

Association of Cognitive Impairment in Patients on 3-Hydroxy-3-Methyl-Glutaryl-CoA Reductase Inhibitors

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Abstract

Background: Atherosclerotic cardiovascular diseases are the leading cause of death in the United States. A reduction in cholesterol with 3-hydroxy-3-methyl-glutaryl-CoA reductase inhibitors (statin) significantly reduces mortality and morbidity. Statins may be associated with cognitive impairment or dementia. Our aim was to study the association of cognitive impairment or dementia in patients who were on a statin.

Methods: Electronic medical records of 3,500 adult patients in our suburban internal medicine office were reviewed.

Results: There were 720 (20.6%) patients in the statin treatment group. Dementia or cognitive impairment was an associated comorbid condition in 7.9% patients in the statin treatment group compared to 3.1% patients in the non-statin group ($P < 0.001$). Analysis of all of the patients with cognitive impairment or dementia showed that among the age ranges of 51 years through 100 years, the patients in the statin treatment group had a higher prevalence of cognitive impairment or dementia compared to the non-statin group. In the statin treatment group, we found significantly higher prevalence of hyperlipidemia (86.3%), hypertension (69.6%), diabetes mellitus (36.0%), osteoarthritis (31.5%), coronary artery disease (26.1%), hypothyroidism (21.5%) and depression (19.3%) compared to the non-statin group ($P < 0.001$). About 39.9% of the patients with dementia or cognitive impairment were on statin therapy compared to 18.9% patients who had no dementia or cognitive impairment and were on statin therapy ($P < 0.001$). Among the patients with cognitive deficit or dementia in the statin treatment group, the majority of the patients were either on atorvastatin (43.9%) or simvastatin (35.1%), followed by

rosuvastatin (12.2%) and pravastatin (8.8%). We found greater odds of dementia or cognitive impairment with each year increase in age (1.3 times), in women (2.2 times), African American race (2.7 times), non-consumption of moderate amount of alcohol (two times), diabetes mellitus (1.6 times), hypothyroidism (1.7 times), cerebrovascular accident (3.2 times), and other rheumatological diseases (1.8 times).

Conclusions: The association of dementia or cognitive impairment was significantly higher in the patients who were on statin therapy compared to the patients who were not on a statin.

Keywords: Cognitive function; Cognitive impairment; Dementia; Statin therapy; HMG-CoA reductase inhibitor therapy

Introduction

Atherosclerotic cardiovascular diseases (ASCVDs) include heart disease, stroke and other cardiovascular disorders. According to the current statistics, ASCVD is the underlying cause of one in every three deaths in the United States [1]. A reduction in the low-density lipoprotein cholesterol (LDL-C) has been shown to be associated with a relative risk reduction of 20-30% for myocardial infarction, about 20% for ischemic stroke and up to 15% for all-cause mortality related to ASCVD [2]. The 3-hydroxy-3-methyl-glutaryl-CoA (HMG-CoA) reductase inhibitors (commonly known as “statins”) represent a group of medications that reduce cholesterol levels, especially the LDL-C. Long-term treatment with a statin is considered as safe and it improves survival in patients with ASCVD [3]. Additionally, long-term adherence to statin therapy is associated with progressively increasing clinical benefits in the form of primary and secondary prevention of atherosclerotic cardiovascular events [4].

Cholesterol is an integral component of the cell membrane signal transduction in the neurons and in the nerve endings. In a dry adult human brain, the total lipids in the gray matter, white matter and myelin constitute about 39.6%, 64.6% and 78.0% of dry weight, respectively [5].

Suboptimal lipid levels may potentially alter the composition and impair neuronal function. Several studies have suggested an association between the statins therapy, reduction in the circulating cholesterol levels and neurocognitive disorders

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Table 1. Baseline Characteristics

Variable	All (n = 3,500)	Group 1: statin treatment group (n = 720)	Group 2: non-statin treatment group (n = 2,780)	P value (1 vs. 2)
Age (years), mean (SD)	46.9 (17.6)	65.8 (14.3)	46.9 (16.5)	< 0.001*
Gender				
Male (n, %)	1,590 (45.4)	405 (56.2)	1,185 (42.6)	< 0.001†
Female (n, %)	1,910 (54.6)	315 (43.8)	1,595 (57.4)	< 0.001†
Race				
Caucasian (n, %)	2,179 (62.3)	511 (71.0)	1,668 (60.0)	< 0.001†
African American (n, %)	473 (13.5)	74 (10.3)	399 (14.4)	
Hispanic (n, %)	326 (9.3)	50 (6.9)	276 (9.9)	
Other (n, %)	522 (14.9)	85 (11.8)	437 (15.7)	
Social factors				
Alcohol (n, %)	1,654 (47.3)	318 (44.2)	1,336 (48.1)	0.066†
Cigarettes (n, %)	1,308 (37.4)	363 (50.5)	945 (34.0)	< 0.001†
Drugs (n, %)	149 (4.3)	24 (3.3)	125 (4.5)	0.169†

*Wilcoxon two-sample test. †Fisher's exact test.

[6-11].

