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Original Article

The effect of statins on the occurrence of peptic ulcer

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ABSTRACT

Background: This study was to determine the association between the use of statins and the occurrence of peptic ulcer diseases (PUD).
Methods: Using the National Health Insurance Research Database to conduct a population-based cohort study. We identified 48,562 patients who were newly diagnosed with hyperlipidemia during the period of 1998 to 2011 and who were divided into two groups based on their use of statins. The non-statin cohort (without statin treatment, 24,139 patients) were 1:1 frequency matched with sex, age, year of diagnosis of hyperlipidemia and index-year to the statin cohort (24,423 patients). The relative risk of patients with and without statins treatment on the occurrence of PUD and concomitant use of nonsteroidal anti-inflammatory drugs (NSAIDs) and aspirin were analyzed using the univariable and multivariable Cox proportional hazards regression model.
Results: The incidence of PUD increased with age in both cohorts and female had a higher occurrence rate than male in both cohorts. Compared with the non-statin cohort, the statin cohort was associated with a significant lower risk of PUD for all age group. The concomitant use of aspirin and/or NSAIDs had higher incidence of PUD than those without in both cohorts. Analyzing the cumulative defined daily dose (DDD) of statins indicated that high-dose groups (≧575 DDD) exhibited significantly decreased risk compared with non-statin users.
Conclusion: The results of the present study indicated that statins might be associated with the protection of peptic ulcer in a dose-respondent manner.

1. Introduction

Conglomerated and known as "statin," the hydroxymethylglutaryl coenzyme A (HMG-CoA) reductase inhibitors act to obstruct the synthesis of cholesterol in the liver [1,2]. Since mevalonic acid, the end product of said enzymatic reaction, is one of the foundational baseline substances to various isoprenoid metabolites [1,3], it could potentially lead to pleiotrophic effects of the aforementioned drugs. Also, growing evidence reveals that some other beneficial influence of these agents may have a significant effect on lowering plasma cholesterol levels [4–8]. As it appears, the positive effect surpasses the cholesterol-lowering result of statins through its protective effects on atherosclerotic plague stabilization and endothelial nitric oxide bioactivity [9,10]. Moreover, evidences point to statins affecting angiogenesis therapeutically; endothelial functions and angiogenesis are impaired by hypercholesterolemia, therefore, by reducing cholesterol and strengthening endothelial functions, statins could potentially ameliorate angiogenesis [11].

Peptic ulcer disease (PUD) is one of the most prevalent causes of gastrointestinal bleeding, which leads to hospitalization and/or mortalities. It is known that nonsteroidal anti-inflammatory drugs (NSAIDs) and *Helicobacter pylori* (*H. pylori*) are what cause peptic ulcers. While the cases of *H. pylori* have been decreasing over the last decade due to improved cleanliness and eradication therapy, the rate of PUD has not decreased dramatically in some countries. This leads us to conclude that the usage of NSAIDs and aspirin in the elderly, then, is the reason why PUD is still common [12–14].

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Despite that, an increase in statin related side effects such as gastrointestinal (GI) symptoms and GI hemorrhage has been reported [15–17]. Contrarily, much research on gastroprotective effects and the preservation of vascular integrity are on animal subjects, and it appears that statin use actually lowers the rate of peptic ulcer development when administering antithrombotic treatment and NSAID to a patient [15,26,27]. Consequently, it is unknown how relevant it is to human models. Though experiments suggest that an imbalance between gastrointestinal toxic agents and protective mechanisms provokes inflammation leading to peptic mucosa injury [24,25]. Our study was one of the leads to investigate the effects of statin on the occurrence of PUD.

Since many patients are treated with statins, and because epidemiological evidence for a connection between statin use and the risk of PUD is minimal, we committed ourselves to the study in Taiwan to deduce whether statin use can reduce PUD incidences, and to ascertain the dosage-dependent effects of statins.

2. Methods

2.1. Source of data

In March, 1995, the Taiwanese government commenced its state-run National Health Insurance (NHI) program, which provides universal health insurance coverage to 99% of Taiwan's entire population and has contracted with 97% of the hospitals. For research purpose, the National Health Research Institute (NHRI) compiled all medical claims in NHI program and released the database annually to the public. The National Health Insurance Research Database (NHIRD) contains medical information including inpatient and outpatient care facilities, drug prescriptions, insurant's sex and the date of birth, date of visit or hospitalization, and diagnoses coded in the ICD-9-CM format (International Classification of Disease, 9th Revision, Clinical Modification).

The NHRI established several randomly selected claim databases representative of the whole population. This cohort study used the randomly selected insurance claim data of one million insurants. Sets of information available for the database cover all medical services received by each enrollee from 1996 to 2011.

