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Primary Care Toolkit Understanding Diabetic Kidney Disease

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Learning Outcomes

- To increase knowledge and understanding of:
  - Connection between Diabetes and CKD
  - Monitoring of kidney function (NICE guidance)
  - Slowing progression
  - Referral to Renal Team
  - Medicines management (Hypertension, oral glycaemics, cardio vascular risk)
  - Managing diabetes specifically when having haemodialysis

Who should be screened for CKD?

- People with the following conditions should be screened for CKD:
  - Diabetes
  - Hypertension
  - Acute kidney injury
  - Cardiovascular disease (ischaemic heart disease, chronic heart failure, peripheral vascular disease or cerebral vascular disease)
  - Known structural renal tract disease, recurrent renal calculi or prostatic hypertrophy
  - Prescribed drugs that have an impact on kidney function, e.g. calcineurin inhibitors, lithium, NSAIDs

Causes & Risk Factors of CKD

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Causes

- Type 1 or type 2 diabetes
- Hypertension
- Glomerulonephritis
- Interstitial nephritis
- Autosomal dominant polycystic kidney disease (ADPKD)
- Prolonged obstruction of the urinary tract, e.g enlarged prostate, kidney stones and some cancer
- Vesicoureteral reflux, (urine forced back into the kidneys when the bladder contracts
- Recurrent kidney infection

Risk Factors

- Diabetes
- Hypertension
- Cardiovascular disease
- Smoking
- Obesity
- Race: African-American, Native American or Asian-American
- Family history of kidney disease
- Abnormal kidney structure
- Older age

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Diagnosing CKD

Two eGFR estimations <60ml/min/1.73m^2 over a period of at least 90 days (with or without markers of kidney damage)

or

Normal eGFR with albumin:creatinine ratio (ACR) >3 mg/mmol

- Symptoms
  - Often asymptomatic, disease only identified once a routine blood or urine test detects a possible problem
    - Symptoms: weight loss, poor appetite, oedema, shortness of breath, tiredness, haematuria frequency of micturition, insomnia, muscle cramps, nausea, headaches

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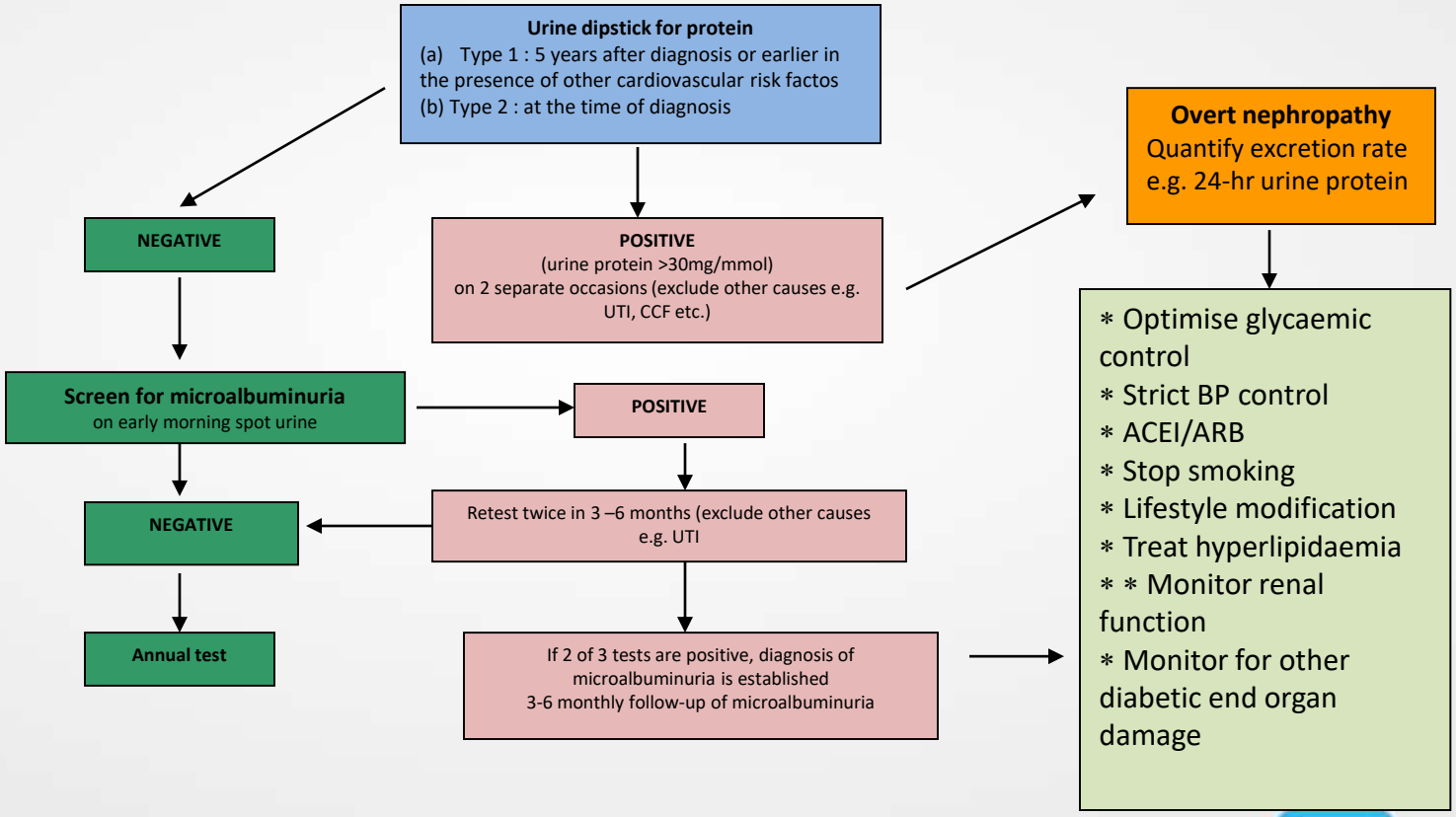
Algorithm : Screening for Proteinuria