In 2014, the United States Food and Drug Administration (FDA) released its report on expanded adverse effects of statins [12]. According to the report memory loss, forgetfulness and confusion span all statin products and all age groups. This report was based on the review of the database and recorded reports of clinical trials on statins that included assessment of cognitive function [6, 7, 11, 13-21]. The report also included the post-marketing adverse event reports of documented but reversible memory loss and cognitive impairment. The post-marketing adverse reports, reported via the Adverse Event Reporting System (AERS), upon which the FDA based its warnings, generally described individuals older than 50 years age who experienced ill-defined memory loss, confusion, and foggy thinking with variable onset of symptoms ranging from 1 day to years after statin exposure. The statins involved were primarily the lipophilic statins simvastatin and atorvastatin. These symptoms resolved after discontinuation of the statins and in some instances recurred with resumption. The reported cases did not appear to be associated with fixed or progressive dementia, such as Alzheimer's disease [12].

On the contrary, some studies have shown either no effect [22, 23], or neuroprotective benefits of statins for dementia or cognitive impairment [4, 24-29]. Similarly, hyperlipidemia and the sequelae of ASCVD are risk factors for dementia, hence according to other studies, it has been proposed that statins could play a role in protection from cognitive impairment [7]. Yet, reports of memory loss are mentioned in the second paragraph of the expanded advice to the consumers on statin risks reported by the FDA in the consumer health information [12]. The specific statin, dose, patient characteristics, and other comorbidities have not yet been determined by the available studies. The objective of our retrospective study was to determine the association of cognitive impairment and dementia in patients in our clinical practice who were on a statin.

Materials and Methods

Study selection

This study was a retrospective electronic medical record review that observed the association between a multitude of factors and cognitive impairment in patients who were on statin and compared with the patients who were not on statin. Patients who were seen between July 1, 2015 and December 31, 2015 were included in this study. The study was reviewed and approved by the Institutional Review Board of the Cooper Health System, Camden, New Jersey, USA. The inclusion criterion was adult patients of age 18 years or older who were either on statin therapy, or not. The exclusion criterion was patients under the age of 18 years.

Data collection

The following data were collected for each patient: age, gender, race (Caucasian, African American, Hispanic or other), social history (tobacco use, alcohol use, and/or recreational drug use), diagnosis of cognitive deficit or dementia, family history of dementia, comorbid medical conditions, such as hypertension, hyperlipidemia, hypothyroidism, coronary artery disease, cerebral vascular attack, carotid artery stenosis, congestive heart failure, chronic obstructive pulmonary disease, asthma, chronic kidney disease, liver disease, HIV, other immunodeficiencies, post-organ transplant immunodeficiency, cancer, other endocrine disorders, psychiatric conditions (depression, bipolar, anxiety disorder, and schizophrenia), arthritis and other rheumatologic diseases. We also collected systolic and diastolic blood pressures, body mass index, statin use, name of the statin, statin dose, and medication for dementia. Measure-

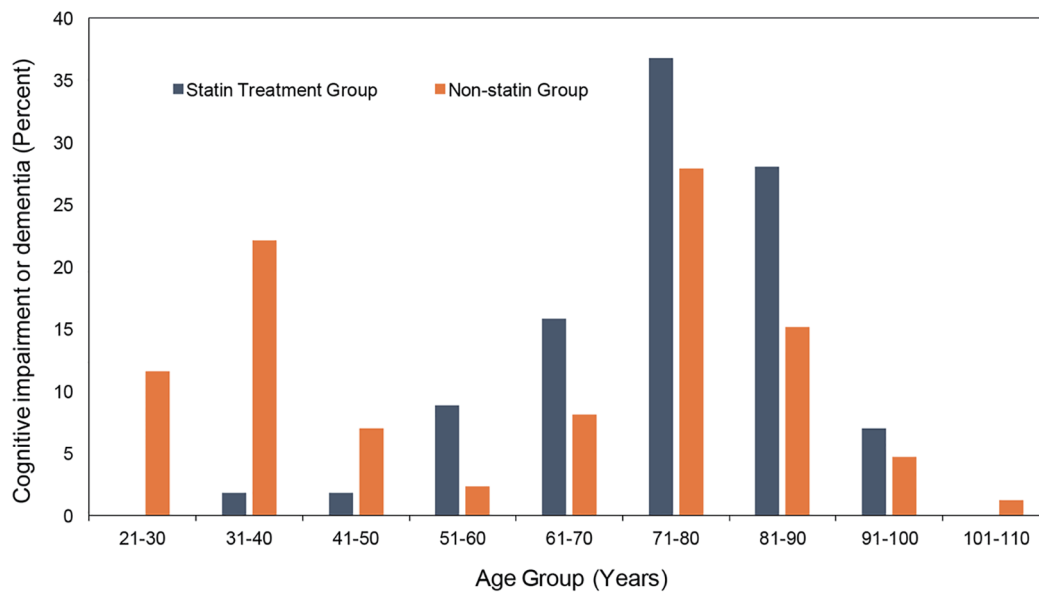


Figure 1. Comparative frequency of all cases of cognitive impairment or dementia based on age group.

ments of total cholesterol, triglycerides, high-density lipoprotein cholesterol (HDL-C), and LDL-C were also included in this study.

