Impact of Air Pollution and Statins Use on Stroke among Hypertension Patients: A Population-Based Cohort Study in Taiwan

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There is growing evidence of the association between air pollution and the incidence and mortality of cardiovascular diseases especially stroke, which disease have had high risk to suffer among people who had hypertension. Stains are widely used for hyperlipidemia and cardiovascular disease by their cholesterol-lowering effect. Due to pleiotropy of statins, there are many study reported that statins are related to improve outcome and survival after stroke and may reduce the risk of stroke by their anti-inflammatory and neuroprotective effect. The objective of this study is to assess the modification of air pollution on using statins related to attack of stroke among hypertension patients. The study design was a retrospective cohort and the medical records of subjects including stroke events and statins use were collected by Longitudinal Health Insurance Database 2000 (LHID2000). Air pollution data including SO_2, CO, O_3, NO_2, PM_{10} and $PM_{2.5}$ were collected by high-density Taiwan Environmental Protection Administration monitoring stations and used in estimating exposure by Geographic Information Systems (GIS). Cox proportion regression models were used to estimate the relationship between air pollution and stroke occurring with statins using among hypertension patients. The results show that air pollution increases the risk of first attack of stroke and statins may reduce the risk of stroke occurring among hypertension patients. There are potential antagonistic effects between air pollution and statins use on stroke occurring among hypertension patients who were statins user. It is worth to be further studied to clarify this relationship among general population.

Keywords: Stroke; Air Pollution; Statins; Hypertension Patients; Longitudinal Health Insurance Database 2000 (LHID2000)

Introduction

Cerebrovascular diseases are the third of leading causes of death in Taiwan. There is growing evidence of the association between air pollution and the incidence of cardiovascular diseases especially stroke, which disease has had high risk to suffer among people who having hypertension. Stains are widely used for hyperlipidemia and cardiovascular disease by their cholesterol-lowering effect. Due to pleiotropy of statins, there are many studies reported that statins are related to improving outcome and survival after stroke. Statins may reduce the risk of stroke by their anti-inflammatory and neuroprotective effect. There are no study to research the association between air pollution and stroke occurring with statins use among hypertension patients.

Objective

The objective of this study is to estimate the effects of air pollution on stroke among hypertension patients with using statin.

Methods

The study design was a retrospective cohort study. We used outpatient visits and admissions records which included information on patient characteristics, such as sex, date of birth, dates of visits, date of admission, date of discharge, and diagnoses for outpatient visits and admissions(using the International Classification of Diseases, ninth revision [ICD-9], classification system). Our cohort was defined patients who had first-time diagnosis of hypertension (ICD-9 codes 401, 402, 403, 404, and 405) and age >18 years between January 1, 2000 and December 31, 2009 (n=124137). We collected and analyzed their first-time occurring of stroke (ICD-9 codes 430, 431, 432, 433, 434, 435, 436, 437) after first-time diagnosis of hypertension and statin use records for calculating the defined daily dose (cDDD). Air pollution data including NO, NO_2, NO_x, CO, SO_2, O_3, $PM_{2.5}$ and PM_{10} were collected by high-density Taiwan Environmental Protection Administration monitoring stations and used in estimating every district’s air pollutants concentration in Taiwan by

Geographic Information Systems (GIS). Air pollution was assessed twelve months prior to first-time occurring of stroke. Cox proportion regression models were used to estimate the relationship between air pollution and stroke occurring among hypertension patients stratified by statin status. Hypothesis testing was two-sided at the 0.05 significance level and was performed using SAS software version 9.4.

