Glucose-Lowering Therapy in Patients With Postpancreatitis Diabetes Mellitus: A Nationwide Population-Based Cohort Study

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OBJECTIVE

Postpancreatitis diabetes mellitus (PPDM) is a type of secondary diabetes that requires special considerations for management. The main objective was to examine prescription patterns of glucose-lowering therapy among adults with PPDM compared with type 1 and type 2 diabetes.

RESEARCH DESIGN AND METHODS

In a Danish nationwide population-based cohort study, we identified all individuals with adult-onset diabetes in the period 2000–2018 and categorized them as having type 1 diabetes, type 2 diabetes, or PPDM. We ascertained diabetes incidence rates, clinical and demographic characteristics, and classifications and prescription patterns of glucose-lowering therapy and compared these parameters across diabetes subgroups.

RESULTS

Among 398,456 adults with new-onset diabetes, 5,879 (1.5%) had PPDM, 9,252 (2.3%) type 1 diabetes, and the remaining type 2 diabetes (96.2%). The incidence rate of PPDM was 7.9 (95% CI 7.7–8.1) per 100,000 person-years versus 12.5 (95% CI 12.2–12.7) for type 1 diabetes (incidence rate ratio 0.6 [95% CI 0.6–0.7]; $P < 0.001$). A sizeable proportion of patients with PPDM were classified as having type 2 diabetes (44.9%) and prescribed sulfonylureas (25.2%) and incretin-based therapies (18.0%) that can potentially be harmful in PPDM. In contrast, 35.0% of patients never received biguanides, which are associated with a survival benefit in PPDM. Increased insulin requirements were observed for patients with PPDM compared with type 2 diabetes (hazard ratio 3.10 [95% CI 2.96–3.23]; $P < 0.001$) in particular for PPDM associated with chronic pancreatitis (hazard ratio 4.30 [95% CI 4.01–4.56]; $P < 0.001$).

CONCLUSIONS

PPDM is a common type of secondary diabetes in adults but is often misclassified and treated as type 2 diabetes, although PPDM requires special considerations for management.

Postpancreatitis diabetes mellitus (PPDM) is a frequent complication of acute and chronic pancreatitis, and, after type 2 diabetes, it is one of the most prevalent types of adult-onset diabetes (1,2). Due to a globally increasing incidence of acute

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and chronic pancreatitis, the incidence of PPDM is expected to increase, which makes it an important and evolving clinical problem (3–5). However, until now, PPDM has not been widely recognized as a unique entity and is often classified as type 2 diabetes (2).

Although guidelines and recommendations for management of PPDM have been underdeveloped, most experts in the field agree that PPDM needs special considerations for management. Due to misclassification, most patients with PPDM are initially treated as having type 2 diabetes but often have an increased risk of poor glycemic control and complications, excess mortality, and early requirements for insulin therapy (2,6). Consequently, patients with PPDM are often changed to insulin therapy (monotherapy) following a short trial of oral glucose-lowering therapy or started directly on insulin. However, biguanides (metformin) seem to promote a survival benefit in individuals with PPDM, as opposed to insulin, and may also possess antineoplastic effects (7). This is particularly important in people with a history of pan-creatitis who have an excess risk of pancreatic cancer (8,9). Therefore, most experts recommend that biguanides are prescribed and maintained in all individuals with PPDM irrespective of their requirement for insulin (10,11). Also, misclassification of PPDM as type 2 diabetes may lead to prescription of incretin-based therapies, which should be used with caution in patients with pancreatitis (12). Likewise, sulfonylureas (SU) are, by most experts, considered unsafe in patients with PPDM due to their increased risk of inducing hypoglycemia (10). Notwithstanding these important considerations for management, there are currently no population-based studies describing the use of oral glucose-lowering therapies in this context. A detailed characterization of glucose-lowering drugs prescribed for patients with PPDM may highlight pitfalls in current management strategies and stimulate development of management guidelines.

We hypothesized that a large proportion of individuals with PPDM are classified and treated as having type 2 diabetes and consequently receive potentially harmful glucose-lowering drugs (incretin-based therapies or SU) or are withheld from potentially beneficial treatments (biguanides). The aims of this population-based study were to: *1*) calculate and compare incidence rates (IR) of diabetes subgroups; *2*) compare demographic and clinical characteristics of diabetes subgroups; *3*) analyze classification patterns of PPDM; and *4*) investigate prescription patterns of glucose-lowering therapies for patients with PPDM, type 1 diabetes, and type 2 diabetes.

