Clinical Practice Guideline on management of patients with diabetes and chronic kidney disease stage 3b or higher (eGFR <45 mL/min)

ERBP

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Introduction

Diabetes mellitus is becoming increasingly prevalent and is considered a rapidly growing concern for healthcare systems. Besides the cardiovascular complications, diabetes mellitus is associated with chronic kidney disease (CKD). CKD in patients with diabetes can be caused by true diabetic nephropathy, but can also be caused indirectly by diabetes, e.g. due to polyneuropathic bladder dysfunction, increased incidence of relapsing urinary tract infections or macrovascular angiopathy. However, many patients who develop CKD due to a cause other than diabetes will develop or may already have diabetes mellitus. Finally, many drugs that are used for management of CKDs, e.g. corticosteroids or calcineurin inhibitors, can cause diabetes.

Despite the strong interplay between diabetes and CKD, the management of patients with diabetes and CKD stage 3b or higher (eGFR <45 mL/min) remains problematic. Many guidance-providing documents have been produced on the management of patients with diabetes to prevent or delay the progression to CKD, mostly defined as the presence of micro and macroalbuminuria. However, none of these documents specifically deal with the management of patients with CKD stage 3b or higher (eGFR <45 mL/min). There is a paucity of well-designed, prospective studies in this population, as many studies exclude either patients with diabetes, or with CKD stage 3b or higher (eGFR<45mL/min), or both. This limits the evidence base to these approaches.

In addition, due to some new developments in this area, the advisory board of ERBP decided that a guideline on the management of patients with diabetes and CKD stage 3b or higher (eGFR <45 mL/min) was needed and timely: 1. The clear recognition of the importance of evidence-based approaches to patient care to enhance quality, improve safety and establish a clear and transparent framework for service development and healthcare provision. 2. The advent of new diagnostics and therapeutics in this area, highlighting the need for a valid, reliable and transparent process of evaluation to support key decisions. In addition to a rigorous approach to methodology and evaluation, we were keen to ensure that the document focused on patient-important outcomes and had utility for clinicians involved in everyday practice.

We hope you will enjoy reading this guideline and that you will find it useful in your everyday management of patients with diabetes and CKD stage 3b or higher.

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http://european-renal-best-practice.org/

CHAPTER 1: ISSUES RELATED TO RENAL REPLACEMENT MODALITY SELECTION IN PATIENTS WITH DIABETES AND END-STAGE RENAL DISEASE

Chapter 1.1. Should patients with diabetes and CKD stage 5 start with peritoneal dialysis or haemodialysis as a first modality?

1.1.1 We recommend giving priority to the patient's general status and preference in selecting renal replacement therapy as there is an absence of evidence of superiority of one modality over another in patients with diabetes and CKD stage 5 (1C).

1.1.2 We recommend providing patients with unbiased information about the different available treatment options (1A).

1.1.3 In patients opting to start haemodialysis (HD), we suggest prefering high flux over low flux when this is available (2C).

1.1.4 We suggest diabetes has no influence on the choice between HD or haemodiafiltration (HDF) (2B).

Advice for clinical practice

Make sure that all the different renal replacement therapy modalities (peritoneal dialysis (PD), in-centre HD, satellite HD, home HD, nocturnal dialysis, different modalities of transplantation) can be made equally available for all patients is indispensable to allow free modality choice.

Chapter 1.2. Should patients with diabetes and CKD stage 5 start dialysis earlier, i.e. before becoming symptomatic, than patients without diabetes?

1.2.1 We recommend initiating dialysis in patients with diabetes on the same criteria as in patients without diabetes (1A).

Advice for clinical practice

1. Distinguish complaints due to long-standing diabetes (polyneuropathy, gastroparesis versus nausea on uraemia etc.) from uraemic complaints might be cumbersome in clinical practice.

2. In patients opting for HD, take into account and discuss with the patient the following factors to determine the decision on and optimal timing of vascular access creation:

(a) speed of deterioration of renal function
(b) pojected probability that a functioning vascular access will be achieved
(c) projected life expectancy.

Chapter 1.3. In patients with diabetes and CKD stage 5, should a native fistula, graft or tunnelled catheter be preferred as initial access?

