Association of venous thromboembolism between hydrophilic and lipophilic statin users among diabetic subjects

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Abstract

This retrospective analysis aimed to compare the risk of venous thromboembolism (VTE) between patients with diabetes mellitus who received hydrophilic statin treatment to those who receive lipophilic statin. There were 6639 patients receiving hydrophilic statin therapy and 10,854 patients receiving lipophilic statin therapy in the study. The hazard ratios and 95% confidence intervals for VTE were estimated using univariate and multivariate Cox proportional hazards models when the study cohorts were compared. Among all patients, the incidence rate of VTE was 4.27 per 1000 person-years in the control cohort, 4.18 per 1000 person-years in the hydrophilic statin use cohort, and 3.91 per 1000 person-years in the lipophilic statin use cohort. After adjusting for age, sex, and comorbidities, the risk of VTE in the hydrophilic statin use cohort was 0.90 (0.72, 1.12) lower than that in the control cohort, the risk of VTE in the lipophilic statin use cohort was 0.87 (0.72, 1.05) lower than that in the control cohort, and the risk of VTE in the lipophilic statin use cohort was 0.97 (0.78, 1.21) lower than that in the hydrophilic statin use cohort. However, all were not statistically significant. Our result showed that there was no significant difference among the study cohorts regarding the outcome of VTE.

Keywords: diabetes mellitus, statin, venous thromboembolism

1. Introduction

Diabetes mellitus (DM) is considered as a major issue in endemic area and mainly for related complications and high mortality.[1,2] Statin could have been taken into consideration as a risk-reduction factor for DM associated adverse events.[1,2] Indeed, statin is stratified into 2 categories, the hydrophilic and lipophilic one according to the pharmacologic property. To date, there is no consensus regarding which one is superior to the other for outcomes prevention. Due to inconclusive results from prior investigations, there is still controversy regarding the statements.[3–8] The relationship between the risk of cardiovascular outcomes and DM is well-known. Despite higher incidence of associated higher morbidity and mortality, venous thromboembolism (VTE) attracts less attention compared to other adverse outcomes among DM subjects.[9,10] In order to comment this information on whether one statin is superior to the other for VTE risk among DM individuals, this study focuses on the relationship of incident VTE between hydrophilic and lipophilic statin users in people affected by DM with further subgroup analytical approach.

2. Methods

2.1. Data source

The National Health Insurance (NHI) program in Taiwan was launched in March 1995 and had provided universal health coverage of 99.9% of the population who had resided in Taiwan (approximately 23 million people) by a single-payer system for healthcare. The database derived from the NHI program was known as the National Health Insurance Research Database (NHIRD). For privacy protection, the data in the NHIRD were de-identified and encrypted. The dataset from the Longitudinal Health Insurance Database (LHID) was used in the study.[11,12] It was randomly sampled from the NHIRD and contained claims data of 1 million individuals on demographics, diagnoses of diseases, prescriptions, and inpatient and outpatient visits. The diagnostic classification was according to the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM). This study was approved by the Central Regional Research Ethics Committee, China Medical University, Taichung, Taiwan (CMUH104-REC2-115(CR-7)).

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2.2. Study population

The case cohort was defined as patients diagnosed with type II DM (ICD-9-CM: 250.x0 and 250.x2) and receiving hydrophilic or lipophilic statin therapy for at least 6 months (180 days) between 2000 and 2012. The index date was the date of the first prescription of the statin. The control cohort was defined as patients who did not receive hydrophilic or lipophilic statin therapy between 2000 and 2012, and it was matched with the case cohort by the index year, sex, and age in a 1:1 ratio using frequency matching. The end date of the follow-up was the date of onset of VTE (ICD-9-CM: 415, 452, 453, except 415.1), the date of patient withdrawal from the NHI program, or December 31, 2013. The study excluded patients younger than 20 years, diagnosed with VTE before the index date, or with incomplete medical information at enrollment.

