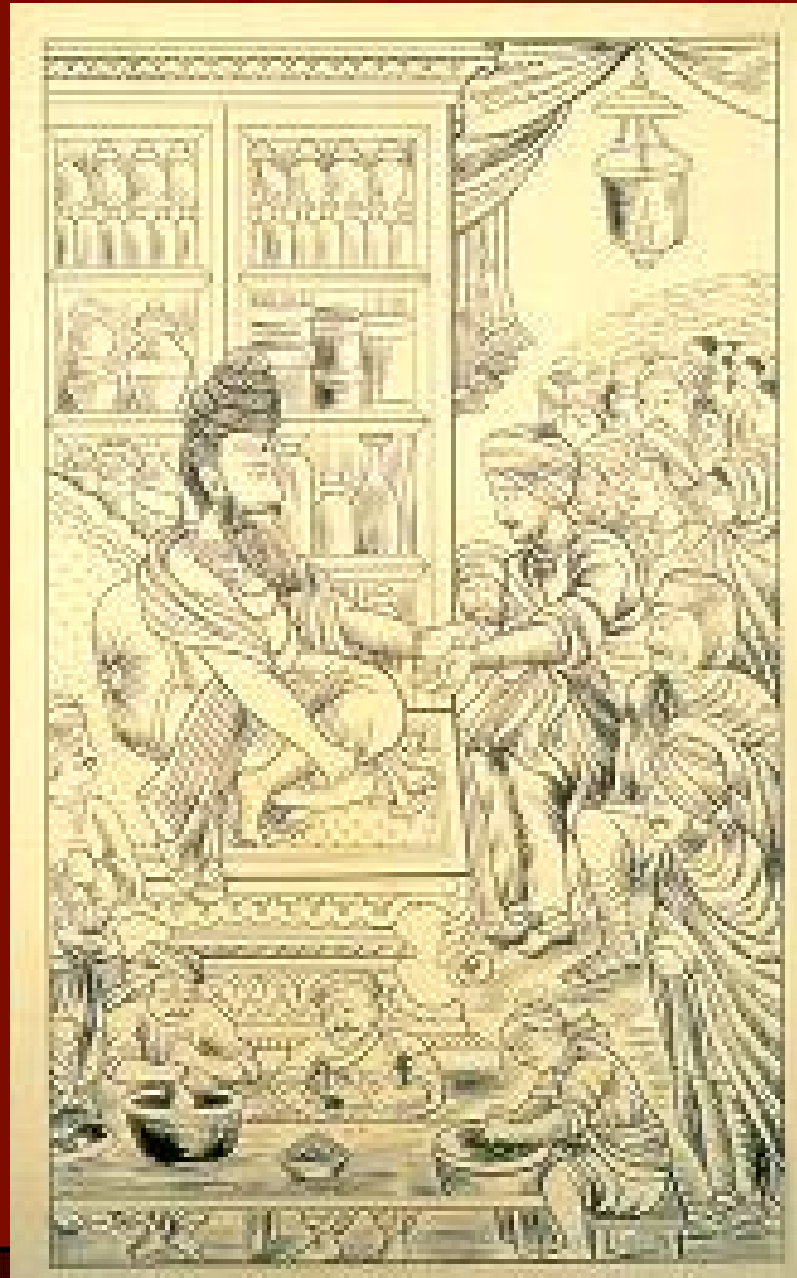


DM Management in 2010

*Dr. K W Lo
Diabetes and Endocrine Centre
HK Sanatorium & Hospital*







Milestones for Management of Diabetes

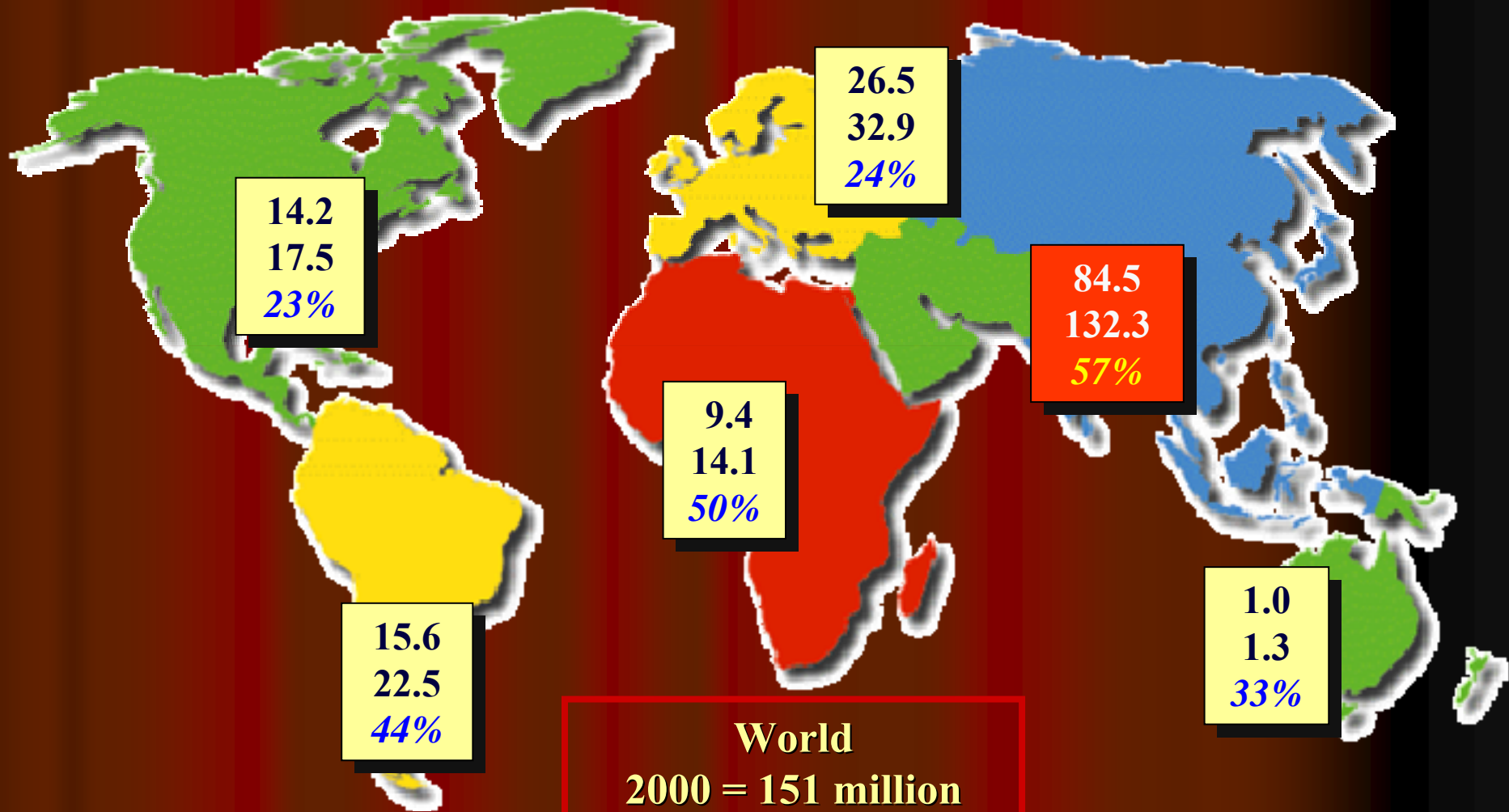
- *1552 B.C. - describe in Egyptian Papyrus*
- *1869 - Paul Langerhans*
- *1870 - Bouchardat*
- *1921 - Banting's*
- *1922 - 1st patient (Leonard Thompson) treated by insulin*

Milestones for Management of Diabetes

- *1955 - OHA introduced*
- *1960 - HBGM devices*
- *1993 - Discovery of ID1-1 gene*
- *1993 - DCCT*
- *1998 - UKPDS*

