LECTURE 1: DIABETES MEDICATIONS FOR TYPE 2 DIABETES

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Disclosures:

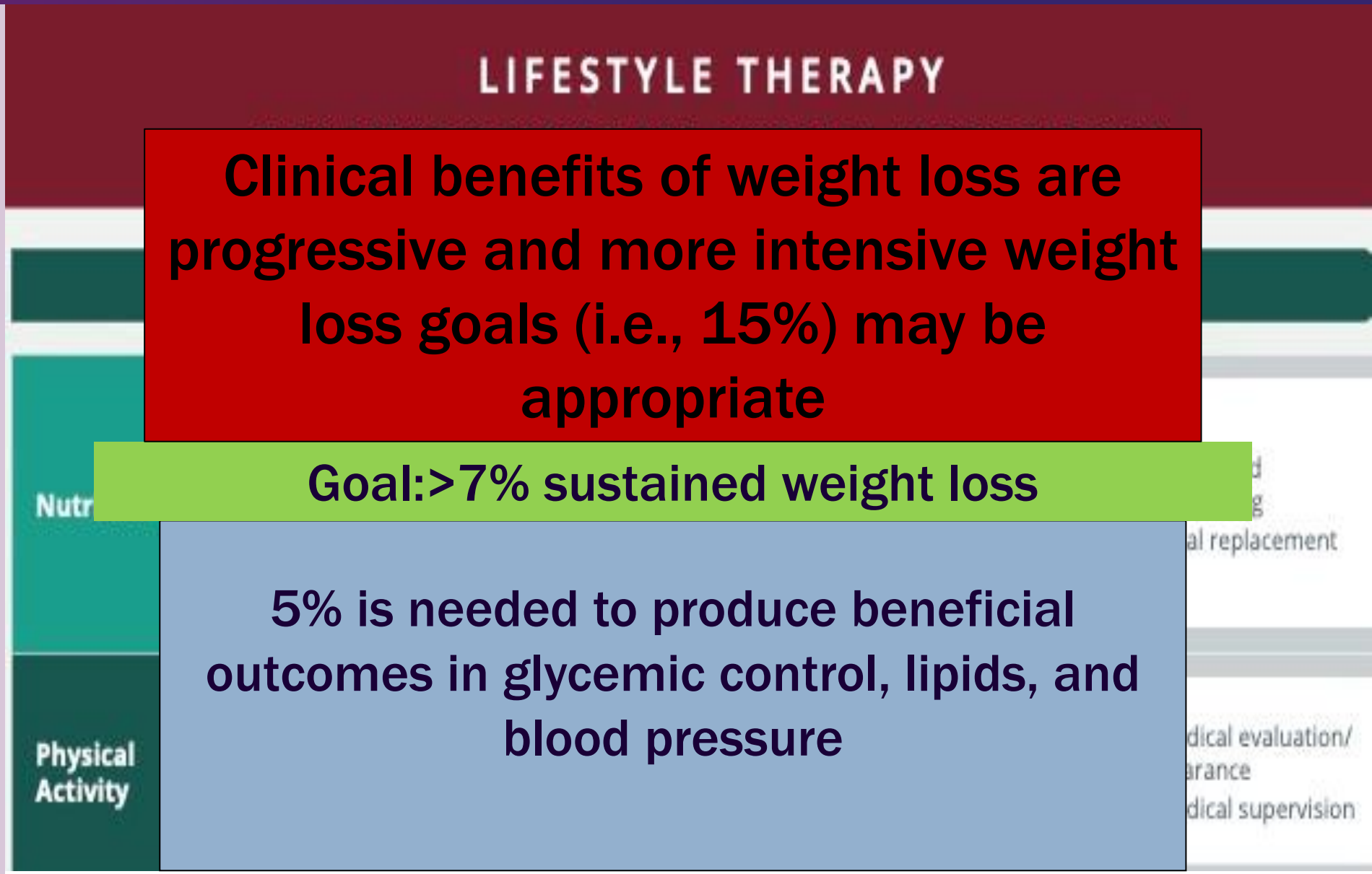
- Dr. Ehrhardt has received a consulting fee from Novo Nordisk and received investigator-initiated grants from Dexcom and educational grants from Merck and NovoNordisk

Objectives:

- Understand how to safely prescribe and use older diabetes medications
- Understand physiology and mechanism of action, efficacy, safety, tolerability, managing side effects, dosing and administration of individual drugs.
- Assess the cardiac and renal benefits or lack of cardiac benefits in these older medications
- Understand use in renal disease and liver disease

Recommendations **ADA**

- Diet, physical activity, and behavioral therapy designed to achieve >5% weight loss should be prescribed for overweight and obese patients with type 2 diabetes ready to achieve weight loss. **A**
- Such interventions should be high intensity (≥16 sessions in 6 months) and focus on diet, physical activity, and behavioral strategies to achieve a 500–750 kcal/day energy deficit. **A**
- Diets should be individualized, as those that provide the same caloric restriction but differ in protein, carbohydrate, and fat content are equally effective in achieving weight loss. **A**
- For patients who achieve short-term weight-loss goals, long-term (≥1 year) comprehensive weight maintenance programs should be prescribed. Such programs should provide at least monthly contact and encourage ongoing monitoring of body weight (weekly or more frequently), continued consumption of a reduced-calorie diet, and participation in high levels of physical activity (200–300 min/week). **A**



Franz MJ, et al. J Acad Nutr Diet 2015; 115:1447–146
Lean ME et al. Lancet 2018;391:541–551
American Diabetes Association Diabetes Care 2019 Jan; 42(Supplement 1): S46-S60
Endocrine Practice: January 2020, Vol. 26, No. 1, pp. 107-139

Insulin

As glucose toxicity resolves, simplifying the regimen and consider changing to insulin sparing agents if possible

Do not be afraid to use early!

American Diabetes Association. 2020 Jan;43(Suppl 1):S98-S110.

