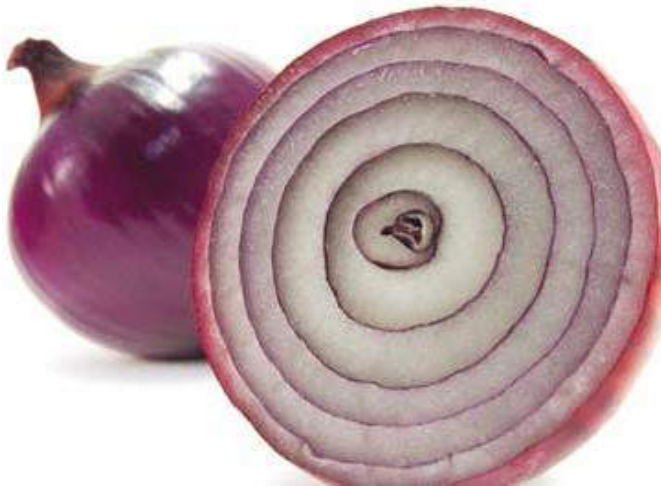


Type 2 diabetes, insuline resistentie

Hoe behandelen?



Prof. Dr. Frank Nobels

Endocrinologie-Diabetologie
OLV Ziekenhuis, Aalst-Asse-Ninove

type 2 diabetes, insuline resistentie



- 56 j
- G 92 kg, L 1.65 m, BMI 33.8 kg/m²
- metformine 850 mg 1-1-1
Apidra 32-20-28 E
Lantus 35-0-0-35 E
- HbA1c (%) 7.3 → 8.0 → 8.4
(mmol/mol) 56 → 64 → 68
- 10 kg bijgekomen sinds insuline opstart

glycemiebehandeling:

enorme ontwikkeling

glycemie verlagers

- metformine
- sulfonylureum

... en combinaties

- insuline

glycemie verlagers

- metformine
- sulfonylureum
- glinide
- acarbose
- glitazone
- DPP-4 inhibitor
- SGLT2 inhibitor
- GLP-1 analoog
- insuline

... en combinaties

Mono-therapy

Efficacy*
Hypo risk
Weight
Side effects
Costs*

Dual therapy†

Efficacy*
Hypo risk
Weight
Side effects
Costs*

Triple therapy

Combination injectable therapy‡

Healthy eating, weight control, increased physical activity, and diabetes education

Metformin

high
low risk
neutral / loss
GI / lactic acidosis
low

If A1C target not achieved after ~3 months of monotherapy, proceed to 2-drug combination (order not meant to denote any specific preference—choice dependent on a variety of patient- and disease-specific factors):

Metformin +	Metformin +	Metformin +	Metformin +	Metformin +	Metformin +
Sulfonylurea	Thiazolidinedione	DPP-4 inhibitor	SGLT2 inhibitor	GLP-1 receptor agonist	Insulin (basal)
high	high	intermediate	intermediate	high	highest
moderate risk	low risk	low risk	low risk	low risk	high risk
gain	gain	neutral	loss	loss	gain
hypoglycemia	edema, HF, fxs	rare	GU, dehydration	GI	hypoglycemia
low	low	high	high	high	variable

If A1C target not achieved after ~3 months of dual therapy, proceed to 3-drug combination (order not meant to denote any specific preference—choice dependent on a variety of patient- and disease-specific factors):

Metformin +	Metformin +	Metformin +	Metformin +	Metformin +	Metformin +
Sulfonylurea +	Thiazolidinedione +	DPP-4 inhibitor +	SGLT2 inhibitor +	GLP-1 receptor agonist +	Insulin (basal) +
TZD	SU	SU	SU	SU	TZD
or DPP-4-i	or DPP-4-i	or TZD	or TZD	or TZD	or DPP-4-i
or SGLT2-i	or SGLT2-i	or SGLT2-i	or DPP-4-i	or Insulin ^S	or SGLT2-i
or GLP-1-RA	or GLP-1-RA	or Insulin ^S	or Insulin ^S		or GLP-1-RA
or Insulin ^S	or Insulin ^S				

If A1C target not achieved after ~3 months of triple therapy and patient (1) on oral combination, move to injectables; (2) on GLP-1-RA, add basal insulin; or (3) on optimally titrated basal insulin, add GLP-1-RA or mealtime insulin. In refractory patients consider adding TZD or SGLT2-i:

Metformin +

Basal insulin + Mealtime insulin or GLP-1-RA

ADA-EASD position statement.

Inzucchi S, et al. Diabetes Care 2015;38:140

fysiopatho-logica

evidentie

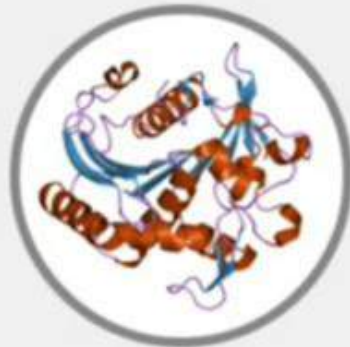
hoe kiezen?

**fysiopatho-logica
evidentie (veiligheid, uitkomst)**

THE METABOLIC SYNDROME



HEART DISEASE



LIPID PROBLEMS



HYPERTENSION



TYPE 2 DIABETES



DEMENTIA



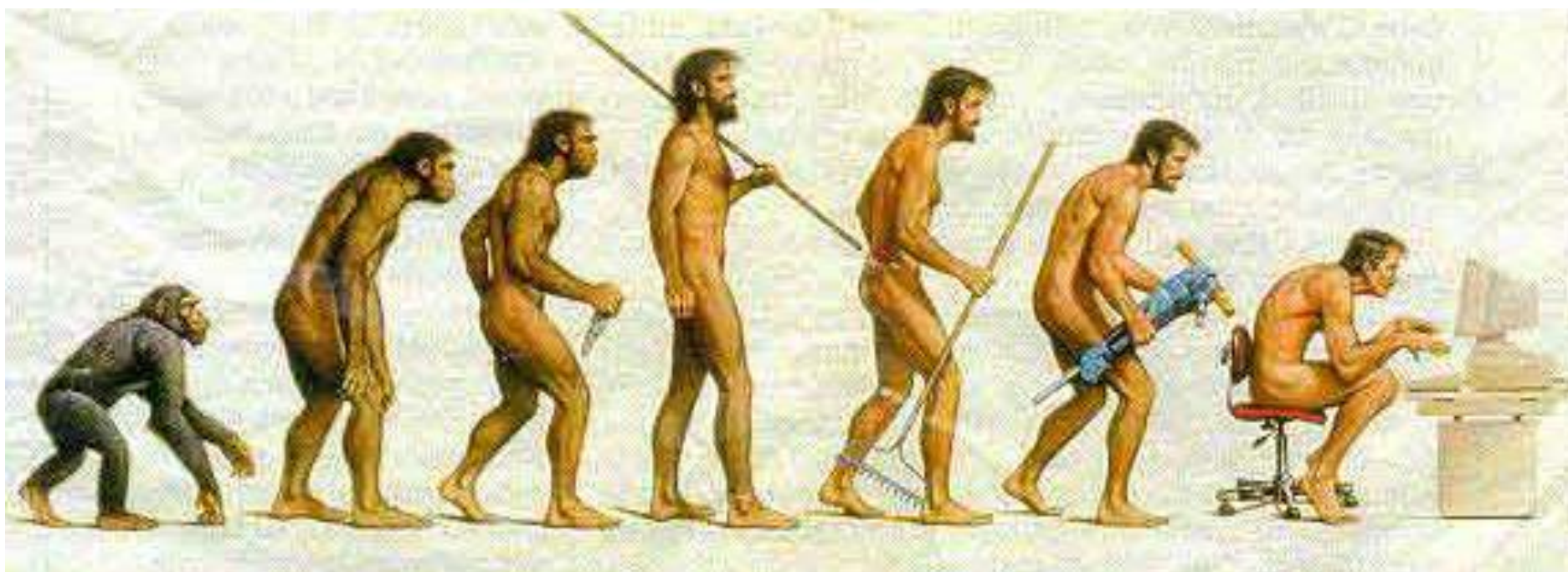
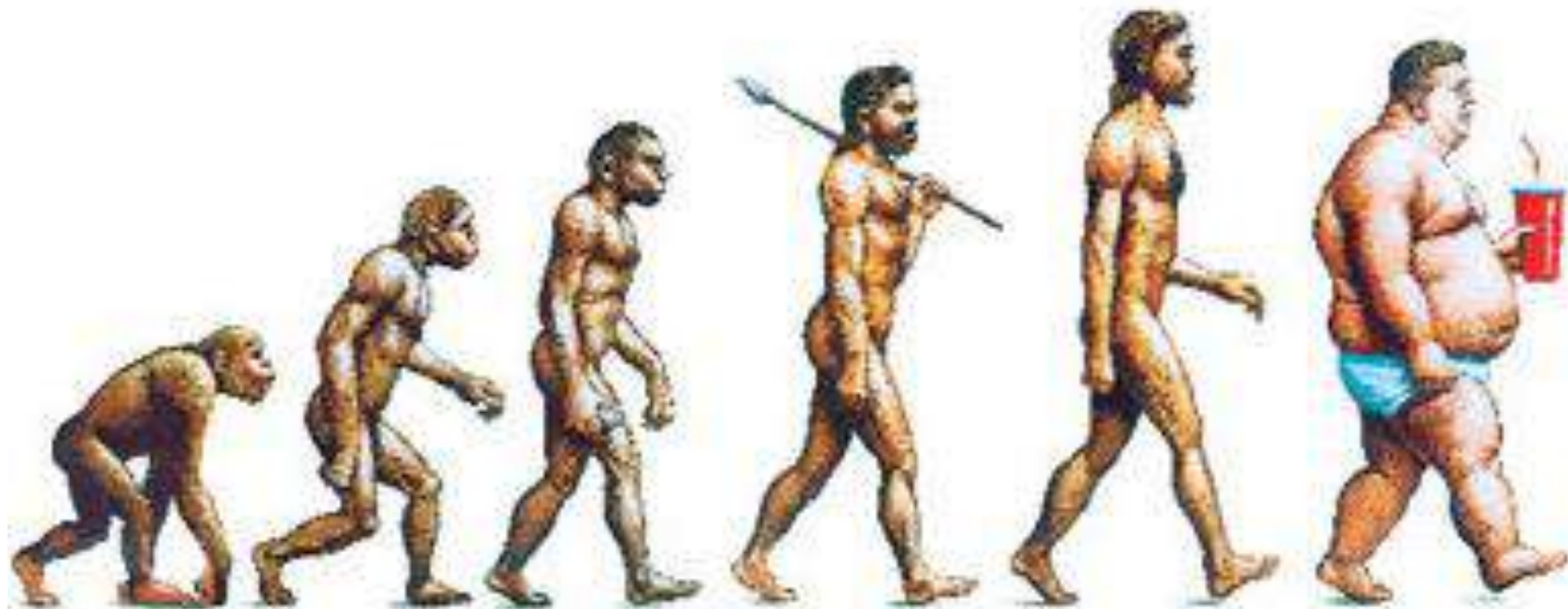
CANCER



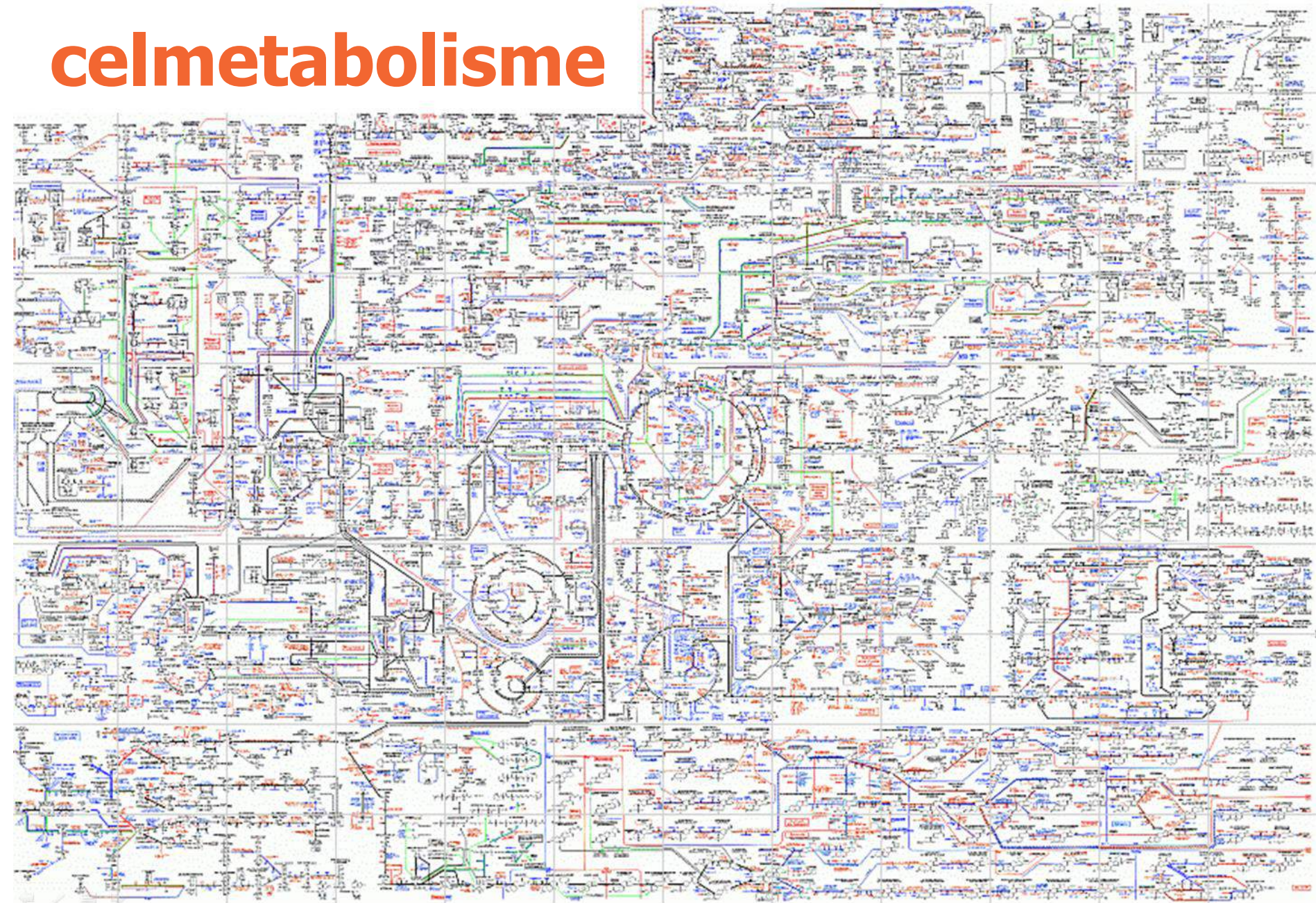
**POLYSYSTIC
OVARIAN
SYNDROME**



**NON-ALCOHOLIC
FATTY LIVER
DISEASE**



celmetabolisme



zuinige 'verbranding'



