Research Letters

DPP-4 Inhibitor Dose Selection According to Manufacturer Specifications: A Contemporary Experience From UK General Practice

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ABSTRACT

Recently, 2 dipeptidyl peptidase-4 (DPP-4) inhibitors, sitagliptin and saxagliptin, adjusted dosing specification from creatinine clearance to glomerular filtration rate, more typically reported in routine laboratory tests. This cross-sectional study examines all DPP-4 inhibitor initiations that require dose adjustment and the dose selection using data from UK general practice. Results indicate that 34% of patients taking a nonlinagliptin DPP-4 inhibitor were given a higher dose and 11% a lower dose than specified in the Summary of Product Characteristics. This reinforces the deviation from Summary of Product Characteristics prescription of DPP-4 inhibitors identified in earlier studies despite improvement in compatibility with routine reporting. (*Clin Ther*. 2019;41:1622–1630) © 2019 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Keywords: dose selection, DPP-4 inhibitors, summary of product characteristics, renal impairment, Type 2 diabetes mellitus, UK general practice.

INTRODUCTION

Dipeptidyl peptidase-4 (DPP-4) inhibitors (alogliptin, linagliptin, saxagliptin, sitagliptin, vildagliptin) are indicated to improve glycemic control in patients with type 2 diabetes mellitus (T2DM). The first DPP-4 inhibitor was introduced in the United Kingdom in 2009,[1] offering an additional treatment option for patients with T2DM and renal impairment.[2] According to their Summaries of Product Characteristics (SmPCs), all nonlinagliptin DPP-4 inhibitors require dose adjustment according to patients' renal function.[3–6] Linagliptin is the only member of the class that does not require dose adjustment, regardless of the degree of renal insufficiency, because of its primarily nonrenal mode of excretion.[7,8]

Until January 2018, the SmPC-specified common upper threshold for dose adjustment for all nonlinagliptin DPP-4 inhibitors was a creatinine clearance (CrCl) level of 50 mL/min. Previous UK observational studies have found that 32% of patients with T2DM with a CrCl <50 mL/min who began taking a nonlinagliptin DPP-4 inhibitor were taking a higher than the SmPC-recommended dose.[9] A subsequent study also found that 14% patients with T2DM treated with a nonlinagliptin DPP-4 inhibitor whose renal function did not indicate dose adjustment were treated with a lower than the SmPC-specified dose.[10] For patients with chronic kidney disease, clinical guidelines issued by the National Institute for Health and Care Excellence (NICE) recommend use of the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) creatinine equation for estimating glomerular filtration rate (GFR), an index of kidney function.[11] A possible explanation for the discrepancy in dose selection reported in the previous studies might be the discordance between the CrCl

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thresholds noted for dose adjustment in the SmPCs and the estimated GFR values used in clinical practice.

In January and July 2018, respectively, the SmPCs for sitagliptin and saxagliptin were updated to specify a renal threshold for dose adjustment of GFR <45 mL/min. In line with the previous studies, the aim of this analysis was to examine dose selection in a more recent cohort of patients with T2DM treated with DPP-4 inhibitors after the update, adopting variable renal threshold of GFR or CrCl, depending on the SmPC of the relevant prescribed DPP-4 inhibitor. This study therefore will provide insights on the extent to which the change of renal thresholds from CrCl to GFR has improved dose selection of DPP-4 inhibitors in UK general practice.

METHODS

Patients with T2DM treated with DPP-4 inhibitors on or after July 15, 2018, were identified in the Clinical Practice Research Datalink (CPRD). This date was chosen to account for the last change on renal adjustment specifications for a DPP-4 inhibitor. The index prescription was the first prescription on or after July 15, 2018, which was assessed via product codes captured by CPRD. Patients included in the analysis were of acceptable research standard, had a T2DM diagnostic code before the index date, and were registered to a general practice for 12 months, which had to be up to standard at the time of index prescription. Patients were at least 18 years old at T2DM diagnosis with no history of type 1 diabetes mellitus. Patients' renal function was estimated from the last serum creatinine record before or at index prescription. To account for outliers, serum creatinine records below the first percentile and above the 99th percentile were excluded from the analysis.