2.3. Baseline comorbidities

Baseline comorbidities were as follows: hypertension (ICD-9-CM: 401-405), hyperlipidemia (ICD-9-CM: 272), coronary artery disease (ICD-9-CM: 410-414), chronic obstructive pulmonary disease (ICD-9-CM: 491, 492, 496), peripheral artery disease (ICD-9-CM: 440.0, 440.2, 440.3, 440.8, 440.9, 443, 444.0, 444.22, 444.8, 444.9, 447.8, and 447.9), chronic kidney disease (ICD-9-CM: 585), hyperthyroidism (ICD-9-CM: 242), sleep disorder (ICD-9-CM: 307.4, 780.5), gout (ICD-9-CM: 274), cirrhosis (ICD-9-CM: 571), depression (ICD-9-CM: 296.2, 296.3, 300.4, 311), anxiety (ICD-9-CM: 300.00), and migraine (ICD-9-CM: 346).

2.4. Statistical analysis

The demographics and comorbidities in each study cohort were summarized by numbers and percentages for categorical variables and means and standard deviations for continuous variables. The distributions of demographics and comorbidities were compared between the statin use patients and controls by chi-square tests for categorical variables and t tests for continuous variables. The incidence rates (IRs) of VTE were calculated as the number of the events divided by the person-years during the follow-up. The hazard ratios (HRs) and 95% confidence intervals (CIs) for VTE were estimated using univariate and multivariate Cox proportional hazards models when the study cohorts were compared. Covariates used in the multivariate models included age, sex, and comorbidities mentioned above. Significance was defined as a $P < .05$. All data were analyzed using SAS 9.4 software (SAS Institute Inc., Cary, NC).

3. Results

Table 1 shows comparisons of demographics and comorbidities between statin use patients and controls. There were 6639 patients receiving hydrophilic statin therapy and 10,854 patients receiving lipophilic statin therapy in the study. The average ages was 63.9 ± 11.6 in the hydrophilic statin use cohort and 63.3 ± 11.8 years in the lipophilic statin use cohort. Females accounted for 52.5% of patients in the hydrophilic statin use cohort and 52.0% of patients in the lipophilic statin use cohort.

Table 2 shows comparisons of incidence rates of VTE among the study cohorts. Among all patients, the IR of VTE was 4.27 per 1000 person-years in the control cohort, 4.18 per 1000 person-years in the hydrophilic statin use cohort, and 3.91 per 1000 person-years in the lipophilic statin use cohort. After adjusting for age, sex, and comorbidities, the risk of VTE in the hydrophilic statin use cohort was 0.90 (0.72, 1.12) lower than that in the control cohort, the risk of VTE in the lipophilic statin use cohort was 0.87 (0.72, 1.05) lower than that in the control cohort, and the risk of VTE in the lipophilic statin use cohort was 0.97 (0.78, 1.21) lower

Table 1

Comparison of demographics and comorbidity between statin use patients and controls.

