

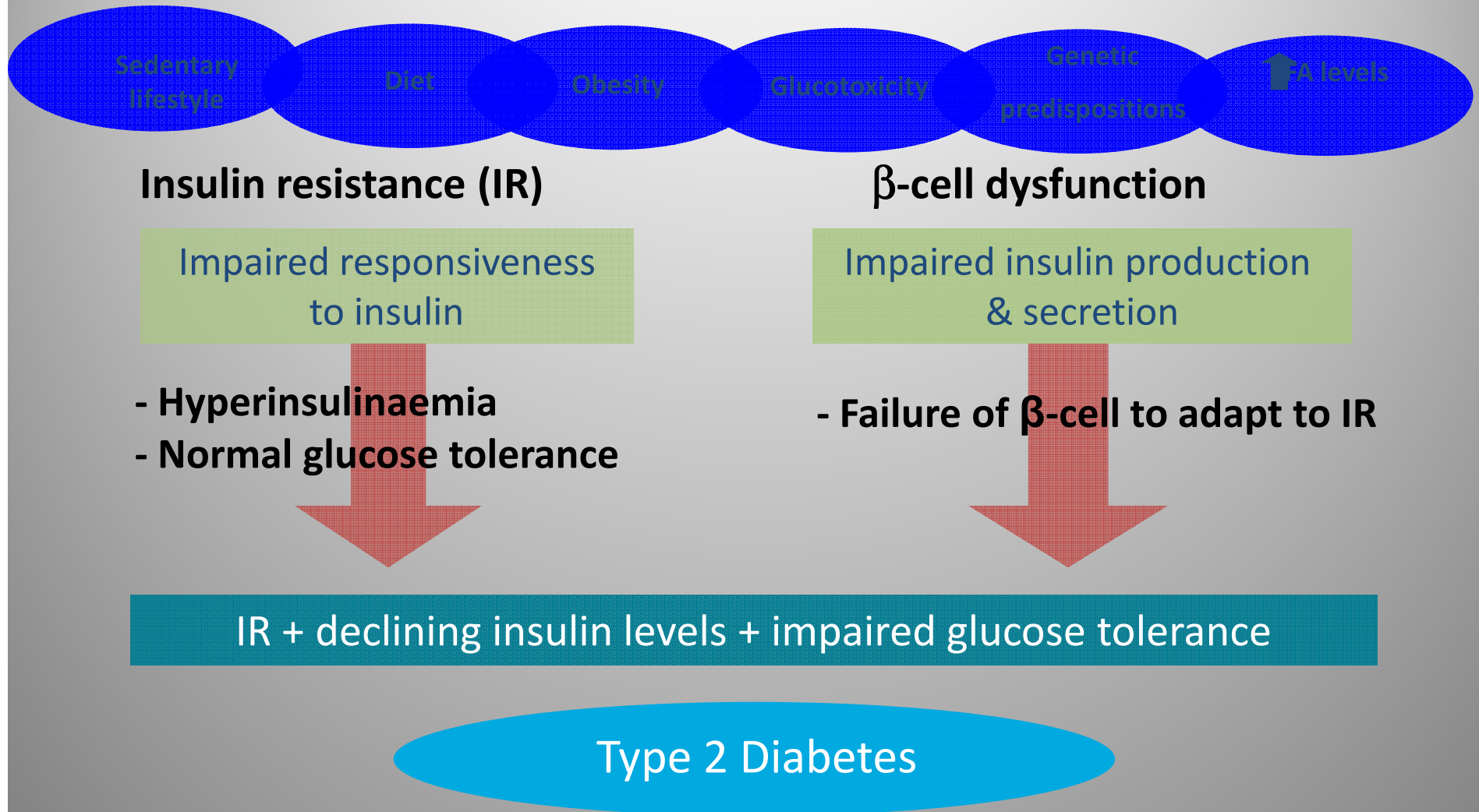
Treatment pathways in Type 2 diabetes

JAY/NOV11

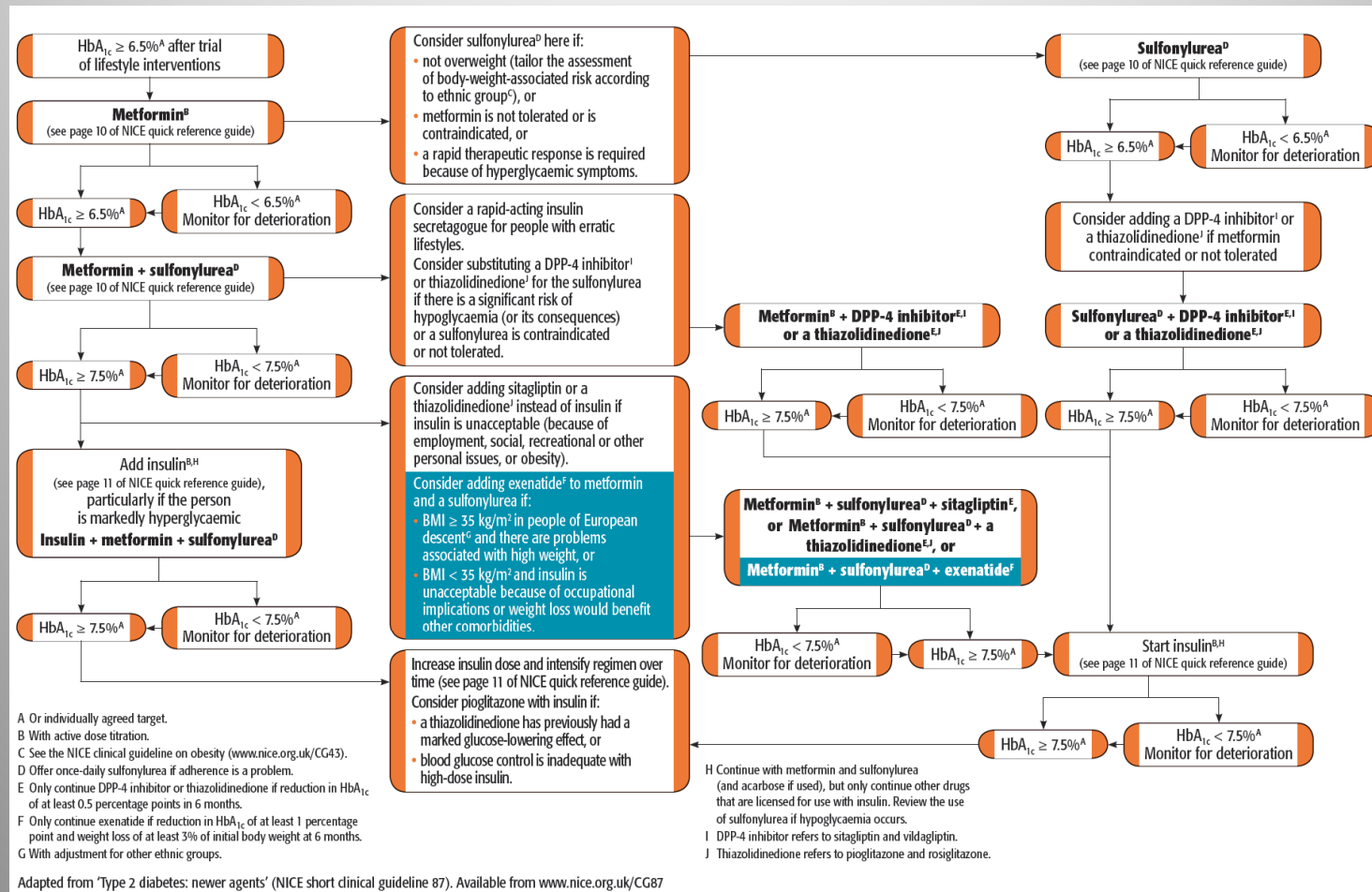
Contents

- The pathway Type 2 diabetes
- NICE and oral agents : a progression
- Newer agents
- Insulin therapy
- Safe use of insulin

Core underlying defects in type 2 diabetes: Insulin resistance and β -cell dysfunction



