ORIGINAL ARTICLE

WILEY **Endocrinology, Diabetes & Metabolism** Open Access

Preferential prescribing and utilization trends of diabetes medications among patients with renal impairment: Emerging role of linagliptin and other dipeptidyl peptidase 4 inhibitors

Elisabetta Patorno[1] | Chandrasekar Gopalakrishnan[1] (iD) | Dorothee B. Bartels[2,3] |
Kimberly G. Brodovicz[4] | Jun Liu[1] | Sebastian Schneeweiss[1]

[1]Division of Pharmacoepidemiology and Pharmacoeconomics, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA

[2]Corporate Department Global Epidemiology, Boehringer Ingelheim GmbH, Ingelheim, Germany

[3]Hannover Medical School, Institute for Epidemiology, Social Medicine and Health Systems Research, Hannover, Germany

[4]Global Epidemiology, Boehringer Ingelheim Pharmaceuticals, Inc., Ridgefield, CT, USA

Correspondence
Chandrasekar Gopalakrishnan,
Division of Pharmacoepidemiology and Pharmacoeconomics, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA.
Email: cgopalakrishnan@bwh.harvard.edu

Summary

Objectives: Although many newer diabetes medications have become available in the last decade, most have not been widely studied in populations with chronic kidney disease under routine care. Linagliptin, a recently marketed dipeptidyl peptidase 4 (DPP-4) inhibitor, is the only agent in the U.S. that does not require dose adjustment in patients with diabetes mellitus type 2 (T2DM) and renal impairment. We sought to describe baseline kidney function and other key characteristics among patients with diabetes mellitus type 2 (T2DM) initiating linagliptin and other diabetes medications, and to explore prescribing patterns among T2DM patients with moderate to severe renal impairment before and after the launch of linagliptin.

Design: Using a population-based cohort study design nested in a large U.S. commercial healthcare dataset linked to laboratory values, we described characteristics of T2DM patients initiating linagliptin and other diabetes medications between May 2011 (launch of linagliptin) and September 2015. We also explored prescribing trends among T2DM patients with moderate to severe renal impairment (ICD-9 diagnosis code 585.3x-6x) who initiated linagliptin and other diabetes medications between January 2006 to September 2015 (before and after the launch of linagliptin).

Patients: We identified 1,174,476 T2DM patients initiating a diabetes medication (28,900 linagliptin initiators) between 05/2011-09/2015. We also identified 100,847 T2DM patients with moderate to severe renal impairment initiating a diabetes agent between 01/2006-09/2015.

Results and Conclusion: Among patients initiating newer diabetes medications between 05/2011-09/2015, those initiating linagliptin had the highest prevalence of moderate to severe renal impairment, suggesting preferential prescribing in routine care. DPP-4 inhibitors overall were among the most frequently chosen agents among T2DM patients with moderate to severe renal impairment between 01/2006-09/2015. Further investigation of the safety and effectiveness of DPP-4 inhibitors in

1 | INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a leading cause of chronic kidney disease (CKD) in the United States, with approximately 40% of diabetes patients having CKD.[1] Reduced renal function can complicate diabetes management resulting in an increased risk of adverse events, for example severe hypoglycaemia, or decreased efficacy. Although many newer diabetes medications have become available in the last decade, most have not been widely studied in CKD populations under routine care, leaving clinicians caring for these patients with little evidence regarding best practices, particularly in patients with more severe renal impairment. Among the recently marketed medications, linagliptin, a dipeptidyl peptidase 4 (DPP-4) inhibitor, is the only agent in the United States that does not require dose adjustment in T2DM patients with renal impairment, suggesting it may be preferentially prescribed among these patients.

We sought to describe baseline kidney function and other key characteristics among T2DM patients initiating linagliptin and other diabetes medications and to explore prescribing patterns among T2DM patients with moderate to severe renal impairment before and after the launch of linagliptin.

