Incrétinomimétiques et Diabète de type 2 :

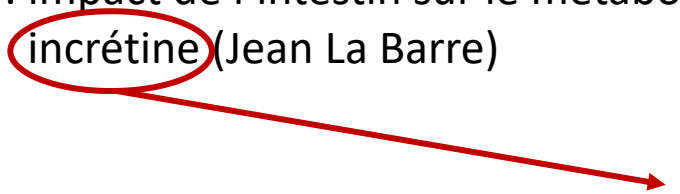
D’un traitement alternatif à un traitement incontournable ?

Dr Luc Derdelinckx

Clinique Saint-Luc
Bouge

1902 : rôle endocrine de l'intestin (sécrétine)

1932 : impact de l'intestin sur le métabolisme glucosé
incrétine (Jean La Barre)



Intestine Se**cret**ion Insul**in**

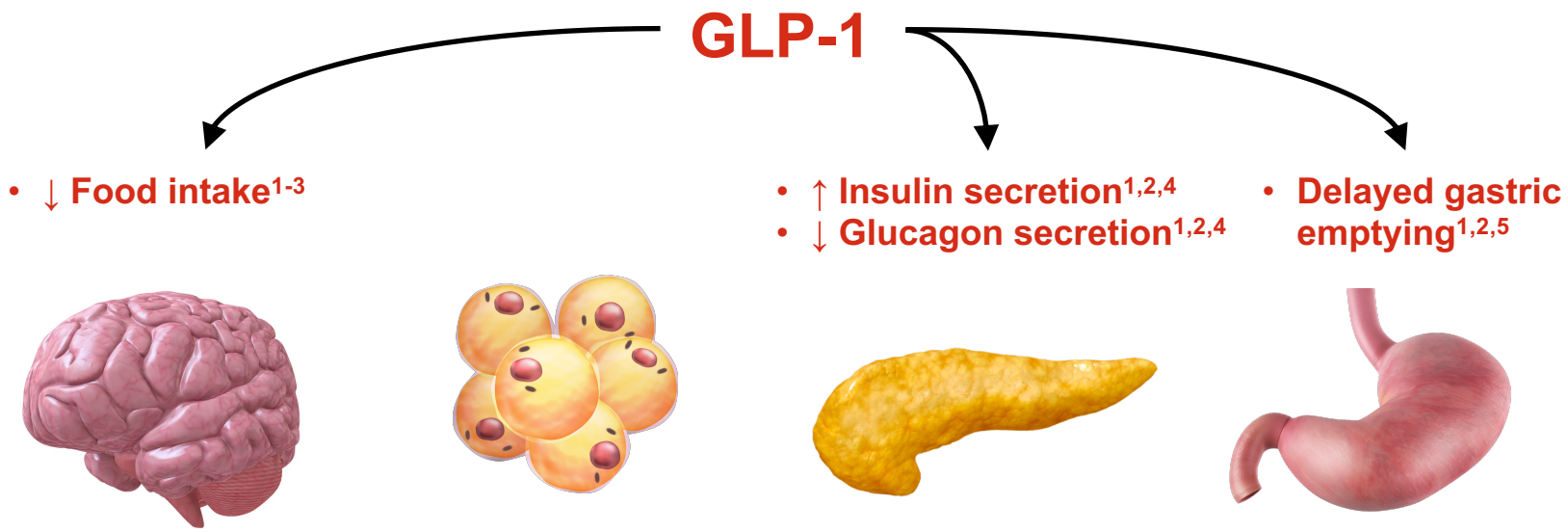
Hormones intestinales dont la sécrétion est stimulée par la prise alimentaire de glucides et qui potentialisent l'effet du glucose sur la sécrétion d'insuline

1960 : dosages RIA : effet incrétine (réponse insulinique amplifiée par la prise orale de glucose)

1980 : identification des peptides intestinaux (GIP, GLP1)

2000… : exploitation thérapeutique de l'effet incrétine

- Le GLP-1 a des effets directs sur le SNC, les ilôts de Langerhans et l'estomac[1-5]

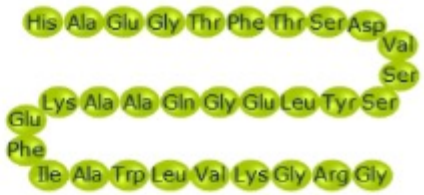


CNS = central nervous system; GIP = glucose-dependent insulinotropic polypeptide; GIPR = glucose-dependent insulinotropic polypeptide receptor; GLP-1 = glucagon-like peptide 1; GLP-1R = glucagon-like peptide 1 receptor.

1. Aronoff SL, et al. *Diabetes Spectr*. 2004;17(3):183-190. 2. Drucker JD, Nauck MA. *Lancet*. 2006;368(9548):1696-1705. 3. Szayna M, et al. *Endocrinology*. 2000;141(6):1936-1941. 4. Kreymann B, et al. *Lancet*. 1987;330(8571):1300-1304. 5. Willms B, et al. *J Clin Endocr Metab*. 1996;81(1):327-332. 6. Samms RJ, et al. *Trends Endocrin Met*. 2020;31(6):410-421. 7. Usdin TB, et al. *Endocrinology*. 1993;133(6):2861-2870. 8. Kaplan AM, Vigna SR. *Peptides*. 1994;15(2):297-302. 9. Mohammad S, et al. *J Biol Chem*. 2011;286(50):43062-43070. 10. Starich GH, et al. *Am J Physiol-Endoc M*. 1985;249(6):E603-E607. 11. Dupre J, et al. *J Clin Endocr Metab*. 1973;37(5):826-828.

Les analogues GLP1

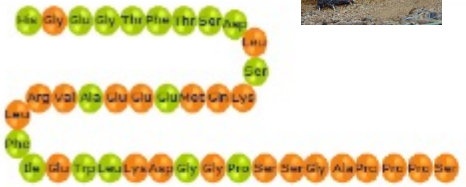
GLP-1 humain natif



GLP-1RA

- Traitements à base de GLP-1 humain
  - **Hebdomadaire**
    - dulaglutide (59,67 kDa) — SC
    - sémaglutide (4,11 kDa) — SC
  - **Une fois par jour**
    - liraglutide (3,75 kDa) — SC
    - sémaglutide (4,11 kDa) — Oral
- Traitements à base d'exendine
  - **Hebdomadaire**
    - exénatide LP (4,19 kDa) — SC
  - **Une fois/deux fois par jour**
    - exénatide (4,19 kDa) — SC
    - lixisénatide (4,86 kDa) — SC

