Perspective in Diabetes Drug Treatment

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Conflict of Interest

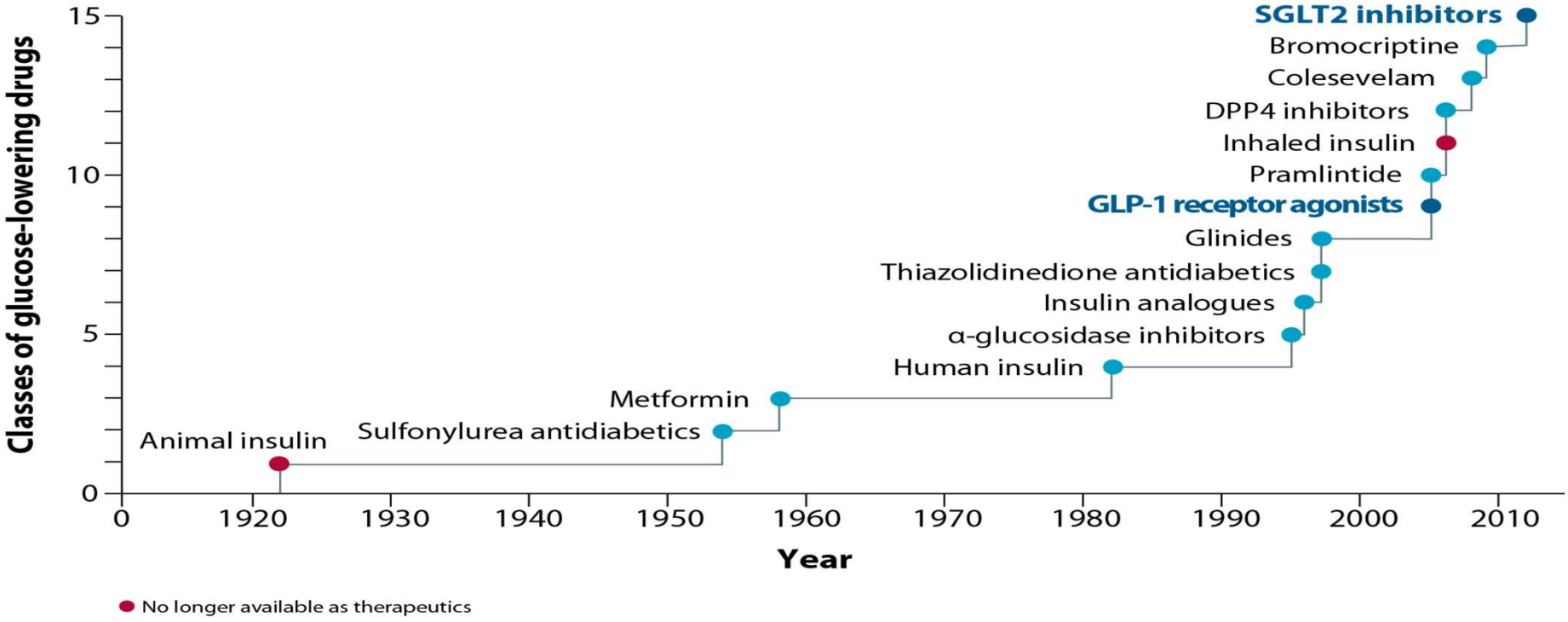
- **Consulting**

MSD,BI,SANOFI,NOVONORDISK,ASTRAZENCA,PFIZER,TEVA,NOVARTIS

- **Lecture**

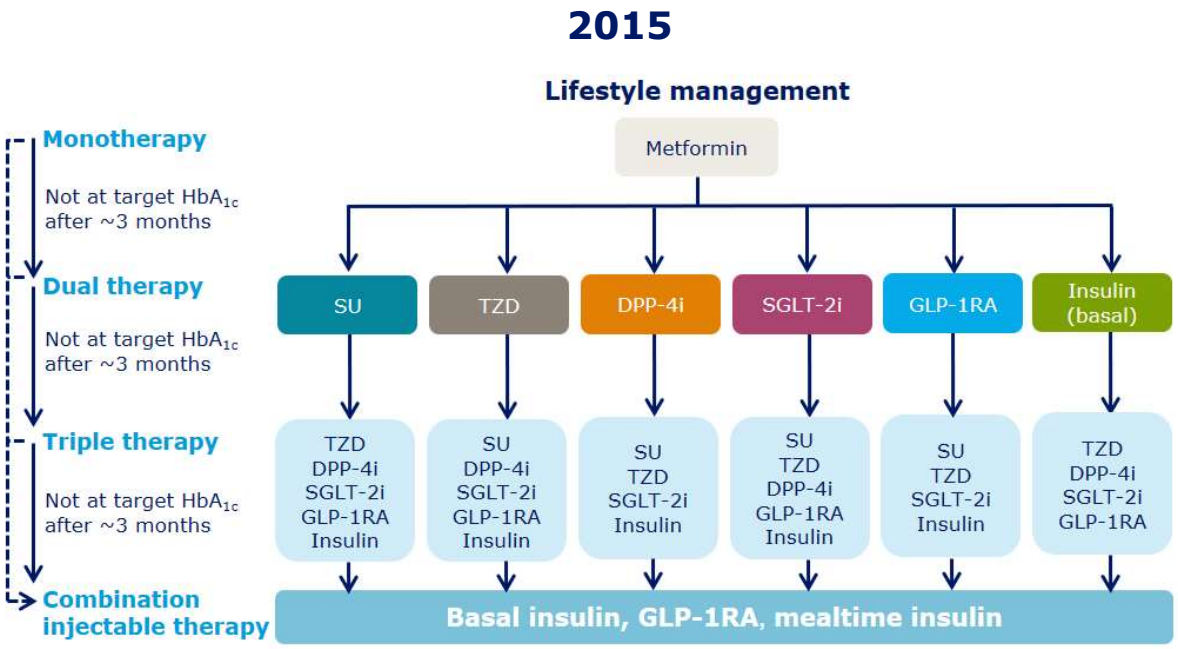
MSD,BI,SANOFI,NOVONORDISK,ASTRAZENCA,PFIZER,TEVA,NOVARTIS, DEXON

The History of Treatment for T2D



Adapted from: Kahn et al. lancet, 2014

Management of hyperglycaemia in type 2 diabetes – 2015 version



DPP-4i, dipeptidyl peptidase-4 inhibitor; GLP-1RA, glucagon-like peptide-1 receptor agonist; HbA_{1c}, glycosylated haemoglobin; SGLT2i, sodium-glucose cotransporter-2 inhibitor; SU, sulphonylurea; T2D, type 2 diabetes; TZD, thiazolidinedione
Inzucchi SE et al. *Diabetologia* 2015;58:429–442

"***Glucose control remains a major focus*** *in the management of patients with T2D. However, this should always be in the* ***context*** *of a* ***comprehensive cardiovascular risk factor program****….including blood pressure control, lipid management and, in some circumstances, anti-platelet therapy"*

"*The* ***impact of glucose control on cardiovascular complications remains uncertain****; a more modest benefit is likely to be present, but probably emerges only after many years of improved control"*

"***More long-term data*** *regarding the cardiovascular impact of our glucose-lowering therapies will be* ***available over the next 1–3 years****. Information from these will further assist us in optimizing treatment strategies"*

Second-line therapy for T2D in patients with established ASCVD or heart failure

What is the background for the changes?

Major adverse cardiovascular events

LEADER[1]	Hazard ratio (95% CI)
MACE	**0.87** (0.78; 0.97)
CV death	**0.78** (0.66; 0.93)
Non-fatal MI	**0.88** (0.75; 1.03)
Non-fatal stroke	**0.89** (0.72; 1.11)

SUSTAIN 6[2]	Hazard ratio (95% CI)
MACE	**0.74** (0.58; 0.95)
CV death	**0.98** (0.65; 1.48)
Non-fatal MI	**0.74** (0.51; 1.08)
Non-fatal stroke	**0.61** (0.38; 0.99)

EMPA-REG OUTCOME[3]	Hazard ratio (95% CI)
MACE	**0.86** (0.74; 0.99)
CV death	**0.62** (0.49; 0.77)
Non-fatal MI	**0.87** (0.70; 1.09)
Non-fatal stroke	**1.24** (0.92; 1.67)

CANVAS Program[4]	Hazard ratio (95% CI)
MACE	**0.86** (0.75; 0.97)
CV death	**0.87** (0.72; 1.06)
Non-fatal MI	**0.85** (0.69; 1.05)
Non-fatal stroke	**0.90** (0.71; 1.15)

ASCVD, atherosclerotic cardiovascular disease; CI, confidence interval; CV, cardiovascular; MACE, major adverse cardiovascular event; MI, myocardial infarction; T2D, type 2 diabetes

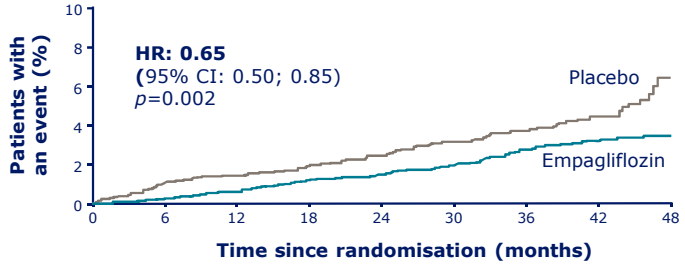
1. Marso SP et al. *N Engl J Med* 2016;375:311–322; 2. Marso SP et al. *N Engl J Med* 2016;375:1834–1844; 3. Zinman B et al. *Cardiovasc Diabetol* 2014;13:102; 4. Neal B et al. *N Engl J Med* 2017;377:644–657

Second-line therapy for T2D in patients with established ASCVD or HF

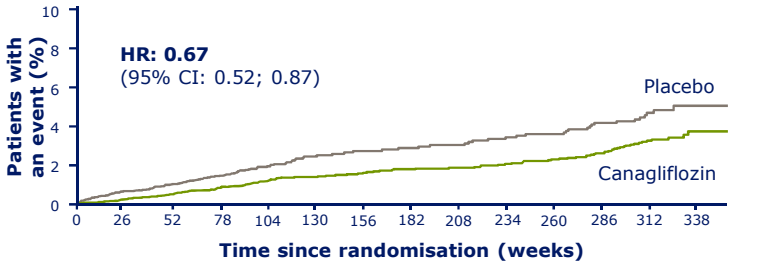
What is the background for the changes?

Hospitalisation for HF

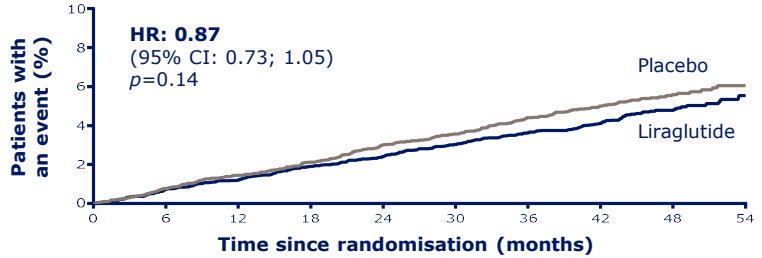
EMPA-REG OUTCOME[1]



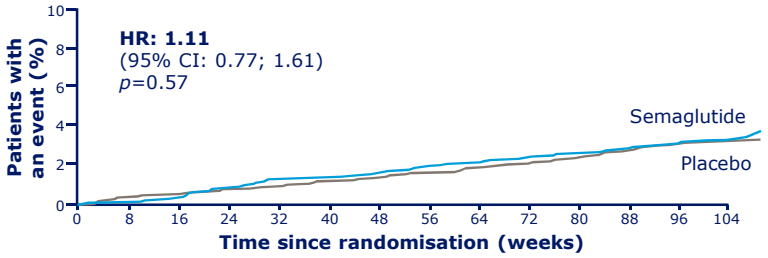
CANVAS Program[2]



LEADER[3]



SUSTAIN 6[4]



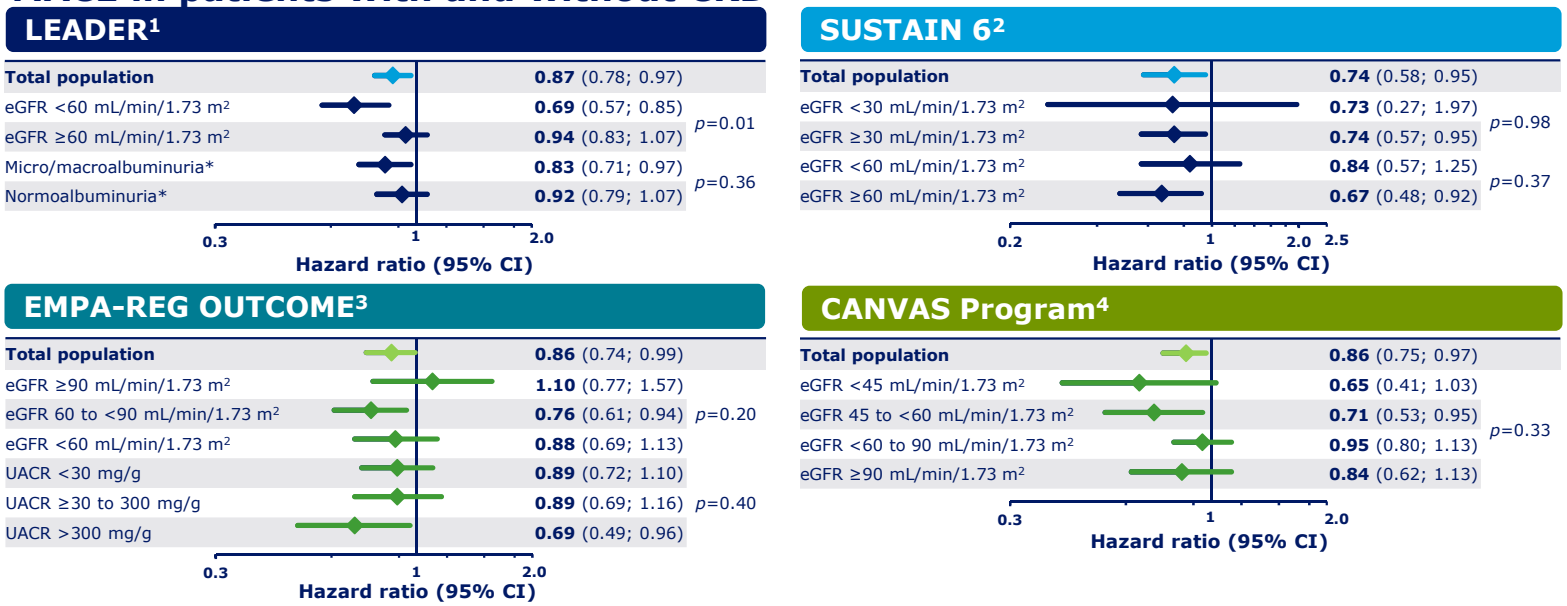
ASCVD, atherosclerotic cardiovascular disease; CI, confidence interval; HF, heart failure; HR, hazard ratio; T2D, type 2 diabetes

1. Zinman B et al. *Cardiovasc Diabetol* 2014;13:102; 2. Neal B et al. *N Engl J Med* 2017;377:644–657; 3. Marso SP et al. *N Engl J Med* 2016;375:311–322; 4. Marso SP et al. *N Engl J Med* 2016;375:1834–1844

Considerations related to chronic kidney disease

What is the background for the changes?

MACE in patients with and without CKD



*Only patients with albuminuria measurements at baseline (n=9137) included in albuminuria group

CI, confidence interval; eGFR, estimated glomerular filtration rate; HR, hazard ratio; MAC, major adverse cardiovascular event; UACR, urinary albumin-to-creatinine ratio

1.Mann J et al. *Circulation* 2018; [In Press]; 2. Marso SP et al. *N Engl J Med* 2016;375:1834–1844; 3. Zinman B et al. *N Engl J Med* 2015;373:2117–2128; 4. Neuen BL et al. *Circulation* 2018; doi: 10.1161/CIRCULATIONAHA.118.035901. [Epub ahead of print]

Summary of the efficacy and safety findings in SGLT-2i CVOTs

	Endpoint	DECLARE[1]	EMPA-REG[2]	CANVAS[3]
Efficacy	MACE Non-inferiority	✓	✓	✓
	hHF/CV Death	✓	Nominal	Nominal
	MACE Superiority	✗	✓	✓
	Renal Composite	Nominal	Nominal	Nominal
Safety	Amputations	No	No	Yes
	Fractures	No	No	Yes
	Bladder cancer	No	No	No
	Genital infections	Yes	Yes	Yes
	DKA	Yes	Yes	Yes

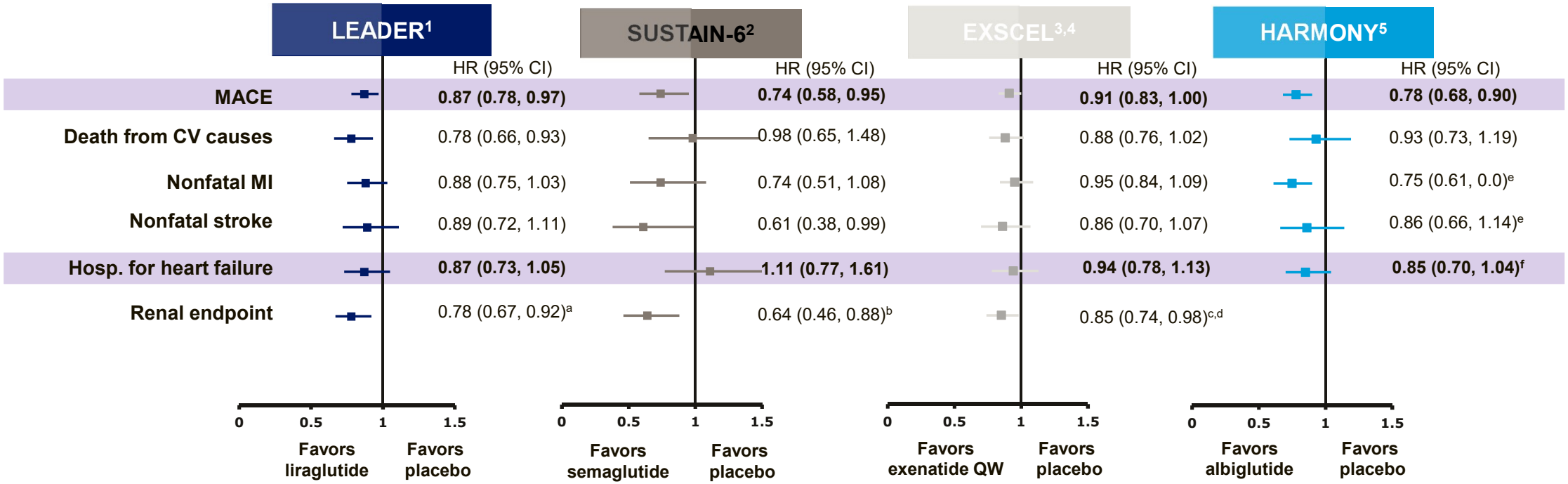
✓ Statistically significant ✗ Not statistically significant Nominal Not formally significant as pre-specified in statistical analysis plan

No No imbalance Yes Imbalance observed

CV, cardiovascular; CVOT, CV outcome trials; DKA, diabetic ketoacisdosis; hHF, hospitalizations for heart failure; MACE, major adverse CV events; SGLT-2i, sodium-glucose co-transporter 2 inhibitor; T2D, type 2 diabetes

1. Wiviott SD et al. Online ahead of print. *N Engl J Med.* 2018; 2. Zinman B, et al. *N Engl J Med* 2015;373:2117–2128; 3. Neal B, et al. *N Engl J Med* 2017;377:644–657

While earlier studies with diabetes treatments did not definitively show benefit for CV disease and HF, GLP-1 RAs are shown to have CV benefits driven by less atherosclerotic events….

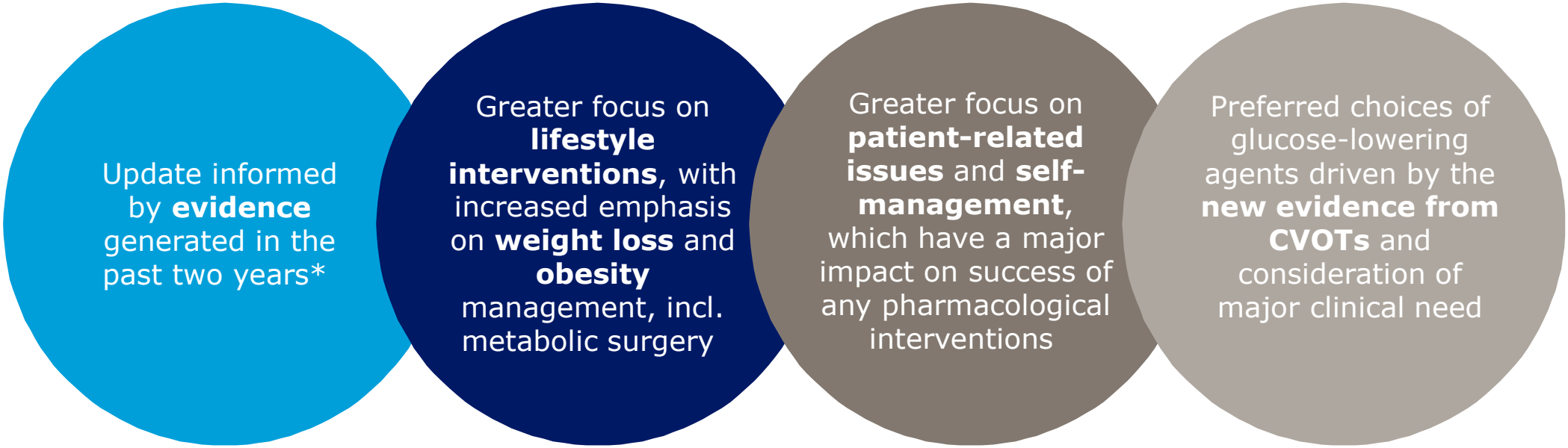


[a]New onset of macroalbuminuria or a doubling of the serum creatinine level and an eGFR of ≤45 ml/min/1.73 m^2, the need for continuous renal-replacement therapy, or death from renal disease; [b]New or worsening nephropathy includes persistent macroalbuminuria, persistent doubling of the serum creatinine level and a creatinine clearance of less than 45 ml/min/1.73 m^2 (according to the Modification of Diet in Renal Disease criteria), or the need for continuous renal-replacement therapy; [c]40% eGFR decline, renal replacement, renal death, or new-onset macroalbuminuria; [d]Adjusted for age, sex, ethnicity, race, region, duration of diabetes, prior history of CV event, insulin use, baseline glycated hemoglobin, eGFR, and body-mass index [e]Includes fatal and nonfatal events; [f]Composite of CV death or hospitalization for heart failure. CI, confidence interval; CV, cardiovascular; eGFR, estimated glomerular filtration rate; GLP-1 RA, GLP-1 receptor agonists; HR, hazard ratio; MACE, major adverse cardiovascular events; MI, myocardial infarction; QW, once weekly

1. Marso SP, et al. *N Engl J Med* 2016;375:311–322; 2. Marso SP, et al. *N Engl J Med* 2016;375:1834–1844; 3. Holman RR, et al. Article and supplementary appendix. *N Engl J Med* 2017;377:1228-1239;
4. Bethel MA, et al. Presented at: ADA 78th Scientific Sessions; June 22-26, 2018; Orlando, FL. Poster 522-P; 5. Hernandez AF, et al. Online ahead of print. *Lancet.* 2018.

Management of hyperglycaemia in type 2 diabetes – 2018 version

Key points to emphasise



*Between 1 January 2014 and 28 February 2018

ADA, American Diabetes Association; CVOT, cardiovascular outcomes trial; EASD, European Association for the Study of Diabetes

Management of hyperglycaemia in type 2 diabetes – 2018 version

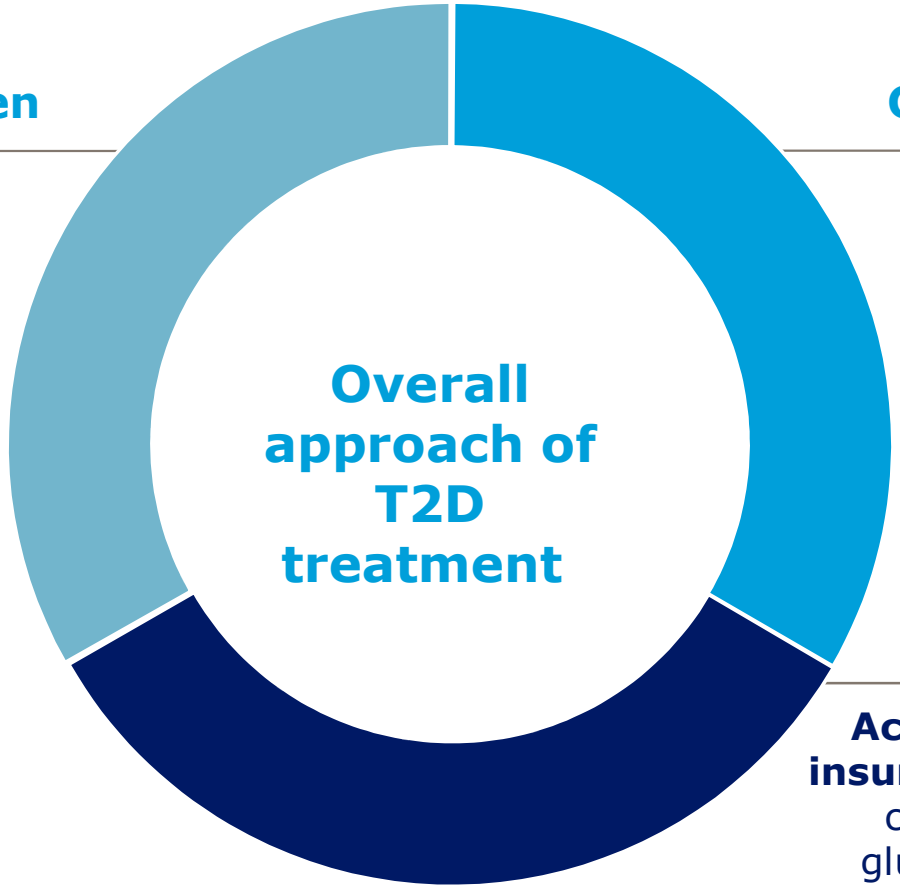
Overall approach

Overall diabetes regimen

Based on **patient preferences** and **clinical characteristics**

Goals of diabetes care

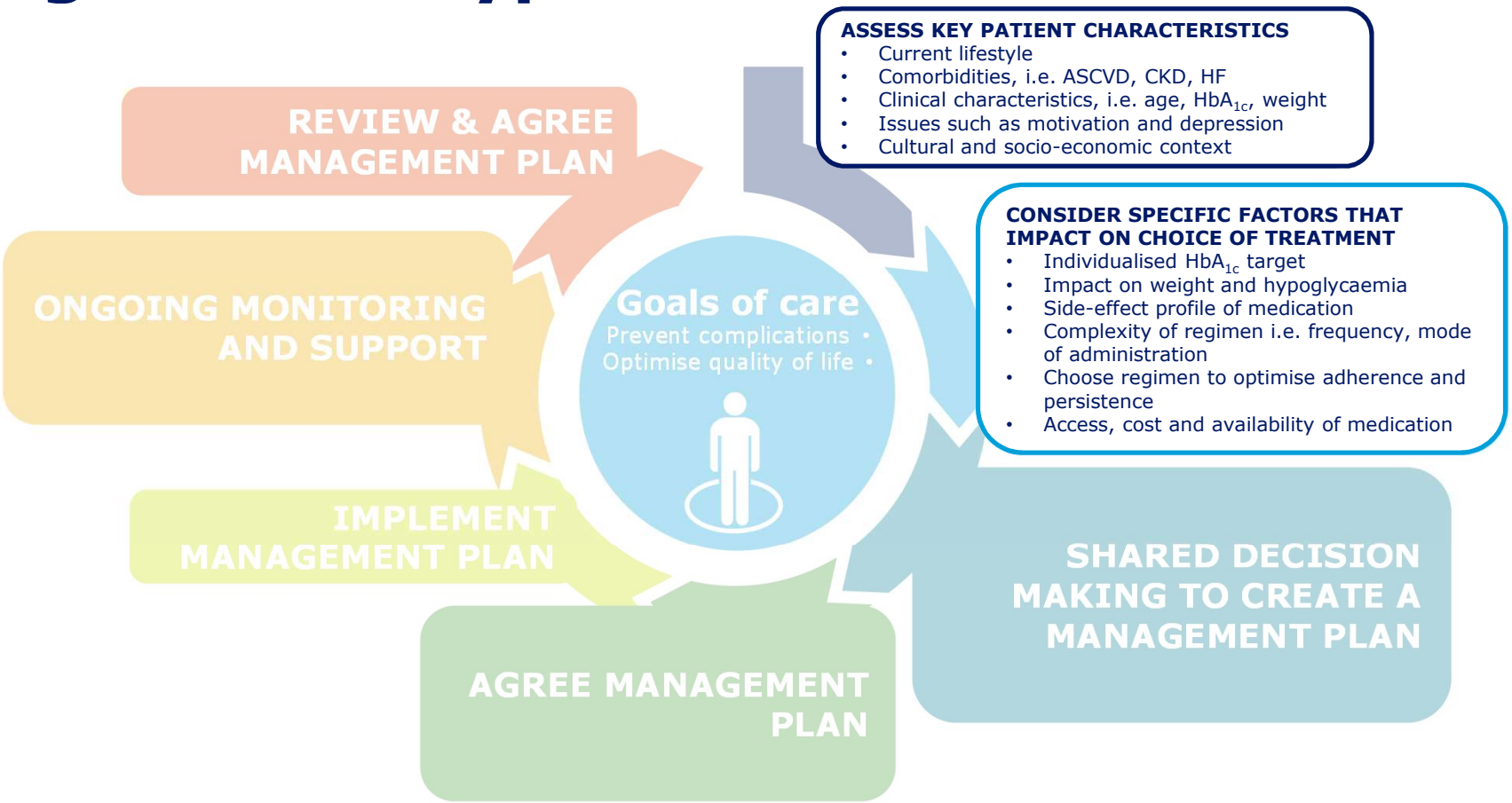
Prevent complications and optimise quality of life