2 | METHODS

Within a large U.S. commercial insurance data set (Clinformatics™ DataMart; OptumInsight, Eden, Prairie, MN, USA), we identified T2DM patients (ICD-9 diagnosis250.x0 or250.x2) initiating linagliptin or other diabetes agents between 05/2011 (linagliptin launch) and 09/2015 (Table 1), with no use of that agent in the previous 6 months. Patient characteristics were measured during the 6 months prior to treatment initiation, and for approximately 30% of the population, included baseline estimated glomerular filtration rate (eGFR)[2] and haemoglobin A1c (HbA1c). In a separate cohort of T2DM patients with moderate to severe renal impairment (ICD-9 diagnosis code of CKD stage 3 or higher [585.3x-6x]), patterns of diabetes therapy initiation before and after the launch of linagliptin (01/2006-09/2015) were plotted by year for DPP-4 inhibitors (by class and individual agents), metformin, 2nd generation sulphonylureas, GLP-1 receptor agonists, glitazones, SGLT-2 inhibitors, meglitinides and insulin.

3 | RESULTS

Of 1 174 476 T2DM patients initiating a diabetes medication between 05/2011 and 09/2015, 28 900 (2.5%) were linagliptin initiators. The proportion of baseline kidney disease (overall kidney dysfunction, any stage of CKD,[3] respectively) was higher among patients initiating linagliptin (22.4%, 12.9%), meglitinides (28.7%, 16.7%) or insulin (27.0%, 13.5%), resulting in a higher burden of comorbidities[4] compared to patients initiating other diabetes medications. In particular, patients initiating linagliptin, meglitinides or insulin had higher proportions of baseline CKD stage 3 or higher or eGFR <60 mL/min per 1.73 m^2 (Table 1).

When assessing the prescribing patterns among T2DM patients with moderate to severe renal impairment between 01/2006 and 09/2015 (N = 100 847), initiation of DPP-4 inhibitors, metformin and SGLT-2 inhibitors increased over time, whereas initiation of sulphonylureas, glitazones, meglitinides and insulin decreased (Figure 1). After its launch, linagliptin use among T2DM patients with moderate to severe renal impairment increased over time, whereas the use of other DPP-4 inhibitors either decreased (sitagliptin and saxagliptin) or remained stable (alogliptin) (Figure 1). Secondary analyses restricted to patients with baseline eGFR <60 mL/min per 1.73 m^2 confirmed observed utilization trends.

4 | DISCUSSION

Among patients initiating newer diabetes medications, those initiating linagliptin had the highest prevalence of moderate to severe renal impairment, suggesting preferential prescribing in routine care. These patterns should be accounted for in the design of non-interventional studies related to linagliptin. Despite the increase in linagliptin use, insulin, sulphonylureas, metformin and other DPP-4 inhibitors, that is sitagliptin, remain the most frequently chosen agents among T2DM patients with moderate to severe renal impairment. While the choice of traditional antidiabetic agents that is insulin, short-acting sulphonylureas and meglitinides is acknowledged,[5] and the increasing role of metformin has been previously observed,[6,7] the prominent role of DPP-4 inhibitors among T2DM patients with kidney disease in recent years has been largely undocumented. Such extensive use in clinical practice is unforeseen, as the data on the effects of DPP-4 inhibitors in patients with diabetes

TABLE 1 Baseline characteristics of patients with a new diabetes treatment episode after the launch of linagliptin (May 2011-Sep 2015)