1.3.1 We recommend that reasonable effort be made to avoid tunnelled catheters as primary access in patients with diabetes starting HD as renal replacement therapy (1C).

1.3.2 We recommend that the advantages, disadvantages and risks of each type of access be discussed with the patient.

Advice for clinical practice

When deciding whether or not to create a native vascular access, the following points should be considered:

- expected life expectancy of the patient
- expected QoL of the patient
- probability of success of native access creation, as predicted based on ultrasound and Doppler results (Figure 2).

Chapter 1.4 Is there a benefit to undergoing renal transplantation for patients with diabetes and CKD stage 5?

1.4.1 We recommend providing education on the different options of transplantation and their expected outcomes for patients with diabetes and CKD stage 4 or 5 who are deemed suitable for transplantation (Table 5) (1D).

Statements only for patients with type 1 diabetes and CKD stage 5

1.4.2 We suggest living donation kidney transplantation or simultaneous pancreas kidney transplantation to improve survival of suitable patients (2C).

1.4.3 We suggest against islet transplantation after kidney transplantation with the aim to improve survival (2C).

1.4.4 We suggest pancreas grafting to improve survival after kidney transplantation (2C).

Statements only for patients with type 2 diabetes and CKD stage 5

1.4.5 We recommend against pancreas or simultaneous kidney pancreas transplantation (1D).

1.4.6 We recommend diabetes in itself should not be considered a contraindication to kidney transplantation in patients who otherwise comply with inclusion and exclusion criteria for transplantation *(1C).*

Advice for clinical practice

- Successful simultaneous pancreas–kidney transplantation improves QoL, neuropathy, glycaemic control and diabetic retinopathy in type 1 diabetes.
- Perioperative comorbidity of simultaneous pancreas kidney transplantation can be substantial.

- We refer to the ERBP guideline [60] on kidney transplant donor and recipient evaluation and peri-operative management for assessing whether or not a patient is deemed suitable for transplantation.

CHAPTER 2. ISSUES RELATED TO GLYCAEMIC CONTROL IN PATIENTS WITH DIABETES AND CKD STAGE 3B OR HIGHER (eGFR <45 mL/min)

Chapter 2.1
A. Should we aim to lower HbA1C by tighter glycaemic control in patients with diabetes and CKD stage 3b or higher (eGFR <45 mL/min)?

B. Is an aggressive treatment strategy (in numberof injections and controls and follow-up) superior to a more relaxed treatment strategy in patients with diabetes and CKD stage 3b or higher (eGFR <45 mL/min) and using insulin?

2.1.1 We recommend against tighter glycaemic control if this results in severe hypoglycaemic episodes (1B).

2.1.2 We recommend vigilant attempts to tighten glycaemic control with the intention to lower HbA1C when values are >8.5% (69 mmol/mol) (1C).

2.1.3 We suggest vigilant attempts to tighten glycaemic control with the intention to lower HbA1C according to the flow chart in Figure 4 in all other conditions (2D).

2.1.4 We recommend intense self-monitoring only to avoid hypoglycaemia in patients at high risk for hypoglycaemia (2D).

Advice for clinical practice

- Severity of hypoglycaemic episodes are defined as 'mild' when it can be treated by the patient himself and as 'severe' when assistance is required.
- The most important concern is to avoid episodes of hypoglycaemia.
- Empower patients at moderate and high risk for hypoglycaemia to perform regular follow-up of blood glucose level by using validated point of care devices.
- Patients and conditions at low, moderate and high risk for hypoglycaemic episodes are depicted in Figure 5.

Chapter 2.2. Are there better alternatives than HbA1c to estimate glycaemic control in patients with diabetes and CKD stage 3b or higher (eGFR <45 mL/min/ 1.73 m2)?

2.2.1 We recommend the use of HbA1C as a routine reference to assess longer term glycaemic control in patients with CKD stage 3b or higher (eGFR <45 mL/min/1.73 m2) (1C).

Advice for clinical practice

- Continuous glucose measurement devices can be considered in high-risk patients in whom a very tight control of glycaemia is deemed of benefit.
- The association between HbA1C and longer term glycaemic control might be different in patients with versus without CKD stage 3b or higher (eGFR <45 mL/min), and this both for the absolute value as well as for the slope of the association curve.
- The following factors are potentially associated with a lower than expected HbA1C:
  - decreased red blood cell survival
  - increased red blood cell formation (use of iron, RhuEpo).
- The following factors are potentially associated with a higher than expected HbA1C:
  - accumulation of uraemic toxins.

