

Diabetes and CKD Workshop

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Consultant

DM is a main cause of CKD (25%)

- Onset at 5-15 years of T₁DM
- Can be present at diagnosis of T₂DM
- Detect in regular MA/Cr screening (2X first urine sample, no UTI, no other causes)

- Contributing Factors
 - HbA_{1c}
 - Hypertension (140/90 vs 130/80 mmHg) (ACE/ARBs)
 - Increased vasoactive hormones and growth factors
 - Genetic factors
 - Smoking

Microalbuminuria

Macroalbuminuria

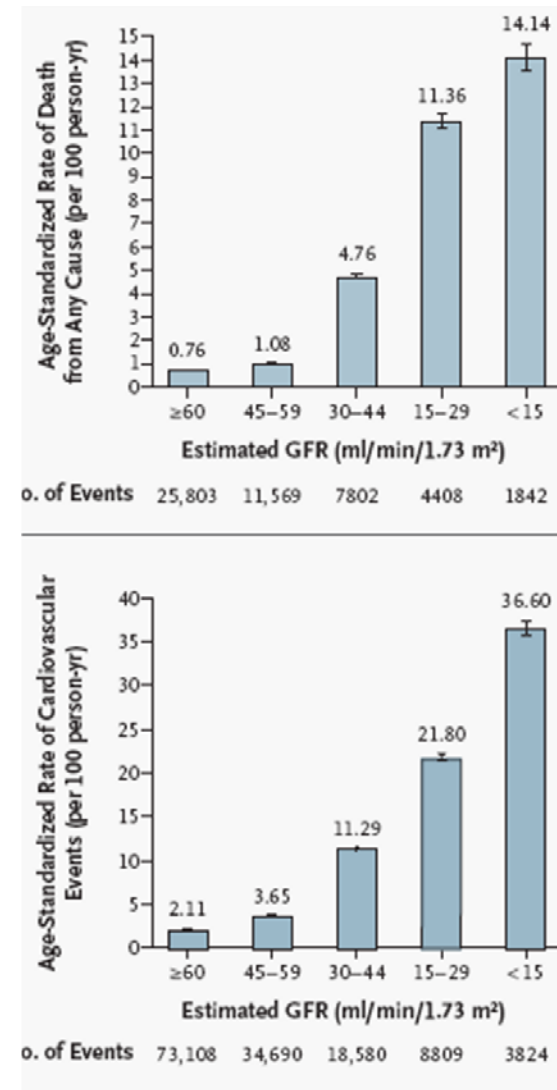
↑Cr and ↓eGFR

>CKD 3b - CKD strikes back

CKD increases risk of CV events and death

1,120,295 US pts from the health-care register

Adjusted for all other risk factors for CV and death



Safe diabetes control

- **UKPDS follow up***
- 5102 T2DM pts
- intensive v conventional treatment no HbA1C target
- Differences in HbA1C lost after 1 y, but legacy effect remained
microvascular disease (24%, P=0.001), MI (15%, P=0.01) and death from
any cause (13%, P=0.007)

- **ACCORD study****
- 10251 pts with T2DM
- Intensive treatment (HbA1C 6%) v standard treatment (HbA1C 7-7.9%)
- CV outcomes ns
- increased risk of death in intensive treatment group (1.22; 95% CI, 1.01 to
1.46; P=0.04)
- Hypoglycemia requiring assistance and weight gain of more than 10 kg
were more frequent in the intensive-therapy group

*Holman et al N Engl J Med 2008 359: 1577-1589

** . N Engl J Med. 2008;358:2545-59

HbA₁C and BG monitoring in CKD

HbA₁C misleading

1 RBC turnover

2 blood transfusion

3 EPO and Fe infusion

Hypos more frequent with deterioration of CKD independent of medication*

* Haneda M and Morikawa A. *Nephrol Dial Transplant* 2009;24:338-341.
Moen M, et al. *Clin J Am Soc Nephrol* 2009;4:1121-1127.

Hypoglycaemia risk

drug	Mechanism	Risk
Metformin	Decreases hepatic glucose output	Low
SGLT inhibitors (-glifozin)	Inhibit glucose reabsorption in the kidney	Low
Meglitinides (-glinide)	Stimulates insulin secretion	High
Sulphonylurea	Enhances insulin secretion	High
Thiazolidinedione (Pioglitazone)	Increases sensitivity of muscles, fat, and liver to endogenous and exogenous insulin	Low
GLP-1 agonists Exenatide/	Potentiates glucose-stimulated insulin secretion	Low
DPP-4 inhibitors (gliptin)	Enhances effects of GLP-1 and GIP; increases glucose-mediated insulin secretion and suppressed glucagon secretion	Low
Insulin	Replaces natural secretion	High

