Type 2 Diabetes Mellitus Pathogenesis and Management

Alireza Esteghamati, MD

Professor of Endocrinology and Metabolism

TUMS

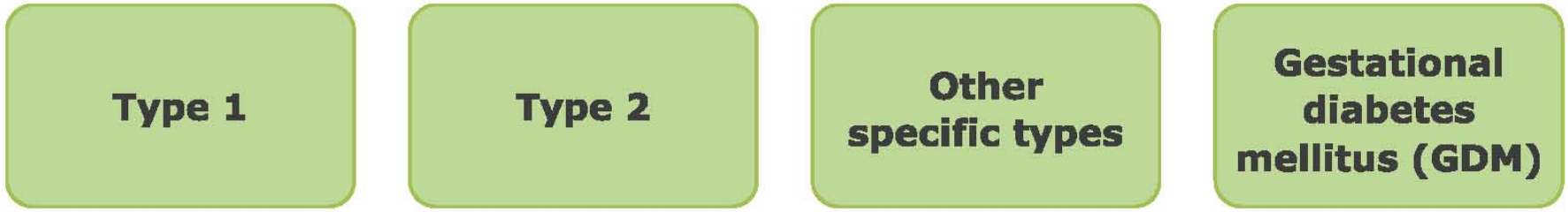
Definition

Diabetes mellitus

A chronic disorder characterized by a deficiency of insulin secretion and/or insulin effect

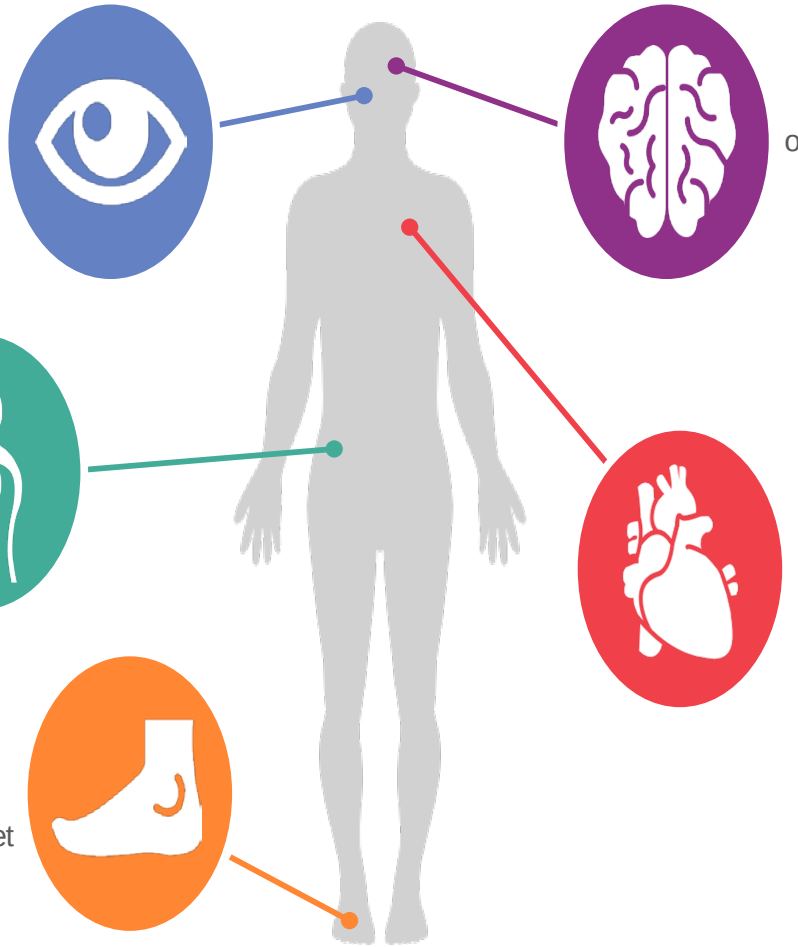
1. Which causes hyperglycemia
2. Disturbances of carbohydrate, fat and protein metabolism
3. Constellation of chronic complications .

The major forms of diabetes



Diabetes Care 2005; 28(Suppl 1): S37-S42.

T2D is a complex metabolic disease, with vascular complications affecting multiple organ systems



Diabetic retinopathy[1]

A leading cause of preventable blindness

Stroke[1,2]

2–6 times increased risk of ischaemic attacks compared with adults without diabetes

Renal disease[1]

A leading cause of dialysis and kidney transplant

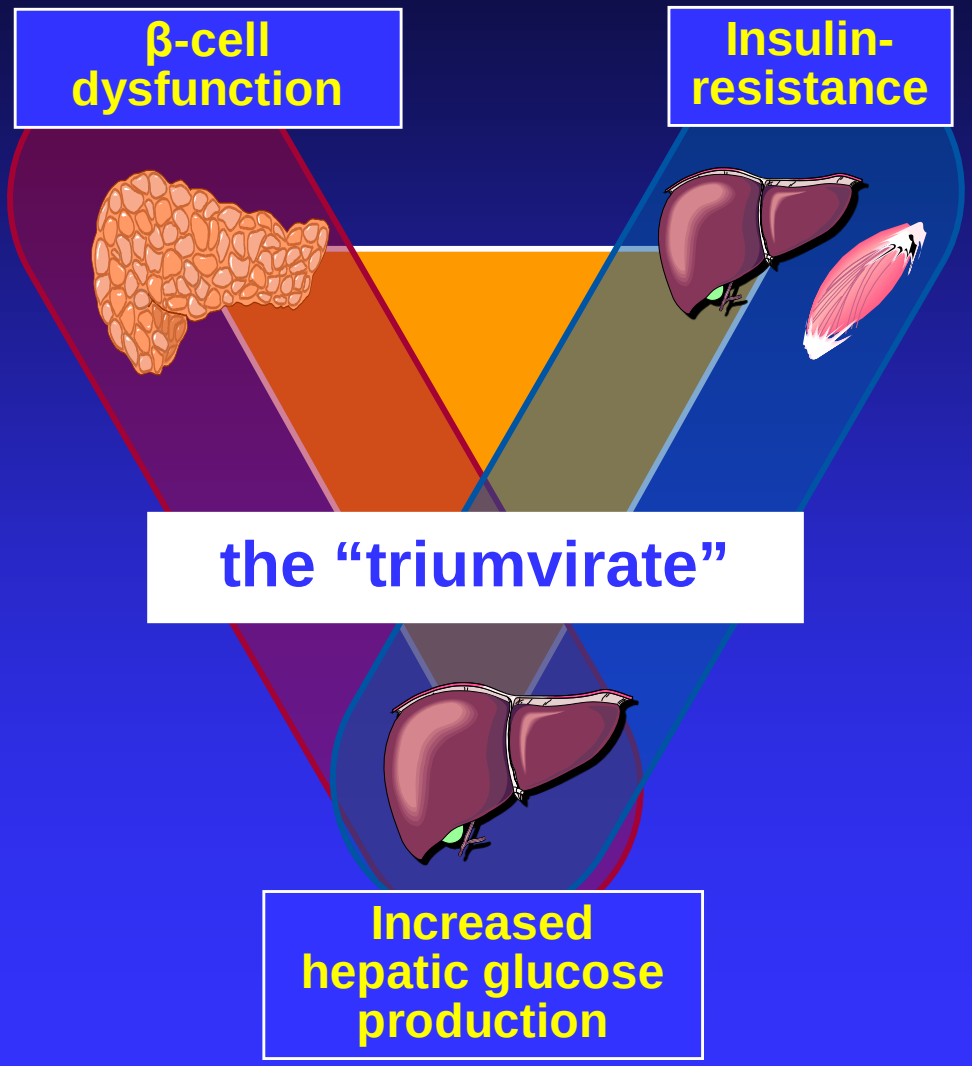
Cardiovascular disease[1,2]

2–4 times increased risk of developing cardiovascular disease compared with adults without diabetes

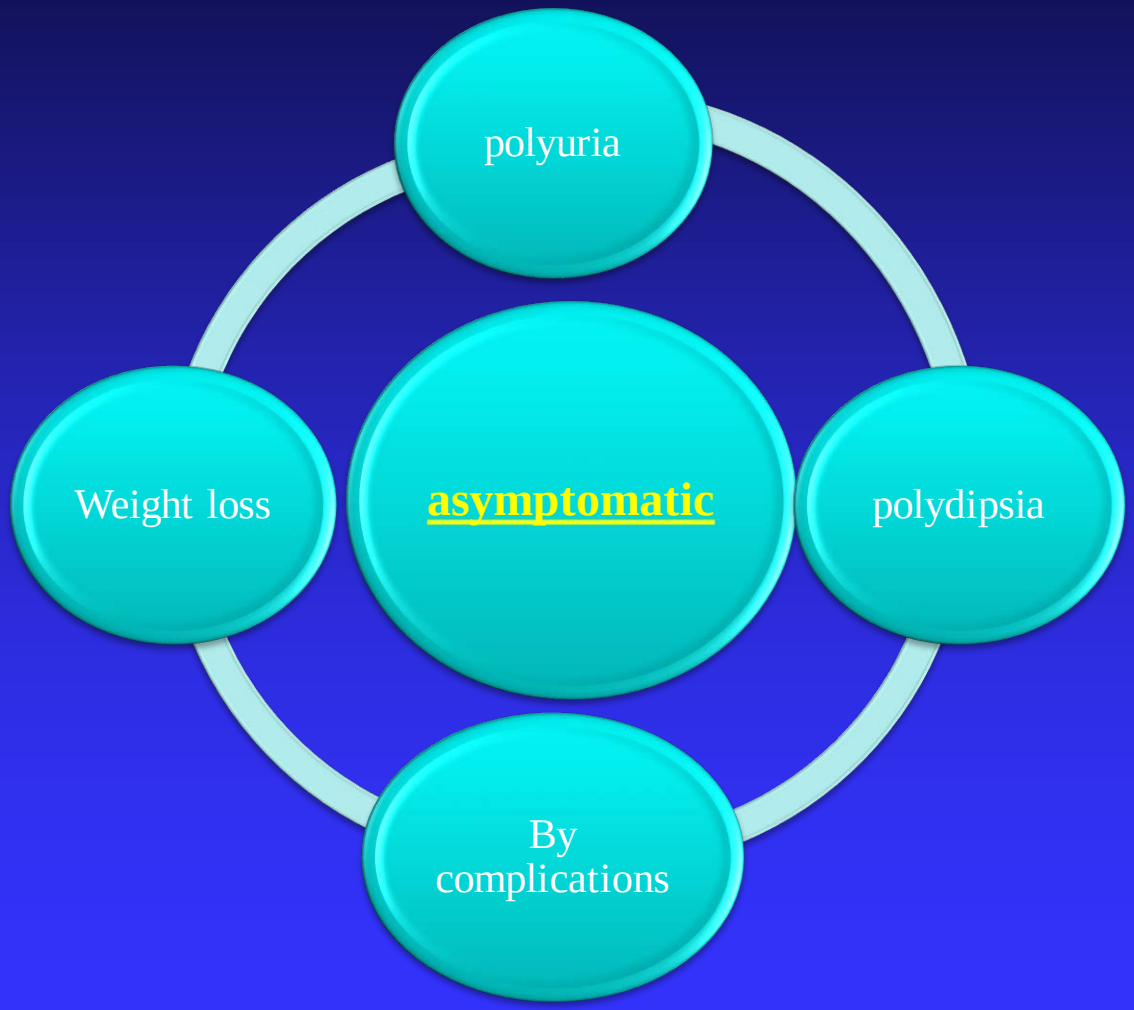
Diabetic neuropathy[1,3]

The most common complication of diabetes; up to 50% of people with T2D have neuropathy and at-risk feet

The 3 main pathophysiological defects of Type 2 diabetes



symptoms


polyuria
Weight loss
asymptomatic
polydipsia
By complications

Symptoms of marked hyperglycemia

- Polyuria, polydipsia
- Weight loss, sometimes with polyphagia
- Blurred vision.
- Impairment of growth
- Susceptibility to certain infections may also accompany chronic hyperglycemia.

Diagnostic tests for diabetes

Criteria for the Diagnosis of Diabetes

A1C ≥6.5%

OR

Fasting plasma glucose (FPG) ≥126 mg/dl (7.0 mmol/l)

OR

Two-hour plasma glucose ≥200 mg/dl (11.1 mmol/l) during an OGTT

OR

A random plasma glucose ≥200 mg/dl (11.1 mmol/l)

American Diabetes Association.

ADA. I. Classification and Diagnosis. *Diabetes Care* 2011;34(suppl 1):S13. Table 2.

Criteria for the Diagnosis of Diabetes

A1C ≥6.5%

The test should be performed in a laboratory using an NGSP-certified method standardized to the DCCT assay*

*In the absence of unequivocal hyperglycemia, result should be confirmed by repeat testing.

American Diabetes Association.

ADA. I. Classification and Diagnosis. *Diabetes Care* 2011;34(suppl 1):S13. Table 2.

Criteria for the Diagnosis of Diabetes

Fasting plasma glucose (FPG)
≥126 mg/dl (7.0 mmol/l)

Fasting: no caloric intake for
at least 8 h*

*In the absence of unequivocal hyperglycemia, result should be confirmed by repeat testing.

American Diabetes Association.

ADA. I. Classification and Diagnosis. *Diabetes Care* 2011;34(suppl 1):S13. Table 2.

Criteria for the Diagnosis of Diabetes

Fasting plasma glucose (FPG)
≥126 mg/dl (7.0 mmol/l)

Fasting: no caloric intake for
at least 8 h*

*In the absence of unequivocal hyperglycemia, result should be confirmed by repeat testing.

American Diabetes Association.

ADA. I. Classification and Diagnosis. *Diabetes Care* 2011;34(suppl 1):S13. Table 2.

Criteria for the Diagnosis of Diabetes

Two-hour plasma glucose ≥200 mg/dl (11.1 mmol/l) during an OGTT

The test should be performed as described by the World Health Organization, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water*

*n the absence of unequivocal hyperglycemia, result should be confirmed by repeat testing.

American Diabetes Association.

ADA. I. Classification and Diagnosis. *Diabetes Care* 2011;34(suppl 1):S13. Table 2.

Criteria for the Diagnosis of Diabetes

In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥200 mg/dl (11.1 mmol/l)

American Diabetes Association.

ADA. I. Classification and Diagnosis. *Diabetes Care* 2011;34(suppl 1):S13. Table 2.

Prediabetes: IFG, IGT, Increased A1C

Categories of increased risk for diabetes (Prediabetes)*

FPG 100-125 mg/dl (5.6-6.9 mmol/l): IFG

or

2-h plasma glucose in the 75-g OGTT
140-199 mg/dl (7.8-11.0 mmol/l): IGT

or

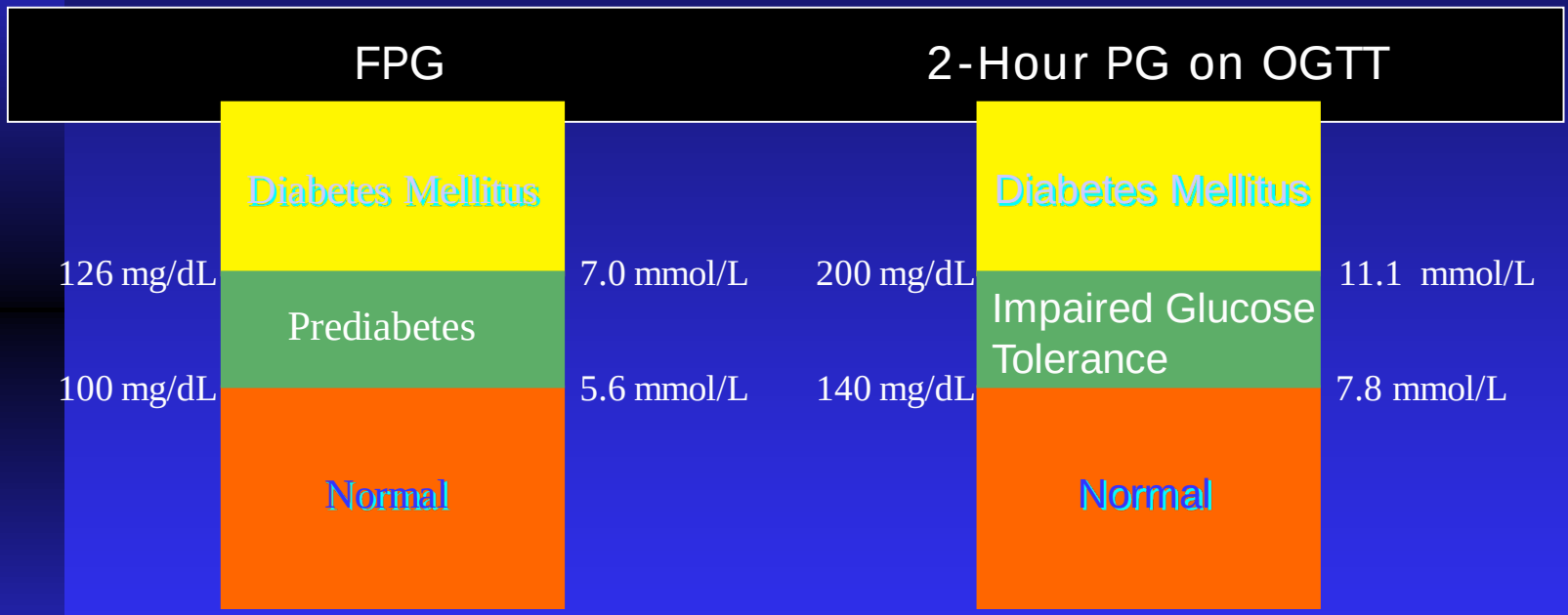
A1C 5.7-6.4%

*For all three tests, risk is continuous, extending below the lower limit of a range and becoming disproportionately greater at higher ends of the range.

American Diabetes Association.

ADA. I. Classification and Diagnosis. *Diabetes Care* 2011;34(suppl 1):S13. Table 3.

Diagnostic Criteria Associated with Glucose Abnormalities

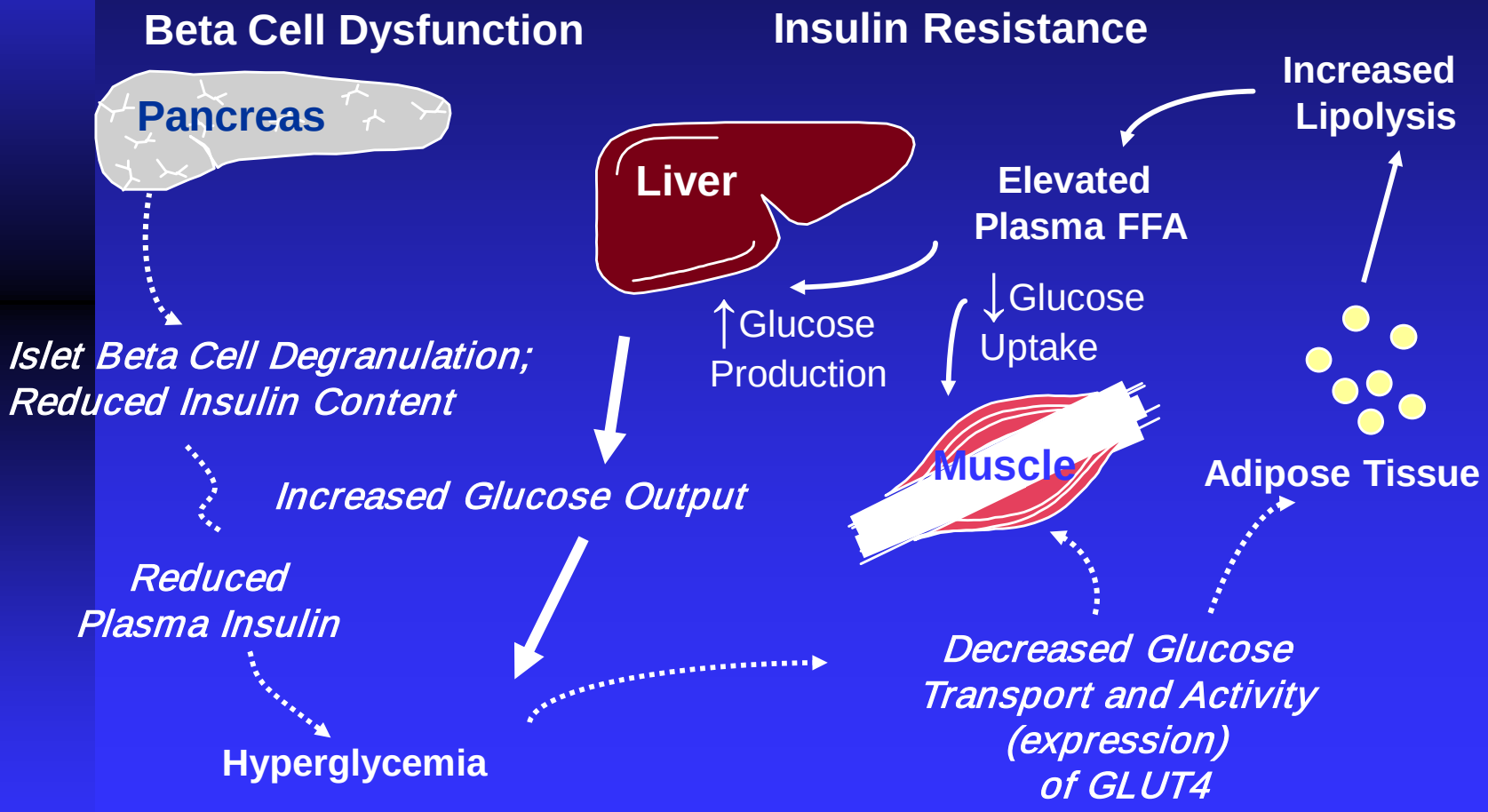


TYPE 2 DM

Central to the development of type 2 DM are:

1. Insulin resistance
2. Abnormal insulin secretion.

Beta Cell Dysfunction and Insulin Resistance Produce Hyperglycemia in Type 2 Diabetes

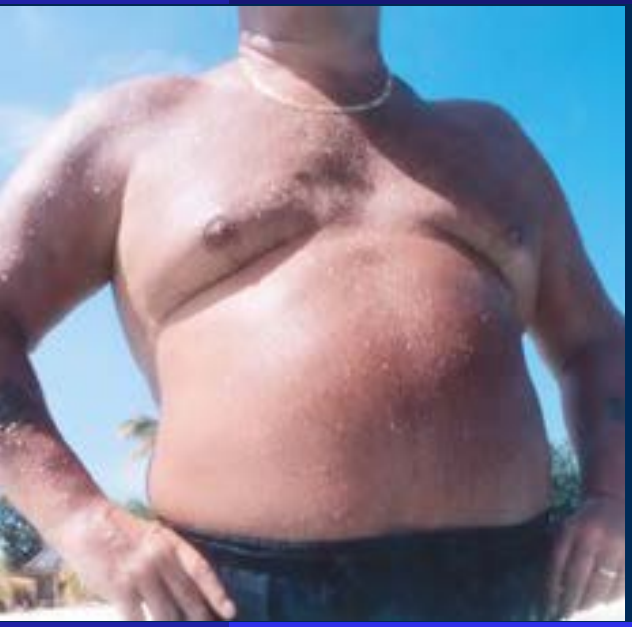


Genetic Considerations

Although controversy remains, most studies support the view that insulin resistance precedes insulin secretory defects

Type 2 DM has a strong genetic component.

disease is polygenic and multifactorial.



~90% of people with type 2 diabetes are overweight or obese

World Health Organization, 2005. http://www.who.int/dietphysicalactivity/publications/facts/obesity

Genetic Considerations

Genes that predispose to type 2 DM are incompletely identified

TCF7 L2

Most prominent is a variant of **the transcription factor 7-like 2 gene that has** been associated with type 2 diabetes

in addition to genetic susceptibility, environmental factors (such as obesity, nutrition, and physical activity) modulate the phenotype.

Genetic Considerations

Genetic polymorphisms associated with type 2 diabetes found in the genes encoding

- Peroxisome proliferators-activated receptor- γ
- K channel in β cells
- zinc transporter in β cells
- IRS
- calpain 10

The interaction between genetics and the environment. “The Pima Indian experience”

Pima Indian from Mexico

Prevalence of diabetes:
11% (W) and **6%** (M)

Pima Indian from Arizona

Prevalence of diabetes:
37% (W) and **54%** (M)

Diabetes Care 1994; 17:1067-1074.

Genetic Considerations

The concordance of type 2 DM in identical twins is between 70 and 90%.

Individuals with a parent with type 2 DM have an increased risk of diabetes

If both parents have type 2 DM, the risk in offspring may reach 40%.

