# Risk heterogeneity of bullous pemphigoid among dipeptidyl peptidase-4 inhibitors: A population-based cohort study using Japanese Latter-Stage Elderly Healthcare Database

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# Risk heterogeneity of bullous pemphigoid among dipeptidyl peptidase-4 inhibitors: A population-based cohort study using Japanese Latter-Stage Elderly Healthcare Database

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**Keywords**
Bullous pemphigoid, DPP-4 inhibitor, Drug adverse reaction

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## ABSTRACT

**Aims/Introduction:** Although the association between dipeptidyl peptidase-4 (DPP-4) inhibitors and bullous pemphigoid (BP) has begun to be established, some studies have suggested there are risk differences among DPP-4 inhibitors. We conducted a population-based cohort study to examine the risk differences.

**Materials and Methods:** Using the claims databases of the Fukuoka Prefecture Wide-Area Association of Latter-Stage Elderly Healthcare between April 1, 2013 and March 31, 2017, we conducted a retrospective cohort study to compare patients receiving one DPP-4 inhibitor with those who were prescribed another antidiabetic drug. The primary outcome was an adjusted hazard ratio (HR) of the development of bullous pemphigoid during a 3-year follow-up. The secondary outcome was the development of BP requiring systemic steroids immediately after the diagnosis. These were estimated using Cox proportional hazards regression models.

**Results:** The study comprised 33,241 patients, of which 0.26% ($n$ = 88) developed bullous pemphigoid during follow-up. The percentages of patients with bullous pemphigoid who required immediate systemic steroid treatment was 0.11% ($n$ = 37). We analyzed four DPP-4 inhibitors: sitagliptin, vildagliptin, alogliptin, and linagliptin. Vildagliptin and linagliptin raised the risk of BP significantly (primary outcome, vildagliptin, HR 2.411 [95% confidence interval (CI) 1.325–4.387], linagliptin, HR 2.550 [95% CI 1.266–5.136], secondary outcome, vildagliptin HR 3.616 [95% CI 1.495–8.745], linagliptin HR 3.556 [95% CI 1.262–10.024]). A statistically significant risk elevation was not observed with sitagliptin and alogliptin (primary outcome, sitagliptin, HR 0.911 [95% CI 0.508–1.635], alogliptin, HR 1.600 [95% CI 0.714–3.584], secondary outcome, sitagliptin, HR 1.192 [95% CI 0.475–2.992], alogliptin, HR 2.007 [95% CI 0.571–7.053]).

**Conclusions:** Not all the DPP-4 inhibitors could induce bullous pemphigoid significantly. Therefore, the association warrants further investigations before generalization.

## INTRODUCTION

Diabetes mellitus is one of the most common chronic diseases which predispose to various complications such as atherosclerotic illnesses, nephropathy, and neuropathy. Approximately 30.2 million citizens in the United States were reported as being diagnosed with diabetes mellitus[2]. Similarly, a national Health and Nutrition Survey reported that approximately 20 million Japanese citizens were estimated to have impaired

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glucose tolerance[1]. The strict management of diabetes is required to prevent long-term complications such as diabetic nephropathy. However, this strategy could impose a risk of iatrogenic hypoglycemia. Therefore, recent management strategy, especially for the elderly, has shifted from aggressive glycemic control to safe and comprehensive management with less chance of hypoglycemia[3,4]. Dipeptidyl peptidase-4 (DPP-4) inhibitors were reported to have less risk of hypoglycemia than sulfonylureas[5]. Metformin has been used widely for safety reasons and for being affordable[6]. However, the Japanese government and general practitioners have been reluctant to prescribe biguanides for elderly diabetic patients because of concern for lactic acidosis and renal toxicity[7]. With this background, the administration of DPP-4 inhibitors to Japanese elderly patients has been growing rapidly since approval and has become one of the most important therapeutic options. In recent years, there have been a number of case reports of bullous pemphigoid (BP) in patients treated with DPP-4 inhibitors. This dermatologic disorder could be caused by autoimmune mechanisms, which were not discussed in detail[8–10]. Kridin and colleagues suggested that an increased administration of a DPP-4 inhibitor could contribute to the growing incidence of bullous pemphigoid[11]. There have been some case–control studies and a cohort study suggesting a statistically significant association between DPP-4 inhibitors and bullous pemphigoid[12–16]. In these previous studies, associations between DPP-4 inhibitors and bullous pemphigoid were established. However, the results could suggest that there could be a risk heterogeneity among them. For example, Kridin *et al.* also reported that vildagliptin and linagliptin were associated with bullous pemphigoid, whereas sitagliptin had no statistically significant association[12]. On the other hand, Lee *et al.* concluded that they all had an increased risk of bullous pemphigoid[13]. A disproportionality analysis based on the Japanese adverse drug event report database stated that reporting the odds ratios of some DPP-4 inhibitors, sitagliptin, saxagliptin, and alogliptin were reduced to a not statistically significant level, while those of teneligliptin, vildagliptin, and linagliptin retained significance after stratification by time trend of the reports[17]. Douros *et al.* in their population-based study addressed this issue and concluded that vildagliptin and linagliptin were likely to raise the risk of the development of bullous pemphigoid[14]. However, the focus of their article was the association between all DPP-4 inhibitors and bullous pemphigoid. On the grounds of the confidentiality policies of the Clinical Practice Research Datalink, a part of the risk differences was not fully elucidated.

