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SHORT COMMUNICATION

Effects of a Sitagliptin Safety Alert on Prescription Behaviour for Oral Antihyperglycaemic Drugs: A Propensity Score-Matched Cohort Study of Prescription Receipt Data in Japan

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Abstract

Background Sitagliptin, the first of a new class of dipeptidyl peptidase-4 (DPP-4)-inhibitory oral antihyperglycaemic drugs (OHDs), was introduced in Japan in December 2009. In April 2010 a safety alert was issued regarding the risk of serious hypoglycaemic events, and prescribers were recommended to reduce the dose of sulfonylurea (i.e. glimepiride, glibenclamide [glyburide] or gliclazide) in patients receiving a combination of sulfonylurea and sitagliptin.

Objective A propensity score-matched cohort study was performed using Japanese pharmacy prescription receipt data for OHDs in order to confirm reported changes in OHD prescription behaviour for patients receiving sitagliptin before and after the safety alert.

Methods Prescription data from about 6,500 medical institutions throughout Japan during December 2009 to 31 December 2010 were randomly collected from 300 pharmacies, covering 82,064 patients with 629,955 prescriptions for OHDs. Patients who had received a sulfonylurea and sitagliptin (1,788 patients/3,576 prescriptions) before the safety alert were designated as the DPP-4 group. Patients who had received a sulfonylurea but not sitagliptin (30,963 patients/61,926 prescriptions) before the alert were designated as the non-DPP-4 group. Propensity score matching was employed to match baseline characteristics, such as age, sex, type of OHD, metformin use, type of prescribers period for measuring baseline period and type of prescribers' institutions, for 1,783 patients from each group. In the matched cohort, logistic regression analysis was conducted to compare prescription trends before and after the alert. The primary outcome measure of this study was dose of glimepiride, glibenclamide or gliclazide prescribed for DPP-4 and non-DPP-4 patients.

Results In the propensity score-matched cohort, the proportion of glimepiride dose >2 mg of DPP-4 patients was reduced from 45.8 % in Period 1 (before the alert) to 37.5 % in Period 2 (after the alert) (odds ratio [OR] 0.71; 95 % CI 0.579–0.870), whereas in the case of non-DPP-4 patients the proportion was changed from 28.9 % to 29.5 % in the matched cohort (OR 1.03; 95 % CI 0.868–1.215). The mean prescribed glimepiride dose in DPP-4 patients was also reduced from 2.79 ± 1.81 mg in Period 1 (before the alert) to 2.38 ± 1.71 mg in Period 2 (after the alert) [$p < 0.0001$], whereas the corresponding change in the case of non-DPP-4 patients was from 2.01 ± 1.56 mg to 2.01 ± 1.54 mg ($p = 0.94$). The difference between the mean prescribed doses in the two groups was statistically significant in both periods. Similar trends of prescription pattern changes were seen for glibenclamide and gliclazide. The reduction of prescribed sulfonylurea dose in DPP-4 patients following the safety alert coincided with a decrease of adverse event reports.

Conclusion Our results indicate that propensity score matching to control for baseline characteristics of individual patients and prescribers is a useful approach to avoid selection bias and confounding effects in evaluating the influence of an event on prescription behaviour. This case-matched study indicated that sulfonylurea prescription behaviour changed significantly after the sitagliptin safety alert. There was a significant reduction in sulfonylurea dose after the alert in DPP-4 patients, but not in non-DPP-4

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patients. Our findings should be helpful for assessing and improving the effectiveness of other regulatory safety alerts.

1 Introduction

1.1 Background

In December 2009, sitagliptin was launched in Japan as the first dipeptidyl peptidase-4 (DPP-4) inhibitor for use either alone or in combination with sulfonylureas or other oral antihyperglycaemic drugs (OHDs) in patients with type 2 diabetes [1, 2, 3]. The OHD-associated hypoglycaemia rate was expected to be lower in the case of sitagliptin therapy than in conventional OHD therapy with sulfonylureas [4].

On 7 April 2010, The Japan Diabetes Society also published a recommendation that the dose of sulfonylureas should be reduced when sitagliptin or another DPP-4 inhibitor is added to the regimen for patients already receiving sulfonylureas [5]. The Society recommended that when sitagliptin is prescribed with sulfonylureas (glimepiride, glibenclamide [glyburide] or gliclazide), the dose of these sulfonylureas should be reduced to 2 mg/day or less, 1.25 mg/day or less, or 40 mg/day or less, respectively, whereas the normal maintenance dose ranges of these sulfonylureas in Japan are 1–4 (highest 6) mg/day for glimepiride, 1.25–7.5 (highest 10) mg/day for glibenclamide and 40–120 (highest 160) mg/day for gliclazide. On 27 April 2010, the label of sitagliptin was revised to warn of the risk of serious hypoglycaemia for the situation when sitagliptin is combined with sulfonylureas. Based on The Japan Diabetes Society's recommendation, physicians were recommended to reduce the dose level of sulfonylureas prescribed in combination with sitagliptin [6, 7].

