View metadata, citation and similar papers at core.ac.uk
brought to you by CORE
provided by Via Medica Journals



Endokrynologia Polska
DOI: 10.5603/EP.a2019.0064
Volume/Tom 71; Number/Numer 1/2020
ISSN 0423–104X

# Diagnosis and treatment of type 2 diabetes mellitus in patients with chronic kidney disease and eGFR < 60 mL/min — a position statement of the Polish Society of Nephrology Working Group on Metabolic and Endocrine Disorders in Kidney Diseases

*Tomasz Stompór[1], Marcin Adamczak[2], Anna Masajtis-Zagajewska[3], Oktawia Mazanowska[4], Katarzyna Maziarska[4], Agnieszka Witkowska[2], Andrzej Więcek[2]*

[1]*Department of Internal Medicine, Clinic of Nephrology, Hypertension, and Internal Diseases, University of Warmia and Mazury, Olsztyn, Poland*
[2]*Department of Nephrology, Transplantation, and Internal Medicine, Medical University of Silesia, Katowice, Poland*
[3]*Department of Nephrology, Hypertension, and Kidney Transplantation, Medical University of Lodz, Lodz, Poland*
[4]*Department and Clinic of Nephrology and Transplant Medicine, Wroclaw Medical University, Wroclaw, Poland*

**Abstract**
Diabetes mellitus is one the most frequent co-morbid conditions in patients with chronic kidney disease (CKD), frequently leading to chronic kidney failure. Progression of CKD accelerates several metabolic disorders, predominantly those related to abnormalities of carbohydrate metabolism. Patients with CKD are usually characterised by an insulin resistance additionally aggravated by several co-morbid conditions (for example chronic low-grade inflammation). Treatment with anti-diabetic medications in patients with CKD remains a challenge because, along with the disease progression, the dosing of several drugs needs to be adjusted to the reduced kidney function (especially those that are excreted intact with urine or as active metabolites). Progression of CKD also increases the risk of hypoglycaemia in patients treated with anti-diabetic drugs, and other adverse drug reactions may occur more frequently. Usefulness of the new generation drugs has not yet been verified in patients with advanced kidney disease (although some of them act through kidney-related mechanisms). The current position statement of the Polish Society of Nephrology Working Group provides practical recommendations for the diagnosis and treatment of type 2 diabetes mellitus in patients with CKD and reduced kidney function. **(Endokrynol Pol 2020; 71 (1): 3–14)**

**Key words:** *type 2 diabetes mellitus; chronic kidney disease; glucose metabolism; oral anti-diabetic drugs; incretin-based therapy; insulin; adverse events*

## Introduction

It is estimated that 8 to 9% of the world population suffers from diabetes mellitus (in up to 90% of them it is classified as diabetes type 2 — T2D) [1]. Epidemiological analyses suggest that in 15–20% of diabetic patients the glomerular filtration rate (GFR) is lower than 60 mL/min/1.73 m$^2$ [2–4].-

Chronic kidney disease (classified according to KDIGO into stages 1–5), in particular — stages 3a–5, may significantly worsen metabolic regulations in diabetic patients and influence the efficacy and safety of several glucose-lowering drugs. The aim of this Position Statement paper is to analyse and discuss the differences in the clinical course, diagnosis, and treatment of T2D in patients with CKD. Our statement is largely limited to patients with GFR lower than 60 mL/min/1.73 m$^2$ (above this GFR most of the diagnostic and therapeutic approaches do not differ from those applied in patients with normal kidney function). The Working Group aimed to develop the opinions (summarised in Tab. 1) that might be helpful for nephrologists and other practitioners in the treatment of T2D in the setting of co-existing CKD of any aetiology.

## Statement 1

*Chronic kidney disease causes a potentially "diabetogenic" milieu because it leads per se to carbohydrate metabolism disturbances and enhances insulin resistance. Several drugs used in the treatment of kidney diseases impair glucose metabolism. Conversely, because renal tissue contributes to*

Prof. dr hab. n. med. Tomasz Stompór, Katedra Chorób Wewnętrznych, Klinika Nefrologii, Hipertensjologii i Chorób Wewnętrznych Wydział Lekarski, Collegium Medicum, Uniwersytet Warmińsko-Mazurski w Olsztynie, ul. Żołnierska 18, 10–561 Olsztyn, tel: (+48) 89 5386219, fax: (+48) 89 5386550; e-mail: stompin@mp.pl

**Table 1.** ***Diagnosis and treatment of type 2 diabetes (T2D) in patients with chronic kidney disease (CKD): summary of the Working Group statements***

1. CKD is potentially "diabetogenic" state since it leads per se to the carbohydrate metabolism disturbances and enhances insulin resistance. Several drugs used in the treatment of kidney diseases impair glucose tolerance. In opposite, since renal tissue contributes to insulin catabolism, decreasing kidney function resulting in impaired insulin clearance may lead to the decreased demand for exogenous insulin.
2. Concomitant CKD does not influence the diagnostic criteria of T2D commonly accepted in the general population. $HbA_{1c}$ is less precise and accurate in monitoring of diabetes control, but — since no other tool has been developed and validated – it should also be used in diabetic patients with CKD. Along with CKD progression higher values of $HbA_{1c}$ (i.e. 7–8%) should be accepted acceptable for optimal metabolic control in patients with T2D.
3. The glomerular filtration rate (GFR) is one of the key factors in choosing the type of glucose-lowering agent. The risk of adverse events of glucose-lowering drugs increases along with decreasing GFR. In the treatment of T2D with concomitant CKD drugs with proven cardiovascular benefits (i.e.: metformin, SGLT2 inhibitors, and GLP1 receptor agonists) should be preferred unless not contraindicated in a certain GFR range.
4. Demand for exogenous insulin decreases with decreasing GFR, although the relationship between GFR and insulin doses is non-linear, and several other factors influence the need for exogenous insulin.



*insulin catabolism, decreasing kidney function resulting in impaired insulin clearance may lead to the decreased demand for exogenous insulin.*

### *Commentary to Statement 1*

Chronic kidney disease influences the carbohydrate metabolism, which may result in so-called "pseudodiabetes" in non-diabetic patients with CKD, and worsening of metabolic control in those with established T2D. The most important factors accompanying CKD that may influence carbohydrate metabolism include [5–7]:

— impaired insulin secretion (caused, among others, by secondary hyperparathyroidism);
— increasing insulin resistance (which becomes apparent when GFR falls below 50 mL/min/1.73 $m^2$);
— impaired renal and hepatic catabolism of insulin, with impaired clearance of this hormone;
— reduced renal gluconeogenesis.

The above-mentioned disturbances are even more advanced in patients with end-stage renal diseases (ESRD) treated with dialysis (both peritoneal dialysis and haemodialysis) and following kidney transplantation. In the latter group of patients, disturbances typical for CKD without diabetes are additionally complicated by *de novo* development of diabetes (post-transplantation diabetes mellitus — PTDM) [8].

Severe proteinuria is frequently present in patients with chronic kidney diseases; resulting in hypoproteinaemia and hypoalbuminaemia. The most obvious consequence of hypoalbuminaemia is increased free fraction of protein-bound glucose-lowering drugs. This may unpredictably increase their pharmacological activity and lead to unexpected hypoglycaemia. It should be kept in mind that several primary and secondary proteinuric kidney diseases are treated with 'diabetogenic' drugs, such as steroids (used in high doses and in prolonged courses) and calcineurin inhibitors (cyclosporine, and especially tacrolimus). These and other drugs may adversely influence the carbohydrate metabolism but are also prone to interactions with other therapeutic agents (including glucose-lowering ones) [9].

