Metformin and Risk of Hypertension in Taiwanese Patients With Type 2 Diabetes Mellitus

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Background—Whether metformin use may reduce hypertension risk has not been studied. This study investigated such possibility in patients with type 2 diabetes mellitus.

Methods and Results—Newly diagnosed patients with type 2 diabetes mellitus during 1999–2005 were enrolled from the reimbursement database of the Taiwan’s National Health Insurance and followed to December 31, 2011. Hypertension was defined either by a diagnosis or by a diagnosis plus the use of angiotensin converting enzyme inhibitors/angiotensin receptor blockers and/or calcium channel blockers. Analyses were conducted in a propensity score matched-pair cohort of 4810 ever users and 4810 never users. Cox proportional hazards regression model was used to estimate the hazard ratios. Results showed that when hypertension was defined by a diagnosis, 2261 never users and 1908 ever users developed hypertension. The overall hazard ratio was 0.724 (0.681–0.769) and the hazard ratios for the first (<2.0 months), second (2.0–13.0 months) and third (>13.0 months) tertiles of cumulative duration were 0.820 (0.745–0.903), 0.692 (0.634–0.756), and 0.687 (0.630–0.749), respectively. When cumulative duration of metformin therapy was treated as a continuous variable, the hazard ratio was 0.991 (0.989–0.994) for every 1-month increment of metformin use. When hypertension was defined by a diagnosis plus the use of antihypertensive drugs, the overall hazard ratio was 0.831 (0.771–0.895), the hazard ratios for the respective tertiles were 0.868 (0.769–0.980), 0.852 (0.767–0.946), and 0.787 (0.709–0.874), and the hazard ratio was 0.994 (0.991–0.997) for every 1-month increment of metformin use.

Conclusions—A reduced risk of hypertension is observed in metformin users in a dose-response pattern. (J Am Heart Assoc. 2018;7:e008860. DOI: 10.1161/JAHA.118.008860.)

Key Words: database • diabetes mellitus • hypertension • metformin

Hypertension is a common comorbidity associated with diabetes mellitus. An estimated 54.5% of the Taiwanese patients with diabetes mellitus may have hypertension.1 Hypertension is the most important risk factor of ischemic heart disease2 and is highly predictive for stroke,3 peripheral artery disease4 and non-cancer-related deaths5 in the Taiwanese patients with diabetes mellitus.

The high correlation between diabetes mellitus and hypertension may be because of the common pathophysiology of insulin resistance.6 However, the use of antidiabetic drugs such as insulin7 and sulfonylurea8 may also be responsible for the significant increase of hypertension within a few years after diabetes mellitus diagnosis. Both of these 2 classes of drugs significantly increase insulin levels among users. On the other hand, metformin exerts an insulin sensitizing effect;9 and therefore, may potentially reduce hyperinsulinemia and the risk of hypertension in patients who use the drug.

To the best of our knowledge, no previous epidemiological studies have ever investigated whether long-term use of metformin might reduce the risk of hypertension in patients with type 2 diabetes mellitus. The present population-based study investigated such a possible association in Taiwanese patients.

Materials and Methods

The Taiwan’s National Health Insurance (NHI) is a unique and universal healthcare system that covers >99% of the population. It has been implemented since March 1995, and all in-hospitals and nearly 93% of all medical settings have
Clinical Perspective

What Is New?

• This population-based observational study, using a nationwide administrative database, shows that patients with type 2 diabetes mellitus who were prescribed metformin may have a reduced risk of hypertension in a dose-response pattern, when compared with those who did not receive metformin.

What Are the Clinical Implications?

• Amongst patients with type 2 diabetes mellitus, a routine and an early use of metformin may reduce the incidence of hypertension; and thereby, potentially reduce the cardiovascular risk.
• Findings of this study reinforce the use of metformin, a cheap anti-hyperglycemic agent with a minimal risk of hypoglycemia, as a first-line agent for treatment of those with type 2 diabetes mellitus.

contracts with the Bureau of the NHI. The NHI keeps records of all disease diagnoses, medication prescriptions, and clinical procedures used for reimbursement. Investigators may use the database for academic research if approved after ethics review. The present study was granted an approval number of 99274 for analyses. Because of the local law restriction on the release of individualized data to the public for the protection of privacy, the data and study materials will not be made available to other researchers.

