

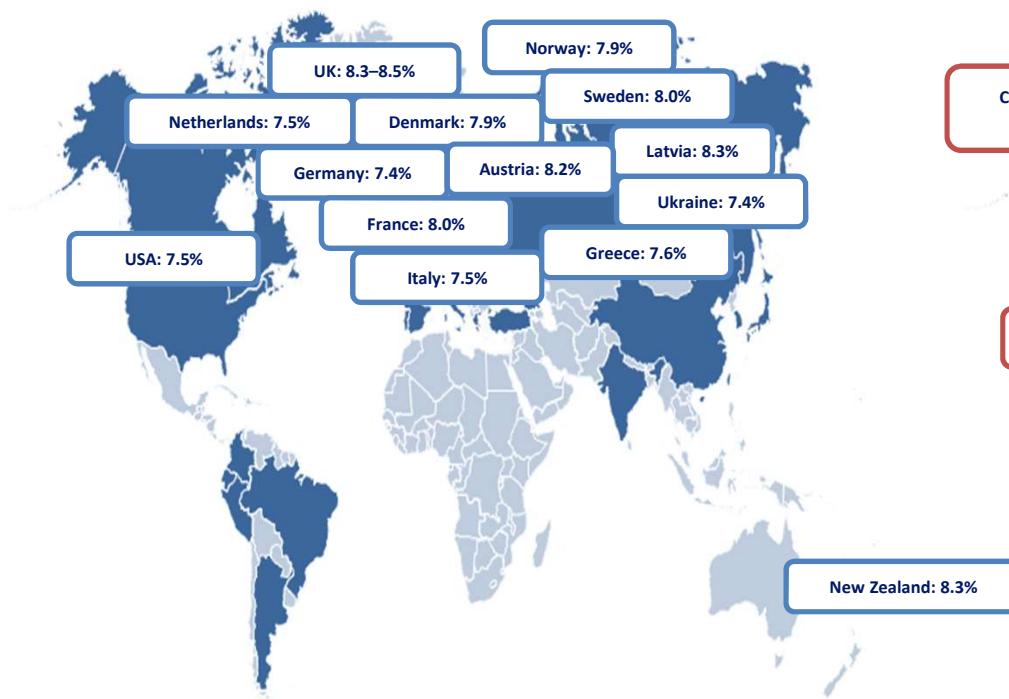
Nieuwe medicatie in de behandeling van Type 2 diabetes Diabetes Liga

Dr Mortzos Nikolaos
Jessa Ziekenhuis

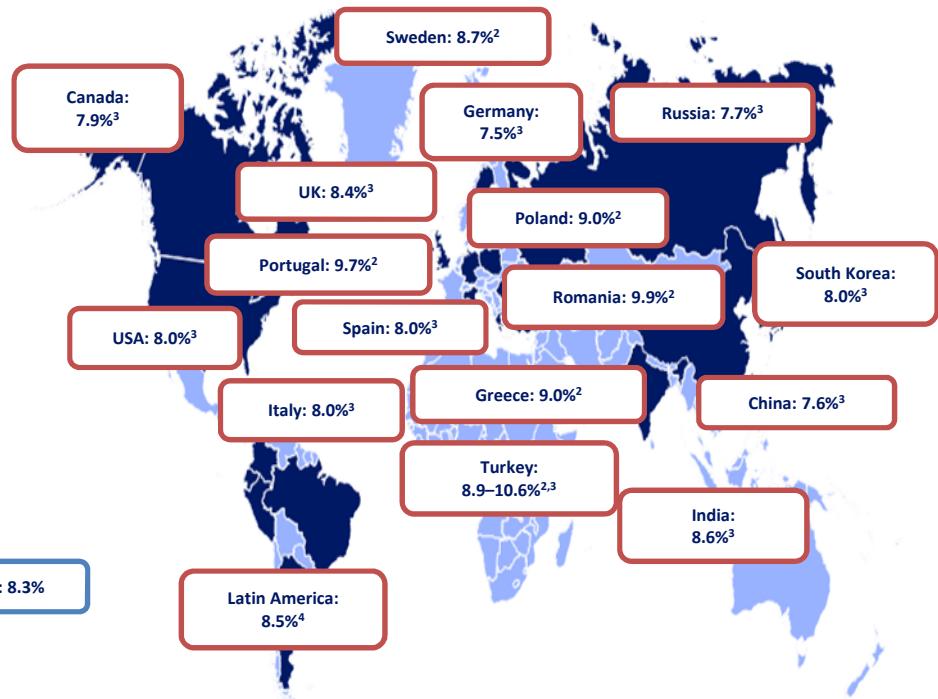
The worldwide challenge of glycaemic control

HbA_{1c} in T1D and T2D

T1D^{1*}



T2D^{2–4}



*Data are median and in adults (25+ years)

T1D, type 1 diabetes; T2D, type 2 diabetes

1. McKnight *et al.* *Diabet Med* 2015;32:1036–50; 2. Oguz *et al.* *Curr Med Res Opin* 2013;29:911–20; 3. Polinski *et al.* *BMC Endocr Disord* 2015;15:46; 4. Mendivil *et al.* *Curr Med Res Opin* 2014;30:1769–76



