ORIGINAL RESEARCH

Metformin Use Is Associated With a Lower Risk of Hospitalization for Heart Failure in Patients With Type 2 Diabetes Mellitus: a Retrospective Cohort Analysis

Chin-Hsiao Tseng, MD, PhD

***Background*—**A beneficial effect of metformin on heart failure requires confirmation.

***Methods and Results*—**Patients with new-onset type 2 diabetes mellitus during 1999 to 2005 were enrolled from Taiwan's National Health Insurance database and followed up from January 1, 2006, until December 31, 2011. Main analyses were conducted in an unmatched cohort (172 542 metformin ever users and 43 744 never users) and a propensity score matched-pair cohort (matched cohort I, 41 714 ever users and 41 714 never users). Hazard ratios were estimated by Cox hazard regression incorporated with the inverse probability of treatment weighting using the propensity score in the unmatched cohort and by naïve method in the matched cohort I. Results showed that the respective incidence rates of heart failure hospitalization in ever users and never users were 304.25 and 864.31 per 100 000 person-years in the unmatched cohort (hazard ratio, 0.350; 95% CI, 0.329–0.373) and were 469.66 and 817.01 per 100 000 person-years in the matched cohort I (hazard ratio, 0.571; 95% CI, 0.526–0.620). A dose-response pattern was consistently observed while estimating hazard ratios for the tertiles of cumulative duration of metformin therapy. Findings were supported by another propensity score–matched cohort created after excluding 10 potential instrumental variables in the estimation of propensity score (matched cohort II). An approximately 40% lower risk was consistently observed among ever users in different models derived from the matched cohorts I and II, but models from the matched cohort II were less subject to model misspecification.

***Conclusions*—**Metformin use is associated with a lower risk of heart failure hospitalization. **(*J Am Heart Assoc*. 2019;8: e011640. DOI: 10.1161/JAHA.118.011640.)**

Key Words: diabetes mellitus • heart failure • hospitalization • metformin • Taiwan

Heart failure (HF) is a common and serious clinical entity that has always been neglected. According to epidemiological studies using the reimbursement database of the National Health Insurance (NHI) in Taiwan, the annual incidence of hospitalization for HF (HHF) in 2005 was 88 and 2181 per 100 000 population in younger (20–64 years old) and elderly (≥65 years old) people, respectively.[1,2] Age and male sex are major risk factors, and diabetes mellitus, hypertension, chronic obstructive pulmonary disease, nephropathy, ischemic heart disease, and peripheral arterial disease are common comorbidities seen in patients with HF.[2] The mean length of stay for the first episode of HHF was 15.8 days, and the in-hospital mortality was 3.9% in Taiwan.[2]

Metformin, now a first-line oral antidiabetic drug recommended for the treatment of type 2 diabetes mellitus, exerts an insulin-sensitizing effect.[3] Because of a potential risk of fatal lactic acidosis, metformin has long been underprescribed, especially in patients with HF.[4] This condition has much improved after recent epidemiological studies showing that the risk of lactic acidosis associated with metformin use is not greater than with other antidiabetic drugs[5] and that metformin use in patients with diabetes mellitus and HF does not necessarily increase the risk of lactic acidosis.[6]

To the best of our knowledge, no previous epidemiological studies in either Asian or non-Asian populations have ever investigated whether metformin might reduce the risk of HF in patients with type 2 diabetes mellitus. The present

From the Department of Internal Medicine, National Taiwan University College of Medicine, Taipei, Taiwan; Division of Endocrinology and Metabolism, Department of Internal Medicine, National Taiwan University Hospital, Taipei, Taiwan; and Division of Environmental Health and Occupational Medicine, National Health Research Institutes, Zhunan, Taiwan.

Correspondence to: Chin-Hsiao Tseng, MD, PhD, Department of Internal Medicine, National Taiwan University Hospital, No. 7 Chung-Shan South Rd, Taipei (100), Taiwan. E-mail: ccktsh@ms6.hinet.net

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Clinical Perspective

What Is New?

- This population-based retrospective cohort study, using Taiwan's nationwide administrative database, shows that metformin use in patients with type 2 diabetes mellitus is associated with a lower risk of hospitalization for heart failure in a dose-response pattern, when compared with patients who have never been treated with metformin.

What Are the Clinical Implications?

- An early and continuous use of metformin in patients with type 2 diabetes mellitus may provide a protection against heart failure.
- Metformin should always be considered as a first-line treatment for type 2 diabetes mellitus because it is an inexpensive drug with minimal risk of hypoglycemia and shows beneficial effects on cardiovascular disease, including heart failure.

population-based retrospective cohort study investigated such a possible effect by comparing the risk of HHF between ever users and never users of metformin in Taiwanese patients.

Materials and Methods

Study Population

Taiwan's NHI is a unique and universal healthcare system covering >99% of the population. It has been implemented since March 1995, and all hospitals have contracts with the Bureau of the NHI. The Bureau of the NHI keeps records of all disease diagnoses, medication prescriptions, and clinical procedures used for reimbursement purposes. Investigators may use the database for academic research if approved after an ethics review. The present study was granted an approval number 99 274 by the National Health Research Institutes. According to local law, public availability of the individualized data was not permitted and informed consent was not required for the use of the deidentified database.

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. HHF was defined by a primary diagnosis of HF during an admission to a hospital (*ICD-9-CM* codes 398.91, 402.11, 402.91, 404.11, 404.13, 404.91, 404.93, and 428).

The database was described in detail in a previously published article.[7] The present study first enrolled an unmatched original cohort and a propensity score (PS)–matched cohort (the matched cohort I) for main analyses after the procedures shown in the Figure. At first, 423 949 patients who had new-onset diabetes mellitus during 1999 to 2005 in the outpatient clinics and had received ≥2 prescriptions of antidiabetic drugs were identified. 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) patients with type 1 diabetes mellitus (n=2062), (3) patients with missing data (n=424), (4) patients with a diagnosis of HF at outpatient clinics or during hospitalization before entry or within 6 months of diabetes mellitus diagnosis (n=4444), and (5) patients with follow-up <180 days (n=16 896). As a result, 172 542 ever users and 43 744 never users of metformin were identified as the unmatched original cohort. PS was created from all characteristics listed in Table 1 plus the date of entry by logistic regression. A matched-pairs cohort of 41 714 ever users and 41 714 never users (the matched cohort I) was then created by matching the PS based on the Greedy 8→1 digit match algorithm, as detailed elsewhere.[8,9]

