Glucose-lowering drugs in patients with chronic kidney disease: a narrative review on pharmacokinetic properties

Paul Arnouts¹, Davide Bolignano²,³, Ionut Nistor²,⁴, Henk Bilo⁵,⁶, Luigi Gnudi⁷, James Heal⁸ and Wim van Biesen²,⁹

¹Nephrology-Diabetology Department, AZ Turnhout, Belgium, ²European Renal Best Practice Methods Support Team, Ghent University Hospital, Ghent, Belgium, ³CNR-IBIM, Clinical Epidemiology and Physiopathology of Renal Diseases and Hypertension of Reggio Calabria, Calabria, Italy, ⁴Nephrology Department, Gr. T. Popa University of Medicine and Pharmacy, Iasi, Romania, ⁵Departments of Internal Medicine, Isala Clinics, Zwolle, the Netherlands, ⁶University Medical Center, Groningen, the Netherlands, ⁷Unit For Metabolic Medicine, Department Diabetes and Endocrinology, Cardiovascular Division, Guy’s and St Thomas Hospital, King’s College London, London SE1 9NH, UK, ⁸Department of Nephrology B, Herlev Hospital, University of Copenhagen, Copenhagen, Denmark and ⁹Renal Division, Ghent University Hospital, Ghent, Belgium

Correspondence and offprint requests to: Wim van Biesen; E-mail: wim.vanbiesen@ugent.be

ABSTRACT

The achievement of a good glycaemic control is one of the cornerstones for preventing and delaying progression of microvascular and macrovascular complications in patients with both diabetes and chronic kidney disease (CKD). As for other drugs, the presence of an impaired renal function may significantly affect pharmacokinetics of the majority of glucose-lowering agents, thus exposing diabetic CKD patients to a higher risk of side effects, mainly hypoglycaemic episodes. As a consequence, a reduction in dosing and/or frequency of

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administration is necessary to keep a satisfactory efficacy/safety profile. In this review, we aim to summarize the pharmacology of the most widely used glucose-lowering agents, discuss whether and how it is altered by a reduced renal function, and the recommendations that can be made for their use in patients with different degrees of CKD.

Keywords: chronic kidney disease, diabetes, dialysis, glucose lowering drugs, pharmacokinetics

INTRODUCTION

Diabetes mellitus is a leading cause of chronic kidney disease (CKD) and a major cause of morbidity and mortality worldwide. Registry data show that the incidence of type 2 diabetes has more than doubled in the last 30 years [1], and time projections of diabetes burden over the next decades paint a global scenario with dramatic perspectives for public health [2]. Furthermore, the coexistence of diabetes and CKD, be it as a direct consequence of diabetic nephropathy or as an association of separate diseases, is increasingly prevalent. The presence of CKD influences glycaemic control, making the therapeutic management of diabetes patients challenging. On the one hand, progressive loss of renal function impairs renal dynamics of glucose-lowering drugs is thus a timely issue, with different degrees of CKD.

From a general point of view, all aspects of drug pharmacokinetics (absorption, distribution, metabolism and excretion) can be influenced by CKD [5]; consequently, the complexity of drug prescription increases as kidney function worsens and, particularly in dialysis patients (CKD-5D) where the impact of renal replacement therapy on insulin sensitivity and clearance of various drugs should also be taken into account [6].

Absorption

A reduced or slowed drug absorption decreases drug bioavailability, i.e. the fraction of the total dose of a drug that reaches the systemic circulation. In CKD, gastric acidity is usually altered due to the presence of uraemic gastritis or by the ingestion of medications with antiacid effects (e.g. phosphate binders and proton pump inhibitors). Moreover, gastric emptying is often delayed in these patients when they also have diabetes, quite often due to diabetic and/or uraemic gastroparesis. Many CKD patients also take chelating agents, such as phosphate binders or resins, which can also absorb part of the drugs, especially when concomitantly ingested. In addition, uraemia-induced vomiting may reduce the time drugs remain in the gastrointestinal tract, thus limiting the time for absorption. Gut oedema, often associated with congestive heart failure, chronic fluid overload, cirrhosis, nephrotic syndrome or other conditions of anasarca, may further impair intestinal absorption.

Distribution

Under normal conditions, the kidney plays a major role in regulating the volume of distribution (V_d) of a drug—that is the association between the total amount of a drug in the body and its serum concentration. Drugs with a small V_d (such as hydrophilic compounds) tend to maintain higher serum concentrations for lower dosages given, and vice versa. Fluid status is an important determinant of V_d. When extracellular fluids are increased, such as in hypervolaemic or oedematous CKD patients, the increase in V_d leads to a reduction in serum levels of the drug. Conversely, an increase in serum concentrations may be expected in fluid-depleted patients or patients with CKD-associated muscle wasting, where V_d is reduced. Obesity, a condition often associated with CKD and diabetes, may affect V_d in different ways depending on the characteristics of the drug (lipo- or hydrophilic). Both CKD and diabetes might be associated with hypo-albuminaemia and CKD may also significantly impair the capacity of plasma protein to bind and transport drugs. This is a major issue because the consequent rise in the free fraction of drugs (unbound molecules) will enhance the pharmacologic effects for the same total concentration. The total binding capacity can also be influenced by uraemic molecules, the absolute reduction in circulating protein (e.g. albumin) levels, e.g. as the consequence of inflammation, severe renal protein leakage or impaired hepatic production or due to alterations in blood pH.

Metabolism

Biotransformation generates inactive or pharmacologically active agents with a chemical, biological and pharmacotherapeutic profile similar or different from parent compounds. Although most drug metabolism takes place in the liver, other organs such as the intestinal tract, lungs and kidney, can also contribute in a relevant way. CKD can impair the ability of the kidneys to metabolize drugs [7] and, as a consequence, in CKD patients an increased half-life has been observed even for drugs not undergoing renal excretion (be it tubular or glomerular) [8]. This can be partly explained by the retention of uraemic mediators and the accumulation of cytokines which deregulate hepatic and intestinal cytochrome enzyme activities as well as P-glycoprotein (Pgp) and organic anion-transporting polypeptide (OATP) function [9], resulting in an altered intestinal
uptake, liver metabolism and bile excretion of drugs [10] in patients with CKD. Accordingly, the removal of uraemic toxins by renal replacement therapy can improve cytochrome activity [11] and can thus alter the elimination of drugs, even if they are not cleared by the dialysis itself.

Excretion

Typically, drugs and active drug metabolites for which the kidney represents the major route of elimination (via glomerular excretion, tubular secretion or both) accumulate as kidney function is impaired. For these drugs, a dose adjustment or an extended dose interval is usually needed in CKD patients in order to keep an optimal safety/efficacy profile. Generally, it is accepted that reducing the dose without altering dosing frequency has a higher risk of overdosing the drug (due to progressive accumulation), but assures continuous coverage, whereas giving the same dose but increasing the dosing interval has a lower risk of accumulation but a higher risk of having periods of underdosaging. Although the alteration in drug clearance is usually proportional to the reduction in the estimated GFR (eGFR), certain populations (e.g. elderly and neonates) are at high risk of inappropriate drug dosage due to the intrinsic imprecision of some eGFR creatinine-based formulas.

