Systematic Review and Meta-Analysis

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Relationship between statins and the risk of amyotrophic lateral sclerosis

A PRISMA-compliant meta-analysis

Min Cheol Chang, MD[a], Sang Gyu Kwak, PhD[b], Jin-Sung Park, MD[c], Donghwi Park, MD[d,*]

Abstract

Objective: Previous studies on overlapping surveillance databases have suggested that statin use was associated with the development of amyotrophic lateral sclerosis (ALS)-like syndrome. However, the association between statin use and ALS incidence has not been clearly elucidated. To further explore this issue, we performed a systemic review and meta-analysis of all available clinical studies on the association between statin use and ALS incidence.

Methods: A comprehensive database search on PubMed, Embase, Cochrane Library, and SCOPUS was conducted. We included studies up to January 31, 2020 that fulfilled our inclusion and exclusion criteria. Statin use between the ALS and control groups was collected for the meta-analysis.

Results: Three case-control studies and 1 cohort study, that related the risk of ALS to statin use, satisfied the inclusion criteria for the meta-analysis. There was no statistically significant difference in statin use between the ALS and control groups (odds ratio, 0.75 [95% confidence interval, 0.53–1.08]).

Conclusion: No definite association was found between statin use and the development of ALS. Further large-scale prospective randomized control studies are necessary to draw definite conclusions.

Abbreviations: ALS = amyotrophic lateral sclerosis, MND = motor neuron disease, HMG-CoA = 3-hydroxy-methylglutaryl-coenzyme A.

Keywords: amyotrophic lateral sclerosis, meta-analysis, statin

1. Introduction

Amyotrophic lateral sclerosis (ALS) is an incurable neurodegenerative disease characterized by progressive loss of motor neurons in the spinal cord, brainstem, and cerebral cortex.[1–4] Globally, the annual incidence rates of ALS are 0.4 to 2.4 cases per 100,000, and the prevalence rates of ALS are 4 to 10 cases per 100,000.[5–10]

Statins are competitive inhibitors of 3-hydroxy-methylglutaryl-coenzyme A (HMG-CoA) reductase, a rate-limiting enzyme in cholesterol biosynthesis.[11] Statins were first approved in 1987, and large randomized clinical trials have shown that statins reduced the risk of cardiovascular mortality, such as acute myocardial infarction and stroke.[12] Statins have been commonly prescribed for and well-tolerated by patients worldwide. However, statin use was associated with neuromuscular adverse effects, such as myopathy, rhabdomyolysis, and myalgia.[13] Recently, statin use has been associated with peripheral neuropathy but the mechanism is not well understood.[14]

Two previous analyses of overlapping surveillance databases have suggested that statin use was associated with developing an ALS-like syndrome.[15,16] Additionally, Dupuis et al and Yoshii et al indicated that increased serum lipid level was a neuroprotective factor in ALS patients. Physicians were recommended to exercise caution when prescribing statins in patients with ALS.[17,18]

Conversely, Iwamoto et al reported that statins exerted neuroprotective effects on degenerating motor neurons and denervated muscles in mouse animal models.[19] Moreover, statins were shown to reduce the risk of neurodegenerative

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[a] Department of Rehabilitation Medicine, College of Medicine, Yeungnam University, Daegu, Republic of Korea, [b] Department of Medical Statistics, College of Medicine, Daegu Catholic University, Daegu, Republic of Korea, [c] Department of Neurology, School of Medicine, Kyungpook National University, Kyungpook National University Chilgok Hospital, Daegu, Republic of Korea, [d] Department of Physical Medicine and Rehabilitation, Ulsan University Hospital, University of Ulsan College of Medicine, Ulsan, Republic of Korea.

[*] Correspondence: Donghwi Park, Department of Physical Medicine and Rehabilitation, Ulsan University Hospital, University of Ulsan College of Medicine, 877, Bangeojinsunghwndo-ro, Dong-gu, Ulsan 44033, Republic of Korea (e-mail: bdome@hanmail.net).

