The failing beta-cell: the problem and the prospects

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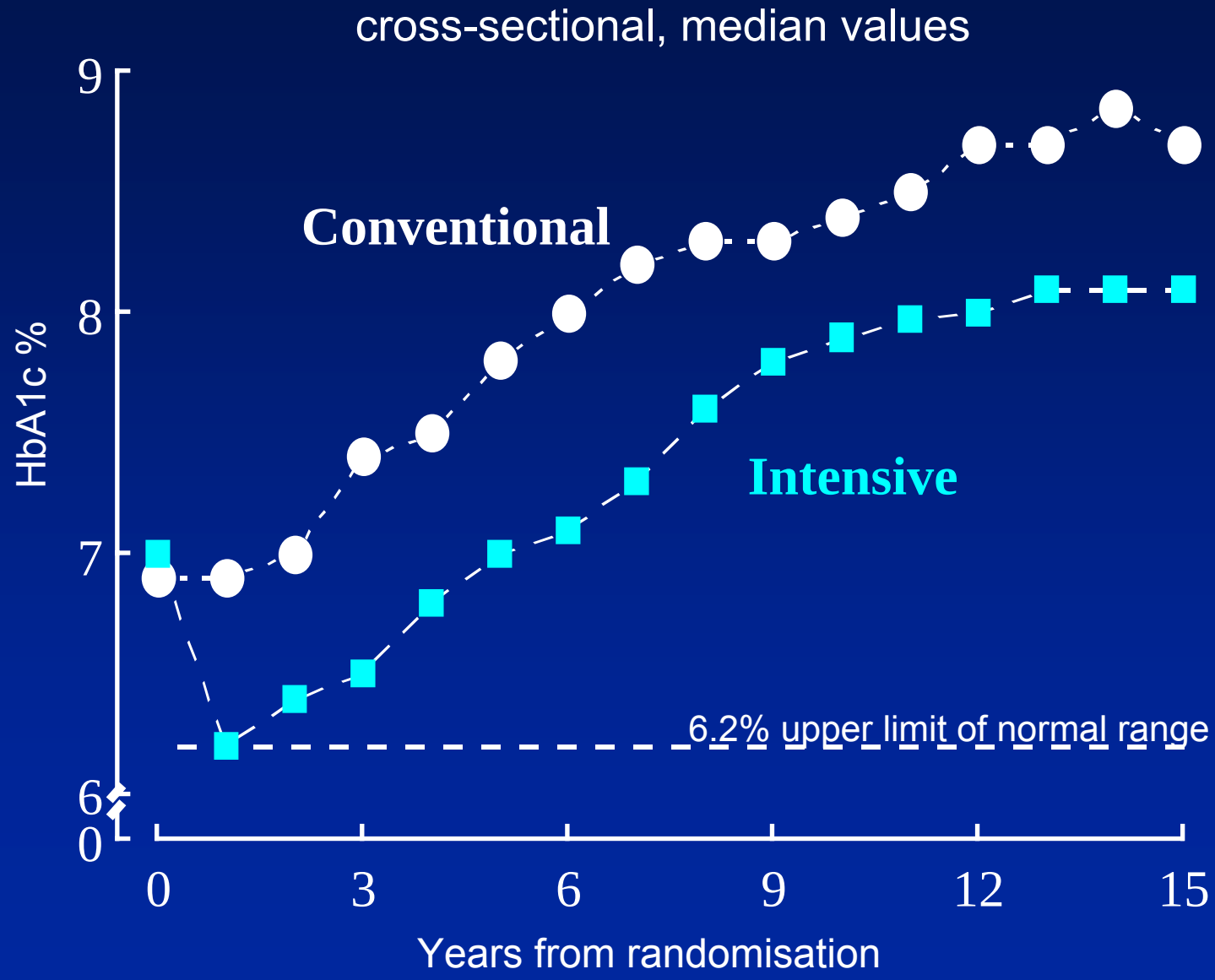
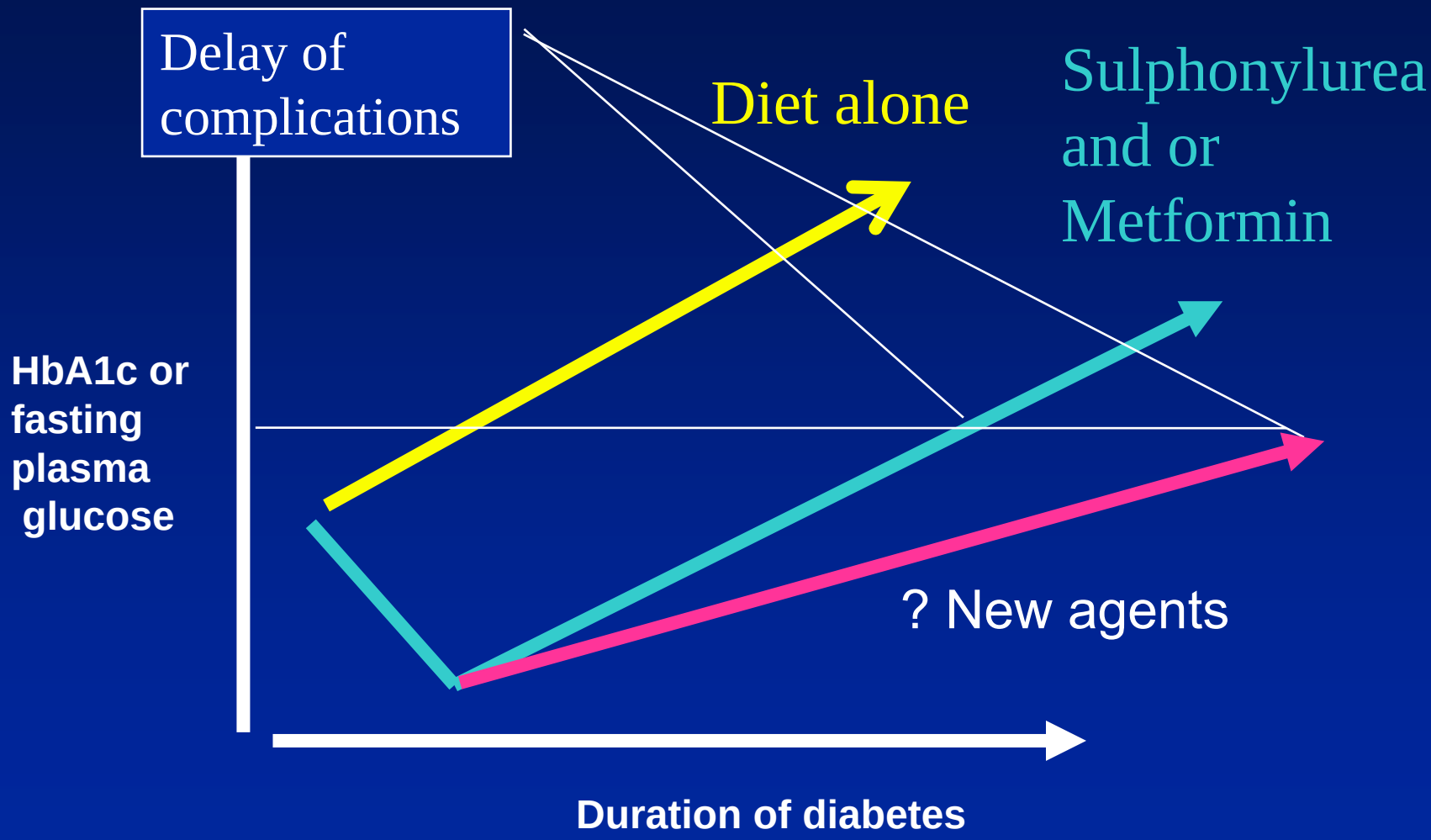
The Oxford Centre
for Diabetes, Endocrinology and Metabolism

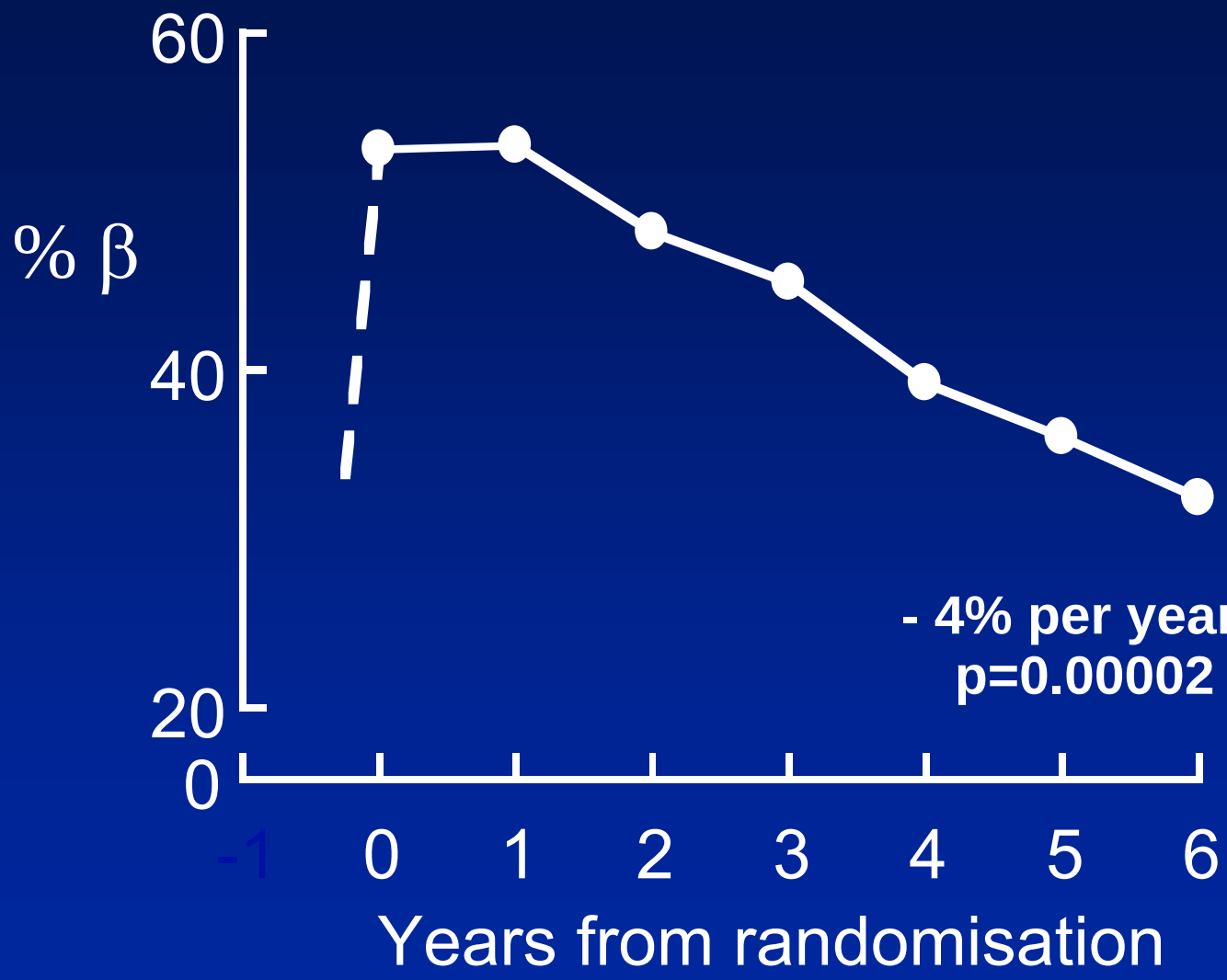
UKPDS: HbA_{1c}


cross-sectional, median values
9
8
7
6
0
HbA1c %
Conventional
Intensive
6.2% upper limit of normal range
0
3
6
9
12
15
Years from randomisation

