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Submitted to Expert Opinion on Drug Metabolism & Toxicology

Pharmacokinetic considerations for the treatment of diabetes in patients with chronic kidney disease

André J. Scheen

Division of Diabetes, Nutrition and Metabolic Disorders
and Division of Clinical Pharmacology,
Department of Medicine, CHU Sart Tilman, University of Liège, Liège, Belgium

Running title : Management of T2DM in patients with CKD

Word count : 9981

Address for correspondence : Pr André J. SCHEEN
Department of Medicine
CHU Sart Tilman (B35)
B-4000 LIEGE 1
BELGIUM
Phone : 32-4-3667238
FAX : 32-4-3667068
Email : andre.scheen @ chu.ulg.ac.be

SUMMARY

Introduction : People with chronic kidney disease (CKD) of stages 3-5 (creatinine clearance < 60 ml/min) represent 25-30% of patients with type 2 diabetes (T2DM), but the problem is underrecognized or neglected in clinical practice. However, most oral antidiabetic agents have limitations in case of renal impairment, either because they require a dose adjustment or because they are contraindicated for safety reasons.

Area covered: An extensive literature search was performed to analyze the influence of renal impairment on the pharmacokinetics (PK) of glucose-lowering agents and the potential consequences for clinical practice. The following pharmacological classes will be considered : biguanides (metformin), sulfonylureas, meglitinides (glinides), alpha-glucosidase inhibitors, thiazolidinediones (glitazones), dipeptidyl peptidase-4 (DPP-4) inhibitors, sodium-glucose

cotransporters 2 (SGLT2) inhibitors, glucagon-like peptide-1 (GLP-1) receptor agonists, insulin and insulin analogues.

Expert Opinion : Because of potential important PK interferences and for safety reasons, the pharmacological management of T2DM should be adjusted according to kidney function. In general, the daily dose should be reduced according to glomerular filtration rate (GFR) or even the drug is contraindicated in presence of more severe CKD. This is the case for metformin (risk of lactic acidosis) and for many sulfonylureas (risk of hypoglycemia). At present, however, the exact GFR cutoff for metformin use is controversial. New antidiabetic agents are better tolerated in case of CKD, although clinical experience remains quite limited for most of them. The dose of DPP-4 inhibitors should be reduced (except for linaglitpin) whereas both the efficacy and safety of SGLT2 inhibitors are questionable in presence of CKD.

Key-words : Chronic kidney disease – Glomerular filtration rate – Glucose-lowering therapy – Pharmacokinetics – Oral antidiabetic agent – Renal impairment – Type 2 diabetes mellitus

1. Introduction

The prevalence of type 2 diabetes mellitus (T2DM) is rapidly increasing worldwide. Numerous patients with T2DM have some degree of renal impairment (RI), which may be assessed by a reduction in glomerular filtration rate (GFR) and classified in various stages according to severity (from stage 1 to stage 5)[1, 2]. The presence of RI may impact on the management of T2DM[3, 4]. The prevalence of chronic kidney disease (CKD) associated with diabetes in the United States increased from 1988 to 2008 in proportion to the prevalence of diabetes and among persons with diabetes, the prevalence of CKD was stable despite the implementation of specific therapies[5]. The causes of CKD in T2DM patients are numerous, most generally combining the effects of diabetic nephropathy resulting from chronic hyperglycemia (which may remain unknown for a long time because of the lack of symptoms), nephroangiosclerosis secondary to arterial hypertension (a common comorbidity in patients with T2DM), urinary infections (generally asymptomatic), coadministered potentially nephrotoxic agents (among which widely used non steroidal antiinflammatory drugs) or simply advance in age[3].

In the US National Health and Nutrition Examination Survey (NHANES), 39.7 % of patients with T2DM had CKD of various degrees[6]. The proportion of patients treated by at least one oral antidiabetic agent (OAD) significantly progresses from 36.3% in patients with stage 1 CKD to 62.9% in patients with stages 4-5 CKD. These observations support the availability of efficacious and safe glucose-lowering agents to be prescribed in T2DM patients with CKD. In the Kidney Early Evaluation Program (KEEP) involving 77,077 participants, 26.2% had CKD and 29.9% had diabetes. Among those with both diabetes and CKD, only 9.4% were aware of the existence of RI[7]. Interestingly, patients with a documented RI diagnosis have lower odds of progression to end-stage renal disease (ESRD). The presence of CKD may influence the adequate use of glucose-lowering agents in T2DM[8-10]. Not surprisingly, commonly prescribed OADs such as metformin and sitagliptin are frequently administered at inappropriate doses in patients with RI[11]. These observations reinforce the need for a better sensitization of both physicians and diabetic patients regarding the problem of CKD. The general objectives are that T2DM patients should be regularly checked as far as their renal function and that glucose-lowering agents are used in an efficacious and safe manner in presence of CKD[12-14]. Finally, besides specific hyperglycemia management, other

risk factors (hypertension, dyslipidemias, …) should also be treated in order to improve cardiovascular and renal outcomes[2, 3, 12, 15].

Evidence that intensive glucose-lowering treatment has an effect on loss of glomerular filtration rate (GFR) is sparse. The 2012 update of the KDOQI (Kidney Disease Outcomes Quality Initiative) clinical practice guidelines for diabetes and CKD recommends a target hemoglobin A1c (HbA1c) of ≈ 7.0% to prevent or delay progression of the microvascular complications of diabetes, including CKD (level of evidence *1A*); recommends not treating to an HbA1c target of <7.0% in patients at risk of hypoglycemia (level of evidence *1B*); and suggests that target HbA1c be extended above 7.0% in individuals with co-morbidities or limited life expectancy and risk of hypoglycemia (level of evidence *2C*) [3]. This patient-centered approach is in agreement with the 2012 ADA (American Diabetes Association) – EASD (European Association for the Study of Diabetes) position statement[16].

Kidney plays a major role in the clearance of drugs, in general[17], and of glucose-lowering agents used for T2DM, in particular[13]. Therefore, the management of glycemia in patients with diabetes and CKD is quite challenging[10] and the questions of which hypoglycemic agents to use in T2DM subjects with CKD and how to use them are of major practical importance[18]. Besides the mode of action of glucose-lowering agents[19], renal function should also be taken into account by the physician. Indeed, the presence of RI may deeply impact the pharmacokinetics (PK) and thereby should influence choices, dosing, and monitoring of hypoglycemic agents according to the reduction of GFR[9]. The situation is even more complex in the frail elderly population, where RI and polymedication are very common[20].

The aim of this paper is to provide an updated analysis of the use of OADs and injectable agents in T2DM patients with CKD[8-10]. After a brief description of how to assess kidney function in patients with T2DM, we will describe the PK characteristics as well as the efficacy/safety profile of each glucose-lowering compound in patients with various degrees of RI (Table 1, Table 2).

To identify relevant studies, an extensive literature search of MEDLINE was performed from 1970 to December 2012, with the names of the following pharmacological classes biguanides, sulfonylureas, meglitinides (glinides), alpha-glucosidase inhibitors, thiazolidinediones (TZDs), dipeptidyl peptidase-4 (DPP-4) inhibitors, sodium-glucose cotransporter-2 (SGLT2) inhibitors, glucagon-like peptide-1 (GLP-1) receptor agonists,

human insulin or insulin analogs combined with any of the following terms : “chronic kidney disease”, “renal insufficiency”, “renal impairment” or “nephropathy”. Each generic name - “metformin”, glibenclamide (glyburide), glimepiride, glipizide, gliclazide, gliquidone, repaglinide, nateglinide, acarbose, miglitol, voglibose, pioglitazone, rosiglitazone, sitagliptin, vildagliptin, saxagliptin, linagliptin, alogliptin, dapagliflozin, canagliflozin, empagliflozin, exenatide, liraglutide, insulin, insulin lispro, insulin aspart, insulin glulisine, insulin glargine, insulin detemir - was also combined with the various terms corresponding to CKD. No language restrictions were imposed. Reference lists of original studies, narrative reviews and previous systematic reviews were also carefully examined.

2. Assessment of kidney function and stratification of CKD in diabetes

Renal function is classically assessed by the GFR, which can be estimated by the creatinine clearance (CL_{CR}) using the Cockroft-Gault formula[1]. However, such formula may be biased by body weight as a confounding factor leading to overestimation of true GFR in overweight/obese individuals, a common situation in patients with T2DM. Currently, the MDRD (« Modification of Diet in Renal Disease «) formula is preferred as the method of choice for estimating GFR (eGFR), although it underestimates GFR in patients with GFR > 60 mL/min/1.73 m² body surface area and is not validated for all populations. The corresponding values to the various stages of RI are summarized in Table 3. More appropriate new formulae have been recently proposed by nephrologists, although they are not used yet in clinical practice by diabetologists[21]. However, the coexistence of two formulae, such as Cockroft-Gault and MDRD, may lead to some discrepancies in dosing adjustment as recently illustrated with the use of sitagliptin in clinical practice[22].

3. Biguanides (metformin)

Among biguanide compounds, only metformin remains on the market. The two other agents, phenformin and buformin, were withdrawn because of a too high risk of lactic acidosis, especially when the compound accumulates in case of RI[23]. Although this complication may also occur with metformin, it is a rare event when the contraindications are respected but, interestingly enough, also in patients who may be considered at higher risk (see below)[24]. Metformin is currently accepted as the first choice OAD in the management of T2DM[16]. Paradoxically, there are numerous contraindications to the use of metformin because of a theoretical risk of lactic acidosis[24]. However, such a risk has been probably overestimated in many circumstances. Therefore, contraindications to the use of metformin may deprive

numerous T2DM patients from a drug that may provide more benefits than risks[25, 26]. This is especially the case of patients with mild to moderate CKD who deserve much attention because they represent an increasing proportion of the T2DM population, notably in the elderly[20].