RESEARCH DESIGN AND METHODS

Study Design and Data Sources

This was a historical nationwide Danish cohort study including all cases of adult new-onset diabetes between 1 January 2000 and 31 December 2018. Information on diabetes diagnoses, comorbidities, demographic and clinical characteristics, and a history of acute or chronic pancreatitis was obtained through linkage with the Danish National Patient Registry. This nationwide registry covers all nonpsychiatric hospital admissions since 1977 and all outpatient and emergency room contacts since 1995. Data have been coded according to the ICD-10 since 1994 and include relevant discharge diagnoses and corresponding dates (13). Information on glucose-lowering drug prescriptions was obtained from the Danish National Health Service Prescription Registry (14). Data on sex, birth date, as well as emigration date and date of death (if applicable) were retrieved from the Danish Central Person Registration system, which ensures complete follow-up with respect to emigration and death (15,16).

Study Population

The cohort eligible for this study comprised all adult individuals (≥18 years) with new-onset diabetes during the study period. Eligible individuals were included and categorized into diabetes subgroups through linkage with National Health Registries using the criteria described below. We excluded individuals with missing or misinformed data on sex, birth date, or date of death (if applicable). In addition, we excluded people with a diagnosis of pancreatic cancer between 1 January 1996 and the end of the study period in order to focus the study on PPDM. An overview of study enrollment and timeline are shown in Supplementary Figs. 1 and 2, respectively.

Definition and Classification of Type 1 and Type 2 Diabetes

A diagnosis of diabetes was based on a previously published algorithm (17–19) by either an Anatomical Therapeutic Chemical code (ATC-code) of glucose-lowering drugs used in diabetes (A10) or any ICD-10 code related to diabetes (E10.x, E11.x, E12.x, E13.x, E14.x, G63.2, H28.0, H36.0, M14.2, O24, and R73), including both primary or secondary diagnoses. Therefore, all people diagnosed with diabetes were defined either from a hospital visit and/or by prescription of glucose-lowering drugs. The diabetes cohort was further classified as having type 1 or type 2 diabetes. People with type 1 diabetes were defined by at least one E10.x ICD-10 code (type 1 diabetes) and at least one A10A ATC-code (insulins and analogs) and no A10B ATC-code (blood glucose-lowering drugs exclusive of insulins); all other individuals were classified as having type 2 diabetes.

Definition and Classification of PPDM

Among people initially diagnosed with type 1 or type 2 diabetes, PPDM cases were defined by a past diagnosis of pancreatitis (either acute or chronic) at least 3 months prior to but no later than 4 years before the diabetes diagnosis (i.e., at the earliest on 1 January 1996 and the latest on 31 September 2018). This definition is in keeping with recently published criteria for the diagnosis of PPDM (3,7,20). The diagnoses of acute and chronic pancreatitis were ascertained by the ICD-10 code: K85.x (acute pancreatitis) and K86.0 or K86.1 (chronic pancreatitis). These codes have a positive predictive value of 93% for acute pancreatitis and 80% for chronic pancreatitis in the Danish registers (21). PPDM cases were further subclassified based on a history of acute pancreatitis (PPDM-A) or chronic pancreatitis (PPDM-C). Participants who had a preceding diagnosis of both acute and chronic pancreatitis were classified as PPDM-C. Thus, four mutual exclusive diabetes subgroups were identified (i.e., type 1 diabetes, type 2 diabetes, PPDM-A, and PPDM-C).

Baseline Characteristics

Baseline characteristics were identified in the period from start date of data collection, 1 January 1996, until date of diabetes diagnosis by means of ICD-10 and ATC-codes (Supplementary Fig. 2 and Supplementary Table 1). Age at baseline was calculated based on date of birth and date of diabetes diagnosis.

We approximated smoking status by identification of ICD-10 codes related to lung diseases associated with tobacco exposure as well as nicotine poisoning and psychiatric tobacco-related diagnosis (22). In addition, we identified ATC-codes corresponding to dispense of treatments for tobacco dependence (e.g., nicotine replacement therapy at any time or dispense of drugs for obstructive airway diseases after 40 years of age). With respect to potential underestimation, we chose to classify this group as heavy smokers.

An estimate of alcohol abuse was assessed by either one relevant ICD-10 or ATC-code covering diseases and drugs with direct affiliation to alcohol (e.g., intoxication, abuse, alcoholic liver disease, alcoholic cardiomyopathy, alcoholic polyneuropathy, alcoholic gastritis, alcohol-induced pancreatitis, or alcohol-related psychiatric disorders, etc.) (22).

