

Type 2 Diabetes and Renal Impairment

How to Manage?

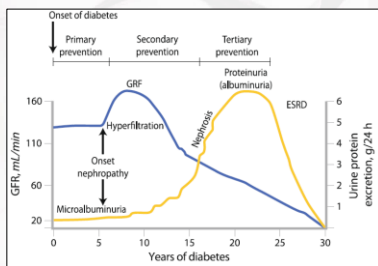
Dr Ivan Kuo

Diabetes & Renal Impairment

- 1 in 18 (5.4%) Australian adults have diabetes
- 30% diabetics have nephropathy
 - Making diabetes the most common cause of CKD
- Nephropathy progresses over time
- Worsening nephropathy increases mortality

ABS 2014

Check GFR and microalbuminuria...



William Curr Diab Rep 2011

Relevance – Progression to ESRD

Kidney Function Stage	GFR (mL/min/1.73m ²)	Albuminuria Stage		
		Normal (urine ACR mg/mmol) Male: < 2.5 Female: < 3.5	Microalbuminuria (urine ACR mg/mmol) Male: 2.5-25 Female: 3.5-35	Macroalbuminuria (urine ACR mg/mmol) Male: > 25 Female: > 35
1	≥90	Not CKD unless haematuria, structural or pathological abnormalities present	10x	20x
2	60-89		7x	50x
3a	45-59	5x	20x	100x
3b	30-44	50x	70x	1000x
4	15-29	500x	1000x	2000x
5	<15 or on dialysis			

KIDGO 2012

Relevance – Mortality

Kidney Function Stage	GFR (mL/min/1.73m ²)	Albuminuria Stage		
		Normal (urine ACR mg/mmol) Male: < 2.5 Female: < 3.5	Microalbuminuria (urine ACR mg/mmol) Male: 2.5-25 Female: 3.5-35	Macroalbuminuria (urine ACR mg/mmol) Male: > 25 Female: > 35
1	≥90	Not CKD unless haematuria, structural or pathological abnormalities present	1.5x	5x
2	60-89		1.5x	3x
3a	45-59	1.5x	2x	4x
3b	30-44	2x	3x	5x
4	15-29	5x	5x	7x
5	<15 or on dialysis			

KIDGO 2012

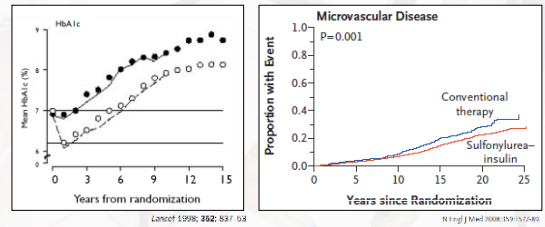
How to Manage?

- Therapy choices affect CKD
 - HbA1c
 - BP
 - ACE/ARB, CCB
 - SGLT-2i
 - GLP-1a
- CKD affect therapy choices
 - Metformin
 - SU, Acarbose, Glitazones
 - SGLT-2i, DPP-4i
 - GLP-1a, Insulin

Therapy Choices affect CKD

- HbA1c
- BP
- ACE/ARB
- CCB
- SGLT-2i
- GLP-1a

HbA1c (UKPDS)

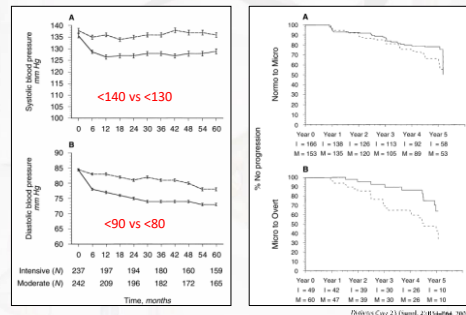


HbA1c target

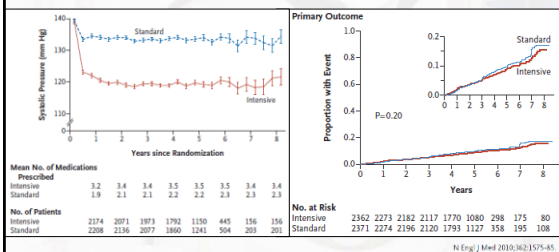
Specific Clinical Situations	HbA1c
General	≤7%
Diabetes of short duration and no clinical CVD	≤6.0%
• Requiring lifestyle modification ± metformin	≤6.5%
• Requiring any antidiabetic agents other than metformin or insulin	≤6.5%
• Requiring insulin	≤7.0%
Pregnancy or planning pregnancy	≤6%
Diabetes of longer duration or clinical CVD (any therapy)	≤7.0%
Recurrent severe hypoglycaemia or hypoglycaemia unawareness (any therapy)	≤8.0%
Major comorbidities likely to limit life expectancy (any therapy)	Symptomatic therapy of hypoglycaemia

