GLP1-RA – LÉČIT OBEZITU NEBO DIABETES?

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Centrum diabetologie, IKEM

Obsah přednášky

- Nový ADA/EASD konsensus léčby DM 2. typu
- GLP-1 RA v léčbě diabetu
- GLP-1 RA v léčbě obezity

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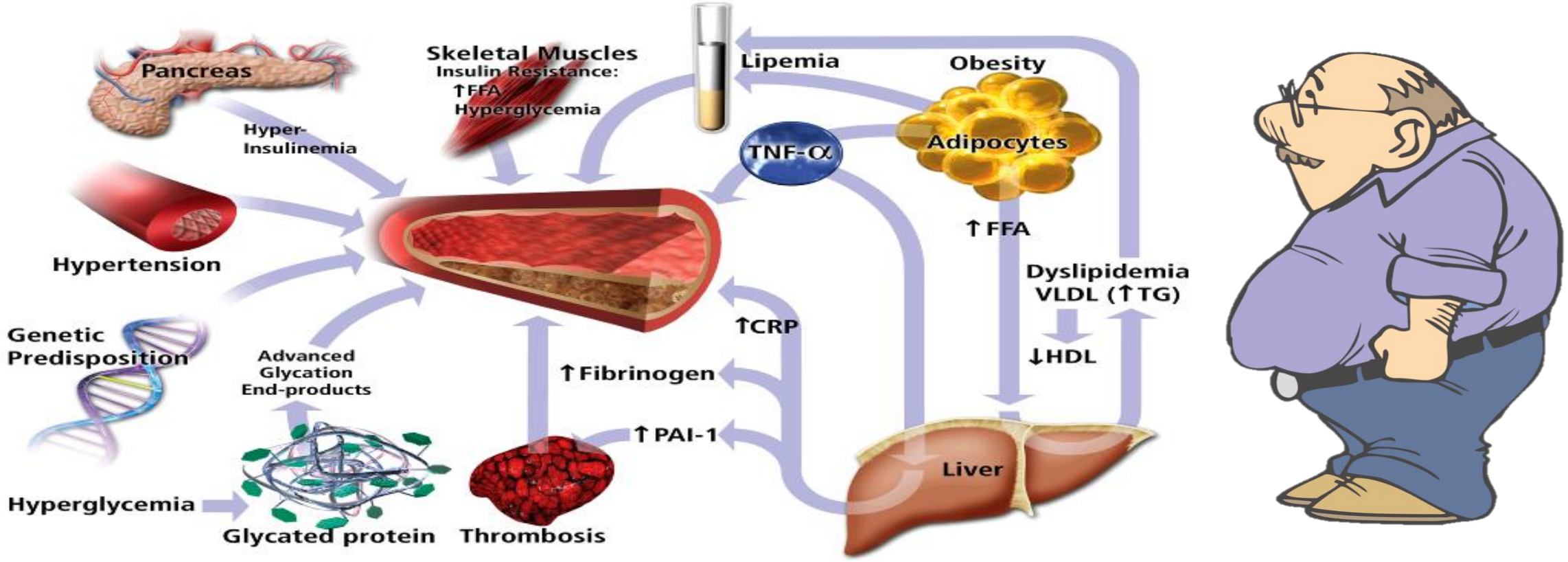
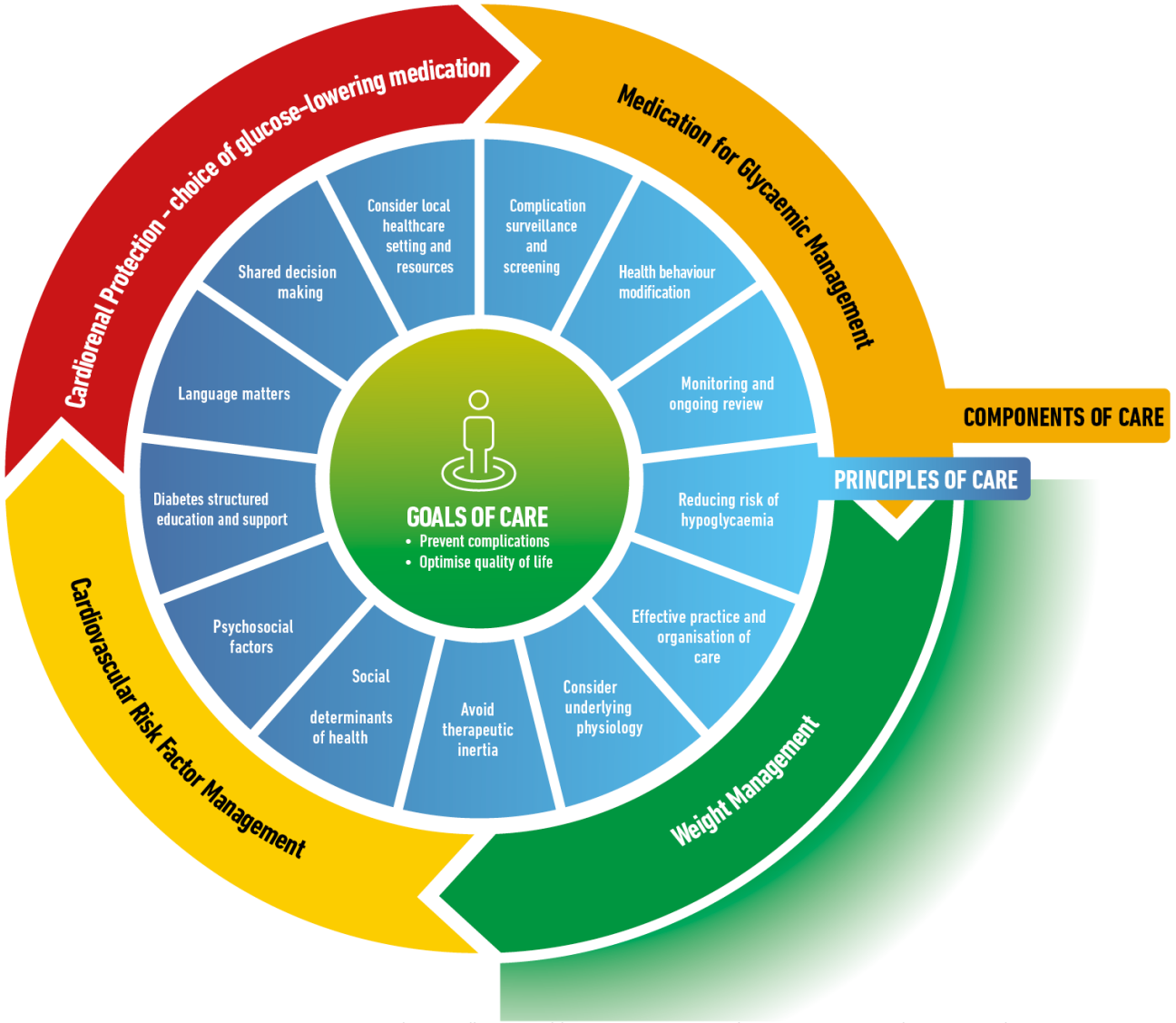
Diabetes 2. typu se vyskytuje v kombinaci s řadou komorbidit



90% of T2D patients are overweight or obese[2]
70% of T2D patients have hypertension[3]
70% of T2D patients have dyslipidemia[4,5]

CV, cardiovascular; FFA, free fatty acids; HDL, high-density lipoprotein; PAI-1, plasminogen activator inhibitor-1; T2D, type 2 diabetes; TG, triglyceride; TNF-α, tumour necrosis factor-α; VLDL, very low-density lipoprotein. 1. Libby et al. Circulation 2002;106:2760–2763; 2. World Health Organization. Obesity and Overweight Fact Sheet. http://www.who.int/dietphysicalactivity/media/en/gsfs_obesity.pdf (accessed Aug 2017); 3. Fox CS et al. Diabetes Care 2015;38:1777–1803; 4. Canadian Diabetes Association Clinical Practice Guidelines. http://guidelines.diabetes.ca/browse/chapter24 (accessed Aug 2017); 5. Dixit AK et al. J Diabetes Metab Disord 2014,13:58

Nový konsensus ADA/EASD pro léčbu DM 2. typu



Goal: Achievement and Maintenance of Glycaemic and Weight Management Goals

Glycaemic Management: Choose approaches that provide the efficacy to achieve goals:

Metformin OR Agent(s) including COMBINATION therapy that provide adequate EFFICACY to achieve and maintain treatment goals

Consider avoidance of hypoglycaemia a priority in high-risk individuals

In general, higher efficacy approaches have greater likelihood of achieving glycaemic goals

Efficacy for glucose lowering

Very High:
Dulaglutide (high dose), Semaglutide, Tirzepatide

Insulin

Combination Oral, Combination Injectable (GLP-1 RA/Insulin)

High:
GLP-1 RA (not listed above), Metformin, SGLT2i, Sulfonylurea, TZD

Intermediate:
DPP-4i

Achievement and Maintenance of Weight Management Goals:

Set individualised weight management goals

General lifestyle advice: medical nutrition therapy/eating patterns/ physical activity