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diseases, such as Parkinson and Alzheimer diseases.[20,21] However, the association between statin use and ALS incidence has not been clearly elucidated. To further explore this issue, we performed a meta-analysis of all available clinical studies on the association between statin use and ALS incidence.

2. Methods

2.1. Search strategy

This meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines. Institutional Review Board approval was waived due to the use of retrospective and de-identified data. We systematically searched the relevant literature in PubMed, Embase, Cochrane Library, and SCOPUS for studies published up to January 31, 2020. The following keywords were used in the database search: (*amyotrophic lateral sclerosis* or *ALS* or *motor neuron disease* or *MND*) and (*3-hydroxy-methyl glutaryl coenzyme A reductase* or *HMG-CoA reductase* or *statin* or *lipid-lowering medication* or *cholesterol-lowering drug*).[22] The filters were used to select studies with human participants. We only included articles published in English.

2.2. Study selection

Population-based case-control studies on ALS incidence in statin- and non-statin-treated populations were considered suitable for inclusion. The following studies were excluded: studies with populations that did not include patients with ALS; those in which statins were not part of the intervention; those in which the measure of incidence rate in case-control trials was unreported; and trials in which the studied populations possessed multiple diseases aside from ALS.[22] We excluded review articles, letters, and case reports. We also excluded 15 studies that reported no or insufficient data/results. A previous study, which was included in the previous meta-analysis, was excluded because it was a poster presentation.[23]

2.3. Data extraction

All data were independently extracted by 2 researchers (DP and MCC) using a standardized data collection form. Discrepancies were resolved through discussions with another investigator (SGK) and by referring to the original articles. In the 3 case-control and cohort studies, the data of a total of 242,320 participants (11,747 patients with ALS and 230,573 controls) were extracted. Additionally, the research characteristics, study design, number of study and control groups, number of included participants, follow-up period, diagnostic criteria, number of participants using statins in the ALS and control groups, the incidence rate of statin use between the ALS and control groups, and sex ratio in the study group were investigated.

2.4. Quality assessment

Quality assessment was performed using the Newcastle–Ottawa Scale (NOS).[24] This scale criticizes case-control and cohort studies according to 3 domains, namely selection of study groups (4 items), comparability of study groups (2 items), and exposure and outcome measurement (3 items). Studies with an NOS score of at least 6 were considered high-quality studies.[24]

2.5. Statistical analysis

RevMan 5.3 software (http://tech.cochrane.org/revman) and R statistical software program were used for statistical analysis of the pooled data. In each analysis, a heterogeneity test was performed using I^2 statistics, which measures the extent of inconsistency among the results.[25] P values $<.05$ were considered significantly heterogenous, and the random-effects model was used for the data analysis. In contrast, when P values were $\geq.05$, pooled data were considered homogenous, and the fixed effects model was applied. We analyzed the odds ratio (OR) for association measures in case-control studies. The fixed and random effects models were selected according to the different heterogeneity levels of the ratio outcomes. Further, the 95% confidence interval (CI) was used in the analysis. A P value $<.05$ was considered statistically significant.

2.6. Data availability

Data availability depended on the agreement between the participating studies subject to their regulatory requirements and appropriate data-sharing arrangements.

3. Results

In the databases, 644 articles were obtained, and 51 duplicated articles were removed (Fig. 1). Eligibility screening was conducted by reviewing the title and abstract, and 20 articles were included for full-text reading. After a detailed assessment, 16 articles were excluded: 15 studies reported insufficient results, and 1 study was a poster presentation. Four studies were included in our meta-analysis (Table 1). Therefore, a total of 4 studies (3 case-control studies[26–28] and 1 cohort study[16]) on the incidence of ALS in statin- and non-statin-treated individuals were included in determining the effect of statins on ALS incidence. The characteristics of the studies included in the analysis are also presented in Table 1.

