# Antidiabetic Medications and Mortality Risk in Individuals With Pancreatic Cancer–Related Diabetes and Postpancreatitis Diabetes: A Nationwide Cohort Study

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## OBJECTIVE

**There are no specific treatment guidelines for diabetes of the exocrine pancreas. High-quality studies are warranted to investigate whether the use of antidiabetic medications has survival benefit in individuals with diabetes of the exocrine pancreas. The objective was to determine the risk of mortality associated with the use of antidiabetic medications in individuals with pancreatic cancer–related diabetes (PCRD) and postpancreatitis diabetes mellitus (PPDM).**

## RESEARCH DESIGN AND METHODS

**Nationwide pharmaceutical dispensing data (2006–2015) linked to hospital discharge data were used to identify 1,862 individuals with PCRD or PPDM. Multivariable Cox regression analysis was conducted, and the risk was expressed as hazard ratios and 95% CIs. A 6-month lag was used to minimize reverse causality.**

## RESULTS

**In individuals with PCRD, ever users of metformin (adjusted hazard ratio 0.54; 95% CI 0.46–0.63) and ever users of insulin (adjusted hazard ratio 0.46; 95% CI 0.39–0.55) had significantly lower risks of mortality compared with never users of antidiabetic medications. These associations attenuated toward the null with the use of a 6-month lag. In individuals with PPDM, ever users of metformin had a significantly lower risk of mortality (adjusted hazard ratio 0.51; 95% CI 0.36–0.70), whereas ever-users of insulin did not have a significantly changed risk of mortality (adjusted hazard ratio 0.75; 95% CI 0.49–1.14) compared with never users of antidiabetic medications. The former association remained significant with the use of a 6-month lag.**

## CONCLUSIONS

**Metformin promotes a survival benefit in individuals with PPDM but not PCRD. Reverse causality may play a role in the association between insulin use and mortality in PCRD.**


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Adults with diabetes are at 1.6 to 2.1 times higher risk of mortality than those without diabetes (1,2). Glycemic control by antidiabetic medications reduces the risk of mortality in individuals with type 2 diabetes, as suggested by several randomized trials (3–5). Diabetes of the exocrine pancreas (DEP), previously called "type 3c diabetes," is the second most common type of new-onset diabetes in adults, surpassing type 1 diabetes (6). The largest contributors to DEP are post-pancreatitis diabetes mellitus (PPDM) and pancreatic cancer–related diabetes (PCRD) (7). A recent population-based study by the COSMOS (Clinical and epidemiOlogical inveStigations in Metabolism, nutritiOn, and pancreatic diseaseS) group showed that PPDM leads to excess overall mortality (14.8 per 1,000 person-years) compared with type 2 diabetes (8). Pancreatic cancer is the most lethal disease of the exocrine pancreas, with a 5-year survival rate of <5%, and individuals with PCRD have a 1.5 times higher risk for mortality compared with pancreatic cancer patients without diabetes (9,10). However, there are no specific published guidelines on how best to treat DEP. Further, the multidisciplinary nature of management of DEP (involving both diabetologists and gastroenterologists, surgeons, oncologists, primary care physicians) requires a holistic and concerted management plan that considers not only short-term outcomes (e.g., lowering high blood glucose levels) but also long-term outcomes (e.g., mortality) (7).

More than two-thirds of individuals with pancreatic cancer have diabetes or prediabetes (11). Some population-based studies showed a significantly lower mortality risk associated with the use of metformin (12–16), whereas others (17–19) found no significant survival benefit of metformin in individuals with PCRD. Part of the reason for conflicting findings might be biases inherent in study design and analysis. In particular, findings of previous pharmacoepidemiological studies might have been influenced by immortal time bias and reverse causality. The fact that follow-up time between the time of diabetes diagnosis and first prescription of metformin (the so-called "immortal time") was either misattributed as exposure time or ignored completely might have led to an overestimation of the protective effect of metformin in the published studies (12–15), although it can be mitigated by using a time-dependent analysis (20). Similarly, given that patients with pancreatic cancer are less likely to be prescribed medications when they are close to death, the use of an exposure lag time is recommended to reduce the likelihood of reverse causality (21,22).

Pancreatitis, one of the most frequent risk factors for pancreatic cancer and the most frequent cause of DEP, is known to lead to PPDM in up to 83% of patients (23–25). A 2017 population-based study of new-onset diabetes found that individuals with PPDM are 9.6 times more likely to receive insulin within 1 year after diagnosis of diabetes (and 7.4 times more likely within 5 years) compared with individuals with type 2 diabetes (6). It also showed that mean glycated hemoglobin ($HbA_{1c}$) levels were significantly higher in PPDM versus type 2 diabetes at the time of the diabetes diagnosis and 1 year and 5 years after the diagnosis. Insulin is known to be the first-line treatment option for individuals at high risk of poor glycemic control (26), but its usefulness might be limited to the short-term effect on hyperglycemia. This is supported by the results of a meta-analysis of 22 randomized controlled trials that showed no survival benefit of insulin therapy compared with oral hypoglycemic medications in type 2 diabetes (27). However, no study has examined long-term outcomes of antidiabetic medications in individuals with PPDM.