PK characteristics of metformin are well known since a long time ago[27], even if new interesting mechanistic data have been published more recently[28]. Metformin is absorbed predominately from the small intestine and is excreted unchanged in urine. The elimination half-life ($t_{1/2}$) of metformin during multiple dosages in patients with good renal function is approximately 5 hours. The population mean renal clearance (CL_R) and apparent total clearance after oral administration (CL/F) of metformin were estimated to be (mean±SD) 510±130 mL/min and 1140±330 mL/min, respectively, in healthy subjects and diabetic patients with good renal function. Over a range of renal function, the population mean values of CL_R and CL/F of metformin are 4.3±1.5 and 10.7±3.5 times as great, respectively, as the CL_{CR}. As the CL_R and CL/F decrease approximately in proportion to CL_{CR}, the dosage of metformin should be reduced in patients with CKD in proportion to the reduced CL_{CR}[28]. However, rather few PK data are available in T2DM patients with various degrees of RI. More recent data revealed that the renal excretion of metformin (as its oral absorption and hepatic uptake) is mediated largely by organic cation transporters (OCTs)[28]. CL_R of metformin in healthy Caucasian men varied 3.8-fold and was significantly dependent not only on CL_{CR} and age but also on OCT1 polymorphisms[29]. Finally, promoter variants of multidrug and toxin extrusion protein (MATE)1 and MATE2 were recently shown to be also important determinants of metformin disposition, by influencing its renal and secretory clearances, and glucose-lowering response in healthy volunteers and diabetic patients[30].

3.1 PK of metformin after single dose in patients with RI

PK parameters of metformin were determined in volunteers with normal renal function and in patients with different degrees of RI. The $t_{1/2}$ for the elimination of metformin from plasma after intravenous injection was much longer (4.94±1.11 h) in patients with RI than in normal subjects (1.52±0.3 h). A significant correlation was observed between $t_{1/2}$ and CL_{CR}. After oral administration of metformin tablets, drug recovery in urines was only 37.6%, possibly as a consequence of binding to the intestinal wall. Metformin is rapidly eliminated through active secretion by the kidney, with a mean CL_R of 440 ml/min (almost 3-4 times the value of CL_{CR})[31]. Another study in healthy subjects and T2DM patients with various degrees of RI gave information about metformin clearance over a range of CL_{CR} from 47 to 179

mL/min. Plasma CL_R of metformin was found to be highly correlated with CL_{CR} (r = 0.85, P<0.001). However, a weaker relationship between total oral clearance of the drug and CL_{CR} suggested that the latter may not always be a reliable indicator of potential metformin accumulation. CL_R values for metformin well in excess of CL_{CR} confirmed tubular secretion of this highly ionized compound as a major mechanism of urinary excretion[32].

In a detailed study evaluating the effects of RI and age on the PK of metformin, healthy adults (young, middle-age, elderly) and adults with various degrees of CKD (mild to severe) were given a single, 850 mg metformin HCl tablet[33]. In the control group (CL_{CR} : 112±8 mL/min), average metformin CL_R was 636±84 mL/min, whereas in mild CKD (CL_{CR} : 61–90 mL/min) metformin CL_R was reduced at 384±122 mL/min. The mean CL_R of metformin was lower in subjects with moderate (CL_{CR} : 31–60 mL/min) and severe (CL_{CR} : 10–30 mL/min) CKD, measuring 108±57 and 130±90 mL/min, respectively. Maximum concentration (C_{max}) and the area under the concentration time curve (AUC) were increased in individuals with moderate to severe CKD compared with those with mild CKD or normal renal function. In the moderate and severe CKD groups, all clearance values were 74-78% lower than in the healthy young/middle-age group, and all other evaluable PK parameters (with the exception of t_{max}) differed significantly in this group. In the mild CKD group, however, clearance values of metformin, which were 23-33% lower than in the young/middle-age group, were the only parameters that differed significantly. Based on a regression analysis of the combined data, both CL_{CR} and age were predictors of metformin clearance[33].

In healthy elderly subjects (mean age : 71 years; range : 65-81 years), total plasma clearance of metformin was decreased, the half-life was prolonged, and C_{max} was increased, compared to healthy young subjects. From these data, it appears that the change in metformin PK with aging is primarily accounted for by a change in renal function. Metformin CL_R averaged 412±98 mL/min in elderly subjects compared to 522±139 mL/min in younger subject (reduction by 21%)[33].

3.2 PK of metformin after multiple doses and chronic administration

T2DM patients aged between 70-88 years received metformin at a dosage of either 850 mg or 1,700 mg/day dependent on CL_{CR} values of 30-60 mL/min and greater than 60 mL/min, respectively. After 2 months, metformin concentrations remained in the therapeutic range and lactate levels within the reference limits in all participants, with no statistically differences between those with and without RI[34].

Trough serum levels of metformin were measured in 137 T2DM patients with varying renal function and followed repeatedly during 2 months in 20 patients with eGFR <60 mL/min/1.73 m². Patients with eGFR >60, 30-60, and <30 mL/min/1.73 m² had median trough metformin concentrations of 4.5, 7.71 and 8.88 µmol/L, respectively. Notably, there were wide variations in these levels within each group, with few patients having serum levels > 20 µmol/L (> ~2.6 µg/mL). The median intra-individual overall coefficient of variation was around 30%[35]. In patients with severe RI (CL_{CR} 15-40 mL/min), who were prescribed a range of metformin doses (250-2000 mg daily), few had high lactate concentrations (>2.7 mmol/L) and few had high metformin concentrations (3-5 mg/L), without correlation between metformin and lactate concentrations[36]. Whether the measurement of metformin levels actually can aid in the prediction of lactic acidosis risk remains unclear and thereby is not recommended in clinical practice[37].

3.3 Metformin and hemodialysis

Metformin is not bound to plasma proteins, and thus should be easily dialyzable[27]. A study determined the characteristics of metformin elimination by dialysis. Metformin may be removed even after reaching an equilibrium between blood and dialysate levels in a recirculating system, suggesting a storage of metformin in a deep compartment with a gradient of concentration between this compartment and the blood. Metformin is highly dialyzable with a clearance of up to 170 mL/min under good hemodynamic conditions. Thus, hemodialysis can efficiently remove metformin, especially from patients in whom overdose is suspected, and corrects metabolic acidosis in patients with metformin-induced lactic acidosis[38]. Accurate recognition of metformin-associated lactic acidosis and prompt initiation of hemodialysis are paramount steps towards rapid recovery[39].

3.4 Controversy about the risk of metformin in patients with CKD

Classically, CKD (CL_{CR} < 60 mL/min) represents a contraindication to the use of metformin in patients with T2DM[40]. In case of RI, metformin may, indeed, accumulate, block gluconeogenesis and cause lactic acidosis, a harmful complication that may be fatal[41, 42]. However, recent data suggested that metformin may be administered with caution in patients with CL_{CR} 45-60 mL/min or even lower (30-45 mL/min), provided that the daily dose is reduced by half and kidney function is regularly monitored[37]. In patients without comorbid conditions that would predispose them to lactic acidosis, elevated serum creatinine levels (or

reduced GFR) should be considered a risk factor for the development of lactic acidosis but not an absolute contraindication[43]. In daily clinical practice, development of contraindications, including RI, rarely results in discontinuation of metformin therapy; nevertheless, lactic acidosis remains a rare event[44, 45]. In some studies, the prevalence of T2DM receiving metformin despite having a contraindication (including a GFR < 60 mL/min) was over 80%. Nevertheless, metformin use in such conditions did not appear to increase the risks of lactic acidosis, hospitalization and death[46]. At least three scenarios can be proposed to explain the use of metformin in patients with RI: *1*) creatinine levels are not appropriately or consistently assessed, *2*) levels are normal at the time of the initial prescription of metformin and subsequent elevations go unrecognized, or *3*) physicians judge that benefits of therapy outweigh potential risks[47]. In patients having T2DM with established atherothrombosis participating in the Reduction of Atherothrombosis for Continued Health (REACH) Registry, the 2-year mortality rate associated with metformin vs. other glucose-lowering agents was significantly lower in patients with an eGFR of 30 to 60 mL/min/1.73 m² (adjusted hazard ratio 0.64; 95% CI, 0.48-0.86; P=0.003)[48]. There are more and more data suggesting that meformin can be used in stable mild to moderate CKD and that not prescribing metformin in these patients may cause more harm compared to the benefits of avoiding potentially rare complications[25, 49, 50]. These observations led to a recent position statement from the ADA-EASD in which metformin may be used down to a GFR of 30 mL/min, with dose reduction advised at 45 mL/min (Table 4). This would lead to safely prescribing OADs in patients with an eGFR < 60 mL/min/1.73 m², and more importantly in medical practice, according to the law[51]. However, the risk of lactic acidosis should not be neglected [42, 50, 52] and the drug should be immediately stopped in presence of unstable RI, any acute event (high fever for instance), gastrointestinal disorders (diarrhea, vomiting), dehydration, ...[42, 52].

4. Sulfonylureas

Sulfonylureas remain largely used in the management of T2DM and are positioned as second-line treatment after failure of metformin monotherapy[16]. They are associated with a higher risk of severe hypoglycemia, compared with metformin and more recent glucose-lowering therapies[53], especially in the elderly population and in patients with CKD[20, 54]. In a German study investigating the incidence of severe hypoglycemia and clinical characteristics to demonstrate typical risk constellations, T2DM patients were characterized by old age, low CL_{CR} (46±24 mL/min) with RI in 73% and extensive co-medication[55]. The excessive

mortality associated with hypoglycemia makes this complication a significant threat to patient safety in CKD[56].

Surprisingly, a recent retrospective analysis of the national Veterans Administration database showed that, compared to patients using metformin, sulfonylurea users had an increased risk for renal outcomes (persistent decline in eGFR from baseline of 25% or more or diagnosis of ESRD and/or death), with an adjusted hazard ratio of 1.20[57]. The reasons for these intriguing observations, which should be confirmed in further analyses, remain unknown.

Most sulfonylureas are excreted by the kidney, either the parent compound or metabolites (some of them being pharmacologically active)[41, 58]. Clinical PK of sulfonylureas has been extensively reviewed[59]. However, rather few PK studies have been performed with sulfonylureas in patients with RI and most of them are rather old and of poor quality in terms of number of subjects and PK parameters description (Table 1). Sulfonylureas of first generation, like tolbutamide[60] or chlorpropamide[61], were shown to be excreted by the kidney, leading to a higher risk of severe hypoglycemia in patients with CKD. Currently, they have been replaced by second-generation sulfonylureas.