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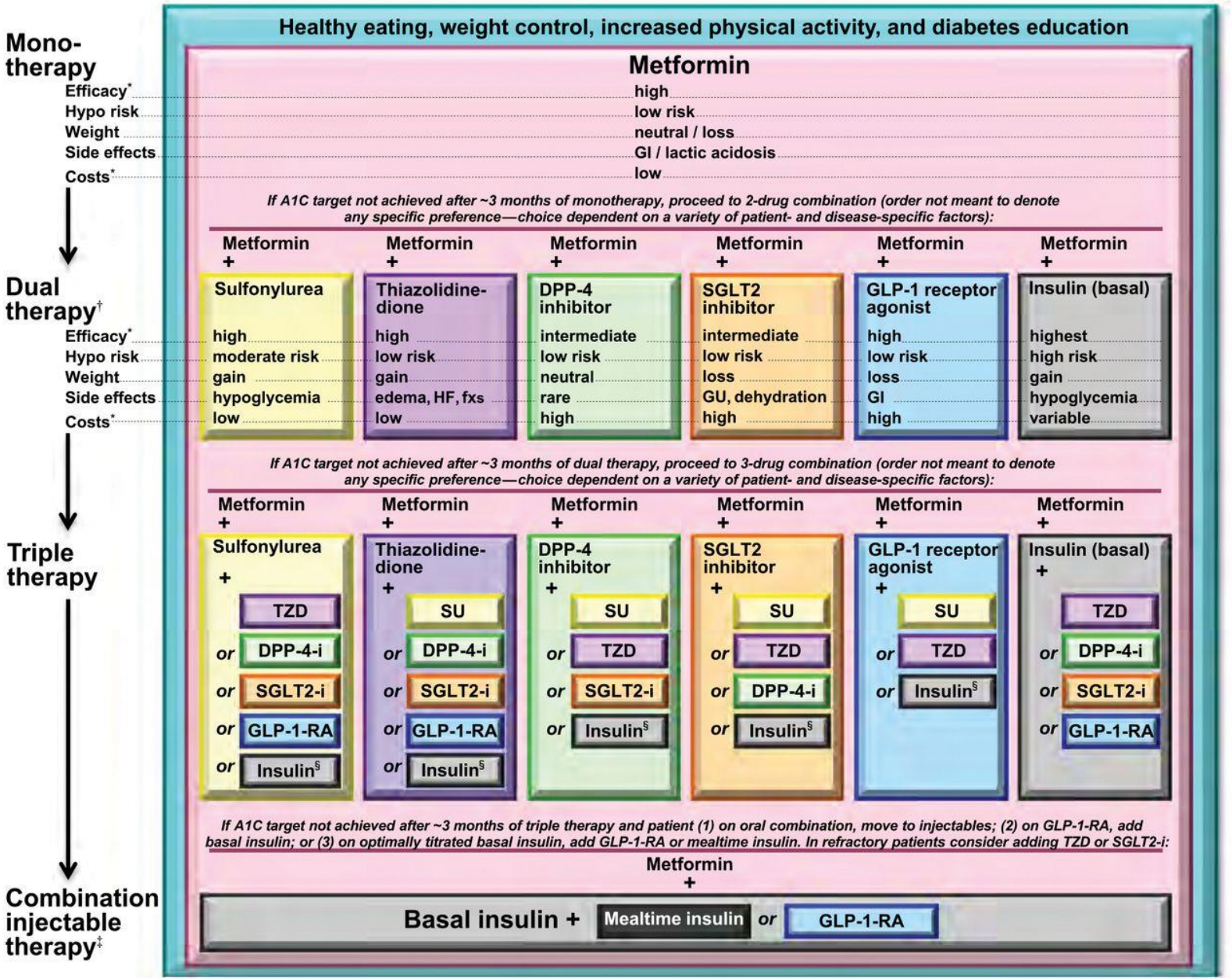
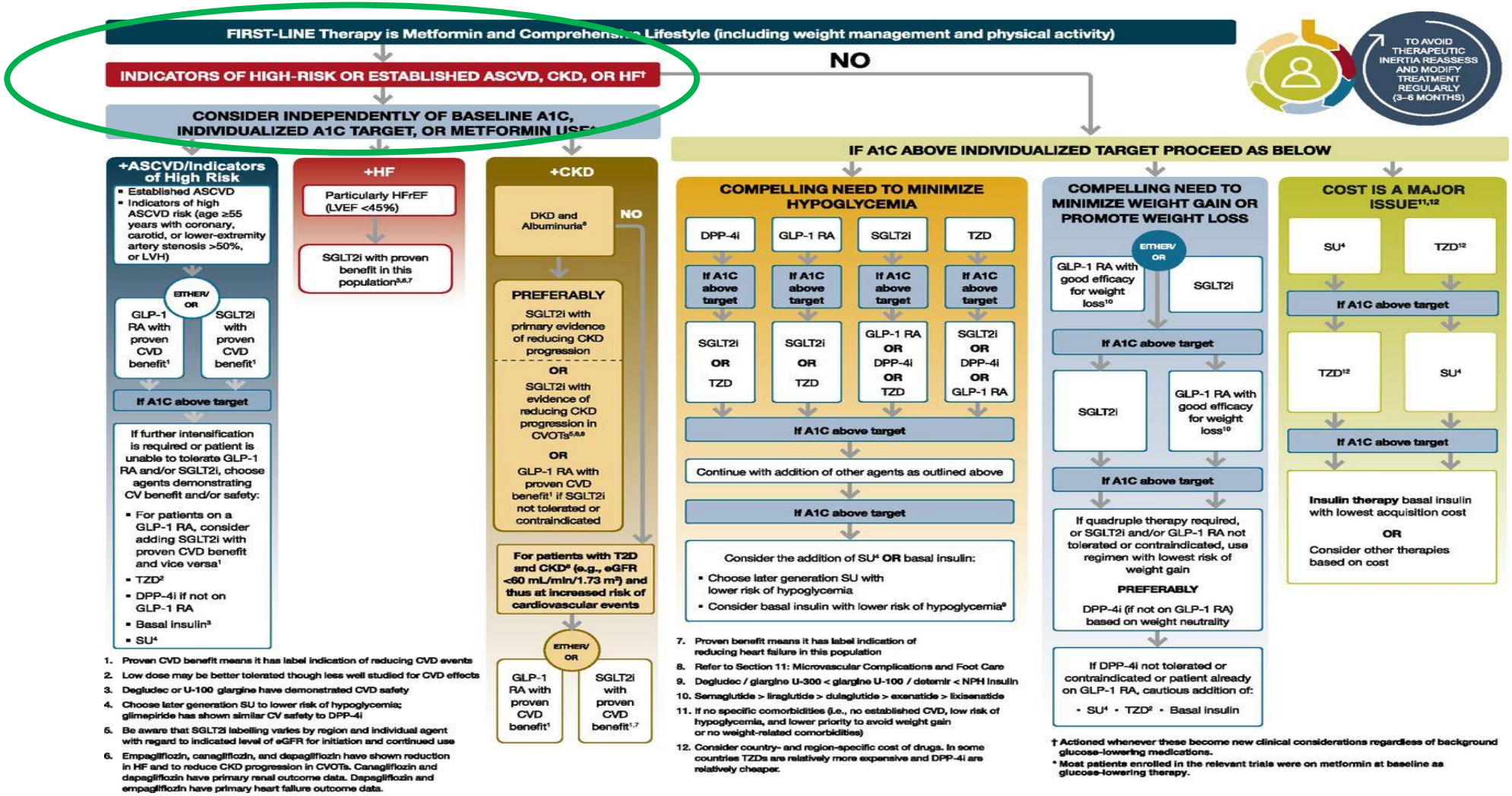


Inzucchi SE et al. Management of hyperglycemia in type 2 diabetes, Diabetes Care 2015;38:140– 14.

Glucose-lowering medication in type 2 diabetes: 2021 ADA Professional Practice Committee (PPC) adaptation of Davies et al.



1. Proven CVD benefit means it has label indication of reducing CVD events
2. Low dose may be better tolerated though less well studied for CVD effects
3. Degludec or U-100 glargine have demonstrated CVD safety
4. Choose later generation SU to lower risk of hypoglycemia; glimepiride has shown similar CV safety to DPP-4i
5. Be aware that SGLT2i labelling varies by region and individual agent with regard to indicated level of eGFR for initiation and continued use
6. Empagliflozin, canagliflozin, and dapagliflozin have shown reduction in HF and to reduce CKD progression in CVOTs. Canagliflozin and dapagliflozin have primary renal outcome data. Dapagliflozin and empagliflozin have primary heart failure outcome data.
7. Proven benefit means it has label indication of reducing heart failure in this population
8. Refer to Section 11: Microvascular Complications and Foot Care
9. Degludec / glargine U-300 < glargine U-100 / detemir < NPH insulin
10. Semaglutide > liraglutide > dulaglutide > exenatide > lixisenatide
11. If no specific comorbidities (i.e., no established CVD, low risk of hypoglycemia, and lower priority to avoid weight gain or no weight-related comorbidities)
12. Consider country- and region-specific cost of drugs. In some countries TZDs are relatively more expensive and DPP-4i are relatively cheaper.