Pathophysiology

Type 2 DM is characterized by

Impaired insulin secretion

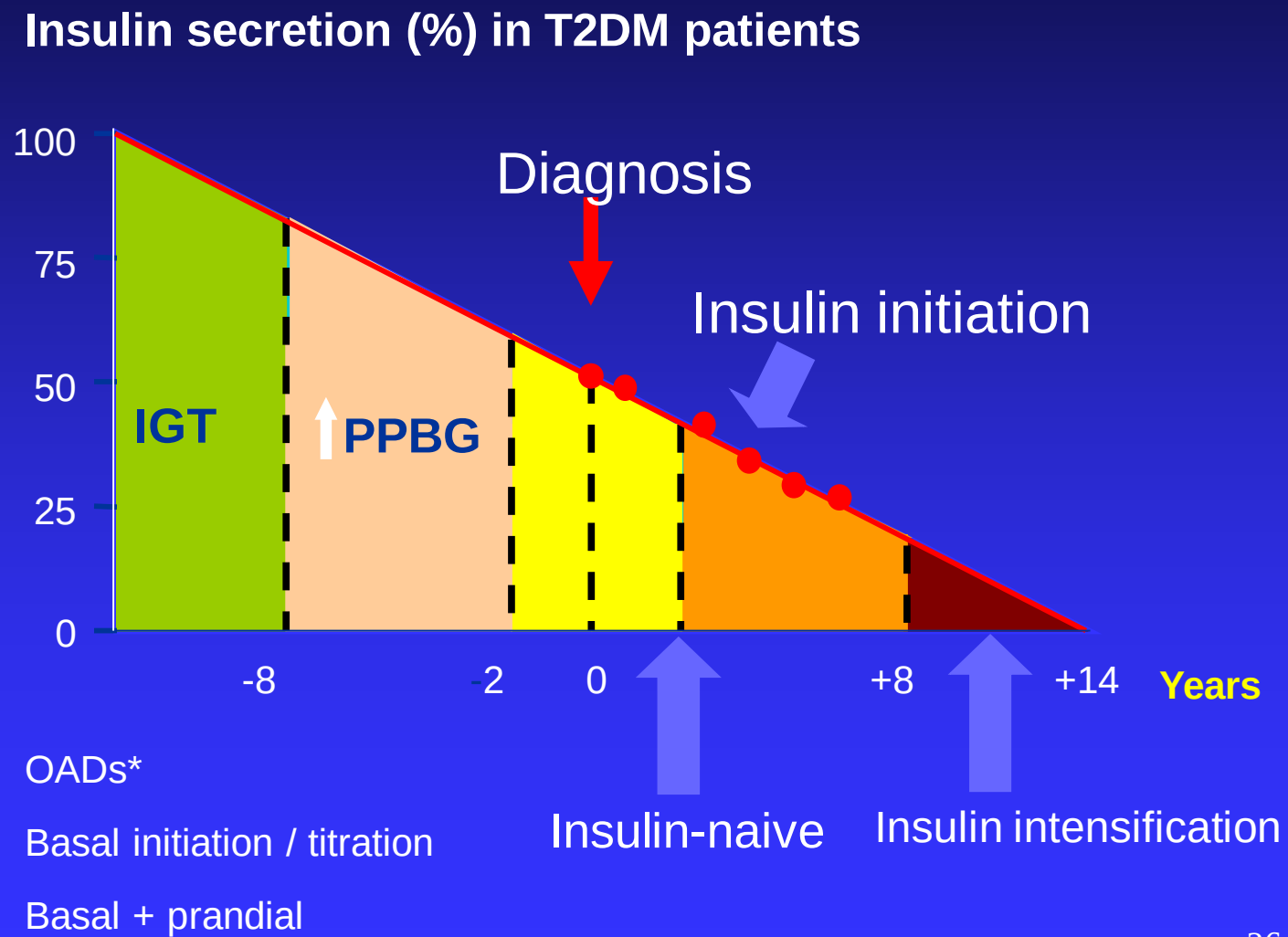
Peripheral insulin resistance

Excessive hepatic glucose production.

Abnormal fat metabolism

Obesity, particularly visceral or central (as evidenced by the hip-waist ratio), is very common in type 2 DM

T2DM is a progressive disease with β-cell function decrease over time



Lebovitz. *Diab Rev* 1999;7:139.

Role of Incretin hormones in the pathogenesis of type 2 diabetes

What are incretins?

- Hormones produced by GIT in response to incoming nutrients, and have important actions that contribute to glucose homeostasis.

Two hormones:

- Glucose-dependent insulinotropic polypeptide (GIP)
- Glucagon-like peptide-1 (GLP-1).

Incretin

Incretins are released from neuroendocrine cells of GI tract following food ingestion and amplify glucose-stimulated insulin secretion and suppress glucagon secretion.

Glucagon-like peptide 1 (GLP-1), the most potent incretin, is released from L cells in the small intestine and stimulates insulin secretion only when blood glucose is above fasting

Incretin analogues, such as exenatide, are being used to enhance endogenous insulin secretion

Glucagon-like peptide-1 (GLP-1)

- 30-amino acid peptide secreted in response to the oral ingestion of nutrients by L cells, primarily in the ileum and colon.

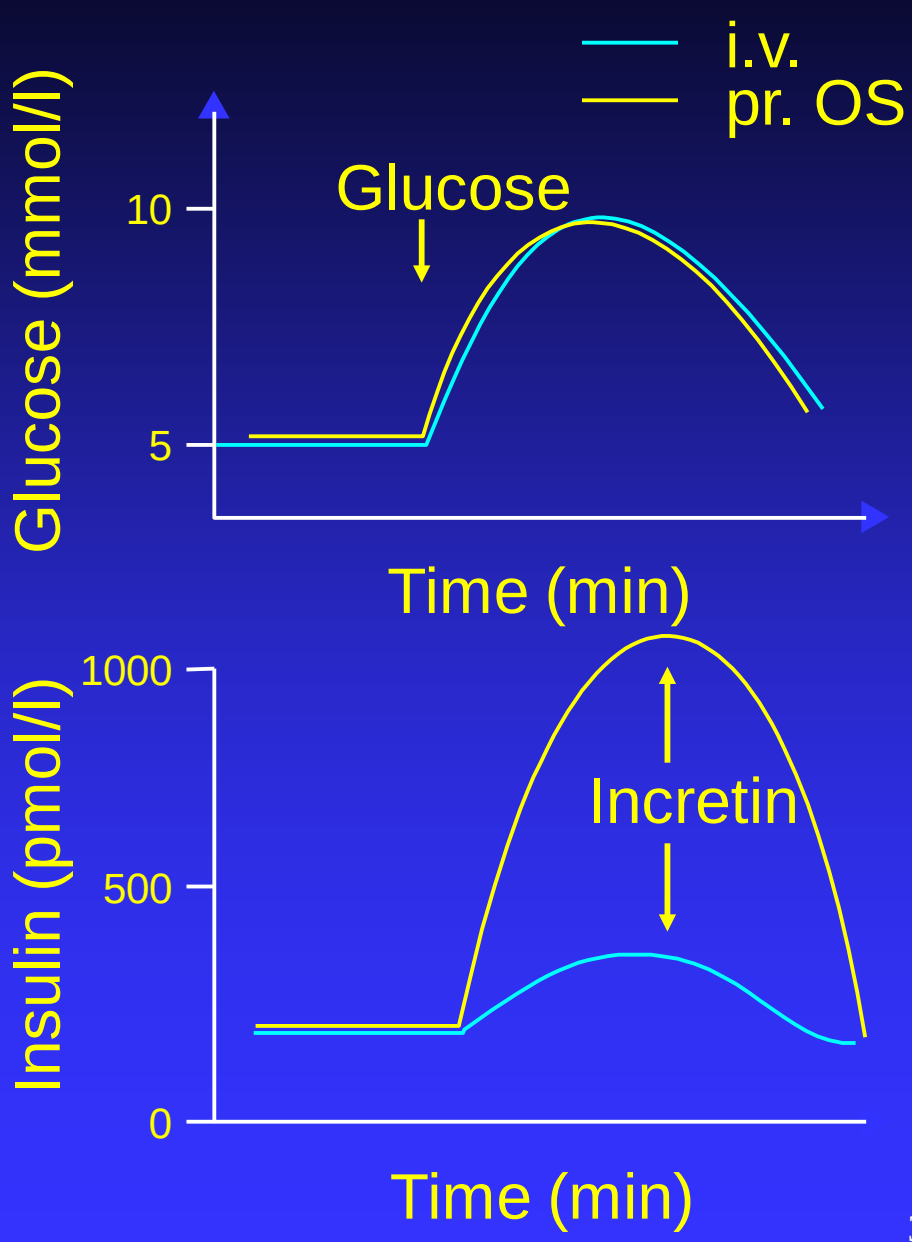
There are GLP-1 receptors in:

- islet cells
- CNS
- and other places.

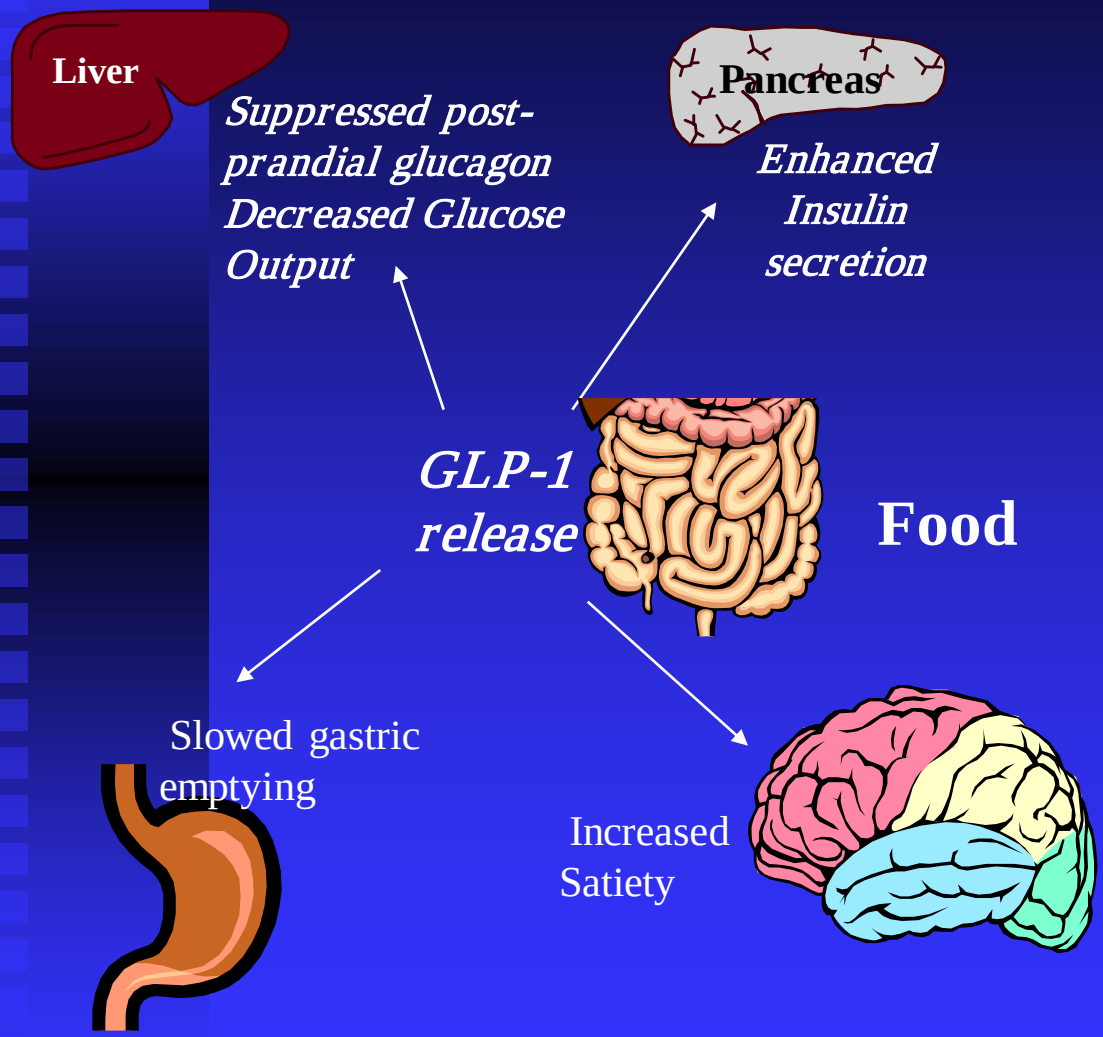
- GLP-1 is metabolized by the enzyme **dipeptidyl peptidase-IV (DPP-IV)** .

The incretin effect

- Up to 70% of post-glucose insulin secretion is due to the effects of incretins
- The incretin effect is due to gut hormones – the incretin hormones



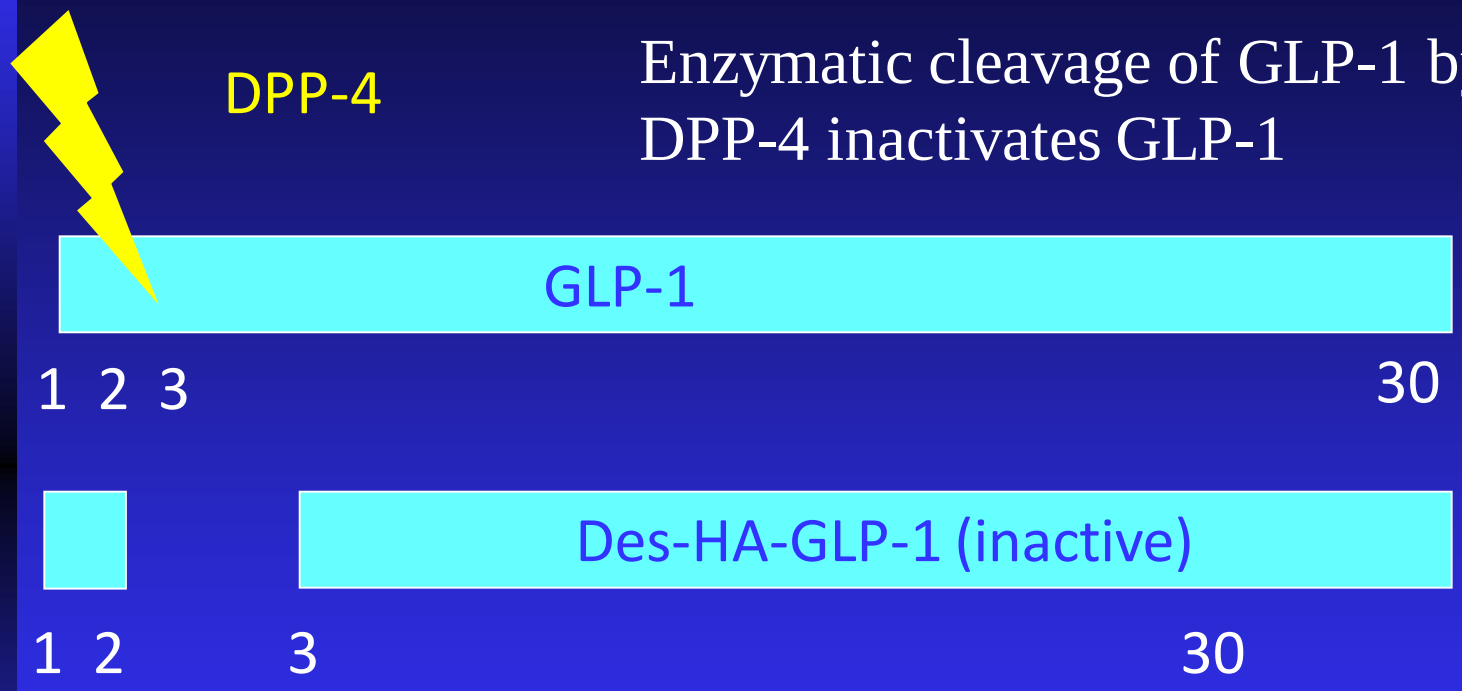
Diabetes is a Multi-System Disorder:
"The Incretin Effect"



GLP-1 and other gut hormones released in response to food: "entero-insular axis"

This ability is reduced or lost in type 2 diabetes

Degradation of GLP-1

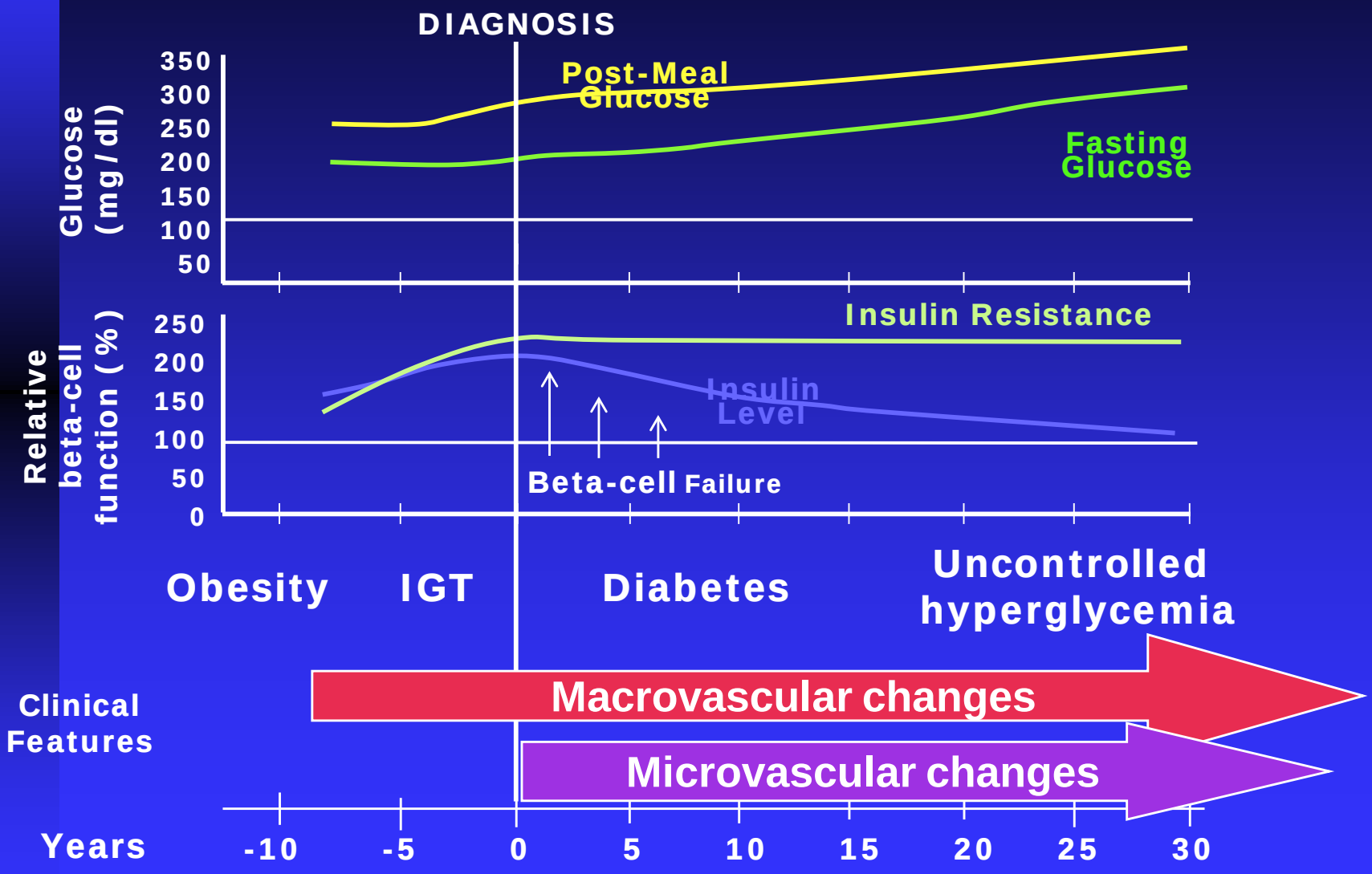


Two possible solutions to utilize GLP-1 action therapeutically:

1) Long-acting DPP-4-resistant GLP-1 analogues / incretin mimetics
2) DPP-4 inhibitors / incretin enhancers

Mentlein et al. *Eur J Biochem.* 1993; Gallwitz et al. *Eur J*

Natural Progression of Type 2 Diabetes



Adapted from *Type 2 Diabetes BASICS*. Minneapolis, MN: International Diabetes Center; 2000.

Metabolic Abnormalities

This is also responsible for dyslipidemia found in type 2 DM:

- Elevated triglycerides
- Reduced HDL
- Increased small dense LDL particles

Metabolic Abnormalities

Glucose toxicity : Chronic hyperglycemia paradoxically impairs islet function and leads to a worsening of hyperglycemia.

Improvement in glycemic control is often associated with improved islet function.

Lipotoxicity: elevation of free fatty acid levels also worsens islet function.

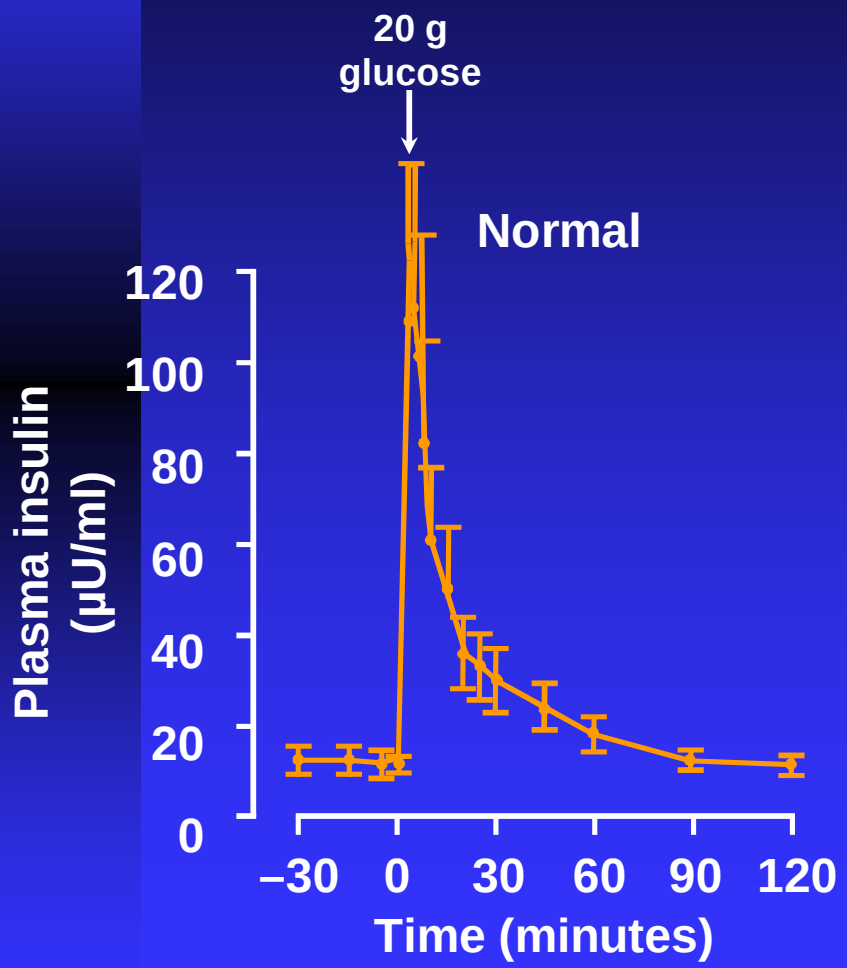
Metabolic Abnormalities

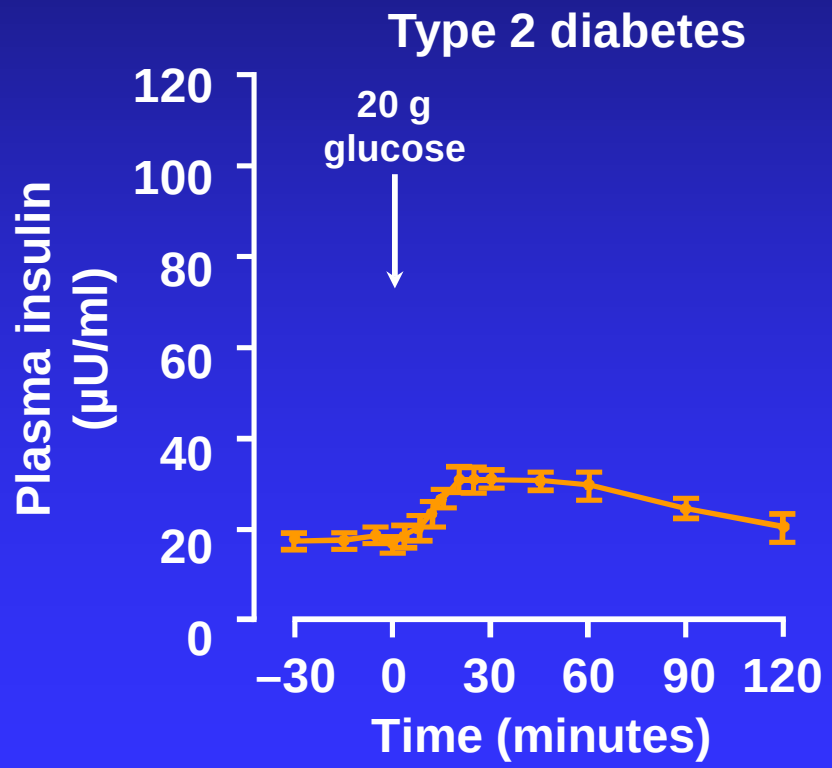
Impaired Insulin Secretion

In type 2 DM, insulin secretion initially increases in response to insulin resistance in order to maintain normal glucose tolerance.

Initially, the insulin secretory defect is mild and selectively involves glucose-stimulated insulin secretion.

