Pharmacological Management of Diabetes

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Based on the a Position Statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD)

American Diabetes Association.

References:
Diabetes Care 2015;38:140–149
Diabetologia 2015;58:429–442

EASD

OUTLINE OF THE PRESENTATION

1. IMORTANCE OF PATIENT-CENTERED CARE

2. BACKGROUND

- Epidemiology and health care impact
- Relationship and importance of glycemic control to outcomes
- Overview of the pathogenesis of Type 2 diabetes

3. ANTI-HYPERGLYCEMIC THERAPY

- Glycemic targets
- Therapeutic options
  - 3.0. Lifestyle modifications
  - 3.1. Insulin
  - 3.2. Oral agents & non-insulin injectables

Diabetes Care 2012;35:1364–1379; *Diabetologia* 2012;55:1577–1596
Diabetes Care 2015;38:140-149; *Diabetologia* 2015;58:429-442

OUTLINE OF THE PRESENTATION

4. ANTIHYPERGLYCEMIC THERAPY

- Drug combinations, and drug interactions
- Special consideration in case of hypoglycemia, weight gain

5. SPECIAL CONDITIONS/CONSIDERATIONS

- Treatment of ketoacidotic coma
- Treatment of hypoglycemia
- Age, Weight, Sex/racial/ethnic/genetic differences
- Comorbidities *(CAD, HF, CKD, Liver disease, Hypoglycemia-prone)*

6. CLINICAL GUIDE FOR ANTIHYPERGLYCEMIC THERAPY

- Implementation Strategies
  - Initial drug therapy
  - Advancing to dual combination therapy
  - Advancing to triple combination therapy
  - Transitions to and titrations of insulin

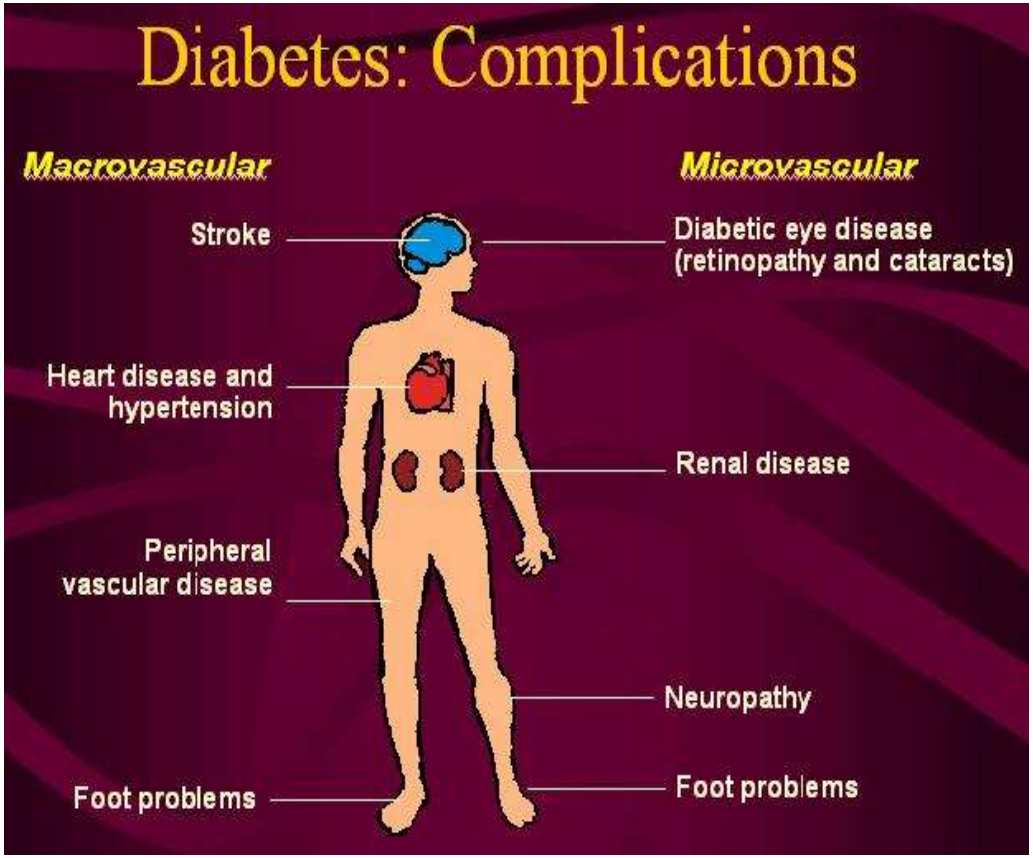
1. Patient-Centered, evidence-based approach

"…providing care that is respectful of and responsive to individual patient preferences, needs, and values - ensuring that patient values guide all clinical decisions."

- **Gauge patient's preferred level of involvement.**
- **Explore, where possible, therapeutic choices. Consider using decision aids.**
- **<u>Shared Decision Making</u> – a collaborative process between patient and clinician, using best available evidence and taking into account the patient's preferences and values**
- **Final decisions regarding lifestyle choices ultimately lie with the patient.**

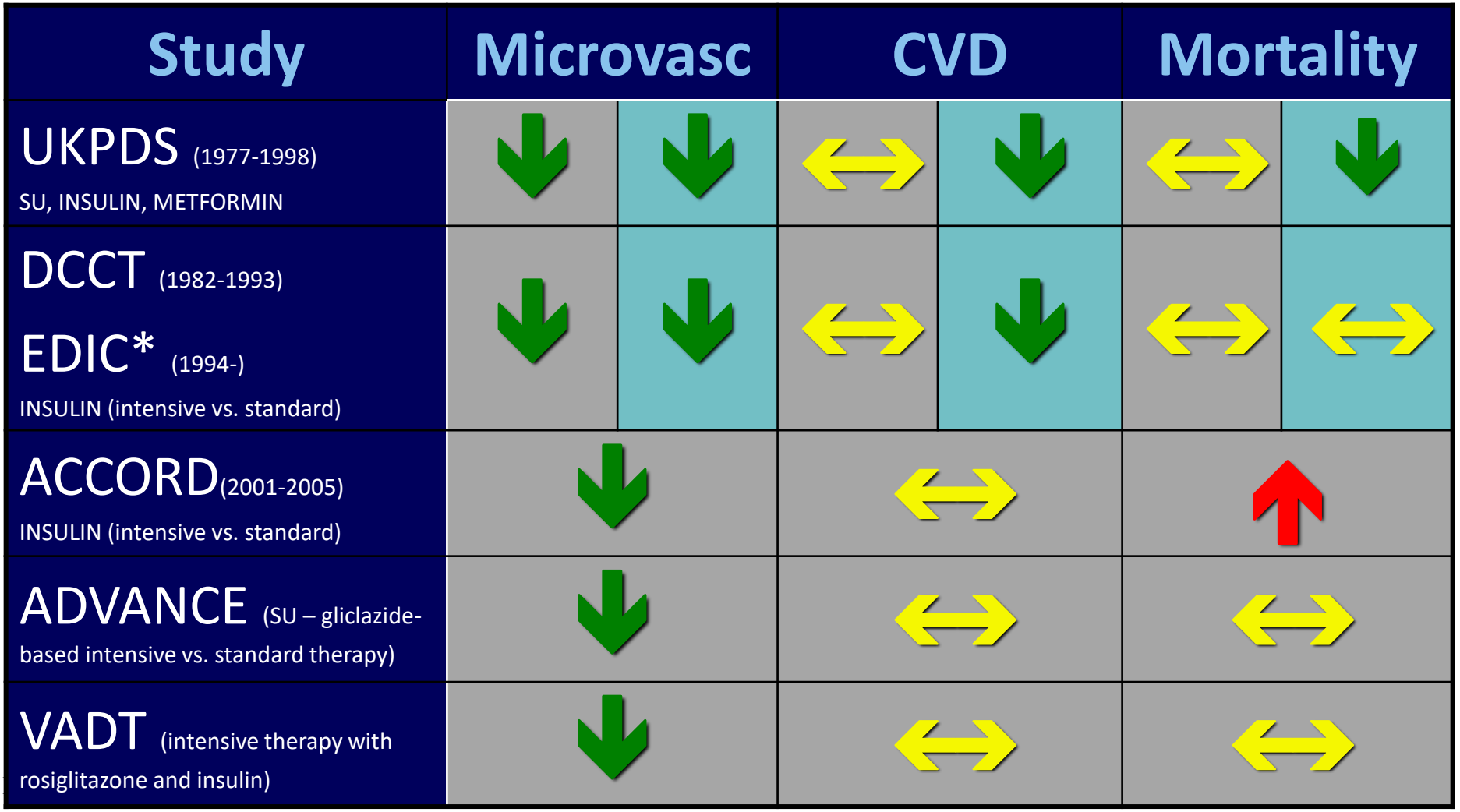
2. BACKGROUND

- About 27% of the population over 65 has diabetes. If this trend is going on by 2050 every third adult will be diabetic (USA data)



- There is a tight relationship of glycemic control to microvascular and macrovascular outcomes.

Impact of Intensive Therapy for Diabetes: Summary of Major Clinical Trials



UK Prospective Diabetes Study (UKPDS) Group. *Lancet* 1998;352:854.
Holman RR et al. *N Engl J Med*. 2008;359:1577. DCCT Research Group. N Engl J Med 1993;329;977.
Nathan DM et al. *N Engl J Med*. 2005;353:2643. Gerstein HC et al. *N Engl J Med.* 2008;358:2545.
Patel A et al. N Engl J Med 2008;358:2560. Duckworth W et al. N Engl J Med 2009;360:129.
Moritz T. *N Engl J Med* 2009;361:1024)

Initial Trial

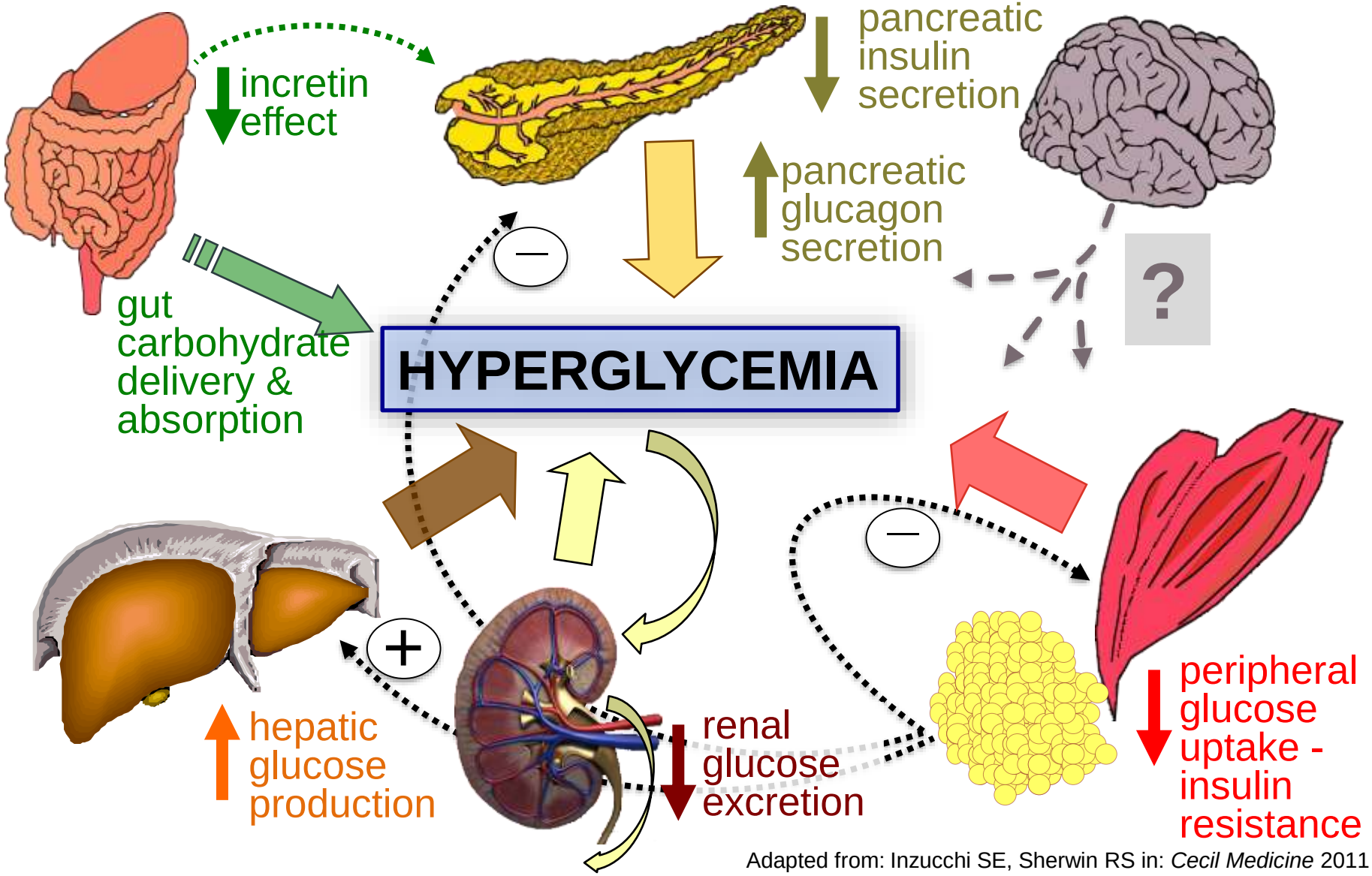
Long Term Follow-up

* in T1DM

2. BACKGROUND

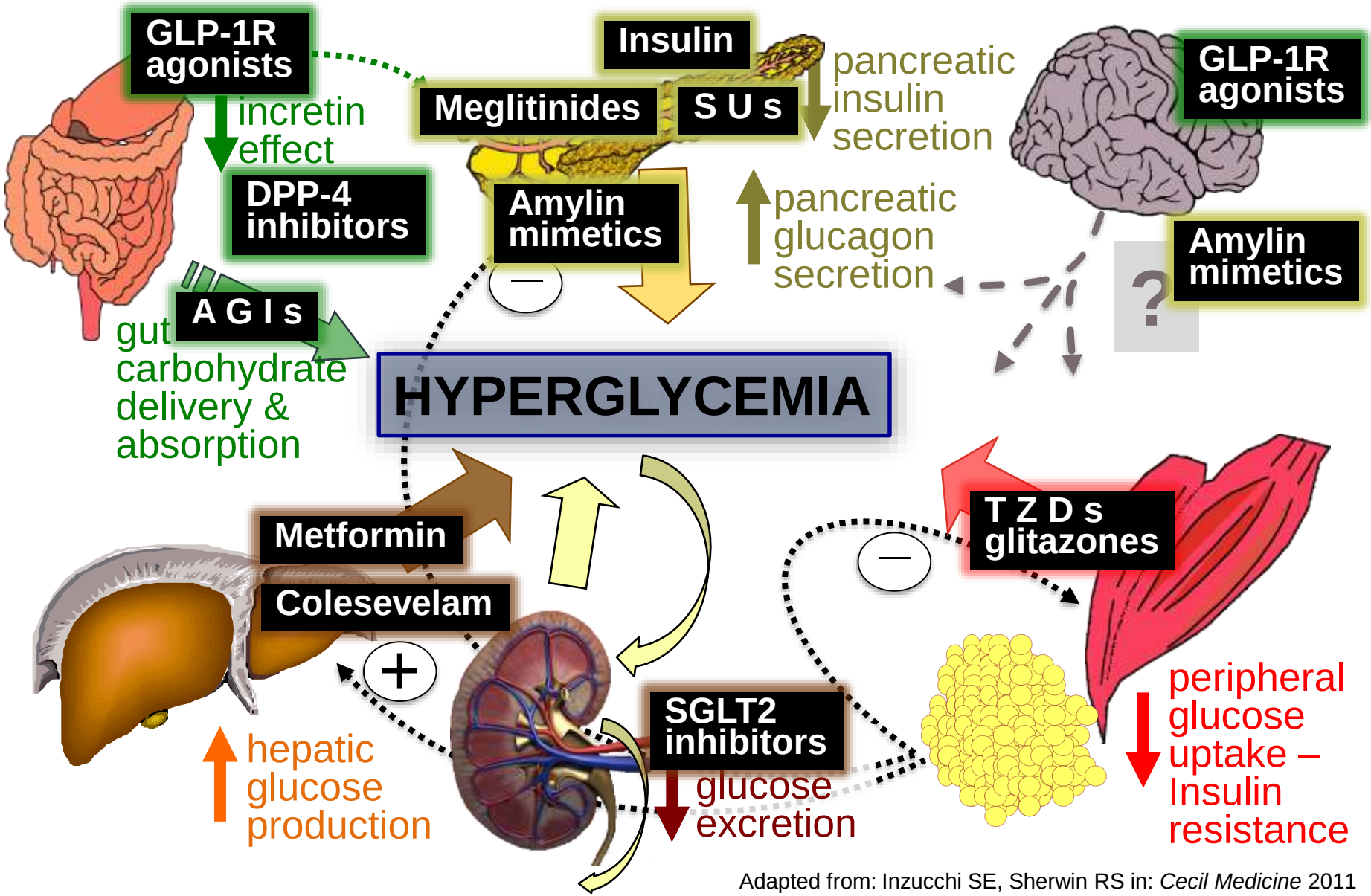
- **Overview of the pathogenesis of T2DM**
  - Insulin secretory dysfunction
  - Insulin resistance (muscle, fat, liver)
  - Increased endogenous glucose production
  - Decreased incretin effect
  - Deranged adipocyte biology
  - …

Multiple, Complex Pathophysiological Abnormalities in T2DM



Adapted from: Inzucchi SE, Sherwin RS in: *Cecil Medicine* 2011

Multiple, Complex Pathophysiological Abnormalities in T2DM



Adapted from: Inzucchi SE, Sherwin RS in: *Cecil Medicine* 2011

3. THERAPEUTIC AIMS OF ANTI-HYPERGLYCEMIC THERAPY

- **To reach glycemic targets**
  - **HbA1c < 7.0%** (mean PG ~150-160 mg/dl [8.3-8.9 mmol/l])
  - Pre-prandial PG <130 mg/dl (7.2 mmol/l)
  - Post-prandial PG <180 mg/dl (10.0 mmol/l)
  - ***Individualization*** is key:
    - Tighter targets (6.0 - 6.5%) - younger, healthier
    - Looser targets (7.5 - 8.0%$^{+}$) - older, comorbidities, hypoglycemia prone, etc.
  - Avoidance of hypoglycemia

PG = plasma glucose

3. ANTI-HYPERGLYCEMIC THERAPY

3.0. Therapeutic options: Lifestyle

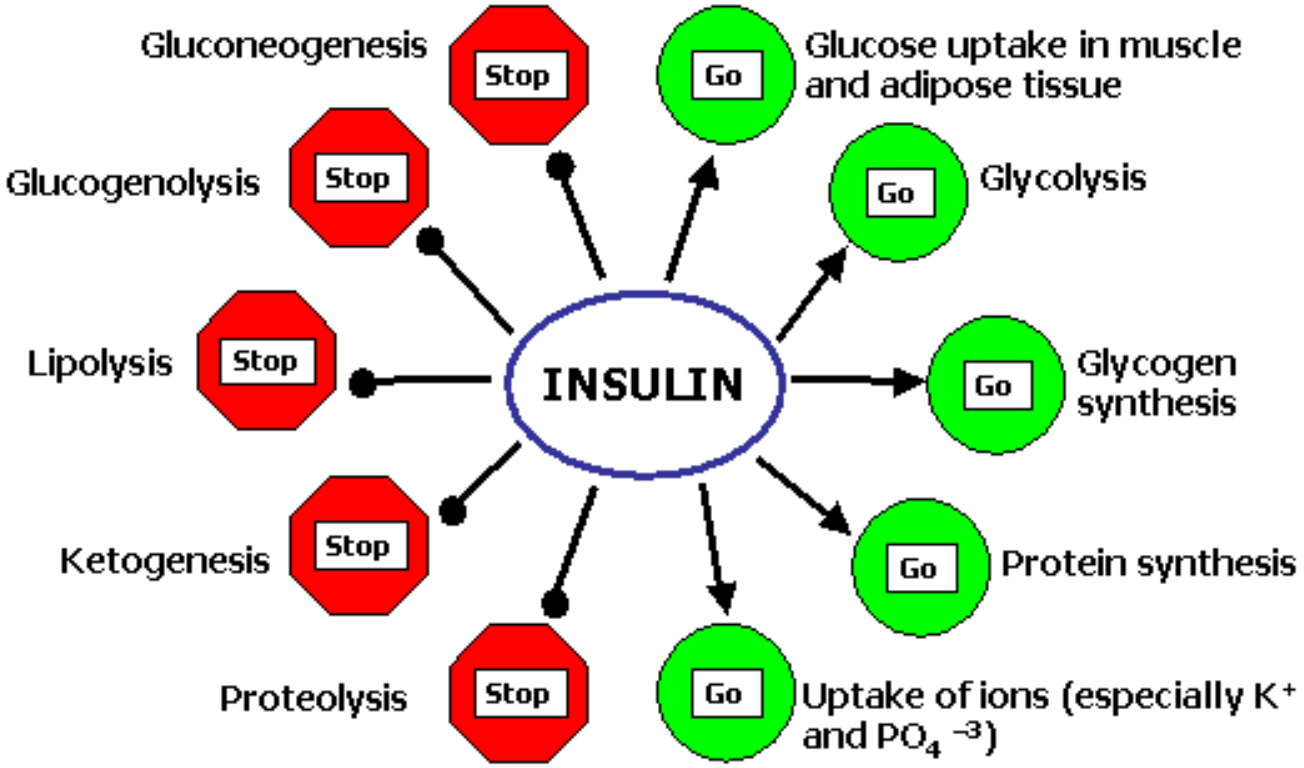
- **Weight optimization**

- **Healthy diet**

- **Increased physical activity level**

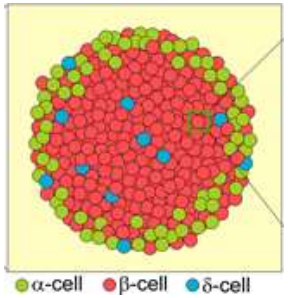
3. ANTI-HYPERGLYCEMIC THERAPY

3.1. Insulin



Modified from Clinical Biochemistry, A. Gaw et al, Churchill Livingstone, Edinburgh, 1995.