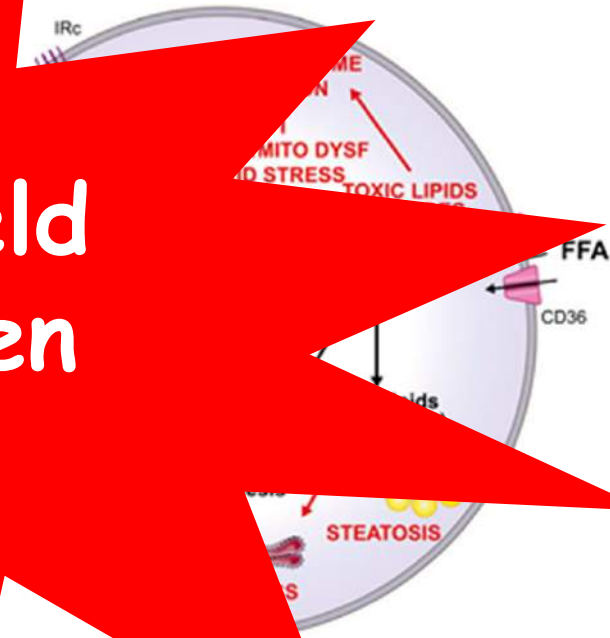
abdominale obesitas en 'zuinige verbranding'

cellen overspoeld
door nutriënten
→ toxisch



cytokines

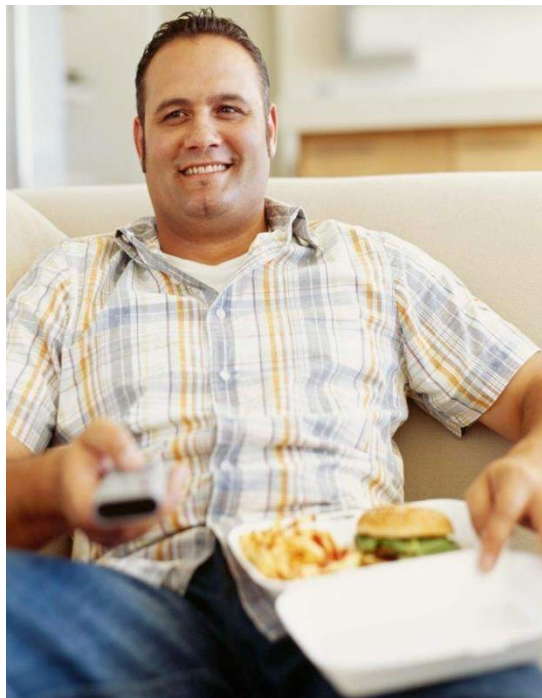
→ inflammatie,
metabole ontregeling



boosdoeners



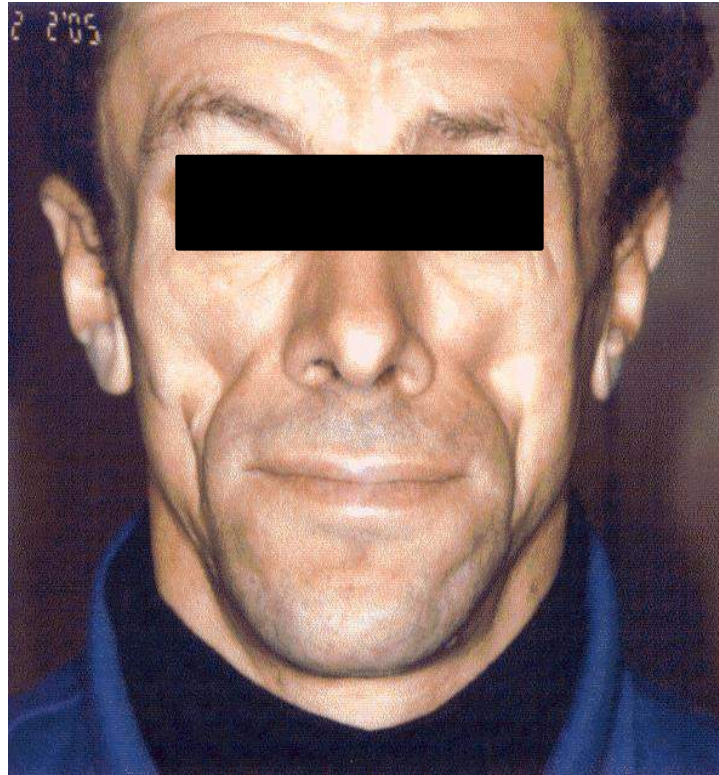
+



+



een bewijs hiervoor: lipoatrofie



insuline resistentie:

hoe herkennen?

klinisch beeld herkennen

- abdominale vetverdeling
- huidafwijkingen (bij extreme IR)
- lab:
 - dyslipidemie (TG↑, HDL↓)
 - licht gestoorde levertesten
 - urinezuur↑
 - glucose↑
 - (insuline, Cpeptide meten niet nodig)

insuline resistentie: huid

skin tags



acanthosis nigricans



= groeihormoonachtig effect van insuline

pseudoacromegalie



behandeling

nutrienten in cellen↓



cellen overspoeld
door nutrienten
→ toxisch

- calorie-inname ↓
 - aanpassing voeding
 - bariatrische chirurgie

- beweging ↑
 - aerob

- medicatie
 - metformine
 - GLP-1 farmaca
 - SGLT2 inhibitoren

'nutrient off-loading'

'Mediterrane' voeding

fruit en groenten ↑

vezelrijk (snelle suikers ↓)

cholesterol, verzadigde vetten ↓

- ◆ magere vlees- en zuivelproducten
- ◆ max. 1x /14d gefrituurde bereidingen
- ◆ beperk smeer- en bereidingsvet

onverzadigde vetten ↑

- ◆ olijfolie als bereidingsvet
- ◆ noten
- ◆ minstens 2x vis / wk
- ◆ max. 2 eieren / wk



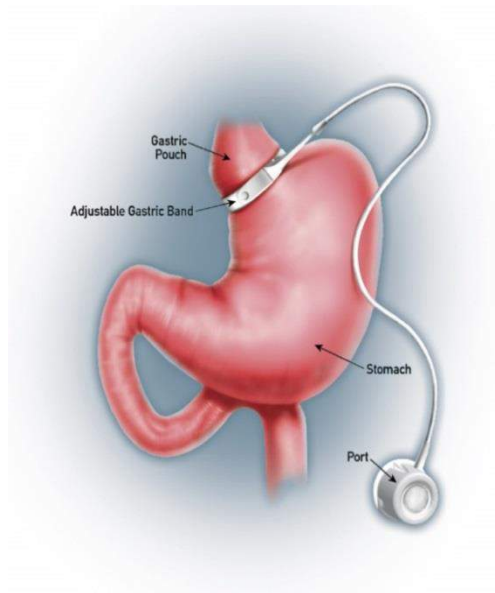
beweging:

- hoeft niet intensief te zijn
- maar wel frequent
- gecombineerd aeroob - kracht

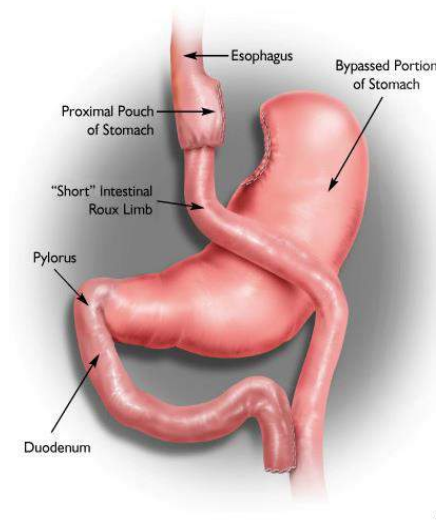


Bariatrische heelkunde

Lap Gastric Band
Restrictief

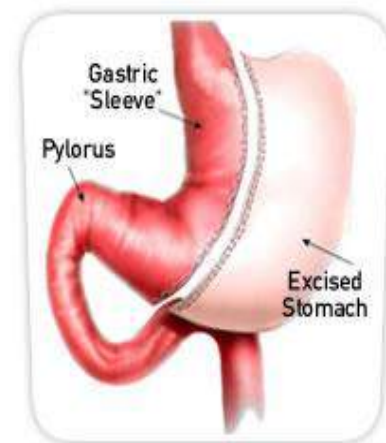


Lap Gastric Bypass
Malabsorptief + Restrictief



hormonaal
(Ghrelin ↓, GLP1 ↑, PYY ↑, ...)

Sleeve gastrectomie
Restrictief



hormonaal
(Ghrelin ↓)

medicatie

nutrient off-loading

metformine

DPP-4 inhibitoren

GLP-1 analogen

SGLT-2 inhibitoren

overrulen van IR

sulfonylurea

glitazones

insuline

Metformine

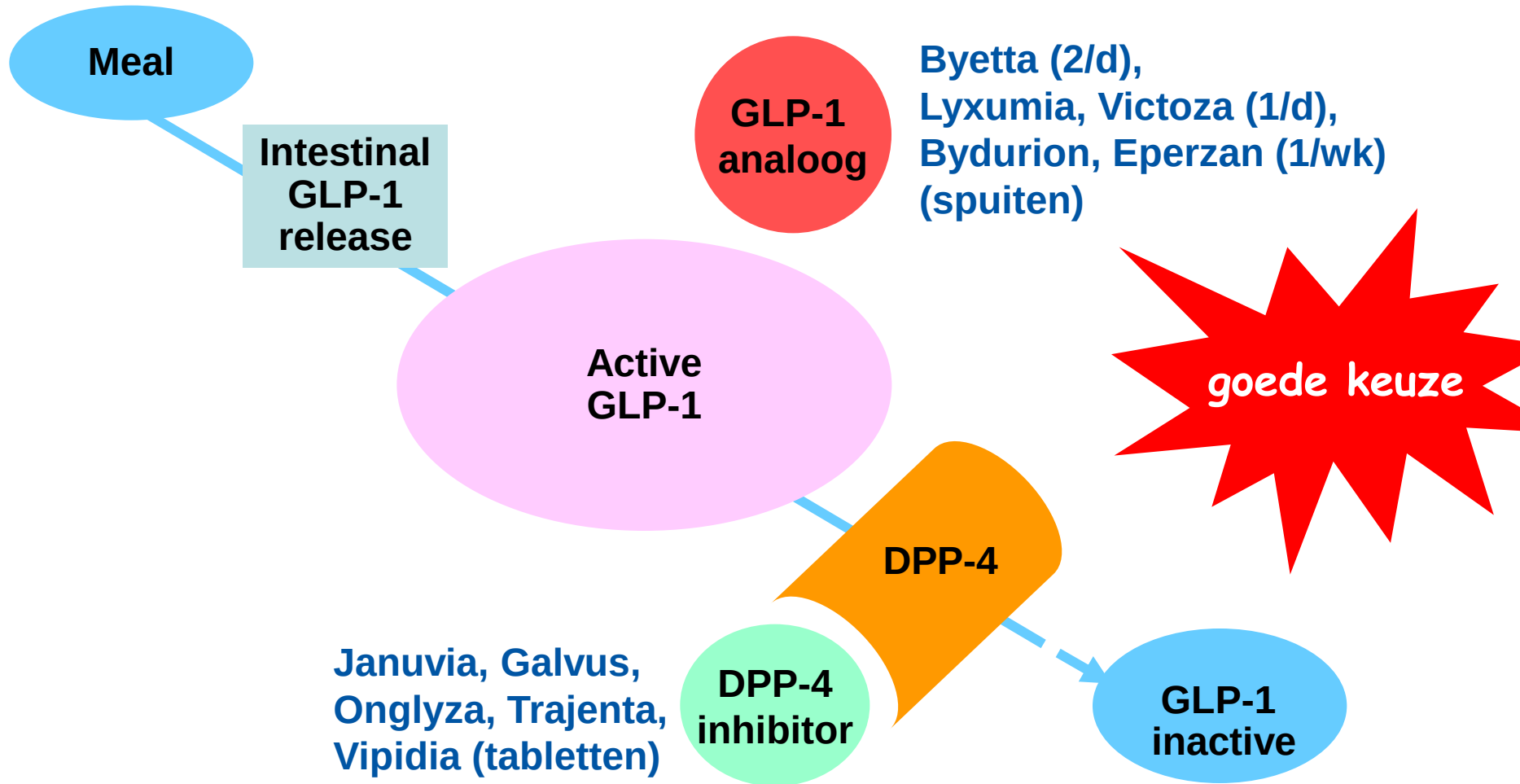
hepatische glucoseproductie ↓



goede keuze

- geen hypoglycemie
- geen gewichtstoename
- overbelast de β -cel niet
- reduceert microvasculaire complicaties (UKPDS)
- reduceert macrovasculaire complicaties (UKPDS)
- vermindert mogelijk kans op kanker

Metabolisme van GLP-1

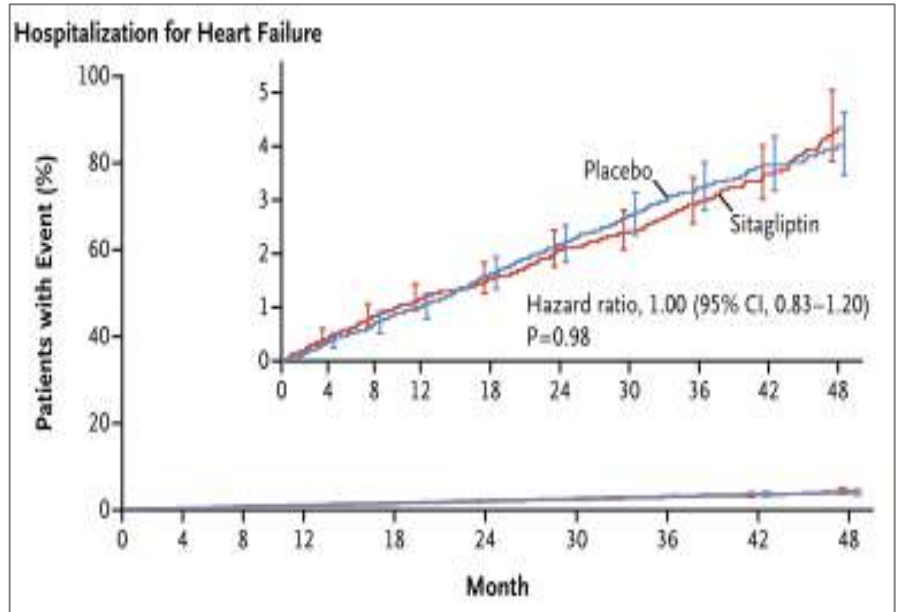
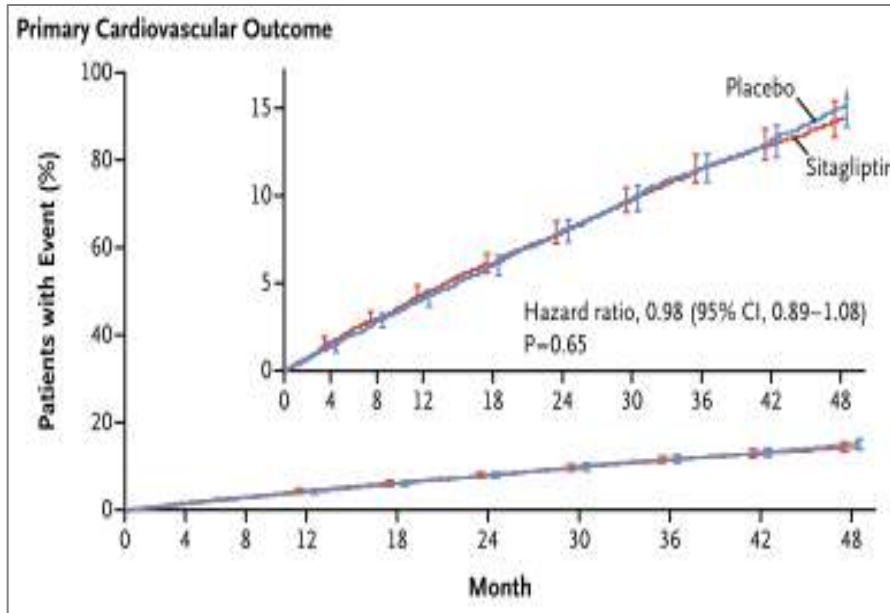


DPP-4 inhibitoren (gliptines)

+ metformine

- | | | |
|------------------|-----------------------|-------------------------|
| - alogliptine: | Vipidia [®] | Vipdomet [®] |
| - linagliptine: | Trajenta [®] | Jentadueto [®] |
| - saxagliptine: | Onglyza [®] | Komboglyze [®] |
| - sitagliptine: | Januvia [®] | Janumet [®] |
| - vildagliptine: | Galvus [®] | Eucreas [®] |

safety of DPP4i



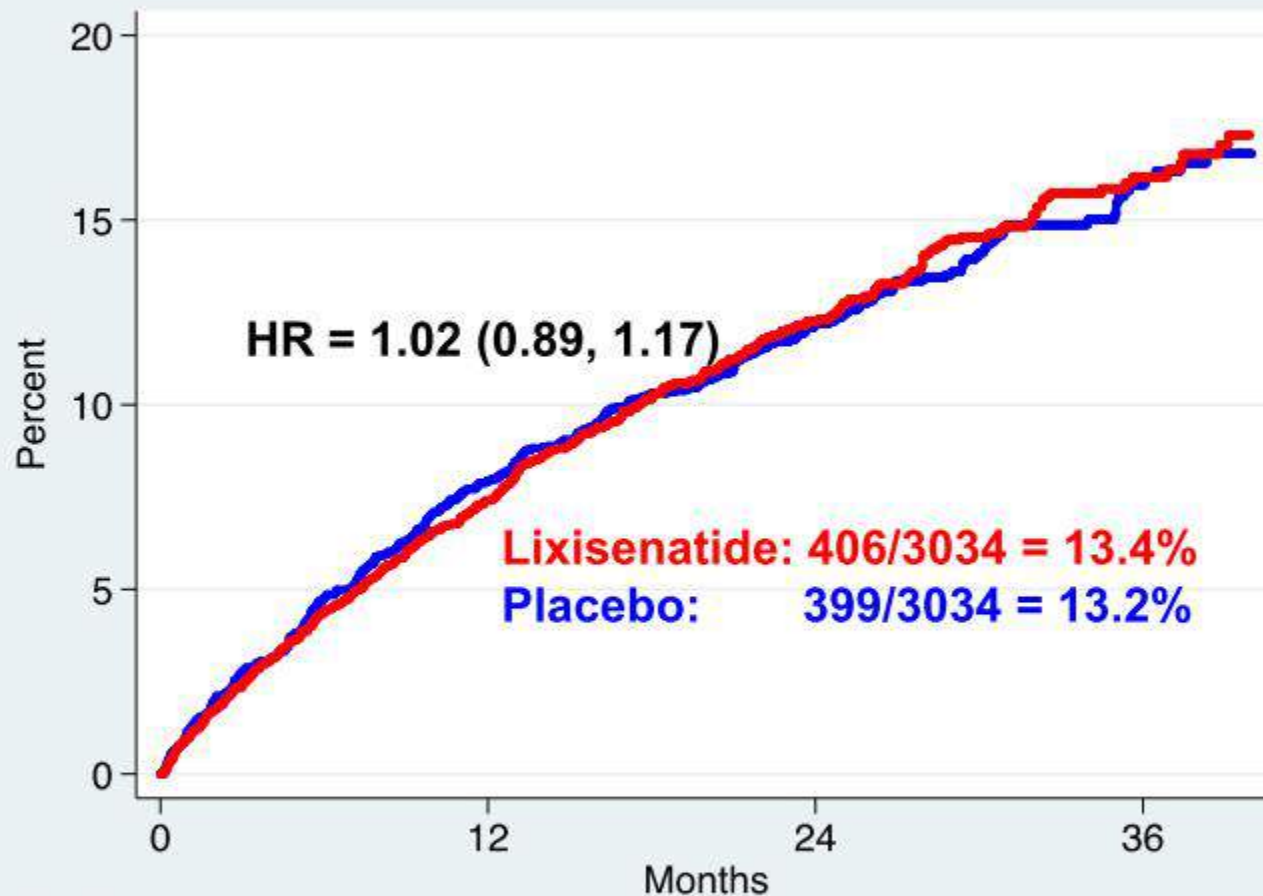
Ook niet méér pancreatitis of pancreasca.

