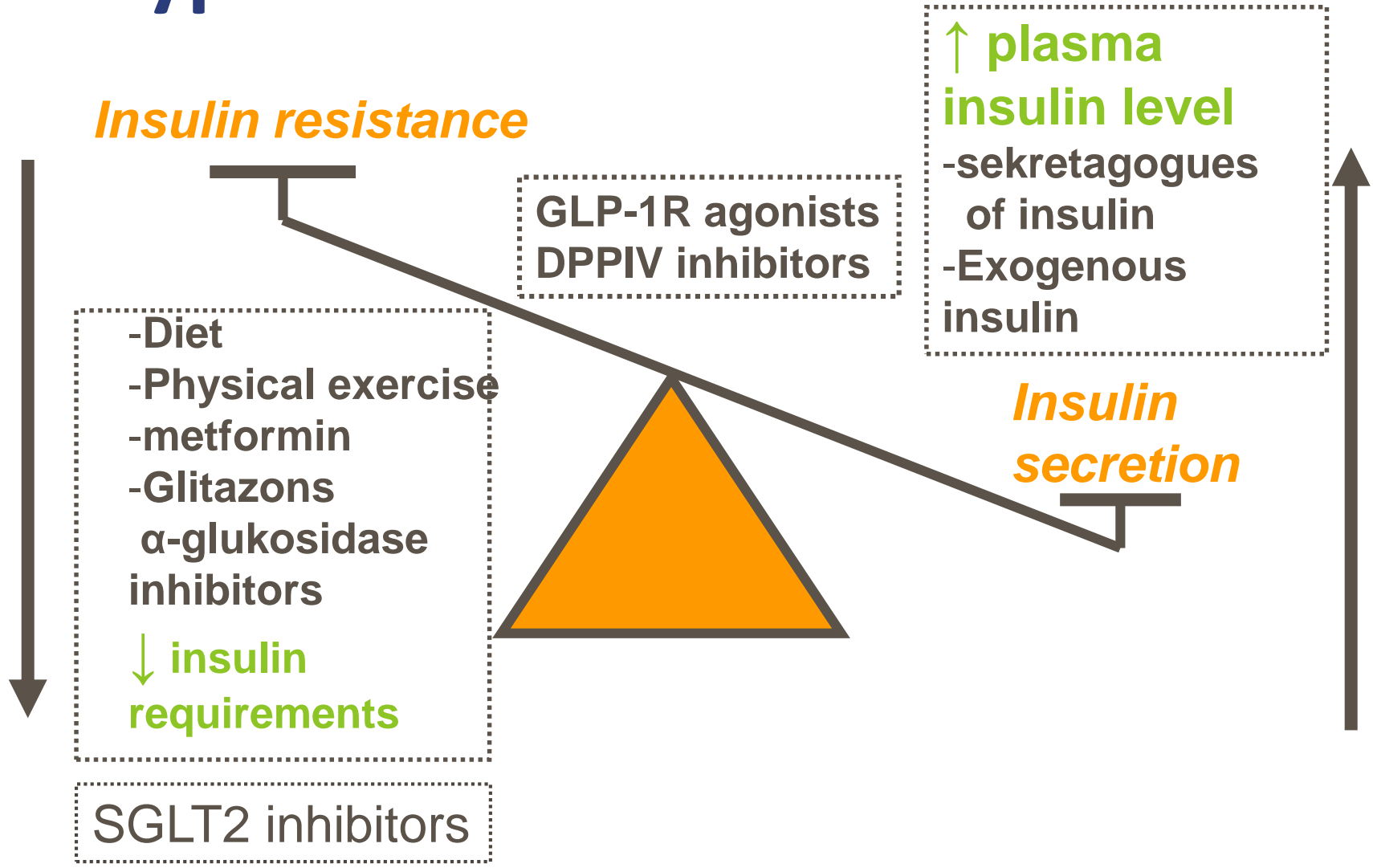


Treatment of Type 2 diabetes mellitus Oral antidiabetics



Pavλίna Piťhová

Type 2 diabetes treatment





Metformin

- Used over 50 years
- activates enzyme adenosinmonofosfate(AMP)-
proteinkinase
- **Key regulator of glucose and lipid metabolism**
- Responsible for cell sensitivity for insulin action
- Enhances activity of glucose **transporters** GLUT 4
and GLUT-1
- Normalizes activity of enzymatic pathway in insulin
signalling
- Result of this action: decreasing of hepatic glucose
production and increasing of glucose disposal in
muscles



