عنوان برنامه

درمان ومدیریت دیابت

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فوق تخصص غدد و متابولیسم

استاد دانشگاه علوم پزشکی تبریز

a A silent killer.

b Kills one person every 6 seconds.

c Global problem with devastating human, social and economic impact.

d Today more than 400 million people worldwide are living with diabetes.

▶ diabetes is common and its frequency is rising dramatically worldwide.

▶ It is a life-threatening condition.

▶ A full and healthy life is however possible with diabetes.

▶ In many cases, diabetes can be prevented

Prevalance of type 2 diabetes was > 400 million in year 2015, and is likely to rise to > 500 million by year 2035

Premature mortality

- Life expectancy   ↓5-10 years
- Fatal CHD   ↑ 2-4 fold
- Fatal stroke   ↑ 2-3 fold

Morbidity

- Non-fatal CHD   ↑ 2-3 fold
- Retinopathy will develop in ~80%
- Nephropathy will develop in ~ 30%
- Foot ulcers will develop in ~ 5%

Direct cost

- 9-15% of total
- Healthcare budgets of most westernized countries

EPIDEMIOLOG

Estimated number of people with diabetes worldwide
and per region in 2015 and 2040 (20-79 years)

World
2015 **415 million**
2040 **642 million**

North America and Caribbean
2015 **44.3 million**
2040 **60.5 million**

Europe
2015 **59.8 million**
2040 **71.1 million**

Middle East and North Africa
2015 **35.4 million**
2040 **72.1 million**

Western Pacific
2015 **153.2 million**
2040 **214.8 million**

South East Asia
2015 **78.3 million**
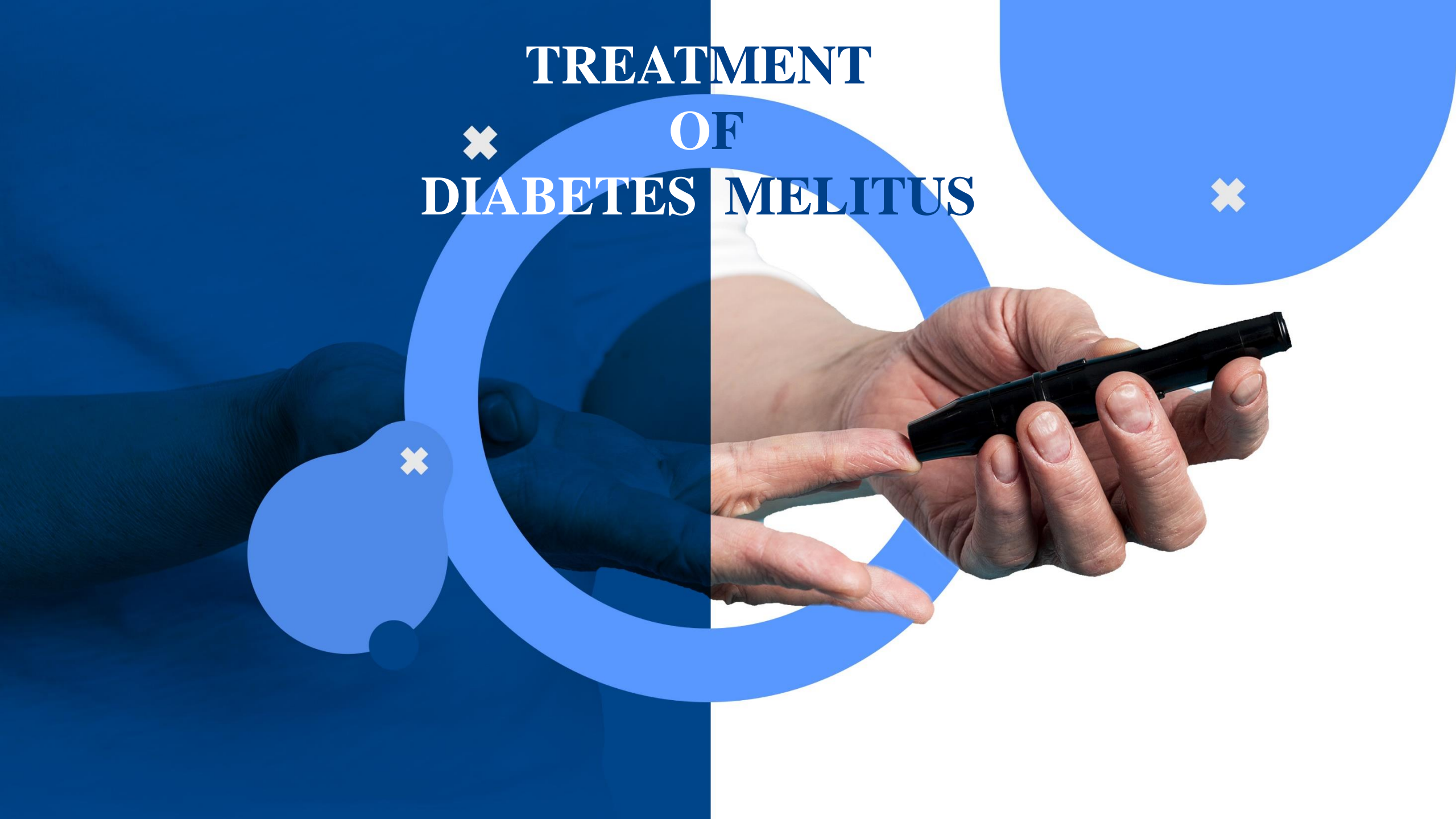2040 **140.2 million**

South and Central America
2015 **29.6 million**
2040 **48.8 million**

Africa
2015 **14.2 million**
2040 **34.2 million**

TREATMENT
OF
DIABETES MELITUS

Diabetes care should be managed by a multidisciplinary team that may draw from:

- primary care physicians
- subspecialty physicians
- nurse practitioners
- physician assistants
- dietitians, exercise specialists
- pharmacists, dentists, podiatrists, and mental health professionals.

▶ **Education**
  ▶▶ **Diabetes Self-Management Education, Support**
▶ **Nutrition**
  ▶▶ **Medical Nutrition Therapy (MNT)**
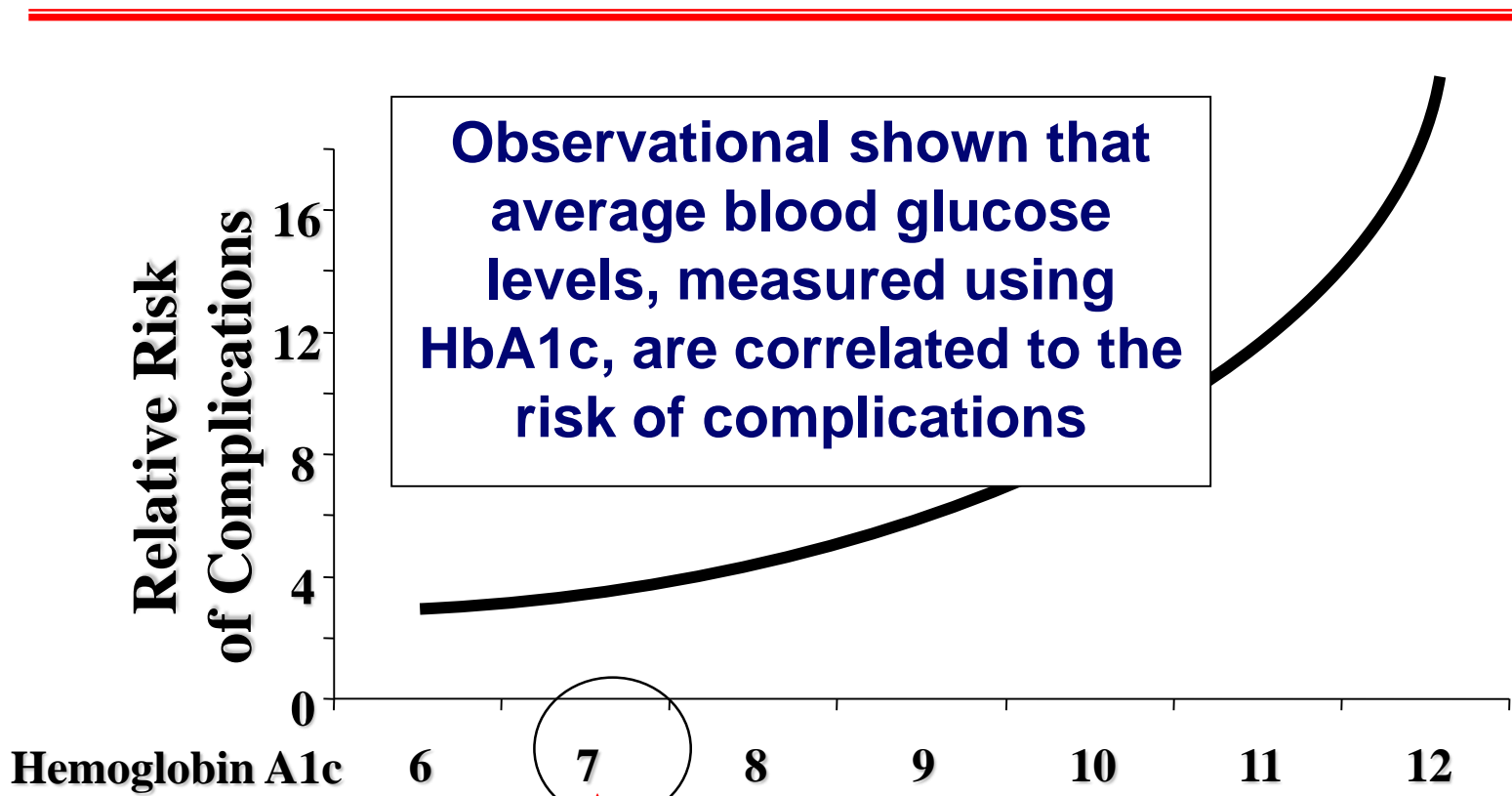▶ **Immunization**
▶ **Physical Activity**
▶ **Smoking Cessation**
▶ **Psychosocial Assessment and Care**
▶ **Prevention and Delay of Type**
▶ **Pharmacotherapy**

A close relationship between blood glucose levels and complications of diabetes

Relative Risk of Complications

16

12

8

4

0

Observational shown that average blood glucose levels, measured using HbA1c, are correlated to the risk of complications

Hemoglobin A1c   6   7   8   9   10   11   12

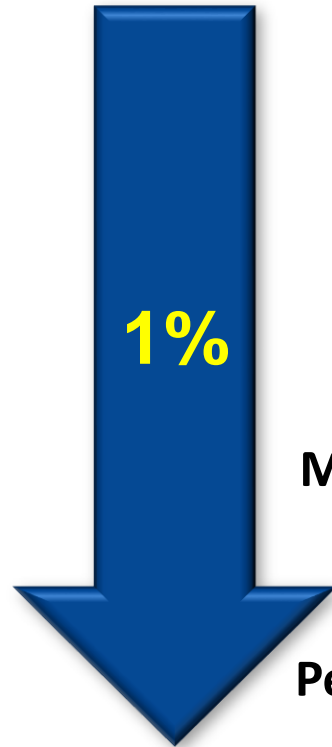Target value in the guidelines: < 7%

UKPDS 33: Lancet 1998; 352, 837-853.
DCCT Study Group. N Engl J Med 329:977, 1993

Better control in T2DM means fewer complications

1% reduction in HbA$_{1c}$ **Risk reduction***

1%

Deaths from diabetes   **-21%**

Myocardial Infarction   **-14%**

Microvascular complications   **-37%**

Peripheral vascular disorders   **-43%**

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

Study	Micro		Macro		Mortality	
UKPDS	☐	☐	☐☐	☐	☐☐	☐
DCCT / EDIC	☐	☐	☐☐	☐	☐☐	☐☐
ACCORD	☐		☐☐		☐	
ADVANCE	☐		☐☐		☐☐	
VADT	☐		☐☐		☐☐	

☐ **Initial Trial**   ☐ **Long Term Follow-up**

Goals of Treatment

① **Eliminate symptoms related to hyperglycemia,**

② **Reduce or eliminate the long-term microvascular and macrovascular complications of DM, and**

③ **Allow the patient to achieve as normal a life-style as possible**

❯ **Identify a target level of glycemic control for each patient,**

❯ **provide the patient with the educational and pharmacologic resources necessary to reach this level, and**

❯ **monitor/treat DM-related complications.**

Glycemic control

AIC	<7.0%*
Preprandial plasma glucose	90–130 mg/dl
Postprandial plasma glucose	<180 mg/dl

Lipids

LDL	<100 mg/dl
Triglycerides	<150 mg/dl
HDL	>40 mg/dl for man
	>50 mg/dl for woman

Key concepts in setting glycemic goals:

►Goals should be individualized

► Certain populations (children, pregnant women, and elderly) require special considerations

► Less intensive glycemic goals may be indicated in patients with severe or frequent hypoglycemia

► More stringent glycemic goals (i.e. a normal A1C, _6%) may further reduce complications at the cost of increased risk of hypoglycemia

(particularly in those with type 1 diabetes)

► Postprandial glucose may be targeted if AIC goals are not met despite reaching preprandial glucose goals