Renal function was expressed in CrCl if the index prescription was alogliptin or vildagliptin, using the Cockroft-Gault formula.[12] Patients whose renal function was estimated in CrCl also had at least 1 record of weight measurement to input into the formula. Because the NICE national guidelines recommend that clinical laboratories should report an estimated GFR (eGFR) using the CKD-EPI equation,[13] the GFR was estimated using the CKD-EPI formula[14] for patients whose index prescription was sitagliptin or saxagliptin. The CKD-EPI requires ethnicity information for accurate estimation. Ethnicity is poorly reported in CPRD; therefore, the CKD-EPI equation was not adjusted for ethnicity because the overall effect on study results is expected to be minimal as reported in earlier studies.[15]

Two analytical cohorts were defined. Cohort 1 included patients with an index prescription for saxagliptin or sitagliptin and an eGFR <45 mL/min, as well as patients with an index prescription for alogliptin or vildagliptin and a CrCl $\leq$50 mL/min and <50 mL/min, respectively. Cohort 2 included patients with an index prescription for saxagliptin or sitagliptin and an eGFR $\geq$45 mL/min, as well as patients with an index prescription for alogliptin and vildagliptin and a CrCl >50 and $\geq$ 50 mL/min, respectively.

Cohort 1 (Higher than SmPC-Specified analysis)

Patients in cohort 1 were expected to have their dose adjusted for the level of their renal function as recommended in the individual SmPC for each DPP-4 inhibitor. Numbers and percentages were estimated for patients prescribed alogliptin 25 mg, saxagliptin 5 mg, sitagliptin 100 mg, or vildagliptin 50 mg twice daily. In addition, patients prescribed alogliptin 12.5 mg and sitagliptin 50 mg with more severe levels of renal impairment (CrCl <30 mL/min and eGFR <30 mL/min, respectively) were included in the estimates.

Cohort 2: lower than SmPC-Specified analysis

Patients in cohort 2 were expected to receive the full dose of their DPP-4 inhibitor. Numbers and percentages were estimated for patients prescribed alogliptin 12.5 mg or 6.25 mg, saxagliptin 2.5 mg, sitagliptin 50 mg or 25 mg, or vildagliptin 50 mg once daily. Patients with a record of sulfonylurea prescription within 30 days of vildagliptin prescription were not included in the estimate because it is possible that they were taking these medicines concomitantly; this would require patients to receive a reduced vildagliptin dose (in line with the vildagliptin SmPC).[3]

For class-level estimates, patients with T2DM with linagliptin index prescription and CrCl <50 mL/min were included in cohort 1; those with linagliptin prescription and CrCl $\geq$50 mL/min were included in cohort 2. These thresholds were documented in the linagliptin SmPC to specify the threshold of moderate renal impairment.

This study was approved by the Independent Scientific Advisory Committee for Medicines and Healthcare Products Regulatory Agency database research (protocol 18_268R).

RESULTS

A total of 18,395 patients were prescribed a DPP-4 inhibitor during the study period, of whom 17,102 (93%) met the study inclusion criteria (Appendix). Of the 17,102 patients, 2580 patients should have had their dosage adjusted for their level of renal function as per the relevant SmPC (cohort 1), and 14,522 patients were expected to have received full dosage (cohort 2). Table I gives the baseline characteristics for all patients. Patients in cohort 1, who by definition had a lower level of renal function, were older, more likely to be female, and had longer disease duration but comparable body mass index and glycosylated hemoglobin to patients in cohort 2 (Table I).