Cheung et al. JAMA, 2009;301:339-344

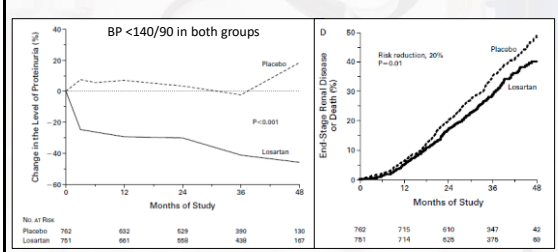
Blood Pressure <130/80 (ABCD)



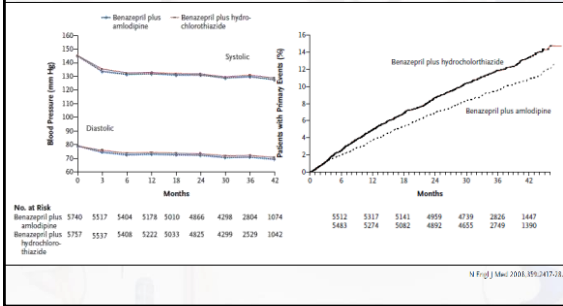
<120 not better (Accord BP)



ACE/ARB beneficial (Renaal)

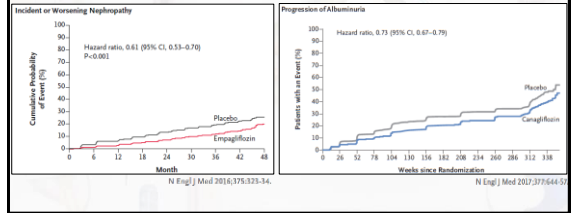


CCB beneficial (Accomplish)

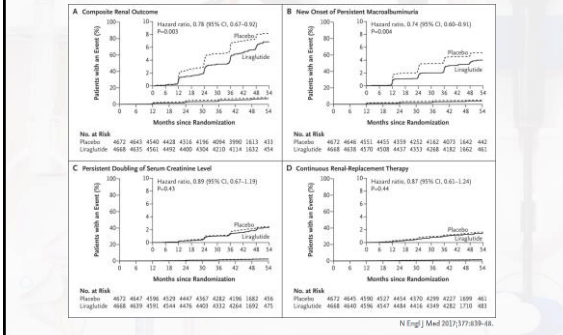


SGLT-2i beneficial

- Prevents worsening of Nephropathy
 - Empa-Reg, CANVAS
 - Declare-Timi just completed



GLP-1a beneficial (Leader)



GLP-1a beneficial (EXSCEL)

	Exenatide		Placebo		HR (95% CI)	p
	# with event, n/N (%)	Incidence/100 pyr	# with event, n/N (%)	Incidence/100 pyr		
Renal composite 1	246/6456 (3.8%)	1.2	273/6458 (4.2%)	1.4	0.88 (0.74, 1.05)	0.164
<i>Adjusted HR*</i>					0.87 (0.73, 1.04)	0.128
40% eGFR decline	239		266			
Renal replacement	7		7			
Renal death	0		0			
Renal composite 2	366/6256 (5.8%)	1.9	407/6222 (6.5%)	2.2	0.88 (0.76, 1.01)	0.065
<i>Adjusted HR*</i>					0.85 (0.73, 0.98)	0.027
40% eGFR decline	216		228			
Renal replacement	7		6			
Renal death	0		0			
New macroalbuminuria	143		173			

*Adjusted for age, sex, ethnicity, race, region, duration of diabetes, prior history of CV event, insulin use, baseline HbA1c, eGFR, and BMI.

CKD can affect therapy choices

- Metformin
- Sulphonylurea
- Acarbose
- Thiazolidinediones
- DPP-IV inhibitors
- SGLT-2 inhibitors
- GLP-1 agonist
- Insulin

Metformin in CKD

- No guideline specifically about renal dosing
- Concern regarding lactic acidosis...
 - Phemformin withdrawn due to lactic acidosis
 - Evidence lacking for Metformin lactic acidosis
 - Cochrane Review 2005
 - Metformin – 8.4 cases per 100,000 patient years
 - Non-metformin – 9 cases per 100,000 patient years

Metformin dose reduction in CKD



Prescribing in renal disease

Randall Faull, Senior Consultant Nephrologist, Royal Adelaide Hospital, and Associate Professor of Medicine, University of Adelaide, and Lisa Lee, Renal Pharmacist, Royal Adelaide Hospital

