Dipeptidyl Peptidase-4 Inhibitors Use and Relative Risk of Ischemic Cerebrovascular Disease in Type 2 Diabetic Patients in a Case-Control Study

Shih-Wei Lai¹,², Kuan-Fu Liao³,⁴, Cheng-Li Lin¹,⁵ and Hsien-Feng Lin²,⁶*

¹ Department of Medicine, China Medical University, Taichung, Taiwan, ² Department of Family Medicine, China Medical University Hospital, Taichung, Taiwan, ³ Department of Medicine, Tzu Chi University, Hualien, Taiwan, ⁴ Department of Internal Medicine, Tzu Chi University, Hualien, Taiwan, ⁵ Management Office for Health Data, China Medical University Hospital, Taichung, Taiwan, ⁶ Department of Chinese Medicine, China Medical University, Taichung, Taiwan

Background and Objectives: Limited research focuses on the risk of ischemic cerebrovascular disease associated with use of dipeptidyl peptidase-4 inhibitors (DPP-4 inhibitors) in patients with type 2 diabetes mellitus in Taiwan. This study aimed to investigate the association between DPP-4 inhibitors use and the first episode of ischemic cerebrovascular disease.

Methods: We designed a case-control study using the database of the Taiwan National Health Insurance Program. There were 1999 type 2 diabetic subjects aged 20–84 years with the first episode of ischemic cerebrovascular disease from 2000 to 2013 as the cases, and 7996 sex- and age-matched, randomly selected type 2 diabetic subjects aged 20–84 years without any type of cerebrovascular diseases as the matched controls. We estimated the odds ratio (OR) and 95% confidence interval (CI) of ischemic cerebrovascular disease associated with cumulative duration of DPP-4 inhibitors use by the multivariable logistic regression model.

Results: After adjustment for confounding variables, the adjusted OR of ischemic cerebrovascular disease was 0.96 (95% CI 0.95, 0.97) in subjects with ever use of DPP-4 inhibitors as increase in use duration for every 1 month, compared with never use. The sub-analysis disclosed that the adjusted ORs of ischemic cerebrovascular disease were 1.57 (95% CI 1.36, 1.80) for subjects with cumulative duration of DPP-4 inhibitors use <1 year, and 0.70 (95% CI 0.57, 0.87) for subjects with cumulative duration of DPP-4 inhibitors use ≥1 year, compared with never use.

Conclusion: Our findings suggest that DPP-4 inhibitors use correlates with relative risk reduction of the first episode of ischemic cerebrovascular disease in type 2 diabetic patients in a duration-dependent response. The beneficial effect will be marked when DPP-4 inhibitors use is ≥1 year.

Keywords: diabetes mellitus, DPP-4 inhibitors, ischemic cerebrovascular disease, National Health Insurance Program, Taiwan
INTRODUCTION

Dipeptidyl peptidase-4 inhibitors (DPP-4 inhibitors) are classified as a new oral anti-diabetic medication and are widely used for management of type 2 diabetes mellitus (Baetta and Corsini, 2011). In addition to their glucose-lowering effects, current evidence discloses that DPP-4 inhibitors have beneficial effects on the major adverse cardiovascular events (Monami et al., 2011; Scheen, 2013; Davidson, 2014; Kaneko and Narukawa, 2016).

Cerebrovascular disease ranked the fourth leading cause of death and diabetes mellitus ranked the fifth leading cause of death in Taiwan in 2016, respectively (Ministry of Health and Welfare, 2017a). To date, conclusive results on the risk of ischemic cerebrovascular disease associated with DPP-4 inhibitors use in Taiwan are limited. If the association between the risk of ischemic cerebrovascular disease and DPP-4 inhibitors use substantially exists, the drug of choice for management of type 2 diabetes mellitus can be suggested in Taiwan. Therefore, we designed a case-control study using the database of the Taiwan National Health Insurance Program to investigate the association between DPP-4 inhibitors use and the first episode of ischemic cerebrovascular disease.