Fit for real-world use

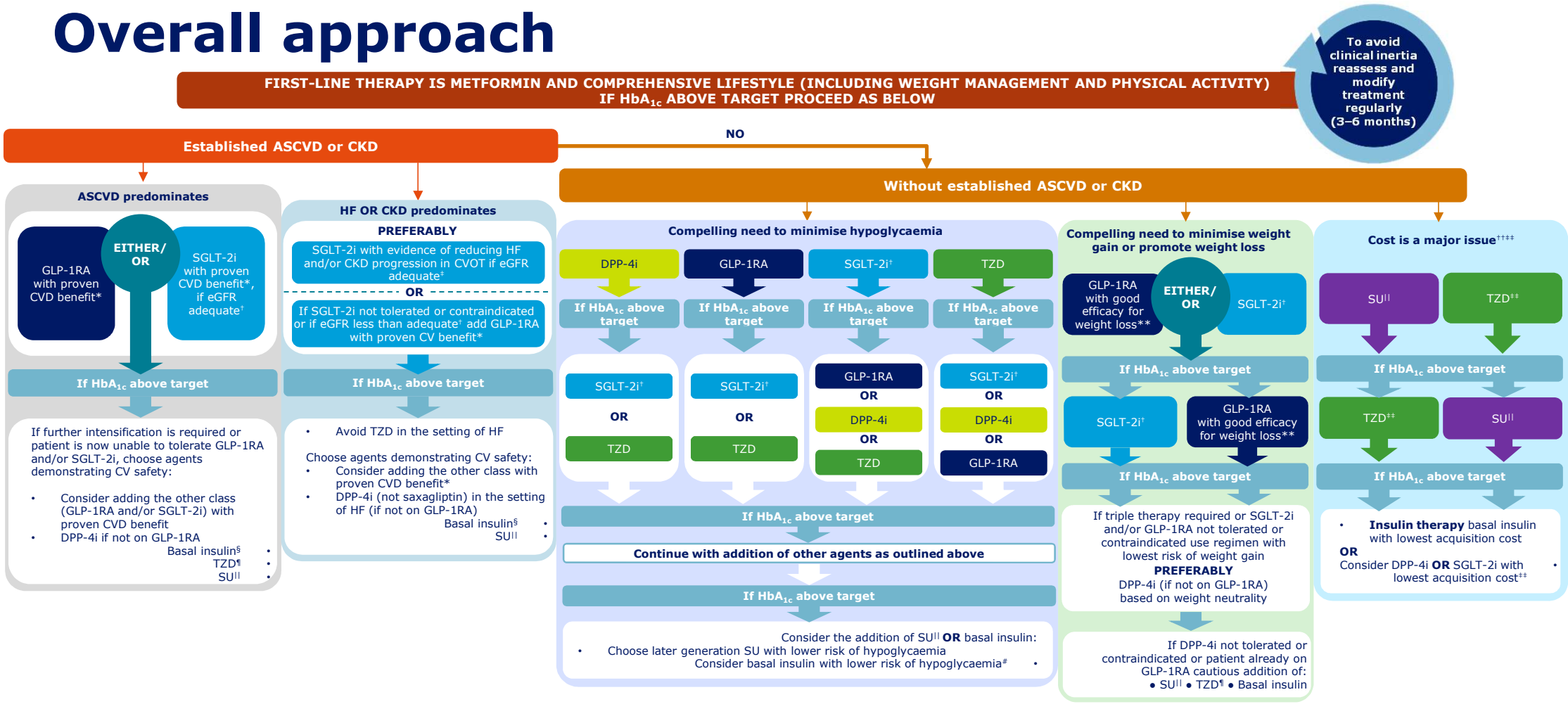
Access, **treatment cost**, and **insurance coverage** should all be considered when selecting glucose-lowering medications

Decision cycle for patient-centred glycaemic management in type 2 diabetes



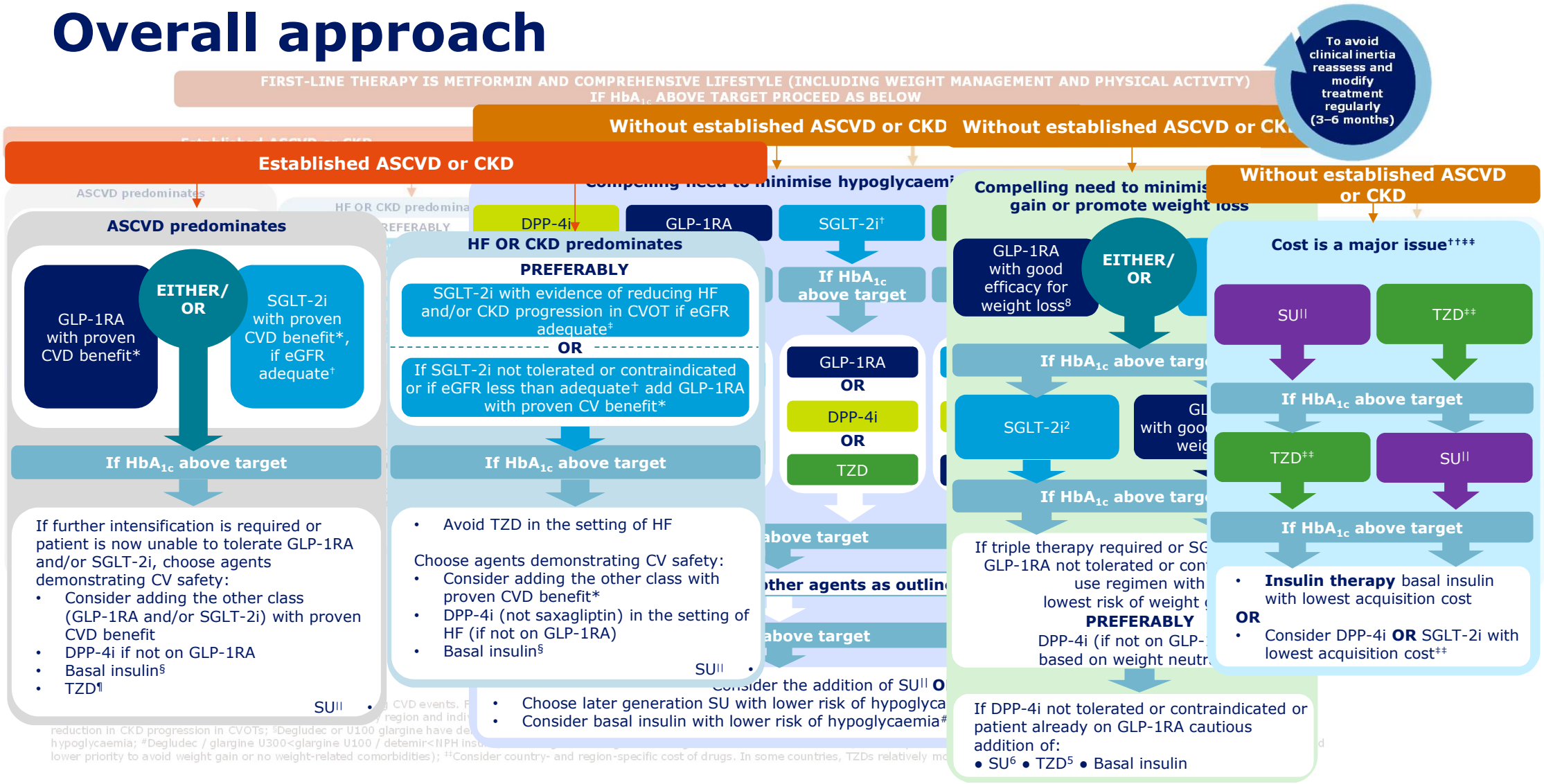
ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; HbA_{1c}, glycosylated haemoglobin; HF, heart failure

Glucose-lowering medication in type 2 diabetes: Overall approach



*Proven CVD benefit means it has label indication of reducing CVD events. For GLP-1RA strongest evidence for liraglutide>semaglutide>exenatide extended release. For SGLT-2i evidence modestly stronger for empagliflozin>canagliflozin; †Be aware that SGLT-2i vary by region and individual agent with regard to indicated level of eGFR for initiation and continued use; ‡Both empagliflozin and canagliflozin have shown reduction in HF and reduction in CKD progression in CVOTs; §Degludec or U100 glargine have demonstrated CVD safety; ¶Low dose may be better tolerated though less well studied for CVD effects; ||Choose later generation SU with lower risk of hypoglycaemia; #Degludec / glargine U300<glargine U100 / detemir<NPH insulin; **Semaglutide>liraglutide>dulaglutide>exenatide>lixisenatide; ††If no specific comorbidities (i.e. no established CVD, low risk of hypoglycaemia and lower priority to avoid weight gain or no weight-related comorbidities); ‡‡Consider country- and region-specific cost of drugs. In some countries, TZDs relatively more expensive and DPP-4i relatively cheaper

Glucose-lowering medication in type 2 diabetes: Overall approach

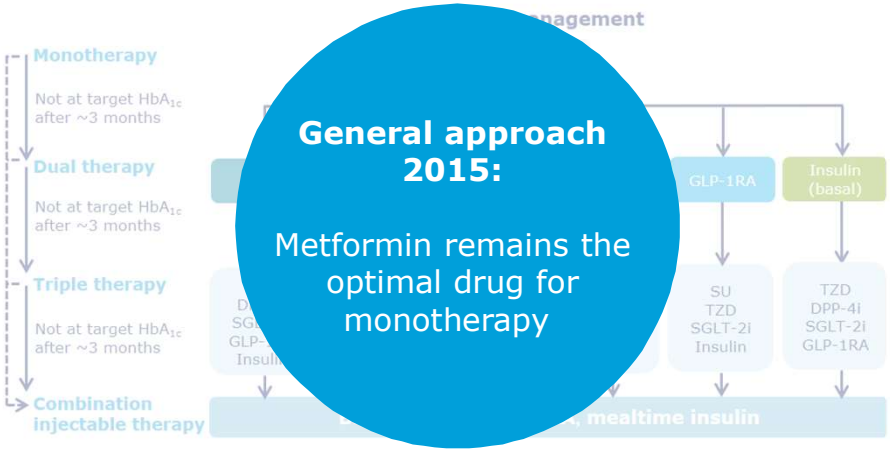


First-line therapy

First-line glucose-lowering medication for T2D

What are the changes?

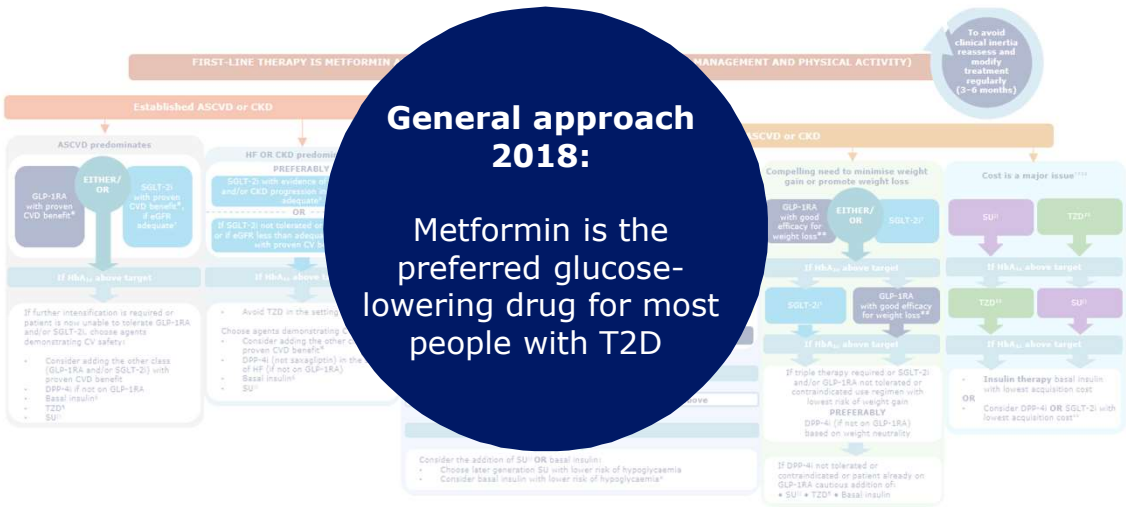
2015



General approach 2015:

Metformin remains the optimal drug for monotherapy

2018



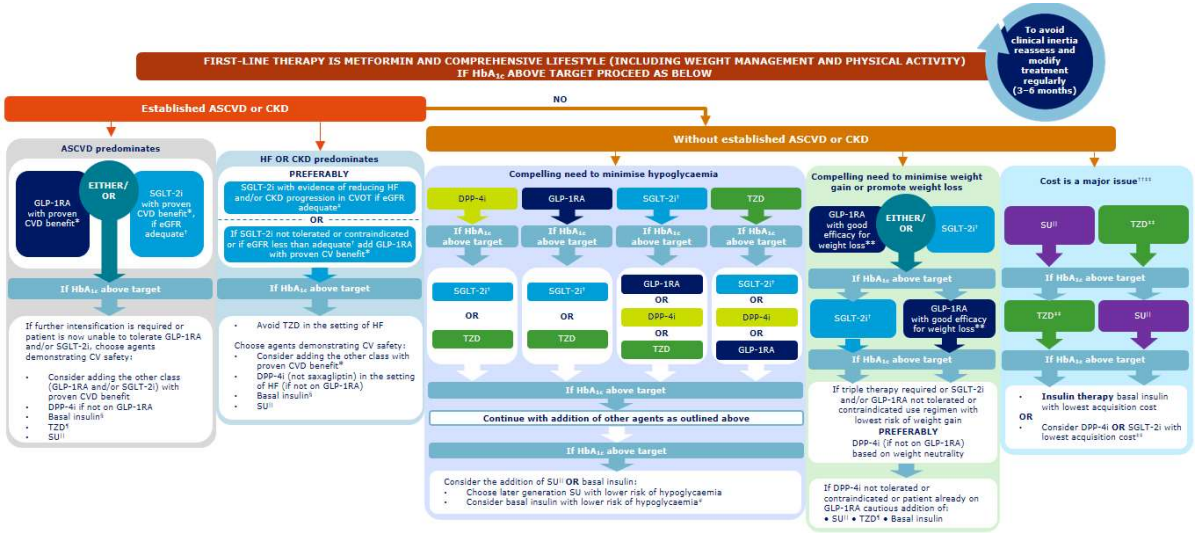
General approach 2018:

Metformin is the preferred glucose-lowering drug for most people with T2D

T2D, type 2 diabetes

First-line glucose-lowering medication for T2D

2018



- **Metformin**, on top of lifestyle intervention, remains as the recommended first line glucose-lowering medication for patients with T2D

T2D, type 2 diabetes

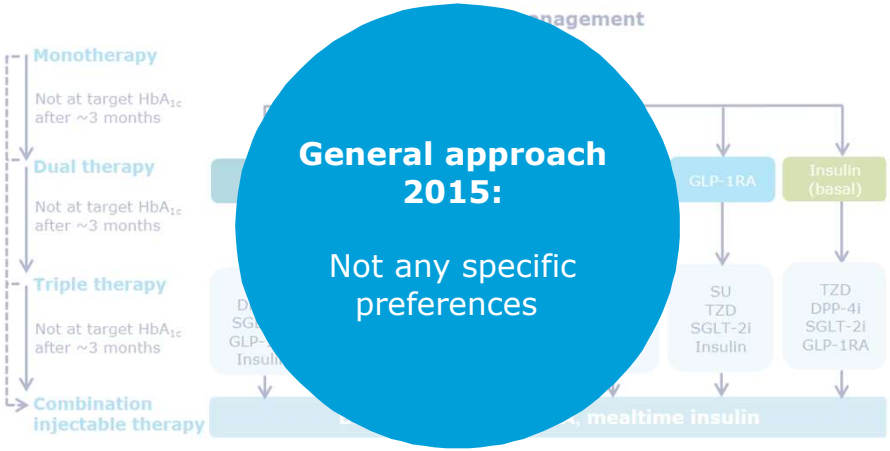
Patients with established ASCVD, CKD or HF

ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; HF, hearth failure

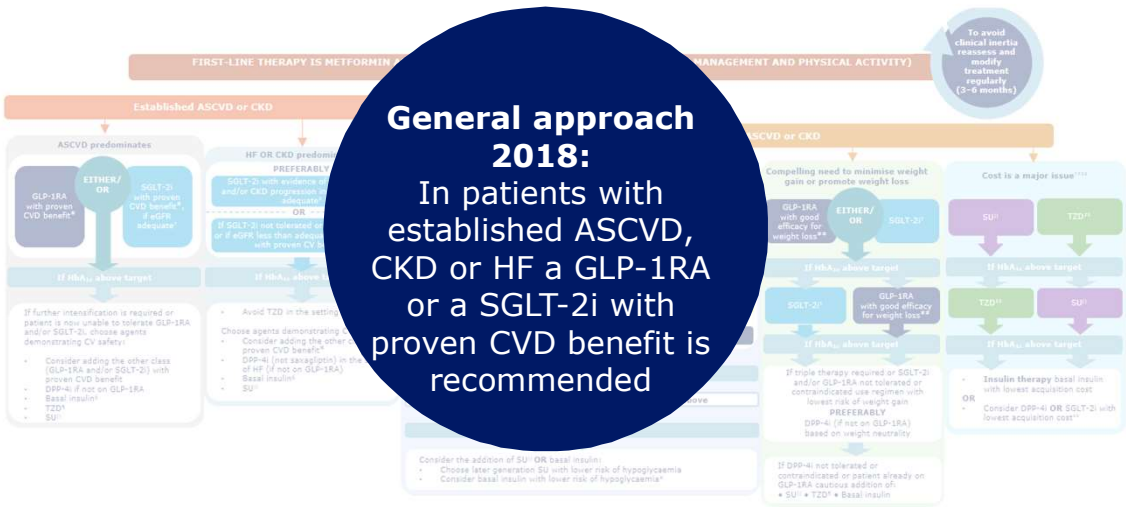
Second-line therapy for T2D in patients with established ASCVD, CKD or HF

What are the changes?

2015

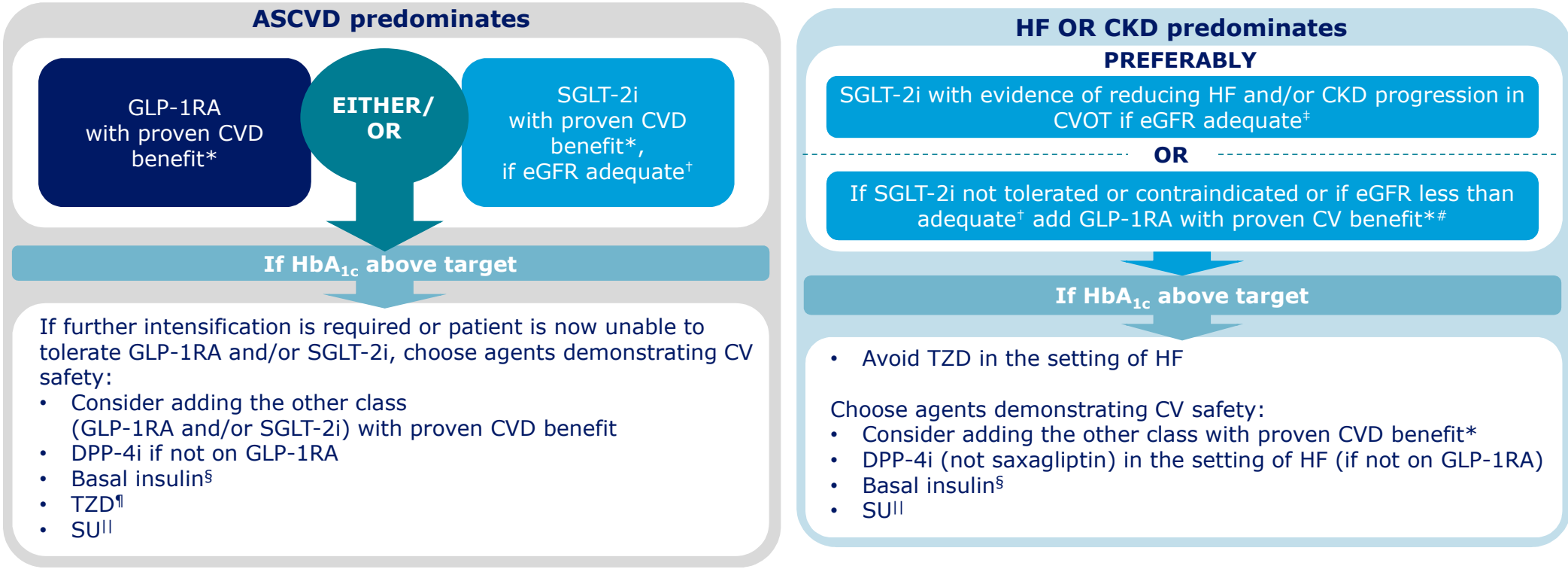


2018



ASCVD, atherosclerotic cardiovascular disease; GLP-1RA, glucagon-like peptide-1 receptor agonist; HF, heart failure; SGLT-2i, sodium-glucose cotransporter-2 inhibitor

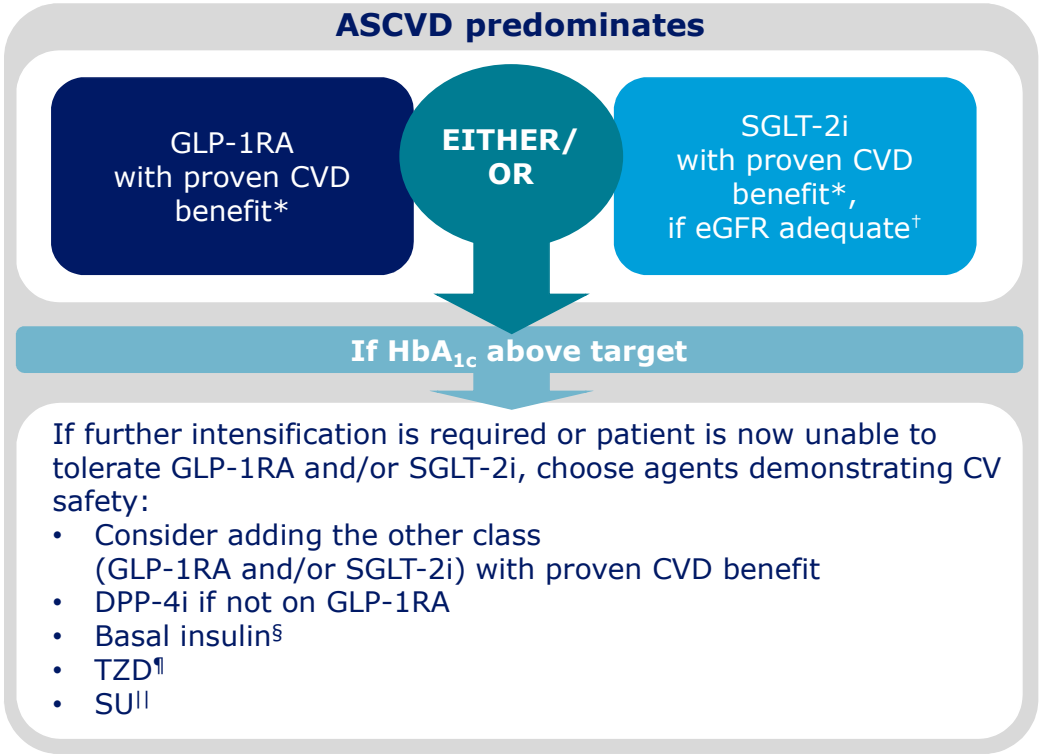
Second-line therapy for T2D in patients with established ASCVD or HF

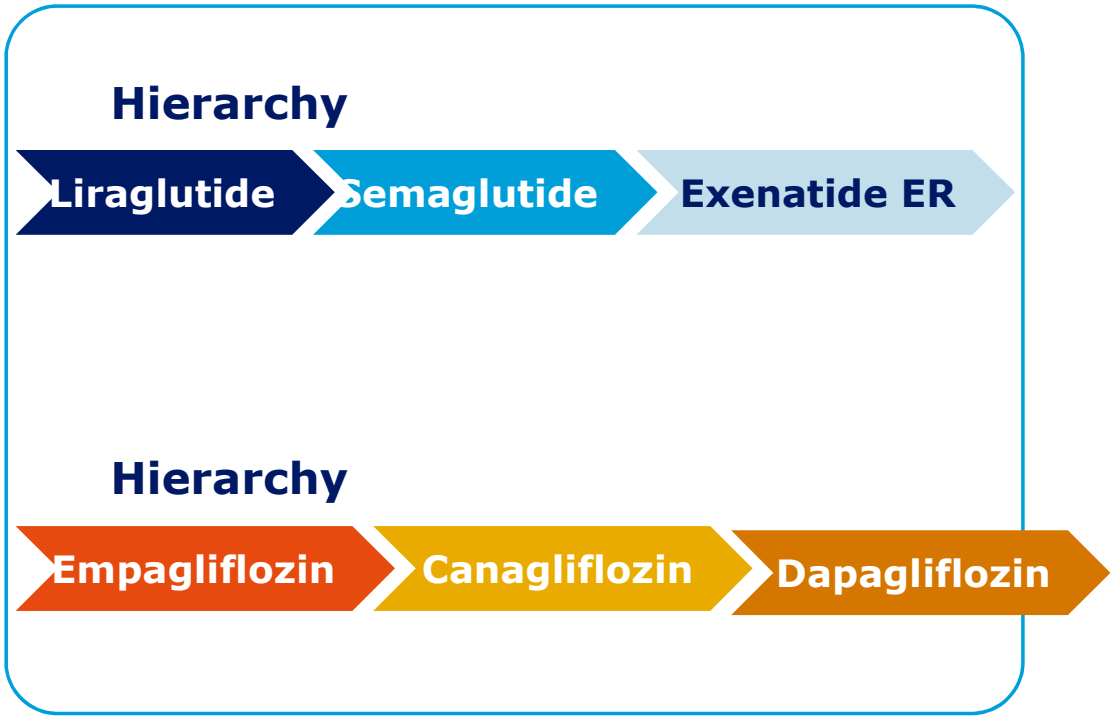


*Proven CVD benefit means it has label indication of reducing CVD events. For GLP-1RA strongest evidence for liraglutide>semaglutide>exenatide extended release. For SGLT-2i evidence modestly stronger for empagliflozin>canagliflozin; †Be aware that SGLT-2i vary by region and individual agent with regard to indicated level of eGFR for initiation and continued use; ‡Both empagliflozin and canagliflozin have shown reduction in HF and reduction in CKD progression in CVOTs; §Degludec or U100 glargine have demonstrated CVD safety; ¶Low dose may be better tolerated though less well studied for CVD effects; ||Choose later generation SU with lower risk of hypoglycaemia'; #Caution with GLP-1RA in ESRD