10 Jan 2007 US Congress passed the resolution and recognized DM as global threat

GLOBAL PROJECTIONS FOR THE DIABETES EPIDEMIC: 2000-2010



World
2000 = 151 million
2010 = 221 million
Increase 46%

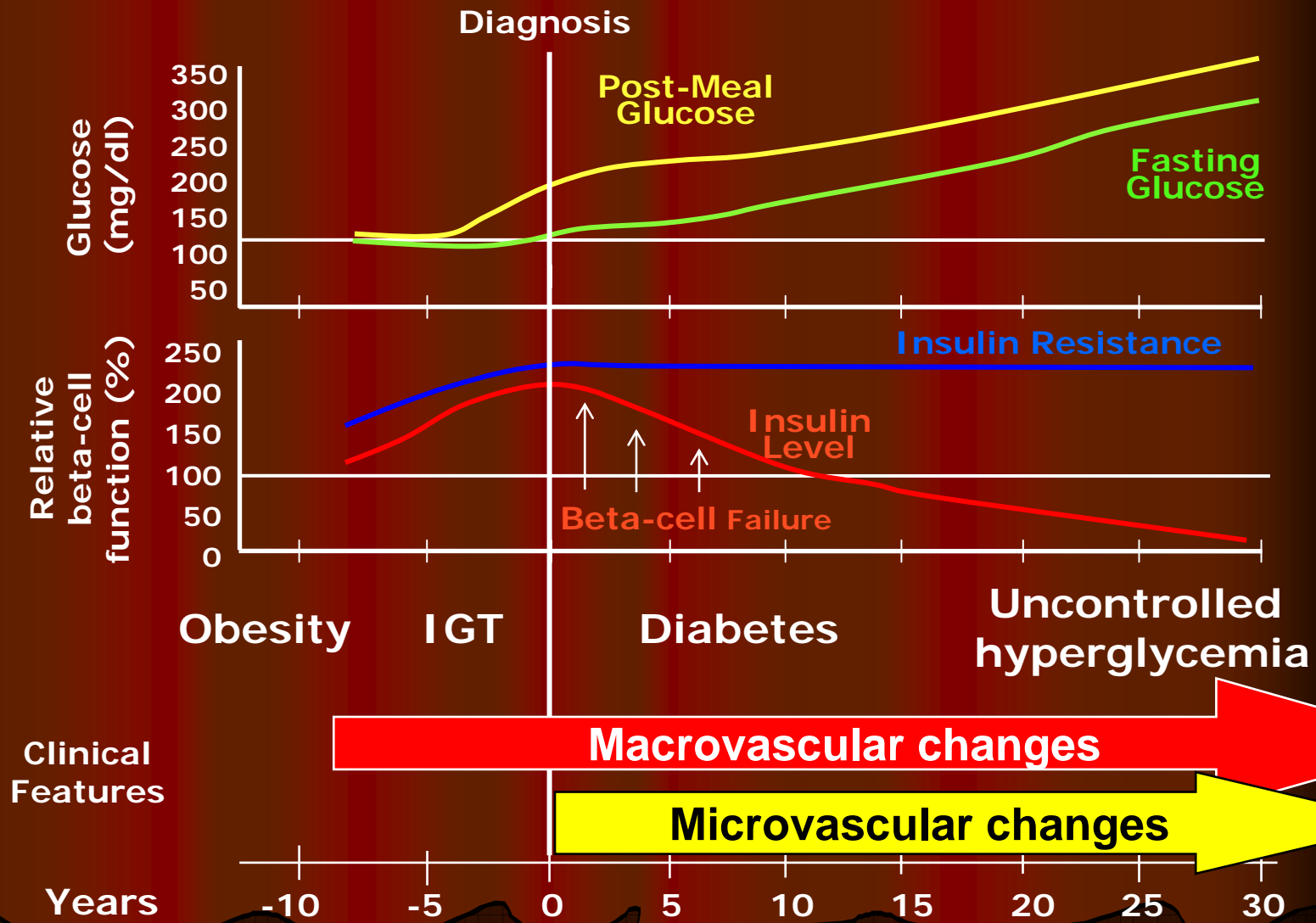
Barriers to quality diabetes care

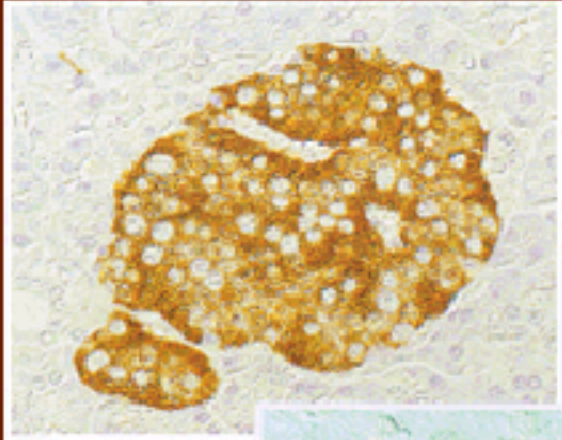
- *> 50% undiagnosed*
- *40-50 % of patients are non-compliant*
- *FACTORS*
 - *Illness*
 - *Patient*
 - *Doctor*

ILLNESS

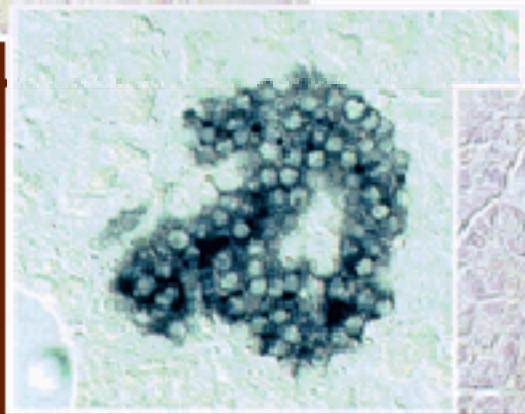
- *Absence of symptoms*
- *Incurable chronic* **PROGRESSIVE**
illness

Natural Progression of Type 2 Diabetes

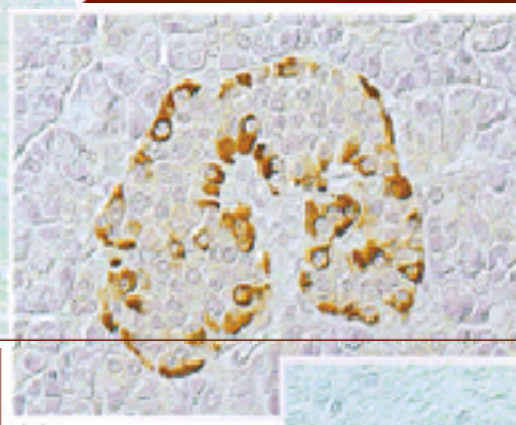




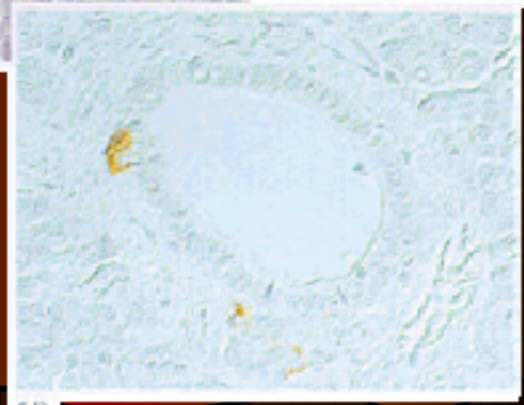
(a)



(b)

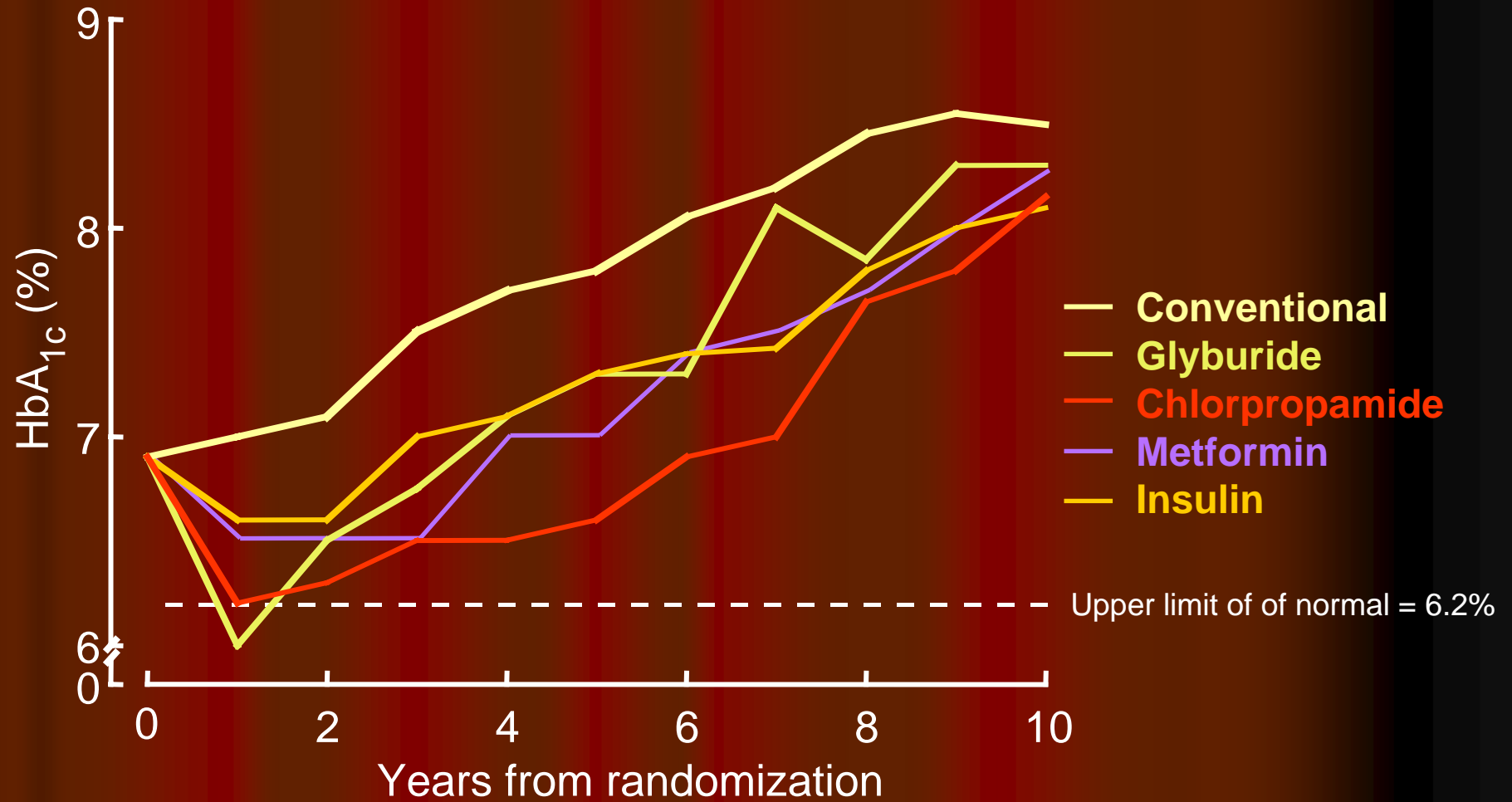


(c)



