

عنوان برنامه

درمان
و مدیریت
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

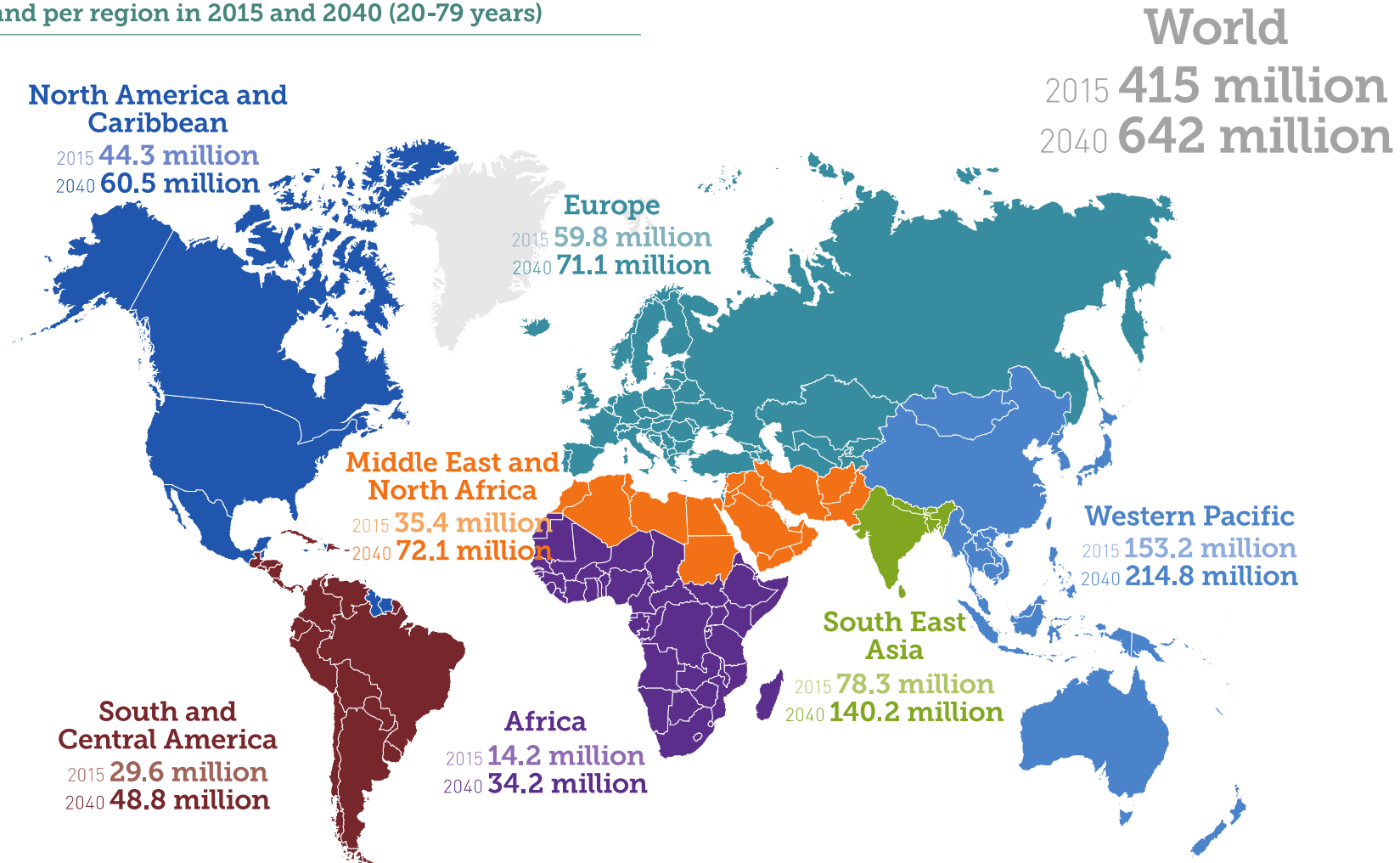
- 9-15% of total
- Healthcare budgets of most westernized countries

EPIDEMIOLOG

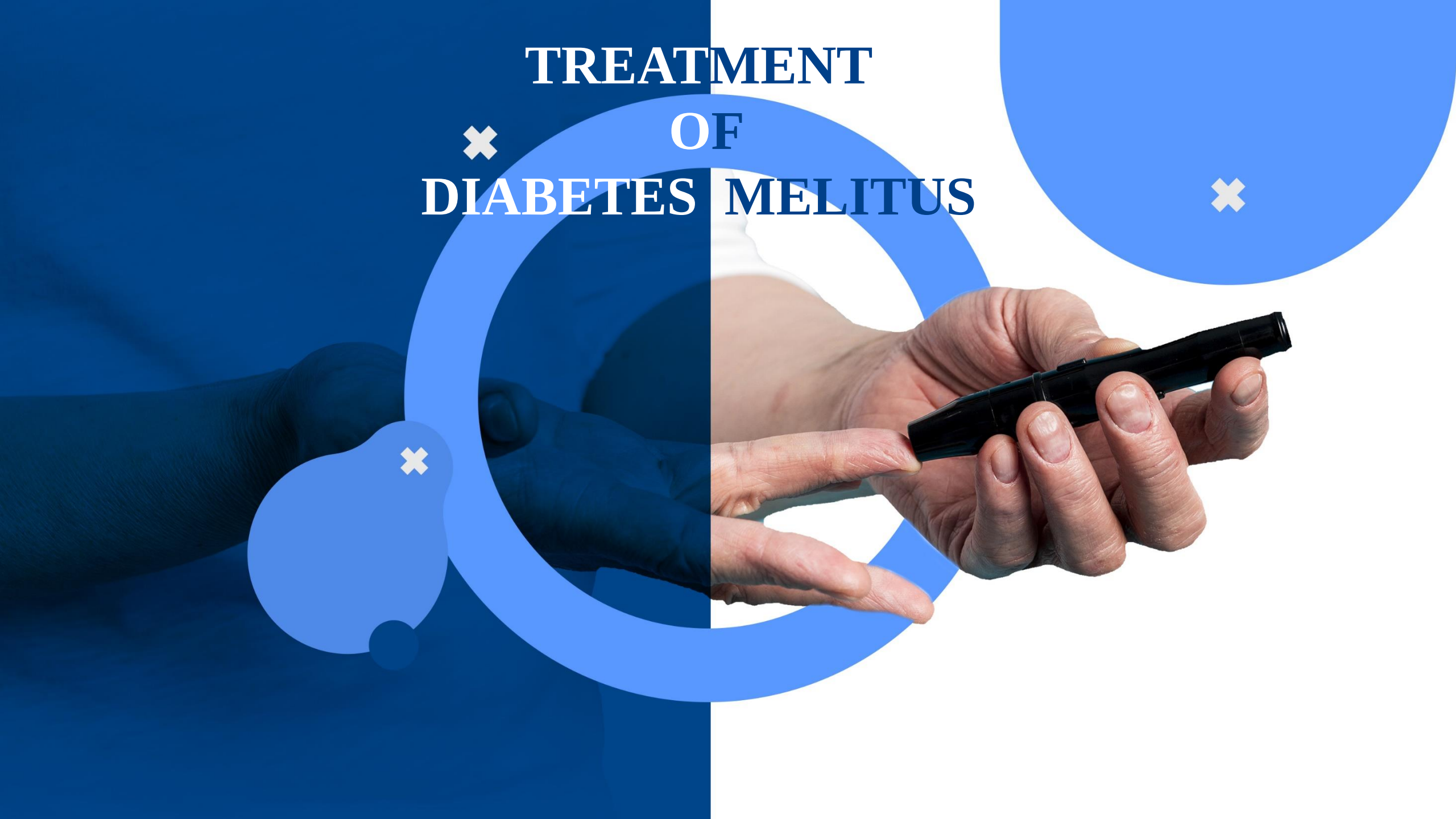




Estimated number of people with diabetes worldwide and per region in 2015 and 2040 (20-79 years)



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**

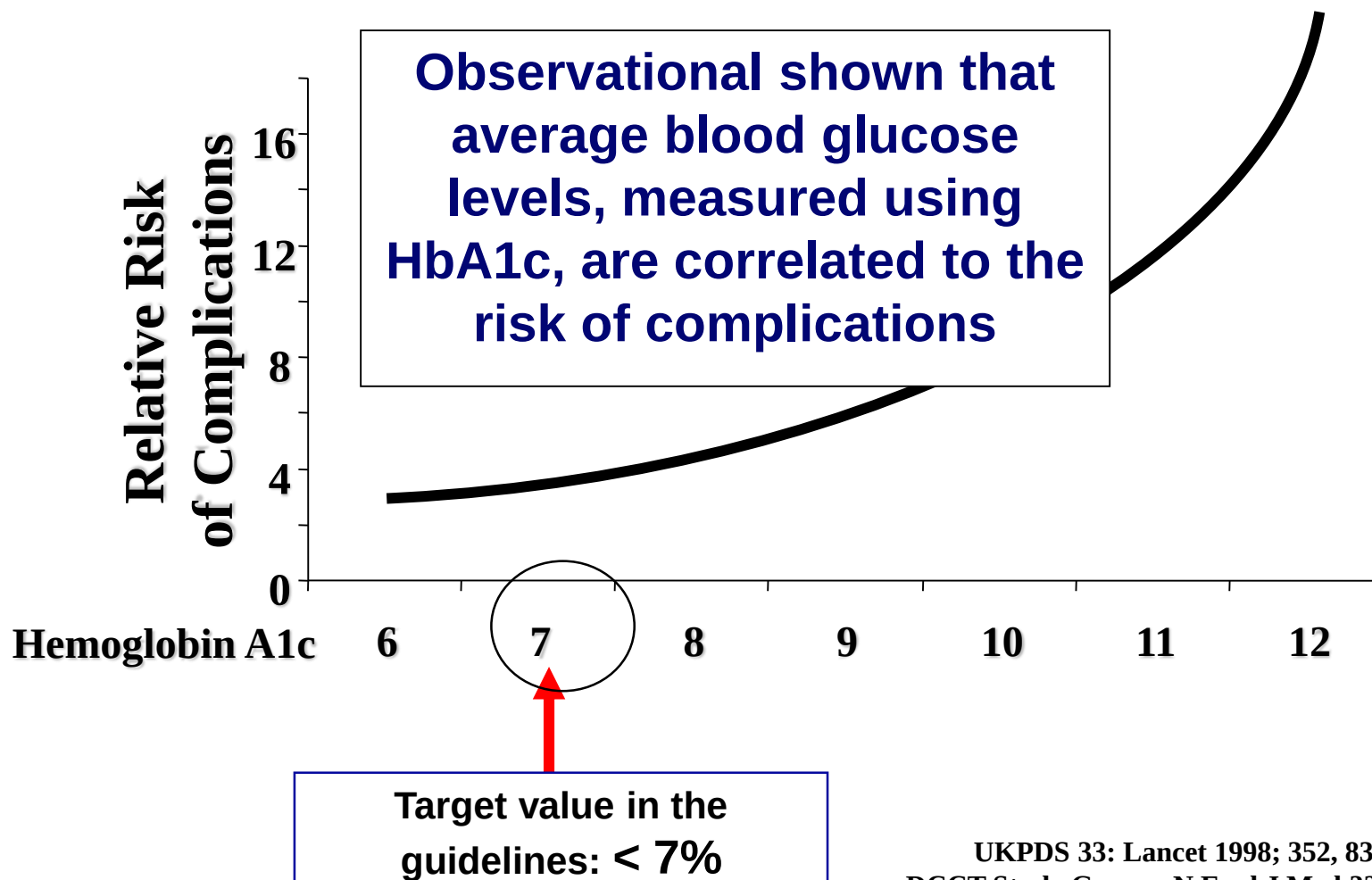
➤ **Psychosocial Assessment and Care**

➤ **Prevention and Delay of Type**

➤ **Pharmacotherapy**



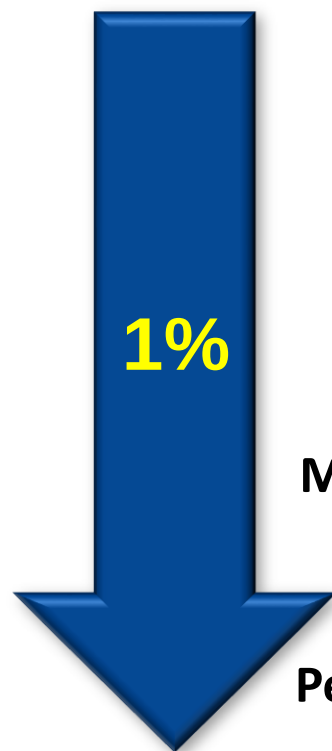
➤ A close relationship between blood glucose levels and complications of diabetes



