The Oral Hypoglycaemic Drugs

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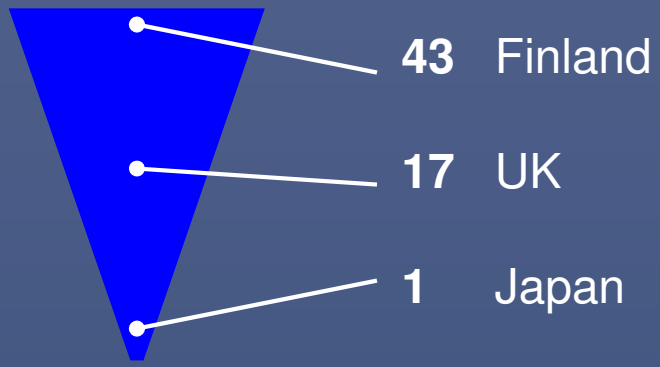
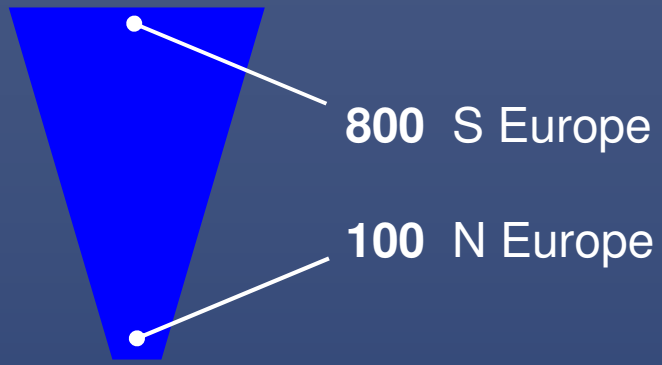
Incidence of Diabetes (/100,000)

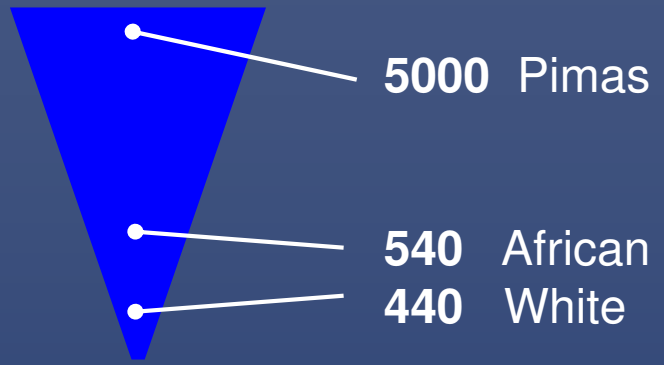
IDDM



NIDDM



Ethnic variation (USA)



Treatment Goals

The goal is to correct the metabolic complications of insulin deficiency:

- **ACUTE** — hyperglycaemia (causing polyuria/thirst)
  ketoacidosis

- **CHRONIC**
  - ↗ macro vascular — atherosclerotic e.g. stroke/AMI
  - ↘ micro vascular — nephropathy
    retinopathy
    neuropathy

NB Progression of CHRONIC complications are directly related to the degree of hyperglycaemia - long-term efficacy of tight glycaemic control demonstrated by UKPDS (type 2) and DCCT (type 1) trials.

Classification of Hypoglycaemic drugs

A] Agents that promote insulin release (Secretogogues)

1. Sulfonylureas:

   1st Generation:

   - Tolbutamide, tolazamide, acetohexamide, chlorpropamide

   2nd Generation:

   - Glyburide, glipizide, glimepiride, glibenclamide,gliclazide

2. Meglitinides:

   - Repaglinide, nateglimide

3. The Incretin Analogues:

   - Exenatide

4. Dipeptidyl Peptidase – IV Inhibitors:

   - Sitagliptin

Classification of Hypoglycaemic drugs

B] Drugs that alter insulin action

1. Biguanides:
   - Metformin
2. Thiazolidinediones:
   - Rosiglitazone, pioglitazone

C] Drugs affecting the absorption of glucose

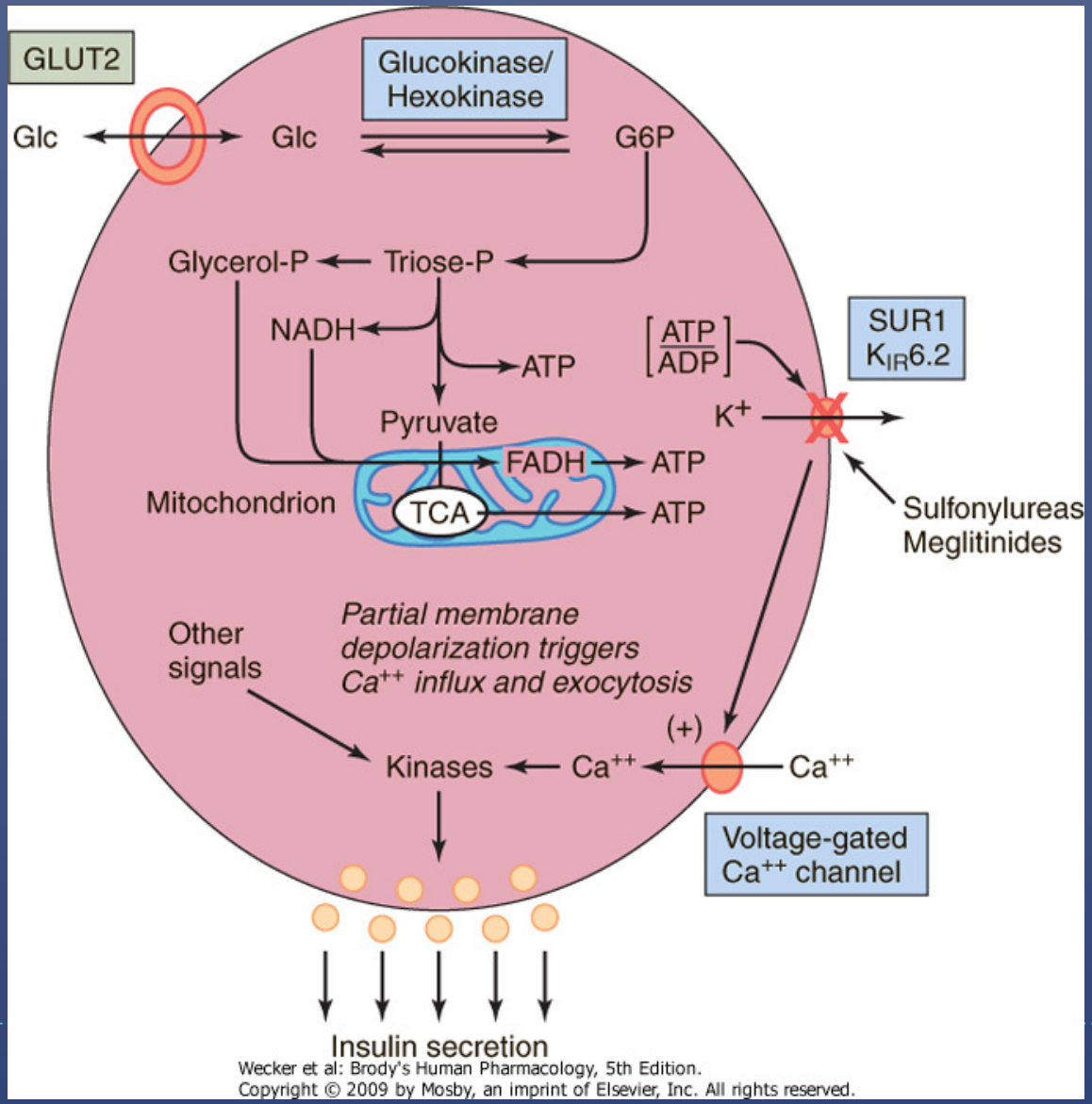
1. α-Glucosidase Inhibitors:
   - Acarbose, miglitol

D] Drugs that compliment the action of insulin

1. Amylin analogues:

   Pramlinide

Stimulation of Insulin secretion



Secretogogues

- MOA:

  Bind to the sulfonylurea subunit (SUR1) of the SUR1 / Kir 6.2 ATD-sensitive K^+ channel → inhibition of channel conductance → Partial depolarization

  → Activation of the voltage-sensitive Ca^{2+} channels

  → ↑ cytosolic Ca^{2+}

  → Exocytosis of secretory granules

  → **INSULIN RELEASE**

1]1st Generation SULFONYLUREAS

- Tolbutamide:
  - 500mg T. D. S. A. C.
  - Duration of effects is 6-12hrs
  - Oxidized in the liver
  - Hypoglycaemia rare
  - Interaction with sulfonamides, phenylbutazone and azole-antifungals

2nd Generation SULFONYLUREAS

- 100+ times more potent than tolbutamide
- Glyburide: 2.5mg / D → 5- 10mg / D mane
- Use with caution in CV disease and the elderly – hypoglycaemia
- Tabs: 1.25mg, 2.5mg and 5mg
- Flushing after alcohol ingestion
- C / I: Hepatic impairment
- Others: Glipizide, gliclazide, glimepiride

2] Meglitinides - Repaglinide

- Rapid absorption, complete metabolism $t_{1/2}$ = 1hr
- Brief but rapid pulse of insulin
- Dose: 0.5- 4mg T.D.S A.C.
- Used in combination with metformin
- S / E: hypoglycaemia, weight gain

3] Incretin Analogues

- Oral glucose → 3- 4x higher insulin response than I.V. glucose
- Oral glucose →release of gut hormones = glucagon-like peptide-1(GLP1) and glucose-dependent insulinotropic peptide-1(GIP1) → amplify the glucose-induced insulin release
- Type 2: GLP1 secretion is impaired

3] Incretin Analogues

- Exenatide: has an amino acid sequence like GLP1 – binds the receptor on the β-cell → increased cAMP + $GLUT_2$ transporters
- Increased glucose uptake + ATP formation

  → closure of the kir 6.2 ATP-sensitive K^+ channel

  → release of insulin from β-cells in the presence of increased glucose
- Combine with metformin and SU's
  - Dose: 100mg O.D.

4] Dipeptidyl Peptidase IV Inhibitors

- Sitagliptin: Inhibits the enzyme DPP-1V which is responsible for the inactivation of endogenous incretin hormones, such as glucagon-like peptide-1 (GLP-1). This results in increased insulin.

  - Oral DPP-IV inhibitors prolong the action of endogenously released GLP1 and GIP1.
  - Effective alone, + metformin or pioglitizone
  - Improves HbA_{1c} 0.5- 1.4%
  - Dose: 100mg O. D.

B] Drugs that alter insulin action

I] Biguanides – metformin

- MOA:
  - ↓ liver gluconeogenesis by activating adenosine monophosphate-activated protein kinase (AMPK) which acts as an intracellular energy sensor
  - $t_{1/2}$ = 1.5- 3hrs; Dose: 500mg T.D.S c.c.
  - Use in obese patients
  - S / E: GIT-N, V, D, abdominal pain

B] Drugs that alter insulin action

2] Thiazolidinediones

- MOA:
  - Bind a nuclear receptor called peroxisome proliferator - activated receptor gamma – PPARγ
  - Affects the expression of a number of genes
  - Regulates the release of the adiposekines – resistin and adiponectin – from adipocytes. Adiponectin sensitizes tissues to the effects of insulin. Resistin secretion is inhibited → ↓ insulin resistance

    Increased glucose transporter expression $GLUT_{1+4}$

B] Drugs that alter insulin action

2] Thiazolidinediones

- Rosiglitazone and Pioglitazone
  - Effective as monotherapy and in combination with SU's, insulin or metformin.