Regarding the relative risk among DPP-4 inhibitors, the conclusion in preceding studies was controversial. Before regarding bullous pemphigoid as a common adverse reaction of DPP-4 inhibitors, we should improve understanding as to the association. The aim of the present study is to conduct a population-based cohort study to explore additional evidence of the association between each DPP-4 inhibitor and bullous pemphigoid by evaluating their individual risk elevation.

## MATERIALS AND METHODS

### Data source

A retrospective cohort study was conducted using the healthcare claims database and the master database of Fukuoka Prefecture Wide-Area Association of Latter-Stage Elderly Healthcare between April 1, 2013 and March 31, 2017. Among this 4-year database, we used the 1-year record between April 1, 2013 and March 31, 2014 to select study subjects and the rest of the 3-year records between April 1, 2014 and March 31, 2017 was utilized to follow up outcomes. In Japan, the majority of people aged ≥75 years enroll into lifelong public health insurance. The number of the insured belonging to that age group in the area under study was reported to be 624,579, as of March 2017[18]. Considering the census report, the enrollment rate was estimated at 94.7%[19]. The healthcare claims database included data of the International Classification of Diseases 10th Revision (ICD-10), the date of diagnosis and hospitalization, and drug prescriptions. The master database records the date of insurance enrollment, withdrawal, and death. As the majority of the healthcare insured subjects have sustainable long-term eligibility, there were few study subjects lost to follow-up. The majority of these databases are computer administered. According to a report by the Japanese Ministry of Health, Labour and Welfare, the penetration rate of the computer-administered claims database was 98.6% in April 2015[20]. The Japanese Health Insurance Claims Review and Reimbursement services has a responsibility for quality control. The Institutional Review Board of Kyushu University (Clinical Bioethics Committee of the Graduate School of Healthcare Sciences, Kyushu University) approved this study.

### Study population

We identified patients treated with one antidiabetic drug in the healthcare database by checking prescription records 3 months before start of follow-up as a cohort entry. We made a comparison between patients treated by administration of one DPP-4 inhibitor and those who were receiving another antidiabetic drug. As mentioned in the Data source section, we used a 1 year record from the healthcare claims database to which Japanese people aged ≥75 years old were enrolled. Therefore, the study population must have been insured for at least 1 year, meaning that they were aged ≥76 years.

We excluded patients treated with multiple antidiabetic drugs to exclude synergetic effects or interactions of antidiabetic drugs, because some articles suggested tolbutamide, a classical sulfonylurea, could induce bullous pemphigoid[21,22]. We also excluded those with concerns over the possibility of increasing variation of glycemic control. With the aim of removing potential confounding, we selected those who received another antidiabetic drug as a reference group, whose sum risk was the general risk of bullous pemphigoid for patients with diabetes. We analyzed the DPP-4 inhibitors that more than 1500 study participants used, considering the calculation of the sample size described in the Statistical Analysis Section. Furthermore, by

reviewing ICD-10 code (= L120) of the study subjects until the start of follow-up, we excluded individuals with a past medical history of bullous pemphigoid so revealing a new incidence rate. Finally, we excluded study subjects treated with systemic steroid regularly, because systemic steroid, regardless of the therapeutic purpose, could have an inhibitory influence on bullous pemphigoid. We reviewed the prescription records 6 months before the start of observation and calculated the medication possession ratio (MPR) of systemic steroids[23]. We regarded a study subject as a regular systemic steroid user if the MPR was greater than 0.8.

### Outcomes

In the present study, the primary outcome was a new incidence of bullous pemphigoid within the follow-up period, and the secondary outcome was the new development of bullous pemphigoid requiring systemic steroid treatment within 1 day of the diagnosis. The diagnosis of bullous pemphigoid was confirmed by identifying the ICD-10 code (= L120) in the claims database. We considered the secondary outcome as a surrogate indicator of moderate–severe BP because localized or mild bullous pemphigoid was likely to be treated by drug discontinuation or topical corticosteroid at the diagnosis[24]. The healthcare claims database did not always include information about causal relationships between diseases and prescriptions. By way of checking and matching the date of diagnosis and prescription, we deduced a plausible causal relation that the steroid prescription was filled for BP treatment. Therefore, we defined the secondary outcome as the development of BP requiring systemic steroid treatment within 1 day of the diagnosis.

### Statistical analysis

We conducted survival analyses to compare the outcomes of patients taking each DPP-4 inhibitor with those prescribed with another antidiabetic drug. In the present study, a priori sample size calculation was conducted to detect a hazard ratio of 1.50 at the 3-year follow-up, with 80% power, two-sided 5% $\alpha$ level[25]. At first, we generated Kaplan–Meier plots to estimate the time to event distributions of each group. The differences between the groups were evaluated for statistical significance using the log-rank test. Furthermore, we used a multivariate Cox proportional hazards method to control for the potential confounding effects of the patients' sex, age, comorbidities, and socioeconomic status. We checked Schoenfeld residuals to investigate the validity of each proportional hazards assumption[26]. To evaluate the patients' comorbidities, we used the Charlson Comorbidity Index (CCI) at the time of diagnosis as an explanatory variable[27–29]. The CCI includes an item for a variable designated 'diabetes mellitus'. We calculated the CCI without the item and classified the CCI into tertiles. A two-sided $P$ value <0.05 was considered statistically significant. Analyses were conducted using Stata software, version 14 (Stata Corp, College Station, Texas).