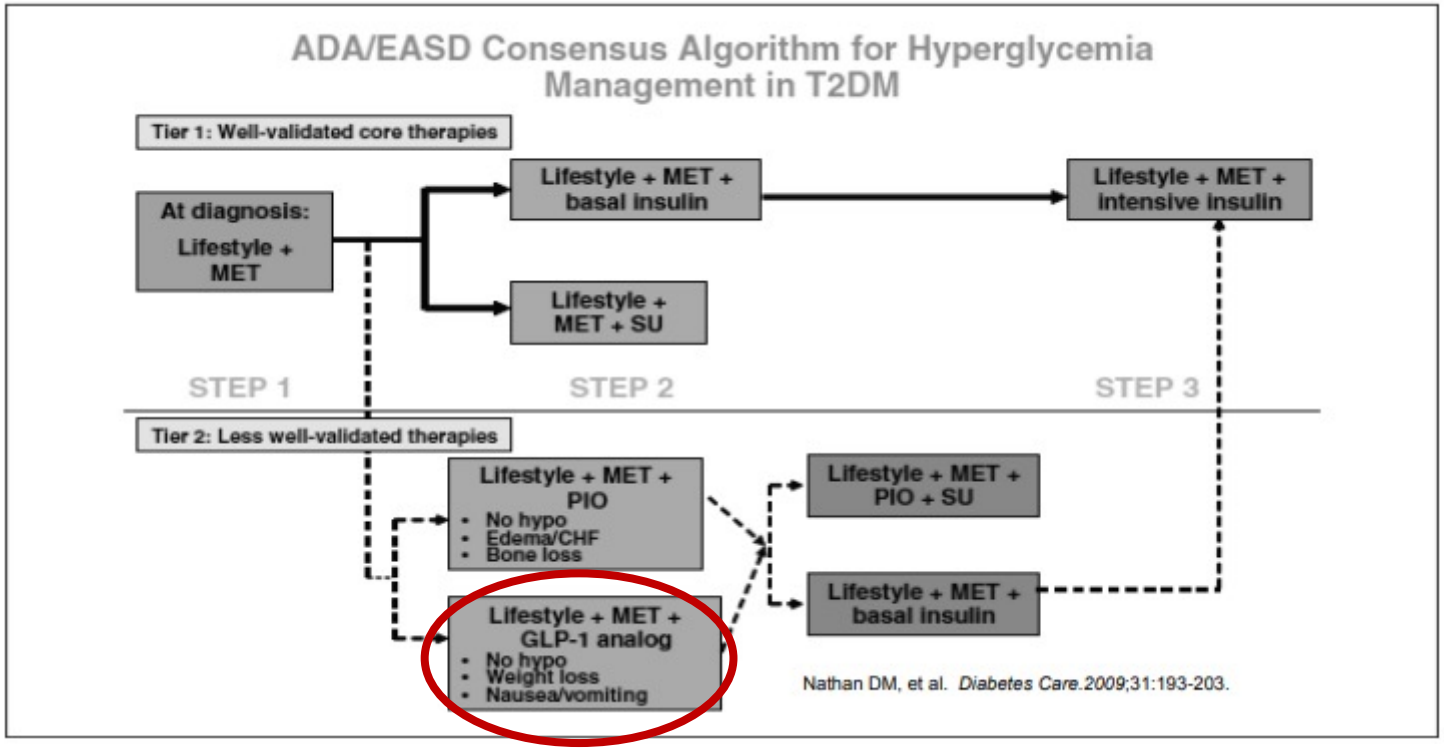
Exendine-4



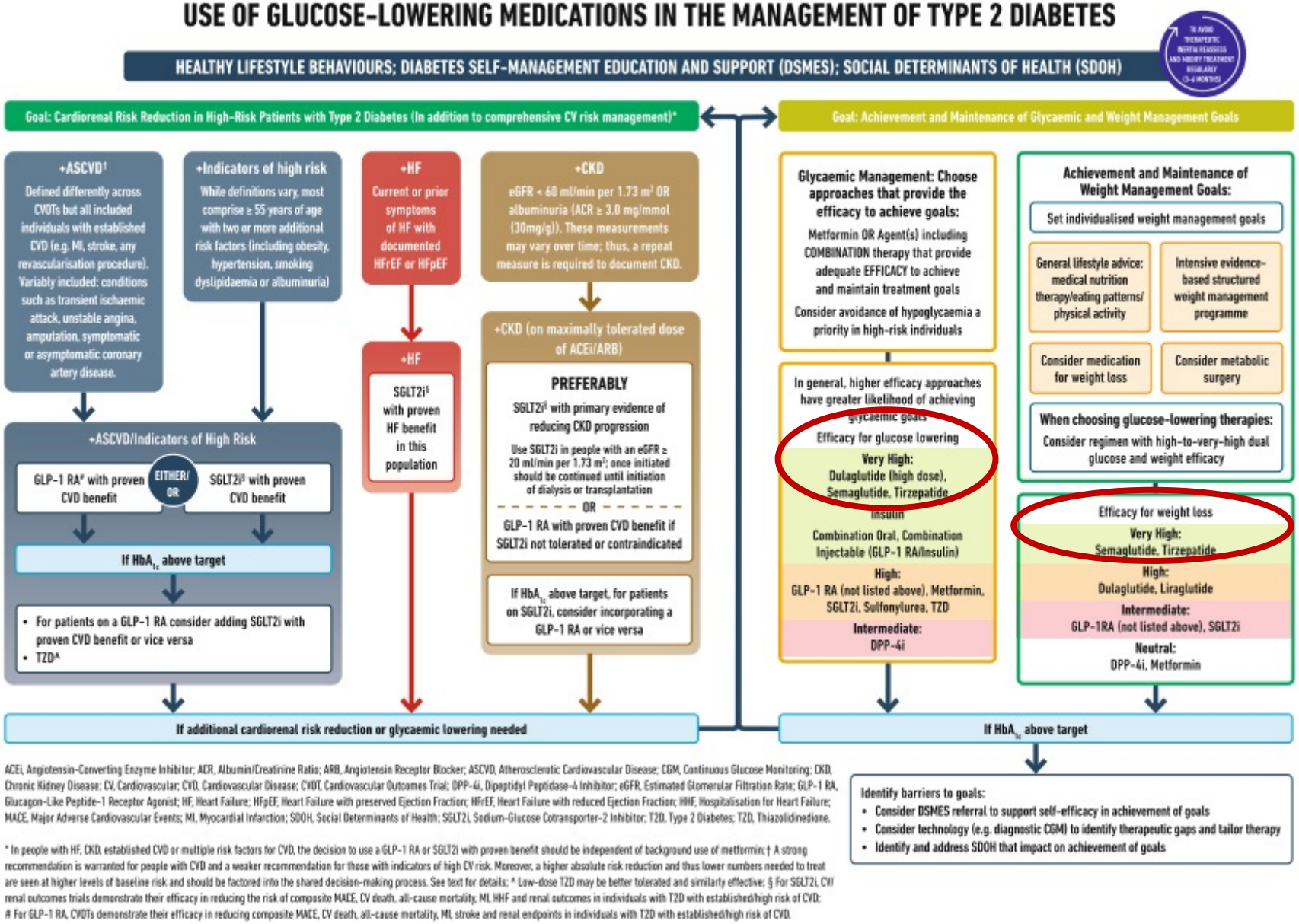
ER, extended release; GLP-1, glucagon-like peptide-1; GLP-1RA, glucagon-like peptide-1 receptor agonist; s.c., subcutaneous.

1. Wick A, Newlin K. *J Am Acad Nurse Pract* 2009;21:623–30; 2. White J. *J Am Pharm Assoc* 2009;49(Suppl. 1):S30–40;
3. Madsbad S, et al. *Diabetes Obes Metab* 2011;13:394–407.

ADA EASD 2009



ADA EASD 2022

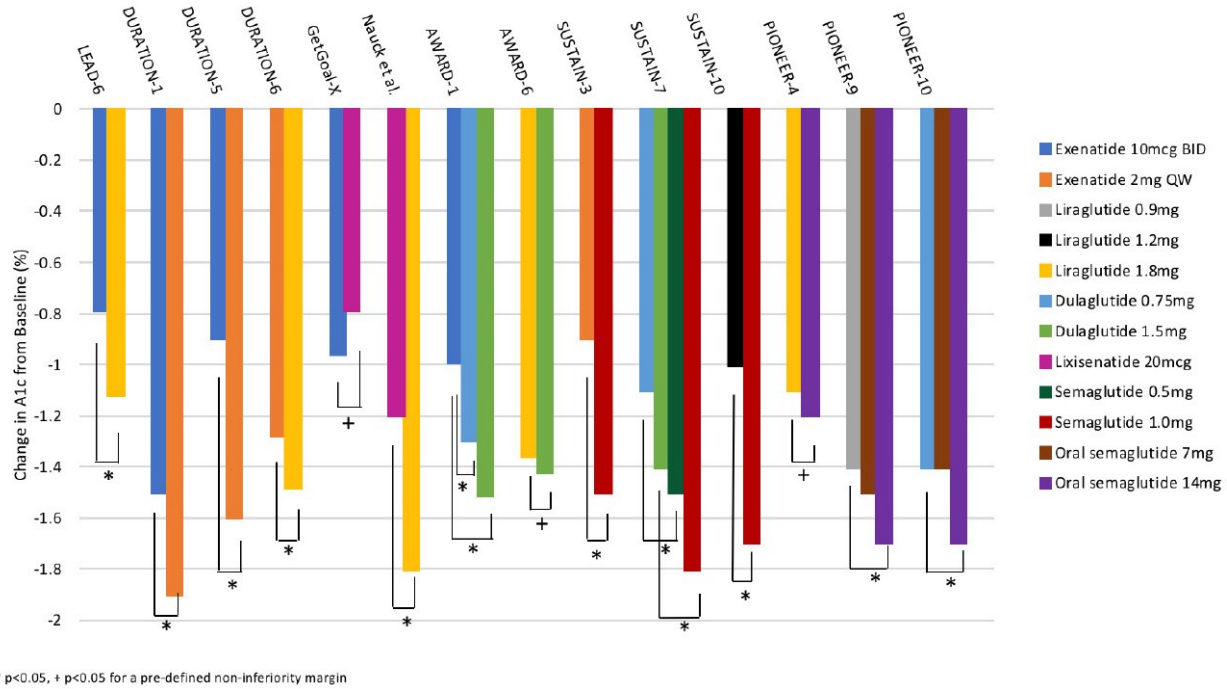


ACEi, Angiotensin-Converting Enzyme Inhibitor; ACR, Albumin/Creatinine Ratio; ARB, Angiotensin Receptor Blocker; ASCVD, Atherosclerotic Cardiovascular Disease; CGM, Continuous Glucose Monitoring; CKD, Chronic Kidney Disease; CV, Cardiovascular; CVD, Cardiovascular Disease; CVOT, Cardiovascular Outcomes 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.

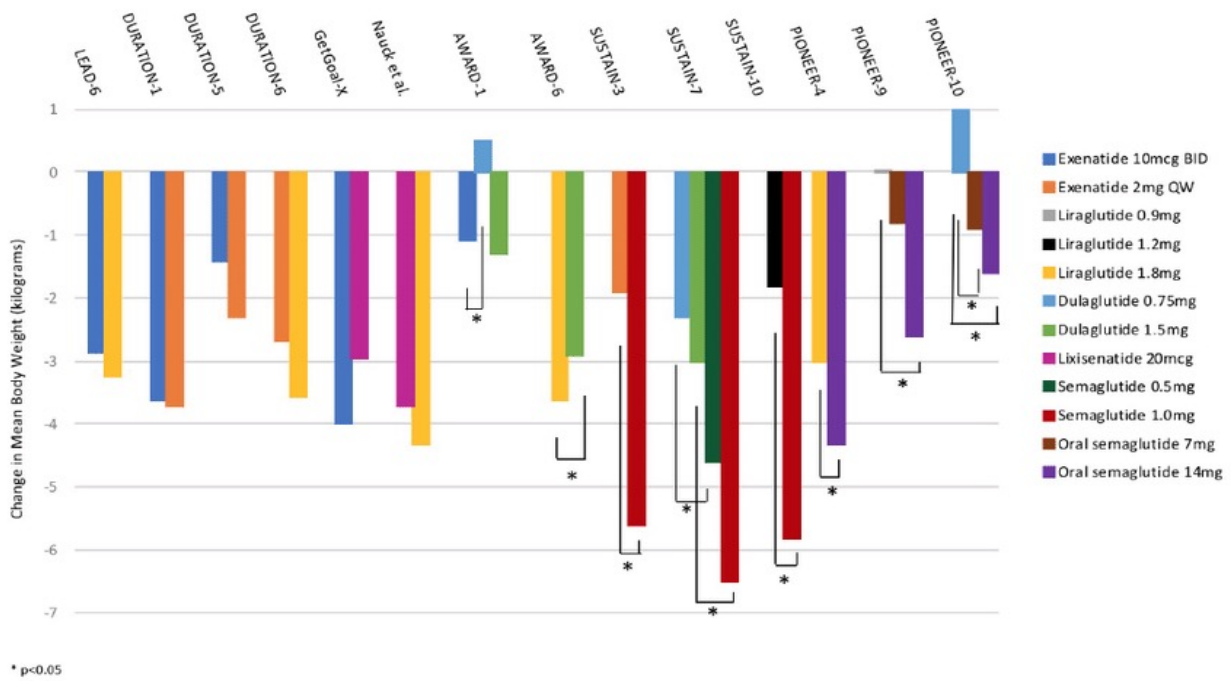
Les analogues GLP1:

Impact sur l' HbA1C



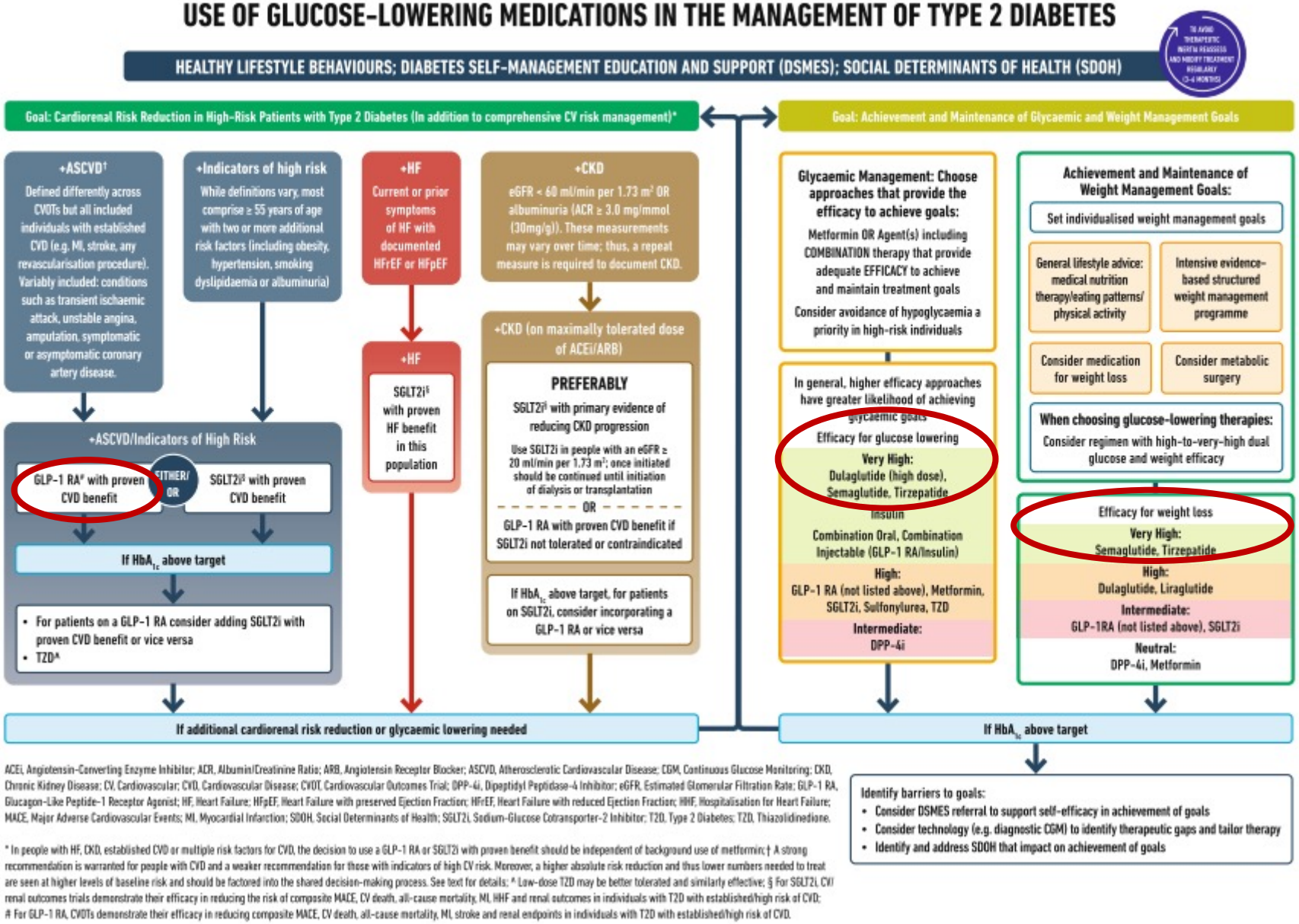
* p<0.05, + p<0.05 for a pre-defined non-inferiority margin