Categories of Proteinuria

A1	A2	A3
Normal to mild ↑ <3mg/mmol	Moderate ↑ 3-30mg/mmol	Severe ↑ >30mg/mmol

Factors that may affect ACR results

- Poor glycaemic control
- Poor blood pressure control
- Exercise
- Gender
- Race

ACR >70 **REFER**

Managing proteinuria

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- Early identification of proteinuria can limit progression of CKD
- How to measure
  - –ACR (albumin creatinine ratio)
  - –PCR (protein creatinine ratio)
  - –Reagent strips detect albumin not protein so not quantitative

Normalbuminuria, Microalbuminuria, –Macroalbuminuria- old terminology

- NICE recommend ACR in preference to PCR, because it has greater sensitivity for low levels of proteinuria.

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NICE CG182 CKD guidelines

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Reviews and monitoring:

- Agree the frequency of monitoring (eGFR creatinine and ACR) with the person with, or at risk of, CKD; bear in mind that CKD is not progressive in many people[1]
- Use the table shown to guide the frequency of GFR monitoring for people with, or at risk of CKD[1]
- The frequency of monitoring should be tailored to the individual, according to:
  - The underlying cause of CKD[1]
  - Past patterns of eGFR and ACR[1]
  - Comorbidities[1]
  - Changes to their treatment[1]
  - Intercurrent illness[1]
  - Whether they have chosen conservative management of CKD[1]

The numbers in this table indicate recommended frequency of monitoring per year		ACR categories (mg/mmol), description and range		
		A1 <3 Normal to mildly increased	A2 3-30 Moderately increased	A3 >30 Severely increased
GFR categories (ml/min/1.73 m²), description and range	G1 ≥90 Normal and high	≤1	1	≥1
	G2 60-89 Mild reduction related to normal range for a young adult	≤1	1	≥1
	G3a 45-59 Mild-moderate reduction	1	1	2
	G3b 30-44 Moderate-severe reduction	≤2	2	≥2
	G4 15-29 Severe reduction	2	2	3
	G5 <15 Kidney failure	4	≥4	≥4

Increasing risk

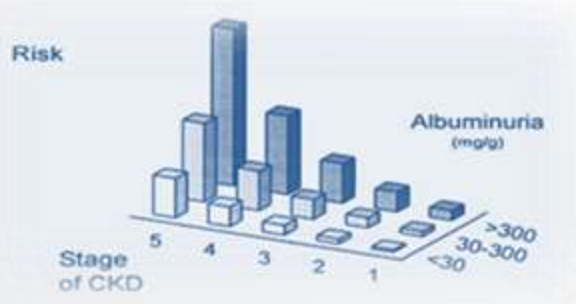
Increasing risk

Adapted from: NICE clinical guideline 182. Chronic kidney disease early identification and management of chronic kidney disease in adults in primary and secondary care. July 2014.