(Sinds 2007 op markt)

GLP1 analogen

- exenatide: Byetta[®] 2x /d
- liraglutide: Victoza[®] 1x /d
- lixisenatide: Lyxumia[®] 1x /d
- exenatide LA: Bydurion[®] 1x /wk
- albiglutide: Eperzan[®] 1x /wk

1° Outcome (CV Death, MI, Stroke or UA)



Number at risk

Placebo 3034

Lixisenatide 3034

2759

2785

1566

1558

476

484

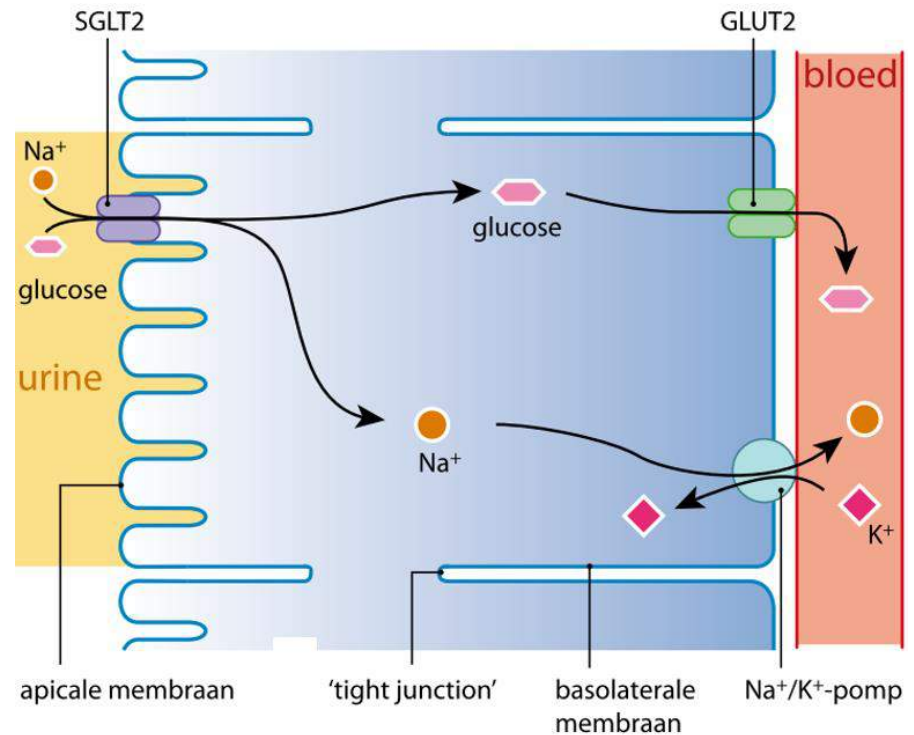
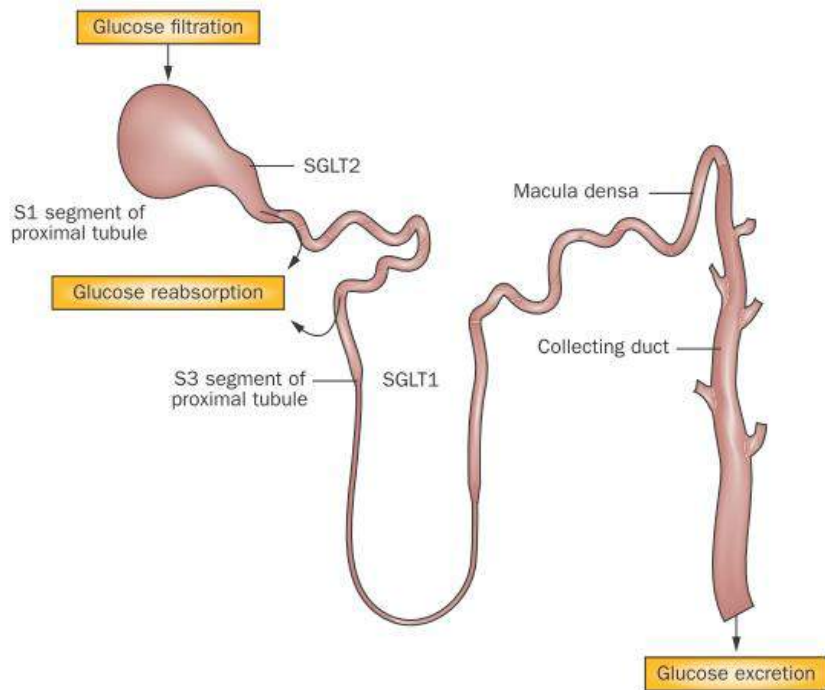


SGLT2 inhibitoren (gliflozines)

+ metformine

- canagliflozine: Invokana[®] Vokanamet[®]
- empagliflozine: Jardiance[®]
- ...
- ...
- ...

SGLT2= Sodium-GLucose coTransporter-2

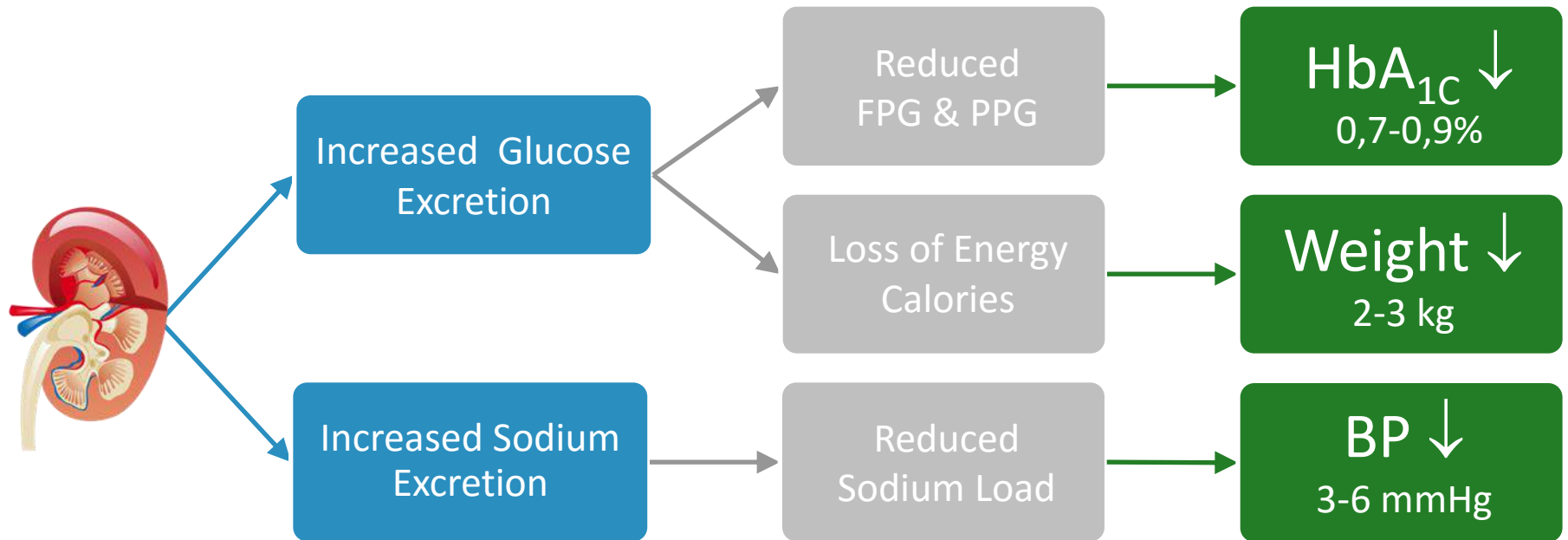


genetisch defect van SGLT2 → benigne renale glucosurie

SGLT2 inhibitie: verwachte (neven)effecten

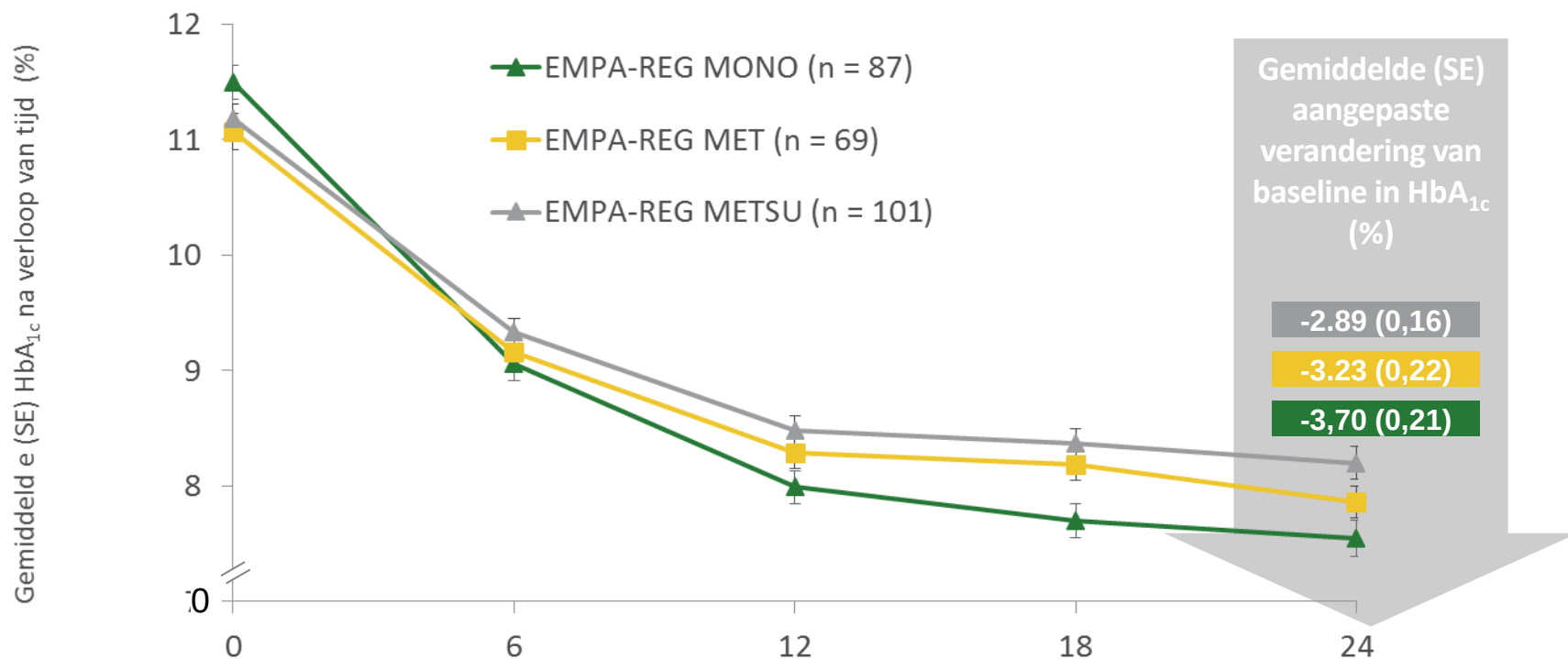
- goede nierfunctie nodig
- glycemie ↓, HbA1c ↓
- weinig hypoglycemie
- BD ↓ (natriurese, osmotische diurese)
- gewicht ↓ (glucosurie, diurese)
- urogenitale infecties (glucosurie)
- veilig op lange termijn ('benigne renale glucosurie')

Expected Clinical Effects of SGLT2 Inhibition Based on the Mode of Action



EMPA-REG MONO/MET/METSU™ (open-label) studies – Empagliflozin 25 mg

Changes in HbA_{1c} at week 24 in patients with baseline HbA_{1c} ≥ 10



N/Week	BL	6	12	18	24
Monotherapie	87	77	74	73	66
Add-on voor metformine	69	66	60	58	48
Add-on voor metformine + SU	101	94	89	77	70

BL, baseline; HbA_{1c}, geglycosyleerde hemoglobine; QD, eenmaal per dag; SE, standaardafwijking; SU, sulfonyleurea.

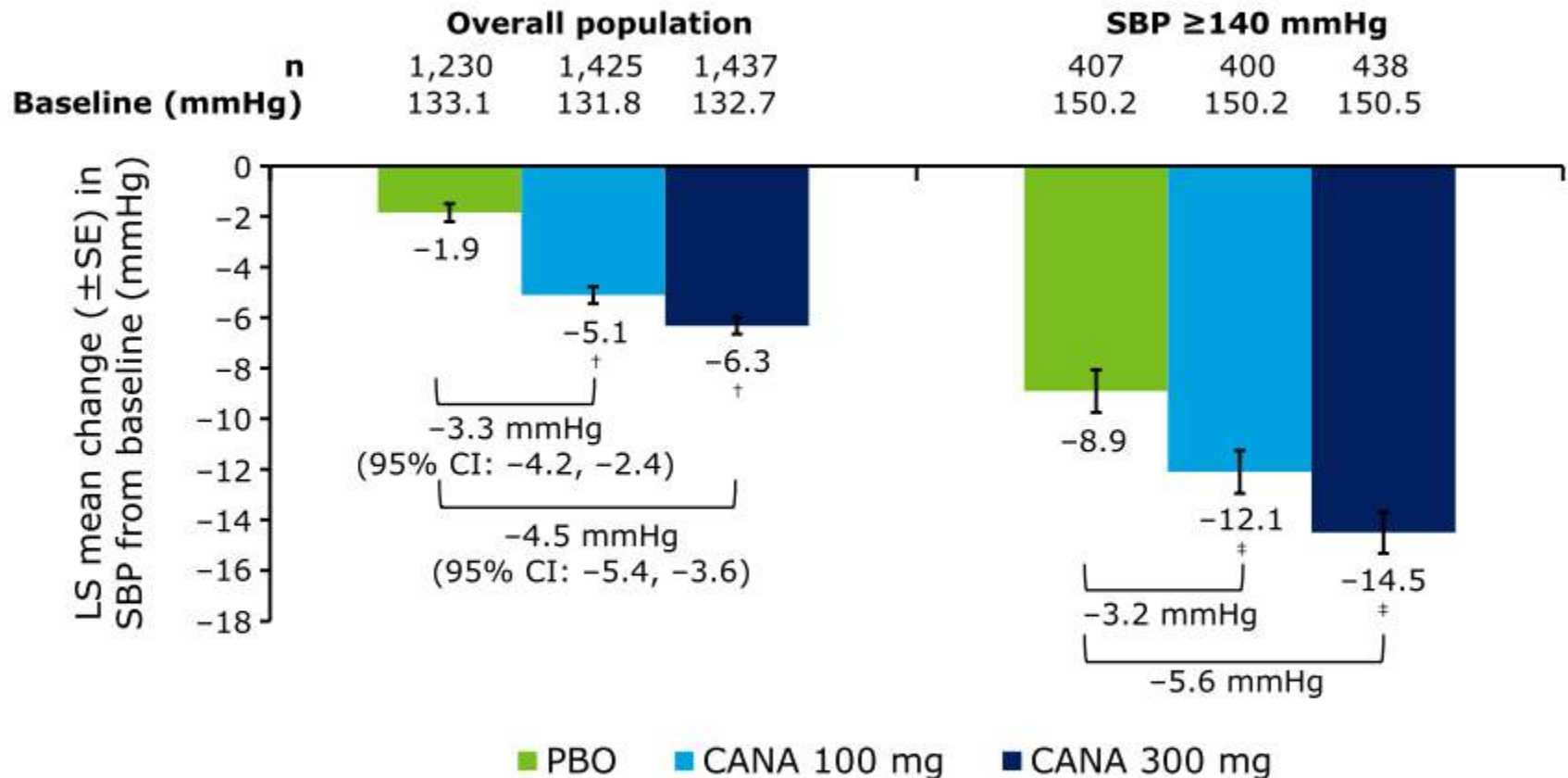
Sources: 1. Adapted from Roden M, et al. Lancet Diabetes Endocrinol. 2013;1(3):208–219;

2. Adapted from Häring H-U, et al. Diabetes Care. 2014 (In druk);

3. Adapted from Häring H-U, et al. Diabetes Care. 2013;36:3396–404.

JARDIANCE® [samenvatting van productkenmerken]. Product Information – EMA

Change in SBP for Overall Population and for Subjects With SBP ≥ 140 mmHg (6 Pooled PBO-controlled Studies, LOCF)*



Absolute reductions in SBP were greater in the elevated BP subgroup than in the overall population.

