Combination of OHA Therapy in Type 2 Diabetes Mellitus

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DIABETES MELLITUS

↓

β-Cell Dysfunction

↓

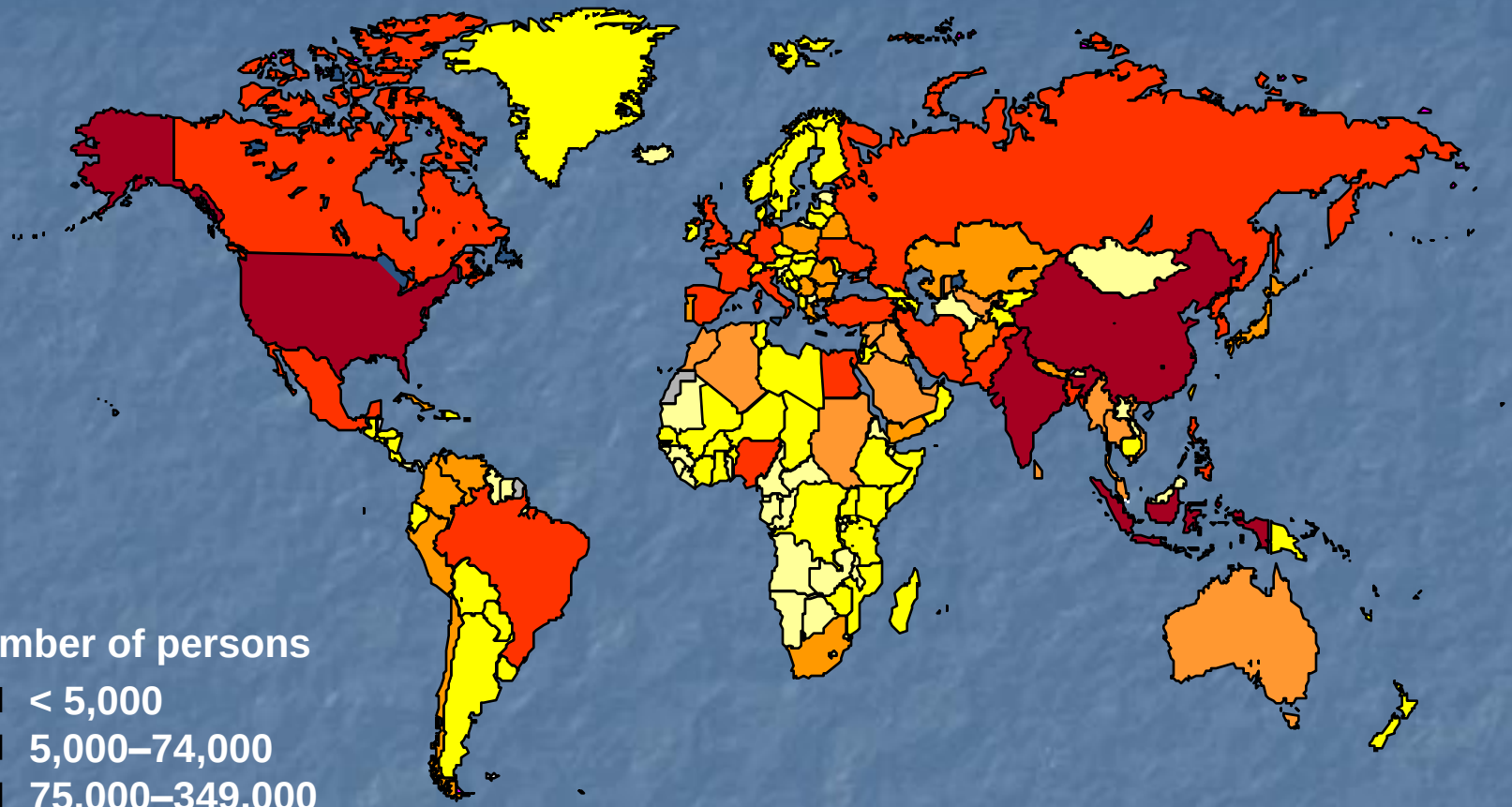
INSULIN

HOLDS TRUE

FOR

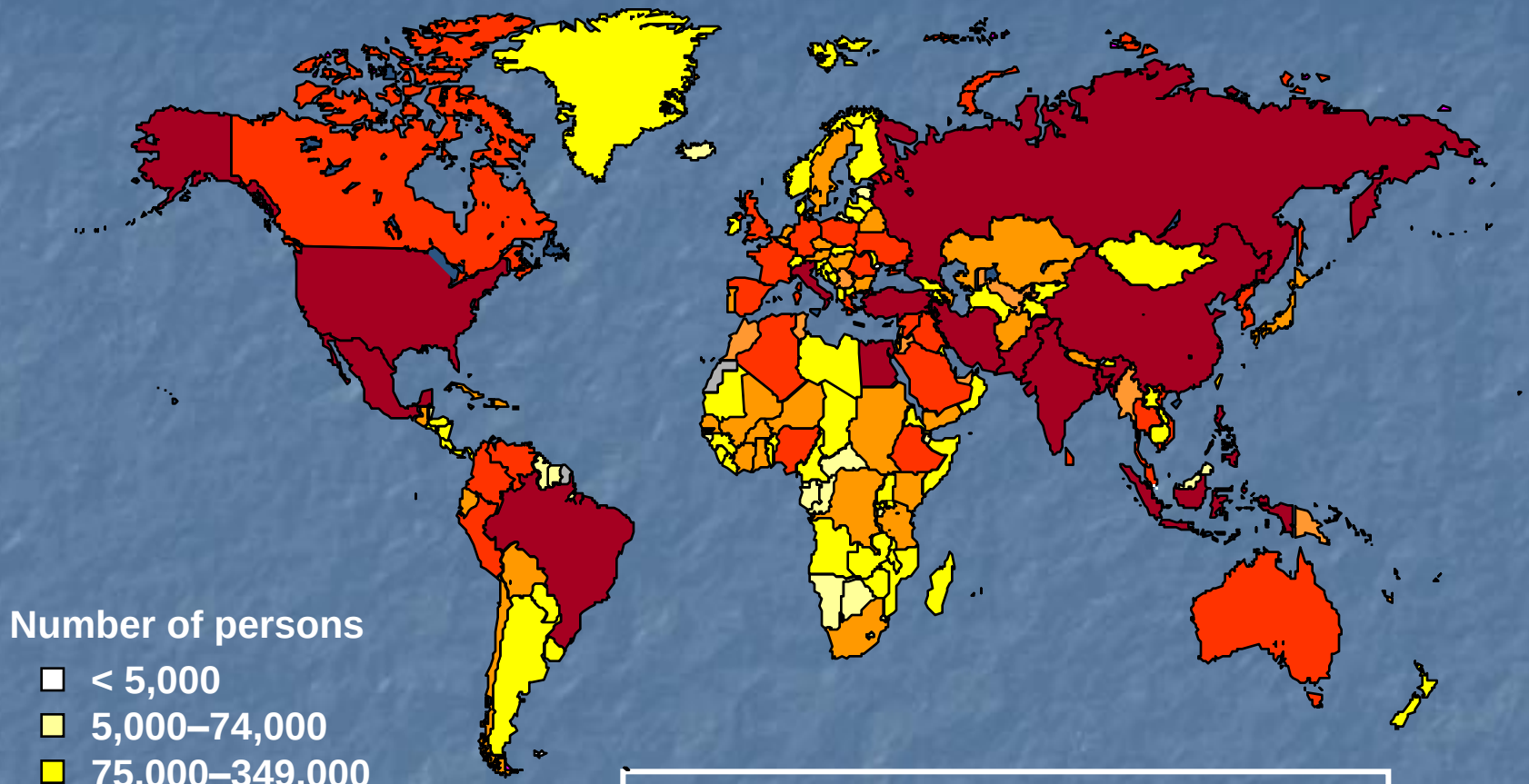
TYPE 1 D.M.

Worldwide prevalence of diabetes in 2000



Adapted from WHO Diabetes Programme Facts and Figures: www.who.int/diabetes/facts/world_figures/en. Accessed 1 August, 2006.

Worldwide prevalence of diabetes in 2030 (projected)



Total cases > 300 million adults

Adapted from WHO Diabetes Programme Facts and Figures: www.who.int/diabetes/facts/world_figures/en. Accessed 1 August, 2006.

Type 2 diabetes: a growing problem

- A serious, progressive disease, characterized by two fundamental defects
  - Insulin resistance
  - β-cell dysfunction
- Accounts for > 95% on diabetes cases worldwide
- Represents a significant disease burden
  - Associated with serious microvascular and macrovascular complications
  - Significant impact on overall healthcare costs

Characteristics of type 2 diabetes

- Chronic hyperglycaemia with disturbances of carbohydrate, fat and protein metabolism
- Defects in insulin action (insulin resistance), insulin secretion (β-cell dysfunction) or both

ORAL HYPOGLYCEMIC AGENTS

O.H.A. are the most common form of treatment of Type 2 D.M. worldwide. When used judiciously they are important agents in the management of the most common form of Diabetes.

O. H. A.

For economic, logistic and general effectiveness, oral agents are a dependable means of treating a large population of diabetics world wide when used correctly

