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Prevalence of Antilipemic Drug Use in Taiwan: Analysis of a Sampling Cohort within the National Health Insurance

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Background. Hyperlipidemia is a major risk factor of cardiovascular diseases. We investigated the utilization of antilipemic drugs at the outpatient sector within the National Health Insurance in Taiwan.

Methods. We obtained the first cohort (n = 50,000) dataset from the National Health Insurance Research Database and analyzed the outpatient claim files of the cohort in 2000. The antilipemic drugs were defined as the drug items belonging to the group C10 (serum lipid reducing agents) of the Anatomical Therapeutic Chemical classification system.

Results. Among the cohort with 46,614 eligible people, 760 patients had ever received antilipemic drugs (prevalence: 1.6%). The group 60 - 69 years of age had the greatest age-specific prevalence (7.2%), followed by the group over 70 years of age (6.0%). There were more male than female patients, but female patients outnumbered male patients before the age of 49 years. The antilipemic drugs had been prescribed 3,850 times to tally with 70,272 defined daily doses (DDDs). On an average age, a patient with antilipemic therapy received 5.1 (± 4.5) prescriptions of antilipemic drugs in one year and a prescription contained 18.3 (± 11.5) DDDs. We measured 4.1 DDDs per 1,000 inhabitants per day for all antilipemic drug use in 2000. The statins and fibrates predominated the antilipemic drug use. While gemfibrozil was most popular in respect of recipients and prescription items, simvastatin had the largest amount of use in unit of DDDs. Diabetes mellitus co-existed in 37.8% of the patients with antilipemic therapy and the standardized morbidity ratio (SMR) was 3.34. The other concomitant diseases included essential hypertension (rate: 48.8%, SMR: 2.40) and other heart disease (rate: 30.7%, SMR: 2.36).

Conclusions. Statins were the leading antilipemic drugs in Taiwan. The users of antilipemic drugs were more likely to have concomitant diabetes mellitus, hypertension and heart disease.

Although hyperlipidemia has been recognized as a major risk factor of cardiovascular diseases for decades, the benefit of lipid lowering was demonstrated late in 1994 by a large, randomized clinical trial.[1] Despite the clinical and economic significance associated with the antilipemic drugs, little was known about their utilization at the national level.[2,3] Among the member countries of the OECD (Organisation for Economic Co-operation and Development), only seven countries had data based on national pharmaceutical sales in 1998.[4] Since 1995, a National Health Insurance (NHI) program covering nearly all population has been implemented in Taiwan. With the availability of longitudinal medication data of individual patients within the NHI, we had the opportunity of studying not only the national consumption of antilipemic drugs, but also the prevalence of antilipemic drug use in this country.

In this current study, we surveyed the outpatient dataset of the NHI claims from a 50,000-person cohort in the calendar year 2000. Beside calculating the age- and

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sex-specific prevalence of antilipemic drug use and the consumption of single antilipemic drugs in Taiwan, we investigated the health conditions of the patients with antilipemic therapy by evaluating their concomitant diseases.

METHODS

Data sources

We obtained the first cohort dataset from the National Health Insurance Research Database (NHIRD; http://www.nhri.org.tw/nhird/). The cohort included 50,000 people randomly sampled from 23,753,407 people who had ever been insured under the NHI since 1995. The dataset included all insurance claims of these 50,000 people from 1996 to 2000. The purpose of the NHIRD and the structure of the NHI claim files had been described in details in our previous study.[5]

In the current study, we analyzed only the outpatient visit and order files of the cohort dataset in 2000 (R01_CD2000.DAT, and R01_OO2000.DAT). These files contained the claims of outpatient (including emergency) visits to clinics of Western medicine, dentistry and traditional Chinese medicine. Besides, we obtained a complete file of 21,146 approved drug items of Western medicine in Taiwan from the web site of the Bureau of National Health Insurance (BNHI; http://www.nhi.gov.tw/; accessed May 25th, 2001). The BNHI also offered a list of ATC (the Anatomical Therapeutic Chemical classification system) codes (4th level) for each drug item.[6] We added the 5th level coding for the relevant drug items and found their Defined Daily Dose (DDD), respectively.[6]

