

Diabetes and Obesity

Considerations for weight loss management in prevention and treatment of type 2 diabetes

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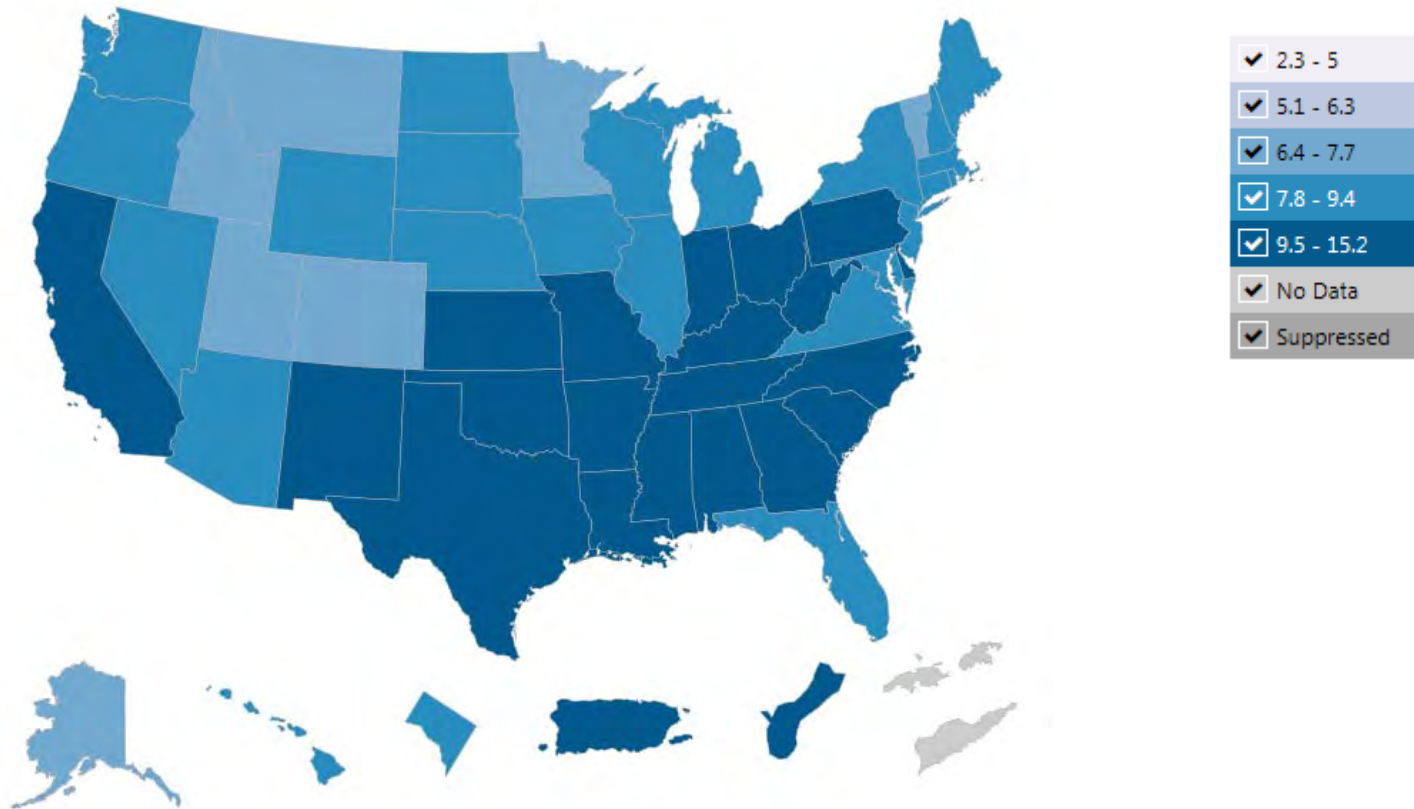
Disclosures

- Novo Nordisk – Consultant, Speaking Honoraria
- Sanofi – Consultant
- Lilly - Consultant

D Diabetes

1. “Diabesity”
2. Diabetes prevention
3. Effects of weight loss in diabetes
4. Choosing anti-diabetes pharmacotherapy
5. Choosing surgery
6. Medication adjustment

30.3 Million Adults with Diabetes



By 2050 there will be roughly 84 million (21% of population)
Costs for diabetes in the US \$327 billion in 2017

CDC, October 2019

Illinois

Health and Economic Burden



- Prevalence 9.9% = 971,000 people
- Incidence 66,000 new diagnosed cases/yr
- Total Cost \$8,585,600,000 per year

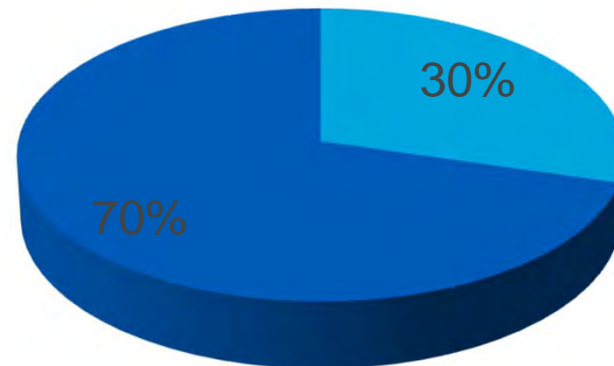
Diabetes at NorthShore

Diabetes and Obesity Prevalence

**% of Diabetes Among BMI >25
150,000 patients**



■ Diabetes
■ No Diabetes



Weight loss in diabetes prevention: DPP

The New England Journal of Medicine

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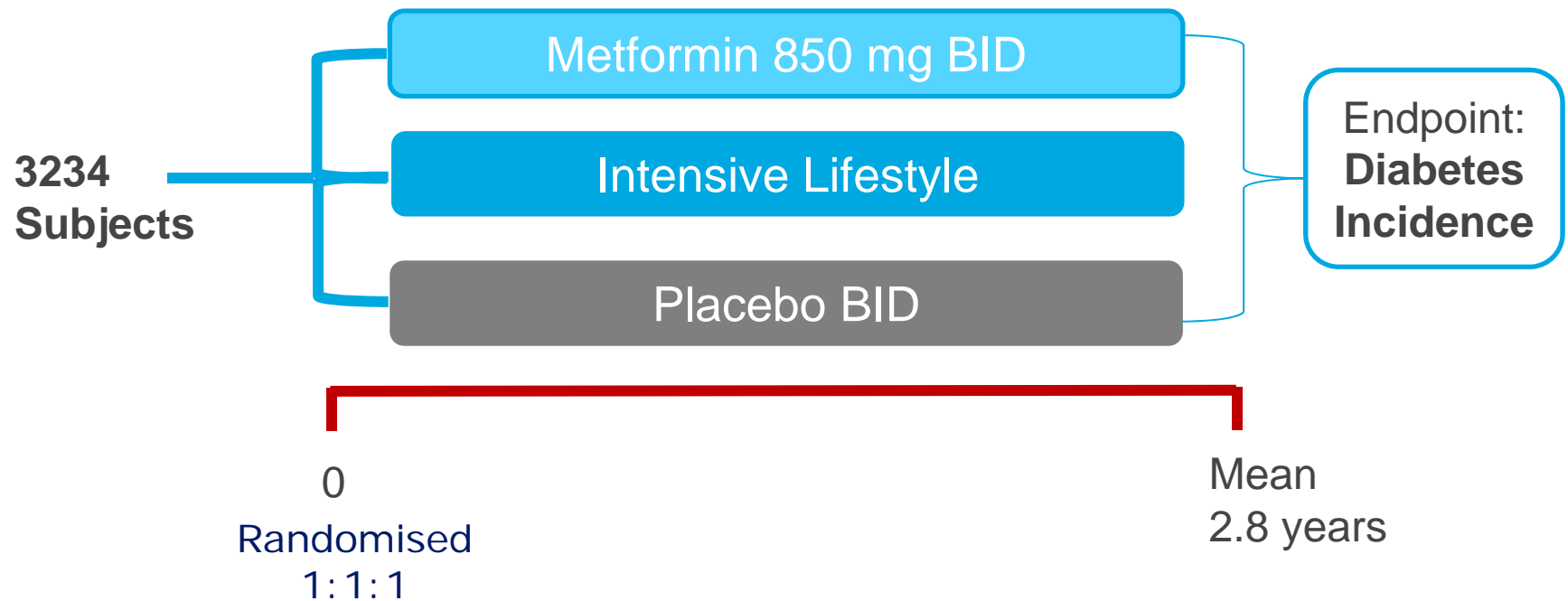
REDUCTION IN THE INCIDENCE OF TYPE 2 DIABETES WITH LIFESTYLE
INTERVENTION OR METFORMIN

