Curriculum Vitae

Dr. Mursyid Bustami, SpS(K), KIC, MARS.

- **Data Pribadi**
  - Nama : dr. Mursyid Bustami, SpS(K), KIC, MARS.
  - Tempat/tgl lahir : Bukittinggi/ 13 September 1962
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  - Telp/ email : bmursyid@yahoo.com
- **Riwayat Pendidikan**
  - Dokter : FK UGM Yogyakarta, th 1987.
  - Spesialis Saraf : FKUI Jakarta, th 2000.
  - Intensivist : Program Pendidikan KIC, Kolegium Anestesiologi dan Reanimasi Indonesia, th 2005.
  - Konsultan Neurotrauma dan Neuroemergensi, PERDOSSI, th 2007.
  - Kajian Administrasi Rumah Sakit, FKMUI Jakarta 2014.
- **Fellowship/Pelatihan**
  - Neurosonologi and Stroke, National Cerebrocardiovascular Center, Osaka, Japan, tahun 2002
  - Pelatihan Kepemimpinan Nasional Tk. II, Angkatan VII Tahun 2019.

Dr. Mursyid Bustami, SpS(K), KIC, MARS.

Pekerjaan

- Dirut RSPON. Prof. Mahar Mardjono, Jakarta, tahun 2013-sekarang.
- Departemen Neurologi FKUI/ RSCM, tahun 2000-2013.
- Anggota tim khusus dokter spesialis ke daerah konflik Lhokseumawe, NAD, tahun 2002

Organisasi

- Pengurus Perdossi/KNI 2007 – sekarang
- Pengurus Perhimpunan Dokter Intensive Care Indonesia (PERDICI)
- Pengurus Perhimpunan Dokter Emergensi Indonesia (PDEI)
- Pengurus Indonesian Society of Hypertension (Ina SH)

Piagam Penghargaan

- Dokter Puskesmas Teladan Nasional, tahun 1991.
- Satya Lencana Karya Satya 10 tahun, 20 tahun dan 30 tahun
- Bakti Karya Husada Dwi Windu 16 tahun dan 24 tahun.
- Top 5 PPT Teladan, Kemenpan RB tahun 2019.

Is **Statin safe** for *cognitive impairment & other neurologic diseases ?*

dr. Mursyid Bustami, Sp.S(K), KIC, MARS.
Brain Center Hospital Prof. DR. Mahar Mardjono, SpS(K)

Principal risk factors for stroke

Risk factor	Odds ratio
Hypertension	2.64
Cardiac causes[a]	2.38
Smoking	2.09
Dyslipidemia[b]	1.89
Waist-to-hip ratio (tertile 3 vs tertile 1)	1.65
Alcohol intake > 30 drinks/month	1.51
Diabetes	1.36

Odds ratios for stroke in 22 countries worldwide, adjusted for age, sex and region

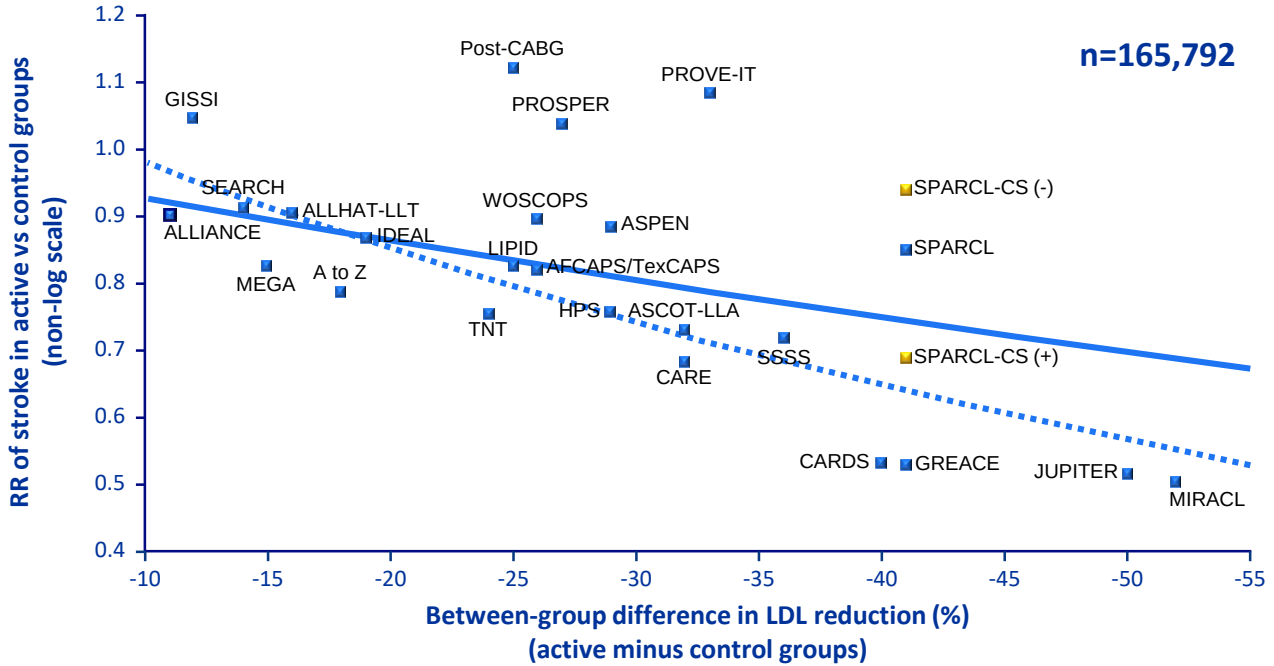
[a]Includes atrial fibrillation or flutter, previous myocardial infarction, rheumatic heart disease, or prosthetic heart valve

[b] Ratio of apolipoprotein B to A1 (tertile 3 vs tertile 1)

