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Use of the Japanese health insurance claims database to assess the risk of acute pancreatitis in patients with diabetes: comparison of DPP-4 inhibitors with other oral antidiabetic drugs

This study was initiated to evaluate the association of acute pancreatitis (AP) with the use of dipeptidyl peptidase-4 (DPP-4) inhibitors among patients with diabetes in Japan. A retrospective cohort study of a large medical and pharmacy claims database was performed to compare the incidence of AP among those receiving DPP-4 inhibitors and those receiving other oral antidiabetic drugs. The incidence of all AP and hospitalizations for AP was similar between the two groups. Previous exposure to DPP-4 inhibitors did not affect occurrence of AP in patients on other oral antidiabetic drugs. The Kaplan–Meier curve for time to AP was similar between the two groups, and was not affected by previous exposure to DPP-4 inhibitors. The Cox proportional hazard models showed the incidence of AP was not significantly higher in those receiving DPP-4 inhibitors. Despite numerous, important limitations related to claims database-based analyses, our results indicate that there is no increased risk of AP with use of DPP-4 inhibitors among patients with diabetes in Japan.

Keywords: acute pancreatitis, claims database, dipeptidyl peptidase-4 inhibitor

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Introduction

Dipeptidyl peptidase-4 (DPP-4) inhibitors are widely used in the management of type 2 diabetes worldwide [1]. Their superior glucose-lowering effect in Asian people with type 2 diabetes, which is characterized by non-obesity and impaired insulin secretion, has promoted the use of these drugs in Asia [2–4]. The potential risk of pancreatitis and pancreatic cancer has been of concern from the early stages of DPP-4 inhibitor development. To ascertain whether or not DPP-4 inhibitors are associated with pancreatitis or pancreatic cancer, several investigations have been undertaken [5–7], including studies using claims databases, spontaneous reporting of clinical events, and brain-dead donors, in addition to systematic reviews based on various randomized clinical trials addressing the efficacy and the safety of DPP-4 inhibitors; however, published data on pancreatitis and/or pancreatic cancer associated with DPP-4 inhibitors focused on type 2 diabetes in Asian populations is limited.

In this study, we analyse a Japanese medical and pharmacy claims database to evaluate any association of acute pancreatitis (AP) with the use of DPP-4 inhibitors in Japanese patients with diabetes.

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Materials and Methods

We used the Japan Medical Data Centre Claims Database (Japan Medical Data Centre Co., Ltd, Tokyo, Japan), which contains the following information on individuals aged <75 years in employment-based health insurance programmes: age and gender of patient; diagnosis of disease using International Classification of Diseases (ICD)-10 code; and prescribed drugs. The data can be tracked for each individual in chronological order, even if they used multiple medical institutions.

Patients aged 30–74 years with pharmacy and medical claims data for a continuous period of at least 12 months from 1 June 2009 to 31 August 2013 were included. This allowed a 6-month period for baseline observations and at least 6 months of observation after initiation of the index medication. Patients with diabetes were identified by the presence of at least one ICD-10 code of E10–E14 during the study. Patients with E11 (n = 27 962) and E14 (n = 93 280) were subjected to further analyses, while those with E10 (n = 2090), E12 (n = 4) and E13 (n = 614) were excluded. The index date was defined as the prescription date of the first claim for a new oral antidiabetes drug during the target period, 1 December 2009 to 28 February 2013. An antidiabetic drug was considered new if there were no claims for the medication during the preceding ≥6-month period. Patients with AP ≥6 months before or on the index date were excluded. Patients with other pancreatic diseases, for example, chronic pancreatitis, were not excluded. Patients treated with glucagon-like peptide-1 (GLP-1) receptor agonists before or on the index date were also excluded. The use of insulin was not taken into consideration. The observation period started on the index date and ended at the occurrence of

Table 1. Incidence of all acute pancreatitis (AP) and hospitalizations for AP in patients on different oral antidiabetic drugs.