3.1. Study characteristics

In the 4 studies,[16,26–28] 111,747 participants with ALS and 230,573 participants without ALS (controls) were recruited. In a study by Colman et al[16], 9 out of 19 ALS patients used statins. Among 118,245 non-ALS patients, 64,593 patients used statins (OR, 0.75; 95% CI 0.30–1.84). In a study by Sorensen et al[26], 79 out of 556 ALS patients used statins. Among 5560 non-ALS patients, 806 used statins (OR, 0.98; 95% CI 0.76–1.25). In a study by Seelen et al[27], 79 out of 722 ALS patients used statins. Among 2268 non-ALS patients, 476 used statins (OR, 0.46; 95% CI 0.36–0.60). In a study by Freedman et al[28], 4870 out of 10,450 ALS patients used statins. Among 10,4500 non-ALS patients, 50,738 used statins (OR, 0.92; 95% CI 0.89–0.96). However, data on the classes and doses of statins administered to the ALS and control groups were not available.

3.2. Risk of bias

The 4 studies were assessed using NOS. All studies garnered 8 stars and were considered high-quality studies (selection of subjects, 4 stars; comparability of groups, 2 stars; and assessment of outcome, 2 stars).

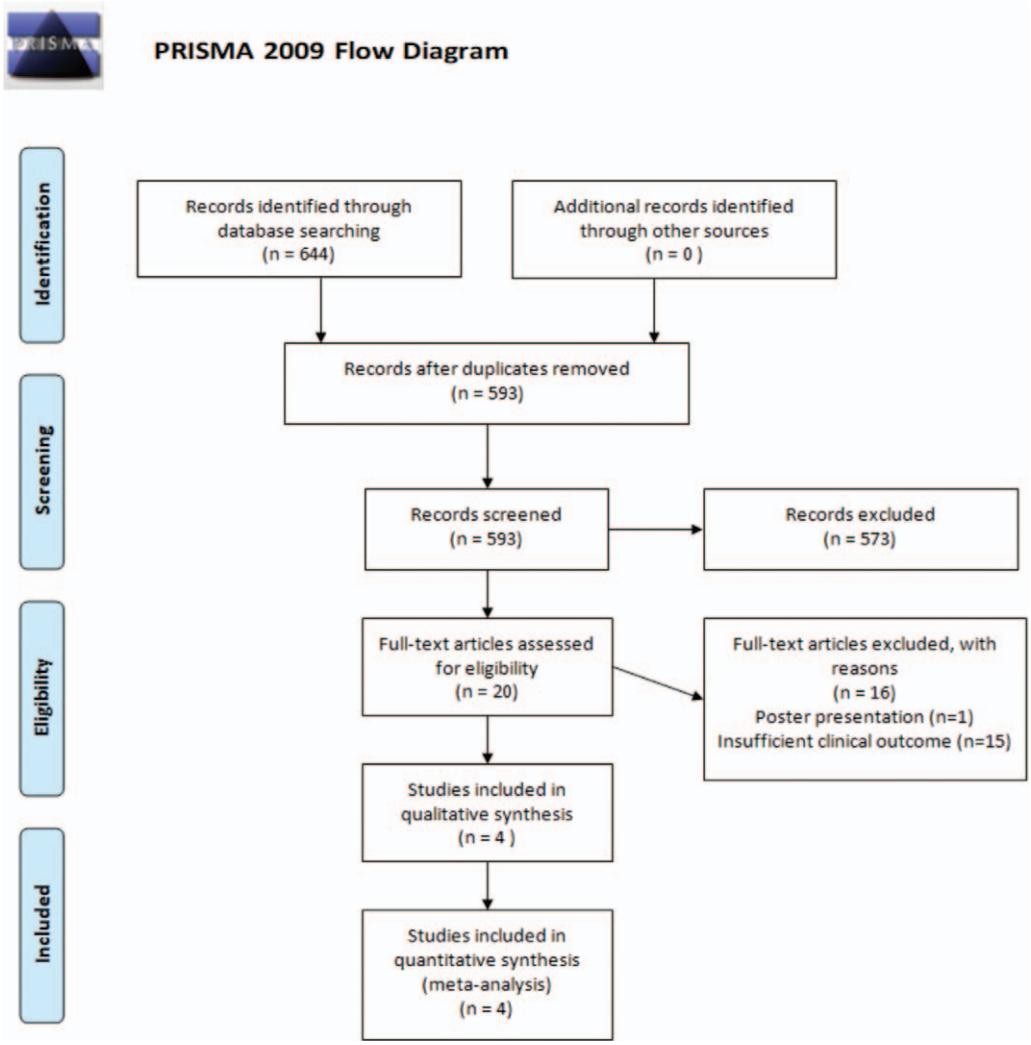

Figure 1. Flowchart showing the search results of the meta-analysis.

3.3. Meta-analysis results

Since the *P* values for heterogeneity of all our analyses were <.05, a random-effects model was adopted. The OR of the 4 studies is presented in Figure 2. There was no statistical difference in ALS incidence between the statin and non-statin groups (OR, 0.75 [95% CI 0.53–1.08]).

3.4. Publication bias

Based on a few distinct methods, 2 authors (DP and MCC) individually assessed the risk of bias.[29,30] The risk of publication bias was determined using a funnel plot and Egger test.[31] Additionally, a fail-safe N was calculated to determine the number of studies with a null result needed to increase the *P* value