The study aim was to investigate the risk of mortality associated with the use of antidiabetic medications in a nationwide cohort of individuals with PCRD and PPDM with comprehensive data on dispensed medications, taking into account the possible impact of immortal time bias and reverse causality.

## RESEARCH DESIGN AND METHODS

### Data Source

The Ministry of Health Analytical Services (National Health Board, New Zealand) performed data extraction and linkage and provided the data with encrypted identifiers of all individuals. All publicly funded hospital discharge data were extracted for individuals who were ever diagnosed with acute pancreatitis (ICD-10, K85), chronic pancreatitis (K86.0, K86.1), pancreatic cancer (C25), and diabetes (E10, E11, E13) between 1 January 1998 and 31 December 2015. The data were contained to individuals' demographics (age, sex, ethnicity, area of residence) and admission (ICD-10 codes and date of admission). These data were linked to a mortality database (date of death) and a pharmaceutical dispensing database (dispensed date, chemical name, dose, and days of supply). Pharmaceutical dispensing data (covering primary, secondary, and tertiary health care in the entire country) were available between 1 January 2006 and 31 December 2015. This study was exempt from ethical approval according to the Ministry of Health guidelines.

### Study Individuals

To identify individuals with PPDM, we selected those who were ever diagnosed with pancreatitis but never with pancreatic cancer during the entire study period ($n$ = 19,641). After that, individuals aged 21 years and older who were first diagnosed with diabetes from 2006 to 2015 (based on the availability of pharmaceutical dispensing data) and >90 days after the first pancreatitis diagnosis (to rule out preexisting diabetes or stress-induced hyperglycemia) (7,28, 29) were selected ($n$ = 2,332). Three exclusion criteria were applied then: diagnosis of type 1 diabetes (ICD-10, E10) during the entire study period, any other diagnosis of diabetes before or at the time of the first pancreatitis admission, and diagnosis of diabetes within 90 days after the first pancreatitis diagnosis (7,28,29). Finally, 836 individuals with PPDM were identified (Supplementary Fig. 1).

To identify individuals with PCRD, two complementary nonoverlapping approaches were used. First, individuals with a diagnosis of pancreatic cancer were identified ($n$ = 7,432). Then, individuals aged 21 years and older who were first diagnosed with diabetes between 2006 and 2015 during and after the first admission for pancreatic cancer were selected ($n$ = 603). Two exclusion criteria were applied then: diagnosis of type 1 diabetes (ICD-10, E10) and any other diagnosis of diabetes before the first pancreatic cancer diagnosis. Second, individuals with a diagnosis of diabetes during the entire study period were first identified ($n$ = 225,391). Among them,

individuals aged 21 years and older who were first diagnosed with diabetes between 2006 and 2015 and subsequently diagnosed with pancreatic cancer within 36 months after the first diagnosis of diabetes (i.e., new-onset diabetes in presymptomatic pancreatic cancer [30,31]) were selected ($n$ = 582). After those with a diagnosis of type 1 diabetes were excluded, 1,026 individuals with PCRD were identified (Supplementary Fig. 1).

To identify individuals with type 2 diabetes (and without PPDM or PCRD), individuals who were first diagnosed with type 2 diabetes (ICD-10, E11) between 2006 and 2015 ($n$ = 116,402) were selected. Those with the diagnoses of pancreatitis, pancreatic cancer, type 1 diabetes, and other specified diabetes during the entire study period were excluded. Finally, 114,202 individuals with type 2 diabetes were identified (Supplementary Fig. 1).

### Follow-up

The primary end point was overall mortality. The secondary end points were mortality from cardiovascular disease (ICD-10, Ixx), cancer (Cxx), and other causes. Date of the first admission with a diagnosis of diabetes in any position from 2006 to 2015 was set as the index date. All individuals were monitored to the end of the observation period (31 December 2015) or date of death, whichever occurred first.

### Antidiabetic Medications

Dispensing of antidiabetic medications was used as a proxy for use of antidiabetic medications. Antidiabetic medications included oral hypoglycemic medications (metformin, sulfonylureas, α-glucosidase inhibitors, and thiazolidinediones) and insulin. The exposure to insulin during the entire observation period (i.e., 2006–2015) was categorized as no antidiabetic medications (never users of antidiabetic medications), any antidiabetic medications with insulin never used (insulin never users), and insulin ever used alone or in combination with other antidiabetic medications (insulin ever users). The identical categorization was applied for the exposure to metformin.

### Covariates

Individuals who ever had ICD codes for alcohol abuse (ICD-10, F10) and tobacco smoking (Z72.0, Z86.43, Z87.891) (32) were identified throughout the entire observation period. The Charlson comorbidity index, a widely used method of predicting mortality by weighting comorbid conditions, was calculated in line with the published recommendations (33). Ethnicity was categorized as European, Māori or Pacific Islander, Asian, and others. The social deprivation index (ranging from 1 to 10) was matched with each individual's area of residence (32) and was categorized into quartiles; those with missing values were classified into a separate category.