Result

Table 1 showed the demographic variables of hypertension patients. A total of 86,893 hypertension patients were included as our study cohort. Among these patients, 25,906(29.8%) patients had used statin (≥28 cDDDs), and 10,025(11.5%) patients had first-time occurring of stroke in the following period. Among hypertension patients with statin use, female was 52.5% and age group 40–49 has high percentage (31.16%). Table 2 exhibited twelve months air pollution patterns prior to first-time occurring of stroke. The mean concentration and interquartile range (IQR) of CO were 0.58 ppm and 0.23 ppm. Table 3 showed that the Spearman's rank correlation coefficient between air pollutants and O_3 had negative correlations with NO, NO_2, NO_x, and CO. The effects of air pollution and statin use on occurring of stroke demonstrated in table 4. There were significant effects of NO, NO_2, NO_x, CO, SO_2, $PM_{2.5}$ and PM_{10} on increasing the risks of first-time occurring of stroke. CO had highest adjusted hazard ratio (Adjusted HR, 2.835; 95% CI, 2.757 to 2.916). Statin use had significantly protection effects on first-time occurring of stroke (Adjusted HR<1). Furthermore, NO, NO_x, CO, SO_2, $PM_{2.5}$ and PM_{10} had significant interaction with statin use (*P*-value<0.05). In subgroup analysis, all air pollutants had significantly adverse effects on stroke among hypertension patients for both statin user and statin nonuser. The effects of CO, SO_2, $PM_{2.5}$ and PM_{10} on first-time occurring of stroke among statin users were more harmful than which among statin nonusers. The risks of NO and NO_X on first-time occurring of stroke among statin users were lesser than which among statin nonusers (Table 5).

Discussion and Conclusion

Based on results, CO may have strongest effect on stroke occurring among hypertension patients, especially for statin user. Further investigations on biological mechanism and pathogenesis are in need. In addition, air pollution and statin use have interaction to first-time occurring of stroke. It should more research about different trends of interaction between different pollutants and statin use to stroke among hypertension patients. This study is first study to discuss the relationship between air pollution and occurring of stroke with statins use among hypertension patients. The strengths of this study are the large sample sizes, and complete medical and medication records. However, our research limitations are less information like other environmental risk factors and personal living habits.

In conclusion, air pollution may increase the risk of first-time occurring of stroke among hypertension patients even for statin user. It is necessary to protect public from the adverse effects of air pollution, especially such high risk group like hypertension. This issue should be more concerned and further researched.

Table1. Patient demographics of the hypertension cohort

	Patients With Statin Use (≥28 cDDDs; n= 25,906)		Patients Without Statin Use (<28 cDDDs; n= 60,987)	
	No	%	No	%
First-time occurring of stroke	2,074	8.01	7,951	13.04
Sex				
Male	12,306	47.50	31,913	52.33
Female	13,600	52.50	29,074	47.67
Age, year				
18-29	675	2.61	2,952	4.84
30-39	3,032	11.70	9,118	14.95
40-49	8,073	31.16	16,168	26.51
50-59	7,122	27.49	12,574	20.62
≥60	7,004	27.04	20,175	33.08
Income, NT$				
0	6,007	23.19	13,721	22.50
1-15840	3,352	12.94	9,051	14.84
15841-25000	10,748	41.49	26,575	43.57
≥25001	5,799	22.38	11,640	19.09
Urbanization level				
Ⅰ	9,029	34.85	17,616	28.88
Ⅱ	11,655	44.99	27,630	45.30
Ⅲ	3,573	13.79	10,673	17.50
Ⅳ(rural area))	1,649	6.37	5,068	8.31

Abbreviations: cDDD, cumulative defined daily dose.

Table 2. Hypertension Patients average concentrations of the ambient air pollutants and meteorological factors.

Pollutant	Mean	Minimum	Maximum	IQR	Percentile		
					25^{th}	50^{th}	75^{th}
NO, ppb	8.27	0.58	45.40	7.54	3.94	6.04	11.49
NO_2, ppb	19.75	2.61	33.43	6.70	16.29	19.56	22.99
NO_X, ppb	28.00	3.26	78.72	13.34	20.27	26.15	33.62
CO, ppm	0.58	0.17	5.14	0.23	0.45	0.54	0.67
SO_2, ppb	4.29	0.77	12.15	1.23	3.39	3.64	4.62
O_3, ppb	29.14	17.62	41.48	4.49	26.76	29.73	31.25
$PM_{2.5}$, $\mu g/m^3$	34.38	15.42	60.78	12.03	28.46	33.03	40.50
PM_{10}, $\mu g/m^3$	59.97	27.78	94.60	24.44	48.99	58.01	73.43
RH, %	72.98	62.31	86.55	2.40	71.51	72.81	73.91
Temp, ℃	24.01	19.75	26.47	0.95	23.51	23.84	24.45

Abbreviations: RH, relative humidity; Temp, temperature; IQR, interquartile range.