Statistical analysis

Collected data were entered into a Microsoft Excel (2013, Redmond, WA, USA) spreadsheet. Statistical analysis was done using SPSS (Statistical Package for the Social Sciences, version 15.01, IBM, Armonk, NY, USA). Subjects were divided into two groups. Group 1 represented the patients who were on statin (stain treatment group). Group 2 represented the patients who were not on statin (non-stain group). Baseline group characteristics of the study population were compared using univariate analysis and multivariate analysis. For univariate analysis, the independent *t*-test or Mann-Whitney U test was used to compare continuous variables between the two study groups and between those with diagnosis of cognitive deficit or dementia and those who did not have cognitive deficit or dementia. Chi-square tests were used to compare categorical variables between the groups. For multivariate analysis, logistic regression was used. The dependent variable was cognitive deficit or dementia and the independent variable was statin use. Other independent variables in the model were determined by the univariate analysis. Those with a P value of 0.20 or less were included in the regression model. In this study, significance was defined as a $P < 0.05$.

Results

A total of 3,500 patients were included in the study. The age range of our study population was 19 - 103 years. There were 720 (20.6%) patients who were on a statin (group 1: statin

treatment group). The remaining 2,780 (79.4%) patients were not on a statin (group 2: non-statin group).

The mean age of the patients in the statin treatment group was 65.8 ± 14.3 years and in the non-statin group was 46.9 ± 16.5 years. The difference in the mean age was statistically significant ($P < 0.001$) (Table 1).

There were significantly more male patients (56.2%) compared to the female patients (43.8%) in the statin treatment group ($P < 0.001$). Moreover, among all of the male patients in our study, there were significantly more male patients (56.2%) in the statin treatment group than in the non-statin group (42.6%) ($P < 0.001$).

The race analysis showed that the majority of the patients in the statin treatment group were Caucasian (71.0%), followed by African American (10.3%), other race (11.8%) and Hispanic (6.9%) (Table 1). We found similar hierarchy of the frequency of race in the non-statin group as well, but there were significantly more Caucasians in the statin treatment group (71.0%) compared to the non-statin group (60.0%) ($P < 0.001$), while there were significantly less African Americans, other races and Hispanics in the statin treatment group (10.3%, 11.8% and 6.9%, respectively) compared to the non-statin group (14.4%, 15.7% and 9.9%, respectively) ($P < 0.001$) (Table 1).

The analysis of the social factors such as alcohol intake, cigarette smoking and use of recreational drugs was observed in 47.3%, 37.4%, and 4.5% of all patients, respectively. Inter-group comparison showed no statistically significant difference in alcohol use or recreational drug use between the statin treatment group and the non-statin group, but there were significantly more patients in the statin treatment group (50.5%) compared to the non-statin group (34.0%) who smoked cigarettes ($P < 0.001$) (Table 1).

Dementia or cognitive impairment was identified as an associated comorbid condition in 7.9% patients in the statin treatment group compared to 3.1% patients in the non-statin

Table 2. Associated Comorbid Conditions

Variable	Group 1: statin treatment group (n = 720)	Group 2: non-statin treatment group (n = 2,780)	P* value (1 vs. 2)
Hyperlipidemia (n, %)	621 (86.3)	677 (24.4)	< 0.001
Hypertension (n, %)	501 (69.6)	683 (24.6)	< 0.001
Diabetes mellitus (n, %)	259 (36.0)	237 (8.5)	< 0.001
Osteoarthritis (n, %)	227 (31.5)	396 (14.2)	< 0.001
Coronary artery disease (n, %)	188 (26.1)	56 (2.0)	< 0.001
Hypothyroidism (n, %)	155 (21.5)	266 (9.6)	< 0.001
Depression (n, %)	139 (19.3)	421 (15.1)	< 0.001
Anxiety disorder (n, %)	118 (16.4)	426 (15.3)	0.482
Other rheumatological disease (n, %)	115 (16.0)	240 (8.6)	< 0.001
Cancer (n, %)	104 (14.4)	183 (6.6)	< 0.001
Asthma (n, %)	96 (13.3)	343 (12.3)	0.474
Other endocrine disorder (n, %)	88 (12.2)	173 (6.2)	< 0.001
Cerebrovascular accident (n, %)	73 (10.1)	34 (1.2)	< 0.001
Chronic kidney disease (n, %)	67 (9.3)	75 (2.7)	< 0.001
Liver disease (n, %)	66 (9.2)	137 (4.9)	< 0.001
Congestive heart failure (n, %)	61 (8.5)	36 (1.3)	< 0.001
Dementia-cognitive impairment (n, %)	57 (7.9)	86 (3.1)	< 0.001
Chronic obstructive airway disease (n, %)	55 (7.6)	48 (1.7)	< 0.001
Carotid stenosis (n, %)	30 (4.2)	6 (0.2)	< 0.001
Family history of dementia (n, %)	19 (2.6)	40 (1.4)	0.026
Bipolar disorder (n, %)	18 (2.5)	72 (2.6)	0.892
Immunodeficiency disease (n, %)	2 (0.3)	3 (0.1)	0.274
Post-transplant immunosuppression (n, %)	2 (0.3)	57 (2.1)	0.001
Schizophrenia (n, %)	1 (0.1)	11 (0.4)	0.479
Human immunodeficiency virus infection (n, %)	1 (0.1)	7 (0.3)	1.000

*Fisher's exact test.