NICE guidance

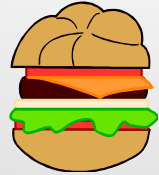


Newer agents

GLP-1 receptor agonists and DPP-4 inhibitors

- Target the incretin system
- Blood glucose lowering agents
- Injectable or oral
- No weight gain and variable weight loss
- Low rate of hypoglycaemia

incretin axis: sites for therapeutic intervention



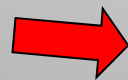
GLP-1 analogs



GLP-1

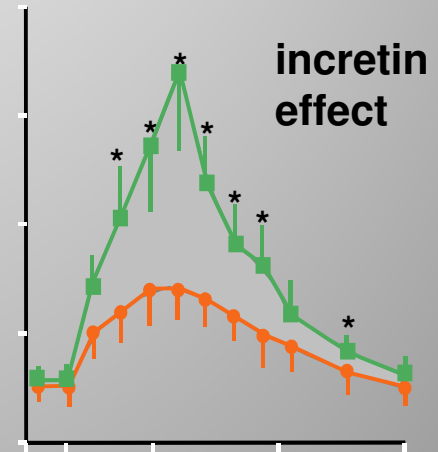


DPP-IV inhibitors



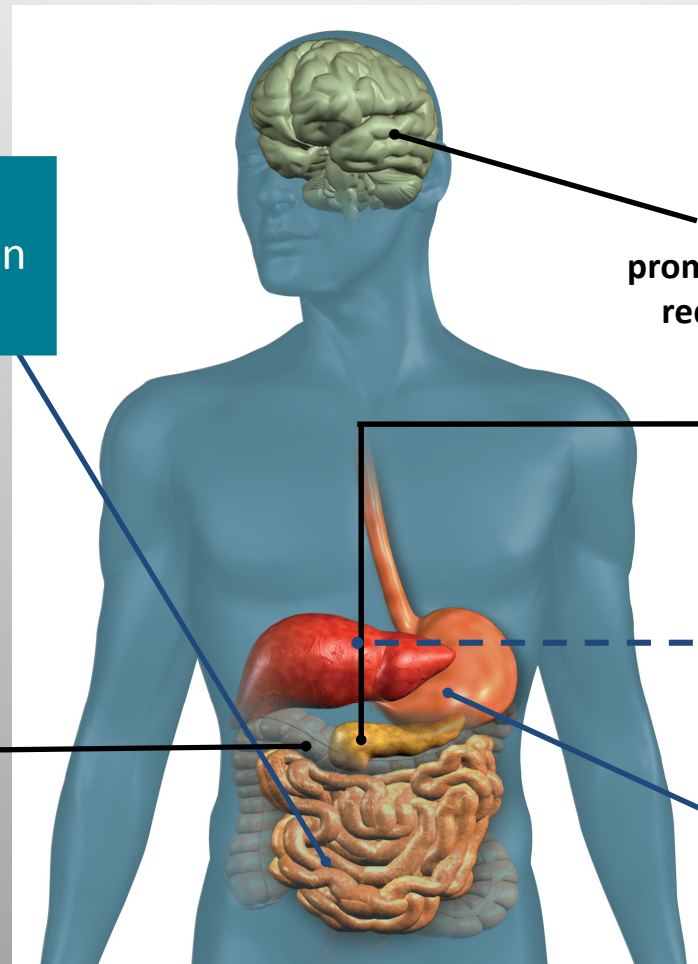
DPP-IV
 $t_{1/2} \sim 1.5$ min

inactive GLP-1



GLP-1: Self-regulating blood glucose levels through multiple mechanisms of action

GLP-1 secreted upon the ingestion of food



Brain:
promotes satiety and
reduces appetite

α-cell:
suppresses postprandial
glucagon secretion

Liver:
reduces hepatic glucose
output

Stomach:
slows the rate of gastric
emptying

β-cell:
enhances glucose-dependent
insulin secretion in the
pancreas

Exenatide (Byetta) Glucagon – like peptide -1 receptor antagonist or GLP -1

Modes of action (class effect)

- Acts by binding to and activating the GLP-1 receptor
- Increases glucose dependent insulin secretion from the pancreatic beta cells, as glucose concentrations decrease, insulin secretion subsides
- Suppresses inappropriately elevated glucagon levels
- Slows gastric emptying thus reducing the rate of which meal derived glucose appears in the circulation
- Patient should reach satiety sooner and thus eat less!
- Caution if eGFR 30-50mL/min , avoid if eGFR < 30mL/min/1.73m²