* Haneda M and Morikawa A. *Nephrol Dial Transplant* 2009;24:338-341.
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METFORMIN

- Renal clearance proportional to creatinine clearance (CrCl)
- NICE
 - Review metformin if eGFR <45 ml/min/1.73m²
 - Stop metformin if eGFR <30 ml/min/1.73m²
- Studies measuring MF concentration in CKD have small numbers (n=9 <30 ml/min, n=21 30-60mL/min) -QJM 2013
- Association with lactic acidosis
- No correlation, no increased mortality with MF
- Cochrane 2014 meta-analysis of 347 trials/studies –no increase in incidence Lactic acidosis

METFORMIN

MF can be used under specialist supervision in pts with eGFR 30-45 ml/min/1.73m² (Cr 150-200 μmol/L)

Needs to be omitted in dehydration due to any cause, or patient unwell with increased oxidative stress (liver failure, acute heart failure, sepsis)

Renal function needs to be checked regularly

GLICLAZIDE

- Protein-bound – can be displaced by other drugs – unpredictably increased effect
- Half-life in healthy volunteers 10-12 hrs
- Metabolised in the liver BUT
- Active metabolite renally excreted
- Duration of action can be much longer in renal failure
- High risk of hypoglycaemia in CKD
- Unpredictable in fluctuating renal function

Other medication

Repaglinide

- Half-life in healthy volunteers 1 hr
- Metabolised almost completely in the liver

Pioglitazone

Metabolised in the liver, no dose adjustment

Concerns – fluid retention, fracture risk, bladder Ca

DPP₄ inhibitors

Only Linagliptin does not require dose adjustment

GLP-1 analogues

Exenatide excreted via kidneys – Risk of AKI - not recommended in eGFR < 30 ml/min

Liraglutide metabolised in the liver – no dose adjustment in CKD, renal license applied for

Insulins

- Generally recommended in CKD 3-5
- Exogenous insulin excreted by kidneys – reduced elimination in CKD
- **Increased risk of hypos – reduced awareness**
- Am Coll Phys - 25% dose reduction GFR 10-50, 50% reduction GFR<10
- Dialysis – ↑ peripheral insulin sensitivity-↓ insulin requirement
- Dose reduction on HD days

Take home messages - DM and CKD

- HbA_{1c} may be misleading
 - Risk of unrecognised hypos
 - Reliable CBG monitoring needed
 - Where possible, use agents with low hypo risk
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- Traditional treatment algorithms (NICE, Herts Diabetes) might not be suitable due to specifics not considered
 - New guidelines on the way

Take home messages - DM and CKD

- ACE/ARB for BP control
- Smoking cessation (Aspirin if do not stop)
- Lipid management
- Consider anaemia and bone disease when eGFR <45ml/min

Case Study 1: 81 year old male

- T2DM x 13 years
- IHD
- Retinopathy
- AAA
- Obstructive Uropathy
- Meds:
 - Gliclazide 80mg mane
 - Atenolol
 - Atorvastatin
 - Clopidogrel
- BMI 27.4
- BP 120/70
- HbA1c = 50 (6.7%)
- Cholesterol 3.6
- Creatinine 217
- eGFR 26
- ACR 3.0
- Hb 130

Case Study 2: 65 year old male

- T2DM x 11 years
- IHD
- Retinopathy
- PVD
- Hypertension
- Ca Bladder
- Meds:
 - Humulin M3
 - Metformin 500mg BD
 - Atenolol, Ramipril, Aspirin, Atorvastatin
- BMI 32.5
- BP 140/70
- HbA1c = 62 (7.8%)
- Cholesterol 4.1
- Creatinine 125
- eGFR 50
- ACR 12.1
- Hb 159
- No intention of stopping smoking

Case Study 3: 75 year old female

- T2DM x 6 years
- Hypertension
- AF
- Depression
- Osteoarthritis
- Meds:
 - Gliclazide 80mg bd
 - (Metformin intolerant)
 - Bisoprolol, Doxazocin, Perindopril, BFZ, Warfarin, Sertraline
- BMI 32.5
- BP 135/60
- HbA1c = 47 (6.5%)
- Cholesterol 3.4
- Creatinine 123
- eGFR 37
- Hb 133

Case Study 4: 70 year old male

- T2DM x 18 years
- Ca Bladder
- BPH
- Postural Hypotension
- Meds:
 - Gliclazide 160mg BD
 - Sitagliptin 100mg mane
 - BFZ, Atenolol, Amlodipine, Losartan, Aspirin, Atorvastatin
- BMI 32.4
- BP 170/90
- HBA1c – 75 (9.0%)
- Cholesterol 4.1
- Creatinine 143
- eGFR 40
- ACR 2.8
- Hb 115