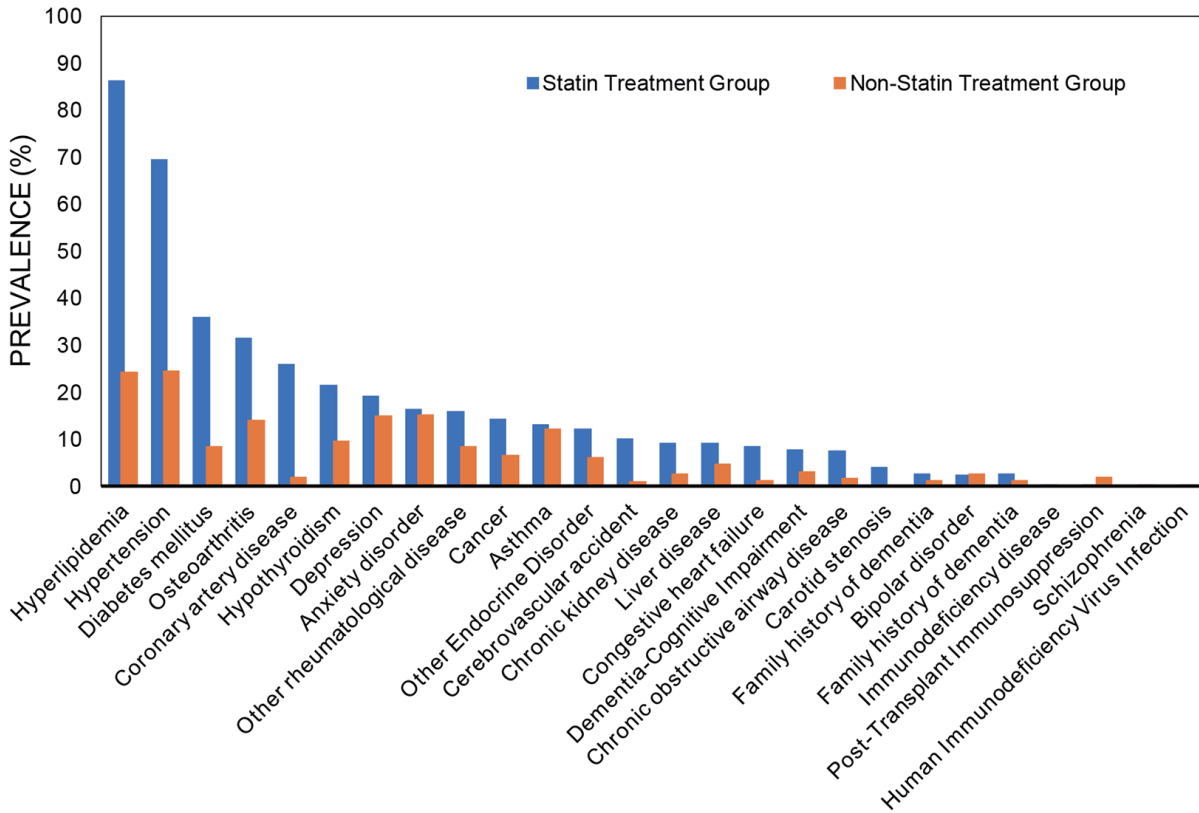
group. The difference was statistically significant ($P < 0.001$).

Further analysis of all of the patients with cognitive impairment or dementia showed that among the age ranges of 51 years through 100 years, the patients in the statin treatment group had a higher prevalence of cognitive impairment or dementia compared to the non-statin group (Fig. 1). We found a higher prevalence of cognitive impairment or dementia in the younger population (ages 21 - 50) due to cognitive deficits associated with childhood onset developmental disorders, such as mental retardation, cerebral palsy, autism spectrum disorder and other childhood onset cognitive disorders (Fig. 1). Although there was a higher prevalence of family history of dementia in the statin treatment group (2.6%) compared to the non-statin group (1.4%), the difference was not statistically significant ($P = 0.026$).

In the statin treatment group, more than two-thirds of the patients had hyperlipidemia (86.3%) and hypertension (69.6%), about one-third had diabetes mellitus (36.0%) and osteoarthritis (31.5%), about a quarter had coronary artery disease (26.1%), and about one-fifth had hypothyroidism (21.5%)

and depression (19.3%). The prevalence of all of these associated comorbid conditions was significantly higher in the statin treatment group than in the non-statin group ($P < 0.001$) (Table 2, Fig. 2). Similarly, patients in the statin treatment group had a significantly higher prevalence of other rheumatological disorders (12.2%), cerebrovascular accidents (10.1%), chronic kidney disease (9.3%), liver disease (9.2%), congestive heart failure (8.5%), chronic obstructive airway disease (7.6%) and carotid stenosis (4.2%) compared to the non-statin group (Table 2). The prevalence of other associated comorbid conditions, such as anxiety disorder, asthma, bipolar disorder, immunodeficiency disease, post-transplant immunosuppression, schizophrenia and HIV infection was comparable in both the groups.

The majority of the patients ($n = 511$, or 70.9%) in the statin treatment group were in the age range of 51 - 80 years (Fig. 3). This subgroup was further analyzed and compared with the patients in the age group of 51 - 80 years in the non-statin group (Table 3). The mean age of the patients in this subgroup of patients who were in the age range of 51 - 80 years and were



ASSOCIATED COMORBID CONDITIONS

Figure 2. Associated comorbid conditions.

