Εξελίξεις στη θεραπεία του διαβήτη

Υπό εξέλιξη θεραπείες

ΚΩΝΣΤΑΝΤΙΝΟΣ ΜΑΚΡΥΛΑΚΗΣ
ΚΑΘΗΓΗΤΗΣ ΠΑΝ/ΜΙΟΥ ΑΘΗΝΩΝ
Πρόεδρος Ελληνικής Διαβητολογικής Εταιρείας

Α΄ ΠΡΟΠΑΙΔΕΥΤΙΚΗ ΠΑΘΟΛΟΓΙΚΗ ΚΛΙΝΙΚΗ &
ΔΙΑΒΗΤΟΛΟΓΙΚΟ ΚΕΝΤΡΟ
ΛΑΪΚΟ ΝΟΣΟΚΟΜΕΙΟ ΑΘΗΝΩΝ

Στόχοι της φροντίδας του διαβήτη

- Πρόληψη επιπλοκών
- Βελτιστοποίηση ποιότητας ζωής

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.

Αντιμετώπιση του ΣΔ

Οι 9 κατηγορίες των υπογλυκαιμικών ουσιών

Κλάση	Φαρμακευτικές Ουσίες
1. Διγουανίδια	Μετφορμίνη
2. Σουλφονυλουρίες	Γλιβενκλαμίδη, Γλικλαζίδη, Γλιμεπιρίδη
3. Θειαζολιδινεδιόνες	Πιογλιταζόνη
4. Μεγλιτινίδια	Ρεπαγλινίδη, Νατεγλινίδη
5. Αναστολείς α-γλυκοσιδασών	Ακαρβόζη
6. Ινκρετίνες	
α) Αγωνιστές GLP-1/GIP	Εξενατίδη (LAR), Λιραγλουτίδη, Λιξισενατίδη, Ντουλαγλουτίδη, Σεμαγλουτίδη, Τιρζεπατίδη
β) DPP-IV αναστολείς	Σιταγλιπτίνη, Βιλνταγλιπτίνη, Σαξαγλιπτίνη Λιναγλιπτίνη, Αλογλιπτίνη
8. SGLT2 αναστολείς	Νταπαγλιφλοζίνη, Εμπαγλιφλοζίνη, Καναγλιφλοζίνη (Ερτουγλιφλοζίνη)
9. Ινσουλίνη	

Οι 9 κατηγορίες των υπογλυκαιμικών ουσιών

Κλάση	Φαρμακευτικές Ουσίες
1. Διγουανίδια	Μετφορμίνη
2. Σουλφονυλουρίες	Γλιβενκλαμίδη, Γλικλαζίδη, Γλιμεπιρίδη
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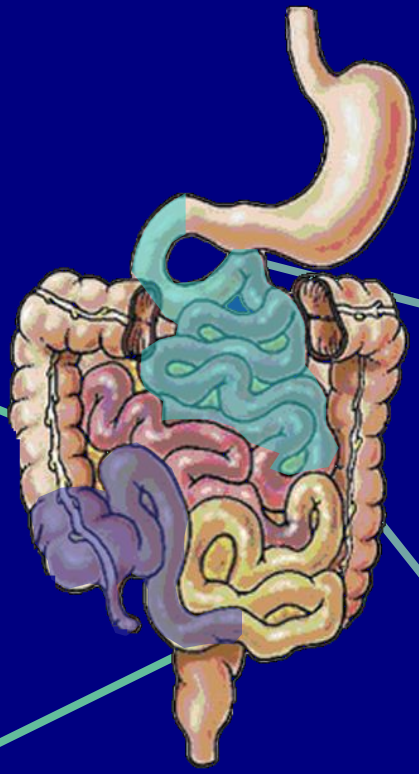
5. Αναστολείς α-γλυκοσιδασών	Ακαρβόζη
6. Ινκρετίνες	
α) Αγωνιστές GLP-1/GIP	Εξενατίδη (LAR), Λιραγλουτίδη, Λιξισενατίδη, Ντουλαγλουτίδη, Σεμαγλουτίδη, Τιρζεπατίδη
β) DPP-IV αναστολείς	Σιταγλιπτίνη, Βιλνταγλιπτίνη, Σαξαγλιπτίνη Λιναγλιπτίνη, Αλογλιπτίνη
8. SGLT2 αναστολείς	Νταπαγλιφλοζίνη, Εμπαγλιφλοζίνη, Καναγλιφλοζίνη (Ερτουγλιφλοζίνη)
9. Ινσουλίνη	

Οι πιο σημαντικές Ινκρετίνες

L-cells
(ειλεός)

K-cells
(12/δάκτυλο, νήστιδα)

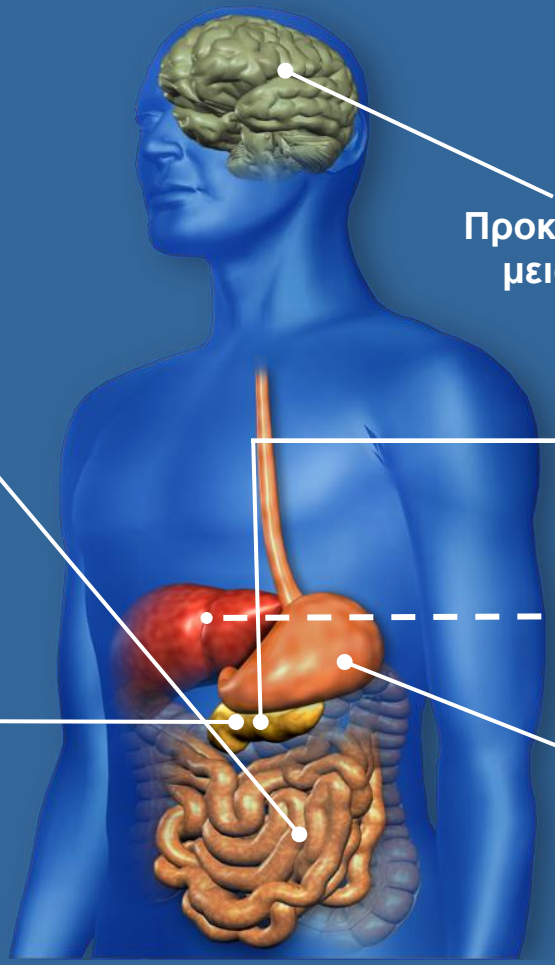


GLP-1

GIP

GLP-1=glucagon-like peptide-1; GIP=glucose-dependent insulinotropic polypeptide

Ο ΓΛΥΚΟΡΥΘΜΙΣΤΙΚΟΣ ΡΟΛΟΣ ΤΟΥ GLP-1



GLP-1 secreted upon the ingestion of food

↑ Beta-cell response

↓ Beta-cell workload

Προκαλεί κορεσμό και μειώνει την όρεξη

α-κύτταρα:
↓ μεταγευματική έκκριση γλυκαγόνης

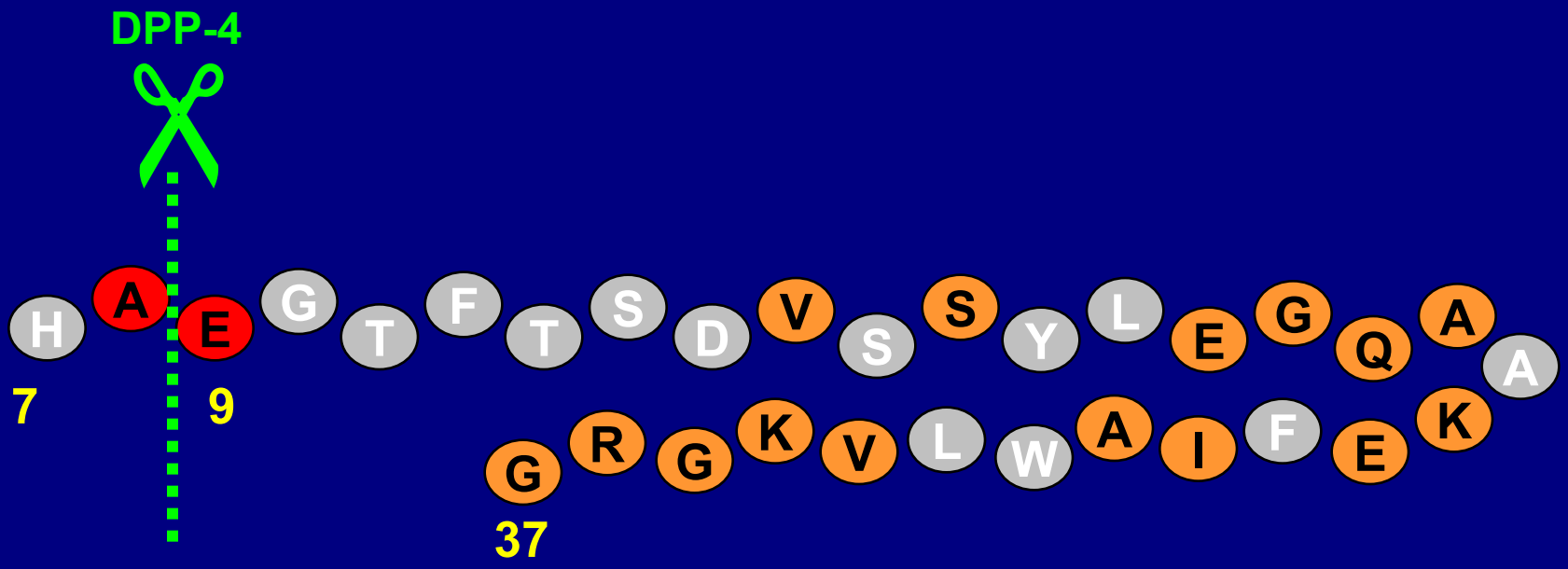
ήπαρ:
↓ γλυκαγόνη
μειώνει την ηπατική παραγωγή γλυκόζης

β-κύτταρα:
αυξάνει τη γλυκοεξαρτώμενη έκκριση ινσουλίνης

Στόμαχος:
ρυθμίζει τη γαστρική κένωση

Adapted from Flint A, et al. *J Clin Invest.* 1998;101:515-520.; Adapted from Larsson H, et al. *Acta Physiol Scand.* 1997;160:413-422.; Adapted from Nauck MA, et al. *Diabetologia.* 1996;39:1546-1553.; Adapted from Drucker DJ. *Diabetes.* 1998;47:159-169.

Το ενδογενές GLP-1 αδρανοποιείται ταχέως από το ένζυμο DPP-4



$T_{½}$ = 1–2 minutes

Amino acids shown in gold are homologous with the structure of glucagon.

DPP-4=dipeptidyl peptidase-4

Στρατηγικές θεραπείας με GLP-1

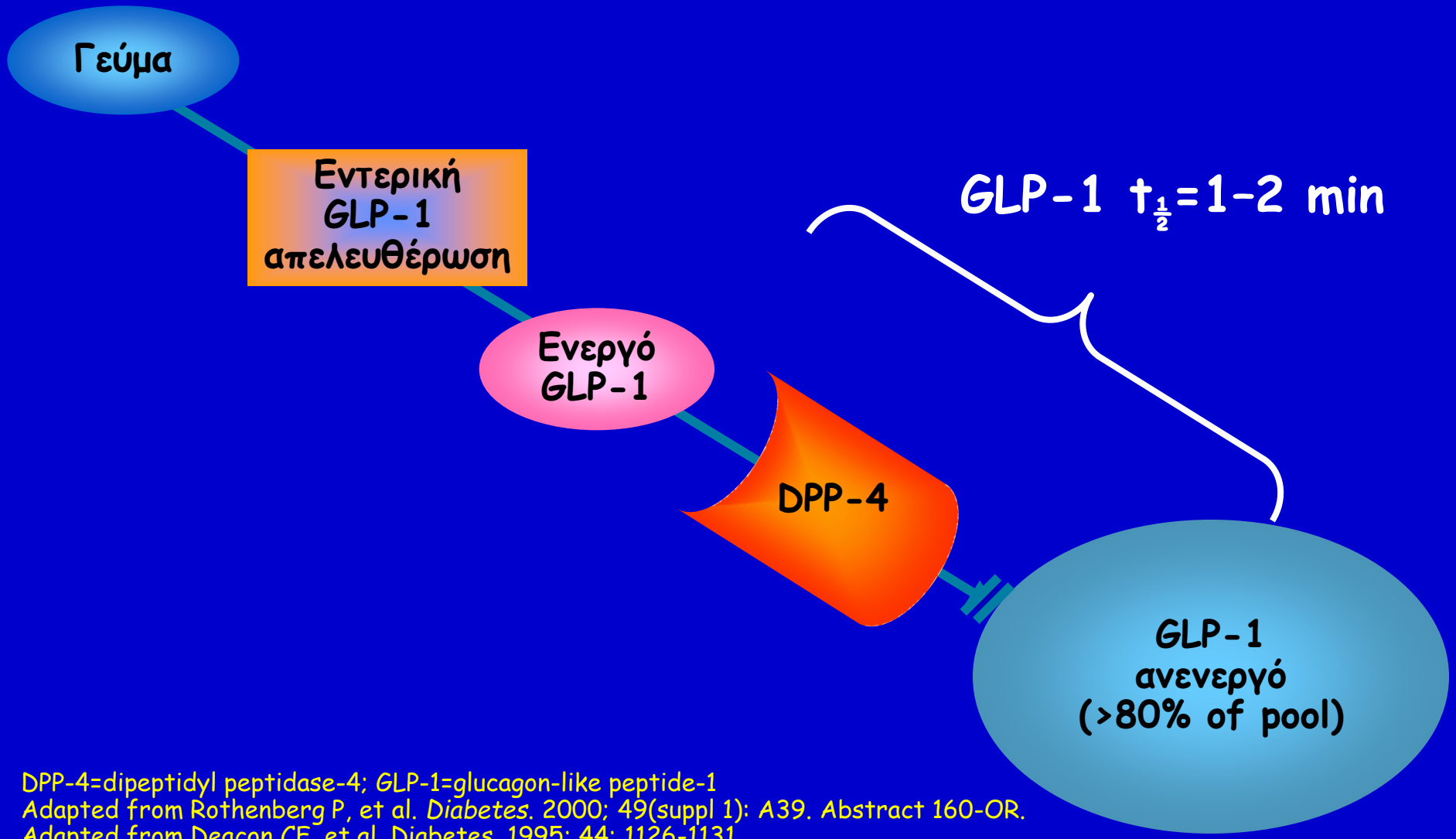
- **GLP-1 receptor agonists**
  - GLP-1 mimetics; GLP-1 analogues
    - Exenatide, Exenatide LAR
    - Liraglutide
    - Lixisenatide
    - Dulaglutide
    - Semaglutide
- **DPP-4 inhibitors**
  - incretin enhancers, incretin potentiators
    - Sitagliptin
    - Vildagliptin
    - Saxagliptin
    - Linagliptin
    - Alogliptin

DPP-IV ΑΝΑΣΤΟΛΕΙΣ

DPP-IV ΑΝΑΣΤΟΛΕΙΣ

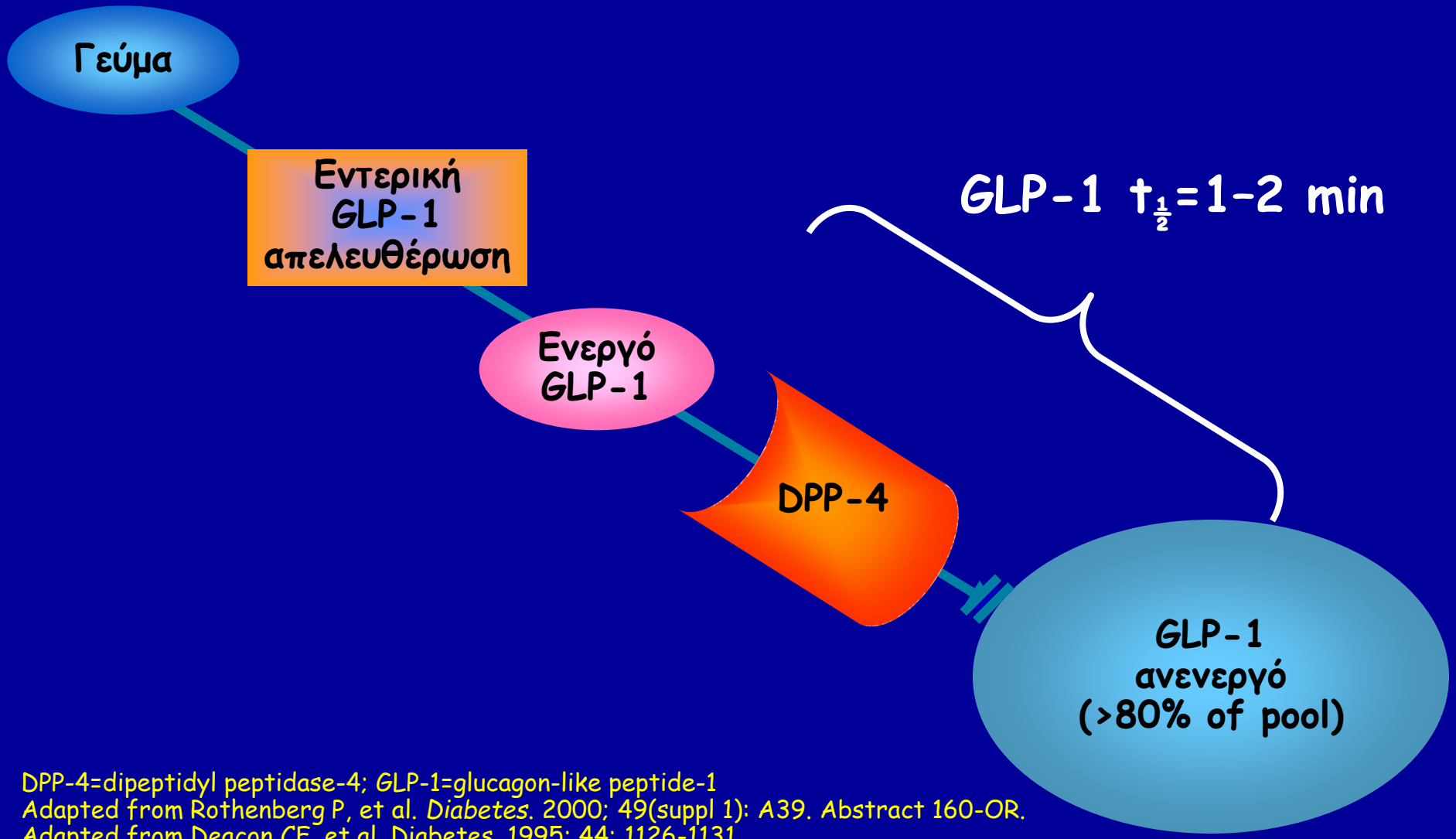
ΣΙΤΑΓΛΙΠΤΙΝΗ (Januvia)
ΒΙΛΝΤΑΓΛΙΠΤΙΝΗ (Galvus)
ΣΑΞΑΓΛΙΠΤΙΝΗ (Onglyza)
ΛΙΝΑΓΛΙΤΠΙΝΗ (Trajenta)
ΑΛΟΓΛΙΠΤΙΝΗ (Vipidia)

ΟΙ ΑΝΑΣΤΟΛΕΙΣ ΤΟΥ DPP-4 ΑΥΞΑΝΟΥΝ ΤΟ ΕΝΕΡΓΟ GLP-1



DPP-4=dipeptidyl peptidase-4; GLP-1=glucagon-like peptide-1
Adapted from Rothenberg P, et al. *Diabetes*. 2000; 49(suppl 1): A39. Abstract 160-OR.
Adapted from Deacon CF, et al. Diabetes. 1995; 44: 1126-1131.

ΟΙ ΑΝΑΣΤΟΛΕΙΣ ΤΟΥ DPP-4 ΑΥΞΑΝΟΥΝ ΤΟ ΕΝΕΡΓΟ GLP-1



DPP-4=dipeptidyl peptidase-4; GLP-1=glucagon-like peptide-1
Adapted from Rothenberg P, et al. *Diabetes*. 2000; 49(suppl 1): A39. Abstract 160-OR.
Adapted from Deacon CF, et al. Diabetes. 1995; 44: 1126-1131.

Δοσολογία DPP4is στη Νεφρική Δυσλειτουργία

Αναστολείς της DPP-4	Αλογλιπτίνη	Λιναγλιπτίνη	Σιταγλιπτίνη	Βιλνταγλιπτίνη	Σαξαγλιπτίνη
Ήπια (Cl cr >50 mL/min)	25mg	5mg	100mg	50mgx2	5mg
Μέτρια (Cl_{cr} 50→30 mL/min)	½ δόσης	»	½ δόση	½ δόσης	½ δόσης
Σοβαρή (Cl_{cr} <30 mL/min)	¼ δόσης	»	¼ δόσης	½ δόσης	½ δόσης
Νεφρική Ανεπάρκεια Τελικού Σταδίου (ESRD)	¼ δόσης	»	¼ δόσης	½ δόσης	Δεν ενδείκνυται
Αιμοκάθαρση	¼ δόσης	»	¼ δόσης	½ δόσης	Δεν ενδείκνυται

SmPC Vipedia, SmPC Januvia, SmPC Galvus, SmPC Trajenta, SmPC Onglyza valid Jan 2018

DPP4i: Χρήση σε Ηπατική Ανεπάρκεια

	αλογλιπτίνη	Linagliptin	Saxagliptin	Sitagliptin	Vildagliptin
Χρόνος ημίσειας ζωής, ώρες	12–21	10–40	2–4 (parent) 3–7 (active metabolite)	8–24	1.5–4.5
Ηπατική Ανεπάρκεια					
Ήπια	**Ναι**	**Ναι**	**Ναι**	**Ναι**	**Όχι**
Μέτρια	**Ναι**	**Ναι**	**Ναι**	**Ναι**	**Όχι**
Σοβαρή	**Όχι**	**Ναι**	**Όχι**	**Όχι**	**Όχι**
Monitoring Ηπατικής λειτουργίας	**Όχι**	**Όχι**	**Όχι**	**Όχι**	**Ναι**

*Renal insufficiency: Mild: CrCl ≥50 mL/min, Moderate: CrCl ≥30–<50 mL/min, Severe/ESRD: CrCl <30 mL/min
CrCl=creatinine clearance; DPP4i=dipeptidyl peptidase-4 inhibitor; ESRD=end-stage renal disease; EU=Europe; min=minute; NR=not recommended; US=United States

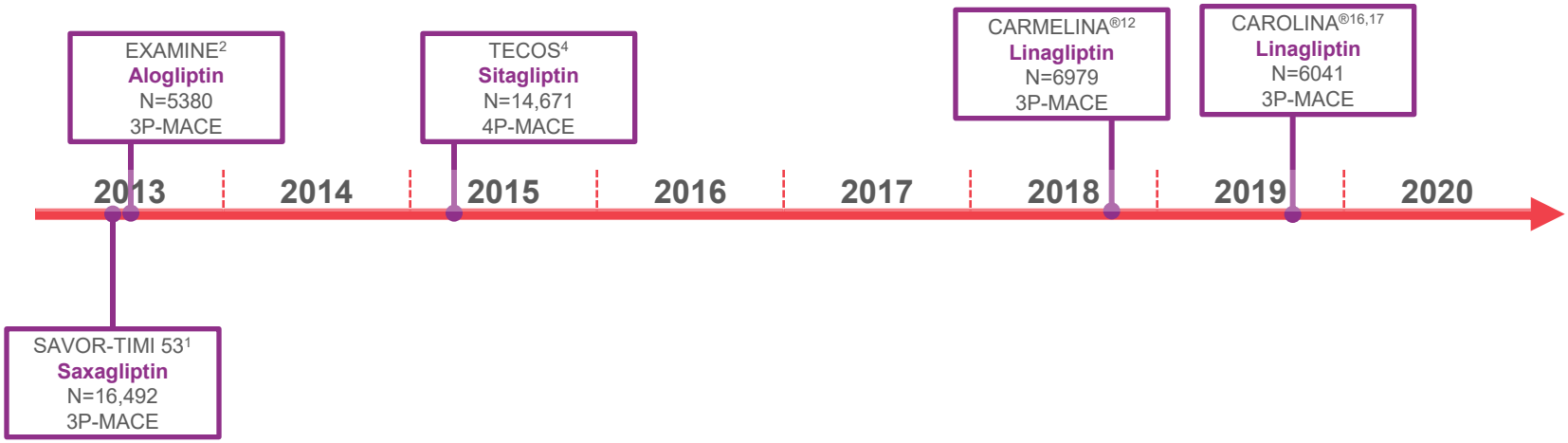
Adapted from: 1. Deacon CF. *Diabetes Obes Metab.* 2011;13:7-18. 2. Deacon CF, et al. *Expert Opin Pharmacother.* 2013;14:2047-2058.

Χαρακτηριστικά αντιδιαβητικών φαρμάκων

Παρεμβάσεις	Αναμενόμενη ↓ HbA_{1c} (%)
Δίαιτα & Άσκηση	1.0-2.0
Διγουανίδια Μετφορμίνη	1.0-2.0
Αναστολείς α-Γλυκοσιδάσης Ακαρβόζη	0.5-0.8
Σουλφονυλουρίες 1.Γλιβενκλαμίδη 2.Γλικλαζίδη MR 3.Γλιμεπιρίδη	1.0-2.0
Μεγλιτινίδες 1.Ρεπαγλινίδη 2.Νατεγλινίδη	0.5-1.5
Γλιταζόνες Πιογλιταζόνη	0.5-1.4
Αναστολείς DPP-4 1.Σιταγλιπτίνη 2.Βιλνταγλιπτίνη 3.Σαξαγλιπτίνη	0.5-0.8
Μιμητικά GLP-1 1.Εξενατίδη 2.Λιραγλουτίδη	0.5-1.0

ΕΔΕ 2011-13

Μελέτες Καρδιαγγειακών εκβάσεων των DPP-4 αναστολέων

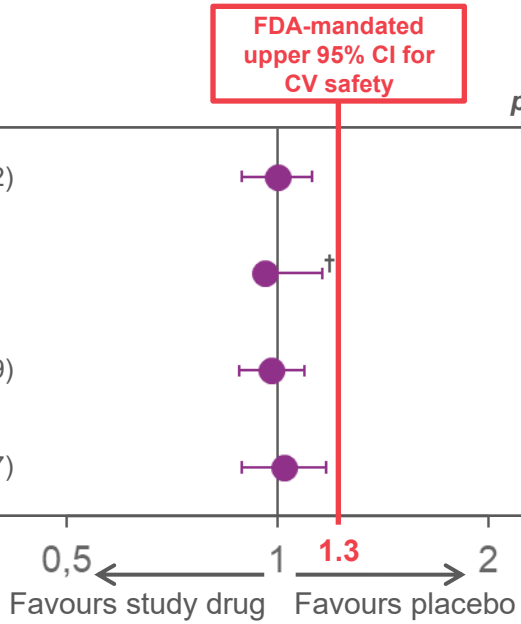


Markers on timeline represent trial completion and estimated disclosure dates, all of which come from ClinicalTrials.gov
See slide notes for abbreviations and full list of references

Πρωτεύον τελικό στις μελέτες ΚΔ εκβάσεων των DPP-4 αναστολέων

Οι DPP-4 αναστολείς στις μελέτες ΚΔ εκβάσεων τεκμηρίωσαν την ζητούμενη από τον FDA καρδιαγγειακή τους ασφάλεια

	Study drug	Placebo		
	n with event/N analysed (%)		HR (95% CI)	*p*-value*
SAVOR-TIMI 53[1] (saxagliptin)	613/8280 (7.3)	609/8212 (7.2)	1.00 (0.89, 1.12)	0.99
EXAMINE[2] (alogliptin)	305/2701 (11.3)	316/2679 (11.8)	0.96 (≤1.16)	0.32
TECOS[3] (sitagliptin)	695/7257 (9.6)	695/7266 (9.6)	0.98 (0.88, 1.09)	0.65
CARMELINA®[4] (linagliptin)	434/3494 (12.4)	420/3485 (12.1)	1.02 (0.89, 1.17)	0.74



Comparison of trials should be interpreted with caution due to differences in study design, populations and methodology

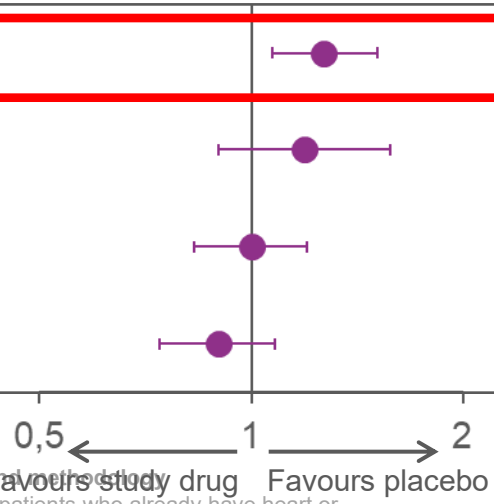
**p*-value for superiority; †Upper boundary of one-sided repeated CI. CV, cardiovascular; CVOT, cardiovascular outcomes trial; DPP-4, dipeptidyl peptidase-4

1. Scirica BM *et al. N Engl J Med* 2013;369:1317; 2. White WB *et al. N Engl J Med* 2013;369:1327; 3. Green JB *et al. N Engl J Med* 2015;373;232; 4. Rosenstock J *et al. JAMA* 2019;321:69

Νοσηλεία για Καρδιακή Ανεπάρκεια στις μελέτες ΚΔ εκβάσεων των DPP-4 αναστολέων

Η σαξαγλιπτίνη συνδέθηκε με σημαντική αύξηση του κινδύνου για νοσηλεία από καρδιακή ανεπάρκεια συγκριτικά με το εικονικό φάρμακο

	Study drug	Placebo		
	n with event/N analysed (%)		HR (95% CI)	*p*-value
SAVOR-TIMI 53*[1] (saxagliptin)	289/8280 (3.5)	228/8212 (2.8)	1.27 (1.07, 1.51)	0.007
EXAMINE*[2] (alogliptin)	106/2701 (3.9)	89/2679 (3.3)	1.19 (0.90, 1.58)	0.22
TECOS†[3] (sitagliptin)	228/7332 (3.1)	229/7339 (3.1)	1.00 (0.83, 1.20)	0.98
CARMELINA®[4] (linagliptin)	209/3494 (6.0)	226/3485 (6.5)	0.90 (0.74, 1.08)	0.26



Comparison of trials should be interpreted with caution due to differences in study design, populations and methodology

*According to an FDA safety review, saxagliptin and alogliptin may increase the risk of heart failure, particularly in patients who already have heart or kidney disease. A warning has been added to the labels of these drugs[5]; †Heart failure risk was not assessed at the time of the trial

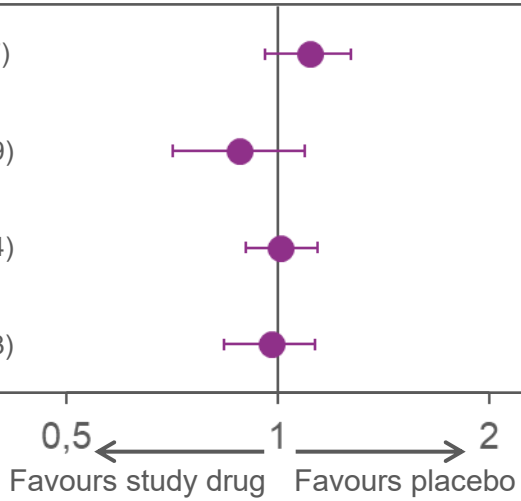
CVOT, cardiovascular outcomes trial; DPP-4, dipeptidyl peptidase-4

1. Scirica BM *et al. N Engl J Med* 2013;369:1317; 2. Zannad F *et al. Lancet* 2015;385:2067; 3. Green JB *et al. N Engl J Med* 2015;73:232; 4. Rosenstock J *et al. JAMA* 2019;321:69; 5. FDA Drug Safety Communication. Feb 2014. https://www.fda.gov/drugs/drugsafety/ucm486096.htm (accessed Mar 2019)

Θάνατος κάθε αιτιολογίας στις μελέτες ΚΔ εκβάσεων των DPP-4 αναστολέων

Δεν αναφέρθηκε για τους DPP-4 αναστολείς καμία επίδραση στο θάνατο κάθε αίτιας

	Study drug	Placebo		
	n with event/N analysed (%)		HR (95% CI)	*p*-value
SAVOR-TIMI 53[1] (saxagliptin)	42/8280 (4.9)	378/8212 (4.2)	1.11 (0.96,1.27)	0.15
EXAMINE[2] (alogliptin)	153/2701 (5.7)	173/2679 (6.5)	0.88 (0.71, 1.09)	0.23
TECOS[3] (sitagliptin)	547/7332 (7.5)	537/7339 (7.3)	1.01 (0.90, 1.14)	0.88
CARMELINA®[4] (linagliptin)	367/3494 (10.5)	373/3485 (10.7)	0.98 (0.84, 1.13)	0.74



Comparison of trials should be interpreted with caution due to differences in study design, populations and methodology

CVOT, cardiovascular outcomes trial; DPP-4, dipeptidyl peptidase-4

1. Scirica BM *et al. N Engl J Med* 2013;369:1317; 2. White WB *et al. N Engl J Med* 2013;369:1327; 3. Green JB *et al. N Engl J Med* 2015;73:232; 4. Rosenstock J *et al. JAMA* 2019;321:69