Variables	Type 2 diabetes								P value
	Total (N = 17,493)		Hydrophilic statin use (N = 6639)		Lipophilic statin use (N = 10,854)		Controls (N = 17,493)		
	n	%	n	%	n	%	n	%	
Age, yr									.99
≤ 49	2185	12.5	756	11.4	1429	13.2	2185	12.5	
50–64	7044	4.3	2686	4.5	4358	4.2	7044	4.3	
≥ 65	8264	47.2	3197	48.2	5067	46.7	8264	47.2	
Mean (SD)*	63.5	11.7	63.9	11.6	63.3	11.8	63.7	12.1	.29
Gender									.99
Women	9130	52.2	3486	52.5	5644	52.0	9130	52.2	
Men	8363	47.8	3153	47.5	5210	48.0	8363	47.8	
Comorbidity									
Hypertension	15,017	85.6	5803	87.4	9214	84.9	12,419	71.0	<.001
Hyperlipidemia	15,775	9.2	6090	91.7	9685	89.2	6967	39.8	<.001
Coronary artery disease	9150	52.3	3703	55.8	5447	5.2	6385	36.5	<.001
Chronic obstructive pulmonary disease	4680	26.8	1845	27.8	2835	26.1	4621	26.4	.48
Peripheral artery disease	1955	11.2	813	12.3	1142	1.5	1338	7.65	<.001
Chronic kidney disease	1598	9.14	678	1.2	920	8.48	920	5.26	<.001
Hyperthyroidism	517	2.96	226	3.40	291	2.68	433	2.48	.01
Sleep disorder	6517	37.3	2648	39.9	3869	35.7	6083	34.8	<.001
Gout	4822	27.6	1904	28.7	2918	26.9	3392	19.4	<.001
Cirrhosis	7828	44.8	2969	44.7	4859	44.8	8000	45.7	.06
Depression	1887	1.8	811	12.2	1076	9.91	1692	9.67	<.001
Anxiety	2893	16.5	1197	18.0	1696	15.6	2471	14.1	<.001
Migraine	928	5.30	413	6.22	515	4.74	780	4.46	<.001

Chi-square test.

SD = standard deviation.

* t test.

Table 2

Comparisons of incidence densities and HR of venous thromboembolism in study cohorts.

Variable	Controls		Crude HR*	Adjusted HR†	Hydrophilic statin use		Crude HR*	Adjusted HR†	Lipophilic statin use		Crude HR*	Adjusted HR†
	Event	Rate‡	(95% CI)	(95% CI)	Event	Rate‡	(95% CI)	(95% CI)	Event	Rate‡	(95% CI)	(95% CI)
All	373	4.27	1(Reference)	1(Reference)	132	4.18	0.98(0.80,1.19)	0.90(0.72,1.12)	241	3.91	0.92(0.78,1.08)	0.87(0.72,1.05)
Men	208	4.40	1(Reference)	1(Reference)	75	4.39	0.94(0.69,1.27)	1.01(0.72,1.41)	138	4.13	0.90(0.70,1.15)	0.98(0.74,1.31)
Women	165	4.11	1(Reference)	1(Reference)	57	3.92	1.01(0.78,1.32)	0.81(0.61,1.09)	103	3.64	0.93(0.75,1.16)	0.78(0.61,1.00)
All							1(Reference)	1(Reference)			0.94(0.76, 1.16)	0.97(0.78,1.21)
Men							1(Reference)	1(Reference)			0.96(0.70, 1.33)	1.00(0.72,1.39)
Women							1(Reference)	1(Reference)			0.92(0.69,1.22)	0.96(0.72,1.27)

CI = confidence interval, HR = hazard ratio.

*Relative HR.

†Multivariable analysis including age, sex, comorbidities of hypertension, hyperlipidemia, coronary artery disease, chronic obstructive pulmonary disease, peripheral artery disease, chronic kidney disease, hyperthyroidism, sleep disorder, gout, cirrhosis, depression, anxiety, and migraine.

‡Incidence rate, per 1000 person-years.

than that in the hydrophilic statin use cohort. However, all were not statistically significant. Among male patients, the IR of VTE was 4.40 per 1000 person-years in the control cohort, 4.39 per 1000 person-years in the hydrophilic statin use cohort, and 4.13 per 1000 person-years in the lipophilic statin use cohort. After adjusting for age, sex, and comorbidities, the risk of VTE in the hydrophilic statin use cohort was 1.01 (0.72, 1.41) higher than that in the control cohort, the risk of VTE in the lipophilic statin use cohort was 0.98 (0.74, 1.31) lower than that in the control cohort, and the risk of VTE in the lipophilic statin use cohort was 1.00 (0.72, 1.39) equal to that in the hydrophilic statin use cohort. However, all were not statistically significant. Among female patients, the IR of VTE was 4.11 per 1000 person-years in the control cohort, 3.92 per 1000 person-years in the hydrophilic statin use cohort, and 3.64 per 1000 person-years in the lipophilic statin use cohort. After adjusting for age, sex, and comorbidities, the risk of VTE in the hydrophilic statin use cohort was 0.81 (0.61, 1.09) lower than that in the control cohort, the risk of VTE in the lipophilic statin use cohort was 0.78 (0.61, 1.00) lower than that in the control cohort, and the risk of VTE in the lipophilic statin use cohort was 0.96 (0.72, 1.27) lower than that in the hydrophilic statin use cohort. However, all were not statistically significant.