DIABETES PREVENTION PROGRAM RESEARCH GROUP*

Diabetes Prevention Program (DPP) Study Design

Inclusion Criteria:

- >25 y/o
- Fasting glucose 95-124 mg/dl
- 2hr post 75g OGTT 140-199 mg/dl



DPP.NEJM.2002

DPP: Standard vs Intensive Lifestyle

Standard Lifestyle

- Written Instructions
- 20-30 minute individual session
- Reference to healthy diets
- Increase exercise

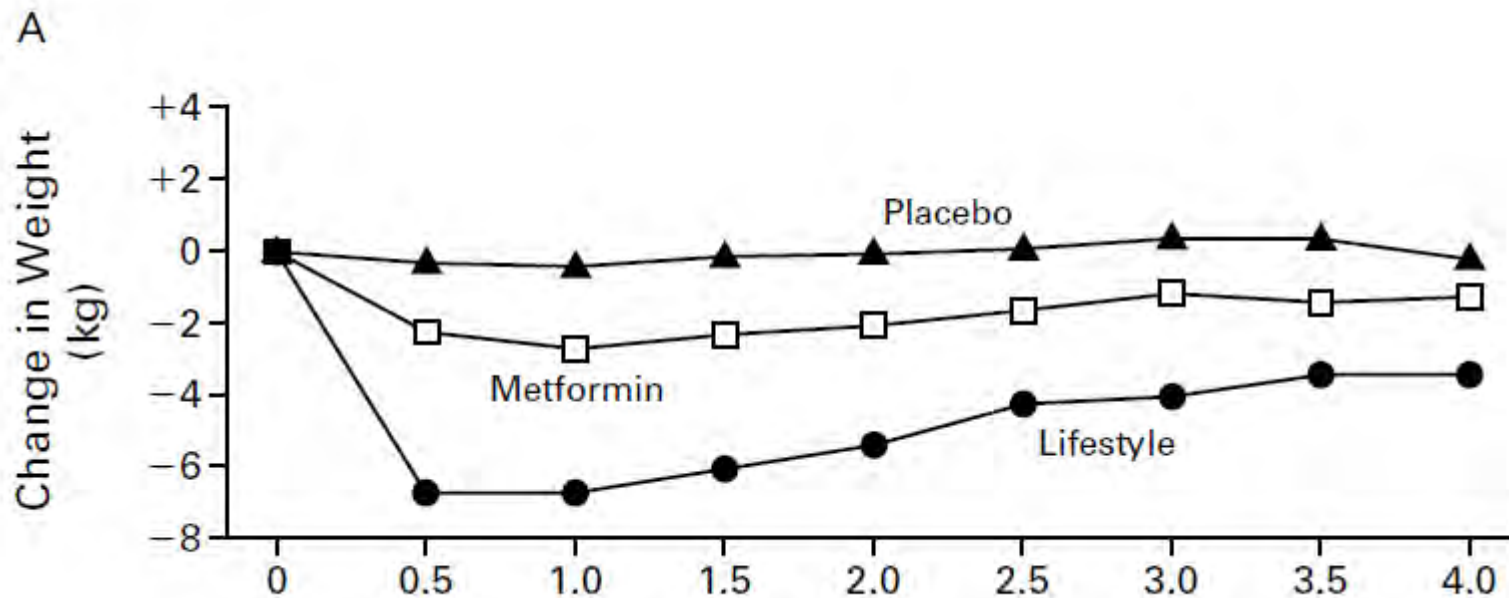
Intensive Lifestyle

- Weight loss (7% body weight)
- Healthy low calorie, low-fat diet
- 150 minutes/week of moderate intensity physical activity
- 16-lesson curriculum in-person one-on-one during first 24 weeks

DPP.NEJM.2002

Weight loss by treatment group

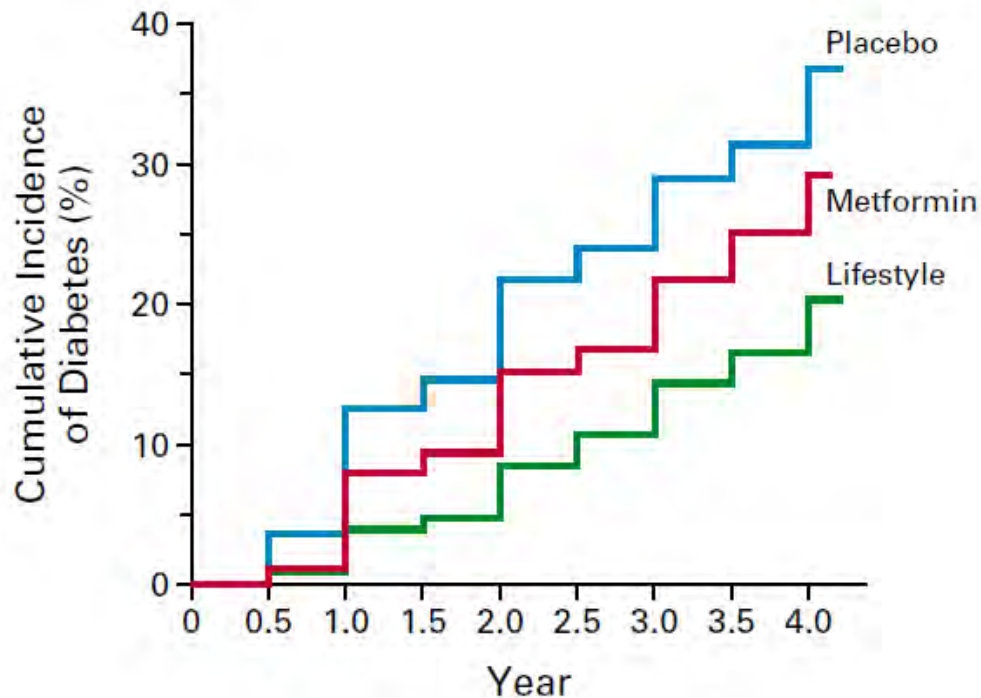
Lifestyle group lost on average 7% body weight



DPP.NEJM.2002

DPP Results – Weight loss is important

Key take-away – Lower risk and low number needed to treat to prevent diabetes



Risk of DM was:
58% lower in Lifestyle
31% lower in Metformin
compared to placebo

Number need to treat
(NNT) to prevent DM
7 people in Lifestyle
14 in Metformin

DPP.NEJM.2002

Question 1

The participants in the Diabetes Prevention trial were randomized to standard of care with placebo pill, metformin 850mg twice daily, or lifestyle intervention. Compared to placebo the following interventions lowered diabetes risk as follows:

- A) Metformin 20%, Lifestyle 10%
- B) Metformin 10%, Lifestyle 30%
- C) Metformin 31%, Lifestyle 58%