Data Collection

Potential confounders included the following categories of variables: (1) demographic data: age, sex, occupation, and living region; (2) major comorbidities: hypertension, dyslipidemia, and obesity; (3) diabetes mellitus–related complications: nephropathy, eye diseases, stroke, ischemic heart disease, and peripheral arterial disease; (4) antidiabetic drugs: insulin, sulfonylurea, meglitinide, acarbose, rosiglitazone, and pioglitazone; (5) commonly encountered comorbidities: chronic obstructive pulmonary disease (a surrogate for smoking), tobacco abuse, alcohol-related diagnoses, hepatitis B virus infection, hepatitis C virus infection, cirrhosis of liver without mention of alcohol, other chronic nonalcoholic liver disease, and cancer; and (6) commonly used medications in patients with diabetes mellitus: angiotensin-converting enzyme inhibitor/angiotensin receptor blocker, calcium channel blocker, statin, fibrate, and aspirin. The classifications of living region and occupation were detailed elsewhere.[10] 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 sea people), class III (farmers or fisher people), and class IV (low-income families supported by social welfare or veterans). The *ICD-9-CM* codes for the above diagnoses were as follows: hypertension (codes 401–405), dyslipidemia (codes 272.0–272.4), obesity (code 278), nephropathy (codes 580–589), eye diseases (coded 250.5 [diabetes mellitus with ophthalmic manifestations], 362.0 [diabetic retinopathy], 369 [blindness and low vision], 366.41

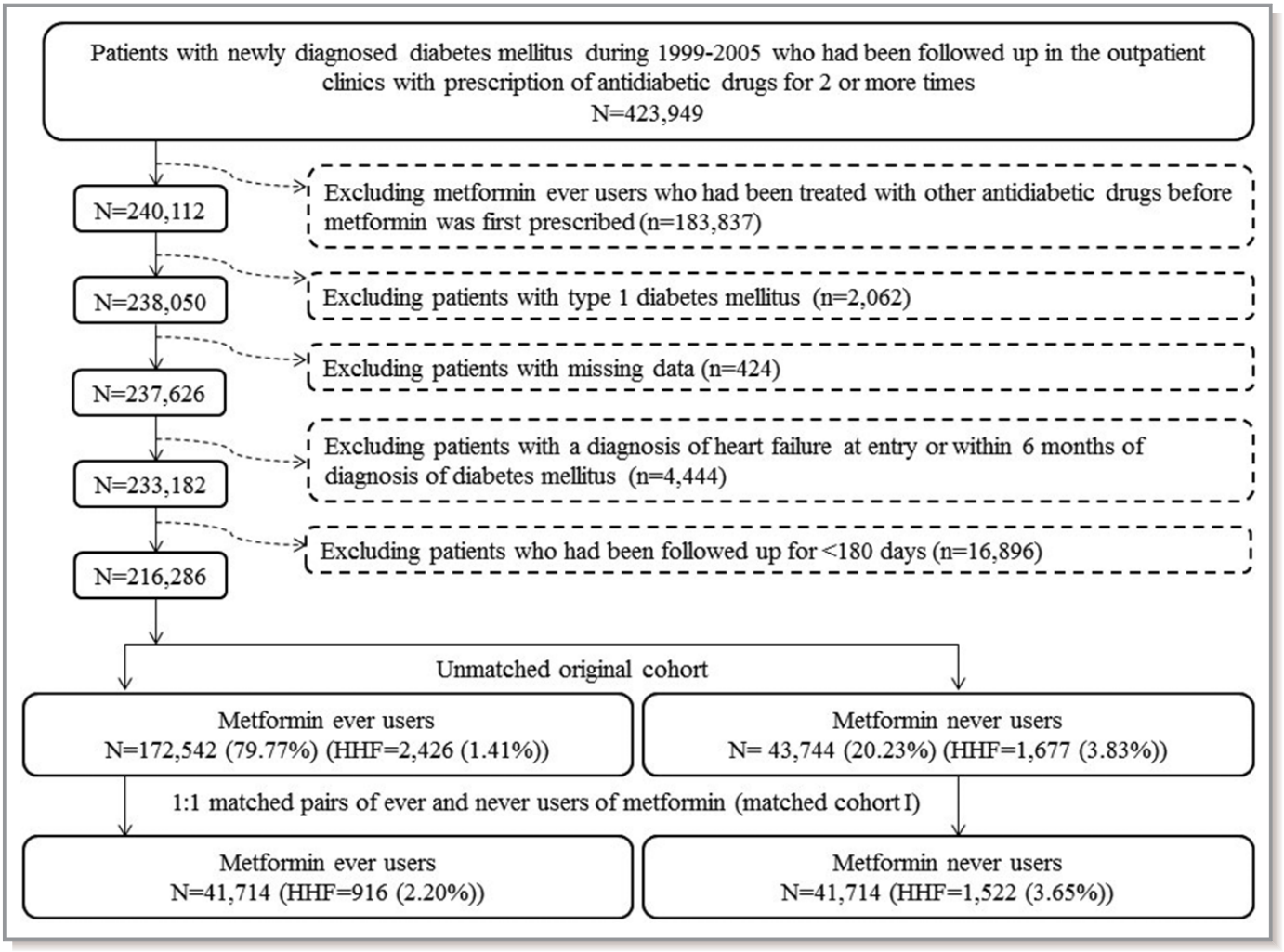

Figure. Flowchart showing the procedures in creating a cohort of 1:1 matched pairs of metformin ever and never users (matched cohort I) from the reimbursement database of the National Health Insurance. HHF indicates hospitalization for heart failure.

[diabetic cataract], and 365.44 [glaucoma associated with systemic syndromes]), stroke (codes 430–438), ischemic heart disease (codes 410–414), peripheral arterial disease (codes 250.7, 785.4, 443.81, and 440–448), chronic obstructive pulmonary disease (codes 490–496), tobacco abuse (codes 305.1, 649.0, and 989.84), alcohol-related diagnoses (codes 291, 303, 535.3, 571.0–571.3, and 980.0), hepatitis B virus infection (codes 070.22, 070.23, 070.32, 070.33, and V02.61), hepatitis C virus infection (codes 070.41, 070.44, 070.51, 070.54, and V02.62), cirrhosis of liver without mention of alcohol (code 571.5), other chronic nonalcoholic liver disease (code 571.8), and cancer (codes 140–208).

Statistical Analyses

Several principles have been recommended for the selection of variables in the estimation of PS to reduce bias.[11,12] These include an inclusion of all variables associated with the outcome irrespective of their association with the treatment and the exclusion of potential instrumental variables that are strongly related to the treatment but not to the outcome.[11,12] Therefore, Pearson correlation coefficients between HHF, metformin use, and all the covariates were first calculated from the unmatched cohort and a new set of PS was created by including variables correlated with HHF (regardless of their correlations with metformin use) and excluding variables correlated with metformin use but not with HHF in the estimation of PS. A new matched cohort (the matched cohort II), based on this new set of PSs, was then created by applying the Greedy 8→1 digit match algorithm.[8,9]

Analyses were conducted in the unmatched original cohort, matched cohort I, and matched cohort II. Results derived from different cohorts allowed the examination of the consistency of the findings and to check model misspecification in models created from the different cohorts.

