ORIGINAL RESEARCH

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

Chin-Hsiao Tseng, MD, PhD

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 disease[2] and is highly predictive for stroke,[3] peripheral artery disease[4] and non-cancer-related deaths[5] 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 insulin[7] and sulfonylurea[8] 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

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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.[10] 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=2062), (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=6189), (7) use of calcium channel blockers before entry (n=4138); (8) aged <25 years at entry (n=4565), (9) aged >75 years at entry (n=1557), and (10) follow-up <180 days (n=3908). As a result, 36 432 ever users and 4813 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.[11,12]

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.[13] 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.[14]

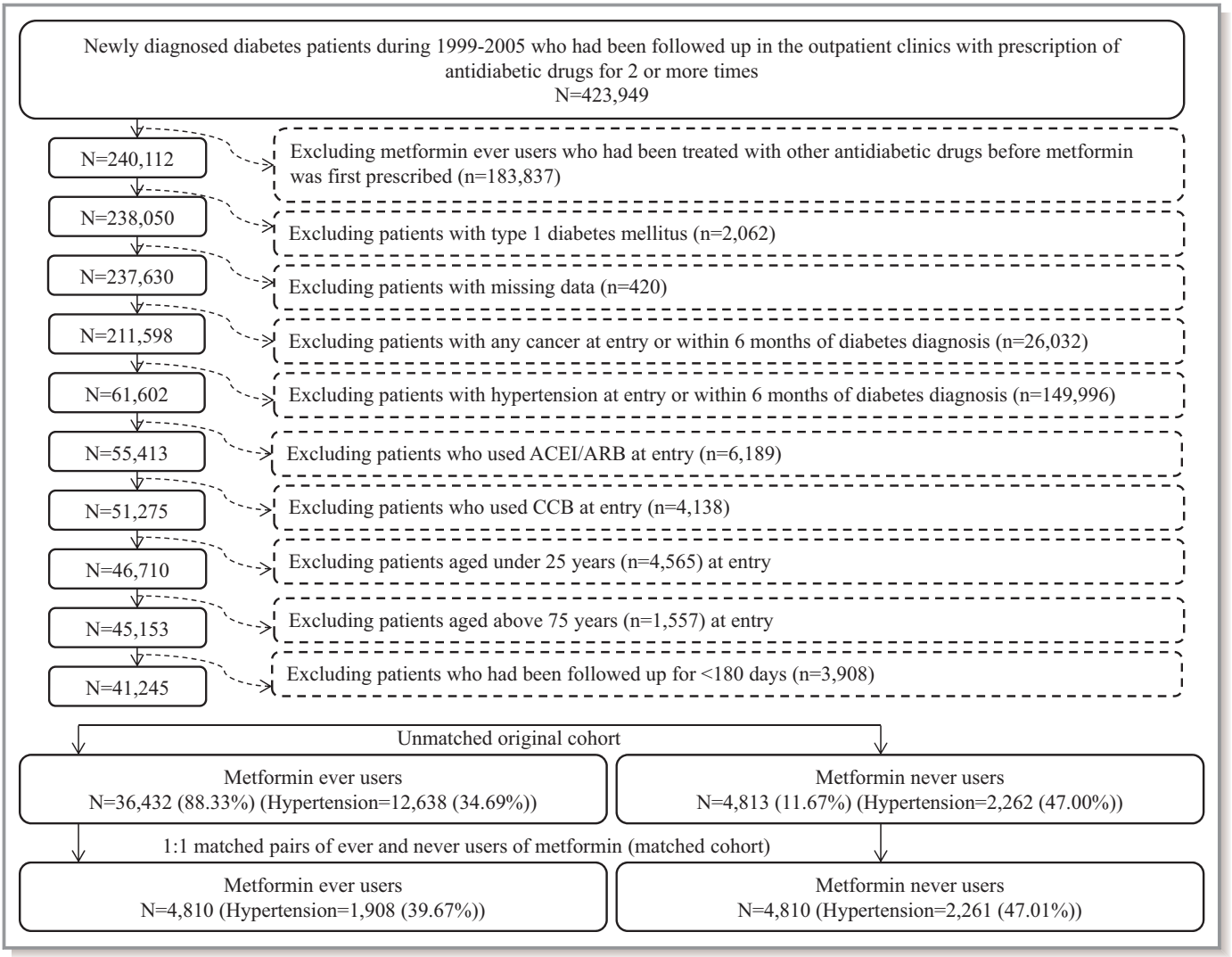

Figure. Flowchart showing the procedures in creating the unmatched original cohort and a cohort of 1:1 matched-pairs of metformin ever and never users from the reimbursement database of the National Health Insurance. ACEI indicates angiotensin converting enzyme inhibitors; ARB, angiotensin receptor blockers;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

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

Table 1. Characteristics in Never and Ever Users of Metformin

Variable	Never Users (n=4810)		Ever Users (n=4810)		*P* Value	Standardized Difference
	n	%	n	%		
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.

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							
For every 1-month increment					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).

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 prevalence of insulin use was slightly higher in never users of metformin (Table 1) and our previous epidemiological study suggested an increased risk of hypertension after prolonged use of insulin.[7] However, the standardized difference did not suggest a potential confounding from insulin use (Table 1). Because sulfonylureas may also potentially increase the risk of hypertension,[8] the higher prevalence of sulfonylureas use in ever users of metformin (Table 1) might only underestimate the beneficial effect of metformin if this would cause residual confounding.

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[15,16] and clinical trials supported an antiatherogenic effect of metformin.[17] Metformin inhibits the formation of advanced glycation end products,[18,19] attenuates glucose-induced endothelial dysfunction,[20] and increases nitric oxide production and improves angiogenic functions.[21]

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.[22] This bias can be introduced when

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[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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