Do second-line oral antidiabetic drugs have different long-term effects on persons with young-onset type 2 diabetes? —A nationwide population base cohort study

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Original investigation

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Abstract

Background: People with young-onset diabetes (YOD) exhibit a higher risk of morbidity and mortality than those with late-onset diabetes. Few studies have explored the preferred management of diabetes in such patients; therefore, we compared the risks of hospitalization and mortality among people with YOD to whom second-line oral antidiabetic drugs (OADs) were administered.

Methods: We conducted a nationwide cohort study using the National Health Insurance Research Database (Taiwan). A total of 7257 people taking second-line OADs after initial metformin therapy were enrolled during 2009–2014. Using add-on sulfonylureas (SUs) as a reference, the multivariable Cox regression model was used to compare the risks of hospitalization and mortality among 5 categories of second-line OADs: alpha-glucosidase inhibitors, meglitinide, dipeptidyl peptidase-4 (DPP-4) inhibitors, SUs, and thiazolidinediones.

Results: The mean age of patients, duration of diabetes, and follow-up period were 31.6, 3.3, and 1.9 years, respectively. After baseline characteristics, comorbidities, duration of diabetes, and cardiovascular drug use were controlled, the adjusted hazard ratios and 95% confidence interval for all-cause, cardiovascular, and non-infection hospitalization and all-cause mortality for metformin plus DPP-4 inhibitors were 0.62 (0.52–0.73), 0.49 (0.29–0.85), 0.64 (0.54–0.76), and 0.50 (0.27–0.92), respectively, when compared with the data for metformin plus SUs.

Conclusions: We found that among people with YOD, taking add-on DPP-4 inhibitors was associated with lower risks of all-cause hospitalization and mortality than taking add-on SUs. DPP-4 inhibitors thus seem to be a suitable second-line OAD for such patients.

Trial registration: retrospectively registered

Background

Given widespread changes in dietary habits and lifestyle, type 2 diabetes mellitus (T2DM) is becoming increasingly prevalent among younger people in some countries [1]. In 2000, approximately 23 million young adults aged 20–39 years had T2DM worldwide (13% of 177 million individuals with T2DM), with the prevalence increasing to 63 million young adults in 2013 (16% of 382 million individuals with T2DM) [1]. This situation is particularly obvious among Asians [2]. T2DM in people aged <40 years is referred to as young-onset diabetes (YOD) [3]. In Asia, YOD is observed in approximately 20% of adults with T2DM [2]; in China specifically, YOD is seen in 4%–6% of individuals with T2DM [4]. The prevalence of YOD in Taiwan also exhibits an upward trend (approximately 12% in 2012) [5]. In Australia, in 2011, roughly 9% of newly diagnosed cases of T2DM were YOD [6]. Further, the prevalence of YOD in the United Kingdom increased from 5.9% in 1991 to 12.4% in 2010 [7].

Patients with YOD are destined to live with diabetes for a long time; moreover, most of them have other metabolic risk factors [2]. In the literature, using age-matched persons without diabetes as the
benchmark, adults with YOD have been found to have a significantly higher risk of premature death, macro- and microvascular complications, and hospitalization than those with late-onset T2DM [8–11]. Further, T2DM seems to rapidly progress in adults with YOD. Given that young adults tend to be the primary source of income within a family and actively contribute to the economic growth of a nation, optimal measures for those with YOD should be taken to enhance their health as well as quality of life.

Most randomized controlled trials recruited people aged >50 years [12]; because the number of participants under the age of 40 years is low, subgroup analyses involving those with YOD are challenging. Therefore, the current treatment strategies for YOD are extrapolated from the standard treatment guidelines for T2DM. Metformin is administered as the first-line drug, and second-line drugs are introduced when appropriate. Achieving the glycemic target in people with YOD is often difficult [13], and they also need to use insulin earlier than persons with more typical T2DM [8]. Treating people with YOD is difficult, and to date, few studies have evaluated the impact of different treatments in this population. Therefore, we conducted this retrospective cohort study to compare the risks of hospitalization and all-cause mortality among adults with YOD being treated with different second-line oral antidiabetic drugs (OADs).

**Methods**

**Data source**

The National Health Insurance (NHI) program was implemented in Taiwan in 1995, and in 2000, it involved >99% of the 23 million residents, >450 hospitals, and >10,000 clinics in Taiwan [14]. We used the full-population dataset from the NHI Research Database (NHIRD), which includes details pertaining to each insured’s residency/working location, gender, age, and the diagnoses and prescriptions they received in hospitals and clinics. The *International Classification of Diseases, Ninth Revision, Clinical Modifications (ICD-9-CM)* was used to code disease diagnoses. Death-related information of all residents is available in the National Death Registry, and the NHIRD was linked to this registry to verify information pertaining to mortality. To protect privacy, all information that could disclose the identity of residents was encrypted before release. This study was approved by the Institutional Review Board of the National Health Research Institutes (EC1060704-E); the requirement for informed consent was waived.

**Study population and design**

We used data from the NHIRD belonging to patients who were newly diagnosed with T2DM (*ICD-9-CM: 250.x*) in 2009–2014. Dipeptidyl peptidase-4 (DPP-4) inhibitors have been marketed in Taiwan since 2009; therefore, our study began in 2009 and attempted to achieve a fair comparison of second-line OADs. Patients were included if they had a discharge diagnosis of T2DM with at least 2 outpatient or 1 inpatient claim within a year [15]. We further selected our study population using the following criteria: 1) an age at T2DM diagnosis of 20–39 years; 2) continuous use of metformin for >1 year without using other OADs and insulin; and 3) adding only 1 OAD for >90 days after metformin monotherapy. The 91st day after add-on of the second-line OAD was defined as the index date in this study.
Five categories of second-line OADs were taken by patients in this study: alpha-glucosidase inhibitors (AGIs), meglitinide, DPP-4 inhibitors, sulfonylureas (SUs), and thiazolidinediones (TZDs). Sodium glucose cotransporter-2 inhibitors were launched in Taiwan in 2018. Glucagon-like peptide-1 receptor agonists were marketed in Taiwan in 2011; they represented only 0.01% of all antidiabetic drug prescriptions in 2011 and 0.19% in 2014. Thus, we did not investigate these two drugs in this study. For comparing clinical outcomes, we used SUs—the most frequently used second-line OAD—as a reference. The follow-up was stopped if the second-line therapy was discontinued or switched or if add-on third-line OADs were identified. Moreover, we excluded patients with type 1 diabetes mellitus (ICD-9-CM: 250.1) with a catastrophic illness card. For those with gestational diabetes (ICD-9-CM: 648.0 and 648.8), their records for the current year were not be considered, but their data were recalculated 1 year later.