† Actioned whenever these become new clinical considerations regardless of background glucose-lowering medications.
* Most patients enrolled in the relevant trials were on metformin at baseline as glucose-lowering therapy.

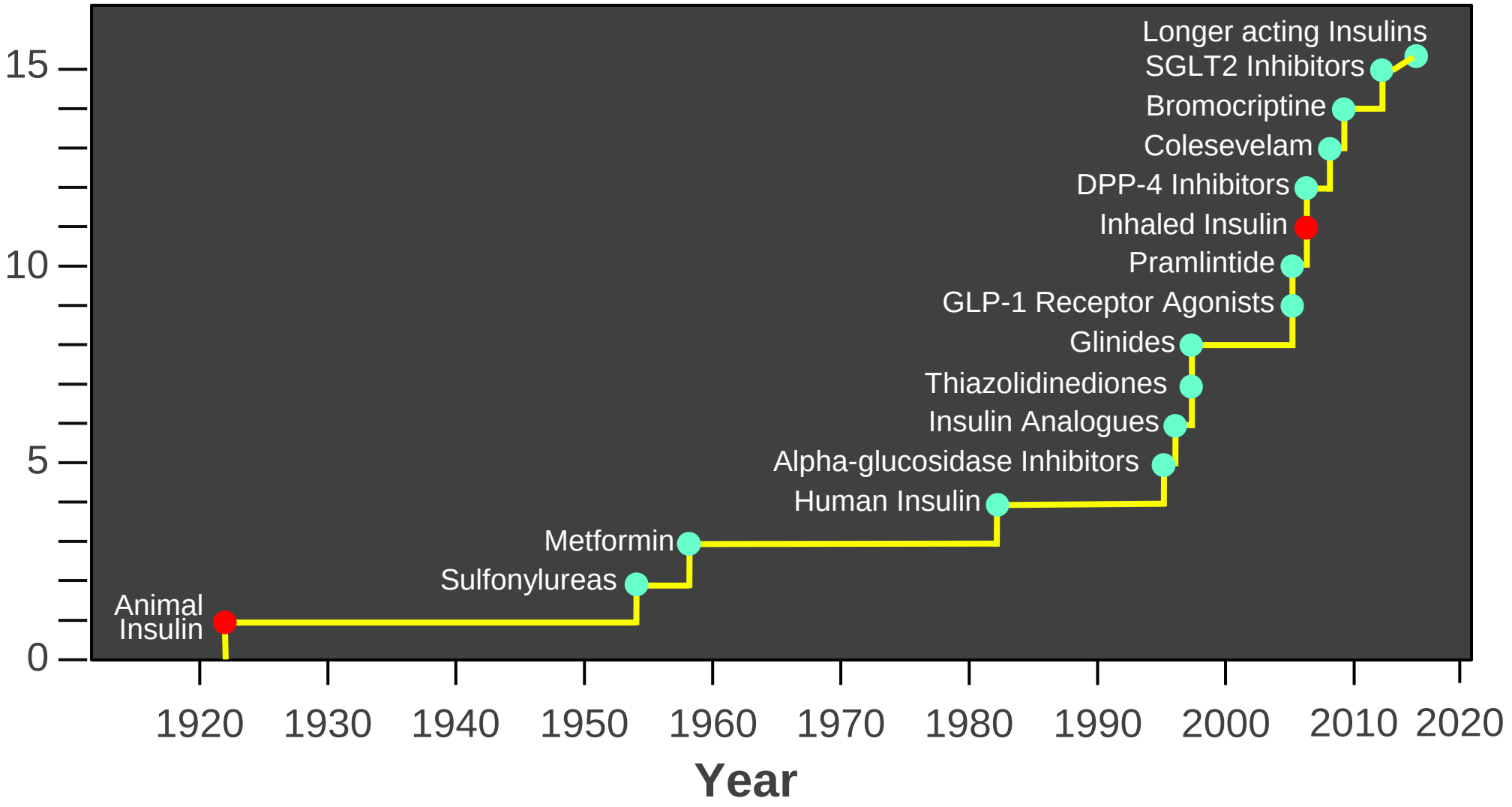
American Diabetes Association Dia Care 2021;44:S111-S124

American Diabetes Association.

How to Think about Selecting the Appropriate Diabetes Medication(s)

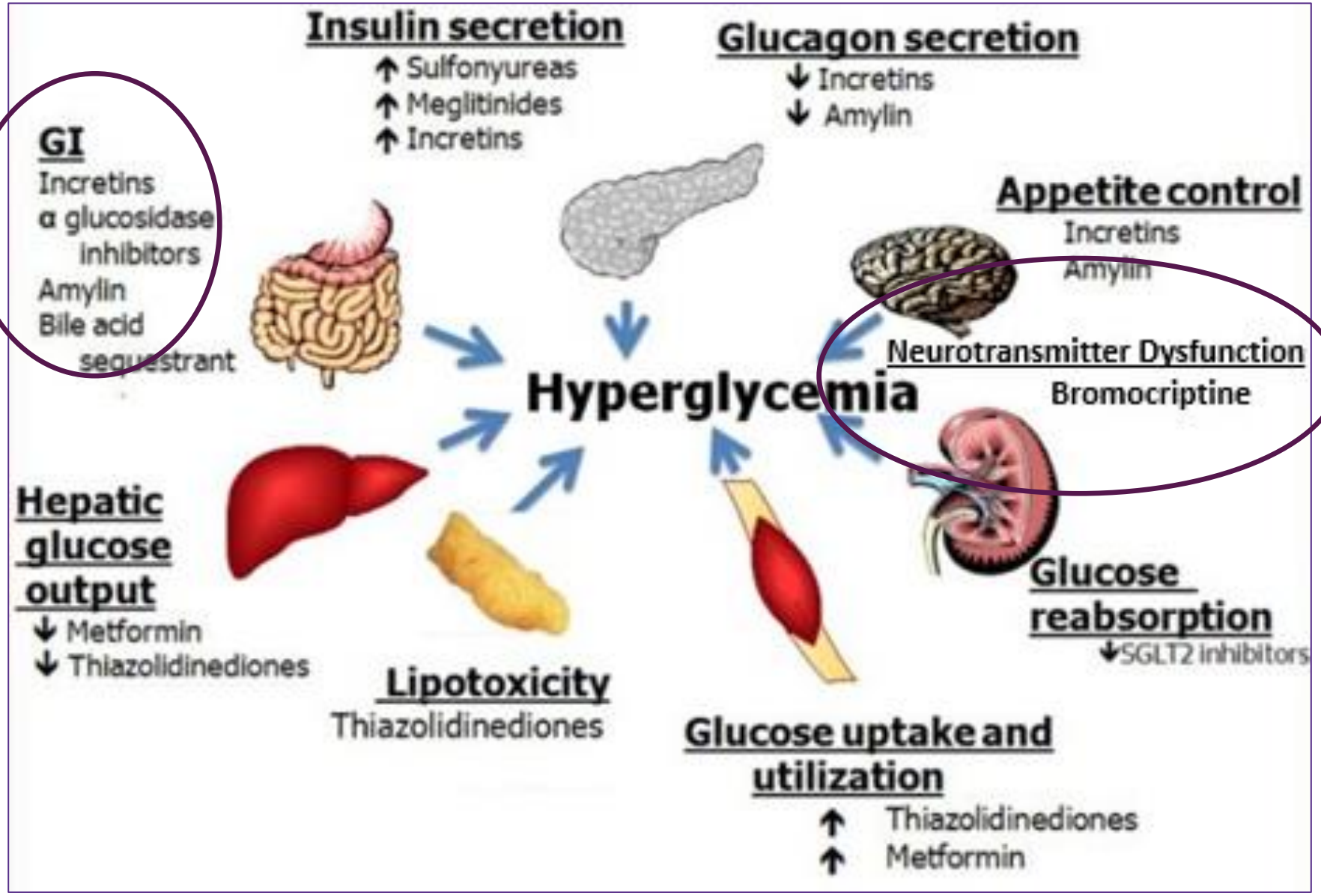
- Mechanism of action
- Efficacy (on average how much does it lower blood sugar)
- Does it cause hypoglycemia yes/no
- Weight gain/Weight loss/Weight neutral
- **Cardiovascular effects**
- **Use in CKD and liver disease and renal/liver protective effect**
- Common side-effects
- Serious side-effects