Choosing glucose-lowering medication

In patients with established ASCVD





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Choosing glucose-lowering medication

In patients with established HF or CKD

HF OR CKD predominates

PREFERABLY

SGLT-2i with evidence of reducing HF and/or CKD progression in CVOT if eGFR adequate‡

OR

If SGLT-2i not tolerated or contraindicated or if eGFR less than adequate† add GLP-1RA with proven CV benefit*#

If HbA_{1c} above target

- Avoid TZD in the setting of HF

Choose agents demonstrating CV safety:

- Consider adding the other class with proven CVD benefit*
- DPP-4i (not saxagliptin) in the setting of HF (if not on GLP-1RA)
- Basal insulin§
- SU||

- SGLT-2is preferred over GLP-1RAs as significant, consistent reductions in hospitalisation for HF have been seen in SGLT-2i trials
- SGLT-2i

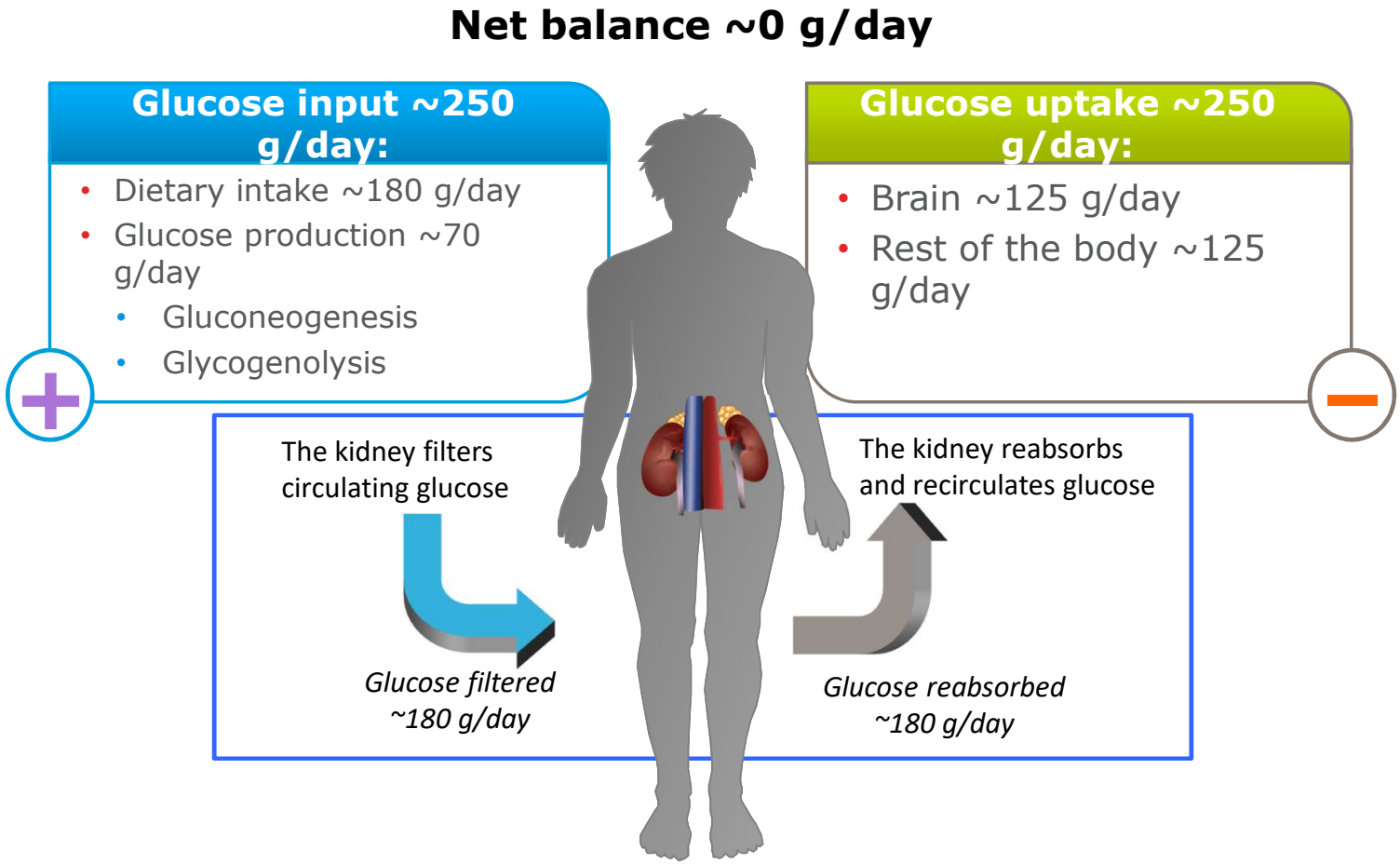
  Empagliflozin, Cnagliflozin , Dapagliflozin
- GLP-1RA

  Liraglutide preferred

*Proven CVD benefit means it has label indication of reducing CVD events. For GLP-1RA strongest evidence for liraglutide>semaglutide>exenatide extended release. For SGLT-2i evidence modestly stronger for empagliflozin>canagliflozin; †Be aware that SGLT-2i vary by region and individual agent with regard to indicated level of eGFR for initiation and continued use; ‡Both empagliflozin and canagliflozin have shown reduction in HF and reduction in CKD progression in CVOTs; §Degludec or U100 glargine have demonstrated CVD safety; ||Choose later generation SU with lower risk of hypoglycaemia; #Caution with GLP-1RA in ESRD

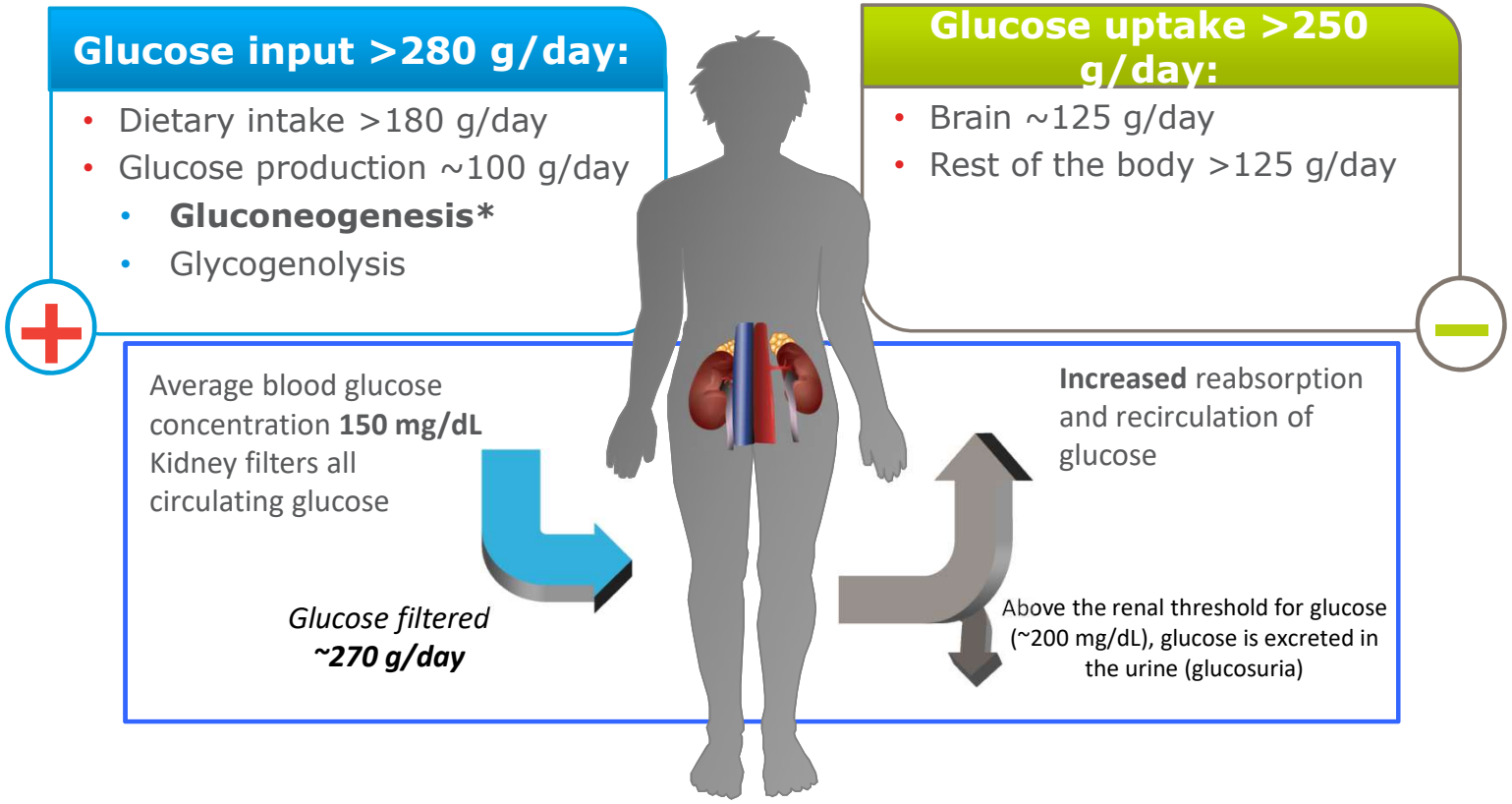
The sodium-glucose cotransporter-2 (SGLT2) therapy

Normal glucose homeostasis[1,2]



1. Wright EM. *Am J Physiol Renal Physiol* 2001;**280**:F10–18.
2. Gerich, JE. *Diabetes Obes Metab* 2000;**2**:345–50.

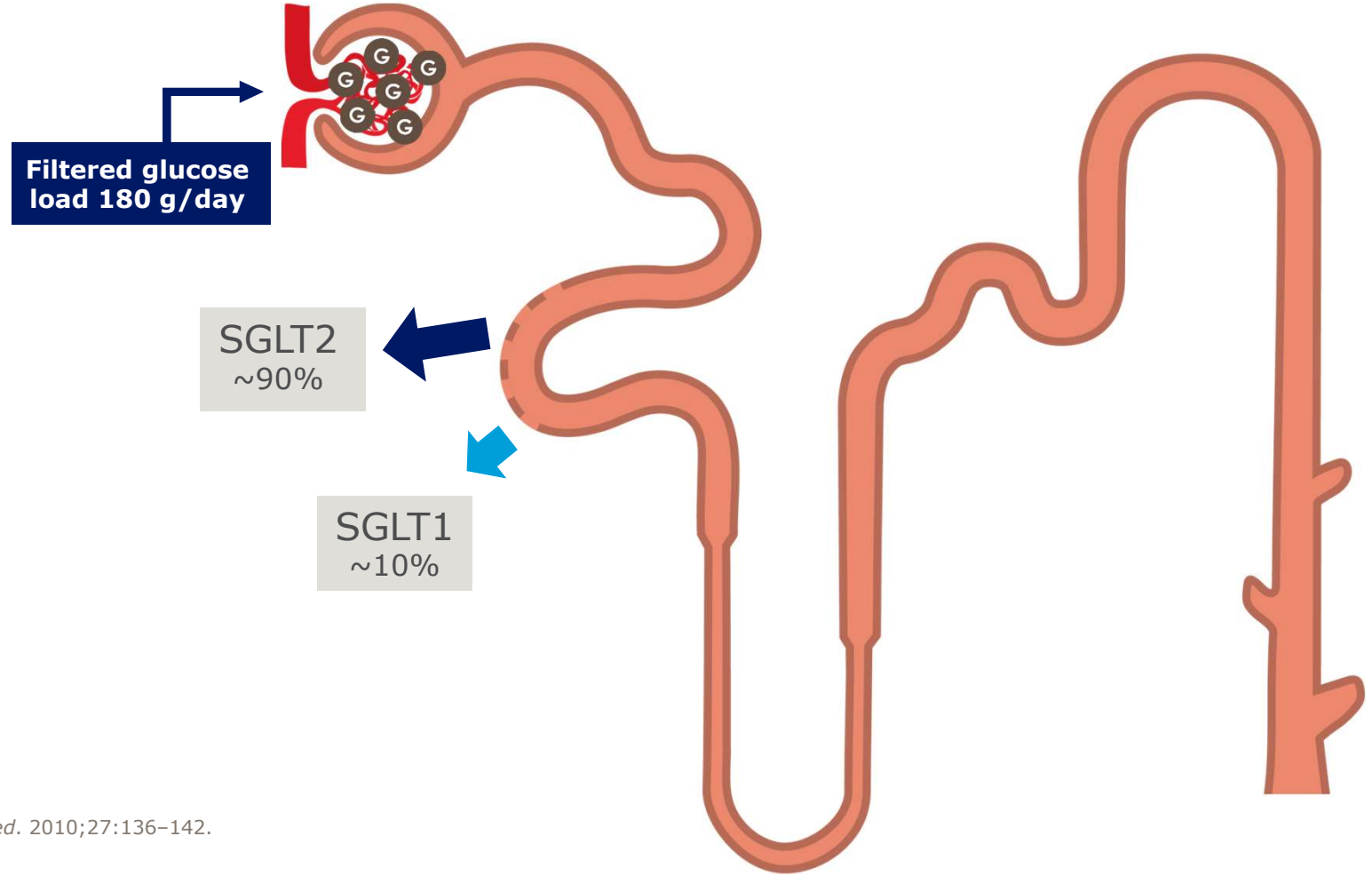
Glucose handling in Type 2 diabetes[1,2]



*Elevated glucose production in patients with Type 2 diabetes attributed to hepatic and renal gluconeogenesis.[2]

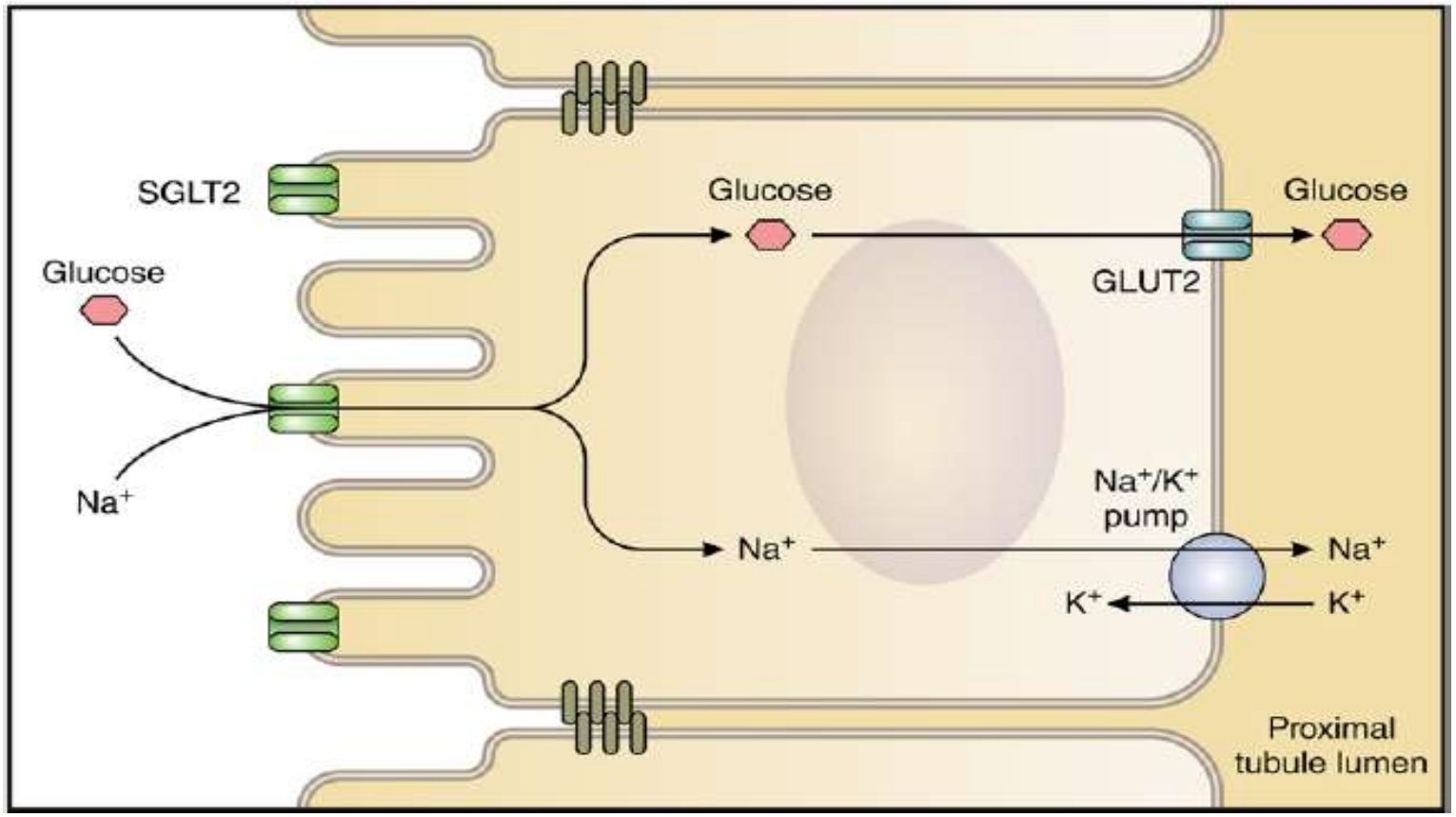
1. Gerich JE. *Diabet Med* 2010;**27**:136–42; 2. Abdul-Ghani MA, DeFronzo RA. *Endocr Pract* 2008;**14**:782–90.

Renal glucose reabsorption in healthy individuals



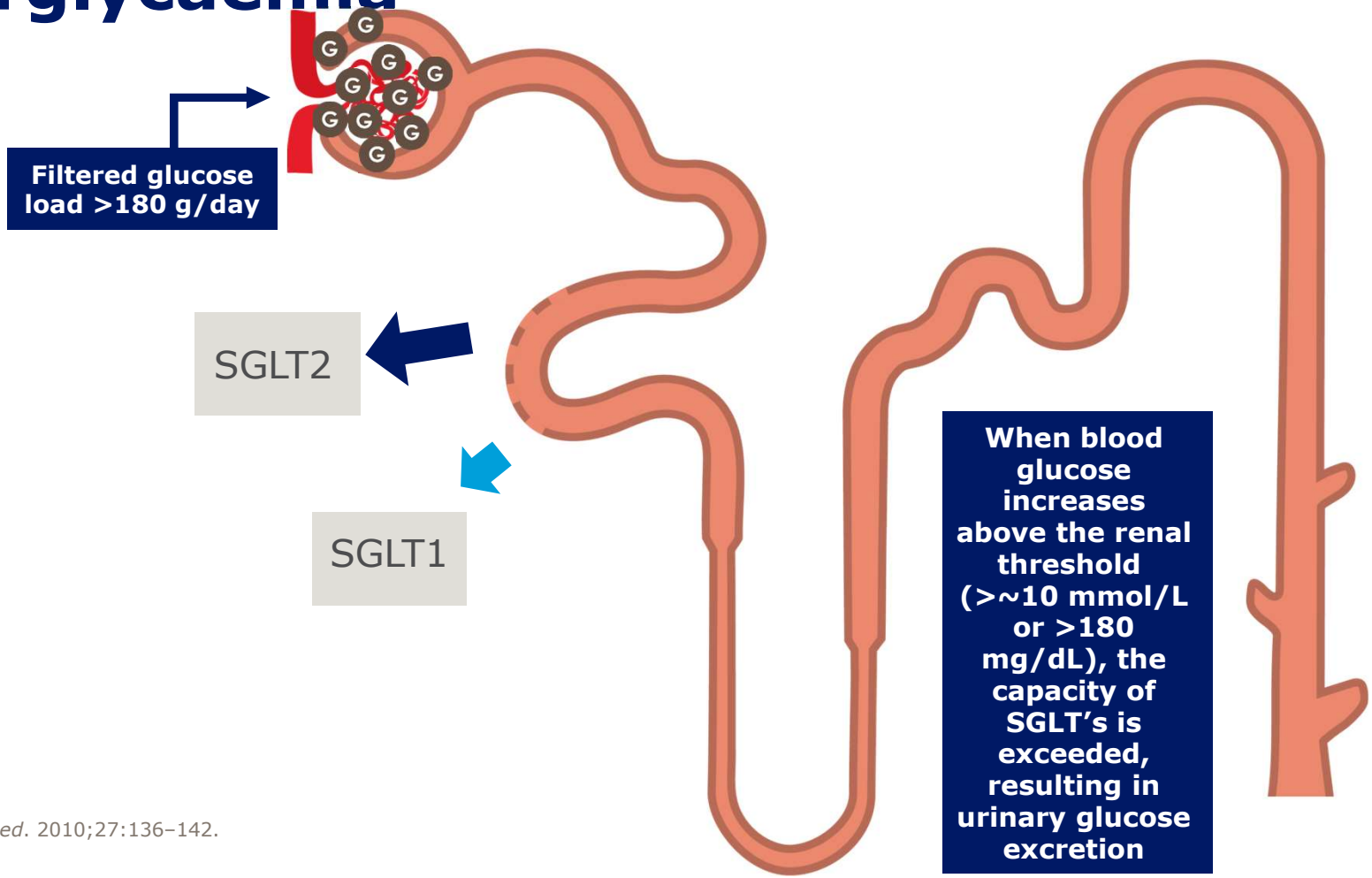
Gerich JE. *Diabet Med*. 2010;27:136–142.

The sodium-glucose cotransporter-2 (SGLT2) mechanism in the proximal tubule



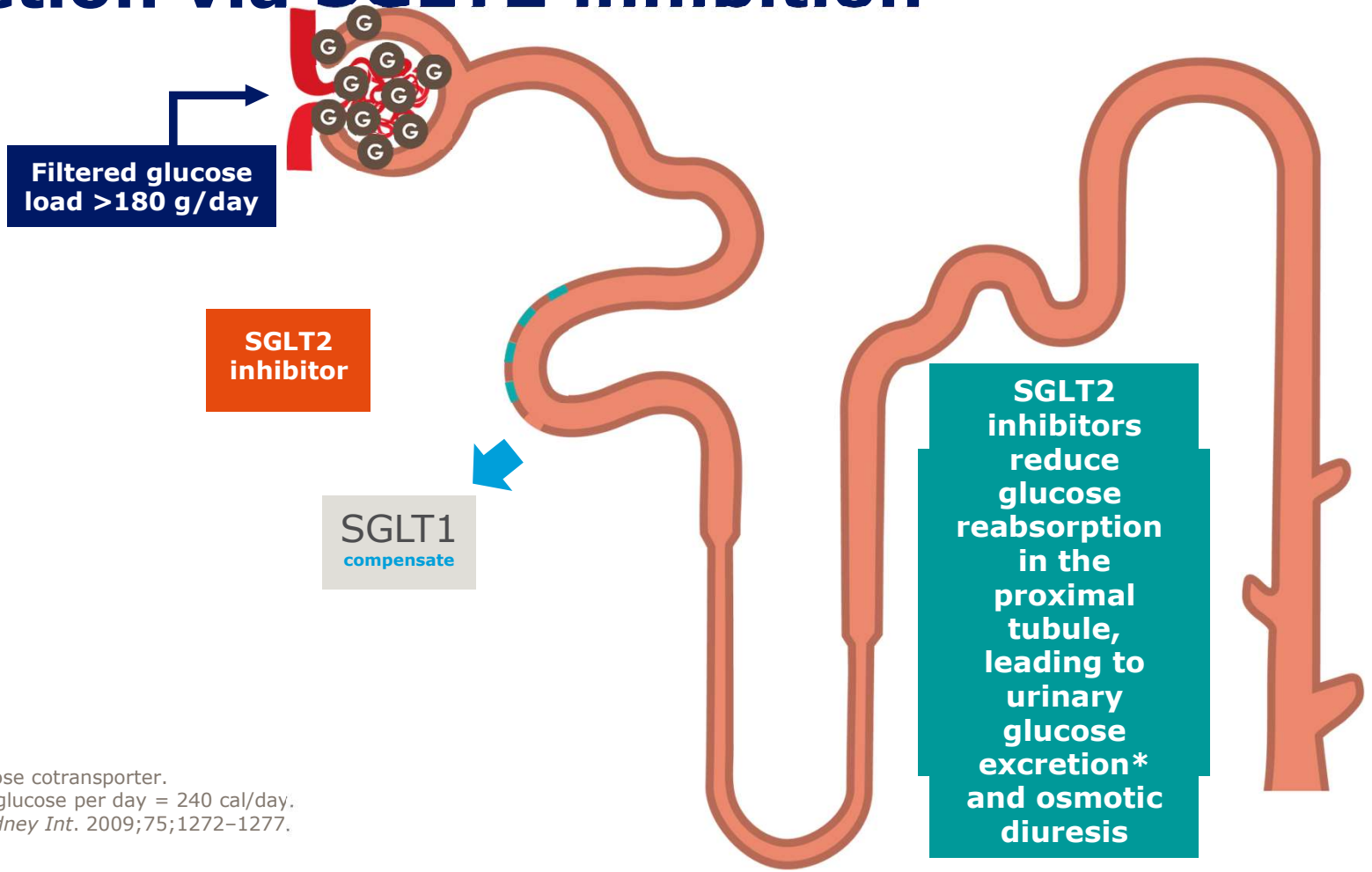
Hiddo J.L, Circulation. Sep 2016

Renal glucose reabsorption in patients with hyperglycaemia



Gerich JE. *Diabet Med*. 2010;27:136–142.

Empagliflozin increases urinary glucose excretion via SGLT2 inhibition



SGLT, sodium glucose cotransporter.
*Loss of ~ 80 g of glucose per day = 240 cal/day.
Bakris GL, et al. *Kidney Int*. 2009;75;1272–1277.