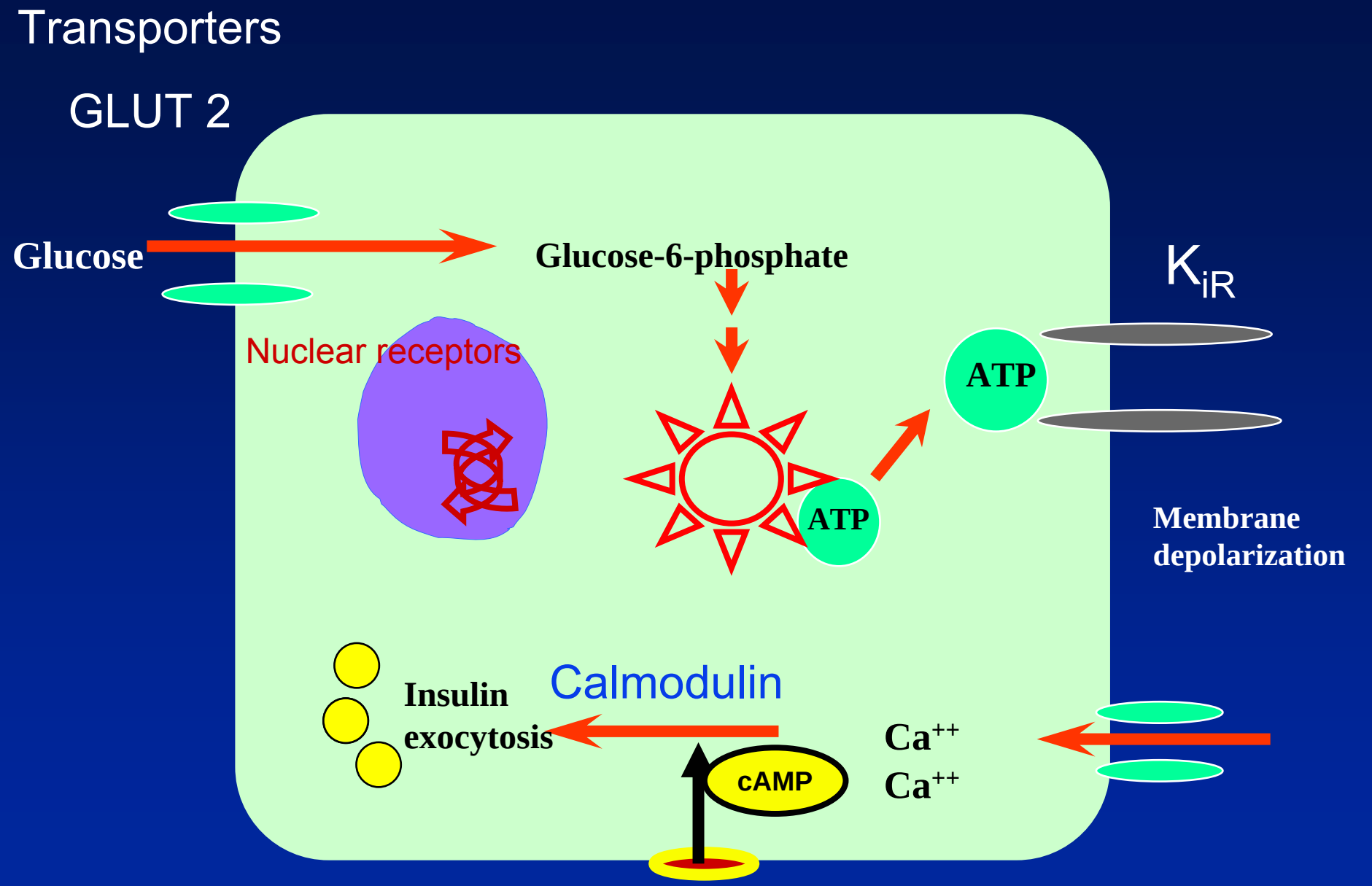
Management of Type 2 diabetes.



β-cell function (UKPDS)



Patients allocated to and remaining on diet alone


Transporters
GLUT 2
Glucose
Glucose-6-phosphate
K_{iR}
Nuclear receptors
ATP
ATP
Membrane depolarization
Insulin exocytosis
Calmodulin
Ca^{++}
Ca^{++}
cAMP
G-protein receptors

Glucose transporters

- Thiazolidinediones Increase glut4 in fat and muscle.
- ? Changes in glut 2 in the pancreas
- Glut4 transporter defects not apparent in man and not thought to be a major cause of T2DM

Prospects for therapy

Thiazolidinediones

MODY

- MODY 2
  - Monogenic defect
  - Heterozygous condition = whence 50% glucokinase function
  - Rare cause of T2DM (and not the commonest MODY)
  - <2% of T2DM explicable

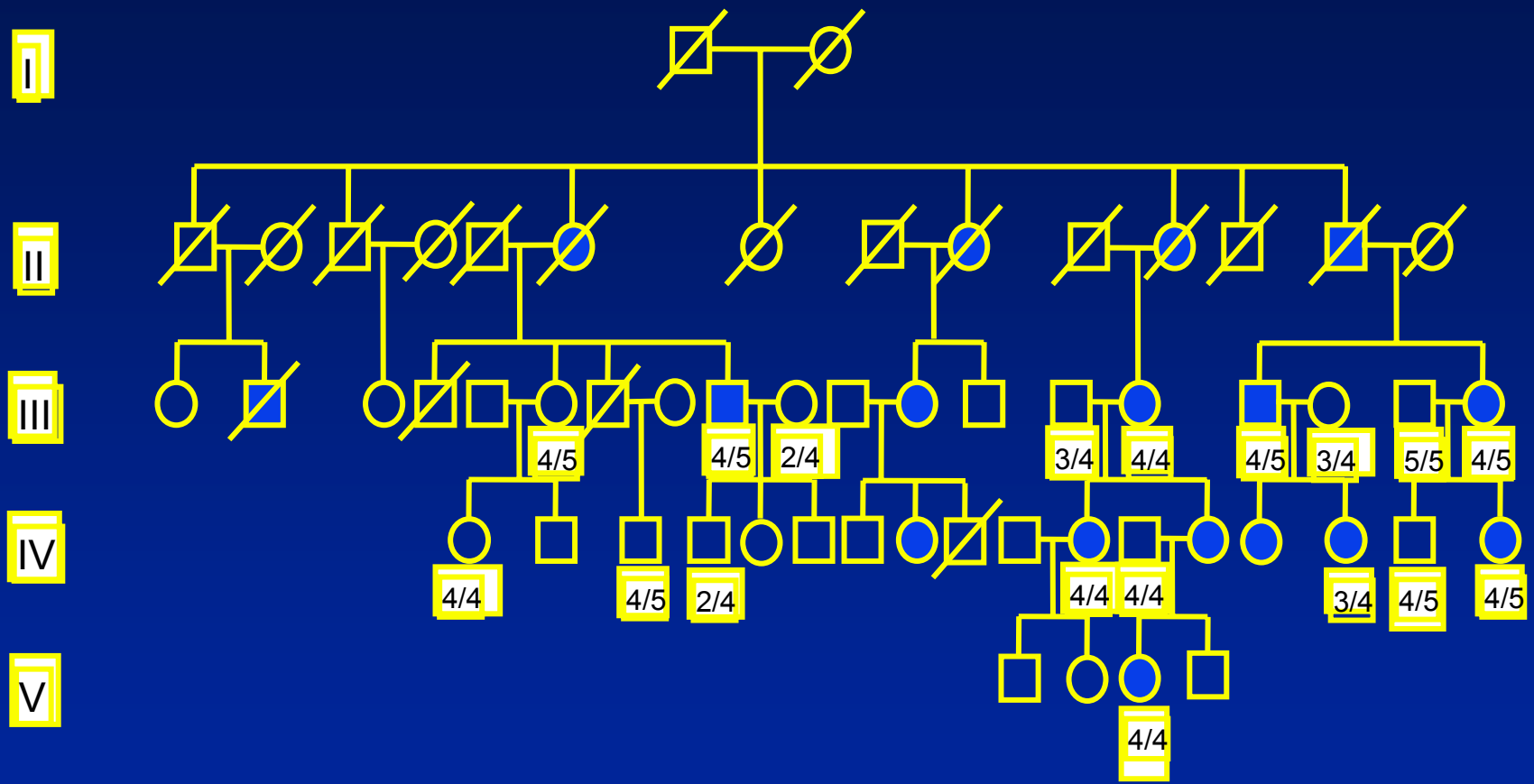
- MODY 3
  - HNF1α
  - Autosomal dominant

Prospects for therapy

Thiazolidinediones reported to increase glucokinase, but usually sulphonylureas have been used (downstream of the defect)

Low-dose sulphonylureas especially efficacious in HNF1α defects

MODY 2 (Heterozygous for glucokinase)



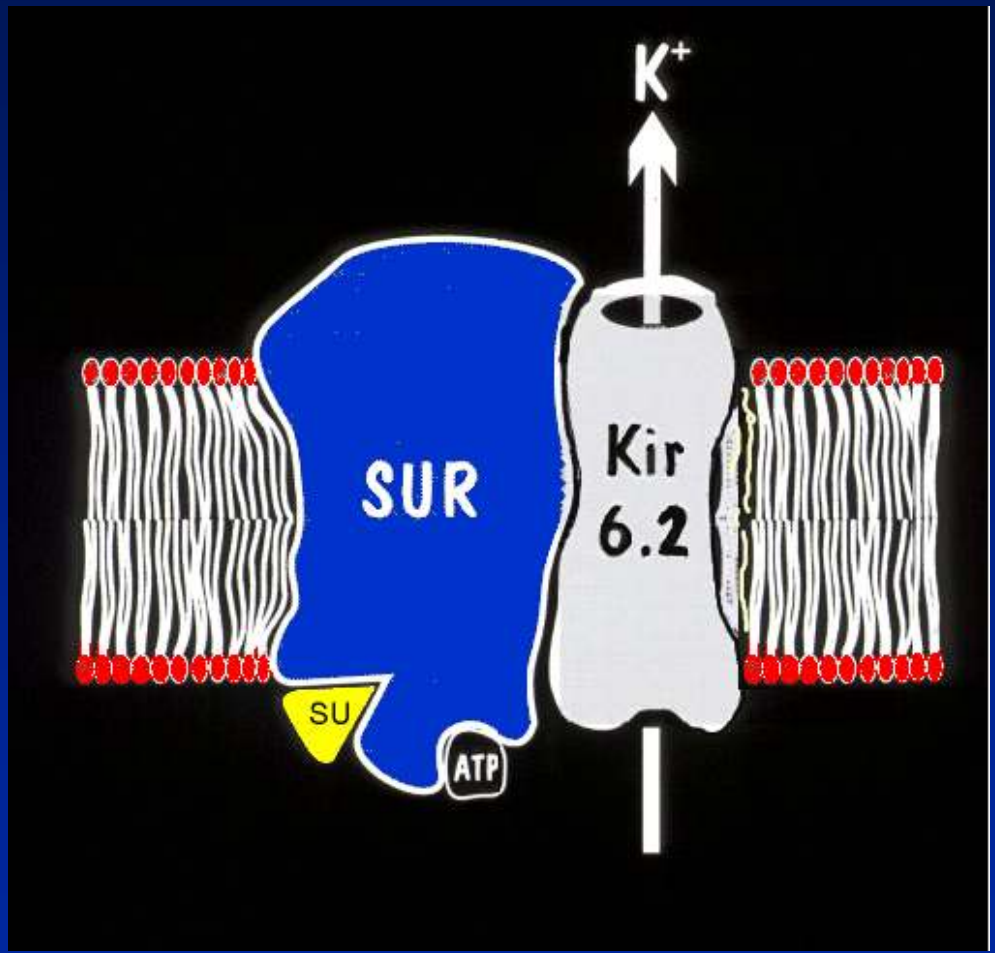
SUR receptors

- No evidence that sulphonylureas wear out the pancreatic beta cell, but different sulphonylureas have different effects
- Kir 6.2 defects have been found in some patients with hypoglycaemia
- Systematic searches for SUR gene defects have been disappointing, but there is heterogeneity of the SUR receptor binding
- Glinides (repaglinide and nateglinide) bind to the SUR receptor at different domains