4.1 Glibenclamide (glyburide)

Contrasted observations regarding glibenclamide (glyburide) have been reported with no increase in concentrations of the parent drug in patients with various degrees of CKD, but a higher incidence of severe hypoglycemia reported in T2DM patients with RI. This may be explained by the presence of two active metabolites (M1 and M2), which are also cleared by the kidneys[62].

4.1.1 Glibenclamide PK in patients with RI

The PK of ^{14}C-labeled glyburide was studied in men with varying degrees of RI, who received a single, 5 mg oral dose of glyburide as a solution (10 microCi/ml/mg) after a high-carbohydrate breakfast. Patients with normal to moderate RI (CL_{CR} of 29 to 131 ml/min/1.73 m²) had glyburide plasma $t_{1/2}$ values of 2.0 to 5.0 h, with no relationship between CL_{CR} and glyburide clearance. One subject with severe RI (CL_{CR} = 5 ml/min/1.73 m²) had decreased glyburide clearance that resulted in a $t_{1/2}$ of 11 h. The elimination of metabolites was more dependent on renal status but, in this study, was only significantly affected in the patient with severe RI[63].

The PK of glibenclamide and its active metabolites, 4-trans-hydroxyglibenclamide (M1) and 3-cis-hydroxy-glibenclamide (M2) was compared after a single oral 7 mg dose in two groups of diabetic patients with RI (iohexol clearance range : 7-42 mL/min/1.73 m²) or normal renal function (iohexol clearance range : 75-140 mL/min/1.73 m²)[64]. Peak serum values of M1 (24-85 vs 16-57 ng/mL) and M2 (7-22 vs <5-18 ng/mL) were higher in the group with RI. AUC and C_{max} of glibenclamide were lower and the clearance to bioavailability ratio (CL/F) was higher in the RI group. In contrast, AUC and C_{max} of M1 were higher and CL/F lower in the RI group. Much lower amounts of M1 and M2 were excreted in the urine in the RI group (7.2% vs. 26.4% in 24 h). The fraction of the glibenclamide dose excreted as metabolites correlated significantly with renal function measured by iohexol clearance. The differences in AUC, C_{max} and CL/F of glibenclamide may be explained by a higher free fraction in the RI group which would increase glibenclamide metabolic clearance. The inverse findings regarding M1 may be explained by the fact that the metabolites are primarily eliminated by the kidneys. As only small amounts of M1 and M2 were excreted in the urine, this may indicate one or several complementary non-renal elimination routes[64].

Finally, PK of glyburide was compared in subjects with T2DM and ESRD requiring hemodialysis and in T2DM patients with normal renal function. The mean serum glyburide blood levels and PK parameters did not differ after initial or chronic glyburide (3 mg once daily) administration in patients with ESRD treated with hemodialysis compared with controls. Glyburide $t_{1/2}$ averaged 3.3 h in control subjects and 5.0 h in hemodialysis subjects[65].

4.1.2 Hypoglycemia in glibenclamide-treated patients with RI

In a cohort of 33,243 sulfonylurea users, the rate of diagnosis of hypoglycemia made by physicians was higher for glibenclamide than for other sulfonylureas (glipizide, gliclazide, tolbutamide). Furthermore, RI was shown to be associated with an increased risk of hypoglycemia (odds ratio, OR : 4.32 ; 95% CI 2.40-7.77)[66]. A Canadian case-control study described the potentially devastating effect of sulfonylurea-based (mostly glibenclamide/glyburide) oral hypoglycemic therapy in patients with ESRD with the occurrence of severe and prolonged hypoglycemia. Patients at greatest risk appear to be those with reduced intake, previous hypoglycemic episodes, and longer duration of diabetes so that alternative drugs should be considered in these patient groups[67]. However, opposite

conclusion was reported in another nested case-control study using administrative records and laboratory data from Ontario, Canada, which included outpatients 66 years of age and older with T2DM. Compared to metformin, glyburide was associated with a greater risk of hypoglycemia in patients with both normal [adjusted odds ratio – OR - : 9.0; 95% CI 4.9-16.4) and impaired renal function (OR: 6.0; 95% CI 3.8-9.5). The conclusion of this population-based study was that RI does not augment the risk of hypoglycemia associated with glyburide use in T2DM patients[68]. Nevertheless, a one-time intervention in a risk reduction project decreased glyburide use over a 3-month period in elderly outpatients with RI without compromising glucose control and with a trend for a reduction in the incidence of hypoglycemia[69].

4.2 Glimepiride

The PK of glimepiride was investigated in a single (3 mg)- and a multiple-dose (1-8 mg daily over 3 months) open study in patients with T2DM and RI[70]. Patients were divided into three groups with CL_{CR} above 50 mL/min, 20-50 mL/min and 10-20 mL/min. Mean relative total clearance and mean volume of distribution of single dose of glimepiride (41.6 mL/min and 8.47 L, respectively, in patients with CL_{CR} above 50 mL/min) increased in proportion to the degree of RI (up to 91.1 mL/min and 14.98 L, respectively, when CL_{CR} was below 20 mL/min), whereas the terminal $t_{1/2}$ and mean time remained unchanged. Similar results were obtained after multiple doses of glimepiride. Lower relative total clearance and CL_R of glimepiride metabolites correlated significantly with lower CL_{CR} values. Glimepiride was well-tolerated without drug-related adverse events. The increased plasma elimination of glimepiride with decreasing kidney function can be explained on the basis of altered protein binding with an increase in unbound drug[58, 70].

Glimepiride was associated with fewer episodes of severe hypoglycemia than glibenclamide in routine clinical use[53]. However, severe hypoglycemia did occur with glimepiride, especially in elderly T2DM patients with RI[71]. Uncritical prescription of sulfonylureas (including a high proportion of glimepiride in a German study) neglecting crucial contraindications - particularly RI - contributed substantially to the risk of sulfonylurea-induced hypoglycemia in these mainly geriatric patients[55].

4.3 Glipizide

In healthy volunteers, the $t_{1/2}$ of glipizide elimination averaged 3.3 h both after intravenous and oral administration. The total plasma clearance of glipizide was 42.2±5.4

mL/min. Glipizide CL_R was dependent on urinary pH, but on the average it contributed to the total clearance of the parent drug only by 5%[72]. In subjects receiving 5 mg ^{14}C-glipizide, 85% of the total radioactivity in plasma corresponded to unchanged glipizide. In urine, 98% of the radioactivity corresponded to more polar and more readily excreted metabolites. The administration of ^{14}C-glipizide to patients with RI showed that the rate of disappearance of the unchanged glipizide was approximately the same as in normal subjects, but that apparent $t_{1/2}$ of the hydroxylated metabolites was increased to 20 h and more. Because these metabolites are metabolically inactive, such accumulation of metabolites could not lead to a higher risk of hypoglycemia in T2DM patients with RI[73].

Glipizide (2.5 mg once daily, adjusted based on glycemic control to a 10-mg twice a day maximum dose) was evaluated in patients with T2DM and moderate-to-severe CKD and inadequate glycemic control. A higher incidence of symptomatic hypoglycemic episodes was observed with glipizide versus sitagliptin (17.0% versus 6.2%, respectively; P=0.001), for a comparable glucose-lowering efficacy, an observation similar to that previously reported in patients without RI[74]. Similar results were obtained in a recent study that compared the efficacy and safety of sitagliptin and glipizide monotherapy in patients with T2DM and ESRD on dialysis therapy[75]. Thus, glipizide does not increase hypoglycemia in patients with CKD and its use appears more suitable than glibenclamide (glyburide) or even glimepiride in this population.

4.4 Gliclazide

Gliclazide is metabolized by the liver to inactive metabolites, which are eliminated mainly in the urine (80%). The PK of gliclazide was studied in 6 diabetic (mean CL_{CR}=44 mL/min) and 11 non-diabetic (mean CL_{CR}=13 mL/min) patients with various degrees of RI, and compared to that of 9 healthy volunteers (mean CL_{CR}=118 mL/min). Gliclazide was absorbed similarly in all three groups. Once maximum plasma levels of gliclazide had been reached, they tended to decline more slowly in the RI groups (mean elimination-half-life in diabetic group: 14.8 hours and non-diabetic group: 22.4 hours) as compared to the healthy volunteer group (12.7 hours). However, the inter-subject variability was large and the differences were not statistically significant. There were no significant differences for the other parameters measured and no significant correlation was found between any of the measured PK parameters and CL_{CR} (data only reported as abstract form)[76].

Although no extensive data are available in patients with severe RI, studies have shown neither PK modifications of the drug nor a higher risk of hypoglycemia in patients with

a GFR > 40 ml/min[41]. In Switzerland, gliclazide is the only sulfonylurea that can be used in subjects with a GFR of 40-60 ml/min, but it has to be stopped once GFR falls below 40 ml/min[78].

Since many years, gliclazide is available as a modified release formulation[73]. The long-term efficacy and safety of gliclazide modified release in T2DM patients with mild to moderate RI were confirmed by the results of phase III studies. Among the 507 patients who completed 2 study years, 20% of them had mild to moderate RI defined on CL_{CR} between 20 and 80 mL/min. In these patients, the mean change in HbA1c from baseline to 2 years was similar to that of the patients with normal renal function, with no excess of hypoglycemic episodes[79].

In the European GUIDE study, which randomized 845 T2DM patients (almost 42% with a CL_{CR} < 80 mL/min) to either gliclazide modified release 30-120 mg daily or glimepiride 1-6 mg daily, gliclazide was as effective as glimepiride, but with a significantly lower risk of hypoglycemia[80]. One proposed explanation was that the two drugs show different PK profiles with the occurrence of an active metabolite eliminated by the kidney for glimepiride and no circulating active metabolite for gliclazide, consistent with the higher incidence of hypoglycemia in patients with RI[80].