Obesity was evaluated either by the overweight/obesity ICD-10 code or use of antiobesity pharmaceuticals. Previous cholelithiasis and enzyme-replacement therapy were assessed to evaluate the validity of the PPDM classification into acute and chronic subtypes, respectively (23,24). The use of enzyme replacement was identified by ATC code, and previous cholelithiasis was evaluated by the corresponding ICD-10 code.

The analysis of comorbidity and malignancy was assessed by Charlson Comorbidity Index (CCI) (25). This was based on discharge diagnoses registered by ICD-10 codes.

Glucose-Lowering Therapy

The concordance between actual use and prescription of diabetes-related medications is, in general, high (26–30). Thus, we identified prescriptions of glucose-lowering drugs by ATC-codes and applied this as a proxy for use (Supplementary Table 3). The glucose-lowering drugs included insulin (all types of insulin), biguanides, dipeptidyl peptidase 4 inhibitors (DPP-4i), glucagon-like peptide 1 analogs (GLP-1a), sodium–glucose cotransporter 2 inhibitors (SGLT2i), SU, and glitazones. Any first prescription of any glucose-lowering drug during the study period after diabetes diagnosis was categorized as "ever use" of that specific drug, and, if no prescription occurred, it was categorized as "never use."

Statistical Analyses

Exposure was type of diabetes (type 1 diabetes, type 2 diabetes, PPDM-A, or PPDM-C). The primary outcome was differences in glucose-lowering drug prescriptions between diabetes groups. The secondary outcome was time to event of first insulin prescription. Date of diabetes diagnosis at any time between 1 January 2000 and 31 December 2018 was set as index date. All individuals were followed to the end of study period (31 January 2018)or date of death or emigration (i.e., people who leave Denmark in the period), whichever occurred first.

Descriptive statistics are presented as numbers (percentage), means (SD), or medians (interquartile range [IQR). Unpaired t tests and χ^2 tests were used to compare continuous and dichotomous variables across diabetes subgroups. Group differences are presented as mean differences or risk ratios (RR) with 95% CI.

IR of diabetes subgroups were calculated as the number of incident cases during the study period (numerator) divided by the time at risk (in 100,000 person-years) using the total Danish population (denominator). Differences in IR between diabetes subgroups were calculated as IR ratios.

To visualize time to insulin use in the diabetes subgroups, we constructed a Kaplan-Meier curve of the estimated cumulative incidence. For the analysis of time to insulin use between diabetes subgroups, we performed a competing risk regression analysis fitted by Fine and Gray's proportional subdistribution hazard ratio (HR) models (31) with death as a competitive event and type 2 diabetes as comparator. Crude and adjusted HR models with 95% CI were performed, including sex, age category, year of diabetes diagnosis, history of heavy smoking, alcohol abuse, obesity, and CCI score in the most adjusted model. We examined the assumption of proportionality by graphical plots, and no violation was identified. All analyses were conducted in STATA 16.1 (StataCorp, College Station, TX).

Data and Resource Availability

Data were available and anonymized by Statistics Denmark (Danmarks Statistik, project identifier 703382). All authorized Danish research organizations can apply for access. Ethics committee approval is not required for epidemiology studies in Denmark.

RESULTS

During the period from 2000 to 2018, we identified 658,615 individuals with a diagnosis of diabetes (Supplementary Fig. 1). After exclusion of 246,762 prevalent cases and further exclusion of 7,907 individuals $<$18 years of age and 5,496 individuals with a diagnosis of pancreatic cancer, the final study cohort comprised 398,456 new diagnoses of adult-onset diabetes (incident cases) with a median follow-up of 6.7 (IQR 1.9–10.8) years. Among these individuals, 383,325 (96.2%) were classified as having type 2 diabetes, 9,252 (2.3%) as having type 1 diabetes, and 5,879 (1.5%) as having PPDM. The subgroup of PPDM was further classified into 3,418 (0.9%) individuals with PPDM-A and 2,461 (0.6%) individuals with PPDM-C. Among individuals included based on an ICD-10 code, 63% were classified by a primary ICD-10 diabetes diagnosis and 37% by a secondary diabetes-related diagnosis; 35% of the cohort was included based on A10 ATC-codes (prescription of glucose-lowering drugs) only.