Pharmacokinetics

Metformin is a hydrophilic drug for which the absorption occurs almost exclusively in the upper gastrointestinal tract [20]. After administration, the maximum peak in plasma concentration (2 µg/mL) is reached within 2 h [21]. A dose-response study demonstrated that 2000 mg daily is the most effective dose of metformin, resulting in a mean 2% lowering of HbA1c when compared with placebo, while 85% of the maximal effect of metformin is observed at a dose of 500 mg three times daily [22]. The absolute bioavailability of a 500 mg dose of metformin is ~50–60%. The bioavailability is reduced by food and tends to decrease with the increase of the dose administered, suggesting the existence of a saturation- or permeability/transit time-limited absorption mechanism. The overall volume of distribution is 3.1 L/kg. As metformin is highly distributed in erythrocytes, the blood mean terminal elimination half-life (t1/2) is notably higher (17.6 h) than the plasma t1/2 (1.5–4.9 h) [21, 23]. Metformin is only minimally bound to serum proteins (plasma protein-binding capacity 1.1–2.8%) and is not metabolized and is eliminated unchanged by the kidney through glomerular filtration and tubular secretion [18]. The last mechanism (involving the human organic cation transporter-2) accounts for most of metformin elimination and explains the high renal clearance of the drug (~450 mL/min). The elimination half-life ranges from 1.5 to 8.7 h and ~90% of the dose is excreted in urine within 12–24 h [24, 25]. When renal function is impaired, the clearance of metformin decreases in parallel with the decrease of eGFR. In patients with mild-to-moderate CKD, the plasma half-life of metformin can be notably prolonged and a dangerous accumulation can be observed in subjects with a severely impaired renal function (eGFR < 15 mL/min/1.73 m²) or in dialysis [24, 25]. As demonstrated by single-dose and steady-
FIGURE 1: Main tissue and organ targets of glucose-lowering drugs.
Table 1. Pharmacokinetics properties of main hypoglycaemic drugs and main modifications in CKD

<table>
<thead>
<tr>
<th>Class/Drug</th>
<th>Mechanism of action</th>
<th>Disadvantages/side effects</th>
<th>Usual Dose</th>
<th>Biotransformation and clearance</th>
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<tr>
<td>BIGUANIDES</td>
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| Metformin  | Decreases hepatic glucose production; increases insulin sensitivity; increases insulin-mediated utilization of glucose in peripheral tissues and decreases glucose intestinal absorption | -Diarrhoea  
-Abdominal pain  
-Vitamin B12 deficiency  
-Lactic acidosis (very rare) | 500–1000 mg orally one to three times daily | Eliminated unchanged by the kidney through glomerular filtration and tubular secretion and excreted in the urine (80%). No metabolite generation | Decrease in the clearance parallel to that of eGFR. Increase in the maximum serum concentrations in patients with moderate to severe CKD. Increase in the maximum serum concentrations in patients with moderate to severe CKD which can contribute to the development of hypoglycaemia | In CKD-3, the dosage should not exceed 1.5 g/day especially in the presence of acidosis, hypoxia, dehydration. Awaiting further pharmacokinetics data | Consider carefully |
| SULFONYLUREAS |                      |                           |            |                                 |                                   |                |                |
| Chlorpropamide | Stimulates insulin secretion from the pancreas; closes K-ATP channels on β-cell plasma membranes | -Hypoglycaemia (frequent)  
-Flush after alcohol ingestion  
-Hyponatremia  
-Increased cardiovascular risk and mortality  
-Hypoglycaemia  
-May be associated with increased cardiovascular risk and mortality  
-Sulphonamide allergy | 250–500 mg orally one daily | Eliminated almost exclusively by the kidney and excreted in the urine as unchanged drug and hydroxylated or hydrolyzed metabolites | Decrease in the clearance parallel to that of eGFR. Increase in the maximum serum concentrations in patients with moderate to severe CKD which can contribute to the development of hypoglycaemia. Increase in serum concentrations in patients with moderate to severe CKD which can contribute to the development of hypoglycaemia | Reduce dosage  
-In CKD-3: 100 to 125 mg daily  
-Avoid in CKD-4 | Contraindicated |
| Acetohexamide | Stimulates insulin secretion from the pancreas; closes K-ATP channels on β-cell plasma membranes | -Hypoglycaemia  
-May be associated with increased cardiovascular risk and mortality  
-Sulphonamide allergy | 500–750 mg orally one to two times daily | Eliminated almost exclusively by the kidney; it is excreted in the urine as hydroxylated or hydrolyzed metabolites | Decrease in the clearance parallel to that of eGFR. Increased serum concentrations in patients with moderate to severe CKD which can contribute to the development of hypoglycaemia | Contraindicated | Contraindicated |
| Tolazamide | Stimulates insulin release from pancreatic β cells; reduces glucose output from the liver; increases insulin secretion from the pancreas; decreases glucose output from the liver; reduces insulin sensitivity at peripheral target sites | -Hypoglycaemia  
-Increased cardiovascular risk and mortality  
-Sulphonamide allergy | 250–500 mg orally one to two times daily | Eliminated almost exclusively by the kidney; metabolized to active metabolites eliminated in the urine | Decrease in clearance parallel to that of eGFR. Increased serum concentrations in patients with moderate to severe CKD which can contribute to the development of hypoglycaemia | Contraindicated | Contraindicated |
| Tolbutamide | Stimulates pancreatic insulin secretion from the pancreas; closes K-ATP channels on β-cell plasma membranes | -Hypoglycaemia  
-Increased cardiovascular risk and mortality  
-Sulphonamide allergy | 1000–2000 mg orally one to two times daily | Liver metabolism to hydroxymethyltolbutamide (mildly active) and carboxytolbutamide (inactive); metabolites are excreted in urine and faeces | No variations | Preferably dose titration to 250 mg one to three times/day (especially in elderly patients) | Contraindicated |
| Glipizide | Stimulates insulin release from pancreatic β cells | -Hypoglycaemia  
-Gastrointestinal disturbances | 2.5–10 mg daily | Primarily eliminated by hepatic transformation into inactive metabolites; 80% excreted in urine, 10% excreted in faeces and 10% excreted unchanged | No active metabolites are excreted by the kidney | The drugs should be started at low doses and the dose titrated up every 1–4 weeks | Contraindicated |
| Gliclazide | Stimulates insulin release from pancreatic β cells | -Hypoglycaemia  
-Gastrointestinal disturbances | 40–240 mg daily | Hepatic transformation into several inactive metabolites; 60–70% excreted in urine, 10–20% excreted in faeces and 1% excreted unchanged | No active metabolites are excreted by the kidney | The drugs should be started at low doses and the dose titrated up every 1–4 weeks | Contraindicated |
| Glyburide/Glibenclamide | Stimulates insulin release from pancreatic β cells | -Hypoglycaemia  
-Cholestatic jaundice  
-Hepatitis  
-Increased transaminases  
-Allergic skin reactions  
-Hypoglycaemia  
-Nausea  
-Flu-like syndrome  
-Increased transaminases | 2.5–20 mg once daily | Metabolized in the liver to weakly active metabolites excreted in urine (50%) and bile/fece (50%) | Reduced urinary excretion of weakly active metabolites might prolong the hypoglycaemic effect | To be avoided | To be avoided |
| Glimepiride | Stimulates insulin release from pancreatic β cells  
-reduces glucose output from the liver | -Hypoglycaemia  
-May be associated with increased cardiovascular risk and mortality  
-Sulphonamide allergy | 2–4 mg once daily | Metabolized by oxidative biotransformation which generates two major metabolites: M1 (40% of glimepiride activity) and M2; 58% is excreted in urine, 35% excreted in feces and 5.5% excreted unchanged | Glimepiride serum levels increase as renal function decreases while M1 and M2 serum levels (mean AUC values) increase | Reduce dosage to 1 mg daily | To be avoided |
| Metformin  | Decreases hepatic glucose production; increases insulin sensitivity; increases insulin-mediated utilization of glucose in peripheral tissues and decreases glucose intestinal absorption | -Diarrhoea  
-Abdominal pain  
-Vitamin B12 deficiency  
-Lactic acidosis (very rare) | 500–1000 mg orally one to three times daily | Eliminated unchanged by the kidney through glomerular filtration and tubular secretion and excreted in the urine (80%). No metabolite generation | Decrease in the clearance parallel to that of eGFR. Increase in the maximum serum concentrations in patients with moderate to severe CKD. Increase in the maximum serum concentrations in patients with moderate to severe CKD which can contribute to the development of hypoglycaemia | In CKD-3, the dosage should not exceed 1.5 g/day especially in the presence of acidosis, hypoxia, dehydration. Awaiting further pharmacokinetics data | Consider carefully |
| Tolazamide | Stimulates insulin release from pancreatic β cells; reduces glucose output from the liver; increases insulin secretion from the pancreas; decreases glucose output from the liver; reduces insulin sensitivity at peripheral target sites | -Hypoglycaemia  
-Increased cardiovascular risk and mortality  
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-Allergic skin reactions  
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-Nausea  
-Flu-like syndrome  
-Increased transaminases | 2.5–20 mg once daily | Metabolized in the liver to weakly active metabolites excreted in urine (50%) and bile/fece (50%) | Reduced urinary excretion of weakly active metabolites might prolong the hypoglycaemic effect | To be avoided | To be avoided |
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-reduces glucose output from the liver | -Hypoglycaemia  
-May be associated with increased cardiovascular risk and mortality  
-Sulphonamide allergy | 2–4 mg once daily | Metabolized by oxidative biotransformation which generates two major metabolites: M1 (40% of glimepiride activity) and M2; 58% is excreted in urine, 35% excreted in feces and 5.5% excreted unchanged | Glimepiride serum levels increase as renal function decreases while M1 and M2 serum levels (mean AUC values) increase | Reduce dosage to 1 mg daily | To be avoided |