ORAL HYPOGLYCEMIC AGENTS

SULFONYLUREAS

BIGUANIDES

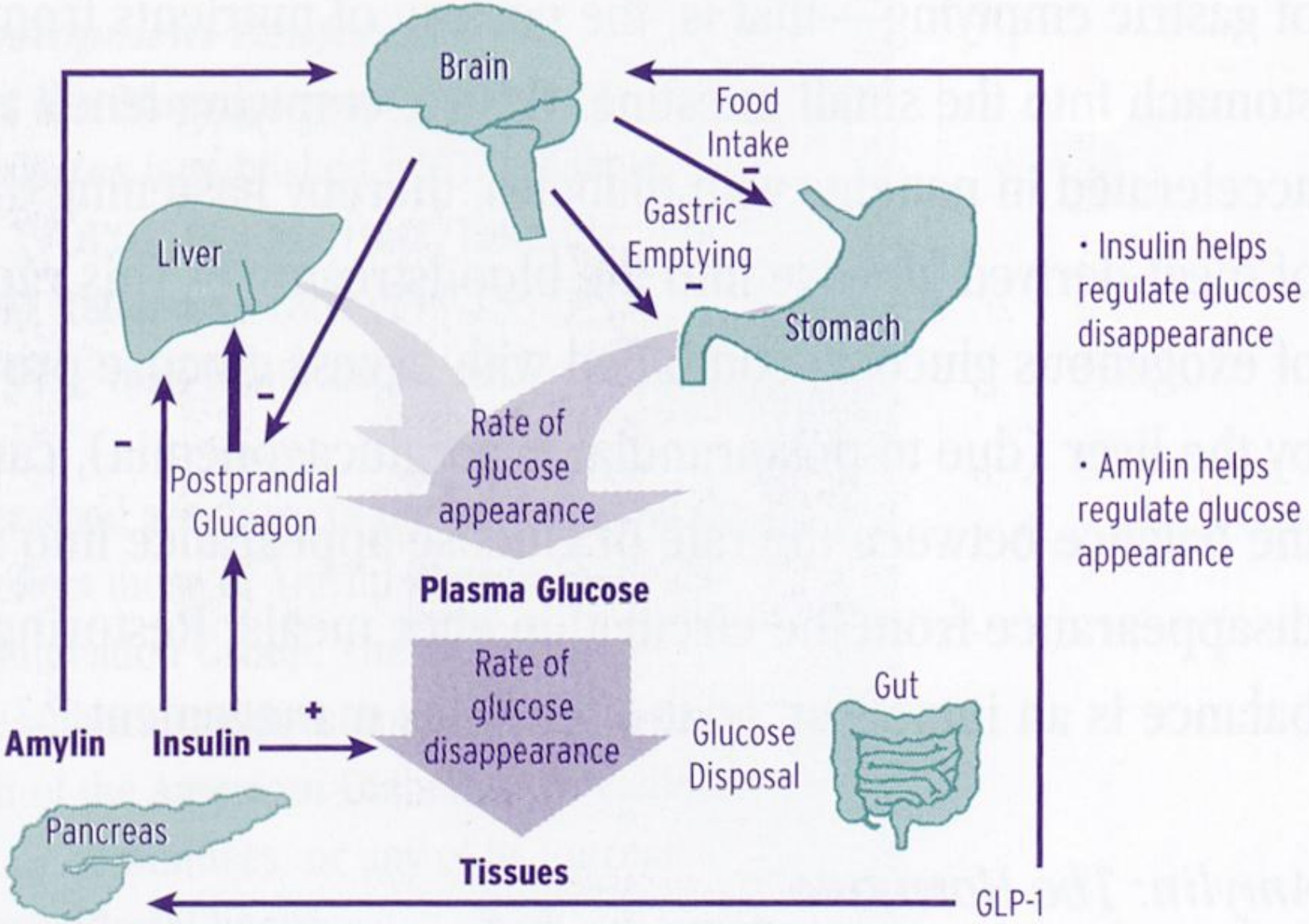
MEGLITINIDES

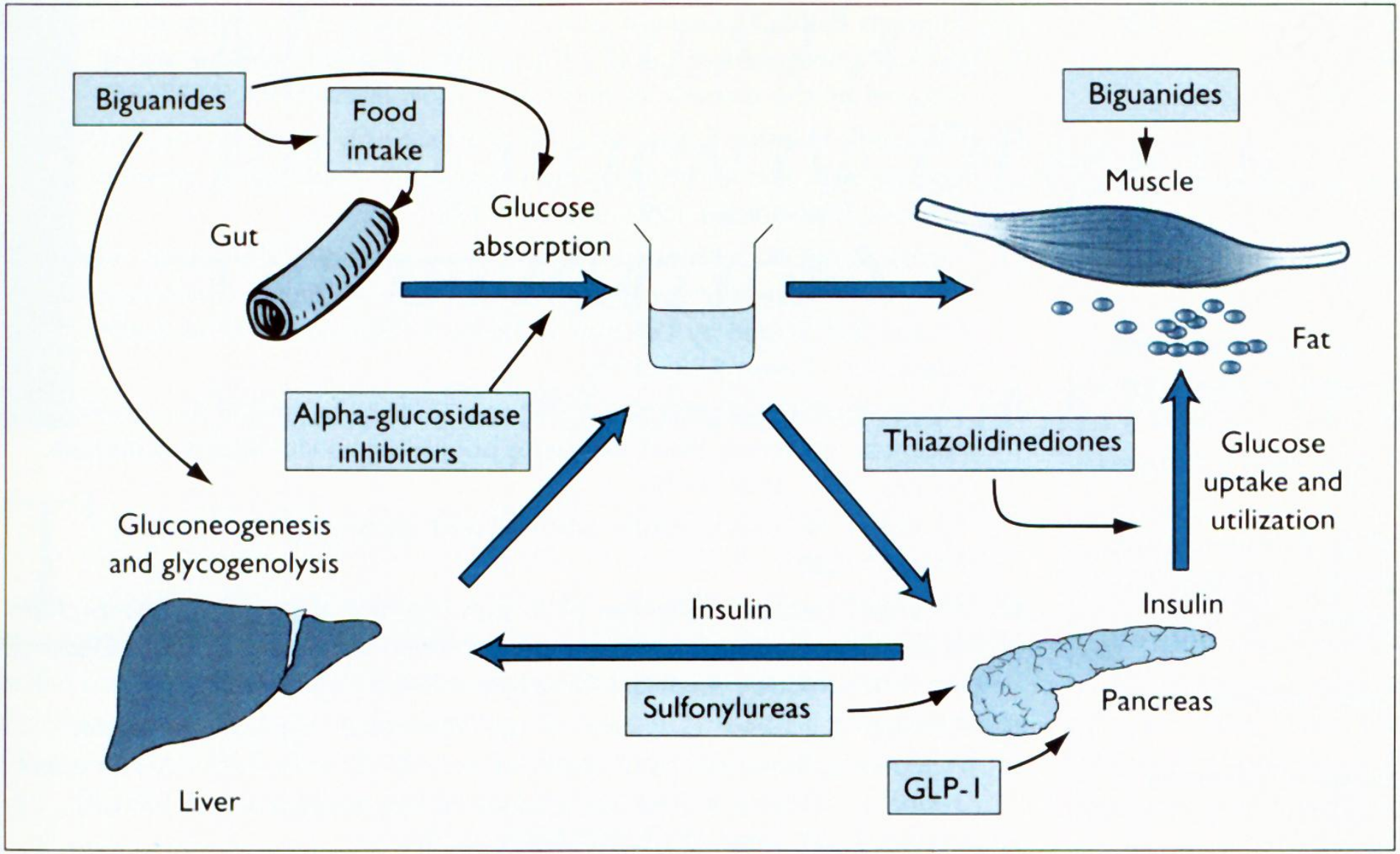
ALPHA GLUCOSIDASE INHIBITORS

THIAZOLIDINEDIONES

CLINICAL BARRIERS TO O.H.A.S.

