Behandeling Type 2 Diabetes Mellitus

Gids voor de huisarts
Diabetes Liga & ABD

INHOUD

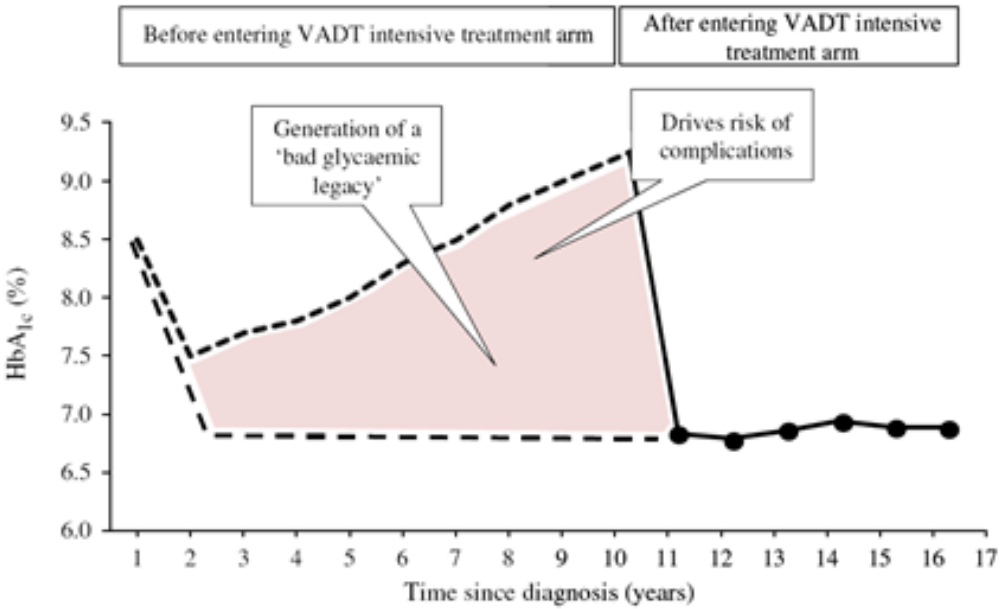
- **EASD/ADA recommendations**
- Cases:
  - Nieuw gediagnosticeerde patiënt (prof. F. Nobels)
  - Intensificatie na metformine (prof. A. Scheen)
  - Metformine + SU (Prof. M. Buysschaert)
  - Metformine + DPP4i (prof. C. De Block)
  - Metformine + SGLT2i (prof. L. Crenier)
  - GLP1-receptor agonist (dr. A. Verhaegen)
  - Basale insuline (prof. C. Mathieu)
- Aandachtspunten:
  - Leeftijd, baseline HbA1c, BMI, nierfunctie, CV disease

EASD/ADA Guidelines 2015

MEDICAL NEED

HbA1c		
	As low as possible →	Indivualised
	As soon as possible →	↓inertia
	For as long as possible →	↓ complications
	As safely as possible →	↓hypo, CV, renal
	As rationally as possible →	No weight gain

METABOLIC MEMORY



Inzucchi et al – Diabetes Care 2015

Challenges in type 2 diabetes

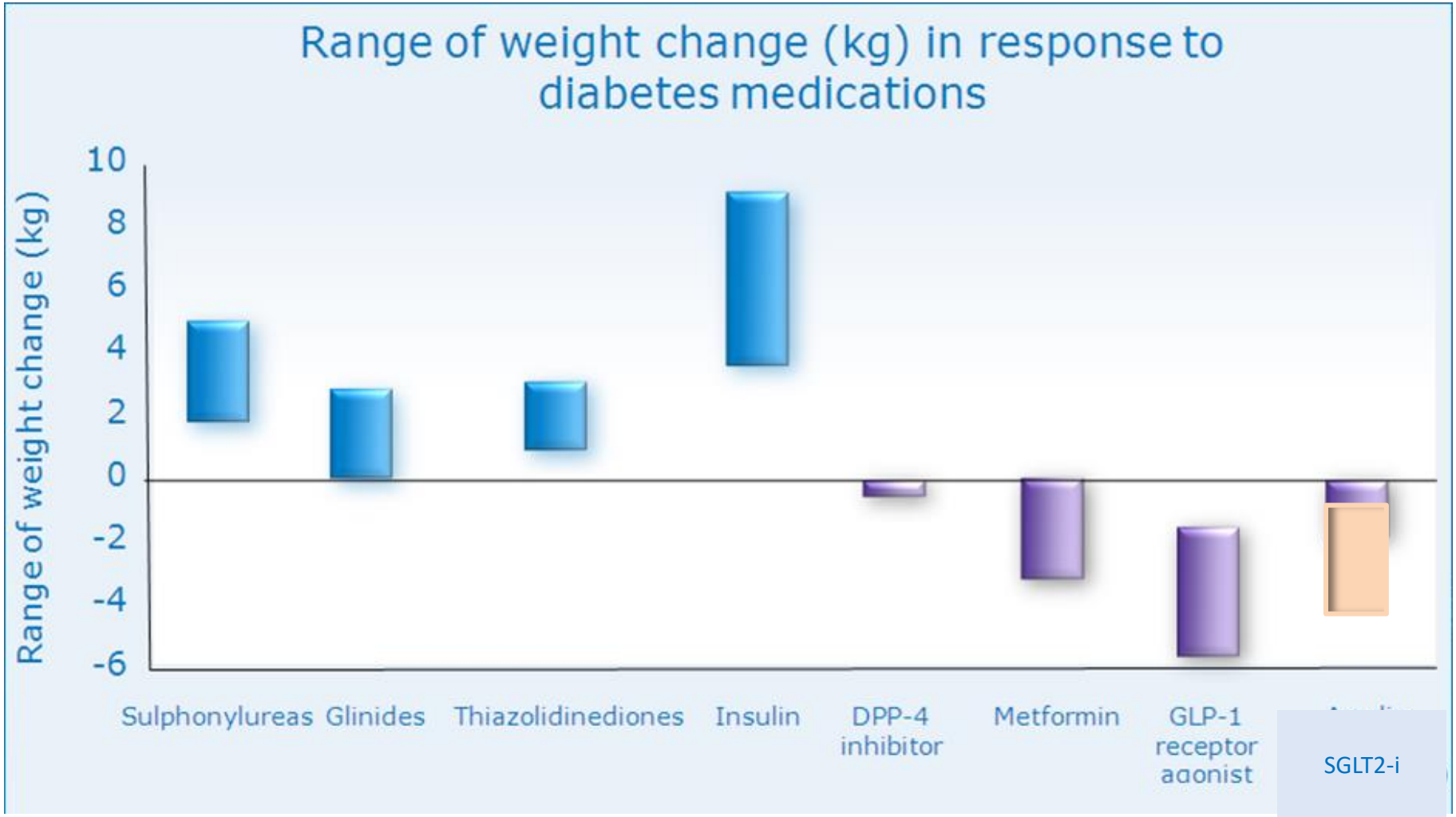
Hypoglycemia is a frequent acute complication of treatment

High risk[1]	Low risk[1,2]
Insulin	Metformin
Sulphonylureas	α-glucosidase inhibitors
Meglitinides	Thiazolidinediones
	GLP-1 receptor agonists
	DPP-4 inhibitors
	SGLT2- inhibitors

1. Nathan DM, et al. Diabetologia. 2009;52:17-306.
2. Cefalu WT. Nature. 2007;81:636-49.

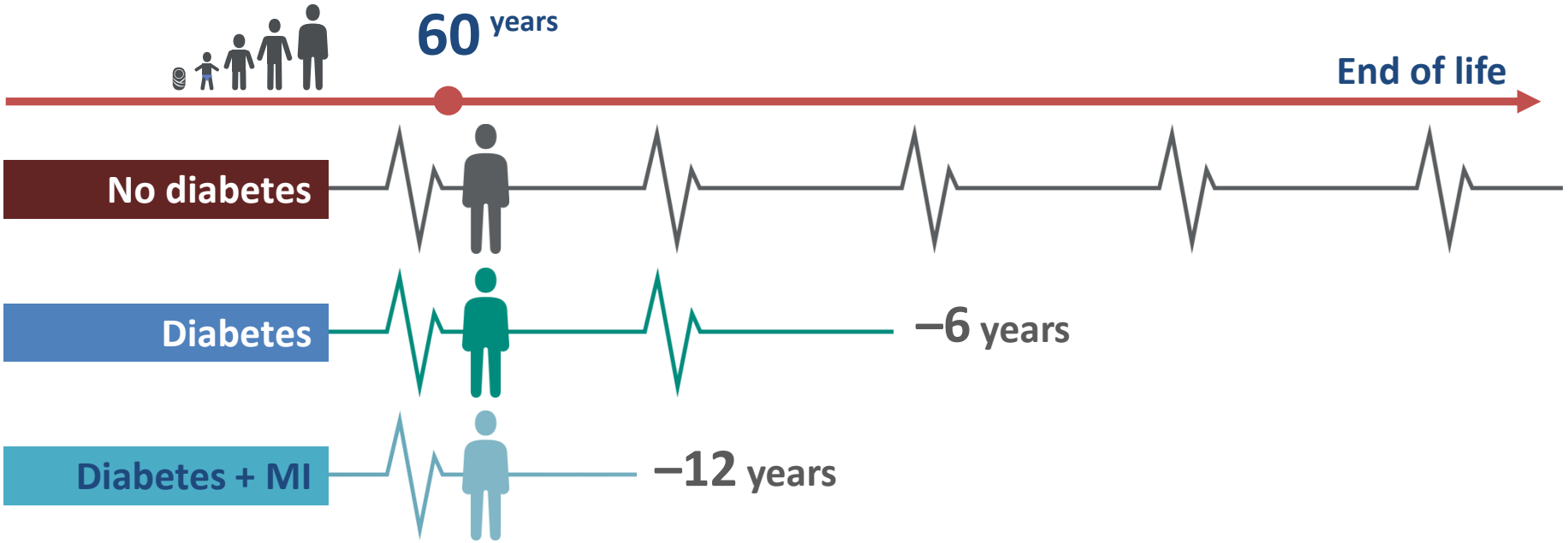
Challenges in type 2 diabetes

Weight increases with time



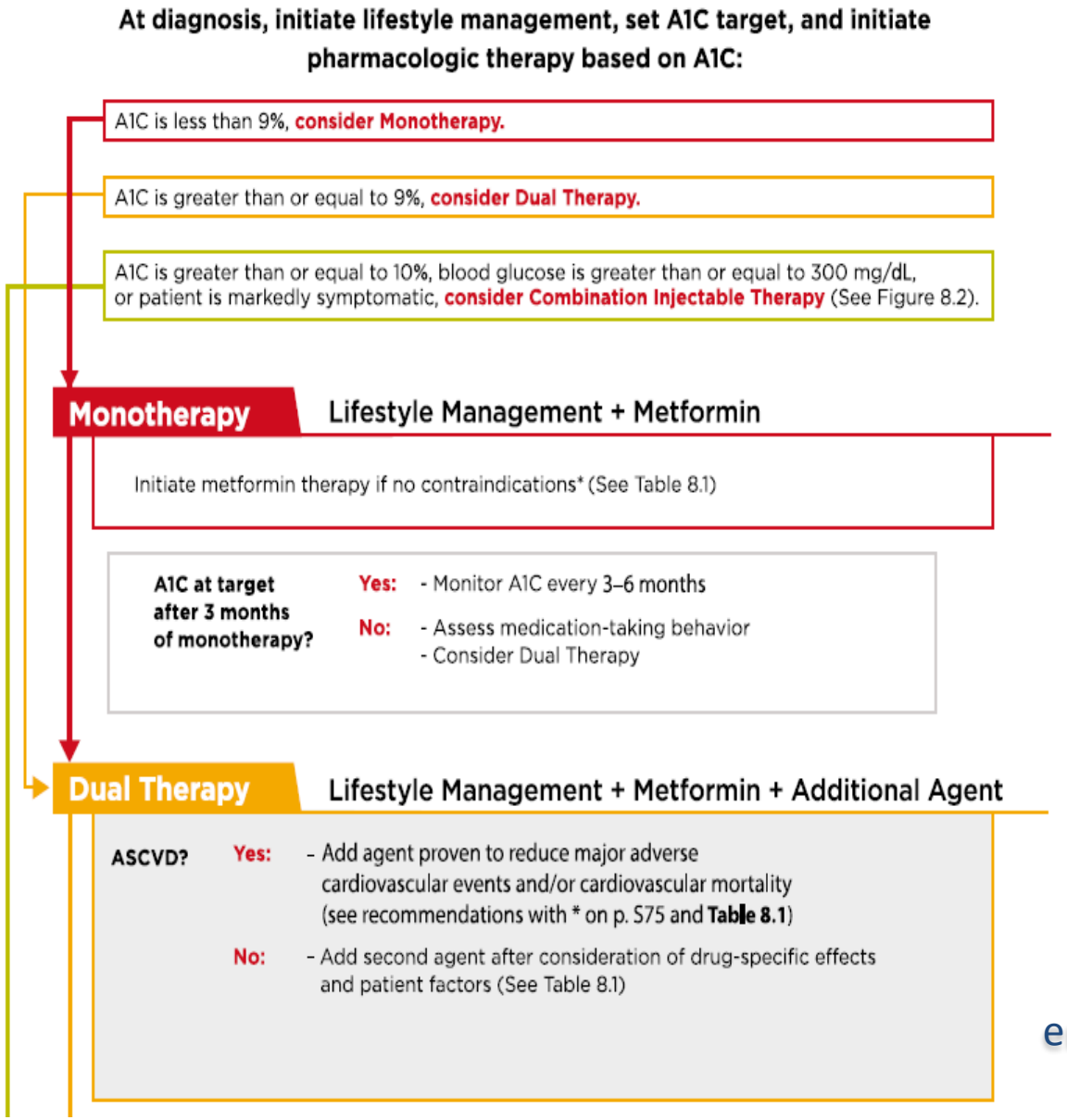
Adapted from: Joanna Mitri & Osama Hamdy Expert Opin. Drug Saf. (2009) 8(5)

Life expectancy is significantly decreased in patients with T2D and established CV disease*



In this case, CV disease is represented by MI or stroke. *Male, 60 years of age with history of MI or stroke
CV, cardiovascular; MI, myocardial infarction; T2D, type 2 diabetes
The Emerging Risk Factors Collaboration. *JAMA* 2015;314:52

Antihyperglycemic Therapy in Adults with Type 2 Diabetes



American Diabetes Association

8. Pharmacologic Approaches to Glycemic Treatment: *Standards of Medical Care in Diabetes—2018*

Diabetes Care 2018;41(Suppl. 1):S73–S85 | https://doi.org/10.2337/dc18-S008

- In patients with type 2 diabetes and established atherosclerotic cardiovascular disease, antihyperglycemic therapy should begin with lifestyle management and metformin and subsequently incorporate an agent proven to reduce major adverse cardiovascular events and cardiovascular mortality (currently empagliflozin and liraglutide), after considering drug-specific and patient factors

empagliflozin & liraglutide : class A
canagliflozin : class C

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- Aandachtspunten:
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CASUS

Dame:

- Leeftijd: 55 jaar
- Beroep: lerares

Medische voorgeschiedenis:

- type 2 diabetes sinds 5 jaar
- Hypercholesterolemie & hypertensie
- Cardiovasculaire voorgeschiedenis: blanco

Usus:

- Roken: negatief
- Ethyl: sporadisch

Medicatie:

- Metformine 850 mg 2/d
- Statine, ACE-inhibitor

CASUS

Klinisch onderzoek:

- BMI 28,5 kg/m^2
- BD: 140/85 mmHg

Laboratoriumonderzoek:

- HbA1c: 8,7%
- Tot chol 190 mg/dl; HDL 45 mg/dl; LDL 110 mg/dl; TG 175 mg/dl
- eGFR: 85 ml/min/1,73 m^2

Antihyperglycemic therapy in type 2 diabetes: EASD/ADA recommendations.

Monotherapy **Metformin** **Lifestyle Management**

EFFICACY*	high
HYPO RISK	low risk
WEIGHT	neutral/loss
SIDE EFFECTS	GI/lactic acidosis
COSTS*	low

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

Dual Therapy **Metformin +** **Lifestyle Management**

	Sulfonylurea	Thiazolidinedione	DPP-4 inhibitor	SGLT2 inhibitor	GLP-1 receptor agonist	Insulin (basal)
EFFICACY*	high	high	intermediate	intermediate	high	highest
HYPO RISK	moderate risk	low risk	low risk	low risk	low risk	high risk
WEIGHT	gain	gain	neutral	loss	loss	gain
SIDE EFFECTS	hypoglycemia	edema, HF, fxs	rare	GU, dehydration, fxs	GI	hypoglycemia
COSTS*	low	low	high	high	high	high

Theoretisch: kies voor medicatie

- met laag hypo risico
- gewichts-neutraal of -verlies
- cardiovasculair neutraal of protectief

Diabeters Care 2017

Intensificatie na metformine

Prescribe sulphonylurea

- Only in patients not at risk of hypoglycaemia
- Avoid in elderly patients living alone
- Avoid in obese patients
- Avoid in patients with CV disease
- Avoid in patients with renal impairment
- Give preference to gliclazide modified release (UniDiamicron)
- Lower cost

Prescribe DPP-4 inhibitor

- In elderly frail patients
- In patients with renal impairment (dose reduction except for linagliptin)
- In patients with CV disease (CV neutrality)

Intensificatie na metformine

Prescribe a DPP-4 inhibitor

Prescribe an SGLT-2 inhibitor

FIG 1 — **Approche phénotypique schématique orientant le choix thérapeutique**

C-I: contre-indications; CV: cardiovasculaire; DFG: débit de filtration glomérulaire.

