Aspects of Diabetes including renal impairment

Dr Bob Wilkinson

HbA1c

%	mol/mol
6.0	42
6.5	48
7.0	53
7.5	59
8.0	64
9.0	75
10.0	86
11.0	97
12.0	108

Was planned to change in June 2011 but only implimented in January 2012

Diabetes

- Type1

  insulin deficiency. Ketone prone

  Treat with insulin

- Type2

  insulin resistance. Not ketone prone

  Treat with metformin, GLP-1 mimetics

- Type1.5

  type 1 with obesity. Deficiency of insulin plus insulin resistance

Structure of Lecture

- An Approach to patients with Obesity
- Gliptins
- Effect of Renal Impairment on Diabetic Medications

Type 2 Diabetes

My clinic population

- either Good HbA1c and Weight gain
- or Less Good HbA1c and less weight gain

Sulphonylureas, glitazones and insulin put on weight

Type 2 Diabetes

Catch 22 situation

For each 10mol/mol HbA1c reduction get 2kg weight gain

For each 5kg weight increase get 30% increase in cardiovascular risk

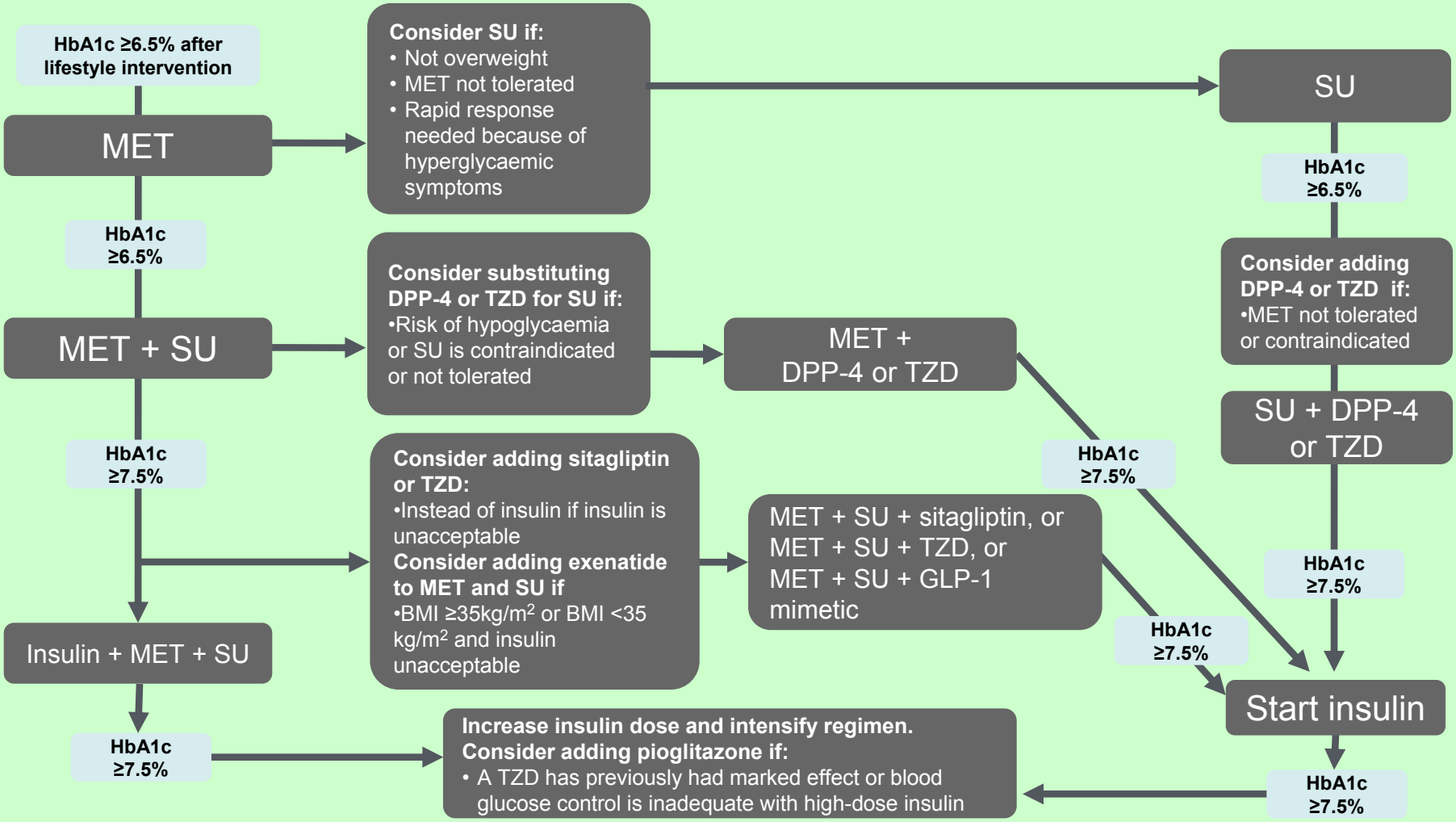
	O/R death
Diabetes	2.73
Obesity	1.78
Both	6.81

Need a Good Treatment for Insulin Resistance

Type 2 Diabetes

- More than 80% of type 2 diabetics are obese or over weight
- Some are massively over weight BMI > 40
- Waist circumference (abdominal visceral fat) closely reflects cardiovascular risk

National Institute for Health and Clinical Excellence (NICE): T2D treatment algorithm[1]



MET = metformin, SU = sulphonylureas, TZD = thiazolidinedione, DPP-4= dipeptidyl peptidase-4 inhibitor

1. Adapted from: National Institute for Health and Clinical Excellence. Clinical Guideline 87. Type 2 diabetes - newer agents (a partial update of CG66): quick reference guide.

Scottish Intercollegiate Guidelines Network (SIGN): T2D treatment algorithm[1]

1st LINE OPTIONS in addition to lifestyle measures; START ONE OF

Metformin (MET)	**Sulphonylurea* (SU)** • If intolerant to metformin • If weight loss/osmotic symptoms

Review and if not reaching target move to 2nd line

	Usual approach
	Alternative approach
*	**Continue medication if EITHER individualised target achieved OR HbA1c falls >0.5% (5.5 mmol/mol) in 3-6 months**

2nd LINE OPTIONS in addition to lifestyle measures, adherence to medication and dose optimisation; ADD ONE OF

SU*	**Thiazolidinedione*** • If hypos a concern (e.g. driving, occupational hazards, at risk of falls) and if no congestive heart failure	**DPP-4 inhibitor*** • If hypos a concern (e.g. driving, occupational hazards, at risk of falls, or if weight gain a concern

Review and if not reaching target move to 3rd line

3rd LINE OPTIONS in addition to lifestyle measures, adherence to medication and dose optimisation; ADD OR SUBSTITUTE WITH ONE OF

ORAL (continue MET/SU if tolerated)		INJECTABLE (if willing to self inject; continue MET/SU if tolerated)	
Thiazolidinedione* If no congestive heart failure	**DPP-4 inhibitor*** If weight gain a concern	**Insulin* (inject before bed)** • If osmotic symptoms/rising HbA1c; NPH insulin initially • If hypos a concern, use basal analogue • Add prandial insulin with time if required	**GLP-1 agonists*** •If BMI > 30 kg/m^2 •If a desire to lose weight •Usually <10 years from diagnosis

DPP-4= dipeptidyl peptidase-4 inhibitor; GLP-1 = glucagon-like peptide 1

1. Adapted from: Scottish Intercollegiate Guidelines Network. Management of diabetes: a national clinical guideline. March 2010. Prescribers should refer to the British National Formulary (www.bnf.org) and the Scottish Medicines Consortium (www.scottishmedicines.org.uk) for updated guidance on licensed indications, full contraindications and monitoring requirements.