Chapter 2.3

A. Is any oral drug superior to another in terms of mortality/ complications/glycaemic control in patients with diabetes type 2 and CKD stage 3b or higher (eGFR <45 mL/min/ 1.73 m2)?

B. In patients with diabetes type 2 and CKD stage 3b or higher (eGFR <45 mL/min/1.73 m2), is maximal oral therapy better than starting/adding insulin at an earlier stage?

2.3.1 We recommend metformin in a dose adapted to renal function as a first line agent when lifestyle measures alone are insufficient to get HbA1C in the desired range according to Figure 4 (1B).

2.3.2 We recommend adding on a drug with a low risk for hypoglycaemia (fig 5, 6 and 7) as additional agent when improvement of glycaemic control is deemed appropriate according to Figure 4 (1B).

2.3.3 We recommend instructing patients to temporarily withdraw metformin in conditions of pending dehydration, when undergoing contrast media investigations, or in situations with an increased risk for AKI (1C).

Advice for clinical practice

- Consider instructing patients by using credit-card type flyers on when to temporarily withdraw metformin.
- Conditions considered as low, moderate or high risk for hypoglycaemia are depicted in Figure 5.
- Hypoglycaemia risk for different drugs is presented in Figures 5 and 7.
- In patients with diabetes type 2 and CKD stage 3b or higher (eGFR <45 mL/min/1.73 m2) who are on metformin, the decision to withhold the drug 48 h before and after administration of contrast media

should be taken by the treating physician, balancing the probability of emergence of contrast-induced nephropathy (type and amount of contrast,intravenous versus intra-arterial), and presence of other coexisting factors that might cause sudden deterioration of kidney function (dehydration, use of NSAID, use of inhibitors of the RAAS system) against the potential harms by stopping the drug (which should be considered low in view of the short period that it should be withheld).

- As renal clearances of different glycaemia-lowering agents might differ, combining different glycaemia-lowering drugs in a one pill formulation can lead to overdosing of one of the constituents in patients with CKD stage 3b or higher.

CHAPTER 3. ISSUES RELATED TO MANAGEMENT OF CARDIOVASCULAR RISK IN PATIENTS WITH DIABETES AND CKD STAGE 3B OR HIGHER

Chapter 3.1
In patients with diabetes andCKDstage 3b or higher (eGFR <45 mL/min/1.73 m2) or on dialysis and with CAD, is percutaneous coronary intervention (PCI), coronary artery bypass grafting (CABG) or conservative treatment to be preferred?

3.1.1 We recommend not omitting coronary angiography with the sole intention of avoiding potential contrast-related deterioration of kidney function in patients with diabetes and CKD stage 3b or higher (eGFR<45mL/min) in whom a coronary angiography is indicated (1D).

3.1.2 We recommend that optimal medical treatment should be considered as preferred treatment in patients with diabetes and CKD stage 3b–5 who have stable CAD, unless there are large areas of ischaemia or significant left main or proximal LAD lesions (1C).

3.1.3 We recommend that when a decision is taken to consider revascularization, CABG is preferred over PCI in patients with multivessel or complex (SYNTAX score >22) CAD (1C).

3.1.4 We recommend that patients with diabetes and CKD stage 3b or higher (eGFR <45 mL/min) who present with an acute coronary event should be treated no differently than patients with CKD stage 3b or higher (eGFR <45 mL/min) without diabetes or patients with diabetes without CKD stage 3b or higher (eGFR <45 mL/min) (1D).

Advice for clinical practice

For patients with stable CAD,

- Optimal medical treatment is the preferred treatment.
- When there are large areas of ischaemia, or indications

of significant left main or proximal LAD lesions, elective CABG is the preferred treatment.

For patients presenting with ST-elevation myocardial infarcton (STEMI), primary PCI is recommended over fibrinolysis if it can be performed within the recommended time limits.

