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 naive 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
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 99274 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 250XX. HF 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. 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, 423949 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=183837); (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=16896). As a result, 172542 ever users and 43744 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 41714 ever users and 41714 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 (codes 250.5 [diabetes mellitus with ophthalmic manifestations], 362.0 [diabetic retinopathy], 369 [blindness and low vision], 366.41...
Patients with newly diagnosed diabetes mellitus during 1999-2005 who had been followed up in the outpatient clinics with prescription of antidiabetic drugs for 2 or more times

N=423,949

- Excluding metformin ever users who had been treated with other antidiabetic drugs before metformin was first prescribed (n=183,837)
- Excluding patients with type 1 diabetes mellitus (n=2,062)
- Excluding patients with missing data (n=424)
- Excluding patients with a diagnosis of heart failure at entry or within 6 months of diagnosis of diabetes mellitus (n=4,444)
- Excluding patients who had been followed up for <180 days (n=16,896)

Unmatched original cohort

Metformin ever users
N=172,542 (79.77%) (HHF=2,426 (1.41%))

Metformin never users
N=43,744 (20.23%) (HHF=1,677 (3.83%))

1:1 matched pairs of ever and never users of metformin (matched cohort I)

Metformin ever users
N=41,714 (HHF=916 (2.20%))

Metformin never users
N=41,714 (HHF=1,522 (3.65%))

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.

Statistical Analyses

Several principles have been recommended for the selection of variables in the estimation of PS to reduce bias.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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 $\chi^2$ test for other variables. Balance for
Table 1. Baseline Characteristics in Never and Ever Users of Metformin in the Unmatched Cohort

| Variable                                      | Never Users   | Ever Users    | P Value      | Standardized Difference |
|-----------------------------------------------|---------------|---------------|--------------|--------------------------|
|                                               | (n=43 744)    | (n=172 542)   |              |                          |
|                                               | 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                                            | 7 378         | 16.87         | 36 985       | 21.44                    |         | 14.08  |
| III                                           | 11 952        | 27.32         | 38 283       | 22.19                    |         | −13.08 |
| IV                                            | 9 907         | 22.65         | 31 697       | 18.37                    |         | −12.86 |
| Living region                                 |               |               |              |                          |
| Taipei                                        | 14 109        | 32.25         | 54 858       | 31.79                    | <0.0001 |         |
| Northern                                      | 5 165         | 11.81         | 19 703       | 11.42                    |         | −1.43  |
| Central                                       | 7 763         | 17.75         | 31 266       | 18.12                    |         | 0.25   |
| Southern                                      | 8 185         | 18.71         | 31 266       | 18.12                    |         | −4.64  |
| Kao-Ping and Eastern                          | 8 522         | 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                                       | 1 221         | 2.79          | 5 432        | 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                                  | 4 484         | 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                   | 9 413         | 21.52         | 29 750       | 17.24                    | <0.0001 | −12.95 |
| Antidiabetic drugs                            |               |               |              |                          |
| Insulin                                       | 3 098         | 7.08          | 4 006        | 2.32                     | <0.0001 | −29.06 |
| Sulfonylurea                                   | 33 236        | 75.98         | 123 823      | 71.76                    | <0.0001 | 2.49   |
| Meglitinide                                    | 3 612         | 8.26          | 6 922        | 4.01                     | <0.0001 | −21.85 |
| Acarbose                                      | 4 604         | 10.52         | 9 276        | 5.38                     | <0.0001 | −18.65 |
| Rosiglitazone                                 | 1 401         | 3.20          | 8 318        | 4.82                     | <0.0001 | 10.43  |
| Pioglitazone                                  | 970           | 2.22          | 4 469        | 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          | 3 431        | 1.99                     | <0.0001 | 4.52   |
| Alcohol-related diagnoses                     | 2 300         | 5.26          | 9 191        | 5.33                     | 0.5658  | 0.64   |
| Hepatitis B virus infection                   | 794           | 1.82          | 2 918        | 1.69                     | 0.0747  | −0.86  |
| Hepatitis C virus infection                   | 2 110         | 4.82          | 6 328        | 3.67                     | <0.0001 | −6.46  |
| Cirrhosis of liver without mention of alcohol | 2 655         | 6.07          | 6 702        | 3.88                     | <0.0001 | −12.18 |
| Other chronic nonalcoholic liver disease      | 3 950         | 9.03          | 14 731       | 8.54                     | 0.0011  | −1.92  |
| Cancer                                        | 6 516         | 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 |
|----------|------------------------|------------------------|---------|-------------------------|
| 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.