Loss of first-phase insulin response





Pfeifer MA et al. Am J Med 1981;70:579–88

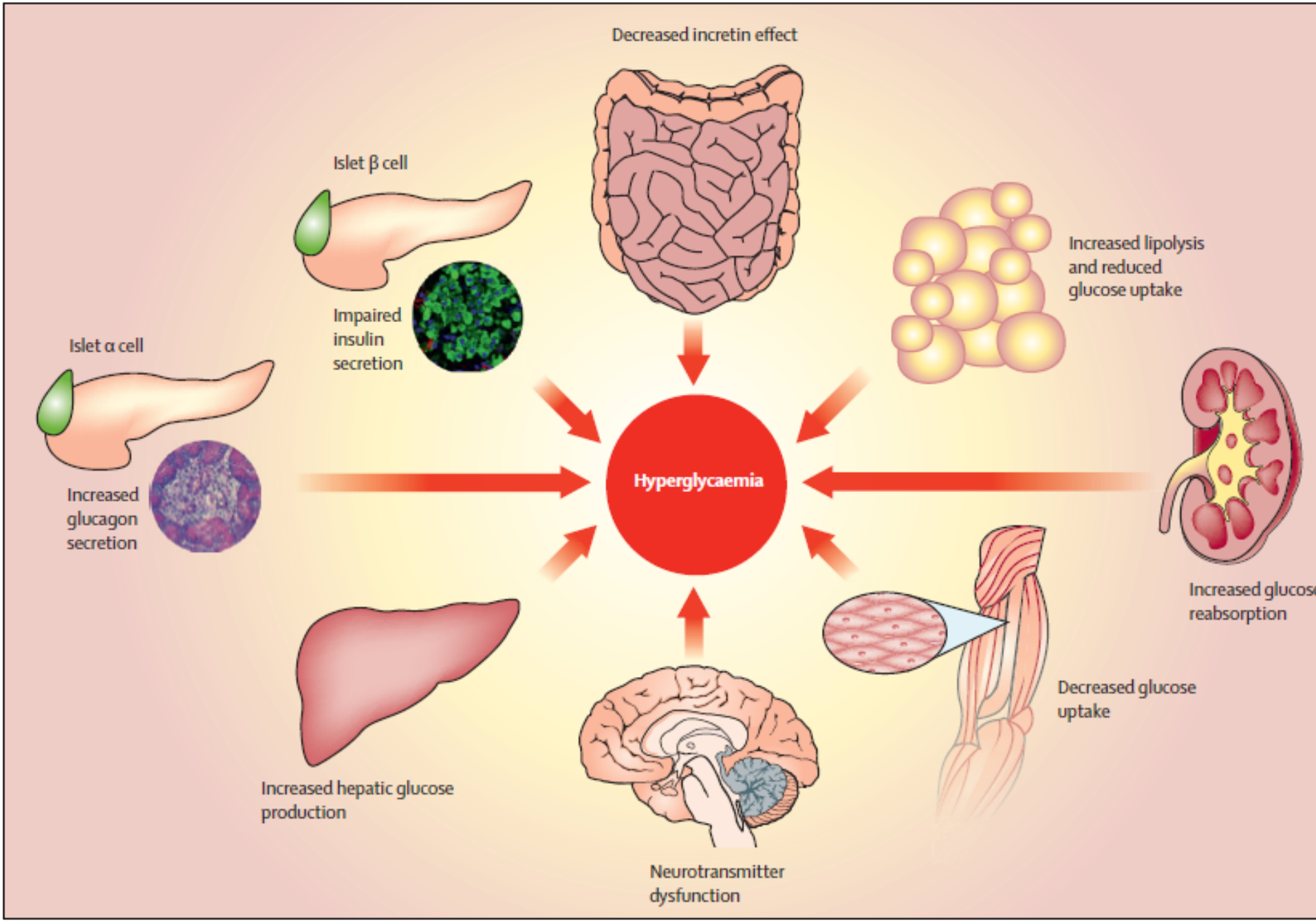


Figure 1: **Typical pathogenic features of hyperglycaemia in type 2 diabetes**
Adapted from DeFronzo[8] with permission.

Features of Type 2 Diabetes

- Most common after age 40
- Abdominal obesity present in 90%
- Insulin resistance/hyperinsulinemia
- Ketosis resistance (not always)
- Hypertension common
- High VLDL, low HDL cholesterol
- Accelerated atherosclerosis
- Increased risk in many ethnic groups

LONG-TERM TREATMENT

OVERALL PRINCIPLES

- The goals of therapy for type 1 or type 2 DM are to:

(1) Eliminate symptoms related to hyperglycemia

(2) Reduce or eliminate the long-term microvascular and macrovascular complications of DM

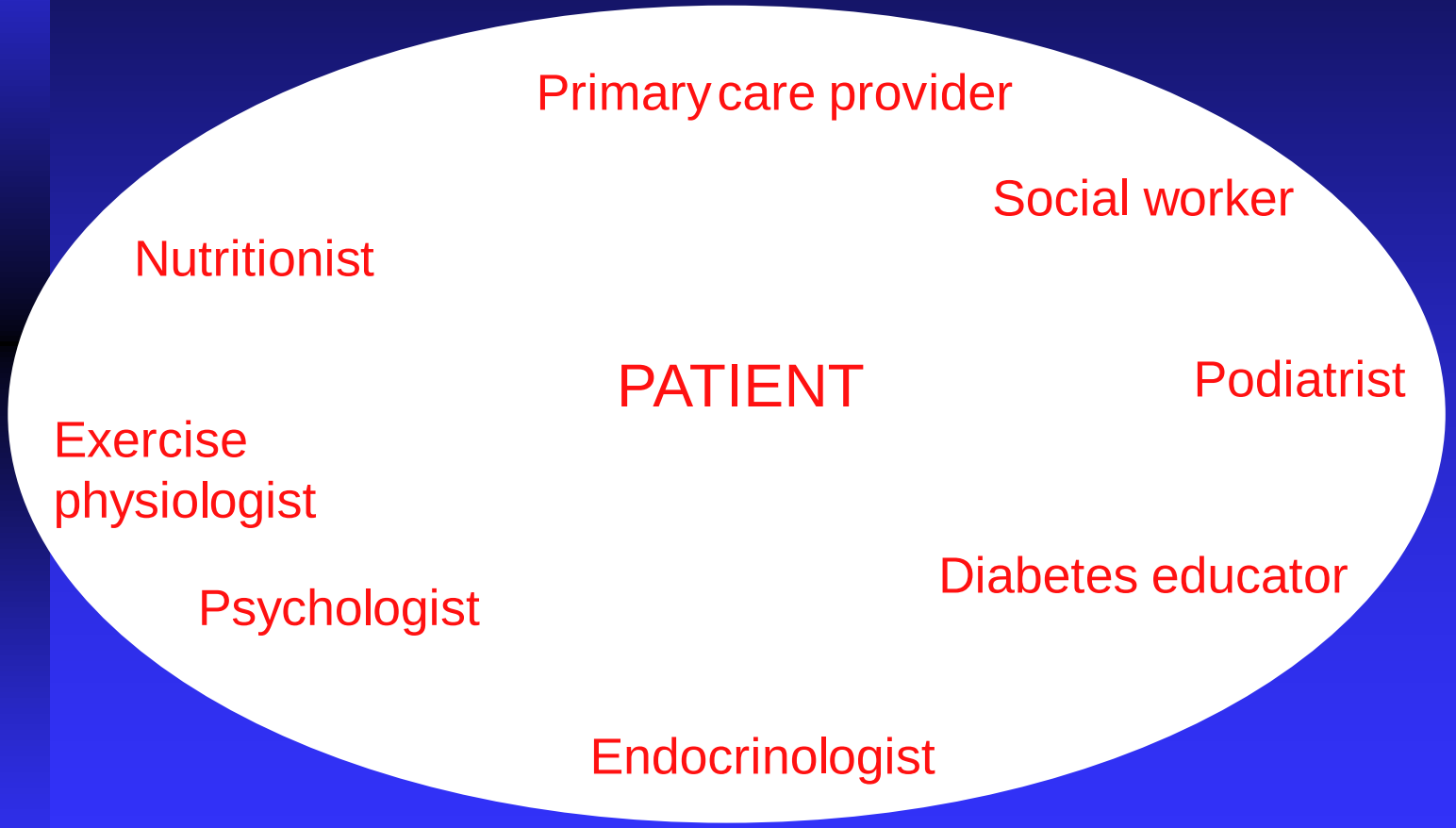
(3) Allow the patient to achieve as normal a life-style as possible.

Long-Term Treatment

- The care of either type 1 or type 2 DM requires a multidisciplinary team.

- Central to the success of this team are the patient's participation

Diabetes Team



Patient-Centered Care: The Team Approach

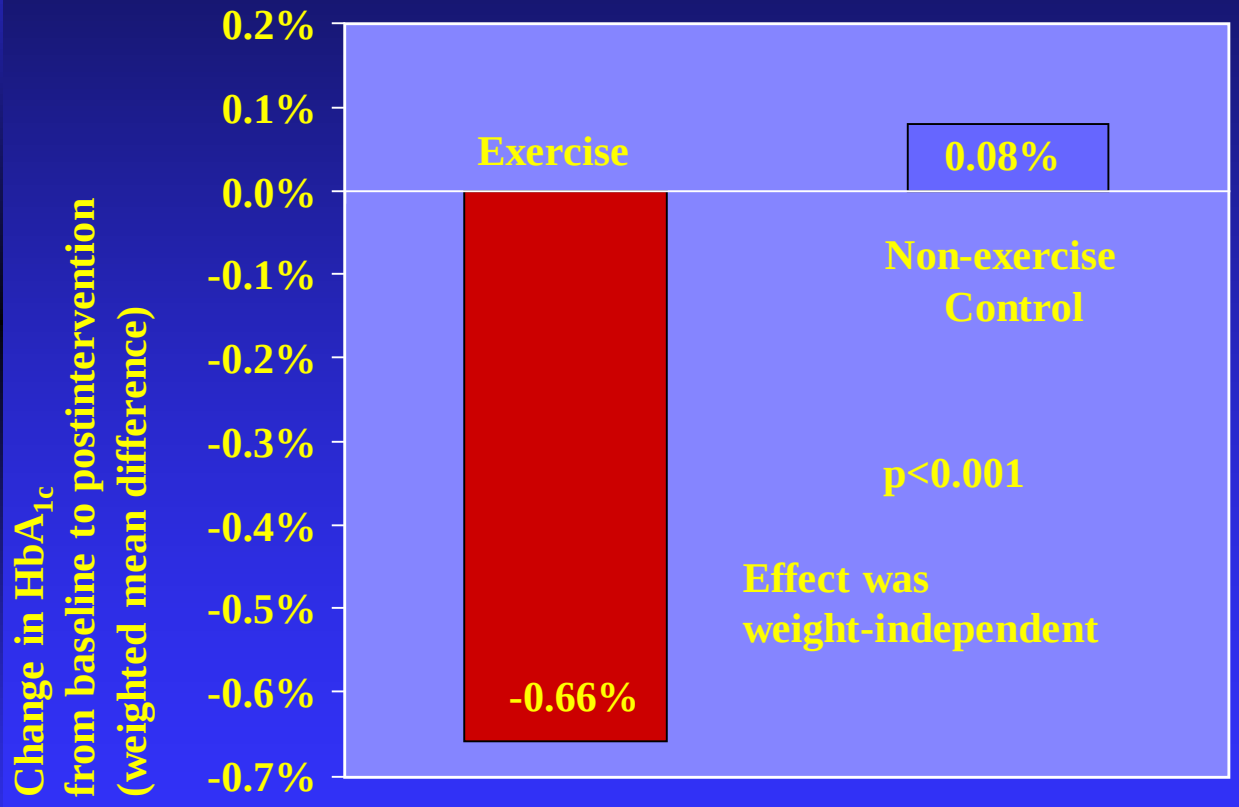
- Partner with the patient: do not scold or scare!
- A mutually respectful and trusting patient-provider relationship
- Use and collaborate with diabetes education programs: team management!
- "Refresher Courses" are often necessary
- Frequent communication is key






education monitoring communication early insulin multifactorial therapy

Pooled Meta-Analysis of 14 Exercise Trials: Exercise Significantly Reduces HbA_{1c}



Boulé NG *et al. JAMA* 2001;286:1218-27.

Nutrition

- *Medical nutrition therapy* is a term to describe the optimal coordination of caloric intake with other aspects of diabetes therapy (insulin, exercise, weight loss).

- Historically, nutrition has imposed restrictive, complicated regimens on the patient.

Nutrition

Modern MNT now includes:

- Foods with sucrose
- Modify other risk factors such as hyperlipidemia and hypertension

Rather than focusing exclusively on weight loss in type 2 DM.

Nutrition

The goals of MNT in type 2 DM

- Address the greatly increased prevalence of CV risk factors (hypertension, dyslipidemia, obesity)
- The majority of are obese, and weight loss is strongly encouraged.

Nutrition

Therefore MNT for type 2 should emphasize

- Modest caloric reduction
- Increased physical activity
- Reduction of hyperlipidemia and hypertension
- Increased consumption of soluble, dietary fiber may improve glycemic control in type 2 DM.

MNT Goals (cont)

- Address individual nutritional needs
- Taking into consideration personal and cultural preferences and
- lifestyle
- Respecting the individual's wishes and willingness to change.

Physical Activity: Recommendations

Children and adolescents with diabetes or prediabetes:

1-Should engage in:

a) 60 min/day or more

b) Moderate- or vigorous-intensity

c) Aerobic activity

2-with vigorous muscle-strengthening and bone-strengthening activities at least 3 days/week.

Physical Activity: Recommendations

Most adults with type 1 and type 2 diabetes:

- Should engage in 150 min or more of moderate-to-vigorous intensity aerobic activity per week, spread over at least 3 days/week, with no more than 2 consecutive days without activity.

- Shorter durations (75 min/week) of vigorous-intensity or interval training may be sufficient for younger and more physically fit individuals.

Recommendations: Physical Activity (2)

- Adults with type 1 and type 2 diabetes should engage in 2-3 sessions/week of resistance exercise on nonconsecutive days.
- All adults, and particularly those with type 2 diabetes, should decrease the amount of time spent in daily sedentary behavior.
- Prolonged sitting should be interrupted every 30 min for blood glucose benefits, particularly in adults with type 2 diabetes.
- Flexibility training and balance training are recommended 2–3 times/week for older adults with diabetes. Yoga and tai chi may be included based on individual preferences to increase flexibility, muscular strength, and balance.

Lifestyle Management:
Standards of Medical Care in Diabetes - 2018. Diabetes Care 2018; 41 (Suppl. 1): S38-S50

Exercise

- To avoid exercise-related hyper- or hypoglycemia, individuals with type 1 DM should:

(1) Monitor blood glucose before, during, and after exercise

(2) Delay exercise if blood glucose is >250 <100 mg/dL, or if ketones are present

Exercise

(3) Eat a meal 1 to 3 h before exercise and take supplemental carbohydrate at least every 30 min during prolonged exercise

(4) Decrease insulin before exercise and inject insulin into a nonexercising area

Exercise

- Untreated proliferative retinopathy is a relative contraindication to vigorous exercise, since this may lead to vitreous hemorrhage or retinal detachment.

Type 2 Diabetes: pharmacological treatment
which medications

1. Metformin
2. Sulfonylureas/Glinides
3. α-glucosidase-inhibitors
4. DPP4-inhibitors
5. Pioglitazone
6. *SGLT2-inhibitors*
7. GLP1r-agonists
8. Insulins

Oral agents

injections

Insulin therapy

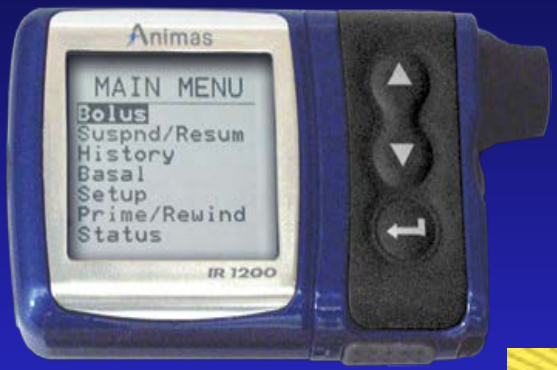
- Used to treat all patients with Type I diabetes
- 1/3 of patients with Type 2 diabetes
- Women with GDM
- DKA , NKHC
- Acute stress

Intensive Management

Insulin regimens usually include

- Multiple-component insulin regimens
- Multiple daily injections (MDI)
- Insulin infusion

Pump Technology



Intensive Management

- The benefits of intensive diabetes management and improved glycemic control include :
- Reduction in the microvascular complications
- Possible delay or reduction in the macrovascular complications

Intensive Management

- In pregnancy reduces fetal malformation and morbidity.
- Strongly encouraged in newly diagnosed type 1 because it may prolong the period of C-peptide production, which may result in better glycemic control

Insulin preparations

Five different preparations are available

- Short-acting insulin: regular
- Rapid-acting insulin(analogues): lispro, Aspart, Glulisine
- Intermediate –acting insulin: NPH or Lente
- Long-acting insulin : Ultralente
- Basal insulin(analogues): glargine, detemir,degludec

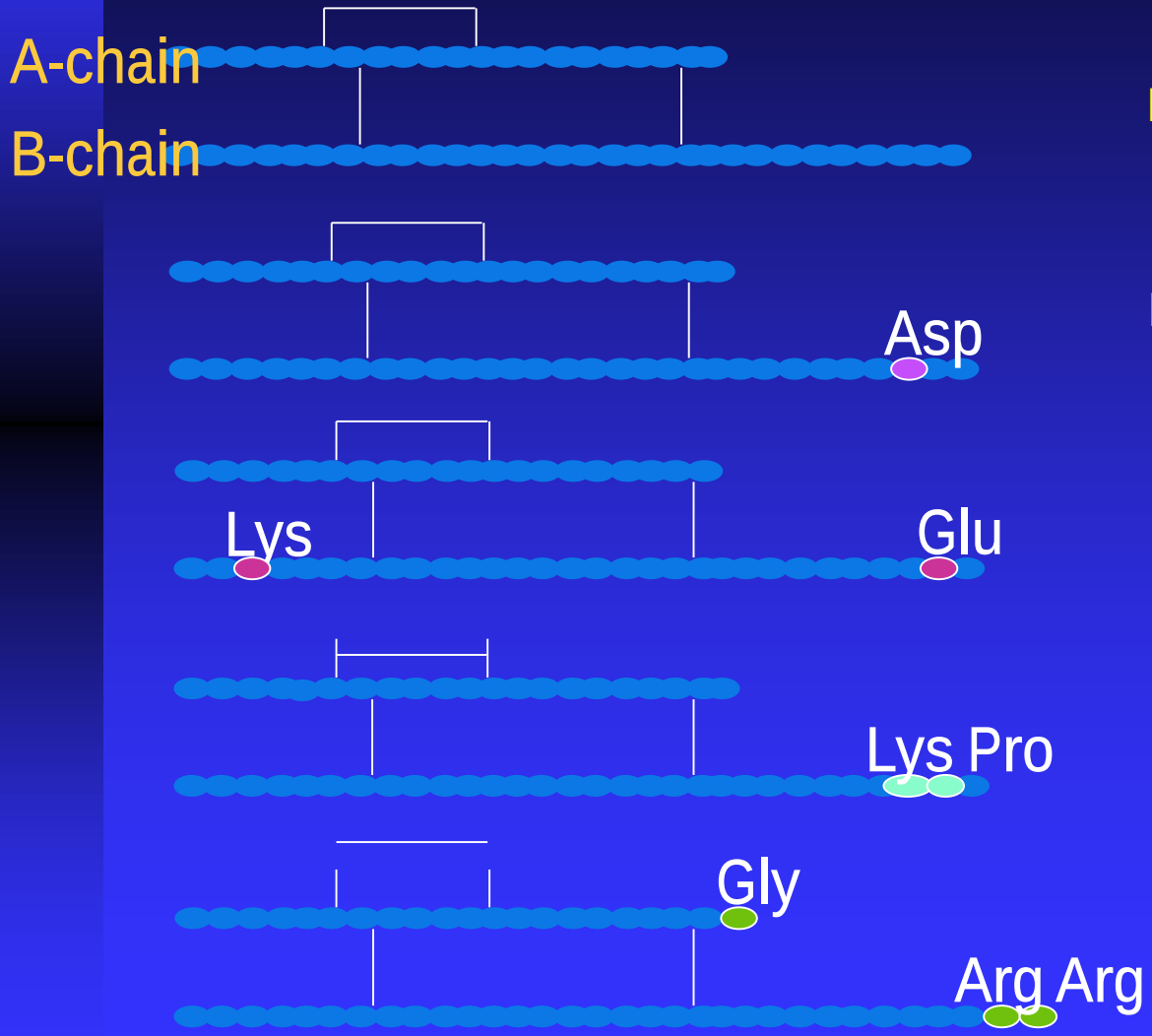
The Basal/Bolus Insulin Concept

- Basal Insulin
  - Suppresses glucose production between meals and overnight
  - Nearly constant levels
  - 50% of daily needs

- Bolus Insulin (mealtime or prandial)
  - Limits hyperglycemia after meals
  - Immediate rise and sharp peak at 1 hour
  - 10% to 20% of daily requirement at each meal

Owens DR, et al. *Lancet*. 2001;358:739-746.

Insulin Analogues



Human Insulin
Dimers and hexamers
in solution

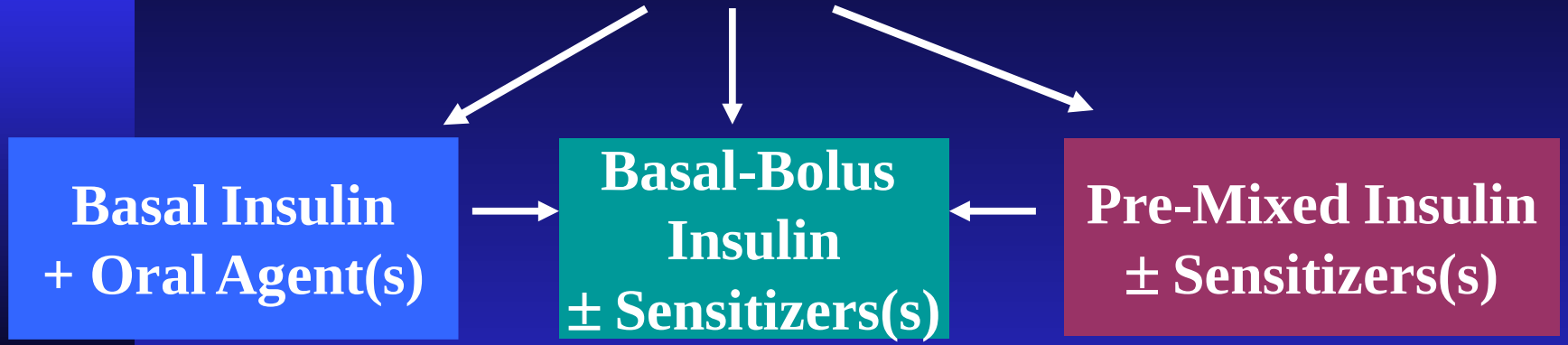
Aspart
Limited self-aggregation
Monomers in solution

Glulisine
Limited self-aggregation
Monomers in solution

Lispro
Limited self-aggregation
Monomers in solution

Glargine
Soluble at low pH
Precipitates at
neutral (subcutaneous) pH

Insulin Therapies



Mazze R et al. *Staged Diabetes Management: Prevention, Detection and Treatment of Diabetes in Adults Quick Guide.* 4th ed. Minneapolis, Minn: Matrex; 2005.