Baseline characteristics between never and ever users of metformin were compared by Student *t* test for age as a continuous variable and by χ^2 test for other variables. Balance for

Table 1. Baseline Characteristics in Never and Ever Users of Metformin in the Unmatched Cohort

Variable	Never Users (n=43 744)		Ever Users (n=172 542)		*P* Value	Standardized Difference
	No.	%	No.	%		
Demographic data						
Age, y*	65.81	12.58	59.17	11.94	<0.0001	−64.76
Sex (men)	21 915	50.10	92 374	53.54	<0.0001	7.19
Occupation						
I	14 507	33.16	65 577	38.01	<0.0001	
II	7378	16.87	36 985	21.44		14.08
III	11 952	27.32	38 283	22.19		−13.08
IV	9907	22.65	31 697	18.37		−12.86
Living region						
Taipei	14 109	32.25	54 858	31.79	<0.0001	
Northern	5165	11.81	19 703	11.42		−1.43
Central	7763	17.75	31 266	18.12		0.25
Southern	8185	18.71	31 266	18.12		−4.64
Kao-Ping and Eastern	8522	19.48	37 538	21.76		7.11
Major comorbidities						
Hypertension	37 066	84.73	120 706	69.96	<0.0001	−39.20
Dyslipidemia	27 671	63.26	117 150	67.90	<0.0001	12.51
Obesity	1221	2.79	5432	3.15	<0.0001	2.26
Diabetes mellitus–related complications						
Nephropathy	12 429	28.41	28 875	16.74	<0.0001	−36.94
Eye diseases	4484	10.25	27 479	15.93	<0.0001	19.19
Stroke	15 479	35.39	37 061	21.48	<0.0001	−37.85
Ischemic heart disease	24 668	56.39	59 126	34.27	<0.0001	−52.46
Peripheral arterial disease	9413	21.52	29 750	17.24	<0.0001	−12.95
Antidiabetic drugs						
Insulin	3098	7.08	4006	2.32	<0.0001	−29.06
Sulfonylurea	33 236	75.98	123 823	71.76	<0.0001	2.49
Meglitinide	3612	8.26	6922	4.01	<0.0001	−21.85
Acarbose	4604	10.52	9276	5.38	<0.0001	−18.65
Rosiglitazone	1401	3.20	8318	4.82	<0.0001	10.43
Pioglitazone	970	2.22	4469	2.59	<0.0001	4.85
Commonly encountered comorbidities						
Chronic obstructive pulmonary disease	23 829	54.47	68 568	39.74	<0.0001	−36.45
Tobacco abuse	648	1.48	3431	1.99	<0.0001	4.52
Alcohol-related diagnoses	2300	5.26	9191	5.33	0.5658	0.64
Hepatitis B virus infection	794	1.82	2918	1.69	0.0747	−0.86
Hepatitis C virus infection	2110	4.82	6328	3.67	<0.0001	−6.46
Cirrhosis of liver without mention of alcohol	2655	6.07	6702	3.88	<0.0001	−12.18
Other chronic nonalcoholic liver disease	3950	9.03	14 731	8.54	0.0011	−1.92
Cancer	6516	14.90	16 989	9.85	<0.0001	−19.33

Continued

Table 1. Continued

Variable	Never Users (n=43 744)		Ever Users (n=172 542)		*P* Value	Standardized Difference
	No.	%	No.	%		
Commonly used medications in patients with diabetes mellitus						
Angiotensin-converting enzyme inhibitor/angiotensin receptor blocker	31 993	73.14	99 414	57.62	<0.0001	−36.78
Calcium channel blocker	30 774	70.35	86 997	50.42	<0.0001	−45.82
Statin	18 716	42.79	76 395	44.28	<0.0001	4.88
Fibrate	13 574	31.03	55 482	32.16	<0.0001	3.76
Aspirin	27 349	62.52	81 632	47.31	<0.0001	−35.66

*Age is expressed as mean and SD.

each covariate was evaluated by the calculation of standardized difference, as proposed by Austin and Stuart.[13] Because there is no consensus for the cutoff value of standardized difference to indicate the presence of meaningful confounding, some investigators recommended a cutoff of >10%.[13]

Cumulative duration of metformin therapy in months was calculated, and its tertiles were used for dose-response analyses. All patients should be alive until after January 1, 2006, and follow-up started after this date. Incidence density of HHF 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 HHF observed during follow-up. The denominator in person-years was the follow-up duration, which ended on December 31, 2011; at the time of a new-onset HHF; or on the date of death or the last reimbursement record.

As main analyses, hazard ratios and their 95% CIs for ever users and for each tertile of cumulative duration in comparison to never users were estimated in the unmatched cohort and the matched cohort I. For the unmatched cohort, Cox hazard regression analysis, incorporated with the inverse probability of treatment weighting using the PS (proposed by Austin, who showed that this method reduces the potential confounding from the differences in characteristics[14]), was used to estimate the hazard ratios and their 95% CIs. For the matched cohort I, naïve Cox models were created. Age was treated as a continuous variable in the estimation of PS in these main analyses.

To examine the consistency of the findings, analyses were also conducted with age modified in the estimation of PS in the following 4 conditions: (1) age as a continuous variable with log transformation; (2) age divided into 2 subgroups of <65 and ≥65 years; (3) age divided into 2 subgroups (<65 and ≥65 years) with addition of interaction term of age and chronic obstructive pulmonary disease; and (4) age divided into 2 subgroups (<65 and ≥65 years) with addition of interaction term of age and nephropathy. Both chronic obstructive pulmonary disease and nephropathy have been identified as important risk factors for HHF in our previous study.[2] However, among the patients with HHF, chronic obstructive pulmonary disease was more common in the older subgroup (8.6% versus 21.9%; $P<0.0001$) and nephropathy was more common in the younger subgroup (17.8% versus 11.1%; $P<0.0001$). The above analyses were conducted in both the unmatched cohort and the matched cohort I to examine the consistency of the findings before and after matching for PS.

Additional models for the unmatched cohort, the matched cohort I, and the matched cohort II were created to examine whether models adjusted for all covariates, as done in a traditional Cox regression or Cox models adjusted for PS (as either a continuous variable or a categorical variable divided into quintiles) would be less subject to model misspecification. In these models, age was either treated as a continuous variable or modified in 1 of the 4 conditions, as mentioned above. The Ramsey Regression Specification Error Test was conducted, and $P>0.05$ indicated that there would be no functional form misspecification.[15]

Because Austin has proposed 3 approaches (ie, naïve Cox model, stratified Cox model, and robust Cox model) to estimate marginal hazard ratios after PS matching,[14] these additional models were created to estimate the hazard ratios comparing ever users versus never users of metformin in the matched cohort I and the matched cohort II. In the estimation of PS, age was either treated as a continuous variable or modified in 1 of the 4 conditions, as mentioned above.