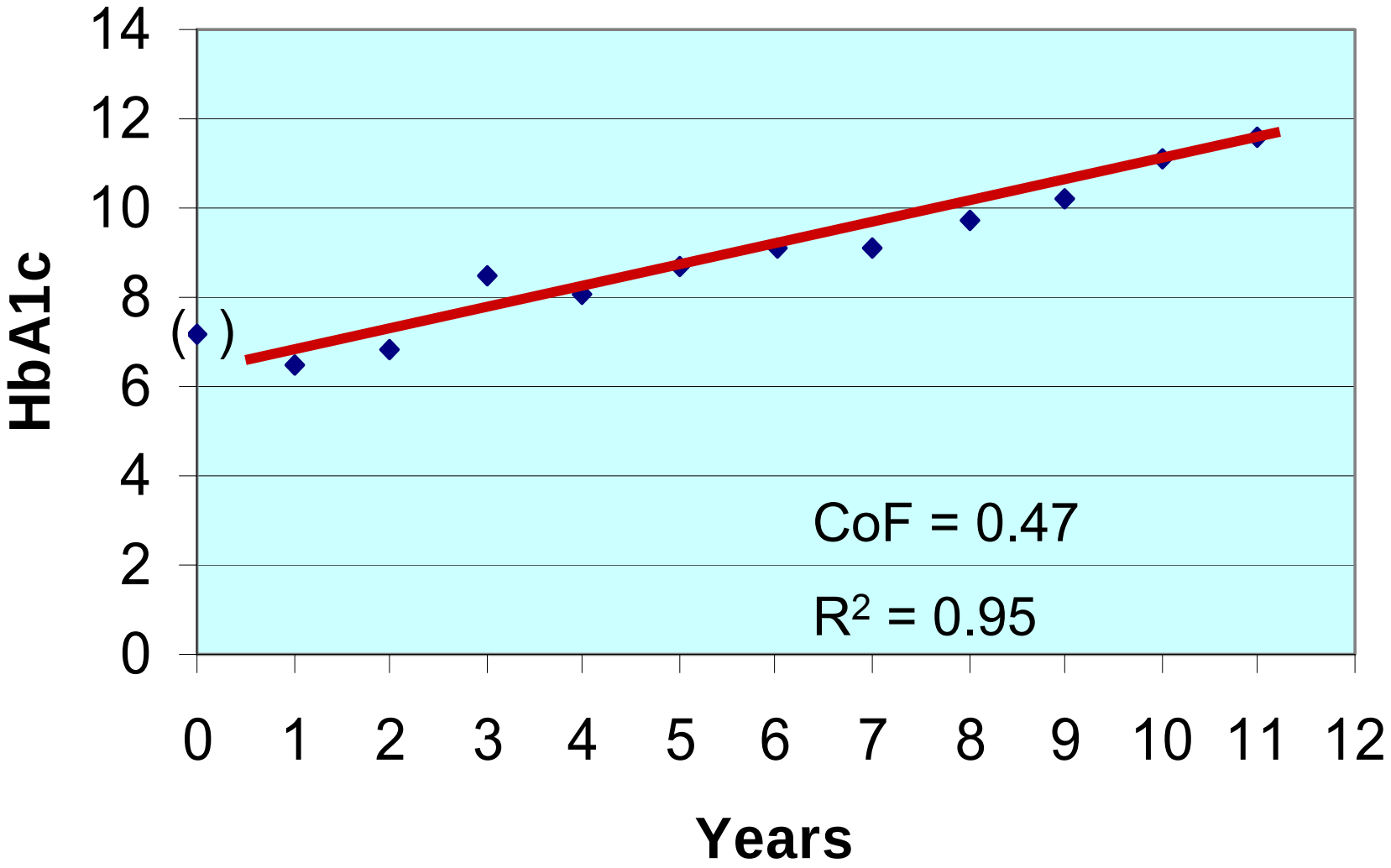
Prospects for therapy

Sulphonylureas and glinides are therapeutically effective

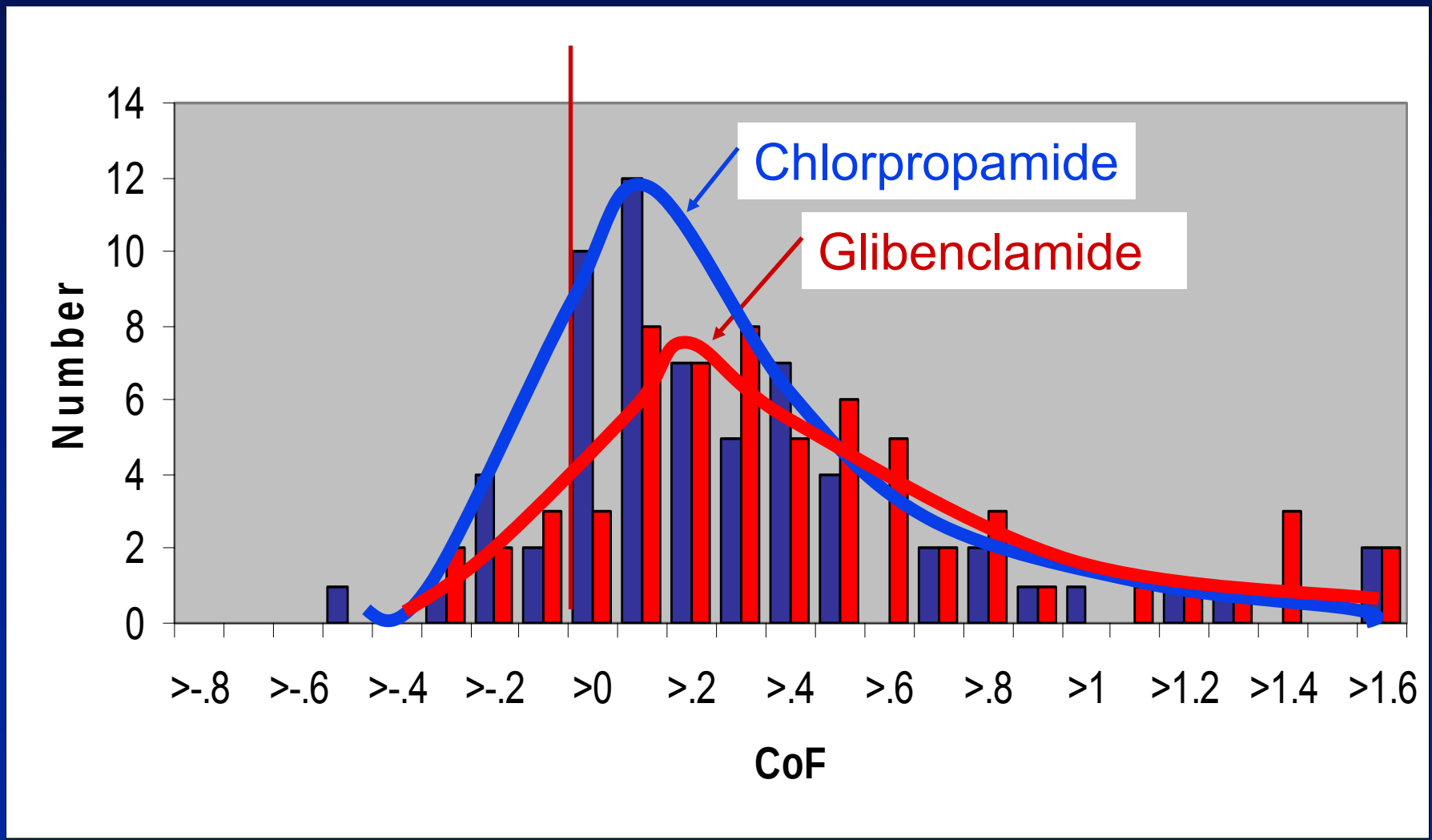
No evidence that they preserve beta cell function


K+
SUR
Kir
6.2
SU
ATP

Coefficient of failure (Glibenclamide)



Distribution of Coefficient of Failure



Membrane depolarisation

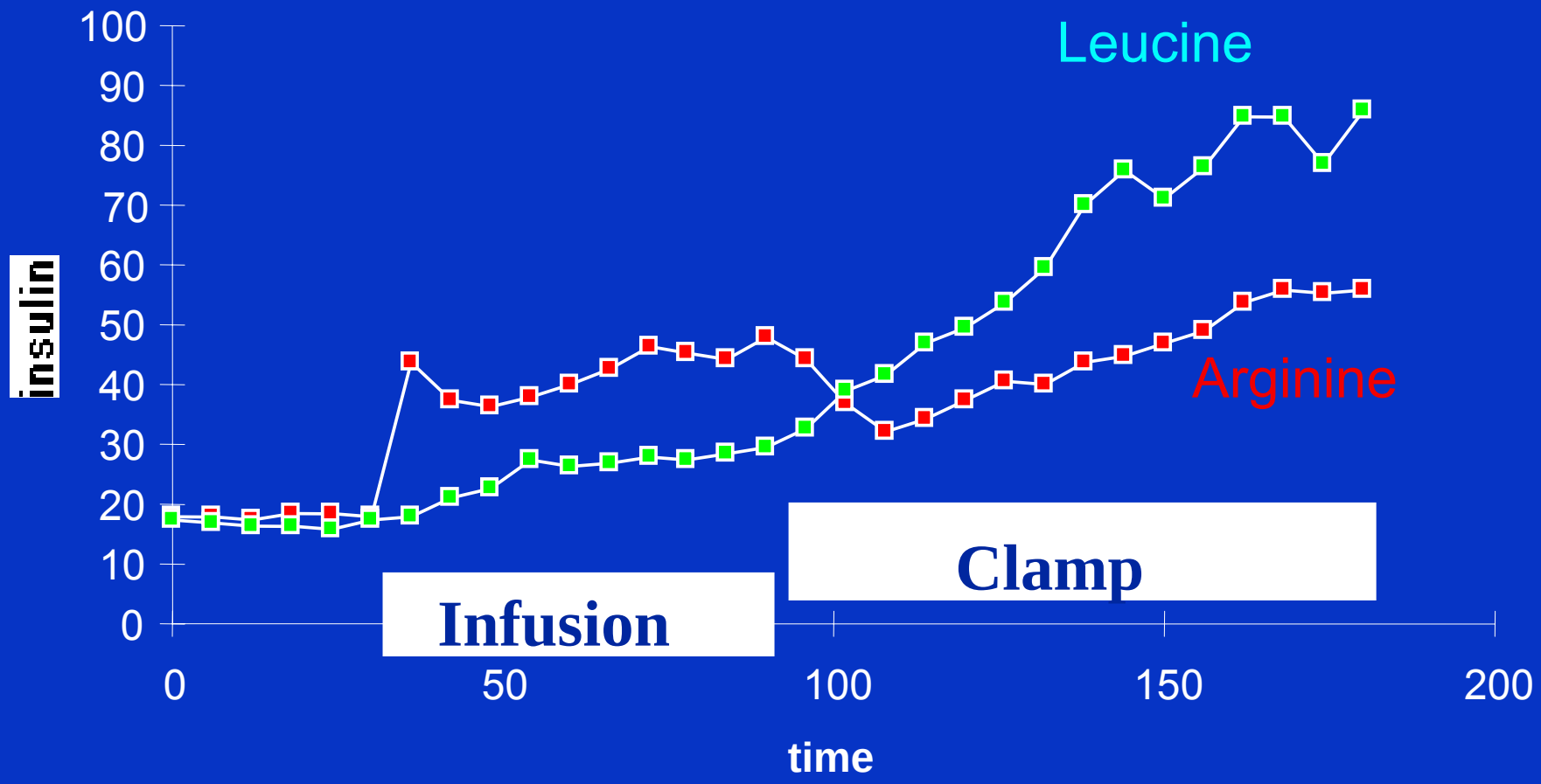
- Arginine's direct effect on the membrane is probably via the Ca++ channels or direct depolarisation
- Paralysing the depolarisation (isolated beta-cells given voltage shock) abolishes most of the Sulphonylurea effects
- Pulsatile insulin secretion may be co-ordinated electrically / neurally

Prospects for therapy

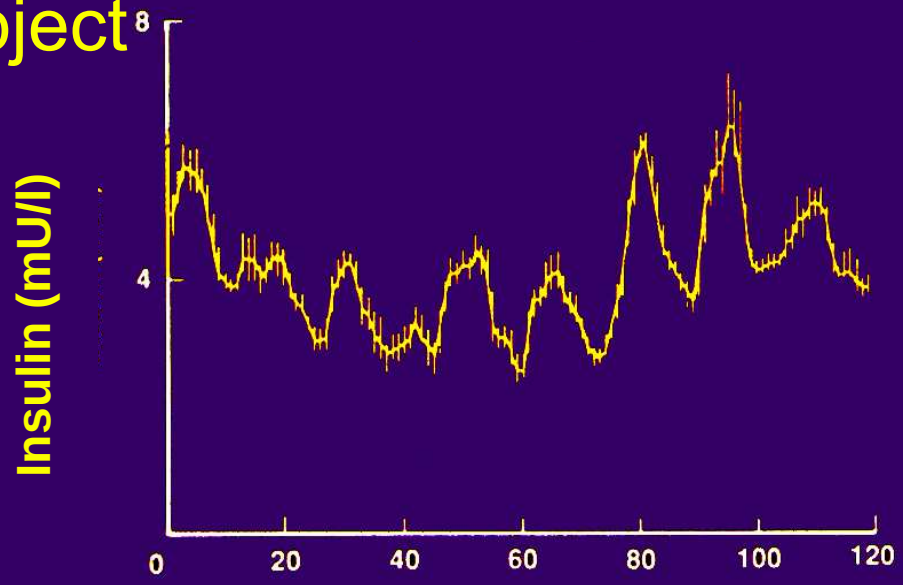
Amino-acid derivatives; pacemaker?