LOCF, last observation carried forward; LS, least squares; SE, standard error.

*Statistical testing was pre-specified for the elevated SBP population only; 95% CIs are provided for the overall population.

[†]95% CI vs PBO excluded 0.

[‡] $P < 0.001$ vs PBO.

Summary of Adverse Drug Reactions

≥2% in Four Placebo-controlled 26-week Studies (n=2313)

	Placebo N=646 (%)	CANA 100 mg N=833 (%)	CANA 300 mg N=834 (%)
Gastrointestinal Disorders			
Constipation	0.9	1.8	2.3
Thirst	0.2	2.8	2.3
Nausea	1.4	2.2	2.2
Renal and Urinary Disorders			
Polyuria or pollakiuria	0.8	5.3	4.6
Urinary tract infection (UTI)	4.0	5.9	4.3
Reproductive System Disorders			
Balanitis or balanoposthitis	0.6	4.2	3.7
Vulvovaginal candidiasis	3.2	10.4	11.4

The most commonly reported AEs overall were vulvovaginal candidiasis, UTI and polyuria or pollakiuria. When CANA was used in combination with insulin or insulin secretagogues the most commonly reported AEs included hypoglycaemia

cardiovasculaire outcome

EMPA-REG outcome



NIEUW

Key inclusion and exclusion criteria

- Key inclusion criteria
 - Adults with type 2 diabetes
 - BMI ≤ 45 kg/m²
 - HbA1c 7–10%*
 - Established cardiovascular disease
 - Prior myocardial infarction, coronary artery disease, stroke, unstable angina or occlusive peripheral arterial disease
- Key exclusion criteria
 - eGFR < 30 mL/min/1.73m² (MDRD)

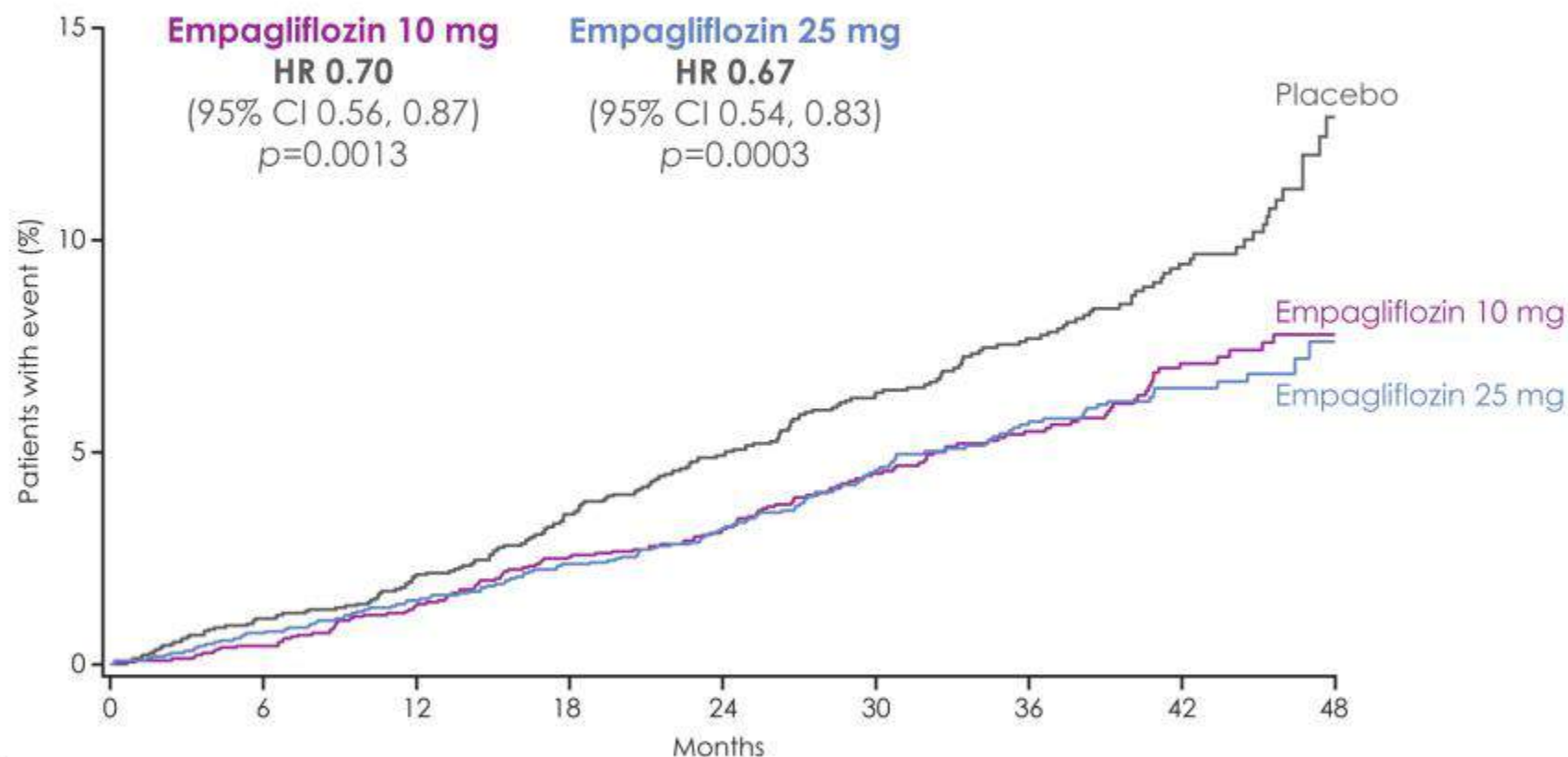
BMI, body mass index; eGFR, estimated glomerular filtration rate; MDRD, Modification of Diet in Renal Disease

*No glucose-lowering therapy for ≥ 12 weeks prior to randomisation or no change in dose for ≥ 12 weeks prior to randomisation or, in the case of insulin, unchanged by $> 10\%$ compared to the dose at randomisation



**EMPA-REG
OUTCOME®**

All-cause mortality

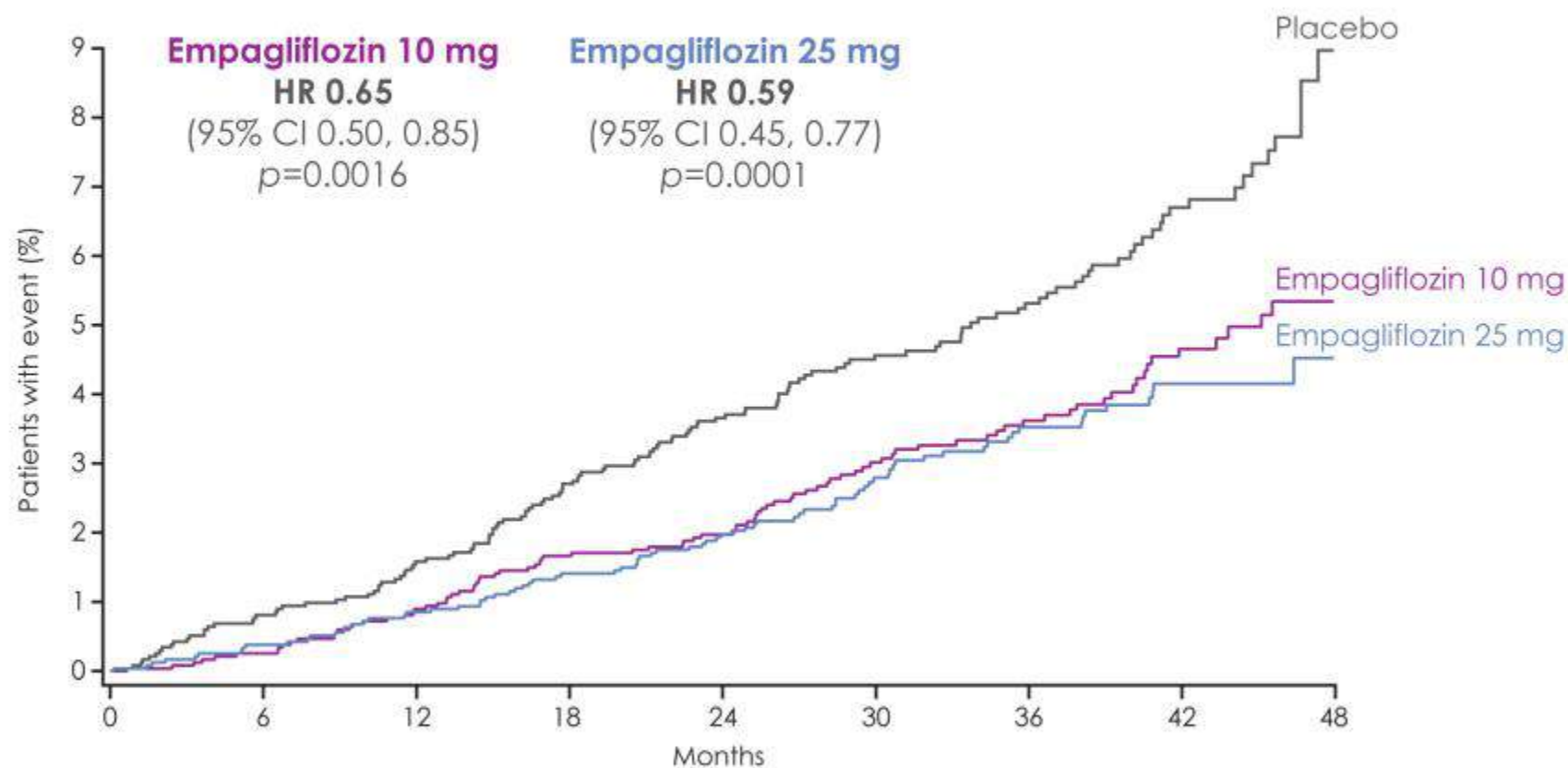


No. of patients

Empagliflozin 10 mg	2345	2327	2305	2274	2055	1542	1303	847	201
Empagliflozin 25 mg	2342	2324	2303	2282	2073	1537	1314	875	213
Placebo	2333	2303	2280	2243	2012	1503	1281	825	177

Kaplan-Meier estimate. HR, hazard ratio

CV death

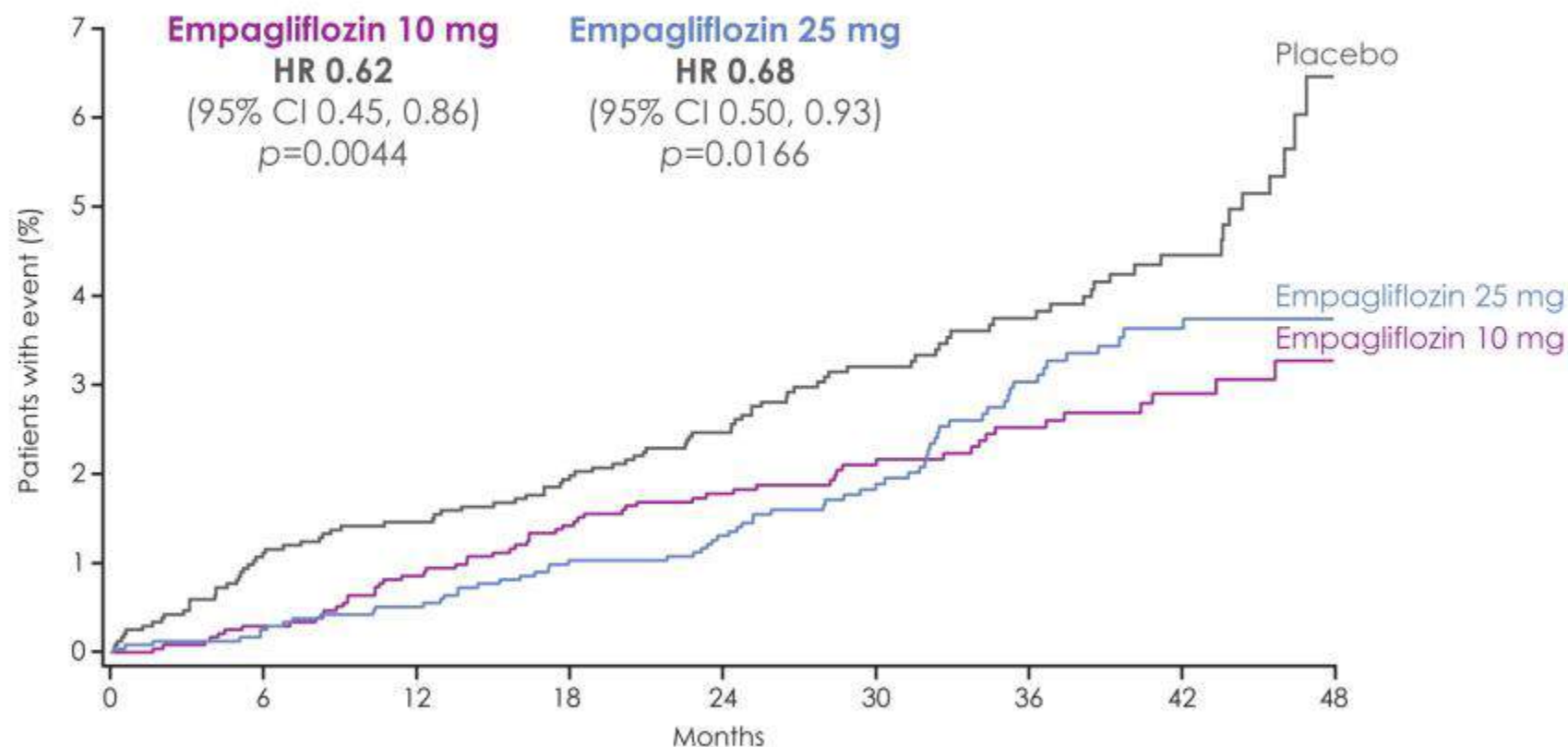


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Placebo	2333	2303	2280	2243	2012	1503	1281	825	177

