EXPLORING INCRETIN-BASED THERAPY

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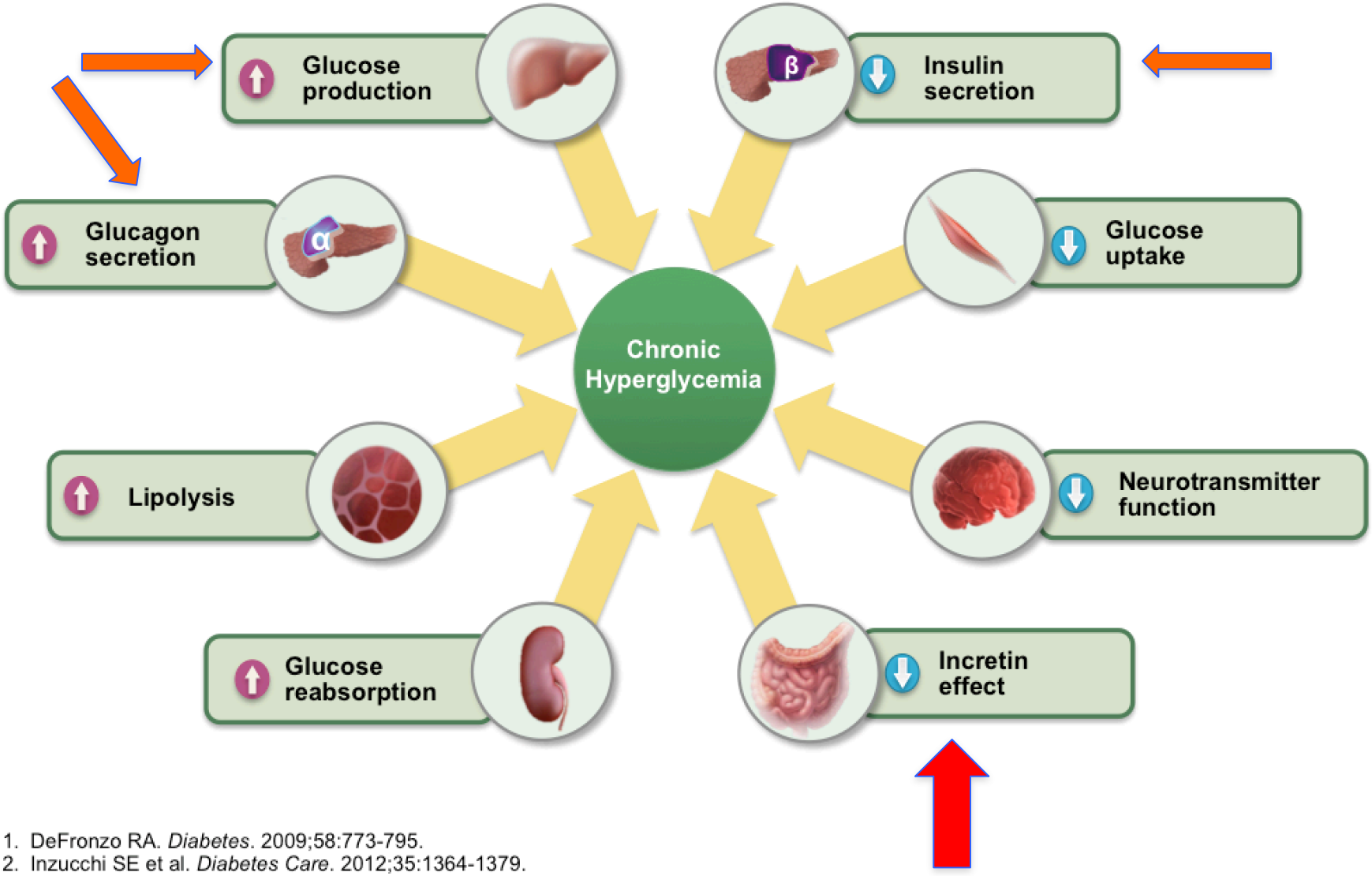
URBAN FARM & WINE BAR

Disclosures

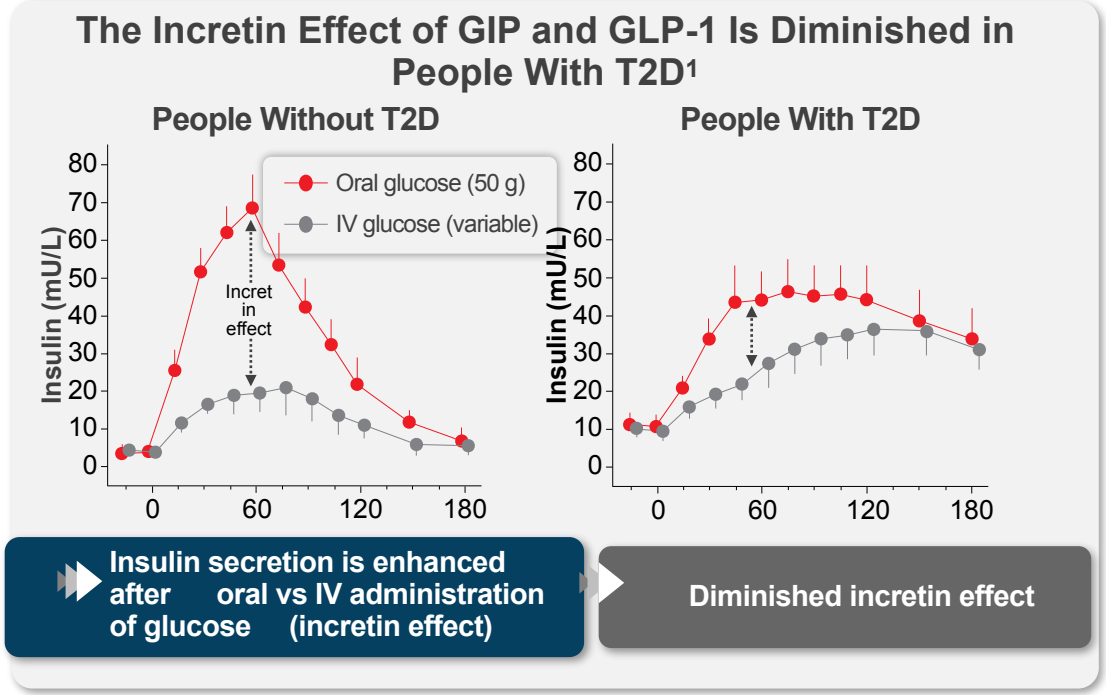
- I currently speak on behalf of:
  - Abbvie
  - Lilly
  - NovoNordisk

The Multifactorial Pathophysiology of Type 2 Diabetes Is a Key Factor for Optimizing Individualization of Therapy[1-2]



1. DeFronzo RA. *Diabetes*. 2009;58:773-795.
2. Inzucchi SE et al. *Diabetes Care*. 2012;35:1364-1379.

GLP-1 and GIP are signals from the gut that reflect the fed state.

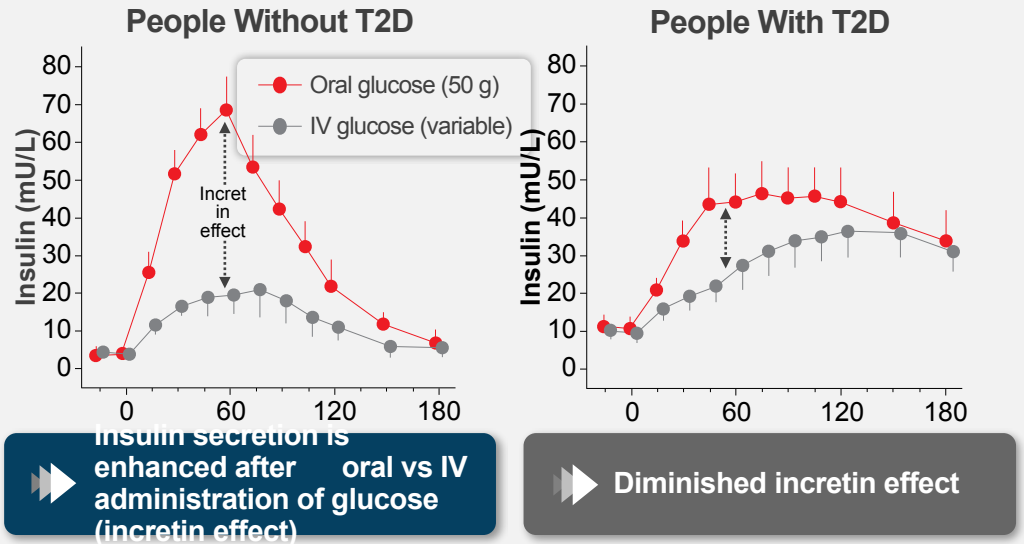


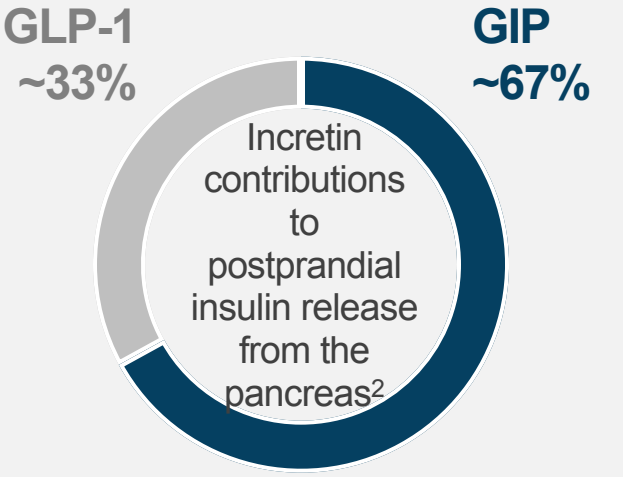
*P<0.05 vs oral glucose.[1]
IV=intravenous.

1. Nauck MA, et al. *Diabetes Obes Metab*. 2018;20(suppl 1):5-21. 2. Nauck MA, et al. *Diabetes*. 2019;68(5):897-900.

Relative contributions of GLP-1 and GIP to the Incretin Effect.[1,2]

The Incretin Effect of GIP and GLP-1 Is Diminished in People With T2D[1]

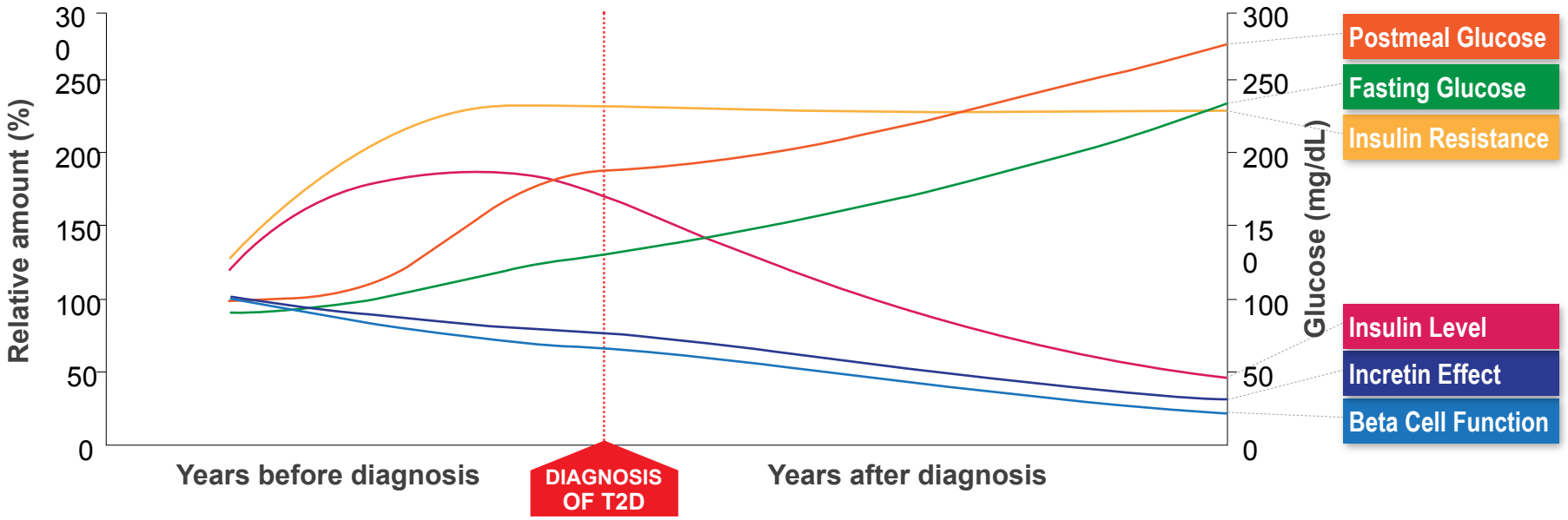




GIP is responsible for nearly **two-thirds** of the incretin effect in people without T2D, contributing more to insulin secretion than GLP-1.[2]

*$P<0.05$ vs oral glucose.[1]
IV=intravenous.
1. Nauck MA, et al. *Diabetes Obes Metab*. 2018;20(suppl 1):5-21. 2. Nauck MA, et al. *Diabetes*. 2019;68(5):897-900.

T2D IS A PROGRESSIVE INSULIN SECRETORY DEFECT AGAINST THE BACKGROUND OF INSULIN RESISTANCE[1-3,*]



*Representative depiction of the natural history of T2D highlighting the role of insulin resistance, insulin deficiency, and impaired incretin effect. Both the time course and relative function are descriptive.
T2D=type 2 diabetes.

1. Kendall DM, et al. *Am J Med*. 2009;122(suppl 6A):S37-S50.
2. Esser N, et al. *Diabetologia*. 2020;63(10):2007-2021.
3. Skyler JS, et al. *Diabetes*. 2017;66(2):241-255.

