Diabetes mellitus

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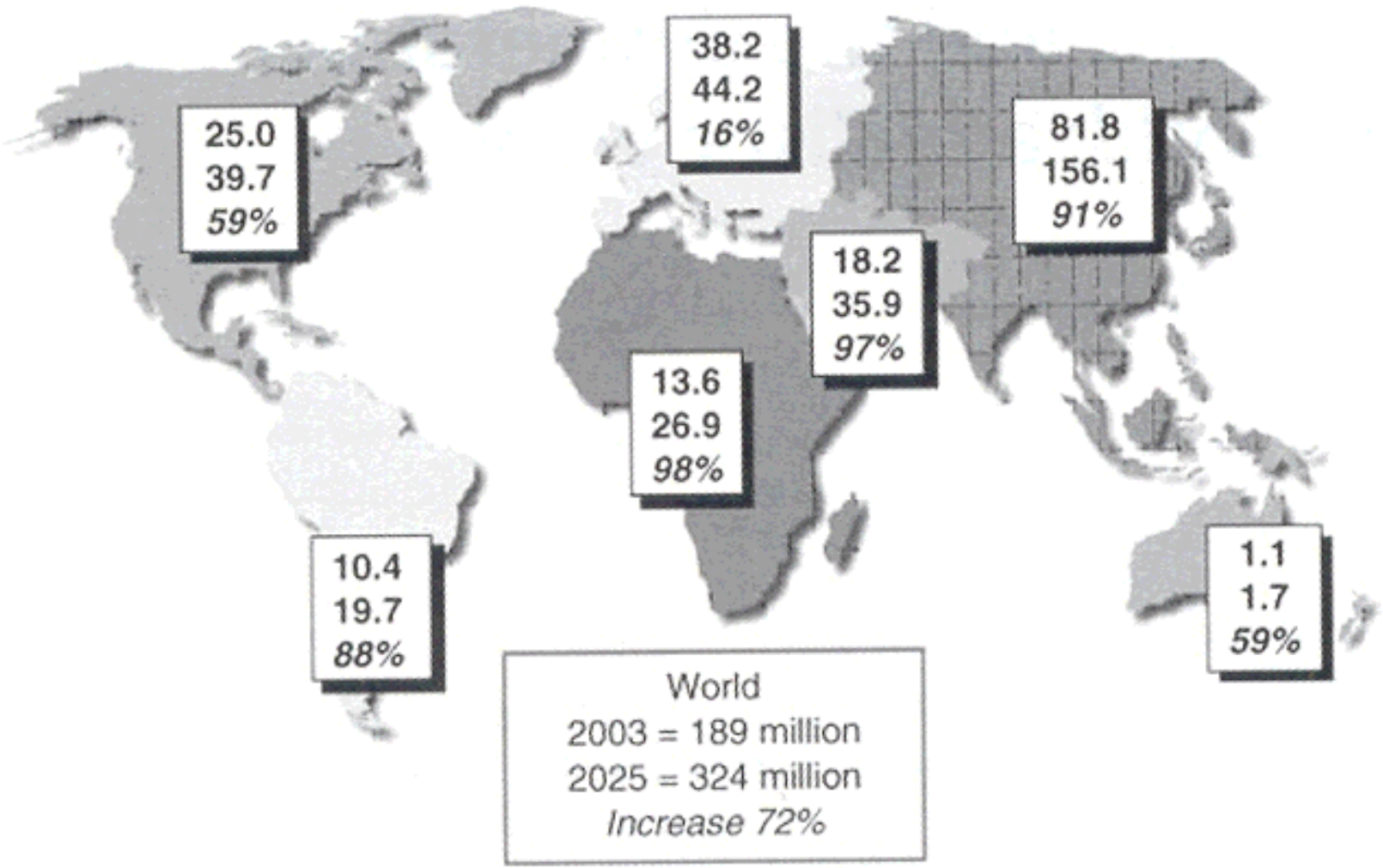
- The most frequent metabolic disease
- Relative or absolute insufficiency of insulin
- Hyperglycaemia

- The most frequent cause of blidness
- The most frequent cause of amputation of lower extremities
- 40 % patients on chronic dialysis



- Zimmet,P.: Preventing type 2 diabetes and dysmetabolic syndrome in the real word: a realistic view, Diabetic Medicine, 20, 2003

Classification of Diabetes

- Type 1 diabetes mellitus
- Type 2 diabetes mellitus
- Gestational diabetes mellitus
- Specific types of diabetes due to other causes

Other specific types

- Genetic defects
- Disease of the exocrine pancreas
- Endocrinopathies
- Infections

- Drug – or chemical – induced diabetes (glucocorticoids)
- Uncomon forms

- **Type 1 DM**

- an absolute insulin deficiency

- a) immune-mediated (95%)
- b) idiopathic (mostly African or Asian ancestry)

- **Type 2 DM**

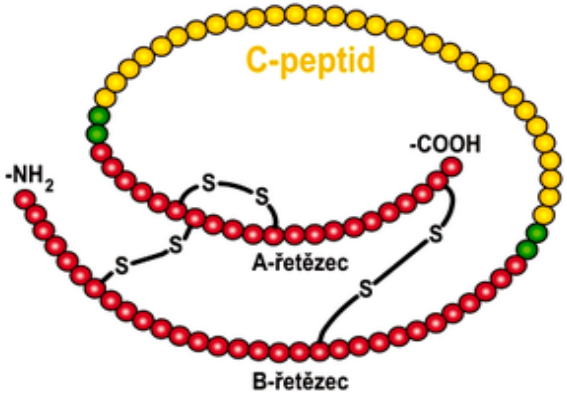
- a relative insulin deficiency

- a) predominantly insulin resistance (Latinos)
- b) predominantly an insulin secretory defect (East Asians)

Type 1 Diabetes mellitus

- 6 % of all diabetics
- mostly immune-mediated (autimmune destruction of beta-cells - insulitis) – in 96%
  - presence of antibodies: anti-GAD (glutamic acid decarboxylase), anti IA-2 (tyrosine phosphatase), antibodies to islet cells
  - strong HLA associations with DQA and DQB genes

  - low C-peptide levels
  - low genetic predisposition (probability: 5 % in DM1 women, 8 % in DM1 men)



- **C-peptid**
  - part of **proinsulin**
  - its concentration tells us about the amount of production of insulin

Risk factors – Type 1 DM

- Respiratory viruses ?
- Enteroviruses ?

- Casein of cow milk ?

Type 2 Diabetes mellitus

- 94 % of all diabetics
  - heterogenous and multigenous
  - monogenous only in a very small percent
  - + changes in life-style („coca - colonization“, „pandemic“)
  - strong genetic predisposition (probability: one parent – 50 %, both parents – 100 %)

Diabetes mellitus typ 2

- a) insulin resistance (muscle, liver, fat)
- b) an insulin secretory defect
- c) progressively declining of beta-cell mass - declining of function of pancreas)

  - GIT: incretin deficiency and/or resistance
  - Pancreas: hyperglucagonemia
  - Kidneys: enhanced glucose reabsorption
  - CNS: insulin resistance

Risk Factors – Type 2 DM

- strong familial aggregation
- age
- obesity
- physical inactivity
- racial and ethnic subgroups (Native American, Polynesian, Micronesian, Asian-Indian, Hispanic, Afro-American)

Diagnosis of DM

- fasting plasma glucose level (FPG) - 7,0 mmol/l or more
- 2 – hour postload plasma glucose level or casual plasma glucose level - 11,1 mmol/l or more

- without clinical symptoms - 2x

- Oral Glucose Tolerance Test (oGTT) - Czech
  - 75 g glucose load, usually dissolved in water

Glycosylated/glycated haemoglobin (HbA1C)

- fusion glucose + haemoglobin (….compensation of DM for last 6- 8 weeks..)
-
- in some countries – dg of DM (only adult populations, 6.5 % and more - by DCCT – US, Europe: 48 mmol/mol and more …)

- in all countries – compensation of DM

Prediabetes…..

microvascular complications - 7 mmol/l (fasting)
macrovascular complications - 6 mmol/l (fasting)

Prediabetes („people with high risk of developing diabetes“)

- **1) Impaired glucose tolerance (IGT)**
  - 7,8 – 11,0 mmol/l postprandial (2-hour postload)
  - *independent risk factor for ischemic heart disease*
- **2) Impaired fasting glucose (IFG)**
  - 5,6 - 6,9 mmol/l fasting

3) Glyk. Hb 5.7-6.4 % (USA)…39-47 mmol/mol in Europe

Symptomatology of Type 1 Diabetes

- beginning is quick (hours, dayes)
- thirst, increasing urination, fatigue
- hyperglycaemia, ketoacidosis, thirst, fatigue, coma….