Characteristics and comorbidities

Comorbidities were calculated according to patients’ NHI records 1 year before the index date; comorbidities were defined as ≥2 outpatient diagnoses or at least 1 inpatient claim. We considered the following comorbidities in this study: hypertension (ICD-9-CM: 401–405 and A26), dyslipidemia (272 and 278), chronic kidney disease (403.01, 403.11, 403.91, 404.02, 404.03, 404.12, 404.13, 404.92, 404.93, V42.0, V45.1, V56.x, and 790), coronary artery disease (410–414), asthma (493, 786.07, and V17.5), and psychotic disorders (290–299). We also considered Charlson comorbidity index (CCI) [16] and Diabetes Complications Severity Index (DCSI) scores [17]. In addition, we observed the use of antihypertensive drugs, statins, and aspirin within 1 year before the index date.

Main outcomes

The primary outcome was all-cause hospitalization. We also assessed the risks of all-cause mortality, cardiovascular (CV) hospitalization, and non-infection hospitalization. The following CV diseases were investigated: cardiovascular diseases (ICD-9-CM: 398.91, 402.xx, 404.xx, 410.xx- 414.xx, 00.66, and 36.xx), heart failure (428.x), and ischemic stroke (433.x, 434.x, or 436.x). The incidence of outcomes was calculated in the follow-up period. The outcomes were identified as when they first occurred or at the end of the study. The date and cause of mortality were determined from the National Death Registry.

Statistical analysis

Baseline characteristics, premium levels, urbanization, comorbidities, CCI and DCSI scores, duration of diabetes, and medications were compared among patients receiving the 5 categories of second-line OADs. Baseline characteristics were compared using analysis of variance (ANOVA) or chi-square tests when conditions were appropriate. The stratified log-rank test and Kaplan–Meier analyses were used to compare the cumulative incidence of hospitalization and mortality. In the multivariable Cox regression model, hazard ratios (HRs) and 95% confidence intervals (CIs) were used to estimate treatment effects after adjusting for the aforementioned variables. We adopted the 2-sided trial, and \( P < 0.05 \) indicated statistical significance. SAS 9.4 (SAS Institute Inc., Cary, NC) and STATA 15.1 (STATA Corp, College Station, TX) were used for statistical analyses.
Results

From 2009 to 2014, we recruited 457, 283, 1241, 4975, and 301 people with YOD who were administered AGIs, meglitinide, DPP-4 inhibitors, SUs, and TZDs, respectively, as an add-on to metformin. As evident from Table 1, most of their baseline characteristics were different. The mean age of people in these 5 categories was 31.4, 31.8, 31.5, 31.7, and 31.5 years, respectively; the mean duration of T2DM was 3.2, 3.2, 3.4, 3.4, and 3.4 years, respectively; and the mean follow-up time was 1.9, 2.4, 1.2, 2.3, and 1.9 years, respectively.
Table 1 Basic characteristics of 20–39-year-old patients with type 2 diabetes taking add-on second-line oral antidiabetic drugs after metformin monotherapy

|                  | Alpha glucosidase (AGIs) | Meglitinide | Dipeptidyl peptidase 4 (DPP4i) | Sulfonylurea (TZD) | Thiazolidinediones | \( P \) value |
|------------------|--------------------------|-------------|-------------------------------|-------------------|-------------------|--------------|
| **N**            | 457                      | 283         | 1,241                         | 4,975             | 301               |              |
| **Age group**    |                          |             |                               |                   |                   |              |
| 20-24            | 40 (8.8)                 | 21 (7.4)    | 115 (9.3)                     | 380 (7.6)         | 27 (9)            | 0.35         |
| 25-29            | 103 (22.5)               | 56 (19.8)   | 248 (20)                      | 943 (19)          | 62 (20.6)         | 0.40         |
| 30-34            | 183 (40)                 | 120 (42.4)  | 478 (38.5)                    | 2,144 (43.1)      | 120 (39.9)        | 0.042        |
| 35-39            | 131 (28.7)               | 86 (30.4)   | 400 (32.2)                    | 1,508 (30.3)      | 92 (30.6)         | 0.63         |
| **Mean(SD)**     | 31.4 (4.3)               | 31.8 (4.2)  | 31.5 (4.5)                    | 31.7 (4.2)        | 31.5 (4.4)        | 0.26         |
| **Gender**       |                          |             |                               |                   |                   | <0.001       |
| Male             | 228 (49.9)               | 186 (65.7)  | 766 (61.7)                    | 3,412 (68.6)      | 188 (62.5)        |              |
| Female           | 229 (50.1)               | 97 (34.3)   | 475 (38.3)                    | 1,563 (31.4)      | 113 (37.5)        |              |
| **Premium level**|                          |             |                               |                   |                   |              |
| (NTD)            |                          |             |                               |                   |                   |              |
| <22,000 or poor  | 193 (42.2)               | 110 (38.9)  | 486 (39.2)                    | 2,167 (43.6)      | 122 (40.5)        | 0.042        |
| 22,000-44,999    | 220 (48.1)               | 145 (51.2)  | 612 (49.3)                    | 2,362 (47.5)      | 143 (47.5)        | 0.62         |
| \( \geq 45,000 \) | 44 (9.6)                 | 28 (9.9)    | 143 (11.5)                    | 446 (9)           | 36 (12)           | 0.049        |
| **Urbanization** |                          |             |                               |                   |                   |              |
| Highly           | 111 (24.3)               | 81 (28.6)   | 291 (23.4)                    | 1,267 (25.5)      | 97 (32.2)         | 0.19         |
| Median           | 198 (43.3)               | 130 (45.9)  | 489 (39.4)                    | 2,264 (45.5)      | 119 (39.5)        | 0.001        |
| Township         | 44 (9.6)                 | 24 (8.5)    | 118 (9.5)                     | 512 (10.3)        | 32 (10.6)         | 0.79         |
| Rural area       | 104 (22.8)               | 48 (17)     | 343 (27.6)                    | 932 (18.7)        | 53 (17.6)         | <0.001       |
| **Comorbidity**  |                          |             |                               |                   |                   |              |
| Condition     | Group 1 | Group 2 | Group 3 | Group 4 | Group 5 | p-value |
|---------------|---------|---------|---------|---------|---------|---------|
| Hypertension  | 96 (21) | 63 (22.3)| 92 (7.4)| 1,175 (23.6)| 53 (17.6)| <0.001  |
| Dyslipidemia  | 74 (16.2)| 44 (15.5)| 59 (4.8)| 908 (18.3)| 49 (16.3)| <0.001  |
| CKD           | 20 (4.4)| 15 (5.3)| 8 (0.6)| 249 (5)| 13 (4.3)| <0.001  |
| CAD           | 10 (2.2)| 5 (1.8)| 13 (1)| 163 (3.3)| 9 (3)| <0.001  |
| Stroke        | 5 (1.1)| 5 (1.8)| 8 (0.6)| 78 (1.6)| 7 (2.3)| 0.076   |
| Asthma        | 30 (6.5)| 14 (4.9)| 52 (4.2)| 170 (3.4)| 10 (3.3)| 0.010   |
| Psychotic     | 18 (3.9)| 9 (3.2)| 19 (1.5)| 201 (4)| 7 (2.3)| <0.001  |