### Statistical Analysis

All analyses were performed using SAS 9.4 software (SAS Institute, Cary, NC). A two-sided $P < 0.05$ was set as statistical significance. The Kaplan-Meier curves were created to compare survival probability according to antidiabetic medication use. The significance of the differences in survival probability was tested by a log-rank test (across the three groups) and by the Šidák correction of multiple comparisons (between two groups). Mortality rate was calculated as the number of deaths per 100 person-years. Crude and multivariable Cox regression analyses (adjusting for age, sex, ethnicity, social deprivation index, alcohol abuse, tobacco smoking, and the Charlson comorbidity index) were performed to yield the risk of mortality related to antidiabetic medication use in individuals with PPDM or PCRD. In all Cox regression models, the reference category was never use of antidiabetic medications. Graphical plots were used to examine the assumption for proportionality, and no violations were identified. The risk of mortality associated with the use of antidiabetic medications was expressed as hazard ratios (HRs) with 95% CIs.

Four prespecified sensitivity analyses were performed in PPDM and PCRD individuals separately. First, in the analysis constrained to first prescribed antidiabetic medications, a subset of individuals first diagnosed with diabetes between 2007 and 2015 were analyzed. Given that there are no specific recommendations on the first-line therapy for DEP, this sensitivity analysis enabled us to investigate antidiabetic medications first prescribed to individuals with DEP in current clinical practice. To ensure the inclusion of first prescribed antidiabetic medications, individuals with at least one dispensing record of antidiabetic medications during 1 year before the index date were excluded. First prescribed antidiabetic medications were categorized as follows: no antidiabetic medications, metformin monotherapy, insulin as monotherapy or in combination with other antidiabetic medications, and others.

Second, the same analyses were repeated when constrained to long-term use of antidiabetic medications. Long-term use of antidiabetic medications was defined as at least one dispensing record over 1 month after the first dispensing record or two dispensing records within a 2-month period after the first dispensing record.

Third, to account for varied drug initiation date among individuals and to minimize immortal time bias, a time-varying Cox regression analysis was used (34). This analysis was constrained to dispensing records after the index date, and never users of antidiabetic medications were treated as nonusers of metformin or insulin. In the time-varying Cox regression analysis, the use of metformin or insulin was included as a time-dependent variable. Individuals were classified as nonusers during the time from follow-up start to their first dispensing records (i.e., immortal time), from which point they were then reclassified as users until the end of follow-up. As a result of this approach, the protective effect of antidiabetic medications on mortality was less prone to overestimation (20).

Fourth, to reduce the possibility of reverse causation (i.e., individuals with longer survival have a greater chance of receiving antidiabetic medications), we constrained the analysis to individuals with long-term (≥6 months) follow-up.

In addition, a post hoc analysis was performed in PPDM to examine a dose-response relationship between the first prescribed daily metformin dose and the risk of mortality, constrained to individuals without any antidiabetic medications during 1 year before the index date. This analysis enabled us to investigate initial daily doses of metformin and their associations with survival in individuals with PPDM. This analysis excluded individuals without information on the metformin dose (defined as a total amount prescribed divided by days of supply) and those with metformin combined with insulin. The reference

**Table 1—Characteristics of the study population**

| | PPDM (*n* = 836) | PCRD (*n* = 1,026) | Type 2 diabetes (*n* = 114,202) |
|---|---|---|---|
| Age, mean (SD), years | 64.6 (16.1) | 70.0 (11.4) | 63.7 (14.5) |
| Men, *n* (%) | 485 (58.0) | 539 (52.5) | 59,689 (52.3) |
| Ethnicity, *n* (%) | | | |
| European | 557 (66.6) | 748 (72.9) | 65,118 (57.0) |
| Māori/Pacific Islander | 220 (26.3) | 185 (18.0) | 32,281 (28.3) |
| Asian | 48 (5.7) | 59 (5.8) | 11,761 (10.3) |
| Other | 11 (1.3) | 34 (3.3) | 5,042 (4.4) |
| Social deprivation index, *n* (%) | | | |
| Quartile 1 | 163 (19.5) | 262 (25.5) | 25,086 (22.0) |
| Quartile 2 | 161 (19.3) | 201 (19.6) | 30,944 (27.1) |
| Quartile 3 | 209 (25.0) | 228 (22.2) | 30,945 (27.1) |
| Quartile 4 | 272 (32.5) | 276 (26.9) | 19,909 (17.4) |
| Missing | 31 (3.7) | 59 (5.8) | 7,318 (6.4) |
| Alcohol abuse, *n* (%) | 128 (15.3) | 13 (1.3) | 2,587 (2.3) |
| Tobacco smoking, *n* (%) | 576 (68.9) | 578 (56.3) | 59,737 (52.3) |
| Charlson comorbidity index, mean (SD) | 1.3 (0.8) | 2.2 (1.3) | 1.3 (0.9) |
| Never users of antidiabetic medications, *n* (%) | 258 (30.9) | 295 (28.8) | 22,270 (19.5) |
| Insulin use, *n* (%) | | | |
| Never insulin | 377 (45.1) | 291 (28.4) | 63,632 (55.7) |
| Ever insulin | 201 (24.0) | 440 (42.9) | 28,300 (24.8) |
| Metformin use, *n* (%) | | | |
| Never metformin | 80 (9.6) | 170 (16.6) | 7,334 (6.4) |
| Ever metformin | 498 (59.6) | 561 (54.7) | 84,598 (74.1) |

group was individuals who did not receive metformin. Natural cubic spline Cox regression analysis with four knots at 5, 25, 75, and 95 percentiles was used (35).