Obese Type 2 Diabetic

- Loose weight
  - decrease insulin requirement
  - decrease insulin resistance
- Exercise
  - increases insulin sensitivity
- Dietitian
  - less calories, less CHO
* Food Plan
  - for 3 months unless glucose very high
  - reinforced by dietitian
- Metformin
  - gradually build up dose
  - decreases insulin resistance
- Reinforce food plan

- If you add sulphonylurea or insulin the weight will go up and appetite will be stimulated

Myths about Obesity/Dieting

- I do not eat very much!
  - eat more than need.
  - underestimate what do eat.
  - total calories in that counts
- I eat healthily!
  - maybe but TOO Much. Portion size. Smaller plate
- I can not exercise because of back/heart
  - exercise does not burn many calories
  - can exercise in chair
- I have a slow metabolism
  - Rubbish obese have higher BMR than normal weight
- Its my glands
  - Rubbish if thyroid is ok
  - v.v.v.rare metabolic problems associated with obesity
  - only gland that's wrong is …….

OBESE

- Need to eat less permanently
  -not diet – short term.
  - alter eating habits permanently – food plan/life style
  - difficult – food is pleasurable + social

. Respond to Satiety signals
  -eating is a habit. Stop eating when full. LEAVE FOOD ON PLATE.

. Never tell obese T2D to snack between meals/ have a supper unless they have gone hypo.

. Anticipate exercise and take less medication before it rather than snack to cover it.

. EAT + DRINK LESS

Case Study

- Keep on with Food Plan alone for 3 months (but see them regularly)
- Then add METFORMIN gradually 500mg with main meal for two weeks then 500mg BD etc
- Never liquid metformin use sachets
- Try Metformin SR if bowel intolerant
- If not to target send to NASTY dietitian

Diabetes is Different

- It is not like hypertension, lipid problems or even IHD – take the medication

- Diabetes take the medication
  PLUS
  Monitor BM
  24/7 stick to the food plan
  Balance food, activity + medication
  No Holidays from it

  WILL ONLY WORK IF PATIENT WILLING TO INPUT

  Waste of time & money – if patient is not willing to help themselves

Scottish Intercollegiate Guidelines Network (SIGN): T2D treatment algorithm[1]

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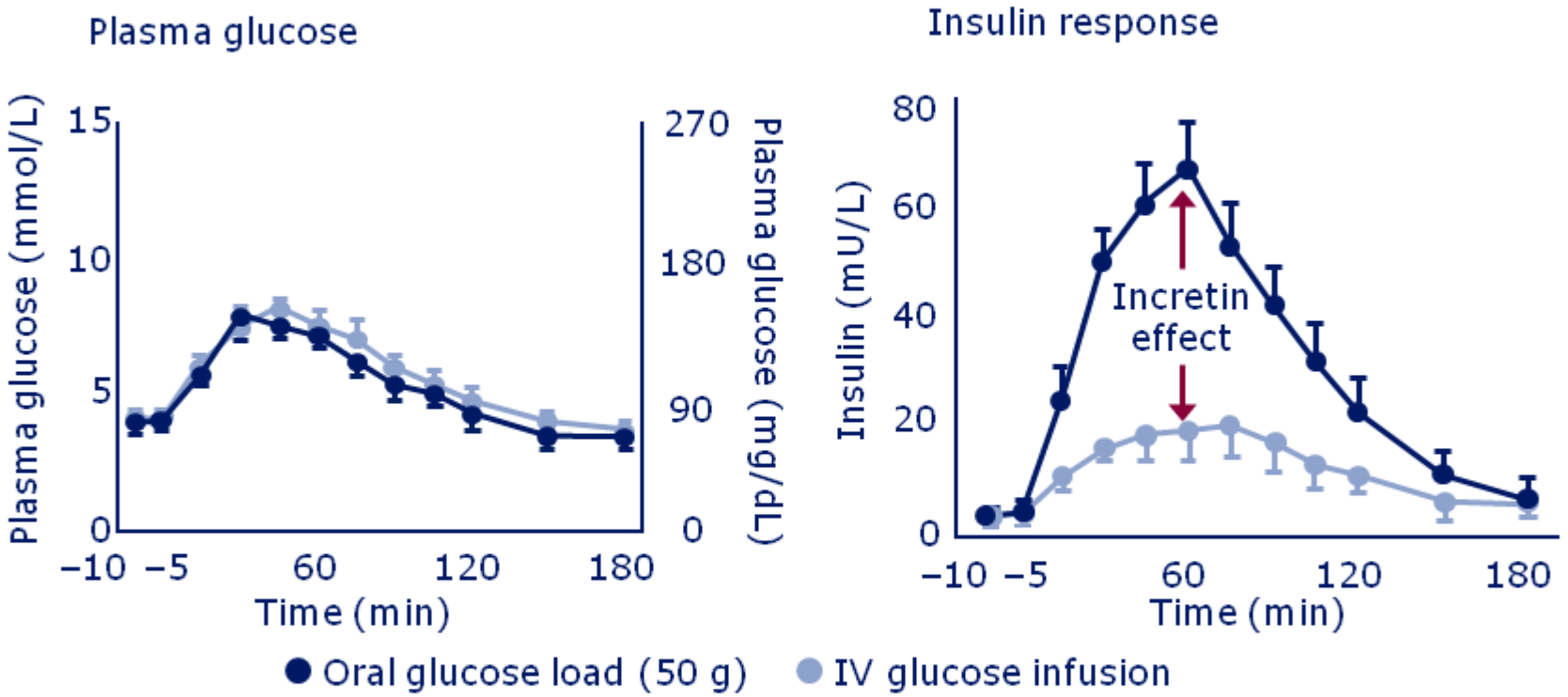
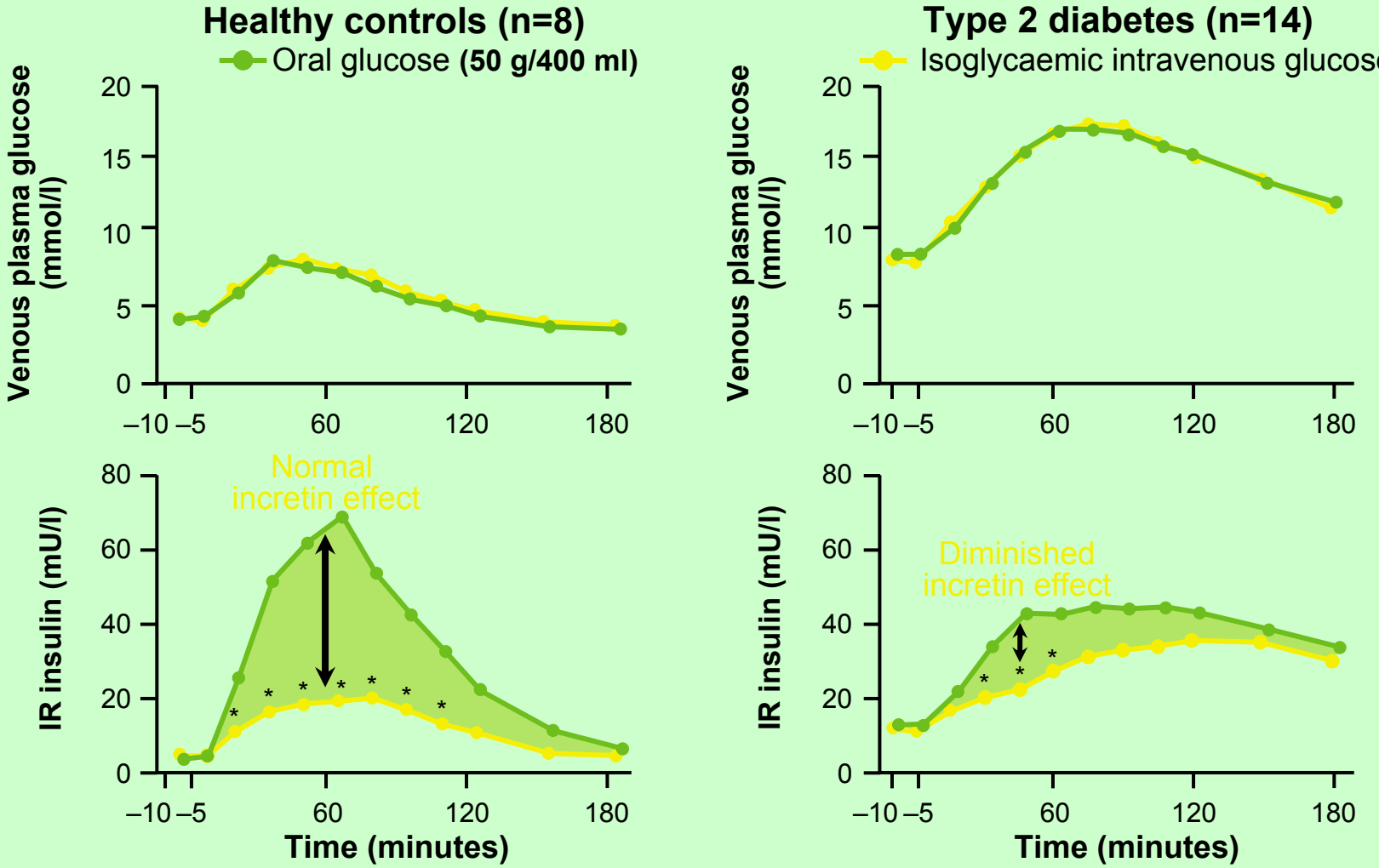
Incretin hormones play an important role in a healthy insulin response