Symptomatology of Type 2 Diabetes

- very often without any problems (many years…)
- finding the complications (skin, kidney, eyes, neuropathy..)

- can be thirst, increasing urination, fatigue
- hyperglycaemia, mostly without ketoacidosis

Screening for Type 2 DM and prediabetes

- In all adults who are overweight (BMI 25 kg/m^2 or more) and have additional risk factors in any time:
  - physical inactivity, first-degree relative with diabetes, members of high-risk ethnic population, women with GDM or PCOS or who delivered a baby weighing more than 9 lb (?), subjects with IGT or/and IFG, subjects with hypertension, dyslipidemia or history of CVD

Screening for Type 2 DM and prediabetes

- In the absence of these criteria, testing should begin at age 40 (30…35?) years

- Testing should be repeated at 1-3 years intervals

GDM (Gestational diabetes mellitus) – in Czech

- In the first three months
  - at every pregnant women – normal fasting plasma glucose level (FPG) - less than 5,0 mmol/l
  - fasting plasma glucose level (FPG) 5,1-6,9 mmol/l – GDM
  - fasting plasma glucose level (FPG) ≥ 7 mmol/l or HbA1c ≥ 48 mmol/mol - DM

  - No clear result → oGTT

GDM
(Gestational diabetes mellitus)

- In 24-28 week of pregnancy
  - at every woman oGTT
  - (dg:
    - fasting plasma glucose level (FPG)
      - 5,1 mmol/l and more
      - after 1. hour - 10,0 mmol/l and more
      - after 2. hour - 8,5 mmol/l and more)

GDM (Gestational diabetes mellitus) Treatment

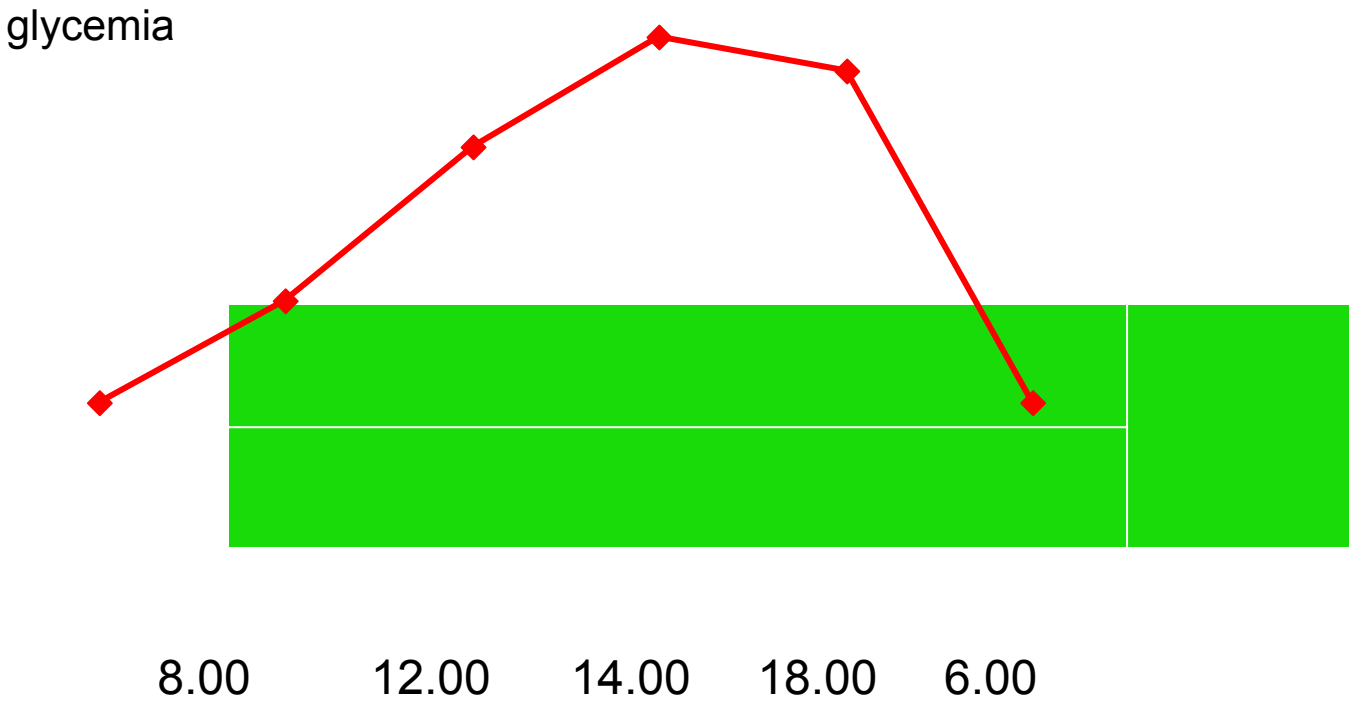
- 80 % lifestyle intervention
- 20 % - + metformin
- - + insulin (does not cross placenta)
- (- + glibenclamid in US ?)

Long therapy with glucocorticoids - drug or chemical – induced diabetes (glucocorticoids)

- there are problems with regulation of glucose in all patients
- almost 25 % (4-44 %) patients develop DM
- there is worsening of glucose in diabetics

- level of glycaemia starts to increase 4-6 hours after application of glucocorticoids and lasts about 12 hours
  - the highest levels of glucose are in the afternoon and in the evening
  - the lowest levels of glucose are during the night and in the morning

Drug – or chemical – induced diabetes (glucocorticoids)



PS-PP
IHOK

- Increasing of previous medications
- Insulin – the highest levels at noon, the lowest at night (in the evening)…..

Short acting insulin: 6 IU – 12 IU – 4 IU

The high levels of glucose should continue several dayes after termination of therapy with glucocorticoids

Treatment of patients with Diabetes Mellitus

- Management of Hyperglycemia in Type 2 Diabetes: A Patient-Centered Approach (Position Statement of ADA and EASD): Inzucchi, Bergenstal, Buse et all., in Diabetes Care, April 2012

- „within the context of the needs, preferences, and tolerances of each patient,
- individualization of treatment is the corneston of success“
- „the synthesis of best available evidence from the literature with the clinician´s expertise and patient´s own inclinations“