➤ Better control in T2DM means fewer complications

1% reduction in HbA_{1c}

Risk reduction*



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			 		 	 
<i>ACCORD</i>			 			
<i>ADVANCE</i>			 		 	
<i>VADT</i>			 		 	



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

A1C	<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, $\leq 6\%$) 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 A1C goals are not met despite reaching preprandial glucose goals





Patient/Disease Features

Risks potentially associated with hypoglycemia and other drug adverse effects

Disease duration

Life expectancy

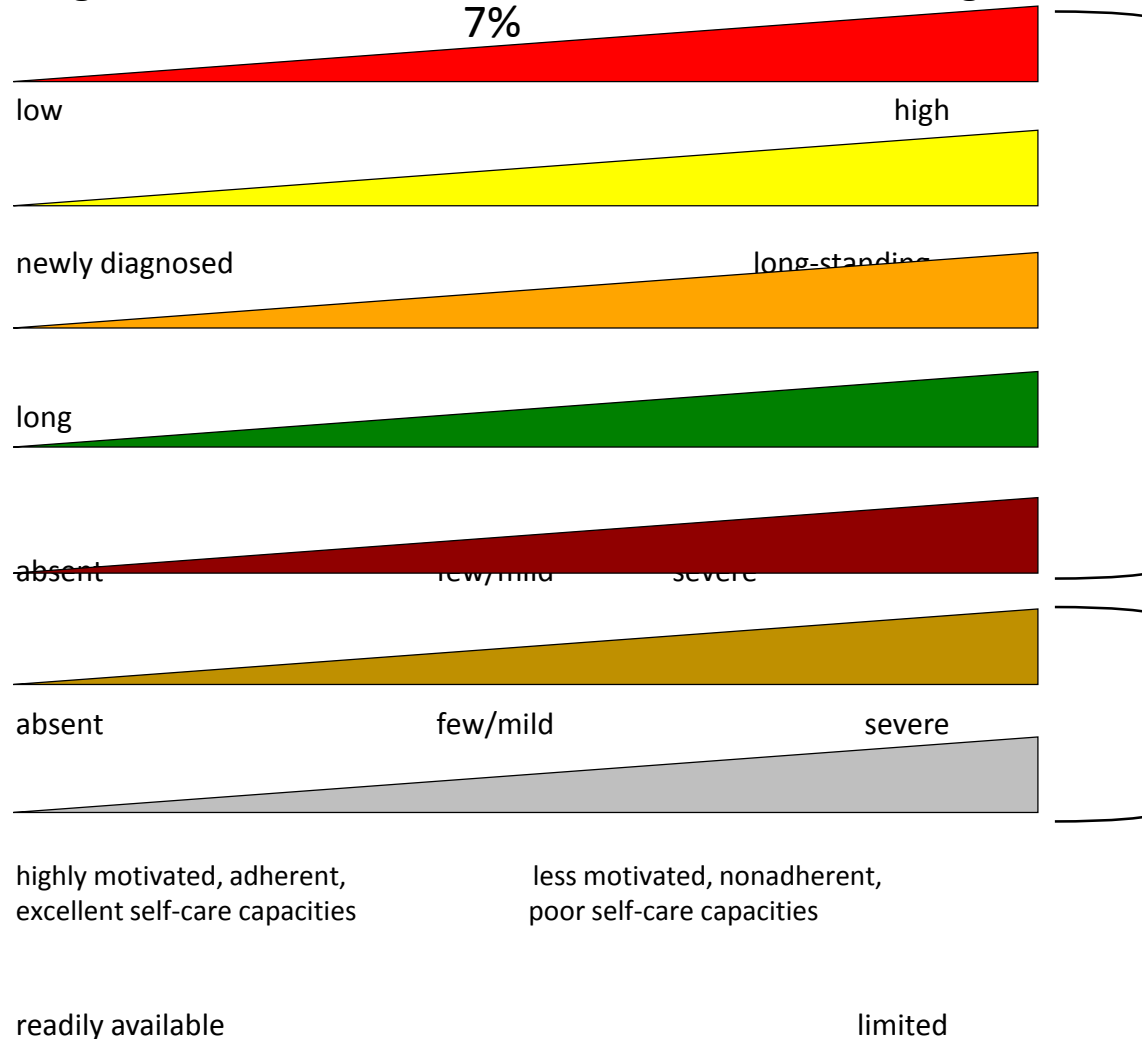
Important comorbidities

Established vascular complications

Patient attitude and expected treatment efforts

Resources and support system

more stringent ← A1c 7% → less stringent





➤ 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 ($>15\%$), a blood pressure target of $<130/80$ mm Hg maybe appropriate, if it can be safely attained





Current Age  *

Age must be between 20-79

Sex *

Male

Female

Race *

White

African American

Other

Systolic Blood Pressure (mm Hg) *

Value must be between 90-200

Diastolic Blood Pressure (mm Hg) 

Value must be between 60-130

Total Cholesterol (mg/dL) *

Value must be between 130 - 320

HDL Cholesterol (mg/dL) *

Value must be between 20 - 100

LDL Cholesterol (mg/dL) 

Value must be between 30-300

History of Diabetes? *

Yes

No

Smoker?  *

Current 

Former 

Never 

On Hypertension Treatment? *

Yes

No

On a Statin? 

Yes

No

On Aspirin Therapy? 

Yes

No

Do you want to refine current risk estimation using data from a previous visit? 

Yes

✓ No





Comprehensive care of diabetes Prospective approach



Reduce macrovascular risk

1. Lipid control
2. BP normalization
3. Smoking cessation
4. Glycemic control
5. Weight control
6. Regular exercise
7. Aspirin

Minimize microvascular/ neuropathic complications

1. Glycemic control
2. BP normalization
3. Regular eye exams
4. Regular testing for albuminuria
5. Foot care

Improve sense of well-being

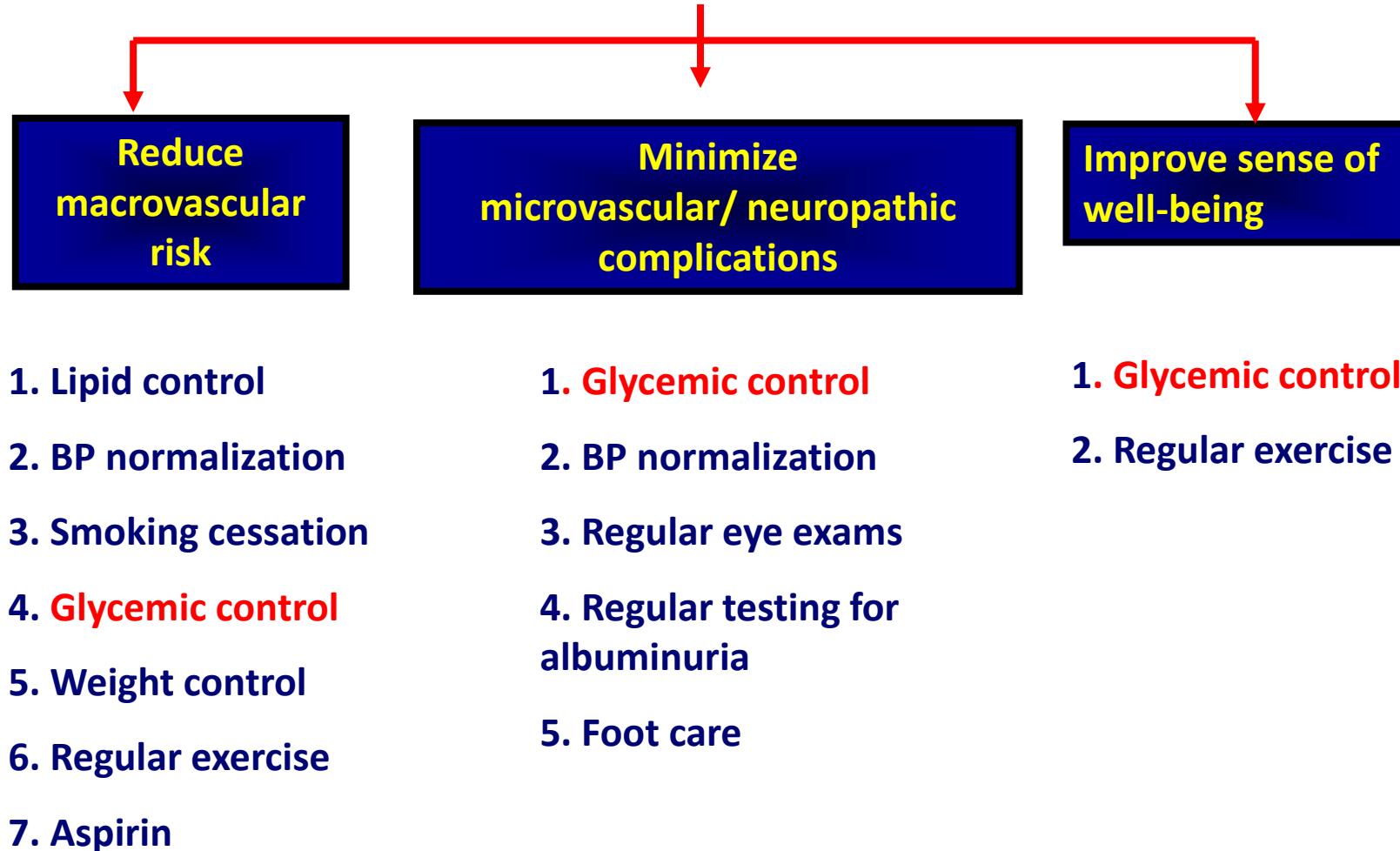
1. Glycemic control
2. Regular exercise

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

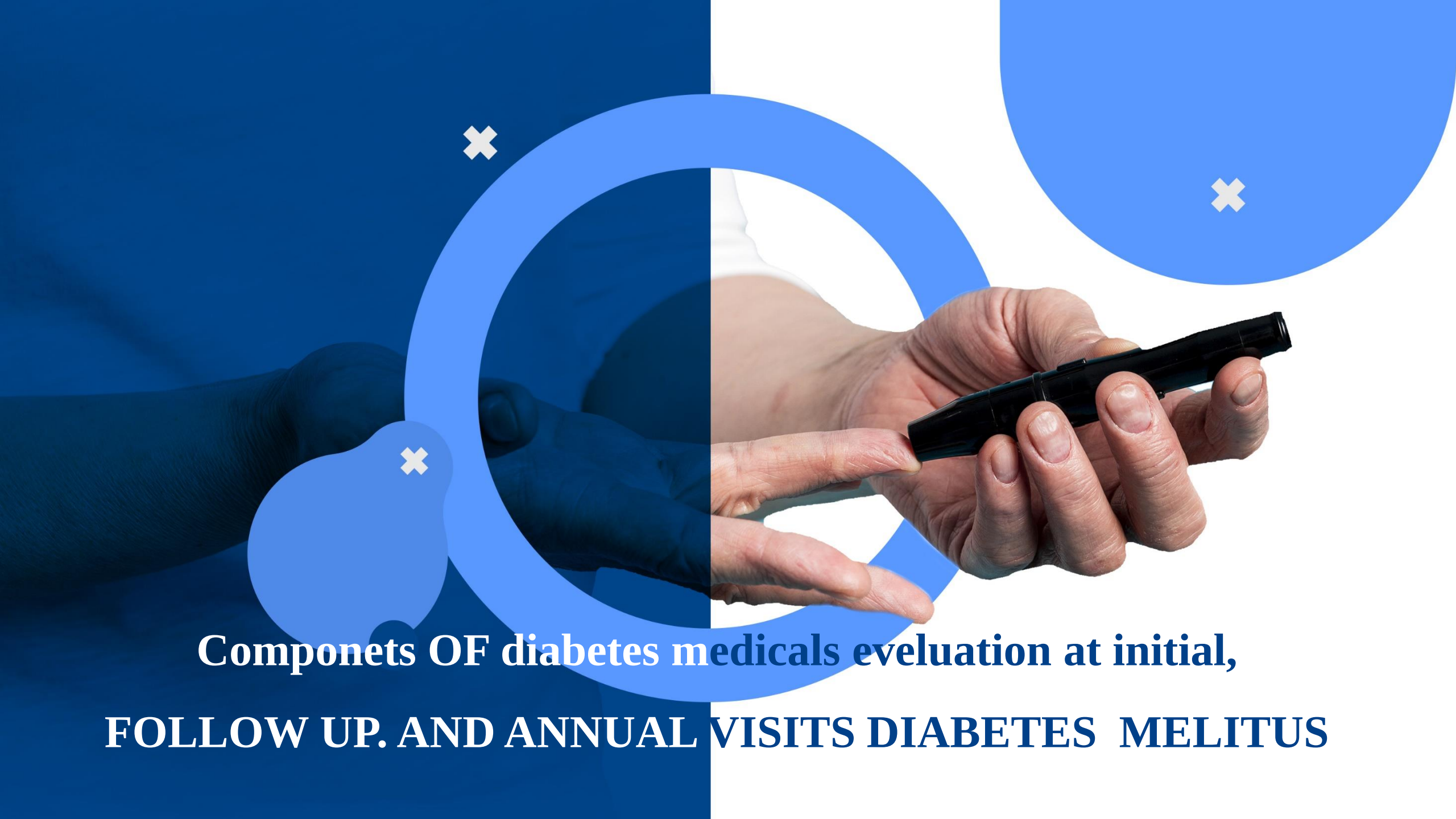




Comprehensive care of diabetes Prospective approach



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



**Components OF diabetes medicals evaluation 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 patterns and weight history



