Association between Use of Oral Anti-Diabetic Drugs and the Risk of Sepsis: A Nested Case-Control Study

Chia-Jen Shih1,2,*, Yueh-Lin Wu1,3,*, Pei-Wen Chao4,5, Shu-Chen Kuo1,6,7, Chih-Yu Yang1,8,9, Szu-Yuan Li1,8,9, Shuo-Ming Ou1,8,9 & Yung-Tai Chen1,9,10

Although oral antidiabetic drugs (OADs) have been associated with immunomodulation in preclinical studies, little is still known about the association between the use of OADs and the risk of sepsis. Using a cohort of patients, extracted from Taiwan’s National Health Insurance Research Database, with type 2 diabetes who were newly diagnosed between 2010 and 2012 and treated with OADs, we conducted a nested case-control study involving 43,015 cases (patients who were first hospitalized for sepsis) and 43,015 matched controls. Compared with non-use, metformin use was associated with a decreased risk of developing sepsis (adjusted odds ratio [OR] 0.80, 95% confidence interval [CI] 0.77–0.83, \( P < 0.001 \)), but meglitinide (adjusted OR 1.32, 95% CI 1.25–1.40, \( P < 0.001 \)) use was associated with the increased risk of developing sepsis. The risk for development of sepsis was also lower among current (adjusted OR 0.87, 95% CI 0.78–0.96) and recent (adjusted OR 0.83, 95% CI 0.73–0.94) thiazolidinedione users. Current or recent sulfonfonyurea use and dipeptidyl peptidase-4 inhibitor use were not significantly associated with the development of sepsis. Our results highlight the need to consider the potential pleiotropic effect of OADs against sepsis in addition to the lowering of blood glucose.

Between 1980 and 2008, the number of people with type 2 diabetes (T2D) worldwide increased from approximately 150 million to 350 million1. According to the World Health Organization, the global economic burden of T2D is tremendous, consuming 2.5–15% of countries’ primary healthcare budgets2.

Till now, the use of oral antidiabetic drugs (OADs) remains the preferred pharmacological therapy due to many patients’ fear of insulin administration and its adverse effects, such as hypoglycemia and weight gain3,4.

Several classes of OAD are available on the market, including biguanide (metformin), sulfonylureas, alpha-glucosidase inhibitors, meglitinides, thiazolidinediones (TZDs), dipeptidyl peptidase-4 (DPP-4) inhibitors, and newer sodium-glucose cotransporter 2 (SGLT2) inhibitors. In addition to mediating
glucose reduction, OADs have been associated with immunomodulation in preclinical studies\(^5\)\(^–\)\(^7\). In fact, patients with T2D are susceptible to infection and sepsis which may also impact on T2D lethality and medical costs in health systems; however, the possible pleiotropic effect of OADs on sepsis outcomes has not yet been well validated in large-scale clinical studies.

Previous studies\(^8\)\(^–\)\(^10\) exploring the association between OADs and sepsis have produced conflicting results, which may be attributed to methodological issues such as small samples, limited follow-up periods, unconfirmed diagnosis of infection events, unknown OAD exposure periods relative to sepsis onset, or the confounding effects of differences in diabetes severity between groups. To investigate whether susceptibility to sepsis differed among patients with T2D taking different classes of OAD, we used the Taiwan National Health Insurance Research Database (NHIRD) to conduct a nationwide nested case-control study that controlled for the effects of predisposing the host factors to sepsis.

**Methods**

**Data sources.** Medical care in Taiwan has been provided under Taiwan's National Health Insurance (NHI) since 1995. This system covers more than 99% of Taiwan's inhabitants for most medical expenses related to inpatient, outpatient, and emergency care, Chinese medicine, and dental services. For administrative and reimbursement purposes, the Bureau of the NHI audited patients' diagnosis, procedure, and medication data to ensure correct coding and appropriateness; these data were recorded and stored in the NHIRD, which has been described in detail in our previous studies\(^11\),\(^12\). To examine OAD use among patients with T2D, we extracted the Longitudinal Cohort of Diabetes Patients dataset from the NHIRD. This dataset includes all available medical registry data for 120,000 patients with incident T2D per year during the period 1999–2012. This study was exempted from full review by the Institutional Review Board of Taipei City Hospital because it used de-identified and secondary claims data released by the NHIRD for research purposes.

