Prescription of DPP-4 Inhibitors to Patients With Adult Type 2 Diabetes Mellitus and Creatinine Clearance >50 mL/min: The UK Primary Care Experience

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ABSTRACT

The aim of the study was to examine the extent to which patients with type 2 diabetes mellitus (T2DM) initiating a dipeptidyl peptidase 4 (DPP-4) inhibitor, who had no recorded objective evidence to justify dose adjustment, were initiated on the manufacturer-specified dose. Adopting a cross-sectional study design and using data from the UK General Practice, this study showed that at least 10% of patients with T2DM and a creatinine clearance level >50 mL/min initiating treatment with a DPP-4 inhibitor were prescribed a dose lower than specified in the Summary of Product Characteristics. This study provides further insights regarding DPP-4 inhibitor dose selection with respect to manufacturer specification in relation to renal function. (*Clin Ther*. 2018;■:1–9) © 2018 Elsevier Inc. All rights reserved.

Key Words: dose selection, DPP-4 inhibitors, renal function, general practice, type 2 diabetes mellitus.

INTRODUCTION

Dipeptidyl peptidase 4 (DPP-4) inhibitors are a commonly prescribed drug class in patients with type 2 diabetes mellitus (T2DM) and renal impairment; they are both efficacious and well tolerated when used at appropriate doses according to renal impairment severity.[1] With the exception of linagliptin, which does not require dose adjustment,[2] Summaries of Product Characteristics (SPCs) note that the dose of DPP-4 inhibitors should only be reduced according to the patient's renal function.[3–6] In addition, the dose of vildagliptin should be reduced to 50 mg once daily regardless of renal function when used in combination with a sulfonylurea.[6]

Nevertheless, 2 recent real-world evidence studies, adopting a range of renal impairment definitions (including those specified in the respective DPP-4 inhibitor SPCs), concluded that at least one third of patients with T2DM and renal impairment when initiated on a DPP-4 inhibitor requiring dose adjustment were prescribed a higher than the SPC-specified dose.[7,8] These findings call into question whether all patients initiated on a DPP-4 inhibitor whose renal function does not indicate dose adjustment are treated in accordance with SPCs.

Using data from primary care, the aim of the present study was to examine the extent to which patients with T2DM whose renal function does not indicate dose adjustment by renal threshold common to all non-linagliptin DPP-4 inhibitor SPCs at the time of treatment (creatinine clearance [CrCl] >50 mL/min) were initiated on the manufacturer-specified dose.

PATIENTS AND METHODS

Patients who had been initiated on a DPP-4 inhibitor (see **Appendix I** in the online version at doi:10.1016/j.clinthera.2018.06.002) between April 2012 and June 2017, when the common threshold for dose adjustment for all non-linagliptin DPP-4 inhibitors was a creatinine clearance (CrCl) level of 50 mL/min according to the respective SPCs,[3–6] were identified in the Clinical

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Practice Research Datalink (CPRD). CPRD is a large, anonymized general practice database representative of the UK population.[9] Quality criteria described previously were applied[7] to define the patient cohort eligible for inclusion in the analysis. In particular, patients were to be of an acceptable CPRD research standard and registered to a general practice for at least 12 months, which had to be of "Up to Standard" at DPP-4 inhibitor initiation.

Patients should have had a record of a T2DM-related medical code (see **Appendix II** in the online version at doi:10.1016/j.clinthera.2018.06.002) before initiation of the DPP-4 inhibitor, with no history of type 1 diabetes mellitus and be at least 18 years of age at T2DM diagnosis. Patients were to have at least 1 record of serum creatinine measurement before DPP-4 inhibitor initiation and at least 1 weight record around the time of DPP-4 inhibitor initiation. Patients initiated on vildagliptin should have had information on their daily dose recorded in their first prescription. To account for outliers and incorrect entries in patient records, serum creatinine and weight values <1st percentile and >99th percentile were excluded from the analysis. In addition, patients with a CrCl level >50 mL/min before or at DPP-4 inhibitor initiation who had a record of renal impairment in their clinical files were not included in the analysis.

Patients included in the analysis were to have a CrCl level >50 mL/min with no recorded history of renal impairment and were assessed toward SPCs valid at the time of treatment. The analysis generated counts and percentages of patients with a CrCl level >50 mL/min who were initiated on alogliptin 12.5mg or 6.25mg, sitagliptin 50mg or 25mg, saxagliptin 2.5 mg, and vildagliptin 50 mg once daily that were lower than the SPC-specified doses, overall and according to DPP-4 inhibitor separately. CrCl levels were estimated by using the Cockcroft-Gault formula[10] from the last serum creatinine measurement recorded before DPP-4 inhibitor initiation and also the weight measurement closest to the DPP-4 inhibitor initiation date. Patients who were prescribed vildagliptin 50 mg once daily but had a record of treatment with a sulfonylurea within 30 days of vildagliptin initiation were classified as treated in accordance with SPCs.

Sensitivity analyses were conducted applying restrictions on the time period between serum creatinine records and weight measurements to DPP-4 inhibitor initiation to a maximum of 90 days; this method was chosen to account for secular volatility of inputs used to estimate CrCl. Patients were also further stratified according to level of renal function at DPP-4 inhibitor initiation (>50−80 mL/min, >80−120 mL/min, and >120 mL/min) to explore consistency of the effect across patient categories representing graded levels of renal function.

RESULTS

Of the 36,874 patients initiated on a DPP-4 inhibitor during the study period, 30,346 (82.3%) met the eligibility criteria. Of the 30,346 eligible patients, 3142 (10.4%) had a CrCl value >50 mL/min before DPP-4 inhibitor initiation coupled with a record of renal impairment in their clinical files, and they were therefore excluded from the analysis. Among the remaining 27,204 patients, 4011 (14.7%) had a CrCl value ≤50 mL/min before DPP-4 inhibitor initiation and were also excluded from the analysis. The remaining 23,193 (85.3%) patients with a CrCl value >50 mL/min according to their last serum creatinine measurement before or at DPP-4 inhibitor initiation with no history of renal impairment were included in the analytical cohort (**Table I**).

The majority of patients with CrCl values >50 mL/min were initiated on sitagliptin (14,779 of 23,193 [64%]), of whom 14% (2061 of 14,779) were on a lower dose than that specified in the SPC. Overall, 12% (2764 of 23,193) of patients with CrCl values >50 mL/min initiated on a DPP-4 inhibitor were on a lower dose than the SPC specified, which increased to 14% when patients initiated on linagliptin who were not at risk of being prescribed a lower dose were excluded (**Table II**). Sensitivity analysis restricting the time period between last creatinine and weight

Table I. Patient distribution according to creatinine clearance levels based on last measurement before initiation of dipeptidyl peptidase 4 inhibitors.

Creatinine Clearance Level	No. (%)
>50 mL/min	23,193 (85.3)
≤50 mL/min	4011 (14.7)
Total	27,204 (100)