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A Population-Based Study on the Association between Statin Use and Sudden Sensorineural Hearing Loss

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Abstract

Objectives. No study has reported the relationship between statin use and sudden sensorineural hearing loss (SSNHL). In this study, we examined the association between statin use and SSNHL using a population-based dataset.

Study Design. A case-control study.

Setting. Taiwan.

Subjects and Methods. The study sample was selected from the Taiwan Longitudinal Health Insurance Database. We identified 1263 subjects aged ≥40 years with SSNHL and 6315 sex-, age-, hypertension-, and coronary heart disease–matched controls. We used conditional logistic regression to compute the odds ratio (OR) for having been a previous statin user between cases and controls. Furthermore, we performed conditional logistic regression to explore the relationship of regular and irregular statin users with SSNHL.

Results. There was a significant difference in the prevalence of statin use between cases and controls (27.2% vs 21.3%, respectively; $P < .001$). The OR of statin use before the index date for cases was 1.36 (95% confidence interval [CI], 1.18-1.57) compared to controls after taking gender, age group, hypertension, coronary heart disease, diabetes, renal disease, and hyperlipidemia into consideration. Furthermore, compared to controls, the adjusted ORs of regular and irregular statin use for cases were 1.30 (95% CI, 1.11-1.52) and 1.49 (95% CI, 1.11-1.93), respectively, compared to controls.

Conclusion. This study found that SSNHL was significantly associated with previous statin use.

Keywords

sudden hearing loss, hearing loss, statin

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Sudden sensorineural hearing loss (SSNHL) is most commonly defined as sensorineural hearing loss of ≥30 dB over at least 3 contiguous audiometric frequencies occurring within a 72-hour period.[1] The incidence of SSNHL is 5 to 20 per 100,000 person-years, but some consider this estimate to be lower than the actual number of cases.[2] It can affect anyone, but for unknown reasons, it most often occurs in people aged 30 to 60 years.[1] There are more than 100 possible causes of SSNHL, but it is rare for a specific cause to be identified. Only 10% to 15% of patients with SSNHL know what caused their loss.[3] Oral steroids are considered the gold standard for treating SSNHL. In some cases, intratympanic steroids are considered with or without systemic steroids according to the AAO-HNSF clinical practice guideline.[4] A report by Shemirani et al[5] found that about 98% of otolaryngologists in the United States used oral steroids to treat idiopathic SSNHL. Steroids improve idiopathic SSNHL by reducing inflammation and edema in the inner ear.[6]

Statins competitively inhibit 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR). This enzyme catalyzes the rate-limiting step in cholesterol biosynthesis, with a resultant reduction in cholesterol concentrations in plasma and an increase in the expression of low-density lipoprotein

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(LDL) receptors, which clears LDL and LDL precursors from circulation.[7] In addition, statins inhibit the synthesis of isoprenoids along the mevalonate pathway, which reduces the extent of isoprenylation of a variety of intracellular proteins (ie, Rho and Ras) that play central roles in both cell growth and signal transduction pathways, such as low molecular weight GTP-binding proteins that are strictly involved in regulating mitogenic pathways and many other cardiovascular functions. This means that statin use can directly and indirectly modulate functional responses of vessel walls.[8] Therefore, statin can be highly beneficial in vascular beds where any systemic hemodynamic response could negatively affect local responses, such as cochlear circulation. Statins have been proposed to be potential therapeutic agents in the treatment of SSNHL.[9] However, one case study reported irreversible hearing loss in a 32-year-old man 18 months after beginning atorvastatin therapy.[10] In addition, Olzowy et al's[11] study found that atorvastatin had no effect on the development of the hearing threshold, and it did not retard the progression of presbycusis. Therefore, the relationship between statin use and SSNHL is still unclear. According to our clinical experience, these incidences are intriguing since we have encountered many patients with SSNHL who are also statin users. In this study, we examined the association between statin use and SSNHL using a population-based dataset.

Methods

Database

The study sample for this case-control study was selected from the Longitudinal Health Insurance Database (LHID2000), which is part of the Taiwan National Health Insurance (NHI) program and is available to scientists in Taiwan for research purposes. Taiwan initiated this single-payer NHI program in 1995. Each year, the Taiwan National Health Research Institute collects data from the NHI program and sorts it into data files, including registration files and original claims data for reimbursement. The LHID2000 mainly includes the medical claims of 1,000,000 enrollees who were systematically and randomly selected from all enrollees. Hundreds of researchers have used the data from the NHI program to publish studies in international peer-reviewed journals. The LHID2000 gives researchers in Taiwan an excellent opportunity to trace all medical utilizations of these 1,000,000 enrollees starting from initiation of the NHI program in 1995. This study was exempt from full review by the institutional review board of Taipei Medical University because the LHID2000 consists of de-identified secondary data released to the public for research purposes.