Phénotype orientant vers une gliptine	Phénotype orientant vers une gliflozine
• pas trop obèse	• obèse
• peu hyperglycémique	• hypertendu
• relativement âgé	• hyperuricémique
• profil fragilisé	• antécédents CV
• C-I gliflozines (*)	• insuffisance cardiaque
• insuffisant rénal	• DFG > 45-60 ml/min/1,73 m²
• non à risque (**)	• non à risque (*)

* Infections urogénitales, déshydratation/hypotension

** Pancréatite

casus

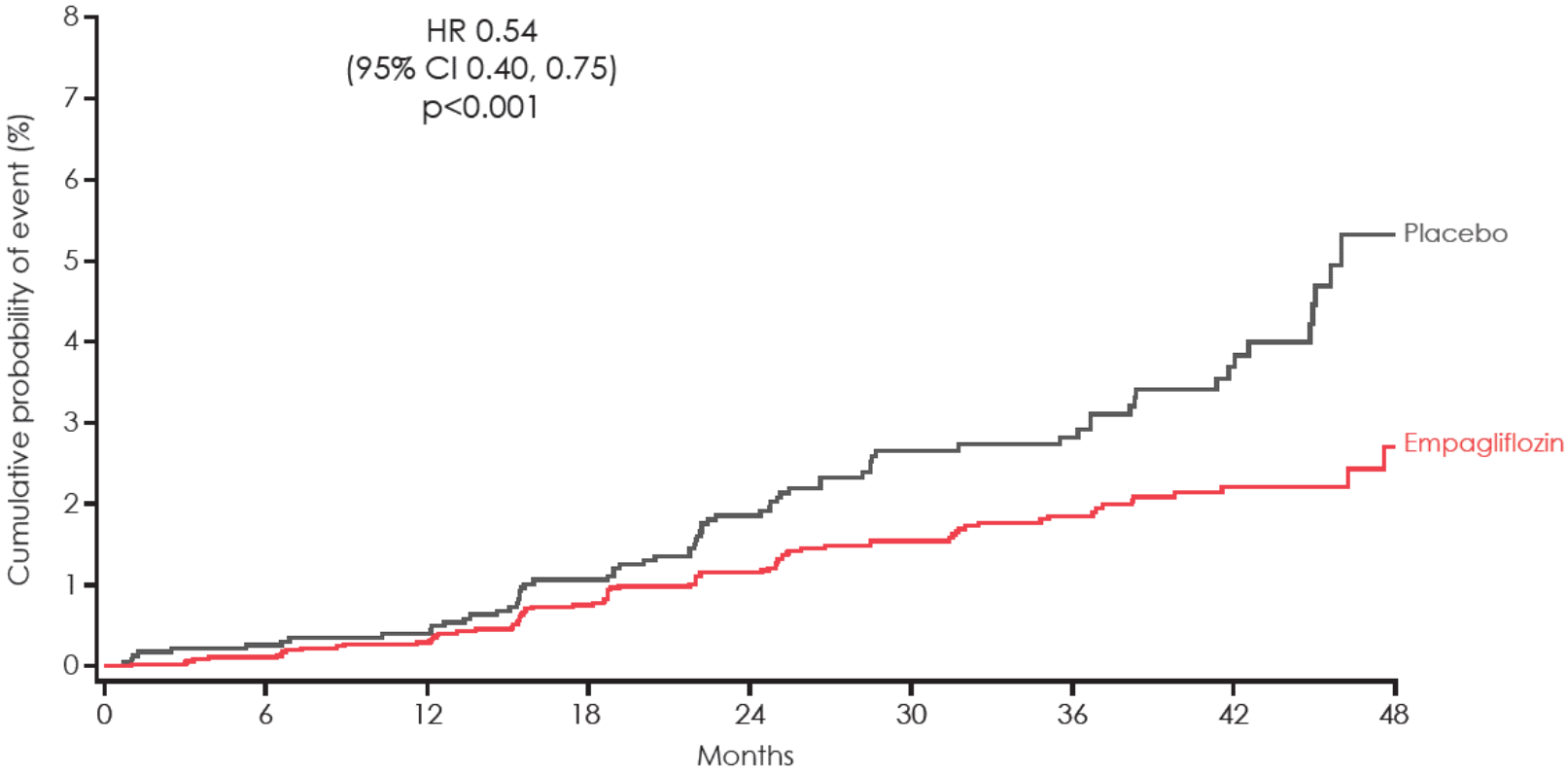
- *Medicatie:*
  - *Metformine 850 mg 2/d; wat toevoegen?*
  - *Stel:*
    - *Nierinsufficiënt*
    - *Voorgeschiedenis van cardiovasculair event*
    - *Hoge BMI*
    - *Hoogbejaard: mevrouw is 80 jaar ipv 55 jaar*
    - *Hoog HbA1c*

Intensificatie na metformine

Casus variation: Based on renal function

- ***Metformin:*** ***stop if eGFR < 30ml/min/1.73m² (reduced dose by half if < 45 ml/min/1.73 m²)***
- ***Sulphonylureas*** ***: be careful for hypoglycaemia (more fragile patients)***
  - *Gliquidone : no renal excretion, thus OK (same for repaglinide)*
  - *Gliclazide : no active metabolite, thus OK with caution*
- ***DPP-4 inhibitors*** ***: no increased risk, still active***
  - *Linagliptin : no renal excretion, thus no dose reduction*
  - *Alo-, saxa-, sita- and vildagliptin : dose reduction according to eGFR*
- ***SGLT-2 inhibitors*** ***: reduced glucose-lowering activity***
  - *No inititiation if eGFR < 60 ml/min/1.73 m²*
  - *Stop if eGFR < 45 ml/min/1.73 m²*
  - *Subject to modified rules in the future (because evidence of renal protection)*

Empagliflozin: Doubling of serum creatinine*, initiation of renal replacement therapy, or death due to renal disease



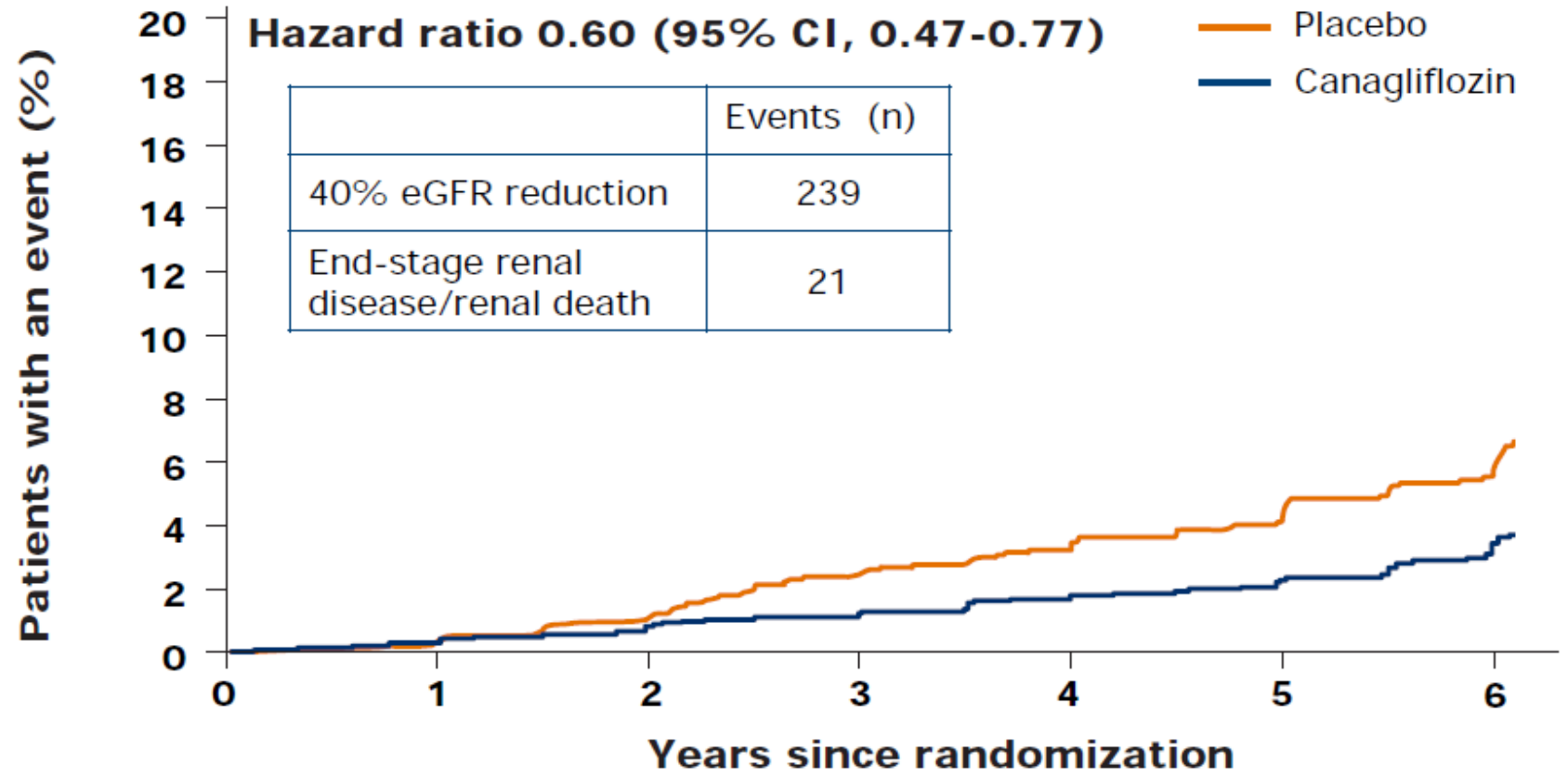
No. of patients									
Empagliflozin	4645	4500	4377	4241	3729	2715	2280	1496	360
Placebo	2323	2229	2146	2047	1771	1289	1079	680	144

Kaplan-Meier estimate in patients treated with ≥1 dose of study drug.
Hazard ratios are based on Cox regression analyses.
*Accompanied by eGFR [MDRD] ≤45 ml/min/1.73m^2.
HR, hazard ratio; CI, confidence interval. *Post-hoc* analyses.

Wanner C et al. NEJM 2016

Canagliflozin: Renal outcome

Composite of 40% Reduction in eGFR, End-stage Renal Disease, or Renal Death



No. of patients

Placebo	4347	4227	3029	1274	1229	1173	819
Canagliflozin	5795	5664	4454	2654	2576	2495	1781

casus

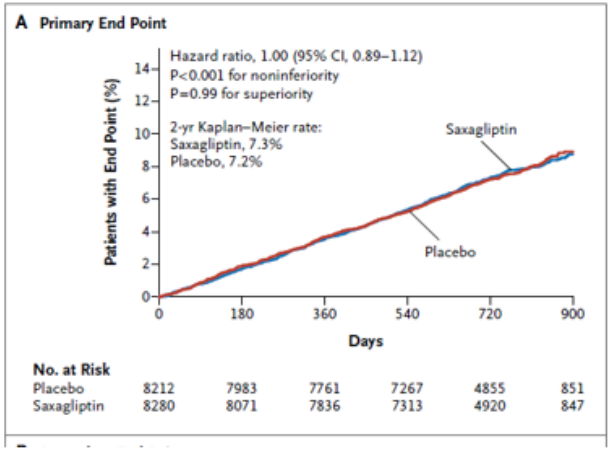
- *Medicatie:*
  - *Metformine 850 mg 2/d; wat toevoegen?*
  - *Stel:*
    - *Nierinsufficiënt*
    - *Voorgeschiedenis van cardiovasculair event*
    - *Hoge BMI*
    - *Hoogbejaard: mevrouw is 80 jaar ipv 55 jaar*
    - *Hoog HbA1c*

Cardiovascular safety/efficacy of DPP-4 inhibitors (gliptins)

Non-inferiority versus placebo

Saxagliptin and Cardiovascular Outcomes in Patients with Type 2 Diabetes Mellitus

SAVOR TIMI 53
Scirica et al. NEJM 2013; 369: 1317-26



SAVOR: saxagliptin vs placebo

3-point MACE : +0 % (p=0.99)

CV death : +3 % (p=0.72)

All-cause death : +11 % (p=0.15)

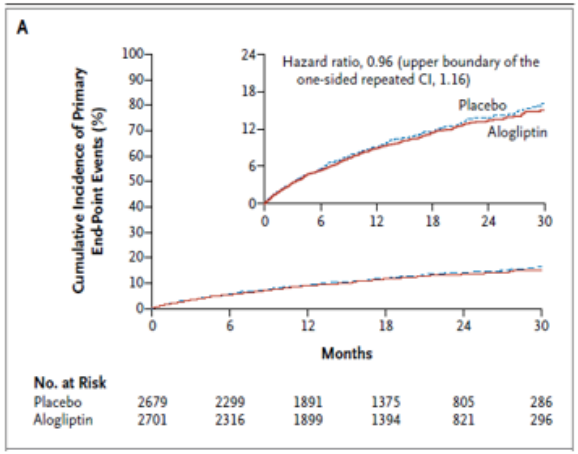
Hospitalisation HF : +27 % (p=0.007)

Total MI : -5 % (p=0.55)

Total stroke : +11 % (p=0.38)

Alogliptin after Acute Coronary Syndrome in Patients with Type 2 Diabetes

EXAMINE
White et al. NEJM 2013; 369:1327-35



EXAMINE: alogliptin vs placebo

3-point MACE : -4 % (p=0.32)

CV death : -15 % (p=0.31)

All-cause death : -12 % (p=0.23)

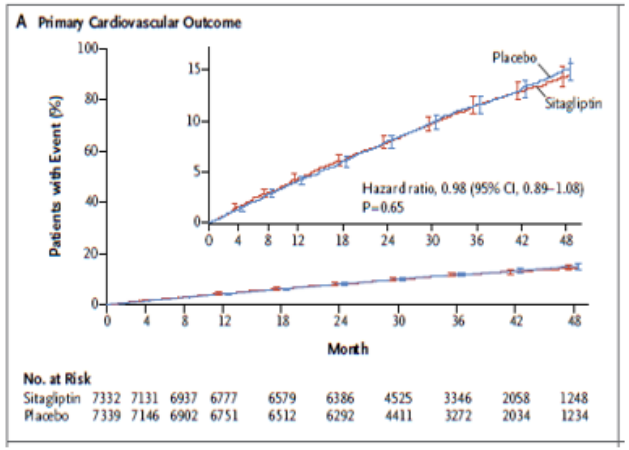
Hospitalisation HF : +7% (NS)

Total MI : +8 % (p=0.47)

Total stroke : -9 % (p=0.71)

Effect of Sitagliptin on Cardiovascular Outcomes in Type 2 Diabetes

TECOS
Green et al. NEJM 2015; 373: 232-42



TECOS: sitagliptin vs placebo

4-point MACE : -2 % (p=0.65)

CV death : +3 % (p=0.71)

All-cause death : +1 % (p<0.88)

Hospitalisation HF : 0 % (p=0.98)

Total MI : -5 % (p=0.49)

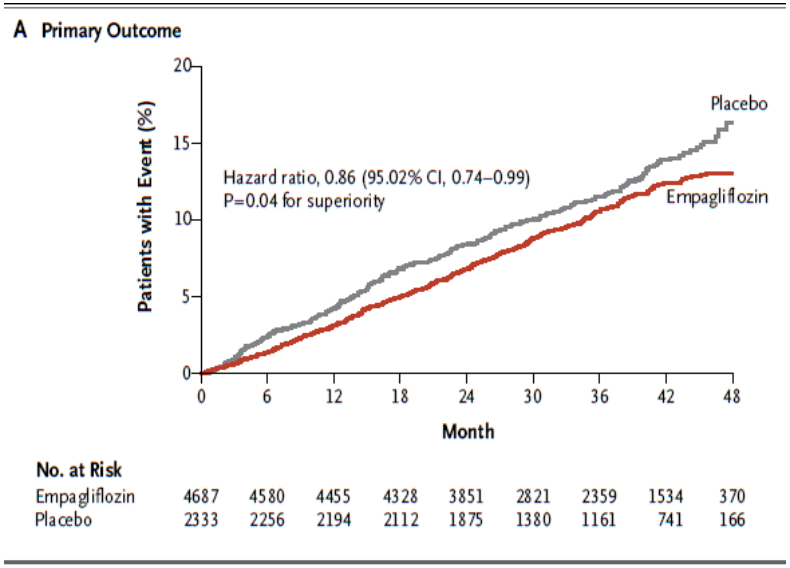
Total stroke : -3 % (p=0.76)

Cardiovascular safety/efficacy of two SGLT2-is

Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes

EMPA-REG OUTCOME Investigators

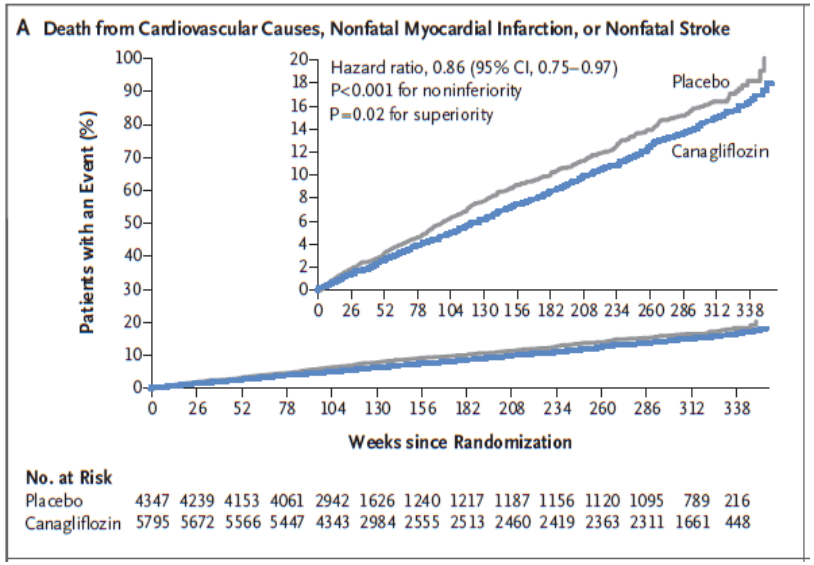
N Engl J Med. 2015 Nov 26;373(22):2117-28.



Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes

CANVAS Program Collaborative Group

N Engl J Med. 2017 Aug 17;377(7):644-657.



EMPA-REG OUTCOME

Triple MACE : -14 % (p=0.04)

CV death : -38 % (<0.001)

All-cause death : -32 % (p<0.001)

Hospitalisation for HF : -35 % (p=0.002)

Renal outcomes : -39 % (p<0.001)

CANVAS

Triple MACE : -14 % (p=0.02)

CV death : -13 % (NS)

All-cause death : -13 %

Hospitalisation for HF : -33 %

Renal outcomes : -40 %

Intensificatie na metformine

Casus variation: Based on CV Disease

- ***Metformin*** *: to be continued (UKPDS, observational studies)*
- ***Sulphonylurea*** *: be cautious, especially if risk of hypoglycaemia (CV safety still controversial)*
- ***DPP-4 inhibitors*** *: CV safety demonstrated, but no protection in patients with established CV disease (SAVOR-TIMI 53, EXAMINE, TECOS)*
- ***SGLT-2 inhibitors*** *: CV protection demonstrated in EMPA-REG OUTCOME and CANVAS; confirmation in observational studies (CVD-REAL, EASEL)*
- ***According to updated guidelines of the American Diabetes Association 2018 :*** *if CV disease, after metformin, the best choice is:*
  - ***either liraglutide (not reimbursed on top of metformin in Belgium)***
  - ***or empagliflozin (grade A) or canagliflozin (grade C) (but not reimbursed in Belgium if HbA1c > 9%)***

Intensificatie na metformine

Casus variation: Patient with heart failure

- ***Sulphonylureas*** *: no specific data available*
- ***DPP-4 inhibitors*** *: saxagliptin should be avoided (increased risk of hospitalisation for heart failure in SAVOR-TIMI 53)*
- ***SGLT-2 inhibitors*** *:*
  - *best choice as a reduction in hospitalization for heart failure was reported with empagliflozin (EMPA-REG) and canagliflozin (CANVAS).*
  - *For dapagliflozin , data will be reported soon in DECLARE.*
  - *CVD REAL showed a reduction in heart failure for all SGLT-2 inhibitors.*

Recognized by the European Society of Cardiology

Ponikowski P et al. *Eur Heart J*. 2016;37:2129-2200
Seferovic PM et al. Eur J Heart Fail 2018

Comparison between glucose lowering drugs

	SGLT2i	SU	DPP4i	GLP1RA	insulin
HbA1c	↓	↓	↓	↓↓	↓↓
Hypo	=	↑	=	=	↑
Bodyweight	↓	↑	=	↓	↑
CVD risk	↓	= / ↑	=	↓ (lira)	=
hHF	↓	=	= (except saxa)	=	=
Renal risk	↓	= / ↓	=	↓	=
Ease of use	oral	oral	oral	injection	injection/titration
Cost	intermediate	low (direct)	intermediate	high	intermediate

hHF : hospitalization for heart failure
Inzucchi et al – Diabetes Care 2015
ADA guidelines -Diabetes Care - January 2018 Volume 41, Supplement 1

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CASUS: opstarten GLP-1 RA

- ***Man , 62 jaar***

- ***Medische voorgeschiedenis***
  - *Type 2 diabetes sinds 6 jaar*
  - *Arteriele hypertensie*
  - *Hypercholesterolemie*
  - *Cardiovasculaire voorgeschiedenis: blanco*

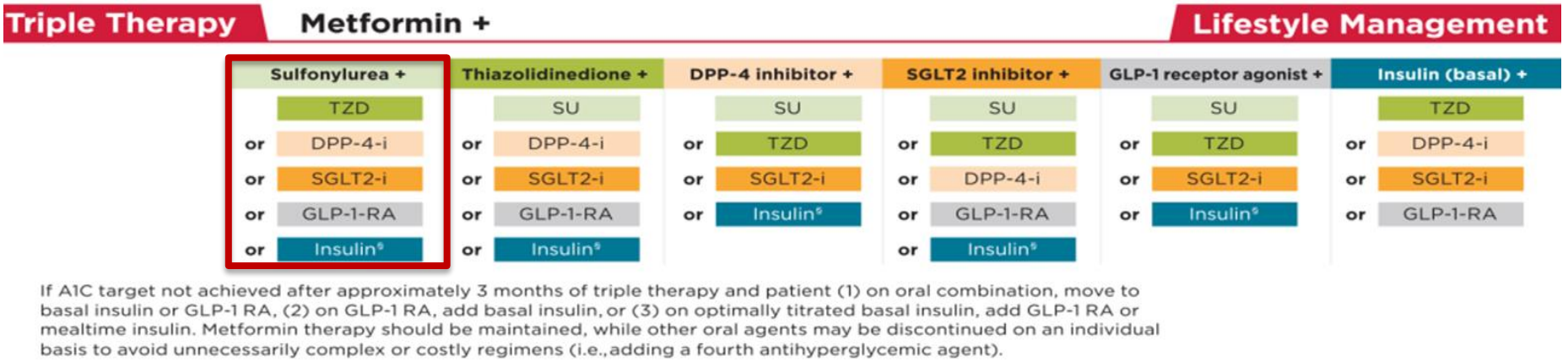
- *Beroep: vrachtwagenchauffeur*
- *Roken: stop 3 jaar geleden*
- *Alcohol gebruik: enkele pintjes in weekend*

CASUS: opstarten GLP-1 RA

- ***Klinisch onderzoek***
  - *BMI 33,5 kg/m², buikomtrek 114 cm*
  - *Blood Pressure 142/82*
- ***Laboratoriumonderzoek:***
  - *HbA1c 7,8 %*
  - *Tot chol 167 mg/dl; HDL38 mg/dl; LDL 93 mg/dl; Triglycerides 182 mg/dl*
  - *eGFR 95 ml/min/1,73m²*
- ***Huidige therapie:***
  - *Metformin 850 mg, 2 x 1 per dag; Uni Diamicron 60 mg, 1 x 2 per dag*
  - *Atorvastatine 20 mg, 1 x 1 per dag*
  - *Lisinopril 20 mg, 1 x 1 per dag; Nobiten 5 mg, 1 x 1 per dag*
  - *Asaflow 80 mg, 1 x 1 per dag*

CASUS: opstarten GLP-1 RA

Mogelijk therapeutische opties



If A1C target not achieved after approximately 3 months of triple therapy and patient (1) on oral combination, move to basal insulin or GLP-1 RA, (2) on GLP-1 RA, add basal insulin, or (3) on optimally titrated basal insulin, add GLP-1 RA or mealtime insulin. Metformin therapy should be maintained, while other oral agents may be discontinued on an individual basis to avoid unnecessarily complex or costly regimens (i.e., adding a fourth antihyperglycemic agent).

Theoretisch: kiezen voor medicatie

- Gewichtsreductie
- Lage kans op hypoglycemie
- Cardiovasculair protectief

Specifiek voor deze casus:

- SGLT-2: frequenter urineren (<-> vrachtwagenchauffeur)
- DPP-4: vermoedelijk onvoldoende effectief in triple therapie
- TZD: verdere gewichtstoename
- Basale insuline: hypo risico

GLP1-receptor agonisten

exenatide (Byetta) 10 of 20 µg 2/d
lixisenatide (Lyxumia) 10 of 20 µg 1/d
liraglutide (Victoza) 0.6 à 1.8 mg 1/d

exenatide QW (Bydureon) 2 mg 1/week
dulaglutide (Trulicity) 0.75 of 1.5 mg 1/week

GLP1 receptor agonisten

glycaemic effects

Reduced FPG & PPG

↓ 1.0 to 1.5 % HbA_{1C}

low risk of hypoglycaemia

non-glycaemic effects

Satiety, fullness, gastric motlity

2 to 3 kg weight Loss

Improved lipid profile

↑ natriuresis

↓ 3 to 5 mm Hg BP

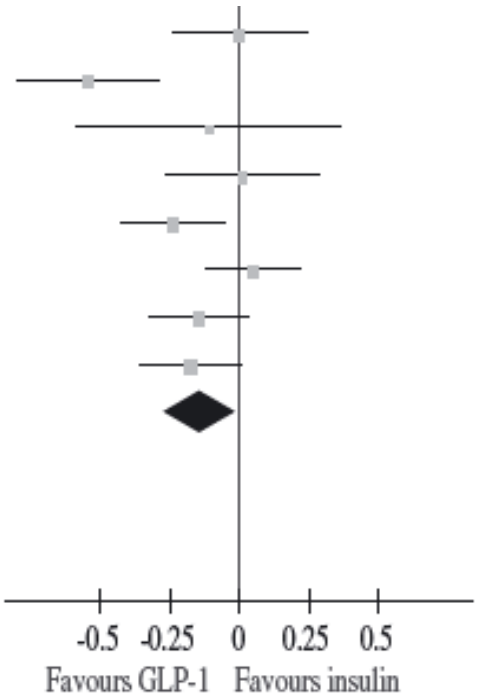
↑ heart rate (2-5 bpm)

GLP1-RA vs insulin: HbA1c

Barnett et al. [17]	-1.36	1.03	136	-1.36	1.01	127	12.1%	0.00 [-0.24, 0.24]
Bergenstal et al. [18]	-2.67	1.79	124	-1.75	1.57	124	11.6%	-0.54 [-0.80, -0.29]
Bunck et al. [19]	-0.8	0.6	36	-0.7	1.15	33	5.4%	-0.11 [-0.58, 0.36]
Davies et al. [20]	-1.25	0.89	98	-1.26	0.9	102	10.6%	0.01 [-0.27, 0.29]
Diamante et al. [21]	-1.5	0.76	228	-1.3	0.92	220	14.7%	-0.24 [-0.42, -0.05]
Heine et al. [12]	-1	1	275	-1.05	0.97	260	15.5%	0.05 [-0.12, 0.22]
Nauck et al. [13]	-1.04	1.11	253	-0.89	0.94	248	15.2%	-0.15 [-0.32, 0.03]
Russell-Jones et al. [22]	-1.33	1.37	232	-1.09	1.38	234	14.9%	-0.17 [-0.36, 0.01]
Subtotal (95% CI)			1382			1348	100.0%	-0.14 [-0.27, -0.02]

Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 18.26$, df = 7 (P = 0.01); $I^2 = 62\%$

Test for overall effect: Z = 2.20 (P = 0.03)



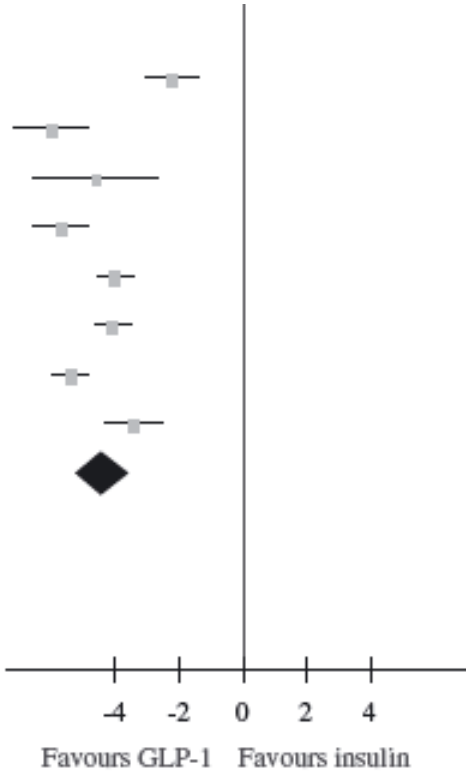
Wang et al. *Diabetes, Obesity and Metabolism* 13: 972–981, 2011

GLP1-RA vs insulin: weight

4.1.4 total								
Barnett et al. [17]	-1.6	3.5	136	0.6	3.38	127	13.0%	-2.20 [-3.03, -1.37]
Bergenstal et al. [18]	-1.9	3.8	124	4.1	5.4	124	11.6%	-6.00 [-7.16, -4.84]
Bunck et al. [19]	-3.6	3.6	36	1	4.6	33	8.2%	-4.60 [-6.56, -2.64]
Davies et al. [20]	-2.73	3.1	100	2.98	3.16	104	12.9%	-5.71 [-6.57, -4.85]
Diamante et al. [21]	-2.6	3.1	233	1.4	3	223	13.9%	-4.00 [-4.56, -3.44]
Heine et al. [12]	-2.32	3.19	231	1.75	3.28	244	13.9%	-4.07 [-4.65, -3.49]
Nauck et al. [13]	-2.5	3.2	253	2.9	3.1	248	14.0%	-5.40 [-5.95, -4.85]
Russell-Jones et al. [22]	-1.8	5	230	1.6	5.03	232	12.6%	-3.40 [-4.31, -2.49]
Subtotal (95% CI)			**1343**			**1335**	**100.0%**	**-4.40 [-5.23, -3.56]**

Heterogeneity: $Tau^2 = 1.23$; $Chi^2 = 63.52$, df = 7 ($P < 0.00001$); $I^2 = 89\%$

Test for overall effect: $Z = 10.28$ ($P < 0.00001$)



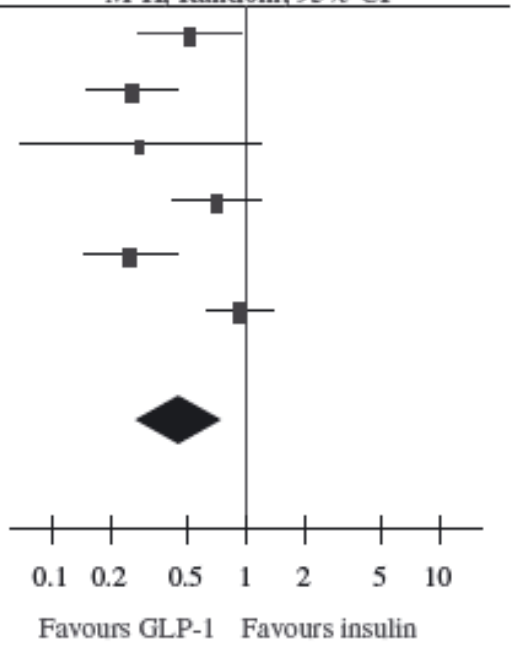
Wang et al. *Diabetes, Obesity and Metabolism* 13: 972–981, 2011

GLP1-RA vs insulin: hypo

Study or Subgroup	GLP-1 Events	GLP-1 Total	insulin Events	insulin Total	Weight	Odds Ratio M-H, Random, 95% CI
Barnett et al. [17]	20	136	32	127	17.1%	0.51 [0.28, 0.95]
Bergenstal et al. [18]	36	124	76	124	18.3%	0.26 [0.15, 0.44]
Bunck et al. [19]	3	36	8	33	8.3%	0.28 [0.07, 1.18]
Davies et al. [20]	59	118	68	116	18.5%	0.71 [0.42, 1.18]
Diamante et al. [21]	19	233	58	223	18.0%	0.25 [0.14, 0.44]
Russell-jones et al. [22]	63	230	67	232	19.9%	0.93 [0.62, 1.39]
Total (95% CI)		**877**		**855**	**100.0%**	**0.45 [0.27, 0.76]**
Total events	200		309			

Heterogeneity: $Tau^2 = 0.30$; $Chi^2 = 23.03$, df = 5 (P = 0.0003); $I^2 = 78\%$

Test for overall effect: Z = 3.03 (P = 0.002)



Wang et al. *Diabetes, Obesity and Metabolism* 13: 972–981, 2011

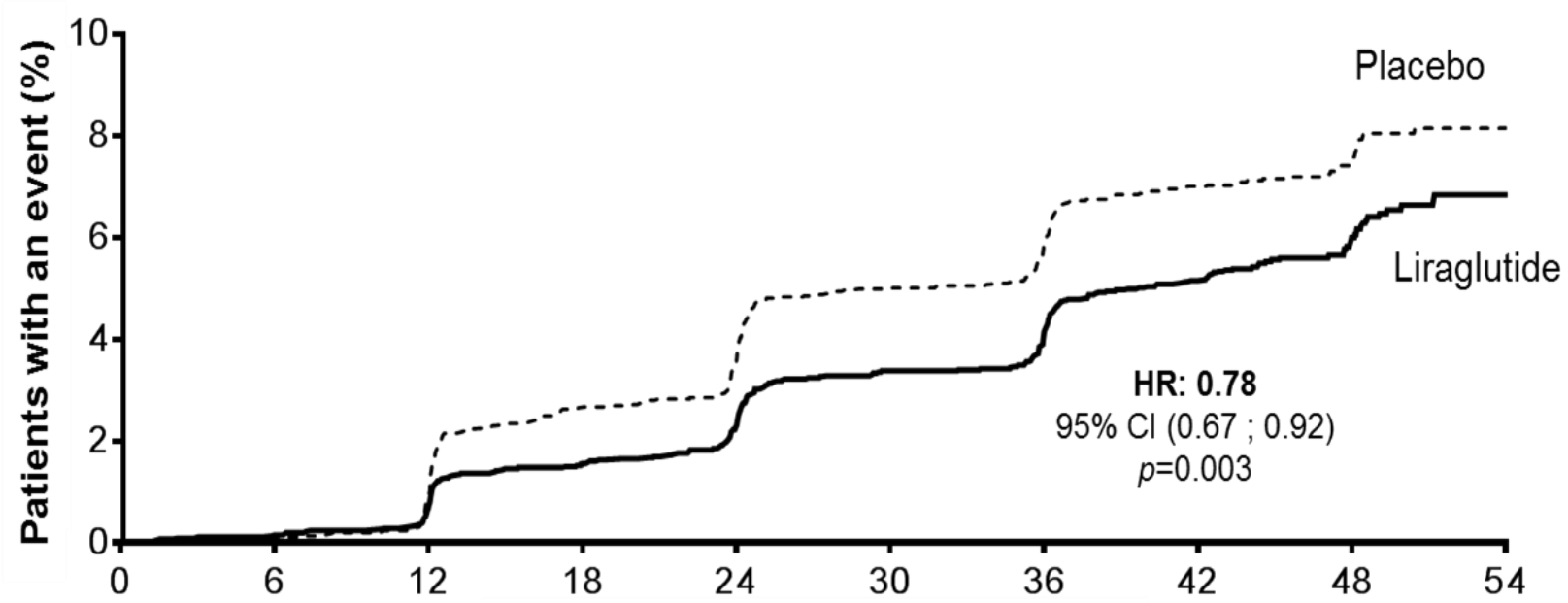
casus

- *Medicatie:*
  - *Metformine 850 mg 2/d + SU*
  - *Stel:*
    - *Nierinsufficiënt*
    - *Voorgeschiedenis van cardiovasculair event*
    - *BMI*
    - *Hoogbejaard*
    - *Hoog HbA1c*