Among patients in cohort 1, a total of 1000 were treated with nonlinagliptin DPP-4 inhibitors and therefore required a dose adjustment according to SmPC recommendations. However, 336 (33.6%) were treated with a higher than the SmPC-specified dose. In cohort 1, a total of 45 of 160 patients (28.1%) treated with saxagliptin and 172 of 526 patients (32.7%) treated with sitagliptin were taking a higher than SmPC-specified dosage. In addition, 116 of 298 patients (38.9%) treated with alogliptin and 3 of 16 patients (19%) treated with vildagliptin were taking a higher than SmPC-specified dosage (Table II). Of the 14,522 patients in cohort 2, a total of 11,411 were treated with a nonlinagliptin DPP-4 inhibitor, of whom 1296 (11.4%) were taking a lower than SmPC-specified dosage. In cohort 2, the proportion of patients prescribed saxagliptin and sitagliptin who were taking a lower than SmPC-specified dose was similar to the class mean (10.2% and 11.3%, respectively). Furthermore, in cohort 2, a total of 358 of 3067 patients (12%) treated with alogliptin and 19 of 95 patients (20%) treated with vildagliptin were taking a lower than SmPC-specified dosage.

Information regarding higher than SmPC-specified dose with nonlinagliptin DPP-4 inhibitors in patients with renal impairment is limited. However, regulators provide guidance on dosing for all nonlinagliptin DPP-4 inhibitors for patients with renal impairment in their respective SmPCs because of increased systemic drug exposure with increasing degrees of impairment.[3–6] Information regarding

Table I. Baseline characteristics of the study patients.[a]

Characteristic	All (n = 17,102)	Cohort 1 (n = 2580)	Cohort 2 (n = 14,522)
Age at index year, y	67.9 (12.0)	79.9 (7.9)	65.7 (11.3)
Sex			
Male	10,093 (59.0)	1274 (49.4)	8819 (60.7)
Female	7009 (41.0)	1306 (50.6)	5703 (39.3)
BMI at index, kg/m^2	31.2 (5.9)	29.0 (5.2)	31.6 (5.9)
HbA_{1c} before index, % of total hemoglobin	8.0 (1.6)	8.1 (1.5)	8.1 (1.5)
GFR before or at index, mL/min	36.3 (10.4)	79.7 (18.6)	73.1 (23.5)
CrCl before or at index, mL/min	38.3 (9.8)	102.3 (40.3)	92.7 (43.8)
Disease duration, mo	347 (213)	300 (194)	307 (198)

Abbreviations: BMI = body mass index; CrCl = creatinine clearance; GFR = glomerular filtration rate; HbA_{1c} = glycosylated hemoglobin.
[a] Data are presented as mean (SD). Numbers do not total because of missing data.

Table II. DPP-4 inhibitor dose selection based on SmPC renal thresholds.

DPP-4 Inhibitor	Cohort 1 (n = 2580)		Cohort 2 (n = 14,522)	
	Total No.	No. (%) Higher Than SmPC Specified	Total No.	No. (%) Lower Than SmPC Specified
Alogliptin	298	116 (38.9)	3067	358 (11.7)
Linagliptin	1580	NA	3081	NA
Saxagliptin	160	45 (28.1)	1415	145 (10.2)
Sitagliptin	526	172 (32.7)	6864	774 (11.3)
Vildagliptin	16	3 (18.8)	95	19 (20.0)
All DPP-4 inhibitors	2580	336 (13.0)	14,522	1296 (8.9)
All DPP-4 inhibitors excluding linagliptin	1000	336 (33.6)	11,411	1296 (11.4)

Abbreviations: DPP-4 = dipeptidyl peptidase-4; NA = not applicable; SmPC = Summary of Product Characteristics.

lower than SmPC-specified dose with nonlinagliptin DPP-4 inhibitors is also limited, but reduced plasma concentrations may lead to altered pharmacodynamic properties and therapeutic efficacy.

CONCLUSIONS

In addition to previous studies,[9,10] this study provides further evidence on DPP-4 inhibitor dose selection in relation to newly defined renal thresholds for 2 members of the class. Of all patients with diabetes taking nonlinagliptin DDP-4 inhibitors who required dose adjustment, 33.6% were prescribed a DPP-4 inhibitor at a higher dose than specified in the SmPC. Furthermore, 11.4% of patients who did not require dose adjustment were prescribed a lower dose than specified in the SmPC. For saxagliptin and sitagliptin, the 2 DPP-4 inhibitors that recently updated the dose adjustment thresholds recommended in their SmPC from CrCl to GFR, 28.1% and 32.7% of patients were taking a higher than SmPC-specified dosage, whereas 10.2% and 11.3% were taking lower than SmPC-specified dosage, respectively. Despite changes in measures that are more compatible with laboratory results, prescription of DPP-4 inhibitors at doses outside those recommended in the SmPC is still common in general practice. We recommend that clinicians are given further education on dose adjustment of DPP-4 inhibitors in patients with T2DM and renal impairment.