Intensive evidence-based structured weight management programme

Consider medication for weight loss

Consider metabolic surgery

When choosing glucose-lowering therapies:

Consider regimen with high-to-very-high dual glucose and weight efficacy

Efficacy for weight loss

Very High:
Semaglutide, Tirzepatide

High:
Dulaglutide, Liraglutide

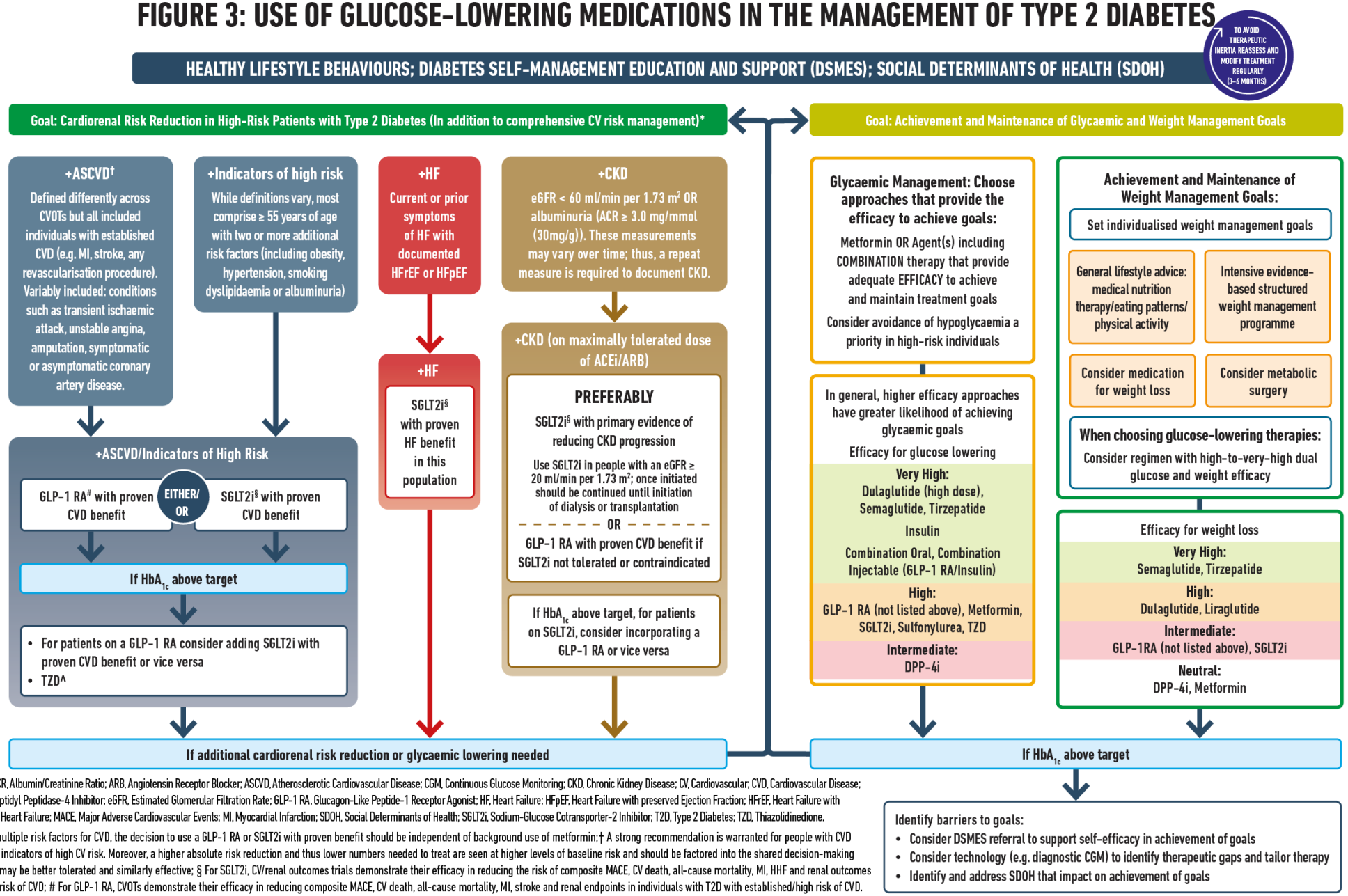
Intermediate:
GLP-1RA (not listed above), SGLT2i

Neutral:
DPP-4i, Metformin

Davies MJ, Aroda VR, Collins BS, Gabbay RA, Green J, Maruthur NM, Rosas SE, Del Prato S, Mathieu C, Mingrone G, Rossing P, Tankova T, Tsapas A, Buse JB

Diabetes Care 2022; https://doi.org/10.2337/dci22-0034. *Diabetologia* 2022; https://doi.org/10.1007/s00125-022-05787-2.

FIGURE 3: USE OF GLUCOSE-LOWERING MEDICATIONS IN THE MANAGEMENT OF TYPE 2 DIABETES



ACEi, Angiotensin-Converting Enzyme Inhibitor; ACR, Albumin/Creatinine Ratio; ARB, Angiotensin Receptor Blocker; ASCVD, Atherosclerotic Cardiovascular Disease; CGM, Continuous Glucose Monitoring; CKD, Chronic Kidney Disease; CV, Cardiovascular; CVD, Cardiovascular Disease; CVOT, Cardiovascular Outcomes Trial; DPP-4i, Dipeptidyl Peptidase-4 Inhibitor; eGFR, Estimated Glomerular Filtration Rate; GLP-1 RA, Glucagon-Like Peptide-1 Receptor Agonist; HF, Heart Failure; HFpEF, Heart Failure with preserved Ejection Fraction; HFrEF, Heart Failure with reduced Ejection Fraction; HHF, Hospitalisation for Heart Failure; MACE, Major Adverse Cardiovascular Events; MI, Myocardial Infarction; SDOH, Social Determinants of Health; SGLT2i, Sodium-Glucose Cotransporter-2 Inhibitor; T2D, Type 2 Diabetes; TZD, Thiazolidinedione.

* In people with HF, CKD, established CVD or multiple risk factors for CVD, the decision to use a GLP-1 RA or SGLT2i with proven benefit should be independent of background use of metformin; † A strong recommendation is warranted for people with CVD and a weaker recommendation for those with indicators of high CV risk. Moreover, a higher absolute risk reduction and thus lower numbers needed to treat are seen at higher levels of baseline risk and should be factored into the shared decision-making process. See text for details; ^ Low-dose TZD may be better tolerated and similarly effective; § For SGLT2i, CV/renal outcomes trials demonstrate their efficacy in reducing the risk of composite MACE, CV death, all-cause mortality, MI, HHF and renal outcomes in individuals with T2D with established/high risk of CVD; # For GLP-1 RA, CVOTs demonstrate their efficacy in reducing composite MACE, CV death, all-cause mortality, MI, stroke and renal endpoints in individuals with T2D with established/high risk of CVD.

Davies MJ, Aroda VR, Collins BS, Gabbay RA, Green J, Maruthur NM, Rosas SE, Del Prato S, Mathieu C, Mingrone G, Rossing P, Tankova T, Tsapas A, Buse JB

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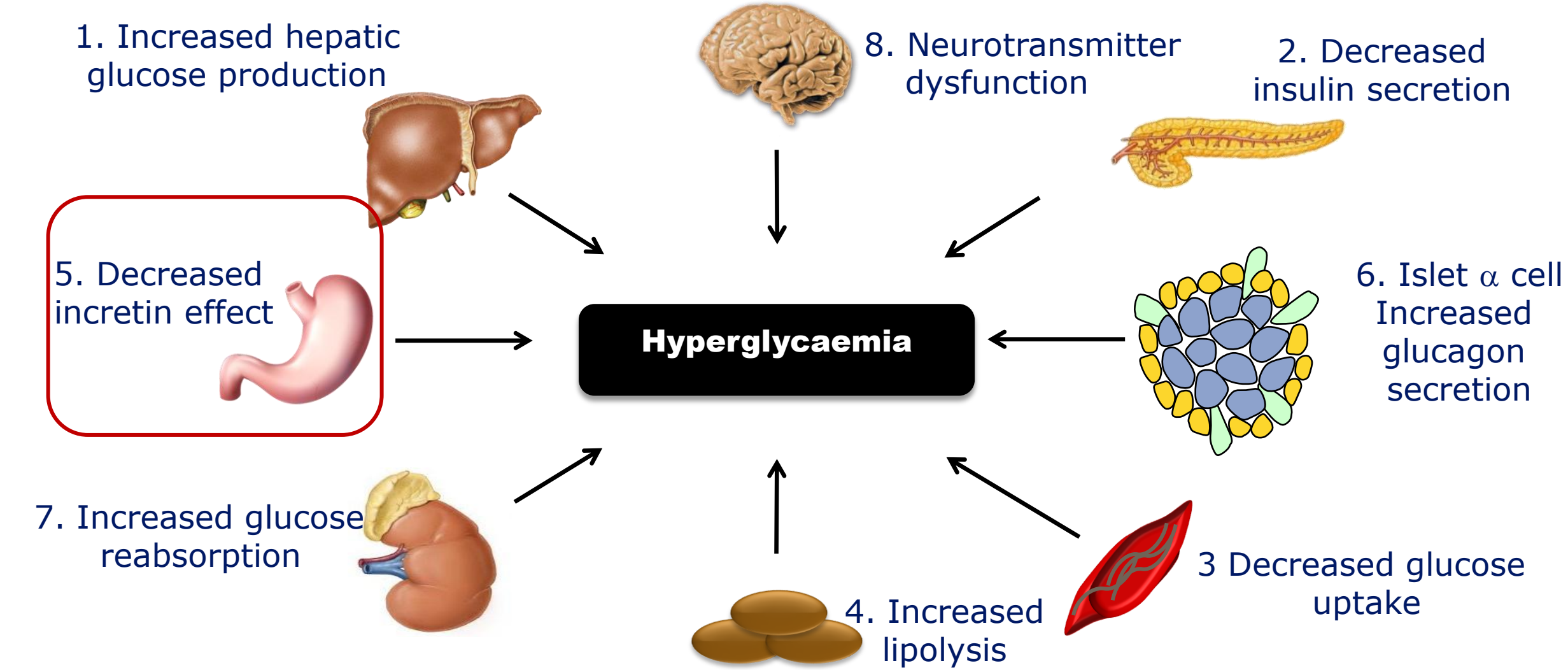
Pathophysiology of type 2 diabetes: the ominous octet



