Oral Hypoglycaemic Agents and Insulin

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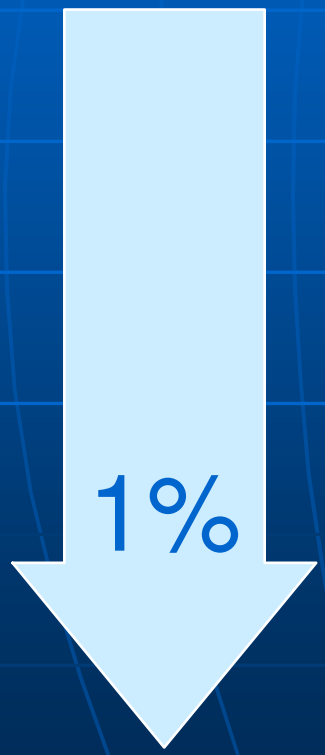
Hypoglycaemic Agents

- α glucosidase inhibitors
- Metaglinides
- Metformin
- Sulphonylureas
- Thiazolidindiones
- GLP – 1 analogues
- DPP IV inhibitors
- SGLT2 inhibitors

Lessons from UKPDS: Better Control Means Fewer Complications

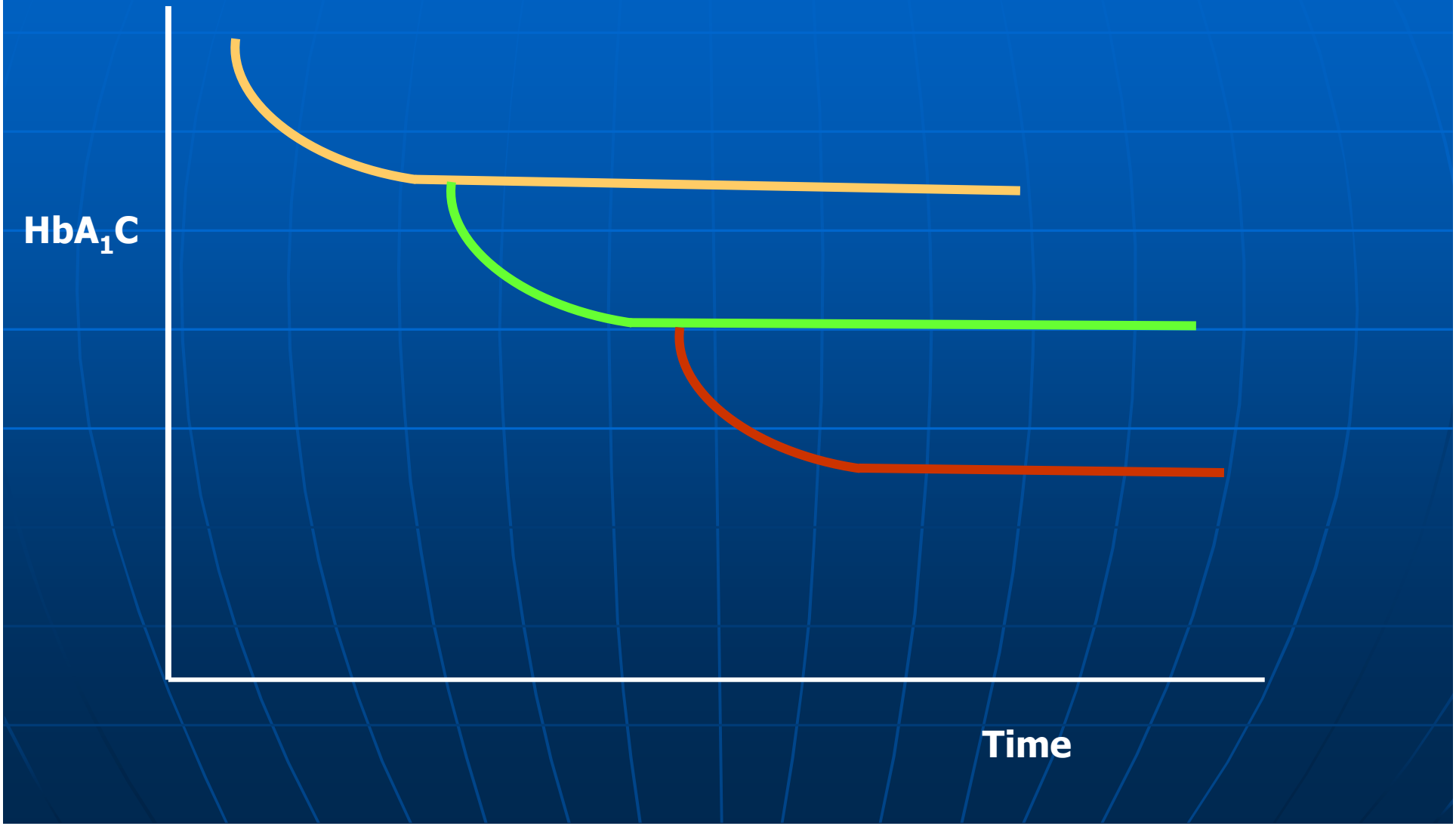


	REDUCED RISK*
Deaths from diabetes	–21%
Heart attacks	–14%
Microvascular complications	–37%
Peripheral vascular disorders	–43%

UKPDS 35. BMJ 2000;321:405–12

*p<0.0001

Their Effects Are Additive



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Acarbose

- Marginal benefit – no overall effect on hyperinsulinaemia or insulin sensitivity
- Best for individuals with normal fasting glucose but high postprandial glucose levels
- Maximum HbA_1C reduction of 0.75%
- Can be used in combination with insulin, metformin or SU's

Acarbose

- GI side effects abound therefore dose gradually built up
- Contraindicated in inflammatory bowel disease, cirrhosis, severe renal impairment, history of abdominal surgery

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Metaglinides

- Repaglinide and Nateglinide
  - First introduced in 1998
  - Work by binding to the sulphonylurea receptor and 'squeezing' the β cell to release insulin
  - They stimulate first-phase insulin release in a glucose-sensitive manner

Metaglinides

- Short acting
- Taken only with meals
- Marginal benefit
- Best for individuals with normal fasting glucose but high postprandial glucose levels
- Maximum HbA_1C reduction of 1.0%

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Metformin

- Used since medieval times in some form or other