Diabetes epidemie

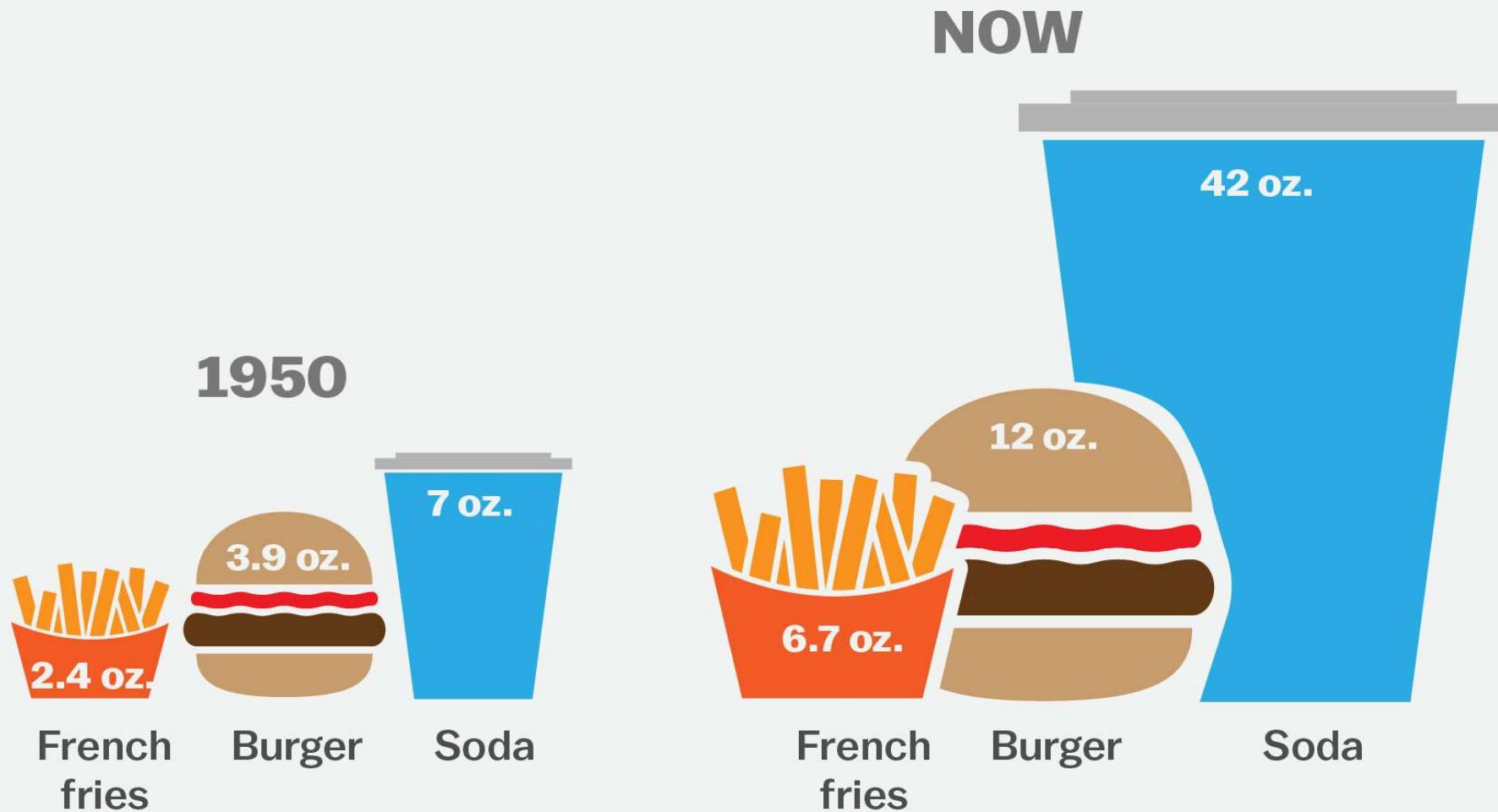
Dieet



Beweging



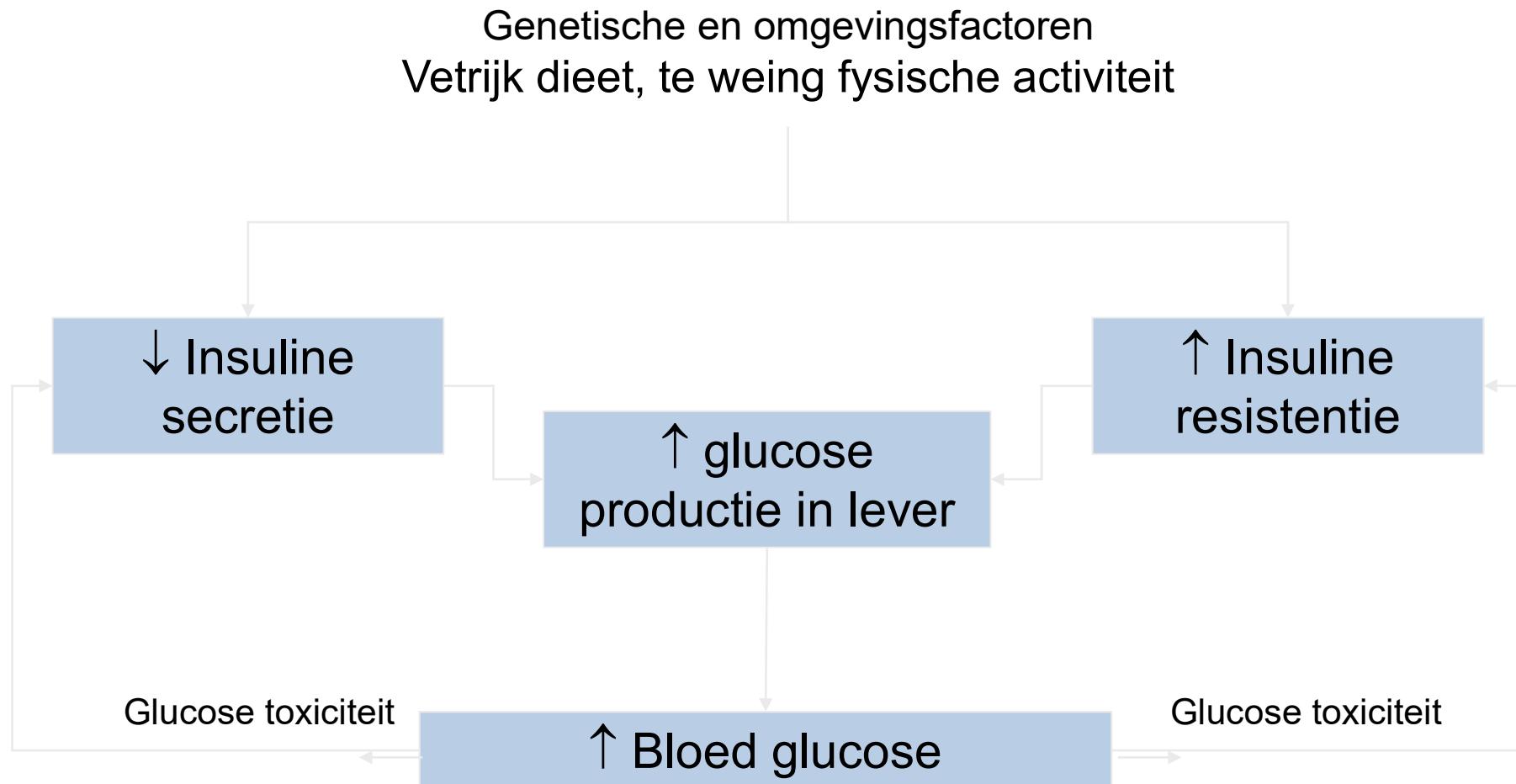
The average restaurant meal today is more than four times larger than in the 1950s