Classes of Glucose Lowering Agents for Treating Type 2 Diabetes



Modified from Kahn SE et al: Lancet 2014; 383 (9922)

Target Sites of Action



Feingold KR. Endotext [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2000.

Biguanides/Metformin

Biguanides/Metformin

Class/Main Action	Name(s)	Daily Dose Range	Considerations
Biguanides • Decreases hepatic glucose output • First line med at diagnosis of type 2	metformin (Glucophage) Riomet (liquid metformin)	500 - 2500 mg (usually BID w/ meal) 500 - 2500mg 500mg/5mL	**Side effects:** nausea, bloating, diarrhea, B12 deficiency. To minimize GI Side effects, use XR and take w/ meals. **Obtain GFR before starting.** • If GFR <30, do not use. • If GFR <45, don't start Meformin • If pt on Metformin and GFR falls to 30-45, eval risk vs. benefit; consider decreasing dose. **For dye study,** if GFR <60, liver disease, alcoholism or heart failure, restart metformin after 48 hours if renal function stable. **Benefits:** lowers cholesterol, no hypo or weight gain, cheap. Approved for pediatrics, 10 yrs + Lowers A1c 1.0%-2.0%.
	Extended Release-XR (Glucophage XR) (Glumetza) (Fortamet)	(1x daily w/dinner) 500 – 2000 mg 500 – 2000 mg 500 – 2500 mg	

https://diabetesed.net/pocket-cards-insulin-and-diabetes-medication/

Metformin/Risk for Lactic Acidosis

Previous US Food and Drug Administration Prescribing Guidelines for Metformin as Related to Kidney Function

- "DO Not Use"
- Serum creatinine levels:
  - ≥ 1.5 mg/dL males
  - ≥ 1.4 mg/dL females

Source: Metformin final printed labeling

Metformin in Patients With T2D and Kidney Disease: A Systematic Review

Table 2. Possible Approach to Metformin Prescribing in the Setting of CKD[a]

CKD Stage	eGFR, mL/min per 1.73 m^2	Maximal Total Daily Dose, mg	Other Recommendations
1	≥90	2550	
2	60 -<90	2550	
3A	45 -<60	2000	Avoid if kidney function is or expected to become unstable Consider more cautious follow-up of kidney function
3B	30 -<45	1000	Do not initiate therapy at this stage but drug may be continued Avoid if kidney function is or expected to become unstable Consider more cautious follow-up of kidney function
4	15 -<30	Do not use	
5	<15	Do not use	

Abbreviations: CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate.

[a] This strategy has not been evaluated or validated in a clinical trial; there are no data to support its efficacy, safety, or potential to improve clinical outcomes.

- 3 per 100,000 person-years to 10 per 100,000 person-years
-Indistinguishable from the background rate in the overall population with diabetes.

Metformin: FDA Safety Review of Metformin-Containing Drugs April 2016 updated

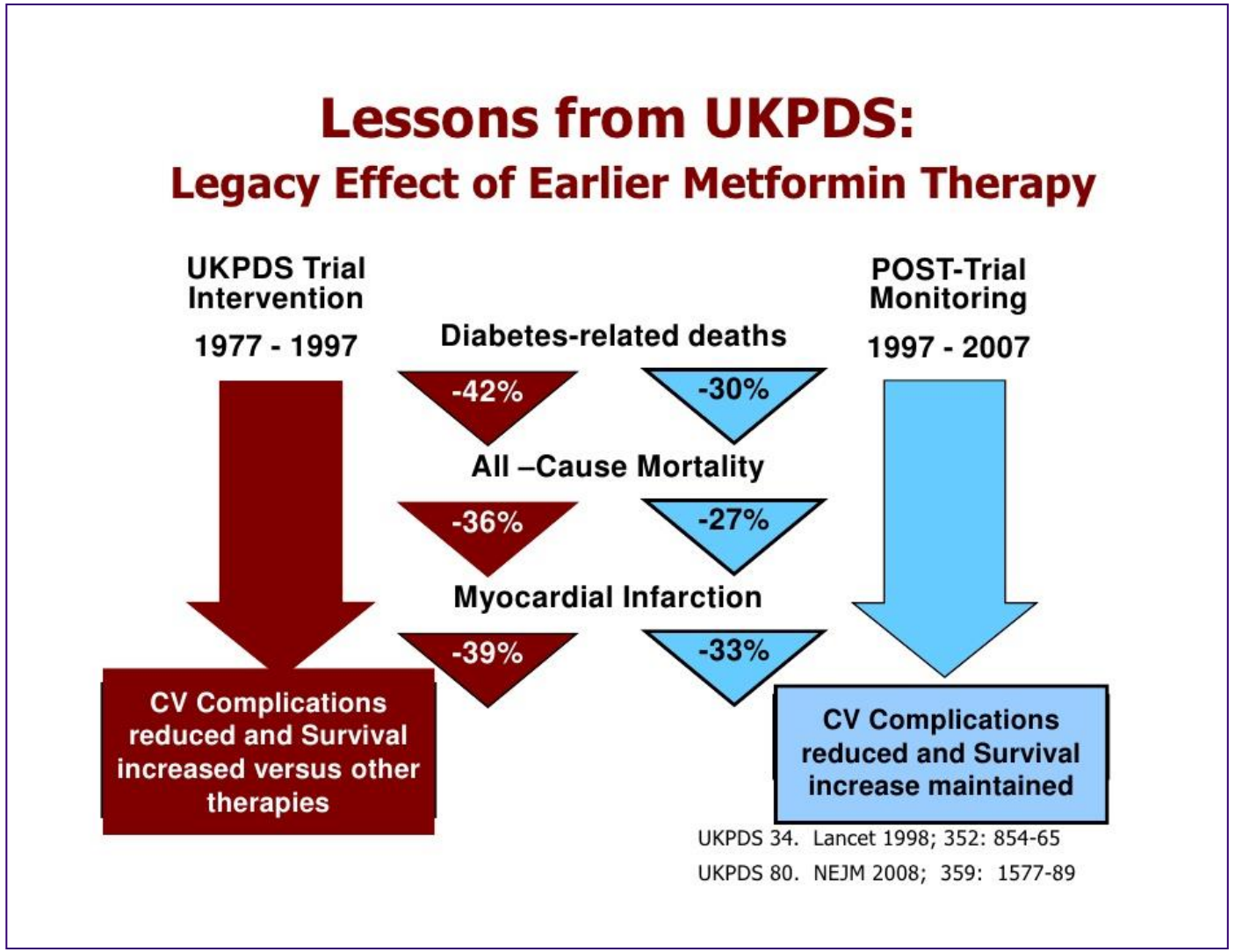
Inzucchi SE et. Al JAMA. 2014;312(24):2668-2675.