**Study population.** In this nationwide population-based study, we assembled a cohort of patients who received new diagnoses of diabetes between 2010 and 2012, as the marketing of DPP-4 inhibitors was approved in Taiwan in 2009. The definition of diabetes was based on the presence of one primary discharge diagnosis of diabetes (International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM] code 250.x), two ambulatory visits with a diagnosis of diabetes (ICD-9-CM code 250.x), or use of any antidiabetic drug. The accuracy of coded DM diagnoses in the NHIRD has been validated\(^13\). The date of cohort entry was the first day on which a patient fulfilled the diabetes diagnosis criteria (NHI) since 1995. This system covers more than 99% of Taiwan’s inhabitants for most medical expenses; however, the possible pleiotropic effect of OADs on sepsis outcomes has not yet been well validated in large-scale clinical studies.

The baseline demographic characteristics of the cohort were analyzed using descriptive statistics. We conducted conditional logistic regression with adjustment for potential confounding factors, including OAD use, insulin use, and all other predefined comorbidities associated with the risk of sepsis (Table 1). ORs were computed to compare OAD exposure of cases and controls. The Microsoft SQL Server 2012 (Microsoft Corp., Redmond, Washington, USA) was used for data linkage, processing, and sampling. All analyses were performed using STATA statistical software (version 13.0; StataCorp., College Station, Texas, USA). Statistical significance was defined as P < 0.05.

**Case definition and control selection.** Because OAD exposure may be a time-dependent property associated with sepsis occurrence, we conducted a nested case-control analysis to estimate the odds ratios (ORs) for sepsis, comparing each OAD user with a nonuser of that drug. Cases were all patients hospitalized for sepsis (defined as a primary diagnosis of septicemia [ICD-9-CM code 038.x] plus the prescription of antibiotics) during the study period. We previously validated the accuracy of this definition of sepsis\(^11\). The index date was the day of the case’s hospital admission. For each case, we randomly selected a control matched according to age (±1 year), sex, month and year of cohort entry, level of urbanization, monthly income, Charlson Comorbidity Index score\(^14\), adapted Diabetes Complications Severity Index (aDCSI) score\(^15\), and duration of follow up.

**Exposure assessment.** All OAD prescriptions for each subject in the year before the index date were identified. The OADs of primary interest in the present study were metformin, sulfonylureas, TZDs, meglitinides, and DPP-4 inhibitors. Given that preclinical studies\(^16\),\(^17\) have found that glibenclamide may have anti-inflammatory responses, but other sulfonylureas did not, we further stratified sulfonylureas into glibenclamide and non-glibenclamide sulfonylureas. For each OAD prescription, we collected the following information: dispensing date, drug type, quantity, and duration of drug supply. The pattern of OAD use was categorized as current (on index date), recent (<30 days before index date), or past (31–365 days before index date).

**Statistical analysis.** The baseline demographic characteristics of the cohort were analyzed using descriptive statistics. We conducted conditional logistic regression with adjustment for potential confounding factors, including OAD use, insulin use, and all other predefined comorbidities associated with the risk of sepsis (Table 1). ORs were computed to compare OAD exposure of cases and controls. The
Results