During the study period, the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) was used for disease diagnoses and diabetes mellitus was coded 250.XX. Hypertension was defined either by a diagnosis of hypertension (ICD-9-CM: 401–405) alone or by using a more stringent criterion of combining a diagnosis of hypertension plus the use of angiotensin converting enzyme inhibitors/angiotensin receptor blockers and/or calcium channel blockers.

The database was described in detail in a previously published paper. The present study enrolled a matched cohort following the procedures shown in Figure. At first, 423,949 patients were identified with new-onset diabetes mellitus during 1999–2005 in the outpatient clinics and had received ≥2 prescriptions of antidiabetic drugs. The following patients were then excluded: (1) Ever users of metformin who had received other antidiabetic drugs before metformin was initiated (n=183,837); (2) type 1 diabetes mellitus (n=20,622), (3) missing data (n=420), (4) diagnosis of any cancer before entry or within 6 months of diabetes mellitus diagnosis (n=26,032), these patients were excluded because they might have distorted follow-up time because of shortened lifespan), (5) diagnosis of hypertension before entry or within 6 months of diabetes mellitus diagnosis (n=149,996), (6) use of angiotensin converting enzyme inhibitors/angiotensin receptor blockers before entry (n=61,189), (7) use of calcium channel blockers before entry (n=41,388); (8) aged <25 years at entry (n=45,657), (9) aged >75 years at entry (n=15,577), and (10) follow-up <180 days (n=39,088). As a result, 36,432 ever users and 48,13 never users of metformin were enrolled as the unmatched original cohort. Propensity score was created from all characteristics (collected until the end of follow-up) listed in Table 1 plus the date of entry by logistic regression. A matched-pair cohort (the matched cohort) was then created by matching the propensity score based on the Greedy 8→1-digit match algorithm, as detailed elsewhere.

Potential confounders included the following categories of variables: (1) demographic data: age, sex, occupation, and living region; (2) major comorbidities: dyslipidemia and obesity; (3) diabetes mellitus-related complications: nephropathy, eye diseases, stroke, ischemic heart disease, and peripheral artery disease; (4) antidiabetic drugs: insulin, sulfonylureas, meglitinide, acarbose, rosiglitazone, and pioglitazone; (5) commonly encountered comorbidities: chronic obstructive pulmonary disease (a surrogate for smoking), tobacco abuse, alcohol-related diagnoses, and heart failure; and (6) commonly used medications in patients with diabetes mellitus: statins, fibrates, and aspirin. The classifications of living region and occupation were detailed elsewhere. In brief, the living region was classified as Taipei, Northern, Central, Southern, and Kao-Ping/Eastern. Occupation was classified as class I (civil servants, teachers, employees of governmental or private businesses, professionals, and technicians), class II (people without a specific employer, self-employed people, or seamen), class III (farmers or fishermen), and class IV (low-income families supported by social welfare or veterans). The ICD-9-CM codes for the above diagnoses were: dyslipidemia (272.0–272.4), obesity (278), nephropathy (580–589), eye diseases (250.5, diabetes mellitus with ophthalmic manifestations; 362.0, diabetic retinopathy; 369, blindness and low vision; 366.41, diabetic cataract; and 365.44, glaucoma associated with systemic syndromes), stroke (430–438), ischemic heart disease (410–414), peripheral artery disease (250.7, 785.4, 443.81, and 440–448), chronic obstructive pulmonary disease (490–496), tobacco abuse (305.1, 649.0, and 989.84), alcohol-related diagnoses, (291, 303, 535.3, 571.0–571.3, and 980.0) and heart failure (398.91, 402.11, 402.91, 404.11, 404.13, 404.91, 404.93, and 428).