Dynamic insulin secretion is more efficacious than steady state

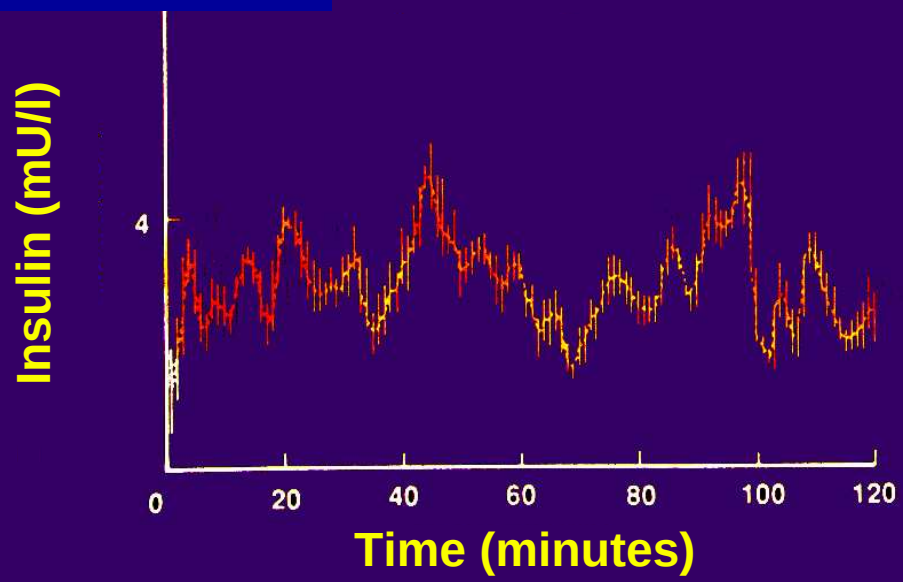
Arginine and leucine infusions



Control subject



First degree relative



Lipotoxicity

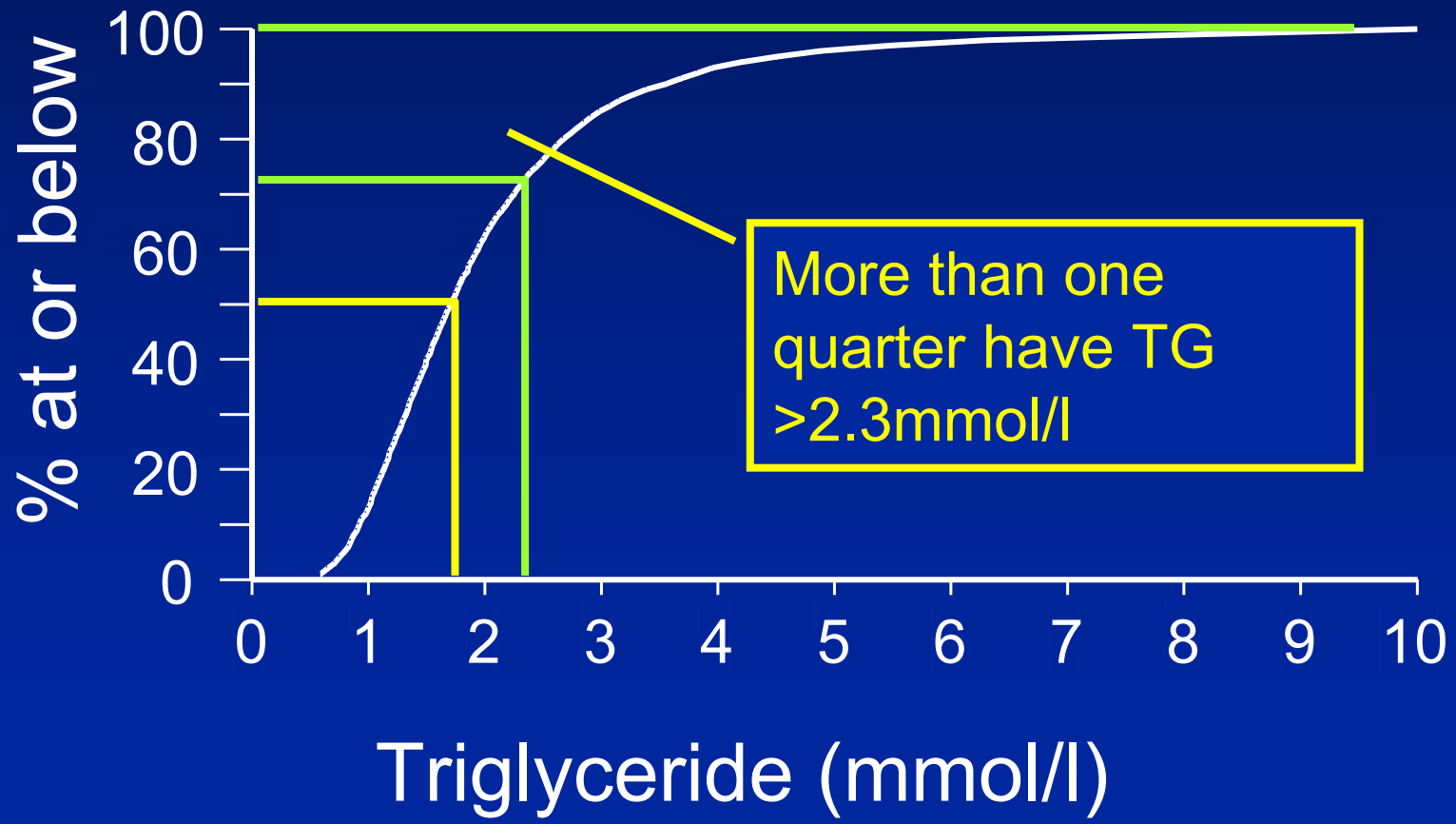
- Lipid accumulation may impair beta-cell function
- Likely to be via FFA and Triglycerides
- Explains beta-cell deterioration in the metabolic syndrome, but does not explain why some dyslipidaemias may last for years without T2DM
- PPARγ and α activation in the Liver and muscle increase glucose utilisation and decrease fatty acid oxidation

Prospects for therapy

Thiazolidinediones

Fibrates

Triglyceride at entry to UKPDS



G-protein receptors

- Exendin 4 and GLP1 stimulate the beta-cell
- “Liraglutide” in phase 3 development with Novo Nordisk
- Mechanism is downstream of the SUR receptor
- May act as an amplifier of action
- Agents tested in primates suggest that they do not cause clinical hypoglycaemia (i.e. “smart” agents)
- Only available in injectable form so far

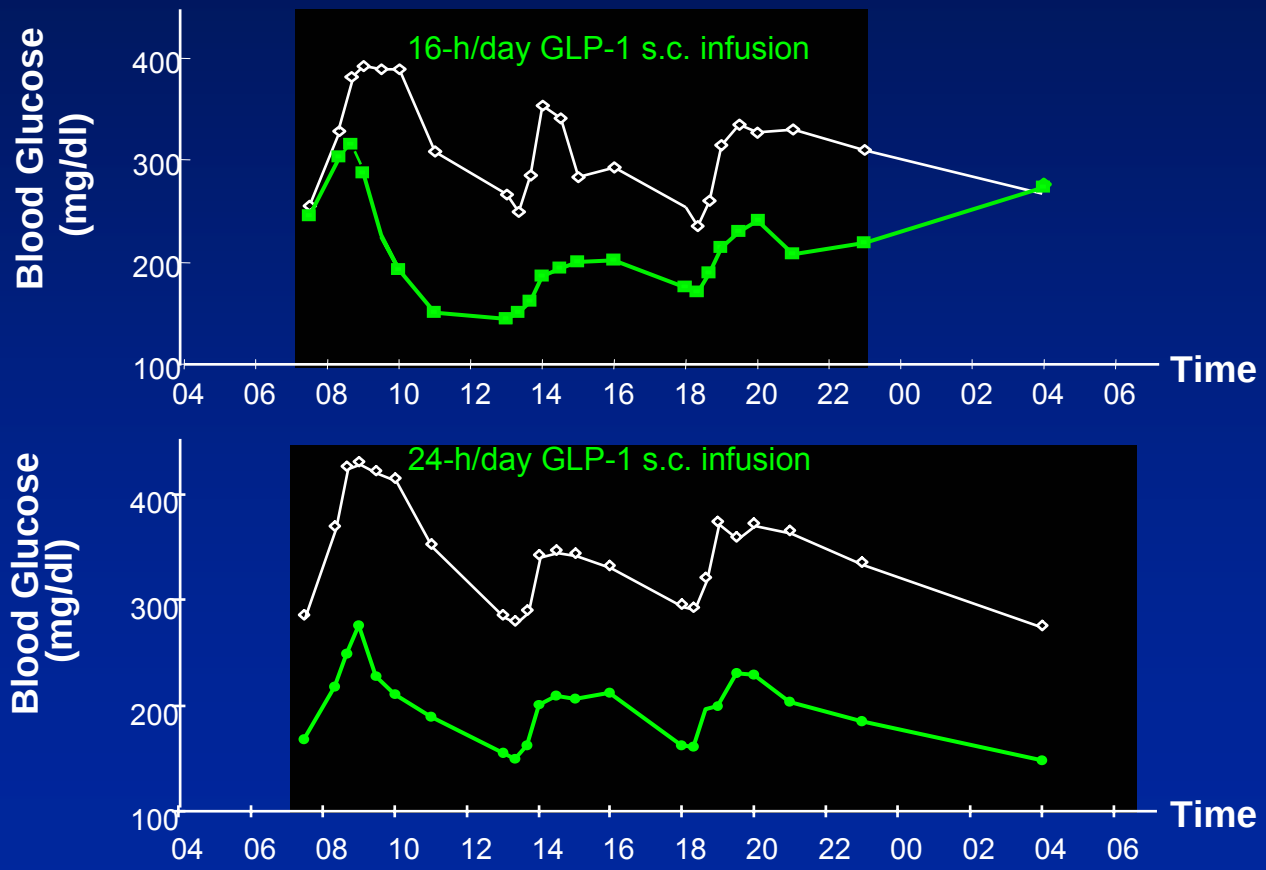
Prospects for therapy

GLP-1 derivatives may augment other therapies

Effect on beta-cell preservation looks promising

GLP-1 analogues

GLP-1 is short-acting



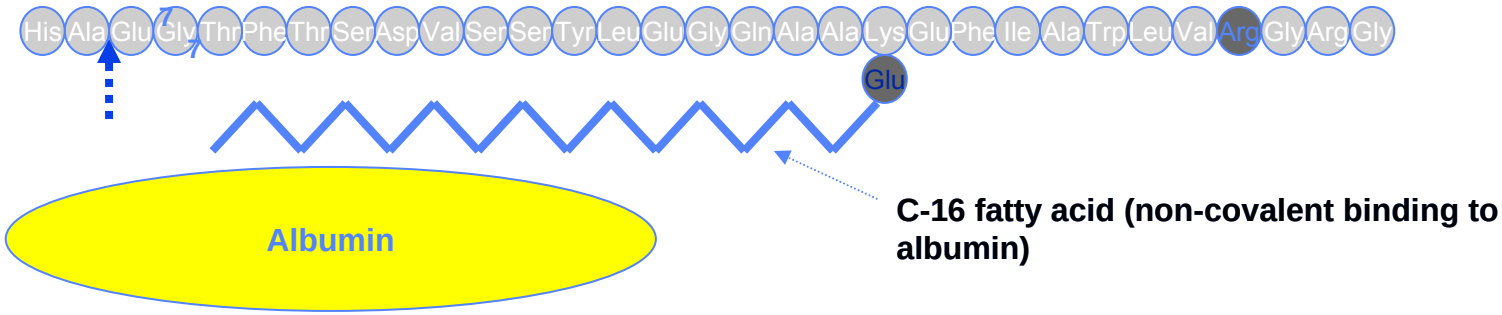
Blood glucose profiles

- Control
- After 7 days

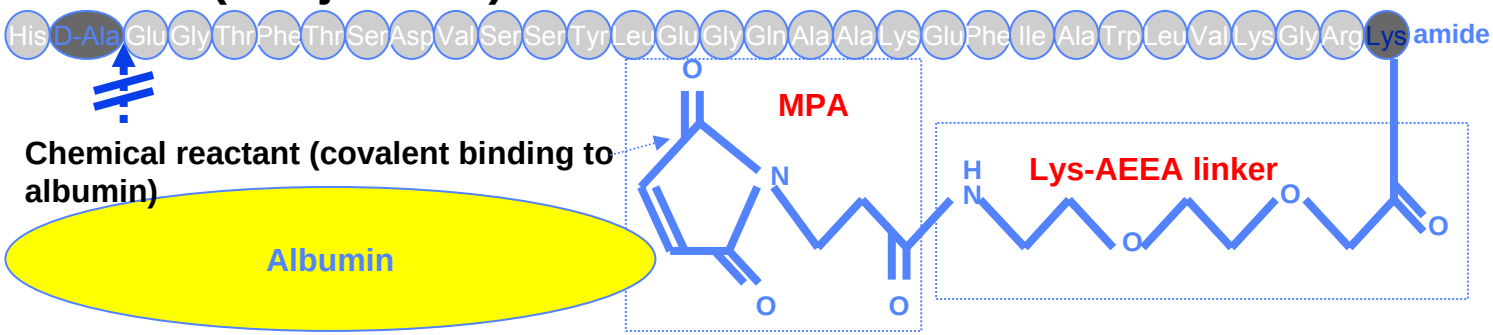
Modified from J Larsen et al: Diabetes Care 2001; 24:1416-1421