As 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 characteristics14), 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****                      | 0.026****      |
| Occupation                                        | 0.038****                       | -0.065****     |
| Living region                                     | -0.003                          | 0.011****      |
| Hypertension                                      | 0.053****                       | -0.134****     |
| Dyslipidemia                                      | -0.012****                      | 0.040****      |
| Obesity                                           | -0.006*                         | 0.006****      |
| 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
| Variable | Matched Cohort I | Matched Cohort II | Matched Cohort I | Matched Cohort II | Matched Cohort I | Matched Cohort II |
|----------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
|          | Never Users     | Ever Users      | P Value         | Standardized    | Never Users     | Ever Users      |
|          | (n=41 714)      | (n=41 714)      |                 | Difference      | (n=41 909)      | (n=41 909)      |
|          | 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          | 0.50            | 14 029 33.47    | 14 032 33.48    | 0.8407          | ...             |
| II       | 7205 17.27      | 7211 17.29      | -0.06           | 0.20            | 7233 17.26      | 7257 17.32      | 0.06            | 0.06            |
| III      | 11 271 27.02    | 11 102 26.61    | -0.81           | 0.00            | 11 341 27.06    | 11 237 26.81    | -0.47           |                 |
| IV       | 9264 22.21      | 9205 22.07      | -0.23           | 0.16            | 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
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 models consistently supported a 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, 7).
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                 |         |
| 26.2–57.7            | 1032             | 56 883           | 192198.69    | 536.94                                    | 0.643 (0.595–0.696)   | <0.0001 |
| >57.7                | 536              | 58 682           | 332705.04    | 161.10                                    | 0.178 (0.162–0.196)   | <0.0001 |
| Matched cohort †     |                  |                  |              |                                           |                       |         |
| 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                 |         |
| 29.5–61.6            | 377              | 13 763           | 48121.71     | 783.43                                    | 1.010 (0.902–1.131)   | 0.8624  |
| >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 (<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 naive 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, 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
| 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.
| Model/Metformin Use | Matched Cohort I | Matched Cohort II | 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 |
| 1. Age as a continuous variable | | | | | | |
| Never users | 1.00 | <0.0001 | 1.0000 | 1.0600 | 0.1660 |
| Ever users | 0.567 (0.523–0.616) | <0.0001 | 0.579 (0.533–0.628) | <0.0001 | 0.2000 |
| Tertiles of cumulative duration of metformin therapy, mo | | | | | | |
| Never users | 1.00 | <0.0001 | 1.0000 | 0.2000 | 0.0928 |
| I | 0.947 (0.844–1.061) | 0.3470 | 0.979 (0.875–1.096) | 0.7093 | 0.0928 |
| II | 0.571 (0.506–0.644) | <0.0001 | 0.583 (0.517–0.658) | <0.0001 | 0.0928 |
| III | 0.340 (0.295–0.391) | <0.0001 | 0.338 (0.294–0.389) | <0.0001 | 0.0928 |
| 2. Age as a continuous variable with log transformation | | | | | | |
| Never users | 1.00 | 0.1312 | 1.0000 | 0.1773 | 0.0164 |
| Ever users | 0.574 (0.528–0.623) | <0.0001 | 0.583 (0.538–0.633) | <0.0001 | 0.0164 |
| Tertiles of cumulative duration of metformin therapy, mo | | | | | | |
| Never users | 1.00 | 0.1944 | 1.0000 | 0.1773 | 0.0164 |
| I | 0.993 (0.886–1.113) | 0.9011 | 1.014 (0.907–1.135) | 0.7531 | 0.0164 |
| II | 0.576 (0.510–0.650) | <0.0001 | 0.588 (0.522–0.663) | <0.0001 | 0.0164 |
| III | 0.333 (0.289–0.384) | <0.0001 | 0.334 (0.290–0.384) | <0.0001 | 0.0164 |
| 3. Age divided into 2 subgroups of <65 and ≥65 y | | | | | | |
| Never users | 1.00 | <0.0001 | 1.0000 | 0.2123 | 0.0164 |
| Ever users | 0.569 (0.524–0.617) | <0.0001 | 0.580 (0.535–0.630) | <0.0001 | 0.0164 |
| Tertiles of cumulative duration of metformin therapy, mo | | | | | | |
| Never users | 1.00 | <0.0001 | 1.0000 | 0.2123 | 0.0164 |
| I | 0.947 (0.845–1.062) | 0.3500 | 0.982 (0.878–1.099) | 0.7531 | 0.0164 |
| II | 0.576 (0.507–0.646) | <0.0001 | 0.586 (0.519–0.660) | <0.0001 | 0.0164 |
| III | 0.340 (0.296–0.392) | <0.0001 | 0.338 (0.294–0.389) | <0.0001 | 0.0164 |
| 4. Age divided into 2 subgroups (<65 and ≥65 y) with addition of interaction term of age and chronic obstructive pulmonary disease | | | | | | |
| Never users | 1.00 | <0.0001 | 1.0000 | 0.2123 | 0.0164 |
| Ever users | 0.576 (0.531–0.625) | <0.0001 | 0.586 (0.540–0.636) | <0.0001 | 0.0164 |
| Tertiles of cumulative duration of metformin therapy, mo | | | | | | |
| Never users | 1.00 | 0.0001 | 1.0000 | 0.2123 | 0.0164 |
| I | 0.974 (0.869–1.091) | 0.6438 | 1.000 (0.894–1.119) | 0.9980 | 0.0164 |
| II | 0.578 (0.512–0.652) | <0.0001 | 0.591 (0.525–0.667) | <0.0001 | 0.0164 |
| III | 0.340 (0.295–0.392) | <0.0001 | 0.339 (0.294–0.390) | <0.0001 | 0.0164 |
| 5. Age divided into 2 subgroups (<65 and ≥65 y) with addition of interaction term of age and nephropathy | | | | | | |
| Never users | 1.00 | <0.0001 | 1.0000 | 0.1781 | 0.0164 |
| Ever users | 0.569 (0.524–0.617) | <0.0001 | 0.580 (0.535–0.630) | <0.0001 | 0.0164 |
| Tertiles of cumulative duration of metformin therapy, mo | | | | | | |
| Never users | 1.00 | <0.0001 | 1.0000 | 0.1781 | 0.0164 |
| I | 0.946 (0.844–1.061) | 0.3424 | 0.981 (0.877–1.098) | 0.7449 | 0.0164 |