In the large prospective ADVANCE ("Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation") trial, a strategy of intensive glucose control, involving gliclazide (modified release) and other drugs as required, that lowered the glycated hemoglobin (HbA_{1c}) value to 6.5% yielded a 21% significant reduction in the incidence of nephropathy (4.1% vs. 5.2%; hazard ratio, 0.79; 95% CI 0.66-0.93; P=0.006). The component of new or worsening nephropathy most clearly reduced through intensive glucose control was the development of macroalbuminuria, with only a trend toward a reduction in the need for renal-replacement therapy or death from renal causes but no effect on the doubling of serum creatinine level. In this population, which comprised a majority of patients with normal kidney function, gliclazide was well tolerated, with uncommon hypoglycemia[81].

4.5 Gliquidone

Gliquidone is rapidly and almost completely absorbed after oral administration, and has a short elimination half-life (around 1.5 h). It is metabolized in the liver so that accumulation does not take place in patients with RI[41, 82]. However, there are no large scale studies published with this sulfonylurea, which is only commercialized in few countries.

5. Meglitinides (glinides)

Compared to sulfonylureas, glinides are characterized by shorter half-lifes as well as by the absence of significant renal excretion[83, 84]. Thus, in principle, they may be used in patients with CKD, without dose adjustment[85]. This conclusion may be drawn from PK studies in patients with RI, with repaglinide[86] and nateglinide (although some caution is required for nateglinide because of the presence of an active metabolite that is cleared by the kidney).[87] However, there are no large scale studies having assessed both the efficacy and the safety of glinides in T2DM patients with CKD[83]. Furthermore, these compounds are exposed, as sulfonylureas, to drug-drug interactions[88].

5.1 Repaglinide

PK comparison with single and multiple doses of repaglinide (2 mg repaglinide for 7 days) was performed in subjects with normal renal function and subjects with various degrees of RI (mild to moderate; severe; hemodialysis). PK parameters did not show significant changes after single or multiple doses of repaglinide, although the elimination rate constant in the group with severe RI decreased after 1 week of treatment. Subjects with severe RI had significantly higher exposure (AUC values) after single and multiple doses of repaglinide than subjects with normal renal function (Table 1). No significant differences in values for serum C_{max} or T_{max} were detected between subjects with RI and those with normal renal function. Hemodialysis did not significantly affect repaglinide clearance. Repaglinide was safe and well tolerated in subjects with varying degrees of RI. Although adjustment of starting doses of repaglinide is not necessary for RI or renal failure, severe impairment may require more care when upward adjustments of dosage are made[89].

In clinical trials of up to 52 weeks' duration and in the clinical practice setting, recommended dosages of repaglinide (0.5-4 mg three times daily) provided effective glycemic control and were generally well tolerated in patients with T2DM, including those with RI[83]. Thus, repaglinide is an appropriate treatment choice, even for individuals with more severe degrees of RI[86].

5.2. Nateglinide

Diabetic patients with RI or ESRD undergoing hemodialysis received a single 120 mg dose of nateglinide immediately before breakfast. Plasma nateglinide concentrations increased

rapidly and similarly in patients undergoing dialysis and matched healthy subjects and was comparable in patients with RI and controls. There were no statistically significant differences for C_{max} or AUC between the groups (Table 1). Nateglinide was eliminated rapidly in all groups ($t_{1/2}$ = 1.9-2.8 h). There was no correlation between the level of renal function and systemic exposure. There was a low extent of renal excretion of nateglinide in healthy subjects (11%) and diabetic patients with RI (3%). Nateglinide was well tolerated. These data suggested that nateglinide is suitable for use in diabetic patients with CKD or with ESRD undergoing dialysis. No dose adjustment appears necessary in renally impaired patients[87].

In another study, single 90 mg dose of nateglinide was safe and effective in patients with renal failure[90]. However, repeated administrations could cause prolonged hypoglycemia due to accumulation of M1, a metabolite that is known to have a modest hypoglycemic activity[91]. Hemodialysis may help to eliminate excessive accumulation of M1[90].

5.3 Mitiglinide

Although mitiglinide was effective as a treatment for diabetic patients on hemodialysis therapy, it should be initiated at a lower dose in this population, compared with the general population of diabetic patients, in order to avoid hypoglycemia[92].

6. Alpha-glucosidase inhibitors

Alpha-glucosidase inhibitors are not recommended as part of the management of T2DM in the recent ADA-EASD position statement[16], most probably because of their lower glucose-lowering efficacy and of their rather poor gastrointestinal tolerance in Caucasian people. Nevertheless, they are a popular therapy in Asian countries. Various compounds belong to this pharmacological class, but the available data regarding their use in patients with CKD are rather scarce[13]. Because of their PK characteristics, no dose adjustment is required in case of RI, although their use in patients with moderate to severe CKD is not recommended in absence of available data[41].

6.1 Acarbose

Acarbose acts locally within the gastrointestinal tract and is characterized by a low systemic bioavailability[93]. Although <2% of an oral dose of acarbose was absorbed as active drug, patients with severe RI (CL_{CR} <25 mL/min) attained increases about 5-fold higher for peak plasma concentration of acarbose and 6-fold higher for AUC values than subjects with

normal renal function[13]. Because long-term clinical trials in diabetic patients with significant renal dysfunction have not been conducted, treatment of T2DM patients with acarbose is not recommended [2].

6.2 Miglitol

Miglitol is systemically absorbed but is not metabolized, and is rapidly eliminated by renal excretion as unchanged drug[94]. Patients with CL_{CR} <25 mL/min taking miglitol 25 mg 3 times daily exhibited a greater than 2-fold increase in miglitol plasma levels when compared to subjects with CL_{CR} >60 mL/min[13]. Dose adjustment to correct for the increased plasma concentrations is not feasible because miglitol acts locally in the gut. Treatment of patients with CL_{CR} <25 mL/min with miglitol is not recommended because the safety of miglitol in these patients has not yet been elucidated[13].

6.3 Voglibose

Voglibose is an alpha-glucosidase inhibitor only commercialized in Japan. It has no renal excretion[13]. Two studies showed that it can be safely used in diabetic patients on hemodialysis, in combination with pioglitazone or mitiglinide[95, 96].

7. Thiazolidinediones

The experimental studies that evaluated the potential beneficial effects of peroxisome proliferator-activated receptor-gamma (PPARγ) agonists (TZDs : pioglitazone, rosiglitazone) on renal function have been reviewed. In that paper, the efficacy, tolerability and safety results of TZD use in patients with different degrees of RI, in dialysis patients, and in diabetic patients after kidney transplantation were revised[97]. Data from several animal and human studies support the notion that TZDs reduce urine albumin excretion and may prevent development of renal injury[98]. From a PK point of view, TZDs are metabolized in the liver and not excreted by the kidney. Therefore, no dose adjustments are required in patients with CKD. However, the safety of TZDs has been questioned and some safety concerns may be even more relevant in a diabetic population with CKD[99]. The risk of fluid retention and congestive heart failure, a well known adverse event associated with TZD therapy[100], may be a concern, especially in the fragile population with CKD. Preclinical and pilot clinical data attest to the fact that at least part of the fluid retention derives from a direct effect of TZDs on sodium reabsorption via the renal medullary collecting duct. This mechanism is sensitive to

diuretic agents that have this nephron segment as their site of action (spironolactone, amiloride and hydrochlorothiazide) but the efficacy of those diuretics is limited and/or their safety is questionable in patients with CKD[100]. Furthermore, TZDs may increase the incidence of bone fractures[101], a complication already more frequently observed in patients with CKD independently of TZD therapy because of insufficient vitamin D activation and renal osteodystrophy. Finally, cardiovascular safety of TZDs, especially rosiglitazone, has been questioned[99] and it is well known that T2DM patients with CKD are at higher risk of cardiovascular complications. Contradictory results have been reported regarding the mortality in diabetic patients with ESRD treated by dialysis and receiving TZD therapy with either increased mortality[102] or better survival[103]. Thus, despite favorable PK properties, TZDs do not appear as the drug of choice in T2DM patients with CKD. Nevertheless, a small study showed that TZD therapy was safe and effective for ambulatory patients receiving hemodialysis, even if some cases of heart failure have been reported[104].

7.1 Pioglitazone

Because pioglitazone and its active metabolites are excreted mainly via the liver, these PK properties are ideally suited for patients with CKD[105]. Healthy subjects with normal renal function (CL_{CR} > 80 mL/min), patients with moderate RI (CL_{CR} 30-60 mL/min) and patients with severe RI (CL_{CR} < 30 mL/min) received single and multiple oral doses of pioglitazone 45 mg. The serum PK profiles of pioglitazone and its metabolites M-III and M-IV were assessed for the first and last dose administered (day 1 and day 12, respectively). PK data were similar in subjects with normal and with moderate RI and revealed no significant accumulation of pioglitazone or its metabolites in patients with RI. Mean AUC values were decreased (rather than increased) in patients with severe RI compared with healthy subjects with normal renal function for pioglitazone and its M-III and M-IV metabolites (Table 1) This may be explained by reduced protein binding, which is common in patients with RI, resulting in increased free pioglitazone concentrations and increased total clearance of the drug (assuming that the intrinsic capacity of the liver remains unchanged). In this study, pioglitazone was well tolerated in patients with varying degrees of RI so that adjustment of starting and maintenance doses in these patients is probably unwarranted[106]. PK profile of pioglitazone was also shown to be similar in patients with ESRD undergoing hemodialysis and in patients with normal renal function[107]. In T2DM patients on hemodialysis, pioglitazone treatment resulted in better glycemic control, improved lipid levels, an increase in insulin

sensitivity and adiponectin levels, a decrease in inflammatory markers and a reduction in erythropoietin dose, thus improving the risk factors of cardiovascular disease[108]. Interestingly, a post hoc analysis from PROactive ("PROspective pioglitAzone Clinical Trial In macroVascular Events") investigated the effects of pioglitazone 45 mg treatment on recurrent CV disease in a population of patients with T2DM and documented macrovascular disease according to the level of GFR. Patients who had CKD (eGFR < 60 mL/min/1.73m²) and were treated with pioglitazone were less likely to reach a composite endpoint of all-cause death, myocardial infarction and stroke (HR=0.66, 95% CI 0.45-0.98), independent of the severity of RI [109, 110].