Study design

The antilipemic drugs defined in our study included all drug items belonging to the group C10 (serum lipid reducing agents) of the ATC classification system. The C10 group had only one 3rd-level subgroup C10A (cholesterol- and triglyceride reducers) with five 4th-level subgroups: C10AA (HMG CoA reductase inhibitors), C10AB (fibrates), C10AC (bile acid sequestrants), C10AD (nicotinic acid and derivatives), and C10AX (other cholesterol- and triglyceride reducers). Totally, 145 items of antilipemic drugs have been registered in the NHI drug file since 1995.

We first identified the order records with prescriptions of antilipemic drugs in the R01_OO2000.DAT and then found their associated visit records in the R01_CD2000.DAT. These records were extracted for further analyses. Because the bile acid sequestrants, especially cholestyramine, were not solely used in treating hyperlipidemia, we excluded their records without a related diagnosis, *i.e.* 272 as the first three digits of diagnostic codes in ICD-9-CM (International Classification of Diseases, 9th Revision, Clinical Modification). In a visit record, up to three diagnoses were coded according to the ICD-9-CM.

The use of antilipemic drugs among the cohort was stratified by the recipients' age/sex to determine the prevalence. We also stratified the prescriptions of antilipemic drugs by their chemical substances (ATC 5th level) and calculated the number of recipients, the number of prescribed items, and the total prescribed amount in unit of DDDs in each main ingredient. Besides, the numbers of DDDs per 1,000 inhabitants per day were calculated to reflect the proportion of the Taiwanese population treated daily with each kind of antilipemic drugs at the outpatient sector.

Hyperlipidemia usually co-existed with other diseases. To calculate the frequency of concomitant diseases in the patients receiving antilipemic drugs, we extracted the identification numbers of these patients and found out all of their visit records and diagnoses, not limited to the records with prescriptions of antilipemic drugs. Because more than 12,000 codes in the ICD-9-CM had difficulties in analysis, we adopted the grouping system developed by the National Center of Health Statistics of the United States for use with the data of the National Ambulatory Medical Care Survey (NAMCS) and the National Hospital Ambulatory Medical Care Survey (NHAMCS).[7] All of the original ICD-9-CM codes were reclassified into 22 main categories and 194 groups. Beside calculating the crude rates of major concomitant diseases in the patients receiving antilipemic drugs, we also computed the standardized morbidity ratios (SMR) (the indirect method of rate adjustment) to eliminate the confounding effect from age factor.[8]

Data processing and statistical analysis

The database software of Microsoft SQL Server 2000 was used for data linkage and calculation. For the age- and sex-specific prevalence, the denominators were those people who were still insured under the NHI in 2000. Among the 50,000 people of the sampling cohort, 46,614 were still insured in 2000. In calculating the numbers of DDDs per 1,000 inhabitants per day for each kind of antilipemic drugs, the total numbers of DDDs from the cohort were at first divided by 46,614 (people insured under the NHI at the end of 2000) and 366 (days in year 2000), and then multiplied by 1,000 (inhabitants). In calculating the SMR, the standard population was also the cohort. The prevalence rates and SMRs were displayed with 95% confidence intervals.[9]

RESULTS

Among the cohort with 46,614 people who were still insured under the NIH in 2000, only 41,333 (88.7%) people had the outpatient visit of Western medicine within the NHI during the whole year. Antilipemic drugs had been ever prescribed to 760 people (Table 1). The total prevalence of antilipemic drug use was 1.6% (95% CI: 1.5% to 1.7%). Nearly a half of the patients with antilipemic therapy were more than 60 years of age. The age-specific prevalence rate jumped after the age of 40 years and was the highest in the age group of 60-69 years (7.2%). The prevalence rate in the age group over 70 years was higher than that in the age group of 50 - 60 years (6.0% *vs.* 4.5%). The trend of age-specific prevalence rates was similar in both sexes. Although the total number of patients with antilipemic therapy was larger in male than that in female, the female patients still outnumbered the male patients before the age of 49 years.