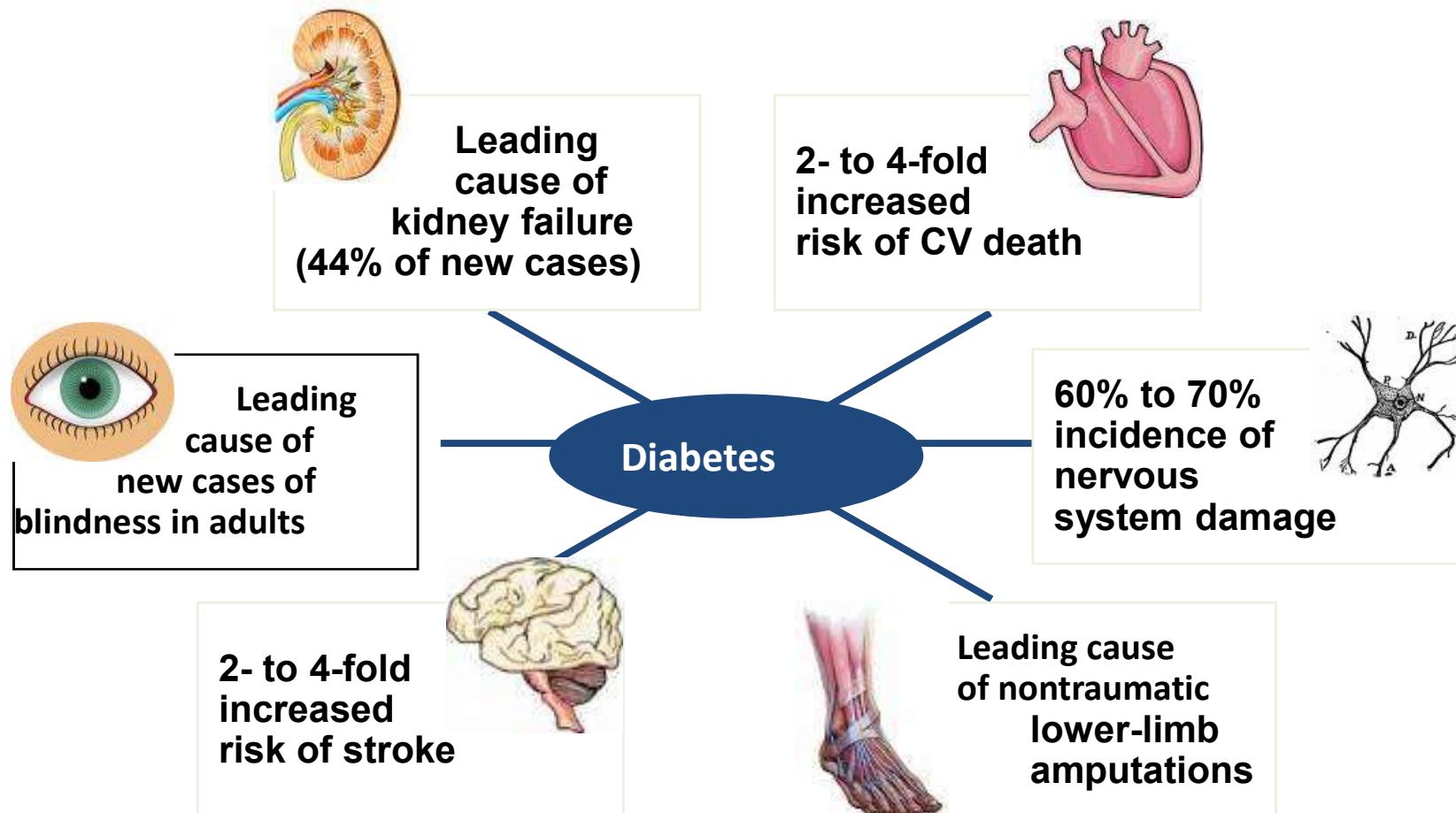
SOURCE: CDC

Vox

PATHOGENESE VAN DMT2



Microvascular and Macrovascular Complications Are Serious

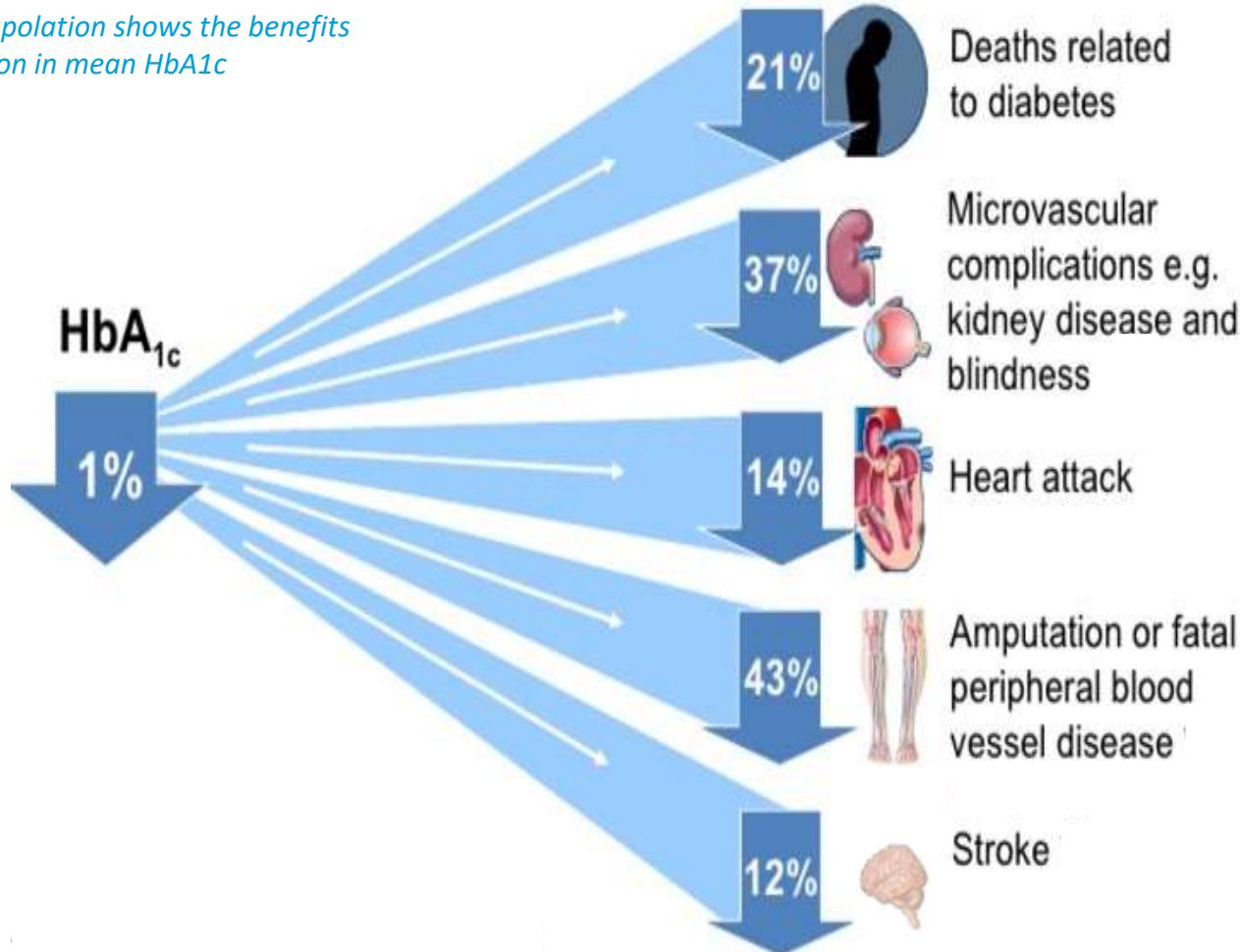


CV = cardiovascular.