Treatment of Type 1 Diabetes

Insulin

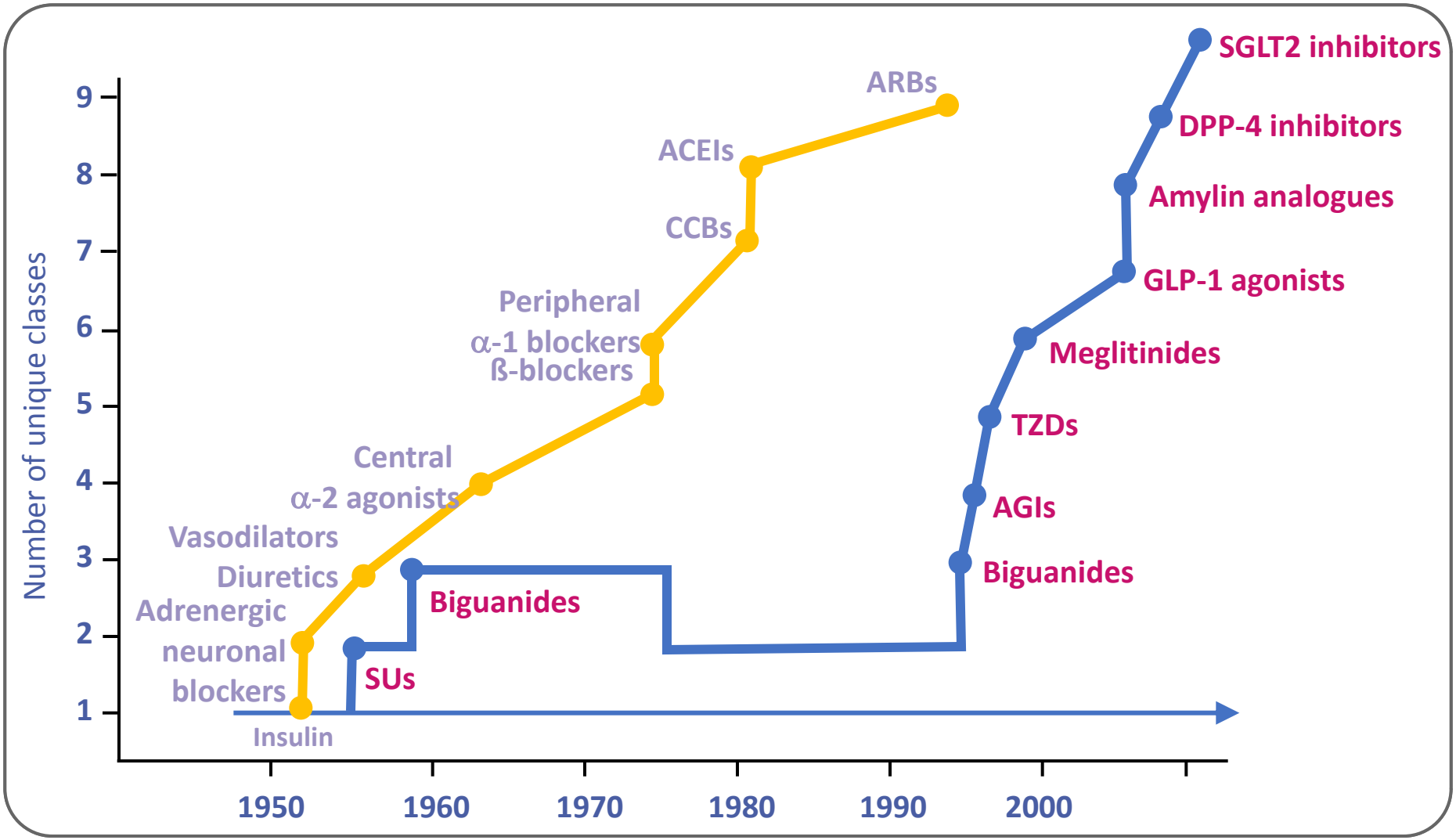
- Insulin
- (+ amylin agonist (pramlintid-inhibition of glucagon secretion and slowing gastric emtying) – in USA
- p.o. antidiabetics – „do not work“ - Europe

Transplantation (pancreas, pankreatic islets)

Treatment of Type 2 Diabetes

- 1) Non – pharmacological (life style intervention)
- 2) Pharmacological (drugs, insulin)
- 3) Surgery + **metabolic** intervention – gastric and intestine operation (gastric banding etc…) - **metabolic surgery**

Antidiabetics



Adapted from: Inzucchi SE in *Clinical Diabetes*, Fonseca VA ed., 2006.

Treatment of Type 2 Diabetes

Biguanides (metformin)

- the main drug for treatment Type 2 DM
- reduces hepatic glucose output and reduces hepatic insulin resistance
- rarely if ever causes hypoglycemia

Prediabetes and metformin

- BMI > 35 kg/m2
- Aged < 60 years
- Women with prior GDM

Metformin – systemic effects

- decreasing of cancers
- pozitive cardiovascular effect
- stimulation of immunity response
- anabolic effect on bone
- pozitive effect on ovulation (PCOSy)
- reduction of weight and waist circumferrence
- pozitive effect on steatosis hepatis
- decreasing of chronnic inflammatory process in a body
- increasing activity of GLP-1
- hypolipidemic acivity
- decreasing aggregability of trombocytes

Treatment of Type 2 Diabetes

Sulphonylureas

- stimulate insulin secretion from beta cells of pankreas – exhaustion of pancreas
- can cause severe hypoglycemia

There are not often used now….

Treatment of Type 2 Diabetes

Thiazolidinediones

- reduce peripheral insulin resistance
- preserve residual function of beta-cells
- can cause heart insufficiency (rosiglitazon)

(only pioglitazon is used….)

„Incretin effect“…

…the insulin response to oral glucose is greater than for i.v. glucose

- Incretins (intestinal hormones) - GLP-1 (glucagon-like peptid):
  - stimulates insulin release from beta-cells
  - without hypoglycaemia
  - slowes gastric emptying (decreases glucose excursion and feeling of hunger)
  - centrally reduces food intake
  - promotes beta cell survival and their regeneration

Treatment of Type 2 Diabetes

Incretin mimetics and enhancers:

GLP-1 (glucagon-like peptid - 1) – receptor agonists

usually s.c. aplication (twice…once daily)

DPP-4 inhibitors (inhibitors of dipeptidyl peptidase-4 – inhibition of enzyme which degrades GLP-1)

p.o. use

Treatment of Type 2 Diabetes

Gliflozins – inhibition of reabsorbtion of glucose from kidney (SGLT2-inhibitors)

- decreasing of increase reabsorbtion of glucose from kidney – DM Type 2
- decreasing of glycaemia, blood pressure and weight

New information: improvement of kidney and heart insufficiency also in non–diabetic people!!