### Sensitivity analysis

To confirm the robustness of our study, we performed three sensitivity analyses. First, many previous articles have shown that bullous pemphigoid could be associated with malignancy, although some meta-analyses concluded that those results might be controversial[30–32]. In this study, we considered the past medical history of malignancy in the CCI variable. In this first sensitivity analysis, we included a variable for ongoing malignancy follow-up by identifying a payment package reimbursed only when hospitals performed cancer follow-ups for patients with established malignancy diagnosis. The Japanese government has conducted a bundled payment associated with ongoing malignancy management. In the reimbursement of the payment named 'malignancy specific substance management fee', the Japanese government required medical practitioners to establish the diagnosis of malignant disease and to manage them on the basis of assessments of disease activity by way of tumor marker measurements. We conducted a secondary sensitivity analysis to evaluate the effects of the drugs prescribed concurrently. Previous studies reported associations between bullous pemphigoid and various drugs[33,34]. Although there was no established evidence about the association, we reviewed previous articles on drug-induced bullous pemphigoid[34–36]. We selected angiotensin converting enzyme (ACE) inhibitors as a potential confounding drug because they were frequently prescribed for patients with diabetes mellitus. The ACE inhibitors detected in this study included alacepril, imidapril, enalapril, captopril, quinapril, cilazapril, temocapril, delapril, trandolapril, benazepril, perindopril, and lisinopril. Finally, we created a study model for third sensitivity analysis to consider diabetes management during follow-up. In original analyses, we adopted a study model close to the 'intention to treat model' and we did not consider switching or adding another antidiabetic drug during follow-up. In the third sensitivity analysis, we excluded DPP-4 users switching to another antidiabetic drug and non DPP-4 users adding or switching to DPP-4 inhibitors by checking the latest prescription records before the end of follow-up. This model was close to the 'per protocol' model, which could provide important complementary information about the impact of protocol deviation, albeit with a danger of attrition bias and risk overestimation.

## RESULTS

### Patient characteristics

Following screening according to our inclusion and exclusion criteria (Figure 1), the final number of study subjects was 33,718. In total, 477 patients were lost to follow-up and the completeness of follow-up was 98.6%.

The number of males was 15,261 (45.9%). The mean age of the study population was 82.1 ± 4.81 years. The DPP-4 inhibitors and other treatment groups represented 15,503 (46.6%) and 17,738 (53.4%), respectively. The number in each group who died during follow-up with no development of bullous pemphigoid was 3,379 (21.8%) and 3,791 (21.4%), respectively.

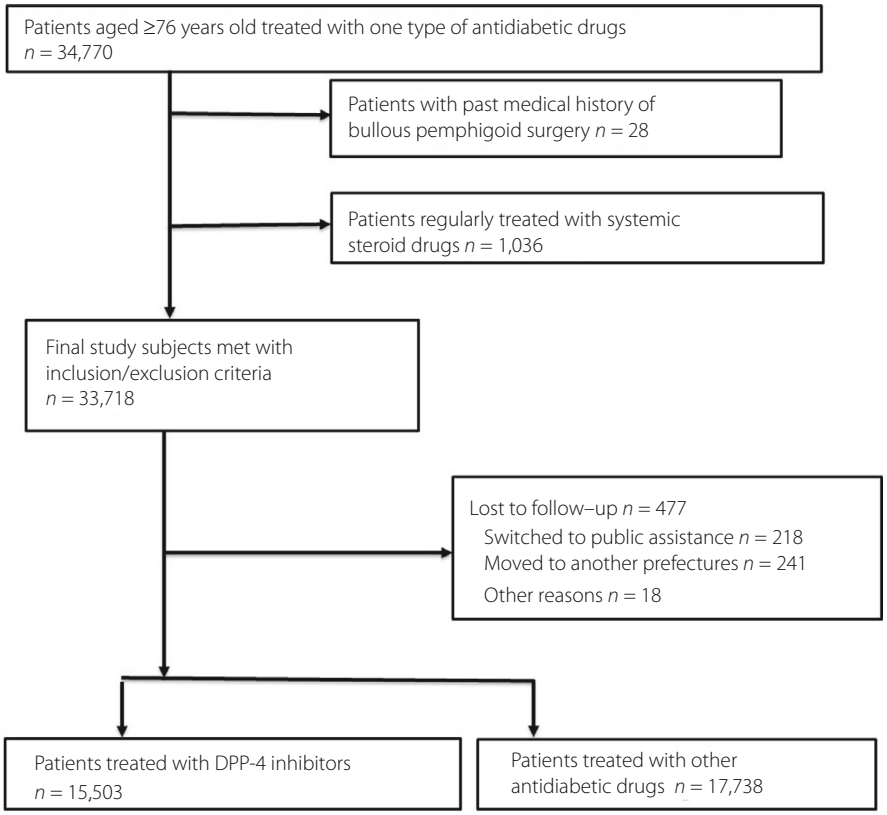


**Figure 1** | Flow diagram of inclusion/exclusion criteria. DPP-4, dipeptidyl-peptidase 4.

There were four DPP-4 inhibitors for which the number of study participants was greater than 1,500; sitagliptin, vildagliptin, alogliptin, and linagliptin. The patients' baseline characteristics are shown in Table 1.