## Statement 2

*Concomitant CKD does not influence the diagnostic criteria of T2D commonly accepted in the general population. $HbA_{1c}$ is less precise and accurate in monitoring diabetes control, but, since no other tool has been developed and validated, it should also be used in diabetic patients with CKD for this purpose. Along with CKD progression, in T2D patients higher values of $HbA_{1c}$ (i.e. 7–8%) should be accepted as targets of metabolic control.*

### *Commentary to Statement 2*

The diagnostic criteria of T2D in patients with CKD are the same as for the general population (regardless of the CKD stage); the same applies for the criteria of metabolic control in T2D. The target $HbA_{1c}$ in CKD patients (depending of the disease stage) remains the subject of controversies. Renal anaemia, iron deficiency, haemolysis, and shortened life-span of red blood cells, but — on the other hand — increase production of new red blood cells upon stimulation with the erythropoiesis stimulating agents, comprise the factors that may have an impact on the interpretation of $HbA_{1c}$ as a marker of long-term metabolic control in diabetes with concomitant CKD. It is generally accepted that in CKD patients, the level of $HbA_{1c}$ tends to underestimate the true exposure to hyperglycaemia. Despite these controversies and the fact that in advanced CKD there is no clear relationship between $HbA_{1c}$ and long-term patient prognosis, $HbA_{1c}$ and glycaemia remain the only tools for the assessment of metabolic control in diabetic patients with concomitant CKD. Other proposed markers used for control monitoring

in diabetic patients (such as fructosamine or glycated albumin) are also influenced by CKD-dependent factors, and — in addition — none of them was validated in CKD patients [10].

It is generally assumed that the "standard" targets of metabolic control are less achievable with decreasing values of GFR. Advanced CKD is associated with higher risk of hypoglycaemia, and the consequences of hypoglycaemia may be more pronounced in this patient group. In addition, several advanced comorbidities (especially cardiovascular disease) impair the overall prognosis of CKD patients, and therefore strict metabolic control of glycaemia may not be beneficial and prolong survival. Thus, higher values of $HbA_{1c}$ are generally acceptable, especially in CKD stages 3b–5. European experts from the *European Renal Best Practice* (ERBP) group suggest 8.5 as a target for $HbA_{1c}$ in patients with GFR lower than 45 mL/min/1.73 $m^2$ [11]. Most other guidelines aimed at an $HbA_{1c}$ level of 7% or less to prevent microvascular complications of diabetes also in patients with concomitant CKD, but achievement of these values should not be attempted in patients with high risk of hypoglycaemia. Experts agreed that $HbA_{1c}$ exceeding 7% should be accepted in patients with multiple and advanced comorbidities, short expected survival, and high risk of hypoglycaemia [12–14]. Studies demonstrated that an association between $HbA_{1c}$ and outcome in CKD is "J"-shaped — prognosis worsens with $HbA_{1c}$ below 6.5% and above 8%. A similar relationship was also observed in dialysis patients [15]. Higher values of $HbA_{1c}$ (i.e. between 7% and 8%) as a criterion of long-term metabolic control were based on studies comprising high-risk patient groups (ACCORD, ADVANCE, VADT) and applied also to patients with CKD stages 3–5 [13].

## Statement 3

*The glomerular filtration rate (GFR) is one of the key factors in choosing a glucose-lowering agent. The risk of adverse events of glucose-lowering drugs is higher in patients with lower GFR. In the treatment of T2D with concomitant CKD drugs with proven cardiovascular benefits (i.e. metformin, SGLT2 inhibitor, and GLP1 receptor agonist) should be preferred unless not contraindicated in a certain GFR range.*

## Statement 4

*Demand for exogenous insulin decreases in patients with decreased GFR, although the relationship between GFR and insulin doses is not linear, and several other factors influence the need for exogenous insulin.*

### *Commentaries to Statements 3 and 4*

Whereas the diagnostic criteria of T2D in CKD are universal and shared with those accepted in the general population, the choice of hypoglycaemic drug is largely influenced by the GFR value. Modification of pharmacological therapy in T2D with concomitant CKD (especially stages 3–5) should take into account the following aspects [16, 17]:

— different pharmacokinetic and pharmacodynamic characteristics of the drug (depending on the contribution of the kidneys to the drug metabolism and/or elimination, as well as the presence and renal clearance of active metabolites); all mentioned circumstances mandate the adjustment of drug dose to the GFR;
— potential toxic effects of the drug to the organs and systems other than the kidneys in case of renal elimination of the drug or its active metabolites (due to their accumulation in CKD stages 3–5); severe adverse effects may include the risk of unpredictable and profound hypoglycaemia;
— difficulties in predicting the drug absorption in the case of uremic gastroparesis (frequently present in diabetic patients) and GI mucous oedema (in patients with severe fluid retention and/or severe proteinuria);
— the impact of other drugs commonly used for the treatment of CKD and concomitant diseases on glucose-lowering drug absorption. These include: proton pump inhibitors (overused in the general population and CKD patients), phosphate binders, oral iron supplementation, and drugs used as alkalinising agents;
— the impact of hypoproteinaemia caused by severe proteinuria on free (unbound) fraction of glucose-lowering drugs;
— insulin resistance, increasing in patients with decreased GFR.

The question remains whether the targets of metabolic control that are expected to be achieved using a particular drug in a patient with certain stage of CKD (i.e. glycaemia or $HbA_{1c}$) would translate into clinically important end points, such as decreased risk of cardio-vascular or cerebrovascular events, or prolonged survival. Before reviewing the use of glucose-lowering drugs in CKD we would like to emphasise that along with progressive loss of GFR the expected benefits from using a particular drug and better metabolic control are reduced. CKD is one of the strongest predictors of adverse outcome in patients with T2D. Intensive hypoglycaemic treatment and/or achieving-targets of glycaemic control has little impact on patients' outcome when GFR is reduced below 60 mL/min/1.73 $m^2$. The same applies to other interventions, such as lipid-lowering treatment.

## Non-pharmacological treatment of T2D with concomitant CKD

The diet prescribed to T2D patients is generally beneficial also in patients with chronic kidney disease (i.e. it may slow down the CKD progression). Unfortunately, in CKD stages 3 to 5, establishing a well-balanced and valuable diet becomes more difficult because new restrictions must be introduced along with GFR loss. The most important one is the need to limit potassium intake, with a reduction of vegetable content in the diet. One of the dietary restrictions of paramount importance for both nephroprotection and reduction of organ damage in CKD is reduced phosphate intake. This is a special challenge in patients with CKD because a low-phosphate diet is usually low in protein as well. Advanced CKD is a catabolic and "inflammatory" state — restricting protein intake may further impair nutritional status and eventually lead to sarcopaenia, cachexia, and MIA syndrome (malnutrition, inflammation, atherosclerosis). Therefore, it is recommended that the daily protein intake should not be lower than 0.8 g/kg body weight (unless not supplemented with amino acid ketoanalogues).

## Using glucose-lowering drugs in CKD

### *Metformin*

Metformin is entirely excreted by the kidneys. Metformin is not nephrotoxic per se; however, kidney failure may promote extra-renal toxicities of this drug. No controlled trials have been completed to prospectively demonstrate the renal (nephroprotective) benefits of metformin. Retrospective, observational studies suggest that patients treated with metformin experience slower progression of CKD (in terms of lower rate of the GFR loss and progression to ESRD) as compared to those treated with sulphonylurea agents. These data indirectly suggest nephroprotective properties of metformin. The most important factor that limits the use of metformin in patients with reduced GFR is a risk of severe lactic acidosis. The risk of this life-threatening complication prompted all groups of experts to suggest adjustment of drug dosing to GFR and withdrawal of metformin in advanced stages of CKD [18–20].