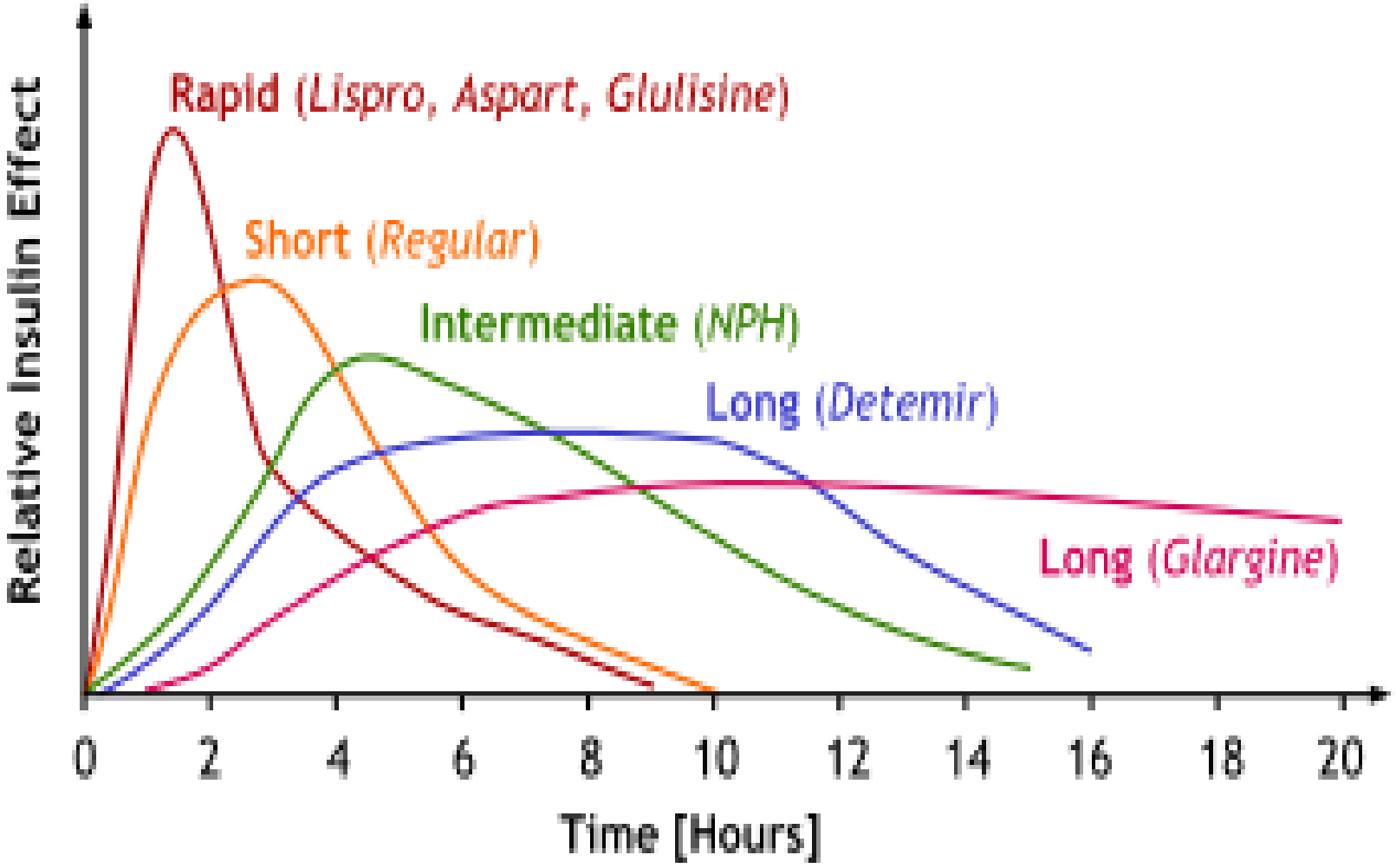
Insulin

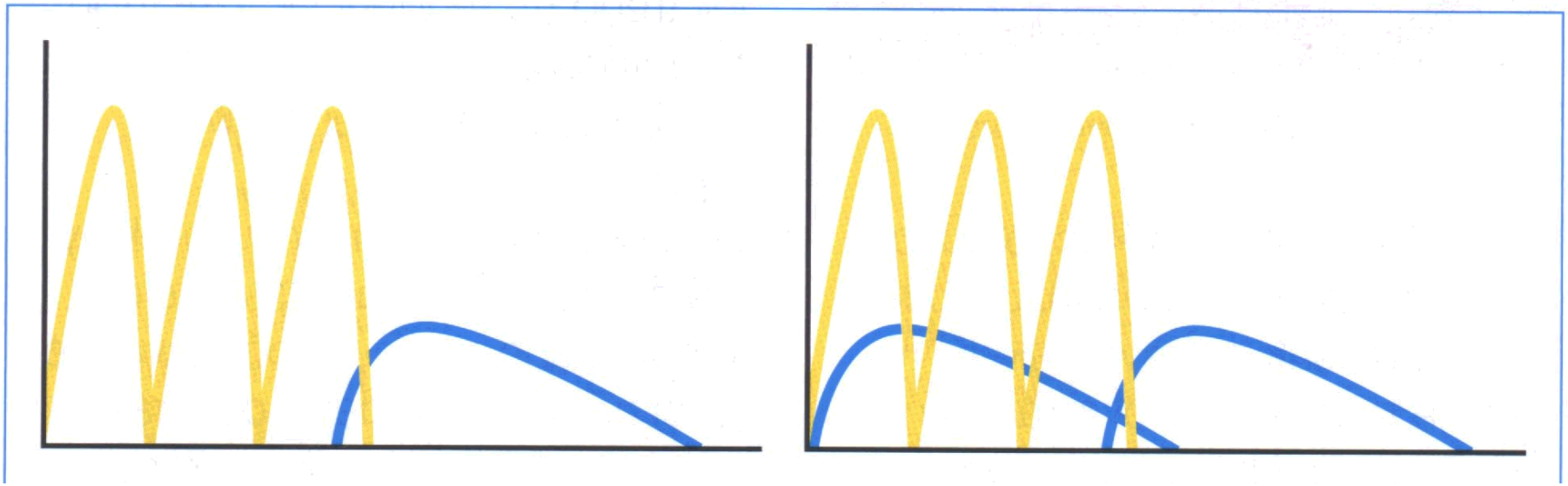
- essential in Type 1 DM (and GDM?)

- Type 2 DM:
- - glucose plasma level more than 15 mmol/l - decompensation of DM
- - acidosis
- - other serious diseases
- - poor compensation of diabetes
- - as a second step

Type of insulin

- Short (acting) human insulin (Regular)
- Rapid (acting) insulin analogues
- Intermediate (acting) human insulin (NPH)
- Long (acting) insulin analogues


Relative Insulin Effect
Rapid (Lispro, Aspart, Glulisine)
Short (Regular)
Intermediate (NPH)
Long (Detemir)
Long (Glargine)
0
2
4
6
8
10
12
14
16
18
20
Time [Hours]



Compensation

- FPG („fasting“ plasma glucose)
- PPG („postprandial“ plasma glucose)
- Glycosylated/glycated haemoglobin (HBA1C)

New information in the past years….

- 1) good compensation of diabetes at the beginning of the disease leads to less complications afterwards („glycemic memory“)

- 2) there are more deaths when we try to have a good compensation of diabetes in patients with long duration of diabetes

Glycemic targets

Glycosylated/glycated haemoglobin (HbA1C) up to 45 mmol/mol at the beginning of the disease, long life expectancy, no CVD

Glycosylated/glycated haemoglobin (HbA1C) up to 60 mmol/mol in people with complications of diabetes, e. g. severe hypoglycemia

(Glycosylated/glycated haemoglobin more than 53 mmol/mol (7 % DCCT) – revise therapy)

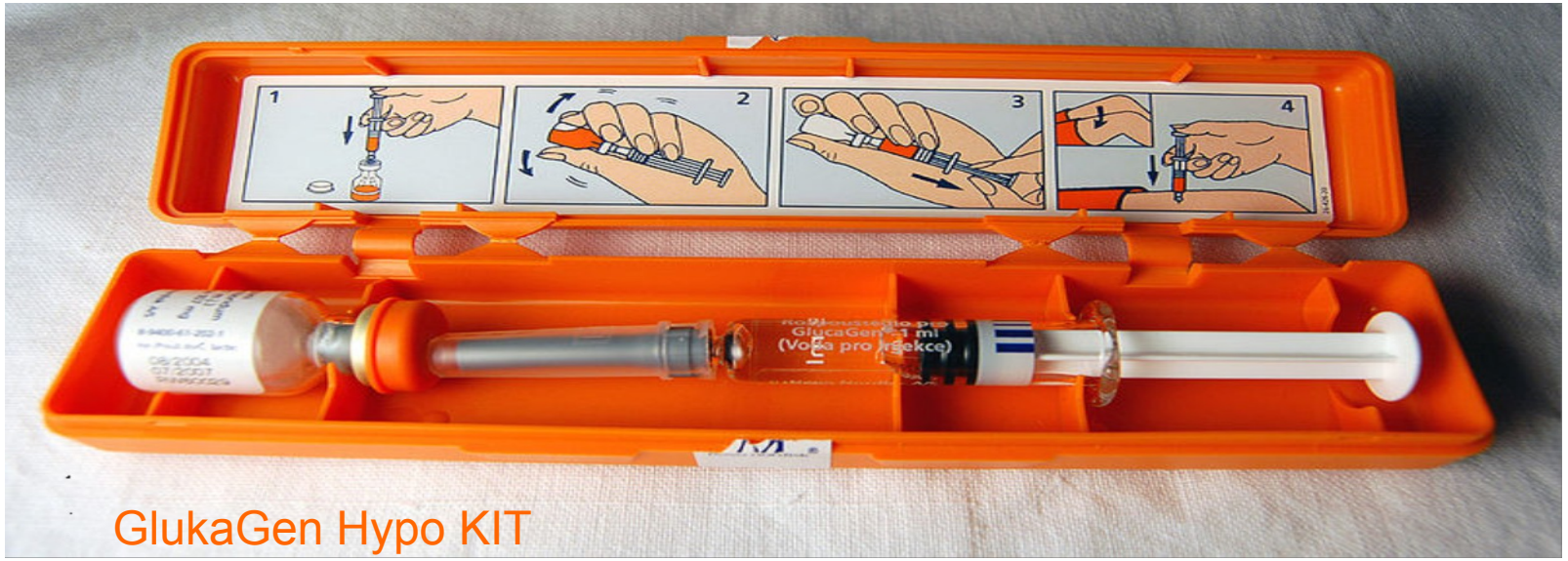
- Blood pressure
- Lipids
- Antiplatelet treatment (??)
- Retinopathy screening
- Micro and macroalbuminuria and function of kidney screening
- Neuropathy screening
- Foot care

Parametr	Kompenzace výborná	Kompenzace uspokojivá	Kompenzace u pac. s vysokým KV rizikem
Glykémie nalačno (mmol/l)	4,0-6,0	6,0-7,0	< 7,0-8,0
Glykémie za 1-2 hod po jídle (mmol/l)	5,0-7,5	7,5-9,0	< 9,0
HbA_1c - glykovaný hemoglobin mmol/mol	< 45	45 - 54	54-60
Celkový cholesterol (mmol/l)	do 4,5?		
HDL - cholesterol (mmol/l)	>1,1		
LDL - cholesterol (mmol/l)	**2,5 – 1,8**		**1,4 - 1,8**
Triglyceridy (mmol/l)	< 1,7		
Krevní tlak (mm Hg)	< 130/80		< do 140/90
Hmotnostní index BMI (body mass index) (kg/ m^2) muži	21 - 25	25 - 27	
Hmotnostní index BMI (body mass index) (kg/ m^2) ženy	20 - 24	24 - 26	

Acute complications

- acute life threatening - coma
- HYPOGLYCAEMIA
- HYPERGLYCAEMIA:
  1. Hyperglycaemic ketoacidotic coma
  2. Hyperglycaemic hyperosmolary coma
  3. Laktacidotic coma

Glukagon



GlukaGen Hypo KIT

Powder…talc….