Incidence of Diabetes Subgroups

The mean IR of PPDM was 7.9 (95% CI 7.7–8.1) per 100,000 person-years compared with 12.5 (95% CI 12.2–12.7) per 100,000 person-years for type 1 diabetes (IR ratio 0.64; 95% CI 0.61–0.66, $P <$ 0.001). The highest IR was observed for type 2 diabetes (IR 516.0; 95% CI 514.4–517.7) per 100,000 person-years.

Characteristics of Diabetes Subgroups

Demographic and clinical characteristics of the diabetes subgroups are reported in Table 1. Individuals with PPDM and type 2 diabetes showed similar age distributions, while individuals with type 1 diabetes were younger. A male predominance was observed in the PPDM subgroup (62.9%) compared with type 2 diabetes (50.1%) (RR 1.24 [95% CI 1.22–1.33]; $P <$ 0.001). Also, individuals with PPDM were more likely to be heavy smokers (RR 1.29 [95% CI 1.24–1.34]; $P <$ 0.001) and alcohol abusers (RR 7.35 [95% CI 7.10–7.61]; $P <$ 0.001) and had a higher

Table 1—Demographic and clinical characteristics

	Type 1 diabetes (*n* = 9,252)	Type 2 diabetes (*n* = 383,325)	All PPDM (*n* = 5,879)	PPDM-A (*n* = 3,418)	PPDM-C (*n* = 2,461)
Age (years), mean (SD)	46 (20)	59 (17)	59 (14)	60 (15)	57 (12)
Age category (years), *n* (%)					
18–29	2,649 (28.6)	26.544 (6.9)	123 (2.1)	85 (2.5)	38 (1.5)
30–39	1,615 (17.5)	36,468 (9.5)	416 (7.1)	269 (7.9)	147 (6.0)
40–49	1,296 (14.0)	45,021 (11.7)	1,027 (17.5)	508 (14.9)	519 (21.1)
50–59	1,141 (12.3)	78,874 (20.6)	1,549 (26.4)	784 (22.9)	765 (31.1)
60–69	1,130 (12.2)	93,860 (24.5)	1,397 (23.8)	802 (23.5)	595 (24.2)
70–79	896 (9.7)	67,562 (17.6)	915 (15.6)	621 (18.2)	294 (4.2)
≥80	525 (5.7)	34,996 (9.1)	452 (7.7)	349 (10.2)	103 (4.2)
Sex, *n* (%)					
Female	3,428 (37.1)	191,278 (49.9)	2,223 (37.8)	1,440 (42.1)	783 (31.8)
Male	5,824 (62.9)	192,047 (50.1)	3,656 (62.2)	1,978 (57.9)	1,678 (68.2)
Heavy smoker, *n* (%)	1,130 (12.2)	90,157 (23.5)	1,785 (30.4)	1,014 (26.7)	771 (31.3)
Alcohol abuse, *n* (%)	783 (8.5)	20.938 (5.5)	2,361 (40.2)	787 (23.0)	1,574 (65.0)
Obesity, *n* (%)	557 (6.0)	80,329 (21.0)	1,067 (18.2)	800 (23.4)	257 (10.9)
Enzyme treatment, *n* (%)	90 (1.0)	549 (0.1)	931 (15.8)	78 (2.3)	853 (34.7)
Cholelithiasis, *n* (%)	218 (2.4)	16,792 (4.4)	1,978 (33.7)	1,543 (45.1)	435 (17,7)
CCI, mean (SD)	1.8 (1.4)	1.6 (1.1)	2.1 (1.5)	2.0 (1.4)	2.2 (1.6)
Charlson category, *n* (%)					
1–2	6,369 (68.8)	263,921 (68.9)	2,908 (49.5)	1,798 (52.6)	1,110 (45.1)
>2	2,883 (31.2)	119,404 (31.1)	2,971 (50.5)	1,620 (47.4)	1,351 (54,9)
Follow-up time (years)	6.8	6.7	5.0	5.1	4.9
Median follow-up (IQR)	(2.6–12.1)	(2.9–10.8)	(2.0–8.9)	(2.0–8.9)	(2.0–9.0)

frequency of comorbidities compared with type 2 diabetes (CCI score 2.12 ± 1.53 vs. 1.60 ± 1.11, mean difference 0.52 [95% CI 0.48–0.56]; $P < 0.001$).