Physical activity and sleep behaviors



Tobacco, alcohol and substance use



Medications and vaccinations

Current medication regimen	☐	☐	☐
Medication-taking behavior	☒	☐	☐
Medication intolerance or side effects	☒	☒	☐
Complementary and alternative medicine use	☒	☒	☐
Vaccination history and needs	☒	☐	☐



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 dietitian/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 evaluation

A1c if the results are not available within the past 3 months	☐	☐	☐
If not performed/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 β -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
- 

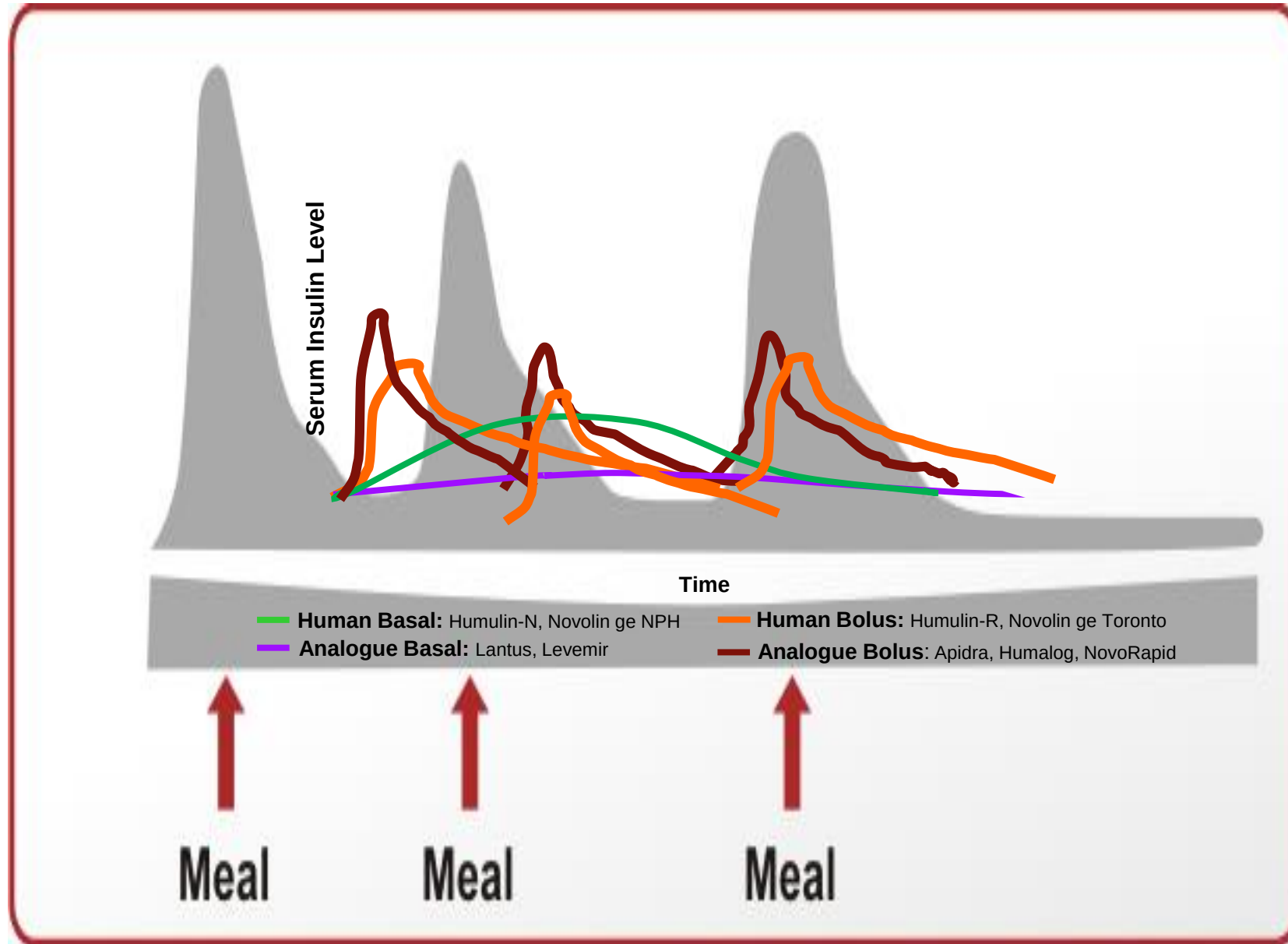
- Education is fundamental to diabetes management & metabolic control. Teaching about diabetes is best handled by a diabetes management team, including a physician, nurse, educator, dietitian, & mental health professional.
- The family of diabetic patient must be taught the following basic of treatment:
 - 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.







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 فرایند چرخه تصمیم گیری بازنگری شده و مجدداً انجام گیرد.

ویژگی های اصلی بیمار را ارزیابی کنید

- شیوه زندگی فعلی
- بیماری های 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 انتخاب 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.

اهداف مراقبت

- جلوگیری از عوارض
- بهینه سازی کیفیت زندگی



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 خانگی قند خون (SMBG)، وزن، شمارش تعداد قدم های پیموده شده، HbA1c، فشار خون، چربی های خون بازخوردهای تشویقی به بیمار بدهید (بیوفیدبک)

اجرای مدیریت درمان طراحی شده

- بیمارانی که قادر به دستیابی به اهداف درمان نمی شوند معمولاً 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)

- ویژه Specific

- قابل اندازه گیری Measurable

- قابل دستیابی Achievable

- واقع بینانه Realistic

- زمان بندی شده Time limited باشد.

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 خوشن در دیابت و پشتیبانی مستمر) را تضمین می کند.

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

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



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



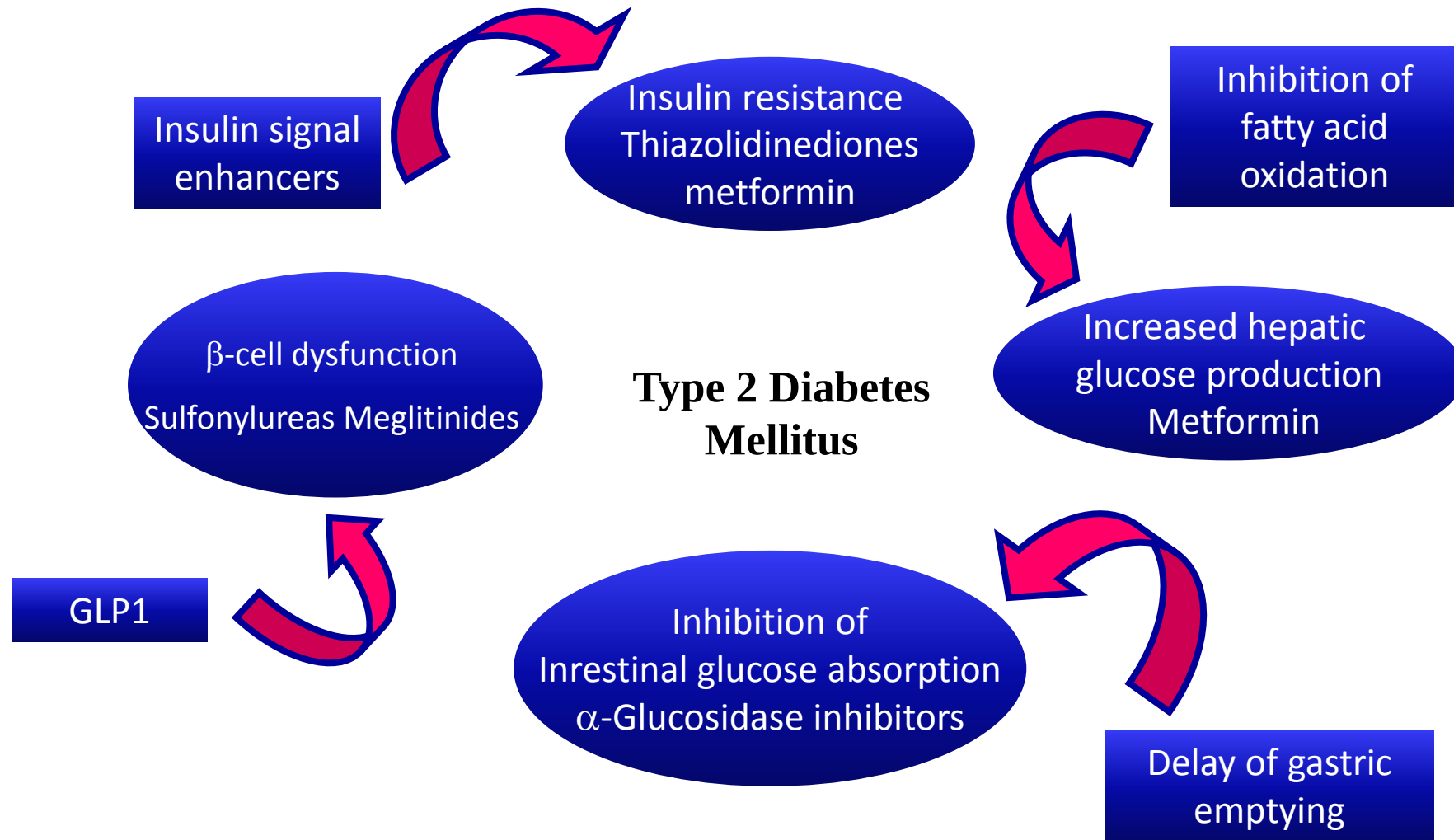
- ① Effectiveness of nutrition therapy
- ② Energy balance
- ③ Eating patterns and macronutrients
- ④ distribution
 - Carbohydrates
- ⑤ Protein

- ⑥ Dietary fat
- ⑦ Micronutrients and herbal supplements
- ⑧ Alcohol
- ⑨ Sodium
- ⑩ Nonnutritive sweeteners