3.1. Insulin: Structure of proinsulin



Bovine:
B_{30} alanine
A_8 alanine
A_{10} valine

Connecting peptide
(C-peptide)

NH_2 -

A-chain

B-chain

-COOH

Porcine:
B_{30} alanine

3.1. Insulin: The fate of secreted/administered insulin

half-life in plasma < 9 min

The main sites of degradation

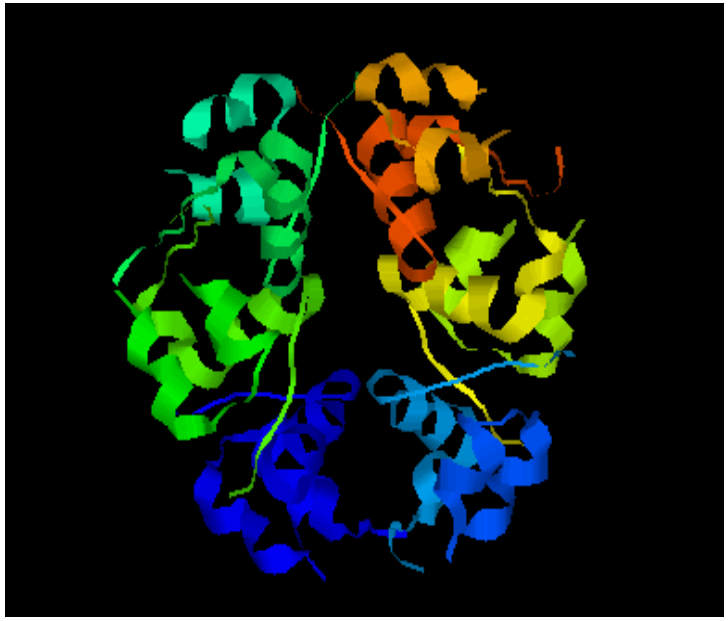
liver - about 50% is destroyed in a single passage without reaching the general circulation

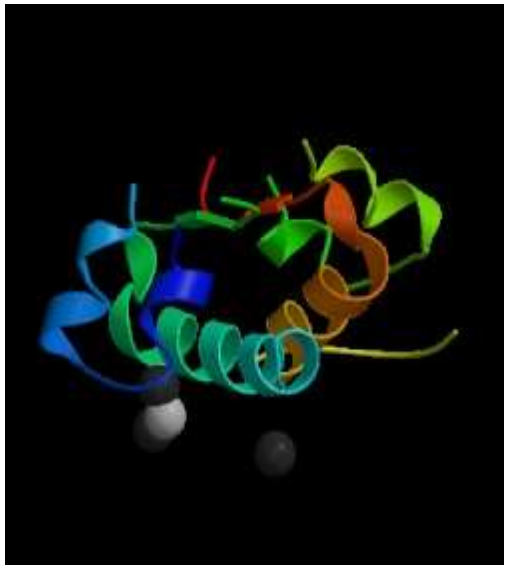
kidney - filtration by glomeruli, reabsorption by tubuli, degradation in the tubuli

muscle - of minor significance

In severe impairment of renal function, or in liver cirrhosis breakdown of insulin decreases – increased risk of hypoglycemia

3.1. Insulin: Hexamer/monomer form of human insulin





in the pancreas

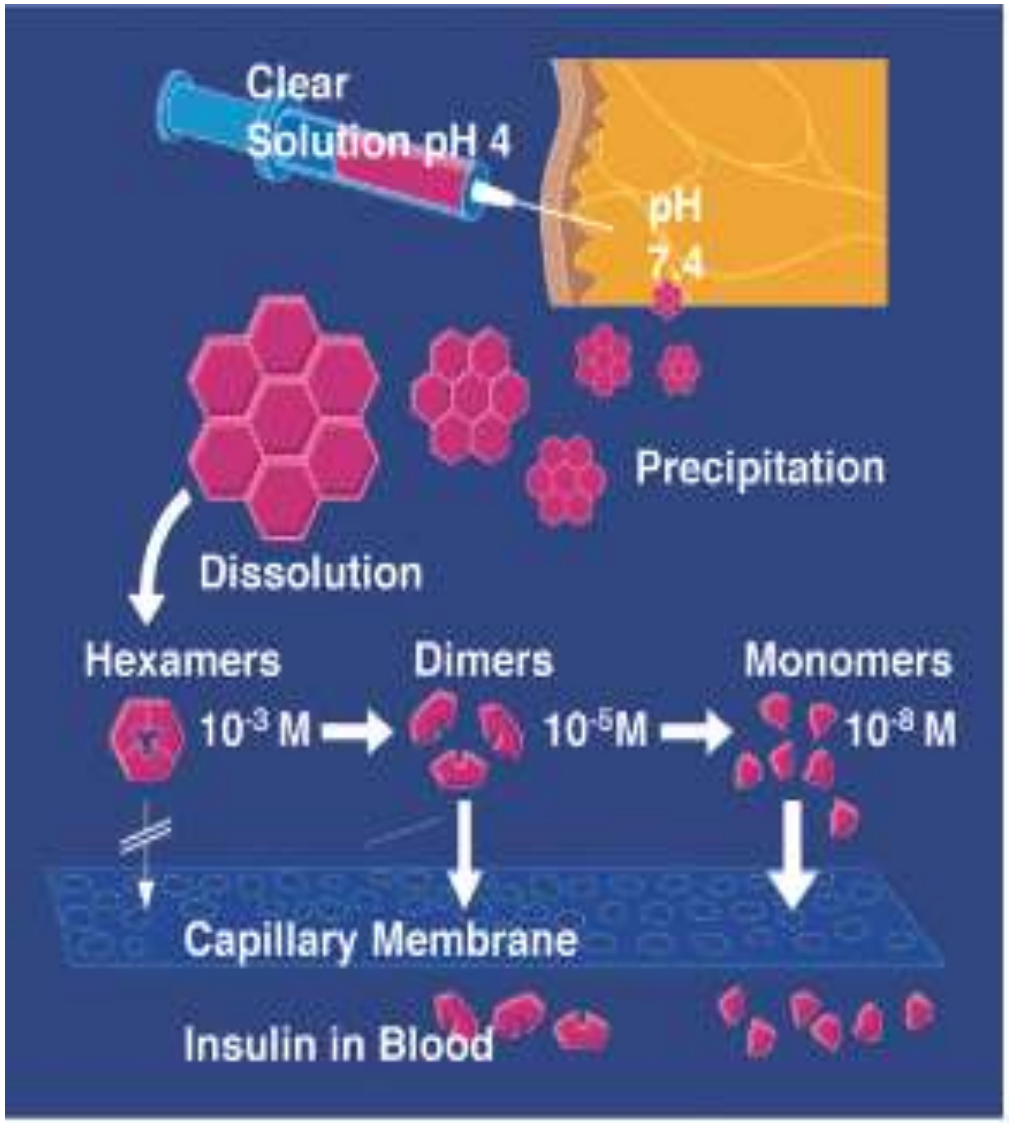
in case of sc. administration

hexamer

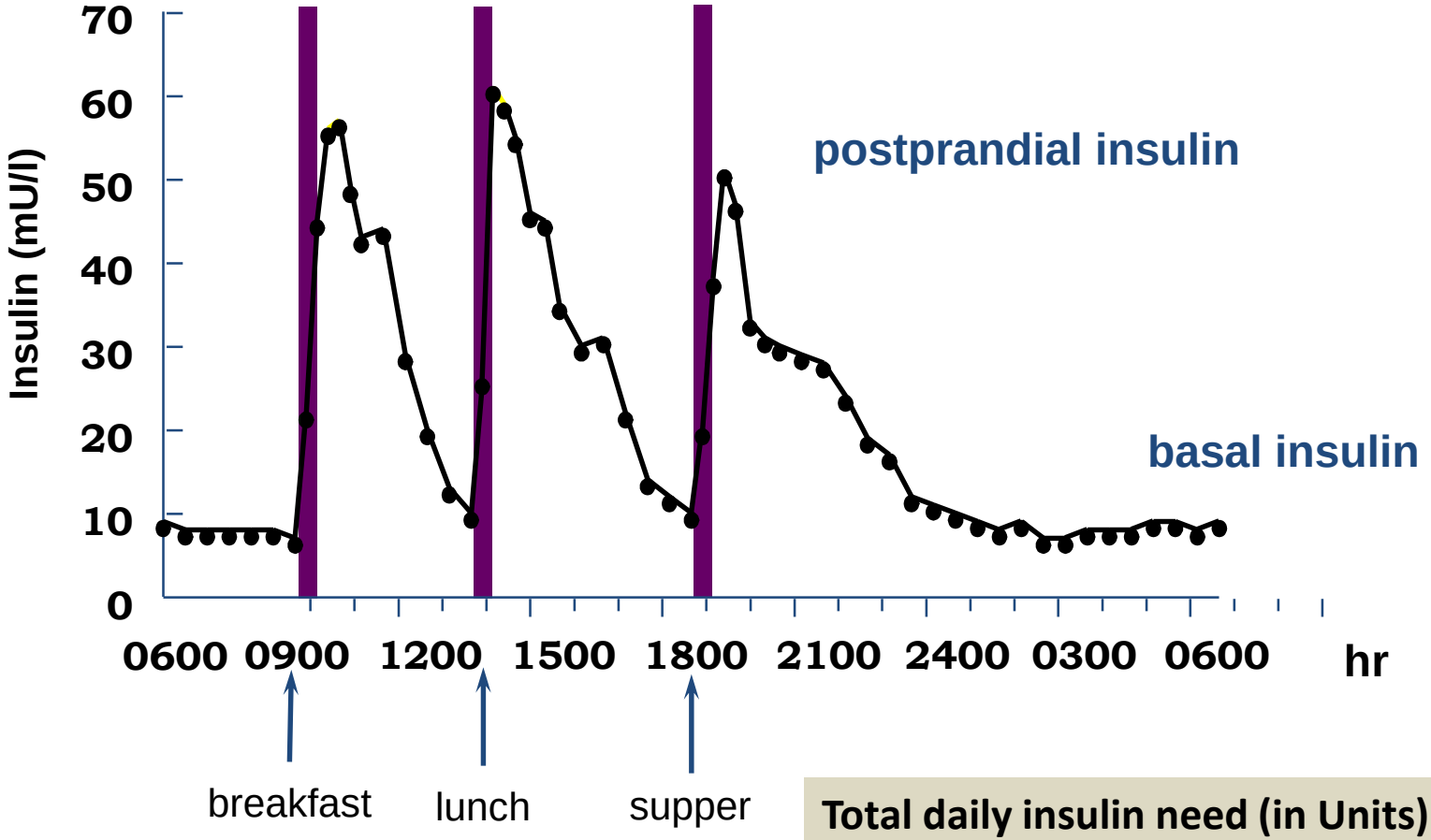
in the circulation

monomer

3.1. Insulin: Dissociation of insulin hexamers to monomers after s.c. injection



3.1. Insulin: Daily Insulin levels in healthy humans



Adapted from Polonsky et al. 1988

Total daily insulin need (in Units)
= weight (kg) x 0.55
= weight (pound) / 4

3.1. Insulin classes: According to the duration of action I

- **short acting - regular human insulin**

  (onset ~ 30min-1 hr, duration ~ 5-6 hr)

- Good for i.v. administration (e.g. for diabetic ketoacidosis/hyperkalemia)

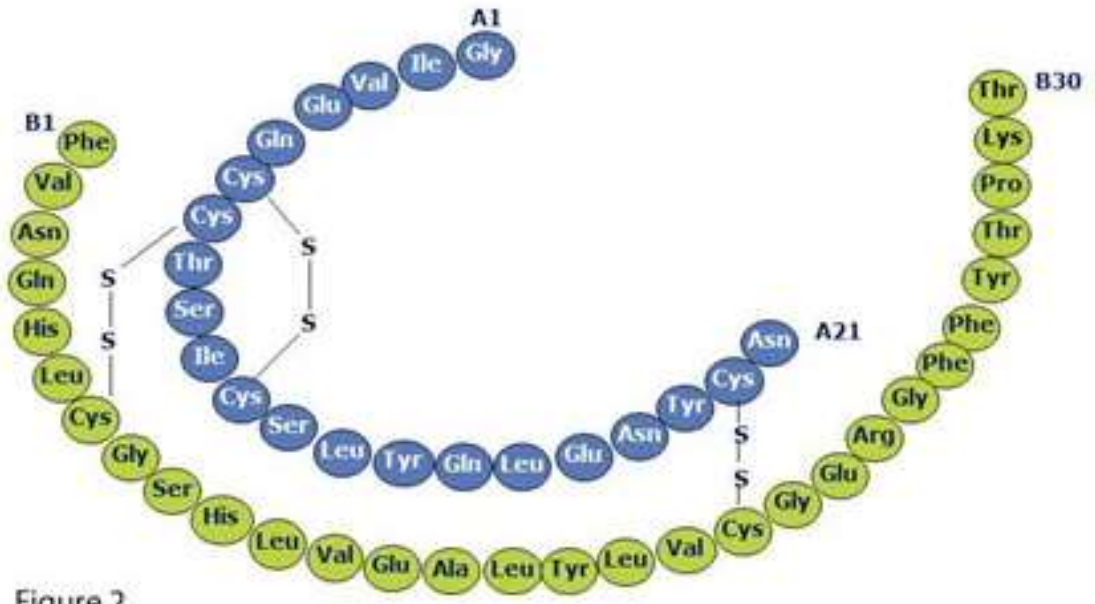
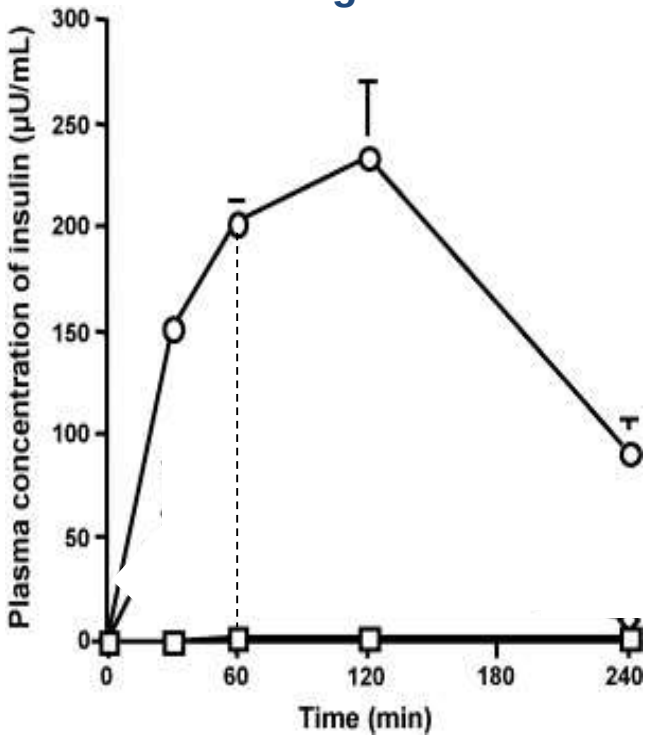


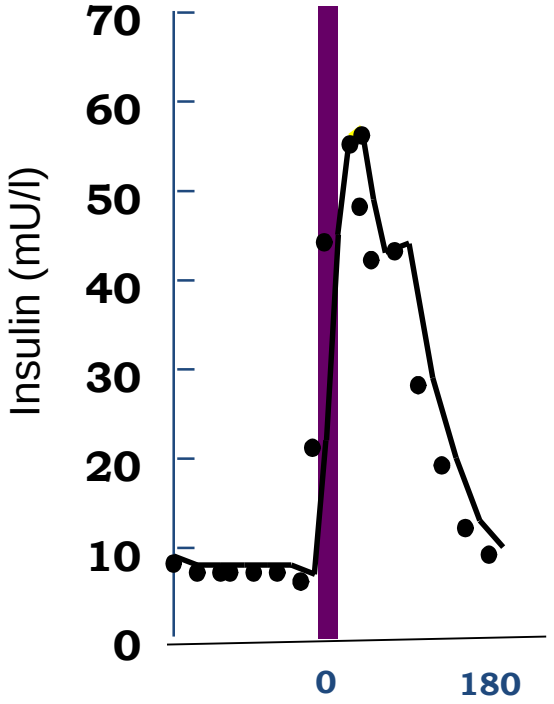
Figure 2

3.1. Insulin: Activity profile of regular insulin

insulin level after
sc regular insulin



insulin level in
non-diabetics



Optimal time for preprandial sc. injection - 60 min before meal

If given at the time of meal:

– prandial hyperglycemia, postprandial hypoglycemia

3.1. Insulin classes: According to the duration of action II

- **fast (ultra-short) acting insulin analogs**

  (onset ~ 20-30 min, duration ~ 3-4 hr)

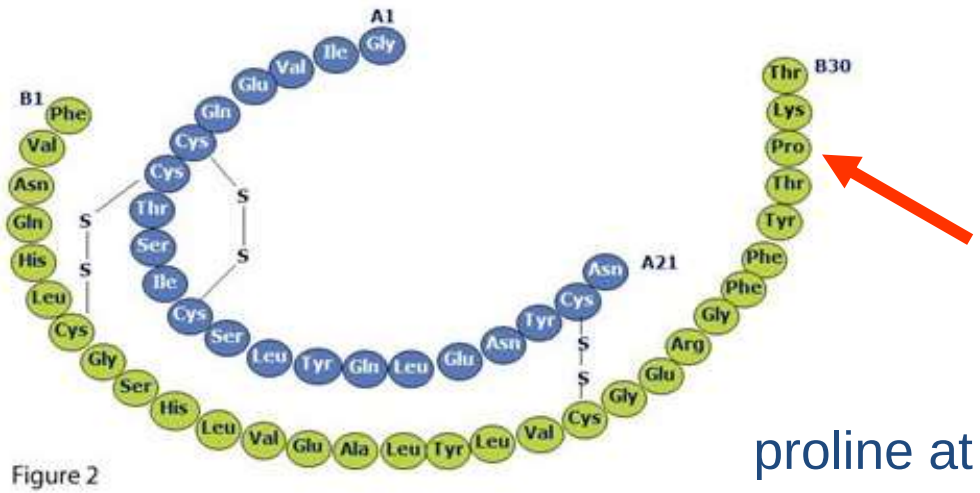
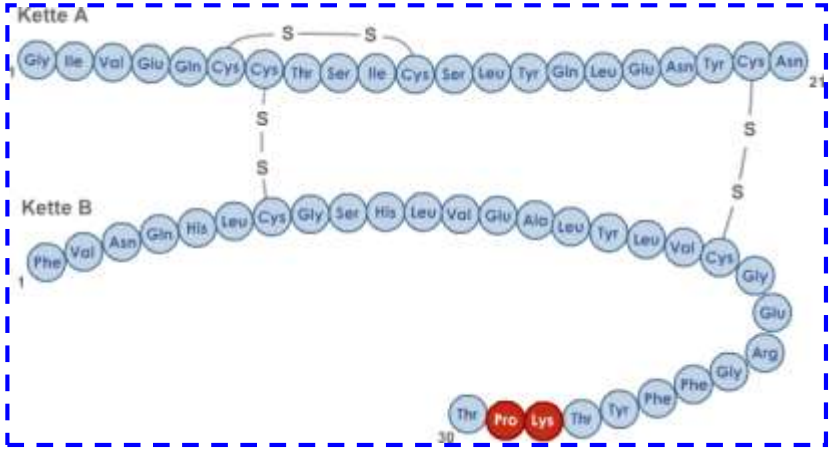


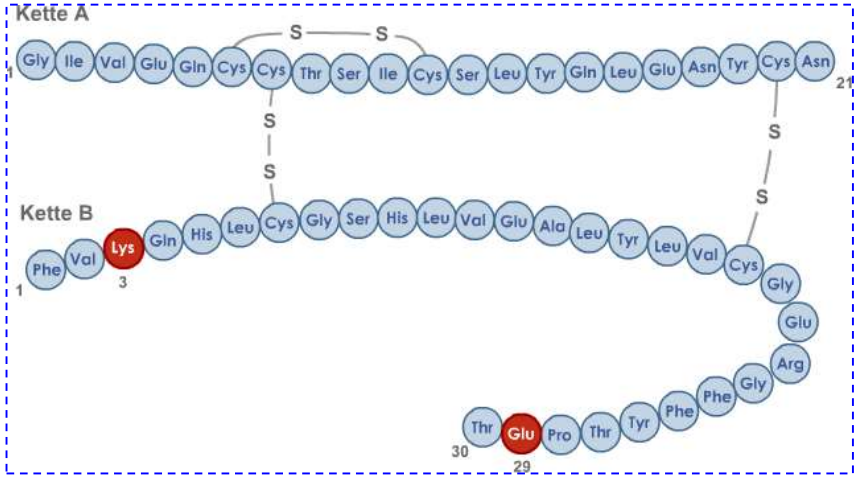
Figure 2

proline at B28 position is rather active in the formation of hexamer binding – target of modifications – no hexamer production – rapid action – to mimic normal post-prandial insulin spike

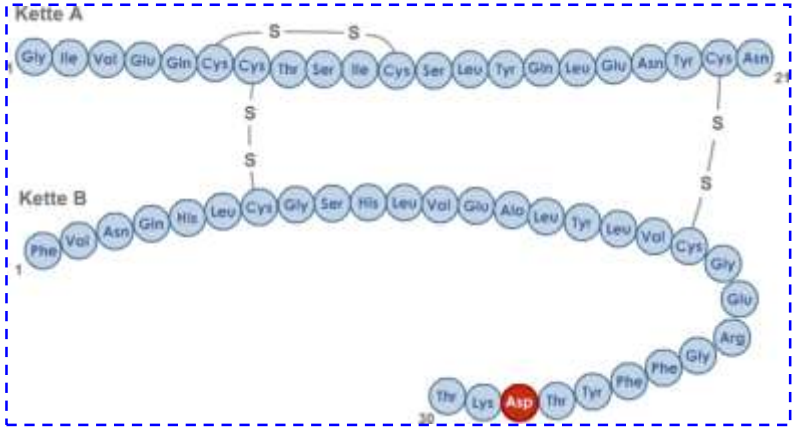
3.1. Insulin classes: Fast acting insulin analogs



lispro



glulisine

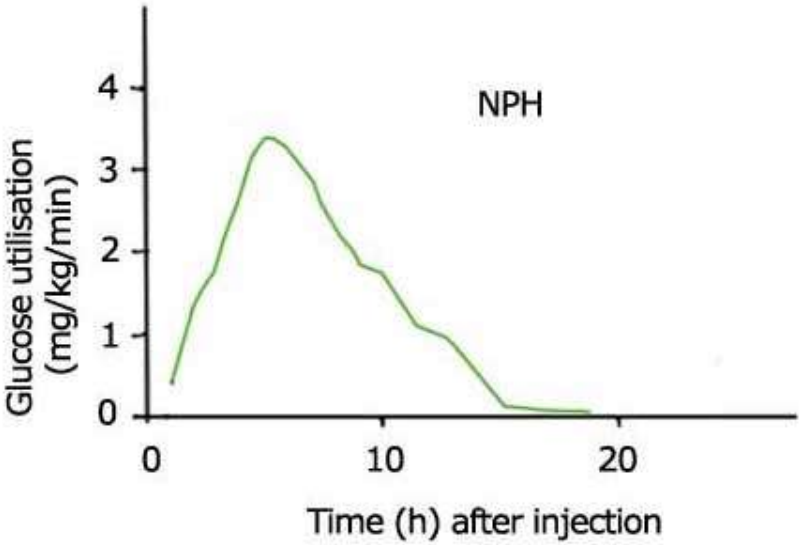


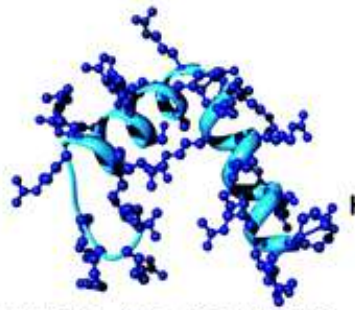
aspart

3.1. Insulin classes: According to the duration of action III

- **intermediate acting - isophane/NPH insulin – (Neutral Protamine Hagedorn)**

- (onset ~ 4-5 hr, duration ~ 12-14 hr)