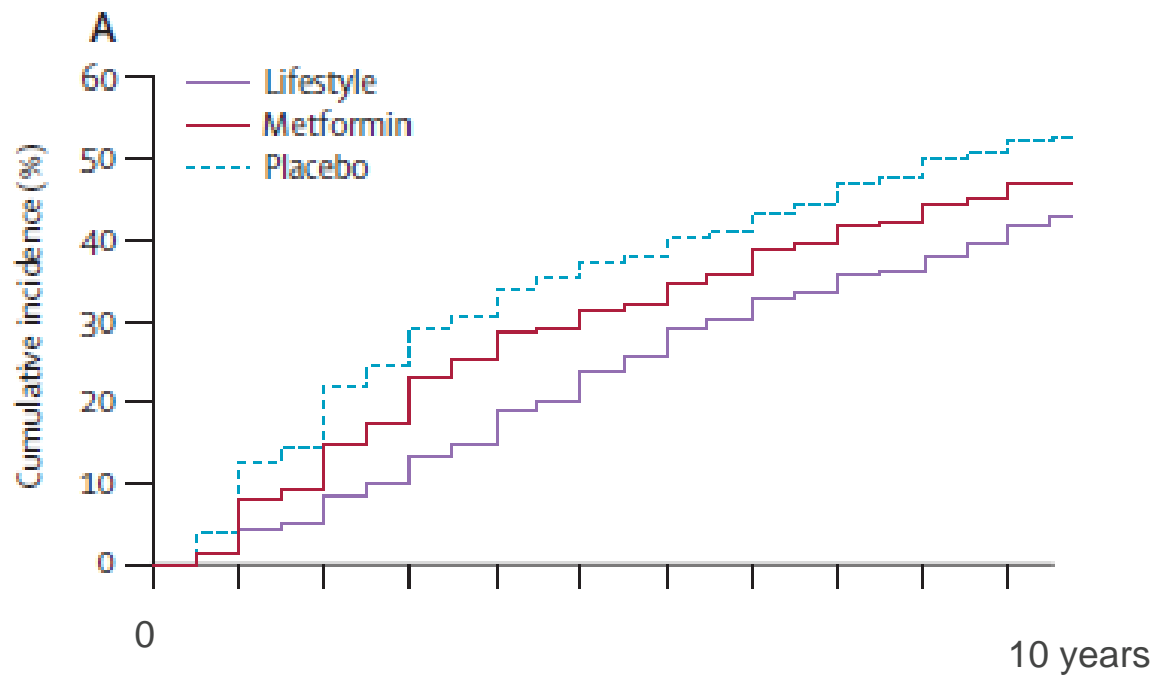
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Long-term follow-up in DPP → DPPOS

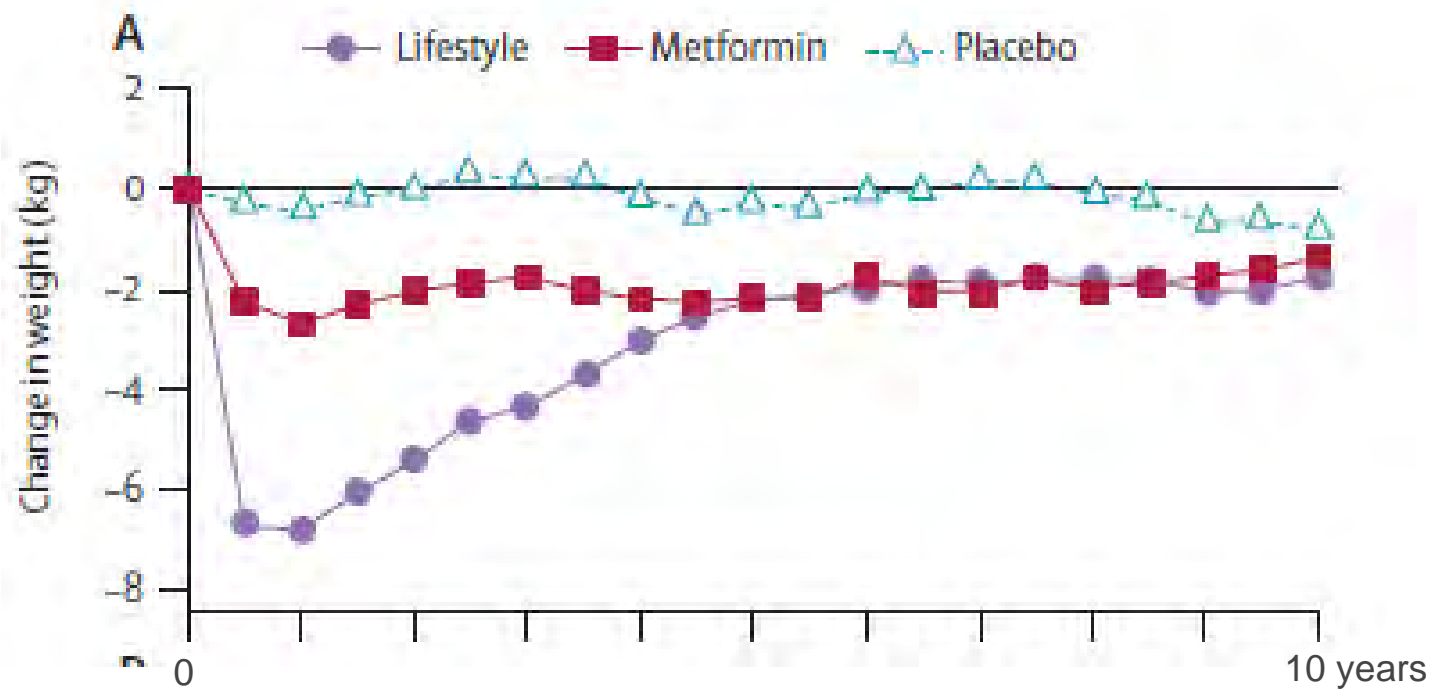
10 years of follow-up since randomization



Risk of DM was:
35% lower in Lifestyle
18% lower in Metformin
compared to placebo