Table 1

Characteristics of studies included in the systematic review.

Trial, year	Location	Number of participants (cases/controls)	Period of recruitment	Incidence rate (%)		Age (mean [SD])	% Men
				Cases	Controls		
Sorensen, 2010	Denmark	556/5560	1999–2008	14.2 (79/556)	14.5 (806/5560)	66.2 (12.0)	54
Colman, 2008	United States	19/118245	1991–2006	47.3 (9/19)	54.6 (64593/118245)	NM	NM
Freedman, 2018	United States	10450/104500	2008–2014	46.6 (4870/10450)	48.5 (50738/104500)	NM	48.76
Seelen, 2014	Netherlands	722/2268	2006–2011	10.9 (79/722)	21.0 (476/2268)	63.16 (2.61)	58.50

Case-control trials assessing statin use and incidence of ALS.
ALS = amyotrophic lateral sclerosis, NM = not mentioned.

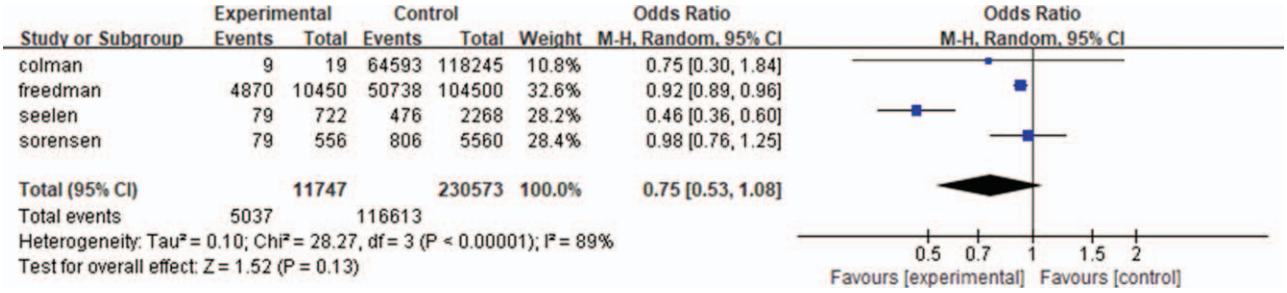

Figure 2. Forest plot of statin use in patients with amyotrophic lateral sclerosis vs controls. Note: Three case-control studies and 1 cohort study were included. The odds ratio was 0.75 (95% confidence interval, 0.53–1.08), indicating no statistical difference in ALS incidence between the statin and non-statin groups. ALS = amyotrophic lateral sclerosis.

for an overall effect size >.05. A funnel plot was constructed to investigate the risk of publication bias, as shown in Figure 3. Performing a visual inspection suggested some funnel plot asymmetry. However, Egger test was not significant ($z = -0.880$, $P = .471$), indicating no publication bias risk. Moreover, the fail-safe Ns were 35, which were larger than the recommended cutoff (ie, fail-safe N|>|5n|+|10, where n = the number of published studies).[32]