Liver Disease and Metformin

- 50%-70% reduction in HCC risk among those treated with metformin
- Hep C : reduced in risk for HCC, liver related mortality, and transplantation,.
- Reduce the incidence of overt hepatic encephalopathy by 8 folds through inhibition of glutaminase activity
- Metformin is often withheld from patients with liver diseases due to an exaggerated concern for metformin-associated lactic acidosis (MALA)
- MALA is an exceedingly rare condition with an estimated incidence of < 10 per 100000 patient-years of exposure in patients without significant renal impairment

Ampuero J et al. PLoS One. 2012;7:e49279
Nkontchou G et al.. J Clin Endocrinol Metab. 2011;96:2601-2608
hang X et al. Hepatology. 2014 Dec;60(6):2008-16

UKPDS:CV risk reduction



- The number needed to treat to avoid one death was 14
- ARR 0.07

Summary: Metformin

- Try again low dose with Extended release (XR) in those with hx of GI intolerance
- Do not stop if GFR > 30 and can start GFR> 45
- Cheap, low risk hypoglycemia, causes slight weight loss
- May have cancer benefit effects, may have CV benefits
- Consider use in prediabetes (hx of GDM, BMI >30, Age <60)

Sulfonylureas

Sulfonylureas

- Glimepiride and glipizide associated with a reduced likelihood of hypoglycemia
- Glimepiride also improves first-phase insulin secretion

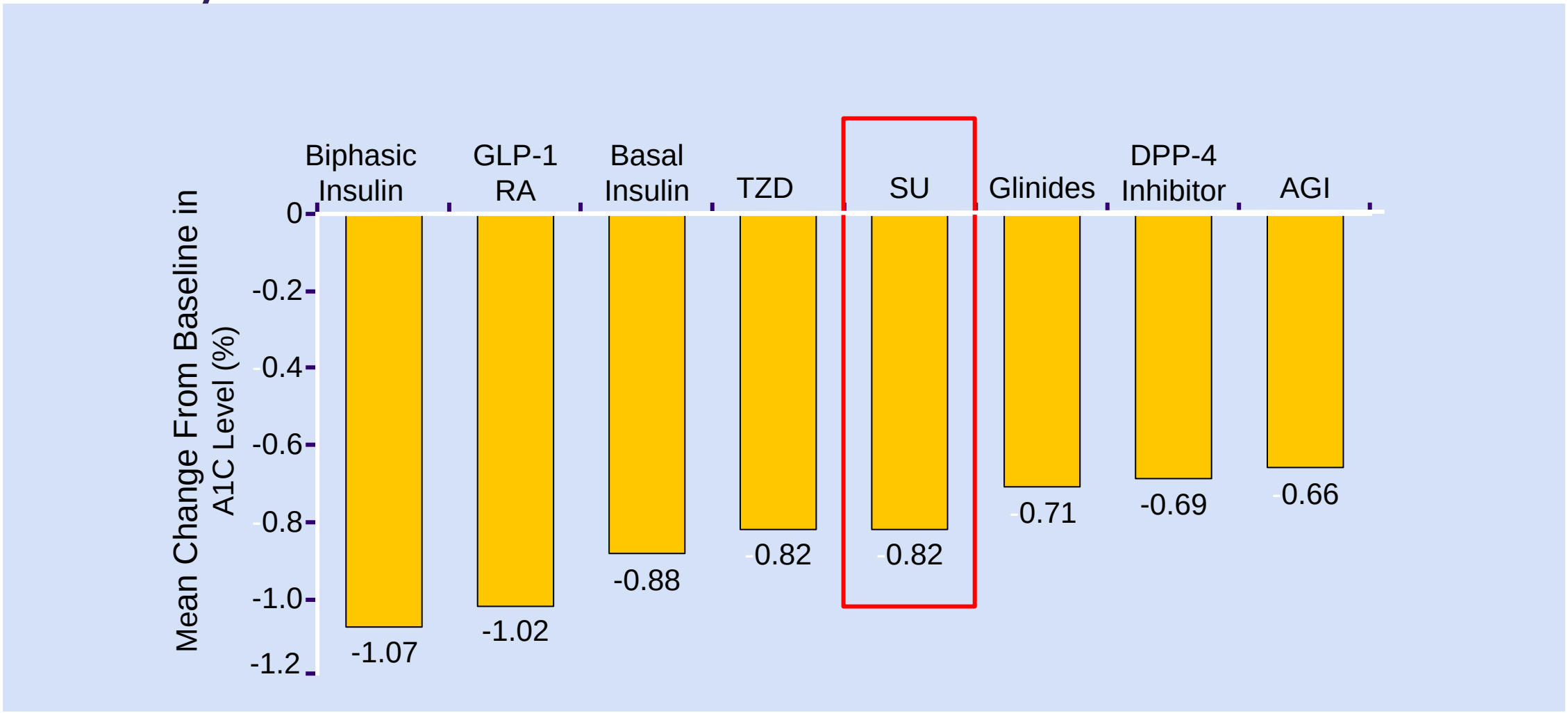
  -reducing postprandial hyperglycemia.
- Glyburide more associated with hypoglycemia

Sulfonylureas • Stimulates sustained insulin release	glyburide: (Diabeta) (Glynase PresTabs)	 1.25 – 20 mg 0.75 – 12 mg	Can take once or twice daily before meals. Low cost generic. **Side effects**: hypoglycemia and weight gain. Eliminated via kidney. **Caution**: Glyburide most likely to cause hypoglycemia. Lowers A1c 1.0% – 2.0%.
	glipizide: (Glucotrol) (Glucotrol XL)	2.5 – 40 mg 2.5 – 20 mg	
	glimepiride (Amaryl)	1.0 – 8 mg	

https://diabetesed.net/pocket-cards-insulin-and-diabetes-medication/

Diabetes Care 2002 Sep; 25(9): 1607-1611.

Efficacy added to Metformin



Liu SC, et al. Diabetes Obes Metab. 2012;14:810-820.

Sulfonylureas in CKD

Stage 2(eGFR 60-90)**& Stage 3a&b** (eGRF 59-30):

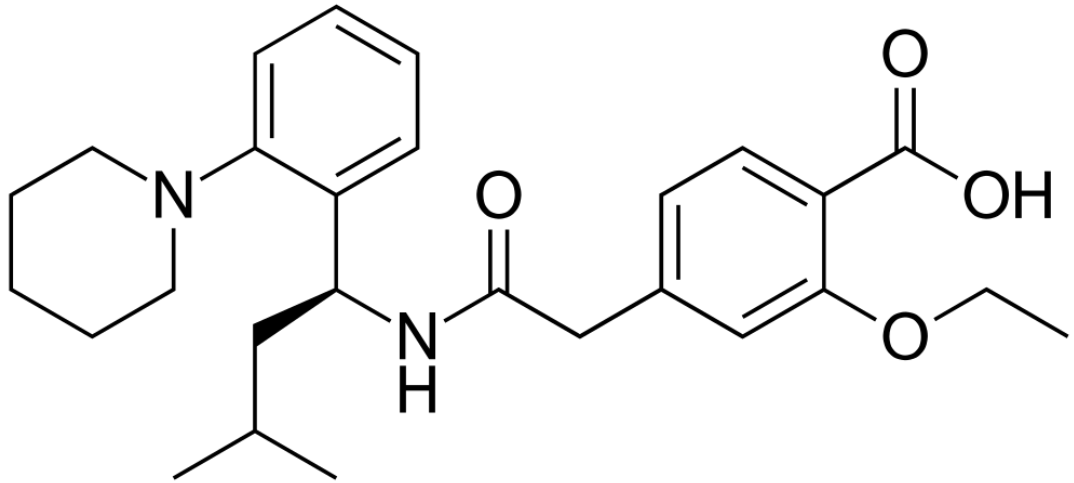
- Glyburide (Glibenclamide): Limit use in stage 2. Not recommended Stage 3
- Glimiperide: Start at reduced dose 1-2mg daily for Stage 2 -3 . Not recommended Stage 4.