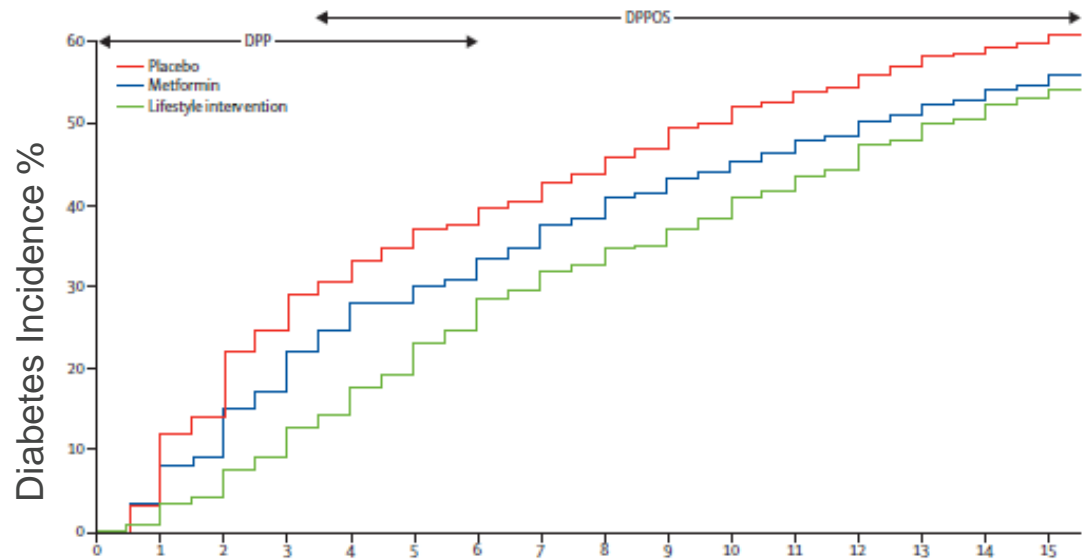
DPPOS.Lancet.2009

An illustration of metabolic memory



DPPOS. *Lancet*. 2009

Weight loss is worth the investment



DPPOS.Lancet.2015

Weight loss in diabetes

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

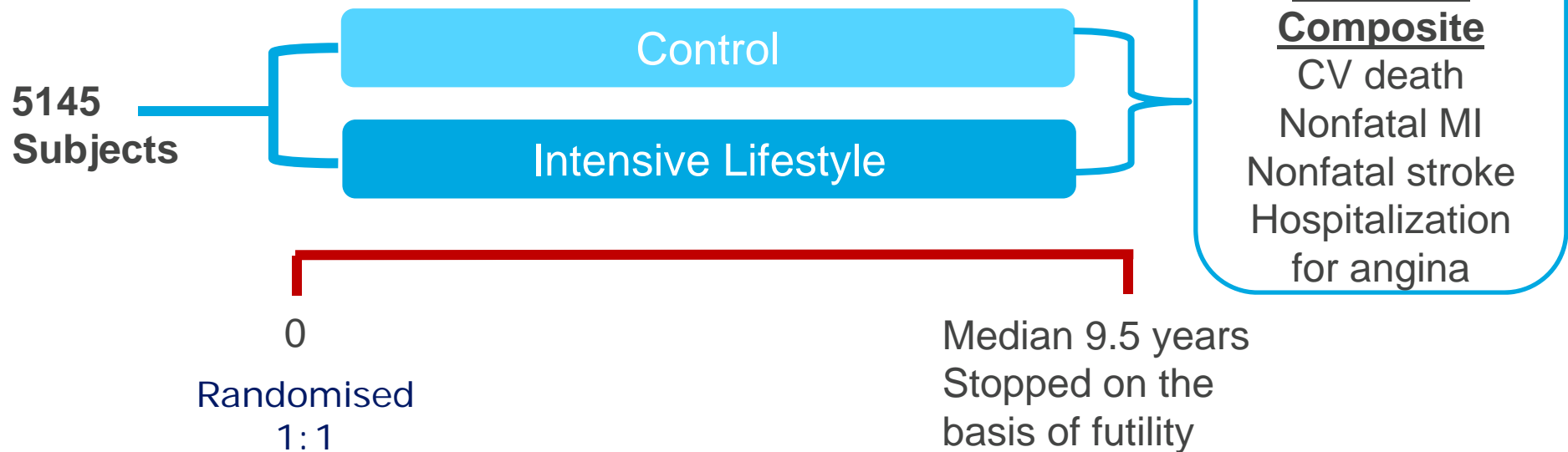
Cardiovascular Effects of Intensive Lifestyle Intervention in Type 2 Diabetes

The Look AHEAD Research Group*

Look AHEAD Study Design

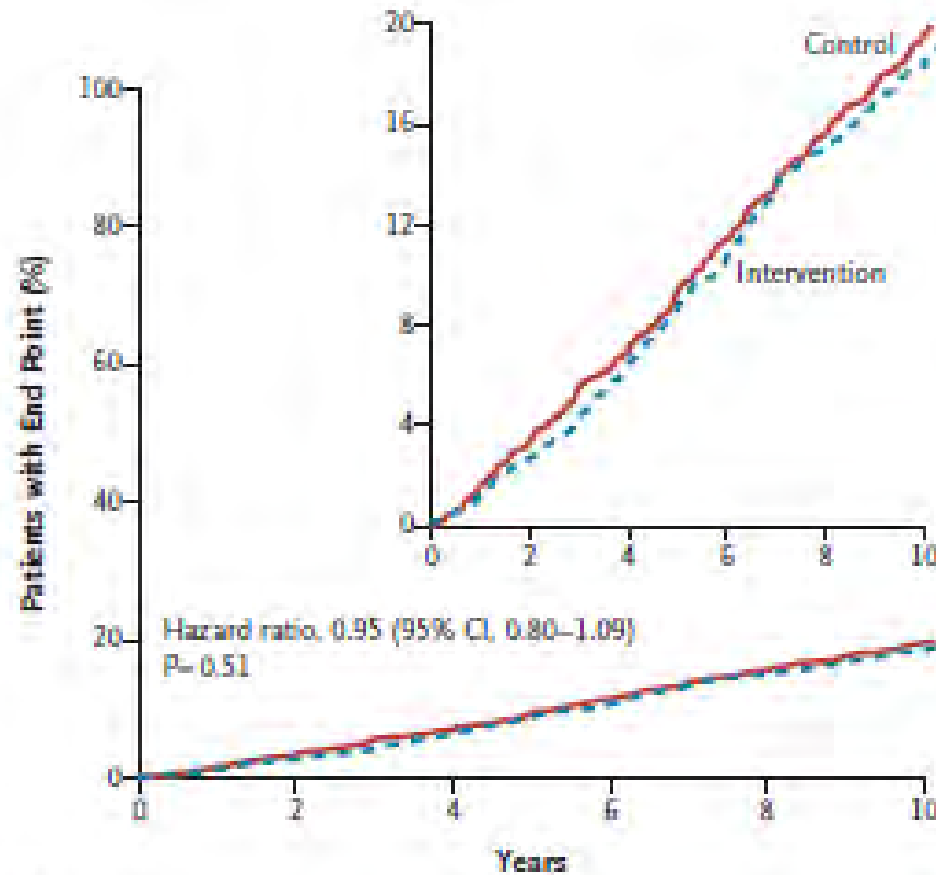
Inclusion Criteria:

- >45-75 y/o
- T2D
- BMI \geq 25
- HbA1c \leq 11%



Look AHEAD. *NEJM*. 2013

Look AHEAD: No benefit in terms of 4P MACE

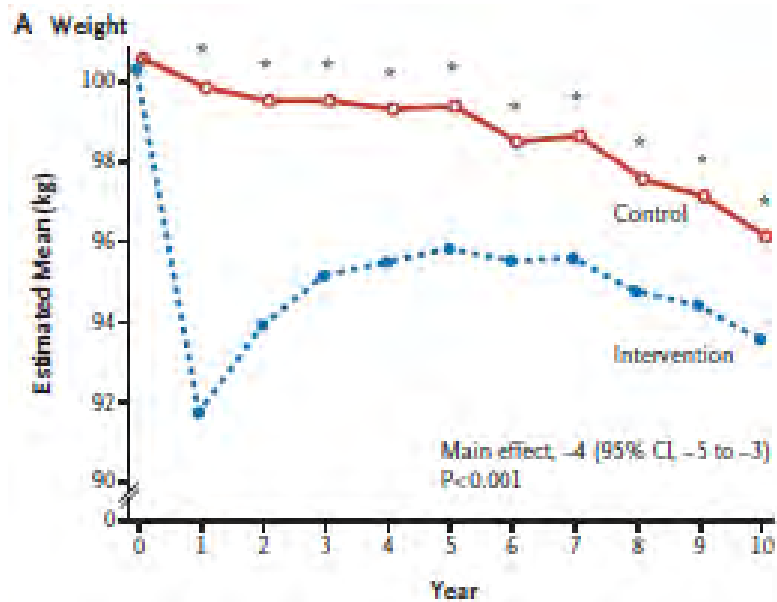


No. at Risk						
Control	2575	2425	2296	2156	2019	688
Intervention	2570	2447	2326	2192	2049	505