Large observational studies focusing on the incidence of lactic acidosis in metformin-treated patients suggest that the risk of this complication is very low and largely comparable to the risk observed in patients who are treated with the other glucose-lowering agents. In one of the analyses the frequency of lactic acidosis was 3.3 per 100,000 metformin users and 4.8 per 100,000 patients not using this drug. In the same-study hypoglycaemia was found in 60 out of 100,000 patients treated with metformin and 110 per 100,000 who were using other drugs. Frequency of severe hypoglycaemia was 20 times higher in patients who were treated with other drugs as compared to metformin users [18]. Overall, it seems that between 25% and 33% of patients with T2D and CKD stage 3 are treated with metformin (frequently without proper dose adjustment) [21]. Some experts argue that metformin can be used in a dose of 500 mg once daily also in T2D patients with GFR 15–30 mL/min (with temporary withholding or withdrawal, when GFR is lower than 15 mL/min) [22]. In the NHANES study as many as 40% of patients with T2D and CKD3 were treated with metformin. The incidence of lactic acidosis increased along with the GFR reduction, but it was usually without important clinical consequences [23].

In patients with lactic acidosis apparently associated with the use of metformin, the blood concentration of the drug was either normal or elevated. There was also no significant correlation between metformin blood concentration and the severity of lactic acidosis [18]. When prescribing metformin, it is advisable to take into account a few additional "safety rules":

— cimetidine inhibits tubular excretion of metformin – its concomitant use may promote retention of metformin, even when GFR is preserved;
— temporary drug withdrawal may be considered (although is not mandatory in all patients) in clinical settings that expose patients to the risk of CKD worsening (for example, when intra-arterial contrast media are injected);
— patients treated with metformin should monitor their kidney function and consult with their doctors regarding further treatment in such situations as: fever, vomiting, diarrhoea, dehydration, any noticed decrease in urine volume (also due to "post-renal" causes);
— special attention should be paid to patients using metformin, CKD patients, and those with concomitant liver failure (that impairs lactate metabolism) or clinical situations that increase the risk of hypoxia (i.e. worsening of chronic obstructive pulmonary disease, congestive heart failure, etc.).

Recently, changes were made to the summaries of product characteristics of some metformin preparations. In some of them it has been stated that the drug can be used when GFR decreases to the range between 30 and 60 mL/min; if GFR is between 30 and 44 mL/min, the initial dose should not exceed 50% of the maximum dose (i.e. 1000 mg/d), whereas in the GFR range of 45–59 mL/min it may be used in a full dose of 2000 mg/d (being still contraindicated when GFR falls below 30 mL/min). This means that metformin may not only be continued in a reduced dose, but also initiated in moderate stages of CKD. We emphasise this fact because

**Table 2.** *Dosing recommendations of metformin adjusted to the kidney function (based on [18, 19])*

| eGFR [mL/min/1.73 m²] | Dosage | Maximum daily dose [mg] |
|---|---|---|
| ≥ 90 (G1) | Dose modification unnecessary | 3000 |
| 60–89 (G2) | Renal function assessment annually | |
| 45–59 (G3a) | Treatment can be continued<br>Renal function assessment every 3–6 months<br>Should not be used in patients with unstable renal function or when significant renal function worsening can be expected* | 2000 |
| 30–44 (G3b) | Can be used with caution<br>The treatment should not be started<br>The dose should not exceed 50% of the maximum registered dose<br>Renal function assessment at least every 3 months<br>Should not be used in patients with unstable renal function or when significant renal function worsening can be expected* | 1000 |
| < 30 (G4–G5) | Contraindicated | – |

eGFR — estimated glomerular filtration rate; *using metformin in patients with CKD stage 3 is not in accordance with the summary of product characteristics (SPC): SPCs of available preparations state that they are contraindicated if creatinine clearance is lower than 60 mL/min

such changes in the product characteristics follow the data obtained from clinical observations and meet the needs of practitioners.

Recommendations concerning metformin dosing according to expert groups in relation to GFR are shown in Table 2.

### *Pioglitazone*

Taking into account its pharmacokinetic (PK) properties, pioglitazone seems to be an "ideal" drug for patients with all stages of CKD (including advanced renal failure) — it is not excreted by the kidneys and does not accumulate in patients with advanced CKD. In addition, the PROactive trial demonstrated that treatment with pioglitazone reduced the risk of cardio-vascular events, and the beneficial effects were independent from the renal function [26]. Nevertheless, there are several important limitations to the use of this drug in patients with CKD, despite the above-mentioned PK properties [17, 20, 25]:

— the drug promotes water and sodium retention and oedema formation – these are common problems in CKD patients;
— the drug should not be used in patients with heart failure (up to 40% of patients with T2D and advanced CKD suffer from heart failure of varying severity);
— the albumin-bound fraction of a drug is close to 98%, which makes the pharmacokinetic and pharmacodynamic properties of the drug largely unpredictable in CKD patients with severe proteinuria;
— the drug is metabolised by the cytochrome P450, which contributes to the metabolism of several other drugs used in the treatment of patients with chronic kidney diseases (including calcineurin inhibitors); in addition, several drugs can inhibit or activate cytochrome P450, modifying the drug inactivation rate. These data indicate that in the case of pioglitazone (more than in the case of other glucose lowering agents) potential drug interactions may be expected.

### *Sulphonylurea derivates (SU)*

Each of the drugs in this group has slightly different characteristics in relations to kidney function. All have strong affinity to plasma proteins, are predominantly eliminated by the liver, and to a small degree are excreted by kidneys (although kidneys may significantly contribute to the clearance of their metabolites, they usually do not exert glucose-lowering properties). Other drugs with high affinity to protein (among others, $\beta$-receptor antagonists and warfarin) may lead to an increase in free SU blood concentration. Glipizide is metabolised exclusively to non-active metabolites by the liver, and less than 10% of the drug is excreted with urine. PK of glipizide is virtually unchanged in patients with CKD, and therefore glipizide is considered a very 'convenient' drug for these patients. The same applies to gliquidone. Gliclazide is also metabolised to inactive by-products, and its dosing should not be adjusted to the GFR value (although the treatment should always be started from low doses, then up-titrated). Extended release formulations of gliclazide are generally considered safe in terms of risk of hypoglycaemia in patients with reduced GFR. It is generally thought that hypoglycaemic episodes following SU may be more pronounced in patients

with reduced GFR; this is especially true in the case of glimepiride, which is metabolised to active products that may accumulate in the setting of CKD. For this reason, the drug should not be used in patients with CKD stage 5, and the dose of 1 mg should not be exceeded in CKD stages 3–4 [16, 17, 20, 27, 28].

### *Acarbose*

Less than 2% of acarbose dose is absorbed from the GI lumen; however, some metabolites possessing glucose-lowering activity may achieve clinically important concentrations in the blood in patients with advanced CKD. Although the excess rate of side effects in CKD was not confirmed, the drug is contraindicated when GFR falls below 25 mL/min or serum creatinine exceeds 2 mg/dL [16, 17, 20].

### *Repaglinide*

The PK properties of repaglinide in patients with CKD are similar to those described above for SU: the drug is almost entirely metabolised by the liver and only 8–10% is excreted unchanged with the urine. Dose adjustment is not necessary in patients with CKD, although caution is advised because the drug may eventually lead to profound hypoglycaemia when used in advanced stages of CKD (especially with other glucose-lowering agents) [14, 16, 27].

### *GLP-1 analogues (GLP-1 receptor agonists)*

GLP1 analogues available in the market differ in their PK characteristics. Liraglutide is not excreted by the kidneys: dosing does not need any adjustment until GFR value falls below 30 mL/min (when GFR is lower than 30 mL/min/1.73 m$^2$ the drug is not contraindicated, but limited experience in this range of GFR is emphasised by the manufacturer). The drug should not be prescribed in advanced CKD (< 15 mL/min/1.73 m$^2$) and ESRD. In the LEADER trial, it was demonstrated that treatment with liraglutide decreased the rate of cardiovascular and all-cause death and greater benefit was obtained in patients with eGFR < 60 mL/min/1.73 m$^2$, as compared to those with eGFR above this limit (a small number of patients with eGFR < 30 mL/min/1.73 m$^2$ were also included in this trial, and the benefits in this group were also comparable) [29–32].