Liraglutide: Renal function

Time to primary composite nephropathy outcome

Macroalbuminuria, doubling of serum creatinine*, ESRD, renal death (N= 605)



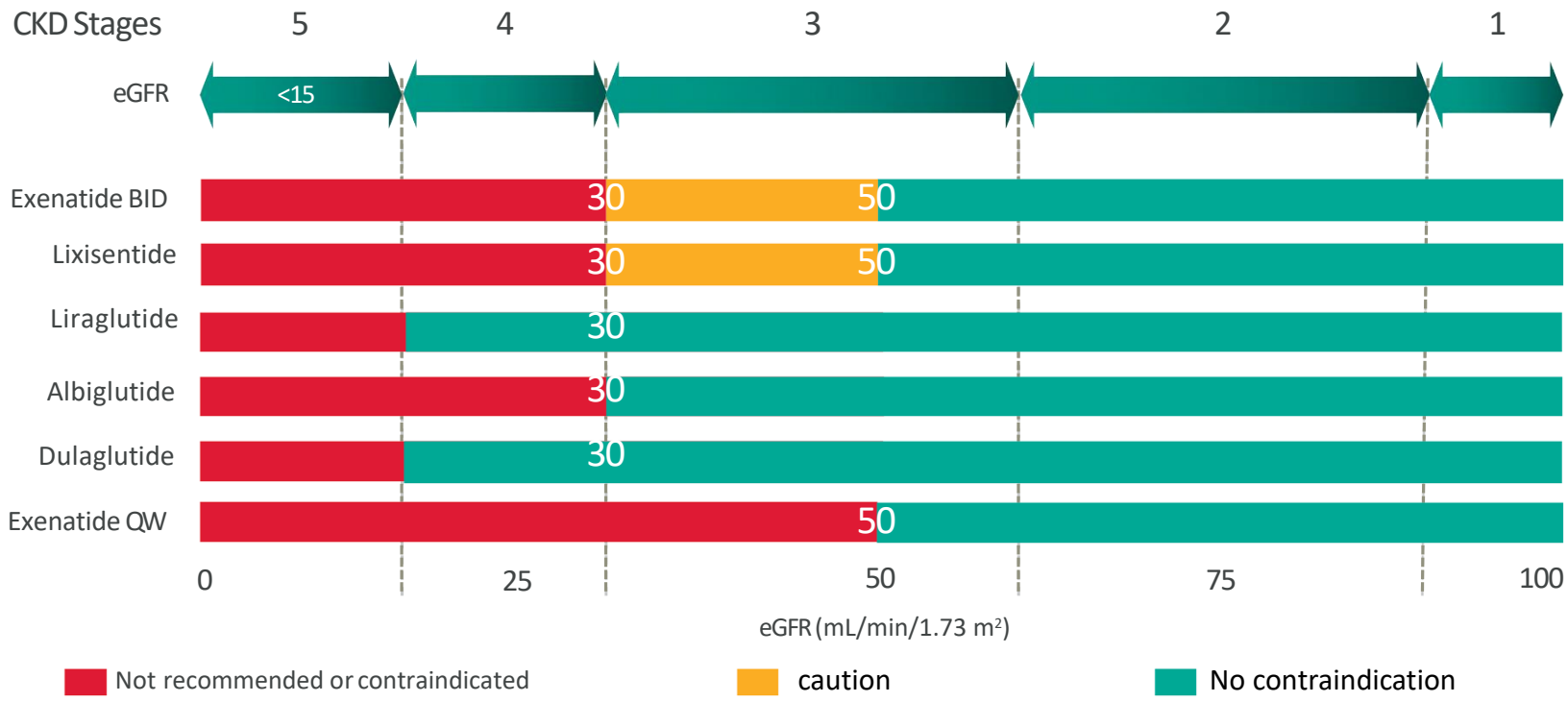
Patients at risk										
Liraglutide	4668	4635	4561	4492	4400	4304	4210	4114	1632	454
Placebo	4672	4643	4540	4428	4316	4196	4094	3990	1613	433

*and eGFR ≤45 mL/min/1.73 m^2 per MDRD. The cumulative incidences were estimated with the use of the Kaplan–Meier method, and the HRs with the use of the Cox proportional-hazard regression model. The data analyses are truncated at 54 months because less than 10% of the patients had an observation time beyond 54 months. CI: confidence interval; eGFR, estimated glomerular filtration rate; ESRD: end-stage renal disease; HR: hazard ratio; MDRD: modification of diet in renal disease. Presented at ASN Kidney week, 19 November 2016, Chicago, USA.

Marso et al. NEJM. 2017

Nierinsufficiëntie

GLP-1 RA en nierinsufficientie



CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate

BYETTA European Product Information. AstraZeneca AB. Available at: http://www.ema.europa.eu/ema/ Accessed May 4, 2015; LYXUMIA European Product Information. Sanofi-aventis groupe. Available at: http://www.ema.europa.eu/ema/ Accessed May4, 2015; VICTOZA European Product Information. Novo Nordisk A/S. Available at: http://www.ema.europa.eu/ema/ Accessed May4, 2015; EPERZAN European Product Information. GlaxoSmithKline. Available at: http://www.ema.europa.eu/ ema/ Accessed May 4, 2015; TRULICITY European Product Information. Eli Lilly and Company. Available at: http://www.ema.europa.eu/ema/ Accessed May 4, 2015;

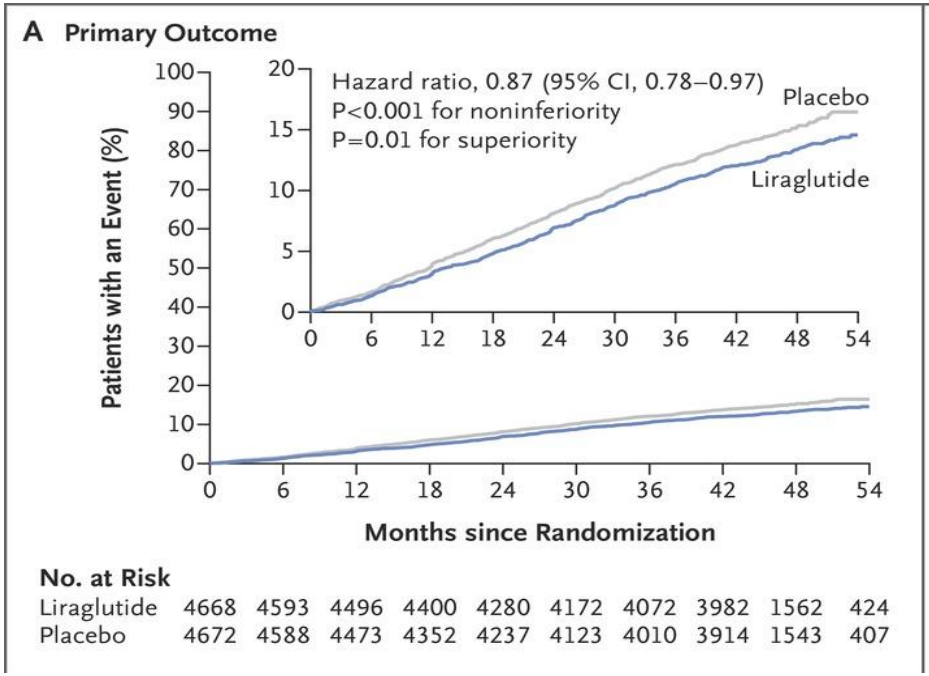
BYDUREON European Product Information. AstraZeneca AB. Available at: http://www.ema.europa.eu/ema/ Accessed May 4, 2015.

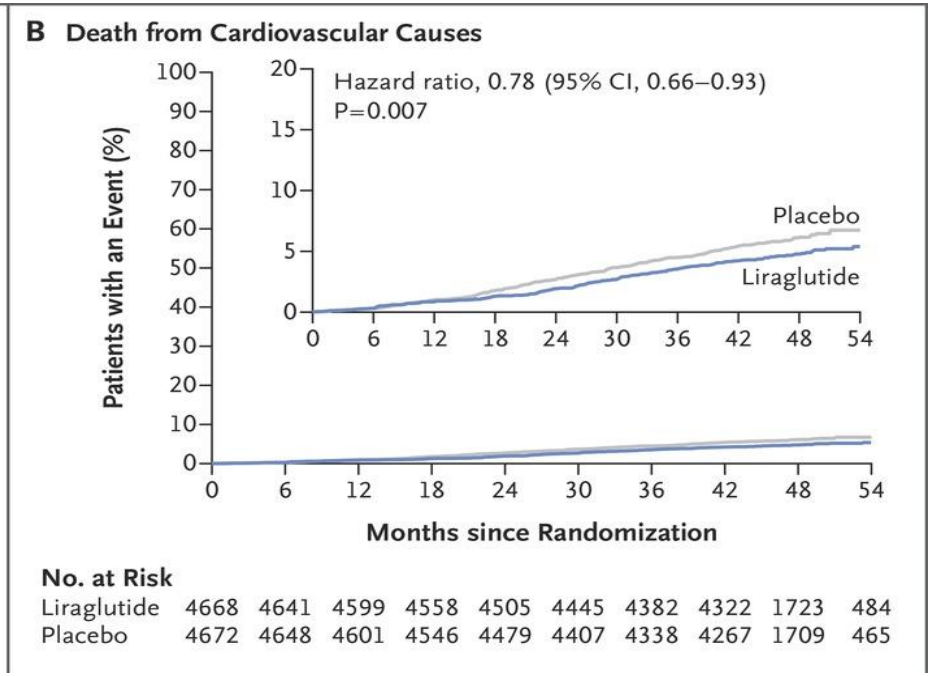
casus

- *Medicatie:*
  - *Metformine 850 mg 2/d + SU*
  - *Stel:*
    - *Nierinsufficiënt*
    - *Voorgeschiedenis van cardiovasculair event*
    - *BMI*
    - *Hoogbejaard*
    - *Hoog HbA1c*

GLP1-RA & Cardiovasculaire status

LEADER trial
Liraglutide - Primary Outcomes.





13 % reductie 3 punts MACE
CV death, non fatal stroke, non fatal MI

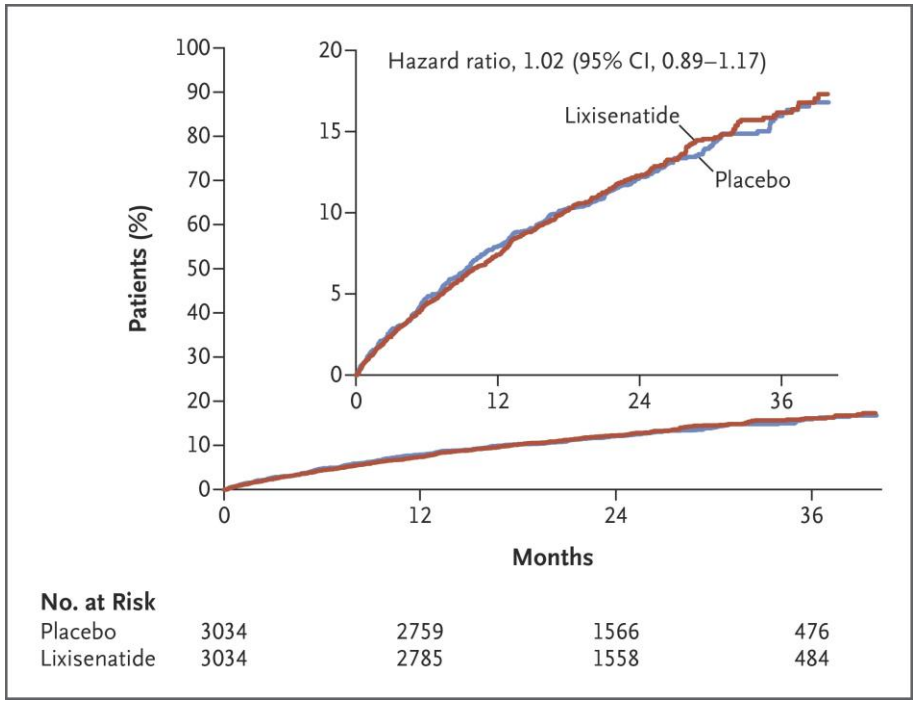
22 % reductie CV overlijden (p=0.007)
15 % reductie death of any cause (p=0.02)

Marso SP et al. N Engl J Med 2016;375:311-322

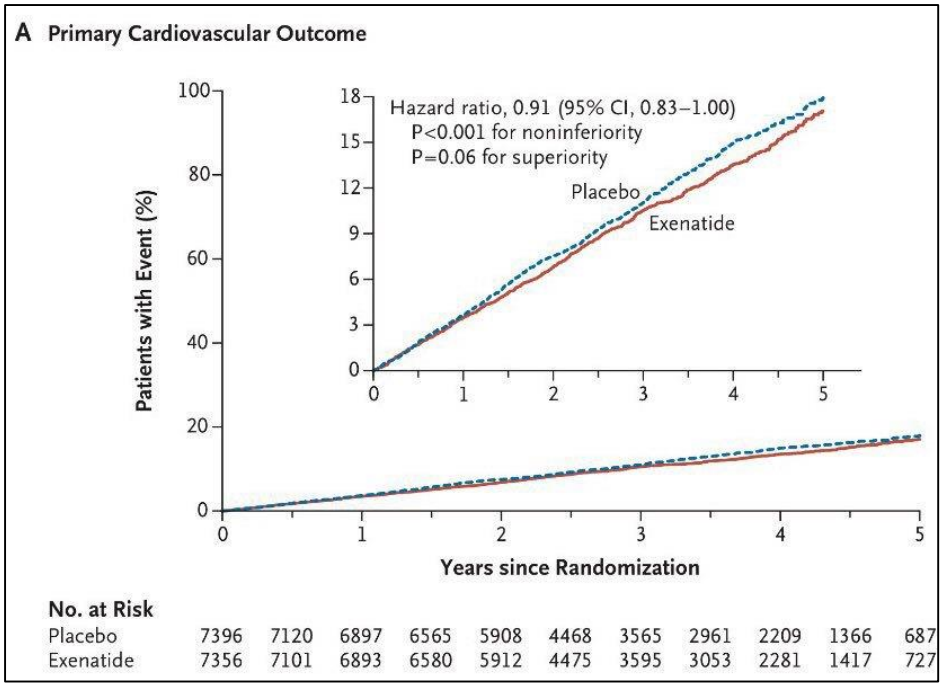
GLP1-RA & Cardiovasculaire status

CV outcome trials

Elixa (lixisenatide) trial

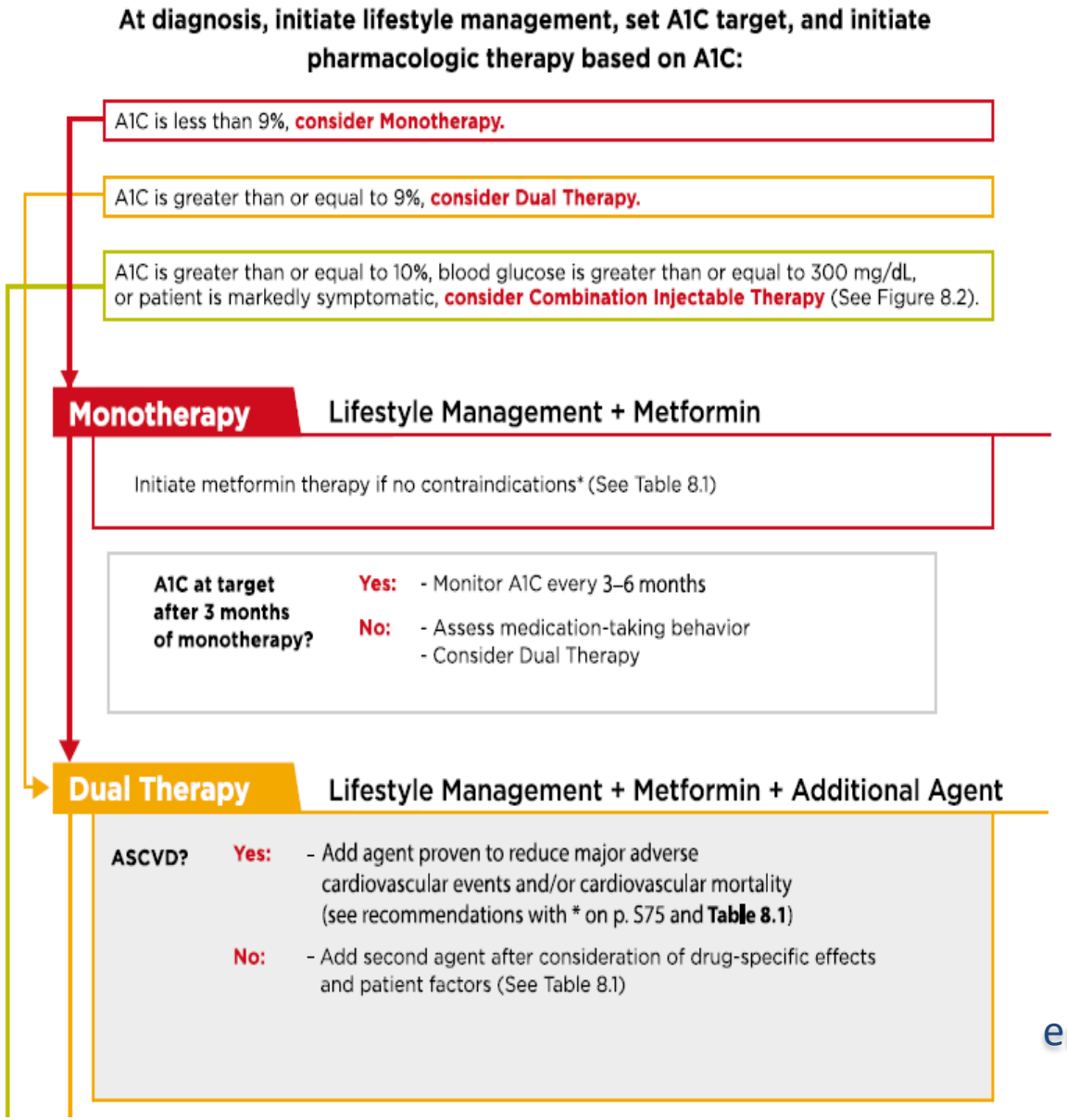


Exscel (exenatide LAR) trial



Pfeffer MA et al. N Engl J Med 2015;373:2247-2257
Holman N Engl J Med 2017; 377:1228-1239