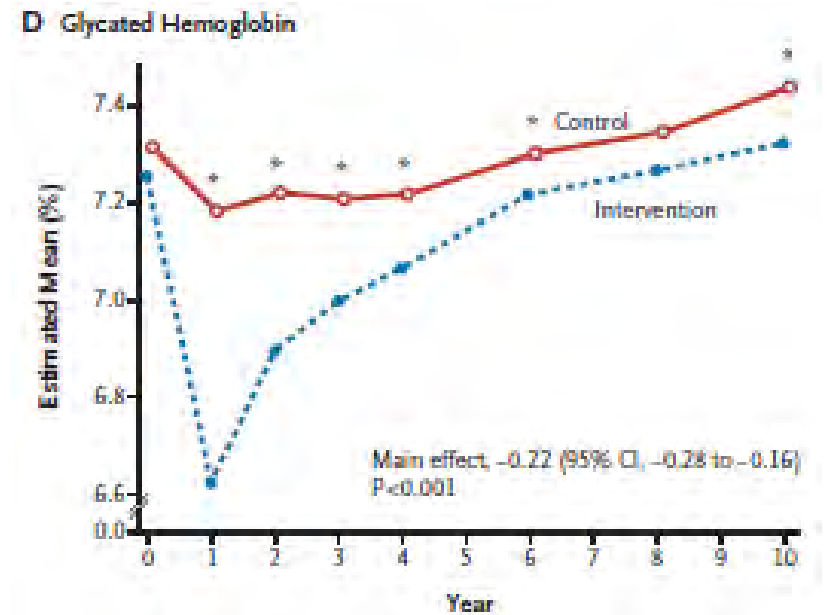
Look AHEAD. *NEJM*. 2013

A1c and weight loss in Look AHEAD

Weight



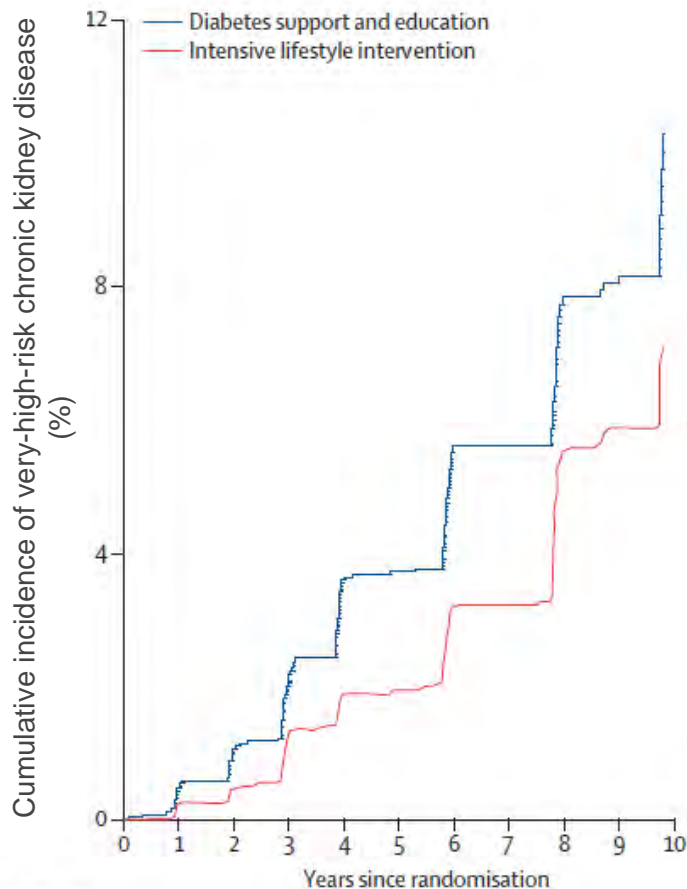
HbA1c



Look AHEAD. *NEJM*.2013

Weight loss in T2D influences CKD risk

Lower cumulative risk of high-risk CKD in patients in the Intensive Arm



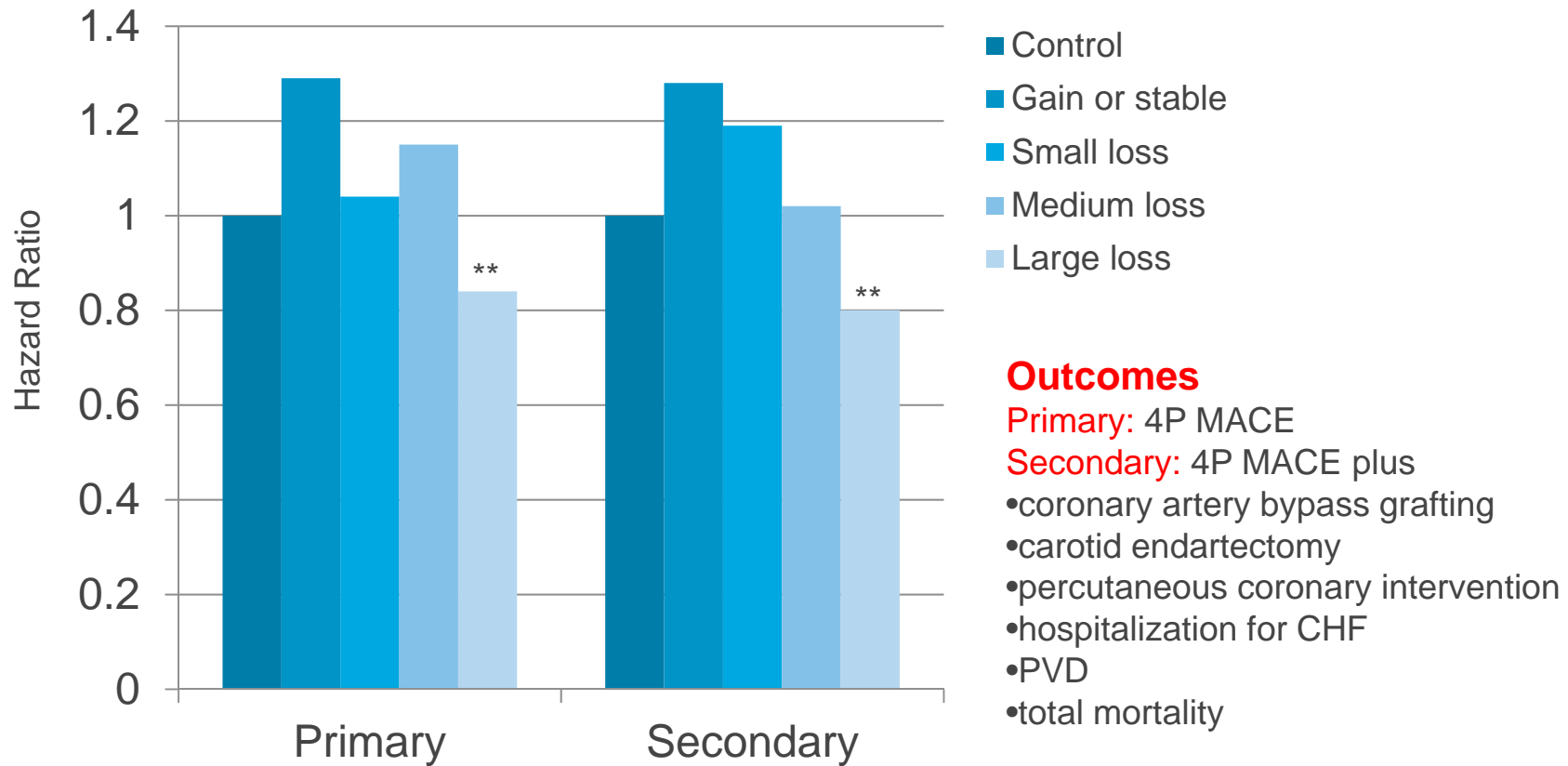
Number at risk	0	1	2	3	4	5	6	7	8	9	10
Diabetes support and education	2408	2325	2203	2092	1914	854					
Intensive lifestyle intervention	2423	2371	2275	2180	1987	889					

Outcome: High-risk CKD

- eGFR less than 30, or
- eGFR less than 45 and urine ACR at least 30
- eGFR less than 60 mL/min and urine ACR
- than 300
- Renal replacement therapy

