


Association between dipeptidyl peptidase-4 inhibitors and increased risk for bullous pemphigoid within 3 months from first use: A 5-year population-based cohort study using the Japanese National Database

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ABSTRACT

Aims/Introduction: We assessed the association between dipeptidyl peptidase-4 inhibitors (DPP-4is) and bullous pemphigoid (BP) and time-dependent changes in the risk for developing BP after DPP-4i initiation.

Materials and Methods: The present population-based, real-world study was carried out using the Japanese National Database dataset collected between 2013 and 2018. To assess independent correlations between DPP-4is and the development of BP, the self-controlled case series method was used.

Results: Among the cohort followed up for a median of 1,540 days, 53,027 patients were likely to develop BP. The possible incidence rate of BP in all 150,328,339 patients was 10.4/100,000 person-years. Among the 9,705,814 patients with type 2 diabetes, 15,634 were likely to develop BP. The possible incidence rate of BP in patients with type 2 diabetes was 38.1/100,000 person-years, whereas that in patients with type 2 diabetes who did and did not use DPP-4is was 40.7 and 30.0/100,000 person-years, respectively. Analysis of the 28,705 patients with type 2 diabetes likely to develop BP after initial DPP-4i use showed a risk ratio of 2.15 (95% confidence interval [CI] 1.75–2.63), 1.70 (95% CI 1.37–2.11), 1.44 (95% CI 1.15–1.82), 1.25 (95% CI 0.98–1.59), 0.84 (95% CI 0.63–1.10), 0.84 (95% CI 0.64–1.11) and 1.05 (95% CI 0.92–1.20), for the risk period of ≤ 30 , 31–60, 61–90, 91–120, 121–150, 151–180 and 181–365 days, respectively.

Conclusions: Although DPP-4is were associated with increased risk for BP, the risk was particularly significant within 3 months from first use.

INTRODUCTION

Bullous pemphigoid (BP), a rare acquired autoimmune blistering skin disease that is prevalent in the elderly population, is characterized by an autoimmune reaction directed against two hemidesmosomal proteins (BP180 and BP230) of the dermoepidermal junction^{1,2}. Although multiple drugs have been

implicated in the development of BP^{2,3}, an increasing number of case reports have suggested its association with dipeptidyl peptidase-4 inhibitors (DPP-4is)^{4–8}.

The prevalence of type 2 diabetes mellitus has increased significantly worldwide. Several pharmacological interventions, such as oral antidiabetic drugs, have allowed for achieving and maintaining good glycemic control^{9–11}. Among such interventions, DPP-4is have been a mainstay in the management of type 2 diabetes mellitus.

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Epidemiological evidence has shown an association between DPP-4i use and BP. Accordingly, studies have reported DPP-4i use to be associated with increased BP in patients with type 2 diabetes^{12–18}. Furthermore, a systematic review suggested an association between DPP-4i use and BP¹⁹.

However, the aforementioned studies were relatively small, with almost all of them being case reports or case-control studies. Furthermore, these studies did not investigate time-dependent changes in the risk of developing BP after DPP-4i initiation. The current study utilized data from the Japanese National Database (NDB), which contains data on all patients using any type of insurance program that covers Japan's 127 million citizens, to elucidate the relationship between DPP-4is and BP over a 5-year follow-up period.

MATERIALS AND METHODS

Design

The present population-based, real-world retrospective study was carried out using the NDB dataset and was approved by the Ethics Committee of Nara Medical University (1123-5).

Our cohort consisted of individuals enrolled in the NDB, with all patient data being anonymized. The NDB data provide information on personal identifier (ID0 variable²⁰), date, age group, sex, description of the procedures carried out, diagnostic codes established by the World Health Organization's International Classification of Diseases (ICD-10), medical care received, medical examinations conducted (without results) and prescribed drugs, which are independent of doctor's or patient's reports. Drug information included prescription amount, brand name, generic name, dosage and number of days prescribed. The present study defined a person's age as the age at the last insurance use. Our study cohort was designed such that all patient data were included from the NDB dataset (collected between April 2013 and March 2018).