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CONFLICTS OF INTEREST

M. Busse, A. Tebboth, N.D. Gollop, and M.W. Marcus are all employees of Boehringer Ingelheim. D. Spanopoulos was an employee of Boehringer Ingelheim at the time the study was conducted. J. Webb is an employee of Eli Lilly and Company. The authors have indicated that they have no other conflicts of interest regarding the content of this article.

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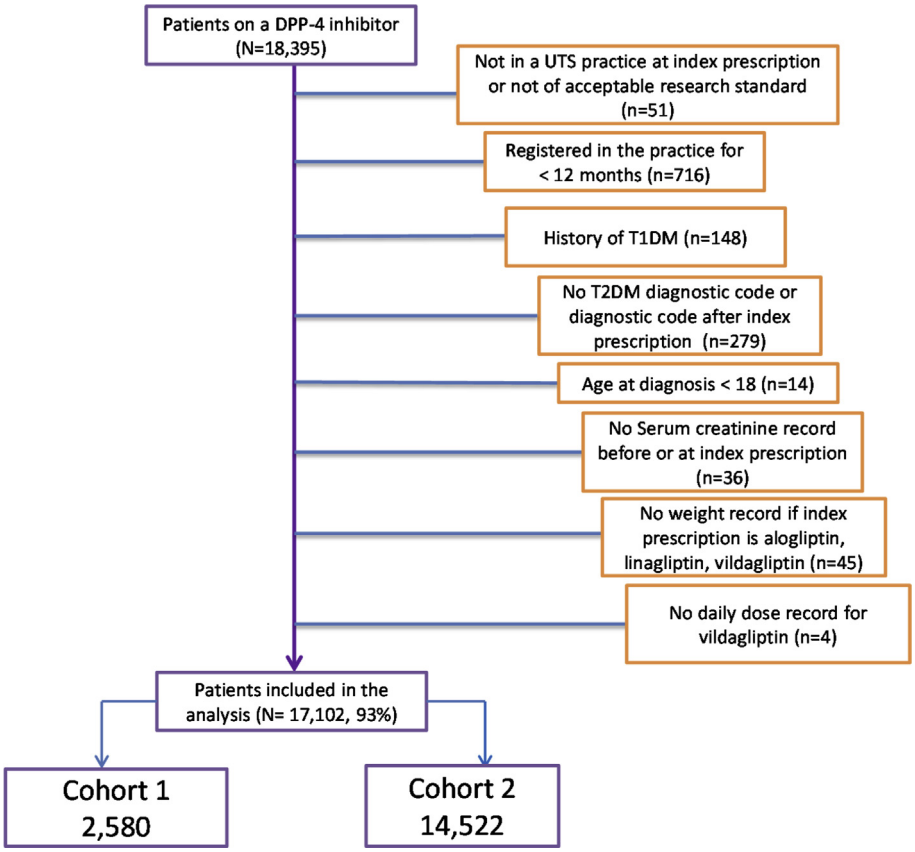
D. Spanopoulos, M. Busse, J. Webb, A. Tebboth, N.D. Gollop, and M.W. Marcus contributed to the study design, data interpretation, and writing of the manuscript. D. Spanopoulos conducted data analysis,

and M.W. Marcus conducted data quality control. All authors listed contributed to the study design, data handling, data analysis and interpretation, writing of the report, and the decision to submit the article for publication.

APPENDIX 1. PATIENT FLOW DIAGRAM.



Abbreviations: DPP-4, dipeptidyl peptidase-4; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; UTS, up-to-standard.

Appendix II. Product codes for DPP-4 inhibitors.

