Contemporary Management Strategies in Diabetes 2022

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Conflict of Interest Disclosure

Enrico Cagliero, MD

has no significant relationships with industry to report

Contemporary Management Strategies in Diabetes

- Current guidelines
  - A1c goals
  - Pharmacologic treatment of hyperglycemia
- Novel Therapies
  - GLP-1 Receptor Agonists
  - DPP-4 Inhibitors
  - SGLT-2 Inhibitors
- CVD/CKD risk reduction

Goals of Treatment

- Avoid acute complications of diabetes
- Prevent micro and macrovascular complications
- Minimize hypoglycemia
- Minimize weight gain and/or help weight loss
- Increase quality of life

HbA1c Goals

- 2018 American College of Physicians: *Clinicians should aim to achieve an HbA_{1c} level between 7% and 8% in most patients with type 2 diabetes.*
- 2018 American Association of Clinical Endocrinologists: *the AACE supports a goal A1c of < 6.5% for most patients*
- 2021 American Diabetes Association: *An A1c goal for many nonpregnant adults of < 7% is appropriate. Less stringent goals (A1c < 8.0%) may be appropriate for patients with a history of severe hypoglycemia, limited life expectancy, advanced micro or macrovascular complications, or extensive comorbid conditions.*

Individualize A1c goals !

Standards of Medical Care in Diabetes - 2022

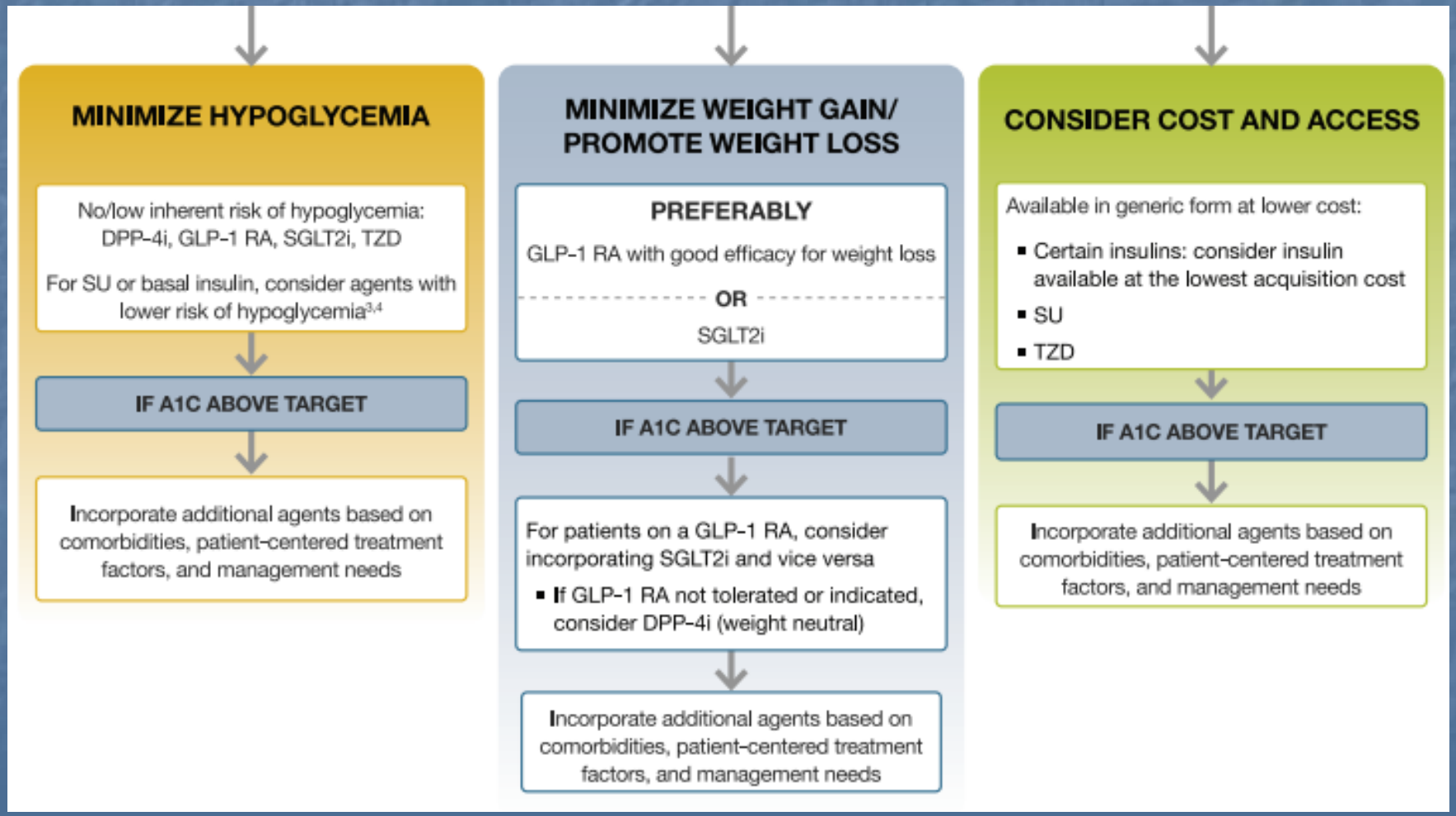
Pharmacologic Approaches to Glycemic Management

Diabetes Care 2022;45 (supplement1):S125-S143
Diabetes Care 2020;43:487-493

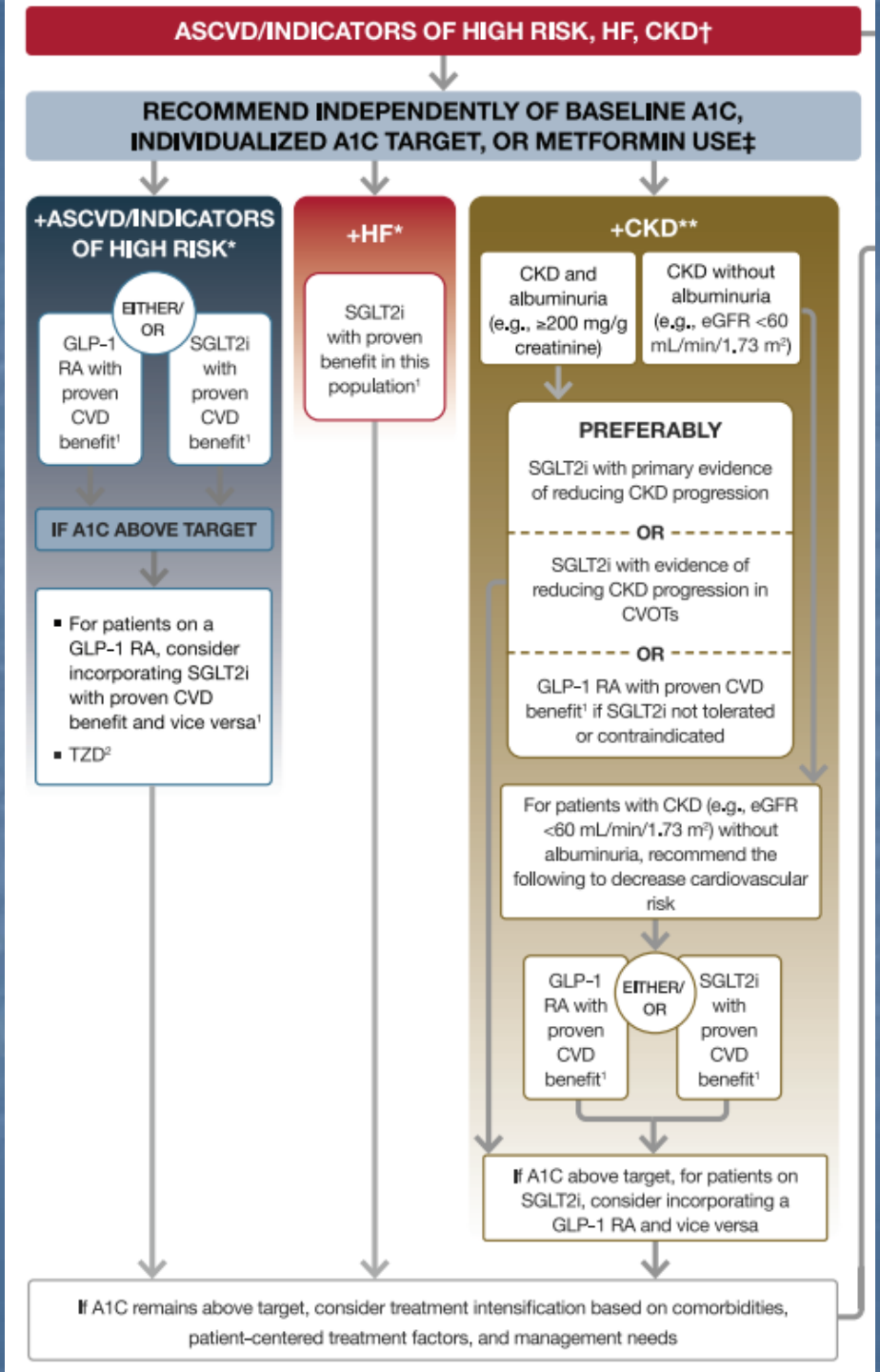
Pharmacologic Treatment of Hyperglycemia in Adults with Type 2 diabetes

First line therapy generally includes Metformin and Lifestyle modifications

In absence of ASCVD, indicators of high risk, heart failure, CKD



Diabetes Care 2022;45 (supplement1):S125-S143



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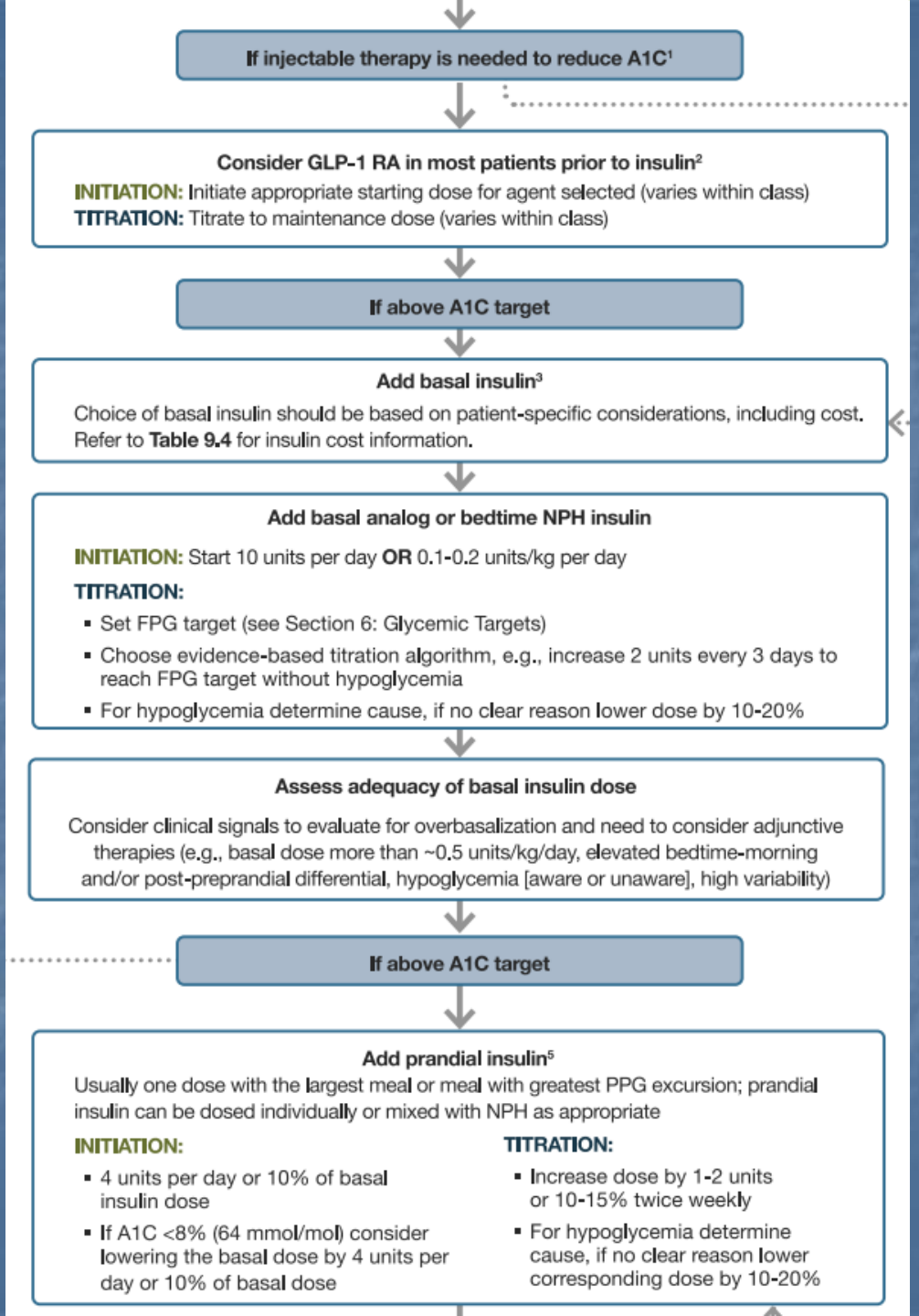


Diabetes Care 2022;45 (supplement1):S125-S143

Summary

- Start with monotherapy with Metformin unless A1c > 9% (consider starting with dual therapy), or A1c > 10% (consider injectable therapy)
- If monotherapy not effective after 3 months, proceed to dual therapy
- For patients with CVD, CKD or HF use GLP-1 RA or SGLT-2 inhibitors independent of baseline A1c
- If injectable therapy is needed, consider GLP-1 RA in most patients prior to insulin