Side metformin actions

- Protective influence on **β – cells** (oxidative stress reduction, increases survival rate of β – cells)
- Decreases levels of **PAI-1** 43 – 100% \rightarrow \downarrow risk of thrombotic complication in insulinresistant patients
- **Direct protective effect against damage of endothelial cells** caused by chronic high glucose level \rightarrow reduction in cardiovascular complication rate
- \downarrow **free oxygen radicals formation**
- \downarrow vWf, \downarrow E-selektin, \downarrow tPA = improvement in endothelial function



Next metformin action

- ↓ **TG** (30%), **total cholesterol** and **LDLchol** (
- ↓ **C – reactive protein level**
- **Doesn't cause weigh gain**
- ↓ **IR** = ↓ plasma insulin level
- Absence of low glucose levels = reduction of „extra snacks“ (very often of sweet taste) = reduction of energy intake
- **EBM – reduction of cardiovascular complication in diabetic patients (UKPDS 36% lower mortality and morbidity)**



Metformin contra-indication

Risk of lactic acidosis

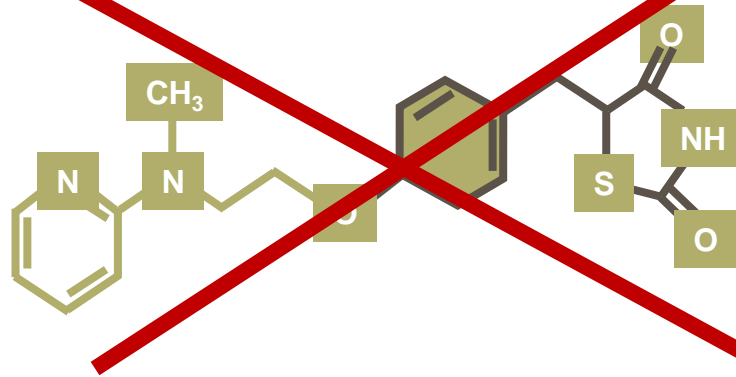
- Limited liver function
- **Limited kidney function**
 - **GF < 1.0ml/s not start new therapy + in treatment 1/2 dose reduction**
 - **GF < 0.5 ml/s EX – not used**
- Respiratory and heart failure
- Alcohol abus^{us}



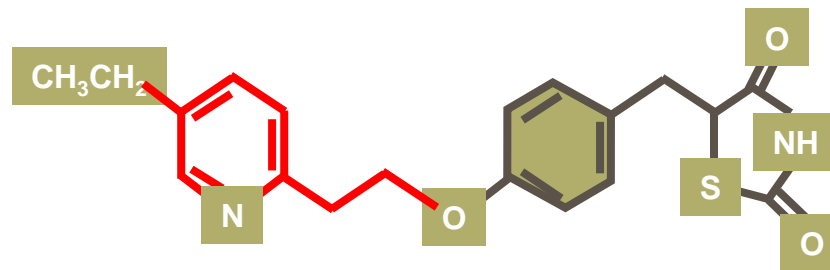
Metformin – drugs and dosage

- 500 – 850– 1000mg 3x daily
- GLUCOPHAGE (tbl, XR tbl, eff)
- SIOFOR
- METFIREX
- STADAMET
- Metformin GAL, AL, TEVA...

Thiazolidindions - glitazones



rosiglitazon



pioglitazon

1. ciglitazon 1982 – derivát klofibrátu
2. troglitazon (Rezulin®) – antidiabetikum 1996 uveden na trh v USA a 1997 ve VB
3. rosiglitazon a pioglitazon – 2000
4. netoglitazon



Benefits x risk of glitazons treatment

Benefits:

- Better metabolic control
- ↓insulin rezistance
- ↓visceral adipose tissue (redistribution)
- ↓blood pressure
- improving β -cell function
- Improving endotelial function
- ↓fat deposits in liver (NASH)

Risk:

- Hepatotoxicity
- Weight gain/ ↑ body adipose tissue/
↑subcutaneous adipose tissue
- Fluid retention/edema
- Pulmonary edema
- Risk of heart failure
- Risk of ischemic vascular attacks????