Impact sur le poids



* p<0.05

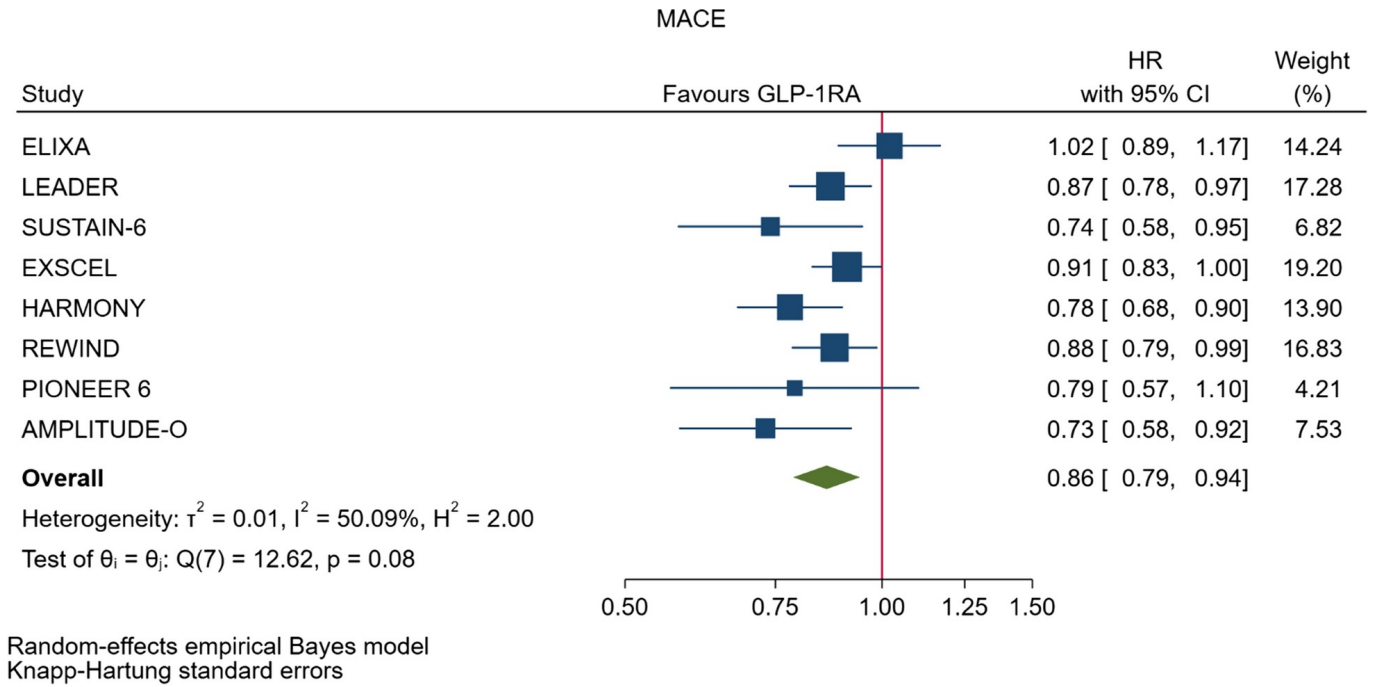
ADA EASD 2022



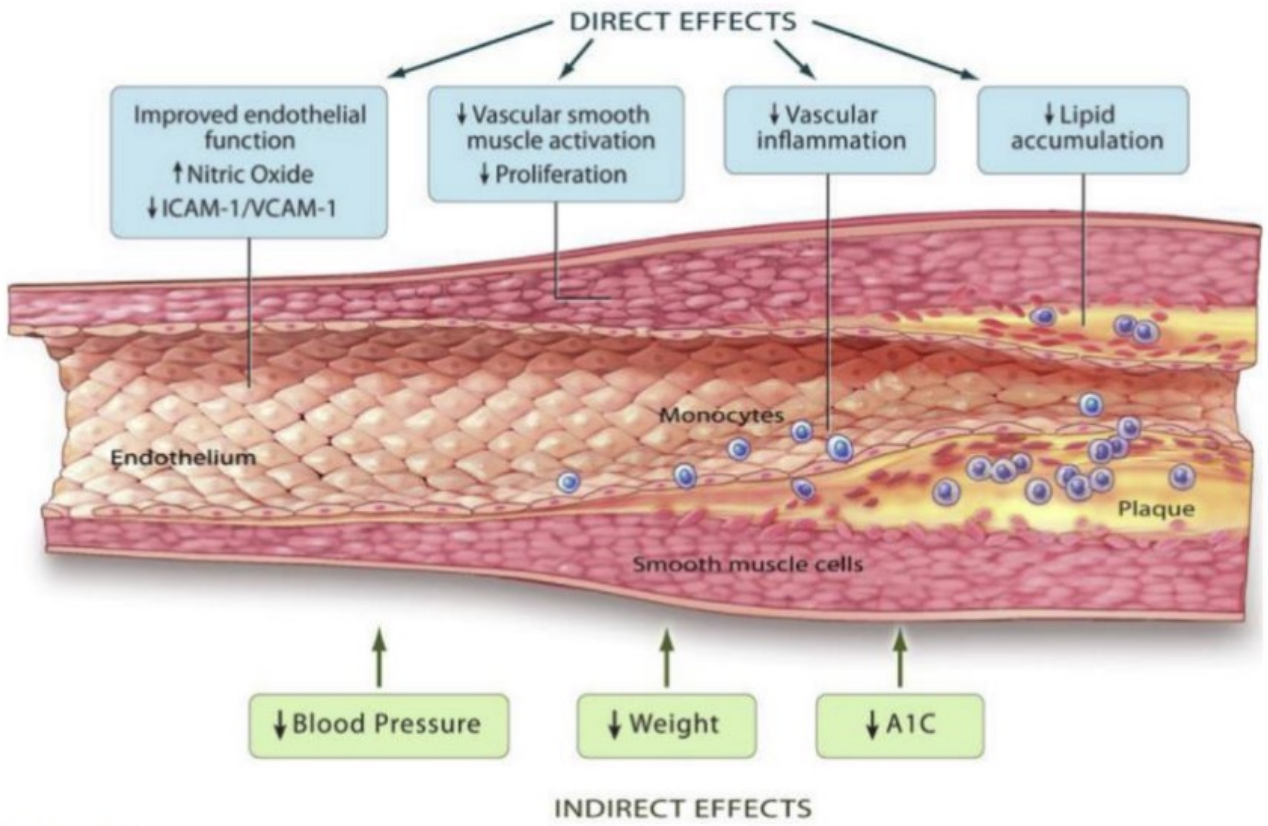
ACEi, Angiotensin-Converting Enzyme Inhibitor; ACR, Albumin/Creatinine Ratio; ARB, Angiotensin Receptor Blocker; ASCVD, Atherosclerotic Cardiovascular Disease; CGM, Continuous Glucose Monitoring; CKD, Chronic Kidney Disease; CV, Cardiovascular; CVD, Cardiovascular Disease; CVOT, Cardiovascular Outcomes 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.

Analogues GLP1 et protection cardio-vasculaire

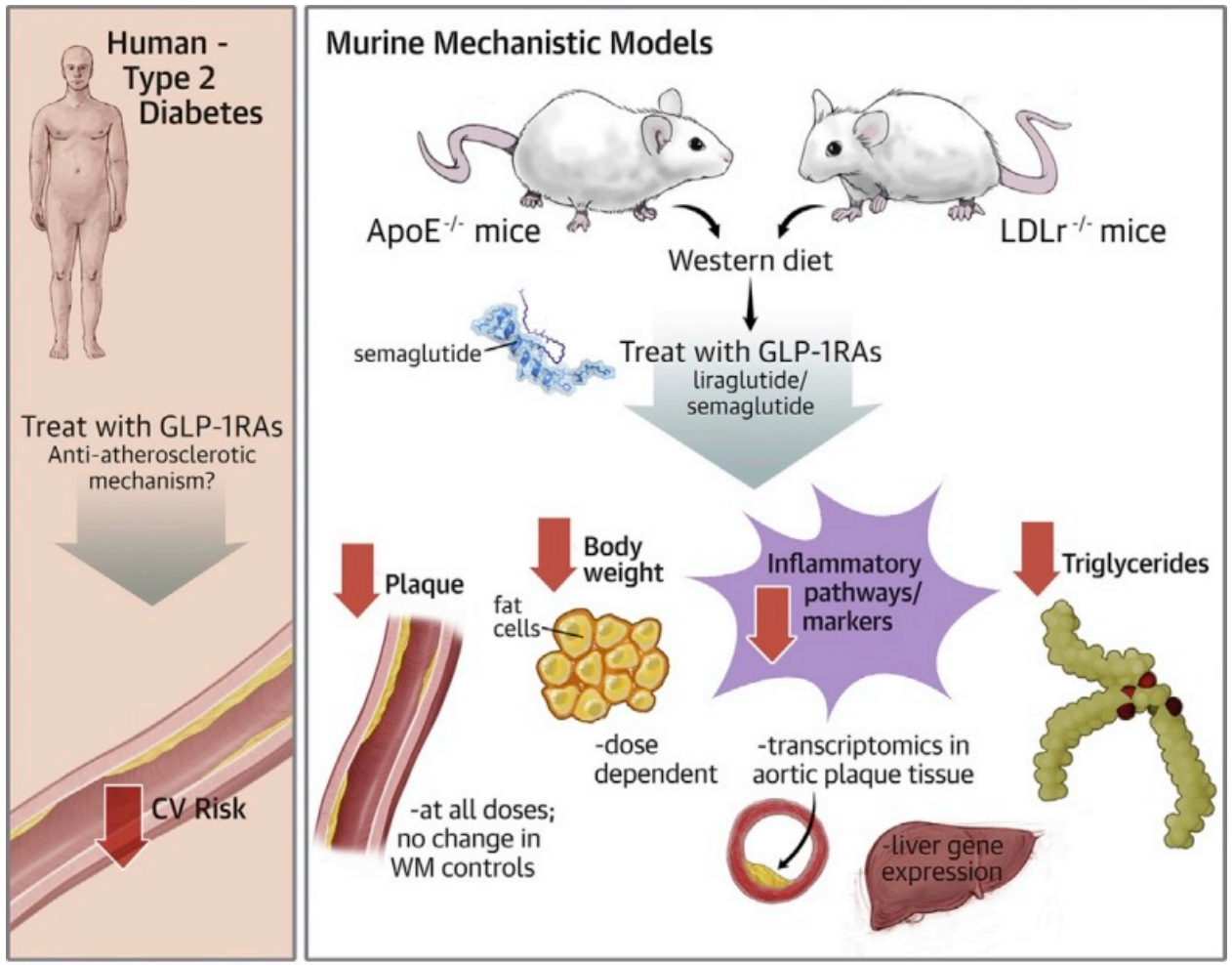


Analogues GLP1 et protection cardio-vasculaire : Mécanismes directs et indirects



A. Sharma, S. Verma / Can J Diabetes 44 (2020) 93e10295
A1C,glycated hemoglobin;ICAM-1, intercellular adhesionmolecule 1;VCAM-1, vascular cell adhesion molecule 1

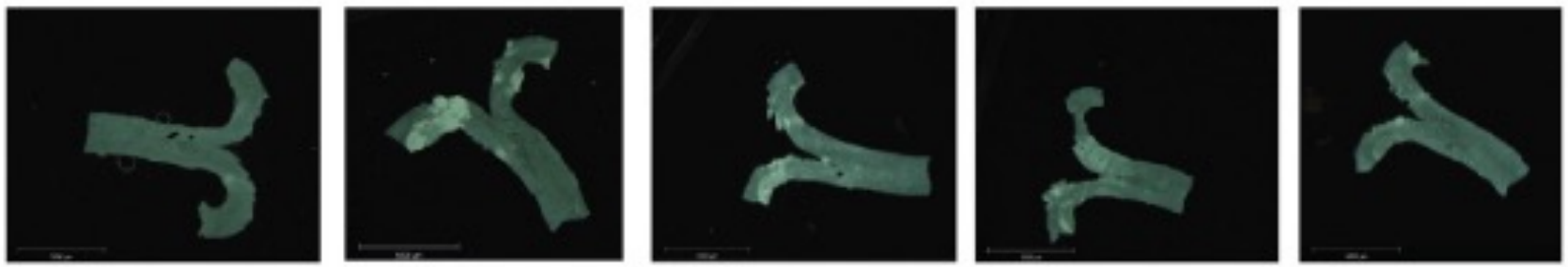
Analogues GLP1 et protection cardio-vasculaire



Rakipovski, G. et al. J Am Coll Cardiol Basic Trans Science. 2018;3(6):844-57.