Novel Therapies

GLP-1 agonists

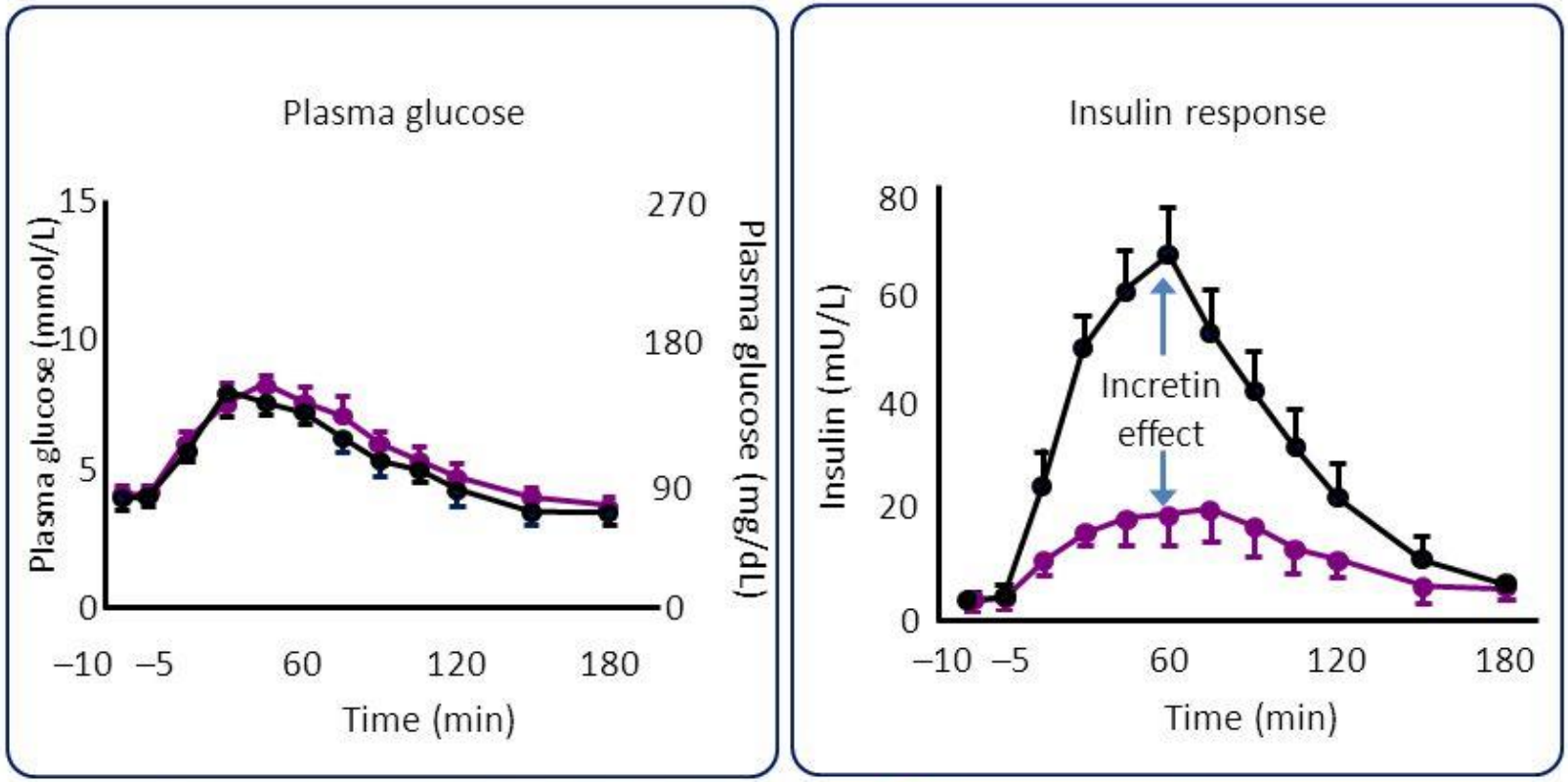
DPP-4 inhibitors

SGLT-2 inhibitors

Incretin Hormones

- Peptide hormones released by cells in the GI tract in response to nutrient stimulus
- Most potent is Glucagon-Like Peptide 1 (GLP-1)
- GLP-1 stimulates insulin secretion, suppresses glucagon secretion, delays GI tract motility and decreases appetite
- In patients with type 2 diabetes GLP-1 levels are decreased
- GLP-1 is rapidly degraded by the enzyme dipeptidyl peptidase IV (DPP IV)

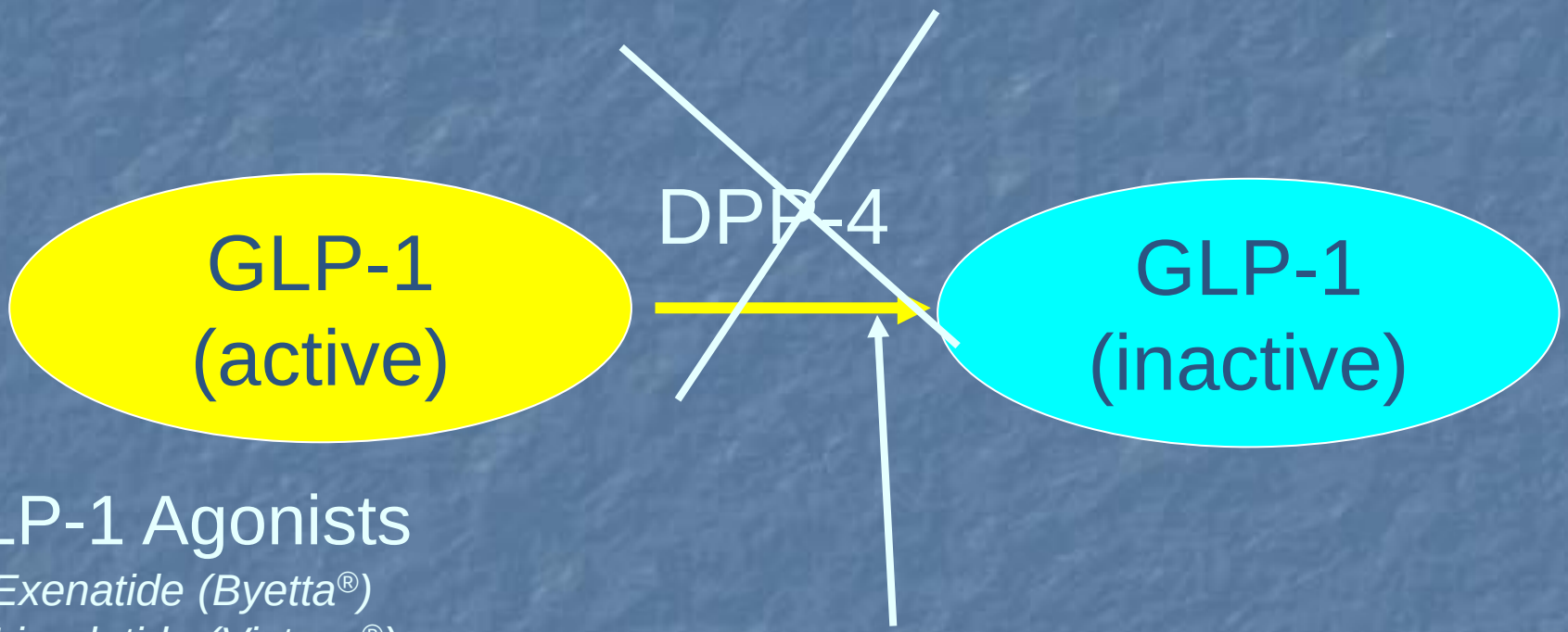
The Incretin Effect



Insulin response is greater following oral glucose than IV glucose, despite similar plasma glucose concentration.

Nauck *et al. Diabetologia* 1986;29:46–52.

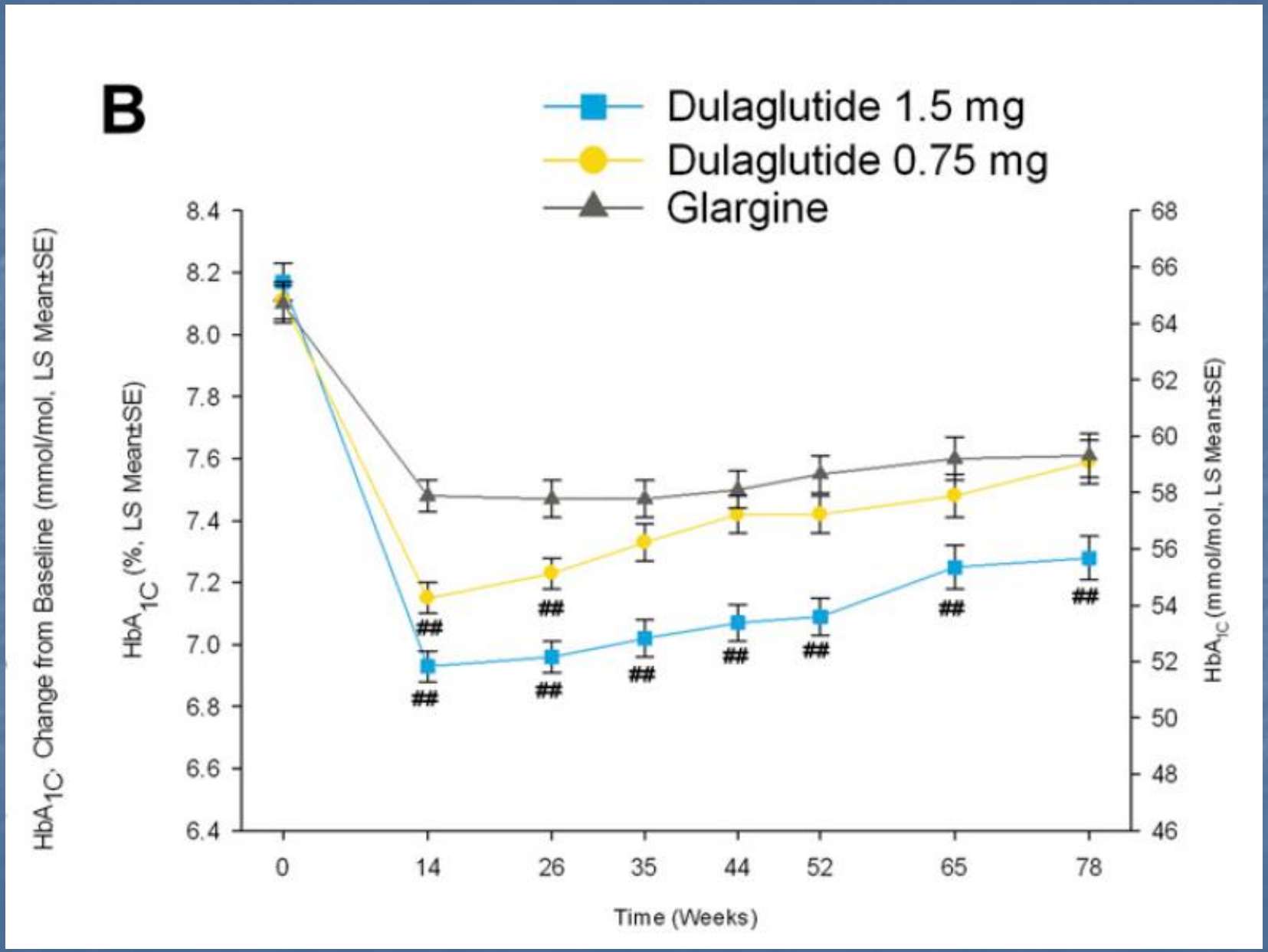
Strategies To Prolong GLP-1 Action



1. GLP-1 Agonists
   - *Exenatide (Byetta®)*
   - *Liraglutide (Victoza®)*
   - *Exenatide ER (Bydureon®)*
   - *Dulaglutide (Trulicity®)*
   - *Lixisenatide (Adlyxin®)*
   - *Semaglutide (Ozempic®)*
   - *Oral Semaglutide (Rybelsus®)*

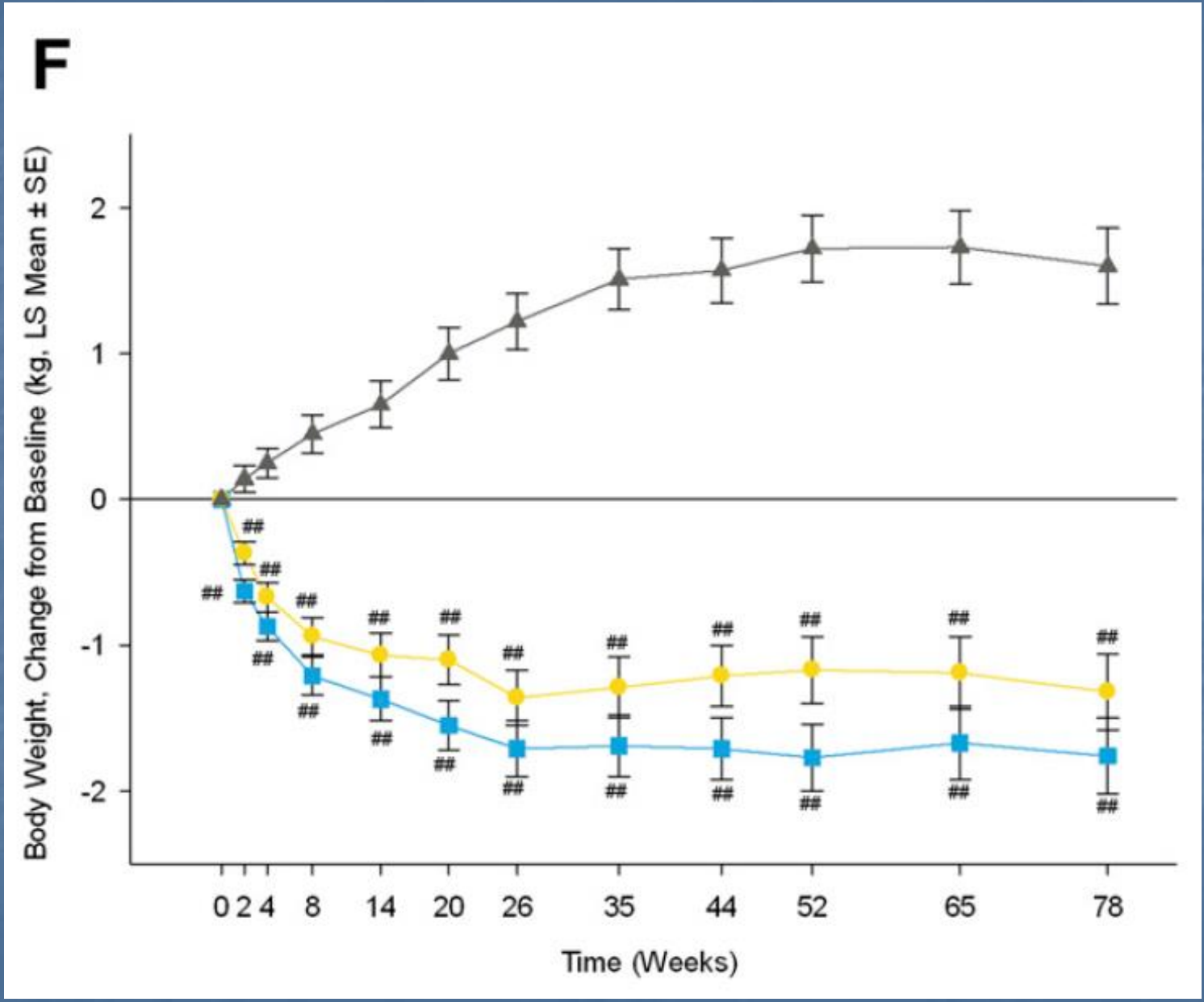
2. DPP-4 Inhibitors
   - *Sitagliptin (Januvia®)*
   - *Saxagliptin (Onglyza®)*
   - *Linagliptin (Tradjenta®)*
   - *Alogliptin (Nesina®)*