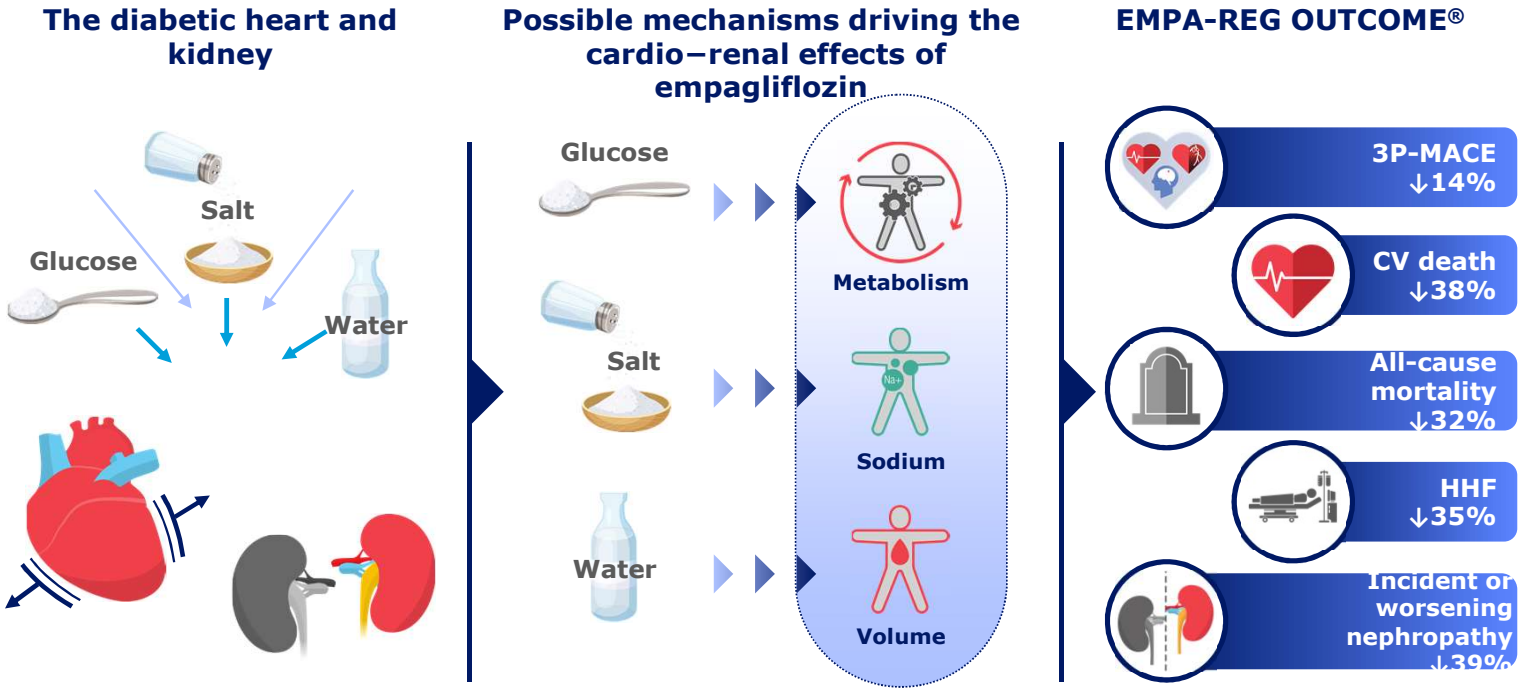
Mean difference and heterogeneity in meta-analyses of double blind, randomised controlled trials comparing SGLT2-i versus

SGLT2-i	Total n	Mean difference(confidence interval)	I^2(Q)%	Subgroup differences
Fasting plasma glucose (mg/dL)	8,914	-28.1 (-31.1; -25.1)	79.1	P = 0.04
Body weight (kg)	9,612	-2.1 (-2.3; -2.0)	44.5	P < 0.01
Systolic blood pressure (mmHg)	9,336	-3.9 (-4.6; -3.3)	33.6	P = 0.03
Diastolic blood pressure (mmHg)	7,402	-2.0 (-2.4; -1.6)	6.3	P = 0.82
Heart rate (bpm)	4,587	-0.6 (-1.3; 0.0)	48.4	P = 0.04
HDL cholesterol (mmol/L)	4,698	0.05 (0.04; 0.07)	31.0	P = 0.03
Triglycerides (mmol/L)	4,704	-0.09 (-0.16; 0.02)	29.8	P < 0.01
LDL cholesterol (mmol/L)	5,431	0.09 (0.04; 0.14)	55.5	P < 0.01
Alanine aminotransferase (U/L)	3,719	-2.8 (-4.0; -1.7)	44.3	P = 0.59
Creatinine (µmol/L)	5,445	0.6 (0.1; 1.1)	11.3	P = 0.05
Dapagliflozin	**Total n**	**MD (CI)**	**I^2(Q)%**	
Fasting plasma glucose (mg/dL)	3,844	-24.6 (-28.7; -20.4)	74	
Body weight (kg)	4,432	-2.0 (-2.2; -1.8)	24	
Systolic blood pressure (mmHg)	3,943	-3.5(-4.3; -2.7)	1	
Diastolic blood pressure (mmHg)	2,009	-2.1 (-2.9; -1.3)	8	
Heart rate (bpm)	2,148	-0.7 (-2.1; 0.7)	63	
HDL cholesterol (mmol/L)	175	0.09 (-0.03; 0.21)	NA	
Triglyceride (mmol/L)	175	0.00 (-0.12; 0.12)	NA	
LDL cholesterol (mmol/L)	175	-0.15 (-0.32; 0.02)	NA	
Alanine aminotransferase (U/L)	1,817	-2.1 (-3.8; -0.5)	30	
Creatinine (µmol/L)	2,335	0.3 (-0.4; 1.0)	0	
Empagliflozin	**Total n**	**MD (CI)**	**I^2(Q)%**	
Fasting plasma glucose (mg/dL)	2,955	-29.5 (-33.1; -25.9)	60	
Body weight (kg)	3,063	-2.0 (-2.2; -1.7)	9	
Systolic blood pressure (mmHg)	3,185	-3.2 (-4.2; -2.3)	11	
Diastolic blood pressure (mmHg)	3,185	-1.9 (-2.5; -1.2)	31	
Heart rate (bpm)	1,103	0.5 (-0.7; 1.6)	0	
HDL cholesterol (mmol/L)	2,417	0.04 (0.02; 0.06)	27	
Triglyceride (mmol/L)	2,435	0.00 (-0.09; 0.08)	0	
LDL cholesterol (mmol/L)	3,173	0.06 (0.01; 0.10)	0	
Alanine aminotransferase (U/L)	673	-3.4 (-6.1; -0.6)	46	
Creatinine (µmol/L)	1,872	0.3 (-0.6; 1.1)	15	

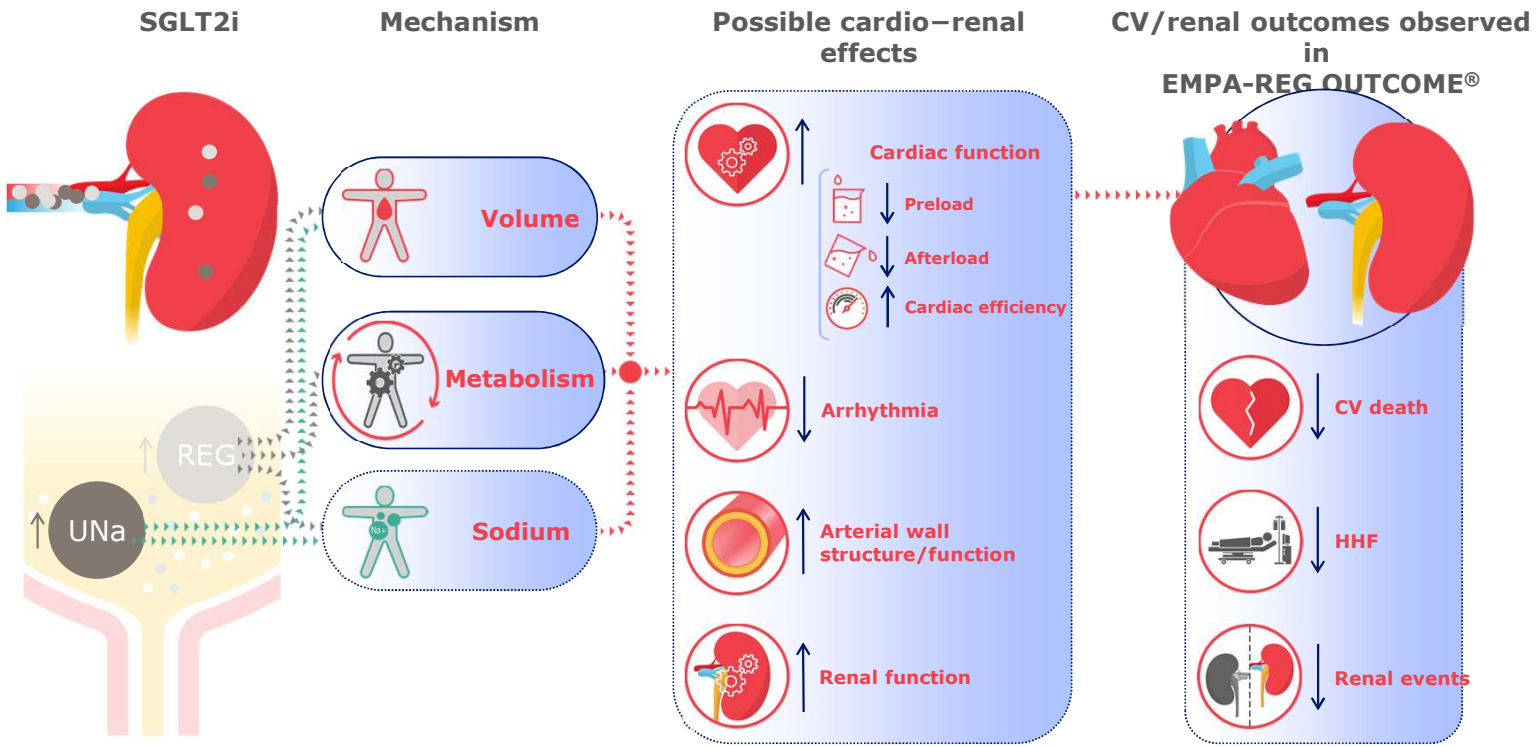
Storgaard H, PLOS ONE November 11, 2016

What is SGLT2 doing?

SGLT2 may produce changes in metabolism, sodium and volume to unburden the diabetic heart and kidney

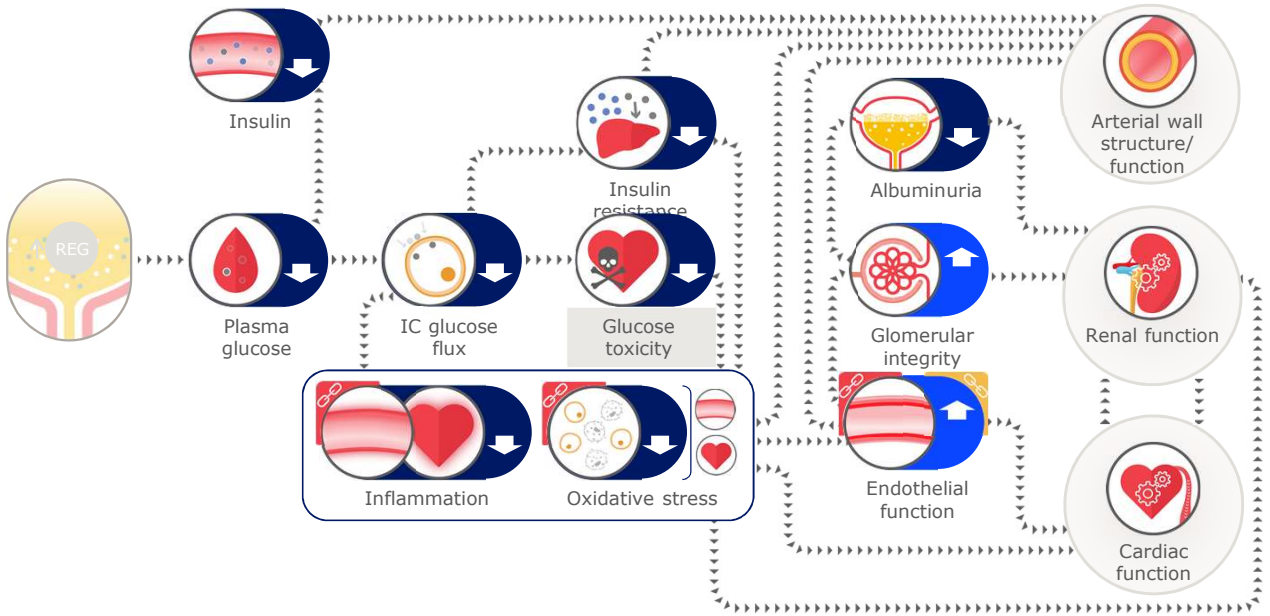


Possible CV and renal mechanisms of SGLT2



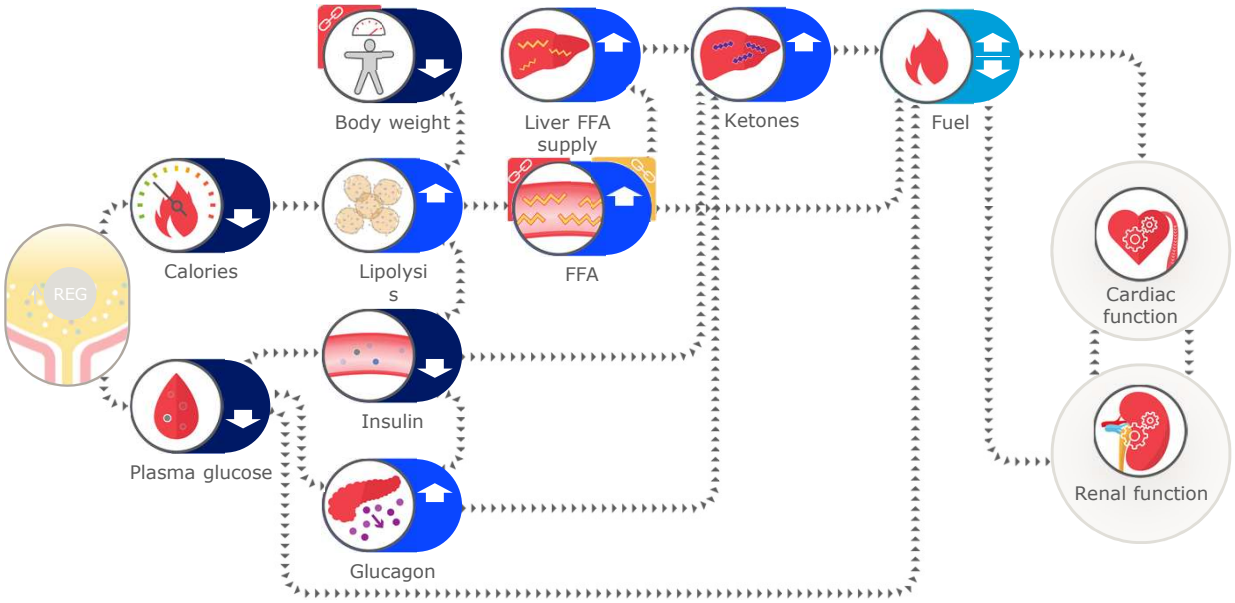
REG, removal of excess glucose; UNa, urinary sodium

Empagliflozin may improve arterial wall structure/function, and cardiac and renal function, by reducing glucose toxicity



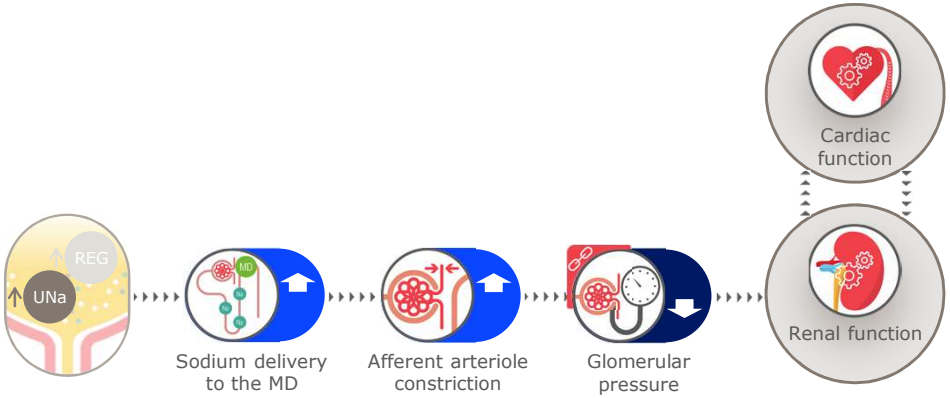
The available evidence to support the hypothesis may be incomplete; specific evidence for empagliflozin may not be available for the hypothesis or parts thereof.
IC, intracellular; REG, removal of excess glucose

Empagliflozin may influence cardiac and renal function via changes in energy supply



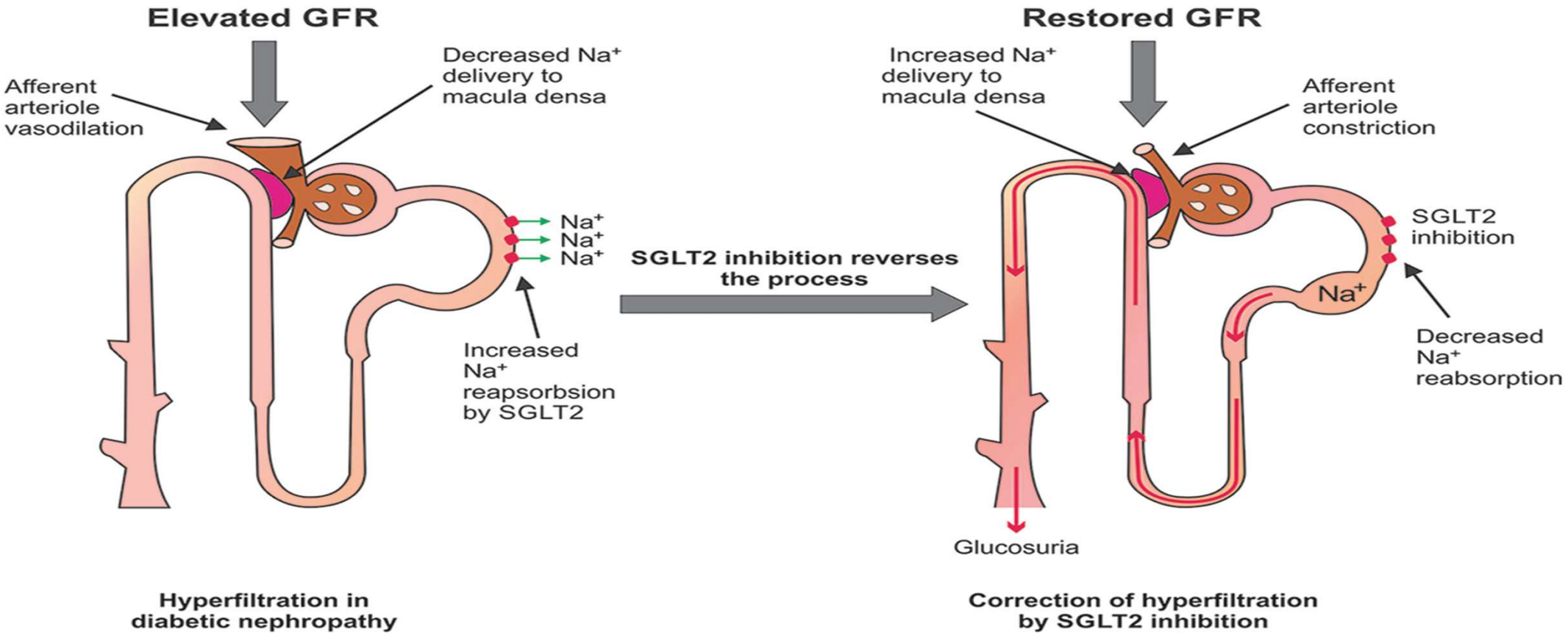
The available evidence to support the hypothesis may be incomplete; specific evidence for empagliflozin may not be available for the hypothesis or parts thereof.
FFA, free fatty acids; REG, removal of excess glucose

Empagliflozin may reduce glomerular pressure by activating tubuloglomerular feedback



The available evidence to support the hypothesis may be incomplete; specific evidence for empagliflozin may not be available for the hypothesis or parts thereof.
MD, macula densa; UNa, urinary sodium

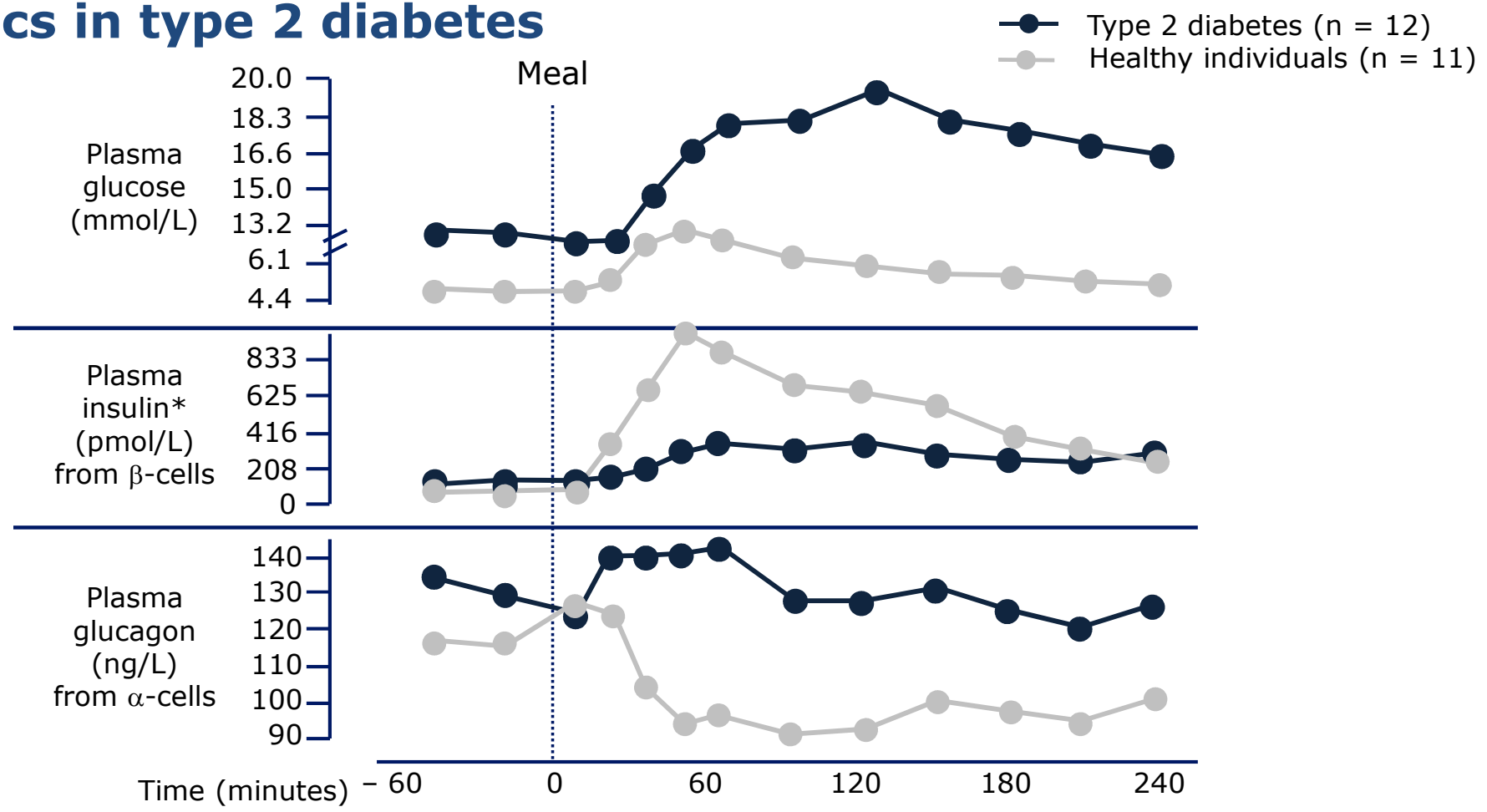
Hyperfiltration in diabetic nephropathy and reduction of hyperfiltration by SGLT2 inhibitors



Sanjay K, Adv Ther (2016)

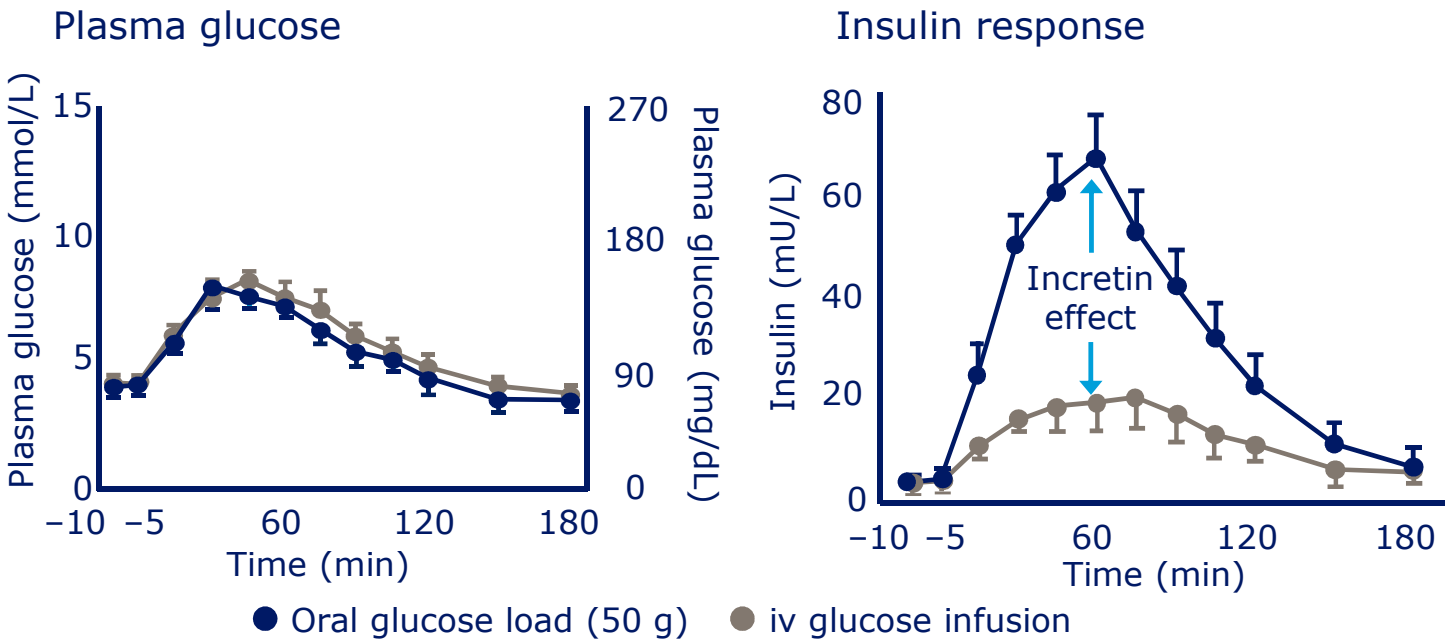
The Glucagon Like Peptide-1(GLP-1) Receptor Analog therapy

Islet cell dysfunction leads to abnormal insulin and glucagon dynamics in type 2 diabetes



Adapted from Müller WA, et al. *N Engl J Med*. 1970;283:109–115.