Selection of Cases and Controls

For cases, we identified 1263 subjects aged $\geq$40 years with a first-time principal diagnosis of sudden hearing loss (International Classification of Diseases [ICD-9-CM] code 388.2) at an ambulatory care visit (including to outpatient departments of hospitals and clinics) from January 1, 2008, to December 31, 2011. We also ensured that all selected cases had at least 2 diagnoses of SSNHL coded in their ambulatory care claims with at least 1 of those diagnoses being made by a certified otolaryngologist to increase the validity of the SSNHL diagnosis. We assigned the first ambulatory care visit for the treatment of SSNHL as the index date for cases. We also ensured that no selected cases had a history of other types of hearing loss (ICD-9-CM codes 389 or 389.0-389.9).

To form our control group, we selected 5 controls for each case from the remaining patients of the LHID2000. We first excluded all subjects with a history of SSNHL or other types of hearing loss since the beginning of the NHI program in 1995. Thereafter, we randomly selected 6315 controls to match the cases in terms of gender, age group (40-49, 50-59, 60-69, 70-79, and $>$79 years), hypertension (ICD-9-CM codes 401-405), coronary heart disease (CHD) (ICD-9-CM codes 410-414 or 429.2), and index year. For cases, the year of the index date was the year in which the patients received their first diagnosis of SSNHL; for controls, the year of the index date was simply a matched year in which subjects had a medical utilization. We further assigned the first instance of medical care occurring in the index year as the index date for controls.

Exposure Assessment

This study attempted to investigate the association between SSNHL and prior statin use. The LHID2000 also provides data on ambulatory care medical orders, and this allowed us to determine which subjects had ever filled prescriptions for statins before the index date. In this study, we selected simvastatin, lovastatin, atorvastatin, fluvastatin, pravastatin, and rosuvastatin as the major drugs of interest. In addition, to explore the association between SSNHL and prior statin use, we further defined subjects who had received continuous statin prescriptions for $\geq$60 days within 6 months before the index date as regular statin users. All other subjects who had been prescribed statin within 6 months before the index date were defined as irregular statin users. All prior statin users included regular and irregular statin users.

Statistical Analysis

This study used the SAS System for Windows (version 8.2, SAS Institute, Cary, North Carolina) to carry out all statistical analyses. χ^2 tests were conducted to compare statistical differences in monthly income (New Taiwan [NT] $ 0-NT$15,840, NT$15,841-NT$25,000, and $\geq$NT$25,001; in 2010, the average exchange rate was US$1.00 $\approx$ NT$30), geographic location (Northern, Central, Eastern, and Southern Taiwan), and medical comorbidities (diabetes [ICD-9-CM code 250] and renal disease [ICD-9-CM codes 585 and 586]) between cases and controls. To calculate the odds ratio (OR) and 95% confidence interval (CI) for SSNHL between cases (any use of statins) versus controls, a conditional logistic regression model was utilized, controlling for gender, age group, hypertension, CHD, and index year. A second conditional logistic regression model

Table 1. Demographic Characteristics of Patients with Sudden Hearing Loss and Controls after Matching for Gender, Age Group, Hypertension, Coronary Heart Disease, and Index Year (N = 7578).

	Patients with Sudden Hearing Loss (n = 1263)	Controls (n = 6315)	
Variable	n (%)	n (%)	*P* Value
Diabetes	369 (29.2)	1511 (23.9)	<.001
Renal disease	75 (5.9)	223 (3.5)	<.001
Hyperlipidemia	445 (36.0)	1877 (29.7)	<.001
Monthly income[a]			.403
≤NT$15,840	453 (35.9)	2386 (37.8)	
NT$15,841-NT$25,000	488 (38.6)	2397 (38.0)	
≥NT$25,001	322 (25.5)	1532 (24.3)	
Geographic region			.015
Northern	574 (45.5)	3062 (48.5)	
Central	306 (24.2)	1566 (24.8)	
Southern	359 (28.4)	1535 (24.3)	
Eastern	24 (1.9)	152 (2.4)	

[a]In 2012, the average exchange rate was US$1.00 ≈ New Taiwan (NT) $30.

Table 2. Crude Relationship between SSNHL and Statins, Stratified according to Regular or Irregular Use.