In the previous study by our research group, using simple logistic regression analysis of the prescription behavioural change for patients receiving sitagliptin before and after the alert issued on 27 April 2010, we found that the glimepiride dose was reduced from 2.78 ± 1.86 mg to 2.32 ± 1.68 mg after the safety alert [8]. However, as that was not a controlled study the result might have been affected by biases and confounding baseline factors that might have influenced diabetes treatment selection. In order to evaluate more robustly the effectiveness of the alert in terms of prescription behavioural change, we therefore attempted to perform an analysis in the framework of a matched case-control study, using the propensity score matching method to minimize or eliminate selection biases and confounding effects related to diabetes treatment selection.

Diabetes treatment selection is considered to be influenced by the characteristics of not only patients, but also those of prescribers [9], and the baseline characteristics of subjects receiving a particular treatment regimen often differ systematically from those of subjects receiving an alternative regimen. This is an important issue when estimating the effect of treatments or exposures on outcomes using observational data. One approach to reduce or eliminate the effect of treatment selection bias and confounding effects is the use of propensity score matching, which allows one to design and analyse an observational (non-randomized) study so that it mimics some of the characteristics of a randomized controlled trial [10]. Propensity score matching is a statistical matching technique that attempts to estimate the effect of an intervention by accounting for the covariates that predict receiving the intervention, reducing the bias due to confounding that could affect an estimate of the effect obtained from simply comparing outcomes with controls [11]. In this study, we used this approach to examine the effect of the sitagliptin safety alert on prescription trends of OHD. Specifically, because patients were not randomized to receive a DPP-4 inhibitor, we performed a one-to-one matched analysis without replacement on the basis of the estimated propensity score of each patient.

1.2 Objectives

The objective of this study was to examine the effect of the sitagliptin safety alert on prescribing behaviour by comparing the OHD prescription data of a propensity score-matched cohort of patients receiving a sulfonylurea and sitagliptin (DPP-4 patients) and patients receiving a sulfonylurea but not sitagliptin (non-DPP-4 patients) before the safety alert.

2 Methods

2.1 Study Design

This study was a retrospective cohort study of prescription data from about 6,500 medical institutions throughout Japan, randomly collected from 300 pharmacies. The number of prescriptions included in the cohort from 1 December 2009 to 31 December 2010 was approximately 12,285,000 prescriptions (11,340,000 patients/year), among which 629,955 prescriptions included OHDs.

2.2 Setting

The prescription data were collected from 1 December 2009 to 31 December 2010, which covers the first year of DPP-4 inhibitor (e.g. sitagliptin) introduction and includes the safety alert issued in April 2010.

2.3 Participants

We identified a cohort of 82,064 patients with 629,955 prescriptions for OHDs, among which 353,818 included sulfonylureas (e.g. glimepiride: 246,182). The original cohort was composed of the following non-DPP-4 and DPP-4 patient populations. The non-DPP-4 patients (30,963 patients/61,926 prescriptions) consisted of those who received a sulfonylurea in Period 1 (before the alert: from 1 December 2009 to 26 April 2010) and continued it in Period 2 (after the alert: from 27 April 2010 to 31 December 2010), but did not receive sitagliptin at least in Period 1. The DPP-4 patients (1,788 patients/3,576 prescriptions) consisted of those who received both a sulfonylurea and sitagliptin in Period 1 and continued OHD treatment in Period 2. We focused on glimepiride, glibenclamide and gliclazide as sulfonylureas because dose reduction of these three drugs was explicitly recommended by The Japan Diabetes Society. We extracted the data of two prescription points, one each in Period 1 and Period 2, in each patient group. The two points consisted of the earliest prescription point in Period 1 and the latest prescription point in Period 2.

2.4 Variables

The primary outcomes of this study were numbers of combined OHDs and prescribed doses of sulfonylureas (glimepiride, glibenclamide and gliclazide) for DPP-4 and non-DPP-4 patients before and after the safety alert issued in April 2010.

2.5 Bias

To reduce the effect of treatment selection bias and potential confounding effects, we performed adjustments for differences in baseline characteristics by means of propensity score matching. The propensity scores were estimated using multiple logistic regression analysis. Prespecified covariates listed in Table 1 were included for the calculation of propensity scores.