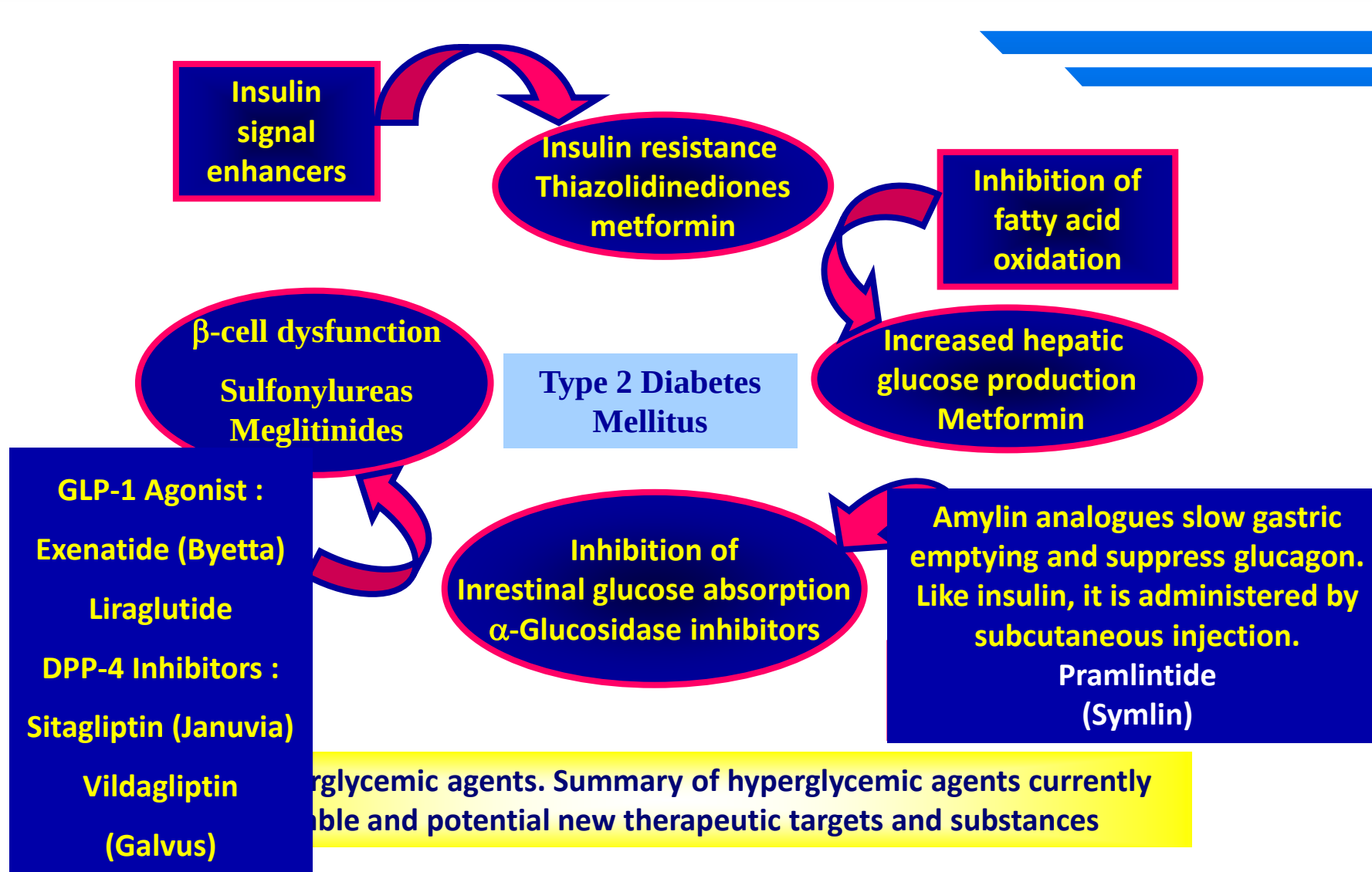
	Mechanism of Action	Examples	A1C Reduction (%)	Agent Specific Advantages	Agent-Specific Disadvantages
Medical nutrition therapy and physical activity	↓ Insulin, resistance, ↑ insulin secretion	Low-calorie, low-fat diet, exercise	1–2	Other health benefits	Compliance difficult, long-term success low





and potential new therapeutic targets and substances

Antihyperglycemic agents. Summary of hyperglycemic agents currently available 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

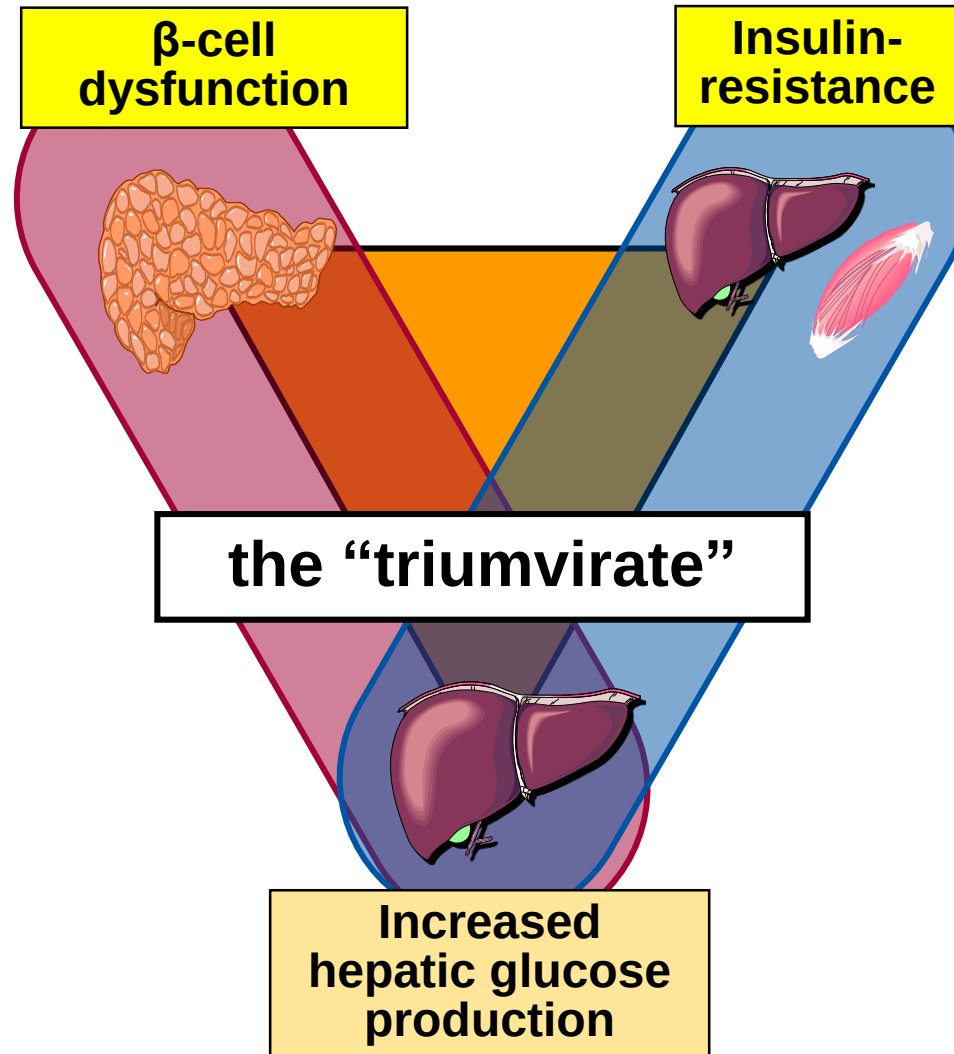


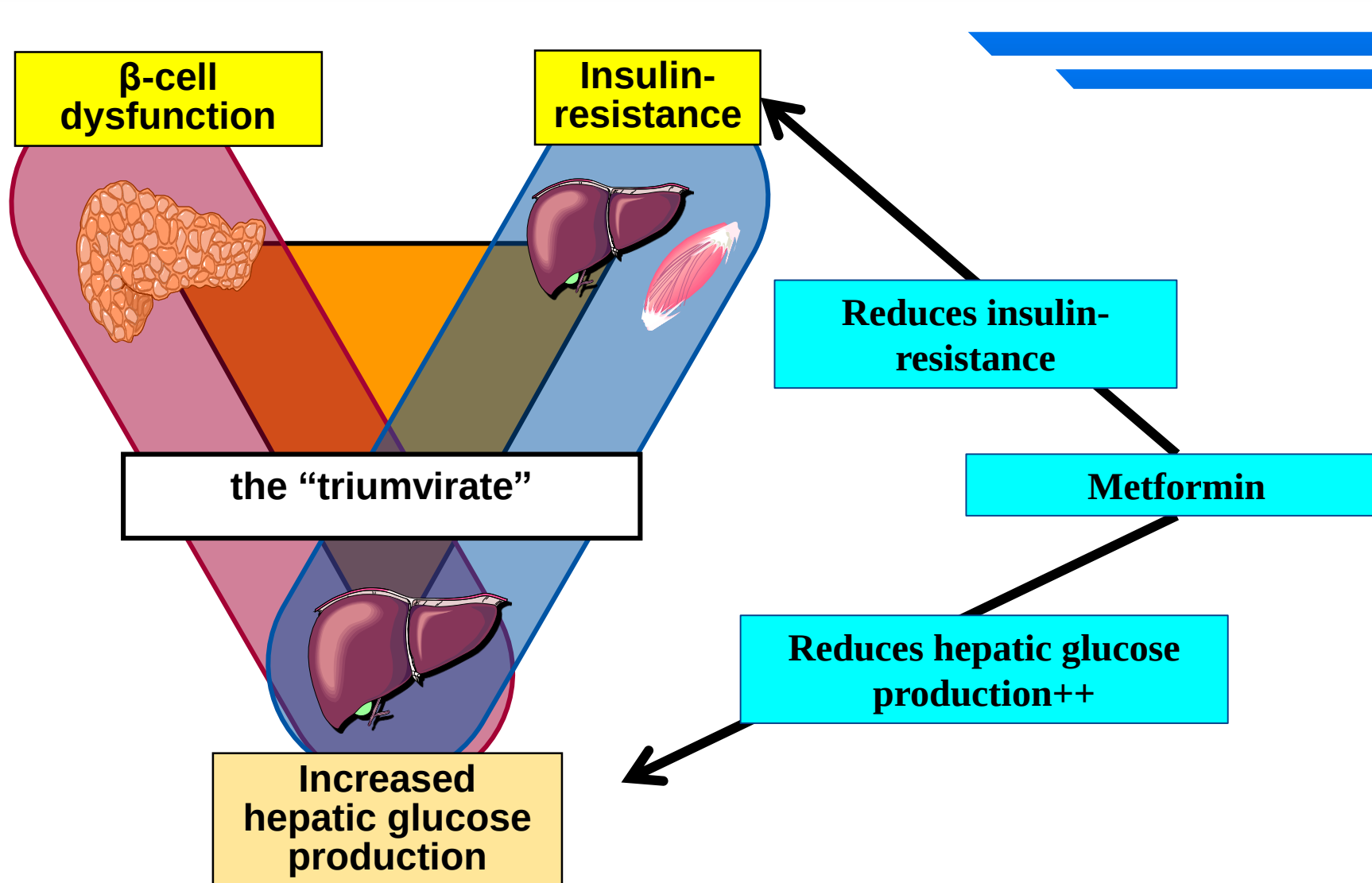
BIGUANIDES



- 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







① Metformin is widely accepted as the 1st line agent

② and next as the background medication of the intensification strategy

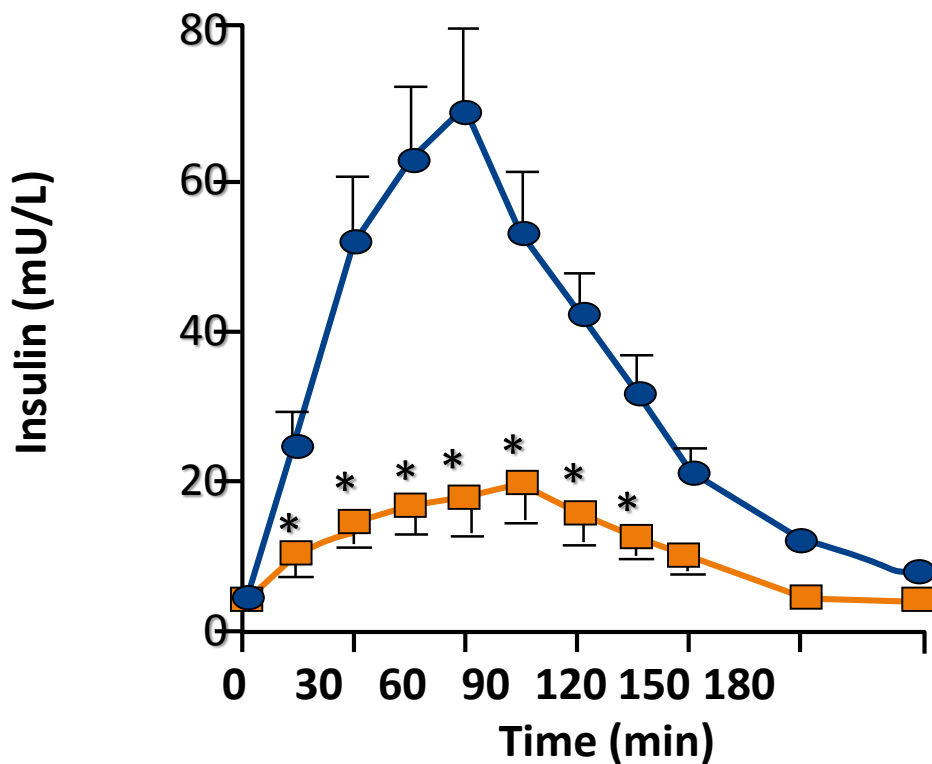
- An insulin-sensitizer which fits with the physiopathological features of the disease
- A powerful agent which decreases HbA1c by >1%
- No weight gain
- No hypoglycaemia
- Possible cardio-vascular protective effect
- Possible protective effect against cancer
- Safe : low level of serious side effects
- Cheap