The frequency of obesity was lower among patients with PPDM compared with type 2 diabetes (RR 0.87 [95% CI 0.82–0.91]; $P < 0.001$). Individuals with PPDM-A were more likely to be obese compared with PPDM-C (RR 1.99 [95% CI 1.71–2.32]; $P < 0.001$) and had a higher occurrence of cholelithiasis (RR 2.55 [95% CI 2.33–2.80]; $P < 0.001$). In contrast, individuals with PPDM-C were more likely to receive enzyme replacement therapy (indicative of exocrine pancreatic insufficiency) (RR 15.19 [95% CI 12.12–19.04]; $P < 0.001$) and had a higher degree of comorbidity compared with PPDM-A (CCI score 2.24 ± 1.63 vs. 2.02 ± 1.45, mean difference 0.22 [95% CI 0.14–0.30]; $P < 0.001$).

Classification of PPDM

The first ICD-10 code related to diabetes for individuals with PPDM is reported in Supplementary Table 4. Individuals with PPDM were most often assigned a diagnose code of type 2 diabetes (45%) followed by type 1 diabetes (14%), while other ICD codes were assigned in 14% of cases. In a large proportion of participants (27%), no specific diabetes-related diagnosis code was allocated, and these cases were identified based on prescription of glucose-lowering therapy. Individuals with PPDM-C were more often assigned a diagnosis of type 1 diabetes (20%) compared with individuals with PPDM-A (10%) (RR 1.88 [95% CI 1.66–2.13]; $P < 0.001$).

Glucose-Lowering Therapy

Use of glucose-lowering drugs stratified by diabetes subgroups is reported in Table 2. The majority of people with type 2 diabetes used biguanides (76.3%), while they were less frequently used by people with PPDM (64.5%) (RR 0.85 [95% CI 0.83–0.86]; $P < 0.001$). In contrast, people with PPDM more often used insulin (42.5%) compared with individuals with type 2 diabetes (17.8%) (RR 2.40 [95% CI 2.32–2.47]; $P < 0.001$). The use of SU was largely proportionate between PPDM (25.2%) and type 2 diabetes (26.5%) (RR 0.95 [95% CI 0.91–0.99]; $P = 0.02$), while individuals with type 2 diabetes used incretin-based drugs more frequently compared with PPDM (24.0% vs. 17.8%; RR 0.73 [95% CI 0.69–0.77]; $P < 0.001$). However, a significant proportion of individuals with PPDM were ever users of DPP-4i (14.1%) and GLP-1a (6.3%).

The use of glucose-lowering drugs changed during the study period due to introduction of new antidiabetic medications (i.e., DPP-4i, GLP-1a, and SGLT2i) (Supplementary Fig. 3). The temporal trends in prescription patterns were largely comparable between patients with type 2 diabetes and PPDM, although the decline in prescription of SU was observed 2 years later in patients with PPDM compared with type 2 diabetes.

Kaplan-Meier curves of time to first insulin use after diabetes diagnosis can be seen in Fig. 1. There was an earlier and increased use of insulin in both PPDM-A and PPDM-C compared with type 2 diabetes. The HRs obtained from competing risk regression analysis are presented in Table 3. Both crude and adjusted HRs indicated significantly increased insulin use in the PPDM subgroup compared with type 2 diabetes (HR 3.10 [95% CI 2.96–3.23]; $P < 0.001$). In keeping with this, both the PPDM-A subgroup (HR 2.45 [95% CI 2.30–2.61]; $P < 0.001$) and PPDM-C subgroup (HR 4.30

Table 2—Any use of glucose-lowering drugs during the study period

	Type 1 diabetes (*n* = 9,252)	Type 2 diabetes (*n* = 383,325)	All PPDM (*n* = 5,879)	PPDM-A (*n* = 3,418)	PPDM-C (*n* = 2,461)
Insulin, *n* (%)					
Never	0 (0.0)	315,249 (82.2)	3,378 (57.5)	2,281 (66.7)	1,097 (44.6)
Ever	9,252 (100.0)	68,076 (17.8)	2,501 (42.5)	1,137 (33.3)	1,364 (55.4)
Biguanide, *n* (%)					
Never	9,252 (100.0)	90,842 (23.7)	2,085 (35.5)	997 (29.2)	1,088 (44.2)
Ever	0 (0.0)	292,483 (76.3)	3,794 (64.5)	2,421 (70.8)	1,373 (55.8)
SGLT2i, *n* (%)					
Never	9,252 (100.0)	349,525 (91.2)	5,496 (93.5)	3,157 (92.4)	2,339 (95.0)
Ever	0 (0.0)	33,800 (8.8)	383 (6.5)	261 (7.6)	122 (5.0)
GLP-1a, *n* (%)					
Never	9,252 (100.0)	344,557 (90.0)	5,509 (93.7)	3,157 (92.4)	2,352 (95.6)
Ever	0 (0.0)	38,768 (10.1)	370 (6.3)	261 (7.6)	109 (4.4)
DPP-4i, *n* (%)					
Never	9,252 (100.0)	311,336 (81.2)	5,051 (85.9)	2,871 (84.0)	2,180 (88.6)
Ever	0 (0.0)	71,989 (18.8)	828 (14.1)	547 (16.0)	281 (11.4)
SU, *n* (%)					
Never	9,252 (100.0)	281,641 (73.5)	4,400 (74.8)	2,609 (76.3)	1,791 (71.8)
Ever	0 (0.0)	101,684 (26.5)	1,479 (25.2)	809 (23.7)	670 (27.2)
Glitazone, *n* (%)					
Never	9,252 (100.0)	377,846 (98.6)	5,819 (99.0)	3,382 (98.9)	2,437 (99.0)
Ever	0 (0.0)	5,479 (1.4)	60 (1.0)	36 (1.1)	24 (1.0)