Definition of patients with type 2 diabetes

Patients with type 2 diabetes were defined as those who had any of the diagnostic codes associated with type 2 diabetes and were prescribed diabetes medication at least once. The diagnosis and medicine codes are shown in the Tables S1 and S2. All patients with any type of diabetes who fulfilled the aforementioned criteria were included.

Definition of patients with type 1 diabetes

Patients with type 1 diabetes were defined as those who had any of the medical procedure codes associated with type 1 diabetes.

Bullous pemphigoid definition

Patients with BP were defined as those who had diagnostic codes associated with BP and were billed the dermatology-specific disease guidance management fee (I). The time of onset was defined as the date on which BP was diagnosed. Almost all patients with BP in Japan are charged this management fee.

However, because the NDB does not include laboratory data or immunohistological evaluation, diseases other than BP might be included in the patients defined as having BP.

Inclusion and exclusion criteria

Patients with type 1 diabetes were excluded. To calculate the incidence rate of BP, all patients without type 1 diabetes were included. For the analysis of a self-controlled case series method, only patients with type 2 diabetes who first developed BP were included, regardless of the use of other antidiabetic drugs (Figure 1).

Statistical analysis

The present study used patients' health insurance information from April 2013 to March 2018 for analysis. From this data, incidence rates of BP for all patients in the NDB and those with type 2 diabetes were calculated. For patients with type 2 diabetes, incidence rates of BP were calculated separately according to whether or not DPP-4i was prescribed. The standardized incidence ratio (SIR) of BP was then analyzed according to daily and weekly DPP-4is, taking patients with type 2 diabetes who have never been prescribed DPP-4is as the reference population.

The incidence rate ratios of each risk period after using DPP-4is (≤ 30 , 31–60, 61–90, 91–120, 121–150, 151–180, 181–365, 366–549 and 550–730 days) to the control period (other than those stated above) were calculated using a self-controlled case series method (generalized linear Poisson regression model)^{21,22}. BP onset, which does not occur more than once per person, was the primary outcome. The model accounted for DPP-4i use (exposure). Independent variables in the model included age classes by 5-year age groups, sex, seasonal categories (fall, winter, spring and summer), years after observation (0, 1 or 2 years) and each type of DPP-4i.

All statistical tests were two-tailed, and were carried out using Microsoft SQL Server 2016 Standard® (Microsoft Corp., Redmond, WA, USA) and IBM SPSS for Windows, version 25.0 (IBM, Armonk, NY, USA), with *P*-values < 0.05 showing significance.

RESULTS

Patient characteristics

Table 1 shows the demographic characteristics of the patients included in the present study. A total of 150,328,339 individuals (186,836,905,265 person-days) enrolled in the NDB used their health insurance from April 2013 to March 2018. At baseline, patients had a mean age of 45.9 years, with 52.8% of them being women. The mean age of the 9,705,814 patients with type 2 diabetes was 70.0 years, with 41.0% being women. Among the cohort followed up for a median of 1,540 days (interquartile range 756–1777), 53,027 patients were likely to develop BP. The possible incidence rate of BP for all patients was 10.4/100,000 person-years (men and women: 9.8 and 10.8/100,000 person-years, respectively). Meanwhile, among the