Table 3 shows development of VTE in patients receiving statin therapy in different genders. The risk of VTE was lower in men compared to women when both genders received hydrophilic statin therapy (adjusted HR: 0.91, 95% CI: 0.64–1.29) and was lower in patients receiving lipophilic statin therapy compared to women receiving hydrophilic statin therapy (adjusted HR: 0.98, 95% CI: 0.74–1.30 in women with lipophilic statin; adjusted HR: 0.88, 95% CI: 0.64–1.19 in men with lipophilic statin). However, all were not statistically significant.

4. Discussion

The study investigated the association of VTE between hydrophilic and lipophilic statin users among diabetic subjects with further stratified analysis and no significant difference among the study cohorts regarding the outcome of VTE was concluded.

The strength of this research is a relatively large sample size with the novelty and plausible reasons of the key findings. Indeed, this is an aspect because the relationship between the 2 categories has never been reported before. The main contribution of this paper is that we demonstrated no significant difference between these 2 categories and also in the subgroup sex stratified analysis.

There is difference of hydrophilic and lipophilic statins regarding the tissue selectivity, which might have impact on the subsequent pharmacologic therapeutic effect.[13] Indeed, pleomorphic beneficial effects of statin have been provided, especially for cardiovascular events risk reduction.[14–16] Interesting, we observed a nonsignificant trend toward reduced risk of VTE events in lipophilic statins users compared to hydrophilic statins users. A plausible mechanism and reasonable hypothesis for this phenomenon is that lipophilic has higher penetration capacity for any cells.[13] Given the statistically nonsignificant results here, it seems relatively premature to draw a firm conclusion. To this end, further investigation seems to be needed for further clarification.

DM is a major contributing factor for cause of morbidity and mortality in the world. Recently, VTE has been considered an emerging threat and burden, especially in those affected by DM.[9,10] The presented rationale for this research also makes it simple to place the results in context of previous research or study hypotheses. We observed that men conferred a trend toward reduced VTE incidence in spite of hydrophilic or

Table 3

Development of venous thromboembolism in patients with statin use associated with gender in Cox regression analysis.

Hydrophilic statin use	Lipophilic statin use	Gender	N	Case	Rate‡	Crude HR* (95% CI)	Adjusted HR† (95% CI)
Yes	No	Women	3486	75	4.39	1(Reference)	1(Reference)
Yes	No	Men	3153	57	3.92	0.89(0.63, 1.26)	0.91(0.64, 1.29)
No	Yes	Women	5644	138	4.13	0.94(0.71, 1.25)	0.98(0.74, 1.30)
No	Yes	Men	5210	103	3.64	0.83(0.62, 1.12)	0.88(0.64, 1.19)

CI = confidence interval, HR = hazard ratio.

*Relative HR.

†Multivariable analysis including age, sex, comorbidities of hypertension, hyperlipidemia, coronary artery disease, chronic obstructive pulmonary disease, peripheral artery disease, chronic kidney disease, hyperthyroidism, sleep disorder, gout, cirrhosis, depression, anxiety, and migraine.

‡Incidence rate, per 1000 person-years.

lipophilic statin use. It seems that hormone might play a role in statin effect on VTE among DM subjects. Future works are mandatory to identify the possible mechanism.