As shown in Table 1, there was substantial variation between the two groups. Therefore, patient selection was performed by using the propensity score-matching method with the Greedy 5-to-1 digit-matching algorithm [12, 13] for baseline characteristics, i.e. age, sex, type of OHD, type of prescriber, type of prescribers' institution, metformin use and period for measuring baseline characteristics. In the Japanese medical environment, the pattern of prescribing metformin is likely to be a confounding factor, which represents the patients' disease baseline characteristics. Although biguanides are also recommended as a first-line treatment [14], sulfonylureas have been preferred for patients with decreased insulin secretion capacity associated with the development of type 2 diabetes in Japan [15]. Thus, we chose metformin as one of the factors to be adjusted in this study because it may be related to disease baseline characteristics, such as decreased secretion capacity or increased insulin resistance.

2.6 Statistical Method

Summary statistics were constructed employing frequencies and proportions for categorical data, and means and standard deviations for continuous variables. We compared prescription trends using the Chi-square test for categorical outcomes and t-tests for continuous variables, as appropriate.

After propensity score matching, logistic regression analysis was conducted to compare mean daily dose and proportions for categorical dose of concomitant sulfonylureas (glimepiride, glibenclamide and gliclazide) and number of OHDs combined (1, 2, $\geq$3) between Period 1 and Period 2.

All comparisons were planned and the tests were two-sided. A p-value of less than 0.05 was considered to indicate a statistically significant difference. All statistical analyses were conducted by using SAS software, version 9.2 (SAS Institute Inc., NC, USA).

3 Results

3.1 Participants and Descriptive Data

After propensity score matching, we compared baseline covariates between the two groups. Of the 1,788 DDP-4 patients, we successfully matched 99.7 % of patients 1:1 with a control patient (N = 3,566; 1783 patients for each group), and their demographic characteristics are summarized in Table 1. In the original cohort, there were statistically significant differences in the age of patients, prescribers' scale of medical institution, department, metformin use and dosing period between DPP-4 patients and non-DPP-4 patients. In contrast, there were less statistically significant differences in any of the demographic characteristics between the propensity score-matched groups.

3.2 Outcome Data

Tables 2, 3 and 4 show the numbers of patients in each category of sulfonylurea drug use and time period (Period 1: before the alert was issued on 27 April 2010; Period 2: after the alert).

Table 1 Characteristics of the original cohort (DPP-4 patients and non-DPP-4 patients [control]) and the propensity score-matched cohort

Factor	Original cohort			Propensity score-matched cohort		
	DPP-4 patients [n = 1,788] (%)	Non-DPP-4 patients [n = 30,963] (%)	p-value	DPP-4 patients [n = 1783] (%)	Non-DPP-4 patients [n = 1783] (%)	p-value
Sex						
Male	1,041 (58.2)	18,375 (59.4)	0.35	1,039 (58.3)	1,083 (60.7)	0.13
Female	747 (41.8)	12,588 (40.6)		744 (41.7)	700 (39.3)	
Age (y)						
0 (<55)	388 (21.7)	3,840 (12.4)	<0.0001	387 (21.7)	482 (27.0)	0.003
1 (55–64)	518 (29.0)	8,397 (27.1)		517 (29.0)	523 (29.3)	
2 (65–74)	521 (29.1)	10,096 (32.6)		519 (29.1)	487 (27.3)	
3 (≥75)	361 (20.2)	8,630 (27.9)		360 (20.2)	291 (16.3)	
Scale of medical institution						
200 or more beds	627 (35.1)	13,863 (44.8)	<0.0001	627 (35.2)	667 (37.4)	0.027
Less than 200 beds	220 (12.3)	5,476 (17.7)		220 (12.3)	256 (14.4)	
General practitioners	941 (52.7)	11,624 (37.5)		936 (52.5)	860 (48.2)	
Department						
Metabolic medicine	317 (17.7)	4,787 (15.6)	0.14	317 (17.8)	356 (20.0)	0.087
General internal medicine	1,214 (67.9)	20,783 (67.8)		1214 (68.1)	1152 (64.6)	
Others	257 (14.4)	5,086 (16.6)		252 (14.1)	275 (15.4)	
Metformin						
Used	614 (34.3)	8,847 (28.6)	<0.0001	612 (34.3)	607 (34.0)	0.86
Not used	1,174 (65.7)	22,116 (71.4)		1171 (65.7)	1176 (66.0)	
Period for measuring baseline characteristics						
Dosing period (median: min, max)	9.1 months (0.30–12.6)	11.3 months (0.29–12.9)	<0.0001	9.2 months (0.30–12.6)	9.2 months (0.30–12.9)	0.30

DPP-4 patients: patients who received sulfonylurea (glimepiride, glibenclamide or gliclazide) and sitagliptin before the safety alert

Non-DPP-4 patients: patients who received sulfonylurea (glimepiride, glibenclamide or gliclazide) but did not receive sitagliptin before the safety alert