GLP-1 ΑΓΩΝΙΣΤΕΣ

GLP-1RAs - φαρμακοκινητική

Αύξηση διάρκειας δράσης

Κατηγορία	Σκεύασμα	Χρόνος ημίσειας ζωής	Cmax
Ταχείας δράσης <24 ώρες	Exenatide BD	2.4 ώρες	2 ώρες
	Lixisenatide OD	2.7-4.3 ώρες	1.25-2.25 ώρες
Μακράς δράσης ≥24 ώρες	Liraglutide OD Semaglutide p.o. OD	13 ώρες	8-12 ώρες
	Dulaglutide OW	90 ώρες	24-48 ώρες
	Albiglutide OW	6-7 ημέρες	3-5 ημέρες
	Exenatide OW Semaglutide OW	7-14 ημέρες	6-7 εβδομάδες

BD: twice a day; Cmax: maximum concentration; GLP-1RA: glucagon-like peptide-1 receptor agonist; OD: once a day; OW: once weekly

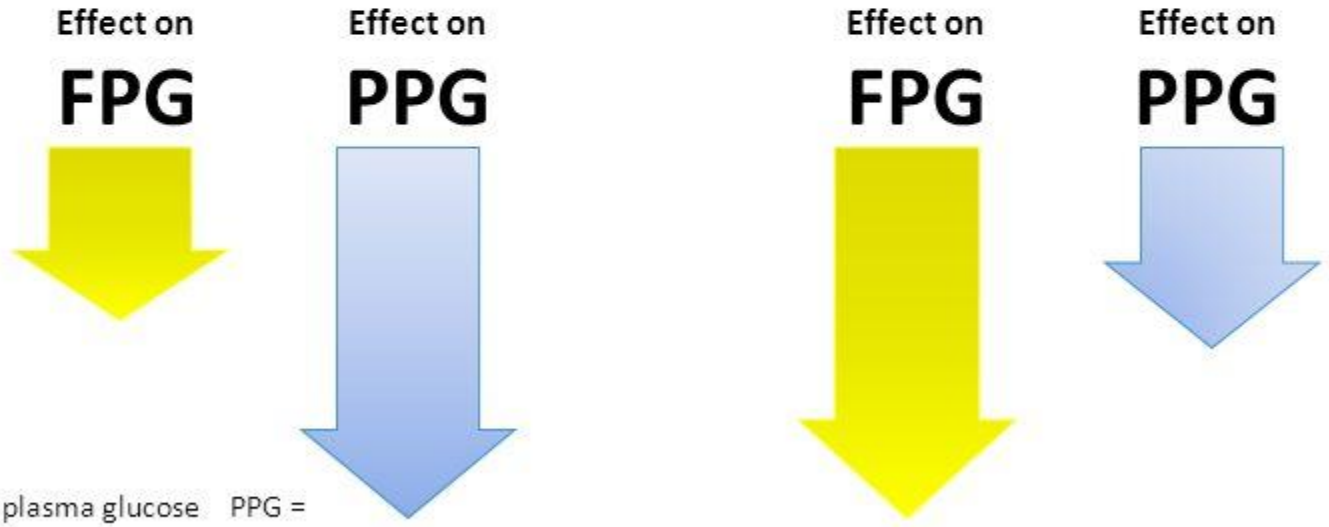
Choice of GLP-1 receptor agonist: short acting versus long acting

The pharmacological profile and half-life of a GLP-1 receptor agonist influences its effects on postprandial and basal (fasting) glycaemia

SHORT ACTING
GLP-1 receptor agonists
Lixisenatide OD, Exenatide BD

or

LONG ACTING
GLP-1 receptor agonists
Liraglutide OD, Exenatide/Dulaglutide QW



FPG = fasting plasma glucose PPG = postprandial glucose

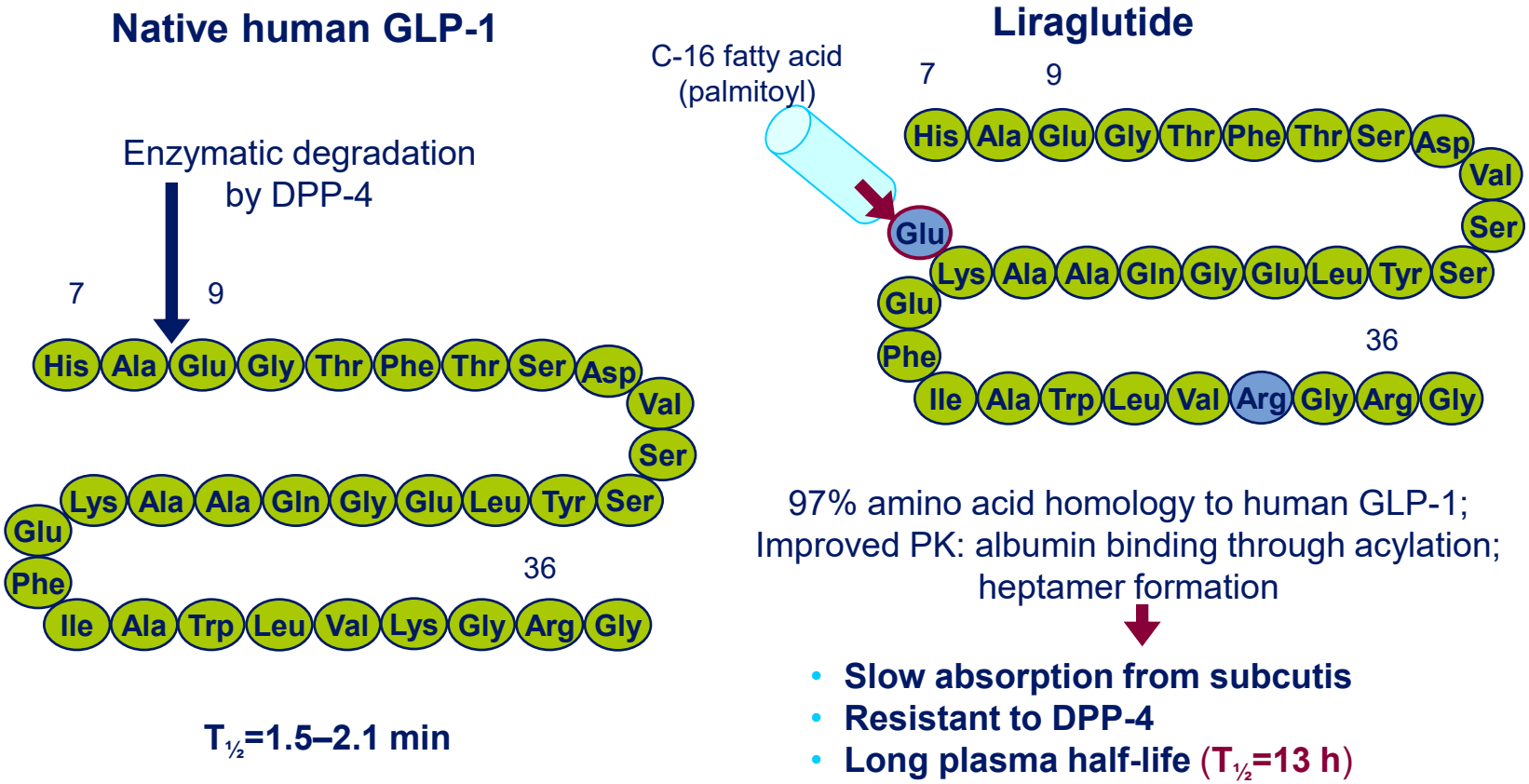
Fineman MS et al. Diabetes Obes Metab 2012;14:675-88

Gila monster

Εξενατίδη (Byetta): Το πρώτο μόριο


Lyxumia® 10 micrograms
Lyxumia® 20 micrograms
solution for injection
lixisenatide
Subcutaneous use
Treatment initiation pack
Each pack of 2 pre-filled pens for a 4 week treatment schedule contains:
1 pre-filled pen for 14 doses of 10 micrograms
1 pre-filled pen for 14 doses of 20 micrograms
SANOFI
Lyxumia® 20mcg
injection
lixisenatide
Lyxumia® 10mcg
injection
lixisenatide

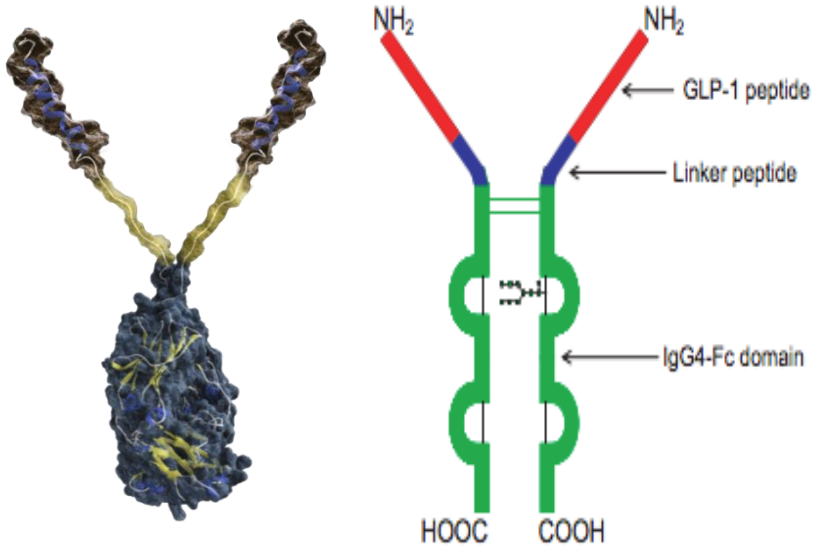
Liraglutide: Ανθρώπινο ανάλογο GLP-1 που χορηγείται μια φορά την ημέρα



Knudsen *et al. J Med Chem* 2000;43:1664–9; Degn *et al. Diabetes* 2004;53:1187–94

Ντουλαγλουτίδη (Trulicity):
Σχεδιασμένη με βάση τις ανάγκες των ασθενών

Αποσκοπώντας στη βελτίωση της εμπειρίας των ασθενών από την έναρξη ενέσιμης θεραπείας, τόσο το μόριο της ντουλαγλουτίδης όσο και η πένα χρήσης της έχουν σχεδιασθεί με βάση τις ανάγκες των ασθενών[1,2]



Το μόριο της ντουλαγλουτίδης

Η έτοιμη προς χρήση πένα

1. Glaesner W, et al. *Diabetes Metab Res Rev*. 2010;26(4):287-296. 2. Matfin G, et al. *Diabetes*. 2014;63(Suppl 1A):LB31.

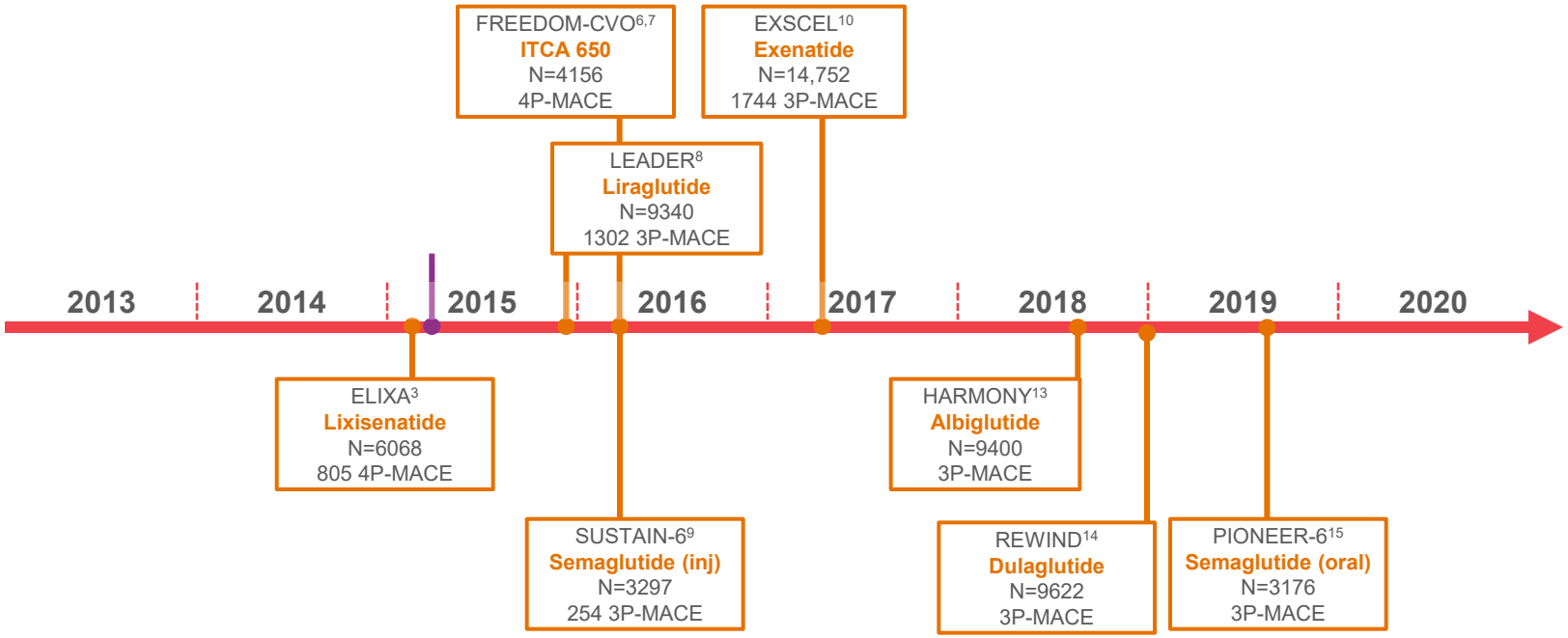

OZEMPIC®
(semaglutide) injection
For Single Patient Use Only
8 mg/3 mL (2.68 mg/mL) Prefilled pen
Pen delivers doses in
2 mg increments only
For subcutaneous use only
Use OZEMPIC once weekly
NDC 0169-4772-12 List 477212
NDC 0169-4772-11 List 477211
0
mg
novo nordisk®


RYBELSUS®
3 mg
tablets
semaglutide
Oral use
30 tablets
novo nordisk®


RYBELSUS®
7 mg
tablets
semaglutide
Oral use
30 tablets
novo nordisk®

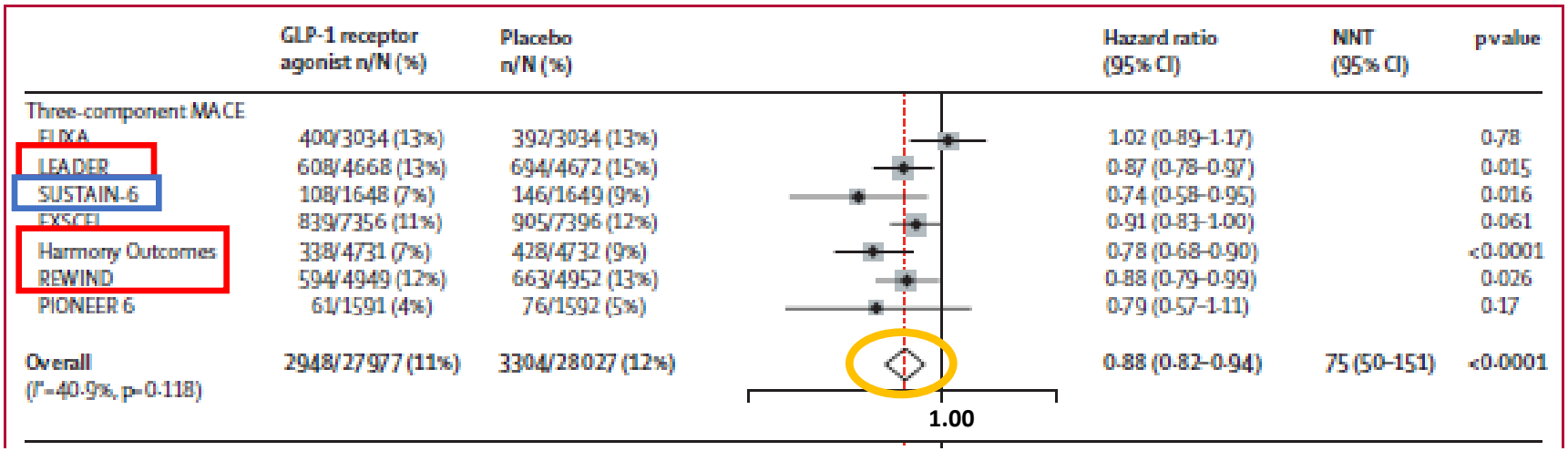

RYBELSUS®
14 mg
tablets
semaglutide
Oral use
30 tablets
novo nordisk®

Μελέτες Καρδιαγγειακών εκβάσεων των GLP-1 αγωνιστών



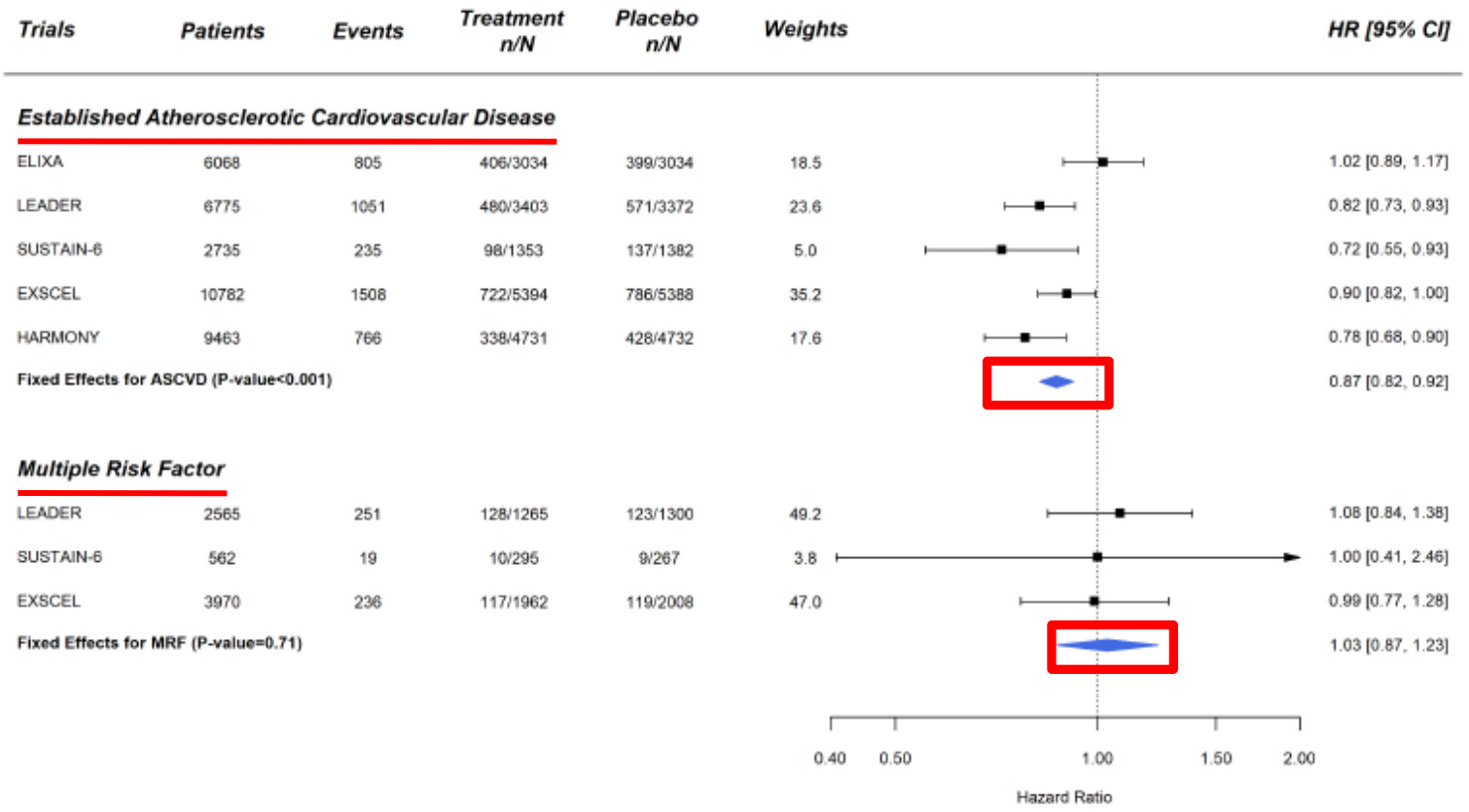
All trial completion and estimated disclosure dates come from ClinicalTrials.gov
3P-MACE, 3-point major adverse cardiovascular events; 4P-MACE, 4-point major adverse cardiovascular events; 5P-MACE, 5-point major adverse cardiovascular events; CV, cardiovascular; DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; SGLT2, sodium-glucose co-transporter-2; SU, sulphonylurea
Adapted from: Johansen OE. *World J Diabetes* 2015;6:1092. See notes for full list of references

Risk of MACE with GLP1 RAs



Kristensen et al. Lancet Diabetes Endocrinol 2019

Supplemental Figure 3: Pooled GLP1-RA trials stratified by presence of established atherosclerotic cardiovascular disease for the composite of myocardial infarction, stroke, and cardiovascular death (MACE)

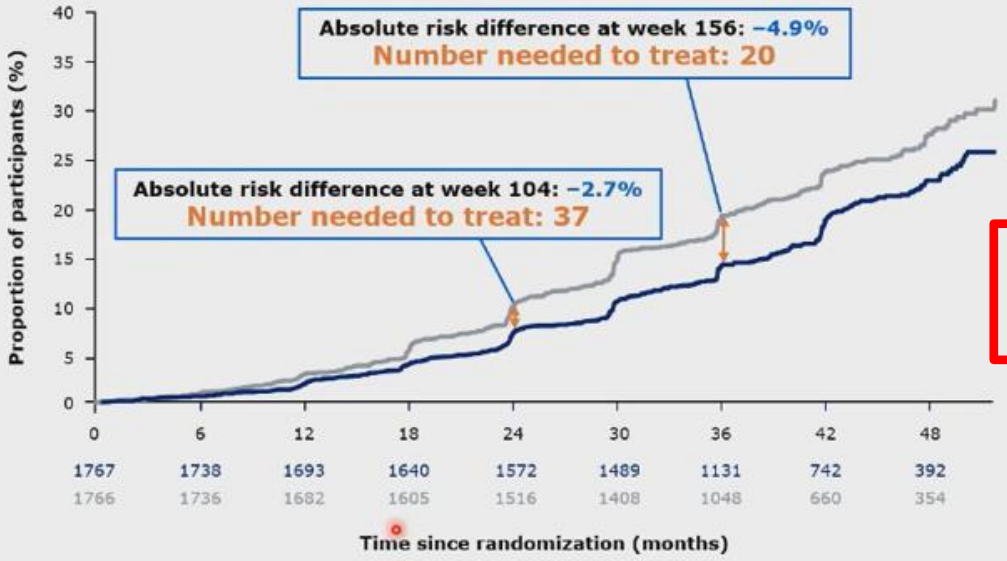


Zelniker et al. GLP1-RA and SGLT2i in Type 2 Diabetes Mellitus. *Circulation. 2019;139:2022–2031*

Composite kidney outcome

Primary outcome

FLOW
semaglutide | renal outcomes trial



Placebo 23.2%
(410/1766)

Semaglutide 18.7%
(331/1767)

HR 0.76 (95% CI 0.66, 0.88)
p=0.0003

Full analysis set. Data from the in-trial period. Numbers shown in the lower panels represent the number of participants at risk.
Event rates: 5.8 and 7.5 per 100 patient-years of follow-up for participants receiving semaglutide and placebo, respectively.
CI, confidence interval; HR, hazard ratio.
Perkovic V et al. *N Engl J Med* 2024; doi: 10.1056/NEJMoa2403347.

Superiority if two-sided
p value <0.0322

N Engl J Med 2024;391:109-121

Composite kidney outcome

FLOW
semaglutide | renal outcomes trial

Full analysis set. Data from the in-trial period. CV death includes undetermined cause of death.
†Data on file. Kidney failure was a three-component composite outcome consisting of initiation of chronic replacement therapy (dialysis or kidney transplantation), onset of persistent eGFR <15 mL/min/1.73 m², and kidney death.
CI, confidence interval; CV, cardiovascular; eGFR, estimated glomerular filtration rate; HR, hazard ratio.
Perkovic V et al. *N Engl J Med* 2024; doi: 10.1056/NEJMoa2403347.

N Engl J Med 2024;391:109-121

Summary of results from meta-analyses evaluating changes in metabolic outcomes with maximal doses of GLP-1RAs and SGLT2 inhibitors vs placebo

	A1C, % (95% CI)	Weight, kg (95% CI)	Systolic blood pressure, mm Hg (95% CI)
GLP-1RAs			
Albiglutide QW	−0.94 (−0.64 to −1.24)	−0.41 (+1.5 to -2.32)	—
Dulaglutide QW	−1.12 (−1.05 to −1.36)	−1.57 (−0.66 to −2.48)	−3.35 (−2.10 to −4.61)
Exenatide BID	−0.70 (−0.59 to -0.81)	−1.67 (−1.05 to −2.29)	−3.43 (−2.17 to −4.69)
Exenatide QW	−1.08 (−0.89 to −1.27)	−1.49 (−0.40 to −2.58)	−3.65 (−2.13 to −5.15)
Liraglutide QD	−1.15 (−1.03 to −1.27)	−1.96 (−1.25 to −2.67)	−4.04 (−2.90 to −5.19)
Lixisenatide QD	−0.55 (-0.42 to −0.68)	−0.78 (−0.09 to −1.48)	—
Semaglutide QD (oral)	−0.95 (−0.74 to −1.17)	−3.28 (−2.71 to −3.85)	−3.35 (−2.10 to −4.61)
Semaglutide QW	−1.38 (−1.16 to −1.59)	−3.98 (−3.43 to −4.54)	−5.94 (−4.02 to −7.89)
SGLT2 inhibitors			
Canagliflozin	−0.86 (−0.76 to −0.96)	−2.47 (−2.11 to −2.84)	−4.87 (-3.87 to −5.87)
Dapagliflozin	−0.66 (−0.58 to -0.74)	−2.18 (−1.90 to −2.47)	−3.01 (−2.13 to −3.89)
Empagliflozin	−0.66 (−0.56 to -0.76)	−2.24 (−1.91 to −2.58)	−3.66 (−2.77 to −4.54)
Ertugliflozin	−0.90 (−0.80 to −1.00)	−1.80 (−1.40 to −2.20)	−3.50 (−2.00 to −4.90)

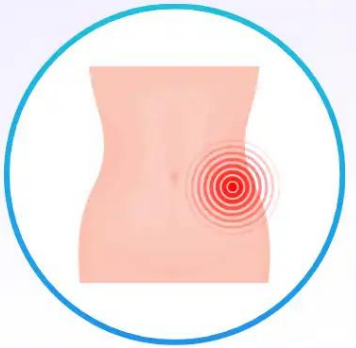
BID, twice daily; *CI*, confidence interval; *GLP-1RAs*, glucagon-like peptide-1 receptor agonists; *QD*, once daily; *QW*, once weekly; *SGLT2*, sodium-dependent glucose cotransporter-2.

Note: Data adapted from Avgerinos et al (86), Giorgino et al (3), Htike et al (5), Kanters et al (87) and Liu et al (88).

R.M. Goldenberg et al. / Can J Diabetes (2020) 1-12

Side Effects of GLP-1 Receptor Agonists

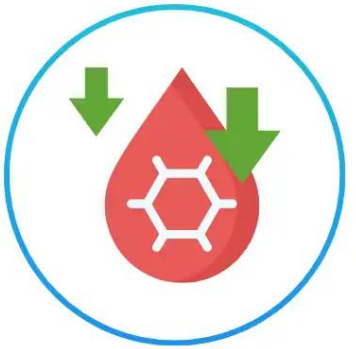
Gastrointestinal problems



Injection site reactions

Decrease in appetite

Risk of pancreatitis



Hypoglycemia

Risk of thyroid cancer

GLP-1 ανάλογα – αντενδείξεις - ανεπιθύμητες ενέργειες

Γαστρεντερικές διαταραχές:
ναυτία (25-60%), έμετοι (5-15%), διάρροιες(10-20%) , δυσκοιλιότητα

- Λιγότερο συχνά με τα μακράς δράσεις ανάλογα
- Συνήθως αυτοπεριορίζονται μετά την αρχική περίοδο

Αποφυγή:

- Γαστροπάρεση ή σοβαρή γαστροοισοφαγική παλινδρόμηση
- Ιστορικό παγκρεατίτιδας/παγκρεατικής νεοπλασίας
- Ατομικό ή οικογενειακό ιστορικό μυελοειδούς καρκινώματος θυρεοειδούς ή συνδρόμου πολλαπλής ενδοκρινικής νεοπλασίας τύπου 2

Hinnen Diabetes Spectr. 2017 Aug;30(3):202
Meier et al Nat Rev Endocrinol 2012;8:728

ΣΥΜΠΕΡΑΣΜΑΤΑ

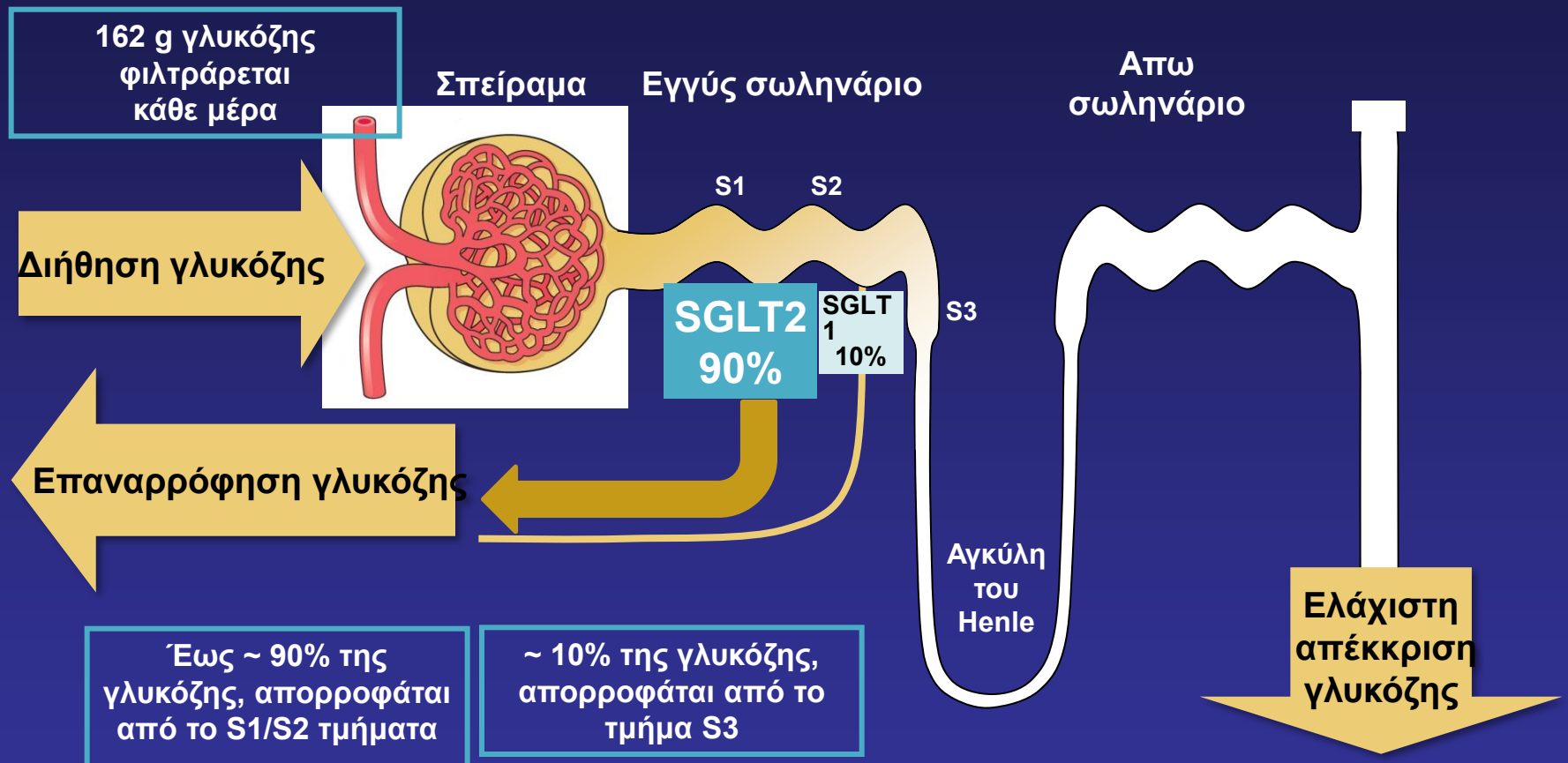
- GLP-1 αγωνιστές: αποτελεσματική και ασφαλής αγωγή, θέση σε όλα τα βήματα μετά τη μετφορμίνη
- Βραχείας διάρκειας: κυρίως μεταγευματική γλυκόζη
- Μακράς διάρκειας: κυρίως γλυκόζη νηστείας, καλύτερη HbA1c, μείωση βάρους
- Μακράς διάρκειας: εναλλακτική επιλογή έναντι βασικής ινσουλίνης
- Κύρια ανεπιθύμητη ενέργεια: ναυτία
- Ερωτηματικό για την μικρή αύξηση στη συχνότητα οξείας παγκρεατίτιδας
- Μειώνουν τα καρδιαγγειακά συμβάματα σε άτομα με αυξημένο ΚΑΝ κίνδυνο