Adapted from DeFronzo RA. *Diabetes Care* 2009;58:773–795

Albiglutide was withdrawn from the worldwide market in July 2018

GLP-1 agonisté se liší molekulární strukturou a velikostí molekuly

Exendin-4-based GLP-1RAs

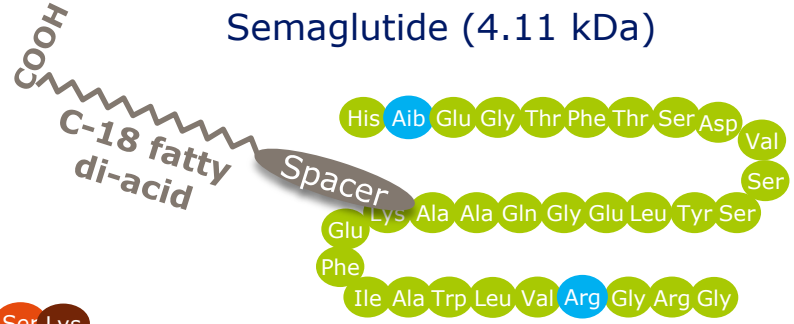
Exenatide (4.19 kDa)

Lixisenatide (4.86 kDa)

Acylated hGLP-1RAs

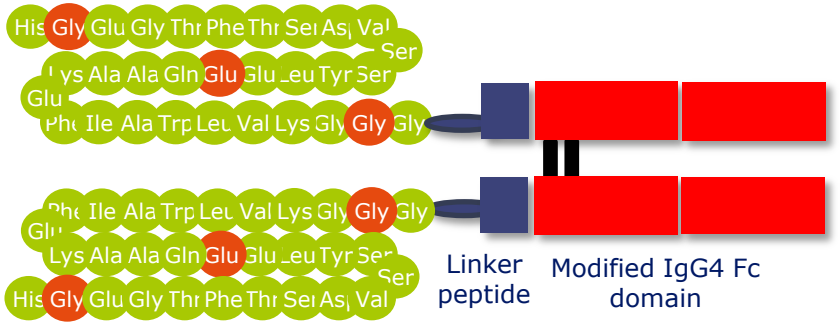
Liraglutide (3.75 kDa)

Semaglutide (4.11 kDa)



Macromolecular hGLP-1RAs

Dulaglutide (~63 kDa)



Albiglutide (72.97 kDa)

GLP-1RA, glucagon-like peptide-1 receptor agonist; hGLP-1RA, human glucagon-like peptide-1 receptor agonist; IgG4 Fc, immunoglobulin-G4 fragment crystallisable.

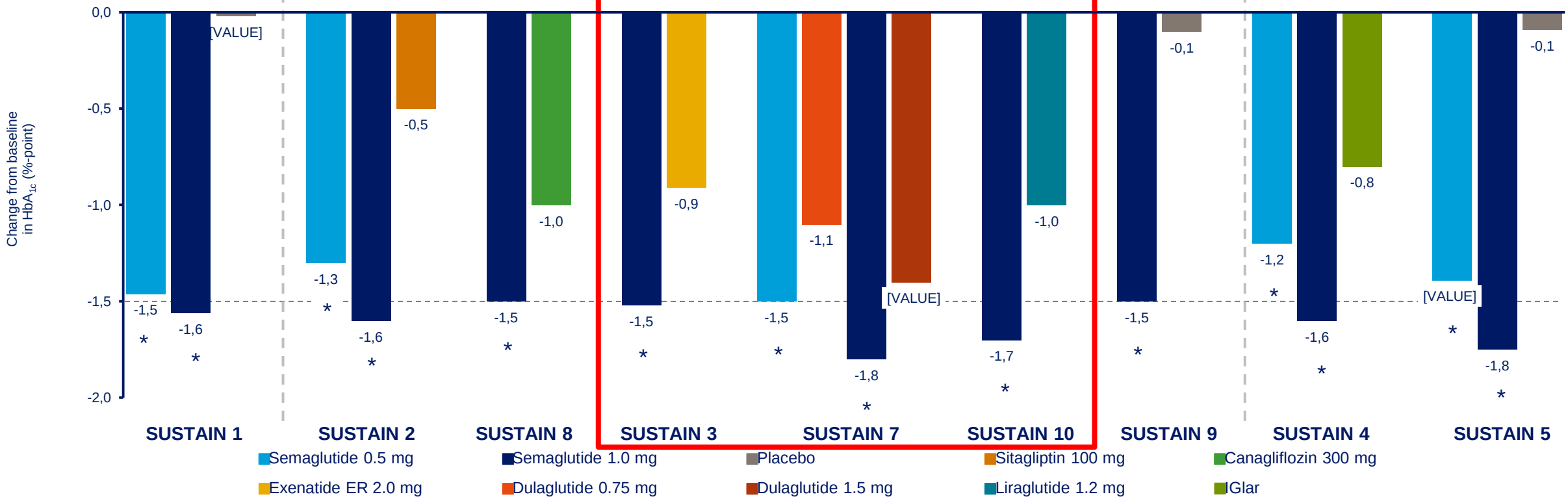
s.c. semaglutid vs. komparátory: změny HbA_{1c}

Novo Nordisk®

SUSTAIN 1–5 AND 7–10

1.3 – 1.8%

	MONOTHERAPY	VS OADs		VS OTHER GLP-1RAs			ADD-ON TO SGLT-2i	VS/ADD-ON TO BASAL INSULIN	
Comparator:	**Placebo[1]**	**Sitagliptin[2]**	**Canagliflozin[3]**	**Exenatide ER[4]**	**Dulaglutide[5]**	**Liraglutide[6]**	**Placebo[7]**	**IGlar[8]**	**Placebo[9]**
Background:	N/A	MET±TZD	MET	1–2 OADs MET/TZD/SU	MET	1–3 OADs MET±SU±SGLT-2i	SGLT-2i ±MET±SU	MET±SU	Basal insulin±MET
Treatment dur. (w):	30	56	52	56	40	30	30	30	8.4
Baseline HbA_{1c} (%):	8.1	8.1	8.3	8.3	8.2	8.2	8.0	8.2	



*p<0.0001 vs comparator. dur., duration; exenatide ER, exenatide extended release; GLP-1RA, glucagon-like peptide-1 receptor agonist; IGlar, insulin glargine; MET, metformin; N/A, not applicable; OAD, oral antidiabetic drug; SGLT-2i, sodium–glucose cotransporter-2 inhibitor; SU, sulphonylurea; TZD, thiazolidinedione; w, weeks.