DPP-4 dipeptidyl peptidase-4, *max* maximum, *min* minimum

3.3 Main Results

The main variables in both the original cohort before matching and the propensity score-matched cohort are presented in Table 2. In the cohort before propensity score matching, for example, the mean daily prescribed dose of glimepiride for DPP-4 patients was reduced from 2.81 ± 1.82 mg (782 patients; Period 1) to 2.39 ± 1.72 mg (773 patients; Period 2) [$p \leq 0.0001$] after the alert, while the corresponding change for non-DPP-4 patients was from 2.07 ± 1.55 mg (21,038 patients) to 2.09 ± 1.56 mg (21,628 patients). In the propensity score-matched cohort, the mean daily prescribed dose of glimepiride for DPP-4 patients was similarly reduced from 2.79 ± 1.81 mg (778 patients; Period 1) to 2.38 ± 1.71 mg (769 patients; Period 2) [$p \leq 0.0001$], while for non-DPP-4 patients, the doses in Period 1 and Period 2 were 2.01 ± 1.56 mg (1,304 patients) and 2.01 ± 1.54 mg (1,324 patients), respectively. There was no statistically significant difference between the doses in Period 1 and Period 2 for non-DPP-4 patients ($p = 0.94$) in the matched cohort. The mean daily glimepiride dose in either Period 1 or Period 2 for DPP-4 patients was statistically significantly higher than that of non-DPP-4 patients in the corresponding period ($p < 0.0001$ and $p < 0.0001$, respectively). The proportion of glimepiride dose >2 mg for DPP-4 patients was reduced from 46.0 % to 37.8 % in the original cohort and from 45.8 % to 37.5 % in the matched cohort (odds ratio [OR] 0.71; 95 % CI: 0.579–0.870), while that of non-DPP-4 patients changed from 29.2 % to 30.1 % in the original cohort and from 28.9 % to 29.5 % in the matched cohort (OR 1.03; 95 % CI: 0.868–1.215).

The dose changes between Period 1 and Period 2 of other sulfonylureas (glibenclamide and gliclazide) showed a similar trend to glimepiride, as presented in Tables 3 and 4. However, in the case of glibenclamide for DPP-4 patients, there was no statistically significant reduction of mean daily dose after the alert in the matched cohort.

Table 2 Daily dose of glimepiride in DPP-4 and non-DPP-4 patients of the original cohort and propensity score-matched cohort

	Period 1 (before alert)		Period 2 (after alert)		OR/p-value	Difference in difference analysis
	No. of patients (prescriptions)	Glimepiride dose/day	No. of patients (prescriptions)	Glimepiride dose/day		
Original cohort						
DPP-4 patients	782 (782)	≤2 mg 422 (54.0 %) >2 mg 360 (46.0 %) Average: 2.808 ± 1.817 mg (0.50–6.0) [95 % CI 2.680–2.935]	773 (773)	≤2 mg 481 (62.2 %) >2 mg 292 (37.8 %) Average: 2.393 ± 1.721 mg (0.13–6.0) [95 % CI 2.272–2.515]	OR 0.71 (95 % CI 0.581–0.871) $p < 0.0001$	$p < 0.0001$
Non-DPP-4 patients	21,038 (21,038)	≤2 mg 14,887 (70.8 %) >2 mg 6,151 (29.2 %) Average: 2.071 ± 1.551 mg (0.25–9.0) [95 % CI 2.050–2.092]	21,628 (21,628)	≤2 mg 15,111 (69.9 %) >2 mg 6,517 (30.1 %) Average: 2.092 ± 1.564 mg (0.125–10.0) [95 % CI 2.072–2.113]	OR 1.04 (95 % CI 1.001–1.088) $p = 0.16$	
Propensity score-matched cohort						
DPP-4 patients	778 (778)	≤2 mg 422 (54.2 %) >2 mg 356 (45.8 %) Average: 2.791 ± 1.808 mg (0.50–6.0) [95 % CI 2.664–2.918]	769 (769)	≤2 mg 481 (62.5 %) >2 mg 288 (37.5 %) Average: 2.375 ±1.706 mg (0.125–6.0) [95 % CI 2.254–2.495]	OR 0.71 (95 % CI 0.579–0.870) $p < 0.0001$	$p < 0.0001$
Non-DPP-4 patients	1,304 (1,304)	≤2 mg 927 (71.1 %) >2 mg 377 (28.9 %) Average: 2.014 ± 1.558 mg (0.25–6.0) [95 % CI 1.929–2.098]	1,324 (1,324)	≤2 mg 934 (70.5 %) >2 mg 390 (29.5 %) Average: 2.009 ± 1.544 mg (0.25–6.0) [95 % CI 1.926–2.092]	OR 1.03 (95 % CI 0.868–1.215) $p = 0.94$	