Liraglutide (Victoza)

- Licensed at 1.2mgs in combination with Metformin & a SU or metformin TZD (thiazolidinedione) or dual therapy if intolerant to Metformin or a SU, or treatment with either is contraindicated and the patients is intolerant of TZD and DPP-4 inhibitors
- Advantage: Patients benefit from a once daily injection and timing does not have to be at a meal time
- Disadvantage : More costly than Byetta and little evidence for the use of 1.8mg (each pen 30 doses of 0.6mgs or 15 of 1.2mgs cost)
- Avoid if eGFR < 60mL/min/1.73m² (no experience)

DPP-4

(dipeptidyl peptidase-4 inhibitors)

NICE CG87

- The use of Sitagliptin or Vildagliptin is recommended instead of an SU as second line therapy if BG control remains or becomes inadequate if the person is at significant risk of hypoglycaemia or its consequences

Barnett A, Brice R, Hall G, Holt R, Kanumilli N, Mulnier H, 2010, "Nice technology Appraisal on liraglutide : Interpretation and practical implications. Supplement to Diabetes & primary care Vol 12, No 6

BYDUREON

- Alternative to other GLP-1 agonists in a weekly preparation (same day)
- BYDUREON is exenatide incorporated into polymer based microspheres.
- Following s/c injection the microspheres slowly biodegrade and release the exenatide gradually at a controlled rate over an extended period of time
- Therapeutic levels are achieved in 2 weeks and steady state is achieved at 6-7weeks
- Target patient=
- Cost for 28 days = £73.36
- Lower incidence of nausea then BD exenatide or 1.8mgs liraglutide
- Some problems with skin pruritus/nodules/erthema at injection sites

Compare and contrast

	GLP-1	DPP-4
GLP-1 conc. in plasma	Supraphysiological levels of GLP-1 Not limited by endogenous secretion of GLP-1	Increased levels of GLP-1 in physiological range Limited by endogenous secretion of GLP-1
Effects on insulin & glucagon	++ insulin release when glucose elevated - -Glucagon release when glucose elevated	+ insulin release when glucose elevated -Glucagon release when glucose elevated
GI side effects	-Food intake - gastric emptying	No significant effect
Tolerability	Mild & transient nausea in 10-30% Low rates of hypo unless with SU	Low rates of hypos unless with SU or insulin (sitagliptin only)

Compare and contrast

	GLP-1	DPP-4
Method of administration	s/c injection	Oral
Approximate reduction in HbA1c in phase III clinical trails	~1.0-1.5% (~11-16mmols/mol)	~0.5-1.0% (~ 5-11mmol/mol)
Typical effect on body weight	Weight loss	Weight neutral