Antihyperglycemic Therapy in Adults with Type 2 Diabetes



American Diabetes Association

8. Pharmacologic Approaches to Glycemic Treatment: *Standards of Medical Care in Diabetes—2018*

Diabetes Care 2018;41(Suppl. 1):S73–S85 | https://doi.org/10.2337/dc18-S008

- In patients with type 2 diabetes and established atherosclerotic cardiovascular disease, antihyperglycemic therapy should begin with lifestyle management and metformin and subsequently incorporate an agent proven to reduce major adverse cardiovascular events and cardiovascular mortality (currently empagliflozin and liraglutide), after considering drug-specific and patient factors

empagliflozin & liraglutide : class A
canagliflozin : class C

INHOUD

- EASD/ADA guidelines
- Cases:
  - Nieuw gediagnosticeerde patiënt (prof. F. Nobels)
  - Intensificatie na metformine (prof. A. Scheen)
  - Metformine + SU (prof. M. Buysschaert)
  - Metformine + DPP4i (prof. C. De Block)
  - Metformine + SGLT2i (prof. L. Crenier)
  - GLP1-receptor agonist (dr. A. Verhaegen)
  - **Basale insuline (prof. C. Mathieu)**
- Aandachtspunten:
  - Leeftijd, baseline HbA1c, BMI, nierfunctie, CV disease

CASUS

Beschrijving van de patiënt

- *54 jaar*
- *vertegenwoordiger; te druk voor lifestyle aanpassingen*
- *Type 2 diabetes sinds 7 jaar, gediagnosticeerd nav screening bij nieuwe job*
- *Momenteel behandeld met metformine 3x850mg/d en uni-gliclazide 120mg*
- *Poging met SGLT2i faalde omwille van balanitis*
- *Poging met GLP1 receptor agonist faalde omwille van diarree*
- *Niet roker*

Klinisch onderzoek

- *BMI 29kg/m^2 lengte 184cm en gewicht 97kg*
- *Bloeddruk 142/78mmHg*
- *Buikomtrek 92cm*

CASUS

Laboratoriumonderzoek:

- *HbA1c 8,4%*
- *LDL cholesterol 75mg/dl; HDL cholesterol 45mg/dl; Triglyceriden 214mg/dl*
- *eGFR 98ml/min/1,73m^2*

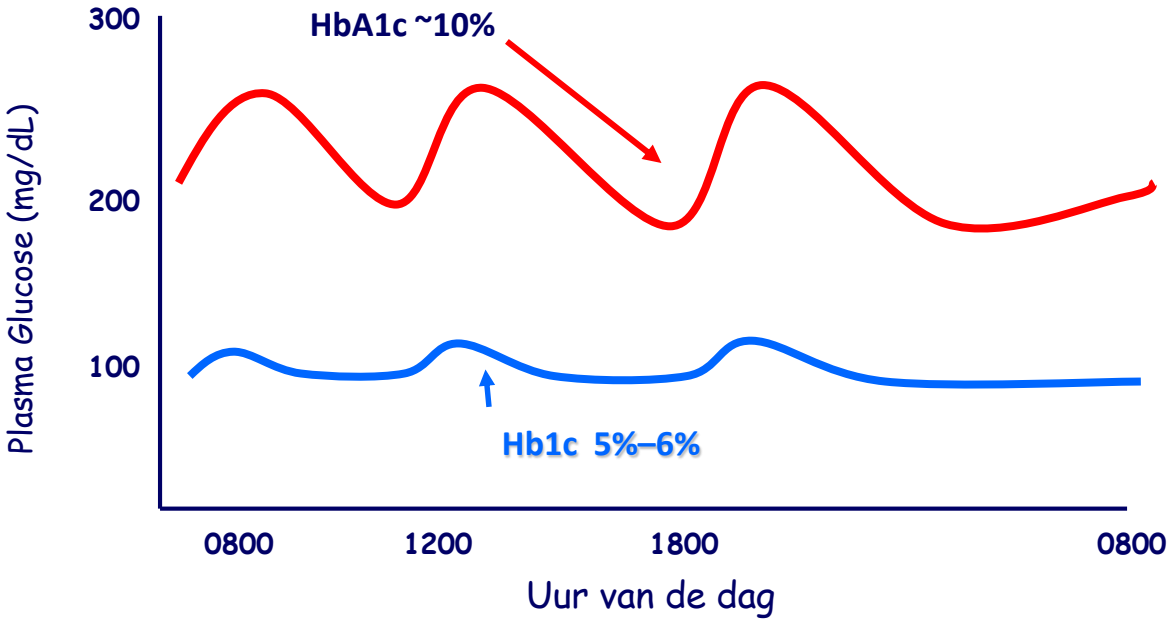
Medicatie

- *Atorvastatine/ezetimibe 40/10mg*
- *Enalapril 20mg*
- *Bisoprolol 10mg*
- *Asaflow 80mg*
- *Metformine 3x850mg*
- *Uni-gliclazide 120mg*

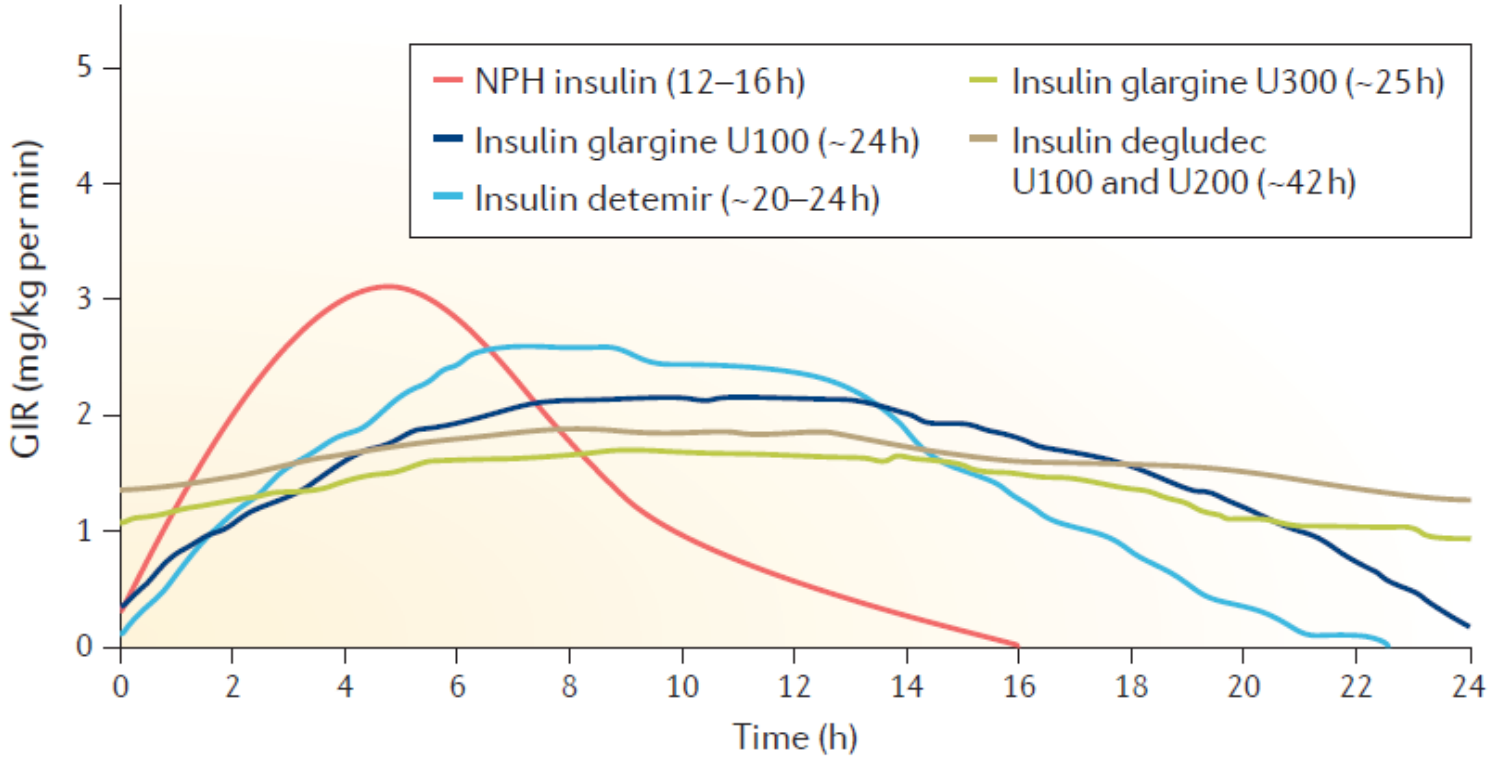
Basale insulines

Doel van basale insuline:
Hepatische glucose output onderdrukken in de nacht
Fix Fasting First

Glycemisch profiel in type 2 diabetes



Basale insulines



Mathieu C. et al Nat Rev Endocrinol 2017

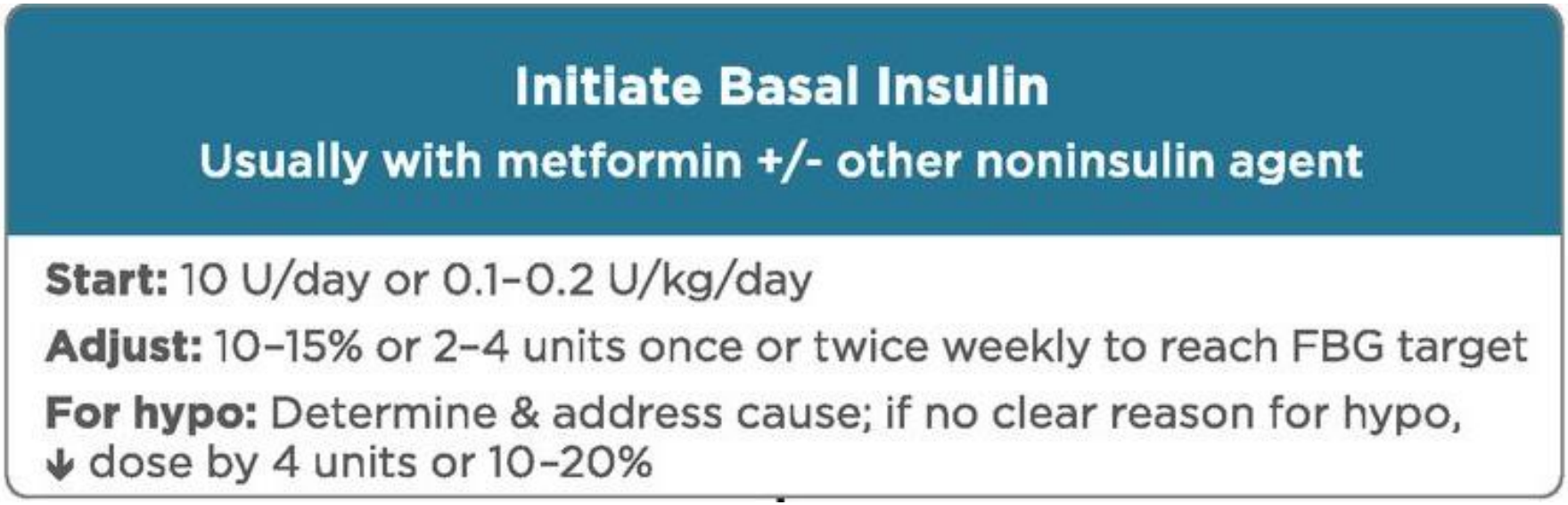
Praktisch starten, rekening houdend met Terugbetaling in België

- *Starten met NPH insuline bij het slapengaan 0,1^{E}/kg of 10^{E}*
- *Start met Zorgtraject- Overleg met Endocrinoloog, toegang tot educatie, toegang tot meetmateriaal*

Let op voor:

- *Hypoglycemie, vooral tijdens de nacht*
- *Gewichtstoename: belang educatie!*
- *Toename complexiteit therapie: injectie, nood tot zelfcontrole*

Basal insulin therapy



American Diabetes Association Dia Care 2017;40:S64-S74

Praktisch starten, rekening houdend met Terugbetaling in België

- *Drijf de dosis met 2 E per week op tot je in het streefgebied komt*
- *Als de ochtendglykemie veel te hoog is, kan dit eventueel sneller gebeuren*
- *Een praktisch schema is:*

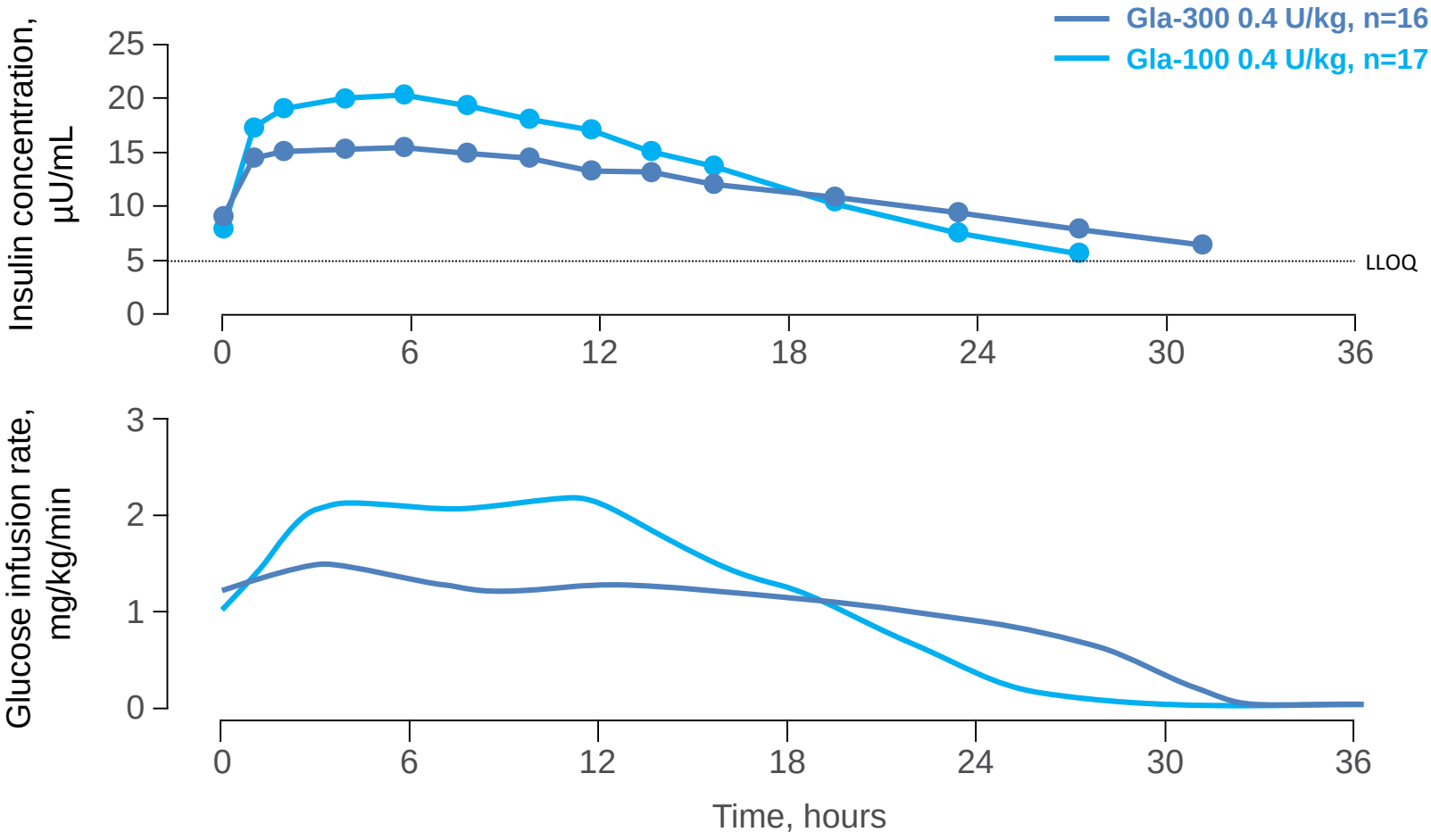
Bij een nuchtere glykemiewaarde van	Verhoog met
>120-140 mg/dL	2 E
>160 mg/dL	4 E
>180 mg/dL	6 E
>200 mg/dL	8 E