### The association between the use of DPP-4 inhibitors and the risk of BP

The percentage of bullous pemphigoid within 3 years was 0.26% ($n$ = 88) and 0.32% ($n$ = 50) in the DPP-4 inhibitors group and 0.21% ($N$ = 38) in the other treatments group, respectively (Table 2).

The overall incidence rate of bullous pemphigoid was estimated at 96.6 (95% confidence interval (CI): 78.4–119.1) per 100,000 person-years. Regarding vildagliptin and linagliptin, there were significant differences in the Kaplan–Meier plots, compared with the reference group (vildagliptin $P$ = 0.001, linagliptin $P$ = 0.002). In contrast, no significant differences were observed with sitagliptin and alogliptin (sitagliptin $P$ = 0.73, alogliptin $P$ = 0.25). In multivariate Cox proportional hazards analyses, individuals treated with vildagliptin and linagliptin seemed to incur a significantly greater risk of bullous pemphigoid (vildagliptin, adjusted HR, 2.411, 95% CI, 1.325 to 4.387, linagliptin, adjusted HR, 2.550, 95% CI, 1.266 to 5.136) (Table 2). On the other hand, a statistically significant risk elevation was not observed with sitagliptin and alogliptin (sitagliptin, adjusted HR, 0.911, 95% CI, 0.508 to 1.635, alogliptin, adjusted HR, 1.600, 95% CI, 0.714 to 3.584) (Table 2). The result of Schoenfeld residuals revealed no violation of the proportional hazards assumption.

### The association between the use of DPP-4 inhibitors and the risk of BP requiring systemic steroid therapy

The percentage of patients with bullous pemphigoid receiving systemic corticosteroids within 1 day of the diagnosis was 0.11% ($n$ = 37), 0.15% ($n$ = 24) in the DPP-4 inhibitors group, and 0.07% ($n$ = 13) in the other treatments group (Table 3), respectively. The overall incidence rate of bullous pemphigoid was estimated at 40.6 (95% CI: 29.4–56.0) per 100,000 person-years. Regarding vildagliptin and linagliptin, there were significant differences in the Kaplan–Meier plots, compared with the other treatments group (vildagliptin $P < 0.001$, linagliptin $P$ = 0.003). In contrast, no significant differences were observed with sitagliptin and alogliptin (sitagliptin $P$ = 0.76, alogliptin $P$ = 0.27). In multivariate Cox proportional hazards analyses, vildagliptin and linagliptin are likely to raise the risk of bullous pemphigoid development significantly (vildagliptin, adjusted HR, 3.616, 95% CI 1.495 to 8.745, linagliptin, adjusted HR, 3.556, 95% CI, 1.262 to 10.024) (Table 3). Sitagliptin and

**Table 1** | Baseline characteristics of patients in the present study

| DPP-4 inhibitors ($n$ = 15,503) | | | Other antidiabetic drugs ($n$ = 17,738) | | |
|---|---|---|---|---|---|
| Drug name | Number | | Drug name | Number | |
| Sitagliptin | 8,281 | 53.4% | Sulfonylureas | 6,244 | 35.2% |
| Vildagliptin | 2,711 | 17.5% | Biguanides | 1,738 | 9.8% |
| Alogliptin | 2,039 | 13.2% | Insulins | 3,718 | 21.0% |
| Linagliptin | 1,657 | 10.7% | αGIs | 3,771 | 21.3% |
| Others | 815 | 5.3% | Thiazolidines | 1,047 | 5.9% |
| | | | Glinides | 1,070 | 6.0% |
| | | | GLP-1 receptor agonist | 150 | 0.8% |

| | Number | | Number | | *P* value* |
|---|---|---|---|---|---|
| Gender: Male | 7,045 | 45.4% | 8,216 | 46.3% | 0.110 |
| Mean age (SD) | 82.2 | (±4.83) | 81.9 | (±4.79) | |
| Median age | 81 | | 81 | | |
| Age categories | | | | | |
| 76 ≤ ≤ 80 | 6,765 | 43.6% | 8,193 | 46.2% | <0.001 |
| 81 ≤ ≤ 85 | 5,095 | 32.9% | 5,691 | 32.1% | |
| 86≤ | 3,643 | 23.5% | 3,854 | 21.7% | |
| Income categories | | | | | |
| Low | 6,180 | 39.9% | 7,078 | 39.9% | 0.435 |
| Middle | 8,322 | 53.7% | 9,575 | 54.0% | |
| High | 1,001 | 6.5% | 1,085 | 6.1% | |
| Death during follow-up without BP development | 3,379 | 21.8% | 3,791 | 21.4% | 0.300 |
| CCI categories | | | | | |
| Low (≤2) | 4,395 | 28.3% | 5,362 | 30.2% | 0.001 |
| Intermediate (3 ≤ ≤ 5) | 5,919 | 38.2% | 6,586 | 37.1% | |
| High (6≤) | 5,189 | 33.5% | 5,790 | 32.6% | |
| Comorbidities | | | | | |
| Acute myocardial infarction | 928 | 6.0% | 930 | 5.2% | 0.003 |
| Congestive heart failure | 6,213 | 40.1% | 6,296 | 35.5% | <0.001 |
| Peripheral vascular disease | 5,932 | 38.3% | 6,463 | 36.4% | <0.001 |
| Cerebral vascular disease | 8,252 | 53.2% | 9,168 | 51.7% | 0.005 |
| Dementia | 3,251 | 21.0% | 3,002 | 16.9% | <0.001 |
| Chronic pulmonary disease | 7,217 | 46.6% | 7,728 | 43.6% | <0.001 |
| Connective tissue disorder | 1,070 | 6.9% | 1,080 | 6.1% | 0.003 |
| Peptic ulcer | 5,901 | 38.1% | 6,586 | 37.1% | 0.079 |
| Mild liver disease | 4,839 | 31.2% | 5,604 | 31.6% | 0.457 |
| Hemiplegia | 556 | 3.6% | 582 | 3.3% | 0.127 |
| Moderate to severe renal disease | 3,839 | 24.8% | 4,167 | 23.5% | 0.007 |
| Diabetes with end-organ damage | 2,859 | 18.4% | 4,137 | 23.3% | <0.001 |
| Tumor | 4,037 | 26.0% | 4,848 | 27.3% | 0.008 |
| Leukemia | 47 | 0.3% | 68 | 0.4% | 0.214 |
| Lymphoma | 198 | 1.3% | 179 | 1.0% | 0.742 |
| Moderate to severe liver disease | 256 | 1.7% | 402 | 2.3% | <0.001 |
| Metastatic solid tumor | 667 | 4.3% | 789 | 4.4% | 0.517 |
| AIDS | 3 | 0.0% | 4 | 0.0% | 1.000 |