4. Discussion

Currently, ALS is incurable, but treatments, such as edaravone and riluzole, have been reported to delay ALS progression.[33–36] Therefore, identifying risk factors for ALS is essential in preventing and treating this disease. Based on Cohen study [37], this effect size can suggest that statins were unlikely to be associated with ALS incidence (OR, 0.75 [95% CI 0.53–1.08]). ALS incidence tended to decrease slightly in the statin group, but there was no statistical significance.

To date, there have been several debates regarding statin use and the development of ALS. It is important to remain cautious of reporting bias when consulting debates that reported ALS development in patients taking statins. The typical age of onset of ALS was similar to the modal age of statin users. Thus, it is possible that some ALS patients were recently prescribed statins. In the previous case series on ALS, statin treatment was initiated within 1 year of the onset of symptoms in >50% of ALS patients.[16] These biases may have influenced previous findings that associated statin use with ALS.

A previous in vitro study reported that statins reduced inflammatory cytokine production by microglia and astrocytes, a process implicated in the pathogenesis of ALS.[38] The anti-inflammatory effect of statins in the central nervous system was the basis for an ongoing study testing the hypothesis that atorvastatin favorably affects the clinical course of ALS patients.[16] However, testing this hypothesis requires large-scale prospective randomized control studies.

There were a few limitations. First, only 4 studies were included in this meta-analysis. Additionally, most patient data were included in 2 studies (Colman et al[16] and Freedman et al[28]). Therefore, more large-scale studies are necessary. Second, age was not analyzed as a confounding factor. However, only 2 of the 4 studies in this meta-analysis had information on the patients' ages. Therefore, further studies, analyzing confounding factors, such as age, are necessary.

In conclusion, no definite association was found between statin use and the development of ALS. Considering the essential clinical advantages of statins in treating and preventing cardiovascular diseases, we recommend continuous statins when clinically indicated. Further large-scale prospective randomized control studies are necessary to draw definite conclusions.

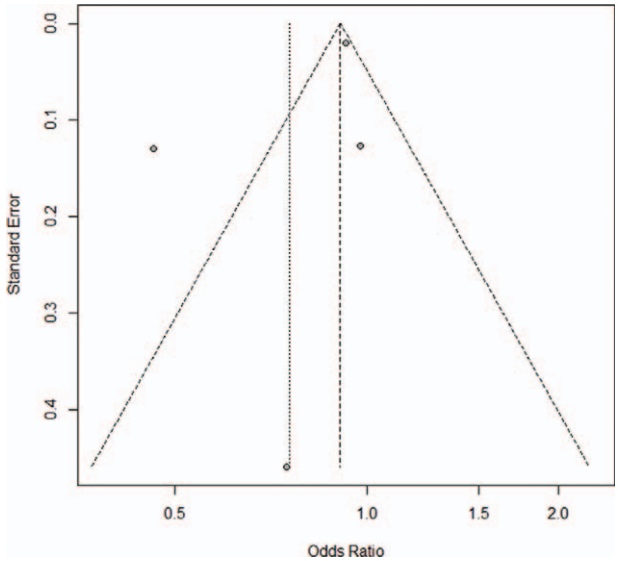

Figure 3. Graphic funnel plot of included studies.

Author contributions

Min Cheol Chang: study concept and design, acquisition of data, revision of the manuscript, and critical revision of the manuscript for intellectual content.
Sang Gyu Kwak: analysis of data.
Jin-Sung Park: study concept and design.
Donghwi Park: study concept and design, analysis of data, and critical revision of the manuscript for intellectual content.
Data curation: Sang Gyu Kwak.
Formal analysis: Sang Gyu Kwak.
Supervision: Jin-Sung Park.
Writing – original draft: Min Cheol Chang, Donghwi Park.
Writing – review & editing: Min Cheol Chang, Donghwi Park.

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