Insulin therapy

An option appraisal

Insulin therapy in Type 2 Diabetes

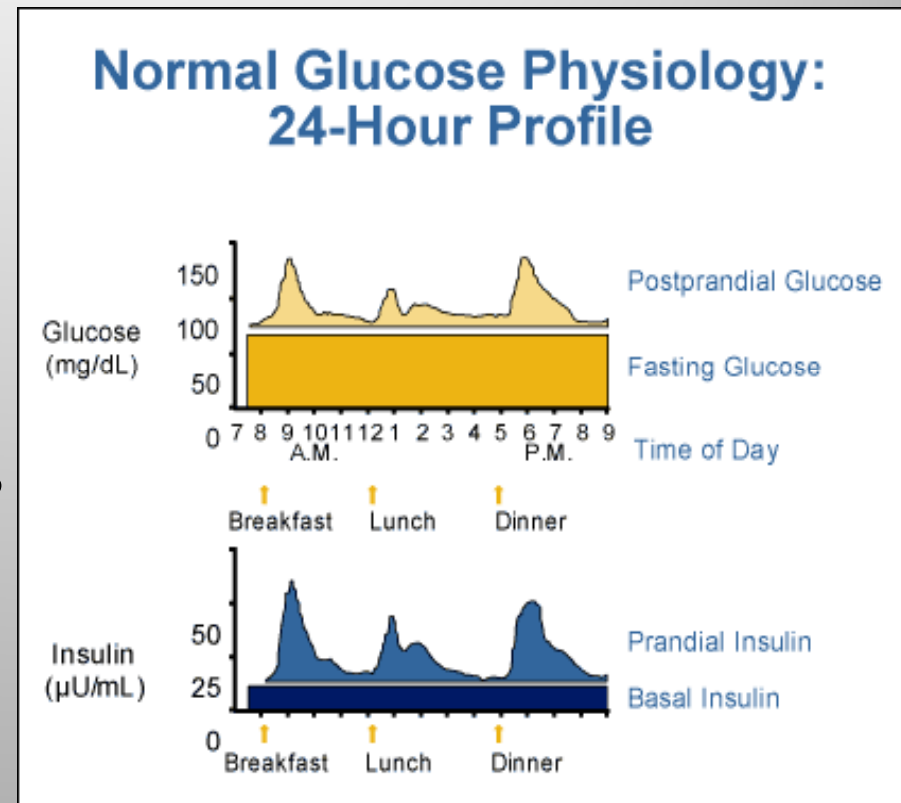
- Accounts for majority of people commencing insulin
- The younger patient is at presentation ↑ risk of needing insulin
- Quicker need to increase O.H.As ↑ risk of earlier introduction of insulin
- The progressive nature of Type 2 diabetes means that a substantial proportion of patients may require insulin within 10 years of diagnosis

Type 2 diabetes and insulin

- Does insulin help?
 - Mostly
- When should insulin be started?
 - Often too late
 - Depends on goals of therapy
- Which is the best insulin and regimen?
 - No evidence base for this
- What is the correct starting dose?
 - Variable nationally
- How are oral therapies managed?

Normal glucose/ insulin physiology

- Insulin is secreted at a low basal rate which accounts for about 50% of insulin produced¹
- Post-prandially insulin is secreted in relation to post-meal glucose¹



What currently guides choice of insulin?

- Aim of treatment
 - What are the goals of therapy (from HCP & patient perspective)
- Individual capabilities
 - Knowledge, skills and competence
- Lifestyle/social aspects
 - Dietary patterns, employment etc
- Patient choice (What does this actually look like ?)
 - Are patients given a choice re number of injections, pen devices, regimens?
 - Patients want to know the full information to be able to make an informed choice
 - Unless a treatment is asked for, it may not ever be offered. It was felt this amounted to gate keeping of information

DUK , "What does choice mean to people with diabetes?" DUK: London 2005

Further points to consider when choosing insulin regimens in Type 2

- Not achieving goals of therapy
- Was failure of previous medication due to non-compliance/adherence
- Mismatched goals
- Weight gain
 - Variable depending upon regimen and pre-therapy state
- Availability or lack of, dietary support
- Hypoglycaemia
 - Risk is lower in type 2 diabetes

4-T study: 3 year efficacy of complex insulin regimens in Type 2 diabetes⁷

- Sponsored by Novo Nordisk, independently designed run and reported by an academic group (Oxford)
- 1 year results published in 2007
- First phase
 - 1 yr head to head comparison of the efficacy of 3 different types on insulin (Prandial Insulin Aspart (Novorapid) three times daily, biphasic insulin aspart (NovoMix 30) twice daily, basal insulin detimir (Levemir) once daily (twice if required))
- 3 yr study in 708 Type 2s in 58 UK / Irish centres
- Second phase
 - Evaluation over 2 further years for the need for more complex insulin regimens and overall efficacy of insulin strategies above