AIDS, acquired immunodeficiency syndrome; CCI, Charlson comorbidity index; GLP-1, glucagon-like peptide-1; SD, standard deviation; αGI, α-glucosidase inhibitor. **P* values determined with the $\chi^2$ test or Fisher exact test, as appropriate.

alogliptin did not seem to elevate the risk of bullous pemphigoid significantly (sitagliptin, adjusted HR, 0.911, 95% CI, 0.508 to 1.635, alogliptin, adjusted HR, 2.007, 95% CI, 0.571 to 7.053) (Table 3). The result of Schoenfeld residuals revealed no violation of the proportional hazards assumption.

### Sensitivity analysis

In the first sensitivity analysis, we analyzed the same outcomes, adding a variable identifying ongoing cancer follow-up. The results of the multivariate Cox proportional hazards analysis were consistent with the original analysis. A statistically

**Table 2** | Crude and adjusted HR for the association between the use of DPP-4 inhibitors and the risk of bullous pemphigoid

| | No. | BP within 3 years (%) | Incidence rate (100,000 person-years) | Univariate HR (95% CI) | *P* value | Adjusted HR (95% CI)* | *P* value |
|---|---|---|---|---|---|---|---|
| DPP-4 inhibitor | 15,503 | 50 (0.32) | 118.0 (89.42-155.66) | 1.513 (0.992-2.306) | 0.054 | 1.458 (0.956-2.224) | 0.080 |
| Sitagliptin | 8,281 | 16 (0.19) | 70.4 (43.11-114.86) | 0.902 (0.503-1.617) | 0.728 | 0.911 (0.508-1.635) | 0.754 |
| Vildagliptin | 2,711 | 15 (0.55) | | | 0.002 | | 0.004 |
| | | | 203.6 (122.75-337.75) | 2.610 (1.436-4.744) | | 2.411 (1.325-4.387) | |
| Alogliptin | 2,039 | 7 (0.34) | 124.4 (59.30-260.91) | 1.595 (0.712-3.571) | 0.257 | 1.600 (0.714-3.584) | 0.254 |
| Linagliptin | 1,657 | 10 (0.60) | 226.6 (121.92-421.14) | 2.914 (1.452-5.848) | 0.003 | 2.550 (1.266-5.136) | 0.009 |
| Other DPP-4 inhibitors | 815 | 2 (0.25) | | | | | |
| Other antidiabetic drugs | 17,738 | 38 (0.21) | 78.0 (56.77-107.22) | REF | | REF | |

BP, bullous pemphigoid; CI, confidence interval; CI, confidence interval; DPP-4, dipeptidyl-peptidase 4; HR, hazard ratio; HR, hazard ratio; OS, overall survival; REF, reference. *Adjusted HR was estimated according to sex, age, comorbidities (Charlson comorbidity index), and socioeconomic status.

**Table 3** | Crude and adjusted HR for the association between the use of DPP-4 inhibitors and the risk of bullous pemphigoid requiring systemic steroid therapy

| | No. | BP within 3 years (%) | Incidence rate (100,000 person-years) | Univariate HR (95% CI) | *P* value | Adjusted HR (95% CI)* | *P* value |
|---|---|---|---|---|---|---|---|
| DPP-4 inhibitor | 15,503 | 24 (0.15) | 56.6 (37.94-84.45) | 2.122 (1.080-4.167) | 0.029 | 1.990 (1.013-3.912) | 0.046 |
| Sitagliptin | 8,281 | 7 (0.08) | 30.8 (14.67-64.56) | 1.154 (0.460-2.891) | 0.760 | 1.192 (0.475-2.992) | 0.709 |
| Vildagliptin | 2,711 | 8 (0.30) | 108.4 (54.21-216.74) | 4.062 (1.684-9.801) | 0.002 | 3.616 (1.495-8.745) | 0.004 |
| Alogliptin | 2,039 | 3 (0.15) | 53.3 (17.19-165.21) | 1.998 (0.569-7.011) | 0.280 | 2.007 (0.571-7.053) | 0.277 |
| Linagliptin | 1,657 | 5 (0.30) | 113.2 (47.11-271.92) | 4.251 (1.515-11.92) | 0.006 | 3.556 (1.262-10.02) | 0.016 |
| Other DPP-4 inhibitors | 815 | 1 (0.12) | | | | | |
| Other antidiabetic drugs | 17,738 | 13 (0.07) | 26.7 (15.49-45.94) | REF | | REF | |

