GLP-1 RA and SGLT2i: New Treatment Strategies for Diabetes and Obesity in the Context of HIV

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Objectives

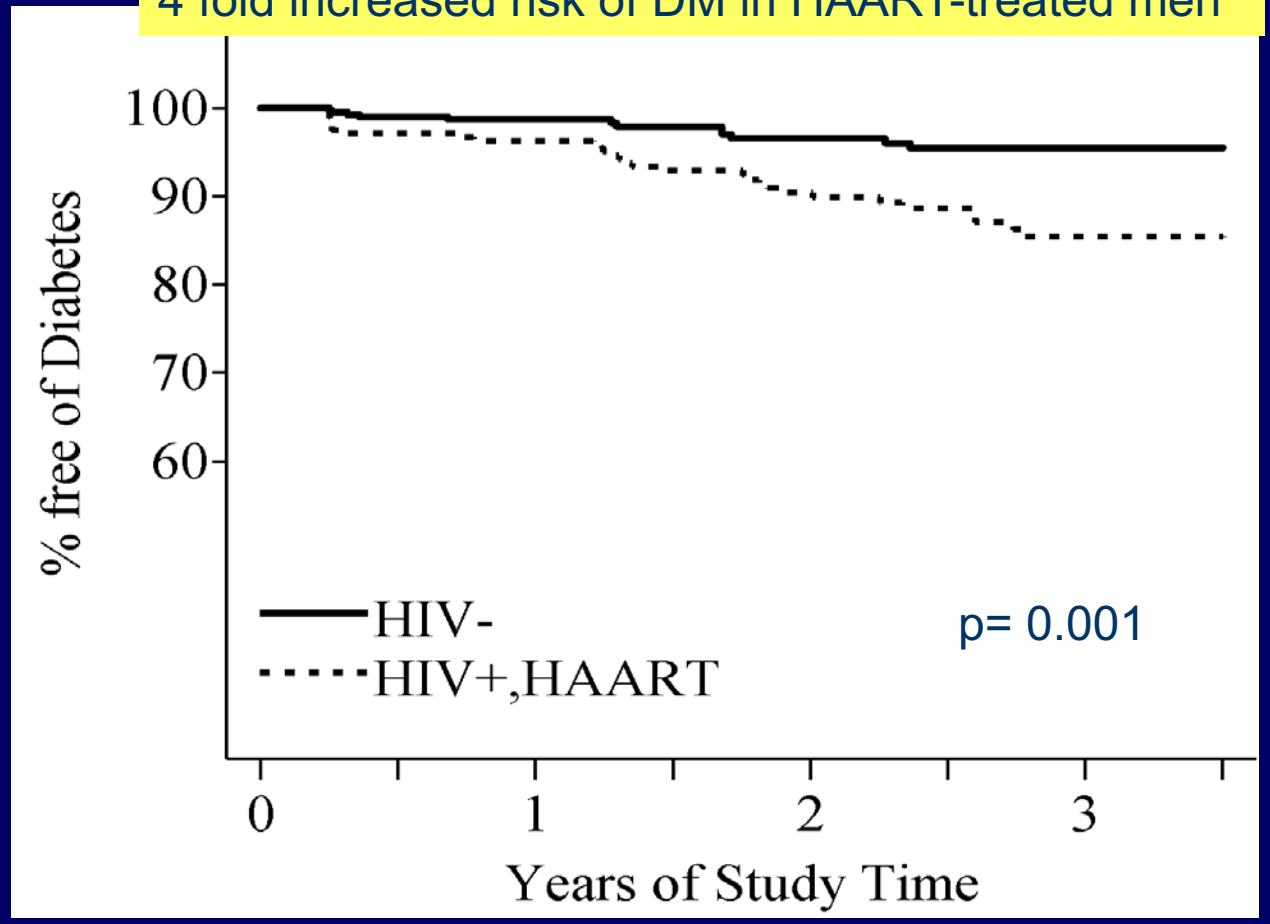
- To describe how GLP-1 receptor agonists and SGLT2 inhibitors work
- To list the risks and benefits of GLP-1 receptor agonists and SGLT2 inhibitors and where they fit in for the treatment of diabetes
- To explain the impact of GLP-1 receptor agonists for the treatment of obesity and be familiar with unanswered questions about their long-term safety and efficacy

Why Care about Diabetes?

- Very common with rapidly increasing prevalence
- One of leading causes of cardiovascular disease, blindness, ESRD, amputations, hospitalizations
- Common in Populations with HIV
- Diabetes can be controlled, but management is complicated and requires individualization

Risk of Incident Diabetes Mellitus in the Multicenter AIDS Cohort Study (1999-2003)

4 fold increased risk of DM in HAART-treated men



* Adjusted for age and BMI at study entry

Brown, Arch Int Med, 2005

Pathogenesis of Diabetes in People with HIV

- **Host Factors**
  - **Adiposity**
  - **HCV**
  - **Genetic Factors: Family History, Race**
  - **Concomitant Medications: Corticosteroids/Atypical Antipsychotics**
- **Antiretroviral Medication Factors**
  - **Thymidine analogues, older PIs**
  - **? Integrase Inhibitors**
- **HIV Factors**
  - **Residual immune activation/inflammation**

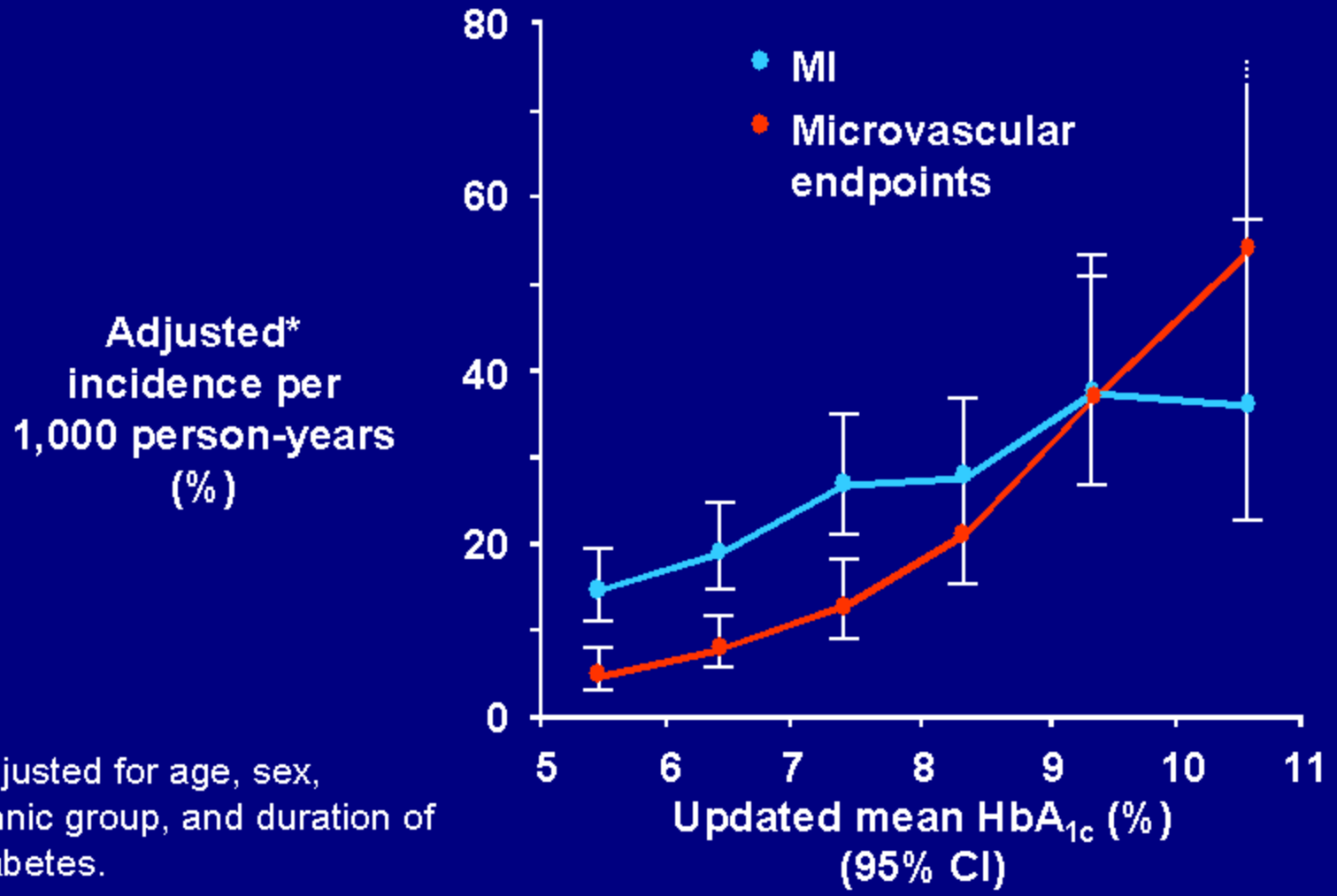
Key Concepts in Diabetes Management

- What should be the glycemic target?

What should be the glycemic target?

HbA1c < 7%

UKPDS: MI and Microvascular Endpoints Associated With Increasing HbA_{1c}

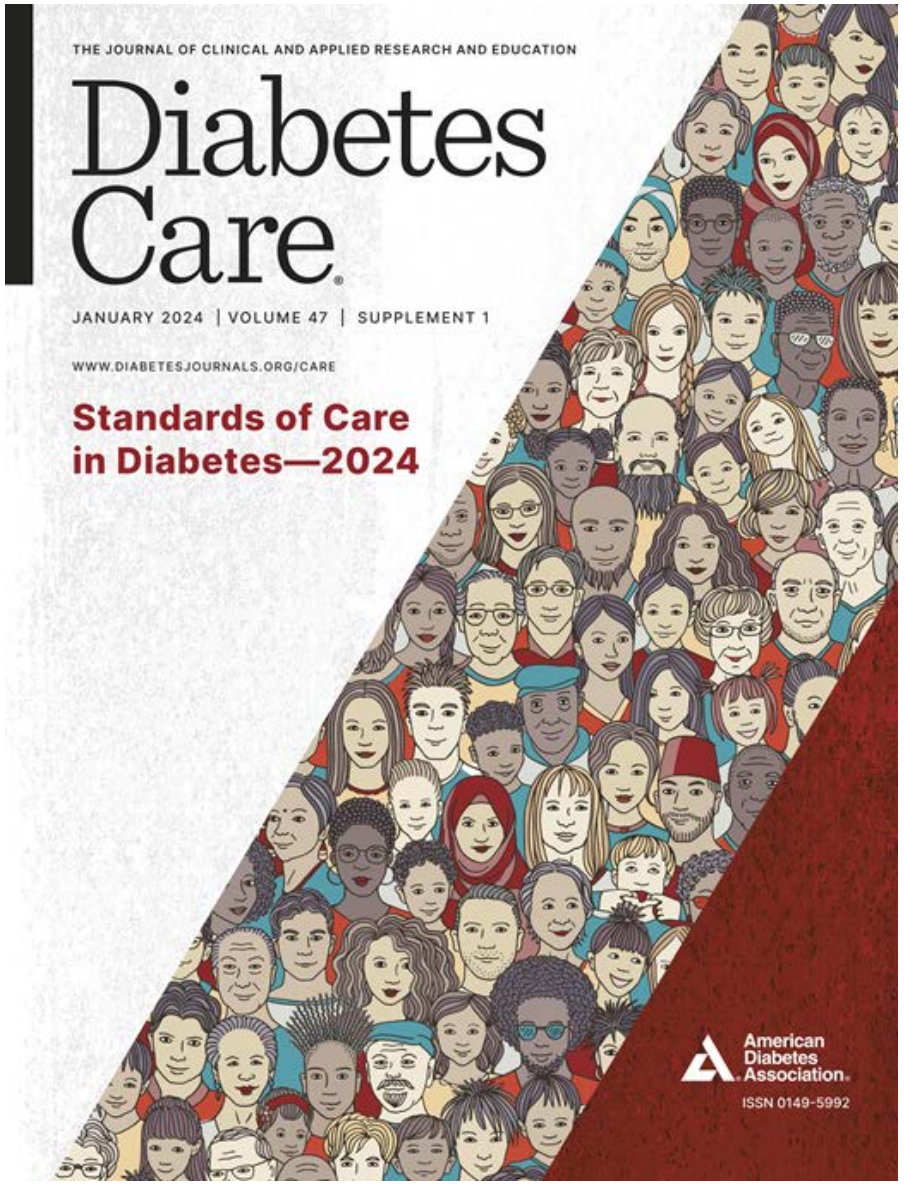


*Adjusted for age, sex, ethnic group, and duration of diabetes.

Stratton IM et al. *BMJ.* 2000;321:405-412.

Key Concepts in Diabetes Management

- What should be the glycemic target?
- Which diabetes medications should be used to achieve that target?



The Reign of Metformin as THE First Line Drug
2007-

Metformin: Pros and Cons

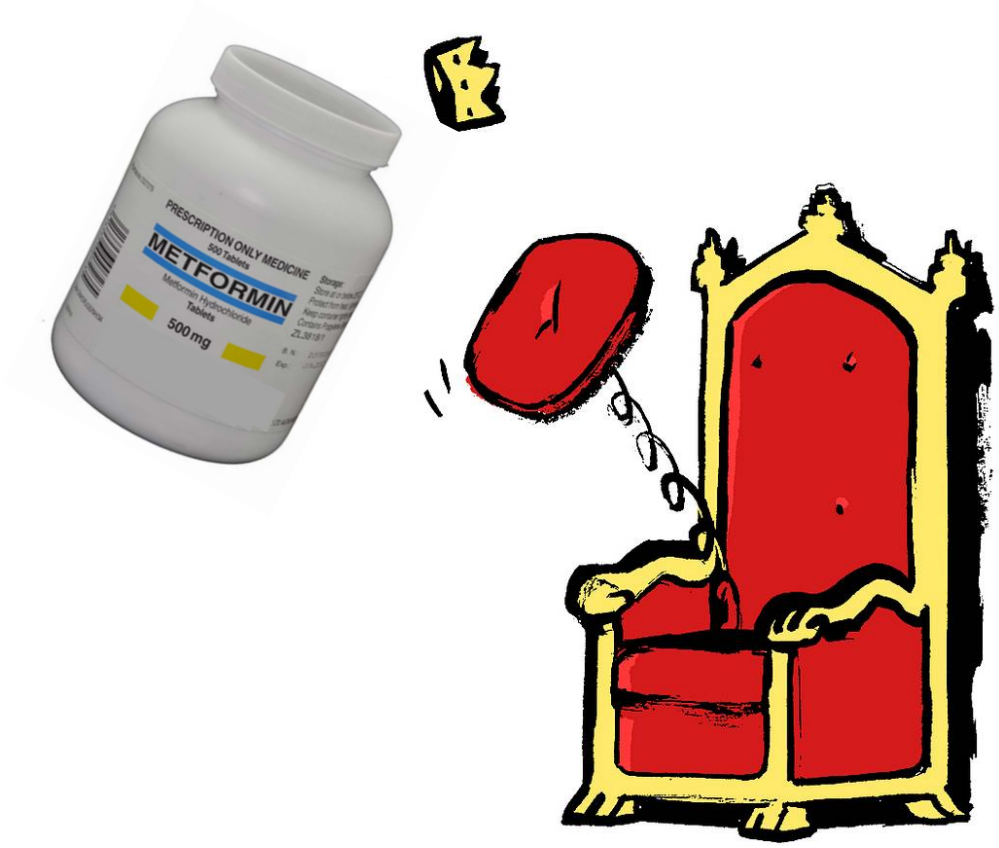
Pros

- ↓ A1c ~1%
- Long Track Record
- No Hypoglycemia
- No Weight Gain
- CVD benefit
- Low Cost (NADAC $3/month)

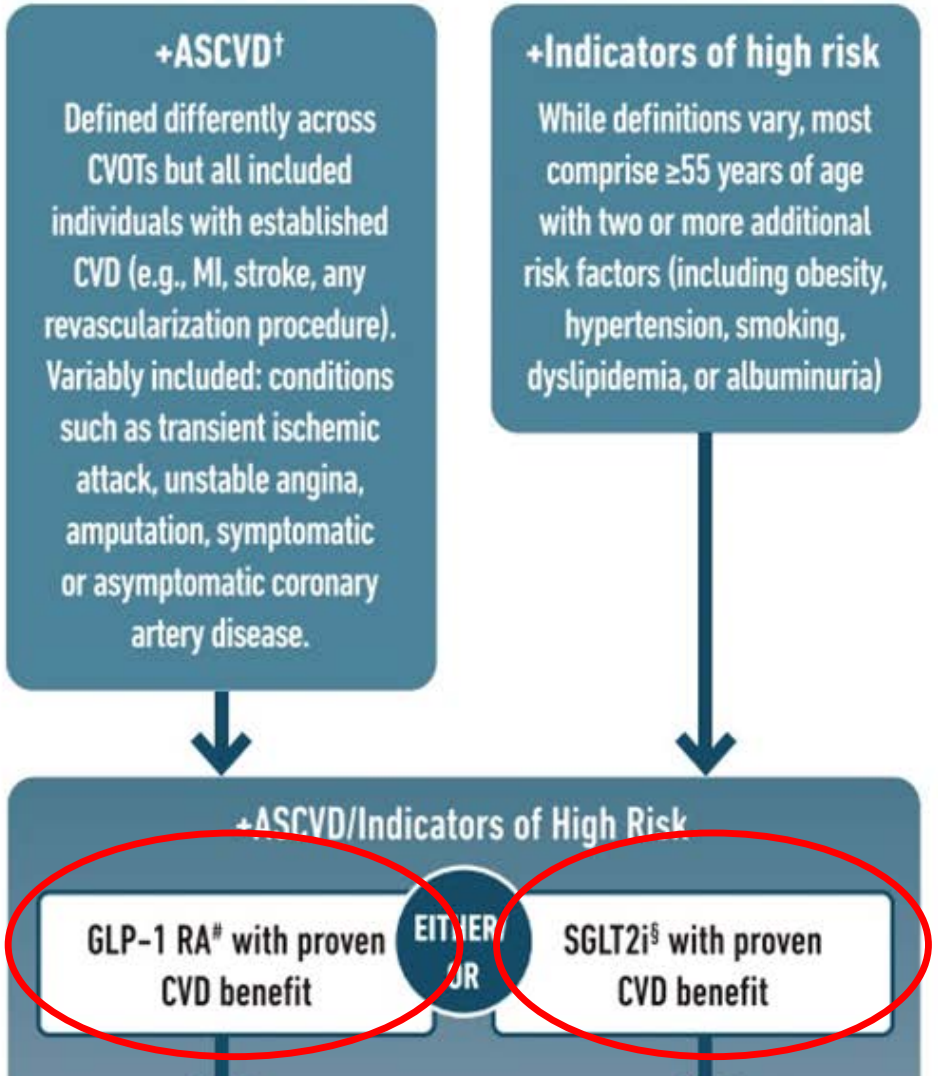
Cons

- GI side effects
- Lactic Acidosis (rare)
- Contraindications:
  - CKD (OK eGFR > 30 cc/min/1.73 m^2)
  - Hypoxia
  - Decompensated Liver Disease
  - Severe CHF
  - Alcohol Abuse
  - Past H/O Lactic Acidosis
- Interaction with DTG