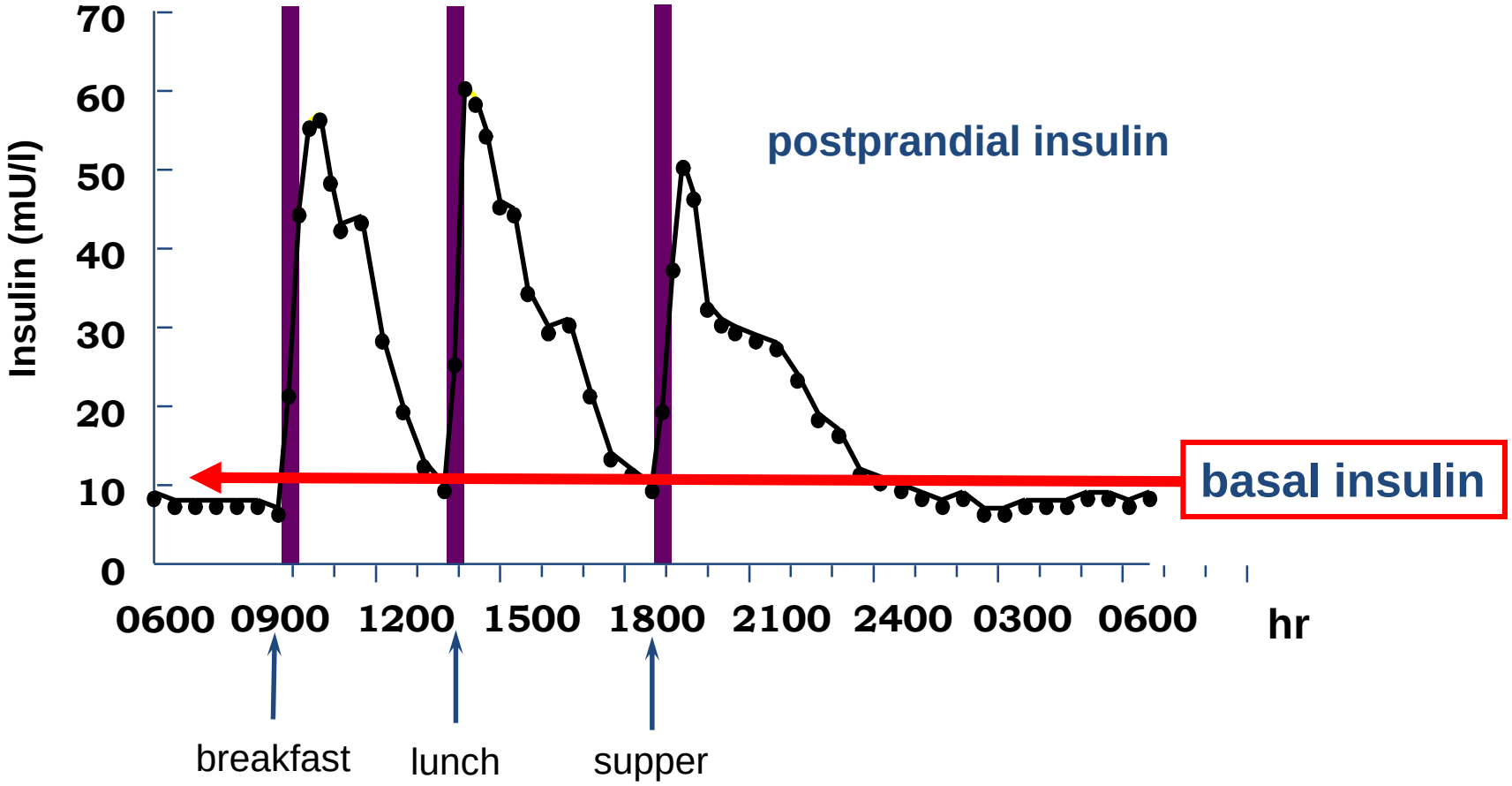


H_2N–Pro–Arg_4–Ser–Arg–Pro–
Val–Arg_5–Pro–Arg_2–Pro–Arg_2–
Val–Ser–Arg_6–Gly–Arg_4–COOH

PROTAMINE

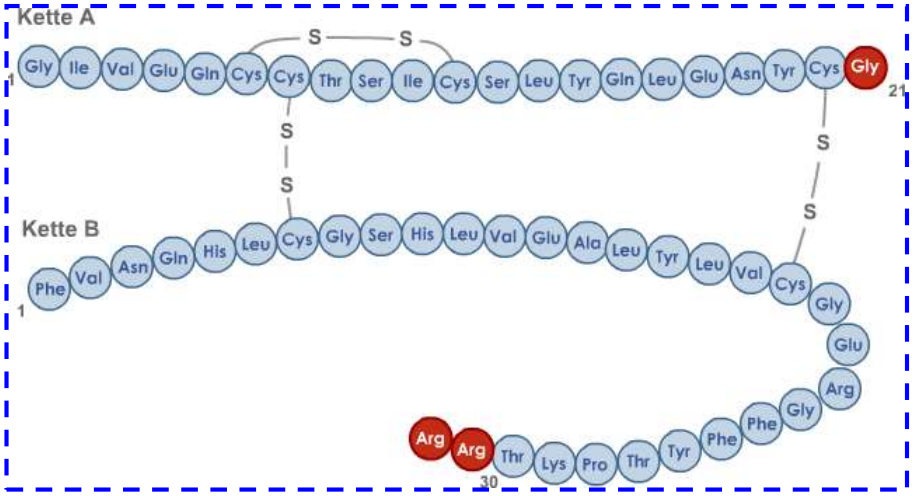
Protamine hypersensitivity is more common in males after vasectomy or in patients who are allergic to fish.

3.1. Insulin classes: Ultra long acting insulin analogs IV



Adapted from Polonsky et al. 1988

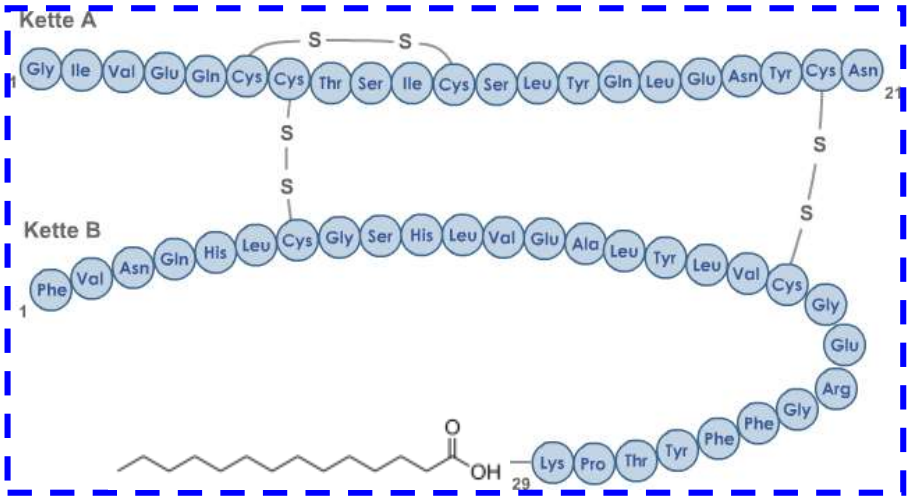
3.1. Insulin classes: Ultra long acting insulin analogs



glargin

Addition of two Arg after B30 –Thr

Isoelectric point - human insulin pH 5.4; glargin insulin pH ~7.0

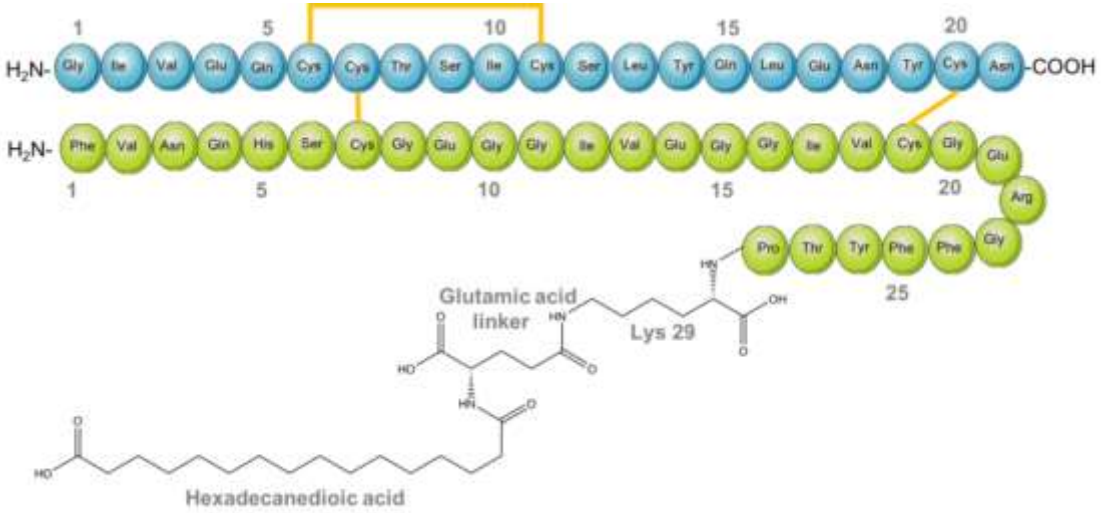


detemir

Thr in position B30 has been omitted and myristic acid was coupled to B29-Lys

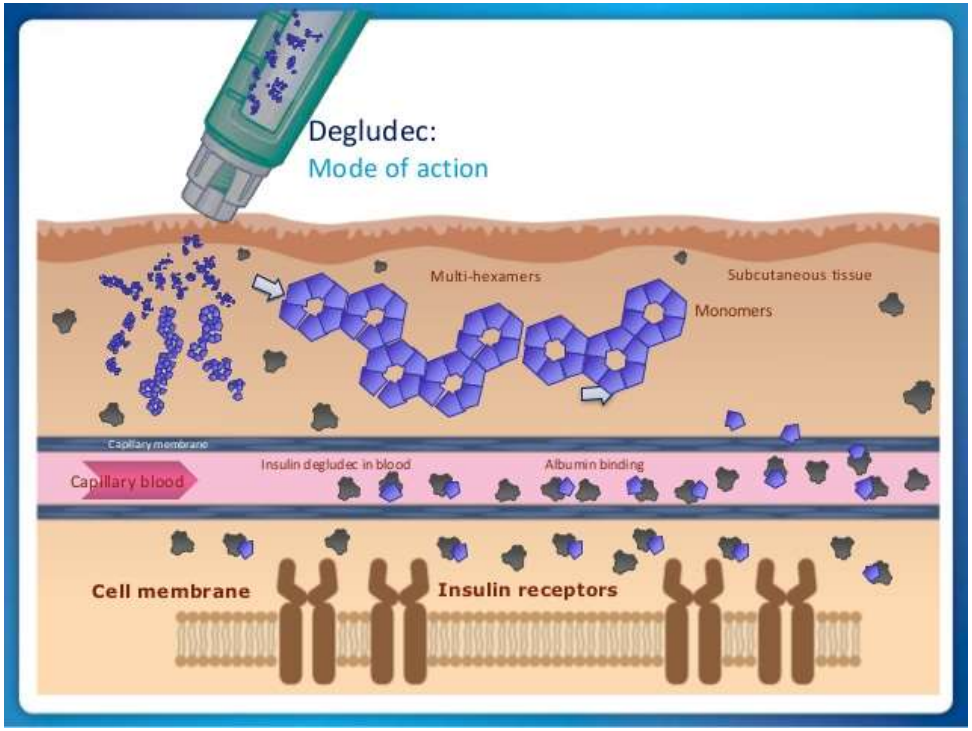
→ More apolar character and enhanced albumin binding

3.1. Insulin classes: Ultra long acting insulin analogs

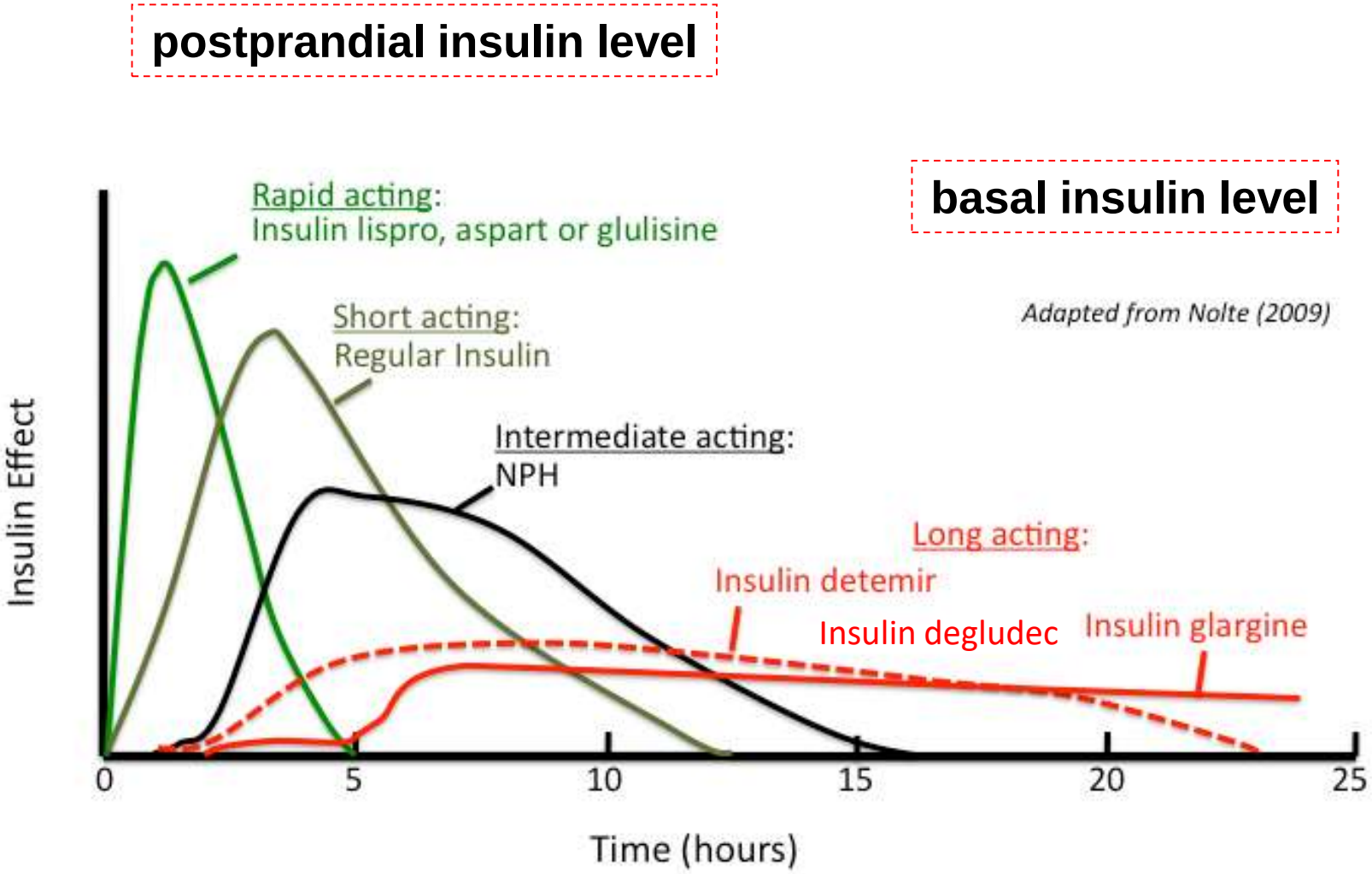


degludec

Thr - B30 has been omitted and the Lys - B29 has been coupled to **hexadecanedioic acid** via a glutamic acid linker.



3.1. Insulin: Duration of action of insulin preparations



3.1. Insulin: Preparations of insulin according to the solubility

watery (clear) solution

regular (human) insulin

insulin analogs

suspension (cloudy solution)

protamine insulin

The various insulin preparations contain generally 40-100 NE/ml insulin

3.1. Insulin: Routes of administration

i.v. Only clean solution (human and fast acting analogs)

Emergency situations e.g. coma due to diabetic ketoacidosis

s.c. – retarded absorption

Clean solution and suspension

„artificial pancreas" / insulin pumps human and fast acting analogs

- closed system - according to actually monitored glucose level (for children only this system is prescribed)
- open system - according to a program

by inhalation – only clean solution for adults

– withdrawn from the market in 2016 due to safety concerns

(decline in pulmonary function and a slight increased incidence of lung cancer)

3.1. Insulin: CLINICAL USAGE OF INSULIN

- **Diabetes mellitus**: Type 1 always, Type 2 – in case the endogenous insulin stores are exhausted

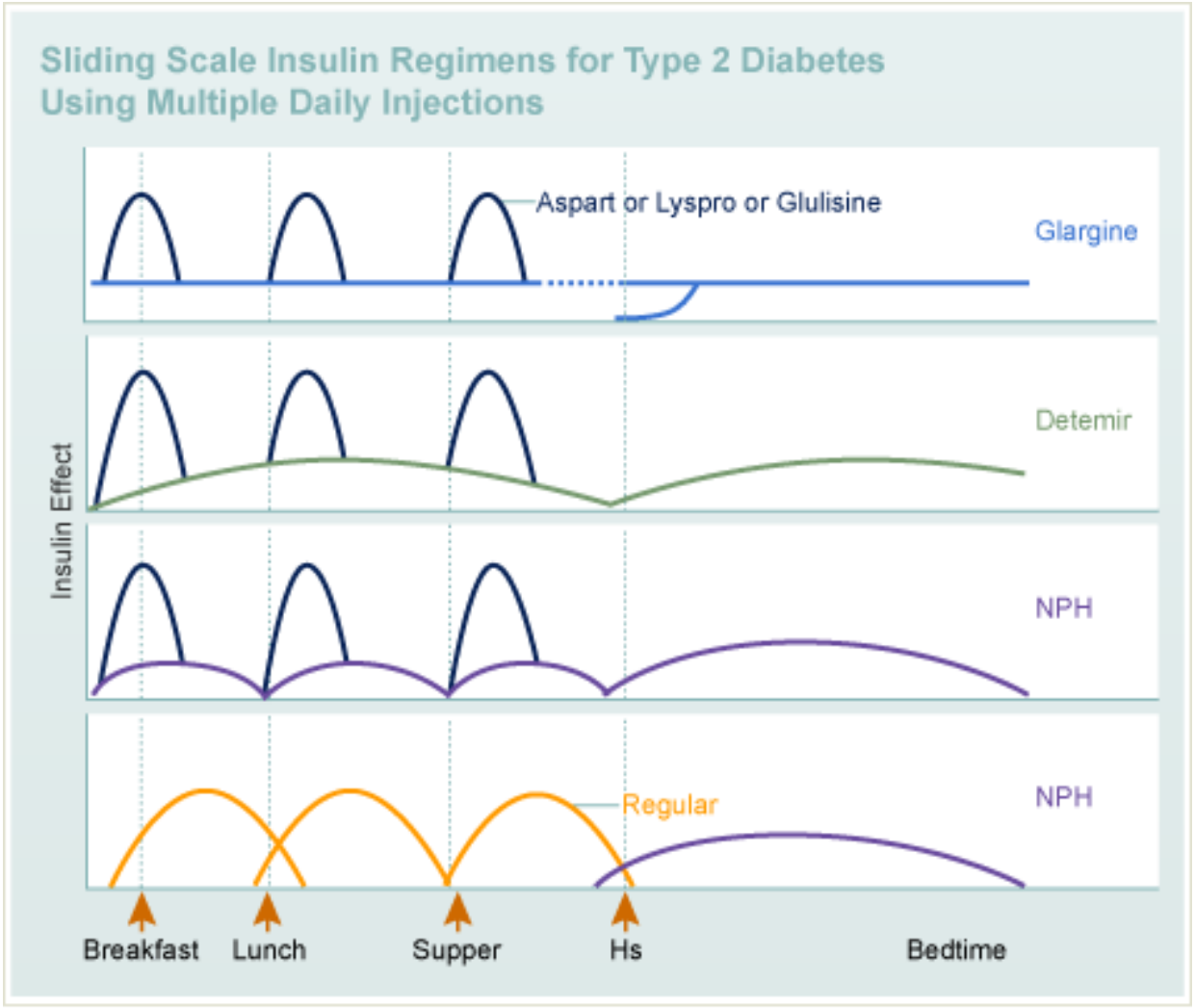
- **Gestational diabetes**: oral antidiabetics are contraindicated !!

