Diabetes Therapies Part 2:

Pioglitazone AND DDP-4 Inhibitors - Cardiovascular, Renal, and Liver Effects

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ECHO

Objectives

- Understand the mechanism of action, efficacy, and side-effects of pioglitazone on cardiovascular, renal, and liver

- Understand the mechanism of action, efficacy, and side-effects of DPP-4 inhibitors on cardiovascular, renal, and liver

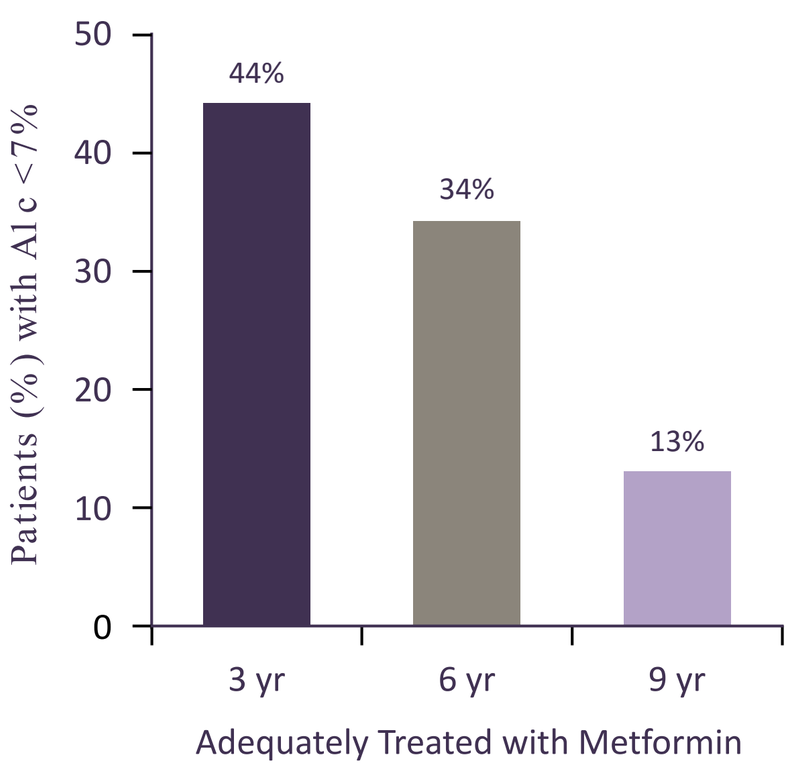
Case

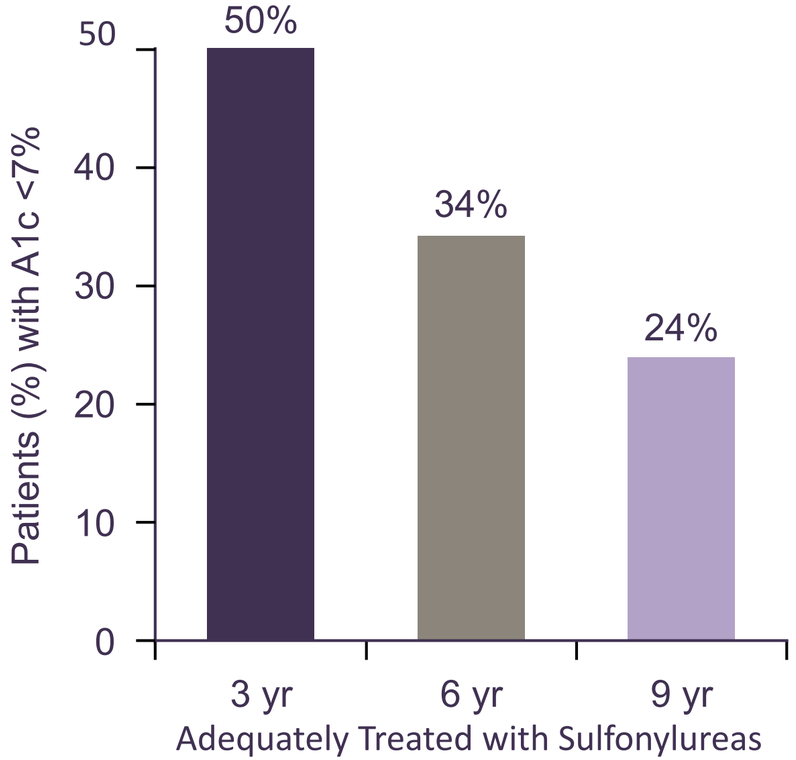
- 54 year old male with 5 years of type 2 diabetes, no complications
- On metformin 1000mg twice daily
- Has gained 12 lbs working from home over the past 2 years
- Self-pay
- A1C 8.6-9% over recent 12 months (8.6 → 8.9 → 9.2%)

What is the next step?

Glycemic control declines over time with traditional monotherapy

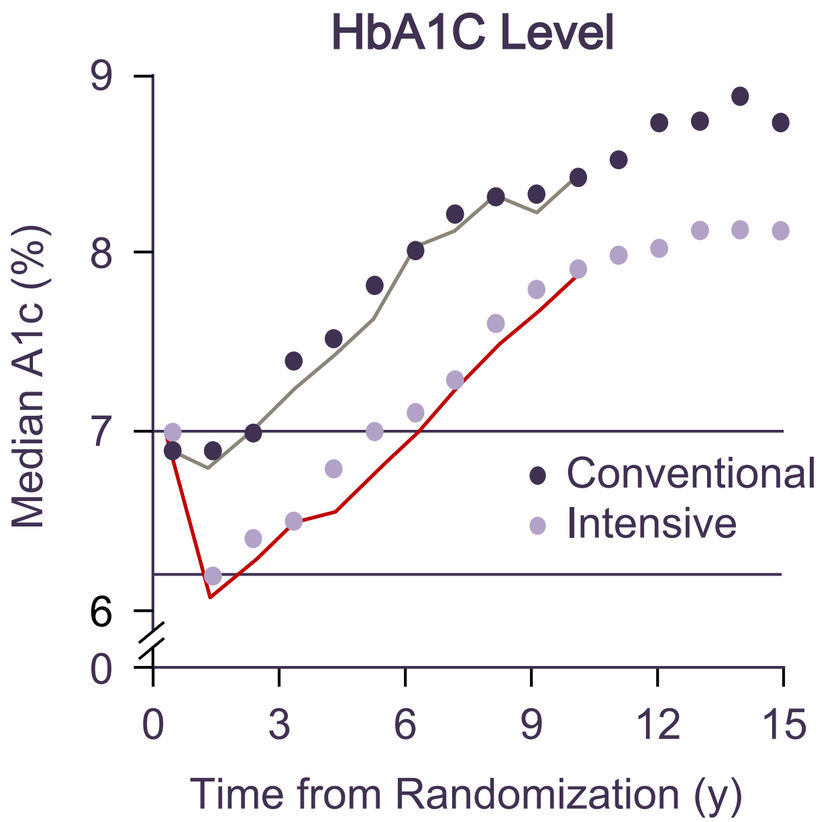
Most patients on traditional therapies will require another agent to maintain long-term glycemic control

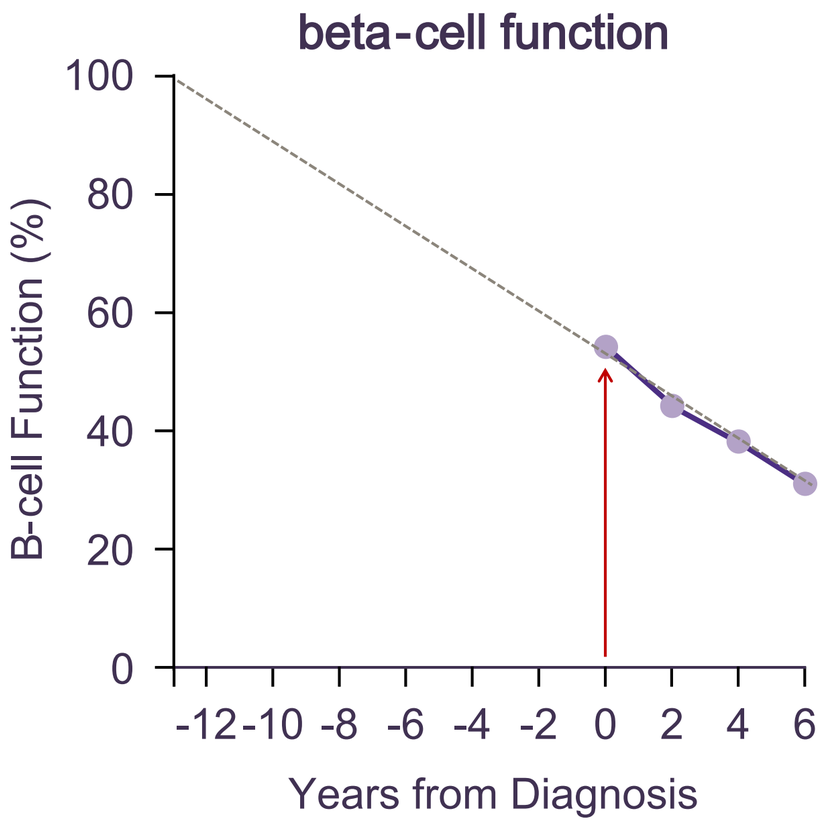




Turner RC, et al. *JAMA* 1999;281:2005

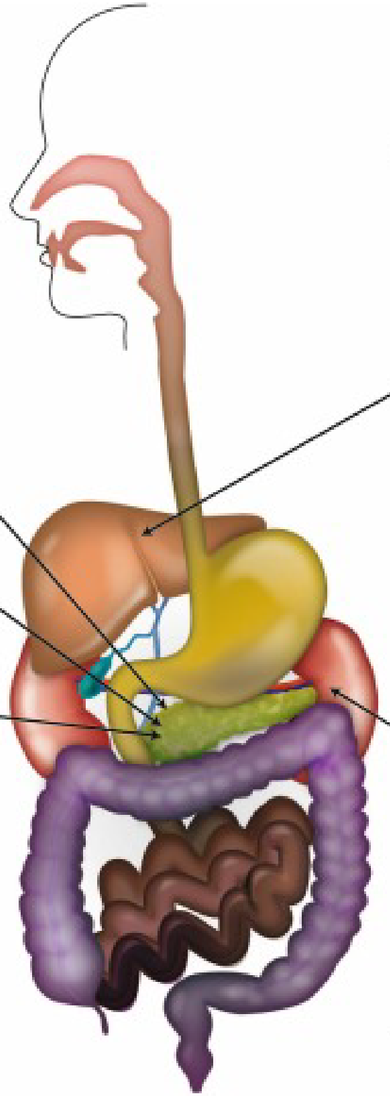
Progressive deterioration in glycemic control over time





UKPDS Group. *Lancet*. 1998;352:837 -853. Holman RR. *Diabetes Res Clin Pract* 1998;40(suppl):S21 -S25.