Exenatide is excreted by the kidneys, but it can still be used in quite a wide range of GFR values. If GFR is higher than 50 mL/min, the dose does not need adjustment; careful dose titration from 2 × 5 $\mu$g/d to 2 × 10 $\mu$g/d is recommended when GRF drops to the range of 30–50 mL/min. Regular (short-acting) formulation of exenatide should not be used in patients with creatinine clearance of less than 30 mL/min; interestingly, the manufacturer does not recommend its use even in patients with ClCr of 30–50 mL/min in the case of long-acting formulation [33].

Dulaglutide (similarly to extended-release exenatide) is given once weekly. No significant correlation was found between the PK of the drug and creatinine clearance; patients with reduced GFR did not experience more adverse effects of the drug [25]. Nevertheless, treatment with dulaglutide is now contraindicated in CKD patients with ClCr lower than 30 mL/min, mostly due to limited experience in CKD stages 4 and 5 [25]. Dose adjustment is not necessary across the whole ClCr range exceeding 30 mL/min. Dulaglutide demonstrated its efficacy in reduction of the composite cardio-vascular end-point ($p = 0.026$ *vs.* placebo) in the cardio-vascular outcome trial (CVOT), but did not reduce any of the separate contributing events, except for non-fatal stroke. Dulaglutide also failed to reduce the mortality of patients participating in the REWIND trial [34, 35]. In the REWIND trial a very small percentage of patients (1%) suffered from advanced CKD (i.e. eGFR < 30 mL/min/1.73 m$^2$) at baseline. Dulaglutide was nephroprotective, significantly reducing composite renal outcome, which was entirely due to reduction of new onset of macroalbuminuria [35].

### *DPP4 inhibitors*

Sitagliptin, predominantly (in up to 90%) excreted with urine as an active drug, accumulates in CKD. Despite precautions suggested by the manufacturer for CKD patients, the drug was generally well tolerated and effective in improving metabolic control of T2D also in this patient group [36]. Vildagliptine is also safe and effective in CKD patients, despite the fact that the drug is metabolised by the kidneys and excreted with urine. In adjusted doses it can still be used even in the advanced stages of CKD [37]. The same is true for saxagliptin, which is considered a safe and effective drug across all stages of CKD and even in patients treated with dialysis (when the dose needs to be reduced to 2.5 mg/d vs. standard 5 mg/d). Vildagliptin and saxagliptin bind to plasma proteins in less than 10%; sitagliptin is protein-bound in 30–40%, whereas linagliptin — in more than 80%. Only 1% of linagliptin dose is eliminated by the kidneys, and thus linagliptin does not need any dose adjustment across all stages of CKD [27]. It seems to be the most convenient drug to be used in CKD patients at present (unless not contraindicated for other reasons). Unfortunately the drug did not reduce the risk of cardiovascular and renal events in the high-risk population of patients included in the CARMELINA trial (in 75% of patients eGFR was lower than 60 mL/min/1.73 m$^2$ and/or proteinuria higher than 300 mg/g of creatinine; 15.2% of patients suffered from advanced CKD with eGFR < 30 mL/min/1.73 m$^2$). This

study seems to be the largest trial to date that was focused particularly on patients with T2D and CKD. It should be mentioned that treatment with linagliptin in this high-risk population was not associated with an increased risk of hospitalisation due to heart failure (which was the case of alogliptin and saxagliptin in previous trials) [38]. Because heart failure is a very frequent co-morbid condition in patients with T2D and CKD, the latter finding may be of particular importance when choosing glucose-lowering drugs in advanced CKD.

### *SGLT-2 inhibitors (SGLT2i)*

Sodium — glucose co-transporter type 2 (SGLT-2) inhibitors have recently attract the attention of the nephrological community because the glucose-lowering (metabolic) effects of these drugs as well as their impact on "hard" outcomes are achieved (among others) through the "renal" mechanisms of action, resulting in enhanced ("therapeutic") glycosuria and augmented natriuresis.

In the human physiology SGLT-2 is responsible for almost complete (up to 100%) reabsorption of glucose in proximal tubules. Hyperglycaemia upregulates the SGT2 expression, which enhances reabsorption capacity. This mechanism has a negative impact on the metabolism, and blocking activity of SGLT-2 with specific inhibitors (resulting in 'therapeutic glycosuria') constitutes a novel approach to the treatment of T2D (which is entirely independent from glucose synthesis, secretion, or sensitivity) [39–42]. Recently published papers pivotally demonstrated that SGLT2 inhibitors significantly reduce the risk of cardiovascular events, cardiovascular mortality, and all-cause mortality. Depending on the drug (empagliflozin, canagliflozin, dapagliflozin), these effects differ slightly, but in principle the cardio-protective mechanisms can be attributed to all of them (class effect). Similarly, all these drugs contribute also to nephroprotection in T2D [43]. The positive impact of the mentioned drug class on cardio-vascular endpoints is not only due to better metabolic control of T2D (in fact, their impact on glycaemia and $HbA_{1c}$ is relatively modest). These drugs also decrease body weight, reduce blood pressure, improve heart function with decreased oxygen demand for myocardium, reduce oxidative stress, decrease sympathetic nervous system activation, reduce serum uric acid level, and possess properties of weak diuretics. In the kidney they reduce oxygen consumption by the proximal tubules because less energy is needed when sodium and glucose reabsorption are substantially limited. An additional mechanism that may impact on blood pressure and natriuresis is the blockade of sodium — proton exchanger type 3 (NHE3). SGLT2i also activates tubulo-glomerular feedback: the increased sodium load in the region of macula densa triggers constriction of the afferent arteriole, thus reducing intraglomerular pressure and hyperfiltration. This mechanism, although based on a different principle, largely resembles the effect of ACEI or ARBs, and — as in the case of these drugs — may be associated with transient ("acute") but reversible reduction in GFR [39]. At present, the summaries of product characteristics of all mentioned SGLT2 inhibitors state that they should not be used in patients with GFR of less than 60 mL/min/1.73 $m^2$. It has been assumed that the significantly reduced number of intact proximal tubules and nephrons (i.e. the target for SGLT2i) in this stage of CKD precludes the effectiveness of these drugs. However, an increasing body of evidence suggests that — although less efficient in metabolic control of diabetes in more advanced CKD — these drugs may still reduce body weight and blood pressure. Dapagliflozin was effective in reducing $HbA_{1c}$, fasting blood glucose, body weight, and systolic blood pressure also in patients with eGFR ranging between 45 and 59 mL/min/1.73 $m^2$ (CKD stage 3a; DERIVE study) [44, 45]. It is worth emphasising that pivotal outcome trials, namely EMPA-REG (with empagliflozin) and CANVAS (with canagliflozin), enrolled only a small proportion of patients with eGFR between 30 and 60 mL/min/1.73 $m^2$ [46–48]. In the EMPA-REG trial cardiovascular outcomes were independent of CKD stage (eGFR value), whereas in the CANVAS trial the most significant risk reduction of cardio-vascular endpoints was observed in patients with eGFR between 30 and 60 mL/min/1.73 $m^2$. Several ongoing trials are testing the hypothesis that SGLT21 and GLP1R agonists are beneficial also in patients with significantly reduced eGFR. Recently, the CREDENCE trial repeatedly proved the renoprotective efficacy of the SGLT2 inhibitor canagliflozin in patients with eGFR reduced to less than 60 mL/min/1.73 $m^2$ at baseline. The drug decreased the risk of primary outcome comprising end-stage renal disease, doubling of serum creatinine from baseline, or death from renal or cardiovascular causes, with highly significant difference vs. placebo ($p = 0.00001$; the effect was achieved due to reduction in doubling of serum creatinine, onset of ESRD, and cardiovascular death) [49]. Cardiovascular benefit achieved in this trial was — as in the case of cardio-vascular outcome trials performed with other drugs — predominantly demonstrated in patients with the lowest baseline GFR (i.e. < 45 mL/min/1.73 $m^2$) [50].