**NDT PERSPECTIVES**

Continued
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<td>GLUCOSIDASE INHIBITORS</td>
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<tr>
<td>Acarbose</td>
<td>Blocks the action of the α-glucosidase with reduced hydrolysis of complex saccharides.</td>
<td>- Flatulence - Diarrhoea</td>
<td>75–300 mg/day</td>
<td>Intestinal production of several metabolites, some of which biologically active. Intact acarbose excreted by the kidney</td>
<td>Severe renal impairment (eGFR &lt; 25 mL/min) increases plasma concentrations and plasma exposure</td>
<td>No evidence of dose adjustment required for GFR values higher than 25 mL/min</td>
<td>To be avoided</td>
</tr>
<tr>
<td>Miglitol</td>
<td>Blocks the action of the α-glucosidase with reduced hydrolysis of complex saccharides</td>
<td>-Flatulence - Diarrhoea</td>
<td>75–300 mg/day</td>
<td>Not metabolized. Excreted by the kidney as unchanged compound</td>
<td>Accumulates when renal function is impaired</td>
<td>No evidence available on efficacy and safety in the long term</td>
<td>No evidence available on efficacy and safety in the long term</td>
</tr>
<tr>
<td>Proglitazone</td>
<td>Reduces insulin resistance, increases glucose uptake in muscles and adipose tissue, decreases hepatic glucose production</td>
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<td>15–45 mg orally, once daily</td>
<td>Hepatic biotransformation produces active metabolites. Unchanged drug and metabolites are excreted in bile and faeces. About 15–30% of the dose is excreted in the urine</td>
<td>No changes</td>
<td>No dose adjustment necessary</td>
<td>No dose adjustment necessary</td>
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<td>DPP-IV INHIBITORS</td>
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<td>Sitagliptin</td>
<td>Inhibits DPP-4, which inactivates endogenous incretins</td>
<td>-Generally modest effect on HbA1c - Urticaria/angioedema -Pancreatitis</td>
<td>50 mg twice daily, orally</td>
<td>Hepatic metabolism. No generation of metabolites. Excreted in urine (87%) and feces (13%)</td>
<td>Plasma exposures and peak plasma concentrations increase as eGFR decreases</td>
<td>Reduce dosage - In CKD 3: 50 mg - In CKD 4: 25 mg</td>
<td>Reduce dosage to 25 mg. Administration irrespective of HD timing</td>
</tr>
<tr>
<td>Vildagliptin</td>
<td>Inhibits DPP-4, which inactivates endogenous incretins</td>
<td>Generally modest effect on HbA1c - Urticaria/angioedema -Pancreatitis</td>
<td>50 mg orally, once or twice daily</td>
<td>Tissue metabolism (hydrolysis) with generation of non-active metabolites; 85% of the dose is excreted via the kidney</td>
<td>Plasma exposure increases in CKD without relationships with eGFR -CKD 3–5: reduce dose to 50 mg once daily -CKD 1–2: no dose adjustment necessary</td>
<td>Reduce dosage to 50 mg once daily</td>
<td>Halve dosage to 2.5 mg once daily. Administration after HD session</td>
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<tr>
<td>Saxagliptin</td>
<td>Inhibits DPP-4, which inactivates endogenous incretins</td>
<td>Generally modest effect on HbA1c - Urticaria/angioedema -Pancreatitis</td>
<td>5 mg orally, once daily</td>
<td>Hepatic metabolism producing an active metabolite. Eliminated by both hepatic and renal (75%) routes. Approximately 95% of the administered dose is recovered in urine</td>
<td>Slight increase in plasma levels of inactive drug and active metabolite in CKD 1–2. Relevant increase in CKD 3–5</td>
<td>No dose adjustment necessary</td>
<td>No dose adjustment necessary</td>
</tr>
<tr>
<td>Linagliptin</td>
<td>Inhibits DPP-4, which inactivates endogenous incretins</td>
<td>Generally modest effect on HbA1c - Urticaria/angioedema -Pancreatitis</td>
<td>5 mg orally, once daily</td>
<td>No production of active metabolites by liver metabolism. 84.7% of the dose eliminated via the entero-hepatic system and 5.4% via the kidney</td>
<td>No increase in plasma exposure</td>
<td>No dose adjustment necessary</td>
<td>No dose adjustment necessary</td>
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<tr>
<td>Alogliptin</td>
<td>Inhibits DPP-4, which inactivates endogenous incretins</td>
<td>Generally modest effect on HbA1c - Urticaria/angioedema -Pancreatitis</td>
<td>25 mg orally, once daily</td>
<td>Production of two inactive metabolites by the liver. 60–70% of the dose eliminated through the renal route</td>
<td>1.7-, 2.3- and 3.2-fold increase in the patients with mild, moderate and severe renal impairment</td>
<td>-CKD 1–2: no dose adjustment necessary</td>
<td>Reduce dosage to 6.25 mg once daily</td>
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<tr>
<td>Saxagliptin</td>
<td>Inhibits DPP-4, which inactivates endogenous incretins</td>
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<td><strong>INCRETIN MIMETICS</strong></td>
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<td>Exenatide</td>
<td>Promotes glucose dependent insulin secretion by pancreatic β cells - suppresses glucagon secretion and slows gastric emptying</td>
<td>- Nausea/vomiting - Acute pancreatitis</td>
<td>5–10 mcg once/twice daily, subcutaneously</td>
<td>Clearance and degradation via the kidney. No active metabolites production</td>
<td>Renal clearance decreases progressively in CKD 2–5D. Plasma exposure is unchanged in CKD 1–3 and increase in CKD 4–5</td>
<td>- CKD 2–3: reduce dose to 5 mcg once/twice daily - CKD 4–5: to be avoided</td>
<td>Not recommended</td>
</tr>
<tr>
<td>Liraglutide</td>
<td>Promotes glucose-dependent insulin secretion by pancreatic β cells - suppresses glucagon secretion and slows gastric emptying</td>
<td>- Nausea/vomiting - Thyroid tumours</td>
<td>0.6–1.8 mg once daily, subcutaneously</td>
<td>Metabolization to inactive metabolites. Excretion via the kidney</td>
<td>Plasma exposure is unchanged in CKD</td>
<td>Limited experience</td>
<td>No experience available</td>
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<tr>
<td>Lixisenatide</td>
<td>Promotes glucose dependent insulin secretion by pancreatic β cells - suppresses glucagon secretion and slows gastric emptying</td>
<td>- Gastrointestinal disturbances</td>
<td>10–20 mcg, once daily, subcutaneously</td>
<td>Metabolisation to inactive peptides. Excretion via the kidney</td>
<td>Increase in plasma exposure (AUC) by 24% and 46% in subjects with moderate (GFR 30–50 mL/min) and severe (GFR 15–30 mL/min) renal impairment</td>
<td>No dose adjustment in patients with GFR 50–80 mL/min. Careful use in patients with GFR 50–15 mL/min</td>
<td>Limited experience</td>
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<td><strong>AMYLIN ANALOGUES</strong></td>
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<td>Pramlintide</td>
<td>Regulates glucose levels in response to food intake – controls gastric emptying and postprandial glucagon secretion - reduces food intake by increasing satiety</td>
<td>- Nausea/vomiting - Abdominal pain - Anorexia</td>
<td>30–120 mcg once to thrice daily, subcutaneously</td>
<td>Mainly metabolized by the kidney with the production of a biologically active metabolite. Excretion via the kidney</td>
<td>Unchanged exposure and clearance in patients with moderate to severe renal impairment (eGFR 20–50 mL/min)</td>
<td>Limited experience available</td>
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<td><strong>SGLT-2 INHIBITORS</strong></td>
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<td>Dapagliflozin</td>
<td>Blockade of the sodium-glucose transport protein subtype 2 with increased renal loss of glucose - tiredness - excessive weight loss - dehydration - urinary infections</td>
<td>- Pollakiuria - Nasopharyngitis - Constipation - Headache</td>
<td>5–10 mg once daily, orally</td>
<td>Metabolized partly in the kidney and partly in the liver with generation of active metabolites only if high doses are administered</td>
<td>Increased exposure (C_{\text{max}}) with decrease in renal function</td>
<td>Limited experience available</td>
<td>Limited experience available</td>
</tr>
<tr>
<td>Canagliflozin</td>
<td>Blockade of the sodium-glucose transport protein subtype 2 with increased renal loss of glucose - Hyperkalaemia - tiredness - Excessive weight loss - Dehydration - Urinary infections</td>
<td></td>
<td>100–300 mg once daily, orally</td>
<td>O-Glucuronidation is the major metabolic elimination pathway with generation of inactive metabolites. Approximately 33% of the dose is excreted in urine, mainly as O-glucuronide metabolites</td>
<td>Plasma AUC of is increased by approximately 15, 29, and 53% in subjects with mild, moderate and severe renal impairment</td>
<td>Reduced efficacy</td>
<td>To be avoided</td>
</tr>
<tr>
<td>Empagliflozin</td>
<td>Blockade of the sodium-glucose transport protein subtype 2 with increased renal loss of glucose</td>
<td></td>
<td>10–100 mg once daily, orally</td>
<td>Kidney, liver and tissue metabolism with no generation of active metabolites</td>
<td>AUC values increased by 18, 20, 66 and 48% in subjects with mild, moderate, severe renal impairment and ESKD</td>
<td>Reduced efficacy</td>
<td>Reduced efficacy</td>
</tr>
</tbody>
</table>