    Can ↓ insulin dose by 30- 50%
  - Can be used in Type-1 with insulin – Insulin resistance
  - S / E: anemia, weight gain, oedema
  - Dose: rosig: 4- 8mg / D; Pioglit: 15- 45mg /D

C] Drugs affecting the absorption of glucose

α-Glucosidase Inhibitors

- MOA:
  - Competitively inhibit the α-glucosidase enzymes in the gut that digest dietary starch and sucrose
- Potent inhibitors of glucoamylase, α-amylase and sucrase – involved in the degradation of complex carbohydrates
- Prevents the generation of monosaccharides

  → blunts the rise in glucose after a meal

C] Drugs affecting the absorption of glucose

1] Acarbose:

- Dose: 50mg B. D. → 100mg T. D. S. c.c.
- Reduces postprandial hyperglycaemia by 30- 50%
- S / E: Flatulence – 30%:, D, no risk of hypoglycaemia

2] Miglitol:

- MOA ≡ Acarbose
- Dose: 25mg T. D. S. →50mg T. D. S.
- S / E: GIT
- Excreted unchanged by the kidney

D] Drugs that compliment the action of insulin

Pramlintide

- A synthetic analogue of islet amyloid polypeptide (IAPP or amylin)
- Amylin = a peptide hormone synthesized by β-cells that is co-secreted with insulin in response to increased blood glucose
- Pramlintide delays gastric emptying , suppresses glucagon secretion and decreases appetite
- It inhibits glucagon secretion from pancreatic α-cells and increases hepatic insulin sensitivity by increasing glucose use and reducing gluconeogenesis
- Decreases HbA_{1c} and total cholestrol
- Adjunctive treatment for both type 1 and 2
- Admin: Subcut, immediately prior to meals-Decrease ins by 50%(rapid& Short) to avoid severe hypoglycaemia

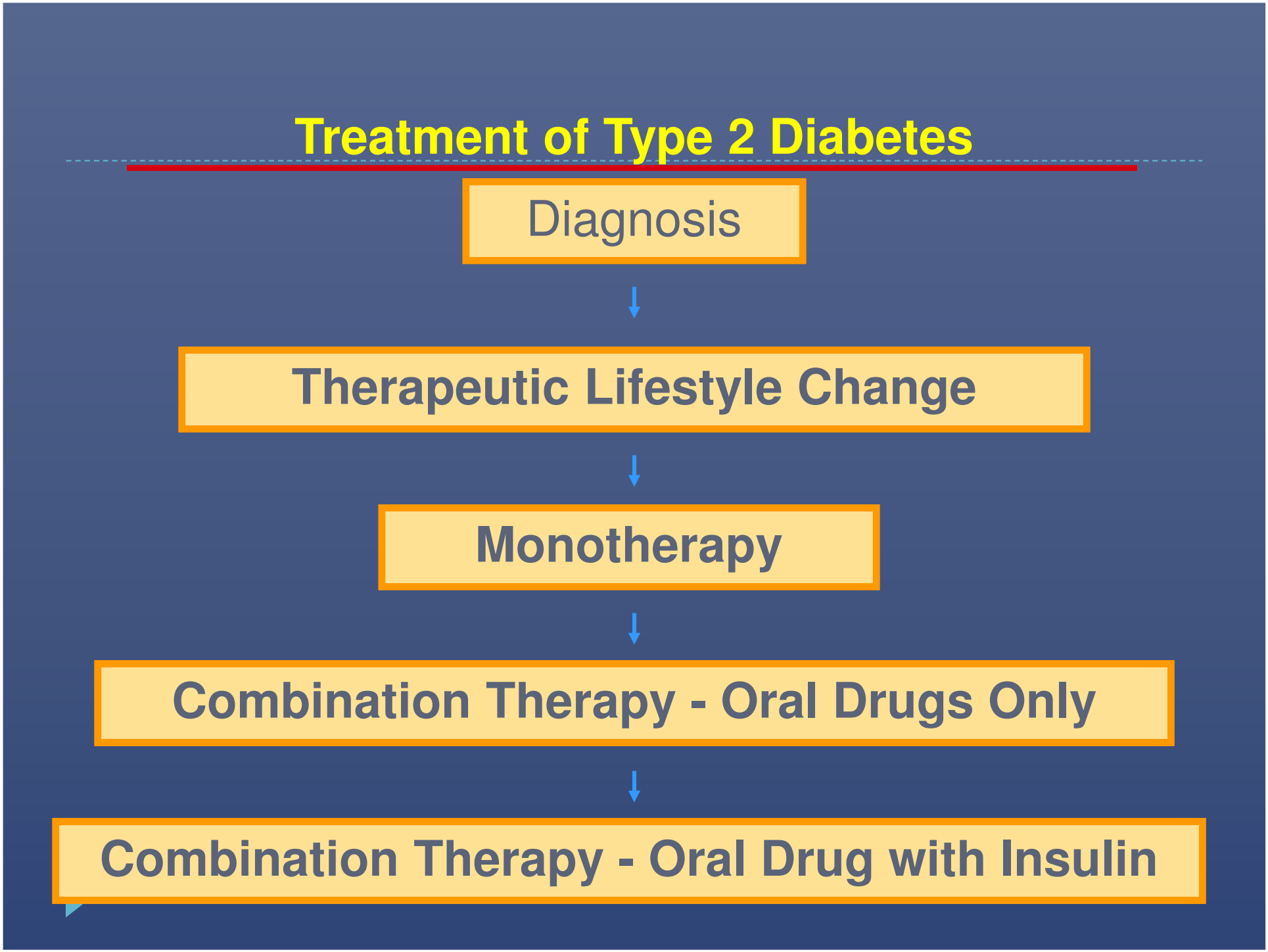
Efficacy of Monotherapy with Oral Diabetes Agents