GLP-1 Glycine-extended form (7-37)

NN2211 (NovoNordisk)



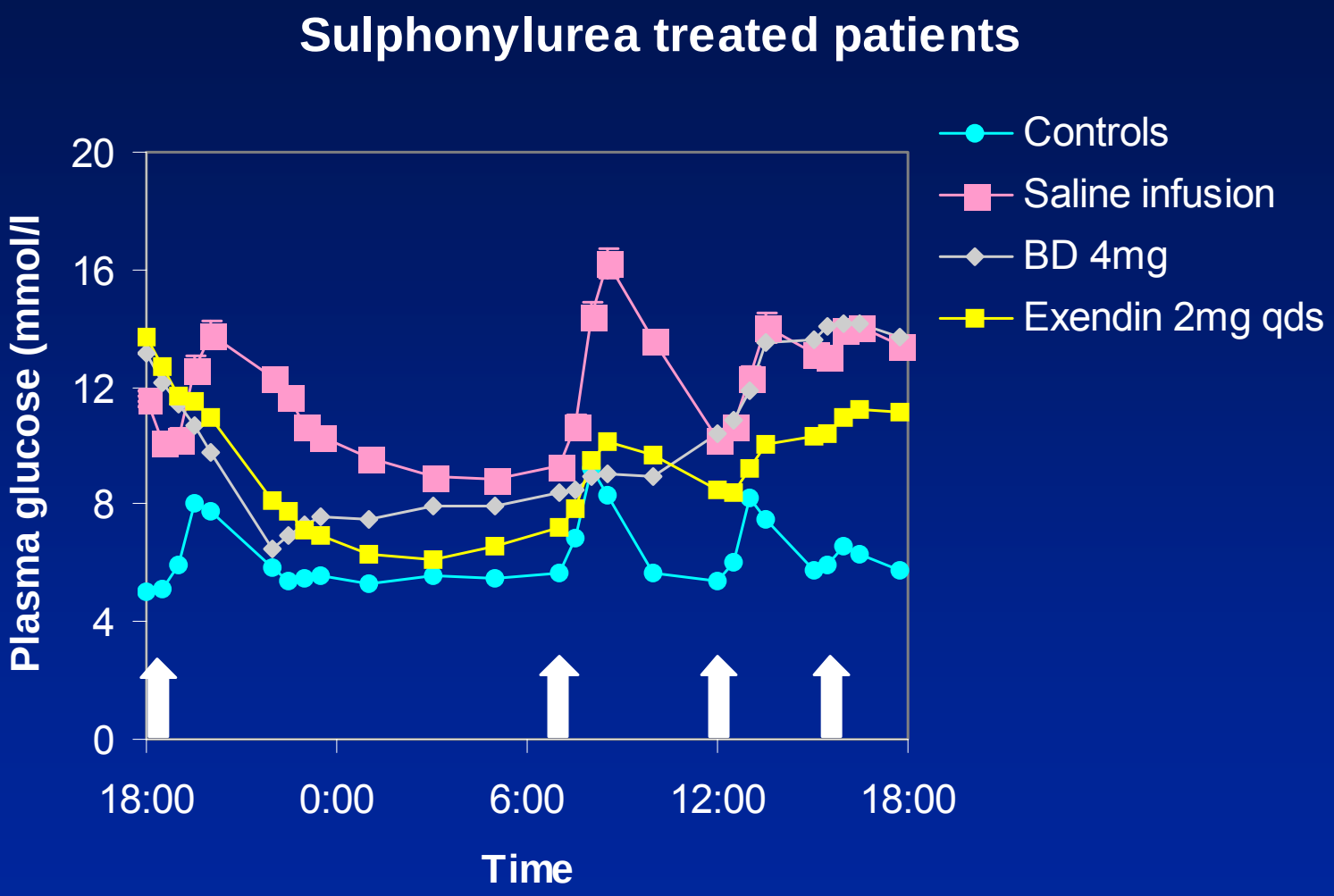
CJC-1131 (Conjuchem)



AC2993 (Exendin-4, Amylin Pharmaceuticals)

Exendin-4

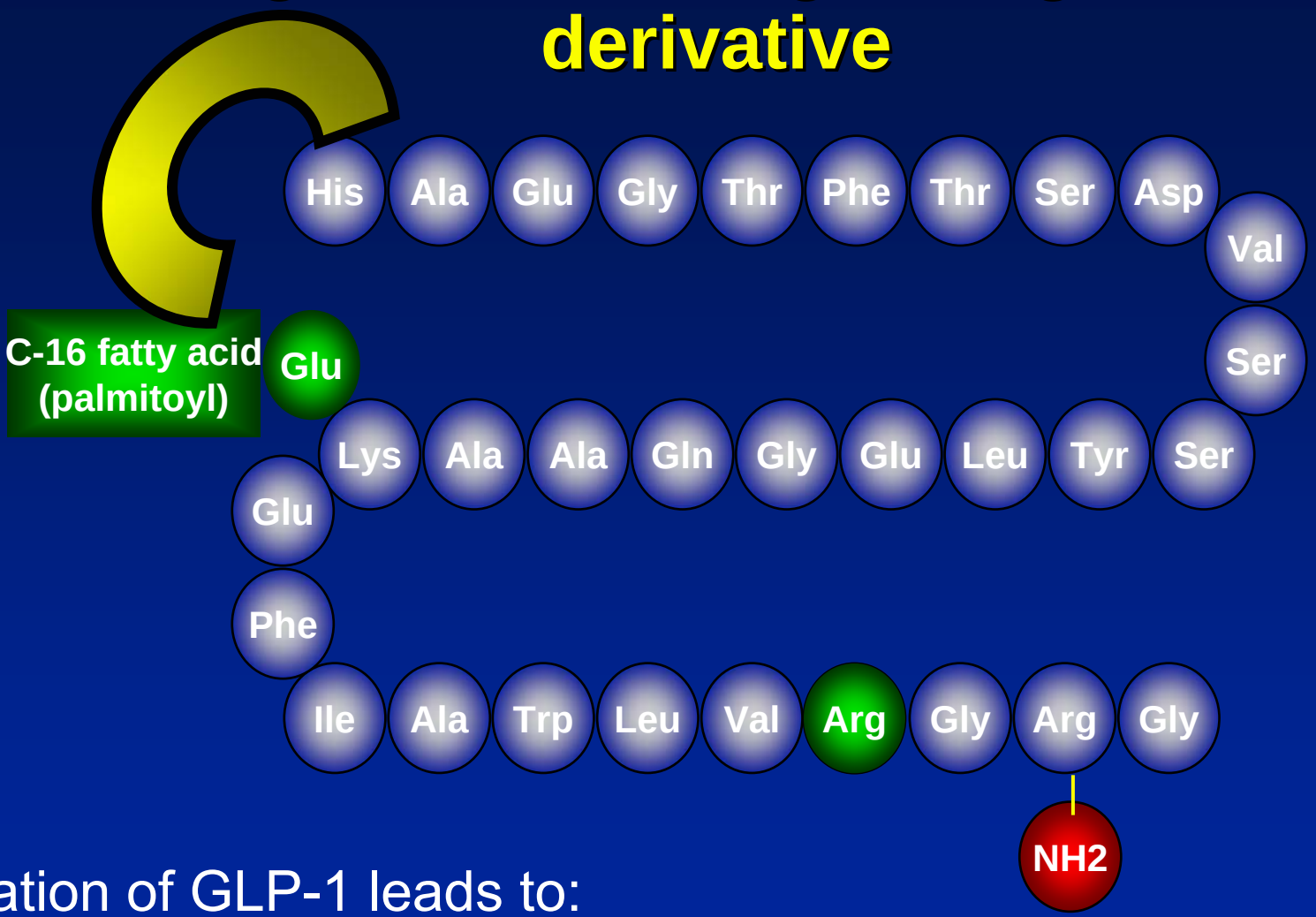
Exendin-4



Maksoud et al. Diabetes 2000

Liraglutide

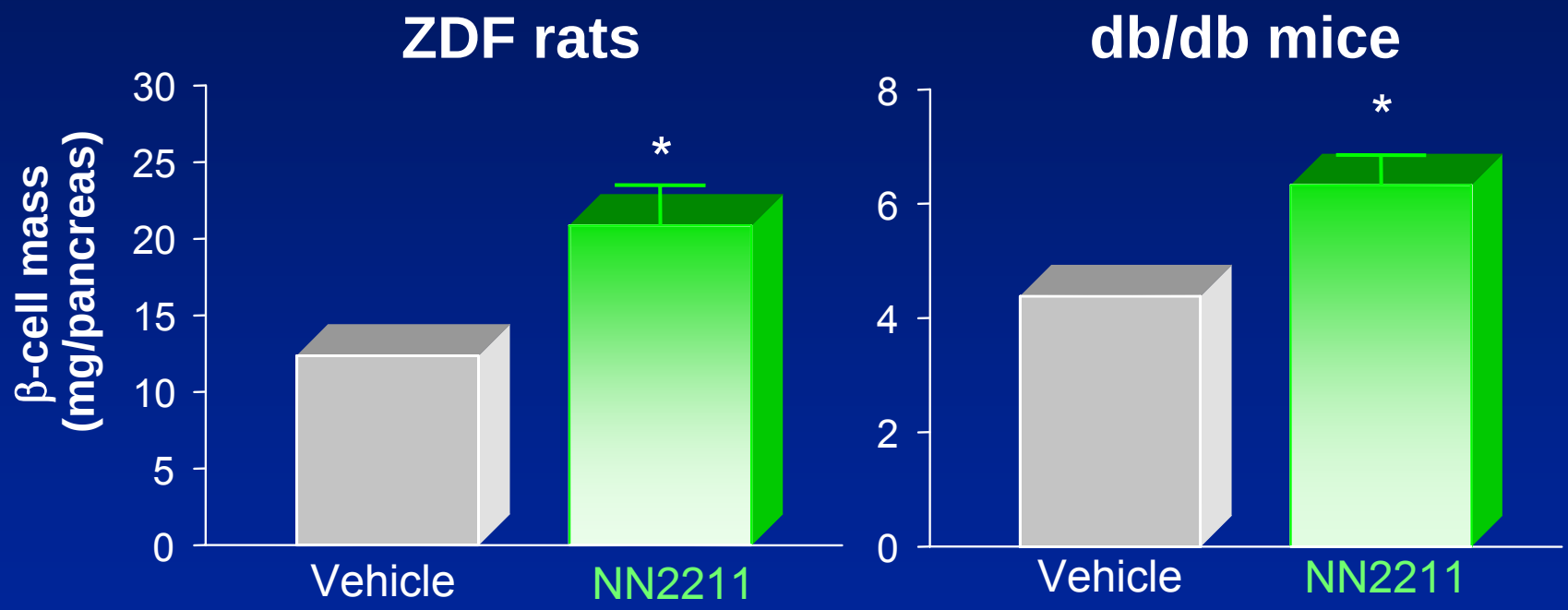
Liraglutide is a long-acting GLP-1 derivative



Acylation of GLP-1 leads to:

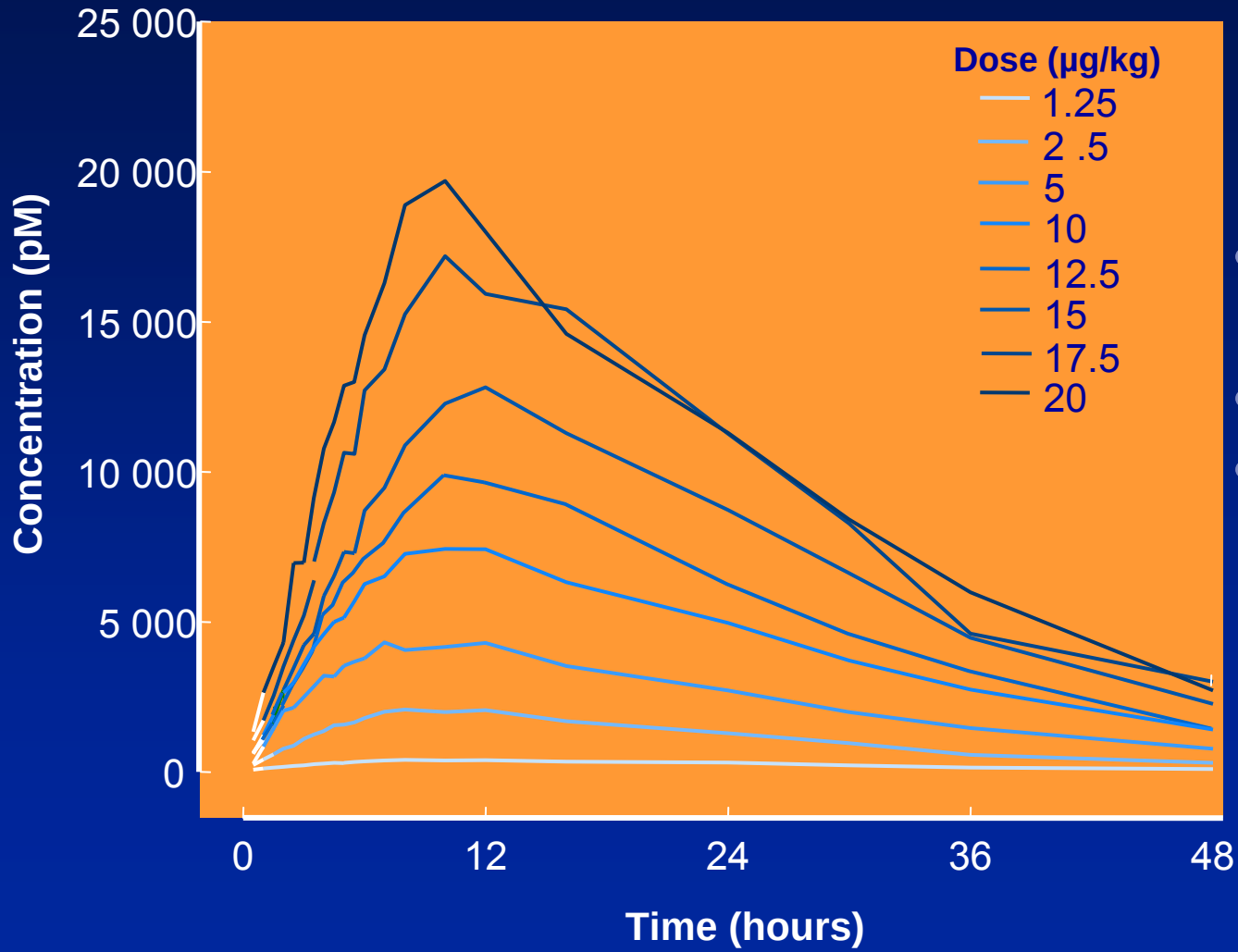
- Slow absorption
- Albumin binding
- Reduced renal clearance

Increases in β-cell mass



J Sturis et al: Diabetes 2000; 49 (Suppl 1): A228 [943-P]; C Gotfredsen et al: Diabetes 2001; 50 (Suppl 2): A31