Prodcode	Product Name
Alogliptin	
59809	Alogliptin 6.25mg tablets
60328	Alogliptin 12.5mg tablets
59177	Alogliptin 25mg tablets
60682	Vipidia 25mg tablets
60681	Vipidia 12.5mg tablets
62326	Vipidia 6.25mg tablets
Linagliptin	
46665	Linagliptin 5mg tablets
46716	Trajenta 5mg tablets
Saxagliptin	
41204	Saxagliptin 5mg tablets
45775	Saxagliptin 2.5mg tablets
41431	Onglyza 5mg tablets
45821	Onglyza 2.5mg tablets
Sitagliptin	
35022	Sitagliptin 100mg tablets
48401	Sitagliptin 50mg tablets
48533	Sitagliptin 25mg tablets
35462	Januvia 100mg tablets
50087	Januvia 50mg tablets
50124	Januvia 25mg tablets
Vildagliptin	
37875	Vildagliptin 50mg tablets

Appendix III. Medical codes for T2DM

Medcode	Read Code	Read Term
758	C10F.00	Type 2 diabetes mellitus
506	C100112	Non-insulin dependent diabetes mellitus
4513	C109.00	Non-insulin dependent diabetes mellitus
17859	C109.12	Type 2 diabetes mellitus
1407	C10FJ00	Insulin treated Type 2 diabetes mellitus
18219	C109.13	Type II diabetes mellitus
18390	C10FM00	Type 2 diabetes mellitus with persistent microalbuminuria
5884	C109.11	NIDDM - Non-insulin dependent diabetes mellitus
18278	C109J00	Insulin treated Type 2 diabetes mellitus

(*continued on next page*)

Appendix III. (*Continued*)

Medcode	Read Code	Read Term
26054	C10FL00	Type 2 diabetes mellitus with persistent proteinuria
12640	C10FC00	Type 2 diabetes mellitus with nephropathy
22884	C10F.11	Type II diabetes mellitus
18496	C10F600	Type 2 diabetes mellitus with retinopathy
8403	C109700	Non-insulin dependant diabetes mellitus - poor control
25627	C10F700	Type 2 diabetes mellitus - poor control
32627	C10FN00	Type 2 diabetes mellitus with ketoacidosis
34912	C109400	Non-insulin dependent diabetes mellitus with ulcer
47954	C10F900	Type 2 diabetes mellitus without complication
34450	C10FK00	Hyperosmolar non-ketotic state in type 2 diabetes mellitus
36695	C10D.00	Diabetes mellitus autosomal dominant type 2
29979	C109900	Non-insulin-dependent diabetes mellitus without complication
34268	C10F200	Type 2 diabetes mellitus with neurological complications
53392	C10F911	Type II diabetes mellitus without complication
18777	C10F000	Type 2 diabetes mellitus with kidney complications
35385	C10FH00	Type 2 diabetes mellitus with neuropathic arthropathy
25591	C10FQ00	Type 2 diabetes mellitus with exudative maculopathy
17262	C109600	Non-insulin-dependent diabetes mellitus with retinopathy
18425	C10FB00	Type 2 diabetes mellitus with polyneuropathy
60796	C10FL11	Type II diabetes mellitus with persistent proteinuria
49074	C10F400	Type 2 diabetes mellitus with ulcer
41389	C105100	Diabetes mellitus, adult onset, + ophthalmic manifestation
63762	C10z100	Diabetes mellitus, adult onset, + unspecified complication
44982	C10FE00	Type 2 diabetes mellitus with diabetic cataract
50609	L180600	Pre-existing diabetes mellitus, non-insulin-dependent
59365	C109C00	Non-insulin dependent diabetes mellitus with nephropathy
46917	C10FD00	Type 2 diabetes mellitus with hypoglycaemic coma
47321	C10F100	Type 2 diabetes mellitus with ophthalmic complications
62674	C10FA00	Type 2 diabetes mellitus with mononeuropathy
47315	C10F711	Type II diabetes mellitus - poor control
18264	C109J12	Insulin treated Type II diabetes mellitus
24458	C109711	Type II diabetes mellitus - poor control
12736	C10F500	Type 2 diabetes mellitus with gangrene
36633	C109K00	Hyperosmolar non-ketotic state in type 2 diabetes mellitus
63690	C10FR00	Type 2 diabetes mellitus with gastroparesis
64668	C10FJ11	Insulin treated Type II diabetes mellitus
45913	C109712	Type 2 diabetes mellitus - poor control
51756	C10FP00	Type 2 diabetes mellitus with ketoacidotic coma
58604	C109611	Type II diabetes mellitus with retinopathy
49655	C10F611	Type II diabetes mellitus with retinopathy
37806	C10FF00	Type 2 diabetes mellitus with peripheral angiopathy
59253	C10FG00	Type 2 diabetes mellitus with arthropathy
37648	C109J11	Insulin treated non-insulin dependent diabetes mellitus
55075	C109411	Type II diabetes mellitus with ulcer

