ABCD-RA guidelines on management of glycaemia in DM-CKD

Glycaemic Targets

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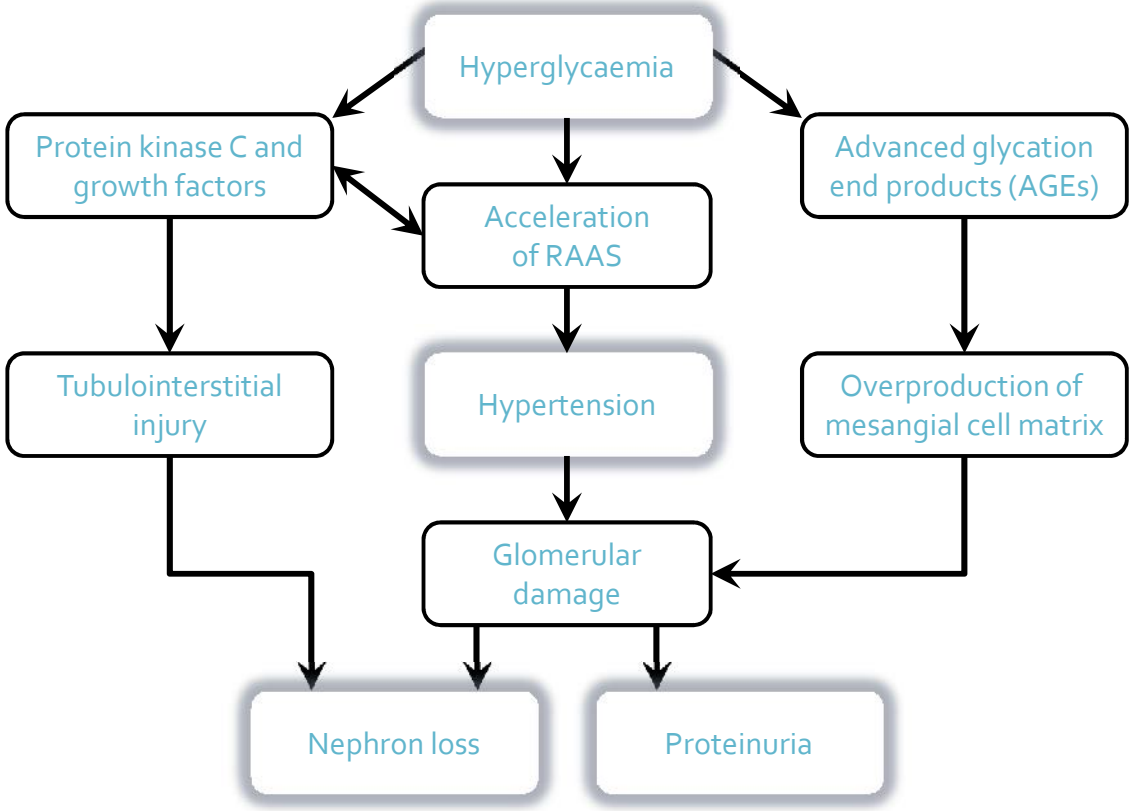
Hyperglycaemia and DM-CKD

Three mechanisms have been postulated that explain how hyperglycaemia causes tissue damage in the kidney:

1. Activation of PKC
2. Over-activation of the RAAS
3. Non-enzymatic glycation that generates AGE products



Glycaemic Targets

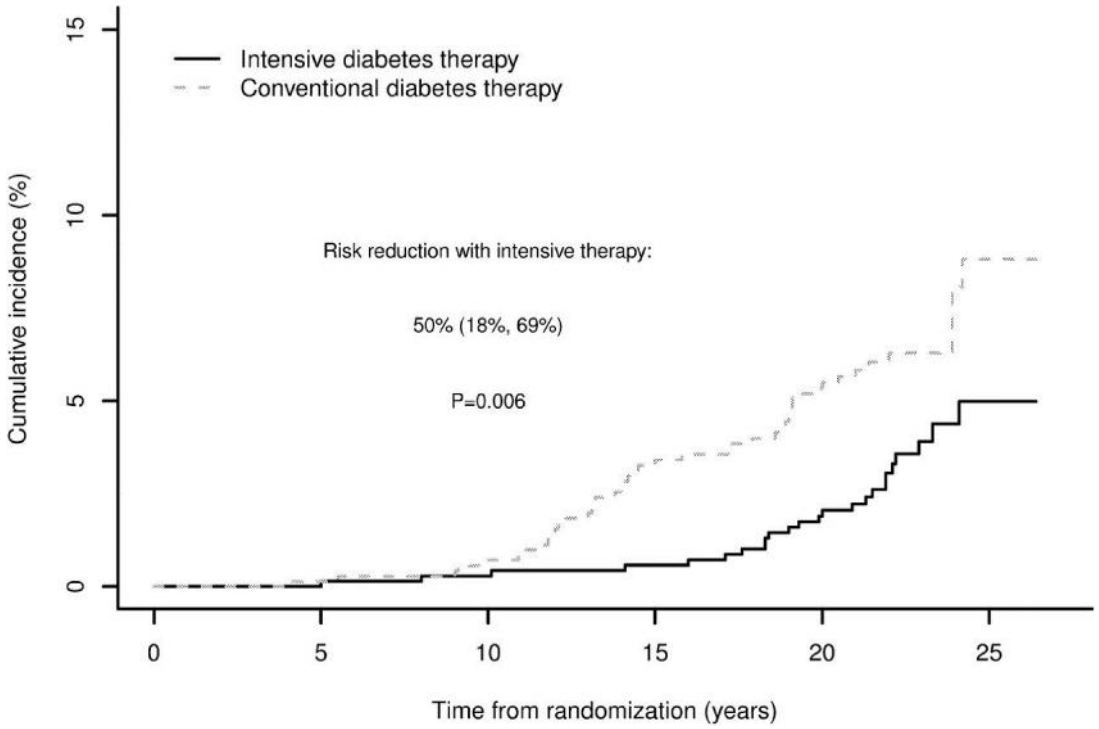
- Does intensive glucose control prevent *development* of DM-CKD?
- Does intensive glucose control prevent *progression* of DM-CKD?
- What glycaemic targets should we aim for in DM-CKD?