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 baseline characteristics in never and ever users of metformin in the unmatched cohort. It is evident that,

Table 2. Pearson Correlation Coefficients in the Unmatched Cohort

Variable	Hospitalization for Heart Failure	Metformin Use
Metformin use	−0.071****	. . .
Entry date	−0.048****	0.054****
Age	0.092****	−0.216****
Sex	−0.008***	0.028****
Occupation	0.038****	−0.065****
Living region	−0.003	0.011****
Hypertension	0.053****	−0.134****
Dyslipidemia	−0.012****	0.040****
Obesity	−0.006*	0.008***
Nephropathy	0.037****	−0.119****
Eye diseases	0.028****	0.064****
Stroke	0.051****	−0.130****
Ischemic heart disease	0.067****	−0.182****
Peripheral arterial disease	0.036****	−0.045****
Insulin	0.021****	−0.107****
Sulfonylurea	0.008***	−0.038****
Meglitinide	0.007***	−0.079****
Acarbose	0.006**	−0.084****
Rosiglitazone	0.001	0.031****
Pioglitazone	−0.002	0.010****
Chronic obstructive pulmonary disease	0.036****	−0.120****
Tobacco abuse	−0.002	0.015****
Alcohol-related diagnoses	−0.011****	0.001
Hepatitis B virus infection	−0.011****	−0.004
Hepatitis C virus infection	−0.001	−0.024****
Cirrhosis of liver without mention of alcohol	−0.003	−0.043****
Other chronic nonalcoholic liver disease	−0.004	−0.007**
Cancer	0.003	−0.065****
Angiotensin-converting enzyme inhibitor/angiotensin receptor blocker	0.061****	−0.128****
Calcium channel blocker	0.060****	−0.161****
Statin	0.003	0.012****
Fibrate	0.001	0.010****
Aspirin	0.061****	−0.122****

*P<0.05, **P<0.01, ***P<0.001, ****P<0.0001.

except for alcohol-related diagnoses and hepatitis B virus infection, all other baseline characteristics differed significantly between never and ever users of metformin. Values of standardized difference were >10% in 21 comparisons of the 31 covariates, suggesting that never and ever users of metformin in the unmatched cohort were imbalanced in the distribution of baseline characteristics.

The Pearson correlation coefficients between baseline characteristics and HHF and metformin use are shown in Table 2. Ten variables (ie, living region, rosiglitazone, pioglitazone, tobacco abuse, hepatitis C virus infection, cirrhosis of liver without mention of alcohol, other chronic nonalcoholic liver disease, cancer, statin, and fibrate) were identified as potential instrumental variables because they were correlated with metformin use but not with HHF. Therefore, these 10 variables were excluded in the estimation of PS that was used for the creation of the matched cohort II and in the analyses of the matched cohort II when PS was applied.

The baseline characteristics between never and ever users of metformin in the matched cohort I and matched cohort II are shown in Table 3. After matching, only a few baseline characteristics remained significantly different between never and ever users of metformin, but the values of standardized difference were <10% for all covariates, suggesting that never and ever users of metformin in both matched cohorts were well matched and they were balanced in the distribution of baseline characteristics.

Table 4 shows the incidence of HHF and the hazard ratios by metformin exposure in the main analyses. The results consistently supported a lower risk of HHF associated with metformin use in a dose-response pattern. In general, hazard ratios estimated from the unmatched cohort deviated further away from unity compared with the corresponding hazard ratios derived from the matched cohort I. The overall risk reduction estimated from the unmatched cohort was 65%, but was 43% in the matched cohort I. Metformin use for >29.5 months (or approximately 2.5 years) in the second and third tertiles in the matched cohort I showed a significantly reduced risk. Age was treated as a continuous variable in the data shown in Table 4. However, the results were similar when age was modified in the estimation of PS in the following conditions (data not shown): (1) age as a continuous variable with log transformation; (2) age divided into 2 subgroups of <65 and ≥65 years; (3) age divided into 2 subgroups (<65 and ≥65 years) with addition of interaction term of age and chronic obstructive pulmonary disease; and (4) age divided into 2 subgroups (<65 and ≥65 years) with addition of interaction term of age and nephropathy.

The P values of Ramsey Regression Specification Error Test for the various models investigating model misspecification are shown in Table 5. All P<0.0001 in the unmatched cohort for all the corresponding models that considered the 2 sets of covariates (with or without excluding the 10 potential instrumental variables) for adjustment or for estimating PS (data not shown), suggesting functional form misspecification in all analyses in the unmatched cohort. In the matched cohort I, only the models created with age treated as a continuous

Table 3. Baseline Characteristics in Never and Ever Users of Metformin in the Matched Cohort I and the Matched Cohort II

	Matched Cohort I						Matched Cohort II					
	Never Users (n=41 714)		Ever Users (n=41 714)		*P* Value	Standardized Difference	Never Users (n=41 909)		Ever Users (n=41 909)		*P* Value	Standardized Difference
Variable	No.	%	No.	%			No.	%	No.	%		
Demographic data												
Age, y*	65.25	12.46	64.93	11.50	0.0001	−2.32	65.28	12.46	64.96	11.50	<0.0001	−2.46
Sex (men)	20 917	50.14	21 211	50.85	0.0418	1.37	21 044	50.21	21 319	50.87	0.0575	1.31
Occupation												
I	13 974	33.50	14 196	34.03	0.3594		14 029	33.47	14 032	33.48	0.8407	. . .
II	7205	17.27	7211	17.29		−0.06	7233	17.26	7257	17.32		0.06
III	11 271	27.02	11 102	26.61		−0.81	11 341	27.06	11 237	26.81		−0.47
IV	9264	22.21	9205	22.07		−0.23	9306	22.21	9383	22.39		0.53
Living region												
Taipei	13 398	32.12	13 523	32.42	0.7277	. . .	. . .	. . .	. . .	. . .	. . .	. . .
Northern	4909	11.77	4905	11.76		0.00	. . .	. . .	. . .	. . .	. . .	. . .
Central	7373	17.68	7374	17.68		0.00	. . .	. . .	. . .	. . .	. . .	. . .
Southern	7781	18.65	7633	18.30		−0.85	. . .	. . .	. . .	. . .	. . .	. . .
Kao-Ping and Eastern	8253	19.78	8279	19.85		0.16	. . .	. . .	. . .	. . .	. . .	. . .
Major comorbidities												
Hypertension	35 093	84.13	34 897	83.66	0.0649	−1.05	35 274	84.17	35 200	83.99	0.4848	−0.33
Dyslipidemia	26 677	63.95	26 656	63.90	0.8797	−0.11	26 756	63.84	26 672	63.64	0.5462	−0.39
Obesity	1176	2.82	1174	2.81	0.9666	−0.07	1182	2.82	1159	2.77	0.6297	−0.40
Diabetes mellitus–related complications												
Nephropathy	11 140	26.71	11 034	26.45	0.4061	−0.57	11 240	26.82	11 074	26.42	0.1945	−0.85
Eye diseases	4429	10.62	4352	10.43	0.3850	−0.83	4428	10.57	4404	10.51	0.7872	−0.39
Stroke	14 136	33.89	13 838	33.17	0.0289	−1.29	14 258	34.02	13 981	33.36	0.0429	−1.23
Ischemic heart disease	22 868	54.82	22 790	54.63	0.5875	−0.16	23 031	54.95	22 786	54.37	0.0891	−0.99
Peripheral arterial disease	8807	21.11	8745	20.96	0.5984	−0.36	8875	21.18	8697	20.75	0.1309	−1.04
Antidiabetic drugs												
Insulin	2496	5.98	2454	5.88	0.5382	−1.56	2560	6.11	2497	5.96	0.3608	−1.87
Sulfonylurea	32 195	77.18	32 796	78.62	<0.0001	2.18	32 320	77.12	33 018	78.78	<0.0001	2.95
Meglitinide	3190	7.65	3139	7.53	0.5049	−0.81	3200	7.64	3189	7.61	0.8861	−0.40
Acarbose	4235	10.15	4533	10.87	0.0008	0.84	4221	10.07	4543	10.84	0.0003	0.97
Rosiglitazone	1378	3.30	1474	3.53	0.0674	0.64	. . .	. . .	. . .	. . .	. . .	. . .
Pioglitazone	954	2.29	1078	2.58	0.0054	1.22	. . .	. . .	. . .	. . .	. . .	. . .
Commonly encountered comorbidities												
Chronic obstructive pulmonary disease	22 147	53.09	21 888	52.47	0.0725	−1.09	22 350	53.33	22 097	52.73	0.0800	−1.02
Tobacco abuse	639	1.53	632	1.52	0.8432	−0.16	. . .	. . .	. . .	. . .	. . .	. . .
Alcohol-related diagnoses	2202	5.28	2202	5.28	0.9999	−0.02	2217	5.29	2222	5.30	0.9385	0.01