Analogues GLP1 et protection cardio-vasculaire

E Representative *En Face* Images

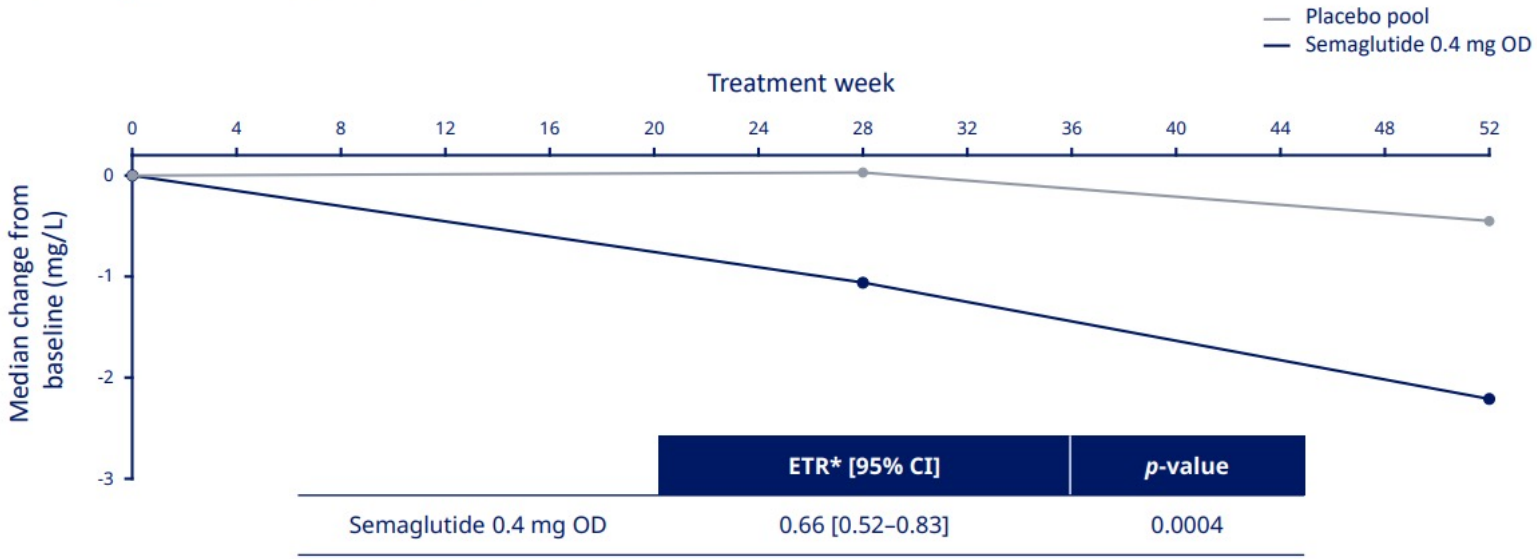


Analogues GLP1 et protection cardio-vasculaire

Novo Nordisk®

Semaglutide reduces inflammatory markers

Change from baseline in hsCRP

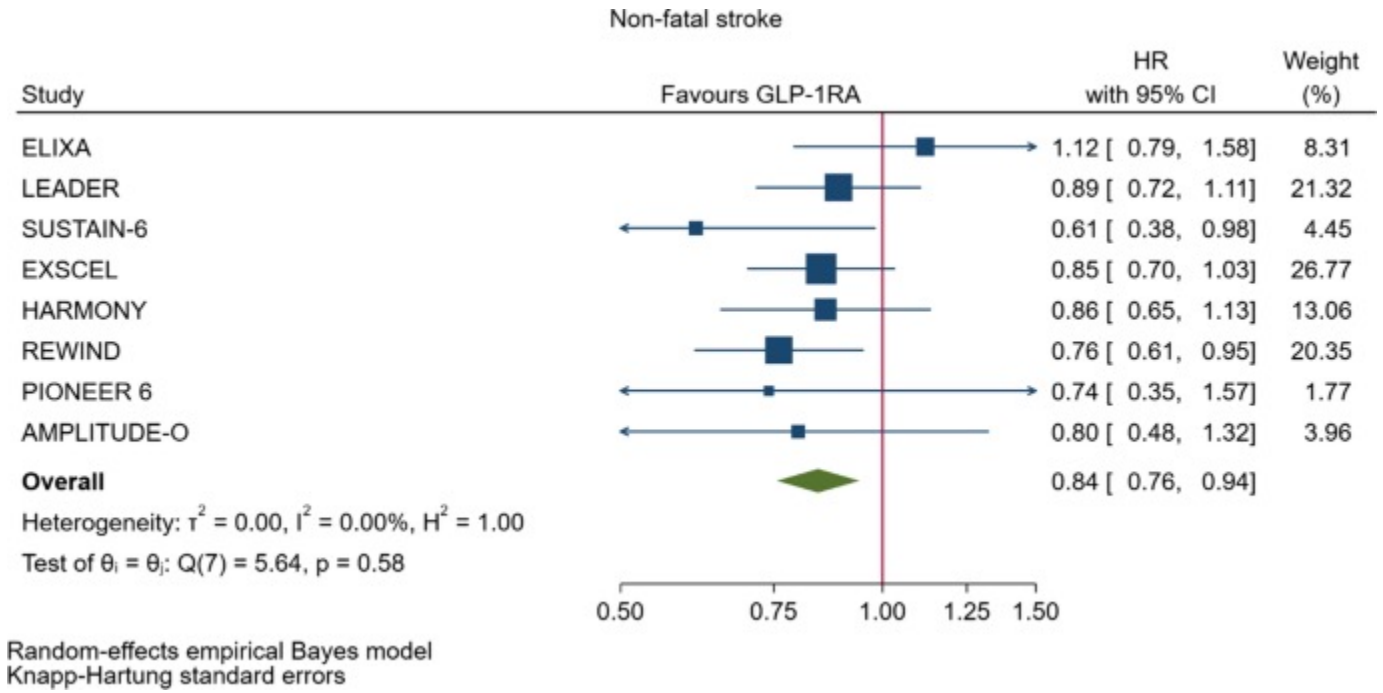


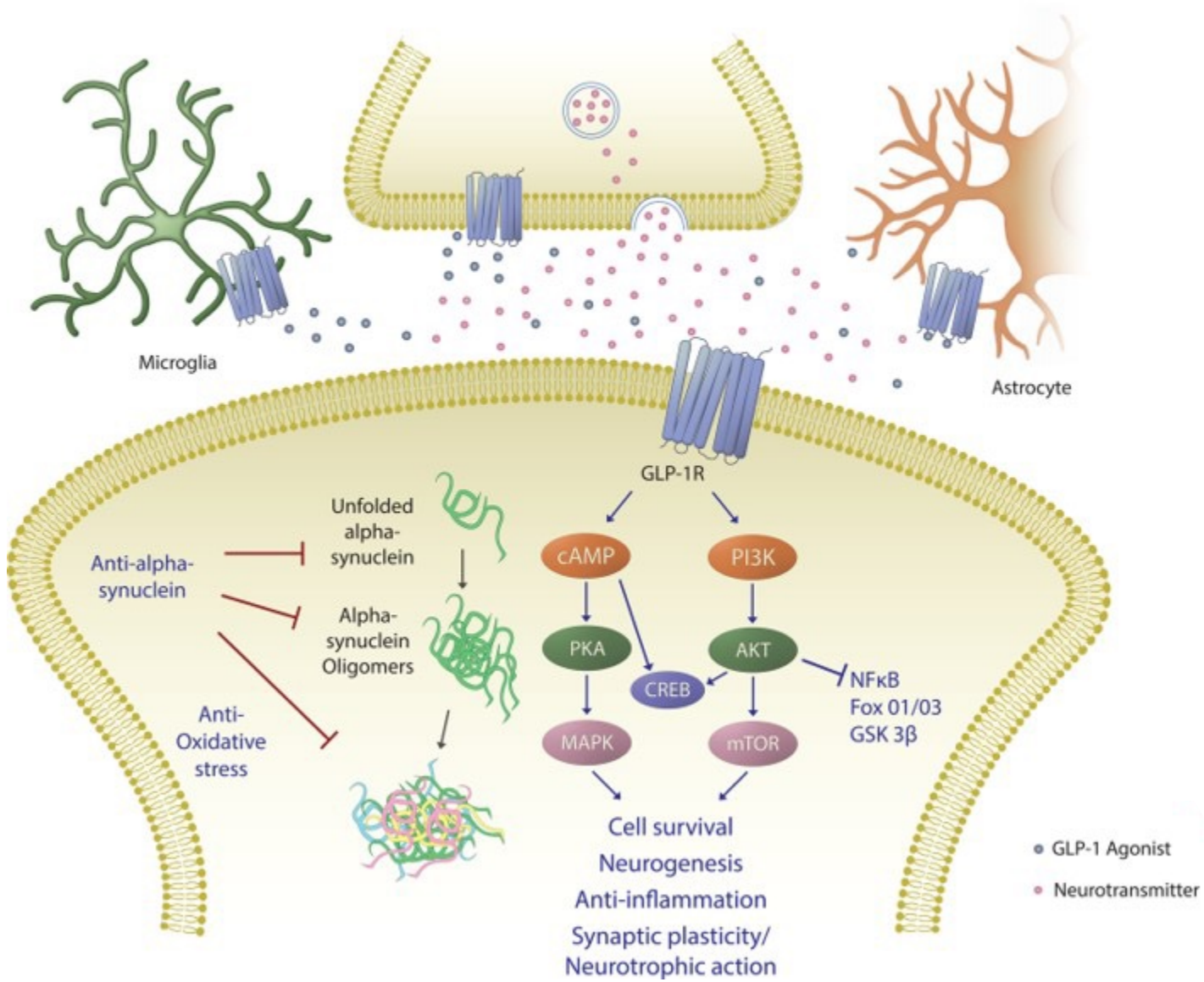
	ETR* [95% CI]	*p*-value
Semaglutide 0.4 mg OD	0.66 [0.52–0.83]	0.0004

Data are from a phase 2 weight management study. Observed data.
**Semaglutide 0.4 mg compared with placebo pool.*
CI, confidence interval; ETR, estimated treatment ratio; hsCRP, high-sensitivity C-reactive protein; OD, once-daily.
Newsome PN et al. Poster presented at The Liver Meeting® 2018; Poster 0749;9–13 November 2018; San Francisco, USA; Novo Nordisk. Data on file.