Tight glycaemic control on DM-CKD in T1D

DCCT-EDIC

- 6.5 yrs intensive: target 42 mmol/mol (6%) – achieved 55 mmol/mol (7.2%)
- Reduced incidence of microalbuminuria and macroalbuminuria
- 25 yr follow up – 50% reduction in CKD

Cumulative incidence eGFR < 60



Tight glycaemic control on DM-CKD in T1D

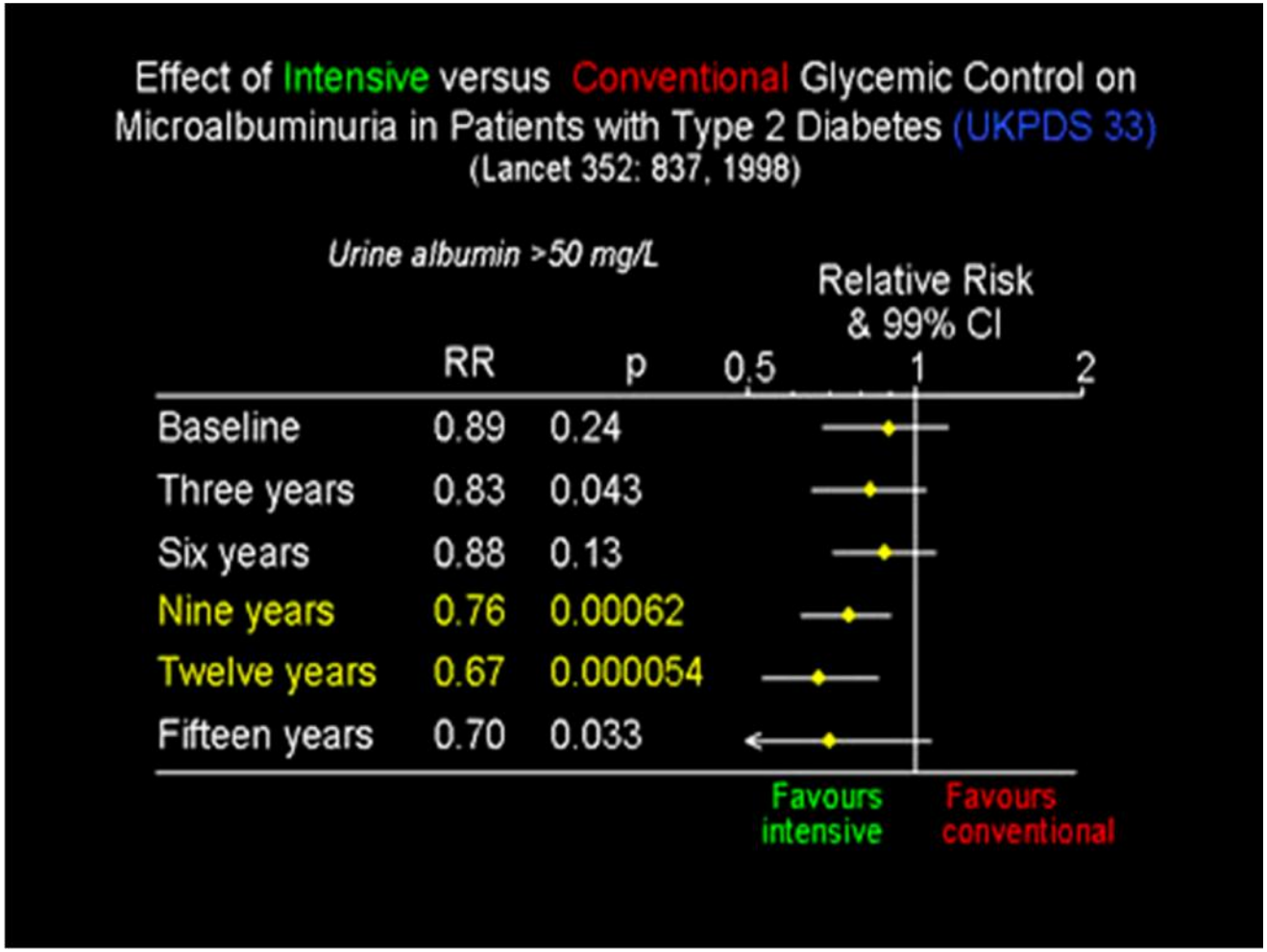
- No intervention study in T1D with *established* DM-CKD to suggest tight glucose control reduces progression of CKD