## RESULTS

### Characteristics of Study Individuals

The main analysis included 836 individuals with PPDM and 1,026 individuals with PCRD (Table 1). The median follow-up periods were 835 days (interquartile range 327–1,431) in individuals with PPDM and 259 days (interquartile range 76–692) in individuals with PCRD. Insulin use was recorded in 24.0% (*n* = 201) of individuals with PPDM and in 42.9% (*n* = 440) of individuals with PCRD. Metformin use was recorded in 59.6% (*n* = 498) of individuals with PPDM and in 54.7% (*n* = 561) of individuals with PCRD.

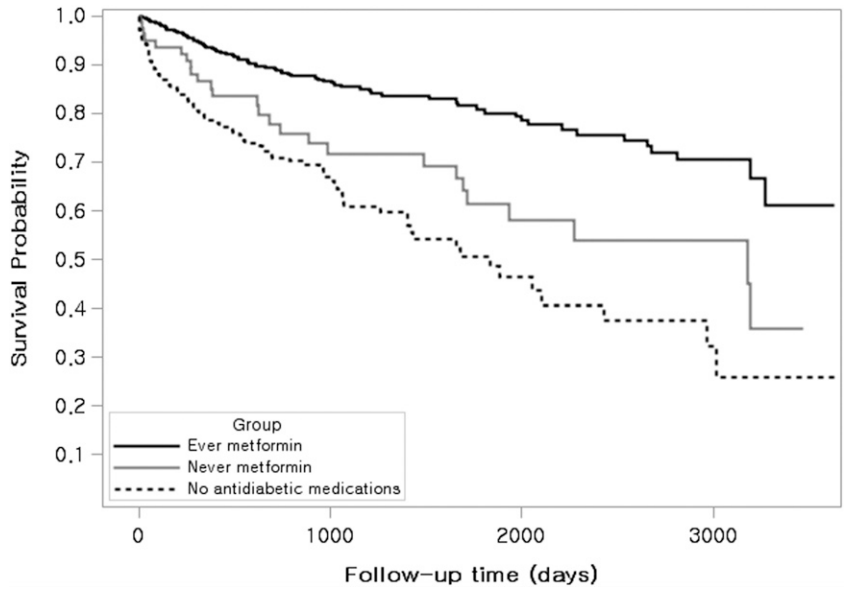


**Figure 1**—Survival probability of individuals with PPDM stratified by the use of antidiabetic medications.

### Associations Between Metformin Use and Mortality

Among individuals with PPDM, there were statistically significant differences in mortality risk across the metformin exposure groups in the main analysis (Fig. 1). Never users of antidiabetic medications had the lowest survival probability, followed by metformin never users and metformin ever users (log-rank test $P < 0.001$). The differences in survival probabilities were statistically significant for all the pairwise comparisons ($P < 0.001$). Compared with never users of antidiabetic medications, ever users of metformin had a significantly lower risk of mortality (adjusted HR 0.51; 95% CI 0.36–0.71) (Table 2). The lower mortality risk associated with metformin use was more pronounced in individuals with PPDM compared with those with type 2 diabetes (adjusted HR 0.75; 95% CI 0.72–0.77). There was no significant association between metformin use and cause-specific mortality in individuals with PPDM (Supplementary Table 1).

In the sensitivity analysis constrained to long-term use of antidiabetic medications, the lower risk of mortality associated with ever use of metformin (adjusted HR 0.50; 95% CI 0.36–0.70) remained statistically significant compared with never use of antidiabetic medications in individuals with PPDM (Table 3). In the sensitivity analysis constrained to individuals with long-term follow-up, the lower risk of mortality associated with ever use of metformin (adjusted HR 0.65; 95% CI 0.44–0.96) remained statistically significant. In the sensitivity analysis constrained to metformin as a time-varying variable, the lower risk of mortality associated with ever use of metformin was statistically significant in the unadjusted analysis (HR 0.53; 95% CI 0.39–0.71) but not in the adjusted analysis (HR 0.88; 95% CI 0.63–1.21). In the sensitivity analysis constrained to first prescribed antidiabetic medications, individuals who were prescribed metformin monotherapy had a significantly lower risk of mortality compared with never users of antidiabetic medications (adjusted HR 0.22; 95% CI 0.09–0.53). In the post hoc analysis, the median first prescribed metformin dose