7.2 Rosiglitazone

Rosiglitazone is mainly metabolized by CYP2C8 into inactive metabolites, and < 1% of the parent drug appears in the urine in unchanged form[111]. To investigate the effect of varying degrees of CKD on the PK of rosiglitazone after a single dose of 8 mg, subjects were stratified by estimated CL_{CR} : normal (> 80 mL/min), mild RI (60-80 mL/min), moderate RI (30-59 mL/min), and ESRD not requiring dialysis (< 30 mL/min)[112]. Slight increases (approximately 10%-20%) in mean unbound AUC_∞ values were observed for each RI group compared to the normal group but were not considered to be clinically relevant. Patients with severe RI exhibited a 38% increase in mean fraction unbound, leading to an increase in total clearance, which resulted in a 19% to 24% lower mean total AUC_∞ and C_{max} values relative to the normal group. The rates of adverse events were similar for all groups. As RI does not markedly alter the PK of total or unbound rosiglitazone following a single dose of rosiglitazone, the starting dose does not need to be adjusted in patients with CKD. Subsequent dose adjustments should be based on individual patient response[112].

The PK and tolerability of a single 8 mg oral dose of rosiglitazone were compared in ESRD patients undergoing hemodialysis and 10 healthy volunteers. Hemodialysis did not influence rosiglitazone PK, and dialytic clearance was low (0.10 L/h). Mean AUC_∞, C_{max} and $t_{1/2}$ for rosiglitazone were similar in hemodialysis patients and healthy individuals. Thus, rosiglitazone dose adjustments are not warranted in patients with T2DM with ESRD on hemodialysis[113]. The PK of a single 8 mg oral dose of rosiglitazone was studied in patients with ESRD and requiring long-term chronic ambulatory peritoneal dialysis. Mean AUC_∞ and C_{max} of rosiglitazone in patients with peritoneal dialysis appear no different from those reported in healthy volunteers[114].

In a post-hoc analysis of data pooled from 3 randomized, double-blind, placebo-controlled studies, the effects of rosiglitazone 4 mg when added to a sulfonylurea regimen were investigated in patients with T2DM and mild to moderate RI (baseline CL_{CR} of 30 to 80 mL/min). Rosiglitazone was effective and well tolerated in this population, with no obvious differences with results observed in patients with normal kidney function[115]. In two other studies, rosiglitazone was well tolerated and beneficial in patients with T2DM on peritoneal dialysis therapy[116] or undergoing regular hemodialysis[117].

8. DPP-4 inhibitors

DPP-4 inhibitors (gliptins) are a new class of OADs belonging to the incretin-based glucose-lowering agents. They improve glucose control without inducing hypoglycemia (in contrast to sulfonylureas) and are weight-neutral[118]. Several molecules are already available, which are characterized by different PK properties[119, 120]. DPP-4 inhibitors have been particularly well studied in patients with CKD[121]. Sitagliptin,[122] vildagliptin[123, 124], saxagliptin[125] and alogliptin[126] are largely excreted by the kidneys. Results from dedicated PK studies in subjects with various degrees of RI suggest that the daily doses of these four DPP-4 inhibitors should be adjusted according to eGFR to reach almost similar plasma levels[121]. Several studies have demonstrated that the glucose-lowering efficacy is maintained while a good safety profile when reduced doses of these gliptins are used in patients with RI[127-130]. In contrast, linagliptin is mainly excreted by the biliary route rather than by the kidney (< 5 %)[131]. Therefore, this DPP-4 inhibitor does not require any dose adjustment in case of RI and can be used in patients with various degrees of CKD (Table 5)[132, 133]. In all studies involving DPP-4 inhibitors, the following populations were tested : normal kidney function, CL_{CR} > 80 ml/min; mild RI, 50–80 mL/min; moderate RI, 30–50 mL/min; severe RI, <30 mL/min; ESRD, <30 mL/min undergoing hemodialysis.

DPP-4 inhibitors are playing an increasing role in the management of T2DM, especially in combination with metformin. Several fixed-dose combinations (FDCs) are currently available or will be commercialized very soon[118]. Such FDCs may only be prescribed when both compounds are not contraindicated because of the presence of RI and appropriate adjustments of individual doses may be required[134-136].

8.1 Sitagliptin

The PK of single doses of sitagliptin 50 mg was evaluated in patients with various degrees of RI : mild, moderate, severe, ESRD on hemodialysis, and normal renal function[122]. Increases in sitagliptin AUC_{∞} were ~1.6-fold, ~2.3-fold, ~3.8-fold, and ~4.5-fold higher for patients with mild, moderate, severe RI and ESRD, respectively, as compared to levels obtained in subjects with normal renal function (Table 1). Based on these findings, sitagliptin dose adjustments are recommended for patients with moderate RI (50 mg daily) or severe RI or ESRD (25 mg daily) to provide plasma sitagliptin exposure comparable to patients with normal renal function (100 mg daily) (Table 5).

Sitagliptin was generally well tolerated and provided effective glycemic control in patients with T2DM and moderate to severe RI, including patients with ESRD on dialysis[128]. In patients with T2DM and moderate to severe CKD, sitagliptin (50 to 25 mg/day respectively) and glipizide provided similar HbA_{1c}-lowering efficacy. Sitagliptin was generally well-tolerated, with a lower risk of hypoglycemia and weight loss versus weight gain, relative to glipizide[74]. In patients with T2DM and ESRD on dialysis therapy, sitagliptin 25 mg/day was almost as effective in reducing HbA1c as glipizide (non significant difference of 0.15% after 54 weeks), with a lower incidence of symptomatic hypoglycemia (6.3 % vs. 10.8%) and severe (0% vs. 7.7%) hypoglycemia[75].

8.2 Vildagliptin

Vildagliptin is primarily metabolized via hydrolysis and the metabolites are predominantly excreted by the kidneys. To a smaller extent, vildagliptin is also excreted by the kidneys as the unchanged drug (23% after an oral dose). Therefore, RI may have certain effects on the PK of vildagliptin[123]. The mean AUC values increased by 32–134% and the C_{max} values increased by 8–66% in subjects with mild, moderate and severe RI, and ESRD on hemodialysis, compared with healthy subjects. CL_R of vildagliptin in healthy volunteers averaged 12.4 L/h, and decreased in subjects with varying degrees of RI with a significant correlation with the reduction in GFR (r^2=0.75). However, the total exposure (AUC) to vildagliptin did not show a clear correlation with the severity of RI (assessed by GFR). Vildagliptin was removed by hemodialysis to a limited extent (3%). Compared with values in healthy subjects, exposure (AUC) to the major and inactive hydrolysis metabolite (LAY151) in subjects with mild, moderate and severe RI, and in those with ESRD was increased by 1.6-, 2.4-, 5.4- and 6.7-fold, respectively, with a good correlation between changes in exposure to LAY151 and GFR reduction[124] (Table 1). The lack of a clear correlation between the

increased exposure to vildagliptin and the severity of RI may indicate that the kidneys contribute not only to the excretion but also, and predominantly, to the hydrolysis metabolism of vildagliptin. From a PK perspective, the approximate 2-fold increase in exposure suggests that the dose of vildagliptin for patients with moderate and severe RI should be reduced to half of the daily dose for patients with normal renal function (50 mg once daily instead of 50 mg twice daily) (Table 5)[123].

In a 24-week study of 515 patients with T2DM and moderate or severe RI, vildagliptin (50 mg once daily) added to ongoing antidiabetic therapy had a safety profile similar to placebo and elicited a statistically and clinically significant decrease in HbA_{1c}[129]. These results were confirmed after a 1-year observation[130]. In another study, the safety profile of vildagliptin 50 mg as an add-on to metformin was similar in patients with mild RI and normal renal function[137]. In a pooled analysis of 38 studies where vildagliptin was given for 12-104 weeks in patients with T2DM, the presence of mild RI did not adversely affect the safety of vildagliptin relative to patients with normal renal function[138]. Finally, vildagliptin was also effective and safe as a treatment for diabetic patients undergoing hemodialysis[139] or in patients with severe RI (eGFR < 30 mL/min/1.73 m² and longstanding T2DM not adequately controlled with insulin therapy[140].

8.3 Saxagliptin

The PK of saxagliptin and its pharmacologically active metabolite, 5-hydroxy saxagliptin, in nondiabetic subjects with mild (CL_{CR} 50–80 ml/min), moderate (30–50 ml/min), severe RI (<30 ml/min), or ESRD were compared with saxagliptin and metabolite PK and tolerability in healthy adult subjects.[125] All subjects received a single oral dose of saxagliptin 10 mg. Using a model-based approach and compared with healthy subjects, the geometric mean AUC_∞ for saxagliptin was 16%, 41% and 108% higher in subjects with mild, moderate or severe RI, respectively. AUC_∞ values for 5-hydroxy saxagliptin were 67%, 192% and 347% higher in subjects with mild, moderate or severe RI, respectively (Table 1). Elimination $t_{1/2}$ of saxagliptin and 5-hydroxy saxagliptin progressively increased while corresponding CL_R progressively decreased according to the reduction of CL_{CR}. Consequently, one-half the usual dose of saxagliptin 5 mg (i.e. 2.5 mg orally once daily) is recommended for patients with moderate or severe RI or ESRD on hemodialysis, but no dose adjustment is recommended for those with mild RI.

A 12-week study evaluated the efficacy and safety of saxagliptin 2.5 mg versus placebo in patients with T2DM and RI (CL_{CR} < 50 mL/min)[141]. Oral antihyperglycemic drugs

and insulin therapy present at enrolment were continued throughout the study. Adjusted mean HbA_{1c} decreases from baseline to week 12 were numerically greater with saxagliptin than with placebo in the subgroups of patients with moderate ($\geq$ 30 CL_{CR} < 50 mL/min) and severe (CL_{CR} < 30 mL/min) RI, but not in ESRD patients on hemodialysis. After an extended follow up of 52 weeks, adjusted mean decrease in HbA_{1c} was greater with saxagliptin than placebo (difference, -0.73%, $p<0.001$). Reductions in HbA_{1c} were numerically greater with saxagliptin 2.5 mg than placebo in patients with RI rated as moderate or severe, but similar to placebo for those with ESRD on hemodialysis. Saxagliptin was generally well tolerated, with similar proportions of patients reporting hypoglycemic events as in the placebo group. Thus, saxagliptin 2.5 mg once daily offers sustained efficacy and good tolerability for patients with T2DM and moderate to severe RI, but should not be recommended in patients with ESRD (Table 5)[127].