**CCI scores**

| CCI scores | Group 1 | Group 2 | Group 3 | Group 4 | Group 5 | p-value |
|------------|---------|---------|---------|---------|---------|---------|
| <=1        | 336 (73.5)| 203 (71.7)| 1,146 (92.3)| 3,585 (72.1)| 231 (76.7)| <0.001 |
| 2          | 77 (16.8)| 51 (18)| 55 (4.4)| 820 (16.5)| 40 (13.3)| <0.001  |
| 3          | 17 (3.7)| 13 (4.6)| 24 (1.9)| 257 (5.2)| 16 (5.3)| <0.001  |
| >=4        | 27 (5.9)| 16 (5.7)| 16 (1.3)| 313 (6.3)| 14 (4.7)| <0.001  |
| Mean(SD)   | 1.9 (1.3)| 1.7 (1.1)| 1.7 (1.2)| 1.8 (1.3)| 1.7 (1.1)| <0.001  |

**DCSI score**

| DCSI score | Group 1 | Group 2 | Group 3 | Group 4 | Group 5 | p-value |
|------------|---------|---------|---------|---------|---------|---------|
| 0          | 392 (85.8)| 230 (81.3)| 1,193 (96.1)| 4,170 (83.8)| 256 (85)| <0.001  |
| 1          | 49 (10.7)| 36 (12.7)| 24 (1.9)| 492 (9.9)| 33 (11)| <0.001  |
| >=2        | 16 (3.5)| 17 (6)| 24 (1.9)| 313 (6.3)| 12 (4)| <0.001  |
| Mean(SD)   | 1.3 (0.5)| 1.5 (0.8)| 1.6 (0.7)| 1.6 (0.9)| 1.3 (0.6)| <0.001  |

**Diabetic duration, years**

| Group     | Group 1 | Group 2 | Group 3 | Group 4 | Group 5 | p-value |
|-----------|---------|---------|---------|---------|---------|---------|
| ACEi /ARBS| 119 (26)| 57 (20.1)| 432 (34.8)| 1110 (22.3)| 92 (30.6)| <0.001  |
| Beta blocker| 70 (15.3)| 26 (9.2)| 219 (17.6)| 573 (11.5)| 37 (12.3)| <0.001  |
| CCB       | 93 (20.4)| 43 (15.2)| 291 (23.4)| 840 (16.9)| 57 (18.9)| <0.001  |
| Diuretics | 61 (13.3)| 33 (11.7)| 184 (14.8)| 516 (10.4)| 35 (11.6)| <0.001  |
| Statin    | 111 (24.3)| 52 (18.4)| 429 (34.6)| 1100 (22.1)| 101 (33.6)| <0.001  |
| Aspirin   | 33 (7.2)| 10 (3.5)| 96 (7.7)| 315 (6.3)| 20 (6.6)| <0.001  |
The incidence rates of all-cause hospitalization were 76.52, 100.15, 47.44, 92.86, and 75.54 per 1000 person-years, respectively, for add-on AGIs, meglitinide, DPP-4 inhibitors, SUs, and TZDs (Table 2). With add-on SUs used as a reference, the adjusted HR (95% CI) for all-cause hospitalization in the case of add-on DPP-4 inhibitors was 0.62 (0.52–0.73, \( P < 0.001 \)). Furthermore, the cumulative incidence of all-cause hospitalizations per Kaplan–Meier analyses indicated a significantly lower risk of hospitalization in people administered add-on DPP-4 inhibitors than in those administered add-on SUs (log-rank test, \( P < 0.001 \), Fig. 1). Similarly, with add-on SUs used as a reference, the adjusted HR of CV hospitalization showed statistically significant difference \( \text{aHR} 0.49 (0.29-0.85), \ P = 0.011 \), and the adjusted HR (95% CI) for non-infection hospitalization in the case of add-on DPP-4 inhibitors was 0.64 (0.54–0.76, \( P < 0.001 \), Table 2).
Table 2 Mortality and admission-related data of 20–39-year-old patients with type 2 diabetes taking add-on second-line oral antidiabetic drugs after metformin monotherapy