For patients presenting with non-STEMI (NSTEMI)

- CABG results in improved outcomes (mortality,MACE) when compared with PCI when they have main stem lesions and/or advanced multivessel disease.
- Pharmacological treatment, including anti-thrombotic therapy, has a place provided the doses of the medications are adapted to renal function.

Chapter 3.2
In patients with diabetes and CKD stage 3b or higher (eGFR <45 mL/min/1.73m2) or on dialysis and with a cardiac indication (heart failure, ischaemic heart disease, hypertension) should we prescribe inhibitors of the RAAS system as cardiovascular prevention?

3.2.1 We recommend that adults with CKD stage 3b or higher (eGFR <45 mL/min/1.73 m2 or on dialysis) and diabetes who have a cardiovascular indication (heart failure, ischaemic heart disease) be treated ith an ACE-I at maximally tolerated dose (1B).

3.2.2 We suggest there is insufficient evidence to justify the start of an angiotensin-receptor blocker (ARB) in adults with CKD stage 3b or higher (eGFR <45 mL/min/1.73 m2 or on dialysis) and diabetes who have a cardiovascular indication (heart failure, ischaemic heart disease) but intolerance for ACE-I (2B).

3.2.3 We recommend not combining different classes of renin angiotensin-blocking agents (ACE-I, ARBs or direct renin inhibitors) (1A).

Advice for clinical practice

There is insufficient evidence whether or not RAAS inhibitors should be stopped in patients with CKD progressing to CKD stage 5. A trial stopping the RAAS inhibitor with the aim to delay the need to start renal replacement therapy can be discussed with the patient.

Chapter 3.3. In patients with diabetes and CKD stage 3b or higher (eGFR <45 mL/min/1.73 m2) or on dialysis, should we prescribe beta blockers to prevent sudden cardiac death?

3.3.1 We suggest starting a selective beta-blocking agent as primary prevention in patients with diabetes and CKD stage 3b or higher and then continuing it when tolerated (2C).

3.3.2 We suggest prescribing lipophilic rather than hydrophylic beta-blocking agents in patients with diabetes and CKD stage 3b or higher (eGFR <45 mL/min) (2C).

Chapter 3.4 In patients with diabetes and CKD stage 3b or higher (eGFR <45 mL/min/1.73 m2), should we aim at lower blood pressure targets than in the general population?

3.4.1 We suggest against applying lower blood pressure targets in patients with diabetes and CKD stage 3b or higher (eGFR <45 mL/min/1.73 m2) than in the general population (2C).

3.4.2 We suggest that in patients with diabetes and CKD stage 3b or higher (eGFR <45 mL/min/ 1.73 m2) but without proteinuria, all blood pressure-lowering drugs can be used equally to lower blood pressure (2C).

Advice for clinical practice

- Blood pressure should be carefully titrated to a target <140 mmHg SBP, while monitoring tolerance and avoiding side effects.
- Patients with diabetes and CKD stage 3b or highermight suffer from autonomic dysfunction and are thus more prone to complications associated with sudden hypotension.
- A diastolic blood pressure that is too low can jeopardize coronary perfusion.

Chapter 3.5 In patients with diabetes and CKD stage 3b or higher (eGFR <45 mL/min/1.73 m2) or on dialysis, should we prescribe lipid-lowering therapy in primary prevention?

3.5.1 We recommend starting a statin in patients with diabetes and CKD stage 3b and 4 (1B).

3.5.2 We suggest a statin be considered in patients with diabetes and CKD stage 5 (2C).

3.5.3 We recommend against starting a statin in patients with diabetes and CKD stage 5D (1A).

3.5.4 There was no consensus in the guideline development group on whether or not statins should be stopped in patients with diabetes with CKD stage 5D.

3.5.5 We suggest fibrates can replace statins in patients with CKD stage 3b who do not tolerate statins (2B).

Advice for clinical practice

- Doses of lipid-lowering agents should be adapted according to renal function (Table 8).
- As the doses in Table 8 should be considered maximal doses in patients with CKD, repetitive measurement of lipid levels does not add diagnostic or therapeutic value.
- For patients with CKD stage 5 or CKD stage 5D, patient preference and motivation to take another pill with its risk of side effects and limited expected benefit should guide management.

