

# Serum low-density lipoprotein levels, statin use, and cognition in patients with coronary artery disease

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**Aim:** Statins have been associated with decreased cognition due to the effects of low concentrations of low-density lipoprotein (LDL) on brain function. This has remained controversial and is particularly relevant to patients with coronary artery disease (CAD), who have an increased risk of cognitive decline and are frequently prescribed statins. This study hypothesized that low concentration of LDL is associated with poor cognition in CAD patients using statins. It also explored the association between high-dose versus low-dose statins on cognition in this population.

**Patients and methods:** Baseline cross-sectional data from a longitudinal study of 120 statin-using CAD patients were examined (mean statin duration 25±43 months). The main outcomes were measures of global cognition and cognitive domains, with poor cognition defined as cognitive performance ≤1 standard deviation below the population age and education adjusted means. A battery of cognitive tests was used to assess verbal memory, executive function, speed of processing, visuospatial memory, and global cognition. Adjusting for age, sex, education, and other covariates, multivariable logistic regression analyses assessed associations between low LDL levels (<1.5 mmol/L), statin use, and poor cognition.

**Results:** LDL levels were not associated with global cognition or individual cognitive domains. High-dose statin use was associated with higher visuospatial memory (odds ratio, OR [95% confidence interval, CI] =0.12 [0.02–0.66], *P*=0.01) and executive functioning (OR =0.25 [0.06–0.99], *P*=0.05). This effect was independent of covariates such as LDL levels.

**Conclusion:** Low LDL levels do not appear to be associated with poor cognition in CAD patients using statins. Whether high-dose statin use may have positive effects on cognition in CAD patients could be investigated in future studies.

**Keywords:** cholesterol, visuospatial cognition, heart disease, psychopharmacology, adverse drug events

## Introduction

HMG-CoA reductase inhibitors (statins) are believed to have positive cognitive effects. Meta-analyses have found associations between statins and decreased risk of cognitive decline and cognitive disorders,<sup>1</sup> especially with long-term use.<sup>2-4</sup> These potential protective effects of statins may be related to cerebrovascular health; statin use has been linked with better white matter integrity in community dwelling elders.<sup>5</sup> Although controversial,<sup>6</sup> some early evidence has suggested that statins may be useful in the prevention of dementia in high-risk populations,<sup>7</sup> particularly in patients with poorly controlled hypercholesterolemia.<sup>8</sup> This may be explained in part by the pleiotropic effects of statins, such as improved endothelial functioning, atherosclerotic plaque

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stability, decreased oxidative stress, inflammation, and inhibition of vascular thrombogenic response, in addition to their cholesterol-lowering effects.<sup>9</sup>

On the contrary, statins have been recently associated with worse cognition due to their low-density lipoprotein (LDL) cholesterol-lowering effects. It is thought that low LDL levels (eg,  $<1.5$  mmol/L) interfere with cholesterol and phospholipid concentrations in neuronal membranes, thereby affecting cell signaling and neuronal functioning.<sup>10</sup> Novel animal data have demonstrated that gene knockout of the LDL receptor may be associated with hippocampal apoptosis.<sup>11</sup> Recent human studies suggest that statin users are more likely to suffer from cognitive impairment than non-statin users,<sup>12</sup> with impairments in executive functioning, episodic memory, and other cognitive domains associated with low LDL levels.<sup>13,14</sup> This remains controversial, as well-designed prospective longitudinal studies and randomized controlled trials have not necessarily found an association between LDL and cognition.<sup>15–17</sup>

These issues are particularly relevant in those with coronary artery disease (CAD). CAD and cognitive disorders such as Alzheimer's, vascular, and mixed dementias have a shared biological etiology, with both being associated with oxidative stress, inflammation, lipid/glucose dysregulation, endothelial dysfunction,<sup>18,19</sup> and common genetic risk factors.<sup>20</sup> As such, CAD patients have a substantially increased risk of Alzheimer's disease and other dementias.<sup>21–24</sup> CAD patients often have poor white matter microstructural integrity, which in turn has been associated with executive function, processing speed, and other cognitive deficits.<sup>25,26</sup> Statins are very frequently prescribed in CAD patients. Statin pharmacotherapy in CAD is recommended irrespective of a patient's lipid profile, even in normocholesterolemic patients, as they have been shown to reduce premature death, myocardial infarction, and other cardiovascular events.<sup>27</sup> Therefore, the risk/benefit of statins vis-à-vis cognitive dysfunction is important in this population.

