-4.14 to -2.59)	-3.19 (-4.06 to -2.31)	-0.18 (-0.63 to 0.25)	5
Diastolic BP	-1.66 (-2.15 to -1.16)	-0.89 (-1.45 to -0.32)	-0.77 (-1.05 to -0.49)	46
Pulse pressure	-1.71 (-2.25 to -1.17)	-2.30 (-2.91 to -1.69)	0.59 (0.30 to 0.88)	-35
Central systolic BP	-3.02 (-3.78 to -2.26)	-2.57 (-3.43 to -1.71)	-0.45 (-0.88 to -0.02)	15
Central diastolic BP	-1.69 (-2.20 to -1.19)	-0.95 (-1.52 to -0.38)	-0.75 (-1.03 to -0.47)	44
Central pulse pressure	-1.33 (-1.80 to -0.85)	-1.62 (-2.16 to -1.09)	0.29 (0.03 to 0.54)	-22

Mediation model between statin use, LDL-c levels, and BP parameters: path A represents the direct and total effects, path B and path C together represent the indirect effect. Adjusted for age; sex; body mass index; presence of diabetes mellitus; active smoking status; heart rate; eGFR; serum uric acid levels; and use of β -blockers, calcium channel blockers, diuretics, renin-angiotensin system blockers, and aspirin. Effects represent changes of BP parameter per 1 SD of LDL (95% confidence interval). BP indicates blood pressure; eGFR, estimated glomerular filtration rate; and LDL-c, low-density lipoprotein cholesterol.

statins and that these pleiotropic effects mostly associate with lower pulsatile BP components (systolic and pulse pressures). On the contrary, LDL-c reduction seems to be primarily associated with lower steady BP components (diastolic BP).

Central BP may be associated with cardiovascular mortality, myocardial infarction, heart failure, stroke, and peripheral vascular disease more strongly than brachial BP.^{8,9,22-26} In addition, antihypertensive agents differ in their ability to reduce central BP compared with peripheral BP. For example, β -blockers have been shown to be less effective in reducing central BP compared with other classes of antihypertensive drugs.^{9,15} Two large meta-analyses have demonstrated a relationship between statin use and brachial BP. The first meta-analysis (20 trials and 828 patients) found a significant decrease in systolic BP of 1.9 mmHg with statins and a trend toward lower diastolic BP of 0.9 mmHg.⁶ In the second meta-analysis of 40 randomized clinical trials including 45 113 subjects, statin decreased brachial BP by 2.6/0.9 mmHg compared with placebo.⁷ A reduction in central BP parameters¹⁰⁻¹² and decreased arterial stiffness²⁷⁻³² with statin use were shown in small-scale randomized controlled trials. In contrast, the CAFE-LLA study (Conduit Artery Function Evaluation-Lipid-Lowering Arm) found that statins had no influence on central nor brachial BP.¹³ However, the addition of antihypertensive medication during follow-up may have hidden the BP-lowering effect of statins. Studies on the association between lower serum LDL-c levels and lower BP have produced inconsistent results.^{7,10,33-38}

LDL-c is known to be detrimental to endothelial function, with elevated serum LDL-c levels resulting in higher vascular tone through an increased response of vascular smooth muscle cells to angiotensin II and a lower bioavailability of NO.³⁹⁻⁴¹ These pathophysiologic pathways are consistent with this study's finding that LDL-c levels are mostly associated with

elevated steady component of BP, which is primarily determined by arterial resistance.⁴²⁻⁴⁵

Other potential LDL-c-independent mechanisms of the BP-lowering effects of statins are to be considered. First, a reduction in oxidative stress could result in improvement of vascular function.⁴⁶ Second, the synergistic effects of statins and renin-angiotensin antagonists on BP may suggest an implication of the renin-angiotensin-aldosterone system, possibly through a downregulation of angiotensin II receptor type 1.^{47,48} Finally, randomized studies tend to suggest that statins improve arterial stiffness, although data remains conflicting in this regard.^{10-12,27-32,49} Although experimental studies will always have difficulties separating the BP-lowering effects of statins that are mediated by concomitant changes in LDL-c levels from other pleiotropic effects, these findings suggest that these effects may contribute through mechanisms related to an improvement of pulsatile components of BP, which depend primarily on arterial stiffness. Although the lack of association between pulsatile pressures and both statin use and LDL-c levels in the secondary prevention subgroup may be partly because of the lower power of these analyses, the greater use of antihypertensive treatment in statin users may have partly masked the beneficial effects on arterial stiffness, as was seen in the CAFE-LLA trial.¹³