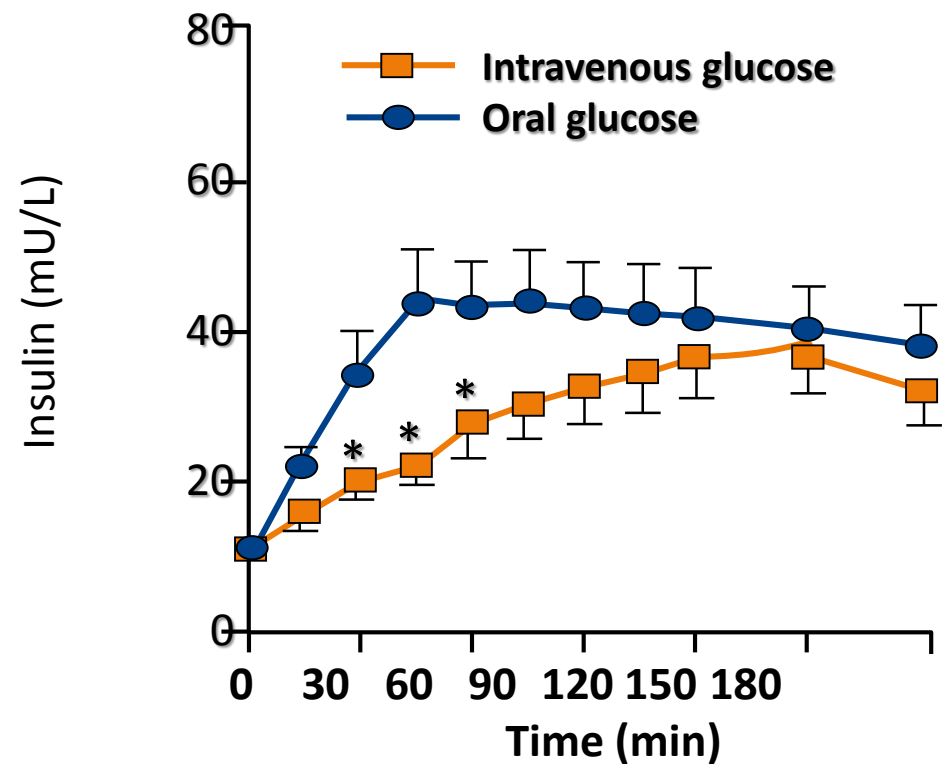
DIPEPTIDYL PEPTIDASE-4 INHIBITORS
And
GLP- 1 Agonists

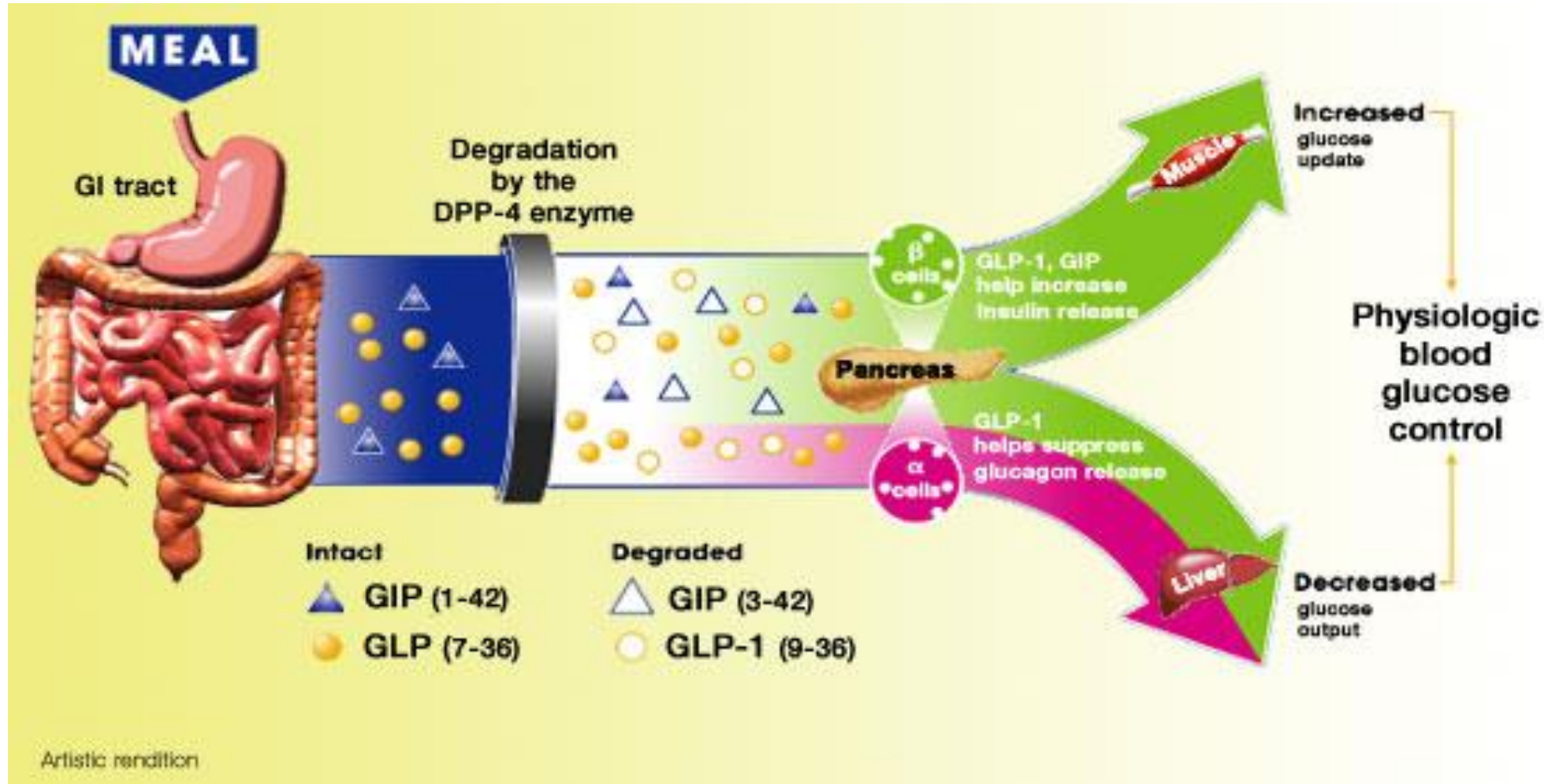


Control subjects



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

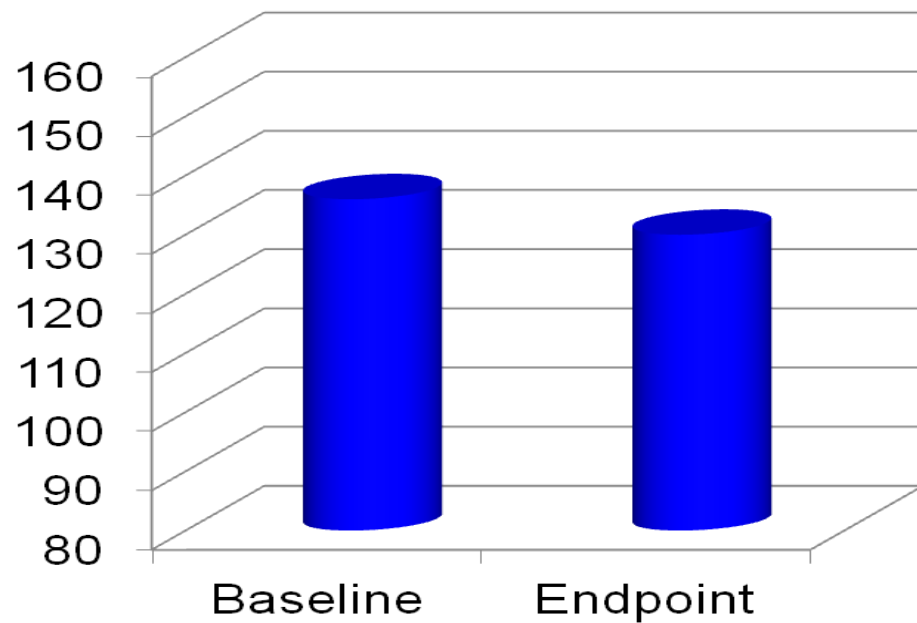
- Oral
- No hypoglycemia when used as
- monotherapy
- Weight neutral
- Generally well tolerated

➤ Disadvantages

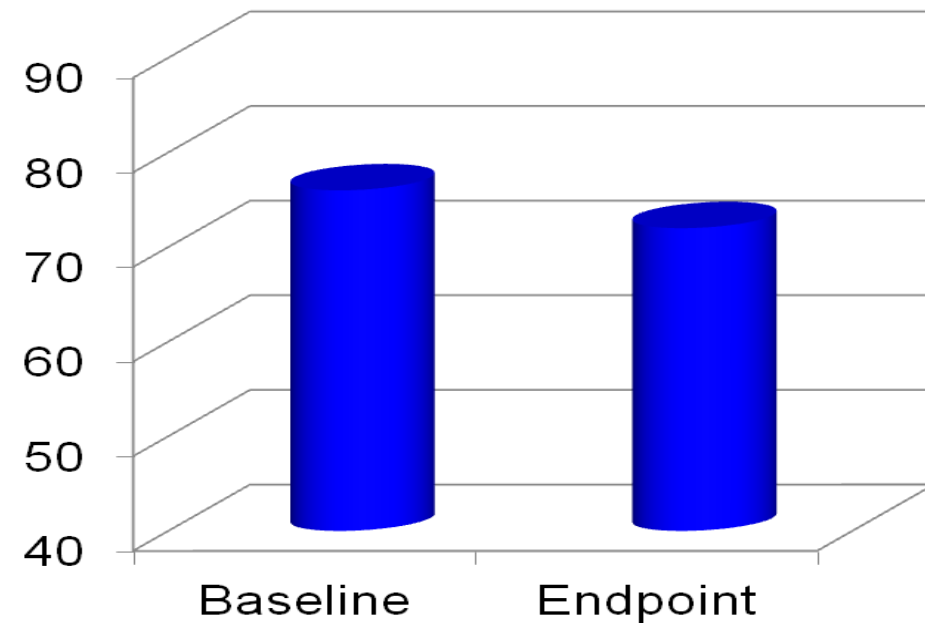
- Dosage modification required with renal impairment (sitagliptin, saxagliptin, alogliptin)
- CYP3A4 interactions (saxagliptin, linagliptin)
- May be associated with pancreatitis
- May worsen heart failure (saxagliptin)
- May cause severe joint pain