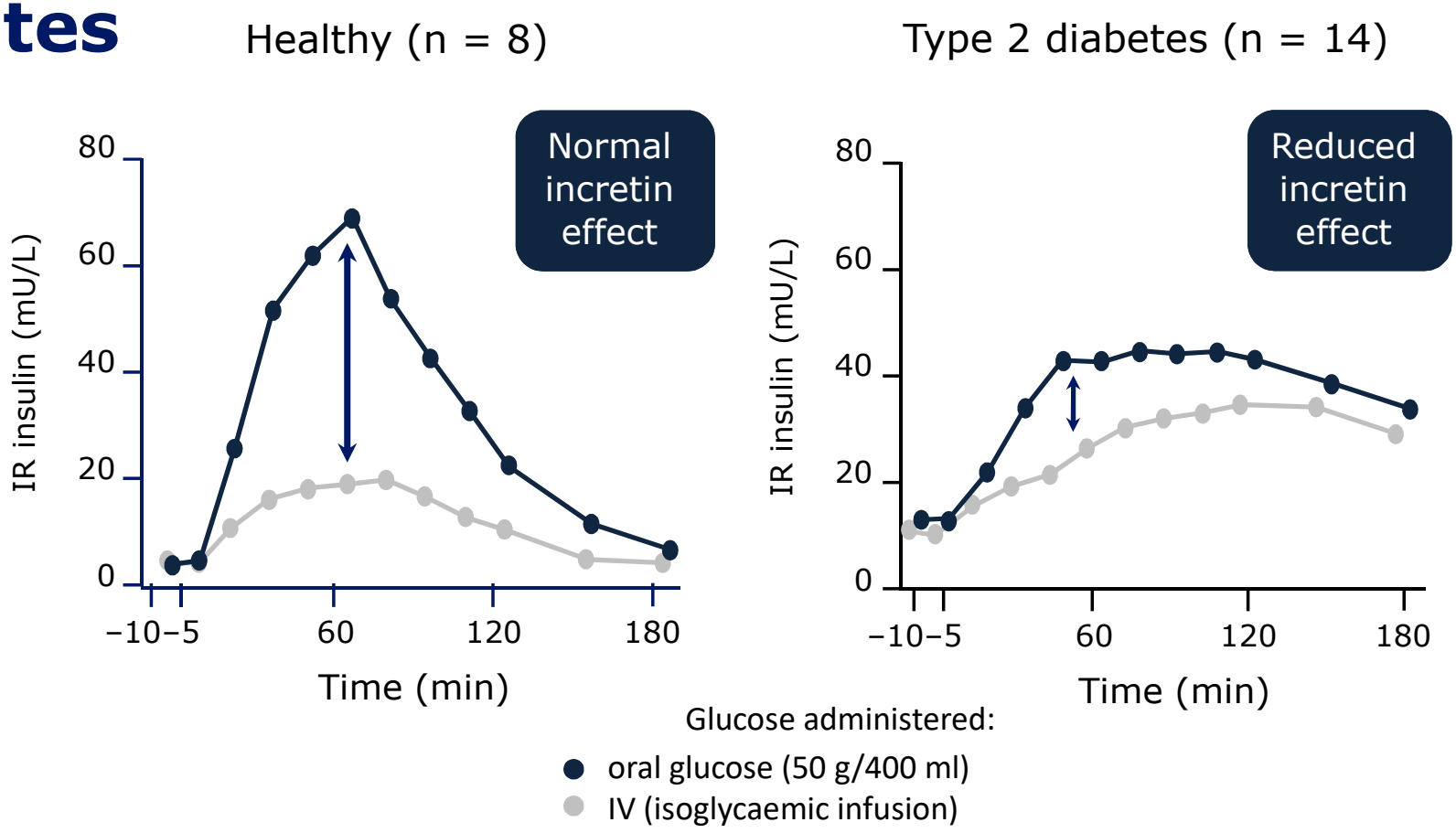
The incretin hormones play a crucial role in a healthy insulin response



- Insulin response is greater following oral glucose than iv glucose, despite similar plasma glucose concentration

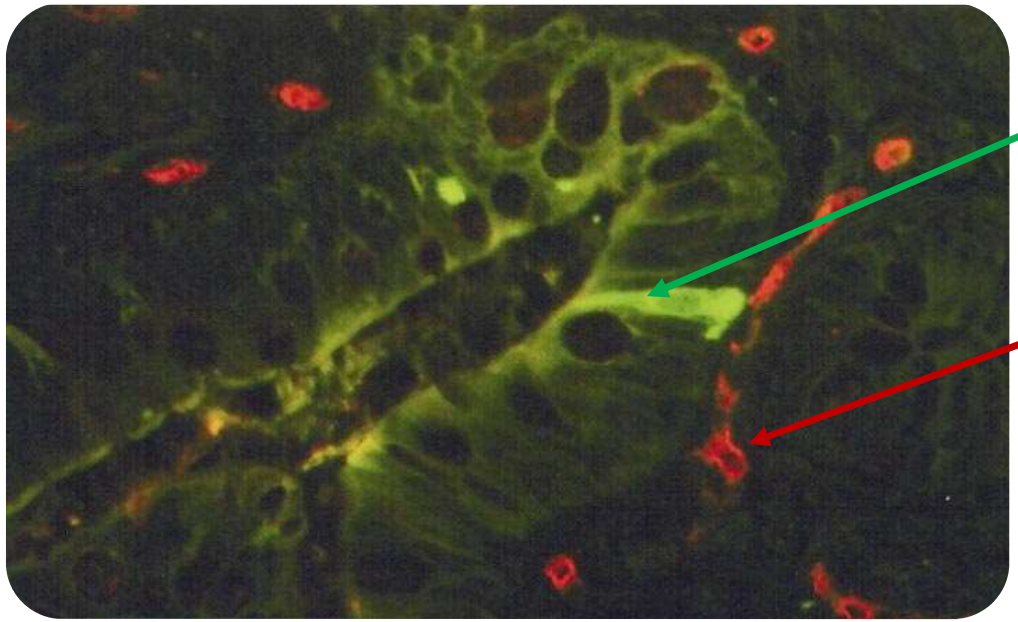
Nauck *et al. Diabetologia* 1986;29:46–52, healthy volunteers (n=8)

The absolute incretin effect is reduced in type 2 diabetes



Nauck *et al. Diabetologia* 1986;29:46–52, healthy volunteers (n=8)

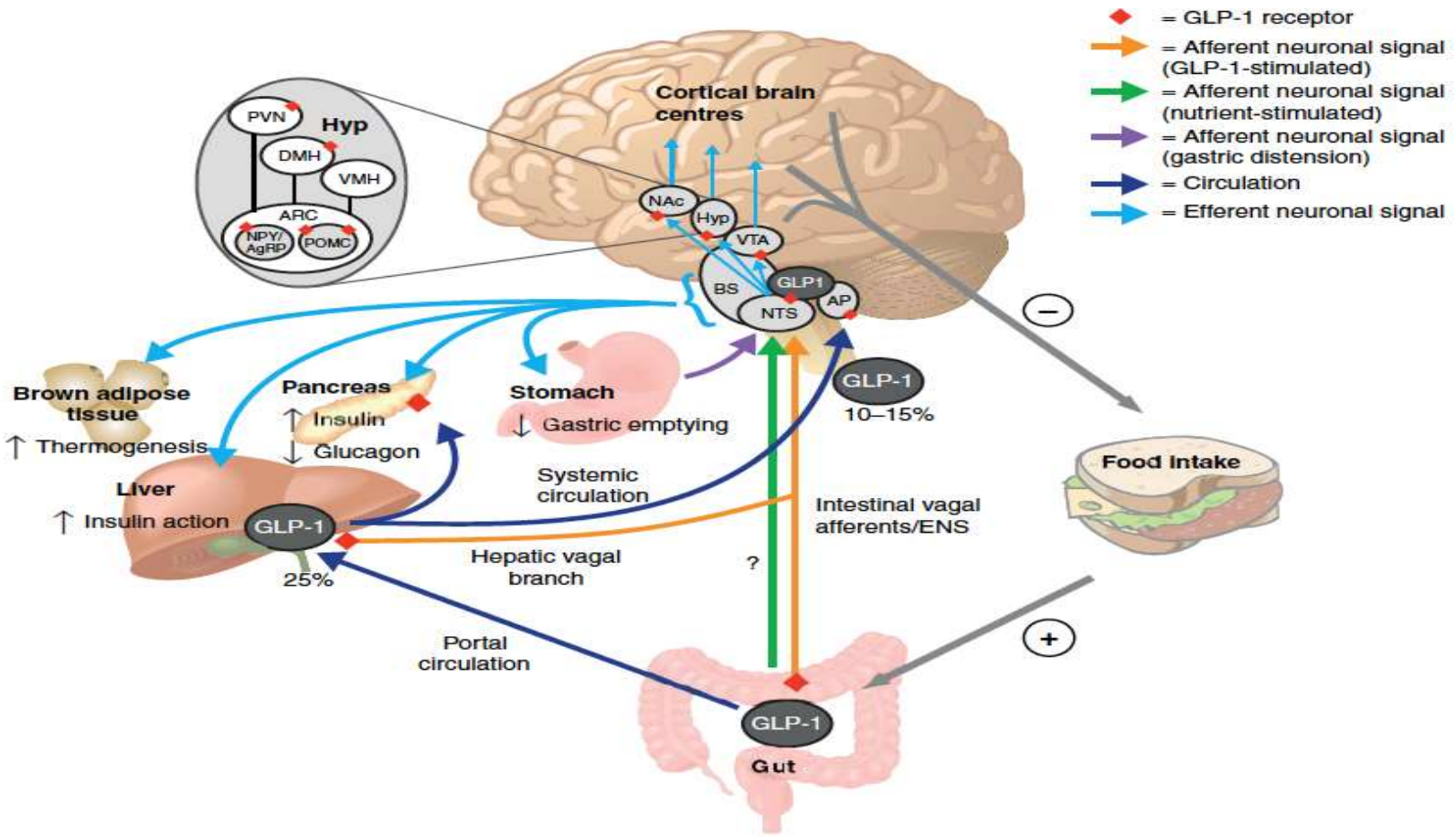
Native GLP-1 is rapidly degraded by DPP-4



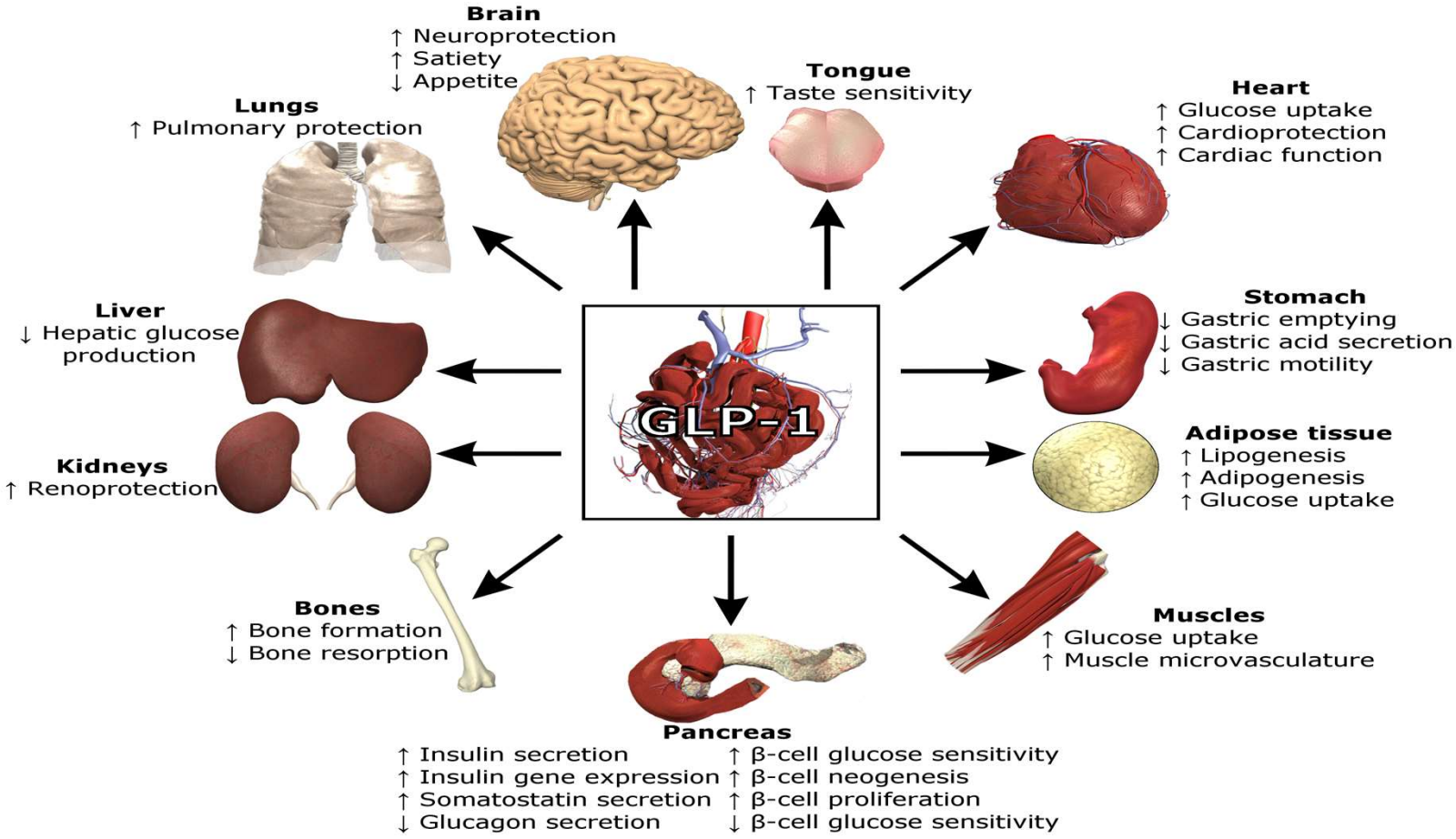
Double immunohistochemical staining for DPP-4 (red) and GLP-1 (green) in the human ileum

Adapted from: Hansen *et al. Endocrinology* 1999;140:5356–63

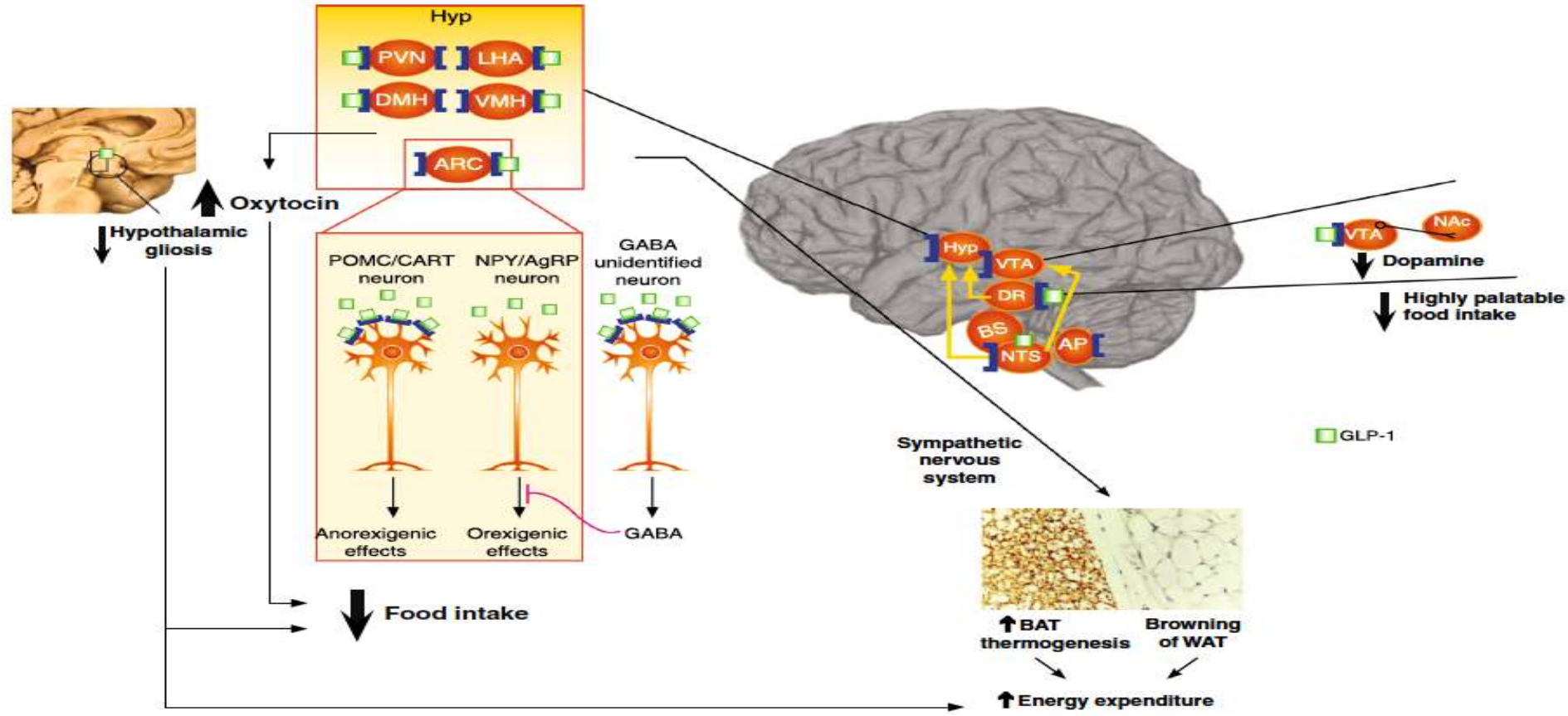
Proposed routes of action of GLP-1 in the central regulation of feeding and glucose metabolism



GLP-1RAs have multifactorial effects



(GLP-1 action in the central nervous system.



Geloneze B, Drugs (2017)

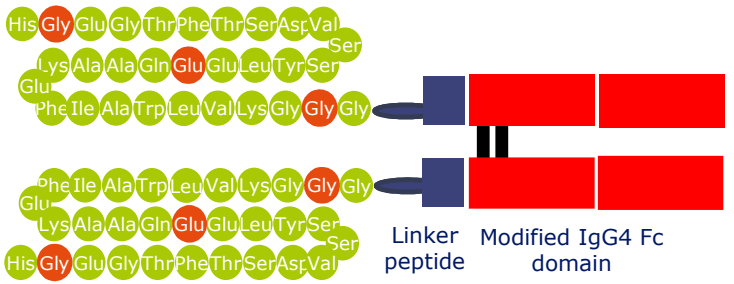
GLP-1RAs for the treatment of T2D

Exendin-4 based	Human-based	
	Small	Large

Exenatide

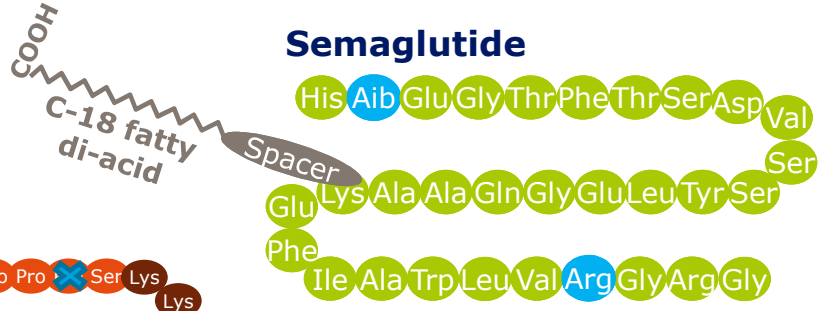
Liraglutide

Dulaglutide

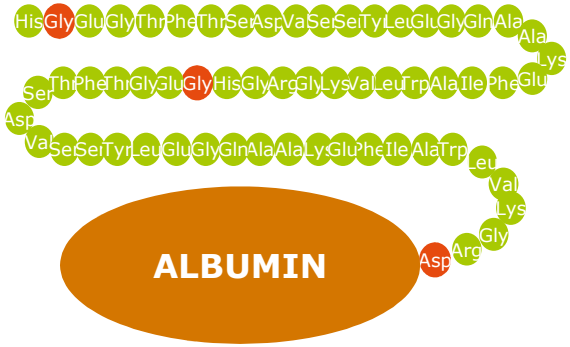


Lixisenatide

Semaglutide

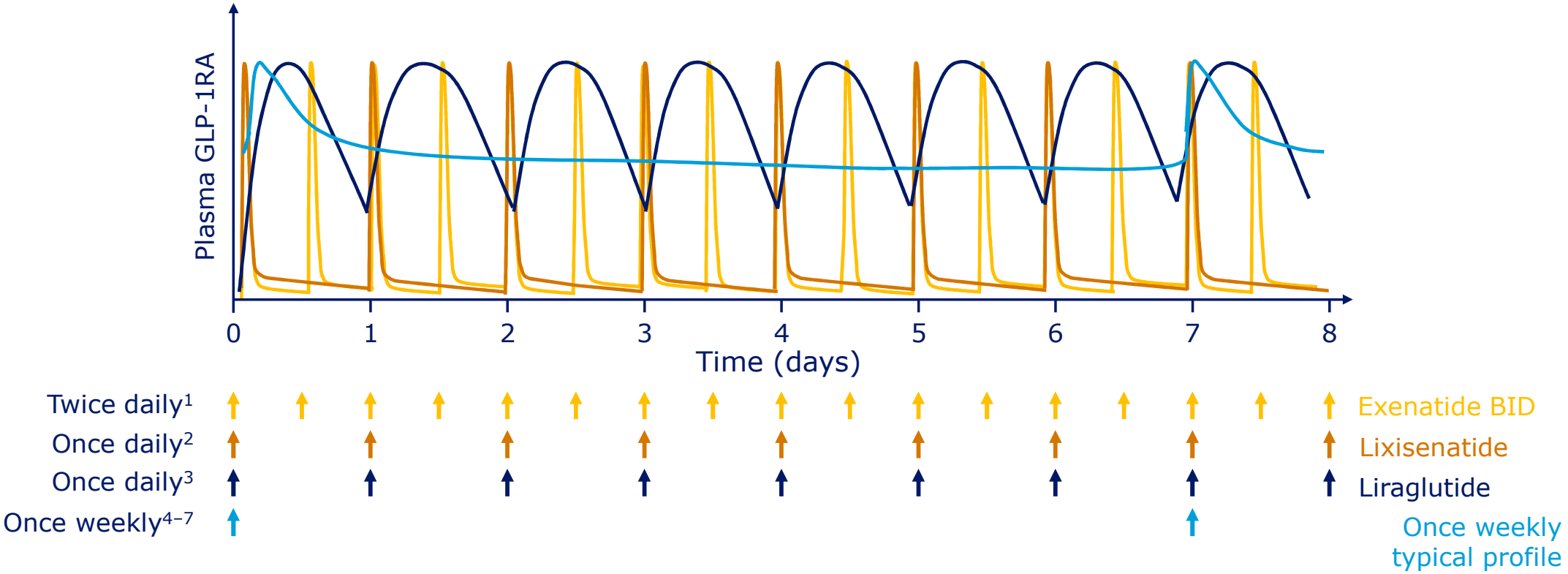


Albiglutide*



*Albiglutide will be withdrawn by July 2018 for commercial reasons.
GLP-1RA, glucagon-like peptide-1 receptor agonist; IgG4 Fc, immunoglobulin-G4 fragment crystallisable.
Lund A et al. *Eur J Intern Med* 2014;25:407–14.

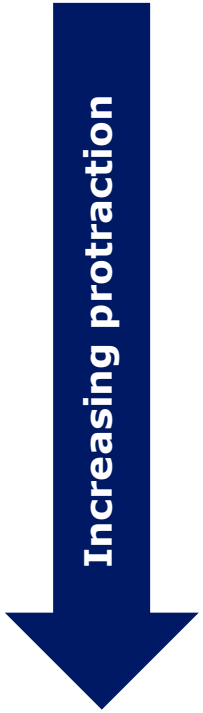
Typical GLP-1RA PK profiles at steady state by dosing frequency



BID, twice daily; GLP-1RA, glucagon-like peptide-1 receptor agonist; PK, pharmacokinetics.

1. Reddy S et al. *AAPS J* 2005;7:M1285; 2. Christensen M et al. *IDrugs* 2009;12:503–13; 3. Elbrønd B et al. *Diabetes Care* 2002;25:1398–404; 4. Kapitza C et al. *J Clin Pharmacol* 2015;55:497–504; 5. Marbury TC et al. *Clin Pharmacokinet* 2017;56:1381–1390; 6. Kuritzky L et al. *Postgrad Med* 2014;126:60–72; 7. Fineman M et al. *Clin Pharmacokinet* 2011;50:65–74.

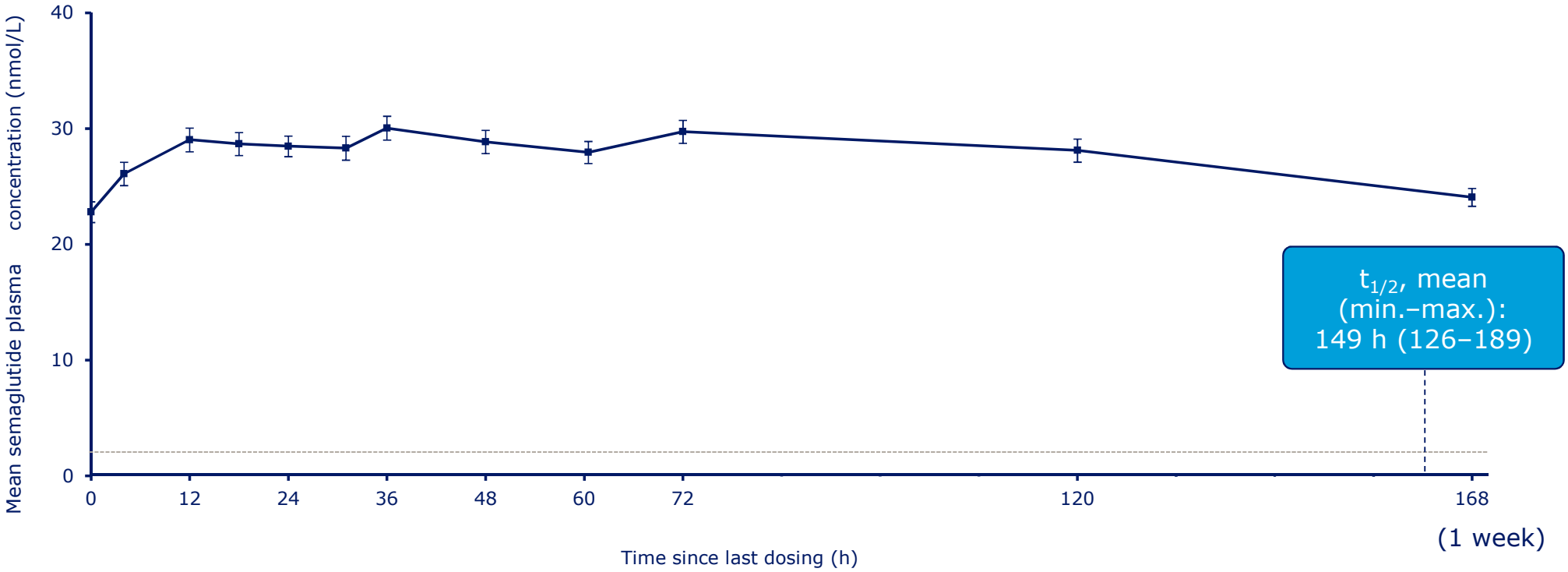
Summary: pharmacokinetic profiles of approved GLP-1RAs and semaglutide



Agent	$t_{1/2}$	t_{max}
Exenatide BID[1]	2.4 h	0.6 h
Lixisenatide OD[2]	3 h	1–3.5 h
Liraglutide OD[3]	13 h	8–12 h
Dulaglutide QW[4]	~4 days	24–48 h
Albiglutide QW[5]*	~5 days	3–5 days
Exenatide QW[6]	7–14 days	6–7 weeks
Semaglutide QW[7,8]	~7 days	1–3 days

*Albiglutide will be withdrawn by July 2018 for commercial reasons.
BID, twice daily; GLP-1RA, glucagon-like peptide-1 receptor agonist; OD, once daily; QW, once weekly; $t_{1/2}$, half-life; t_{max}, time to maximum concentration.
1. Byetta®. Summary of Product Characteristics. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000698/WC500051845.pdf Accessed January 2018;
2. Lyxumia®. Summary of Product Characteristics. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002445/WC500140401.pdf Accessed January 2018;
3. Victoza®. Summary of Product Characteristics. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/001026/WC500050017.pdf Accessed January 2018;
4. Barrington P et al. *Diabetes Obes Metab* 2011;13:434–8; 5. Tanzeum™. Prescribing Information. Available at: https://www.gsksource.com/pharma/content/dam/GlaxoSmithKline/US/en/Prescribing_Information/Tanzeum/pdf/TANZEUM-PI-MG-IFU-COMBINED.PDF Accessed January 2018; 6. Fineman M et al. *Clin Pharmacokinet* 2011;50:65–74; 7. Marbury T et al. *Diabetes* 2014;63(Suppl.1):A260(1010-P); 8. Kapitza C et al. *J Clin Pharm* 2015;55:497–504.

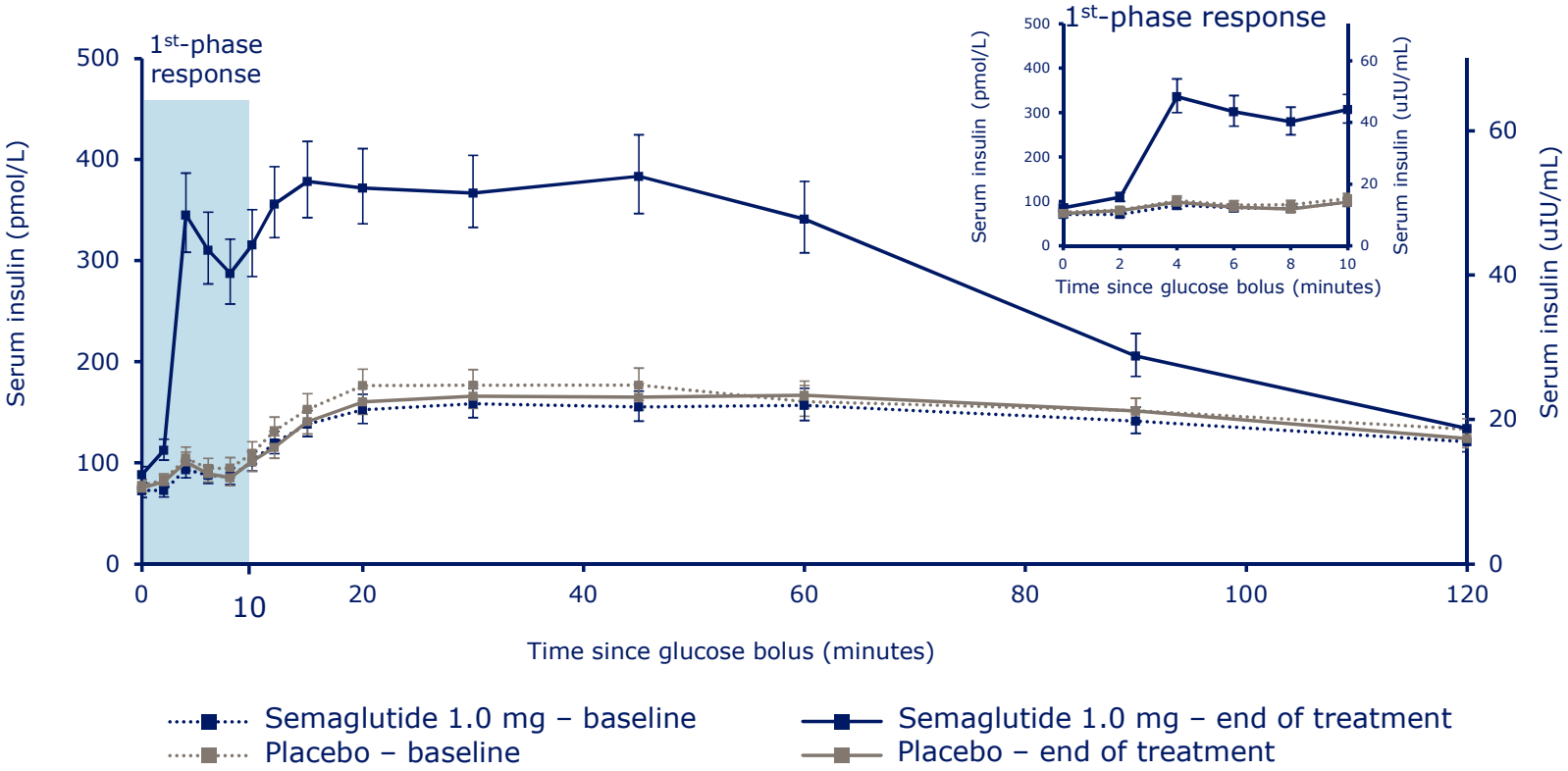
The PK profile of semaglutide at steady state makes it suitable for once-weekly dosing



In this trial investigating the effects of semaglutide on different aspects of beta-cell function (study 3635), assessment of plasma semaglutide level was conducted after 12 weeks of treatment at 1.0 mg steady state in subjects with T2D (n=37).
Data are presented as mean (standard deviation). Dashed line indicates lower limit of quantification.
PK, pharmacokinetic; $t_{1/2}$, half-life.
Novo Nordisk. Data on file.