SGLT-2 ΑΝΑΣΤΟΛΕΙΣ

Οι 9 κατηγορίες των υπογλυκαιμικών ουσιών

Κλάση	Φαρμακευτικές Ουσίες
1. Διγουανίδια	Μετφορμίνη
2. Σουλφονυλουρίες	Γλιβενκλαμίδη, Γλικλαζίδη, Γλιμεπιρίδη
3. Θειαζολιδινεδιόνες	Πιογλιταζόνη
4. Μεγλιτινίδια	Ρεπαγλινίδη, Νατεγλινίδη
5. Αναστολείς α-γλυκοσιδασών	Ακαρβόζη
6. Ινκρετίνες	
α) Αγωνιστές GLP-1	Εξενατίδη (LAR), Λιραγλουτίδη, Λιξισενατίδη, Ντουλαγλουτίδη, (Σεμαγλουτίδη)
β) DPP-IV αναστολείς	Σιταγλιπτίνη, Βιλνταγλιπτίνη, Σαξαγλιπτίνη Λιναγλιπτίνη, Αλογλιπτίνη
8. SGLT2 αναστολείς	Νταπαγλιφλοζίνη, Εμπαγλιφλοζίνη, Καναγλιφλοζίνη (Ερτουγλιφλοζίνη)
9. Ινσουλίνη	

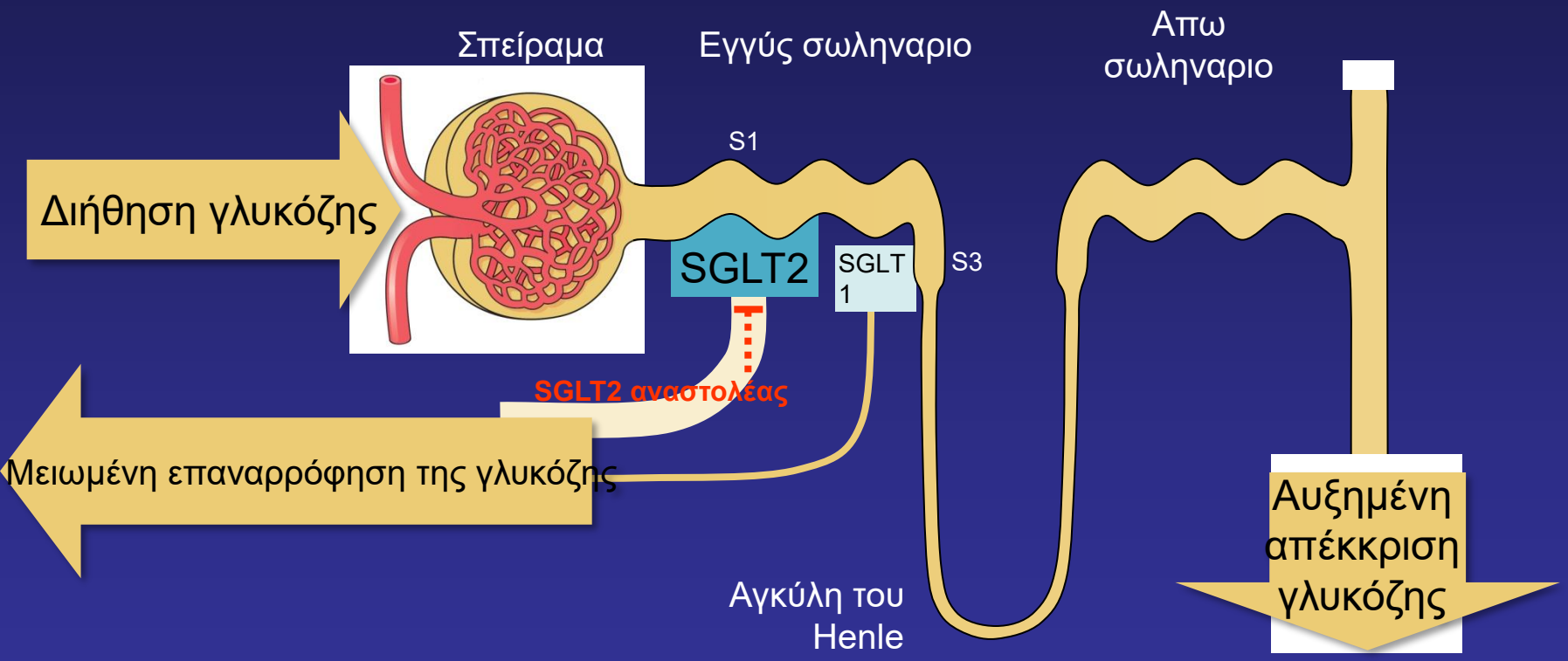
Οι νεφροί φιλτράρουν και απορροφούν 162 g γλυκόζης την ημέρα στους νεφρώνες μέσω της ενεργούς μεταφοράς



Ειδικοί μεταφορείς γλυκόζης (SGLT) είναι υπεύθυνοι για αυτήν την επαναρρόφηση στους νεφρούς

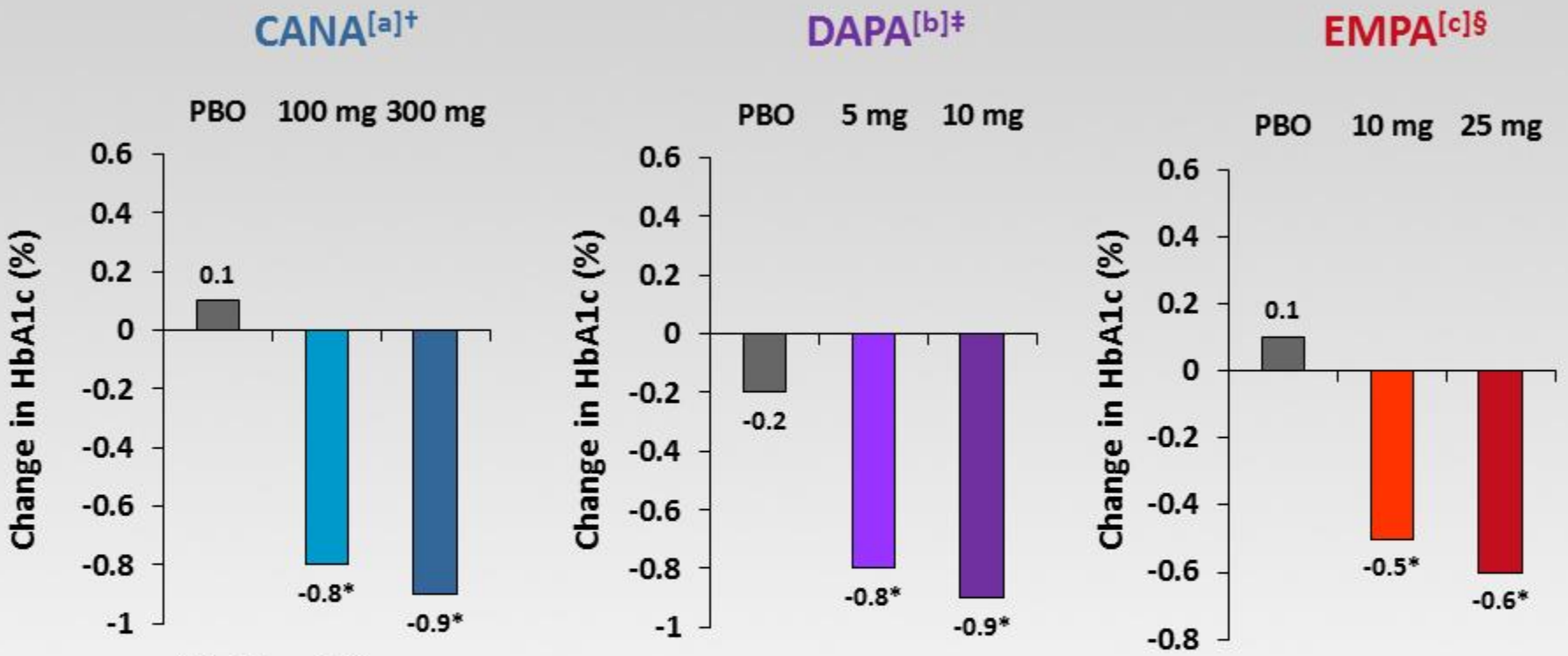
Wright EM. *Am J Physiol Renal Physiol* 2001;280:F10–8; Lee YJ, et al. *Kidney Int Suppl* 2007;106:S27–35; Brown GK. *J Inherit Metab Dis* 2000;23:237–246.

Η αναστολή των SGLT2 μειώνει τη νεφρική επαναρρόφηση της γλυκόζης και αυξάνει την αποβολή γλυκόζης



Wright EM. *Am J Physiol Renal Physiol* 2001;280:F10–8; Lee YJ, et al. *Kidney Int Suppl* 2007;106:S27–35; Han S. *Diabetes* 2008;57:1723–1729.

SGLT2 Inhibitors: Glycemic Efficacy as Monotherapy



*P<.05 vs PBO

†12 weeks; baseline HbA1c = 8.1%

‡24 weeks; baseline HbA1c = 7.8%-8.0%

§ 12 weeks; baseline HbA1c = 7.9%

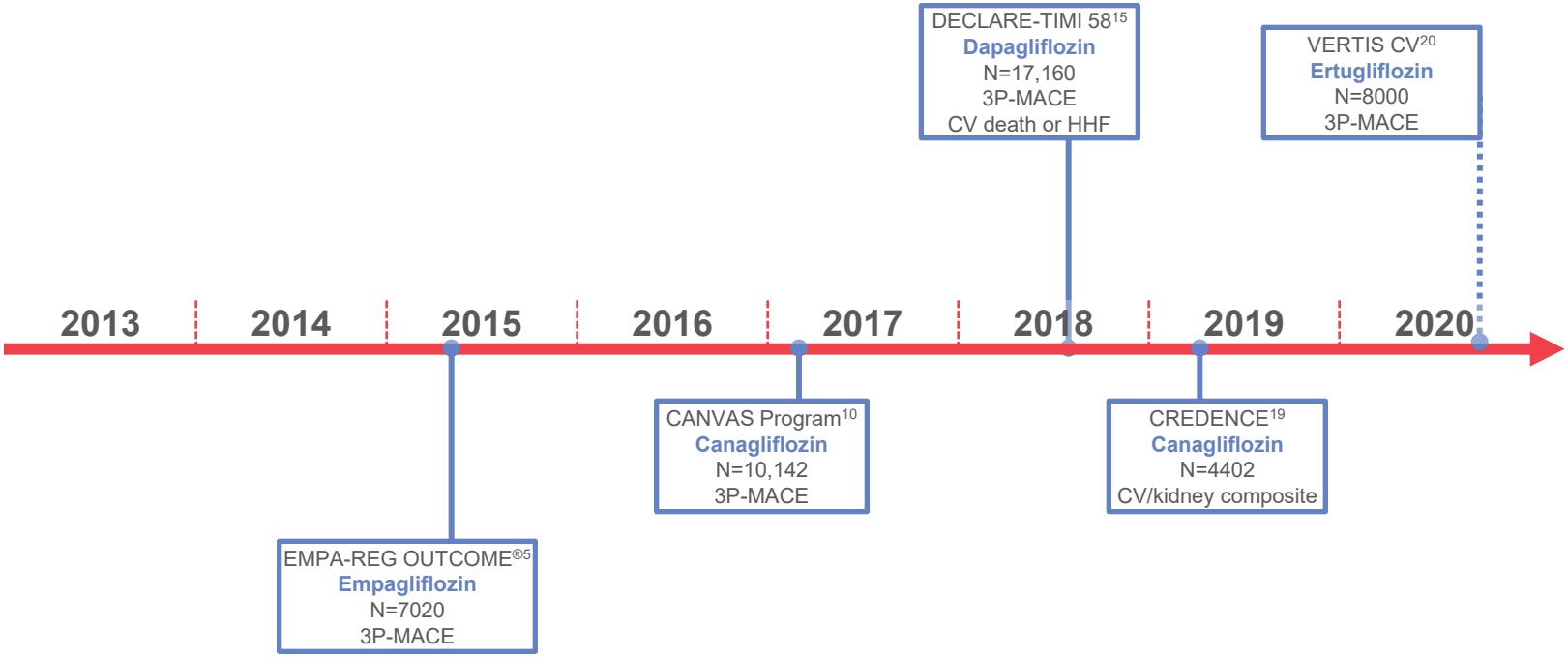
CANA = canagliflozin; DAPA = dapagliflozin; EMPA = empagliflozin; PBO = placebo

a. Inagaki N, et al. *Diabetes.* 2011;60(Suppl 1):999-P.

b. Ferrannini E, et al. *Diabetes Care.* 2010;33:2217-2224.

c. Ferrannini E, et al. *Diabetologia.* 2010;53(Suppl 1):877.

Μελέτες Καρδιαγγειακών εκβάσεων των SGLT2 αναστολέων

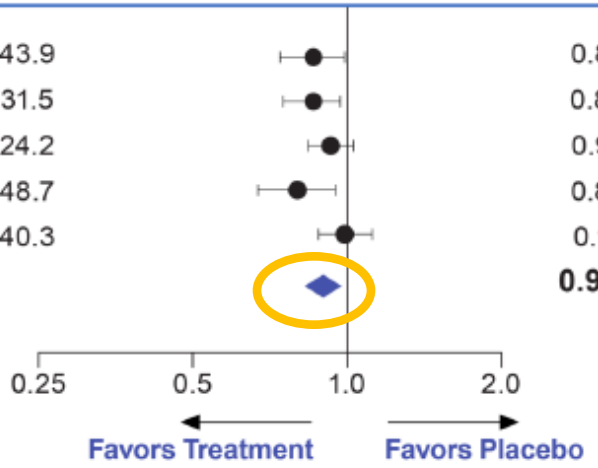


Markers on timeline represent trial completion and estimated disclosure dates, all of which come from ClinicalTrials.gov

Time to first MACE

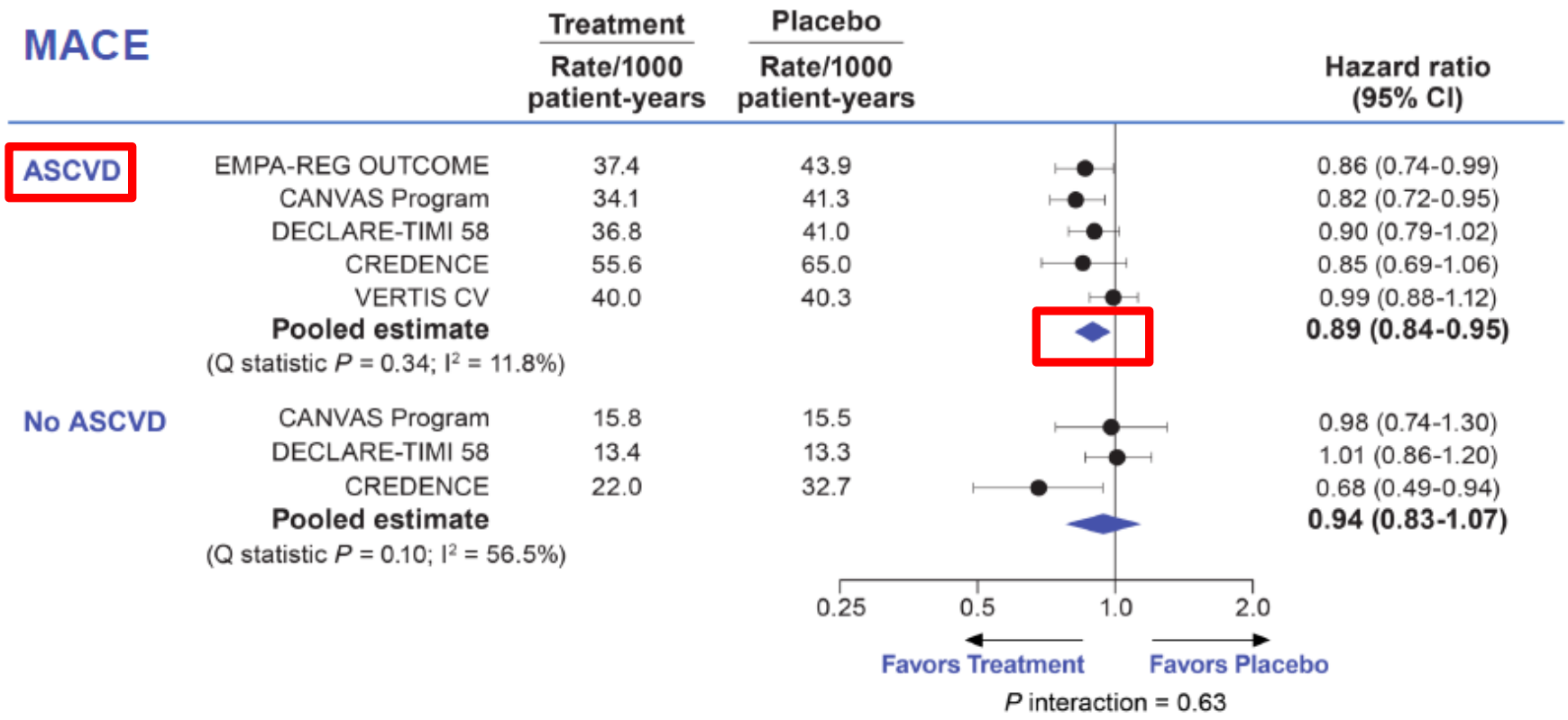
MACE

	Treatment Rate/1000 patient-years	Placebo Rate/1000 patient-years	Hazard ratio (95% CI)
EMPA-REG OUTCOME	37.4	43.9	0.86 (0.74-0.99)
CANVAS Program	26.9	31.5	0.86 (0.75-0.97)
DECLARE-TIMI 58	22.6	24.2	0.93 (0.84-1.03)
CREDENCE	38.7	48.7	0.80 (0.67-0.95)
VERTIS CV*	40.0	40.3	0.99 (0.88-1.12)
Pooled estimate			**0.90 (0.85-0.95)**
(Q statistic $P = 0.27$; $I^2 = 23.4\%$)			



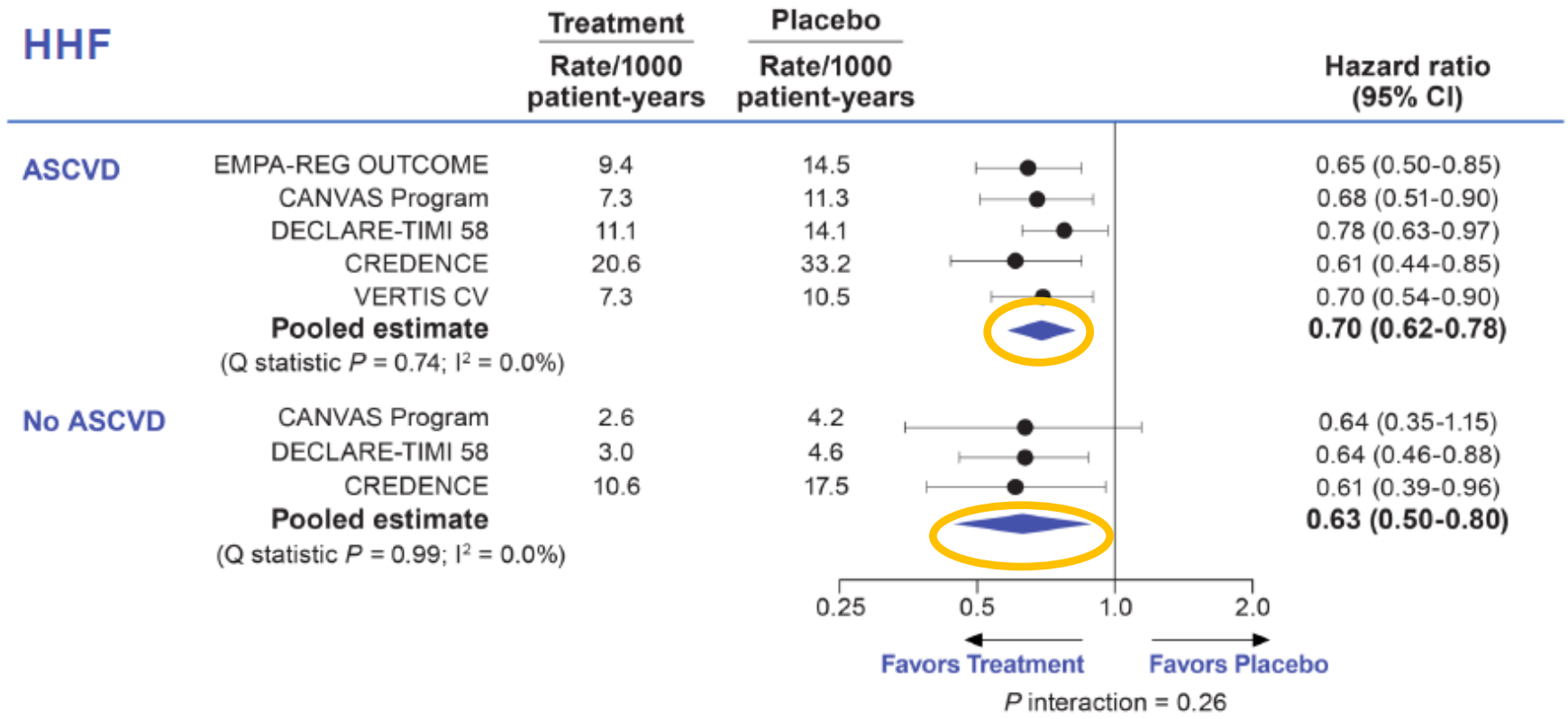
*Intention-to-treat population was used for consistency with other trials.
CI, confidence interval; MACE, major adverse cardiovascular events.

Time to first MACE – subgroup analysis by ASCVD



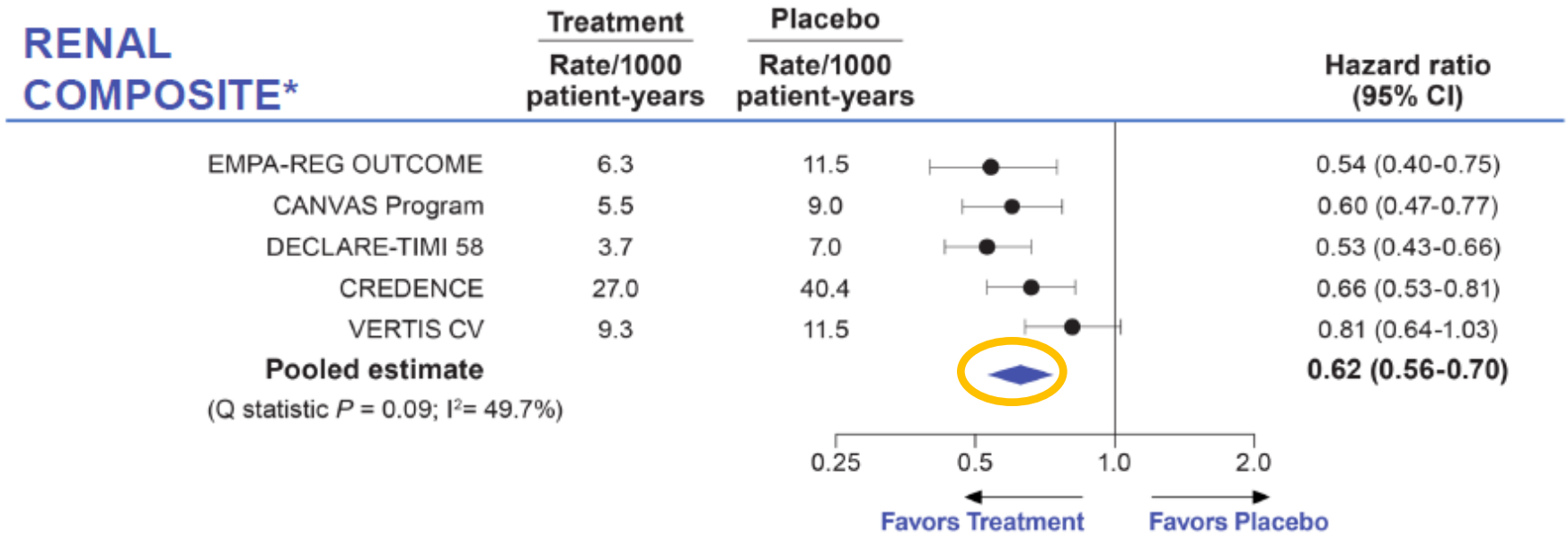
ASCVD, atherosclerotic cardiovascular disease; CI, confidence interval; MACE, major adverse cardiovascular events.

Time to first HHF – subgroup analysis by ASCVD

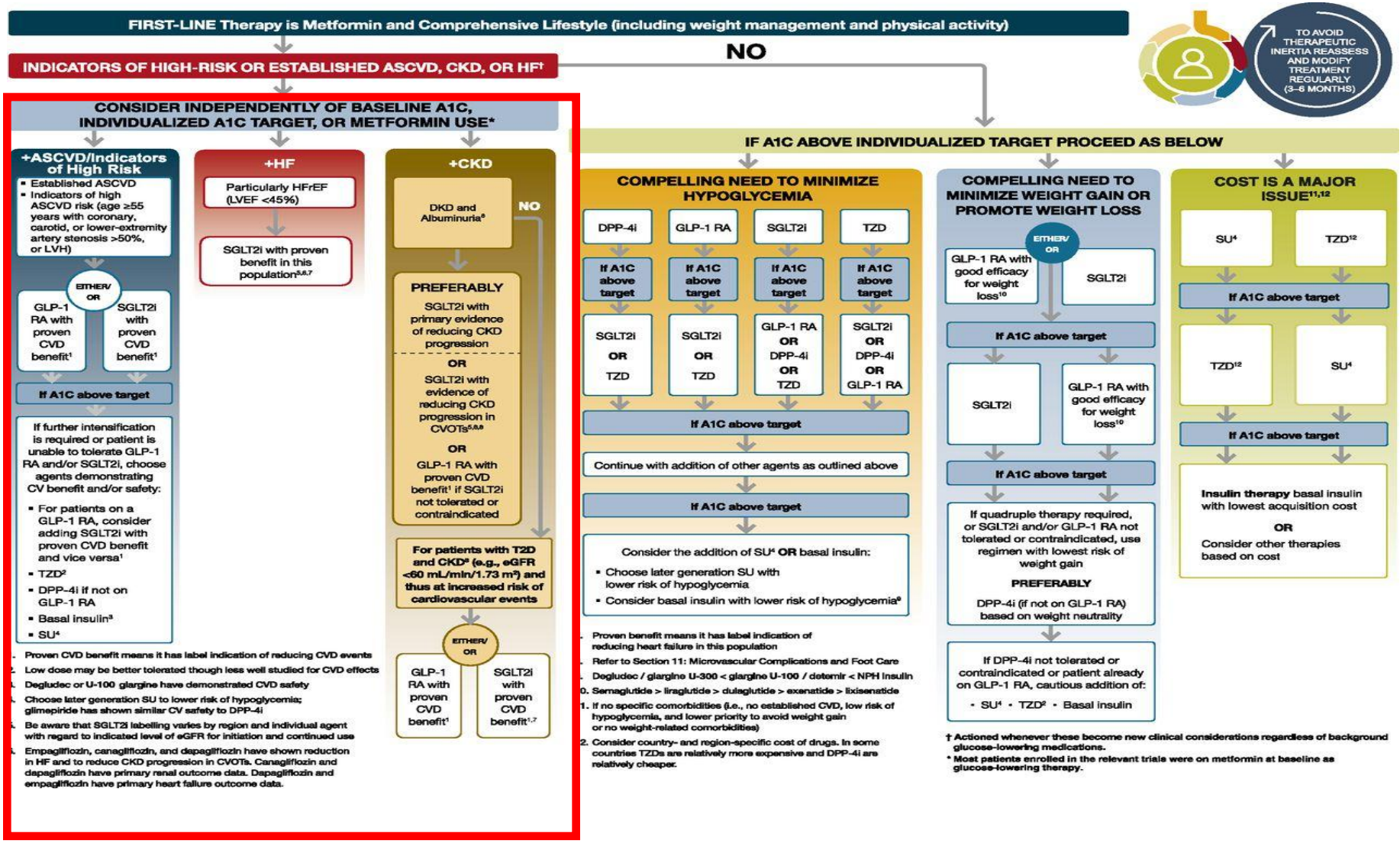


ASCVD, atherosclerotic cardiovascular disease; CI, confidence interval; HHF, hospitalization for heart failure.

Time to first renal composite outcome



*Renal composite outcome definitions varied across trials.
CI, confidence interval.



1. Proven CVD benefit means it has label indication of reducing CVD events
2. Low dose may be better tolerated though less well studied for CVD effects
3. Degludec or U-100 glargine have demonstrated CVD safety
4. Choose later generation SU to lower risk of hypoglycemia; glimepiride has shown similar CV safety to DPP-4i
5. Be aware that SGLT2i labelling varies by region and individual agent with regard to indicated level of eGFR for initiation and continued use
6. Empagliflozin, canagliflozin, and dapagliflozin have shown reduction in HF and to reduce CKD progression in CVOTs. Canagliflozin and dapagliflozin have primary renal outcome data. Dapagliflozin and empagliflozin have primary heart failure outcome data.
7. Proven benefit means it has label indication of reducing heart failure in this population
8. Refer to Section 11: Microvascular Complications and Foot Care
9. Degludec / glargine U-300 < glargine U-100 / detemir < NPH insulin
10. Semaglutide > liraglutide > dulaglutide > exenatide > lixisenatide
11. If no specific comorbidities (i.e., no established CVD, low risk of hypoglycemia, and lower priority to avoid weight gain or no weight-related comorbidities)
12. Consider country- and region-specific cost of drugs. In some countries TZDs are relatively more expensive and DPP-4i are relatively cheaper.

† Actioned whenever these become new clinical considerations regardless of background glucose-lowering medications.

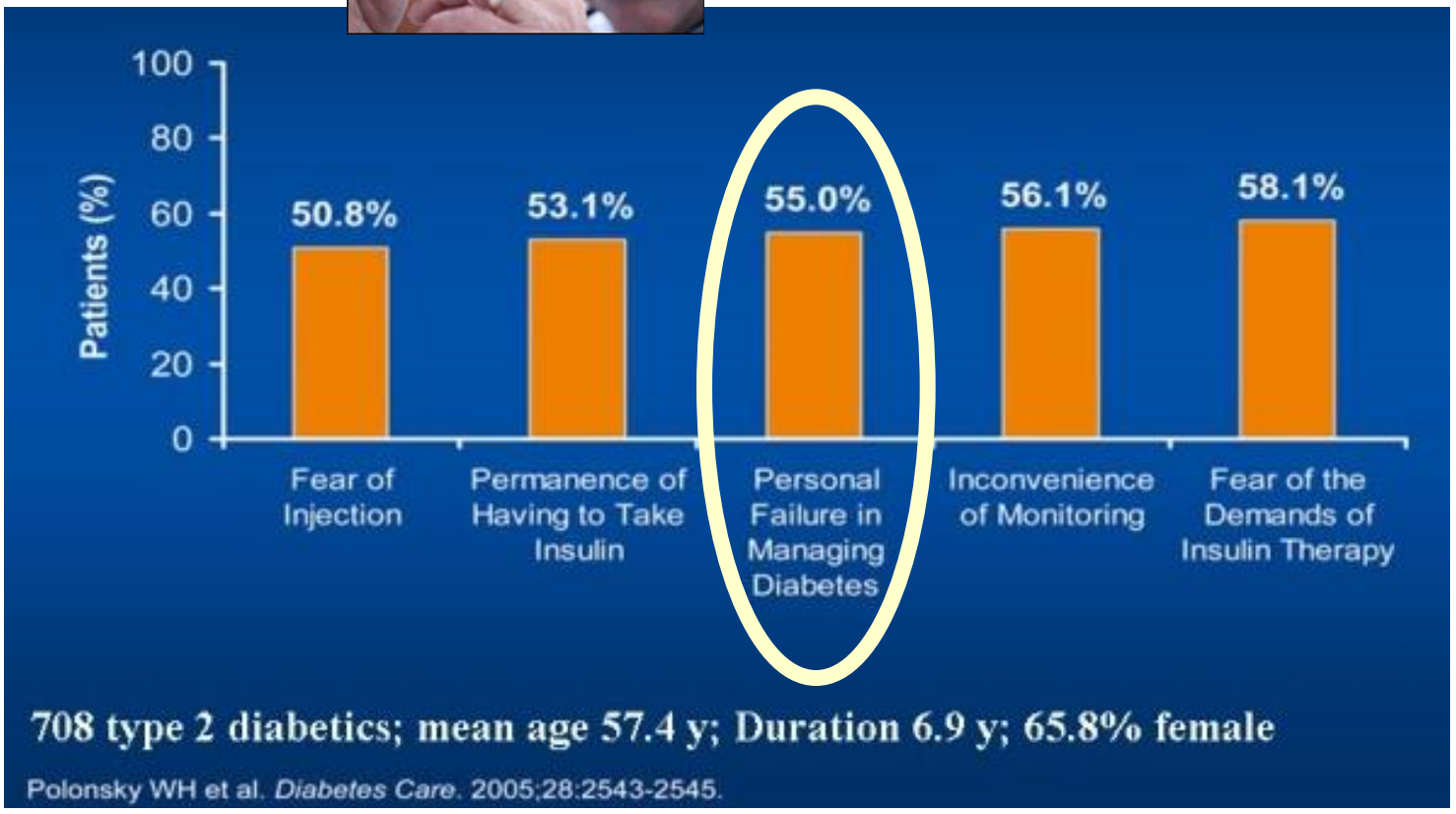
* Most patients enrolled in the relevant trials were on metformin at baseline as glucose-lowering therapy.