Continued...
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. 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 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 al16) 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

| 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.
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 NHII 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 peptidase-4 inhibitors and a protective effect on HF for a new class of oral antidiabetic drugs of the sodium glucose cotransporter 2 inhibitors, including empagliﬂozin, canagliﬂozin, and dapagliﬂozin. Whether a combination of metformin with dipeptidyl peptidase-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, 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, 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. 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). 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. 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 McAllister et al 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 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. Tsoulaki 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. 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. 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. Besides, metformin improves insulin resistance by increasing the expression of the insulin receptor and activation of tyrosine kinase, 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. Metformin improves the endothelial function, reduces oxidative stress and inflammation, and reverses the effects of angiotensin II. It attenuates ischemia-reperfusion injury 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.

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.

Acknowledgments

The study is based, in part, on data from the National Health Insurance Research Database provided by the Bureau of National Health Insurance, Department of Health, and managed by the National Health Research Institutes. The interpretation and conclusions contained herein do not represent those of the Bureau of National Health Insurance, Department of Health, or National Health Research Institutes. The guarantor of this article is Dr Tseng.

Sources of Funding

The study was partly supported by the Ministry of Science and Technology (MOST) (National Science Council [NSC] 101-2314-B-002-117, NSC 102-2314-B-002-067, and MOST 107-2221-E-002-129-MY3) of Taiwan and the Yee Fong Charity Foundation. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the article.

Disclosures

None.