- Should be the first line oral hypoglycaemic agent for almost all individuals with type 2 diabetes
- BMI is no longer an issue

Ungar G, Freedman L, Shapira S. Pharmacological studies of a new oral hypoglycaemic drug. Proceedings of the Society for Experimental Biology and Medicine. 1957;95:190-192

Metformin

- Works by decreasing hepatic gluconeogenesis, decreasing gut glucose uptake and increasing peripheral insulin sensitivity
- Relies on adequate β cell function
- Weight neutral
- Can be used in combination with other oral agents or insulin

Metformin

- GI disturbance is common so dose titrated
- Maximum HbA_1C reduction is 1.5%

Metformin

- Hypoglycaemia is NOT a side effect of treatment
- Avoid in conditions predisposing to renal insufficiency and/or hypoxia
- Lactic acidosis is a theoretical risk

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Sulphonylureas

- Have been around since the 1950's
- Act by binding to the SU receptor causing an influx of Ca^{2+} and an exocytosis of insulin containing vesicles
- Relies on adequate β cell function
- Good for rapid symptom relief

Sulphonylureas

- Use limited to individuals with a BMI < 25 or in whom metformin is contraindicated
- When used in combination, they flatten glucose excursions
- Can be used in combination with most other oral hypoglycaemic agents

Sulphonylureas

- Their long half life makes hypoglycaemia more likely, especially in the elderly
- Avoid in hepatic or renal failure
- Maximum HbA_1C reduction is 1.5%
- Weight gain is common

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Thiazolidinediones

- Pioglitazone (rosiglitazone was withdrawn in 2010)
- Work by increasing peripheral insulin sensitivity at a nuclear level on peroxisome proliferator-activated receptor γ (PPAR γ)
- "First do no harm"