ΙΝΣΟΥΛΙΝΗ

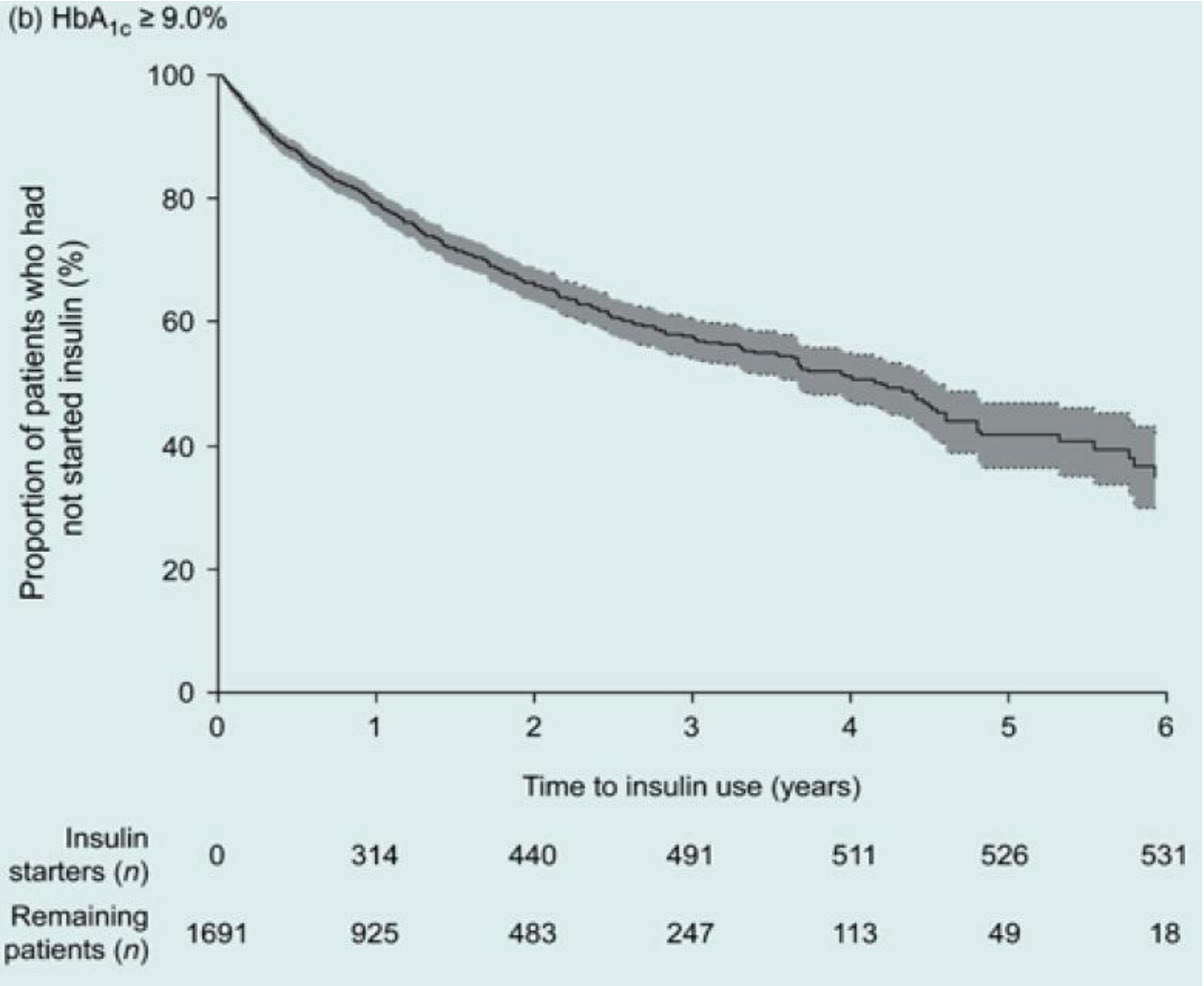
ΕΝΑΡΞΗ ΙΝΣΟΥΛΙΝΗΣ στο ΣΔτ2

Αιτίες άρνησης έναρξης ινσουλίνης

Επί αποτυχίας θα πρέπει
να κάνετε ινσουλίνη

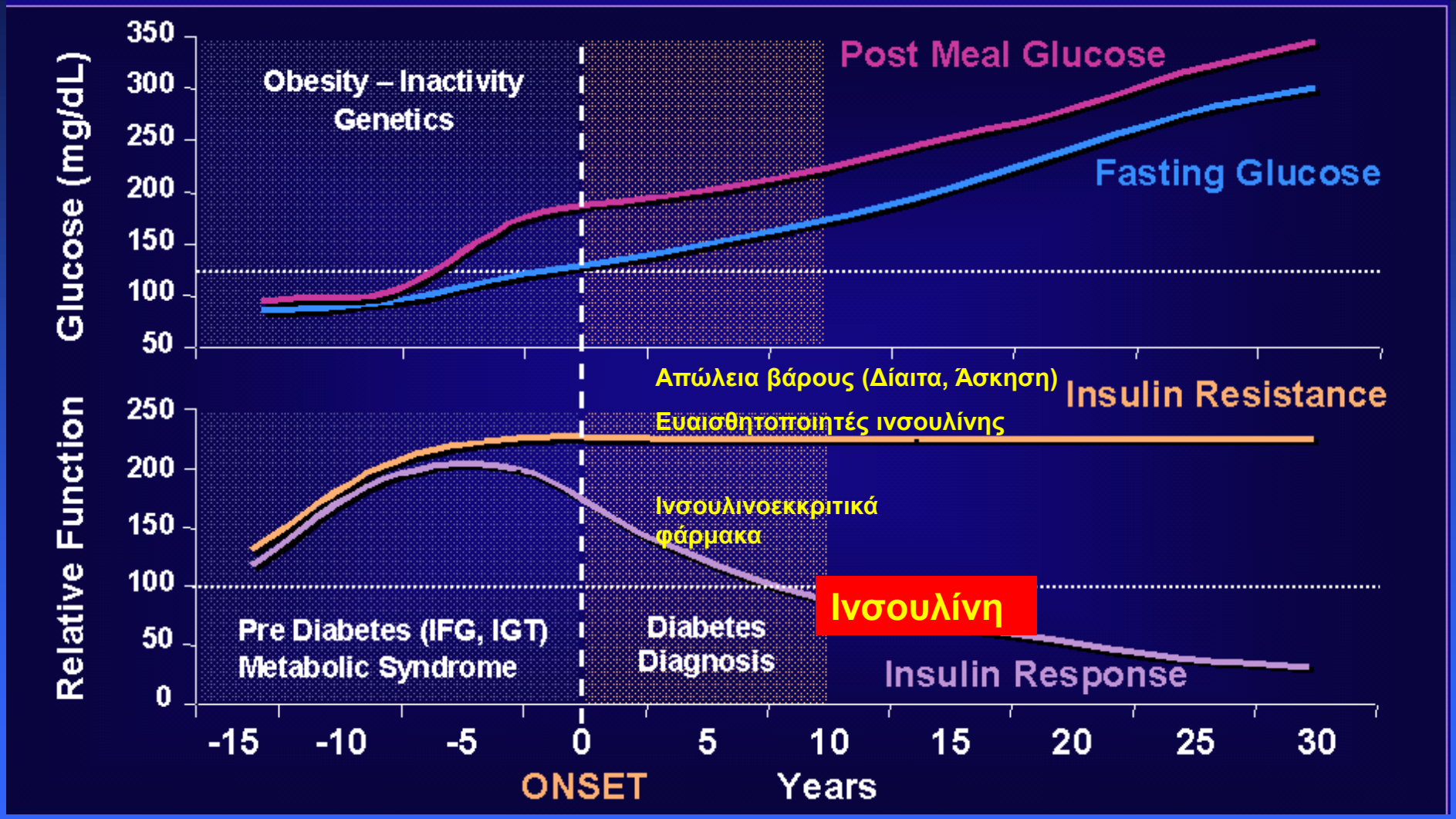


Οι ασθενείς αρχίζουν ινσουλίνη πολύ αργά!

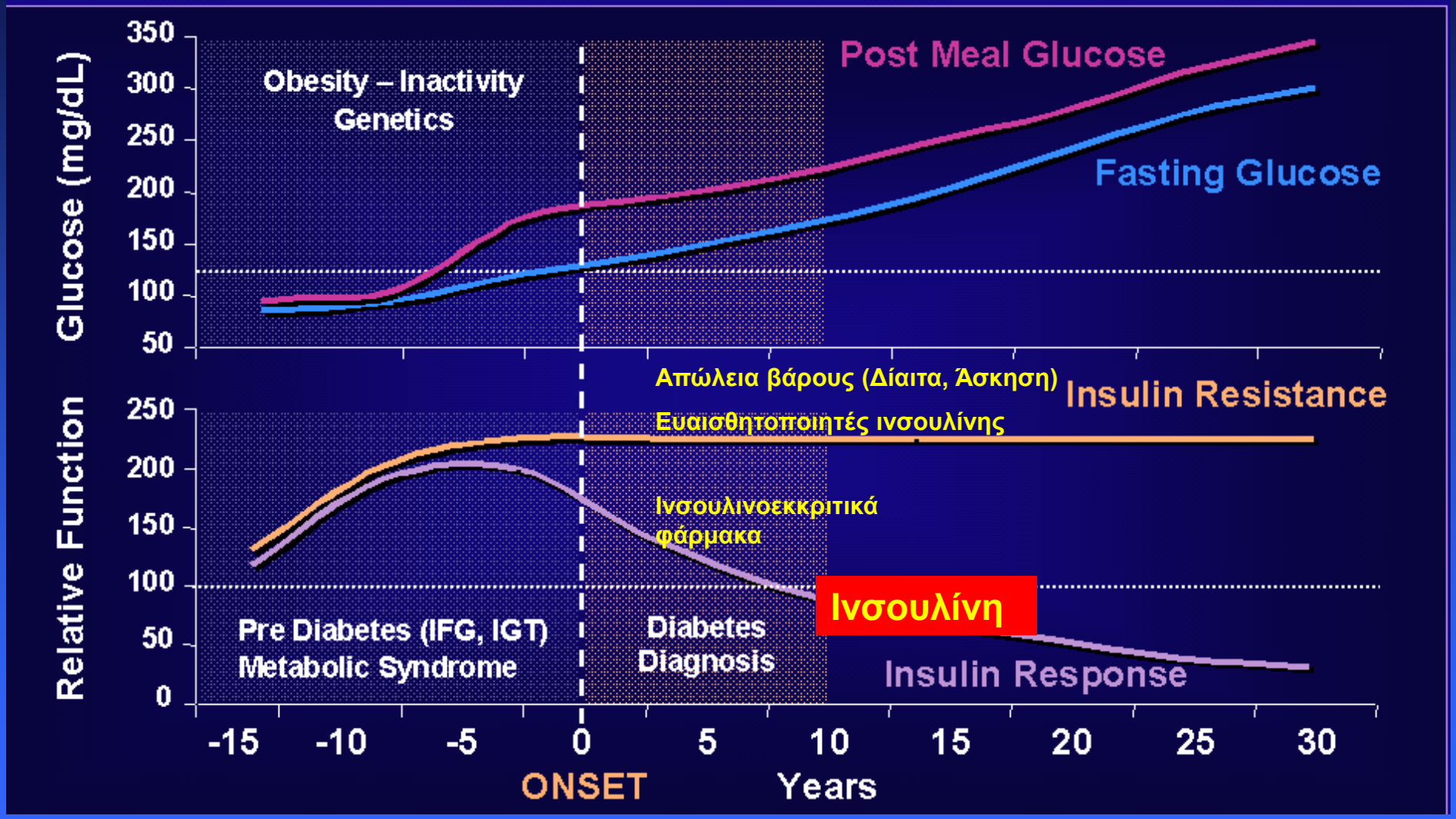


A. Rubino, Journal compilation © 2007 Diabetes UK. Diabetic Medicine, 24, 412–1418

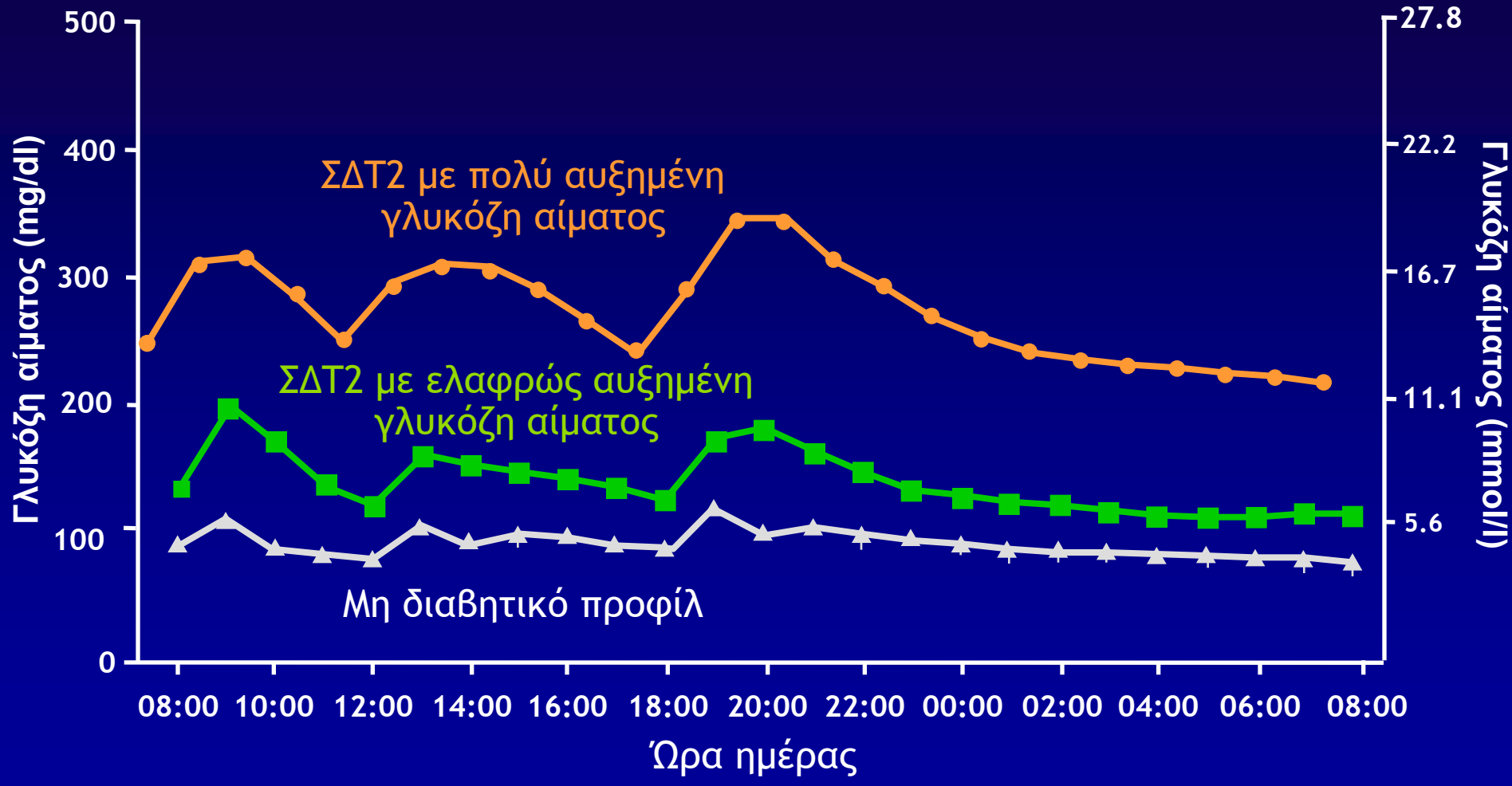
Φυσική Ιστορία ΣΔ2
Τροποποίηση με τη Θεραπεία



Φυσική Ιστορία ΣΔ2
Τροποποίηση με τη Θεραπεία



Σημασία της ρύθμισης της γλυκόζης νηστείας



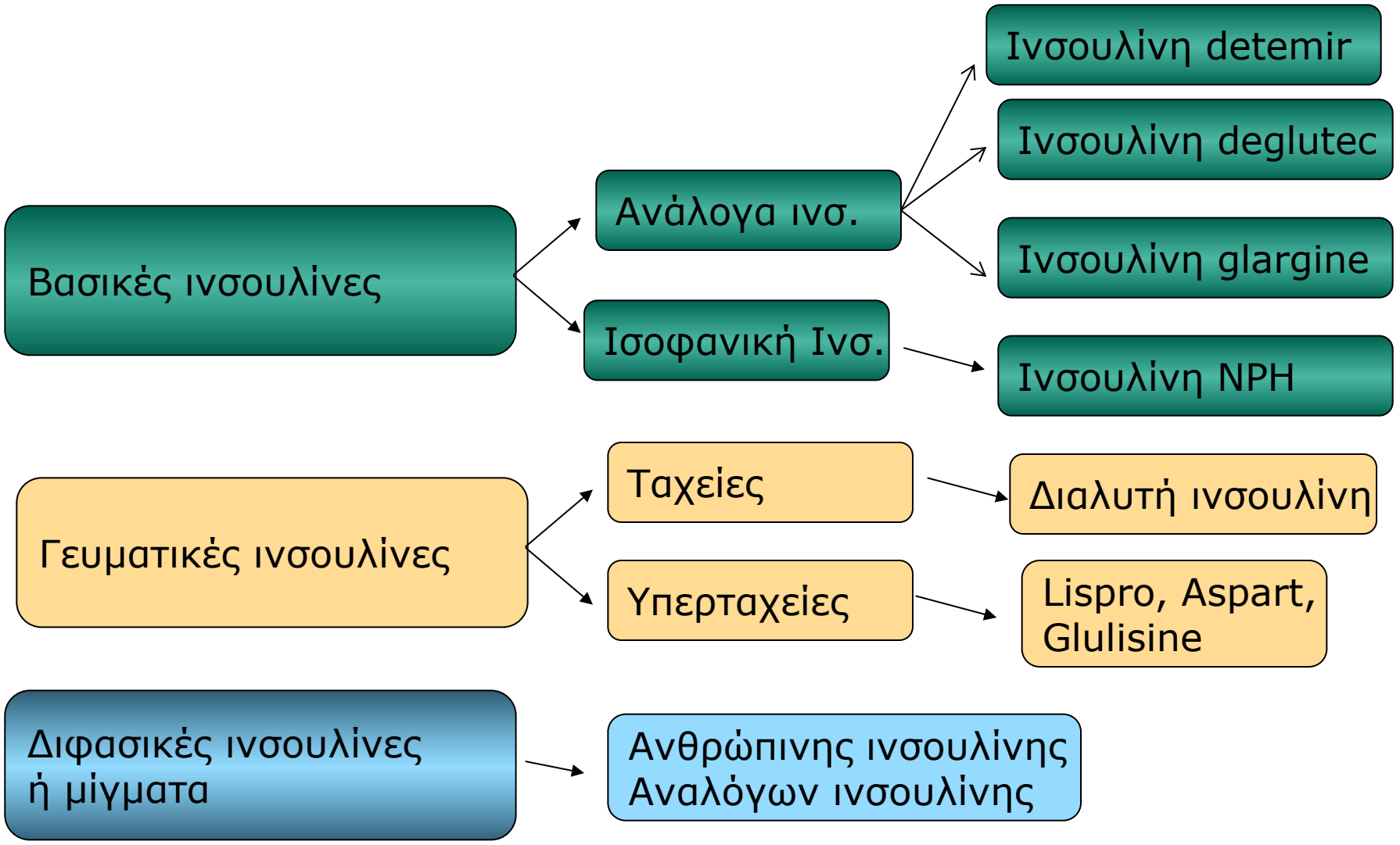
Reaven G. Diabetes 1988;37:1020–4.

Πόση βασική ινσουλίνη; Έναρξη-τιτλοποίηση

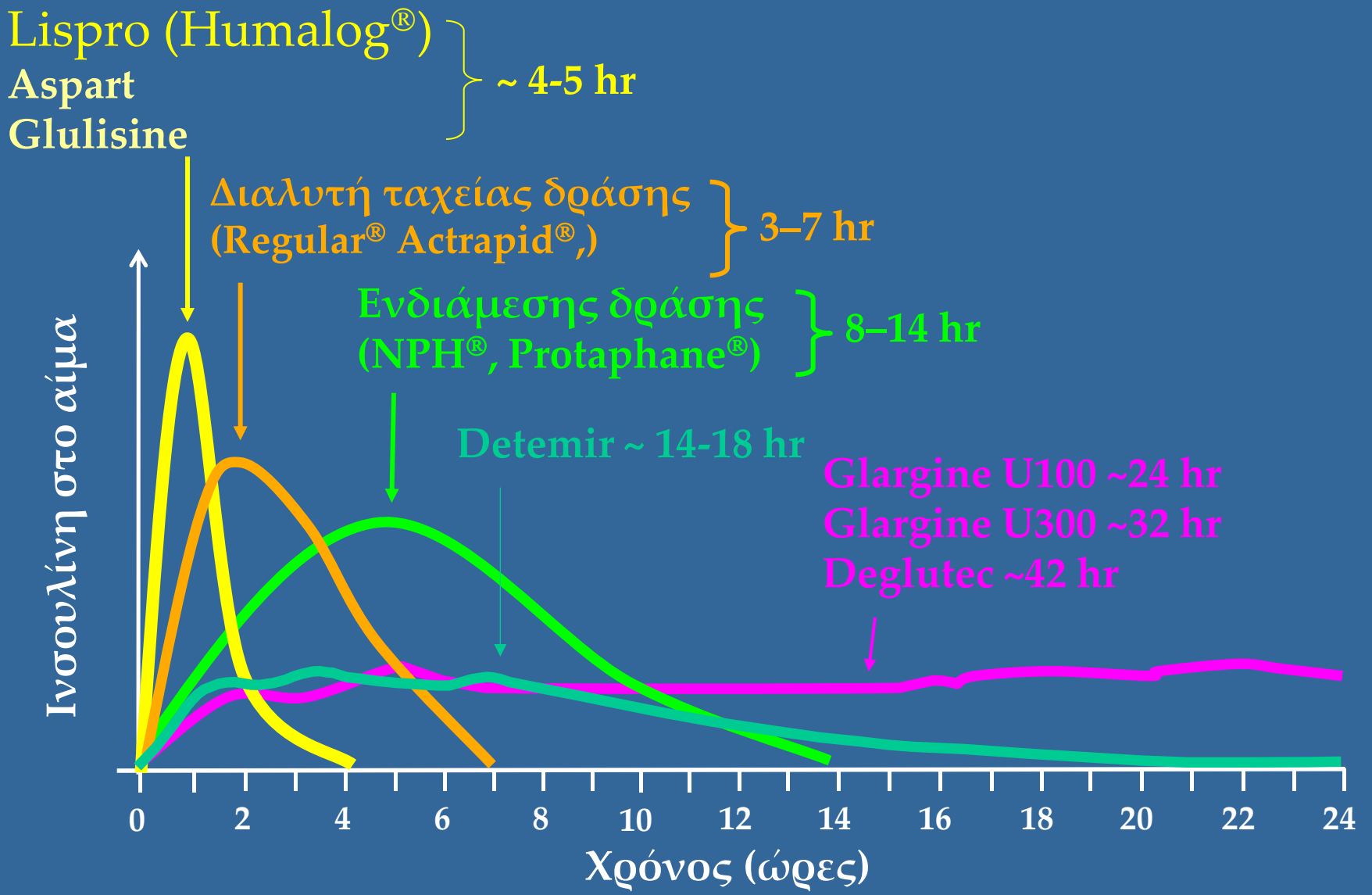
- **ΕΝΑΡΞΗ**
- **Σταθερή δόση: 10 μονάδες**
- **Σε BMI>30 kg/m^2: 0,2 μον/kg βάρους**
- **ΘΕΣΠΙΣΗ ΣΤΟΧΟΥ**
- **Τιτλοποίηση με βάση τη μέση τιμή των τριών τελευταίων πρωινών μετρήσεων νηστείας**

- ***Παράδειγμα αλγόριθμου τιτλοποίησης*:**
- **Στόχος πρωινού σακχάρου νηστείας 80-120 mg/dl:**
- **< 80 επιστροφή στην προηγούμενη δόση**
- **80-120 0**
- **121-180 +2**
- **>181 +4**
- **Υπογλυκ - 2 έως 4 μον**

Ποιούς τύπους ινσουλίνης έχουμε;

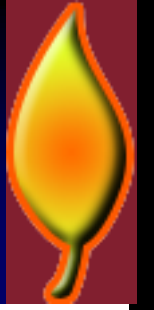


Καμπύλες δράσης των διαφόρων ινσουλινών



Τροποπ. από Rosenstock J. Clin Cornerstone. 2001; 4: 50-64

ΙΝΣΟΥΛΙΝΟΘΕΡΑΠΕΙΑ



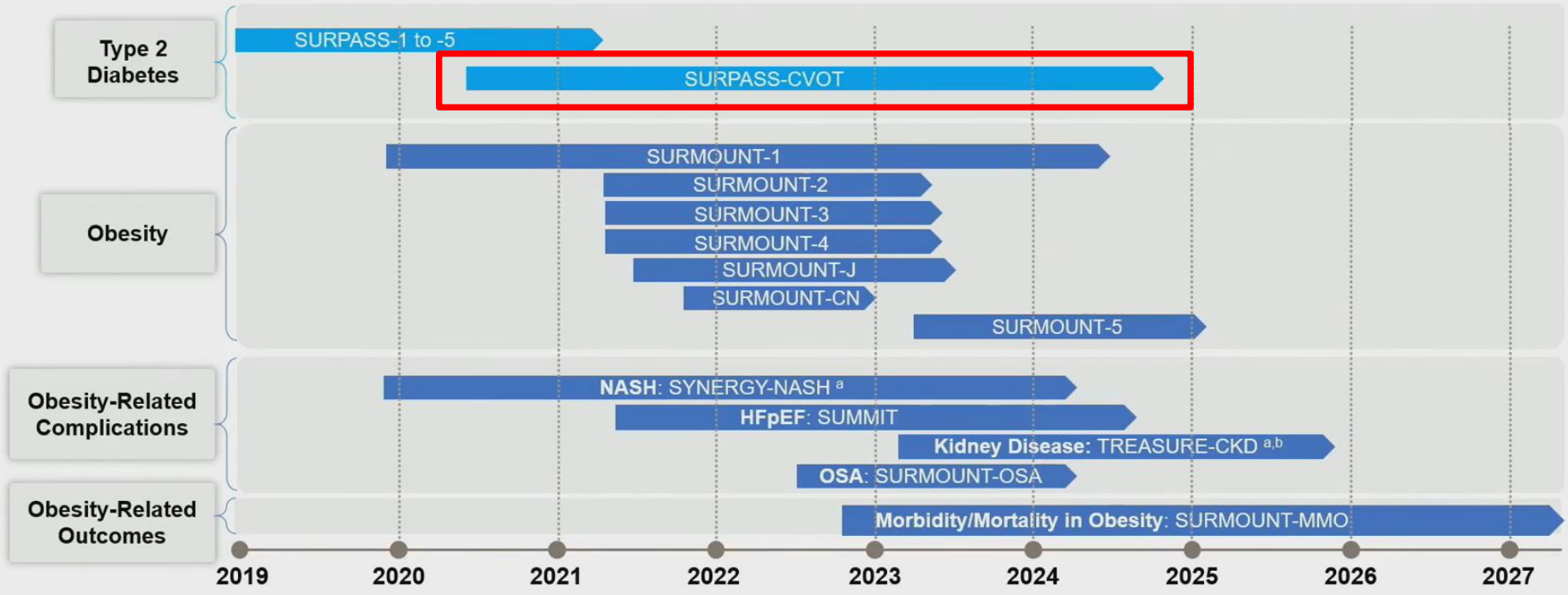
ΕΚΠΑΙΔΕΥΣΗ ΣΤΗΝ ΤΕΧΝΙΚΗ ΤΗΣ ΕΝΕΣΗΣ!!!!

ΚΑΙ ΣΤΗΝ ΤΙΤΛΟΠΟΙΗΣΗ ΤΗΣ ΙΝΣΟΥΛΙΝΗΣ

ΔΙΠΛΟΙ GLP-1/GIP ΑΓΩΝΙΣΤΕΣ

Tirzepatide Clinical Development Program

T2D, Obesity, and Obesity-Related Outcomes



[a] Phase 2 study.
[b] Not an outcomes study.
CKD=Chronic Kidney Disease; CVOT=Cardiovascular Outcomes; HFpEF=Heart Failure With Preserved Ejection Fraction; MMO=Morbidity/Mortality in Obesity; MoA=Mechanism of Action; NASH=Non-alcoholic Steatohepatitis; OSA=Obstructive Sleep Apnea.

The dual GIP-GLP-1 agonist tirzepatide: Unprecedented weight loss in long-term obesity studies

2

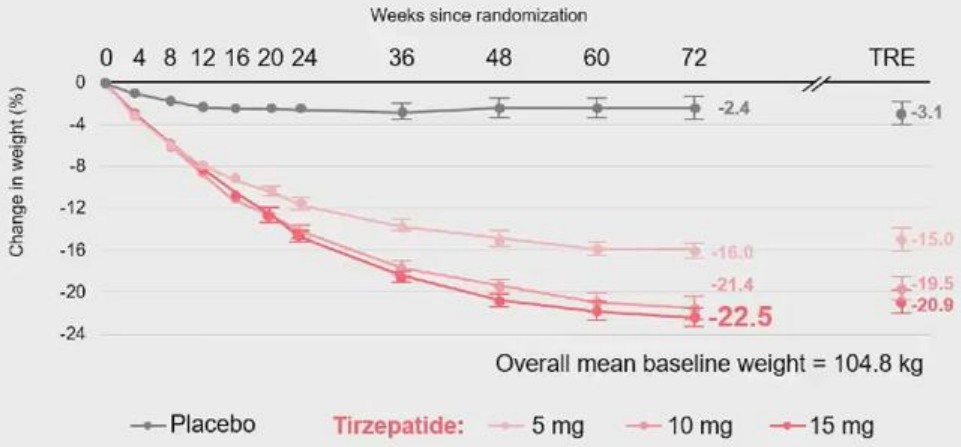
Study

2022

Phase 3

Obese adults

Body weight is decreased dose-dependently

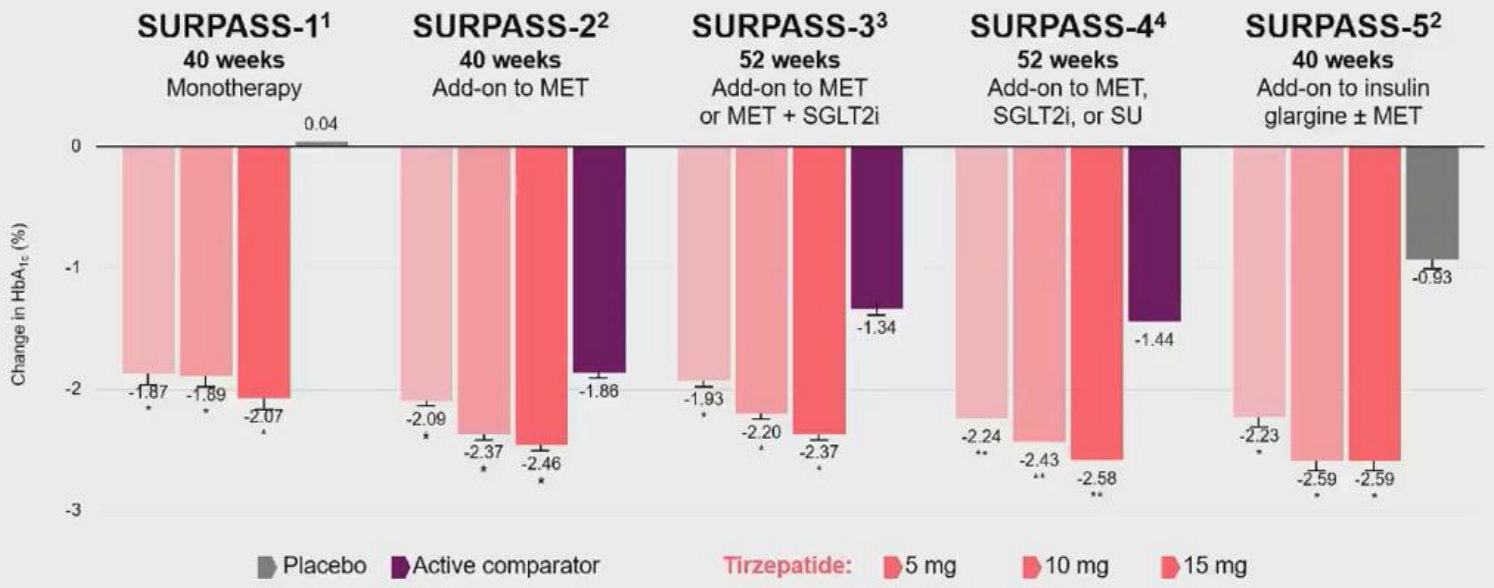


TRE, treatment regimen estimand

Jastreboff AM, et al. *N Engl J Med*. 2022;387(3):205-216.