O'Donnell MJ, et al. Lancet. 2010;376(9735):112–123

Stroke risk and LDL lowering

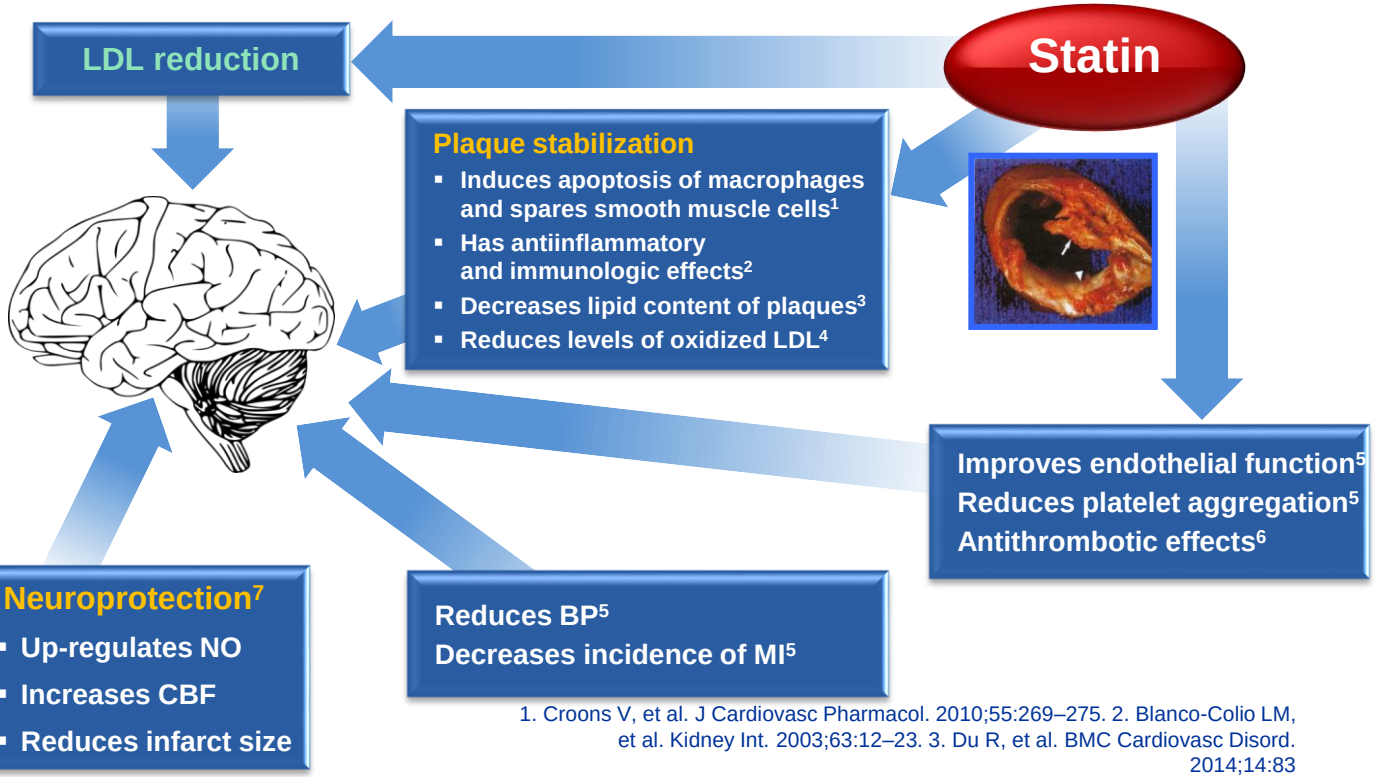
Each 1 mmol/L (39 mg/dL) LDL reduction reduced the relative risk of stroke by 21% (95% CI: 6.3–33.5; p=0.009)



Solid line, all trials. Dashed line, excluding trials with clearly defined groups in secondary stroke prevention
RR, risk ratio

Amarenco P, Labreuche J. Lancet Neurol. 2009;8:453–463

The Role of Statins in Reducing Stroke

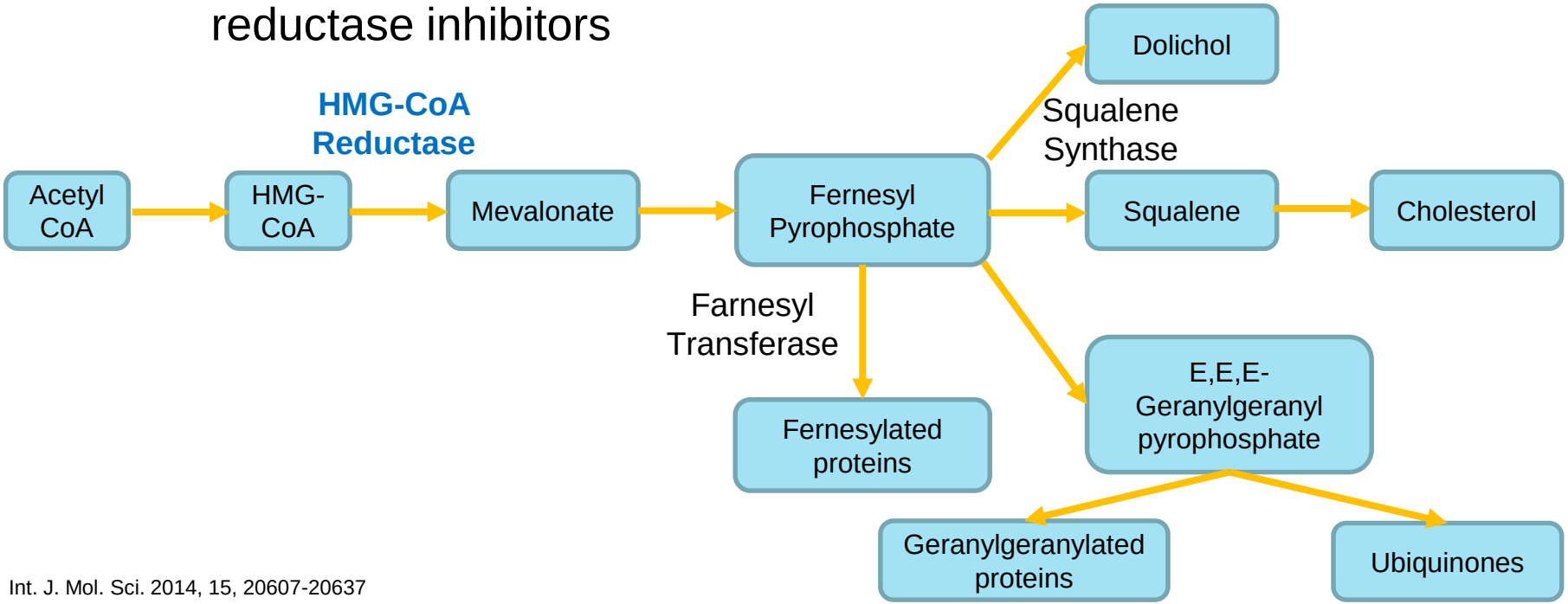


BP, blood pressure; CBF, cerebral blood flow; MI, myocardial infarction; NO, nitric oxide