Centers for Disease Control and Prevention. National diabetes fact sheet, 2007. http://www.cdc.gov/diabetes/pubs/pdf/ndfs_2007.pdf. Accessed February 26, 2010.

Glycaemic control matters!

*Epidemiologic extrapolation shows the benefits
of every 1% reduction in mean HbA_{1c}*



Diabetes behandeling

Waar beginnen we?



Guidelines for Glycemic, BP, & Lipid Control

	American Diabetes Assoc. Goals
HbA1C	< 7.0% (<i>individualization</i>)
Preprandial glucose	70-130 mg/dL (3.9-7.2 mmol/l)
Postprandial glucose	< 180 mg/dL
Blood pressure	< 130/80 mmHg
Lipids	<p>LDL: < 100 mg/dL (2.59 mmol/l) < 70 mg/dL (1.81 mmol/l) (with overt CVD)</p> <p>HDL: > 40 mg/dL (1.04 mmol/l) ♂ > 50 mg/dL (1.30 mmol/l) ♀</p> <p>TG: < 150 mg/dL (1.69 mmol/l)</p>

HDL = high-density lipoprotein; LDL = low-density lipoprotein; PG = plasma glucose; TG = triglycerides.

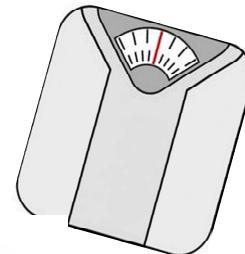
ADA. *Diabetes Care*. 2012;35:S11-63

ADA-EASD Position Statement: Management of Hyperglycemia in T2DM

ANTI-HYPERGLYCEMIC THERAPY

- Therapeutic options: Lifestyle

- Weight optimization



- Healthy diet

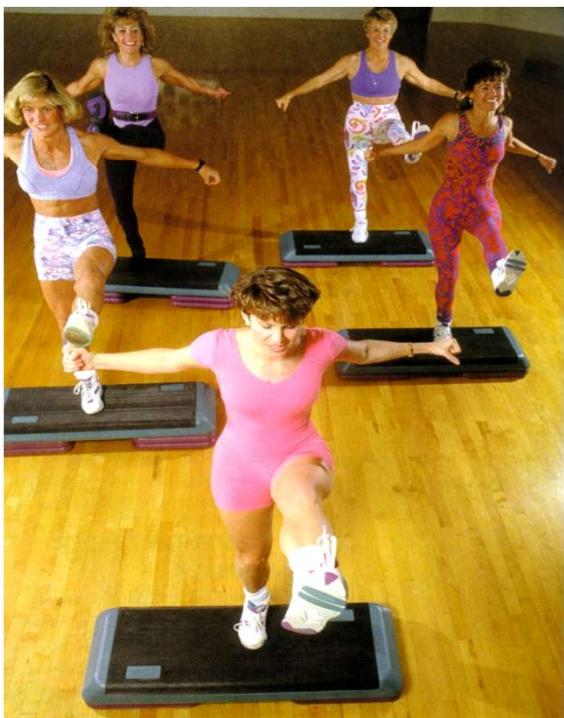
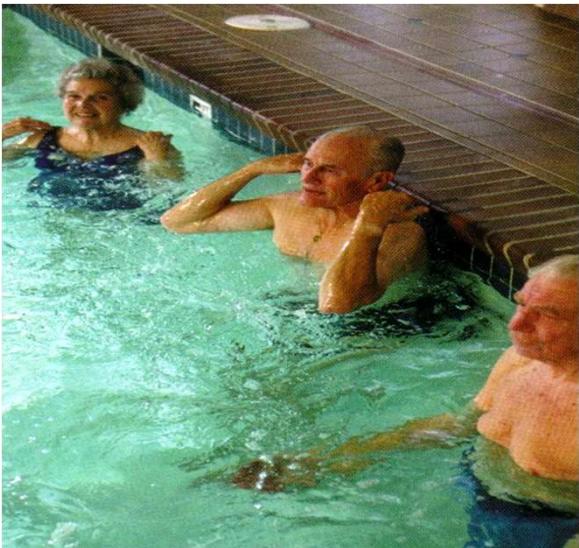


- Increased activity level



Vermijd snel werkende koolhydraten





DOEN & VOLHOUDEN !!!

ANTI-HYPERGLYCEMIC THERAPY

- Therapeutic options:

Oral agents & non-insulin injectables

- Metformin
- Sulfonylureas
- DPP-4 inhibitors
- SGLT-2 inhibitors
- GLP-1 receptor agonists



Metformin

- Metformin decreases hepatic glucose production and increases insulin-mediated peripheral glucose uptake (primary effect)
- Efficacy
 - Decrease fasting plasma glucose 60-70 mg/dL (3.3-3.9 mmol/L)
 - Reduce HbA1c 1.0-2.0%
- Other Effects
 - Diarrhoea and abdominal discomfort
 - Lactic acidosis if improperly prescribed
 - Causes small decrease in LDL cholesterol level and triglycerides
 - No weight gain, with possible modest weight loss
 - Contraindicated in patients with impaired renal function
(Serum Cr >1.4 mg/dL for women, or 1.5 mg/dL for men)