MATERIALS AND METHODS

Study Design and Study Population

The methodology was adapted from previous studies (Lai et al., 2016, 2017j; Liao et al., 2017b). It did not need to write published protocol details. We summarized them as follows and cited the relevant references. We designed a case-control study using the database of the Taiwan National Health Insurance Program. Taiwan is an independent country with more than 23 million persons (Chan et al., 2016; Chang and Yu, 2016; Chang et al., 2016; Chen and Wu, 2016; Chen S.Y. et al., 2016; Chen Y.F. et al., 2016; Hsieh et al., 2016; Hsu and Yin, 2016; Huang and Chang, 2016; Lin and Lin, 2016; Maa and Leu, 2016; Ooi, 2016; Yu et al., 2016; Lai et al., 2017g; Lee et al., 2017; Liang et al., 2017; Liao et al., 2017a,c; Lin et al., 2017a; Liu et al., 2017b). Briefly, subjects with at least a prescription for medications studied before index date were classified into "ever use." Subjects without a prescription of medications studied before index date were classified into "never use."

Statistical Analysis

At first, we made a comparison of sex, age, medications, and comorbidities between the cases and the matched controls by using the Chi-square test for categorized variables and the t-test for continuous variables. Then, variables which were significantly associated with ischemic cerebrovascular disease in the univariable logistic regression model were further tested by the multivariable logistic regression model. We estimated the odds ratio (OR) and 95% confidence interval (CI) for the relative risk of ischemic cerebrovascular disease associated with cumulative duration of DPP-4 inhibitors use. The probability value < 0.05 was considered statistically significant (SAS software version 9.2, SAS Institute, Inc., Cary, NC, United States).

RESULTS

Basic Characteristics of the Study Population

Table 1 discloses the basic characteristics of the study population. There were 1999 cases with the first episode of ischemic cerebrovascular disease in 2000–2013 and 7996 matched controls without any type of cerebrovascular diseases, with similar distributions of sex and age. The mean ages (standard deviation) were 67.8 (10.6) years in cases and 67.7 (10.6) years in matched controls, without statistical significance (t-test, \( P = 0.67 \)).
cases were more likely to have higher proportions of ever use of DPP-4 inhibitors, ever use of other anti-diabetic medications, alcohol-related disease, atrial fibrillation, chronic kidney disease, coronary artery disease, hyperlipidemia, and hypertension than the matched controls, with statistical significance (Chi-square test, \( P < 0.05 \), for all).

**Relative Risk of Ischemic Cerebrovascular Disease Associated with Cumulative Duration of DPP-4 Inhibitors Use**

After adjustment for confounding variables including other anti-diabetic medications, alcohol-related disease, atrial fibrillation, chronic kidney disease, chronic obstructive pulmonary disease, coronary artery disease, hyperlipidemia, and hypertension, the adjusted OR of ischemic cerebrovascular disease was 0.96 (95% CI 0.95, 0.97) in subjects with ever use of DPP-4 inhibitors as increase in use duration for every 1 month, compared with never use. The sub-analysis disclosed that the adjusted ORs of ischemic cerebrovascular disease were 1.57 (95% CI 1.36, 1.80) for subjects with cumulative duration of DPP-4 inhibitors use < 1 year, and 0.70 (95% CI 0.57, 0.87) for subjects with cumulative duration of DPP-4 inhibitors use \( \geq 1 \) year, compared with never use (Table 2).

**DISCUSSION**

In this case-control study, we found that DPP-4 inhibitors use was associated with decreased odds of the first episode of ischemic cerebrovascular disease in type 2 diabetic patients in a