Cumulative incidence function, HR, hazard ratio

Hospitalisation for heart failure

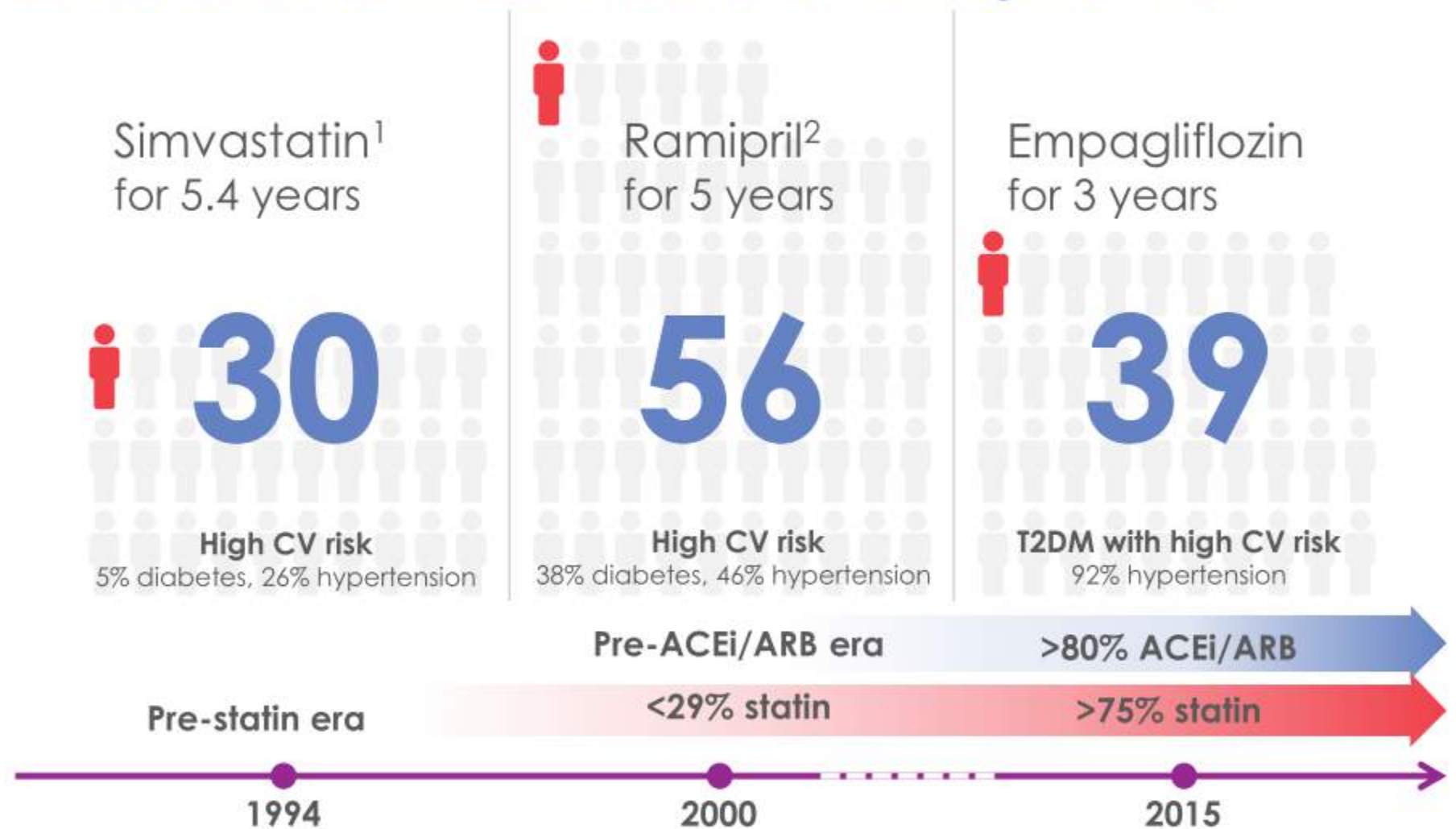


No. of patients

Empagliflozin 10 mg	2345	2306	2256	2204	1981	1473	1240	804	188
Empagliflozin 25 mg	2342	2308	2267	2223	2007	1477	1247	830	207
Placebo	2333	2271	2226	2173	1932	1424	1202	775	168

Cumulative incidence function, HR, hazard ratio

Number needed to treat (NNT) to prevent one death across landmark trials in patients with high CV risk



1. 4S investigator, Lancet 1994; 344: 1383-89, <http://www.trialresultscenter.org/study2590-4S.htm>;

2. HOPE investigator N Engl J Med 2000;342:145-53, <http://www.trialresultscenter.org/study2606-HOPE.htm>



EMPA-REG
OUTCOME®

medicatie

nutrient off-loading

metformine

overrulen van IR

sulfonylurea

glitazones

DPP-4 inhibitoren

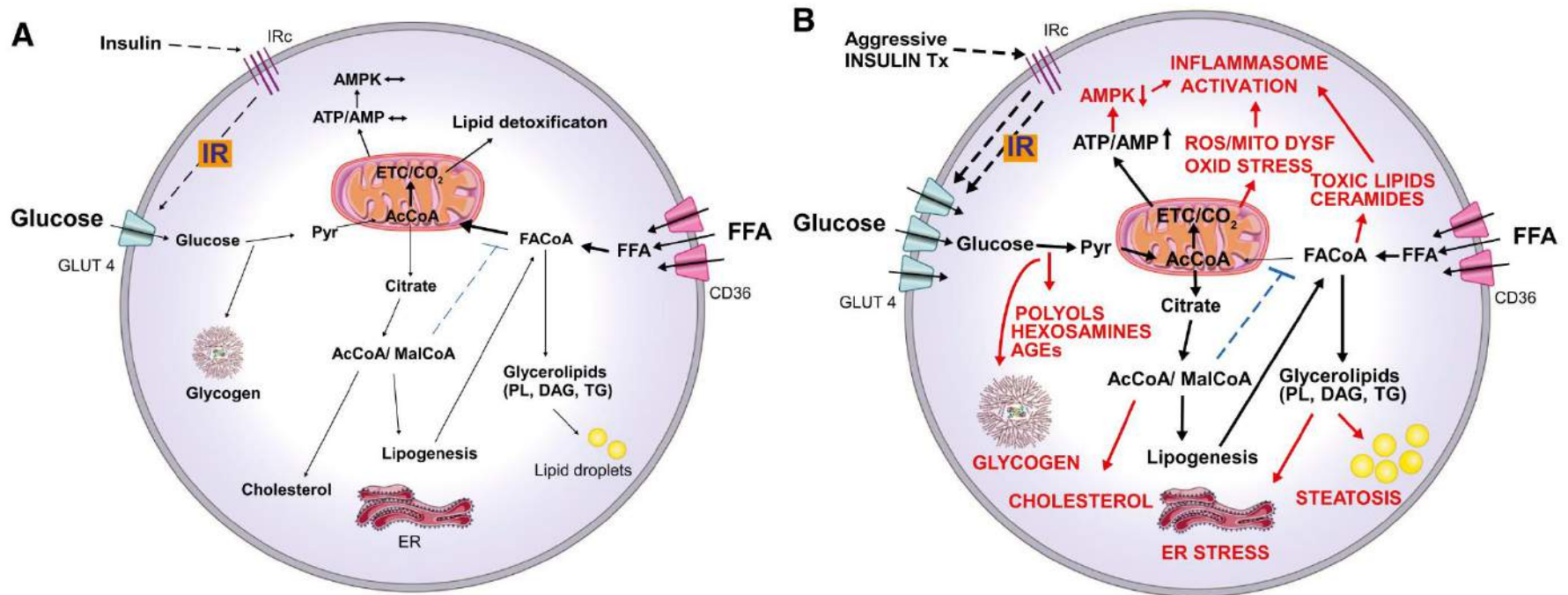
GLP-1 analogen

SGLT-2 inhibitoren

insuline

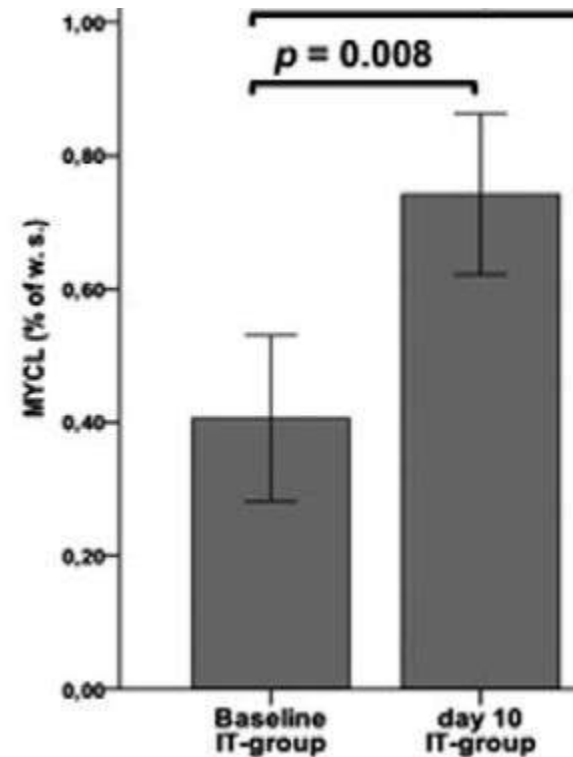
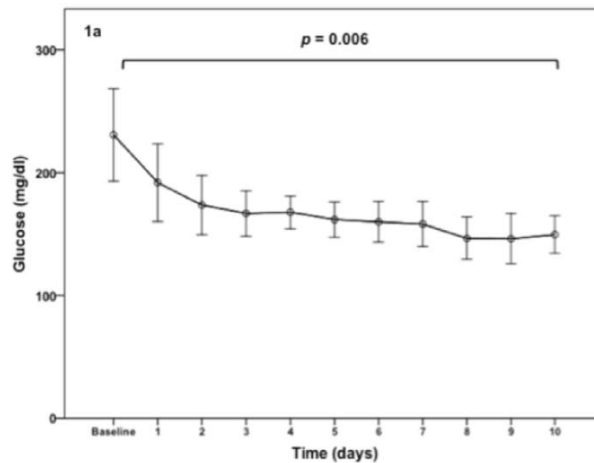
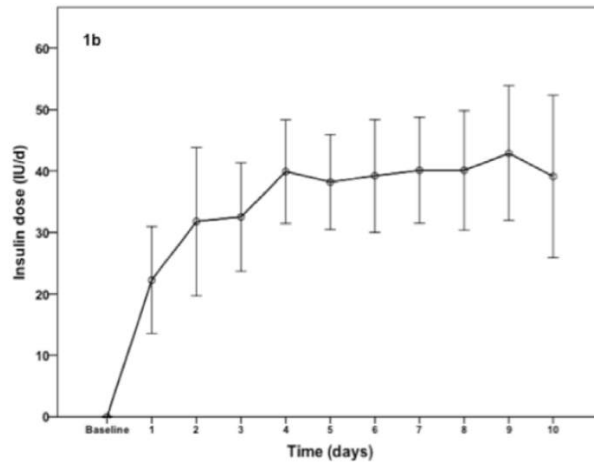
**oppassen met
meer nutriënten
in de cellen te duwen**

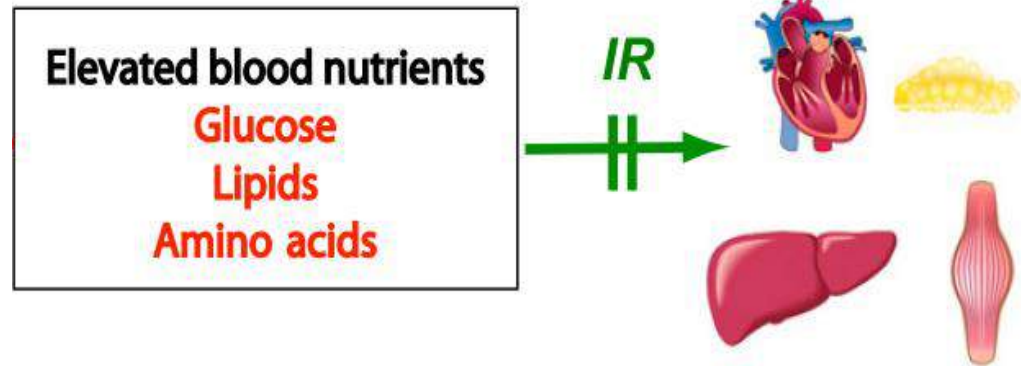
Insulin Resistance as a Physiological Defense Against Metabolic Stress: Implications for the Management of Subsets of Type 2 Diabetes