Appendix III. (*Continued*)

Medcode	Read Code	Read Term
52303	C109000	Non-insulin-dependent diabetes mellitus with kidney comps
42762	C109612	Type 2 diabetes mellitus with retinopathy
24836	C109C12	Type 2 diabetes mellitus with nephropathy
45467	C109B00	Non-insulin dependent diabetes mellitus with polyneuropathy
45919	C109212	Type 2 diabetes mellitus with neurological complications
50429	C109100	Non-insulin-dependent diabetes mellitus with ophthalm comps
69278	C109E00	Non-insulin depend diabetes mellitus with diabetic cataract
40401	C109500	Non-insulin dependent diabetes mellitus with gangrene
43785	C109D00	Non-insulin dependent diabetes mellitus with hypoglyca coma
44779	C109E12	Type 2 diabetes mellitus with diabetic cataract
47816	C109H11	Type II diabetes mellitus with neuropathic arthropathy
55842	C109200	Non-insulin-dependent diabetes mellitus with neuro comps
18209	C109012	Type 2 diabetes mellitus with kidney complications
48192	C109E11	Type II diabetes mellitus with diabetic cataract
50225	C109011	Type II diabetes mellitus with kidney complications
62107	C109511	Type II diabetes mellitus with gangrene
65267	C10F300	Type 2 diabetes mellitus with multiple complications
65704	C109412	Type 2 diabetes mellitus with ulcer
43227	C10F311	Type II diabetes mellitus with multiple complications
46150	C109512	Type 2 diabetes mellitus with gangrene
64571	C109C11	Type II diabetes mellitus with nephropathy
66965	C109H12	Type 2 diabetes mellitus with neuropathic arthropathy
24693	C109G00	Non-insulin dependent diabetes mellitus with arthropathy
54899	C109F11	Type II diabetes mellitus with peripheral angiopathy
61071	C109D12	Type 2 diabetes mellitus with hypoglycaemic coma
67905	C109211	Type II diabetes mellitus with neurological complications
47409	C109B11	Type II diabetes mellitus with polyneuropathy
50527	C10FB11	Type II diabetes mellitus with polyneuropathy
57278	C10F011	Type II diabetes mellitus with kidney complications
59725	C109111	Type II diabetes mellitus with ophthalmic complications
60699	C109F12	Type 2 diabetes mellitus with peripheral angiopathy
62146	C109300	Non-insulin-dependent diabetes mellitus with multiple comps
72320	C109A00	Non-insulin dependent diabetes mellitus with mononeuropathy
18143	C109G11	Type II diabetes mellitus with arthropathy
49869	C109G12	Type 2 diabetes mellitus with arthropathy
50813	C109A11	Type II diabetes mellitus with mononeuropathy
56268	C109D11	Type II diabetes mellitus with hypoglycaemic coma
70316	C109112	Type 2 diabetes mellitus with ophthalmic complications
85991	C10FM11	Type II diabetes mellitus with persistent microalbuminuria
91646	C10F411	Type II diabetes mellitus with ulcer
93727	C10FE11	Type II diabetes mellitus with diabetic cataract

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