The differences between never and ever users of metformin were compared by Student t test for age and by Chi-square test for other variables. Standardized difference for each covariate was calculated as a test of balance diagnostic proposed by Austin and Stuart, who recommended a cutoff value >10% to indicate potential confounding from the variable.
Cumulative duration of metformin therapy (in months) was calculated as time before the start of follow-up which was set on January 1, 2006. Incidence density of hypertension was calculated for never users, ever users, and the tertiles of cumulative duration of metformin therapy. The numerator of the incidence was the case number of new-onset hypertension observed during follow-up. The denominator in person-years was the follow-up duration, which ended on December 31, 2011, at the time of new-onset hypertension, or on the date of death or the last reimbursement record.

Hazard ratios and their 95% confidence intervals for ever user and for each tertile of cumulative duration in comparison to never users were estimated by Cox proportional hazards regression model. Additionally, hazard ratios for cumulative duration of metformin therapy being treated as a continuous variable were estimated. All models were adjusted for the covariates shown in Table 1.

Analyses were conducted using SAS statistical software, version 9.3 (SAS Institute, Cary, NC). P<0.05 was considered statistically significant.

Results

Table 1 shows the characteristics between never and ever users of metformin. Age, sex, and most variables were not different significantly, except for insulin and sulfonylureas. None of the variables had a value of standardized difference >10%.

Table 2 shows the incidence of hypertension and the hazard ratios by metformin exposure. The overall hazard ratios indicated a significantly lower risk of hypertension in metformin users in models using either definition of hypertension. Analyses by categorizing cumulative duration of

Figure. Flowchart showing the procedures in creating the unmatched original cohort and a cohort of 1:1 matched-pairs of metformin ever and never users from the reimbursement database of the National Health Insurance. ACEI indicates angiotensin converting enzyme inhibitors; ARB, angiotensin receptor blockers; CCB, calcium channel blockers.
Table 1. Characteristics in Never and Ever Users of Metformin

| Variable                                | Never Users (n=4810) | Ever Users (n=4810) | P Value | Standardized Difference |
|-----------------------------------------|----------------------|---------------------|---------|-------------------------|
| **Demographic data**                   |                      |                     |         |                         |
| Age, y*                                 | 56.99 10.39          | 56.90 9.96          | 0.6804  | -0.39                   |
| Sex (men)                               | 3042 63.24           | 3048 63.37          | 0.8990  | 0.03                    |
| Occupation                              |                      |                     |         |                         |
| I                                       | 2072 43.08           | 2086 43.37          | 0.8604  |                         |
| II                                      | 1047 21.77           | 1032 21.46          | -0.67   |                         |
| III                                     | 854 17.75            | 877 18.23           | 1.59    |                         |
| IV                                      | 837 17.40            | 815 16.94           | -1.53   |                         |
| Living region                           |                      |                     |         |                         |
| Taipei                                  | 1446 30.06           | 1481 30.79          | 0.1152  |                         |
| Northern                                | 493 10.25            | 433 9.00            | -4.57   |                         |
| Central                                 | 813 16.90            | 830 17.26           | 1.13    |                         |
| Southern                                | 937 19.48            | 886 18.42           | -2.63   |                         |
| Kao-Ping and Eastern                    | 1121 23.31           | 1180 24.53          | 3.27    |                         |
| **Major comorbidities**                |                      |                     |         |                         |
| Dyslipidemia                            | 3034 63.08           | 3024 62.87          | 0.8328  | -0.09                   |
| Obesity                                 | 80 1.66              | 76 1.58             | 0.7468  | -0.84                   |
| **Diabetes mellitus-related complications** |                    |                     |         |                         |
| Nephropathy                             | 820 17.05            | 779 16.20           | 0.2615  | -2.55                   |
| Eye diseases                            | 644 13.39            | 628 13.06           | 0.6301  | -1.56                   |
| Stroke                                  | 586 12.18            | 529 11.00           | 0.0695  | -3.95                   |
| Ischemic heart disease                  | 841 17.48            | 806 16.76           | 0.3435  | -1.96                   |
| Peripheral artery disease               | 621 12.91            | 605 12.58           | 0.6247  | -0.98                   |
| **Antidiabetic drugs**                  |                      |                     |         |                         |
| Insulin                                 | 448 9.31             | 375 7.80            | 0.0078  | -7.49                   |
| Sulfonylureas                           | 3756 78.09           | 3883 80.73          | 0.0014  | 6.82                    |
| Meglitinide                             | 275 5.72             | 280 5.82            | 0.8269  | 0.32                    |
| Acarbose                                | 429 8.92             | 444 9.23            | 0.5944  | -0.41                   |
| Rosiglitazone                           | 97 2.02              | 95 1.98             | 0.8841  | -0.55                   |
| Pioglitazone                            | 66 1.37              | 59 1.23             | 0.5286  | -0.41                   |
| **Commonly encountered comorbidities**  |                      |                     |         |                         |
| Chronic obstructive pulmonary disease   | 1646 34.22           | 1705 35.45          | 0.2067  | 2.43                    |
| Tobacco abuse                           | 133 2.77             | 128 2.66            | 0.7537  | -0.68                   |
| Alcohol-related diagnoses               | 450 9.36             | 417 8.67            | 0.2400  | -2.93                   |
| Heart failure                           | 153 3.18             | 130 2.70            | 0.1652  | -3.13                   |
| **Commonly used medications in diabetes mellitus patients** |        |                     |         |                         |
| Statins                                 | 1726 35.88           | 1718 35.72          | 0.8649  | -0.27                   |
| Fibrates                                | 1069 22.22           | 1057 21.98          | 0.7681  | -0.32                   |
| Aspirin                                 | 1230 25.57           | 1187 24.68          | 0.3121  | -2.05                   |