5. Limitations

The major flaw of this study is possibly related to coding based study despite the nationwide dataset has been validated. Furthermore, several parameters are missing here, such as current smoking, current alcohol consumption and body mass index. Finally, this study in conducted in Asia, and whether the results presented here could be translated to other races remained questionable.

6. Conclusion

Statistically nonsignificant difference of incident VTE among the study cohorts was found.

Author contributions

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References

[1] Rabar S, Harker M, O'Flynn N, Wierzbicki AS; Guideline Development Group. Lipid modification and cardiovascular risk assessment for the primary and secondary prevention of cardiovascular disease: summary of updated NICE guidance. BMJ. 2014;349:g4356–g4356.

[2] Stone NJ, Robinson JG, Lichtenstein AH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines. J Am Coll Cardiol. 2014;63(25 pt B):2889–934.

[3] Komatsu T, Tachibana H, Sato Y, Ozawa M, Kunugita F, Nakamura M. Long-term efficacy of upstream therapy with lipophilic or hydrophilic statins on antiarrhythmic drugs in patients with paroxysmal atrial fibrillation: comparison between atorvastatin and pravastatin. Int Heart J. 2011;52:359–65.

[4] Oh J, Kang SM, Hong N, et al. Effect of high-dose statin loading on biomarkers related to inflammation and renal injury in patients hospitalized with acute heart failure. Randomized, controlled, open-label, prospective pilot study. Circ J. 2014;78:2447–54.

[5] Takano H, Mizuma H, Kuwabara Y, et al. Effects of pitavastatin in Japanese patients with chronic heart failure: the Pitavastatin Heart Failure Study (PEARL Study). Circ J. 2013;77:917–25.

[6] Izawa A, Kashima Y, Miura T, et al. Assessment of lipophilic vs. hydrophilic statin therapy in acute myocardial infarction—ALPSAMI study. Circ J. 2015;79:161–8.

[7] Kim MC, Ahn Y, Jang SY, et al. Comparison of clinical outcomes of hydrophilic and lipophilic statins in patients with acute myocardial infarction. Korean J Intern Med. 2011;26:294–303.

[8] Sakamoto T, Kojima S, Ogawa H, et al. Usefulness of hydrophilic vs lipophilic statins after acute myocardial infarction: subanalysis of MUSASHI-AMI. Circ J. 2007;71:1348–53.

[9] Ageno W, Becattini C, Brighton T, Selby R, Kamphuisen PW. Cardiovascular risk factors and venous thromboembolism: a meta-analysis. Circulation. 2008;117:93–102. [PubMed] [Google Scholar].

[10] Bai J, Ding X, Du X, Zhao X, Wang Z, Ma Z. Diabetes is associated with increased risk of venous thromboembolism: a systematic review and meta-analysis. Thromb Res. 2014;135:90–5.

[11] Hu WS, Lin CL. Hemorrhoid is associated with increased risk of peripheral artery occlusive disease: a nationwide cohort study. J Epidemiol. 2017;27:574–7.

[12] Hu WS, Lin CL. Association between cataract and risk of incident atrial fibrillation: a nationwide population-based retrospective cohort study. Mayo Clin Proc. 2017;92:370–5.

[13] Schachter M. Chemical, pharmacokinetic and pharmacodynamic properties of statins: an update. Fundam Clin Pharmacol. 2005;19:117–25.

[14] Aikawa M, Rabkin E, Sugiyama S, et al. An HMG-CoA reductase inhibitor, cerivastatin, suppresses growth of macrophages expressing matrix metalloproteinases and tissue factor in vivo and in vitro. Circulation. 2001;103:276–83.

[15] Dangas G, Badimon JJ, Smith DA, et al. Pravastatin therapy in hyperlipidemia: effects on thrombus formation and the systemic hemostatic profile. J Am Coll Cardiol. 1999;33:1294–304.

[16] Laufs U, La Fata V, Plutzky J, Liao JK. Upregulation of endothelial nitric oxide synthase by HMG CoA reductase inhibitors. Circulation. 1998;97:1129–35.