- *Bij optreden van nachtelijke hypoglycemies, verlaag de dosis NPH met 2^{E} of switch naar glargine (Lantus®, Abasaglar®, Toujeo®)*

Praktisch starten, rekening houdend met Terugbetaling in België

- *Bij optreden van nachtelijke hypoglycemies, verlaag de dosis NPH met 2^{E} of switch naar glargine (Lantus®, Abasaglar®, of Toujeo®)*
- *Bij optreden van hypoglycemies overdag, reduceer de dosis orale glucoseverlagende middelen die hypoglycemie kunnen geven: sulfonylurea*
- *Controleer HbA1c na 3 maanden*
- *Zo streefcijfer niet bereikt (HbA1c 7% of afhankelijk van profiel patiënt), laat patiënt een volledig dagprofiel verrichten*
- *Indien nuchter niet op streefcijfer: switch naar glargine (Lantus®, Abasaglar® of Toujeo®)*

More constant and stable PK/PD profile with Gla-300 vs Gla-100

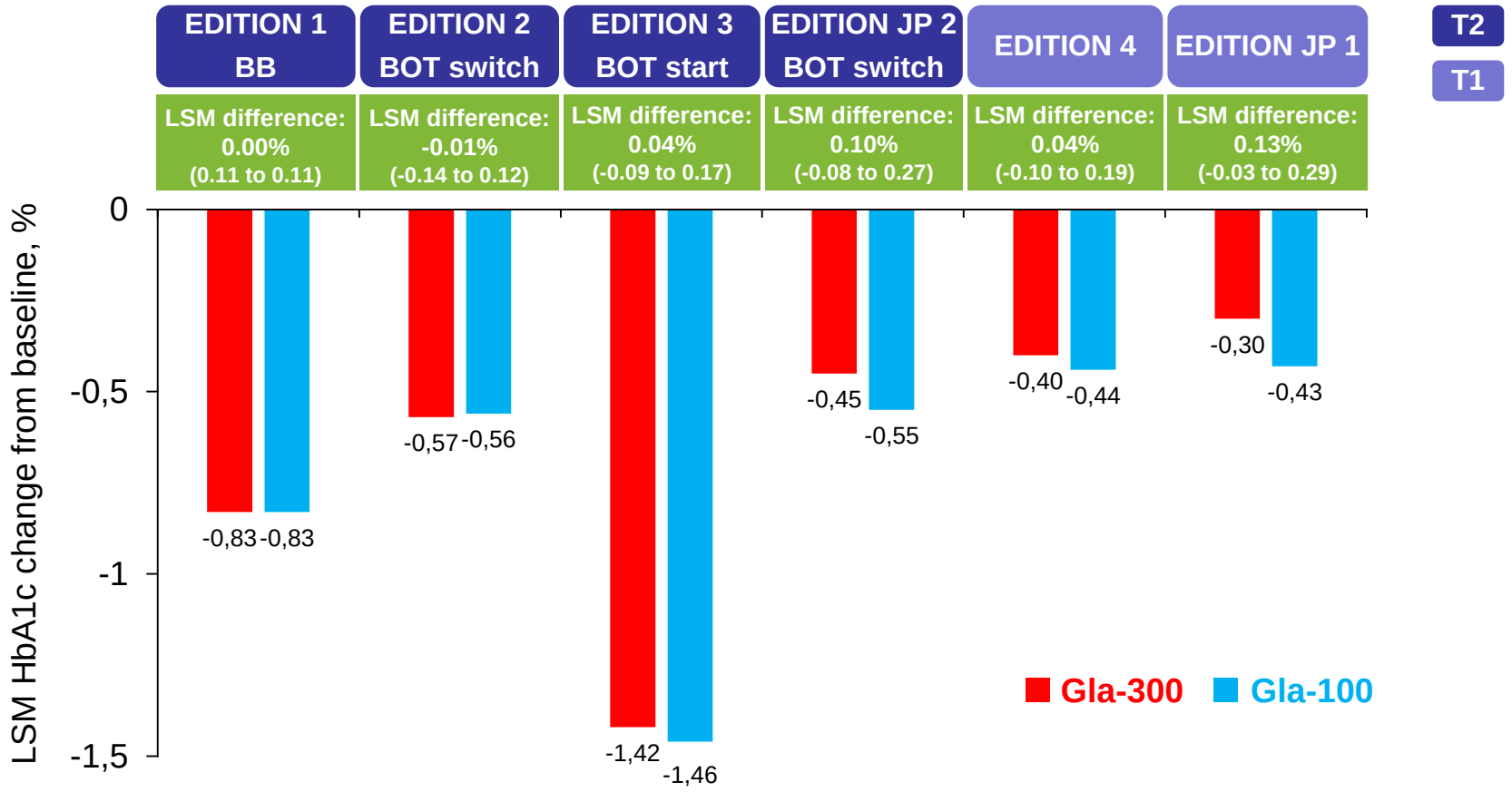


LLOQ, lower limit of quantification

Further details on study design can be found in the back-up

Becker RH et al. Diabetes Care. 2014 Aug 22. pii: DC_140006. [Epub ahead of print]

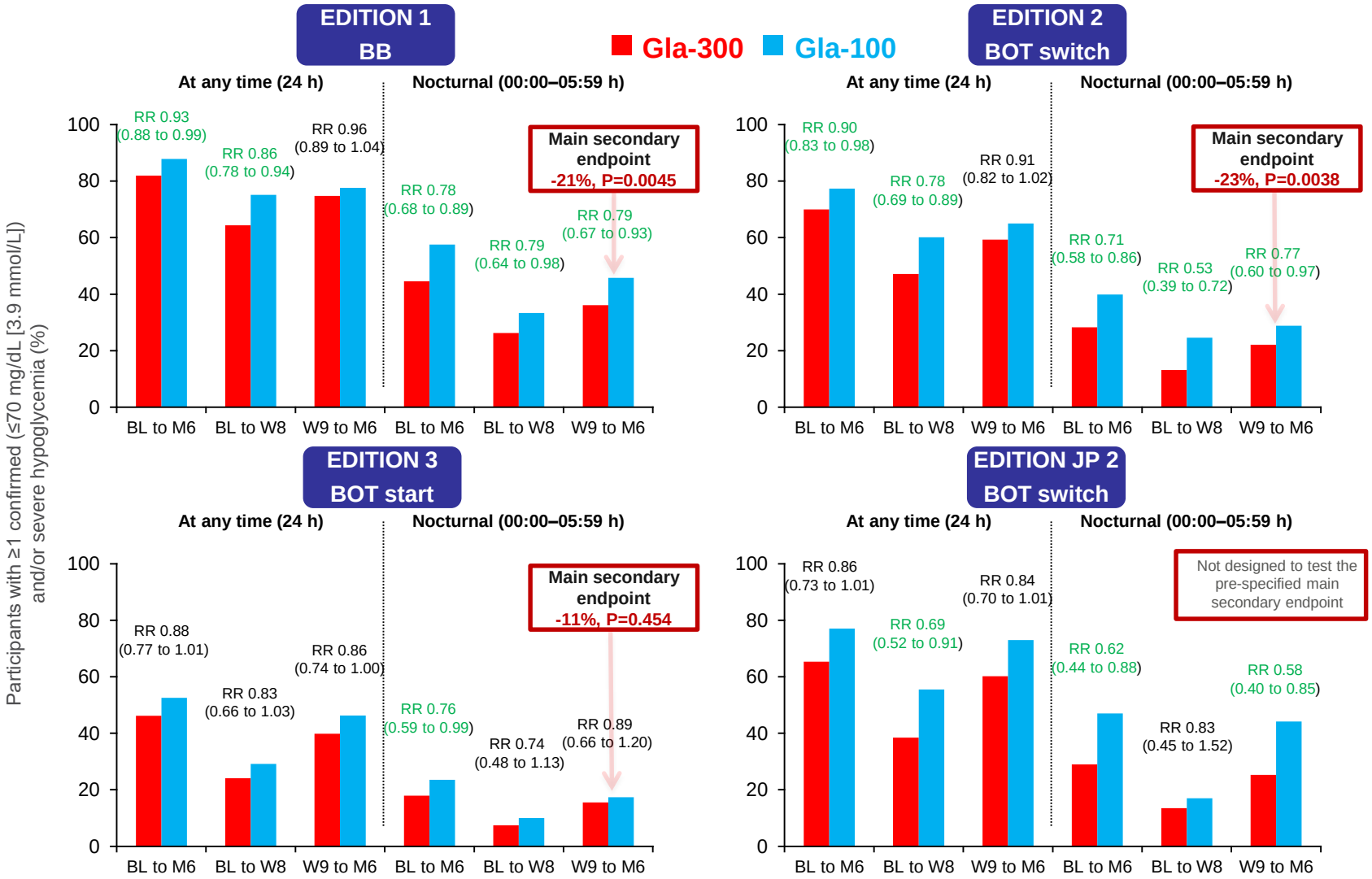
Primary endpoint was successfully achieved in all EDITION trials



Primary endpoint: non-inferiority in HbA1c change with Gla-300 vs Gla-100 at Month 6

Data on file, EDITION 1 CSR, pg 72; EDITION 2 CSR, pg 73; EDITION 3 CSR pg 83; EDITION JP 2 CSR pg 86; EDITION 4 CSR pg 88; EDITION JP 1 CSR pg 80
Riddle MC et al. Diabetes Care. 2014;37:2755-62; Yki-Järvinen H et al. Diabetes Care. 2014;37:3235-43; Bolli GB et al. Diabetes Obes Metab. 2015 Jan 14. doi: 10.1111/dom.12438. [Epub ahead of print]; Terauchi Y et al. Poster presentation at EASD 2014; Abstract 976; Home PD et al. Poster presentation at ADA 2014; Abstract 80-LB; Matsuhisa M et al. Poster presentation at EASD 2014; Abstract 975

Incidence of confirmed (≤70 mg/dL [3.9 mmol/L]) or severe hypoglycemia in T2DM studies



mITT population for main secondary endpoint; safety population for other data; BL, baseline; M6, Month 6; W8, Week 8; W9, Week 9; RR, relative risk

Riddle MC et al. Diabetes Care. 2014;37:2755-62; Yki-Järvinen H et al. Diabetes Care. 2014;37:3235-43; Data on file, saf_hypo_ph2_3 pg 221, 275-6; Bolli GB et al. Diabetes Obes Metab. 2015 Jan 14. doi: 10.1111/dom.12438. [Epub ahead of print]; Bolli GB et al. Poster presentation at EASD 2014; Abstract 947; Data on file, saf_hypo_ph2_3, pg 222, 276; Terauchi Y et al. Poster presentation at EASD 2014; Abstract 976

Basal insulin doses at Month 6

Basal insulin dose at Month 6, U/kg

	T2DM studies				T1DM studies	
	EDITION 1 BB	EDITION 2 BOT switch	EDITION 3 BOT start	EDITION JP 2 BOT switch	EDITION 4	EDITION JP 1
Gla-300	0.98	0.93	0.62	0.35	0.47	0.36
Gla-100	0.88	0.85	0.53	0.30	0.40	0.29
Relative difference for Gla-300 vs Gla-100, %	+11.55	+10.44	+16.58	+17.87	+17.5[1]	+22.47

T2

T1

Data on file, E19_Insulin dose_Absolute and Relative differences_M12_2014-09-03.doc, pg 6, 12, 14, 22, 38, 44

[1]US Prescribing Information, 27 Feb 2015

CASUS

Casus variatie

Taxichauffeur

Wees NOG bewuster op gevaar hypoglycemie

Pas het streefcijfer HbA1c aan naar minder strikte waarden
als deze enkel kunnen bereikt worden met hypoglycemie

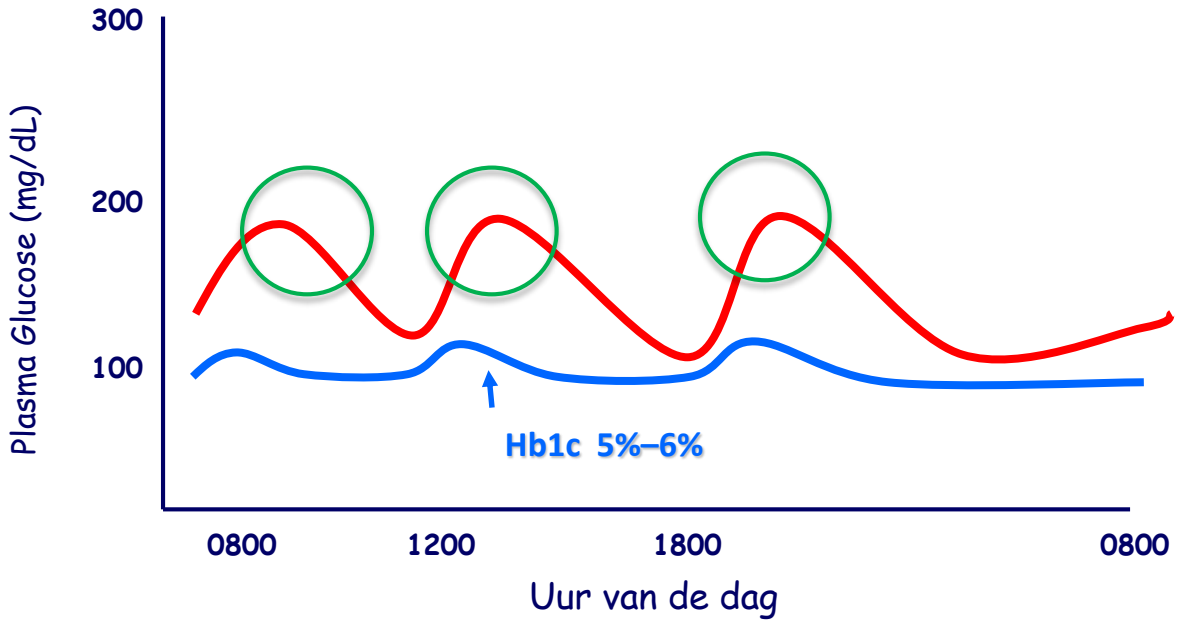
Patiënt dient grondige educatie te krijgen rond hypoglycemie en het belang van zelfcontrole van de bloedsuiker alvorens het stuur te nemen

Vergeet het rijbewijs niet aan te passen!

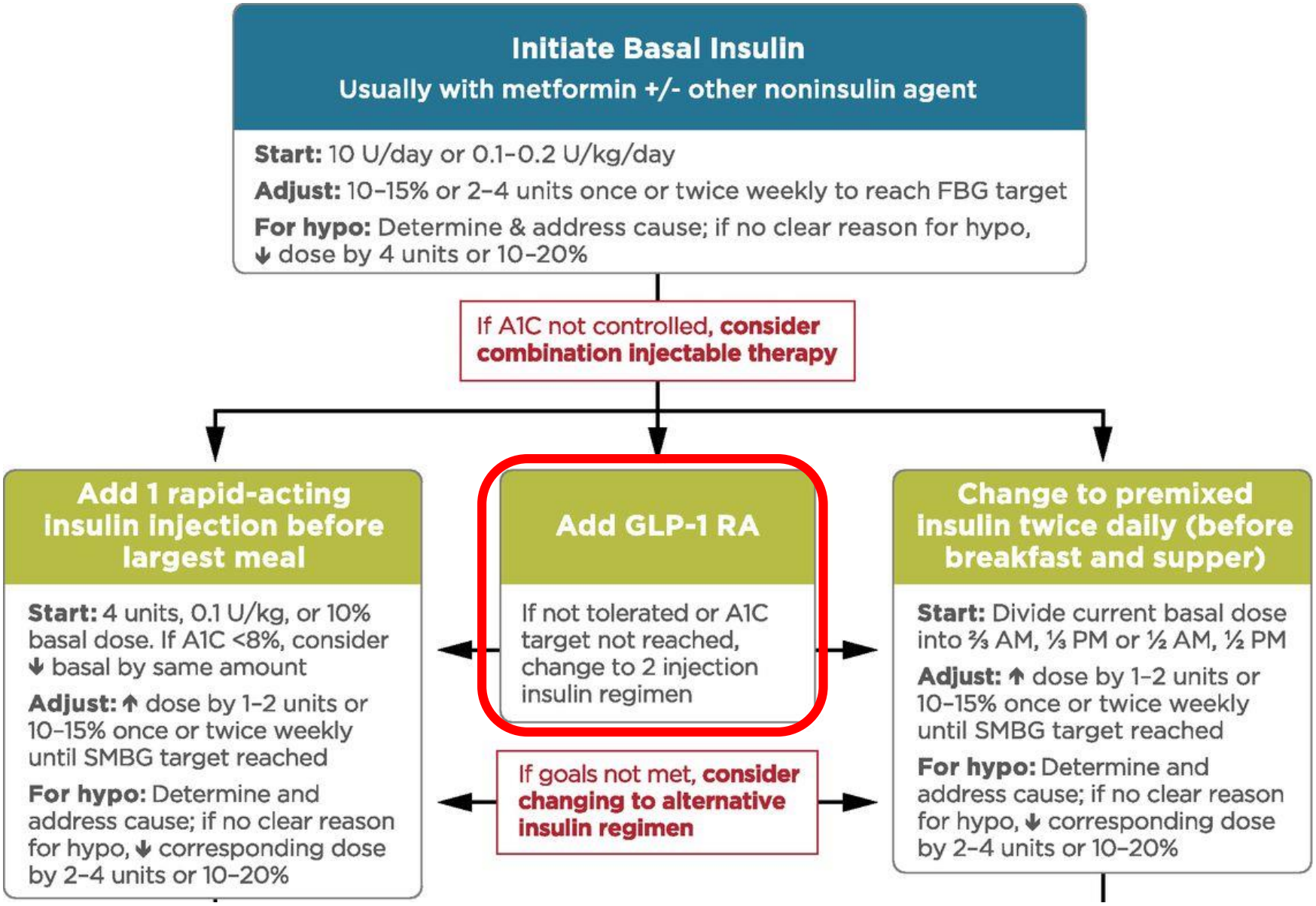
www.diabetes.be

Praktisch starten

Indien nuchter op streefcijfer, maar overdag te hoog: intensifieer overleg met endocrinoloog voor intensifiëring schema met GLP1RA, SGLT2i of maaltijdinsuline.