				Age, years		All acute pancreatitis						Hospitalized AP					
						Observation period, months			Total observation, patient-years	Cases (%)	Incidence rate, cases/100 000 patient-years	Observation period, months			Total observation, patient-years	Cases (%)	Incidence rate, cases/100 000 patient-years
Oral antidiabetic drugs	Previous exposure to DPP-4 inhibitors	n	% male	Mean	95% CI	Median	First quartile	Third quartile				Median	First quartile	Third quartile			
All		16 901	71.1	52.4	52.2–52.5	13	7	22	21 064	67 (0.40)	318	13	7	22	21 116	20 (0.12)	95
DPP-4 inhibitors		11 075	71.6	53.3	53.1–53.4	12	7	21	13 164	42 (0.38)	319	13	7	21	13 195	10 (0.09)	76
Others		5826	70.1	50.6	50.4–50.9	14	8	23	7900	29 (0.50)	367	14	8	23	7921	11 (0.19)	139
	Yes	1483	68.8	50.7	50.2–51.2	13	9	20	1877	7 (0.47)	373	13	9	20	1882	2 (0.13)	106
	No	4343	70.6	50.6	50.3–50.9	14	8	24	6024	22 (0.51)	365	14	8	24	6039	9 (0.21)	149
Sulphonylureas		3348	72.6	51.8	51.5–52.1	11	6	19	3786	12 (0.36)	317	11	6	19	3798	2 (0.06)	53
	Yes	1308	71.3	51.6	51.2–52.1	11	7	18	1395	5 (0.38)	358	11	7	18	1400	1 (0.08)	71
	No	2040	73.4	51.9	51.4–52.3	11	6	21	2391	7 (0.34)	293	11	6	21	2398	1 (0.05)	42
Glinides		902	71.6	52.0	51.4–52.6	9	4	17	908	3 (0.33)	330	9	4	17	909	1 (0.11)	110
	Yes	301	74.1	51.8	50.7–52.8	8	4	13	251	1 (0.33)	399	8	4	13	251	0 (0.00)	0
	No	601	70.4	52.1	51.3–52.9	10	5	19	657	2 (0.33)	304	10	5	19	658	1 (0.17)	152
Biguanides		4747	70.1	51.0	50.7–51.2	11	6	19	5231	11 (0.23)	210	11	6	19	5237	5 (0.11)	95
	Yes	1659	71.7	51.8	51.3–52.2	11	7	17	1706	4 (0.24)	234	11	7	17	1707	2 (0.12)	117
	No	3088	69.2	50.5	50.2–50.9	11	6	20	3525	7 (0.23)	199	11	6	20	3530	3 (0.10)	85
Thiazolidines		2125	71.4	51.9	51.5–52.3	11	6	18	2359	7 (0.33)	297	11	6	18	2365	1 (0.05)	42
	Yes	710	67.3	51.9	51.3–52.6	10	6	15	666	2 (0.28)	300	10	6	15	668	0 (0.00)	0
	No	1415	73.4	51.9	51.4–52.4	11	6	21	1694	5 (0.35)	295	11	6	21	1697	1 (0.07)	59
α-glycosidase inhibitors		2691	72.1	52.1	51.7–52.5	11	6	19	2956	18 (0.67)	609	11	6	19	2968	7 (0.26)	236
	Yes	808	70.4	52.2	51.6–52.9	10	6	16	762	4 (0.50)	525	10	6	16	763	1 (0.12)	131
	No	1883	72.8	52.0	51.6–52.5	11	5	21	2194	14 (0.74)	638	11	5	21	2205	6 (0.32)	272

No statistically significant differences were observed in incidences of all AP and hospitalizations for AP between DPP-4 inhibitors and others (Fisher's exact tests). Previous exposure to DPP-4 inhibitors did not significantly affect incidences of all AP and hospitalizations for AP in patients on other oral antidiabetic drugs, sulphonylureas, glinides, biguanides, thiazolidines and α- glycosidase inhibitors (Fisher's exact tests). Other antidiabetic drugs include sulphonylureas, glinides, biguanides, thiazolidindiones and α-glycosidase inhibitors. CI, confidential interval; DPP-4, dipeptidyl peptidase-4; AP, acute pancreatitis.