A total of 43,015 cases and 43,015 matched controls were identified, with Table 1 showing their baseline characteristics. Hypertension, heart failure, cerebrovascular disease, and drug abuse were more prevalent among cases than among controls.
Table 2 presents the crude and adjusted ORs for the development of sepsis requiring hospitalization (cases) in association with OAD use compared with controls, after adjusting for all potential confounders in Table 1. Metformin use was associated with decreased odds of developing sepsis (adjusted OR 0.80, 95% confidence interval [CI] 0.77–0.83, \( P < 0.001 \)), whereas sulfonylurea (adjusted OR 1.06, 95% CI 1.02–1.10, \( P = 0.001 \)) and meglitinide (adjusted OR 1.32, 95% CI 1.25–1.40, \( P < 0.001 \)) use were associated with increased odds of developing sepsis (Table 2). In addition, the timing of OAD use may be related with the onset of sepsis. Adjusted ORs for sepsis were 0.77 (95% CI 0.73–0.80) for current metformin use, 0.74 (95% CI 0.70–0.79) for recent metformin use, and 0.90 (95% CI 0.86–0.95) for past metformin use. Neither current sulfonylurea use (adjusted OR 1.03, 95% CI 0.98–1.08) nor recent (adjusted OR 0.97, 95% CI 0.91–1.03) sulfonylurea use significantly increased the risk of sepsis. The results remained similar when sulfonylureas were classified as either glibenclamide or non-glibenclamide (Supplementary Table 1). Current (adjusted OR 0.87, 95% CI 0.78–0.96) and recent (adjusted OR 0.83, 95% CI 0.73–0.94) TZD use significantly decreased the risk of sepsis.

| No. (%) | cases (n = 43,015) | Control (n = 43,015) | Crude | Adjusted* | P Value | Adjusted* | P Value |
|---------|-------------------|---------------------|-------|-----------|---------|-----------|---------|
| No Metformin use† | 26,430 (61.4) | 25,062 (58.3) | 1 | 1 | 1 | 1 | 1 |
| Metformin use | | | | | | | |
| Any‡ | 16,585 (38.6) | 17,953 (41.7) | 0.87 (0.94–0.89) | <0.001 | 0.80 (0.77–0.83) | <0.001 |
| Current§ | 6,755 (15.7) | 7,828 (18.2) | 0.81 (0.78–0.84) | <0.001 | 0.77 (0.73–0.80) | <0.001 |
| Recent‖ | 3,647 (8.5) | 4,532 (10.5) | 0.76 (0.72–0.79) | <0.001 | 0.74 (0.70–0.79) | <0.001 |
| Past¶ | 6,183 (14.4) | 5,593 (13.0) | 1.04 (1.00–1.08) | 0.060 | 0.90 (0.86–0.95) | <0.001 |
| No DPP-4 inhibitor use† | 39,492 (91.8) | 39,739 (92.4) | 1 | 1 | 1 | 1 | 1 |
| DPP-4 use | | | | | | | |
| Any‡ | 3,523 (8.2) | 3,276 (7.6) | 1.09 (1.03–1.14) | 0.001 | 1.01 (0.95–1.06) | 0.042 |
| Current§ | 1,148 (2.7) | 1,152 (2.7) | 1.01 (0.93–1.09) | <0.890 | 0.97 (0.89–1.07) | 0.543 |
| Recent‖ | 897 (2.1) | 887 (2.1) | 1.02 (0.93–1.12) | 0.657 | 1.06 (0.95–1.18) | 0.289 |
| Past¶ | 1,478 (3.4) | 1,237 (2.9) | 1.21 (1.12–1.30) | <0.001 | 1.01 (0.92–1.10) | 0.903 |
| No Sulfonylurea use† | 27,733 (64.5) | 27,687 (64.4) | 1 | 1 | 1 | 1 | 1 |
| Sulfonylurea use | | | | | | | |
| Any‡ | 15,282 (35.5) | 15,328 (35.6) | 1.00 (0.97–1.02) | 0.736 | 1.06 (1.03–1.10) | 0.001 |
| Current§ | 6,364 (14.8) | 6,964 (16.2) | 0.91 (0.88–0.95) | <0.001 | 1.03 (0.98–1.08) | 0.220 |
| Recent‖ | 897 (2.1) | 887 (2.1) | 1.02 (0.93–1.12) | 0.657 | 1.06 (0.95–1.18) | 0.289 |
| Past¶ | 5,786 (13.5) | 4,716 (11.0) | 1.22 (1.17–1.28) | <0.001 | 1.18 (1.12–1.24) | <0.001 |
| No Meglitinide use† | 39,329 (91.4) | 40,330 (93.8) | 1 | 1 | 1 | 1 | 1 |
| Meglitinide use | | | | | | | |
| Any‡ | 3,686 (8.6) | 2,685 (6.2) | 1.42 (1.35–1.50) | <0.001 | 1.32 (1.25–1.40) | <0.001 |
| Current§ | 1,357 (3.2) | 1,016 (2.4) | 1.38 (1.27–1.50) | <0.001 | 1.29 (1.17–1.41) | <0.001 |
| Recent‖ | 721 (1.7) | 565 (1.3) | 1.32 (1.18–1.47) | <0.001 | 1.28 (1.13–1.44) | <0.001 |
| Past¶ | 1,608 (3.7) | 1,104 (2.6) | 1.51 (1.40–1.63) | <0.001 | 1.32 (1.22–1.44) | <0.001 |
| No Thiazolidinedione use† | 40,025 (93.0) | 39,901 (92.8) | 1 | 1 | 1 | 1 | 1 |
| Thiazolidinedione use | | | | | | | |
| Any‡ | 2,990 (7.0) | 3,114 (7.2) | 0.96 (0.91–1.01) | 0.093 | 0.95 (0.89–1.01) | 0.085 |
| Current§ | 745 (1.7) | 913 (2.1) | 0.81 (0.74–0.89) | <0.001 | 0.87 (0.78–0.96) | 0.009 |
| Recent‖ | 534 (1.2) | 731 (1.7) | 0.73 (0.65–0.81) | <0.001 | 0.83 (0.73–0.94) | 0.003 |
| Past¶ | 1,711 (4.0) | 1,470 (3.4) | 1.16 (1.08–1.24) | <0.001 | 1.07 (0.98–1.16) | 0.114 |