8.4 Alogliptin

The results of a single-dose (50 mg) PK study in patients with RI showed an increase in alogliptin exposure compared with healthy volunteers: approximately 1.7-, 2.1-, 3.2-, and 3.8-fold increase in patients with mild, moderate, and severe RI, and in patients with ESRD, respectively (Table 1)[126]. Based on these findings, to achieve plasma alogliptin concentrations comparable to those in patients with normal renal function, alogliptin dose adjustments are recommended for patients with T2DM and moderate to severe RI, including those with ESRD requiring dialysis (Table 5).

8.5 Linagliptin

The influence of various degrees of RI on the exposure of linagliptin was assessed in subjects with and without T2DM[142]. Linagliptin PK (5 mg once daily) was studied under single-dose and steady-state conditions (administration for 7-10 days) in subjects with mild, moderate, and severe CKD and ESRD on hemodialysis, and compared with the PK in subjects with normal renal function. Renal excretion of unchanged linagliptin was <7% in all groups. Although there was a tendency towards slightly higher (20-60%) exposure in subjects with CKD compared with subjects with normal renal function, the steady-state AUC and C_{max} values showed a large overlap and were not affected by the degree of RI (Table 1). Thus, CKD has a minor effect on linagliptin PK, a finding that has been confirmed in post-hoc analyses of the trough plasma levels of linagliptin in the global Phase III program

investigating linagliptin 5 mg once daily for 24-52 weeks in patients with T2DM and various degrees of RI[143].

A pooled analysis of 3 clinical trials evaluated the effect of renal function on the efficacy and safety of linagliptin. Data were available for 2,141 patients with T2DM who were grouped by renal function as normal (n=1684), mild CKD (n=418), or moderate CKD (n=39). Linagliptin showed consistent placebo-corrected adjusted mean HbA_{1c} changes after 24 weeks across all 3 groups: normal renal function (-0.63%), mild CKD (-0.69%), and moderate CKD (-0.69%), with no significant inter-group difference. Linagliptin was generally well tolerated, with an incidence rate of adverse events with linagliptin similar to placebo.[132]

Finally, a recent phase 3 trial evaluated the efficacy and safety of linagliptin in patients with T2DM and severe CKD (GFR <30 mL/min/1.73 m^2).[133] Patients were treated with either linagliptin 5 mg once daily or placebo. Linagliptin induced significantly greater HbA_{1c} reductions at week 12 compared to baseline in the full analysis set (-0.8% versus -0.2% with placebo) and in the subgroup of poorly controlled patients (baseline $HbA_{1c} \geq 9\%$) (-1.5% vs. -0.3%). Hypoglycemia occurred more frequently in linagliptin-treated patients than in placebo-treated patients, an observation that may be explained by unchanged doses of insulin and/or sulfonylurea background therapy. Other adverse event rates were similar for linagliptin and placebo.

9. SGLT2 inhibitors

The kidney plays a major role in glucose homeostasis because of its role in gluconeogenesis and the glomerular filtration and reabsorption of glucose in the proximal convoluted tubules. The transport of glucose from the tubule into the tubular epithelial cells is accomplished by sodium-glucose co-transporters (SGLTs), especially SGLT2, a high-capacity, low-affinity transporter expressed chiefly in the kidney. SGLT2 accounts for approximately 90% of glucose reabsorption. SGLT2 inhibitors are new glucose-lowering agents, which specifically target the kidney by blocking the reabsorption of filtered glucose, thus leading to glucosuria. This mechanism of action holds potential promise for patients with T2DM not only in terms of improvements in glycemic control, but also potential benefits on weight loss and arterial blood pressure reduction[144]. Dapagliflozin is the SGLT2 inhibitor with the most clinical data available to date[145]. Other SGLT2 inhibitors (canagliflozin, empagliflozin) are currently in late phase of development, but no specific PK studies in patients with RI have been published so far with these last two compounds[144]. In a study investigating potential drug-drug interactions between empagliflozin and metformin in

healthy men, the renal clearance of empagliflozin and metformin were unaffected by co-administration[146].

A study assessed the effect of differences in renal function on the PK/PD of dapagliflozin. A single 50 mg dose of dapagliflozin was administered in five groups of individuals: healthy nondiabetic subjects; patients with T2DM and normal kidney function; and patients with T2DM and mild, moderate or severe RI based on eGFR. Subsequently, multiple doses (20 mg once daily) were evaluated in the patients with T2DM. Plasma concentrations of dapagliflozin and D3OG, an inactive metabolite, were incrementally increased with declining kidney function. Steady-state C_{max} for dapagliflozin were 4%, 6% and 9% higher and for D3OG were 20%, 37% and 52% higher in patients with mild, moderate, and severe RI, respectively, compared to normal function. $AUC_{0\text{-}tau}$ was likewise higher (Table 1). Compared to patients with normal renal function, glucose-lowering effects were attenuated with RI. Steady-state renal glucose clearance was reduced by 42%, 83%, and 84% in patients with mild, moderate, or severe RI, respectively. These results indicate that the kidney, besides the liver, significantly contributes to dapagliflozin metabolism, resulting in higher systemic exposure with declining kidney function. Dapagliflozin reduced pharmacodynamics in diabetic subjects with moderate to severe RI are consistent with the observation of reduced efficacy in terms of HbA_{1c} diminution in this patient population[147].

10. GLP-1 receptor agonists

When oral therapy is not sufficient to control blood glucose, injectable agents may be used. Besides insulin therapy, GLP-1 receptor agonists (exenatide and liraglutide, soon lixisenatide) offer new opportunities for the management of T2DM[16]. However, because of PK properties of these compounds, some limitations have been pointed out in presence of RI (Table 5).

Published case reports have documented the relationship between exenatide[148, 149] or liraglutide[150] use and acute kidney injury in patients with T2DM. The proposed explanation was the occurrence of gastrointestinal side effects with recurrent vomiting leading to dehydration and secondary acute RI. Physicians should be aware of this adverse event and patients should also be educated about the need to report unusual or prolonged gastrointestinal symptoms. However, a retrospective cohort study of a large medical and pharmacy claims database revealed an increased incidence of acute renal failure in diabetic versus non-diabetic patients but no association between use of exenatide and acute renal failure[151].

10.1 Exenatide

PK, safety and tolerability of a single exenatide dose were evaluated in patients with RI. Exenatide (5 or 10 μg) was injected subcutaneously in 31 subjects (only one with T2DM) stratified by renal function : normal (CL_{CR} >80 mL/min, mild RI (51-80 mL/min), moderate RI (31-50 mL/min) or end-stage renal disease (ESRD) requiring hemodialysis[152]. PK data were combined with four previous single-dose studies in patients with T2DM to explore the relationship of exenatide clearance (CL/F) and CL_{CR}. Mean $t_{1/2}$ for healthy, mild RI, moderate RI and ESRD groups were 1.5, 2.1, 3.2 and 6.0 h, respectively. After combining data from multiple studies, least squares geometric means for CL/F in subjects with normal renal function, mild RI, moderate RI and ESRD were 8.14, 5.19, 7.11 and 1.3 L/h, respectively. Thereby, exposure (AUC) to exenatide was markedly increased in patients with ESRD (Table 1). Exenatide was generally well tolerated in the mild and moderate RI groups, but not in subjects with ESRD due to nausea and vomiting. Since tolerability and PK changes were considered clinically acceptable in patients with mild to moderate RI, it would be appropriate to administer exenatide to these patients without dosage adjustment. However, poor tolerability and significant changes in PK make the currently available therapeutic doses (5 and 10 μg) unsuitable in severe RI or ESRD[152].

10.2 Liraglutide

To investigate whether dose adjustment of the once-daily human GLP-1 analogue liraglutide is required in patients with varying stages of RI, 30 subjects were given a single dose of liraglutide, 0.75 mg subcutaneously. No clear trend for change in PK was evident across groups with increasing renal dysfunction. The regression analysis of log(AUC) for subjects with normal renal function and mild-to-severe RI showed no significant effect of decreasing CL_{CR} on the PK of liraglutide. Degree of RI did not appear to be associated with an increased risk of adverse events. Because renal dysfunction was not found to increase exposure of liraglutide, T2DM patients with RI should use standard treatment regimens of liraglutide. There is, however, currently limited experience with liraglutide in patients beyond mild-stage CKD[153].

To determine the effect of mild RI on the efficacy and safety of liraglutide in patients with T2DM, the six LEAD ("Liraglutide Effect and Action in Diabetes") clinical trials were examined in a meta-analysis focusing on data from patients with normal renal function (CLCR > 89 mL/min), mild RI (60-89 mL/min), and moderate or severe RI (< 60 mL/min). The population contained patients administered once-daily liraglutide (1.2 or 1.8 mg) or

placebo as either monotherapy or in combination with oral antidiabetes drugs for 26 weeks. Mild RI did not affect the estimated treatment differences in HbA1c, body weight and systolic blood pressure. Liraglutide treatment was safe and well tolerated in patients with mild RI, as there were no significant differences in changes in rates of renal injury, minor hypoglycemia, or nausea vs. placebo. Nevertheless, a trend towards increased nausea was observed in patients with moderate or severe RI receiving liraglutide although the number of patients in this treatment group was too low to determine statistical significance. The conclusion was that mild RI had no effect on the efficacy and safety of liraglutide[154].

11. Insulin and insulin analogs

11.1 Human Insulin

The kidney plays a pivotal role in the clearance and degradation of circulating insulin[155]. Almost 50% of circulating insulin (a higher proportion for exogenous than endogenous insulin) is cleared by the kidneys via two distinct routes : 1) glomerular filtration and subsequent luminal reabsorption of insulin by proximal tubular cells by means of endocytosis; and 2) diffusion of insulin from peritubular capillaries and subsequent binding of insulin to the contraluminal membranes of tubular cells. As renal failure progresses, peritubular insulin uptake increases, compensating for the decline in degradation of filtered insulin until the GFR decreases to less than approximately 20 mL/ min. With lower levels of GFR insulin clearance decreases further and overall requirements for exogenous insulin often decline. If this is not anticipated, the risk of symptomatic hypoglycemia can increase.