- Insulin response is greater following oral glucose than IV glucose, despite similar plasma glucose concentration

Nauck *et al. Diabetologia* 1986;29:46–52, healthy volunteers (n=8)
Wick & Newlin. *J Am Acad Nurse Pract* 2009;21:623–30

Incretin effect after oral glucose was diminished in type 2 diabetes[6]

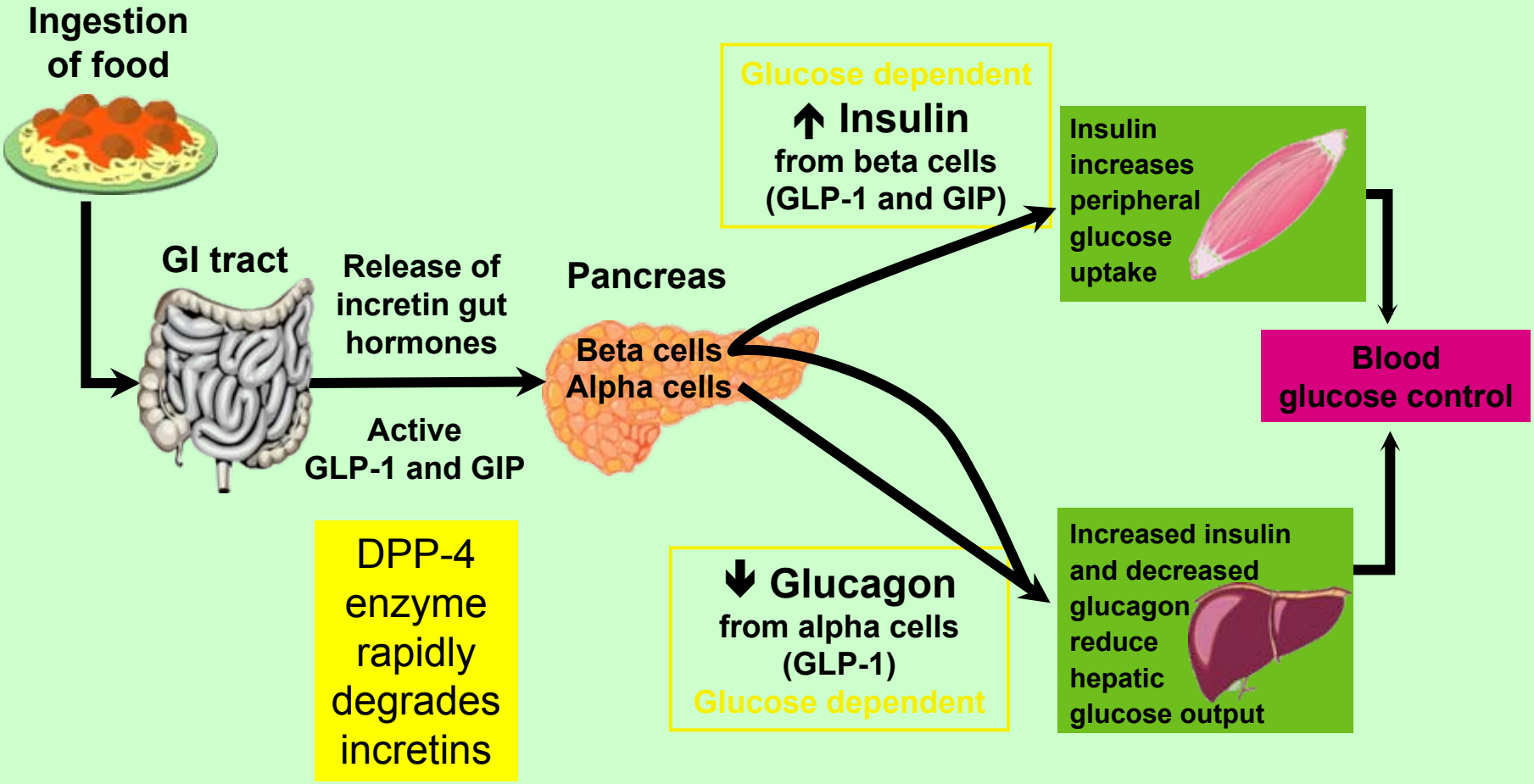


*p≤0.05 vs. respective value after oral load

IR=immunoreactive

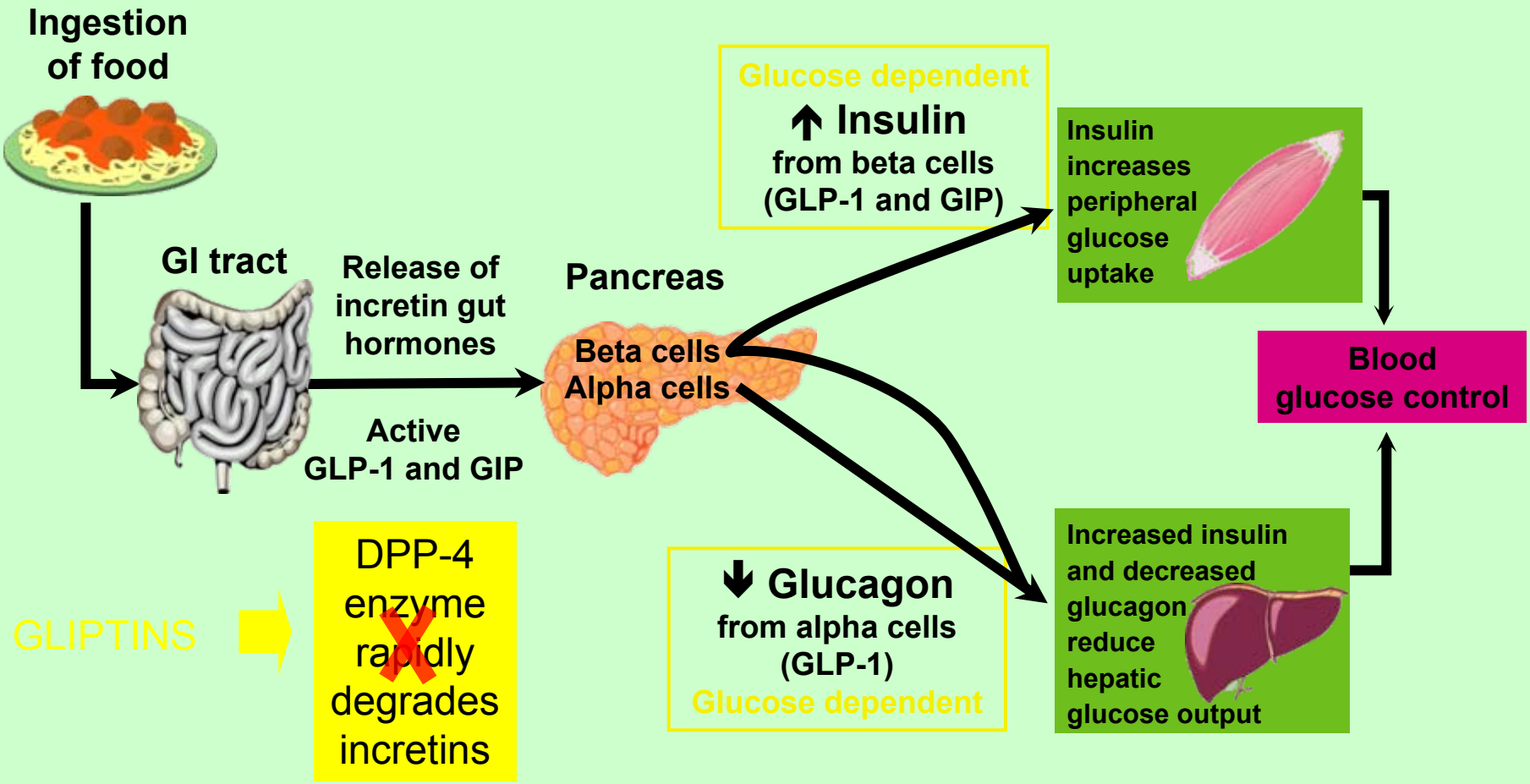
6. Adapted from Nauck M et al *Diabetologia* 1986;29:46–52.