| Event                      | Incidence | Crude model                  | Adjusted model |
|----------------------------|-----------|------------------------------|----------------|
|                            |           | Hazard ratio (95% confidence interval) | Hazard ratio (95% confidence interval) | P value | P value |
|                            |           | Crude model                   | Adjusted model |
| All-cause mortality         |           |                              |                |
| Alpha glucosidase inhibitors (AGIs) | 7          | 8.02                          | 0.57 (0.27-1.22) | 0.16     | 0.62 (0.29-1.33) | 0.22     |
| Meglitinide                 | 7          | 10.50                         | 0.79 (0.37-1.68) | 0.53     | 0.83 (0.39-1.78) | 0.64     |
| Dipeptidyl peptidase 4     | 11         | 7.70                          | 0.46 (0.25-0.85) | 0.014    | 0.50 (0.27-0.92) | 0.026    |
| Sulfonarylurea              | 154        | 13.48                         | 1.0 (reference) | 1.0 (reference) |               |
| Thiazolidinediones          | 5          | 8.94                          | 0.63 (0.26-1.54) | 0.31     | 0.68 (0.28-1.66) | 0.40     |
| (TZD)                       |           |                              |                |
| All-cause hospitalization   |           |                              |                |
| Alpha glucosidase inhibitors (AGIs) | 121       | 76.52                         | 0.84 (0.70-1.01) | 0.65     | 0.90 (0.74-1.10) | 0.30     |
| Meglitinide                 | 101        | 100.15                        | 1.07 (0.87-1.31) | 0.32     | 1.10 (0.88-1.38) | 0.39     |
| Dipeptidyl peptidase 4     | 158        | 47.44                         | 0.57 (0.49-0.67) | <0.001   | 0.62 (0.52-0.73) | <0.001   |
| Sulfonarylurea              | 1,640      | 92.86                         | 1.0 (reference) | .        | 1.0 (reference) |          |
| Thiazolidinediones          | 77         | 75.54                         | 0.81 (0.65-1.02) | 0.25     | 0.86 (0.67-1.11) | 0.24     |
| (TZD)                       |           |                              |                |
| Cardiovascular hospitalization |       |                              |                |
| Alpha glucosidase inhibitors (AGIs) | 9          | 4.89                          | 0.66 (0.33-1.28) | 0.22     | 0.65 (0.33-1.28) | 0.21     |
The event rates of all-cause mortality for add-on AGIs, meglitinide, DPP-4 inhibitors, SUs, and TZDs were 7, 7, 11, 154, and 5 cases, respectively (Table 2). With add-on SU used as a reference, the adjusted HR of all-cause mortality showed statistically significant difference [aHR 0.50 (0.27-0.92), \( P = 0.026 \), Table 2]. The cumulative incidence of survival in the aforementioned 5 categories has been depicted using the Kaplan–Meier method in Fig. 2: a significantly higher probability of survival was found in people administered add-on DPP-4 inhibitors than in those administered add-on SUs (log-rank test, \( P = 0.014 \)).

As per stratified analyses, among people administered add-on DPP-4 inhibitors, those who were aged 20–34 years; both men and women; whose duration of diabetes was < 3 or > 5 years; who did not have hypertension or dyslipidemia; whose CCI score was < 4 and DCSI score was < 2; and who did not use angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, \( \beta \)-blockers, calcium channel blockers, and diuretics had lower risks of all-cause hospitalization compared with those administered add-on SUs (Table 3).
Table 3 Subgroup analysis of all-cause hospitalization involving 20–39-year-old patients with type 2 diabetes taking add-on second-line oral antidiabetic drugs after metformin monotherapy