| NDT PERSPECTIVES | | | | | | | |
| 1290 P. Arnouts et al. | | | | | | | |
state pharmacokinetic assessment, the maximum serum concentration ($C_{\text{max}}$) and the AUC were increased to 173 and 390%, respectively, in patients with moderate-to-severe CKD (eGFR < 60 mL/min/1.73 m$^2$) compared with subjects with normal renal function [18]. In patients with impaired renal function (eGFR < 60 mL/min), a reduction in the daily dosage is recommended. However, recent evidence [26, 27] indicate a strong reduction in mortality in CKD 3 diabetic patients under metformin treatment. Metformin could therefore be used in this range of renal function, provided that the daily dose is decreased to no more than 1.5 g per day (eGFR > 45 mL/min) or 850 mg/day (eGFR between 30 and 45 mL/min) [28, 29]. It is important to realise that in CKD4 patients with unstable kidney function (e.g. during episodes of diarrhoea or of haemodynamic instability), it might be advisable to (temporarily) withhold the drug, as in these patients small absolute increases in GFR might result in large variations in serum concentration of metformin. The mechanism of metformin-associated lactic acidosis (MALA) includes the suppression of liver gluconeogenesis and lactate metabolism with consequent lactate accumulation [30]. Tissue hypoxia and dehydration are two important co-risk factors of MALA. Severe dehydration may cause acute renal failure, hypoperfusion and dysfunction of the liver. Metformin and lactate may then accumulate as a consequence of a combination of the decreased clearance by the liver (decreased gluconeogenesis) and the kidney (reduced urinary excretion) [30]. However, mortality in subjects who develop lactic acidosis is not associated with metformin levels, reflecting that the primary underlying causes of acidosis (e.g. hypoxia, haemodynamic compromise) than the metformin on itself are the major drivers of mortality [31].

Sulfonlureas bind pancreatic β-cells and stimulate insulin release independently from blood glucose concentrations [32]. As a consequence, the hypoglycaemic efficacy decreases over time when β-cell function is impaired [33, 34]. Sulfonlureas are strongly protein-bound (particularly to albumin) and their displacement by β-blockers, salicylates and warfarin can lead to hypoglycaemia [35]. The first generation of sulfonlureas (acetohexamide, chlorpropamide, tolazamide and tolbutamide) has been largely replaced by the second generation, which includes gliclazide, glimepiride, glipizide and glibenclamide (or glyburide). Sulfonlureas are usually well tolerated. Hypoglycaemia, the most common side effect, is more frequently observed with long-acting sulfonlureas (such as chlorpropamide and glyburide), especially in CKD patients because of the fall in renal gluconeogenesis and accumulation [36]. Nausea, skin reactions (including photosensitivity) and abnormal liver function tests represent other low-incidence side-effects.

Pharmacokinetics
First-generation sulfonlureas

Chlorpropamide. Chlorpropamide has a molecular weight of 276.74 Da. The drug interacts with ATP-sensitive potassium-channel receptors on the pancreatic cell surface, promoting the secretion of insulin [37]. Therapeutic dosage usually ranges from 250 to 500 mg daily. Chlorpropamide is rapidly absorbed in the gastrointestinal tract, reaching the highest circulating levels in 2–4 h. It is metabolized in the liver (~80%), primarily via CYP2C9, and the metabolites are mainly excreted in the urine [38]. The average biological half-life is 36 h.
In patients with renal impairment, due to the prolonged elimination, the dose should be reduced by 50% when the GFR is 90–30 mL/min and the drug should be avoided for GFR values <30 mL/min and in dialysis patients [39].

Acetohexamide. Acetohexamide is an intermediate-acting, first-generation oral sulfonylurea with a molecular weight of 324.40 Da. Acetohexamide is rapidly absorbed and extensively metabolized in the liver to the active metabolite hydroxyhexamidine, which exhibits greater hypoglycaemic potency than the parent drug and is believed to be responsible for prolonged hypoglycaemic effects. The drug is eliminated almost exclusively by the kidney and excreted in the urine as hydroxylated or hydrolyzed metabolites. These compounds can accumulate in patients with impaired kidney function, contributing to the development of hypoglycaemia [25].

Tolazamide. Tolazamide is usually administered at the therapeutic dose of 100–1000 mg/day with starting doses of 100–250 mg. The drug is rapidly well absorbed in the gastrointestinal tract, and the average biological half-life is 7 h [40]. Tolazamide is extensively metabolized in the liver with generation of five major active metabolites, which are principally excreted in the urine. Over a 5-day period, 85% of the administered dose of tolazamide is found in urine and only 7% in the faeces [41], making dose adaptations of this drug in patients with impaired renal function (CKD Stage 3–5 or in dialysis) necessary. However, precise data on how to obtain correct dose adaptation in function of renal impairment are not available, making the use of the drug in patients with advanced CKD not advisable.

Tolbutamide. Tolbutamide is usually administered at the therapeutic dose of 0.25–3 g/day, although a maintenance dose >2 g/day is rarely required or advised. Tolbutamide is rapidly absorbed in the gastrointestinal tract and detectable levels are present in the plasma within 20 min after oral ingestion, with peak levels occurring at 3–4 h. The half-life of tolbutamide is 4.5–6.5 h.

The metabolism of tolbutamide is mainly hepatic via CYP2C9 with the generation of hydroxymethyltolbutamide (mildly active) and carboxytolbutamide (inactive). It is excreted in urine (75–85%, primarily as metabolites) and faeces (15–25%) [42]. In patients with renal impairment dose, adjustment is not necessary but since the major risk associated with the use of tolbutamide is hypoglycaemia (which occurs more commonly than with other sulfonylureas), the use of this drug should not be recommended in this population.