Look AHEAD. *Lancet Diabetes Endo*.2014

Magnitude of weight loss influence outcomes



Look AHEAD. *Lancet Diabetes Endo*.2016

Choosing Anti-diabetes therapy that promote weight loss

Supported by ADA guidelines

GLP-1RA

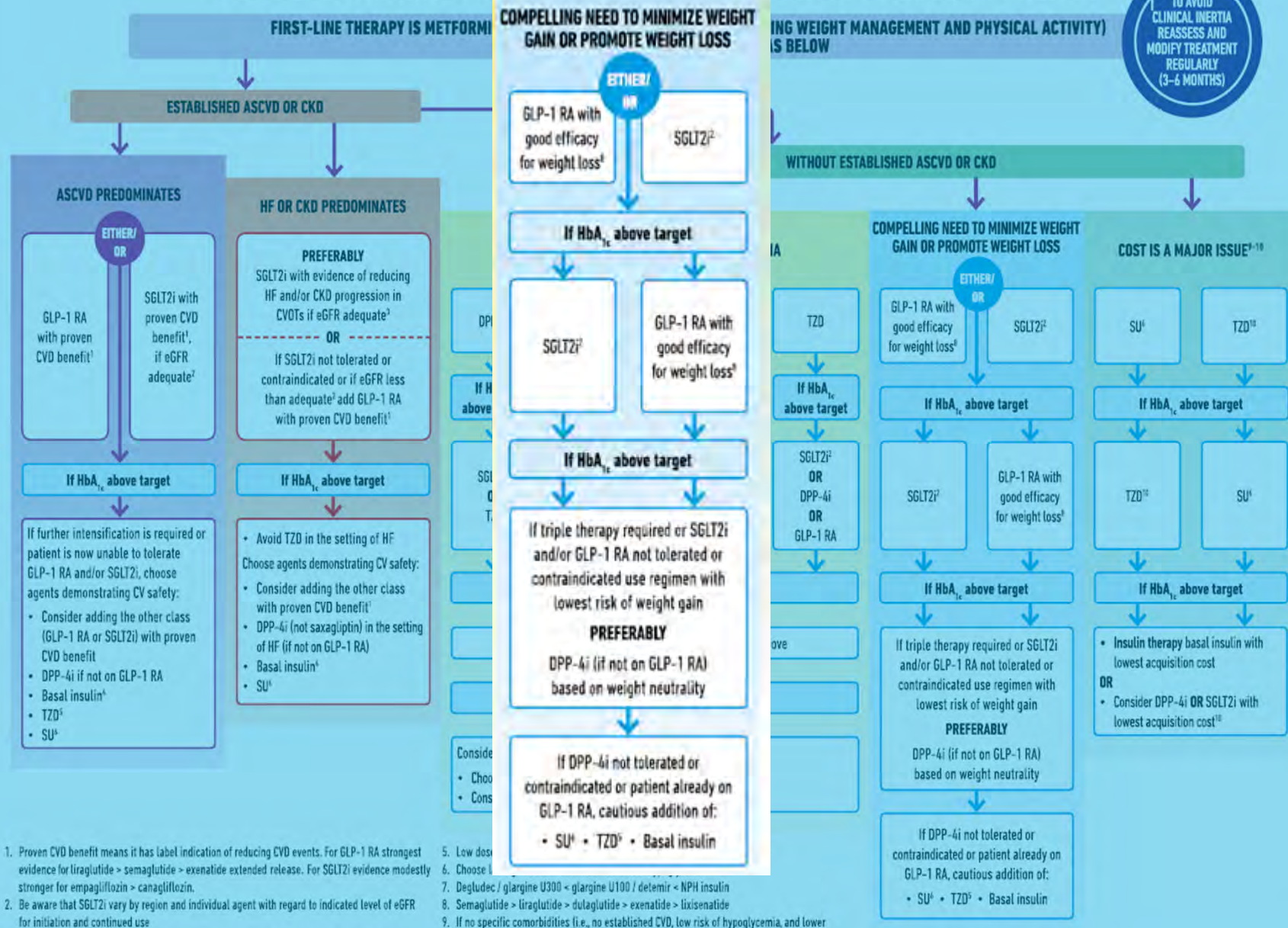


SGLT2i/GLP-1RA (oral semaglutide)



GLUCOSE-LOWERING MEDICATION IN TYPE 2 DIABETES: OVERALL APPROACH

TO AVOID CLINICAL INERTIA REASSESS AND MODIFY TREATMENT REGULARLY (3-6 MONTHS)



1. Proven CVD benefit means it has label indication of reducing CVD events. For GLP-1 RA strongest evidence for liraglutide > semaglutide > exenatide extended release. For SGLT2i evidence modestly stronger for empagliflozin > canagliflozin.

2. Be aware that SGLT2i vary by region and individual agent with regard to indicated level of eGFR for initiation and continued use

3. Low dose

4. Choose

5. Degludec / glargine U300 < glargine U100 / detemir < NPH insulin

6. Semaglutide > liraglutide > dulaglutide > exenatide > lixisenatide

7. If no specific comorbidities (i.e., no established CVD, low risk of hypoglycemia, and lower

Targeting the underlying pathophysiology

Actions of a GLP-1RA

BRAIN

*Decreased energy intake
Increased satiety*



PANCREAS

*Glucose-dependent insulin
and glucagon secretion
Insulin synthesis*



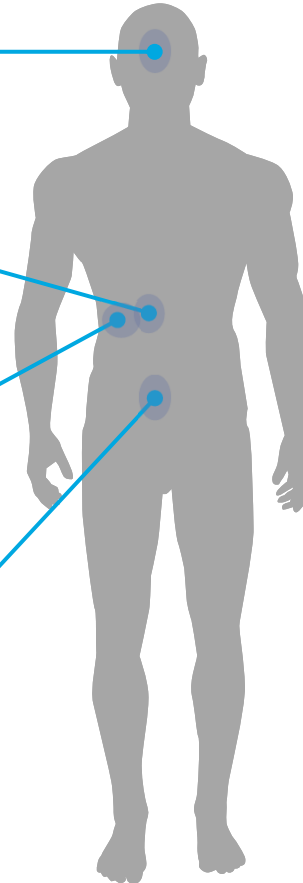
LIVER

*Inhibition of hepatic
glucose production*



GI TRACT

Inhibition of gastric emptying

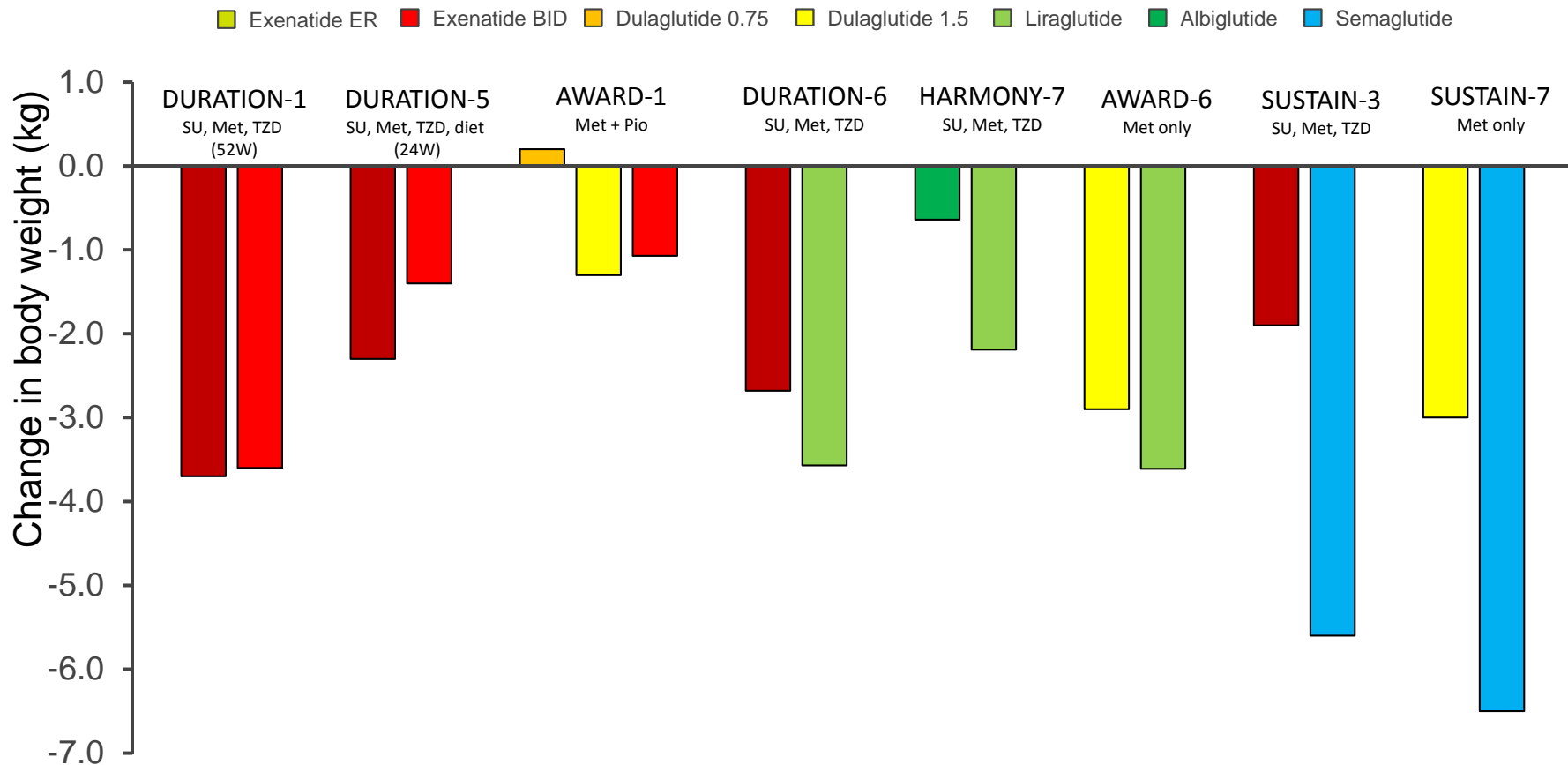


GLP-1RA

- Exenatide
- Exenatide ER
- Liraglutide
- Lixisenatide
- Dulaglutide
- Semaglutide
- Semaglutide (Oral)