▶ Individualizing Glycemic Targets

more stringent ⬅ A1c 7% ➡ less stringent

Patient/Disease Features

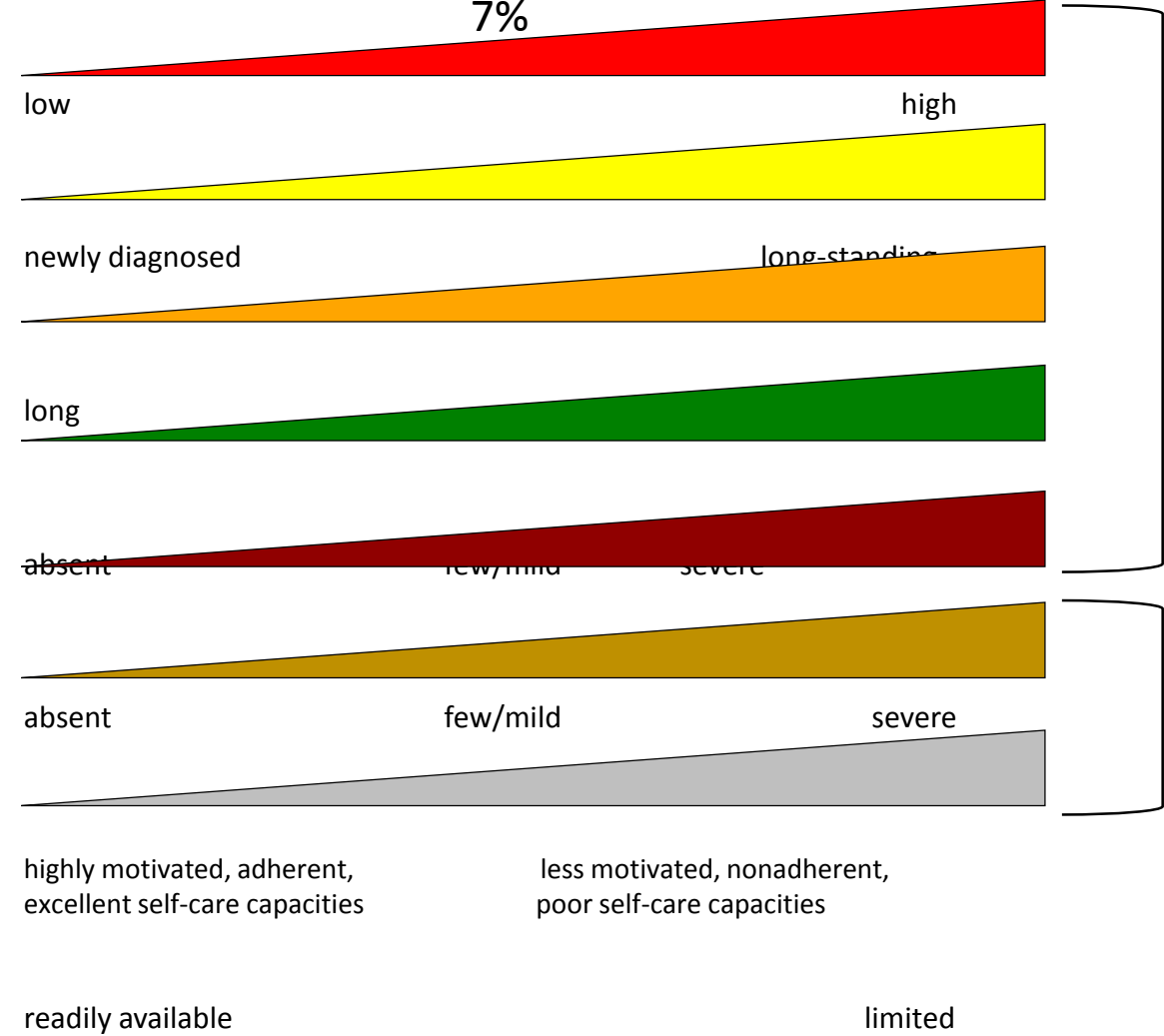**Risks potentially associated with hypoglycemia and other drug adverse effects**

low   high

Disease duration

newly diagnosed   long-standing

Life expectancy

long

Important comorbidities

absent   few/mild   severe

Established vascular complications

absent   few/mild   severe

Patient attitude and expected treatment efforts

highly motivated, adherent, excellent self-care capacities   less motivated, nonadherent, poor self-care capacities

Resources and support system

readily available   limited

> **For patients with diabetes and hypertension, blood pressure targets should be individualized through a shared decision making process that addresses cardiovascular risk, potential adverse effects of antihypertensive medications, and patient preferences.**

▶ **For individuals with diabetes and hypertension at lower risk for cardiovascular disease (<15%), treat to a blood pressure target of <140/90 mmHg.**

For individuals with diabetes and hypertension at higher cardiovascular risk: with use risk Calculator (>15%), ablood pressure target of <130/80mm Hg maybe appropriate, if it can be safely attained

Comprehensive care of diabetes
Prospective approach

Reduce macrovascular risk	Minimize microvascular/ neuropathic complications	Improve sense of well-being

1. Lipid control

2. BP normalization

3. Smoking cessation

4. Glycemic control

5. Weight control

6. Regular exercise

7. Aspirin

1. Glycemic control

2. BP normalization

3. Regular eye exams

4. Regular testing for albuminuria

5. Foot care

1. Glycemic control

2. Regular exercise

The key elements of a comprehensive management plan for patients with diabetes.

Comprehensive care of diabetes
Prospective approach

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Reduce macrovascular risk

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Minimize microvascular/ neuropathic complications

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3. Regular eye exams

4. Regular testing for albuminuria

5. Foot care

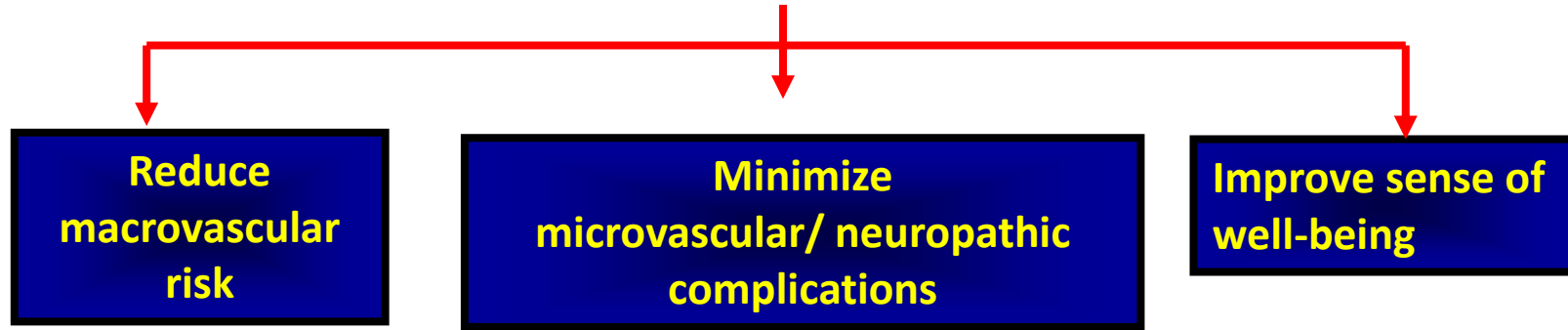**Improve sense of well-being**

1. Glycemic control

2. Regular exercise

The key elements of a comprehensive management plan for patients with diabetes.

Componets OF diabetes medicals eveluation at initial,
FOLLOW UP. AND ANNUAL VISITS DIABETES MELITUS

PAST MEDICAL AND FAMILY HISTORY			
Diabetes history			
▪ Characteristics at onset (e.g., age, symptoms)	✓		
▪ Review of previous treatment regimens and response	✓		
▪ Assess frequency/cause/severity of past hospitalizations	✓		
Family history			
▪ Family history of diabetes in a first-degree relative	✓		
▪ Family history of autoimmune disorder	✓		
Personal history of complications and common comorbidities			
▪ Macrovascular and microvascular	✓		✓
▪ Common comorbidities (e.g., obesity, OSA)	✓		✓
▪ Hypoglycemia: awareness/frequency/causes/timing of episodes	✓	✓	✓
▪ Presence of hemoglobinopathies or anemias	✓		✓
▪ High blood pressure or abnormal lipids	✓		✓
▪ Last dental visit	✓		✓
▪ Last dilated eye exam	✓		✓
▪ Visits to specialists	✓	✓	✓
Interval history			
▪ Changes in medical/family history since last visit		✓	✓

Lifestyle factors	Eating pattens and weight history			
	Physical activity and sleep behaviors	■	□	□
	Tobacco, alcohol and substance use	■		□

Technology use	Assess use of health apps, online education, patients portals, etc		□		□
	Glucose monitoring(meter/CGM): results and data use	■		□	□
	Review insulin pump settings and use	■		□	□

BEHAVIORAL AND DIABETES SELF-MANAGEMENT SKILLS				
	Psychosocial conditions			
	▪ Screen for depression, anxiety, and disordered eating; refer for further assessment or intervention if warranted	✓		✓
	▪ Identify existing social supports	✓		✓
	▪ Consider assessment for cognitive impairment*	✓		✓
	Diabetes self-management education and support			
	▪ History of dietician/diabetes educator visits/classes	✓	✓	✓
	▪ Assess diabetes self-management skills and barriers	✓		✓
	▪ Assess familiarity with carbohydrate counting (type 1 diabetes)	✓		
	Pregnancy planning			
	▪ For women with childbearing capacity, review contraceptive needs and preconception planning	✓	✓	✓

Laboratory evalution	A1c if the results are not available within the past 3 months	☐	☐	☐
	If not perfomed/available within the past year	■		☐
	Lipid profile, including total, LDL and HDL cholesterol and triglycerides	■		☐
	Liver function tests	■		☐
	Spot urinary albumin-to-creatinine ratio	■		☐
	Thyroid-stimulating hormone in patients with type 1 diabetes	■		☐
	Vitamin B12 if on metformin (when indicated)	■		☐
	Serum potassium levels in patients on ACE inhibitors, ARBs or diuretics	■		☐

PHYSICAL EXAMINATION				
	▪ Height, weight, and BMI; growth/pubertal development in children and adolescents	✓	✓	✓
	▪ Blood pressure determination	✓	✓	✓
	▪ Orthostatic blood pressure measures (when indicated)	✓		
	▪ Fundoscopic examination (refer to eye specialist)	✓		✓
	▪ Thyroid palpation	✓		✓
	▪ Skin examination (e.g., acanthosis nigricans, insulin injection or insertion sites, lipodystrophy)	✓	✓	✓
	▪ Comprehensive foot examination			
	• Visual inspection (e.g., skin integrity, callous formation, foot deformity or ulcer, toenails)**	✓		✓
	• Screen for PAD (pedal pulses–refer for ABI if diminished)	✓		✓
	• Determination of temperature, vibration or pinprick sensation, and 10-g monofilament exam	✓		✓

- ➤ **Type 1 diabetes accounts for >90% of cases.**

- ➤ **Type 2 diabetes is increasingly recognized in children.**

- ➤ **Permanent neonatal diabetes**

- ➤ **Transient neonatal diabetes**

- ➤ **MODY**

- ➤ **Others diabetes e.g. in cystic fibrosis or Cushing syndrome.**

➤ **MODY is a monogenic form of diabetes with an autosomal dominant mode of inheritance:**

➤ Mutations in any one of several transcription factors or in the enzyme glucokinase lead to insufficient insulin release from pancreatic ß-cells, causing MODY.

➤ Different subtypes of MODY are identified based on the mutated gene.

➤ **Originally, diagnosis of MODY was based on presence of non-ketotic hyperglycemia in adolescents or young adults in conjunction with a family history of diabetes.**

➤ **However, genetic testing has shown that MODY can occur at any age and that a family history of diabetes is not always obvious.**

Management of Type 1 diabetes

❯ **Prevent death & alleviate symptoms**

❯ **Achieve biochemical control**

❯ **Maintain growth & development**

❯ **Prevent acute complications**

❯ **Prevent or delay late-onset complications**

> **Diabetes**

> **Insulin**

> **Life-saving skills**

> **Recognition of Hypo & DKA**

> **Meal plan**

> **Sick-day management**

➤ **Education is fundamental to diabetes management & metabolic control. Teaching about diabetes is best handled by a diabetes management team, including a physician, nurse, educator, dietitian, & mental health professional.**

➤ **The family of diabetic patient must be taught the following basic of treatment:**

1. monitoring the child's blood glucose and urine ketones.
2. preparing and injecting the correct insulin dose subcutaneously at the proper time.
3. recognizing and treating low blood glucose reactions.
4. having a basic meal plan.

> Physical fitness and regular exercise are to be encouraged in all children with type 1 diabetes.

> Regular exercise improves glycemic control through

1. increased utilization of glucose by muscles.
2. increased rate of absorption of insulin from its injection site.
3. increasing insulin receptor number.

> In patients who are in poor metabolic control, vigorous exercise may precipitate ketoacidosis because of the exercise-induced increase in the counter-regulatory hormones.