To our knowledge, this is the first study to examine the LDL-c-dependent and -independent BP-lowering effects of statin use and the largest to examine the association between central BP, LDL-c, and statin use. The mediation analyses suggest novel insights into the mechanisms of the BP-lowering effects of statin use. The CARTaGENE study is large, well-characterized cohort study, with a high quality of data collection. Brachial and central BPs were recorded in accordance to guidelines, with averages of multiple readings.

This study has some specific limitations to be discussed. First, because all individuals included in CARTaGENE were

randomly selected from the Quebec population, this database included participants with different health profiles. In this context, stratification according to indication for treatment (primary and secondary prevention) was required to create more homogenous groups, but to what extent these findings can be generalized to other populations remains uncertain. Although the participants were randomly recruited from the general population, a selection bias cannot be excluded. Presence of cardiovascular disease was self-reported and not validated, which may have resulted in misclassification in either primary or secondary prevention subgroups. The information on the dose and duration of statin therapy was not available. To what degree this could have influenced the findings on pulsatile and steady BP parameters remains unknown. Finally, as for all cross-sectional studies, only association can be inferred and not causation.

Perspectives

Overall, this large cross-sectional observational study suggests that statin use is associated with lower central BP to a similar degree as brachial BP. More importantly, the mediation analysis suggests that mechanisms independent of LDL-c reduction may play a predominant role through their effects on pulsatile pressure. On the contrary, LDL-c reduction with statin use was predominantly associated with lower steady components of BP. This is of specific interest given the ongoing debate regarding the pleiotropic effects of statins and their clinical significance.

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Disclosures

None.

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Novelty and Significance

What Is New?

- This is the first study to quantify the magnitude of the peripheral and central blood pressure (BP)-lowering effects of statins attributable to change in serum low-density lipoprotein cholesterol (LDL-c).
- LDL-c reduction with statin use was associated with lower steady components of BP.
- The direct effects of statin use (independent of LDL-c reduction) explained most of the association with lower brachial and central BP, with predominant effects on pulsatile components of BP.

What Is Relevant?

- This study confirms the association between statin use on both central and peripheral BP in a large populational cohort.

- It shows a difference in LDL-dependent and LDL-independent effects of statins on steady and pulsatile components of BP, while suggesting an overall predominance of the pleiotropic effect.

Summary

Statin use is associated with lower central and peripheral BP. Reduction of LDL-c explained only a fraction of their BP-lowering effects and was mostly associated with improvement of steady BP, whereas non-LDL-c-mediated pathways were mostly associated with changes in pulsatile pressure.

Central and Brachial Blood Pressures, Statins, and Low-Density Lipoprotein Cholesterol: A Mediation Analysis

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ONLINE SUPPLEMENT

Central and Brachial Blood Pressures, Statins and LDL-cholesterol: A Mediation Analysis

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SUPPLEMENTAL METHODS

Central pulse wave analysis and BP measurement

Brachial BP measurement was recorded as per guidelines with participants seated for ten minutes in an isolated room ¹. An automated device, Omron 907L (BP monitor, Omron 907L; Omron Lake Forest, IL), recorded and averaged three measurements at two minutes intervals. Pulse wave analysis with applanation tonometry was also performed during the same session with brachial systolic and diastolic BPs used for calibration. Two recordings were performed by trained operators with a SphygmoCor Px (AtCor Medical, Lisle, Illinois, USA) and subsequently averaged. Central pulse wave analysis profiles were obtained from the applanation tonometry data with a generalized transfer function ². Quality of acquisition was assessed visually and using the operator index. Central systolic BP, diastolic BP and pulse pressure were derived from the pulse wave analysis.

Propensity score matching

In an attempt to evaluate the potential strong confounding effect of the use of antihypertensive drugs in statin users, we performed a propensity score matching analysis using participants included in the primary prevention subgroup ³. The probability (propensity score) of receiving a statin was derived using a binary logistic regression and the following covariables: age, gender, heart rate, BMI, diabetes, treated hypertension, active smoking, eGFR, uric acid and use of aspirin. These covariables were pre-specified based on literature and biological plausibility and are related to the exposure or the outcome ⁴. Subsequently, a nearest-neighbor 1:1 match (without replacement) was performed using caliper widths equal to 0.2 of the standard deviation of the logit of the propensity score and forced matching of treated hypertension status ⁵. Absolute standardized differences less than 10% between each covariate are indicative of appropriate matching between the groups ⁶.