A small number of studies have examined statins and cognitive dysfunction,<sup>3,13</sup> with few specifically examining this association in CAD patients as a primary outcome.<sup>28</sup> Because high-dose statins are often prescribed in CAD,<sup>29</sup> the potential risk of low LDL levels on cognition are of particular concern. This study hypothesized that low LDL levels will be associated with poor cognition in CAD patients using statins and then examined the association between high-dose versus low-dose statins on cognition in this population. It also explored associations between cognition and other lipid

parameters (high-density lipoprotein [HDL], total cholesterol [TC], TC/HDL ratio, and triglyceride levels).<sup>13,30</sup>

## Methods

### Study design and study population

This was a cross-sectional analysis of data from CAD patients aged 50–75 years just before starting a cardiac rehabilitation exercise program at the University Health Network-Toronto Rehabilitation Institute (UHN-Toronto Rehab), Toronto, Canada. All recruited participants had CAD, defined as a previous hospitalization for acute myocardial infarction, coronary angiographic evidence of  $\geq 50\%$  blockage in one or more major coronary artery, or prior revascularization. Only CAD patients currently being treated with statins were included in this study. The diagnosis of dyslipidemia was assumed (current statin use). Patients with any duration of previous statin exposure were included, and statin duration was described in the results of this study. Participants were excluded if they had previously diagnosed neurodegenerative illness (including dementia), active cancer, surgery planned within 12 months, schizophrenia, bipolar affective disorder, or substance abuse. The Mini Mental Status Examination (MMSE) was used to screen for dementia and subjects with MMSE  $<24$  were excluded.<sup>31</sup> A complete description of eligibility criteria and recruitment has been previously reported.<sup>32</sup> The protocol, including acquisition of written informed consent, for this prospective study was approved by the Sunnybrook Health Sciences Centre Research Ethics Board and the University Health Network Research Ethics Board.

### LDL and statin exposures

The main exposure was serum LDL levels. This study examined associations with the outcomes primarily using a dichotomous LDL definition (LDL  $<1.5$  mmol/L), but also explored relationships using continuous measures. This dichotomous threshold for low LDL was chosen because of the high frequency of LDL  $<2.0$  mmol/L in statin-treated CAD patients<sup>33</sup> and data suggesting that cognition/brain functioning is theoretically most adversely affected when LDL serum concentrations are  $<1.5$  mmol/L.<sup>1,34</sup>

The secondary exposure variable was high-dose versus low-dose statin use. High dose was defined as atorvastatin, pravastatin, or fluvastatin 40–80 mg/day and rosuvastatin or simvastatin 20–40 mg/day, whereas lower dose was defined as 10–20 mg/day and 5–10 mg/day of those medications, respectively.

## Exploratory lipid profile and statin exposure variables

This study explored other potential lipid profile exposures: HDL, non-HDL cholesterol, TC, TC/HDL ratio, and triglyceride levels. These factors have previously had both positive and negative associations with cognition, with high TC, low HDL, and low triglycerides being mostly associated with decreased cognition (where an association had been reported).<sup>13,30</sup> This study also explored whether there was an association between 1) lipophilic statins (atorvastatin, lovastatin, simvastatin, pitavastatin) versus hydrophilic statins (pravastatin, rosuvastatin, fluvastatin) and 2) statin duration, on cognition.

## Covariates

Data on potential covariates associated with cognition were collected, which included age, sex, education, ethnicity, employment, marital status, body mass index, hypertension, diabetes mellitus, hemoglobin A1c, CAD severity (% blockage), concomitant heart failure, coronary artery bypass graft, smoking, alcohol, nonsteroidal anti-inflammatory drugs, platelet inhibitors (eg, clopidogrel), anti-coagulants, calcium channel blockers, beta-blockers, antiarrhythmics, diuretics, insulin/oral hypoglycemic, antioxidant use, omega-3, ginkgo biloba/policosanols, corticosteroid use, non-statin lipid-lowering agents (cholesterol absorption inhibitors and niacin), hormone replacement therapy, thyroid medications, antipsychotic use, and benzodiazepine/zopiclone use. Demographic, clinical characteristics, and a detailed medical history were collected from patient interviews, whereas cardiac, medical history, current use of concomitant medications, and cardiac health indicators (body mass, height, dyslipidemia, hypertension, diabetes mellitus, and waist circumference) were obtained from patient charts. Body mass index was calculated per standard definition [mass (kg)/height (m)<sup>2</sup>].