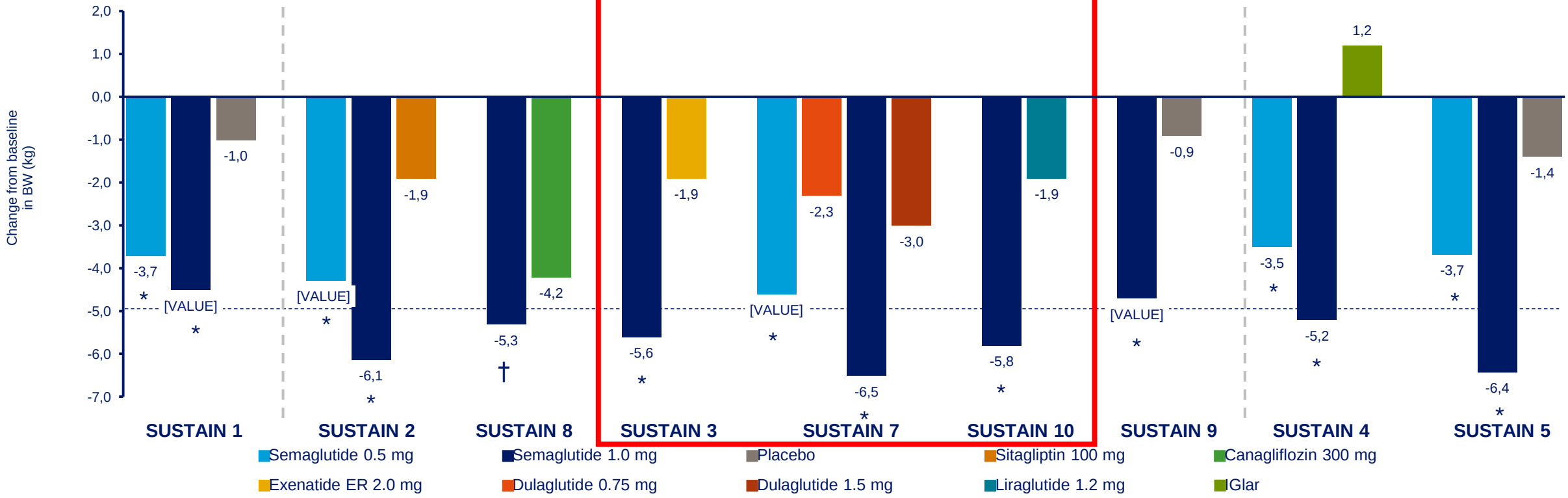
1. Sorli C et al. Lancet Diabetes Endocrinol 2017;5:251–60; 2. Ahrén B et al. Lancet Diabetes Endocrinol 2017;5:341–54; 3. Lingvay I et al. Lancet Diabetes Endocrinol 2019;7:834–44; 4. Ahmann AJ et al. Diabetes Care 2018;41:258–66; 5. Pratley RE et al. Lancet Diabetes Endocrinol 2018;6:275–86; 6. Capehorn MS et al. Diabetes Metab 2020;46:100–9; 7. Zinman B et al. Lancet Diabetes Endocrinol 2019;7:356–67; 8. Aroda VR et al. Lancet Diabetes Endocrinol 2017;5:355–66; 9. Rodbard HW et al. J Clin Endocrinol Metab 2018;103:2291–301.

s.c. semaglutid vs. komparátory: Změny tělesné hmotnosti

SUSTAIN 1–5 AND 7–10

4 – 6.5kg

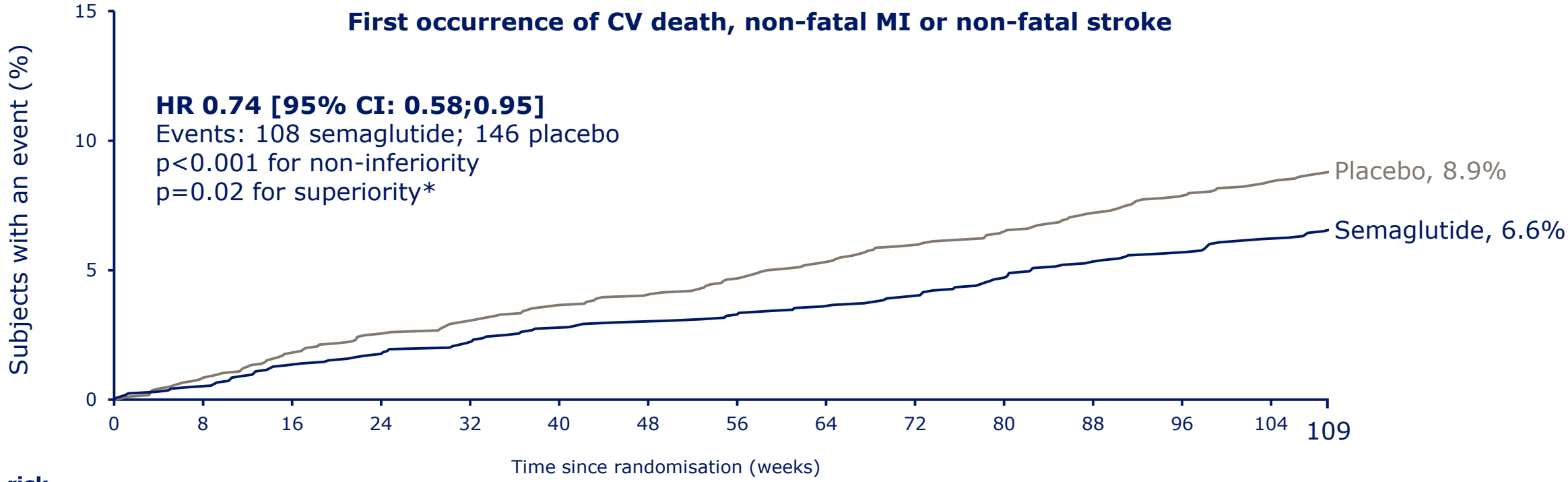
	MONOTHERAPY	VS OADs		VS OTHER GLP-1RAs			ADD-ON TO SGLT-2i	VS/ADD-ON TO BASAL INSULIN	
Comparator:	**Placebo[1]**	**Sitagliptin[2]**	**Canagliflozin[3]**	**Exenatide ER[4]**	**Dulaglutide[5]**	**Liraglutide[6]**	**Placebo[7]**	**IGlar[8]**	**Placebo[9]**
Background:	N/A	MET±TZD	MET	1–2 OADs MET/TZD/SU	MET	1–3 OADs MET±SU±SGLT-2i	SGLT-2i ±MET±SU	MET±SU	Basal insulin±MET
Treatment dur. (w):	30	56	52	56	40	30	30	30	91.7
Baseline BW (kg):	91.9	89.5	90.2	95.8	95.2	96.9	91.7	93.5	



**p<0.0001 vs comparator; †p<0.005 vs comparator. BW, body weight; dur., duration; exenatide ER, exenatide extended release; GLP-1RA, glucagon-like peptide-1 receptor agonist; IGlar, insulin glargine; MET, metformin; N/A, not applicable; OAD, oral antidiabetic drug; SGLT-2i, sodium–glucose cotransporter-2 inhibitor; SU, sulphonylurea; TZD, thiazolidinedione; w, weeks. 1. Sorli C et al. Lancet Diabetes Endocrinol 2017;5:251–60; 2. Ahrén B et al. Lancet Diabetes Endocrinol 2017;5:341–54; 3. Lingvay I et al. Lancet Diabetes Endocrinol 2019;7:834–44; 4. Ahmann AJ et al. Diabetes Care 2018;41:258–66; 5. Pratley RE et al. Lancet Diabetes Endocrinol 2018;6:275–86; 6. Capehorn MS et al. Diabetes Metab 2020;46:100–9; 7. Zinman B et al. Lancet Diabetes Endocrinol 2019;7:356–67; 8. Aroda VR et al. Lancet Diabetes Endocrinol 2017;5:355–66; 9. Rodbard HW et al. J Clin Endocrinol Metab 2018;103:2291–301.*

Kombinace smrti z KV příčin, nefatálního IM a CMP (semaglutid vs. placebo)