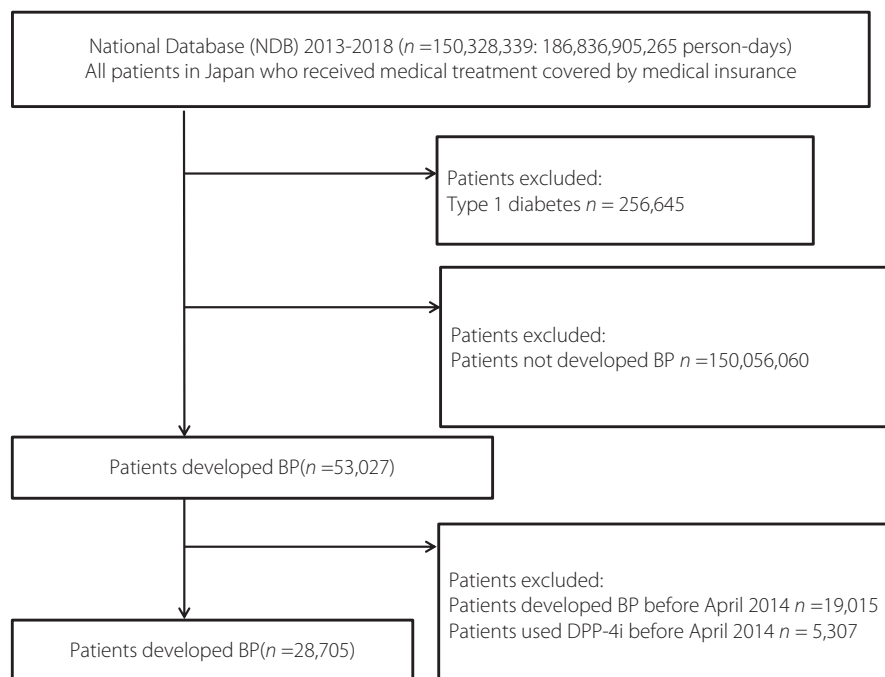


Figure 1 | Flow chart showing the inclusion of patients. BP, bullous pemphigoid.

Table 1 | Baseline participant characteristics

	All patients		
	All	Male	Female
<i>n</i>	150,328,339	70,958,283	79,370,056
Mean age, years (SD)	45.9 (24.2)	44.6 (25.0)	47.1 (23.9)
No. patients developing BP	53,027	23,278	29,749
Incidence ratio of BP/100,000 person-years	10.4	9.8	10.8
	Patients with type 2 diabetes		
<i>n</i>	9,705,814	5,721,666	3,984,148
Mean age, years (SD)	70.0 (13.5)	68.2 (13.0)	72.6 (13.7)
No. patients developing BP	15,634	8,601	7,033
Incidence ratio of BP/100,000 person-years	38.1	36.0	41.1
	Patients with type 2 diabetes		
<i>n</i>	7,227,504	2,478,310	4,749,194
Mean age, years (SD)	70.2 (12.9)	69.4 (15.0)	71.0 (12.8)
No. patients developing BP	12,712	2,922	9,790
Incidence ratio of BP/100,000 person-years	40.7	30.0	41.1

Note: Data are means \pm standard deviation unless otherwise indicated. BP, bullous pemphigoid; DPP-4i, dipeptidyl peptidase-4 inhibitor; SD, standard deviation.

9,705,814 patients with type 2 diabetes, 15,634 were likely to develop BP. The possible incidence rate of BP in patients with type 2 diabetes was 38.1/100,000 person-years (men and women: 36.0 and 41.1/100,000 person-years, respectively). Possible incidence rates of BP in patients with type 2 diabetes who

did and did not use DPP-4is was 40.7 and 30.0/100,000 person-years (see Table 1).

Table 2 summarizes the possible incidence rates of BP according to age and sex. Accordingly, older patients with or without type 2 diabetes tended to show higher incidence rates