John Brown, PhD DSc, FRSC

Department of Cellular and Physiological Sciences
University of British Columbia

GIP

- Isolated around 1970
- “Gastric Inhibitory Polypetide”
- Decrease in stomach acid production

- Later re-named, keeping GIP acronym

- Glucose-dependent Insulinotropic Polypeptide

Holst and Habener

Jans Juus Holst, MD, DMSc

University of Copenhagen
Biomedical Sciences

Joel Francis Habener, MD

Professor of Medicine
Harvard Medical School

Director of Molecular Endocrinology
Massachusetts General Hospital

GLP-1

- Simultaneously isolated in 1986
- “Glucagon-like Peptide 1”
- Accentuation of beta cell production of insulin
- Delay in gastric emptying
- Satiety effect realized around 1996

John Eng, MD

Department of Endocrinology Veteran's Affairs
Mount Sinai Hospital
Bronx, NY

Exendin-4

- Isolated in 1990
- Similar in structure and function to GLP-1
- Present in venom of various reptiles
- Isolated from saliva of *Heloderma suspectum*

Exendin-4

Gila monster

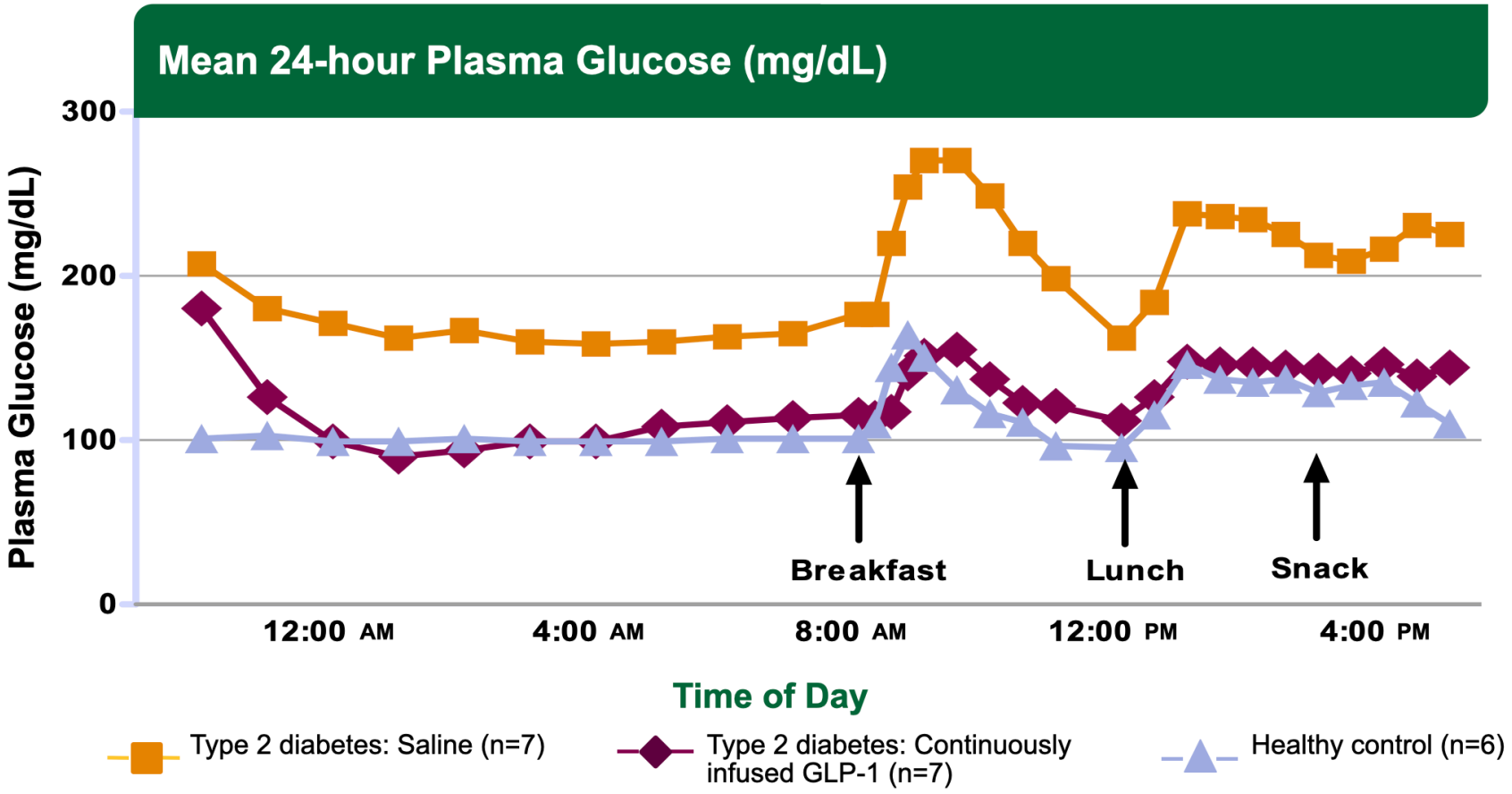
Exendin-4

- *H. suspectum* - normal glucose's while fasting
- Exposure to animals increased beta cell mass
- 1999 - daily injection normalized glucose in diabetic mice
- Increased insulin production in humans
- Longer-acting than endogenous GLP-1
- 2005 - FDA approval of Exenatide

Exenatide

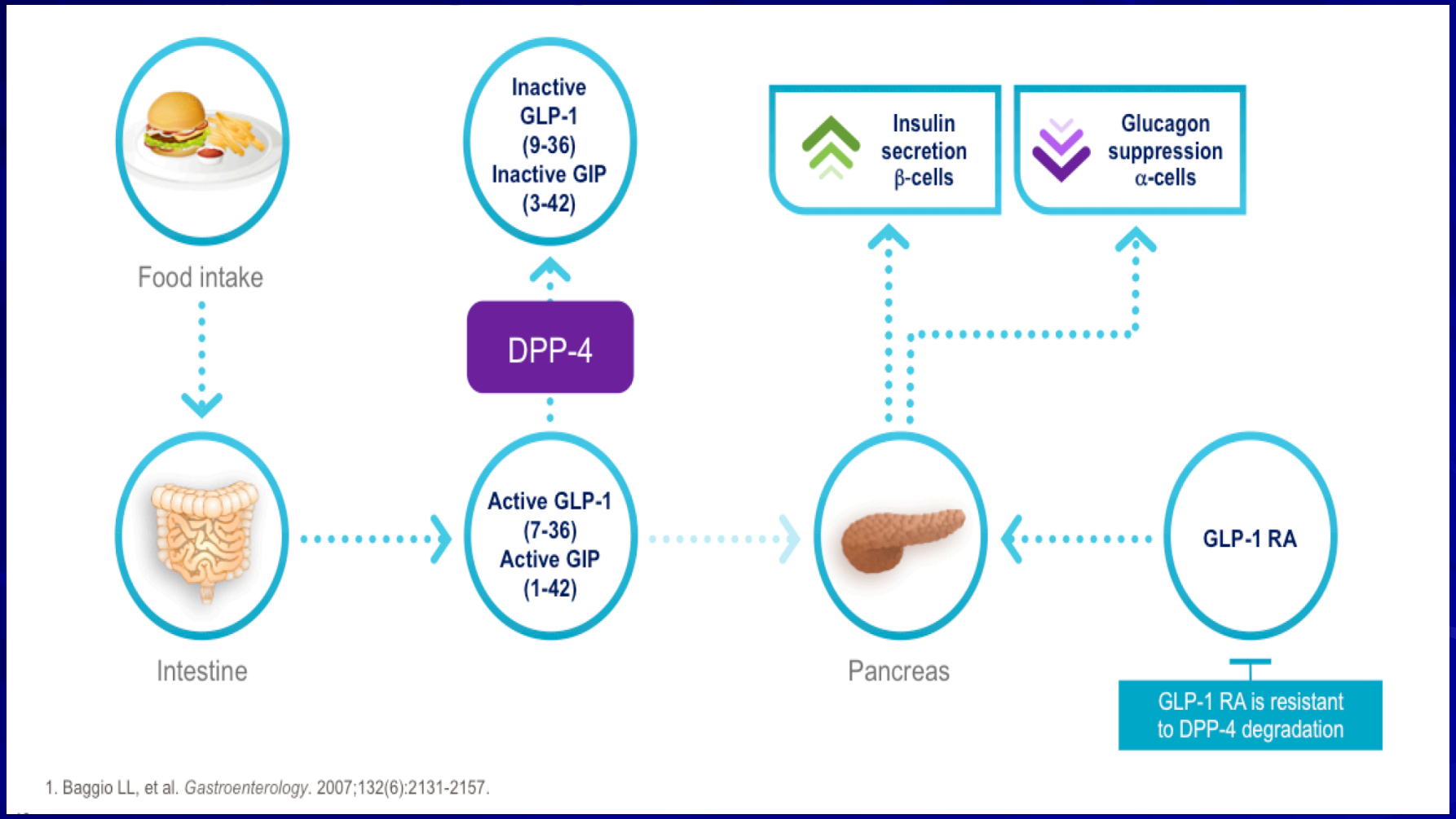
- Treatment of T2DM
- BID dosing
- Very rapid-acting

GLP-1



GLP=glucagon-like peptide.
Adapted from Rachman J et al. *Diabetologia*. 1997;40(2):205-211.

GLP-1



1. Baggio LL, et al. *Gastroenterology*. 2007;132(6):2131-2157.

Liraglutide

- Analog of endogenous GLP-1
- Modified to resist degradation by DPP-4
- Daily dosing (half-life 13hrs)
- 1996 - Invented (NovoNordisk)
- 2010 - Approval for adult use (T2DM)
- 2019 - Approval for pediatric use (T2DM)

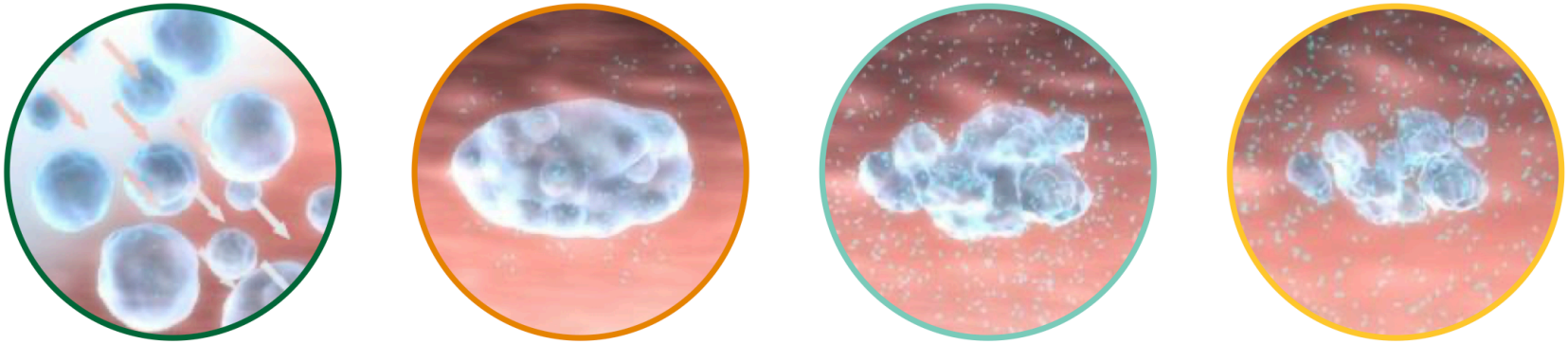
Liraglutide

- Treatment of T2DM
- Daily dosing
- Longer-acting

Exenatide

- Exenatide bound to subcutaneous microspheres
- First agent for weekly dosing
- Steady-state reached in 6-10 weeks
- 2014 - FDA approval of Bydureon (adults with T2DM)

Exenatide


Subcutaneous injection
Microsphere aggregation
Microsphere degradation
Continued release

Exenatide


Bydureon
2 mg/vial
Bydureon
2 mg/vial
Bydureon
Instructions for Use

Exenatide


Este Kit de demostración
es una marca registrada de
AstraZeneca Pharmaceuticals LP.
EXP: AGO-2017
Bydureon®
Exenatida
Suspensión

Exenatide


Once weekly
BYDUREON® BCise™
exenatide extended-release
injectable suspension 2 mg
For subcutaneous use only

Dulaglutide

- GLP-1 analogue resistant to DPP-4 degradation
- Bound to FC portion of IgG4 molecule
- Does not cross blood-brain barrier
- Weekly dosing (half-life 5 days)
- 2014 - FDA approval of Trulicity (adults with T2DM)
- Eli Lilly

Dulaglutide

Semaglutide

- GLP-1 analogue resistant to DPP-4 degradation
- Bound to albumin
- Can cross blood-brain barrier
- Weekly dosing (half-life 7 days)
- 2017 - FDA approval of Ozempic (adults with T2DM)
- NovoNordisk

Semaglutide

Tirzepatide

- GIP analoge that agonizes both GLP-1-*R* and GIP-*R*
- Bound to albumin
- Can cross blood-brain barrier
- Weekly dosing (half-life 5 days)
- 2022 - FDA approval of Mounjaro (adults with T2DM)
- Eli Lilly

Terzepatide

Treatment of Diabetes Mellitus

- GOALS OF TREATMENT:
  - Diabetic Goals:

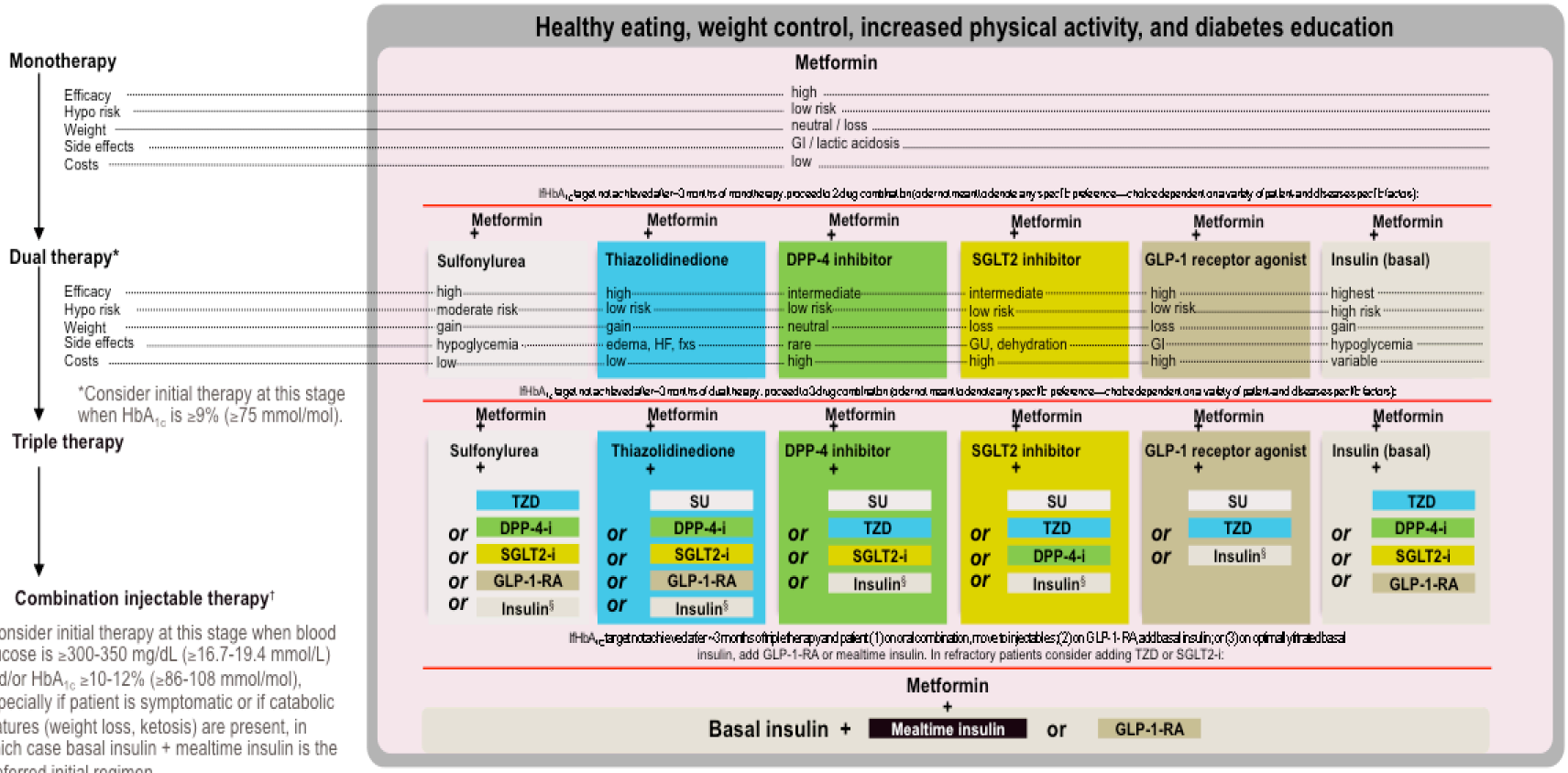
	ADA	ACE
A1c:	< 7%	< 6.5%
Preprandial:	70-130	< 110
Postprandial:	< 180	< 140

- How aggressive should we be?
  - Age
  - Risk of hypoglycemia
  - Pre-existing cardiovascular disease burden
  - Does the drug impact CV risk ?