(d)

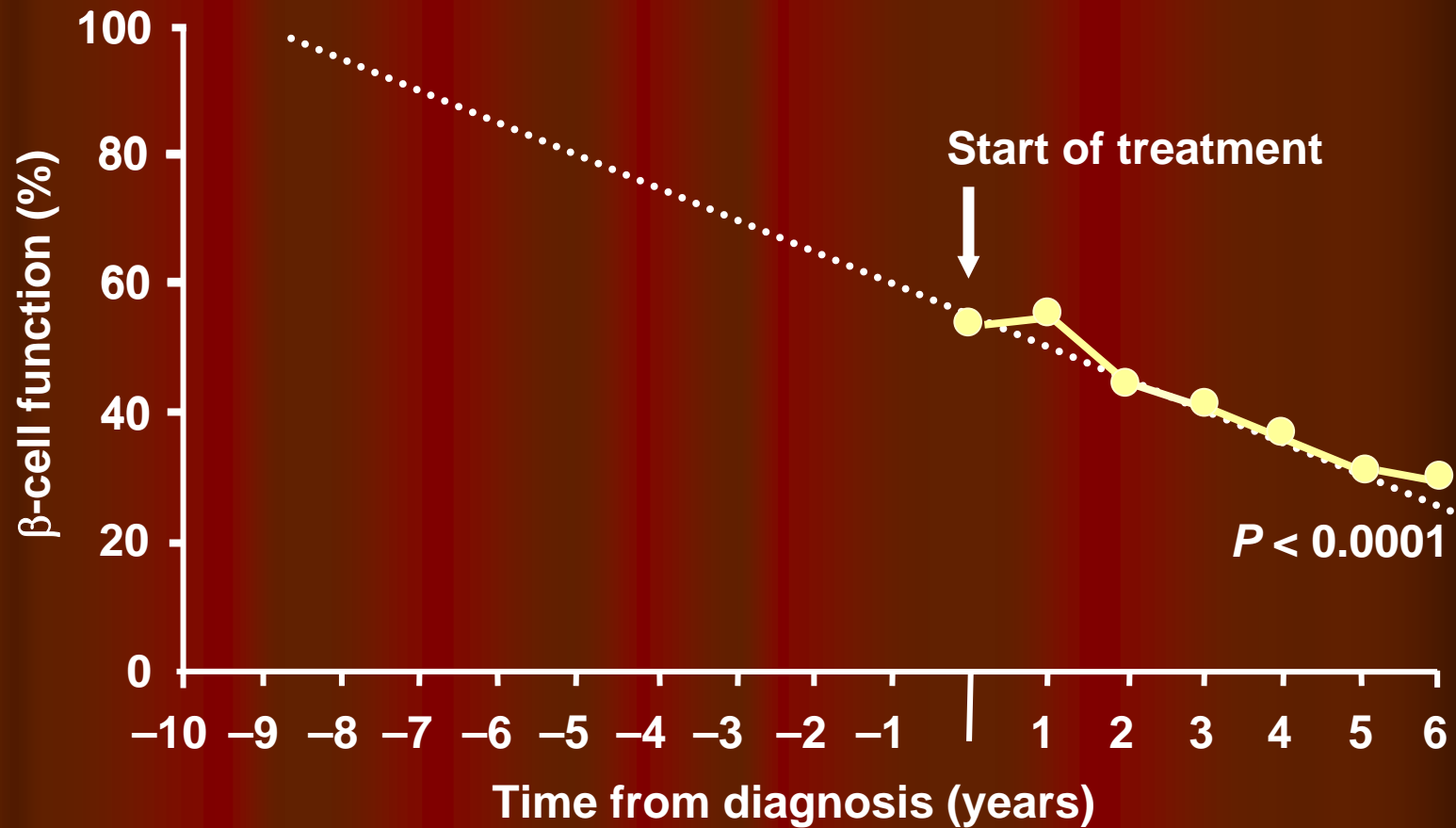
UKPDS demonstrated loss of glycemc control with all agents studied



Overweight patients cohort, median values

UK Prospective Diabetes Study (UKPDS) Group. *Lancet* 1998; 352:854–865.

The UKPDS demonstrated progressive decline of β -cell function over time

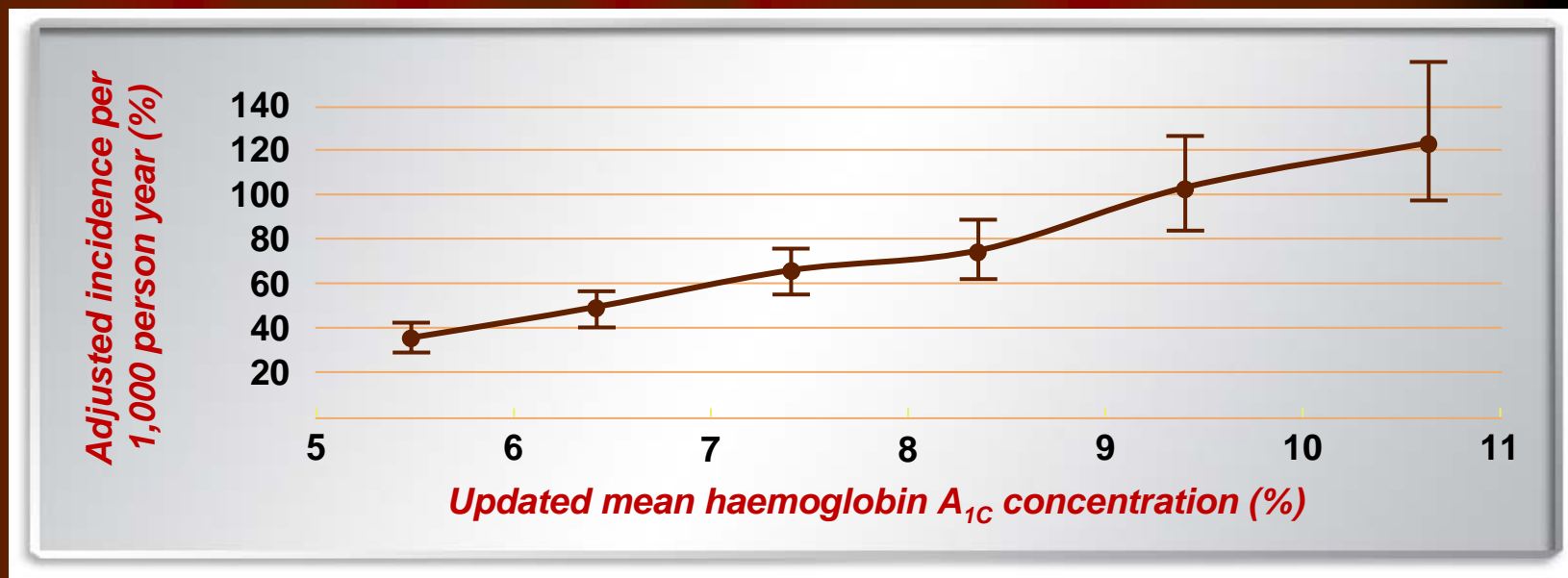


HOMA model, diet-treated
n = 376

Adapted from Holman RR. *Diabetes Res Clin Pract* 1998; 40 (Suppl.):S21–S25.

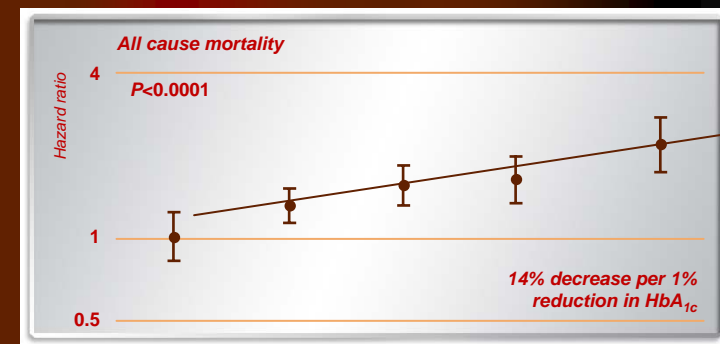
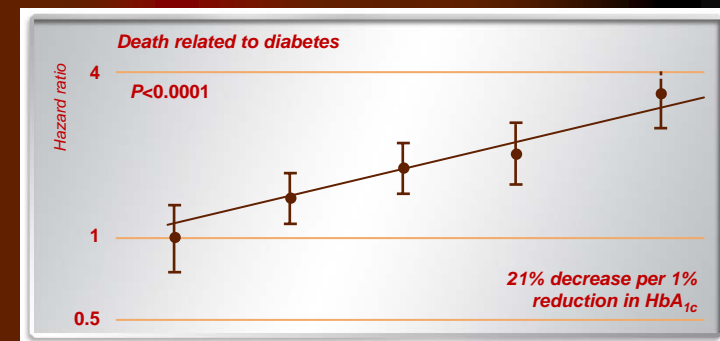
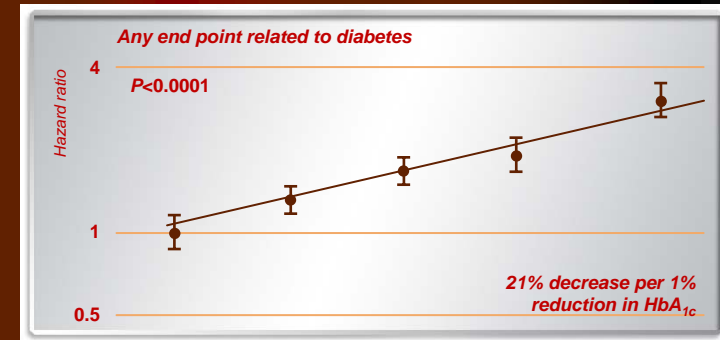
UKPDS 35 - Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes: prospective observational study