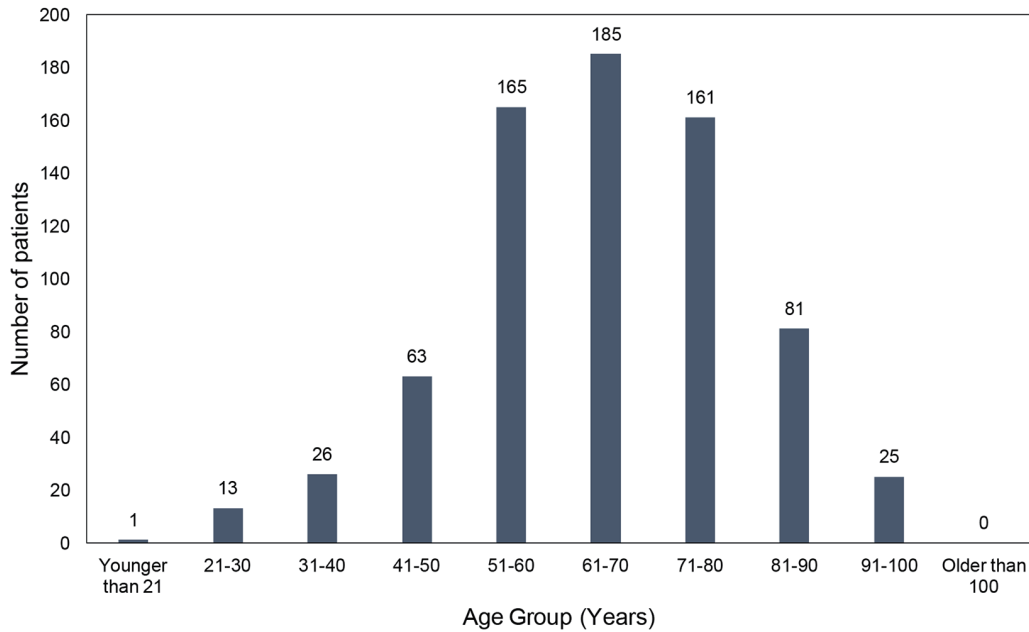


Figure 3. Age distribution of the patients in the statin treatment group.

Table 3. Associated Comorbid Conditions in the 51 - 80 Years Age Subgroup

Variable	Group 1: statin treatment group (n = 511)	Group 2: non-statin treatment group (n = 1,004)	P* value (1 vs. 2)
Age (years), mean (SD)	56.6 (8.3)	61.2 (8.1)	NS
Hyperlipidemia (n, %)	460 (90.0)	431 (42.9)	< 0.001
Hypertension (n, %)	363 (71.0)	426 (42.4)	< 0.001
Diabetes mellitus (n, %)	194 (37.9)	141 (14.0)	< 0.001
Osteoarthritis (n, %)	163 (31.9)	252 (25.1)	< 0.001
Coronary artery disease (n, %)	130 (25.4)	38 (3.8)	< 0.001
Hypothyroidism (n, %)	101 (19.8)	147 (14.6)	NS
Depression (n, %)	102 (19.9)	172 (17.2)	NS
Anxiety disorder (n, %)	78 (15.3)	158 (15.7)	NS
Other rheumatological disease (n, %)	77 (15.1)	150 (14.9)	NS
Cancer (n, %)	71 (13.9)	120 (12.0)	NS
Asthma (n, %)	73 (14.3)	127 (12.6)	NS
Other endocrine disorder (n, %)	60 (11.7)	88 (8.8)	NS
Cerebrovascular accident (n, %)	42 (8.2)	20 (2.0)	< 0.001
Chronic kidney disease (n, %)	67 (9.3)	49 (4.9)	< 0.001
Liver disease (n, %)	49 (9.6)	67 (6.7)	NS
Congestive heart failure (n, %)	37 (7.2)	18 (1.8)	< 0.001
Dementia-cognitive impairment (n, %)	35 (6.8)	33 (3.3)	< 0.001
Chronic obstructive airway disease (n, %)	35 (6.8)	34 (3.4)	< 0.001
Carotid stenosis (n, %)	19 (3.7)	5 (0.5)	< 0.001
Family history of dementia (n, %)	15 (2.9)	23 (2.3)	NS
Bipolar disorder (n, %)	12 (2.3)	18 (1.8)	NS
Immunodeficiency disease (n, %)	2 (0.4)	2 (0.2)	NS
Post-transplant immunosuppression (n, %)	2 (0.4)	57 (5.7)	< 0.001
Schizophrenia (n, %)	0 (0.0)	6 (0.6)	NS
Human immunodeficiency virus infection (n, %)	0 (0.0)	2 (0.2)	NS

*Fisher's exact test. NS: not significant.

Table 4. Comparative Vitals and Lipid Analysis

Variable	Group 1: statin treatment group (n = 720)	Group 2: non-statin treatment group (n = 2,780)	P* value (1 vs. 2)
Vitals			
BMI (kg/m ²), mean (SD)	29.7 (6.5)	29.5 (10.9)	0.556
SBP (mm Hg), mean (SD)	127.4 (14.9)	123 (13.7)	< 0.001
DBP (mm Hg), mean (SD)	75.9 (9.6)	76.5 (9.1)	0.141
Lab tests			
TC (mg/dL), mean (SD)	176.5 (47.4)	185.1 (35.9)	< 0.001
TG (mg/dL), mean (SD)	136.1 (102.3)	113.4 (70.8)	< 0.001
HDL-C (mg/dL), mean (SD)	51.2 (15.8)	54.5 (17.9)	< 0.001
LDL-C (mg/dL), mean (SD)	98.0 (40.8)	108.2 (30.8)	< 0.001

BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; TC: total cholesterol; TG: triglyceride; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol. *Wilcoxon two-sample test.