- **Diabetic critical care states** : diabetic ketoacidosis, hyperosmolar hyperglycemic state
  (human insulin/ultrashort acting insulin analogs)

- **Hyperkalemia critical treatment**: insulin + glucose enhances the K^+ intake of the cells
  (human insulin/ultrashort acting insulin analogs)

3.1. Insulin: INTENSIVE INSULIN THERAPY

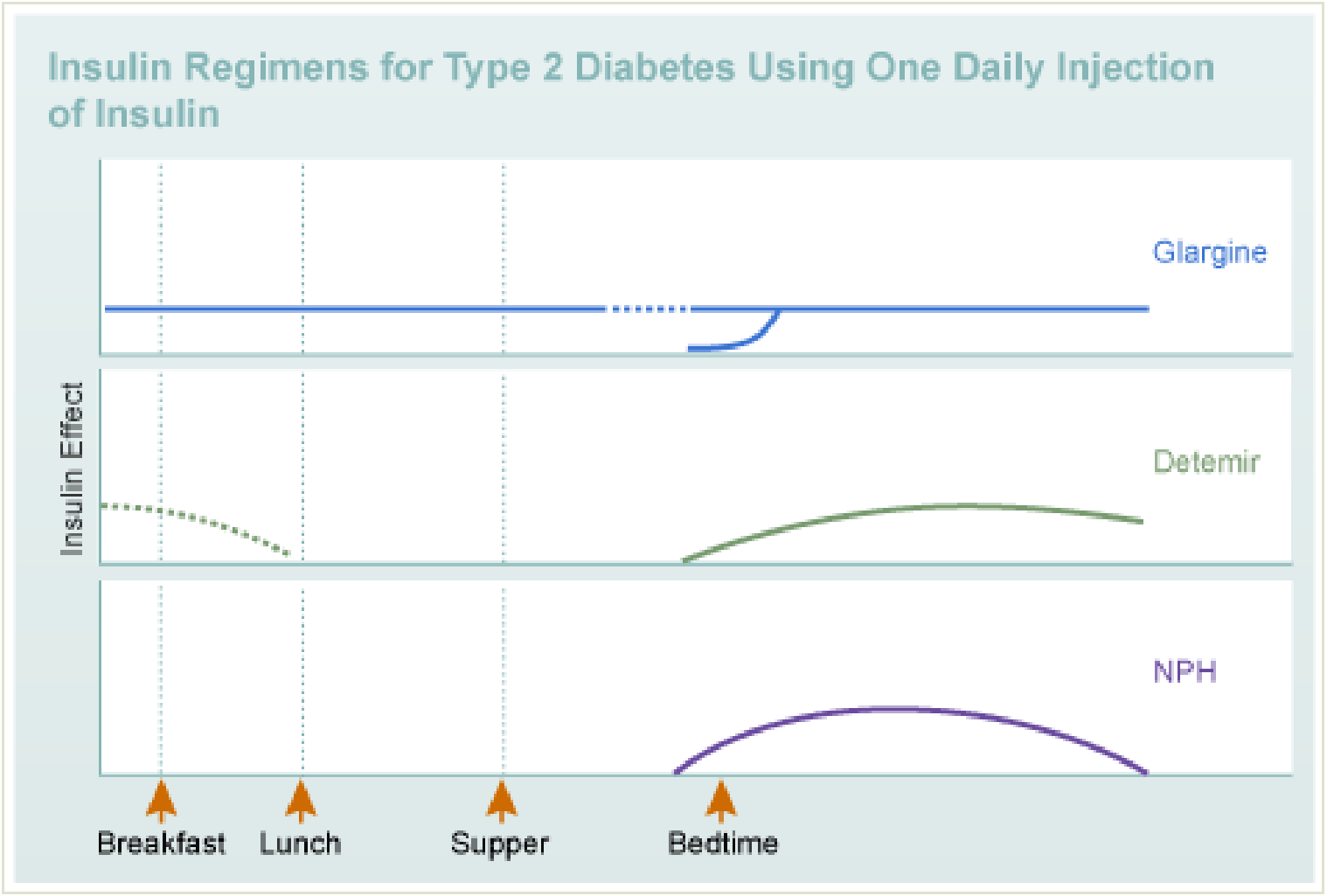
Tight glycemic control with multiple daily injections



https://dtc.ucsf.edu/types-of-diabetes/type1/treatment-of-type-1-diabetes/medications-and-therapies/type-1-insulin-therapy/designing-an-insulin-regimen/

3.1. Insulin: INTENSIVE INSULIN THERAPY

Glycemic control with single daily injections

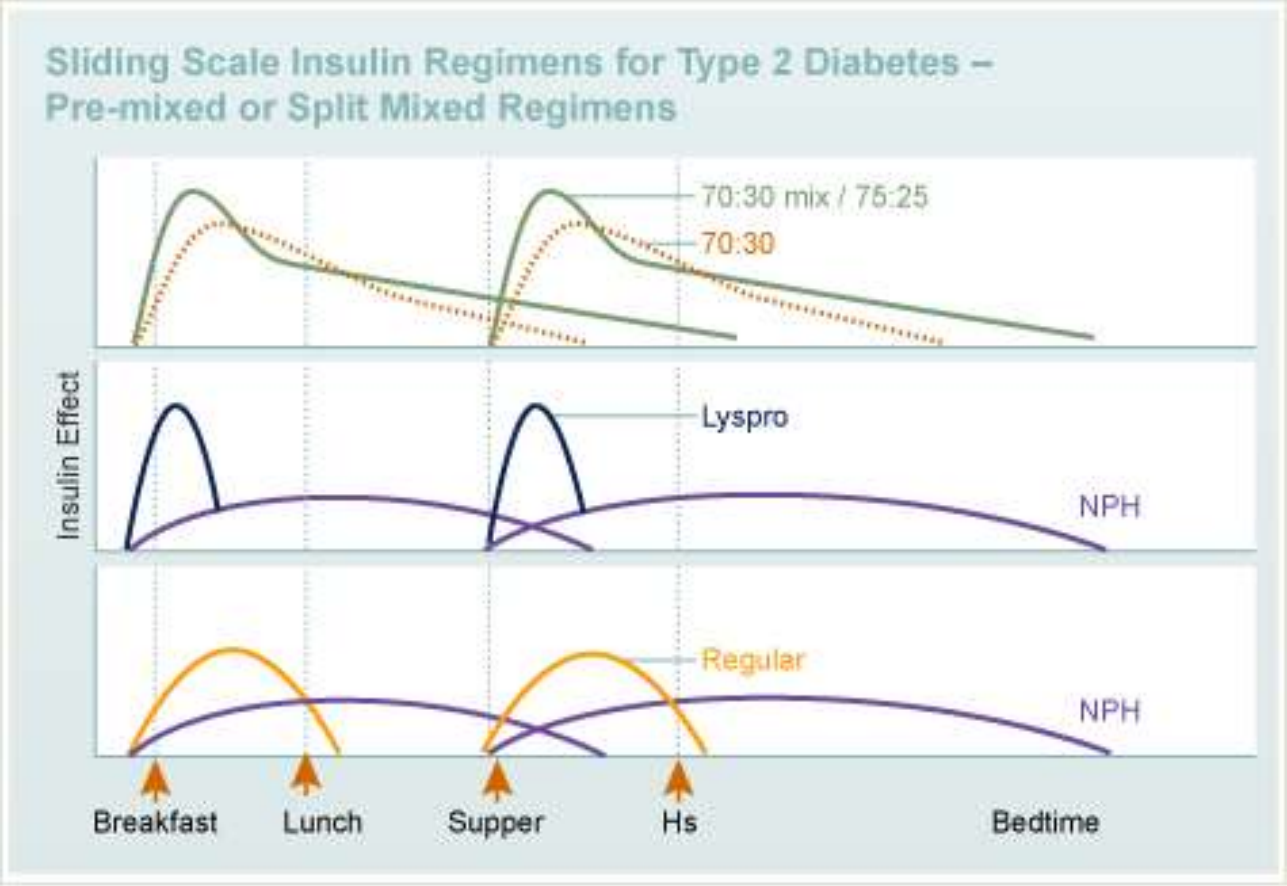


https://dtc.ucsf.edu/types-of-diabetes/type1/treatment-of-type-1-diabetes/medications-and-therapies/type-1-insulin-therapy/designing-an-insulin-regimen/

3.1. Insulin: Premixed preparations for better glycemic control and patient compliance

Premixed prep.: - NPH form + water soluble (most common 30:70 ratio)

- degludec + aspart (70:30 ratio)



https://dtc.ucsf.edu/images/graphs/graph_sliding_mixed.gif

3.1. Insulin: ADVERSE EFFECTS OF INSULIN

➢ Hypoglycemia

with rapid onset sympathetic and parasympathetic stimulation

with slow onset - CNS symptoms

th: glucose orally or i.v.
glucagon i.m. 0.5-1 mg (only within 45 min)

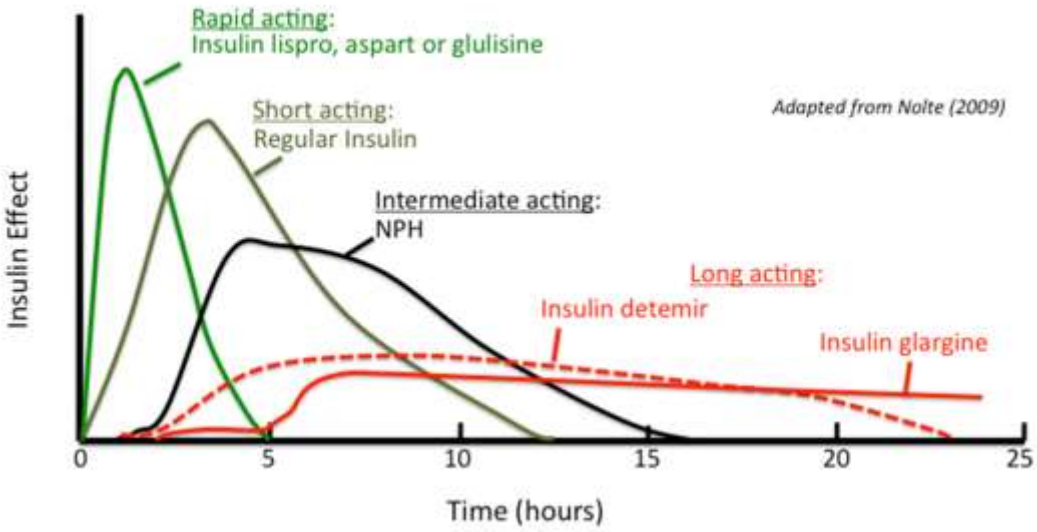
- lipodystrophy (hypertrophy/atrophy)
- oedema
- allergic skin symptoms
- anaphylaxia (rare)
- hypokalaemia (insulin enhances K^+ influx into the cells)

special adverse effect of inhaled insulin

acute bronchospasm, decrease of lung function, lung tumor ?

3.1. Insulin: Summary of insulins

- short acting –regular human insulin
- fast (ultra-short) acting insulin analogs:
  - Lispro, Aspart, Glulisin
- intermediate acting insulins:
  - Isophane/NPH insulin (Neutral Protamine Hagedorn)
- ultra-long acting insulin analogs:
  - Glargin, Detemir, Degludec



Hans Christian Hagedorn (1888 – 1971)
The creator of NPH insulin

3.2. ANTI-HYPERGLYCEMIC THERAPY

Oral agents

Sulfonylureas

Meglitinides

insulin release enhancing (insulinotrop/secretagog) compounds

Metformin (biguanides)

Thiazolidinediones (glitazones)

insulin effect enhancing compounds

DPP-4 inhibitors

incretin effect prolonging compounds

insulin-dependent compounds

α-glucosidase inhibitors (AGIs)

SGLT-2 inhibitors

insulin-independent compounds

Dopamine-2 agonist (low dose bromocriptine – only in US)

Bile acid sequestrants

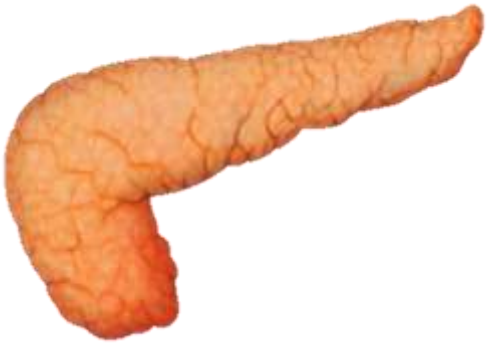
Non-insulin injectables

GLP-1 receptor agonists

Amylin mimetics

parenteral – non-insulin injectables

3.2. Insulinotrop (hypoglycemic) compounds



sulfonylureas

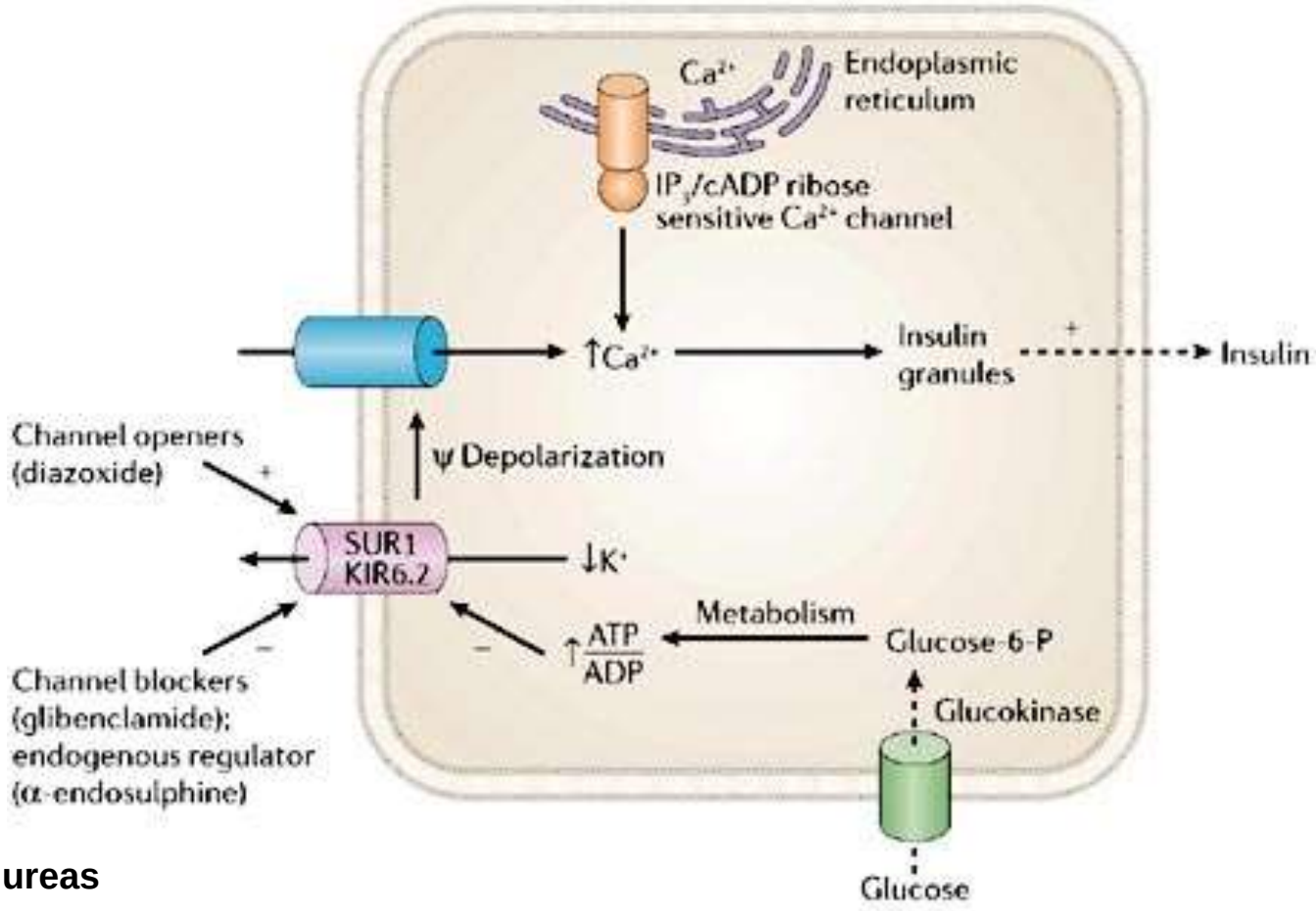
- **stimulate release of insulin from β-cells**
  (~ 30% activity is necessary)
  - **reduce serum glucagon level (via insulin release ?)**
  - **do have effect on K^+-channels in extrapancreatic tissue**

non-sulfonylureas

PRG - prandial regulators of glucose

- **acute increase of insulin release**
  (should be taken in connection with meals)

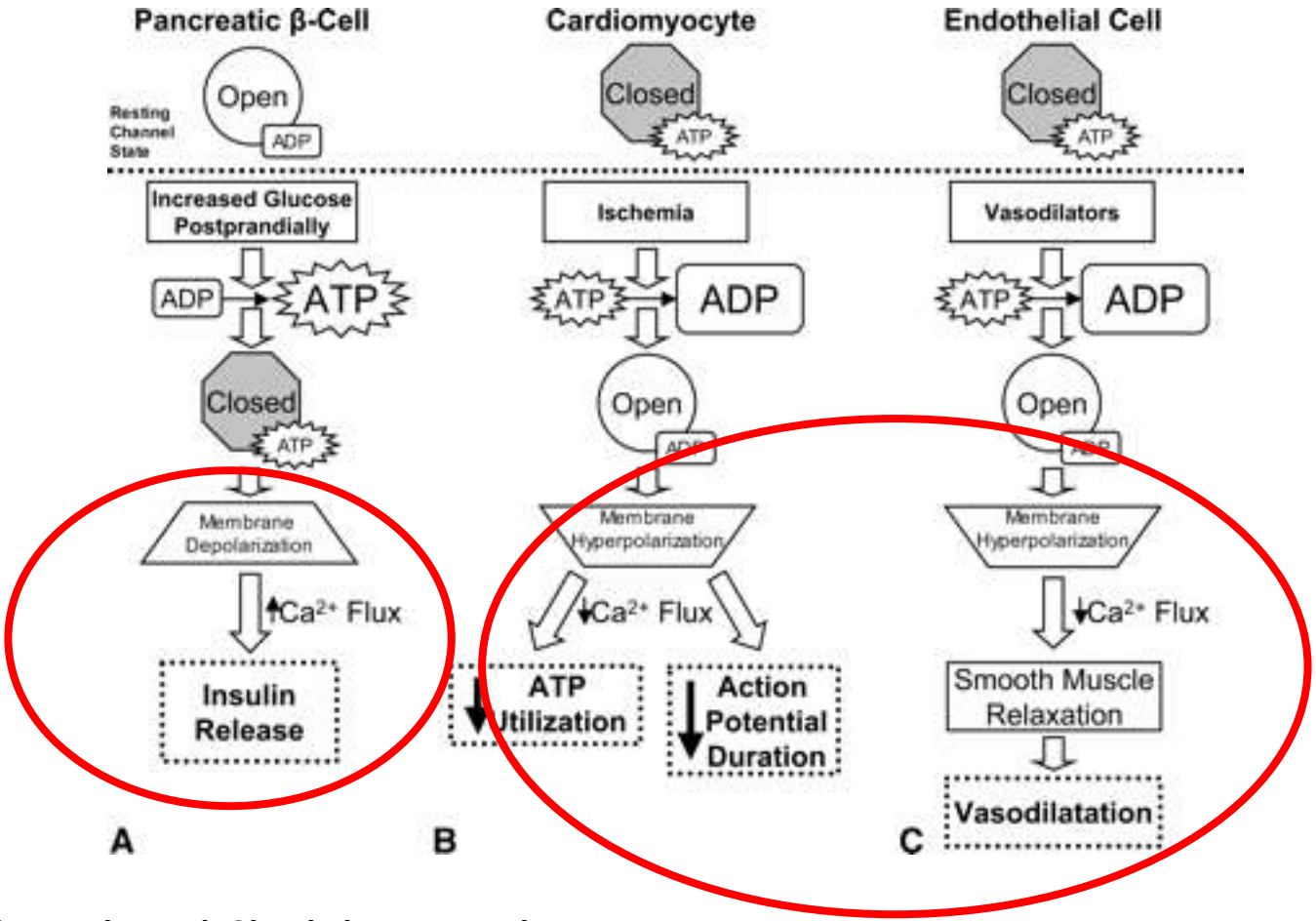
3.2. Effect of insulinotropic agents on the pancreatic β-cells



sulfonylureas

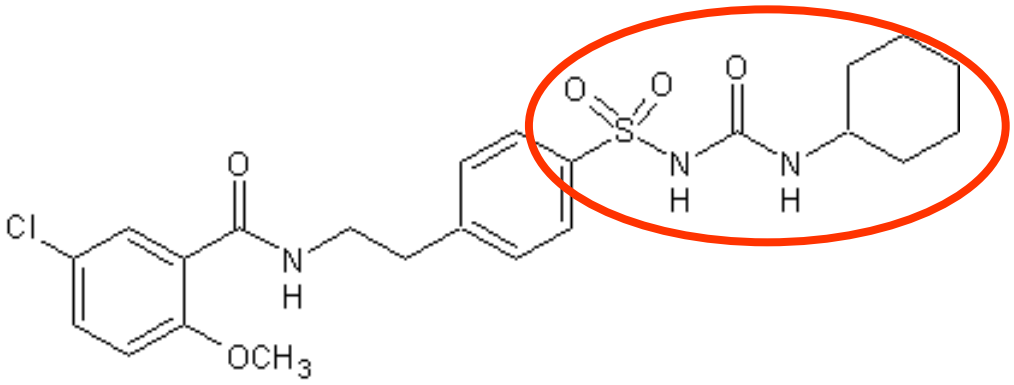
3.2. SU receptor

Combination of subunits is different in pancreatic β cells, vascular smooth muscle and in cardiomyocytes



Michael A. Burke et al. Circulation Research. 2008;102:164-176

3.2. Sulfonylureas



First generation – long duration of action

tolbutamide, tolazamide, chlorpropamide

Second generation

glyburide (aka. glybenclamide): high hypoglycemia risk

gliclazide, glimepiride: pancreas selective drugs

glipizide: shortest duration of action (less hypoglycemia risk)

3.2. Advantages of sulfonylureas

- potent drugs
- generally the action is maintained for longer period
- pancreas-selective drugs (gliclazide, glimepiride) are safer
- gliclazide - SUR 1 selective
  antioxidant and antiproliferative effect
  does not enhance Epac 2 (transcription factor affecting the glucose sensitivity) expression
  smaller risk of hypoglycemia (action rather on the first phase of insulin release)

3.2. Disadvantages of sulfonylureas

- risk of hypoglycemia (prolonged)

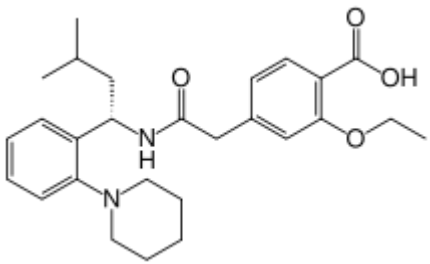
- increased food intake 5 x /day – weight gain is associated with SU use (and meglitinide use)

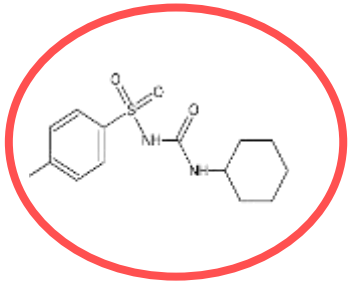
- cardiovascular risk due to inhibition of cardiac SU receptor

- hematological abnormalities (thrombocytopenia, leukopenia, hemolytic anemia)

3.2. Meglitinides (PRGs – prandial regulators of glucose)

repaglinid

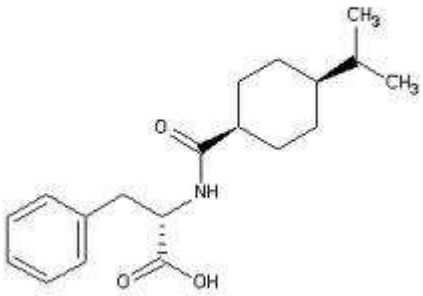




Sulfonylurea group is not present in meglitinides:

A cause of „sulfa”-allergy

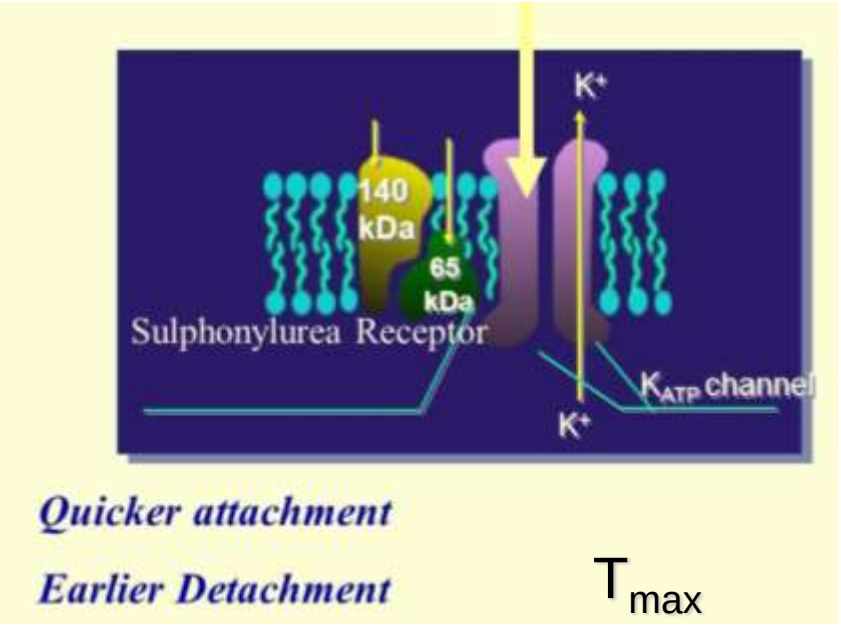
nateglinid

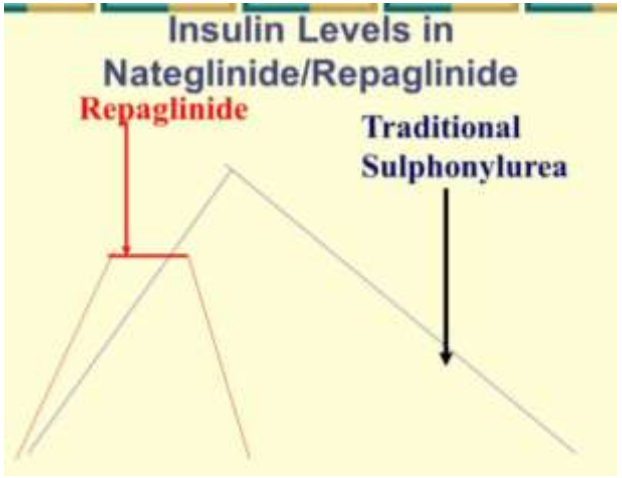


3.2. Meglitinides

repaglinide **nateglinide**

They bind to specific sites in the SUR with different binding characteristics





	T_{max}	Plasma half-life	Duration of action
Glibenclamide	4-6 hrs	10 hrs	16-24 hrs
PGR	40 min	1-1,5 hrs	4-5 hrs

should be taken in connection with meals

3.2. ANTI-HYPERGLYCEMIC THERAPY

Oral agents

Sulfonylureas ✓
Meglitinides ✓

insulin release enhancing (insulinotrop/secretagog) compounds

Metformin (biguanides)
Thiazolidinediones (glitazones)

insulin effect enhancing compounds

DPP-4 inhibitors

incretin effect prolonging compounds

insulin-dependent compounds

α-glucosidase inhibitors (AGIs)
SGLT-2 inhibitors

insulin-independent compounds

Dopamine-2 agonist (low dose bromocriptine – only in US)

Bile acid sequestrants

Non-insulin injectables

GLP-1 receptor agonists
Amylin mimetics

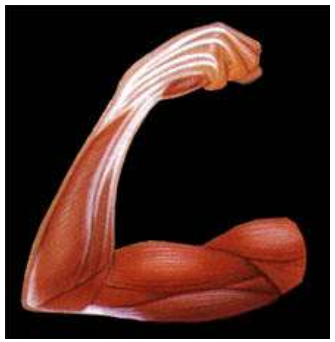
parenteral – non-insulin injectables

3.2. Non-insulinotrop (euglycemic) compounds

- Biguanids

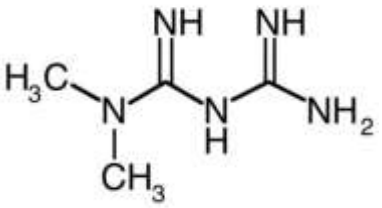
Decrease of
hepatic glucose production,
intestinal glucose absorption, and
increase of peripheral insulin
sensitivity/glucose utilization

- Thiazolidenediones (glitazones)



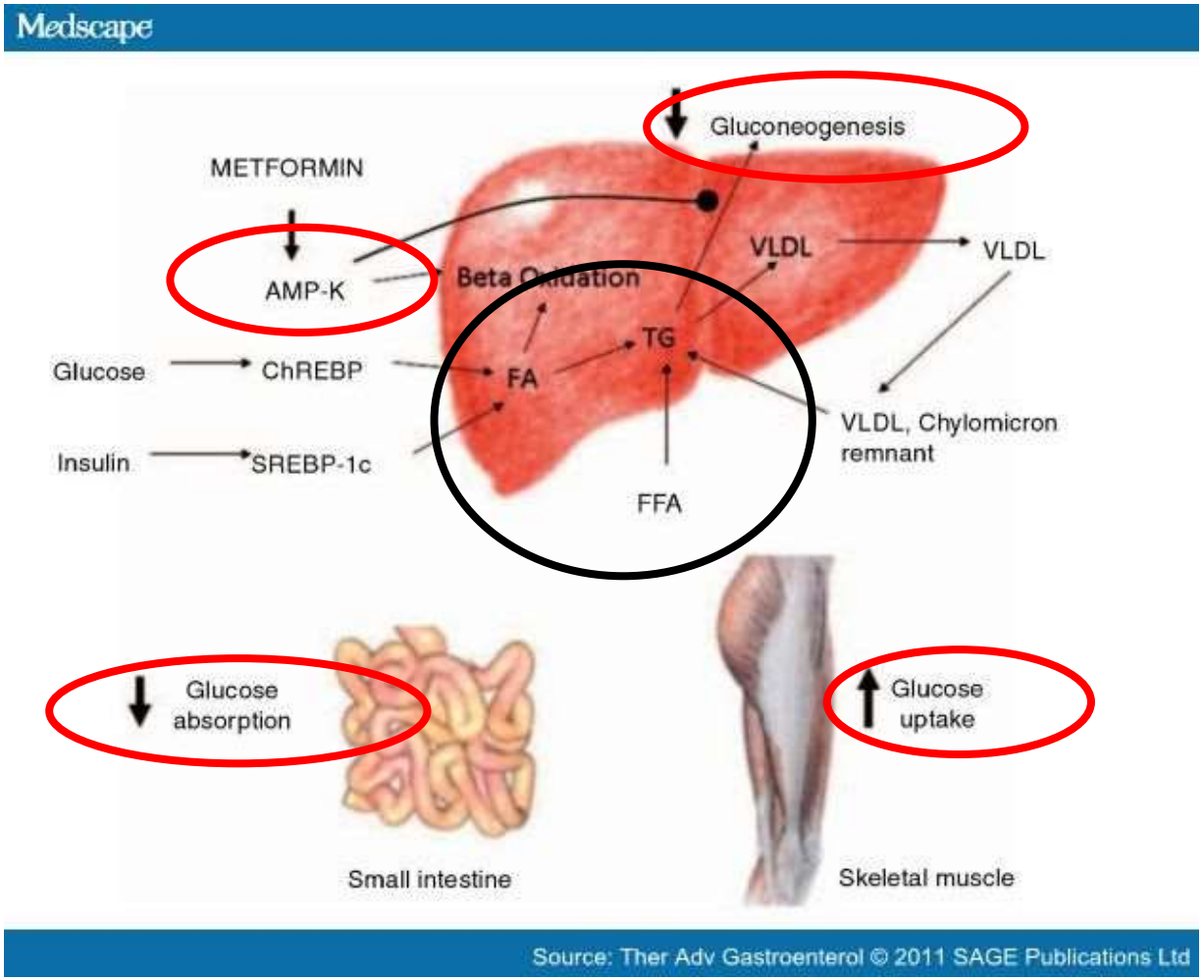
Increase of insulin
sensitivity and peripheral
glucose uptake

3.2. Biguanids



Metformin (Phenformin, Buformin)

Pharmacodynamic



Via acting on the AMP-activated protein kinase (AMPK) it harmonizes the carbohydrate and fat metabolism

3.2. Metformin

Other pharmacodynamic effects

- reduction of plasma glucagon level (inhibition of glucagon mobilization)
- reduction of triglyceride level
- antioxidant effect – decrease of formation of advanced glycation end products

Side effects

- GI: nausea, anorexia, vomiting, diarrhea, metallic taste
- Impaired vitamin B12 absorption – anaemia
- Lactic acidosis (see on next slide)

3.2. Disadvantages of Metformin

- rare, but very significant adverse effect could be lactic acidosis

Contraindications:

- acute metabolic acidosis
- **severe kidney impairment** (GFR < 30 mL/min)
- acute states, which may affect the kidney function, (e.g. dehydration, severe infection, shock)
- states may induce tissue hypoxia (e.g. cardiac or respiratory insuff., MI)
- liver impairment, acute alcoholic intoxication, alcoholism

Conditions that increase the overall risk of lactic acidosis

3.2. Advantages of Metformin

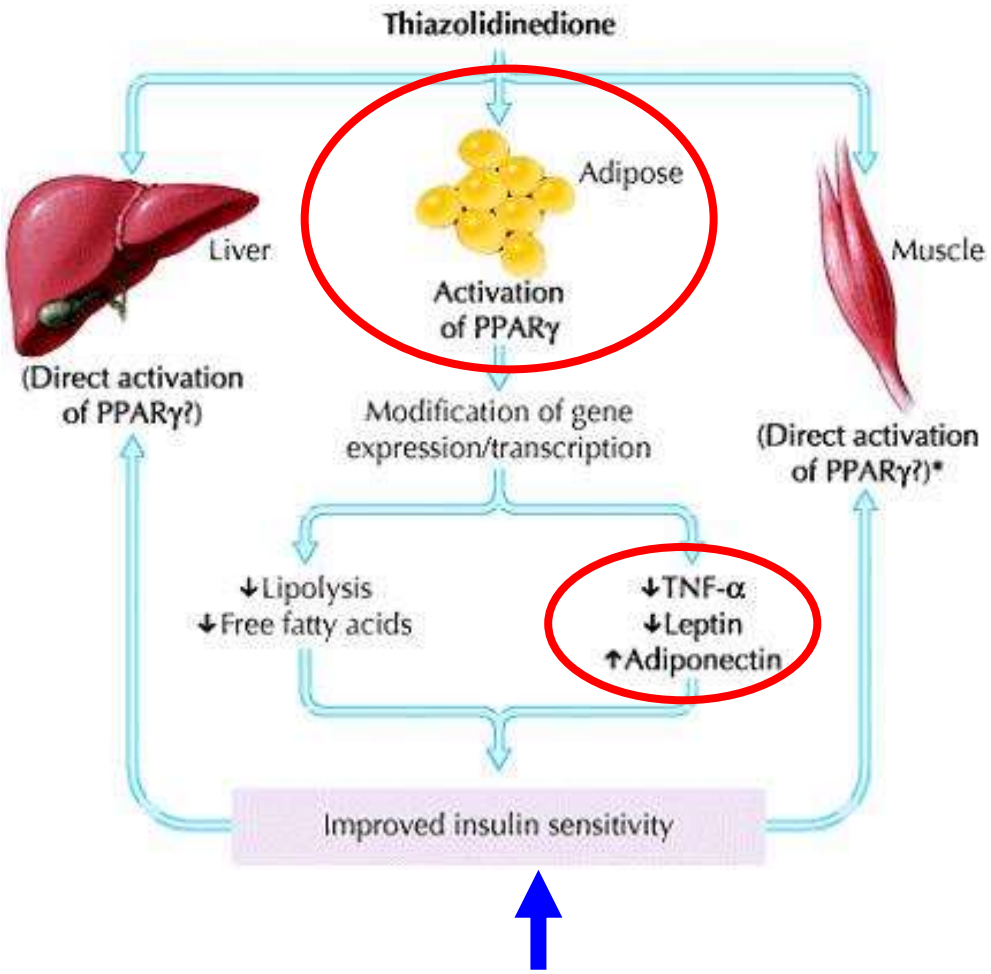
Acts on determining factors involved in the pathogenesis

- decreases insulin resistance
- decreases body weight
- positively affects lipid levels

First drug of choice in type 2 diabetes

- Additional benefit in:
  - polycystic ovary syndrome (hyperinsulinemic state)
  - Hyperinsulinemia / insulin resistance

3.2. Thiazolidenediones (glitazones)



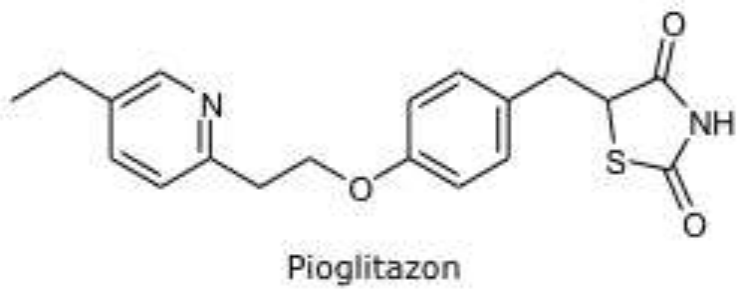
Advantages

PPARγ stimulators

PPAR – intracellular nuclear receptor family

Rosiglitazone
(withdrawn from market)

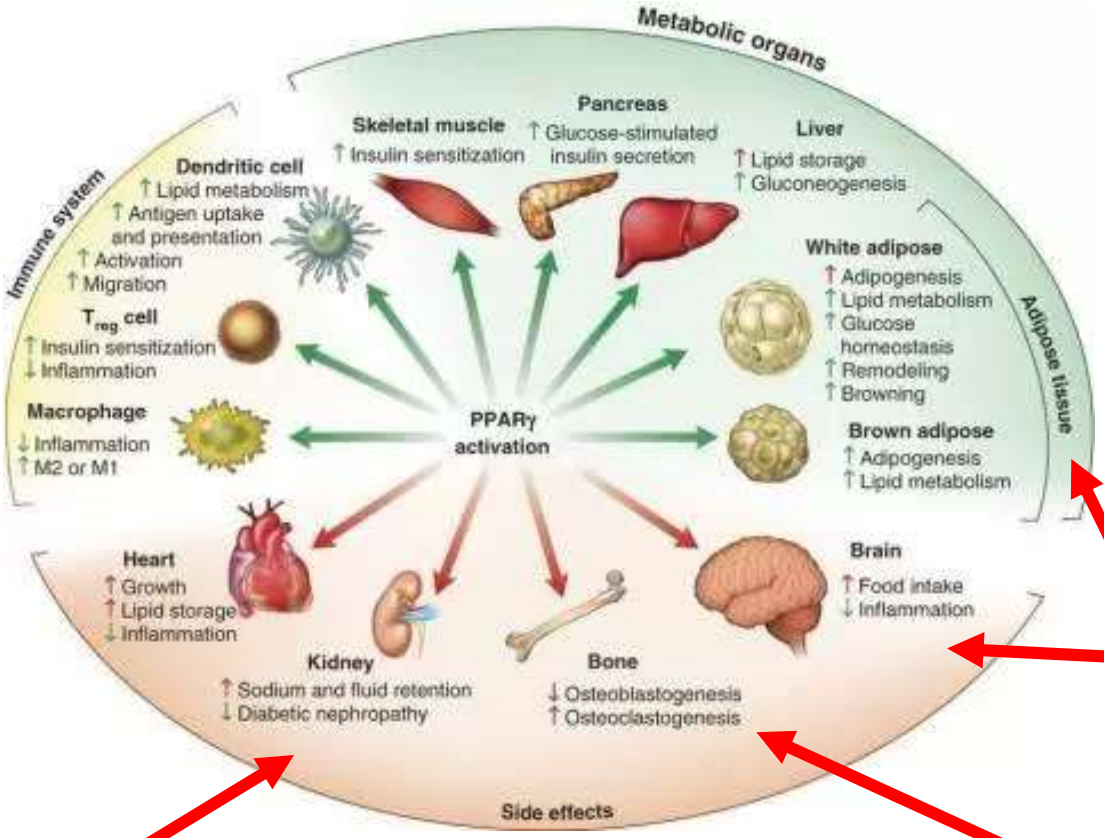
pioglitazone



Pioglitazon

http://www.pharmainfo.net/files/images/stories/article_images/Mechanism%20of%20action%20of%20thiazolidinediones.jpg

3.2. Disadvantages of thiazolidenediones



- Side effect: increase of body weight – adipocyte proliferation

- increase of plasma volume (edema formation – contraindicated in heart failure,
- decrease of hemoglobin and hematocrit level)

- Side effect: increased risk of bone fracture (osteoporosis??)

https://www.selfhacked.com/blog/ppargamma-role-weight-gain-inflammation-natural-activators/

3.2. ANTI-HYPERGLYCEMIC THERAPY

Oral agents

Sulfonylureas ✓
Meglitinides ✓

→ insulin release enhancing (insulinotrop/secretagog) compounds

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→ insulin effect enhancing compounds

DPP-4 inhibitors

→ incretin effect prolonging compounds

→ insulin-dependent compounds

α-glucosidase inhibitors (AGIs)
SGLT-2 inhibitors

→ insulin-independent compounds

Dopamine-2 agonist (low dose bromocriptine – only in US)

Bile acid sequestrants

Non-insulin injectables

GLP-1 receptor agonists
Amylin mimetics

→ parenteral – non-insulin injectables

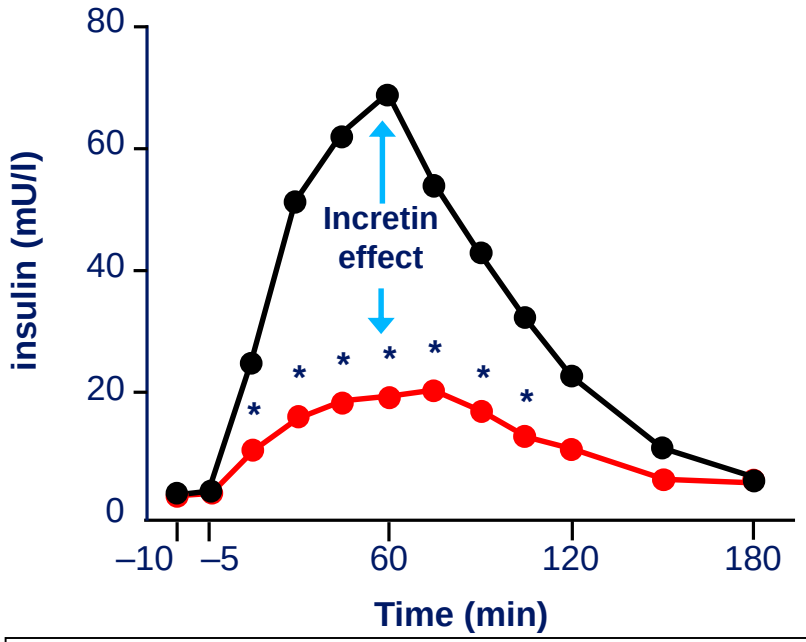
3.2. insulin-dependent, incretin effect prolonging compounds - definition of incretins and their functions

GLP-1 – produced in the ileum and colon - insulin release ↑; glucagon release ↓

GIP – produced in the duodenum and jejunum - insulin release ↑

GLP-1 – glucagon like peptide
GIP – glucose-dependent insulinotropic peptide

EFFECTS ARE GLUCOSE-DEPENDENT

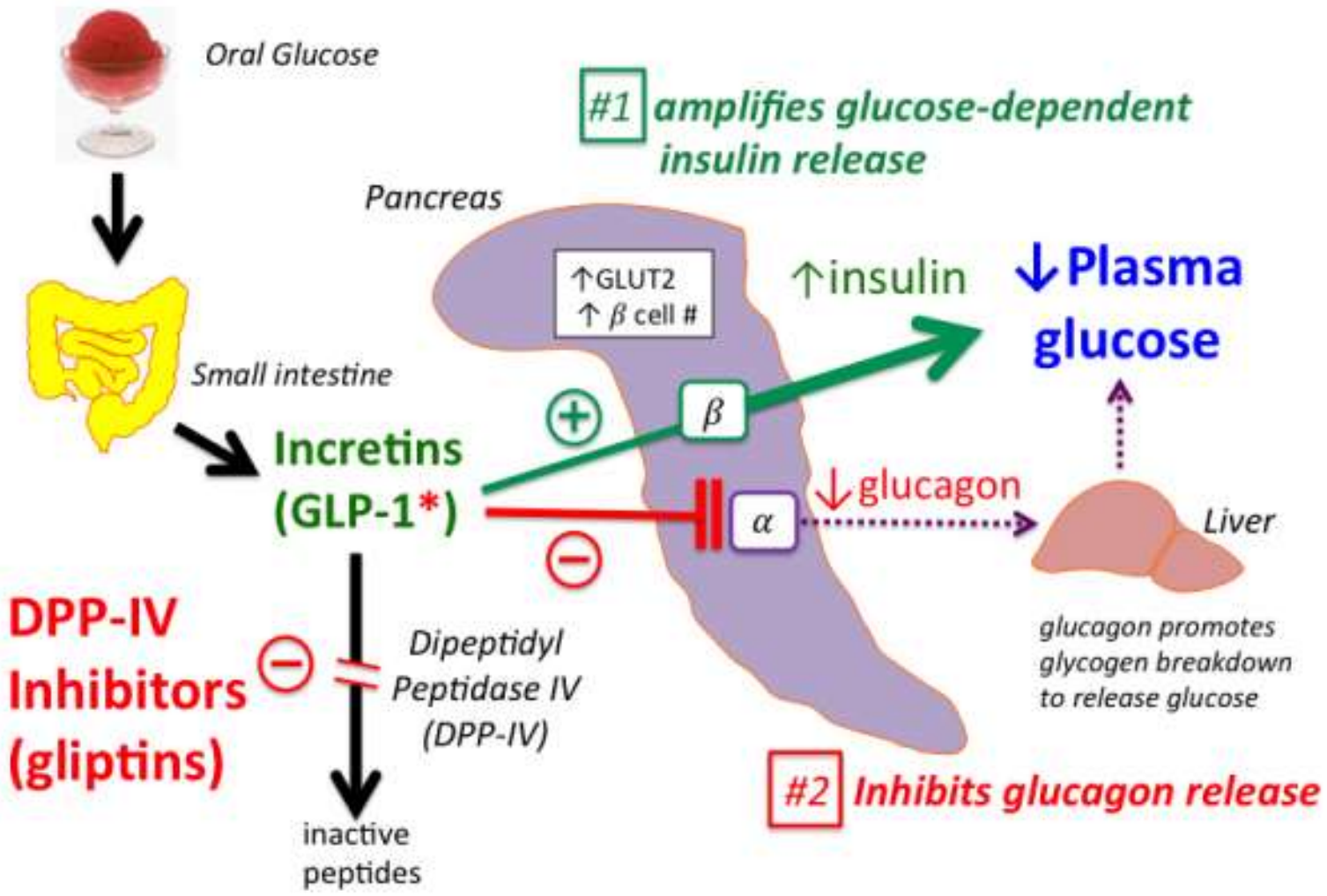


Insulin response to oral glucose load (50 g/400 ml, ●) and during isoglycemic i.v. glucose IV (●)

In T2DM the effect of GIP on insulin release is lost.

