Management of chronic kidney disease (CKD) and diabetes.

Dr. Peter Winocour
Conflicts of Interest

• There are no relevant declarations of interest to declare
Diabetes and CKD
An Exemplar of MultiMorbidity

Glucose
HBP
Lipids
Diabetic renal disease is the most common cause of renal failure in the UK

DM - 4 million in UK (6%)
10% prevalence projected by 2025

### Staging of CKD

<table>
<thead>
<tr>
<th>GFR categories (mL/min/1.73 m²), description and range</th>
<th>ACR categories (mg/mmol), description and range</th>
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</thead>
<tbody>
<tr>
<td>GFR and ACR categories and risk of adverse outcomes</td>
<td>ACR categories (mg/mmol), description and range</td>
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<tr>
<td></td>
<td>&lt;3 Normal to mildly increased</td>
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<tr>
<td>≥90 Normal and high</td>
<td>A1</td>
</tr>
<tr>
<td>60–89 Mild reduction related to normal range for a young adult</td>
<td>G1</td>
</tr>
<tr>
<td>45–59 Mild–moderate reduction</td>
<td>G3a</td>
</tr>
<tr>
<td>30–44 Moderate–severe reduction</td>
<td>G3</td>
</tr>
<tr>
<td>15–29 Severe reduction</td>
<td></td>
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<tr>
<td>&lt;15 Kidney failure</td>
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</table>

Factors that may cause a misleading ACR or eGFR result

- **ACR**: measured in a fresh early-morning sample; misleading increase may result from exercise or from regular daytime ambulant activity or
  - Urinary tract infection
  - Congestive cardiac failure
  - Acute febrile-inflammatory illness
  - Menstruation or vaginal discharge

- **eGFR**: is estimated. Not validated aged < 18yrs and the elderly. Inaccurate in:
  - Pregnancy, Oedema
  - Extremes of Muscle mass, **Obesity**
  - Acutely changing renal function
  - Anything that affects creatinine – high meat intake, Hydration
  - N.B. Ageing – The ‘renopause’
Nonlinear regression analysis of the relationship between age and eGFR

Solini et al JAGS 2013; 61 1253-61
QUESTION 1

• HOW MANY INDIVIDUALS IN THE UK HAVE BOTH DIABETES AND IMPAIRED GFR (<60)
  a. Approximately 100,000
  b. Approximately 250,000
  c. Approximately 500,000
  d. Approximately 750,000
  e. Approximately 1,00,000
Prevalence of CKD in Type 2 Diabetes

- Over 1 in 3 people with T2D have impaired kidney function (CKD 2-5)

N.B. Based solely on eGFR

Impaired kidney function (33.8%)
Epidemiology of Renal Disease in DM

- **T1DM** – linked to glycaemia, BP – nephropathy 20%
  - Incidence declining with better glycaemia control.

- **T2 DM**: Associated with insulin resistance, endothelial dysfunction, CVD risk factors – **30% Microalbuminuria**
  - Microalbuminuria may be present at diagnosis
  - More often non DM basis for CKD - proteinuria the key to true DN in T2DM
CVD risk greatest when Diabetes and CKD co-exist

CHF=congestive heart failure; AMI=acute myocardial infarction; CVA/TIA=cerebrovascular accident/transient ischemic attack; PVD=peripheral vascular disease; ASVD=atherosclerotic vascular disease. *ASVD was defined as the first occurrence of AMI, CVD/TIA, or PVD.
Assessing and Achieving Glycaemic control in DM-CKD

- Targets and utility of HbA1c differs through CKD
- Hierarchy of targets: HBP and Dyslipidaemia-CVD
- Evidence from intervention studies in non CKD: DCCT and ACCORD-ADVANCE
- Benefit of Legacy effect if achieved early in DM
- Caution in older DM with CVD
HbA1c- glycaemic control

- Diagnostic threshold 48 mmol/mol (6.5%)

- Older recommended targets in CKD:
  - Renal Association 2010: 48-58 (6.5-7.5%)
  - NKF-KDOQI 2012: < 53 mmol/mol (7%)

  **BUT**

- Individualised targets ADA-EASD-NICE.