Once-daily injection PK profile in man

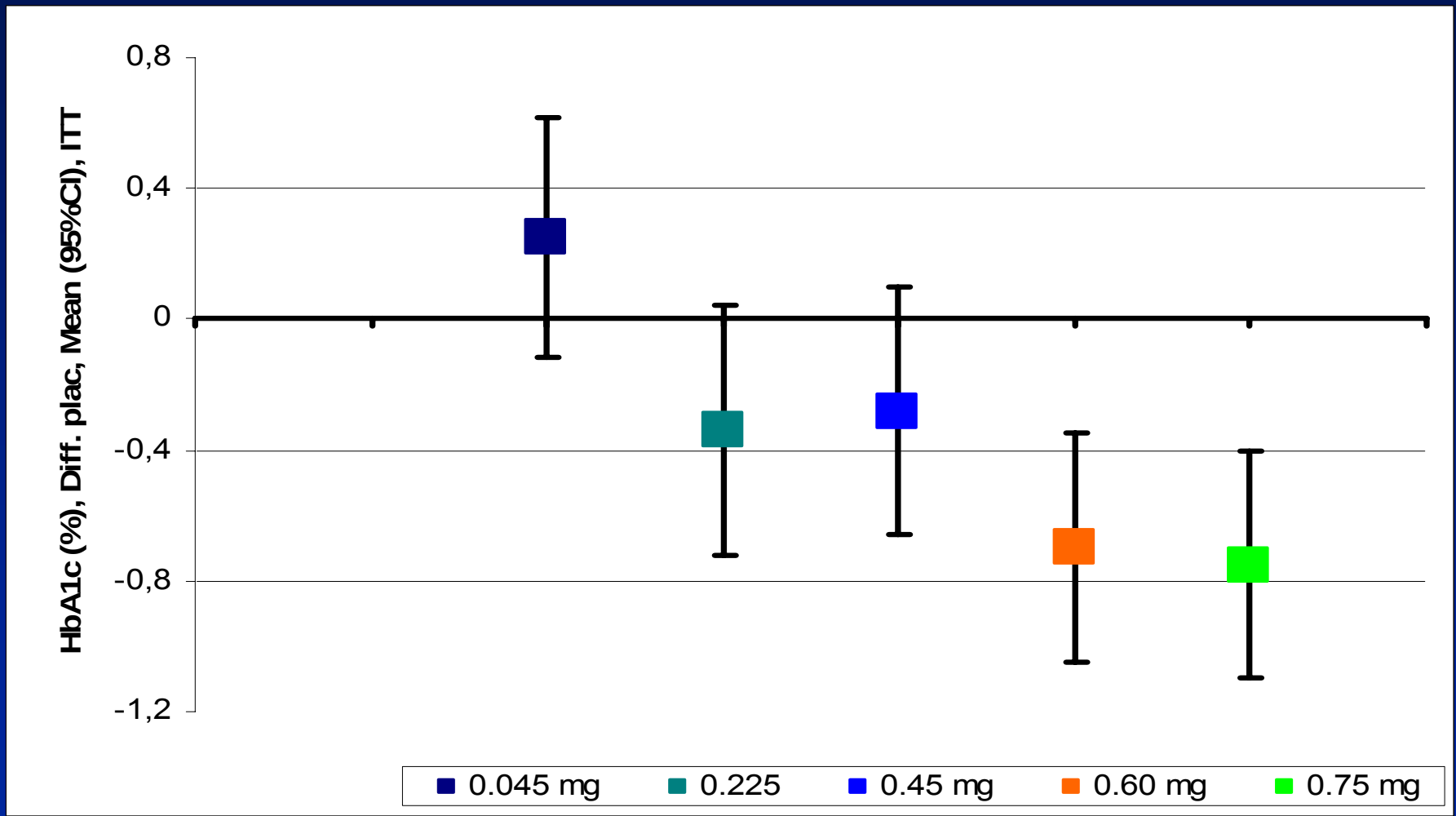


- Slow absorption: T_{max} 9-12 hrs
- Plasma $t_{½}$ 12h
- Bioavailability 55%

Adapted from Elbrønd et al. (2002): Diabetes Care, *in press*

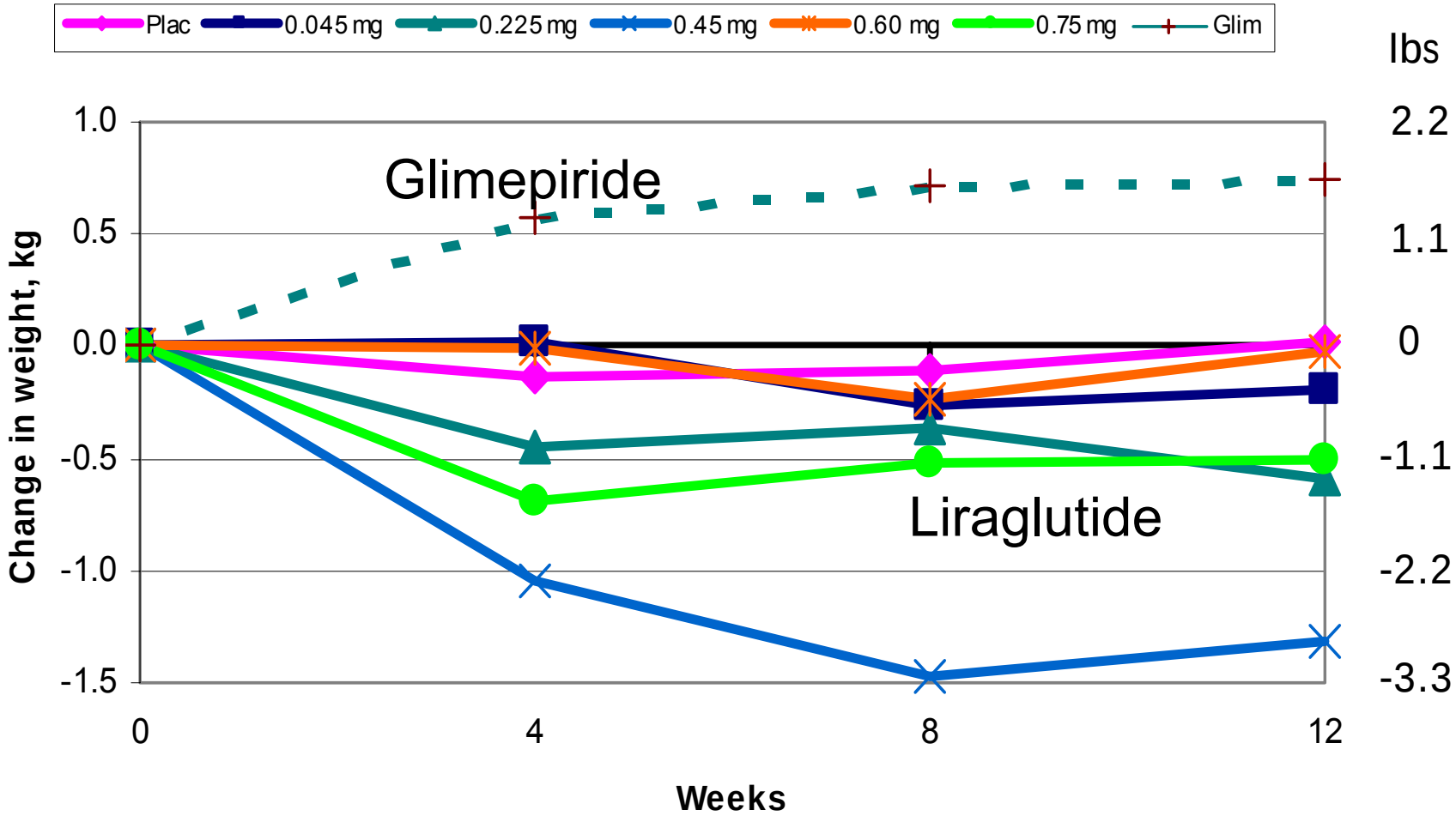
Placebo comparison for HbA1c

12 week randomised, placebo-controlled multicentre trial



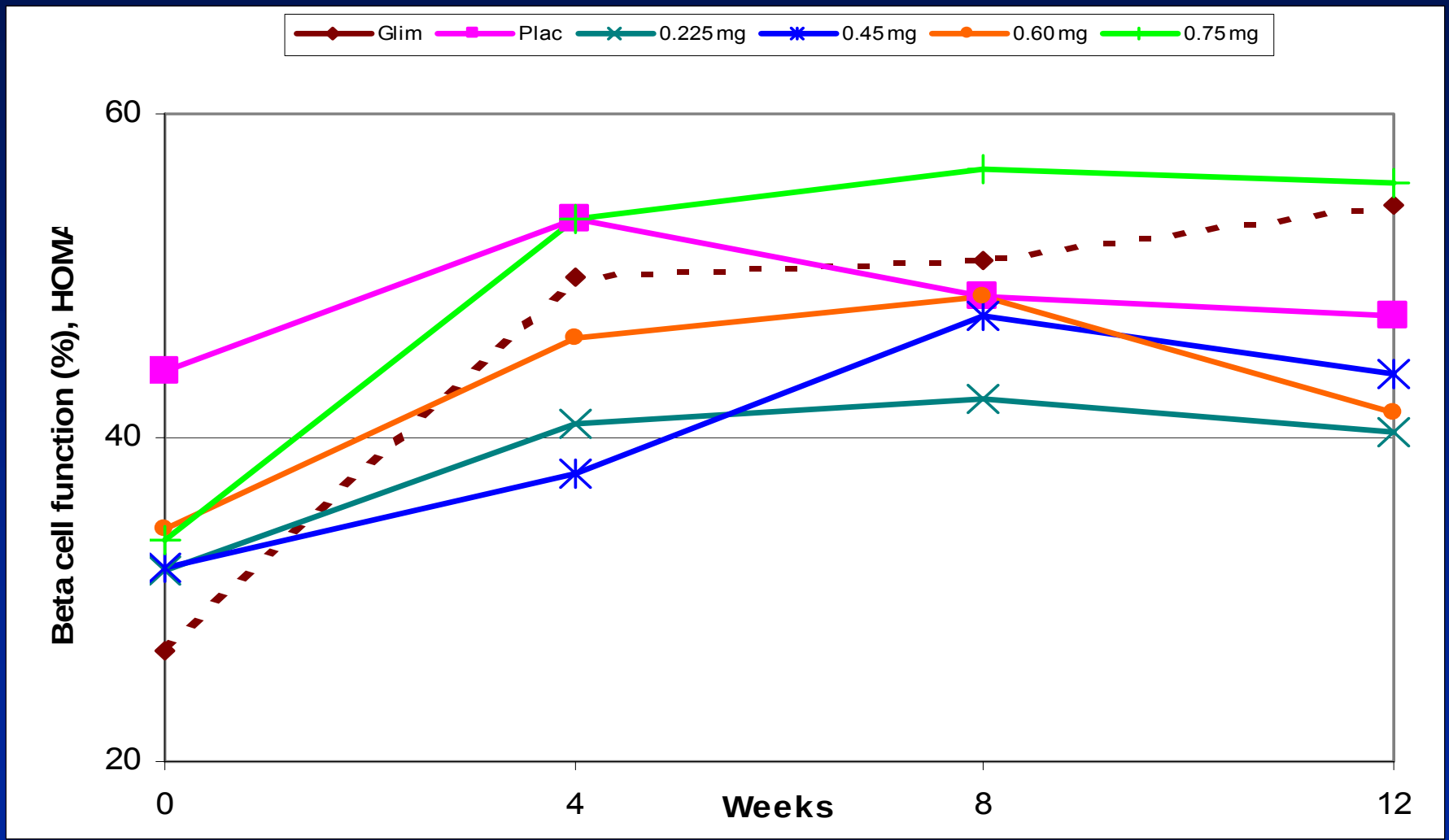
Novo Nordisk: Liraglutide

Weight, change from baseline



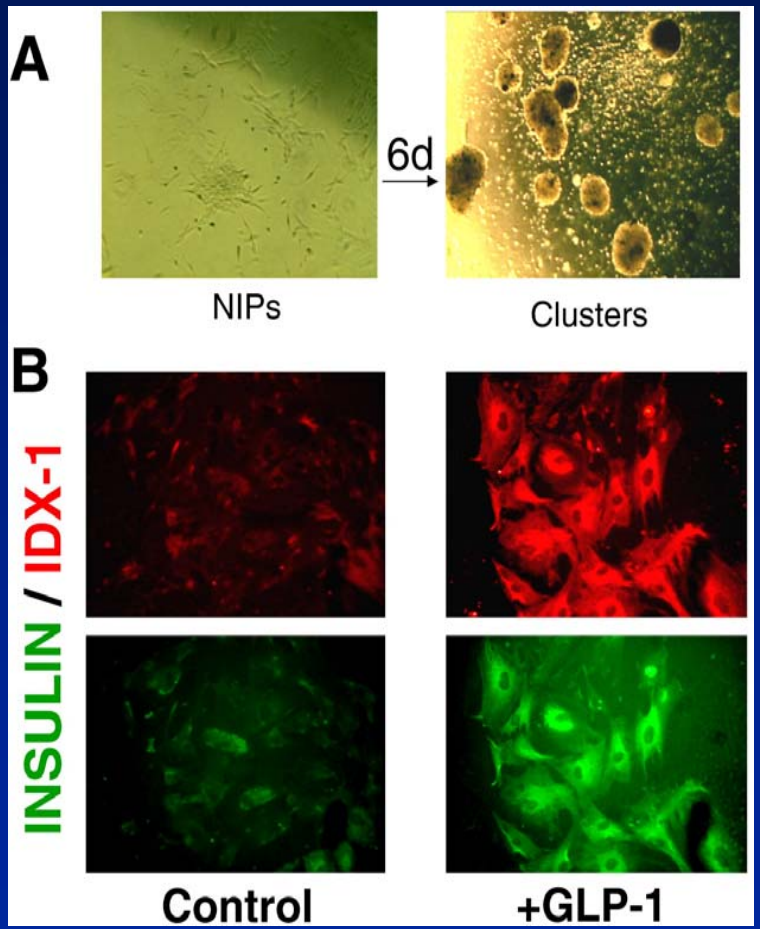
Novo Nordisk: Liraglutide

Beta-cell function, HOMA, week 12, mean, ITT



Novo Nordisk: Liraglutide

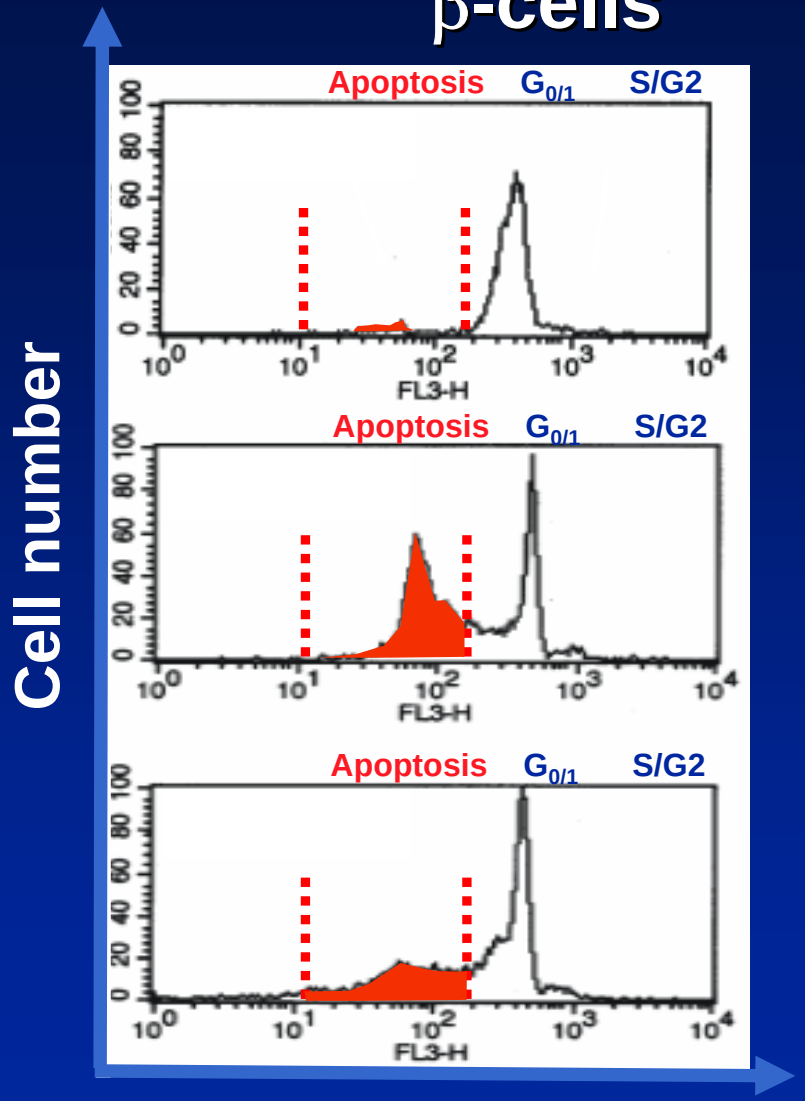
From stem cells to b-cells:
GLP-1 stimulates differentiation of NIPs



- **nestin-positive islet-derived progenitor cells (NIPs)**, isolated from adult pancreatic islets, can differentiate in culture into cells with pancreatic exocrine, endocrine, and hepatic phenotypes

Abraham EJ, Leech CA, Lin JC, Zulewski H, Habener JF. Endocrinology. 2002 Aug;143(8):3152-61

Liraglutide inhibits FFA-induced apoptosis in β-cells



Control
2.7 % apoptotic β-cells

Fatty acids
55.3 % apoptotic β-cells

Fatty acids+ NN2211
26.9 % apoptotic β-cells

Rømer et al. (2002): Diabetes 51: A343

GLP-1

- GLP-1 axis modulation is a promising new approach to diabetes management
- The disadvantage is injection therapy
- Advantages include:
  - simple regimen
  - negligible or no hypoglycaemia
  - glycaemic control comparable to sulphonylureas
  - no weight gain
  - can be able to be combined with SU
  - possibility of preservation (?augmentation) of beta-cell mass

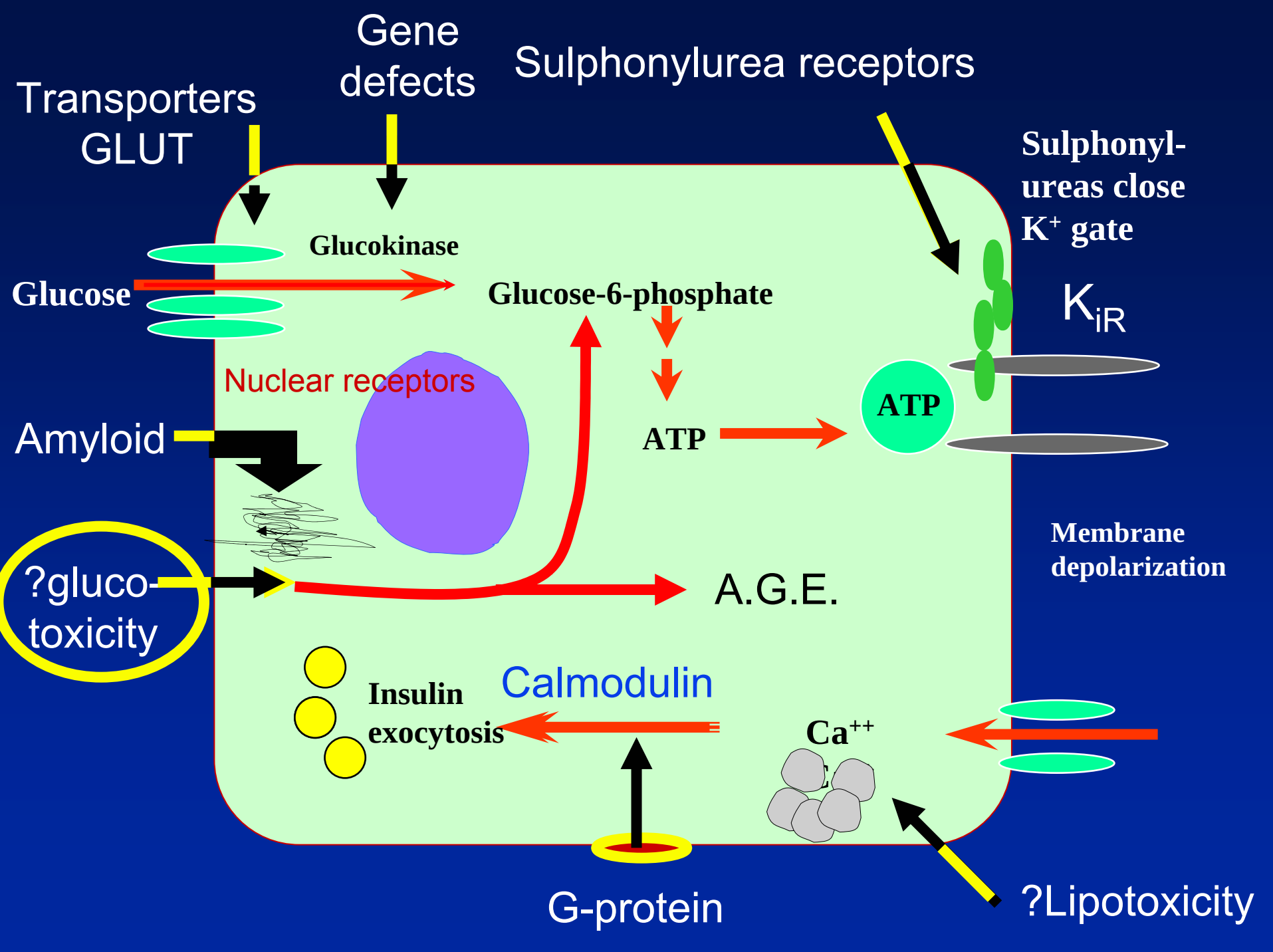
Gluco-toxicity

- Very little evidence of glucotoxicity theory as progenitor of diabetes.
- Glycation certainly implicated in genesis of *complications*
- AGE (glycosylation) may affect secretion eventually
- In man short-term infusions (53hrs) did not cause beta-cell deficit in normal subjects (function actually increased)
- 2 years treatment with gliclazide in fasting hyperglycaemia did not improve beta-cell function despite successfully lowering the glucose

Prospects for treatment

Anti-glycation products disappointing so far

?anything that lowers the glucose


Transporters
GLUT
Gene
defects
Sulphonylurea receptors
Sulphonyl-
ureas close
K+ gate
Glucokinase
Glucose
Glucose-6-phosphate
KiR
Nuclear receptors
ATP
ATP
Amyloid
?gluco-
toxicity
A.G.E.
Membrane
depolarization
Insulin
exocytosis
Calmodulin
Ca++
G-protein
?Lipotoxicity