The cardio-vascular and renal benefits associated with the treatment of SGLT2i and GLP-1R agonists led several groups of experts (such as the American Diabetes Association [ADA] and the European Association for the Studies in Diabetes [EASD]) to publish updated algorithms of treatment in high-risk patients with T2D. The most recent guidelines published by the ADA and EASD suggests the use of SGLT1i and/or GLP1R agonist with proven cardio-vascular efficacy in patients with

atherosclerotic cardiovascular disease, (ACVD), heart failure (HF), or CKD, when metabolic control of T2D cannot be achieved with metformin. In terms of reduction of ACVD in CKD patients with T2D, both drugs are considered equally efficient; however, SGLT2i should be preferred when HF predominates, whereas GLP1R agonist seems to be a better choice in patients with more significantly reduced GFR [51]. The ADA/EASD guidelines were recently upheld and supported by the European Society of Cardiology guidelines on cardiovascular disease in diabetes and prediabetes (published with collaboration of the EASD). This document made a step forward and challenged the "dogma" of modern diabetology; namely, it suggested that patients with T2D and very high or high cardiovascular risk, who are naïve to treatment, should not start treatment with metformin as the first drug. Metformin should remain an option for patients with low or moderate cardiovascular risk. The experts suggested starting therapy in high- and very high-risk patients from SGLT2 inhibitor or GLP1R agonist, listing all available drugs with completed CVOTs from both groups. However, they specifically pointed out liraglutide and empagliflozin as drugs that may reduce not only the risk of a CV event, by also the risk of premature death [52]. These guidelines seem to be relevant for all patients with T2D and CKD of all stages because in most of them the CV risk is considered as high or very high. Currently, liraglutide seems to be best option for patients with advanced CKD (eGFR between 15 and 45 mL/min/1.73 m$^2$).

In Table 3 and 4 we have summarised the available data for oral glucose lowering agents and GLP-1R

**Table 3.** ***The use of oral glucose lowering agents and GLP-1R agonists in patients with type 2 diabetes (T2D) and chronic kidney disease (CKD)***

| Groups of drugs/ /drugs | Limitations for use in patients with CKD (as stated in SPC) | Method of kidney function assessment (stated in the SPC) |
|---|---|---|
| Metformin | Contraindicated if CrCl[1] less than 60 mL/min | Cockcroft-Gault formula |
| Pioglitazone | No need for dose adjustment unless CrCl > 4 mL/min<br>Should not be used in patients on dialysis | Not stated[2] |
| Repaglinide | CKD does not influence drug elimination<br>No special guidelines in CKD patients<br>AUC of the drug in different CrCl ranges described in SPC | Not stated[2] |
| Acarbose | Contraindicated in severe kidney failure (CrCl < 25 mL/min) | Not stated[2] |
| **Sulphonylurea** | | |
| Glipizide | CKD/kidney failure not listed as contraindications | Not stated[2] |
| Glimepiride | Contraindicated in the severe kidney failure ("severe kidney failure" not defined) | Not stated |
| Gliclazide | Contraindicated in the severe kidney failure ("severe kidney failure" not defined) | Not stated |
| Gliquidone | CKD/kidney failure not listed as contraindications CKD<br>In severe kidney failure (not defined) manufacturer recommends careful medical supervision | Not stated |
| **GLP1R agonists** | | |
| Exenatide | Dose adjustment not needed in the CrCl range between 50 and 80 mL/min<br>Conservative dose escalation from 5 to 10 $\mu$g recommended in patients with CrCl 30–50 mL/min<br>Not recommended for use in patients with CrCl < 30 mL/min and ESRD | Not stated[2] |
| Liraglutide | No dose adjustment is required for patients with mild, moderate, or severe renal impairment. There is no therapeutic experience in patients with end-stage renal disease, and the drug is therefore not recommended for use in these patients | Not stated |
| Dulaglutide | No dosage adjustment is required in patients with mild, moderate, or severe renal impairment (eGFR < 90 to ≥15 mL/min/1.73 m$^2$)<br>There is very limited experience in patients with end-stage renal disease (eGFR < 15 mL/min/1.73 m$^2$); therefore, the drug cannot be recommended in this population | CKD-EPI |
| **DPP4 inhibitors** | | |
| Linagliptin | For patients with renal impairment, no dose adjustment for linagliptin is required | 24-hour urine collection-based CrCl or Cockcroft--Gault formula mentioned as used in clinical trials |

**Table 3.** *The use of oral glucose lowering agents and GLP-1R agonists in patients with type 2 diabetes (T2D) and chronic kidney disease (CKD)*

| Groups of drugs/ /drugs | Limitations for use in patients with CKD (as stated in SPC) | Method of kidney function assessment (stated in the SPC) |
|---|---|---|
| Saxagliptin | No dose adjustment is recommended for patients with mild renal impairment or in patients with moderate renal impairment that have GFR ≥ 45 mL/min/1.73 m$^2$<br>The dose should be reduced to 2.5 mg once daily in patients with moderate renal impairment and GFR < 45 mL/min/1.73 m$^2$ and in patients with severe renal impairment<br>Saxagliptin is not recommended for patients with ESRD requiring haemodialysis | Not stated |
| Sitagliptin | For patients with mild renal impairment (GFR < 60 to < 90 mL/min/1.73 m$^2$), no dose adjustment is required<br>For patients with moderate renal impairment (GFR< 45 to < 60 mL/min//1.73 m$^2$), no dosage adjustment is required<br>For patients with moderate renal impairment (GFR > 30 to < 45 mL/min/1.73 m$^2$), the dose is 50 mg once daily<br>For patients with severe renal impairment (GFR ≥ 15 to < 30 mL/min/1.73 m$^2$) or with ESRD (GFR < 15 mL/min/1.73 m$^2$), including those requiring haemodialysis or peritoneal dialysis, the dose is 25 mg once daily<br>Treatment may be administered without regard to the timing of dialysis | Not stated |
| Vildagliptin | No dose adjustment is required in patients with mild renal impairment (CrCl ≥ 50 mL/min)<br>Recommended daily dose 50 mg BID<br>In patients with moderate or severe renal impairment or with ESRD, the recommended dose is 50 mg once daily<br>Due to limited experience it should be used with caution in patients on haemodialysis | Not stated |
| **SGLT2 inhibitors** | | |
| Dapagliflozin | Should not be initiated in patients with GFR< 60 mL/min/1.73 m$^2$ and should be discontinued in patients with GFR persistently < 45 mL/min/1.73 m$^2$ | Not stated |
| Empagliflozin | No dose adjustment is required for patients with an eGFR ≥ 60 mL/min/1.73 m$^2$ or CrCl ≥ 60 mL/min[2]<br>Empagliflozin should not be initiated in patients with an eGFR < 60 mL/min/1.73 m$^2$ or CrCl < 60 mL/min<br>In patients tolerating empagliflozin, whose eGFR falls persistently below 60 mL/min/1.73 m$^2$ or CrCl below 60 mL/min, the dose of empagliflozin should be adjusted to or maintained at 10 mg once daily<br>Empagliflozin should be discontinued when eGFR is persistently below 45 mL/min/1.73 m$^2$ or CrCl persistently below 45 mL/min (see sections 4.4, 4.8, 5.1, and 5.2).<br>Empagliflozin should not be used in patients with ESRD or in patients on dialysis because it is not expected to be effective in these patients | Not stated for CrCl measurement or eGFR calculation; MDRD formula mentioned in SPC as used in one of the clinical trials |
| Canagliflozin | For patients with an eGFR 60 mL/min/1.73 m$^2$ to < 90 mL/min/1.73 m$^2$ or CrCl 60 mL/min to < 90 mL/min, no dose adjustment is needed[2]<br>Canagliflozin should not be initiated in patients with an eGFR < 60 mL/min/1.73 m$^2$ or CrCl < 60 mL/min<br>In patients tolerating canagliflozin, whose eGFR falls persistently below 60 mL/min/1.73 m$^2$ or CrCl 60 mL/min, the dose of canagliflozin should be adjusted to or maintained at 100 mg once daily<br>Canagliflozin should be discontinued when eGFR is persistently below 45 mL/min/1.73 m$^2$ or CrCl persistently below 45 mL/min | Not stated for CrCl measurement or eGFR calculation |