Analogues GLP1 et protection cardio-vasculaire :

Effet spécifique sur le risque d'AVC non fatal




Microglia
Astrocyte
GLP-1R
Unfolded alpha-synuclein
Alpha-synuclein Oligomers
Anti-alpha-synuclein
Anti-Oxidative stress
cAMP
PI3K
PKA
AKT
CREB
MAPK
mTOR
NFκB
Fox 01/03
GSK 3β
Cell survival
Neurogenesis
Anti-inflammation
Synaptic plasticity/
Neurotrophic action
GLP-1 Agonist
Neurotransmitter

1902 : rôle endocrine de l'intestin (sécrétine)

1932 : impact de l'intestin sur le métabolisme glucosé
incrétine (Jean La Barre)

Intestine Se**cret**ion Insul**in**

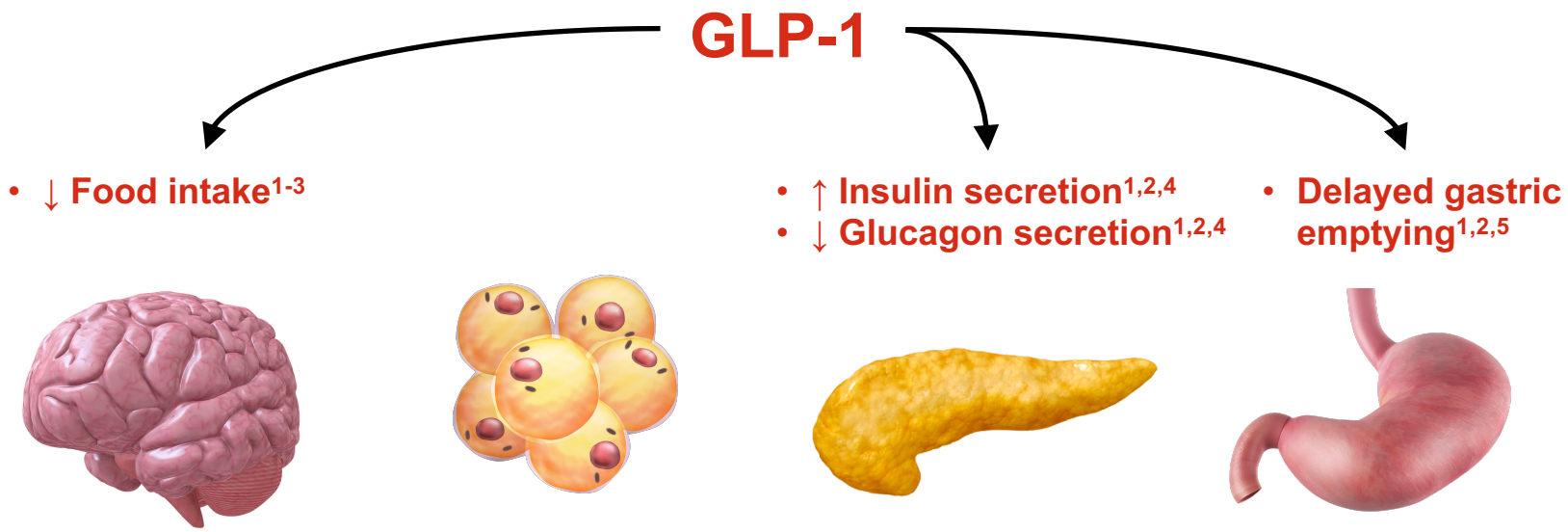
Hormones intestinales dont la sécrétion est stimulée par la prise alimentaire de glucides et qui potentialisent l'effet du glucose sur la sécrétion d'insuline

1960 : dosages RIA : effet incrétine (réponse insulinique amplifiée par la prise orale de glucose)

1980 : identification des peptides intestinaux (GIP, GLP1)

2000… : exploitation thérapeutique de l'effet incrétine

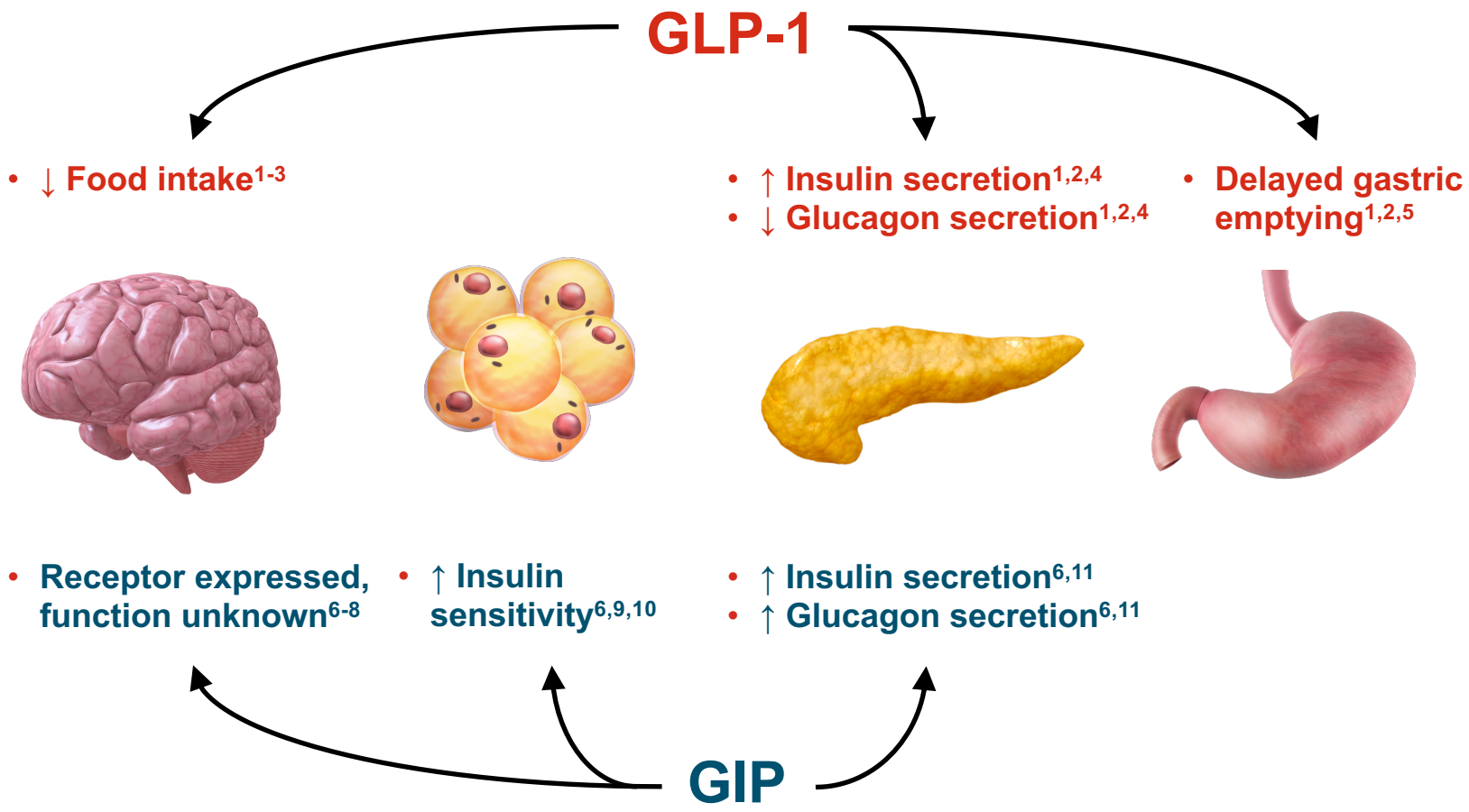
- Le GLP-1 a des effets directs sur le SNC, les ilôts de Langerhans et l'estomac[1-5]



CNS = central nervous system; GIP = glucose-dependent insulinotropic polypeptide; GIPR = glucose-dependent insulinotropic polypeptide receptor; GLP-1 = glucagon-like peptide 1; GLP-1R = glucagon-like peptide 1 receptor.

1. Aronoff SL, et al. *Diabetes Spectr*. 2004;17(3):183-190. 2. Drucker JD, Nauck MA. *Lancet*. 2006;368(9548):1696-1705. 3. Szayna M, et al. *Endocrinology*. 2000;141(6):1936-1941. 4. Kreymann B, et al. *Lancet*. 1987;330(8571):1300-1304. 5. Willms B, et al. *J Clin Endocr Metab*. 1996;81(1):327-332. 6. Samms RJ, et al. *Trends Endocrin Met*. 2020;31(6):410-421. 7. Usdin TB, et al. *Endocrinology*. 1993;133(6):2861-2870. 8. Kaplan AM, Vigna SR. *Peptides*. 1994;15(2):297-302. 9. Mohammad S, et al. *J Biol Chem*. 2011;286(50):43062-43070. 10. Starich GH, et al. *Am J Physiol-Endoc M*. 1985;249(6):E603-E607. 11. Dupre J, et al. *J Clin Endocr Metab*. 1973;37(5):826-828.