A Revolution in Diabetes Management



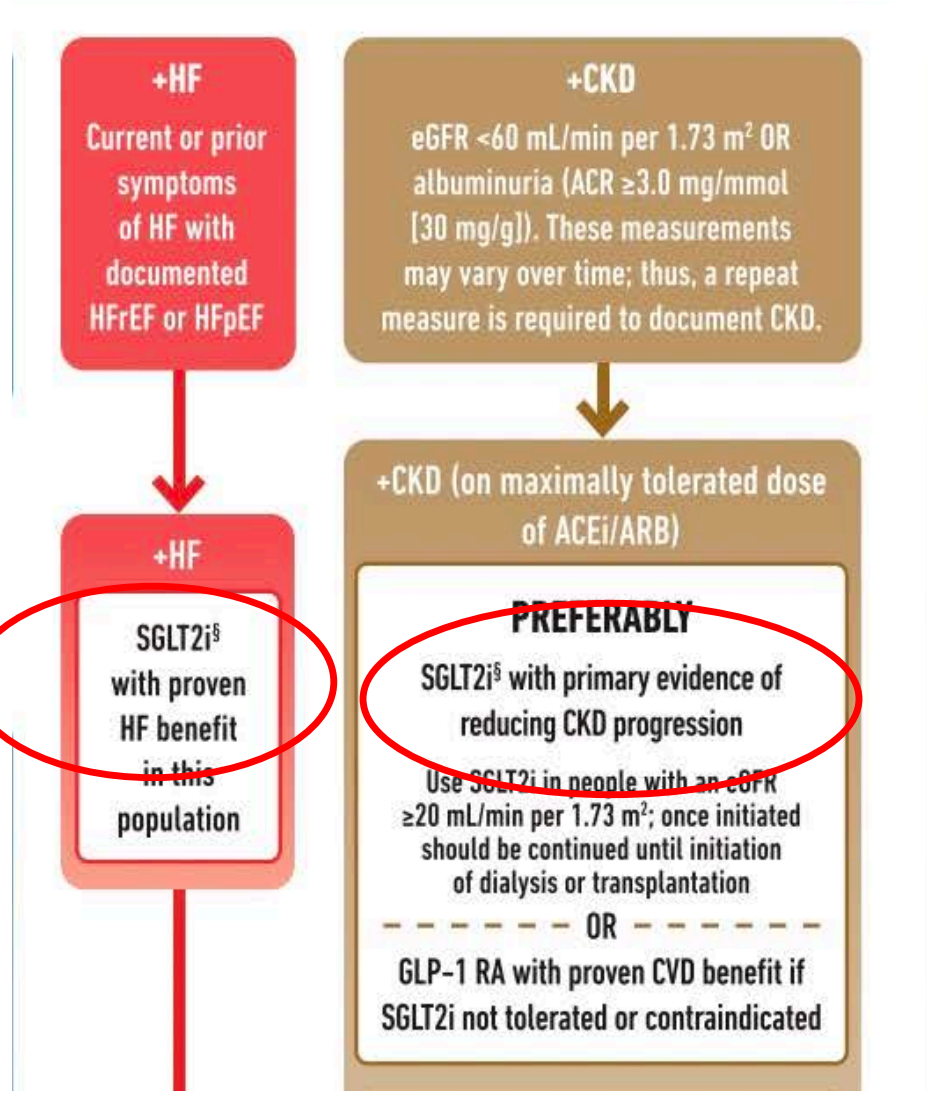
The Reign of Metformin as THE First Line Drug
2007-2023



ADA, Standard of Medical Care in Diabetes, 2023

A Revolution in Diabetes Management

The Reign of Metformin as THE First Line Drug
2007-2023

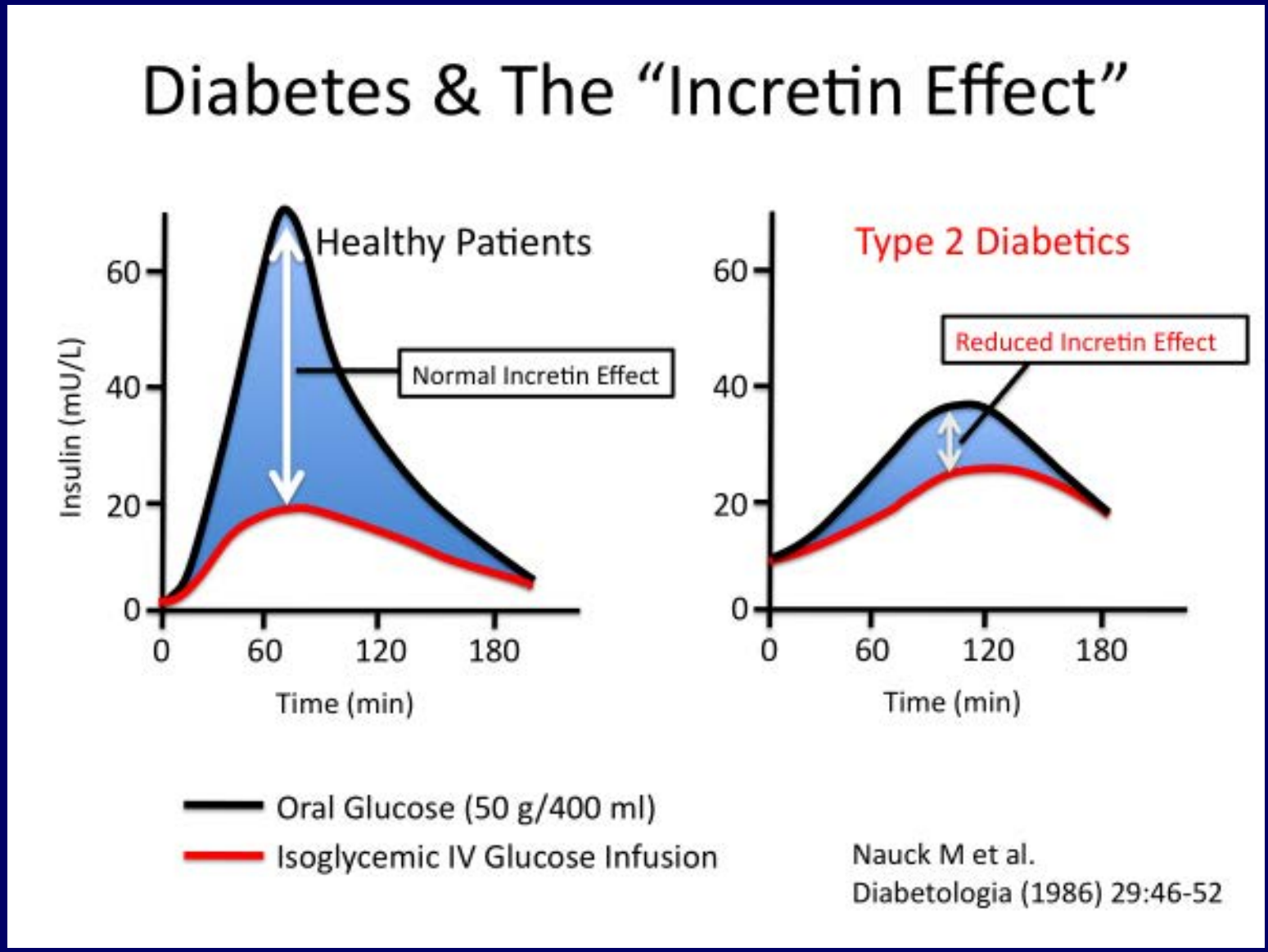


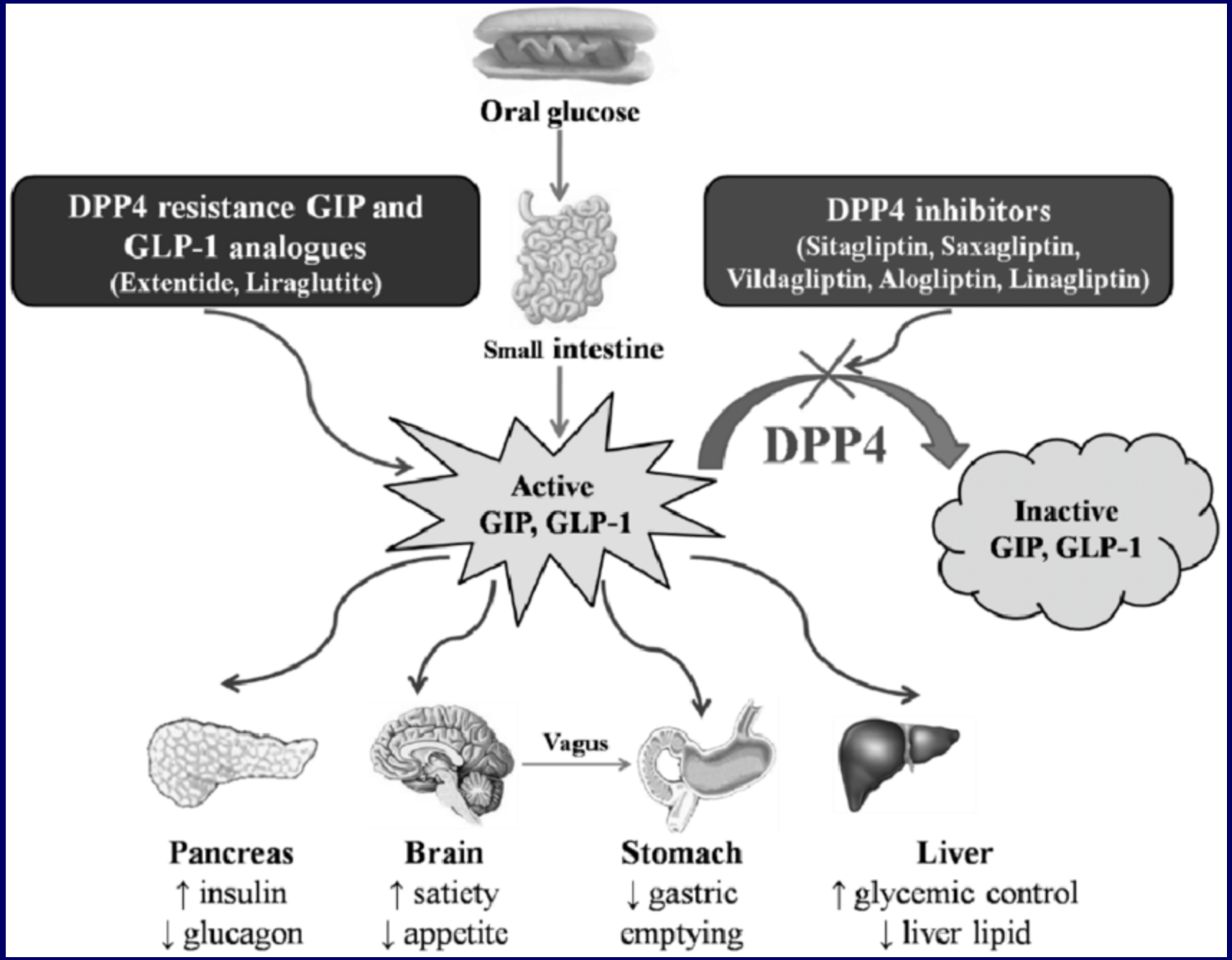
ADA, Standard of Medical Care in Diabetes, 2023

Newer Diabetes Drugs: The Roots of a Quiet Coup

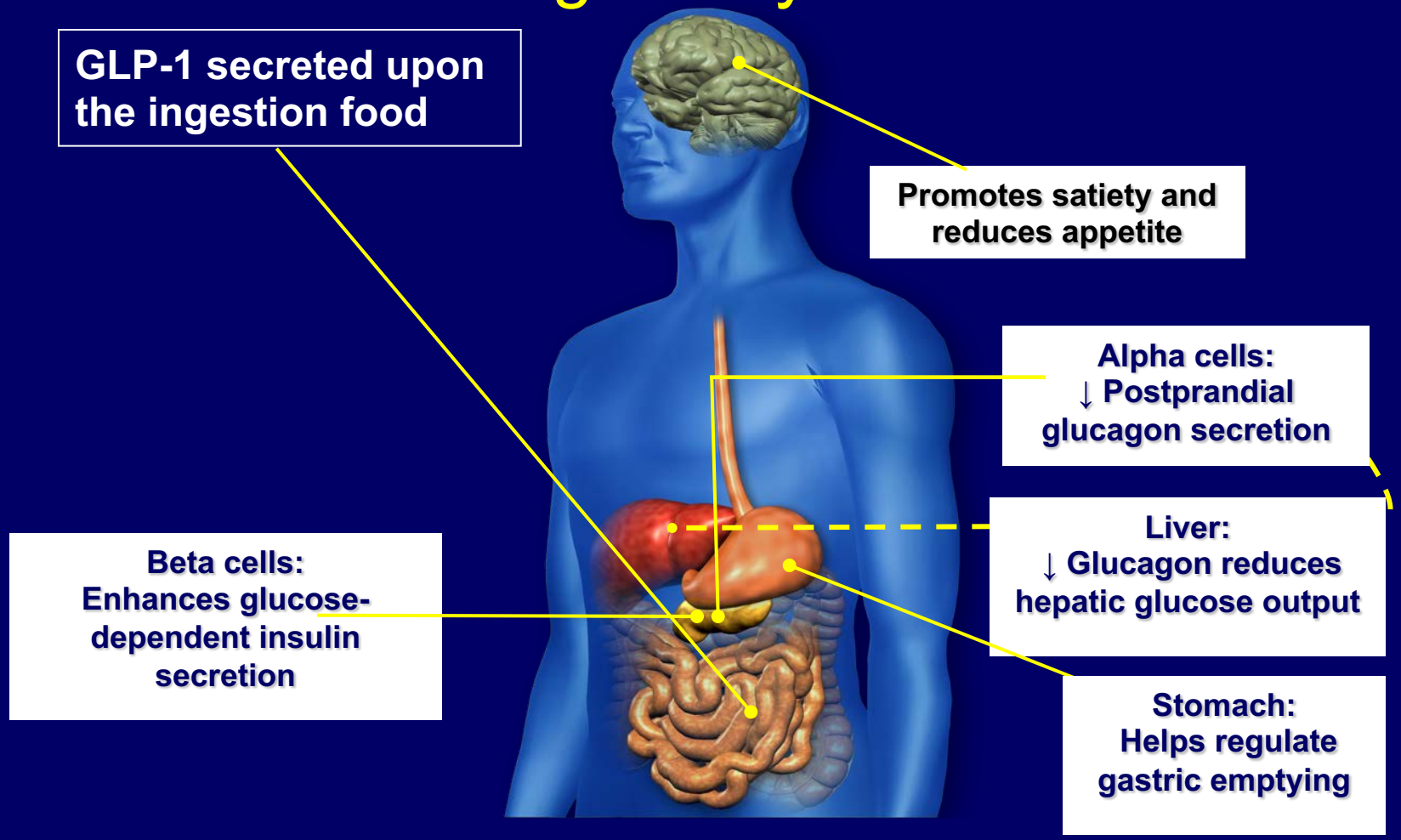
- GLP-1 Receptor Agonists
  - First Approval 2005 (exenatide)
- Sodium Glucose Co-transporter 2 inhibitors (SGLT2i)
  - First approval 2012 (dapaglifozin)

The Incretin Effect



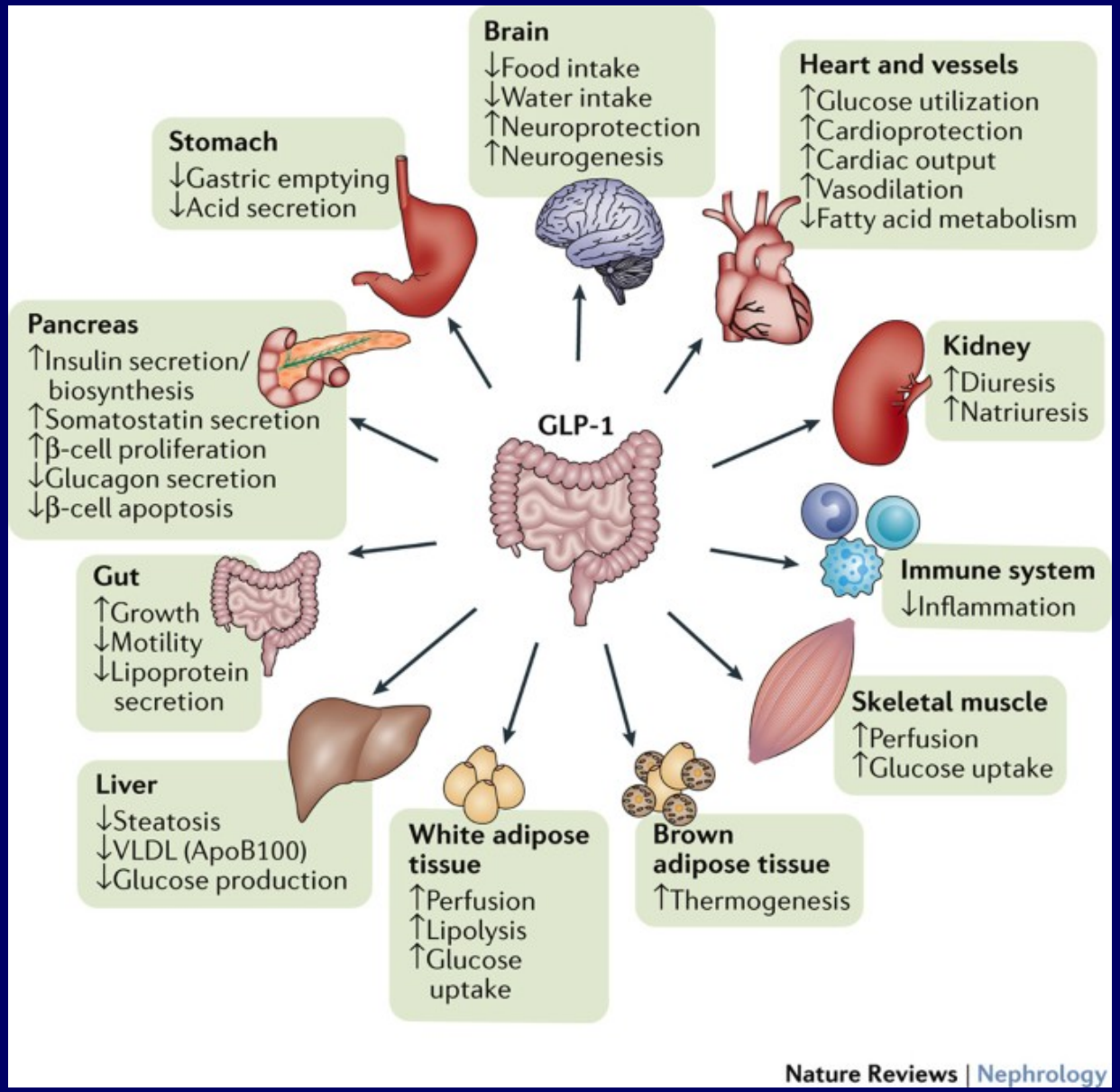

Oral glucose
DPP4 resistance GIP and GLP-1 analogues (Extentide, Liraglutite)
DPP4 inhibitors (Sitagliptin, Saxagliptin, Vildagliptin, Alogliptin, Linagliptin)
Small intestine
Active GIP, GLP-1
DPP4
Inactive GIP, GLP-1
Vagus
Pancreas
↑ insulin
↓ glucagon
Brain
↑ satiety
↓ appetite
Stomach
↓ gastric emptying
Liver
↑ glycemic control
↓ liver lipid

GLP-1 Effects in Humans: Understanding the Glucoregulatory Role of Incretins



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.