*bid* — twice a day; CKD-EPI — Chronic Kidney Disease-Epidemiology Collaboration; CrCl — creatinine clearance; ESRD — end-stage renal disease; GFR — glomerular filtration rate; MDRD — Modification of Diet in Renal Disease; SPC — summary of product characteristics;

[1]the terms "creatinine clearance" (ClCr), "estimated glomerular filtration rate" (eGFR), or both were used in Table 3 according to the terms used in SPCs of the respective products; [2]presumably the Cockcroft-Gault formula; [2]we believe that the statement of "eGFR or CrCl" is highly imprecise because both values may significantly differ in the same person using the same serum creatinine value for calculations

**Table 4.** *The dose adjustments of antidiabetic agents (except of insulin) in patients with chronic kidney disease (CKD). Green — use full dose of the drug; yellow — reduce dose of the drug; orange — continue the treatment in reduced dose of the drug but do not initiate treatment of the drug, red — do not start the drug in any dose*

| Group of antidiabetic agents | | BG | Sulfonylureas | | | | | GLP1 analogues *sc* | | | | | | DPP4 inhibitors | | | | | SGLT2 inhibitors | | | | | Others | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Agents | | Metformin | Gliclazide | Glimepiride | Gliquidone | Glipizide | Glibenclamide | Exena1tide | Lixisenatide | Liraglutide | Semaglutide | Dulaglutide | Albiglutide | Linagliptin | Sitagliptin | Vildagliptin | Alogliptin | Saxagliptin | Dapagliflozin | Canagliflozin | Empagliflozin | Ertugliflozin | Sotagliflozin | Acarbose | Pioglitazone |
| **CKD** | **eGFR** | Dosage in mg (or $\mu$g) — maintenance dose bolded | | | | | | | | | | | | | | | | | | | | | | | |
| G1 | > 90 | *tid* | *bid* | **qd** | *tid* | **qd** | | *bid* | *bid* | *qd* | *qw* | *qw* | *qw* | *qd* | *qd* | *qd* | *qd* | *qd* | *qd* | *qd* | *qd* | *qd* | *qd* | *qd* | *qd* |
| G2 | 89–60 | 500 | 40 | | | **(GITS)** | | | | | | | | | | *bid* | | | | | | | | | |
| | | **850** | 80 | | | *bid* | | | | | | | | | | | | | | | | | | | |
| | | 1000 | 160 | 1 | 15 | 2.5 | | 5 | 10 | 0,6 | 0.25 | 0.75 | **30** | **5** | 100 | **50** | 6.25 | **5** | **10** | 100 | **10** | 5 | 200 | 50 | 15 |
| | | | | 2 | **30** | 5 | | 10 | 20 | **1.2** | **0.5** | **1.5** | 50 | | | | 12.5 | | | **300** | 25 | **15** | 400 | **100** | **30** |
| | | **1 × d E** | **1 × d** | 3 | 45 | **10** | | | | **1.8** | **1.0** | | | | | | **25** | | | | | | | 200 | 45 |
| | | **(XR/MR)** | **(MR)** | **4** | | **15** | | | | | | | | | | | | | | | | | | | |
| | | 500 | 30 | 6 | | 20 | | | | | | | | | | | | | | | | | | | |
| | | 750 | **60** | | | | | | | | | | | | | | | | | | | | | | |
| | | 1000 | **120** | | | | | | | | | | | | | | | | | | | | | | |
| | | **1500** | | | | | | | | | | | | | | | | | | | | | | | |
| | | **2000** | | | | | | | | | | | | | | | | | | | | | | | |
| G3a | 59-45 | Max. 2 g/d | | 1 | | | | 5 | 10 | | | | | | | | | | | 100 | 10 | 5 | 200 | | |
| G3b | 44–30 | Max. 1 g/d | | | | | | | | | | | | | 50 | 50 | 12.5 | 2.5 | | | | | | | |
| G4 | 29–15 | | | | | | | | | | | | | | 25 | | 6.25 | | | | | | | | |
| G5 | < 15 | | | | | | | | | | | | | | | | | | | | | | | | |

BG — biguanide; *bid* — twice a day; E — evening dose; eGFR — estimated glomerular filtration rate; max. — maximum dose; *qd* — once daily; *qw* — once weekly; *s.c.* — subcutaneous; *tid* — three times a day; XR/MR/GITS — drug of extended release

agonists used in patients with T2D and CKD that are available in Poland, with particular focus on their dosage adjustment to the GFR range.

## Insulin

As mentioned above, advanced CKD impairs insulin secretion and enhances insulin resistance; on the other hand, reduced contribution of the kidneys to insulin catabolism and clearance may paradoxically increase the effect of exogenous insulin (up to 30% of insulin inactivation or elimination is performed in the kidneys). It is believed (but this opinion is entirely expert based, not supported by clinical trials) that the demand for exogenous insulin is decreased on average by 20% to 30% when GFR is reduced to 10 to 50 mL/min, as compared to GFR > 50 mL/min. In CKD stage 5 (ESRD) this demand may be even halved compared to normal kidney function. Particular dialysis techniques used for the treatment of ESRD generate special challenges. In patients treated with peritoneal dialysis additional intraperitoneal glucose load must be handled because a significant amount of glucose is absorbed into the bloodstream. Additional doses of insulin need to be prescribed to manage this extra glucose load. A very unique challenge of haemodialysis (HD) when treating diabetes is the "intermittent" nature of therapy — every second day (i.e. day with a dialysis session) is substantially different from the days off dialysis in terms of the metabolic situation: patients have their routine daily schedule (including physical activity, meals, etc.) disturbed by dialysis treatment itself, travelling to and from the dialysis unit (which may together last up to 8–10 hours every second day), substantial changes in volume status, acid-base balance parameters, electrolytes, etc. There is an ongoing discussion in the literature about which type of insulin would be more suitable for patients treated with intermittent HD. No clear recommendations could be established until now — some authors prefer short-acting insulins, whereas others suggest long-acting formulas. Sometimes different dosing schedules are proposed for days on dialysis and off dialysis, although such an approach remains largely impractical and inconvenient. It seems that the PK characteristics of insulin analogues are less disturbed compared to human insulin formulas in HD patients. Specific guidelines for insulin therapy in the maintenance of dialysis patients have not been developed; generally accepted approaches are also adopted for this group of patients (with special considerations applicable for specific types of dialysis). Less stringent goals of metabolic control should certainly be applied in this patient group [5, 53, 54].

*Acknowledgments*

This position statement was kindly reviewed by Professor Krzysztof Strojek, National Consultant in Diabetes. The authors would like to express their deepest thanks for his effort to improve this manuscript; all his valuable comments and corrections were implemented into the final version of the manuscript.