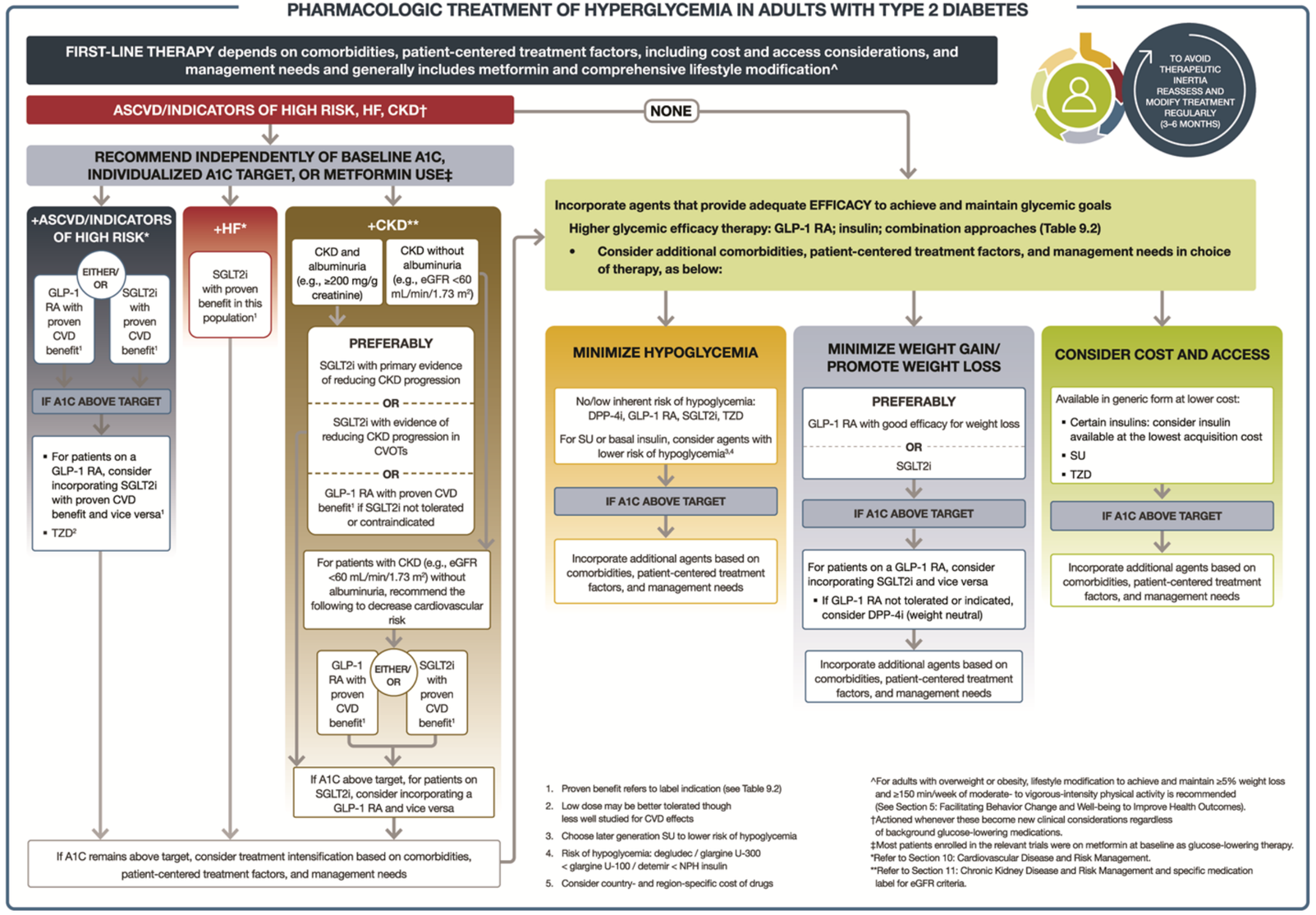
Add-on oral therapies to metformin

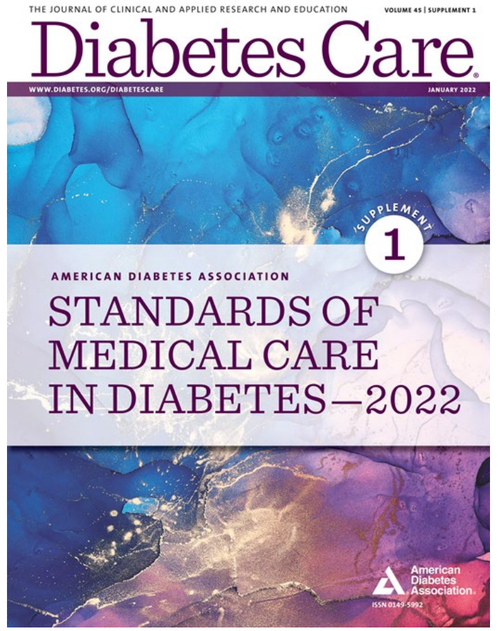


- Sulfonylureas
  - Increase insulin secretion
- DPP-4 inhibitors
  - Inhibit the breakdown of GI hormones that stimulate insulin release (GLP-1 and GIP)
- GLP-1 receptor agonists
  - Stimulate the release of insulin in the pancreas
- **Meglitinides**
- **Alpha glucosidase inhibitors**
- **Bromocriptine**
- **Colesevelam**

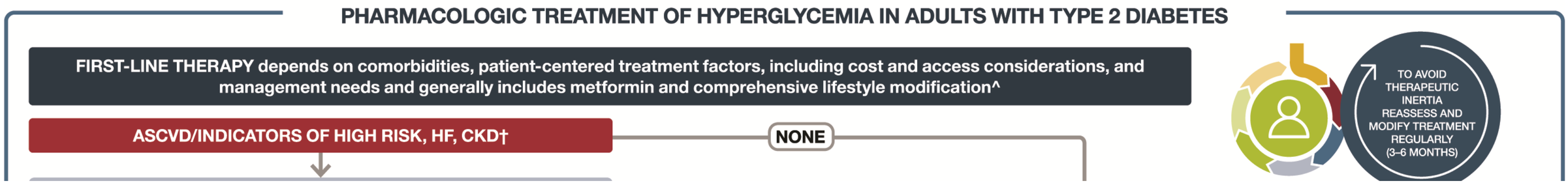
- Biguanides
  - Reduce hepatic gluconeogenesis
  - Decrease insulin resistance
- Thiazolidinediones
  - Modulate expression of insulin-sensitive genes in adipocytes and skeletal muscle
- SGLT2 inhibitors
  - Inhibit reabsorption of glucose in kidney

Algorithm for Type 2 Diabetes Treatment – 2022



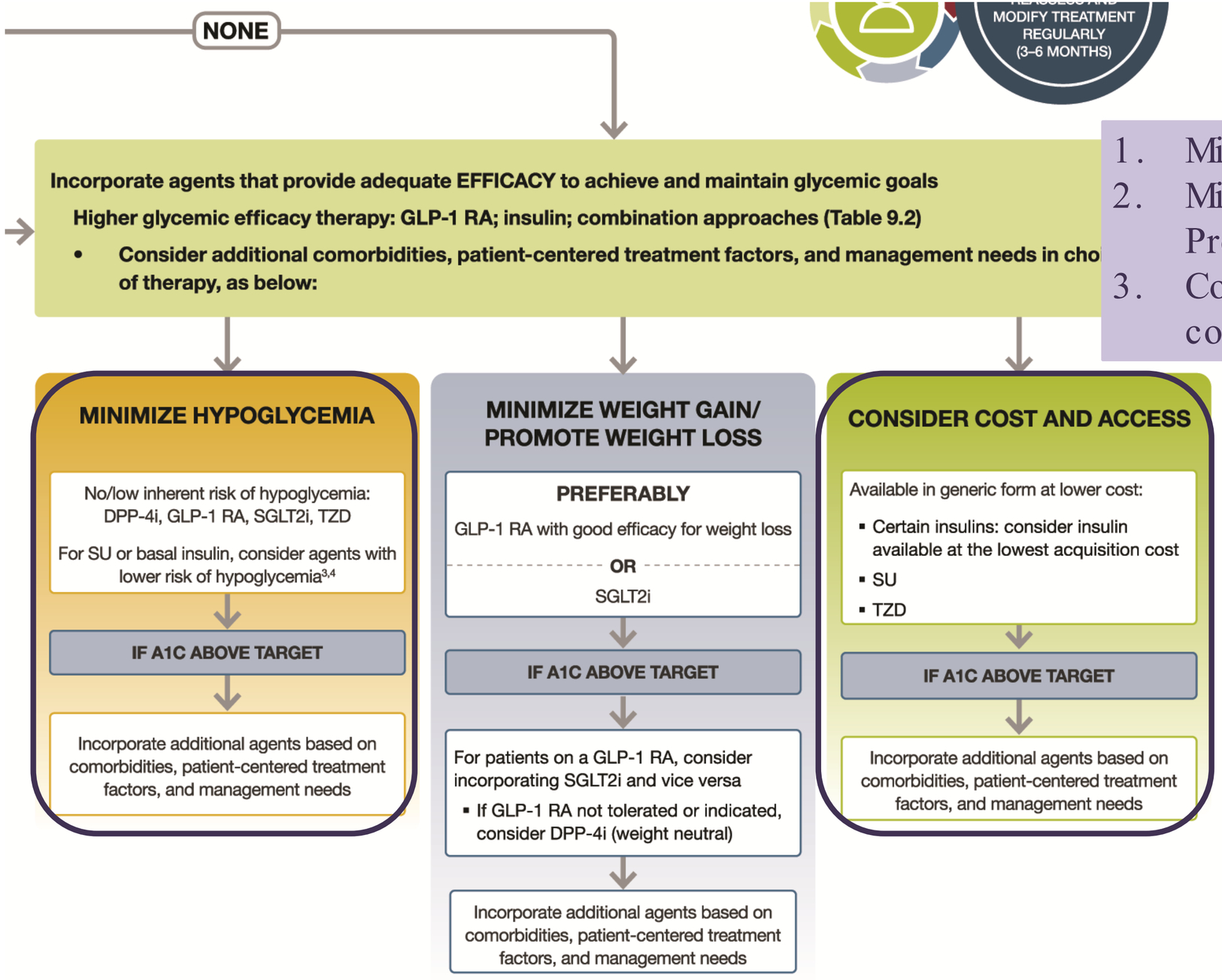


Pharmacologic Approaches to Glycemic Management: *Standards of Medical Care in Diabetes - 2022*. *Diabetes Care 45: S125-143*