- Result:
 - The incidence rates of diabetes complications were significantly associated with glycaemia
 - There was no threshold of risk observed for any complication



UKPDS 35 - Association of glycemia with macrovascular and microvascular complications of type 2 diabetes: prospective observational study

- Result:
 - Each 1% reduction in HbA_{1c} is associated with
 - 21% for any end point related to diabetes ($P < 0.0001$)
 - 21% for deaths related to diabetes ($P < 0.0001$)
 - 14% for myocardial infarction ($P < 0.0001$)
 - There was no threshold of risk observed for any complication

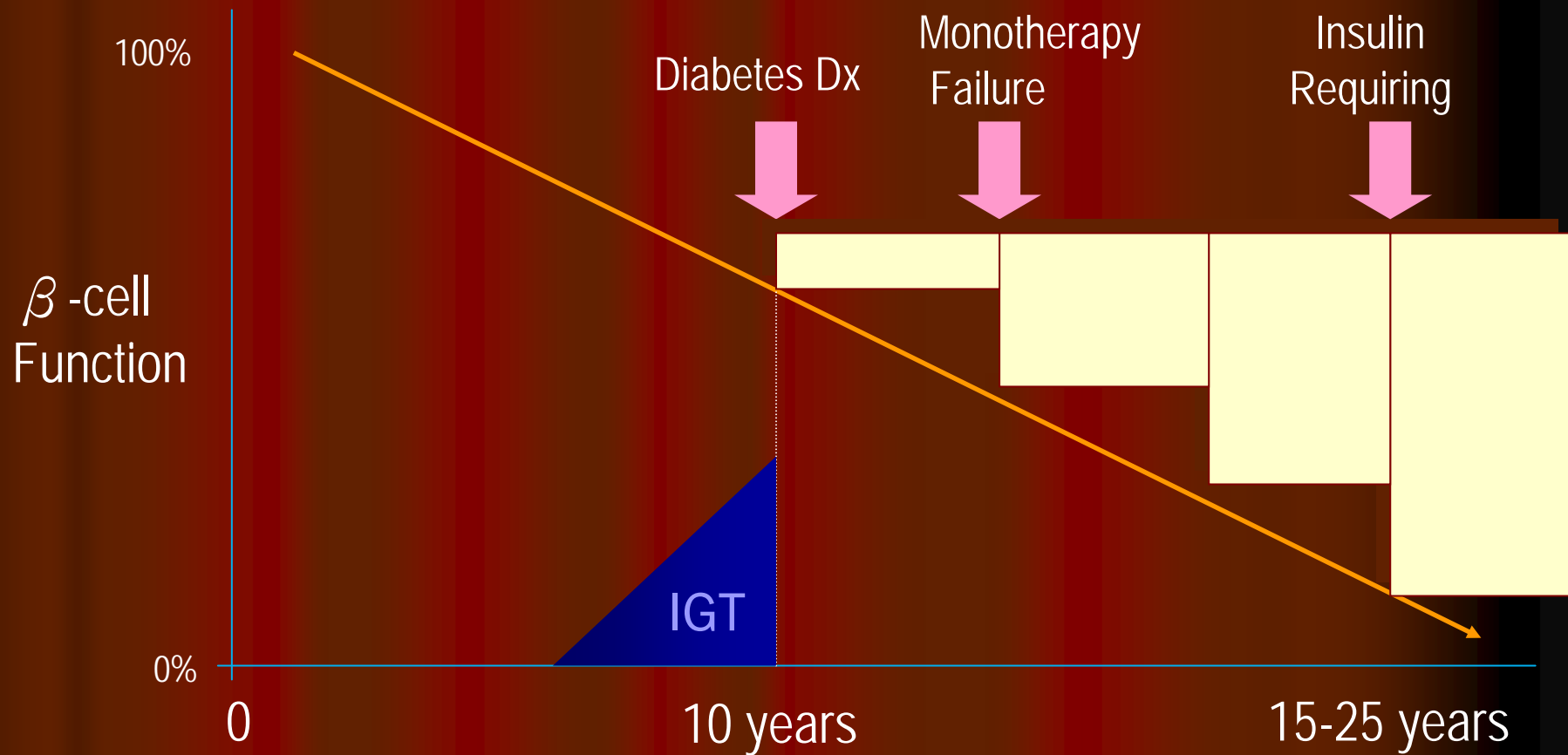


Lessons from the UKPDS

- Too few patients achieved target HbA_{1c} levels, and progression to combination therapy was almost inevitable¹
- After 3 years of monotherapy, 50% of patients required combination therapy¹
- Progression of type 2 diabetes was associated with deterioration of glycemic control²
- No therapy studied reduced disease progression²

Type 2 Diabetes

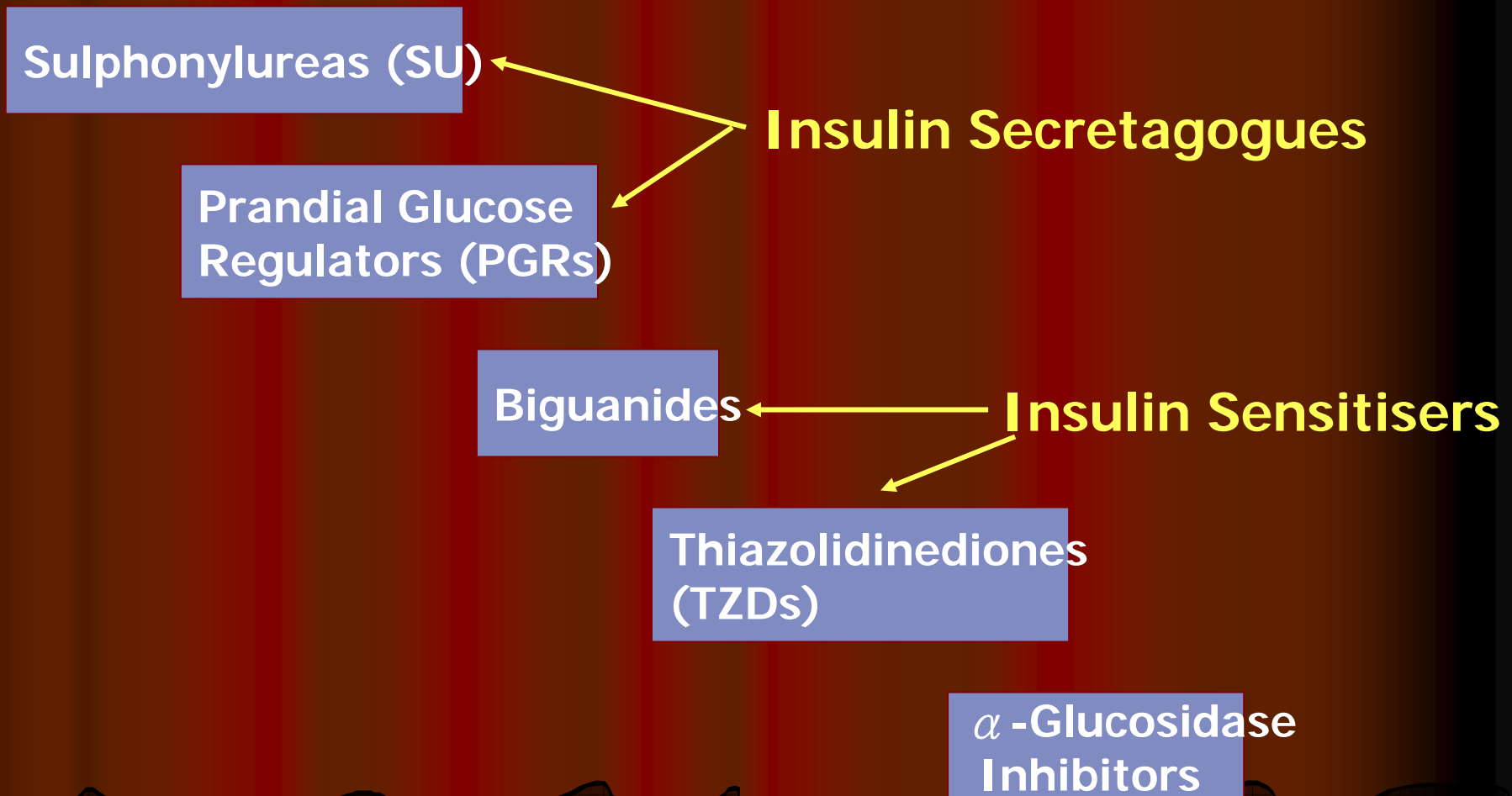
Implications of Progressive Beta-Cell Loss