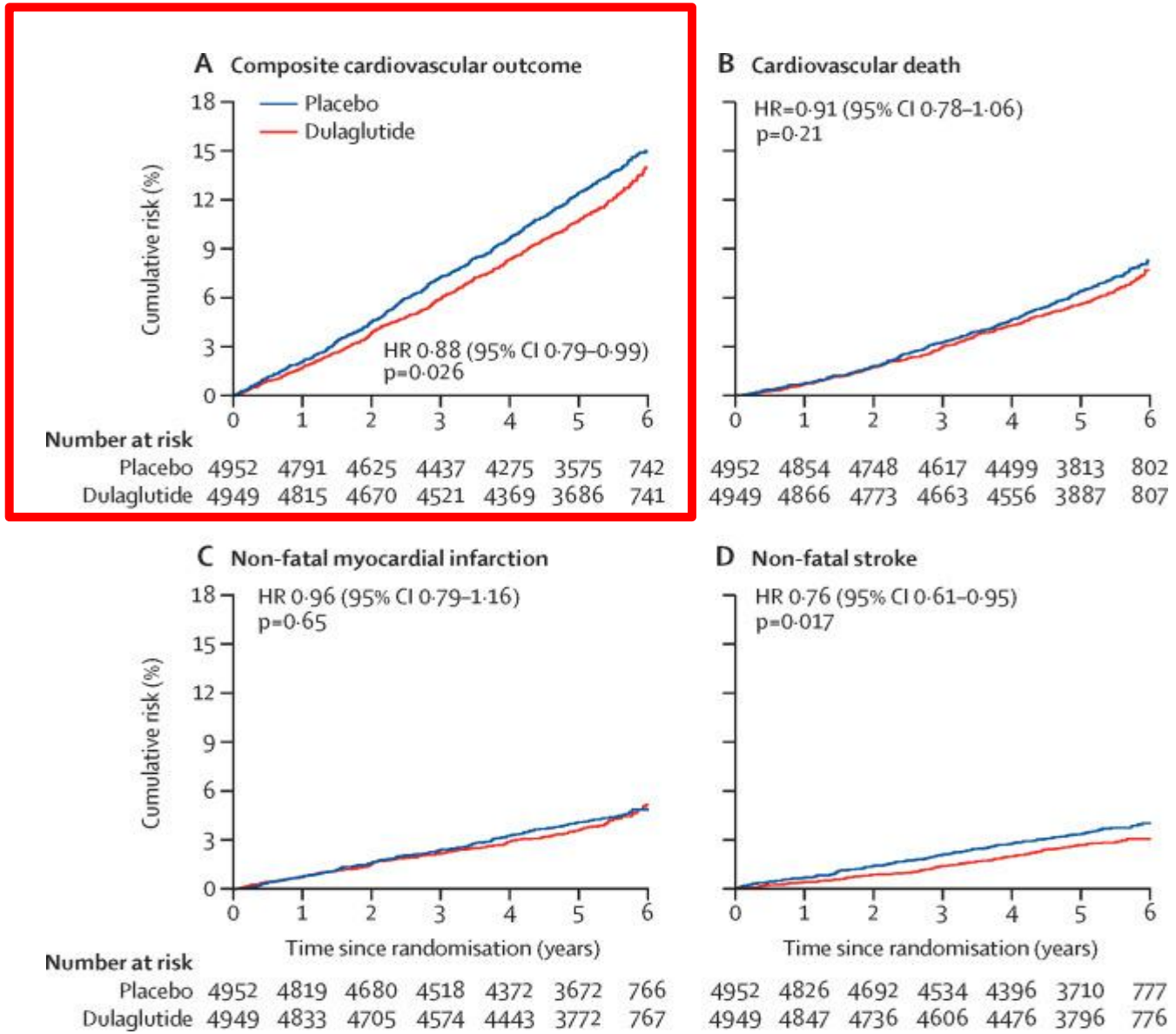
SUSTAIN 6



No. at risk								
Semaglutide	1,648	1,619	1,601	1,584	1,568	1,543	1,524	1,513
Placebo	1,649	1,616	1,586	1,567	1,534	1,508	1,479	1,466

Kaplan–Meier plot for first event adjudication committee-confirmed CV death, non-fatal MI and non-fatal stroke using 'in-trial' data from subjects in the full analysis set. *Not prespecified.
CI, confidence interval; CV, cardiovascular; HR, hazard ratio; MI, myocardial infarction.
Marso SP et al. *N Engl J Med* 2016;375:1834–44.

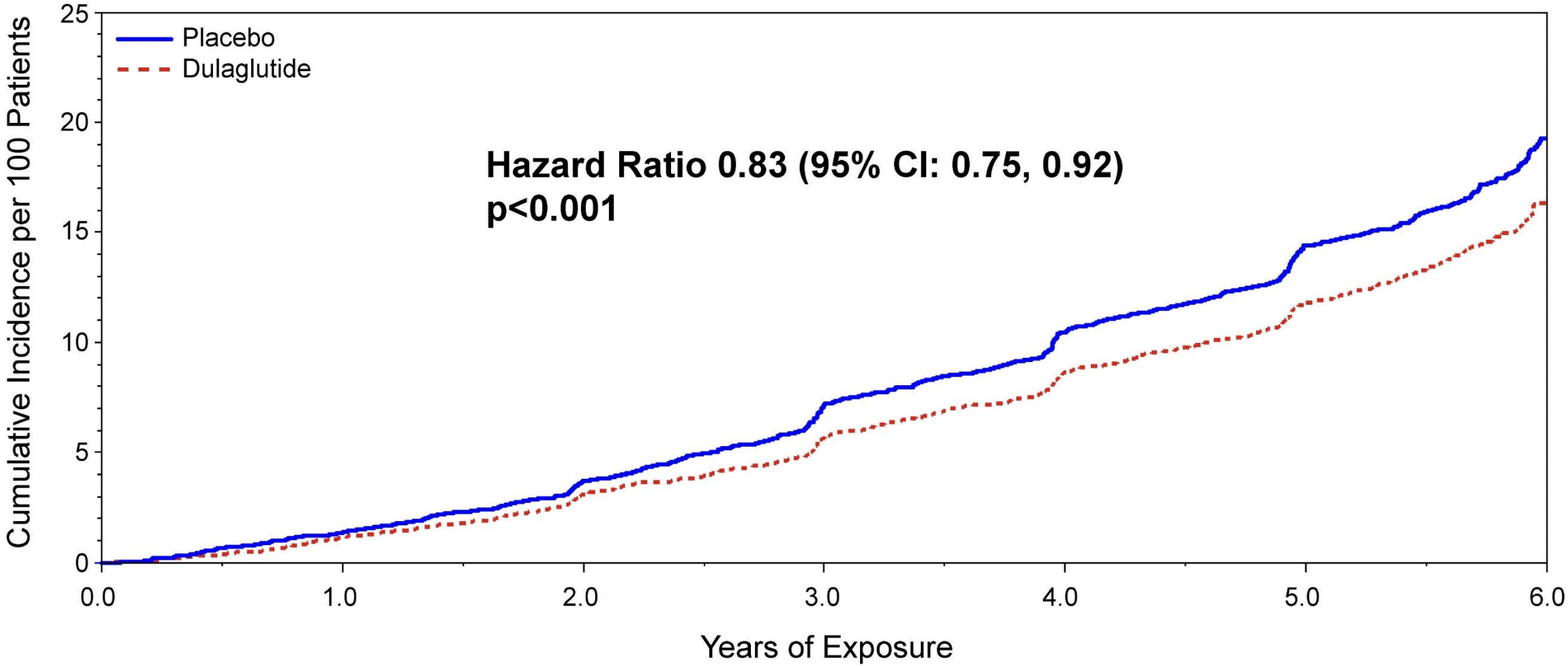
KV studie REWIND: dulaglutid v.s placebo



Dulaglutid: vliv na renální enpointy

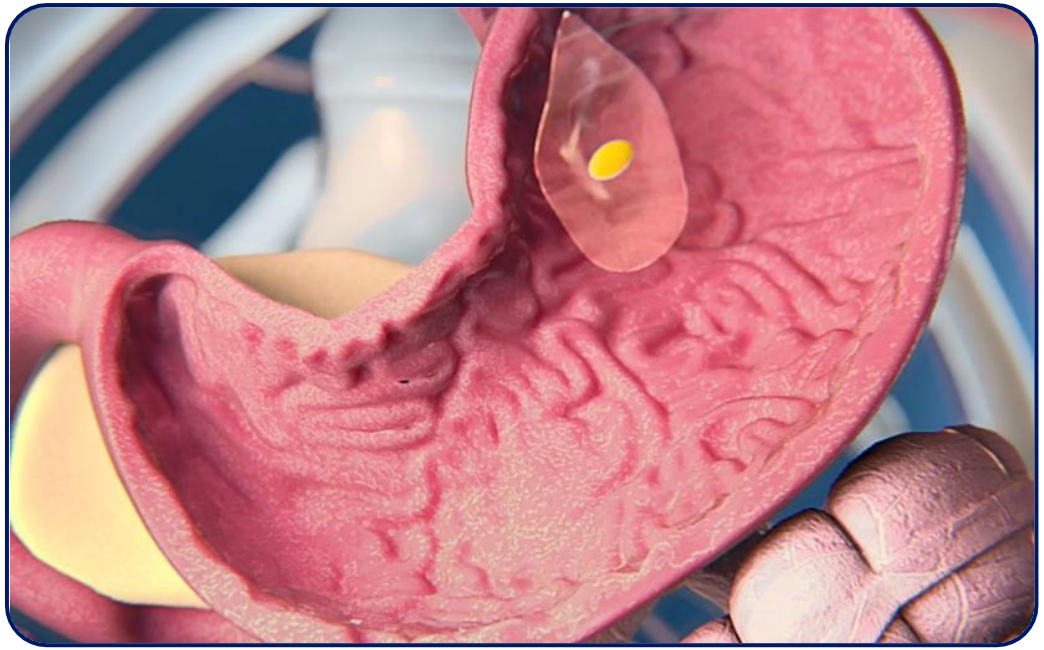
REWIND
Dulaglutide CV Outcomes Trial

Outcome: sustained eGFR decline ≥40%, ESRD, or all-cause death



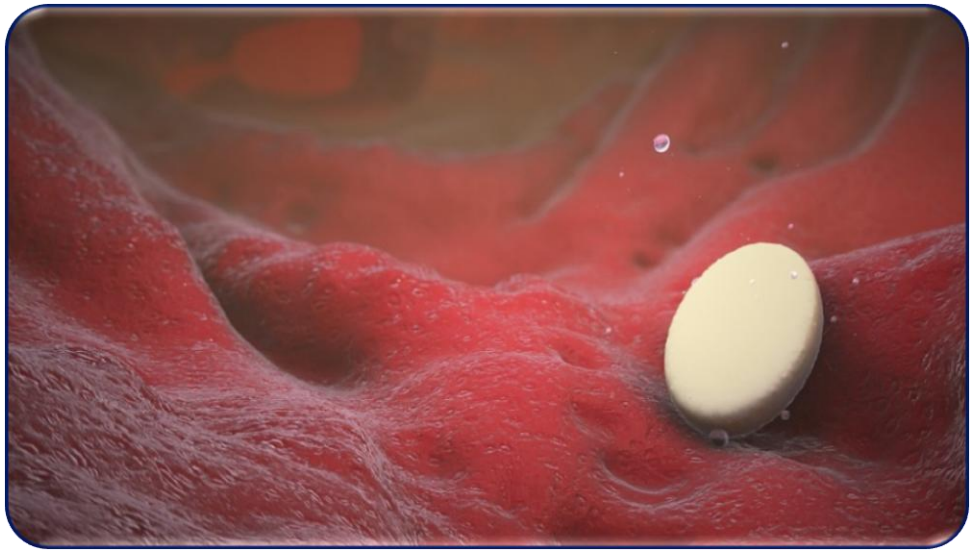
První p.o. GLP-1 RA – semaglutid

K absorpci semaglutidu dochází v žaludku



- Absorption of semaglutide requires co-formulation with SNAC to achieve effective absorption.
- The effect of SNAC is strictly time-, and concentration-dependent, and fully reversible.