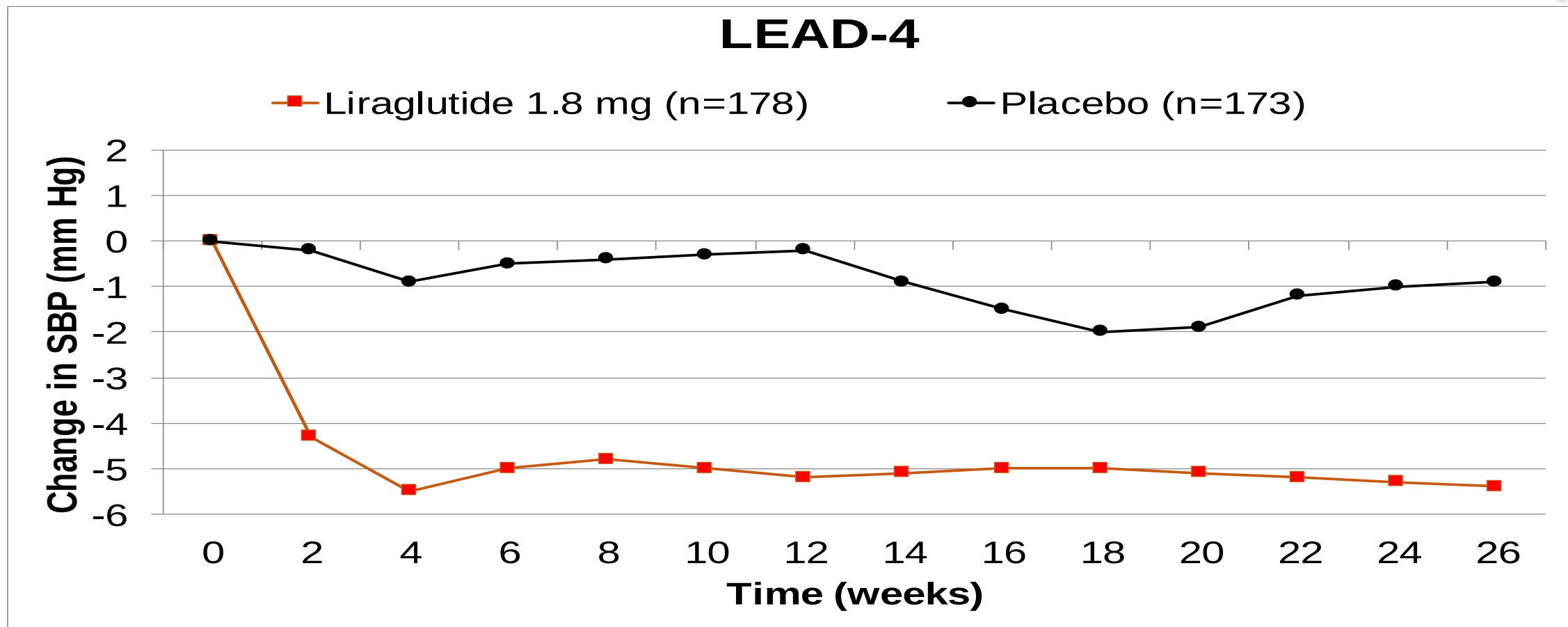
****After 12 weeks of monotherapy**

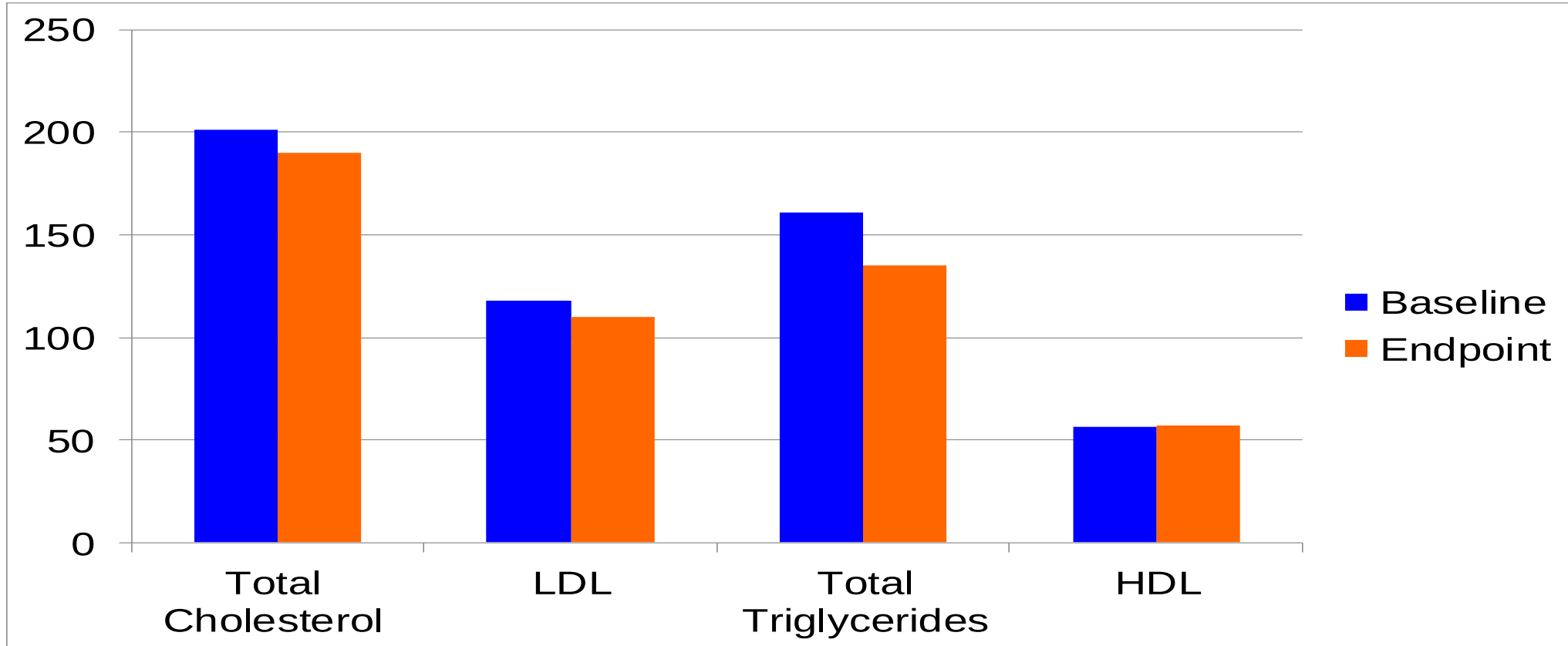
Systolic Blood Pressure



Diastolic Blood Pressure









➤ GLP-1 Ras

➤ Reduce postprandial triglycerides,
FFA, and LDL

➤ DPP-4 inhibitors

➤ Reduce fasting LDL and
triglycerides

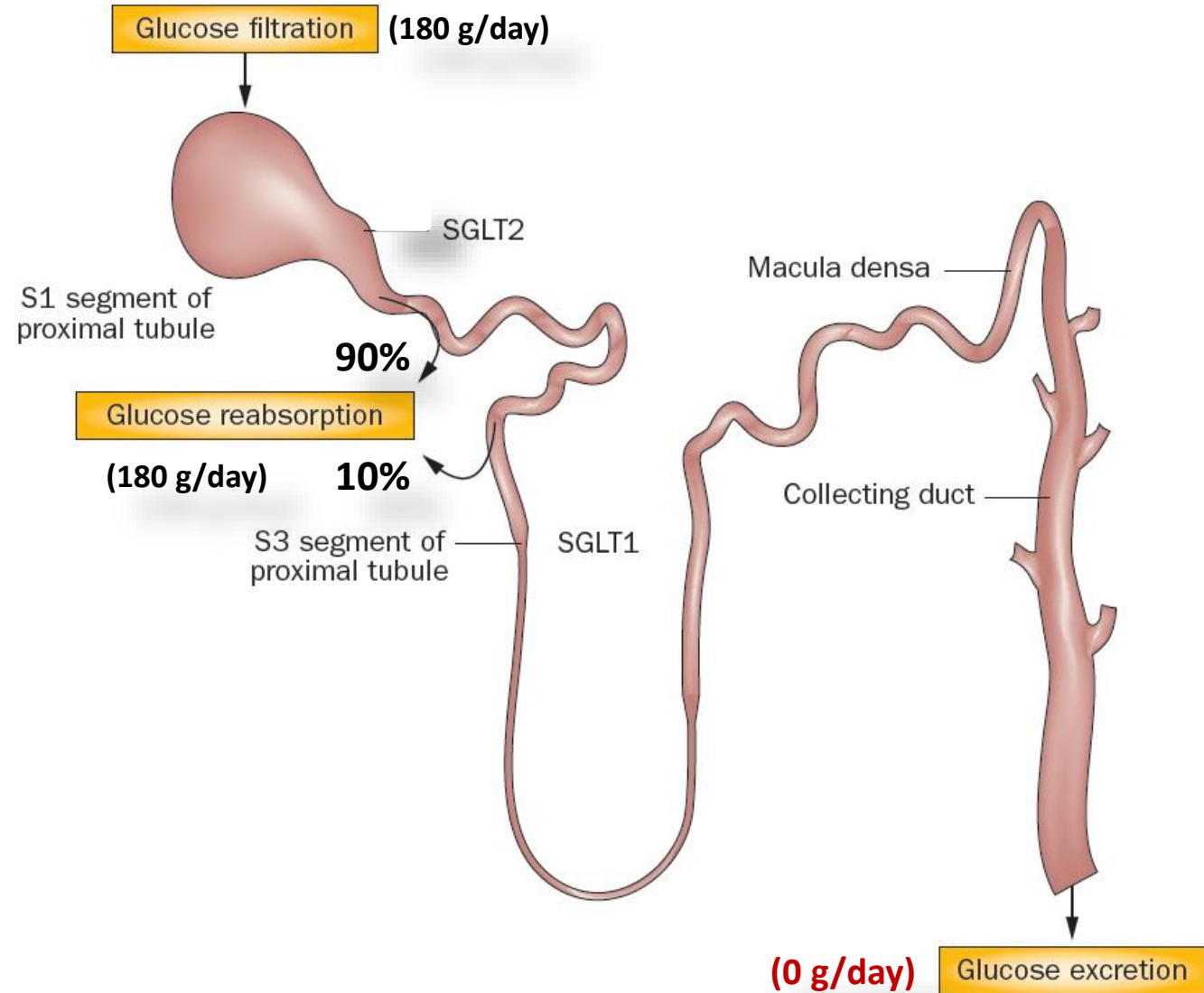
➤ Small increase in HDL

➤ Parallels weight loss



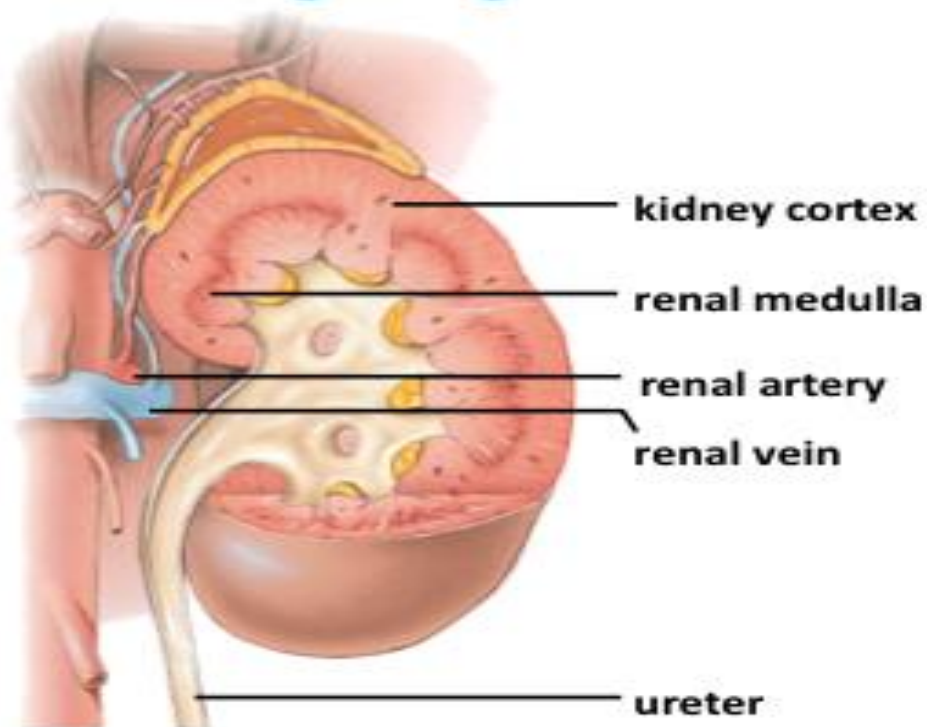


SGLT2 INHIBITO





Renal Handling of Glucose: A Potential New Drug Target?