Pioglitazon (ACTOS), 15 – 45mg 1x daily

Contra-indications:

- **Hypersensitivity**
- **Heart failure** present or in history (NYHA III – IV)
- Restricted liver function
- Pregnancy and breast feeding
- Glitazons are not to use in combination therapy with insulin
- Be careful in vascular patients



Acarbose

- pseudotetrasacharide, doesn't absorb
- **inhibits alfa-glukosidase**
- → glucose absorption is limited and delayed; ↓ **PPG**
1,5-3 mmol/l
- ↓ **FGP**
- ↓ **TG** (↓ syntesis VLDL in hepatocytes) and ↓ **chol**
- ↓ **risk of cardiovascular complication**

- GLUCOBAY – 100mg tbl – 1 - 2 tbl 3x daily



Sulfonylurea - insulin secretagogues

- stimulate insulin secretion
- B-cell function must be efficient



Sulfonylurea – insulin secretagogues

- Glibenclamid – MANINIL, GLUCOBENE (3,5 – 5mg 3x daily), risk of hypoglycemia!!!
- Gliclazid – DIAPREL MR 1 – 4tbl 1 – 2x daily
- Glipizid - MINIDIAB
- Glimepirid – 1 – 4mg 1x(2x) daily – AMARYL, GLYMEXAN
- Gliquidon – GLURENORM 1tbl 3x daily – possible to use in patients with restricted kidney function



Incretin mimetics and incretin „enhancers“

- mimic the normal effect of incretin hormones
- Glucagon like peptid 1

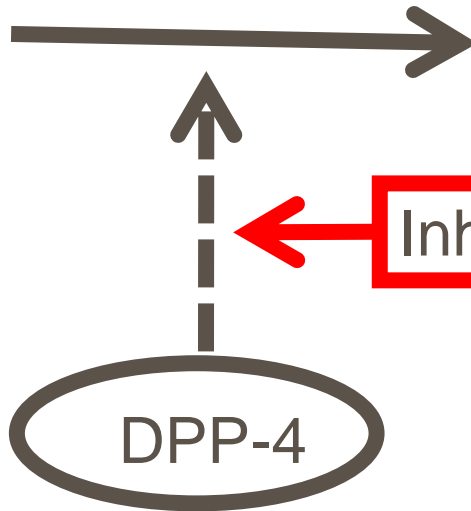
GLP-1 Receptor agonists

GLP - 1

metabolites

Inhibition of DPP-4

DPP-4





Incretins

- GLP-1 receptor agonists
 - exenatid (Byetta – 2x daily 5 – **10**ug)
 - liraglutid (Victoza – 1x daily 0,6 – **1,2** – 1,8mg)
- Inhibitors of dipeptidyl-peptidase IV
 - Sitagliptin (JANUVIA – 100mg 1x daily), combination with metformin JANUMET 50/850, 50/1000mg 2x daily
 - Vildagliptin (GALVUS), with metformin EUCREAS
 - Saxagliptin (ONGLYZA)



Glucuretics

—

glycosuria as
diabetes
treatment?

dapagliflozin
Canagliflozin
empagliflozin



Insulin indications

a/ type 1 diabetes

b/ type 2 diabetes:

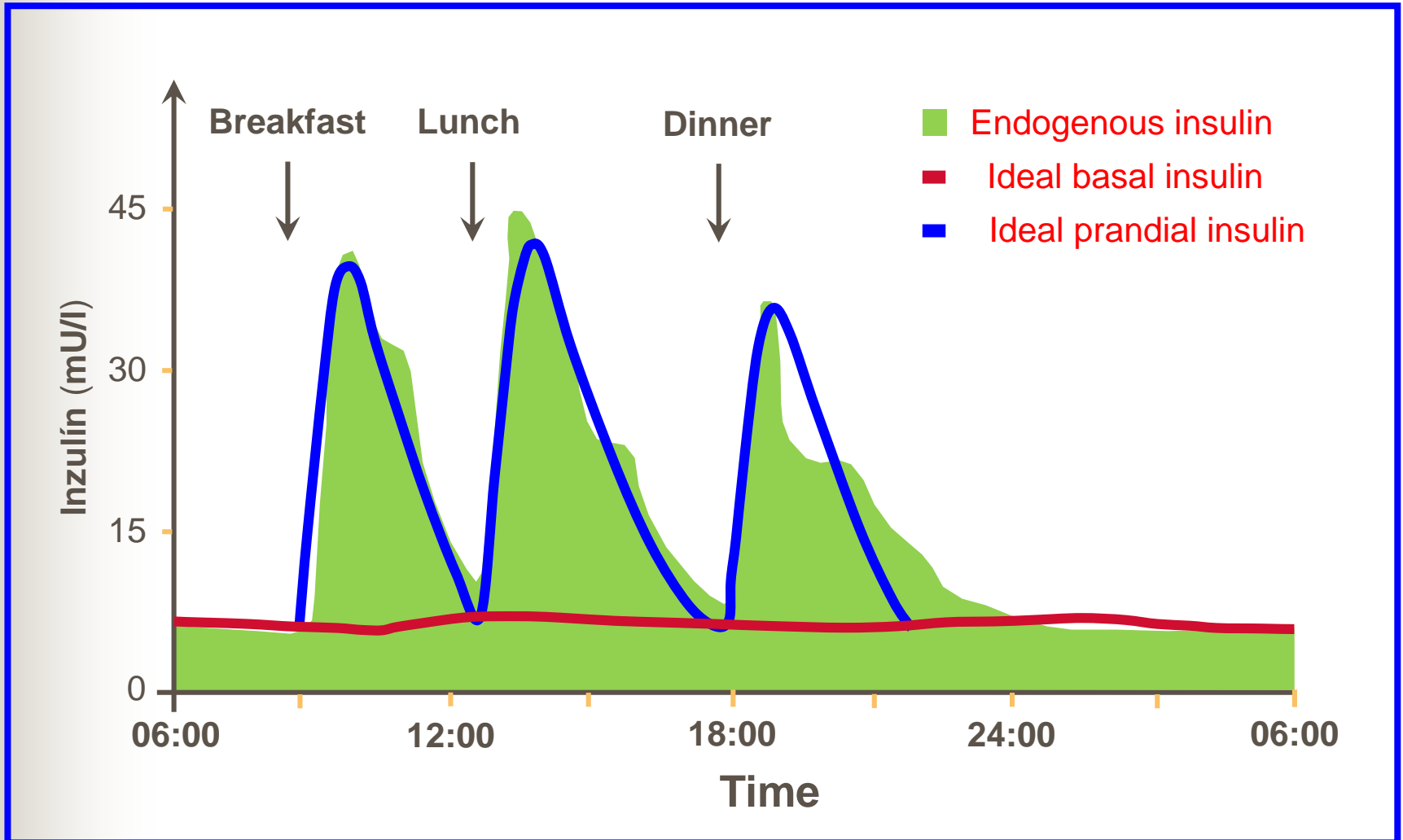
- Oral agent treatment failure
- Allergy
- Acute situation (surgery, injury, infection)
- Pregnancy
- Painful diabetic neuropathy