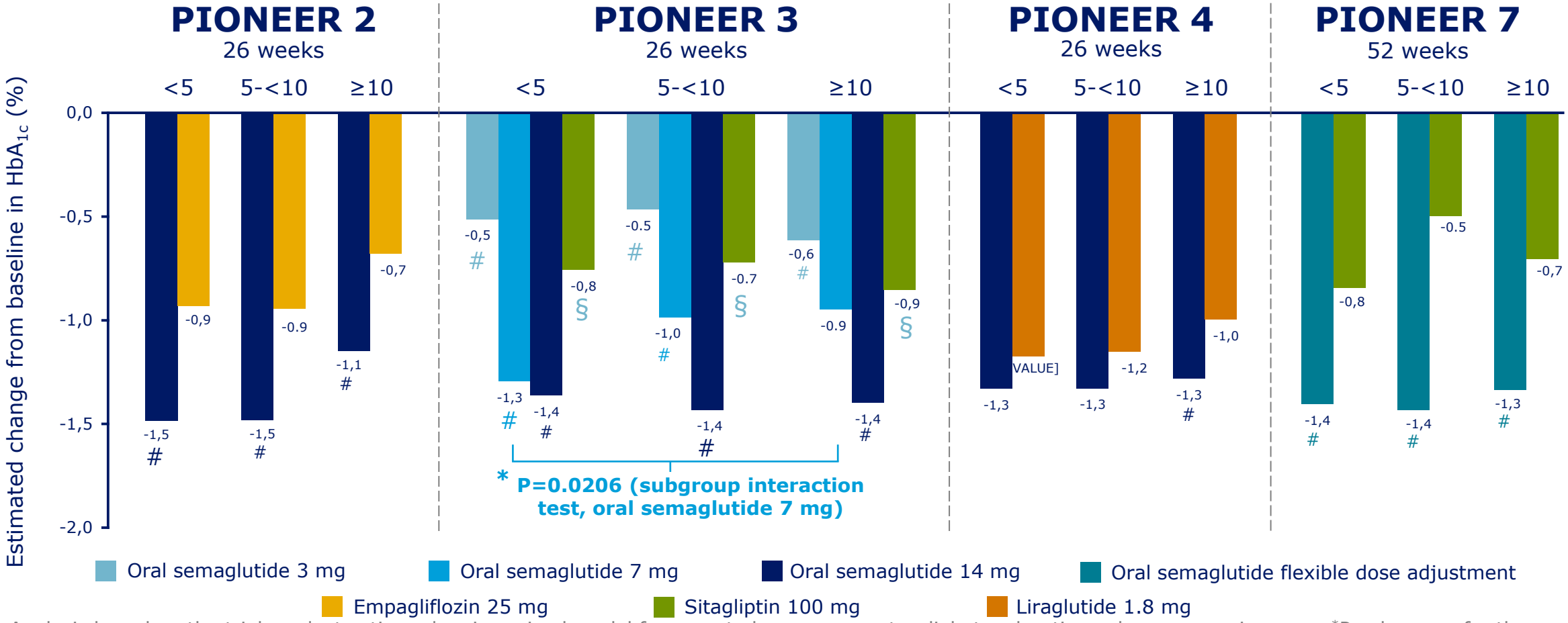
- SNAC causes a local increase of pH leading to higher solubility and protection from proteolytic degradation.
- Approximately 1% of semaglutide is absorbed; the rest is degraded in the GI tract.



SNAC, Sodium N-(8-(2-hydroxybenzoyl) amino) caprylate.
Buckley ST et al. *Sci Transl Med* 2018;10(467) pii: eaar7047.

p.o. semaglutid: změny HbA_{1c} : studie s aktivním komparátorem

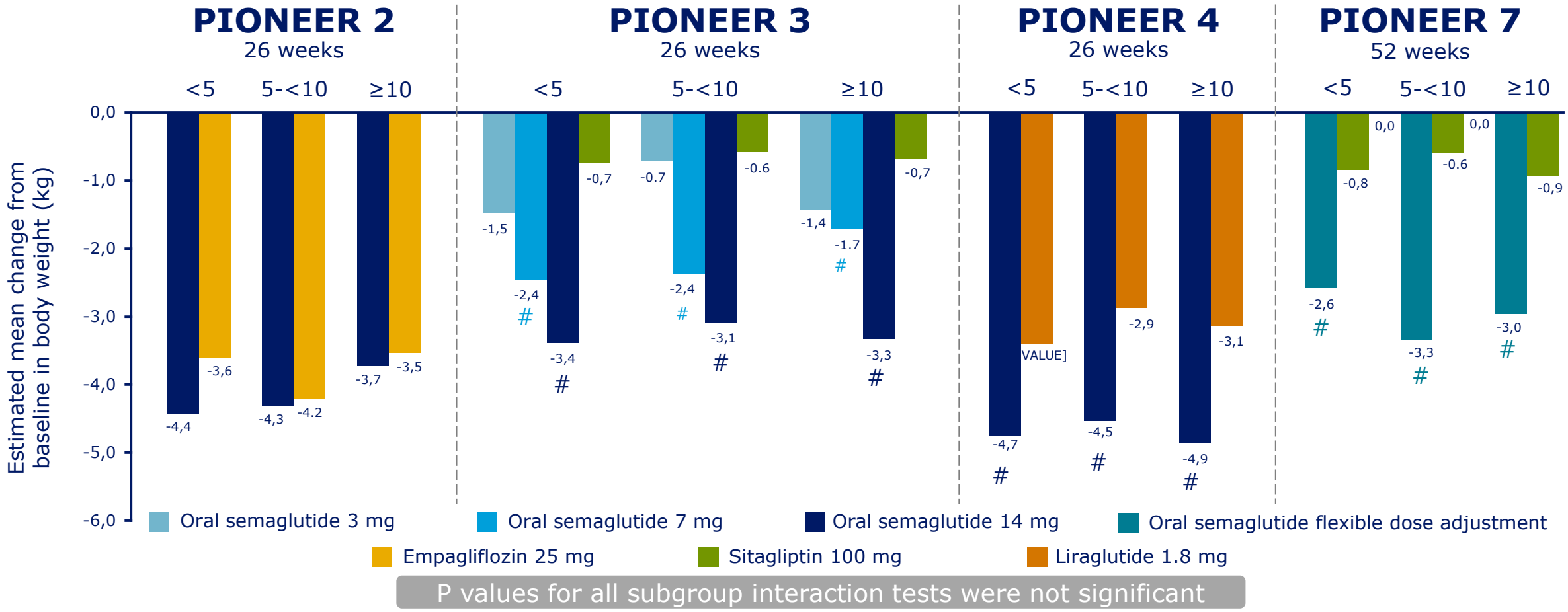
Estimated mean change from baseline



Analysis based on the trial product estimand, using mixed model for repeated measurements; diabetes duration subgroups are in years; *P values are for the test for treatment by subgroup interaction; #95% CI for ETD do not cross 0 vs comparator; §Lower limit of 95% CI for oral semaglutide 3 mg ETD vs comparator above 0. ETD, estimated treatment difference; HbA_{1c}, glycated haemoglobin. CI, confidence interval; ETD, estimated treatment difference.