In the outpatient claims of the cohort in 2000, there were 74 different drug items of antilipemic drugs with 18 main ingredients. Although atorvastatin (C10AA05) has been available within the NHI since November 2000, it did not appear in our cohort dataset. The antilipemic drugs had been prescribed totally 3,850 times with 70,272 DDDs (Table 2). On an average, a patient with antilipemic therapy received 5.1 (SD 4.5) prescriptions of antilipemic drugs in one year, where a prescription contained 18.3 (SD 11.5) DDDs. Besides, we measured 4.1 DDDs per 1,000 inhabitants per day for all antilipemic drug use in 2000. The statins and fibrates predominated the antilipemic drug use. While gemfibrozil was most popular in respect of recipients and prescription items, simvastatin had the largest amount of use in unit of DDDs.

In 2000, the cohort in our study had 657,038 visits where 901,977 diagnostic codes with 6,335 distinct diagnoses had been specified. The 760 patients with antilipemic therapy had 24,240 visits where 44,320 diagnostic codes with 1,752 distinct diagnoses had been specified. Table 3 lists the top 12 diagnosis groups that were most frequently observed in the patients with antilipemic therapy. In order to illustrate the SMRs, the frequencies of these diagnoses among the cohort were also displayed. Diabetes mellitus co-existed in 37.8% of the patients with antilipemic therapy and the SMR was 3.34 (95% CI: 2.61 to 4.17). The other significant concomitant diseases included other endocrine nutritional

Table 1. Age-sex distribution of the sampling cohort, and patients receiving the antilipemic therapy

Age (years)	Sampling cohort[a]			Patients with antilipemic therapy			Prevalence of antilipemic therapy (95% confidence intervals)		
	Total	Male	Female	Total	Male	Female	Total	Male	Female
0 - 9	6486 (13.91%)	3368	3118	6 (0.79%)	2	4	0.1% (0.0%, 0.2%)	0.1% (0.0%, 0.2%)	0.1% (0.0%, 0.3%)
10 - 19	7106 (15.24%)	3587	3518	3 (0.39%)	1	2	0.0% (0.0%, 0.1%)	0.0% (0.0%, 0.2%)	0.1% (0.0%, 0.2%)
20 - 29	8116 (17.41%)	4028	4088	13 (1.71%)	5	8	0.2% (0.1%, 0.3%)	0.1% (0.0%, 0.3%)	0.2% (0.1%, 0.4%)
30 - 39	8075 (17.32%)	4104	3971	48 (6.32%)	14	34	0.6% (0.4%, 0.8%)	0.3% (0.2%, 0.6%)	0.9% (0.6%, 1.2%)
40 - 49	7179 (15.40%)	3530	3649	137 (18.03%)	47	90	1.9% (1.6%, 2.2%)	1.3% (1.0%, 1.8%)	2.5% (2.0%, 3.0%)
50 - 59	3920 (8.41%)	1920	2000	175 (23.03%)	98	77	4.5% (3.8%, 5.1%)	5.1% (4.1%, 6.2%)	3.9% (3.0%, 4.8%)
60 - 69	3014 (6.47%)	1493	1521	216 (28.42%)	140	76	7.2% (6.2%, 8.1%)	9.4% (7.9%, 10.9%)	5.0% (3.9%, 6.3%)
> = 70	2718 (5.83%)	1468	1250	162 (21.32%)	104	58	6.0% (5.1%, 6.9%)	7.1% (5.8%, 8.4%)	4.6% (3.5%, 6.0%)
Total	46614 (100.00%)	23498	23115	760 (100.00%)	411	349	1.6% (1.5%, 1.7%)	1.7% (1.6%, 1.9%)	1.5% (1.4%, 1.7%)

[a] The status of sex was unknown in one insured.