1. Croons V, et al. J Cardiovasc Pharmacol. 2010;55:269–275. 2. Blanco-Colio LM, et al. Kidney Int. 2003;63:12–23. 3. Du R, et al. BMC Cardiovasc Disord. 2014;14:83
4. Tsai NW, et al. Crit Care. 2014;18:R16. 5. Amarenco P, Labreuche J. Lancet Neurol. 2009;8:453–463. 6. Timmis AD. Heart. 2003;89:1268–1272
7. Amarenco P, Moskowitz MA. Stroke. 2006;37:294–296

Mechanism of Statin

- 3-Hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors



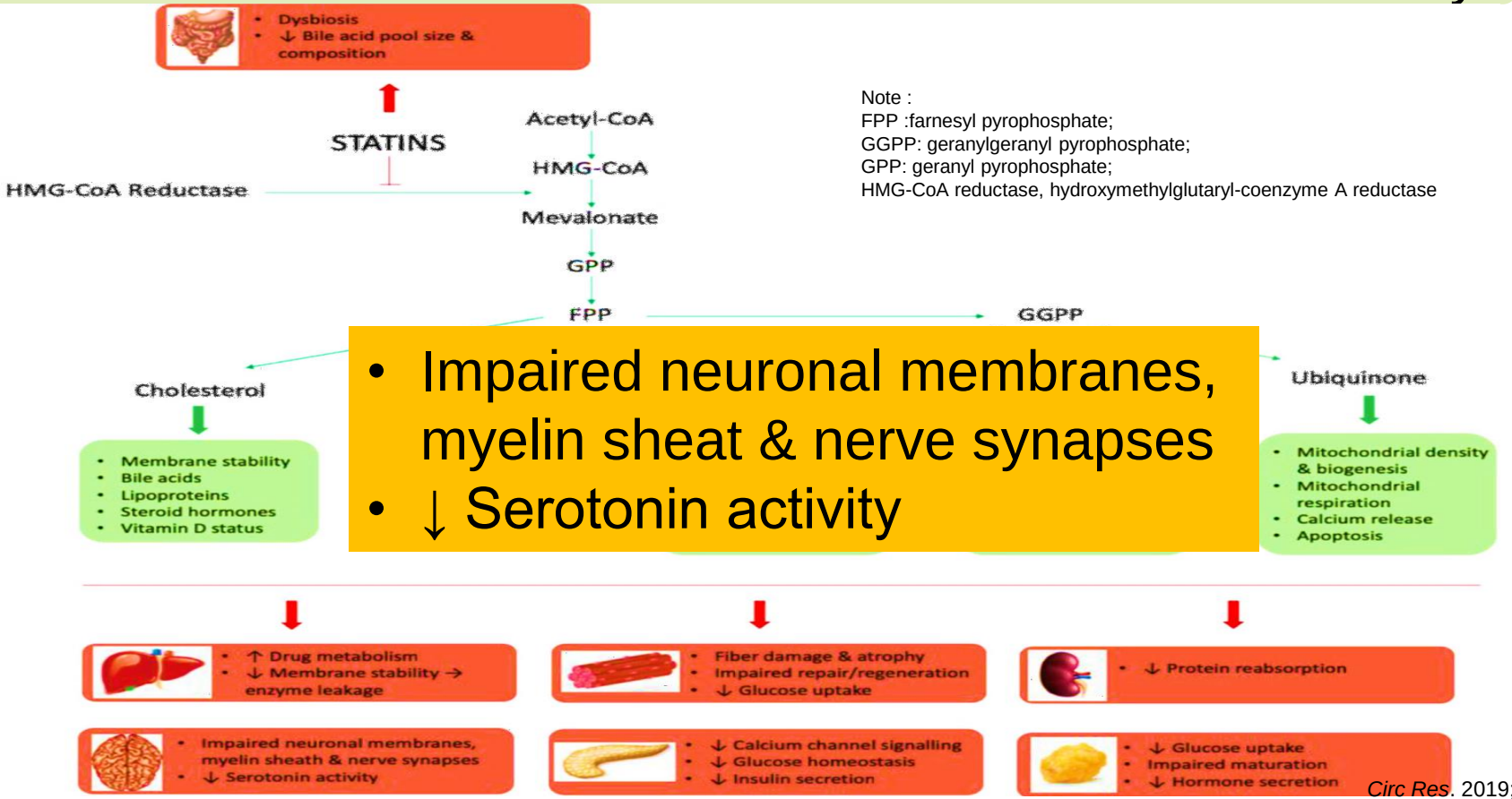
Int. J. Mol. Sci. 2014, 15, 20607-20637

Statin Drug Characteristic

Drug Name	Derivate	Side Ring	Solubility	Form Administration	Metabolism	Clearance	Half Life
Atorvastatin	Synthetic	Pyrrole	Lipophilic	Active Hydroxy acid	CYP3A4	Hepatic	14 h
Cerivastine	Synthetic	Pyridine	Lipophilic	Active Hydroxy acid	Various CYP3A	Hepatic	
Fluvastatin	Synthetic	Indole	Lipophilic	Active Hydroxy acid	CYP2C9	Hepatic	2-3 h
Lovastatin	Fungal	Naphthalene	Lipophilic	Inactive lactone	CYP3A4	Hepatic	3 h
Pitavastatin	Synthetic	Quinoline	Lipophilic	Active Hydroxy acid	Non-CYP450 Limited CYP2C9/19	Hepatic	12 h
Pravastatin	Fungal	Naphthalene	Hydrophilic	Active Hydroxy acid	Non-CYP450	Hepatic and Renal	1.3-2.7 h

Circ Res. 2019;124:328-350.; Int. J. Mol. Sci. 2014, 15, 20607-20637

Mechanism for the development of Statin Toxicity



Note :
FPP :farnesyl pyrophosphate;
GGPP: geranylgeranyl pyrophosphate;
GPP: geranyl pyrophosphate;
HMG-CoA reductase, hydroxymethylglutaryl-coenzyme A reductase

- Impaired neuronal membranes, myelin sheat & nerve synapses
- ↓ Serotonin activity

Circ Res. 2019;124:328-350

Statin Toxicity/ Effect

- Cognitive impairment, Alzheimer diseases
- Hemorrhagic stroke
- Muscle symptom.
- Pheripheral polyneuropathy.