Efficacy and Safety of Once-Weekly Dulaglutide Versus Insulin Glargine



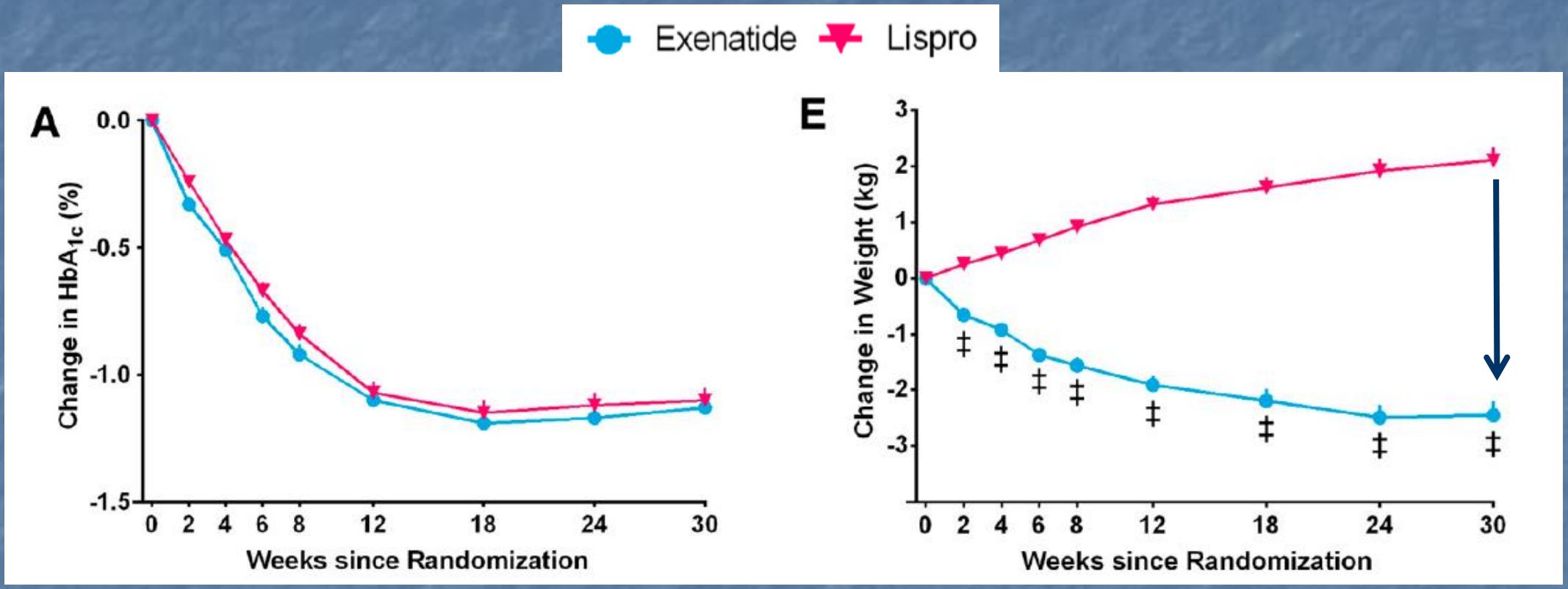
Giorgino et al: *Diabetes Care* 2015;38:2241-2249

Efficacy and Safety of Once-Weekly Dulaglutide Versus Insulin Glargine



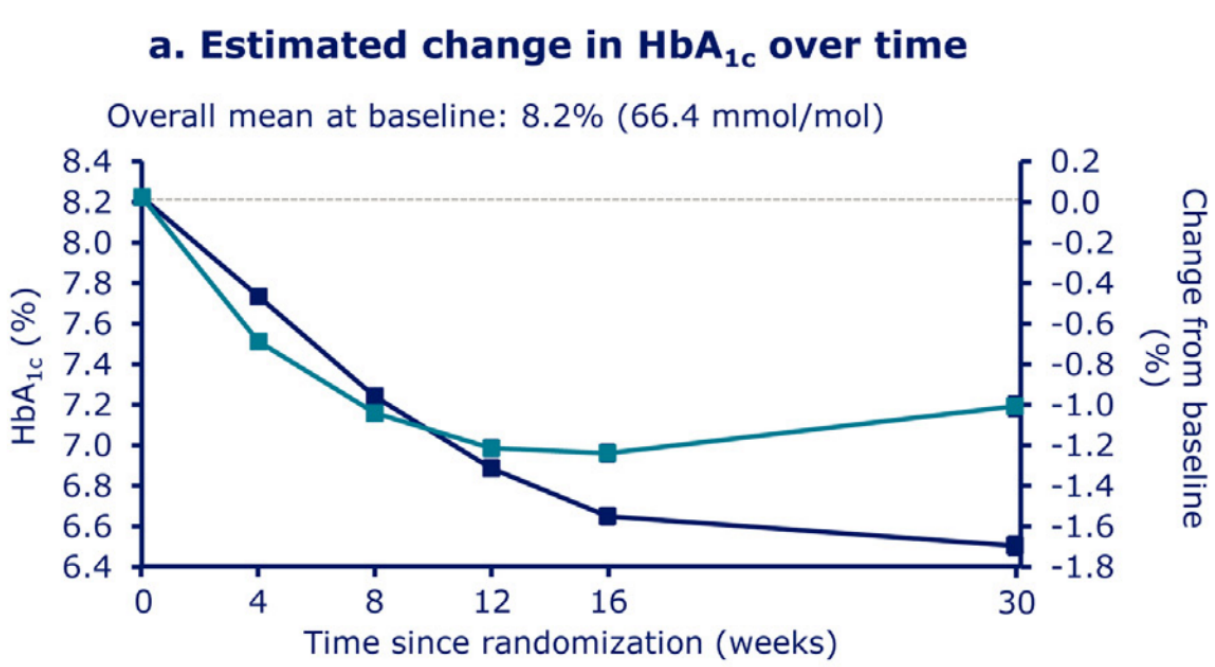
Giorgino et al: *Diabetes Care* 2015;38:2241-2249

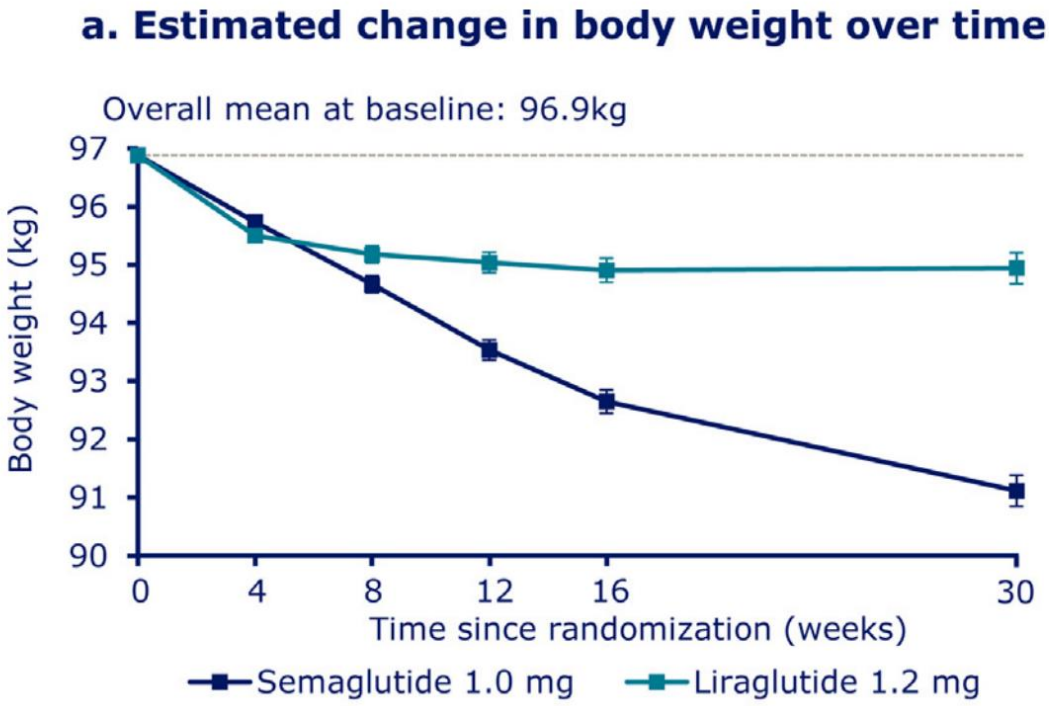
Glucagon-Like Peptide 1 Receptor Agonist or Bolus Insulin with Optimized Basal Insulin in Type 2 diabetes



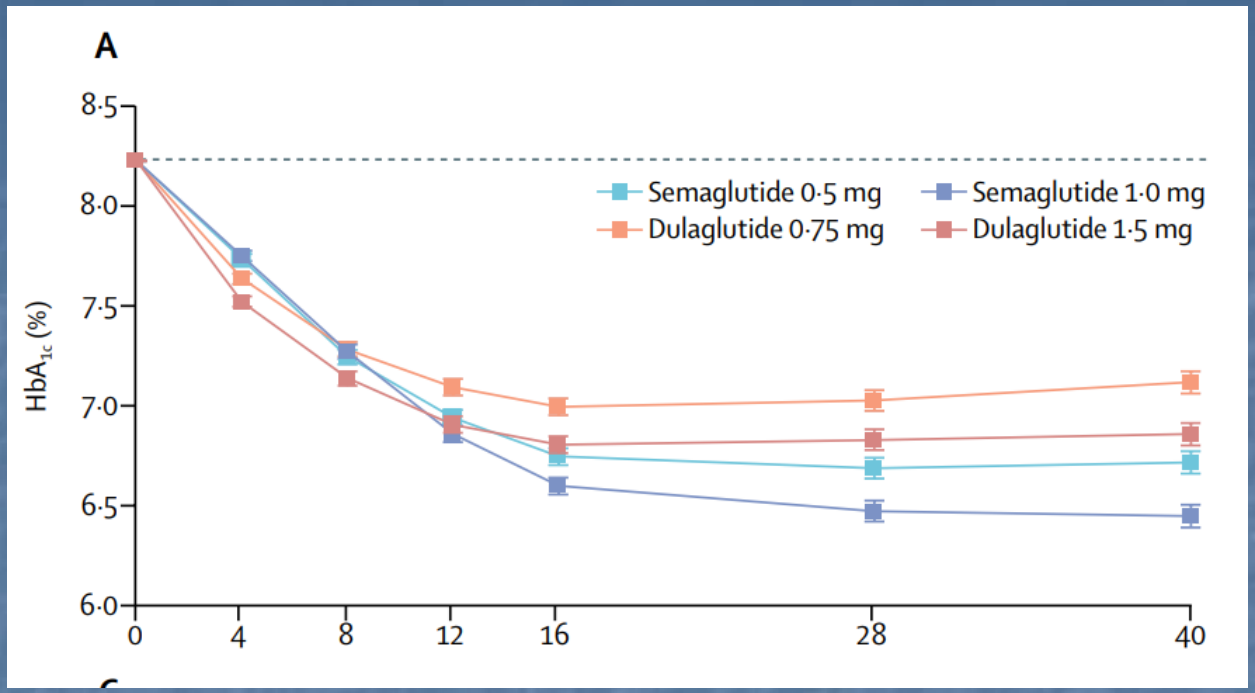
Diabetes Care 2014;37:2763-2773

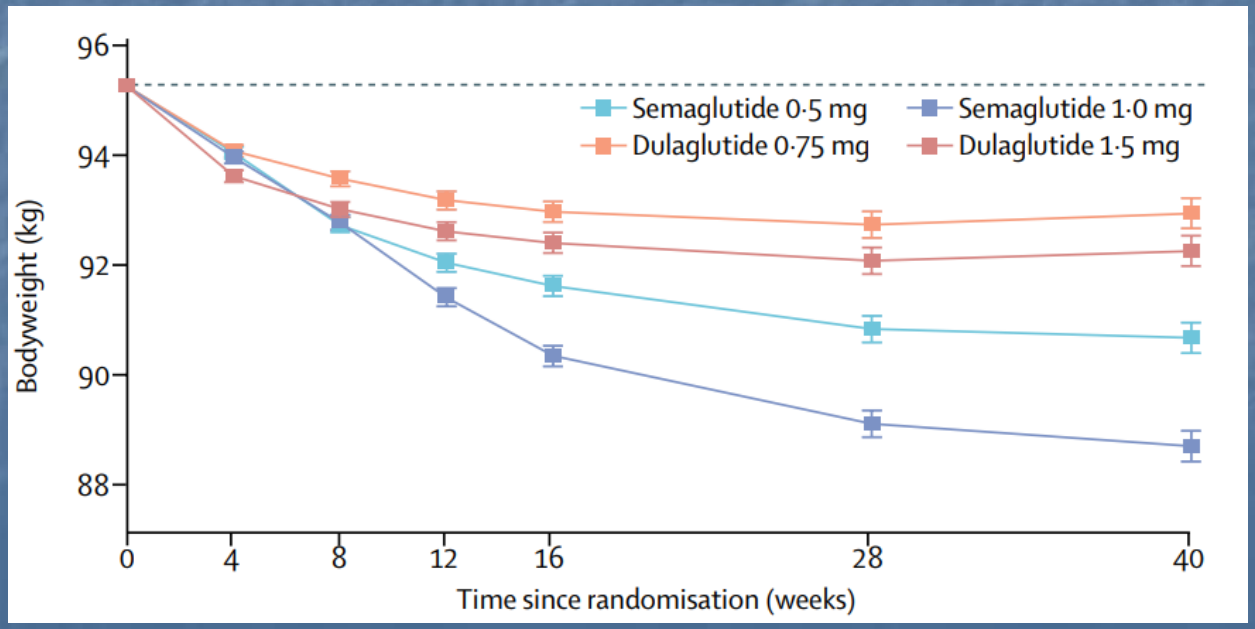
Efficacy and safety of once-weekly Semaglutide 1.0 mg vs once-daily Liraglutide 1.2 mg as add-on to 1–3 oral antidiabetic drugs in subjects with type 2 diabetes (SUSTAIN 10)