Table 5. Statin Therapy and Dementia or Cognitive Impairment

Variable	Dementia or cognitive impairment (n = 143)	No dementia or cognitive impairment (n = 3,357)	P
Statin therapy (n, %)	57 (39.9)	662 (18.9)	< 0.001

in the statin treatment group was 56.6 ± 8.3 years and in the non-statin group was 61.2 ± 8.1 years. Although the mean age of the patients in this subgroup of patients who were in the statin treatment group was lower than subgroup of the patients in the non-statin group, the difference was not statistically significant (Table 3). The prevalence of cognitive impairment or dementia among the patients who were in the age range of 51 - 80 years was 6.8% in the statin treatment group and 3.3% in the non-statin group (Table 3). The difference was statistically significant ($P < 0.001$). Although there was a higher prevalence of ASCVD defining conditions (such as coronary artery disease, cerebrovascular accidents, carotid artery stenosis and congestive heart failure), ASCVD risk factors (such as hyperlipidemia, hypertension and diabetes mellitus), and certain comorbid conditions (such as osteoarthritis, chronic obstructive pulmonary disease and chronic kidney disease), none of the factors can be directly attributed as a cause of cognitive impairment resulting in a higher prevalence of cognitive deficit or dementia in the statin treatment group. Additionally, there was no difference in the prevalence of certain known risk factors for cognitive impairment or dementia between the two groups, such as hypothyroidism, liver disease, other endocrine disorders and family history of dementia (Table 3).

The mean (SD) systolic blood pressure was higher in the statin treatment group (127.4 ± 14.9) compared to the non-statin group (123 ± 13.7) ($P < 0.001$) (Table 4). There were no statistically significant differences in the mean body mass indices and diastolic blood pressures between the two groups (Table 4). In the statin treatment group, the mean total cholesterol, LDL-C and HDL-C were lower (176.5, 98.0 and 51.2 mg/dL, respectively) compared to the non-statin group (185.1, 108.2 and 54.5 mg/dL, respectively). All the differences were statistically significant ($P < 0.001$). The mean triglyceride level was higher (136.1 mg/dL) in the statin treatment group compared to the non-statin group (113.4 mg/dL) ($P < 0.001$) (Table 4).

Further analysis of the association of statin therapy and dementia or cognitive impairment showed that 39.9% of patients with dementia or cognitive impairment were on statin therapy compared to 18.9% patients who had no dementia or cognitive impairment and were on statin therapy. The difference was statistically significant ($P < 0.001$) (Table 5). Among the patients with cognitive deficit or dementia in the statin treatment group, the majority of the patients were either on atorvastatin (43.9%) or simvastatin (35.1%), followed by rosuvastatin (12.2%) and pravastatin (8.8%) (Fig. 4).

The retrospective review of the medical records provided

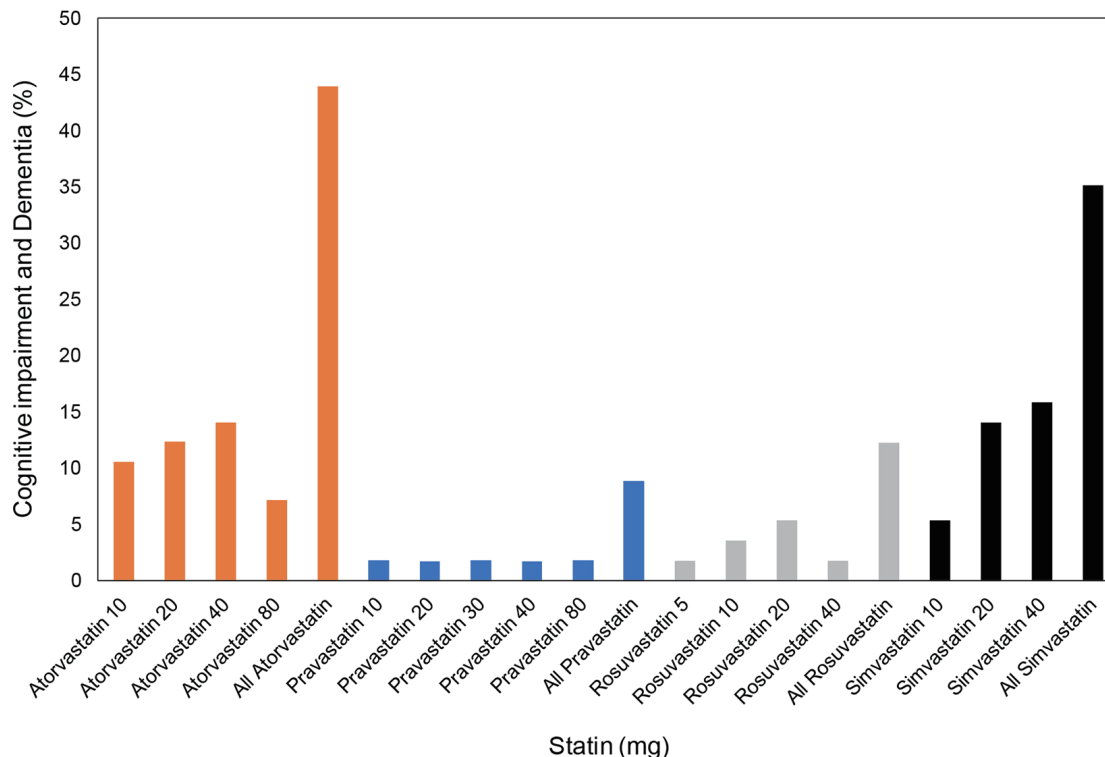


Figure 4. Type of statin and cognitive impairment or dementia.