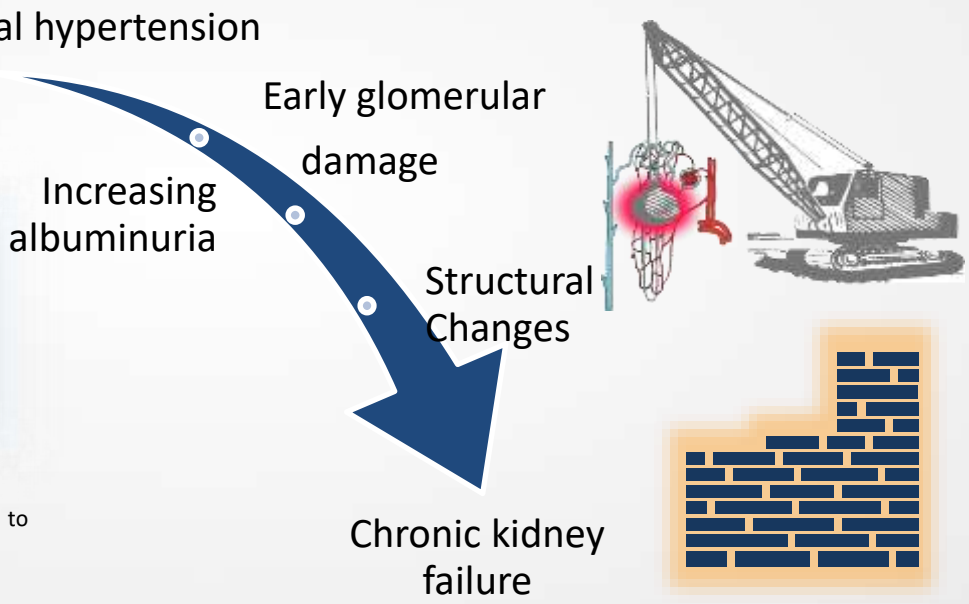
Reference:
1. NICE clinical guideline 182. Chronic kidney disease early identification and management of chronic kidney disease in adults in primary and secondary care. July 2014.

Untreated diabetic kidney disease leads to kidney failure

- Without specific interventions, 20-40% of people with type 2 diabetes with albuminuria progress to overt kidney disease[1]



Relationship of stage of kidney disease and level of albuminuria to prognosis in CKD[2]



References: 1. American Diabetes Association. *Diabetes Care* 2004;27(suppl 1):s79-s83. **2. NKF K/DOQI Guidelines. Available at: http://www.kidney.org/professionals/kdoqi/guidelines_bp/background.htm. Figure 13.**

Statistics

- An estimated 40% of patients with T2DM have some form of CKD; 18 – 30% have CKD stage 3 – 5
- The proportion of T2DM patients with kidney disease is increasing
  - The prevalence of Stage 3 – 5 CKD in T2DM patients from 12 European countries is projected to rise by approximately 50% between 2012 and 2025
- Markers of diabetic kidney disease (declining eGFR and proteinuria) are associated with
  - Increased mortality
    - Patients with T2DM and kidney disease have a higher mortality rate than those without kidney disease
    - CKD accounts for 11% of all deaths in T2DM patients
  - Renal events
  - CV events
  - CV death

Benefits of Glycaemic Control in Diabetic Kidney Disease

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- Reduces rates of renal function decline
  - Particularly if combined with blood pressure control
  - Can reverse hyper-filtration and glomerular hypertrophy
  - Can delay development of albuminuria and overt kidney disease
  - Can slow down the progression of established renal insufficiency
- Reduces complications
  - Autonomic neuropathy, fluid overload
- Improves outcomes
  - Delays the need for dialysis, improves the chances of a successful transplant
- Reduces costs
  - Care for a patient on dialysis costs the NHS around £27,000 a year, while the cost of slowing down kidney deterioration is around £235 a year[1]
- Optimise glycaemic control <48mmol

References: 1. NHS Kidney Care. Addressing Low Chronic Kidney Disease Prevalence in Primary Care. Project report. March 2013. Available at: http://www.cmkcn.nhs.uk/attachments/article/37/Addressing%20Low%20Chronic%20Kidney%20Disease%20Prevalence%20in%20Primary%20Care[1].pdf.

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HbA1c: factors that influence targets

- Haemoglobin A1c (HbA1c) measures circulating Hb and glucose over a 120-day cycle
- HbA1c:
  - Normal level <42mmol
  - Impaired Glucose Tolerance 42–48mmol
  - Diabetes diagnosed > 48mmol
- Measured by three different elements
  - Amount of Hb found in reticulocytes when they leave the bone marrow.
  - Rate of Hb glycation as the red cells age. This is a specific function of the amount of glucose that Hb is subjected to.
  - The average age of the red cell

How does anaemia affect HbA1c readings?

- RBC lifespan shortened by anaemia
- CKD shortened erythrocyte survival (90 days)
- Falsely lowers HbA1c results (regardless of which assay is used)
- Iron replacement therapy also lowers HbA1c and fructosamine concentrations
- Caution when interpreting A1c and management of glycaemia when based on this measurement alone
- Suggest use of home blood glucose monitoring for these patients

Hypoglycaemia with type 2 diabetes and CKD when taking oral glucose control therapies

- Progressive CKD increases the risk of hypoglycaemia
- Risk of 'hypos' more difficult to predict in these patients
- Drug clearance is variable with ↓eGFR
- Symptoms of 'hypos' are often reduced