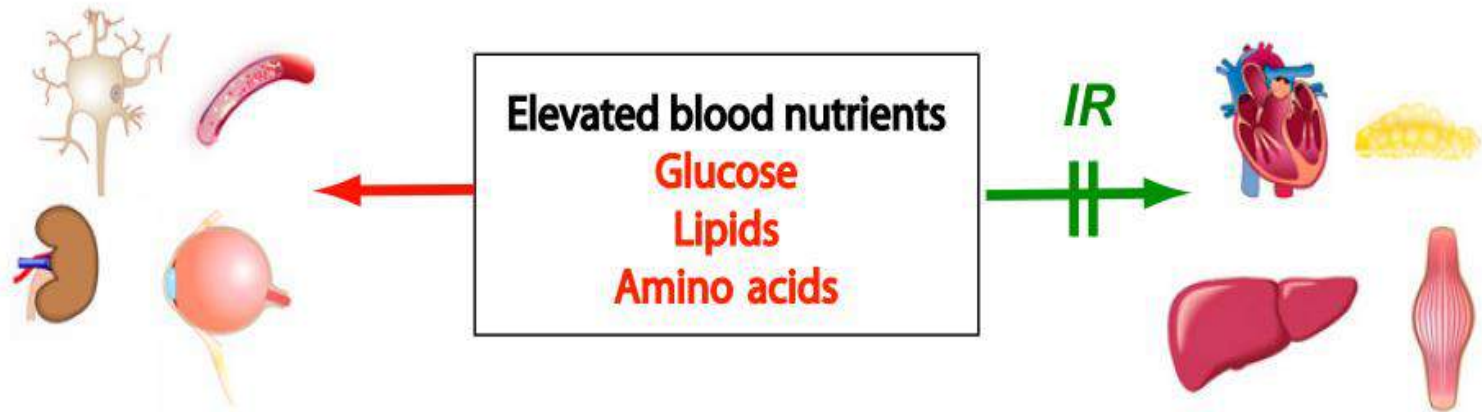


oppassen met 'overruling' van IR

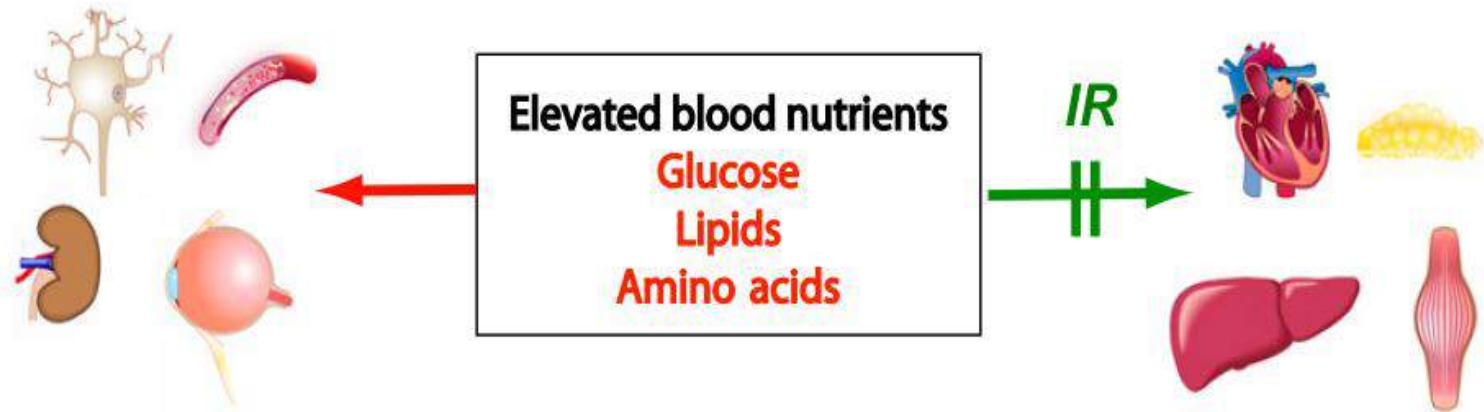
insuline doet myocard lipiden ↑



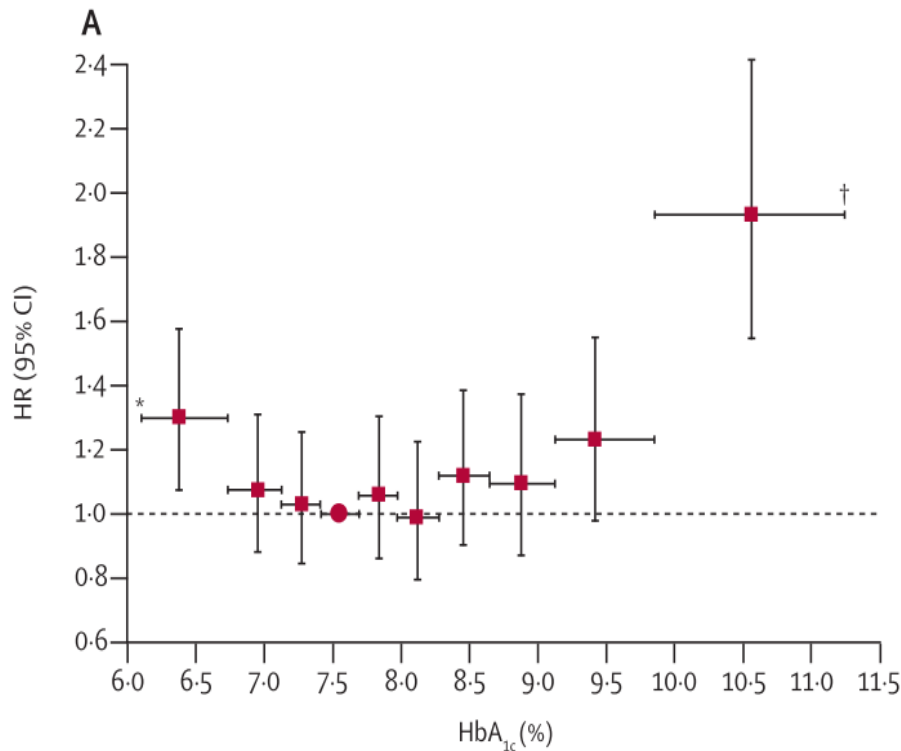




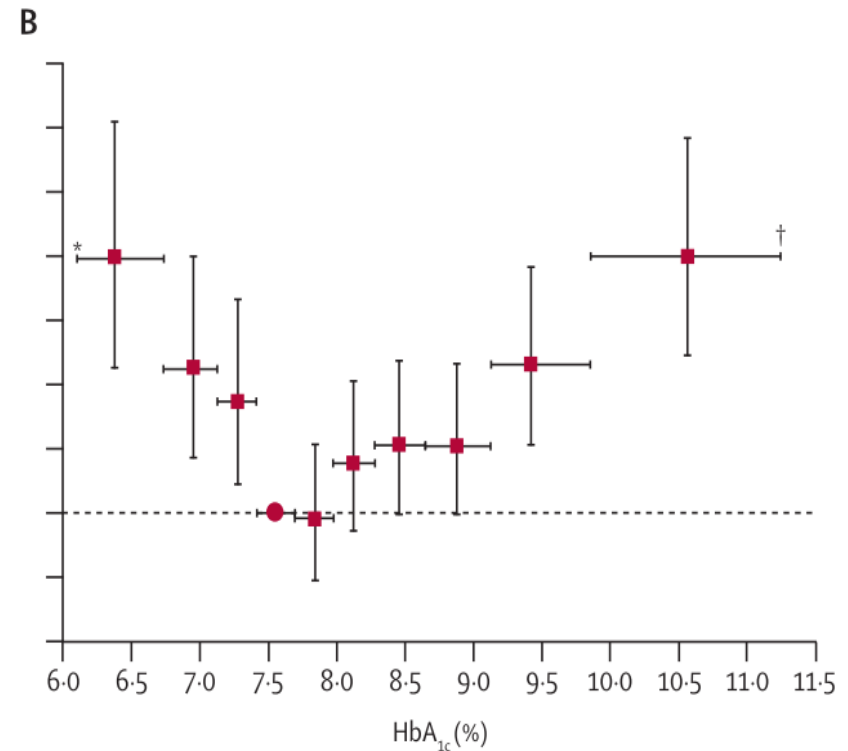
de kerk in het midden houden



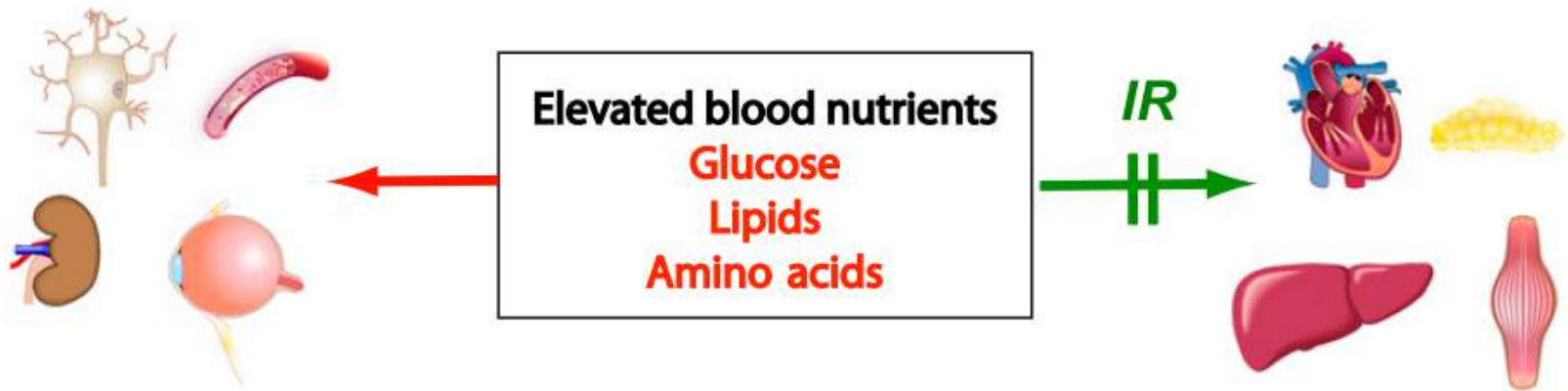
Survival $\sim$ HbA1c in type 2 diabetes: retrospective cohort study.

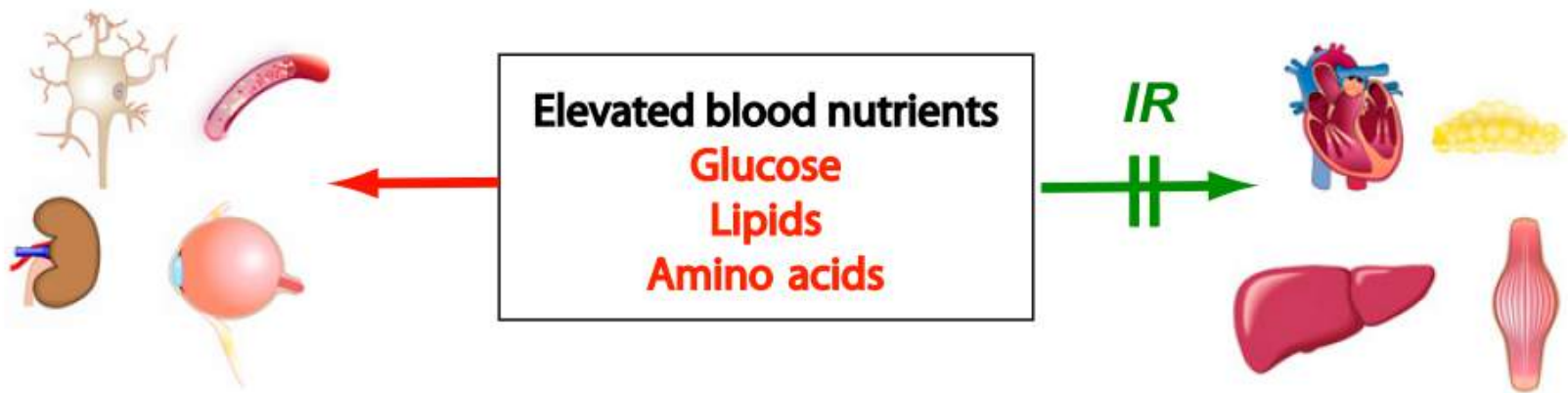


on OAD



on insulin





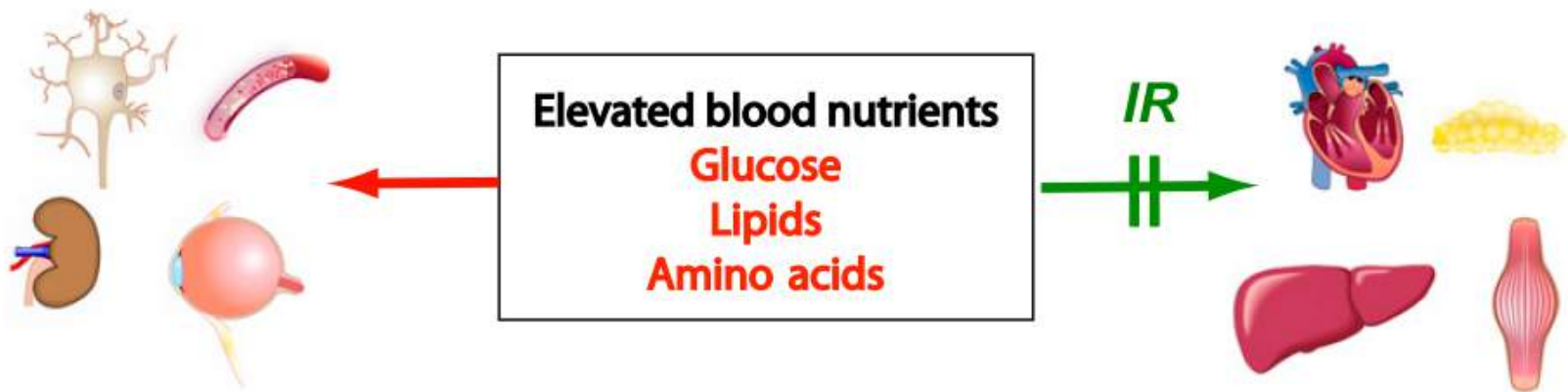
***Nutrient off-loading
+/- low-dose insulin***

Lifestyle
Bariatric surgery
GLP-1R agonists
 α -glucosidase inhibitors

Metformin
SGLT2 inhibitors
Thiazolidinediones?
DPP-4 inhibitors ?



Reduced metabolic stress in ALL tissues
Reduced short- and long-term complications



***Nutrient off-loading
+/- low-dose insulin***

Lifestyle
Bariatric surgery
GLP-1R agonists
 α -glucosidase inhibitors

Metformin
SGLT2 inhibitors
Thiazolidinediones?
DPP-4 inhibitors ?



Reduced metabolic stress in ALL tissues
Reduced short- and long-term complications

***Overriding insulin resistance in
refractory patients***

High-dose insulin
Sulfonylureas?



Insulin-induced metabolic stress
Short-term injury of insulin-sensitive tissues

onze patiënt

type 2 diabetes, insuline resistentie



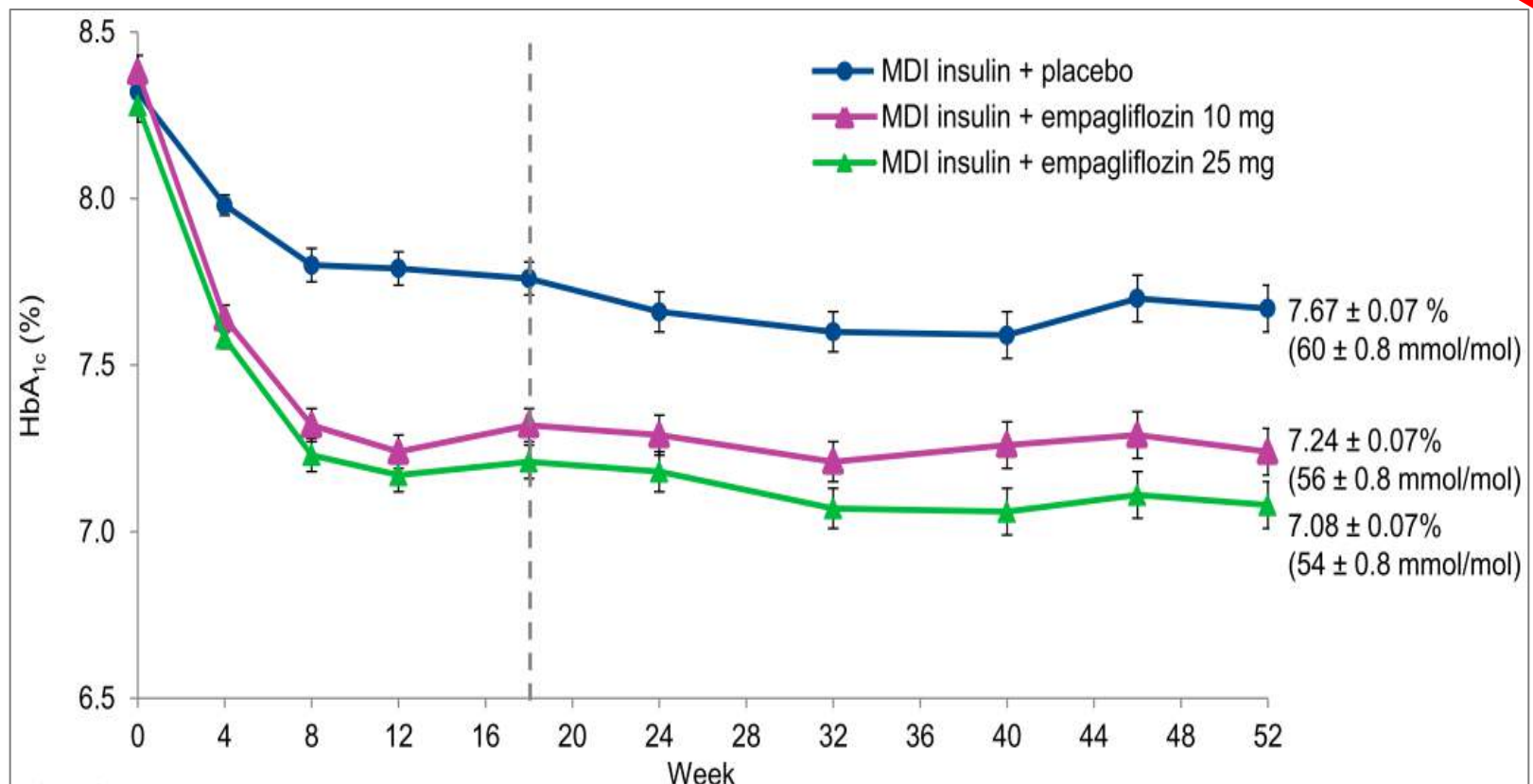
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- metformine 850 mg 1-1-1
Apidra 32-20-28 E
Lantus 35-0-0-35 E
- HbA1c (%) 7.3 → 8.0 → 8.4
(mmol/mol) 56 → 64 → 68
- 10 kg bijgekomen sinds insuline opstart

de insuline resistente patiënt

- on MDI ± metformin: HbA_{1c} 8.3%; BMI 34.8 kg/m²; insulin 92 U/d
- empagliflozin 10 mg (n=186), 25 mg (n=189), placebo (n=188) for 52 weeks

off-label

HbA_{1c}

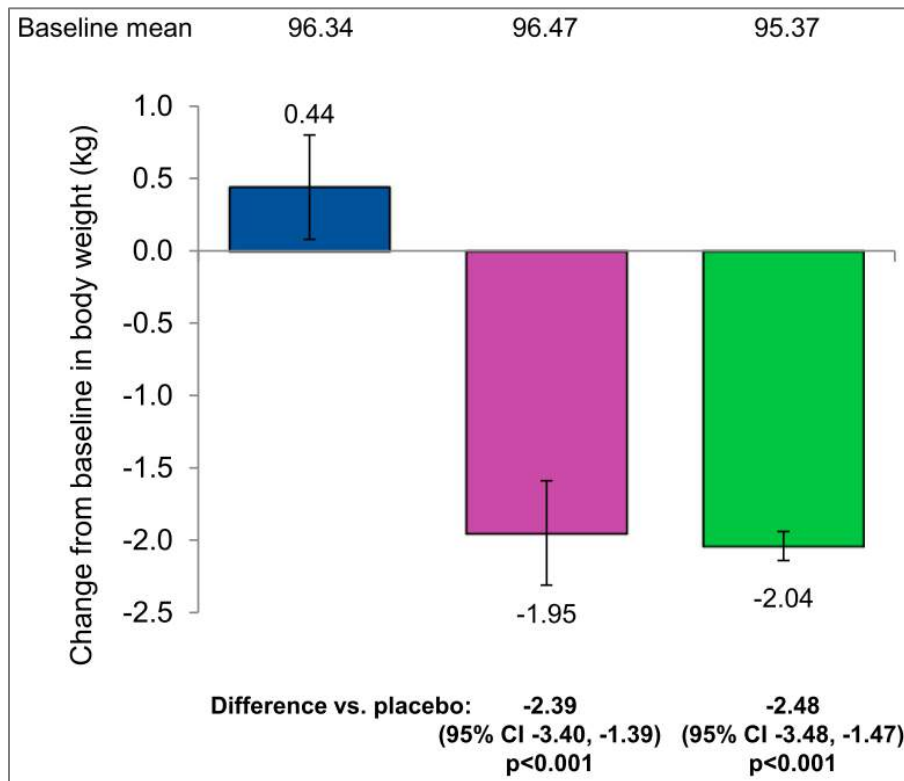


de insuline resistente patiënt

- on MDI ± metformin: HbA1c 8.3%; BMI 34.8 kg/m²; insulin 92 U/d
- empagliflozin 10 mg (n=186), 25 mg (n=189), placebo (n=188) for 52 weeks