Capehorn MS et al. *Diabetes & Metabolism* 2020;46:100–109

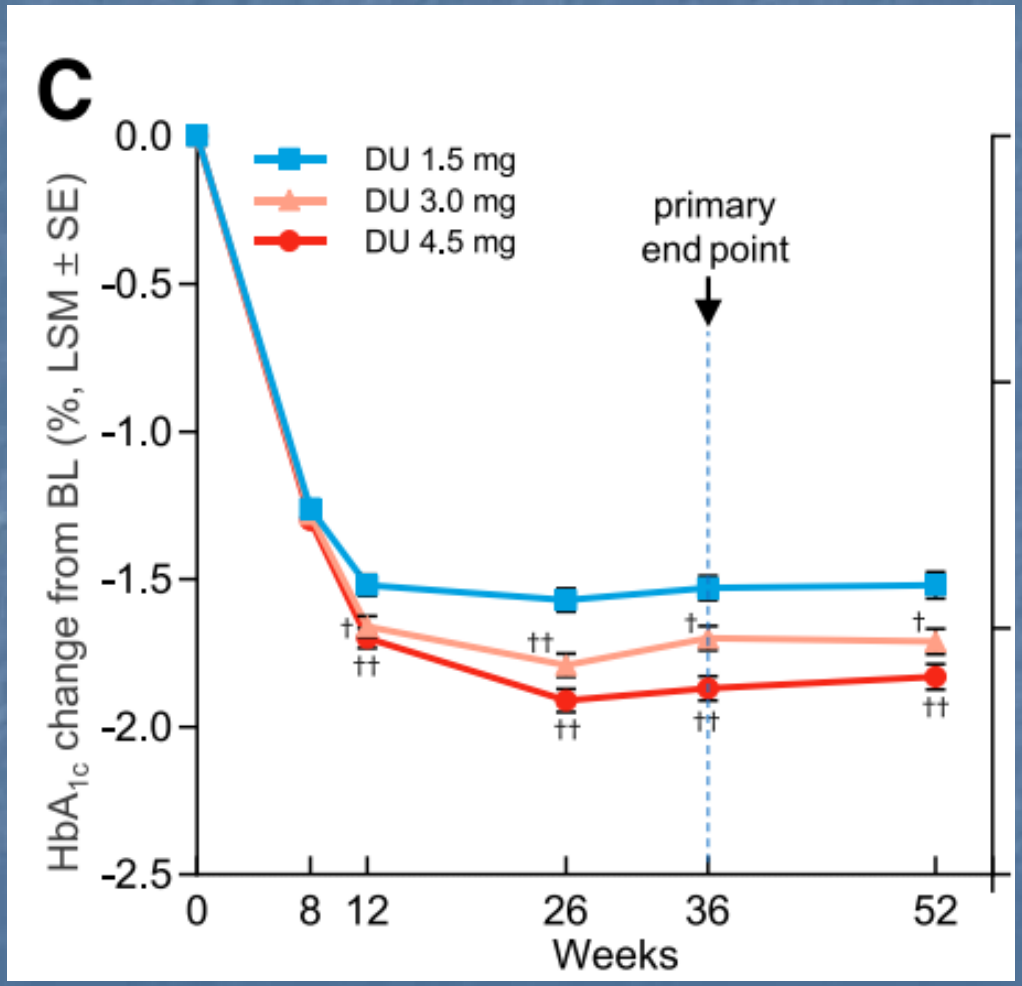


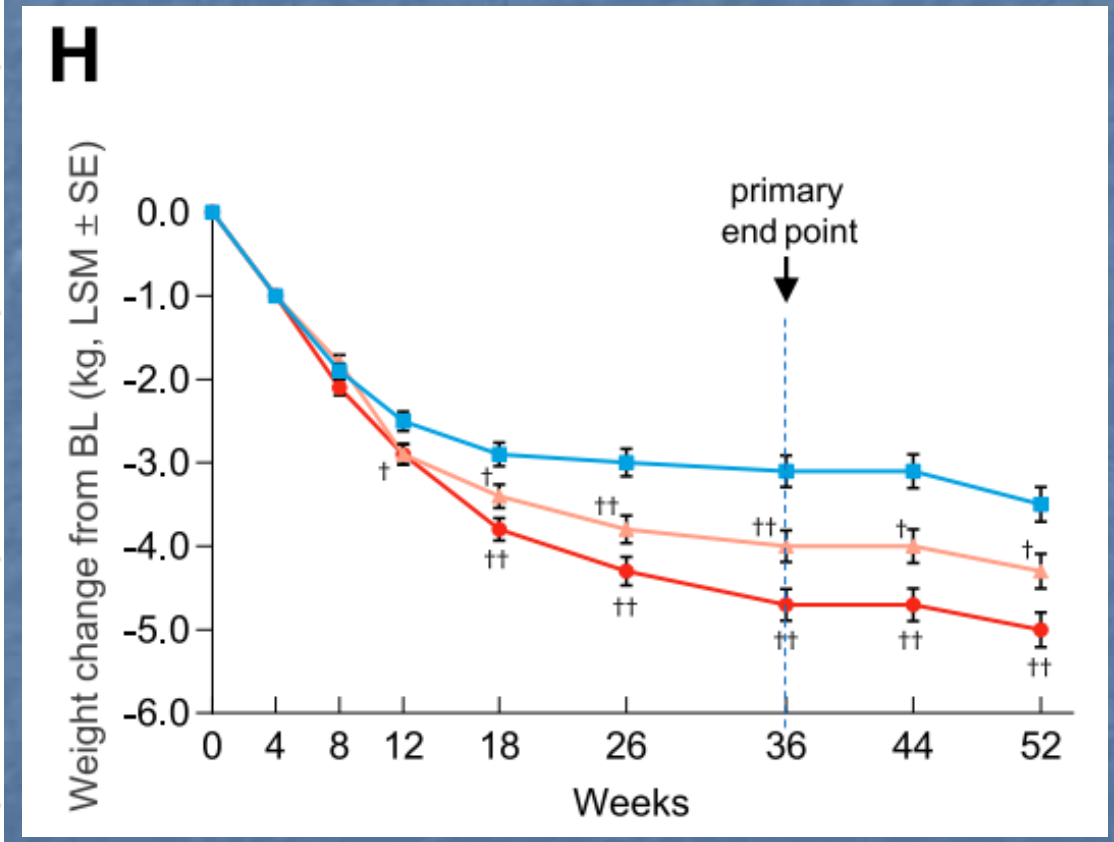


Semaglutide versus Dulaglutide once weekly in patients with type 2 diabetes (SUSTAIN 7): a randomized, open label, phase 3b trial

Pratley et al: *Lancet Diabetes Endocrinol* 2018;6:275-86

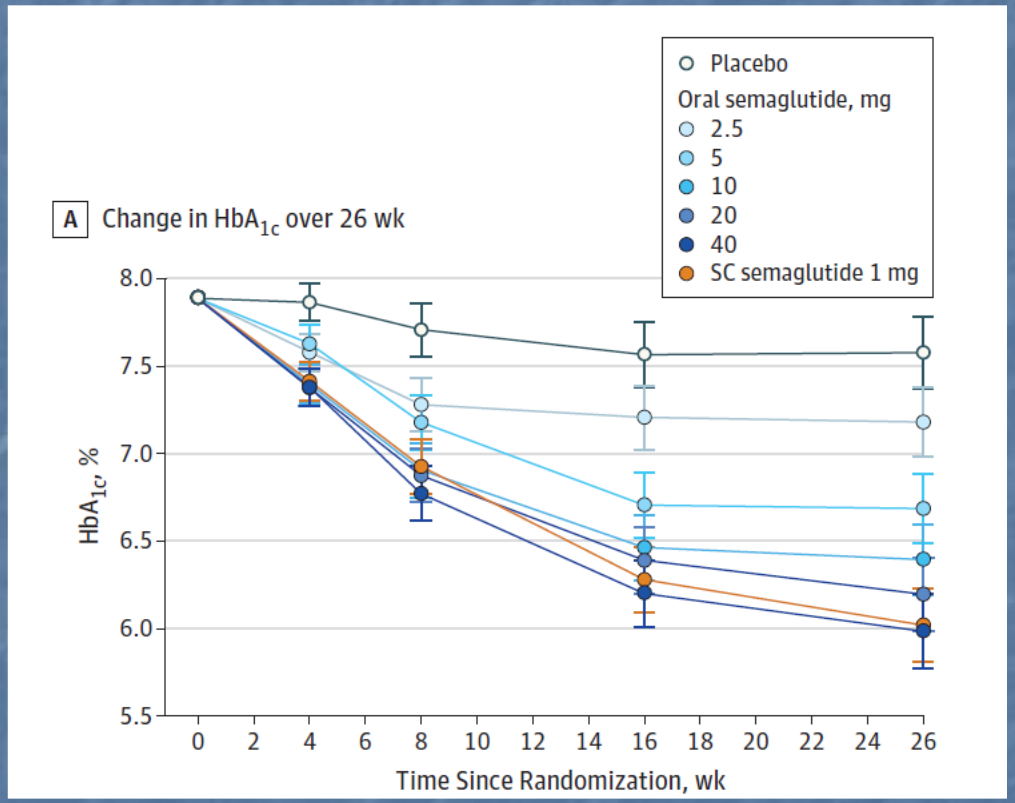
Efficacy and Safety of Dulaglutide 3.0 mg and 4.5 mg versus Dulaglutide 1.5 mg in Metformin-Treated Patients with Type 2 Diabetes

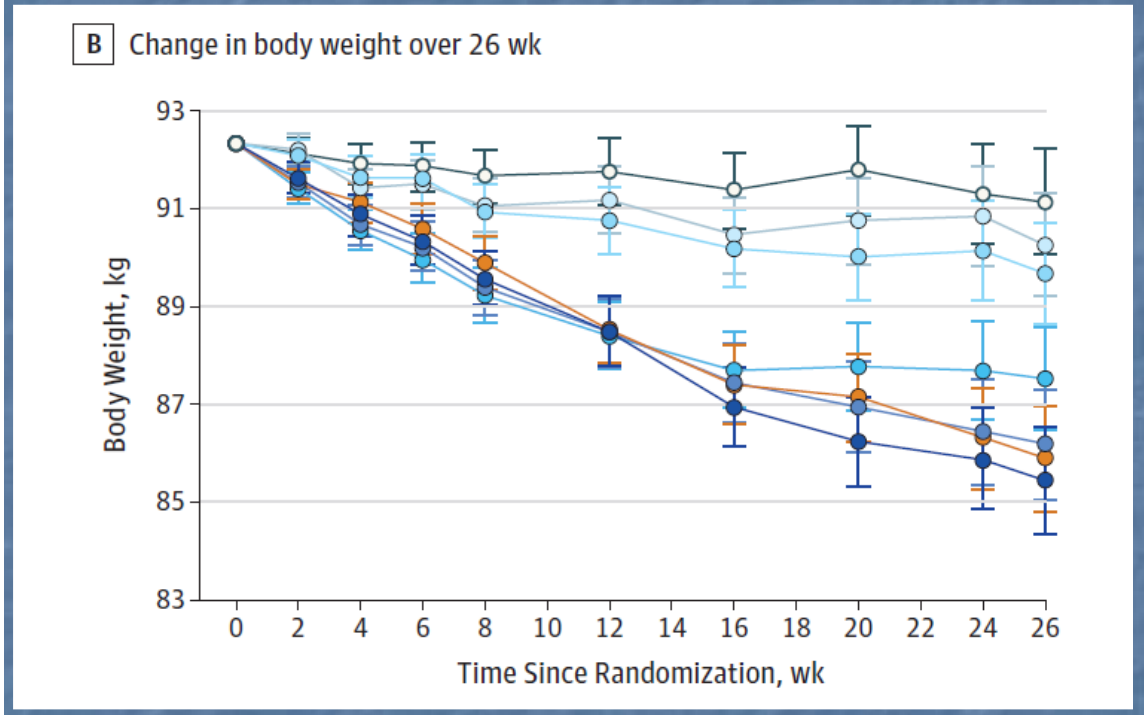




Diabetes Care 2021;44:765-773

Oral versus Subcutaneous Semaglutide





Davies et al: *JAMA* 2017;318:1460-1470

GI adverse events of Liraglutide

(A Randomized clinical trial of 3.0 mg of Liraglutide in Weight Management)

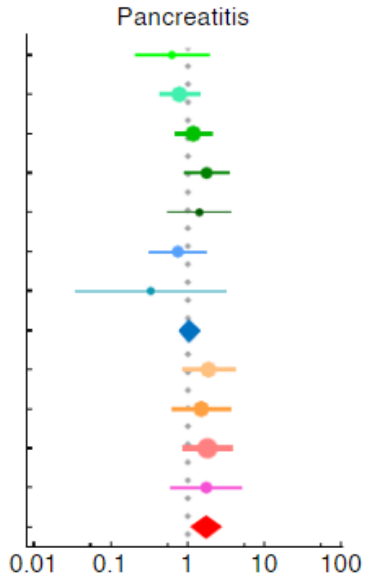
	Liraglutide	Placebo	Difference
Nausea	40	15	25%
Diarrhea	21	9	12
Constipation	20	9	11
Vomiting	16	4	12
Dyspepsia	9	3	6
Abdominal Pain	5	3	2

N Engl J Med 2015;373:11-22

Incretin-based glucose-lowering medications and the risk of acute pancreatitis and malignancies: a meta-analysis based on cardiovascular outcomes trials