Table 2 | Incidence ratio of bullous pemphigoid in each age group

Age (years)	All patients			Patients with type 2 diabetes			Patients with type 2 diabetes	
	All	Male	Female	All	Male	Female	DPP-4i use (+)	DPP-4i use (-)
0-4	*	*	*	*	*	*	*	*
5-9	*	*	*	*	*	*	*	*
10-14	*	*	*	*	*	*	*	*
15-19	0.1	*	0.1	*	*	*	*	*
20-24	0.2	0.2	0.2	*	*	*	*	*
25-29	0.4	0.4	0.4	*	*	*	*	*
30-34	0.5	0.5	0.6	*	*	*	*	*
35-39	0.8	0.7	0.9	3.1	*	*	*	*
40-44	1.3	1.1	1.5	3.7	3.1	5.3	2.77	5.95
45-49	2.0	1.8	2.2	4.4	3.7	6.7	4.38	5.11
50-54	3.0	2.7	3.3	6.5	5.3	9.6	6.38	6.95
55-59	4.4	4.1	4.8	9.2	7.8	12.4	9.38	8.89
60-64	6.4	7.2	5.6	14.1	14.8	12.8	14.36	13.20
65-69	9.2	11.1	7.5	18.6	19.6	16.0	18.23	18.29
70-74	13.1	16.3	10.3	27.0	29.7	22.6	28.73	20.33
75-79	21.0	26.1	16.8	40.3	46.3	32.1	44.19	25.93
80-84	35.1	41.4	30.5	65.3	73.1	56.5	70.21	47.93
85-89	56.3	60.6	53.8	98.2	105.4	92.5	106.01	74.42
90-94	81.5	82.7	81.0	132.3	147.1	125.2	143.91	102.44
95-99	105.1	107.2	104.5	162.1	191.6	151.2	173.79	131.22
≥100	123.9	118.5	124.8	175.8	199.7	172.3	214.97	116.71
Total	10.4	9.8	10.8	37.9	35.9	40.5	40.71	29.96

Note: Incidence ratio/100,000 person-years. Abbreviation: DPP-4i, dipeptidyl peptidase-4 inhibitor. *Data could not be presented based on the Japanese National Database guidelines, because each number of incidents was <10.

of BP. Furthermore, patients with type 2 diabetes had a clearly higher risk for developing BP than the general population. In patients with type 2 diabetes, especially among those aged >70 years, those who used DPP-4is had a higher incidence of BP than those who did not (Table 2).

Table 3 details the SIR of BP according to daily and weekly DPP-4is. Each patient using DPP-4is had an SIR of 139 (95% CI 138.1–140.5), 138 (95% CI 126.4–151.6) and 139 (95% CI 136.7–141.6) for daily, weekly and total DPP-4is, respectively. Little difference in SIR was observed between daily and weekly DPP-4is. To avoid misinterpretation, the SIRs for each DPP-4i were not presented; however, all DPP-4is were associated with

increasing risk for the estimated incidence of BP, with each SIR in the range being approximately twice as much as the other.

The risk ratios for developing BP after DPP-4i use for each period are shown in Table 4. A total of 28,705 patients (11,993 men and 16,712 women), including 4,843 patients with first DPP4i prescription (2,581 men and 2,262 women), were likely to develop BP from April 2014 to August 2017. Risk ratios for developing BP after using DPP-4is were 2.15 (95% confidence interval [CI] 1.75–2.63), 1.70 (95% CI 1.37–2.11), 1.44 (95% CI 1.15–1.82), 1.25 (95% CI 0.98–1.59), 0.84 (95% CI 0.63–1.10), 0.84 (95% CI 0.64–1.11), 1.05 (95% CI 0.92–1.20), 1.18 (95% CI 1.03–1.34) and 1.09 (95% CI 0.95–1.25) for the risk periods ≤30 days, 31–60, 61–90, 91–120, 121–150, 151–180, 181–365, 366–549 and 550–730 days, respectively.

Table 3 | Standardized incidence ratio of bullous pemphigoid by each dipeptidyl peptidase-4 inhibitor

	n	number of development of BP	SIR	95% CI
Daily DPP-4i	7,059,655	12,459	139	138.1–140.5
Weekly DPP-4i	167,849	253	138	126.4–151.6
Total	7,227,504	12,712	139	136.7–141.6

Abbreviations: CI, confidence interval; DPP-4i, dipeptidyl peptidase-4 inhibitor; SIR, standardized incidence ratio.