**TABLE 1** | Basic characteristics between cases with ischemic cerebrovascular disease and matched controls.

| Variable                        | Matched controls | Cases with ischemic cerebrovascular disease |
|---------------------------------|------------------|--------------------------------------------|
|                                 | \( N = 7996 \)   | \( N = 1999 \)                          |
|                                | \( N \) (\%)     | \( N \) (\%)                          |
| Sex                             |                  |                                            |
| Female                          | 3580 (44.8)      | 895 (44.8)                               |
| Male                            | 4416 (55.2)      | 1104 (55.2)                              |
| Age group (years)               |                  |                                            |
| 20–49                           | 496 (6.2)        | 124 (6.2)                                |
| 50–64                           | 2500 (31.3)      | 625 (31.3)                               |
| 65–84                           | 5000 (62.5)      | 1250 (62.5)                              |
| Age (years), mean ± standard deviation† | \( 67.7 \pm 10.6 \) | \( 67.8 \pm 10.6 \)                  |
| Ever use of DPP-4 inhibitors    | 1485 (18.6)      | 446 (22.3)                               |
| Ever use of other anti-diabetic medications | 7741 (96.8) | 1960 (98.1)                           |
| Comorbidities before index date |                  |                                            |
| Alcohol-related disease         | 720 (9.00)       | 209 (10.5)                               |
| Atrial fibrillation             | 220 (2.75)       | 158 (7.90)                               |
| Chronic kidney disease          | 1602 (20.0)      | 441 (22.1)                               |
| Chronic obstructive pulmonary disease | 2617 (32.7) | 597 (29.9)                               |
| Coronary artery disease         | 3586 (44.9)      | 948 (47.4)                               |
| Hyperlipidemia                  | 5697 (71.3)      | 1480 (74.0)                              |
| Hypertension                    | 6517 (81.5)      | 1830 (91.6)                              |

Data are presented as the number of subjects in each group with percentages given in parentheses. *Chi-square test and †t-test comparing subjects with and without ischemic cerebrovascular disease.

**TABLE 2** | Relative risk of ischemic cerebrovascular disease associated with cumulative duration of DPP-4 inhibitors use.

| Variable                                    | Case number/control number | Crude OR (95% CI) | Adjusted OR† (95% CI) |
|---------------------------------------------|----------------------------|-------------------|-----------------------|
| Never use of DPP-4 inhibitors as a reference| 1553/6511                  | 1.00 (Reference)  | 1.00 (Reference)      |
| Cumulative duration of DPP-4 inhibitors use (increase in use duration for every 1 month) | 446/1485                  | 0.96 (0.95, 0.98) | 0.96 (0.95, 0.97)     |
| <1 year                                     | 340/880                    | 1.62 (1.41, 1.86) | 1.57 (1.36, 1.80)     |
| \( \geq 1 \) year                           | 106/605                    | 0.74 (0.59, 0.91) | 0.70 (0.57, 0.87)     |

†Variables found to be statistically significant in the univariable logistic regression model were further tested by the multivariable logistic regression model. Only other anti-diabetic medications use, alcohol-related disease, atrial fibrillation, chronic kidney disease, chronic obstructive pulmonary disease, coronary artery disease, hyperlipidemia, and hypertension could be further tested.
duration-dependent response. The effect would be marked when DPP-4 inhibitors use was \(\geq 1\) year. This finding was consistent with previous studies disclosing that DPP-4 inhibitors use was associated with lower risk of ischemic cerebrovascular disease (Ou et al., 2015; Shih et al., 2016). We found that if DPP-4 inhibitors use was less than 1 year, the odds would be high (adjusted OR1.57). That is, short-term of DPP-4 inhibitors use does not have the beneficial effect. Clinicians should keep in mind about the risk of ischemic cerebrovascular disease during the first year of DPP-4 inhibitors use in type 2 diabetic patients. We suggest that only long-term of DPP-4 inhibitors use for 1 year or longer, type 2 diabetic patients can have the beneficial effect on risk reduction of ischemic cerebrovascular disease.

Hemoglobin A1c is an important indicator for long-term glycemic control. Previous studies disclosed that high levels of hemoglobin A1c were associated with increased risk of cerebrovascular disease (Goto et al., 2015; Cavender et al., 2016). Although DPP-4 inhibitors are not the drug of first choice for type 2 diabetes mellitus by the guidelines of American Diabetes Association (American Diabetes Association, 2017), DPP-4 inhibitors use still can reduce hemoglobin A1c by 0.5–1% (Madsbad et al., 2008; Grunberger, 2014). In our opinion, patients using other anti-diabetic medications but poor glycemic control would additionally use DPP-4 inhibitors. When initiating DPP-4 inhibitors, Hemoglobin A1c levels of these patients should be high. The risk for ischemic cerebrovascular disease was still greater. Only using DPP-4 inhibitors for 1 year or longer and then hemoglobin A1c gradually reducing, these patients could have a chance to be in good glycemic control. Thus, the risk of ischemic cerebrovascular disease was further reduced. That at least partially explains why the odds of ischemic cerebrovascular disease would be high during the first year of DPP-4 inhibitors use, and then the odds would be reduced after 1 year.