- Lind et al. NEJM 2014 - Swedish registry study:
  - CV mortality in T1D with renal disease - same in pts with time averaged HbA1c 53-62 mmol/mol (7.0-7.8%) vs < 52 mmol/mol (6.9%)

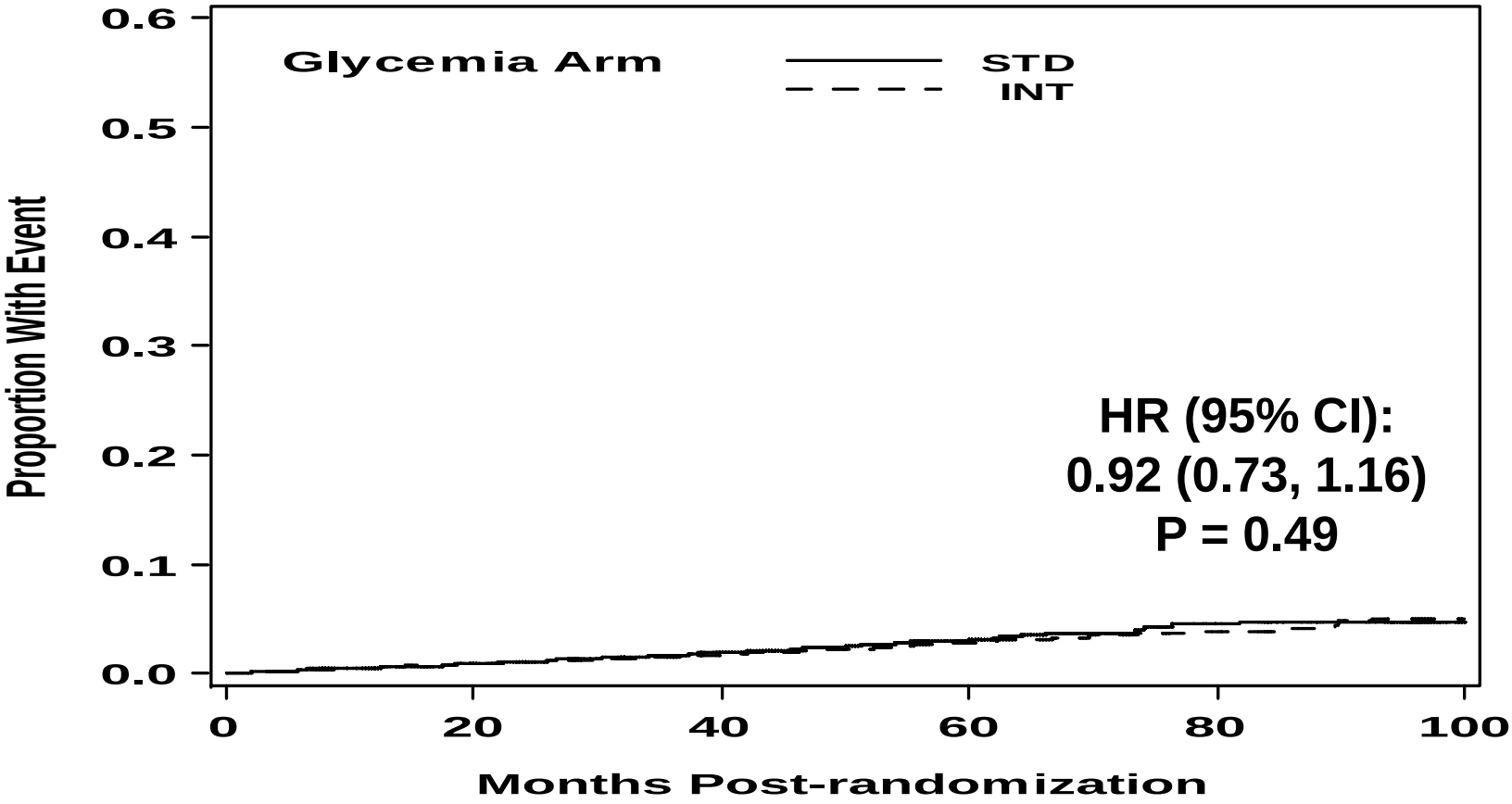
Glycaemic targets in T1D DM-CKD

- <40 years old
  - 48-58 mmol/mol, provided recurrent hypoglycaemia is avoided
- Others
  - 58-62 mmol/mol may be reasonable