| Subgroup                  | Event | Incidence rate (per 1000 person-years) | Crude model | Adjusted model<sup>a</sup> |
|---------------------------|-------|----------------------------------------|-------------|-----------------------------|
|                           |       |                                        | Hazard ratio (95% confidence interval) P value | Hazard ratio (95% confidence interval) P value |
| Overall                   |       |                                        | 0.96 (0.79-1.16) 0.65 | 0.96 (0.79-1.17) 0.70 |
| Alpha glucosidase inhibitors |       |                                        | 0.96 (0.79-1.16) 0.65 | 0.96 (0.79-1.17) 0.70 |
| Meglitinide               | 82    | 78.90                                  | 1.12 (0.90-1.40) 0.31 | 1.10 (0.88-1.38) 0.41 |
| Dipeptidyl                | 156   | 46.43                                  | 0.62 (0.53-0.74) <0.001 | 0.73 (0.62-0.87) <0.001 |
| Dipeptidyl-4 inhibitors   |       |                                        | 0.001        |                              |
| Sulfonylurea              | 1279  | 70.38                                  | reference    | reference                   |
| Thiazolidinediones        | 64    | 61.06                                  | 0.86 (0.67-1.11) 0.24 | 0.89 (0.69-1.14) 0.36 |
| Age 20-29 years-old       |       |                                        | 0.91 (0.64-1.30) 0.62 | 0.93 (0.65-1.34) 0.71 |
| Alpha glucosidase inhibitors |       |                                        | 0.91 (0.64-1.30) 0.62 | 0.93 (0.65-1.34) 0.71 |
| Meglitinide               | 28    | 102.15                                 | 1.41 (0.96-2.08) 0.08 | 1.45 (0.99-2.14) 0.0+  |
| Dipeptidyl                | 41    | 40.90                                  | 0.54 (0.39-0.74) <0.001 | 0.58 (0.42-0.81) 0.001 |
| Dipeptidyl-4 inhibitors   |       |                                        | 0.001        |                              |
| Sulfonylurea              | 339   | 71.87                                  | reference    | reference                   |
| Thiazolidinediones        | 16    | 54.86                                  | 0.75 (0.46-1.25) 0.27 | 0.76 (0.46-1.26) 0.28 |
| Age 30-34 years-old       |       |                                        | 0.90 (0.66-1.23) 0.52 | 0.92 (0.67-1.26) 0.59 |
| Alpha glucosidase inhibitors |       |                                        | 0.90 (0.66-1.23) 0.52 | 0.92 (0.67-1.26) 0.59 |
| Meglitinide               | 35    | 82.01                                  | 1.12 (0.80-1.57) 0.52 | 1.14 (0.81-1.61) 0.45 |
| Dipeptidyl                | 67    | 51.72                                  | 0.66 (0.52-0.86) 0.002 | 0.78 (0.60-1.01) 0.06 |
| Drug Class               | N    | Risk Ratio | 95% CI | p-value | RR 95% CI     | 95% CI | p-value |
|-------------------------|------|------------|--------|---------|----------------|--------|---------|
| Sulfonylurea            | 571  | 73.18      |        |         | reference       |        |         |
| Thiazolidinediones      | 23   | 51.39      | 0.70 (0.46-1.06) | 0.09 | 0.72 (0.48-1.10) | 0.13 |
| **Age 35-39 years-old**|      |            |        |         |                |        |         |
| Alpha glucosidase       | 33   | 71.92      | 1.09 (0.76-1.56) | 0.64 | 1.01 (0.70-1.44) | 0.98 |
| inhibitors              |      |            |        |         |                |        |         |
| Meglitinide             | 19   | 56.14      | 0.86 (0.54-1.37) | 0.53 | 0.83 (0.52-1.32) | 0.43 |
| Dipeptidyl              | 48   | 45.21      | 0.66 (0.49-0.90) | 0.008 | 0.87 (0.64-1.19) | 0.39 |
| peptidase-4 inhibitors  |      |            |        |         |                |        |         |
| Sulfonylurea            | 369  | 65.28      |        |         | reference       |        |         |
| Thiazolidinediones      | 25   | 80.92      | 1.23 (0.82-1.85) | 0.32 | 1.32 (0.87-1.98) | 0.19 |
| **Men**                 |      |            |        |         |                |        |         |
| Alpha glucosidase       | 46   | 57.66      | 0.85 (0.63-1.14) | 0.28 | 0.86 (0.64-1.16) | 0.33 |
| inhibitors              |      |            |        |         |                |        |         |
| Meglitinide             | 51   | 71.91      | 1.07 (0.81-1.43) | 0.62 | 1.08 (0.81-1.43) | 0.59 |
| Dipeptidyl              | 97   | 46.43      | 0.65 (0.52-0.80) | <   | 0.77 (0.62-0.95) | 0.016 |
| peptidase-4 inhibitors  |      |            |        |         |                |        |         |
| Sulfonylurea            | 841  | 67.01      |        |         | reference       |        |         |
| Thiazolidinediones      | 39   | 59.99      | 0.89 (0.64-1.22) | 0.47 | 0.93 (0.68-1.29) | 0.67 |
| **Women**               |      |            |        |         |                |        |         |
| Alpha glucosidase       | 64   | 77.65      | 0.99 (0.76-1.29) | 0.96 | 1.04 (0.80-1.36) | 0.77 |
| inhibitors              |      |            |        |         |                |        |         |
| Meglitinide             | 31   | 93.91      | 1.20 (0.84-1.73) | 0.32 | 1.14 (0.79-1.64) | 0.48 |
| Dipeptidyl              | 59   | 46.44      | 0.57 (0.44-0.75) | <   | 0.68 (0.51-0.89) | 0.006 |
| peptidase-4 inhibitors  |      |            |        |         |                |        |         |
| Sulfonylurea            | 438  | 77.92      |        |         | reference       |        |         |
| Thiazolidinediones      | 25   | 62.8       | 0.80 (0.54-1.20) | 0.29 | 0.83 (0.55-1.25) | 0.37 |
| **Diabetes duration < 3 years** | | | | | | |
|                         | 68   | 64.39      | 1.01 (0.78-1.28) | 0.99 | 0.97 (0.75-1.25) | 0.80 |
| Drug Class            | Duration          | Group 1 | Group 2 | Group 3 | Group 4 | Group 5 |
|-----------------------|-------------------|---------|---------|---------|---------|---------|
| Alpha glucosidase     |                   |         |         |         |         |         |
| Meglitinide           | 3-5 years         | 72.20   | 0.96    | 0.87    | 1.01    | 0.97    |
| Dipeptidyl peptidase-4 inhibitors | 3-5 years | 84.57   | 1.13    | 0.57    | 1.14    | 0.55    |
| Sulfonlurea           | 3-5 years         | 74.80   | reference | reference |         |         |
| Thiazolidinediones    | 3-5 years         | 58.32   | 0.77    | 0.35    | 0.78    | 0.37    |
| Alpha glucosidase     | > 5 years         | 76.83   | 0.89    | 0.63    | 0.92    | 0.74    |
| Meglitinide           | > 5 years         | 86.38   | 1.02    | 0.95    | 1.07    | 0.80    |
| Dipeptidyl peptidase-4 inhibitors | > 5 years | 50.96   | 0.56    | 0.003   | 0.60    | 0.012   |
| Sulfonlurea           | > 5 years         | 84.87   | reference | reference |         |         |
| Thiazolidinediones    | > 5 years         | 41.55   | 0.49    | 0.044   | 0.51    | 0.06    |
| Alpha glucosidase     | With hypertension| 80.97   | 0.98    | 0.89    | 1.05    | 0.80    |
| Meglitinide           | With hypertension|         |         |         |         |         |
| Dipeptidyl peptidase-4 inhibitors | With hypertension |         |         |         |         |         |
| Sulfonlurea           | With hypertension|         |         |         |         |         |
| Thiazolidinediones    | With hypertension|         |         |         |         |         |
| Drug Class                   | N  | Mean (SD) | p-value | Reference Mean (SD) | Reference p-value |
|-----------------------------|----|-----------|---------|---------------------|------------------|
| **Dipeptidyl peptidase-4 inhibitors** |    |           |         |                     |                  |
| Sulfonylurea                | 399| 82.74     | reference |                      | reference         |
| Thiazolidinediones          | 20 | 94.88     | 1.15 (0.74-1.81) | 0.53 | 1.24 (0.79-1.94) | 0.35 |
| **Without hypertension**   |    |           |         |                     |                  |
| Alpha glucosidase           | 78 | 63.58     | 0.96 (0.76-1.21) | 0.71 | 0.95 (0.75-1.20) | 0.67 |
| **Dipeptidyl peptidase-4 inhibitors** |    |           |         |                     |                  |
| Meglitinide                 | 62 | 81.92     | 1.24 (0.96-1.61) | 0.10 | 1.24 (0.96-1.60) | 0.11 |
| Dipeptidyl                  | 133| 43.46     | 0.62 (0.52-0.75) | <   | 0.70 (0.58-0.85) | <   |
| **With Dyslipidemia**       |    |           |         |                     |                  |
| Alpha glucosidase           | 27 | 87.12     | 1.15 (0.77-1.70) | 0.49 | 1.05 (0.71-1.57) | 0.80 |
| **Dipeptidyl peptidase-4 inhibitors** |    |           |         |                     |                  |
| Meglitinide                 | 12 | 65.07     | 0.86 (0.48-1.54) | 0.61 | 0.81 (0.45-1.45) | 0.48 |
| Dipeptidyl                  | 16 | 79.22     | 1.02 (0.62-1.69) | 0.93 | 1.03 (0.62-1.71) | 0.92 |
| **Without Dyslipidemia**   |    |           |         |                     |                  |
| Alpha glucosidase           | 83 | 63.26     | 0.91 (0.73-1.14) | 0.41 | 0.92 (0.74-1.16) | 0.48 |
| **Dipeptidyl peptidase-4 inhibitors** |    |           |         |                     |                  |
| Meglitinide                 | 70 | 81.88     | 1.19 (0.93-1.52) | 0.16 | 1.17 (0.92-1.49) | 0.20 |
| Dipeptidyl                  | 140| 44.34     | 0.61 (0.51-0.73) | <   | 0.71 (0.59-0.86) | <   |
| **peptidase-4 inhibitors** |    |           |         |                     |                  |
| Sulfonylurea                | 991| 68.95     | reference |                      | reference         |
| Thiazolidinediones          | 47 | 55.90     | 0.80 (0.60-1.08) | 0.14 | 0.83 (0.62-1.11) | 0.21 |
CCI scores ≥ 4