Stages to reach and maintain the targets

- Diet and exercise
- Oral hypoglycaemic agents – monotherapy
- Oral hypoglycaemic agents – combination therapy
- OHA s + Nocte Insulin therapy
- OHAs (IS) + Insulin Therapy

OADs – 5 classifications



Oral antidiabetic agents: physiological effects

	Insulin secretagogues	Metformin	α -glucosidase inhibitors	TZDs
Effect on FPG/HbA _{1c}	↓	↓	↓	↓
Effect on plasma insulin	↑	↓	-	↓
Effect on LDL-cholesterol	-	↓	-	↑
Effect on HDL-cholesterol	-	↑/-	-	↑
Effect on triglycerides	-	↓	-	↓/-

Oral antidiabetic agents: side effects

	Insulin secretagogues	Metformin	α -glucosidase inhibitors	TZDs
Risk of hypoglycemia	✓	-	-	-
Weight gain	✓	-	-	✓
GI side-effects	-	✓	✓	-
Lactic acidosis	-	✓*	-	-
Edema	-	-	-	✓
Anemia	-	✓	-	✓

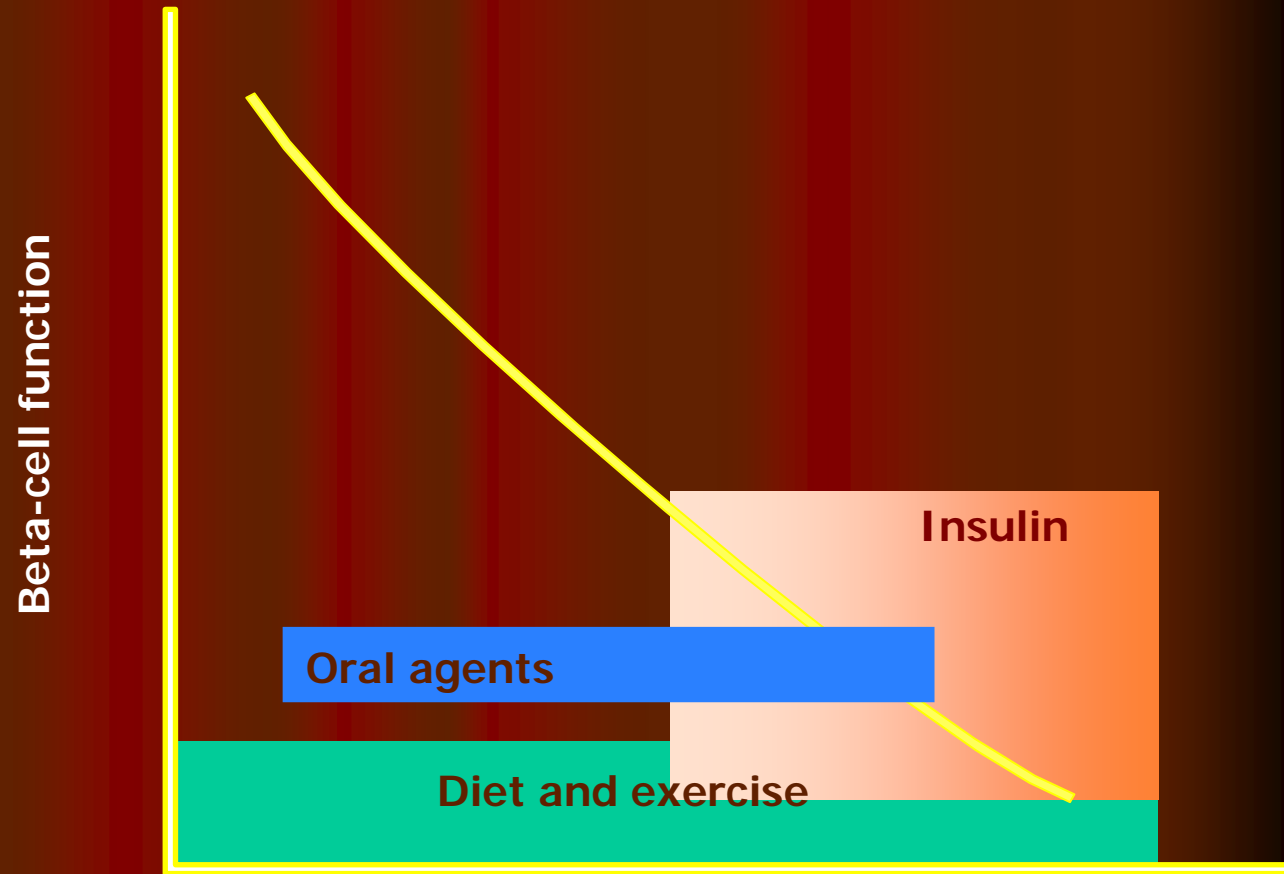
*Observed in patients with renal impairment

Adapted from DeFronzo RA. *Ann Int Med* 1999; 131(4):281–303.

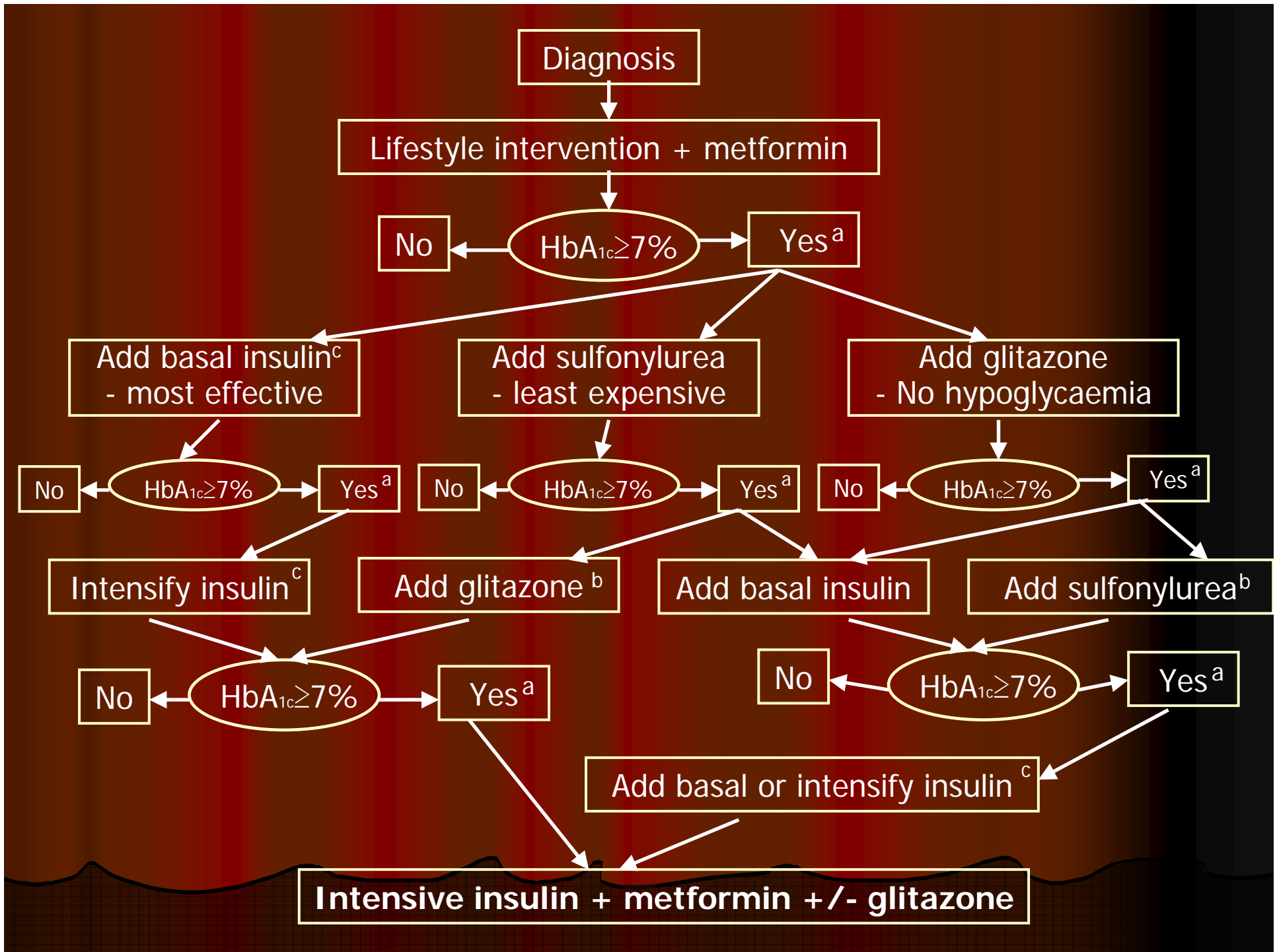
OHA FOR DIABETES

<u>Class</u>	<u>Efficacy in HbA₁C reduction</u>
α_1 -glucosidase inhibitors	0.5 - 1%
Sulphonylureas	1 - 2%
Biguanides	1 - 2%
Thiazolidinedione	1 - 2%

Monotherapy and Combination Therapy



*A consensus statement from the
American Diabetes Association and
the European Association for the
Study Of Diabetes*