Insulin Glargine -analogue

- Is a long-acting biosynthetic human insulin that differs from normal insulin in that:

- Asparagine is replaced by glycine at amino acid 21

- Two arginine residues are added to the C-terminus of the B chain.
- Two forms : U100 and U 300

Insulin Glargine - analogue

Compared to NPH insulin

1. The onset of action is later
2. The duration of action is longer (~24 h)
3. There is no pronounced peak.
4. A lower incidence of hypoglycemia, especially at night, was reported

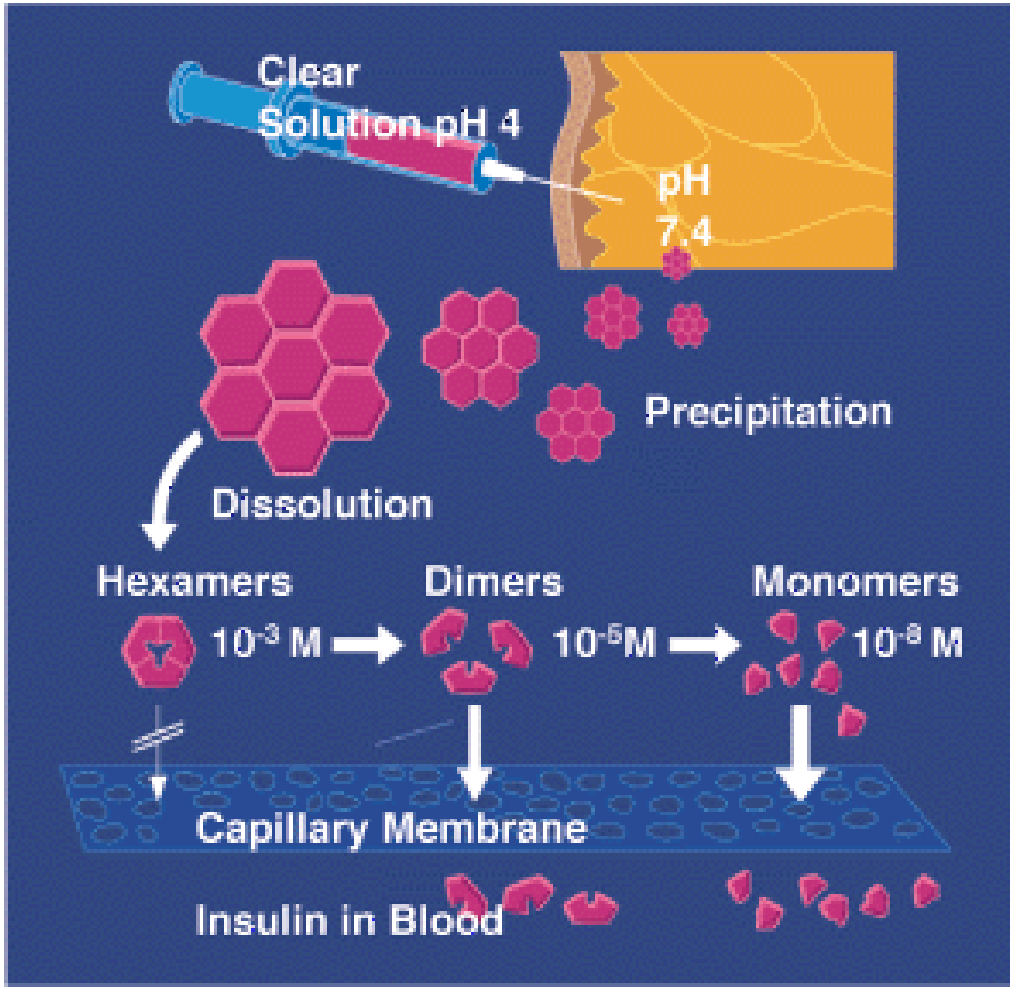
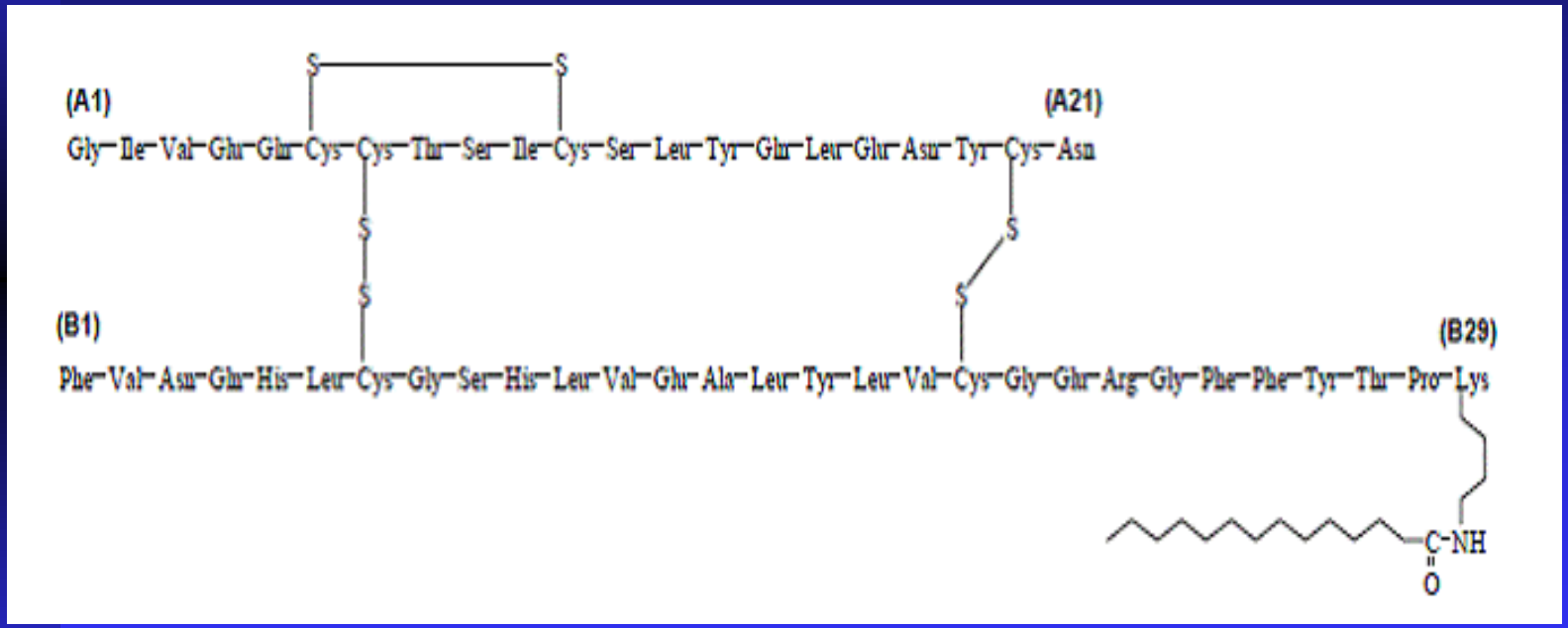


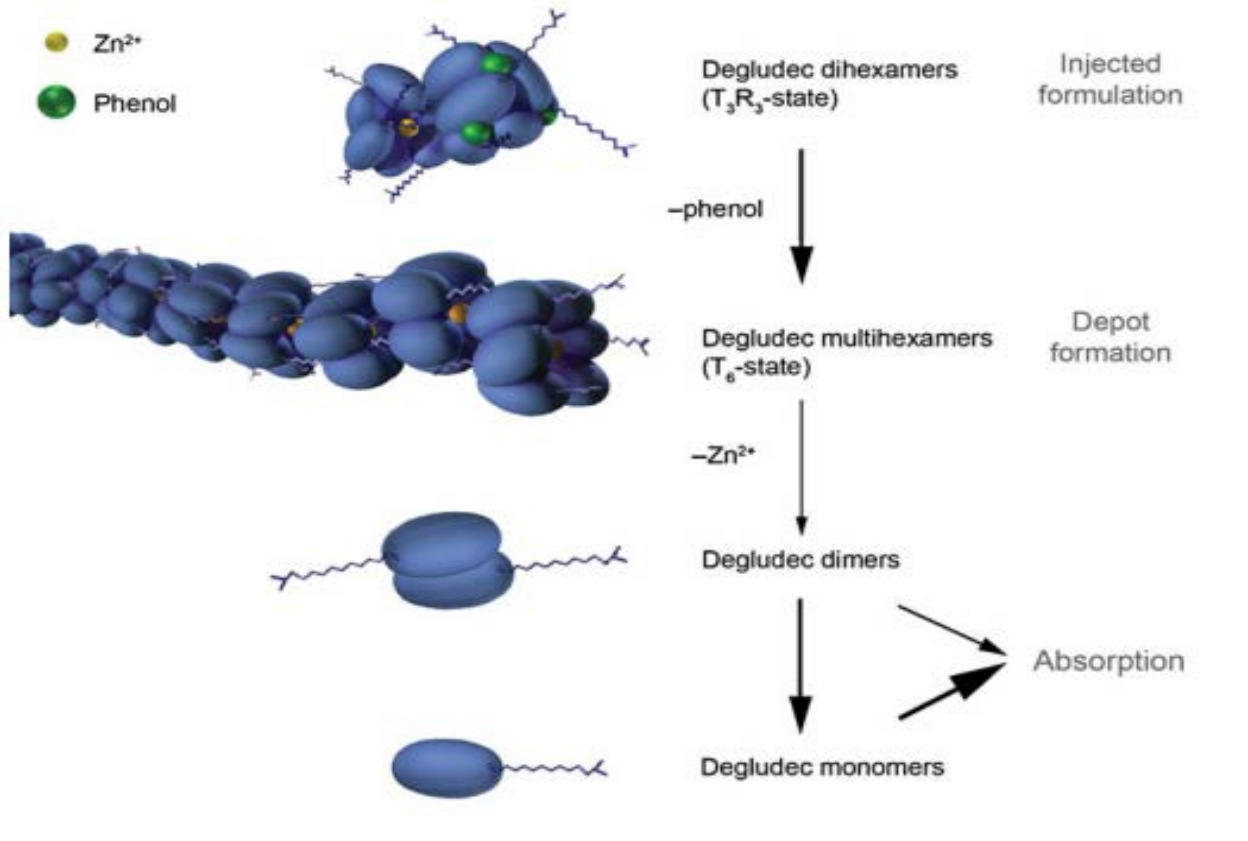
Figure 3. Mechanism of action of insulin glargine. Glargine, which has an acidic pH, is injected into subcutaneous space with normal pH, where it forms microprecipitates. Microprecipitates dissociate to hexamers, dimers, and finally, to monomers, which are absorbed across the capillaries.

Adapted from Kramer W. Exp Clin Endocrinol Diabetes 1999;107(Suppl 2): P42.

Insulin Determir



Insulin Degludec



Jonassen I, et al. Pharm Res 29:2104–2114, 2012

Insulin regimen

One commonly used regimen consists of split-mixed

Twice-daily injections of an intermediate insulin (NPH or lente) mixed with a short-acting insulin before the morning and evening meal .

Split-mixed

Such regimens usually prescribe

- 2/3 of the total daily insulin in the morning (with 2/3 as intermediate-acting and 1/3 as short-acting)

- 1/3 before the evening meal (1/2 given as intermediate-acting and 1/2 as short-acting).

Multiple Daily Injections

- One regimen, consists of a basal insulin with NPH twice a day and preprandial lispro.

An alternative consists of:

1- Bedtime intermediate

2- small dose of intermediate at breakfast (20 to 30% of bedtime dose)

3- preprandial short-acting

Insulin Pens

- More convenient than traditional vial and syringe
- Repeatedly more accurate dosages
- Easier to use for those with visual or fine motor skills impairments
- Less injection pain

Basal -bolus

- Multiple-component insulin regimens refer to the combination of basal insulin; preprandial short-acting insulin; (basal –bolus)

- Changes in short-acting insulin doses to accommodate the results of :
- Frequent SMBG
- Food intake
- physical activity.

Type 2 Diabetes Mellitus

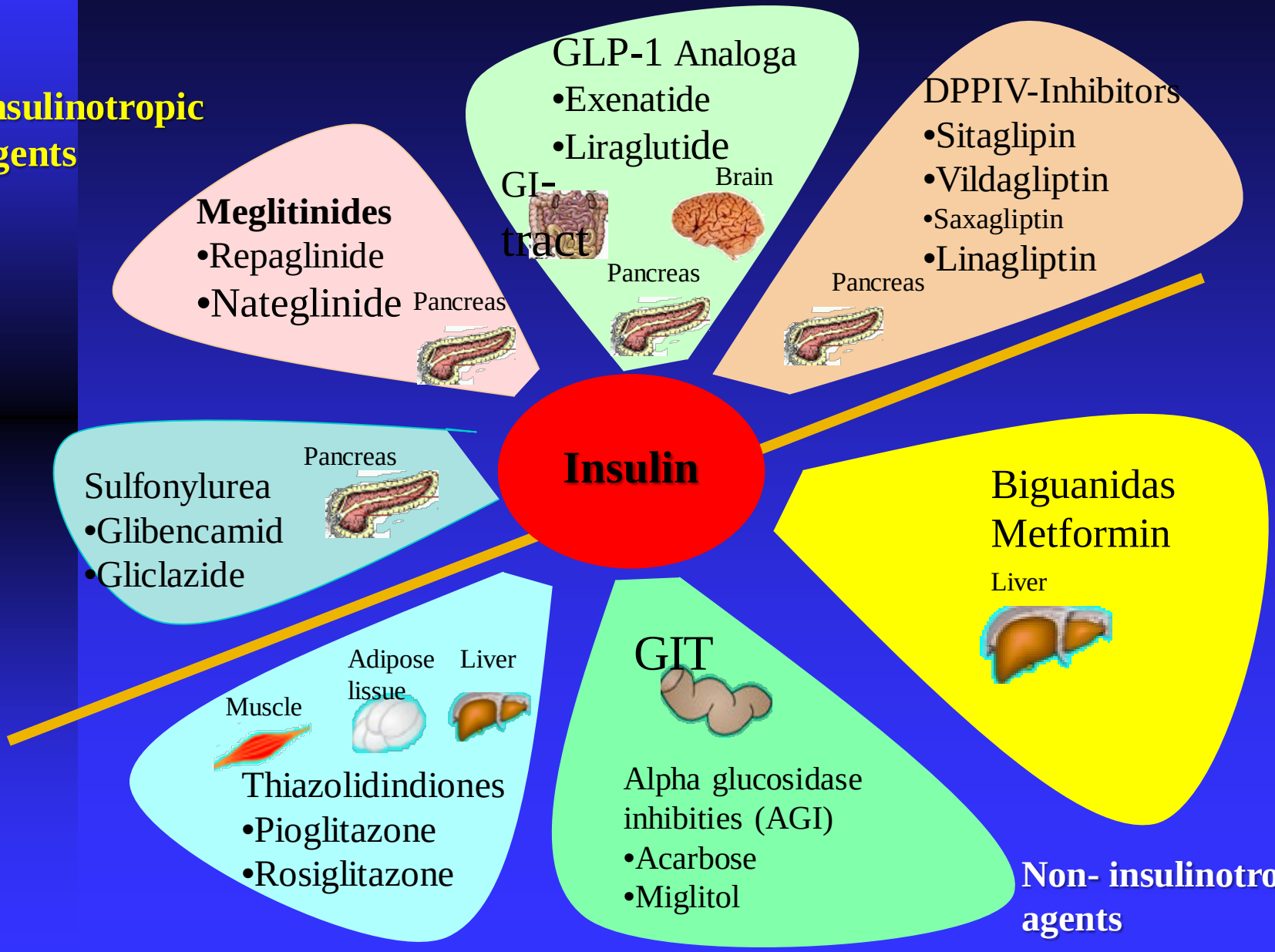
- Pharmacologic approaches to the management of type 2 DM include both oral glucose-lowering agents and insulin

- Most physicians and patients prefer oral glucose-lowering agents as the initial choice.

Glucose-Lowering Agents

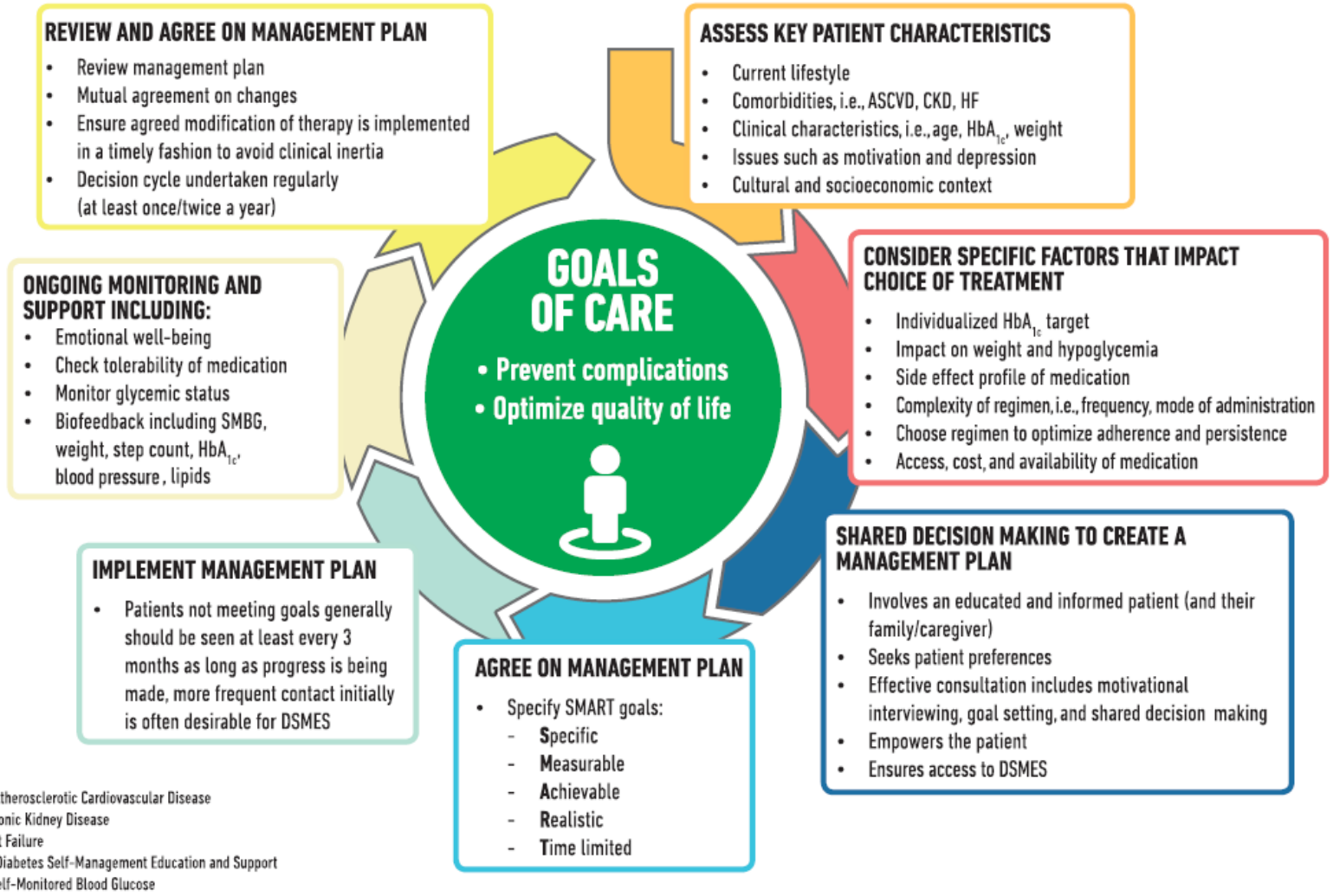
- Based on their mechanisms of action, oral glucose-lowering agents are subdivided:
- Increase insulin secretion
- Reduce glucose production or renal absorption.
- Increase insulin sensitivity .

The focus should be to intensify pharmacological treatment



Management of hyperglycemia in type 2 diabetes
standards of care 2020

Goals of care



ASCVD = Atherosclerotic Cardiovascular Disease
CKD = Chronic Kidney Disease
HF = Heart Failure
DSMES = Diabetes Self-Management Education and Support
SMBG = Self-Monitored Blood Glucose

First step of treatment

- Metformin
- comprehensive life style including weight management and physical activity

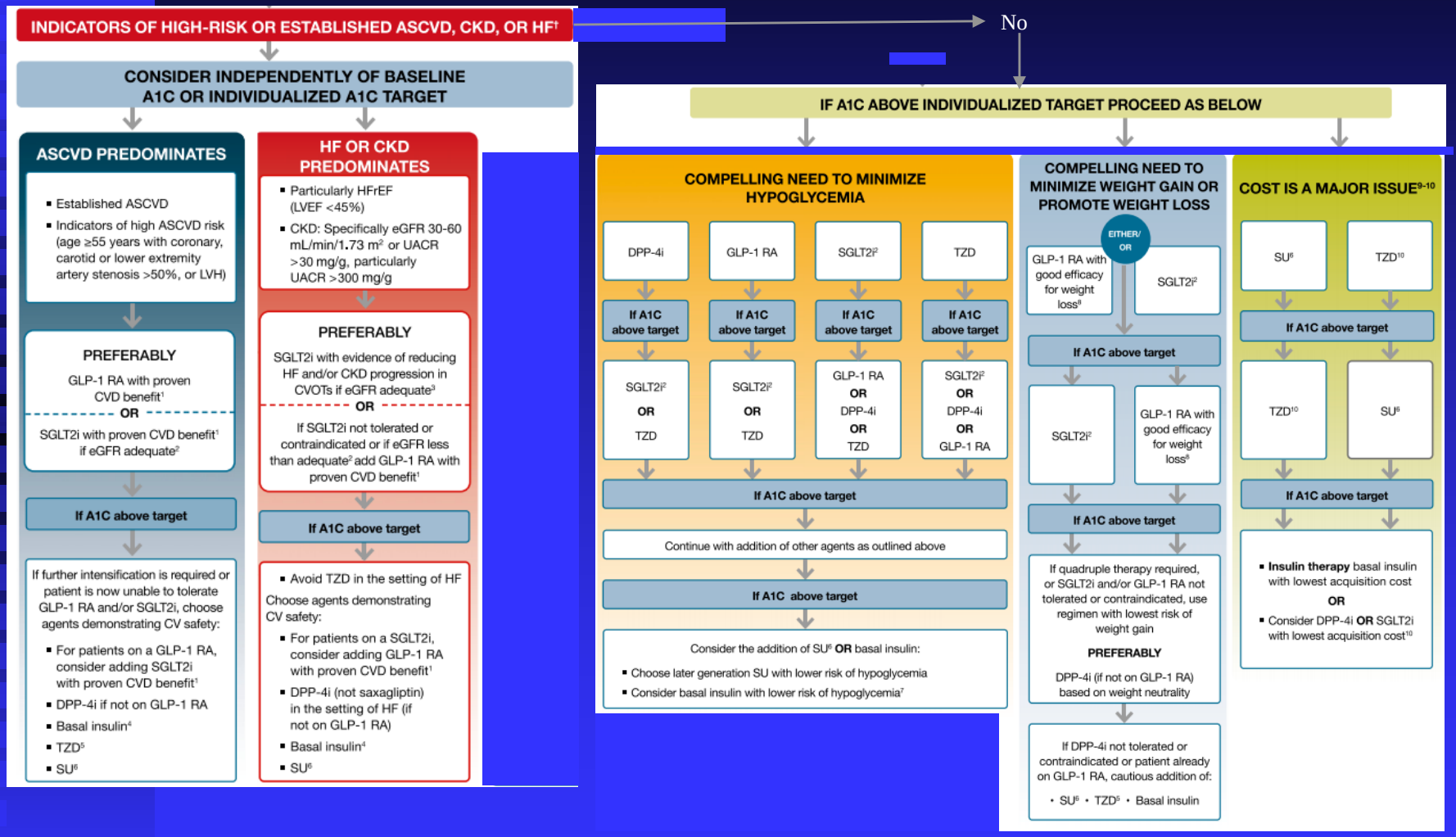
Initial dual therapy

- Consider initiating dual therapy in patients with newly diagnosed type 2 diabetes who have A1C >1.5% above their glycemic target. E

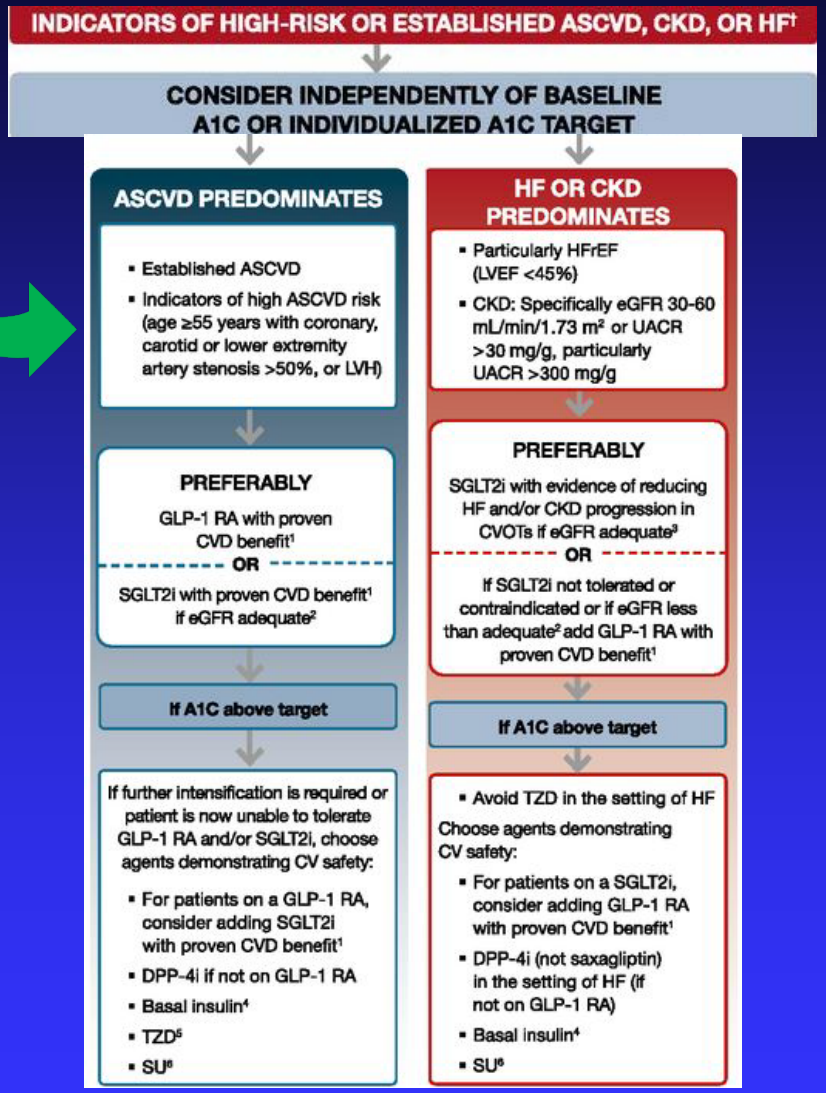
Early Insulin treatment

The early introduction of insulin should be considered :

1. There is evidence of ongoing catabolism (weight loss)
2. symptoms of hyperglycemia are present
3. A1C>10%
4. Blood glucose >300 mg/dL. E



American Diabetes Association®


INDICATORS OF HIGH-RISK OR ESTABLISHED ASCVD, CKD, OR HF†
CONSIDER INDEPENDENTLY OF BASELINE A1C OR INDIVIDUALIZED A1C TARGET
ASCVD PREDOMINATES
▪ Established ASCVD
▪ Indicators of high ASCVD risk (age ≥55 years with coronary, carotid or lower extremity artery stenosis >50%, or LVH)
PREFERABLY
GLP-1 RA with proven CVD benefit[1]
OR
SGLT2i with proven CVD benefit[1] if eGFR adequate[2]
If A1C above target
If further intensification is required or patient is now unable to tolerate GLP-1 RA and/or SGLT2i, choose agents demonstrating CV safety:
▪ For patients on a GLP-1 RA, consider adding SGLT2i with proven CVD benefit[1]
▪ DPP-4i if not on GLP-1 RA
▪ Basal insulin[4]
▪ TZD[5]
▪ SU[6]
HF OR CKD PREDOMINATES
▪ Particularly HFrEF (LVEF <45%)
▪ CKD: Specifically eGFR 30-60 mL/min/1.73 m² or UACR >30 mg/g, particularly UACR >300 mg/g
PREFERABLY
SGLT2i with evidence of reducing HF and/or CKD progression in CVOTs if eGFR adequate[3]
OR
If SGLT2i not tolerated or contraindicated or if eGFR less than adequate[2] add GLP-1 RA with proven CVD benefit[1]
If A1C above target
▪ Avoid TZD in the setting of HF
Choose agents demonstrating CV safety:
▪ For patients on a SGLT2i, consider adding GLP-1 RA with proven CVD benefit[1]
▪ DPP-4i (not saxagliptin) in the setting of HF (if not on GLP-1 RA)
▪ Basal insulin[4]
▪ SU[6]