DISCUSSION

The current study showed that DPP-4i use was independently associated with a higher possible incidence of BP in patients with type 2 diabetes, although this increased risk was only observed within 3 months from first use. To the best of our knowledge, this has been the first large-scale study to evaluate the influence of DPP-4is on BP development in patients with type 2 diabetes over time.

Our research showed that among the 150,328,339 individuals analyzed, 53,027 could have developed new BP during the 5-

Table 4 | Incidence rate ratio of bullous pemphigoid after dipeptidyl peptidase-4 inhibitor use for each period

day after DPP-4i use	Incidence rate ratio	95% CI	P-value
-30	2.15	1.75–2.63	<0.001
31–60	1.70	1.37–2.11	<0.001
61–90	1.44	1.15–1.82	<0.001
91–120	1.25	0.98–1.59	0.071
121–150	0.84	0.63–1.10	0.201
151–180	0.84	0.64–1.11	0.215
181–365	1.05	0.92–1.20	0.472
366–549	1.18	1.03–1.34	0.015
550–730	1.09	0.95–1.25	0.232

Note: Total $n = 28,705$ including 4,843 patients with first dipeptidyl peptidase-4 inhibitor (DPP4i) prescription. Abbreviation: CI, confidence interval.

year observation period. In contrast, Japan has a designated intractable disease registry, with BP registered therein. According to the data available on the registry, 2,031 patients received treatment for BP as a designated intractable disease in 2018²³. Although the estimated incidence of BP (i.e., the number of possible incidences) obtained herein cannot be directly compared with the number of designated incurable disease recipients (i.e., the prevalence of BP), our estimates on new incidences of BP appear to be high.

To validate the present results, we confirmed whether the number of designated incurable disease recipients calculated using the NDB matched the actual number of intractable disease recipients in 2017. After calculating the number of new BP cases with specific procedure codes indicating an intractable disease using the NDB for the year 2017, we found that the values calculated using the NDB were generally consistent with the actual number of designated incurable disease recipients ($n = 2053$). Given the very plausible number of designated intractable disease recipients, as well as the consistency between the number of patients with BP calculated using the NDB and actual figures, we considered our method to be reasonable. However, only severe cases of BP were registered as a designated intractable disease, with the registration being subsequently deleted within a few months when a registered severe case becomes moderate or less due to treatment. Therefore, the number of designated intractable disease recipients could be less than the total number of patients with BP.

Given that the current study adopted a broader definition of BP to include patients with mild disease, patients with BP were herein defined based on diagnostic codes associated with BP and dermatology-specific disease guidance management fees (I). As such, we cannot exclude the possibility that patients other than those with mild pemphigoid were included in the study. We consider our report to be acceptable given the low proportion of recipients with BP as the designated intractable disease, the termination of registrations within a few months, and the

similarity between the number of BP cases obtained herein and those reported in other countries.

The current study showed a possible BP incidence rate of 38.1, 40.7 and 30.0/100,000 person-years among the 9,705,814 patients with type 2 diabetes, among those with type 2 diabetes using DPP-4is and among those not using DPP-4is, respectively (Table 1). A recent cohort study of DPP-4is and BP in the UK or the USA^{24,25} found BP incidence rates of 0.519 and 0.42 (/1,000 person-years) in patients with type 2 diabetes receiving DPP-4is, respectively, a finding consistent with that presented herein. Furthermore, incidence rates of 0.217 and 0.31 (/1,000 person-years) for patients taking other diabetes drugs were also consistent with those reported in the current study, confirming the validity of our report

Given that patients with type 2 diabetes included herein had a higher mean age than all patients, the higher possible incidence of BP was appropriate. However, age- and sex-adjusted analysis also showed a higher possible incidence of BP in patients with type 2 diabetes (Table 5). This indicates that diabetes itself was also associated with an increased risk for developing BP. Furthermore, the possible incidence of BP tended to be higher in elderly individuals, regardless of whether they had diabetes or were using DPP-4is (Table 2).