Table 3. Correlation coefficients of ambient air pollutants average concentration during exposure period.

	NO	NO_2	NO_X	CO	SO_2	O_3	$PM_{2.5}$	PM_{10}	RH	Temp
NO	1.00	0.89	0.96	0.91	0.09	-0.84	-0.47	-0.53	-0.24	-0.28
NO_2		1.00	0.97	0.93	0.27	-0.80	-0.16	-0.25	-0.37	-0.02
NO_X			1.00	0.95	0.17	-0.83	-0.33	-0.41	-0.31	-0.15
CO				1.00	0.12	-0.81	-0.28	-0.38	-0.28	-0.15
SO_2					1.00	0.06	0.40	0.48	0.00	0.40
O_3						1.00	0.46	0.55	0.25	0.38
$PM_{2.5}$							1.00	0.94	-0.06	0.77
PM_{10}								1.00	0.05	0.75
RH									1.00	-0.18
Temp										1

Abbreviations: RH, relative humidity; Temp, temperature

All P-value < 0.001

Table 4. The adjusted hazard ratios and interaction tern between air pollution and statin use for stroke among hypertension patients.

Pollutants	Model 1[a]		Model 2[b]
	Air pollution (aHR, 95% CI)	Statin use (aHR, 95% CI)	Interaction tern (*P*-value)
NO, ppb	1.040 (1.037-1.043)	0.535 (0.509-0.561)	0.0003
NO_2, ppb	1.116 (1.110-1.121)	0.530 (0.505-0.556)	0.4149
NO_X, ppb	1.033 (1.031-1.035)	0.531 (0.505-0.557)	0.0007
CO, ppm	2.835 (2.757-2.916)	0.550 (0.524-0.578)	0.0114
SO_2, ppb	1.127 (1.114-1.140)	0.552 (0.526-0.580)	<.0001
O_3, ppb	0.811 (0.806-0.816)	0.531 (0.506-0.558)	0.1232
$PM_{2.5}$, μg/m^3	1.036 (1.034-1.039)	0.565 (0.538-0.594)	0.0109
PM_{10}, μg/m^3	1.004 (1.003-1.006)	0.553 (0.527-0.581)	0.0005

Abbreviations: aHR, adjusted hazard ratio.

[a]Model 1: without interaction tern between air pollution and statin use.

[b]Model 1: with interaction tern between air pollution and statin use and show *P*-value of interaction tern

All model adjusted for sex, age, income, and urbanization level.

Table 5. Association between air pollution and statin use for stroke among hypertension patients.

Pollutants	All Cases (aHR, 95% CI)	Statin Users (aHR, 95% CI)	Statin Nonusers (aHR, 95% CI)
NO, ppb	1.071 (1.067-1.074)	1.063 (1.055-1.071)	1.073 (1.069-1.078)
NO_X, ppb	1.071 (1.068-1.073)	1.066 (1.060-1.071)	1.072 (1.069-1.075)
CO, ppm	3.257 (3.165-3.351)	3.711 (3.477-3.962)	3.104 (3.006-3.205)
SO_2, ppb	1.140 (1.127-1.154)	1.205 (1.175-1.235)	1.119 (1.104-1.135)
$PM_{2.5}$, μg/m^3	1.038 (1.035-1.041)	1.043 (1.037-1.050)	1.035 (1.032-1.039)
PM_{10}, μg/m^3	1.004 (1.002-1.005)	1.008 (1.004-1.011)	1.002 (1.000-1.004)

Abbreviations: aHR, adjusted hazard ratio.

All model adjusted for sex, age, income, and urbanization level.