## Cognitive testing

A battery of cognitive tests was used to assess verbal memory, executive function, speed of processing, and visuospatial memory. Verbal memory was assessed using the California Verbal Learning Test, 2nd Edition (CVLT-II), which yields a sensitive measure of long delay free recall of a word list after 20 min in addition to measures of verbal learning (recall of a word list over five learning trials) and short delay free recall (recall of a word list after 10 min).<sup>35</sup> Tasks involving an executive component included the Trails-Making Test

Part B (Trails B)<sup>36</sup> and the Controlled Oral Word Association test (COWAT).<sup>37</sup> The Trails-Making Test Part A (Trails A)<sup>36</sup> and the Digit Symbol-Coding task, a measure of complex attention and psychomotor speed from the Wechsler Adult Intelligence Scale, 3rd Edition, were used to assess speed of processing.<sup>38</sup> Visuospatial memory was assessed using the Brief Visuospatial Memory Test-Revised,<sup>39</sup> which yields a measure of visual learning and delayed recall. These instruments were chosen based on the National Institute of Neurological Disorders and Stroke and Canadian Stroke Network (NINDS-CSN) harmonized standards.<sup>35</sup> All cognitive testing was performed by a trained researcher at a standardized time (09:30 AM  $\pm$  30 min) and subjects refrained from eating or drinking any caffeine-containing beverages for at least 4 h before testing.

For each cognitive task, a Z-score was determined from published age- and sex-matched norms. Z-scores follow a normal distribution with a standard deviation (SD) of 1.0; higher Z-scores reflect better performance. Z-scores of related tests can be summed into composite Z-scores to reflect performance in a cognitive domain and avoid multiple comparisons.<sup>40</sup> For memory, Z-scores from the three CVLT-II outcomes (verbal learning and short and long delayed recall) were summed. For executive function, the Z-scores of the Trails B and COWAT were summed. The sum of Digit Symbol-Coding task and Trails A was used to represent speed of processing, whereas Z-scores for the two Brief Visuospatial Memory Test-Revised (BVM-T-R) outcomes (visual learning and delayed recall) were summed for visuospatial memory. For global cognition, the Montreal Cognitive Assessment (MoCA) was used.<sup>41</sup> Impairment in the cognitive domains was defined by a Z-score  $\leq$  1 SD below the mean.

## Outcomes

The primary outcome was global cognition (MoCA), and the secondary outcomes were cognitive domain Z-scores: verbal memory, visuospatial memory, executive function, and processing speed. Dichotomous outcome measures were analyzed: MoCA  $<$  26 points and Z-scores  $\geq$  1 SD below the mean, respectively. The dichotomous outcome measures were used as these would capture more clinically meaningful deficits in cognition.

Usually, cognitive domain Z-score thresholds  $>$  1.5 or  $>$  2 SD below the mean have been traditionally used in defining mild cognitive impairment.<sup>42</sup> However, the study samples, although diagnosed with CAD, were situated in a wealthy borough of metropolitan Toronto, were highly educated,

and had substantially higher cognition than most CAD patients.<sup>42,43</sup> Therefore, a more sensitive, while still clinically meaningful, cognitive Z-score threshold of  $>1$  SD below the mean was chosen. The use of  $>1$  SD below the mean has also been used in older adults with comparatively unimpaired cognition<sup>44</sup> and adults with neuropsychiatric conditions,<sup>45</sup> as well as in a cerebrovascular disease sample.<sup>46</sup>

### Data analysis

Continuous variables were summarized as mean values and SDs, and categorical variables were presented as percentages. Associations between covariates and cognitive outcomes were assessed using chi-square analysis and analyses of variance (cognition  $\leq 1$  SD below the mean). In addition to age, sex, and education, covariates with significant associations (two-tailed  $P < 0.05$ ) were included in the multivariable logistic regression as appropriate.