“Normal” individuals:

- **Filtered glucose load: approximately 180 g/day**
- **Urinary glucose: less than 0.5 g/day**
- **Glucose reabsorption occurs in the proximal tubule through the action of SGLT1 and SGLT2**





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





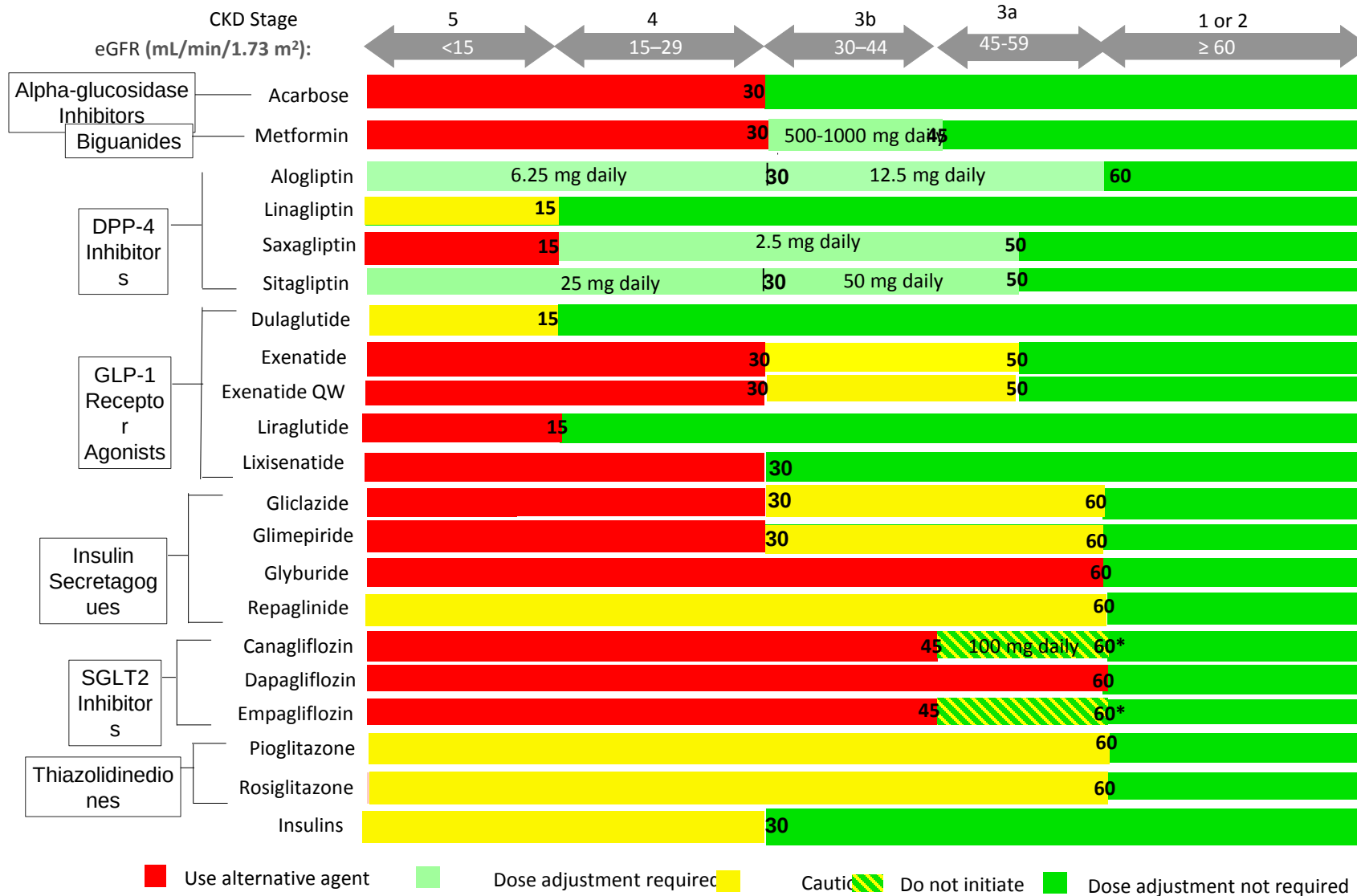
- Secondary failure rate
- Hypoglycemia
- Weight gain
- Low cost
 - Elderly
 - Impaired renal function
 - Irregular meal schedule
- Increase cardiovascular events?



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	<u>University of Toronto</u>
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

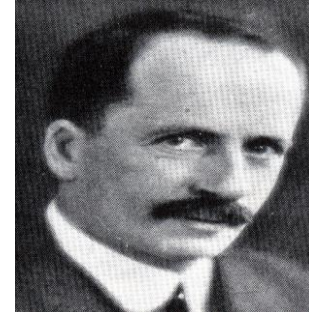




Fred Banting (1891-1941)



Charles H. Best (1899-1978)



John J.R. McLeod (1876-1935)



**James B. Collip
(1892-1965)**



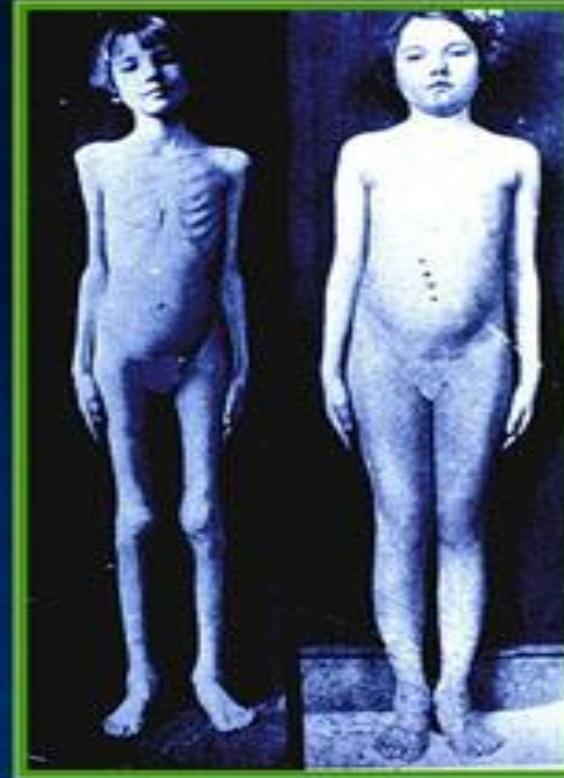
Marjorie (?-?)





Before and After

**One of the first
patients to ever
receive insulin
therapy**



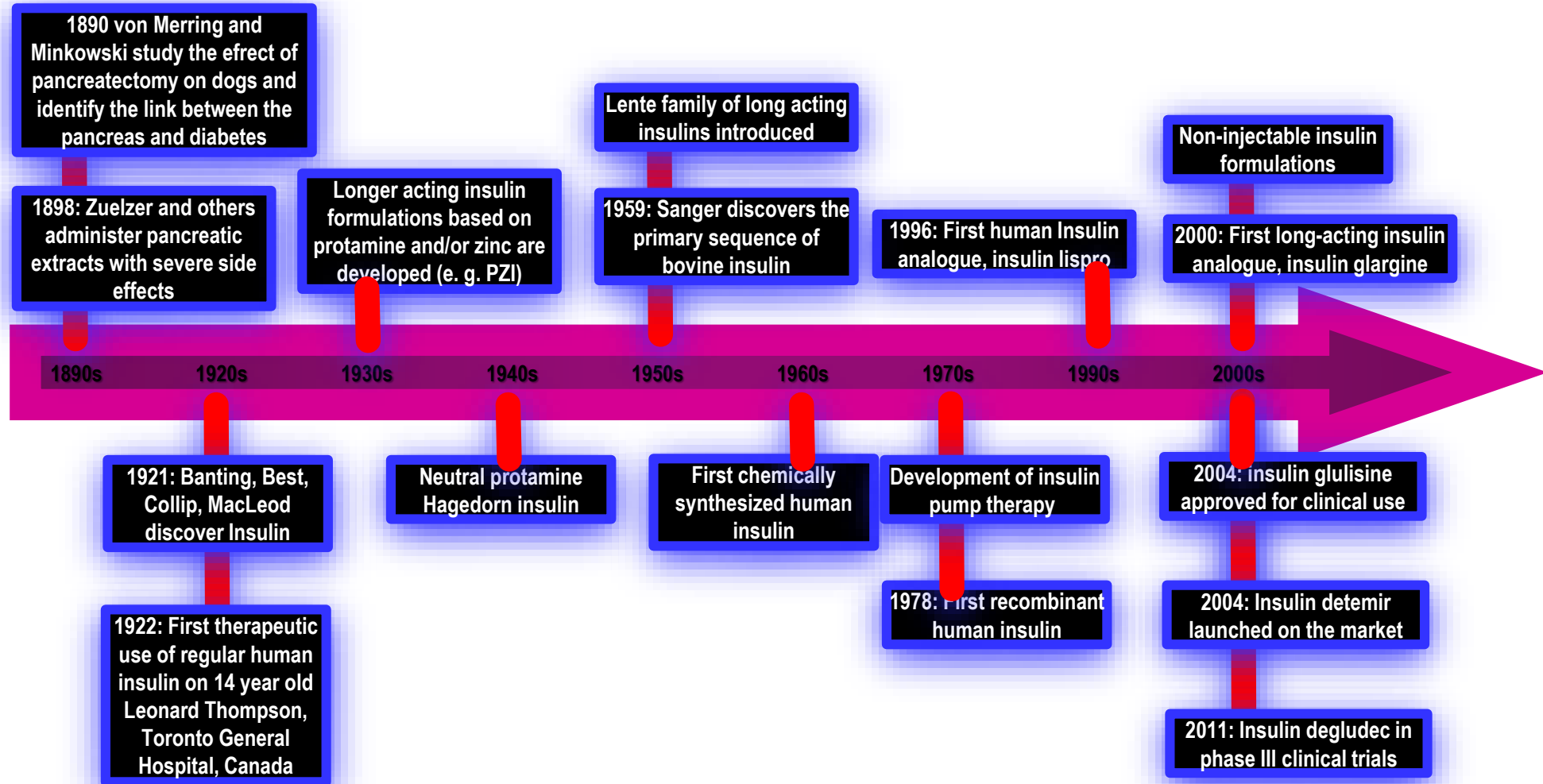
► **Animal insulin**

- Beef insulin
- Beef-pork insulin
- Pork insulin

► **Human insulin by recombinant DNA technology**

- Human insulin
- Analogs of human insulin





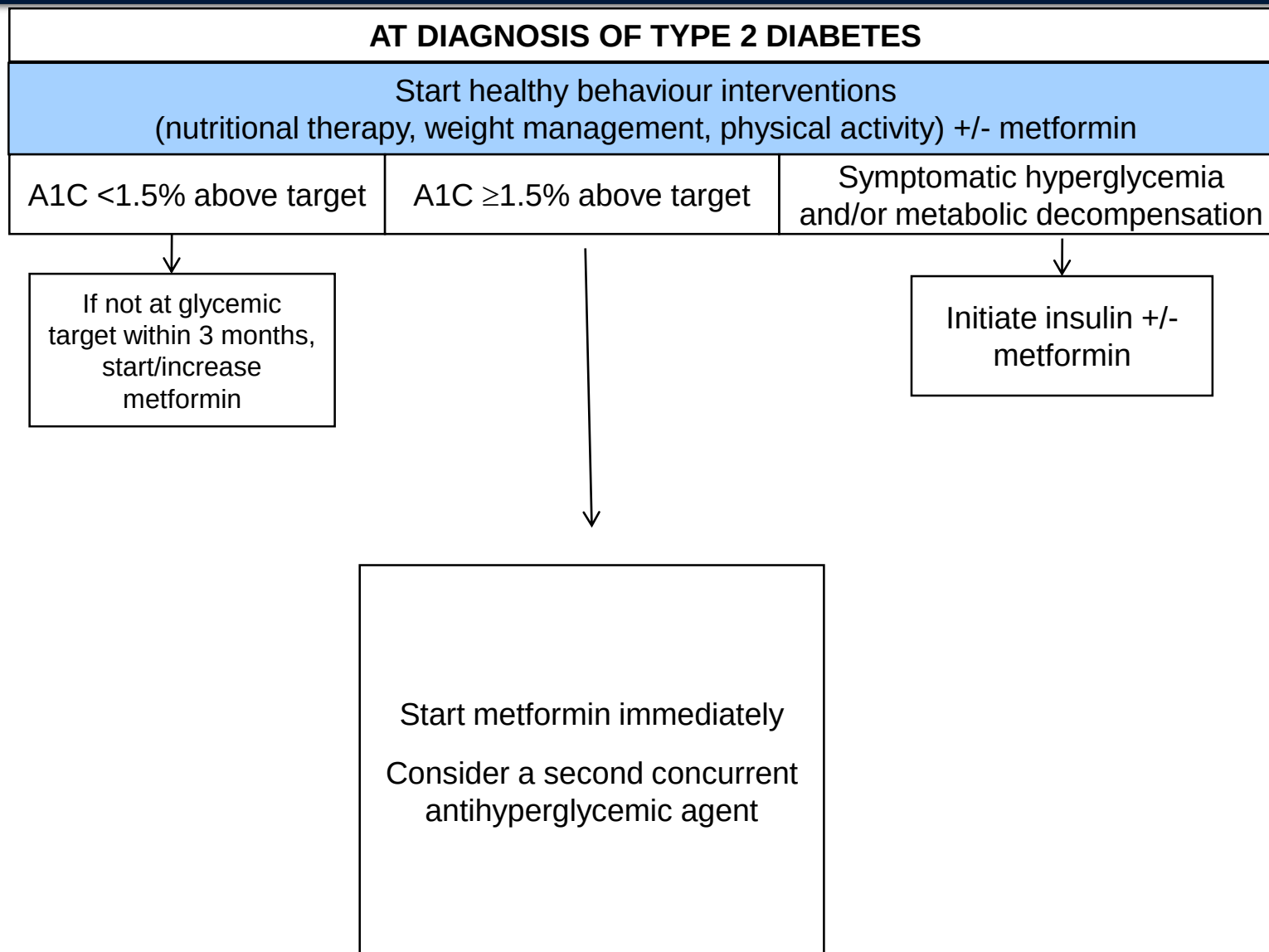
Category/Name of Insulin
Ultra Rapid-Acting
Fiasp [®] —insulin aspart
Rapid-Acting
Insulin Lispro
Insulin Aspart
Insulin Glulisine
Technosphere insulin
Short-Acting
Regular Human
Intermediate-Acting
NPH Human
Long-Acting
Insulin Detemir
Insulin Glargine
Insulin Degludec
Insulin Mixtures
NPH/Regular (70%/30%)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