Drug	Fasting Plasma Glucose Reduction (mmol/l)	A1C Reduction (%)
Thiazolidinedione	**1.9-2.2**	**0.5-1.0**
Sulfonylurea	**3.3-3.9**	**1.0-2.0**
Biguanide	**3.3-3.9**	**1.0-2.0**
Meglitinide	**3.3-3.9**	**1.0-2.0**
Alpha-glucosidase inhibitor	**1.4-1.7**	**0.5-1.0**

DeFronzo *Annals of Internal Medicine* 1999;131:281-303

Nathan *N Engl J Med* 2002; 347:1342-1349

Treatment of Type 2 Diabetes



Combination Therapy for Type 2 Diabetes

Fixed Combination Pills

Sulfonylurea + Biguanide

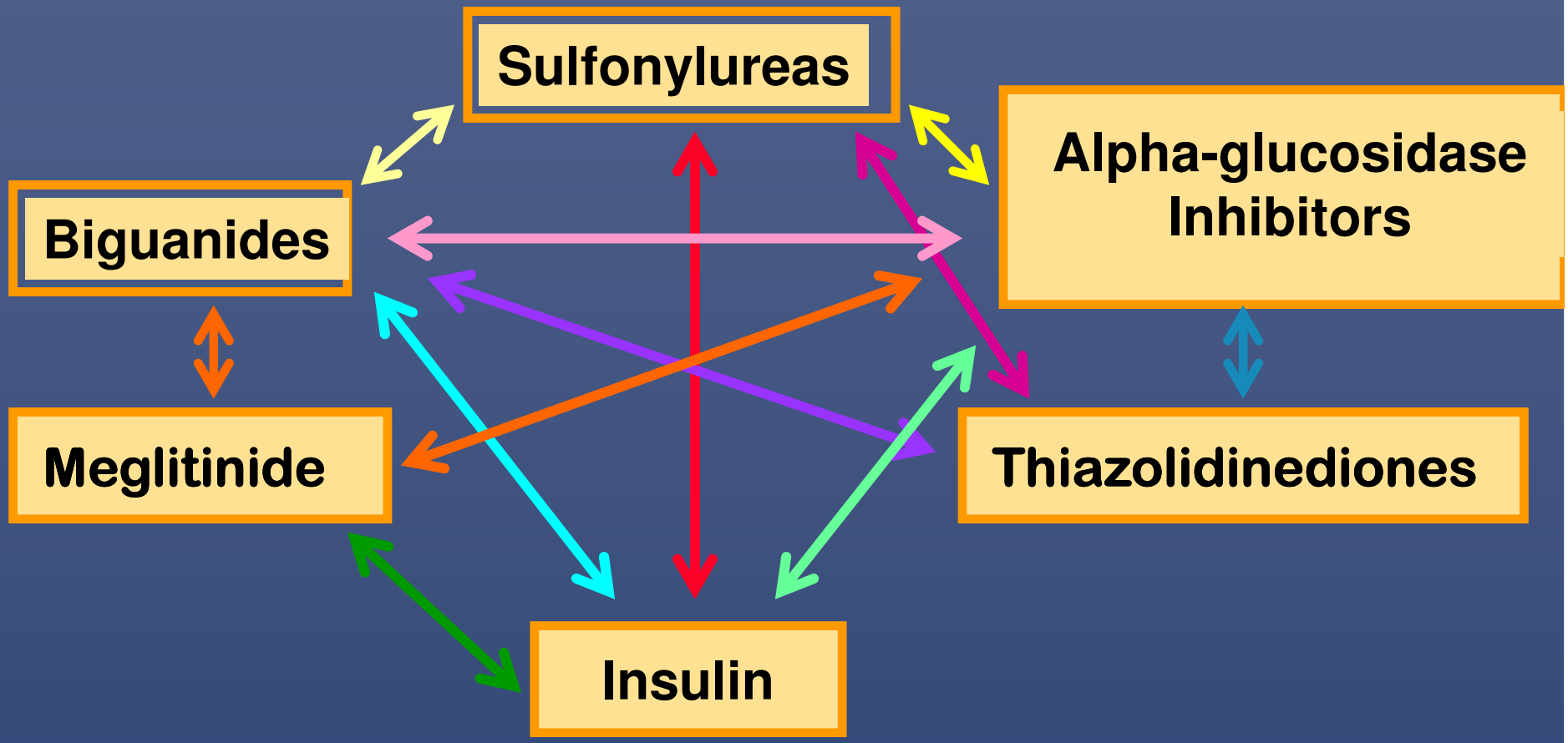
Glybenclamide + Metformin - *Glucovance*