The effect of diabetic nephropathy (Kimmelstiel-Wilson syndrome) on insulin requirements is known for a long time[156]. Impairment of the CL_R of insulin prolongs the $t_{1/2}$ of circulating insulin and often results in a decrease in the insulin requirement of diabetic patients[157]. It is generally recommended that when the GFR decreases to between 10 and 50 mL/ min, the insulin dosage should be reduced by 25%, and when the GFR decreases to <10 mL/min, the insulin dosage should be reduced by 50% from previous amounts[8, 9]. The reduction in insulin requirement in RI is similar in type 1 and insulin-treated T2DM patients. In subjects with T2DM, the residual insulin secretion has no impact on the reduction in insulin requirement dependent on the GFR. As an example, the insulin dose required by T2DM patients was reduced by 51% in patients with a CL_{CR} of 10 mL/min compared to patients with a CL_{CR} of 80 mL/min[158].

11.2. Insulin analogs

Modifications of the insulin molecule have resulted in two long-acting insulin analogs (glargine and detemir) and three rapid-acting insulins (aspart, lispro, and glulisine) with improved PK/PD profiles. As for human insulin, the PK/PD profiles for insulin analogs may be influenced by many variables including renal function, although the available data are rather scarce[159]. Insulin lispro maintains its characteristic PK/PD properties in patients with overt diabetic nephropathy[160]. In hemodialysis patients with diabetes, lispro insulin is absorbed faster than regular insulin, as it is in individuals with normal kidney function[161]. Similarly, RI does not affect the PK of insulin aspart in a clinically significant manner[162]. To our knowledge, there are no published studies that have-specifically tested the PK of the two long-acting insulin analogs, glargine or detemir, in patients with CKD[159]. Reduction of initial glargine/glulisine insulin weight-based dosing in hospitalized patients with T2DM and RI reduced the frequency of hypoglycemia by 50% without compromising the control of hyperglycemia[163]. Short-acting insulin analog can also be used in hemodialysis patients with T2DM[164].

12. Conclusion

A quite large and increasing proportion (currently around 20-25%) of T2DM patients have moderate to severe CKD (stages 3-5), especially in the elderly population, which requires the adaptation of the glucose-lowering therapy. Indeed, RI exerts a major influence on PK of most oral and injectable antidiabetic agents. Therefore, the daily dosage should be reduced in most instances or, if CKD is severe enough, the medication should not be initiated or be stopped for safety reasons (Figure 1). Clinical experience in various countries, however, demonstrates that numerous T2DM patients are not appropriately treated, as they are receiving too high dosages of the medications according to the reduced renal function or even they are treated by drugs that are contraindicated considering the severity of CKD. Despite these inappropriate prescriptions, the incidence of severe adverse events is rather low, even if it may be somewhat underestimated in clinical practice. The most well recognized side effects when glucose-lowering drugs are prescribed in T2DM patients with RI are lactic acidosis with metformin, hypoglycemia with sulfonylureas (more rarely with glinides) but also with insulin (or insulin analogs), and fluid retention with a higher risk of congestive heart failure with TZDs. The PK of DPP-4 inhibitors (except linagliptin) and GLP-1 receptor agonists is also modified by RI, which may require appropriate dose reductions. However, the potential risk

associated with these compounds, even if used in patients with CKD, is less well established. Whatsoever, the risk of hypoglycemia that may be dangerous, and even fatal, with sulfonylureas in patients with CKD could be markedly reduced by using DPP-4 inhibitors instead of sulfonylureas in this population. The case of metformin deserves more attention. Indeed, metformin is the first-line OAD in all guidelines for the management of T2DM, but it is also officially contraindicated in patients with GFR below 60 mL/min. If this rule is strictly respected (which is frequently not the case in real life !), this will deprive numerous patients of the best glucose-lowering agent. This situation should lead to an amendment of the rules of prescription of metformin in patients with mild to moderate RI. Finally, the experience with SGLT2 inhibitors, the only glucose-lowering drugs that specifically target the kidney, is still limited, although this new pharmacological class has already shown a reduced pharmacodynamic activity in patients with CKD and thereby is not best suited for this population.

The increasing prevalence of patients with T2DM and CKD, especially among elderly people, requires regular monitoring of renal function and appropriate selection and dosing of glucose-lowering agents according to GFR. A careful benefit/risk balance assessment should be performed in these more fragile diabetic patients. It would be of clinical interest in the future to develop new antidiabetic agents that may be used efficaciously and safely in the large population with T2DM and CKD.

EXPERT OPINION SECTION

According to the recent ADA-EASD position statement, the management of hyperglycemia of T2DM should be patient-centered. Generally speaking, the objectives and the modalities of therapy should be adapted to the characteristics of the T2DM patient. CKD is a common complication of T2DM, especially in the elderly population whose proportion is rapidly increasing, notably because of a better cardiovascular protection of patients with T2DM. The first step is to use appropriate methods to quantitatively assess and follow renal function. Current non-uniform use of different equations leads to more confusion rather than help with renal dosing and there is need for greater standardization of eGFR estimations.

Secondly, in a patient-centered approach, the presence of CKD is obviously an important condition to be taken into account, more specifically in the selection, dosing and supervision

of pharmacological therapies. In T2DM patients with CKD, the treatment algorithm that may be proposed is the following one, although there are no official guidelines in this specific population.

- The first choice drug may remain metformin provided that RI is stable, the CL_{CR} is above 30 ml/min and the renal function can be regularly monitored. When CL_{CR} is below 45 ml/min, the daily dose of metformin should be reduced by half and the medication should be stopped when CL_{CR} falls below 30 ml/min. Noteworthy, the patient and his/her family should be duly informed that metformin must be stopped in any acute condition, especially any situation that may lead to dehydration (diarrhea, vomiting, …) to reduce the risk of lactic acidosis (a rare but possibly fatal complication).

- In case of contraindication to metformin (CL_{CR} between 30-45 ml/min but at risk of destabilisation or CL_{CR} < 30 ml/min), the physician may chose a DPP-4 inhibitor rather than a sulfonylurea in order to reduce the incidence of sulfonylurea-associated hypoglycemia in patients known to be exposed to this severe complication. Linagliptin, which is not excreted by the kidneys, may be administered at the usual dose whereas the daily dose of other DPP-4 inhibitors should be reduced (generally by half) to reach comparable plasma levels. Thereby, a similar glucose-lowering activity can be achieved, with a good safety profile, in T2DM patients with moderate to severe CKD as compared to patients with normal kidney function. Alternatively, to reduce the cost, a glinide or a sulfonylurea with low renal excretion (and without active metabolite) may also be considered. A thiazolidinedione (currently pioglitazone only, as rosiglitazone is now withdrawn in most countries because of cardiovascular safety) may also be used without dosage adjustment, although the risk of fluid retention and congestive heart failure may be increased in more fragile patients with CKD. In the Asian population, alpha-glucosidase inhibitors might also be a valuable option, although almost no data are available in CKD patients with this pharmacological class that deserves further specific studies in this population.

- When individually-targeted glucose control cannot be achieved or maintained with metformin monotherapy, the addition of a DPP-4 inhibitor appears to offer some advantages compared to sulfonylureas (again, less hypoglycemia, no weight gain, no need of titration). Several gliptin plus metformin FDCs are currently available to

facilitate the use of such combination and improve adherence to therapy. The above-mentioned pharmacological alternatives (repaglinide, pioglitazone, acarbose) may also be considered, although few controlled clinical trials are available in this population with CKD and thus the clinical evidence is rather scarce.

- When the gliptin-metformin combination fails, the shift to insulin therapy is probably the best option, owing to the current limited experience with triple oral therapies or injectable GLP-1 receptor agonists in patients with CKD. It is worth noting that insulin daily doses are generally lower in patients with CKD than in patients without CKD, because the kidneys clear about 50% of circulating insulin and diabetic patients with RI are more exposed to hypoglycemia. The PK of various insulin preparations (including insulin analogs) has not been well studied in patients with varying degrees of RI, and there are no absolute guidelines defining appropriate dosing adjustments of insulin that should be made based on the level of GFR.

- Finally, SGLT2 inhibitors are the only antidiabetic agents that specifically target the kidney to improve glucose control. However, their clinical efficacy vanishes as renal function diminishes so that these novel glucose-lowering medications should not be used in patients with CKD. Their safety profile is also poorly known in this population.

Because of the increasing prevalence of CKD (especially mild to moderate stages) in patients with T2DM, there is an urgent need for a clarification of the use of glucose-lowering agents in this population and for the development of new agents that are efficacious and safe to control hyperglycemia despite impaired renal function.

Funding and conflict of interest

No sources of funding were used to assist in the preparation of this manuscript. No conflicts of interest are directly relevant to the content of this manuscript.
A.J. Scheen has received lecture/advisor fees from AstraZeneca/BMS, Boehringer Ingelheim, Eli Lilly, GlaxoSmithKline, Merck Sharp & Dohme, Novartis, NovoNordisk, and Sanofi-Aventis.

Article highlights

- The reduction in kidney function is a common observation in patients with type 2 diabetes, especially over 65 years, although this problem is frequently overlooked by the physician and unknown by the patient.
- Renal function should be measured in all diabetic patients before prescribing any glucose-lowering agent and regularly monitored to detect worsening, especially when events that may potentially deteriorate renal function occur.
- The pharmacokinetics of almost all glucose-lowering agents may be altered by renal impairment, thus requiring appropriate dosage adjustments according to the reduction in glomerular filtration rate (creatinine clearance).
- Metformin, the first choice oral antidiabetic agent, is officially contraindicated when creatinine clearance is < 60 ml/min/1,73 m², although real life data show that this drug is largely prescribed in patients with lower creatinine clearance without any problem and with potential benefits. In more recent guidelines, a dose reduction is proposed below < 45-60 ml/min/1,73 m², and the drug must be stopped at 30 ml/min/1,73 m².
- Most sulfonylureas are excreted by the kidneys (either parent drug or active metabolites), explaining why these drugs expose to a higher risk of (severe) hypoglycemia in diabetic patients with chronic kidney disease. DPP-4 inhibitors, whose dosage should also be reduced in presence of renal impairment (except linagliptin), offer clear advantages in this regard.
- The efficacy and safety of GLP-1 receptor agonists and new SGLT2 inhibitors remain largely unknown in patients with CKD and warrant further studies before using such agents in this population.