Thiazolidinediones

- Maximum HbA_1C reduction is 1.5%
- But this takes 4 to 6 months to achieve maximal benefit so give it time!
- Avoid if possible – use pioglitazone if you must

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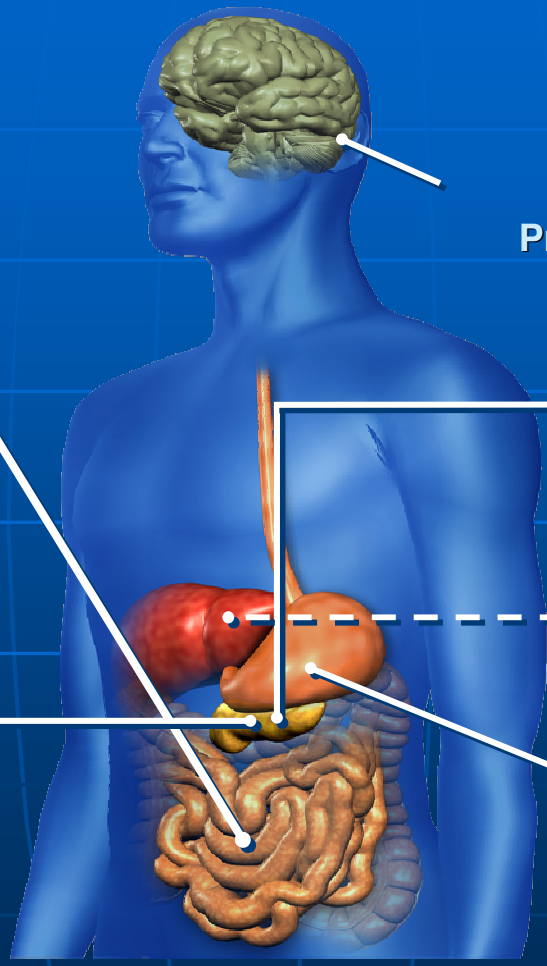
GLP-1 Analogues

- Exentatide and Liragultide

GLP-1 and DPP-IV



GLP-1 secreted upon the ingestion of food

5.Brain:
Promotes satiety and reduces appetite

2.α-cell:
Suppresses postprandial glucagon secretion

3.Liver:
reduces hepatic glucose output

1.β-cell:
Enhances glucose-dependent insulin secretion in the pancreas

4.Stomach:
slows the rate of gastric emptying

Nauck MA et al. *Diabetologia* 1993;36:741–744; Larsson H et al. *Acta Physiol Scand* 1997;160:413–422; Nauck MA et al. *Diabetologia* 1996;39:1546–1553; Flint A et al. *J Clin Invest* 1998;101:515–520; Zander et al. *Lancet* 2002;359:824–830.

Do They Work?

- HbA_1C reduction of about 1.1%
- Extensive weight loss
- ? β cell preservation
- 5mg bd $^{s}/_{c}$ fixed dose
- Expensive
- Haemorrhagic pancreatitis

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DPP-IV Antagonists

- Sitagliptin, saxagliptin and Vildagliptin

Do They Work?

- HbA_1C reduction of about 1.1%
- Oral
- ? B cell preservation
- Weight neutral
- Expensive