Second-generation sulfonylureas

Glipizide. Glipizide is a 445.55 Da second-generation sulfonylurea usually administered at a daily dose of 2.5–10 mg. Peak plasma concentrations occur 1–3 h after a single oral dose and the elimination half-life ranges from 2 to 4 h in normal subjects, whether given intravenously or orally. Glipizide is metabolized primarily by hepatic transformation into several inactive metabolites by aromatic hydroxylation. A minor metabolite (<2% of the totally metabolized compound), an acetylamino-ethylbenzene derivative, is reported to have some hypoglycaemic activity [43]. Ten per cent of a dose is excreted as unchanged in urine and faeces, while ~90% is found as biotransformation products in urine (80%) and faeces (10%). Because glipizide is metabolized by the liver and primarily excreted in the urine as inactive metabolites, it can be used without dose adaptation in patients with advanced CKD or ESRD [43].

Gliclazide. Gliclazide is a 323.41 Da compound usually administered at the therapeutic dose of 40–240 mg/day with peak serum concentrations reached within 4–6 h and a half-life of 10–12 h. Gliclazide is highly bound to serum proteins (85–97%) and is eliminated primarily by hepatic transformation with generation of eight different inactive metabolites. Gliclazide is usually completely eliminated within 144 h post-dose. Faecal elimination accounts for ~11% of the administered dose, while ~70% is excreted in the urine. The renal clearance of unchanged total gliclazide is low (0.5 mL/min, ≤1% of the total administered dose), making it possible to use the drug in renal failure without any adjustment [44, 45]. However, no focus studies on CKD patients are available so far. Furthermore, and quite remarkably, the use of the modified release variety apparently does not lead to more hypoglycaemic episodes compared with the original variant [46].

Glimepiride. Glimepiride is a 490.63 Da second-generation sulfonylurea usually administered at a daily dose of 1–8 mg once daily. Glimepiride is eliminated primarily by hepatic oxidation to two major metabolites (M1 and M2). The M1 metabolite has ~33% activity of the parent compound. Less than 1% of the dose is excreted as the unchanged drug in urine, while ~99% is excreted as biotransformation products in urine (~60%) and faeces (~40%) [47]. In patients with renal insufficiency, M1 and M2 serum levels (mean AUC values) increase as renal function decreases [47]. Since the M1 metabolite has mild hypoglycaemic activity, a starting dose of 1 mg may be given to diabetic CKD patients while maintenance doses need to be titrated on fasting blood glucose levels.

Glyburide/glibenclamide. Glyburide is usually administered at a daily dose of 2.5 to 20 mg. The blood glucose-lowering effect persists for 24 h following single doses in non-fasting diabetic patients. The terminal half-life is ~10 h. The drug undergoes extensive hepatic metabolism to three major metabolites, one of which (four hydroxyglibenclamide) has ~15% of the power of glibenclamide. Metabolites are eliminated by the biliary (50%) and renal (50%) routes [48]; this dual excretory pathway is qualitatively different from that of other sulfonylureas, which are largely excreted in the urine [49]. The use of glyburide in patients with advanced renal impairment demands caution since several reports showed an increased risk of hypoglycaemia, presumably due to the effects of the accumulating active metabolite [50–53].

Gliquidone. Gliquidone is administered at a dose of 45–60 mg, twice to thrice daily. The peak plasma concentration occurs after 2–3 h and the elimination half-life is ~1.5 h. Gliquidone is converted in the liver via hydroxylation and demethylation to largely inactive metabolites, and these metabolic processes are maintained even in patients with hepatic insufficiency [54]. Ninety-five per cent of the gliquidone dose is excreted via bile in the faeces. Less than 5% of the gliquidone dose is eliminated by the renal route [25, 54]. The pharmacokinetic characteristics of gliquidone are equivalent in persons with
and without renal dysfunction [25]. Therefore, although specific studies in CKD individuals are still lacking, in principle no dose adjustments are needed in CKD 3–5 [25].

MEGLITINIDES

Meglitinides (repaglinide, nateglinide) stimulate pancreatic insulin secretion by closing K-ATP channels on β-cell plasma membranes, in a similar manner to sulfonylureas but at a separate binding site. As insulin secretagogues these drugs therefore reduce post-prandial glucose excursion. Common side-effects of meglitinides are hypoglycaemia and weight gain. In addition they have the disadvantage of the need for a frequent dosing schedule.

Pharmacokinetics

Repaglinide. Repaglinide is a compound with a molecular weight of 452.6 Da. It is usually administered with each meal preprandially at a daily dose of 0.5–12 mg. The peak serum level is reached within 30–60 minutes, and the mean absolute bioavailability is 56%. The drug circulates almost totally bound to proteins (98%) with an elimination half-life of 0.5–1 h [55]. Inactive metabolites (M2, a dicarboxylic acid, M1, an aromatic amine and M7, an acyl glucuronide) are generated in the liver by CYP2C8 (70%) and CYP3A4 (30%) and mainly excreted via the bile (∼90%) with M2 accounting for 60% of the administered dose. Only 8% of a given dose of repaglinide is usually excreted in the urine and <2% of the parent drug is recovered in faeces. In CKD Stage 2–3, repaglinide maintains the same pharmacokinetic characteristics as seen in diabetics with normal renal function [56]. In patients with an eGFR <30 mL/min, repaglinide shows a 4-fold increase in half-life after 1 week of treatment and an increased AUC when compared with subjects with normal renal function. However, no difference in maximal plasma concentrations was observed, thus suggesting that CKD somewhat affects metabolism and hepatic clearance of repaglinide, rather than its bioavailability [56]. Nevertheless, no relationship was found between the degree of renal impairment and the risk of hypoglycaemia in patients who were treated with this drug [56]. Initial dose adjustment is not necessary for patients with mild-to-moderate renal dysfunction. However, in the absence of specific studies, doses should be carefully titrated in patients with severe renal function impairment or on dialysis.

Nateglinide. Nateglinide is a 317.43 Da amino acid derivative, administered at a dose of 60–360 mg/day. Following oral administration, nateglinide is rapidly absorbed with the mean peak plasma drug concentrations generally occurring within 1 h after dosing. Absolute bioavailability is estimated to be ∼73% and the elimination half-life is ∼1.2–1.8 h [57]. Nateglinide is extensively bound (98%) to serum proteins, primarily serum albumin, and is predominantly metabolized by CYP2C9 (70%) and CYP3A4 (30%). The main metabolites exert hypoglycaemic effects and the prolonged half-life can then result in hypoglycaemic episodes. Eighty-three per cent of the drug appears in the urine, primarily as metabolites, with only ∼16% as parent drug. Ten per cent appears in faeces. Compared with healthy matched subjects, patients with moderate-to-severe renal insufficiency (eGFR 15–50 mL/min) not on dialysis displayed an apparently similar clearance, AUC and Cmax [58]. In these subjects, it would be preferable to start therapy at the lowest doses (60 mg/day). Conversely, patients on dialysis exhibited reduced overall drug exposure; the drug should therefore be avoided in this population [58].

A-GLUCOSIDASE INHIBITORS

α-Glucosidase inhibitor drugs (acarbose, miglitol) block the action of the homonymous enzyme located in the brush border of the small intestine, which is involved in the hydrolysis of oligosaccharides, trisaccharides and disaccharides into glucose and other monosaccharides [59]. The selective inhibition of this enzyme decreases glucose generation and delays its absorption, consequently reducing postprandial glucose variations without affecting insulin secretion and without inducing an increased risk of hypoglycaemia. Although effective and safe, these drugs are often associated with gastrointestinal side-effects such as flatulence and diarrhea and need a frequent dosing schedule.

Pharmacokinetics

Acarbose. Acarbose is a complex oligosaccharide with a molecular weight of 645.6 Da. In addition to the α-glucosidase inhibition, acarbose exerts a reversible inhibition of the pancreatic enzyme α-amylase, which metabolizes complex starches to oligosaccharides in the lumen of the small intestine. Acarbose is orally administered at a dose of 75 to 300 mg/day, usually before each meal. Metabolism by intestinal bacteria and enzymatic hydrolysis produce over 13 metabolites, at least one of which has some biological activity. Only a small amount of the drug (∼34% of the dose) is absorbed and the bioavailability is very low [60]. The peak plasma concentrations are achieved ∼1 h after administration. Intact acarbose is almost completely excreted by the kidney with an elimination half-life of ∼2 h. Less than 2% of the starting dose is recovered in the urine as an active drug (intact compound and active metabolite) [61]. In patients with impaired renal function, the plasma levels of acarbose and its metabolites increase by several folds. Patients with severe renal impairment (eGFR < 25 mL/min) can attain peak plasma concentrations and plasma exposure of acarbose, respectively, five times and six times higher than the subjects with normal renal function [62].