New Treatment

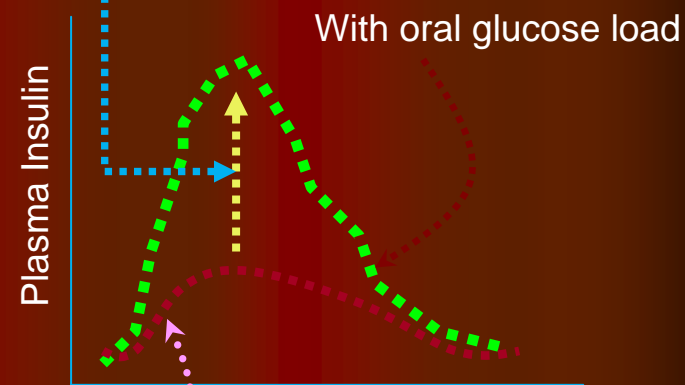
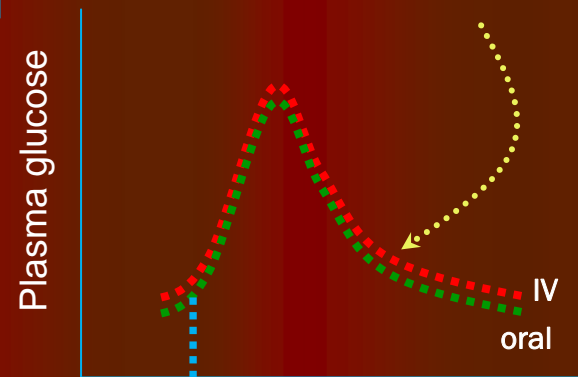
- GLP-1
- Amylin analog
- Dual PPAR agonist
- Inhibition of release or action of counter regulatory hormones
- Inhibition of gluconeogenesis

Incretins: augment insulin secretion

Give a glucose load
IV or oral

Match glycemic profile intravenous
or oral with glucose load

“Incretins”
•GLP-1 (7-36)
•GIP
•? Other incretins



With intravenous
glucose load

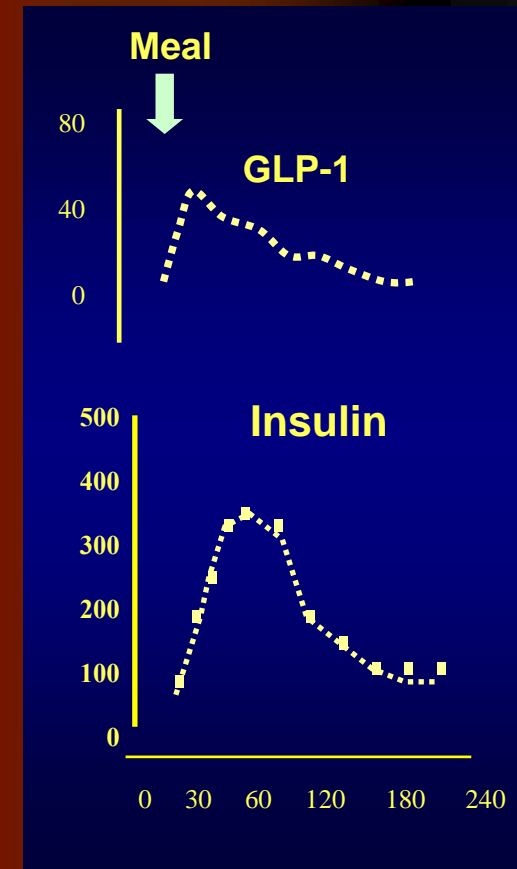
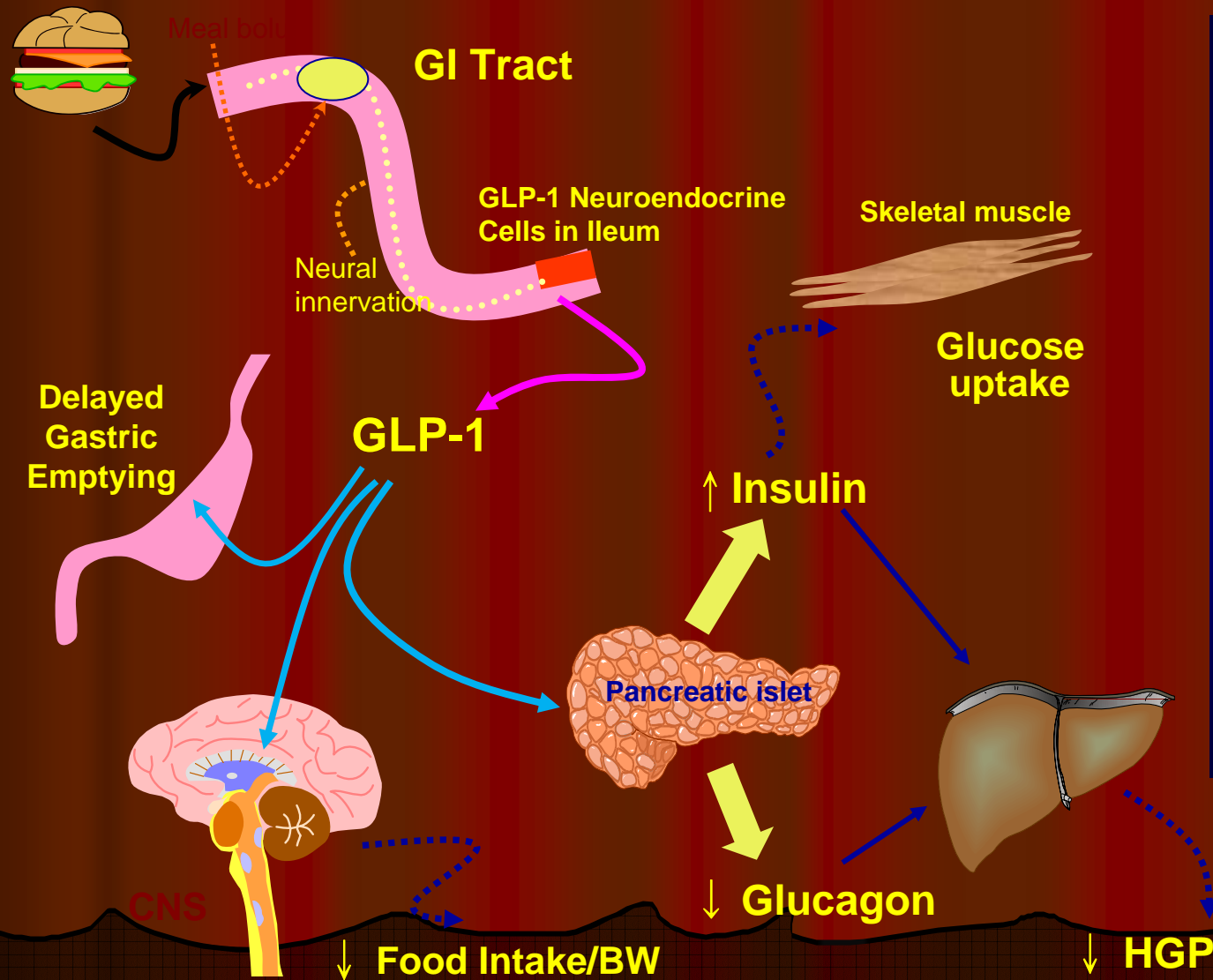
The Main Incretin

- GIP (Glucose-dependent Insulinotropic Peptide)
- GLP (Glucagon Like Peptide)