**Table 2—Associations between the use of antidiabetic medications and mortality in individuals with DEP and type 2 diabetes**

| | Mortality rate per 100 person-years | Crude HR (95% CI) | Adjusted HR (95% CI) |
|---|---|---|---|
| Insulin use | | | |
| PPDM | | | |
| No antidiabetic medications | 16.47 (12.78–20.15) | 1.00 | 1.00 |
| Never insulin | 5.87 (4.42–7.31) | 0.37 (0.27–0.51) | 0.51 (0.36–0.71) |
| Ever insulin | 5.20 (3.51–6.89) | 0.34 (0.23–0.50) | 0.75 (0.49–1.14) |
| PCRD | | | |
| No antidiabetic medications | 126.91 (95.64–158.19) | 1.00 | 1.00 |
| Never insulin | 65.49 (56.74–74.24) | 0.52 (0.44–0.62) | 0.59 (0.49–0.71) |
| Ever insulin | 49.06 (42.99–55.12) | 0.41 (0.35–0.49) | 0.46 (0.39–0.55) |
| Type 2 diabetes | | | |
| No antidiabetic medications | 9.67 (9.42–9.92) | 1.00 | 1.00 |
| Never insulin | 5.05 (4.96–5.15) | 0.53 (0.52–0.55) | 0.80 (0.78–0.83) |
| Ever insulin | 4.10 (3.98–4.21) | 0.45 (0.43–0.47) | 0.86 (0.83–0.90) |
| Metformin use | | | |
| PPDM | | | |
| No antidiabetic medications | 16.47 (12.78–20.15) | 1.00 | 1.00 |
| Never metformin | 10.29 (6.11–14.46) | 0.66 (0.42–1.02) | 0.88 (0.55–1.40) |
| Ever metformin | 4.87 (3.77–5.97) | 0.31 (0.23–0.43) | 0.51 (0.36–0.70) |
| PCRD | | | |
| No antidiabetic medications | 126.91 (95.64–158.19) | 1.00 | 1.00 |
| Never metformin | 48.71 (37.84–59.59) | 0.43 (0.35–0.53) | 0.44 (0.36–0.54) |
| Ever metformin | 57.02 (51.43–62.61) | 0.46 (0.40–0.54) | 0.54 (0.46–0.63) |
| Type 2 diabetes | | | |
| No antidiabetic medications | 9.67 (9.42–9.92) | 1.00 | 1.00 |
| Never metformin | 10.92 (10.51–11.34) | 1.17 (1.12–1.23) | 1.25 (1.20–1.31) |
| Ever metformin | 4.16 (4.09–4.23) | 0.44 (0.43–0.46) | 0.75 (0.72–0.77) |

Mortality rate data are presented as mean (95% CI). Adjusted HRs were from multivariable Cox regression models including age, sex, ethnicity, alcohol abuse, tobacco smoking, social deprivation index, and the Charlson comorbidity index. The "ever insulin" subgroup included individuals who were prescribed insulin alone or in combination with other antidiabetic medications.

was 1,000 mg/day (interquartile range 500–1,000), and the risk of mortality was significantly lower in metformin users with up to 1,200 mg daily dose compared with nonmetformin users (Supplementary Fig. 2).

Among individuals with PCRD, ever users of metformin (adjusted HR 0.54; 95% CI 0.46–0.63) and never users of metformin (adjusted HR 0.44; 95% CI 0.36–0.54) had significantly lower risks of mortality than never users of antidiabetic medications in the main analysis (Table 2). The lower mortality risk associated with ever use of metformin was more pronounced in individuals with PCRD compared with those with type 2 diabetes (adjusted HR 0.75; 95% CI 0.72–0.77). There were significant associations between ever use of metformin and lower risks of cardiovascular and cancer mortality in individuals with PCRD (Supplementary Table 1). The lower risks of mortality associated with never use of metformin (adjusted HR 0.46; 95% CI 0.38–0.56) and ever use of metformin (adjusted HR 0.54; 95% CI 0.46–0.63), compared with never use of antidiabetic medications, remained statistically significant in the sensitivity analysis constrained to long-term use of antidiabetic medications. However, in the sensitivity analyses constrained to individuals with long-term follow-up, to metformin as a time-varying variable, and to first prescribed antidiabetic medications, none of the associations were statistically significant.

### Associations Between Insulin Use and Mortality

Among individuals with PPDM, never use of insulin was associated with a significantly lower risk of mortality compared with never use of antidiabetic medications (adjusted HR 0.51; 95% CI 0.36–0.71), but ever use of insulin did not show significance in the main analysis (Table 2). There were no significant associations between ever use of insulin and risks of cardiovascular and cancer mortality in the adjusted analyses (Supplementary Table 1). In the sensitivity analysis constrained to individuals with long-term follow-up, never use of insulin (vs. never use of antidiabetic medications) was significantly associated with a lower risk of mortality (adjusted HR 0.62; 95% CI 0.41–0.92). The higher risk of mortality associated with ever use of insulin was statistically significant in the sensitivity analysis constrained to insulin as a time-varying variable (adjusted HR 1.75; 95% CI 1.17–2.60). The sensitivity analyses constrained to first prescribed antidiabetic medications and long-term use of antidiabetic medications did not show a statistically significant difference in risk of mortality between ever users of insulin and never users of antidiabetic medications in individuals with PPDM (Table 3).