Diabetes Mellitus and CVD

Macrovascular Outcomes: There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with **XXX** or any other antidiabetic drug.

American Diabetes Association/EASD general therapy recommendations in type 2 diabetes[1]



†Consider initial therapy at this stage when blood glucose is ≥300-350 mg/dL (≥16.7-19.4 mmol/L) and/or HbA_{1c} ≥10-12% (≥86-108 mmol/mol), especially if patient is symptomatic or if catabolic features (weight loss, ketosis) are present, in which case basal insulin + mealtime insulin is the preferred initial regimen.

Trulicity® has not been studied in combination with basal insulin.

§Usually a basal insulin (eg, NPH, glargine, detemir, degludec).

HbA_{1C}=glycated hemoglobin; DPP-4-i=dipeptidyl peptidase-4 inhibitor; EASD=European Association for the Study of Diabetes; fxs=fractures; GU=genitourinary infections; HF=heart failure; SU=sulfonylurea; TD=thiazolidinedione.

1. Inzucchi SE, et al. *Diabetes Care*. 2015;38(1):140-149.

Glycemic Control Algorithm

INDIVIDUALIZE GOALS

A1C ≤ 6.5% For patients without concurrent serious illness and at low hypoglycemic risk

A1C > 6.5% For patients with concurrent serious illness and at risk for hypoglycemia

LIFESTYLE THERAPY (Including Medically Assisted Weight Loss)

Entry A1C < 7.5%

MONOTHERAPY*

- ✓ Metformin
- ✓ GLP-1 RA
- ✓ SGLT-2i
- ✓ DPP-4i
- ! TZD
- ✓ AGi
- ! SU/GLN

If not at goal in 3 months proceed to Dual Therapy

Entry A1C ≥ 7.5%

DUAL THERAPY*

MET or other 1st-line agent +

- ✓ GLP-1 RA
- ✓ SGLT-2i
- ✓ DPP-4i
- ! TZD
- ! Basal Insulin
- ✓ Colesevelam
- ✓ Bromocriptine QR
- ✓ AGi
- ! SU/GLN

If not at goal in 3 months proceed to Triple Therapy

TRIPLE THERAPY*

MET or other 1st-line agent + 2nd-line agent +

- ✓ GLP-1 RA
- ✓ SGLT-2i
- ! TZD
- ! Basal insulin
- ✓ DPP-4i
- ✓ Colesevelam
- ✓ Bromocriptine QR
- ✓ AGi
- ! SU/GLN

If not at goal in 3 months proceed to or intensify insulin therapy

Entry A1C > 9.0%

SYMPTOMS

NO	YES
DUAL Therapy OR TRIPLE Therapy	INSULIN ± Other Agents

ADD OR INTENSIFY INSULIN

Refer to Insulin Algorithm

LEGEND

- ✓ Few adverse events and/or possible benefits
- ! Use with caution

* Order of medications represents a suggested hierarchy of usage; length of line reflects strength of recommendation

PROGRESSION OF DISEASE

 DOI 10.4158/CS-2017-0153

Incretin Receptor Agonists

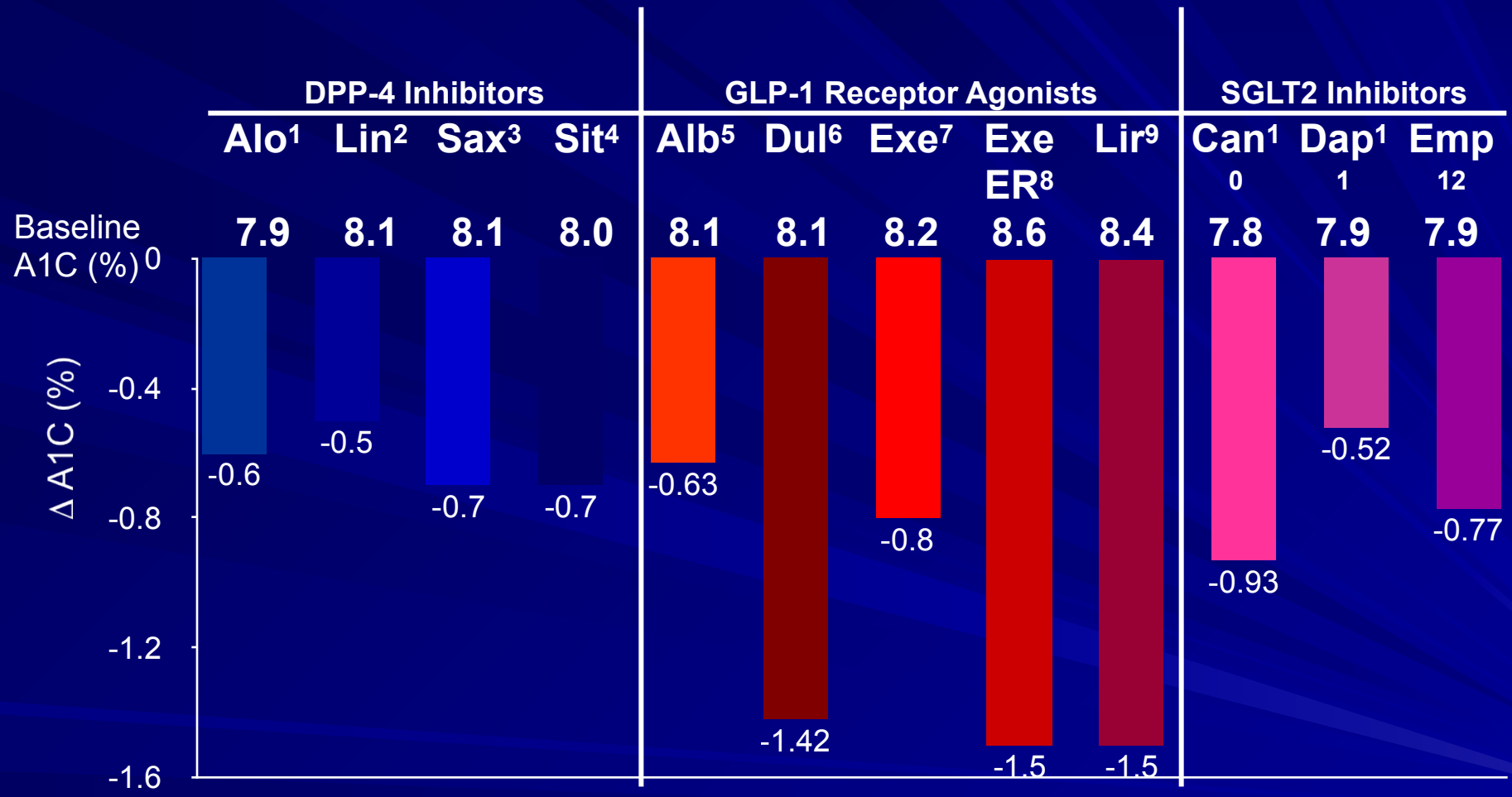
Safety Considerations with GLP-1 RA's

GI adverse events	• Common • Usually dose dependent and transient • Usually reduced with dose titration
Pancreatitis	• Pancreatitis has been reported with postmarketing use of some of incretin agents, although no causal relationship has been established • Extensive review by FDA of studies involving >80,000 patients has not uncovered reliable evidence of increased pancreatic risk with incretins vs other agents • Labeling for all incretins states these agents should be immediately discontinued if pancreatitis is suspected • Labeling for GLP-1 receptor agonists suggests consideration of other therapies for patients with a history of pancreatitis
Pancreatic cancer	• Extensive review by FDA of studies involving >80,000 patients has not uncovered reliable evidence of increased pancreatic risk with incretins vs other agents • Further assessments required from long duration-controlled studies or epidemiological databases

Medullary thyroid cancer	• Animal data showed an increased incidence of C-cell tumors with liraglutide and exenatide ER treatment, but confirmatory population studies are lacking
	• Labeling for liraglutide and exenatide ER:
	  • Patients should be counseled regarding medullary thyroid carcinoma and the signs/symptoms of thyroid tumors
	  • Contraindicated in patients with personal/family history of MTC or multiple endocrine neoplasia syndrome type 2

Renal impairment	• Renal Impairment has been reported postmarketing, usually in association with nausea, vomiting, diarrhea, or dehydration. Use caution when initiating or escalating doses in patients with renal impairment. Exenatide is contraindicated in patients with severe renal insufficiency or ESRD

Glucose Reduction



1. Nauck MA, et al. *Int J Clin Pract*. 2009;63:46-55. 2. Taskinen MR, et al. *Diabetes Obes Metab*. 2011;13:65-74. 3. DeFronzo RA, et al. *Diabetes Care*. 2009;32:1649-1655. 4. Charbonnel B, et al. *Diabetes Care*. 2006;29:2638-2643. 5. Ahrén B, et al. *Diabetes Care*. 2014;37:2141-2148. 6. Dungan KM, et al. *Lancet*. 2014;384:1349-1357. 7. DeFronzo RA et al. *Diabetes Care*. 2005;28:1092-1100. 8. Bergenstal RM, et al. *Lancet*. 2010;376:431-439. 9. Pratley RE, et al. *Lancet*. 2010;375:1447-1456. 10. Cefalu WT, et al. *Lancet*. 2013;382:941-950. 11. Nauck MA, et al. *Diabetes Care*. 2011;34:2015-2022. 12. Haring HU, et al. *Diabetes Care*. 2014;37:1650-1659.

EMPA-REG

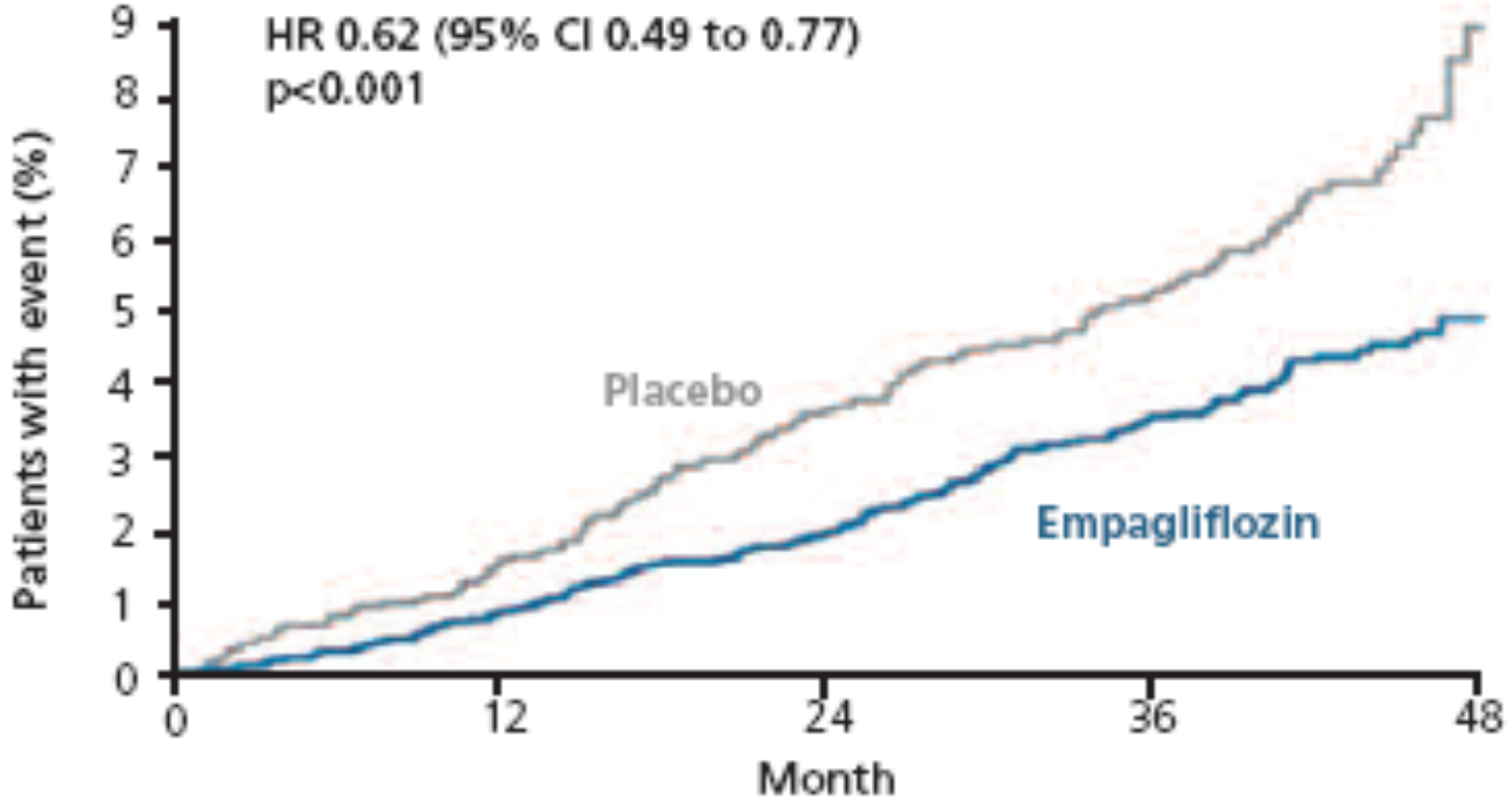
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes

Bernard Zinman, M.D., Christoph Wanner, M.D., John M. Lachin, Sc.D., David Fitchett, M.D., Erich Bluhmki, Ph.D., Stefan Hantel, Ph.D., Michaela Mattheus, Dipl. Biomath., Theresa Devins, Dr.P.H., Odd Erik Johansen, M.D., Ph.D., Hans J. Woerle, M.D., Uli C. Broedl, M.D., and Silvio E. Inzucchi, M.D., for the EMPA-REG OUTCOME Investigators

Figure 1. The cumulative incidence of death from cardiovascular causes in the empagliflozin group versus placebo group in the EMPA-REG OUTCOME



Hazard ratios (HR) are based on Cox regression analysis. Reproduced with permission from ref 2.