Table 2. Crude and Adjusted Rate Ratios for the Risk of Hospitalization for Sepsis With Oral Antidiabetic Drugs. *Adjusted for oral antidiabetic drugs, insulin use, and all confounders in Table 1. Each level of Charlson Comorbidity Index and adapted Diabetes Complications Severity Index was calculated as a separate indicator variable. †During the year prior to the index date. ‡Use of 1 prescription at any time prior to the index date. §A prescription termination date (date of dispensation plus the day supply) overlapping with the index date. ‖A prescription termination date of 1 to 30 days before the index date. ¶A prescription termination date of 31 to 365 days before the index date.
mycosis19 infection, and attenuating hepatitis B virus replication 20. Similar to our findings, a Swedish
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who had received metformin compared with those who had not (OR, 2.49;


gent department events, a significant improvement in short-term survival of sepsis was noted for patients

population-based cohort study 10 with a mean follow-up period of 3.9 years demonstrated that met-

Index and adapted Diabetes Complications Severity Index was calculated as a separate indicator variable.

analyses conducted in RCTs, as some patients were lost to follow up or withdrew from the medication

ent study. Only a modest potential benefit from TZD in sepsis onset may be offset in intention-to-treat

infection risk between the TZD group and active controls; this is consistent with the findings of the pres-

effectiveness of add-on TZD therapy in patients with T2D showed no significant difference in additional

users of other OADs22–24. In a single-center retrospective cohort study of 1,947 patients with septic emer-

to concern about metformin-associated lactic acidosis21, this approach has been controversial because no

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ated with greater risks of upper and lower respiratory-tract infections, but low (< 2% overall) event rates

studies26,27.