Period 1: Before the safety alert was issued on 27 April 2010 (December 2009–April 2010)

Period 2: After the safety alert (April 2010–December 2010)

DPP-4 patients: patients who received glimepiride and sitagliptin in Period 1

Non-DPP-4 patients: patients who received glimepiride but did not receive sitagliptin in Period 1

DPP-4 dipeptidyl peptidase-4, *OR* odds ratio

Table 3 Daily dose of glibenclamide in DPP-4 and non-DPP-4 patients of the original cohort and propensity score-matched cohort

	Period 1 (before alert)		Period 2 (after alert)		OR/p-value	Difference in difference analysis
	No. of patients (prescriptions)	Glibenclamide dose/day	No. of patients (prescriptions)	Glibenclamide dose/day		
Original cohort						
DPP-4 patients	138 (138)	≤1.25 mg 11 (8.0 %) >1.25 mg 127 (92.0 %) Average: 5.539 ± 2.980 mg (0.63–10.0) [95 % CI 5.038–6.041]	117 (117)	≤1.25 mg 12 (10.3 %) >1.25 mg 105 (89.7 %) Average: 5.051 ± 2.843 mg (0.31–10.0) [95 % CI 4.530–5.571]	OR 0.76 (95 % CI 0.321–1.787) p = 0.15	p < 0.0001
Non-DPP-4 patients	6,521 (6,521)	≤1.25 mg 1,503 (23.0 %) >1.25 mg 5,018 (77.0 %) Average: 3.986 ± 2.598 mg (0.31–15.0) [95 % CI 3.923–4.049]	6,029 (6,029)	≤1.25 mg 1,397 (23.2 %) >1.25 mg 4,632 (76.8 %) Average: 3.988 ± 2.608 mg (0.31–15.0) [95 % CI 3.922–4.054]	OR 0.99 (95 % CI 0.914–1.079) p = 0.97	
Propensity score-matched cohort						
DPP-4 patients	138 (138)	≤1.25 mg 11 (8.0 %) >1.25 mg 127 (92.0 %) Average: 5.539 ± 2.980 mg (0.63–10.0) [95 % CI 5.037–6.041]	117 (117)	≤1.25 mg 12 (10.3 %) >1.25 mg 105 (89.7 %) Average: 5.051 ± 2.843 mg (0.31–10.0) [95 % CI 4.530–5.571]	OR 0.76 (95 % CI 0.321–1.787) p = 0.15	p < 0.0001
Non-DPP-4 patients	302 (302)	≤1.25 mg 83 (27.4 %) >1.25 mg 219 (72.5 %) Average: 3.640 ± 2.433 mg (0.63–12.5) [95 % CI 3.365–3.916]	285 (285)	≤1.25 mg 78 (27.4 %) >1.25 mg 207 (72.6 %) Average: 3.643 ± 2.463 mg (0.63–10.0) [95 % CI 3.355–3.930]	OR 1.01 (95 % CI 0.700–1.446) p = 0.99	

Period 1: before the safety alert was issued on 27 April 2010 (December 2009–April 2010)

Period 2: after the safety alert (April 2010–December 2010)

DPP-4 patients: patients who received glibenclamide and sitagliptin in Period 1

Non-DPP-4 patients: patients who received glibenclamide but did not receive sitagliptin in Period 1

DPP-4 dipeptidyl peptidase-4, *OR* odds ratio

Table 4 Daily dose of gliclazide in DPP-4 and non-DPP-4 patients of the original cohort and propensity score-matched cohort

	Period 1 (before alert)		Period 2 (after alert)		OR/p-value	Difference in difference analysis
	No. of patients (prescriptions)	Gliclazide dose/day	No. of patients (prescriptions)	Gliclazide dose/day		
Original cohort						
DPP-4 patients	37 (37)	≤40 mg 16 (43.2 %) >40 mg 21 (56.8 %) Average: 71.351 ± 37.577 mg (20–160) [95 % CI 58.823–83.880]	56 (56)	≤40 mg 37 (66.1 %) >40 mg 19 (33.9 %) Average: 51.786 ± 35.322 mg (20–160) [95 % CI 42.326–61.245]	OR 0.39 (95 % CI 0.167–0.919) p = 0.0020	p = 0.0043
Non-DPP-4 patients	3,443 (3,443)	≤40 mg 2,610 (74.1 %) >40 mg 914 (25.9 %) Average: 45.307 ± 29.619 mg (10–160) [95 % CI 44.317–46.297]	3,342 (3,342)	≤40 mg 2,437 (72.9 %) >40 mg 905 (27.1 %) Average: 45.384 ± 29.955 mg (10–160) [95 % CI 44.364–46.405]	OR 1.06 (95 % CI 0.953–1.180 p = 0.92	
Propensity score-matched cohort						
DPP-4 patients	37 (37)	≤40 mg 16 (43.2 %) >40 mg 21 (56.8 %) Average: 71.351 ± 37.577 mg (20–160) [95 % CI 58.823–83.880]	56 (56)	≤40 mg 37 (66.1 %) >40 mg 19 (33.9 %) Average: 51.786 ± 35.322 mg (20–160) [95 % CI 42.326–61.245]	OR 0.39 (95 % CI 0.167–0.919) p = 0.0033	p = 0.0096
Non-DPP-4 patients	176 (176)	≤40 mg 126 (71.6 %) >40 mg 50 (28.4 %) Average: 44.886 ± 29.587 mg (10–160) [95 % CI 40.485–49.288]	179 (179)	≤40 mg 131 (73.2 %) >40 mg 48 (26.8 %) Average: 45.028 ± 30.194 mg (10–160) [95 % CI 40.574–49.481]	OR 0.92 (95 % CI 0.580–1.470) p = 0.97	