Multiple Sites of Action of GLP-1 RA



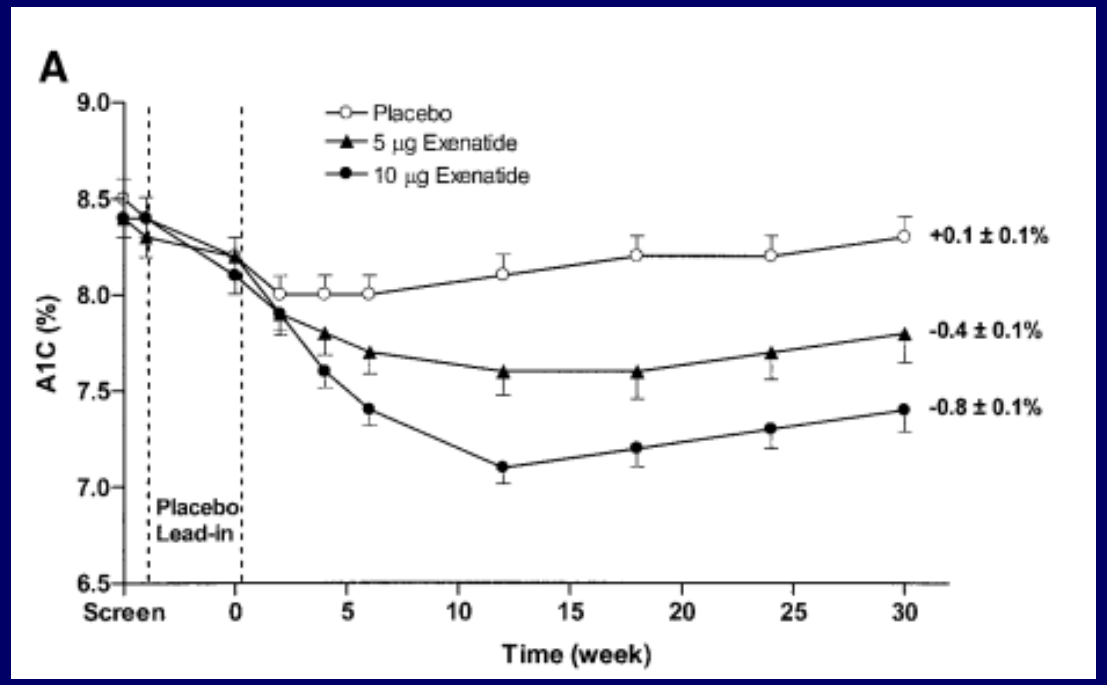
Muskiet, NatureReviewsNephrology, 2017

Exenatide (Byetta)

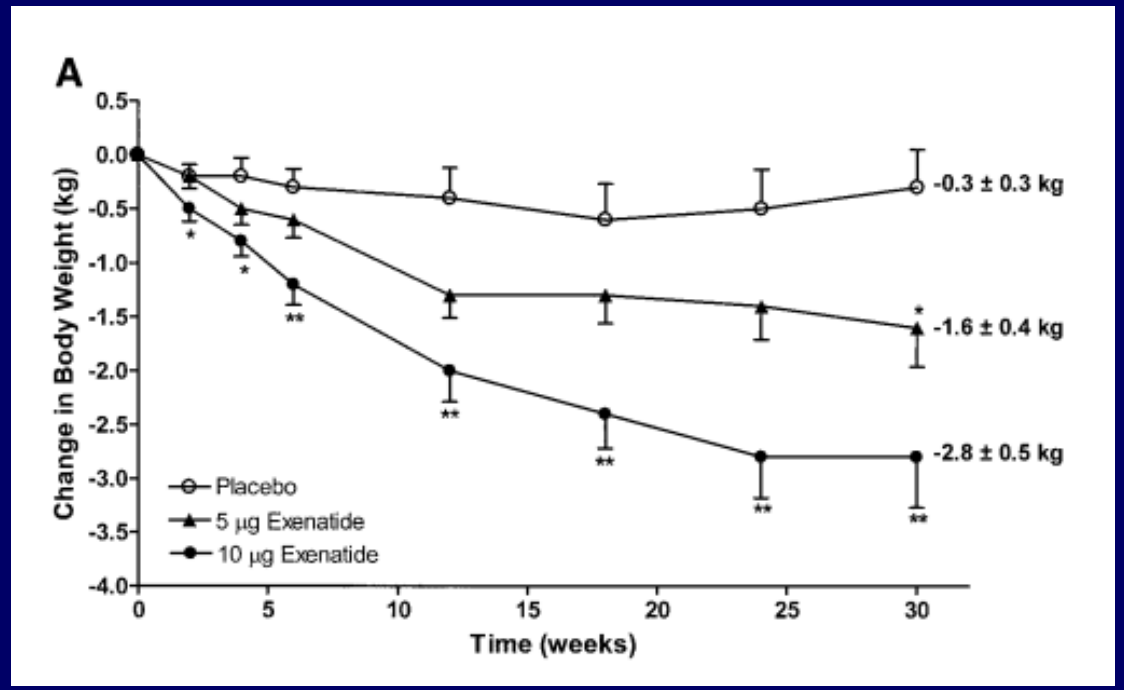
- **Exedin-4: Analog of the gut hormone GLP-1**
- **GI Side Effects**
- **Weight loss (~ 2-4 kg)**
- **Give 5-10 µg SQ bid**
- **Approved in 2005 in type 2 DM patients on sulfonylureas and/or metformin, or TZDs**

Exendin-4 is found in the saliva of the Gila monster

Exenatide (Byetta)



Effects on Glucose



Effects on Weight

DeFronzo, Diabetes Care, 2005

GLP1 RAs in Diabetes: Effects on Glucose

Drug	Duration	Glucose Effect
Exenatide	24 weeks	-0.9%
Liraglutide	52 weeks	-1.1 %
Lixisenatide	24 weeks	-0.72%
Dulaglutide	36 weeks	-1.8%
Semaglutide	40 weeks	-2.1%

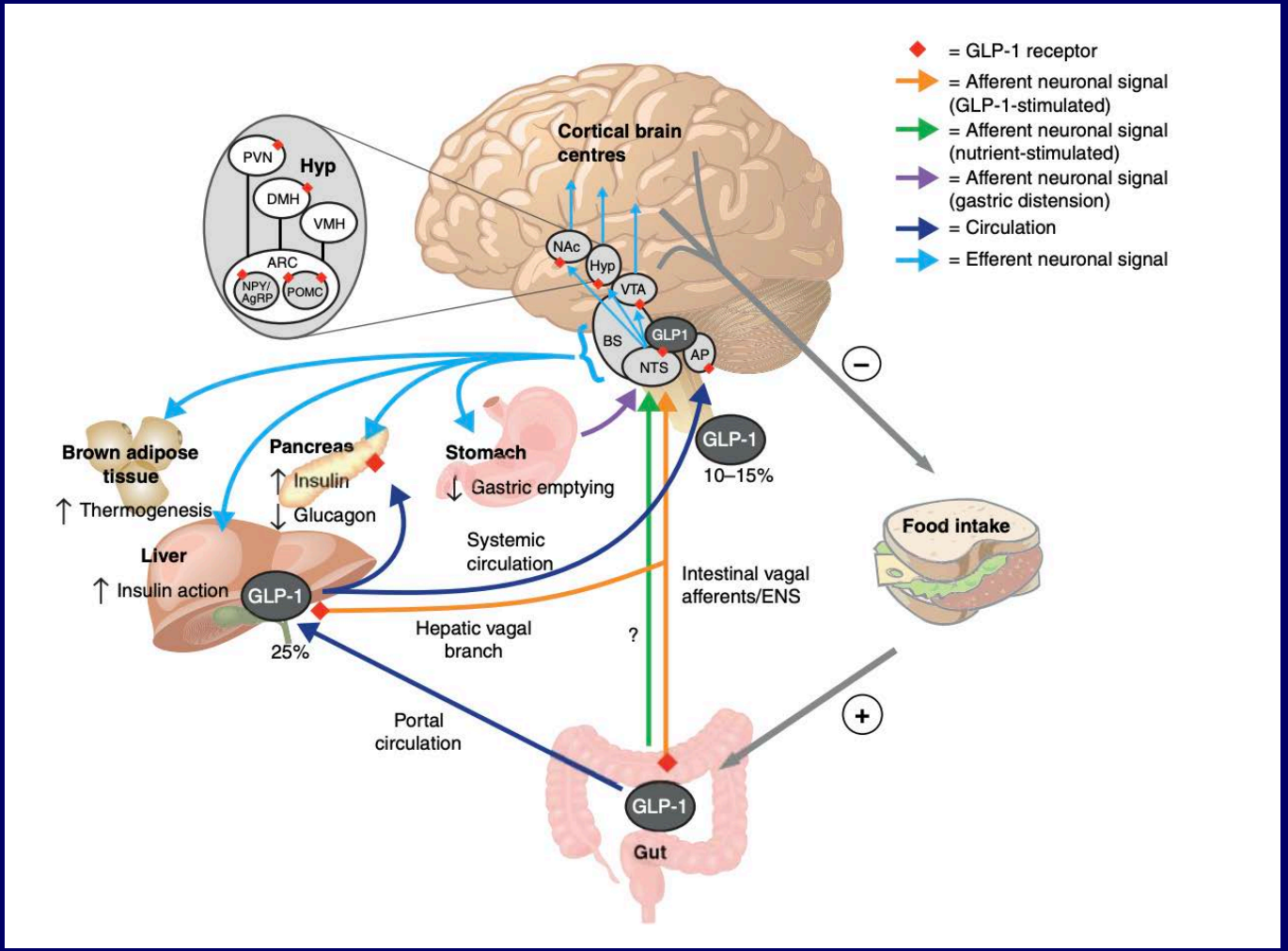
Glucose and weight data from FDA Package Inserts at highest approved dose

GLP1 RAs in Diabetes: Effects on Glucose and Weight

Drug	Duration	Glucose Effect	Weight Effect
Exenatide	24 weeks	-0.9%	-2.9 kg
Liraglutide	52 weeks	-1.1 %	-2.5 Kg
Lixisenatide	24 weeks	-0.72%	-2.7 kg
Dulaglutide	36 weeks	-1.8%	-4.6 kg
Semaglutide	40 weeks	-2.1%	-6.4 kg

Glucose and weight data from FDA Package Inserts at highest approved dose

Central mechanisms of GLP-1RA on feeding behavior



van Bloemendaal, J Endocrinology, 2014

ORIGINAL ARTICLE

Effect of Rosiglitazone on the Risk of Myocardial Infarction and Death from Cardiovascular Causes

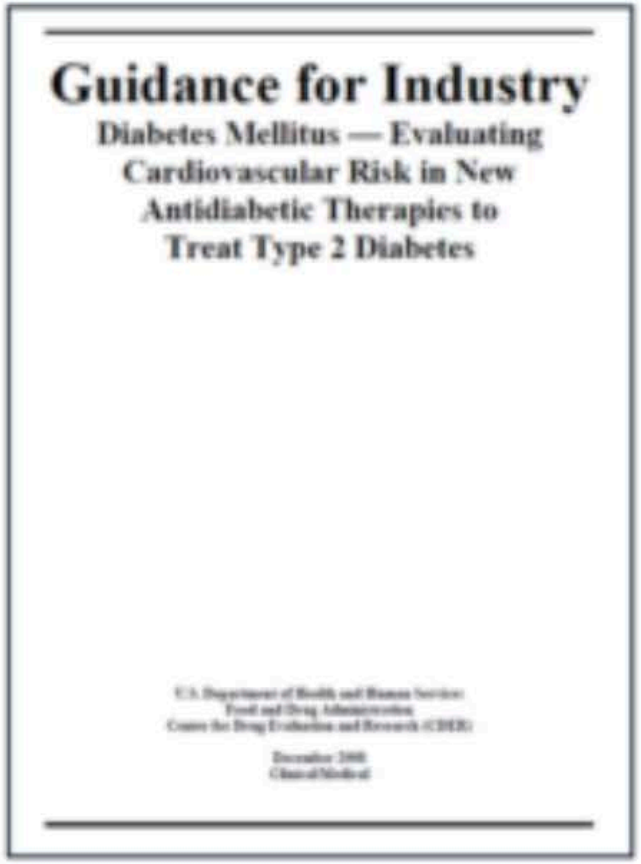
Steven E. Nissen, M.D., and Kathy Wolski, M.P.H.

Table 4. Rates of Myocardial Infarction and Death from Cardiovascular Causes.

Study	Rosiglitazone Group	Control Group	Odds Ratio (95% CI)	P Value
	no. of events/total no. (%)			
Myocardial infarction				
Small trials combined	44/10,285 (0.43)	22/6106 (0.36)	1.45 (0.88–2.39)	0.15
DREAM	15/2,635 (0.57)	9/2634 (0.34)	1.65 (0.74–3.68)	0.22
ADOPT	27/1,456 (1.85)	41/2895 (1.42)	1.33 (0.80–2.21)	0.27
Overall			1.43 (1.03–1.98)	0.03
Death from cardiovascular causes				
Small trials combined	25/6,845 (0.36)	7/3980 (0.18)	2.40 (1.17–4.91)	0.02
DREAM	12/2,635 (0.46)	10/2634 (0.38)	1.20 (0.52–2.78)	0.67
ADOPT	2/1,456 (0.14)	5/2895 (0.17)	0.80 (0.17–3.86)	0.78
Overall			1.64 (0.98–2.74)	0.06

NEJM, 2007

FDA requirements for CV outcome studies for new anti-diabetic agents



Guidance for Industry

Diabetes Mellitus — Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes

2008 FDA guidelines substantially raised the threshold for approval of antidiabetes drugs from proof of glucose lowering to robust assessment of cardiovascular safety

CV risk assessment on phase 2/3 data for all marketed and pipeline antidiabetes treatments: requisite upper bound of two-sided 95% CI for estimated risk ratio

>1.8:	the data are inadequate to support approval; a large safety trial should be conducted
1.3–1.8:	potential for CV harm might still exist; an adequately powered and designed post-marketing trial is necessary to show an upper bound <1.3
<1.3:	overall risk-benefit analysis supports approval; a post-marketing trial is generally not necessary

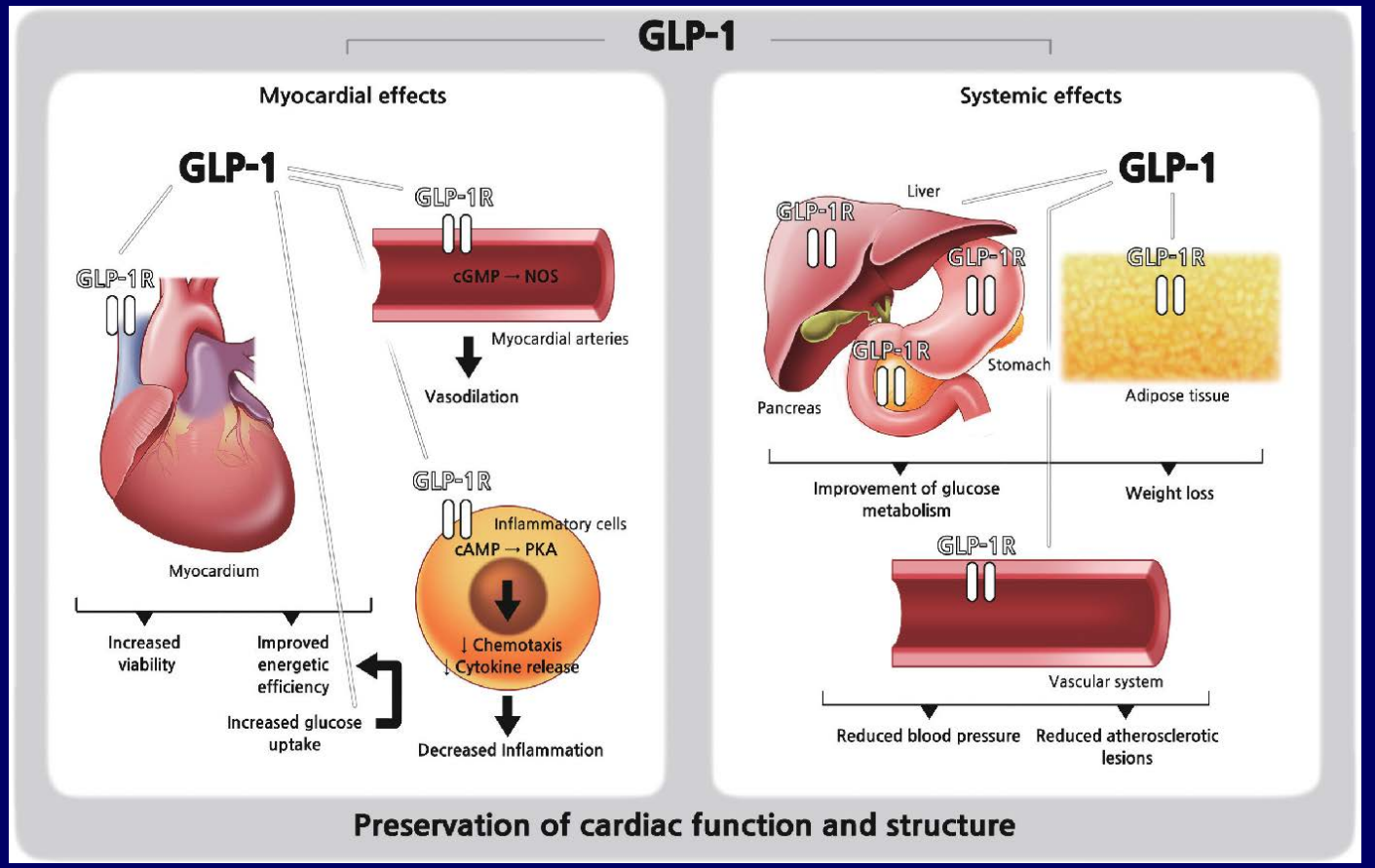
FDA Guidance for Industry. Diabetes mellitus – evaluating cardiovascular risk in new antidiabetic therapies to treat type 2 diabetes. Available from: www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071627.pdf [Accessed July 2014]

GLP1 RAs in Diabetes: Effects on Cardiovascular Events

Drug	Duration	Glucose Effect	Weight Effect	Reduction in MACE
Exenatide	24 weeks	-0.9%	-2.9 kg	NO
Liraglutide	52 weeks	-1.1 %	-2.5 Kg	↓ 14%
Lixisenatide	24 weeks	-0.72%	-2.7 kg	NO
Dulaglutide	36 weeks	-1.8%	-4.6 kg	↓ 12%
Semaglutide	40 weeks	-2.1%	-6.4 kg	↓ 26%

Glucose and weight data from FDA Package Inserts at highest approved dose

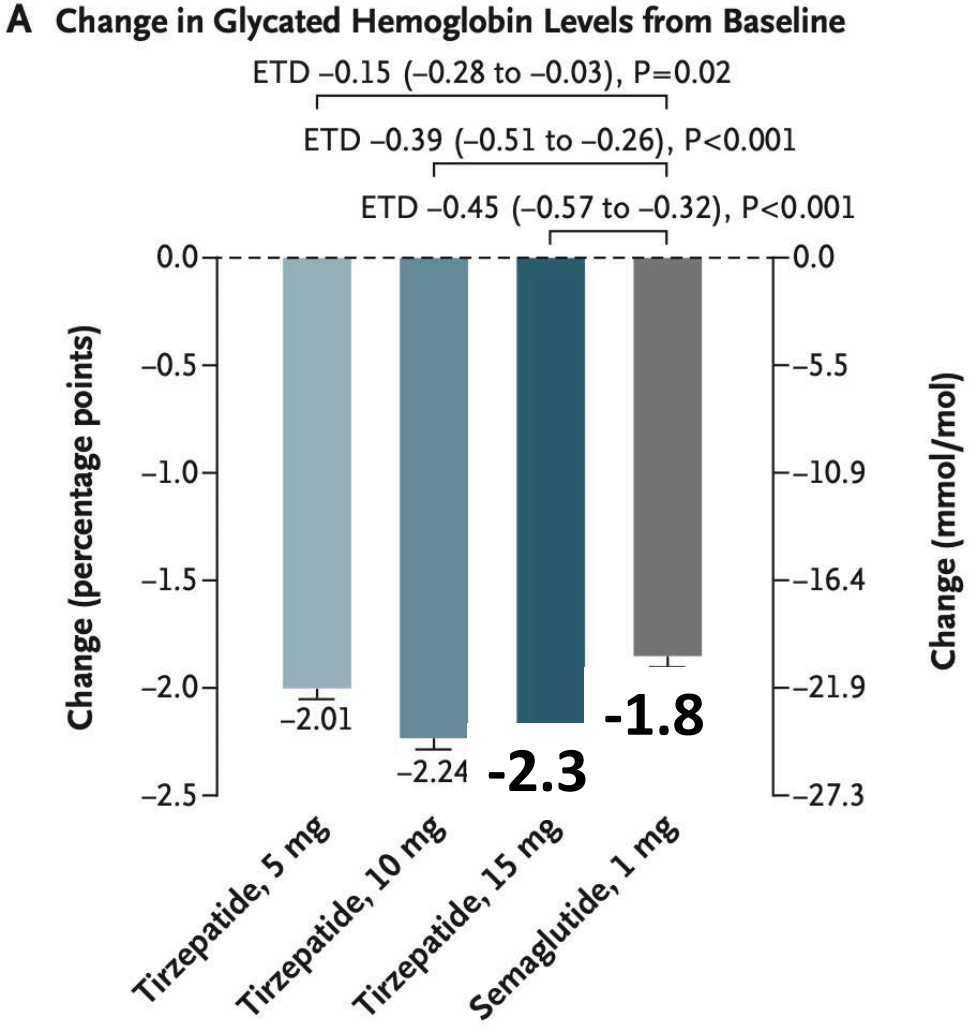
Putative Mechanisms of GLP-1 RAs in Cardiovascular Disease