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SUPPLEMENTAL REFERENCES

Table S1. Characteristics of the study cohort according to statin use

Characteristics	No Statin (n=13,878)	Statin (n=3,133)	p-value
Age (years)	52.1 (47.0, 59.0)	60.0 (53.6, 65.2)	<0.001
Gender	45.0%	64.8%	<0.001
Body mass index (kg/m ²)	27.0 ± 5.1	29.7 ± 5.3	<0.001
Diabetes	5%	29%	<0.001
Cardiovascular disease	2%	22%	<0.001
Smoking (active)	18%	19%	0.8
eGFR (mL/min/1.73m ²)	88.8 ± 14.3	83.9 ± 15.5	<0.001
Uric acid (µmol/L)	295 ± 79	325 ± 78	<0.001
Fasting glucose (mmol/L)	5.6 ± 1.4	6.4 ± 2.4	<0.001
Total cholesterol (mmol/L)	5.3 ± 0.9	4.2 ± 0.9	<0.001
LDL cholesterol (mmol/L)	3.2 ± 0.8	2.2 ± 0.8	<0.001
HDL cholesterol (mmol/L)	1.3 ± 0.4	1.1 ± 0.3	<0.001
Aspirin	6%	51%	<0.001
Treated hypertension	15.7%	57.7%	<0.001
Antihypertensive drugs (n)	0 (0, 0)	1 (0, 2)	<0.001
Renin-angiotensin blockers	10%	43%	<0.001
Diuretics	5%	16%	<0.001
Calcium channel blockers	4%	15%	<0.001
Beta-blockers	3%	20%	<0.001
Controlled BP	84.7%	79.9%	<0.001
Systolic BP (mmHg)	123.0 ± 15.6	127.7 ± 15.0	<0.001
Diastolic BP (mmHg)	73.6 ± 10.2	73.9 ± 10.0	0.07
Pulse pressure (mmHg)	49.4 ± 10.5	53.7 ± 11.6	<0.001
Heart rate (bpm)	67.9 ± 10.7	68.5 ± 11.5	0.01
Central systolic BP (mmHg)	113.3 ± 14.9	117.2 ± 14.6	<0.001
Central diastolic BP (mmHg)	73.6 ± 10.2	73.9 ± 10.0	0.1
Central pulse pressure (mmHg)	38.6 ± 9.7	42.3 ± 11.0	<0.001

Values are expressed as percentages, median (interquartile range) or mean ± standard deviation accordingly. P-value for comparison between statin use and no statin use in the CARTaGENE Lipids cohort. eGFR, estimated glomerular filtration rate; BP, blood pressure. Controlled BP defined as BP < 140/90 mmHg.

Table S2: Characteristics of propensity score and hypertension status-matched statin users and non-users (primary prevention population).