Data are *n* (%). Use of insulin included long-lasting, medium-lasting, and short-acting agents.

[95% CI 4.01–4.56]; $P < 0.001$) had increased use of insulin compared with type 2 diabetes.

CONCLUSIONS

We investigated the prescription patterns of glucose-lowering drugs in a population-derived cohort of adult individuals with PPDM and compared findings to those obtained for individuals with type 1 and type 2 diabetes. The majority of people with PPDM were misclassified as having type 2 diabetes. This had important implications for management, as a large proportion were treated with potentially hazardous medications (incretin-based therapies and SU) not recommended for use in PPDM. In addition, one-third of the PPDM group never received a prescription of a biguanide that has been associated with a survival benefit in PPDM. Collectively, these findings emphasize the current difficulties with misclassification and mistreatment of patients with PPDM and underline the urgent need for improved diagnostic methods and development of evidence-based management guidelines.

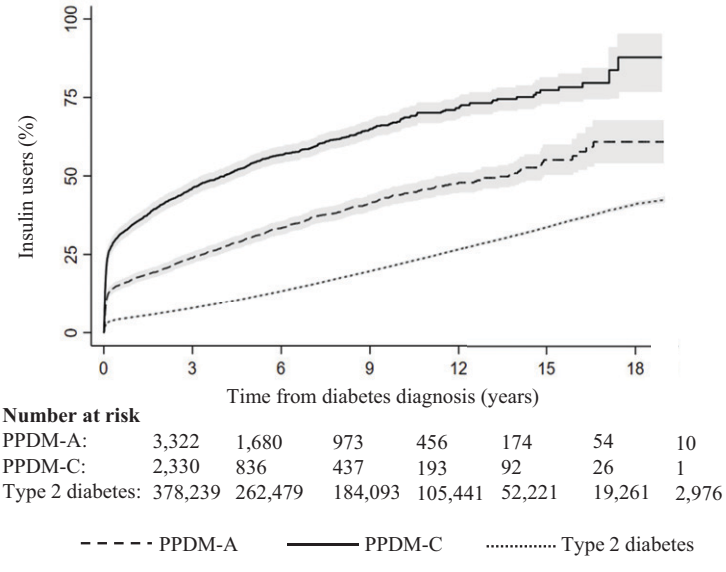

Figure 1—Kaplan-Meier plot. Time to insulin use over time for type 2 diabetes, PPDM-A, and PPDM-C. The gray-shaded areas represent 95% CIs. The table presents the number of patients at risk over time.

Population-based studies on the incidence of PPDM are scarce (2,3). The incidence of diabetes associated with pancreatic diseases (including but not restricted to PPDM) in the U.K. primary care setting was 2.6/100,000 person-years, whereas the incidence of PPDM in the tertiary care setting in New Zealand was 7.9/100,000 person-years (2). Based on these numbers, it was projected that the incidence of PPDM worldwide is ∼6.0/100,000 general population per year (3). This estimate is relatively similar to that obtained from our study (∼8.0/100,000 general population per year) and highlights that PPDM is one of the most common types of adult-onset diabetes after type 2 diabetes. In fact, if patients with

Table 3—Results of crude and adjusted subdistribution HR models of time to first insulin prescription