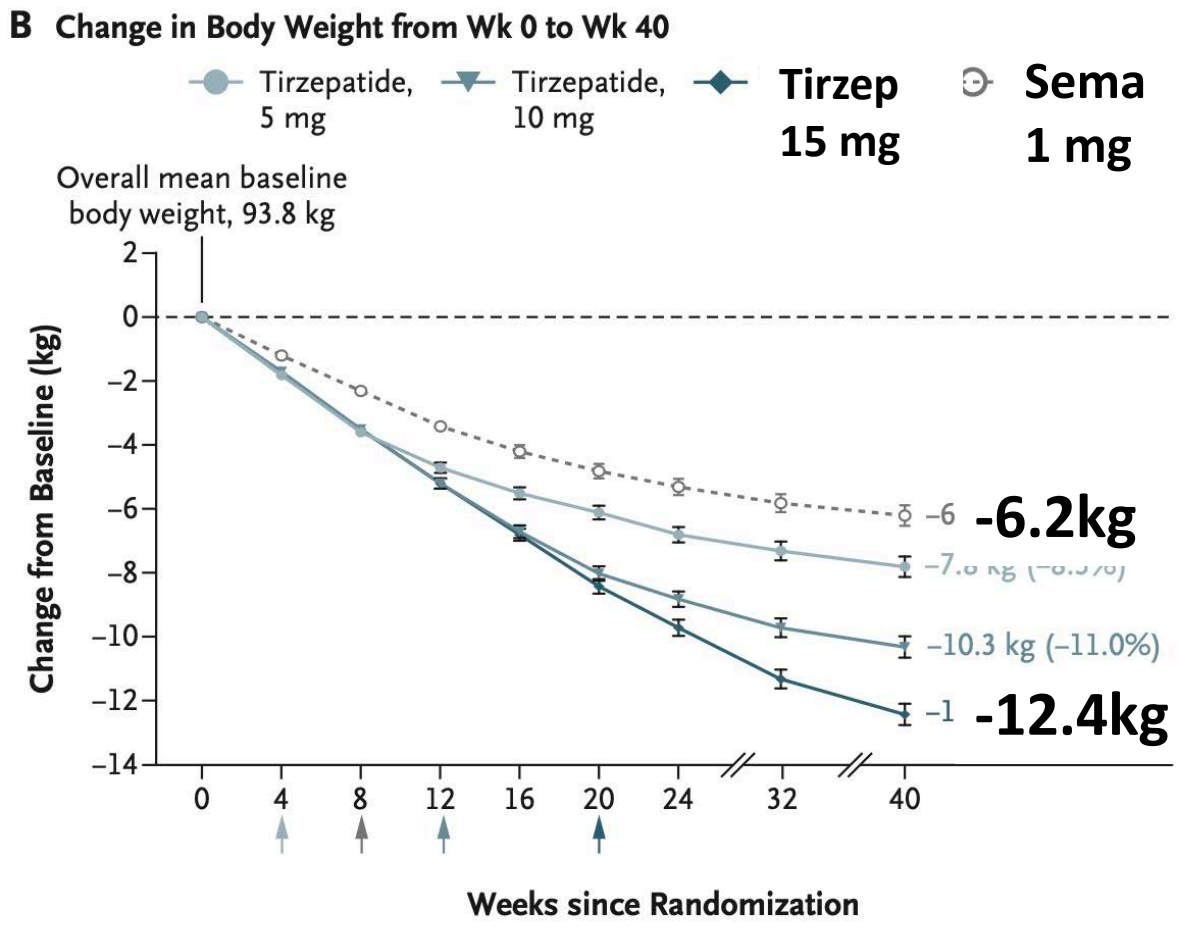
Kang, Endocrinol Metab, 2016

Dual Incretin (GLP-1 & GIP) Receptor Agonist: Tirzepatide

Effect on HbA1c



Effect on Weight



Frias, NEJM, 2021

GLP1 Receptor Agonists: Pros and Cons

Pros

- ↓ A1c ~1.5%
- No Hypoglycemia
- CVD benefit
- Weight Loss
- ↓ Liver Fat
- Weekly Administration

Cons

- Nausea
- ? Pancreatitis
- Cost (NADAC $~770/month)

DPP-IV Inhibitors: Pros and Cons

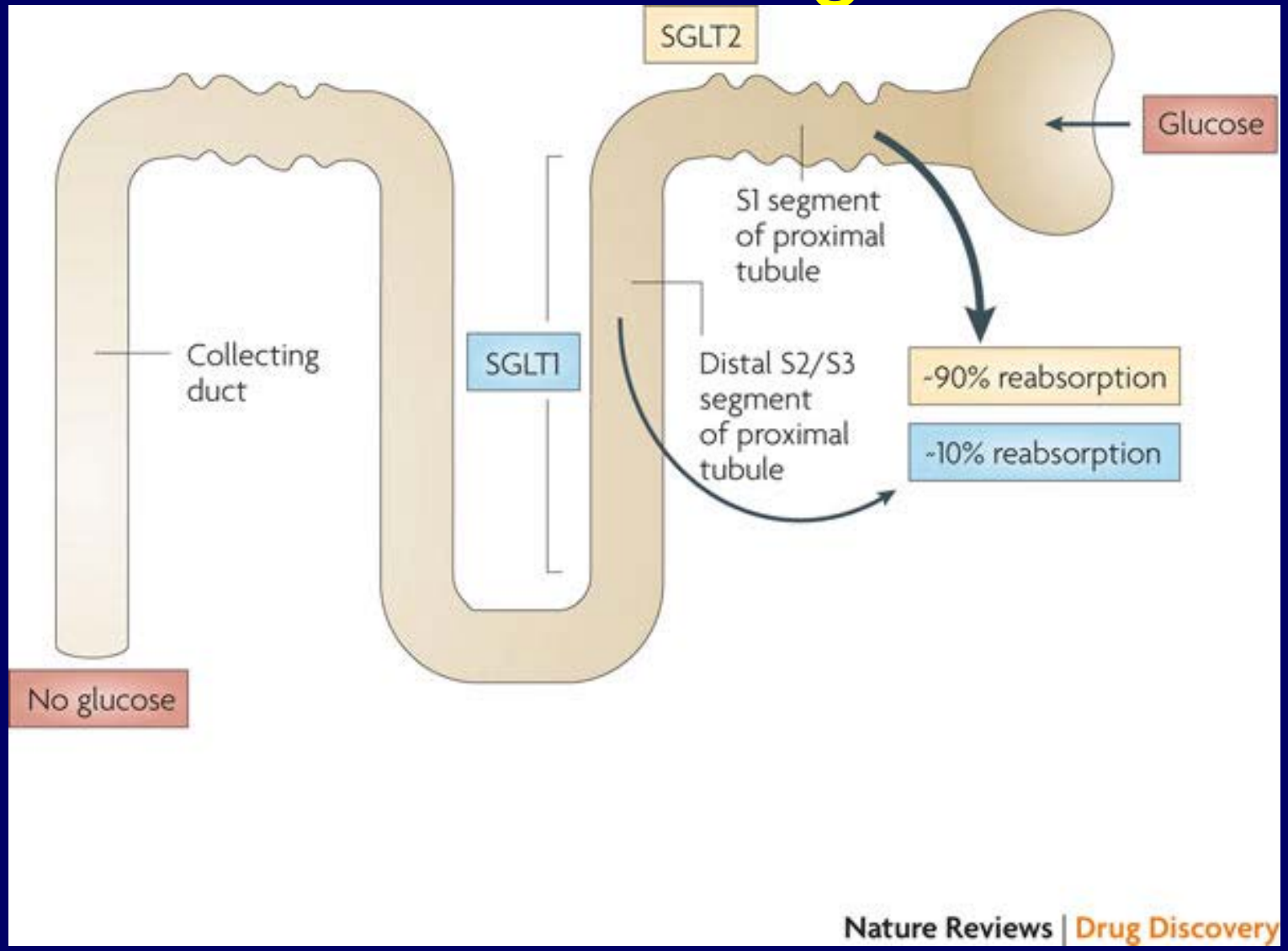
Pros

- No hypoglycemia
- Weight Neutral
- ? ↓ Inflammation

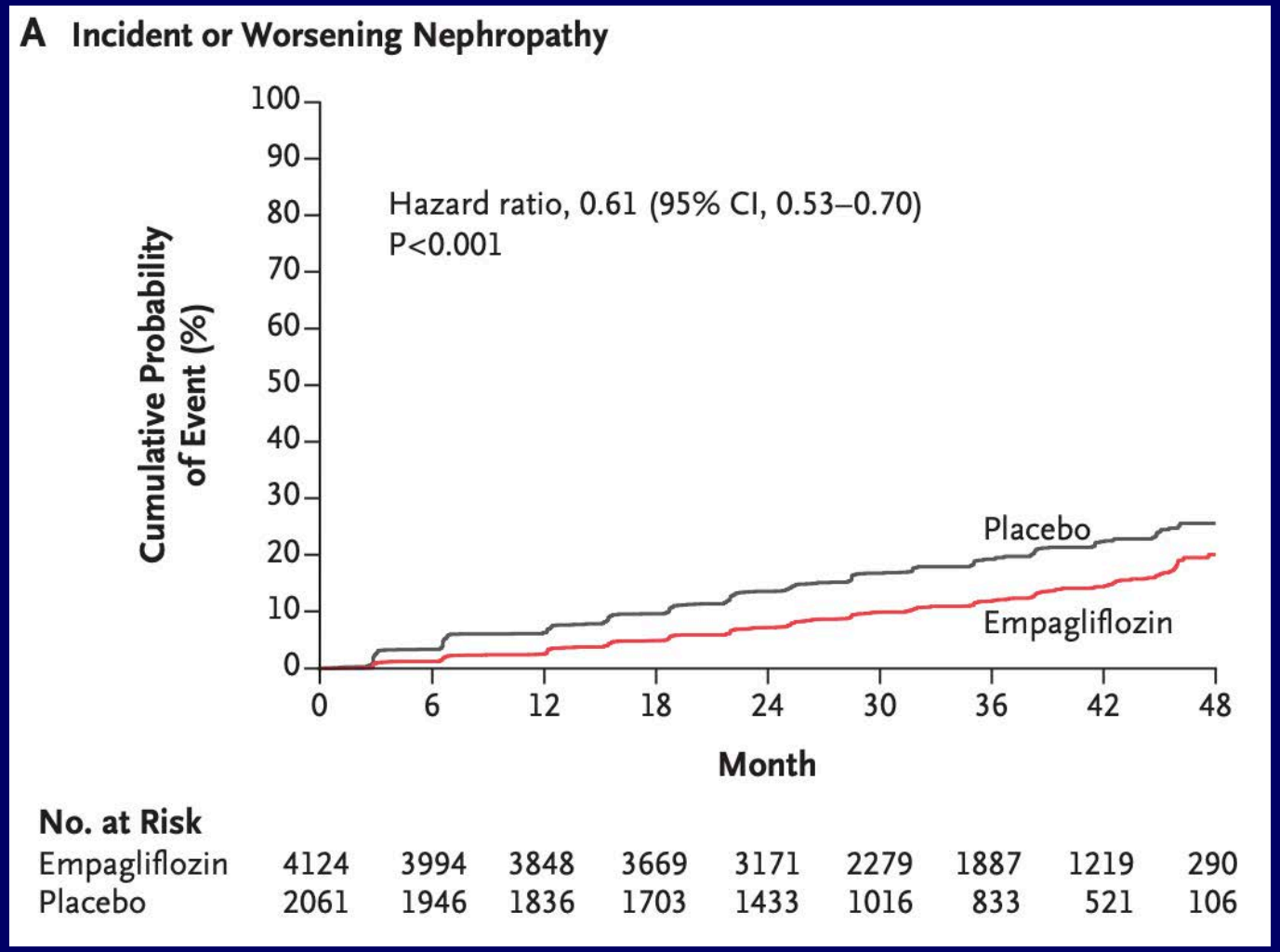
Cons

- ↓ A1c ~0.5%
- GI Side Effects
- ?Pancreatitis
- Hypersensitivity reaction
- No CVD benefit
- Cost (NADAC $~440/month)

Sodium Glucose Co-transporter 2 Inhibitors: The “gliflozins”