NDC 0002-6145-02
baqsimi™
(glucagon) nasal powder
3 mg
For Treatment of Severe Low Blood Sugar
For Nasal Use Only
Contains 1 dose
Rx only
www.baqsimi.com
Lilly
NDC 0002-6145-01
baqsimi™
(glucagon) nasal powder
3 mg
For Nasal Use Only
Rx only

Specific chronic complications

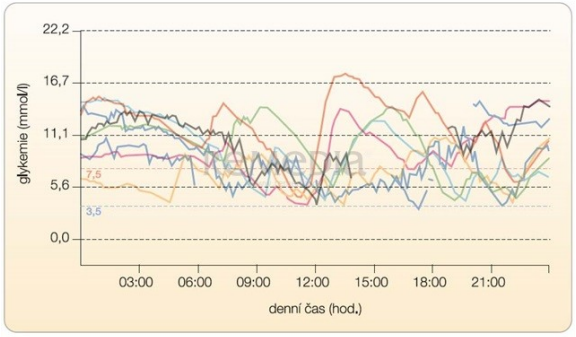
1. Diabetic nephropathy
2. Diabetic retinopathy
3. Diabetic polyneuropathy
4. „Diabetic foot“ (neuropathy + vascular disease)
5. Diabetic osteoartropathy

Measurement of blood glucose

- SMBG (Self Monitoring Blood Glucose)
- CGM (Continual Glucose Monitoring)
- FGM (Flash Glucose Monitoring)

SMBG

CGM


22,2
16,7
11,1
7,5
5,6
3,5
0,0
glykemie (mmol/l)
03:00
06:00
09:00
12:00
15:00
18:00
21:00
denní čas (hod.)

FGM

How to use the FreeStyle Libre System

The FreeStyle Libre system utilises advanced technology that is easy to use.

1 Apply sensor with applicator

- A thin flexible sterile fibre (5mm long) is inserted just below the skin. Most people reported that applying the sensor was painless[5]
- The 14-day sensor stays on the back of your upper arm and automatically captures glucose readings day and night.
- The sensor is water resistant and can be worn while bathing, swimming and exercising[7]

[5]Most people did not feel any discomfort while applying or wearing the FreeStyle Libre Sensor. In a 2013 US study conducted by Abbott Diabetes Care, 100% of patients surveyed (n=30) rated that applying the sensor was painless or almost painless, and 93.4% of patients strongly agree or agree that while wearing the sensor, they did not feel any discomfort under their skin. Data on file. [7] Sensor is water-resistant in up to 1 metre (3 feet) of water for a maximum of 30 minutes

How to use the FreeStyle Libre System

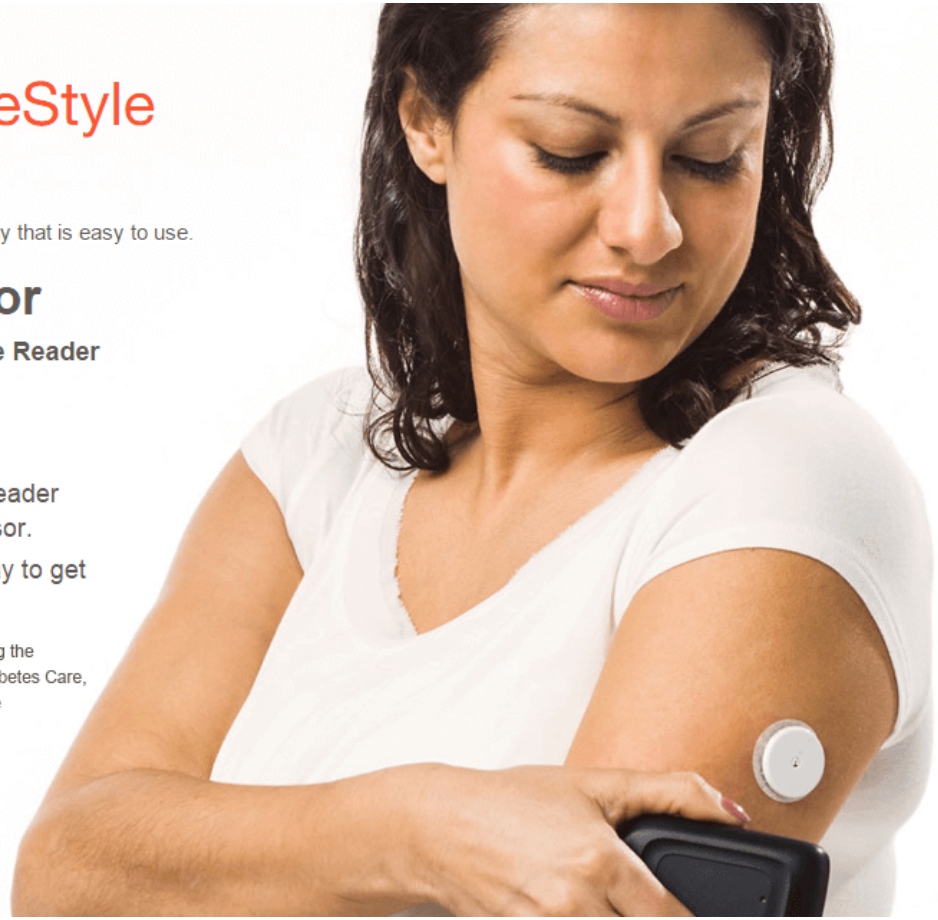
The FreeStyle Libre system utilises advanced technology that is easy to use.

2 Scan sensor

using FreeStyle Libre Reader

- To get a reading, bring the FreeStyle Libre reader close to the sensor and scan it over the sensor.
- A painless[9], 1 second scan offers an easy way to get your glucose reading even through clothing.

[9]Most people did not feel any discomfort under the skin while wearing the FreeStyle Libre sensor. In a 2013 US study conducted by Abbott Diabetes Care, 93.4% of patients surveyed (n=30) strongly agree or agree that while wearing the sensor, they did not feel any discomfort under their skin. Data on file.



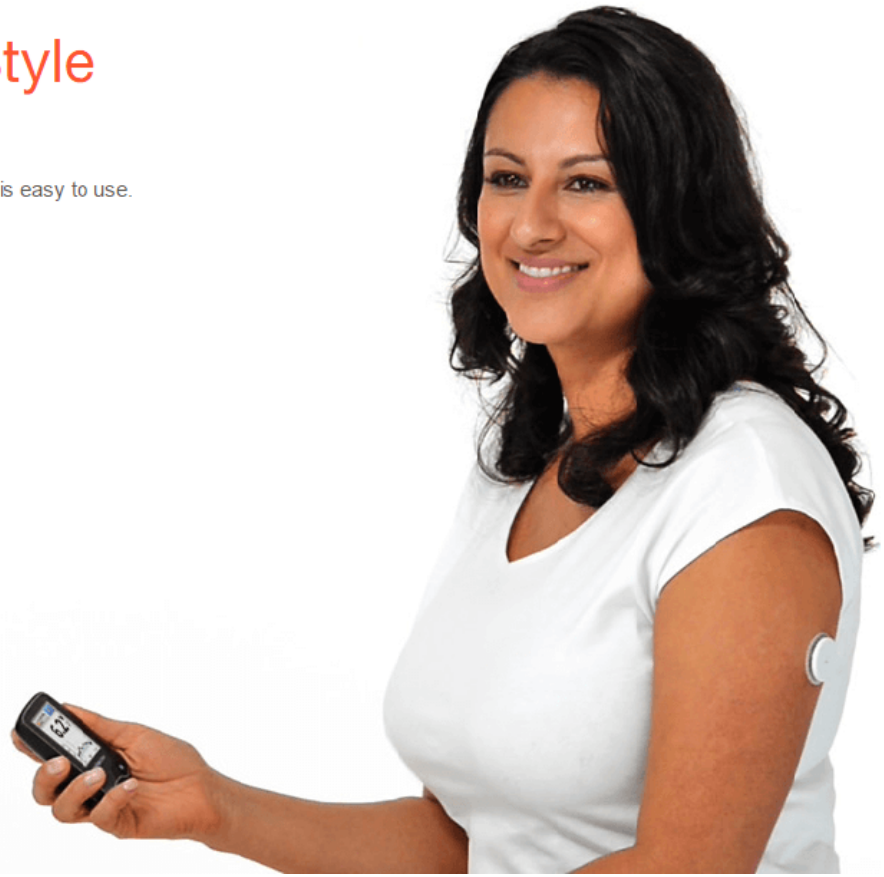
How to use the FreeStyle Libre System

The FreeStyle Libre system utilises advanced technology that is easy to use.