Incretins and glycaemic control[7,8]



Adapted from 7. Drucker DJ. *Cell Metab*. 2006;3:153–165. 8. Miller S, St Onge EL. *Ann Pharmacother* 2006;40:1336-1343.

Mode of action of gliptins[8]



DPP-4= dipeptidyl peptidase 4 inhibitor

Adapted from 8. Miller S, St Onge EL. *Ann Pharmacother* 2006;40:1336-1343.

Summary

- Incretin gut hormones regulate islet cell function in the pancreas
- Incretin secretion in people with type 2 diabetes is impaired, leading to reduced insulin output and non-suppression of glucagon
- Gliptins inhibit DPP-4 enzymes, thereby increasing circulating incretin levels leading to:
  - Increased insulin
  - Decreased glucagon
  - Improved glycaemic control

* Gliptins added on to metformin Reduces HbA_{1c} by 7-8mmol/mmol

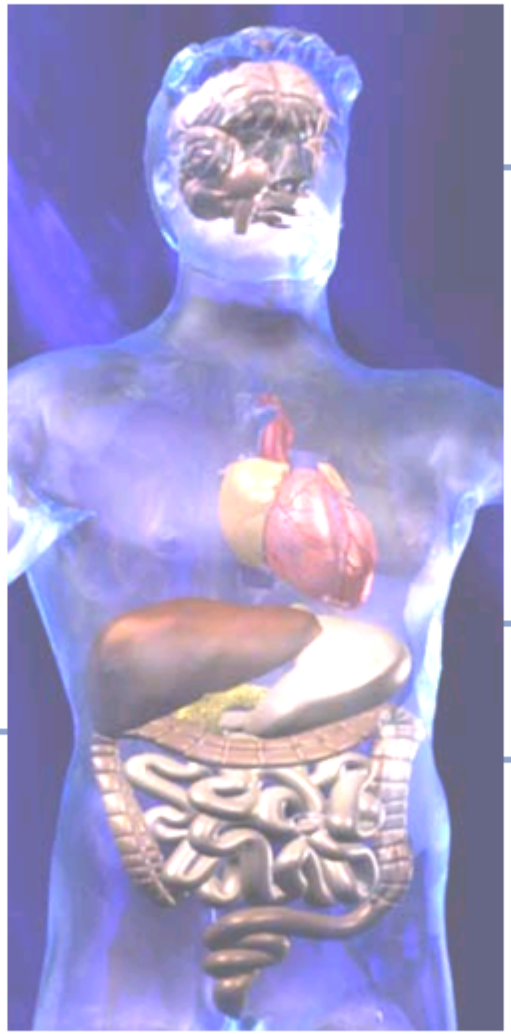
  - Low incidence of hypoglycaemia and low risk of weight gain

Native GLP-1 has multiple direct effects on human physiology

Pancreas

- ↑ Insulin secretion (glucose-dependent)
- ↑ Insulin synthesis
- ↑ Beta-cell mass*
- ↓ Glucagon secretion

*Animal data



Brain

- ↓ Energy intake

Liver

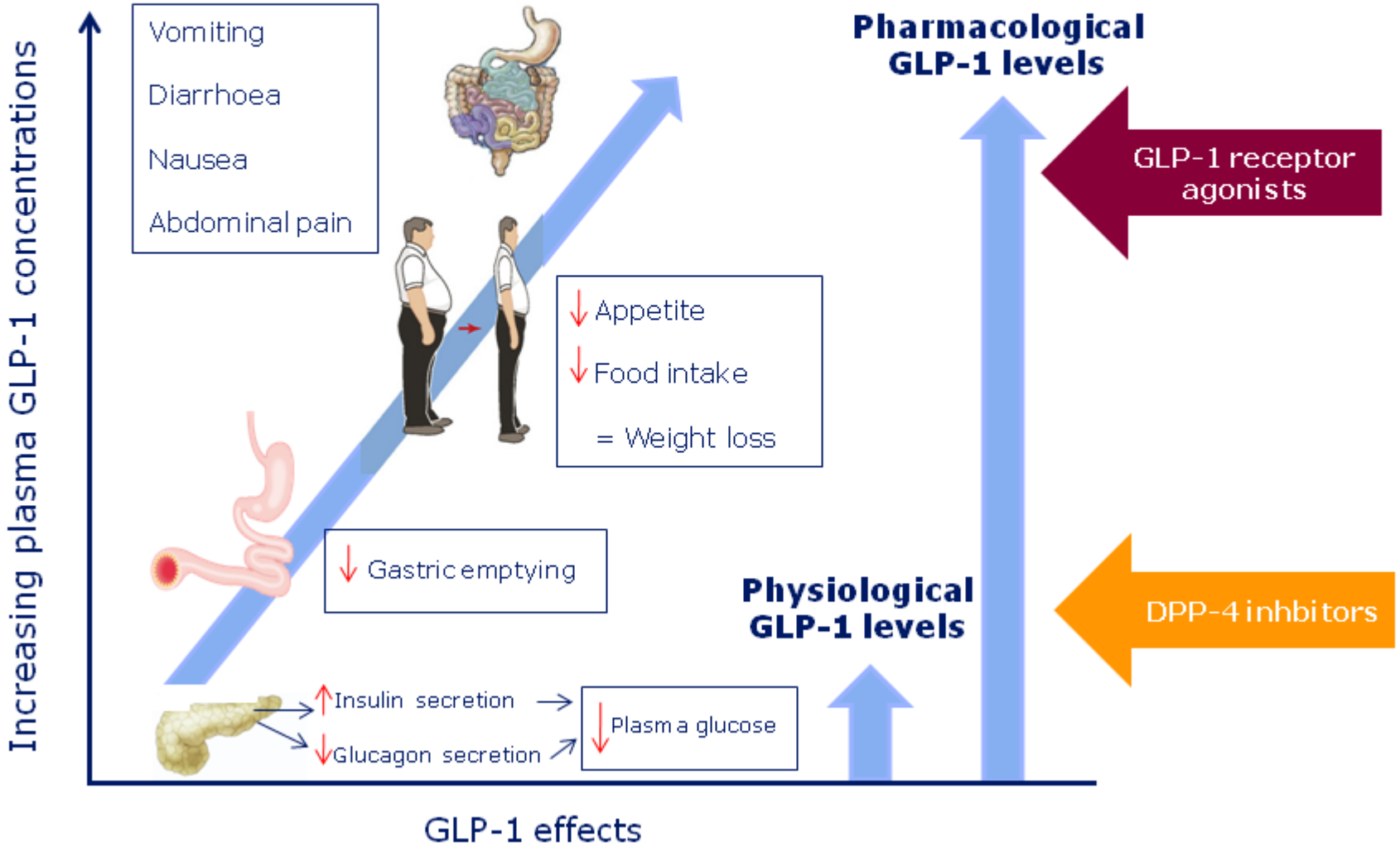
- ↓ Hepatic glucose output

GI tract

- ↓ Motility

Baggio *et al. Gastroenterol* 2007; 132: 2131–57;
Bulotta *et al. J Mol Endocrinol* 2002;29:347–60;
Drucker *et al. Proc Natl Acad Sci USA* 1987;84:3434–8;
Farilla *et al. Endocrinology* 2002;143:4397–408;
Gutzwiller *et al. Gut* 1999;44:81–6;
Kieffer *et al. Endocr Rev* 1999;20:876–913;
Wettergren *et al. Dig Dis Sci* 1993;38:665–73;
Nauck *et al. Diabetologia* 1993;36:741–4;
Zander *et al. Lancet* 2002;359:824–30.