Baggio LL, Drucker DJ. *Gastroenterol* 2007; Niswender KD. *Postgrad Med* 2011

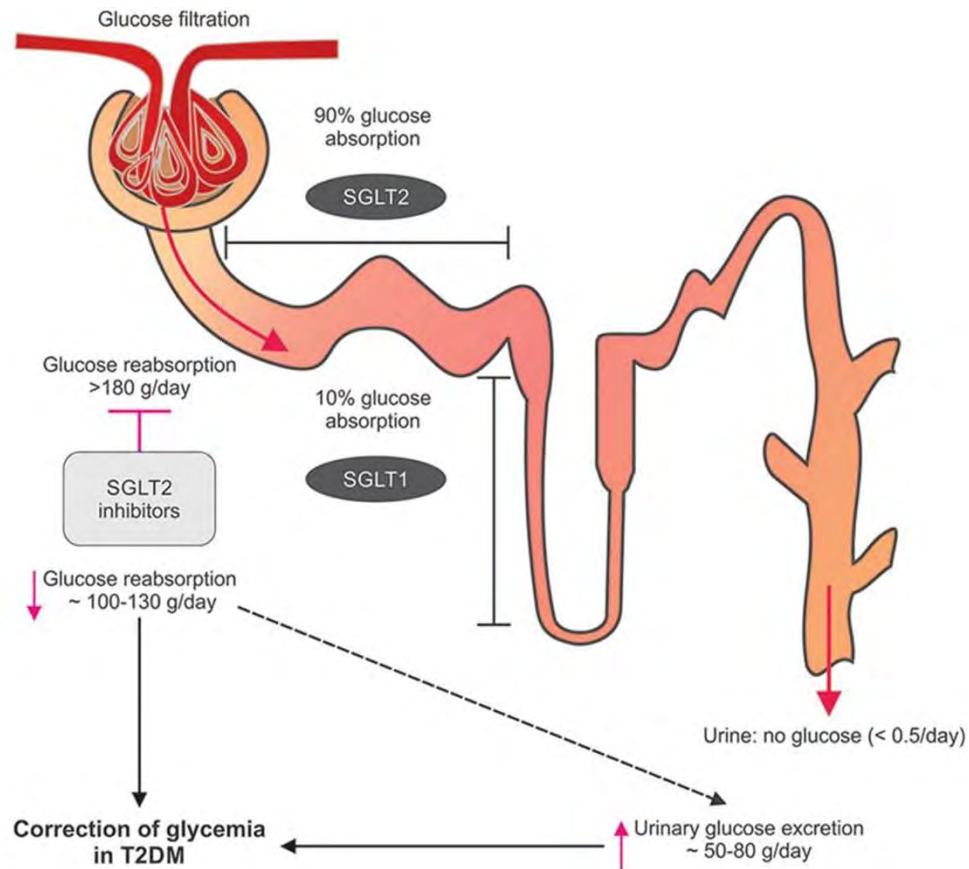
Weight change for GLP-1RAs: Head to Head



Drucker DJ. *Lancet*.2008; Blevins T. *JCEM*.2011; Wysham C. *Diabetes Care*.2014; Buse JB. *Lancet*.2013; Pratley RE. *Lancet Diabetes Endo*.2014; Dungan KM. *Lancet*.2014; Ahmann AJ. *Diabetes Care*.2017; Pratley RE. *Lancet Diab and Endo*. 2018

SGLT2 inhibitors

Block reabsorption of glucose at the proximal tubule of the kidney



SGLT-2 inhibitors

- Canagliflozin
- Dapagliflozin
- Empagliflozin
- Ertugliflozin
- Sotagliflozin

Weight loss: 2-3 kg

Kalra, et al. *Adv Therapy*. 2016

Prevent weight gain when you are considering adding insulin

Scenario #1

HbA1c > 7% on oral medications

Next step: Basal insulin?

Study: DUAL V

Scenario #2

HbA1c > 7% on oral meds and basal

Next step: Bolus insulin?

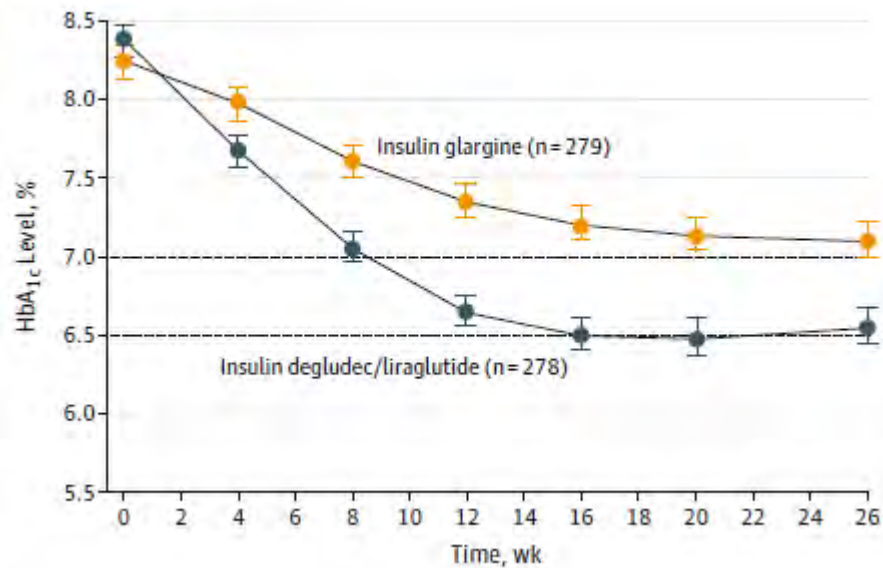
Study: DUAL VII

Adding a GLP1RA can negate weight gain from insulin!

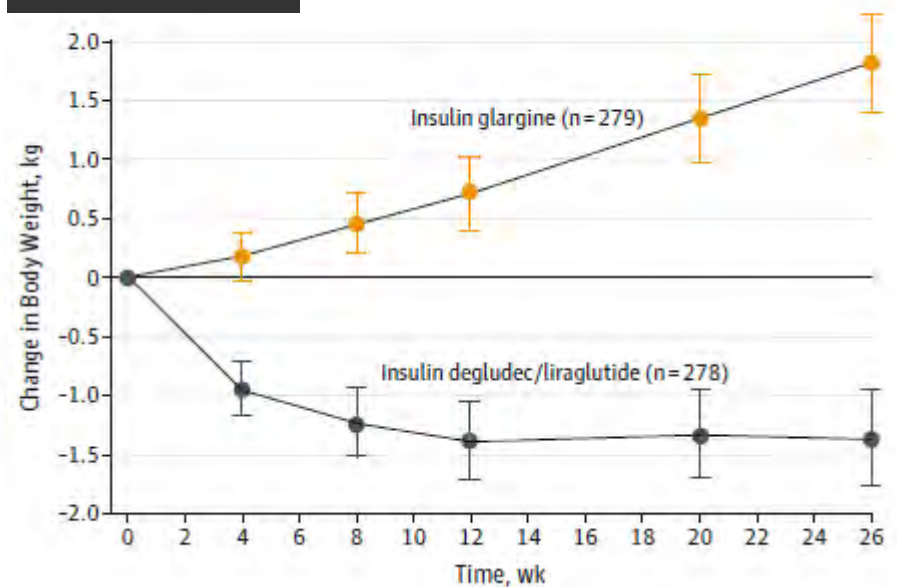
Consider fixed-ratio combination (iDegLira or IGlarLixi) or
Insulin plus GLP1 alone