- Avoided in eGFR <30
- Maximum 1g daily in eGFR 30-60 (1g 30)
- Maximum 2g daily in eGFR 60-90 (2g 60)

(Aust Prescr 2007;30:17-20)

Sulphonylurea OK in CKD

- Many SU metabolites are renally excreted
 - Risk of hypoglycaemia with CKD
 - Esp. with long acting SU
 - Suggest **Gliclazide** (low risk)
- But this can be turned into an advantage...
 - It might work really well in CKD patients

Acarbose C/I in severe CKD

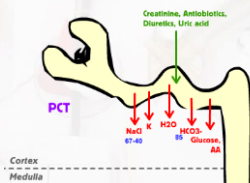
- Effective if tolerated
 - No hypoglycaemic risk, weight neutral
 - >10% flatulence, 1-10% diarrhoea/abdominal pain
- Contraindicated if eGFR <30

Glitazone not the best in CKD

- Low risk of hypoglycaemia
- No need to dose adjust with CKD
- Causes weight gain
- Causes fluid retention
 - Not recommended in CCF
 - Best avoided in CKD

SGLT-2i may be ineffective in CKD

- Dapagliflozin
 - eGFR >60
 - 10mg daily
- Empagliflozin
 - eGFR >45
 - 10mg or 25mg daily
 - 25mg up-titration dose

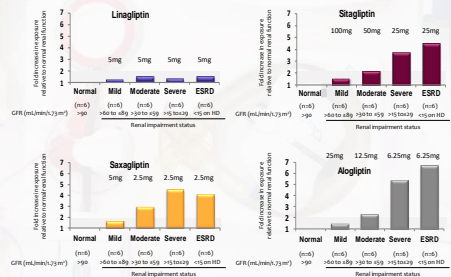


Requires functional nephrons to excrete glucose

Low GFR = ineffective

DPP-4i good in CKD (% and % again)

- Dose reduce in CKD (except Linagliptin)



GLP-1a and CKD

- Exenatide – eGFR >30
- Exenatide weekly – eGFR >30
- Dulaglutide – eGFR <15 not recommended
- Liraglutide – eGFR <15 not recommended

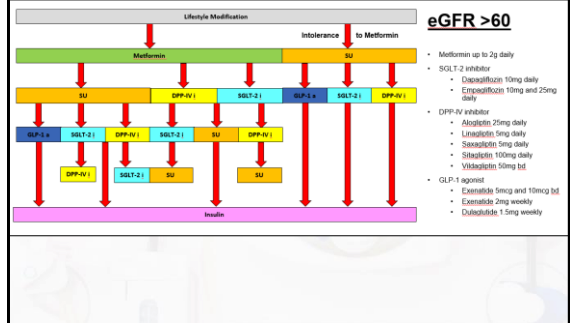
Insulin ok in CKD

- Insulin is renally excreted
 - Up until recently, insulin is the only agent used in severe renal impairment
 - Insulin dose reduction may be needed in severe renal impairment to avoid hypoglycaemia

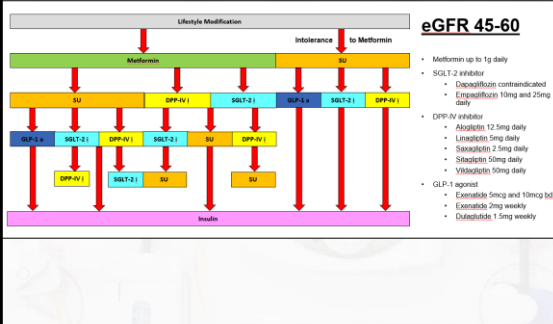
Summary of DM drugs in CKD

	Metformin	SU	Acarbose	TZD	SGLT-2i	DPP-4i	GLP-1a	Insulin
eGFR >60	2g	OK	OK	OK	OK	OK	OK	OK
eGFR 30-60	1g	OK	OK	OK	Empa if eGFR >45	½ dose (except Lin)	OK	OK
eGFR <30	C/I	Hypo risk (Dilcardide lower)	C/I	Fluid retention	Ineffective	½-¾ dose (except Lin)	C/I or not Recom	Hypo risk
Weight	Neutral	Gain	Neutral	Gain	Loss	Neutral	Loss	Gain
Hypo risk	Low	Medium (Dilcardide lower)	Low	Low	Low	Low	Low	High
CKD effect	Good	Neutral	Neutral	Neutral	Good	Neutral	Good	Neutral

CKD, medications and PBS



CKD, medications and PBS



CKD, medications and PBS