The dual GIP-GLP-1 receptor agonist tirzepatide: Superior impact on long-term blood sugar level

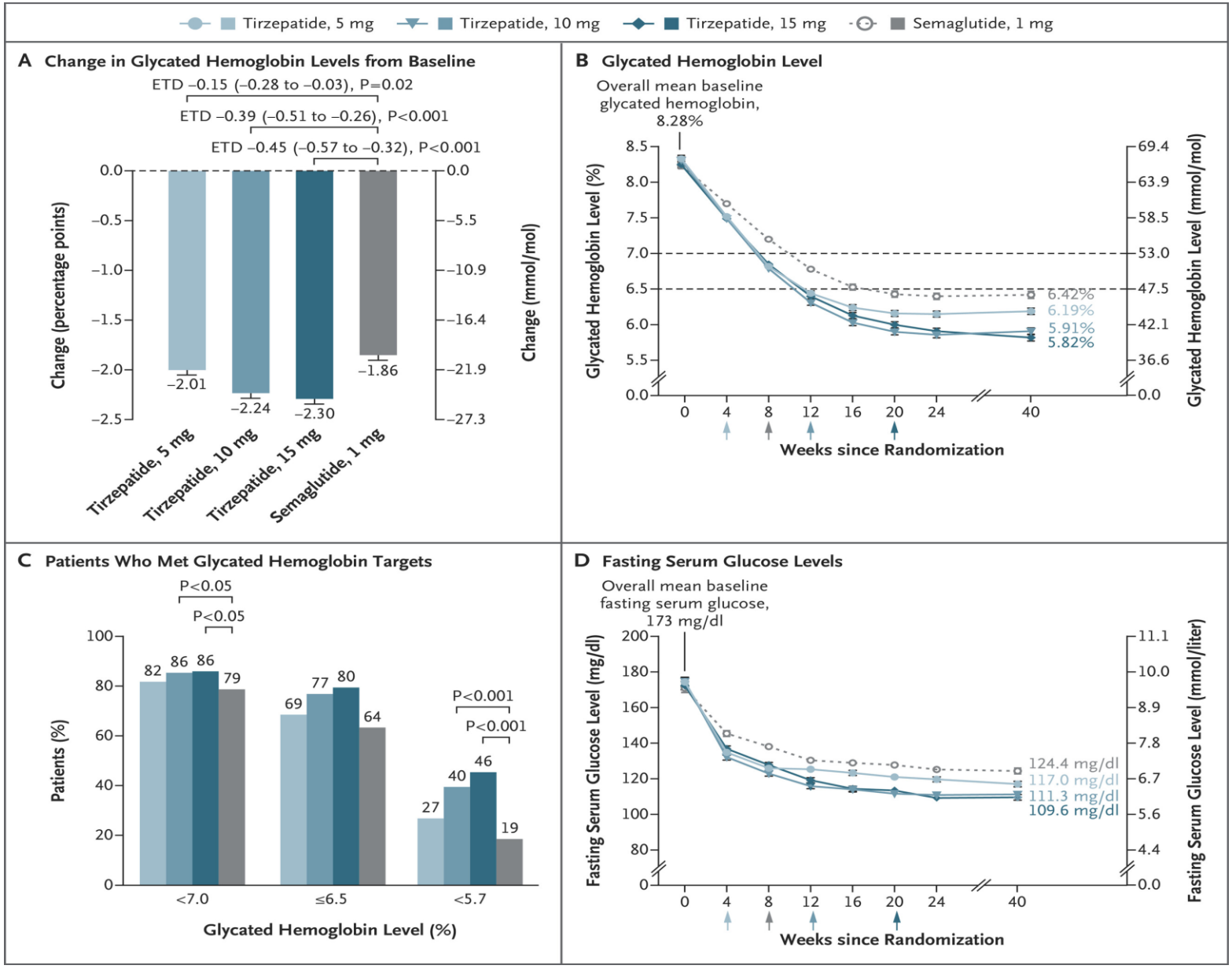
2



*p<0.001; **p<0.0001. HbA_{1c}, glycated hemoglobin A1c; MET, metformin; SGLT2i, sodium dependent glucose co-transporter 2 inhibitor; SU, sulfonylurea

1. Rosenstock J, et al. *Lancet*. 2021;398(10295):143-155. **2.** Frías JP, et al. *N Engl J Med*. 2021;385(6):503-515. **3.** Ludvik B, et al. *Lancet*. 2021;398(10300):583-598. **4.** Del Prato S, et al. *Lancet*. 2021;398(10313):1811-1824. **5.** Dahl D, et al. *JAMA*. 2022;327(6):534-545.

Tirzepatide versus Semaglutide Once Weekly in Patients with Type 2 Diabetes



Frias, et al. Surpass-2. N Engl J Med 2021;385:503-15

TIRZEPATIDE SHOWS CARDIOVASCULAR & MORTALITY BENEFIT IN SURPASS-CVOT TRIAL

>13,000+ ADULTS
30 COUNTRIES

COMPARATOR:
Dulaglutide (Trulicity)

KEY FINDINGS

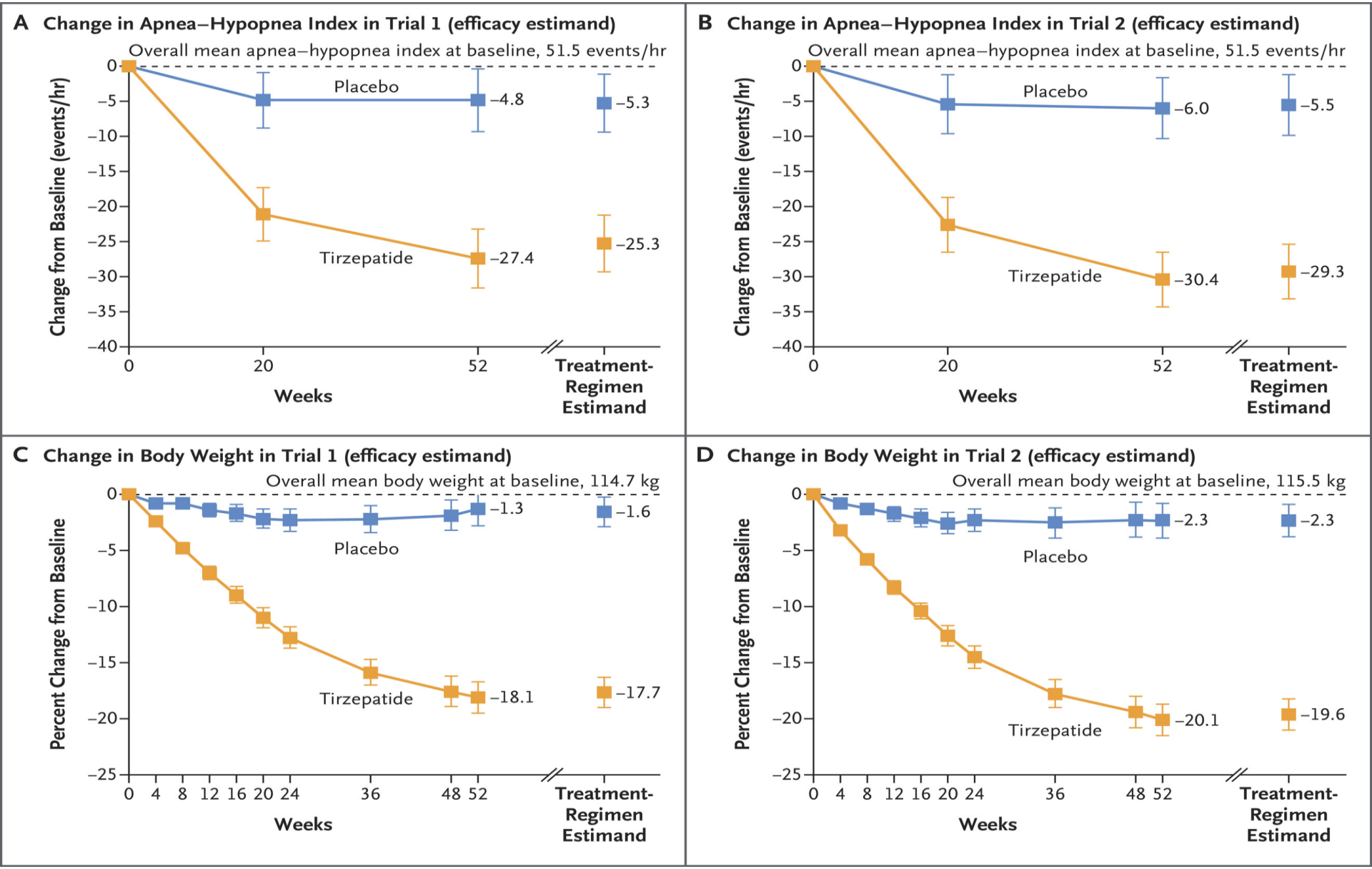
- Non-inferior for MACE-3 (CV death, MI, stroke): HR 0.92
- All-cause mortality ↓16% (HR 0.84; p=0.002)
- HbA1c ↓1,73% vs 0,90% (Δ: -0.83%, p<0.001)
- Weight loss ~11,4 kg vs 4.7 kg
- Slower eGFR decline by 3,54 mL/min CKD subgroups
- Discontinuation due to GI AEs: 13,3% vs 10.2%

WHAT'S NEXT?

- Full results to be presented at EASD 2025
- Regulatory filings expected later this year
- Peer-reviewed publication to follow

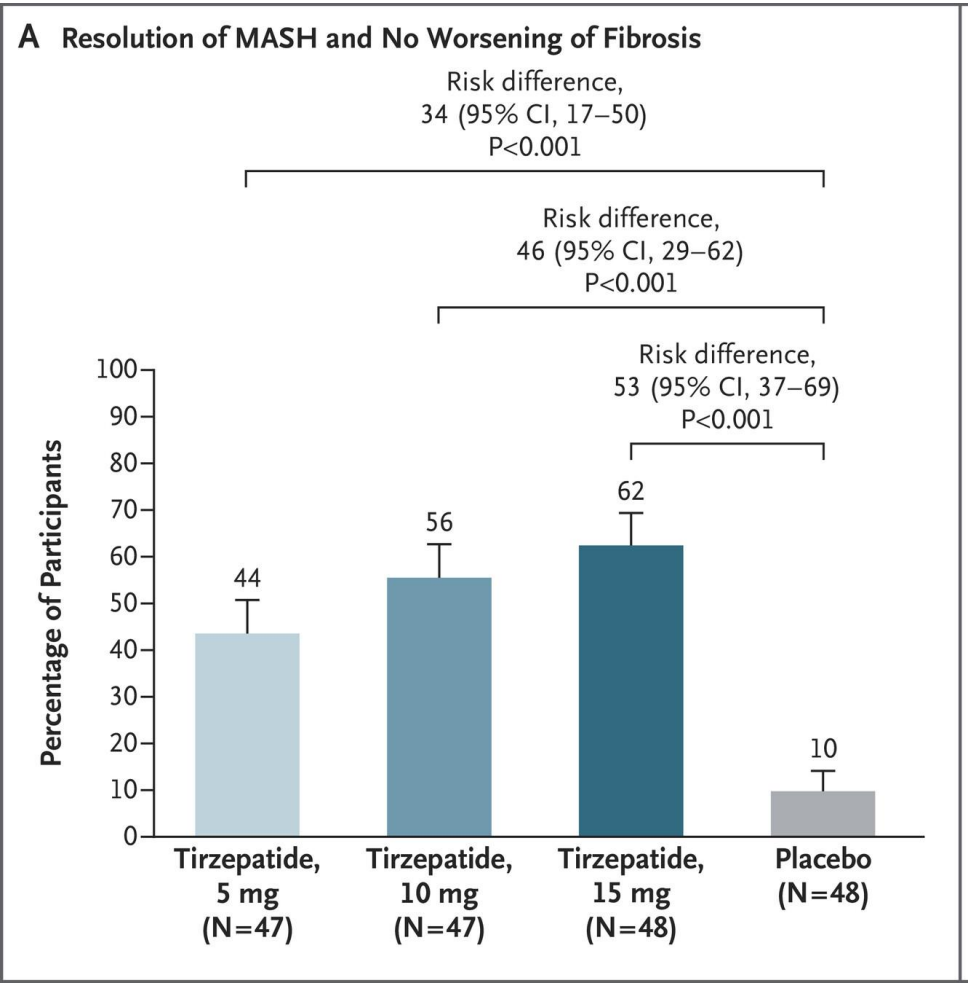
PI from India

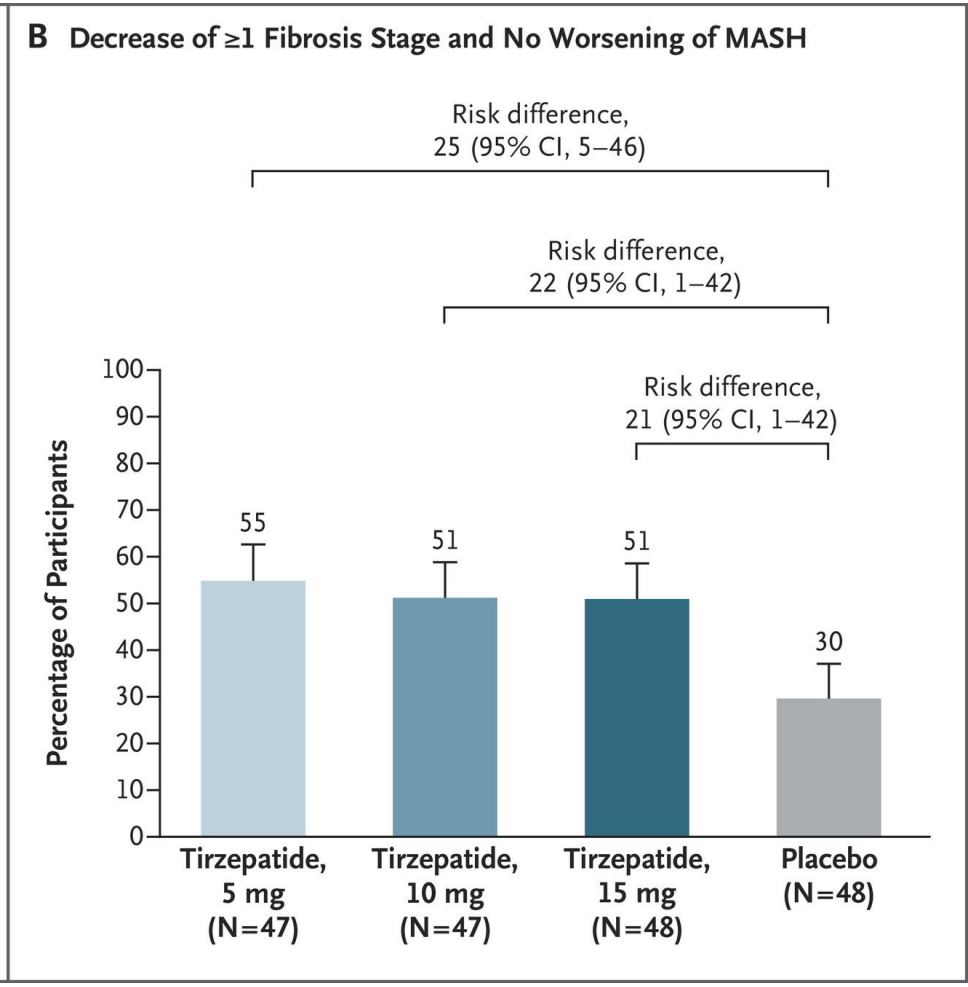
Tirzepatide for the Treatment of Obstructive Sleep Apnea and Obesity



Malhotra et al. N Engl J Med 2024;391:1193-205

Tirzepatide for Metabolic Dysfunction–Associated Steatohepatitis with Liver Fibrosis





Loomba et al., N Engl J Med 2024;391:299-310

Drug	Active molecule	Dosage	Indication
Ozempic®	Semaglutide	1 mg/week (subcutaneous injection)	Type 2 diabetes
Rybelsus®	Semaglutide	7 or 14 mg/day (oral tablets)	Type 2 diabetes
Wegovy®	Semaglutide	2.4 mg/week (subcutaneous injection)	Obesity
Mounjaro™	Tirzepatide	2.5 –15 mg/week (subcutaneous injection)	Type 2 diabetes

Νεώτερες Θεραπείες στον ΣΔ2 (και παχυσαρκία)

- Αυξημένες δοσολογίες GLP-1 RAs
- Μη πεπτιδικοί p.o. GLP-1 RAs
- Διπλοί και τριπλοί αγωνιστές GLP-1/GIP/Glucagen
- Συνδυασμοί GLP-1/αναλόγων αμυλίνης (Cagrilintide)
- Εβδομαδιαίες βασικές ινσουλίνες
- Συνδυασμοί εβδομαδιαίων GLP-1RAs/ινσουλινών
- Ινσουλίνη από του στόματος?

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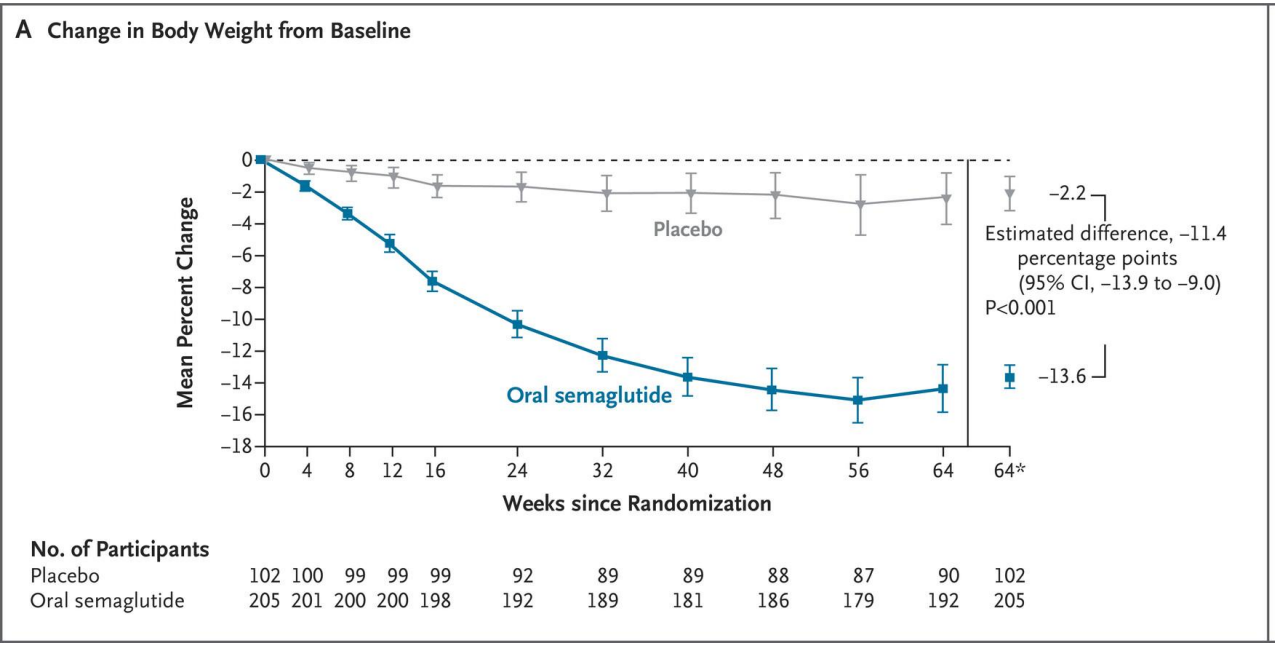
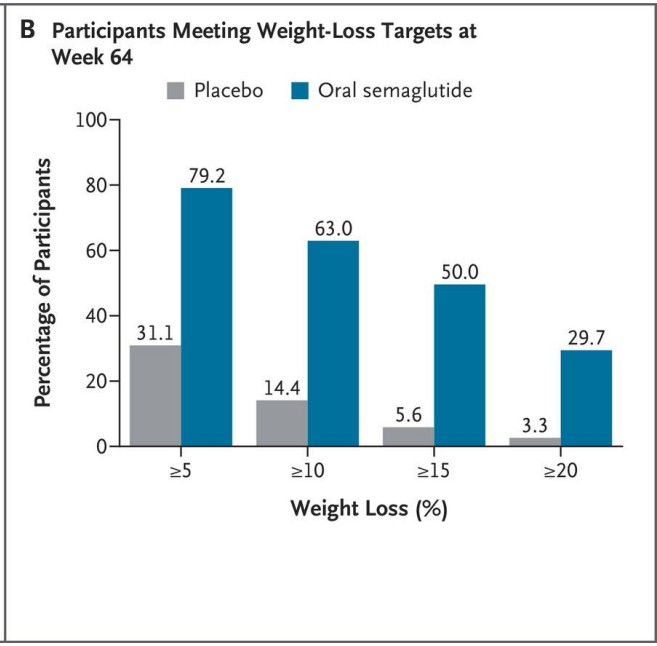
Agents with Significant Weight Loss Potential in Development for Type 2 Diabetes/Obesity

	Class	Name	Phase	Indication
GLP-1 RA	SQ	Semaglutide 7.2 mg (STEP-UP Diabetes - equivalent study)	3	Obesity
	Oral	Semaglutide 25 mg and 50 mg	3	Obesity & T2DM
	Oral	Orfoglipron	2	Obesity & T2DM
	SQ	Semaglutide 8 mg and 16 mg	2	T2DM
	Oral	Danuglipron	2	Obesity
	Oral	Lotiglipron	2	Obesity & T2DM
Dual/Triple Incretin Agonists	GLP-1/GRA	Mazdutide 9 mg	3	Obesity
	GLP-1/GRA	Pemvidutide	2	Obesity
	GLP-1/GRA	BI456906	2	Obesity
	GLP-1/GIP	CT-388	2	Obesity & T2DM
	GLP-1/GIP/GRA	Retatrudide	2	Obesity & T2DM
	GLP-1/amylin	Semaglutide/Cagrilintide (Redifine 2 – equivalent study)	3/2	Obesity/T2DM
Other	GLP-1 RA/ GIP *ANT*agonist	AMG 133	2	Obesity
	TAS2R agonist	ARD-101	2	Obesity
	Type II-B activin rec. modulator	Bimagrumab	2	Obesity
	PYY agonist	PYY 1875	2	Obesity

Information to the best of my knowledge, likely not a comprehensive list. Only agents in phase 2 or later development listed.

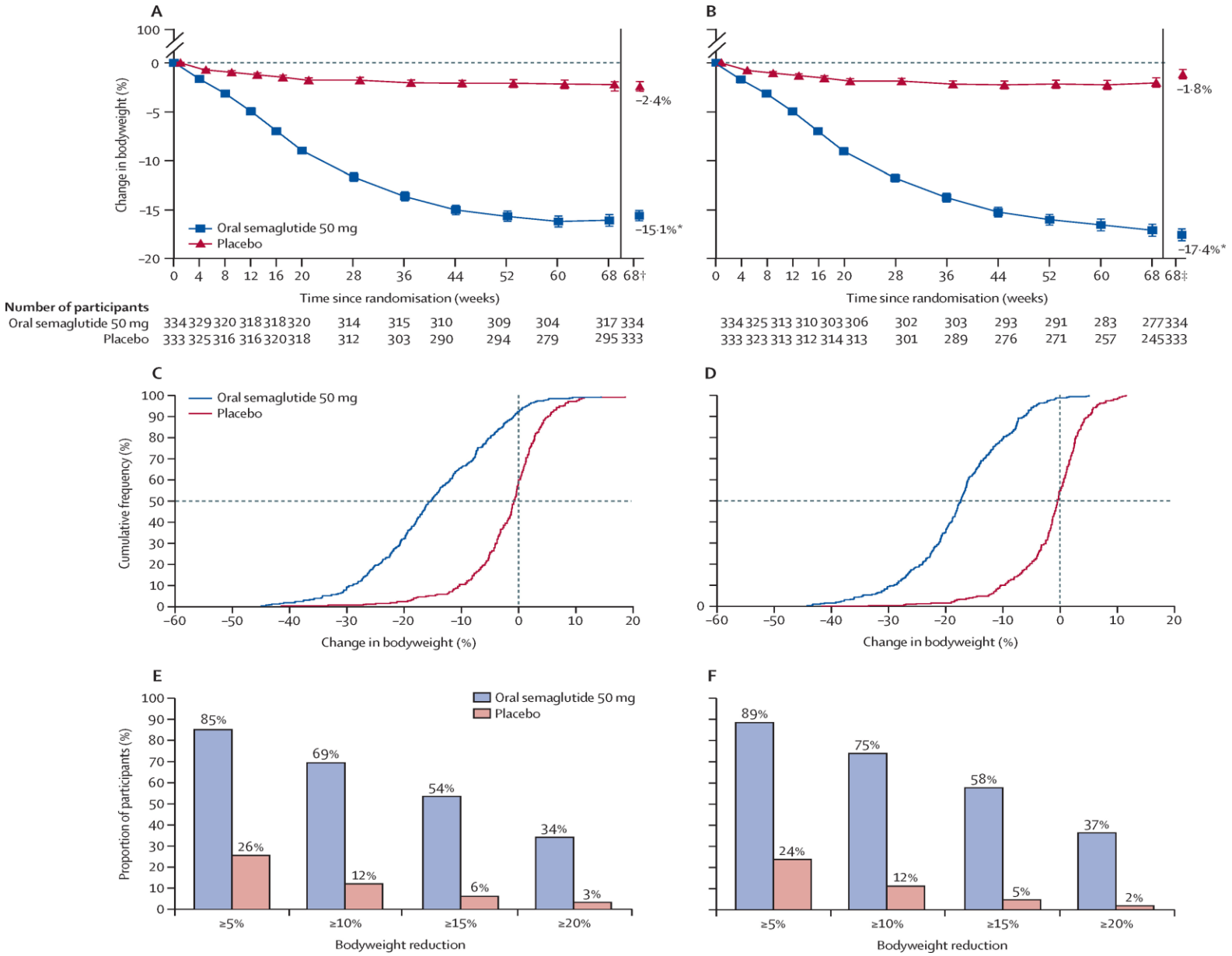
Oral Semaglutide at a Dose of 25 mg in Adults with Overweight or Obesity
OASIS-4 study





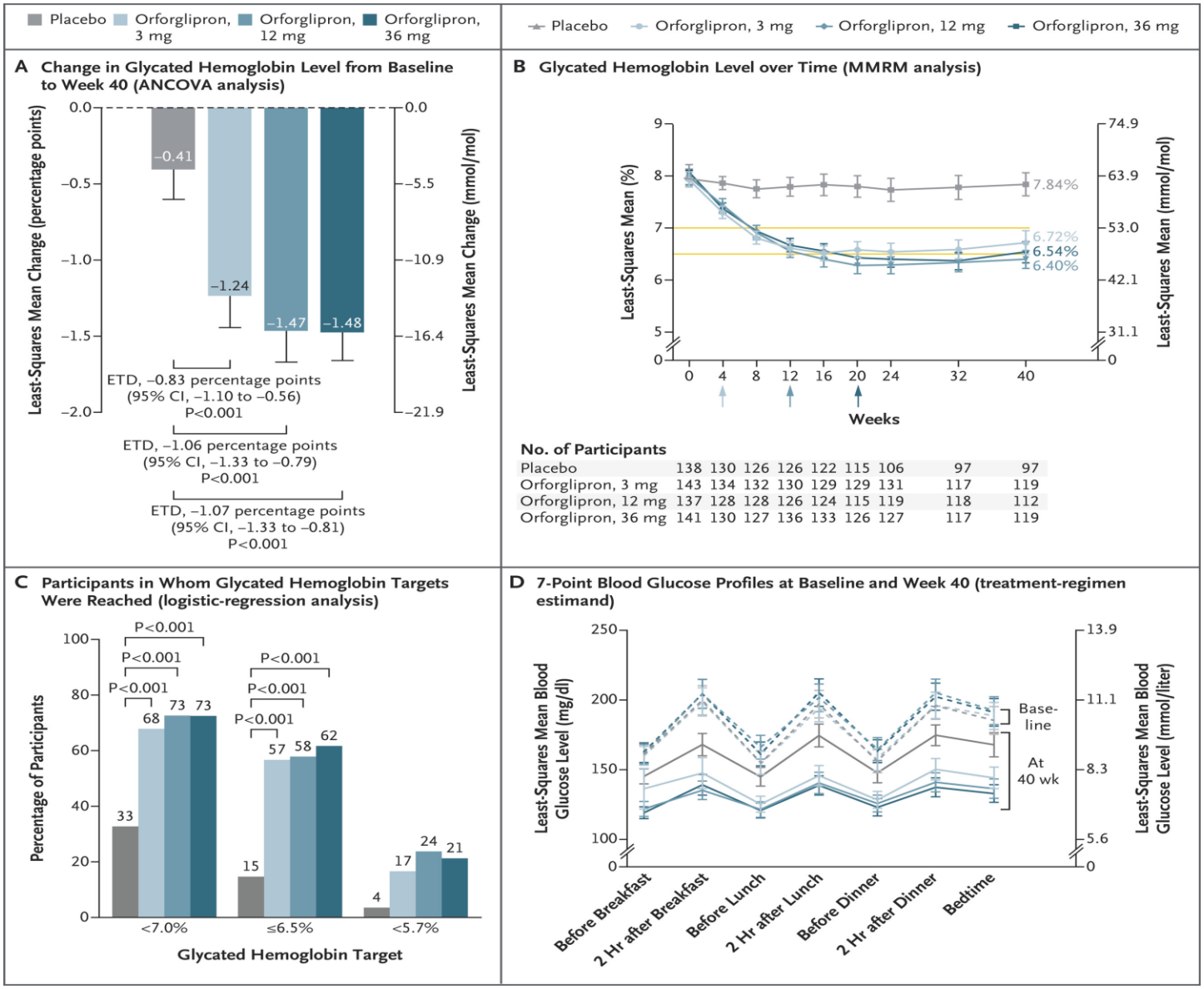
Wharton, et l., N Engl J Med 2025;393:1077-87

Oral semaglutide 50 mg taken once per day in adults with overweight or obesity (OASIS-1 study)



Knop, et al., Lancet 2023; 402: 705–19

Orforglipron, an Oral Small-Molecule GLP-1 Receptor Agonist, in Early Type 2 Diabetes



Rosenstock, et al. N Engl J Med 2025;393:1065-76

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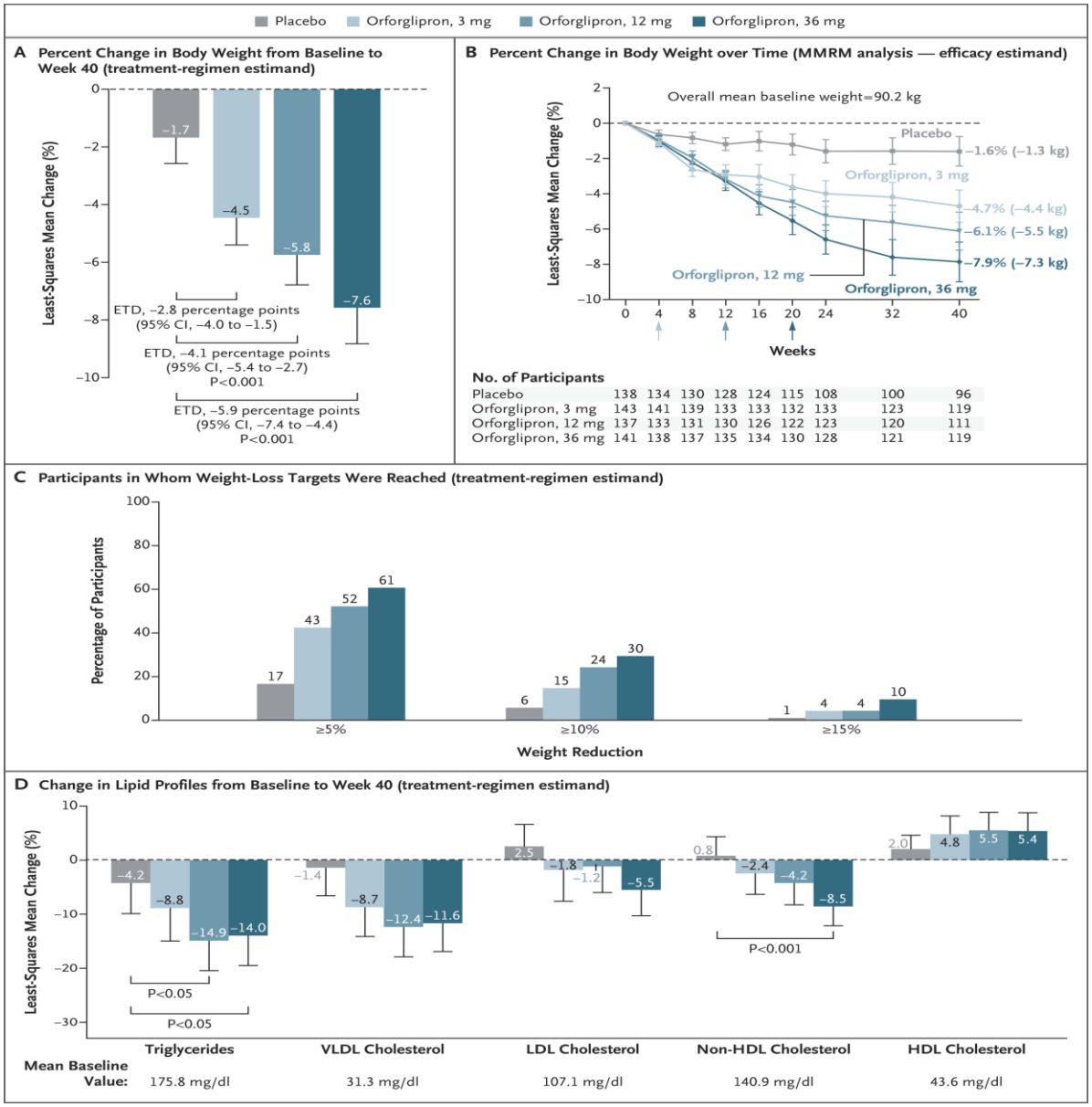