Circ Res. 2019;124:328-350.; Int. J. Mol. Sci. 2014, 15, 20607-20637

Does Statins cause Memory Loss?

FDA Consumer Health Information
www.fda.gov/consumer

FDA Expands Advice on STATIN RISKS

If you're one of the millions of Americans who take statins to prevent heart disease, the Food and Drug Administration (FDA) has important new safety information on these cholesterol-lowering medications.

FDA is advising consumers and health care professionals that:

- Routine monitoring of liver enzymes in the blood, once considered standard procedure for statin users, is no longer needed. Such monitoring has not been found to be effective in predicting or preventing the rare occurrences of serious liver injury associated with statin use.
- Cognitive (brain-related) impairment, such as memory loss, forgetfulness and confusion, has been reported by some statin users.
- People being treated with statins may have an increased risk of raised blood sugar levels and the development of Type 2 diabetes.
- Some medications interact with lovastatin (brand names include Mevacor) and can increase the risk of muscle damage.

This new information should not scare people off statins, says Amy G. Egan, M.D., M.P.H., deputy director for safety in FDA's Division of Metabolism and Endocrinology Products (DMEP). "The value of statins in preventing heart disease has been clearly established," she says. "Their benefit is indisputable, but they need to be taken with care and knowledge of their side effects."

FDA will be changing the drug labels of popular statin products to reflect these new concerns. (These labels are not the sticker attached to a prescription drug bottle, but the package insert with details about a prescription medication, including side effects.)

The statins affected include:

- Altoprev (lovastatin extended-release)
- Crestor (rosuvastatin)
- Lescol (fluvastatin)
- Lipitor (atorvastatin)
- Livalo (pitavastatin)
- Mevacor (lovastatin)
- Pravachol (pravastatin)
- Zocor (simvastatin).

Products containing statins in combination with other drugs include:

- Advicor (lovastatin/niacin extended-release)
- Simcor (simvastatin/niacin extended-release)
- Vytorin (simvastatin/ezetimibe).

"The value of statins in preventing heart disease has been clearly established."

http://www.fda.gov/ForConsumers/ConsumerUpdates/ucm293330.htm

Memory loss is class effect of all Statins

The statins affected include:
- Altoprev (lovastatin extended-release)
- Crestor (rosuvastatin)
- Lescol (fluvastatin)
- Lipitor (atorvastatin)
- Livalo (pitavastatin)
- Mevacor (lovastatin)
- Pravachol (pravastatin)
- Zocor (simvastatin).

This new information should not scare people off statins, says Amy G. Egan, M.D., M.P.H., deputy director for safety in FDA's Division of Metabolism and Endocrinology Products (DMEP). "The value of statins in preventing heart disease has been clearly established," she

Does Statins cause Memory Loss?

Additional Information for Healthcare Professionals

- Healthcare professionals should perform liver enzyme tests before initiating statin therapy in patients and as clinically indicated thereafter. If serious liver injury with clinical symptoms and/or hyperbilirubinemia or jaundice occurs during treatment, therapy should be interrupted. If an alternate etiology is not found, the statin should not be restarted.
- There have been rare post-marketing reports of cognitive impairment (e.g., memory loss, forgetfulness, amnesia, memory impairment, confusion) associated with statin use. These reported symptoms are generally not serious and reversible upon statin discontinuation, with variable times to symptom onset (1 day to years) and symptom resolution (median of 3 weeks).
- Increases in glycosylated hemoglobin (HbA1c) and fasting serum glucose levels have been reported with statin use.
- Healthcare professionals should follow the recommendations in the lovastatin label regarding drugs that may increase the risk of myopathy/rhabdomyolysis when used with lovastatin (see Lovastatin Dose Limitations below).
- Healthcare professionals should report adverse events involving statins to the FDA MedWatch program using the information in the "Contact FDA" box at the bottom of this page.

Journal of Pharmacovigilance
ISSN: 2329-6887

Sahebzamani et al., J Pharmacovigilance 2014, 2:4
DOI: 10.4172/2329-6887.1000141

Research Article Open Access

Examination of the FDA Warning for Statins and Cognitive Dysfunction

Conclusions:
Inconsistent with the FDA class warning, highly lipophilic statins with specific pharmacokinetic properties (atorvastatin, simvastatin) appear to confer a significantly greater risk of adverse cognitive effects compared to other lipophilic statins and those with hydrophilic solubility properties.

Abstract

Background: The ACC/AHA released new guidelines in December of 2013 for treatment of high blood cholesterol to simplify identification and treatment of patients most likely to benefit from statins. These guidelines may result in more patients receiving statin therapy, and at younger ages. In 2012, the U.S. Food and Drug Administration (FDA) mandated warnings for all statin drugs for possible adverse effects on cognitive performance. Statins can be classified as having greater lipophilic or hydrophilic solubility properties with lipophilic statins more readily crossing the blood brain barrier, and possibly differentially inducing detrimental cognitive effects.

Objective: We sought to analyze generalizability of the FDA statin class warning.

Methods: De-identified publicly-available data were analyzed from the FDA Adverse Event Reporting System (AERS) in relation to reports of cognitive dysfunction (primary outcome), and by type of statin (lipophilic, hydrophilic) versus "control" drugs used in the general population.

Results: Significantly higher proportional reporting ratios (PRRs) were observed for lipophilic statins, which more readily cross the blood-brain barrier, (range: 1.47-3.51) compared to hydrophilic statins (range: 0.69-1.64). However, fluvastatin, lovastatin, and pitavastatin (lipophilic) had relatively few adverse reports. The signal of higher risk of cognitive dysfunction was observed for the lipophilic statin atorvastatin (PRR = 2.59, 95% confidence interval: 2.44-2.75) followed by simvastatin (PRR = 2.22, 95% confidence interval: 2.04-2.31). Hydrophilic statins (rosuvastatin, pravastatin) showed essentially no evidence suggestive of heightened risk of cognitive dysfunction. Fluvastatin, lovastatin, and pitavastatin had relatively few adverse reports, and no evidence of a higher proportion of cognitive dysfunction reports compared to the control drugs in aggregate (PRR range: 0.22 to 1.48).

Conclusions: Inconsistent with the FDA class warning, highly lipophilic statins with specific pharmacokinetic properties (atorvastatin, simvastatin) appear to confer a significantly greater risk of adverse cognitive effects compared to other lipophilic statins and those with hydrophilic solubility properties.