GLP-1 dose–response relationships



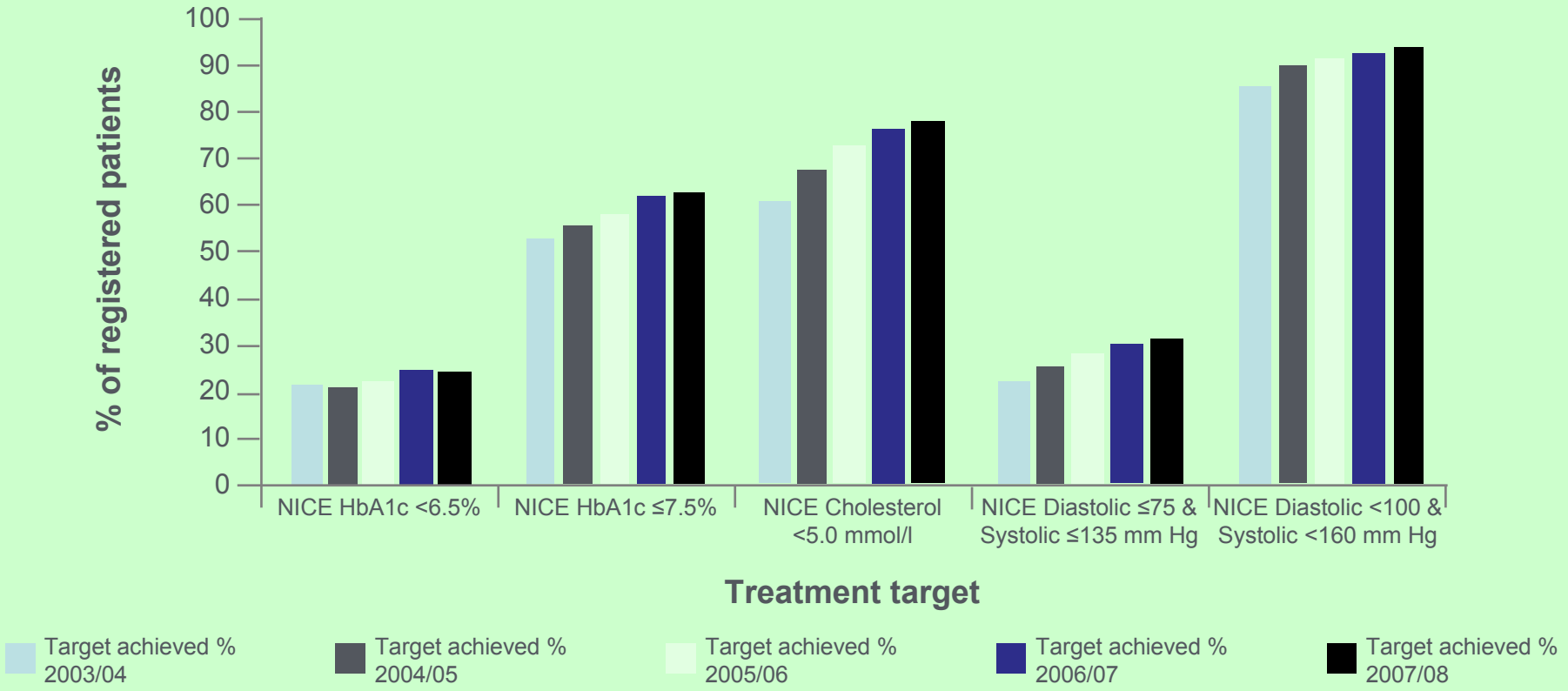
1. Holst. *Trends Mol Med* 2008;14:161–8

Add a Gliptin

- Linagliptin 5mg daily
- No weight gain
- Will reduce HbA1c 7-8 mmol/mmol
- Re-emphasize Food Plan
- Even if renal impairment no dose change needed

Achievement of therapeutic goals in T2D[1]

Percentage of people with diabetes in England by NICE recommended treatment targets, over 5 audit periods



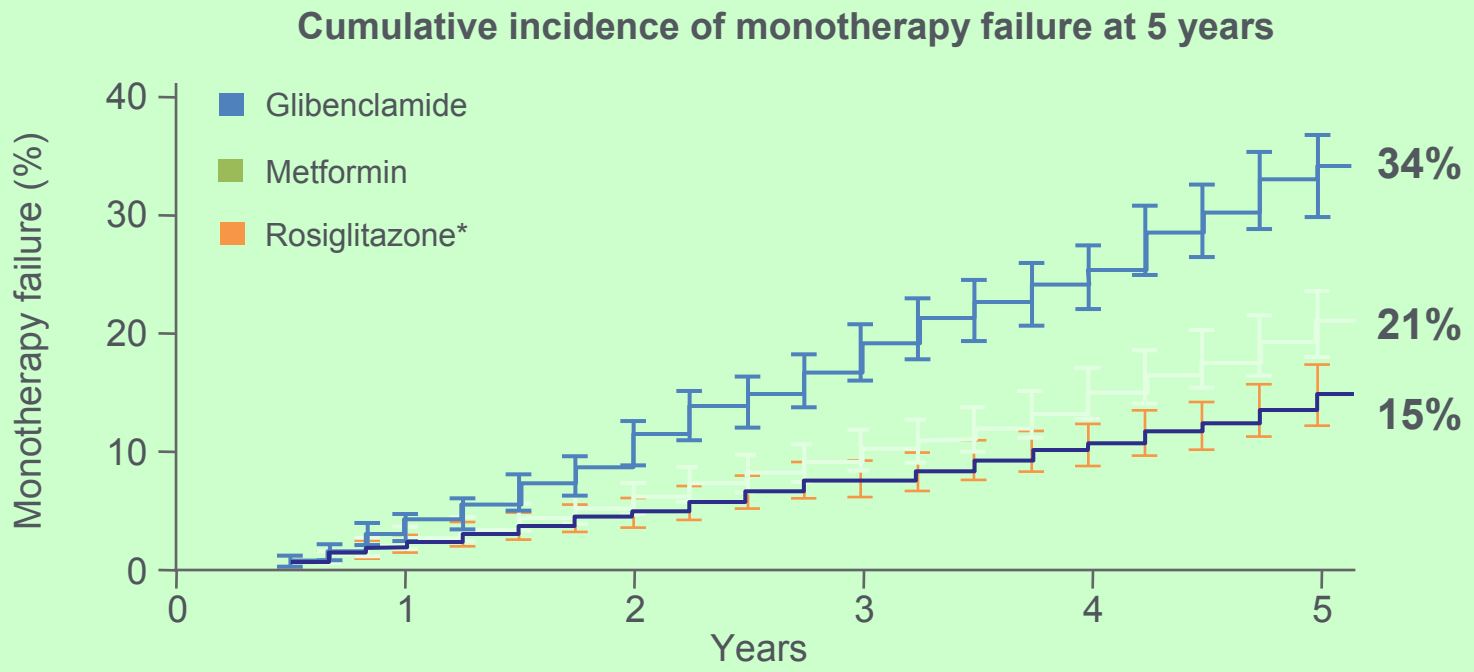
1. Adapted from: National Diabetes Audit. Report for the audit period 2007-2008. NHS. The Information Centre.