Změny hmotnosti: studie s aktivním komparátorem

Estimated mean change from baseline

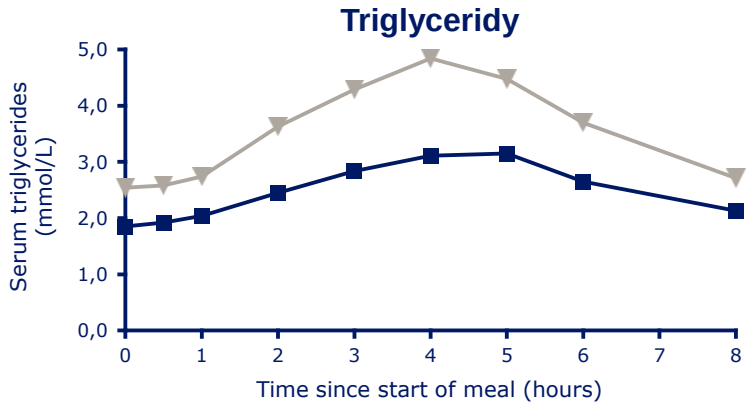


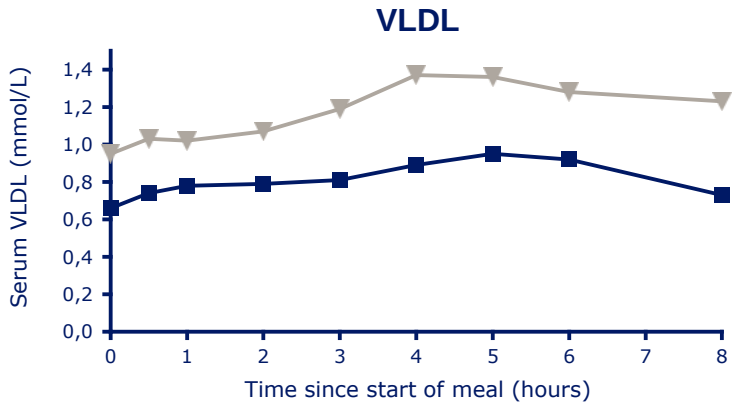
P values for all subgroup interaction tests were not significant

Analysis based on the trial product estimand, using mixed model for repeated measurements; diabetes duration subgroups are in years. #95% CI for ETD do not cross 0 vs comparator. CI, confidence interval; ETD, estimated treatment difference.

Semaglutid: přínosný účinek na lipidy

o 19% nižší triglyceridy
p=0.0036

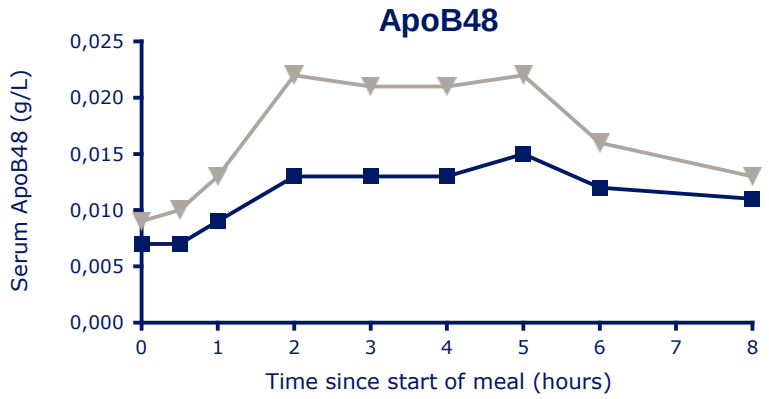




o 20% nižší VLDL
p=0.0161

SPC Rybelsus®

Hladiny lipidů nalačno a postprandiálně
Semaglutid v porovnání s placebem snižoval koncentrace triglyceridů a VLDL cholesterolu nalačno o 19 % [8; 28] a 20 % [5; 33]. Postprandiální odpověď triglyceridů a VLDL cholesterolu na jídlo s vysokým obsahem tuku byla snížena o 24 % [9; 36] a 21 % [7; 32]. Hladina ApoB48 byla snížena ve stavu nalačno i postprandiálně o 25 % [2; 42] a 30 % [15; 43].



o 25% nižší ApoB48
p=0.0350

Oral semaglutide 14 mg Placebo

Data are means unless otherwise specified. Percentages are relative differences ([estimated treatment ratio – 1] × 100).
ApoB48, apolipoprotein B48; AUC, area under the concentration–time curve; iAUC, incremental area under the concentration–time curve; VLDL, very low-density lipoprotein.
Adapted from Figure 3. Mean postprandial lipid metabolism profiles after a fat-rich breakfast.

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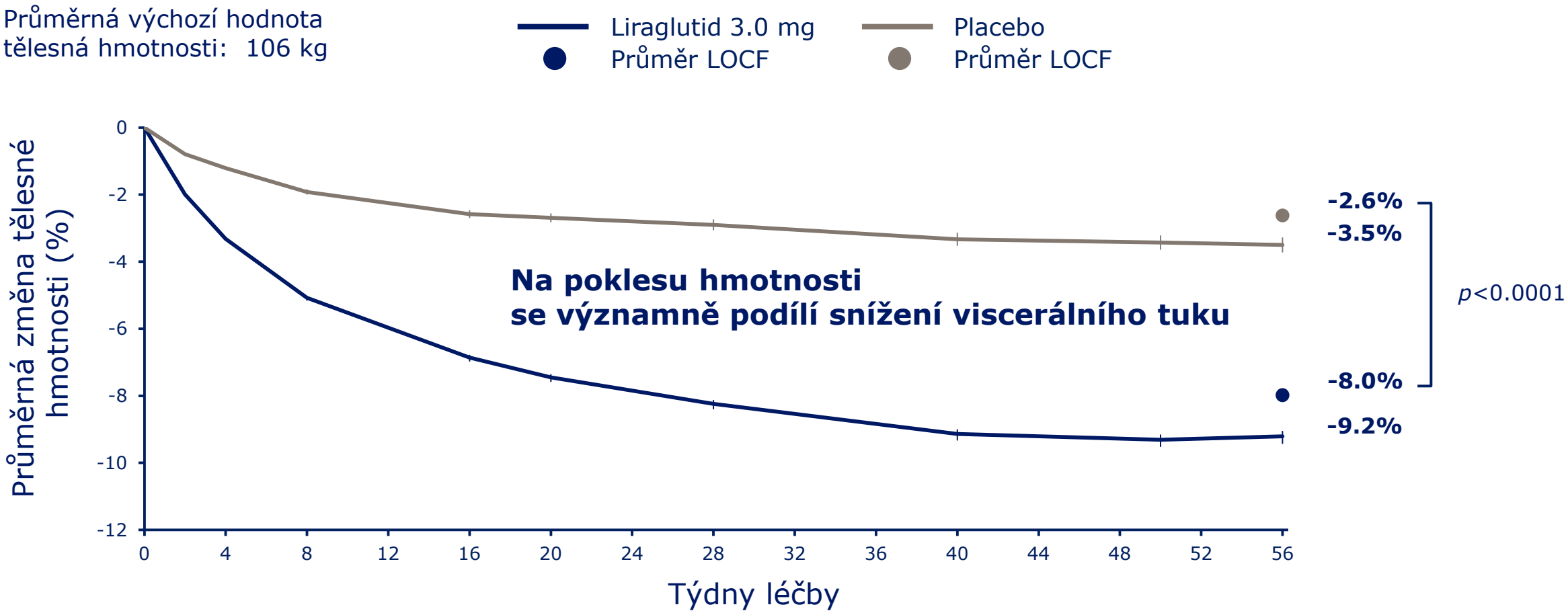
Změna tělesné hmotnosti po 1 roce léčby