LEADER Trial

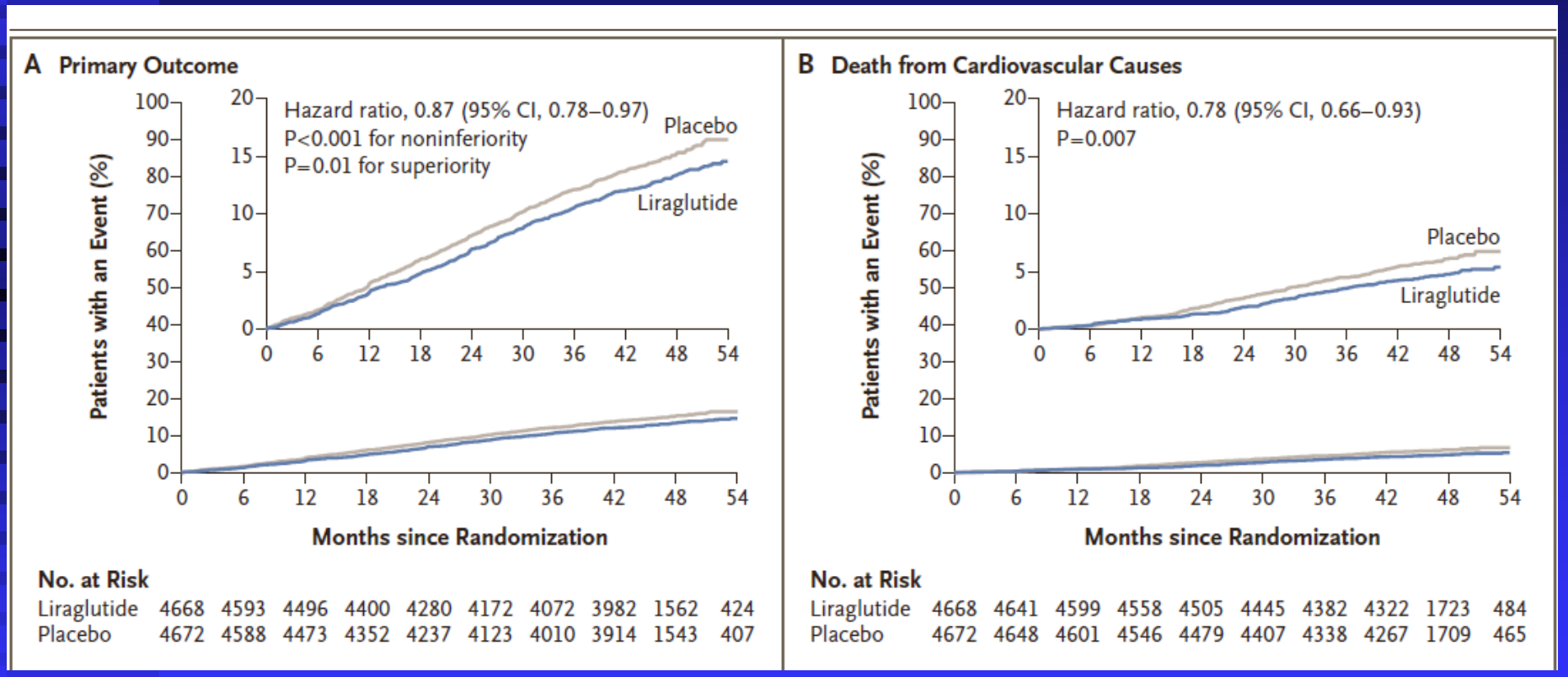
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JULY 28, 2016 VOL. 375 NO. 4

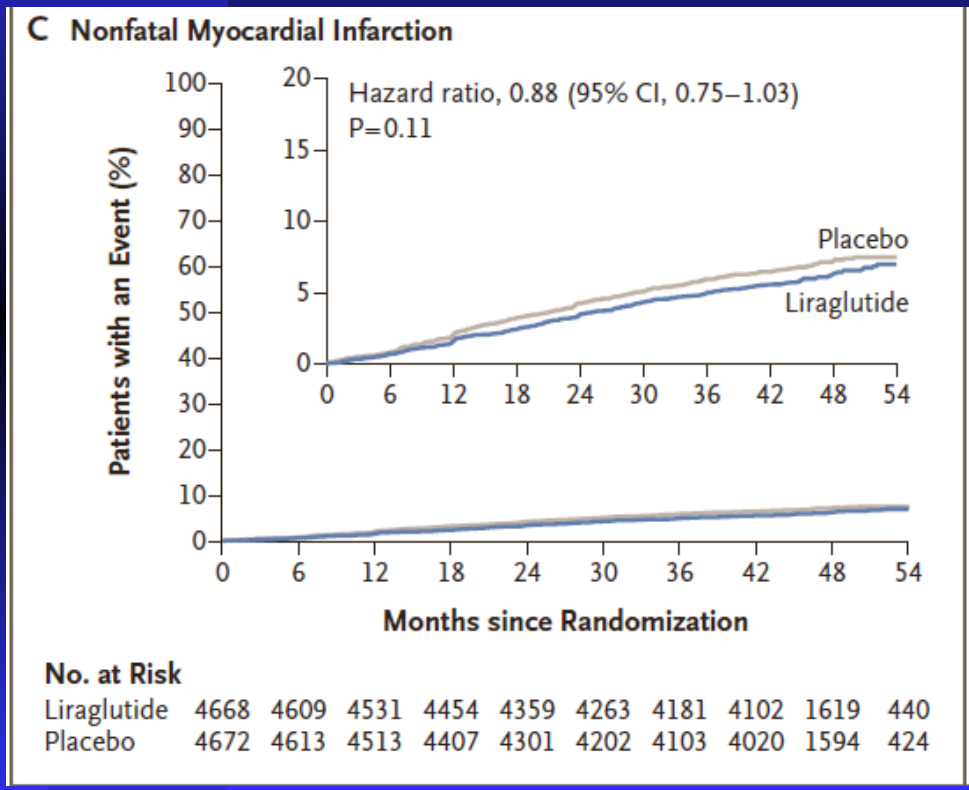
Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes

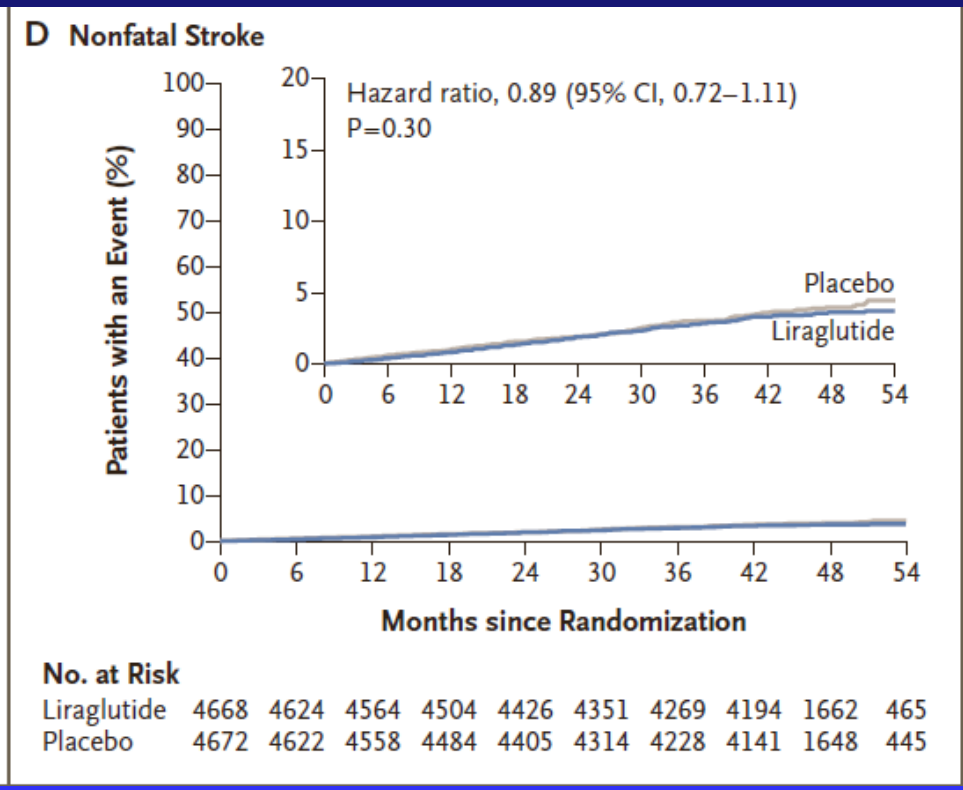
Steven P. Marso, M.D., Gilbert H. Daniels, M.D., Kirstine Brown-Frandsen, M.D., Peter Kristensen, M.D., E.M.B.A., Johannes F.E. Mann, M.D., Michael A. Nauck, M.D., Steven E. Nissen, M.D., Stuart Pocock, Ph.D., Neil R. Poulter, F.Med.Sci., Lasse S. Ravn, M.D., Ph.D., William M. Steinberg, M.D., Mette Stockner, M.D., Bernard Zinman, M.D., Richard M. Bergenstal, M.D., and John B. Buse, M.D., Ph.D., for the LEADER Steering Committee on behalf of the LEADER Trial Investigators*

CV Death


A Primary Outcome
Hazard ratio, 0.87 (95% CI, 0.78–0.97)
P<0.001 for noninferiority
P=0.01 for superiority
Placebo
Liraglutide
Patients with an Event (%)
Months since Randomization
No. at Risk
Liraglutide 4668 4593 4496 4400 4280 4172 4072 3982 1562 424
Placebo 4672 4588 4473 4352 4237 4123 4010 3914 1543 407
B Death from Cardiovascular Causes
Hazard ratio, 0.78 (95% CI, 0.66–0.93)
P=0.007
Placebo
Liraglutide
Patients with an Event (%)
Months since Randomization
No. at Risk
Liraglutide 4668 4641 4599 4558 4505 4445 4382 4322 1723 484
Placebo 4672 4648 4601 4546 4479 4407 4338 4267 1709 465

Nonfatal MI & Stroke





EMPA-REG Trial

The NEW ENGLAND JOURNAL of MEDICINE

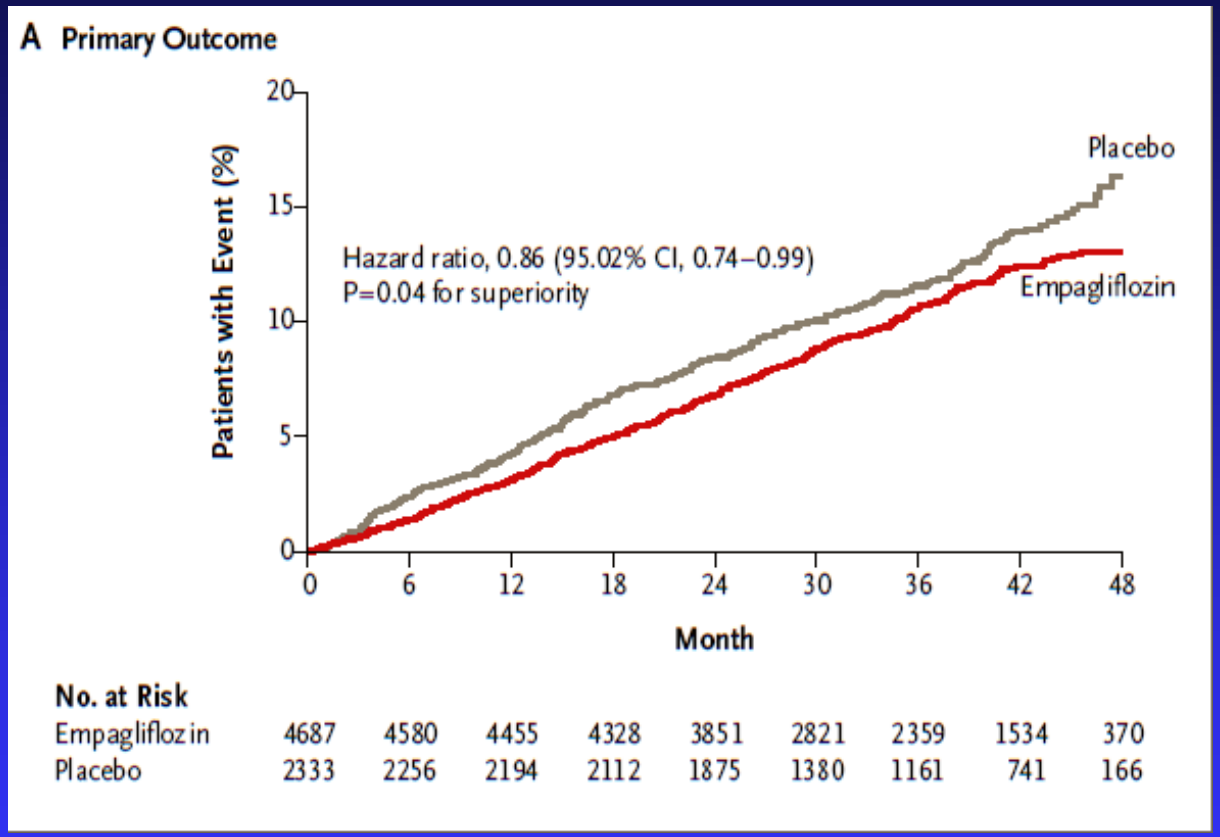
ORIGINAL ARTICLE

Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes

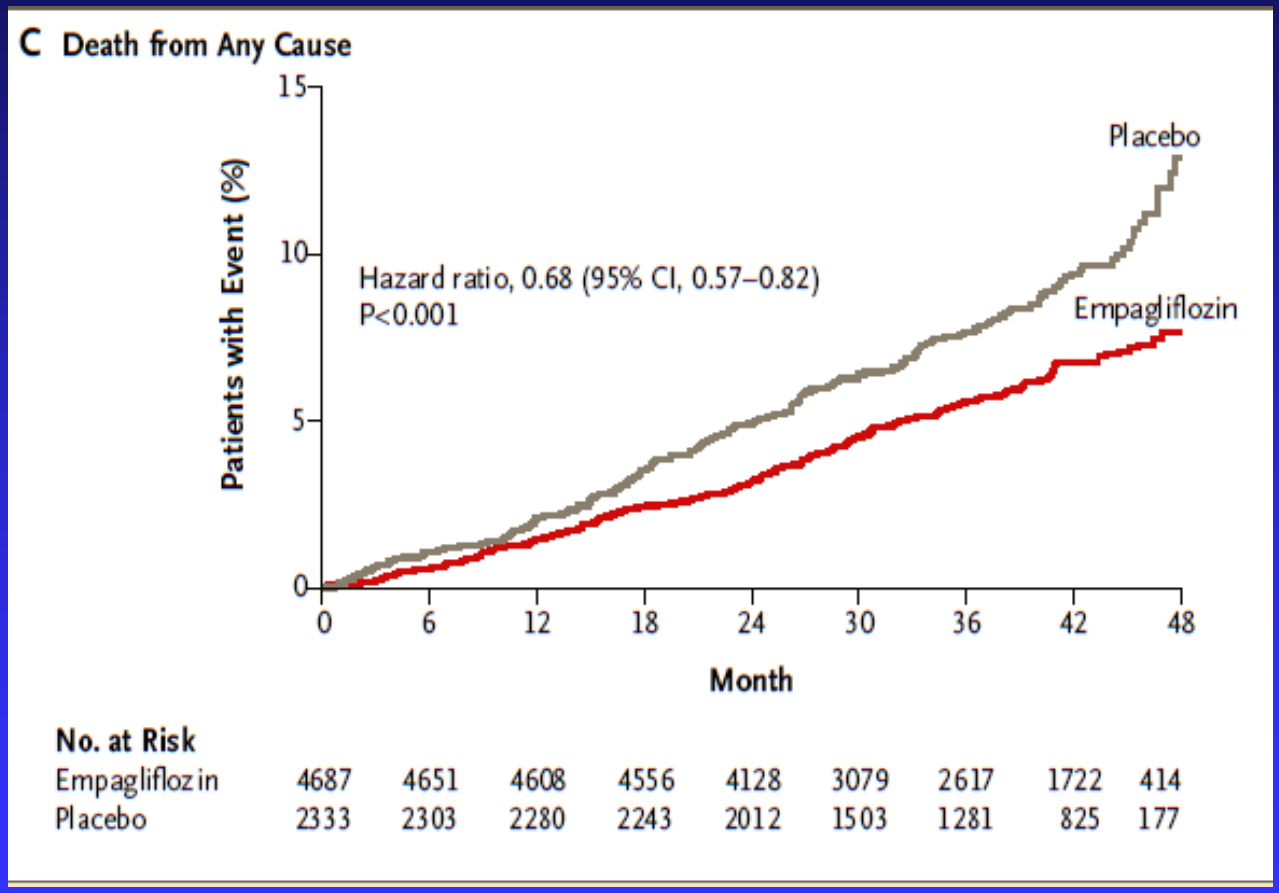
Bernard Zinman, M.D., Christoph Wanner, M.D., John M. Lachin, Sc.D., David Fitchett, M.D., Erich Bluhmki, Ph.D., Stefan Hantel, Ph.D., Michaela Mattheus, Dipl. Biomath., Theresa Devins, Dr.P.H., Odd Erik Johansen, M.D., Ph.D., Hans J. Woerle, M.D., Uli C. Broedl, M.D., and Silvio E. Inzucchi, M.D., for the EMPA-REG OUTCOME Investigators

N ENGL J MED 373;22 NEJM.ORG NOVEMBER 26, 2015

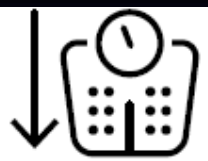
MACE


A Primary Outcome
Patients with Event (%)
20
15
10
5
0
Placebo
Hazard ratio, 0.86 (95.02% CI, 0.74–0.99)
P=0.04 for superiority
Empagliflozin
0
6
12
18
24
30
36
42
48
Month
No. at Risk
Empagliflozin 4687 4580 4455 4328 3851 2821 2359 1534 370
Placebo 2333 2256 2194 2112 1875 1380 1161 741 166

Death from any cause



CHOOSING GLUCOSE-LOWERING MEDICATION IF COMPELLING NEED TO MINIMIZE WEIGHT GAIN OR PROMOTE WEIGHT LOSS



In those WITHOUT established ASCVD OR CKD

Use principles in Figure 1

TO AVOID CLINICAL INERTIA REASSESS AND MODIFY TREATMENT REGULARLY (3–6 MONTHS)

First-line therapy is metformin

If HbA_{1c} is ≥17 mmol/mol (1.5%) above individualized HbA_{1c} target consider early combination therapy

If HbA_{1c} above target

EITHER/ OR

GLP-1 RA with good efficacy for weight loss[1]

SGLT2i if eGFR adequate[2]

If HbA_{1c} above target

Implement strategies for maximizing weight loss

General lifestyle advice

- Medical nutritional therapy
- Eating patterns
- Physical activity

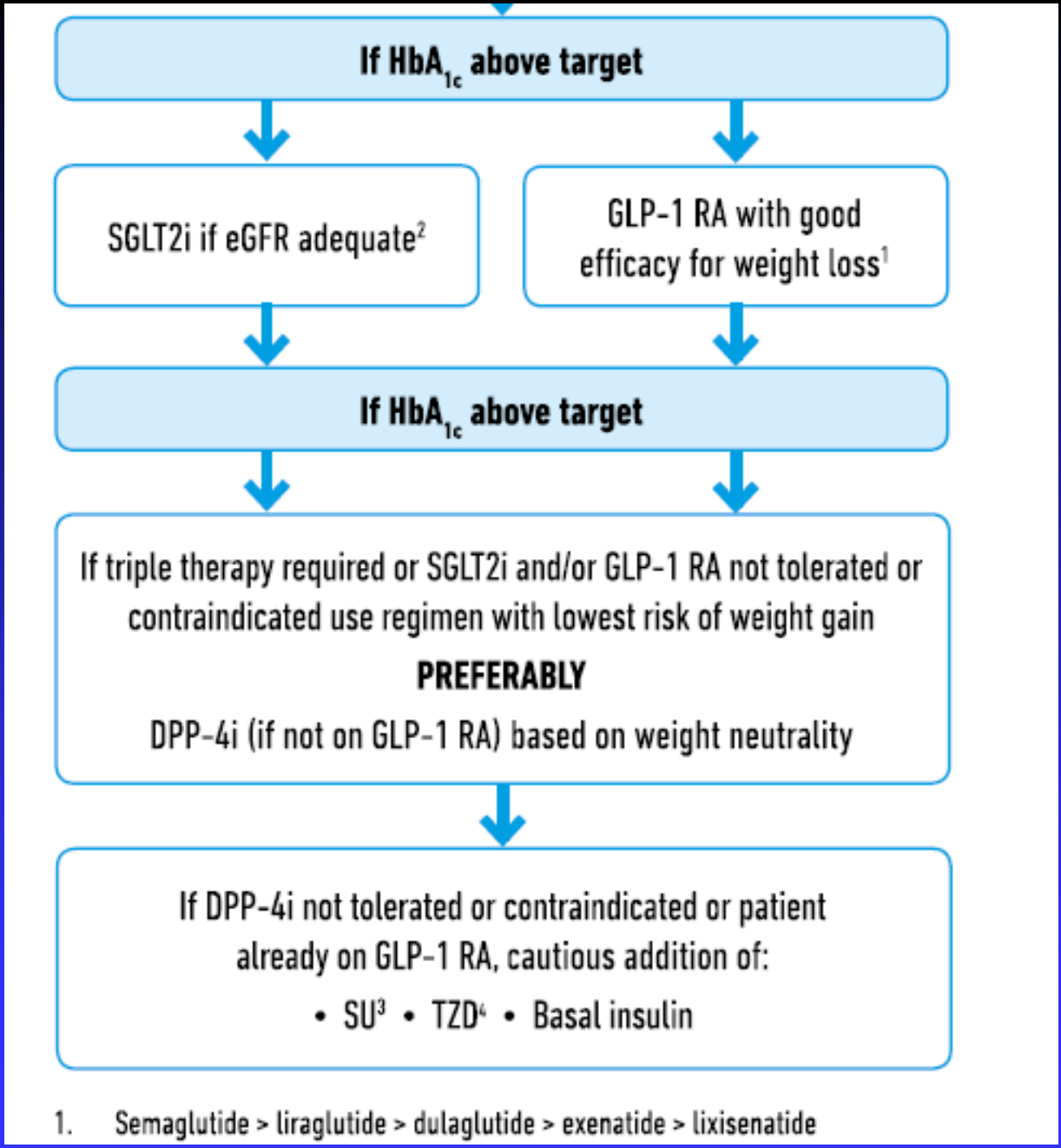
Non-surgical energy restriction for weight loss

Weight loss of 15 kg can lead to remission of T2DM in patient <6 years' duration, **consider evidence-based weight loss programs**