Patient Blood Glucose Monitoring

HbA1c		Average b. glucose
108	12	19.5
97	11	17.5
86	10	15.5
75	9	13.5
64	8	11.5
53	7	9.5

Monotherapy can progressively lose efficacy over time[1]

- Monotherapy treatment failure: patient fasting plasma glucose ≥10 mmol/l



*Rosiglitazone is no longer available in the UK/EU

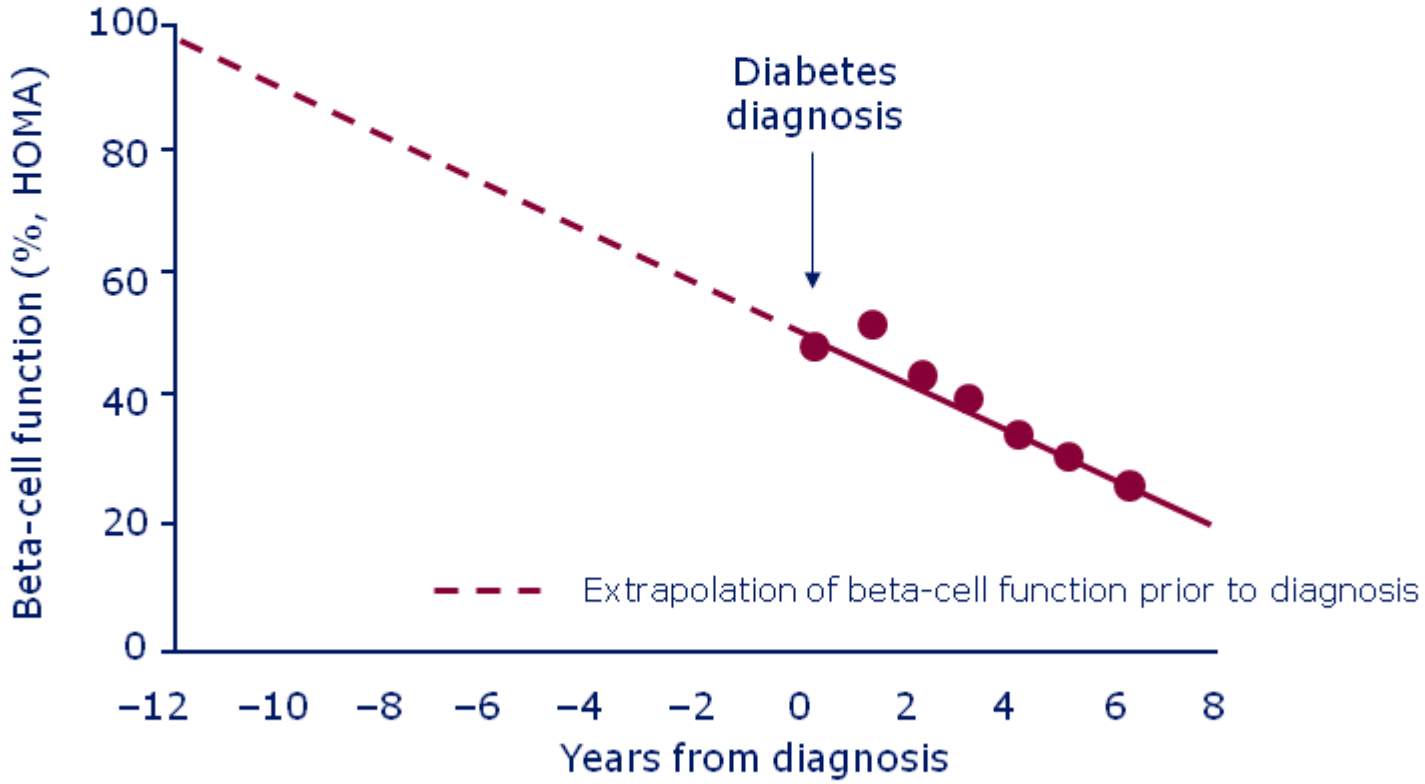
Hazard ratio (95% CI)
Rosiglitazone vs. metformin, CI 0.68 (0.55–0.85); p<0.001
Rosiglitazone vs. glibenclamide, CI 0.37 (0.30–0.45); p<0.001

1. Adapted from: Kahn SE, et al. *N Engl J Med* 2006;355:2427–43.

Date of preparation : September 2010

Challenges of T2D: beta-cell function

Progressive decline of beta-cell function



Lebovitz. *Diabet Rev* 1999;7:139–53 (data are from the UKPDS population)

Chronic kidney disease[1]

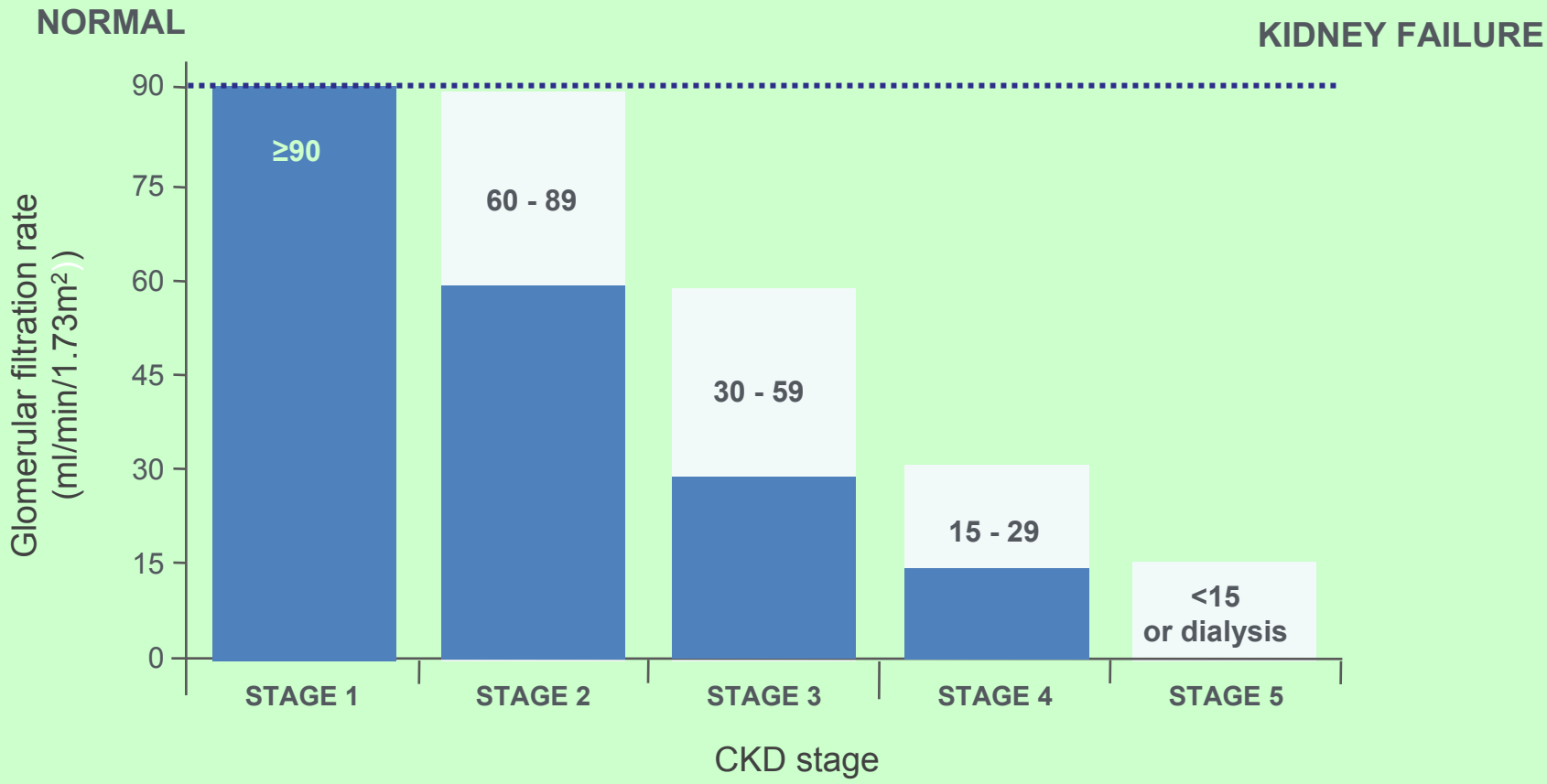
Staging of chronic kidney disease (CKD):