3 Get reading

on the reader

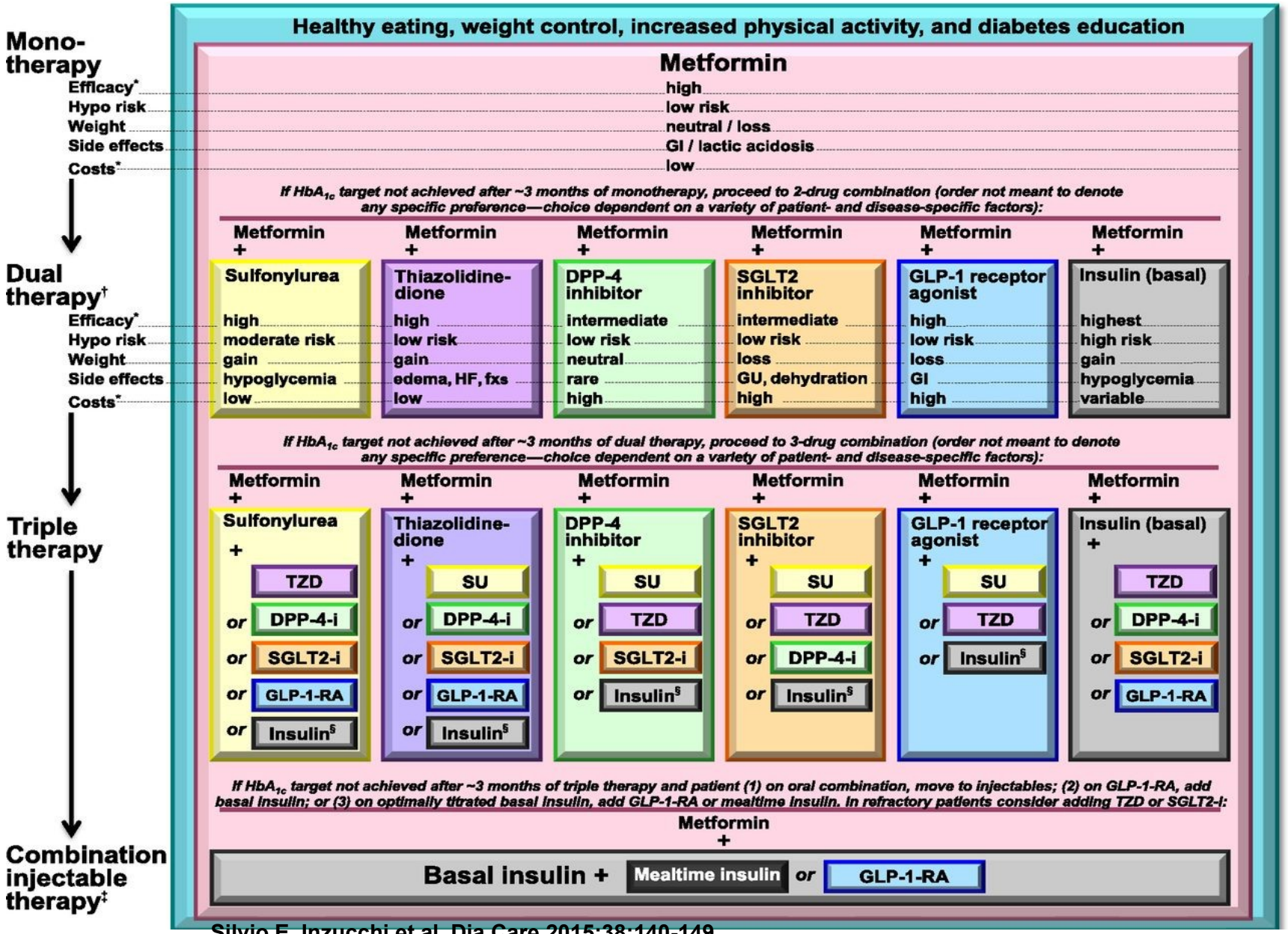
- Get your glucose reading anytime, anywhere
- With every painless 1 second scan you get:
  - Current glucose reading
  - Trend arrow – where your glucose is heading
  - 8 hour glucose history



Treatment of DM type 2 (ADA + EASD from 2015)

- 1) life style intervention + metformin (only highly motivated patients with glyk. Hb near target at diagnosis could be without farmacotherapy for 3-6 month)

- 2) + insulin
- + sulphonylureas
- + thiazolidindiones
- + incretins
- + SGLT2-inhibitor
- 3) combinations of the above



Silvio E. Inzucchi et al. Dia Care 2015;38:140-149

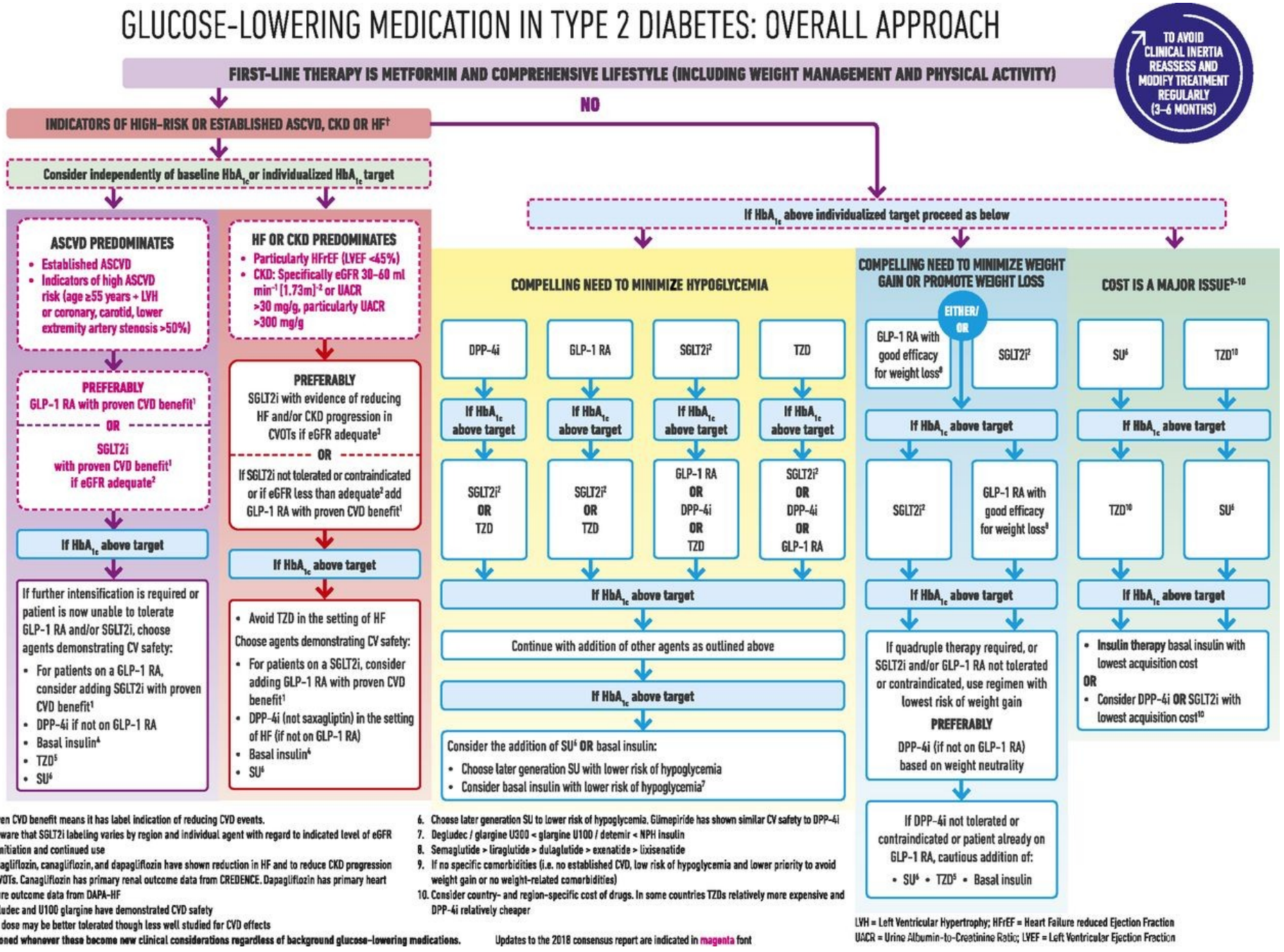
American Diabetes Association.