	Patients with Sudden Hearing Loss	Controls		
Variable	n (%)	n (%)	Crude OR (95% CI)[a]	*P* Value
Presence of prior statin users (including regular and irregular statin users)				<.001
Yes	344 (27.2)	1344 (21.3)	1.39 (1.21-1.59)	
No	919 (72.8)	4971 (78.7)		
Presence of prior regular use of statin				<.001
Yes	274 (21.7)	1095 (17.4)	1.35 (1.17-1.57)	
No	919 (78.3)	4971 (82.6)		
Presence of prior irregular use of statin				<.001
Yes	70 (5.5)	249 (3.9)	1.52 (1.16-2.00)	
No	919 (94.5)	4971 (96.1)		

Abbreviations: CI, confidence interval; OR, odds ratio; SSNHL, sudden sensorineural hearing loss.
[a]For sudden hearing loss. The OR was calculated by conditional logistic regression, which was conditioned on sex, age group, hypertension, coronary heart disease, and index year.

controlling for similar variables was performed that examined the relationship of regular and irregular statin users (ie, 1 independent variable with 3 levels of regular users, irregular users, and nonstatin users) and the odds of SSNHL. The conventional $P \leq .05$ was used to assess statistical significance.

Results

Of the 7578 people in the study sample including 1263 cases and 6315 controls, the mean age was 60.3 ± 11.6 years; the mean age was 60.1 years for cases and 60.3 years for controls ($P = .669$). **Table 1** shows that after matching for gender, age group, hypertension, CHD, and index year, there were no significant differences between cases and controls in terms of monthly income. However, cases had a higher prevalence of medical comorbidities including diabetes, hyperlipidemia, and renal disease than controls.

Table 2 shows the distribution of prior statin users between cases and controls. Of the 7578-person study sample, 1688 (22.3%) were statin users prior to the index date. A χ^2 test revealed a significant difference in the prevalence of statin users between cases and controls (27.2% vs 21.3%, respectively; $P < .001$). The conditional logistic regression analysis (conditioned on gender, age group, hypertension, CHD, and index year) further suggested that the OR for prior statin users among cases was 1.39 (95% CI, 1.21-1.59; $P < .001$) compared to controls. Furthermore, **Table 2** presents the crude relationship between SSNHL and statins, stratified according to regular or irregular use. It consistently indicates that SSNHL was statistically and significantly associated with

Table 3. Adjusted OR for SSNHL among the Sample Subjects: Prior Statin Users versus Controls.

Variables	SSNHL Occurrence, Adjusted OR (95% CI)[a]	*P* Value
Prior statin users	1.36 (1.18-1.57)	<.001
Diabetes	1.18 (1.02-1.36)	.024
Hyperlipidemia	1.13 (0.96-1.34)	.152
Renal disease	1.49 (1.13-1.97)	.005
Geographic region		
Northern	1.00	
Central	1.07 (0.92-1.24)	.405
Southern	1.24 (1.07-1.44)	.004
Eastern	0.79 (0.51-1.24)	.319

Abbreviations: CI, confidence interval; OR, odds ratio; SSNHL, sudden sensorineural hearing loss.
[a]The adjusted OR was calculated by conditional logistic regression, which was conditioned on sex, age group, hypertension, coronary heart disease, and index year.

Table 4. Adjusted OR for SSNHL among the Sample Subjects: Prior Regular Statin Users versus Nonstatin Users and Prior Irregular Statin Users versus Nonstatin Users.

Variables	SSNHL Occurrence, Adjusted OR (95% CI)[a]	*P* Value
Group		
Prior regular statin users	1.30 (1.11-1.52)	<.001
Prior irregular statin users	1.49 (1.11-1.93)	<.001
Nonstatin users	1.00	
Diabetes	1.19 (1.05-1.37)	.015
Hyperlipidemia	1.14 (0.97-1.33)	.134
Renal disease	1.48 (1.14-1.97)	.005
Geographic region		
Northern	1.00	
Central	1.07 (0.92-1.24)	.414
Southern	1.24 (1.07-1.44)	.004
Eastern	0.79 (0.51-1.24)	.296

Abbreviations: CI, confidence interval; OR, odds ratio; SSNHL, sudden sensorineural hearing loss.
[a]The adjusted OR was calculated by conditional logistic regression, which was conditioned on sex, age group, hypertension, coronary heart disease, and index year.

previous statin use, regardless of whether that use was regular or irregular. The crude ORs of regular and irregular statin use for cases were 1.35 (95% CI, 1.17-1.57; $P < .001$) and 1.52 (95% CI, 1.16-2.00; $P < .001$), respectively, compared to controls.