- HYPOGLYCEMIA
- DIURNAL GLUCOSE FLLUCTUATIONS
- EXECESSIVE WEIGHT GAIN
- POST PRANDIAL HYPERGLYCEMIA


Brain
Food Intake
Gastric Emptying
Liver
Stomach
Postprandial Glucagon
Rate of glucose appearance
Plasma Glucose
Rate of glucose disappearance
Amylin
Insulin
Glucose Disposal
Gut
Pancreas
Tissues
GLP-1
• Insulin helps regulate glucose disappearance
• Amylin helps regulate glucose appearance

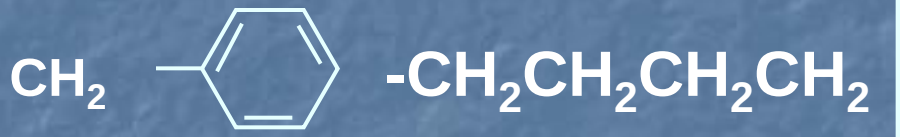

Biguanides
Food intake
Gut
Glucose absorption
Biguanides
Muscle
Fat
Alpha-glucosidase inhibitors
Thiazolidinediones
Glucose uptake and utilization
Gluconeogenesis and glycogenolysis
Insulin
Insulin
Sulfonylureas
Pancreas
GLP-1
Liver

Ideal Therapeutic Agents

- improve the timing and amount of insulin secreted without unduly stressing the already maximally stimulated beta-cells
- enhance insulin actions
- restore inhibition of hepatic gluconeogensis to normal

SULPHONYLUREAS
FIRST GENERATION

Tolbutamide

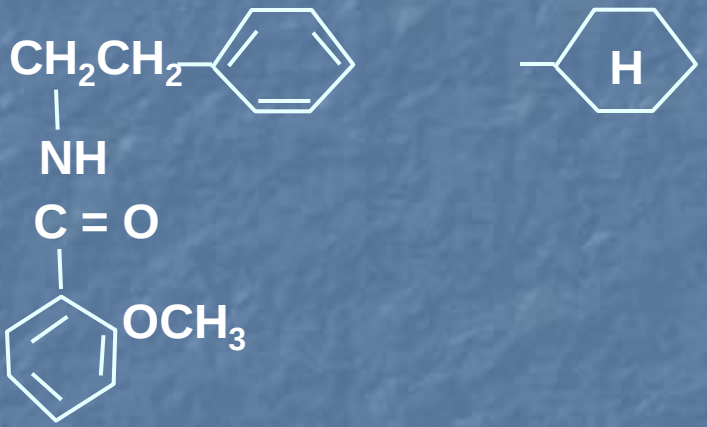


Chlorpropamide

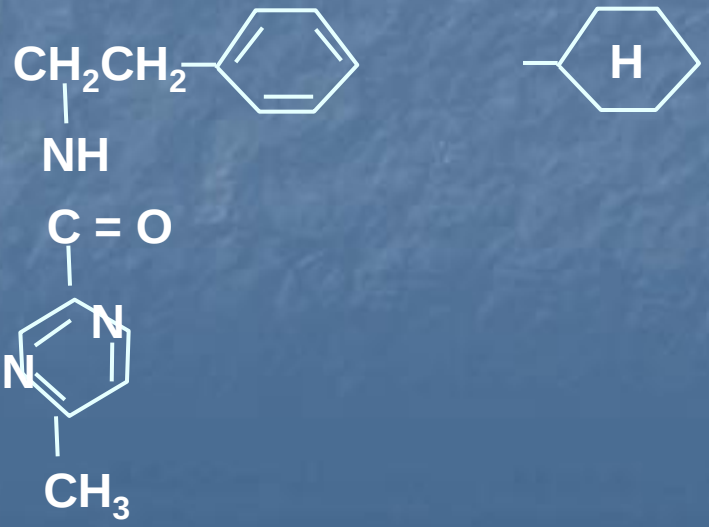
SULPHONYLUREAS
SECOND GENERATION

Gliclazide

GLIBENCLAMIDE



GLIPIZIDE



EFFECTS OF SULPHONYLUREAS

- Increased tissue sensitivity to insulin thus improved insulin action
- Reduced hepatic extraction of insulin from the circulation
- Effects on plasma lipids, i.e. Triglycerides and Cholesterol, Direct effects unlikely
- Effects on platelets and fibrinolysis
- Effects on Basement Membrane to reduce thickness

SULFONYLUREAS:

EXTRAPANCREATIC EFFECTS

1. Increased insulin receptor binding sites
2. Decreased hepatic gluconeogenesis.
   Augmentation of insulin-induced suppression of hepatic glucose release.
3. Inhibition of triglyceride lipase
4. Enteroinsular axis stimulation

OPTIONS FOR SULFONYLUREAS

CHLORPROPAMIDE

TOLBUTAMIDE

GLIBENCLAMIDE

GLIPIZIDE

GLICLAZIDE

GLIMEPIRIDE

BIGUANIDES
MODE OF ACTION

- Inhibition of glucose and aminoacid transport across small bowel
- Enhanced glycolysis in extra hepatic tissues
- Inhibition of hepatic gluconeogenesis
- Direct cellular effect
- Increase in glucose uptake

BIGUANIDES
MODE OF ACTION

- In isolated mitochodria there is intereference with transfer of high energy bonds to A.D.P. suggesting that the compound inhibits oxidative phosphorylation.
- 1/3 is eliminated as metabolite. 2/3 is eliminated unchanged. 30% is excreated in urine in 5 hours and 90% in 24 hours.
- Toxicity associated with hypoxia, renal insufficiency and excessive alcohol intake.
- Hypoglycemia due to phenformin alone is actually unknown.