Glipizide + Metformin - *Metaglip*

Thiazolidinedione + Biguanide

Rosiglitazone + Metformin - *Avandamet*

Combination Therapy for Type 2 Diabetes



Major Therapeutic Trials 1

UKPDS (UK Prospective Diabetes Study) 1977-1997

- 5102 newly diagnosed Type 2 patients from 23 centres
- Median follow up of 11 years
- Randomised to diet or Rx (INS, SU or MF)
- All Rx showed similar efficacy over diet
- Good glycaemic control reduced risk of microvasculopathy
- Approx 35% reduction for each 1% fall in HbA1c
- Macrovascular disease risk not affected *
- β function deteriorated steadily during the study regardless of Rx

* Only reduced by anti-hypertensive Rx in a sub study where the impact of aggressive BP control mirrored HOT trial.

Control Targets in Diabetes

- **Tight glycaemic control should be the goal whenever possible**

e.g. ADA targets: HbA1c <7% and fasting BG 4.4-6.7 mmol/l

- **Are there risks of tight glycaemic control ?**

YES (hypoglycaemia) → elderly – AMI, stroke, syncope

YES (hypoglycaemia) → young (<7) – impaired brain development ?

- **What about other cardiovascular risk factors ?**

Cardiovascular risk factors act synergistically ∴

- Tight control of BP (<140/85) and cholesterol (TC <5)
- Stop smoking
- Aspirin for high-risk patients?

BP control in Diabetics: BHS guidelines

Type I

- prevalence of HT similar to non-DM until nephropathy develops (microalbuminuria or proteinuria)
- ACE-inhibitors 1st-line antihypertensives: reduce rate of decline renal function and progression microalbuminuria → proteinuria
- Target BP <140/80 (<125/75 if proteinuria present)
- ACE-I useful in normotensives?

Type 2

- High prevalence (>70% have BP >140/90)
- No antihypertensive class favoured: >=2 agents often needed to reach target of 140/80

Clinic Checklists

- Glycaemic control- home monitoring, HbA1c, inj site, hypoglycaemia
- Diet, exercise, Smoking, alcohol
- BP
- Weight
- Macrovascular- CVA, IHD
- Microvascular- Retinopathy, microalbuminuria, neuropathy
- Foot Care
- Lipid profile, renal function, TSH

Special circumstances

- Intercurrent illness
- Peri-operative period
- Pregnancy
- Childhood and adolescents
- Others- travelling across time zones

  Exercise

  Alcohol

  Driving

Thank you!!!