Holman RR. et al, New England Journal of Medicine 2007;357: 1716-30

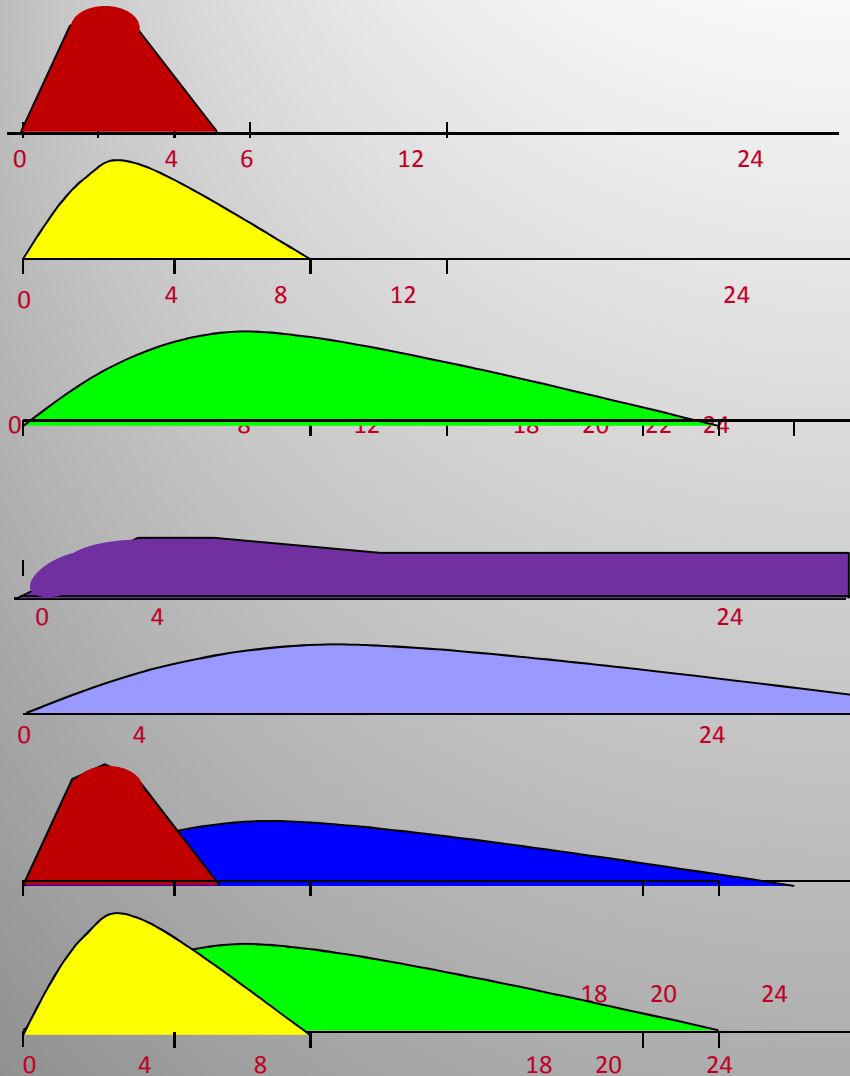
4-T study: 3 year efficacy of complex insulin regimens in Type 2 diabetes⁷

- Demographics
- No difference between 3 groups
 - Age , Duration of diabetes, BMI,
 - HbA1c, Concomitant OHA's

Results

- No statistically difference in median HbA_{1c} between groups
 - Differences in proportions reaching target level
- Hypos lowest in basal group
- Weight gain highest in prandial group
- % of patients who required intensification using a second insulin:-
 - 67.7% for biphasic
 - 73.6% for prandial
 - 81.6% for basal

Onset and Duration of Insulin



Rapid-acting analogue

e.g. Humalog* (insulin lispro), NovoRapid, Apidra

Short-acting (soluble/regular)

e.g., Humulin S (Human insulin), Actrapid, Insuman Rapid

Intermediate acting (Isophane)