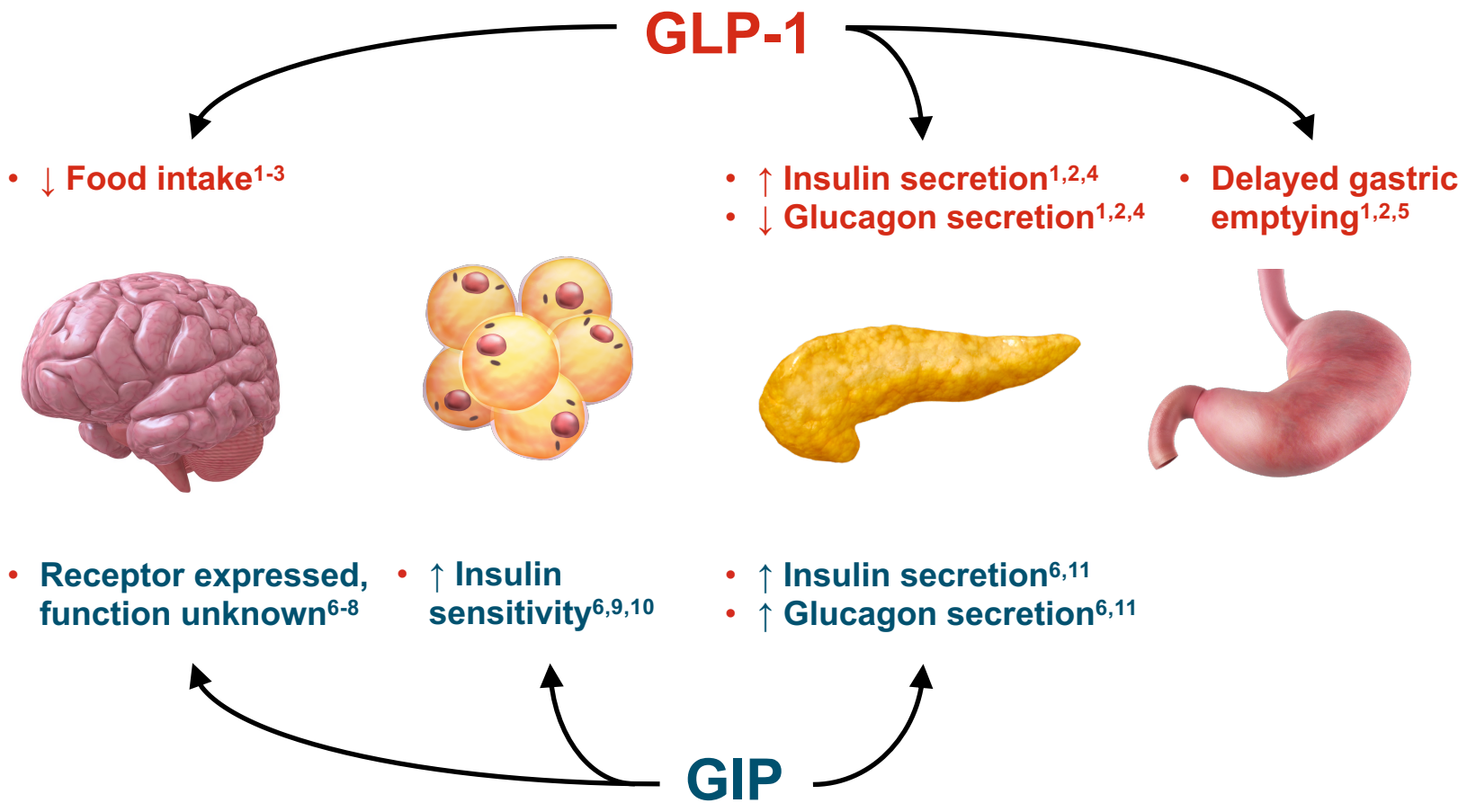
- Le GLP-1 a des effets directs sur le SNC, les ilôts de Langerhans et l'estomac[1-5]
- Le GIP a des effets directs sur le SNC (?), le tissu adipeux et les ilôts de Langerhans[6-11]



CNS = central nervous system; GIP = glucose-dependent insulinotropic polypeptide; GIPR = glucose-dependent insulinotropic polypeptide receptor; GLP-1 = glucagon-like peptide 1; GLP-1R = glucagon-like peptide 1 receptor.

1. Aronoff SL, et al. *Diabetes Spectr*. 2004;17(3):183-190. 2. Drucker JD, Nauck MA. *Lancet*. 2006;368(9548):1696-1705. 3. Szayna M, et al. *Endocrinology*. 2000;141(6):1936-1941. 4. Kreymann B, et al. *Lancet*. 1987;330(8571):1300-1304. 5. Willms B, et al. *J Clin Endocr Metab*. 1996;81(1):327-332. 6. Samms RJ, et al. *Trends Endocrin Met*. 2020;31(6):410-421. 7. Usdin TB, et al. *Endocrinology*. 1993;133(6):2861-2870. 8. Kaplan AM, Vigna SR. *Peptides*. 1994;15(2):297-302. 9. Mohammad S, et al. *J Biol Chem*. 2011;286(50):43062-43070. 10. Starich GH, et al. *Am J Physiol-Endoc M*. 1985;249(6):E603-E607. 11. Dupre J, et al. *J Clin Endocr Metab*. 1973;37(5):826-828.

Effet synergique d'un agoniste uni-moleculaire double GIPR / GLP-1R



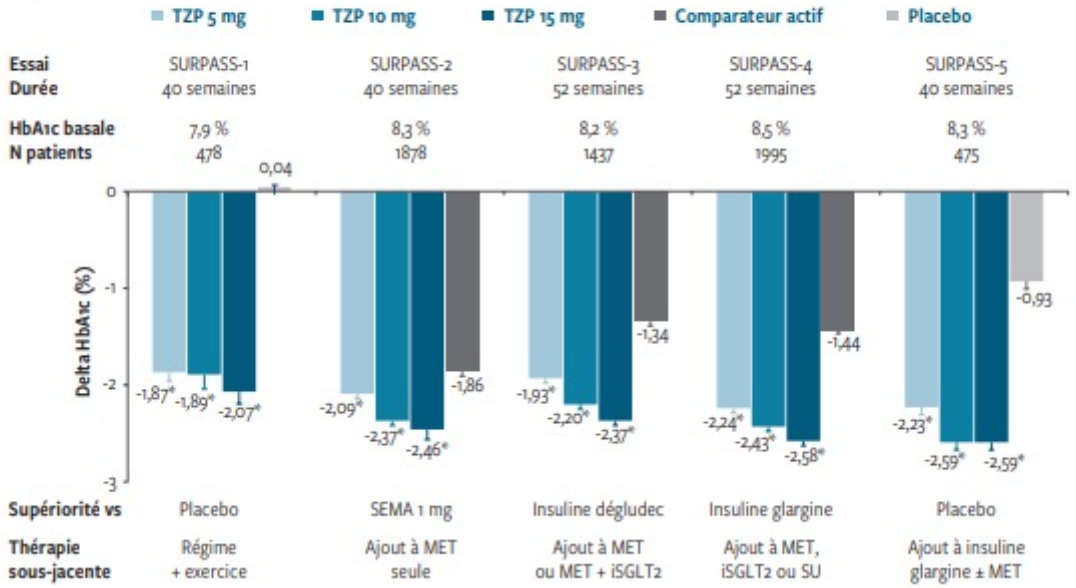
CNS = central nervous system; GIP = glucose-dependent insulinotropic polypeptide; GIPR = glucose-dependent insulinotropic polypeptide receptor; GLP-1 = glucagon-like peptide 1; GLP-1R = glucagon-like peptide 1 receptor.

1. Aronoff SL, et al. *Diabetes Spectr*. 2004;17(3):183-190. 2. Drucker JD, Nauck MA. *Lancet*. 2006;368(9548):1696-1705. 3. Szayna M, et al. *Endocrinology*. 2000;141(6):1936-1941. 4. Kreymann B, et al. *Lancet*. 1987;330(8571):1300-1304. 5. Willms B, et al. *J Clin Endocr Metab*. 1996;81(1):327-332. 6. Samms RJ, et al. *Trends Endocrin Met*. 2020;31(6):410-421. 7. Usdin TB, et al. *Endocrinology*. 1993;133(6):2861-2870. 8. Kaplan AM, Vigna SR. *Peptides*. 1994;15(2):297-302. 9. Mohammad S, et al. *J Biol Chem*. 2011;286(50):43062-43070. 10. Starich GH, et al. *Am J Physiol-Endoc M*. 1985;249(6):E603-E607. 11. Dupre J, et al. *J Clin Endocr Metab*. 1973;37(5):826-828.

Tirzepatide : agoniste double des récepteurs GIP et GLP1

FIG 2 **Réduction moyenne (delta) du taux d'HbA1c dans 5 études SURPASS**

*: p < 0,001 versus placebo ou comparateur actif.
HbA1c: hémoglobine glyquée; iSGLT2: inhibiteur des sodium-glucose transporteur de type 2; MET: metformine; SEMA: sémaglutide; SU: sulfamide hypoglycémiant; TZP: tirzépatide.