Period 1: before the safety alert was issued on 27 April 2010 (December 2009–April 2010)

Period 2: after the safety alert (April 2010–December 2010)

DPP-4 patients: patients who received gliclazide and sitagliptin in Period 1

Non-DPP-4 patients: patients who received gliclazide but did not receive sitagliptin in Period 1

DPP-4 dipeptidyl peptidase-4, *OR* odds ratio

Table 5 Numbers of OHDs used in combination in the DPP-4 population and non-DPP-4 population (control) in the propensity score-matched cohort

	Period 1			Period 2			p-value
	No. of patients	Mean numbers of OHDs [range]	95 % CI	No. of patients	Mean numbers of OHDs [range]	95 % CI	
DPP-4 patients	1783	2.304 ± 1.060	2.255–2.354	1783	2.246 ± 1.049	2.198–2.295	p = 0.068
Number of OHDs [n (%)]	1	490 (27.5)		532 (29.8)			p = 0.099
	2	542 (30.4)		529 (29.9)			
	3	509 (28.5)		506 (28.4)			
	4	203 (11.4)		184 (10.3)			
	5	38 (2.1)		31 (1.7)			
	6	1 (0.06)		1 (0.06)			
Non-DPP-4 patients	1783	1.953 ± 0.841	1.914–1.993	1783	2.012 ± 0.844	1.973–2.052	p = 0.066
Number of OHDs [n (%)]	1	602 (33.8)		545 (30.6)			p = 0.037
	2	733 (41.1)		748 (42.0)			
	3	378 (21.2)		415 (23.3)			
	4	69 (3.9)		73 (4.1)			
	5	1 (0.1)		2 (0.1)			

Period 1: before the safety alert was issued on 27 April 2010 (December 2009–April 2010)

Period 2: after the safety alert (April 2010–December 2010)

DPP-4 patients: patients who received sulfonylurea (glimepiride, glibenclamide or gliclazide) and sitagliptin in Period 1

Non-DPP-4 patients: patients who received sulfonylurea (glimepiride, glibenclamide or gliclazide) but did not receive sitagliptin in Period 1

DPP-4 dipeptidyl peptidase-4, *OHD* oral antihyperglycaemic drugs

We also performed difference-in-difference (DID) analysis on DPP-4 patients and non-DPP-4 patients, comparing before and after the alert. The results of DID showed statistically significant changes after the alert in the matched patients for glimepiride ($p < 0.0001$), glibenclamide ($p < 0.0001$) and gliclazide ($p = 0.0096$) [Tables 2, 3 and 4, respectively].

In the DPP-4 patients, the mean numbers of OHDs used in combination (1, 2, ≥3) in Period 1 and Period 2 were 2.30 ± 1.06 and 2.25 ± 1.05, respectively (no statistically significant difference; Table 5). The non-DPP-4 population showed no statistically significant increase in the mean numbers of OHDs used in combination (from 1.95 ± 0.84 in Period 1 to 2.01 ± 0.84 in Period 2; $p = 0.066$) after the alert.

In addition, adverse events reported to the health authorities showed a peak at around the time of the safety alert and declined afterwards (Table 6).