T2D: Development of macroalbuminuria



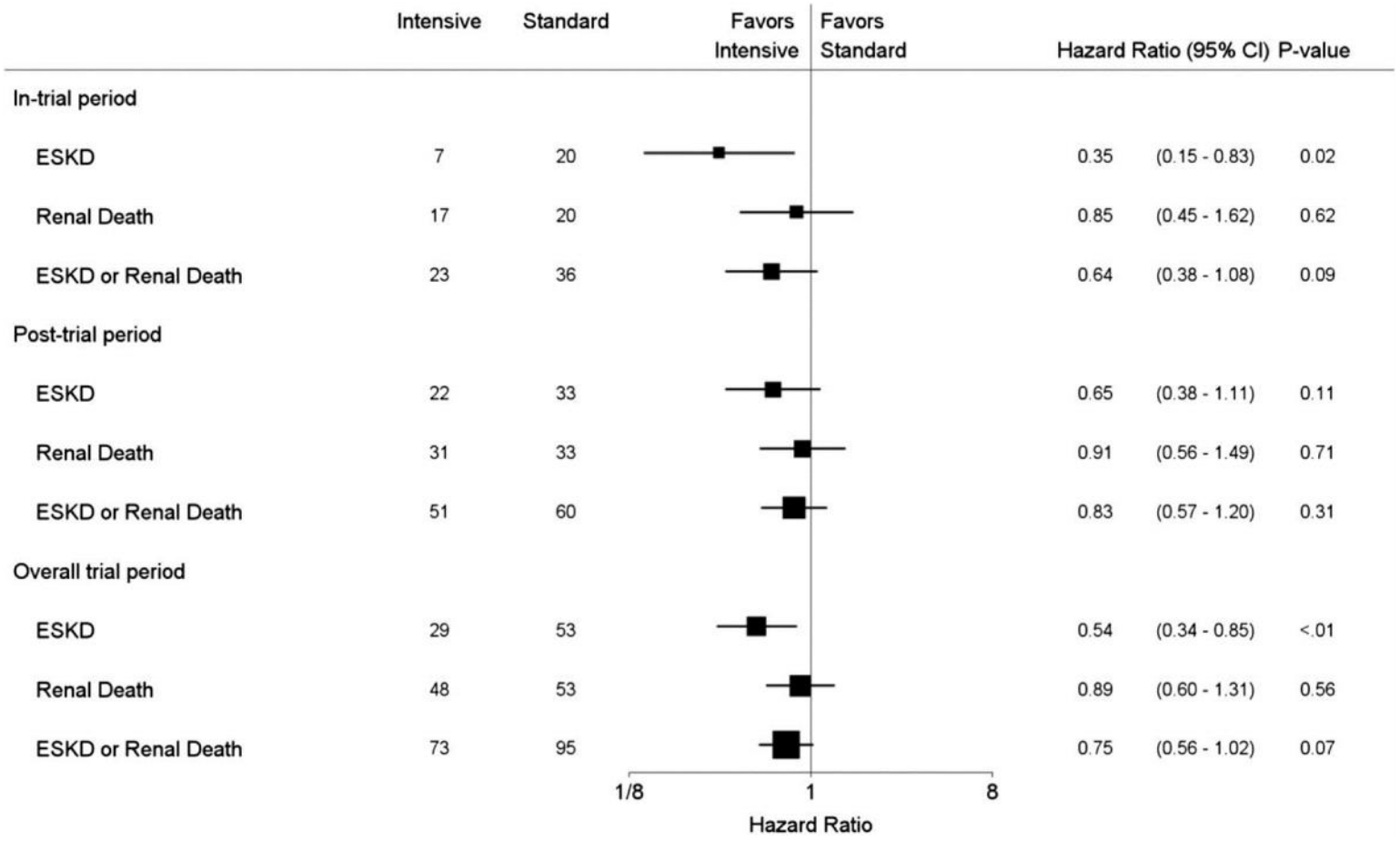
T2D: ESRD - dialysis or renal transplant



ADVANCE

- SU based intensive vs. standard
- Target 48 mmol/mol (6.5%)
- Achieved 48 mmol/mol (6.5%) vs 56 mmol/mol (7.3%)
- 10% RR in major micro- and macrovascular events
- 21% reduction in new nephropathy

ADVANCE-ON (10 yr fu)