INDICATORS OF HIGH RISK OR ESTABLISHED ASCVD, CKD OR HF

CONSIDER INDEPENDENT OF BASELINE A1C OR INDIVIDUALIZED A1C TARGET

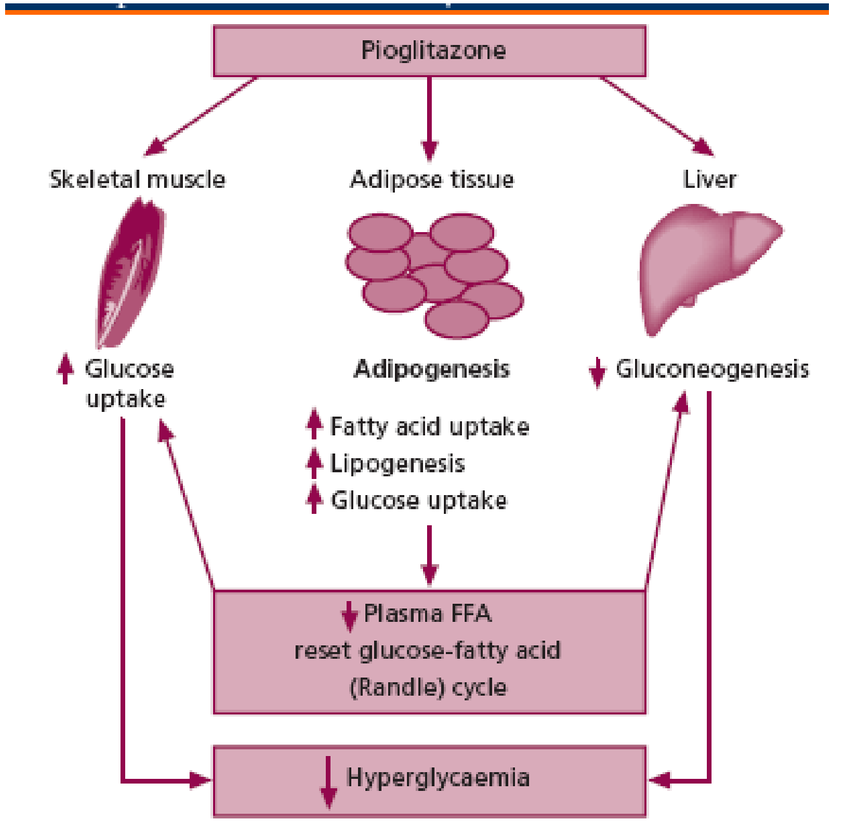


1. Minimize hypoglycemia
2. Minimize weight gain/ Promote weight loss
3. Cost and access considerations

Pioglitazone

Pioglitazone – mechanism of action

- PPAR gamma agonist
- ↑ insulin sensitivity by acting on fat, liver and skeletal muscle to increase glucose utilization and suppress liver glucose production
- Efficacy – A1C reduction 1-1.5%



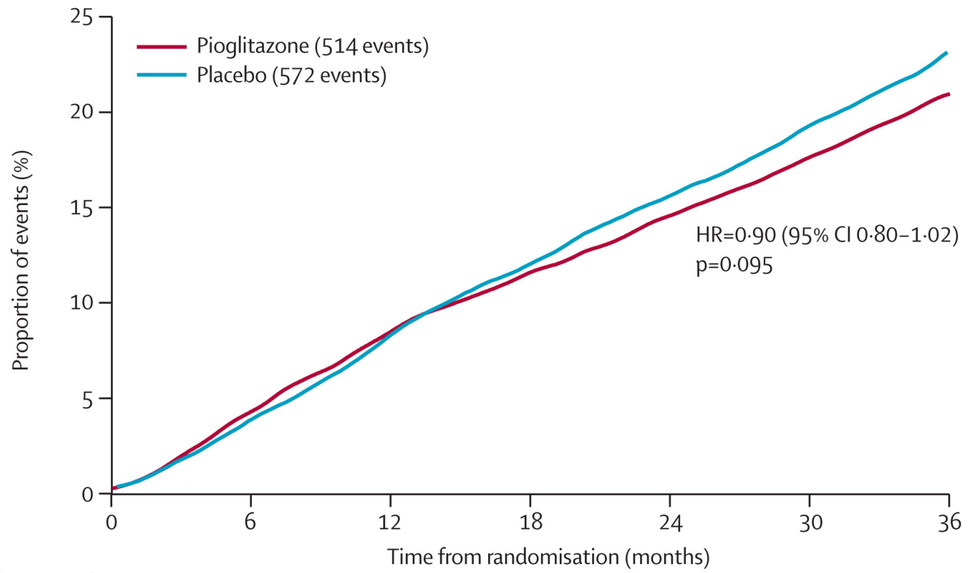
Key: FFA = free fatty acids

Adapted with permission from Bailey CJ, Feher MD, Therapies for Diabetes, Sherborne Gibbs, Birmingham UK, 2004

Cardiovascular effects of pioglitazone

- PROactive
- N=5238 with prior CV event
- Pioglitazone vs placebo for 34.5 months