Human Basal: Humulin-N, Novolin ge NPH   Human Bolus: Humulin-R, Novolin ge Toronto
Analogue Basal: Lantus, Levemir   Analogue Bolus: Apidra, Humalog, NovoRapid
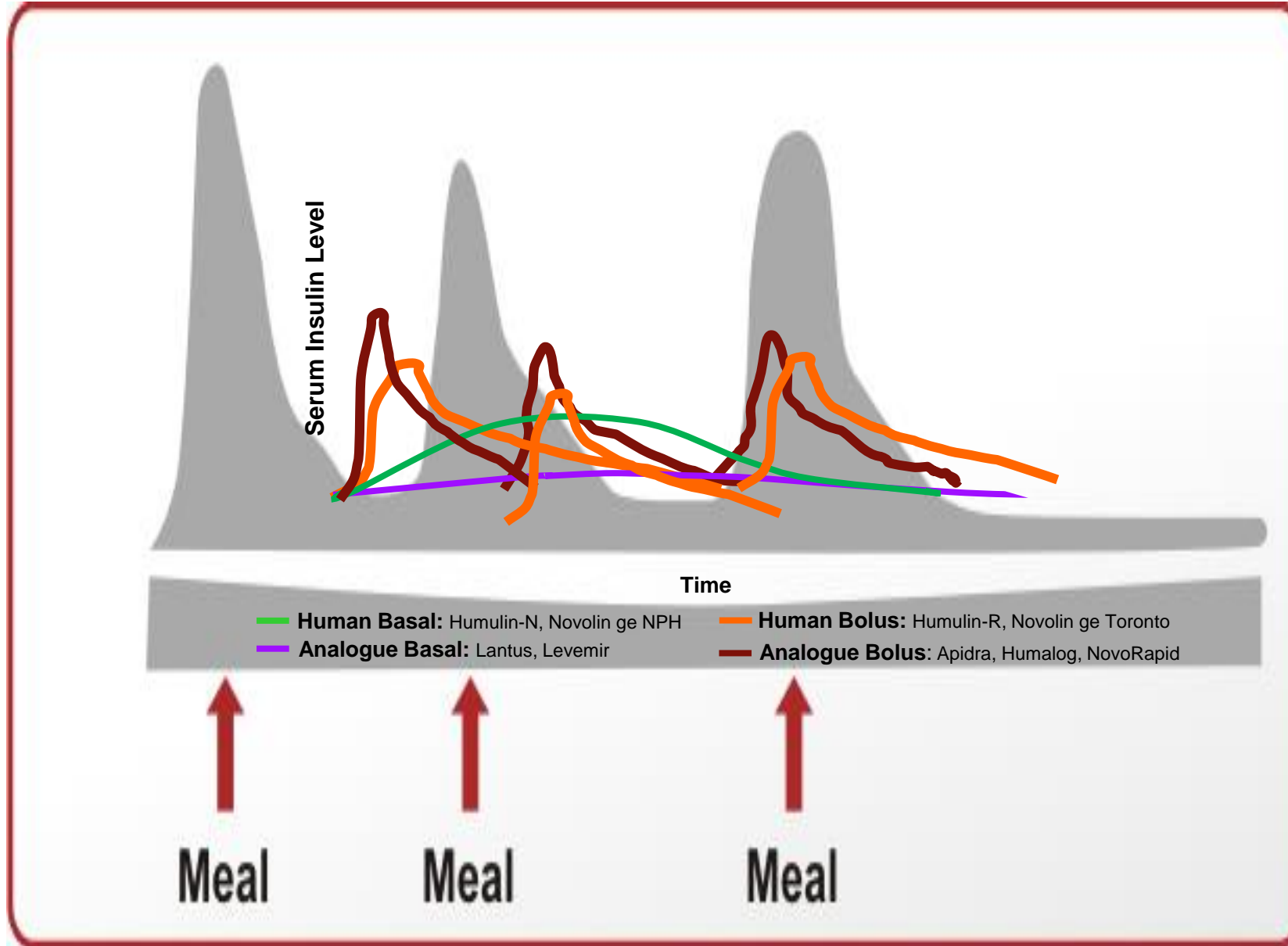
The glycemic management in type 2 diabetes

چرخه تصمیم گیری برای مدیریت هیپرگلیسمی بیمار محور در دیابت نوع 2

INTENSIFYING TO INJECTABLE THERAPIES.

مرور و توافق دوره ای مجدد در مورد طرح مدیریت درمان
- مرور مجدد برنامه مدیریت درمان
- جلب توافق متقابل در مورد تغییرات لازم در رویه درمان
- اطمینان از به اجرا گذاشته شدن تغییرات توافق شده درمانی به صورت زمان بندی شده به منظور جلوگیری از ایجاد بی تفاوتی به روند درمان
- باید به صورت منظم حداقل یک یا دو بار در سال فرآیند چرخه تصمیم گیری بازنگری شده و مجددا انجام گیرد.

ویژگی های اصلی بیمار را ارزیابی کنید
- شیوه زندگی فعلی
- بیماری ها ی همراه نظیر بیماری قلبی عروقی آترواسکلروتیک (ASCVD)، بیماری مزمن کلیه و نارسایی قلب
- ویژگی های بالینی، به عنوان مثال، سن، HbA1c، وزن
- مسائلی مانند انگیزه و افسردگی
- زمینه فرهنگی و اجتماعی و اقتصادی

فاکتورهای خاصی که انتخاب شیوه درمان را تحت تاثیر قرار میدهد را در نظر بگیرید
- هدف فردی HbA1c
- تاثیر درمان بر وزن و هیپوگلیسمی
- اثرات جانبی داروها
- پیچیدگی رژیم درمانی، یعنی دفعات و روش مصرف
- شیوه درمانی را امتخاب کنید تا بیشترین امکان به دست آوردن پایبندی و پایداری در ادامه درمان را فراهم سازد.
- هزینه و امکان در دسترس بودن دارو را ارزیابی کنید.

نظارت و پشتیبانی مستمر شامل موارد زیر خواهد بود:
- دستیابی به احساس عاطفی تندرستی
- قابلیت تحمل داروهای مصرفی را ارزیابی کنید
- وضعیت گلیسمی را پایش کنید
- با ارزیابی مواردی نظیر اندازه گیری قند خون خانگی (SMBG)، وزن، شمارش تعداد قدم های پیموده شده، HbA1C، فشار خون، چربی های خون بازخوردهای تشویقی به بیمار بدهید(بیوفیدبک)

اهداف مراقبت
- جلوگیری از عوارض
- بهینه سازی کیفیت زندگی

طراحی تصمیم سازی برای برنامه ریزی روش درمانی حساب شده با مشارکت بیمار
- شامل یک بیمار (در صورت لزوم خانواده / مراقب یا پرستار) آموزش دیده و آگاه خواهد بود.
- ترجیحات بیمار را دنبال می کند
- مشاوره موثر شامل مصاحبه انگیزشی، تنظیم هدف و تصمیم گیری مشترک خواهد بود.
- بیمار را توانمند می سازد.
- دسترسی به DSMES (آموزش مدیریت بیماری خویشتن در دیابت و پشتیبانی مستمر) را تضمین می کند.

اجرای مدیریت درمان طراحی شده
- بیمارانی که قادر به دستیابی به اهداف درمان نمی شوند معمولا تا زمانی که پیشرفتی دیده می شود باید حداقل هر ۳ ماه یکبار ویزیت شوند، در ابتدا اغلب مطلوبتر است فواصل ویزیت ها کمتر باشد تا برنامه آموزشی (DSMES) پیاده شود.

توافقی دو جانبه بر سر برنامه مدیریت درمان با بیمار برقرار کنید
- اهداف این برنامه باید مشخصاً (SMART) باشند
  - ویژه Specific
  - قابل اندازه گیری Measurable
  - قابل دستیابی Achievable
  - واقع بینانه Realistic
  - زمان بندی شده Time limited باشد.

ASCVD = Atherosclerotic Cardiovascular Disease
DSMES = Diabetes Self-Management Education and Support
SMBG = Self-Monitored Blood Glucose

Glucose-lowering medication in type 2 diabetes: overall approach.

در درمان دیابت برای پیشگیری از پدید آمدن بی تفاوتی و روزمره گی در روند درمان حداقل هر ۳ تا ۶ماه یکبار رویه درمان را مورد باز بینی قرار داده تغییرات لازم را بدهید.

① **Effectiveness of nutrition therapy**

② **Energy balance**

③ **Eating patterns and macronutrients**

④ **distribution**

Carbohydrates

⑤ **Protein**

⑥ **Dietary fat**

⑦ **Micronutrients and herbal supplements**

⑧ **Alcohol**

⑨ **Sodium**

⑩ **Nonnutritive sweeteners**

	Mechanism of Action	Examples	A1C Reduction (%)	Agent Specific Advantages	Agent-Specific Disadvantages
Medical nutrition therapy and physical ac tivity	↓ Insulin, resistance, ↑ insulin secretion	Low-calorie, low-fat diet, exercise	1–2	Other health benefits	Compliance difficult, long-term success low

Insulin signal enhancers

Insulin resistance
Thiazolidinediones
metformin

Inhibition of fatty acid oxidation

β-cell dysfunction
Sulfonylureas Meglitinides

Type 2 Diabetes Mellitus

Increased hepatic glucose production
Metformin

GLP1

Inhibition of
Inrestinal glucose absorption
α-Glucosidase inhibitors

Delay of gastric emptying
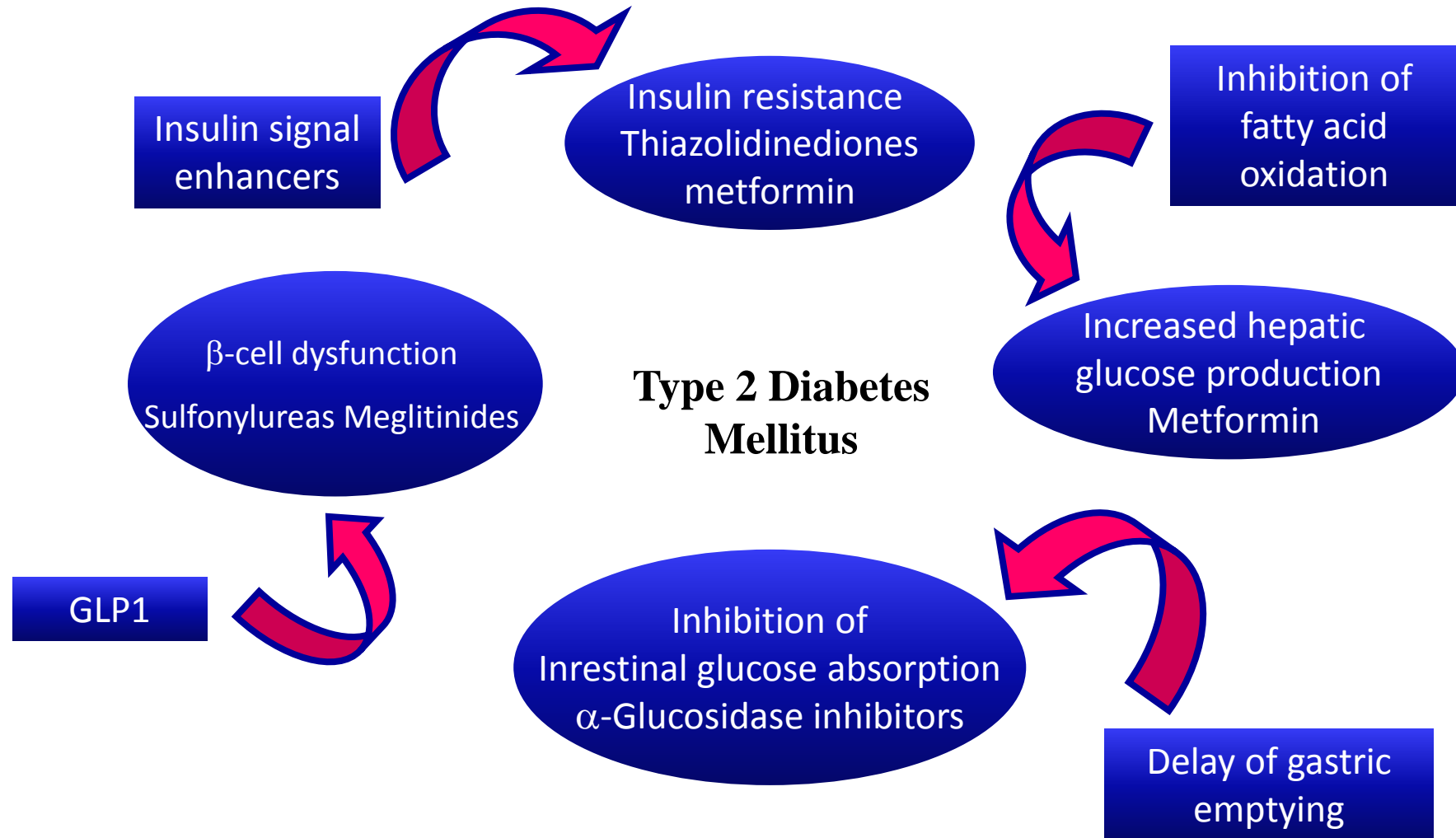
and potential new therapeutic targets and substances

Antihyperglycemic agents. Summary of hyperglycemic agents currently available and potential new therapeutic targets and substances