Details of the adjusted OR for SSNHL are provided in **Table 3**. The conditional logistic regression analysis (conditioned on gender, age group, hypertension, CHD, and index year) shows that compared to controls, the OR of prior statin use for cases was 1.36 (95% CI, 1.18-1.57) after adjusting for geographic region, diabetes, hyperlipidemia, and renal disease. In addition, **Table 4** shows that the adjusted ORs of regular and irregular statin use for cases were 1.30 (95% CI, 1.11-1.52) and 1.49 (95% CI, 1.11-1.93), respectively, compared to controls.

Table 5 shows the comparison between statin users and nonstatin users among patients diagnosed with hyperlipidemia. As exposure (statin use) is dependent on a diagnosis of hyperlipidemia, a comparison between statin users and nonstatin users among patients diagnosed with hyperlipidemia is necessary to avoid bias resulting from this. If more cases had hyperlipidemia, then more cases would be exposed to statins. While there was no difference in statin use between cases and controls who had hyperlipidemia, there was a significant difference in the prevalence of statin use between cases and controls (27.2% vs 21.3%, respectively; $P < .001$). The adjusted OR of statin use before the index date for cases was 1.36 (95% CI, 1.18-1.57) compared to controls. However, we observed no significant difference in the OR of nonstatin users among subjects with hyperlipidemia between cases and controls (OR, 1.05; 95% CI, 0.84-1.31).

Discussion

According to our knowledge, this is the first study to report an association of statin use with SSNHL. We found that SSNHL was significantly associated with previous statin use, and the adjusted OR of statin use before the index date of an SSNHL diagnosis for cases was 1.36 (95% CI, 1.18-1.57) compared to controls.

Although there are more than 100 possible causes of SSNHL, from a meta-analysis of 23 studies of SSNHL, the most identifiable suspected causes included infectious diseases, primary otological diseases, autoimmunological diseases, inner ear trauma, vascular diseases, metabolic diseases, neurological disorders, neoplastic diseases, and drug-induced ototoxicity.[12] Among these etiologies, vascular accidents were regarded as playing a big part with a vascular compromise of the cochlea caused by thrombosis, an embolus, reduced blood flow, or vasospasm in the development of SSNHL. This pathogenesis is supported by the findings that increased risks of cardiovascular and cerebrovascular events have been associated with SSNHL.[13,14] In our study, we also noted that renal disease seems to be related to SSNHL. Although currently there are no reports suggesting that renal diseases might contribute to an increased risk of developing SSNHL, some researchers have reported that the incidence of sensorineural hearing loss among patients with chronic renal failure is considerably higher than in the general population.[15]

Hyperlipidemia has already been recognized as a major risk factor for stroke, and statins have been shown to decrease lipids and exert a pleiotropic effect on intracranial vasculature and inflammatory modulators, leading to neuroprotection.[16] Chang et al[17] reported that individuals with hypertriglyceridemia are at a greater risk of noise-induced hearing loss, which supports the possible relationship between hyperlipidemia and hearing problems. If this rationale is true, we expect that the incidence for the development

Table 5. Prevalence, Crude OR, and 95% CI for Hyperlipidemia among Sample Subjects.

	Patients with Sudden Hearing Loss (n = 1263)	Controls (n = 6315)	
Variable	n (%)	n (%)	Adjusted OR (95% CI)[a]
Presence of prior hyperlipidemia			
Yes	455 (36.0)	1877 (29.7)	1.24[b] (1.08-1.45)
No	781 (64.0)	4438 (71.3)	1.00
Presence of prior hyperlipidemia and statin user			
Yes	344 (27.2)	1344 (21.3)	1.36[c] (1.18-1.57)
No	919 (72.8)	4971 (78.7)	1.00
Presence of prior hyperlipidemia and nonstatin user			
Yes	111 (8.8)	533 (8.4)	1.05 (0.84-1.31)
No	1152 (91.2)	5782 (91.6)	1.00

Abbreviations: CI, confidence interval; OR, odds ratio.
[a]For sudden hearing loss. The OR was calculated by conditional logistic regression, which was conditioned on sex, age group, hypertension, coronary heart disease, and index year; it was also adjusted for patient's urbanization level, diabetes, and renal disease.
[b]$P < .001$.
[c]$P < .01$.

of SSNHL would be lowered in patients with hyperlipidemia if they were under regular statin use. However, as shown in our results, statins actually seem to be associated adversely to the development of SSNHL, and more interestingly, the factor of hyperlipidemia seems to have no significant role in contributing to the development of SSNHL. These results are compatible with the findings that both hyperlipidemia and atherogenic risk factors are not of major pathological importance in sudden hearing loss, as reported by Ullrich et al.[18]