Continued

Table 3. Continued

Variable	Matched Cohort I						Matched Cohort II					
	Never Users (n=41 714)		Ever Users (n=41 714)		*P* Value	Standardized Difference	Never Users (n=41 909)		Ever Users (n=41 909)		*P* Value	Standardized Difference
	No.	%	No.	%			No.	%	No.	%		
Hepatitis B virus infection	750	1.80	760	1.82	0.7951	0.18	766	1.83	760	1.81	0.8768	−0.08
Hepatitis C virus infection	1966	4.71	1920	4.60	0.4498	−0.55	. . .	. . .	. . .	. . .	. . .	. . .
Cirrhosis of liver without mention of alcohol	2420	5.80	2396	5.74	0.7216	−0.25	. . .	. . .	. . .	. . .	. . .	. . .
Other chronic nonalcoholic liver disease	3744	8.98	3801	9.11	0.4914	0.48	. . .	. . .	. . .	. . .	. . .	. . .
Cancer	5926	14.21	5826	13.97	0.3196	−0.63	. . .	. . .	. . .	. . .	. . .	. . .
Commonly used medications in patients with diabetes mellitus												
ACEI/ARB	30 170	72.33	30 030	71.99	0.2795	−0.60	30 333	72.38	30 207	72.08	0.3312	−0.60
Calcium channel blocker	28 924	69.34	28 722	68.85	0.1302	−0.81	29 084	69.40	28 955	69.09	0.3343	−0.48
Statin	18 040	43.25	18 024	43.21	0.9110	−0.15	. . .	. . .	. . .	. . .	. . .	. . .
Fibrate	13 088	31.38	12 984	31.13	0.4373	−0.54	. . .	. . .	. . .	. . .	. . .	. . .
Aspirin	25 658	61.51	25 478	61.08	0.2007	−0.72	25 827	61.63	25 568	61.01	0.0662	−1.11

ACEI/ARB indicates angiotensin-converting enzyme inhibitor/angiotensin receptor blocker.
*Age is expressed as mean and SD.

variable with log transformation in the PS-adjusted models (PS being treated as a continuous variable or as quintiles) were free from model misspecification. In the matched cohort II, misspecification was noted only in the models that adjusted for all covariates, as done in a traditional Cox regression, and all other models adjusted for PS (either as a continuous variable or as quintiles) were free from model misspecification.

Table 6 compares the hazard ratios derived from models after adjustment for PS being treated as a continuous variable in the matched cohort I and the matched cohort II. All results consistently supported a lower risk of HHF associated with metformin use in a dose-response pattern, especially when the cumulative duration of metformin therapy was >2.5 years in the second and third tertiles. Although the Ramsey Regression Specification Error Test might indicate model misspecification in the matched cohort I, the hazard ratios derived from the matched cohort I were similar to the corresponding hazard ratios derived from the matched cohort II, which were free from model misspecification. The conclusions derived from both matched cohorts were basically the same. Results comparing the hazard ratios after adjustment for PS quintiles as categorical variables were similar and not shown in the table.

Table 7 compares the hazard ratios for ever versus never users of metformin, estimated by the naïve, stratified, and robust models in the matched cohort I and the matched cohort II. All models consistently supported a significantly lower risk of HHF associated with metformin use. While comparing the corresponding hazard ratios in different models between the matched cohort I and the matched cohort II, there seemed to be a trend of further deviation from unity for hazard ratios estimated in the matched cohort I. While comparing the different models in the matched cohort I and matched cohort II, there was a trend of deviation toward unity from the naïve to the stratified and to the robust models. However, the differences were small and did not affect the conclusion of a lower risk associated with metformin use. The data shown in Table 7 were analyzed with age treated as a continuous variable, but the results were similar when age was modified in the estimation of PS (data not shown).

Discussion

Main Findings

This is the first population-based observational study that consistently showed a reduced risk of HHF associated with metformin use in patients with type 2 diabetes mellitus in a dose-response pattern and in different analyses (Tables 4, 6,

Table 4. Incidence of HHF and Hazard Ratios by Metformin Exposure in the Main Analyses

Cohort/Metformin Use	Incident Case No.	Cases Followed Up	Person-Years	Incidence Rate (per 100 000 Person-Years)	Hazard Ratio (95% CI)	*P* Value
Unmatched cohort*						
Never users	1677	43 744	194027.40	864.31	1.000	
Ever users	2426	172 542	797634.04	304.15	0.350 (0.329–0.373)	<0.0001
Tertiles of cumulative duration of metformin therapy, mo						
Never users	1677	43 744	194027.40	864.31	1.000	
<26.2	1032	56 883	192198.69	536.94	0.643 (0.595–0.696)	<0.0001
26.2–57.7	858	56 977	272730.31	314.60	0.361 (0.332–0.392)	<0.0001
>57.7	536	58 682	332705.04	161.10	0.178 (0.162–0.196)	<0.0001
Matched cohort I†						
Never users	1522	41 714	186289.30	817.01	1.000	
Ever users	916	41 714	195033.79	469.66	0.571 (0.526–0.620)	<0.0001
Tertiles of cumulative duration of metformin therapy, mo						
Never users	1522	41 714	186289.30	817.01	1.000	
<29.5	377	13 763	48121.71	783.43	1.010 (0.902–1.131)	0.8624
29.5–61.6	317	13 776	66846.49	474.22	0.575 (0.509–0.649)	<0.0001
>61.6	222	14 175	80065.59	277.27	0.327 (0.284–0.377)	<0.0001

Age was treated as a continuous variable in the estimation of propensity scores in the above table. The results were similar when age was modified in the estimation of propensity scores in the following conditions: (1) age as a continuous variable with log transformation; (2) age divided into 2 subgroups of <65 and ≥65 years; (3) age divided into 2 subgroups (<65 and ≥65 years) with addition of interaction term of age and chronic obstructive pulmonary disease; and (4) age divided into 2 subgroups (<65 and ≥65 years) with addition of interaction term of age and nephropathy. HHF indicates hospitalization for heart failure.