Among individuals with PCRD, never users of insulin (adjusted HR 0.59; 95% CI 0.49–0.71) and ever users of insulin (adjusted HR 0.46; 95% CI 0.39–0.55) had significantly lower risks for mortality compared with never users of antidiabetic medications in the main analysis (Table 2). The lower risk for mortality associated with ever use of insulin was more pronounced in individuals with PCRD than in those with type 2 diabetes (adjusted HR 0.86; 95% CI 0.83–0.90). There were significant associations between ever use of insulin and lower risks of cardiovascular and cancer mortality in individuals with PCRD (Supplementary Table 1). In the sensitivity analysis constrained to long-term use of antidiabetic medications, the lower risks of mortality

**Table 3—Sensitivity analyses of the associations between antidiabetic medication use and mortality in individuals with DEP**

| | Deaths, *n* (%) | Crude HR (95% CI) | Adjusted HR (95% CI) |
|---|---|---|---|
| Constrained to first prescribed antidiabetic medications | | | |
| PPDM | | | |
| No antidiabetic medications (*n* = 210) | 66 (31.4) | 1.00 | 1.00 |
| Metformin monotherapy (*n* = 73) | 6 (8.2) | 0.17 (0.07–0.39) | 0.22 (0.09–0.53) |
| Insulin therapy (*n* = 39) | 9 (23.1) | 0.44 (0.22–0.89) | 0.86 (0.40–1.84) |
| Others (*n* = 21) | 6 (28.6) | 0.60 (0.26–1.39) | 0.56 (0.23–1.32) |
| PCRD | | | |
| No antidiabetic medications (*n* = 149) | 120 (80.5) | 1.00 | 1.00 |
| Metformin monotherapy (*n* = 51) | 45 (88.2) | 0.65 (0.46–0.91) | 0.71 (0.50–1.01) |
| Insulin therapy (*n* = 72) | 53 (73.6) | 0.55 (0.40–0.76) | 0.57 (0.41–0.81) |
| Others (*n* = 29) | 25 (86.2) | 0.63 (0.41–0.96) | 0.68 (0.44–1.07) |
| Constrained to long-term use of antidiabetic medications | | | |
| Insulin use | | | |
| PPDM | | | |
| No antidiabetic medications (*n* = 258) | 90 (34.9) | 1.00 | 1.00 |
| Never insulin (*n* = 407) | 74 (18.2) | 0.38 (0.28–0.52) | 0.53 (0.38–0.73) |
| Ever insulin (*n* = 171) | 30 (17.5) | 0.31 (0.21–0.47) | 0.71 (0.45–1.12) |
| PCRD | | | |
| No antidiabetic medications (*n* = 295) | 252 (85.4) | 1.00 | 1.00 |
| Never insulin (*n* = 363) | 317 (87.3) | 0.51 (0.43–0.60) | 0.56 (0.48–0.67) |
| Ever insulin (*n* = 368) | 295 (80.2) | 0.41 (0.34–0.48) | 0.46 (0.39–0.55) |
| Metformin use | | | |
| PPDM | | | |
| No antidiabetic medications (*n* = 258) | 90 (34.9) | 1.00 | 1.00 |
| Never metformin (*n* = 131) | 31 (23.7) | 0.50 (0.33–0.75) | 0.79 (0.51–1.21) |
| Ever metformin (*n* = 447) | 73 (16.3) | 0.32 (0.24–0.44) | 0.50 (0.36–0.70) |
| PCRD | | | |
| No antidiabetic medications (*n* = 295) | 252 (85.4) | 1.00 | 1.00 |
| Never metformin (*n* = 208) | 169 (81.3) | 0.45 (0.37–0.55) | 0.46 (0.38–0.56) |
| Ever metformin (*n* = 523) | 443 (84.7) | 0.46 (0.39–0.53) | 0.54 (0.46–0.63) |
| Constrained to antidiabetic medications as time-varying variables | | | |
| Insulin use | | | |
| PPDM | | | |
| Never insulin (*n* = 646) | 158 (24.5) | 1.00 | 1.00 |
| Ever insulin (*n* = 190) | 36 (19.0) | 0.88 (0.61–1.28) | 1.75 (1.17–2.60) |
| PCRD | | | |
| Never insulin (*n* = 594) | 520 (87.5) | 1.00 | 1.00 |
| Ever insulin (*n* = 432) | 344 (79.6) | 1.06 (0.92–1.22) | 1.08 (0.94–1.25) |
| Metformin use | | | |
| PPDM | | | |
| Never metformin (*n* = 364) | 122 (33.5) | 1.00 | 1.00 |
| Ever metformin (*n* = 472) | 72 (15.3) | 0.53 (0.39–0.71) | 0.88 (0.63–1.21) |
| PCRD | | | |
| Never metformin (*n* = 604) | 509 (84.3) | 1.00 | 1.00 |
| Ever metformin (*n* = 422) | 355 (84.1) | 0.90 (0.78–1.03) | 1.05 (0.91–1.22) |
| Constrained to individuals with long-term follow-up | | | |
| Insulin use | | | |
| PPDM | | | |
| No antidiabetic medications (*n* = 186) | 54 (29.0) | 1.00 | 1.00 |
| Never insulin (*n* = 335) | 51 (15.2) | 0.44 (0.30–0.65) | 0.62 (0.41–0.92) |
| Ever insulin (*n* = 183) | 34 (18.6) | 0.44 (0.29–0.69) | 1.05 (0.65–1.71) |
| PCRD | | | |
| No antidiabetic medications (*n* = 87) | 63 (72.4) | 1.00 | 1.00 |
| Never insulin (*n* = 191) | 166 (86.9) | 1.06 (0.79–1.41) | 1.05 (0.78–1.41) |
| Ever insulin (*n* = 317) | 236 (74.5) | 0.82 (0.62–1.08) | 0.86 (0.64–1.14) |
| Metformin use | | | |
| PPDM | | | |
| No antidiabetic medications (*n* = 186) | 54 (29.0) | 1.00 | 1.00 |
| Never metformin (*n* = 68) | 21 (30.9) | 0.80 (0.48–1.33) | 1.07 (0.62–1.83) |
| Ever metformin (*n* = 450) | 64 (14.2) | 0.39 (0.27–0.56) | 0.65 (0.44–0.96) |
| PCRD | | | |
| No antidiabetic medications (*n* = 87) | 63 (72.4) | 1.00 | 1.00 |
| Never metformin (*n* = 116) | 87 (75.0) | 0.80 (0.58–1.11) | 0.85 (0.61–1.18) |
| Ever metformin (*n* = 392) | 315 (80.4) | 0.94 (0.71–1.23) | 0.96 (0.72–1.26) |