BP, bullous pemphigoid; CI, confidence interval; CI, confidence interval; DPP-4, dipeptidyl-peptidase 4; HR, hazard ratio; HR, hazard ratio; OS, overall survival; REF, reference Adjusted HR was estimated according to sex, age, comorbidities (Charlson comorbidity index), and socioeconomic status.

significant risk elevation was observed with vildagliptin and linagliptin (Table 4). The second sensitivity analysis included a variable indicating a concurrent prescription of ACE inhibitors. Multivariate Cox proportional hazards analysis yielded results consistent with the original analyses (Table 4). In the third analysis, we excluded DPP-4 users switching to another antidiabetic drug and non DPP-4 users adding or switching to DPP-4 inhibitors during follow-up. In spite of further selection of the study population, this statistical analysis revealed consistent results, compared with the original analysis (Table 4). All the results of Schoenfeld residuals revealed no violation of the proportional hazards assumption.

## DISCUSSION

DPP-4 inhibitors belong to a category of antidiabetic drugs, whose hypoglycemic action is achieved by preventing inactivation of endogenous incretins such as glucagon-like peptide-1 (GLP-1) through inhibition of the DPP-4 enzyme. Recently, some observational studies suggested that DPP-4 inhibitors could induce BP[8,12,13,16,37,38]. Bullous pemphigoid is an autoimmune dermatologic disorder whose presentations usually involve the formation of pruritic blisters between the epidermis and dermis. Many patients with moderate to severe bullous pemphigoid need systemic steroid treatment. Therefore, in the case of patients with diabetes developing bullous pemphigoid, their blood glucose could be poorly controlled because of the inflammation reaction and steroid administrations. The concern about this clinical scenario which could increase the disease burden and result in a poor prognosis has accelerated case reports and observational studies. As research has made progress, some articles have suggested that some DPP-4 inhibitors such as vildagliptin might have a higher risk of bullous pemphigoid. Recently, Sugiyama *et al.* conducted a nationwide retrospective observational study in Japan[39]. They analyzed the data of Japanese patients with bullous pemphigoid diagnosed by dermatologists. They concluded that vildagliptin and linagliptin were associated with the development of bullous pemphigoid. However, extrapolation was applied to the study due to lack of information of the parameter which was not a suitable method for risk heterogeneity evaluation. We built study models that enabled us to compare the bullous pemphigoid risk difference for each DPP-4 inhibitor. In the present study, regarding the primary outcome and the secondary outcome, there was substantial risk heterogeneity among the DPP-4

**Table 4** | Sensitivity analyses

| First sensitivity analysis | | Primary outcome | | Secondary outcome | |
|---|---|---|---|---|---|
| | No. | Adjusted HR (95% CI)* | *P* value | Adjusted HR (95% CI)* | *P* value |
| DPP-4 inhibitor | 15,503 | 1.452 (0.952-2.215) | 0.083 | 1.983 (1.009-3.898) | 0.047 |
| Sitagliptin | 8,281 | 0.907 (0.506-1.628) | 0.744 | 1.189 (0.474-2.985) | 0.712 |
| Vildagliptin | 2,711 | 2.399 (1.318-4.367) | 0.004 | 3.605 (1.490-8.723) | 0.004 |
| Alogliptin | 2,039 | 1.603 (0.715-3.591) | 0.252 | 2.010 (0.572-7.064) | 0.276 |
| Linagliptin | 1,657 | 2.489 (1.235-5.017) | 0.011 | 3.509 (1.244-9.902) | 0.018 |
| Other DPP-4 inhibitors | 815 | | | | |
| Other antidiabetic drugs | 17,738 | REF | | REF | |
| **Second sensitivity analysis** | | **Primary outcome** | | **Secondary outcome** | |
| | No. | Adjusted HR (95% CI)* | *P* value | Adjusted HR (95% CI)* | *P* value |
| DPP-4 inhibitor | 15,503 | 1.461 (0.958-2.228) | 0.079 | 1.983 (1.009-3.897) | 0.047 |
| Sitagliptin | 8,281 | 0.916 (0.511-1.645) | 0.770 | 1.187 (0.473-2.979) | 0.715 |
| Vildagliptin | 2,711 | 2.444 (1.343-4.450) | 0.003 | 3.624 (1.498-8.765) | 0.004 |
| Alogliptin | 2,039 | 1.631 (0.728-3.656) | 0.235 | 1.995 (0.567-7.012) | 0.282 |
| Linagliptin | 1,657 | 2.580 (1.280-5.197) | 0.008 | 3.536 (1.255-9.968) | 0.017 |
| Other DPP-4 inhibitors | 815 | | | | |
| Other antidiabetic drugs | 17,738 | REF | | REF | |