Evidence supporting Statin – Cognitive Impairment

Study	Study Type	Statin	Participants	Findings/Relevance
FDA, 2012, [6]	Safety Literature Review	All	N/A	Statin labels should include cognitive impairment however the cardiovascular risks outweigh the small cognitive impairment risk.
Posvar EL, et al., 1996, [12]	Rising single-dose, partially blinded, three period study	Ator	22	Tolerance study that resulted in one participant experiencing cognitive side effects at the 120-mg solution dose. The participant experienced mild, transient restlessness, euphoria, and mental confusion that were considered to be dose-limiting side effects.
Wagstaff LR, et al., 2003, [13]	Review of case reports	Ator(23), Prava (1), Sim (36)	60	Case reports raise the possibility that statins may be associated with cognitive impairment in rare cases.
Muldoon MF, et al., 2000, [14]	Double-blind investigational	lova	209	Lovastatin treatment resulted in small performance decrements on neuropsychological tests of attention and psychomotor speed, the clinical importance of which is uncertain.
Muldoon MF, et al., 2004, [15]	Randomized trial	Sim	308	Patients given placebos performance improved more than statin patients on cognition tests given at day 0 and 6 months.
Evans MA, et al., 2009, [16]	Patient survey-based analysis	All	171	There is a characterizable association between statins and cognitive impairment. 128 patients experienced cogitive adrs determined to be probably or definitely related to statin therapy. Of 143 patients who reported stopping statin therapy, 128 reported improvement in cognitive problems, sometimes within days of statin discontinuation.
M Sahebzamani, 2014, [18]	FDA AERs database analysis	All	4867	Lipophilic statins (especially atorvastatin and simvastatin) have significantly more reports of Cog. Dys. than hydrophilic statins. Estimated Cog Dys reporting with atorvastatin and simvastatin is truly 3,00–30,000 reports/year.

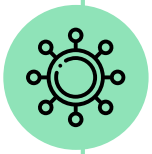
Schultz et al. Translational Neurodegeneration (2018) 7:5

General Cognition

Possible Statin-Induced Mechanism

↓ FPP and/or GGPP; modulation of adult neurogenesis;
↑ expression of neural growth factors.

Strength of Evidence



Limited in vitro and in vivo studies. Conflicting evidence from epidemiological studies and RCT. Case reports of negative effects on cognition. Recent meta-analyses suggest long term statin use may reduce incident of dementia.

Overall Consensus

Long-term statin treatment appears to be beneficial for cognitive function. Whether statins can cause acute cognitive disruption as a rare adverse effect is unclear due to lack of causal evidence from case reports. Identification of underlying mechanisms in vitro or in vivo is difficult due to the subjective nature of acute cognition changes.

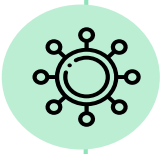
Int. J. Mol. Sci. 2014, 15, 20607-20637

Statin Effect in Alzheimer Disease

Possible Statin-Induced Mechanism

↓ FPP and/or GGPP; ↓ APP production; ↓ ROCK activity;
↓ amyloid-β production;
↑ amyloid-β degradation;
↓ neuro-inflammation; ↓ ROS.

Strength of Evidence



Numerous in vitro and in vivo studies, however some data appears model-dependent so requires careful interpretation. Several randomized controlled trials, and multiple systematic reviews and meta-analyses have

Overall Consensus

Studies suggest statins, if started before old age and without cognitive dysfunction at baseline, may reduce incidence of AD. It is likely different statins have different capacities for inducing this effect.

Int. J. Mol. Sci. 2014, 15, 20607-20637

Summary of evidence evaluating possible effects of statins on cognitive function

Year	Metode	Results	Conclusion
2013	Meta-analysis of 8 prospective cohort studies (n = 57.020 and 2851 cases of dementia)	Statin use was associated with a lower risk of dementia (relative risk 0.62, 95% CI 0.43– 0.81)	Statin use was associated with reduction in the risk of dementia
2013	Systematic review of RCTs and cohort, case–control, and cross-sectional studies and FDA post surveillance marketing database	Among statin users, there was: • No increased incidence of Alzheimer's dementia • No increased incidence of dementia or MCI • FDA post-marketing surveillance database review revealed similar rates of cognitive- related adverse events as compared to other cardiovascular medications	Published data do not suggest an adverse effect of statins on cognition

European Heart Journal (2018) 39, 2526–2539

Summary of evidence evaluating possible effects of statins on cognitive function

Tahun	Metode	Results	Conclusion
2015	Meta-analysis of 25 RCTs (n = 46 836); 23 RCTs included cognitive testing (n = 29 012)	• Adverse cognitive outcomes with statin use were rarely reported in trials involving cognitively normal or impaired subjects • Cognitive test data failed to show significant adverse effects of statins on all tests of cognition in either cognitively normal subjects (P = 0.42) or Alzheimer's dementia subjects (P = 0.38)	Statin therapy is not associated with cognitive impairment
2017	EBBINGHAUS; prospective nested cohort study of the FOURIER study (n = 1204). Cognitive function was assessed prospectively using the Cambridge Neuropsychological Test Automated Battery	• Over a median 19 months follow-up, there were no significant differences between evolocumab and placebo (statin alone) in the change from baseline in the spatial working memory strategy index of executive function (primary end point), or working memory, episodic memory or psychomotor speed (secondary endpoints) • An exploratory analysis showed no association between LDL-C levels and cognitive changes	Low LDL-C levels were not associated with adverse effects on cognitive function as assessed prospectively over 19 months