ADA/EASD (from 2019)

New information: SGLT-2 inhibitors can lead to improvement kidney and heart insufficiency also in non–diabetic people!!

- + GLP-1-rp agonists (liraglutid) or SGLT-2 inhibitors (empagliflozin, canagliflozin, dapagliflozin) in people with CVD or with great risk of development CVD or in people with CKD

GLUCOSE-LOWERING MEDICATION IN TYPE 2 DIABETES: OVERALL APPROACH



1. Proven CVD benefit means it has label indication of reducing CVD events.
2. Be aware that SGLT2i labeling varies by region and individual agent with regard to indicated level of eGFR for initiation and continued use
3. Empagliflozin, canagliflozin, and dapagliflozin have shown reduction in HF and to reduce CKD progression in CVOTs. Canagliflozin has primary renal outcome data from CREDENCE. Dapagliflozin has primary heart failure outcome data from DAPA-HF
4. Degludec and U100 glargine have demonstrated CVD safety
5. Low dose may be better tolerated though less well studied for CVD effects
6. Choose later generation SU to lower risk of hypoglycemia. Glimepiride has shown similar CV safety to DPP-4i
7. Degludec / glargine U300 < glargine U100 / detemir < NPH insulin
8. Semaglutide > liraglutide > dulaglutide > exenatide > lixisenatide
9. If no specific comorbidities (i.e. no established CVD, low risk of hypoglycemia and lower priority to avoid weight gain or no weight-related comorbidities)
10. Consider country- and region-specific cost of drugs. In some countries TZDs relatively more expensive and DPP-4i relatively cheaper

† Actioned whenever these become new clinical considerations regardless of background glucose-lowering medications.

Updates to the 2018 consensus report are indicated in magenta font

LVH = Left Ventricular Hypertrophy; HFrEF = Heart Failure reduced Ejection Fraction
UACR = Urine Albumin-to-Creatinine Ratio; LVEF = Left Ventricular Ejection Fraction

ADA + EASD – 2022

- Individualization of treatment
- Preference of life style-intervention + metabolic surgery
- Preference of using GLP-1-rp analogs or SGLT-2-inhibitors

- Metformin as a first step, but from 2022 we can use as a first step also SGLT2- inhibitor (presence or risk of CVD or CKD),

  or GLP-1-rp analog– liraglutid in people with obesity)

- If we use metformin as a first step, it is recommended to use as a second step GLP-1-rp agonist (liraglutid) or SGLT-2 inhibitor (gliflozin)

Clin Diabetes. 2022;40(1):10–38. doi:10.2337/cd22-as01

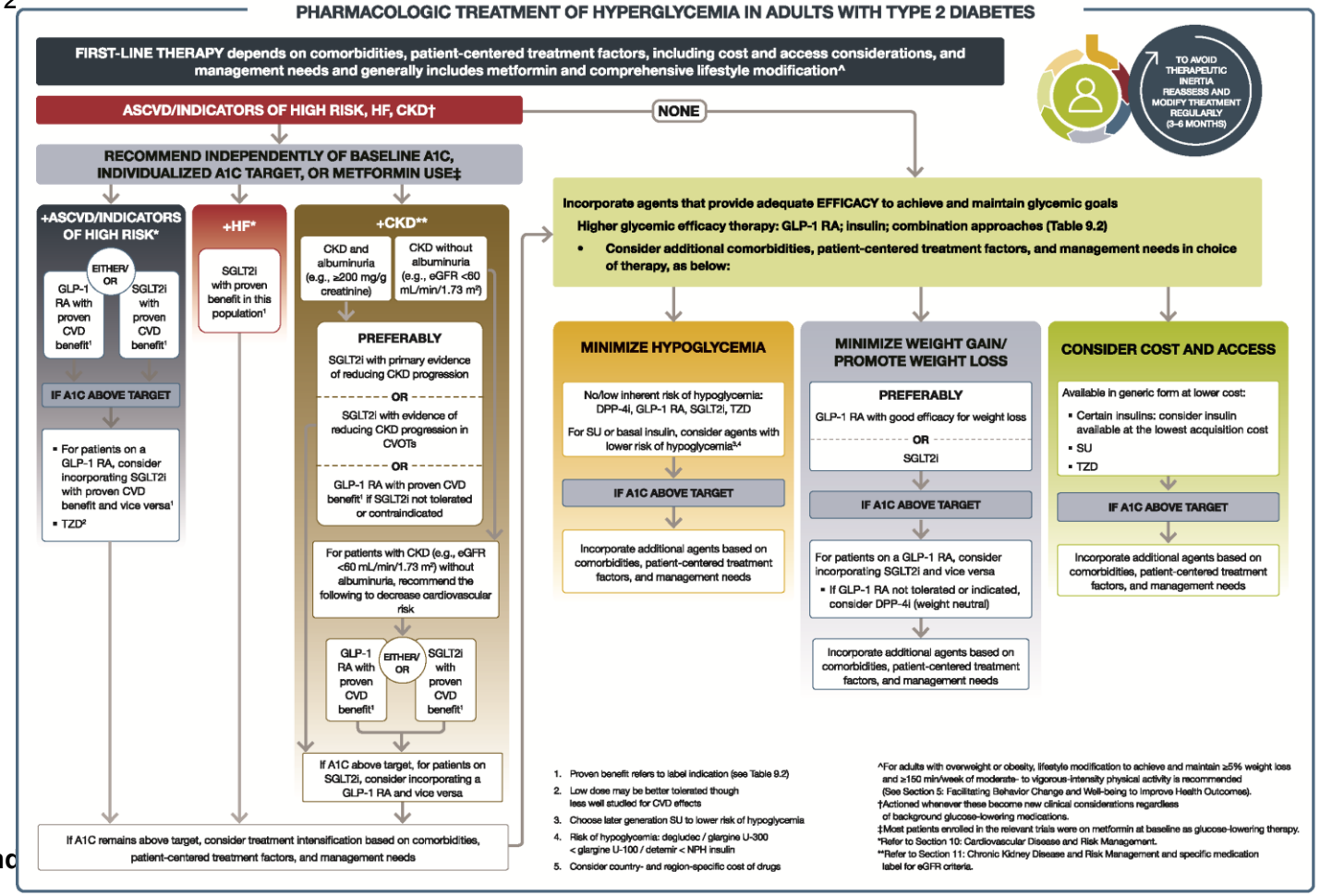


Figure Legend

Pharmacologic treatment of hyperglycemia in adults with type 2 diabetes. 2022 ADA Professional Practice Committee (PPC) adaptation of Davies MJ, D'Alessio DA, Fradkin J, et al. Diabetes Care 2018;41:2669–2701 and Buse JB, Wexler DJ, Tsapas A, et al. Diabetes Care 2020;43:487–493. For appropriate context, see Figure 4.1. The 2022 ADA PPC adaptation emphasizes incorporation of therapy rather than sequential add-on, which may require adjustment of current therapies. Therapeutic regimen should be tailored to comorbidities, patient-centered

Prevention of Type 1 DM

- Insulin
- Nikotinamid
- Imunosupresive therapy (cyclosporin)
    - But none of these exactly works……..