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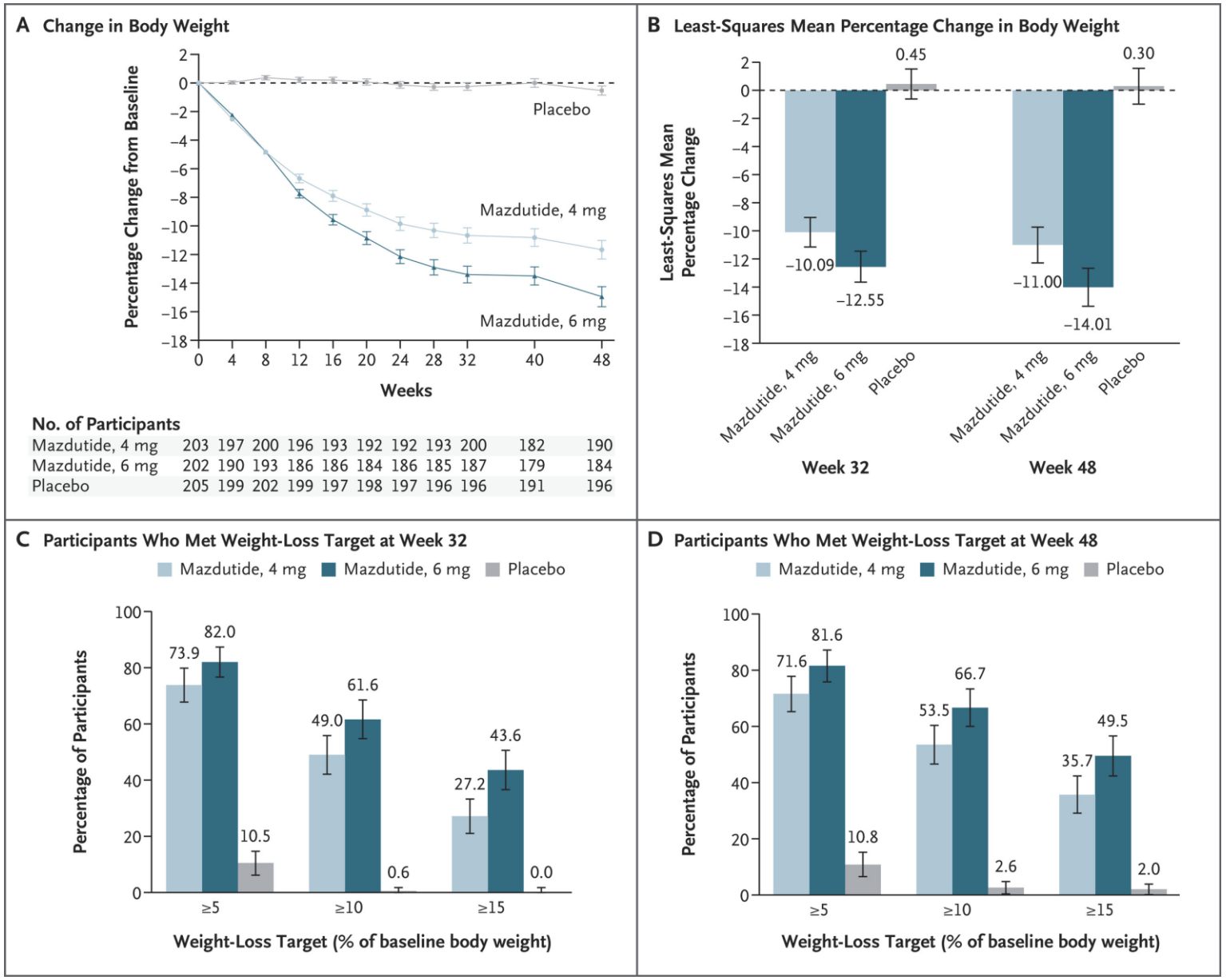
Once-Weekly Mazdutide in Chinese Adults with Obesity or Overweight (GLP-1/Glucagen receptor dual agonist)



Jiang, et al. N Engl J Med 2025;392:2215-25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Next big wave?
tirzepatide
semaglutide

Agents with Significant Weight Loss Potential in Development for Type 2 Diabetes/Obesity

	Class	Name	Phase	Indication
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	PYY agonist	PYY 1875	2	Obesity

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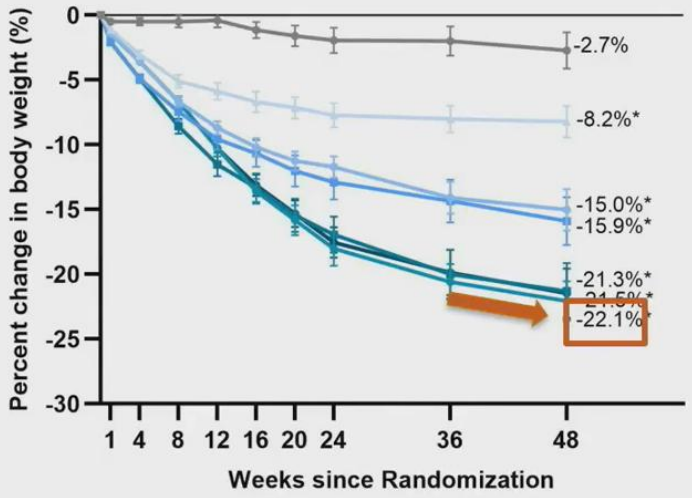
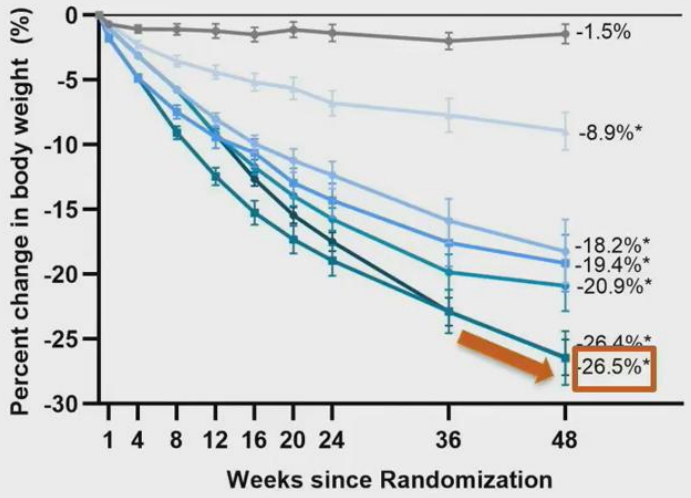
Weight Reduction by Baseline BMI at 48 weeks

Participants with baseline BMI <35 kg/m^2



Participants with baseline BMI ≥35 kg/m^2

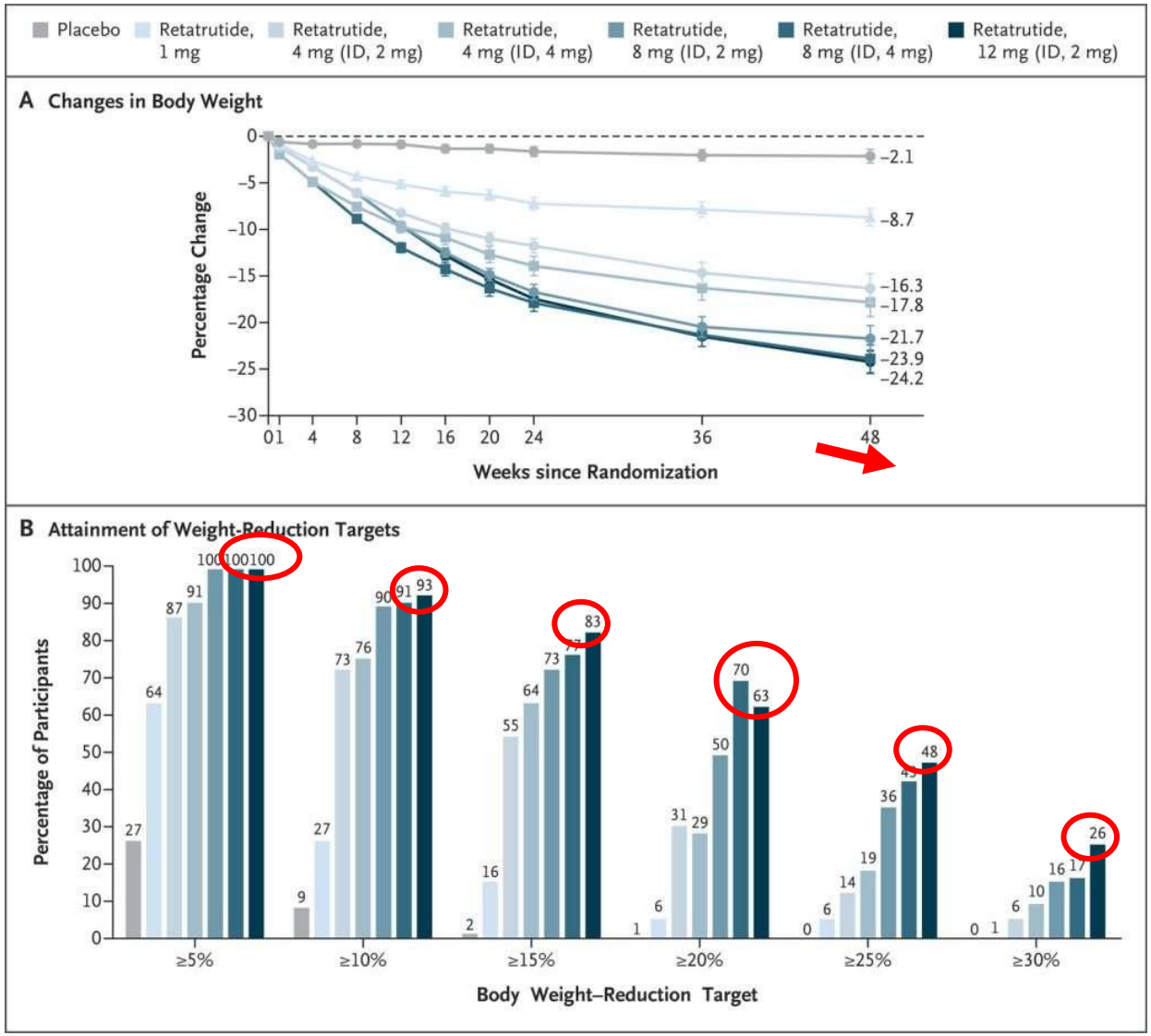


Placebo
RETA 1 mg
RETA 4 mg [ID 2 mg]
RETA 4 mg [ID 4 mg]
RETA 8 mg [ID 2 mg]
RETA 8 mg [ID 4 mg]
RETA 12 mg [ID 2 mg]

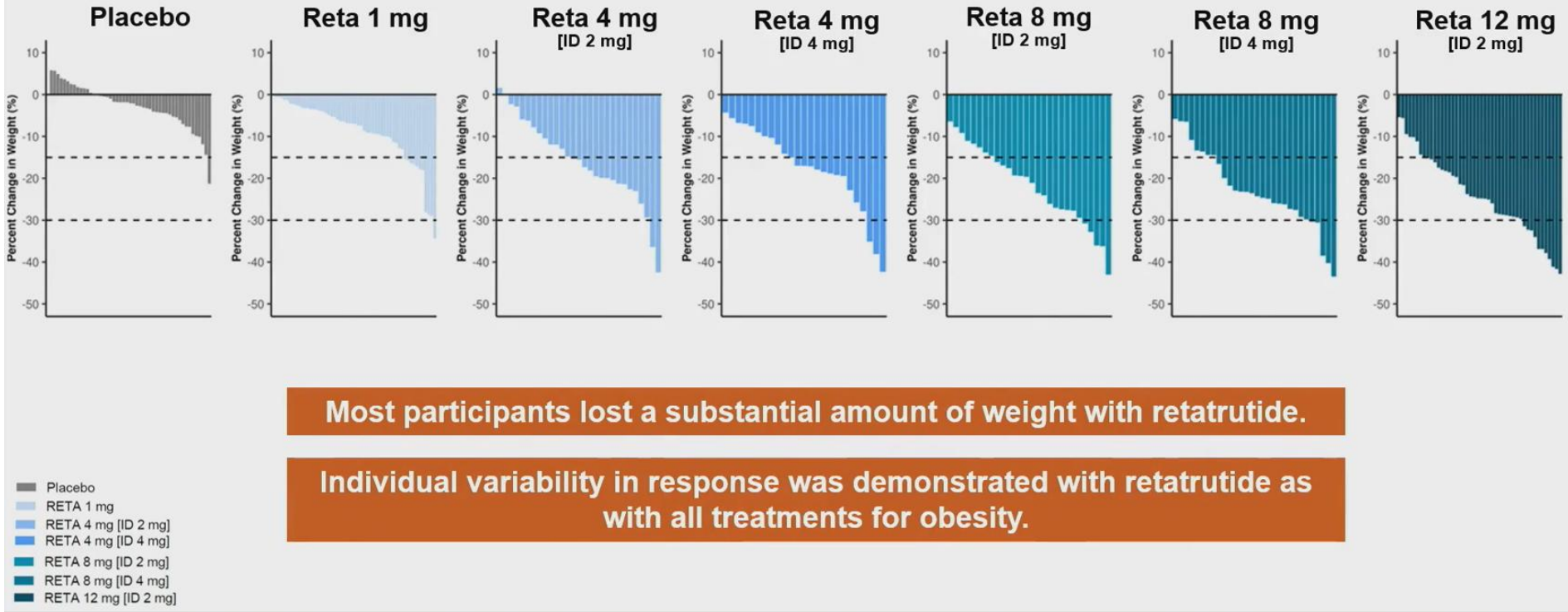
Participants with BMI ≥35 kg/m^2 had numerically greater mean percent reduction with retatrutide compared to participants with BMI <35 kg/m^2.

The efficacy of retatrutide is greater in individuals with more severe obesity.

Retatrutide for Obesity — A Phase 2 Trial (NEJM 2023)



Distribution of Percent Change in Weight For Each Participant (Waterfall Plots)



Most participants lost a substantial amount of weight with retatrutide.

Individual variability in response was demonstrated with retatrutide as with all treatments for obesity.

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- Συνδυασμοί GLP-1/αναλόγων αμυλίνης (Cagrilintide) - Amycretin
- Εβδομαδιαίες βασικές ινσουλίνες
- Συνδυασμοί εβδομαδιαίων GLP-1RAs/ινσουλινών
- Ινσουλίνη από του στόματος?

Rationale for combining amylin and GLP-1RA

Body weight reduction

Amylin and GLP-1RA

- Reduce appetite and energy intake[1–3]
- Increase satiety[1–3]

Glucose control

Amylin

Potential increase in leptin sensitivity[4-7]

GLP-1RA

Increase insulin secretion and biosynthesis[8]

Amylin and GLP-1RA

- Improve insulin sensitivity[9–11]
- Decrease glucagon secretion[8,12]
- Acute delay in gastric emptying[1,13,14]

GLP-1RA, glucagon-like peptide-1 receptor agonist

1. Chapman I, et al. Diabetologia. 2005;48:838–848; 2. Blundell J, et al. Diabetes Obes Metab. 2017;19:1242–1251; 3. Friedrichsen M, et al. Diabetes Obes Metab. 2021;23:754–762; 4. Paz-Filho G, et al. Indian J Endocrinol Metab. 2012;16(Suppl 3):S549–S555; 5. Roth DJ, et al. Proc Natl Acad Sci USA. 2008;105:7257–7262; 6. Ravussin E, et al. Obesity. 2009;17:1736–1743; 7. Trevaskis JL, et al. Endocrinology. 2008;149:5679–5687; 8. Campbell JE & Drucker DJ. Cell Metab. 2013;17:819–837; 9. Kusakabe T, et al. Am J Physiol Endocrinol Metab. 2012;302:E924–E931; 10. Lutz TA. Appetite. 2022;172:105965; 11. Fonseca VA, et al. J Clin Endocrinol Metab. 2019;104:4078–4086; 12. Gedulin BR, et al. Metab Clin Exp. 1997;46:67–70; 13. Tong J & D'Alessio D. Diabetes. 2014;63:407–409; 14. Hay DL, et al. Pharmacol Rev. 2015;67:564–600.

Gasiorek A et al. Presentation #74 (OP-13) at the 60th Annual Meeting of the European Association for the Study of Diabetes (EASD), 9–13 September 2024, Madrid, Spain

Scan QR code or visit the web site below for:
Oral presentation
Poster + slides
Talking head video

https://sciencehub.novonordisk.com/ada2023/Frias.html?cid=qr-w3h0zku1ta

Efficacy and Safety of Co-Administered s.c. Semaglutide and s.c. Cagrilintide in Type 2 Diabetes

Juan P. Frias,[1] Srikanth Deenadayalan,[2] Lars Erichsen,[2] Filip K. Knop,[3,4,5] Ildiko Lingvay,[6] Stanislava Macura,[2] Chantal Mathieu,[7] Sue D. Pedersen,[8] Melanie J. Davies[9]

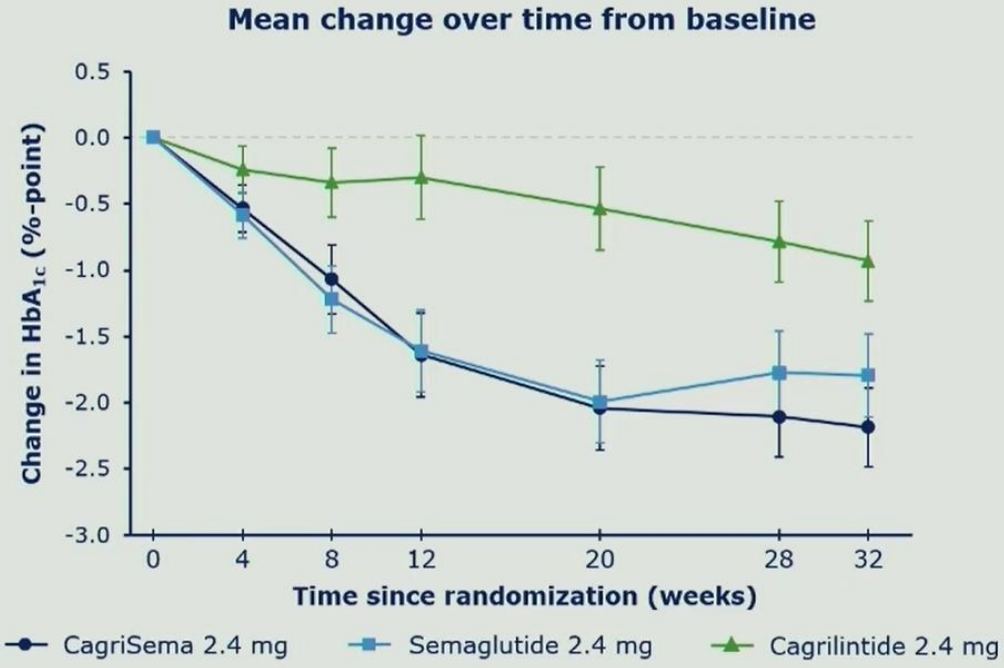
[1]Velocity Clinical Research, Los Angeles, CA, USA; [2]Novo Nordisk A/S, Søborg, Denmark; [3]Center for Clinical Metabolic Research, Gentofte Hospital, University of Copenhagen, Hellerup, Denmark; [4]Steno Diabetes Center Copenhagen, Herlev, Denmark; [5]Department of Clinical Medicine, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark; [6]Division of Endocrinology, Department of Internal Medicine and Peter O'Donnell Jr. School of Public Health, University of Texas Southwestern Medical Center, Dallas, TX, USA; [7]Clinical and Experimental Endocrinology, UZ Gasthuisberg, KU Leuven, Leuven, Belgium; [8]C-ENDO Diabetes and Endocrinology Clinic, Calgary, AB, Canada; [9]Diabetes Research Centre, University of Leicester, Leicester, UK

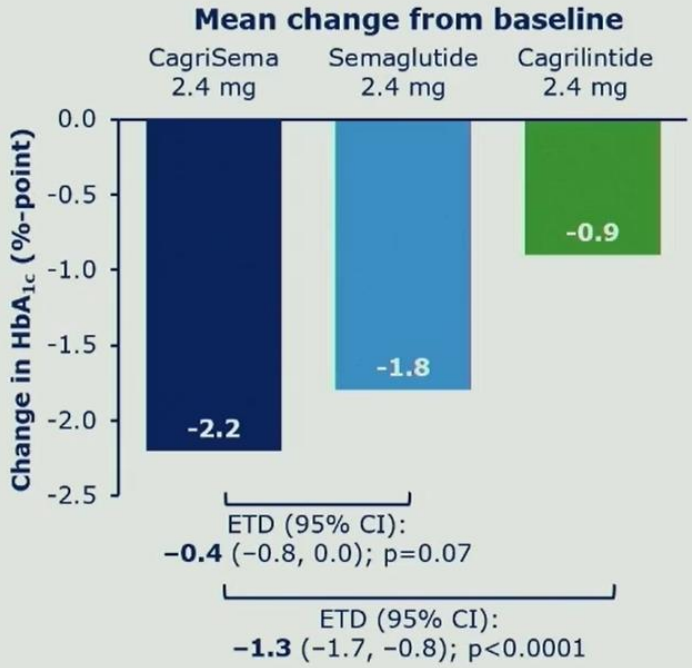
This trial was sponsored by Novo Nordisk and is registered with ClinicalTrials.gov (NCT04982575). The authors acknowledge the medical writing assistance of Abbie Richold and Abbey Pearson of Apollo, OPEN Health Communications, funded by Novo Nordisk, in accordance with Good Publication Practice (GPP) guidelines.

Frias J, et al. Presentation #53-OR at the American Diabetes Association (ADA) 83rd Scientific Sessions, June 23–26, 2023, San Diego, CA, USA.

Change from baseline in HbA_{1c}

Mean baseline HbA_{1c}: 8.4%



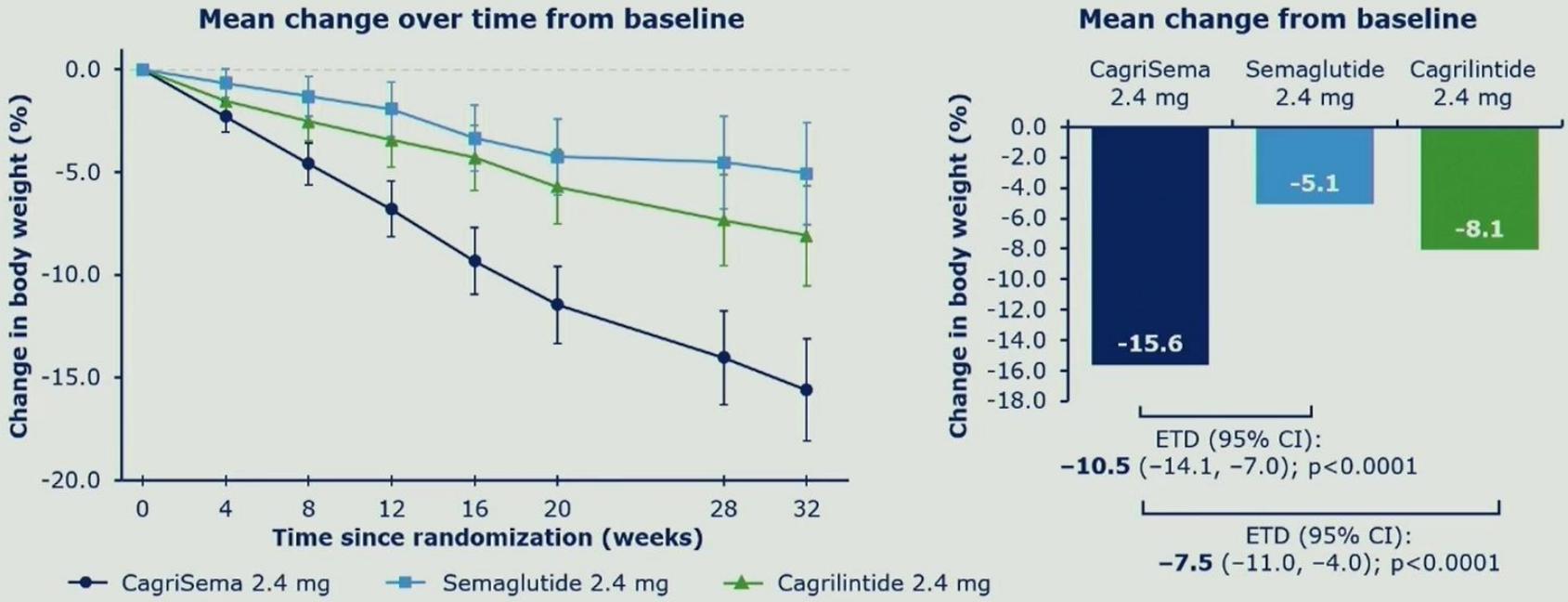


Data are for the trial product estimand (MMRM with treatment and stratification as factors, baseline HbA_{1c} as covariate, all nested within visit and with participants as random effect). Using the treatment policy estimand (ANCOVA model with treatment and stratification as factors and baseline HbA_{1c} as covariate using retrieved participants multiple imputation of missing data regardless of treatment or stratification), mean change in HbA_{1c} from baseline to week 32 was −2.1% with CagriSema, −1.8% with semaglutide, and −0.9% with cagrilintide; the ETD (95% CI) was −0.3% (−0.8, 0.2; p=0.23) for CagriSema vs semaglutide and −1.2% (−1.7, −0.7; p<0.001) for CagriSema vs cagrilintide.
Error bars indicate 95% CIs.
ANCOVA, analysis of covariance; CagriSema, co-administered semaglutide and cagrilintide; CI, confidence interval; ETD, estimated treatment difference; HbA_{1c}, glycated hemoglobin; MMRM, mixed model for repeated measurements.

Mathieu C, et al. Presentation 54-OR at the American Diabetes Association (ADA) 83rd Scientific Sessions, June 23–26, 2023, San Diego, CA, USA.

Change from baseline in body weight

Mean baseline body weight: 105.7 kg



Data are for the trial product estimand (MMRM with treatment and stratification as factors, baseline HbA_{1c} as covariate, all nested within visit and with participants as random effect). Using the treatment policy estimand (ANCOVA model with treatment and stratification as factors and baseline HbA_{1c} as covariate using retrieved participants multiple imputation of missing data regardless of treatment or stratification), mean change in body weight from baseline to week 32 was −14.7% for CagriSema, −5.2% for semaglutide, and −8.1% for cagrilintide, and the ETD (95% CI) was −9.5% (−13.8 to −5.1; p<0.001) for CagriSema versus semaglutide and −6.5% (−10.6 to −2.4; p=0.002) for CagriSema versus cagrilintide. Error bars indicate 95% CIs.
ANCOVA, analysis of covariance; CagriSema, co-administered semaglutide and cagrilintide; CI, confidence interval; ETD, estimated treatment difference; MMRM, mixed model for repeated measures.

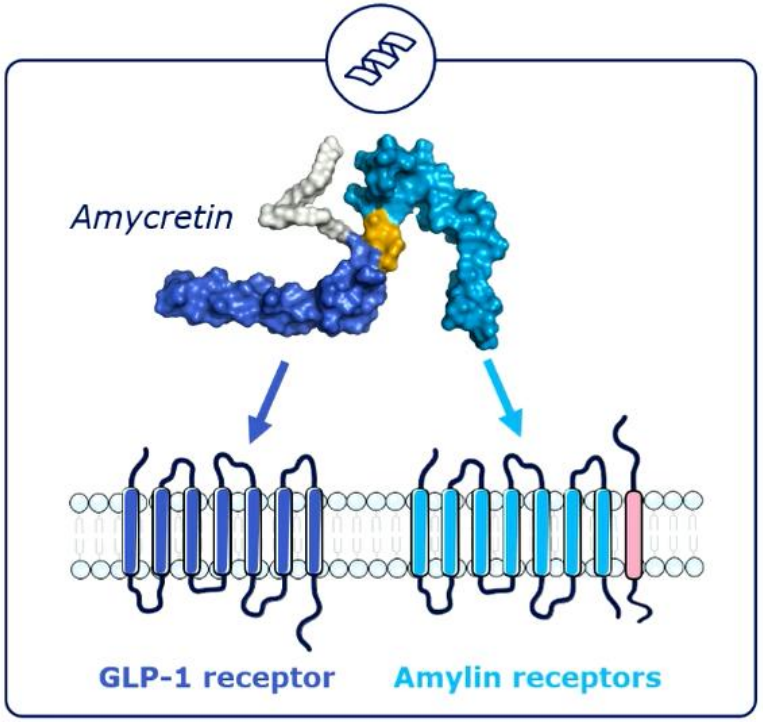
Frias J, et al. Presentation #53-OR at the American Diabetes Association (ADA) 83rd Scientific Sessions, June 23–26, 2023, San Diego, CA, USA.

Amycretin is a long-acting, unimolecular amylin receptor and GLP-1 receptor agonist

Amycretin (NNC0487-0111) is a pioneering, unimolecular dual-acting amylin and GLP-1 receptor agonist

An oral formulation of amycretin has been developed utilising SNAC technology[1]

Pre-clinical findings supported the progression of amycretin to clinical studies

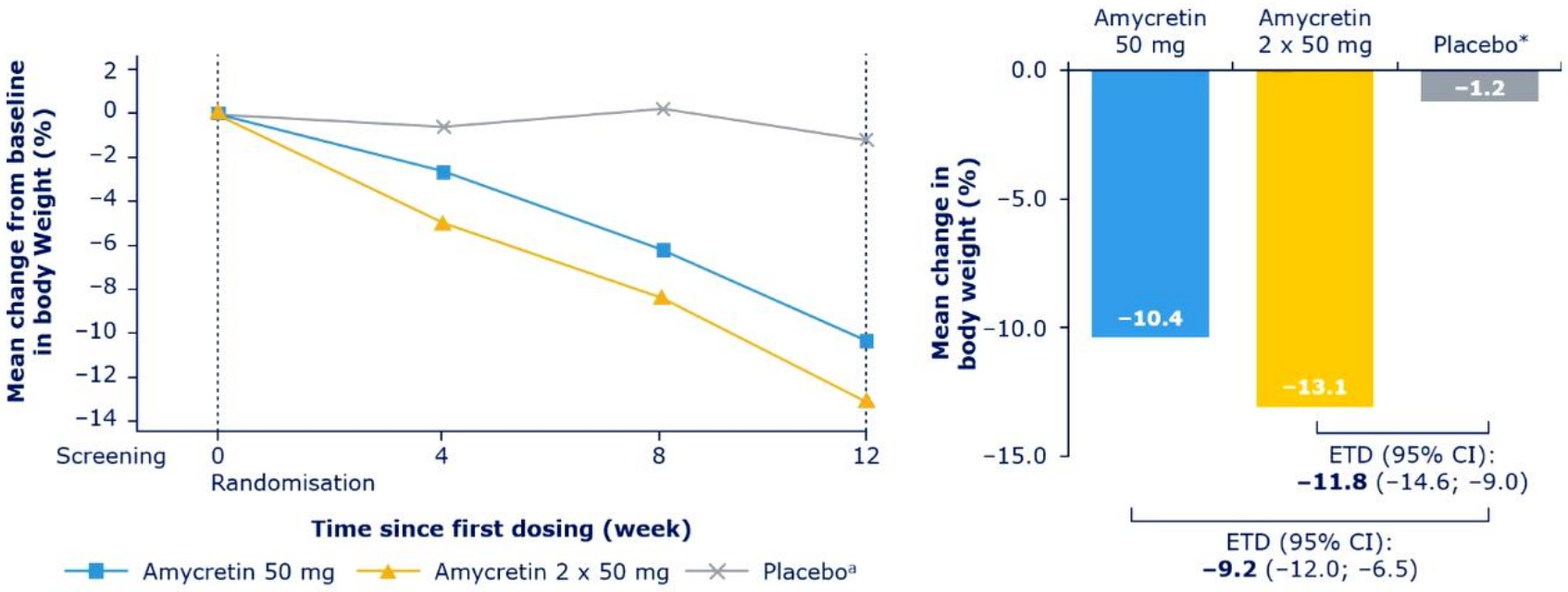


GLP-1, glucagon-like peptide-1; SNAC, sodium N-(8-[2-hydroxybenzoyl] amino) caprylate.