- **ABCD-RA may recommend HbA1c 58-69 in CKD3b-5**
Glycaemic control in CKD

- DM with CKD are at high risk for progressive vascular complications - HbA1c still predictive
- Retinopathy progression and foot disease, esp sepsis, require tailored glycaemic input
- Tight glycaemic control in T2DM reduces development and progression of CKD 1-3 and later CKD in T1DM
- Limited data from prospective studies of T2DM improved glycaemic control reducing ESRD
DCCT- T1DM. Renal and CVD

Target HbA1c 7.5% (58 mmol/mol)

Cumulative incidence eGFR < 60

42% risk reduction

P=0.02

No. at Risk
Conventional 714 688 618 92
Intensive 705 683 629 113

Action to Control Cardiovascular Risk in Diabetes

Older Type 2 DM

TARGET HbA1c 6.5% (48 mmol/mol).

Insulin based regime - no CVD reductions
Type 2DM: ACCORD: Glycaemic control and development of Macroalbuminuria and ESRF

Glycemia Arm

Proportion With Event

0.0
0.1
0.2
0.3
0.4
0.5
0.6

Months Post-randomization

N.B. ADVANCE study suggested benefit
Managing CVD risk in T2DM with CKD

1. High intensity statin - Atorvastatin 20-80 mg – Target TC< 4 , non HDL C < 2.5.

2. ASA 75 mg – JBS3 – proteinuric

3. Tailored BP Rx : Targets <120-140/75-80
   - ACEI or ARB- maximal dosage – monitor K
   - Dual RAAS blockade therapy – ? only for nephrotics

4. Lifestyle advice – weight reduction , smoking cessation , low fat low protein low salt , high fish diet
Intensified multifactorial intervention has sustained beneficial effects at stage of microalbuminuria in T2DM

- In type 2 diabetes with albuminuria, intensified multifactorial intervention* had sustained beneficial effects on vascular complications and on rates of death\(^1\)

- After a mean of 13.3 years\(^\dagger\) there was an absolute risk reduction for death from any cause of 20% among patients on intensive therapy compared to conventional therapy\(^1\)

* tight glucose regulation and the use of renin–angiotensin system blockers, aspirin, and lipid-lowering agents
\(^\dagger\) 7.8 years of multifactorial intervention and an additional 5.5 years of follow-up
CABG=coronary artery bypass graft, PCI=Percutaneous Coronary Intervention

Reference:
Managing Glycaemia in T2DM CKD

- **Glycaemic control HbA1c 58-68 mmol/mol**
  - Metformin, GLP1 agonists, only if eGFR >30ml/min
  - Sulphonylurea - hypo risk in elderly with CKD
  - Insulin - complex and extended range. Hypo risk.
  - Gliptins – Role in advanced CKD
  - SGLT2I - Role if eGFR > 45
Anaemia in DM CKD – it’s complicated!

- Anaemia (< 110) in 30% CKD3
- Seen earlier than in non DM CKD
- Functional/absolute iron or EPO deficit
- Most causes of anaemia reduce HbA1c
- Fe deficiency increases HbA1c
- Consider B12 deficiency - metformin, P.A.
- Don’t forget other causes of anaemia – blood loss, haemolysis
Metabolic Bone Issues in DM CKD

- Abnormal earlier in DM v Non DM CKD (eGFR 20-70)
- Lower levels of calcium and activated vitamin D
- Higher levels of Phosphate and PTH

- eGFR cut off for HPTH: 30-39 DM V 20-29 non DM CKD

- Increased incidence of osteoporosis, adynamic bone disease and hip fractures
Managing DM CKD 3-5 – Also..!

Retinopathy:
Rapid tightening of glycaemic control may accelerate established retinopathy.

Diabetic Foot Disease:
- High prevalence of NeuroVascular Disease and foot ulceration risk.
- Impact of anaemia, hypoxia, reduced wound healing, acidosis, hypoalbuminaemia, oedema, metabolic bone disease and vascular calcification
Conclusions: Managing the 8 Pillars of Care in DM with CKD

1. Avoid both acute and chronic extremes of hypoglycaemia and hyperglycaemia in DM CKD
2. HbA1c and direct measures of glycaemia impart predicting outcomes and clinical utility in patient care. HbA1c target usually 7.5-8.5% (58-69 mmol/mol) - as most DM CKD are older with CVD

3. Monitor for eGFR and proteinuria progression

4-8. Manage CVD risk, feet, eyes, bones and anaemia