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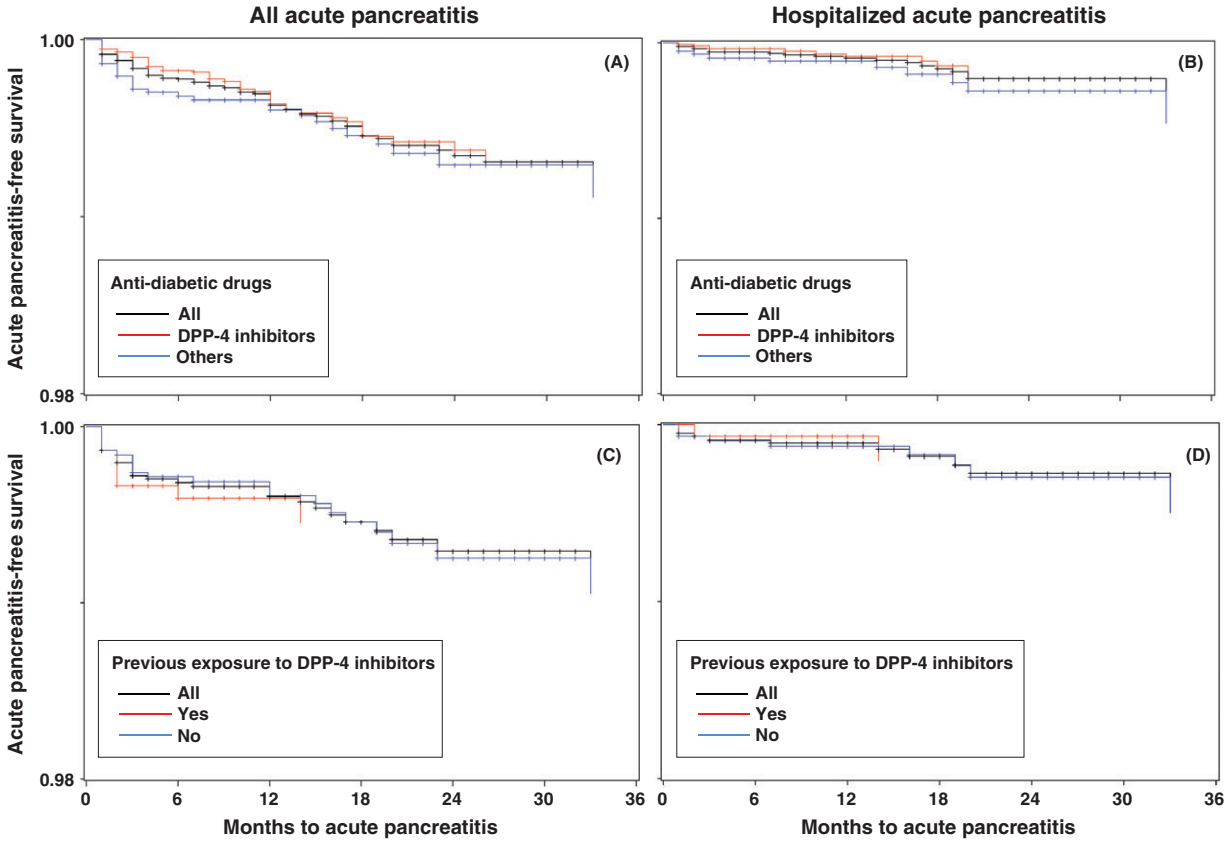