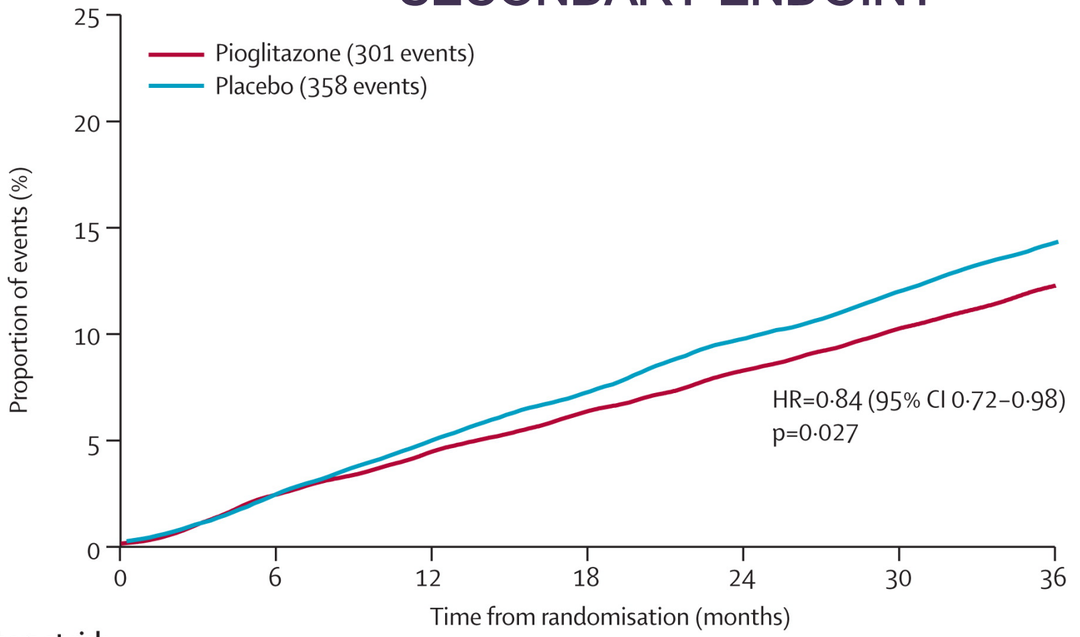
PRIMARY ENDPOINT



Numbers at risk

Pioglitazone	2488	2373	2302	2218	2146	348
Placebo	2530	2413	2317	2215	2122	345

SECONDARY ENDPOINT

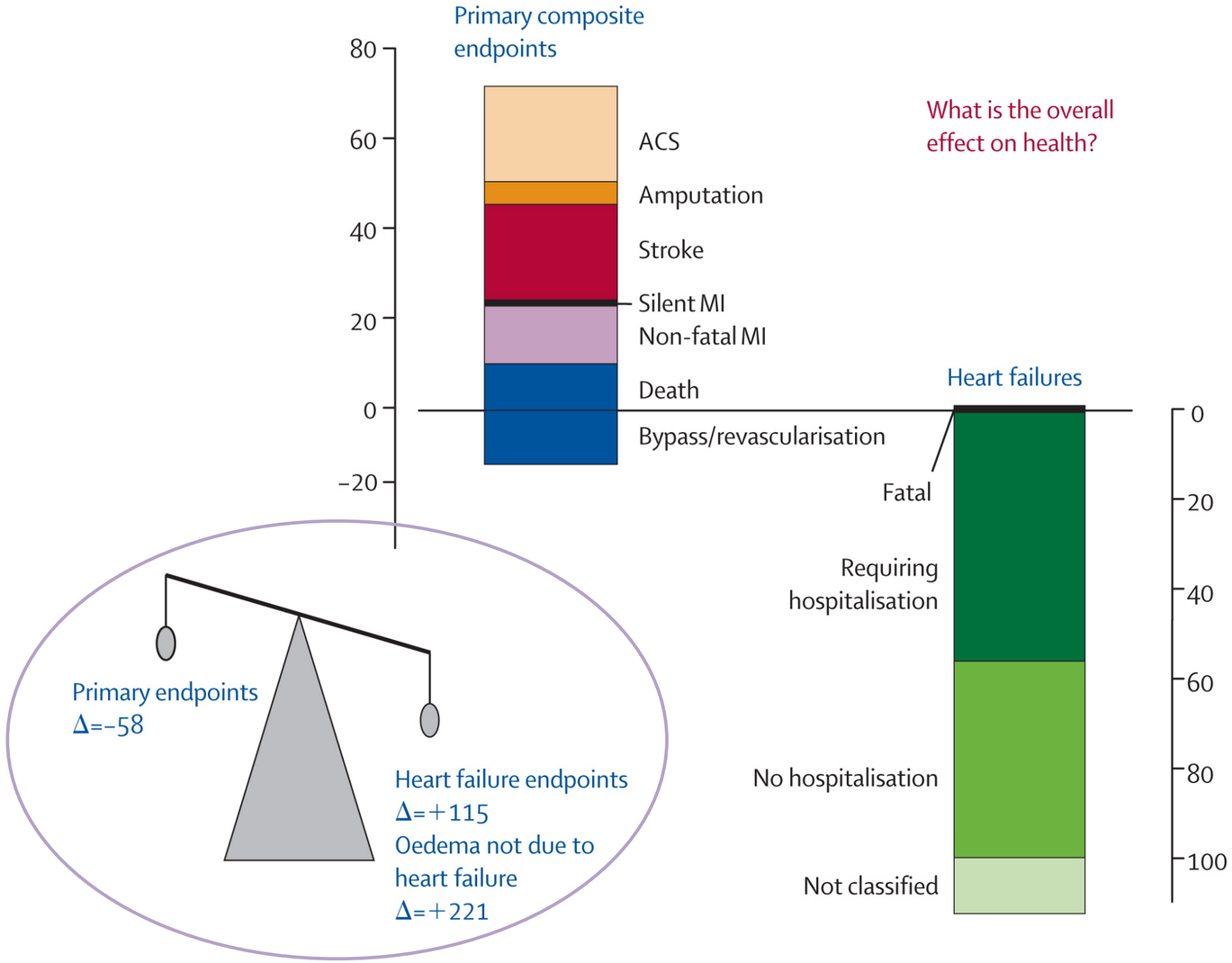


Numbers at risk

Pioglitazone	2536	2487	2435	2381	2336	396
Placebo	2566	2504	2442	2371	2315	390

Dormandy J et al Lancet 2005

PROactive Bad news



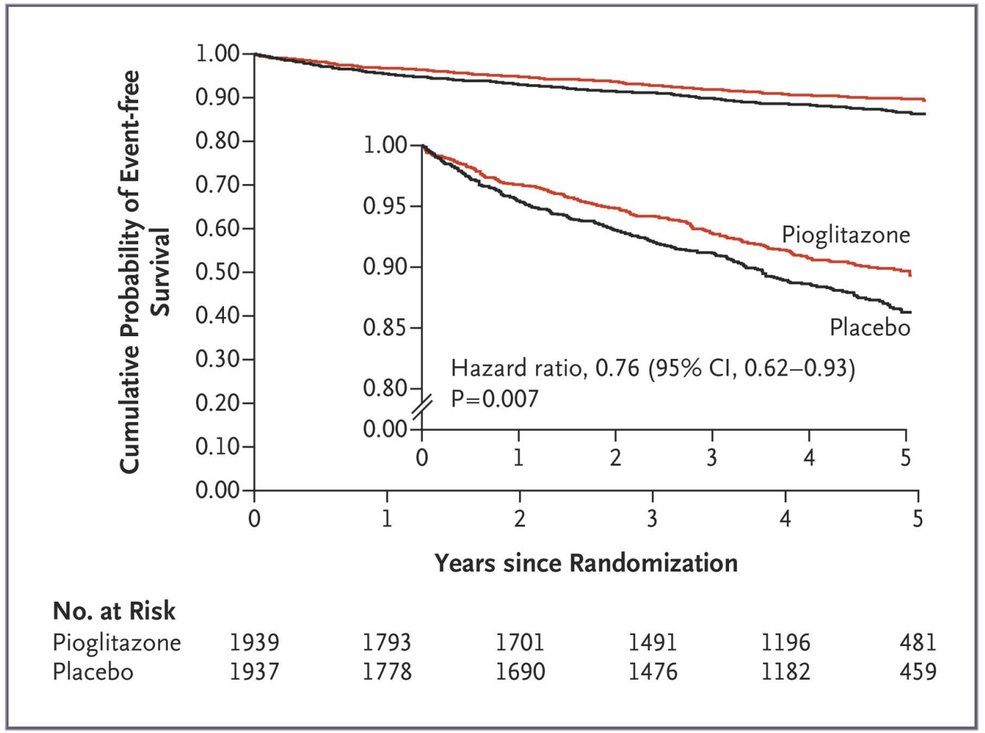
Yki-Jarvinen H Lancet 2005

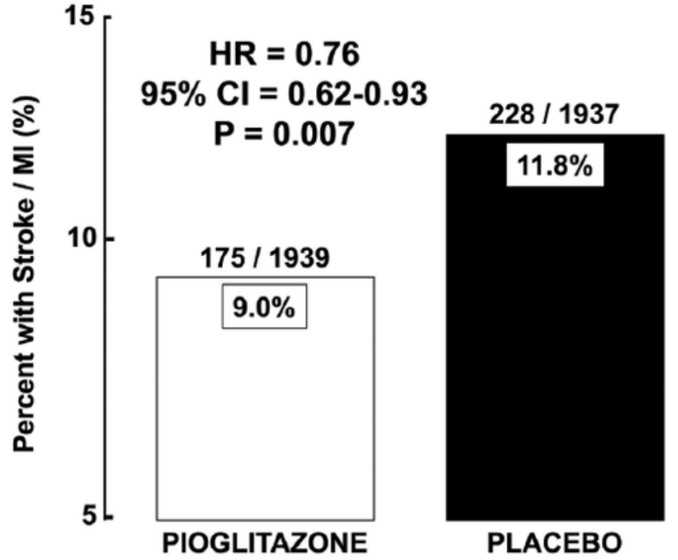
Pioglitazone: IRIS

- N= 3876 individuals without diabetes but with insulin resistance
- Recent h/o TIA or stroke
- Pioglitazone vs placebo for 4.8y

- Pioglitazone ↓ fatal/NF stroke or MI by 24%
- ↓ ACS by 29%
- Mechanism unclear
- Improved insulin sensitivity, blood pressure, plasma glucose, triglycerides, HDL-C, and CRP
- No ↑ in heart failure