Miglitol. Miglitol is an oligosaccharide compound soluble in water with a molecular weight of 207.2 Da. The drug is orally administered at the therapeutic dose of 75–300 mg/day with a variable absorption suggesting the existence of a dose-dependent saturation mechanism (a dose of 25 mg is fully absorbed versus only 50–70% of a 100 mg dose). Plasma peak concentrations are achieved in 2–3 h [63]. Miglitol is only minimally protein bound (<4%) and is not metabolized. The plasma elimination half-life ranges from 0.4 to 2 h and the

Glucose-lowering drugs in CKD
drug is mainly excreted by the kidney as unchanged compound. Over 95% of a 25 mg dose is recovered in the urine [63]. Miglitol accumulates when renal function is compromised. Subjects with eGFR < 25 mL/min assuming 75 mg of miglitol (25 mg/thrice daily) had a 2-fold higher plasma exposure compared to subjects with eGFR > 60 mL/min [64]. There are no long-term studies testing the efficacy and safety of miglitol in CKD populations.

### THIAZOLIDIDINEDIONES (GLITAZONES)

Thiazolidinedione compounds, or glitazones, are insulin sensitizers. These compounds reduce insulin resistance, increase glucose uptake in muscles and adipose tissue and decrease hepatic glucose production [65]. Glitazones target specific peroxisome proliferator-activated receptors (PPARs). When activated, these receptors bind to DNA and, in complex with the retinoid X receptor, modulate generic transcription. Gene modulation improves insulin responsiveness, increases glucose transport, glucose oxidation and glycogen synthesis in the skeletal muscle. In addition, glitazones preserve pancreatic β-cell function, increase adipogenesis, fatty acid uptake and lipogenesis and reduce gluconeogenesis and plasma-free fatty acids levels [65].

**Pharmacokinetics**

**Pioglitazone.** Due to a high incidence of hepatitis, hepatic failure [66] and a suggestion of increased cardiovascular events [67, 68] troglitazone was withdrawn from the market worldwide, while rosiglitazone is currently available only in the US. Therefore, pioglitazone is the only thiazolidinedione compound currently available for clinical use in European countries (except for Germany and France). The drug is a high-molecular weight (392 Da), hydrophobic compound, usually administered once daily at a therapeutic dose of 15–45 mg/day with a high oral bioavailability (83%). Peak concentrations are observed within 2 h. Food slightly delays the time to peak serum concentration to 3–4 h, but does not alter the degree of absorption. $C_{\text{max}}$ increases proportionally at doses of 15 mg and 30 mg per day and the half-life is 5.4 h. The volume of distribution following single-dose administration is about 0.63 L/kg of body weight [69]. Pioglitazone is highly (>98%) protein bound (principally to albumin) and extensively metabolized by the liver via CYP3A4, CYP2C8/9 and CYP4A12. Thus, activators or inhibitors of these CYPs may interact with pioglitazone. Oxidation and hydroxylation produce active metabolites including M-II, M-IV and M-III, whose hypoglycaemic power is reduced by 40–60% with respect of the unmetabolized drug. The mean $t^{1/2}$ of pioglitazone and pioglitazone inclusive of its metabolites is 3–7 h and 16–24 h respectively [69]. After oral administration of the drug, both pioglitazone and its metabolites are excreted predominantly in bile and faeces, while about 15–30% of the dose is found in the urine with an estimated renal clearance of 5–7 L/h [70]. Because of the high molecular weight, high protein-binding capacity and hepatic metabolism, the pharmacokinetic profile of pioglitazone, is similar in subjects with normal or impaired renal function, remaining unaffected even by hemodialysis [70]. Therefore, no dose adjustment is usually required in the presence of CKD. No specific data are known regarding possible differences in fluid retention between subjects with a normal renal function and those with progressive renal insufficiency. Nevertheless, a higher risk of congestive heart failure due to chronic fluid overload might be hypothesized, particularly in CKD patients with cardiac comorbidities.

**Sitagliptin.** Sitagliptin is a highly selective DPP-4 inhibitor, orally administered once daily at the therapeutic dose of 100 mg. After administration, sitagliptin is rapidly absorbed, with peak plasma concentrations occurring after 1–4 h [73]. The drug has a very good bioavailability (87%), long half-life ($t^{1/2}$: 12.4 h) and a distribution volume of 198 l. The hepatic metabolism by CYP3A4 and CYP2C8 is limited and does not produce active metabolites [74]. Sitagliptin is therefore excreted mostly unchanged in urine (87%) and feces (13%). The fraction reversibly bound to proteins is 34–43%. Despite the high molecular weight (523.32 Da), sitagliptin is predominantly eliminated by the kidney through both glomerular filtration and tubular secretion (via the human organic anion transporter-3), as suggested by the high clearance (350 mL/min) [75]. Therefore, the drug tends to accumulate when renal function decreases. In mild-to-moderate CKD, the $C_{\text{max}}$ increases by 1.4- to 1.8-fold [75, 76]. Compared to subjects with normal renal function, patients with eGFR 30–50 mL/min, <30 mL/min or ESRD on dialysis have plasma sitagliptin levels 2.3-, 3.8- and 4.5-fold higher, respectively [75, 76]. Furthermore, $t^{1/2}$ raises to 16.1, 19.1, 22.5 and 28.4 h when the eGFR is reduced to 50–80 mL/min, 30–50 mL/min, <30 mL/min and in haemodialysis patients, respectively [75, 76]. Dose adjustment is therefore necessary in both CKD and ESRD to avoid drug accumulation. Since haemodialysis does not affect sitagliptin levels to a significant extent (only 13.5% is removed if HD is started 4 h after administration), the drug can be administered irrespective of HD timing [76]. Furthermore, in...
a recent 54-week randomized trial of HD patients, dose-adjusted sitagliptin treatment was generally well tolerated and provided clinically meaningful reductions from baseline in haemoglobin A1c and fasting plasma glucose levels [77].

**Vildagliptin.** Vildagliptin is a 303.40 Da powerful DPP-4 blocker, holding an inhibitory concentration 50% (IC50) notably lower (4.5 nM) with respect to sitagliptin (26 nM) [78]. It is usually administered at the therapeutic dose of 50 mg twice daily. Absorption and bioavailability are both very high (>85%), while the half-life is low (2–3 h). The estimated volume of distribution is 71 L [79]. In plasma, the drug circulates unchanged or as a not biologically active metabolite (M20.7) produced by cytochrome P450. The fraction bound to proteins is relatively low (9.3%). The main routes of clearance are hydrolysis by multiple tissues/organs and the kidneys (75%; renal clearance 13 L/h) [79]. Concentrations of the main metabolite M20.7 tend to increase with decreasing eGFR without producing biological effects. Somewhat in contrast to this finding, although the elimination half-life of vildagliptin is not influenced by renal function, the exposure to vildagliptin is increased in patients with CKD (Cmax 8–66%) compared with subjects with normal renal function [80]. However, no correlations have been found between vildagliptin levels and severity of renal impairment, probably because the kidneys contribute to both the excretion and metabolism (by hydrolysis) of the drug [79]. Pooled data from large databases suggest that the drug is well tolerated in CKD Stage 2, so that no dose adjustment is usually required in these patients [80]. In CKD Stage 3–5D, a reduction in the dosage (50 mg once daily) is enough for keeping a satisfactory, safety and efficacy profile [81, 82]. Accordingly, in a recent randomized, controlled trial (RCT) [83], 50 mg of vildagliptin once daily in addition to standard hypoglycaemic therapy showed good efficacy and tolerance over a 1-year follow-up in diabetic subjects with moderate (eGFR 30–60 mL/min) or severe (eGFR < 30 mL/min) renal impairment.