0–56 týdnů

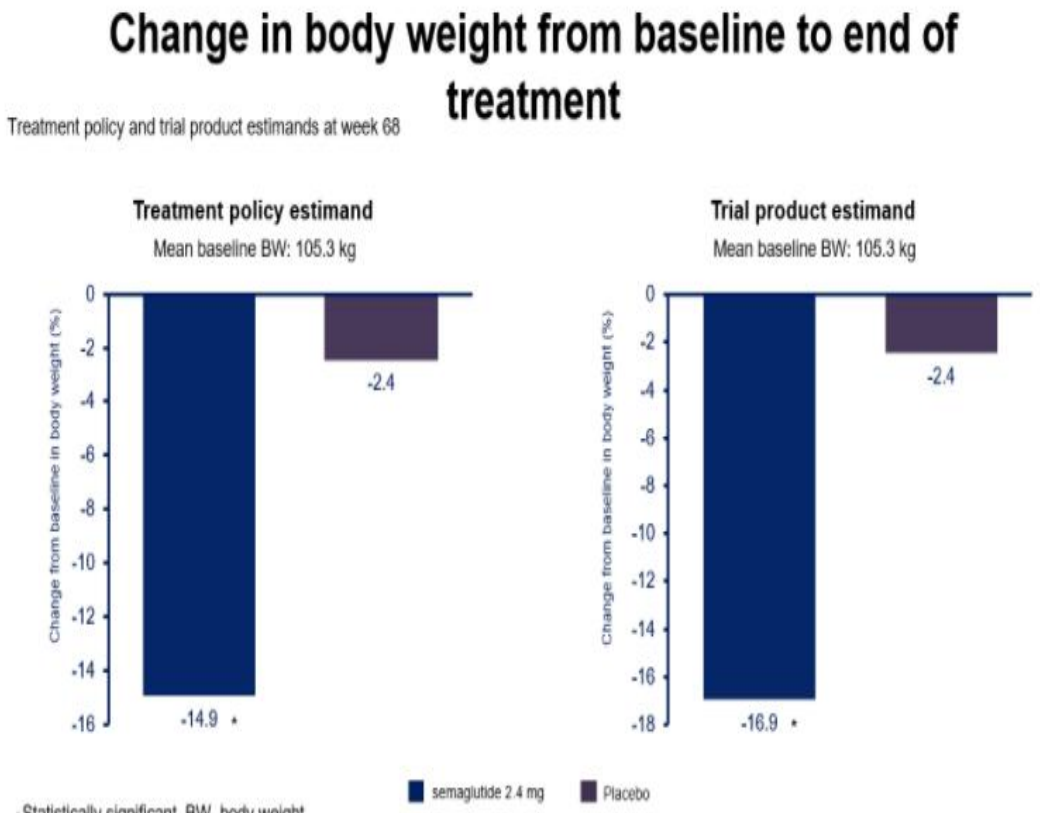


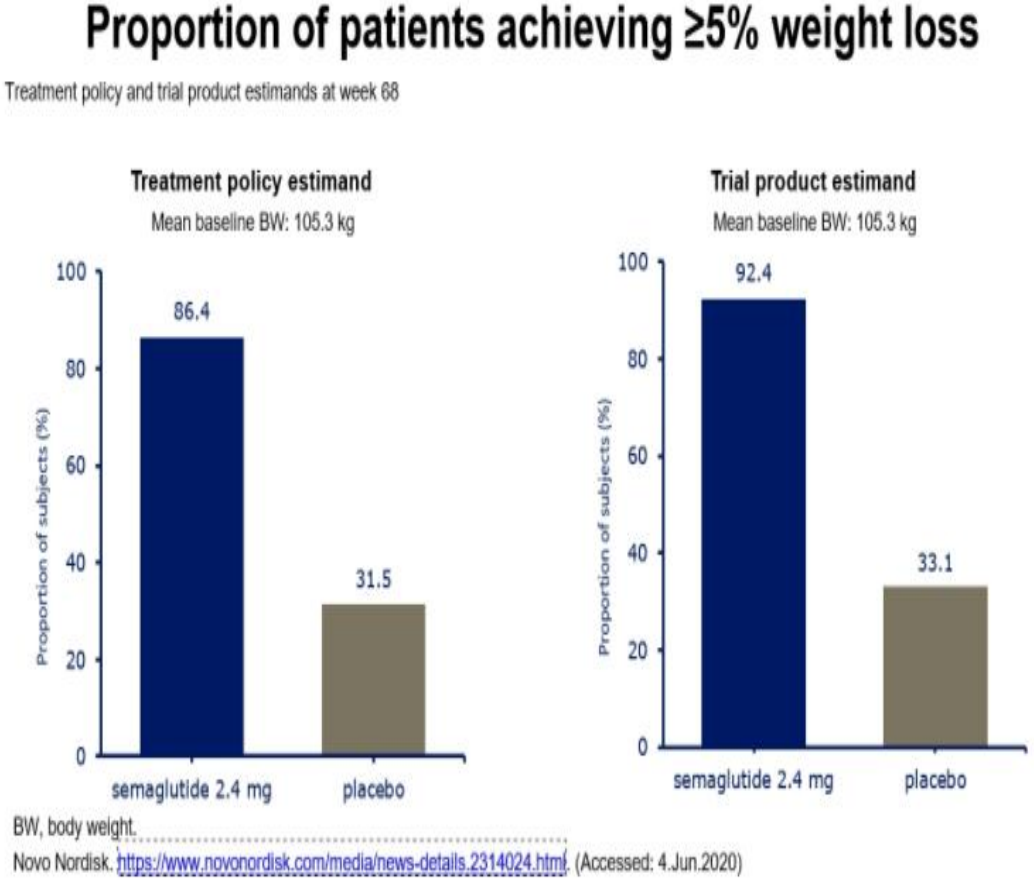
LOCF (Last Observation Carried Forward) - hodnoty z poslední pozorování

FAS, fasting visit data only. Line graphs are observed means (±SE). Statistical analysis is ANCOVA.
FAS, full analysis set; LOCF, last observation carried forward; SE, standard error

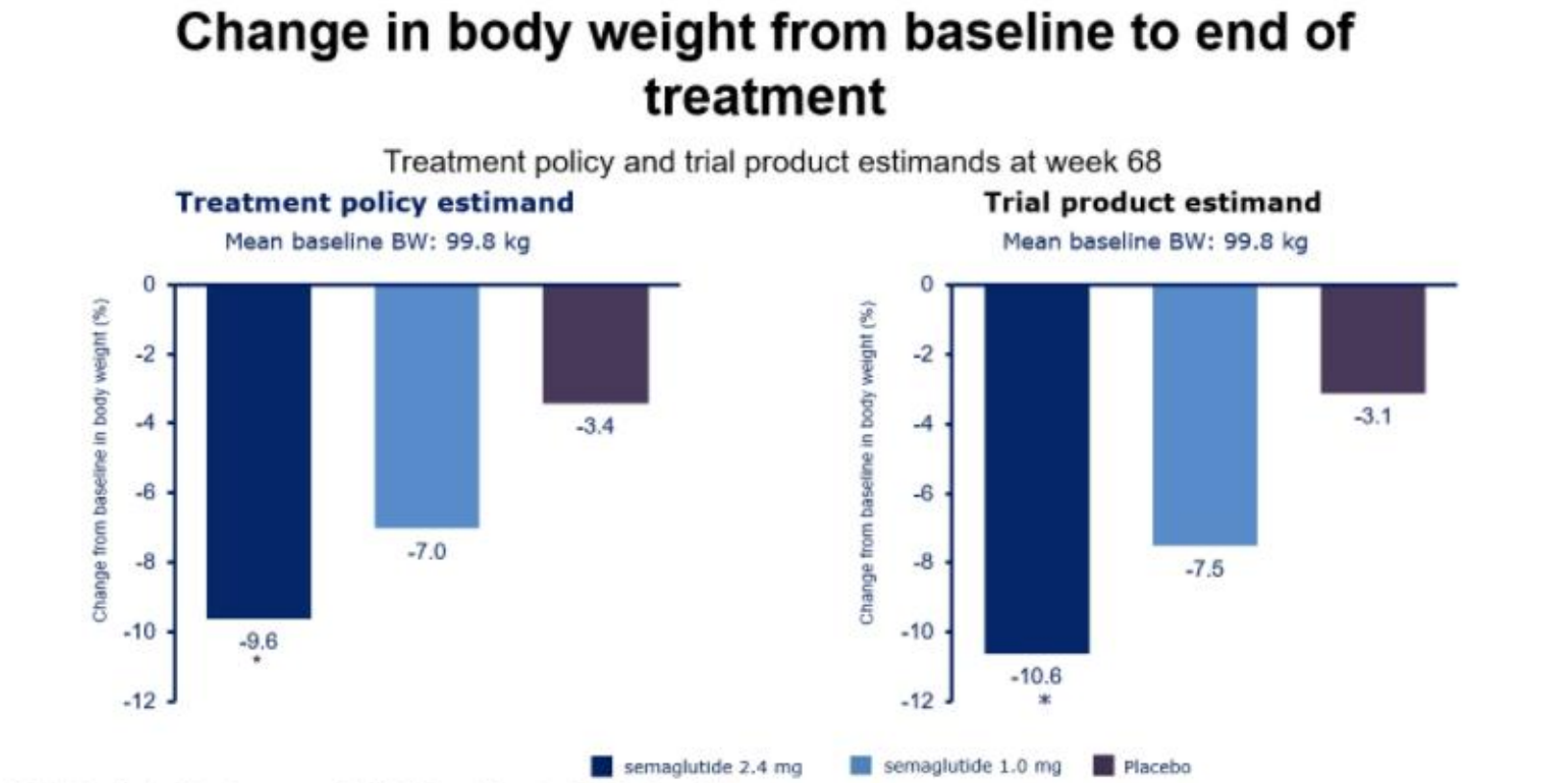
Pi-Sunyer *et al. Diabetologia* 2014;57(Suppl. 1): Abstract 73-OR

Změny hmotnosti po 68 týdnech léčby semaglutidem 2,4 mg 1 x týdně (pacienti s obezitou bez diabetu)





Změny hmotnosti po 68 týdnech léčby semaglutidem 2,4 mg 1 x týdně (pacienti s DM 2. typu)



* Statistically significant vs. semaglutide 1.0 and placebo. BW, body weight.

Novo Nordisk. https://www.novonordisk.com/content/Denmark/HQ/www-novonordisk-com/en_gb/home/media/news-details.2318004.html. (Accessed: Jun.2020)

Duální GLP-1/GIP agonista tirzepatid v léčbě obezity (bez DM)

Závěr

- Obezita představuje závažný problém současného zdravotnictví s ohledem na stoupající prevalenci i výskyt chronických komplikací
- Portfolio možností farmakoterapie obezity se postupně rozšiřuje
- Léky na principu GLP-1 a duálních/triple agonistů mají širší potenciál než „pouhé“ snížení hmotnosti (kardioprotektivita, nefroprotektivita)
- Lze očekávat jejich širší využití v léčbě obezity bez DM i jejich komorbidit (NASH, sy. spánkové apnoe, snížení KV rizika atd.)

Děkuji za pozornost

halm@ikem.cz