BIGUANIDES CONTRA-INDICATIONS

- Patients with renal insufficiency
- Conditions that predispose to tissue hypoxia.
  - Severely uncontrolled diabetes
  - C.C.F., I.H.D., Malignant hypertension, Proliferative retinopathy
  - Pulmonary insufficiency
  - Acute infections, traumatic or inflammatory conditions
  - Advanced age.

BIGUANIDES CONTRA-INDICATIONS

- Hepatic dysfunction (hepatitis, cirrhosis, fatty liver)
- Alcohol abuse
- Patients using barbiturates, salicylates phenothiazines
- General debilitating conditions
- Pre and post operatively (1 week)
- During starvation diet
- Poorly complying patients

OPTIONS FOR BIGUANIDES

- Phenformin
- Metformin

NEWER O.H.A.

- GUAR GUM
- ACARBOSE
- GLIMEPIRIDE
- REPAGLINIDE
- GLITAZONES

ACARBOSE

- Inhibits α Glucosidase Activity
- GI Effects

GLIMEPIRIDE

- Less Hypos
- Less Weight gain
- Less Hyperinsulinemia
- Less early failure of β cells
- Less skipped doses

INSULIN SECRETAGOGUES

Miglitinide Analog – Repaglinide

- **No peripheral effects on muscle, liver and adipose tissue**
- **Excreted via bite – safe in patients with renal disease**
- **Lower risk for hypoglycemia even on skipping a meal!**
- **Good efficacy & safety profile even in the elderly**
- **First line therapy in type 2 patients with diet failure**
- **Good results when used in combination with Metformin**

REPAGLINIDE

- Non Sulfonylurea
- Insulinotropic agent

GLITAZONES
Modes of Action

- It activates the nuclear peroxisome proliferator activated receptor - γ (PPAR- γ)
- It also has partial agonist activity against PPAR α

DIFFERENT TYPES OF PPARS

	α	β	γ
Tissue expression	Skeletal muscle liver, kidney	Not known	Adipose tissue, skeletal, cardiac muscle, liver, kidney SI, bladder & spleen
Also expressed in vascular endothelial cells, VSMC & monocytes /macrophages			
Function	Control of lipoprotein metabolism, fatty acid oxidation	Not known	Adipocyte differentiation
Target Actions	Treatment of dyslipidemia	Not known	Improves insulin sensitivity
Natural ligands	Docosahexanoic acid	Not known	PG metabolite PGJ,
Synthetic ligand	Fibrates	-	Thiazolidinediones

GLITAZONES

- INHIBITS SMOOTH MUSCLE CELLS (SMC) PROLIFERATION IN PATIENTS WITH INSULIN RESISTANCE
- LIVER CELL INJURY IN 1.9% CASES IN CONTROLLED TRIALS
- SUBFULMINANT LIVER FAILURE
- RETENTION OF FLUID
- ANEMIA

GLITAZONES

- INCREASES INSULIN SENSITIVITY IN SKELETAL MUSLCE, HEPATIC AND ADIPOSE TISSUE
- DECREASES ENDOGENOUS INSULIN CONCENTRATION
- DECREASES EXOGENOUS INSULIN REQUIREMENTS
- INDUCES CYTOCHROME p 450 ISOENZYME 3 A 4

Characteristics of Oral Antidiabetic Agents

Efficacy	Insulin secretagogues	Metformin	α-Glucosidase inhibitors	Insulin	TZDs
Effect on FPG / HbA1C	↓	↓	↓	↓	↓
Effect on Plasma insulin	↑	↓	-	↑	↓
Effect on insulin resistance	-	↓/-	-	-	↓
Effect on β-cell function	-	-	-	-	↑
Safety and tolerability					
Risk of hypoglycaemia	✓	-	-	✓	-
Weight gain	✓	-	-	✓	✓
Gastrointestinal side-effects	-	✓	✓	-	-
Lactic acidosis	-	✓	-	-	-
Oedema	-	-	-	-	✓

Effiacy : ↓ = reduced levels; ↑ = increased levels; - = no documented change. Safety and tolerability : ✓ = treat-related adverse event; - no documented association with treatment. FPG = fasting plasma glucose. TZDs = thiazolidinedions.