1. Buckley ST, et al. Sci Transl Med 2018;10:eaar7047.

Gasiorek A et al. Presentation #74 (OP-13) at the 60th Annual Meeting of the European Association for the Study of Diabetes (EASD), 9–13 September 2024, Madrid, Spain

Relative body weight change from baseline to week 12



Full analysis set: all randomised participants. Vertical lines represent first and last dosing of amycretin.
**Placebo group (n=12) includes four participants from Part D.*
CI, confidence interval; ETD, estimated treatment difference; SD, standard deviation.

Gasiorek A et al. Presentation #74 (OP-13) at the 60th Annual Meeting of the European Association for the Study of Diabetes (EASD), 9–13 September 2024, Madrid, Spain

Νεώτερες Θεραπείες στον ΣΔ2 (και παχυσαρκία)

- Αυξημένες δοσολογίες GLP-1 RAs
- Μη πεπτιδικοί p.o. GLP-1 RAs
- Διπλοί και τριπλοί αγωνιστές GLP-1/GIP/Glucagen
- Συνδυασμοί GLP-1/αναλόγων αμυλίνης (Cagrilintide)
- Εβδομαδιαίες βασικές ινσουλίνες
- Συνδυασμοί εβδομαδιαίων GLP-1RAs/ινσουλινών
- Ινσουλίνη από του στόματος?

Once-weekly basal insulins in late-stage clinical development

Efsitora alfa

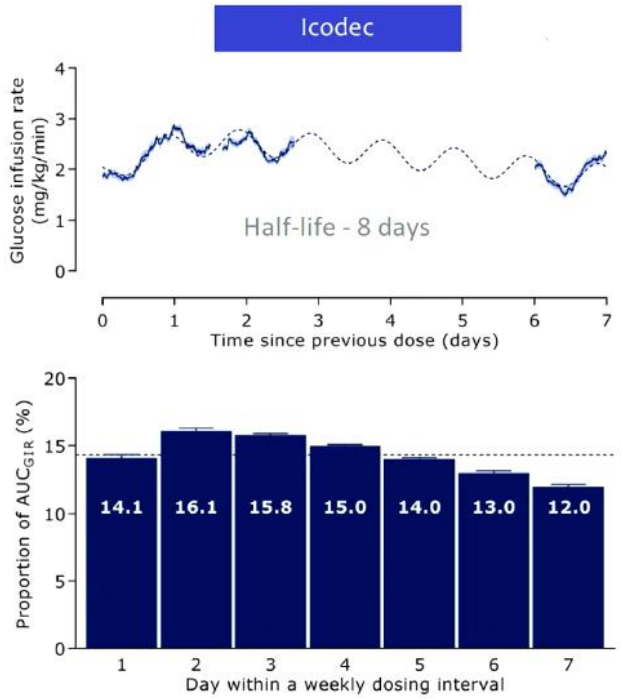
- Fusion protein that combines a single-chain variant of insulin with a human IgG Fc domain
- Eli Lilly
- In Phase 3 of clinical development (QWINT Program)

Moyers JS, et al. Pharmacol Exp Ther. 2022;382:346-355
Heise T, et al. J Endocr Soc. 2021;5(Suppl 1):A329.
https://investor.lilly.com. Accessed June 2023

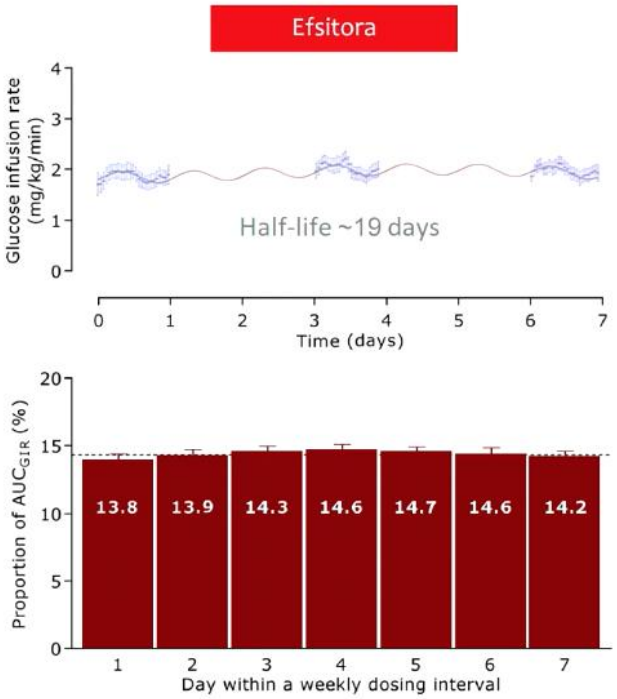
Icodec

- Novel basal insulin analog that strongly, but reversibly, binds to albumin
- Novo Nordisk
- Completed pivotal Phase 3a clinical development program (ONWARDS Program)

Nishimura E, et al. BMJ Open Diabetes Research and Care 2021;9:e002301.
https://www.novonordisk.com/science-and-technology. Accessed June 2023

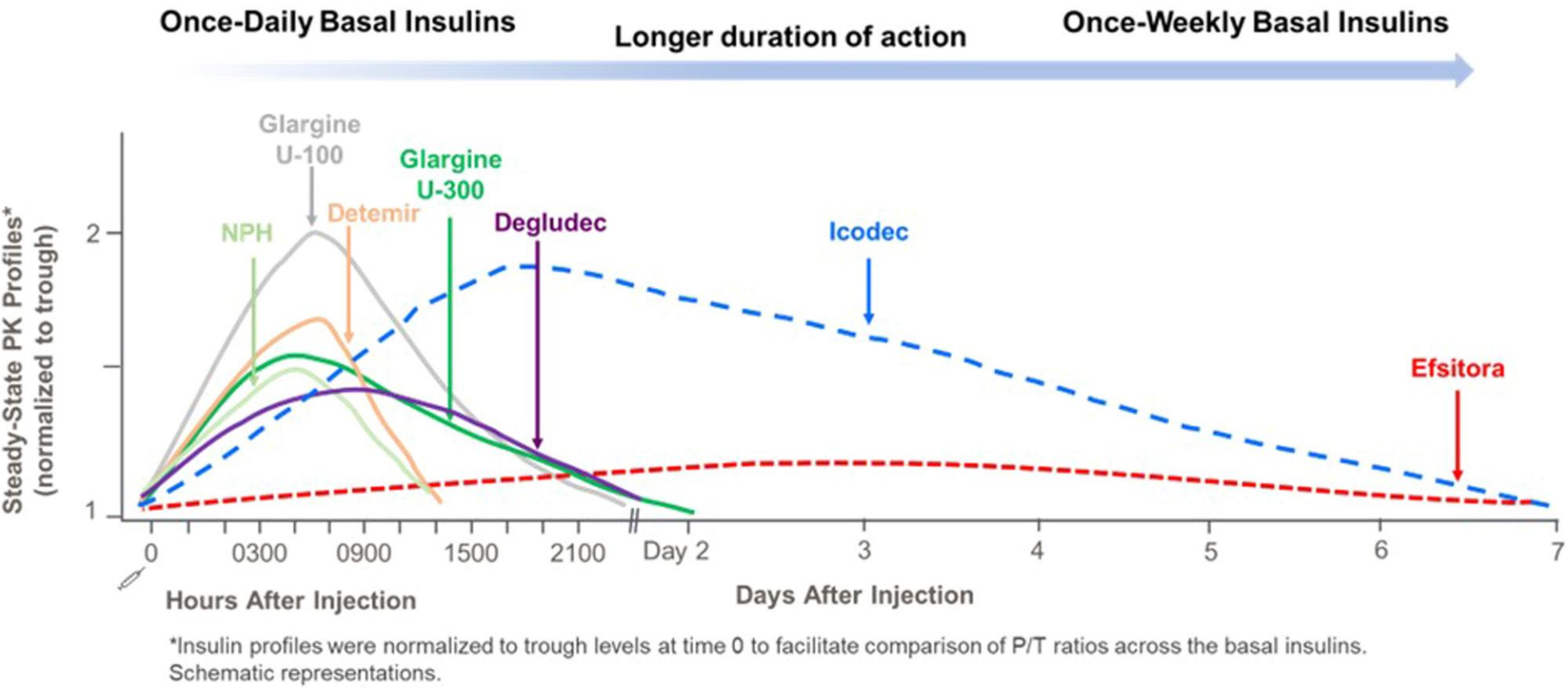


Pieber T et al. Diabetes Obesity Metabolism 2024



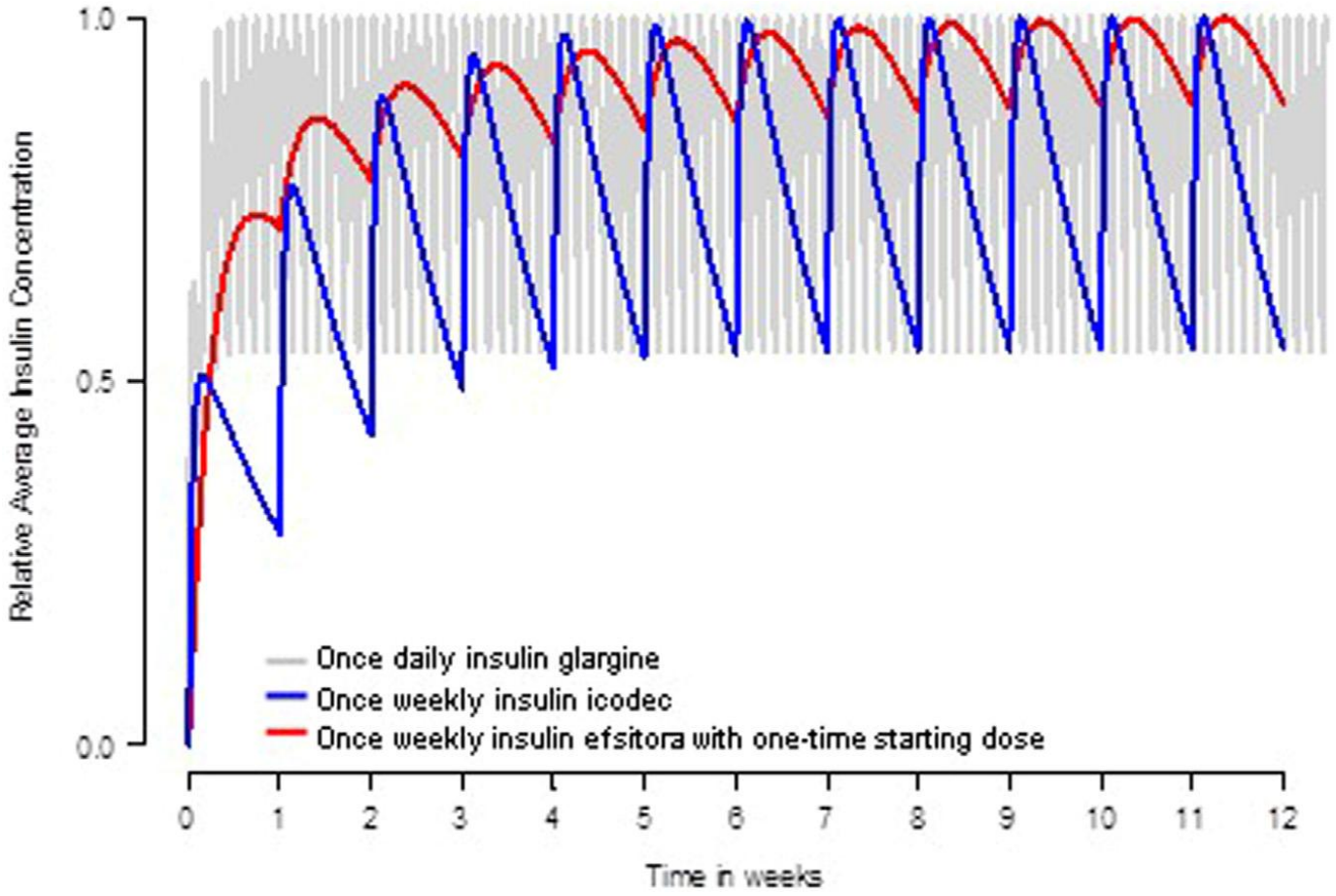
Leohr J et al. Poster 802 ADA, Chicago

Schematic representations of exposure profiles of daily and weekly basal insulins at steady state

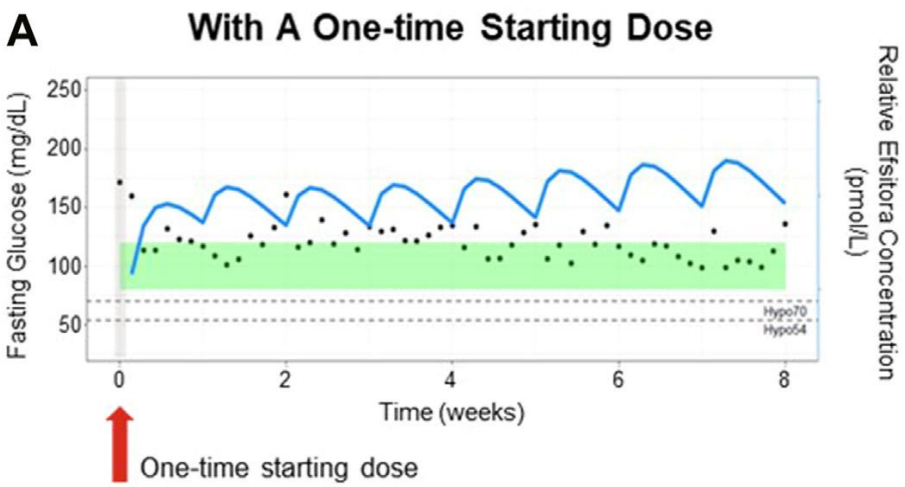


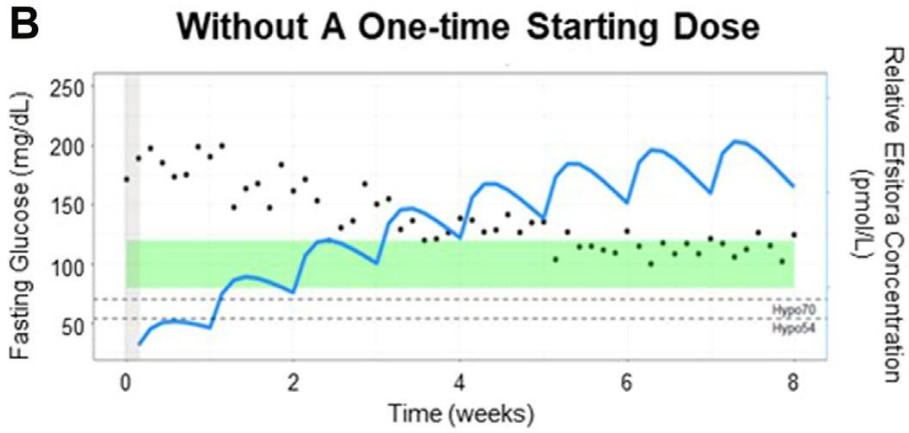
*Insulin profiles were normalized to trough levels at time 0 to facilitate comparison of P/T ratios across the basal insulins.
Schematic representations.

Endocrine Practice 2024; 30: 863-869

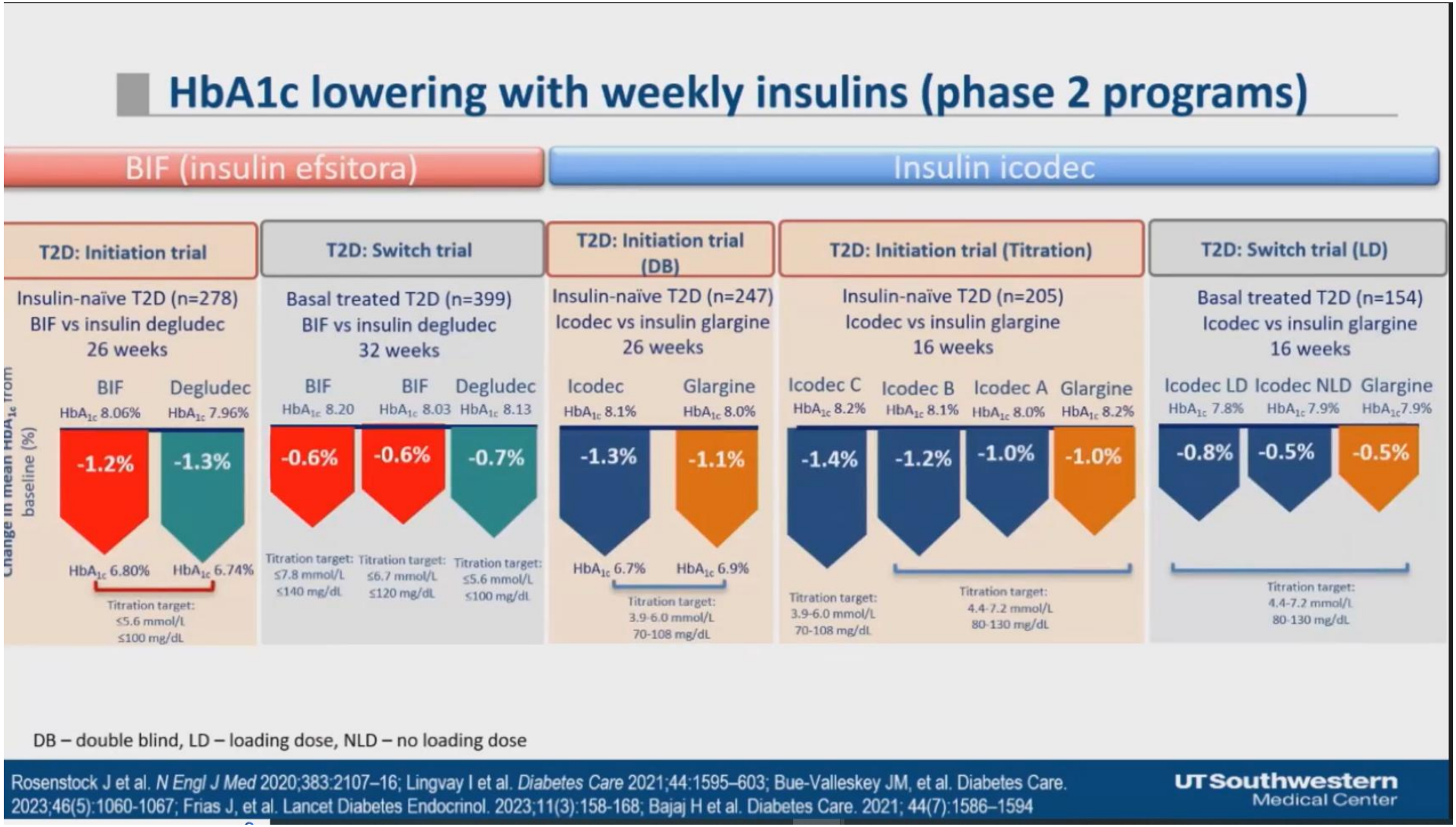


T.R. Pieber, J. Leohr, J.M. Bue-Valleskey et al. Endocrine Practice 2024; 30: 863-869


A
With A One-time Starting Dose
Fasting Glucose (mg/dL)
250
200
150
100
50
0
2
4
6
8
Time (weeks)
Hypo70
Hypo54
Relative Efsitora Concentration (pmol/L)
One-time starting dose


B
Without A One-time Starting Dose
Fasting Glucose (mg/dL)
250
200
150
100
50
0
2
4
6
8
Time (weeks)
Hypo70
Hypo54
Relative Efsitora Concentration (pmol/L)

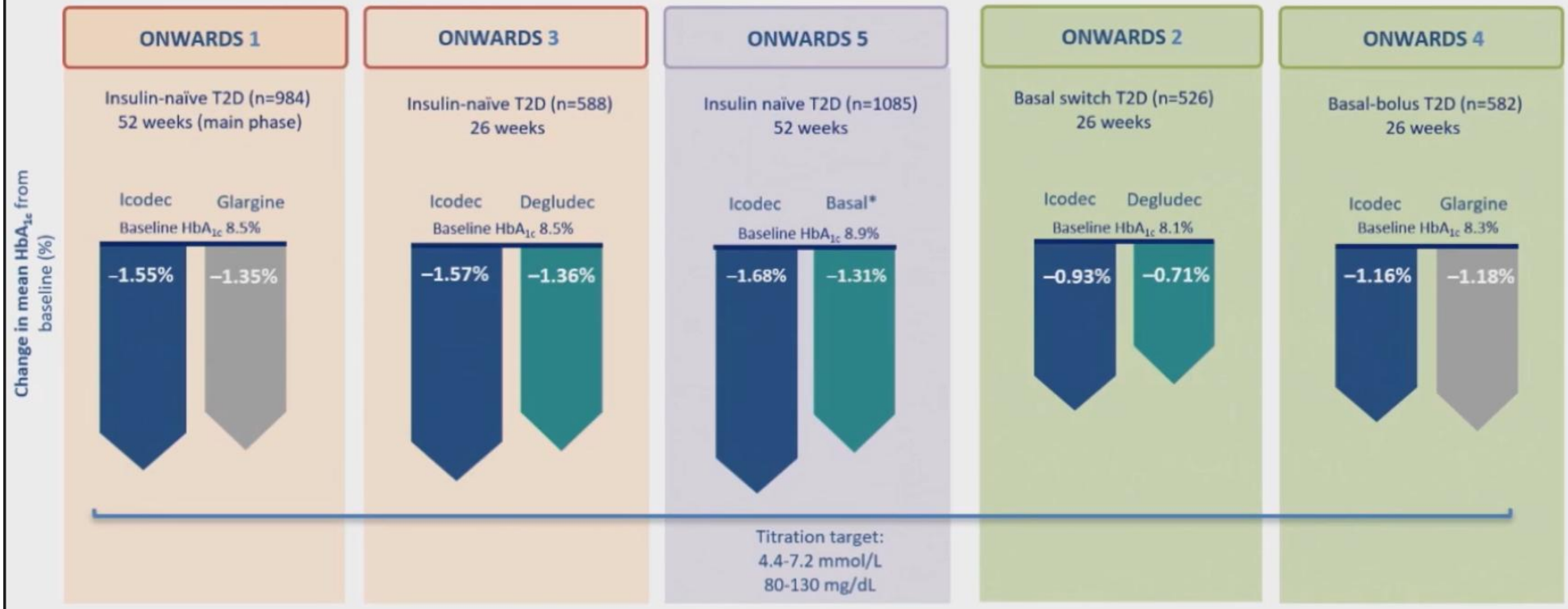
HbA1c lowering with weekly insulins (phase 2 programs)



DB – double blind, LD – loading dose, NLD – no loading dose

Rosenstock J et al. *N Engl J Med* 2020;383:2107–16; Lingvay I et al. *Diabetes Care* 2021;44:1595–603; Bue-Valleskey JM, et al. Diabetes Care. 2023;46(5):1060-1067; Frias J, et al. Lancet Diabetes Endocrinol. 2023;11(3):158-168; Bajaj H et al. Diabetes Care. 2021; 44(7):1586–1594

HbA1c lowering in the ONWARDS Program (insulin icodec)

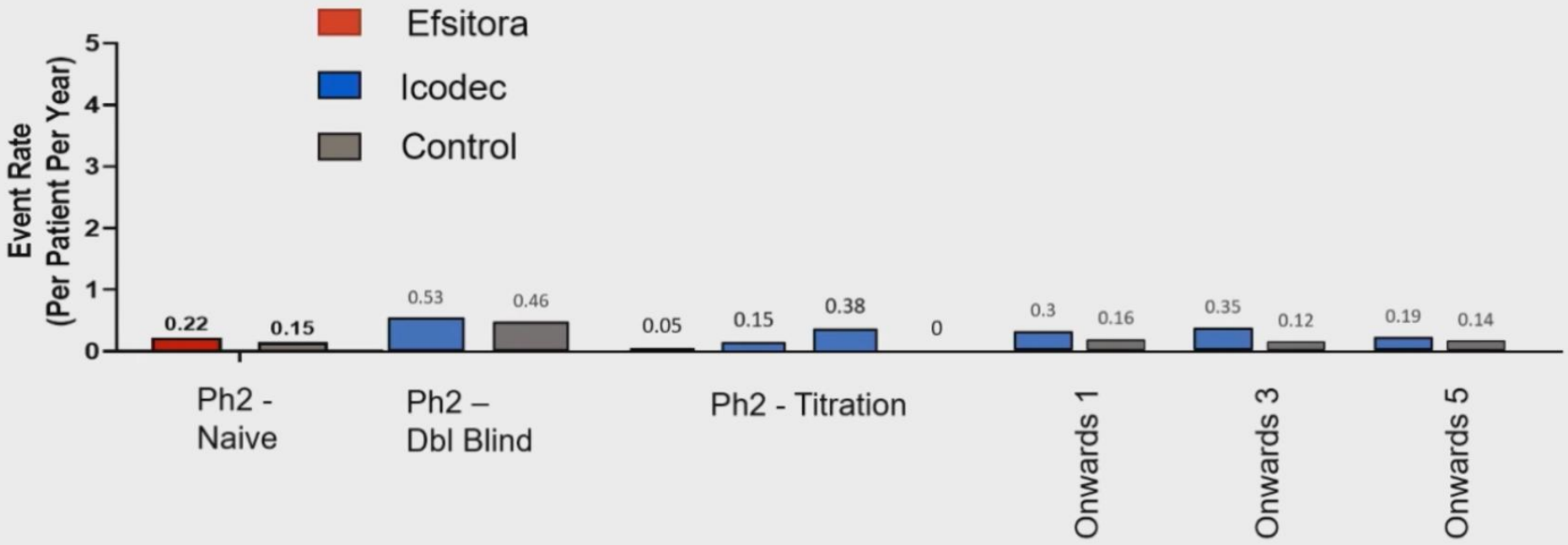


Glargine in ONWARDS 1 and 4 was the U100 formulation. *Basal insulin per provider choice (glargine U100, glargine U300, or degludec U100)
ETD, estimated treatment difference; T1D, type 1 diabetes, T2D, type 2 diabetes.

ONWARDS 1, 3, 5 presented at ADA 2023.
Onwards 2: Philis-Tsimikas et al. Lancet D&E. ePub May 3,2023 ONWARDS 4: Mathieu et al. Lancet D&E. ePub May 5, 2023.

UT Southwestern Medical Center

Rate of Level 2 or 3 Hypoglycemia in Insulin ***Naïve*** Populations



Bue-Valleskey JM, et al. *Diabetes Care*. 2023;46(5):1060-1067.
Rosenstock J et al. *N Engl J Med* 2020;383:2107–16.
Lingvay I et al. *Diabetes Care* 2021;44:1595–603.
Rosenstock J et al. NEJM ePub 24Jun 2023
Lingvay I et al. JAMA ePub 24Jun2023
Bajaj et al. ADA 2023 Poster Presentation

A new way of using basal insulins for clinicians

Insulin-naive people with T2D

Icodec

- Start with 70U

First dose = 70U

From week 2: 70U and titrate

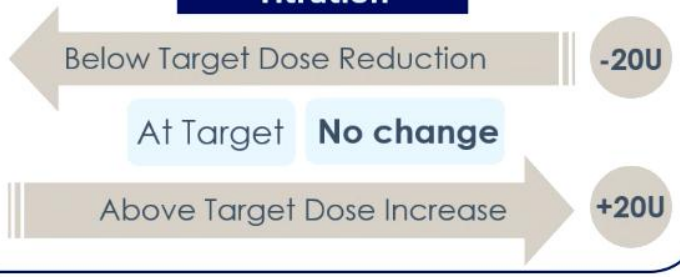
Efsitora

- Start with 300U

First dose = 300U (100 U x 3)

From week 2: 100U and titrate

Titration



A new way of using basal insulins for clinicians

Insulin-experienced people with T2D

Icodec

- Take the original dose and multiply by 7 to cover the week dose
- Add once a loading dose (multiply by 1.5)

Example: In a person injecting 20U basal insulin daily

First dose = 210U (140U x 1.5)

From week 2: 140U and titrate

Efsitora

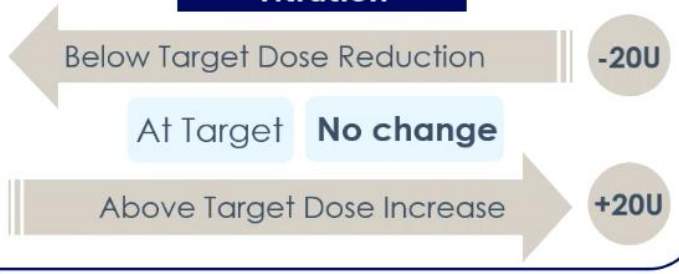
- Take the original dose and multiply by 7 to cover the week dose
- Add once a loading dose (multiply by 3)

Example: In a person injecting 20U basal insulin daily

First dose = 420U (140U x 3)

From week 2: 140U and titrate

Titration



Titration Algorithm for Basal Insulin

Pre-breakfast SMBG		Icodec weekly dose adjustments	Glargine U100 dose adjustments
Up-titration	Mean of the SMBG values >130 mg/dL (>7.2 mmol/L)	+20 U	+3 U
Target	Mean of the SMBG values 80–130 mg/dL (4.4–7.2 mmol/L)	0 U	0 U
Down-titration	Lowest SMBG value <80 mg/dL (<4.4 mmol/L)	–20 U	–3 U

Dose adjustment based on three pre-breakfast SMBG values measured two days prior to titration and on the day of titration

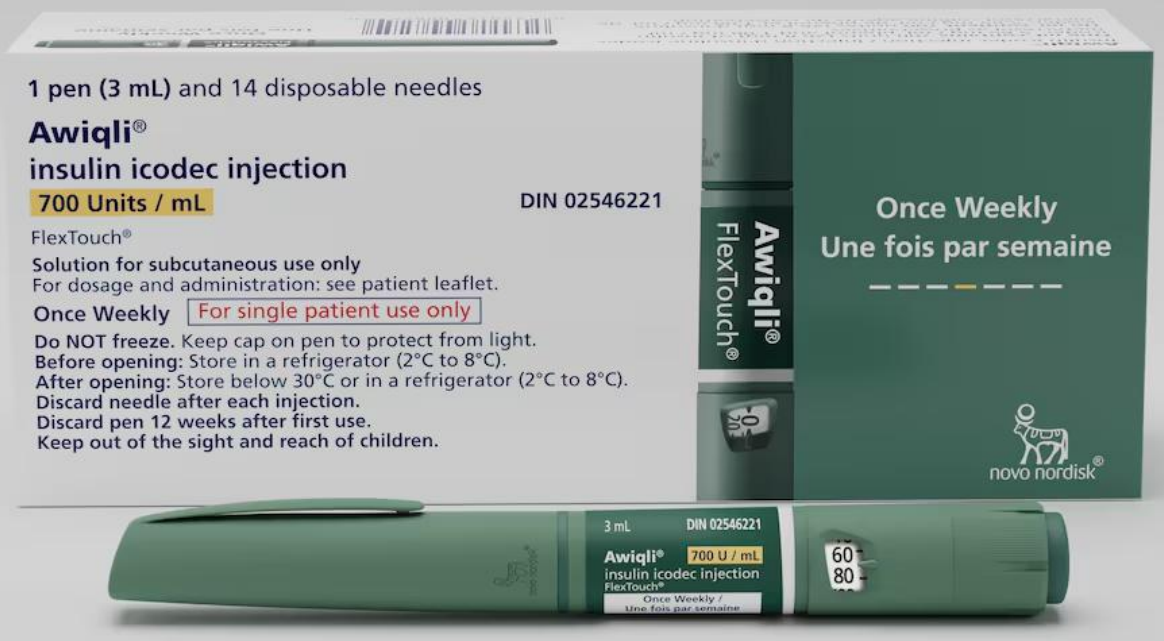
Philis-Tsimikas et al. Diab, Obesity and Metab. 2022; 25(2): 331-341.