Adjusted HRs were from multivariable Cox regression models including age, sex, ethnicity, alcohol abuse, tobacco smoking, social deprivation index, and the Charlson comorbidity index. The "insulin therapy" and "ever insulin" subgroups included individuals who were prescribed insulin alone or in combination with other antidiabetic medications.

associated with never use of insulin (adjusted HR 0.56; 95% CI 0.48–0.67) and ever use of insulin (adjusted HR 0.46; 95% CI 0.39–0.55) remained statistically significant compared with never use of antidiabetic medications. The sensitivity analysis constrained to first prescribed antidiabetic medications showed that insulin therapy was significantly associated with a lower risk of mortality (adjusted HR 0.57; 95% CI 0.41–0.81) compared with never use of antidiabetic medications. In the sensitivity analysis constrained to long-term follow-up, none of the associations were significant in the adjusted analysis (Table 3). In the sensitivity analysis constrained to insulin as a time-varying variable, there was no statistically significant difference in risk of mortality between never users and ever users of insulin (Table 3).

## CONCLUSIONS

This population-based cohort study is the first to investigate the risk of mortality associated with the use of antidiabetic medications specifically in individuals with PPDM or PCRD. The two disorders were identified using an expanded search strategy of automated nationwide data with a long observation period. This approach enabled us to avoid recall bias and information bias in defining exposure and covariates. The use of time-varying drug exposure and a 6-month lag period of follow-up ensured that the probability of immortal time bias and reverse causality was reduced. The use of nationwide prospective dispensing records at all levels of health care suggests that the findings are generalizable. The study showed that individuals with PPDM or PCRD have divergent risks of mortality related to the use of antidiabetic medications. Metformin use was associated with a significantly lower mortality risk in individuals with PPDM, which was consistently observed in the main analysis and most of the prespecified sensitivity analyses. Furthermore, the lower mortality risk associated with metformin use in individuals with PPDM was more pronounced than in those with type 2 diabetes. Individuals with PCRD also showed the association between metformin use and a lower risk of mortality in the main analysis, but this was likely due to reverse causality because the association was not significant in most of the prespecified sensitivity analyses. Similarly, insulin use was associated with a lower mortality risk in individuals with PCRD in the main analysis, but this could be attributed (at least in part) to reverse causality and immortal time bias because the association was not significant in most of the prespecified sensitivity analyses.

There are no evidence-based guidelines on treatment of PPDM, but the findings from a 2017 population-based cohort study on new-onset diabetes from the U.K. showed that insulin is used frequently in this population (6). Specifically, whereas only 1.4% of individuals with type 2 diabetes without prior disease of the exocrine pancreas received insulin within 1 year of diabetes diagnosis, 13.4% of individuals with PPDM received insulin within 1 year of the diabetes diagnosis (6). This practice did not result in improved short-term outcomes (i.e., blood glucose control) in individuals with PPDM, and the effect on long-term outcomes (e.g., mortality) was not investigated. The current study adds to the literature by demonstrating that metformin use is associated with significant survival benefits in individuals with PPDM. This association remained significant after excluding individuals with short-term follow-up, hence, reducing the likelihood of reverse causality (which is important because individuals with PPDM with short survival have less of a chance of receiving metformin, for example, due to acute diabetes complications such as diabetic ketoacidosis or hyperosmolar coma). Consistent with that, PPDM individuals who never used insulin have a significantly lower mortality in the sensitivity analysis constrained to long-term follow-up.