Insulin signal enhancers

Insulin resistance Thiazolidinediones metformin

Inhibition of fatty acid oxidation

β-cell dysfunction

Sulfonylureas Meglitinides

Type 2 Diabetes Mellitus

Increased hepatic glucose production Metformin

GLP-1 Agonist :

Exenatide (Byetta)

Liraglutide

DPP-4 Inhibitors :

Sitagliptin (Januvia)

Vildagliptin

(Galvus)

Inhibition of Inrestinal glucose absorption α-Glucosidase inhibitors

Amylin analogues slow gastric emptying and suppress glucagon. Like insulin, it is administered by subcutaneous injection. Pramlintide (Symlin)

erglycemic agents. Summary of hyperglycemic agents currently ble and potential new therapeutic targets and substances

- **Biguanides**
- **Sulfonylureas**
- **Thiazolidinediones**
- **Meglitinides**
- **Alpha-glucosidase inhibitors**
- **DPP-4 inhibitors**

- **SGLT-2 inhibitors**
- **Dopamine-2 agonists**
- **Bile acid sequestrants**
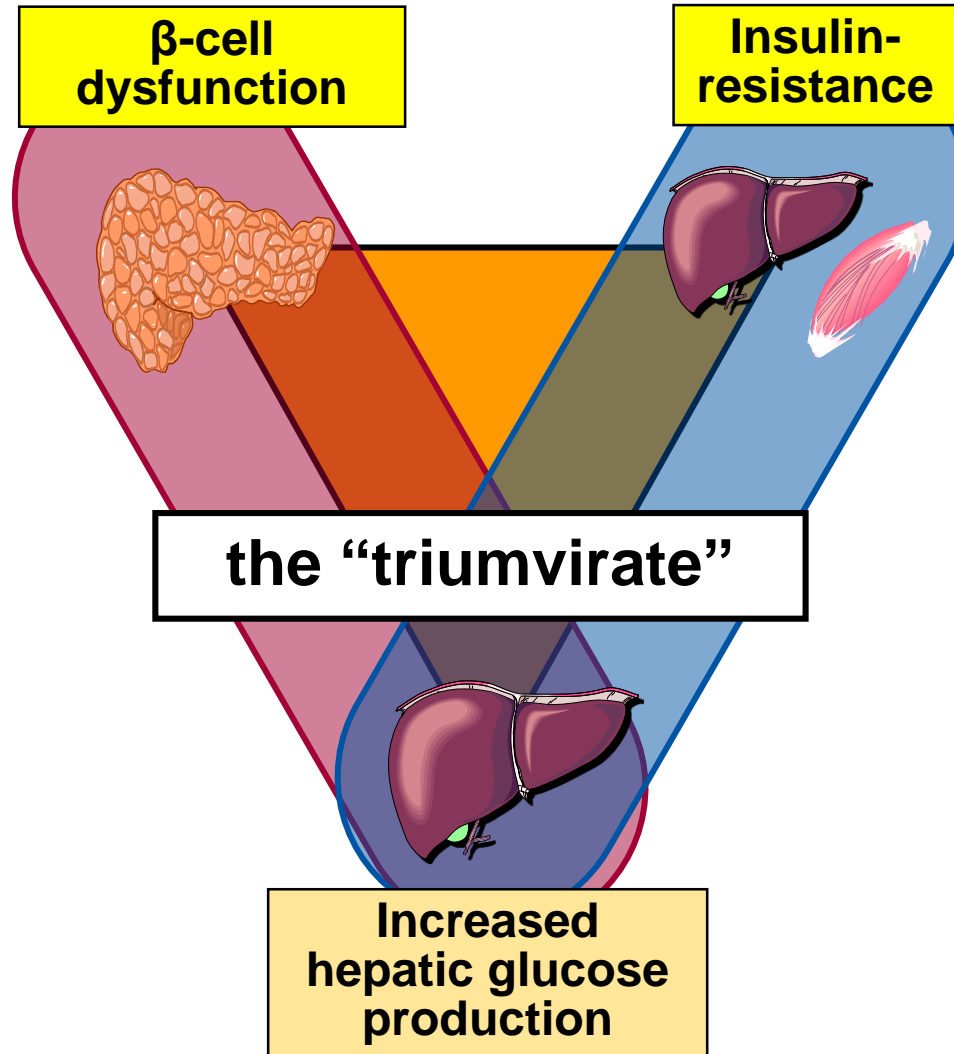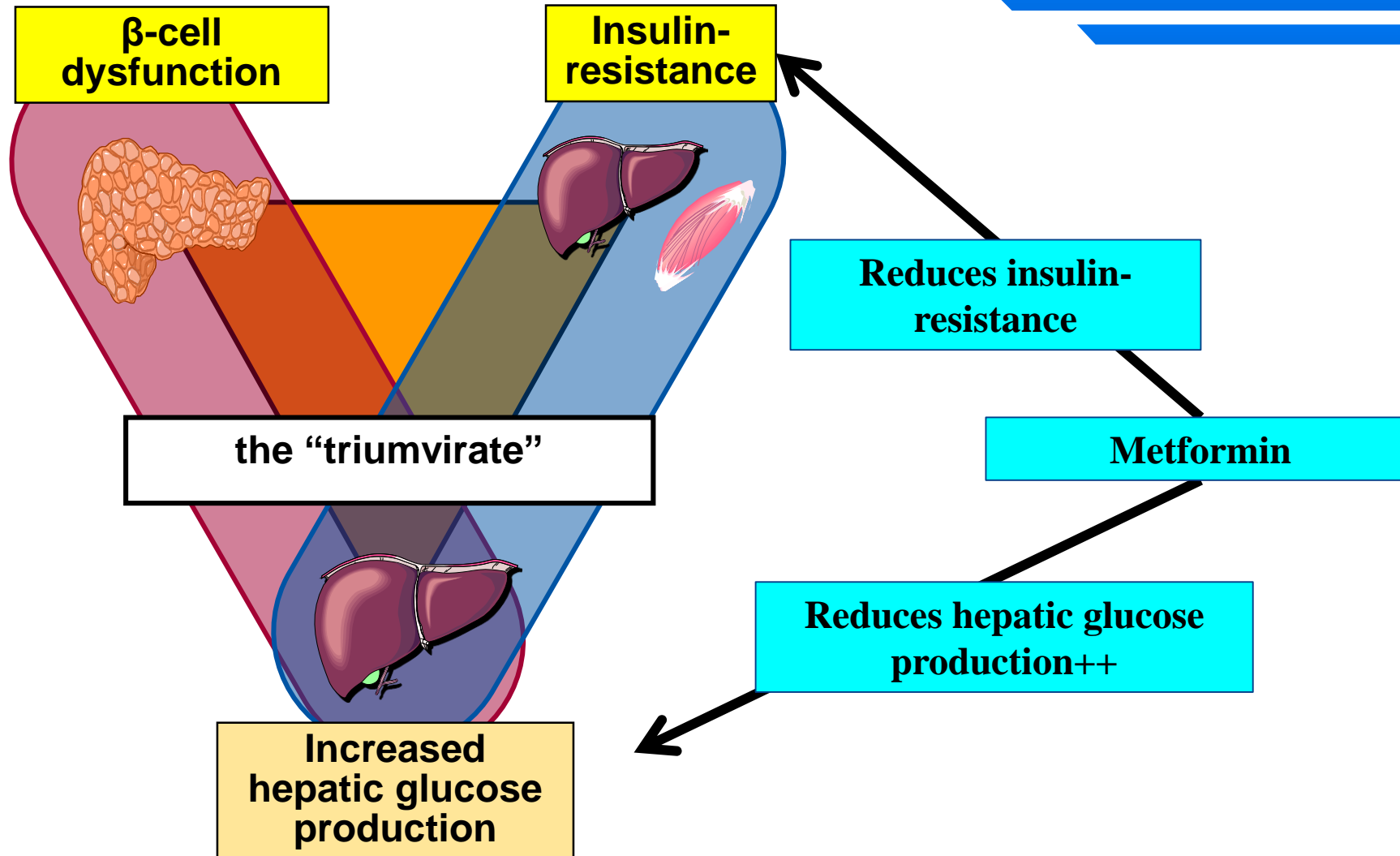- **GLP-1 receptor agonists**
- **Amylinomimetics**

BIGUANIDES

➤ The **Biguanide** class of antidiabetic drugs, originates from the **French lilac** or goat's rue (Galega officinalis), a plant used in folk medicine for several centuries

➤ Metformin became available in the **British National Formulary** in 1958

β-cell dysfunction

Insulin-resistance

the "triumvirate"

Increased hepatic glucose production

β-cell dysfunction

Insulin-resistance

the "triumvirate"

Reduces insulin-resistance

Metformin

Reduces hepatic glucose production++

Increased hepatic glucose production

1 **Metformin is widely accepted as the 1ˢᵗ line agent**

2 **and next as the background medication of the intensification strategy**

> **An insulin-sensitizer which fits with the physiopathological features of the disease**

> **A powerful agent which decreases HbA1c by >1%**

> **No weight gain**

> **No hypoglycaemia**

> **Possible cardio-vascular protective effect**

> **Possible protective effect against cancer**

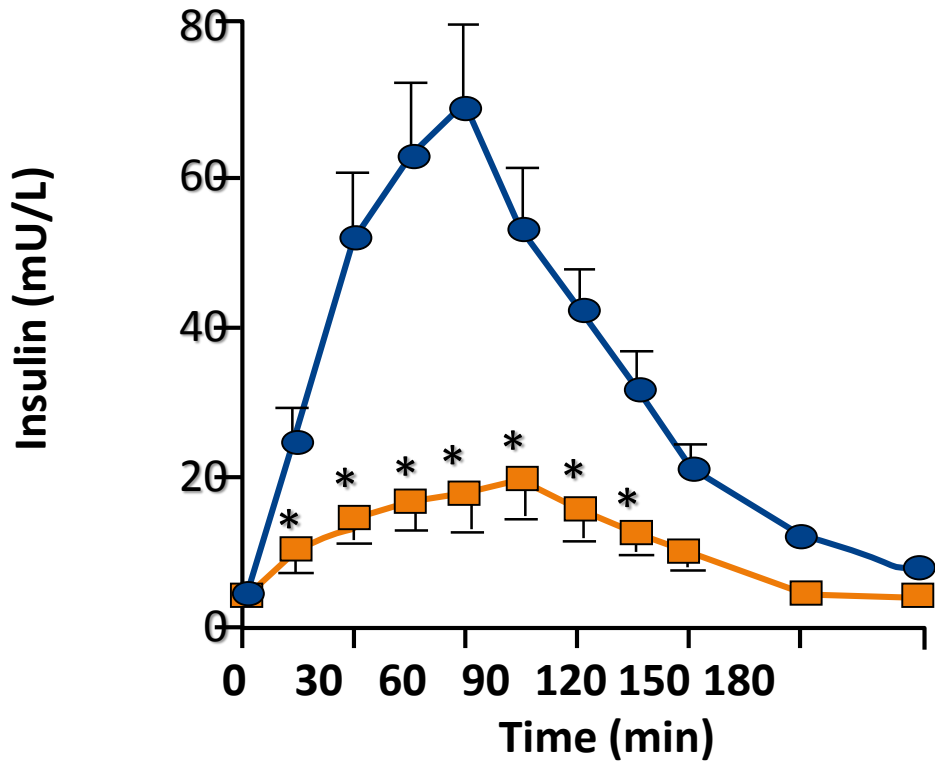> **Safe : low level of serious side effects**