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triphosphate–sensitive potassium channel in pancreatic

cells may also have off–target effects, which

the scope of the present study, their propensities for insulin secretagogues by inhibiting the adenosine

prescriptions had the opposite effect on sepsis development, which appeared to be weaker for sulfon-

of sepsis through the examination of patterns of past, recent, or current use. Furthermore, meglitinide

inhibition and anti-inflammation may be responsible for infection risk in DPP-4 inhibitor users.

Recent/current, but not past, TZD prescription was associated with a modest reduction in sepsis risk,
suggesting that this effect is immediate. Randomized controlled trials (RCTs)28,29 investigating the clinical
effectiveness of add-on TZD therapy in patients with T2D showed no significant difference in additional
infection risk between the TZD group and active controls; this is consistent with the findings of the pres-
ent study. Only a modest potential benefit from TZD in sepsis onset may be offset in intention-to-treat
analyses conducted in RCTs, as some patients were lost to follow up or withdrew from the medication
during the follow-up period. In contrast, a meta-analysis8 of 13 trials showed that TZD use was associ-
ated with greater risks of upper and lower respiratory-tract infections, but low (< 2% overall) event rates
of sepsis and differences in follow-up periods (1–5 years) among trials may have affected the accuracy
of estimates of incident sepsis events.

No association between DPP-4 inhibitors and sepsis risk was observed in the present study. DPP-4
inhibition may have pleiotropic effects, modulating the immune response by binding DPP-4 receptors of
immune cells20 or culprit pathogens, such as coronavirus and hepatitis C virus31,32. The balance between
immune inhibition and anti-inflammation may be responsible for infection risk in DPP-4 inhibitor users.

Table 3. Crude and Adjusted Rate Ratios for the Risk of Hospitalization for Sepsis with Metformin-
Based Combination Therapy. *Adjusted for all confounders in Table 1. Each level of Charlson Comorbidty
Index and adapted Diabetes Complications Severity Index was calculated as a separate indicator variable.

Discussion
To our knowledge, this is the first population-based, nested case-control study to examine the relation-
ship between OAD use and the risk of hospitalization for sepsis.

We found that metformin use was associated with about 20% reduced risk of sepsis compared with
nonuse. In contrast, meglitinides and sulfonylureas was associated with increased risk of future sepsis
events, but this association was not evident among recent and current sulfonylurea users. The effects of
DPP-4 inhibitors and TZDs on sepsis were neutral, but a reduced risk of sepsis occurrence was observed
only in recent/current TZD users. Nevertheless, metformin-based OADs conferred a persistent benefit
on the rate of hospitalization for sepsis.

In-vitro studies have found that metformin treatment had an inhibitory effect on mediators of
sepsis, such as by limiting respiratory Staphylococcus aureus growth8 and tuberculosisis18 and mucor-
mycosis19 infection, and attenuating hepatitis B virus replication20. Similar to our findings, a Swedish
population-based cohort study10 with a mean follow-up period of 3.9 years demonstrated that met-
formin treatment was associated with a reduced risk of composite outcomes of acidosis/serious infection
(adjusted hazard ratio 0.85, 95% CI 0.74–0.97) in patients with T2D, independent of glycemic control,
compared with those receiving other OADs (about 80% of which were sulfonylureas). Although relevant
guidelines for diabetes treatment have suggested withdrawal from metformin for patients with sepsis due
to concern about metformin-associated lactic acidosis23, this approach has been controversial because no
proven evidence supports the increased risk of this condition among metformin users compared with
users of other OADs22–24. In a single-center retrospective cohort study of 1,947 patients with septic emerg-
ent department events, a significant improvement in short-term survival of sepsis was noted for patients
who had received metformin compared with those who had not (OR, 2.49; P < 0.01)25. Our nationwide
study provided more evidence to support the association of metformin prescription with decreased risk
of sepsis through the examination of patterns of past, recent, or current use. Furthermore, meglitinide
prescriptions had the opposite effect on sepsis development, which appeared to be weaker for sulfon-
ylurea users. Although investigation of the mechanism responsible for these relationships was beyond
the scope of the present study, their propensities for insulin secretagogues by inhibiting the adenosine
triphosphate–sensitive potassium channel in pancreatic β cells may also have off–target effects, which
have been found to be related to impaired immune response against invading pathogens in preclinical
studies26,27.