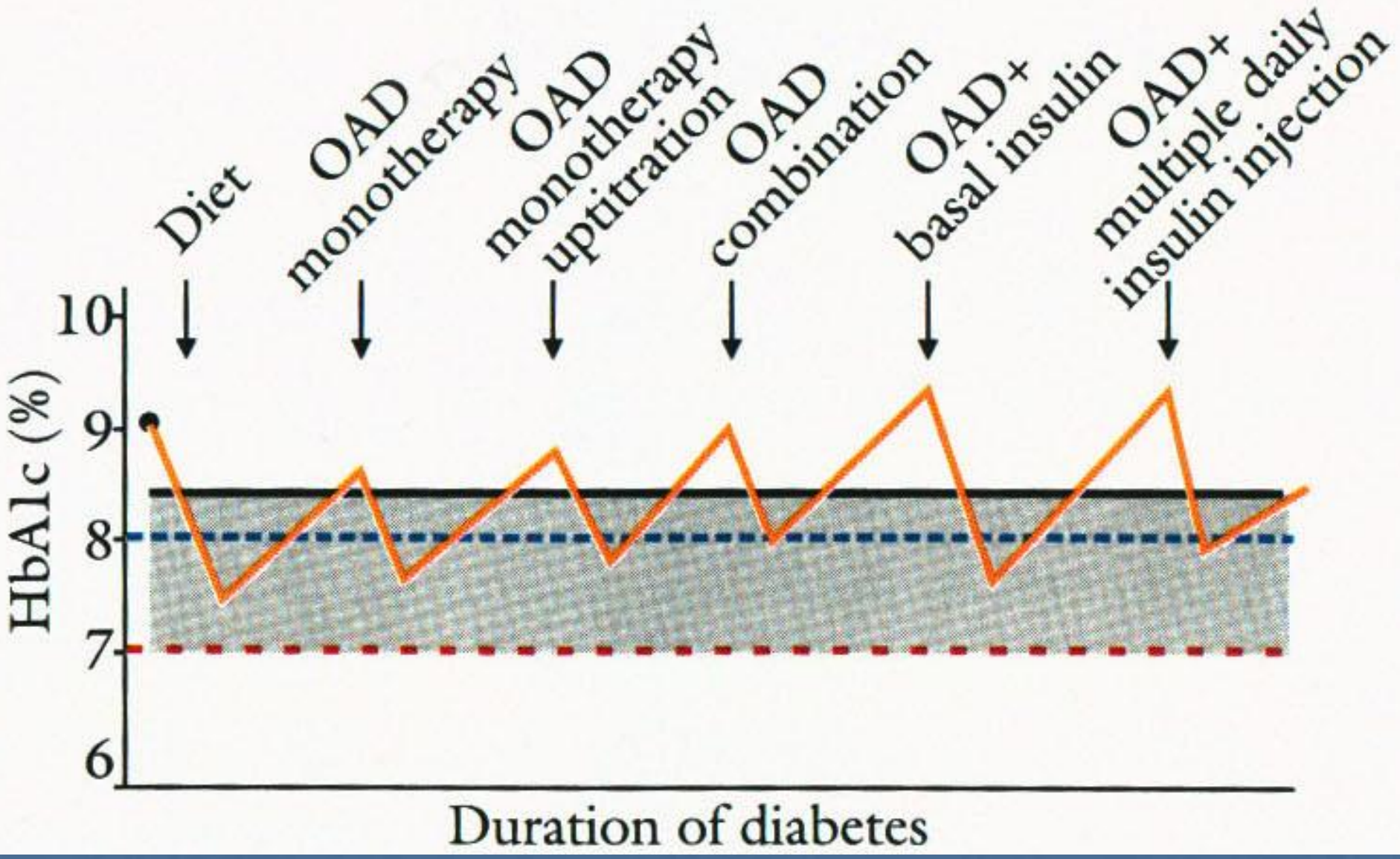
TYPE 2 DIABETES MELLITUS
SECONDARY FAILURE

- Secondary failure rate 5% to 10% a year (UKPDS 7% a year)
  - Decreasing β-cell function
  - Obesity
  - Non-adherence to treatment
  - Lack of exercise
  - Intercurrent illness