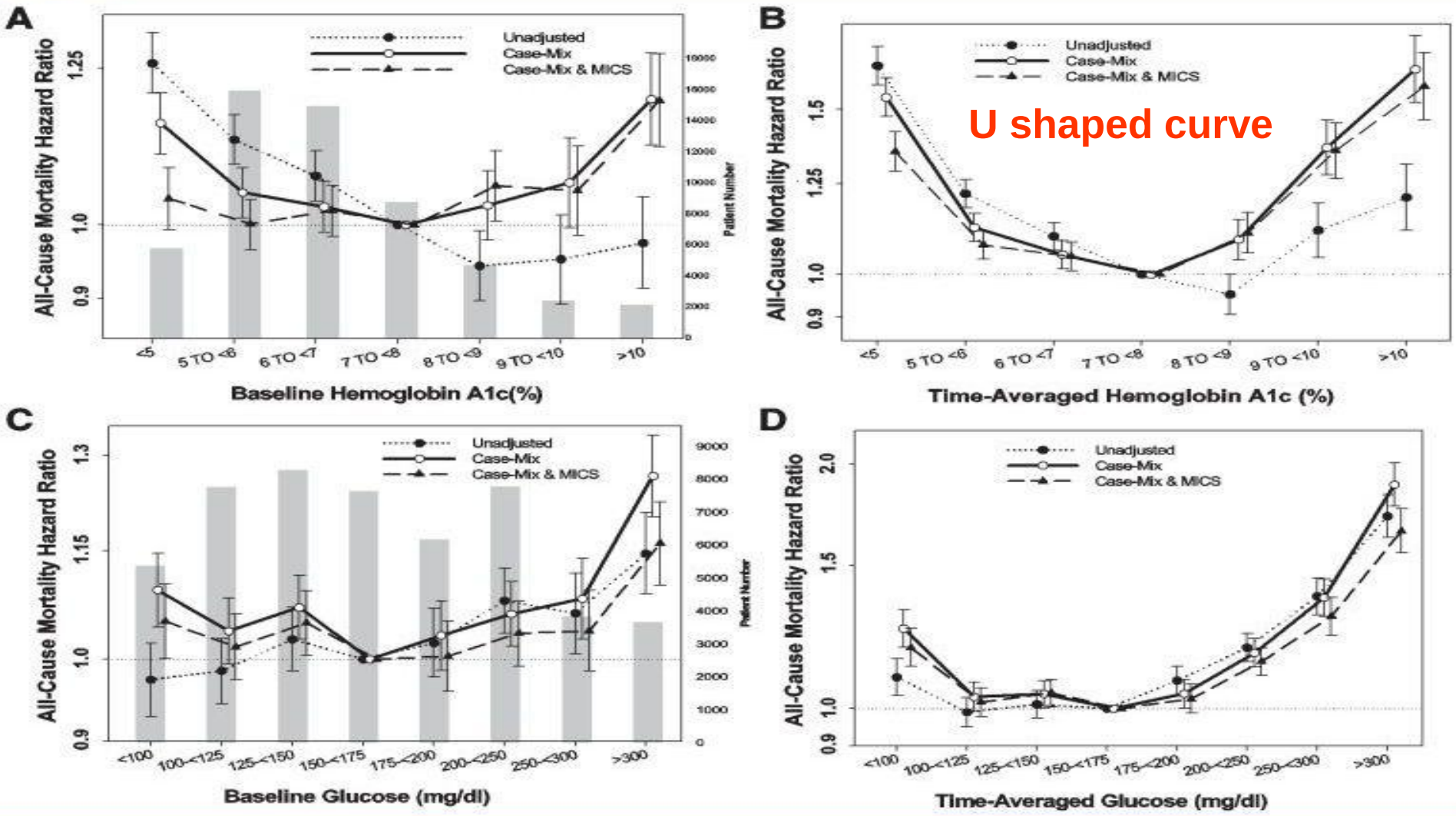


Meta-analyses

- Coca et al, Arch Int Med 2012
- Rodriguez et al, Circulation 2016
  - Reduced microalbuminuria and macroalbuminuria
  - No impact of intensive vs standard glucose control

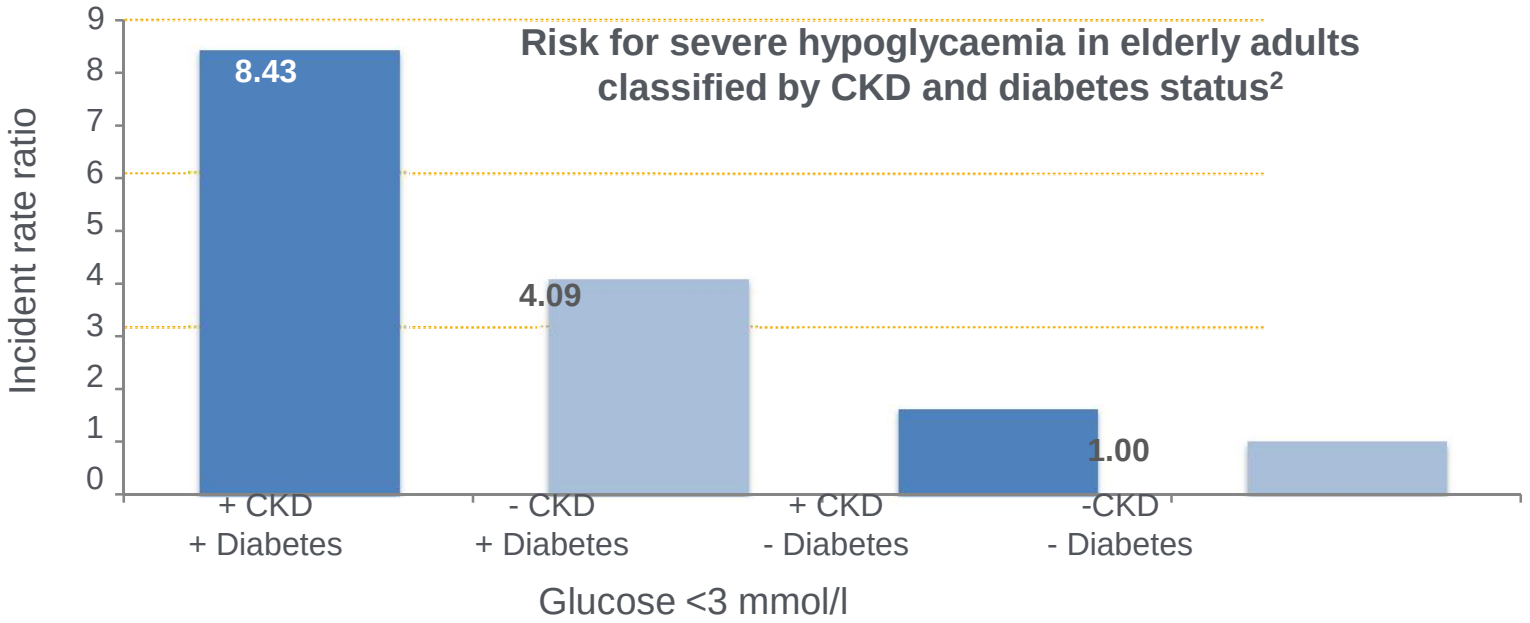
Glycaemic control and CVD mortality in DM on Dialysis