	All PPDM		PPDM-A		PPDM-C	
	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
Model 1	3.38 (3.24–3.52)	<0.0001	2.44 (2.30–2.60)	<0.0001	5.00 (4.72–5.29)	<0.0001
Model 2	3.17 (3.04–3.31)	<0.0001	2.42 (2.27–2.57)	<0.0001	4.41 (4.17–4.67)	<0.0001
Model 3	3.28 (3.15–3.43)	<0.0001	2.51 (2.27–2.67)	<0.0001	4.46 (4.22–4.72)	<0.001
Model 4	3.10 (2.96–3.23)	<0.001	2.45 (2.30–2.61)	<0.001	4.30 (4.05–4.56)	<0.001

End point was time to insulin after diabetes diagnosis. Subdistribution HRs of the competing risk regression analysis are shown with 95% CI and *P* values. Type 2 diabetes HR was set as the denominator. Model 1 represents unadjusted ratios. Model 2 is adjusted for sex and age. Model 3 is additionally adjusted for year of diabetes diagnosis, and model 4 is multiple adjustment for sex, age, year of diabetes diagnosis, Charlson index, smoking, alcohol, and obesity.

pancreatic cancer associated with diabetes were included in the incidence estimates of our study, as was the case for the aforementioned study from the U.K. (2), the IR would exceed that observed for type 1 diabetes.

Clinical characteristics of PPDM have only been scarcely investigated on a population-based level. It is generally assumed that patients with PPDM (chronic pancreatitis, in particular) are characterized by excessive weight loss and malnutrition due to exocrine pancreatic insufficiency (10). However, recent data indicate that patients with PPDM share many clinical characteristics with patients with type 2 diabetes, which makes PPDM difficult to distinguish from the much more prevalent type 2 diabetes in routine clinical practice (32,33). The current study was not designed for detailed characterization of patients with PPDM, but we did confirm a lower frequency of obesity in the PPDM subgroup as compared with type 2 diabetes. Likewise, a higher frequency of heavy smokers and alcohol abusers were observed among people with PPDM, which is plausible, as smoking and excessive alcohol consumption are among the most common pancreatitis risk factors (34,35). Future studies should focus on more detailed clinical phenotyping and biomarkers of patients with PPDM to reveal characteristics that may be useful to identify and discern these patients from individuals with type 2 diabetes (33,36).

Our study corroborates past observations showing that PPDM is underrecognized and that the majority of cases are misclassified as type 2 diabetes (2). Similarities in the clinical presentation of diabetes subgroups may account for this observation, as discussed above (33). Also, the lack of a specific ICD-10 code for PPDM may contribute to this finding, although the prescription pattern of glucose-lowering therapies indicated that most individuals with PPDM were treated as having type 2 diabetes or type 1 diabetes (see discussion below).

A key finding of our study was that a sizeable proportion of people with PPDM did not receive an adequate glucose-lowering therapy. Although the evidence level is limited to observational studies, expert opinions, and extrapolations from type 2 diabetes, biguanides have been recommended for use in patients with PPDM for more than a decade (10,11, 20,37). However, 35% of individuals with PPDM in the current study never received a prescription of biguanides. Recently, a well-conducted epidemiological study highlighted the importance of this recommendation by demonstrating that biguanides were associated with a survival benefit in patients with PPDM (7). The mechanisms underlying this beneficial effect are incompletely understood but may include improved hepatic insulin sensitivity as well as antineoplastic effects (10,11,38).

Another important observation of our study was the prescription of incretin-based drugs in 20% and SU in 25% of individuals with PPDM. Although the benefit-risk profiles of glucose-lowering drugs in patients with PPDM have never been formally validated in randomized controlled trials, the prescription of incretin-based therapies has generally been advised against in patients with PPDM by most experts in the field (10,11,39), which is supported by findings from observational studies (8,9,20). For example, postmarketing surveillance suggested that use of incretin-based therapy was associated with increased risk of pancreatic cancer (12). Although this concern was later dismissed by the U.S. Food and Drug Administration and European Medicines Agency (40), special considerations may apply for PPDM, as patients with acute and chronic pancreatitis have a two- to sevenfold increased pancreatic cancer risk (8,9). Consequently, additional studies on the safety profile of incretin-based therapies in PPDM need to be conducted before these medications can be safely prescribed for this indication. Furthermore, many patients on incretin-based treatment experience gastrointestinal side effects, including nausea, early satiety, and reduced appetite, which may induce weight loss. While these effects are advantageous in people with type 2 diabetes, weight loss is problematic in people with PPDM, chronic pancreatitis in particular, as they often suffer from exocrine pancreatic insufficiency and malnutrition (41).