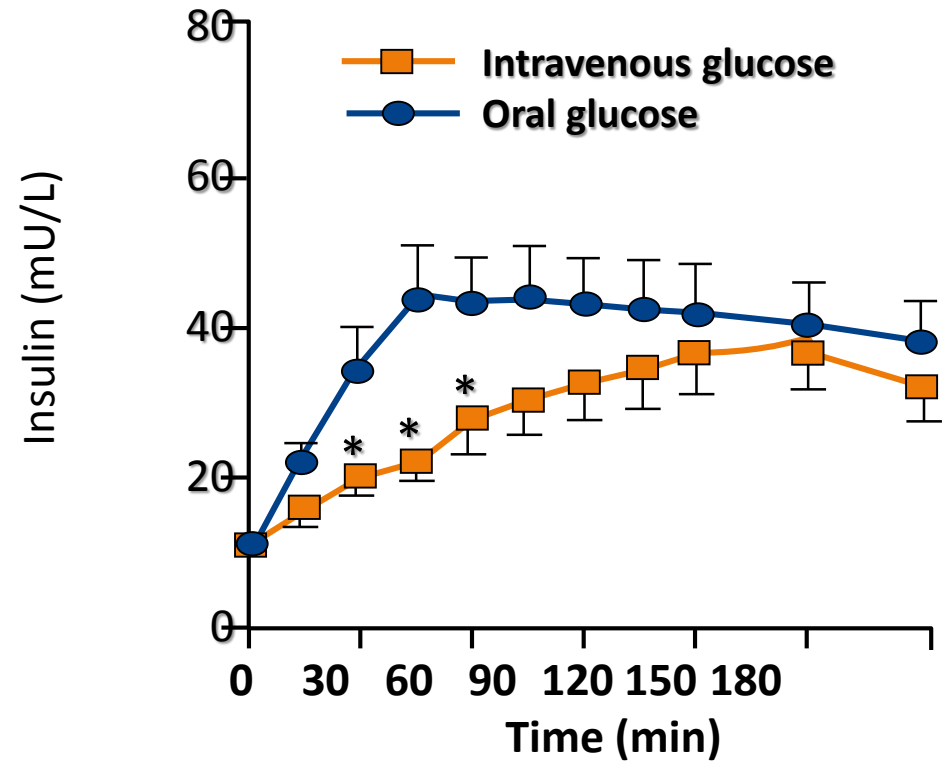> **Cheap**

DIPEPTIDYL PEPTIDASE-4 INHIBITORS
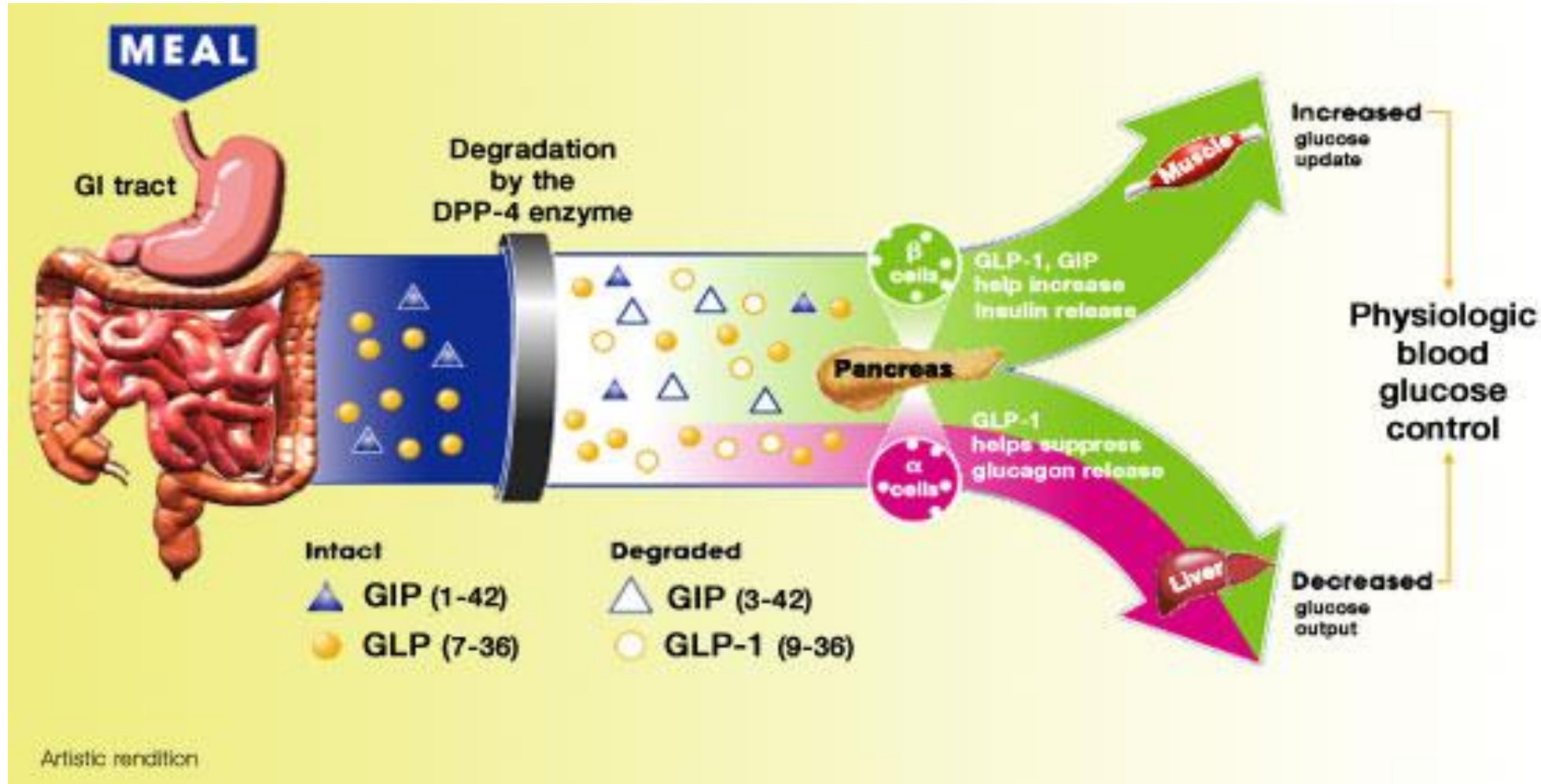## And
GLP- 1Agonists

Control subjects

T2DM patients

- MOA: dipeptidyl peptidase-4 inhibitor, blocks the breakdown of GLP-1 in small intestine increasing concentration in the bloodstream
- A1c ↓ 0.5-0.8%
- FPG ↓ 15-30 mg/dl
- PPG ↓ 34-50 mg/dl
- Dosing: sitagliptin 50 or 100 mg daily, saxagliptin 2.5 or 5 mg daily, linagliptin 5 mg daily (Taken with or without food)
- Side Effects: Possible hypoglycemia when used with insulin or insulin secretagogues
- Often added to metformin for maximum effect

Advantages

- Lack of hypoglycemia when used as monotherapy
- Weight loss
- Reduces PPG values
- Combination of injectable therapies of basal insulin and a GLP-1 RA is a strategy

Disadvantages

- Injectable
- AEs: headache, nausea (often transient), diarrhea

  Dosage modification with renal dysfunction needed (albiglutide, dulaglutide)
- Contraindicated in severe renal impairment (exenatide)
- May be associated with pancreatitis
- Associated with thyroid cell cancer in rodents
- May be associated with renal insufficiency

Advantages

- Oral
- No hypoglycemia when used as monotherapy
- Weight neutral
- Generally well tolerated

Disadvantages

- Dosage modification required with renal impairment (sitagliptin, saxagliptin, alogliptin)
- CYP3A4 interactions (saxagliptin, linagliptin)
- May be associated with pancreatitis
- May worsen heart failure (saxagliptin)
- May cause severe joint pain

After 12 weeks of monotherapy
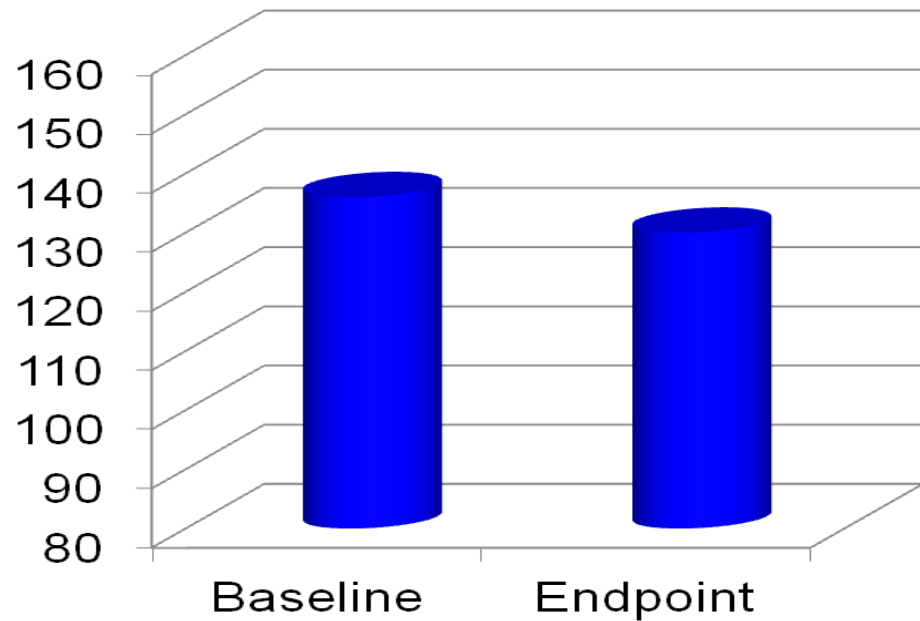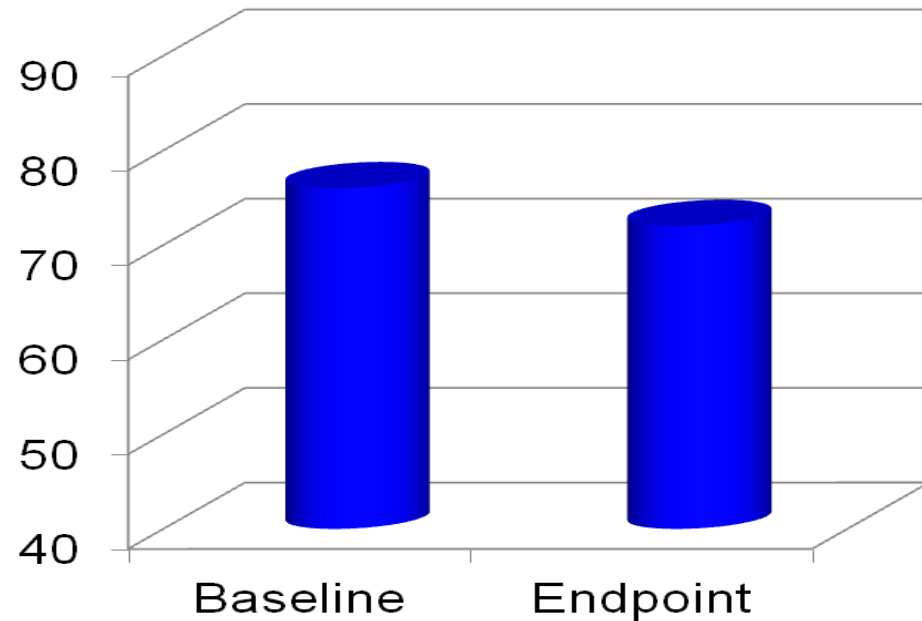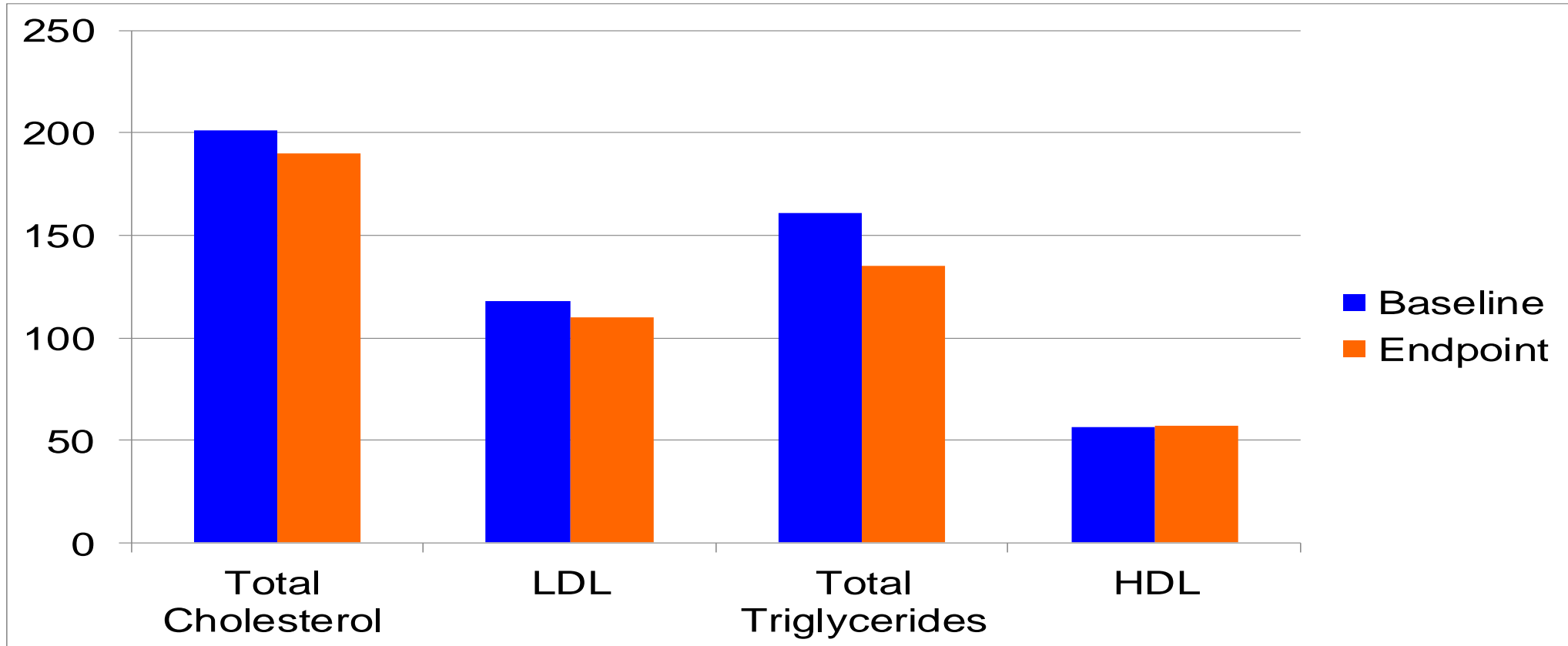
❯ **GLP-1 Ras**