Medscape



CKD in DM and hypoglycaemia risk

- Chronic kidney disease increases hypoglycaemia risk in patients with diabetes
- In elderly subjects (>70 years) hypoglycaemia occurs more frequently in subjects with CKD stages 3–5



What do other guidelines say?

- KDOQI 2012 - <53 mmol/mol (7.0%)
- ERBP 2015 – "vigilant attempts to tighten glycaemic control when values >69 mmol/mol (8.5%)"
- JBDS haemodialysis guidelines 2016 – 58-68 mmol/mol

What do ABCD-RA say?

- In patients with established DM-CKD (especially those with CKD 3b-5)
  - Don't ignore the glucose, but INDIVIDUALISE target
  - Avoid both acute and chronic extremes of hypoglycaemia and hyperglycaemia

- Type 1
  - Younger patients, DM <10 years, CKD 2 — 48-58 mmol/mol (6.5-7.5%)
  - Older patients, DM >10 years, CKD 3-4 — 58-62 mmol/mol (7.5-7.8%)
  - CKD5, dialysis — 58-68 mmol/mol (7.5-8.5%)

- Type 2
  - Age <40, CKD 2 (A1-2) — 48-58 mmol/mol (6.5-7.5%)
  - CKD 3-4 on non-insulin — 52-58 mmol/mol (7.5-7.8%)
  - CKD 3-4 on insulin — 58-68 mmol/mol (7.5-8.5%)
  - CKD5, dialysis — 58-68 mmol/mol (7.5-8.5%)

Dr Ana Pokrajac

ABCD RA clinical guidelines - oral agents in T2DM and CKD

Metformin

- Cheap, efficient, safe
- Half-life 1.5-5 hrs, renal excretion, dialysed
- No hypos / weight gain
- UKPDS – RR reduction 30-40% DM-related outcomes, mortality and all cause mortality
- LA in gen population 1-5 per 100K , mortality 30-50%, tissue hypoperfusion and reduced oxygenation
- In CKD metformin concentrations do go up, but do not correlate with increase in LA concentration or mortality – bystander?
- Deterioration in HbA1C after discontinuation in pts with CKD 3&4, despite insulin and OHA; wt gain; worse lipid profile and BP (4yrs)*

*Rachmani Eur J Med 2002, 13(7) 428

Metformin

- **Metformin can be used in patients with DM down to an eGFR of 30 ml/min. Dose may have to be reduced once eGFR is below 45 ml/min (1B)**
- **eGFR in certain patients may underestimate renal function (obesity)- Cockroft-Gault formula / direct measurement when eGFR does not support it (1C)**
- **Metformin should be withheld during periods of acute illness, particularly when there is AKI. All patients treated with metformin should be given sick day guidance (1B)**

Metformin - research

- Does metformin reduce risk of CVD in patients with T2DM and CKD?
- Can metformin be used safely in more significant CKD 4/5 using metformin levels?
- What is the effect of cessation of metformin on glucose control and renal decline?

SUs

- Old and cheap
- Trigger insulin release from beta cells (lesser extent, glucose uptake in muscle and fat cells)
- Hypos and weight gain
- Metabolised in the liver but some SUs and their active metabolites are cleared via kidneys – caution with falling GFR, risk of hypo increases
- Highly protein bound – not cleared by dialysis, risk of hypo even greater

SUs – little evidence in CKD

- **Patients with T2DM &CKD on SUs are at increased risk of hypoglycaemia - CBG monitoring recommended. If eGFR is <45 ml/min CBG monitoring should be mandatory (2B)**
- **Glicalzide and glipizide are metabolised in the liver- preferred SUs in patients with T2DM and CKD. CV mortality makes gliclazide a preferred choice* (2B).**
- **Gliclazide and glipizide in eGFR <45 ml/min – submaximal doses (2B)**
- **Avoid glicazide and glipizide in eGFR <30 ml/min - off licence (2B)**
- **Safety profiles and pharmacokinetics of glibenclamide, glimepiride and tolbutamide do not support their use in patients with CKD and they should be avoided (2B).**