periodic documentation of lipid levels without specific date of diagnosis of hyperlipidemia or date of statin initiation for a specific statin treatment group. In our institution, the electronic medical records were implemented in 2008. Patient data were manually entered from previous paper charts without specific mention of the onset of the statin therapy or cognitive impairment. Patients with cognitive impairment or dementia were either treated with donepezil, memantine or rivastigmine. All of the patients in the statin treatment group remained on statin at the time of data acquisition, hence there was no documentation of cessation of statin therapy and changes in cognitive function status. Diagnostic documentation of cognitive impairment or dementia was based on mini-mental status examination and/or Montreal cognitive assessment test. We also reviewed the possible negative cognitive influence of psychoactive medications in patients who had psychiatric disorders, such as depression, anxiety, bipolar disorder and/or schizophrenia. We found comparable prevalence of depression, anxiety, bipolar disorder and/or schizophrenia between the patients in the statin treatment group and in the non-statin treatment group who were in the age range of 51 - 80 years (Table 3).

Additionally, we looked into the factors that might have contributed to dementia or cognitive impairment and performed a multivariate analysis. We found that the odds of getting dementia or cognitive impairment increased by 1.3% with each year increase in age. Women had 2.2 times greater odds of having dementia or cognitive impairment. African American patients had 2.7 times greater odds of having dementia or cognitive impairment than other minorities who were non-Hispanic. Patients who did not consume moderate amount of alcohol had two times increased odds of having dementia or cognitive impairment than those who consumed alcohol. We found an opposite relationship between the diastolic blood pressure and dementia or cognitive impairment. The average diastolic blood pressure was lower in patients with dementia or cognitive impairment than those without. Patients with diabetes mellitus had 1.6 times greater odds of having dementia or cognitive impairment. Similarly, patients with hypothyroidism had 1.7 times greater odds of having dementia or cognitive impairment, patients with cerebrovascular accident had 3.2 times greater odds of having dementia or cognitive impairment, and patients with other rheumatological diseases had 1.8 times greater odds of having dementia or cognitive impairment.

Discussion

Our study had three major findings: first, a significantly higher association of dementia or cognitive impairment as a comorbid condition in patients who were on statin therapy compared to the patients who were not on statin therapy; second, a significantly higher number of patients with dementia or cognitive impairment were on statin therapy compared to the patients without dementia or cognitive impairment; third, atorvastatin and simvastatin were the leading statins associated with dementia or cognitive impairment.

Our findings were supported by several studies that have

found a similar association between statins and cognitive impairment and other psychological disorders, such as an increased risk of suicide [6-11].

Muldoon and colleagues compared the changes in performance between lovastatin-treated patients and placebo. They found statistically significant differences in the tests of attention and psychomotor speed indicating greater improvement in the placebo group compared to the lovastatin-treated patients [11]. Another study by Muldoon and colleagues showed that patients on statins demonstrated lack of otherwise expected normal improvements on repeated tests of attention and reaction time taken over the course of 6 months compared with placebo. This study was subsequently focused on simvastatin which partially supported that patients on simvastatin had minor decrements in cognitive function [6]. A study by Evans and Golomb showed negative cognitive effects with statins, and the effects were directly related to the potency of the statins. It offered significant negative impact in the quality of life [7]. According to the 2014 Food and Drug Administration (FDA) report memory loss, forgetfulness and confusion span all statin products across all age groups [12]. A review by Wagstaff and colleagues concluded that statins may be associated with cognitive impairment but they could not determine a causal relationship [14].

Our observation of 7.9% prevalence of cognitive impairment or dementia in our patients who were on a statin corresponds with the findings of Glasser and colleagues who found 8.6% prevalence of cognitive impairment in statin users in a national cohort study of the United States population in which 7,191 participants were on a statin and 17,404 participants were not on statins [30]. It is important to mention that adverse drug reactions due to statins are less likely discussed with the patients by the physicians, unless the patients initiate the discussion. One study found that muscle related adverse effects were the most likely statin related adverse effect discussed, while the cognitive changes were rarely assessed, evaluated or initiated by the physicians [31]. It is fair to estimate that voluntary reporting of adverse event of cognitive impairment due to statins has been variable and mostly under-reported. This might underestimate the prevalence of cognitive impairment associated with the statins.

Kessler and colleagues found that healthcare providers do not think to report adverse events to the FDA that might be associated with medications [32]. Various studies indicate that the percentage of voluntary reporting to the AERS varies between 1% and 10% which is considered to be extremely low reporting [32]. Sahebzamani and colleagues found 2,566 reports of cognitive impairment for atorvastatin and simvastatin documented in AERS over a period of 8 years. They further extrapolated the data based on underreporting assuming 1-10% of reporting and concluded that about 3,000 - 30,000 cognitive impairments each year may be associated with simvastatin and atorvastatin [8].