European Heart Journal (2018) 39, 2526–2539

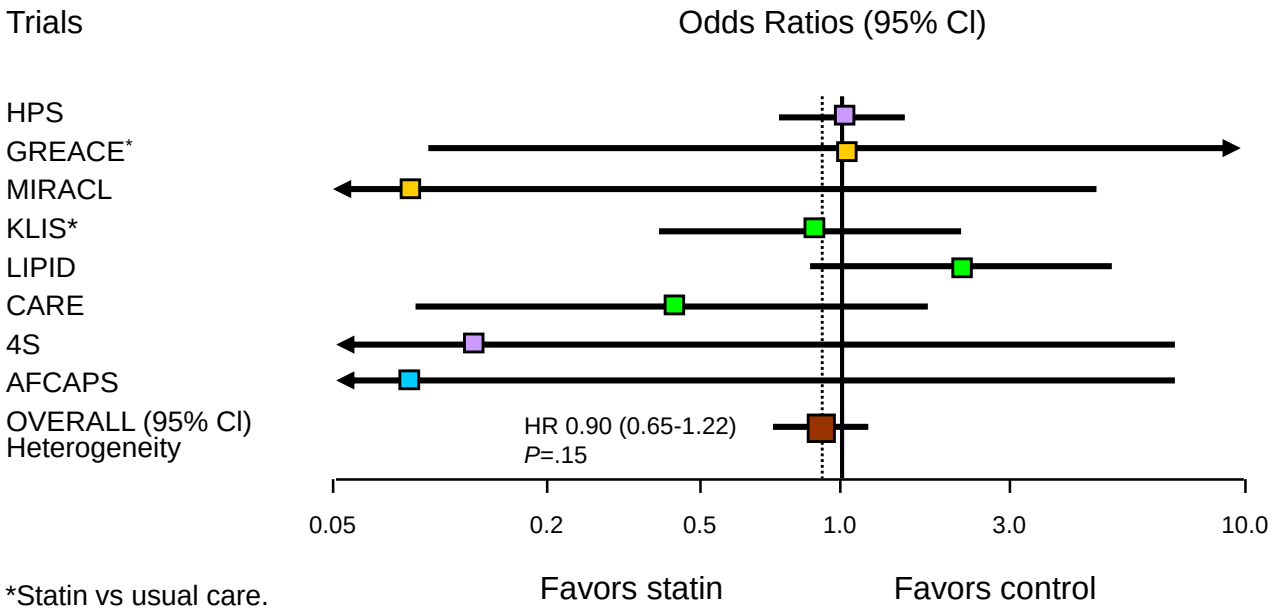
Tahun	Metode	Results	Conclusion
2017	IMPROVE-IT (n = 15 281) FOURIER (n = 25 982)	• In IMPROVE-IT, the incidence of neurocognitive adverse events did not increase at very low LDL-C levels (<0.78 mmol/L or <30 mg/dL) • FOURIER, the incidence of neurocognitive adverse events did not increase at very low LDL-C levels (<0.50 mmol/L or <20 mg/dL)	Very low LDL-C levels do not adversely affect cognitive function
2017	Mendelian randomization studies: 1. 111 194 individuals from the Copenhagen General Population Study and Copenhagen City Heart Study 2. The International Genomics of Alzheimer's Project (n = 17 008 Alzheimer's disease cases and 37 154 controls)	• In the Copenhagen Studies, the hazard ratios for a 1 mmol/L lower observational LDL-C level were 0.96 (95% CI 0.91–1.02) for Alzheimer's disease, 1.09 (95% CI 0.97–1.23) for vascular dementia, 1.01 (95% CI 0.97– 1.06) for any dementia, and 1.10 (95% CI 1.00–1.21) for Parkinson's disease • In genetic, causal analyses in the Copenhagen studies the risk ratios for a lifelong 1 mmol/L lower LDL-C level due to PCSK9 and HMGCR variants were 0.57 (95% CI 0.27–1.17) for Alzheimer's disease, 0.81 (95% CI 0.34–1.89) for vascular dementia, 0.66 (95% CI 0.34– 1.26) for any dementia, and 1.02 (95% CI 0.26–4.00) for Parkinson's disease • Summary level data from the International Genomics of Alzheimer's Project using Egger Mendelian randomization analysis gave a risk ratio for Alzheimer's disease of 0.24 (95% CI 0.02–2.79) for 26 PCSK9 and HMGCR variants, of 0.64 (95% CI 0.52–0.79) for 380 variants of LDL-C lowering omitting the APOE gene, but including nearby variants, and 0.98 (95% CI 0.87–1.09) including all LDL-C related var-iants omitting the wider APOE gene region	Low LDL-C levels due to PCSK9 and HMGCR variants mimicking PCSK9 inhibitor and statin treatment had no causal effect on the risk of Alzheimer's disease, vascular dementia, any dementia, or Parkinson's disease

European Heart Journal (2018) 39, 2526–2539

Is Statin caused of Hemorrhagic Stroke?

Statin Therapy Is Not Associated With Increased Risk for Hemorrhagic Stroke

A recent meta-analysis demonstrated that statin therapy does **not increase risk of hemorrhagic stroke vs control**



*Statin vs usual care.

Adapted with permission from Amarenco P et al. *Stroke*. 2004;35:2902-2909.

Can Low-Density Lipoprotein Be Too Low? The Safety and Efficacy of Achieving Very Low Low-Density Lipoprotein With Intensive Statin Therapy

JACC Vol. 46, No. 8, 2005
October 18, 2005:1411–6

A PROVE IT-TIMI 22 Substudy

Stephen D. Wiviott, MD,*† Christopher P. Cannon, MD, FACC,*†
David A. Morrow, MD, MPH, FACC,*† Kausik K. Ray, MD,† Marc A. Pfeffer, MD, PHD, FACC,*
Eugene Braunwald, MD, MACC,*† for the PROVE IT-TIMI 22 Investigators

Boston, Massachusetts

Table 2. Major Safety and Efficacy Outcomes (Percent of Subjects)

Safety Measure	Achieved LDL Cholesterol (mg/dl) >80–100 n = 256	>60–80 n = 576	>40–60 n = 631	<40 n = 193	p Trend
Muscle side effects*					
Myalgia	6.4	4.3	6.2	5.7	0.75
Myositis	0.4	0.6	0.6	0	0.64
CK >3× ULN	2.3	0.7	1.9	1.0	0.18
CK >10× ULN	0	0	0.3	0	0.45
Rhabdomyolysis	0	0	0	0	1.0
Liver side effects					
ALT >3× ULN	3.2	3.0	3.2	2.6	0.98
Study drug discontinued because of LFT	2.0	2.6	2.4	1.6	0.83
Other					
Hemorrhagic stroke	0.4	0.2	0	0	0.12
Retinal AE	0.4	0.9	1.0	0	0.48
Suicide/trauma death	0	0	0	0	1.0
Study drug discontinued because of any AE	10.2	9.4	9.7	9.8	0.99
Major efficacy measures					
Death	1.1	1.4	1.3	0.5	0.59
CHD death	0.5	0.5	0.6	0.0	0.06
Myocardial infarction	1.0	0.7	0.5	0.6	0.009
Any stroke	0.8	0.9	0.6	1.6	0.32
Primary composite*	26.1	22.2	20.4	20.4	0.10

*Primary composite = percent of subjects with any of the following: death, myocardial infarction, stroke, unstable angina requiring rehospitalization, and revascularization. Myalgia = muscle symptoms without CK elevation; myositis = muscle symptoms with CK elevation; rhabdomyolysis = muscle symptoms with CK >10× ULN and evidence of renal dysfunction (17).