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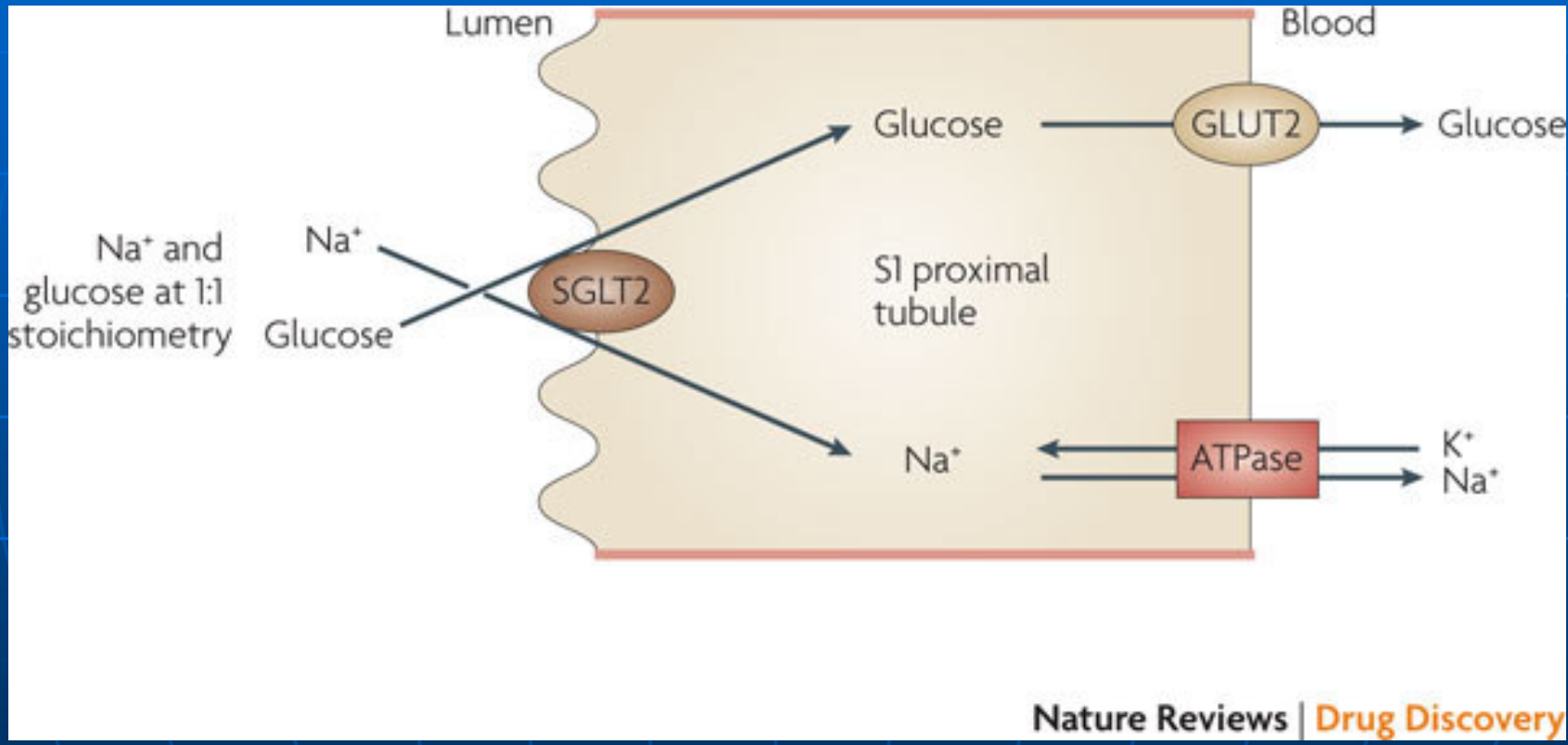
SGLT2 Inhibitors



Chao EC Nature Rev Drug Disc 2010;9(7):551-559

SGLT2 Inhibitors

- Work independently of insulin to inhibit glucose re-uptake from the proximal convoluted renal tubule
- Can be used in type 1 or type 2 diabetes
- Can be used in combination with any other agent