Table 6 Adverse event reports on sitagliptin associated with hypoglycaemic events from December 2009 to March 2011

Reporting period[a]	Adverse events[a]	
	Hypoglycaemia	Coma, hypoglycaemia
December 2009–March 2010	17	0
April 2010–July 2010[b]	69	4
August 2010–November 2010	20	2
December 2010–March 2011	19	0

[a] Data sorted from the periodic cumulative ADR reporting data published on http://www.mhlw.go.jp by the Pharmaceuticals and Medical Devices Agency, Japan (PMDA)/Japanese Ministry of Health, Labour & Welfare (MHLW) [note that the adverse event reporting periods do not coincide with our study periods 1 and 2 shown in Tables 2 and 3]

[b] On 27 April 2010 a safety alert was issued for hypoglycaemia associated with sitagliptin and combined sulfonylureas

ADR adverse drug reaction

4 Discussion

4.1 Key Results

The results of our study of a propensity score-matched cohort of patients showed that there was a statistically significant reduction in the prescribed dose of combined sulfonylurea (e.g. glimepiride) in patients receiving sitagliptin in the period after the regulatory safety alert issued in April 2010 compared with that in the period immediately before, suggesting that the alert had indeed impacted on prescription behaviour. The trend of adverse event reports was consistent with the safety alert and the prescription behaviour change.

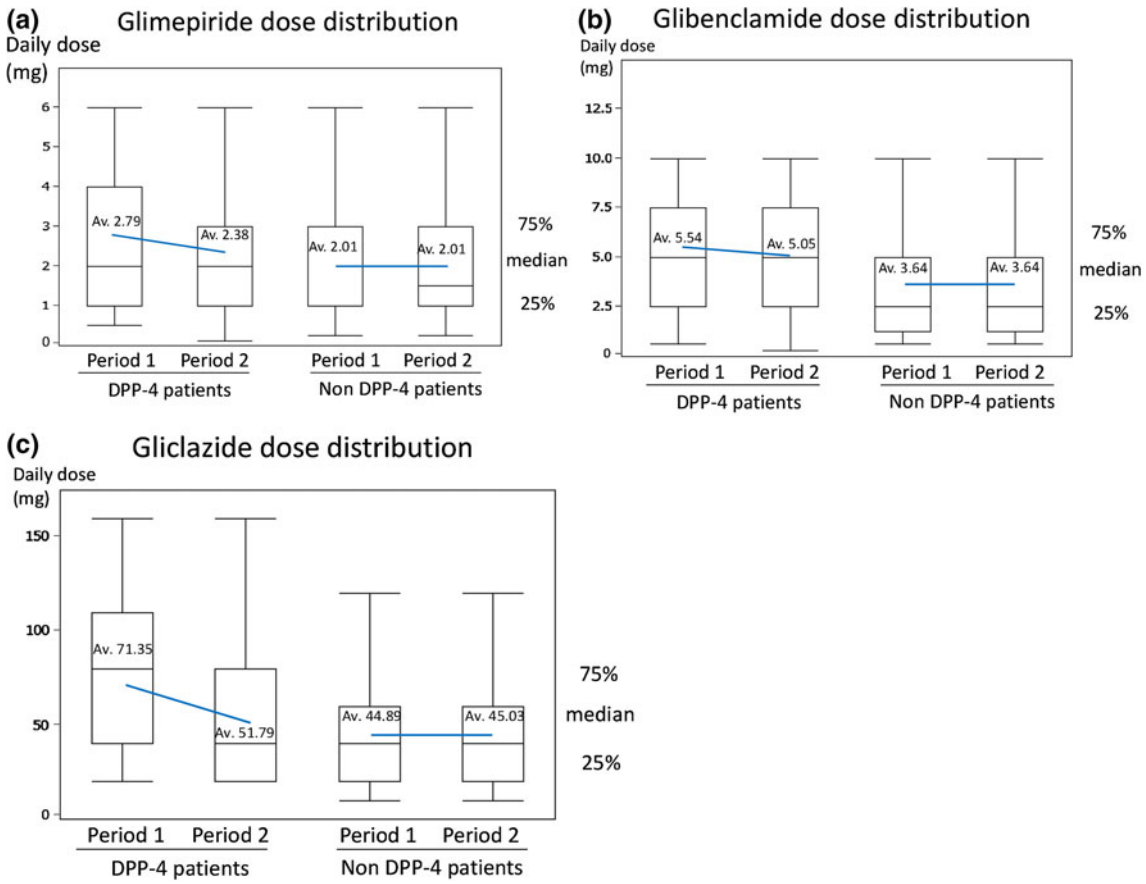

Fig. 1 Dose distribution of three sulfonylureas prescribed for DPP-4 patients and non-DPP-4 patients (propensity score-matched cohort). *Av* average, *DPP-4* dipeptidyl peptidase-4

4.2 Limitations

We used the prescription receipt data as a convenient source of medical information for epidemiological purposes. However, the data do not include diagnostic parameters, such as glycated haemoglobin (HbA1c), indicating disease stage or history [16], so the possibility that unknown confounding factors were overlooked cannot be ruled out. Therefore, the propensity score-matching method used in this study may not have adequately matched the disease state of the two groups (DPP-4 patients and non-DPP-4 patients) in our cohort.