AE = adverse event; ALT = alanine aminotransferase; CHD = coronary heart disease; CK = creatine kinase; LFT = liver function test; LDL = low-density lipoprotein; ULN = upper limit of normal.

Hemorrhagic stroke in the Stroke Prevention by Aggressive Reduction in Cholesterol Levels study

L.B. Goldstein, MD
P. Amarenco, MD
M. Szarek, MS
A. Callahan III, MD
M. Hennerici, MD, PhD
H. Sillesen, MD, DMSc
J.A. Zivin, MD, PhD
K.M.A. Welch, MB, ChB
On behalf of the SPARCL Investigators*

Address correspondence and reprint requests to Larry B. Goldstein, MD, Box 3651, Duke University Medical Center, Durham, NC 27710
golds004@mc.duke.edu

ABSTRACT

Background: In the Str
study, atorvastatin 80
Post hoc analysis foun
tients having hemorrha

Methods: We explored
characteristics, most r
lesterol levels prior to t

Results: Of 4,731 patie
as entry events. In add
Cox multivariable reg
showed that hemorrha
event (HR 5.65, 95% (
0.01), and with age (10
statistical interactions
that having Stage 2 (
increased risk (HR 6.19
LDL-cholesterol level i

Conclusions: Hemorrha
with a hemorrhagic str
hypertension at the las
ment did not dispropor
factors. There were no
tein (LDL) cholesterol level or recent LDL cholesterol level in treated patients.

Neurology® 2008;70:2364–2370

Conclusions :

Hemorrhagic stroke was more frequent in those treated with atorvastatin, in those with a hemorrhagic stroke as an entry event, in men, and increased with age. Those with Stage 2 hypertension at the last visit prior to the hemorrhagic stroke were also at increased risk. Treatment did not disproportionately affect the hemorrhagic stroke risk associated with these other factors.

No relationships between hemorrhage risk and baseline LDL-c. level or recent LDL-c level in treated patients.

Neurology 2008;70:2364-2370

Benefit of Targeting a LDL (Low-Density Lipoprotein) Cholesterol <70 mg/dL During 5 Years After Ischemic Stroke

Pierre Amarenco, MD; Jong S. Kim, MD; Julien Labreuche, BST; Hugo Charles, BST; Maurice Giroud, MD; Byung-Chul Lee, MD; Marie-Hélène Mahagne, MD; Norbert Nighoghossian, MD; Philippe Gabriel Steg, MD; Éric Vicaut, MD; Eric Bruckert, MD; on behalf of the Treat Stroke to Target Investigators*

Background and Purpose—The TST trial (Treat Stroke to Target) evaluated the benefit of targeting a LDL (low-density lipoprotein) cholesterol of <70 mg/dL to reduce the risk of cardiovascular events in 2860 patients with ischemic stroke with atherosclerotic stenosis of cerebral vasculature or aortic arch plaque >4 mm, in a French and Korean population. The follow-up lasted a median of 5.3 years in French patients (similar to the median follow-up time in the SPARCL trial [Stroke Prevention by Aggressive Reduction in Cholesterol Level]) and 2.0 years in Korean patients. Exposure duration to statin is a well-known driver for cardiovascular risk reduction. We report here the TST results in the French cohort.

Methods—One thous
dL (90–110 mg/dL
added ezetimibe o
new symptoms rec

Results—After a mec
mmol/L) on avera
0.74 [95% CI, 0.57
attack was reduce
The primary outco
13 and 11 patients

Conclusions—After
dL during 5.3 yea
intracranial hemor

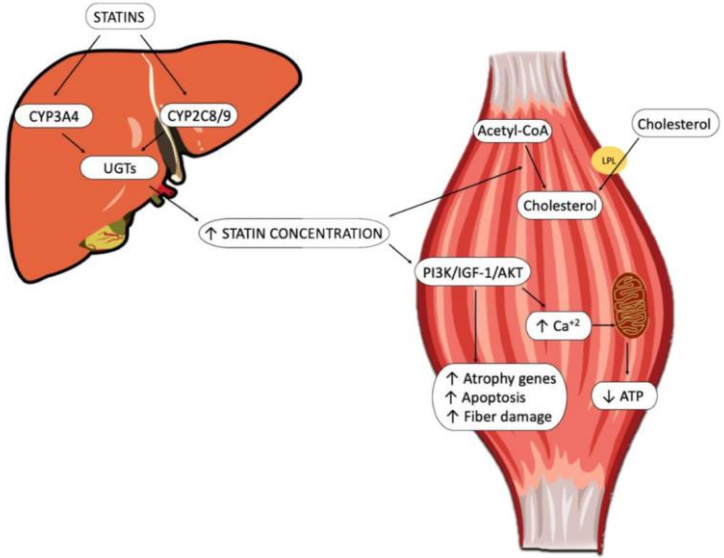
Registration—URL: https://www.clinicaltrials.gov. Unique identifier: NCT01252875. (***Stroke***. **2020;51:00-00. DOI: 10.1161/STROKEAHA.119.028718.)**

Conclusions.

After an ischemic stroke of documented atherosclerotic origin, targeting a LDL cholesterol of <70 mg/dL during 5.3 years avoided 1 subsequent major vascular event in 4 (number needed to treat of 30) and **no increase in intracranial hemorrhage.**

Stroke. 2020;51:00-00.