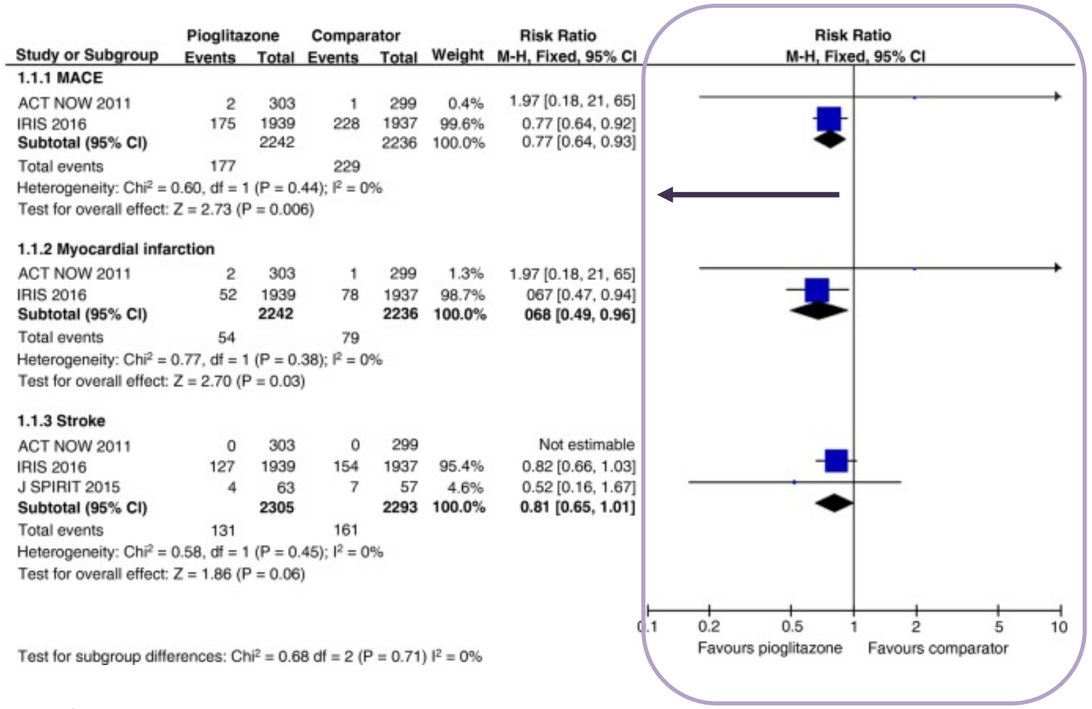
Kernan W et al IRIS Trial, NEJM 2016





Pioglitazone – meta-analysis

Prediabetes, insulin resistance

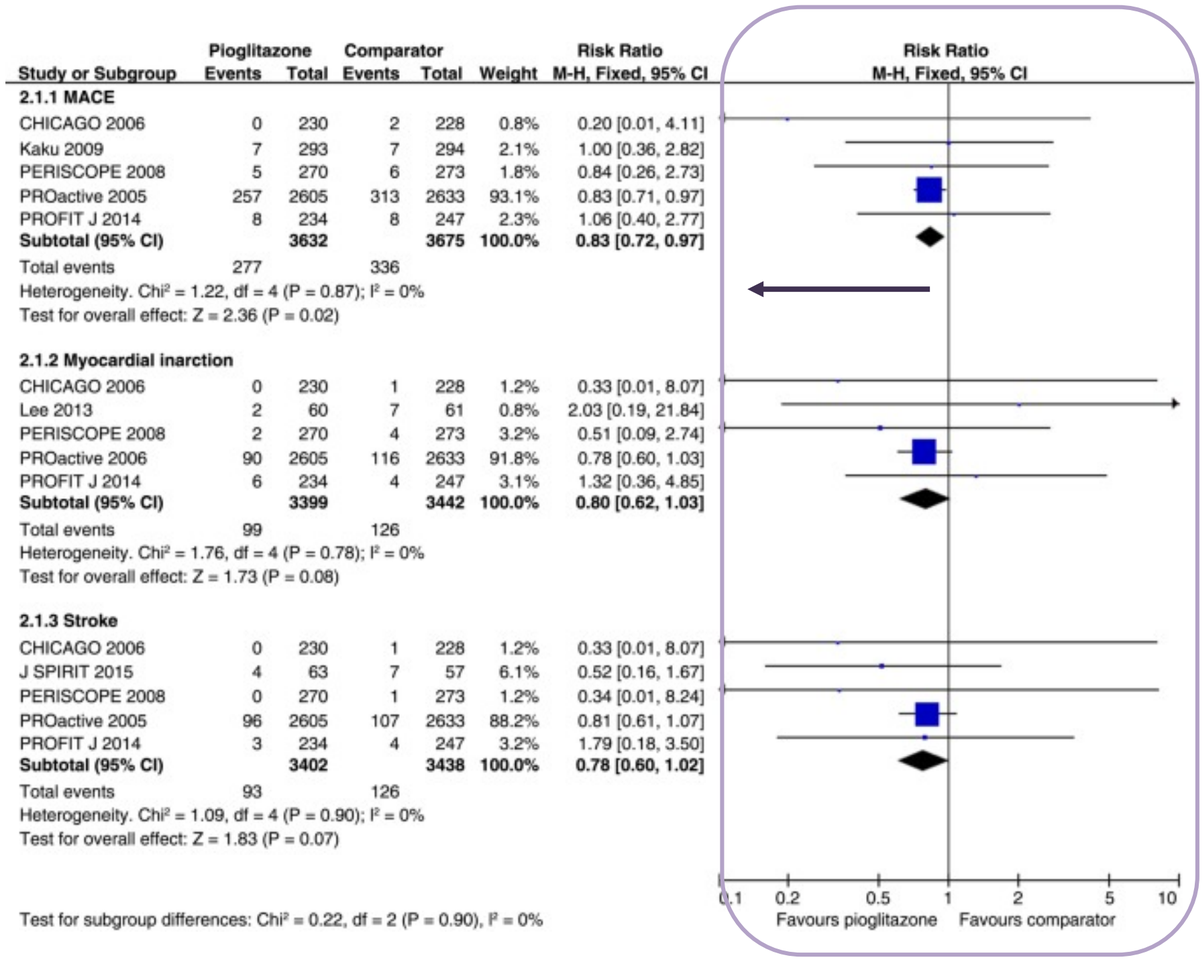


Study or Subgroup	Pioglitazone Events	Total	Comparator Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.1.1 MACE						
ACT NOW 2011	2	303	1	299	0.4%	1.97 [0.18, 21, 65]
IRIS 2016	175	1939	228	1937	99.6%	0.77 [0.64, 0.92]
Subtotal (95% CI)		2242		2236	100.0%	0.77 [0.64, 0.93]
Total events	177		229			
Heterogeneity: Chi² = 0.60, df = 1 (P = 0.44); I² = 0%						
Test for overall effect: Z = 2.73 (P = 0.006)						
1.1.2 Myocardial infarction						
ACT NOW 2011	2	303	1	299	1.3%	1.97 [0.18, 21, 65]
IRIS 2016	52	1939	78	1937	98.7%	067 [0.47, 0.94]
Subtotal (95% CI)		**2242**		**2236**	**100.0%**	**068 [0.49, 0.96]**
Total events	54		79			
Heterogeneity: Chi² = 0.77, df = 1 (P = 0.38); I² = 0%						
Test for overall effect: Z = 2.70 (P = 0.03)						
1.1.3 Stroke						
ACT NOW 2011	0	303	0	299		Not estimable
IRIS 2016	127	1939	154	1937	95.4%	0.82 [0.66, 1.03]
J SPIRIT 2015	4	63	7	57	4.6%	0.52 [0.16, 1.67]
Subtotal (95% CI)		**2305**		**2293**	**100.0%**	**0.81 [0.65, 1.01]**
Total events	131		161			
Heterogeneity: Chi² = 0.58, df = 1 (P = 0.45); I² = 0%						
Test for overall effect: Z = 1.86 (P = 0.06)						
Test for subgroup differences: Chi² = 0.68 df = 2 (P = 0.71) I² = 0%						

↓ MACE RR 0.77
↓ MI RR 0.68

Type 2 diabetes

↓ MACE RR 0.72



Study or Subgroup	Pioglitazone Events	Total	Comparator Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
2.1.1 MACE						
CHICAGO 2006	0	230	2	228	0.8%	0.20 [0.01, 4.11]
Kaku 2009	7	293	7	294	2.1%	1.00 [0.36, 2.82]
PERISCOPE 2008	5	270	6	273	1.8%	0.84 [0.26, 2.73]
PROactive 2005	257	2605	313	2633	93.1%	0.83 [0.71, 0.97]
PROFIT J 2014	8	234	8	247	2.3%	1.06 [0.40, 2.77]
Subtotal (95% CI)		**3632**		**3675**	**100.0%**	**0.83 [0.72, 0.97]**
Total events	277		336			
Heterogeneity. Chi² = 1.22, df = 4 (P = 0.87); I² = 0%						
Test for overall effect: Z = 2.36 (P = 0.02)						
2.1.2 Myocardial inarction						
CHICAGO 2006	0	230	1	228	1.2%	0.33 [0.01, 8.07]
Lee 2013	2	60	7	61	0.8%	2.03 [0.19, 21.84]
PERISCOPE 2008	2	270	4	273	3.2%	0.51 [0.09, 2.74]
PROactive 2006	90	2605	116	2633	91.8%	0.78 [0.60, 1.03]
PROFIT J 2014	6	234	4	247	3.1%	1.32 [0.36, 4.85]
Subtotal (95% CI)		**3399**		**3442**	**100.0%**	**0.80 [0.62, 1.03]**
Total events	99		126			
Heterogeneity. Chi² = 1.76, df = 4 (P = 0.78); I² = 0%						
Test for overall effect: Z = 1.73 (P = 0.08)						
2.1.3 Stroke						
CHICAGO 2006	0	230	1	228	1.2%	0.33 [0.01, 8.07]
J SPIRIT 2015	4	63	7	57	6.1%	0.52 [0.16, 1.67]
PERISCOPE 2008	0	270	1	273	1.2%	0.34 [0.01, 8.24]
PROactive 2005	96	2605	107	2633	88.2%	0.81 [0.61, 1.07]
PROFIT J 2014	3	234	4	247	3.2%	1.79 [0.18, 3.50]
Subtotal (95% CI)		**3402**		**3438**	**100.0%**	**0.78 [0.60, 1.02]**
Total events	93		126			
Heterogeneity. Chi² = 1.09, df = 4 (P = 0.90); I² = 0%						
Test for overall effect: Z = 1.83 (P = 0.07)						
Test for subgroup differences: Chi² = 0.22, df = 2 (P = 0.90), I² = 0%						

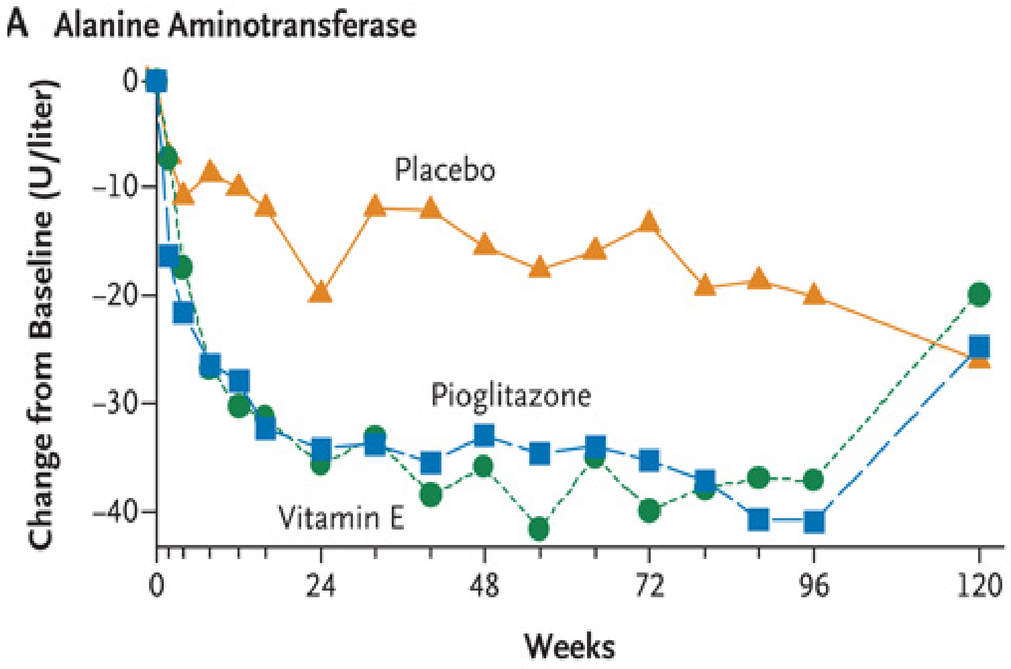
Liao H et al, BMJ open 2017

Pioglitazone: kidney effects

- Decrease in urinary albumin and protein excretion in T2D
- No studies in low eGFR!