Figure 1. Kaplan–Meier curves for time to acute pancreatitis. Time to acute pancreatitis [(A, C) all acute pancreatitis (AP); (B, D) hospitalizations for AP] was analysed for patients on dipeptidyl peptidase-4 (DPP-4) inhibitors and those on other oral antidiabetic drugs (others), and all together [(A, B) All], and for patients on other antidiabetic drugs with or without previous exposure to DPP-4 inhibitors, and all together (C, D). Vertical lines indicate patients excluded for reasons other than AP (e.g. initiation of another new antidiabetic drug or GLP-1 receptor agonist, end of observation period or end of eligibility). The log-rank test did not show significant difference either between patients on DPP-4 inhibitors and those on other drugs (all AP, $p = 0.4440$; hospitalizations for AP, $p = 0.1524$) or between patients on other drugs with or without previous exposure to DPP-4 inhibitors (all AP, $p = 0.9626$; hospitalizations for AP, $p = 0.6908$). Other oral antidiabetic drugs included sulphonylureas, glinides, biguanides, thiazolidiones and α-glycosidase inhibitors.

one of the following events, whichever was earliest: (i) AP, (ii) initiation of another new antidiabetic drug or GLP-1 receptor agonist, (iii) end of observation period and (iv) end of eligibility. The same patients were included multiple times into different index drug groups if they met the criteria, which allowed the consideration of exposure to DPP-4 inhibitors before initiation of the drug whose risk for AP was being studied. AP was determined by a claim for ICD-10 code K85. The AP risk factors, comorbidities and comedications at baseline are summarized in Tables S1–S3, Supporting information.

The primary outcome was the first occurrence of AP after the index date. The DPP-4 inhibitor group was compared with the group of patients on other antidiabetic drugs using Fisher's exact test. Kaplan–Meier curves were constructed for each group to show the time to AP. The log-rank test was performed to analyse any significant difference between two groups in time to AP. Cox proportional hazard models were built to compare the adjusted risk of AP with drug therapy, age, sex and/or risk comorbidities as independent variables. The integrity of the database was tested by examining the adjusted risk of hypoglycaemia of antidiabetic drugs and insulin, which was consistent with our general knowledge (Tables S12–S14).

All analyses were performed using SAS software 9.3 TS1M1 (SAS Institute Inc., Cary, NC, USA). A p value of <0.05 was taken to indicate statistical significance.

Results

The incidence of all AP and hospitalizations for AP in patients on DPP-4 inhibitors and other antidiabetic drugs is summarized in Table 1. The frequency of the occurrence of AP, both all AP and hospitalizations for AP, was found to be similar in patients on DPP-4 inhibitors and those on other drugs (all AP, $p = 0.6241$; hospitalizations for AP, $p = 0.1790$). The presence or absence of previous exposure to DPP-4 inhibitors did not affect the occurrence of AP in patients on other drugs (all AP, $p = 1.0000$; hospitalizations for AP, $p = 1.0000$). The Kaplan–Meier curves for time to all AP and hospitalization for AP was similar in patients on DPP-4 inhibitors and those on other drugs (Figure 1). Time to AP in patients on other drugs, with or without previous exposure to DPP-4 inhibitors, did not

differ (Figure 1). The adjusted AP risk, calculated by the Cox proportional hazard models, did not differ by current or previous exposure to DPP-4 inhibitors (Tables S4 and S5).

Discussion

This study failed to show any association of AP, in both all patients with AP and those hospitalized for AP, with use of DPP-4 inhibitors in Japanese patients with diabetes. Our negative findings are consistent with the claims database-based retrospective observations carried out in the United States [8,9]. Although the incidence of all AP in this study (318 cases per 100 000 patient-years) is much higher than that of previous epidemiological data (5–80 cases per 100 000 patient-years) [10], it is consistent with that reported in claims analyses previously, which show a two- to three-fold higher incidence of AP in patients with diabetes (400–600 cases per 100 000 patient-years) [9,11].