Figure 1 : Use of glucose-lowering medications according to the degree of renal impairment assessed by the glomerular filtration rate (eGFR). (*) The level of GFR may depend on the type of sulfonylurea (see text).

Table 1 : Drug exposure (AUC) in subjects with various degrees of renal impairment (RI ; according to the level of creatinine clearance) compared with subjects with normal renal function. Results are expressed as % changes versus subjects with normal renal function or as geometric mean ratio (GMR) RI/normal renal function (90% confidence intervals). NA : data not available.

	Reference	Mild RI	Moderate RI	Severe RI	Hemodialysis
Metformin	Sambol et al 1995[33]	NA	NA	NA	NA
Glibenclamide M1 + M2 (active metabolites)	Jonsson et al 1998[64]	NA NA	NA NA	- 45% + 98%	NA NA
Glimepiride M2 (active metabolite)	Rosenkranz et al 1998[70]	NA	- 55% + ≈100%	- 55% + ≈400%	NA NA
Glipizide	Balant et al 1973[73]	NA	NA	NA	NA
Gliclazide	McGavin et al 2002[77]	NA	NA	NA	NA
Repaglinide	Marbury et al 2000[89]	NA	+ 19%	+32%	+32%
Nateglinide	Deviveni et al 2003[87]	NA	+ 5%		-15%
Pioglitazone MIII MIV	Budde et al 2003[106]	NA	-17% -43% -21%	-23% -11% -44%	NA
Rosiglitazone	Chapelsky et al 2003[112]	1.08 (+8%) (0.85-1.37)	1.14 (+14%) (0.91-1.43)	0.81 (-19%) (0.64-1.04)	NA
Sitagliptin	Bergman et al 2007[122]	1.61 (+61%) (1.43-1.81)	2.26 (+126%) (2.02-2.53)	3.77 (+277%) (3.37-4.22)	4.50 (+350%) (4.03-5.03)

Vildagliptin LAY151 (inactive metabolite)	He et al 2012[123, 124]	1.40 (+40%) (1.24-1.57) 1.66 (+66%) (1.35-2.04)	1.71 (+71%) (1.52-1.93) 3.20 (+220%) (2.60-3.95)	2.00 (+100%) (1.77-2.26) 7.30 (+630%) (5.90-9.04	NA NA
Saxagliptin Active metabolite	Boulton et al 2011[125] (*)	1.16 (+16%) 1.67 (+67%)	1.41 (+41%) 2.92 (+ 192%)	2.08 (+108%) 4.47 (+ 347%)	NA (**) NA (**)
Alogliptin	Karim et al 2008[126]	1.7 (+70%) (NA)	2.1 (+110%) (NA	3.2 (+220%) (NA)	3.8 (+280%) (NA)
Linagliptin	Graefe-Mody et al 2011[142]	1.29 (+29%) (1.01-1.66)	1.56 (+56%) (1.06-2.32)	1.41 (+41%) (1.04-1.91)	1.54 (+54%) (1.18-2.00)
Dapagliflozin Metabolite D3OG	Kasichayanula et al 2012[147]	1.28 (+28%) (1.19-1.37) 1.50 (+50%) (1.37-1.65)	1.52 (+52%) (1.35-1.72) 2.01 (+101%) (1.71-2.37)	1.75 (+75%) (1.49-2.07) 2.54 (+154%) (2.04-3.16)	NA NA
Exenatide	Linnebjerg et al 2007[152]	0.81 (-19%) (0.66-0.98)	0.97 (-3%) (0.77-1.21)	NA (NA)	3.37 (+227%) (2.80-4.06)
Liraglutide	Jacobsen et al 2009[153]	0.67 (-33%) (0.54-0.85)	0.86 (-14%) (0.70-1.07)	0.73 (-27%) (0.57-0.94)	0.74 (-26%) (0.56-0.97)

(*) Model-derived point estimates for the mid-point of each renal impairment category
(**) NA – not available without post-dose hemodialysis

Table 2 : Clinical practice recommendations regarding the use of glucose-lowering agents in T2DM patients with various degrees of RI according to the level of glomerular filtration rate (GFR). ESRD : End-stage renal disease.

	Exposure (AUC) in patients with RI	**Risk of side effects in patients with RI**	**Use according to GFR (ml/min)**	**Use in patients with ESRD and dialysis**
Biguanides				
- Metformin	Increased	Lactic acidosis	≥ 60 : yes 30-45 : caution (half dose) < 30 : stop	No (dialysis in case of intoxication)
Sulfonylureas				
- Gilbenclamide	Increased (active metabolite)	Hypoglycemia (variable risk according to the molecule)	≥ 60 : yes < 60 : no	No
- Glimepiride	Increased (active metabolite)		≥ 60 : yes < 60 : caution	No
- Glipizide	No change (no active metabolite)		Yes	Yes
- Gliclazide	No change (no active metabolite)		Yes (caution)	No data
- Gliquidone	No change (no renal excretion)		Yes (few data)	No data
Glinides				
- Repaglinide	No change	Hypoglycemia (less than with sulfonylureas)	Yes	Yes
- Nateglinide	Modest change		<60 : caution	No
Alpha-glucosidase inhibitors				
- Acarbose/Miglitol	Increased (metabolite)	Unknown	< 60 : caution ≥ 60 : yes	No

			< 60 : caution	
Thiazolidinediones				
- Pioglitazone/ Rosiglitazone	No change	Fluid retention Congestive Heart failure	≥ 60 : yes < 60 : caution	Limited experience Great caution
DPP-4 inhibitors				
- Sitagliptin	Increased	Unknown	≥ 50 : yes 30-50 : half dose < 30 : quarter dose	Caution
- Vildagliptin	Increased		≥ 50 : yes < 50 : half dose	Caution
- Saxagliptin	Increased (+ active metabolite)		≥ 50 : yes < 50 : half dose < 30 : caution	No
- Alogliptin	Increased		≥ 50 : yes < 50 : reduced dose	Caution
- Linagliptin	No change		Yes (without dose adjustment)	Possibly yes (no data)
SGLT2 inhibitors				
- Dapagliflozin	Increased	Unknown	≥ 60 : yes < 60 : no	No
GLP-1 receptor agonists				
- Exenatide	No change	Unknown	≥ 60 : yes 30-60 : caution < 30 : no	No
- Liraglutide	No change		≥ 50 : yes < 50 : no	No

Insulin				
Insulin & insulin analogs	Increased	Hypoglycemia	Yes (reduced daily dose)	Yes

Table 3 : Various stages of chronic kidney disease (CKD) according to the glomerular filtration rate estimated by the MDRD formula (eGFR) or the creatinine clearance (CL_{CR}) calculated by the Cockroft-Gault formula.

Stage	**Description**	**eGFR derived from MDRD formula**	**CL_{CR} derived from Cockroft-Gault formula**
Formula		**GFR (ml/min/1.73 m^2) = 186.3 x (plasma creatinine [µmol/L]/88.4)$^{-1.154}$ x age$^{-0.203}$**	**GFR (ml/min) = (140-age) x weight (kg)/ plasma creatinine [µmol/L]**
Correction factor		**Woman : x 0.742 Afro-American : x 1.21**	**Woman : x 1.03 Man : x 1.23**
1	Normal renal function	≥90	>80
2	Mild CKD	60-89	50-80
3 (*)	Moderate CKD	30-59	30-50
4	Severe CKD	15-29	<30
5	End-stage renal disease (ESRD)	< 15 (or dialysis)	Dialysis

* Stage 3 may be divided in two categories : 3a between 45 et 59 ml/min/1.73 m² and 3b between 30 and 44 ml/min/1.73 m².

Table 4 : Proposed recommendations for use of metformin based on eGFR (adapted from reference Lipska et al)[37].

eGFR **ml/min/1,73 m²**	**Actions**
≥ 60	No renal contraindication to metformin Monitor renal function annually
< 60 à ≥ 45	Continue metformin use if well tolerated Increase monitoring of renal function (every 3-6 months) Avoid any nephrotoxic drugs Stop metformin in case of serious acute event and dehydration
< 45 à ≥ 30	Prescribe metformin with caution Use lower dose (e.g., 50%, or half-maximal dose) Closely monitor renal function (every 3 months) Avoid any nephrotoxic drugs Stop metformin in case of serious acute event and dehydration Do not start new patients on metformin
< 30	Stop metformin Adjust antidiabetic therapy is necessary Closely monitor renal function (every 6 weeks)

Additional caution is required in patients at risk for acute kidney injury or with anticipated significant fluctuations in renal status, based on previous history, other comorbidities, or potentially interacting medications.

Table 5 : Dose adjustments recommended when using incretin-based therapies in patients with various stages of renal impairment (RI) based on previous pharmacokinetics studies. CL_{CR} : creatinine clearance.NR : not recommended

RI STAGE CL_{CR} ml/min	Mild 1-2 ≥ 50	Moderate 3 ≥30 -<50	Severe 4 <30	ESRD 5 Dialysis
Sitagliptin	100 mg/day	50 mg/day	25 mg/day	25 mg/day
Vildagliptin	2 x 50 mg/day	1 x 50 mg/day	1 x 50 mg/day	1 x 50 mg/day
Saxagliptin	5 mg/day	2,5 mg/day	2,5 mg/day	NR
Alogliptin	25 mg/day	12.5 mg/day	6.25 mg/day	6.25 mg/day
Linagliptin	5 mg/day	5 mg/day	5 mg/day	5 mg/day
Exenatide	2 x 10 µg/day	2 x 10 µg/day	NR	NR
Liraglutide	1.2-1.8 mg/day	NR	NR	NR

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