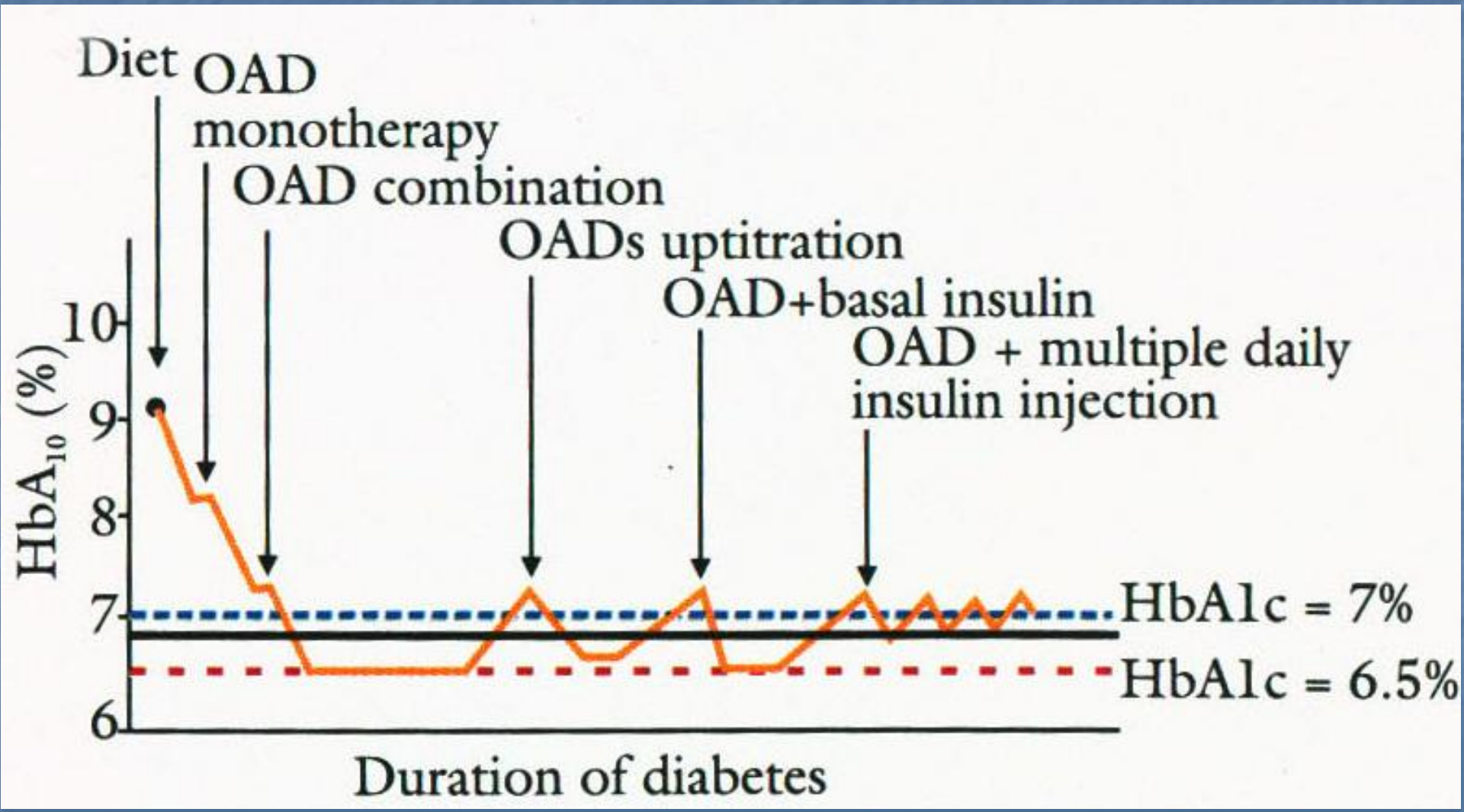
PROBALITY OF REQUIRING POLYTHERAPY

- Young age at diagnosis
- Increased base line Obesity
- Increased base line Glycemia
- Increased baseline Triglycerides

TRADITIONAL STEPWISE APPROACH



EARLY COMBINATION APPROACH. OAD, ORAL ANTIDIABETIC DRUG



ADVANTAGES OF FIXED DOSE COMBINATIONS

- Improved compliance
- Synergism
- Enhanced efficacy
- Reduction of side effects
- Economy