References

1. Tseng CH. The age- and sex-specific incidence and medical expenses of heart failure hospitalization in 2005 in Taiwan: a study using data from the National Health Insurance. J Am Geriatr Soc. 2010;58:611–613.
2. Tseng CH. Clinical features of heart failure hospitalization in younger and elderly patients in Taiwan. Eur J Clin Invest. 2011;41:597–604.
3. Yang X, Xu Z, Zhang C, Cai Z, Zhang J. Metformin, beyond an insulin sensitizer, targeting heart and pancreatic β cells. Biochim Biophys Acta. 2017;1863:1984–1990.
4. Packer M. Is metformin beneficial for heart failure in patients with type 2 diabetes? Diabetes Res Clin Pract. 2018;136:168–170.
5. Salpeter SR, Greyber E, Pasternak GA, Salpeter EE. Risk of fatal and nonfatal lactic acidosis with metformin use in type 2 diabetes mellitus. Cochrane Database Syst Rev. 2010;4:CD002967.
6. Eurich DT, Weir DL, Majumdar SR, Tsuyuki RT, Johnson JA, Tjosvold L, Vanderloo SE, McAlistre FA. Comparative safety and effectiveness of metformin in patients with diabetes mellitus and heart failure: systematic review of observational studies involving 34,000 patients. Circ Heart Fail. 2013;6:399–402.
7. Tseng CH. Metformin is associated with a lower risk of colorectal cancer in Taiwanese patients with type 2 diabetes: a retrospective cohort analysis. Oncotarget. 2017;8:41132–41142.
8. Parsons LS. Performing a 1:N case-control match on propensity score. http://www.google.com.tw/url?sa=t&rct=j&q=&esrc=s&source=web&cd=1&ved=0CBoFjAAahUKEwibi7HllcnIAhUDoJQKHVeZAA&url=http%3A%2F%2Fwww2.sas.com%2Fproceedings%2FSugii29%2F165-29.pdf&usg=AFQjCNDHGwYuJE88n4Bo1TUIkIT987Q. Accessed September 17, 2019.
9. Tseng CH. Metformin and lung cancer risk in patients with type 2 diabetes mellitus. Oncotarget. 2017;8:41132–41142.
10. Tseng CH. Diabetes, metformin use, and colon cancer: a population-based cohort study in Taiwan. Eur J Endocrinol. 2012;167:409–416.
11. Patrick AR, Schneeweiss S, Brookhart MA, Glynn RJ, Rothman KJ, Avorn J, Sturmer T. The implications of propensity score variable selection strategies in pharmacoepidemiology: an empirical illustration. Pharmacoepidemiol Drug Saf. 2011;20:551–559.
12. Ali MS, Groenwold RH, Beltser SV, Pestman WR, Hoes AW, Roels KG, Boer A, Klungel OH. Reporting of covariate selection and balance assessment in propensity score analysis is suboptimal: a systematic review. J Clin Epidemiol. 2015;68:112–121.
13. Austin PC, Stuart EA. Moving towards best practice when using inverse probability of treatment weighting (IPTW) using the propensity score to estimate causal treatment effects in observational studies. Stat Med. 2015;34:3661–3679.
14. Austin PC. The performance of different propensity score methods for estimating marginal hazard ratios. Stat Med. 2013;32:2837–2849.
15. Wooldridge JM. Introductory econometrics: a modern approach (5th edition, chapter 9: More on specification and data issues). Cengage Learning. 2012. Available at: https://economics.ut.ac.ir/documents/3030266/14100645/Jeffrey_M._Wooldridge_Introductory_Econometrics_A_Modern_A Approach___2012.pdf.

16. Lêvesque LE, Hanley JA, Kezouh A, Sussa S. Problem of immortal time bias in cohort studies: example using statins for preventing progression of diabetes. BMJ. 2010;340:b5087.

17. Scirica BM, Bhatt DL, Braunwald E, Hirschberg B, Ohman P, Frederich R, Wiviott SD, Hoffman EB, Cavender MA, Udel RA, Desai NR, Mosenzon O, McGuire DK, Ray KK, Leiter LA, Raz I; SAVOR-TIMI 53 Steering Committee and Investigators. Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. N Engl J Med. 2013;369:1317–1326.

18. Tseng CH. Sitagliptin and heart failure hospitalization in patients with type 2 diabetes. Oncotarget. 2016;7:62687–62696.

19. Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, Mattheus M, Riumar P, Raz I, Bhatt DL, Braunwald E, Cornell C. Reappraisal of metformin efficacy in the treatment of type 2 diabetes: a meta-analysis of randomised controlled trials. PLoS Med. 2012;9:e1001204.

20. McAlister FA, Eurlch DT, Majumdar SR, Johnson JA. The risk of heart failure in patients with type 2 diabetes treated with oral agent monotherapy. Eur J Heart Fail. 2008;10:703–708.

21. Casscells SW, Granger E, Swedorske J, Goldhammer R, Shaheen M, Doris J, Hong A, Wiktor M. A comparison of select cardiovascular outcomes by anti-diabetic prescription drug classes used to treat type 2 diabetes among Military Health System beneficiaries, fiscal year 2003–2006. Am J Ther. 2008;15:198–205.

22. Tzoulaki I, Molokhia M, Curvin V, Little MP, Millett C, Ng A, Hughes RI, Khunti K, Wilkins MR, Majeed A, Elliott P. Risk of cardiovascular disease and all cause mortality among patients with type 2 diabetes prescribed oral antidiabetes drugs: retrospective cohort study using UK general practice research database. BMJ. 2009;339:b4731.

23. Pantalone KM, Kattan MW, Yu C, Wells BJ, Arrigain S, Jain A, Atreja A, Zimmerman RS. The risk of developing coronary artery disease or congestive heart failure, and overall mortality, in type 2 diabetic patients receiving rosiglitazone, pioglitazone, metformin, or sulfonylureas: a retrospective analysis. Acta Diabetol. 2009;46:145–154.

24. Boussageon R, Supper I, Bejan-Coupinant Y, Kellou N, Cucherat M, Boissel JP, Kassai B, Moreau A, Gueyffier F, Cornu C. Metformin and Heart Failure

25. Tseng CH. Sitagliptin and heart failure hospitalization in patients with type 2 diabetes. Oncotarget. 2016;7:62687–62696.

26. McAlister FA, Eurlch DT, Majumdar SR, Johnson JA. The risk of heart failure in patients with type 2 diabetes treated with oral agent monotherapy. Eur J Heart Fail. 2008;10:703–708.

27. Casscells SW, Granger E, Swedorske J, Goldhammer R, Shaheen M, Doris J, Hong A, Wiktor M. A comparison of select cardiovascular outcomes by anti-diabetic prescription drug classes used to treat type 2 diabetes among Military Health System beneficiaries, fiscal year 2003–2006. Am J Ther. 2008;15:198–205.

28. Tzoulaki I, Molokhia M, Curvin V, Little MP, Millett C, Ng A, Hughes RI, Khunti K, Wilkins MR, Majeed A, Elliott P. Risk of cardiovascular disease and all cause mortality among patients with type 2 diabetes prescribed oral antidiabetes drugs: retrospective cohort study using UK general practice research database. BMJ. 2009;339:b4731.

29. Pantalone KM, Kattan MW, Yu C, Wells BJ, Arrigain S, Jain A, Atreja A, Zimmerman RS. The risk of developing coronary artery disease or congestive heart failure, and overall mortality, in type 2 diabetic patients receiving rosiglitazone, pioglitazone, metformin, or sulfonylureas: a retrospective analysis. Acta Diabetol. 2009;46:145–154.

30. Rena G, Pearson ER, Sakamoto K. Molecular mechanism of action of metformin: old or new insights? Diabetologia. 2013;56:1898–1906.

31. Viellet B, Guigas B, Sanz Garcia N, Leclerc J, Foretz M, Andreelli F. Cellular and molecular mechanisms of metformin: an overview. Clin Sci (Lond). 2012;122:253–270.

32. Nesti L, Natali A. Metformin effects on the heart and the cardiovascular system: a review of experimental and clinical data. Nutr Metab Cardiovasc Dis. 2017;27:657–669.

33. Bertrand L, Ginion A, Beauloye C, Hebert AD, Guigas B, Hue L, Vanoverschelde JL. AMPK activation restores the stimulation of glucose uptake in an in vitro model of insulin-resistant cardiomyocytes via the activation of protein kinase B. Am J Physiol Heart Circ Physiol. 2006;291:H239–H250.