ALWAYS ASK ABOUT HYPOGLYCAEMIA

- Assess 'risk and treatment' of hypoglycaemia
- More tailored dosing is required
- Patients need to be monitored more frequently

Perform frequent therapy reviews, especially if patient commences dialysis

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Type 2 medication - considerations

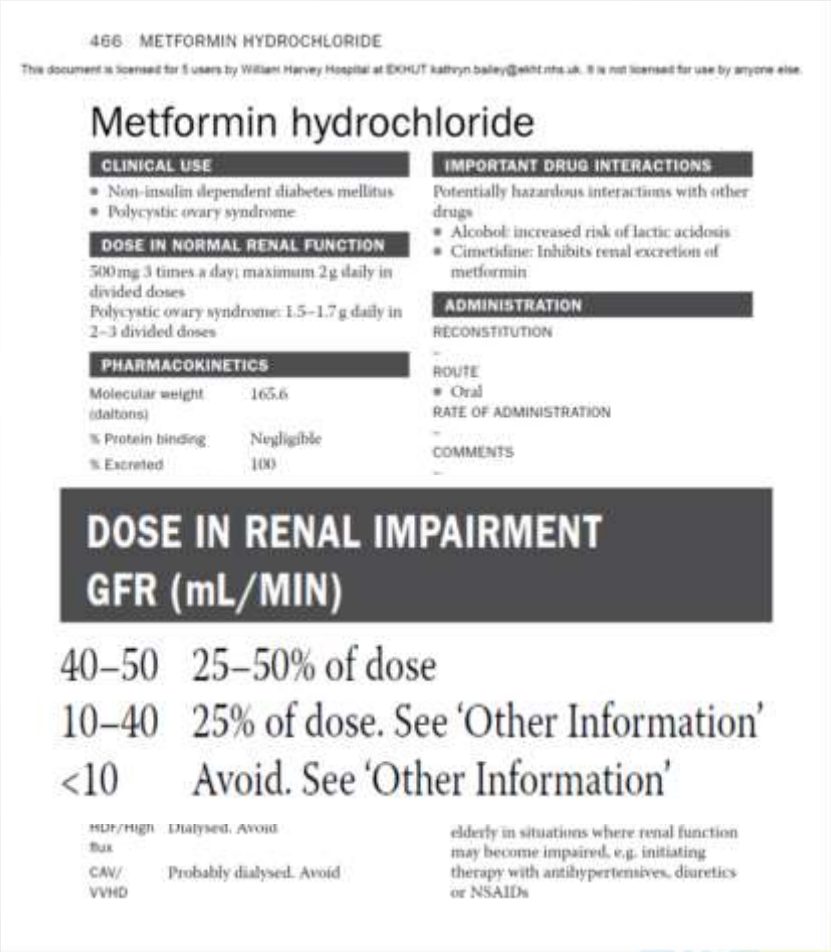
MEDICATION GROUP	DRUGS IN CATEGORY	INSTRUCTIONS IN RENAL IMPAIRMENT
Biguanides	Metformin	Caution in eGFR 30-45 Stop when eGFR <30 (or before if gradual decline) Not recommended on dialysis
Sulphonylureas	Gliclazide, Glimepiride, Glipizide	Caution in eGFR 30-45 Stop when eGFR <30 (or before if gradual decline) Not recommended on dialysis
Thiazolidinedione	Pioglitazone	Considered safe in eGFR down to 15 – but consider other co-morbidities Not recommended on dialysis
DPP4 inhibitors	Linagliptin	No dose reduction, down to eGFR of 15
	Alogliptin, Sitagliptin, Saxagliptin, Vildaglipin	Dose adjustment required (look at individual drugs)
GLP-1 receptor agonists	Lixisenatide, Byetta, Victoza, Bydureon, Dulaglitide.	Stop when eGFR <30 Not recommended on dialysis
Sodium glucose co-transporter 2 inhibitors (SGLT-2)	Dapaglifozin, Canaglifozin, Empaglifozin	New evidence from CREDENCE (eGFR ≥ 60) reviewing license in CKD Not recommended on dialysis

Nice metformin

In adults with type 2 diabetes, review the dose of metformin if the estimated glomerular filtration rate (eGFR) is below 45 ml/minute/1.73m^2:

Stop metformin if the eGFR is below 30 ml/minute/1.73m^2.