INDICATIONS AND LIMITATIONS OF USE

JARDIANCE is indicated to reduce the risk of cardiovascular (CV) death in adults with type 2 diabetes mellitus and established CV disease.

LEADER Trial

ORIGINAL ARTICLE

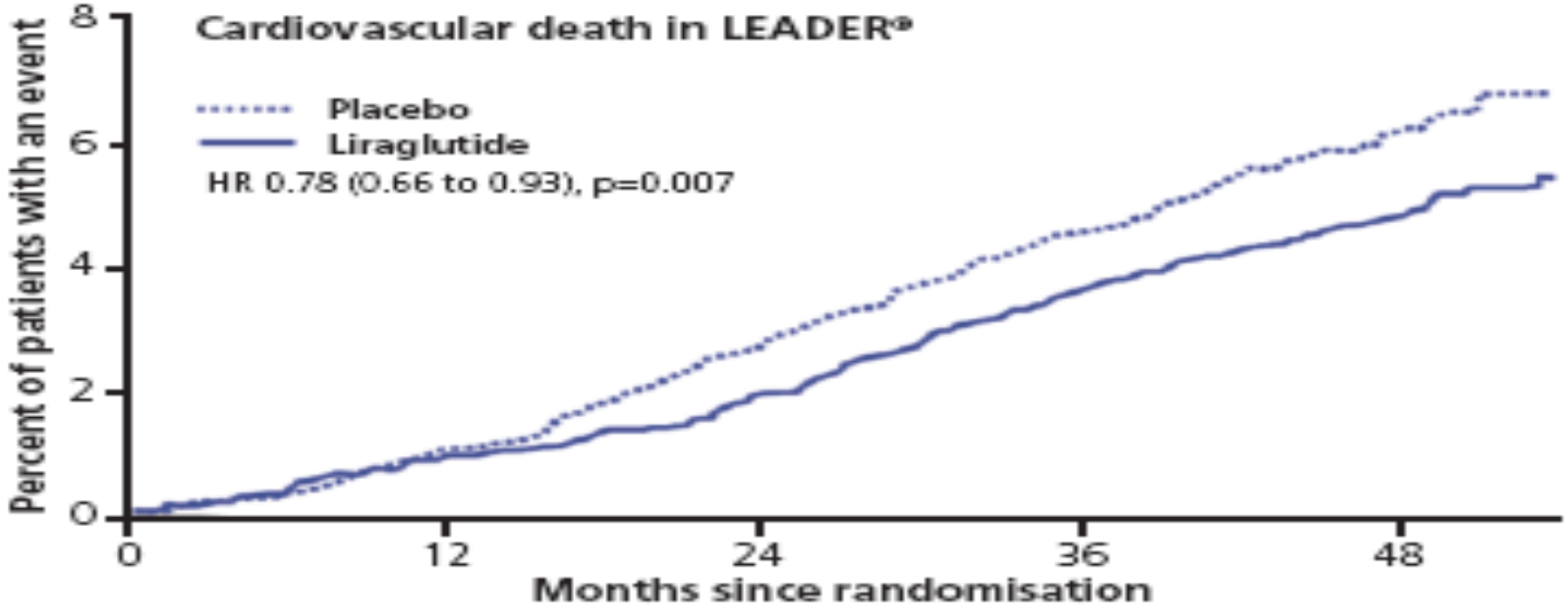
Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes

Steven P. Marso, M.D., Gilbert H. Daniels, M.D., Kirstine Brown-Frandsen, M.D., Peter Kristensen, M.D., E.M.B.A., Johannes F.E. Mann, M.D., Michael A. Nauck, M.D., Steven E. Nissen, M.D., Stuart Pocock, Ph.D., Neil R. Poulter, F.Med.Sci., Lasse S. Ravn, M.D., Ph.D., William M. Steinberg, M.D., Mette Stockner, M.D., Bernard Zinman, M.D., Richard M. Bergenstal, M.D., and John B. Buse, M.D., Ph.D., for the LEADER Steering Committee on behalf of the LEADER Trial Investigators*

ABSTRACT

LEADER Trial

Figure 1. Cumulative incidence of death from cardiovascular causes in the liraglutide group versus placebo group in the LEADER study



Hazard ratios [HR (95%CI)] based on Cox regression analysis
Adapted from reference 6

'Victoza® is indicated:

- as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.
- **as an adjunct to standard treatment of cardiovascular risk factors to reduce the risk of major adverse cardiovascular events (cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke) in adults with type 2 diabetes mellitus and high cardiovascular risk.'**

SUSTAIN-6

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes

Steven P. Marso, M.D., Stephen C. Bain, M.D., Agostino Consoli, M.D., Freddy G. Eliaschewitz, M.D., Esteban Jódar, M.D., Lawrence A. Leiter, M.D., Ildiko Lingvay, M.D., M.P.H., M.S.C.S., Julio Rosenstock, M.D., Jochen Seufert, M.D., Ph.D., Mark L. Warren, M.D., Vincent Woo, M.D., Oluf Hansen, M.Sc., Anders G. Holst, M.D., Ph.D., Jonas Pettersson, M.D., Ph.D., and Tina Vilsbøll, M.D., D.M.Sc., for the SUSTAIN-6 Investigators*

SUSTAIN-6

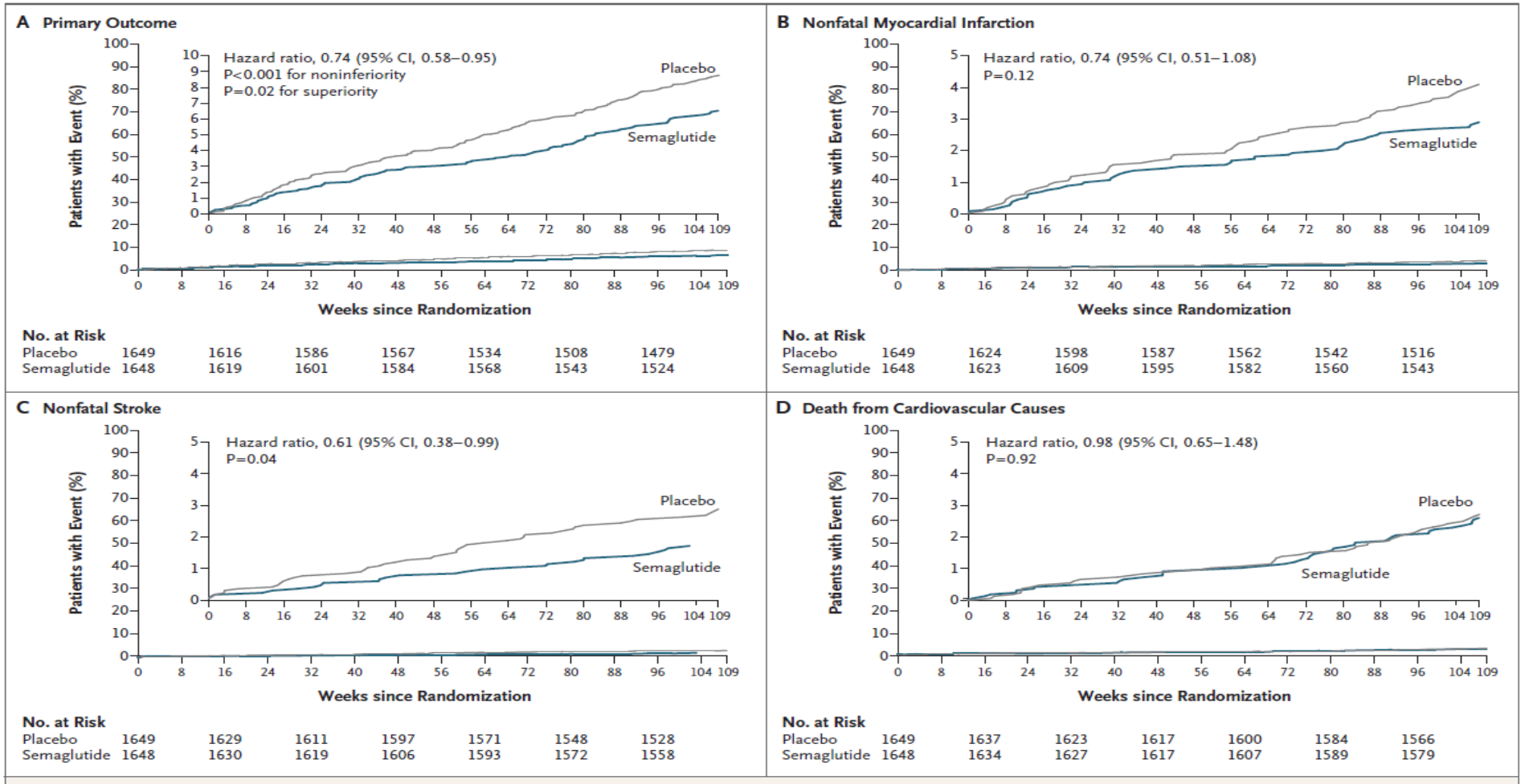
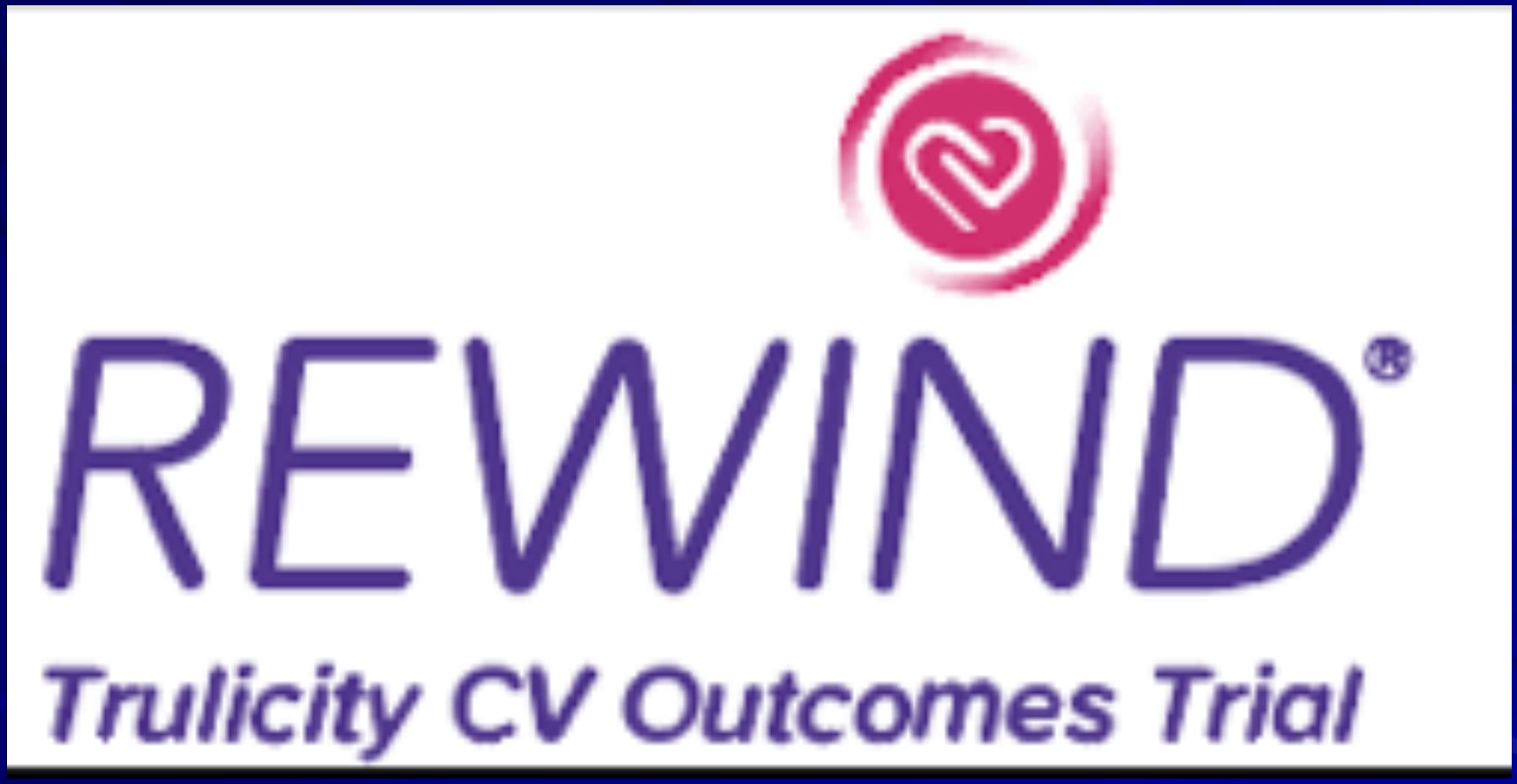


Figure 1. Cardiovascular Outcomes.

Shown are Kaplan–Meier plots of the primary outcome (a composite of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke) (Panel A), nonfatal myocardial infarction (Panel B), nonfatal stroke (Panel C), and death from cardiovascular causes (Panel D). The trial included a planned observation period of 109 weeks for all patients (a 104-week treatment period with a 5-week follow-up period). In Panel C, there were no events in the semaglutide group after week 104. Insets show the same data on an expanded y axis.