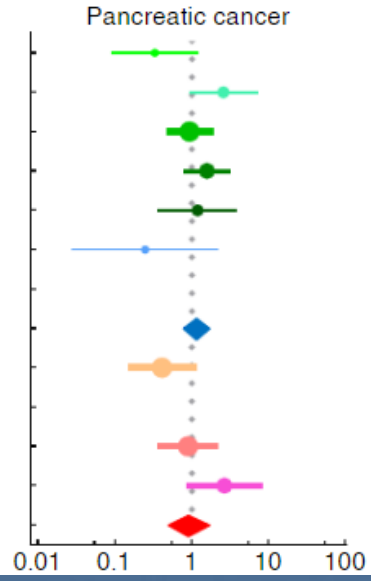
(A)

Study	Compound	Rate ratio (95 % CI)	Z-value	p-value
Pfeffer et al. 2015	Lixisenatide	0.63 (0.20-1.91)	- 0.82-	0.41
Marso et al. 2016 a	Liraglutide	0.78 (0.42-1.45)	- 0.78	0.44
Holman et al. 2017	Exenatide q.w.	1.20 (0.67-2.10)	0.60	0.55
Gerstein et al. 2019	Dulaglutide	1.77 (0.90-3.49)	1.65	0.10
Hernandez et al. 2018	Albiglutide	1.43 (0.54-3.80)	0.72	0.50
Marso et al. 2016	Semaglutide s.c.	0.75 (0.32-1.78)	- 0.65	0.52
Husain et al. 2019	Semaglutide oral	0.33 (0.04-3.21)	- 0.95	0.34
All GLP-1 RAs		**1.05 (0.78-1.41)**	**0.31**	**0.75**
Scirica et al. 2013	Saxagliptin	1.88 (0.84-4.21)	1.53	0.13
White et al. 2013	Alogliptin	1.51 (0.62-3.80)	0.91	0.36
Green et al. 2015	Sitagliptin	1.82 (0.87-3.80)	1.60	0.11
Rosenstock et al. 2019	Linagliptin	1.75 (0.60-5.23)	1.01	0.31
All DPP-4 Is		**1.75 (1.14-2.70)**	**2.56**	**0.01**



(B)

Study	Compound	Rate ratio (95 % CI)	Z-value	p-value
Pfeffer et al. 2015	Lixisenatide	0.33 (0.09-1.23)	- 1.65	0.10
Marso et al. 2016 a	Liraglutide	2.60 (0.93-7.30)	1.82	0.07
Holman et al. 2017	Exenatide q.w.	0.94 (0.47-1.91)	0.16	0.87
Gerstein et al. 2019	Dulaglutide	1.58 (0.77-3.26)	1.25	0.21
Hernandez et al. 2018	Albiglutide	1.20 (0.37-3.93)	0.30	0.76
Marso et al. 2016	Semaglutide s.c.	0.25 (0.03-2.24)	- 1.24	0.22
Husain et al. 2019	Semaglutide oral	No cases described		
All GLP-1 RAs		**1.14 (0.77-1.70)**	**0.70**	**0.51**
Scirica et al. 2013	Saxagliptin	0.41 (0.15-1.17)	- 1.66	0.10
White et al. 2013	Alogliptin	No cases observed		
Green et al. 2015	Sitagliptin	0.90 (0.37-2.22)	- 0.23	0.82
Rosenstock et al. 2019	Linagliptin	2.68 (0.85-8.41)	1.69	0.09
All DPP-4 Is		**0.94 (0.52-1.68)**	**- 0.22**	**0.83**



Abd El Aziz M, et al: *Diabetes Obes Metab* 2020;22:699-704

GLP-1 Receptor Agonists: Daily Agents

- Exenatide (Byetta®)
  - Twice/day sc. Injections
  - Start with 5 mcg bid within 60 minutes of a meal and after 1 month increase the dose to 10 mcg bid if eGFR > 30 ml/min
  - Should not be used in patients with eGFR < 30 ml/min
- Liraglutide (Victoza®)
  - Once day sc injection, "use with caution in renal impairment"
  - Start with 0.6 mg qd for 1 week, then increase to 1.2 mg qd; may go to 1.8 mg qd
  - No dosage adjustment is recommended in patients with renal impairment
- Lixisenatide (Adlyxin®)
  - Initiate at 10 mcg daily, can increase to 20 mcg daily after 2 weeks.
  - No dose adjustments for patients with moderate renal impairment (eGFR >30 ml/min), minimal experience for patients with severe renal impairment
- Oral Semaglutide (Rybelsus®)
  - Daily pill take with water 30 minutes before food, water or medications (3 mg, 7 mg and 14 mg)
  - No dose adjustment is recommended for patients with renal impairment

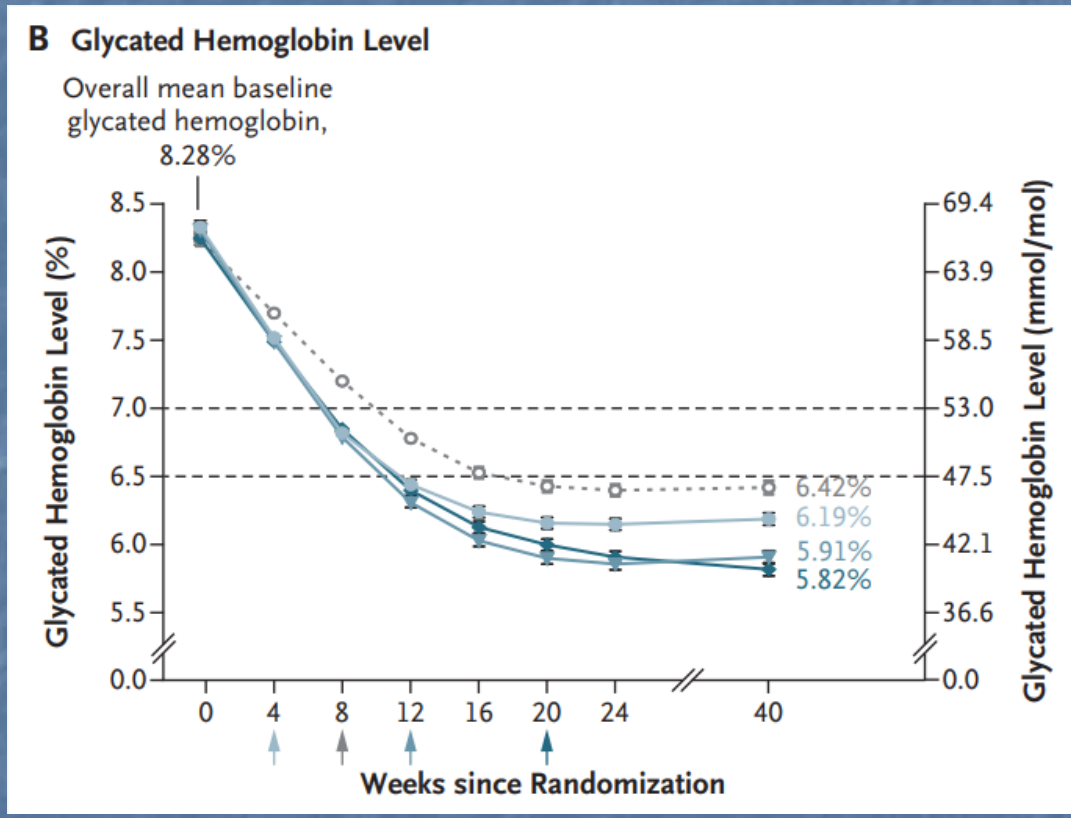
GLP-1 Receptor Agonists: Weekly Agents

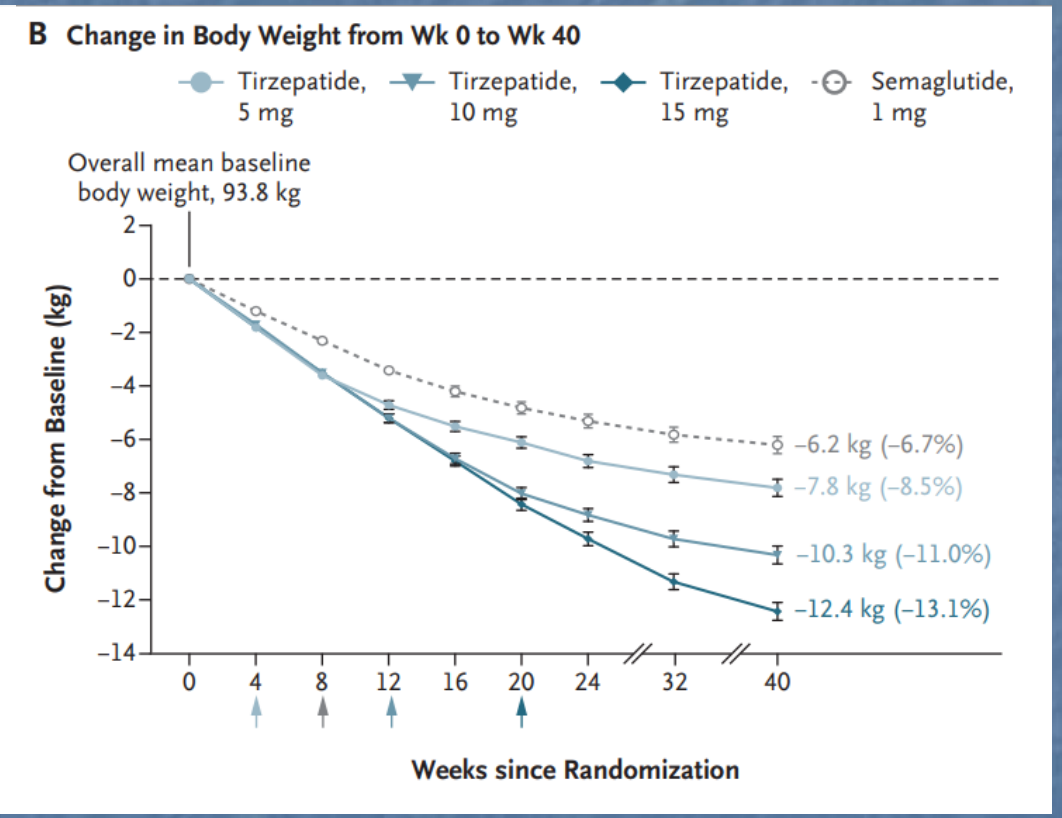
- Exenatide ER (Bydureon®)
  - Once per week injection 2 mg
  - Not recommended in patients with eGFR < 45 ml/min
- Dulaglutide (Trulicity®)
  - Once per week, start 0.75 mg, can increase to 1.5 mg, 3 mg, or 4 mg.
  - No dose adjustment needed in patients with renal impairment including end stage renal disease
- Semaglutide (Ozempic®)
  - Start at 0.25 mg weekly, after 4 weeks can increase to 0.5 mg weekly and if not at goal can increase to 1 mg after another 4 weeks, recently approved dose of 2 mg
  - No dose adjustments for patients with renal impairment including end stage renal disease

Tirzeparide

- Dual GLP-1 and GIP receptor agonists
- Weekly administration (dose starting at 2.5 mg and titrating up to 15 mg)
- Can be used in patients with CKD and ESRD
- Similar side effect profile as GLP-1 RA

Tirzeparide



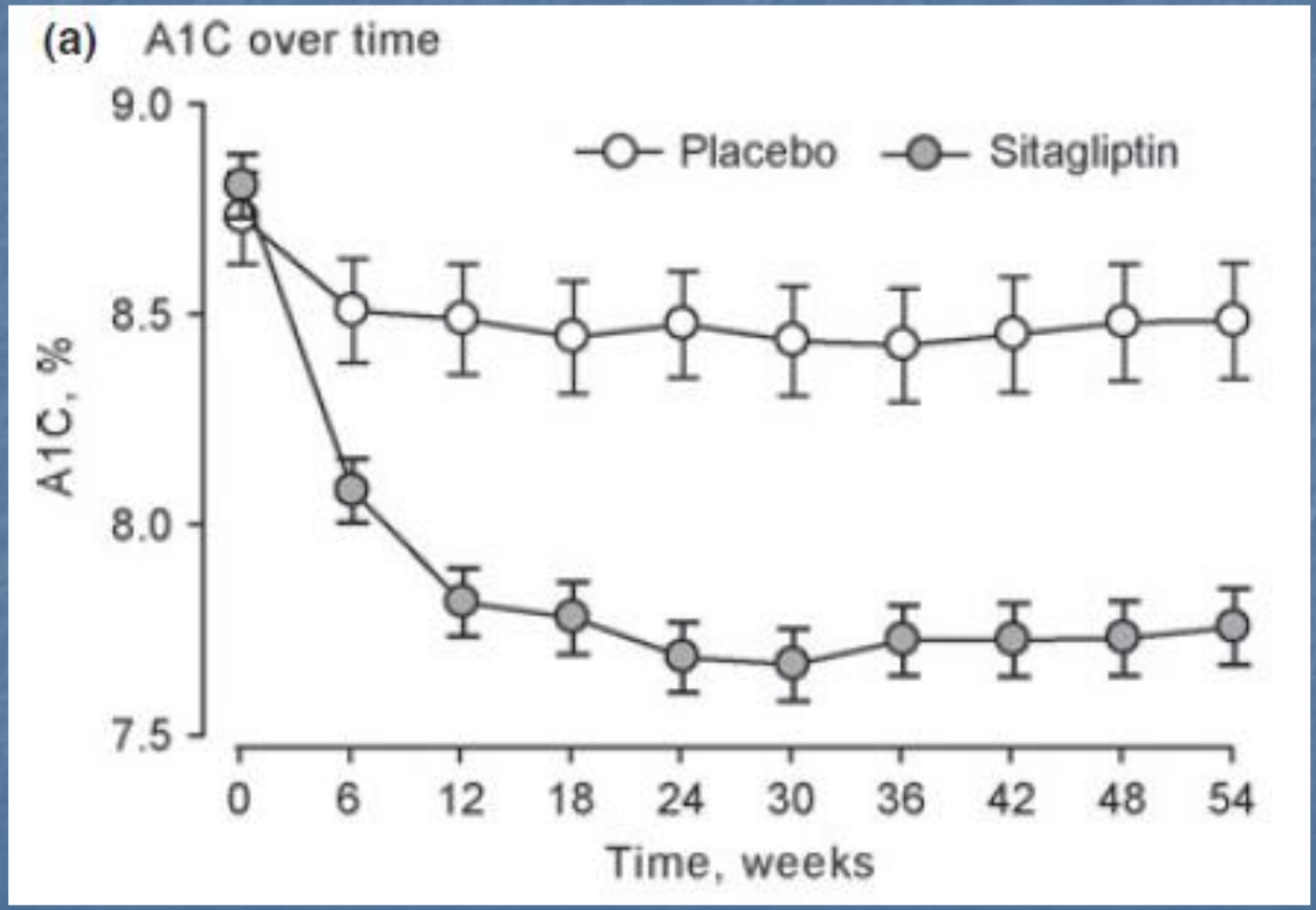


N Engl J Med 2021;385:5033-515

GLP-1 agonist: Take home message

- Powerful hypoglycemic effect with weight loss and no hypoglycemia
- Can be used instead of insulin in most patients with type 2 diabetes
- Can be added to basal insulin instead of adding prandial insulin
- Not tolerated because of GI side effects in ~ 10-15% of patients
- Most, but not all GLP-1 agonists provide CVD benefits in patients with established CVD or at high risk for CVD
- Possible CKD protection