- Defined as kidney damage (pathologic abnormalities, proteinuria), or GFR <60 ml/min/1.73m^2 for >3 months (irrespective of the presence/absence of kidney damage)
- Includes all types of renal disease, irrespective of cause
- Renal impairment: CKD stages 2-5

Stages of CKD	Description	GFR (ml/min/1.73m^2)
1	Kidney damage with normal or ↑GFR	≥90
2	Kidney damage with mild ↓GFR	60-89
3	Moderate ↓GFR	30-59
4	Severe ↓GFR	15-29
5	Kidney failure	<15 (or dialysis)

1. Adapted from: Levey AS, et al. *Ann Intern Med* 2003;139:137-147.

CKD stages and impact on kidney function[1]



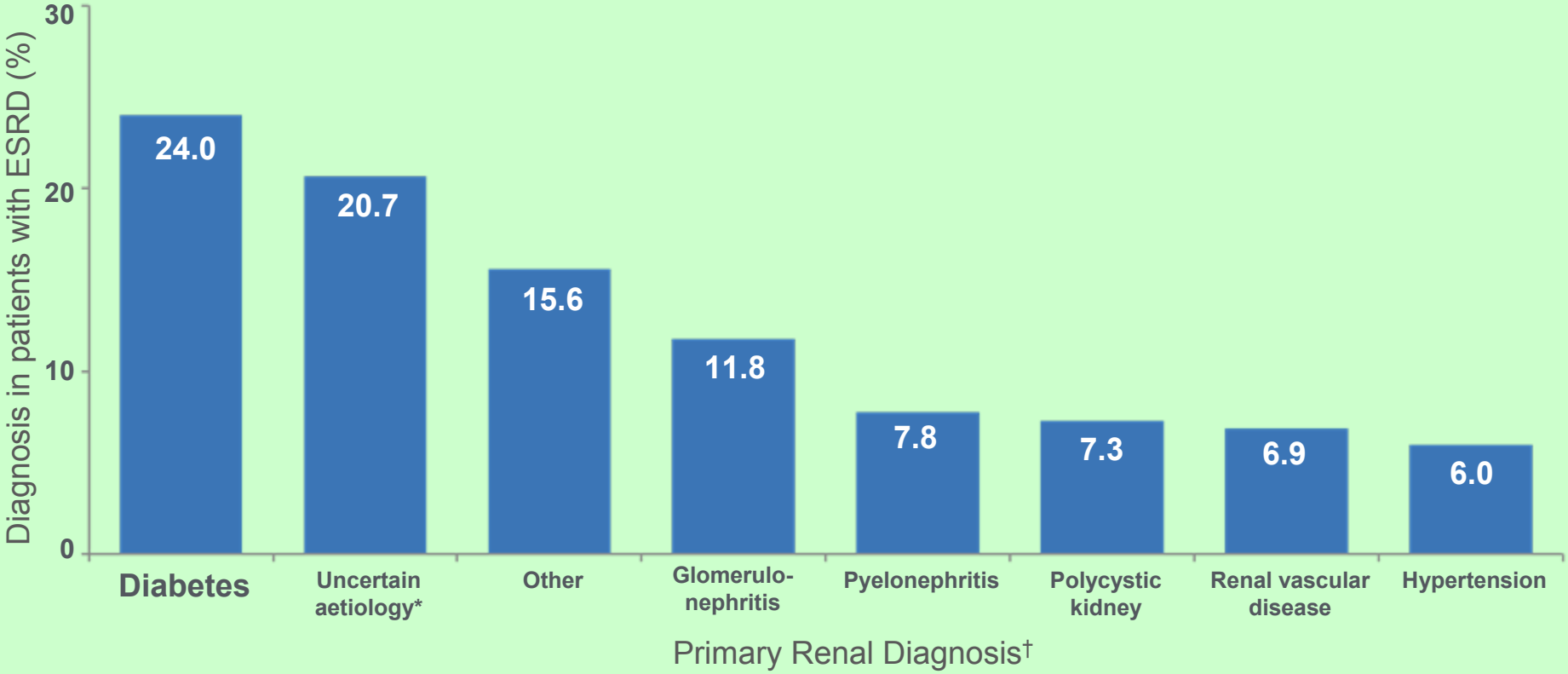
1. Adapted from: Levey AS, et al. *Ann Intern Med* 2003;139:137-147.

Diabetic kidney disease: NICE Guidelines[1]

- The urinary albumin:creatinine ratio is a useful measure of renal function used in diabetic renal disease (using first morning urine sample where practicable)
- **Microalbuminuria** is defined as: albumin:creatinine ratio (ACR) >2.5 mg/mmol (men) or >3.5 mg/mmol (women) or albumin concentration >20 mg/l
- **Proteinuria (macroalbuminuria)** is defined as: albumin:creatinine ratio ≥30 mg/mmol
- **NICE suggest:**
  - All people with diabetes should have urinary albumin/protein excretion quantified
  - The first abnormal result should be confirmed on an early morning sample (if not previously obtained)
  - Quantify by laboratory testing the urinary albumin/protein excretion of people with an eGFR 60 ml/min/1.73m^2 or more if there is a strong suspicion of CKD

1. National Institute for Health and Clinical Excellence. Clinical Guideline 73. Early identification and management of chronic kidney disease of adults in primary and secondary care.

Diabetic renal disease remains the single most common cause of renal failure[1]

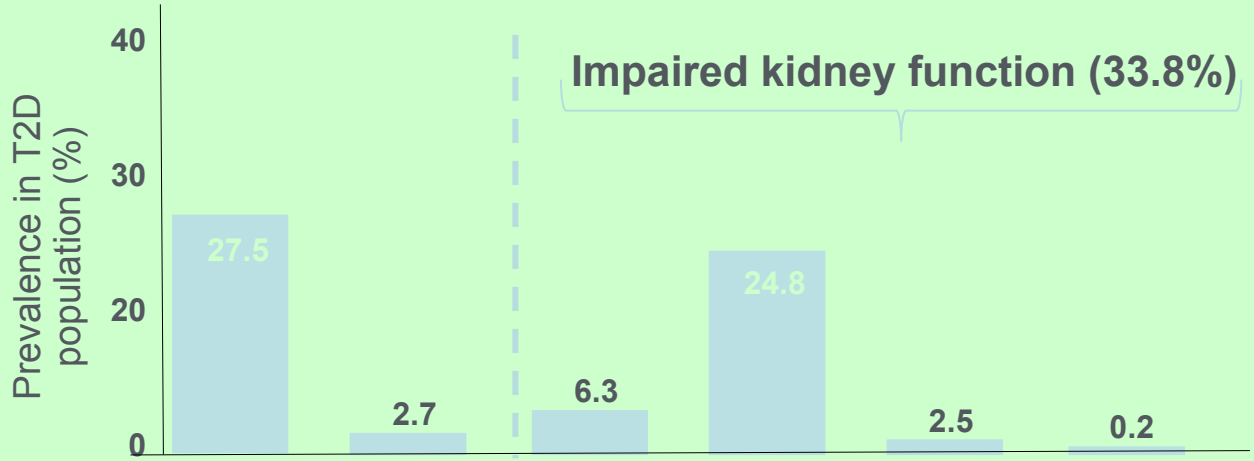


*Includes presumed glomerulonephritis not biopsy proven.
† Figures shown are calculated excluding data not available. Data for primary renal diagnosis (PRD) missing in 10.8% of patients. In centres with >25% missing PRD data, percentages in the other diagnostic categories not calculated. Centres with very high rates of uncertain diagnosis also excluded.