Third sensitivity analysis

| Primary outcome | No. | BP within 3 years (%) | Univariate HR (95% CI) | P value | Adjusted HR (95% CI)* | *P* value |
|---|---|---|---|---|---|---|
| Sitagliptin | 6,020 | 10 (0.17) | 0.932 (0.436-1.991) | 0.855 | 0.938(0.475-2.007) | 0.869 |
| Vildagliptin | 1,635 | 12 (0.73) | 4.214 (2.060-8.621) | <0.001 | 3.848(1.495-7.883) | <0.001 |
| Alogliptin | 1,206 | 5 (0.41) | 2.321 (0.871-6.185) | 0.092 | 2.507(0.571-6.694) | 0.067 |
| Linagliptin | 1,079 | 8 (0.74) | 4.250 (1.872-9.648) | 0.001 | 3.942(1.262-8.972) | 0.001 |
| Other antidiabetic drugs | 11,642 | 20 (0.17) | REF | | REF | |
| Secondary outcome | No. | BP within 3 years (%) | Univariate HR (95% CI) | *P* value | Adjusted HR (95% CI)* | *P* value |
| Sitagliptin | 6,019 | 5(0.08) | 1.875(0.543-6.475) | 0.855 | 1.893(0.547-6.557) | 0.314 |
| Vildagliptin | 1,635 | 8(0.49) | 11.24(3.677-34.354) | <0.001 | 10.127 (3.309-30.997) | <0.001 |
| Alogliptin | 1,204 | 2(0.17) | 3.750(0.728-19.331) | 0.092 | 4.329 (0.835-22.431) | 0.081 |
| Linagliptin | 1,077 | 3(0.28) | 6.417(1.533-26.850) | 0.001 | 5.906 (1.407-24.787) | 0.015 |
| Other antidiabetic drugs | 11,641 | 5 (0.04) | REF | | REF | |

Upper section: First sensitivity analysis. This analysis was conducted by adding a variable. Middle case: Secondary sensitivity analysis. This analysis was performed, considering effects of co-prescriptions of ACE inhibitors. Lower case: Third sensitivity analysis. This analysis was excluded both DPP-4 inhibitor users switching to another antidiabetic drug and non DPP-4 inhibitor users starting DPP-4 inhibitors before the end of follow-up.
*Adjusted HR was estimated according to sex, age, comorbidities (Charlson comorbidity index), and socioeconomic status. ACE, angiotensin converting enzyme; BP, bullous pemphigoid; CI, confidence interval; HR, hazard ratio; DPP-4, dipeptidyl-peptidase 4; OS, overall survival.

inhibitors. Vildagliptin and linagliptin was likely to raise the risk of bullous pemphigoid development significantly, not sitagliptin and alogliptin. Regarding subgroup analyses of four DPP-4 inhibitors, consistent results were observed. On the other hand, the overall analyses of the association between bullous pemphigoid and all DPP-4 inhibitors under the study revealed inconsistent results. In the primary outcome, there was no significant difference in the development of bullous pemphigoid. In contrast, in the secondary outcome, a statistically significant risk elevation of bullous pemphigoid was found. The discrepancy between the primary and the secondary outcome could be explained on the grounds that the majority of the study population consisted of patients treated with sitagliptin which seemed not to have a significant association with bullous pemphigoid, and vildagliptin and linagliptin were likely to have a stronger association with moderate to severe bullous pemphigoid requiring immediate systemic steroid treatment than the overall bullous pemphigoid development. Therefore, inconsistent results could be explained by the risk heterogeneity among the DPP-4 inhibitors. Sitagliptin is the most classical drug among the DPP-4 inhibitors and has been on the market for the longest duration. We examined the possibility that

sitagliptin might have induced bullous pemphigoid before our follow-up period and that the sitagliptin users in the present study were 'BP survivors'. If that were the case, case reports and pharmacovigilance systems should have raised concern that sitagliptin might induce bullous pemphigoid. As long as we searched preceding articles, the majority of them reported that vildagliptin or linagliptin might induce bullous pemphigoid. In addition, the latency times were not always short, and DPP-4 inhibitor induced bullous pemphigoid could occur among long time users[10,40–45].