Chapter 3.6

A. In patients with diabetes and CKD stage 3b or higher (eGFR <45 mL/min/1.73m2), should we recommend interventions aimed at increasing energy expenditure and physical activity?

B. In patients with diabetes and CKD stage 3b or higher (eGFR <45 mL/min/1.73m2), should we recommend interventions aimed at reducing energy intake?

3.6.1 We suggest that patients with diabetes and CKD stage 3b or higher (eGFR <45 mL/min) perform additional physical exercise at least three times

1/2 to 1 hour/week to reduce fat mass and improve QoL (2D).

3.6.2 We suggest that there is no evidence of harm when promoting an individualized regimen of increased physical exercise (2C).

3.6.3 When promoting weight loss in patients with diabetes and with overweight, we recommend supervision of this process by a dietician and to ensure that only fat mass is lost and malnutrition is avoided (1C).

Chapter 3.7 In patients with diabetes and CKD stage 3b or higher (eGFR <45 mL/min/1.73 m2), should antiplatelet therapy be recommended, regardless of the cardiovascular risk?

3.7.1 We recommend against adding glycoprotein IIb/ IIIa inhibitors to standard care to reduce death, myocardial infarction, or need for coronary revascularization in patients with diabetes and CKD stage 3b or higher (eGFR <45 mL/min) and acute coronary syndromes (ACSs) or highrisk coronary artery intervention (1B).

3.7.2 We suggest not adding a thienopyridine or ticagrelor o standard care to reduce death,myocardial infarction, or need for coronary revascularization in patients with diabetes and CKD stage 3b or higher (eGFR <45 mL/min) and ACSs or high-risk coronary artery intervention unless there is no additional risk factor for bleeding (2B).

3.7.3 We recommend starting aspirin as secondary prevention, unless there is a contraindication, side effects or intolerance (1C).

3.7.4 We suggest starting aspirin as primary prevention only in patients without additional risk factors for major bleeding (2C).

Advice for clinical practice

Consider clopidogrel as an alternative for aspirin in patients with clear intolerance or contraindications for aspirin.

Tables

Table 6: Comparison of the different glycaemic markers in patients with diabetes and CKD stage 3b or higher

Marker	Advantages	Disadvantages
HbA1c	• Marker of longer-term glycaemic concentrations • Excellent standardization of HbA1c assays • Universally available primary reference measurement system • Scientific evidence on association with outcomes from several trials • In comparison with blood glucose, less sensitivity to preanalytical variables, lower within subject biological variability, little/no diurnal variations, little/no influence from acute stress and little/no influence from common drugs which are known to influence glucose metabolism • Excellent separation of the HbA1c fraction from other haemoglobin adducts and with no interference from carbamylated haemoglobin due to technological advances in HbA1c measurement	• Falsely increased values with iron deficiency, vitamin B12 deficiency, decreased erythropoiesis, alcoholism, chronic renal failure, decreased erythrocyte pH, increased erythrocyte lifespan, splenectomy, hyperbilirubinaemia, carbamylated haemoglobin, alcoholism, intake of large doses of aspirin, chronic opiate use • Falsely decreased values have been reported after administration of erythropoietin, iron or vitamin B12; with reticulocytosis, chronic liver disease, ingestion of aspirin, vitamin C, vitamin E, certain haemoglobinopathies, increased erythrocyte pH, a decreased erythrocyte lifespan, haemoglobinopathies, splenomegaly, rheumatoid arthritis, drugs such as antiretrovirals, ribavirin and dapsone, hypertriglyceridaemia • Variable changes have been seen in patients with HbF, haemoglobinopathies, methaemoglobin, genetic determinants
Glycated albumin	• Measure of shorter-term glycaemic control (2–3 weeks) • Not influenced by gender, erythrocyte lifespan, erythropoietin therapy or serum albumin concentration • Significant association with markers of vascular injury	• Values can be influenced by lipaemia, hyperbilirubinaemia, haemolysis, increased uric acid, uraemia, intake of high doses of aspirin, low serum protein concentrations/nutritional status, age, albuminuria, cirrhosis, thyroid dysfunction and smoking • Concentration is inversely influenced by body mass index, body fat mass and visceral adipose tissue • Different reference ranges depending on the applied method • Limited data, especially on the impact of using it as a target • Expensive, time consuming, not widely available
Fructosamine	• Correlates with average glucose levels in the previous 10–14 days • Simple, automated analysis	• Contradictory results concerning the correlation between fructosamine and mean glucose concentrations in patients with CKD stage 3b or higher • Values can be influenced by nephrotic syndrome, thyroid dysfunction, glucocorticoid administration, liver cirrhosis, icterus • Concentration in uraemic patients may be influenced by a number of variables other than glycaemia, including hypoalbuminaemia, hyperuricaemia • Within-subject variation is higher than that for HbA1c
1,5-anhydroglucitol	• Reflects day-to-day changes in glucose levels. • Retained metabolic inertness, steady-state levels in all tissues and negligible influence of sampling conditions such as collection time, body weight, age, sex and food intake of the subjects	• Poorer performance in identifying cases of undiagnosed diabetes in comparison with other glycaemic markers • Influenced by traditional Chinese herbal drugs • Limitations for use in subjects with renal tubular acidosis, or advanced renal disease • Not widely available, limited data on its clinical everyday value
Continuous glucose measurement	• Theoretically the most ideal marker for glycaemic control • Allows examination of short-term glycaemic changes around the time of dialysis	• Exhaustion of the sensor, limited data