Combination injectable therapy for type 2 diabetes.

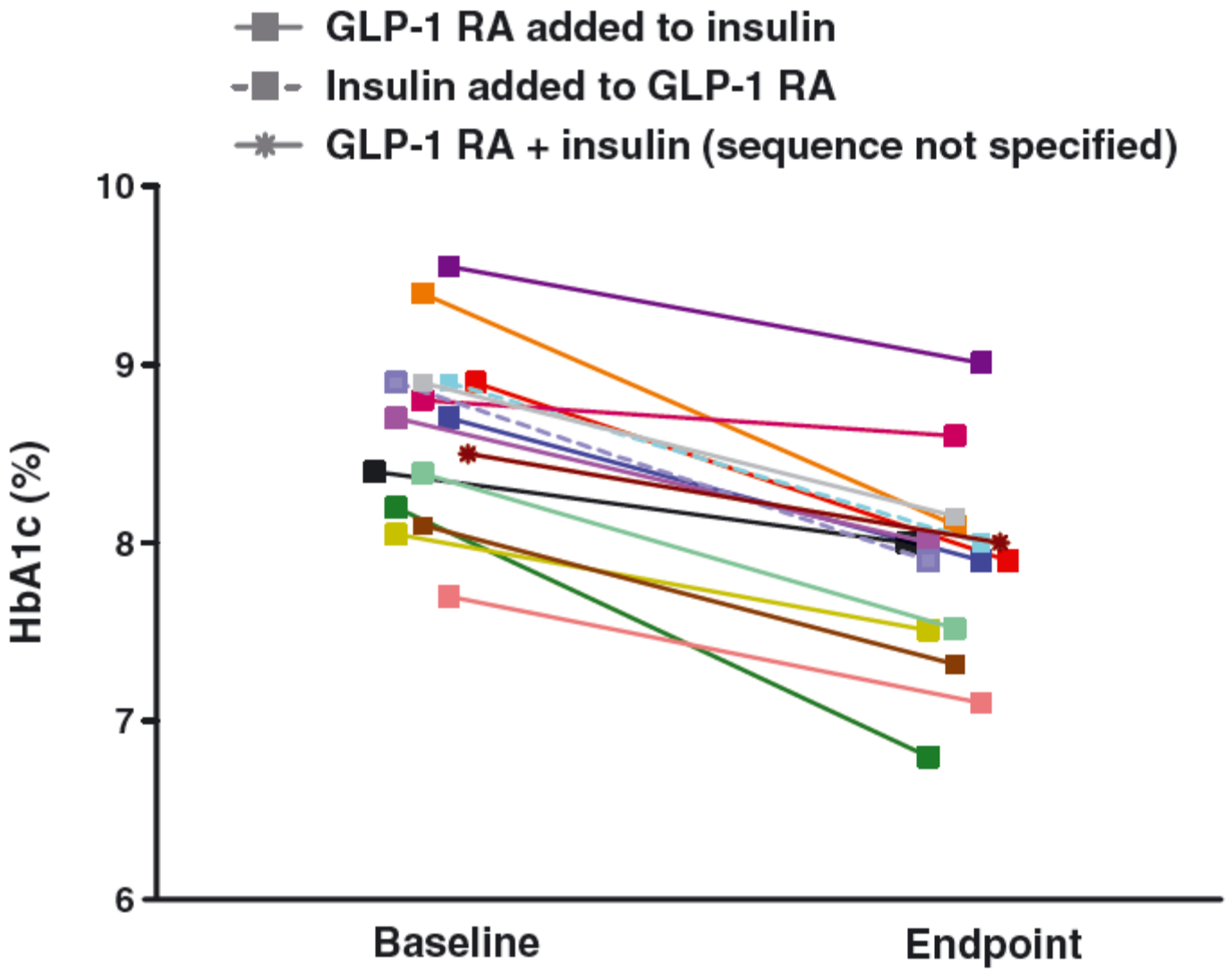


American Diabetes Association Dia Care 2017;40:S64-S74

GLP1RA in combinatie met insuline

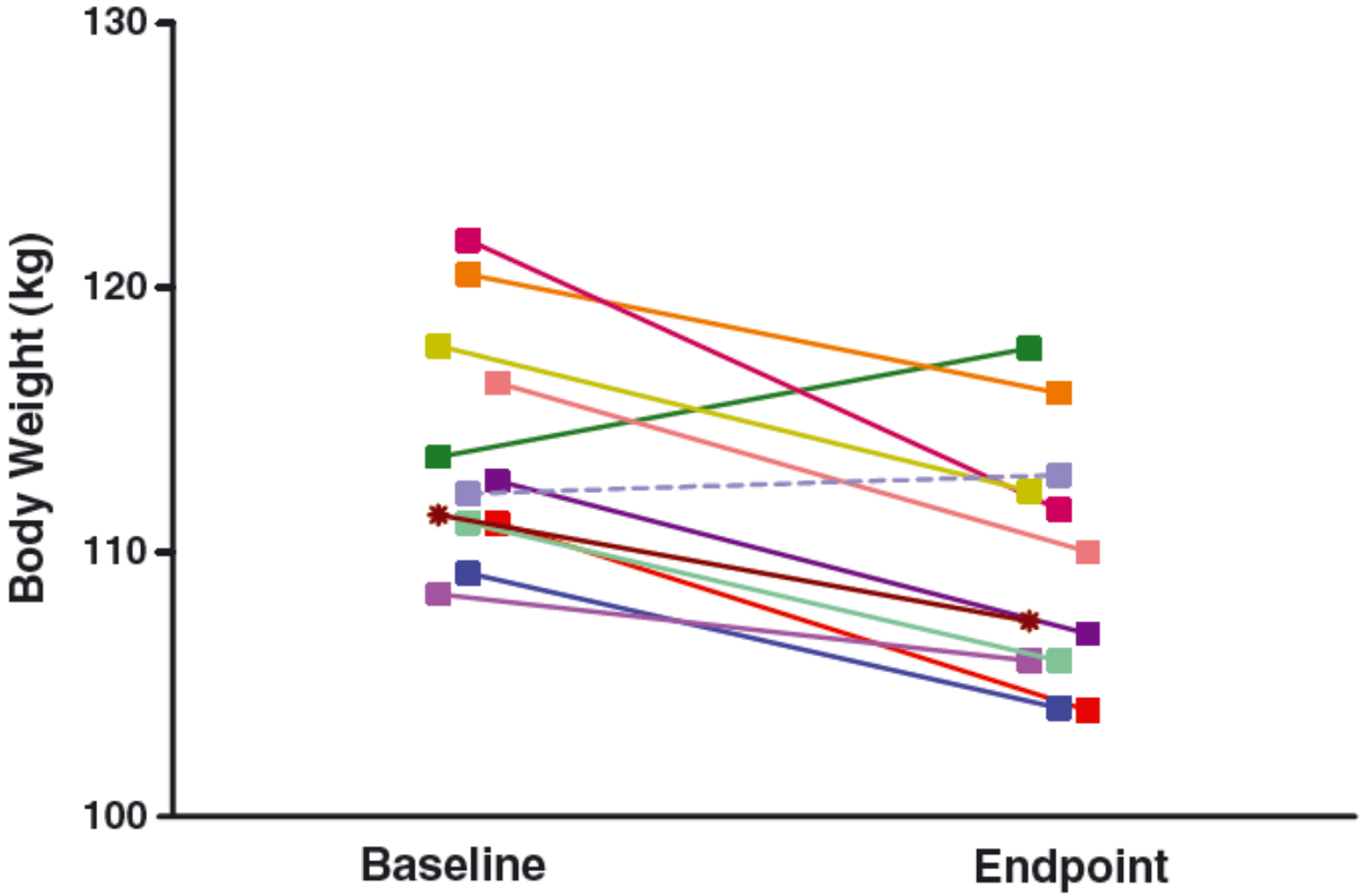
- Welke insuline?
  - Basale insuline
- Welke GLP1RA zijn terugbetaald?
  - Byetta
  - Lyxumia
- Combinatie:
  - Xultophy (insuline degludec + GLP1RA liraglutide)
  - Suliqua (insuline glargine + GLP1RA lixisenatide)

GLP1-RA + Basal Insulin: HbA1c



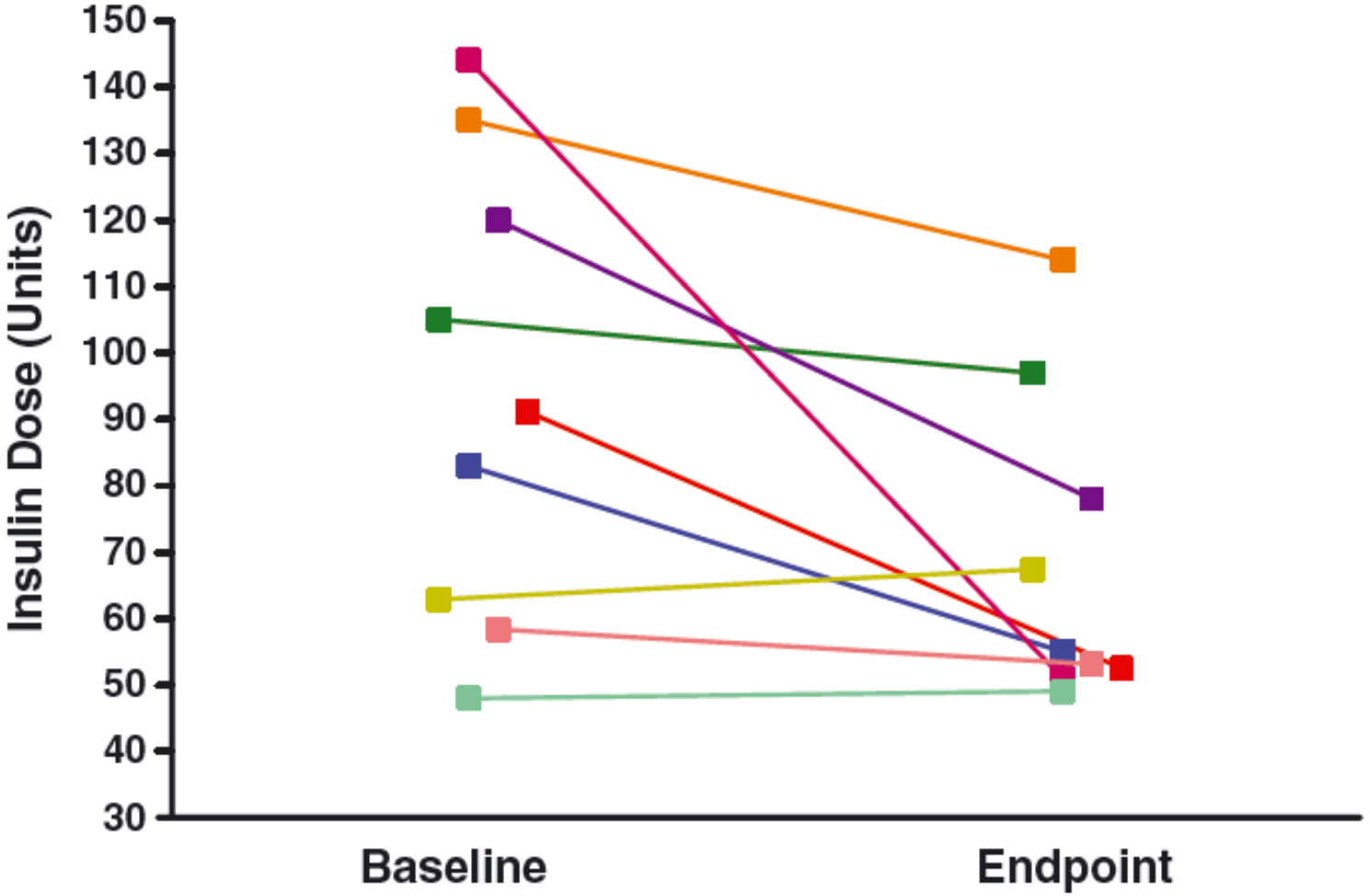
Balena et al, *Diabetes, Obesity and Metabolism* 15: 485–502, 2013.

GLP1-RA + Basal Insulin: weight



Balena et al, *Diabetes, Obesity and Metabolism* 15: 485–502, 2013.

GLP1-RA + Basal Insulin: insulin dose



Balena et al, *Diabetes, Obesity and Metabolism* 15: 485–502, 2013.

Comparing daily treatment with IDegLira and Basal-Bolus

IDegLira

1 pen[1]

1 Injection[1]

1 SMBG test[2]

Daily Regimen

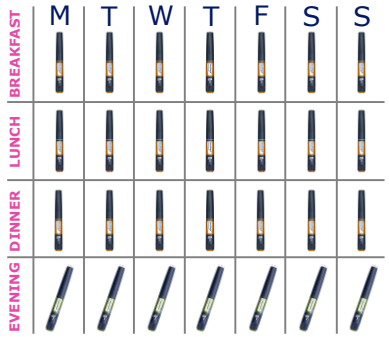
Basal - Bolus

2 pens

2-4 *Injections[3]

2-4 *SMBG test[2]

Daily Regimen



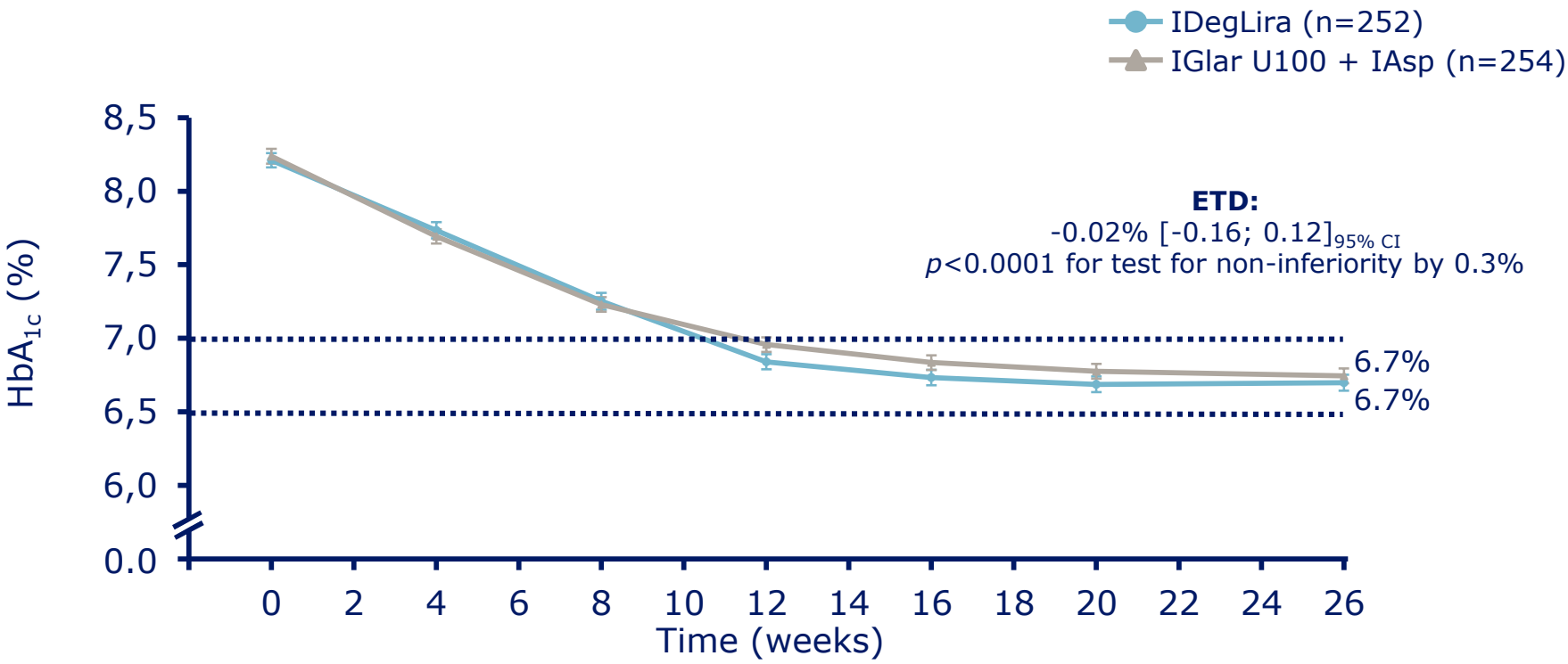
*Based on the number of meals

SMBG, self measured blood glucose

1. Buse JB et al. *Diabetes Care* 2014;37: 2926-2933; 2. Owens D et al. *Diabetes and Primary Care* 2004; 6(1): 8-16; 3. National Institute for Clinical Excellence. Guidance on the use of long-acting insulin analogues for the treatment of diabetes – Insulin glargine. Technology Appraisal number 53 December, 2002