The NHIRD encrypts the patients' personal information for privacy protection and provides researchers with anonymous identification numbers associated with the relevant claim information, which includes the patient's sex, date of birth, registry of medical services, and medication prescriptions. Patient's consent is not required for accessing the NHIRD. This study was approved by the Institutional Review Board of China Medical University in central Taiwan (CMU-REC-101-012).

2.2. Study population

Patients who were newly diagnosed with hyperlipidemia (ICD-9-CM 272.xx) during the period of 1998 to 2011 and who were divided into two groups based on their use of statin. The statin cohort was defined as patients who underwent statin treatment for at least 90 days. The index date for each patent was the first treatment date of statin. Patients were excluded if they were younger than 20 years or with peptic ulcer diseases (ICD-9-CM 531.xx-535.xx) history before the index date. The non-statin cohort (without statin treatment) were 1:1 frequency matched with sex, age, year of diagnosis of hyperlipidemia and index-year to the statin cohort. The same exclusion criteria were also applied to non-statin cohort.

2.3. Outcome measurement, comorbidities and medications

We identified the first diagnosis of PUD from outpatient claims and/or hospitalization records from 1998 to 2011 as the study endpoint. All of the study subjects were followed from the index date to occurrence of endpoint, withdrawal from the database, the end of 2011, whichever date came first.

We also incorporated inpatient and outpatient diagnosis records to ascertain the baseline comorbidities, including hypertension (ICD-9-CM 401-405), stroke (ICD-9-CM 430-438), coronary artery disease (ICD-9-CM 410-414), and end stage renal disease (ESRD) (ICD-9-CM 585). In addition, concomitant uses of NSAIDs and/or aspirin were also analyzed.

2.4. Statistical analysis

The Chi-square test and Mann–Whitney *U* test were used for comparison between the statin and non-statin cohorts. The incidence density rate (IR) stratified by baseline characteristics was estimated in both cohorts. The relative risk of patients with and without statin treatment on the occurrence of PUD was analyzed using the univariable and multivariable Cox proportional hazards regression model. The multivariable models were adjusted for age, gender, and comorbidities of hypertension, stroke, coronary artery disease, end stage renal disease, and the use of aspirin and/or NSAID. The hazard ratio (HR) and 95% confidence interval (CI) were estimated by Cox model. The defined daily dose, recommended by the World Health Organization, is the assumed average maintenance dose per day per drug. The formula of cumulative defined daily dose (DDD) equals to the sums of defined daily dose of any statin in the duration of follow-up (years) of patients. We classified the cumulative DDD of statin use by the third quartile (<575, ≧575 DDD). Further, we estimated the dose–response of statin use on the risk of developing PUD based on cumulative DDD. A two-tailed p value of <0.05 was considered statistically significant. All analyses were performed with SAS statistical software (version 9.2 for Windows; SAS Institute, Inc., Cary, NC, USA).

3. Results

The baseline characteristics of the patients in the two cohorts are presented in Table 1. Of the statin cohort, 54% were men and 46% were women. The median age of the statin cohort and non-statin cohort were 55.2 (range = 20.2–99.9) and 55.6 (range = 20.0–99.0) years, respectively. No significant differences were noted in sex ($p = 0.30$) and age ($p = 0.36$). Statin cohort tended to have hypertension (65.4% vs. 38.2%, $p < 0.0001$), stroke (15.4% vs. 8.25%, $p < 0.0001$), coronary artery disease (26.0% vs. 13.0%, $p < 0.0001$), end stage renal disease (0.60% vs. 0.20%, $p < 0.0001$), and accompanying use of aspirin (36.9% vs. 23.0%, $p < 0.0001$) or NSAID (27.8% vs. 23.4%, $p < 0.0001$).

Table 1
Demographic characteristics of study subjects.

Variables	Statin				
	No N = 24, 139		Yes N = 24, 423		
	n	%	n	%	*p*-Value
Sex					0.30
Women	10,988	45.5	11,232	46.0	
Men	13,151	54.5	13,191	54.0	
Age, years					0.36
<45	4228	17.5	4228	17.3	
45–60	11,304	46.7	11,304	46.3	
60–75	7022	29.1	7226	29.6	
≥75	1585	6.57	1665	6.82	
Median (range)[a]	55.2	(20.2–99.9)	55.6	(20.0–99.0)	<0.0001
Medical history					
Hypertension	9226	38.2	15,965	65.4	<0.0001
Stroke	1991	8.25	3767	15.4	<0.0001
Coronary artery disease	3147	13.0	6354	26.0	<0.0001
End stage renal disease	49	0.20	147	0.60	<0.0001
Medicine status					
Aspirin	5450	23.0	9014	36.9	<0.0001
NSAID	5639	23.4	6779	27.8	<0.0001

Chi-square test.
[a] Mann–Whitney *U* test.