To test the main and secondary hypotheses, multivariable logistic regressions were performed to assess the association between LDL  $< 1.5$  mmol/L and cognitive outcomes and to assess the relationship between high-dose statin use and cognitive outcomes. SPSS 22.0 was used for all analyses.

## Results

### Main hypothesis: LDL concentration and cognition in CAD patients

Of the 120 patients, 54% had LDL  $< 1.5$  mmol/L ( $n=65$ ). Those with LDL  $< 1.5$  mmol/L were more likely to be male ( $\chi^2[1]=4.76$ ,  $P=0.03$ ), less likely to have diabetes ( $\chi^2[1]=8.22$ ,  $P=0.004$ ), or have a percutaneous coronary angioplasty (PTCA) stent ( $\chi^2[1]=8.67$ ,  $P=0.003$ ). Other demographic and clinical characteristics are described in Table 1.

In logistic regressions controlling for covariates (age, sex, years of education, diabetes, PTCA stent), there was

**Table 1** Clinical and demographic characteristics of CAD patients using statins ( $n=120$ )

Variables	LDL $< 1.5$ mmol/L ( $n=65$ ) Mean $\pm$ SD or % (n)	LDL $\geq 1.5$ mmol/L ( $n=55$ ) Mean $\pm$ SD or % (n)
Age, years	63 $\pm$ 7	64 $\pm$ 6
Sex (% male)	78.5 (51)	92.7 (51)
Education, years	17 $\pm$ 3	16 $\pm$ 4
Ethnicity (% Caucasian)	87.7 (57)	78.2 (43)
Employment (% employed)	63.1 (41)	47.2 (25)
Marital status (% married)	69.2 (45)	72.7 (40)
Body mass index	28.9 $\pm$ 4.5	29.5 $\pm$ 5.8
Hypertension	95.4 (62)	92.7 (51)
Diabetes mellitus	7.7 (5)	27.3 (15)
Hemoglobin A1c	0.059 $\pm$ 0.006	0.059 $\pm$ 0.001
CAD severity (number of blocked vessels)	2 $\pm$ 1	2 $\pm$ 1
Heart failure	0 (0)	3.6 (2)
Myocardial infarction	44.6 (29)	52.7 (29)
Coronary artery bypass graft	27.3 (15)	38.5 (25)
Stent	21.8 (12)	78.2 (43)
Smoking history (% past or current smoker)	66.2 (43)	54.5 (30)
Alcohol (number of drinks per week)	3 $\pm$ 4	3 $\pm$ 5
Caffeine (number of caffeinated drinks per day)	2 $\pm$ 1.5	2 $\pm$ 2.5
Depression (major and minor)	12.7 (7)	24.6 (16)
Nonsteroidal anti-inflammatory drugs	3.1 (2)	0 (0)
Corticosteroids	0 (0)	1.8 (1)
Platelet inhibitors (eg, clopidogrel)	95.4 (62)	98.2 (54)
Anti-coagulants	7.7 (5)	1.8 (1)
Calcium channel blockers	13.8 (9)	14.5 (8)
Beta-blockers	80 (52)	80 (44)
Antiarrhythmics	4.6 (3)	1.8 (1)
Diuretics	20 (13)	10.9 (6)
Insulin use	6.2 (4)	23.6 (13)
Non-statin lipid-lowering agents	7.7 (5)	3.6 (2)
Antioxidant use	9.1 (5)	18.5 (12)
Omega-3	25 (15)	22.4 (11)
Hormone replacement therapy	0 (0)	1.8 (1)
Thyroid medications	12.3 (8)	5.5 (3)
Anxiolytic use	6.2 (4)	0 (0)
Alternative medicine	0 (0)	0 (0)

**Abbreviations:** CAD, coronary artery disease; LDL, low-density lipoprotein; SD, standard deviation.

**Table 2** Odds ratio of impairment <1 SD in cognitive domains between CAD patients with LDL <1.5 mmol/L and those with LDL ≥1.5 mmol/L

Cognitive domains	LDL <1.5 mmol/L OR (95% CI) n=65	LDL ≥1.5 mmol/L (reference) n=55	P-value <sup>a</sup> (significance at P≤0.05)
Global cognition	1.78 (0.76–4.20)	1.0	0.19
Verbal memory	2.11 (0.68–6.54)	1.0	0.19
Visuospatial memory	1.57 (0.46–5.29)	1.0	0.47
Processing speed	0.76 (0.27–2.19)	1.0	0.62
Executive function	1.01 (0.35–2.90)	1.0	0.99

**Notes:** <sup>a</sup>Two-tailed significance of differences in cognitive impairment between LDL groups in logistic regressions controlling for age, gender, years of education, percutaneous coronary intervention, and diabetes.