Some limitations should be mentioned. First, due to the inherent limitation, hemoglobin A1c was not recorded in the database. Our study could not prove the association between the risk of ischemic cerebrovascular disease and hemoglobin A1c levels. Second, Table 1 discloses that about 97% of study subjects had ever used other anti-diabetic medications. It is difficult to investigate the absolute risk of ischemic cerebrovascular disease associated with DPP-4 inhibitors use alone due to the small eligible number for DPP-4 inhibitors use alone. The rational option was to investigate the relative risk of ischemic cerebrovascular disease associated with DPP-4 inhibitors use after adjustment for other anti-diabetic medications. Third, a case-control study could not prove the causal relationship. Further prospective cohort research is warranted to focus on the association between the absolute risk of ischemic cerebrovascular disease and DPP-4 inhibitors use alone.

Some strengths should be emphasized. The title clearly and precisely reflects the findings of the study. The statistical methods used validate. The prior works are properly and fully cited. Immortal time bias can be minimized in a case-control study. The results are convincing.

**CONCLUSION**

Our findings suggest that DPP-4 inhibitors use correlates with relative risk reduction of the first episode of ischemic cerebrovascular disease in type 2 diabetic patients in a duration-dependent response. The beneficial effect will be marked when DPP-4 inhibitors use is \(\geq 1\) year.

**ETHICS STATEMENT**

Insurance reimbursement claims data used in this study were available for public access. Patient identification numbers had been scrambled to ensure confidentiality. Patient informed consent was not required.

**AUTHOR CONTRIBUTIONS**

S-WL and K-FL contributed to the conception of the article, initiated the draft of the article, revised the article, and contributed equally to the article. C-LL conducted the data analysis and reviewed the article. H-FL participated in the data interpretation and revised the article.

**ACKNOWLEDGMENTS**

This study was supported in part by Taiwan Ministry of Health and Welfare Clinical Trial Center (MOHW106-TDU-B-212-113004), China Medical University Hospital, Academia Sinica Taiwan Biobank Stroke Biosignature Project (BM10601010036), Taiwan Clinical Trial Consortium for Stroke (MOST 106-2321-B-039-005), Tseng-Lien Lin Foundation, Taichung, Taiwan, Taiwan Brain Disease Foundation, Taipei, Taiwan, and Katsuzo and Kiyo Aoshima Memorial Funds, Japan. These funding agencies did not influence the study design, data collection and analysis, decision to publish, or preparation of the manuscript.

**REFERENCES**

American Diabetes Association (2017). Pharmacologic approaches to glycemic treatment. *Diabetes Care* 40, S64–S74. doi: 10.2337/dc17-S011

Baetta, R., and Corsini, A. (2011). Pharmacology of dipeptidyl peptidase-4 inhibitors: similarities and differences. *Drugs* 71, 1441–1467. doi: 10.2165/11591400-000000000-00000

Cavender, M. A., Scirica, B. M., Raz, I., Steg, P. G., Mcguire, D. K., Leiter, L. A., et al. (2016). Cardiovascular outcomes of patients in SAVOR-TIMI 53 by baseline hemoglobin A1c. *Am. J. Med.* 129, 340e1-8. doi: 10.1016/j.amjmed.2015.09.022

Chan, C. Y., Lien, C. H., Lee, M. F., and Huang, C. Y. (2016). Quercetin suppresses cellular migration and invasion in human head and neck squamous cell carcinoma (HNSCC). *Biomedicine* 6, 15. doi: 10.7603/s40681-016-0015-3