Prescribe metformin with caution for those at risk of a sudden deterioration in kidney function and those at risk of eGFR falling below 45 ml/minute/1.73m^2. **[2015]**



466 METFORMIN HYDROCHLORIDE

Metformin hydrochloride

CLINICAL USE
- Non-insulin dependent diabetes mellitus
- Polycystic ovary syndrome

DOSE IN NORMAL RENAL FUNCTION

500 mg 3 times a day; maximum 2 g daily in divided doses
Polycystic ovary syndrome: 1.5–1.7 g daily in 2–3 divided doses

PHARMACOKINETICS

Molecular weight (daltons)	165.6
% Protein binding	Negligible
% Excreted	100

IMPORTANT DRUG INTERACTIONS

Potentially hazardous interactions with other drugs
- Alcohol: increased risk of lactic acidosis
- Cimetidine: Inhibits renal excretion of metformin

ADMINISTRATION

RECONSTITUTION
–
ROUTE
- Oral

RATE OF ADMINISTRATION
–
COMMENTS
–

DOSE IN RENAL IMPAIRMENT

GFR (mL/MIN)	
40–50	25–50% of dose
10–40	25% of dose. See 'Other Information'
<10	Avoid. See 'Other Information'

HDF/High flux	Dialysed. Avoid	elderly in situations where renal function may become impaired, e.g. initiating therapy with antihypertensives, diuretics or NSAIDs
CAV/VVHD	Probably dialysed. Avoid	

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Optimal care for Diabetic Nephropathy

- Control blood pressure (BP)
- Control blood glucose
- Measure proteinuria
- Measure kidney function
- Assess cardiovascular risk
- Identify progressive disease and refer if appropriate
- Annual eye & foot checks
- Lifestyle advice

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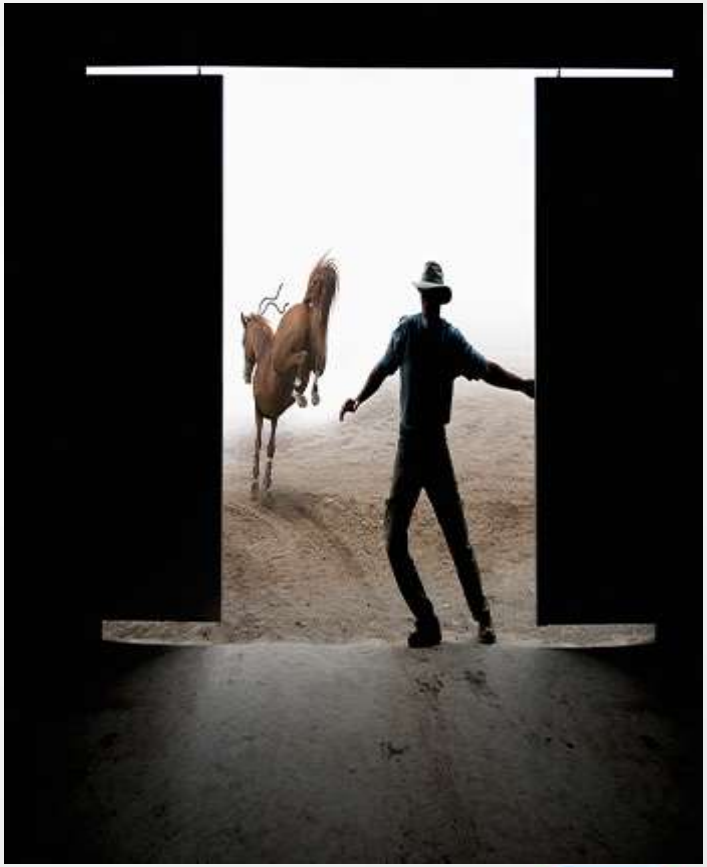
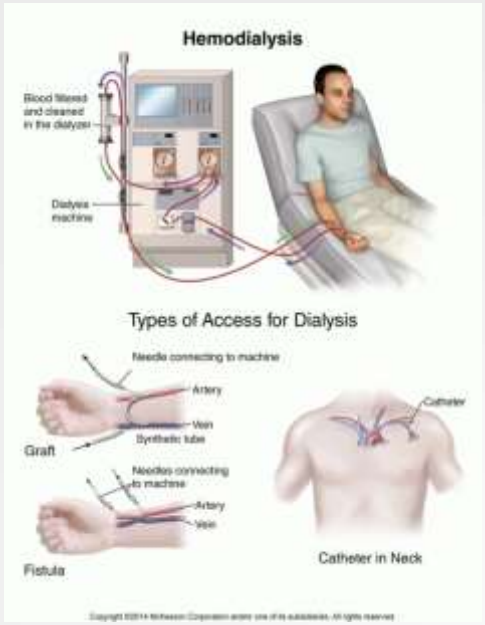
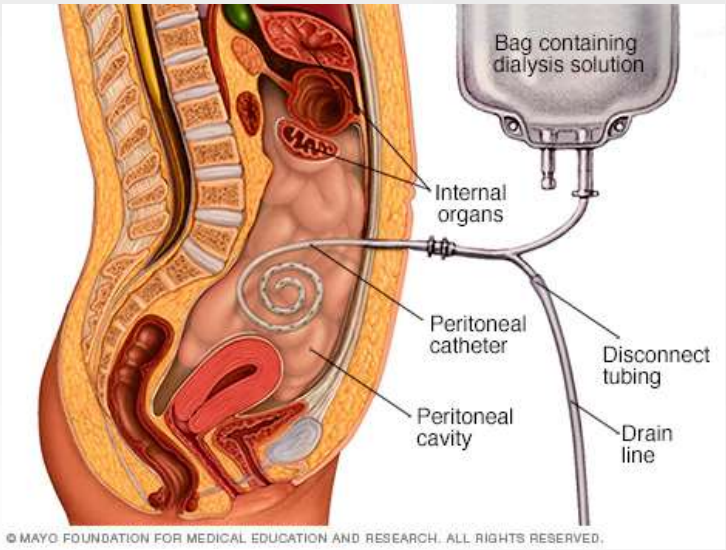
Referral to Kidney Doctors