off-label

gewicht

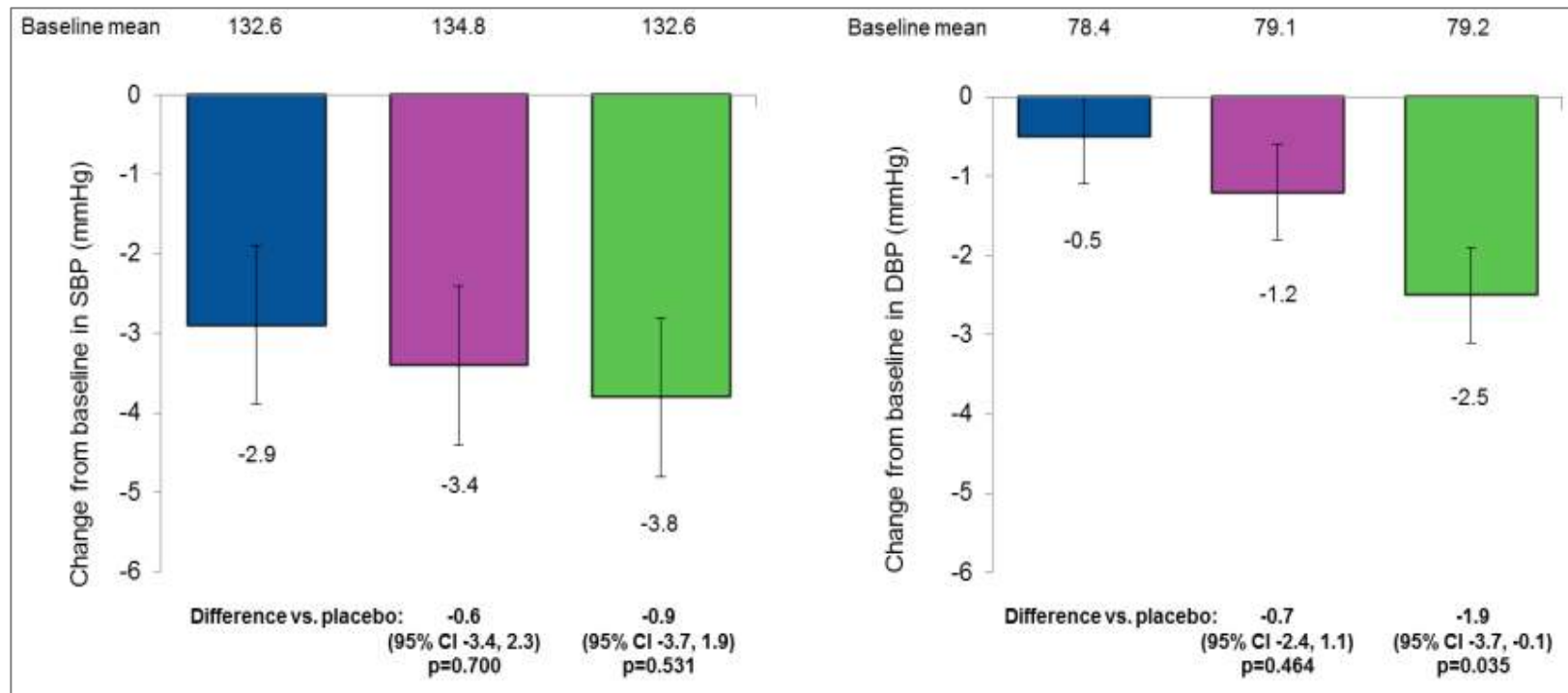


de insuline resistente patiënt

- on MDI ± metformin: HbA1c 8.3%; BMI 34.8 kg/m²; insulin 92 U/d
- empagliflozin 10 mg (n=186), 25 mg (n=189), placebo (n=188) for 52 weeks

off-label

Bloeddruk



andere risicofactoren

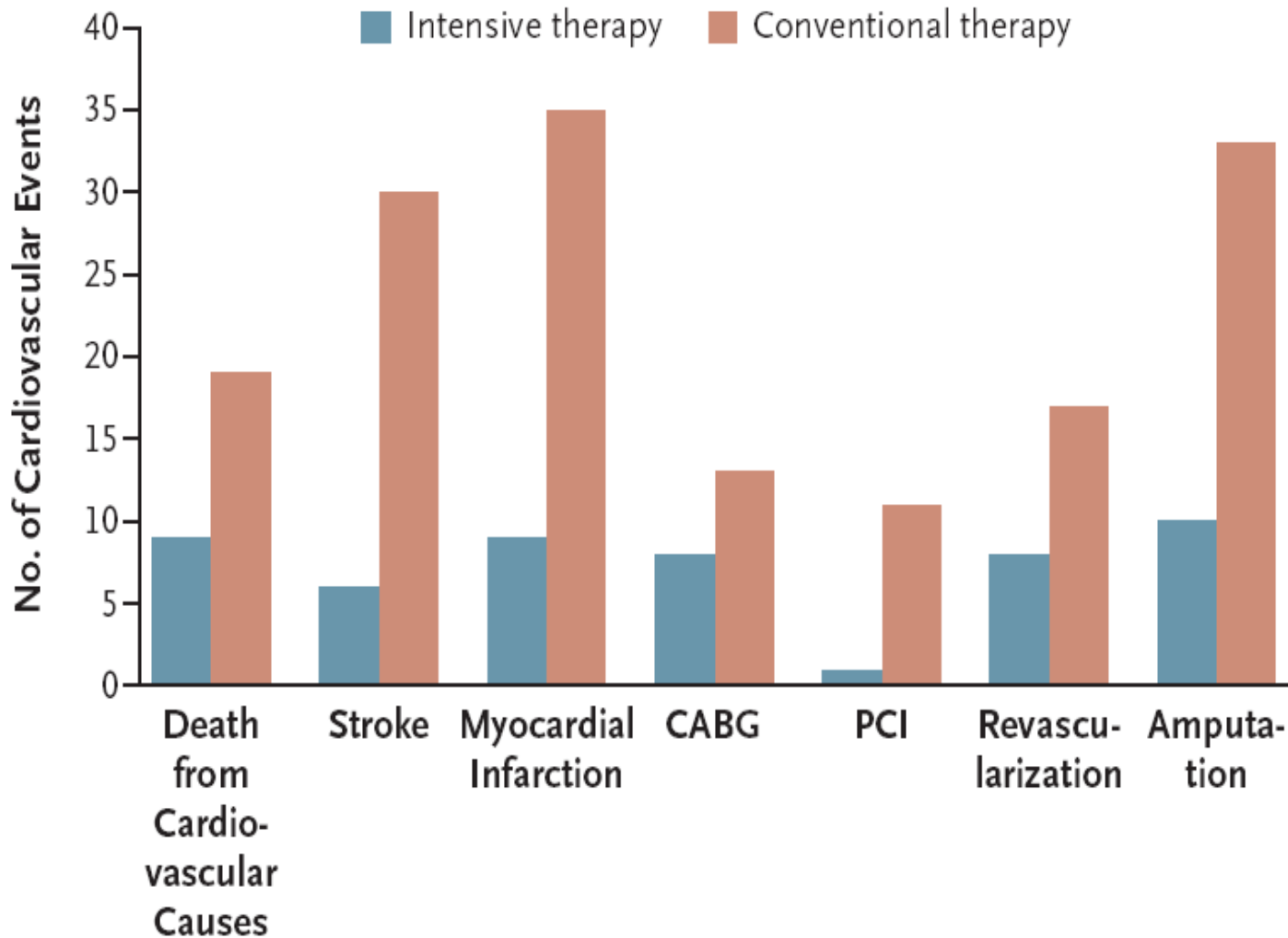
andere risicofactoren behandelen

- cardiovasculair
- slaap apnoe
- kankerscreening

A large, red, multi-pointed starburst graphic with a jagged, sunburst-like shape. It is centered on the right side of the slide and contains the text 'maakt het verschil' in white.

maakt
het verschil

Steno-2



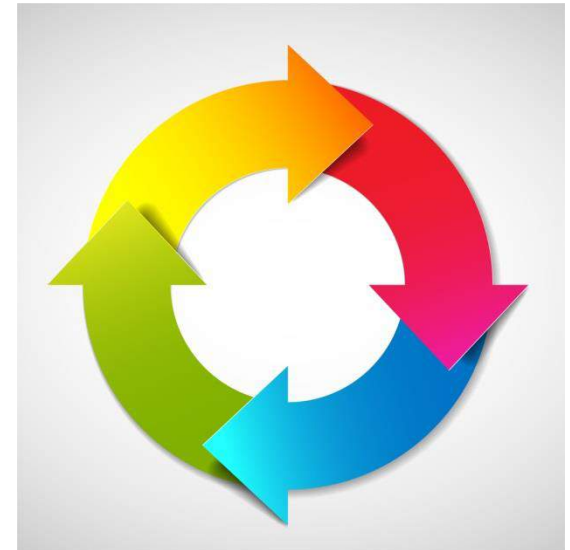
DM 2 + microalbuminuria: 8y intervention, 8+5=13 y follow-up

STENO-2 study. Gaede et al. NEJM 08;358:580

**zeer moeilijke situaties bij
uitgesproken insuline resistentie**

zeer moeilijke situaties bij insuline resistentie ++

- beperkte mobiliteit
- stoppen metformine
- corticoïden (chemotherapie)
- chirurgie, acute ziekte
- zwangerschap



samenvatting

type 2 diabetes/insuline resistentie

- Ernstig multifactorieel probleem
- Cellen overspoeld door nutriënten.
- Behandeling met 'nutrient off-loading'
- Oppassen met 'overrulen' van IR
- Correctie van (cardiovasculaire) risico's
- Blijf de vicieuze cirkel voor

glycemie verlagende medicatie

- verschuiving naar nieuwe producten met beter profiel dan SU
- DPP4i: effectief, meer en meer gerust over veiligheid
- SGLT2i: zeer effectief, ook bij gevorderde diabetes (maar niet bij nierinsufficiëntie), breed effect (G, BD), bewezen gunstig cardiovasculair
- GLP1a: meer en meer vóór insuline of in combinatie met basale insuline

START DIABETESPAS

metformine (MF)

- pro: laag hypo risico
gewicht neutraal
lange ervaring
uitkomststudie gunstig
- con: GFR moet ≥ 30
gastrointestinale hinder

Als MF gecontraïndiceerd of niet verdragen: stap overslaan.

Wij raden het gebruik van glitazones af, gezien veel neveneffecten.

+ DPP4-inhibitor (DPP4i)

- pro: laag hypo risico
gewicht neutraal
weinig neveneffecten
- con: beperkte ervaring
duur

of

+ SGLT2-inhibitor (SGLT2i)

- pro: laag hypo risico
gewicht ↓, BD ↓
uitkomststudie gunstig
- con: zeer beperkte ervaring
GFR moet ≥ 60
neveneffecten (genitaal, orthostatisme)
duur

of

+ sulfonyleureum (SU) (of glinide)

- pro: lange ervaring
uitkomststudie met SU gunstig
- con: gewicht ↑
hypo risico ↑
glycemie zelfcontrole nodig
snellere ↓ betacelfunctie?
cardiovasculair ongunstig?

mogelijke tussenstap:

tripel orale therapie

MF+SU+(SGLT2i of DPP4i)

- pro: geen spuitjes
- con: HbA1c ↓ $\leq 1\%$

START ZORGTRAJECT

+ GLP-1 analoog (GLP1a) met MF (+ SU)

- pro: laag hypo risico
gewicht ↓
sommige slechts 1 spuit/week
- con: beperkte ervaring
pas op bij nierinsufficiëntie
gastrointestinale hinder
erg duur

of

+ basale insuline

- met MF (+ SU) (+DPP4i of SGLT2i)
- pro: matig hypo risico
lange ervaring
- con: gewicht ↑

mogelijke tussenstap:

+ GLP1 analoog en basale insuline

met MF (+ SU)

- pro: GLP1a remt gewicht ↑ van insuline af
minder hypoglycemie dan complex insulineschema
- con: minder krachtig dan complex insulineschema
neveneffecten van GLP1a

START CONVENTIE

complex insulineschema

met MF (+ SU)

kostprijs voor $\pm$ equipotente dosis

kost aan maatschappij: € / 30d

- metformine 2 x 850 mg/d: 6
- gliclazide 3 x 80 mg/d: 15
- sitagliptine 1 x 100 mg/d: 43
- empaglifozine 1 x 10 of 25 mg/d: 44
- exenatide LAR 1 x /wk: 105
- NPH 40 E/d: 30

terugbetalingscriteria

DPP4i:

- A1c 7-9%
- in monotherapie bij nierinsufficiëntie (MDRD < 50)
- in bi- of tritherapie met oude OAD
- mag met basale insuline
- $A1c \leq 9\%$ voor verlenging en niet hoger dan bij start

SGLT2i:

- A1c 7-9%, GFR ≥ 60 ml/min
- niet in monotherapie
- in bi- of tritherapie met oude OAD
- mag met basale insuline
- $A1c \leq 7,5\%$ of daling $> 0,5\%$ en gewichtsdeling voor verlenging

**Mag ik nog iets zeggen
over type 1 diabetes?**

FreeStyle Libre (Flash)



Snapshot

15 september 2015 - 22 september 2015 (8 dagen)

FreeStyle Libre 

Glucose

Geschatte HbA1c **6,4%** of **46 mmol/mol**

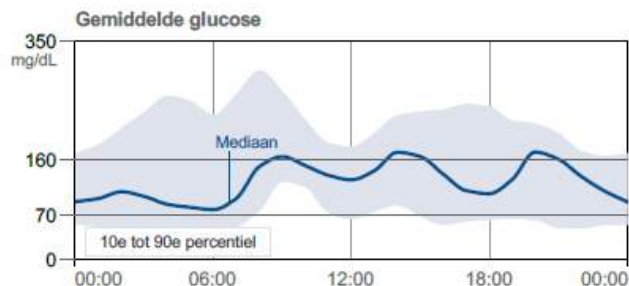
GEMIDDELDE GLUCOSE

136 mg/dL

% boven doel **35** %

% binnen doel **42** %

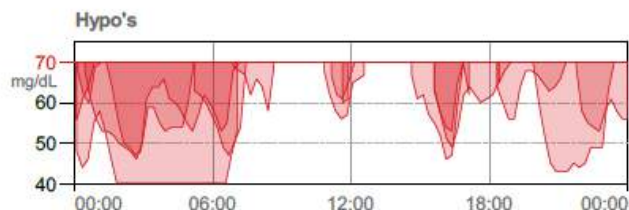
% onder doel **23** %



HYPO'S

14

Gemiddelde duur **208** Min



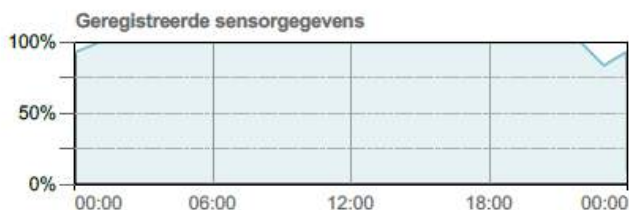
Sensorgebruik

GEREGISTREERDE

SENSORGEGEVEN

100 %

Dagelijkse scans **13**



Opmerkingen

Genoteerde KH

DAGELIJKSE KH

163 gram/dag

Genoteerde insuline

Snelwerkende insuline **36,8** eenheden/dag

Langwerkende insuline **25,0** eenheden/dag

TOTALE DAGELIJKSE INSULINE **61,8** eenheden/dag

wo 16 sep.