Semaglutide treatment increases first- and second-phase insulin secretion

INTRAVENOUS GLUCOSE TOLERANCE TEST

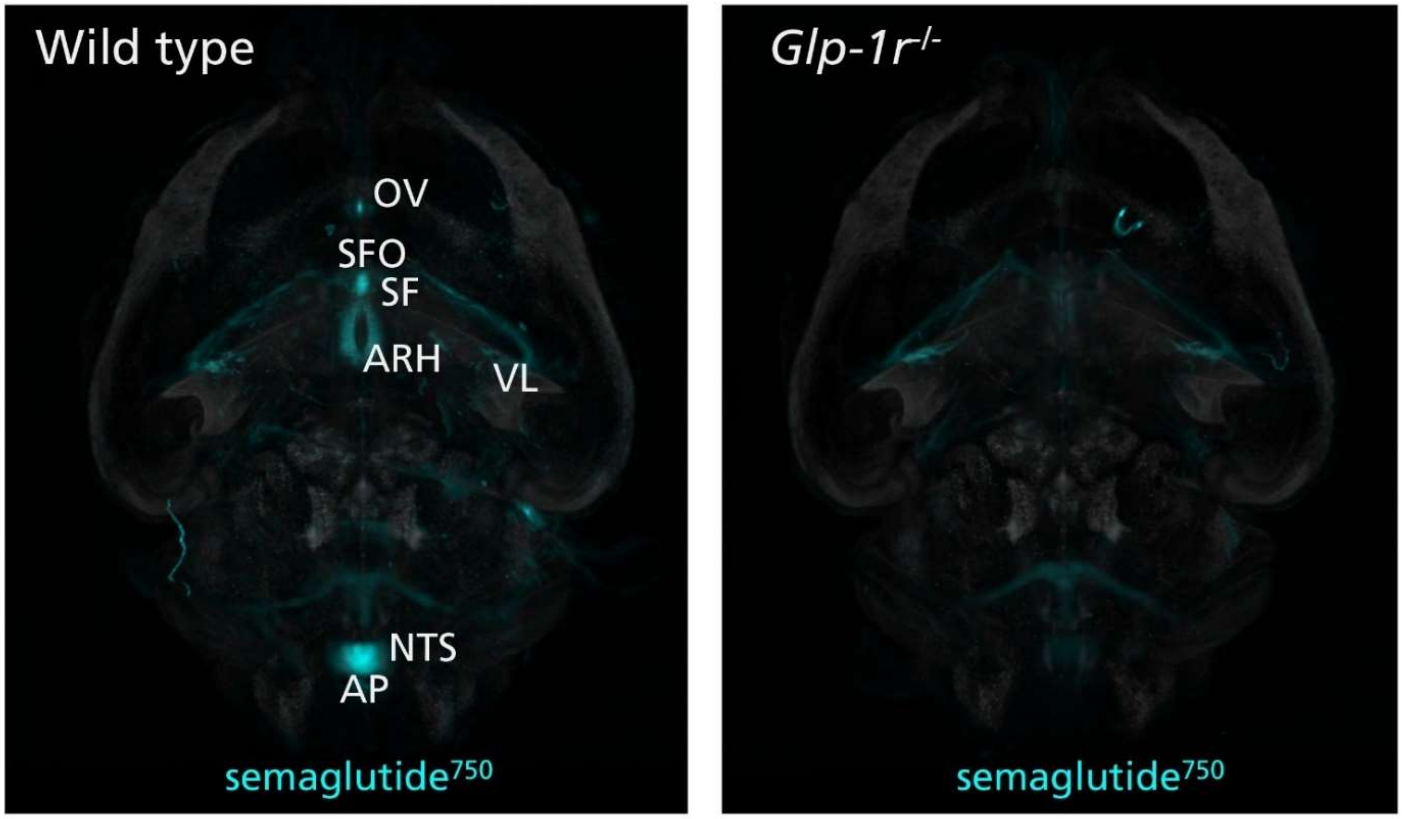


Semaglutide treatment also increased maximum insulin secretory capacity vs placebo in the arginine stimulation test

Mean insulin response to the intravenous glucose tolerance test (25 g glucose bolus load) before and after 12 weeks of treatment with semaglutide or placebo. p<0.0001 for both first- and second-phase semaglutide vs placebo. Values are means (± standard errors) from a mixed model for repeated measurements analysis using 'on-treatment without rescue medication' data from subjects in the full analysis set. Subject 101069 has been removed from all IVGTT statistical analysis due to incorrect amount of glucose infused. IVGTT, intravenous glucose tolerance test.

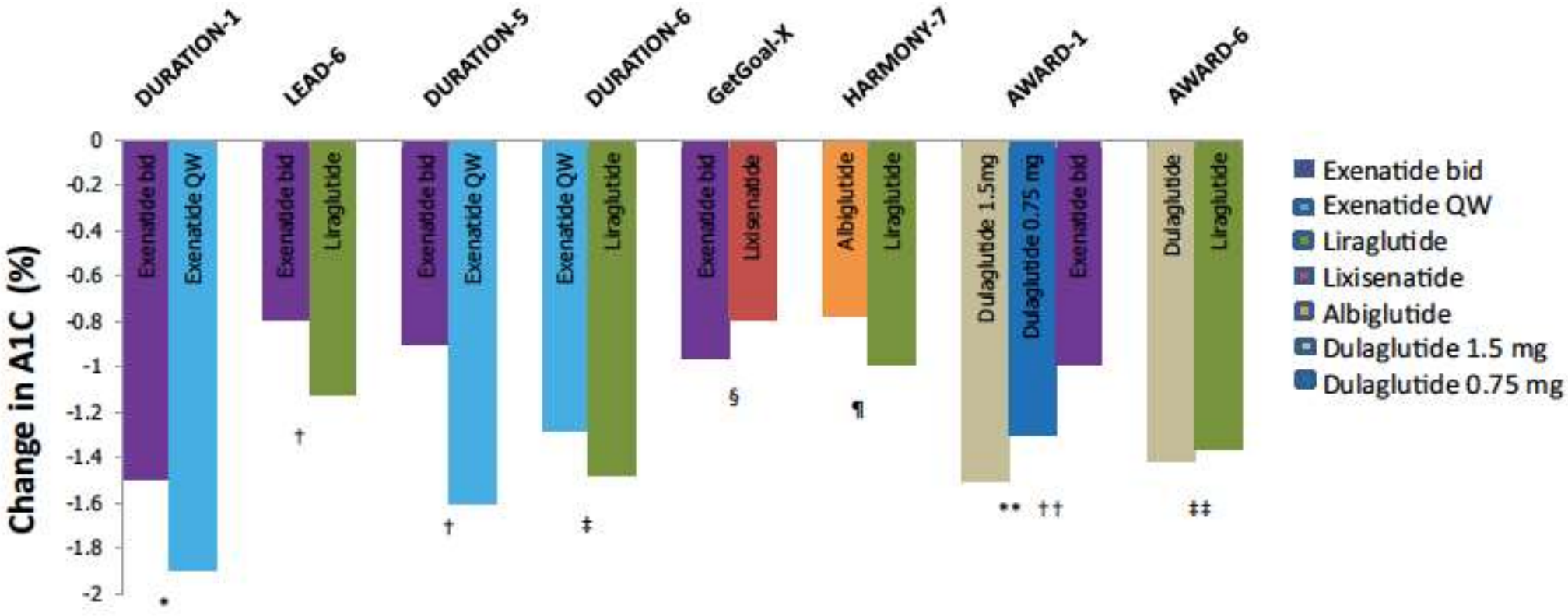
Kapitza C et al. *Diabetologia* 2017;60:1390–9.

The signal of semaglutide^{750} in the brain is GLP-1R-dependent



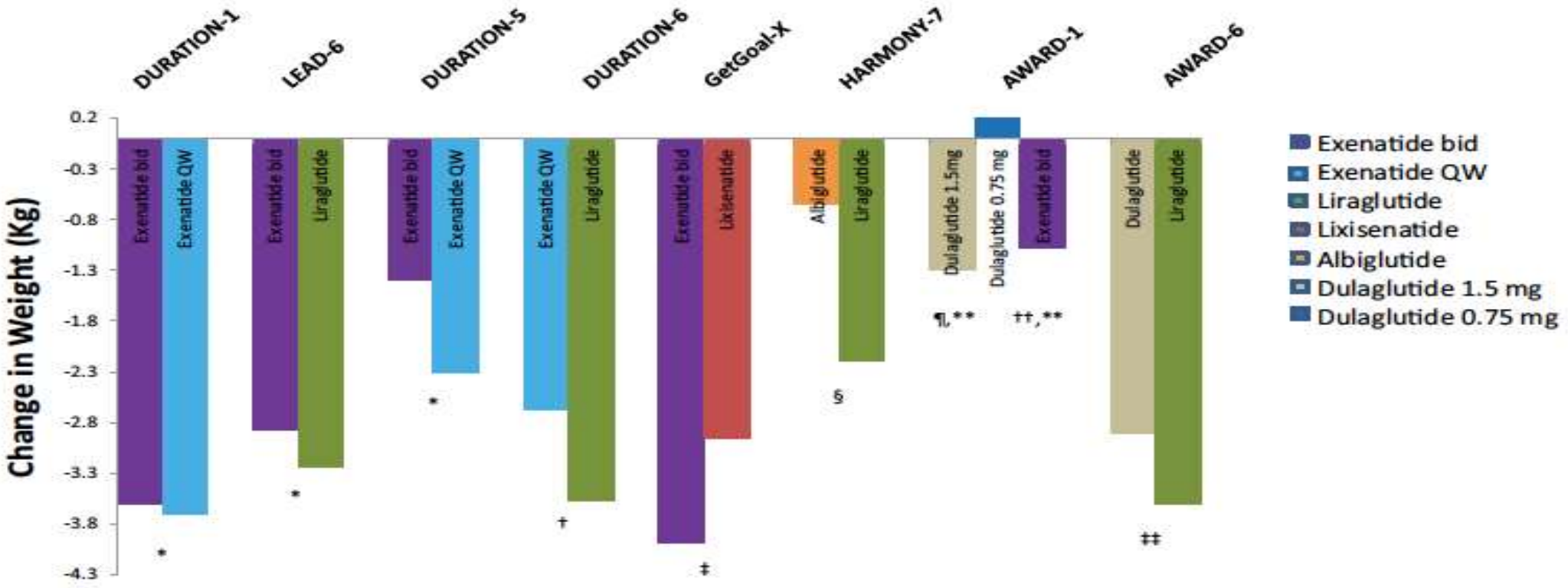
Maximum intensity projection of average (n=4–5) semaglutide^{750} distribution in wild-type C57BL/6 mice (left) and *Glp-1r*$^{-/-}$ mice (right).
AP, area postrema; ARH, arcuate hypothalamic nucleus; NTS, nucleus of the solitary tract; OV, vascular organ of the lamina terminalis; SF, septofimbrial nucleus; SFO, subfornical organ; VL, lateral ventricle.
Jensen CB et al. Presented at the 77th American Diabetes Association Scientific Sessions, 9–13 June 2017, San Diego, CA, USA. Poster Presentation 1145-P.

Changes in A1C values with glucagon-like peptide 1 receptor agonists (GLP-1 RAs) in head-to-head clinical studies.



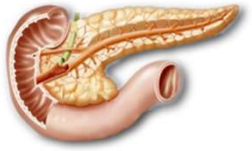
JM Trujillo, Therapeutic Advances in Endocrinology and Metabolism 2015

Changes in weight with glucagon-like peptide 1 receptor agonists (GLP-1 RAs) in head-to-head clinical studies.



JM Trujillo, Therapeutic Advances in Endocrinology and Metabolism 2015

Summary: GLP-1 RA mechanism of action



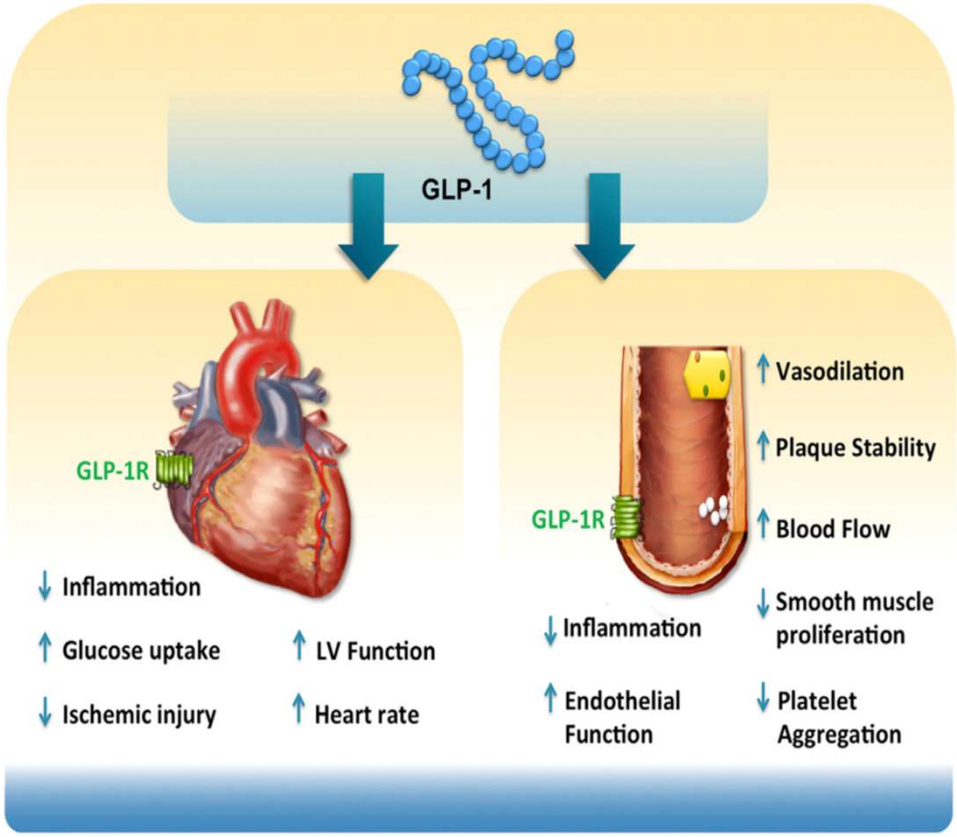
Glp-1RA increases insulin secretion and beta-cell responsiveness, and suppresses hepatic glucose output in a glucose-dependent manner[1,2]

Energy intake, food consumption and body weight are reduced with semaglutide vs placebo[3]

Glp-1RA e attenuates plaque lesion progression in atherosclerotic mouse models[4]

1. Kapitza C et al. *Diabetologia* 2017;60:1390–9; 2. Korsatko S et al. Presented at the 52nd European Association for the Study of Diabetes annual meeting, 12–16 September 2016 Munich, Germany. Poster Number 764; 3. Blundell J et al. *Diabetes Obes Metab* 2017;19:1242–51. 4. Rakipovski G et al. Presented at the 77th Scientific Sessions of the American Diabetes Association, 9–13 June 2017, San Diego, CA, USA. Oral Presentation 244-OR.

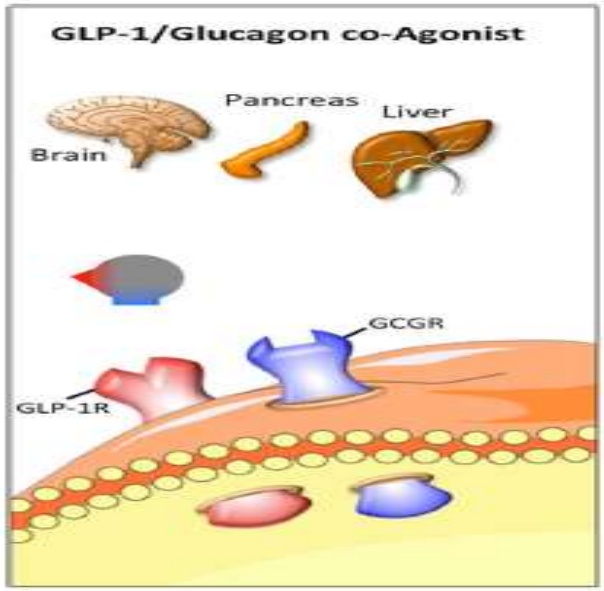
Summary: GLP-1 RA mechanism of action



Drucker DJ. *Cell Metab* 2016;24:15–30

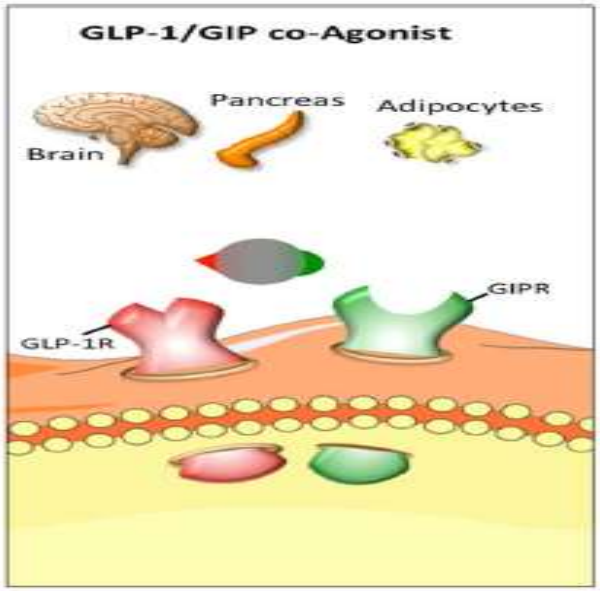
The Multiple Agonist

Gut hormone polyagonists for the treatment of type 2 diabetes



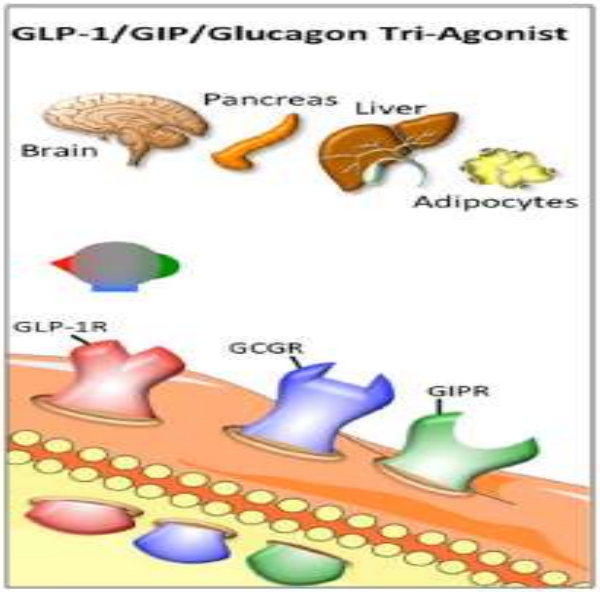
Improves:

Body weight
Energy Expenditure
Glycemic control
Cholesterol



Improves:

Glycemic control
Body weight
Lipolysis
Cholesterol

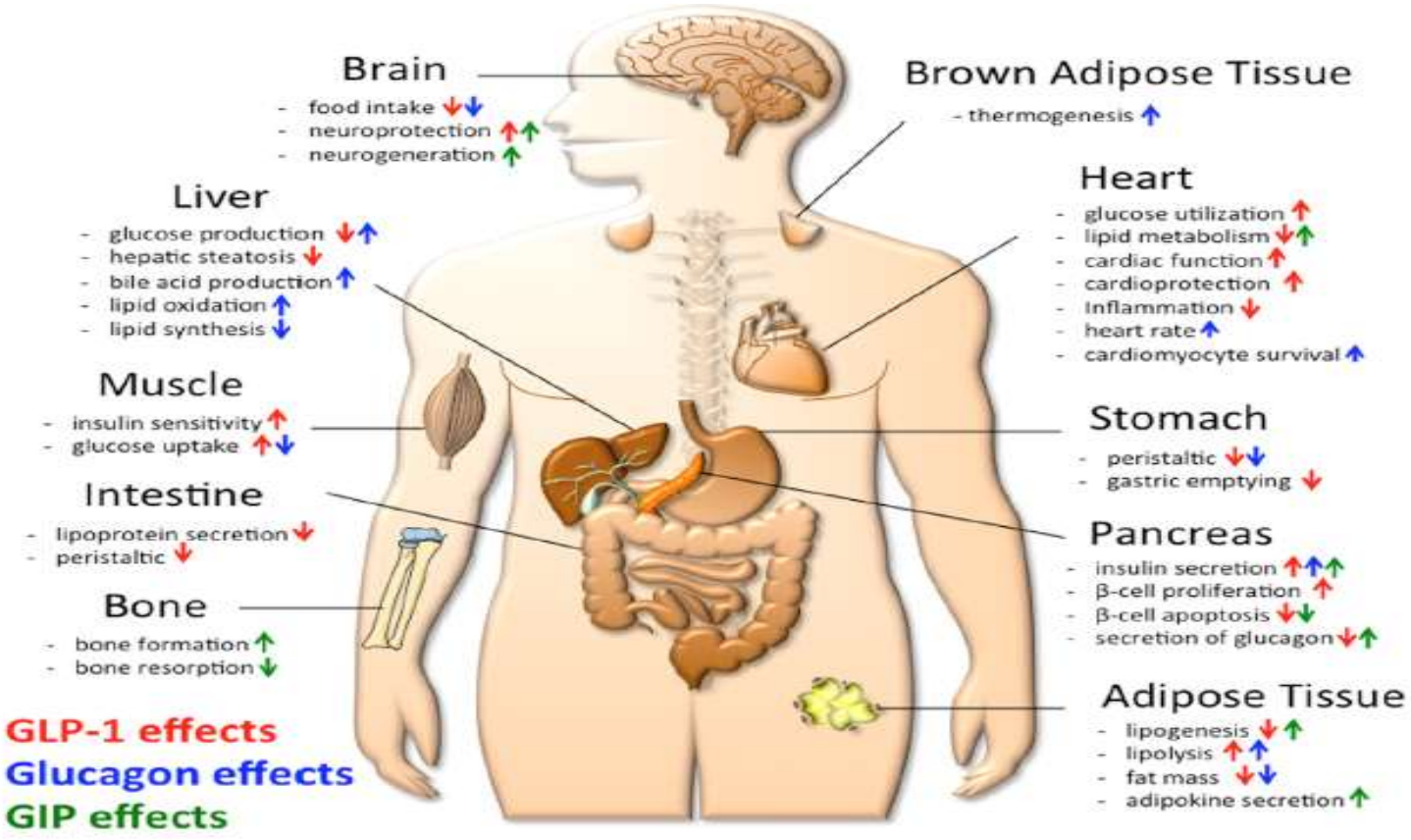


Improves:

Body weight
Glycemic control
Hepatosteatosis
Cholesterol
Energy Expenditure
Lipolysis

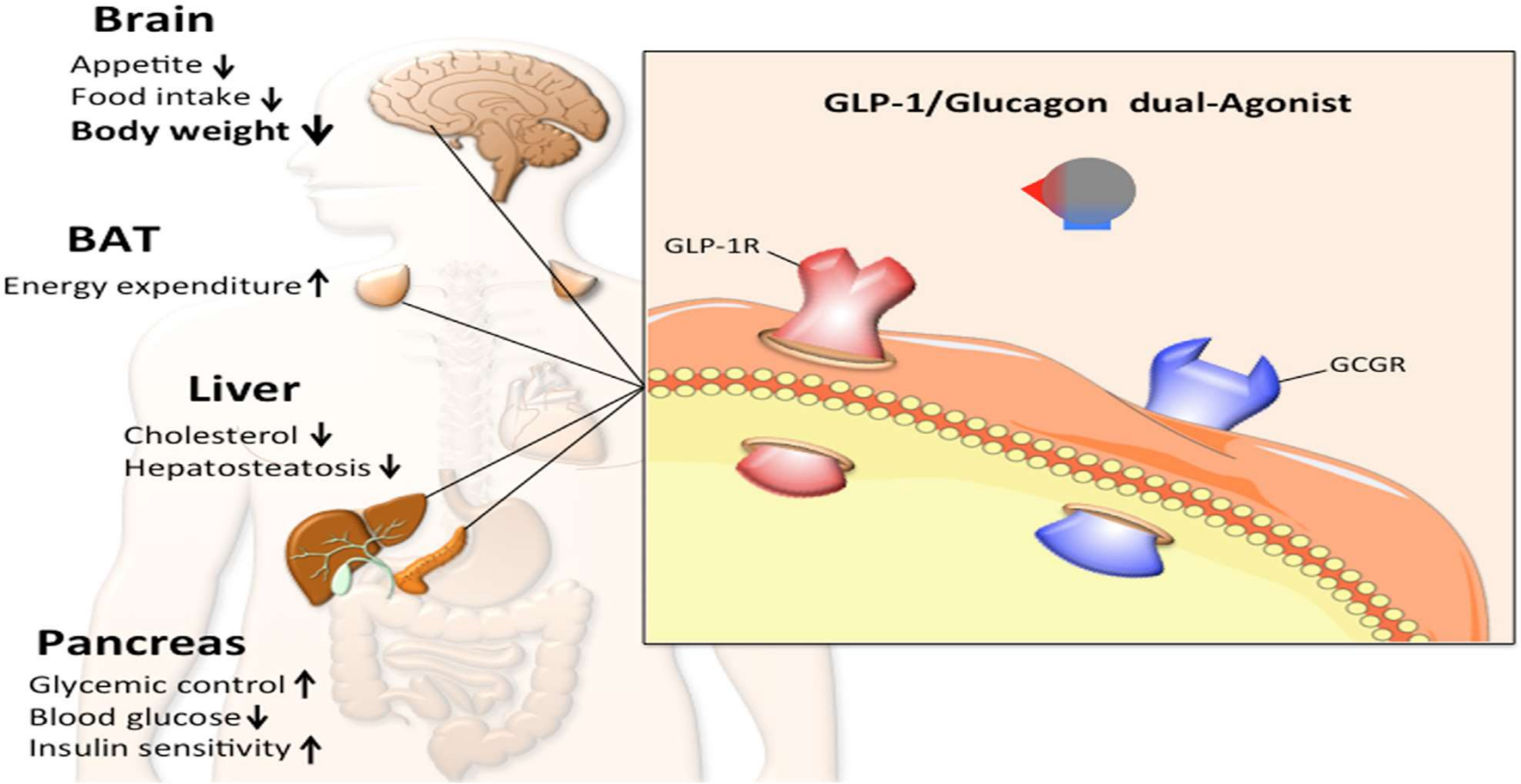
Brandt SJ Peptides *2018*

Schematic demonstrating the qualitative metabolic effects of GLP-1, glucagon and GIP on systems metabolism,