Characteristic	Linagliptin	Other DPP4i	Metformin	2nd gen SU	GLP-1 RA	Glitazones	SGLT2i	Glinides	Insulin
N	28 900	153 596	465 695	227 036	55 083	46 335	39 048	8695	150 088
Age, mean (SD)	60.2 (12.4)	61.8 (12.7)	59.8 (13.2)	62.2 (13.1)	56.2 (11.3)	62.6 (12.7)	56.4 (10.7)	66.9 (12.6)	62.5 (13.5)
Females, N (%)	12 562 (43.5)	69 861 (45.5)	220 873 (47.4)	100 900 (44.4)	29 099 (52.8)	19 487 (42.1)	16 722 (42.8)	4346 (50.0)	70 516 (47.0)
Comorbidity index,[a] mean (SD)	2.0 (1.6)	1.9 (1.5)	1.6 (1.3)	1.9 (1.6)	1.7 (1.2)	1.8 (1.5)	1.6 (1.1)	2.4 (1.9)	2.5 (2.1)
Renal dysfunction, N (%)	6478 (22.4)	25 626 (16.7)	43 873 (9.4)	38 369 (16.9)	7376 (13.4)	8604 (18.6)	4010 (10.3)	2497(28.7)	40 582 (27.0)
CKD, N (%)	3734 (12.9)	13 234 (8.6)	18 292 (3.93)	19 344 (8.5)	3384 (6.1)	4685 (10.1)	1584 (4.06)	1454 (16.7)	20 260 (13.5)
CKD stage, N (%)									
CKD stage 1	174 (0.6)	817 (0.5)	1735 (0.4)	1115 (0.5)	284 (0.5)	295 (0.6)	226 (0.6)	42 (0.5)	830 (0.6)
CKD stage 2	395 (1.4)	2124 (1.4)	4658 (1.0)	2880 (1.3)	592 (1.1)	798 (1.7)	430 (1.1)	146 (1.7)	2325 (1.6)
CKD stage 3	2351 (8.1)	8391 (5.5)	10 935 (2.4)	12 092 (5.3)	2094 (3.8)	2998 (6.5)	872 (2.2)	866 (10.0)	11 420 (7.6)
CKD stage 4	584 (2.0)	1372 (0.9)	619 (0.1)	2159 (1.0)	324 (0.6)	456 (1.0)	43 (0.1)	270 (3.1)	3096 (2.1)
CKD stage 5	57 (0.2)	140 (0.1)	64 (0.0)	199 (0.1)	25 (0.1)	26 (0.1)	2 (0.0)	20 (0.2)	357 (0.2)
End stage renal disease, N (%)	173 (0.6)	390 (0.3)	281 (0.1)	899 (0.4)	65 (0.1)	112 (0.2)	11 (0.0)	110 (1.3)	2232 (1.5)
HbA1C %, mean (SD)	8.3 (4.2)	8.4 (3.3)	7.9 (3.8)	8.6 (4.3)	8.6 (4.3)	8.5 (2.4)	8.8 (3.3)	8.3 (5.1)	9.4 (4.5)
Patients with HbA1c available, N (%)	9644 (33.4)	46 324 (30.2)	123 539 (26.5)	59 299 (26.1)	16 530 (30.0)	14 188 (30.6)	14 768 (37.8)	2697 (31.0)	35 339 (23.6)
eGFR, mean (SD)	88.8 (27.4)	92.7 (23.5)	97.0 (19.0)	91.43 (24.4)	96.87 (21.5)	90.6 (24.4)	100.7 (18.3)	82.1 (26.7)	86.70 (27.8)
Patients with creatinine available, N (%)	10 647 (36.8)	49 984 (32.5)	136 719 (29.4)	65 087 (28.7)	18 170 (33.0)	15 051 (32.5)	15 919 (40.8)	3028 (34.8)	41 146 (27.4)
eGFR Category, N (%)									
eGFR ≥90 mL/min per 1.73 m^2	6242 (58.6)	30 396 (60.8)	91 471 (66.9)	38 078 (58.5)	13 008 (71.6)	8441 (56.1)	12 220 (76.8)	1289 (42.6)	21 823 (53.0)
eGFR 60-89 mL/min per 1.73 m^2	2535 (23.8)	14 450 (28.9)	40 017 (29.3)	19 370 (29.8)	3865 (21.3)	4737 (31.5)	3238 (20.3)	1086 (35.9)	11 952 (29.1)
eGFR <60 mL/min per 1.73 m^2	1870 (17.6)	5138 (10.3)	5231 (3.8)	7639 (11.7)	1297 (7.1)	1873 (12.4)	461 (2.9)	653 (21.6)	7371 (17.9)
eGFR 45-59 mL/min per 1.73 m^2	883 (8.3)	2806 (5.6)	3755 (2.8)	3940 (6.1)	731 (4.0)	1003 (6.7)	332 (2.1)	310(10.2)	3135 (7.6)
eGFR 30-44 mL/min per 1.73 m^2	644 (6.1)	1637 (3.3)	1161 (0.9)	2464 (3.8)	411 (2.3)	617 (4.1)	101 (0.6)	204 (6.7)	2381 (5.8)
eGFR 15-29 mL/min per 1.73 m^2	288 (2.7)	573 (1.2)	245 (0.2)	1020 (1.6)	135 (0.7)	223 (1.5)	24 (0.2)	107 (3.5)	1389 (3.4)
eGFR <15 mL/min per 1.73 m^2	55 (0.5)	122 (0.2)	70 (0.1)	215 (0.3)	20 (0.1)	30 (0.2)	4 (0.0)	32 (1.1)	466 (1.1)