1. Adapted from: The Renal Association. UK Renal Registry. Twelfth Annual Report 2009.

Prevalence of CKD in T2D[1]

- Over a third of people with T2D have impaired kidney function (CKD stage 2-5)



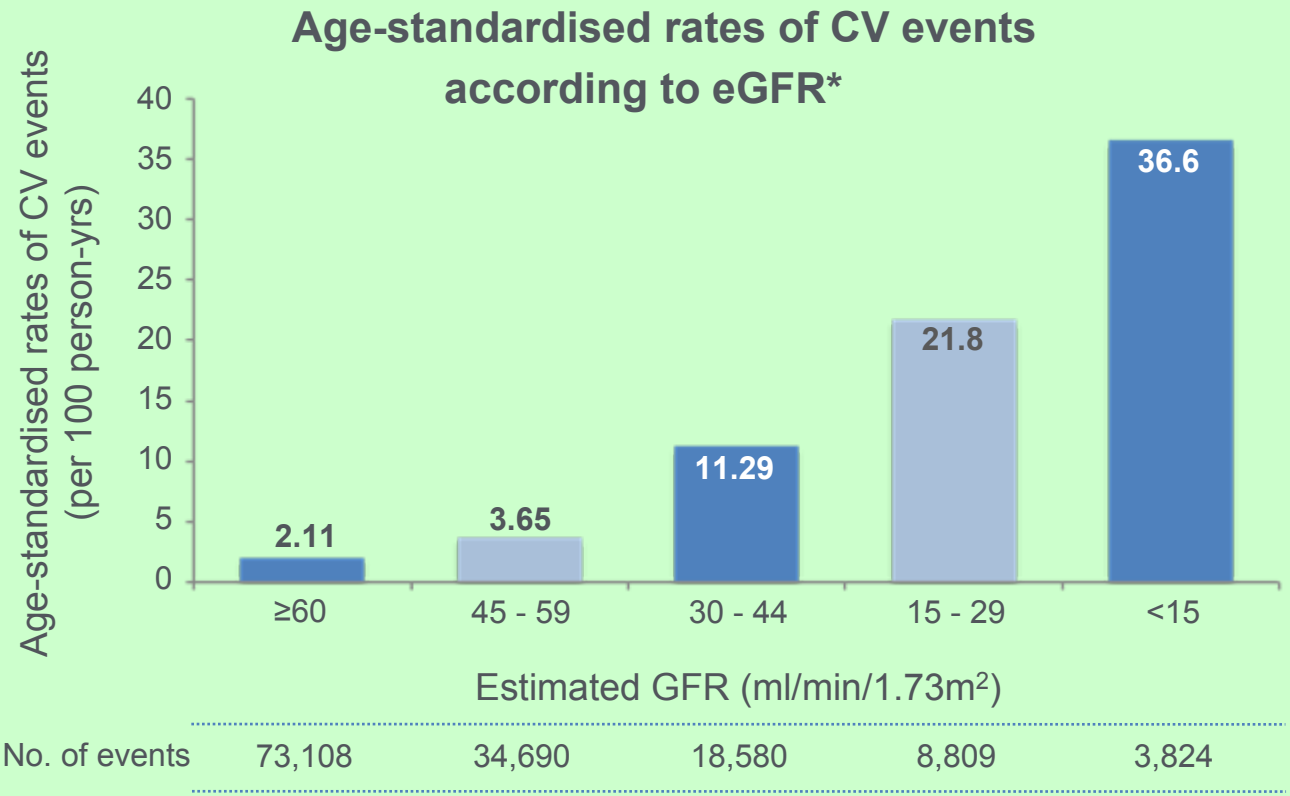
GFR ml/min/1.73m^2	≥90	≥90	60-89	30-59	15-29	<15
Stage	0	1	2	3	4	5
Kidney Function	Kidney normal	Kidney damage with normal GFR	Kidney damage with mild ↓GFR	Moderate ↓GFR	Severe ↓GFR	Kidney failure

Note: 36% of subjects with GFR ≥ 60 ml/min/1.73m^2 without albuminuria data may have no kidney disease or stage 1–2 CKD

1. Adapted from: Middleton RJ et al. *Nephrol Dial Transplant* 2006;21:88-92.

Renal impairment and cardiovascular (CV) risk[1]

- As eGFR decreases, risk of CV events increases



* Adults (1,120,295) within large US integrated healthcare system, with serum creatinine measured: 9.6% had been diagnosed with diabetes.

1. Adapted from: Go AS, et al. *N Engl J Med* 2004;351:1296-1305.

Treatment goals for CKD and T2D

Primary goals of treatment:

- Prevent or slow progression of CKD
- Management of CV risk factors

Manage key risk factors:

- Hyperglycaemia
- Hypertension BP 120/70 ACE inhibitor needed
- Proteinuria
- Dyslipidaemia
- Other CV risk factors (smoking, obesity etc.)

Summary: What we know

- Many patients with T2D face an inevitable decline in renal function
- The majority of people with T2D have renal impairment risk factors
- Renal function is a key predictor of CV risk
- CKD doubles the risk of CV events and death in patients with T2D
- Albuminuria is prevalent and persistent in patients with T2D
- Microalbuminuria is an early warning sign of renal decline

Summary: Treatment considerations

- Renal function should be considered when choosing treatment for T2D

- Patients with CKD are more likely to have poor glucose control and also have an increased risk for hypoglycemia[1]

- Several anti-diabetes medications are either contraindicated or have important side-effects in patients with T2D and impaired renal function[1,2]
  - Fluid retention, oedema and hypoglycaemia

- There is a need for well tolerated and efficacious treatments with:
  - No requirement for dose adjustment for any degree of renal impairment
  - No increased risk of hypoglycaemia
  - No associated weight gain, oedema or fluid retention

1. National Kidney Foundation. *Am J Kidney Dis* 2007;49(Suppl 2):S62–S73.
2. Zelmanovitz T, et al. *Diabetol Metab Syndr* 2009;1:10.

Decline in Renal Function

- If medication is renally excreted then it builds up in blood
- Metformin
- Sulphonylureas
- Insulin
- Gliptins except linagliptin
- GLP-1 agonists
- DANGER OF HYPOGLYCAEMIA unless dose of medication is reduced

HYPOGLYCAEMIA

- Comes on insidiously
  - loss of warning signs
  - confusion even semiconcious
  - especially with sulphonylureas

- Progressive fall eGFR in diabetic kidneys
  Elderly normal decline in eGFR
  Elderly eat less/stop eating when unwell

HYPOGLYCAEMIA

- Hypos on insulin - treat with glucose/food and discharge from casualty in type 1

- Hypos on tablets - treat with iv dextrose for 24 -48 hours in type 2 and change medication to short acting drugs eg glinides. Reduce insulin dose

DPP-4 inhibitors excretion

	Renal excretion
Linagliptin	5%
Sitagliptin	87%
Saxagliptin	75%
Vildagliptin	85%

All need dose reduction as eGFR falls except Linagliptin

LINAGLIPTIN

- DPP-4 inhibitor - WEIGHT NEUTRAL
- Effective - will reduce HbA1c by 7-8 (0.6)
- Safe - few side effects
- Cost neutral
- Once daily dosage
- NO dosage adjustment in renal impairment
- Should be added in Early to obese type2 regimen before sulphonylureas
- My Gliptin of choice

OBESE DIABETIC

- Comply with calorie/CHO restriction
- Metformin
- Linagliptin
- STOP gliptin and use GLP-1 agonist
- Add sulphonylurea/prandial regulator
- Add basal long acting insulin if fasting glucose is above 6mmol/l
- CAN BE VIRTUALLY UNTREATABLE ESPECIALLY IF NON COMPLIANT TO FOOD PLAN