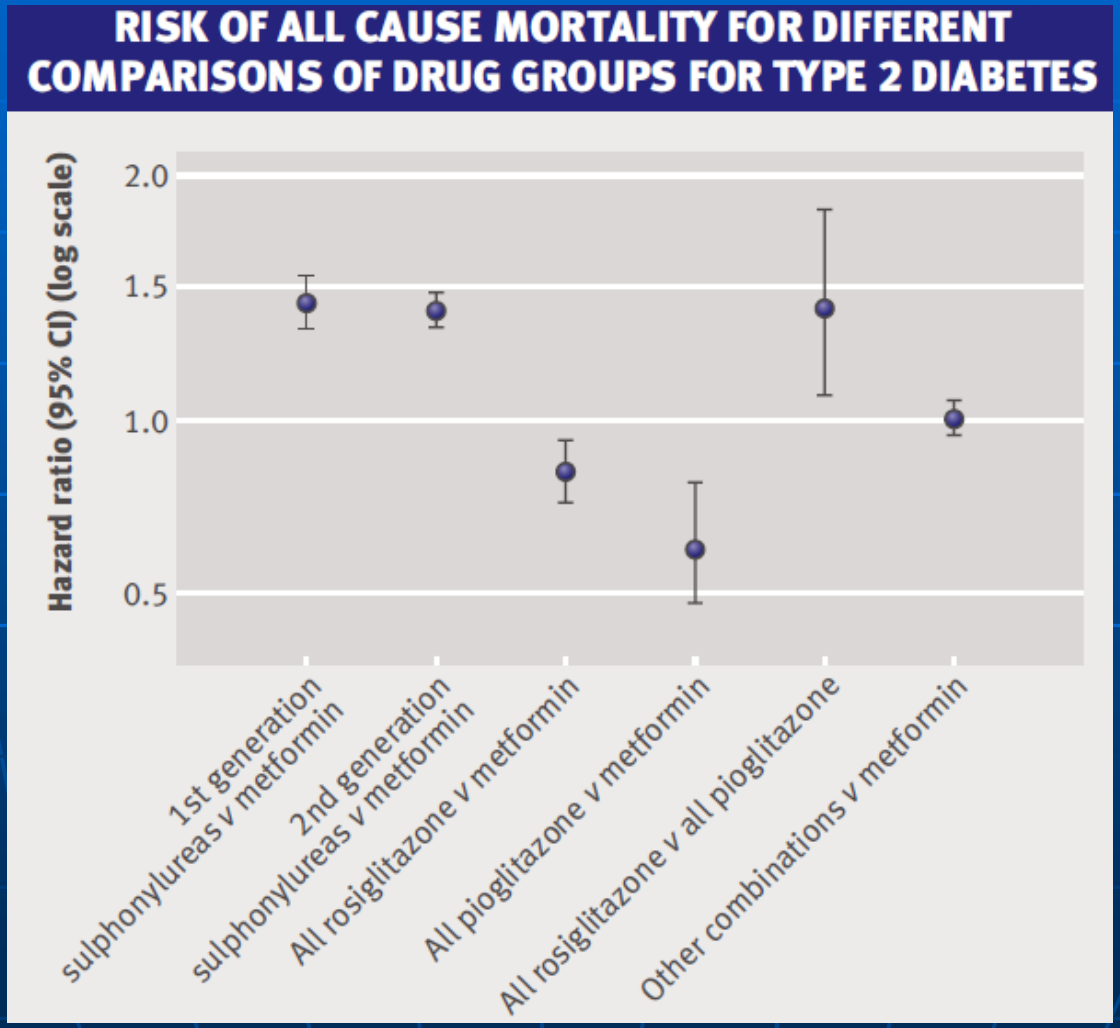
SGLT2 Inhibitors

- Developed from the bark of the apple tree
- Hba1c reduction ~ 6mmol/mol (0.75%)
- Associated with weight loss

SGLT2 Inhibitors

- Safety
  - No increased incidence of hypos
  - No increased incidence of UTI's
  - Increase in urinary volumes by 4-600mls/day
  - Slight increase in thrush

Mortality Differences



Tzoulaki I et al BMJ 2010;340(7736):35

Things That Make the Most Difference

Smoking	OR 2.87
Raised ApoB/ApoA1 ratio	OR 3.25
History of hypertension	OR 1.91
Diabetes	OR 2.37
Abdominal obesity	OR 1.12
Psychosocial factors	OR 2.67
Daily fruit and veg intake	OR 0.7
Regular alcohol consumption	OR 0.9
Regular physical activity	OR 0.86

Yusuf et al Lancet 2004 364:937-952

Any questions?