Table 7: Oral glycaemia-lowering drugs: mechanisms of action

Drug class	Mechanisms of action	Examples (alphabetical order)
Biguanides	- Decrease hepatic glucose production - Increase insulin sensitivity - Increase insulin-mediated utilization of glucose in peripheral tissues - Decrease glucose intestinal absorption	Metformin
Sulfonylureas	- Stimulate insulin secretion from the pancreas - Closes K-ATP channels on β-cell plasma membranes	Acetohexamide, chlorpropamide, glibenclamide, gliclazide, glyburide, glimeperide, glipizide, gliquidone
Meglitinides	- Stimulate pancreatic insulin secretion by closing K-ATP channels on β-cell plasma membranes	Nateglinide, repaglinide
Alfa glucosidase inhibitors	- Block the action of the α-glucosidase with reduced hydrolysis of complex saccharides - Reversible inhibition of the pancreatic enzyme α-amylase	Acarbose, miglitol
Glitazones	- Reduce insulin resistance - Increase glucose uptake in muscles and adipose tissue - Decrease hepatic glucose production	Pioglitazone
DPP-IV inhibitors	- Inhibit DPP-4, which inactivates endogenous incretins	Alogliptin, linagliptin, saxagliptin, sitagliptin, vildagliptin,
Incretin mimetics	- Promote glucose dependent insulin secretion by pancreatic β cells - Suppress glucagon secretion - Slow gastric emptying	Eexenatide, liraglutide, lixisenatide
Amylin analogues	- Regulate glucose levels in response to food intake - Control gastric emptying and postprandial glucagon secretion - Reduce food intake by increasing satiety	Pramlinitide
SLT-2 inhibitors	- Block the sodiumglucose transport protein subtype 2, thus increasing renal loss of glucose	Canagliflozin, dapagliflozin, empagliflozin

Table 8: Dose recommendations of statins in patients with CKD stage 3b or higher (eGFR <45 mL/min). *Adapted from Tonelli and Wanner Ann Intern Med 2014; 160: 182*

Statin	Maximum dose when eGFR <45 mL/min
Lovastatin	No data
Fluvostatin	80 mg
Atorvastatin	20 mg
Rosuvastatin	10 mg
Simvastatin/ezetimibe	20/10 mg
Pravastatin	40 mg
Simvastatin	40 mg
Pitavastatin	2 mg