Chang, L. C., and Yu, Y. L. (2016). Dietary components as epigenetic-regulating agents against cancer. *Biomedicine* 6, 2. doi: 10.7603/s40681-016-0002-8

Chang, W. S., Liu, L. C., Hsiao, C. L., Su, C. H., Wang, H. C., Ji, H. X., et al. (2016). The contributions of the tissue inhibitor of metalloproteinase-1 genotypes to...
Ministry of Health and Welfare (2017a). *Statistics of Causes of Death*. Available at: http://www.mohw.gov.tw/EN/Ministry/Index.aspx

Ministry of Health and Welfare (2017b). *Taiwan Health and Welfare Report*. Available at: http://www.mohw.gov.tw

Monami, M., Dicembrini, I., Martelli, D., and Mannucci, E. (2011). Safety of dipeptidyl peptidase-4 inhibitors: a meta-analysis of randomized clinical trials. *Curr. Med. Res. Opin.* 27(Suppl. 3), 57–64. doi: 10.1185/03007995.2011.602964

Ooi, H. (2016). Bedside pleuroscopy in Taiwan: a great vision for critically-ill patients and intensivists. *Biomedicine* 6, 13. doi: 10.7603/s40681-016-0013-5

Ou, S. M., Shih, C. J., Chao, P. W., Chu, H., Kuo, S. C., Lee, Y. J., et al. (2015). Effects on clinical outcomes of adding dipeptidyl peptidase-4 inhibitors versus sulfonylureas to metformin therapy in patients with type 2 diabetes mellitus. *Ann. Intern. Med.* 163, 663–672. doi: 10.7326/M15-0308

Scheen, A. J. (2013). Cardiovascular effects of dipeptidyl peptidase-4 inhibitors: from risk factors to clinical outcomes. *Postgrad. Med.* 125, 7–20. doi: 10.3810/pgm.2013.05.2659

Shih, C. J., Chen, H. T., Kuo, S. C., Ou, S. M., and Chen, Y. T. (2016). Cardiovascular outcomes of dipeptidyl peptidase-4 inhibitors in elderly patients with type 2 diabetes: a nationwide study. *J. Am. Med. Dir. Assoc.* 17, 59–64. doi: 10.1016/j.jamda.2015.10.009

Tsai, T. Y., Lin, C. C., Peng, C. Y., Huang, W. H., Su, W. P., Lai, S. W., et al. (2016). The association between biliary tract inflammation and risk of digestive system cancers: a population-based cohort study. *Medicine* 95:e4427. doi: 10.1097/MD.000000000004427

Wen, Y. J., and Yin, M. C. (2017). The anti-inflammatory and anti-glycative effects of rosmarinic acid in the livers of type 1 diabetic mice. *Biomedicine* 7:19. doi: 10.1051/bmdcn/2017070319

Wu, M. H., Lee, T. H., Lee, H. P., Li, T. M., Lee, I. T., Shieh, P. C., et al. (2017). Kuei-Lu-Er-Xian-Jiao extract enhances BMP-2 production in osteoblasts. *Biomedicine* 7:2. doi: 10.1051/bmdcn/2017070302

Yang, J. S., Lu, C. C., Kuo, S. C., Hsu, Y. M., Tsai, S. C., Chen, S. Y., et al. (2017). Autophagy and its link to type II diabetes mellitus. *Biomedicine* 7, 8. doi: 10.1051/bmdcn/2017070201

Yang, M. D., Lin, K. C., Lu, M. C., Jeng, L. B., Hsiao, C. L., Yueh, T. C., et al. (2017). Contribution of matrix metalloproteinases-1 genotypes to gastric cancer susceptibility in Taiwan. *Biomedicine* 7, 10. doi: 10.1051/bmdcn/2017070203

Yu, C. C., Chien, C. T., and Chang, T. C. (2016). M2 macrophage polarization modulates epithelial-mesenchymal transition in cisplatin-induced tubulointerstitial fibrosis. *Biomedicine* 6:5. doi: 10.7603/s40681-016-0005-5

**Conflict of Interest Statement**: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Copyright © 2017 Lai, Liao, Lin and Lin. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) or licensor are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.