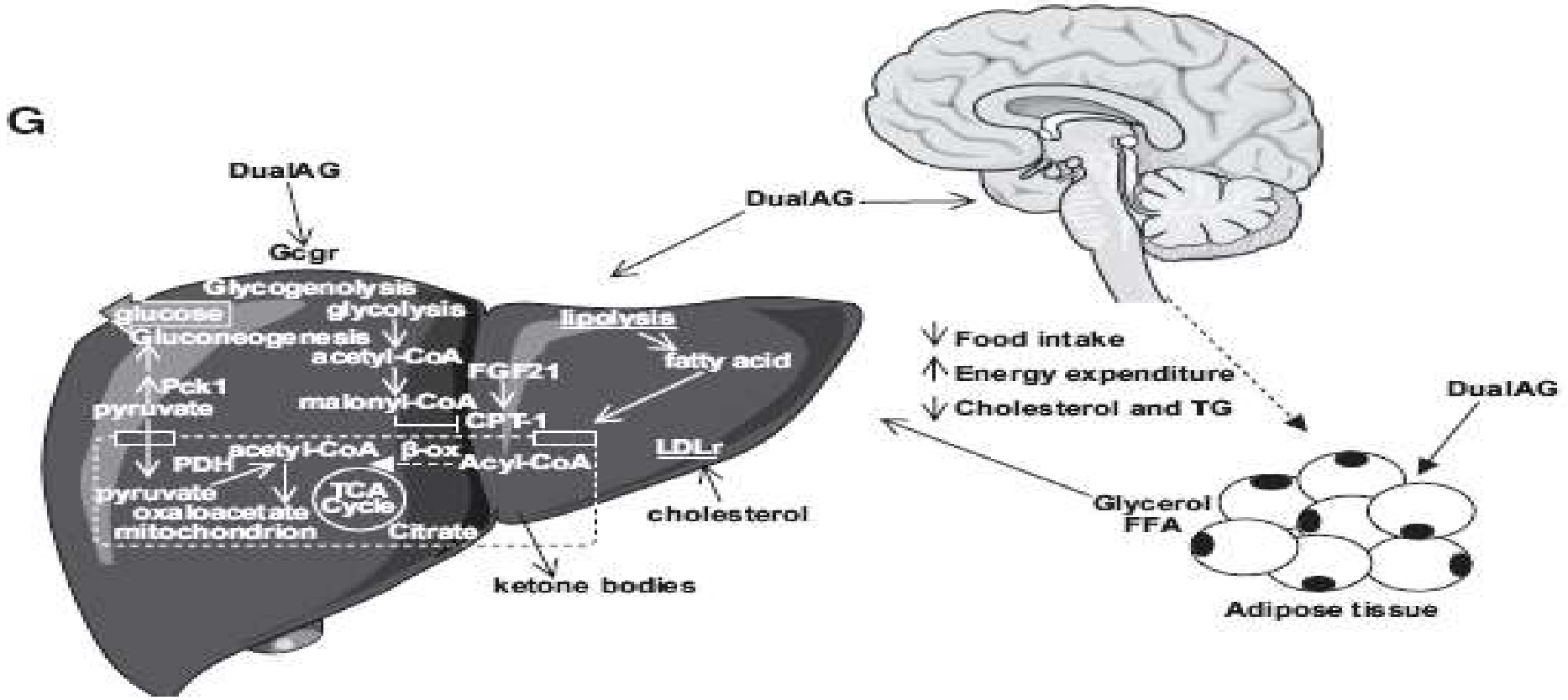
Brandt SJ*Journal of Endocrinology 2018*

Schematic demonstrating the qualitative metabolic effects of GLP-1/glucagon dual agonist on systems metabolism,



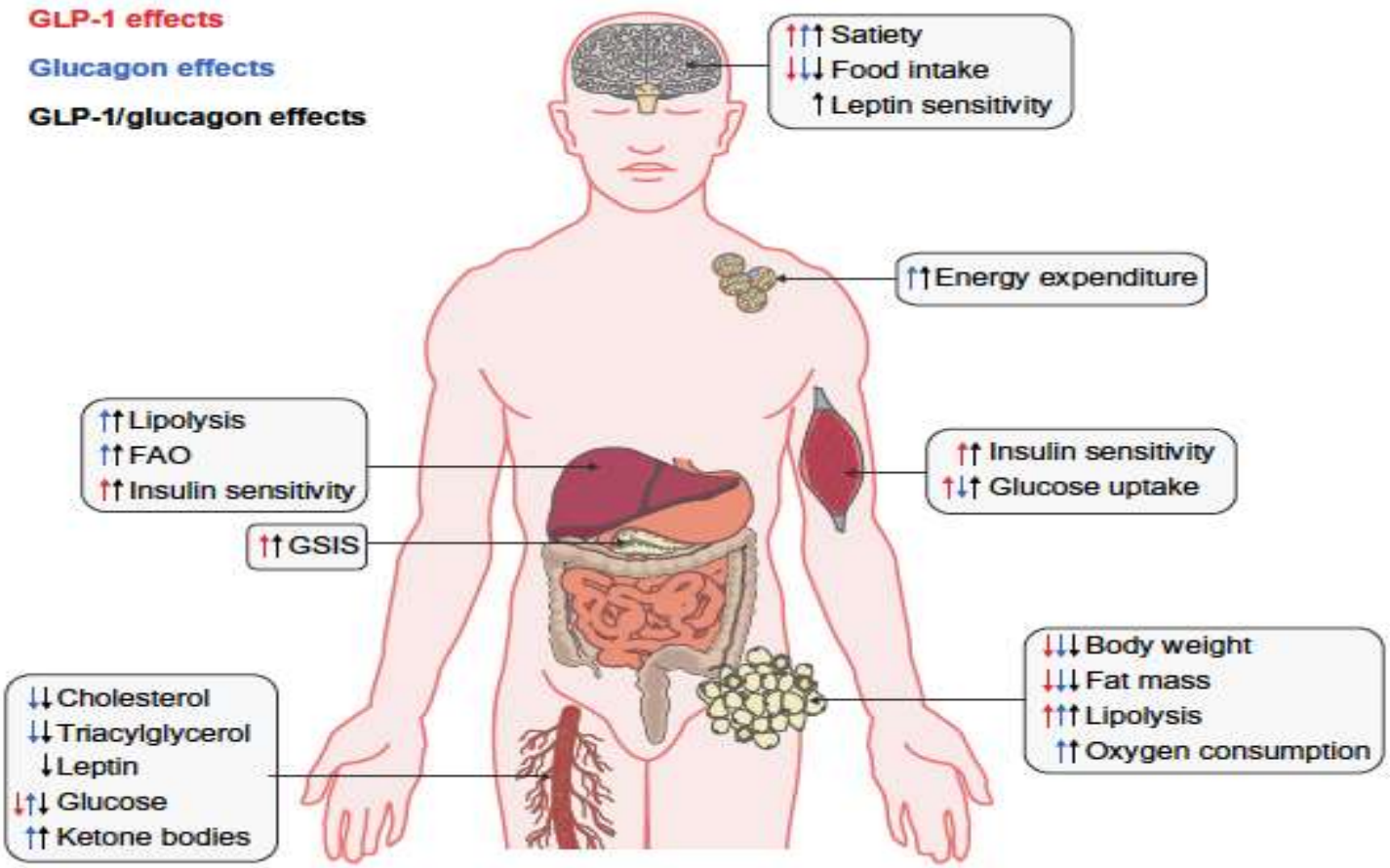
Brandt SJ*Journal of Endocrinology 2018*

Dual AG lowers body weight and food intake via activation of GLP1R and GCGR

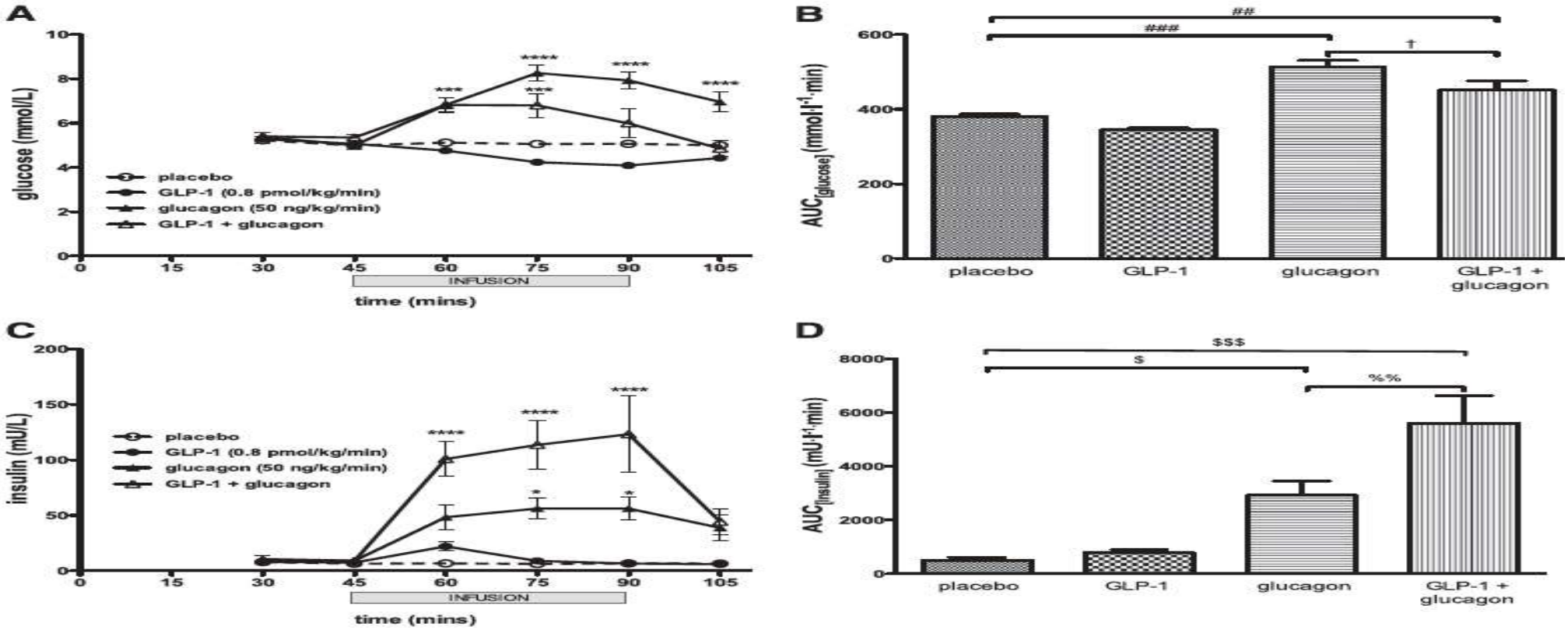


Pocai A, Diabetes 2009

Metabolic actions of GLP-1R agonists and GcgR agonists on key organs

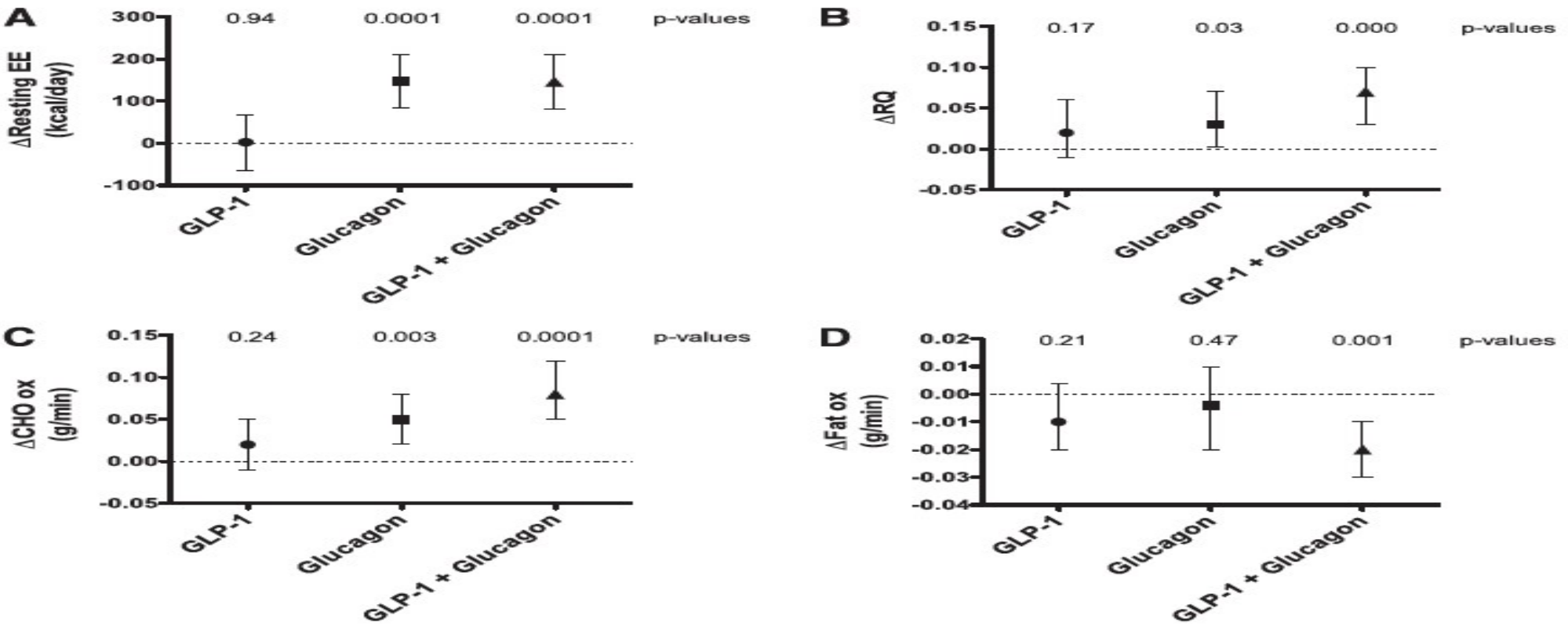


Coadministration of Glucagon-Like Peptide-1 During Glucagon Infusion in Humans Results in Increased Energy Expenditure and Amelioration of Hyperglycemia



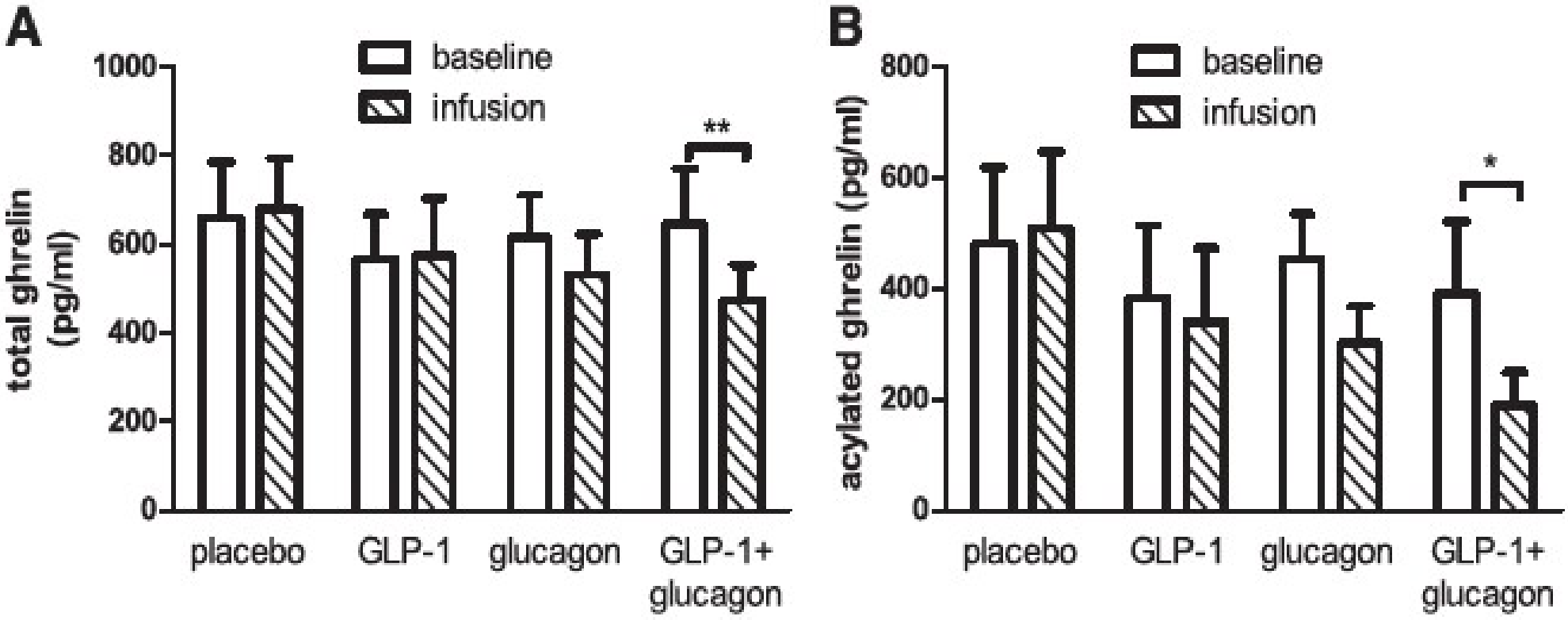
Tan TM, Diabetes 2013

Coadministration of Glucagon-Like Peptide-1 During Glucagon Infusion in Humans Results in Increased Energy Expenditure and Amelioration of Hyperglycemia



Tan TM, Diabetes 2013

Coadministration of Glucagon-Like Peptide-1 During Glucagon Infusion in Humans Results in Increased Energy Expenditure and Amelioration of Hyperglycemia



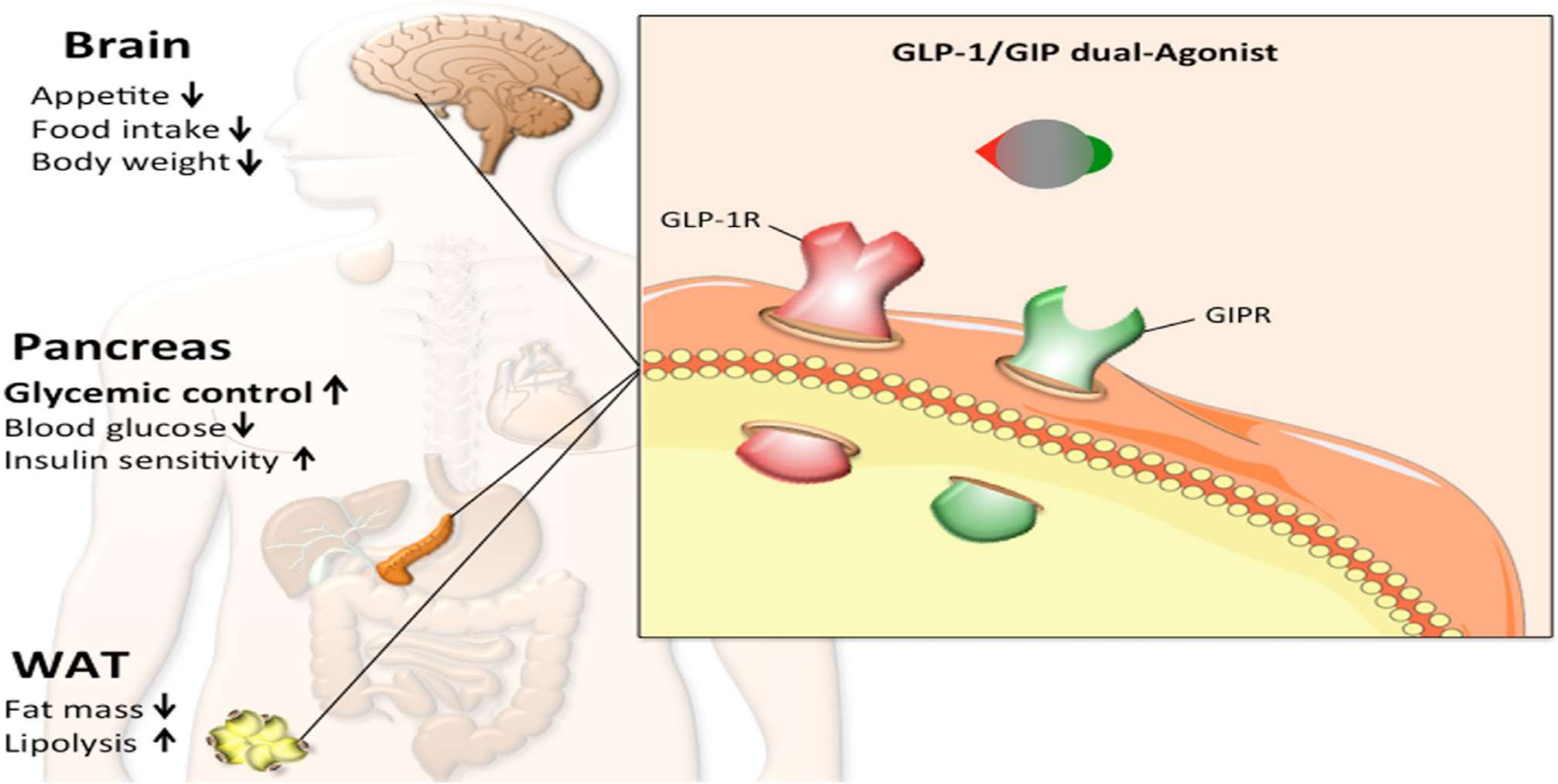
Tan TM, Diabetes 2013

GLP-1/GcgR Dual Analog

SAR425899	Sanofi-Aventis	GLP-1R/GcgR	Phase 1	SC, daily
LY2944876/TT-401	Eli Lilly	GLP-1R/GcgR	Phase 2	SC, weekly
HM12525A	Hanmi Pharmaceuticals	GLP-1R/GcgR	Phase 1	SC, weekly
ZP2929	Zealand	GLP-1R/GcgR	Phase 1	SC, daily
MEDI0382	MedImmune	GLP-1R/GcgR	Phase 1	SC
VPD-107	Spitfire Pharma	GLP-1R/GcgR	Preclinical	SC, weekly
MOD-6031	OPKO Biologics	GLP-1R/GcgR	Phase 1	SC, monthly
Liraglutide + NN9030	Novo Nordisk	GLP-1R + GcgR	Phase 1	SC

Sanchez-Garrido MA, Diabetologia (2017)

Schematic demonstrating the qualitative metabolic effects of GLP-1/GIP dual agonist on systems metabolism,



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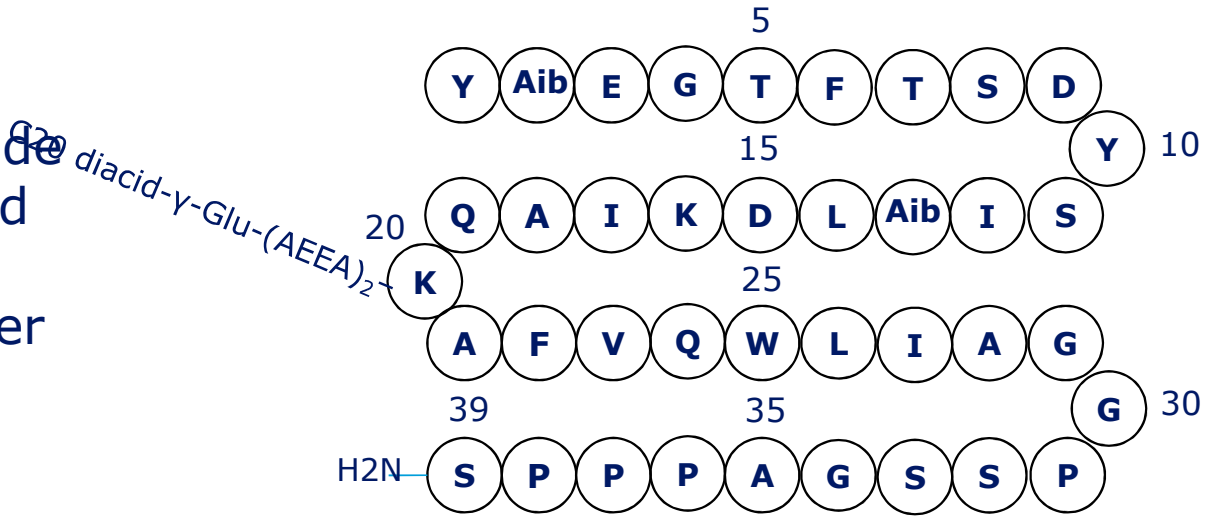
What is LY3298176?

- A 39 amino-acid synthetic peptide (4.8 kDa) with a C20 fatty diacid moiety connected to lysine residue at position 20 via a linker that prolongs the duration of action, allowing once-weekly subcutaneous administration



- Its structure is primarily based on the GIP amino acid sequence with agonist activity at both the GIP and GLP-1 receptors

- Equipotent to native GIP and less potent than native GLP-1

GIP, gastric inhibitory polypeptide; GLP-1, glucagon-like peptide-1.
Coskun T et al. *Mol Metab* 2018. doi: 10.1016/j.molmet.2018.09.009. [Epub ahead of print].

The rationale for developing a GLP-1/GIP dual agonist

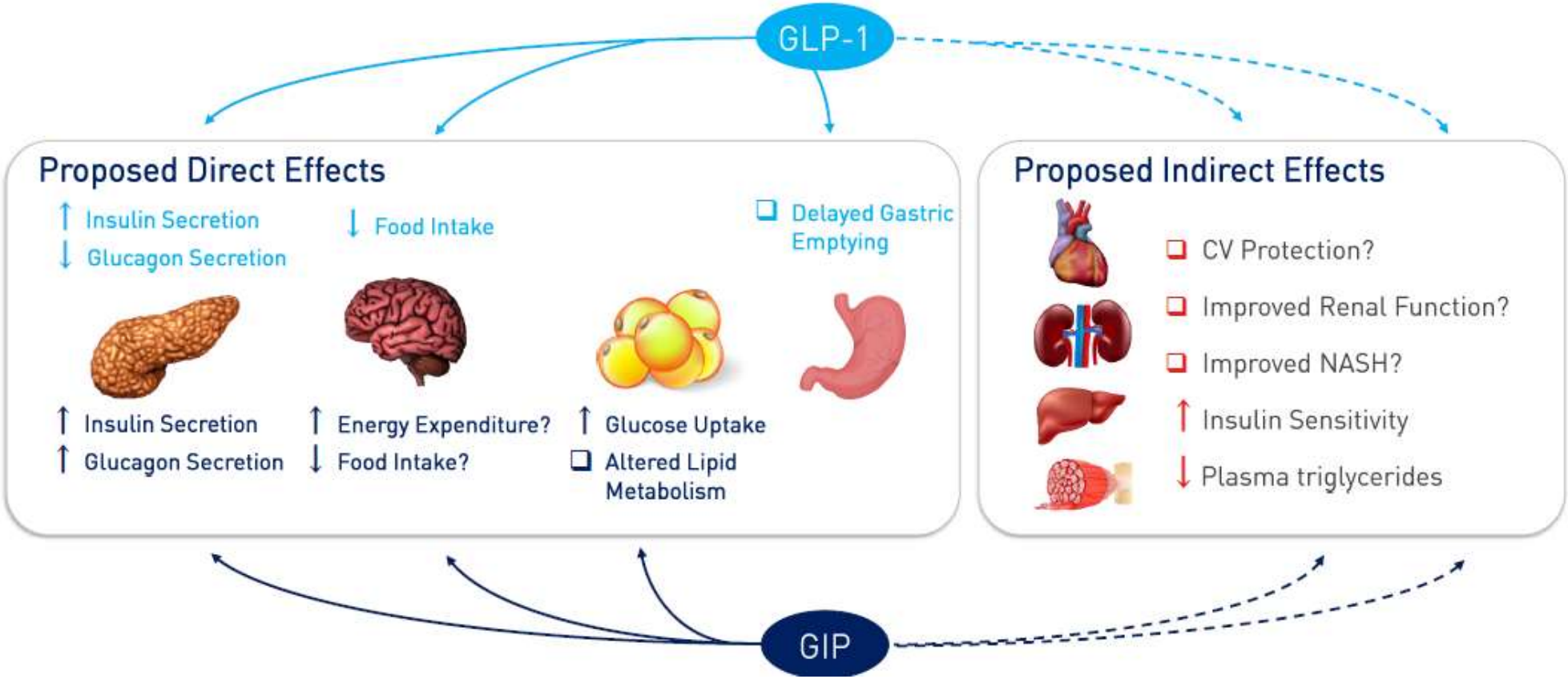
- GLP-1RAs improve glucose control by enhancing glucose-stimulated insulin secretion,[1,2] delaying gastric transit,[3,4] decreasing plasma glucagon levels,[5] and reducing body weight by activating anorexigenic pathways in the brain[6] through activation of GLP-1R signalling

- The GLP-1R is expressed in pancreatic beta cells, cells of the gastric antrum/pylorus, and neurons in the central and peripheral nervous systems[7]

- Despite the broad metabolic benefits of GLP-1RAs, many patients do not achieve glycaemic targets,[8] and weight loss with these agents is less than what can be attained with bariatric surgery[9,10]

GI, gastrointestinal; GLP-1R, glucagon-like receptor; GLP-1RA, glucagon-like receptor agonist. 1. Holst JJ et al. *FEBS Lett* 1987;211:169–74; 2. Kreymann B et al. *Lancet* 1987;2:1300–4; 3. Imeryüz N et al. *Am J Physiol* 1997;273:G920–7; 4. Nauck MA et al. *Am J Physiol* 1997;273:E981–8; 5. Schirra J et al. *J Endocrinol* 1998;156:177–86; 6. Turton MD et al. *Nature* 1996;379:69–72; 7. Richards P et al. *Diabetes* 2014;63:1224–33; 8. Frias JP et al. *Lancet* 2018; http://dx.doi.org/10.1016/S0140-6736(18)32260-8. [Epub ahead of print]. 9. Shah M, Vella A. *Rev Endocr Metab Disord* 2014; 15: 181–7. 10. Kashyap SR et al. *Cleve Clin J Med* 2010; 77: 468–76.