Other DPP-4i, other DPP-4 inhibitors (i.e alogliptin, saxagliptin and sitagliptin); 2nd gen SU, 2nd generation sulphonylureas (i.e glipizide, glimepiride, glyburide); GLP-1 RA, GLP-1 receptor agonists (i.e albiglutide, dulaglutide, exenatide, liraglutide); glitazones, thiazolidinediones (i.e rosiglitazone, pioglitazone); glinides, meglitinides (i.e nateglinide, repaglinide); SGLT2i, SGLT-2 inhibitors (i.e canagliflozin, dapagliflozin, empagliflozin); SD, standard deviation; CKD, chronic kidney disease, assessed through ICD-9 diagnosis codes; HbA1c, haemoglobin A1c; eGFR, estimated glomerular filtration rate.

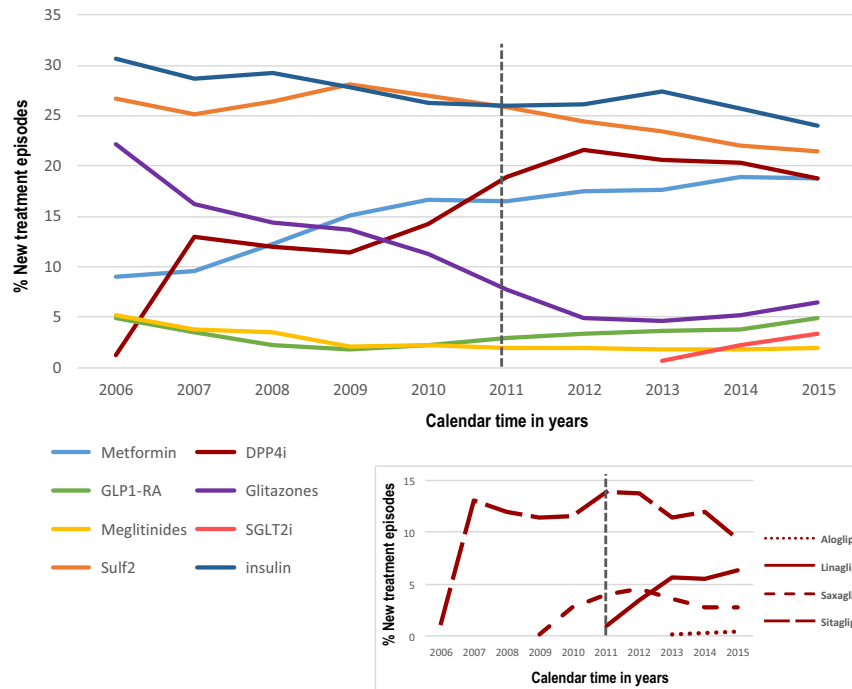[a]As measured by the Romano modification of the Charlson comorbidity score.[4]