Several mechanisms have been explained between the association of cognitive impairment and statins. Ayinyet and colleagues postulate that there happens to be a connection between low serum cholesterol and lower activity of central serotonergic release which influences the mood, cognition and impulsive behavior [9]. Engelberg reviewed available physio-

logical mechanism behind low cholesterol levels and cognitive deficit [33]. It has been observed in the animal models that increase in the brain synaptosomal membrane cholesterol results into a robust increase in the number of serotonin receptors that are responsible for the maintenance of adequate cognitive and behavioral response. Lowering the synaptosomal membrane cholesterol with statins decreases the number of serotonin receptors, which in turn decreases synaptic binding and uptake of serotonin resulting into reduced cognitive and behavioral response [33].

We found that dementia or cognitive impairment was observed in a significantly higher proportion with the lipophilic statins, such as atorvastatin and simvastatin (79%) compared to the hydrophilic statins, such as rosuvastatin and pravastatin (21%). Our findings were supported by many studies that have shown higher association and severity of cognitive deficit with lipophilic statins compared with hydrophilic statins [8, 14, 34-38].

Thelen and colleagues reported significant reduction in the brain cholesterol precursor levels in simvastatin-treated mice (simvastatin 100 mg/kg body weight) compared to hydrophilic pravastatin or controls after 3 days of oral intake [35]. A study by Sahebzamani and colleagues showed a significantly higher proportion of cognitive impairment associated with the commonly prescribed lipophilic statins, atorvastatin and simvastatin, compared to hydrophilic statins, such as rosuvastatin and pravastatin [8].

Studies suggest that hyperlipidemia inhibits intracellular cholesterol synthesis in the neurons and increases intracellular amyloid (Ab) production which results into cell lysis which facilitates inhibition of cholesterol synthesis. Lipophilic statins, such as simvastatin and atorvastatin, further inhibit neuronal cholesterol which exacerbates neuronal degeneration resulting into cognitive impairment and dementia [36]. In a study, Chauhan and colleagues found that lipophilic statin, such as lovastatin significantly increased cerebral levels of IL-1beta and TNF-alpha in the animal model suggesting an enhanced cerebral inflammatory mechanism which may be responsible for the alteration in the function of the neurons [39]. Lipophilic statins cross the blood-brain barrier which may influence the synthesis of cholesterol in the neurons [40]. Reduction in the supply of unesterified cholesterol in the nerve cells affects cell integrity and function. Lipophilic statins diffuse via both passive diffusion and non-selective diffusion into hepatocytes and non-hepatocyte tissues [41-46]. On the contrary, hydrophilic statins are highly hepatoselective and enter into the hepatocytes via active transportation, which makes them less likely associated with non-hepatocytic adverse effects [36, 42]. Among the lipophilic statins, the likelihood of associated adverse effects predominantly depend upon their mechanisms of action.

The most commonly prescribed lipophilic statins atorvastatin and simvastatin are metabolized through CYP3A4. Atorvastatin has a longer half-life (about 11 - 30 h) while simvastatin has a higher percentage of absorption (about 65-85%). Other lipophilic statins, such as fluvastatin go through an extensive first-pass metabolism and protein binding. This may explain why atorvastatin and simvastatin may have higher association with non-hepatocytic adverse effects (such as cognitive impairment and dementia) among all of the lipophilic statins

[36, 42].

Rojas-Fernandez and colleagues analyzed the impact of statin use on cognition. According to their analysis in suspected individuals with statin-induced cognitive impairment switching from lipophilic to hydrophilic statins might resolve cognitive impairment [37].

It is important to mention that there have been many observational studies, randomized studies and reviews that have found no association between statins and cognitive impairment or dementia [47-50].

Other notable findings in our study were a higher association of hyperlipidemia, diabetes mellitus, hypertension and other cardiovascular risk factors or end-organ damages in the statin treatment group. It is appropriate to say that the patients in the statin treatment group fell into a higher ASCVD risk category, hence they were on a statin. It is also important to mention that although we found a higher association of depression in the statin treated patients, nevertheless we did not observe a higher association of other psychological disorders, such as anxiety disorder, bipolar disorder and schizophrenia in the statin treatment group. Our findings do not fully correlate with the previously reported studies [9-11]. Our multivariate analysis identified certain risk categories with higher odds of having cognitive impairment or dementia, such as increasing age, women, African American ethnicity, non-consumption of moderate amount of alcohol, lower diastolic blood pressure, diabetes mellitus, hypothyroidism, cerebrovascular accidents, and rheumatological diseases other than osteoarthritis. Our findings correspond with many studies which support our observation on increasing age [51-53], women [54], African American ethnicity [55], non-consumption of moderate amount of alcohol [56], lower diastolic blood pressure [57], diabetes mellitus [58], hypothyroidism [59-62], cerebrovascular accidents [63], and rheumatological diseases other than osteoarthritis [64, 65].

The major strength of our study was a large sample size from one office location. Patients' subsequent visits with the same healthcare provider allowed somewhat active recognition and documentation of cognitive changes in the electronic medical record. Nevertheless, our study had several limitations, such as retrospective analysis of only documented variables, and analysis limited to a suburban outpatient population, which cannot be generalized.

We conclude that association of dementia or cognitive impairment was significantly higher in our patients who were on statin therapy compared to the patients who were not on a statin.

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Conflicts of Interest

None.

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