    ❯ **Reduce postprandial triglycerides, FFA, and LDL**

❯ **DPP-4 inhibitors**

    ❯ **Reduce fasting LDL and triglycerides**

    ❯ **Small increase in HDL**

    ❯ **Parallels weight loss**

SGLT2 INHIBITO
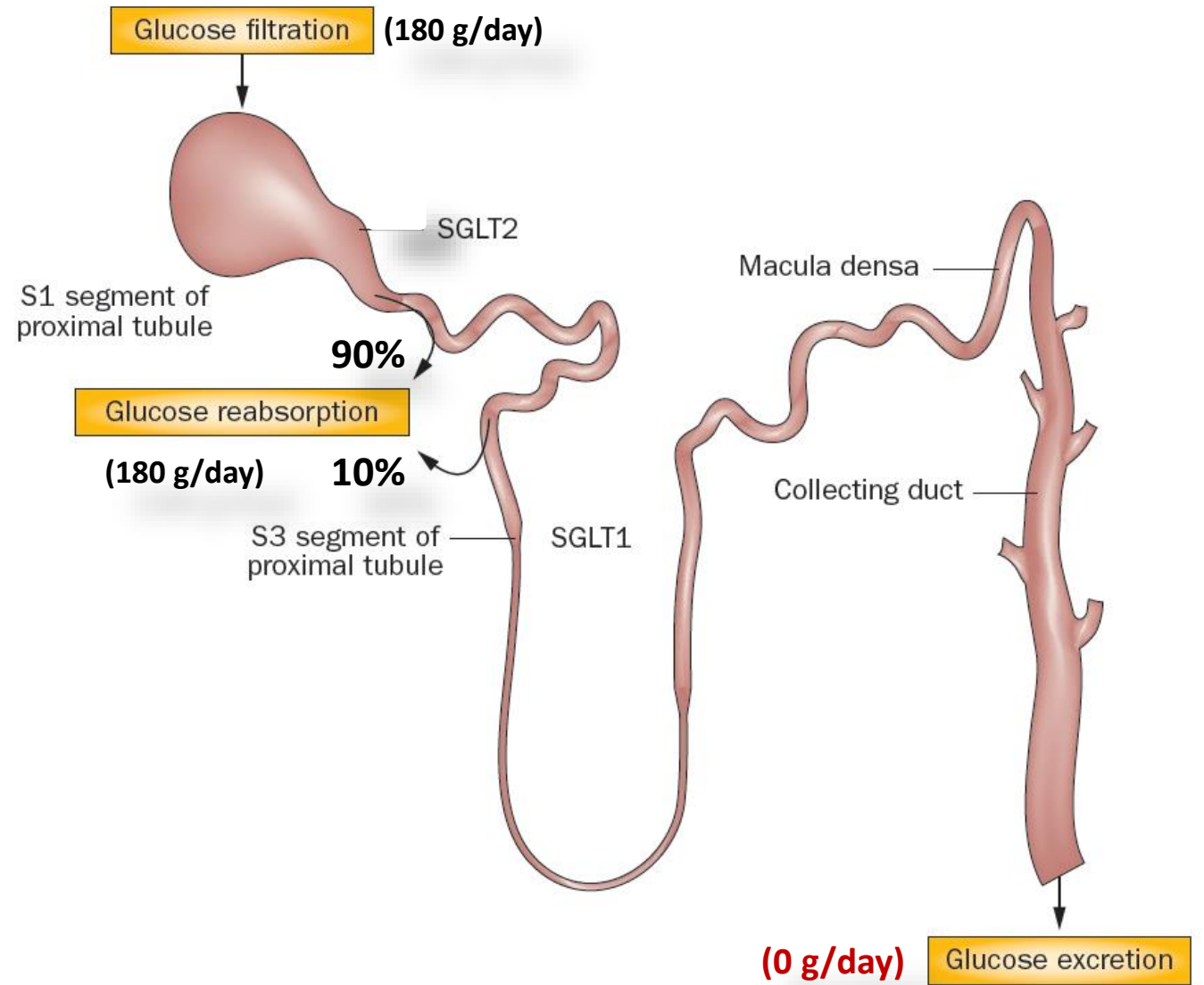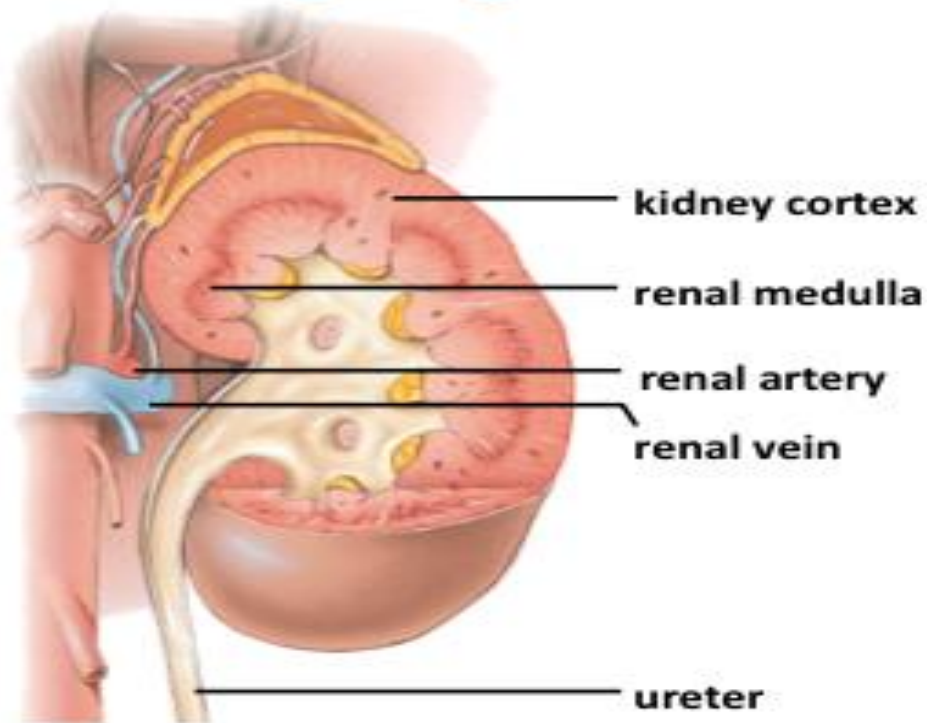
SULFONYLUREAS

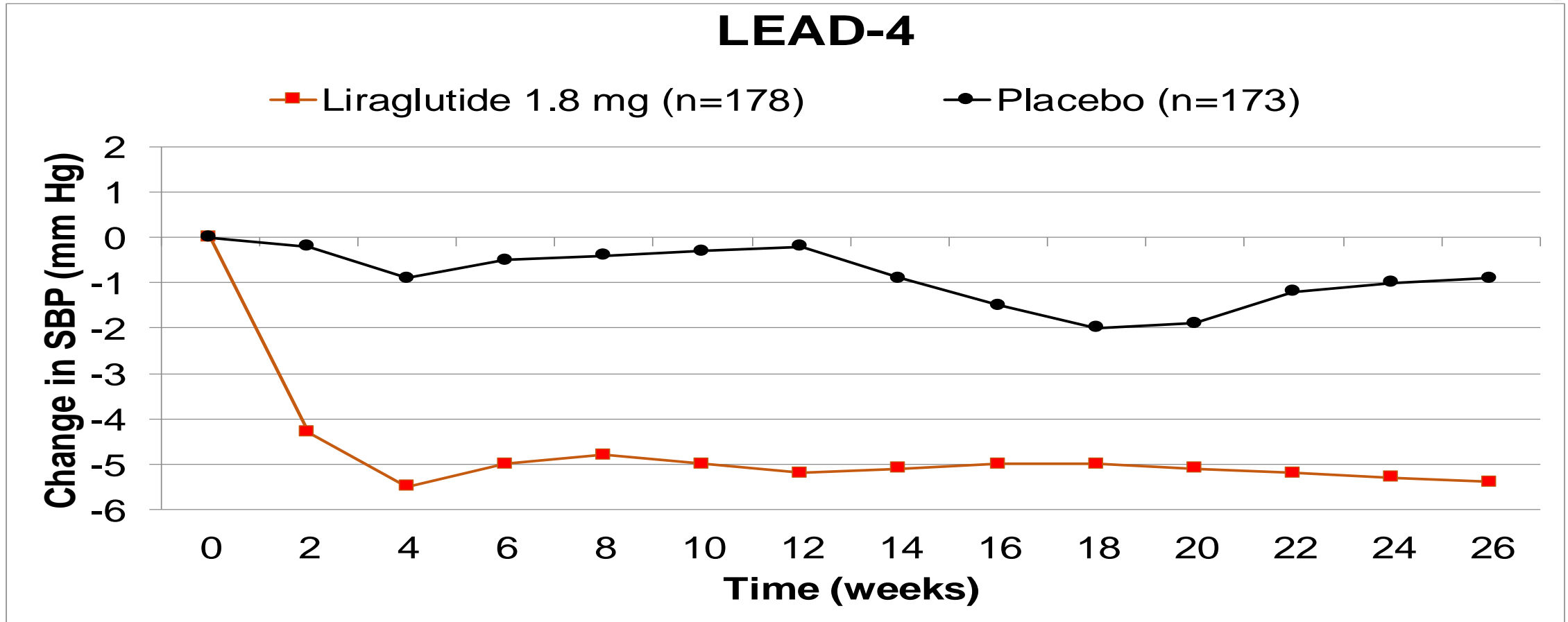| Generic Name	Approved Daily Dosage Range,mg	Duration of Action, h
Sulfonylurea—first generation		
Chlorpropamide	100 – 500	> 48
Tolazamide	100 – 1000	12 – 24
Tolbutamide	500 – 3000	6 – 12
Sulfonylurea—second generation		
Glimepiride	1 – 8	24
Glipizide	25 – 40	12 – 18
Glipizide (extended release)	5 – 15	24
Glyburide	1.25 – 20	12 – 24
Glyburide (micronized)	0.75 – 12	12 – 24
Nonsulfonylureas		
Repaglinide	0.5 – 16	2 – 6
Nateglinide	180 – 360	2 4

- **Secondary failure rate**
- **Hypoglycemia**
- **Weight gain**
- **Low cost**

  - Elderly
  - Impaired renal function
  - Irregular meal schedule

- **Increase cardiovascular events?**

Advantages	**Potent glucose lowering effect** **Favorable adverse effect profile**
Disadvantages	**Hypoglycemia, more with Glyburide** **Glyburide contraindicated in renal impairment?** **Glyburide impairs ischemic preconditioning in heart (UKPDS did not reveal increased cardiac risk)**
Concomitant use with other drugs	**Can be used as monotherapy and with all classes including insulin**

Antihyperglycemic Agents and Renal Function
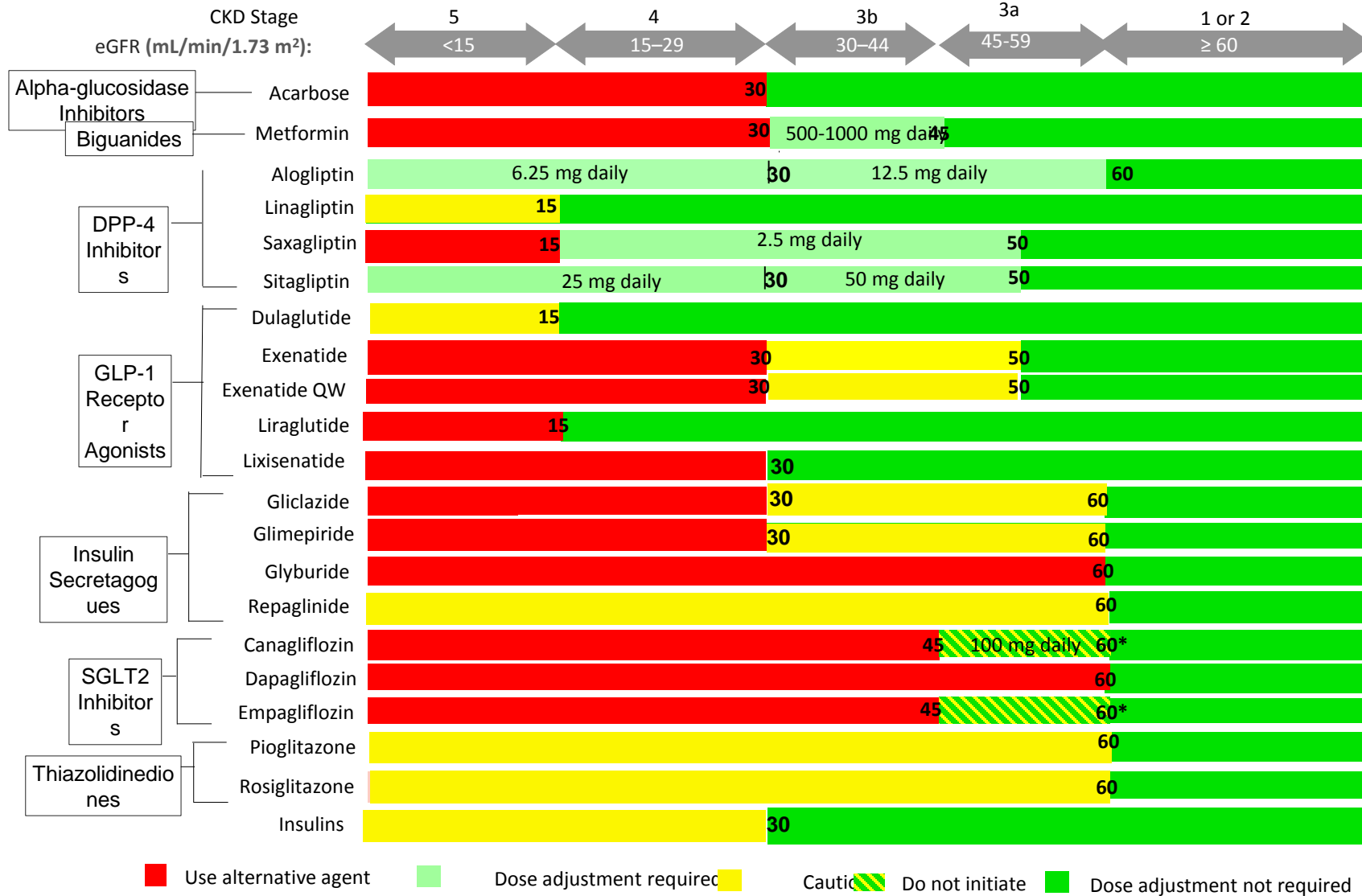
Born	February 27, 1899 West Pembroke, Maine, U.S.
Died	March 31, 1978 (aged 79) Toronto, Ontario, Canada
Nationality	Canadian
Alma mater	University of Toronto
Known for	Co-discoverer of insulin
Awards	Flavelle Medal (1950) Gairdner Foundation International Award (1971) Order of Canada Order of the British Empire Order of the Companions of Honour
Scientific career	
Fields	Physiologist Biochemistry