Sulfonylureas

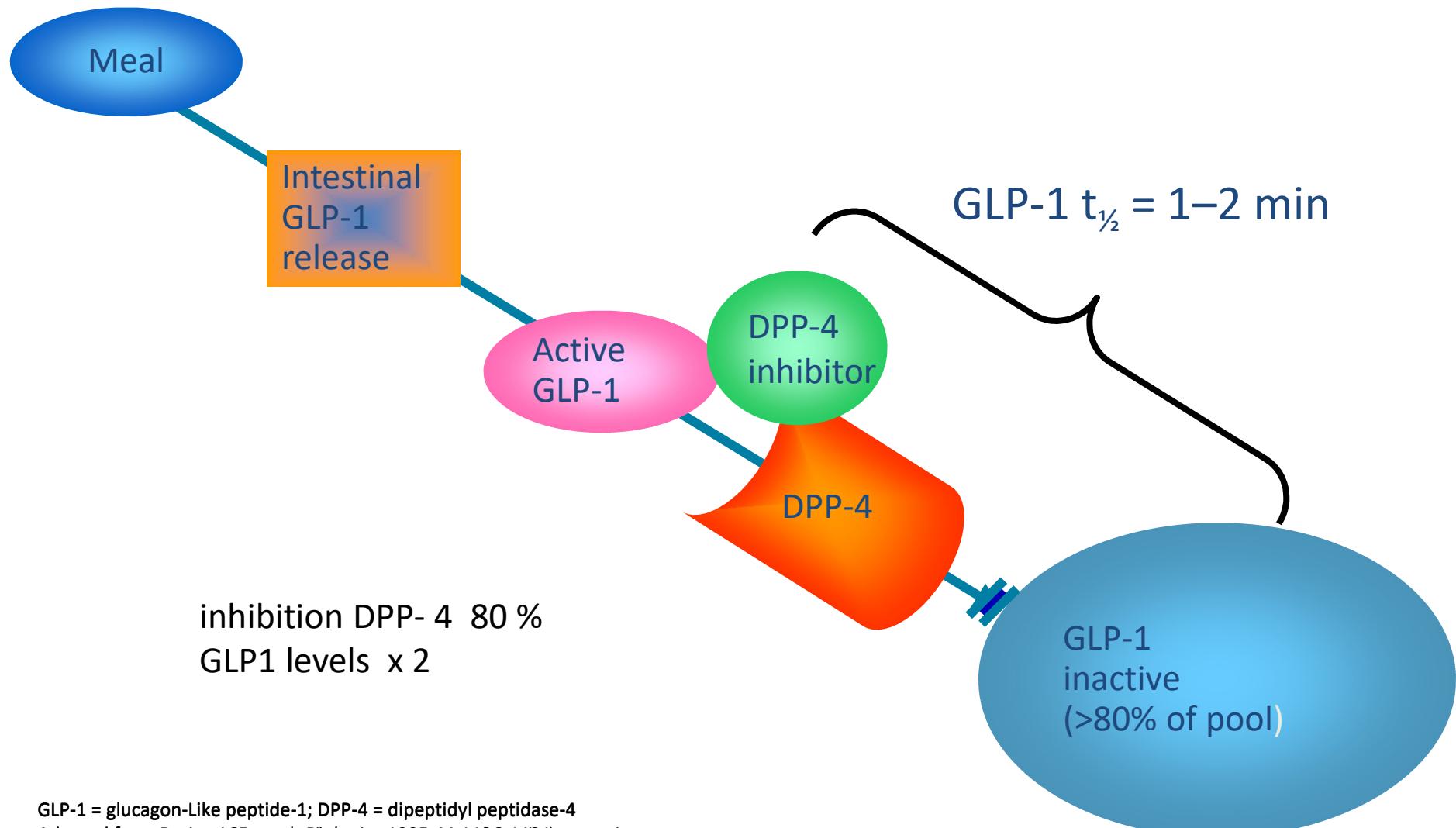
- Gliclazide, Glipizide, Glimepiride, Glibenclamide
- Enhance insulin secretion – independent of glucose
- Only effective when residual pancreatic beta-cell activity is present
- Lower HbA1c by 1.5%
- Weight gain typically 2kg
- Hypoglycaemia risk especially in elderly / renal impairment

DPP4 inhibitors

DPP4 inhibitors

- Januvia (sitagliptine)
- Galvus (vidagliptine)
- Onglyza (saxagliptine)
- Trajenta (linagliptine)
- Vipidia (alogliptine)

Inhibition of DPP-4 Increases Active GLP-1



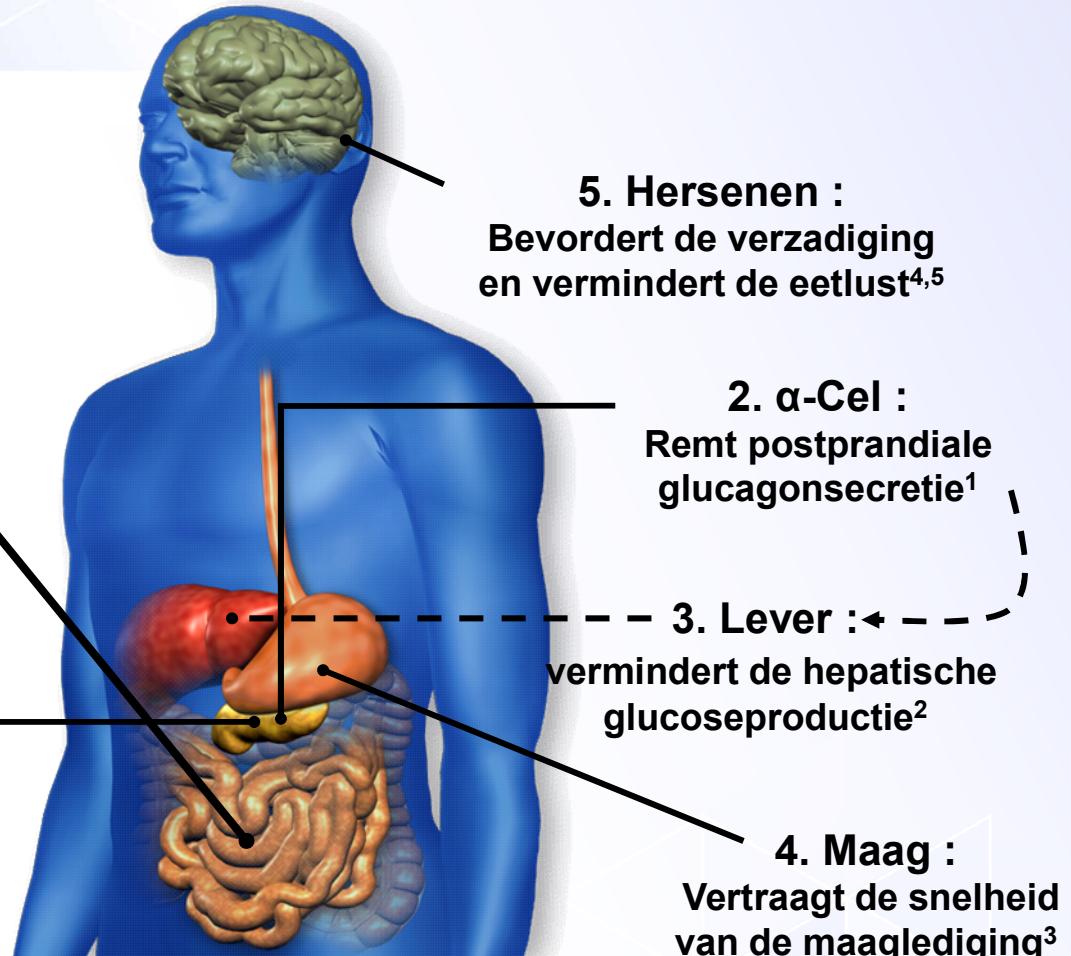
GLP-1 = glucagon-Like peptide-1; DPP-4 = dipeptidyl peptidase-4

Adapted from Betzenhauser et al. *Diabetes* 2000; 49(Suppl 1):A39. Abstract 160-OR.