The first case report to show an association between DPP-4is and BP was published in 2011¹⁶. That report had likewise shown an association between DPP-4is (vildagliptin) and BP in two patients with type 2 diabetes. Since then, several reports on the risk of various DPP-4is and the development of BP have been published^{4–8,12,13}. However, the aforementioned studies were relatively small, with almost all them being case reports or case-control studies. Although recent prospective cohort studies in the UK and USA have shown that DPP-4is was associated with increased risk for developing BP in patients with type 2 diabetes, both studies were quite small and made no mention of time-dependent changes in the risk of developing BP from drug initiation^{24,25}. The current study utilized data obtained from the NDB, which covers 150,328,339 Japanese patients, to elucidate the relationship between DPP-4is and BP over a 5-year follow-up period.

Table 5 | Age-sex-adjusted Incidence ratio of bullous pemphigoid

	All patients	Patients with type 2 diabetes
n (%)	150,328,339	9,705,814
Mean age, years (SD)	45.9 (24.2)	70.0 (13.5)
No. patients developing BP	53,027	15,634
Incidence ratio of BP/100,000 person-years	10.36	38.15
Incidence ratio of BP/100,000 person-years*	3.16	6.53

Abbreviation: SD, standard deviation. *Incidence ratio of bullous pemphigoid (BP) adjusted age and sex.

Benzaquen *et al.*¹⁷ reported that vildagliptin promoted the highest risk for developing BP, whereas sitagliptin and linagliptin were not associated with the development of BP. However, Kridin *et al.*¹⁸ showed that vildagliptin and linagliptin were associated with an increased risk for BP. As stated earlier, although many reports have shown that vildagliptin was associated with the development of BP, it remains controversial whether other DPP-4is were related to the development of BP. Given their relatively small sample size, previous studies could not sufficiently validate whether DPP-4is were associated with the development of BP. In contrast, the larger sample size of our study allowed us to assess the risk associated with each DPP-4i. Accordingly, the present study showed that not only daily DPP-4i (alogliptin, anagliptin, linagliptin, saxagliptin, sitagliptin, teneligliptin and vildagliptin), but also all weekly DPP-4i (such as omarigliptin and trelagliptin) were significantly associated with the risk for developing BP, with both having an approximately similar risk for developing BP (Table 3). The SIRs for each DPP-4i were within the approximately twofold range, although the respective values were not provided to avoid misunderstanding.

To assess time-dependent changes in the risk for developing BP after DPP-4i initiation, a self-controlled case series analysis of 28,705 patients with type 2 diabetes who developed BP was carried out using a model adjusted for each DPP-4i prescription. This included 3,878 patients with type 2 diabetes who used DPP-4i for the first time after April 2014 and first developed BP after using DPP-4i, regardless of the use of other antidiabetic drugs. The current study using the NDB had a sample size larger than any of the previous studies described earlier. The risk ratio for developing BP with DPP-4i was highest within 30 days after initial administration, gradually decreasing thereafter until no risk was observed after 90 days, except for after 366–549 days (Table 4). In contrast, there have been reports on BP developing >90 days after DPP-4i initiation. For instance, one study reported DPP-4i-specific BP, which is histologically different from classical BP, with a latency of 5–26 months²⁶. We hypothesized that BP developing within 90 days of DPP-4i initiation might have a different pathogenic mechanism than BP developing later, because of the different onset times and incidence rates. Particular attention should be paid to the development of BP within 90 days of DPP-4i initiation. Although the incidence of BP is rare, care should be taken even after 3 months of DPP-4i use. This is the first study to show a time-dependent change in the risk of developing BP after DPP-4i initiation. For sensitivity analysis, calculations for risk periods were carried out only for patients with type 2 diabetes who used DPP-4is for the first time after April 2014 and were prescribed other antidiabetic drugs from April 2013 to March 2014. Although 28,705 individuals were included in this analysis, incidence rates of BP according to days after exposure were calculated in those who experienced exposure and outcome. Data for the other patients were used to adjust other variables in the model. Accordingly, results similar to those presented earlier had been obtained (Table S3).