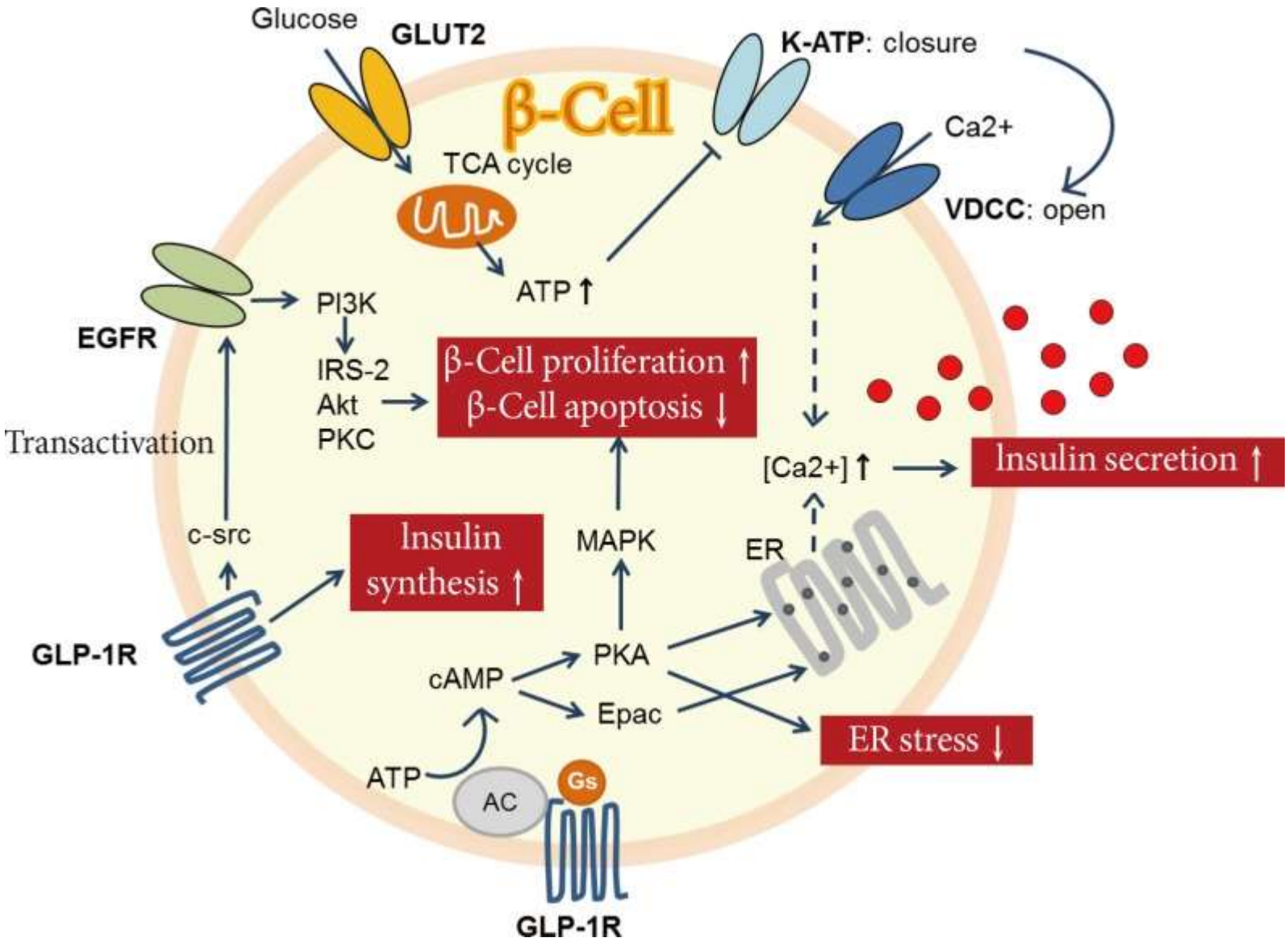
The effect of GLP-1 is still possible.

3.2. Physiological actions of endogenous GLP-1



* Physiological $t_{1/2}$=2 mins due to rapid inactivation by DPP-IV

3.2. Cellular actions of GLP-1 on the β-cell

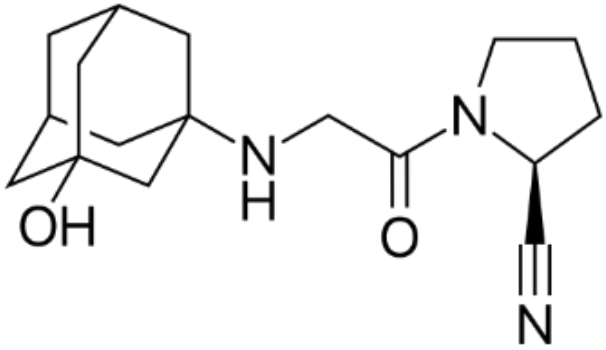


3.2. DPP-4 inhibitors: to increase endogenous GLP-1 levels and GLP-1 action

vildagliptin, sitagliptin, saxagliptin, linagliptin, alogliptin

Advantages

- effect is glucose dependent
- no hypoglycemia
- no change in of body weight



vildagliptin

Disadvantages/side effects

- Nasopharyngitis, headache, nausea, skin hypersensitivity
- Increased risk of pancreatitis and pancreatic cancer? Increased risk of inflammatory bowel disease?
- Saxagliptin may increase the morbidity in patients with heart failure

3.2. ANTI-HYPERGLYCEMIC THERAPY

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} insulin-independent compounds

Dopamine-2 agonist (low dose bromocriptine – only in US)

Bile acid sequestrants

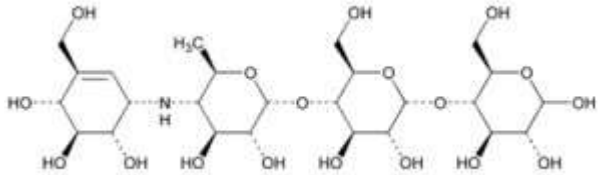
Non-insulin injectables

GLP-1 receptor agonists
Amylin mimetics

} parenteral – non-insulin injectables

3.2. Alpha-glucosidase inhibitors

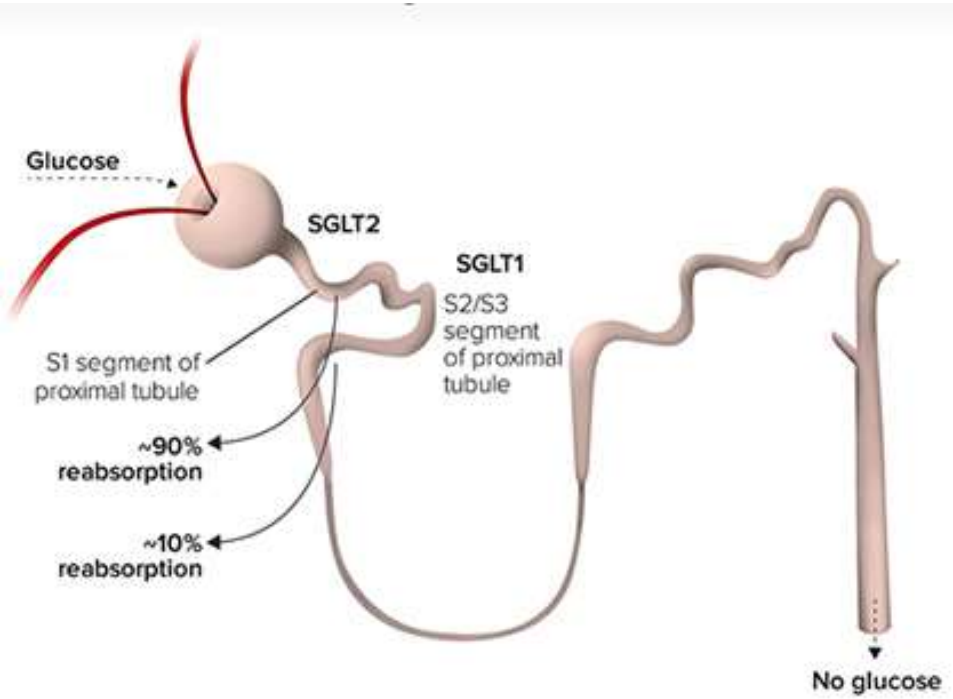
acarbose, miglitol



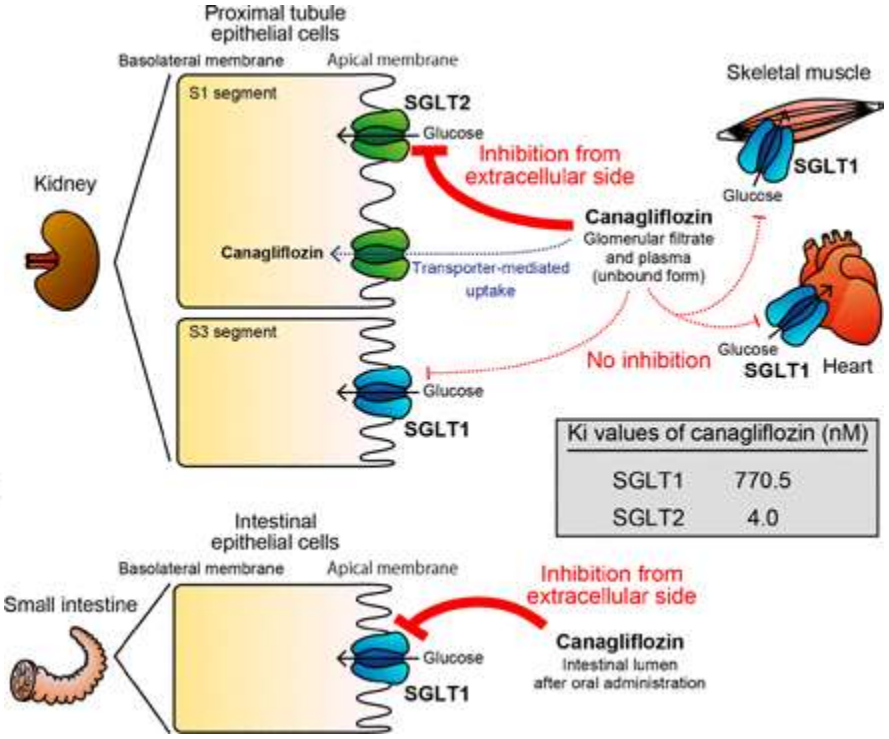
- inhibition of the splitting of di-, oligo- and polysaccharides by enzymes of the intestinal brush border - reduction of carbohydrate absorption (not that of lactose !!)
  Result: reduction of postprandial hyperglycemia
- Recommended for obese patients, taken together with meal
- Side effects: meteorism, abdominal pain, flatulence, diarrhea (due to fermentation of undigested carbohydrates)

3.2. Sodium-glucose transporter-2 (SGLT-2) inhibitors

dapagliflozin, canagliflozin, empagliflozin, ertuglifozin



Advantage: SGLT2 expression is enhanced in tubuli due to DM



They decrease the glucose reabsorption by about 30-50% (the effect on other SGLT might also contribute to the overall efficacy?)

3.2. SGLT-2 inhibitors

Advantages

- The effect does not depend on the beta cell function and they do not influence the function of beta cells
- They decrease the body weight
- They decrease intestinal glucose absorption as well for a small extent.
- They decrease the blood pressure
- Good candidates for treating obese patients with Heart Failure with Preserved Ejection Fraction (HFpEF).

Disadvantages

- Given their mode of action, the SGLT2 inhibitors are less effective in case of impaired kidney function, when eGFR < 60 ml/min they does not work
- Blood pressure may decrease

Side effects

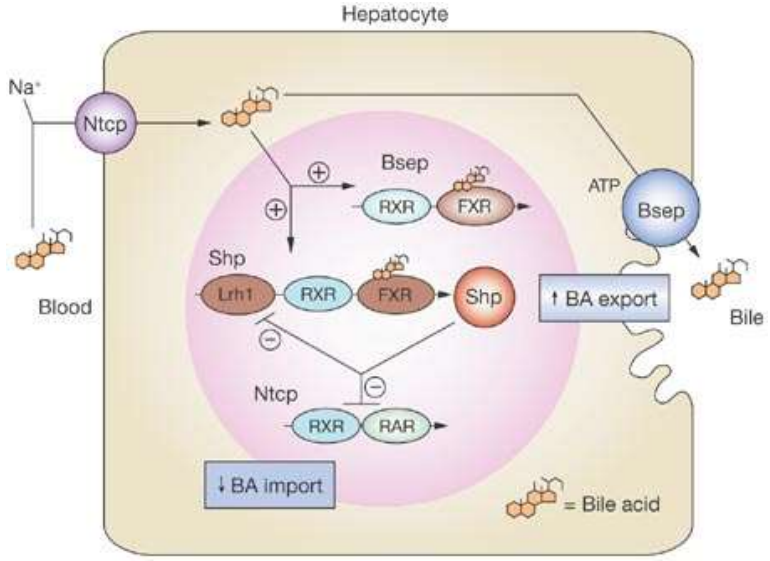
- Urinary tract infections, mycotic infections (e.g. vaginal candidiasis)
- Increased rik of bone fractures
- Increased risk of polyuria, dehydration, hypotension and hypoglycemia.

3.2. Other compounds I

- **Colesevelam** (used as bile acid sequestrant, antihyperlipidemic agent) decreases the blood glucose level, in US registered for treatment of DM too

Mechanism of action not clear, perhaps it activates the farneosid X receptor (FXR).

FXR in the liver has a key role in the regulation of the cholesterol, glucose and bile acid metabolism



- **Bromocriptine** – it decreases the plasma glucose level with an unknown mechanism (registered in the US as adjuvant drug)

3.2. Other compounds II

Drugs in the management of diabetic neuropathia

Benfotiamine – lipid soluble prodrug of vitamin B_1

Thioctic acid (alpha lipoic acid) – a vitamin like compound, essential for aerobic metabolism, antioxidant

3.2. ANTI-HYPERGLYCEMIC THERAPY

Oral agents

Sulfonylureas ✓
Meglitinides ✓

} insulin release enhancing (insulinotrop/secretagog) compounds

Metformin (biguanides) ✓
Thiazolidinediones (glitazones) ✓

} insulin effect enhancing compounds

DPP-4 inhibitors ✓

} incretin effect prolonging compounds

insulin-dependent compounds

α-glucosidase inhibitors (AGIs) ✓
SGLT-2 inhibitors ✓

} insulin-independent compounds

Dopamine-2 agonist (low dose bromocriptine – only in US)

Bile acid sequestrants ✓

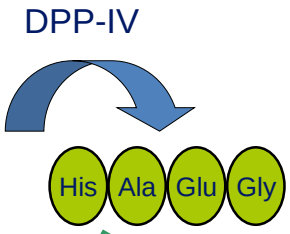
Non-insulin injectables

GLP-1 receptor agonists
Amylin mimetics

} parenteral – non-insulin injectables

3.2. Agents acting on the GLP-1 receptor

exenatide Originally was discovered in the saliva of glia monster



Amino acid changes or variations confer resistance to DPP4

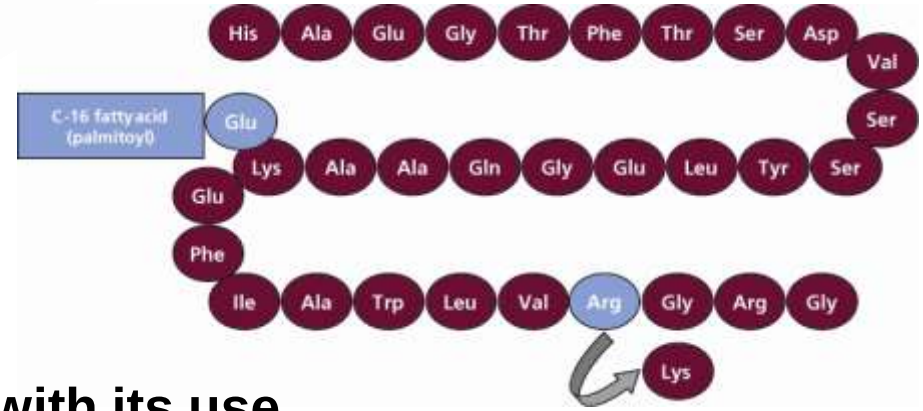
administration sc. twice a day, connected to food intake

retard preparation is available

3.2. Long acting GLP-1 analogs

lixisenatide

liraglutide



sc. once a day

Liraglutide is approved for the treatment of obesity

– 4-6 kg weigth loss is acheiavable with its use

Side effects: **diarrhea, heartburn, indigestion, nausea, and vomiting**

dizziness, headache

acute pancreatitis

may increase thyroid cancer risk

3.2. Ultra long acting GLP-1 analogs

albiglutide

Fusion to human albumin

withdrawn from market in 2018 (probably due to lower efficacy to reduce HbA1c levels)

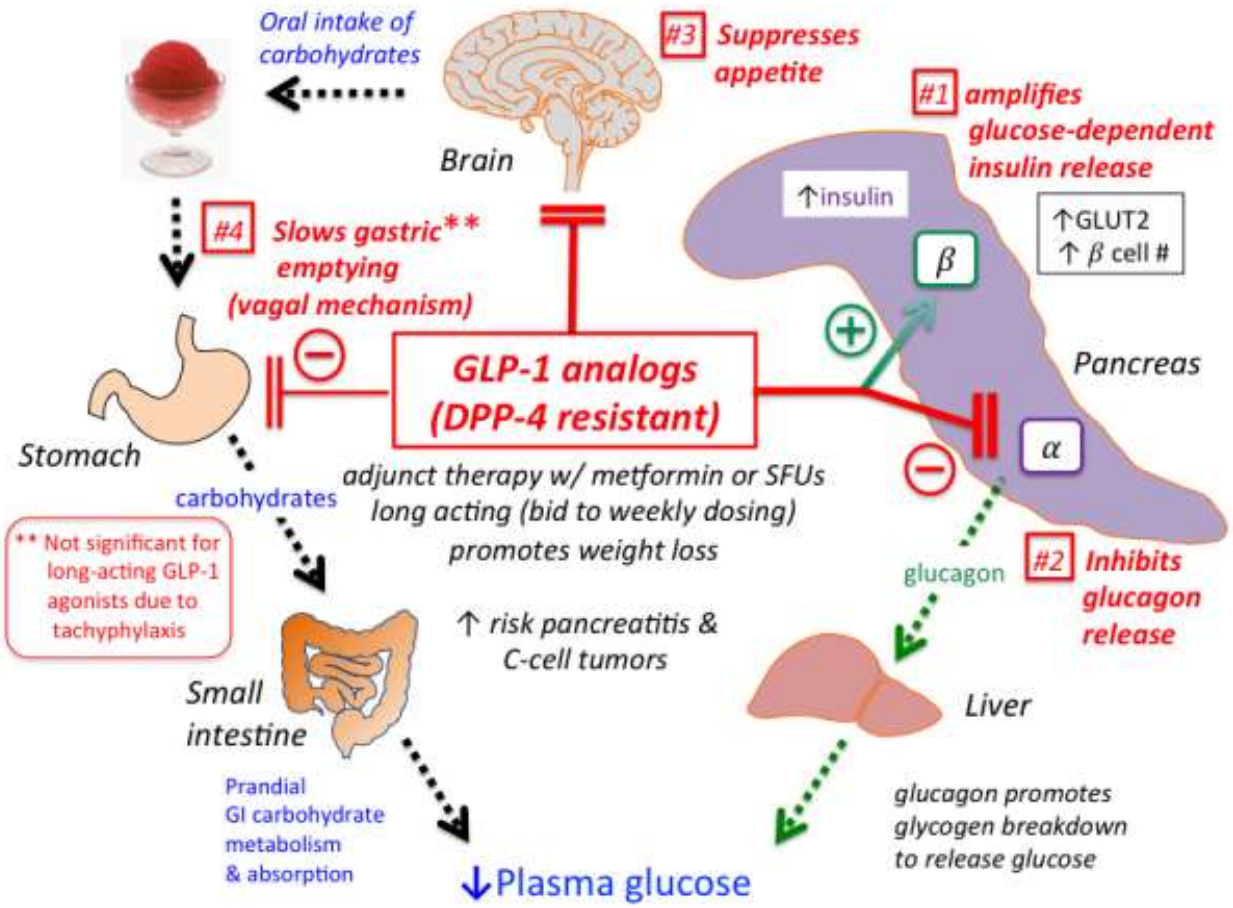
dulaglutide

sc. once a week

3.2. Agents acting on the GLP-1 receptor

Effects of the GLP-1 analogs

- glucose-mediated insulin release
- reduction of the postprandial glucagon release
- delaying gastric emptying
- decrease of appetite (central effect)