Stage 4 CKD (eGFR <30)

*Glipizide short acting is preferred (dose 2.5 to 10 mg/day)

Diabetologia. 1996 Dec; 39(12):1617-24
Jönsson A et al. Eur J Clin Pharmacol. 1998 Feb; 53(6):429-35

Meglitinide(glinide)



Short Acting Secretagogues:

Nateglinide (Starlix 60-120mg with meals)

- CKD stage 5 avoid
- CKD stage 4 reduce to 60 mg TID

Repaglinide (Prandin 0.5 mg to 4 mg before meals)

- CKD stages 4 and 5 without dose reduction.

Diabetes Care 2003 Mar; 26(3): 886-891
Oncotarget 2017 Sep 29; 8(44): 78086–78095

Sulfonylureas and Liver disease

- Main risk hypoglycemia
- Increased odds of HCC development by up to 3 folds amongst patients with T2DM treated with sulfonylureas
- Expert opinions advise that insulin secretagogues be avoided or used with extreme caution in patients with CLD/ESLD

Singh S, et al Am J Gastroenterol. 2013 Jun;108(6):881-91
Lee JY et al.. Sci Rep. 2019;9:853

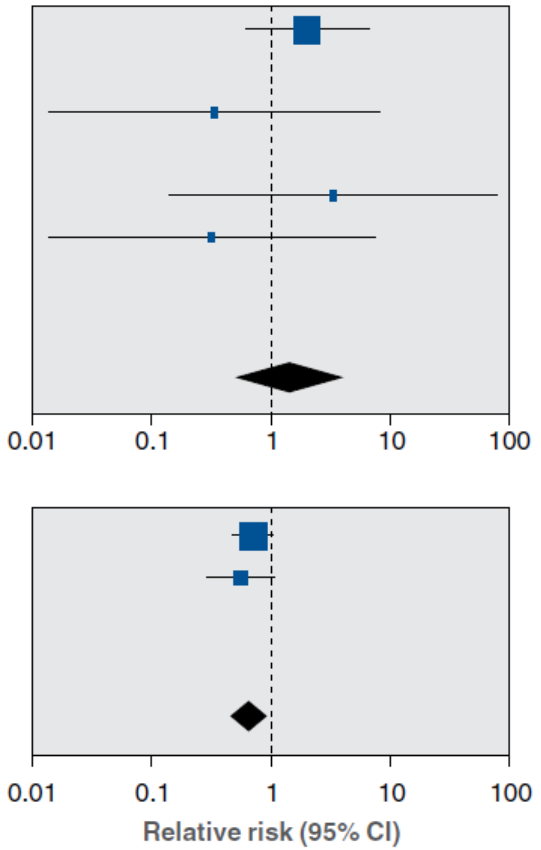
Second and Third Generation Sulfonylurea vs. Metformin Monotherapy in Patients with Type 2 Diabetes

B: Cardiovascular mortality

ADOPT 2006[20–26]	8/1447	4/1455	2.01 (0.61–6.66)
Campbell et al., 1994[27]	0/24	0/24	Not estimable
DeFronzo et al., 1995[29]	0/209	1/210	0.33 (0.01–8.17)
Derosa et al., 2004[42]	0/81	0/83	Not estimable
Hermann et al., 1991b[31–34]	1/34	0/38	3.34 (0.14–79.42)
Lawrence et al., 2004[36]	0/22	1/21	0.32 (0.01–7.42)
Tosi et al., 2003[38]	0/22	0/22	Not estimable
Yamanouchi et al., 2005[43]	0/37	0/39	Not estimable
Overall	9/1876	6/1892	1.47 (0.54–4.01)
Heterogeneity: I^2 = 0%			

C: Nonfatal macrovascular outcomes

ADOPT 2006[20–26]	41/1447	58/1455	0.71 (0.48–1.05)
Hermann et al., 1991b[31–34]	9/34	18/38	0.56 (0.29–1.07)
Tosi et al., 2003[38]	0/22	0/22	Not estimable
Yamanouchi et al., 2005[43]	0/37	0/39	Not estimable
Overall	50/1540	76/1554	0.67 (0.48–0.93)
Heterogeneity: I^2 = 0%			



No increased risk with Sulfonylurea use

Favors Sulfonylurea use

All-cause Mortality: RR 0.98, 95% CI 0.61 to 1.58

Cardiovascular Mortality :RR 1.47 95% CI 0.54 to 4.01

CMAJ Open. 2014 Jul-Sep; 2(3): E162–E175

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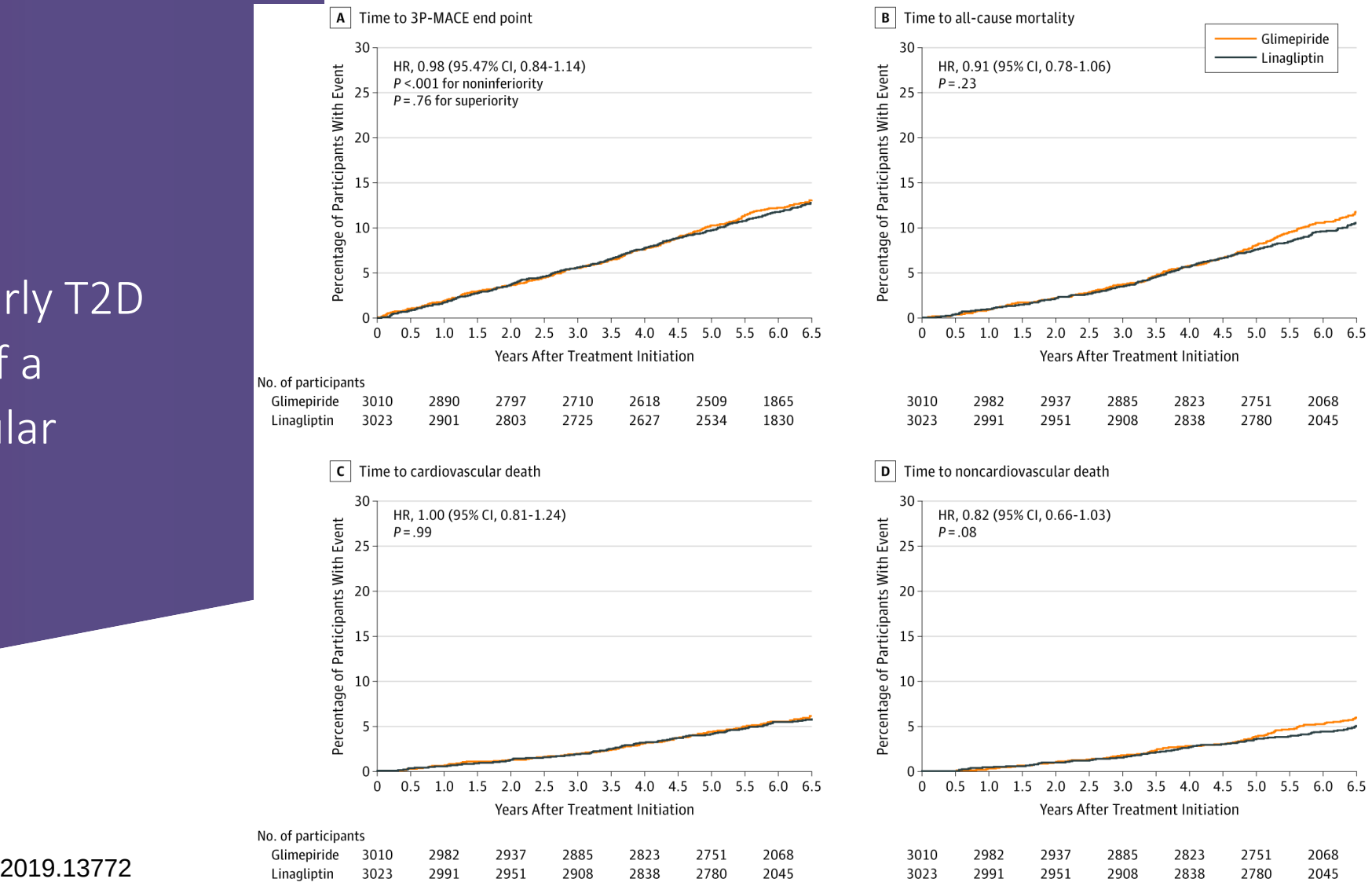
FROM: EFFECT OF LINAGLIPTIN VS GLIMEPIRIDE ON MAJOR ADVERSE CARDIOVASCULAR OUTCOMES IN PATIENTS WITH TYPE 2 DIABETES: THE CAROLINA RANDOMIZED CLINICAL TRIAL