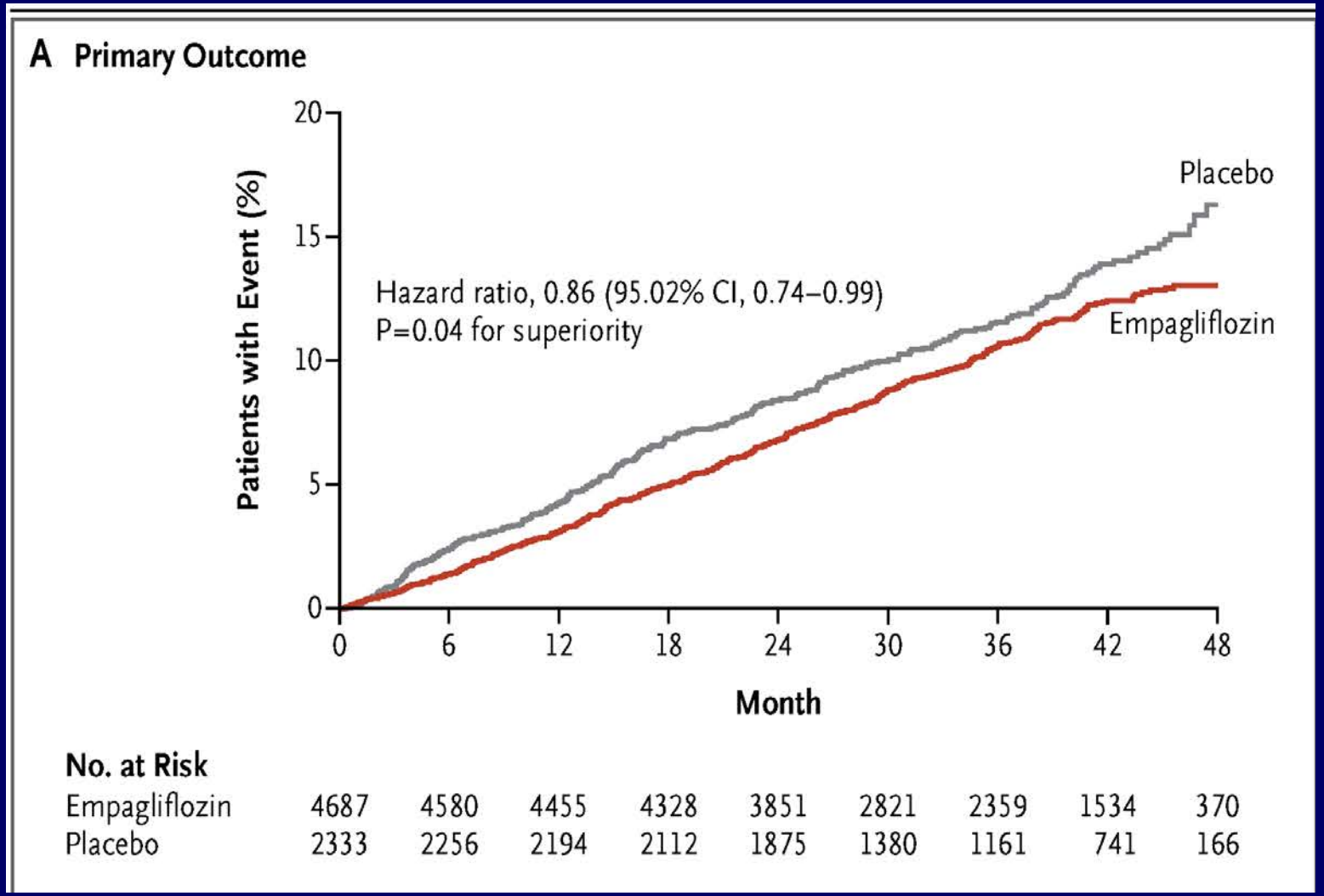


Empagliflozin Decreases Risk of Kidney Disease Progression



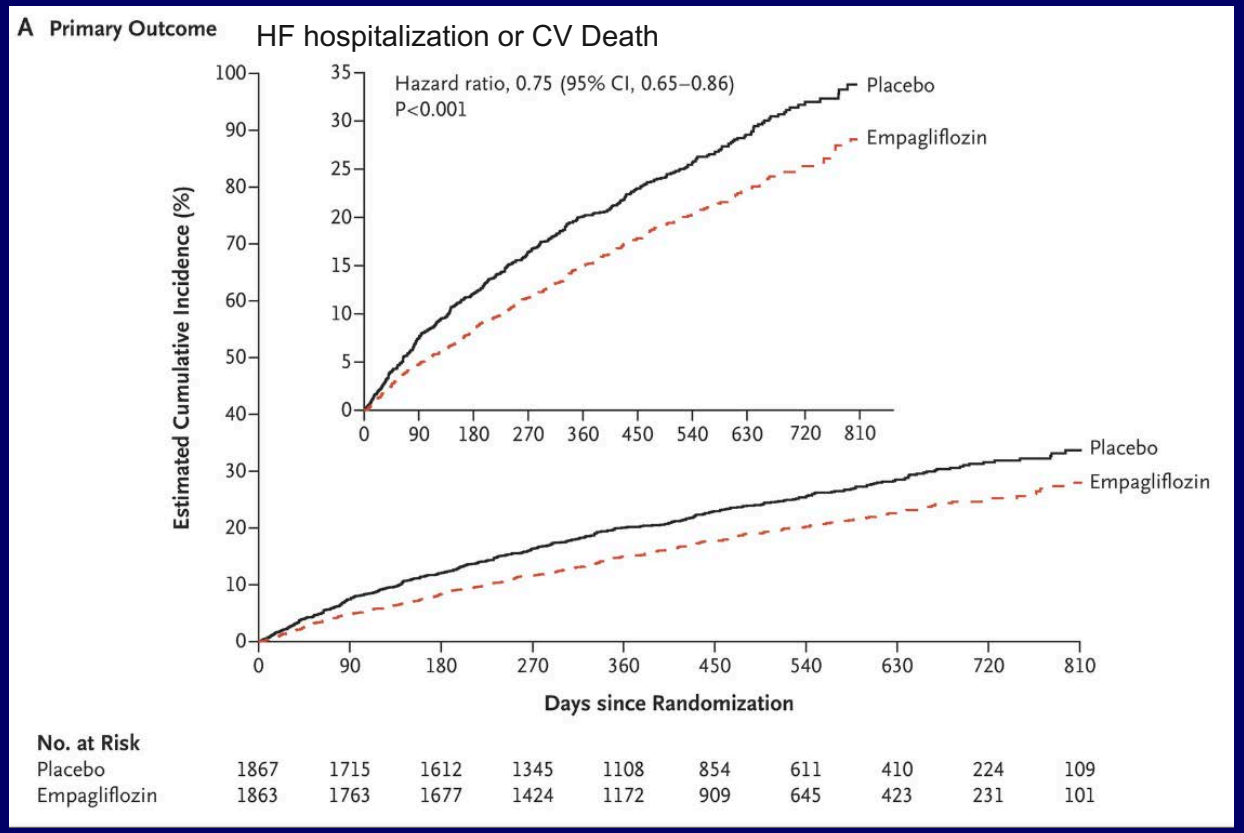
Wanner, NEJM, 2016

Empaglifozin Reduces CVD Events in DM Patients with High CVD Risk



Zinman, NEJM, 2015

SGLT2i in Heart Failure



HFrEF

Packer, NEJM, 2020

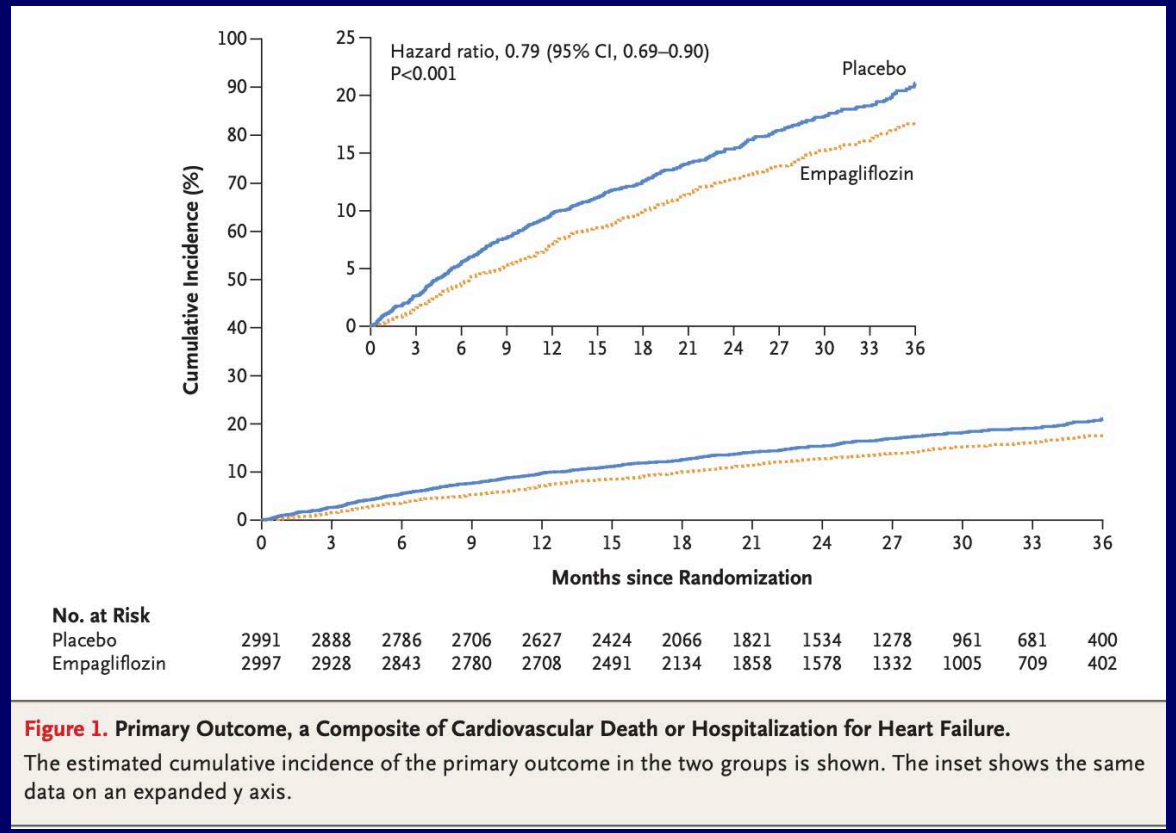
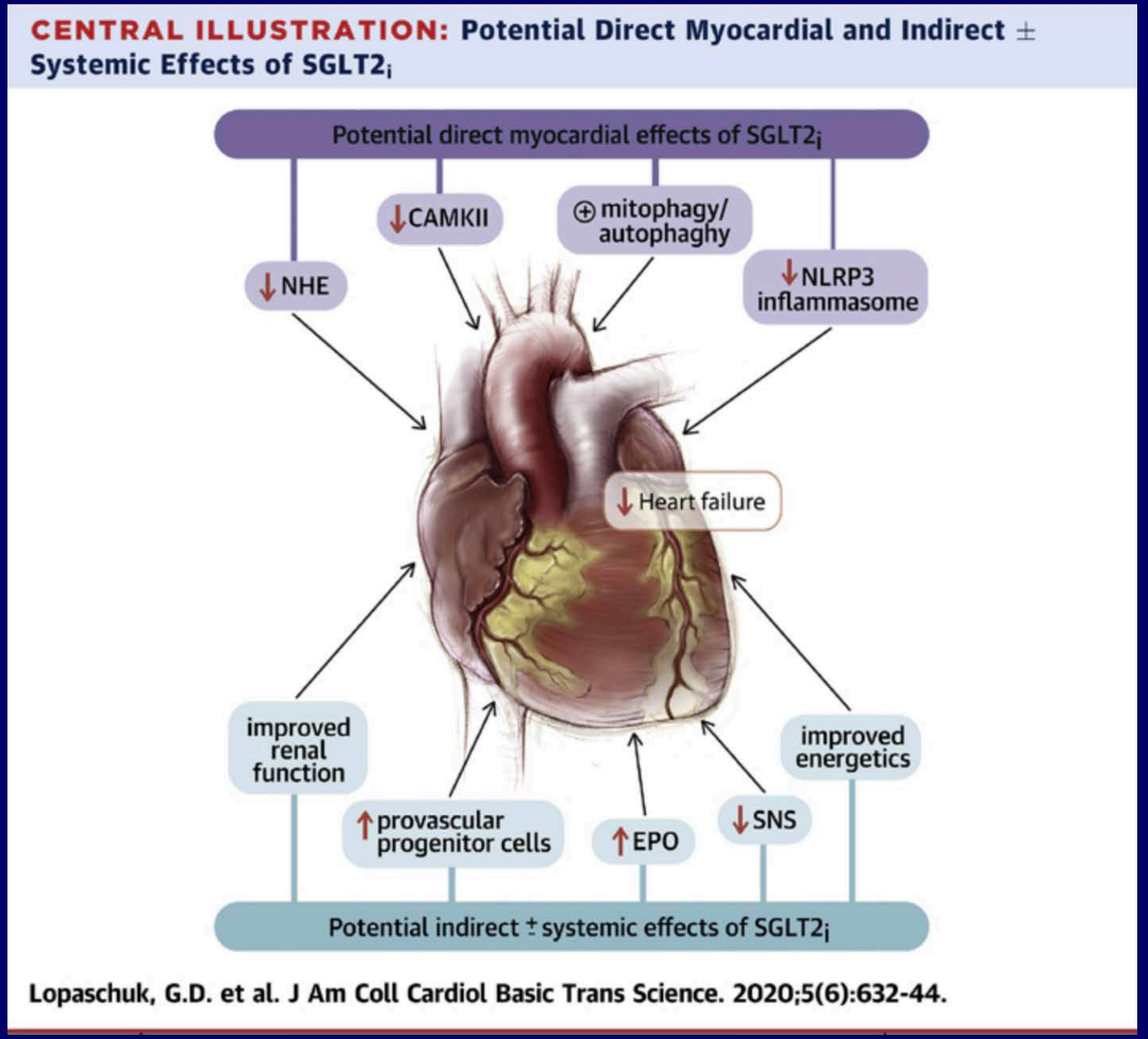


Figure 1. Primary Outcome, a Composite of Cardiovascular Death or Hospitalization for Heart Failure.
The estimated cumulative incidence of the primary outcome in the two groups is shown. The inset shows the same data on an expanded y axis.

HFpEF

Anker, NEJM, 2021

Direct and Indirect Effects of SGLT2i on Cardiac Function



Sodium Glucose Co-transporter 2 Inhibitors: Pros and Cons

Pros

- No hypoglycemia
- Weight Loss
- Lowers BP
- Preserves kidney function
- Decreases heart failure risk

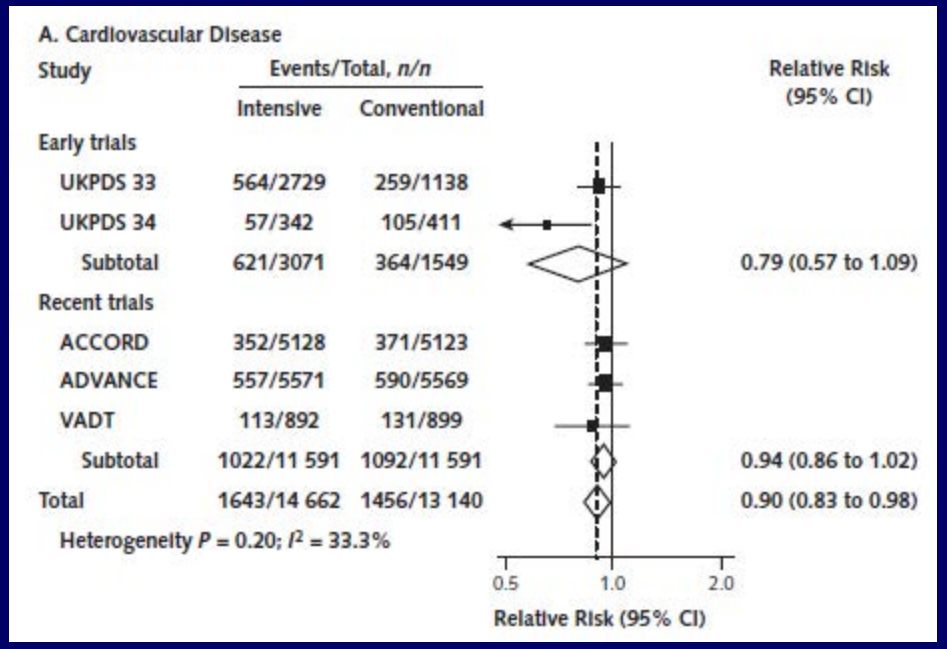
Cons

- ↓ A1c ~0.5-1%
- ↑ urinary tract infections/candidiasis
- Polyuria/dehydration
- ↑ DKA risk
- ↑ Bone Fractures/amputations
- Cost (NADAC $~500/month)

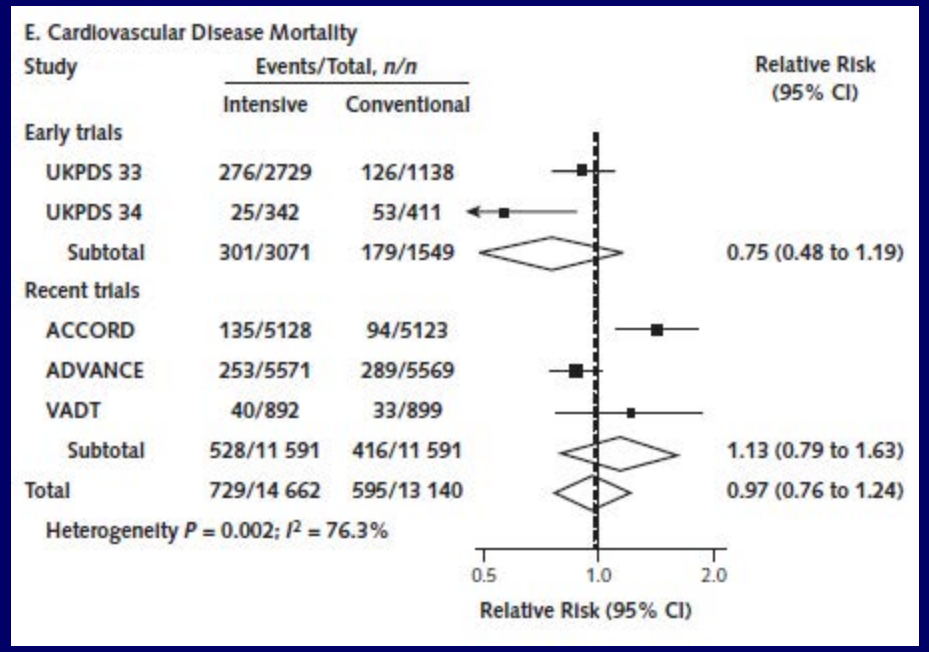
What should be the glycemic target?

HbA1c < 7%

Meta-Analysis of Glycemic Control and CVD in Diabetes



10% Risk Reduction for CVD

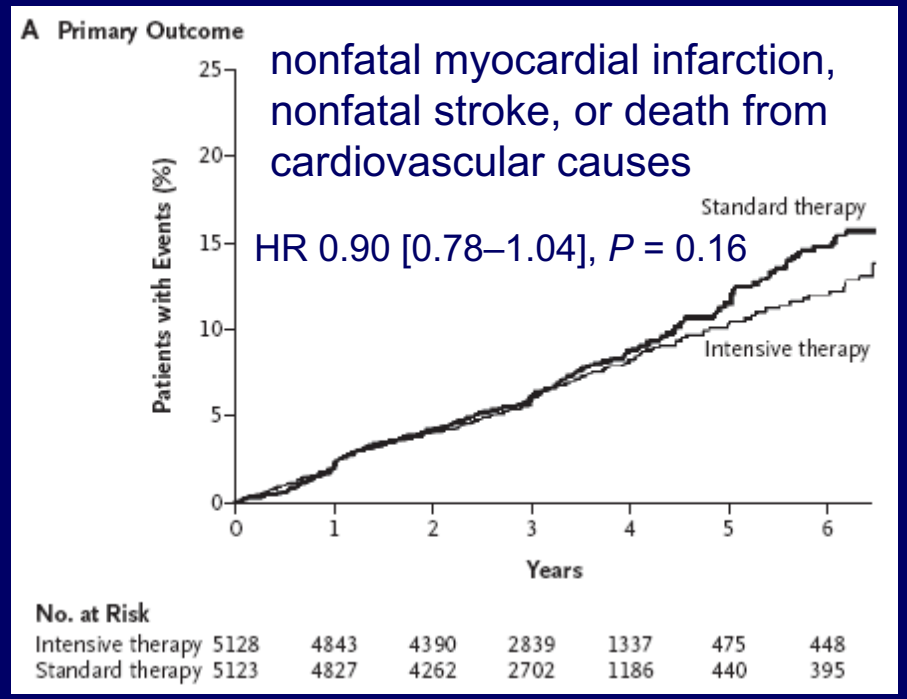


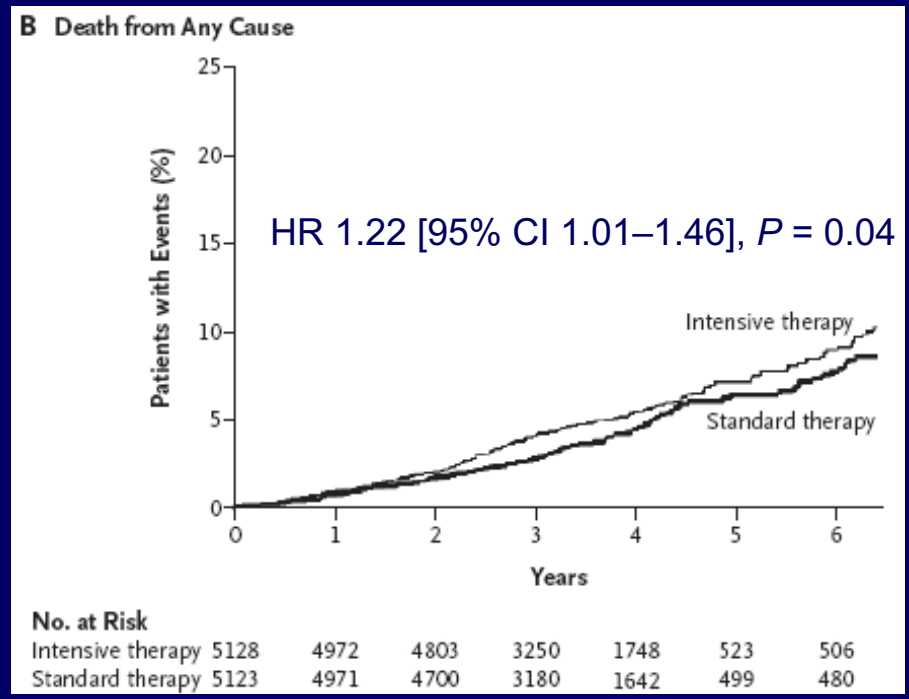
No Benefit on CVD Mortality

2-fold Increase Risk of Severe Hypoglycemia with Intensive Control

Kelly, Annals of Int Med, 2009

Intensive vs Standard Therapy in ACCORD





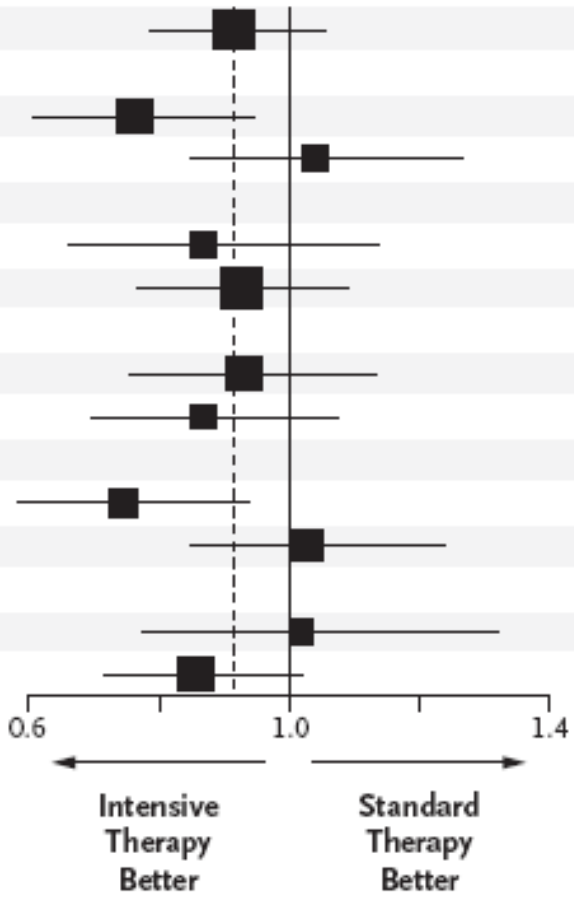
- Age 62 years, DM Duration 10 yrs, A1c 8.2%
- Randomized to intensive (A1c < 6.0%) vs. conventional blood sugar control (A1c 7-8%)

NEJM, 2008

Intensive vs Standard Therapy in ACCORD: Primary Endpoint

A Primary Outcome

Subgroup	No. of Patients	No. of Events	P Value
Total	10,251	723	
Previous cardiovascular event			0.04
No	6,643	330	
Yes	3,608	393	
Sex			0.74
Female	3,952	212	
Male	6,299	511	
Age at baseline			0.65
<65 yr	6,779	383	
≥65 yr	3,472	340	
Glycated hemoglobin at baseline			0.03
≤8.0%	4,868	284	
>8.0%	5,360	438	
Race			0.29
Nonwhite	3,647	222	
White	6,604	501	



NEJM, 2008

A1c Goal

HbA1c < 7%

Individualization is Key:

- Tighter Control (A1c 6.0-6.5%): Younger, Healthier
- Looser Control (A1c 7.5-8.0%+): Older, Hypoglycemia Prone, Co-morbidities

What else should I be doing to prevent complications?: Microvascular

- Retinopathy: Yearly ophthalmologic exams
- Nephropathy:
  - BP Control
  - Spot Urine Microalbumin every 6-12 months
  - ACE-I/ARB with microalbuminuria or HTN
  - Lipid Control
- Neuropathy:
  - Foot exams every 6-12 months
  - Instruction in foot care
  - Podiatry if evidence of neuropathy

What else should I be doing to prevent complications?: Macrovascular

- Attention to all CV risk factors

A: Anti-platelet therapy
B: Blood pressure
C: Cholesterol
D: Diabetes/Glucose Management
S: Smoking Cessation