*Hazard ratios in the unmatched cohort were estimated by Cox regression model, incorporated with the inverse probability of treatment weighting using propensity score.

†Hazard ratios in the propensity score–matched cohort I were estimated by the naïve Cox model.

and 7). Such a beneficial effect was especially significant when metformin had been used for more than ≈2.5 years in the second and third tertiles of cumulative duration of metformin therapy in the matched cohorts (Tables 4 and 6).

Additional Consideration of Potential Residual Confounding

The present study followed up patients up to December 31, 2011, and the data might seem to be a little old. However, it is recognized that metformin is one of the oldest classes of oral antidiabetic drugs. It has been consistently used in clinical practice in Taiwan for over half a century and remained a main treatment option even during the time of its withdrawal in the United States. It has been in use since the implementation of the NHI in 1995. A termination of the observation period by December 31, 2011, also rendered the study less influenced by potential confounding effects of incretin-based therapies and sodium glucose cotransporter 2 inhibitors. These newer classes of antidiabetic drugs introduced into Taiwan in recent years may have an impact on HF.

Sodium glucose cotransporter 2 inhibitors were not available in Taiwan throughout the study period, but some patients might have been treated with incretin-based therapies during follow-up. Secondary analyses after excluding patients who happened to receive incretin-based therapies during follow-up did not remarkably change the results of the study (data not shown). To further exclude the potential impact of irregular follow-up, secondary analyses were conducted after excluding patients who had not received regular refills (ie, having 2 consecutive prescriptions spanning >4 months). The results were also similar and would not change the conclusions of the study (data not shown).

Because aging may potentially increase the risk of HF,[1,2] the older age in never users of metformin in the 2 matched cohorts (Table 3) might exert some residual confounding effect. Although the values of standardized difference did not suggest such a possibility (Table 3), subgroup analyses were conducted for further clarification. The reduced risk of HHF associated with metformin use could be similarly demonstrated in patients aged <65 and ≥65 years (data not shown). Also, some covariates might be significantly different between never and ever users of metformin in the matched cohorts (ie, sex, stroke, sulfonylurea use, acarbose use, and pioglitazone use, as shown in Table 3). Additional analyses conducted in subgroups of these covariates consistently supported a

Table 5. Model Misspecification Evaluated by Ramsey RESET in Various Models in the Matched Cohort I and the Matched Cohort II

Cohort/Model	*P* Value of Ramsey RESET for the Models		
	Adjusted for All Covariates	Adjusted for PS as a Continuous Variable	Adjusted for PS Quintiles as Categorical Variables
Matched cohort I			
1. Age as a continuous variable			
Model evaluating ever vs never users of metformin	<0.0001	<0.0001	<0.0001
Model evaluating tertiles of cumulative duration of metformin therapy	<0.0001	<0.0001	<0.0001
2. Age as a continuous variable with log transformation			
Model evaluating ever vs never users of metformin	<0.0001	0.1312	0.2105
Model evaluating tertiles of cumulative duration of metformin therapy	<0.0001	0.1944	0.0847
3. Age divided into 2 subgroups of <65 and ≥65 y			
Model evaluating ever vs never users of metformin	<0.0001	<0.0001	<0.0001
Model evaluating tertiles of cumulative duration of metformin therapy	<0.0001	<0.0001	<0.0001
4. Age divided into 2 subgroups (<65 and ≥65 y) with addition of interaction term of age and chronic obstructive pulmonary disease			
Model evaluating ever vs never users of metformin	<0.0001	<0.0001	<0.0001
Model evaluating tertiles of cumulative duration of metformin therapy	<0.0001	<0.0001	<0.0001
5. Age divided into 2 subgroups (<65 and ≥65 y) with addition of interaction term of age and nephropathy			
Model evaluating ever vs never users of metformin	<0.0001	<0.0001	0.0002
Model evaluating tertiles of cumulative duration of metformin therapy	<0.0001	<0.0001	0.0003
Matched cohort II			
1. Age as a continuous variable			
Model evaluating ever vs never users of metformin	<0.0001	0.1660	0.6892
Model evaluating tertiles of cumulative duration of metformin therapy	<0.0001	0.2000	0.6764
2. Age as a continuous variable with log transformation			
Model evaluating ever vs never users of metformin	<0.0001	0.0928	0.4546
Model evaluating tertiles of cumulative duration of metformin therapy	<0.0001	0.1164	0.3704
3. Age divided into 2 subgroups of <65 and ≥65 y			
Model evaluating ever vs never users of metformin	<0.0001	0.1773	0.6214
Model evaluating tertiles of cumulative duration of metformin therapy	<0.0001	0.1994	0.6295
4. Age divided into 2 subgroups (<65 and ≥65 y) with addition of interaction term of age and chronic obstructive pulmonary disease			
Model evaluating ever vs never users of metformin	<0.0001	0.2123	0.9092
Model evaluating tertiles of cumulative duration of metformin therapy	<0.0001	0.2689	0.6496
5. Age divided into 2 subgroups (<65 and ≥65 y) with addition of interaction term of age and nephropathy			
Model evaluating ever vs never users of metformin	<0.0001	0.1781	0.4888
Model evaluating tertiles of cumulative duration of metformin therapy	<0.0001	0.1989	0.4356

P>0.05 in Ramsey RESET indicates a lack of functional form misspecification in the model. All Ramsey RESET *P*<0.0001 in the unmatched cohort for all the above corresponding models that considered the 2 sets of covariates (with or without excluding the 10 potential instrumental variables) for adjustment or for estimating PS (data not shown). PS indicates propensity score; RESET, Regression Specification Error Test.