DR. ELLIOT JOSLIN

GOALS OF THERAPY
FOR THOSE WITH DIABETES MELLITUS

SHOULD INCLUDE A SERIOUS EFFORT

TO

ACHIEVE BLOOD GLUCOSE LEVELS

AS CLOSE TO NORMAL AS POSSIBLE

CONFIRMED BY

DCCT

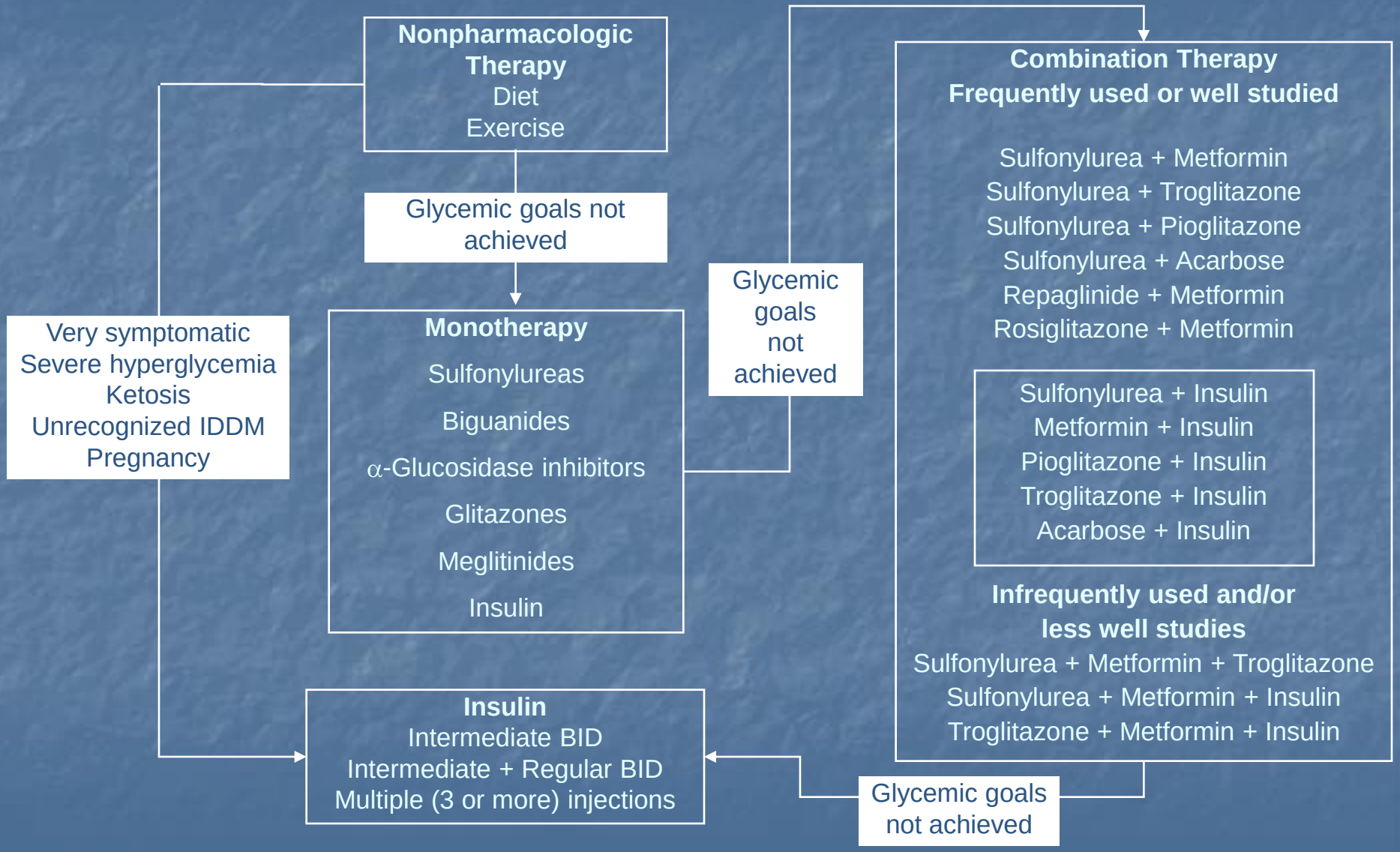
UK PDS

KUOMOTO TRIAL

IDEAL O.H.A.

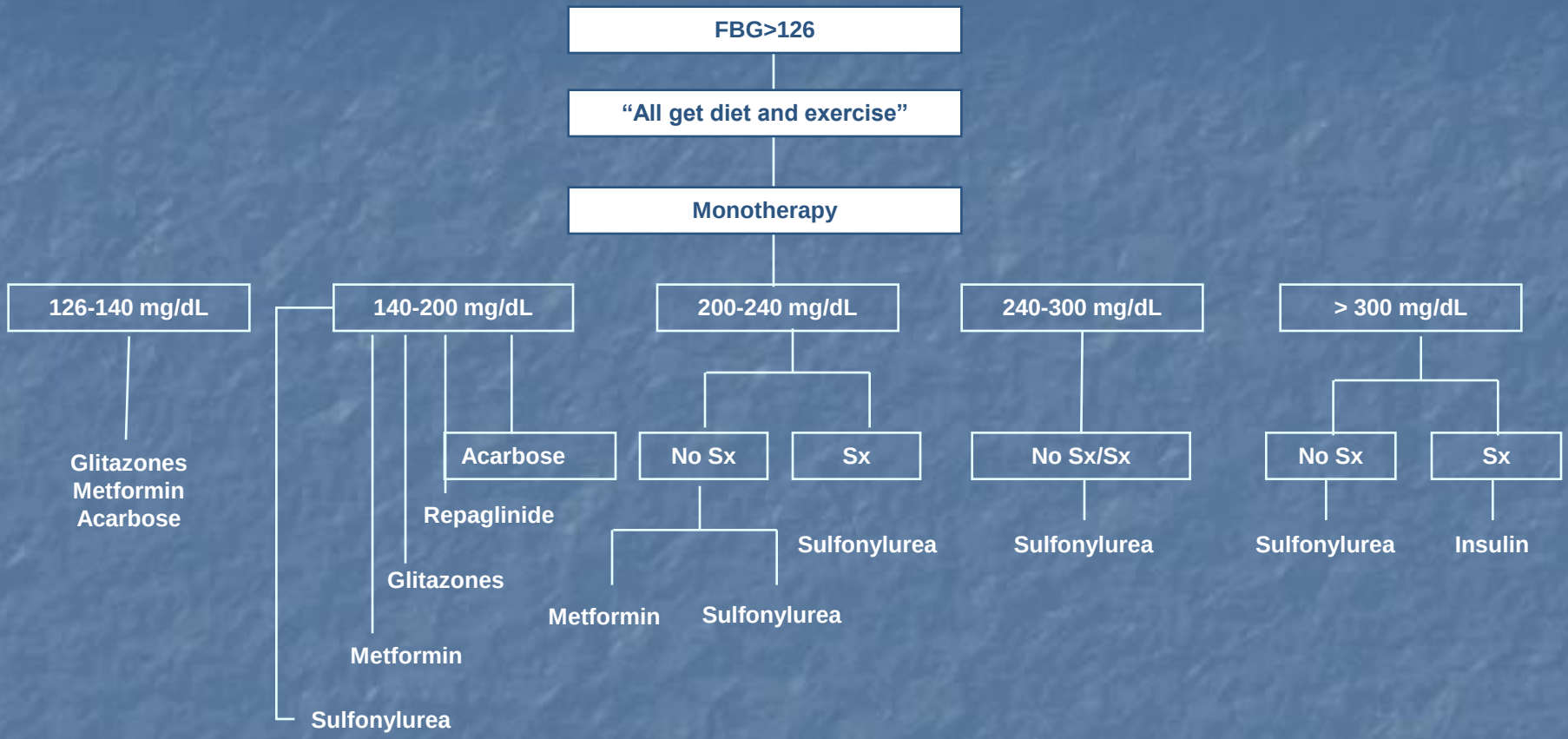
- Combination Efficacy, Safety, Tolerability.
- Metformin
- Thiazolidinediones

ADA "Consensus" on Type 2 Diabetes Therapy



Modified from Zimmerman et al. *Diabetes Care* - 1995.

PRACTICAL MANAGEMENT OF TYPE 2 DIABETES MELLITUS



Oral Combination

- Evolving criteria
  - If FBG>140 mg/dL (126 mg/dL?)
  - HbA_{1c} > 8% (7%?)
    - Add second oral agent and titrate to maximum dose

Triple Therapy

- If no improvement:
  - Try a different sensitizer
  - *Or* try triple therapy?
  - Or Continue oral agent(s) and add insulin Rx at PM or Hs

CONCLUSION

- MONOTHERAPY
- COMBINATION THERAPY

THANK YOU