Amyloidosis

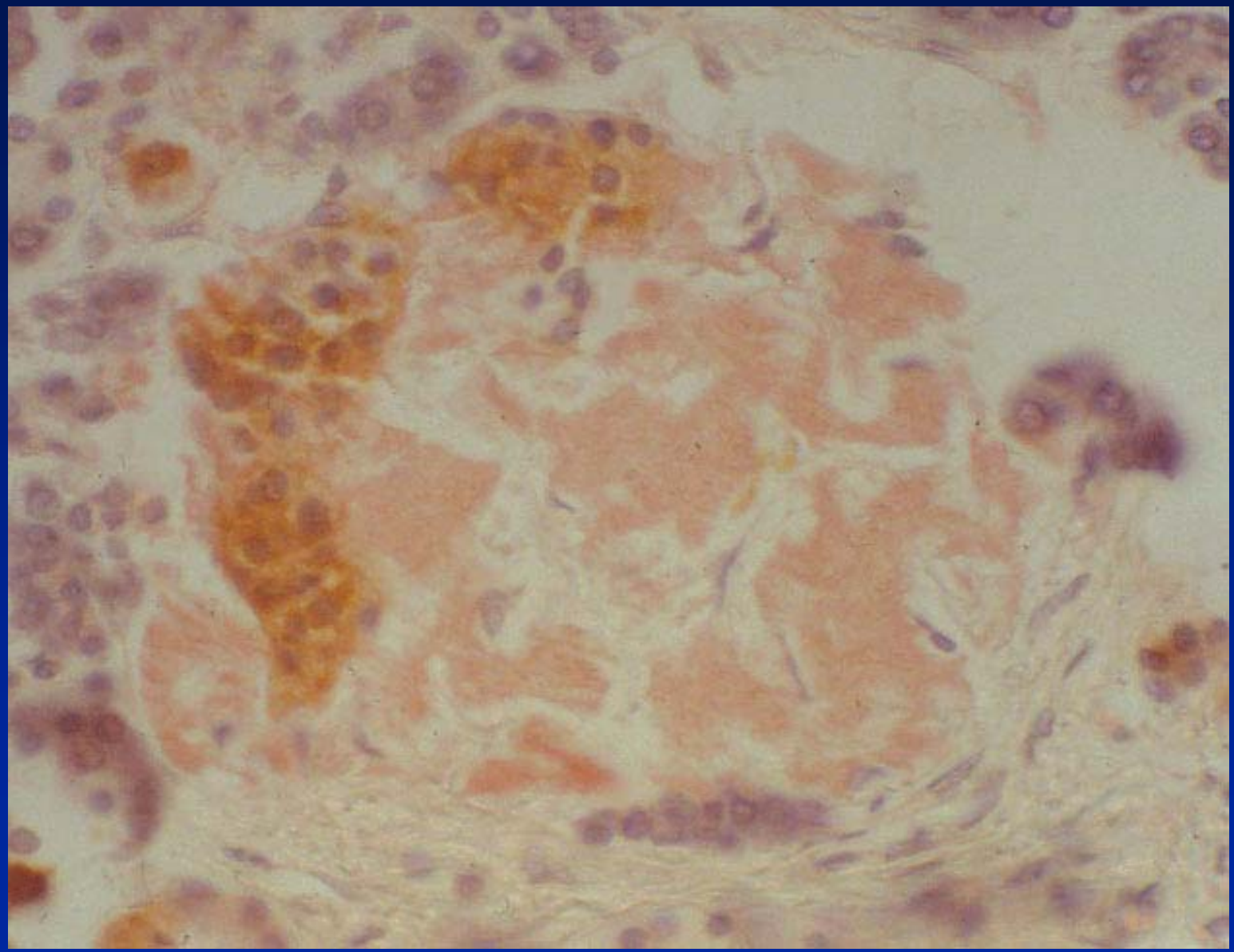
- May not explain all the pathological deterioration
- IAPP is co-secreted with insulin and beta-pleats to form amyloid
- Equivalent to Alzheimer's of the pancreas

Prospects for therapy

?Amyloid pleating blockers

Cellular replacement programmes

Amyloidosis



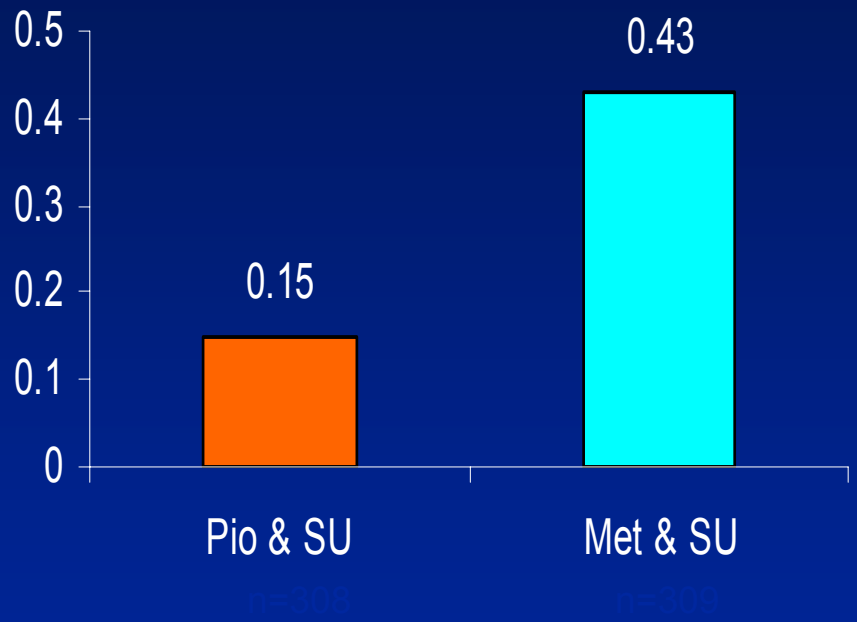
Nuclear receptors

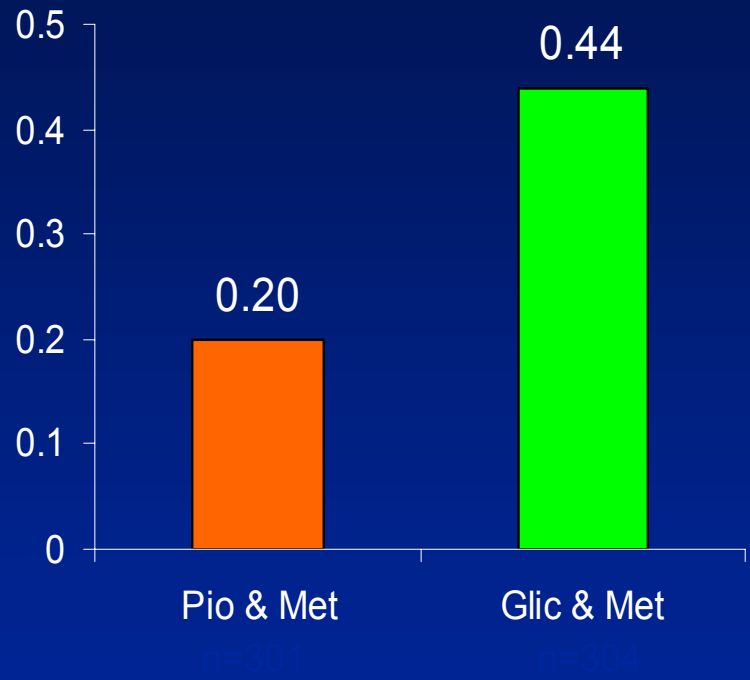
- PPARγ and PPARα receptors
- Increase GLUT4 (?2), decrease FFA deposition
- Decrease body insulin resistance
- Increase measurable beta-cell function

Prospects for therapy

Thiazolidinediones may reduce lipotoxicity and demand on beta-cell by changing peripheral insulin resistance

Coefficient of Failure of HbA_{1c} over 2 years





Pioglitazone v Metformin (as add-on to SU):

Difference (mean): -0.29

95% CI: (-0.56, 0.02)

Pioglitazone v Gliclazide (as add-on to metformin):

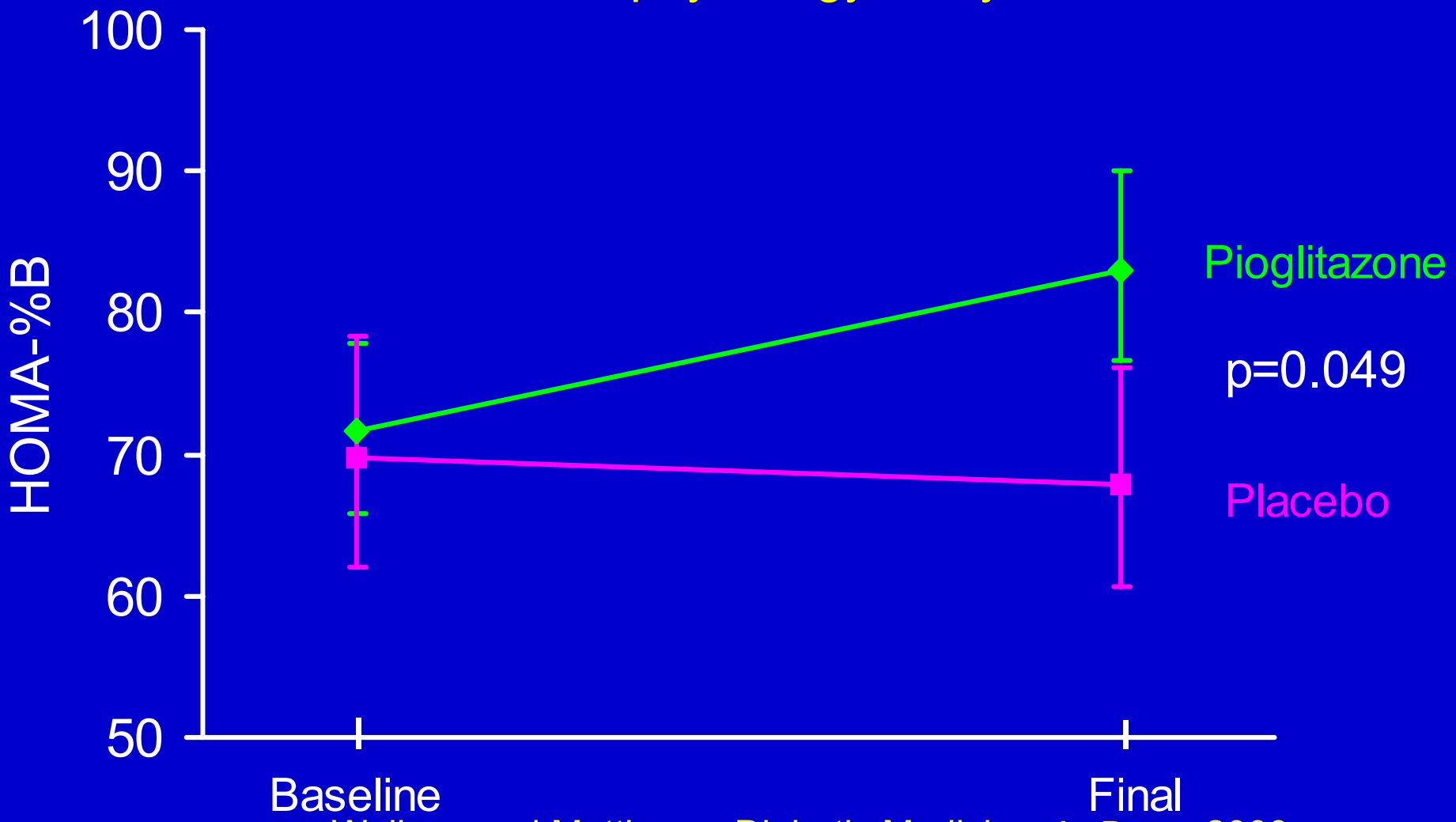
Difference (mean): -0.24

95% CI: (-0.41, -0.07)

Change in HOMA-%B

(geometric mean ± SEM)

12 week physiology study



Wallace and Matthews: Diabetic Medicine. *In Press* 2003

Nuclear receptor modulation

- TZDs increase insulin sensitivity
- Glycaemic control is similar to current agents
- Lipid profiles may improve (Pioglitazone)
- Beta-cell function may be preserved
- TZDs can be safely used in combination with other agents

Prospects for treatment

Beta-cell preservation and delay of onset of diabetes

Conclusions

- As yet no clinical trials have demonstrated conclusive evidence of preservation

BUT…

- Understanding of the beta-cell normal physiology allows definitive interventions
- By contrast the pathophysiology of deterioration is still poorly understood
- Nevertheless there are exciting new prospects for preservation of function