FIGURE 1 Utilization trends before and after the launch of linagliptin among patients with moderate to severe renal impairment (CKD Stage 3 or higher) initiating a glucose-lowering drug. Other DPP-4i, other DPP-4 inhibitors (ie, alogliptin, saxagliptin and sitagliptin); 2nd gen SU, 2nd generation sulphonylureas (ie, glipizide, glimepiride, glyburide); GLP-1 RA, GLP-1 receptor agonists (ie, albiglutide, dulaglutide, exenatide, liraglutide); glitazones, thiazolidinediones (ie, rosiglitazone, pioglitazone); glinides, meglitinides (ie, nateglinide, repaglinide); SGLT2i, SGLT-2 inhibitors (ie, canagliflozin, dapagliflozin, empagliflozin); SD, standard deviation; CKD, chronic kidney disease, assessed through ICD-9 diagnosis codes; HbA1c, haemoglobin A1c; eGFR, estimated glomerular filtration rate. [1]As measured by the Romano modification of the Charlson comorbidity score[4]

and kidney dysfunction in routine care are limited, and current guidelines do not specifically recommend the preferential use of these agents over alternative treatments in this population.[5,8] In the light of this, further investigation of the safety and effectiveness of DPP-4 inhibitors in the routine care of T2DM patients with renal impairment is sorely needed to either corroborate or discourage current prescribing patterns.

CONFLICTS OF INTEREST

EP, CG, JL and SS report receiving a research grant from Boehringer Ingelheim to support this work. DB and KB are employees of Boehringer Ingelheim.

AUTHOR CONTRIBUTIONS

EP, SS, CG were involved in the concept and design of the study; all authors were involved in acquisition, analysis or interpretation of data; EP, SS, CG drafted the manuscript; all authors critically revised the manuscript for important intellectual content; JL, EP, CG were involved in statistical analysis; EP, SS supervised the study.

ORCID

Chandrasekar Gopalakrishnan iD http://orcid.org/0000-0003-2424-2453

REFERENCES

1. Koro CE, Lee BH, Bowlin SJ. Antidiabetic medication use and prevalence of chronic kidney disease among patients with type 2 diabetes mellitus in the United States. *Clin Ther*. 2009;31:2608-2617.
2. Rule AD, Larson TS, Bergstralh EJ, Slezak JM, Jacobsen SJ, Cosio FG. Using serum creatinine to estimate glomerular filtration rate: accuracy in good health and in chronic kidney disease. *Ann Intern Med*. 2004;141:929-937.
3. Winkelmayer WC, Schneeweiss S, Mogun H, Patrick AR, Avorn J, Solomon DH. Identification of individuals with CKD from Medicare claims data: a validation study. *Am J Kidney Dis*. 2005;46:225-232.
4. Romano PS, Roos LL, Jollis JG. Adapting a clinical comorbidity index for use with ICD-9-CM administrative data: differing perspectives. *J Clin Epidemiol*. 1993;46:1075-1079, discussion 81-90.
5. Berns JS, Glickman JD. Management of hyperglycemia in patients with type 2 diabetes and pre-dialysis chronic kidney disease or end-stage

renal disease. ©2017 UpToDate® http://www.uptodate.com. Accessed March 20, 2017

6. Flory JH, Hennessy S. Metformin use reduction in mild to moderate renal impairment: possible inappropriate curbing of use based on food and drug administration contraindications. *JAMA Intern Med*. 2015;175:458-459.

7. Clemens KK, Liu K, Shariff S, Schernthaner G, Tangri N, Garg AX. Secular trends in antihyperglycaemic medication prescriptions in older adults with diabetes and chronic kidney disease: 2004-2013. *Diabetes Obes Metab*. 2016;18:607-614.

8. Tuttle KR, Bakris GL, Bilous RW, et al. Diabetic kidney disease: a report from an ADA Consensus Conference. *Diabetes Care*. 2014;37:2864-2883.