Boehringer Ingelheim

Clinical Study Synopsis for Public Disclosure

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ABSTRACT

Name of company: Boehringer Ingelheim			
Name of finished medicinal product: Trazenta			
Name of active ingredient: Linagliptin			
Report date: 20 October 2017	**Study number:** 1218.178	**Version/Revision:** Version 1	**Version/Revision date:** No appropriate
Title of study:	Clinical characteristics and practice patterns of type 2 diabetes mellitus (T2DM) patients treated with oral antidiabetic drugs (OADs) in Japan: analysis of medical and health care database of the Medical Data Vision (MDV).		
Keywords:	Type 2 diabetes mellitus, oral antidiabetic drugs, real world data, persistence, renal impairment		
Rationale and background:	Renal impairment (RI) is a common complication in patients with T2DM. In Japanese patients with T2DM, about 30% of patients have microalbuminuria, and other report shows that 60% of Japanese patients with T2DM suffer from renal dysfunction. In patients with T2DM and RI, all drugs, including OADs— particularly those that undergo renal metabolism/excretion, should be used according to prescribing information with due consideration to relevant factors such as glomerular filtration rate (GFR). In general, all OADs can be used in patients with mild RI; however, treatment options for patients with moderate-to-severe chronic kidney disease (CKD) or end-stage renal disease (ESRD) are limited because reduced GFR may lead to drug or metabolite accumulation and consequent side effects Thus, proper use of OADs including dose-reduction is important for patient's safety in T2DM patients with RI. However, there are insufficient data on dose adjustment in accordance with the prescription pattern and the risk of RI with OADs, in particular dipeptidyl-peptidase 4 (DPP-4) inhibitors, in clinical practice in Japan. Therefore, we investigated OADs usage conditions in T2DM patients by using MDV clinical database in clinical practice in Japan.		
Research question and objectives:	<u>Research aim:</u> To understand the prescription pattern of each compound and each class for all OADs in T2DM patients, available throughout study period i.e. DPP-4 inhibitors, sulfonylureas, biguanides, thiazolidinediones, alpha-glucosidase inhibitors (AGIs), and meglitinides (glinides). <u>Study objectives:</u> 1. To analyze the demographic and clinical characteristics of T2DM patients who have been treated with OADs		

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	2. To assess time (in months) to the first occurrence of discontinuation, meaning survival analysis for therapy discontinuation about each compound and each class for all OADs. 3. To assess time (in months) to the first occurrence of discontinuation according to baseline renal function about each compound and each class for all OADs in T2DM patients, only when enough number of patients available.
Study design:	Retrospective observational cohort study <u>Statistical analysis methods:</u> • First analysis: number of index dates, and demographics and clinical characteristics of patients by class/drug. • Second analysis: time to the first occurrence of discontinuation for each class/drug was presented as a survival curve, time to the first occurrence of discontinuation according to baseline renal function. Interim analyses were not conducted.
Setting:	MDV clinical database (01/01/2014-30/09/2016) was used.
Subjects and study size, including dropouts:	<u>Inclusion criteria</u> • Patients with T2DM (International Classification of Diseases 10th Revision (ICD-10) code: E11-E14). • Patients having their first prescription (defined as index date) for any study drugs between 01/01/2014 and 30/09/2016. • Patients having at least 6 months enrolment verified by the presence of any record except for the study drug prescriptions within the database (look back period) prior to the index date for each drug. <u>Exclusion criteria</u> • Patients who were under 40 y.o. at the time of diagnosis of diabetes. • Patients with record of type 1 diabetes mellitus (ICD-10 code: E10). • Patients who prescribed the study drugs during 6 month prior to index date for each drug. • Patients whose mean visit interval were more than 92 days.
Variables and data sources:	Valuables • Exposure: OADs available in Japan on January 1, 2014 as follows: 1) AGIs: acarbose, miglitol, voglibose; 2) biguanides: buformin,