GLP effecten bij de mens : de natuurlijke rol van incretines

Uitgescheiden GLP-1 na
inname van voedsel

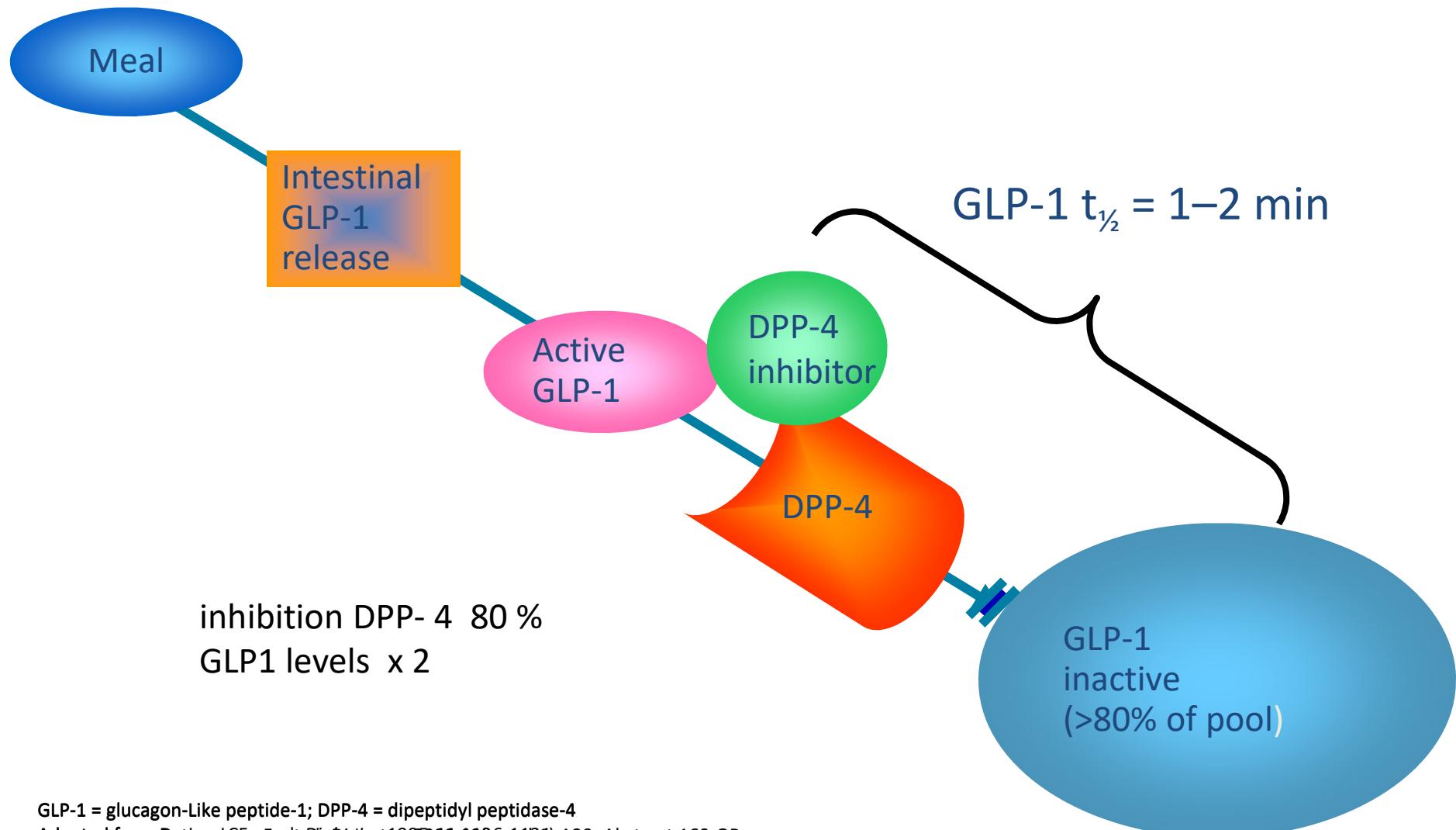
1. β -Cell :
Verhoogt de insuline-
afhankelijke secretie van
insuline in de pancreas¹



GLP-1=glucagon-like peptide-1

1. Nauck MA, et al. *Diabetologia* 1993;36:741–744. 2. Larsson H, et al. *Acta Physiol Scand* 1997;160:413–422. 3. Nauck MA, et al. *Diabetologia* 1996;39:1546–1553.
4. Flint A, et al. *J Clin Invest* 1998;101:515–520. 5. Zander et al. *Lancet* 2002;359:824–830.

Inhibition of DPP-4 Increases Active GLP-1



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GLP-1 receptor agonist

- Eperzan (albiglutide)
- Trulicity (dulaglutide)
- Bydureon (exenatide)
- Victoza (liraglutide)
- Lyxumia (lixisenatide)
- Semaglutide (Ozempic)

Comparison of incretin-based therapies

	DPP-4 inhibitors ¹	GLP-1 RAs ²
Mechanism of action	Increase endogenous GLP-1	<ul style="list-style-type: none">•Mimic GLP-1•Resistant to DPP-4
Route of administration	Oral	Subcutaneous injection
Effect on HbA1c	Less potent	More potent
Effect on weight	Weight neutral	Weight loss
Effect on SBP	Modest	Modest
Risk of hypoglycemia	Low	Low
Adverse events	<ul style="list-style-type: none">•Well tolerated•Monitor for signs and symptoms of pancreatitis	<ul style="list-style-type: none">•Nausea/vomiting (usually transient)•Monitor for signs and symptoms of pancreatitis

1.Garber AJ et al. Endocr Pract. 2013;19(Suppl1):1-48

2. Nauck MA et al. Am J Med. 2009;122(Suppl6):S3-S10

SGLT-2 inhibitors



SGLT-2 inhibitors

- Jardiance (empagliflozine)
- Forxiga (Dapagliflozine)
- Invokana (Canagliflozine)

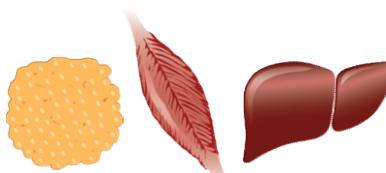
Existing and novel mechanisms to reduce hyperglycaemia in Type 2 diabetes¹⁻⁴

