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

Wei-Syun Hu, MD, PhD, Cheng-Li Lin, MSc

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, and 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 hydrophilic statin use cohort was 0.97 (0.78, 1.21) lower than that in the lipophilic statin use cohort. However, all were not statistically significant.

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.3-10 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.3-10 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 LHID 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, 440.8, 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.

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) |
| Age, yr                          |                  |         |         |                  |
| < 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                             | 8204            | 47.2    | 3197    | 48.2             | 5067            | 46.7    | 8204            | 47.2    |
| Mean (SD)*                       | 63.5            | 11.7    | 63.9    | 11.6             | 63.3            | 11.8    | 63.7            | 12.1    |
| Gender                           |                  |         |         |                  | .99              |         | .29              |         |
| 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    |
| Hyperlipidemia                   | 15,775          | 9.2     | 6090    | 91.7             | 9685            | 89.2    | 6967            | 39.8    |
| Coronary artery disease          | 9150            | 52.3    | 3703    | 55.8             | 5447            | 5.2     | 6385            | 36.5    |
| Chronic obstructive pulmonary disease | 4680      | 26.8    | 1845    | 27.8             | 2835            | 26.1    | 4621            | 26.4    |
| Peripheral artery disease        | 1955            | 11.2    | 813     | 12.3             | 1142            | 1.5     | 1388            | 7.6      |
| Chronic kidney disease           | 1598            | 9.14    | 678     | 1.2              | 920             | 8.48    | 920             | 5.26     |
| Hyperthyroidism                  | 517             | 2.96    | 226     | 3.4              | 291             | 2.68    | 433             | 2.48     |
| Sleep disorder                   | 6517            | 37.3    | 2648    | 39.9             | 3869            | 35.7    | 6083            | 34.8     |
| Gout                             | 4822            | 27.6    | 1904    | 28.7             | 2918            | 26.9    | 3392            | 19.4     |
| Cirrhosis                        | 7828            | 44.8    | 2369    | 44.7             | 4859            | 44.8    | 8000            | 45.7     |
| Depression                       | 1887            | 1.8     | 811     | 12.2             | 1076            | 9.91    | 1602            | 9.67     |
| Anxiety                          | 2893            | 16.5    | 1197    | 18.0             | 1696            | 15.6    | 2471            | 14.1     |
| Migraine                         | 928             | 5.30    | 413     | 6.22             | 515             | 4.74    | 780             | 4.46     |

Chi-square test.
SD = standard deviation.
* t test.
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, 4.39 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. Indeed, pleomorphic beneficial effects of statin have been provided, especially for cardiovascular events risk reduction. Interestingly, 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. 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 2
Comparisons of incidence densities and HR of venous thromboembolism in study cohorts.

| Variable | Controls | Hydrophilic statin use | Lipophilic statin use |
|---------|----------|------------------------|-----------------------|
| All     | Event    | Rate‡                  | HR* (95% CI)          | Rate‡                  | HR* (95% CI)          |
| Men     | 208      | 4.40                   | 0.94 (0.69, 1.27)     | 0.90 (0.72, 1.12)     |
| Women   | 165      | 4.11                   | 1.01 (0.78, 1.32)     | 0.80 (0.61, 1.00)     |
| All     | 373      | 4.27                   | 1 (Reference)         | 1 (Reference)         |
| Crude HR* | 0.98 (0.80, 1.19) | 0.90 (0.72, 1.12) |
| Adjusted HR† | 0.88 (0.64, 1.29) | 0.80 (0.61, 1.00) |

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)    |
| Yes                    | 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)    |

‡Incidence rate, per 1000 person-years.
†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.
*Relative HR.
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

Conceptualization: Cheng-Li Lin.
Formal analysis: Wei Syun Hu.

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