Efficacy of sitagliptin in patients with type 2 diabetes



J Diabetes 2013; 5:68-79

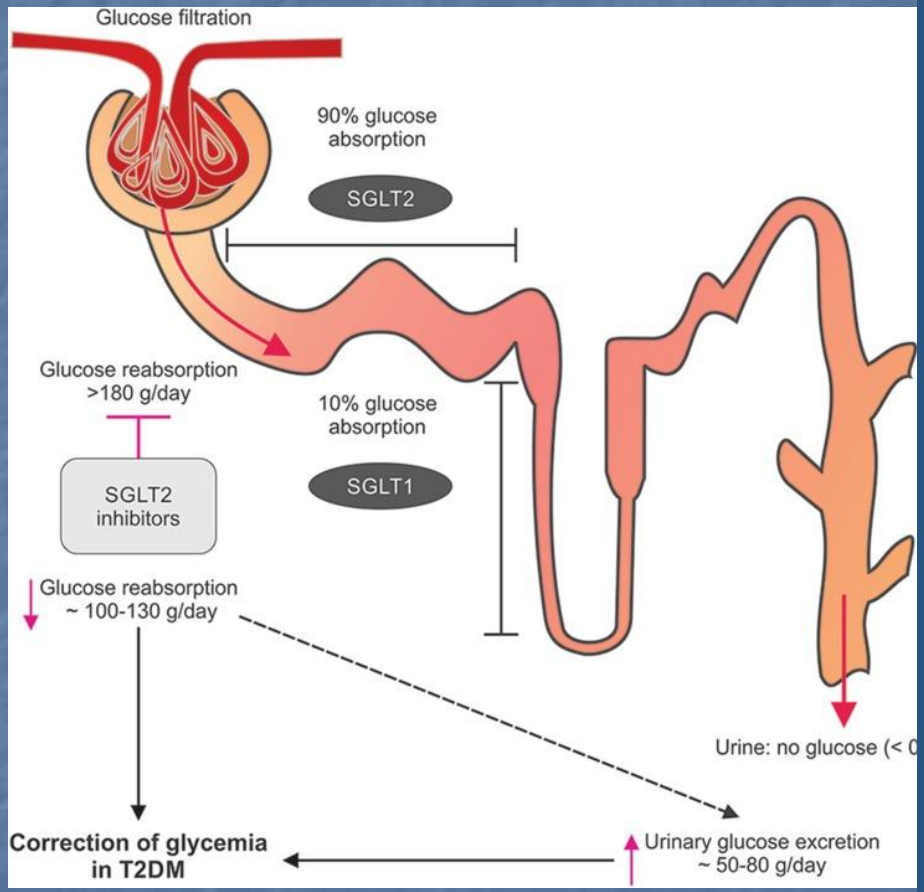
DPP-4 Inhibitors

- Sitagliptin (Januvia®) 2006
  - 100 mg po qd (reduce dose in renal insufficiency)
- Saxagliptin (Onglyza®) 2009
  - 2.5 or 5 mg po qd (reduce dose in renal insufficiency)
- Linagliptin (Tradjenta®) 2011
  - 2.5 mg po qd (no renal adjustment)
- Alogliptin (Nesina®) 2013
  - 25 mg po qd (reduce dose in renal insufficiency)

DPP-4 Inhibitors: Take home message

- Less powerful than sulfonylureas
- Minimal risk of hypoglycemia
- No weight gain
- Easy to use and tolerate
- Neutral effects on cardiovascular disease

Sodium-glucose co-transporter-2 inhibitors

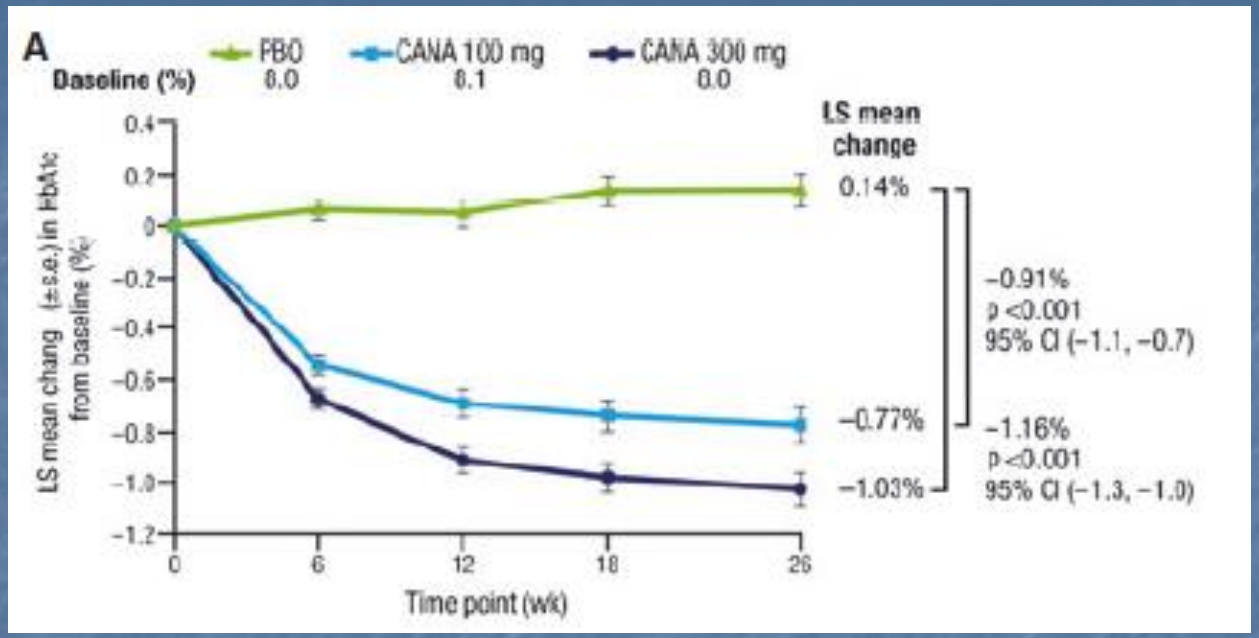


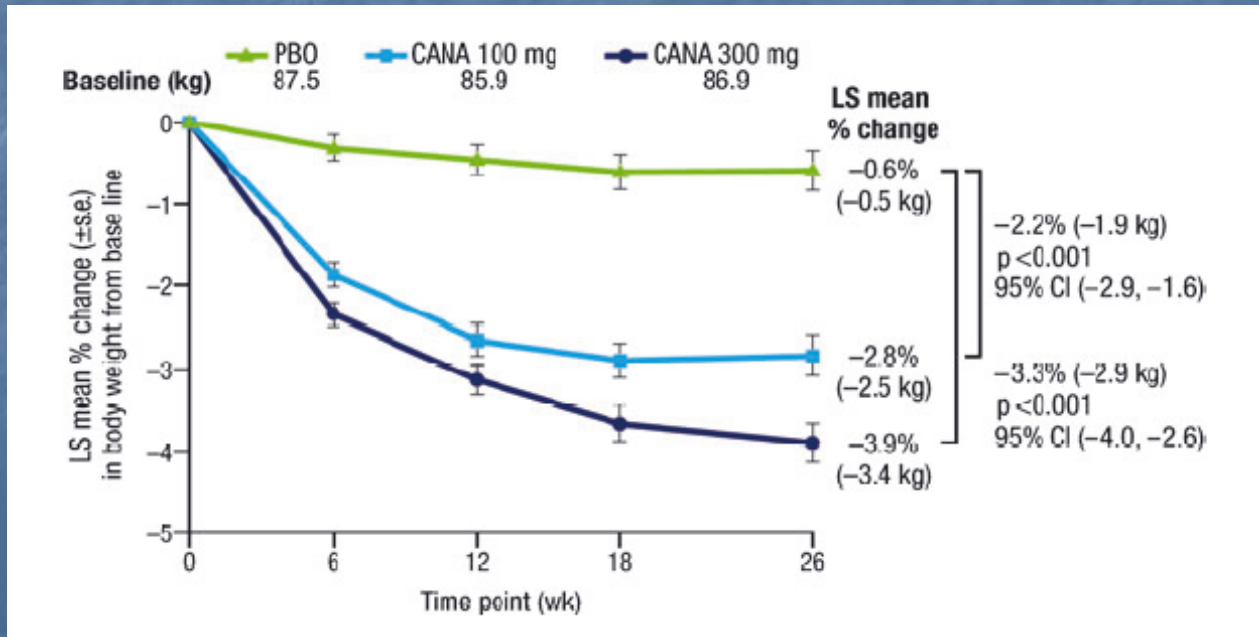
Kalra S, Singh V, Nagrale D. Sodium-Glucose Cotransporter-2 Inhibition and the Glomerulus: A Review. *Advances in Therapy*. 2016;33(9):1502-1518.

- SGLT2:
  - High-capacity, low-affinity: 90% glucose reabsorption, located in segment 1 proximal convoluted tubule
- Blockade of SGLT-2
  - Osmotic diuresis (glucosuria)
  - Lower blood pressure (2-5 mmHg)
  - Decreased uric acid
  - Self-limited glucose lowering
  - Self-limited weight loss
- Drugs
  - Canagliflozin, empagliflozin, dapagliflozin, ertugliflozin

Slide courtesy of Dr. Deborah Wexler

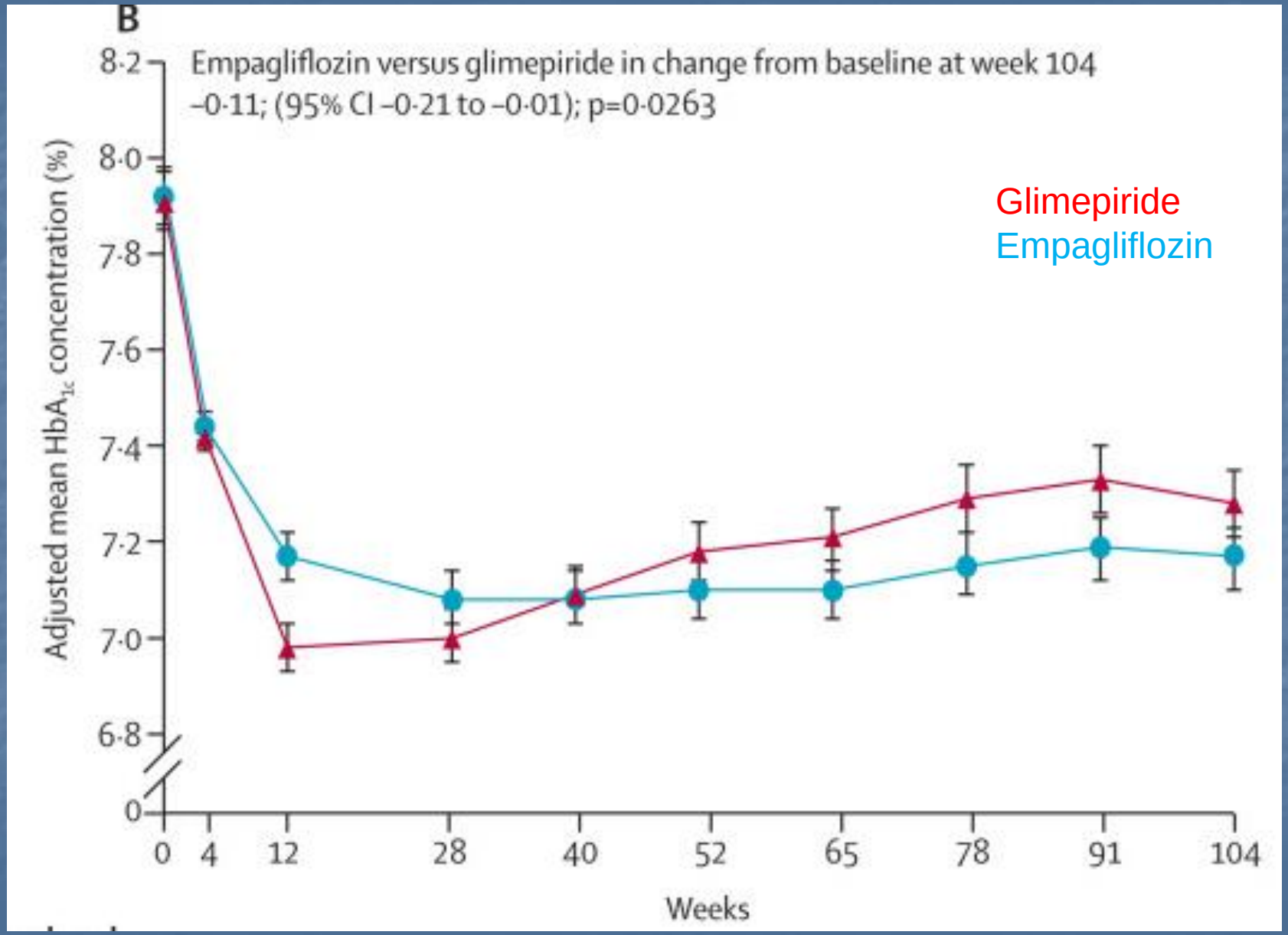
Effects of Canaglifozin in Patients with Type 2 Diabetes





Diabetes, Obesity and Metabolism 15:372-382, 2013

Comparison of Empagliflozin and Glimepiride as add-on to Metformin in patients with type 2 diabetes: a 104 week randomized, active controlled, double-blind, phase 3 trial



Lancet Diabetes Endocrinol 2014;2:691-700

Adverse Events in the EMPA-REG OUTCOME Trial

	Placebo	Empagliflozin 10 mg	Empagliflozin 25 mg
UTI male	9	11	10%
UTI female	41	36	37
Gen. Infection male	2	5	5
Gen Infection female	3	9	11