- eGFR < 30ml/min with or without Diabetes
- ACR ≥ 70 mg/mmol, unless known to be caused by diabetes and already appropriately treated
- Sustained ↓ GFR of ≥25% change in GFR category or sustained ↓ GFR of ≥15 ml/min/1.73 m^2
- ↓ eGFR of >25% after starting ACEi or ARB
- hypertension that remains poorly controlled using at least 4 antihypertensive drugs at therapeutic doses
- Known or suspected rare or genetic causes of CKD
- Suspected renal artery stenosis.




Hemodialysis
Blood filtered and cleaned in the dialyzer
Dialysis machine
Types of Access for Dialysis
Needle connecting to machine
Artery
Vein
Synthetic tube
Graft
Needles connecting to machine
Artery
Vein
Fistula
Catheter
Catheter in Neck


Bag containing dialysis solution
Internal organs
Peritoneal catheter
Disconnect tubing
Peritoneal cavity
Drain line
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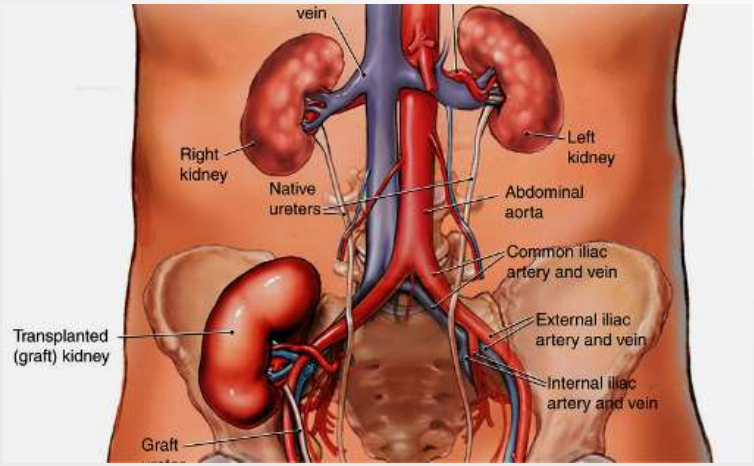
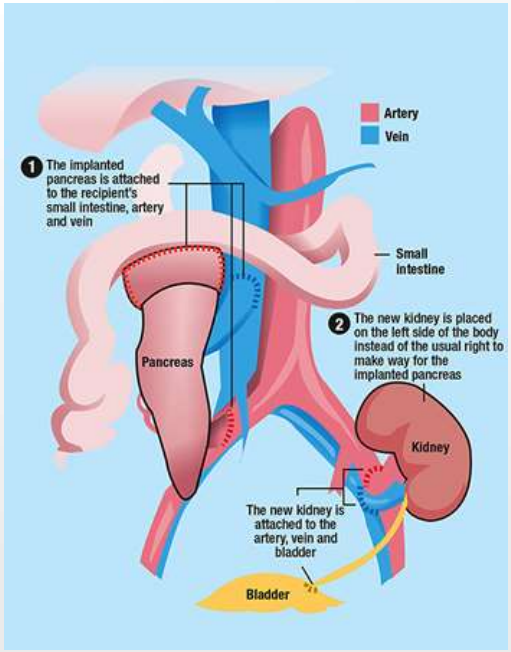

vein
Right kidney
Left kidney
Native ureters
Abdominal aorta
Common iliac artery and vein
Transplanted (graft) kidney
External iliac artery and vein
Internal iliac artery and vein
Graft


Artery
Vein
1 The implanted pancreas is attached to the recipient's small intestine, artery and vein
Small intestine
2 The new kidney is placed on the left side of the body instead of the usual right to make way for the implanted pancreas
Pancreas
Kidney
The new kidney is attached to the artery, vein and bladder
Bladder