We detected a decrease in the use of SU during the study period as novel glucose-lowering drugs were introduced (incretins in 2007 and SGLT2i in 2012). However, the decline in prescription of SU was observed 2 years later in patients with PPDM compared with type 2 diabetes, and SU prescriptions remained significant during the entire study period for patients with PPDM. As these patients often have a "brittle diabetic state" with great variability in glucose homeostasis and excess risk of hypoglycemia, most experts agree that glucose-lowering drugs with increased risk of hypoglycemia, such as SU, should generally be avoided in this condition (17,39).

Another notable finding of our current study was a threefold higher insulin requirement in the PPDM group compared with type 2 diabetes, in particular for PPDM associated with chronic pancreatitis. This finding is in accordance with previous studies (2,7) and supports

the need for and urge toward intensified early glycemic control in patients with PPDM (3). In sum, these findings denote the importance of early identification of PPDM in adults with new-onset diabetes (e.g., by attaining sufficient medical history of previous pancreatic disease).

A strength of the current study is the high quality and validity of the Danish National Registers based on a unique identification number assigned to all Danish citizens (13,16,42,43). In addition, the identification of people diagnosed with diabetes in Denmark was nationwide. Another noticeable strength is the presentation of competing risk analysis expressed by subdistribution hazard models. This is particularly important in studies of PPDM, as patients with acute and chronic pancreatitis have an excess mortality compared with the background population and individuals with type 2 diabetes (6,9,44).

One important limitation is the retrospective data collection and diabetes classification. We excluded all people receiving glucose-lowering drugs exclusive of insulins (A10B) from the group with type 1 diabetes. Thus, people with type 1 diabetes initially misdiagnosed as type 2 diabetes were lost in this investigation. In contrast, we excluded people from the group with type 2 diabetes if they had ever received a DE10 (type 1 diabetes) diagnosis. In Denmark, glucose-lowering drugs besides insulin were not approved as treatment in patients with type 1 diabetes until 2019, and consequently, this is unlikely to impact on the diabetes classification in the current study with a follow-up period from 2000 to 2018. All Danish citizens with type 1 diabetes will eventually be in contact with the hospital and thereby be given an ICD-10 DE10 code. Contrarily, general practitioners outside the hospital will most often be responsible for treatment of people with type 2 diabetes. Thus, only complicated cases of people with type 2 diabetes will be in contact with the hospital and receive an ICD-10 DE11 (type 2 diabetes) code. In addition, we did not have access to laboratory results, and thus, we were unable to differentiate if a subject exclusively identified by ATC-codes was treated with glucose-lowering drugs due to diabetes or other conditions, such as prediabetes or polycystic ovary syndrome. However, according to international guidelines, treatment of prediabetes with glucose-lowering drugs is not recommended (45), and consequently, we only expect people with prediabetes to present a minor proportion of the included subjects, with equal distribution across type 2 diabetes and PPDM subgroups. Likewise, the number of subjects with a diagnosis of polycystic ovary syndrome was very limited (<1% of the total study cohort), and therefore, we do not expect this to significantly impact our results. We expected to underestimate the total prevalence of type 1 diabetes as we excluded all individuals under 18 years of age. Yet, we did not address this issue further, as the focus of this study was new-onset diabetes of adults. Lastly, the registries did not include data on smoking habits, alcohol consumption, etc. We estimated these baseline characteristics based on ICD-10 and ATC-codes and thus only captured patients who had developed smoking or alcohol-related disorders. This may underestimate the effect of lifestyle factors on our hazard estimates, though in a similar manner across subgroups.

Although we used the most recent definition of PPDM (2,3,6,7,46), the diagnostic algorithm for PPDM case finding warrants further validation. Indeed, some patients classified as PPDM may have had classical type 2 diabetes related to the high prevalence in the general population and overlapping risk factors (4,32). Currently, biomarkers for detection of PPDM are under development (47), and, when thoroughly validated for clinical use, these will likely lead to a more accurate diagnosis of PPDM with better separation from type 2 diabetes.

In conclusion, PPDM is a common type of adult-onset diabetes but is underrecognized and often classified as type 2 diabetes. This results in improper treatment strategies and prescription of potentially hazardous glucose-lowering drugs for a sizeable proportion of patients (e.g., incretin-based therapies and SU), while others are withheld from potential beneficial medications (e.g., biguanides). Collectively, our findings emphasize the current difficulties in identification and management of PPDM and urge toward improved diagnostic methods and development of evidence-based management guidelines.

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