This study has some important limitations and the results should be considered with these in mind. Most importantly, the non-random nature of the study might have introduced many confounders, such as obesity and tobacco use, as well as use of medications associated with AP. If physicians were aware of a possible risk of pancreatitis associated with DPP-4 inhibitors, they may have preferentially prescribed other antidiabetic drugs to patients perceived to be at higher risk. The higher AP risk posed by α-glycosidase inhibitors (Fisher's exact tests: all AP, $p = 0.0095$; hospitalization for AP, $p = 0.0147$; Cox proportional hazard models, Table S11) found in this study might be explained by such a prescription bias. In addition, our claims database data do not include potentially relevant demographic or clinical details, such as type and duration of diabetes, obesity, glycaemic and lipid control and alcohol consumption, or AP that may have occurred before the traceable periods within the database. Our analysis did not include adjustment for medication dose or adherence, and did not confirm that patients were taking the prescribed antidiabetic drugs. The limited number of patients on GLP-1 receptor agonists restricted meaningful analysis to only DPP-4 inhibitors (Tables S6–S10).

Despite these limitations, this study provides valuable information for physicians and patients with diabetes, especially those in Japan and other Asian countries. Our claims data analysis has the strength of allowing the observation of a large number of patients treated with antidiabetic drugs throughout the country. Furthermore, our claims data analysis has little chance of missing cases of AP because no secondary insurance policies are allowed in Japan and medical costs are not generally paid out-of-pocket by patients on insurance policies.

In conclusion, the present analysis did not find any increased risk of AP with use of DPP-4 inhibitors among patients with diabetes in Japan.

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Conflict of Interest

D. Y. and Y. S. take responsibility for the contents of the article. D. Y. designed the research, analysed data and wrote the manuscript. M. K., C. I. and R. N. analysed data and contributed to discussion. K. M. contributed to statistical analysis. H. K., K. T. and Y. S. reviewed/edited the manuscript and contributed to discussion.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Pancreatitis risk factors (International Classification of Diseases-10) at baseline in patients on different oral antidiabetic drugs.

Table S2. Pancreatitis risk factors (medications) at baseline in patients on different oral antidiabetic drugs.

Table S3. Lipid-lowering drugs at baseline in patients on different oral antidiabetic drugs.

Table S4. Cox proportional hazards analysis for time to acute pancreatitis, comparing dipeptidyl peptidase-4 inhibitors with other oral antidiabetic drugs.

Table S5. Cox proportional hazards analysis for time to acute pancreatitis, comparing the presence or absence of previous exposure to dipeptidyl peptidase-4 inhibitors in patients on other oral antidiabetic drugs.

Table S6. Incidence of all acute pancreatitis (AP) and hospitalizations for AP in patients on dipeptidyl peptidase-4 inhibitors,

glucagon-like peptide 1 receptor agonists, or other oral antidiabetic drugs.

Table S7. Pancreatitis risk factors (International Classification of Diseases-10) at baseline in patients on dipeptidyl peptidase-4 inhibitors, glucagon-like peptide 1 receptor agonists and other oral antidiabetic drugs.

Table S8. Pancreatitis risk factors (medications) at baseline in patients on dipeptidyl peptidase-4 inhibitors, glucagon-like peptide 1 receptor agonists and other oral antidiabetic drugs.

Table S9. Lipid-lowering drugs at baseline in patients on dipeptidyl peptidase-4 inhibitors, glucagon-like peptide 1 receptor agonists and other oral antidiabetic drugs.

Table S10. Cox proportional hazards analysis for time to acute pancreatitis, comparing glucagon-like peptide 1 receptor agonists with other oral antidiabetic drugs.

Table S11. Cox proportional hazards analysis for time to acute pancreatitis, comparing α-glycosidase inhibitors with other oral antidiabetic drugs.

Table S12. Incidence of all hypoglycaemia and hospitalizations for hypoglycaemia in patients on various antidiabetic drugs.

Table S13. Incidence of all hypoglycaemia and hospitalizations for hypoglycaemia in patients on antidiabetic drugs with or without insulin, sulphonylurea or glinide combinations.

Table S14. Logistic regression analysis for hypoglycaemia risk, comparing various antidiabetic drugs.

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