N Engl J Med 2015;373:2117-28

SGLT-2 Inhibitors: Clinical summary

- Variable HbA1c reduction
  - -0.5% to 2.5%, depending on starting point
- Weight reduction
  - ~2.5 kg, stabilizes
- Hypoglycemia only with insulin or sulfonylurea
- Decreased efficacy with decreasing GFR
  - Contraindicated GFR< 30 ml/min
- Adverse effects
  - Mycotic genital infections
    - Women >> men
  - Fournier Gangrene
    - 1/10,000 men, NS
  - Calciuria
    - Bone loss
  - Rarely, euglycemic DKA
    - Especially in patients with type 1 diabetes, but also in patients with insulin deficient type 2 diabetes
    - Trigger: stress (→increased glucose demand) + ketosis + ongoing osmotic diuresis and glucosuria→DKA)

SGLT-2 Inhibitors

- Canagliflozin (Invokana®) 2013
  - Canagliflozin should not be started in patients with eGFR < 45 mg/min
  - Doubles the risk of lower limb amputation
  - 100 mg qd, if eGFR> 60 mg/min can increase to 300 mg qd
- Dapagliflozin (Farxiga®) 2014
  - 5 or 10 mg qd, do not use if eGFR< 60 mg/min
- Empagliflozin (Jardiance®) 2014
  - 10 to 25 mg qd, do not use if eGFR < 45 mg/min
- Ertugliflozin (Steglatro®) 2017
  - 5 to 15 mg qd, initiation or continuation of use is not recommended in patients with eGFR < 60 mg/min,

SGLT-Inhibitors: Take Home Messages

- Powerful hypoglycemic effect
- Mild weight loss
- No hypoglycemia (unless used in combination with insulin or sulfonylureas)
- Well tolerated with main side effects increase in genital yeast infections
- Do not use when eGFR < 30
- Significant decrease in heart failure hospitalization, CVD events and CKD outcomes

CVD and CKD Reduction

Summary of early CVD Outcomes Trials

- All cardiovascular disease outcomes trials have enrolled people at high risk of CVD outcomes
- Most have had a small difference in glycemic control between the intervention and control group
  - On the order of 0.5% A1C
- It seems likely that differences in glycemic control of this magnitude, in this population, have no impact on cardiovascular disease risk

Large CV Outcomes Trials in Diabetes post-2008

Study	SAVOR	EXAMINE	TECOS	CAROLINA	CARMELINA
DPP4-i	saxagliptin	alogliptin	sitagliptin	linagliptin	linagliptin
Comparator	placebo	placebo	placebo	sulfonylurea	placebo
N	16,500	5,400	14,000	6,000	8,300
Results	2013	2013	2015	2017	2017

NEUTRAL NEUTRAL NEUTRAL NEUTRAL NEUTRAL

Study	LEADER	ELIXA	SUSTAIN 6	EXSCEL	REWIND
GLP1-RA	liraglutide	lixisenatide	semaglutide	exenatide LR	dulaglutide
Comparator	placebo	placebo	placebo	placebo	placebo
N	16,500	14,000	6,000	5,400	8,300
Results	2016	2015	2016	2018	2019

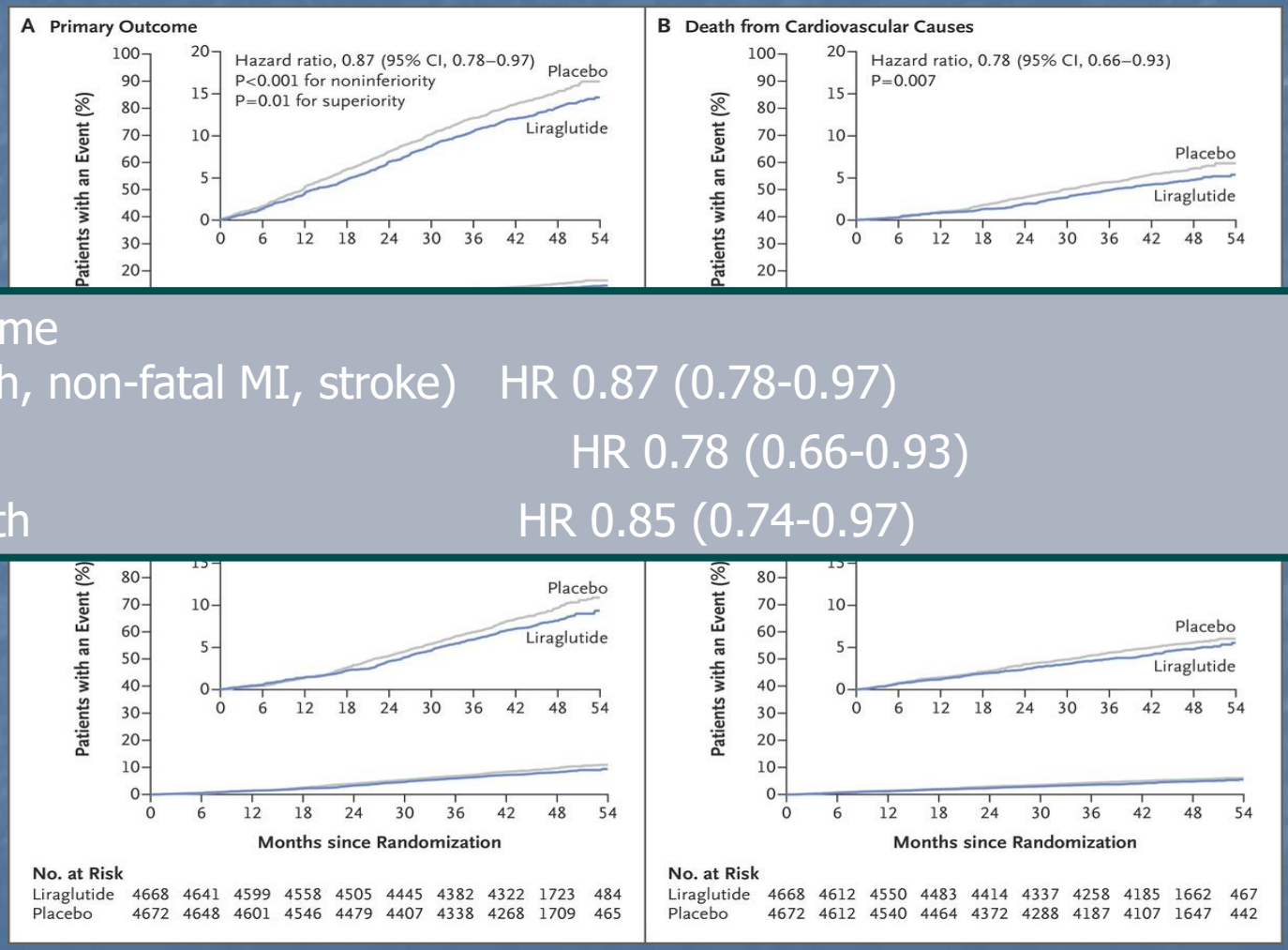
NEUTRAL NEUTRAL

Study	EMPA-REG	CANVAS	DECLARE	VERTIS CV
SGLT-2-i	empaglifozin	canagliflozin	dapagliflozin	ertugliflozin
Comparator	placebo	placebo	placebo	placebo
N	7300	4300	22,200	3900
Results	2015	2017	2019	2020

NEUTRAL

Slide courtesy of Silvio Inzucchi, Yale

Liraglutide: LEADER Outcomes



Primary outcome
(CVD death, non-fatal MI, stroke) HR 0.87 (0.78-0.97)

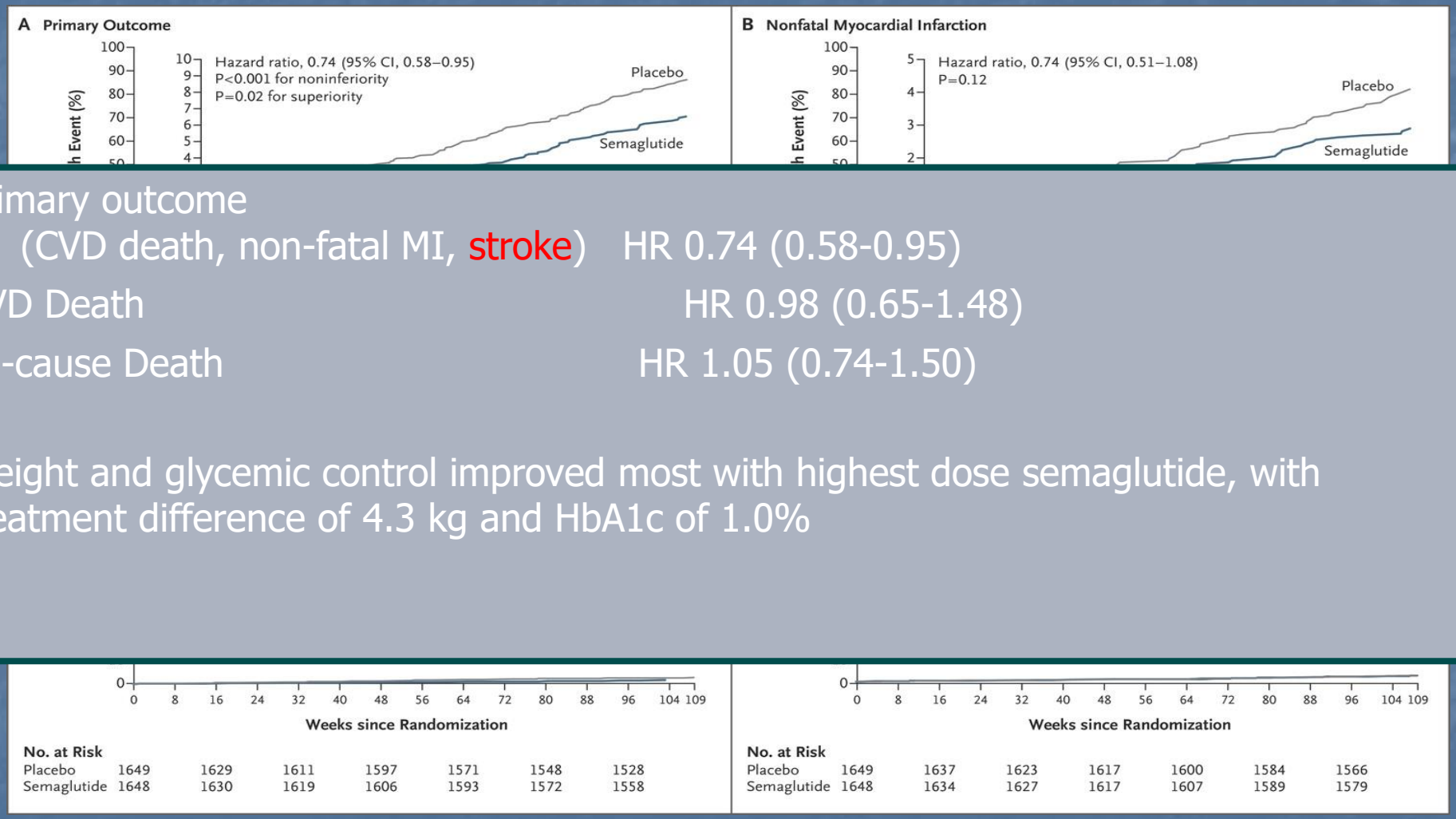
CVD Death HR 0.78 (0.66-0.93)

All-cause Death HR 0.85 (0.74-0.97)

Marso SP et al. N Engl J Med 2016.

Benefit apparent at 1 year

Semaglutide: SUSTAIN-6 Outcomes



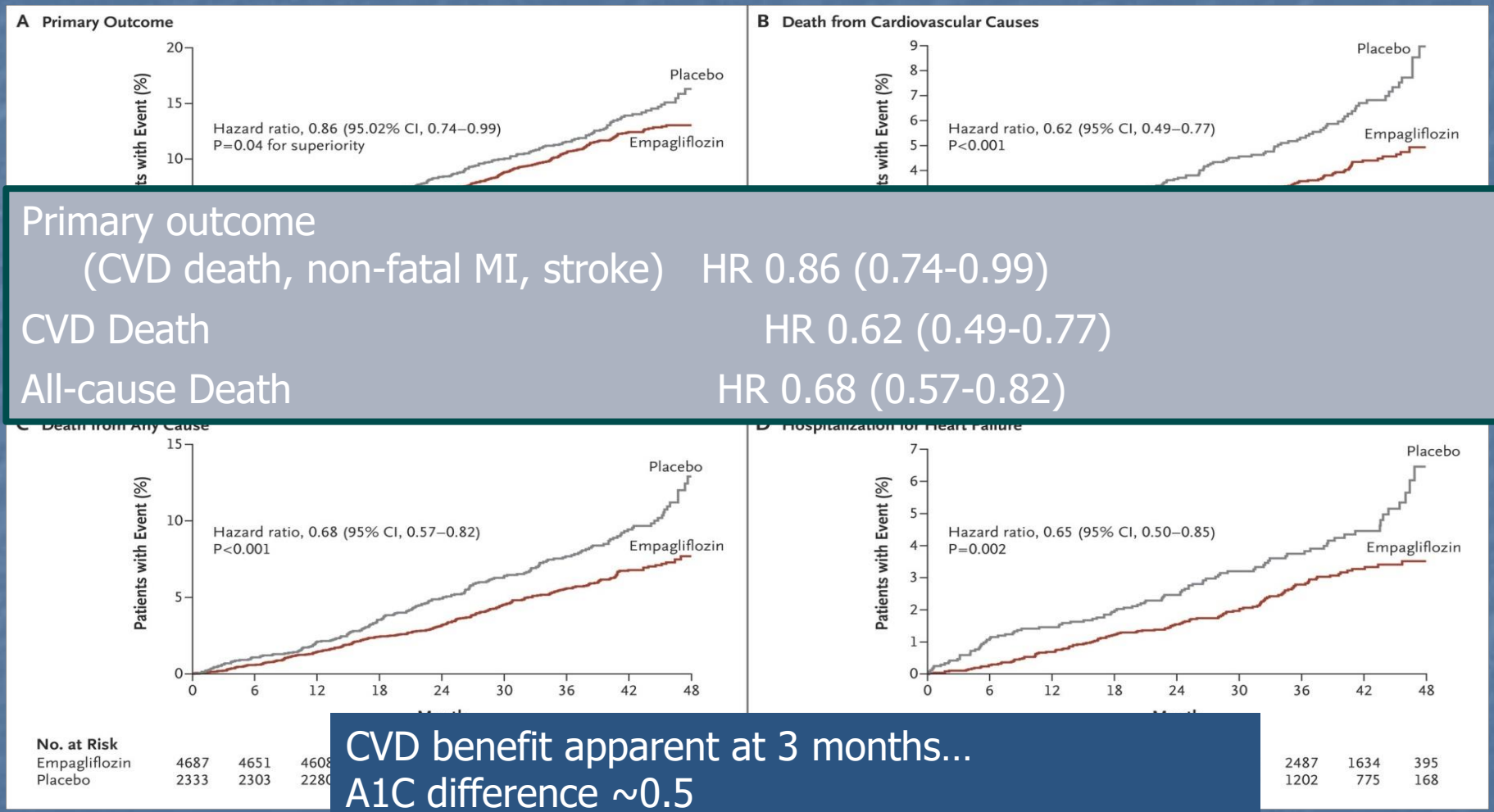
Primary outcome
(CVD death, non-fatal MI, stroke) HR 0.74 (0.58-0.95)