 **Glucose**
mg/dL



 **Snelwerkende
insuline**
eenheden

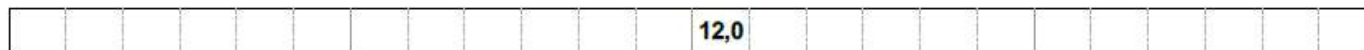
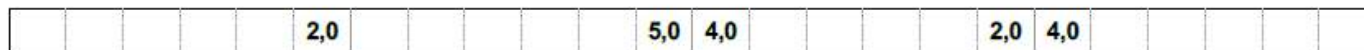
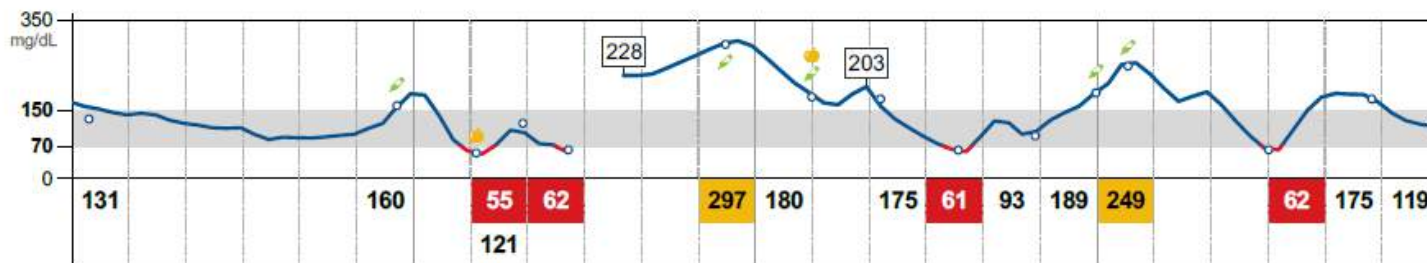
do 17 sep.

 **Glucose**
mg/dL

 **KH**
gram

 **Snelwerkende
insuline**
eenheden

**Langwerkende
insuline**
eenheden



Dagelijkse trends (met glucosemetingen)

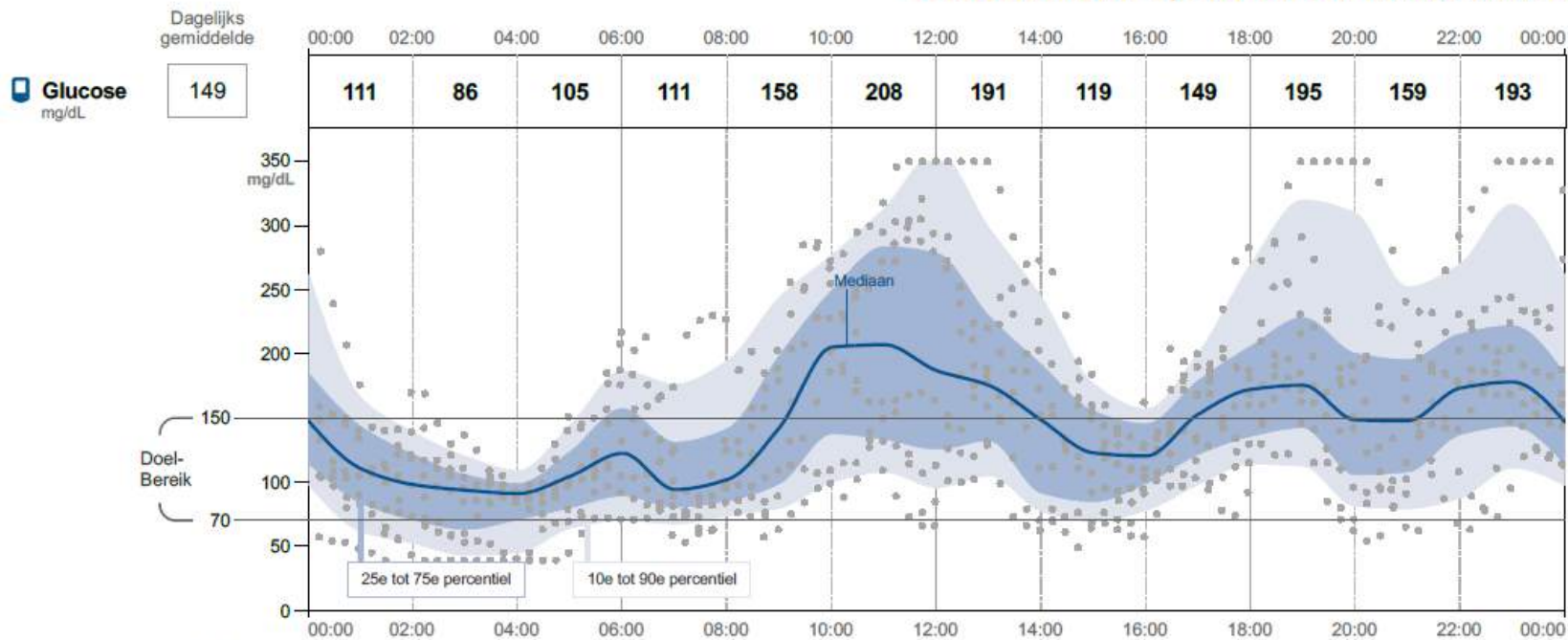
16 september 2015 - 23 september 2015 (8 dagen)

FreeStyle Libre 

Geschatte HbA1c **6,8% of 51 mmol/mol**

PAGINA: 3 / 7
DATUM: 2015-10-20

GEGEBENSBRON: FreeStyle Libre 2.1.2
FreeStyle Libre 1.0



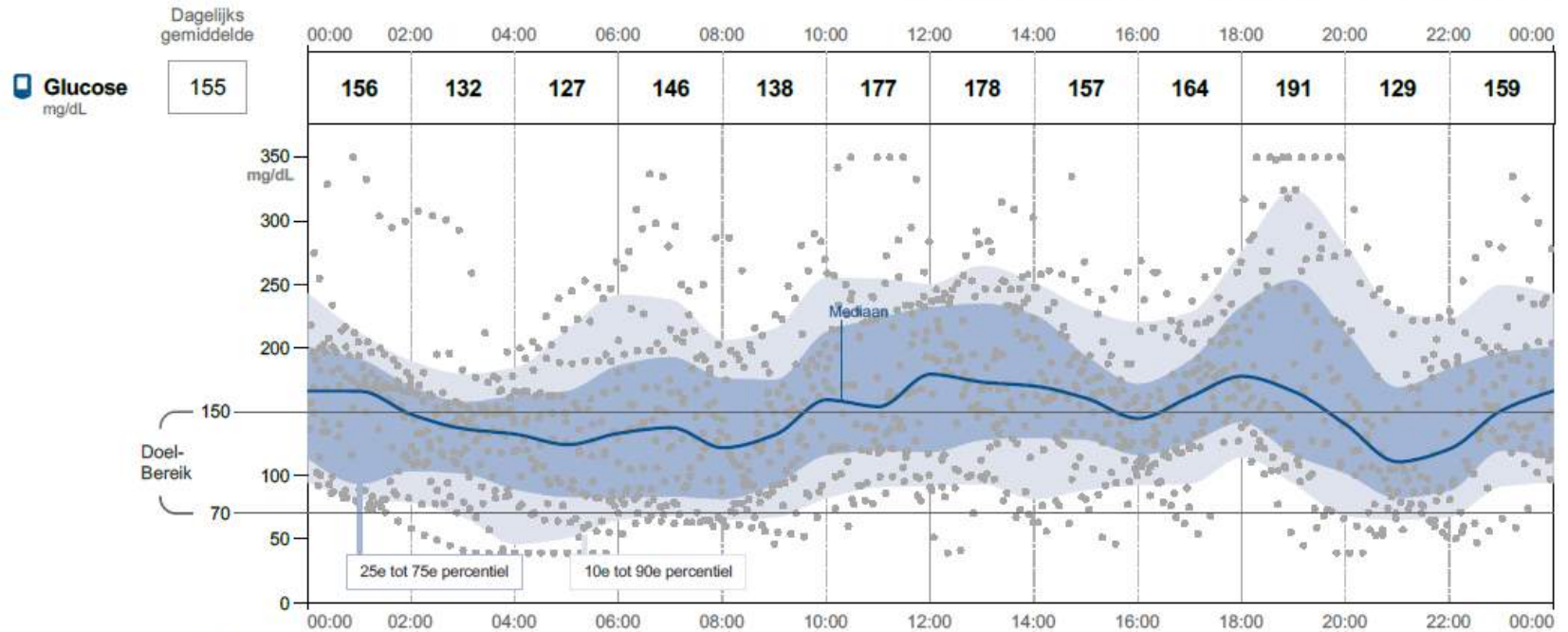
Dagelijks gemiddelde		gemiddelde (aantal dagen waarover is gemiddeld)											
 KH gram	-												
 Snelwerkende insuline eenheden	19,8			0,7 (3)	1,8 (3)	0,3 (1)	3,8 (6)	4,3 (6)		2,1 (5)	5,1 (7)	0,6 (1)	1,1 (3)
 Langwerkende insuline eenheden	9,0							9,0 (6)					

Dagelijkse trends (met glucosemetingen)

28 september 2015 - 12 oktober 2015 (15 dagen)

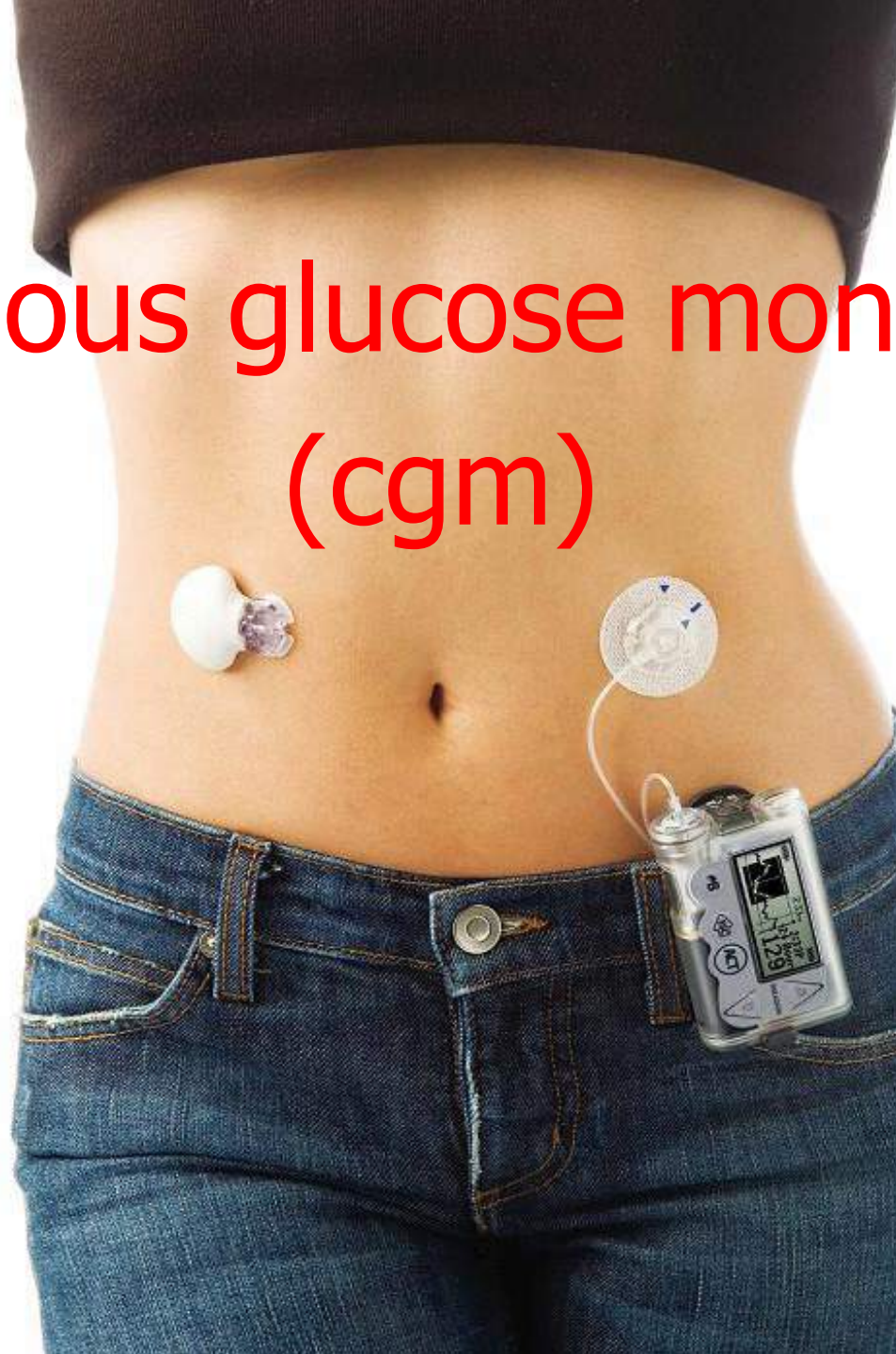


Geschatte HbA1c **7,0%** of **53 mmol/mol**

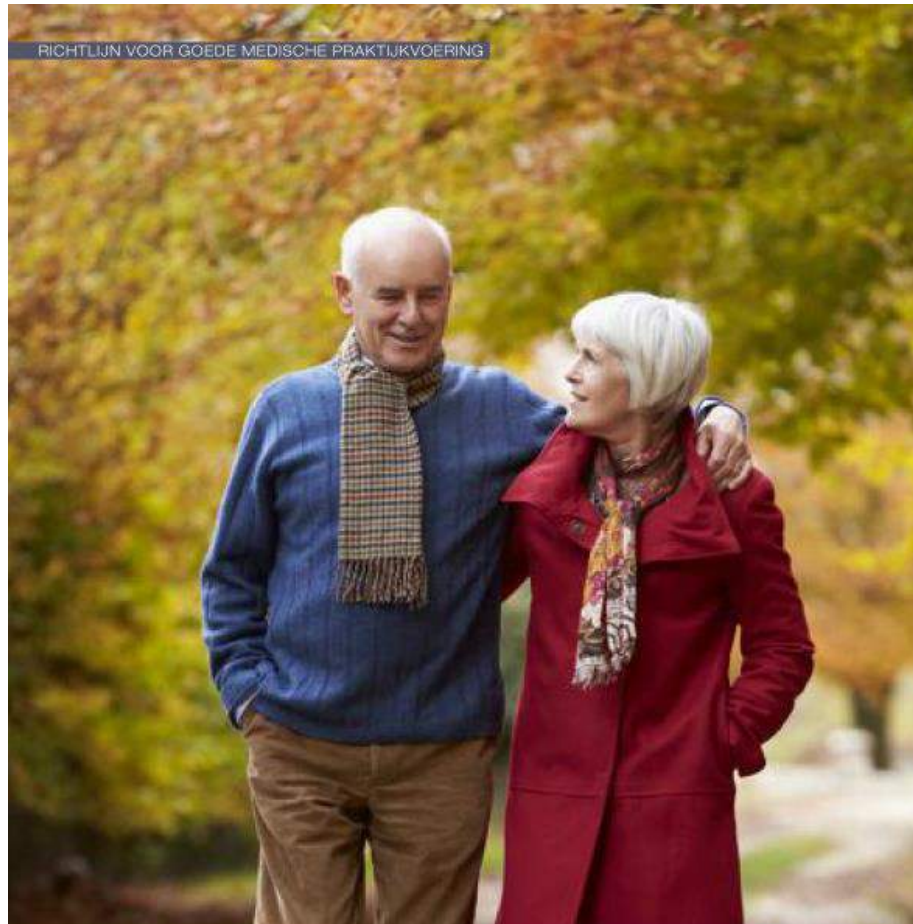


Dagelijks gemiddelde		gemiddelde (aantal dagen waarover is gemiddeld)											
 KH gram	-	40g											
 Snel-werkende insuline eenheden	13,1	0	0,3 (1)	0,2 (1)	1,8 (8)	1,4 (6)	1,9 (6)	2,5 (7)	0,4 (2)	1,4 (8)	2,8 (10)		0,4 (2)
 Lang-werkende insuline eenheden	7,2	10eh						6,4 (8)	0,8 (1)				

continuous glucose monitoring (cgm)



zelfstudie



DIABETES MELLITUS TYPE 2

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L. FEYEN, P. SUNAERT, P. VAN CROMBRUGGE, I. VAN POTTELBERGH,
E. VAN LEEUWEN, A. VERHAEGEN, F. NOBELS

domus
medica



Intro
Diagnose/start behandeling
+ Opvolging onder orale beh.
Overgang naar injecties
+ Opvolging onder injecties
+ Vaststellen van complicaties
Rijbewijs
Downloads

Zwangerschapsdiabetes.org

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DIABETES-WIJZER VOOR DE ZORGVERLENER.

EEN PRODUCT VAN [DIABETESPROJECT AALST](#)