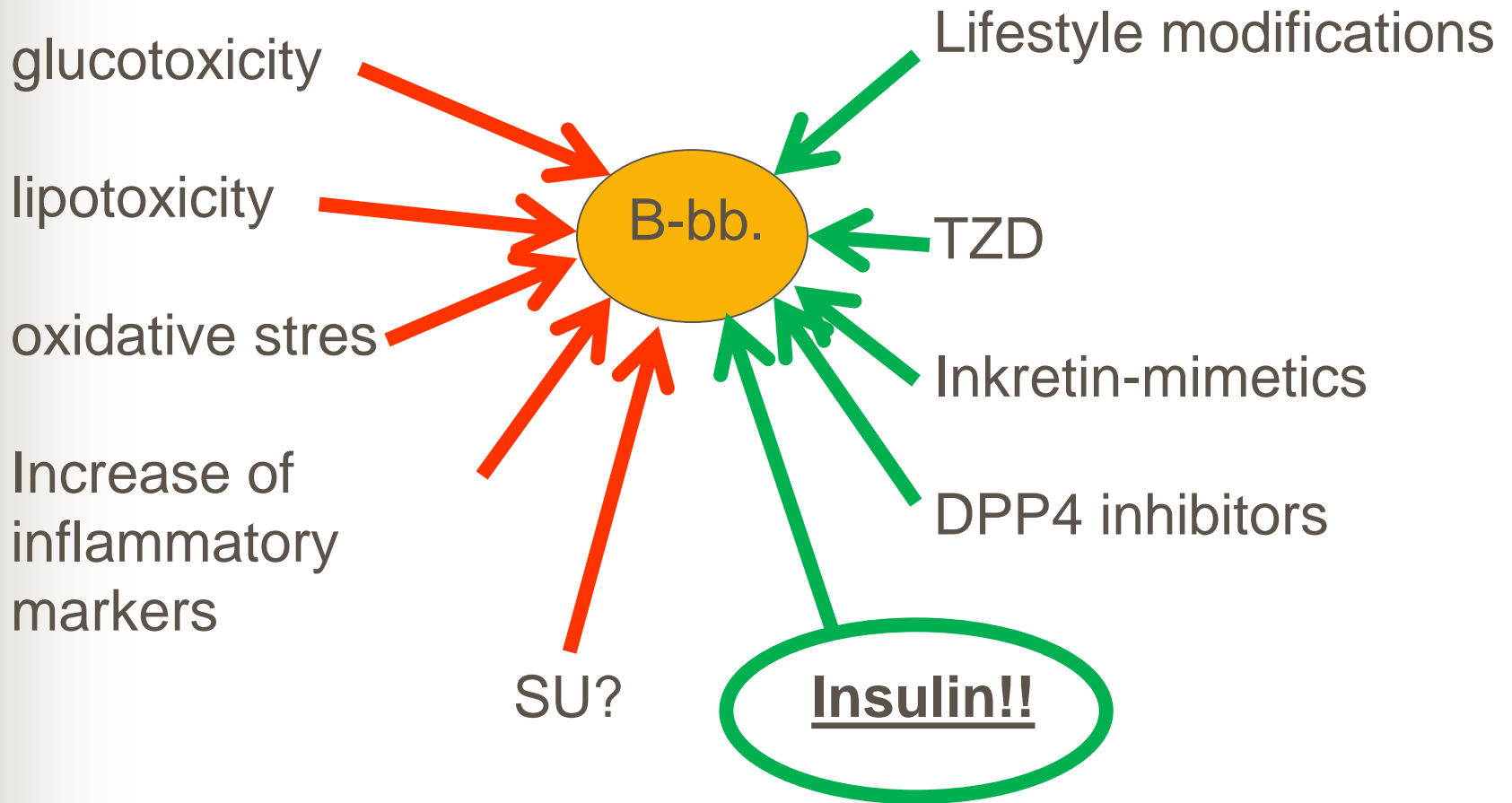
Insulin

- Proteohormon
- contains 51 aminoacids in two chains.
- Produced in pancreatic islets
- $\approx 40\text{U/day}$ - $\frac{1}{2}$ „basal secretion“ – $\frac{1}{2}$ „stimulated secretion“ – after meals

Mimicing the natural insulin secretion...



Injury and protection of B cells



Diagnose

Eraly phase T2DM

Lifestyle changes + metformin

1. stage

in case of metformin intolerance second stage drug

Therapy for 6 month.

Continue

HbA_{1c}<53

HbA_{1c}>53

2. stage

+ inzulin

+ glitazon

+ gliptin

+ GLP-1R agonist

+ gliflozin

+ sulfonylurea

+ glinid

+ akarbóza

Therapy for 6 month.

Continue

HbA_{1c}<53

HbA_{1c}>53

3. stage

Intenified insulin treatment

Combination of drugs

Late phase T2DM

4. stage

Combination therapy – multi-drug including insulin / IIT

HbA_{1c}<60