We proposed 3 possible explanations for the association detected in this study. First, statins may induce apoptosis and neuronal cell death. Park et al[19] found that simvastatin caused neurodegenerative morphological changes and cell death in cultured cochlear neuronal cells. Statins inhibit the conversion of 3-hydroxy-3-methylglutaryl-coenzyme A to mevalonate, a precursor of LDL cholesterol. Mevalonate is also a precursor of coenzyme Q10 (CoQ10), a powerful antioxidant and membrane stabilizer; therefore, statins reduce mevalonate pathway products and cause apoptosis in cochlear neuronal cells. In addition, Salami et al[20] demonstrated improvements in mean air and bone conduction thresholds at 500, 1000, 2000, 4000, and 8000 Hz in patients with age-related sensorineural hearing loss receiving CoQ10. CoQ10 may decrease the number of apoptotic cells, prevent mitochondrial depolarization, and stabilize mitochondrial membranes. In addition, mevalonate gives rise to isoprenoids, such as farnesyl and geranyl groups, which are required for various proteins to attach to membranes. Schulz et al[21] reported that in cultured neurons, statins cause neurite loss by interfering with geranylgeranyl pyrophosphate synthesis.

Second, statins have immunomodulatory capabilities. Inflammation plays a causative role in human atherosclerotic development. Statins have anti-inflammatory effects such as decreasing plasma levels of the acute-phase inflammatory marker C-reactive protein.[22] However, the general view of statins as being anti-inflammatory was contradicted by a report that showed that simvastatin stimulated interleukin-1β secretion by macrophages.[23] Therefore, statin use may induce chronic inflammation in cochlear neurons.

Finally, statins can trigger autoimmunity. Mammen et al[24] described a novel autoantibody that recognizes approximately 200- and 100-kDa proteins associated with autoimmune myopathy and statin use. HMGCR was identified as the approximately 100-kDa autoantigen. In muscle biopsy tissues from anti-HMGCR–positive patients, HMGCR expression was upregulated in cells expressing neural cell adhesion molecules. Among 45 anti-HMGCR–positive patients, 30 (66.7%) had previously taken statins. In addition, 2 reports[25,26] showed that statins induce systemic immune reactions, including dermatomyositis, polymyalgia rheumatica, and serum antineutrophil cytoplasmic antibody–associated systemic vasculitis. Their symptoms all improved after being treated with steroid and/or immunosuppressive therapy, and statins were discontinued.

This study has several noteworthy strengths. First, the large database, which contained information on approximately 1,000,000 people, is likely representative of the Taiwanese population and offered a good opportunity to explore the association between statin use and SSNHL. Second, we ensured that all selected cases had at least 2 diagnoses of SSNHL coded in their ambulatory care claims with at least 1 of those diagnoses being made by a certified otolaryngologist to increase the accuracy of the diagnosis. Third, we took potential risk factors for SSNHL into consideration in the regression models. These included age, gender, monthly income, geographic region, urbanization level, diabetes, hypertension, CHD, and renal disease. Finally, we evaluated the effect of

adherence to statin use. Our results consistently indicated that SSNHL was statistically and significantly associated with previous statin use, regardless of whether it was regular or irregular use.

This study does have several limitations that merit emphasis. First, because we identified patients with SSNHL receiving statins before the index date from the LHID2000, the data did not allow us to know the statin concentration in patients' plasma or to allow for differences in the severity of SSNHL. In addition, the LHID2000 did not contain data on the results of audiometric examinations. We could not evaluate the association between statin concentrations and the severity of SSNHL.

Second, the LHID2000 data provide no information on patients' body mass index, racial information, smoking habits, alcohol consumption, physical activity, or nonprescription medication use. Thus, we could not evaluate the impact of these factors on SSNHL. Third, although we analyzed compliance based on the prescription patterns of statin users, the true compliance of statin use could not be determined in the present dataset. It is believed that patients who had regular statin prescriptions may also have had better compliance or at least equal compliance for medications than patients who had irregular statin prescriptions.

Conclusion

This investigation detected a novel association between statin use and SSNHL after adjusting for comorbid medical disorders. The results consistently showed that SSNHL was significantly associated with previous statin use. It also consistently indicated that SSNHL was statistically and significantly associated with previous statin use, regardless of whether it was regular or irregular use. We suggest that clinicians be aware of the potential association between SSNHL and statin.

Author Contributions

Shiu-Dong Chung, managed the literature searches and wrote the draft; **Chao-Hung Chen**, managed the literature searches and wrote the draft; **Shih-Han Hung**, managed the literature searches and wrote the draft; **Herng-Ching Lin**, designed the study, performed analyses, and wrote the draft; **Li-Hsuan Wang**, designed the study, performed analyses, and wrote the draft.

Disclosures

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