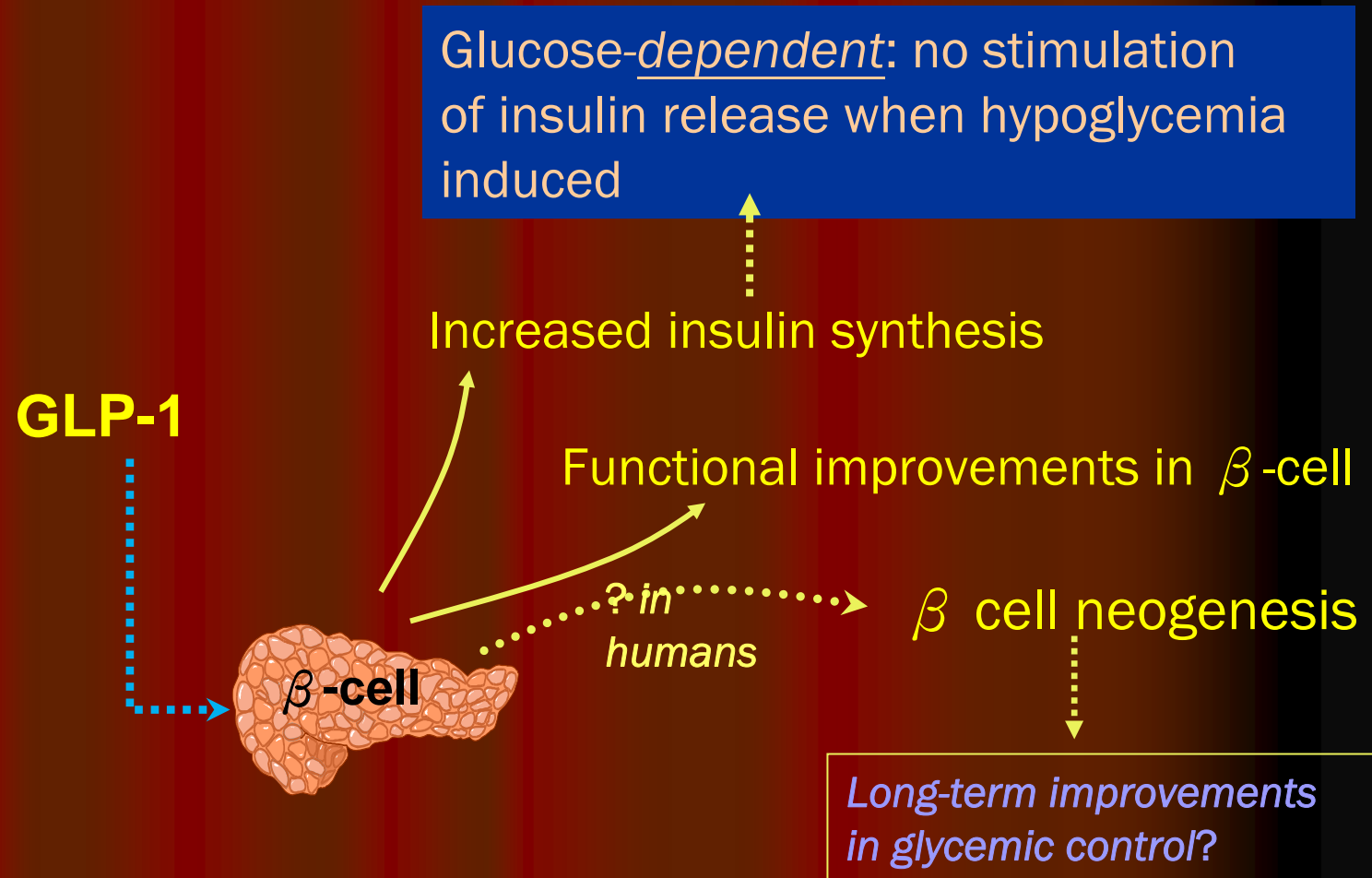
The Incretin: Where they go?

- Both peptides are rapidly cleaved (and thus inactivated) by enzymes
- DPP-IV (Dipeptidyl peptidase)
- Serum T $\frac{1}{2}$ of GIP = 7 mins
- Serum T $\frac{1}{2}$ of GLP-1 = 2 mins

GLP-1: regulation and actions



GLP-1: effects on the β -cell



What does GLP-1 do?

- Enhance insulin secretion
- Decrease glucagon secretion
- Decrease rate of gastric emptying
- Diminish food intake (and obesity)
- Enhance differentiation of progenitor cells to insulin producing cells –neogenesis of β -cells in the islets

Gila Monster (Heloderma Suspectum)

- Biologically active protein in their salivary secretion
- One of these proteins is called **Exendin**
Exocrine gland product that has endocrine functions

Similar biological activities as GLP-1 but a significant different structure

Not susceptible to DPP-IV action

Incretin-based therapies

- GLP-1 Agonist
 - Exenatide
 - Liraglutide
 - CJC-1131
- DPP-IV Inhibitor
 - LAF-237
 - MK-0431
 - ZP-10

Correlation between HbA1c & Plasma Glucose

HbA1c % Mean plasma glucose

6 7.5

7 9.5

8 11.5

9 13.5

10 15.5

11 17.5

12 19.5

Target for Control

? 6.5%

? 7.0%

Individualized

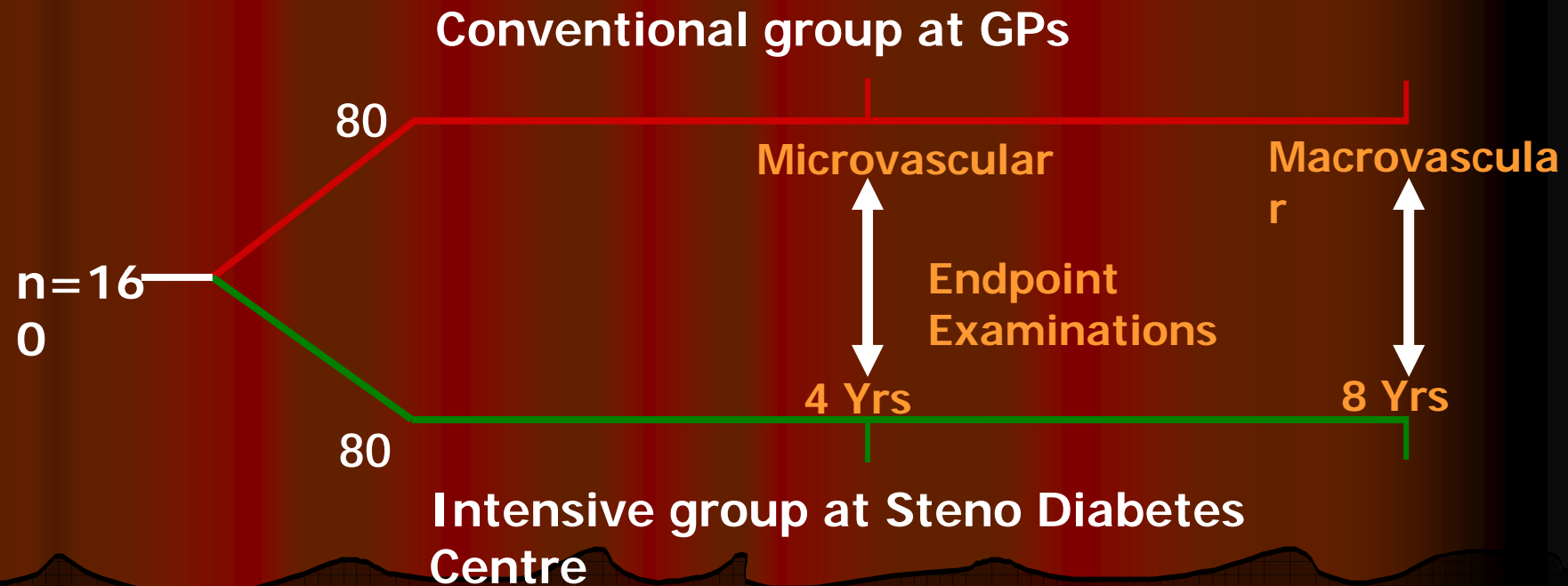
Target for Control

Risk versus benefit

- **Age**
- **Life expectancy**
- **Duration of disease**
- **Presence of microvascular complication**
- **Other co-morbidity**
- **Psychosocial factors**

STENO-2 STUDY

160 patients with T2D and the metabolic syndrome, including microalbuminuria, randomised to either conventional therapy at their GPs, or intensive care at Steno Diabetes Centre.



- **Individualised risk assessment**
- **Ambitious goal setting**
- **More drugs/higher doses**
- **Continued patient education/motivation**

Drug treatment: stepwise and target driven

Hyperglycaemia Metformin - Gliclazide — Insulin per charts

Dyslipidaemia Statins – Fibrates

**Hypertension ACE Inhibitors - Angiotensin II blockers –
Diuretics - Calcium antagonists - Beta-blockers**

Albuminuria ACE Inhibitors

Other CVD prevention Aspirin

STENO-2: Follow up at 8 yrs

	Conventional	Intensive
• HbA_{1C} (%)	9.0	7.9
• Systolic BP (mmHg)	146	131
• Diastolic BP (mmHg)	78	73
• Total chol (mM)	5.6	4.1
• LDL chol (mM)	3.3	2.1
• Triglycerides (mM)	3.0	1.7