Newer Diabetes Drugs in the Treatment of Obesity

Clinical Infectious Diseases

MAJOR ARTICLE

Practical Review of Recognition and Management of Obesity and Lipohypertrophy in Human Immunodeficiency Virus Infection

Jordan E. Lake,[1,a] Takara L. Stanley,[2,a] Caroline M. Apovian,[3,4] Shalendar Bhasin,[3] Todd T. Brown,[5] Jaqueline Capeau,[6] Judith S. Currier,[7] Michael P. Dube,[8] Julian Falutz,[9] Steven K. Grinspoon,[10] Giovanni Guaraldi,[11] Esteban Martinez,[12] Grace A. McComsey,[13] Fred R. Sattler,[8] and Kristine M. Erlandson[14]

2017

Pharmacologic Management of Obesity in HIV

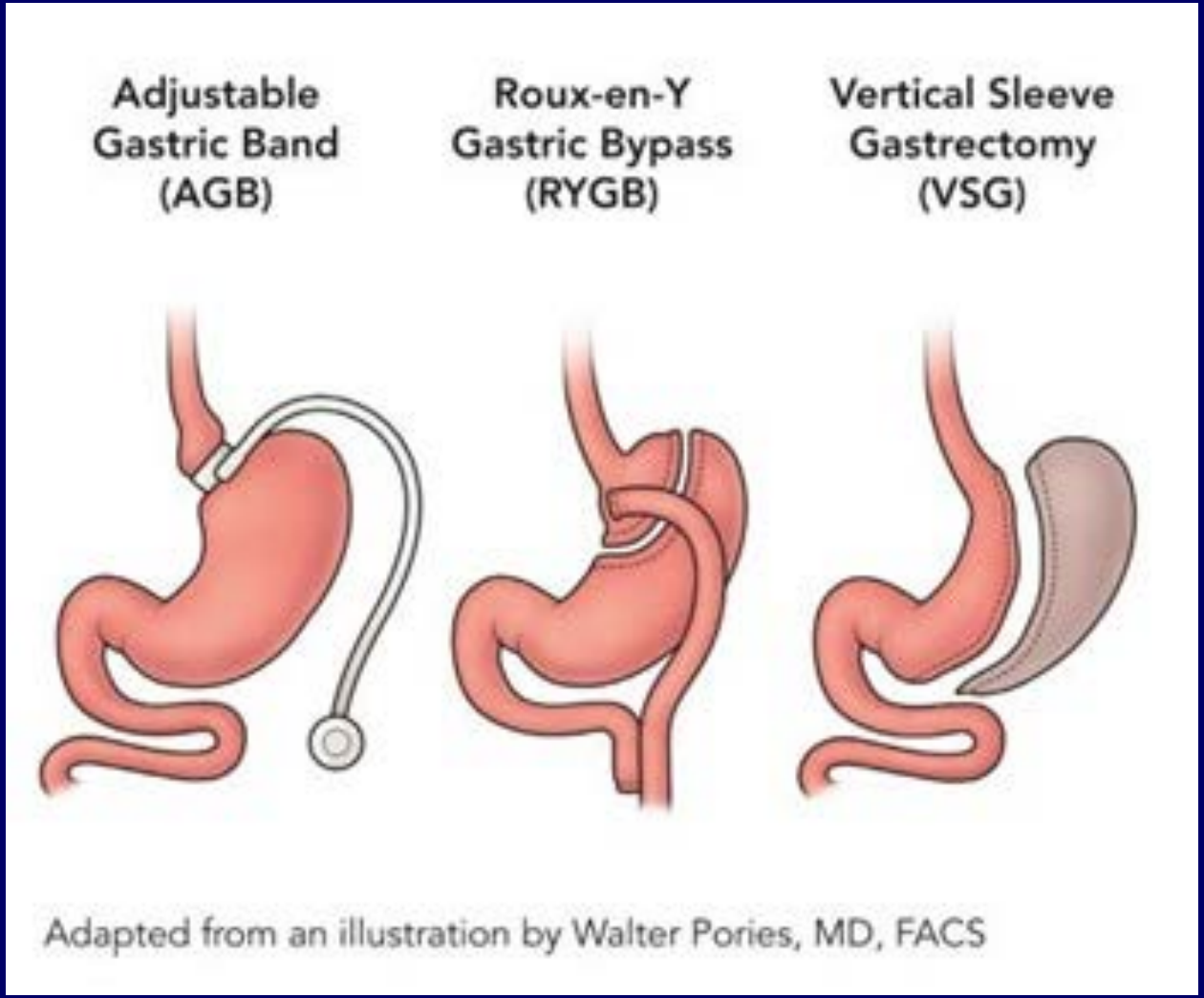
Table 2. Potential Drug Reactions and Interactions Between Antiretroviral Therapy and Antiobesity Medications

Medication	Maximum Dose[a]	Mechanism of Action	Side Effects	ART Interactions
Orlistat	120 mg TID	Pancreatic/gastric lipase inhibitor	↓ fat-soluble vitamin absorption, steatorrhea, fecal incontinence	**Avoid:** Loss of virologic control reported in patients taking ATV/r or EFV [S178, S179].
Phentermine/ Topiramate	7.5 mg/46 mg QD	Norepinephrine releasing agent/ GABA receptor modulation	Insomnia, dry mouth, constipation, paraesthesia, dizziness, dysgeusia	**Caution:** Topiramate is a mild CYP3A4 inducer, but clinical relevance is unlikely [S180].
Lorcaserin	10 mg BID	5HT2c receptor agonist	Headache, nausea, dry mouth, dizziness, fatigue, constipation **Caution if also taking**: SSRI, SNRI/MAOI, St. John's wort, triptans, buproprion, dextromethorphan	None
Naltrexone/ Bupriopion	8 mg/90 mg,2 tabs BID	Dopamine/norepi-nephrine reuptake inhibitor/opioid antagonist	Nausea, constipation, headache, vomiting, dizziness	**Caution**: Bupropion CYP2B6 metabolized [S181]. EFV or RTV use may decrease concentrations. Clinical monitoring and standard bupropion doses recommended.
Liraglutide	3 mg daily	GLP-1 agonist	Nausea, vomiting, pancreatitis	None

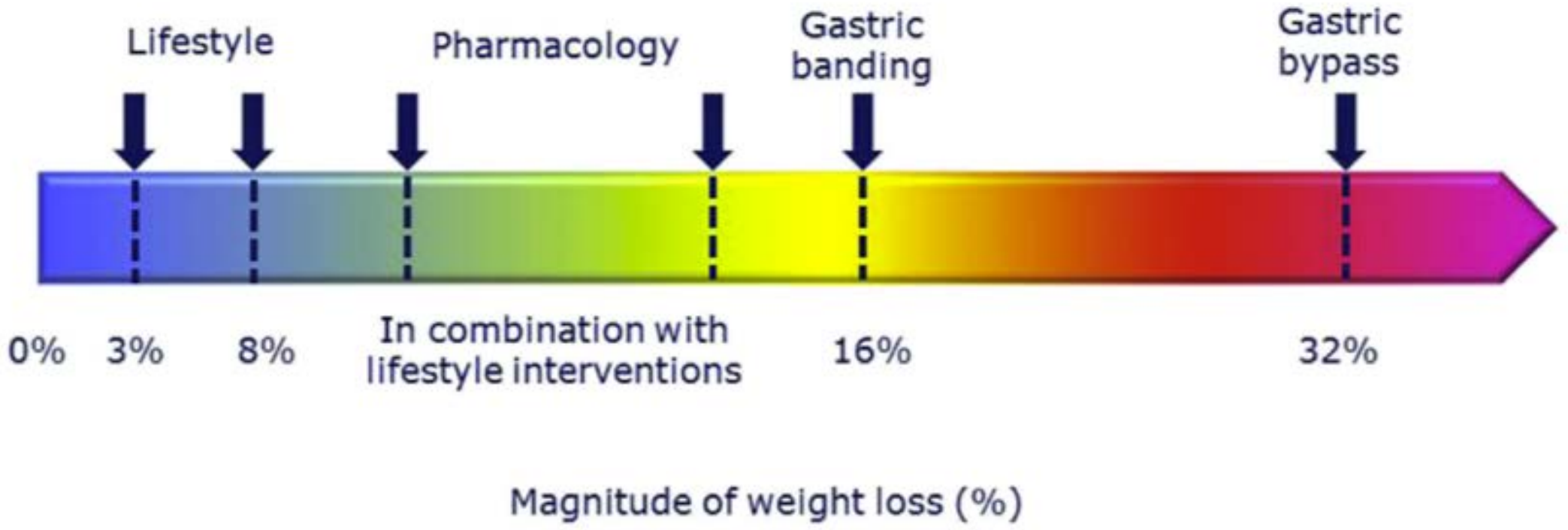
Lake, CID, 2017


Potential Benefits
Cost
Risks

Bariatric Surgery Procedures



Weight loss for different treatment interventions



Tonstad, Obesity Medicine, 2016

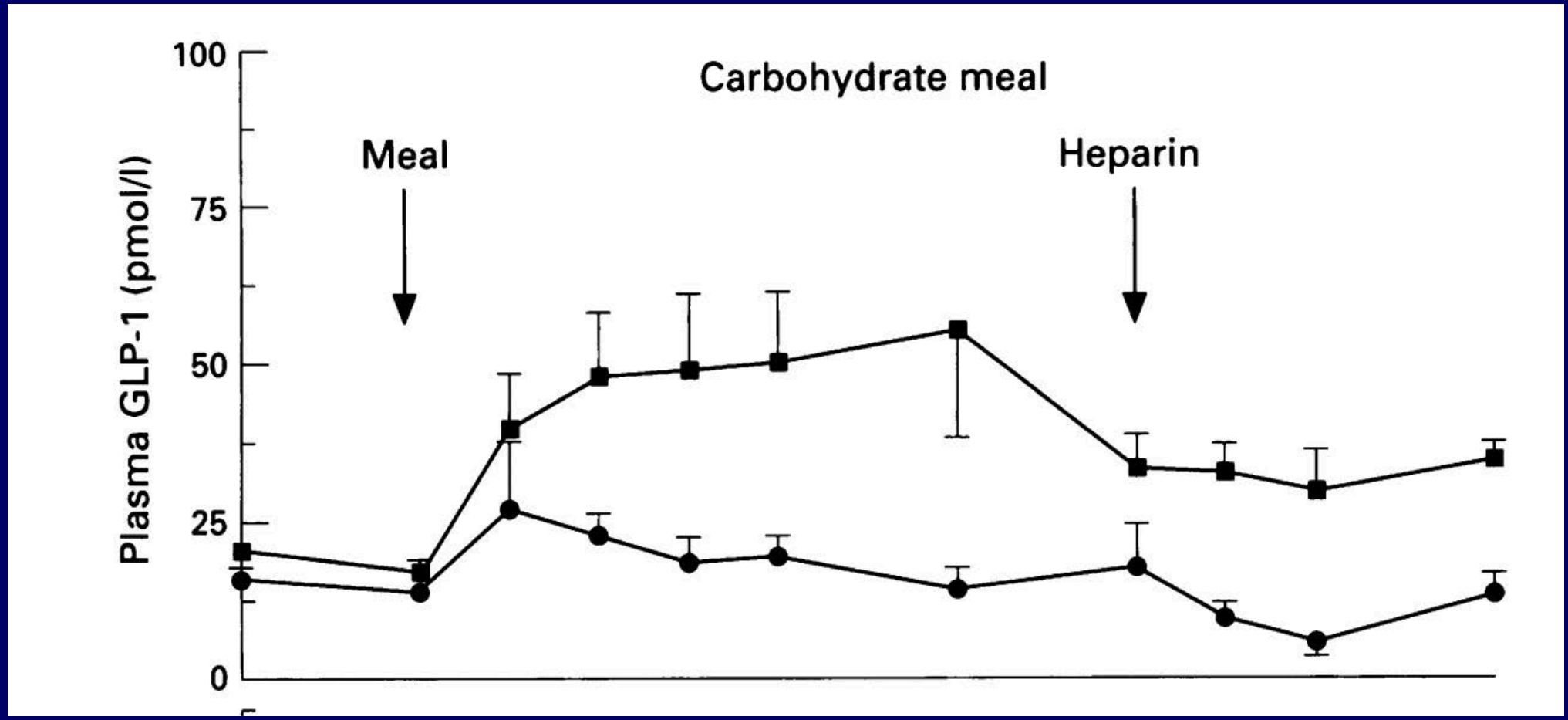
Next Generation Pharmacologic Treatment for Obesity: GLP-1 RA

Dawn of a New Era

Ensign Lake, Boundary Waters Canoe Area, MN

GLP-1 RA Mania

GLP-1 Secretion is Reduced in Obesity



Raganath, Gut, 1996

GLP1 RA for Obesity

Drug	Duration	Max Dose	Weight Effect	% Non-responder*	% D/C in Treatment Arm
Liraglutide	72 w	3.0 mg	-8.4 kg/-8%	46%	9.9%
Semaglutide	68 w	2.4 mg	-18.4 kg/-16%	13%	5.9%
Tirzepatide	72 w	15 mg	-22 kg/-18.4%	12.5%	10%

*weight loss < 5%

Pi-Sunyer, NEJM, 2015; Wadden, JAMA, 2021; Wadden, Nature Med, 2023

GLP1 RA: Adverse Effects & Long-Term Benefits

Possible Adverse Effects

- Nausea/Diarrhea
- Pancreatitis
- Gastroparesis
- Bowel Obstruction
- Decreased muscle mass
- Facial lipoatrophy ("Ozempic Face")
- ~~Suicidal ideation~~ (Wang, Nat Med, 2024)
- ? Medullary thyroid cancer
- ? Decreased effectiveness of oral contraceptives (tirzepatide)

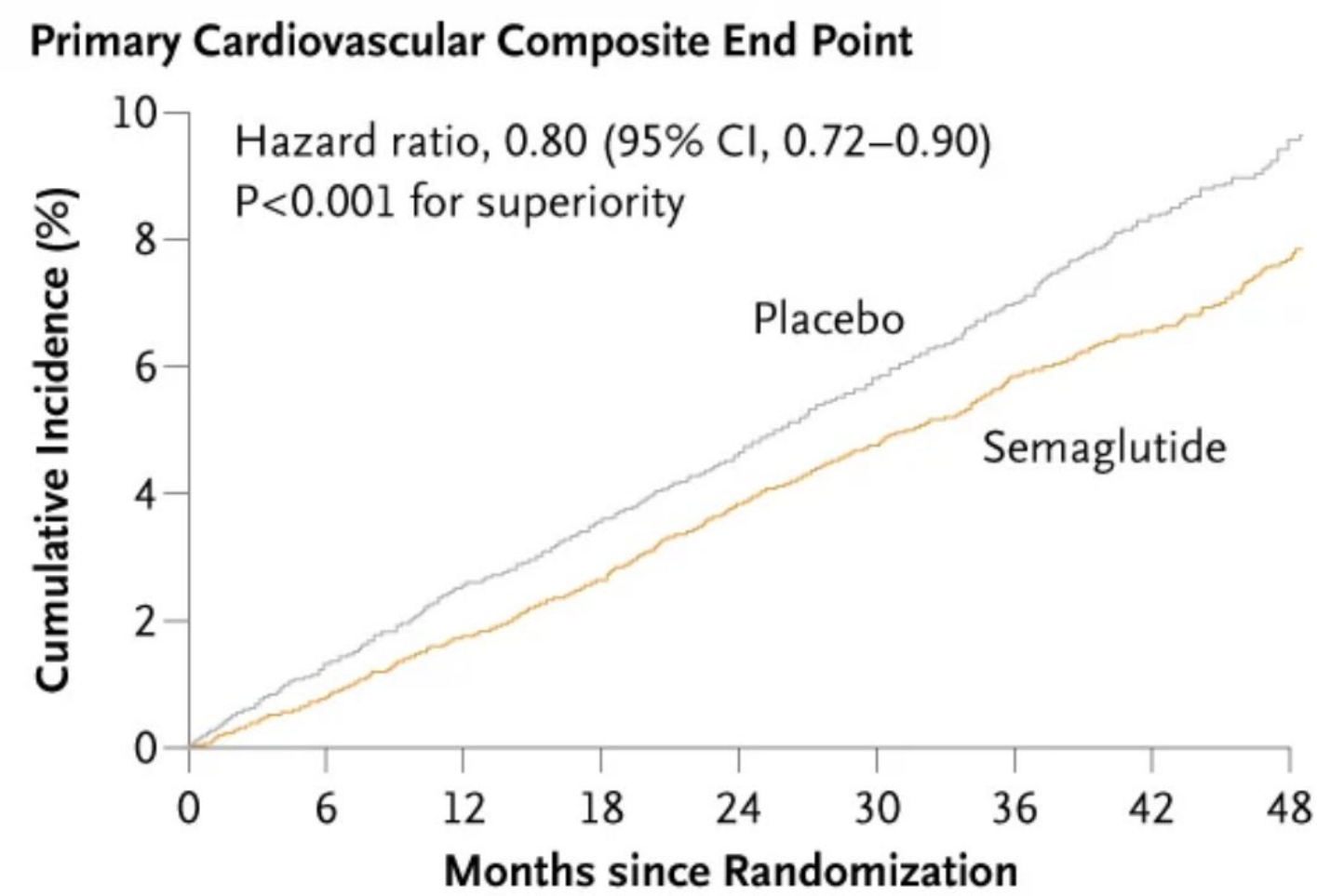
Possible Long-term Benefits

- Diabetes Prevention

ORIGINAL ARTICLE FREE PREVIEW

Semaglutide and Cardiovascular Outcomes in Obesity without Diabetes

A. Michael Lincoff, M.D., Kirstine Brown-Frandsen, M.D., Helen M. Colhoun, M.D., John Deanfield, M.D., Scott S. Emerson, M.D., Ph.D., Sille Esbjerg, M.Sc., Søren Hardt-Lindberg, M.D., Ph.D., G. Kees Hovingh, M.D., Ph.D., Steven E. Kahn, M.B., Ch.B., Robert F. Kushner, M.D., Ildiko Lingvay, M.D., M.P.H., Tugce K. Oral, M.D., et al., for the SELECT Trial Investigators*