3.2. Agents acting on the GLP-1 receptor

Advantageous characteristics

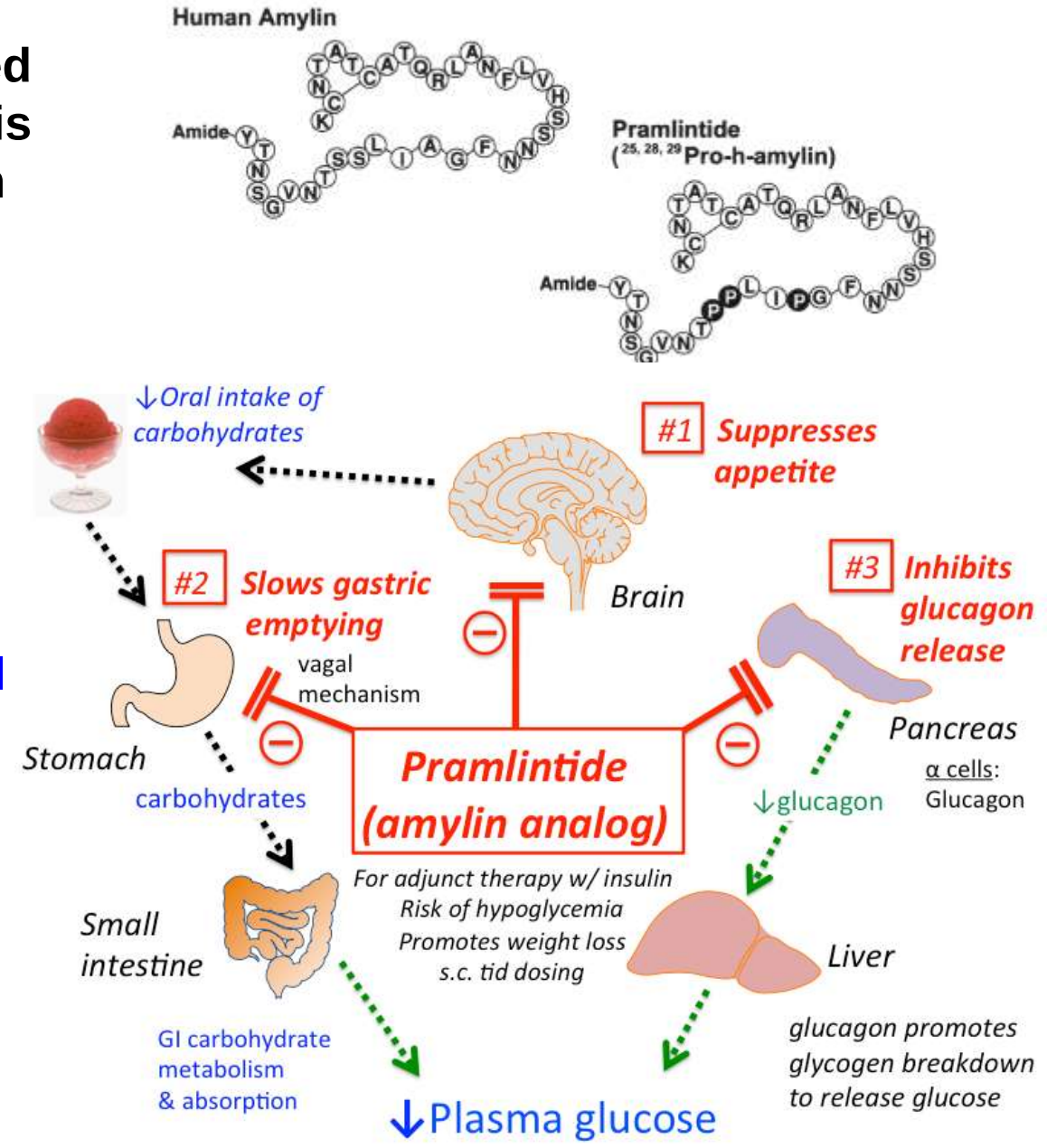
- Effect is glucose dependent, influence the postprandial glucose level – no hypoglycemia
- Decrease of body weight

Therapeutical use

- Adjuvant treatment in T2DM
- Liraglutide is used in obesity for weight reduction

3.2. Amylin analog: *pramlintide*

- **Islet amyloid polypeptied (IAPP – human amylin) is co-secreted with insulin from β-cells.**
- **There is amylin deficinecy in diabetes (Type I and II.)**
- **Synthetic analog: pramlinitide**
- used in Type I and Type II diabetes as well as in morbid obesity sc., preprandial
- **Relatively high risk of hypoglycemia**
- **GI side effects: nausea, anorexia, vomiting**



3.2. ANTI-HYPERGLYCEMIC THERAPY

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Meglitinides ✓

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DPP-4 inhibitors ✓

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Dopamine-2 agonist (low dose bromocriptine – only in US)

Bile acid sequestrants ✓

Non-insulin injectables

GLP-1 receptor agonists ✓
Amylin mimetics ✓

→ parenteral – non-insulin injectables

4. Combination therapy in T2DM

First drug of choice - metformin

- **combination of OADs** (double or triple therapy)
  - metformin + DPP4 inhibitor
  - metformin + sulfonylureas
  - metformin + glitazones
    - + alpha glucosidase inhibitors
    - + SGLT-2 inhibitors

- in case metformin is contraindicated
  - DPP4 inhibitor alone, SGLT2 inhibitor alone, or SU alone
  - DPP4 inhibitor + SGLT2 inhibitor

For better patient compliance fixed drug combinations are available.

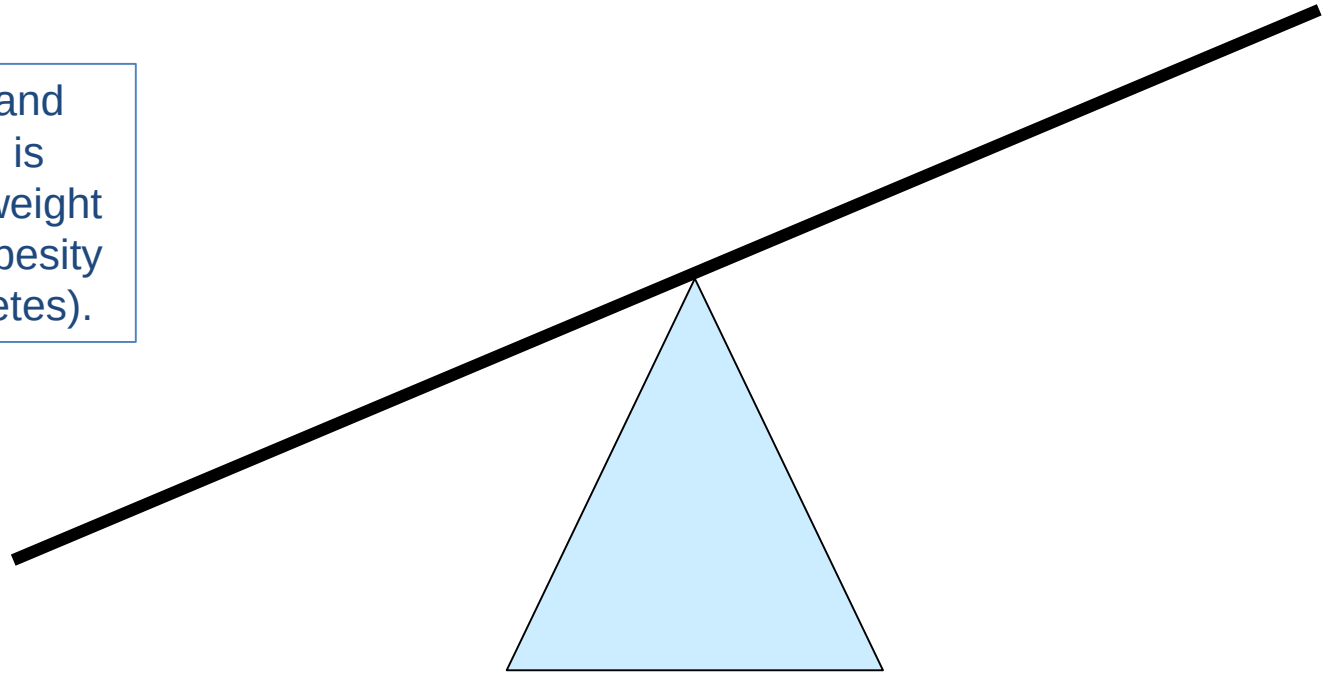
- **combination with insulin** (not the sulfonylureas !!!)
  combination with GLP-1 analogs
- during surgery, serious infection, etc. – **switch to insulin**

in pregnancy always use insulin

4. Effect of antidiabetics on the body weight

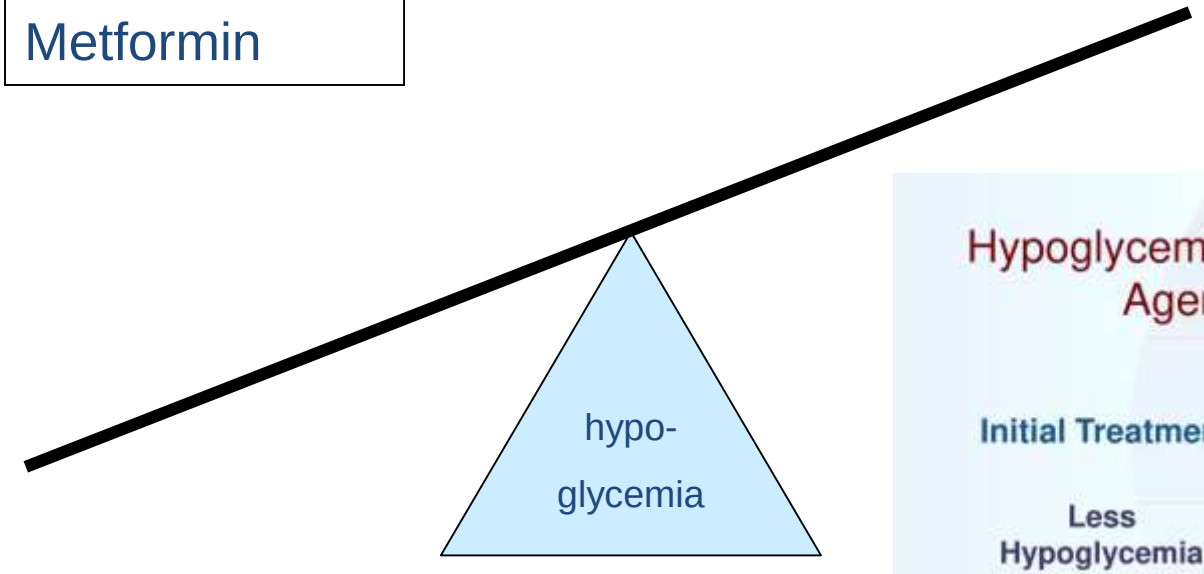
body weight ↓	body weight Ø	body weight ↑
Metformin SGLT-inhibitor GLP-1 analogs	Metformin DPP-4 inhibitors	SU Meglitinides TZD insulin

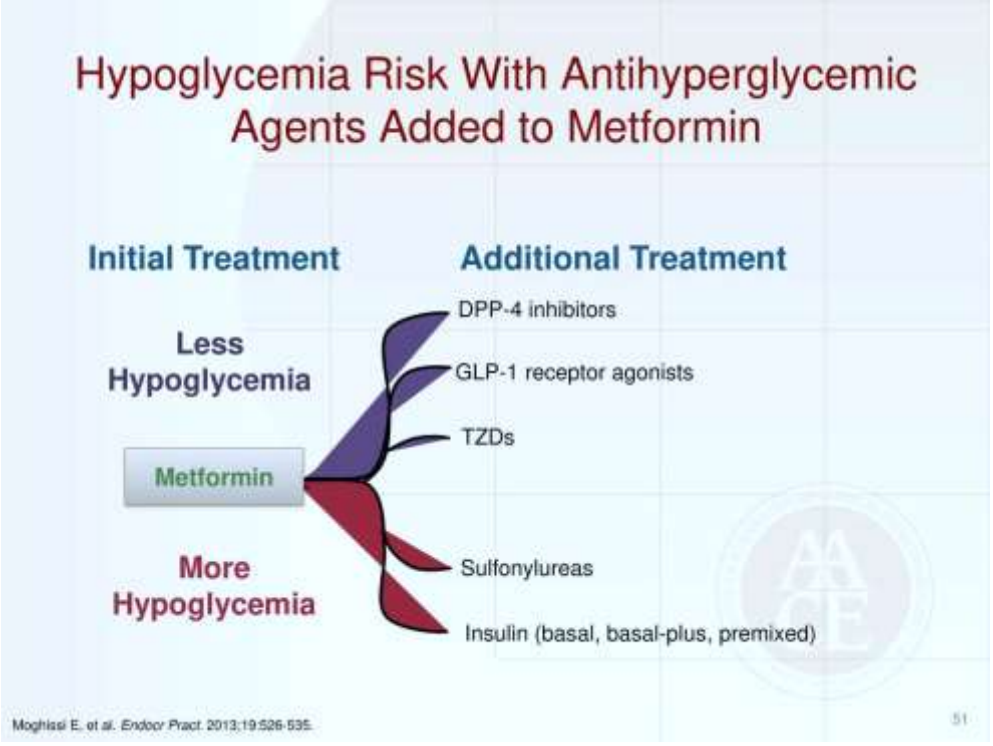
Liraglutide, and pramlintide is indicated for weight reduction in obesity (without diabetes).



4. Risk of hypoglycemia with various antidiabetics

Low risk	Moderate risk	High risk
TZD GLP-1 analogs AGIs DPP-4 inhibitors Metformin	SGLT2-inhibitors	SU Meglitinides Insulin





4. DRUG INTERACTIONS I.

Potentiation of the insulin effect (hypoglycemia)

- **decrease of carbohydrate absorption,**
  anorectic drugs, drugs inducing emesis
  (anticancer therapy!)

- **reduction of gastric emptying - parasympatholytics**,
  opioids

- **inhibition of the sympathetic answer**
  β-blockers, adrenergic neuron blockers
  (they, prolong the hypoglycemia, mask the symptoms of hypoglycemia)

- **Ethanol -** increase in insulin secretion, decrease in glyconeogenesi**s**

- **Salicylates**

4. DRUG INTERACTIONS II

Potentiation of the effect (hypoglycemia)

Oral antidiabetics as with insulin

+

- **agents competing for plasma protein**
  (eg. salicylates, phenylbutazone, sulfonamides, cumarines, etc.)
- **drugs inhibiting the metabolism**
  (eg. sulfonamides, phenylbutazone, chloramphenicol)
- **drugs inhibiting kidney elimination**
  (eg. salicylates, phenylbutazone, probenecid, acidosis in the urine)

4. DRUG INTERACTIONS III

Decrease of insulin effect (hyperglycemia)

- **enhancement of glucose absorption (e.g. cough syrups!)**
- **β-stimulators (dobutamine, terbutaline, e.g.)**
- **insulin antagonist hormones**
  corticosteroids,
  contraceptives,
  thyroid hormone
- **thiazide diuretics**
- **phenytoin by decreasing insulin release**

4. DRUG INTERACTIONS IV

Decrease of insulin effect (hyperglycemia)

Oral antidiabetics as with insulin

+

- **enzyme inducers (phenytoin, barbiturate, rifampin)**
- **enhancement of kidney elimination**

5. TREATMENT OF DIABETIC COMA

- **Volume replacement**
  (isotonic sodium chloride or 0.45%)

- **Insulin**
  aim – slow decrease of blood glucose (max 3 mmol/l/hr)
  below 13 mmol/l very slow decrease (until 8 mmol/l during 12-24 hr)

- **Glucose -** when the blood glucose falls below 10-13 mmol/l

- **K^+** (from the 3rd hours)

- **Bicarbonate** - only if plasma pH< 7.0

Drugs enhancing the blood glucose level

5. TREATMENT OF HYPOGLYCEMIA I

Glucagon – in acute case 0,5-2 mg i.m.

5. TREATMENT OF HYPOGLYCEMIA II (insulinomas)

Diazoxide

mechanism of action: activation of the K^+- dependent ATP channel reduction of insulin secretion, reduction of glucose utilization

adverse effects: oedema, tachycardia

Octreotide

mechanism of action: somatostatin analog – inhibition of insulin secretion

Streptozocine (nitrosourea - cytostatic)

for malignant pancreatic insulinoma

mechanism of action:

reduction of DNA synthesis

adverse effects: tubular necrosis, hepatotoxicity, hematological abnormalities

6. EXTRA SLIDES

- COMPREHENSIVE TABLES

- CLINICAL GUIDE FOR ANTIHYPERGLYCEMIC THERAPY

Oral Class	Mechanism	Advantages	Disadvantages	Cost
Biguanides	• Activates AMP-kinase (?other) • ↓ Hepatic glucose production	• Extensive experience • No hypoglycemia • Weight neutral • ? ↓ CVD	• Gastrointestinal • Lactic acidosis (rare) • B-12 deficiency • Contraindications	Low
Sulfonylureas	• Closes K_{ATP} channels • ↑ Insulin secretion	• Extensive experience • ↓ Microvascular risk	• Hypoglycemia • ↑ Weight • Low durability • ? Blunts ischemic preconditioning	Low
Meglitinides	• **Closes KATP channels** • **↑ Insulin secretion**	• **↓ Postprandial glucose** • **Dosing flexibility**	• **Hypoglycemia** • **↑ Weight** • **? Blunts ischemic preconditioning** • **Dosing frequency**	**Mod.**
TZDs	• PPAR-γ activator • ↑ Insulin sensitivity	• No hypoglycemia • Durability • ↓ TGs (pio) • ↑ HDL-C • ? ↓ CVD events (pio)	• ↑ Weight • Edema/heart failure • Bone fractures • ↑ LDL-C (rosi) • ? ↑ MI (rosi)	Low

Table 1. Properties of oral anti-hyperglycemic agents

Oral Class	Mechanism	Advantages	Disadvantages	Cost
α-Glucosidase inhibitors	• Inhibits a-glucosidase • Slows carbohydrate digestion / absorption	• No hypoglycemia • Nonsystemic • ↓ Postprandial glucose • ? ↓ CVD events	• Gastrointestinal • Dosing frequency • Modest ↓ A1c	Mod.
DPP-4 inhibitors	• Inhibits DPP-4 • Increases incretin (GLP-1, GIP) levels	• No hypoglycemia • Well tolerated	• Angioedema / urticaria • ? Pancreatitis • ? ↑ Heart failure	High
Dopamine-2 Agonist bromocriptine (only in US)	• Activates DA receptor • Alters hypothalamic control of metabolism • ↑ insulin sensitivity	• No hypoglyemia • ? ↓ CVD events	• Modest ↓ A1c • Dizziness, fatigue • Nausea • Rhinitis	High
SGLT2 inhibitors	• Inhibits SGLT2 in proximal nephron • Increases glucosuria	•↓ Weight • No hypoglycemia • ↓ BP • Effective at all stages	• GU infections • Polyuria • Volume depletion • ↑ LDL-C • ↑Cr (transient)	High

Table 2. Properties of oral anti-hyperglycemic agents

Injectable Class	Mechanism	Advantages	Disadvantages	Cost
Amylin mimetics	• Activates amylin receptor • ↓ glucagon • ↓ gastric emptying • ↑ satiety	• ↓ Weight • ↓ Postprandial glucose	• Gastrointestinal • Modest ↓ A1c • Injectable • Hypo if insulin dose not reduced • Dosing frequency • Training requirements	High
GLP-1 receptor agonists	• Activates GLP-1 R • ↑ Insulin, ↓ glucagon • ↓ gastric emptying • ↑ satiety	• ↓ Weight • No hypoglycemia • ↓ Postprandial glucose • ↓ Some CV risk factors	• Gastrointestinal • ? Pancreatitis • ↑ Heart rate • Medullary ca (rodents) • Injectable • Training requirements	High
Insulin	• Activates insulin receptor	• Universally effective • Unlimited efficacy • ↓ Microvascular risk	• Hypoglycemia • Weight gain • ? Mitogenicity • Injectable • Patient reluctance • Training requirements	Variable