Table 6. Comparison of Hazard Ratios Adjusted for Propensity Score as a Continuous Variable in the Matched Cohort I and the Matched Cohort II

	Matched Cohort I			Matched Cohort II		
Model/Metformin Use	Hazard Ratio (95% CI)	*P* Value	Ramsey RESET	Hazard Ratio (95% CI)	*P* Value	Ramsey RESET
1. Age as a continuous variable						
Never users	1.000		<0.0001	1.000		0.1660
Ever users	0.567 (0.523–0.616)	<0.0001		0.579 (0.533–0.628)	<0.0001	
Tertiles of cumulative duration of metformin therapy, mo						
Never users	1.000		<0.0001	1.000		0.2000
I	0.947 (0.844–1.061)	0.3470		0.979 (0.875–1.096)	0.7093	
II	0.571 (0.506–0.644)	<0.0001		0.583 (0.517–0.658)	<0.0001	
III	0.340 (0.295–0.391)	<0.0001		0.338 (0.294–0.389)	<0.0001	
2. Age as a continuous variable with log transformation						
Never users	1.000		0.1312	1.000		0.0928
Ever users	0.574 (0.528–0.623)	<0.0001		0.583 (0.538–0.633)	<0.0001	
Tertiles of cumulative duration of metformin therapy, mo						
Never users	1.000		0.1944	1.000		0.1164
I	0.993 (0.886–1.113)	0.9011		1.014 (0.907–1.135)	0.8059	
II	0.576 (0.510–0.650)	<0.0001		0.588 (0.522–0.663)	<0.0001	
III	0.333 (0.289–0.384)	<0.0001		0.334 (0.290–0.384)	<0.0001	
3. Age divided into 2 subgroups of <65 and ≥65 y						
Never users	1.000		<0.0001	1.000		0.1773
Ever users	0.569 (0.524–0.617)	<0.0001		0.580 (0.535–0.630)	<0.0001	
Tertiles of cumulative duration of metformin therapy, mo						
Never users	1.000		<0.0001	1.000		0.1994
I	0.947 (0.845–1.062)	0.3500		0.982 (0.878–1.099)	0.7531	
II	0.572 (0.507–0.646)	<0.0001		0.586 (0.519–0.660)	<0.0001	
III	0.340 (0.296–0.392)	<0.0001		0.338 (0.294–0.389)	<0.0001	
4. Age divided into 2 subgroups (<65 and ≥65 y) with addition of interaction term of age and chronic obstructive pulmonary disease						
Never users	1.000		<0.0001	1.000		0.2123
Ever users	0.576 (0.531–0.625)	<0.0001		0.586 (0.540–0.636)	<0.0001	
Tertiles of cumulative duration of metformin therapy, mo						
Never users	1.000		0.0001	1.000		0.2689
I	0.974 (0.869–1.091)	0.6438		1.000 (0.894–1.119)	0.9980	
II	0.578 (0.512–0.652)	<0.0001		0.591 (0.525–0.667)	<0.0001	
III	0.340 (0.295–0.392)	<0.0001		0.339 (0.294–0.390)	<0.0001	
5. Age divided into 2 subgroups (<65 and ≥65 y) with addition of interaction term of age and nephropathy						
Never users	1.000		<0.0001	1.000		0.1781
Ever users	0.569 (0.524–0.617)	<0.0001		0.580 (0.535–0.630)	<0.0001	
Tertiles of cumulative duration of metformin therapy, mo						
Never users	1.000		<0.0001	1.000		0.1989
I	0.946 (0.844–1.061)	0.3424		0.981 (0.877–1.098)	0.7449	

Continued

Table 6. Continued

Model/Metformin Use	Matched Cohort I			Matched Cohort II		
	Hazard Ratio (95% CI)	*P* Value	Ramsey RESET	Hazard Ratio (95% CI)	*P* Value	Ramsey RESET
II	0.572 (0.507–0.645)	<0.0001		0.585 (0.519–0.660)	<0.0001	
III	0.341 (0.296–0.392)	<0.0001		0.338 (0.294–0.390)	<0.0001	

Tertile cutoffs are <29.5, 29.5 to 61.6, and >61.6 in the matched cohort I; and are <29.3, 29.3 to 61.3, and >61.3 in the matched cohort II. *P*>0.05 in Ramsey RESET indicates a lack of functional form misspecification in the model. Results for models adjusted for quintiles of propensity score treated as categorical variables are similar and not shown in the table. RESET indicates Regression Specification Error Test.

significantly lower risk of HHF associated with metformin use in all subgroups (data not shown). Therefore, the possibility of residual confounding from the slight, but significant, difference in the distribution of covariates was minimal.

Model Misspecification

In this population-based study, models created from the unmatched cohort were subject to model misspecification (footnote under Table 5). However, this could be corrected by deleting potential instrumental variables in the estimation of PS used for creating the matched cohort (matched cohort II, Table 5) and by using the PS (treated as either a continuous variable or a categorical variable divided into quintiles) as a covariate for adjustment (Table 5). Although model misspecification might exist in the matched cohort I, the results were similar to the analyses conducted in the matched cohort II, which were free from model misspecification (Table 6). Therefore, using a PS-matched cohort with careful exclusion of potential instrumental variables in the estimation of PS and consideration of adjustment for PS in the Cox regression would be a simple way to derive unbiased estimates with models free from misspecification.

Common Methodological Limitations Addressed

Common methodological limitations seen in most pharmacoepidemiological studies, such as selection, prevalent user, immortal time biases, and confounding by indication, have been carefully addressed in the present study.

The use of a nationwide database covering >99% of the population avoided selection bias. Prevalent user bias was avoided by enrolling patients with new-onset diabetes mellitus and new users of metformin. In addition, the impacts of other antidiabetic drugs, which were used before metformin was initiated, were also avoided in the present study by including metformin ever users who received metformin as the first antidiabetic drug (Figure).

Immortal time is the follow-up period during which the outcome cannot happen.[16] Immortal time bias can be introduced when the treatment status or the follow-up time is inappropriately assigned. In the present study, most cases with an indefinite diagnosis of diabetes mellitus had been excluded by enrolling only patients who had received ≥2 prescriptions of antidiabetic drugs (Figure). The treatment status was also unlikely misclassified because the NHI is a universal healthcare system in Taiwan and all prescription information was available during the long follow-up period. Both 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 were not included in the calculation of person-years in the present study. Because patients can get all discharge drugs directly from the hospital at the time of discharge in Taiwan, the immortal time that would result from the waiting period between drug prescription and dispense during discharge (as pointed out by Lévesque et al[16]) would not happen here.