Figures

Figure 2: Decision flow chart for vascular access in patients with diabetes

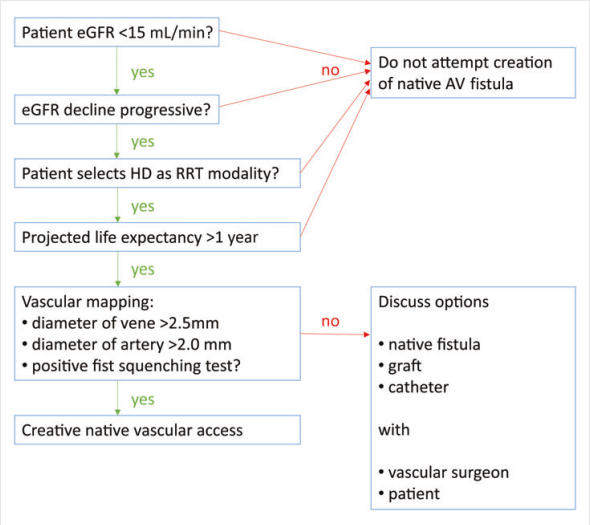

Figure 3: Transplantation decision flow chart for patients with type 1 diabetes

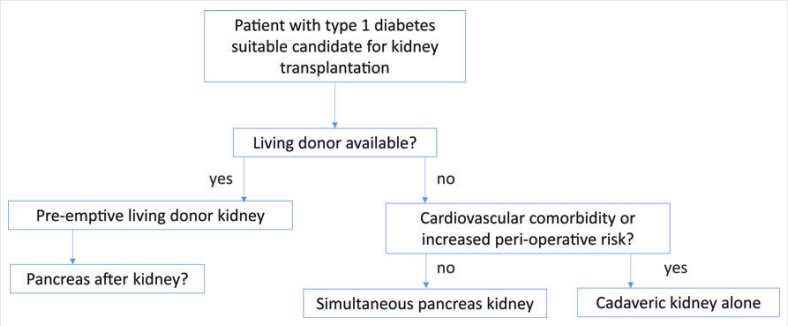

Figure 4: Flowchart of management targets for HbA1C in patients with diabetes and CKD stage 3b or higher (eGFR <45 mL/min)

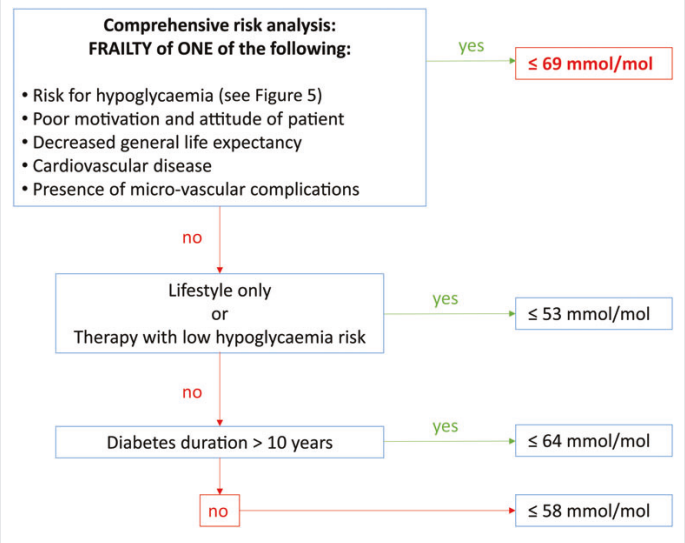

Figure 5: Assessment of risk for hypoglycaemia

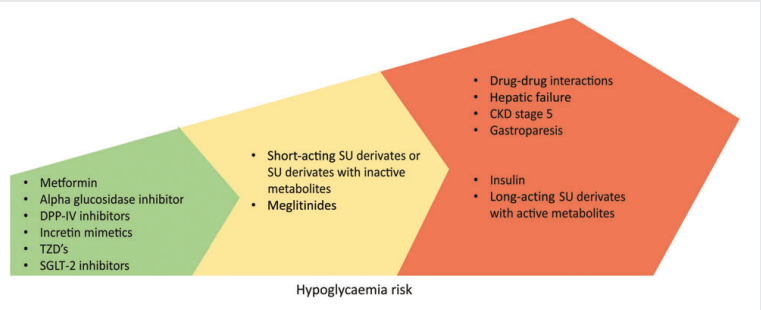

Figure 6: Dose recommendation in CKD

Figure 7: Impact of different classes of glycaemia-lowering drugs on different outcomes Dark green denotes evidence for beneficial effect; red indicates evidence for negative effect; yellow represents not investigated or insufficient data; salmon denotes evidence for weak negative effect; aquamarin represents evidence for neutral to weak positive effect; dark blue indicates evidence for lack of effect/neutral.

Notes:

Notes:

Diabetes 2015