4.3 Interpretation

This study evaluated and clarified the effectiveness of the safety alert on prescribing behavioural change, by adjusting selection biases and confounding related to the demographical factors of patients and prescribers. Our results show that the regulatory safety alert issued in April 2010 did impact on prescription behaviour since we found a statistically significant reduction in the daily dose of the combined sulfonylureas (glimepiride, glibenclamide and gliclazide) when comparing DPP-4 and non-DPP-4 patients before and after the alert, as would be expected if the alert recommendations had been effective. We have also verified the impact from various methods including DID analysis. Our findings suggest that the propensity score-matching method successfully minimized or eliminated selection biases and confounding effects related to diabetes treatment selection.

In the result it was observed that a higher proportion of DPP-4 patients were prescribed 2 mg/day or less of glimepiride after the safety alert (62.5 %) compared with the proportion before the safety alert (54.2 %). Although glimepiride daily dose for DPP-4 patients was recommended to be reduced to 2 mg/day or less, the result in Period 2 for mean glimepiride daily dose (2.38 ± 1.71 mg) and the proportion of glimepiride of 2 mg/day or less (62.5 %) does not seem to reflect full compliance with the recommendation. Similarly, mean daily doses of glibenclamide (5.05 ± 2.84 mg) and gliclazide (51.79 ± 35.32 mg) exceeded the recommended doses of 1.25 mg and 40 mg, respectively. However, even the non-DPP-4 group patients were receiving, on average, 3.64 ± 2.46 mg/day of glibenclamide and 45.03 ± 30.19 mg/day

of gliclazide, which are also over the recommended doses. It seems that The Japan Diabetes Society recommended doses, particularly for glibenclamide (1.25 mg/day), may not reflect the reality of prescription doses from the viewpoint of required potency in practice. A Japanese study comparing the potencies of sulfonylureas (glimepiride, glibenclamide and gliclazide) found that glimepiride 0.43 mg/day was equivalent to glibenclamide 1.25 mg/day and gliclazide 40 mg/day [17]. The lower potency of glibenclamide might partly account for prescribers' low adherence to the warning. The perceived risk-benefit balance of individual patients and range of treatment choices may have influenced prescription behaviours. It is important to note that this does not necessarily indicate that prescribers failed to take note of the warnings. A limitation of this study is the fact that the change of prescription rate/dosing does not quantitatively capture prescribers' response to the alert. Various other factors, such as drug promotion, may also affect the prescribing behaviour in response to safety warnings [18].

Although a reduction of the number of adverse event reports was observed in parallel with the declining prescription trends of sulfonylureas after the alert, the clinical significance of the dose reduction of sulfonylureas is not necessarily confirmed by this as adverse event reporting may sometimes reflect publication bias.

In our study, the higher sulfonylurea-dose group in DPP-4 patients showed shifts to lower doses after the alert (Fig. 1), whereas the dose distribution patterns of glimepiride and gliclazide in Period 2 of DPP-4 patients became closer to those of the non-DPP-4 patients. Overall, it seems reasonable to consider that the prescribing pattern changes after the alert are likely to have impacted on the drug safety of sitagliptin and sulfonylureas in combination.

While the mean prescribed daily dose of each sulfonylurea in DPP-4 patients was reduced after the safety alert, the mean dose of glimepiride of DPP-4 patients remained higher throughout the study period than that of non-DPP-4 patients. It seems plausible that patients receiving higher-dose sulfonylureas as background OHD therapy would have been most likely to have had sitagliptin added to their regimen. This may at least partly explain the frequent onset of serious early-postmarketing-phase hypoglycaemia in this group.

This study on prescription receipts did not consider any other factors that might have induced a change of prescribing patterns at the time of the sitagliptin alert, so it remains important to explore whether other factors could have been involved in changing prescription behaviour at that time.

5 Conclusions

Our analysis of pharmacy prescription receipt data using the propensity score-matching method to adjust for baseline factors indicates that the sitagliptin safety alert had a clear impact on prescription behaviour; there was a highly significant decrease in the doses of concomitantly administered sulfonylureas in DPP-4 patients compared with the change in non-DPP-4 patients. Our results indicate that propensity score matching to control for baseline characteristics of individual patients and prescribers is a useful approach to avoid selection bias and confounding effects in evaluating the influence of an event on prescription behaviour. The changes in prescribed doses after the alert coincided with a decline in reported adverse effects, although this need not necessarily imply a causal relationship since the decline in reported adverse events may reflect publication bias. Overall, our findings indicate the effect of an event on drug treatment pattern, which may depend on baseline characteristics of both individual patients and prescribers. Our findings should be helpful for monitoring drug safety and changes of treatment patterns when new classes of drugs are launched in established therapeutic categories.

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