Global Approvals and Labeling of Insulin Icodec

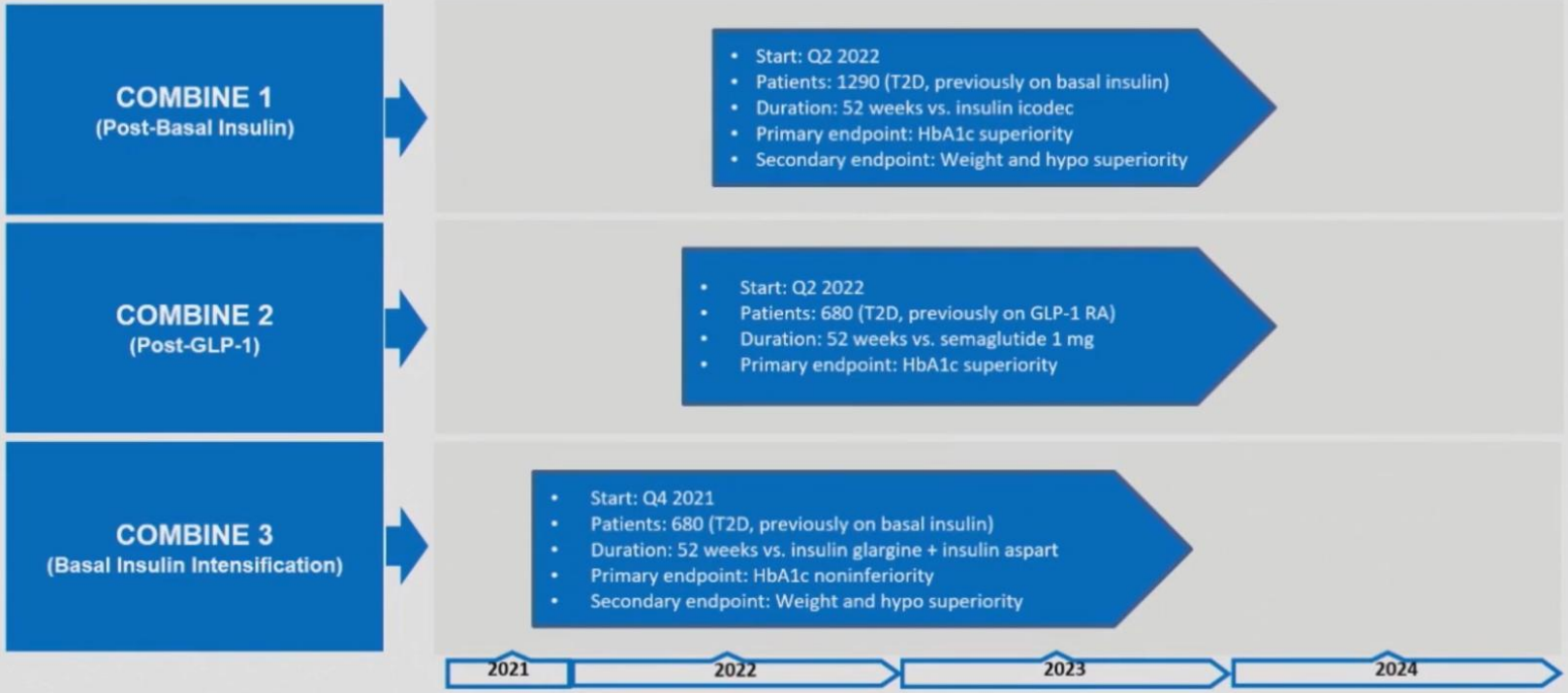
Country	Approval Date	Indication
EMA	May 2024	Treatment of diabetes mellitus in adults[1]
Canada	March 12, 2024	Once-weekly treatment of adults with diabetes mellitus to improve glycemic control[1]
USA	**Not approved**	**FDA Complete Response Letter issued on July 10, 2024[2]**
Switzerland	March 7, 2024	Treatment of diabetes mellitus in adults[1]
Australia	May 17, 2024	Treatment of type 1 and 2 diabetes[3]
Japan	2024	Treatment of type 1 and 2 diabetes[2]
China	2024	Treatment of type 2 diabetes[2]

EMA=European Medicines Agency; FDA=The United States Food and Drug Administration.

Blair HA. *BioDrugs*. 2024;38(5):717-724. 2. https://www.novonordisk.com/news-and-media/news-and-ir-materials/news-details.html?id=168532 (Accessed December 11, 2024).
https://www.tga.gov.au/resources/auspmd/awiqli-insulin-icodec (Accessed December 11, 2024).


1 pen (3 mL) and 14 disposable needles
Awiqli®
insulin icodec injection
700 Units / mL
DIN 02546221
FlexTouch®
Solution for subcutaneous use only
For dosage and administration: see patient leaflet.
Once Weekly
For single patient use only
Do NOT freeze. Keep cap on pen to protect from light.
Before opening: Store in a refrigerator (2°C to 8°C).
After opening: Store below 30°C or in a refrigerator (2°C to 8°C).
Discard needle after each injection.
Discard pen 12 weeks after first use.
Keep out of the sight and reach of children.
Awiqli®
FlexTouch®
Once Weekly
Une fois par semaine
novo nordisk®
3 mL
DIN 02546221
Awiqli®
700 U / mL
insulin icodec injection
FlexTouch®
Once Weekly /
Une fois par semaine
60
80

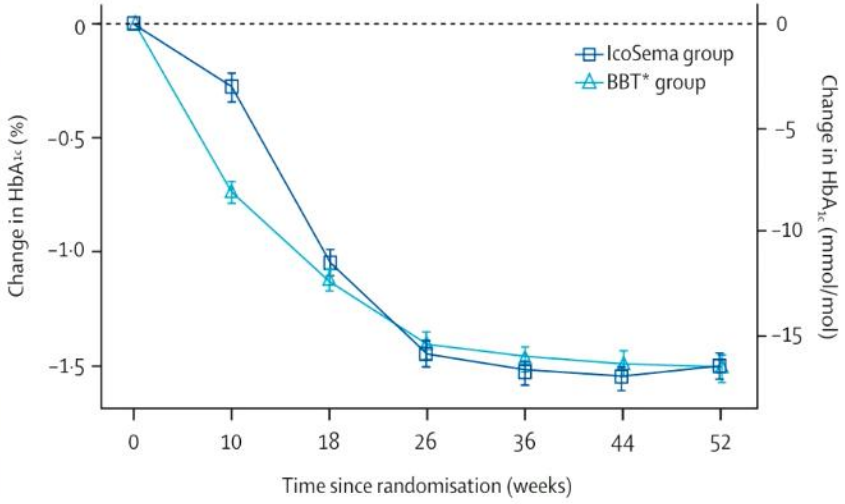
IcoSema (350 units / 1mg) Phase 3 Trial Program

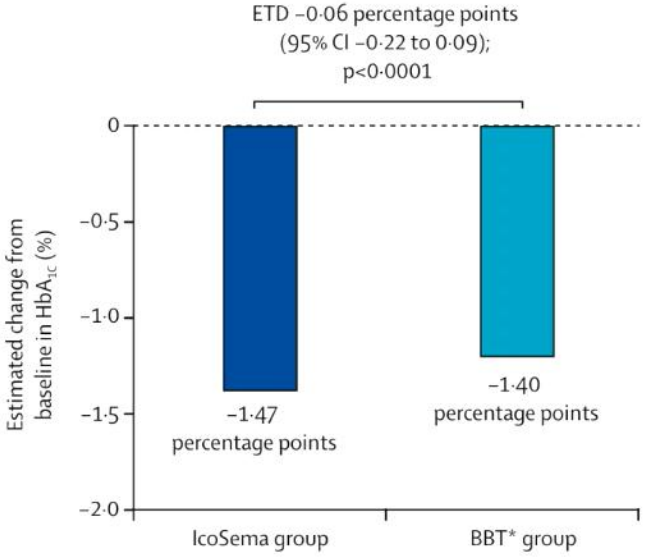


https://investor.novonordisk.com/q3-2022-presentation.

Once-weekly IcoSema versus multiple daily insulin injections in type 2 diabetes management (COMBINE 3): an open-label, multicentre, treat-to-target, non-inferiority, randomised, phase 3a trial

Liana K Billings, Francesco Andreozzi, Marie Frederiksen, Pierre Gourdy, Amoolya Gowda, Linong Ji, Laura Pletsch-Borba, Ryo Suzuki, A G Unnikrishnan, André G D Vianna





Lancet Diabetes Endocrinol 2025

Once-weekly IcoSema versus multiple daily insulin injections in type 2 diabetes management (COMBINE 3): an open-label, multicentre, treat-to-target, non-inferiority, randomised, phase 3a trial

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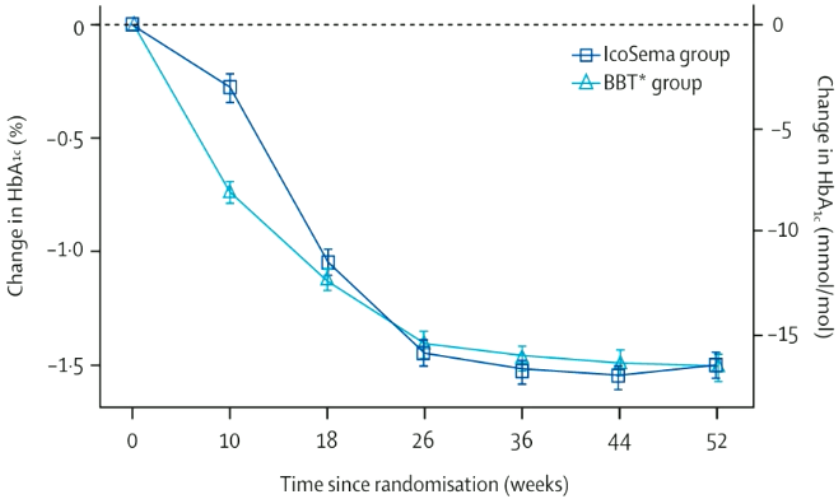

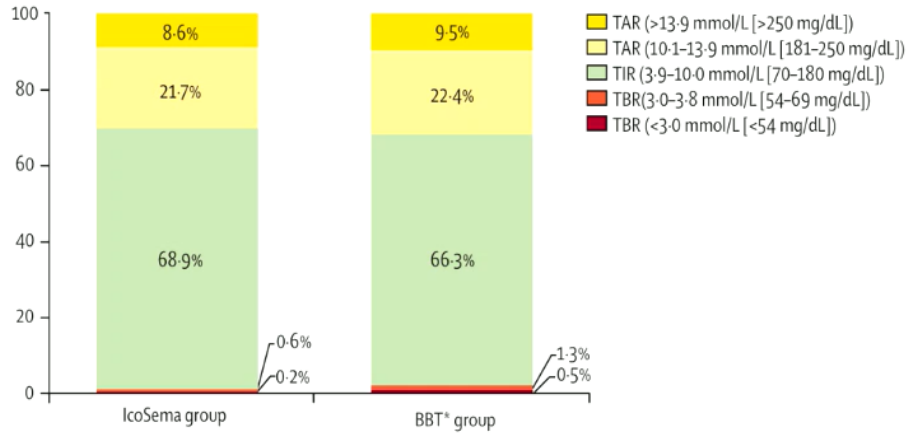

Lancet Diabetes Endocrinol 2025

Νεώτερες Θεραπείες στον ΣΔ2 (και παχυσαρκία)

- Αυξημένες δοσολογίες GLP-1 RAs
- Μη πεπτιδικοί p.o. GLP-1 RAs
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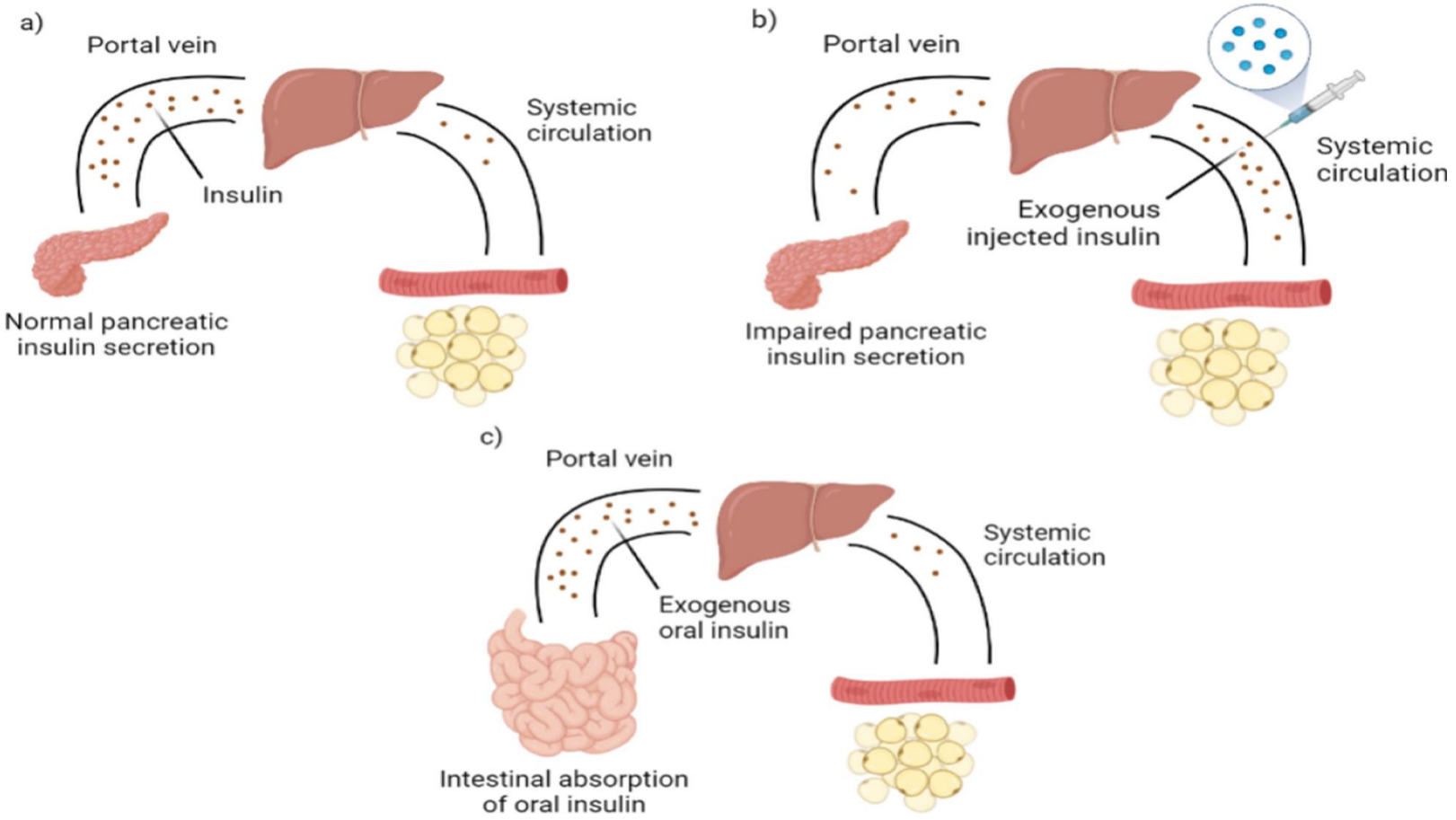
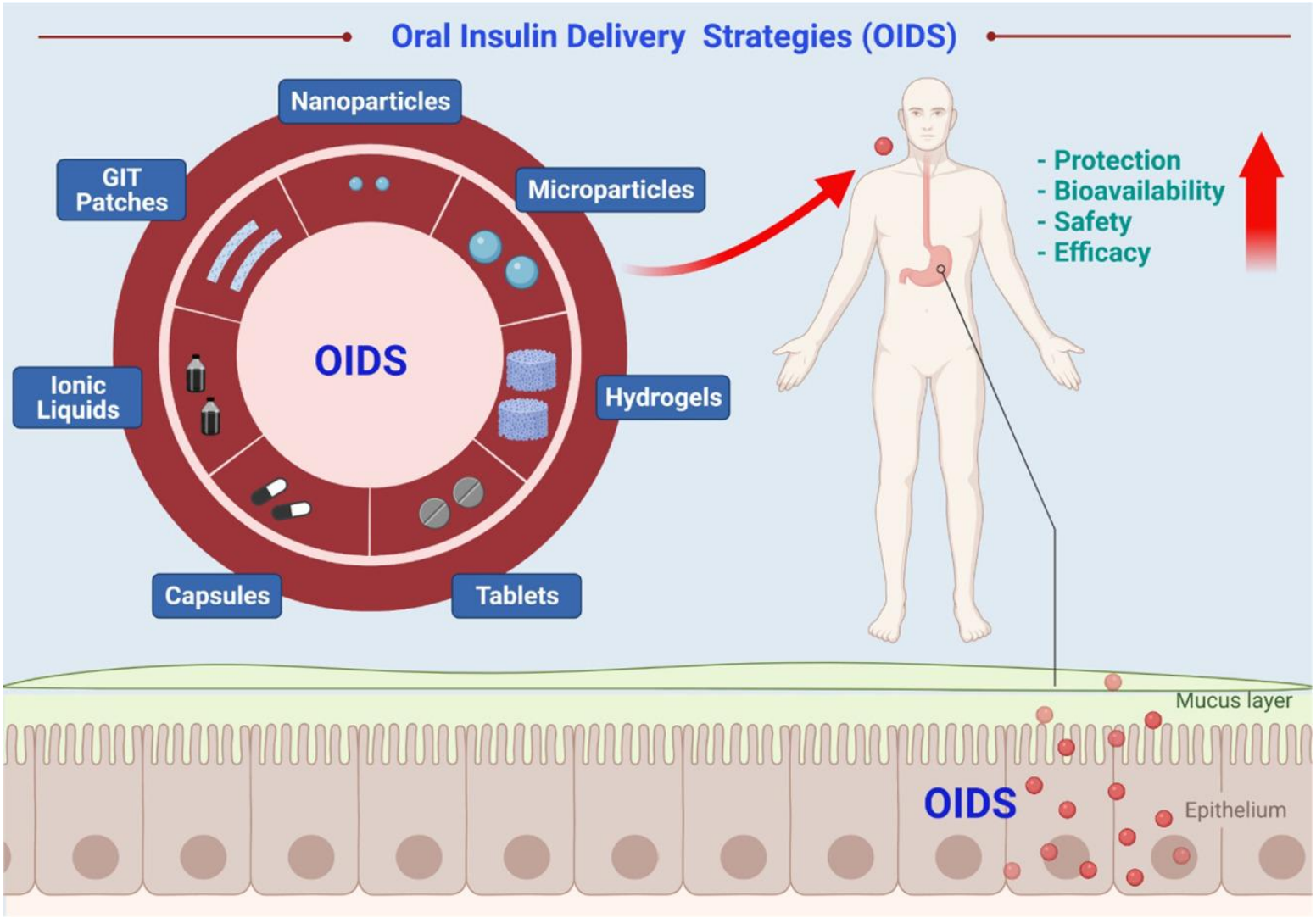
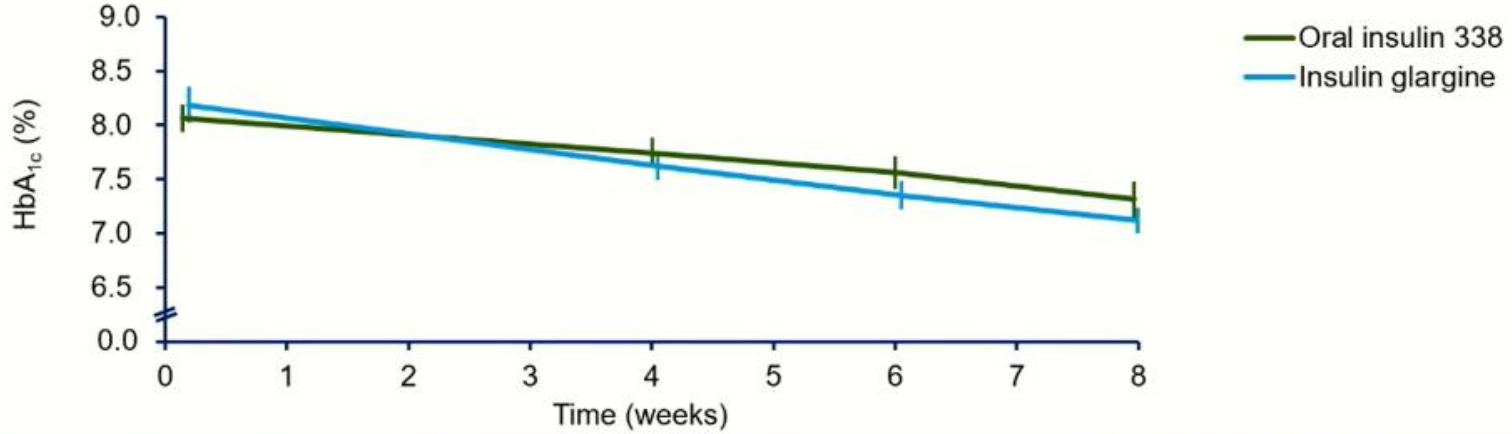
- Συνδυασμοί εβδομαδιαίων GLP-1RAs/ινσουλινών
- Ινσουλίνη από του στόματος – Glucose sensitive insulins?

Portal/systemic insulin gradient in normal physiology and after insulin administration




Oral Insulin Delivery Strategies (OIDS)
Nanoparticles
GIT Patches
Microparticles
OIDS
Ionic Liquids
Hydrogels
Capsules
Tablets
- Protection
- Bioavailability
- Safety
- Efficacy
Mucus layer
OIDS
Epithelium

Oral basal insulin: Glycaemic control
As effective as s.c. insulin glargine U100 in T2DM

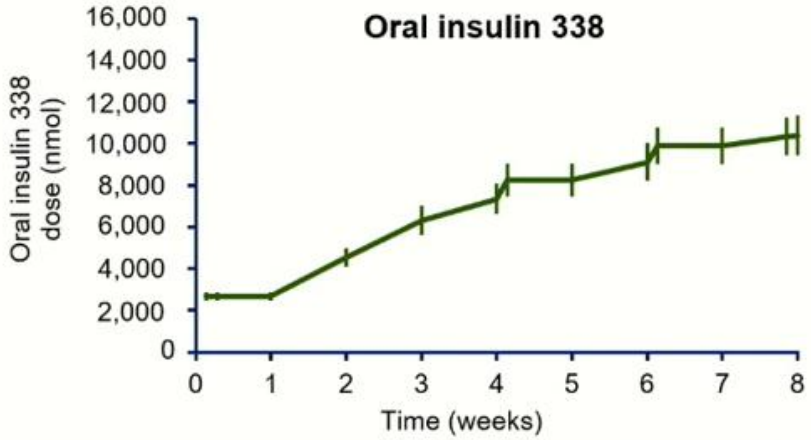


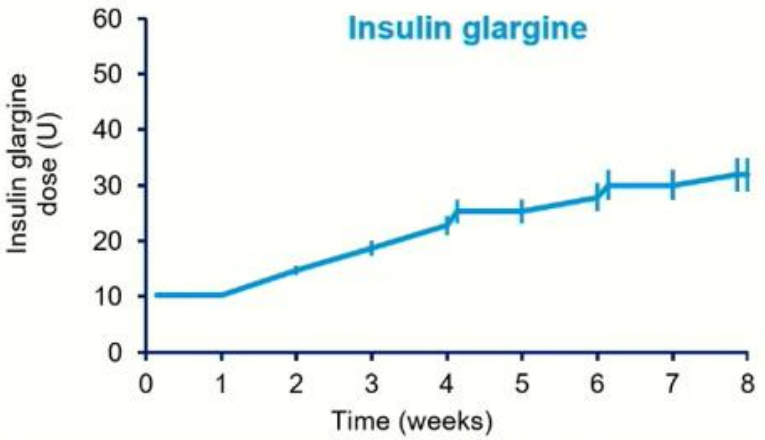
	HbA_{1c} after 8 weeks Mean ± SD
Oral insulin 338	7.3 ± 0.8 %
Insulin glargine	7.1 ± 0.6 %

	Estimated treatment difference after 8 weeks Difference [95% CI]	**p-value**
Oral insulin 338 vs. insulin glargine	0.30 [-0.03; 0.63] %	0.077

Insulin-naive people with type 2 diabetes (n=50)
Halberg I et al. Lancet Diabetes Endocrinol 2019; 7:179-188

Oral basal insulin: much higher insulin doses than with s.c. insulin glargine U100 in T2DM



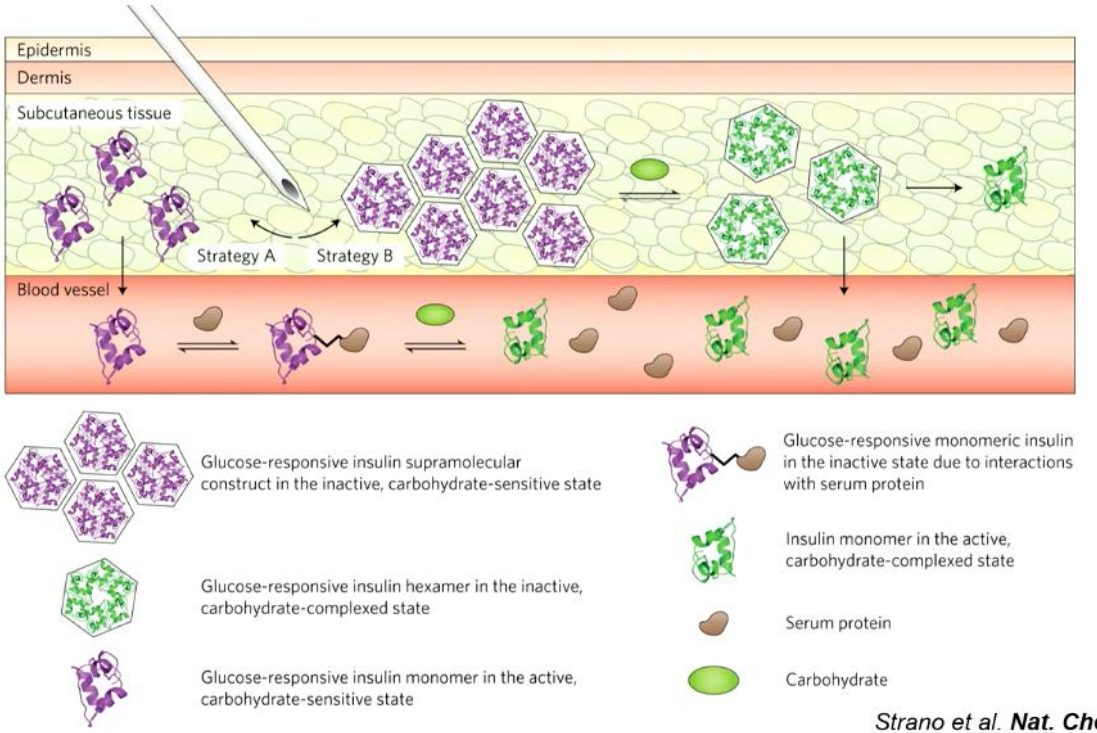


	Daily insulin dose after 8 weeks Mean ± SD
Oral insulin 338	114 ± 51 nmol/kg
Insulin glargine	0.33 ± 0.15 U/kg

	Estimated treatment ratio after 8 weeks Ratio [95% CI]
Oral insulin 338/ insulin glargine	347 [262;459] nmol/U

Halberg I et al. Lancet Diabetes Endocrinol 2019; 7:179-188

“Smart” Insulin to Improve Glucose Control



Strano et al. ***Nat. Chem.*** *2017*

Glucose-responsive “smart” insulin offers a route to ensuring insulin is made available or active precisely at the time of need, according to glucose level

Will we ever have glucose-sensitive insulins?
Reason for hope: pipeline of large pharma companies

Eli Lilly

GS Insulin Receptor Agonist

Diabetes

Cardiometabolic Health
Large Molecule
NME

View more information

GS Insulin Receptor Agonist

"Glucose sensing insulin receptor agonist" is a biologic entity being studied for the treatment of diabetes.

Novo Nordisk

Phase 1

Glucose sensitive insulin

Diabetes
→

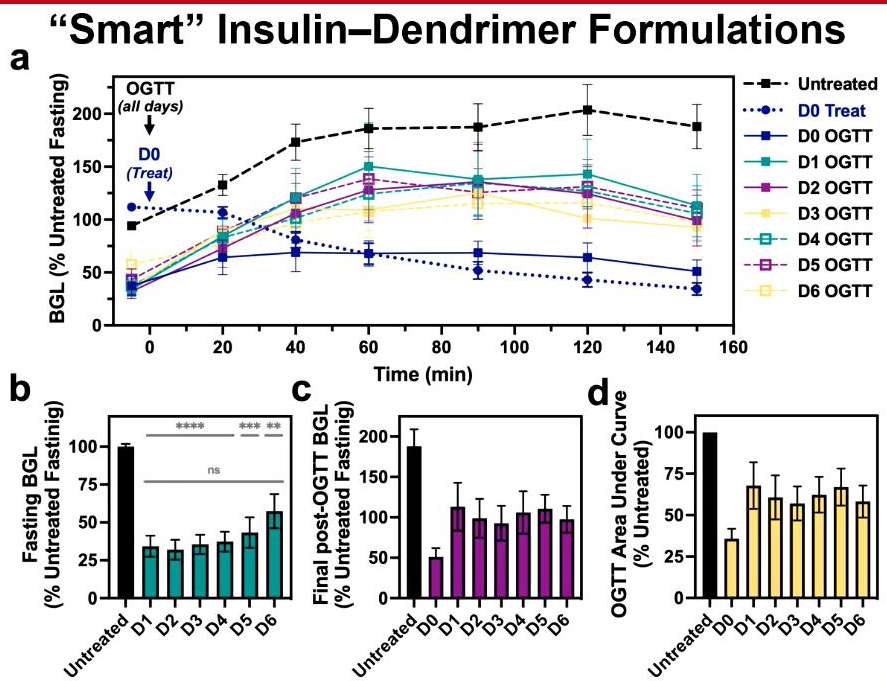
Type 1 and 2 diabetes

A glucose-sensitive insulin analogue intended for once-daily treatment.

https://www.lilly.com/innovation/clinical-development-pipeline#; https://www.novonordisk.com/science-and-technology/r-d-pipeline.html (access 15-Mar-2025)

08:30 - 09:15 Do we need “new” insulins?

CHAIR: HARALD SOURIJ



Diabetic minipigs have substantially improved glucose control for a week following a single injection

Xian,* Xiang,* Webber et. al. *Adv. Mat.* **2024**

University of Notre Dame
Department of Chemical & Biomolecular Engineering
mwebber@nd.edu
www.WebberLab.com
@WebberLab

Matthew Webber

Yes, we need smart insulin

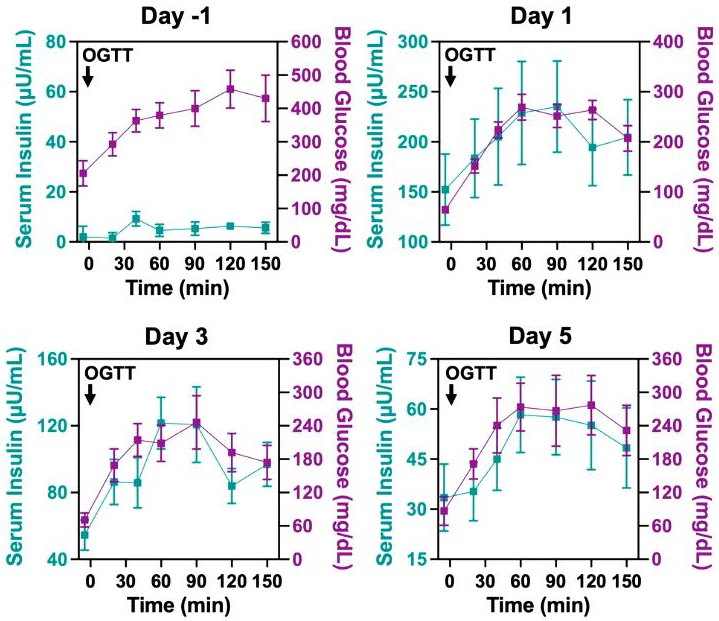
EASD 2025 VIENNA

EASD

08:30 - 09:15 Do we need “new” insulins?

CHAIR: HARALD SOURIJ

“Smart” Insulin–Dendrimer Formulations



Diabetic minipigs have increased serum insulin with glucose challenges for a week after a single dose

Xian,* Xiang,* Webber et. al. *Adv. Mat.* **2024**

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Department of Chemical & Biomolecular Engineering

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www.WebberLab.com

@WebberLab

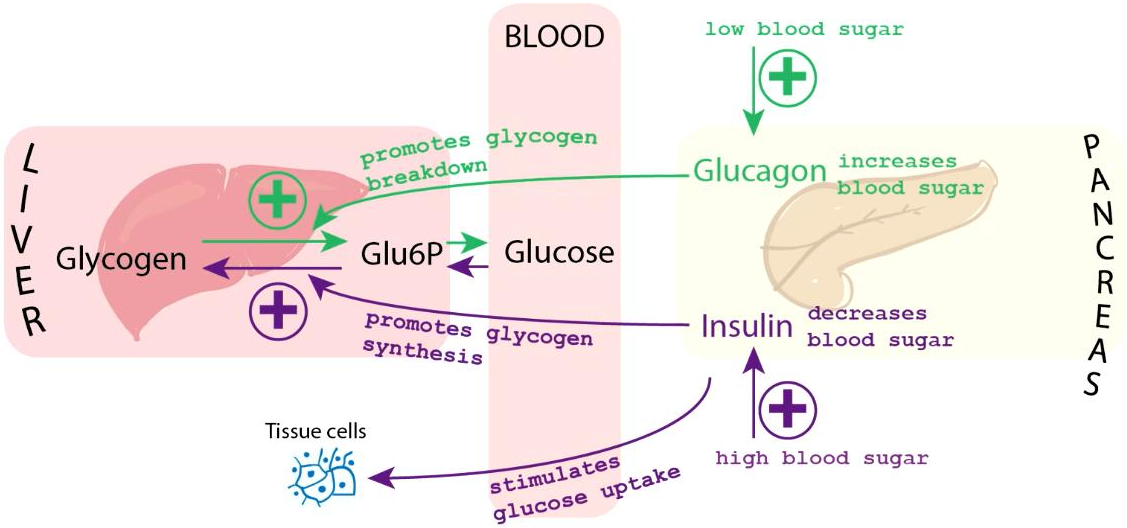
Matthew Webber

Yes, we need smart insulin

08:30 - 09:15 Do we need “new” insulins?

CHAIR: HARALD SOURIJ

But What About Low Glucose? “Smart” Glucagon?



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Matthew Webber

Yes, we need smart insulin

EASD 2025 VIENNA

EASD

Oral and glucose-sensitive insulin: Slowly gaining speed…

ΕΥΧΑΡΙΣΤΩ ΓΙΑ ΤΗΝ ΠΡΟΣΟΧΗ ΣΑΣ