*Scharmm EHJ (2011) 32, 1900–1908

SUs – Research

- SUs-related mortality in patients with CKD

- Head to head comparison of efficiency and hypo risk between Gliclazide/glimepiride and insulin in CKD

Megitinides

- Short acting insulin secretagogues, prandial cover
- Hypo risk but less than with SUs* (?lower efficiency), weight gain like SUs
- Repaglinide excreted fecally, metabolised in the liver but active metabolite cleared via kidneys so accumulation
- Not much evidence in CKD
- CV risk and mortality comparable to MF**

- **Meglitinides can be considered for use in patients with T2DM and CKD as a monotherapy (repaglinide) or in addition to metformin or pioglitazone (nateglinide and repaglinide) if other agents are not tolerated (2C)**
- **In patients with T2DM on meglitinides consider the risk of hypos and advise capillary blood glucose monitoring accordingly (1D)**
- **Dose reduction is recommended in patients with CKD st 4, 5 and on dialysis (2C)**

*Scheen 2007 Clinic pharmaco

**Scharmm EHJ 2011; 32, 1900–1908

Pioglitazone

- Reduces insulin resistance
- Cheap, efficient, no hypos
- Metabolised in the liver – can be used in patients with CKD
- Causes fluid retention* (risk in HF and macular oedema)
- Bone fracture risk with rosiglitazone in ACTOS, with TDZs in Scotish National Database
- Risk of bladder cancer dismissed

- PROActive CKD cohort** – all cause mortality, non-fatal stroke and heart heart attack reduced with pioglitazone (HR 0.66; CI 0.45 to 0.98)
- In patients on dialysis reduces mortality unless given with insulin*** (retrospective)
- Improves lipids, BP and pro-inflammatory markers, reduces microalbuminuria

*Cochrane review 2006
**Schneider 2008 19(1): 182–187.
***Brunelli 2009;75:961-8

Pioglitazone Recommendation

- **Patients with T2DM and CKD of all stages can be considered for pioglitazone (1B)**
- **Monitor for fluid retention initially after 2/52, 3-6/12 there after (1C).**
- **If wt increase >20 % in 2/52 discontinue pioglitazone (2C)**
- **Avoid using pioglitazone in people with documented heart failure and macular oedema (1B)**
- **We recommend against use pioglitazone in patients with CKD who are taking insulin (1B)**
- **Avoid in patients with known osteoporosis or at high risk for osteoporosis (2C) caution in patients with increased risk of hip fractures (1C)**
- **Consider discontinuation in patients who develop hip fracture on pioglitazone (1D)**

Pioglitazone - Research

- Head to head comparison of Pioglitazone with other oral agents in CKD – safety, efficiency, risk of hypoglycaemia and hospitalisation for heart failure across wider range of eGFRs
- Safety and efficiency of Pioglitazone in combination with SGLT2 receptor blockers – benefits of volume-reducing effect of SGLT2 to pioglitazone-induced fluid retention, CV risk reduction, effect on bone fractures, risks of urinary tract cancers with increased exposure to high glucose concentrations.
- Risk of bone fractures in patients on pioglitazone in comparison with meglitinides, SUs and gliptines in patients with T2DM and CKD
- Rate of renal function decline in patients with T2DM treated with pioglitazone

DPP-4 inhibitors

- Prevent hydrolysis of GLP-1
- Not very potent
- Low risk of hypo
- No weight gain

DPP-4 inhibitors

- Sitagliptin – 79% unchanged in urine – dose reduction required when CrCl <50
  - TECOS - Safe in CKD (eGFR>30 ml/min)
  - Ferreira – comparable efficacy to glipizide but less hypos and no wt gain in CKD (eGFR<50 ml/min, excl dialysis)
- Linagliptin – 80% fecally excreted, no dose adjustment required in CKD
  - CARMELINA awaited
- Vildagliptin – 69% hydrolysed in the kidney, 85% urinary eliminated, 23% unchanged, dose reduction in eGFR<30 ml/min
  - Meta-analyses of phase III & IV trials – no increase in 3pt MACE to comparator (McInnis et al 2015; 17(11)1085)
- Alogliptin – dose reduction in CrCl <50 ml/min
  - EXAMINE – no increased risk of HF
- Saxagliptin – dose reduction in CrCl <50 ml/min, avoid in ESRF
  - SAVOUR-TIMI – unexpected risk of HF by 27%

DPP-4 inhibitors

- **We recommend that patients with T2DM and CKD of all stages can be considered for treatment with DPP-4 inh (1B)**
- **We suggest dose reduction of sita-, vilda-, saxa- and alogliptin in accordance with degree of renal impairment (including MHDx) except linagliptin (1B)**
- **Patients with T2DM and CKD can be safely prescribed DPP-4 inh - no risk of hypoglycaemia or weight gain at all stages of renal disease (1B)**
- **There are no current data to recommend use of DPP-4 inhibitors specifically to lower albuminuria in patients with T2DM and CKD (1C)**
- **There are no current data to suggest that DPP-4 inhibitors (except Saxagliptin) are associated with excess risk of heart failure in patients with T2DM and CKD (1A)**
-