e.g. Insulatard, Humulin I (Isophane human), Insuman Basal

Long acting analogue

e.g. Lantus

or Levemir

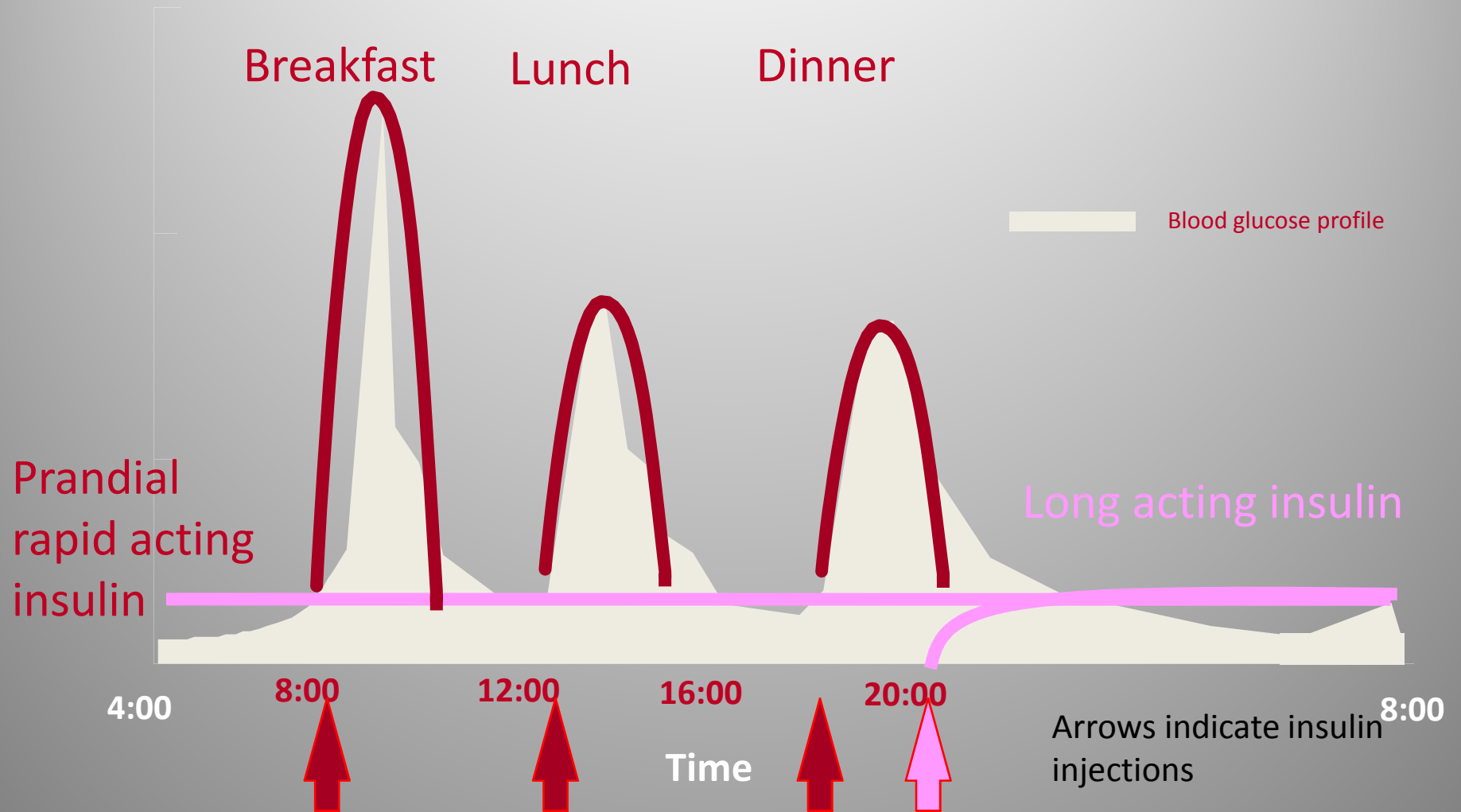
Rapid acting analogue-intermediate mixture

e.g. Humalog Mix25 / Mix50 or NovoMix30

Short acting-intermediate mixture

e.g. Humulin M3, Insuman Comb 15, 25, 50

Basal Bolus regimen aims to physiologically mimic normal endogenous insulin production



Determinants of success

Appropriate insulin regimen

- A need for more evidence in Type 2 diabetes
- Therefore the choice of insulin should be based on presumed likelihood of success.

Appropriate dose titration

- Empowerment for self titration with appropriate instruction
- Pt confidence in self adjustment

Compliance/concordance with treatment

Safe use of insulin

- Safe use of insulin(MHRA)
- Always write UNITS never write IU or U
- All insulin must be administered via a pen device or an insulin syringe
- Common errors?
- Eg Humalog and Humalog Mix 25 are not the same!
- All analogues are clear!

Test your knowledge

Try to undertake a self assessment!

- www.diabetes.nhs.uk/safe_use_of_insulin/learning_course/ -
- Any questions?

Thank you for your attention