| Current exposure                     | Cases (n = 43,015) | Control (n = 43,015) | Crude          | P Value | Adjusted*          | P Value |
|-------------------------------------|------------------|---------------------|----------------|---------|-------------------|---------|
| Metformin Alone                      | 3,135 (7.3)      | 4,467 (10.4)        | 0.64 (0.61–0.67) | < 0.001 | 0.65 (0.62–0.68) | < 0.001 |
| Metformin + Sulfonylurea             | 4,929 (11.5)     | 6,265 (14.6)        | 0.72 (0.69–0.75) | < 0.001 | 0.72 (0.69–0.75) | < 0.001 |
| Metformin + Thiazolinedione         | 132 (0.3)        | 241 (0.6)           | 0.50 (0.41–0.62) | < 0.001 | 0.51 (0.41–0.64) | < 0.001 |
| Metformin + DPP-4 inhibitors        | 215 (0.5)        | 300 (0.7)           | 0.65 (0.55–0.78) | < 0.001 | 0.65 (0.55–0.78) | < 0.001 |
| Metformin + Meglitinides            | 341 (0.8)        | 380 (0.9)           | 0.82 (0.71–0.96) | 0.010   | 0.82 (0.71–0.96) | 0.012   |
In the context of weighing the pros and cons of DPP-4 inhibitor use given the effects of these drugs on immune function, our results show that they have an insignificant influence of sepsis risk. A nested control study based on the World Health Organization Vigibase\(^1\) showed that DPP-4 inhibitor use was associated with a greater risk of infection compared with metformin use. However, this result should be interpreted with caution, as the imprecise definition of infection based on spontaneous reporting introduces reporting bias.

The strengths of the present study include the analysis of large case and control groups respectively representing the nationwide diabetes populations that had previously received OADs either with or without sepsis from 2010–2012, which thus minimized referral bias. Additionally, we investigated whether the impact of OADs on the occurrence of sepsis was immediate or persistent over time by considering OAD exposure intervals. Still, this study has a few potential limitations. First, it was retrospective and observational in nature, and so causality could not be established. Second, the diagnosis of diabetes and sepsis based on ICD-9CM codes may have introduced misclassification bias; however, this bias could be non-differential and robust agreement between diagnoses established by coding and clinical criteria has been demonstrated elsewhere\(^1,3\). Third, the claims database did not include individual baseline data on glycomic control, such as HbA1c levels. Nonetheless, if the impact of OADs on sepsis outcome were mainly the result of the glucose-lowering effect, the tendency of ORs for different OADs should tend toward coherence. Therefore, it is unlikely that this unmeasured confounder biased the results, and its effects were minimized by adjusting for the aDCSI score. Lastly, data on potential confounders such as obesity, smoking habit, and alcohol consumption were also unavailable in the database.

In conclusion, metformin and recent or current TZD use were inversely associated with sepsis occurrence, whereas meglitinide use was positively associated with metformin use. As patients with T2D are predisposed to infection, the direct impacts of OADs on future sepsis events should be considered.

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**Author Contributions**

Y.T.C., S.M.O., C.J.S. and Y.L.W. conceptualised and designed the study and drafted the article; Y.T.C., S.M.O., C.J.S. and Y.L.W. analysed and interpreted the data; Y.T.C., S.M.O., C.J.S. and Y.L.W. critically revised the article for important intellectual content; Y.T.C., S.M.O. and P.W.C. provided final approval of the article; S.C.K. provided study materials and patients; P.W.C., C.Y.Y. and S.Y.L. offered statistical expertise and provided administrative, technical, and logistical support.

**Additional Information**

**Supplementary information** accompanies this paper at http://www.nature.com/srep

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