The source that could contribute to the heterogeneity is yet to be established. The authors of preceding articles considered that DPP-8 or DPP-9, not DPP-4, could have a relationship with the etiology, based on the knowledge that DPP-8/9 were associated with drug induced dermatitis and vildagliptin had a low DPP-4 selectivity against DPP-8/9[13,14]. However, as Douros *et al.* pointed out, linagliptin might have higher selectivity[14]. Therefore, this hypothesis did not seem to fully explain the pathogenesis. Recently, Ujiie *et al.* reported that individuals with DQB1*03:01 could have a genetic susceptibility to DPP-4 inhibitor-induced bullous pemphigoid[46]. At the onset of the development of bullous pemphigoid, the patients (21 cases) took DPP-4 inhibitors as follows: vildagliptin (7 cases, 33.3%), alogliptin (4 cases, 19.0%), teneligliptin (4 cases, 19.0%), linagliptin (4 cases, 19.0%), anagliptin (1 case, 4.8%), sitagliptin (1 case, 4.8%). Interestingly, vildagliptin, which was likely to raise the risk of bullous pemphigoid development significantly in the present study, was prescribed for 33.3% of the noninflammatory bullous pemphigoid patients with DQB1*03:01. On the other hand, sitagliptin, which was likely to have no association with bullous pemphigoid in the present study, was administered to 4.8% of them. This research on the impact of HLA typing did not consider the risk heterogeneity of DPP-4 inhibitors. Taking different DPP-4 inhibitors might affect the risk estimations. Furthermore, in our study, sitagliptin was the most prescribed and the risk of bullous pemphigoid was not significantly increased. If HLA typing were a dominant factor of DPP-4 inhibitor-induced bullous pemphigoid, sitagliptin should have been the most relevant drug, considering that each DPP-4 inhibitor was randomly prescribed to the study population with various HLA typing. In our study, individuals treated with sitagliptin did not have a statistically significant higher risk of bullous pemphigoid. Therefore, our results suggested that HLA typing could not fully explain the source of the risk heterogeneity among the DPP-4 inhibitors, and drug characteristics were likely to be a more determinant factor than patient attributes. Previous well known clinical trials, TECOS, CARMELINA, and EXAMINE trials, suggested that DPP-4 inhibitors might have non-negligible heterogeneity on cardiovascular adverse outcomes[47–49]. Our results warrant further investigations to explain the distinct drug characteristics of DPP-4 inhibitors.

The present study has strengths and limitations. One strength is that this study was based on a healthcare claims database with long-term sustainable eligibility for the majority of elderly people. In general, loss to follow-up in cohort studies could introduce selection bias[50]. However, this public insurance enabled us to conduct a population-based cohort with a high rate of complete follow-up. Another strength is that the healthcare insurance covered almost all people aged ≥75 years. Sampling from the insurance database allowed the study population to be large for multivariate survival analyses with adjustments for sex, age, comorbidities, and socioeconomic status.

A limitation is that this study was performed in Japan and did not have ethnic diversity. Therefore, whether our findings apply to other nations populated by people of other ethnicities remains to be determined. Furthermore, this study population was older, with patients aged ≥76 years. Previous articles revealed that bullous pemphigoid had a sharply increased incidence in the elderly[51,52]. In the present study, the incidence rate could be overestimated because of the age distribution, compared with articles in which the study populations were the general population. However, this study outcomes focused on the risk heterogeneity among DPP-4 inhibitors. Considering that the age-incidence relationship of bullous pemphigoid is not uniform, our study model restricted by a given age distribution could confer more accurate statistical comparison. Hence, the age composition is not likely to impair the generalizability of the findings. Another limitation was that the study design was a retrospective cohort in which residual confounding could not be denied. However, bullous pemphigoid was reported to be a rare disorder with quite a small incidence rate. Conducting a randomized control study seems to be challenging, considering the cost and time. This study model is the most feasible way to handle this rare outcome. Furthermore, this study was based on a claims database in which information concerning skin biopsy upon diagnosis and laboratory tests such as anti-BP180 antibody were not documented. However, some preceding articles reported that the positive rate of anti-BP180NC16a antibody was lower in DPP4 inhibitor related bullous pemphigoid than in non-related cases and the skin pathological finding in DPP-4 related cases could represent a smaller number of eosinophils than in non-DPP4 inhibitor related cases[38,53]. As we examined the secondary sensitivity analysis, preceding articles reported that some drugs could cause bullous pemphigoid. We conducted the analysis, considering the statistical influence of ACE inhibitors which were frequently administered for diabetes management. Another drug might be a potential confounding factor, although the association has not been established yet. The claims database did not include patient information about the glycemic control status and the treatment duration. Although we could not consider them in our analyses, we selected a study population treated with one antidiabetic drug so as not to increase the variation of diabetes mellitus severity. In addition, the healthcare database was lacking the patients' HLA data. However, in general, both patients and healthcare professionals do not have the information. In the present study, the number of study subjects was quite large. Along with the

Law of Large Numbers, patients with various HLA should be randomly allocated to each DPP-4 inhibitor in accordance with the general population[54]. Therefore, the lack of HLA information should not have been a significant confounding factor. Finally, this claims database could have input and coding errors, which are more likely to be random errors and not to have a crucial influence on the statistical inferences.

In conclusion, the present study revealed that there could be a substantial risk heterogeneity of bullous pemphigoid development among DPP-4 inhibitors. Vildagliptin and linagliptin could be highly associated with bullous pemphigoid. This finding suggested that bullous pemphigoid is a common adverse drug reaction of DPP-4 inhibitors might not be accurate. Our study also suggested that the risk differences could be produced mainly by drug compositions, not by the patients' characteristics such as HLA typing. The present study was a retrospective cohort study which was susceptible to statistical bias in spite of the high rate of complete follow-up. Therefore, the validity of our study results should be assured by further extensive studies, meta-analysis or a more integrated pharmacological approach, to reveal the details of the associations.

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## DISCLOSURES

Conflict of interest: N/A.
Approval of the research protocol: The Institutional Review Board of Kyushu University (Clinical Bioethics Committee of the Graduate School of Healthcare Sciences, Kyushu University) approved this study.
Informed consent: The use of claims database was guaranteed by Fukuoka Prefecture Wide-Area Association of Latter-Stage Elderly Healthcare.
Approval date of Registry and the Registration No. of the study/trial: N/A.
Animal Studies: N/A.

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