**Abbreviations:** CAD, coronary artery disease; CI, confidence interval; LDL, low-density lipoprotein; OR, odds ratio; SD, standard deviation.

no association between lower LDL concentrations and risk of impairment in global cognition (OR [95% CI] =0.56 [0.24–1.32],  $P=0.19$ ), verbal memory (OR =0.47 [0.15–1.47],  $P=0.19$ ), visuospatial memory (OR =0.64 [0.19–2.16],  $P=0.47$ ), processing speed (OR =1.31 [0.46–3.76],  $P=0.62$ ), or executive functioning (OR =1.00 [0.35–2.87],  $P=0.99$ ) (Table 2). Similarly, LDL as a continuous measure was not associated with global cognition or any of the cognitive domain Z-scores (data not shown).

## Secondary hypothesis: high-dose versus low-dose statin use and cognition in CAD patients

Seventy-four patients were high-dose statin users, while the remainder were low-dose statin users (n=42). These 116 patients were used to examine statin dose and cognition: of all the 120 statin-using CAD patients in this study, four did not have statin dose information. The average duration of previous statin exposure was 25±43 months (range: 1–200 months). Compared to low-dose users, high-dose statin users were more likely to have had myocardial infarction (70% vs 30%,  $\chi^2[1] = 4.16$ ,  $P=0.05$ ), to be taking an antihypertensive medication (70% vs 30%,  $\chi^2[1] = 3.96$ ,  $P=0.06$ ) and they were significantly younger (63±6 years vs 66±6 years;  $F=7.05$ ,  $P=0.01$ ).

In logistic regressions controlling for covariates (age, sex, years of education, myocardial infarction, anti-hypertensive use, serum LDL concentration, and duration of statin use), high-dose statin use was associated with a lower risk of impairment in visuospatial memory (OR =0.12 [0.02–0.66],  $P=0.01$ ) and executive functioning (OR =0.25 [0.06–0.99],  $P=0.05$ ) but not verbal memory (OR =1.78 [0.47–6.72],  $P=0.39$ ), processing speed (OR =0.41 [0.13–1.29],  $P=0.13$ ), and global cognition (OR =1.11 [0.42–2.93],  $P=0.84$ ) (Table 3).

## Exploratory hypothesis: additional lipid profile variables and cognition

The exploratory analyses did not find any association between HDL, non-HDL cholesterol, TC, TC/HDL ratio, triglyceride levels, and lipophilic statin use with either global cognition or cognitive domain Z-scores (data not shown).

## Discussion

This study found that low LDL levels were not associated with decreased cognition in CAD patients using statins. This is important because CAD patients are at high risk of cognitive dysfunction<sup>21–24</sup> and many CAD patients, particularly statin users, frequently have low LDL concentrations. The findings of this study are consistent with several well-designed and well-powered studies that also did not find

**Table 3** Odds ratio of impairment <1 SD in cognitive domains between CAD patients taking low-dose statins and those taking high-dose statins

Cognitive domains	Low-dose statin (reference)	High-dose statin OR (95% CI)	P-value <sup>a</sup> (significance at P≤0.05)
Global cognition	1.0	1.11 (0.42–2.93)	0.84
Verbal memory	1.0	1.78 (0.47–6.72)	0.39
Visuospatial memory	1.0	0.12 (0.02–0.66)	0.01
Processing speed	1.0	0.41 (0.13–1.29)	0.13
Executive function	1.0	0.25 (0.06–0.99)	0.05

**Notes:** <sup>a</sup>Two-tailed significance of differences in cognitive impairment between statin dose groups in logistic regressions controlling for age, gender, years of education, myocardial infarction, antihypertensive use, serum LDL concentrations, and duration of statin use.