| Category                  | Count | CCI  | Hazard Ratio (95% CI) | p-value | Hazard Ratio (95% CI) | p-value |
|---------------------------|-------|------|-----------------------|---------|-----------------------|---------|
| Alpha glucosidase inhibitors | 11    | 111.68 | 0.86 (0.46-1.58)     | 0.62    | 0.95 (0.50-1.79)     | 0.87    |
| Meglitinide               | 10    | 211.12 | 1.47 (0.78-2.80)     | 0.24    | 1.51 (0.77-2.95)     | 0.23    |
| Dipeptidyl                | 6     | 156.27 | 1.05 (0.47-2.39)     | 0.90    | 1.23 (0.54-2.81)     | 0.62    |
| Sulfonylurea              | 144   | 132.65 | reference             | reference | reference             | reference |
| Thiazolidinediones        | 8     | 183.20 | 1.32 (0.65-2.70)     | 0.44    | 1.59 (0.76-3.31)     | 0.22    |

CCI scores <4

| Category                  | Count | CCI  | Hazard Ratio (95% CI) | p-value | Hazard Ratio (95% CI) | p-value |
|---------------------------|-------|------|-----------------------|---------|-----------------------|---------|
| Alpha glucosidase inhibitors | 99    | 64.98 | 0.97 (0.79-1.19)     | 0.79    | 0.97 (0.79-1.19)     | 0.77    |
| Meglitinide               | 72    | 72.58 | 1.09 (0.86-1.39)     | 0.46    | 1.08 (0.85-1.37)     | 0.55    |
| Dipeptidyl                | 150   | 45.16 | 0.65 (0.55-0.77)     | <       | 0.72 (0.61-0.86)     | <       |
| Sulfonylurea              | 1135  | 66.43 | reference             | reference | reference             | reference |
| Thiazolidinediones        | 56    | 55.75 | 0.84 (0.64-1.09)     | 0.19    | 0.84 (0.64-1.09)     | 0.19    |

DCSI ≥ 2

| Category                  | Count | CCI  | Hazard Ratio (95% CI) | p-value | Hazard Ratio (95% CI) | p-value |
|---------------------------|-------|------|-----------------------|---------|-----------------------|---------|
| Alpha glucosidase inhibitors | 8     | 158.75 | 1.10 (0.54-2.25)     | 0.79    | 1.26 (0.60-2.61)     | 0.54    |
| Meglitinide               | 8     | 123.62 | 0.89 (0.44-1.81)     | 0.75    | 0.86 (0.41-1.80)     | 0.70    |
| Dipeptidyl                | 6     | 111.77 | 0.66 (0.29-1.51)     | 0.33    | 0.61 (0.26-1.40)     | 0.24    |
| Sulfonylurea              | 148   | 141.05 | reference             | reference | reference             | reference |
| Thiazolidinediones        | 6     | 159.03 | 1.19 (0.52-2.69)     | 0.68    | 1.33 (0.57-3.09)     | 0.50    |

DCSI < 2

| Category                  | Count | CCI  | Hazard Ratio (95% CI) | p-value | Hazard Ratio (95% CI) | p-value |
|---------------------------|-------|------|-----------------------|---------|-----------------------|---------|
| Alpha glucosidase inhibitors | 102   | 64.90 | 0.98 (0.80-1.20)     | 0.82    | 0.94 (0.77-1.16)     | 0.58    |
| Meglitinide               | 74    | 75.93 | 1.15 (0.91-1.45)     | 0.25    | 1.14 (0.90-1.44)     | 0.28    |
| Drug Class               | Count | Mean (%) | CI (95%)    | P-value | CI (95%) |
|-------------------------|-------|----------|-------------|---------|----------|
| Dipeptidyl peptidase-4 inhibitors | 150   | 45.37    | <0.65 (0.55-0.78) | <0.001 | 0.74 (0.62-0.88) | <0.001 |
| Sulfonylurea            | 1131  | 66.05    | reference   | reference |
| Thiazolidinediones      | 58    | 57.40    | 0.86 (0.66-1.12) | 0.28    | 0.86 (0.66-1.12) | 0.27 |

**Used ACEi/ARB**

| Drug Class               | Count | Mean (%) | CI (95%)    | P-value | CI (95%) |
|-------------------------|-------|----------|-------------|---------|----------|
| Alpha glucosidase inhibitors | 26    | 60.26    | 0.86 (0.57-1.28) | 0.46    | 0.85 (0.56-1.27) | 0.43 |
| Meglitinide             | 14    | 63.31    | 0.91 (0.53-1.56) | 0.74    | 0.87 (0.51-1.50) | 0.61 |
| Dipeptidyl              | 56    | 48.83    | 0.68 (0.51-0.90) | 0.008   | 0.78 (0.57-1.05) | 0.10 |