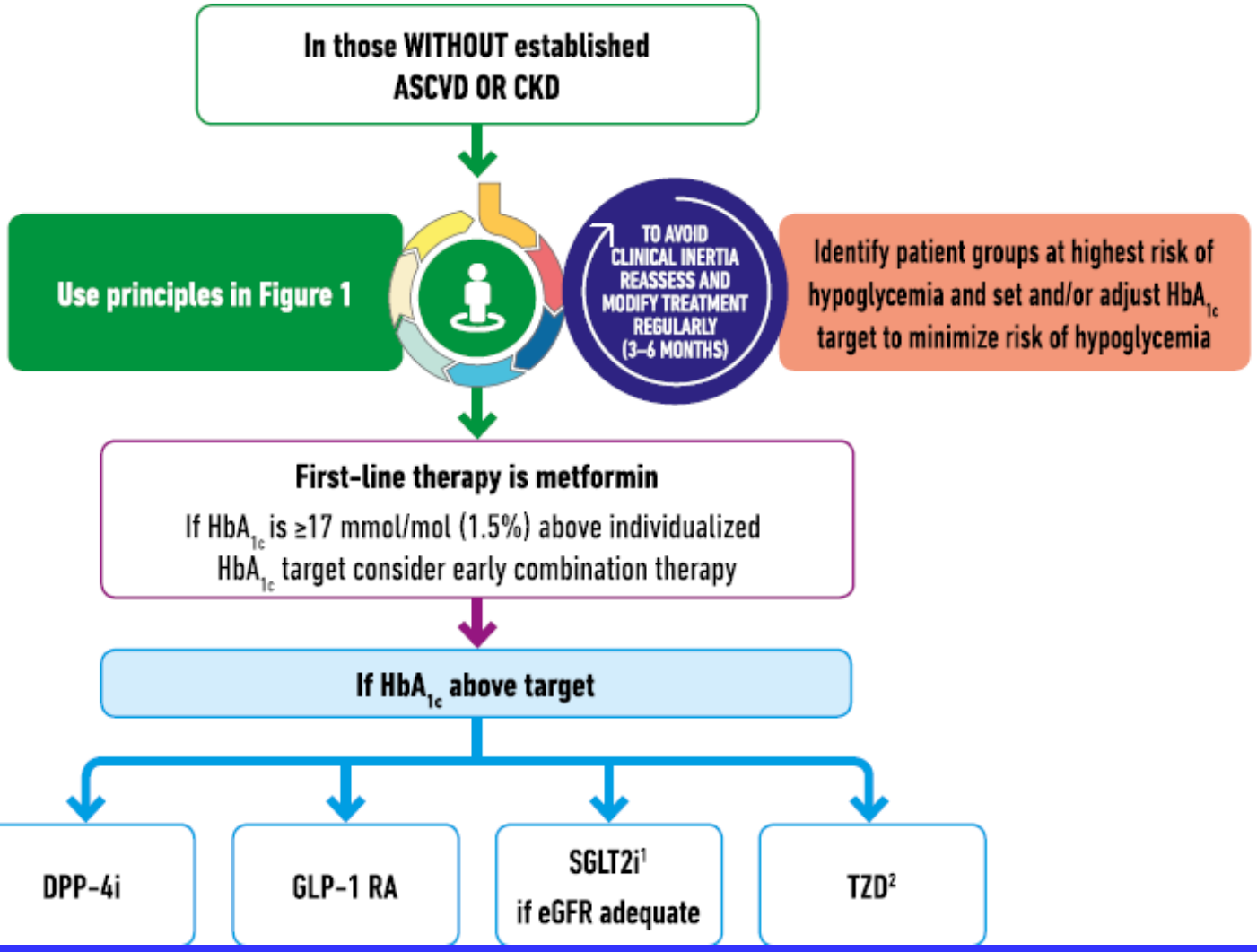
Consider medication for weight loss

Consider metabolic surgery

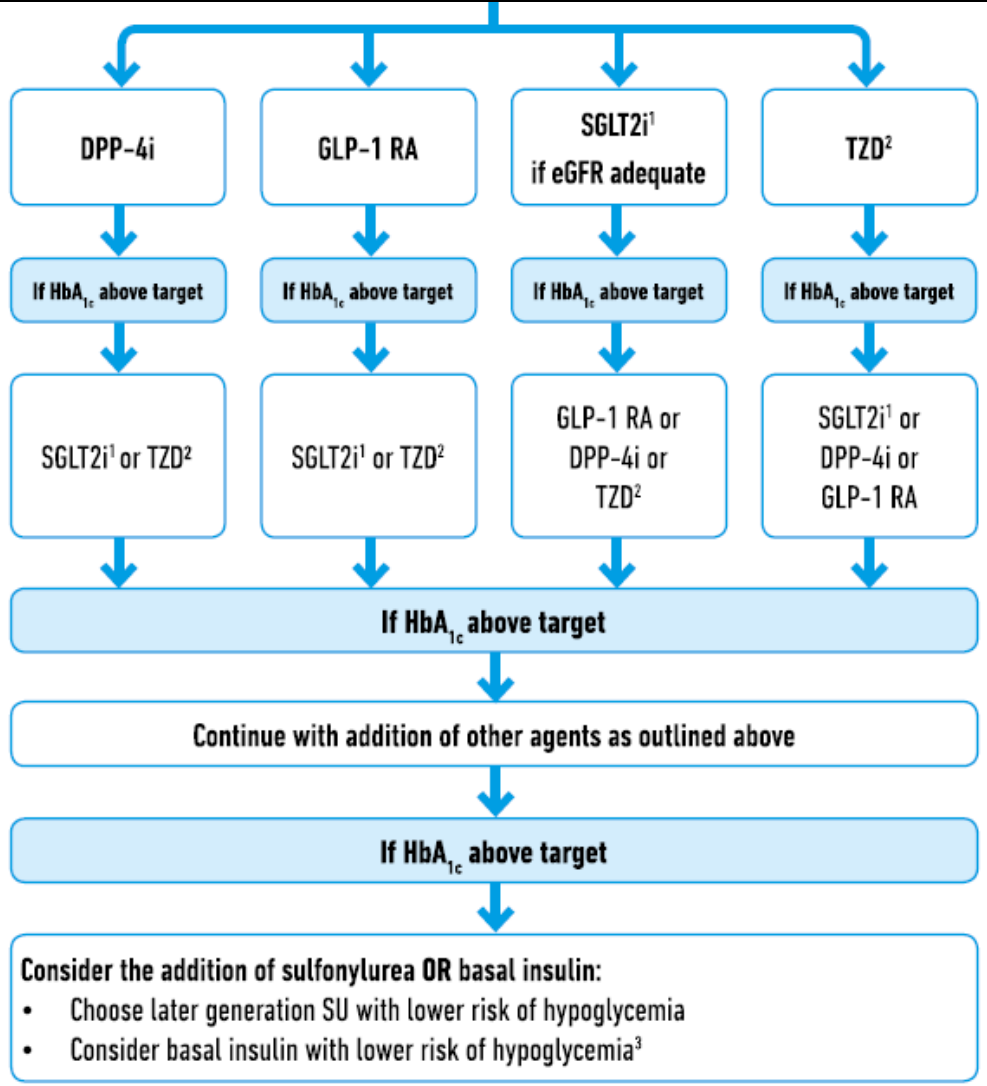
Drugs to minimize weight gain



CHOOSING GLUCOSE-LOWERING MEDICATION IF COMPELLING NEED TO MINIMIZE HYPOGLYCEMIA

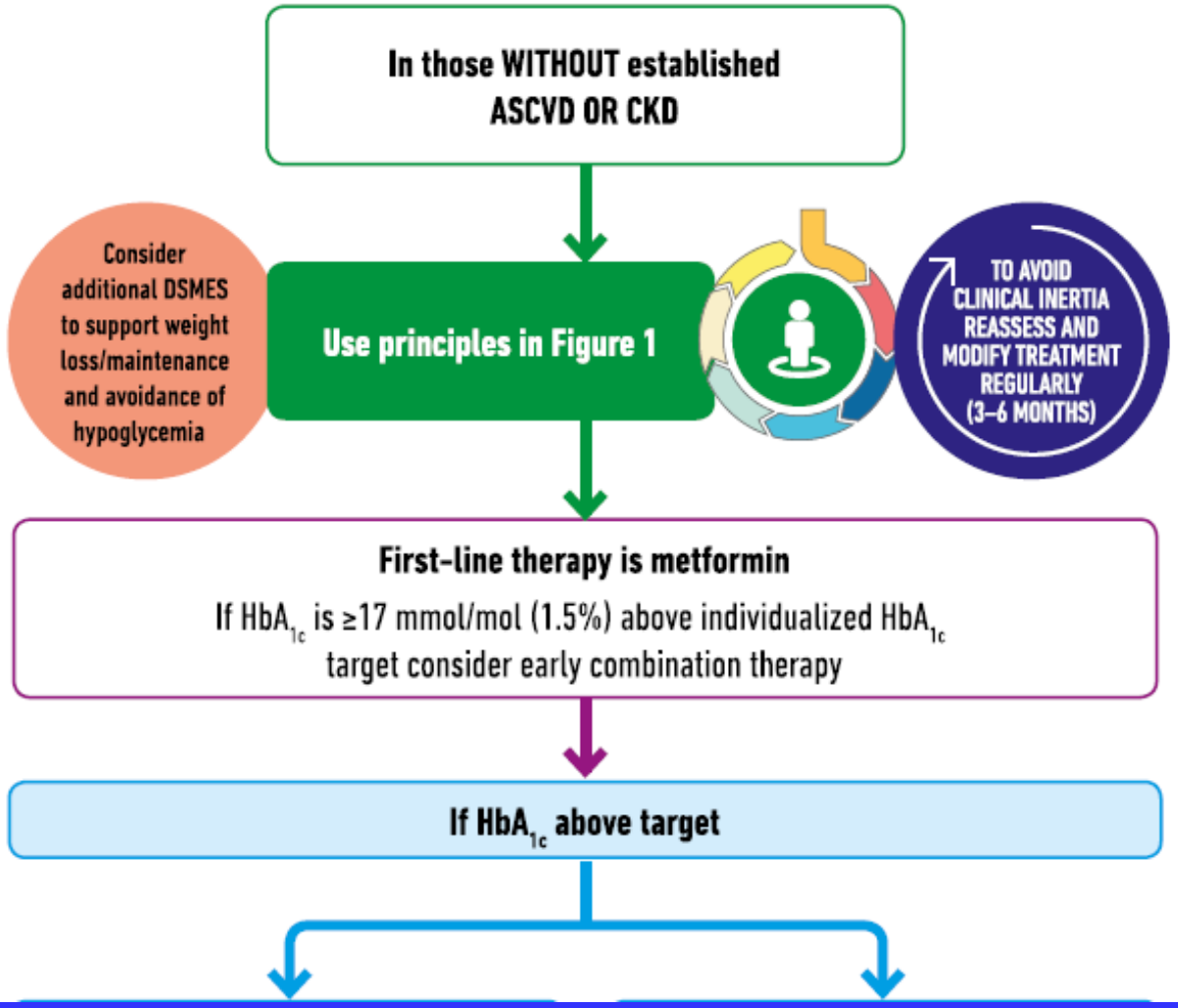


OADs to minimize hypoglycemia

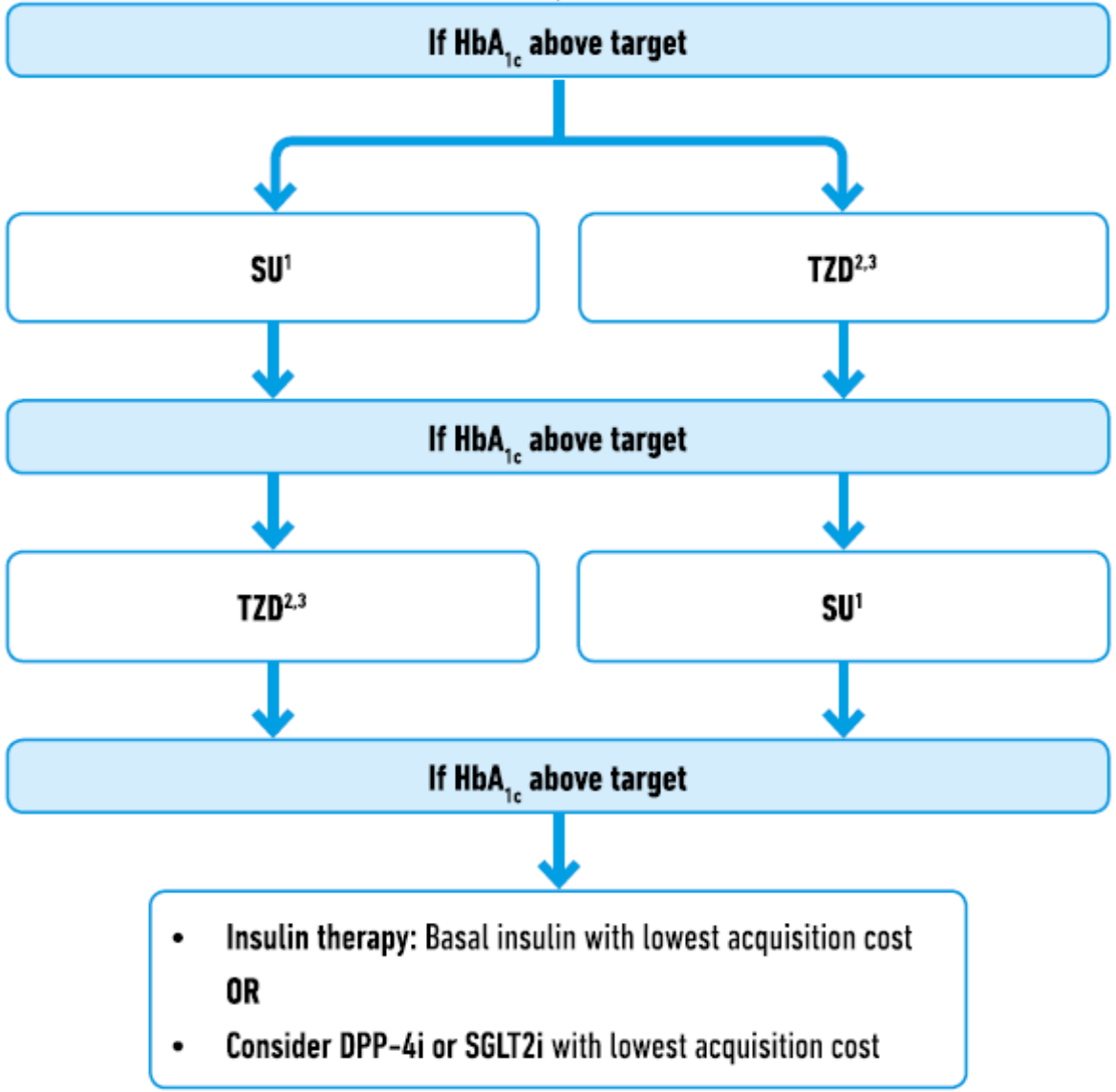


1. Be aware that SGLT2i vary by region and individual agent with regard to indicated level of eGFR for initiation and continued use
2. Low dose TZDs are better tolerated
3. Degludec / glargine U300 < glargine U100 / detemir < NPH insulin

CHOOSING GLUCOSE-LOWERING MEDICATION IF COST IS A MAJOR ISSUE



Cost consideration of OAD

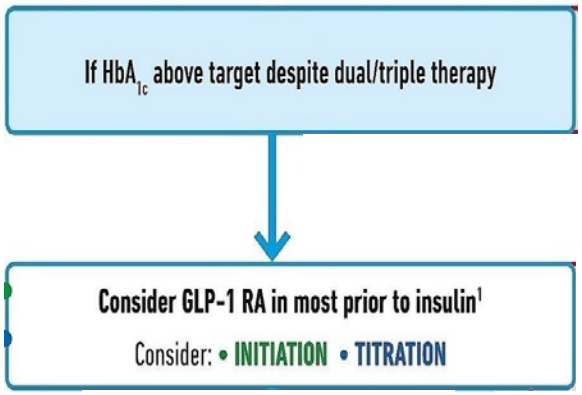


Addition of injectables

Addition of Injectable Medications

Consensus recommendation

- In patients who need the greater glucose-lowering effect of an injectable medication, GLP-1 receptor agonists are the preferred choice to insulin. For patients with extreme and symptomatic hyperglycemia, insulin is recommended (Fig. 7).



Davies MJ, et al. *Diabetes Care*. 2018;41(12):2669-701.

Add basal insulin

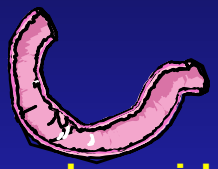
Consider: • **INITIATION** • **TITRATION**

Davies MJ, et al. *Diabetes Care.* 2018 Dec;41(12):2669-2701.

Drug specific and patient factors

- Efficacy
- Hypoglycemia
- Weight change
- CV effects
- Cost
- Oral/SC
- Renal effects
- Additional consideration

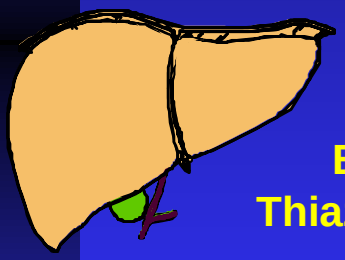
Sites/Mechanisms of Action of Antihyperglycemic Agents



Decreased digestion of complex sugars

Alpha-glucosidase inhibitors

Sulfonylureas
Non-sulfonylurea secretagogues



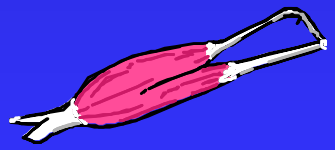
Biguanides
Thiazolidinediones

Normoglycemia

Increased insulin secretion

Decrease in hepatic glucose production

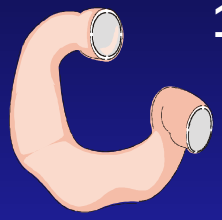
Thiazolidinediones
Biguanides



Increase in glucose uptake

Krenz et al. Spiegelman

Insulin Secretagogues: Mechanisms of Action

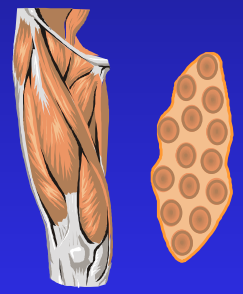


1. Intestine: glucose absorption

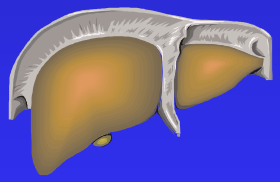
2. Muscle and adipose tissue: glucose uptake

Blood glucose

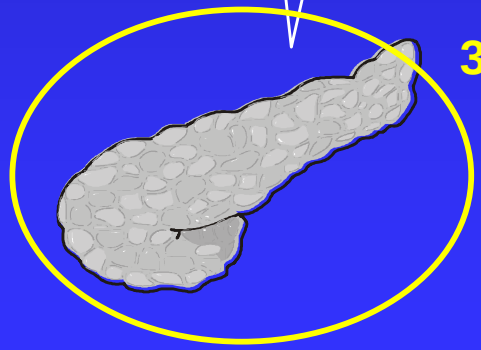
Insulin resistance



4. Liver: hepatic glucose output



Insulin resistance



3. Pancreas:
   Insulin secretion
   Sulfonylureas
   ↑ insulin secretion

Insulin Secretagogues

- Insulin secretagogues stimulate insulin secretion by interacting with the ATP-sensitive potassium channel on the beta cell

These drugs are most effective in individuals with type 2 DM :

1. Relatively recent onset (<5 years)
2. Have endogenous insulin production
3. Obese.

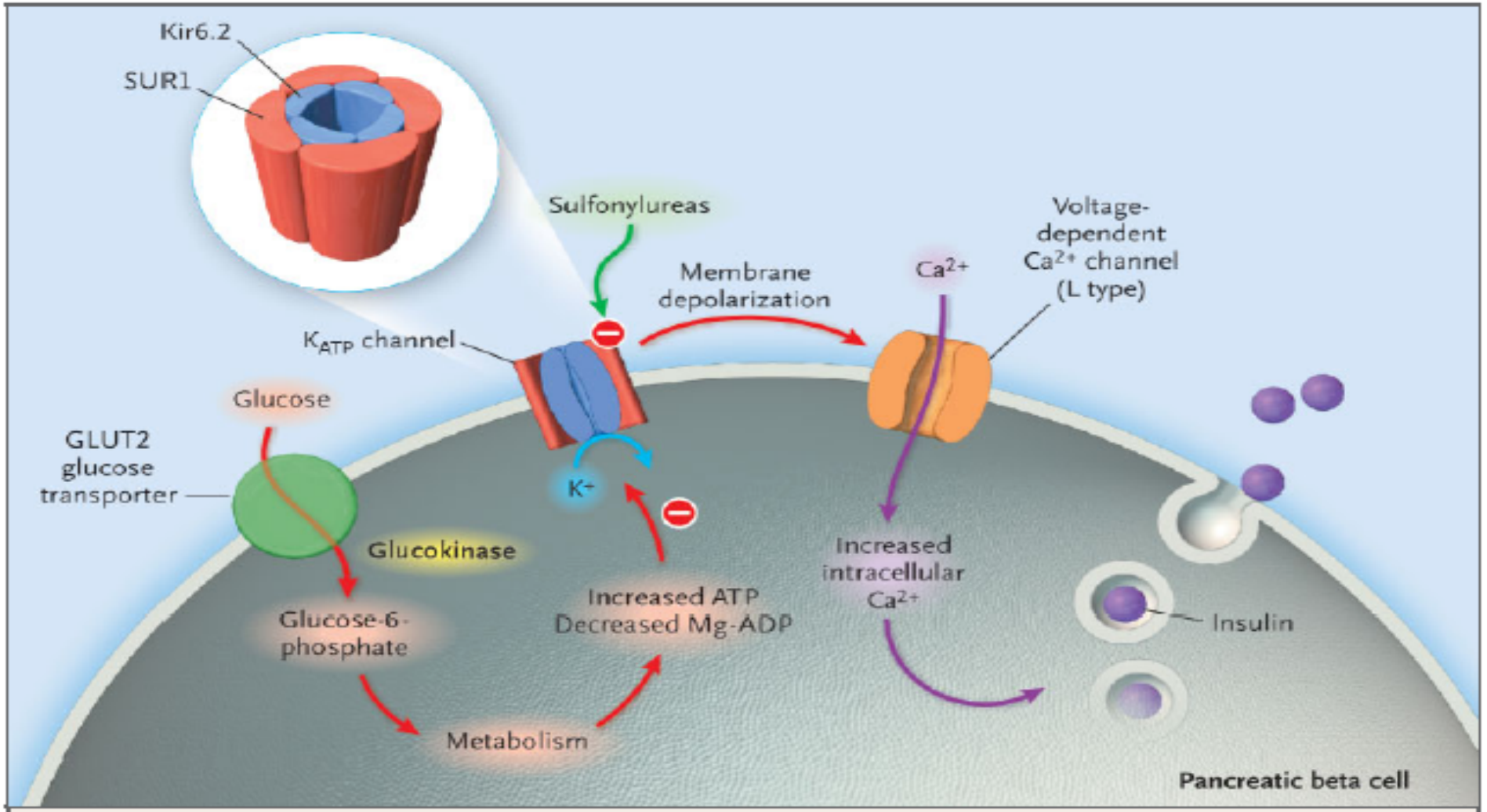


Figure 1. Schematic Representation of the Pancreatic Beta Cell, Illustrating the Role of the ATP-Sensitive Potassium (K_{ATP}) Channel in Insulin Secretion.

Glucose enters the beta cell by way of the GLUT2 glucose transporter. Once inside the cell, glucose is metabolized, leading to changes in the intracellular concentration of adenine nucleotides that inhibit the K_{ATP} channel and thus cause channel closure. The K_{ATP} channel consists of four sulfonylurea-receptor (SUR1) subunits and four Kir6.2 subunits in an octomeric structure. Channel closure leads to membrane depolarization, which subsequently activates voltage-dependent calcium (Ca^{2+}) channels, leading in turn to an increase in intracellular Ca^{2+}, which triggers insulin exocytosis. Sulfonylureas initiate secretion by directly binding to the SUR1 subunits of K_{ATP} channels and causing channel closure. Mg-ADP denotes magnesium ADP.

Sulfonylureas

- Reduce fasting and PPG
- Should be initiated at low doses
- Increased at 1- to 2-week intervals based on SMBG.
- Increase insulin acutely and thus should be taken shortly before a meal
- With chronic therapy, the insulin release is more sustained

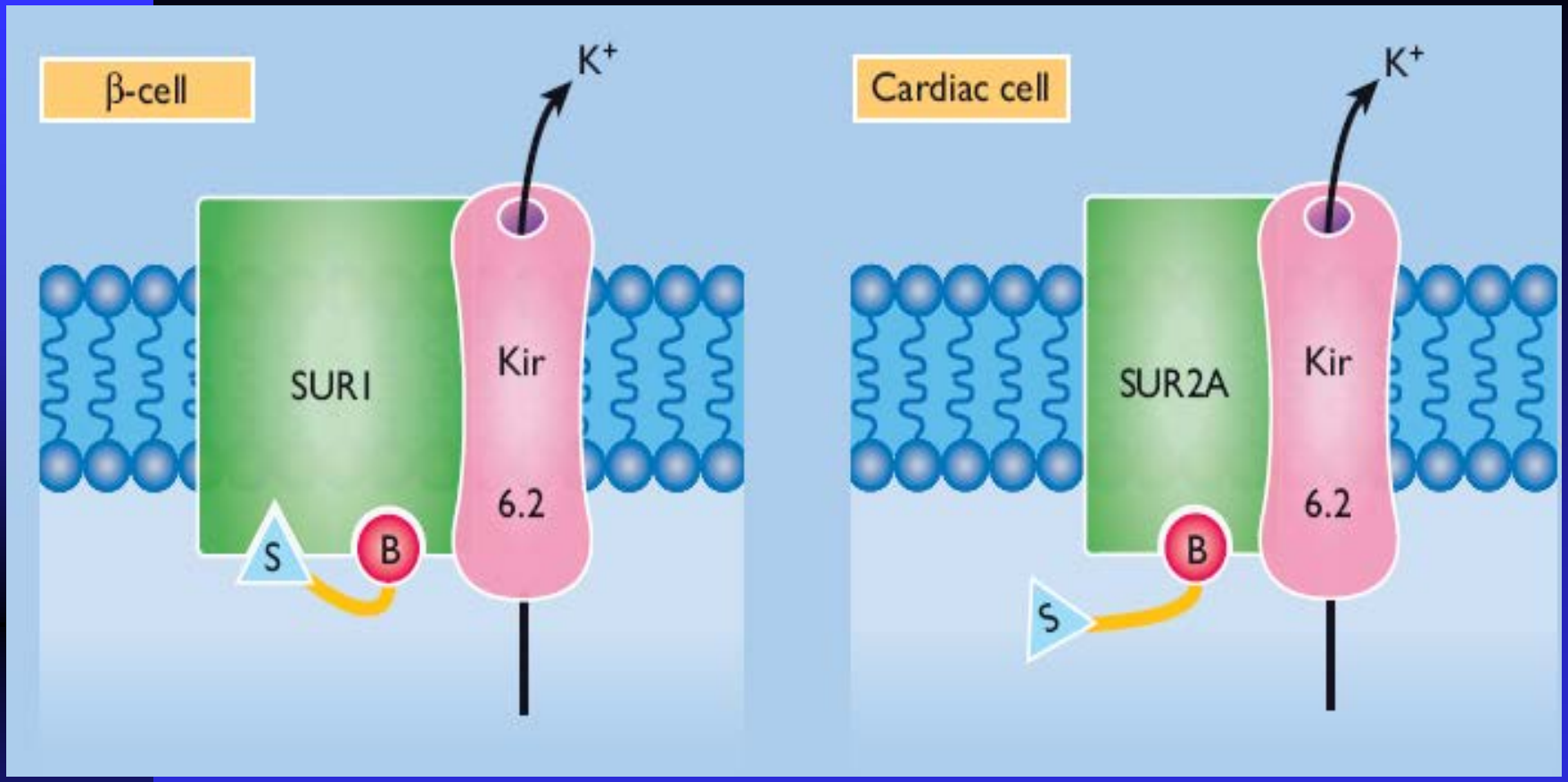
Sulfonylureas

- Most sulfonylureas are metabolized in the liver to compounds that are cleared by the kidney.
- Their use in individuals with significant hepatic or renal dysfunction is not advisable.
- Weight gain, a common side effect of SUD, results from the increased insulin and improvement in glycemic control