Characteristics	No Statin (n=1,853)	Statin (n=1,853)	Absolute standardized difference	p-value
Age (years)	58.7 (52.4, 64.3)	58.6 (52.8, 64.5)	1.8%	0.6
Gender	60.4%	61.1%	1.4%	0.6
Body mass index (kg/m ²)	29.2 ± 5.6	29.2 ± 5.0	0.9%	0.8
Diabetes	16.8%	16.8%	0.0%	1.0
Smoking (active)	18.0%	18.6%	1.6%	0.6
eGFR (mL/min/1.73m ²)	85 ± 15	85 ± 15	1.4%	0.7
Uric acid (µmol/L)	321 ± 78	320 ± 75	1.3%	0.7
Fasting glucose (mmol/L)	6.1 ± 2.1	6.0 ± 1.9	*	0.7
Total cholesterol (mmol/L)	5.5 ± 0.9	4.4 ± 0.9	*	<0.001
LDL cholesterol (mmol/L)	3.5 ± 0.8	2.4 ± 0.8	*	<0.001
HDL cholesterol (mmol/L)	1.2 ± 0.4	1.1 ± 0.3	*	0.054
Aspirin	28.1%	29.6%	3.3%	0.3
Treated hypertension	40.7%	40.7%	0.0%	1.0
Antihypertensive drugs (n)	0 (0, 1)	0 (0, 1)	*	0.5
Renin-angiotensin blockers	28.5%	30.4%	*	0.2
Diuretics	12.6%	13.8%	*	0.3
Calcium channel blockers	9.3%	10.6%	*	0.3
Beta-blockers	7.6%	8.6%	*	0.3
Controlled BP	73.1%	79.8%	*	<0.001
Systolic BP (mmHg)	131.1 ± 14.8	128.0 ± 14.6	*	<0.001
Diastolic BP (mmHg)	77.1 ± 10.0	75.3 ± 9.7	*	<0.001
Pulse pressure (mmHg)	54.0 ± 11.0	52.7 ± 11.1	1.6%	0.6
Heart rate (bpm)	69.2 ± 11.3	69.0 ± 11.0	*	<0.001
Central systolic BP (mmHg)	120.5 ± 14.6	117.7 ± 14.2	*	<0.001
Central diastolic BP (mmHg)	78.2 ± 10.1	76.4 ± 9.8	*	0.003
Central pulse pressure (mmHg)	42.3 ± 10.8	41.3 ± 10.4	1.8%	0.6

Values are expressed mean ± standard deviation or median (interquartile range) as appropriate. Absolute standardized differences < 10% indicate adequate balance. * denotes covariables not included in propensity score. Abbreviations as defined in Table S1.

Table S3: Mediation analysis in the propensity score and hypertension status-matched statin users and non-users (primary prevention population).

BP parameter	Total effect	Direct effect (Path A)	Indirect effect (Path BC)	Percent mediation
Systolic BP	-3.18 (-4.10, -2.25)	-2.07 (-3.21, -0.93)	-1.11 (-1.82, -0.45)	35%
Diastolic BP	-1.65 (-2.24, -1.06)	-0.43 (-1.16, 0.29)	-1.22 (-1.67, -0.77)	74%
Pulse pressure	-1.53 (-2.17, -0.88)	-1.63 (-2.43, -0.83)	0.11 (-0.35, 0.57)	-7%
Central systolic BP	-2.88 (-3.79, -1.97)	-1.66 (-2.77, -0.54)	-1.22 (-1.92, -0.54)	42%
Central diastolic BP	-1.69 (-2.29, -1.10)	-0.48 (-1.21, 0.25)	-1.21 (-1.67, -0.76)	72%
Central pulse pressure	-1.18 (-1.75, -0.62)	-1.17 (-1.87, -0.48)	-0.01 (-0.43, 0.39)	1%

Mediation model between statin use, LDL-c levels and BP parameters: Path A represents the direct and total effects, path B and path C together represent the indirect effect. Adjusted for age, sex, body mass index, presence of diabetes, active smoking status, heart rate, eGFR, serum uric acid levels and use of beta blockers, calcium channel blockers, diuretics, renin-angiotensin system blockers and aspirin. Effects represent changes of BP parameter per 1 standard deviation of LDL (95% confidence interval).

Table S4. Mediation analysis in the primary prevention subgroup after exclusion of individuals with an operator index < 80 (statins user n=1,949 vs non-users n=5,559)

BP parameter	Total effect	Direct effect (Path A)	Indirect effect (Path BC)	Percent mediation
Systolic BP	-3.14 (-3.95, -2.32)	-2.87 (-3.81, -1.93)	-0.26 (-0.76, 0.24)	8%
Diastolic BP	-1.81 (-2.34, -1.29)	-1.00 (-1.60, -0.40)	-0.81 (-1.13, -0.50)	45%
Pulse pressure	-1.32 (-1.89, -0.75)	-1.88 (-2.53, -1.22)	0.55 (0.23, 0.88)	-42%
Central systolic BP	-2.86 (-3.66, -2.06)	-2.36 (-3.28, -1.44)	-0.50 (-1.00, -0.02)	17%
Central diastolic BP	-1.82 (-2.35, -1.29)	-1.03 (-1.63, -0.42)	-0.79 (-1.11, -0.49)	44%
Central pulse pressure	-1.04 (-1.53, -0.54)	-1.33 (-1.90, -0.76)	0.29 (0.01, 0.60)	-28%

Mediation as defined in Table S3