- Pts with CV risk and early T2D had non-inferior risk of a composite cardiovascular outcome over 6.3 yrs.



JAMA. 2019;322(12):1155-1166. doi:10.1001/jama.2019.13772

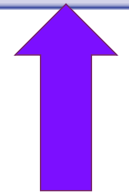
Summary: Sulfonylureas

- Continue both metformin and sulfonylureas(glimiperide) if start basal insulin
- Use glimepiride if possible given has more post meal benefit
- Start low dose if eGFR < 60 i.e. 1mg glimepiride
- If eGFR < 30 use glipizide short acting 2.5mg daily to bid
- Weight gain and no CV benefit but also no harm
- Cost effective but may increase risk for hypo

Dipeptidyl Peptidase (DPP)-4 Inhibitors

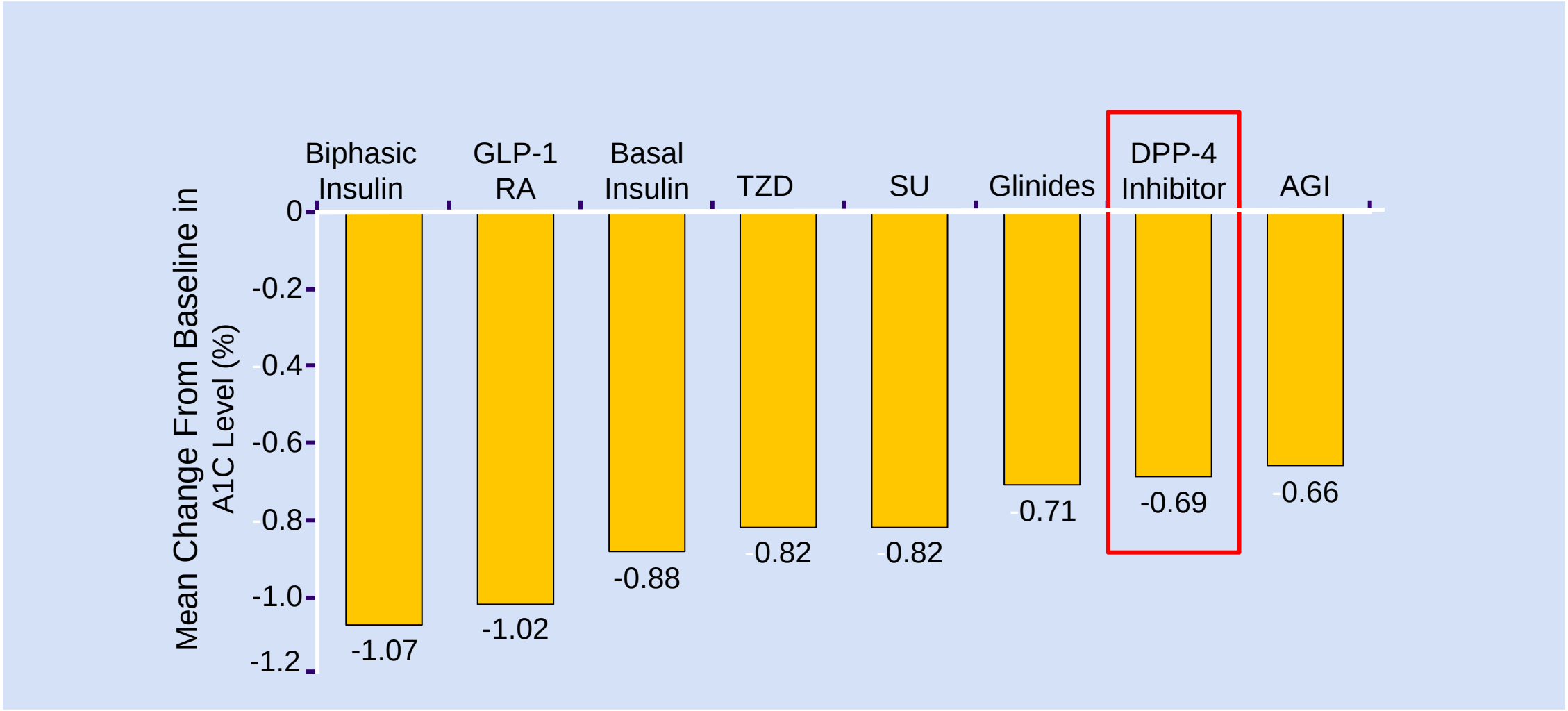
Dipeptidyl Peptidase (DPP)-4 Inhibitors

Class/Main Action	Name(s)	Daily Dose Range	Considerations
DPP – 4 Inhibitors "Incretin Enhancers" • Prolongs action of gut hormones • Increases insulin secretion • Delays gastric emptying	sitagliptin (Januvia)	25 - 100 mg daily – eliminated via kidney*	*If creat elevated, see med insert for dosing. **Side effects:** headache and flu-like symptoms. **Can cause severe, disabling joint pain.** Contact MD, stop med. Report signs of pancreatitis. †Saxagliptin and alogliptin can increase risk of heart failure. Notify MD for shortness of breath, edema, weakness, etc. No wt gain or hypoglycemia. Lowers A1c 0.6%-0.8%.
	saxagliptin (Onglyza)†	2.5 - 5 mg daily – eliminated via kidney*, feces	
	linagliptin (Tradjenta)	5 mg daily – eliminated via feces	
	alogliptin (Nesina)†	6.25 - 25 mg daily – eliminated via kidney*	



http://diabetesed.net/pocket-cards-insulin-and-diabetes-meds

Efficacy added to Metformin



Liu SC, et al. Diabetes Obes Metab. 2012;14:810-820.