- to reduce the risk of major adverse cardiovascular events in adults with type 2 diabetes mellitus and established cardiovascular disease (1).

REWIND



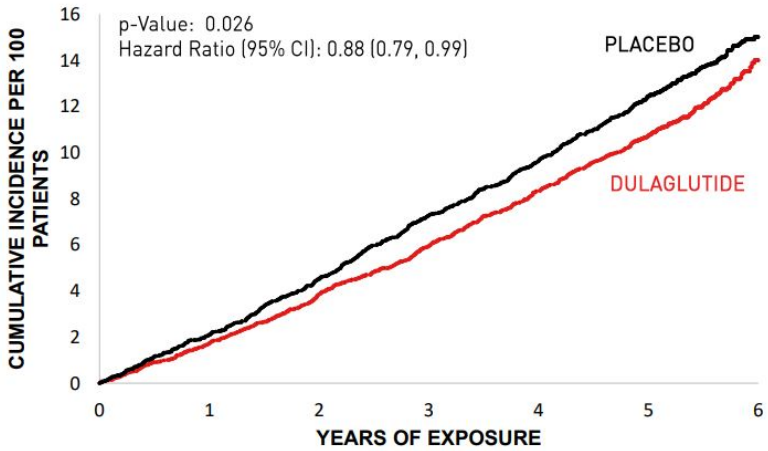
REWIND

TRULICITY CV OUTCOME TRIAL

Lilly

PRIMARY MACE 3 RESULT

- **Dulaglutide significantly reduced the risk of Major Adverse Cardiovascular Events** (MACE 3: CV death, non-fatal MI or non-fatal stroke) **by 12% vs. placebo**

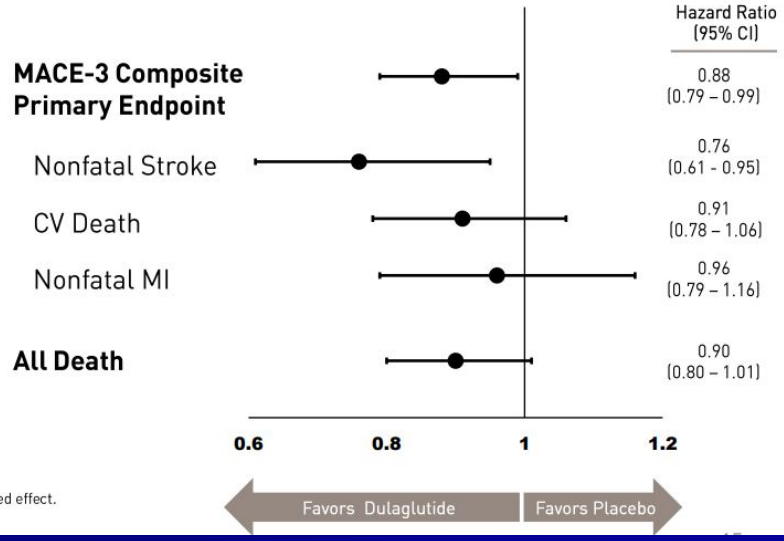


Note: Hazard Ratio and its CI and p-value obtained from Cox Proportional Hazards Regression Model with treatment as a fixed effect.

Gerstein et al. Lancet 2019.

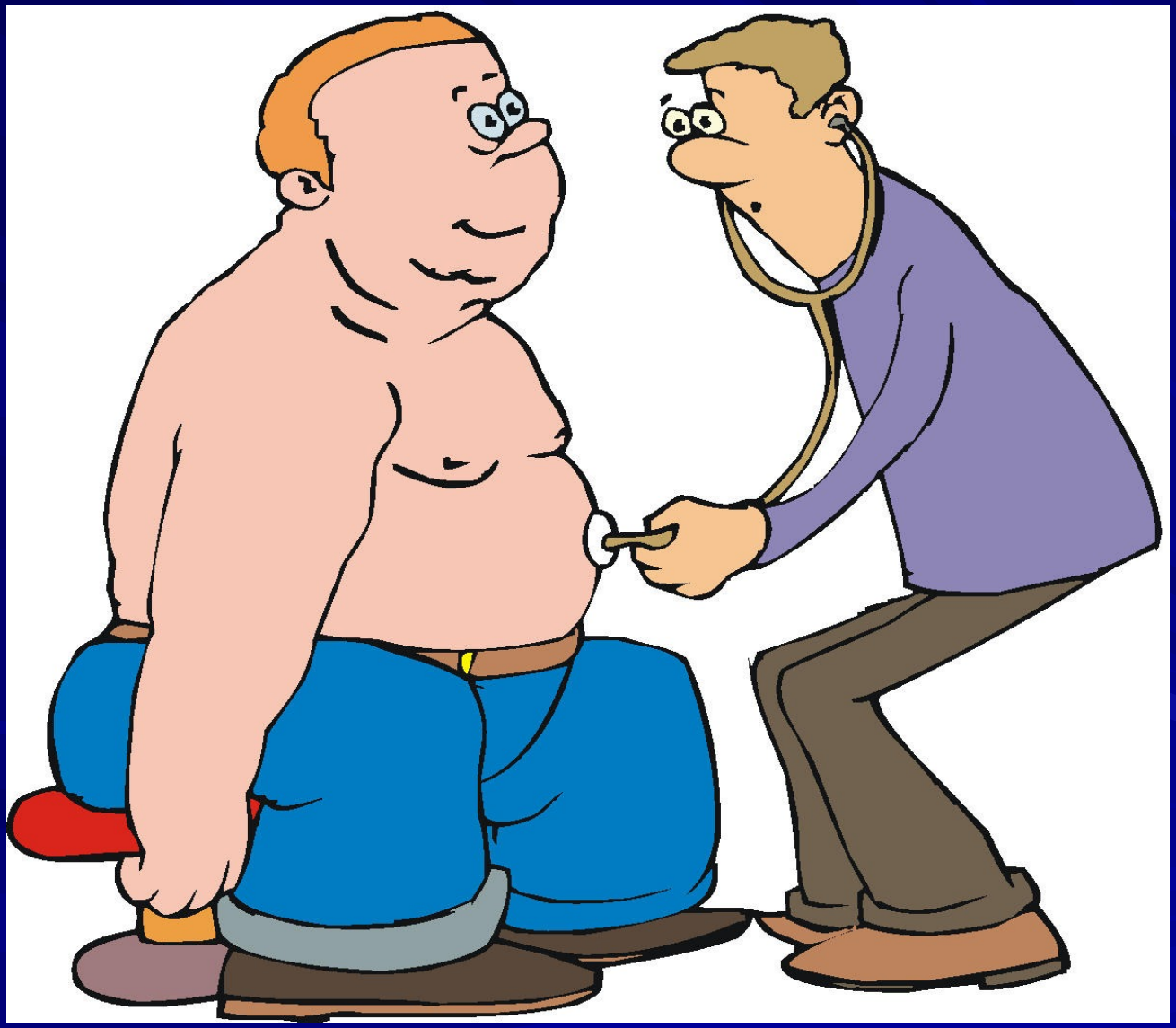
CV OUTCOMES

- **Consistent effect across three components of MACE, greatest difference observed in Nonfatal Stroke**



- To reduce the risk of major adverse cardiovascular events in adults with type 2 diabetes mellitus who have established cardiovascular disease or multiple cardiovascular risk factors.

Incretins for Weight Loss ?



How did we get here?

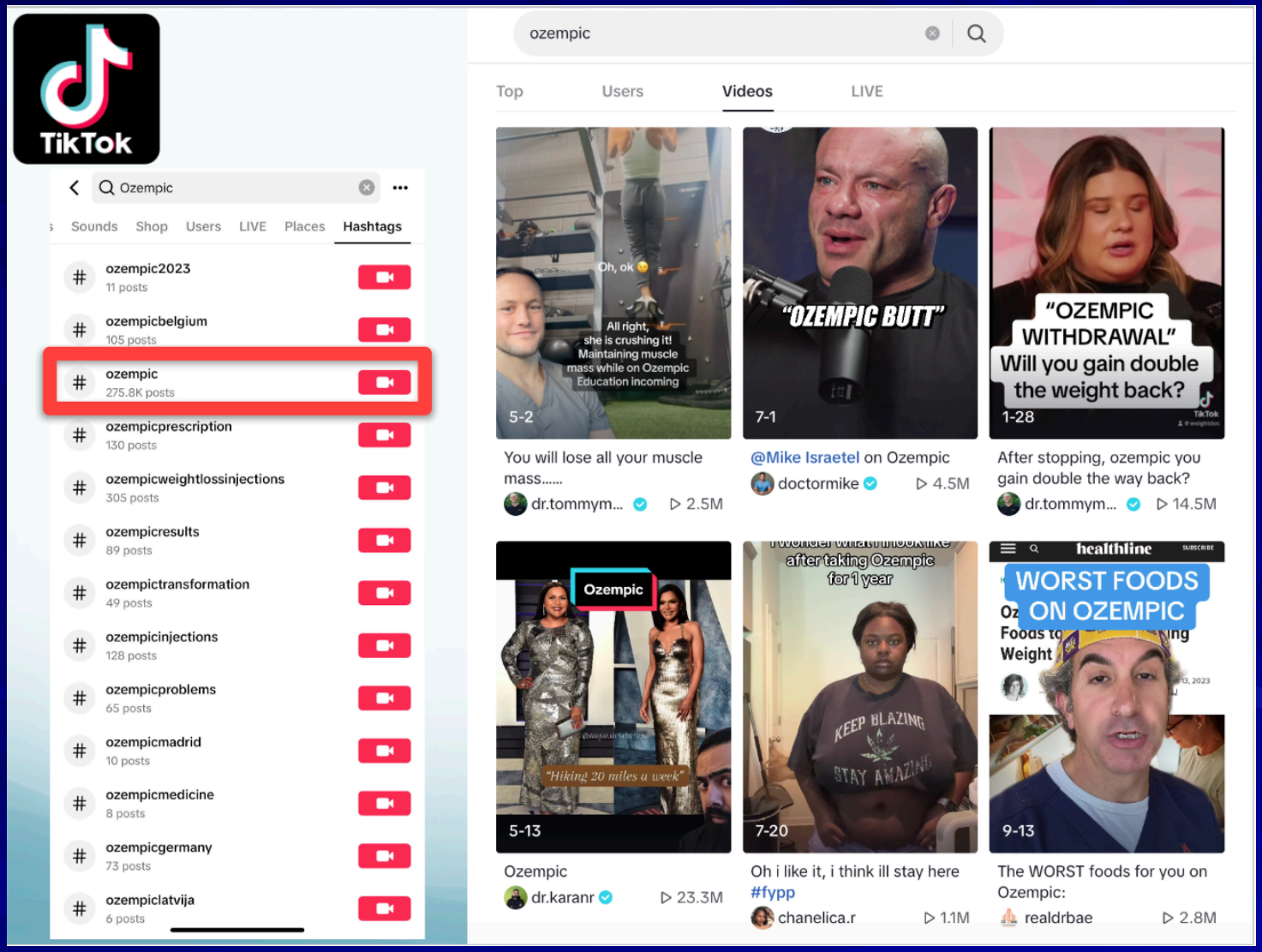
How did we get here?

From your Watch later playlist

Semaglutide, Kardashians, and Female Body Image

PowerfulJRE · 2M views · 7 months ago

How did we get here?



How did we get here?