**Saxagliptin.** Saxagliptin is a 333.43 Da, long-acting DPP-4 inhibitor usually administered once daily at the therapeutic dose of 5 mg. Although the overall half-life is short, metabolism of saxagliptin (mainly by CYP3A4/5) produces an active metabolite (5-hydroxy saxagliptin) which keeps 50% of the power of the primary drug. After administration, the absorption is 67% and the Tmax is 2 h for saxagliptin and 4 h for its active metabolite. Tmax is slightly accelerated by the co-administration of a high-fat meal [84]. Plasma Cmax values of saxagliptin and the active metabolite are 24 and 47 ng/mL, respectively. The fraction of the drug bound to proteins is very low. Saxagliptin is eliminated by both hepatic and renal (75%) routes and ~95% of the administered dose is recovered in urine [84]. Because a mild renal impairment (eGFR 50–80 mL/min) produces only a slight increase in the AUCs of saxagliptin (1.2-fold) and its active metabolite (1.7-fold), dosage adjustment is not usually needed in CKD Stage 1–2 [85, 86]. When a moderate renal impairment (30–50 mL/min) is present, the AUCs of saxagliptin and its active metabolite are 1.4- and 2.9-fold higher, becoming 2.1- and 4.5-fold higher in the presence of severe renal impairment (eGFR < 30 mL/min) [86]. Therefore, in order to achieve and keep plasma levels similar to those in patients with normal renal function, the starting dose should be halved to 2.5 mg/daily in CKD Stage 3–5D. In a RCT of 170 diabetic subjects with eGFR < 50 mL/min, including patients on haemodialysis, 2.5 mg of saxagliptin once daily offered sustained efficacy and good tolerability with no difference in the frequency of hypoglycaemic episodes compared with placebo [87]. Saxagliptin should be taken after the dialysis session since a single 4 h dialysis session removes 23% of the dose [86].

**Linagliptin.** Linagliptin is a 472.54 Da DPP-4 inhibitor administered at the therapeutic dose of 5 mg once daily. The drug has relatively low absorption and bioavailability (~30%) and, unlike the other DPP-4 inhibitors, is highly protein-bound (>80%) [88]. The half-life is long and drug metabolism produces several inactive metabolites. The main one (CD1790) partly contributes to the overall disposition and elimination of linagliptin. Nearly 85% of the ingested dose undergoes faecal excretion via the entero-hepatic system, while renal excretion accounts for only 5.4% of the dose [88, 89]. As renal excretion is a minor elimination pathway of linagliptin at therapeutic dose levels (<1% of unchanged linagliptin appears in urine), no dose adjustments are required in the presence of impaired renal function [89].

**Alogliptin.** Alogliptin is a 339.39 Da highly selective DPP-4 inhibitor administered at a daily dose of 25 mg once daily. After oral administration, alogliptin is rapidly absorbed (median Tmax, 1–2 h) with a 100% bioavailability, a modest protein binding (20%) and a limited metabolism which occurs mainly in the liver (CYP2D6- and 3A4-mediated). The two inactive compounds generated accounted for <2 and <6%, respectively, of total alogliptin concentrations in plasma and urine. The half-life ranges from 12 to 21 h and the excretion is mainly through the renal route (60–70%) [90]. A 1.7-, 2.1- and 3.2-fold increase in alogliptin exposure is observed in patients with mild, moderate and severe renal impairment [91]. No dose adjustment is therefore necessary with eGFR ≥60 mL/min while the daily dose should be reduced to 12.5 mg and 6.25 mg/daily in patients with eGFR 30–60 and <30 mL/min respectively. In a prospective, open-label study of 30 haemodialysis patients, 6.25 mg/day of alogliptin (administered without regard to the timing of dialysis) as monotherapy or in combination with other oral antidiabetic agents improved glycaemic control and were generally well tolerated over a 48-week period [92].

**INCRETIN MIMETICS**

Unlike DPP-4 inhibitors, which prolong endogenous incretin hormones activity by limiting their enzymatic degradation, incretin mimetics (exenatide, liraglutide and lixisenatide) are peptides endowed with direct incretin capacity, as they promote glucose-dependent insulin secretion by pancreatic β-cells, suppress glucagon secretion and slow gastric emptying.
**Pharmacokinetics**

**Exenatide.** Exenatide is a 4186.6 Da peptide with a 39-amino acid sequence partially overlapping that of human GLP-1. The drug is administered subcutaneously with a starting dose of 5 mcg twice daily, to be increased to the dose regimen of 10 mcg twice daily. Peak plasma concentrations are achieved in about 2 h. C_{max} and AUC increased proportionally with the increase of dose administered. After administration of a 10 mcg dose, the volume of distribution is 28.3 L [93]. The kidney is the major route for clearance (via glomerular filtration) and degradation of exenatide into small, biologically inactive peptide fragments [94]. Independent of the dose administered, the mean apparent clearance of exenatide in healthy subjects is 9.1 L/h and the mean terminal half-life is 2.4 h. Exenatide exposure is unchanged in the presence of a mild-to-moderate renal impairment (eGFR 30–80 mL/min), while the AUC increases in CKD Stages 4 and 5 by 1.63- and 6.25-fold, respectively, compared with subjects with normal renal function [95]. In CKD-2 and -3, renal clearance of Exenatide decreases by 13 and 36%, respectively, becoming only 0.9 L/h in CKD-5D (compared with 9.1 L/h in healthy subjects). In order to achieve and keep therapeutic exposures, no dose adjustment is therefore necessary in CKD-2, while caution is required in CKD-3 when initiating or escalating doses from 5 to 10 mcg. Exenatide treatment should be avoided in CKD-4, -5, -SD. Moreover, dialysis patients apparently are not able to tolerate even 5 mcg of Exenatide due to severe gastrointestinal side effects [95]. Although there is no evidence that exenatide may directly produce renal toxicity, several cases of acute renal impairment or renal failure have been reported to the FDA [96]. Renal function should therefore be monitored regularly in all patients receiving exenatide, particularly in those at risk of renal function worsening, e.g. experiencing nausea, vomiting or having transient hypovolaemia or reduced fluid intake.

**Liraglutide.** Liraglutide is an incretin peptide with a high degree of sequence identity (97%) to human GLP-1 [97]. Given the extremely long half-life (13 h), it is usually administered once daily at the starting dose of 0.6 mg that can be increased up to 1.8 mg. The C_{max} (35 ng/mL for a 0.6 mg dose) is usually reached in 8–12 h with an AUC of 960 ng·h/mL [98]. The bioavailability after subcutaneous administration is 55% with a mean apparent volume of distribution of ~13 L [98]. Liraglutide circulates extensively bound to plasma protein (~99%; especially to albumin) and, unlike exenatide, is metabolized by the whole body without a specific organ of elimination. The renal clearance of liraglutide is extremely low (1.2 L/h) and only a small percentage (~5%) of biologically inactive metabolites can be found in urine, while the intact peptide is usually not detectable [98]. Compared with healthy subjects, plasma exposure in CKD Stage 2–5 is on average 35, 19, 29 and 30% lower, respectively [99]. Liraglutide treatment seems to be safe and well tolerated in patients with mild renal impairment [100] with no dose adjustment. Conversely, scarce experience is available in patients with more compromised renal function.

**Lixisenatide.** Lixisenatide is administered subcutaneously, once daily, before one of the main meals at the starting dose of 10 mcg which can be increased up to 20 mcg as maintenance dose. Absorption is rapid and the median T_{max} is 1–3.5 h. Lixisenatide is only moderately bound to human proteins (55%) and the apparent volume of distribution after subcutaneous administration is ~100 L [101]. The drug is eliminated via glomerular filtration (with a mean apparent clearance of about 35 L/h), followed by tubular reabsorption and metabolic degradation with generation of small and inactive peptides. Mild renal impairment does not influence pharmacokinetics or tolerability of lixisenatide [102]. Therefore, no dose adjustment is required for patients with GFR 50–80 mL/min. Conversely, in subjects with moderate (GFR 30–50 mL/min) and severe (GFR 15–30 mL/min) renal impairment the AUC is increased by 24 and 46% respectively. There is limited therapeutic experience in moderate and advanced CKD, so in these patients, the drug should only be used with great caution.