Prevention of Type 2 DM

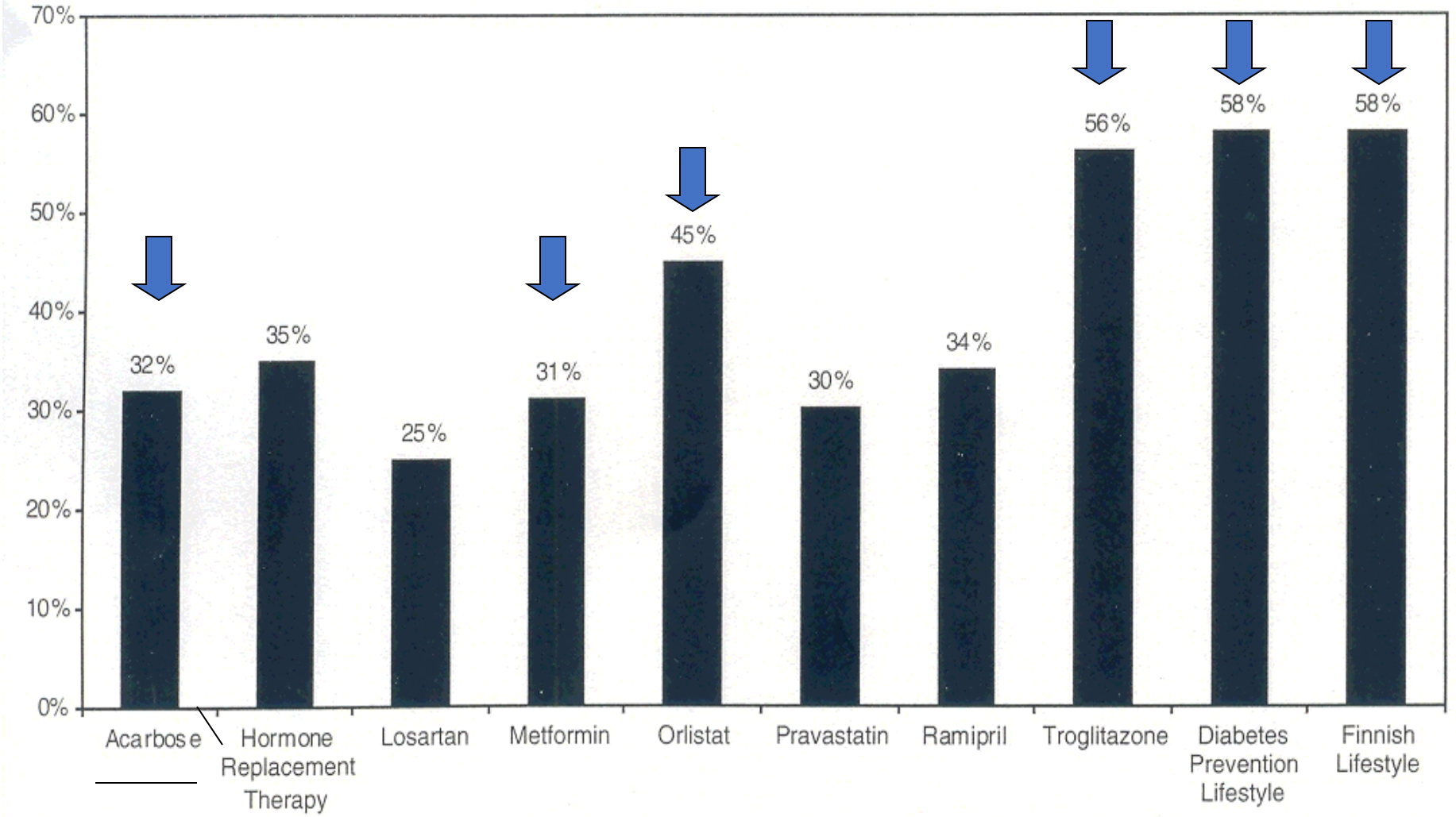
- Life style intervention

- Alfa-glucosidase inhibitors -acarbose
- Metformin
- Thiazolidinediones
- Orlistat

DM and coffee….

- increasing of insulin sensitivity
- includes potassium, magnesium, fibre
- includes antioxidants
- includes polyfenols – Chlorogen- acid – antioxidant + antiinflamatory efect
- includes niacin, B - vitamins B

Prevention/delay of type 2 DM



- Prisant, L.M.:Preventing Type II Diabetes Mellitus. J. Clin. Pharmacol, 44, 2004

FINDRISC (FINnish Diabetes RIsk SCore)

Finnish Diabetes Association

TYPE 2 DIABETES RISK ASSESSMENT FORM

Circle the right alternative and add up your points.

1. Age

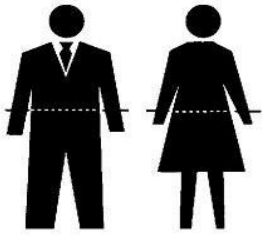
0 p. Under 45 years
2 p. 45–54 years
3 p. 55–64 years
4 p. Over 64 years

2. Body-mass index
(See reverse of form)

0 p. Lower than 25 kg/m²
1 p. 25–30 kg/m²
3 p. Higher than 30 kg/m²

3. Waist circumference measured below the ribs (usually at the level of the navel)

	MEN	WOMEN
0 p.	Less than 94 cm	Less than 80 cm
3 p.	94–102 cm	80–88 cm
4 p.	More than 102 cm	More than 88 cm



4. Do you usually have daily at least 30 minutes of physical activity at work and/or during leisure time (including normal daily activity)?

0 p. Yes
2 p. No

5. How often do you eat vegetables, fruit or berries?

0 p. Every day
1 p. Not every day

6. Have you ever taken medication for high blood pressure on regular basis?

0 p. No
2 p. Yes

7. Have you ever been found to have high blood glucose (eg in a health examination, during an illness, during pregnancy)?

0 p. No
5 p. Yes

8. Have any of the members of your immediate family or other relatives been diagnosed with diabetes (type 1 or type 2)?

0 p. No
3 p. Yes: grandparent, aunt, uncle or first cousin (but no own parent, brother, sister or child)
5 p. Yes: parent, brother, sister or own child

Total Risk Score

☐ **The risk of developing type 2 diabetes within 10 years is**

Lower than 7	**Low:** estimated 1 in 100 will develop disease
7–11	**Slightly elevated:** estimated 1 in 25 will develop disease
12–14	**Moderate:** estimated 1 in 6 will develop disease
15–20	**High:** estimated 1 in 3 will develop disease
Higher than 20	**Very high:** estimated 1 in 2 will develop disease

Please turn over

Test designed by Professor Jaakko Tuomilehto, Department of Public Health, University of Helsinki, and Jaana Lindström, MFS, National Public Health Institute.

Finnish Diabetes Association

WHAT CAN YOU DO TO LOWER YOUR RISK OF DEVELOPING TYPE 2 DIABETES?

You can't do anything about your age or your genetic predisposition. On the other hand, the rest of the factors predisposing to diabetes, such as overweightness, abdominal obesity, sedentary lifestyle, eating habits and smoking, are up to you. Your lifestyle choices can completely prevent type 2 diabetes or at least delay its onset until a much greater age.

If there is diabetes in your family, you should be careful not to put on weight over the years. Growth of the waistline, in particular, increases the risk of diabetes, whereas regular moderate physical activity will lower the risk. You should also pay attention to your diet: take care to eat plenty of fibre-rich cereal products and vegetables every day. Omit excess hard fats from your diet and favour soft vegetable fats.

Early stages of type 2 diabetes seldom cause any symptoms. If you scored 12–14 points in the Risk Test, you would be well advised to seriously consider your physical activity and eating habits and pay attention to your weight, to prevent yourself from developing diabetes. Please contact a public-health nurse or your own doctor for further guidance and tests.

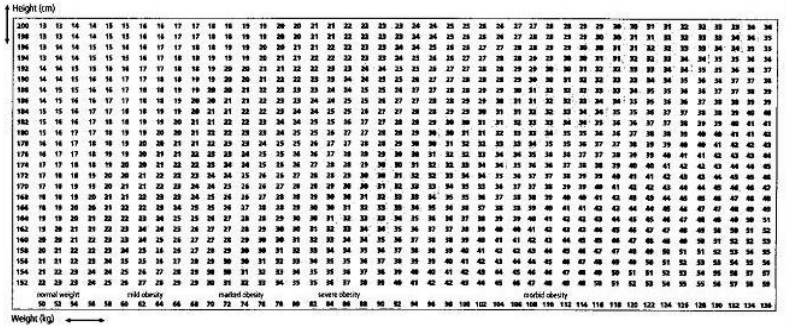
If you scored 15 points or more in the Risk Test, you should have your blood glucose measured (both fasting value and value after a dose of glucose or a meal) to determine if you have diabetes without symptoms.

BODY-MASS INDEX

The body-mass index is used to assess whether a person is normal weight or not. The index is calculated by dividing body weight (kg) by the square of body height (m). For example, if your height is 165 cm and your weight 70 kg, your body-mass index will be 70/(1.65 x 1.65), or 25.7.

If your body-mass index is 25–30, you will benefit from losing weight; at least you should take care that your weight doesn't increase beyond this. If your body-mass index is higher than 30, the adverse health effects of obesity will start to show, and it will be essential to lose weight.

BODY-MASS INDEX CHART




Děkuji vám za pozornost