Fred Banting (1891-1941)   **Charles H. Best (1899-1978)**   **John J.R. McLeod (1876-1935)**

James B. Collip
(1892-1965)

Marjorie (?-?)
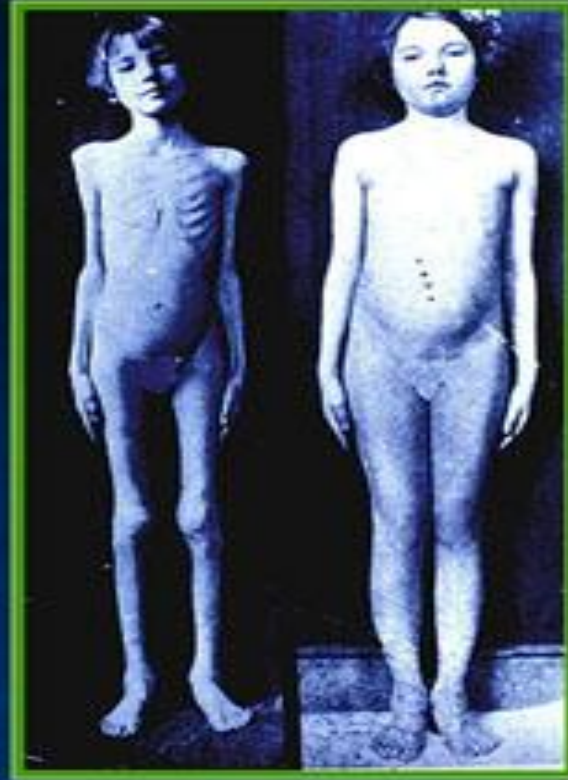
❯ **Animal insulin**

  ➤ **Beef insulin**

  ➤ **Beef-pork insulin**

  ➤ **Pork insulin**

❯ **Human insulin by recombinant DNA technology**

  ➤ **Human insulin**

  ➤ **Analogs of human insulin**
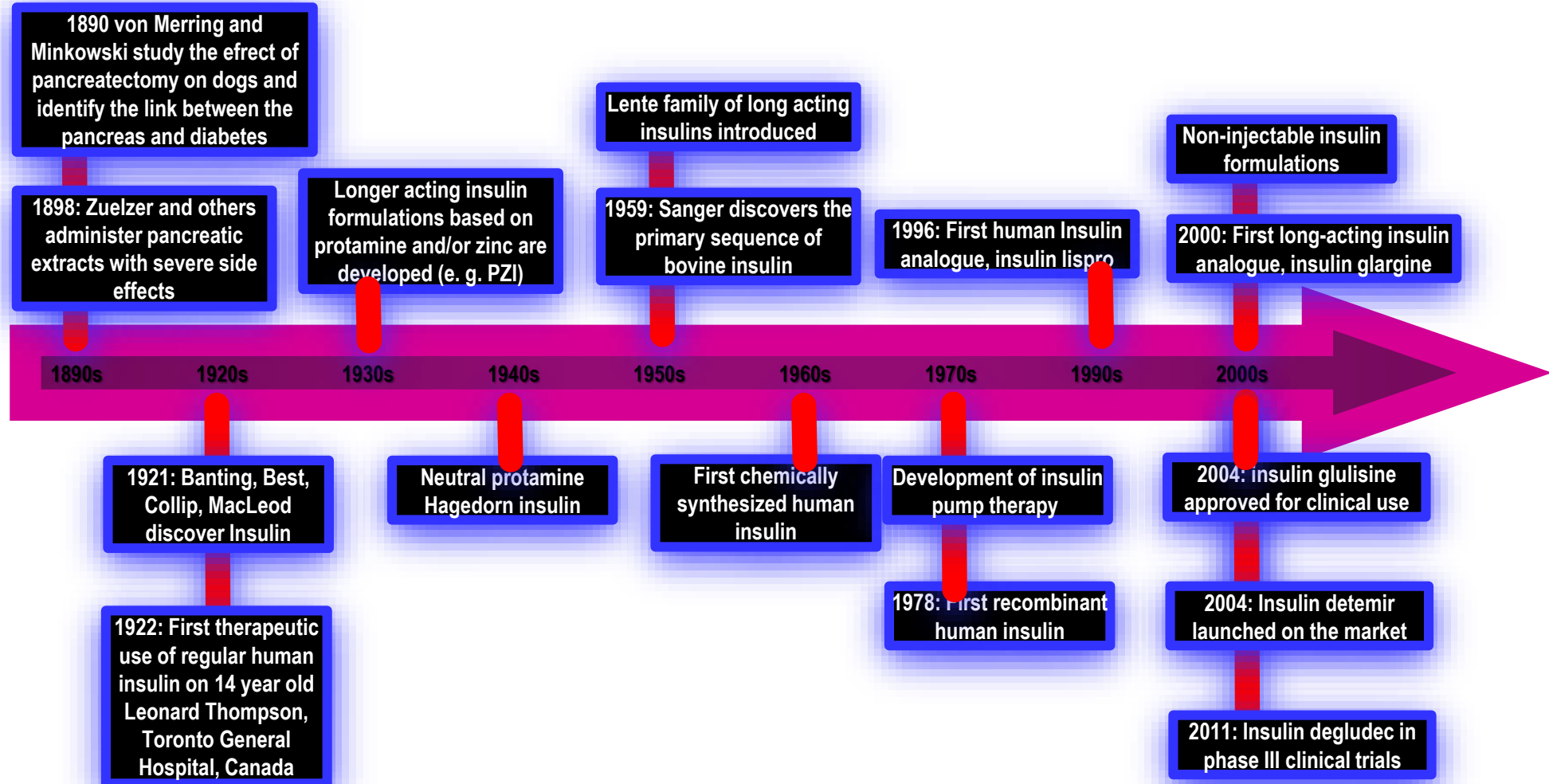
Category/Name of Insulin
Ultra Rapid-Acting
Fiasp®—insulin aspart
Rapid-Acting
Insulin Lispro
Insulin Aspart
Insulin Glulisine
Technosphere insulin
Short-Acting
Regular Human
Intermediate-Acting
NPH Human
Long-Acting
Insulin Detemir
Insulin Glargine
Insulin Degludec
Insulin Mixtures
NPH/Regular (70%/30%)
Protamine/Lispro (50%/50%)
Protamine/Lispro (75%25%)
Protamine/Aspart (70/30)

The glycemic management in type 2 Diabetes

HEALTHY BEHAVIOUR INTERVENTIONS
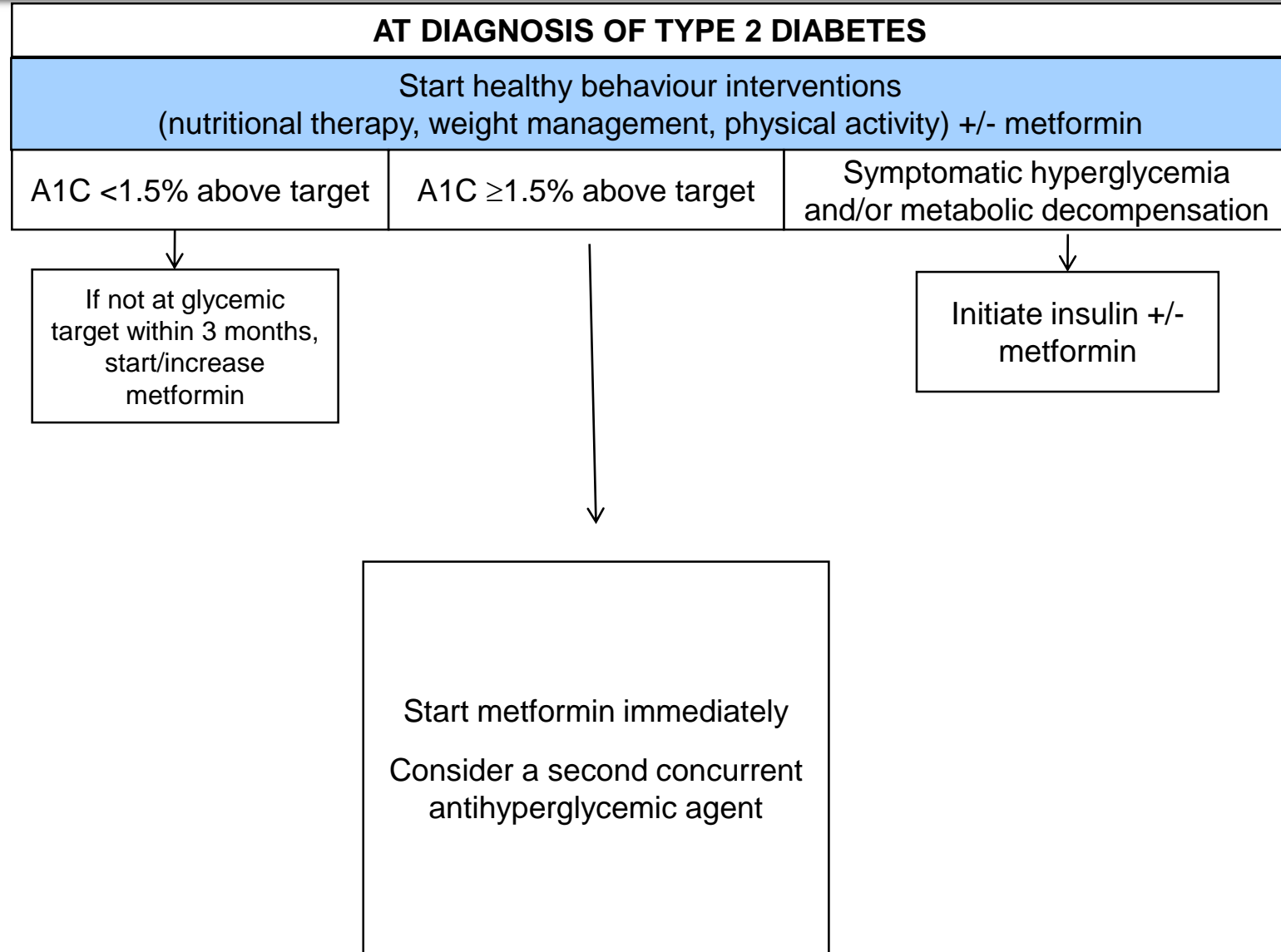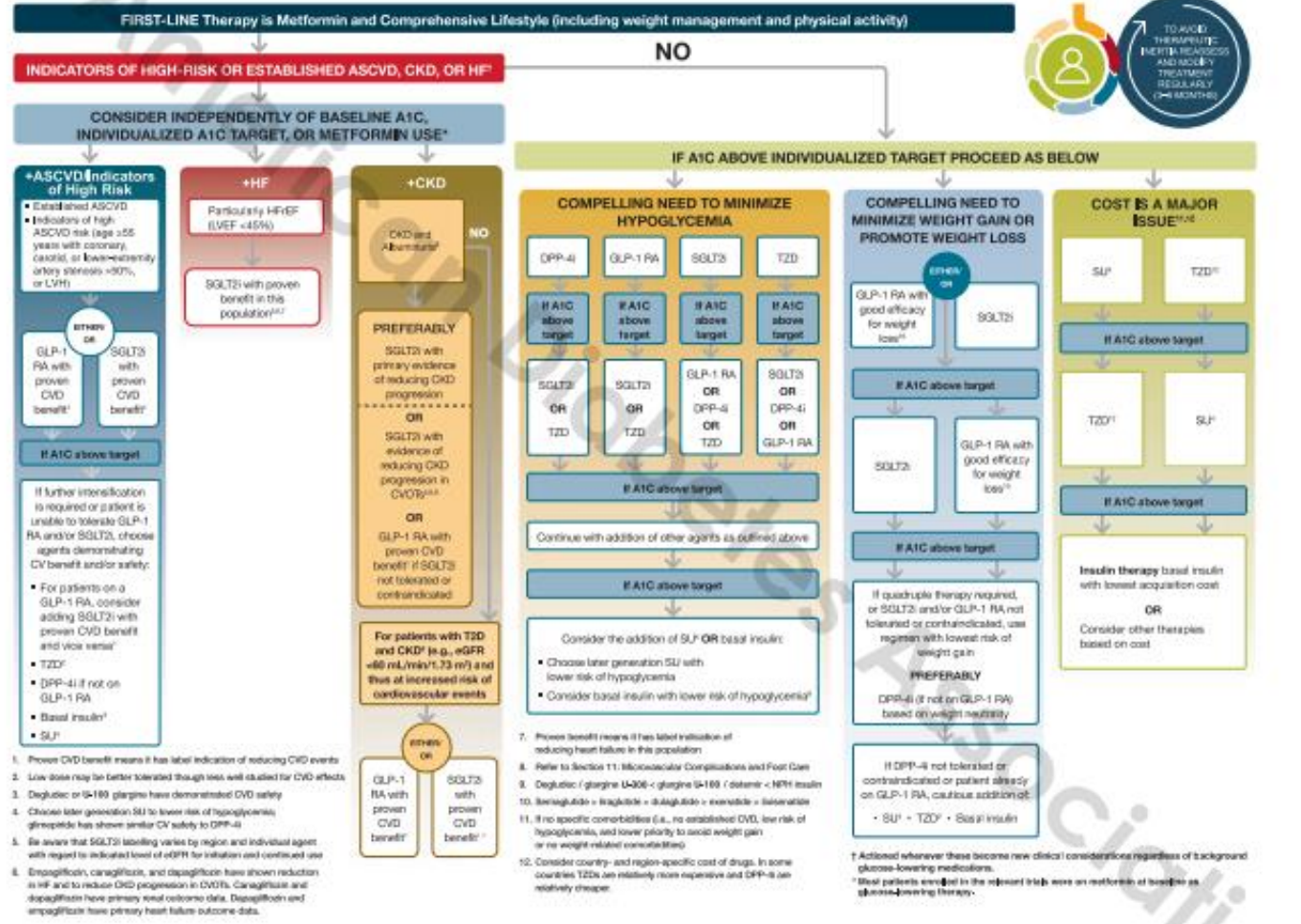
AT DIAGNOSIS OF TYPE 2 DIABETES		
Start healthy behaviour interventions (nutritional therapy, weight management, physical activity) +/- metformin		
A1C <1.5% above target	A1C ≥1.5% above target	Symptomatic hyperglycemia and/or metabolic decompensation