DUAL VII

HbA_{1c} over time



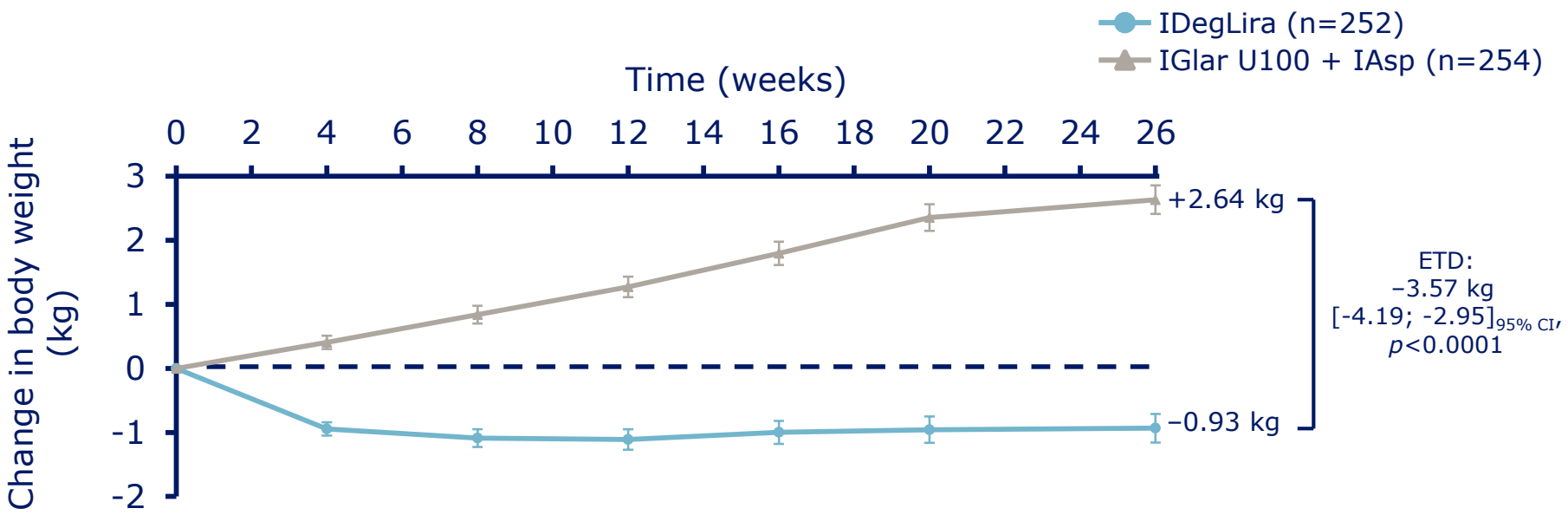
Mean observed values with error bars (standard error mean) based on full analysis set. ETD is based on LSMeans from full analysis set, using mixed model for repeated measurement. ---ADA/EASD HbA_{1c} target <7.0% and AACE HbA_{1c} target ≤6.5%

AACE, American Association of Clinical Endocrinologists; ADA, American Diabetes Association; CI, confidence interval; EASD, European Association for the Study of Diabetes; HbA_{1c}, glycosylated haemoglobin; IAsp, insulin aspart; IDegLira, insulin degludec/liraglutide combination; ETD, estimated treatment difference; IGlar U100, insulin glargine 100 units/mL; LSMean, least square mean.

Billings LK et al. *Diabetes Care.* 2018;41(5):1009-1016

DUAL VII

Change in body weight over time



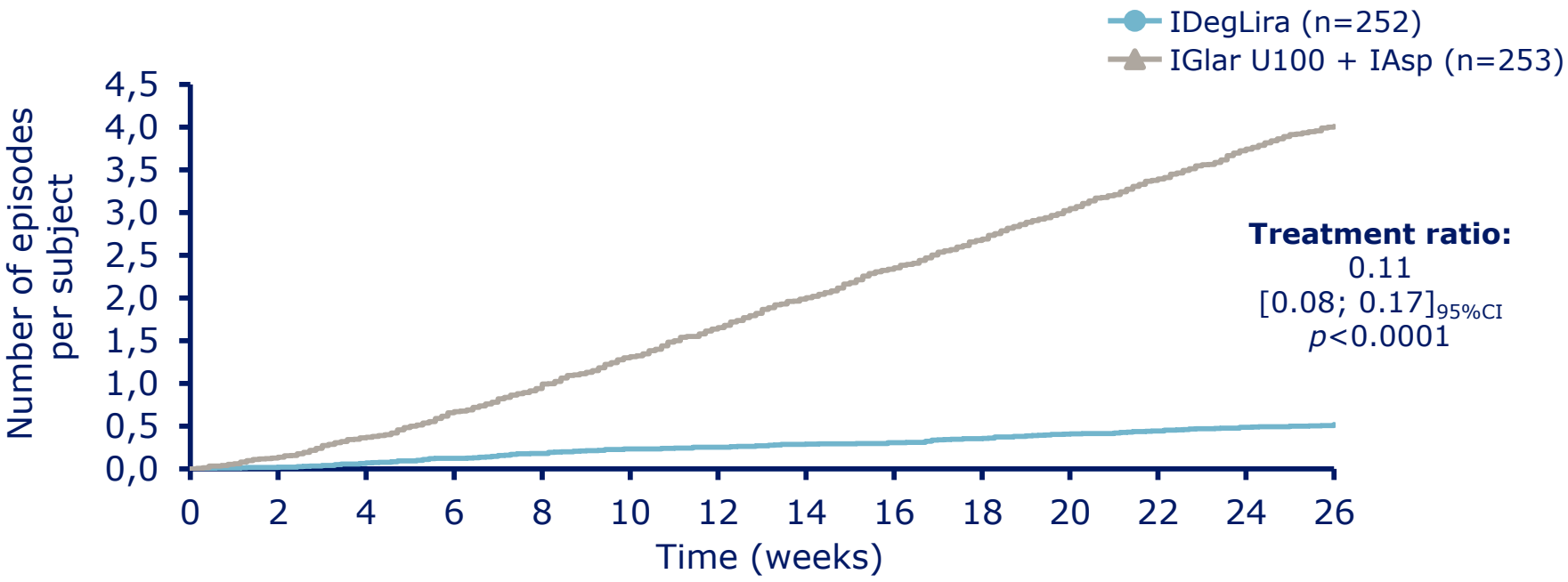
LSMean values with error bars (standard error mean) based on full analysis set, using MMRM. MMRM with treatment, region and visit as factors and baseline value as covariate. Interactions between visit and all other factors and covariate are included.

CI, confidence interval; ETD, estimated treatment difference; IAsp, insulin aspart; IDegLira, insulin degludec/liraglutide combination; IGlar U100, insulin glargine 100 units/mL; LSMean, least square mean; MMRM, mixed model for repeated measurement.

Billings LK et al. *Diabetes Care.* 2018;41(5):1009-1016

DUAL VII

Severe or BG-confirmed symptomatic hypoglycaemia



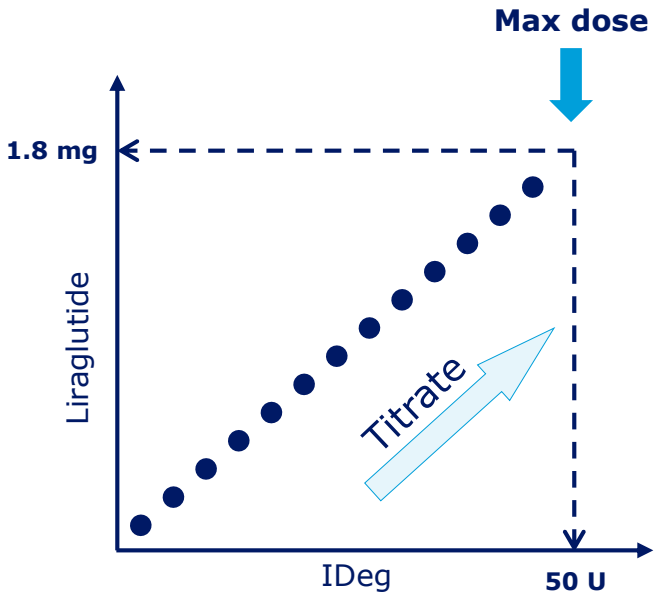
Mean cumulative function based on safety analysis set. Severe or BG-confirmed symptomatic: an episode that is severe according to the ADA classification or BG-confirmed by a plasma glucose value <3.1 mmol/L (<56 mg/dL) with symptoms consistent with hypoglycaemia
ADA, American Diabetes Association; BG, blood glucose; CI, confidence interval; IAsp, insulin aspart; IDegLira, insulin degludec/liraglutide combination; IGlar U100, insulin glargine 100 units/mL.

Billings LK et al. *Diabetes Care.* 2018;41(5):1009-1016

Xultophy® Practical

- **Posology**
  - Xultophy is administered as dose steps

1 dose step	1 unit insulin degludec + 0.036 mg liraglutide
16 dose steps	16 units insulin degludec + 0.58 mg liraglutide
50 dose steps	50 units insulin degludec + 1.8 mg liraglutide



SPC Xultophy® June 2018

Xultophy® indications EU

- Xultophy is indicated for the **treatment of adults with insufficiently controlled type 2 diabetes mellitus** to improve glycaemic control as an adjunct to diet and exercise **in addition to other oral medicinal products** for the treatment of diabetes.

  - Add-on to oral glucose lowering medicinal products
  - Transfer from GLP-1 receptor agonist
  - **Transfer from basal insulin**

Algorithm in Belgium

Healthy eating, weight control, physical activity, diabetes education

Metformin
High efficacy
Low hypo risk
Weight neutral
Side effects: GI, lactic acidosis
Contraindication: GFR < 30 ml/min; NYHA IV

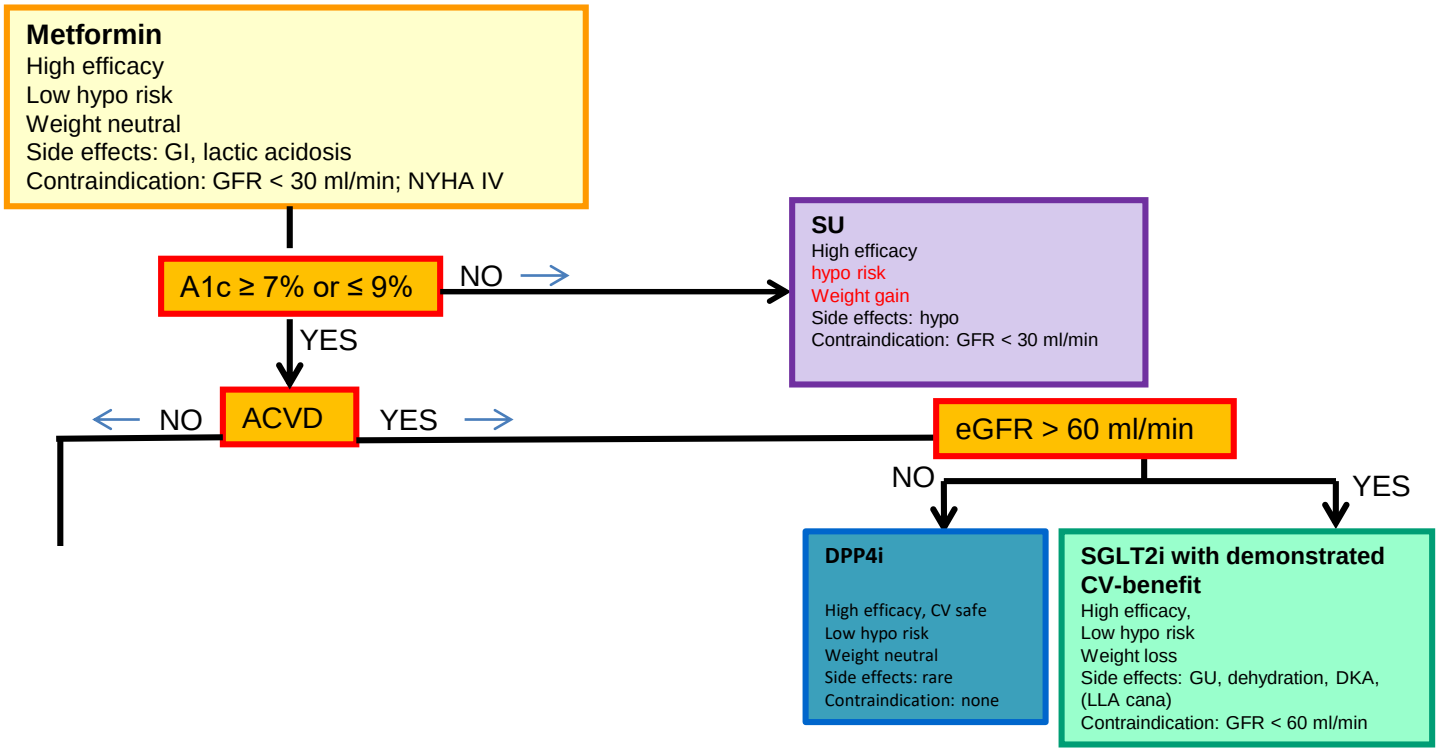
A1c ≥ 7% or ≤ 9%

NO →

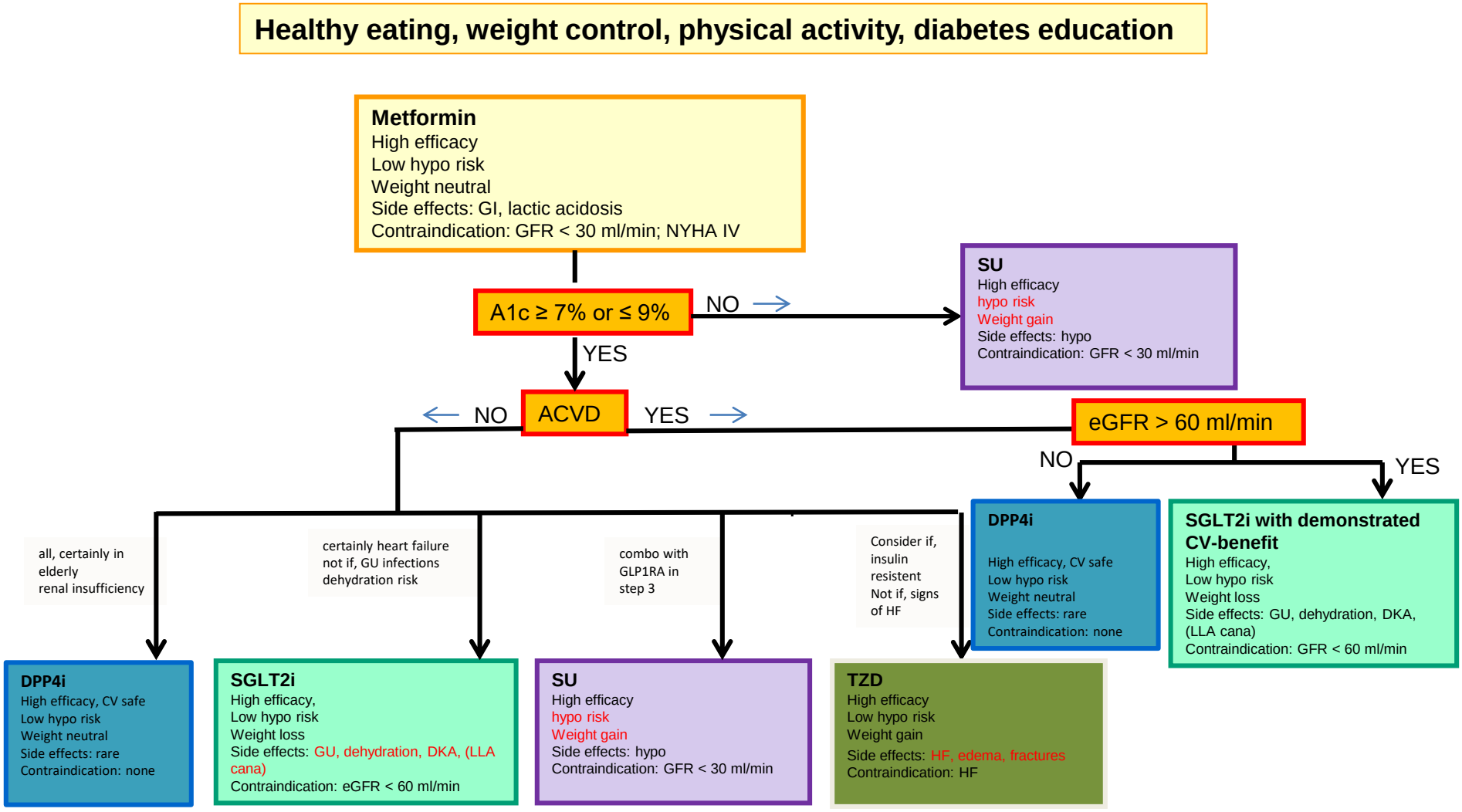
SU
High efficacy
hypo risk
Weight gain
Side effects: hypo
Contraindication: GFR < 30 ml/min

Algorithm in Belgium

Healthy eating, weight control, physical activity, diabetes education



Algorithm in Belgium



Dank u
Merci