## References

1. Jaacks LM, Siegel KR, Gujral UP, et al. Type 2 diabetes: A 21st century epidemic. Best Pract Res Clin Endocrinol Metab. 2016; 30(3): 331–343, doi: 10.1016/j.beem.2016.05.003, indexed in Pubmed: 27432069.
2. Pyram R, Kansara A, Banerji MA, et al. Chronic kidney disease and diabetes. Maturitas. 2012; 71(2): 94–103, doi: 10.1016/j.maturitas.2011.11.009, indexed in Pubmed: 22137331.
3. Wu B, Bell K, Stanford A, et al. Understanding CKD among patients with T2DM: prevalence, temporal trends, and treatment patterns-NHANES 2007-2012. BMJ Open Diabetes Res Care. 2016; 4(1): e000154, doi: 10.1136/bmjdrc-2015-000154, indexed in Pubmed: 27110365.
4. Pugliese G, Solini A, Bonora E, et al. RIACE Study Group. Chronic kidney disease in type 2 diabetes: lessons from the Renal Insufficiency And Cardiovascular Events (RIACE) Italian Multicentre Study. Nutr Metab Cardiovasc Dis. 2014; 24(8): 815–822, doi: 10.1016/j.numecd.2014.02.013, indexed in Pubmed: 24780515.
5. Iglesias P, Díez JJ. Insulin therapy in renal disease. Diabetes Obes Metab. 2008; 10: 811–823, doi: 10.1111/j.1463-1326.2007.00802.x, indexed in Pubmed: 18248491.
6. Xu H, Carrero JJ. Insulin resistance in chronic kidney disease. Nephrology (Carlton). 2017; 22(Suppl 4): 31–34, doi: 10.1111/nep.13147, indexed in Pubmed: 29155496.
7. Leyking S, Fliser D. Insulin resistance in CKD. Clin J Am Soc Nephrol. 2014; 9(4): 638–640, doi: 10.2215/CJN.01290214, indexed in Pubmed: 24677558.
8. Sharif A, Hecking M, de Vries APJ, et al. Proceedings from an international consensus meeting on posttransplantation diabetes mellitus: recommendations and future directions. Am J Transplant. 2014; 14(9): 1992–2000, doi: 10.1111/ajt.12850, indexed in Pubmed: 25307034.
9. Fathallah N, Slim R, Larif S, et al. Drug-Induced Hyperglycaemia and Diabetes. Drug Saf. 2015; 38(12): 1153–1168, doi: 10.1007/s40264-015-0339-z, indexed in Pubmed: 26370106.
10. Kovesdy CP, Sharma K, Kalantar-Zadeh K. Glycemic control in diabetic CKD patients: where do we stand? Am J Kidney Dis. 2008; 52(4): 766–777, doi: 10.1053/j.ajkd.2008.04.011, indexed in Pubmed: 18572289.
11. Guideline development group. Clinical Practice Guideline on management of patients with diabetes and chronic kidney disease stage 3b or higher (eGFR <45 mL/min). Nephrol Dial Transplant. 2015; 30 Suppl 2: ii1–142, doi: 10.1093/ndt/gfv100, indexed in Pubmed: 25940656.
12. Roche-Recinos A, Charlap E, Markell M. Management of glycemia in diabetic patients with stage IV and V chronic kidney disease. Curr Diab Rep. 2015; 15(5): 25, doi: 10.1007/s11892-015-0600-y, indexed in Pubmed: 25772643.
13. American Diabetes Association . Updates to theStandards of Medical Care in Diabetes — 2018. Diabetes Care. 2018; 41(9): 2045–2047, doi: 10.2337/dc18-su09, indexed in Pubmed: 30135199 .
14. Gianchandani RY, Neupane S, Heung M. Hypoglycemia in Hospitalized Hemodialysis Patients With Diabetes: An Observational Study. J Diabetes Sci Technol. 2018; 12(1): 33–38, doi: 10.1177/1932296817747620, indexed in Pubmed: 29291650.
15. Schernthaner G, Ritz E, Schernthaner GH. Strict glycaemic control in diabetic patients with CKD or ESRD: beneficial or deadly? Nephrol Dial Transplant. 2010; 25(7): 2044–2047, doi: 10.1093/ndt/gfq199, indexed in Pubmed: 20388630.
16. Arnouts P, Bolignano D, Nistor I, et al. Glucose-lowering drugs in patients with chronic kidney disease: a narrative review on pharmacokinetic properties. Nephrol Dial Transplant. 2014; 29(7): 1284–1300, doi: 10.1093/ndt/gft462, indexed in Pubmed: 24322578.
17. Di Lullo L, Mangano M, Ronco C, et al. The treatment of type 2 diabetes mellitus in patients with chronic kidney disease: What to expect from new oral hypoglycemic agents. Diabetes Metab Syndr. 2017; 11 Suppl 1: S295–S305, doi: 10.1016/j.dsx.2017.03.005, indexed in Pubmed: 28292575.
18. Inzucchi SE, Lipska KJ, Mayo H, et al. Metformin in patients with type 2 diabetes and kidney disease: a systematic review. JAMA. 2014; 312(24): 2668–2675, doi: 10.1001/jama.2014.15298, indexed in Pubmed: 25536258.
19. Lipska KJ, Bailey CJ, Inzucchi SE. Use of metformin in the setting of mild-to-moderate renal insufficiency. Diabetes Care. 2011; 34(6): 1431–1437, doi: 10.2337/dc10-2361, indexed in Pubmed: 21617112.