To investigate whether the increased risk for developing BP was an event specific to DPP-4i, a similar analysis was conducted with biguanides. Accordingly, we found no such association between biguanides and BP (Table S4), a result consistent with that presented in a Finnish nationwide case-control study²⁷. Therefore, we believe that the increased risk for developing BP was unique to DPP-4is, validating and our self-controlled case series analysis.

The present study had several limitations worth noting. First, the NDB does not include any laboratory data. We defined patients with BP as those who had diagnostic codes associated with BP and the dermatology-specific disease guidance management fee (I). Considering that diseases other than BP might have been included among the patients defined as having BP, we herein described the incidence of BP calculated using the NDB as a possible incidence of BP. However, we are confident in our SIR or time-dependent increase in the risk for developing BP given that these parameters determine the ratio of incidence rates.

Second, medical records of each patient, including body-weight, smoking history and family history, could not be reviewed in detail. However, no reports have shown that these factors were associated with the development of BP, whereas using a self-control case series study design would allow us to adjust for time-independent confounders, including unmeasured time-independent confounding factors. Therefore, although we consider our results to be appropriate, the current study is an observational study and cannot completely adjust for confounding factors.

Third, the present study could not show the possible agent-dependent differences. Although the prescribing history of each of the DPP-4is was adjusted, each effect on BP was not clarified. Finally, given that this was an epidemiological study, residual confounders acting as bystanders or epiphenomena might have affected the association between BP development and DPP-4is. However, given the large scale of the current study of 150,328,339 patients using Japanese insurance claims data, we believe that various confounding factors had been adjusted.

In conclusion, using 5-year data obtained from the NDB, the current study showed the possible incidence of BP in all patients and those with type 2 diabetes. Accordingly, all DPP-4is, including those taken daily and weekly, were associated with an increase in the possible incidence of BP. Furthermore, DPP-4is were associated with an increased risk of developing BP, especially within 3 months from DPP-4i initiation.

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DISCLOSURE

Conflict of interest: Dr Kuwata reports receiving lecture fees and consultant fees from Takeda, Sanofi, Astellas and Novo

Nordisk. Dr Nishioka reports receiving consulting fees from Novo Nordisk. Dr Takahashi reports receiving consultant fees from Novo Nordisk, Otsuka and Recordati, and speaker fees from Novo Nordisk, Sumitomo Dainippon, Eli Lilly, Ono, Novartis, Nippon Boehringer Ingelheim, AstraZeneca and Kyowa Kirin. Dr Ishii reports receiving lecture fees and consulting fees from Takeda, Eli Lilly Japan, Sanofi, Merck & Co., Astellas, Mitsubishi Tanabe, Daiichi Sankyo, Ono, AstraZeneca, Taisho Toyama, Shionogi, Kowa, Boehringer Ingelheim, Novo Nordisk, Sumitomo Dainippon and Kyowa Hakko Kirin. The other authors declare no conflict of interest.

Approval of the research protocol: This study was approved by the ethics committee of Nara Medical University (approval no. 1123-5, 8 October 2015).

Informed consent: The need for informed consent was waived in view of the study design.

Approval date of Registry and the Registration No. of the study/trial: N/A.

Animal Studies: N/A.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1 | Diagnosis code.

Table S2 | Medicine code.

Table S3 | Incidence rate ratio of bullous pemphigoid after dipeptidyl peptidase-4 inhibitor use for each period. ($n = 28,705$ including 1,799 patients with first dipeptidyl peptidase-4 inhibitor prescription and other antidiabetic drugs).

Table S4 | Incidence rate ratio of bullous pemphigoid after biguanides use for each period. ($n = 28,705$ including 2,375 patients with first biguanides prescription).