Table 3. Properties of injectable anti-hyperglycemic agents

CLINICAL RECOMMENDATIONS FOR SEQUENTIAL ANTIHYPERGLYCEMIC THERAPY

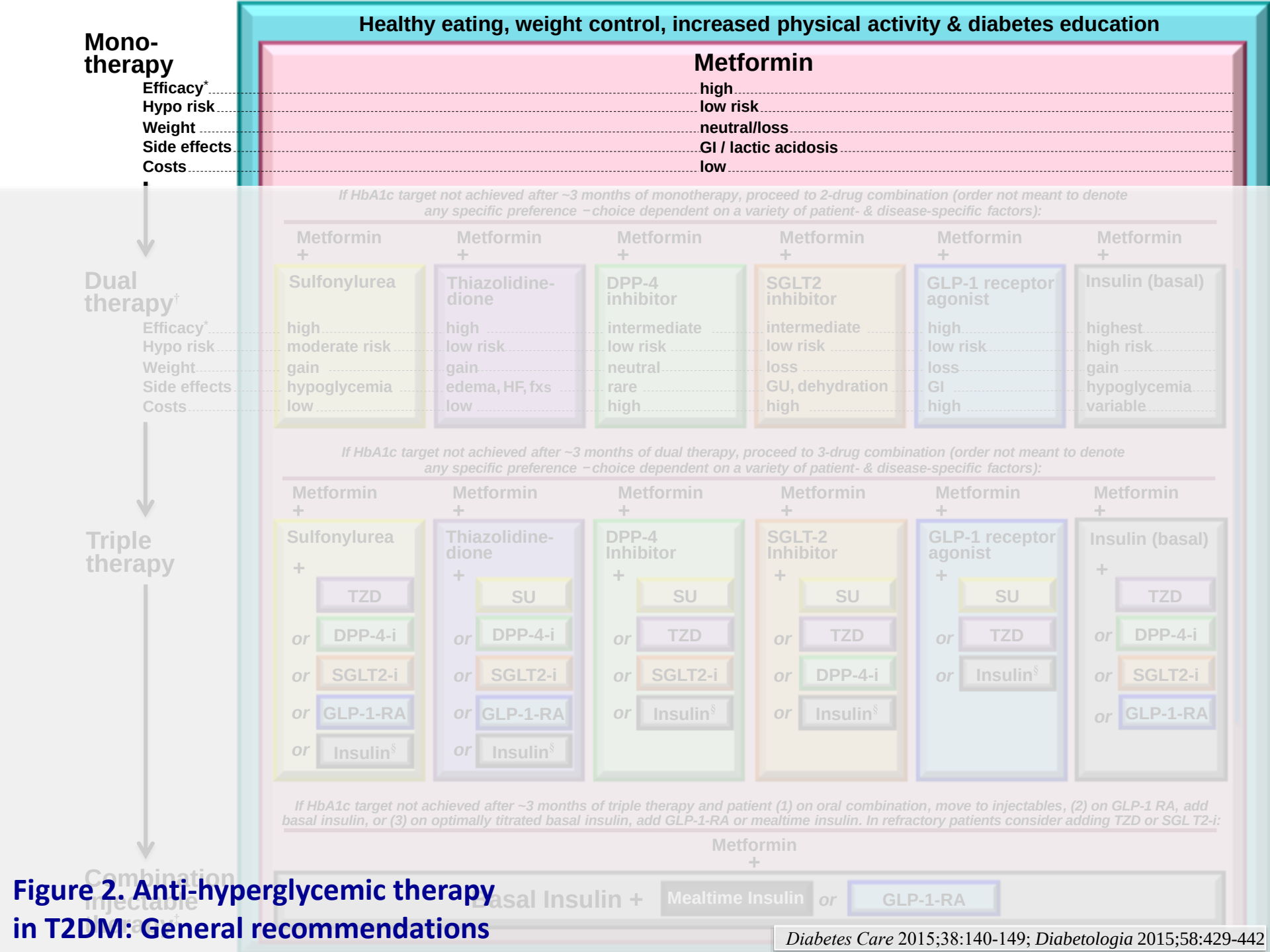


Figure 2. Anti-hyperglycemic therapy in T2DM: General recommendations

Diabetes Care 2015;38:140-149; *Diabetologia* 2015;58:429-442

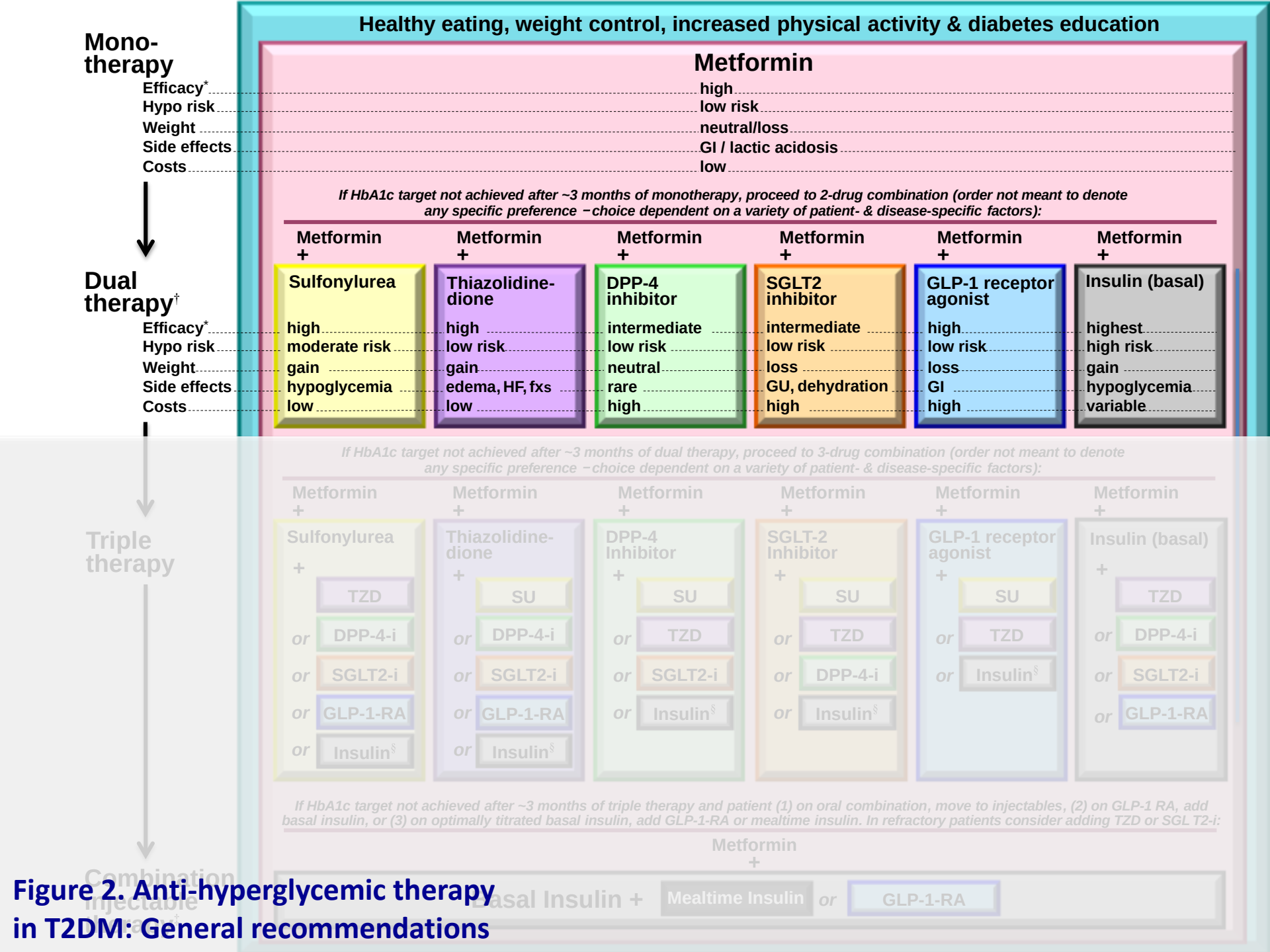


Figure 2. Anti-hyperglycemic therapy in T2DM: General recommendations

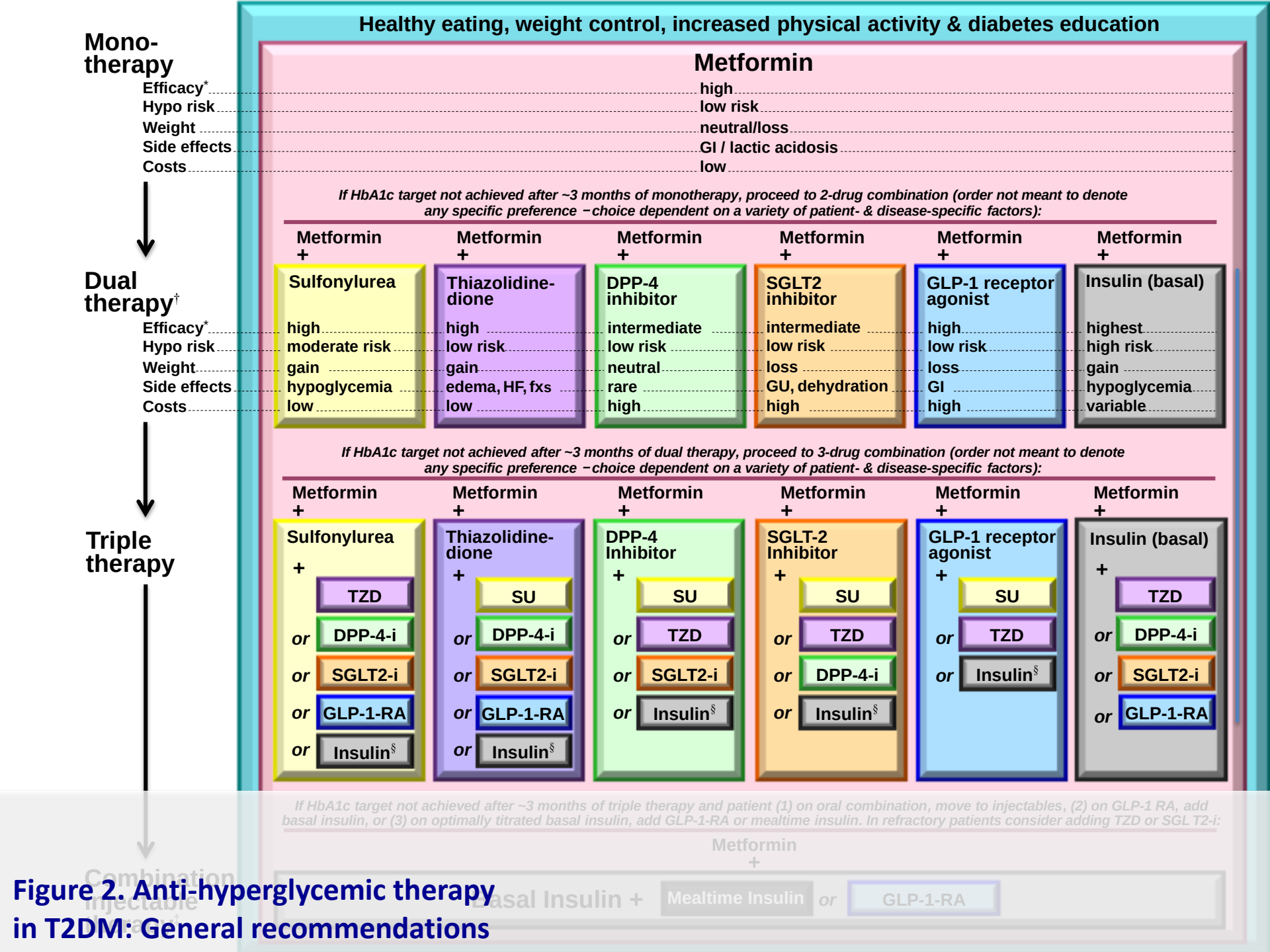
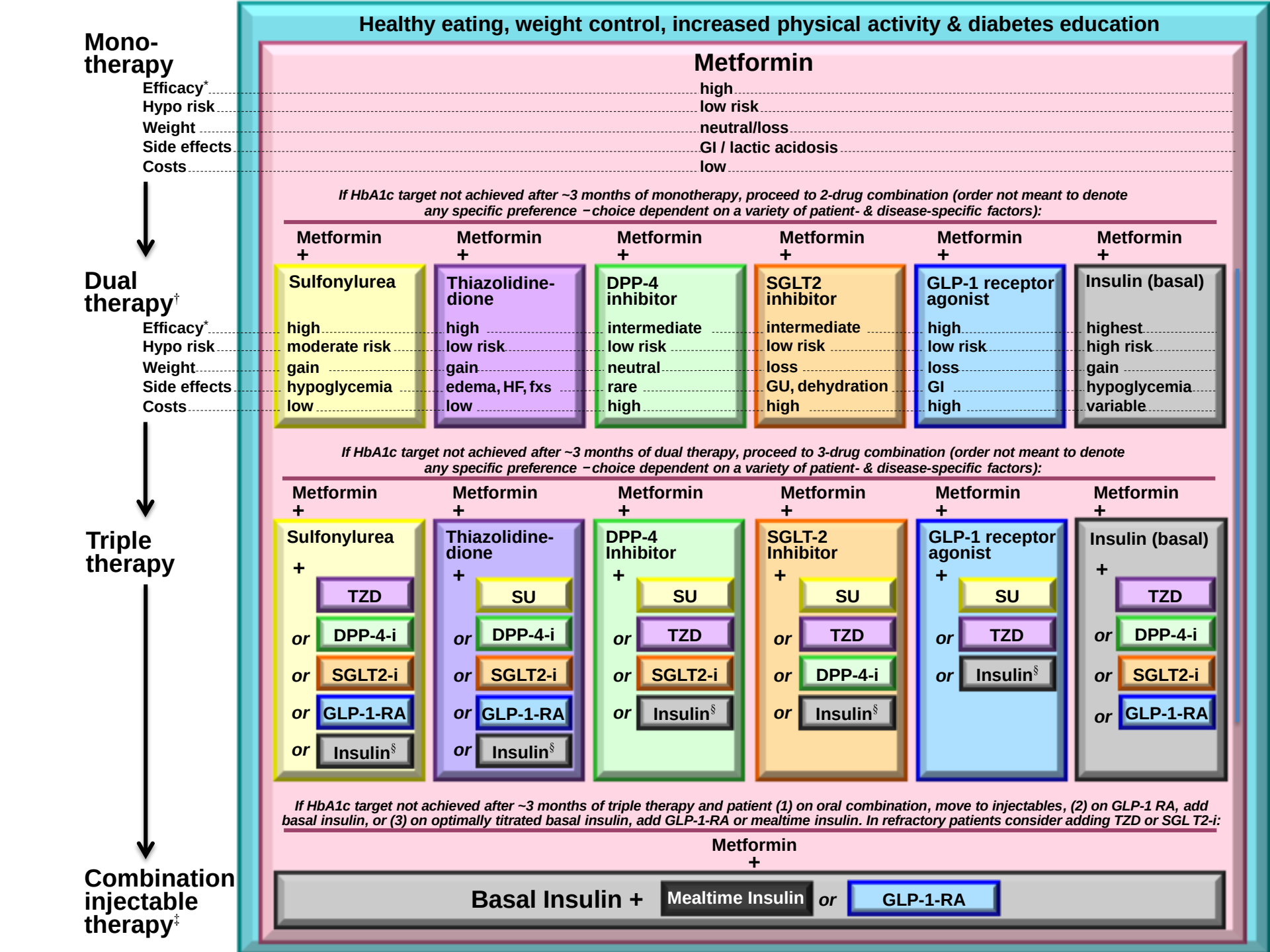


Figure 2. Anti-hyperglycemic therapy in T2DM: General recommendations


Healthy eating, weight control, increased physical activity & diabetes education
Mono-therapy
Metformin
Efficacy*
high
Hypo risk
low risk
Weight
neutral/loss
Side effects
GI / lactic acidosis
Costs
low
If HbA1c target not achieved after ~3 months of monotherapy, proceed to 2-drug combination (order not meant to denote any specific preference −choice dependent on a variety of patient- & disease-specific factors):
Dual therapy†
Metformin + Sulfonylurea
Efficacy* high
Hypo risk moderate risk
Weight gain
Side effects hypoglycemia
Costs low
Metformin + Thiazolidine-dione
high
low risk
gain
edema, HF, fxs
low
Metformin + DPP-4 inhibitor
intermediate
low risk
neutral
rare
high
Metformin + SGLT2 inhibitor
intermediate
low risk
loss
GU, dehydration
high
Metformin + GLP-1 receptor agonist
high
low risk
loss
GI
high
Metformin + Insulin (basal)
highest
high risk
gain
hypoglycemia
variable
If HbA1c target not achieved after ~3 months of dual therapy, proceed to 3-drug combination (order not meant to denote any specific preference −choice dependent on a variety of patient- & disease-specific factors):
Triple therapy
Metformin + Sulfonylurea + TZD or DPP-4-i or SGLT2-i or GLP-1-RA or Insulin§
Metformin + Thiazolidine-dione + SU or DPP-4-i or SGLT2-i or GLP-1-RA or Insulin§
Metformin + DPP-4 Inhibitor + SU or TZD or SGLT2-i or Insulin§
Metformin + SGLT-2 Inhibitor + SU or TZD or DPP-4-i or Insulin§
Metformin + GLP-1 receptor agonist + SU or TZD or Insulin§
Metformin + Insulin (basal) + TZD or DPP-4-i or SGLT2-i or GLP-1-RA
If HbA1c target not achieved after ~3 months of triple therapy and patient (1) on oral combination, move to injectables, (2) on GLP-1 RA, add basal insulin, or (3) on optimally titrated basal insulin, add GLP-1-RA or mealtime insulin. In refractory patients consider adding TZD or SGL T2-i:
Combination injectable therapy‡
Metformin +
Basal Insulin + Mealtime Insulin or GLP-1-RA

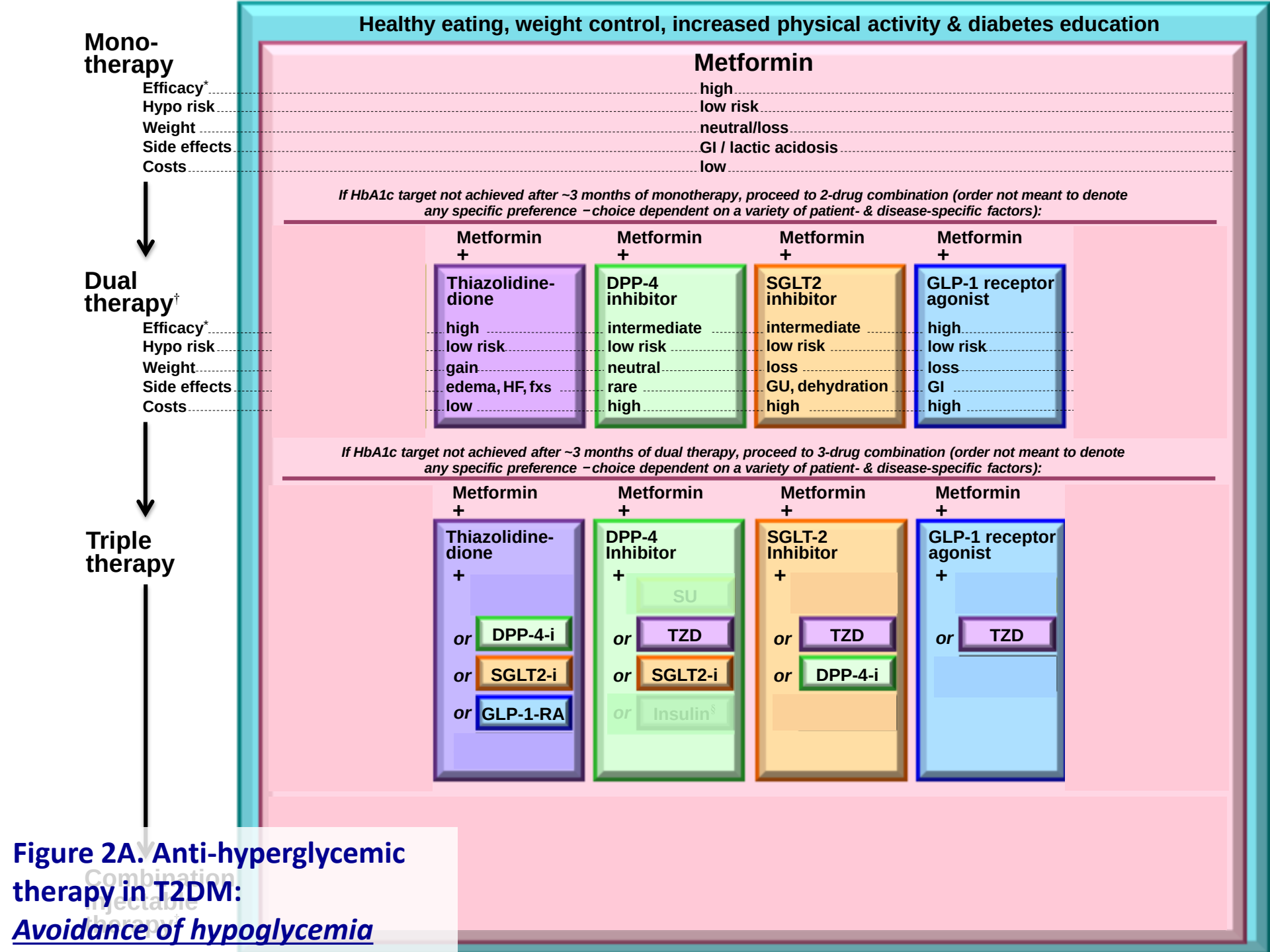


Figure 2A. Anti-hyperglycemic therapy in T2DM: *Avoidance of hypoglycemia*

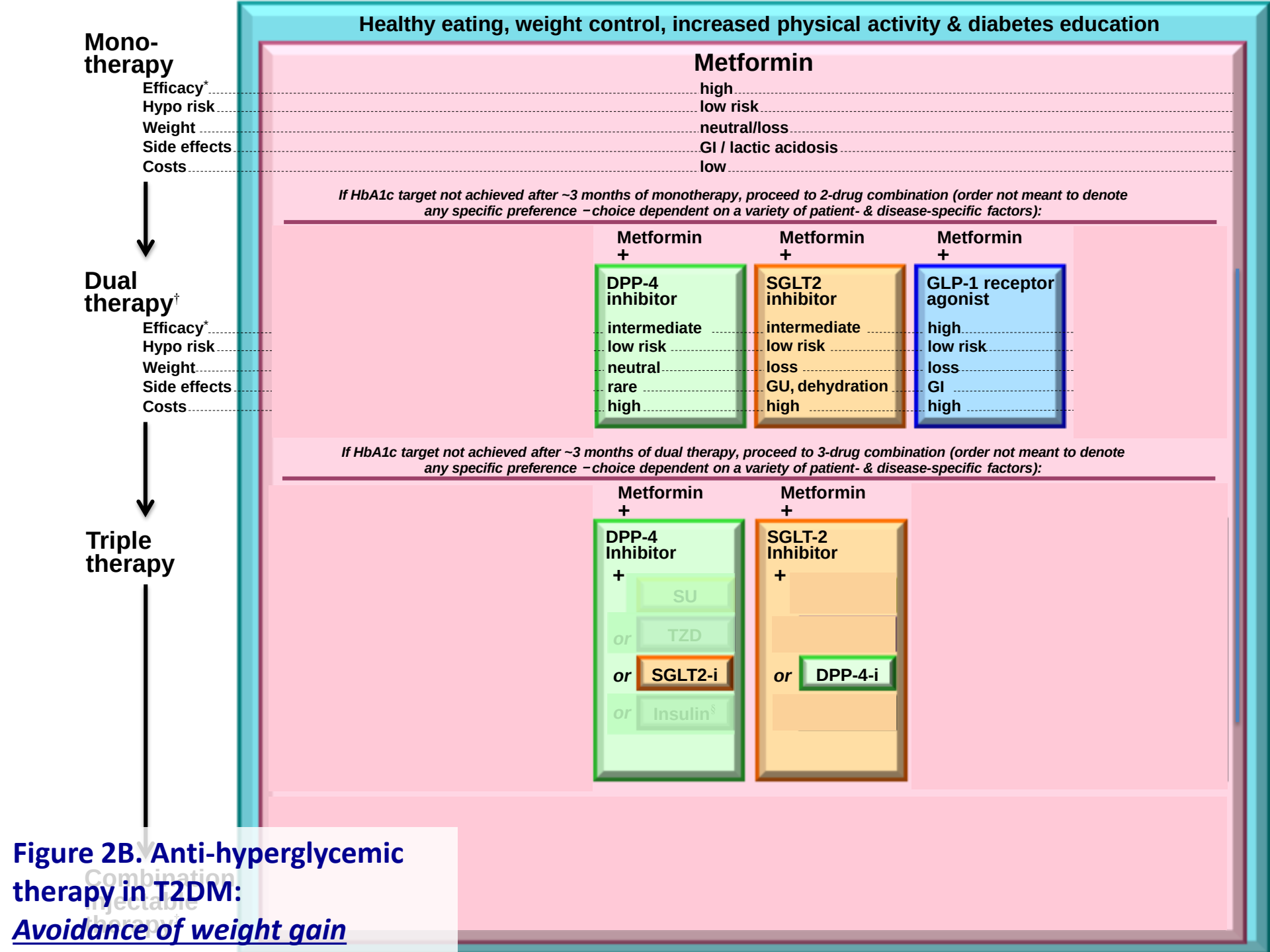


Figure 2B. Anti-hyperglycemic therapy in T2DM:
Avoidance of weight gain

OTHER CONSIDERATIONS

- Age
- Weight
- Sex / racial / ethnic / genetic differences
- Comorbidities
  - Coronary artery disease
  - Heart Failure
  - Chronic kidney disease
  - Liver dysfunction
  - Hypoglycemia-prone

KEY POINTS

- Glycemic targets & BG-lowering therapies must be individualized, based on a variety of patient and disease characteristics.
- Diet, exercise, & education: foundation of any T2DM therapy program.
- Unless contraindicated, metformin remains the optimal first-line drug.
- After metformin, data are limited. Combination therapy with 1-2 other oral / injectable agents is reasonable. Try to minimize side effects.
- Ultimately, many patients will require insulin therapy alone or in combination with other agents to maintain BG control.
- All treatment decisions should be made in conjunction with the patient (focusing on his or her preferences, needs & values.)
- Comprehensive CV risk reduction - a major focus of therapy.