Table 2. Distribution of antilipemic drug prescriptions by main ingredients

ATC[a] coding	Group/ingredient name	No of recipients	No of antilipemic drug items	Total DDDs[b] of antilipemic drugs	DDDs per 1,000 inhabitants per day
C10AA	**HMG CoA reductase inhibitors**	**422**	**1,934**	**40,552**	**2.4**
C10AA01	Simvastatin	170	753	19,115	1.1
C10AA02	Lovastatin	134	475	8,634	0.5
C10AA03	Pravastatin	70	348	4,963	0.3
C10AA04	Fluvastatin	88	358	7,840	0.5
C10AB	**Fibrates**	**395**	**1,700**	**24,850**	**1.5**
C10AB01	Clofibrate	12	49	247	0.0
C10AB02	Bezafibrate	80	347	5,123	0.3
C10AB03	Aluminium clofibrate	1	4	90	0.0
C10AB04	Gemfibrozil	260	1,017	14,648	0.9
C10AB05	Fenofibrate	33	90	2,285	0.1
C10AB06	Simfibrate	1	1	2	0.0
C10AB09	Etofibrate	39	192	2,455	0.1
C10AC	**Bile acid sequestrants**	**7**	**26**	**337**	**0.0**
C10AC01	Cholestyramine	4	20	189	0.0
C10AC03	Detaxtran	3	6	148	0.0
C10AD	**Nicotinic acid and derivatives**	**34**	**172**	**4,384**	**0.3**
C10AD01	Niceritrol	2	16	148	0.0
C10AD03	Nicofuranose	5	15	262	0.0
C10AD06	Acipimox	21	113	3,311	0.2
C10AD-	Nicomol	6	28	663	0.0
C10AX	**Other cholesterol and triglyceride reducers**	**6**	**18**	**148**	**0.0**
C10AX02	Probucol	6	18	148	0.0
Total		**760[c]**	**3,850**	**70,272**	**4.1**

[a] ATC = Anatomical Therapeutic Chemical classification system.
[b] DDD = defined daily dose.
[c] Among 760 patients, 153 patients had received more than one kind of antilipemic drugs during the year 2000.

and metabolic diseases immunity disorders (rate: 25.1%, SMR: 3.01), essential hypertension (rate: 48.8%, SMR: 2.40), and other heart disease (rate: 30.7%, SMR: 2.36).

DISCUSSION

The insurance claims data from the NHI in Taiwan are invaluable to the research of pharmacoepidemiology. The utilization of antilipemic drugs is one of the good examples because nearly all of these drugs have unique indication and the prescription of them has been under rigid restrictions based on the recognized guidelines, *e.g.* the second report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults.[10] Although the prevalence of antilipemic drug use might be significantly lower than the prevalence of hyperlipidemia among the population, the trend and other analyses would help to identify the key points of public health and medical interventions.

The Chinese in Taiwan are known to have low incidence of coronary artery disease and low prevalence of hyperlipidemia in international comparison.[11] But it remains unknown whether the prevalence of patients with antilipemic therapy in Taiwan is also low correspondingly. The international comparison of drug utilizations is usually more dynamic than that of disease epidemiol-

Table 3. Frequency of concomitant diseases in the patients with antilipemic therapy