Isoforms of the Sulfonylurea receptor

ATI'-dependent potassium channels and their physiologic functions

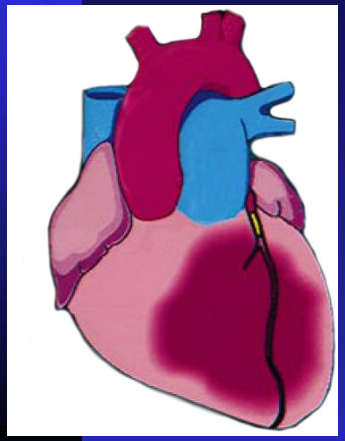
Tissue	Receptor	Basal state	Stimulus	Effect
Pancreatic–β cells	SUR-1	Open	Hyperglycemia	↑ Insulin secretion
Myocardial cells	SUR-2A	Closed	Ischemia Hypoxia	Energy consumption
Vascular smooth	SUR-2B	Closed	Ischemia Hypoxia	Vasodilatation ↓



Glibenclamide & Glipizide : Interact with the cardiac and vascular SUR2A/B

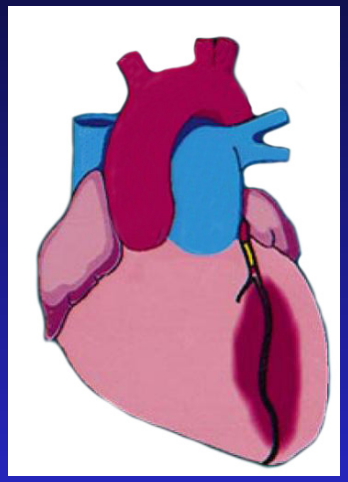
Glimepiride & Gliclazide : Show very little interaction with SUR2A/B

Significance of Ischemic preconditioning



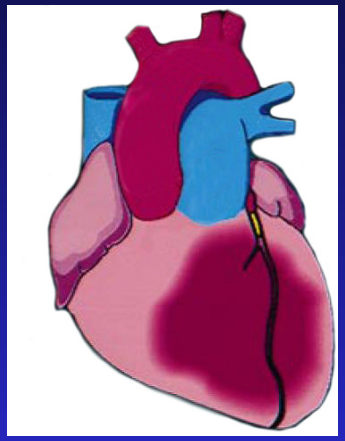
NO ISCHEMIC PRECONDITIONING

Prolonged occlusion of a major coronary artery leads to myocardial infarction



ISCHEMIC PRECONDITIONING

Repeated and brief occlusion of the same vessel preconditions the myocardium such that subsequent prolonged occlusion leads to a smaller infarct



SULFONYLUREAS

Sulfonylureas other than **Glimepiride/Gliclazide** abolish ischemic preconditoning, resulting in large infarction size

J Am Coll Cardiol. 1998 Apr;31(5):950-6.
Klepzig et al. Eur Heart J 1999;20:439-446

Repaglinide

- Is not a sulfonylurea but also interacts with the ATP-sensitive potassium channel.
- Short half-life
- Usually given with or immediately before each meal to reduce meal-related glucose excursions.
- Are well tolerated in general.
- All of these agents, have the potential to cause *profound and persistent hypoglycemia, especially in elderly individuals.*

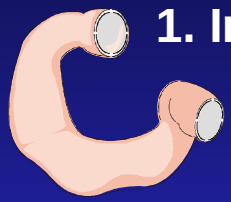
Advantages of Repaglinide

- Flexibility in mealtime dosing- ‘Ramzan Drug’
- No significant increase in bodyweight
- Can be utilized in mild to moderate renal failure

Dosage: Repaglinide:

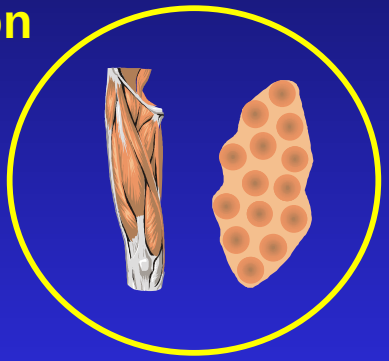
0.5mg/1mg/2mg/4mg per dose per meal

Biguanides: Mechanisms of Action



1. Intestine: glucose absorption

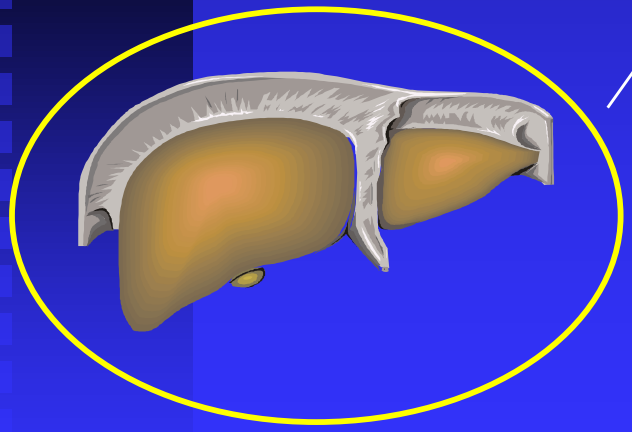
2. Muscle and adipose tissue: Biguanides ↑ glucose utilization



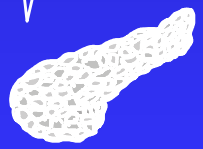
Blood glucose

Insulin resistance

4. Liver: Biguanides ↑ hepatic glucose output



Insulin resistance



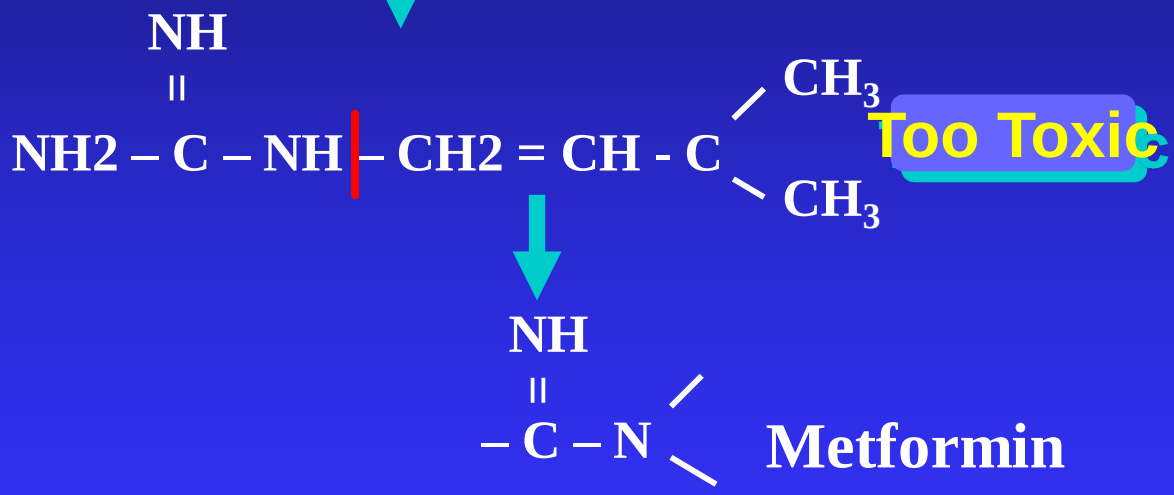
3. Pancreas: insulin secretion

Botanical Heritage of Metformin

Galega Officinalis

Galegine

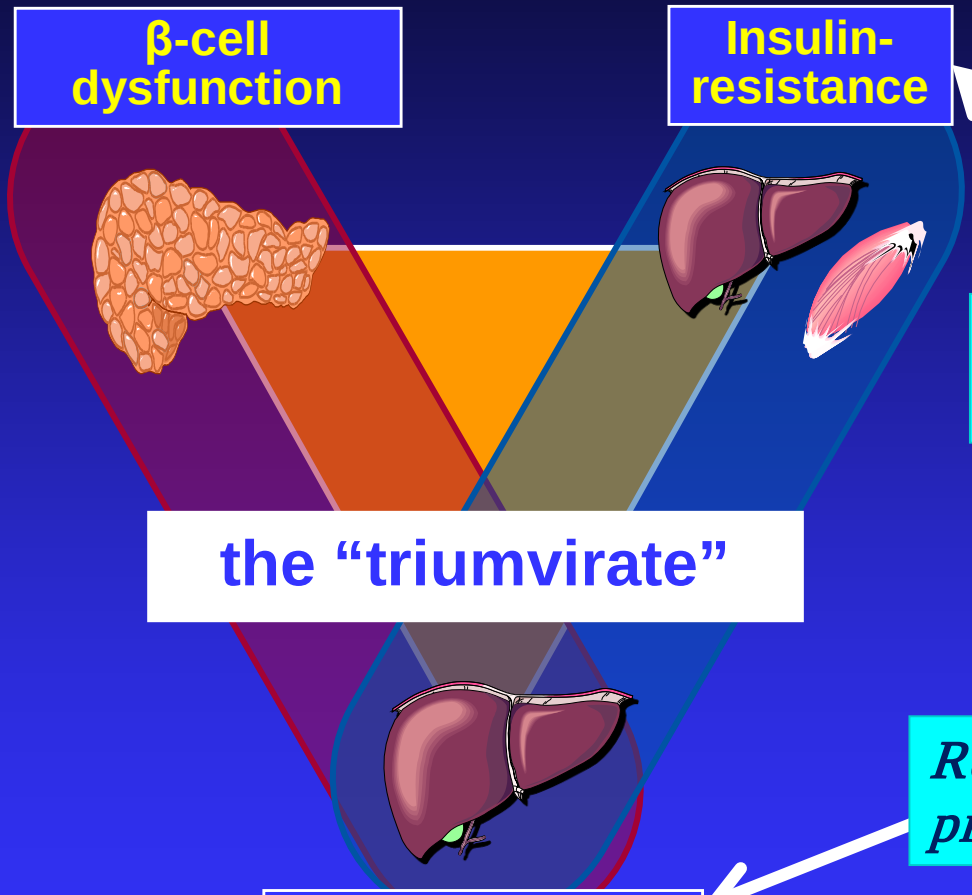
Burger & White (1922)



Elliott P. Joslin, 1927:

"Galegine is the forerunner of better preparations which can be given by mouth and which to some degree will replace insulin"

The 3 main pathophysiological defects of Type 2 diabetes



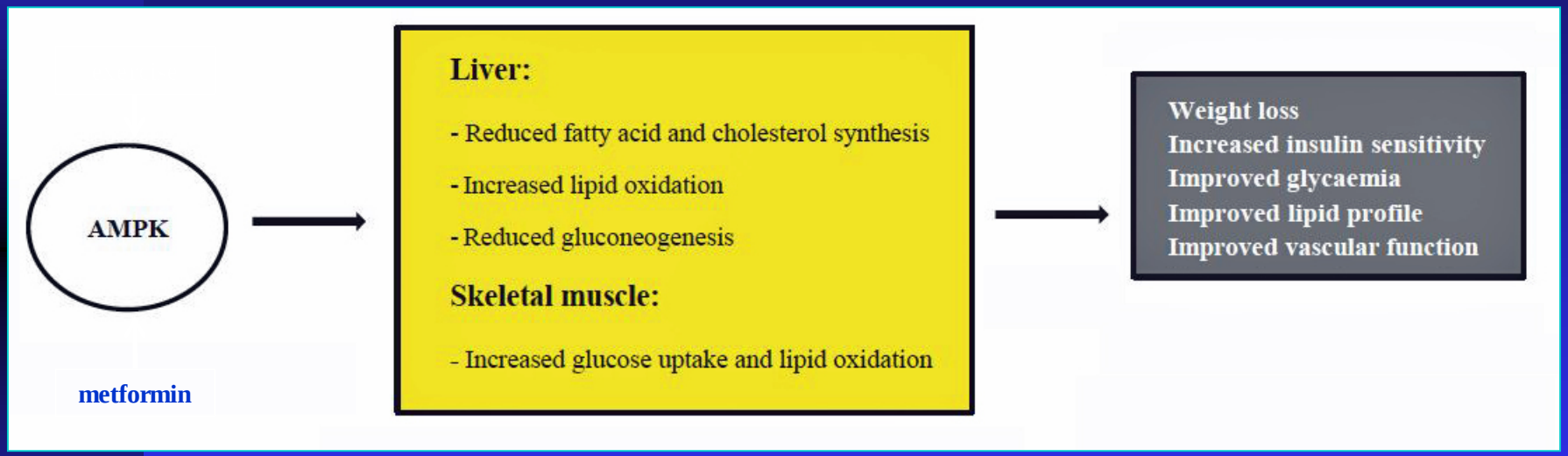
Reduces insulin-resistance

Metformin

Reduces hepatic glucose production++

Metformin: cellular mechanisms of action

Activation of AMP-activated protein kinase (AMPK),
principally in muscle and the liver, is considered a major mode of metformin action



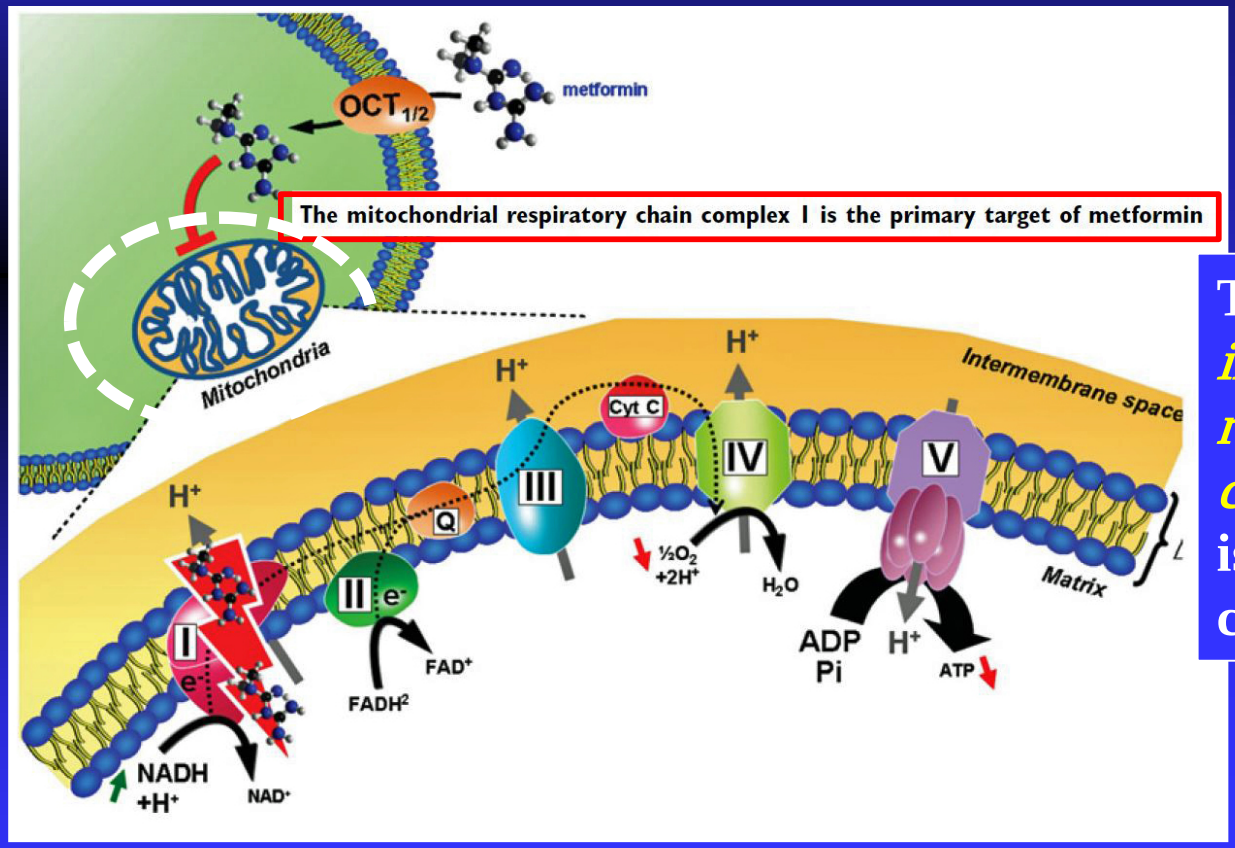
AMPK acts as a sensor of cellular energy status,
coordinating catabolism and anabolism

The concept of energetic stress

Adapted from Diabet. Med. 27, 1097–1106 (2010)

Metformin: cellular mechanisms of action

AMPK activation by metformin is secondary to its effect on **the mitochondria, the primary target of metformin**



Metformin inhibits this complex

The consequence of *inhibition of the respiratory chain complex I by metformin* is a transient reduction in cellular energy status.

AMPK activation

Adapted from Clinical Science (2012) **122**, 253–270

Biguanides

Metformin

- Reduces hepatic glucose production
- May improve peripheral glucose utilization slightly.
- Reduces fasting plasma glucose and insulin levels
- Improves the lipid profile
- Promotes modest weight loss.

Metformin

- The initial starting dose of 500 mg once or twice a day can be increased to 850 mg tid or 1000 mg bid.

- Because of its relatively slow onset of action and gastrointestinal symptoms with higher doses, the dose should be escalated every 2 to 3 weeks

Metformin

- The major toxicity:

lactic acidosis

- Metformin should not be used in patients with eGRF< 30
- Any form of acidosis
- Advanced CHF
- Advanced Liver disease
- Severe hypoxia.

Metformin should be discontinued in patients

Who are seriously ill

Patients who can take nothing orally

Those receiving radiographic contrast

Metformin

- Some develop GI side effects (diarrhea, anorexia, nausea, and metallic taste) that can be minimized by gradual dose escalation.
- Drug is metabolized in the liver
- It should not be used in patients with advanced liver disease or heavy ethanol intake

Metformin is the cornerstone of any pharmacological anti-diabetic treatment: *the 1st line agent and next the background medication of the intensification strategy*

At diagnosis
(in all the guidelines)

Metformin for everybody*

if HbA1c ≥ 6.5 to 7%

***contra-indicated if eGFR<30ml**

Metformin *(if tolerated)* is widely accepted as the 1st line agent

Management of Hyperglycemia in Type 2 Diabetes: A Patient-Centered Approach

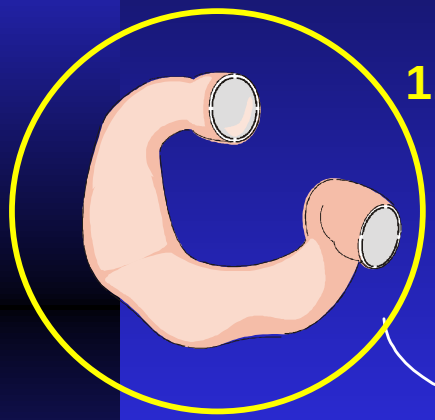
Position Statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD)

American Diabetes Association. EASD

Position Statement

Diabetes Care, 2012, 35: 1364-1379

α-Glucosidase Inhibitors: Mechanisms of Action

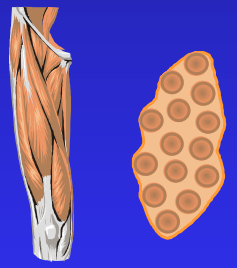


1. Intestine: glucose absorption

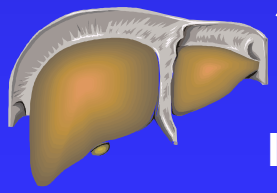
2. Muscle and adipose tissue: glucose uptake

Blood glucose

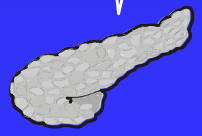
Insulin resistance



4. Liver: hepatic glucose output



Insulin resistance



3. Pancreas: insulin secretion

α- glucosidase inhibitors

- *α* -Glucosidase inhibitors (acarbose and miglitol) reduce postprandial hyperglycemia by delaying glucose absorption
- They do not affect glucose utilization or insulin secretion.
- PP hyperglycemia, contributes significantly to the hyperglycemic state in type 2 DM.

α- glucosidase inhibitors

- The major side effects (diarrhea, flatulence, abdominal distention) are related to increased delivery of oligosaccharides to large bowel
- *α*-Glucosidase inhibitors may increase SUD and increase hypoglycemia.
- Simultaneous treatment with bile acid resins and antacids should be avoided.

α- glucosidase inhibitors

These agents should not be used in :

- IBD
- Gastroparesis
- Creatinine >2.0 mg/dL.

- This agents is not as potent as other oral agents in lowering the HbA1c but is unique in that it reduces the PP glucose rise even in individuals with type 1 .

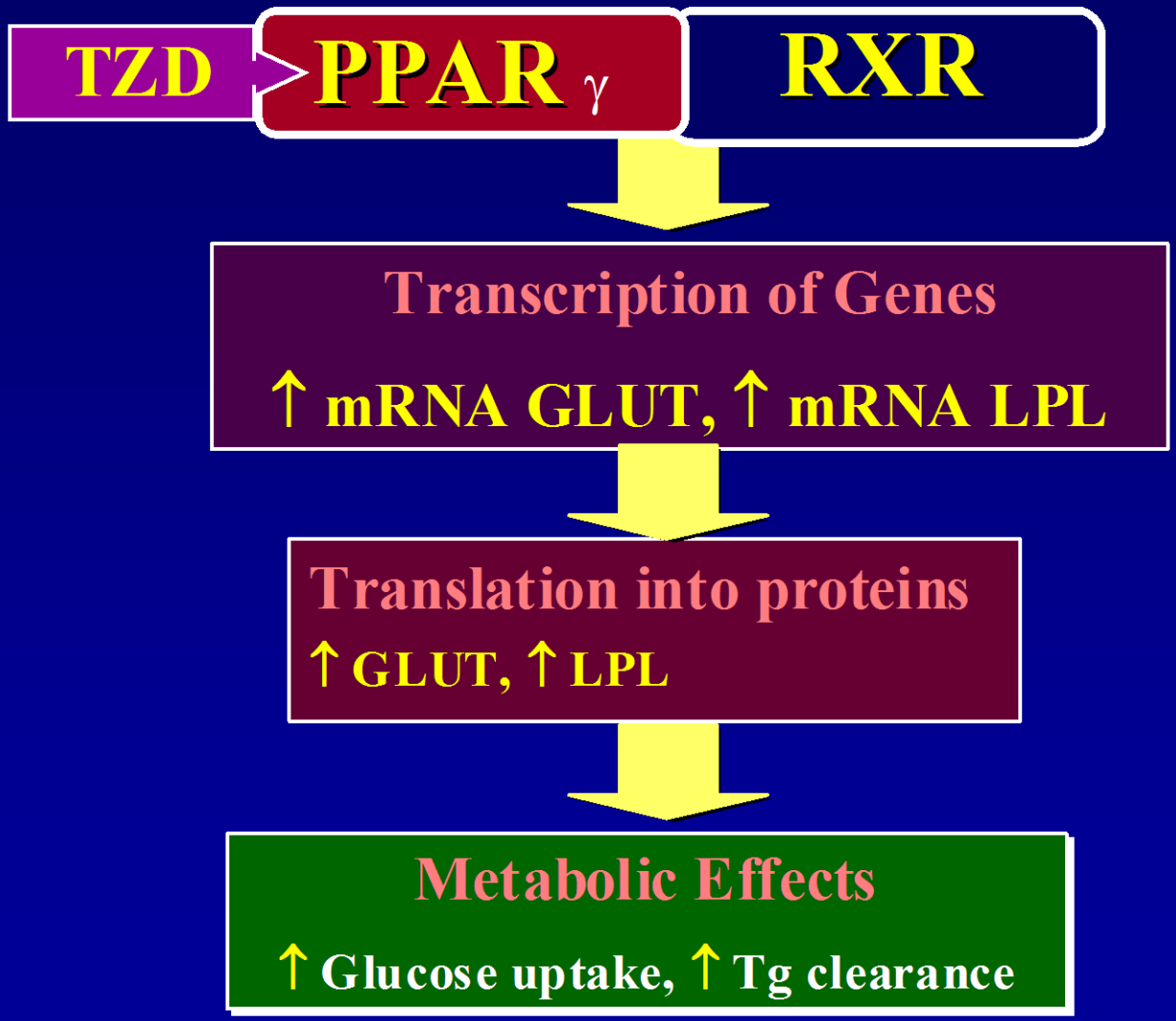
Thiazolidinedione

These drugs bind to a nuclear receptor (peroxisome proliferator-activated receptor, PPAR-γ) that regulates gene transcription.