SGLT2 inhibitors - recommendation

- SGLT2 inhibitors are currently licensed for T2DM eGFR is ≥60 mL/min. For dapagliflozin, the drug should be withheld when the eGFR falls below this level, whilst canagliflozin and empagliflozin may be continued until the eGFR <45 mL/min (lower dose). We support these recommendations (1B)
- Empagliflozin will reduce CV outcomes in patients with T2DM with previous CV event (Grade 1A). Subgroup analysis of these data suggested that patients with an eGFR of 60 to 90 mL/min gained most CV benefit and so this drug might be recommended over other glucose-lowering therapies for this cohort of patients (2B).
- Empagliflozin proven to benefit renal end-points apart from incident rate for albuminuria. Empagliflozin may be recommended for reno-protection for patients who have T2DM and have had a previous CV event (1A).
- Patients with T2DM and CKD treated with SGLT2 inhibitors need only perform frequent self-monitoring of blood glucose when treated with agents which can cause hypoglycaemia (such as SUs and insulins) (1A).

Summary – oral agents

		Renal Impairment - CKD Stage					
Drug	Class of Drug	1 (eGFR >90)	2 (eGFR 60-90)	3a (eGFR 59-45)	3b (eGFR 44-30)	4 (eGFR 29-15)	5 (eGFR<15)
Metformin	Biguanide				Reduce dose to 500mg BD*	in high BMI eGFR underesimate	
Gliclazide	SU	CBG	CBG	CBG	CBG	OFF LICENCE, high risk of	
Repaglinide	Meglitinide	CBG	CBG	CBG	CBG	dose reduction advised CBG	dose reduction advised CBG
Sitagliptin	DPP-4i			<50 ml/min reduce dose to 50 mg	reduce dose to 50 mg	reduce dose to 25 mg	reduce dose to 25 mg
Saxagliptin	DPP-4i			<50 ml/min reduce dose to 2.5 mg	reduce dose to 2.5 mg	reduce dose to 2.5 mg	
Linagliptin	DPP-4i						
Pioglitazone**	TZD						
Dapagliflozin	SGLT-2i						
Canaglifozin	SGLT-2i			reduce dose to 100mg			
Empagliflozin	SGLT-2i			reduce dose to 10 mg			

S C Bain Dualities of interest

Senior clinical academic since 1993, since that time reports having received honoraria, teaching and research sponsorship/grants from the following:
Abbott, Astra-Zeneka, Boehringer Ingelheim, BMS, Cellnovo, Diartis, Eli Lilly, GlaxoSmithKline, Merck Sharp & Dohme, Novartis, Novo Nordisk, Pfizer, Roche, Sanofi-aventis, Schering-Plough, Servier & Takeda

Received funding for the development of educational programmes from Cardiff University, Doctors.net, Elsevier, Onmedica, Omnia-Med & Medscape

Owns a share of Glycosmedia which carries sponsorship declared on site.

Provided expert advice to the All-Wales Medicines Strategy Group and the National Institute for Health and Care Excellence

ABCD RA guidelines on managing glycaemia in DM CKD

- Glucagon-like Peptide-1 Receptor Agonists
- Insulins
- Sick day rules

Glucagon-like Peptide-1 Receptor Agonists

- Licences all limited according by CKD
- Case reports of acute kidney injury
- Isolated reports of interstitial nephritis
- Higher rates of GI side-effects

GLP-1 receptor agonist	Renal recommendations	HbA1c reduction	Renal endpoint data
Exenatide BD (Byetta™)	CC >50mL/min 10µg BD CC 30-50mL/min 'caution' CC <30mL/min 'not recommended'	Pooled analyses; no specific data	No
Liraglutide OD (Victoza™)	CC >30mL/min 1.8mg OD CC <30mL/min 'not recommended'	-0.66% (7.2mmol/mol) in eGFR 30-59mL/min	Reduction in new-onset persistent microalbuminuria (secondary endpoint)
Exenatide QW (Bydureon™)	CC >50mL/min 2mg QW CC <50mL/min 'not recommended'	Pooled analyses; no specific data	No
Lixisenatide OD (Lyxumia™)	CC >50mL/min 20µg OD CC 30-50mL/min 'caution' CC <30mL/min 'not recommended'	Pooled analyses; no specific data	No
Dulaglutide QW (Trulicity™)	CC >30mL/min 1.5mg QW CC <30mL/min 'not recommended'	Awaited (AWARD-7)	No
Albiglutide QW (Eperzan™)	CC >30mL/min 30.0mg QW CC <30mL/min 'not recommended'	-0.83% (9.1mmol/mol) in eGFR 30-59mL/min	No

Insulins

- Little evidence for specific benefit over glucose-lowering
- Initially CKD is associated with insulin resistance, hence higher insulin doses may be required
- Ultimately (eGFR<20mL/min), renal clearance of insulin declines and hypoglycaemia risk increases

‘Sick day rules’ – Vomiting & dehydrating illness

• Metformin	Withhold
• Sulphonylureas	
• Pioglitazone	
• Acarbose	
• Gliptins	
• SGLT-2 inhibitors	Withhold?
• GLP-1 receptor agonists	Withhold?
• Insulins	DON’T STOP