Diagnosis grouping	Sampling cohort (n = 46,614)		Patients with antilipemic therapy (n = 760)		
	No. of patients with a diagnosis	Rate	No. of patients with a diagnosis	Rate	SMR[a] (95% CI[b])
Other acute respiratory infections	30,562	65.6%	526	69.2%	1.14 (0.95, 1.35)
Essential hypertension	3,011	6.5%	371	48.8%	2.40 (1.94, 2.92)
Other diseases of the digestive system	10,466	22.5%	362	47.6%	1.55 (1.25, 1.89)
Diseases of the teeth and supporting structures	15,949	34.2%	294	38.7%	1.23 (0.96, 1.53)
Diabetes mellitus	1,796	3.9%	287	37.8%	3.34 (2.61, 4.17)
Other heart disease	2,019	4.3%	233	30.7%	2.36 (1.80, 3.02)
Conjunctivitis	8,432	18.1%	218	28.7%	1.27 (0.95, 1.64)
Other symptoms/signs and ill-defined conditions	4,656	10.0%	202	26.6%	1.63 (1.21, 2.12)
Other dorsopathies	3,921	8.4%	196	25.8%	1.46 (1.08, 1.91)
Acute bronchitis and bronchiolitis	10,106	21.7%	193	25.4%	1.25 (0.92, 1.63)
Other endocrine nutritional and metabolic diseases immunity disorders	1,971	4.2%	191	25.1%	3.01 (2.21, 3.94)
Gastritis and duodenitis	5,174	11.1%	159	20.9%	1.39 (0.99, 1.87)

[a] SMR = standardized morbidity ratio. The age adjustment was preformed according to the age structure of the sampling cohort.
[b] CI = confidence intervals.

ogy. For example, the Finland and other Nordic countries had slightly lower prevalence of antilipemic drug users and fewer DDDs/1,000 inhabitants/day in early 1990s than Taiwan in 2000.[2,3] However, the antilipemic drug use in those countries increased 6- to 8-fold from 1994 to 2000, mostly due to statins.[4] Further study is needed to investigate whether the strict restrictions within the NHI in Taiwan, *e.g.* mandatory blood analysis in three-month intervals, discourage the antilipemic drug use and hinder the diffusion of newer innovations.

The focus of pharmacoepidemiology study of antilipemic drugs in the literature could be summarized into the following aspects: age-, sex-, disease-, physician-specific drug use, and outcome analysis.[12-21] Some of these investigations could be also repeated in Taiwan with the current NHIRD datasets, but the other could not be done because of the inherent limitations of the NHI claims data.

For example, hyperlipidemia, hypertension and hyperglycemia (so-called 3H) are known to have a clustering tendency. Using SMRs to compare the patients receiving antilipemic therapy with the sampling population in comorbidity, our study showed that those patients in Taiwan did have concomitant diabetes mellitus and essential hypertension more frequently. In the future we would perform another study to know what percentage of patients with diabetes mellitus or essential hypertension also receive antilipemic therapy.

As to the variations of physicians in managing hyperlipidemia or prescribing the antilipemic drugs, the NHIRD did not supply datasets sampled according to consulting physicians. The datasets in our current study and other available datasets with systematic sampling from all visits could only offer aggregate statistics of the physician specialties, not of individual physicians.

A serious drawback of the NHI claims is the absence of laboratory data, let alone other clinical and socioeconomic information. Furthermore, the privacy policy of the BNHI and NHIRD has encrypted the patients' personal identification numbers (PID). Although the encrypted PIDs remain consistent in all the NHIRD datasets, they can not be linked to other outside databases, *e.g.* the mortality database of the Department of Health. Besides, the researchers are forbidden to identify the patients for disease confirmation and follow-ups. That is, the outcome analysis and the study on the appropriateness (over- and undertreatment) of antilipemic drug use are not feasible with the NHI claims.[22-25]

To the best of our knowledge, our current study might be one of the first investigations concerning the

prevalence of antilipemic drug use among a representative population in Taiwan. Because the private use of the drugs outside the NHI is not included in our datasets and the claims fail to offer other significant data, the traditional epidemiological surveys are still needed to facilitate the understanding of hyperlipidemia management and antilipemic drug use in Taiwan.[26]

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