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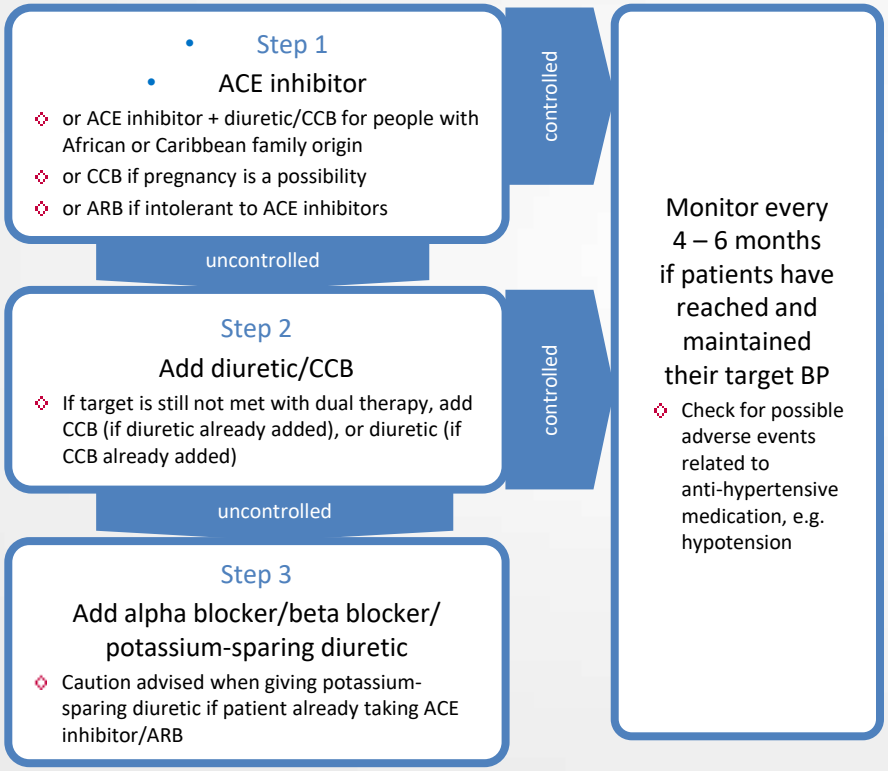
Blood pressure management in type 2 diabetes



If 4 or more anti-hypertensive drugs
Refer to Nephrologist

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Hypertension: choice of agents

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- **CKD (eGFR≤59), diabetes and proteinuria (ACR>3mg/mmol)[1]**
- **CKD and proteinuria (ACR>30mg/mmol)[1]**
- **People < 55yrs (regardless of proteinuria)[2]**

ACE-I (or ARB if intolerant to ACE-I) first line

- **People > 55yrs without proteinuria[2]**
- **Black people of any age without proteinuria[2]**

Calcium channel blocker first line

- Aim systolic blood pressure <140 mmHg (target range 120–139 mmHg) diastolic <80mmHg
  - SBP <130 mmHg (target range 120–129 mmHg)
  - DBP <80 mmHg

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References: 1. NICE clinical guideline 182. Chronic kidney disease early identification and management of chronic kidney disease in adults in primary and secondary care. July 2014. **2.** NICE clinical guideline 127. Clinical management of primary hypertension in adults. August 2011.

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Haemodialysis and Diabetes Management

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What are the challenges?

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Diabetes

- Glycaemic control
- Medication adjustment
  - Insulin
  - Oral glycaemics
- Maintaining patient self-management
  - Lifestyle changes
- Who's job is it?

Impact of HD

- HD causes associated fluid shifts, metabolite and electrolyte changes
- Affects Pharmacokinetics of insulin and oral agents
- Renal gluconeogenesis is reduced in ESRF
- Insulin resistance, exacerbated by HD
- Impact of gastroparesis, malnutrition
- Timing of dialysis shifts
  - eating patterns, long journey times to attend dialysis centres
- HbA1c unreliable
  - Renal Anaemia

Dialysis affects glycaemic control

- Affects insulin secretion, clearance and resistance (periodic improvement in uraemia, acidosis and phosphate metabolism)
- Glucose concentration in dialysate may influence glucose control
  - lower glucose dialysates associated with hypoglycaemia
- Blood glucose falls during a haemodialysis, commonly lowest point being during 3rd hour
- Glucose control on dialysis days may differ to non-dialysis days, leading to unpredictable glucose levels, and glycaemic variability.