Pioglitazone: Effect on the liver

- Improves liver histology in biopsy-proven NASH in patients with or without T2D – decreases steatosis/ hepatic fat
- Improves hepatic fibrosis at any stage of NASH (use up to 24 months)
- Discontinuation of pioglitazone is accompanied by an abrupt ↑ in ALT levels



Sanyal A et al. PIVENS trial. NEJM 2010; Musso G et al. JAMA Int Med 2017

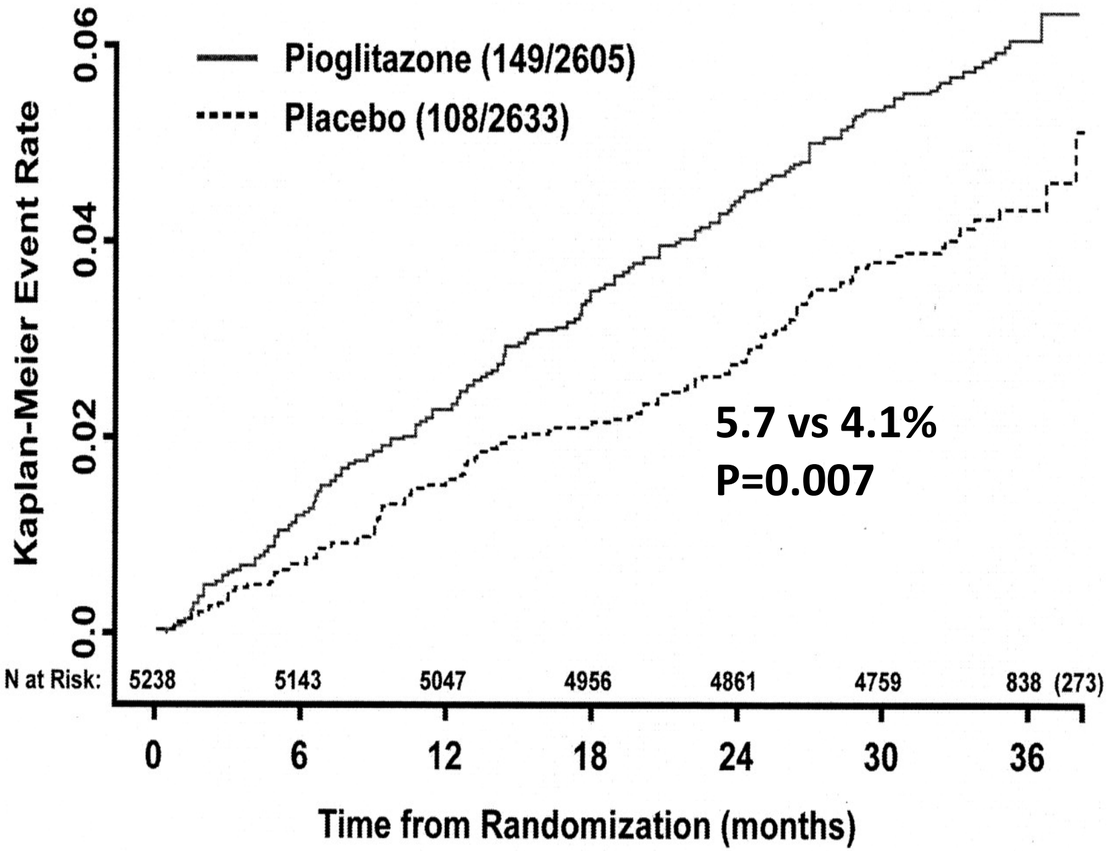
Safety concerns of pioglitazone

Weight gain

- 1-4 kg of adipose tissue mass over 1 yr (2-5% body wt)
- Dose related
- Greater wt gain → greater reductions in A1C → improvements in insulin sensitivity
- ↑ in body weight –due to stimulation of PPARγ receptors in the hypothalamus to augment appetite
- No negative effects of weight gain
- Can be minimized by limiting dose to 30mg

Fluid retention/ heart failure

- Edema – 5-10%
- Dose related; increased with use of sulfonylureas and insulin
  - Causes → renal sodium retention. Peripheral vasodilation
- ↑ serious heart failure events on pioglitazone in PROactive
- Can improve diastolic dysfunction
- *Should not be used in patients with symptomatic HF; if edema present on exam*