- PPARγ - most important receptor isoform
  - Reduces TNF-α and hepatic glucokinase expression (suppresses glucose output)

- Stimulate expression of genes responsible for production of GLUT-1 and GLUT-4 (increases insulin sensitivity 60%)

Thiazolidinedione - Mechanisms of Action

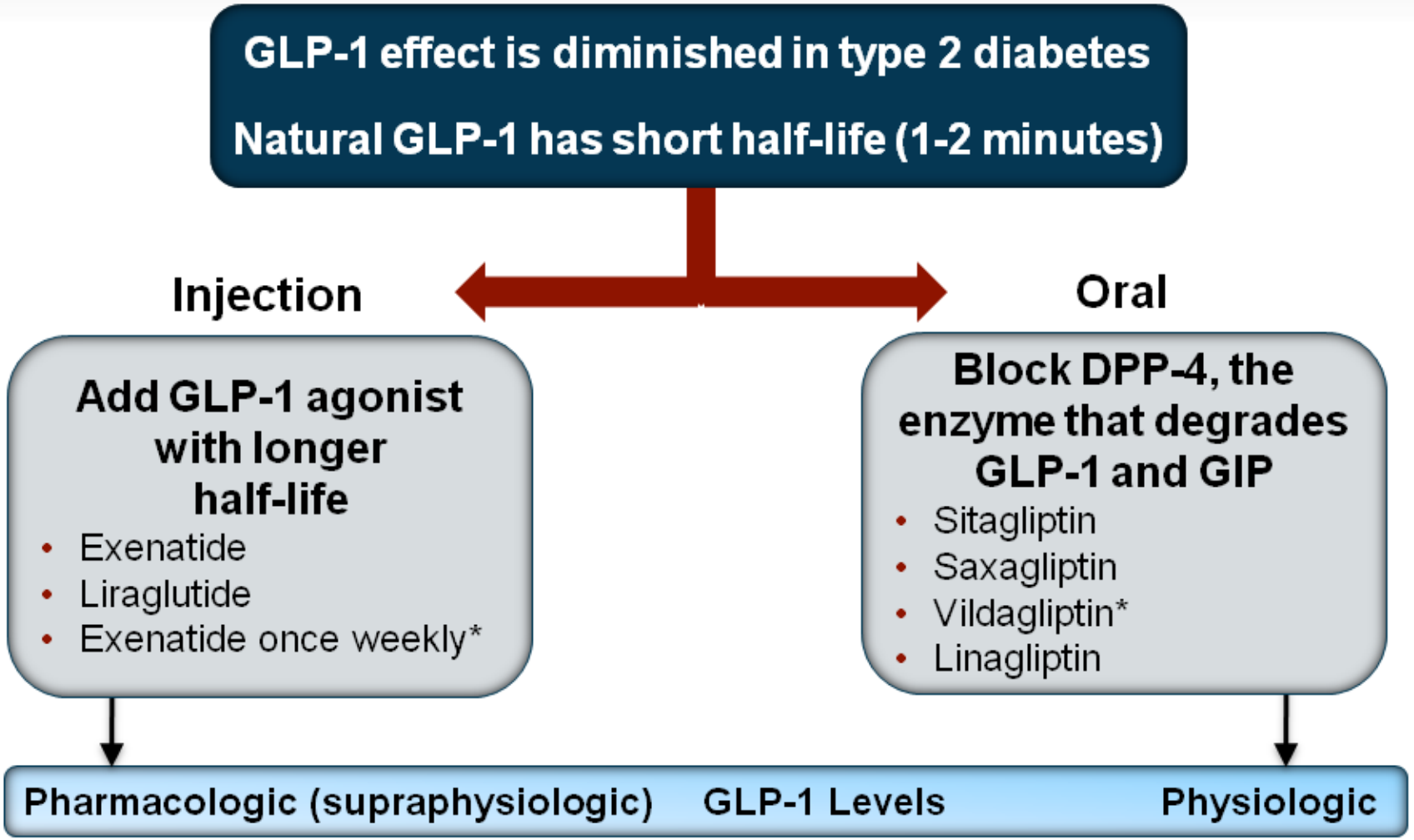


Adapted from: Tan M. (2000) Exp Clin Endocrinol Diabetes Suppl 2 108 :S 224

Thiazolidinedione

- TZD raise LDL and HDL slightly and lower TG by 10 to 15%
- TZD are associated with weight gain (1 to 2 kg)
- small reduction of HCT
- A mild increase in plasma volume.
- Cardiac function is not affected, but the incidence of peripheral edema is increased
- They are contraindicated in patients with liver disease or CHF (class III or IV).
- TZD have been shown to induce ovulation in premenopausal women with polycystic ovary syndrome

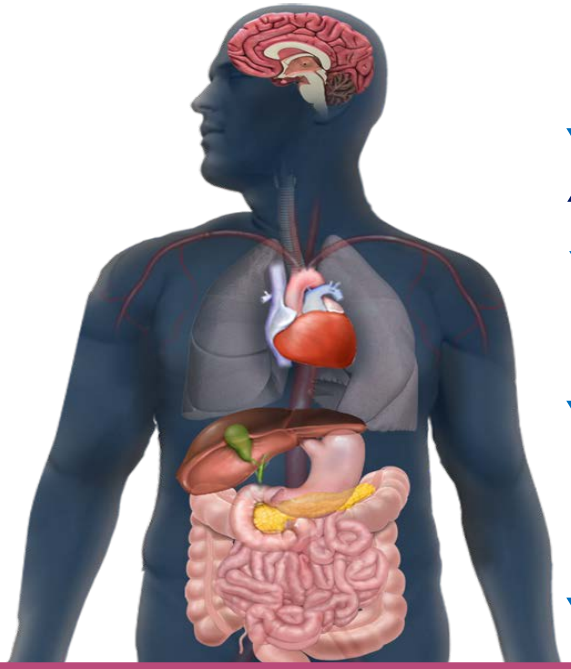
Enhancing the Incretin Effect



*Not yet approved by the US Food and Drug Administration

Drucker DJ, et al. *Lancet*. 2006;368:1696-1705.

GLP-1RA direct effects on human physiology[1]



Pancreas

- ↑ Insulin secretion[2,3] (glucose-dependent) and beta-cell sensitivity
- ↑ Insulin synthesis[4]
- ↓ Glucagon secretion[3] (glucose-dependent)

Brain

- ↓ Body weight[5–7]:
- ↑ Satiety
- ↓ Energy intake

Cardiovascular system

- ↓ Systolic blood pressure[8]

Liver

- ↓ Hepatic glucose output[4]

GLP-1 RA targets six out of eight core defects of T_2DM

1. Holst JJ et al. *Trends Mol Med* 2008;14:161–168; 2. Flint A et al. *Adv Ther* 2011;28:213–226; 3. Degn K et al. *Diabetes* 2004;53:1187–1194; 4. Baggio LL & Drucker DJ. Gastroenterology 2007;132:2131–2157; 5. Horowitz M et al. *Diabetes Res Clin Pract* 2012;97:258–266; 6. Vilsbøll T et al. *BMJ* 2012;344:d7771; 7. Niswender K et al. *Diabetes Obes* Metab 2013;15:42–54; 8. Fonseca V et al. *Diabetes* 2010;59(suppl 1):A79 (296-OR).

Glucagon-like peptide 1 (GLP-1) agonist

Exenatide

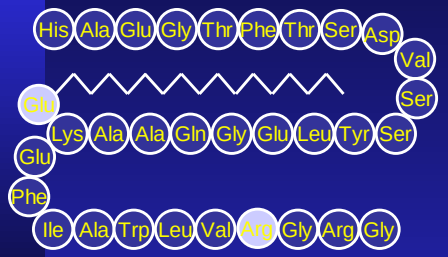
"Insufficient clinical use to be confident regarding safety"

How it works	Potentiates glucose-stimulated insulin secretion
Expected HbA_{1c} reduction	0.5 to 1% (mainly by lowering postprandial glucose)
Adverse events	• GI tract: nausea, vomiting, diarrhea in 30-45% subjects • Pancreatitis?
Weight effects	Weight loss of ~ 2–3 kg over 6 months (may be result of GI side effects)
CV effects	None mentioned

Nathan DM, *et al. Diabetes Care* 2009;32 193-203.

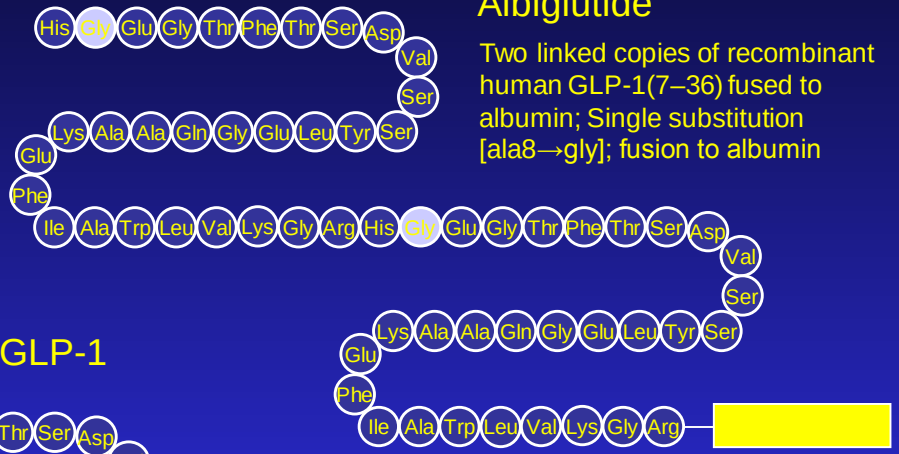
GLP-1 receptor agonists that have been compared

Liraglutide



Single substitution [lys34→gly] and addition [glu26]; acylation with C-16 fatty acid (palmitoyl) confers albumin binding and heptamer formation

Albiglutide

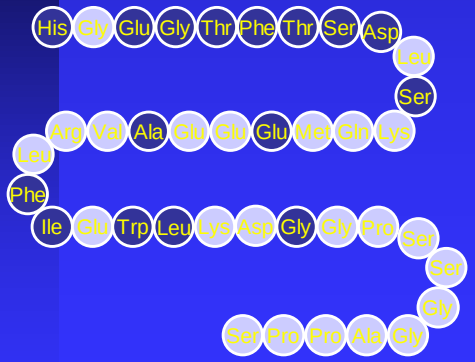


Two linked copies of recombinant human GLP-1(7–36) fused to albumin; Single substitution [ala8→gly]; fusion to albumin

Native human GLP-1

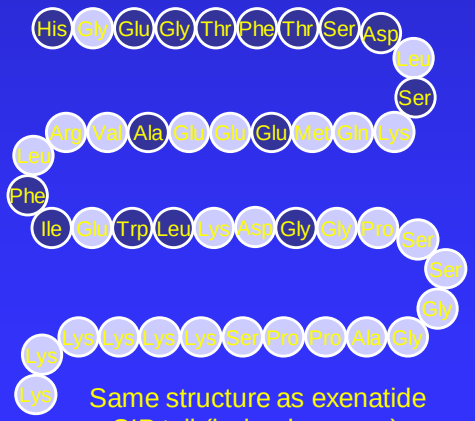
Circulates as GLP-1(7-37) or **GLP-1(7-36) amide**

Exenatide (BID and QW)



Isolated from the saliva of the Gila Monster; 53% AA homology (1-30) to native human GLP-1

Lixisenatide



Same structure as exenatide + SIP tail (lysine hexamer)

SGLT2-inhibitors

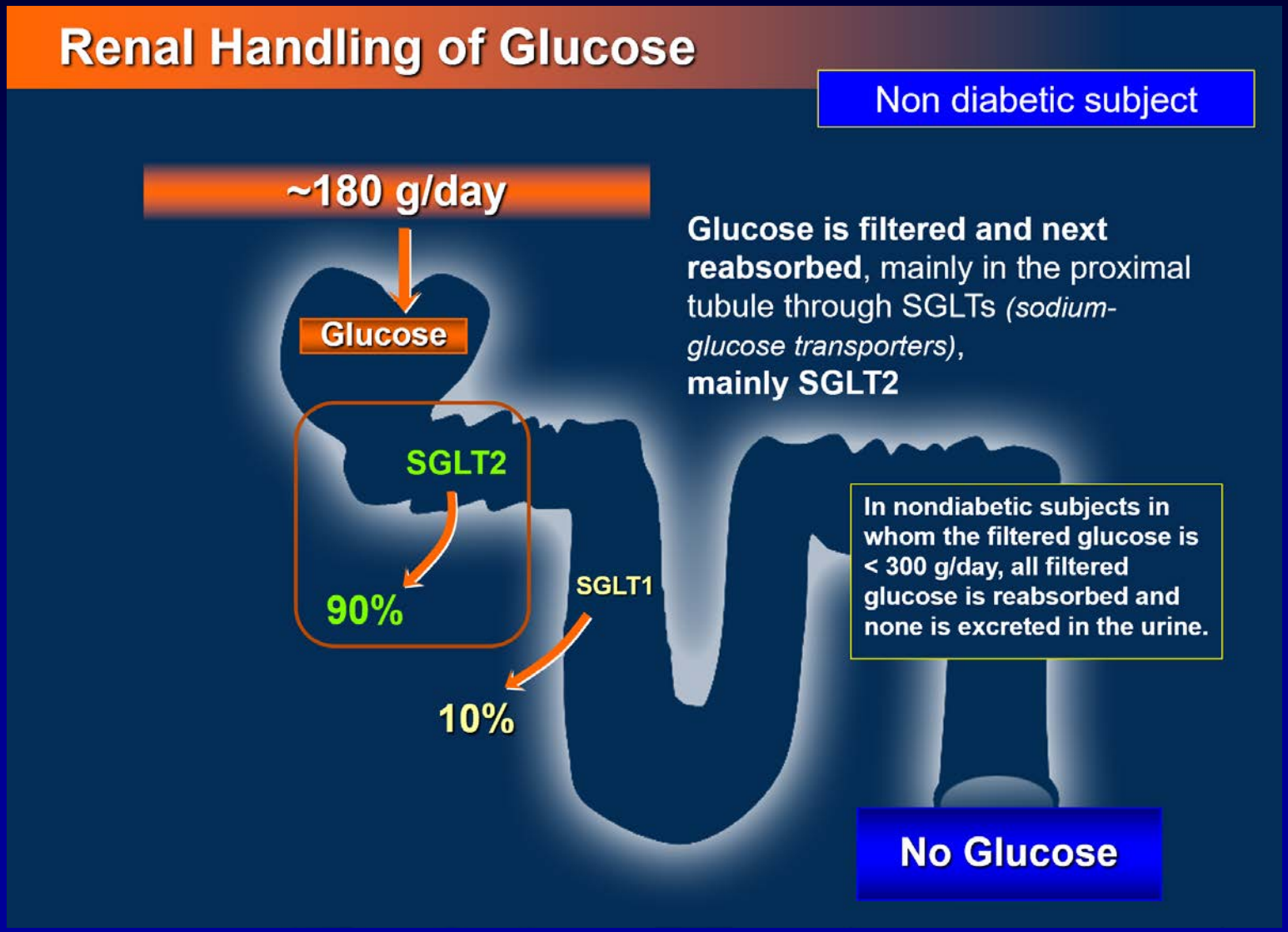
SGLT-2 inhibitors including:

- Dapagliflozin
- Empagliflozin
- Canagliflozin
- Ertugliflozin

Phlorizin (1933): Extracted from Bark of Apple Trees

The example of SGLT2-inhibitors which *both:*

- *improve glucose control*
- *and prevent cardio-vascular events*



SGLT2-inhibitors: induce an osmotic diuresis

Diabetic subjects

> 200 g/day

Glucose

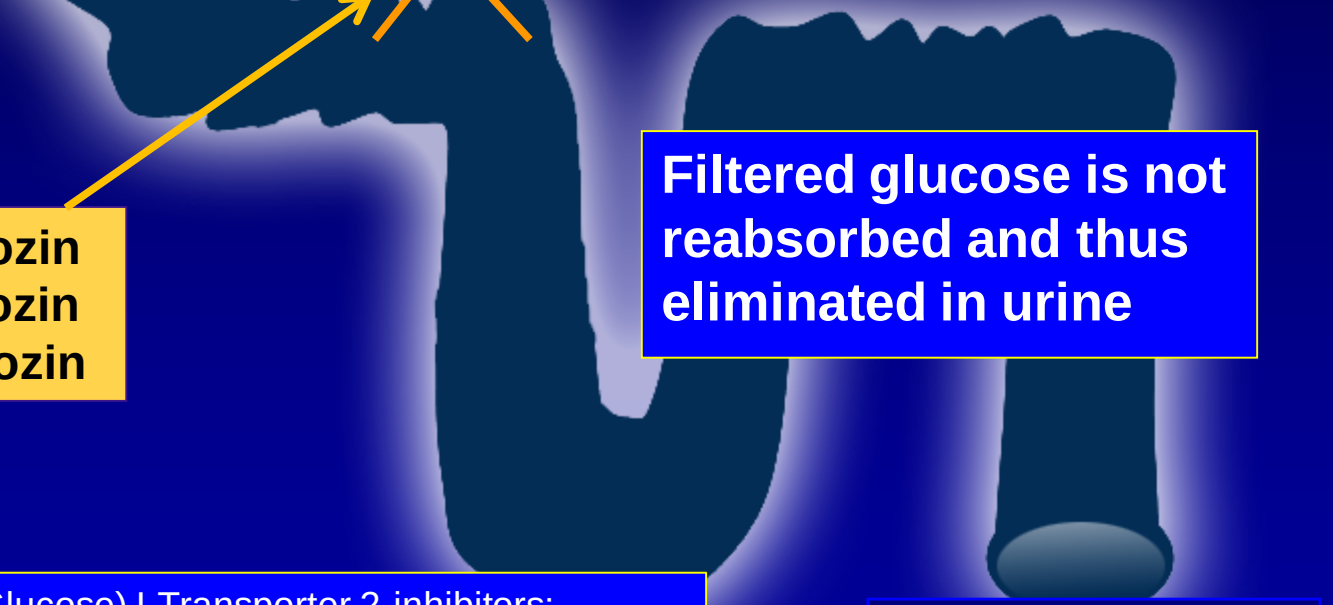
SGLT2

Decrease blood glucose by inducing glycosuria

(loss of glucose but also related calories)

Dapagliflozin
Canagliflozin
Empagliflozin

Filtered glucose is not reabsorbed and thus eliminated in urine



Glycosuria

SG (**Sodium** – Glucose) LTransporter 2-inhibitors:
induce not only glycosuria but also natriuresis

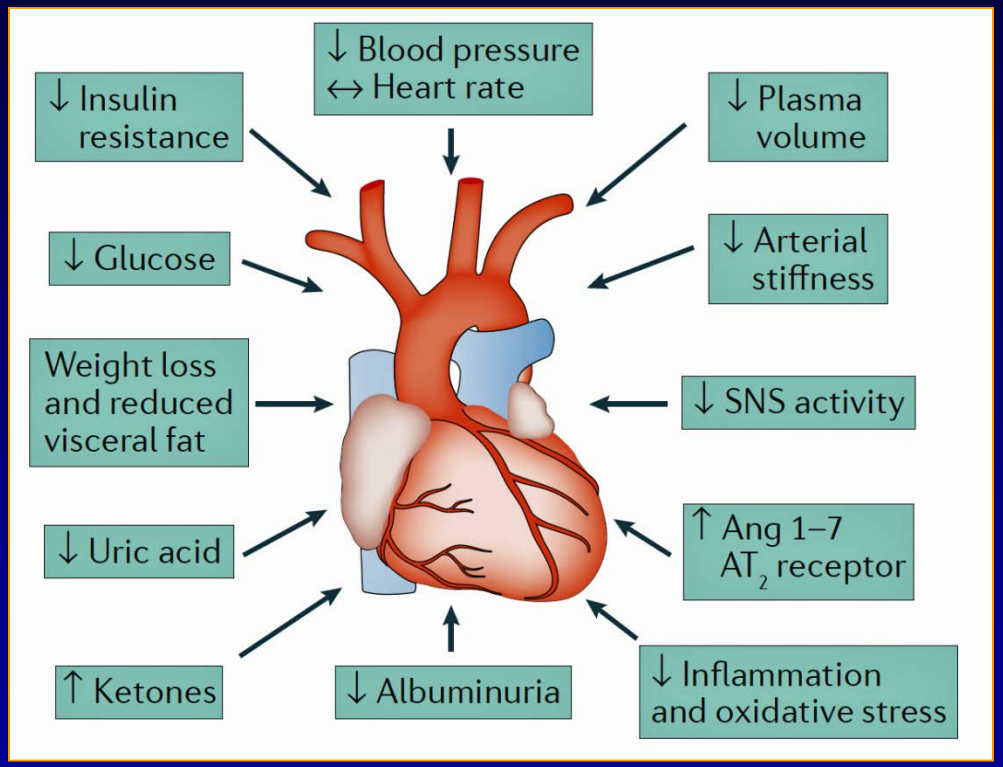
SGLT2-inhibitors

SGLT-2is are proved to be safe:

- No hypos
- No CKD (reduce albuminuria)
- Slightly increased urinary tract infections
- No CV risk (reduced)
- Rare *e*DKA (need education)
- Some genital infections (need educ.)

SGLT2-inhibitors: a positive CV profile

The mechanisms are speculative



The mechanisms of the renal protection (improvement of the tubulo-glomerular feed-back) are different

- **Diuretic effect** of SGLT2i can produce afterload reduction, leading to improved left ventricular function, reduced cardiac workload, and diminished myocardial oxygen demand
- **Preferential ketone oxidation** by myocardial cells could provide an energetic advantage to the failing heart
- **Synergy of metabolic benefits**: reduced blood pressure, reduced body weight, reduced blood glucose…
- **Other potential mechanisms** such as inhibition of cardiac sympathetic nerves, increased glucagon, decreased uric acid…

Adapted from R DeFronzo 2017

GIs and UTIs

UTIs and genital infections

- All events were mild to m
- M
  r
- Most events responded to the initial course of standard therapy

Practical Tips :
Keep Clean , Keep Dry & drink regularly

	Placebo-pool (rm)[2]
(%)	laceb o (N=2295)
UTIs	4.3	3.7
Genital infections	4.8	0.9

- Pyelonephritis was uncommon and occurred at a similar frequency to control[1]

*Genital infection includes the preferred terms: Vulvovaginal mycotic infection, vaginal infection, balanitis, genital infection fungal, vulvovaginal candidiasis, vulvovaginitis, balanitis candida, genital candidiasis, genital infection, genital infection male, penile infection, vulvitis, vaginitis bacterial and vulval abscess.

1. Dapagliflozin. Summary of product characteristics, 2014; 2. EMDAC background document. Available at: http://www.fda.gov/downloads/advisorycommittees/committeesmeetingmaterials/drugs/endocrinologicandmetabolicdrugsadvisorycommittee/ucm378079.pdf. Last accessed March 2015.

Dosage and Administration

- Recommended starting dose 10 mg once daily
- For patients who tolerate 10 mg and need further glycemic control, their dose can be increased to 25 mg once daily
- Can be taken with/without food in the morning
- Can be used alone or in combination with other common therapies

➢No clinically meaningful interactions were observed when empagliflozin was co-administered with other commonly used medications, including pioglitazone

➢A lower dose of insulin or insulin secretagogues (eg, sulphonylureas) may be needed to reduce the risk of hypoglycaemia when empagliflozin is used in combination with these agents

Reference
Jardiance FDA label 2017
Jardiance (empagliflozin) Summary of Product Characteristics. Available at: https://www.medicines.org.uk/emc/medicine/28973 (accessed July 2016).

Approach to the Management of Hyperglycemia

Patient/Disease Features

Risk of hypoglycemia/drug adverse effects

Disease Duration

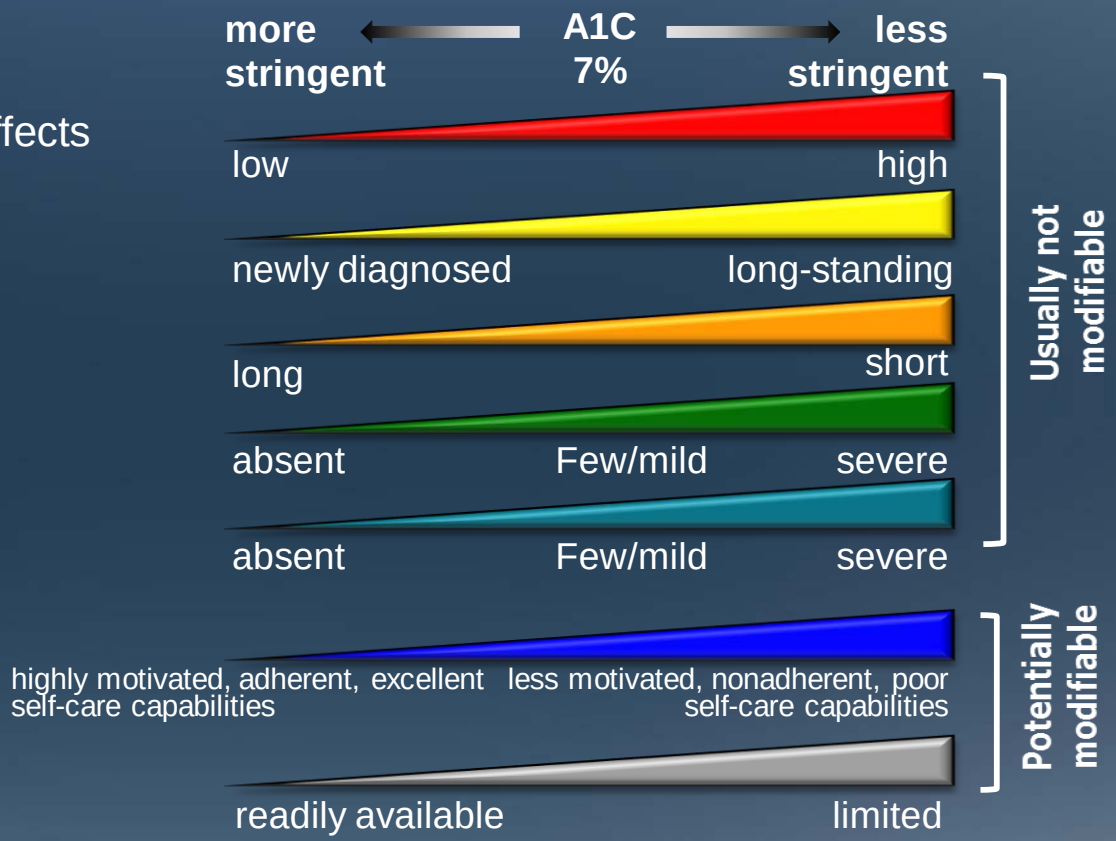
Life expectancy

Relevant comorbidities

Established vascular complications

Patient attitude & expected treatment efforts

Resources & support system



American Diabetes Association Standards of Medical Care in Diabetes. Glycemic targets. Diabetes Care 2017; 40 (Suppl. 1): S48-S56

More Stringent HbA1c Targets (6.0 – 6.5%)

- Short disease duration
- Long life expectancy
- No significant CVD

If this can be achieved without significant hypoglycemia or other adverse effects of treatment

161

Less Stringent HbA1c Targets (7.5 – 8.0% or even slightly higher)

- History of severe hypoglycemia
- Limited life expectancy
- Advanced complications
- Extensive comorbid conditions

In whom the target is difficult to attain despite intensive self-management education, repeated counseling, and effective doses of multiple glucose-lowering agents, including insulin

162

Conclusion:

- Not everyone benefits from aggressive glucose management
- It is important to individualize treatment targets

163

Changing the course of diabetes

The highest cost are the cost of lost opportunities…