Insulin-dependent mechanisms

1

Insulin action

- Thiazolidinediones
- Metformin

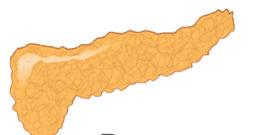


Adipose tissue, muscle and liver

2

Insulin release

- SUs
- GLP-1R agonists*
- DPP4 inhibitors*
- Meglitinides



Pancreas

3

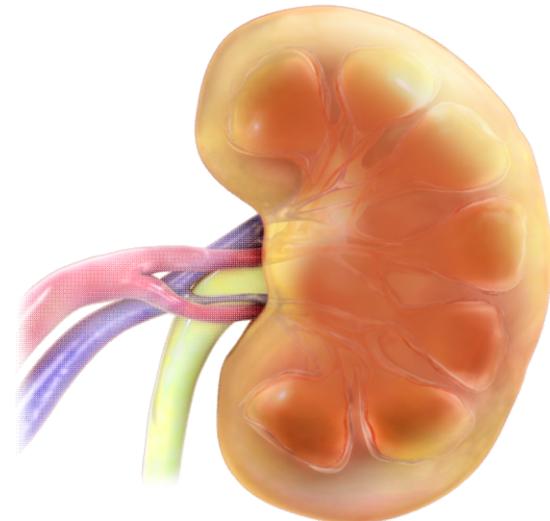
Insulin replacement

- Insulin



Insulin-independent mechanism

SGLT2 inhibition



Glucose utilisation

Glucose excretion/caloric loss

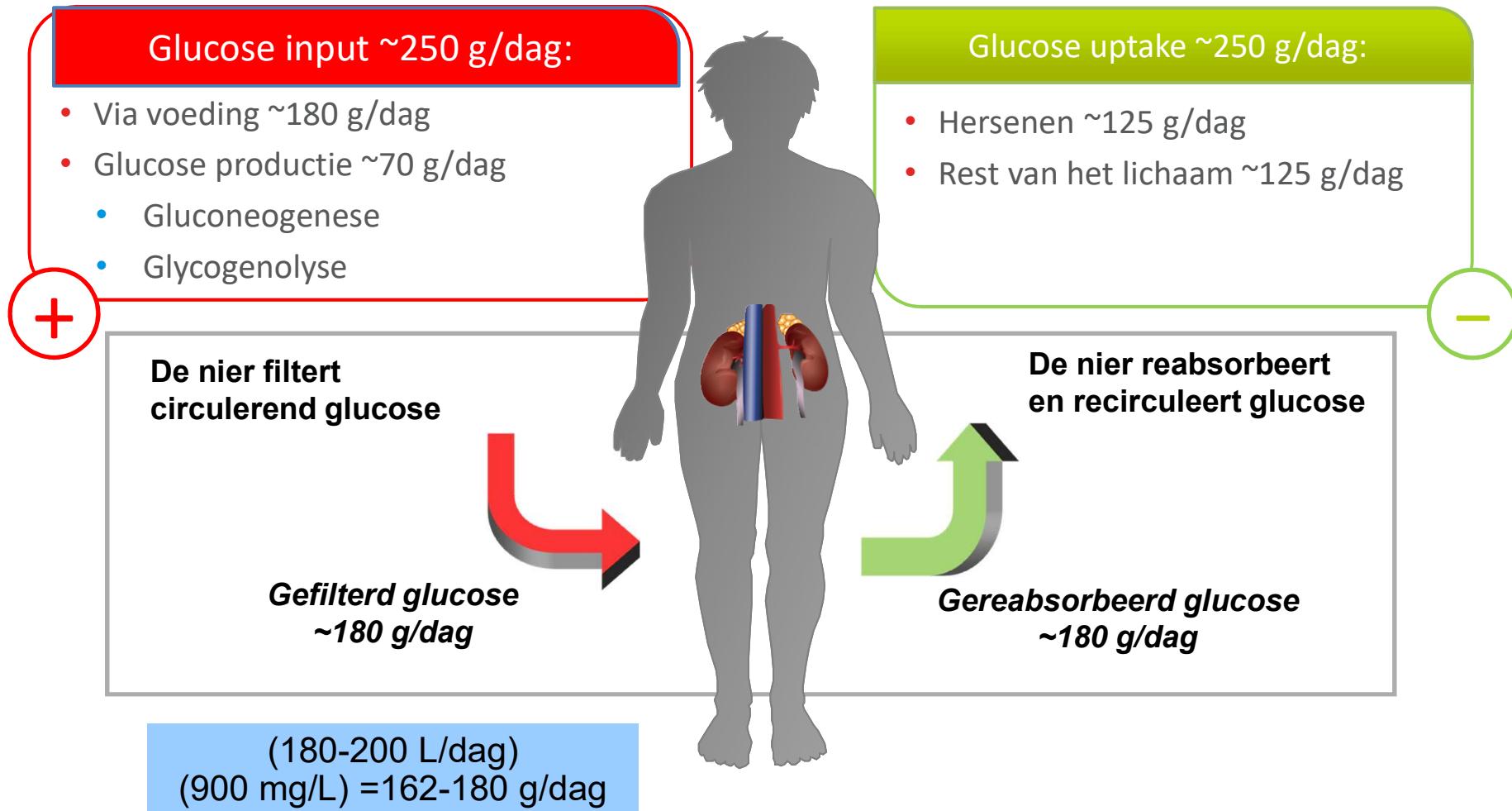
*In addition to increasing insulin secretion, which is the major mechanism of action, GLP-1R agonists and DPP4 inhibitors also act to decrease glucagon secretion.

DPP4, dipeptidyl peptidase-4; GLP-1R, glucagon-like peptide-1 receptor; SUs, sulphonylureas.

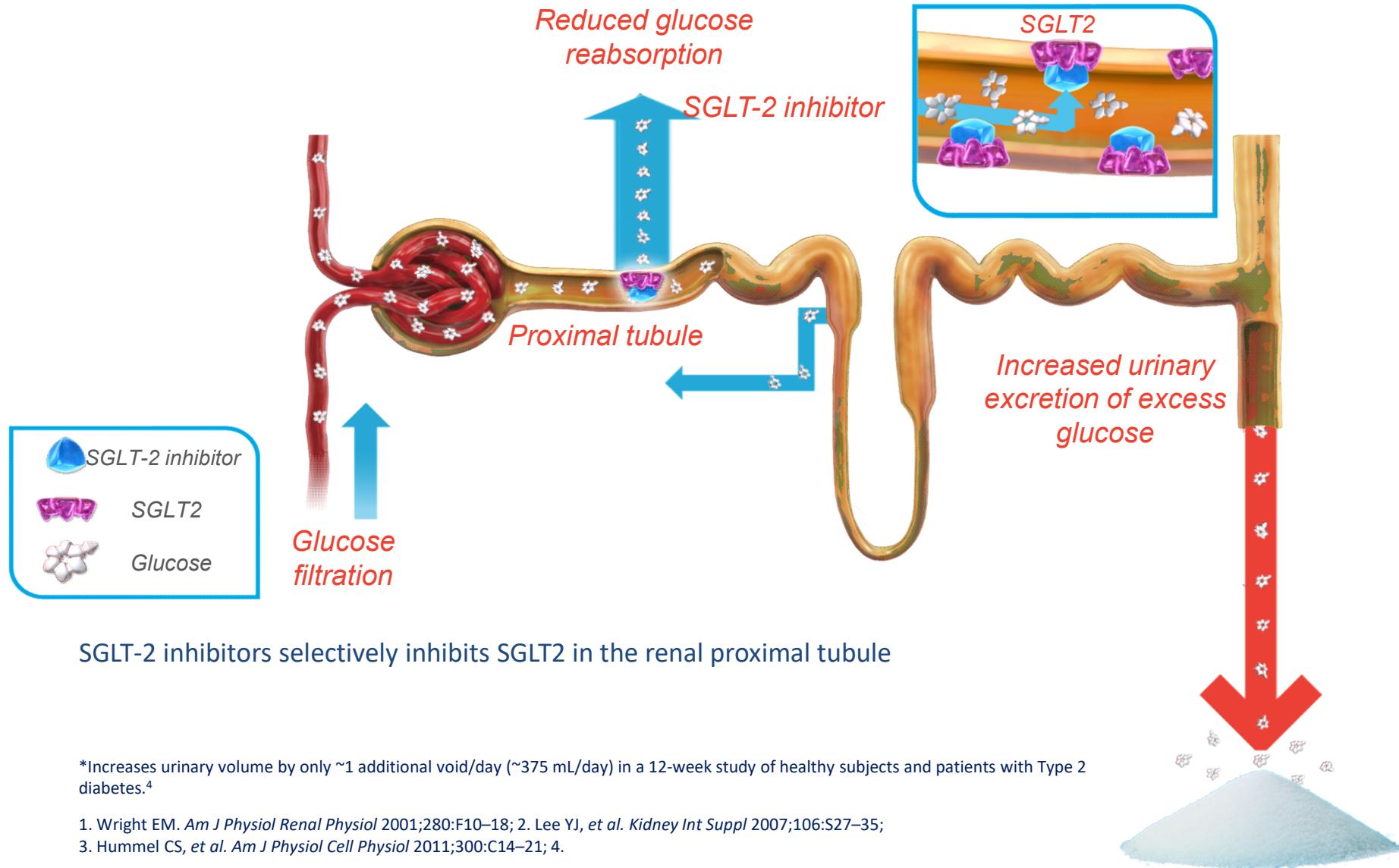
1. Washburn WN. *J Med Chem* 2009;**52**:1785–94; 2. Bailey CJ. *Curr Diab Rep* 2009;**9**:360–7; 3. Srinivasan BT, et al. *Postgrad Med J* 2008;**84**:524–31; 4. Rajesh R, et al. *Int J Pharma Sci Res* 2010;**1**:139–47.