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	metformin; 3) DPP-4 inhibitors: alogliptin, anagliptin, linagliptin, saxagliptin, sitagliptin, teneligliptin, vildagliptin; 4) glinides: mitiglinide, nateglinide, repaglinide: 5) sulfonylureas: acetohexamide, chlorpropamide, glibenclamide, gliclazide, glimepiride, glyclopyramide, tolbutamide; 6) thiazolidinediones: pioglitazone. Combination drugs were analyzed as each single component drug. • Outcomes - Primary outcomes: demographic and clinical characteristics of patients who had a prescription of OADs. - Secondary outcomes: type of drugs they are prescribed as there are different cut-offs for renal functions. - Further outcomes: time to the first occurrence of discontinuation about each compound and each class for all OADs, time to the first occurrence of discontinuation according to baseline parameters. Data sources • MDV clinical database (01/01/2014-30/09/2016)		
Results:	We found 523,585 patients in the database having a diagnosis of T2DM; and then 162,116 patients were included. There were 206,406 index dates for between-class comparisons. Among six classes of OADs, DPP-4 inhibitors had the largest number of index dates (91,634), followed by biguanides (33,238), sulfonylureas (28,211), AGIs (26,192), glinides (16,787), and thiazolidinediones (10,344). Percentage of female was almost the same for all classes ranging from 37% to 39%. Mean age of all patients was 70.7 years old, with 73% of patients aged more than 65. The mean age of patients prescribed biguanides was 66.5 years old, which was the youngest of all the classes, followed by thiazolidinediones (69.7), AGIs and glinides (71.4), DPP-4 inhibitors (71.6), and sulfonylureas (72.0). Data of estimated GFR (eGFR) were available for 25,386 (12.3%) of all index dates (206,406). Patients prescribed biguanides had the highest mean eGFR of all the classes, 74.0 mL/min/1.73m^2, followed by thiazolidinediones (69.7), sulfonylureas (67.4), DPP-4 inhibitors (63.0), AGIs (60.1), and glinides (59.5). The patients prescribed biguanides tended to have the lowest percentages of each comorbidity. For example, 19% of patients prescribed biguanides or thiazolidinediones had comorbid heart failure compared to 24% for the total patient population. On the other hand, those prescribed glinides and AGIs had highest percentages.		

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	Drugs from the study classes (or insulin) were used as previous treatments for other drugs in the study classes. The percentage of previous treatment by study class ranged from 0% to 19%. Nineteen percent of glinides was prescribed by switching from sulfonylureas. Switching from insulin was between 7% and 14% for all classes. The relative frequency of prescription as a concomitant treatment in each class was similar to the relative number of index dates; DPP-4 inhibitors were the highest at 23% overall, and prescribed for 56% of the patients taking glinides and 40% of those taking biguanides. The rate of added use of concomitant treatments was the lowest for DPP-4 inhibitors followed by sulfonylureas at 45% and 55%. The rate of added use of a concomitant treatment was highest for glinides at 80%, including concomitant treatments from two or more classes for 43% patients, followed by thiazolidinediones at 34%. Within the class of DPP-4 inhibitors, a pattern of prescribing linagliptin for patients with RI stage G4+ as well as those with older age, higher complication rate, and insulin use as concomitant treatments was seen. Biguanides and DPP-4 inhibitors showed the longest median survival time followed by glinides, thiazolidinediones, AGIs, and sulfonylureas. The rate declined with lower RI; and DPP-4 inhibitors and biguanides showed similar persistence, which was longer than for the other classes in stage G1 and G2; only DPP-4 inhibitors had longer persistence than biguanides in stages G3 and G4+.		
Discussion:	More than half of index dates were for DPP-4 inhibitors, and the percentage was followed by biguanides, sulfonylureas, AGIs, glinides, and thiazolidinediones. Demographics and clinical characteristics of patients prescribed DPP-4 inhibitors were almost the same as for the total patient population, other than lower rates of concomitant treatment. The patients prescribed biguanides and sulfonylureas tended to have good renal function; on the other hand, those with AGIs and glinides seemed to have lower renal function and more comorbidities. Treatment persistence was highest in the DPP-4 inhibitors and biguanides groups, and the lowest in the sulfonylureas group. Notably, DPP-4 inhibitors showed the highest persistence for the patients with severe RI. Overall, OADs seemed to be prescribed properly for the conditions of patients. However, we found the unexpectedly higher use of biguanides for patients with G3 or G4 of RI stage, and sulfonylureas and thiazolidinediones for those with G4 in this study in spite of recommendation. We believe that OADs should be used		

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	more appropriately to achieve the goals of long-term treatment of T2DM.		
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1. LIST OF ABBREVIATIONS

AGI	α-Glucosidase Inhibitor
CKD	Chronic Kidney Disease
DPC	Diagnostic Procedure Combination
DPP-4	Dipeptidyl-peptidase 4
eGFR	estimated Glomerular Filtration Rate
ESRD	End-Stage Renal Disease
GFR	Glomerular Filtration Rate
ICD-10	International Classification of Diseases 10th Revision
IRB	Institutional Review Board
MDV	Medical Data Vision
OAD	Oral Antidiabetic Drugs
RI	Renal Impairment
T2DM	Type 2 Diabetes Mellitus