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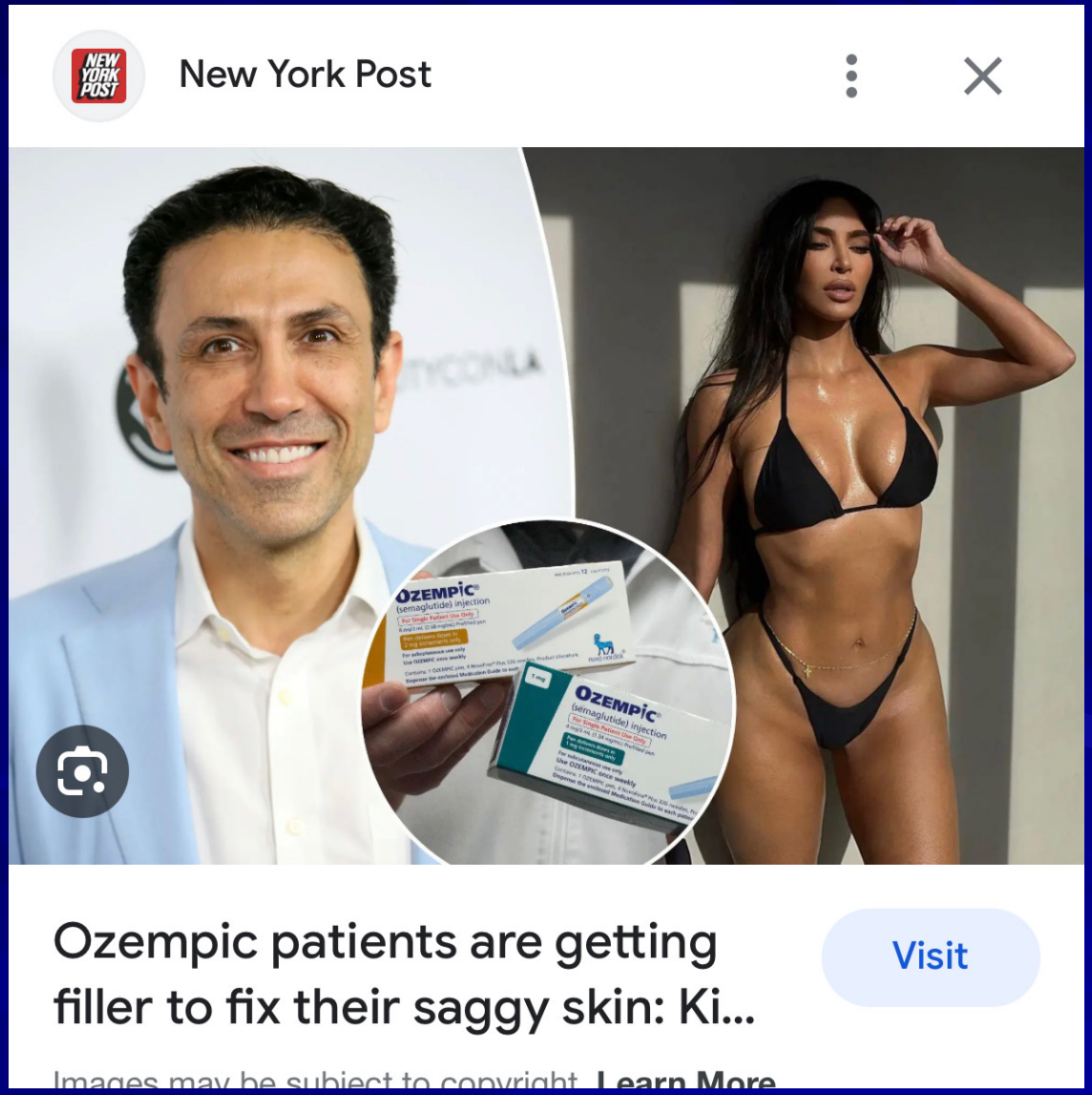
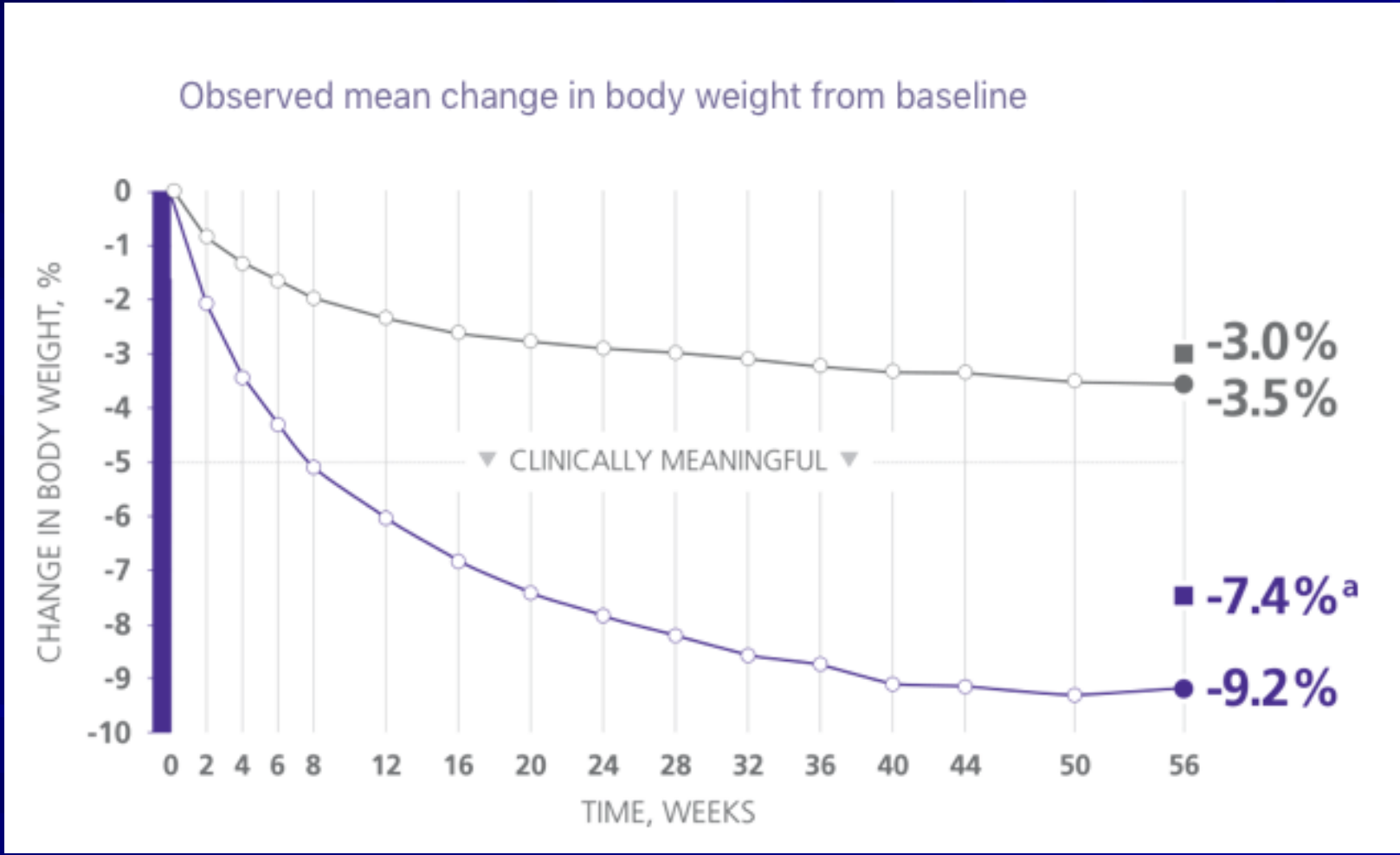


How did we get here?

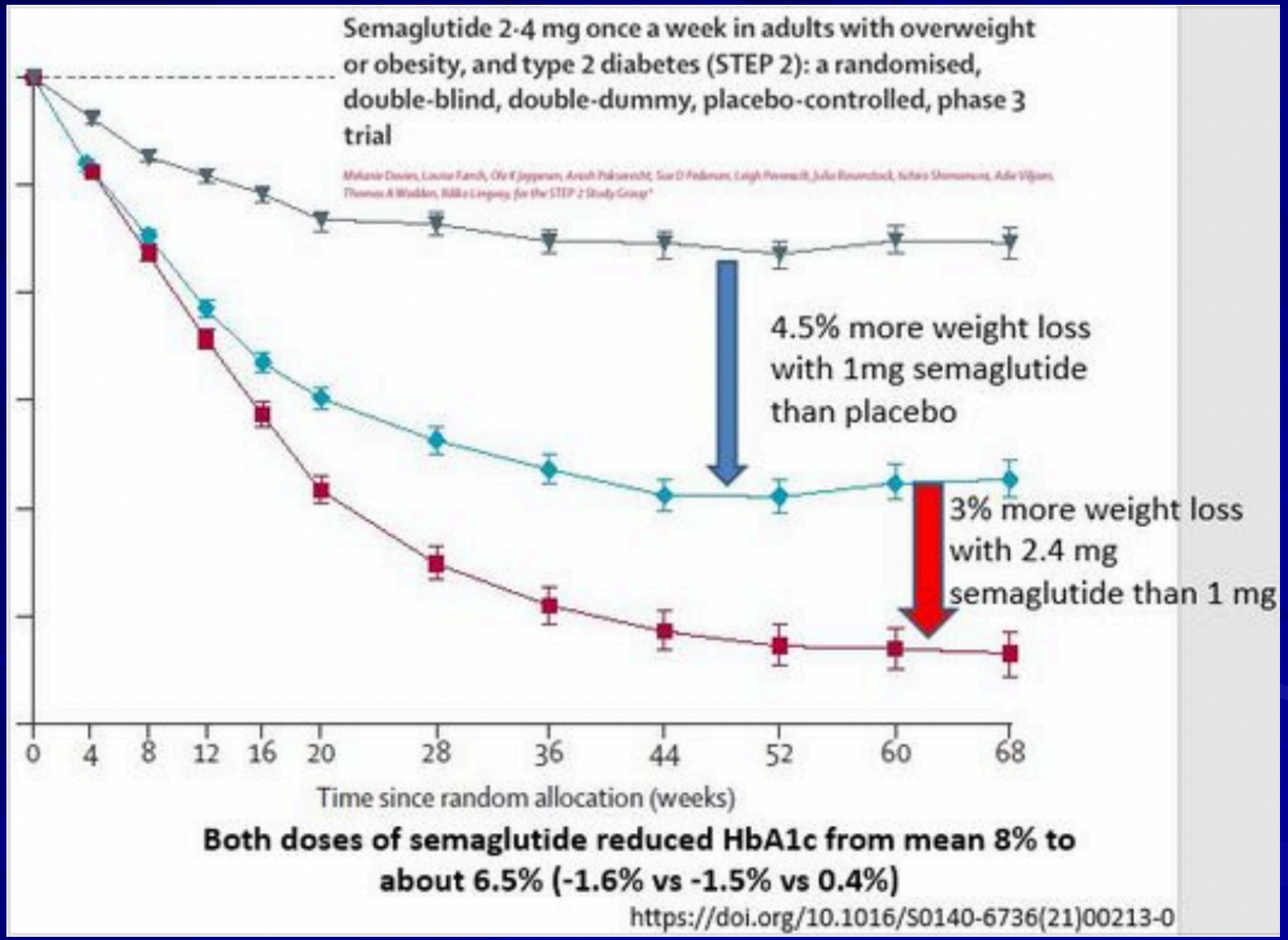
Incretins for Weight Loss

- Saxenda (liraglutide)
- Wegovy (semaglutide)
- Zepbound (tirzepatide)

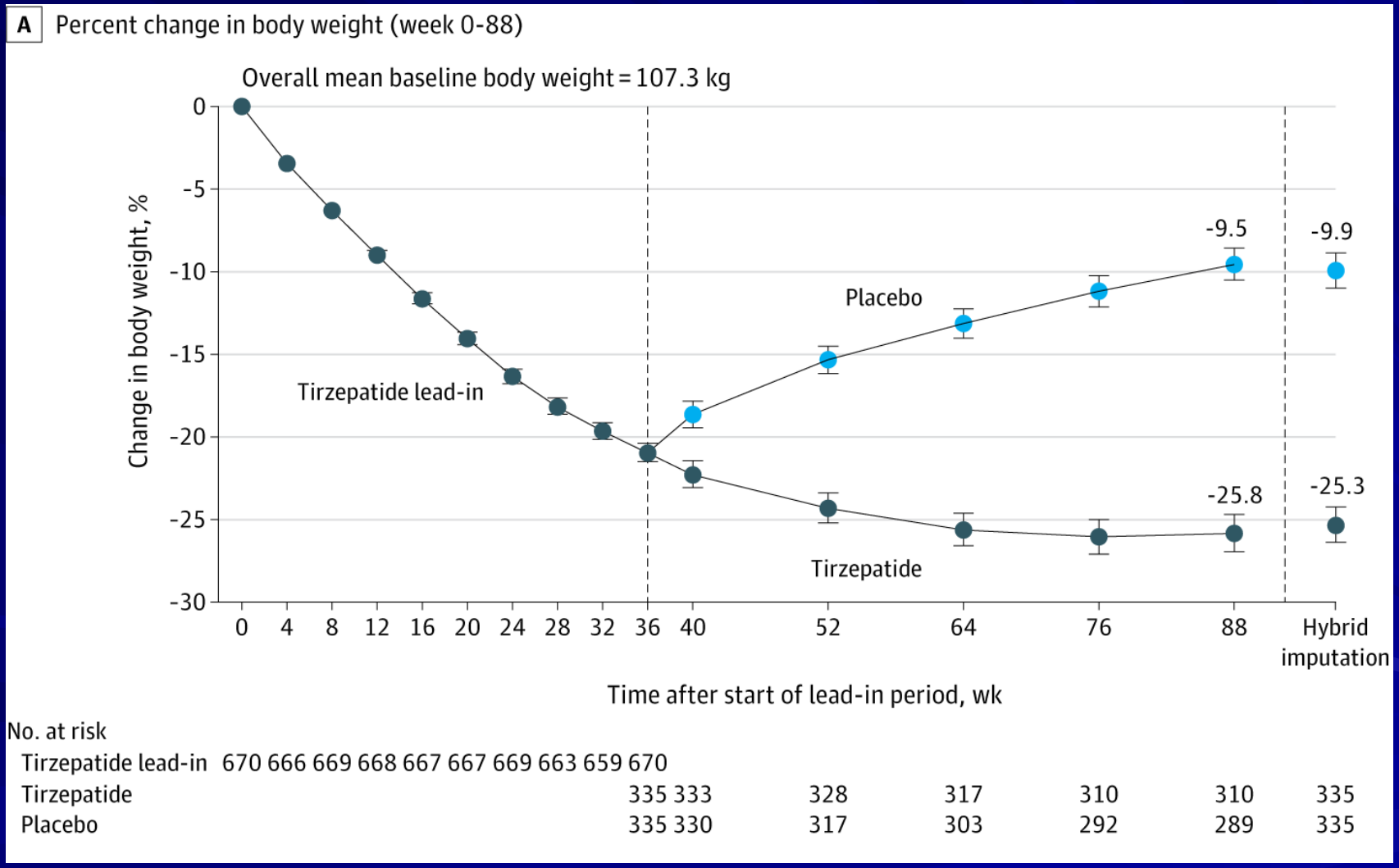
Saxenda (liragulitide)



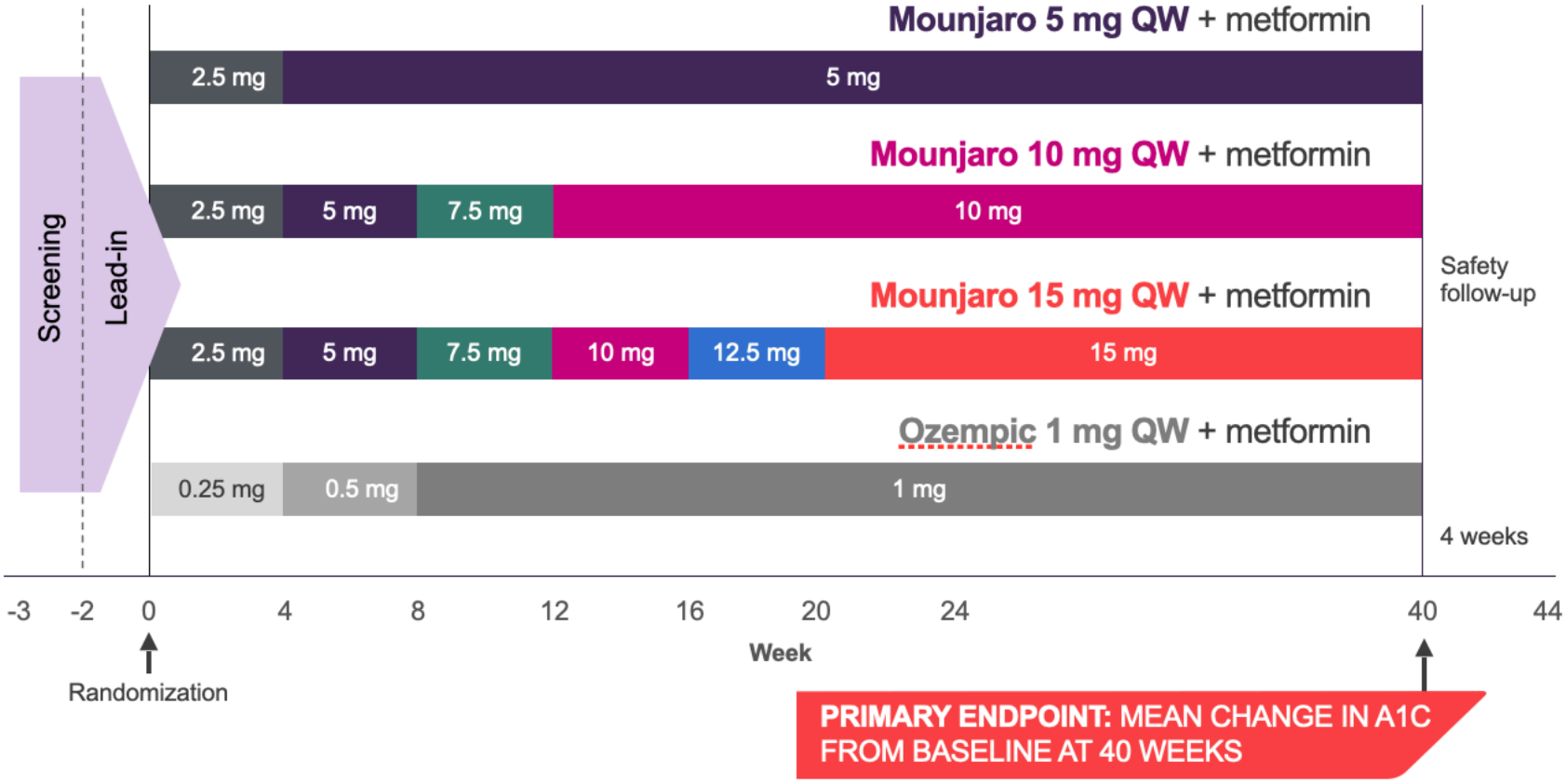
Wegovy (semaglutide)