Glucose in de nier

Netto balans ~0 g/dag



A novel insulin-independent approach to remove excess glucose¹⁻³



Summary

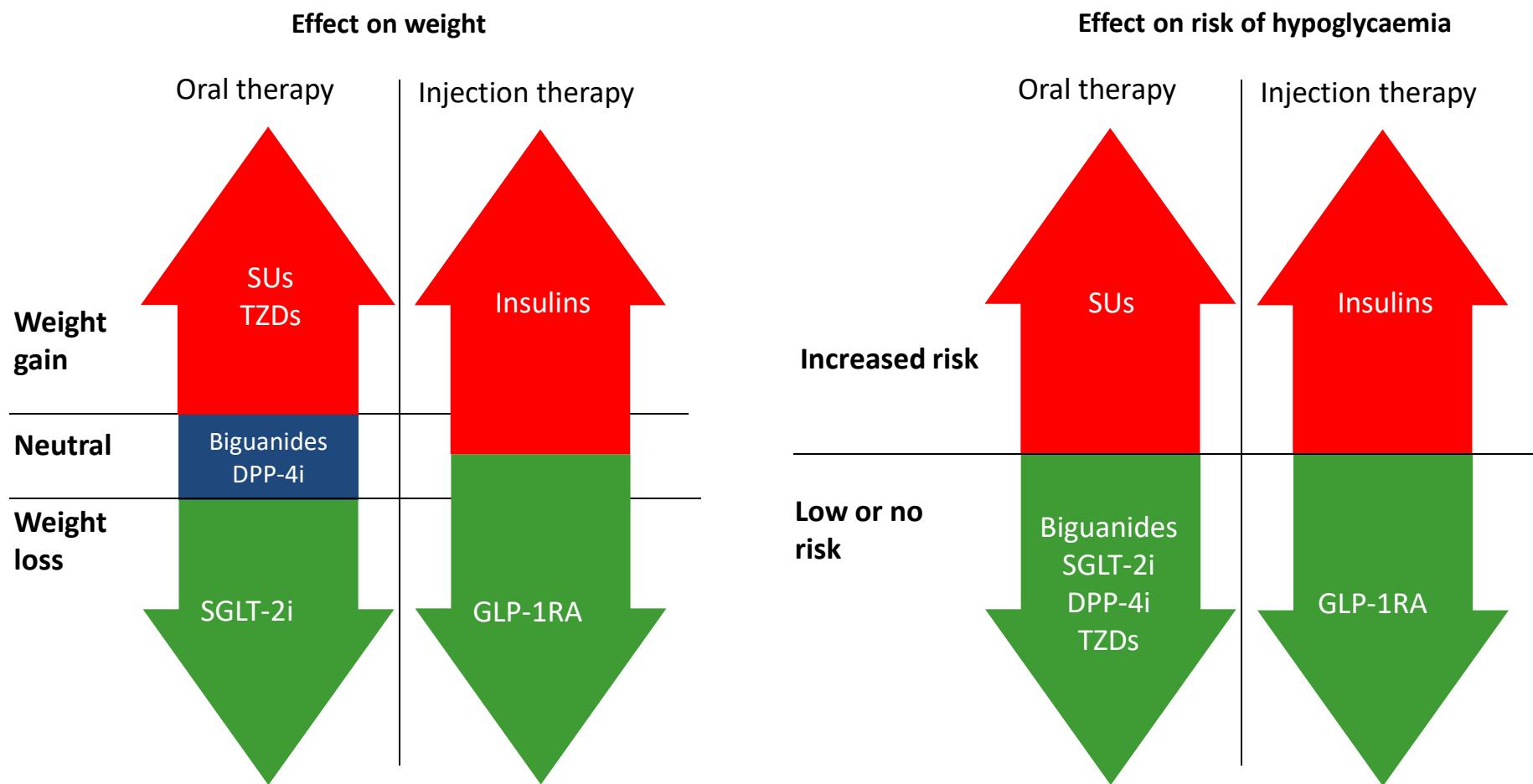
DPP4i

-  HbA1c : +
- Weight neutral
- CV safety proven
 - Saxagliptin
 - Alogliptin
- Low risk of hypoglycemia
- Type 2 diabetes patient with renal impairment : Yes

SGLT2i

-  HbA1c: +
- Weight loss
- CV safety proven
- Low risk of hypoglycemia
- Type 2 diabetes patient with renal impairment :
 - Initiation if eGFR > 60 ml/min.
- UTIs and genital infections

Medications according to effect on weight and risk of hypoglycaemia



DPP-4i, dipeptidyl peptidase-4 inhibitors; GLP-1RA, glucagon-like peptide-1 receptor agonist; HbA_{1c}, glycosylated haemoglobin; SGLT-2i, sodium-glucose cotransporter-2 inhibitors; SU, sulphonylurea; TZD, thiazolidinedione





HYPO

Wisselend
humeur

Hoofdpijn

Moeheid

Bleekheid

Honger

Zweten

Beven

Slecht zien

Duizeligheid



*Maar...
wat is een
goede vraag?*

*Nu vraag je
mij wat!*