**Abbreviations:** CAD, coronary artery disease; CI, confidence interval; LDL, low-density lipoprotein; OR, odds ratio; SD, standard deviation.

an association between LDL and cognition<sup>15–17</sup> in general, though those studies had not been performed specifically in patients with CAD. At least from this initial study, it appears that CAD patients can be safely treated with statins to relatively low LDL levels (<1.5 mmol/L) without concern about cognition, although future longitudinal studies will be helpful to confirm this.

It was also found that high-dose statin use was associated with better visuospatial memory, processing speed, and executive function in CAD patients. This effect seemed to be most robust for visuospatial memory and was independent of covariates such as LDL. This article extends findings from recent meta-analyses and high-quality studies suggesting that statins are associated with lower cognitive risk.<sup>1–4</sup> One paper had previously assessed whether there was any potential relationship between statin dose and cognition.<sup>47</sup> That large observational study of 4,095 community-dwelling participants aged 35–82 years, including 904 statin users, did not find an association between statin use, dose, or duration with their measured cognitive outcomes: the Ruff Figural Fluency Test and the Visual Association Test.<sup>47</sup> It is possible that the in-depth cognitive testing in this study allowed more sensitivity to detect effects on global cognition and cognitive domain scores. Further studies will be needed to replicate these findings and better understand the relationship that was observed between high-dose statin use and higher cognitive function. If this is replicated, it is hypothesized that the potential protective effect of high-dose statins on cognition may be unrelated to statins' effect on LDL. Instead, it is hypothesized that high-dose statins may potentially have positive effects on cognition in CAD patients through an extension of its antioxidant, endothelium-promoting, and anti-inflammatory effects observed at lower doses.<sup>18,19</sup> Such statin effects may be mediated by modified intracellular signaling, particularly the inhibition of small guanosine triphosphate-binding proteins.<sup>9</sup>

## Strengths and limitations

This study had a number of strengths. The patient sample was well-characterized in terms of in-depth cognitive testing and covariates specifically relevant to CAD. The sample size was comparable to other detailed studies of cognition and large enough to detect clinically important effects. There were also some limitations to the data. As this is an observational cross-sectional design, causality cannot be inferred. Medications use covariates that were based on current use and not previous use. There was no access to data regarding

whether patients switched between high- and low-dose statin use during their previous exposure. Longitudinal and ideally randomized controlled study designs would be necessary to strengthen the findings of this study.

## Conclusion

Low LDL levels do not appear to be associated with poor cognition in CAD patients using statins. This is reassuring given the high frequency of LDL concentrations <1.5 mmol/L in CAD patients who are vulnerable to cognitive decline and dementia. High-dose statin use was found to be associated with better executive function and visuospatial cognition in CAD patients, which could be further investigated in future longitudinal and randomized controlled studies.

## Acknowledgments

Funding support was provided by Canadian Institutes of Health Research (Lancet MOP-114913) and the Heart and Stroke Foundation Canadian Partnership for Stroke Recovery.

## Disclosure

Soham Rej receives salary support from the Canadian Institute of Health research (CIHR) Fellowship Award. Mahwesh Saleem was supported by funding from the Alzheimer's Society of Canada. Nathan Herrmann is supported by peer-reviewed grants from the Alzheimer Society of Canada (grant 15–17), Canadian Institute of Health Research, Heart and Stroke Foundation (grant T 6383), Ontario Ministry of Health and Long Term Care AFP Provincial Innovation Fund and Ontario Brain Institute in addition to research contracts funded by F Hoffman-La Roche Ltd. and Lundbeck Canada Inc. Krista L Lancôt is supported by peer-reviewed grants from the Alzheimer Society of Canada (grant 15–17), Alzheimer's Drug Discovery Foundation (grant 20140503), Canadian Institute of Health Research, National Institute on Aging of the National Institutes of Health (grant R01AG046543), and the Heart and Stroke Foundation (grant NA 7220) in addition to research contracts funded by AbbVie Pharmaceuticals, F Hoffman-La Roche Ltd., Elan Pharma International Ltd., and Lundbeck Canada Inc. Anthi Stefatos and Allison Rau report no conflicts of interest in this work.

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