20. Tuttle KR, Bakris GL, Bilous RW, et al. Diabetic kidney disease: a report from an ADA Consensus Conference. Diabetes Care. 2014; 37(10): 2864–2883, doi: 10.2337/dc14-1296, indexed in Pubmed: 25249672.
21. Penfornis A, Blicklé JF, Fiquet B, et al. How are patients with type 2 diabetes and renal disease monitored and managed? Insights from the observational OREDIA study. Vasc Health Risk Manag. 2014; 10: 341–352, doi: 10.2147/VHRM.S60312, indexed in Pubmed: 24966684.
22. Lalau JD, Kajbaf F, Bennis Y, et al. Metformin Treatment in Patients With Type 2 Diabetes and Chronic Kidney Disease Stages 3A, 3B, or 4. Diabetes Care. 2018; 41(3): 547–553, doi: 10.2337/dc17-2231, indexed in Pubmed: 29305402.
23. Kuo CC, Yeh HC, Chen B, et al. Prevalence of Metformin Use and the Associated Risk of Metabolic Acidosis in US Diabetic Adults With CKD: A National Cross-Sectional Study. Medicine (Baltimore). 2015; 94(51): e2175, doi: 10.1097/MD.0000000000002175, indexed in Pubmed: 26705203.
24. Schneider CA, Ferrannini E, Defronzo R, et al. Effect of pioglitazone on cardiovascular outcome in diabetes and chronic kidney disease. J Am Soc Nephrol. 2008; 19(1): 182–187, doi: 10.1681/ASN.2007060678, indexed in Pubmed: 18057215.
25. Davies M, Chatterjee S, Khunti K. The treatment of type 2 diabetes in the presence of renal impairment: what we should know about newer therapies. Clin Pharmacol. 2016; 8: 61–81, doi: 10.2147/CPAA.S82008, indexed in Pubmed: 27382338.
26. Chaudhury A, Duvoor C, Reddy Dendi VS, et al. Clinical Review of Antidiabetic Drugs: Implications for Type 2 Diabetes Mellitus Management. Front Endocrinol (Lausanne). 2017; 8: 6, doi: 10.3389/fendo.2017.00006, indexed in Pubmed: 28167928.
27. Roussel R, Lorraine J, Rodriguez A, et al. Overview of Data Concerning the Safe Use of Antihyperglycemic Medications in Type 2 Diabetes Mellitus and Chronic Kidney Disease. Adv Ther. 2015; 32(11): 1029–1064, doi: 10.1007/s12325-015-0261-x, indexed in Pubmed: 26581749.
28. Abe M, Okada K, Abe M, et al. Antidiabetic agents in patients with chronic kidney disease and end-stage renal disease on dialysis: metabolism and clinical practice. Curr Drug Metab. 2011; 12(1): 57–69, doi: 10.2174/138920011794520053, indexed in Pubmed: 21303332.
29. Scheen AJ. Pharmacokinetics and clinical use of incretin-based therapies in patients with chronic kidney disease and type 2 diabetes. Clin Pharmacokinet. 2015; 54(1): 1–21, doi: 10.1007/s40262-014-0198-2, indexed in Pubmed: 25331711.
30. Muskiet MHA, Tonneijck L, Smits MM, et al. GLP-1 and the kidney: from physiology to pharmacology and outcomes in diabetes. Nat Rev Nephrol. 2017; 13: 605, doi: 10.1038/nrneph.2017.123, indexed in Pubmed: 28869249.
31. Marso SP, Daniels GH, Brown-Frandsen K, et al. LEADER Steering Committee, LEADER Trial Investigators. Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes. N Engl J Med. 2016; 375(4): 311–322, doi: 10.1056/NEJMoa1603827, indexed in Pubmed: 27295427.
32. Mann JFE, Ørsted DD, Buse JB, et al. LEADER Steering Committee and Investigators. Liraglutide and Renal Outcomes in Type 2 Diabetes. N Engl J Med. 2017; 377(9): 839–848, doi: 10.1056/NEJMoa1616011, indexed in Pubmed: 28854085.
33. Mentz RJ, Bethel MA, Merrill P, et al. EXSCEL Study Group, EXSCEL Study Group. Effects of Once-Weekly Exenatide on Cardiovascular Outcomes in Type 2 Diabetes. N Engl J Med. 2017; 377(13): 1228–1239, doi: 10.1056/NEJMoa1612917, indexed in Pubmed: 28910237.
34. Gerstein HC, Colhoun HM, Dagenais GR, et al. REWIND Investigators. Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND): a double-blind, randomised placebo-controlled trial. Lancet. 2019; 394(10193): 121–130, doi: 10.1016/S0140-6736(19)31149-3, indexed in Pubmed: 31189511.
35. Gerstein HC, Colhoun HM, Dagenais GR, et al. REWIND Investigators. Dulaglutide and renal outcomes in type 2 diabetes: an exploratory analysis of the REWIND randomised, placebo-controlled trial. Lancet. 2019; 394(10193): 131–138, doi: 10.1016/S0140-6736(19)31150-X, indexed in Pubmed: 31189509.
36. Engel SS, Suryawanshi S, Stevens SR, et al. TECOS Study Group. Safety of sitagliptin in patients with type 2 diabetes and chronic kidney disease: outcomes from TECOS. Diabetes Obes Metab. 2017; 19(11): 1587–1593, doi: 10.1111/dom.12983, indexed in Pubmed: 28432745.
37. Russo E, Penno G, Del Prato S. Managing diabetic patients with moderate or severe renal impairment using DPP-4 inhibitors: focus on vildagliptin. Diabetes Metab Syndr Obes. 2013; 6: 161–170, doi: 10.2147/DMSO.S28951, indexed in Pubmed: 23650450.
38. Rosenstock J, Perkovic V, Johansen OE, et al. CARMELINA Investigators. Effect of Linagliptin vs Placebo on Major Cardiovascular Events in Adults With Type 2 Diabetes and High Cardiovascular and Renal Risk: The CARMELINA Randomized Clinical Trial. JAMA. 2019; 321(1): 69–79, doi: 10.1001/jama.2018.18269, indexed in Pubmed: 30418475.
39. Wanner C. EMPA-REG OUTCOME: The Nephrologist's Point of View. Am J Med. 2017; 130(6S): S63–S72, doi: 10.1016/j.amjmed.2017.04.007, indexed in Pubmed: 28526179.
40. Heerspink HJL, Perkins BA, Fitchett DH, et al. Sodium Glucose Cotransporter 2 Inhibitors in the Treatment of Diabetes Mellitus: Cardiovascular and Kidney Effects, Potential Mechanisms, and Clinical Applications. Circulation. 2016; 134(10): 752–772, doi: 10.1161/CIRCULATIONAHA.116.021887, indexed in Pubmed: 27470878.
41. Perrone-Filardi P, Avogaro A, Bonora E, et al. Mechanisms linking empagliflozin to cardiovascular and renal protection. Int J Cardiol. 2017; 241: 450–456, doi: 10.1016/j.ijcard.2017.03.089, indexed in Pubmed: 28395981.
42. Schernthaner G, Mogensen CE, Schernthaner GH. The effects of GLP-1 analogues, DPP-4 inhibitors and SGLT2 inhibitors on the renal system. Diab Vasc Dis Res. 2014; 11(5): 306–323, doi: 10.1177/1479164114542802, indexed in Pubmed: 25116004.
43. Wiviott SD, Raz I, Bonaca MP, et al. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. N Engl J Med. 2019; 380: 347–357, doi: 10.1056/NEJMoa1812389, indexed in Pubmed: 30415602.
44. Fioretto P, Del Prato S, Buse JB, et al. DERIVE Study Investigators. Efficacy and safety of dapagliflozin in patients with type 2 diabetes and moderate renal impairment (chronic kidney disease stage 3A): The DERIVE Study. Diabetes Obes Metab. 2018; 20(11): 2532–2540, doi: 10.1111/dom.13413, indexed in Pubmed: 29888547.
45. Dekkers CCJ, Wheeler DC, Sjöström CD, et al. Effects of the sodium-glucose co-transporter 2 inhibitor dapagliflozin in patients with type 2 diabetes and Stages 3b-4 chronic kidney disease. Nephrol Dial Transplant. 2018; 33(11): 2005–2011, doi: 10.1093/ndt/gfx350, indexed in Pubmed: 29370424.
46. Neal B, Perkovic V, Mahaffey KW, et al. Canagliflozin and cardiovascular and renal events in type 2 diabetes. N Engl J Med. 2017; 377(7): 644–657, doi: 10.1056/NEJMoa1611925, indexed in Pubmed: 28605608.
47. Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med. 2015; 373: 2117–2128, doi: 10.1056/NEJMoa1504720, indexed in Pubmed: 26378978 .
48. Wanner C, Inzucchi SE, Lachin JM, et al. Empagliflozin and progression of kidney disease in type 2 diabetes. N Engl J Med. 2016; 375: 323–334, doi: 10.1056/NEJMoa1515920, indexed in Pubmed: 27299675.
49. Perkovic V, Jardine MJ, Neal B, et al. CREDENCE Trial Investigators. Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy. N Engl J Med. 2019; 380(24): 2295–2306, doi: 10.1056/NEJMoa1811744, indexed in Pubmed: 30990260.
50. Mahaffey KW, Jardine MJ, Bompoint S, et al. Canagliflozin and Cardiovascular and Renal Outcomes in Type 2 Diabetes Mellitus and Chronic Kidney Disease in Primary and Secondary Cardiovascular Prevention Groups. Circulation. 2019; 140(9): 739–750, doi: 10.1161/CIRCULATIONAHA.119.042007, indexed in Pubmed: 31291786.
51. Davies MJ, D'Alessio DA, Fradkin J, et al. Management of hyperglycaemia in type 2 diabetes, 2018. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetologia. 2018; 61(12): 2461–2498, doi: 10.1007/s00125-018-4729-5, indexed in Pubmed: 30288571.
52. Cosentino F, Grant PJ, Aboyans V, et al. ESC Scientific Document Group . 2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD. Eur Heart J. 2019 [Epub ahead of print], doi: 10.1093/eurheartj/ehz486, indexed in Pubmed: 31497854.
53. Rajput R, Sinha B, Majumdar S, et al. Consensus statement on insulin therapy in chronic kidney disease. Diabetes Res Clin Pract. 2017; 127: 10–20, doi: 10.1016/j.diabres.2017.02.032, indexed in Pubmed: 28315574.
54. Snyder RW, Berns JS. Use of insulin and oral hypoglycemic medications in patients with diabetes mellitus and advanced kidney disease. Semin Dial. 2004; 17(5): 365–370, doi: 10.1111/j.0894-0959.2004.17346.x, indexed in Pubmed: 15461745.