Guidelines & HbA1C

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HbA1C Targets

- ESRD HbA1c 58-68mmol/mol, (7%-8.2%) [1]
- Higher risk of hypoglycaemia in patients with poor nutrition, low albumin and low BMI
- If taking hypoglycaemia inducing agent consider HbA1c <58 mmol/mol (7.5%) particularly sulphonylureas or insulin[2]

Practical Tips

- Timing of dialysis patients may require snacks
- Patients with gastroparesis are encouraged to have a small meal size but frequent intake.
- A low-fat/low-fibre meal recommended to manage gastroparesis[1]
- Adjust insulin administration times/doses

References: 1.(Joint British Diabetes Societies www.diabetologists-abcd.org.uk/JBDS/JBDS.htm 2016; 2. EDTNA/ERCA Gregory S; Jenkins K: Managing Patients on Haemodialysis with Diabetes Aug 2018 https://www.edtnaerca.org/resource/edtna/files/ManagingHaemodialysiswithDiabetes.pdf

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Adjusting Oral Anti-Glycaemic therapy

Medication Group	Drugs in this category	Instructions in renal impairment
Biguanides	Metformin	Not recommended for those on dialysis
Sulphonylureas	Gliclazide Glimepiride Glipizide Gliblenclamide Tolbutamide	Not recommended for those on dialysis
Alpha glucoside antagonist	Acarbose	Not recommended for those on dialysis
Thiazolidinedione,	Pioglitazone	Not recommended for those on dialysis, and may increase oedema.
DPP4 inhibitors	Linagliptin Alogliptin Sitagliptin Saxagliptin Vildagliptin	Linagliptin requires no dose reduction The following are not recommended for those on dialysis- may be used with caution on individual patient basis Alogliptin – reduce to 6.25mg Sitagliptin – reduce to 25mg Saxaglitpin – reduce dose to 2.5mg Vildagliptin – reduce dose to 50mg
GLP-1 receptor agonists/mimetics		Not recommended for those on dialysis
Sodium glucose co-transporter 2 inhibitors (SGLT-2)	Dapagliflozin Canagligozin Empagliflozin)	Not recommended for those on dialysis
Short-acting oral insulin secretagogues	Nateglinide Repaglinide:	GFR<30ml/min – (Stages G4 & G5) – use with caution and initiate small starting. ↑risk of hypoglycaemia patients should monitor blood glucose frequently

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Adjusting Insulin

Insulin Group	Time of onset	Peak	Duration	Renal Advice (JBDS, 2016)
Intermediate (Human or Animal) Isophane Given OD or BD	1-2hrs	6-8hrs	16-22hrs	Reduce dose by 25% on the morning of dialysis
Short Acting (Human or Animal) Soluble Given 30-45 mins prior to a meal	45 – 75 minutes	2-3hrs	6-8hrs	If am dialysis reduce breakfast dose by 10-15% If pm dialysis reduce lunchtime dose by 10-15% If evening dialysis reduce evening insulin by 10-15%
Human or Animal Mixed Insulin Given BD 30- 45 mins before meal	45 – 75 minutes	2-4hrs	16-22hrs	If am or pm dialysis reduce breakfast dose by 10-15% If evening dialysis reduce evening dose by 10-15%
Long Acting (Analogue) basal insulin Once or twice daily	Continuous	Little or no peak	16 - 36hrs	Reduce dose by 25% on the morning of dialysis
Rapid Acting Analogue With meals	5-15minutes	1.5 - 2hrs	4-5hrs	If am dialysis reduce breakfast dose by 10-15% If pm dialysis reduce lunchtime dose by 10-15% If evening dialysis reduce evening insulin by 10-15%
Mixed Analogue Insulin With meals	5-15minutes	1.5 - 2hrs	12-16hrs	If am or pm dialysis reduce breakfast dose by 10-15% If evening dialysis reduce evening dose by 10-15%

Adapted from SPC information

Considerations for Practice

- Possible reduction of insulin doses during and immediately following dialysis
  - Individualise on basis of Continuous Glucose Monitoring (CGM) data
- Encourage self-monitoring of blood glucose on dialysis and non-dialysis days
- Education on adjusting insulin doses to avoid hypoglycaemia
  - different insulin's work in different ways so the diabetes team should be involved with patients who are on dialysis and need support in managing their doses
- Those with type 2 DM may experience frequent hypoglycaemic episodes resulting in a temporary or permanent cessation of their anti-diabetic therapies
- Joint working between disciplines (diabetes/renal)

- Around 70% patients will require less insulin as kidney function declines
- Around 25% may stop insulin completely
- Action profiles are generally prolonged and less predictable
- Avoid longer-acting analogues unless there are no issues
- TDS pre-mix regimens maybe better tolerated
- Mean glucose is lower on dialysis days
- Frequent monitoring is advised
- Haemodialysis affects glycaemic control
- Pharmacokinetics of insulin & oral agents affected

Summary Key Points

- Remember the basics
- Screen for proteinuria
  - REFER appropriately
- ACE inhibitor or ARB therapy improves outcomes - BUT NOT PRESCRIBED TOGETHER
- Presence of diabetic kidney disease implies generalised vascular disease which requires holistic management
- Oral hypoglycaemic therapy needs adjusting in people with diabetic kidney disease
- Insulin may need adjusting if people with diabetes and kidney disease are receiving dialysis
- Consider referral to a Nephrologist
- Work collaboratively with your local Renal team

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Thank you for listening

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