**Amylin Analogues**

Amylin is a neuroendocrine hormone synthesized and accumulated in pancreatic β-cells and co-released with insulin, which regulates glucose levels in response to food intake, controls gastric emptying and postprandial glucagon secretion and reduces food intake by increasing satiety [103]. Pramlintide is a synthetic analogue of amylin which differs from the original peptide in 3 amino-acids administered to type 1 and 2 diabetic patients already receiving insulin in order to improve glycaemic control.

**Pharmacokinetics**

Pramlintide is administered once to thrice daily by subcutaneous injection with a therapeutic dose ranging from 30 to 120 mcg/day. The absolute bioavailability is ~30–40%. The AUC of a 30 mcg dose is 3750 (pmol·min/L) with a C_{max} of 39 pmol/L, a T_{max} of 21 min and an elimination half-life of 55 min. AUC and C_{max} increase in parallel, while T_{max} and the half-life tend to be similar with respect to the dose administered [104]. Approximately 40% of the drug circulates unbound in plasma. Pramlintide is mainly metabolized by the kidney with the production of a biologically active metabolite (2–37 pramlintide) which holds a similar half-life (48 min) [104]. In patients with moderate-to-severe renal impairment (eGFR 20–50 mL/min) pramlintide exposure and clearance are unchanged [104]. No data are currently available for dialysis patients.

**Sodium Glucose Co-Transporter-2 (SGLT-2) Inhibitors**

Sodium glucose co-transporter-2 (SGLT-2) inhibitors (dapagliflozin, canagliflozin, empagliflozin) block the activation of the sodium–glucose transport proteins subtype 2, a tubular carrier which reabsorbs 90% of the glucose filtered in the glomerulus, thus leading to an increased loss of blood glucose
through the urine [105]. Since the affinity to the SGLT-1 (intestinal subtype) is very low, these drugs do not interfere with glucose absorption at the intestinal level. Human studies have confirmed the efficacy of SGLT2 inhibitors in improving glycaemic control with a low risk of hypoglycaemia plus several pleiotropic effects, including weight loss, the potential of lowering of blood pressure and an improvement in the metabolic milieu (e.g. triglycerides, uric acid and HDL levels) [106].

Adverse effects of SGLT-2 inhibitors are mostly represented by tiredness, dehydration and appearing/worsening of urogenital infections. Dapagliflozin received marketing authorization by the European Medicines Agency, while canagliflozin has been authorized more recently by the Food and Drug Administration (FDA). Both drugs have been approved for the treatment of DM-2.

**Pharmacokinetics**

**Dapagliflozin.** Dapagliflozin is a C-glucoside chemical compound administered at a dose of 5–10 mg once daily alone or in combination with other anti-DM medications, insulin included. The drug is rapidly absorbed after oral administration and circulates highly bound to plasma proteins (91%) [107]. The half-life is long (13.8 ± 9.4 h) and the metabolism is partly renal and partly hepatic by the uridine diphosphate–glucuronosyl transferase 1A9, which converts the parent drug into non-pharmacologically active glucuronides [107]. Active metabolites seem to be generated only if administered doses are >50 mg. Dapagliflozin and its metabolites are only minimally eliminated by the kidney [108], but in patients with impaired renal function plasma concentrations of dapagliflozin increased in parallel with declining kidney function [109]. The $C_{\text{max}}$ of the drug is 4, 6 and 9% higher in patients with mild, moderate and severe renal impairment, respectively, when compared with diabetic subjects with normal function. The glucose-lowering effect is also reduced in the presence of an impaired renal function with an estimated decrease in renal glucose clearance of 42, 83 and 84% in patients with mild, moderate or severe renal impairment, respectively. Hence, dapagliflozin seems to have a reduced efficacy if CKD is present while no long-term data on safety are yet available.

**Canagliflozin.** Canagliflozin is administered once daily at a dose of 100–300 mg, usually before the first meal of the day. Peak plasma concentrations occur within 1–2 h. The apparent terminal half-life ($t_{1/2}$) is 10.6 and 13.1 h for the 100 mg and 300 mg doses, respectively [110]. The mean absolute oral bioavailability of canagliflozin is ~65%. Canagliflozin is broadly bound to proteins in plasma (99%), mainly to albumin, and O-glucuronidation is the major metabolic elimination pathway with generation of inactive metabolites. Approximately 33% of the administered dose is excreted in urine, mainly as O-glucuronide metabolites (30.5%). Renal clearance of canagliflozin 100 mg and 300 mg doses ranges from 1.30 to 1.55 mL/min [111]. Compared with healthy subjects plasma AUC of canagliflozin is increased by ~15, 29, and 53% in subjects with mild, moderate and severe renal impairment, respectively, but is similar for ESRD and healthy subjects [110]. Nevertheless, in a 52-week, randomized, double-blind, placebo-controlled, Phase 3 study, patients with CKD Stage 3 (eGFR ≥30 and <50 mL/min/1.73 m²) receiving 100–300 mg of canagliflozin had less overall glycaemic efficacy and had a higher occurrence of adverse reactions related to reduced intravascular volume, renal-related adverse reactions (such as hyperkalaemia) and decreases in eGFR compared with patients with mild renal impairment or normal renal function (eGFR ≥ 60 mL/min/1.73 m²) [112]. In patients with more advanced CKD or in dialysis, canagliflozin should be avoided because under these conditions, it can be dangerous and is not efficacious [113].

**Empagliflozin.** Empagliflozin is a novel SGLT-2 inhibitor, very close to be introduced in the market. Phase II and III trials have demonstrated a good efficacy and safety profile after administration of single or ascending doses (10–100 mg/day) and a stable pharmacokinetic profile characterized by a rapid absorption, peak levels 1.5–3.0 h after dosing, a biphasic decline and a mean terminal elimination half-life ranging from 10 to 19 h [114]. In a recent study [115], the maximum empagliflozin plasma concentrations attained after a single 50 mg dose were not different in subjects with different degrees of renal impairment compared with subjects with normal renal function, while AUC values increased by 18, 20, 66 and 48% in subjects with mild, moderate, severe renal impairment and end-stage kidney disease, respectively. Although the safety profile was not influenced by the presence/absence or severity of CKD, the ability to induce urinary glucose elimination decreased with decreasing renal function. Therefore, even though in principle no dose adjustment would be required in CKD patients, concerns arise about the efficacy of empagliflozin in patients with more impaired renal function.

**CONCLUSIONS**

Drug dosing is a challenging problem in diabetic-CKD patients. Although a large panel of glucose-lowering agents are currently available to clinicians for the improvement of glycaemic control, it should always be kept in mind that CKD can potentially influence the pharmacokinetics of every therapeutic agent through different mechanisms. For glucose-lowering drugs, this translates into an enhanced risk for hypoglycaemia, side effects and drug-to-drug interactions. Unfortunately, many hypoglycaemic drugs have not been extensively tested yet in CKD population, so that focused studies are eagerly awaited in order to shed light on the true efficacy and safety profile of these drugs in the presence of different degrees of renal impairment. Nevertheless, the proper assessment of renal function, especially in fragile subjects, is a prerequisite for choosing the best therapeutic option. Similarly, renal function should be carefully and periodically monitored during treatment to detect changes that may affect drug metabolism/excretion. In the presence of CKD, drugs undergoing hepatic metabolism or non-renal excretion should probably be preferred. Conversely, if a drug with prevalent renal metabolism has to be implemented, the dosage should be adequately adjusted according to the eGFR. Even though these recommendations are mostly based on...
pharmacokinetic studies in CKD, and may thus be misleading, they still represent a suitable, pragmatic solution in the absence of targeted studies.

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CONFLICT OF INTEREST

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DISCLAIMER

The present text is based upon the information available to the guideline development group at the moment of the preparation of this publication. It has been designed to provide information and assist in decision making, but is not intended to define a standard of care or to improve an exclusive course of treatment. Individual decision making is essential in the approach to any disease and thus also diabetes and advanced CKD. Variations in practice are inevitable when physicians take into account individual patient needs, available resources and limitations specific for a geographical area, country, institution or type of practice. In addition, evidence may change over time as new information becomes available, so that practice may be modified subsequently. Every practitioner using this text is responsible for its application to any particular clinical situation.

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