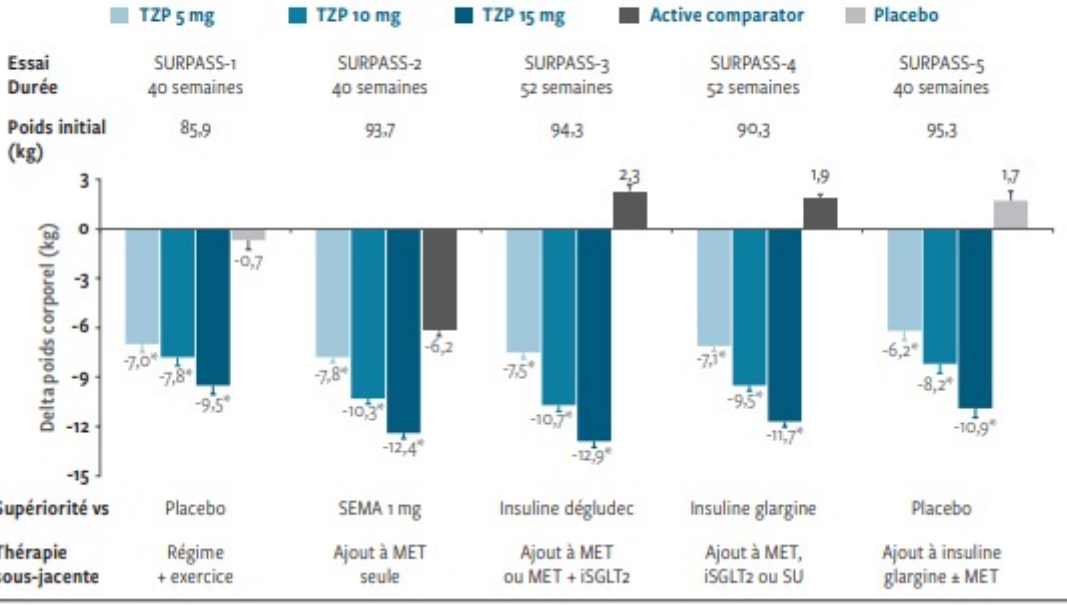


A.J. Scheen,R.P. Radermecker, N. Paquot, Rev Med Suisse 2022 ; 18 : 1539-44 | DOI : 10.53738/REVMED.2022.18.792.1539

Tirzepatide : agoniste double des récepteurs GIP et GLP1

FIG 3 **Réduction moyenne (delta) du poids corporel dans 5 études SURPASS**

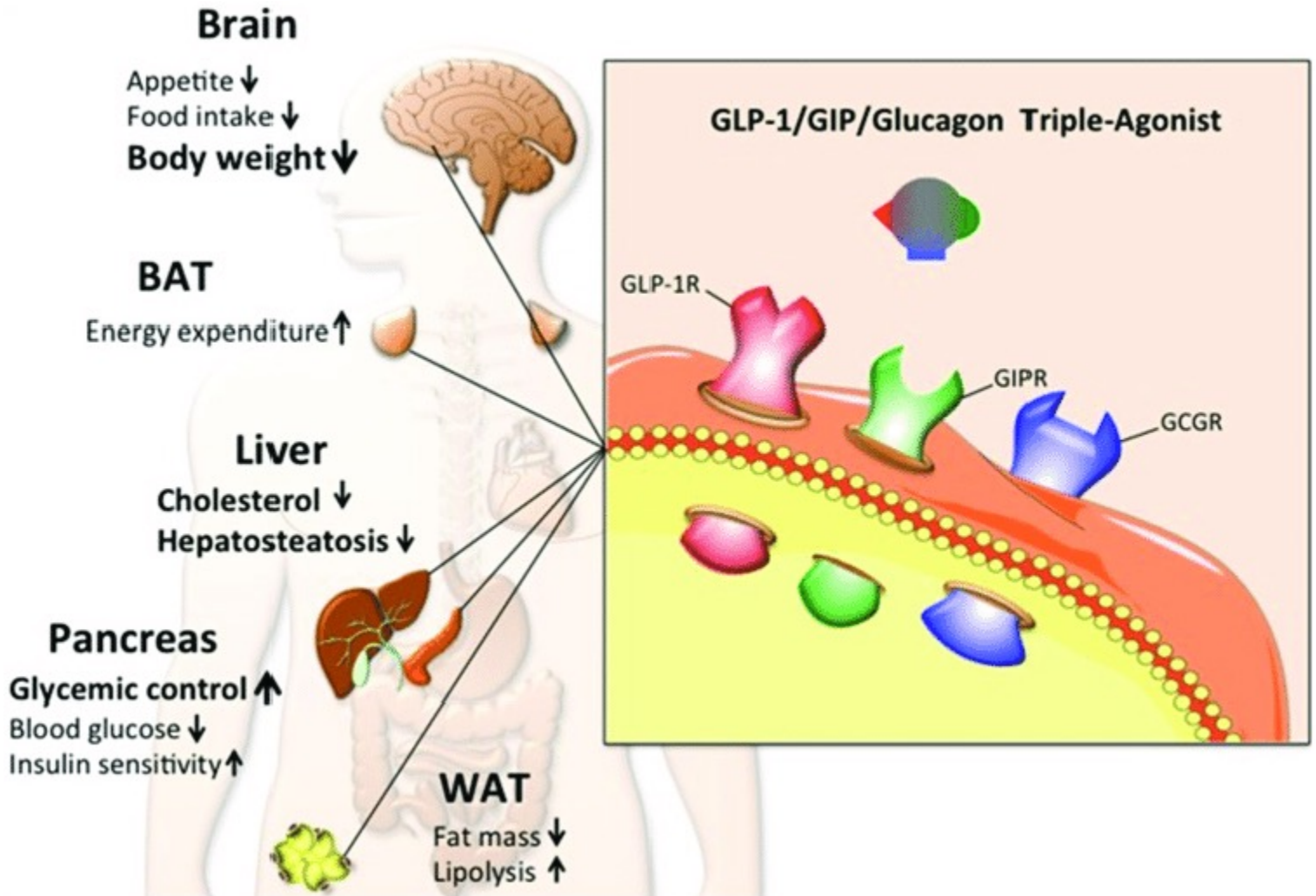
*: p < 0,001 versus placebo ou comparateur actif.
iSGLT2: inhibiteur des sodium-glucose transporteur de type 2; MET: metformine; SEMA: sémaglutide; SU: sulfamide hypoglycémiant; TZP: tirzépatide.



Essai	SURPASS-1	SURPASS-2	SURPASS-3	SURPASS-4	SURPASS-5
Durée	40 semaines	40 semaines	52 semaines	52 semaines	40 semaines
Poids initial (kg)	85,9	93,7	94,3	90,3	95,3
Supériorité vs	Placebo	SEMA 1 mg	Insuline dégludec	Insuline glargine	Placebo
Thérapie sous-jacente	Régime + exercice	Ajout à MET seule	Ajout à MET ou MET + iSGLT2	Ajout à MET, iSGLT2 ou SU	Ajout à insuline glargine ± MET

A.J. Scheen,R.P. Radermecker, N. Paquot, Rev Med Suisse 2022 ; 18 : 1539-44 | DOI : 10.53738/REVMED.2022.18.792.1539

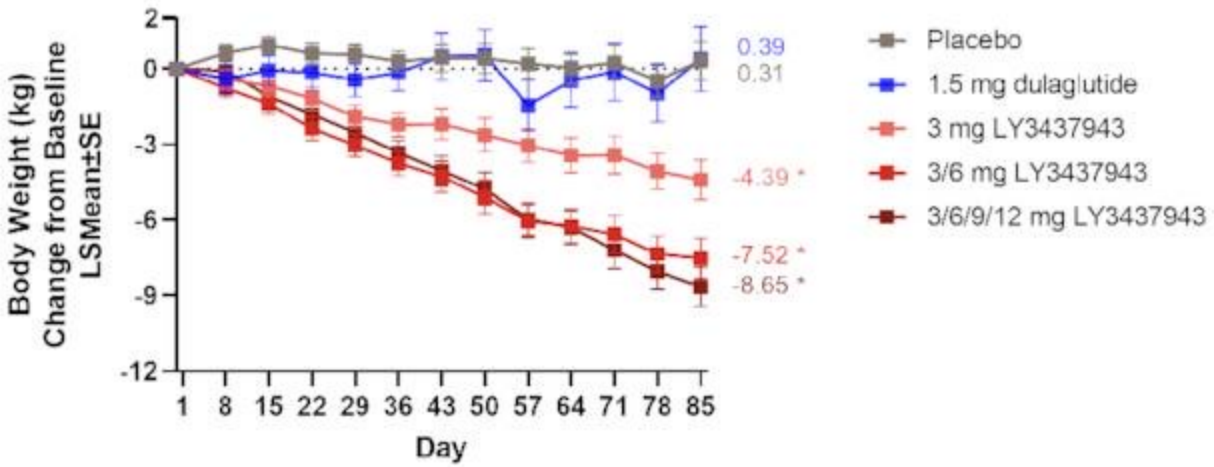
Agoniste triple des récepteurs GIP / GLP1 / Glucagon …



GIP, GLP-1 AND GLUCAGON TRIPLE RECEPTOR AGONIST (GGG LY3437943)

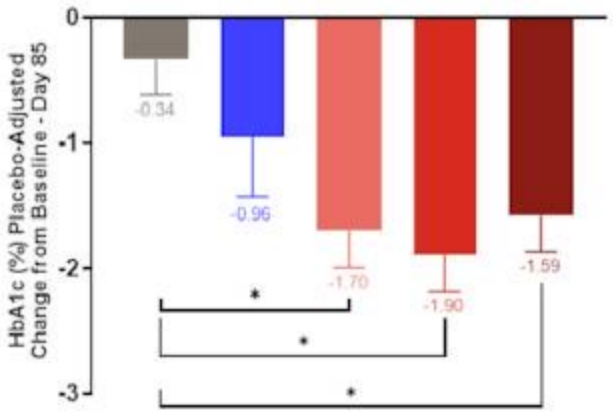
PHASE 1 12-WEEK MULTIPLE ASCENDING DOSE DATA IN T2D

WEIGHT REDUCTION



- Dose-dependent weight reduction of up to 8.65 kg (10.1% change from baseline) within a 12-week study
- Visual analog scoring suggests decreased appetite comparable to dulaglutide 1.5 mg

HBA1C



- Significantly decreased mean HbA1c up to 1.90% from baseline at dose levels of ≥3 mg
- Consistent with incretin effect, notable augmentation of insulin response following OGTT resulting in profound decrease in post-prandial glucose load

Not all arms are shown in the graph above; T2D=type 2 diabetes; OGTT=oral glucose tolerance test


NASH
Neuro-protection
Protection CV obésité
POIDS
Poids
HbA1C
Protection CV diabétique