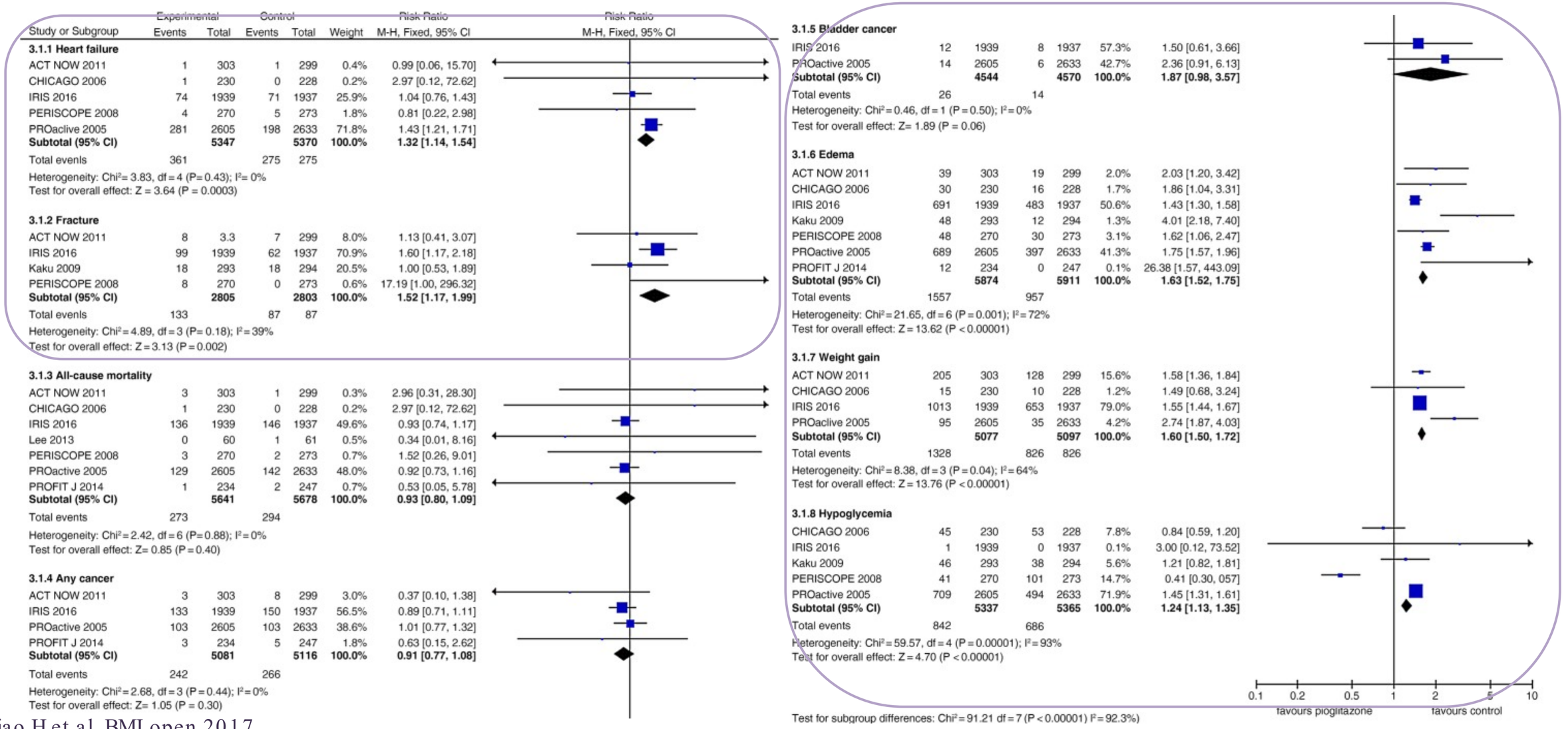


Erdmann E et al Diabetes Care 2007

Other

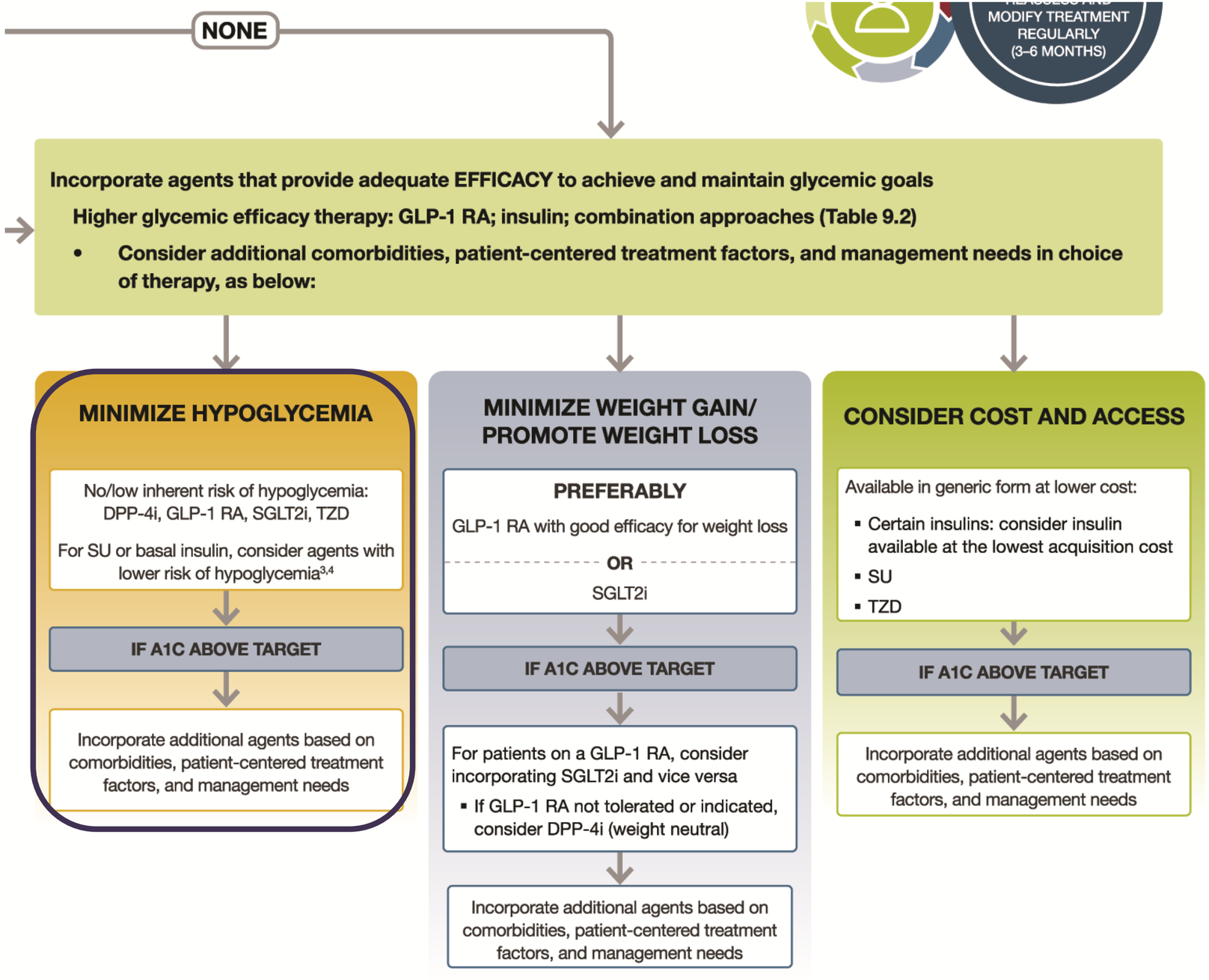
- Bone fractures
- Bladder cancer

Safety outcomes from pioglitazone meta -analysis



Liao H et al, BMJ open 2017

DPP4 inhibitors

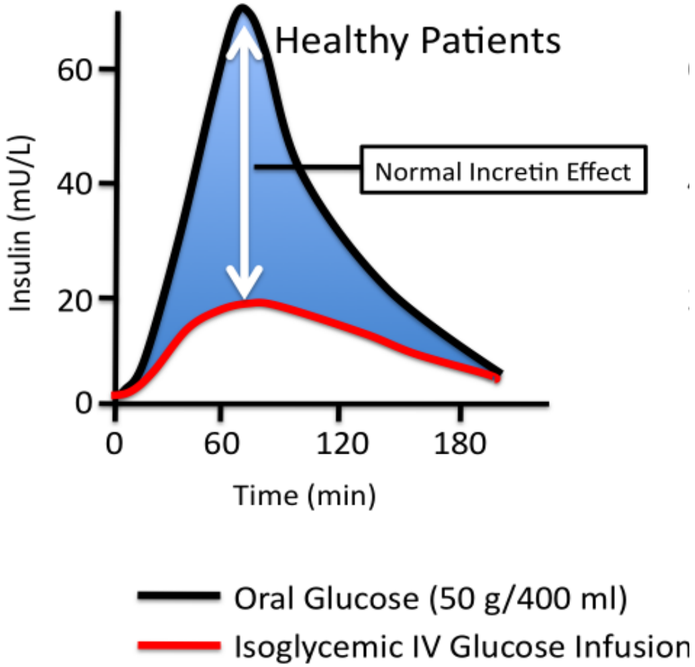

NONE
MODIFY TREATMENT
REGULARLY
(3–6 MONTHS)
Incorporate agents that provide adequate EFFICACY to achieve and maintain glycemic goals
Higher glycemic efficacy therapy: GLP-1 RA; insulin; combination approaches (Table 9.2)
• Consider additional comorbidities, patient-centered treatment factors, and management needs in choice of therapy, as below:
MINIMIZE HYPOGLYCEMIA
No/low inherent risk of hypoglycemia: DPP-4i, GLP-1 RA, SGLT2i, TZD
For SU or basal insulin, consider agents with lower risk of hypoglycemia3,4
IF A1C ABOVE TARGET
Incorporate additional agents based on comorbidities, patient-centered treatment factors, and management needs
MINIMIZE WEIGHT GAIN/ PROMOTE WEIGHT LOSS
PREFERABLY
GLP-1 RA with good efficacy for weight loss
OR
SGLT2i
IF A1C ABOVE TARGET
For patients on a GLP-1 RA, consider incorporating SGLT2i and vice versa
▪ If GLP-1 RA not tolerated or indicated, consider DPP-4i (weight neutral)
Incorporate additional agents based on comorbidities, patient-centered treatment factors, and management needs
CONSIDER COST AND ACCESS
Available in generic form at lower cost:
▪ Certain insulins: consider insulin available at the lowest acquisition cost
▪ SU
▪ TZD
IF A1C ABOVE TARGET
Incorporate additional agents based on comorbidities, patient-centered treatment factors, and management needs

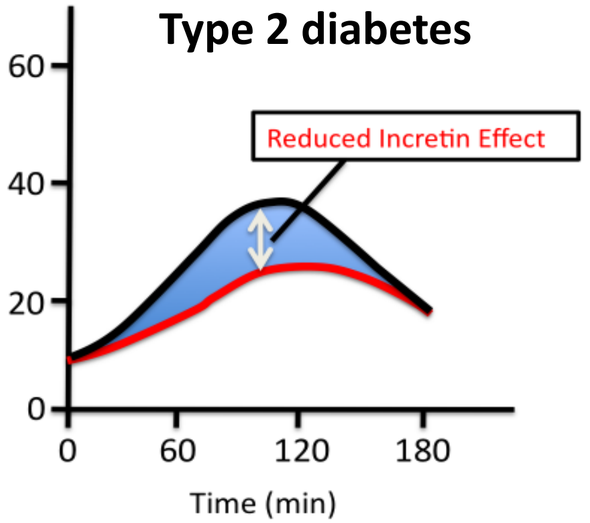
The Incretin Effect

Incretins:

- Glucagon like peptide 1 (GLP-1)
- Gastric inhibitory peptide (GIP)

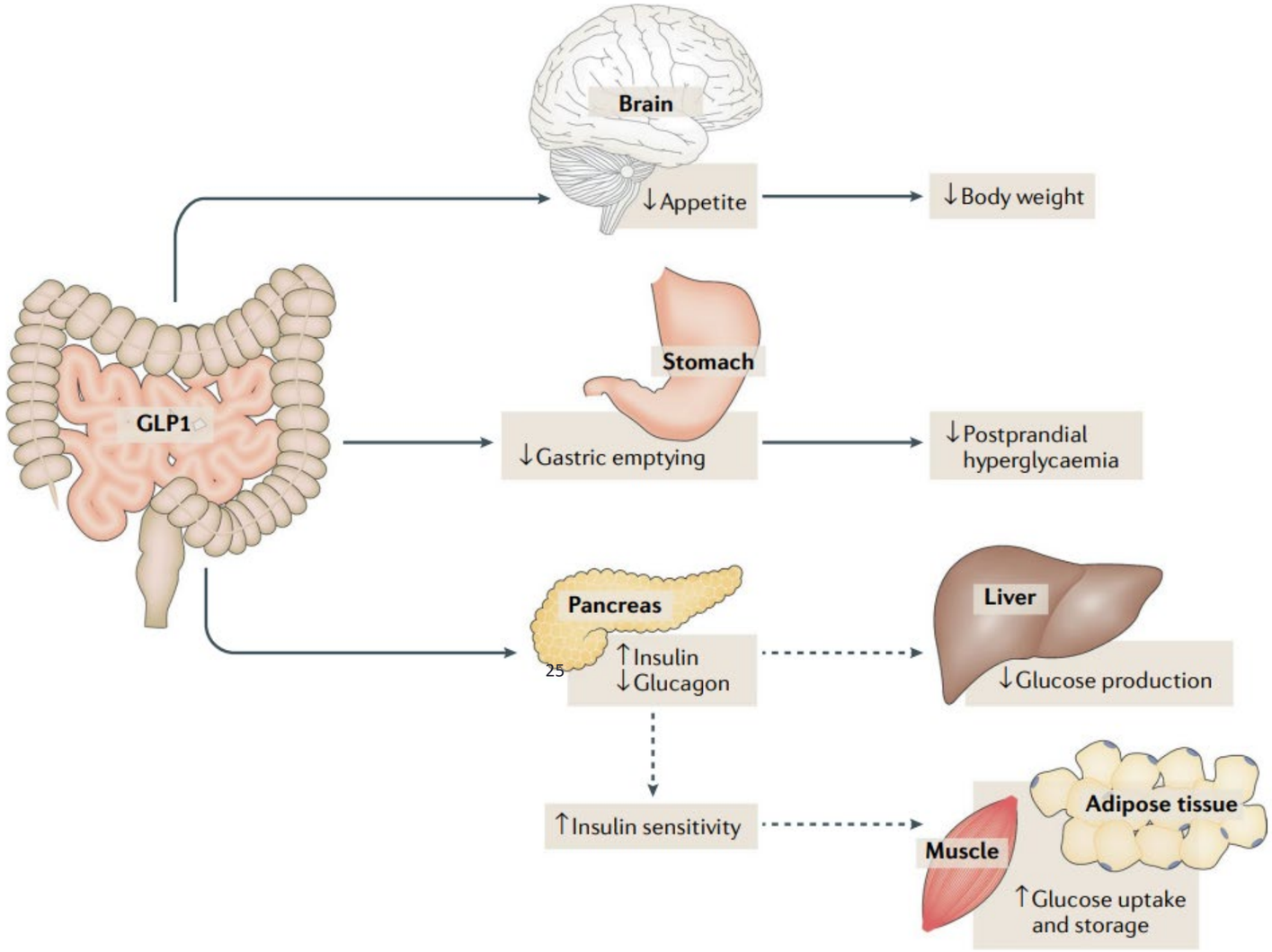
The incretin effect is a term describing greater insulin secretory responses after oral glucose loads than after intravenous glucose infusions that lead to identical glycemic excursions