If not at glycemic target within 3 months, start/increase metformin

Start metformin immediately

Consider a second concurrent antihyperglycemic agent

Initiate insulin +/- metformin

كليات ديابت

FIRST-LINE Therapy is Metformin and Comprehensive Lifestyle (including weight management and physical activity)

INDICATORS OF HIGH-RISK OR ESTABLISHED ASCVD, CKD, OR HF[†] **NO**

CONSIDER INDEPENDENTLY OF BASELINE A1C, INDIVIDUALIZED A1C TARGET, OR METFORMIN USE*

IF A1C ABOVE INDIVIDUALIZED TARGET PROCEED AS BELOW

COMPELLING NEED TO MINIMIZE HYPOGLYCEMIA

DPP-4i	GLP-1 RA	SGLT2i	TZD
If A1C above target	If A1C above target	If A1C above target	If A1C above target
SGLT2i **OR** TZD	SGLT2i **OR** TZD	GLP-1 RA **OR** DPP-4i **OR** TZD	SGLT2i **OR** DPP-4i **OR** GLP-1 RA

If A1C above target

If A1C above target

Continue with addition of other agents as outlined above

If A1C above target

Consider the addition of SU[4] **OR** basal insulin:

- Choose later generation SU with lower risk of hypoglycemia
- Consider basal insulin with lower risk of hypoglycemia[9]

FIRST-LINE Therapy is Metformin and Comprehensive Lifestyle (including weight management and physical activity)

INDICATORS OF HIGH-RISK OR ESTABLISHED ASCVD, CKD, OR HF[1]

CONSIDER INDEPENDENTLY OF BASELINE A1C, INDIVIDUALIZED A1C TARGET, OR METFORMIN USE*

+ASCVD/Indicators of High Risk
- Established ASCVD
- Indicators of high ASCVD risk (age ≥55 years with coronary, carotid, or lower-extremity artery stenosis >50%, or LVH)

EITHER/OR

GLP-1 RA with proven CVD benefit[1]

SGLT2i with proven CVD benefit[1]

If A1C above target

If further intensification is required or patient is unable to tolerate GLP-1 RA and/or SGLT2i, choose agents demonstrating CV benefit and/or safety:

- For patients on a GLP-1 RA, consider adding SGLT2i with proven CVD benefit and vice versa[1]
- TZD[2]
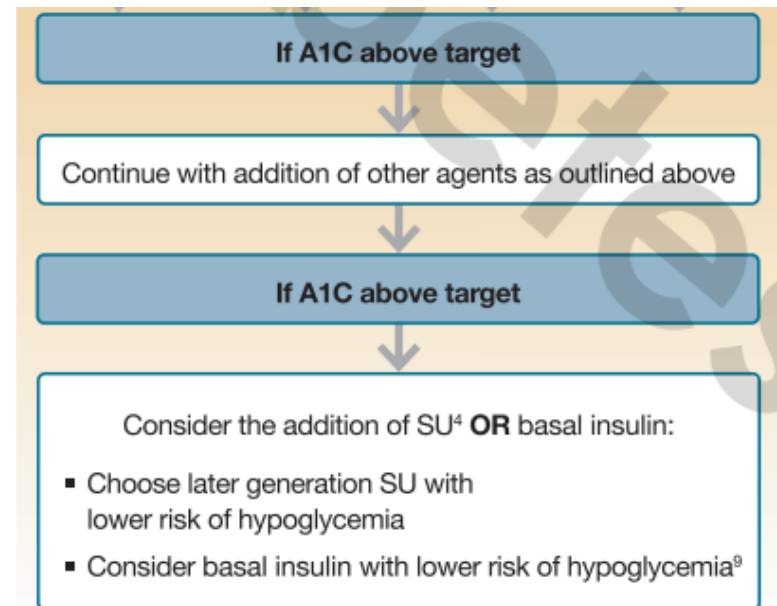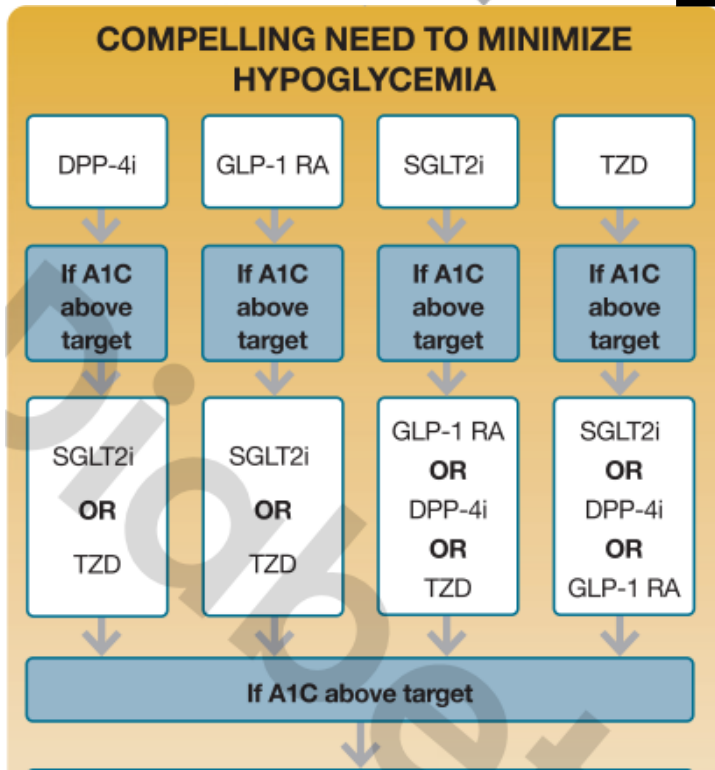- DPP-4i if not on GLP-1 RA
- Basal insulin[3]
- SU[4]

FIRST-LINE Therapy is Metformin and Comprehensive Lifestyle (including weight management and physical activity)

INDICATORS OF HIGH-RISK OR ESTABLISHED ASCVD, CKD, OR HF[1]

CONSIDER INDEPENDENTLY OF BASELINE A1C,
INDIVIDUALIZED A1C TARGET, OR METFORMIN USE*

+HF

Particularly HFrEF
(LVEF <45%)

SGLT2i with proven
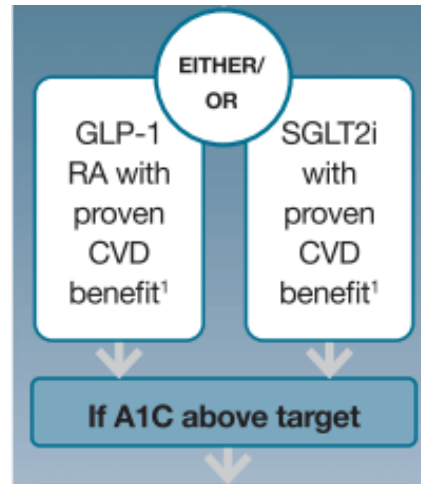benefit in this
population[5,6,7]

FIRST-LINE Therapy is Metformin and Comprehensive Lifestyle (including weight management and physical activity)

INDICATORS OF HIGH-RISK OR ESTABLISHED ASCVD, CKD, OR HF[1]

CONSIDER INDEPENDENTLY OF BASELINE A1C,
INDIVIDUALIZED A1C TARGET, OR METFORMIN USE*

+CKD

DKD and Albuminuria[8]   NO

PREFERABLY

SGLT2i with primary evidence of reducing CKD progression

OR

SGLT2i with evidence of reducing CKD progression in CVOTs[5,6,8]

OR

GLP-1 RA with proven CVD benefit[1] if SGLT2i not tolerated or contraindicated

No →

For patients with T2D and CKD[8] (e.g., eGFR <60 mL/min/1.73 m²) and thus at increased risk of cardiovascular events

EITHER/OR

GLP-1 RA with proven CVD benefit[1]

SGLT2i with proven CVD benefit[1,7]
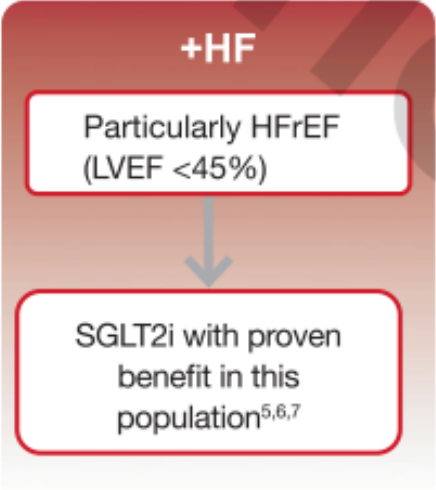
FIRST-LINE Therapy is Metformin and Comprehensive Lifestyle (including weight management and physical activity)

NO

IF A1C ABOVE INDIVIDUALIZED TARGET PROCEED AS BELOW

COST IS A MAJOR ISSUE[11,12]

SU[4]	TZD[12]

If A1C above target

TZD[12]	SU[4]

If A1C above target

Insulin therapy basal insulin with lowest acquisition cost

OR

Consider other therapies based on cost

Use Principles in Figure 9.1, including reinforcement of behavioral interventions (weight management and physical activity) and provision of DSMES to meet individualized treatment goals

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

If injectable therapy is needed to reduce A1C[1]

Consider GLP-1 RA in most patients prior to insulin[2]

INITIATION: Initiate appropriate starting dose for agent selected (varies within class)

TITRATION: Titration to maintenance dose (varies within class)

If already on GLP-1 RA or if GLP-1 RA not appropriate OR insulin preferred

If above A1C target

Add basal insulin[3]

Choice of basal insulin should be based on patient-specific considerations, including cost. Refer to Table 9.3 for insulin cost information.

Add basal analog or bedtime NPH insulin

INITIATION: Start 10 IU a day OR 0.1-0.2 IU/kg a day

TITRATION:

- Set FPG target (see Section 6: Glycemic Targets)
- Choose evidence-based titration algorithm, e.g., increase 2 units every 3 days to reach FPG target without hypoglycemia
- For hypoglycemia determine cause, if no clear reason lower dose by 10-20%

Assess adequacy of basal insulin dose

Consider clinical signals to evaluate for overbasalization and need to consider adjunctive therapies (e.g., basal dose >0.5 IU/kg, elevated bedtime-morning and/or post-preprandial differential, hypoglycemia [aware or unaware], high variability)