Lincoff, NEJM, 2023

GLP1 RA: Adverse Effects & Long-Term Benefits

Possible Adverse Effects

- Nausea/Diarrhea
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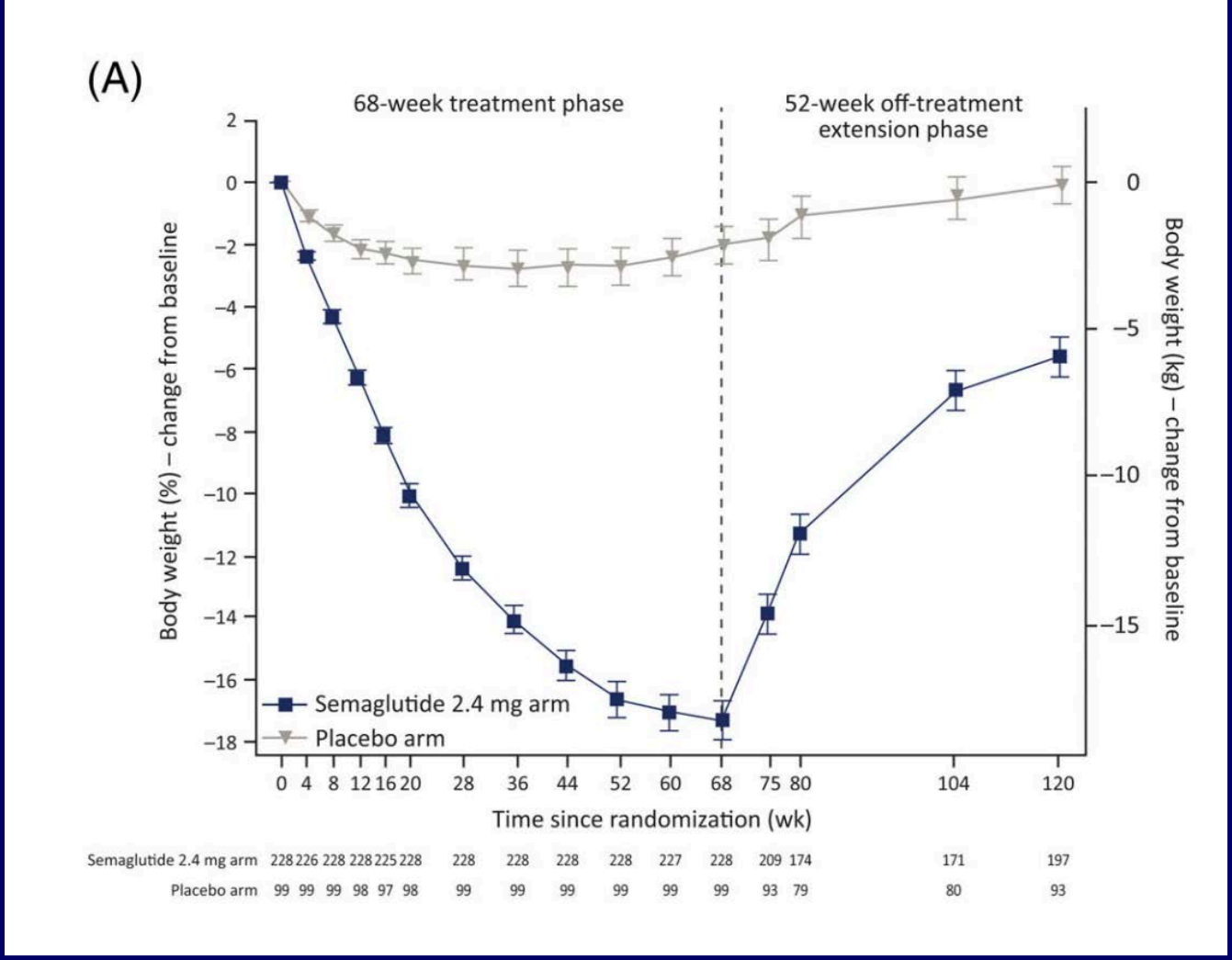
Possible Long-term Benefits

- Diabetes Prevention
- ↓ CVD Risk (SELECT: ↓ 20% MACE)
- ↓ Liver Fat
- ↓ Systemic and Adipose Inflammation
- ↓ Ectopic Fat
- Renal function preservation (FLOW)
- ↑ Physical function (SF-36)

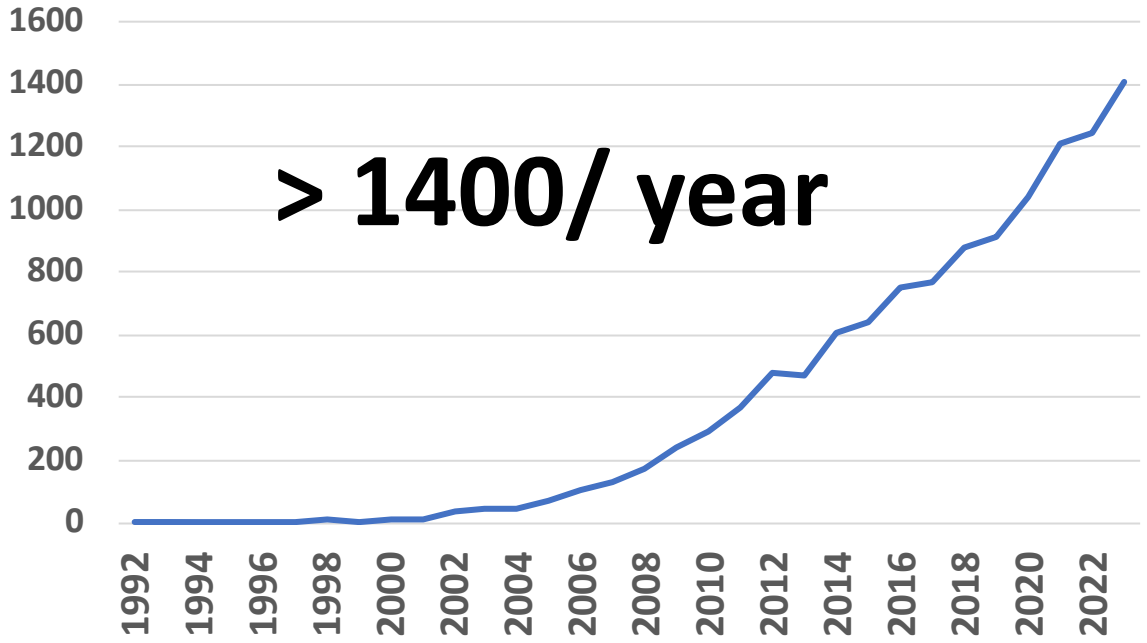
Weight Rebound After Semaglutide Discontinuation



Wilding, Diab Obes Metab, 2022

GLP1 RA and HIV

PubMed Articles: "GLP-1 Receptor Agonists"



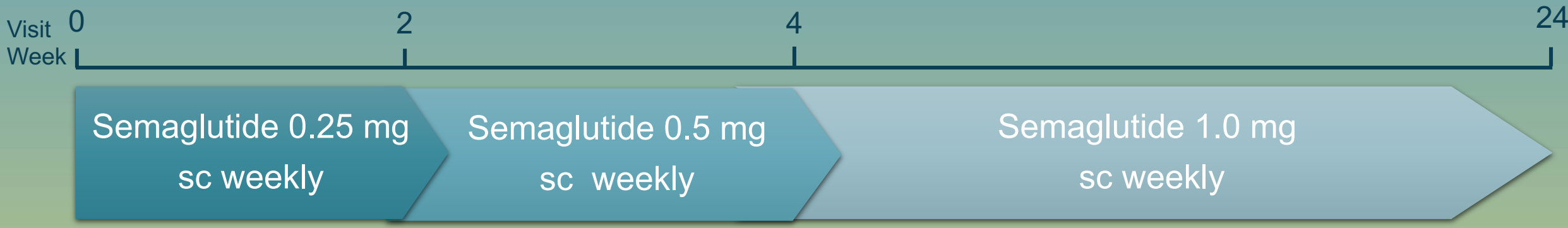
PubMed Articles: "GLP-1 Receptor Agonists, HIV"

ACTG A5371 Study Design

Inclusion Criteria

- Adult PWH on suppressive ART
- Central adiposity
- Insulin resistance or pre-diabetes
- ≥5% IHTG on MRI-PDFF

- **52 enrolled, 49 completed per-protocol**
- Nausea Grade 3 (n=1)
- Withdrawal of Informed Consent (n=1)



N=49; 37% cis women; 6% trans women

Lake, Annals of Internal Medicine, 2024

CROI 2024

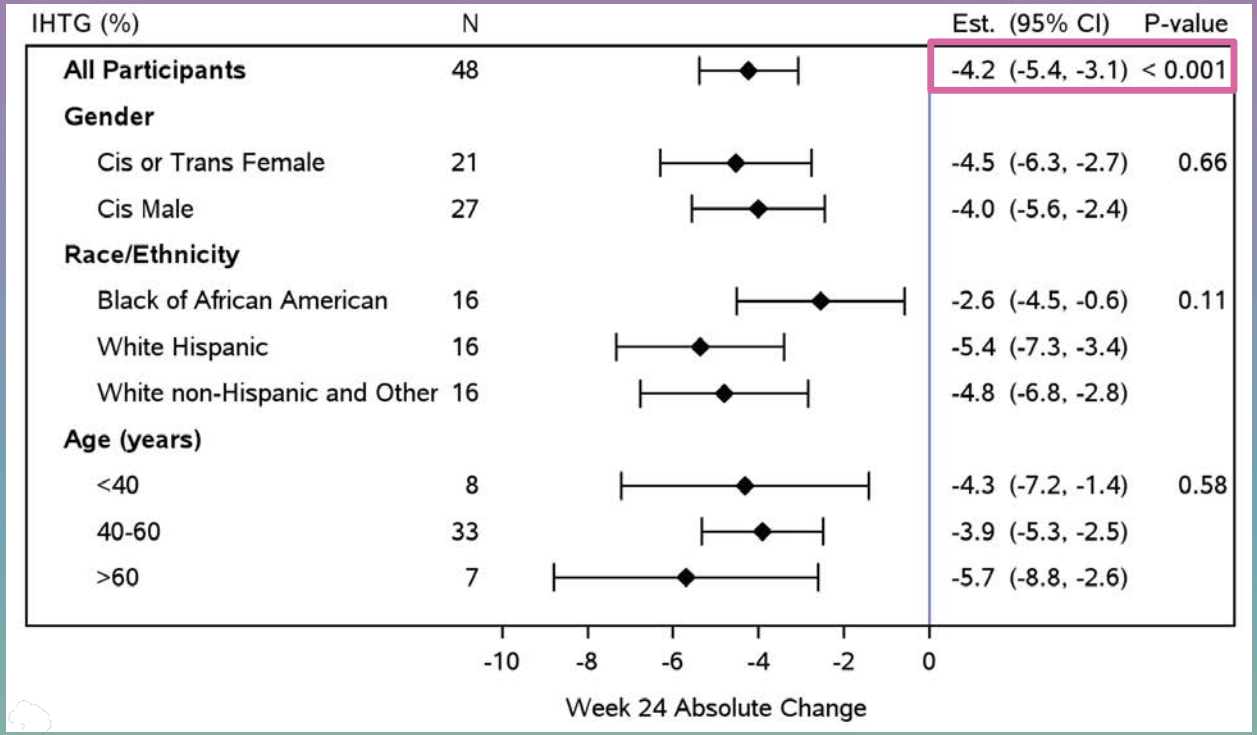
Baseline Characteristics*

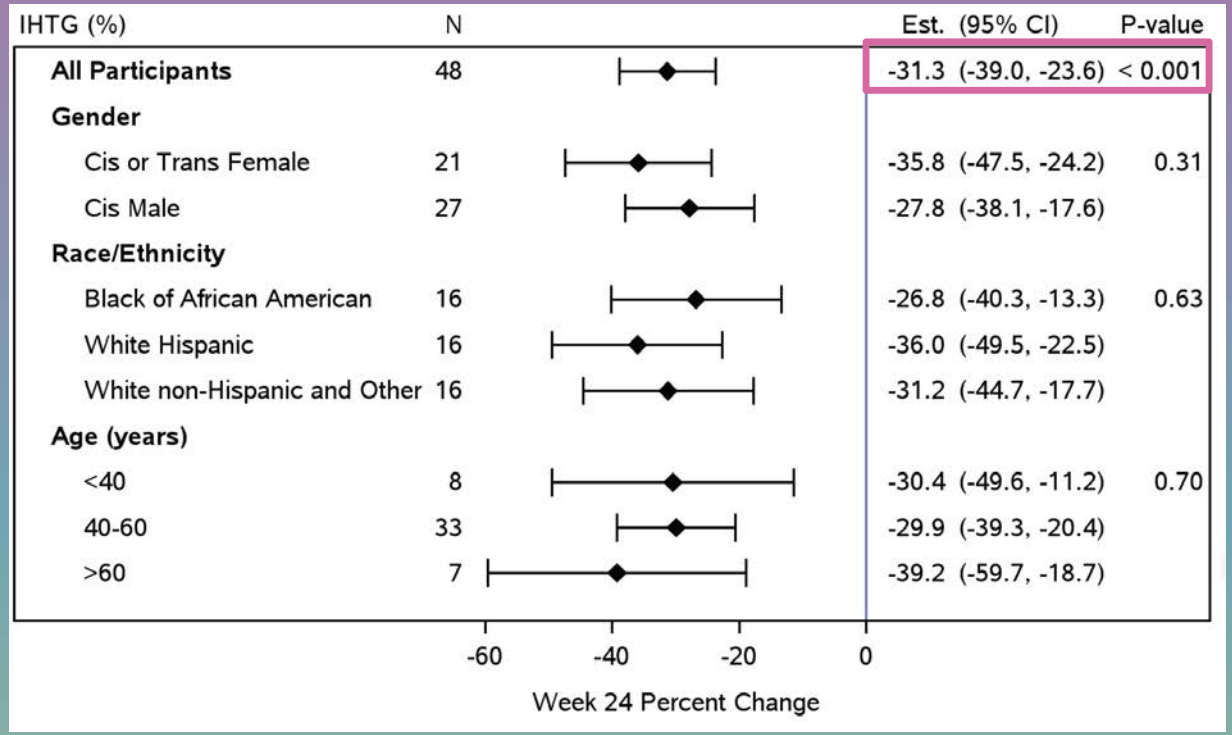
	N=49
Age	52 (42, 58)
Gender	
Cis woman	18 (37%)
Trans woman	3 (6%)
Cis man	28 (57%)
Race/ethnicity	
White non-Hispanic	13 (27%)
Black or African American*	16 (33%)
Hispanic	19 (39%)
American Indian or Alaskan Native	1 (2%)
BMI (kg/m^2)	35 (31, 39)
Waist circumference (cm)	114 (107, 124)
$CD4^+$ T lymphocyte count ($cells/mm^3$)	701 (586, 869)
ART regimen	
PI	2 (4%)
NNRTI	10 (22%)
INSTI	40 (82%)
History of hepatitis C virus	4 (8%)

CROI 2024

*Median with interquartile range or frequency presented

Primary Outcome: Changes in IHTG



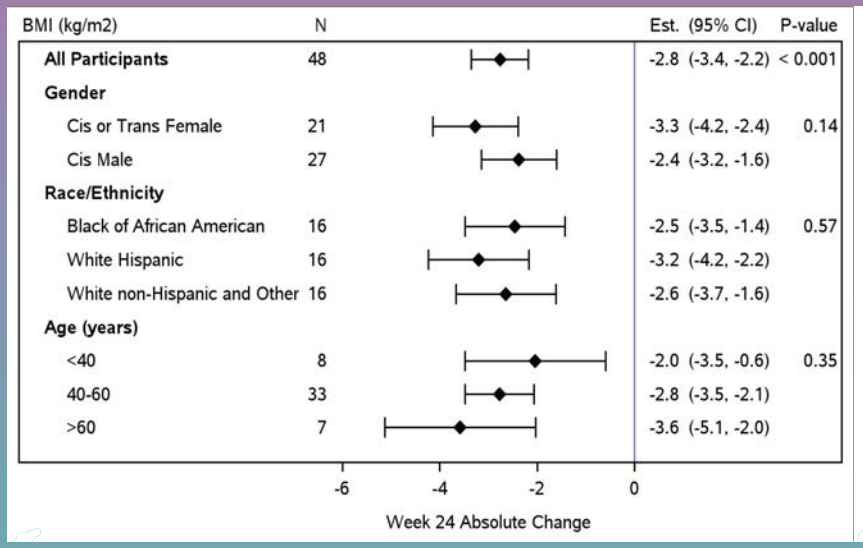


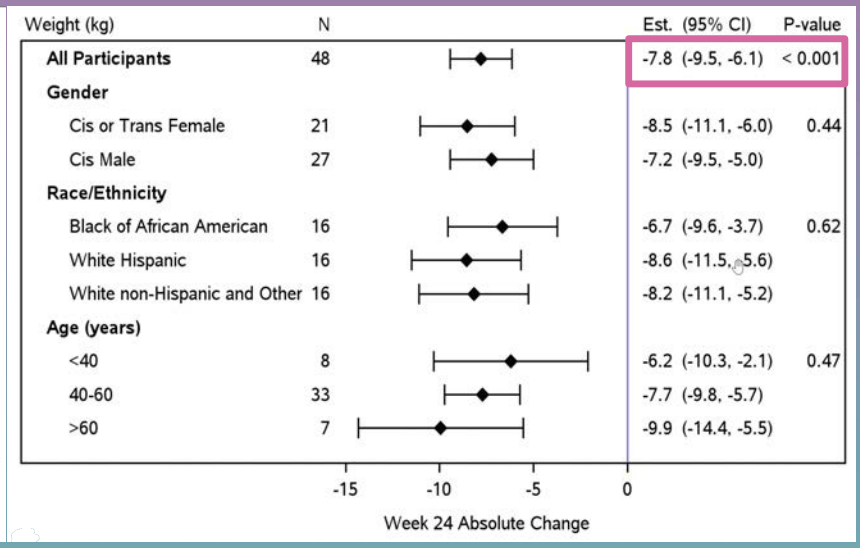
- Overall clinically significant reductions in IHTG
- 29% of participants had complete MASLD resolution (absolute IHTG <5%)
- 58% of participants had a ≥30% relative reduction in IHTG
- Greater reductions in IHTG were observed among*:
  - Women
  - Hispanic and non-Hispanic white participants
  - Participants with age >60 years