Nauck M et al.
Diabetologia (1986) 29:46-52

GLP-1 action



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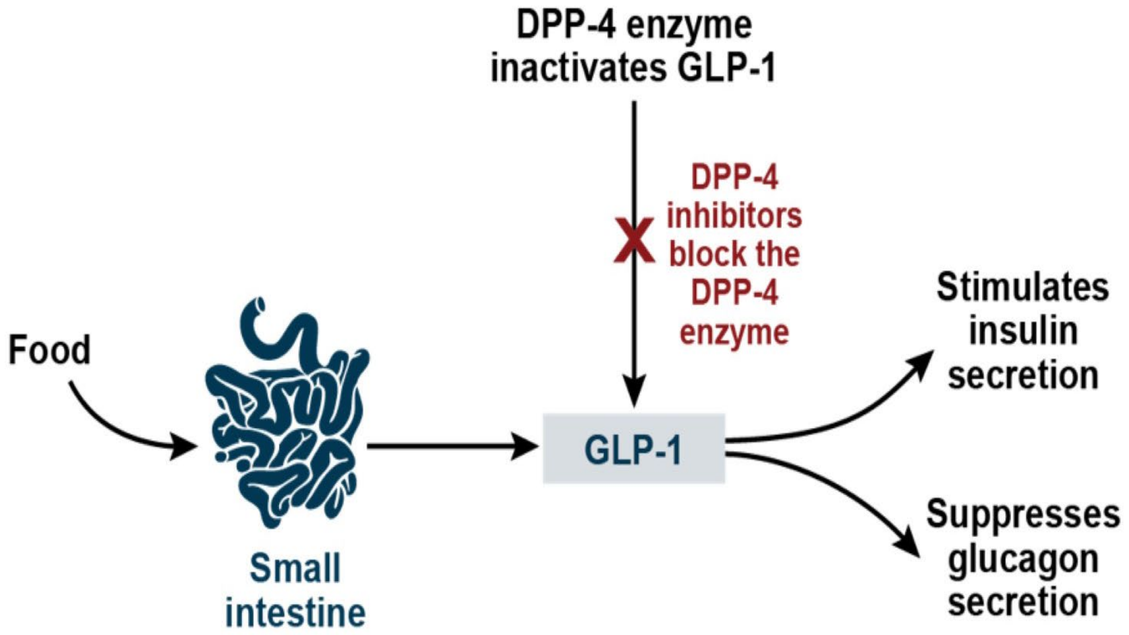
Incretin based therapies – DPP4 inhibitors

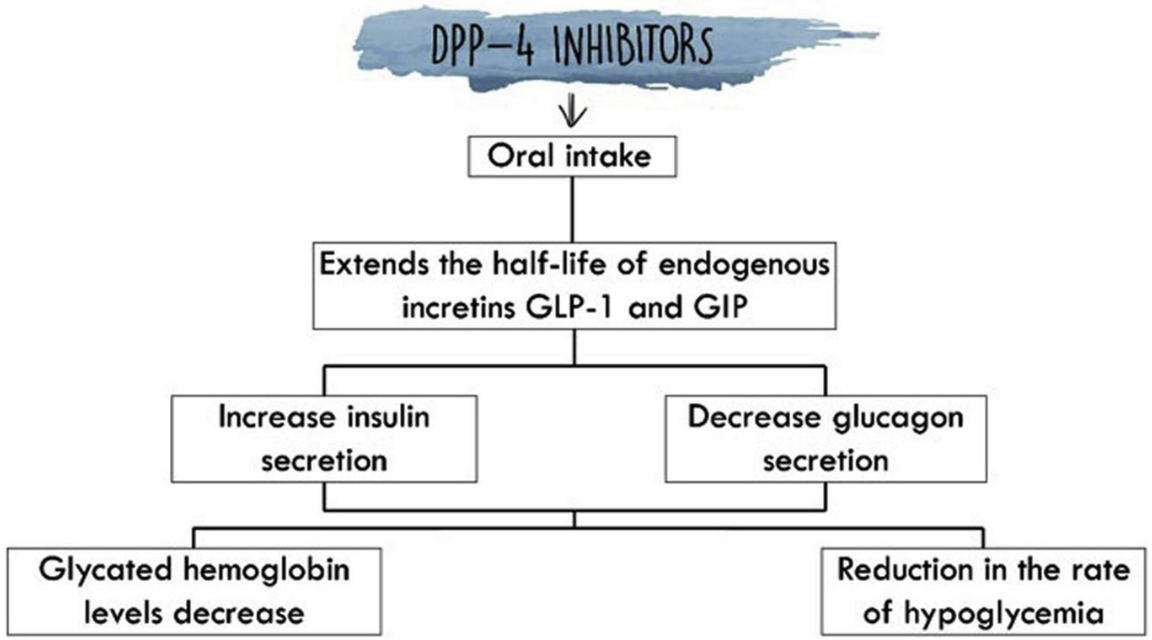
- Incretin enhancers
- Suppress the enzyme dipeptyl peptidase (DPP)-4 that degrades endogenous GLP-1 → increase the concentration of intact, biologically active GLP-1 → augmented interaction with receptors



Lovshin JA and Drucker DJ (2009)

DPP4 inhibitors – glycemic effects

- Reduction in HbA1c ~0.6-0.8%
- Well-tolerated
  - No weight gain when glycemic control improved
  - No hypoglycemia
- Expensive
- Dose adjustment for renal insufficiency for sitagliptin, saxagliptin and alogliptin; Not necessary for linagliptin
- Sitagliptin (Januvia); Saxagliptin (Onglyza); Linagliptin (Tradjenta); Alogliptin (Nesina)



Lovshin JA and Drucker DJ (2009)

DPP-4 inhibitors – cardiovascular effects

- All DPP4 inhibitors are non-inferior to placebo in CVOTs
  - Safe to use in patients with CVD, BUT no demonstrable cardiovascular benefit

Inhibitor	CVOT	Comparator	Cardiovascular safety (MACE), (HR; primary end point)	Risk of hospitalization for heart failure (HR)
Alogliptin	EXAMINE[86]	Placebo	0.96	1.07 ($P = 0.66$)
Linagliptin	CARMELINA[88]	Placebo	1.02	0.90 ($P = 0.26$)
	CAROLINA[89]	Glimepiride	0.98	1.21 ($P = 0.18$)
Saxagliptin	SAVOR-TIMI[85]	Placebo	1.00	1.27 ($P < 0.007$)
Sitagliptin	TECOS[87]	Placebo	0.98	1.00 ($P = 0.98$)
Vildagliptin	None planned[a]	NA	No data	No data

Deacon C 2020

DPP-4 inhibitors - Kidney effects

- CARMELINA – linagliptin vs placebo
- Secondary composite kidney outcome
  - 74% CKD
  - 43% eGFR <45
  - 15% eGFR <30
- Decreased progression of albuminuria

Rosenstock J et al CARMELINA, JAMA 2019

DPP-4 inhibitors - Liver/ NAFLD benefits

- Early uncontrolled trials suggested decrease in plasma ALT levels (sitagliptin)
- In RCTs, DPP-4 inhibitors have been largely negative for treatment of NASH
  - No impact on transaminases or liver fat accumulation
- Recent small study n=75 from China - addition of sitagliptin resulted in similar wt loss compared to liraglutide in pts with “uncontrolled” diabetes

DPP-4 inhibitors – Safety effects

- No pancreatitis or pancreatic cancer signal
- No immune effects
- Saxagliptin - ↑ in heart failure hospitalization (SAVOR-TIMI)
  - Not a class effect
- Vildagliptin – ↑ LV volume but no ↑ in HF; ↑ in liver transaminases
- Safe to use – esp in older individuals, renal impairment, multiple comorbidities

Back to our case

- 54-year-old male with 5 years of type 2 diabetes, no complications
- On metformin 1000mg twice daily
- Has gained 12 lbs working from home over the past 2 years
- Self-pay
- A1C 8.6-9% over recent 12 months (8.6 → 8.9 → 9.2%)

What is the next step?

Take away points

1. Pioglitazone is a cheap, effective drug with likely cardioprotective effects
2. Pioglitazone causes edema, and weight gain; should not be used in people with heart failure
3. Pioglitazone is beneficial in patients with NAFLD
4. DPP4 inhibitors are expensive with no significant CV, renal, or liver benefits
5. DPP4 inhibitors are safe to use in certain populations

Cardiometabolic teleECHO™ Clinic

Patient Recommendation Form

Presentation Date: May 18th, 2022 **Presenter name:** Aristotle Sun, MD

Presenter Facility: UW Valley Medical Clinic

Case Report Recap

- 63 year old Jamaican male with HTN, Sickle cell trait and T2DM
- Taking multiple oral agents for DM, HTN and CVD risk reduction
- Struggles with reducing high starch content of diet and getting physical activity controlled
- On 4 blood pressure medication and 3 oral agents for DM

Medication	Dose	Frequency
metformin	1000 mg	Twice daily
empagliflozin	25 mg	Daily
sitagliptin	100 mg	Daily
benazepril	40 mg	Daily
hydrochlorothiazide	12.5 mg	Daily
atenolol	25 mg	Daily
amlodipine	10 mg	Daily
simvastatin	20 mg	Daily
aspirin	81 mg	Daily
tamsulosin	0.8 mg	Nightly
sildenafil	100 mg	PRN
omeprazole	40 mg	Daily PRN

Case Recommendations:

1. Continue to work on portion size control and offer ideas for food substitutes, given his higher starch traditional intake
2. Due to this patient's sickle cell, continue the current course of overall glycemic control with fructosamine in addition to A1c. An additional option is CGM to confirm average glucose and may also teach about nutrition and activity
3. Encourage this patient to take extra steps during his workday as an uber driver. For example, walking to let passengers out of the car and walking for 5-10 minutes in between picking up new passengers if possible.

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4. There are no changes to consider for this patient's current DM therapy. If appetite cravings continue to be a barrier, consider holding empagliflozin, sitagliptin, and replace with GLP-1 RA (if this medication is available to pt and GERD symptoms on PPI are not limiting).
5. With further nutrition/lifestyle changes, maybe consider holding off on sitagliptin. The goal of minimizing medications may be encouraging to the patient.
6. Consider moderate intensity statin with atorvastatin 20, rather than simvastatin.
7. Screen aldosterone/renin ratio since this patient is currently on four BP medications.
8. There is no indication for ASA therapy.

Nicole Ehrhardt, MD

_____*Nicole Ehrhardt* ____

Physician Signature Nicole Ehrhardt
Represent case July 2022