Refer to "Materials and Methods" for the classification of occupation.

*Age is expressed as mean and standard deviation.
metformin therapy into tertiles and by treating it as a continuous variable supported a reduced risk of hypertension associated with metformin therapy in a dose-response pattern.

Discussion
This is the first population-based observational study showing a preventive effect of metformin on the development of hypertension in a dose-response pattern in patients with type 2 diabetes mellitus (Table 2).

The mechanisms of a reduced risk of hypertension associated with metformin use requires further investigation, but some biological actions of metformin could explain such a beneficial effect. Metformin protects the cardiovascular system from oxidative stress and inflammation via 5′-adenosine monophosphate-activated protein kinase-dependent- and -independent pathways and clinical trials supported an antiatherogenic effect of metformin. Metformin inhibits the formation of advanced glycation end products, attenuates glucose-induced endothelial dysfunction, and increases nitric oxide production and improves angiogenic functions.

The methodological problems commonly seen in pharmacoepidemiological studies such as selection bias, prevalent user bias, immortal time bias, and confounding by indication have been carefully addressed in the study. The use of a nationwide database that covers >99% of the population avoided selection bias and prevalent user bias was prevented by enrolling new-onset diabetes mellitus patients and new users of metformin.

Immortal time is the follow-up period during which the outcome cannot happen. This bias can be introduced when

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### Table 2. Incidence Rates of Hypertension and Hazard Ratios by Metformin Exposure in a Propensity Score Matched-Pair Cohort of Ever and Never Users of Metformin