DUAL V: Glargine v iDegLira on oral med

HbA1c



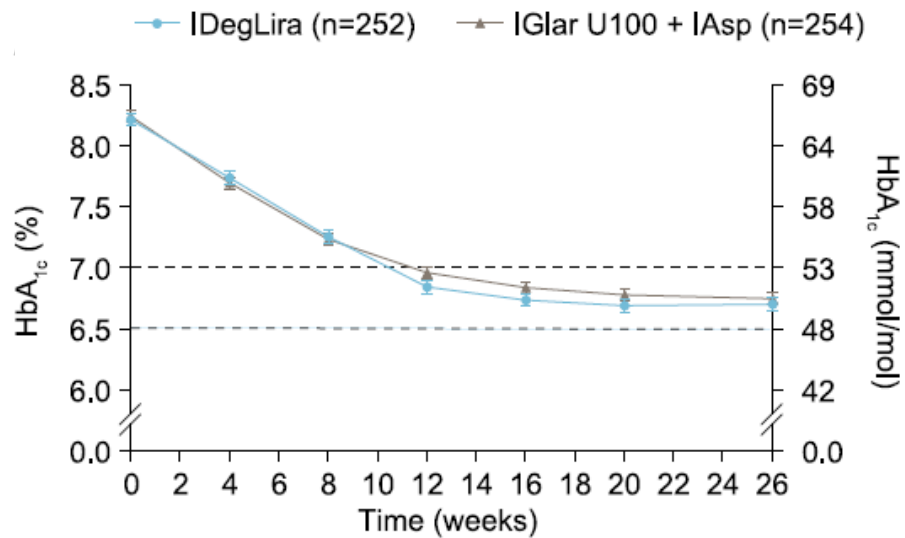
Weight (kg)



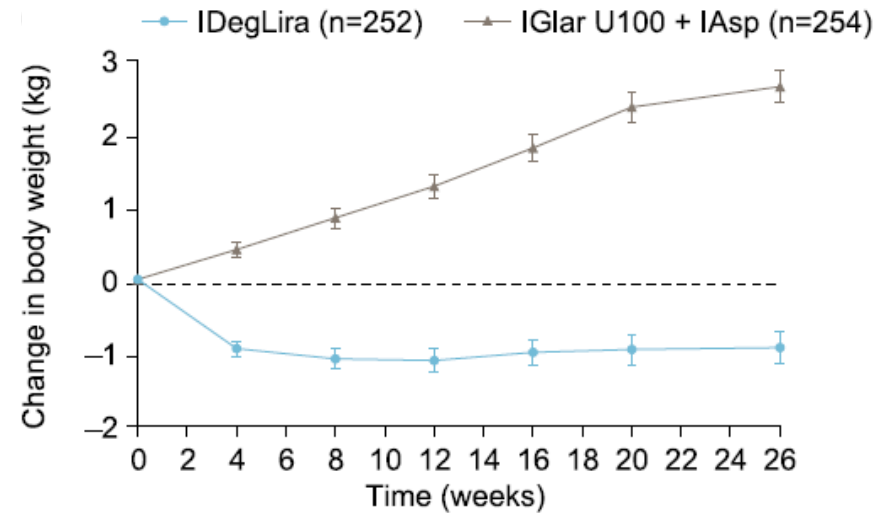
Lingvay. JAMA. 2016

DUAL VII: Basal-bolus v iDegLira add on to basal

HbA1c



Weight (kg)



Billings LK. *Diabetes Care*. 2018

GLP-1RA and SGLT1i are effective in reducing composite MACE

Major Adverse Cardiac Events

MACE 3-Point Composite

- **Non-fatal MI**
- **Non-fatal Stroke**
- **CV-related death**

LEADER (Liraglutide)
SUSTAIN (Semaglutide)
REWIND (Dulaglutide)
EMPA-REG (Empagliflozin)
CANVAS (Canagliflozin)

Question 2

Which medication reduced major adverse cardiovascular events in long-term cardiovascular outcome trials?

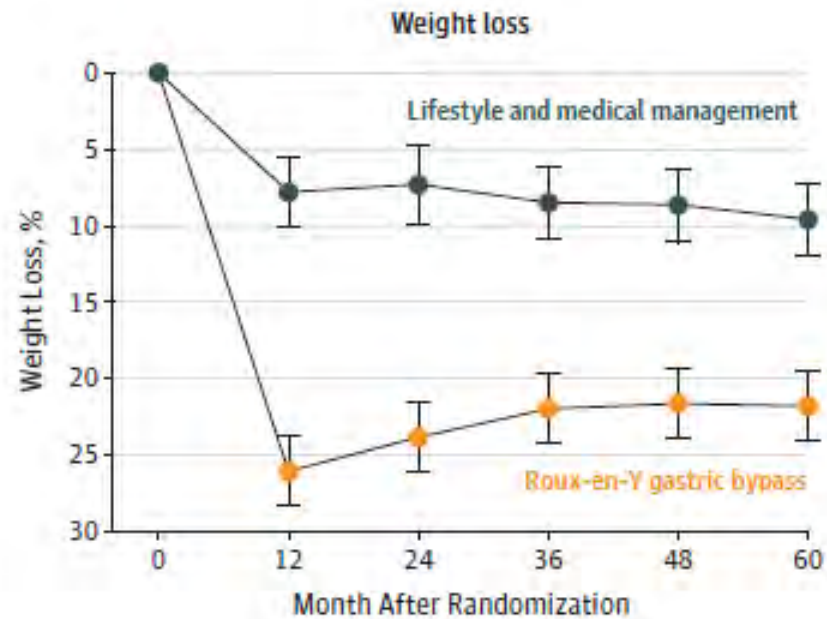
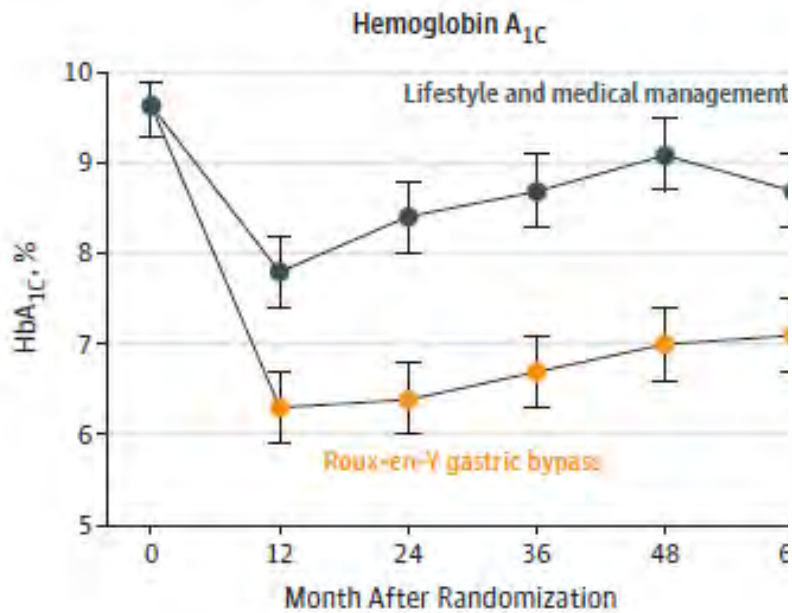
- a) Liraglutide
- b) Exenatide
- c) Dulaglutide
- d) Canagliflozin
- e) Empagliflozin
- f) a, b, c
- g) a, c, d, e
- h) d, e

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- f) a, b, c
- g) a, c, d, e**
- h) d, e

Metabolic Surgery for weight loss and glucose management



Ikramuddin. *JAMA*. 2018

Medication adjustments when starting a low carbohydrate diet (LCD) <130 grams/day in T2D

Drug class	Hypo risk?	Clinical Suggestion
Sulphonylureas	Yes	Reduce (50%)/Stop; Promote weight gain
Insulin	Yes	Reduce/stop. Wean by 30-50%*
SGLT2 inhibitors	No	Continue**
Metformin	No	Continue
GLP-1RA	No	Continue
TZD	No	Stop if possible, promote weight gain
DPP-4i	No	Consider stop; Minimal efficacy; \$\$
SMBG/CGM	N/A	Ensure adequate testing for patients on hypo-risk meds

*Caution when reducing insulin if clinical suspicion of endogenous insulin insufficiency, keep 0.3u/kg/day

**SGLT2i have increased risk of DKA in insulin deficiency

Adapted. Murdoch. *Brit J of Gen Practice*.2019

Thank you!

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