**peptidase-4 inhibitors**

| Drug Class               | Count | Mean (%) | CI (95%)    | P-value | CI (95%) |
|-------------------------|-------|----------|-------------|---------|----------|
| Sulfonylurea             | 278   | 69.97    | reference   | reference |
| Thiazolidinediones       | 17    | 57.90    | 0.82 (0.50-1.34) | 0.43    | 0.89 (0.55-1.47) | 0.66 |

**Nonuse ACEi/ARB**

| Drug Class               | Count | Mean (%) | CI (95%)    | P-value | CI (95%) |
|-------------------------|-------|----------|-------------|---------|----------|
| Alpha glucosidase inhibitors | 84    | 70.55    | 0.99 (0.79-1.24) | 0.93    | 0.99 (0.79-1.24) | 0.94 |
| Meglitinide             | 68    | 83.11    | 1.17 (0.92-1.50) | 0.20    | 1.15 (0.90-1.48) | 0.26 |
| Dipeptidyl              | 100   | 45.19    | 0.60 (0.49-0.74) | <0.001  | 0.70 (0.57-0.87) | 0.001 |

**peptidase-4 inhibitors**

| Drug Class               | Count | Mean (%) | CI (95%)    | P-value | CI (95%) |
|-------------------------|-------|----------|-------------|---------|----------|
| Sulfonylurea             | 1001  | 70.50    | reference   | reference |
| Thiazolidinediones       | 47    | 62.28    | 0.88 (0.66-1.18) | 0.40    | 0.88 (0.65-1.17) | 0.37 |

**Used β-blocker**

| Drug Class               | Count | Mean (%) | CI (95%)    | P-value | CI (95%) |
|-------------------------|-------|----------|-------------|---------|----------|
| Alpha glucosidase inhibitors | 22    | 92.86    | 1.19 (0.76-1.86) | 0.44    | 1.28 (0.81-2.04) | 0.29 |
| Meglitinide             | 7     | 69.75    | 0.91 (0.43-1.95) | 0.82    | 0.90 (0.41-1.95) | 0.78 |
| Dipeptidyl              | 34    | 63.08    | 0.77 (0.53-1.12) | 0.17    | 0.99 (0.66-1.48) | 0.95 |

**peptidase 4 inhibitors**

| Drug Class               | Count | Mean (%) | CI (95%)    | P-value | CI (95%) |
|-------------------------|-------|----------|-------------|---------|----------|
| Sulfonylurea             | 157   | 77.65    | reference   | reference |
| Thiazolidinedones        | 9     | 84.07    | 1.06 (0.54-2.07) | 0.87    | 1.22 (0.61-2.42) | 0.57 |

**Nonuse β-blocker**
| Drug Category                  | Use CCB | Nonuse CCB | Use Diuretic |
|--------------------------------|---------|------------|-------------|
| Alpha glucosidase             |         |            |             |
| Meglitinide                   | 75      | 84         | 11          |
| Dipeptidyl                    | 122     | 109        | 36          |
| Dipeptidase-4 inhibitors      |         |            |             |
| Sulfonylurea                  | 1122    | 228        | 1051        |
| Thiazolidinediones            | 55      | 13         | 51          |
| Nonuse CCB                    |         |            |             |
| Alpha glucosidase             | 26      | 84         | 20          |
| Meglitinide                   | 12      | 70         | 11          |
| Dipeptidyl                    | 47      | 109        | 36          |
| Dipeptidase-4 inhibitors      |         |            |             |
| Sulfonylurea                  | 228     | 1051       |             |
| Thiazolidinediones            | 13      | 51         |             |
| Use Diuretic                  |         |            |             |
| Alpha glucosidase             | 20      | 20         |             |
| Meglitinide                   | 11      | 11         |             |
| Dipeptidyl                    | 36      | 36         |             |
peptidase-4 inhibitors

|                |     |        |        |     |        |
|----------------|-----|--------|--------|-----|--------|
| Sulfonylurea   | 163 | 91.50  | reference | reference |
| Thiazolidinediones | 6  | 53.30  | 0.57 (0.25-1.29) | 0.18 | 0.57 (0.25-1.31) | 0.19 |

Nonuse Diuretic

|                |     |        |        |     |        |
|----------------|-----|--------|--------|-----|--------|
| Alpha glucosidase inhibitors | 90 | 63.82  | 0.93 (0.75-1.15) | 0.51 | 0.93 (0.75-1.15) | 0.50 |

|                |     |        |        |     |        |
|----------------|-----|--------|--------|-----|--------|
| Meglitinide    | 71  | 76.50  | 1.12 (0.88-1.43) | 0.34 | 1.11 (0.87-1.41) | 0.39 |
| Dipeptidyl     | 120 | 41.46  | 0.57 (0.48-0.69) < | 0.68 (0.56-0.82) | <0.001 |

CCI, Charlson comorbidity index; DCSI, Diabetes Complications Severity Index; ACEi, angiotensin-converting enzyme inhibitor; ARBs, angiotensin receptor blockers; CCB, calcium channel blocker

a Adjusted for all variables in Table 1

## Discussion

In this nationwide cohort study, we compared hospitalization and mortality risks among people with YOD taking different second-line OADs. With add-on SUs as a reference, only people taking add-on DPP-4 inhibitors had significantly lower risks of all-cause hospitalizations and mortality. Further, subgroup analyses indicated that among people added on DPP-4 inhibitors, those who were younger, fewer comorbidities and complications seemed to have lower risks of all-cause hospitalization compared with those added on SUs.