CVD Death HR 0.98 (0.65-1.48)

All-cause Death HR 1.05 (0.74-1.50)

Weight and glycemic control improved most with highest dose semaglutide, with treatment difference of 4.3 kg and HbA1c of 1.0%

Empagliflozin: EMPA-REG CVD Outcomes



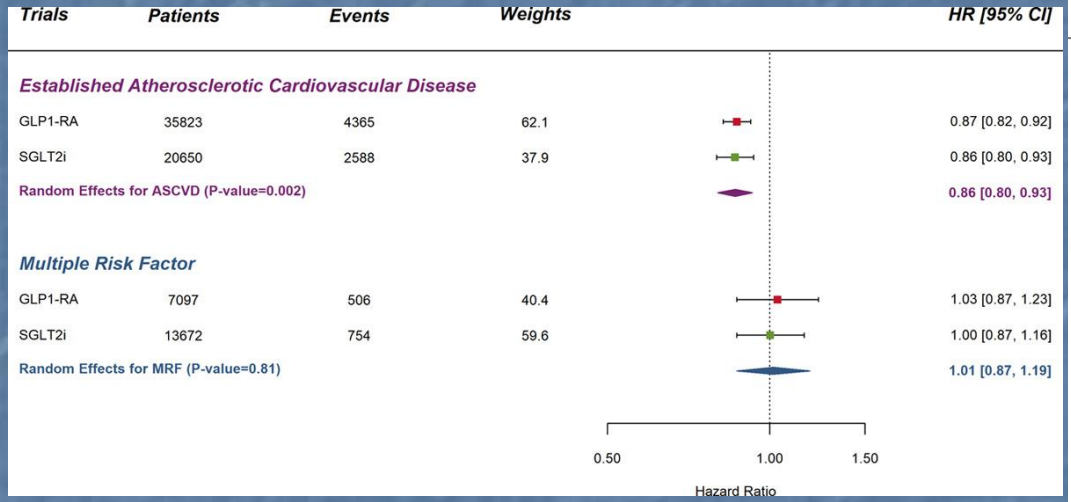
Primary outcome (CVD death, non-fatal MI, stroke)	HR 0.86 (0.74-0.99)
CVD Death	HR 0.62 (0.49-0.77)
All-cause Death	HR 0.68 (0.57-0.82)

CVD benefit apparent at 3 months…
A1C difference ~0.5

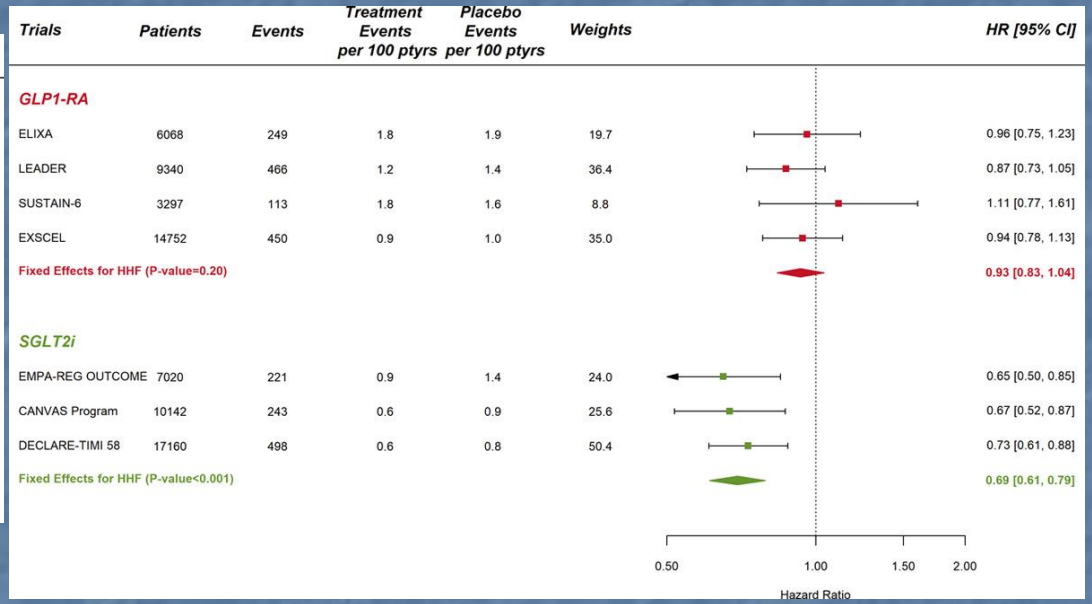
Zinman B et al. N Engl J Med 2015;373:2117-2128

Meta-analysis of Cardiovascular Outcomes Trials

Effect on composite of myocardial infarction, stroke and cardiovascular death

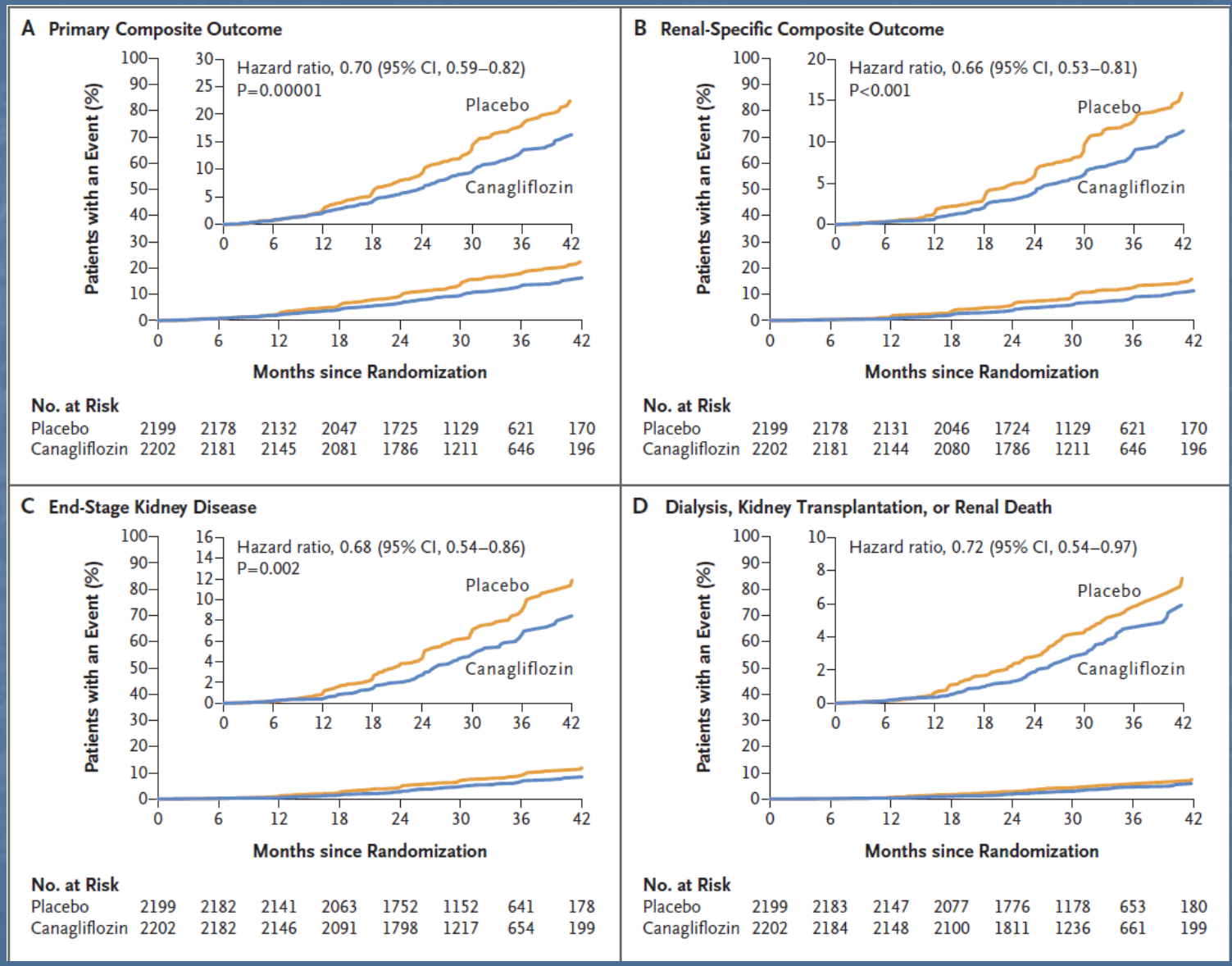


Effect on hospitalization for heart failure



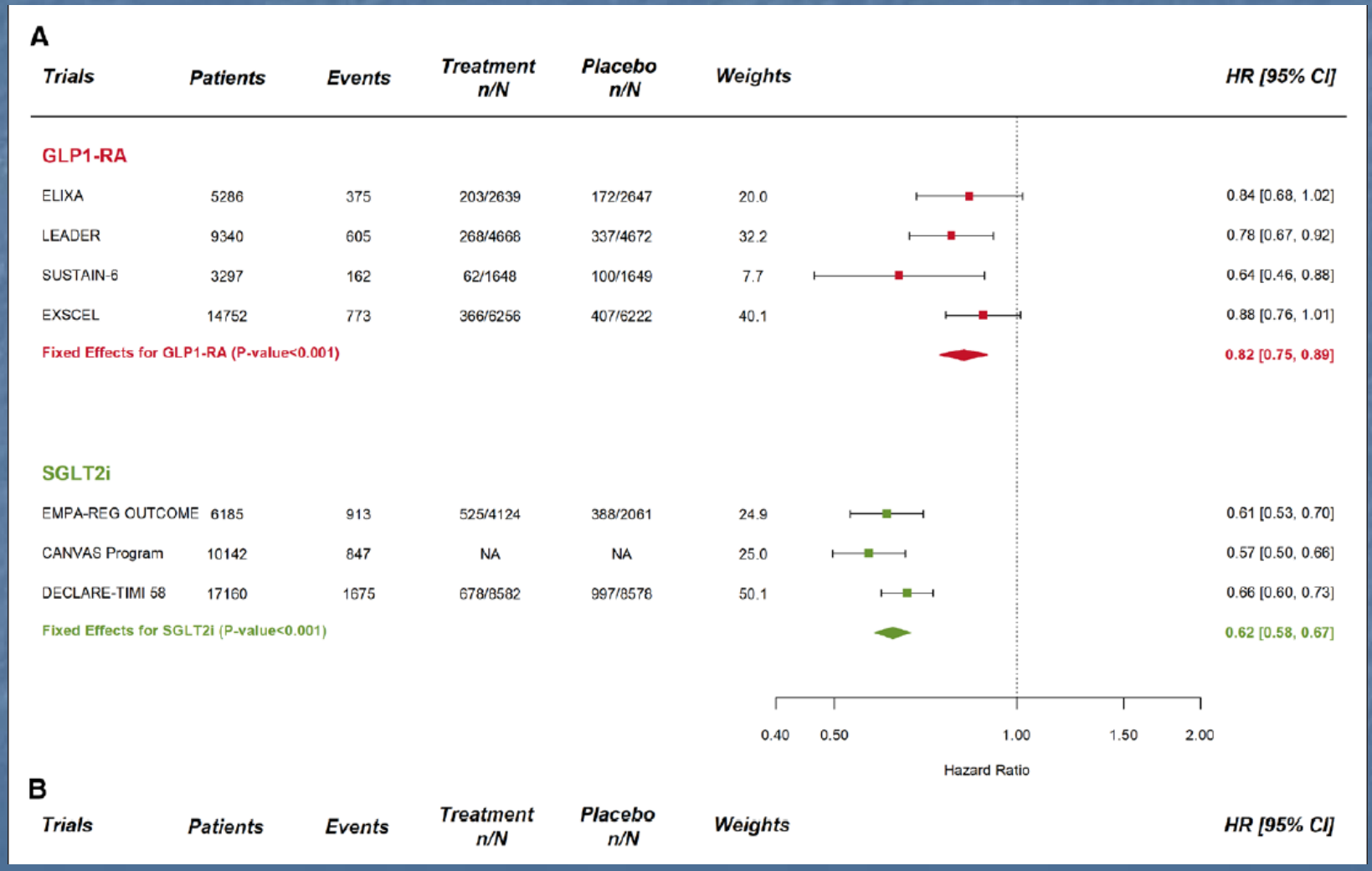
Zelniker et al: *Circulation* 2019;139:2022-2031

Canagliflozin and Renal Outcomes: the Credence Trial



N Engl J Med 2019;380:2295

Meta-analysis of GLP-1 agonists and SGLT-2 inhibitor on Renal End Points



Zelniker et al: *Circulation* 2019;139:2022-2031

CVD and CKD Reduction: Take Home Messages

- Long acting GLP-1 agonists and SGLT-2 inhibitors are both effective at reducing CVD disease in patients with pre-existing CVD or at high risk
- SGLT-2 inhibitors are also effective at reducing hospitalizations in patients with heart failure
- SGLT-2 inhibitors are effective at reducing CKD end points in patients with baseline eGFR > 30 ml/min
- The long acting GLP-1 agonists effects at reducing the CKD end points are mostly driven by a reduction in macroalbuminuria, excluding that particular outcome there was a non significant effect on the risk of doubling serum creatinine


THANK YOU