Zepbound (terzepatide)



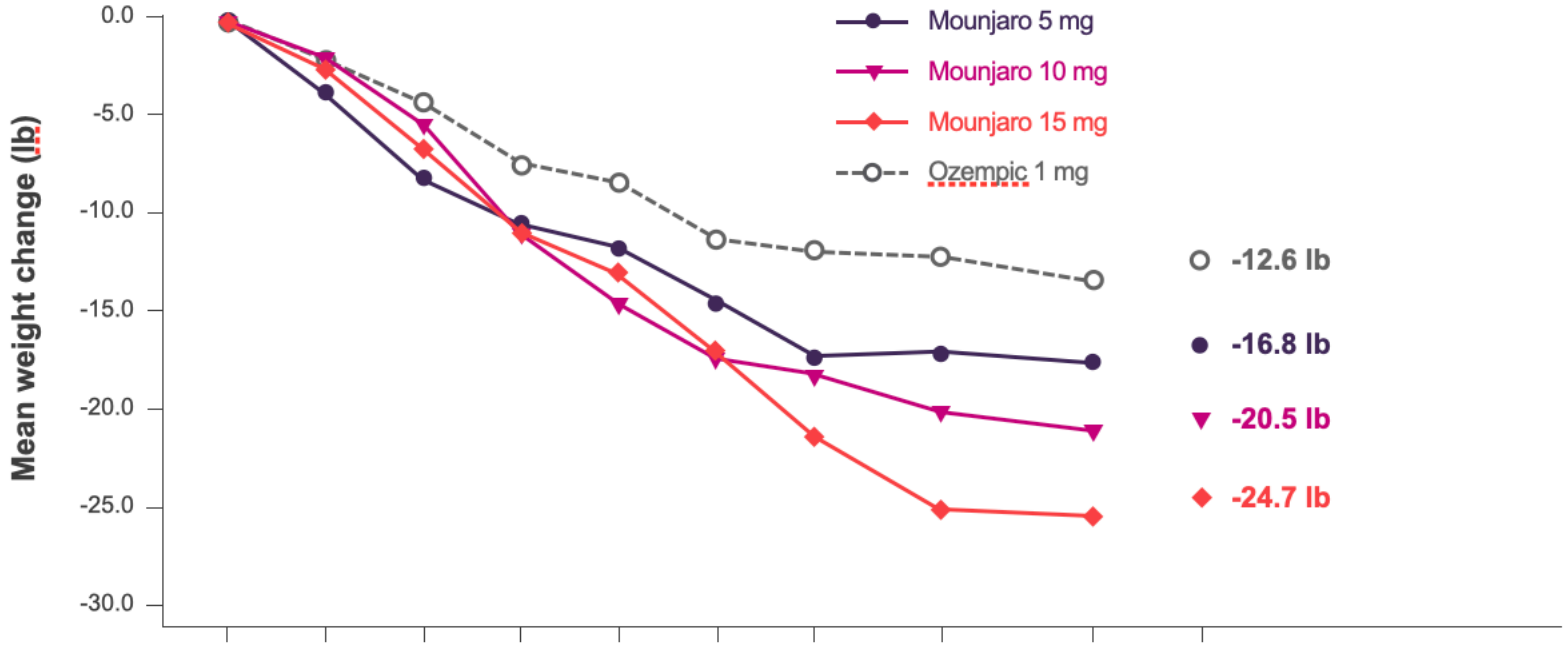
MOUNJARO 5 MG, 10 MG, AND 15 MG VS OZEMPIC 1 MG AS THE ONLY ADD-ON TO METFORMIN[1,2]



PATIENTS TAKING MOUNJARO HAD WEIGHT REDUCTIONS THAT CONTINUED THROUGH 40 WEEKS[1-3,*,†]

Observed mean weight change over time from baseline to 40 weeks[1-3,†]

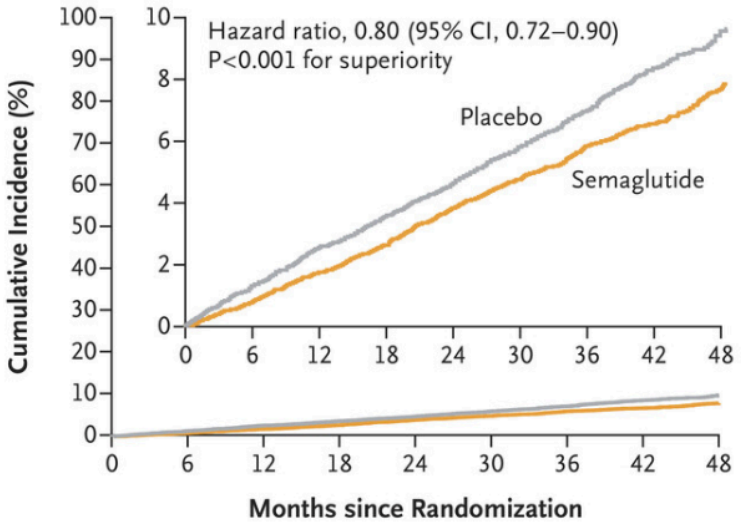
Mean baseline weight: Mounjaro 5 mg, 203.9 lb; Mounjaro 10 mg, 209.1 lb; Mounjaro 15 mg, 206.8 lb; Ozempic 1 mg, 206.6 lb



Number of patients	0	40	Week 40 MI
Mounjaro 5 mg	470	450	470
Mounjaro 10 mg	469	443	469
Mounjaro 15 mg	469	448	469
Ozempic 1 mg	468	444	468

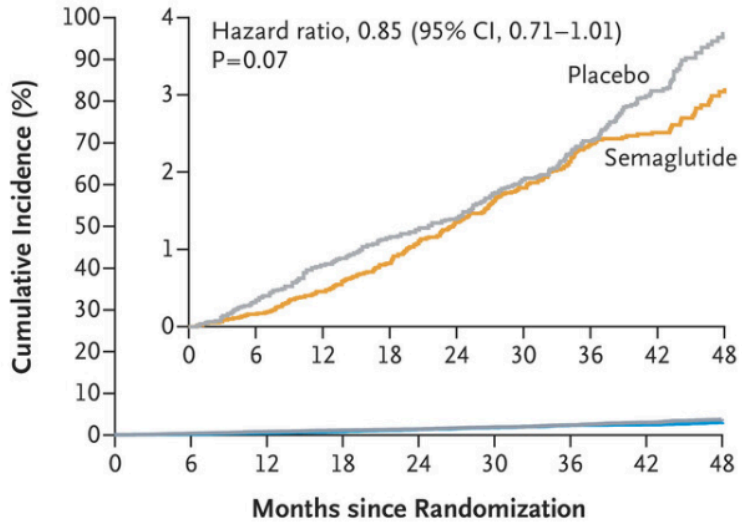
But there is more !

A Primary Cardiovascular Composite End Point



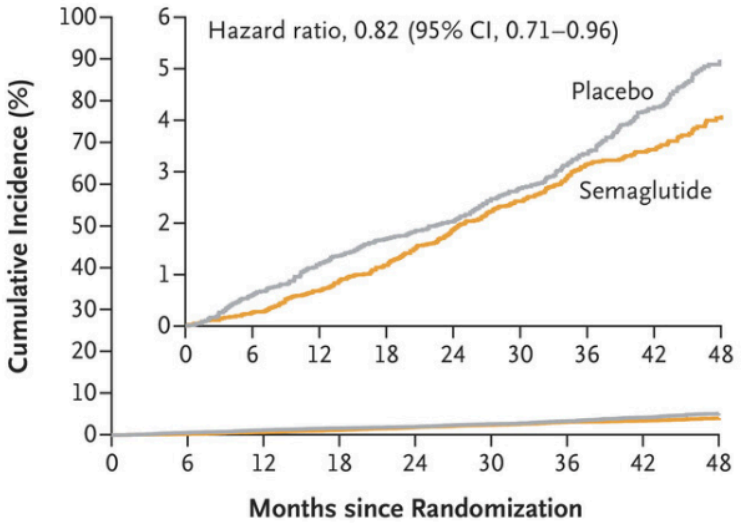
No. at Risk									
Placebo	8801	8652	8487	8326	8164	7101	5660	4015	1672
Semaglutide	8803	8695	8561	8427	8254	7229	5777	4126	1734

B Death from Cardiovascular Causes



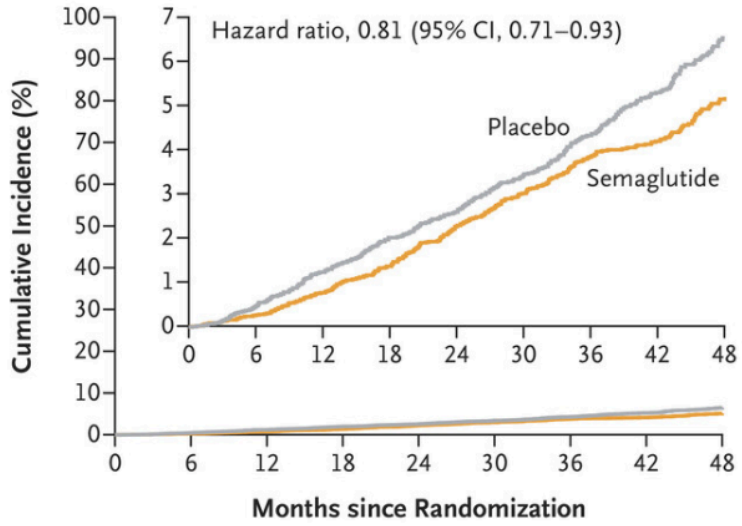
No. at Risk									
Placebo	8801	8733	8634	8528	8430	7395	5938	4250	1793
Semaglutide	8803	8748	8673	8584	8465	7452	5988	4315	1832

C Heart Failure Composite End Point



No. at Risk									
Placebo	8801	8711	8601	8485	8381	7341	5885	4198	1766
Semaglutide	8803	8740	8654	8557	8425	7409	5944	4277	1816

D Death from Any Cause



No. at Risk									
Placebo	8801	8733	8634	8528	8430	7395	5938	4250	1793
Semaglutide	8803	8748	8673	8584	8465	7452	5988	4315	1832

FDA approves Wegovy for CVD reduction in non-diabetic patients

FDA NEWS RELEASE

FDA Approves First Treatment to Reduce Risk of Serious Heart Problems Specifically in Adults with Obesity or Overweight

No change to thyroid dose

March, 2024

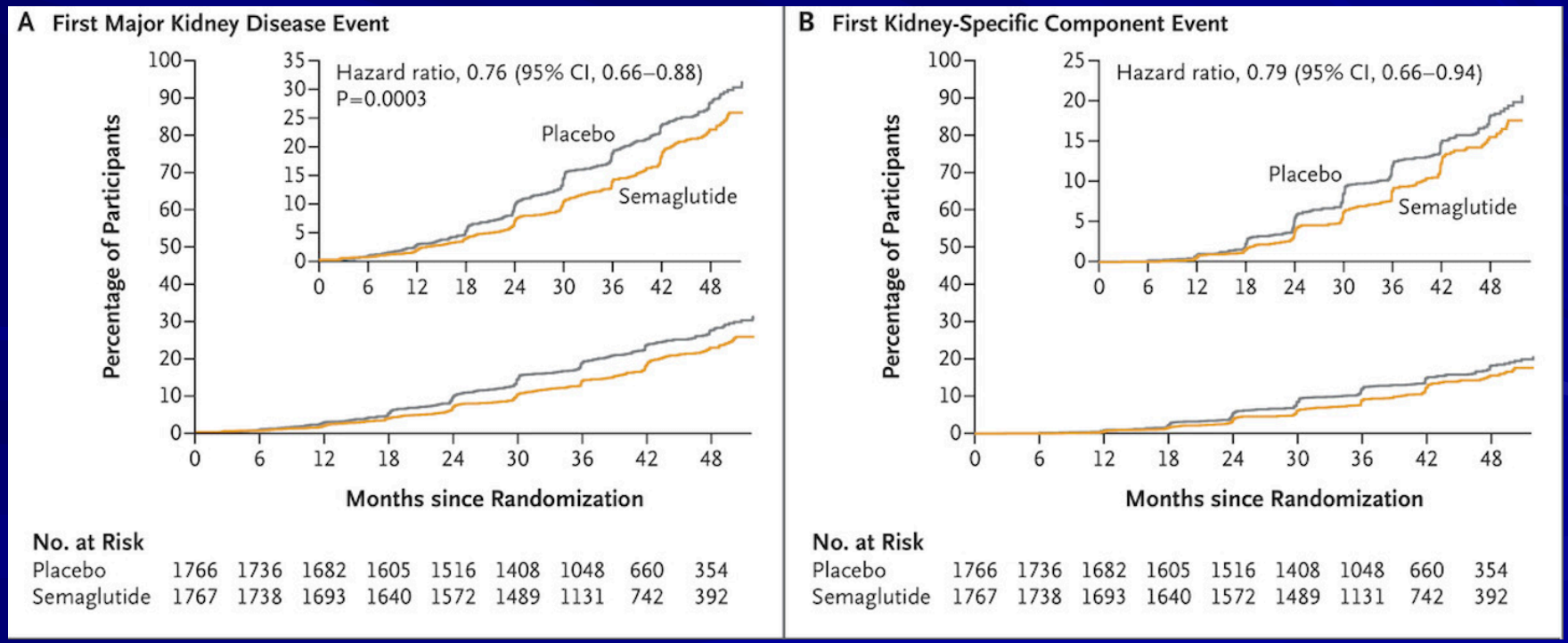
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