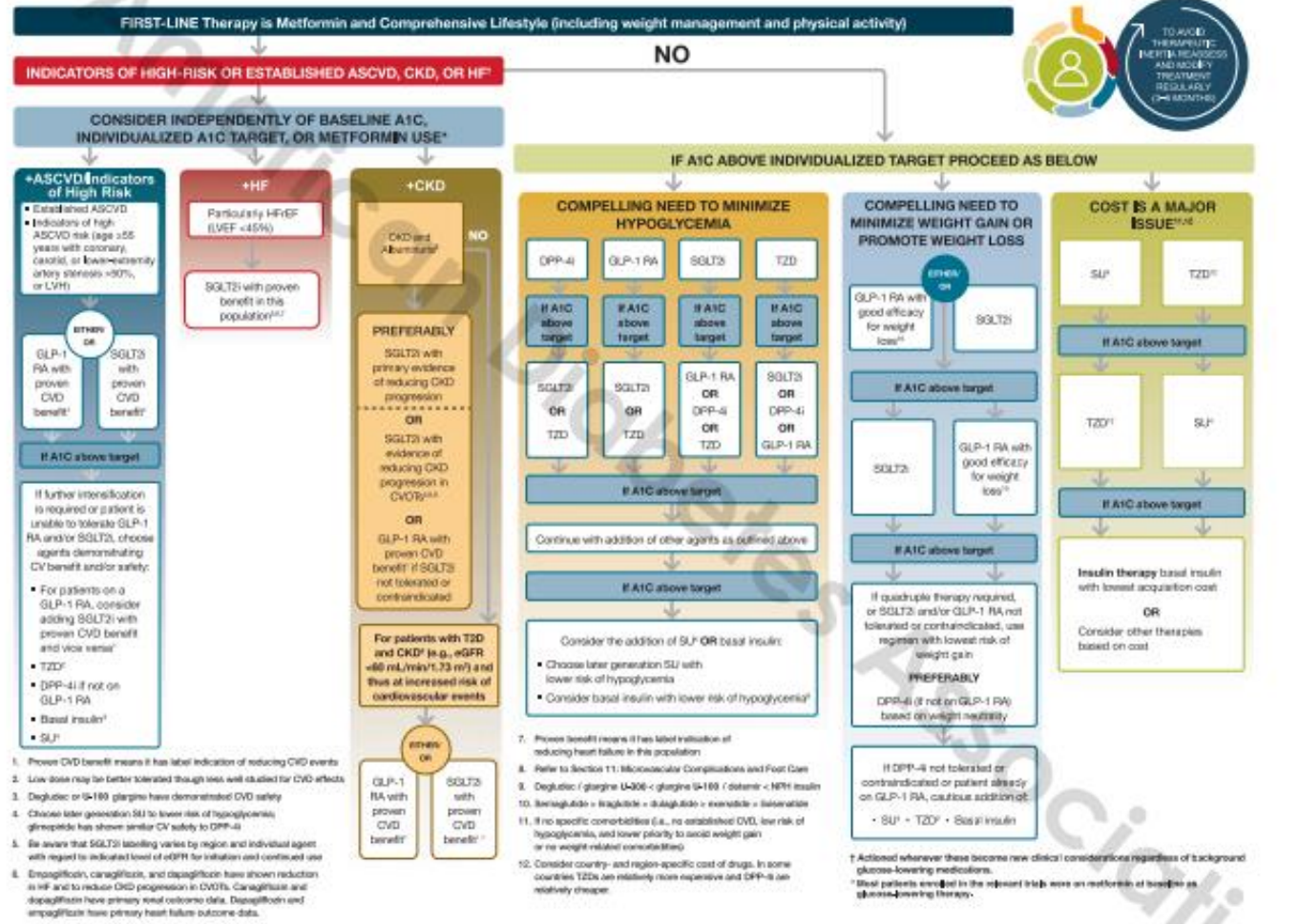


The glycemic management in type 2 Diabetes



HEALTHY BEHAVIOUR INTERVENTIONS







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

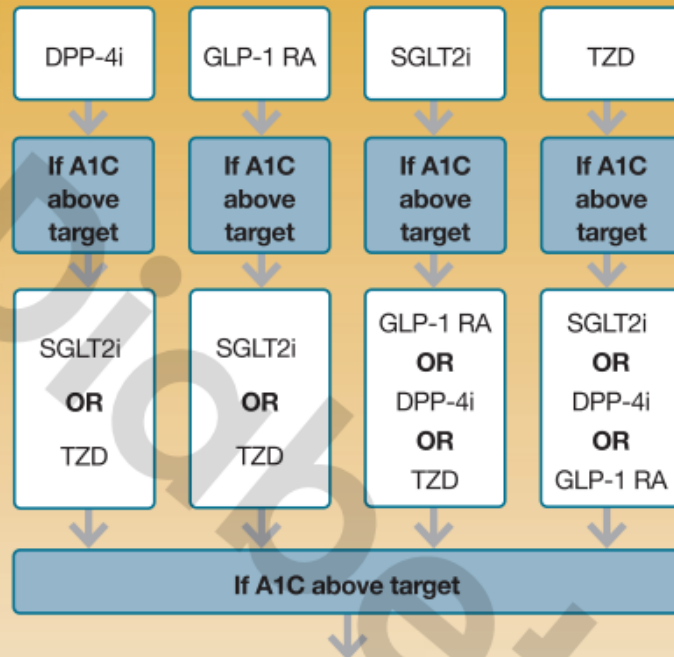
INDICATORS OF HIGH-RISK OR ESTABLISHED ASCVD, CKD, OR HF¹

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**



If A1C above target

Continue with addition of other agents as outlined above

If A1C above target

Consider the addition of SU⁴ **OR** basal insulin:

- Choose later generation SU with lower risk of hypoglycemia
- Consider basal insulin with lower risk of hypoglycemia⁹



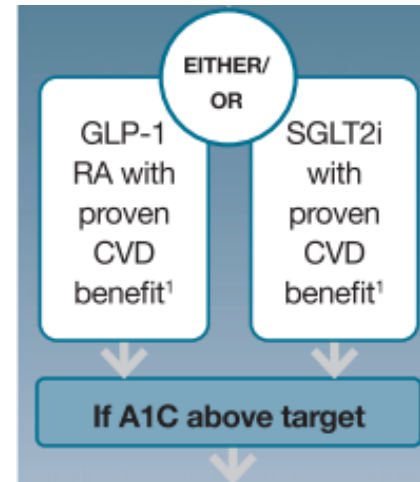
FIRST-LINE Therapy is Metformin and Comprehensive Lifestyle (including weight management and physical activity)

INDICATORS OF HIGH-RISK OR ESTABLISHED ASCVD, CKD, OR HF¹

CONSIDER INDEPENDENTLY OF BASELINE A1C,
INDIVIDUALIZED A1C TARGET, OR METFORMIN USE²

+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)



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 versa¹
- TZD²
- DPP-4i if not on GLP-1 RA
- Basal insulin³
- SU⁴





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

INDICATORS OF HIGH-RISK OR ESTABLISHED ASCVD, CKD, OR HF¹

**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}

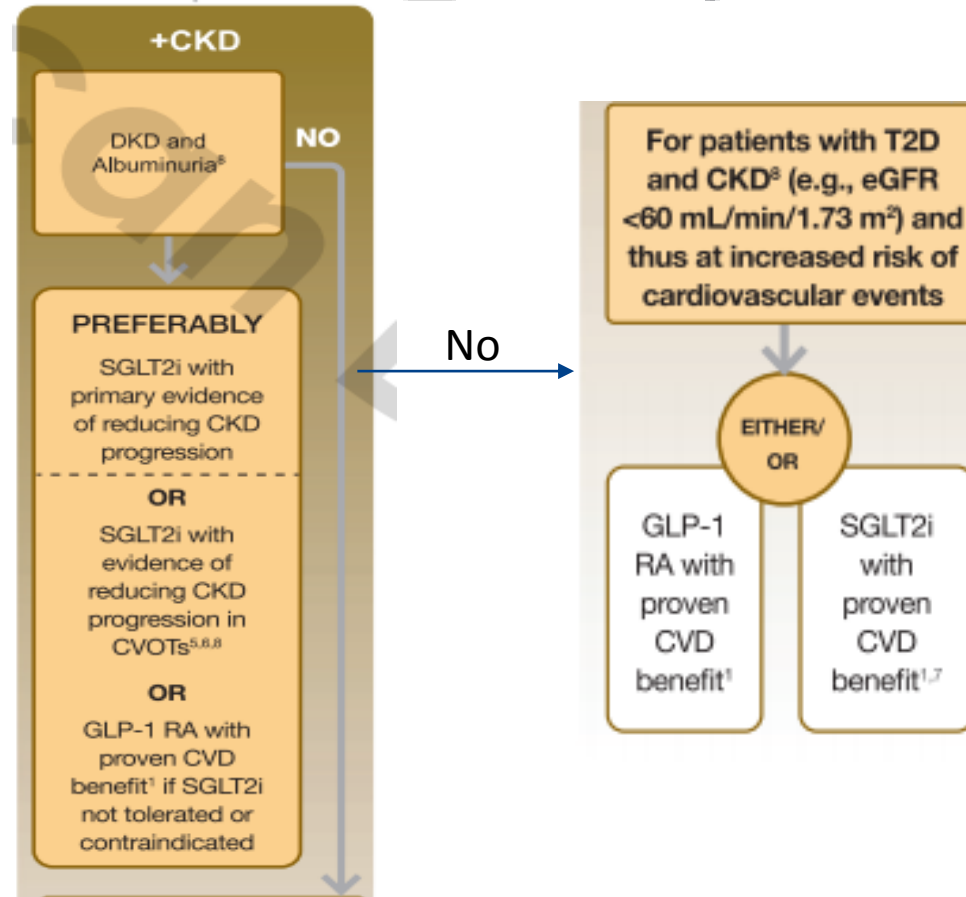




FIRST-LINE Therapy is Metformin and Comprehensive Lifestyle (including weight management and physical activity)

INDICATORS OF HIGH-RISK OR ESTABLISHED ASCVD, CKD, OR HF¹

CONSIDER INDEPENDENTLY OF BASELINE A1C,
INDIVIDUALIZED A1C TARGET, OR METFORMIN USE⁴





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

NO

IF A1C ABOVE INDIVIDUALIZED TARGET PROCEED AS BELOW

**COMPELLING NEED TO
MINIMIZE WEIGHT GAIN OR
PROMOTE WEIGHT LOSS**

**EITHER/
OR**

GLP-1 RA with
good efficacy
for weight
loss¹⁰

SGLT2i

If A1C above target

SGLT2i

GLP-1 RA with
good efficacy
for weight
loss¹⁰

If A1C above target

If quadruple therapy required,
or SGLT2i and/or GLP-1 RA not
tolerated or contraindicated, use
regimen with lowest risk of
weight gain

PREFERABLY

DPP-4i (if not on GLP-1 RA)
based on weight neutrality

If DPP-4i not tolerated or
contraindicated or patient already
on GLP-1 RA, cautious addition of:

• SU⁴ • TZD² • Basal insulin





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}

SU⁴

TZD¹²

If A1C above target

TZD¹²

SU⁴

If A1C above target

Insulin therapy basal insulin
with lowest acquisition cost

OR

Consider other therapies
based on cost