Because metformin is safe, effective, and cheap, unless there are contraindications, it is used as the first-line drug for T2DM treatment in most countries [18]. However, if metformin fails or is insufficient in treating a patient, a second-line OAD is introduced to intensify glycemic management. If patients do not have underlying kidney or CV diseases, all second-line OADs seem to have a similar effect [19, 20]. The GRADE randomized control study investigated the long-term outcomes of glimepiride, sitagliptin, liraglutide, and basal insulin glargine; however, this study is ongoing and thus the results remain unknown [21]. Several studies have compared the clinical outcomes of different second-line OADs added to metformin [22–24]. Morgan et al reported that the combination of metformin plus pioglitazone was associated with a lower risk of combined end points (mortality, CV events, and cancer) compared with the combination of metformin plus SU [22]. Further, Chang et al revealed that glinide plus metformin and
AGIs plus metformin were associated with lower risks of acute myocardial infarction compared with SU plus metformin [23]. Hsu et al demonstrated that acarbose added to metformin was associated with lower risks of major atherosclerotic events compared with the addition of SU to metformin [24]. Few clinical studies have compared the clinical outcomes of different treatments for diabetes in patients with YOD. In the present study, we found that the combination of metformin and DPP-4 inhibitors was associated with a lower risk of all-cause mortality compared with the combination of metformin and SU. Additionally, we found that treatment with metformin plus DPP-4 inhibitors was associated with lower risks of all-cause, cardiovascular and non-infection hospitalization compared with metformin plus SU in multivariable analyses. Ke et al reported that YOD is associated with excess burden of hospitalization compared with late-onset diabetes [10]. Our results indicated that among the tested second-line OADs, DPP-4 inhibitors may be able to lower the risk of hospitalization in people with YOD.

In the subgroup analysis of hospitalization involving people with YOD taking add-on DPP-4 inhibitors, younger people, those with fewer comorbidities and diabetes complications, and those not using any antihypertensive drugs had a lower risk of all-cause hospitalization than those taking add-on SUs. Prevailing evidence suggests that adults with YOD show more rapid β-cell deterioration than those with late-onset T2DM [25]. By prolonging the half-life of glucagon-like peptide-1 and gastric inhibitory polypeptide, DPP-4 inhibitors promote glucose-dependent insulin secretion and are believed to have a β-cell preserving function [26, 27]. Therefore, the use of DPP-4 inhibitors may attenuate β-cell deterioration; by contrast, SUs tend to exhaust β-cell function [28]. This may be particularly important in people with YOD and a rapid decline of β-cell function [25]. Our subgroup analysis further suggested that add-on DPP-4 inhibitors in people with YOD may be as early with young and low complications as better. Moreover, DPP-4 inhibitors have been confirmed to improve glucose excursion, and the risk of hypoglycemia and adverse events is low, even in patients with renal dysfunction [26]. These data thus explain why patients with YOD taking metformin plus DPP-4 inhibitors had a lower risk of hospitalization in this study.

It is noteworthy that people with YOD must live with this condition for most part of their lives. Compared with late-onset diabetes, YOD seems to be associated with a relatively high lifelong risk of vascular complications, hospitalization, and premature mortality. However, only a few studies have explored the optimal management of YOD. Our results suggest that metformin plus DPP-4 inhibitors may reduce the risk of hospitalization compared with metformin plus SUs, which is the most frequently prescribed combination. Further, although the prevalence of YOD is increasing worldwide, the number of patients is still relatively small, and thus, it is difficult to recruit a large number of adults with YOD for randomized control studies. Our study design was thus suitable because we could enroll a sufficient number of people with YOD to compare the outcomes of various second-line OADs.

Our study had some limitations. First, the NHI dataset lacked information on physical activities of patients, alcohol drinking or smoking habits, body weight, blood pressure, renal function, and hemoglobin A1C, glucose, and lipid levels. This lack of data may thus influence the outcomes we assessed. We attempted to decrease the influence of confounders by adjusting for important variables, such as age, gender, premium levels, areas of residence, comorbidities, CCI and DCSI scores, duration of diabetes, and...
CV-related medications. Second, as patients stopped taking an OAD, switched to another OAD, or added a third-line medication, the follow-up was stopped; whereas, information pertaining to the adherence of dosage, timing, and frequency of second-line OADs could not be obtained from the administrative database. The preference of clinicians or patients to prescribe or receive, respectively, any second-line OADs (i.e., confounding by indication) could not be avoided in this study. Third, we believe that future prospective studies with longer follow-up periods of surveillance need to be conducted to elucidate CV and death risks in patients taking the tested second-line OADs. Finally, observational studies are always subject to some residual confounding; randomized control studies are thus warranted to validate our findings.

Conclusions

We herein demonstrated that taking metformin plus DPP-4 inhibitors is associated with lower risks of hospitalization and mortality compared with taking metformin plus SUs among people with YOD. YOD seems to be an aggressive phenotype of T2DM, with a relatively high risk of complications and treatment failure. Thus, our results should be useful for the management of persons with YOD.

Abbreviations

YOD, young-onset diabetes; OAD, oral antidiabetic drug; DPP-4, dipeptidyl peptidase-4; SU, sulfonylurea; T2DM, type 2 diabetes mellitus; TZD, thiazolidinedione; AGI, alpha-glucosidase inhibitor; CCI, Charlson comorbidity index; DCSI, Diabetes Complications Severity Index; CV, cardiovascular.

Declarations

We confirmed that all methods were performed in accordance to Declaration of Helsinki.

Ethics approval and consent to participate

To protect privacy, all information that could disclose the identity of residents was encrypted before release. This study was approved by the Institutional Review Board of the National Health Research Institutes (EC1060704-E).

Consent publication

The requirement for informed consent was waived.

Availability of data and materials

Data are available from the NHIRD, published by Taiwan's NHI Bureau. Requests for data can be sent as a formal proposal to the NHIRD (http://nhird.nhri.org.tw) or by email to nhird@nhri.org.tw.

Competing interest
There were no financial competing interests for this study.

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**Authors’ contributions**

FSY, CMH, and CCH conceptualized, designed, and coordinated the study. JSL, JCW, FSY, and CMH collected the data. JSL, CCH, and CMH analyzed and interpreted the data. JCW, CCH, CMH, JSL, and FSY discussed and interpreted the results. FSY, CCH, JCW, JSL, and CMH wrote and revised the manuscript. CCH and CMH are the guarantors of this work, had full access to all study data, and take responsibility for the integrity and accuracy of data analyses. All authors have approved the final content of this manuscript.

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Figures
Figure 1

Kaplan–Meier curves for hospitalization according to different second-line oral antidiabetic drugs
Figure 2

Kaplan–Meier survival curves according to different second-line oral antidiabetic drugs