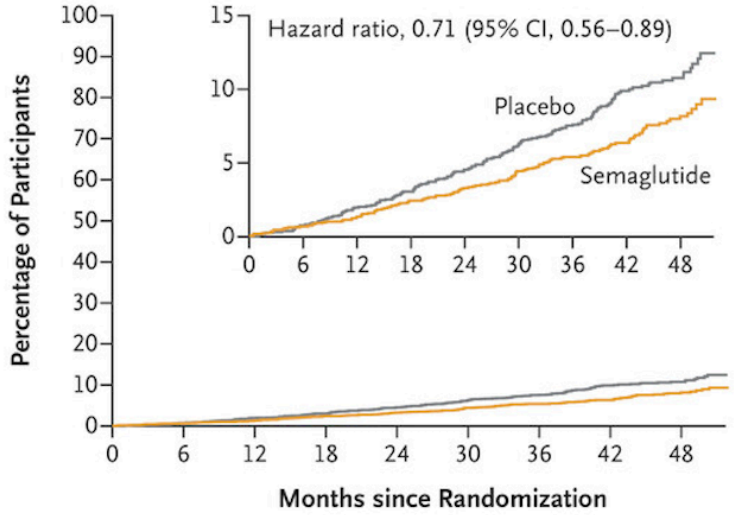
Effects of Semaglutide on Chronic Kidney Disease in Patients with Type 2 Diabetes

Authors: Vlado Perkovic, M.B., B.S., Ph.D., Katherine R. Tuttle, M.D., Peter Rossing, M.D., D.M.Sc., Kenneth W. Mahaffey, M.D., Johannes F.E. Mann, M.D., George Bakris, M.D., Florian M.M. Baeres, M.D., Thomas Idorn, M.D., Ph.D., Heidrun Bosch-Traberg, M.D., Nanna Leonora Lausvig, M.Sc., and Richard Pratley, M.D., for the FLOW Trial Committees and Investigators* Author Info & Affiliations

Published May 24, 2024 | N Engl J Med 2024;391:109-121 | DOI: 10.1056/NEJMoa2403347 | VOL. 391 NO. 2



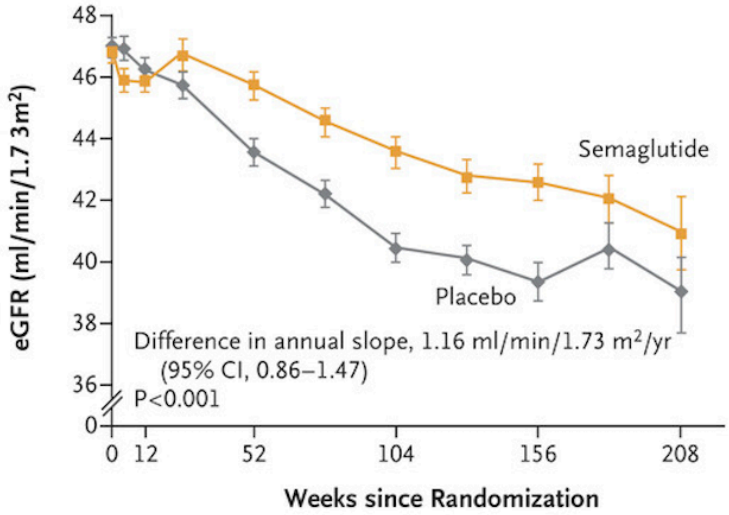
C Death from Cardiovascular Causes



No. at Risk

Placebo	1766	1737	1697	1641	1601	1544	1185	772	437
Semaglutide	1767	1739	1703	1665	1627	1583	1234	838	460

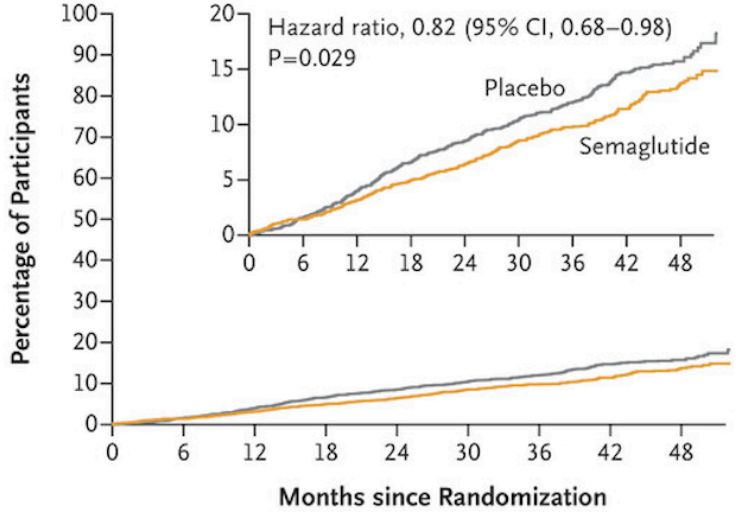
D Total eGFR Slope



No. at Risk

Placebo	1766	1663	1573	1609	1490	1441	1284	876	609	199
Semaglutide	1766	1665	1590	1606	1521	1468	1345	952	651	218

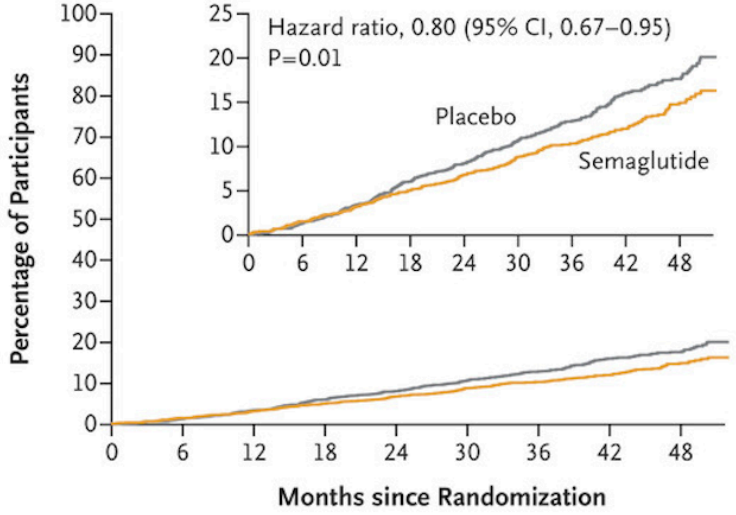
E First Major Cardiovascular Event



No. at Risk

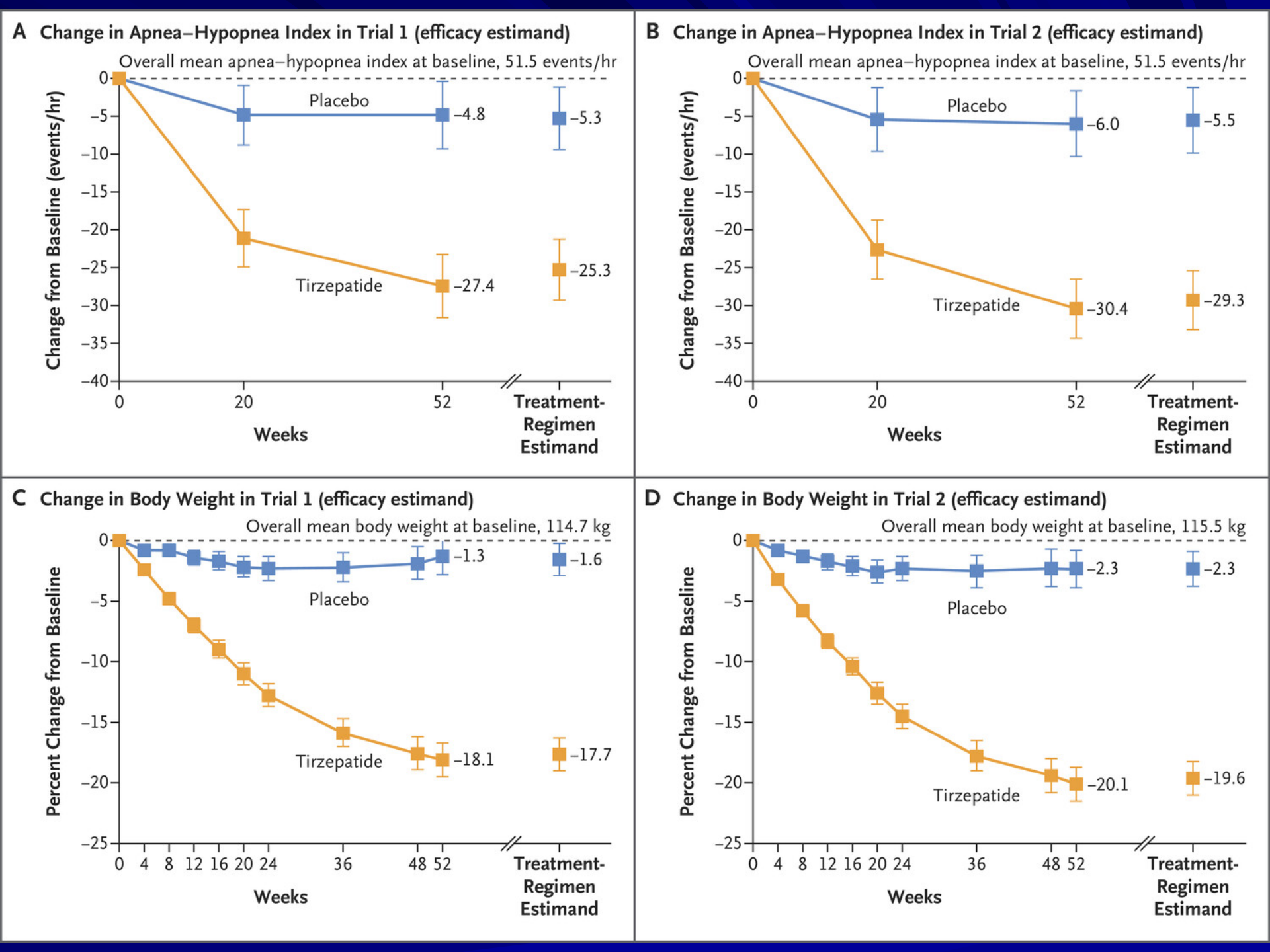
Placebo	1766	1721	1663	1583	1535	1478	1133	731	418
Semaglutide	1767	1725	1672	1622	1575	1515	1176	793	430

F Death from Any Cause



No. at Risk

Placebo	1766	1737	1697	1641	1601	1544	1185	772	437
Semaglutide	1767	1739	1703	1665	1627	1583	1234	838	460


A Change in Apnea–Hypopnea Index in Trial 1 (efficacy estimand)
Overall mean apnea–hypopnea index at baseline, 51.5 events/hr
Change from Baseline (events/hr)
0
−5
−10
−15
−20
−25
−30
−35
−40
Placebo
−4.8
−5.3
Tirzepatide
−27.4
−25.3
0
20
52
Weeks
Treatment-Regimen Estimand
B Change in Apnea–Hypopnea Index in Trial 2 (efficacy estimand)
Overall mean apnea–hypopnea index at baseline, 51.5 events/hr
Change from Baseline (events/hr)
Placebo
−6.0
−5.5
Tirzepatide
−30.4
−29.3
Weeks
Treatment-Regimen Estimand
C Change in Body Weight in Trial 1 (efficacy estimand)
Overall mean body weight at baseline, 114.7 kg
Percent Change from Baseline
0
−5
−10
−15
−20
−25
Placebo
−1.3
−1.6
Tirzepatide
−18.1
−17.7
0 4 8 12 16 20 24 36 48 52
Weeks
Treatment-Regimen Estimand
D Change in Body Weight in Trial 2 (efficacy estimand)
Overall mean body weight at baseline, 115.5 kg
Percent Change from Baseline
Placebo
−2.3
−2.3
Tirzepatide
−20.1
−19.6
Weeks
Treatment-Regimen Estimand

FDA approves Zepbound for treatment of OSA

FDA NEWS RELEASE

FDA Approves First Medication for Obstructive Sleep Apnea

December, 2024

In summary….
Incretin-based therapy has evidence to improve:

- Diabetic control
- Weight / obesity
- CVD risk
- Risk of renal events / progression of CKD
- Obstructive Sleep Apnea

Additionally ….
Incretin-based therapy has evidence to improve:

- A-fib burden
- Cancer risk
- NASH / NAFDL
- CHF
- Pre-diabetes
- PCOS
- Addiction
  - Alcohol use disorder
  - Opiate addiction
  - Smoking
  - Binge-eating

Ongoing incretin-based research:

- Alzheimer's Dimentia
- Parkinson's Disease

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Trial of Lixisenatide in Early Parkinson's Disease

Authors: Wassilios G. Meissner, M.D., Ph.D., Philippe Remy, M.D., Ph.D., Caroline Giordana, M.D., David Maltête, M.D., Pascal Derkinderen, M.D., Ph.D., Jean-Luc Houéto, M.D., Mathieu Anheim, M.D., Ph.D., +37, for the LIXIPARK Study Group* Author Info & Affiliations

Published April 3, 2024 | N Engl J Med 2024;390:1176-1185 | DOI: 10.1056/NEJMoa2312323 | VOL. 390 NO. 13

- DBRPCT, Phase 2
- Diagnosis of Parkinson's Disease (<3 years)
- Stable med regimen, NO motor complications
- Lixisenatide vs. placebo
- Primary outcome: Progression of MC @ 12 mo….

Movement Disorder Society–Unified Parkinson's Disease Rating Scale (MDS-UPDRS) part III (range, 0 to 132, with higher scores indicating greater motor disability)

Placebo: 3.04 (progression)
Lixisenatide: -0.04 (improvement)

QUESTIONS

benseale@yahoo.com