Steno-2: Microvascular complications after 8 years

Nephropathy

Relative Risk 0.39

Retinopathy

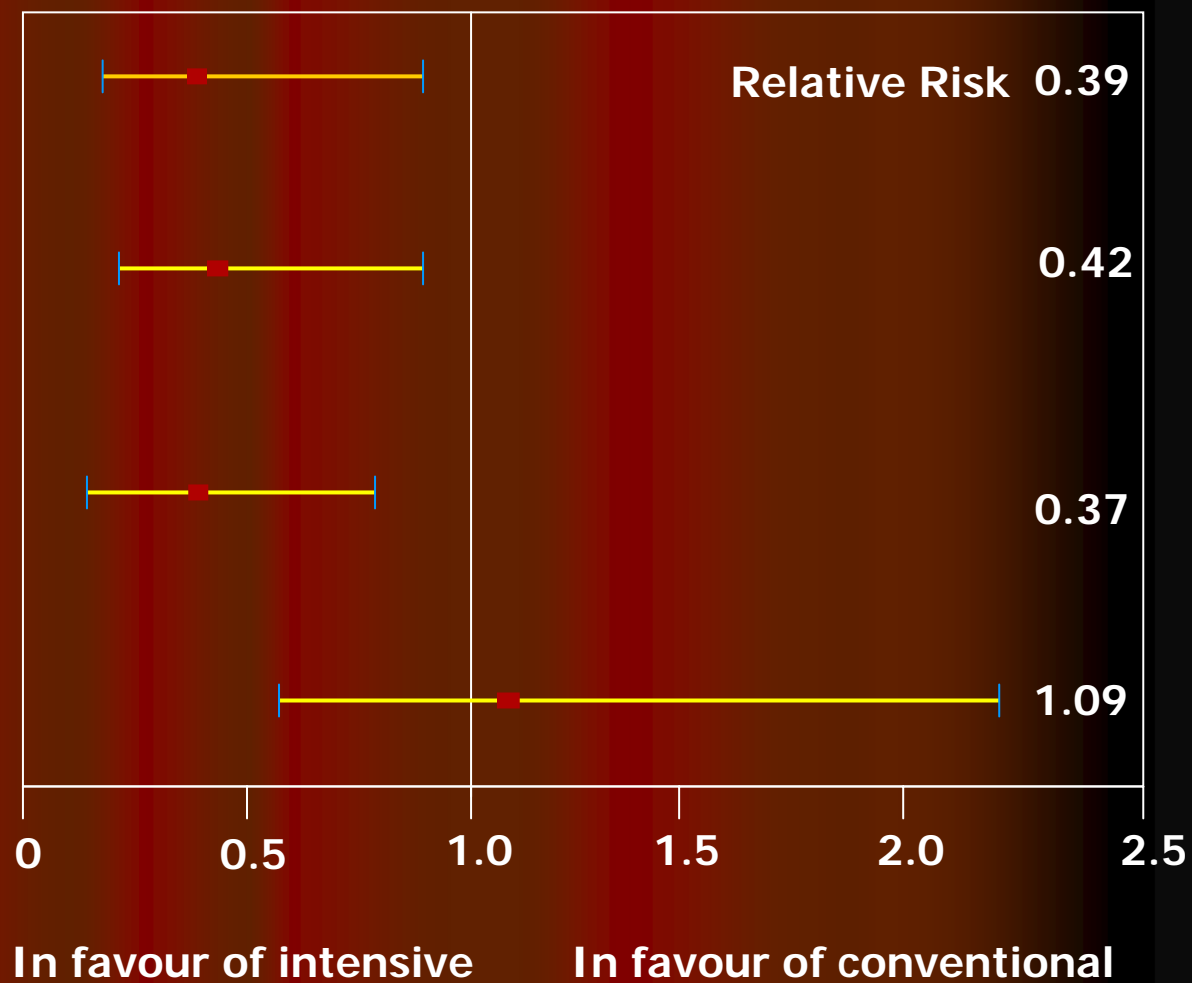
0.42

Auton
Neuropathy

0.37

Periph Neuropathy

1.09

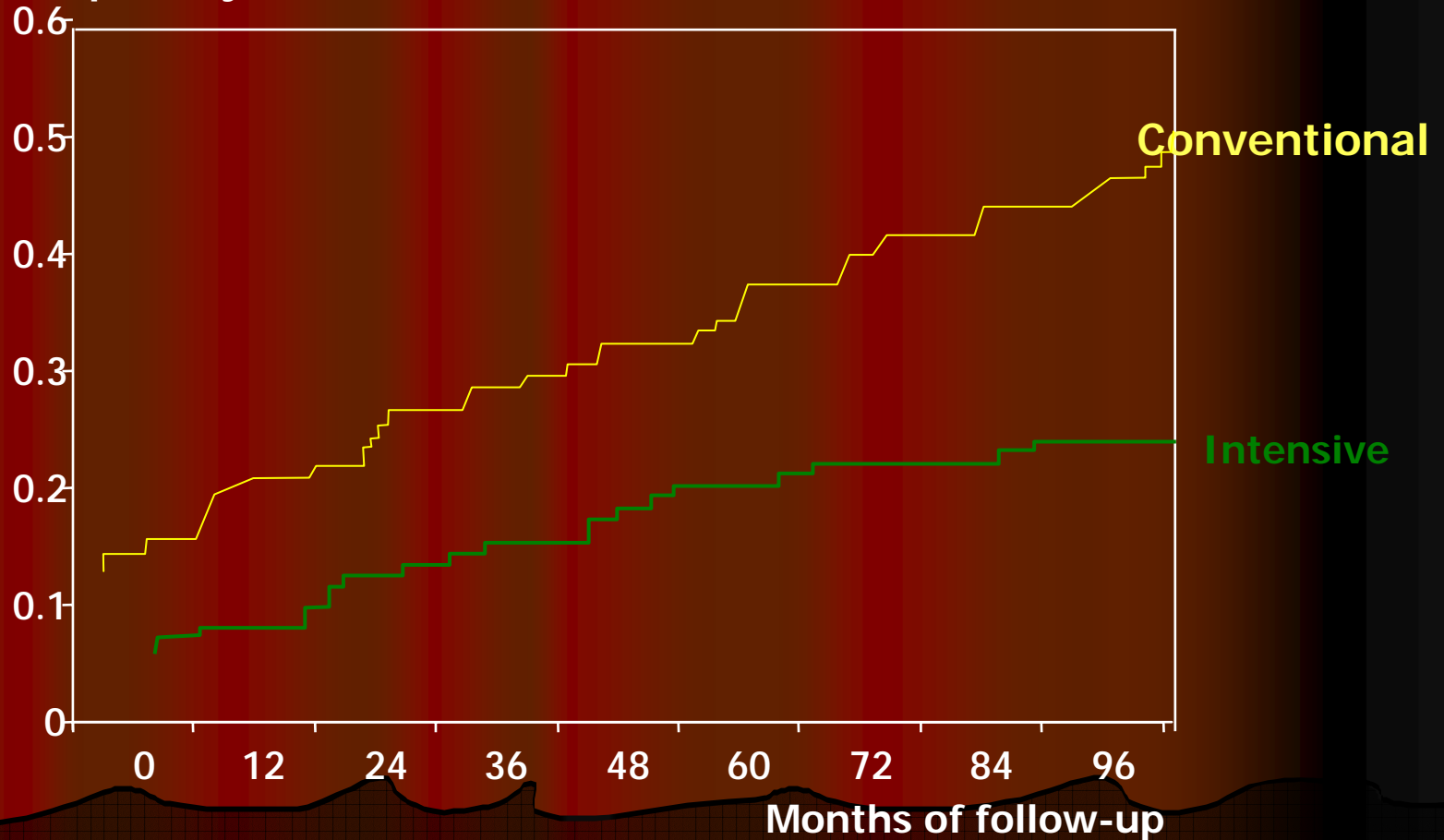


Steno -2: Cardiovascular endpoints after 8 years

65 CVD events in 35 'conventional' patients (44%)

33 CVD events in 19 'intensive' patients (24%)

Probability for primary endpoint



Fundamental message

- Diabetes management - aggressive
- Lifestyle is critical in ALL
- Target all CVRF
- Manage Hyperglycaemia
- Screen for and manage complications

We do not do a good job of reaching targets in this condition

Challenge

PATIENT FACTORS

- Poor acceptance of illness
- Lack of knowledge
- Health beliefs
- Lack of motivation

DOCTORS FACTORS

- Not listening to patient
- Over/Under ambitious treatment objectives
- Not realizing importance of education

MANAGEMENT

- Patient education { doctor(latin): to teach }
 - Therapeutic
 - Correct health beliefs
- Patient empowerment
 - Emphasize importance of self-care
- Multidisciplinary approach
 - Diabetic centre



MULTIDISCIPLINARY CARE

- Self care
 - Modify lifestyle
 - Maintain normal body weight
 - Perform self blood /urine monitoring
 - Attend regular medical follow-up
 - Learn about diabetes

MULTIDISCIPLINARY CARE

- Primary health care providers
 - Provide and reinforce education
 - Adjust medical therapy
 - Assess complication, cardiovascular risk and metabolic control
 - Identify problems that require hospital attention

MULTIDISCIPLINARY CARE

- Diabetes Centre

- Establish communication with primary health care
- Provide ancillary care services, dietitian , podiatrists etc
- Monitoring and quality assurance programmes within community
- Research for new treatment

Frequency of Monitoring in Patients with Diabetes Mellitus

Test	Routine screening frequency	Notes
Smoking cessation counseling	Every visit	For smokers only
Blood pressure	Every visit	
Serum lipids	Annually	
Dilated eye examination	Annually	More often if significant retinopathy
Foot examination	Annually	Every visit if peripheral vascular disease or neuropathy
Microalbuminuria	Annually	After five years in type 1 diabetes; protein excretion and plasma creatinine should also be monitored once persistent microalbuminuria is present
HbA1c	Twice a year	Every three months until goal glycemic control is attained
Education, self-management review	Annually	

Thank You

Interventions	Expected decrease in HbA _{1c} (%)	Advantages	Disadvantages
Steps 1: initial			
Lifestyle to decrease weight and increase activity	1-2	Low cost, many benefits	Fails for most in first year
Metformin	1.5	Weight neutral, inexpensive	GI side effects, rare lactic acidosis
Step 2: additional therapy			
Insulin	1.5-2.5	No dose limit, inexpensive, improved lipid profile	Injections, monitoring, hypoglycaemia, weight gain
Sulfonylureas	1.5	Inexpensive	Weight gain, hypoglycaemia ^a
TZDs	0.5-1.4	Improved lipid profile	Fluid retention, weight gain, expensive
Other drugs			
α -Glucosidase inhibitors	0.5-0.8	Weight neutral	Frequent GI side effects, three times/ day dosing, expensive
Exenatide	0.5-1.0	Weight loss	Injections, frequent GI side effects, expensive, little experience
Glinides	1-1.5 ^b	Short duration	Three times/day dosing, expensive
Pramlintide	0.5-1.0	Weight loss	Injections, three times/day dosing, frequent GI side effects, expensive, little experience