These population-based data are in line with the recent studies by the COMSOS group into early pathogenetic events in PPDM that showed that individuals with PPDM are characterized by hyperinsulinemia, decreased insulin sensitivity, lipolysis of adipose tissue, and gut dysfunction (among other features) (36–44), which can (at least in part) be reverted by metformin. In addition, a 2018 study showed that the antidiabetic effect of metformin in living cells is linked to iron metabolism (45), and two 2018 clinical studies by the COSMOS group independently established the connection between iron metabolism and PPDM (46,47). It is important to acknowledge possible confounding by indication because users of antidiabetic medications may have poorer glycemic control and, hence, may be poised to have a higher mortality risk compared with nonusers of antidiabetic medications, who may have been prescribed lifestyle modifications only. However, metformin use (vs. no antidiabetic medications) was associated with a lower mortality risk in the current study, which suggests that the mortality-reducing effect of metformin outweighs the possible confounding effect of poor glycemic control on mortality. Also, the finding suggests that metformin use can significantly improve survival of individuals with PPDM who are deemed to have a mild form of dysglycemia and, hence, do not receive any antidiabetic medication.

The above findings provide the first evidence-based justification for recommending metformin monotherapy as the first-line therapy in individuals with PPDM. Further, the analysis of the dose-response relationship (Supplementary Fig. 2) suggests that the metformin dose of 1,000 mg/day might be optimal in this population. We acknowledge that a common practice is to start with a low dose of metformin and titrate it up over 4–6 weeks to avoid gastrointestinal side effects. However, this is unlikely to meaningfully affect the recommended metformin dose because the average daily dose of metformin did not vary considerably in our cohort; for example, the average dose on the second dispensing records (median 1,000 mg/day [interquartile range 500–1,500]) was similar to the first ones (median 1,000 mg/day [interquartile range 500–1,000]).

The other notable finding in the current study was that metformin use is not associated with a significant survival benefit among individuals with PCRD in most of the prespecified sensitivity analyses. Specifically, the use of a 6-month exposure lag time (to minimize reverse causality) and recognition of the follow-up time during which individuals could not, by definition, incur the study outcome (to minimize immortal time bias) ensured that the yielded risk of mortality associated with metformin use in PCRD is conservative. Survival

benefits of metformin reported in some of the published population-based studies (12–15) might have been due to immortal time bias, which is frequently observed but rarely accounted for in pharmacoepidemiological studies. Conventional Cox regression analysis is susceptible to this bias and can overestimate the protective effect of a drug (20). The current study minimized immortal time bias by using a time-varying Cox regression analysis and the results were consistent with, to the best of our knowledge, the only other population-based study in the PCRD literature using the similarly robust statistical approach (17). Further, two randomized controlled trials of metformin, published in 2015 and 2016, reported no effect on survival (48,49). An unexpected finding in the current study was that insulin never users were at a significantly 1.3 times higher mortality risk compared with insulin ever users among individuals with PCRD. However, the association did not remain significant in the sensitivity analysis constrained to individuals with long-term follow-up, suggesting that the above significant association might be due to reverse causation. Further well-designed studies on insulin use in individuals with PCRD are warranted to inform the development of treatment guidelines.

There are further points to consider when interpreting the results of the current study. First, diagnosis of diabetes was established using tertiary care data; hence, it is possible that some of the individuals in our cohort were diagnosed with diabetes in the community before the first hospital admission with the diagnosis of diabetes. This might have affected the associations between antidiabetic medications and mortality. However, the pharmaceutical dispensing database used in the study covered all levels of health care, and this enabled us to determine the drug exposure status in a conservative way (based on the entire observation period, including before the first hospital admission). Furthermore, the sensitivity analysis constrained to new users of antidiabetic medications (including in the community, regardless of the need for hospitalization) yielded findings similar to those of the main analysis.

Second, the identification of DEP was based on ICD codes because fasting blood glucose or $HbA_{1c}$ data were not available. Hence, the number of individuals with PCRD and individuals with PPDM might have been underestimated. However, this would not have affected the studied associations differentially.

Third, dispensing of antidiabetic medications was used as a proxy for antidiabetic medications use, and information on antidiabetic medication compliance was not available. Some individuals might not have used antidiabetic medications as prescribed (50). However, the unavailability of compliance data may have resulted in conservative estimates, particularly in examining first prescribed antidiabetic medications. Although information on compliance is not available in most of the nationwide administrative databases, using a proxy such as medication possession ratio (16) could be useful in future investigations.

In conclusion, the use of metformin is associated with significant survival benefits in individuals with PPDM but not PCRD. Metformin monotherapy appears to be the best front-line treatment in individuals with PPDM. The optimal diabetes therapy in individuals with PCRD warrants further investigations. These findings will inform the first evidence-based treatment guidelines for individuals with DEP, development of which should receive attention of all health care specialists (diabetologists, oncologists, gastroenterologists, primary care physicians, and surgeons) involved in the treatment of PPDM and PCRD.

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