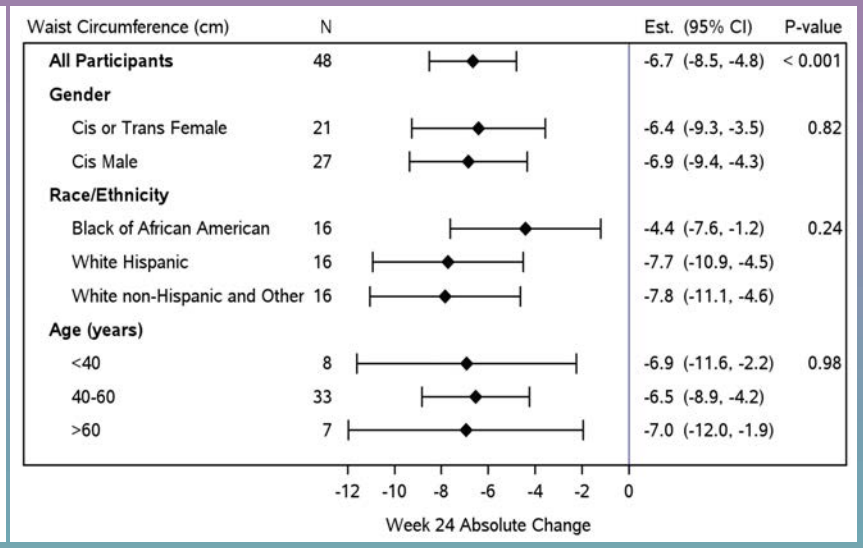
CROI 2024

*Subgroups not powered for statistical significance

Changes in Body Composition





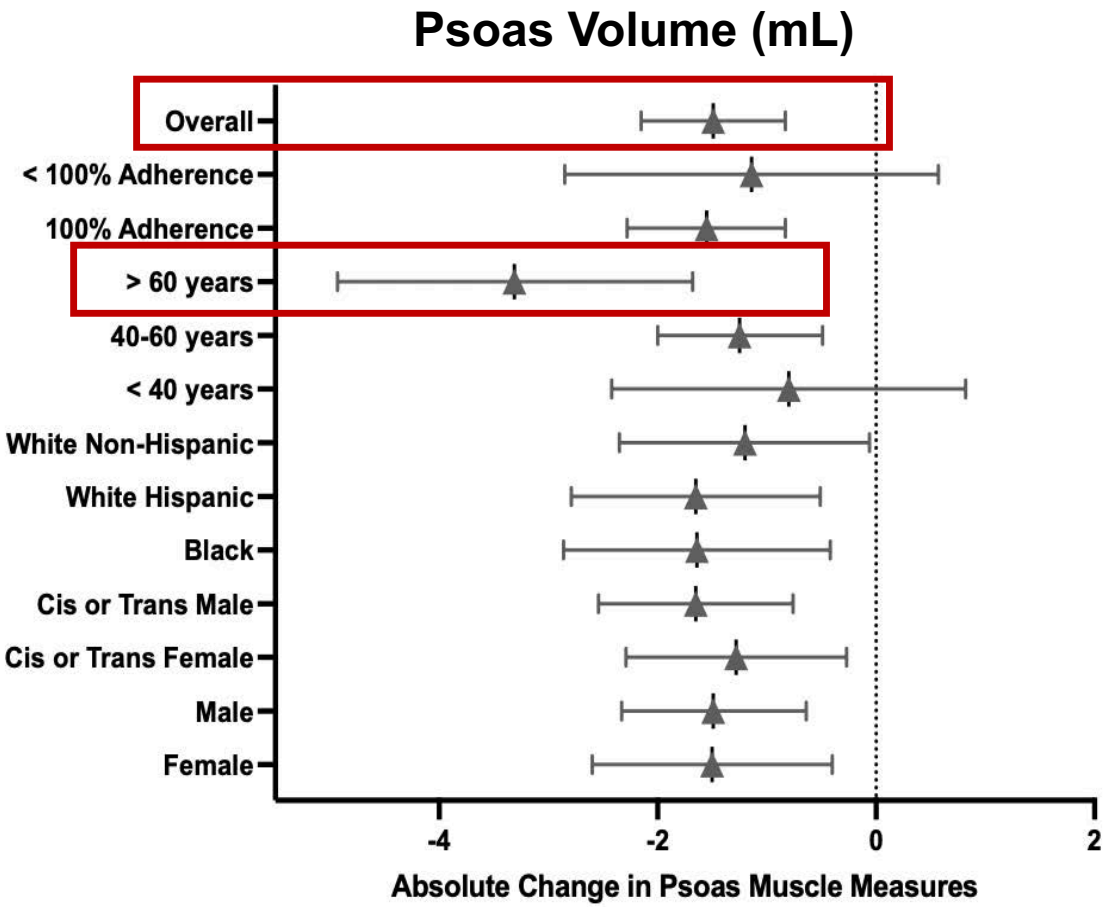


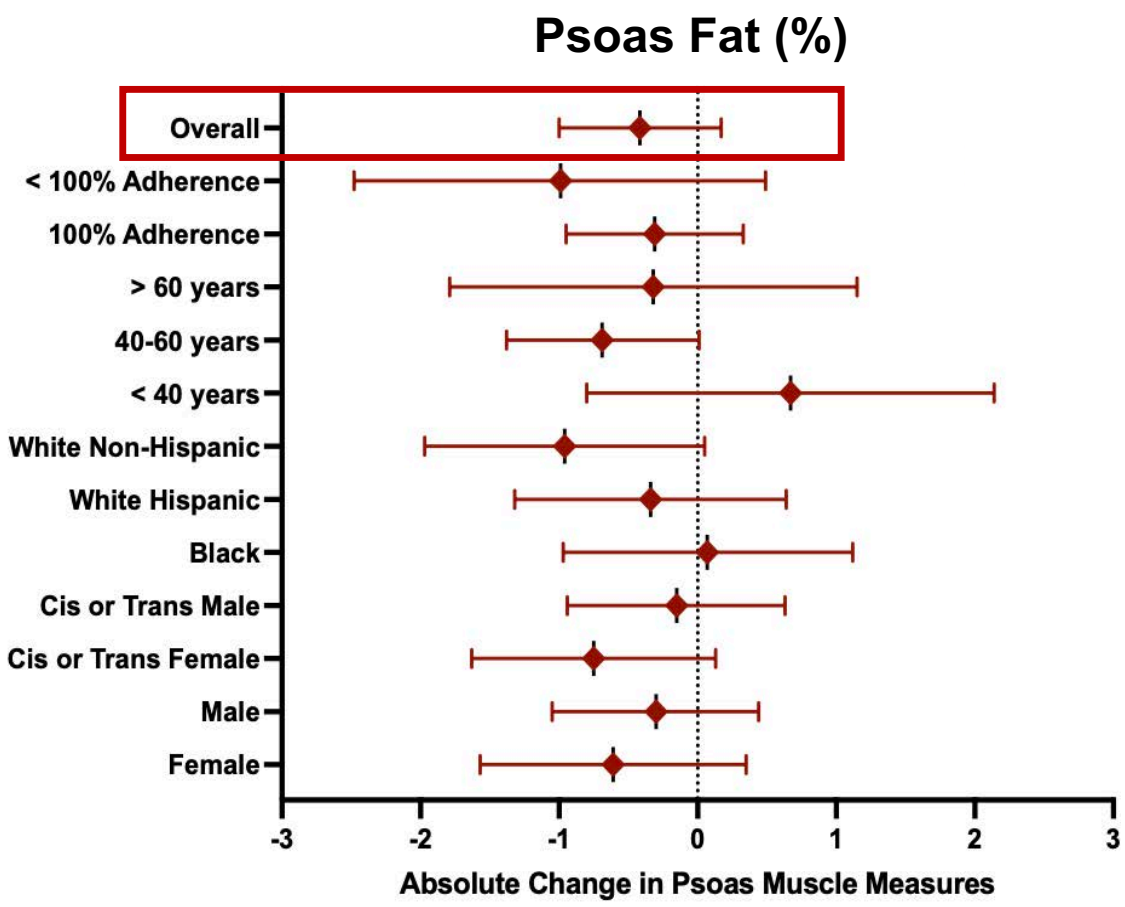
- Mean weight loss was 7.8 kg (17 lbs) over 24 weeks, with greater losses among*
  - Women
  - Hispanic and non-Hispanic white participants
  - Persons ≥40 years of age
- IHTG improvements correlated with weight loss (r=0.54, p<0.0001)
- Amongst persons who lost >2.27 kg (5 lbs) on semaglutide (n=38), the mean absolute and relative changes in IHTG were -5.1% and -39.0%, respectively

CROI 2024

*Subgroups not powered for statistical significance

Results: Change in muscle volume & fat





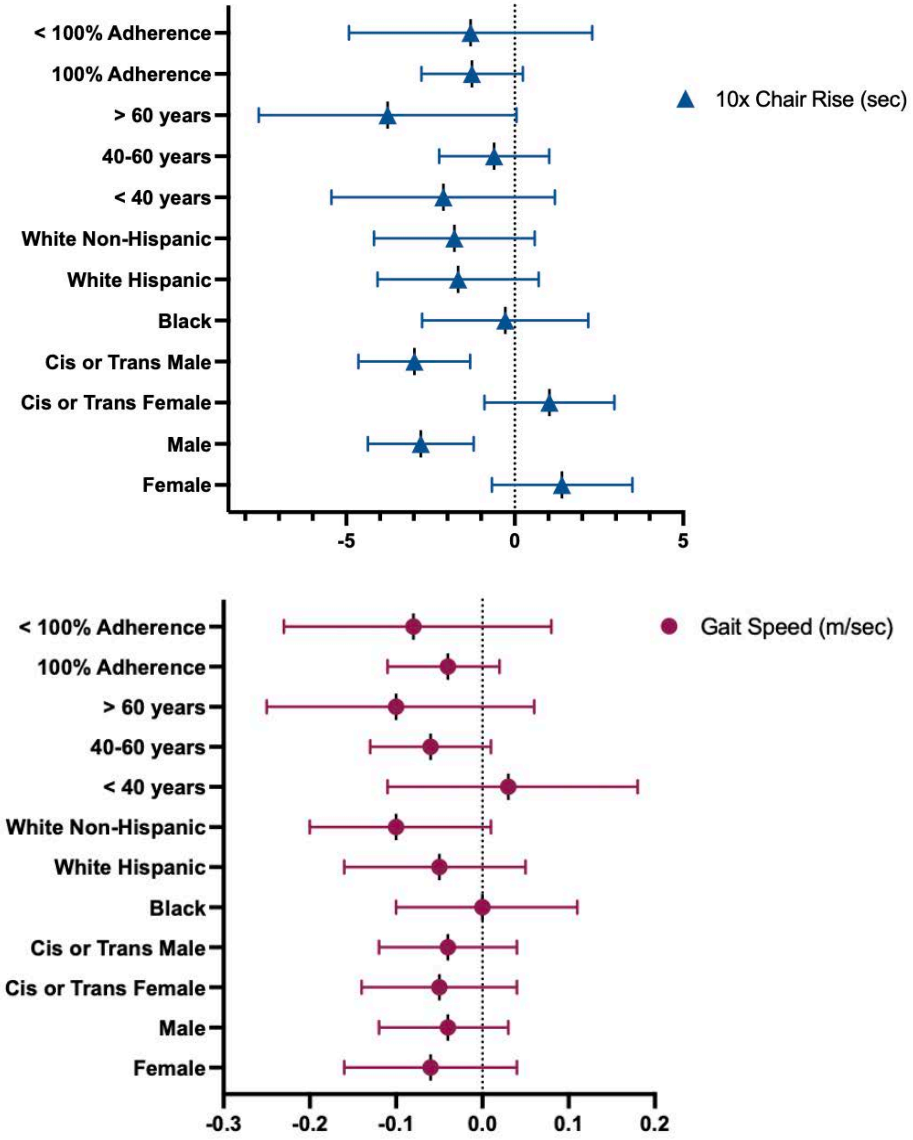
Ditzenbeger, CROI, Abstract 799

Overall psoas muscle volume **declined**, but psoas muscle fat content did not significantly change. PWH >60 years had the greatest decline in muscle volume.

Results: Change in physical function

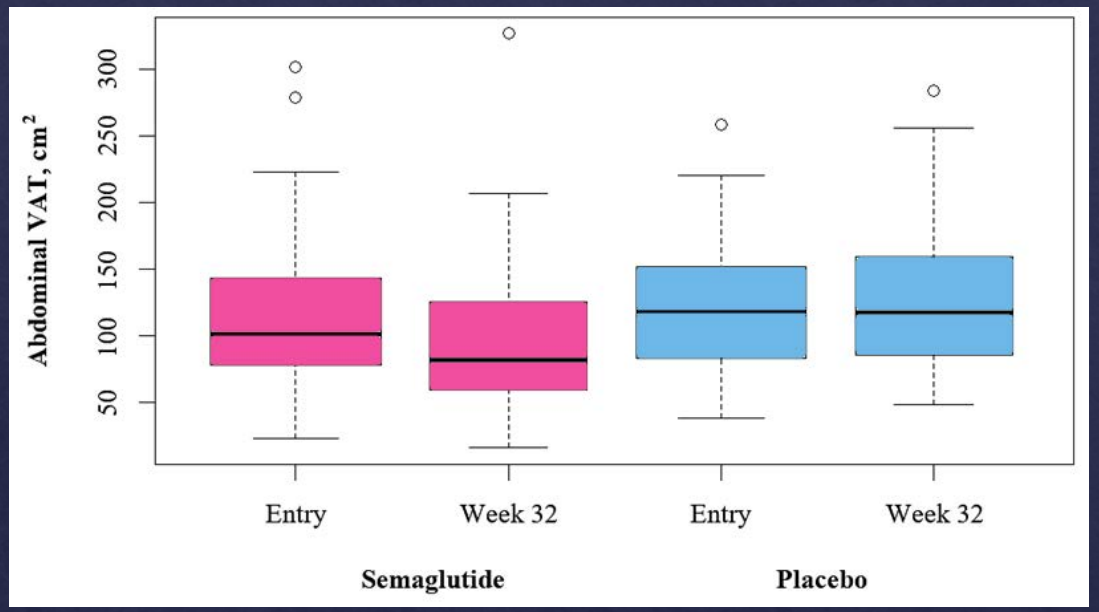
CROI 2024

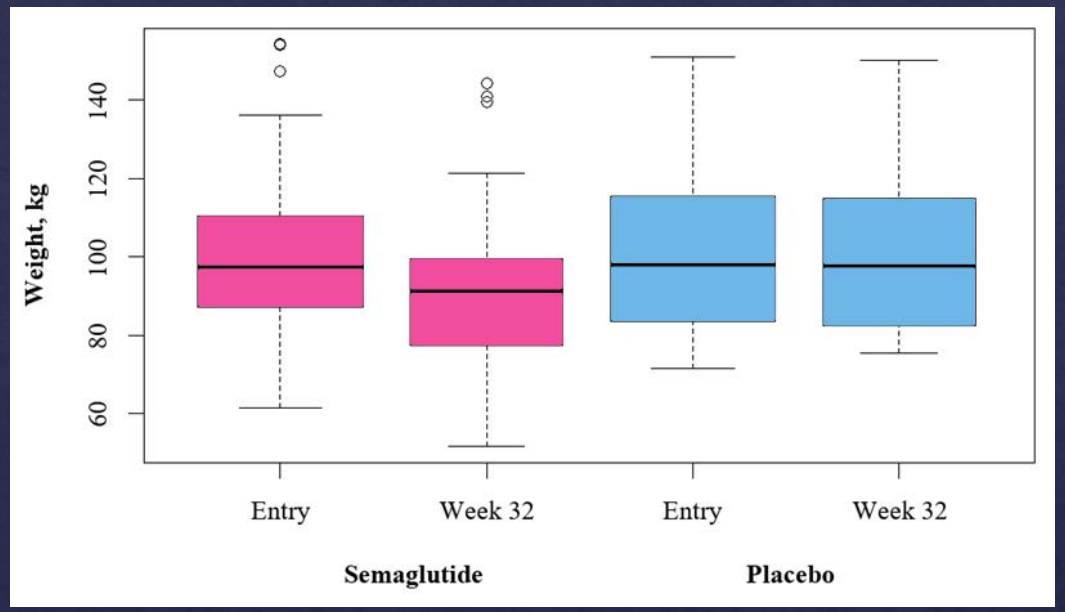
Parameter	Baseline	Week 24	Change, Baseline to Week 24	P-value
5x Chair Rise (seconds)	12.5 (3.6)	11.9 (3.3)	-0.66 (2.5) 95% CI: -1.4, 0.07	0.077
10x Chair Rise (seconds)	26.2 (7.0)	25.0 (6.8)	-1.27 (4.7) 95% CI: -2.7, 0.10	0.069
Gait speed (meters/second)	0.93 (0.23)	0.98 (0.24)	0.05 (0.19) 95% CI: -0.01, 0.10	0.078
Presence of slow gait speed (<1 meters/second)	No: 18 (37%) Yes: 31 (63%)	No: 26 (54%) Yes: 22 (46%)	RR: 0.73 (0.55, 0.97)	0.029



Chair rise time and gait speed was **preserved** despite loss of psoas muscle volume. These changes in function were not correlated with change in overall weight or BMI.

Effect of Semaglutide in PWH with Lipodystrophy





32 weeks of semaglutide use caused significant decreases in abdominal VAT, SAT, TAT, trunk fat, limb fat, total body fat, lean body mass & weight.**

*previously presented at IDWeek 2023, abstract #1984, McComsey

Visceral adipose tissue

-30.6%

Subcutaneous adipose tissue

-11.2%

(abdominal fat area measured by CT at L4-L5)

Body weight

-10.4%

Lean body mass

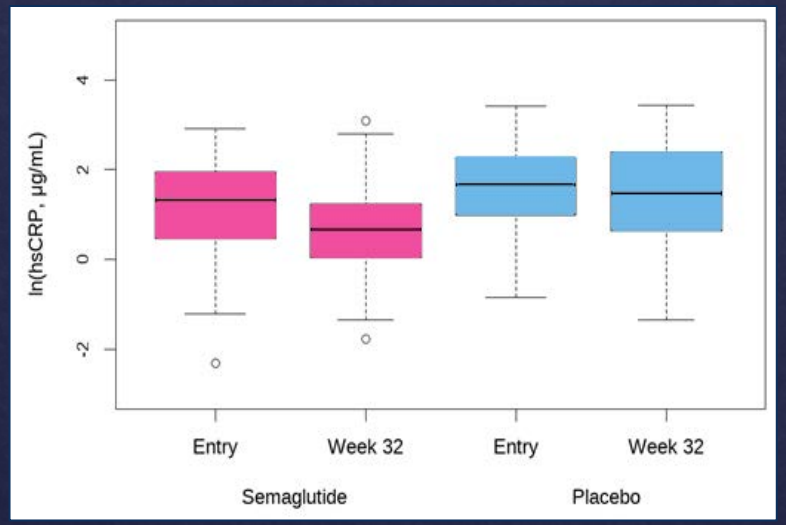
-5.7%

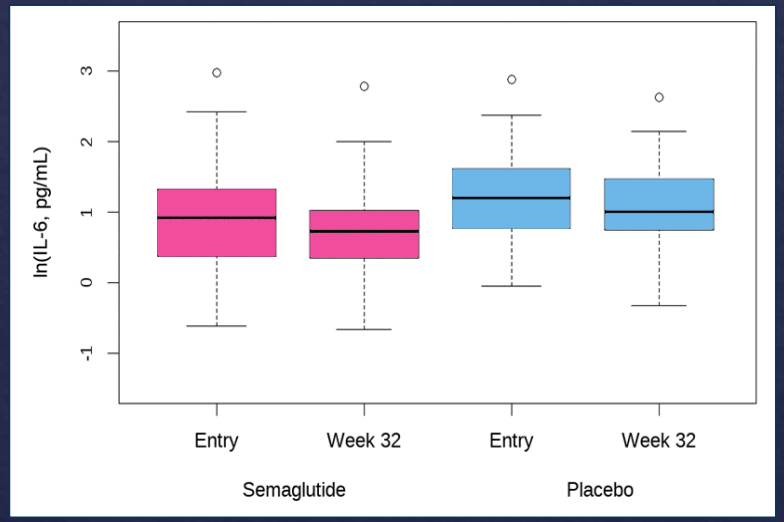
(measured by whole-body DXA)

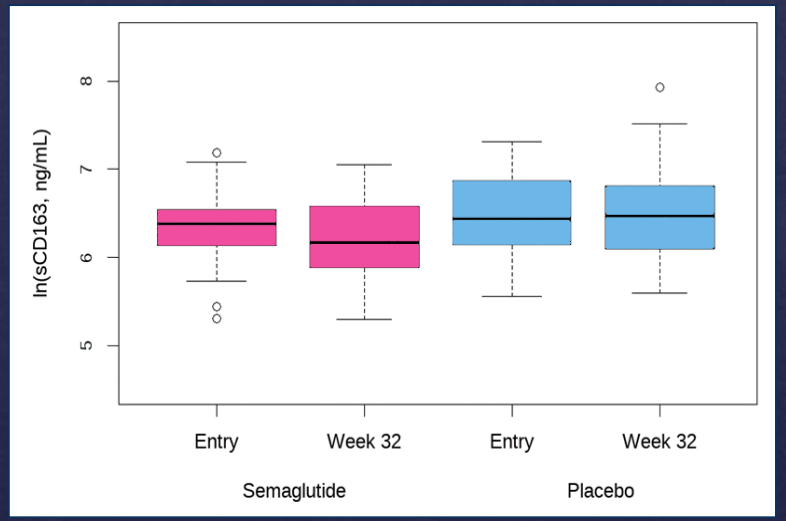
**effect sizes based on β coefficient in sex-adjusted multiplicative GEE regression models; % changes exponentiated with formula: $100(e^{\beta}-1)$

Effects of Semaglutide on Inflammation and Immune Activation

Summary of key linear regression models adjusted for baseline marker values, smoking, male sex ± age*







hsCRP
-39.9%

IL-6
-18.8%

sCD163
-12.3%

Eckard, CROI 2024, Abstract 798

*β coefficients estimate adjusted effects of semaglutide treatment vs. placebo at 32 weeks; % change estimates calculated using the formula: $100(e^{\beta}-1)$

ln(hsCRP): β -0.51, 95% CI [-0.87, -0.15]; p=0.006

ln(sCD163): β -0.13, 95% CI [-0.26, -0.002]; p=0.046

ln(IL-6): β -0.21, 95% CI [-0.44, 0.02]; p=0.074

Conclusions

- The newest diabetes medications have revolutionized the treatment of diabetes
- Metformin no longer always first line
  - CVD--> GLP-1 RA
  - HF-->SGLT2i
  - CKD--> SGLT2i
- GLP-1 RA and SGLT2i also have benefits in people without DM
- GLP-1 RA and dual agonists are also highly effective in treatment of obesity and have a CVD benefit. However, long term safety unclear.
- Studies in PWH are limited. Likely similar weight loss effect.

Thank You for Your Attendance!

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