Statin Associated Muscle Symptoms and Neuropathy



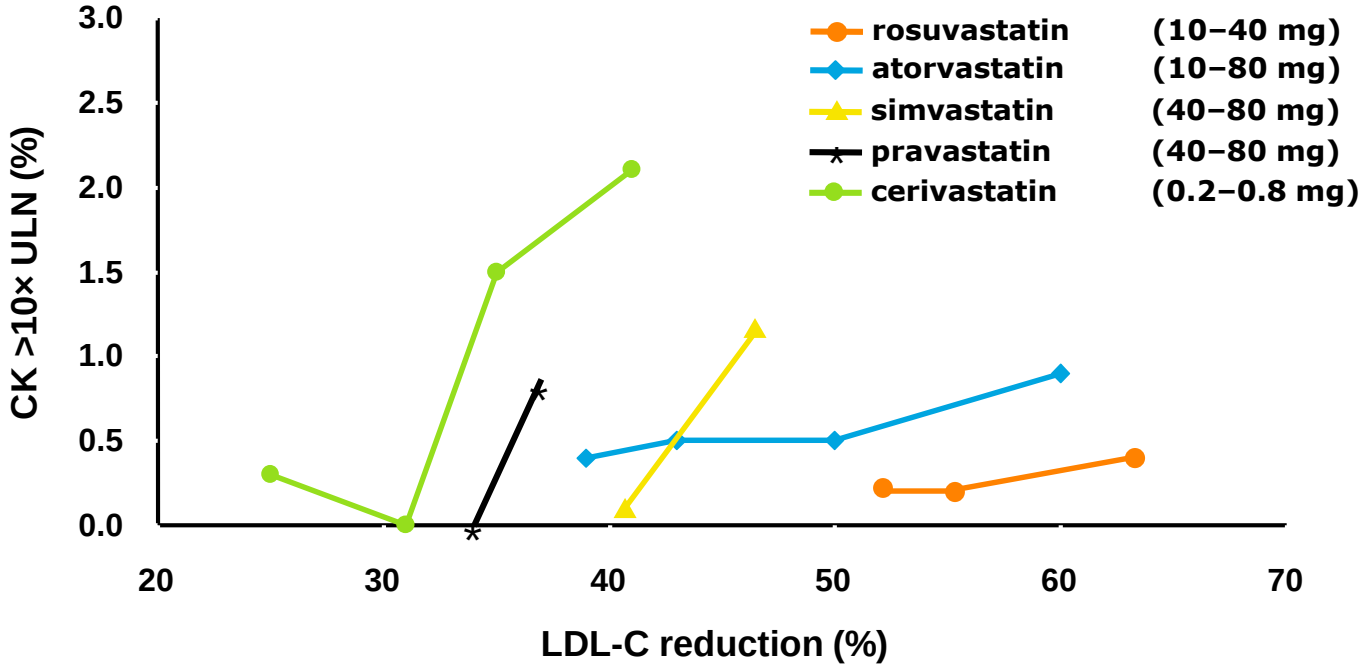
Statin Associated Muscle Symptoms (SAMS)

- **SAMS :** Muscle pain, weakness and aches, usually symmetrical and proximal, affecting the thighs, buttocks, calves and back muscles. Marked: creatine kinase (CK) elevation.
- **When :** early (within 4–6 weeks of starting a statin), after an increase in statin dose, or with initiation of an interacting drug.
- **Who** : elderly (>80 years), female, or with low body mass index or of Asian descent, with a history of muscle disorders, or concurrent conditions (e.g. acute infection, impaired renal or hepatic function, diabetes, HIV) or concomitant interacting medications.
- **How** did the EAS Consensus Panel define SAMS? By the nature of muscle symptoms, and their temporal association with statin initiation, discontinuation, and response to repetitive statin re-challenge.
- **Management :** magnitude of CK elevation, and the patient's global cardiovascular risk.

European Heart Journal (2018) 39, 2526–2539 doi:10.1093/eurheartj/ehy182

Benefit and risk profile of Statin on Muscle

Effect On Muscle :
CK >10x ULN: Frequency by LDL-C Reduction



Brewer HB. Am J Cardiol 2003;92(Suppl):23K–29K

Electronic Physician (ISSN: 2008-5842) http://www.ephysician.ir
March 2018, Volume: 10, Issue: 3, Pages: 6527-6533, DOI: http://dx.doi.org/10.19082/6527

Lipid-lowering drugs (statins) and peripheral neuropathy

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Abstract

Background and aim: statins, are proposed t condition by electrodiag **Methods:** This case-co who had received stati sensory and motor wav (Median, Ulnar, Tibial, software and p<0.05 wa **Results:** Regarding the presented for peripher abnormalities in 2 ner observed in two feature nerve (p=0.036). **Conclusion:** Since stati Even though no signifi neuropathy, there were response. This indicate physicians should be in

Keywords: Hydroxymethylglutaryl-CoA reductase inhibitors, Peripheral nervous system disease, Electrodiagnosis

- Statin might change the function and integrity of cell membranes, in which cholesterol plays a key role.
- Statins also inhibit an important enzyme in mitochondrial respiration named ubiquinone (Coenzyme Q10), which could in turn change the neurons' energy consumption. These are the probable mechanisms of the peripheral neuropathy.

Turk Kardiyol Dern Ars 2019;47(7):554-563 doi: 10.5543/tkda.2019.78379

ORIGINAL ARTICLE

Peripheral polyneuropathy in patients receiving long-term statin therapy

Uzun dönem statin kullanan hastalarda periferik polinöropati gelişimi

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Increased risk of peripheral neuropathy with long-term (>1 year) statin exposure.

ABSTRACT

Objective: Peripheral neuropathy is an important potential side effect of statin use. This study was an investigation of the incidence of peripheral neuropathy in patients taking atorvastatin or rosuvastatin for hypercholesterolemia and the relationship to the dose and duration of the treatment.

Methods: In all, 50 patients using a statin treatment and 50 healthy controls matched for age and gender who had never taken a statin were included in the study. Polyneuropathy was assessed with a neurological examination and electroneuromyography (ENMG).

Results: While no polyneuropathy was detected in the control group, polyneuropathy was seen in 33 (66%) of the patients in the statin group ($p<0.01$). There was no significant difference between the 2 statin groups in the results of the neurological examination or the ENMG findings regarding incidence of polyneuropathy ($p=0.288$ and $p=0.720$, ectively). Neuropathy was observed in a neurological mination performed within the first year in 50% of the rostatin users and 18% of those taking atorvastatin. The erity of the polyneuropathy increased with the duration e treatment in the atorvastatin group ($p=0.030$).

clusion: This study revealed an increased risk of peripheral neuropathy with long-term statin use (>1 year). Electrodiagnostic changes have been detected in motor and sensory nerves in nerve conduction studies of patients on long-term statin treatment. The assessment of neurological symptoms, like tingling, numbness, pain and tremor in the hands and feet, and unsteadiness during walking associated with peripheral neuropathy may be useful in the follow-up of the patients on long-term statin treatment. Early detection of peripheral neuropathy and changing hypercholesterolemia treatment may prevent permanent nerve damage.

Summary

- LDL reduction reduced the relative risk of stroke.
- Statin therapy is not associated with cognitive impairment.
- Statin therapy does not increase risk of haemorrhagic stroke.
- Long-term statin therapy can cause myopathy and polyneuropathy, but temporary.

Thanks