Proposed mode of action of GLP-1/GIP dual agonists



CV, cardiovascular; GIP, gastric inhibitory polypeptide; GLP-1, glucagon-like peptide-1; NASH, non-alcoholic steatohepatitis.
Eli Lilly. Diabetes Update Call. Presented at the 54th Annual Meeting of the European Association for the Study of Diabetes, 1–5 October, 2018, Berlin, Germany.

Efficacy and safety of LY3298176, a novel dual GIP and GLP-1 receptor agonist, in patients with type 2 diabetes: a randomised, placebo-controlled and active comparator-controlled phase 2 trial

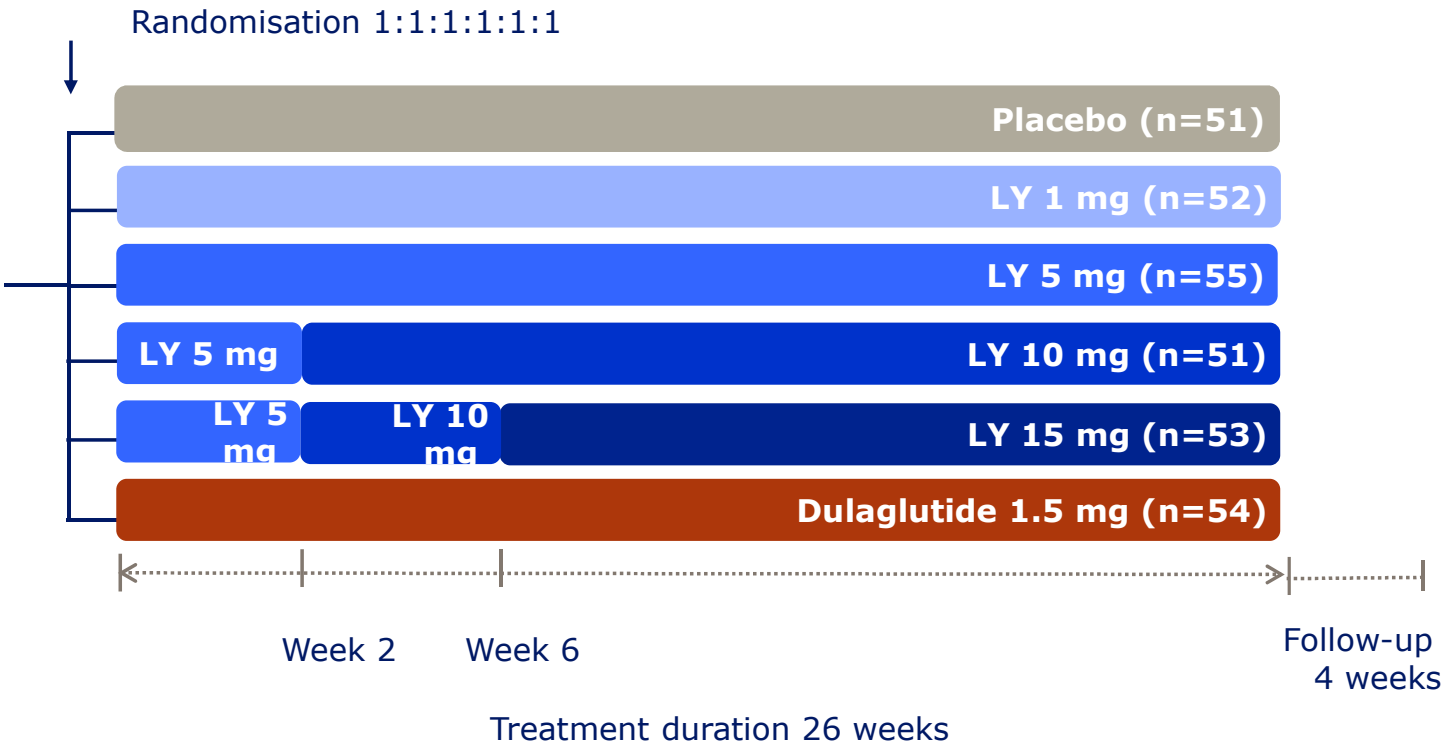
Juan Pablo Frias, Michael A. Nauck, Joanna Van, Mark E. Kutner, Xuewei Cui, Charles Benson, Shweta Urva, Ruth E Gimeno, Zvonko Milicevic, Deborah Robins, Axel Haupt

Frias JP et al. *Lancet* 2018. doi: 10.1016/S0140-6736(18)32260-8

LY3298176 phase 2 trial design

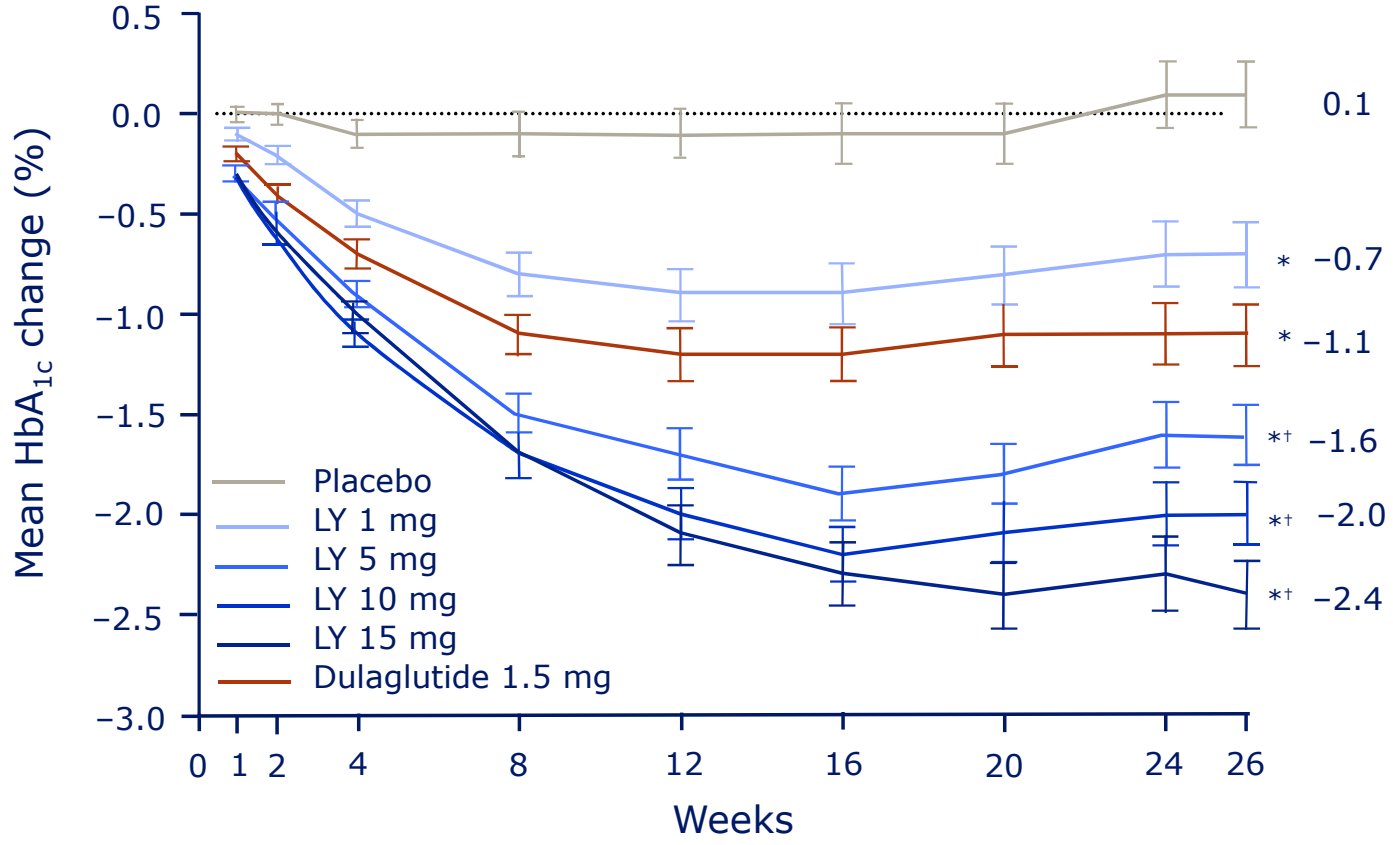
318 subjects with T2D

- Age 18–75 years
- HbA_{1c} 7.0–10.5%
- BMI 23–50 kg/m²
- Diet and exercise ± metformin



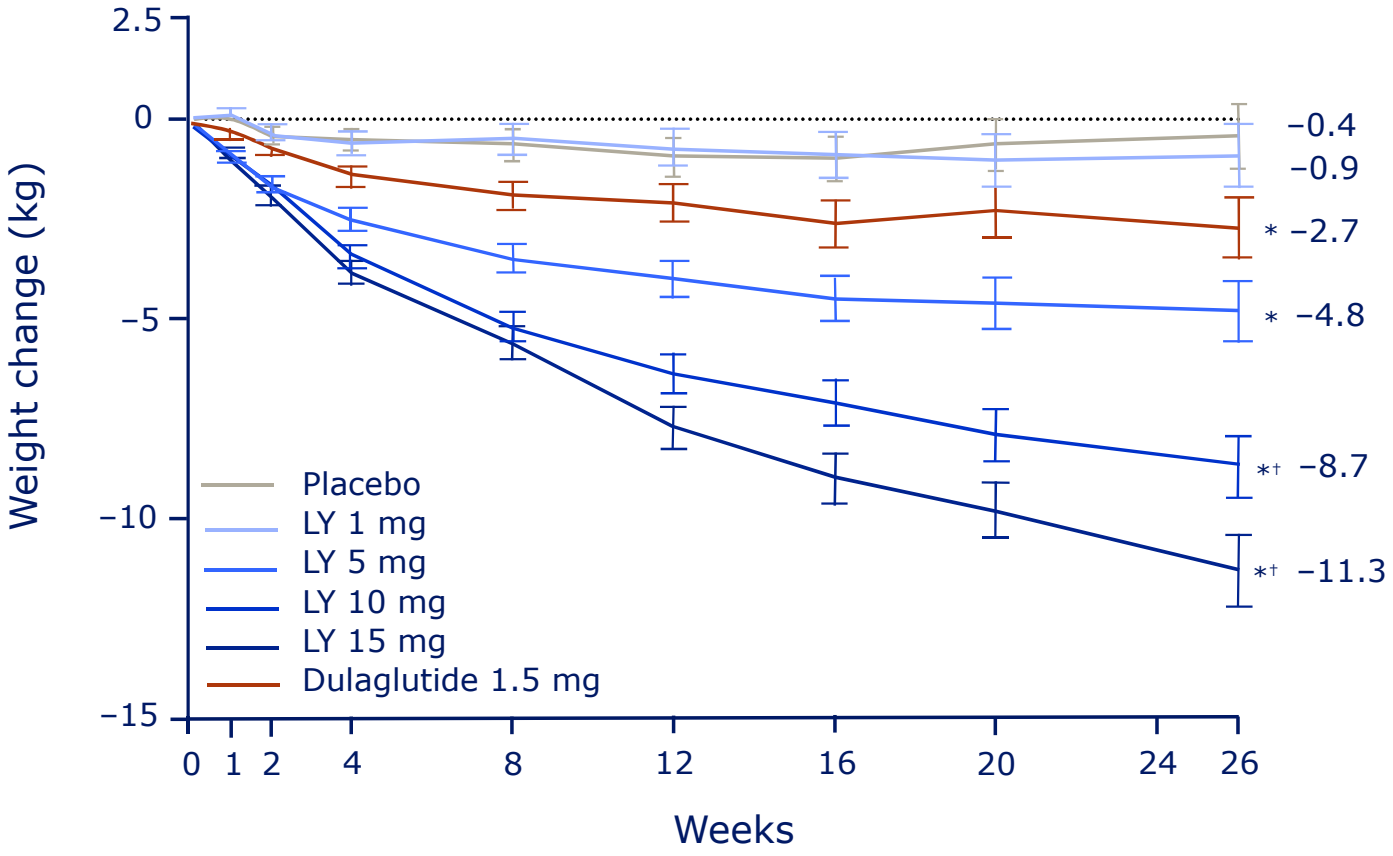
All treatments were administered once-weekly. Stratified randomisation based on: baseline HbA_{1c} (<8.5% or ≥8.5%), metformin use (yes or no), BMI (<30 kg/m² or ≥30 kg/m²).
BMI, body mass index; LY, LY3298176.
Frias JP et al. Lancet 2018. doi: 10.1016/S0140-6736(18)32260-8. [Epub ahead of print].

Change in HbA_{1c} from baseline to week 26



*p<0.05 vs placebo; †p<0.05 vs dulaglutide 1.5 mg. Data presented are LS mean ± SE. MMRM on treatment analysis.
LS, least squares; LY, LY3298176; MMRM, mixed-effect model repeated measure; SE, standard error.
Figure adapted from Frias JP et al. Lancet 2018. doi: 10.1016/S0140-6736(18)32260-8. [Epub ahead of print].

Change in body weight from baseline to week 26



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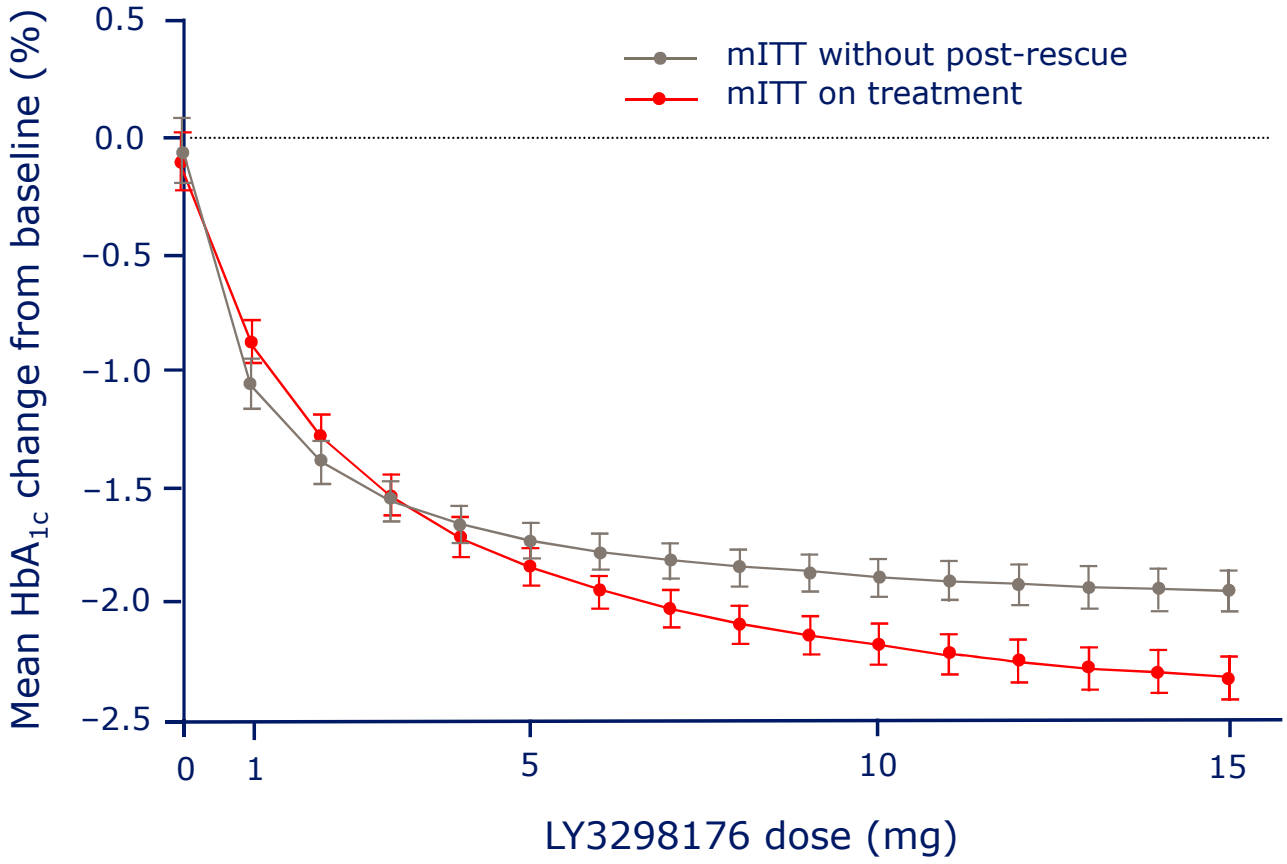
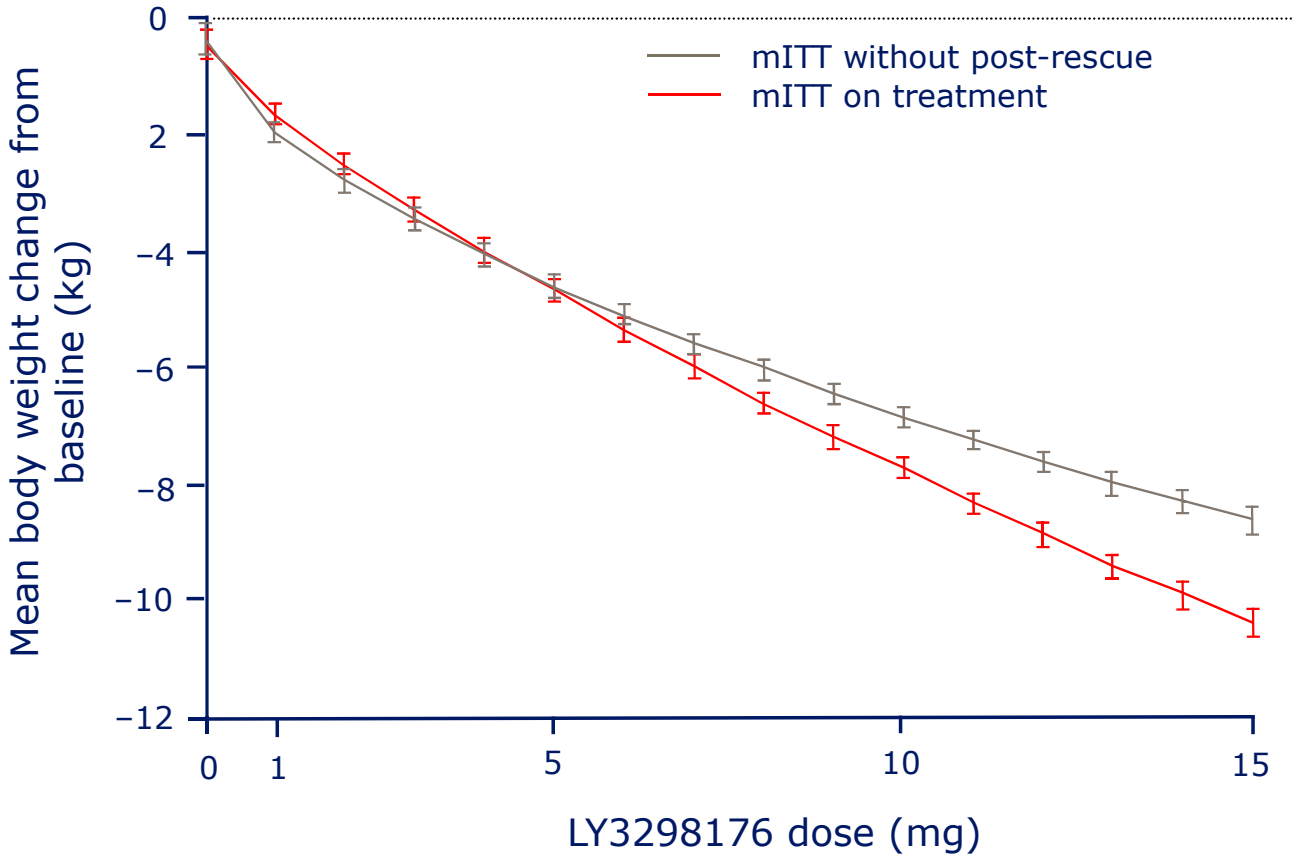
Dose–response modelling for HbA_{1c}



Bayesian dose–response model with interpolated dose levels. Data are posterior mean, with SD error bars.
mITT, modified intention-to-treat; SD, standard deviation.
Frias JP et al. Lancet 2018. doi: 10.1016/S0140-6736(18)32260-8. [Epub ahead of print].

Dose–response modelling for weight



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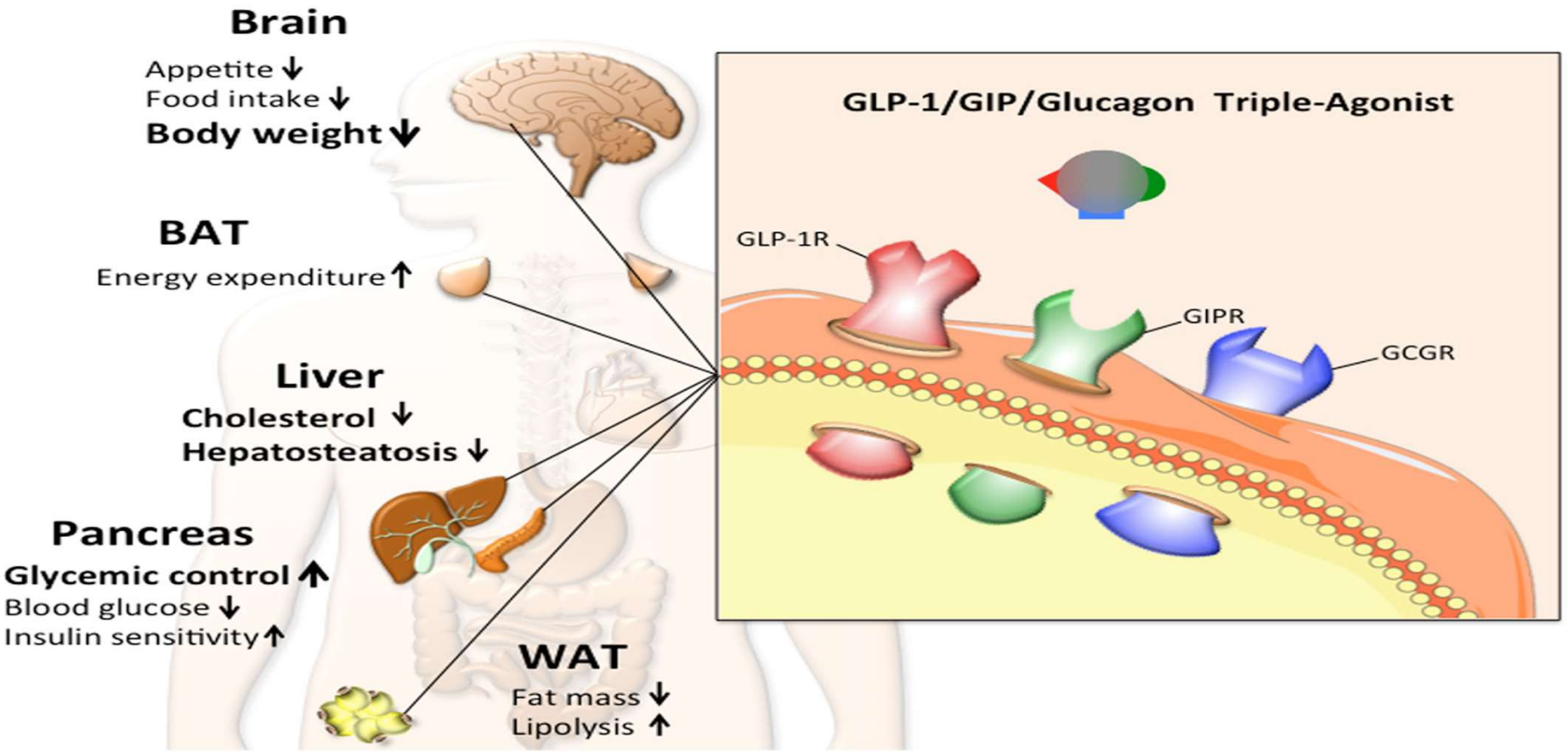
Schematic demonstrating the qualitative metabolic effects of GLP-1/glucagon/GIP triple agonist on systems metabolism



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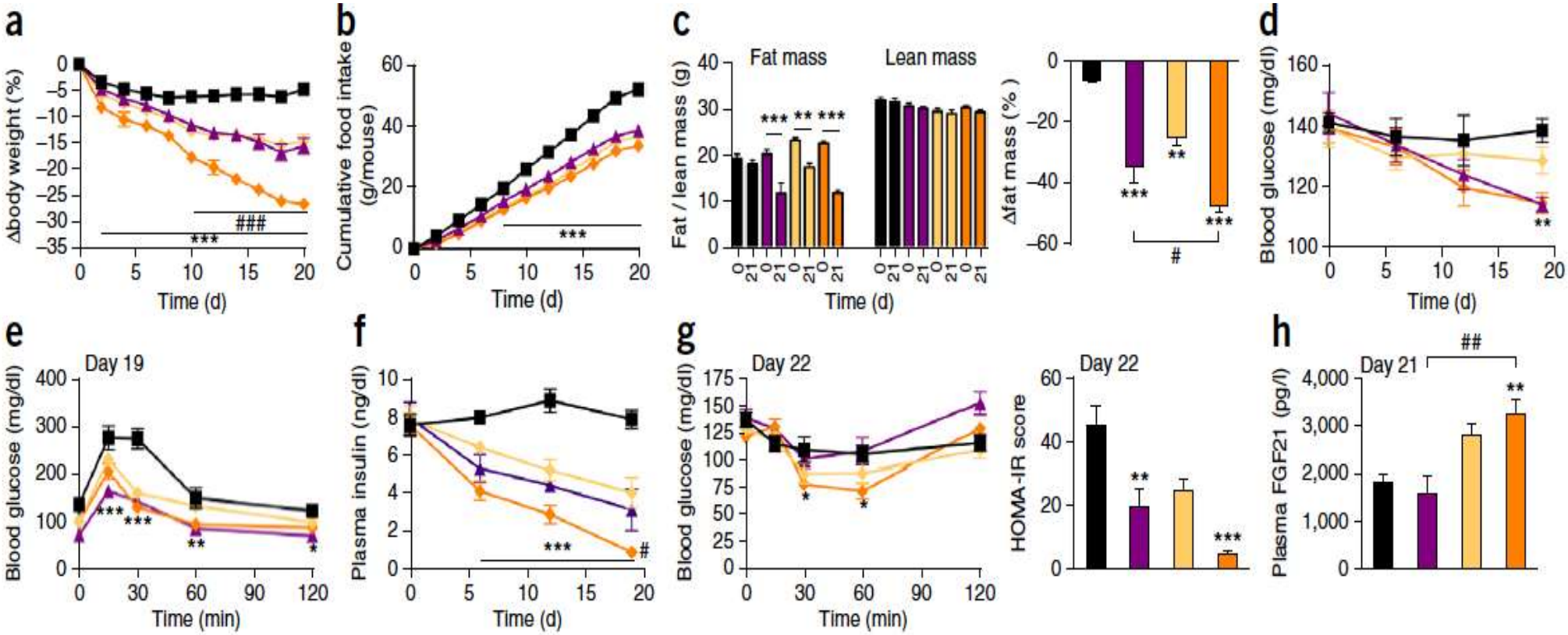
A rationally designed monomeric peptide triagonist corrects obesity and diabetes in rodents



Finan B. nature medicine 2014

Thank You