The use of the PS-matched cohorts (Figure, Table 3), the Cox hazard regression analysis incorporated with inverse probability of treatment weighting (Table 4), and the models adjusted for PS (Table 6) were aimed at reducing confounding by indication. Because none of the standardized differences had a value >10% in the matched cohorts (Table 3), a

Table 7. Hazard Ratios for HHF for Ever Users vs Never Users of Metformin, Derived From Different Cox Models in the Matched Cohort I and the Matched Cohort II

Model	Matched Cohort I		Matched Cohort II	
	Hazard Ratio (95% CI)	*P* Value	Hazard Ratio (95% CI)	*P* Value
Naïve	0.571 (0.526–0.620)	<0.0001	0.581 (0.536–0.630)	<0.0001
Stratified	0.579 (0.522–0.642)	<0.0001	0.586 (0.530–0.648)	<0.0001
Robust	0.607 (0.559–0.659)	<0.0001	0.619 (0.570–0.672)	<0.0001

Age was treated as a continuous variable in the estimation of propensity scores in the above table. The results were similar when age was modified in the estimation of propensity scores in the following conditions: (1) age as a continuous variable with log transformation; (2) age divided into 2 subgroups of <65 and ≥65 years; (3) age divided into 2 subgroups (<65 and ≥65 years) with addition of interaction term of age and chronic obstructive pulmonary disease; and (4) age divided into 2 subgroups (<65 and ≥65 years) with addition of interaction term of age and nephropathy. HHF indicates hospitalization for heart failure.

potential risk of residual confounding from the covariates was less likely in the analyses conducted in the matched cohorts. Furthermore, the protective effect of metformin on HHF was consistently supported by additional analyses after considering the nonlinear effect of age and the potential interaction between age and diseases, such as chronic obstructive pulmonary disease and nephropathy (Tables 4, 6, and 7).

Strengths

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

Limitations

Study limitations may include a lack of measurement data of confounders, like biochemical and humoral data, anthropometric factors, cigarette smoking, alcohol drinking, lifestyle, physical activity, nutritional status, salt intake, family history, and genetic parameters. Because this is a real-world observation study using administrative data, it is deemed that confirmation with prospective cohort studies or open-label trials is at least necessary because further randomized placebo-controlled trials with an old drug of metformin may be unrealistic.

Perspectives

There are some clinical implications of these data with regard to the use of an old antidiabetic drug of metformin. Recent clinical studies suggested a possible risk of HF associated with dipeptidyl dipeptidase-4 inhibitors[17,18] and a protective effect on HF for a new class of oral antidiabetic drugs of the sodium glucose cotransporter 2 inhibitors, including empagliflozin,[19] canagliflozine,[20] and dapagliflozin.[21] Whether a combination of metformin with dipeptidyl dipeptidase-4 inhibitors may counteract or alleviate the potential risk of HF or a combination of metformin with a sodium glucose cotransporter 2 inhibitor may magnify the protective effect against HF is worthy of future investigation. The beneficial effect of sodium glucose cotransporter 2 inhibitors on HF is immediate,[19–21] but it takes at least 2.5 years for metformin to show a protection against HF (Tables 4 and 6). Therefore, an early and continuous use of metformin in combination with later add-on of sodium glucose cotransporter 2 inhibitors if more effective glycemic control is required will probably provide a consistent protection against HF in patients with type 2 diabetes mellitus. The antiaging, anticancer, and antiatherogenic effects of metformin,[22] together with the protection against HF, as shown in the present study, provide good rationale for metformin as a first-line therapy for type 2 diabetes mellitus.

Differences From Earlier Studies

Although favorable effects on diabetes mellitus–related cardiovascular outcomes can be observed in metformin users in a landmark trial, its effect on the incidence of HF could not be demonstrated.[23] This could be because of the small numbers of HF cases observed in the trial (11 and 17 cases in the metformin group and the conventional treatment group, respectively). A meta-analysis including 4 clinical trials with small event numbers also suggested a neutral effect of metformin on HF risk (hazard ratio, 1.03; 95% CI,, 0.67–1.59).[24] None of the previous trials evaluated HF as a primary end point, and they might be underpowered.

Some observational studies comparing HF risk among users of different classes of antidiabetic drugs suggested a lower risk of HF associated with metformin use.[25–28] However, these studies, published approximately 10 years ago, were conducted in western countries and they all had limitations that did not allow a conclusion of a preventive effect of metformin on HF. First, none of them fully addressed the methodological limitations commonly encountered in pharmacoepidemiological studies, such as selection, prevalent users, immortal time biases, and confounding by indication. Second, these previous studies compared HF risk among different classes of drugs and, therefore, a lower risk in metformin users in comparison to users of other classes of drugs did not necessarily imply a protective effect of metformin. Third, some studies evaluated patients treated with various classes of antidiabetic drugs as monotherapy, but most patients are treated with multiple drugs for glycemic control in the real world. For example, the study by McAlister et al[25] retrospectively evaluated the risk of HF in patients treated with monotherapy of metformin or sulfonylurea and found that the incidence of HF was 4.4 per 100 treatment-years in the sulfonylurea group and 3.3 per 100 treatment-years in the metformin group. The findings in this study can only be interpreted as a lower incidence of HF among metformin users while compared with sulfonylurea users, but they should not be interpreted as a preventive role of metformin on HF. The study by Casscells et al[26] was limited by cross-sectional design, enrollment of patients from a Military Health System, and aiming at comparing HF risk between rosiglitazone and other antidiabetic drugs. Tzoulaki et al compared the risk of HF among several classes of oral antidiabetic drugs and showed that the risk was significantly higher among sulfonylurea users while compared with

patients receiving metformin monotherapy.[27] This study had potential risk of residual confounding or confounding by indication, and a lower risk in patients with metformin monotherapy should not be interpreted as a preventive effect of metformin. Pantalone et al retrospectively compared HF risk among 4 groups of patients who received initial prescription of monotherapy of rosiglitazone, pioglitazone, metformin, or sulfonylurea at baseline in a single clinic.[28] Although metformin was associated with a lower risk when compared with sulfonylurea (hazard ratio, 0.76; 95% CI, 0.64–0.91), confounding by indication and selection bias resulting from a single clinic could not be excluded. In addition, a lower risk of HF while comparing metformin monotherapy with sulfonylurea therapy at baseline could not be interpreted as a preventive effect of metformin.

Potential Mechanisms

The mechanisms of a reduced risk of HF associated with metformin use require further investigation, but some biological actions of metformin could explain such a beneficial effect. Metformin inhibits the mitochondrial respiratory-chain complex 1, leading to an activation of the liver kinase B1/5′-AMP kinase pathway, which, in turn, inhibits gluconeogenesis in the liver and lowers blood glucose.[29] Besides, metformin improves insulin resistance by increasing the expression of the insulin receptor and activation of tyrosine kinase,[30] and it has been shown to exert cardiac and vascular protective effects via AMP kinase–dependent and AMP kinase–independent pathways in in vitro and in vivo studies.[31] Metformin improves the endothelial function, reduces oxidative stress and inflammation, and reverses the effects of angiotensin II.[31] It attenuates ischemia-reperfusion injury[31] and has effects on the metabolism and contractile function of myocardial cells in the failing heart by enhancing glucose uptake in the insulin-resistant state.[32]

Conclusions

This population-based retrospective cohort study supports a reduced risk of HHF associated with metformin use in patients with type 2 diabetes mellitus. Because metformin is inexpensive and safe and would not cause hypoglycemia when used as monotherapy, its protection against HF is worthy of more extensive investigation in both patients with diabetes mellitus and people without diabetes mellitus.

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None.

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