| Definition of Hypertension/Metformin Use | n   | N   | Person-Year | Incidence Rate (Per 100 000 Person-Years) | HR   | 95% CI        | P Value |
|-----------------------------------------|-----|-----|-------------|------------------------------------------|------|---------------|---------|
| Diagnosis of hypertension               |     |     |             |                                          |      |               |         |
| Never users                             | 2261| 4810| 16 609.42   | 13 612.76                                | 1.000|               |         |
| Ever users                              | 1908| 4810| 19 022.82   | 10 030.06                                | 0.724| (0.681–0.769) | <0.0001 |
| Tertiles of cumulative duration of metformin therapy, months |     |     |             |                                          |      |               |         |
| Never users                             | 2261| 4810| 16 609.42   | 13 612.76                                | 1.000|               |         |
| <2.0                                    | 568 | 1548| 5242.93     | 10 833.63                                | 0.820| (0.745–0.903) | <0.0001 |
| 2.0 to 13.0                             | 641 | 1614| 6611.52     | 9695.20                                  | 0.692| (0.634–0.756) | <0.0001 |
| >13.0                                   | 699 | 1648| 7168.37     | 9751.17                                  | 0.687| (0.630–0.749) | <0.0001 |
| Cumulative duration of metformin therapy treated as a continuous variable |     |     |             |                                          |      |               |         |
| For every 1-month increment             |     |     |             |                                          | 0.991| (0.989–0.994) | <0.0001 |
| Diagnosis of hypertension+use of ACEI/ARB and/or CCB |     |     |             |                                          |      |               |         |
| Never users                             | 1465| 4747| 18 347.06   | 7984.93                                  | 1.000|               |         |
| Ever users                              | 1311| 4747| 19 636.79   | 6676.24                                  | 0.831| (0.771–0.895) | <0.0001 |
| Tertiles of cumulative duration of metformin therapy, months |     |     |             |                                          |      |               |         |
| Never users                             | 1465| 4747| 18 347.06   | 7984.93                                  | 1.000|               |         |
| <1.9                                    | 358 | 1549| 5522.23     | 6482.88                                  | 0.868| (0.769–0.980) | <0.0001 |
| 1.9 to 13.1                             | 462 | 1584| 6712.06     | 6883.13                                  | 0.852| (0.767–0.946) | <0.0001 |
| >13.1                                   | 491 | 1614| 7402.49     | 6632.90                                  | 0.787| (0.709–0.874) | <0.0001 |
| Cumulative duration of metformin therapy treated as a continuous variable |     |     |             |                                          | 0.994| (0.991–0.997) | 0.0003  |

n: incident case number of hypertension, N: case number followed. ACEI indicates angiotensin converting enzyme inhibitors; ARB, angiotensin receptor blockers; CCB, calcium channel blockers; CI, confidence interval; HR, hazard ratio (adjusted for all covariates in Table 1).
either the treatment status or the follow-up time is inappropriately assigned. In the present study, only patients who had received ≥2 prescriptions of antidiabetic drugs were enrolled (Figure). This would have excluded most cases with indefinite diagnosis of diabetes mellitus. Treatment status was also unlikely misclassified because all prescription information was available during the long follow-up period. The immortal time from diabetes mellitus diagnosis to the start of antidiabetic drugs and in those with a short follow-up period of <180 days was not included in the person-years calculation in the study. It is worth mentioning that the immortal time during the waiting period between drug prescription and dispense when patients are discharged from the hospital (as pointed out by Lévesque et al\textsuperscript{22}) would not happen in Taiwan because the patients can get all discharge medications directly from the hospital when they are discharged.

Confounding by indication was much reduced by the use of the propensity score-matched cohort (Table 2). Because none of the covariates had a value of standardized difference >10% (Table 1), the potential risk of residual confounding was minimal.

The present study has some additional merits. Information bias related to self-reporting could be reduced by using the medical records. Detection bias because of different socioeconomic status can be a problem in some countries, but this was less likely in Taiwan. In general, the drug cost-sharing in the NHI is low and many expenses can be waived for veterans, patients with low-income, or when the patients receive prescription refills for chronic disease.

The study limitations may include a lack of measurement data of confounders like biochemistry, anthropometric factors, cigarette smoking, alcohol drinking, lifestyle, physical activity, nutritional status, salt intake, family history, and genetic parameters. Furthermore, we did not have the data of advanced glycation end products for analyses.

In summary, this population-based retrospective cohort study supports that metformin may have a preventive effect on the development of hypertension in patients with type 2 diabetes mellitus. However, additional confirmation is necessary. Because metformin is cheap and safe and would not cause hypoglycemia when used as monotherapy, its preventive role in hypertension is worthy of more extensive investigation.

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Author Contributions

Tseng researched data and wrote the article. The guarantor of this paper is Tseng.

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Disclosures

None.

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