DPP-4 Inhibitors: Use in CKD

- Most DPP-4 inhibitors reduce dose
  - Example:

    Sitagliptin (Januvia to 50mg : eGFR: 30-45)

    25mg when eGFR< 30

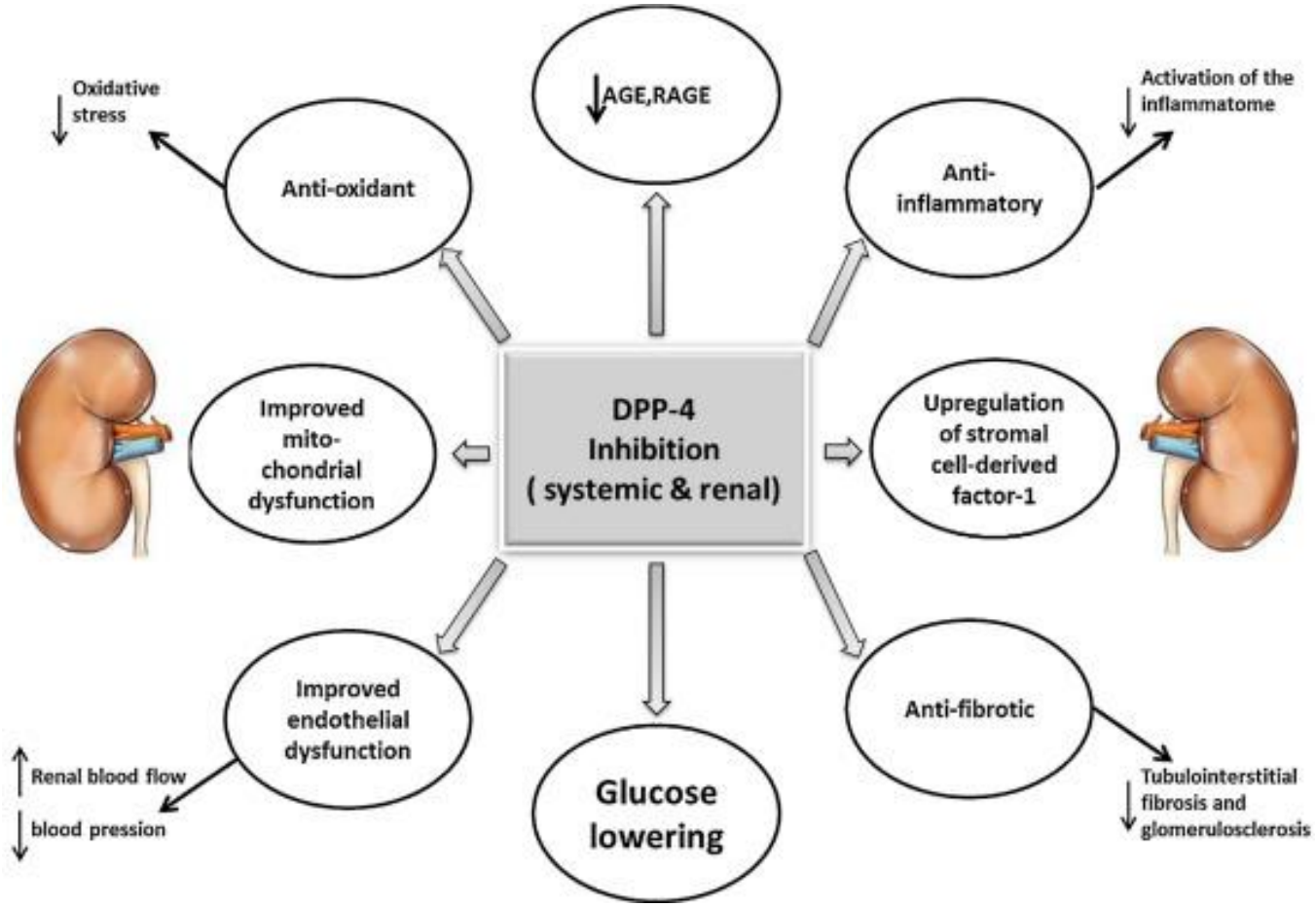
    vs.

    Linagliptin(Tradjenta) not renally cleared
- Safety data stage 1-4 CKD
- Limited data in ESRD

Chen M et al. Ren Fail. 2016;38(4):581-7

DDP-4 Inhibitors and Potential Renal Benefit

Significant reductions in microalbuminuria and in proteinuria



Scheen AJ et al. Diabetes Metab. 2018 Mar;44(2):101-111.

DDP-4 Inhibitors and Liver Disease

- No improvement of fibrosis randomized, placebo-controlled trials of sitagliptin for NASH
- The hepatic protective effects of DPP-4 inhibitors maybe from direct actions on hepatocytes *via* GLP-1 receptors and appear to occur irrespective of the degree of glycemic control
- HCV-infected T-cells may be responsible for the increased serum DPP-4 activity in patients with HCV infection
- Limited human clinical data likely safe to Child stage b

Alam S et al. Hepat Med. 2018; 10:23–31
Zhonget al . Diabetes. 2013;62:149–157

Study	Intervention	Primary endpoint	N	Follow-up time (years)	Mean age	Mean HbA1c levels (%)	CV status of patients
SAVOR TIMI	Saxagliptin versus placebo to standard of care	CV death, AMI, or stroke	18,206	2.1	≥40	≥6.5	CVD or high CV risk
TECOS	Sitagliptin versus placebo	CV death, AMI, unstable angina, or stroke	14,724	3	≥50	6.5–11	Pre-existing CVD
EXAMINE	Alogliptin versus placebo to standard of care	CV death, AMI, or stroke	5380	1.5	≥18	6.5–11	Acute coronary syndrome within previous 15–90 days

CV Outcome Studies for DDP4-Is

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Adapted: Del Olmo-Garcia et al. J Diabetes Res. 2018 Apr 2.

DPP-4 Inhibitors and CV Protection?

- **4 large trials failed to show CV benefit**
  - SAVOR-TIMI 53 (Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus-Thrombolysis in Myocardial infarction) – **May increase CHF**
  - EXAMINE (Study of Alogliptin in Subjects with Type 2 Diabetes and Acute Coronary Syndrome) - **May increase CHF**
  - TECOS (Trial Evaluating Cardiovascular Outcomes with Sitagliptin) - **neutral**
  - CAROLINA Study (Linagliptin) - **neutral**

Summary: DPP-4 Inhibitors

- Mild glycemic benefit (0.6-0.8% HbA1c reduction)
- Can use in renal disease and some potential renal benefit
- Significant cost ($200 to $400/month)
- NO CV benefit -?? Harm for HF in those with or at risk for CHF
- Weight neutral
- Well tolerated/ few side effects

QUESTIONS

Case 1

- Pt newly diagnosed DM. Their HbA1c is 9.0%.
  - What would you do?
  - **What further questions do you need to ask first?**

- A1c Goal
- What type of DM
- Age
- Weight
- renal function
- Symptoms
- What insurance he/she has, if any
- Have they had a primary CV event
- Risk for hypoglycemia

1. Insulin + metformin (symptoms)
2. Metformin + glimepiride 4mg

I would likely not start metformin and DDP-4I

Pt is 45 y/o without renal disease or CVD and BMI 28 with Medicaid insurance

Case 2

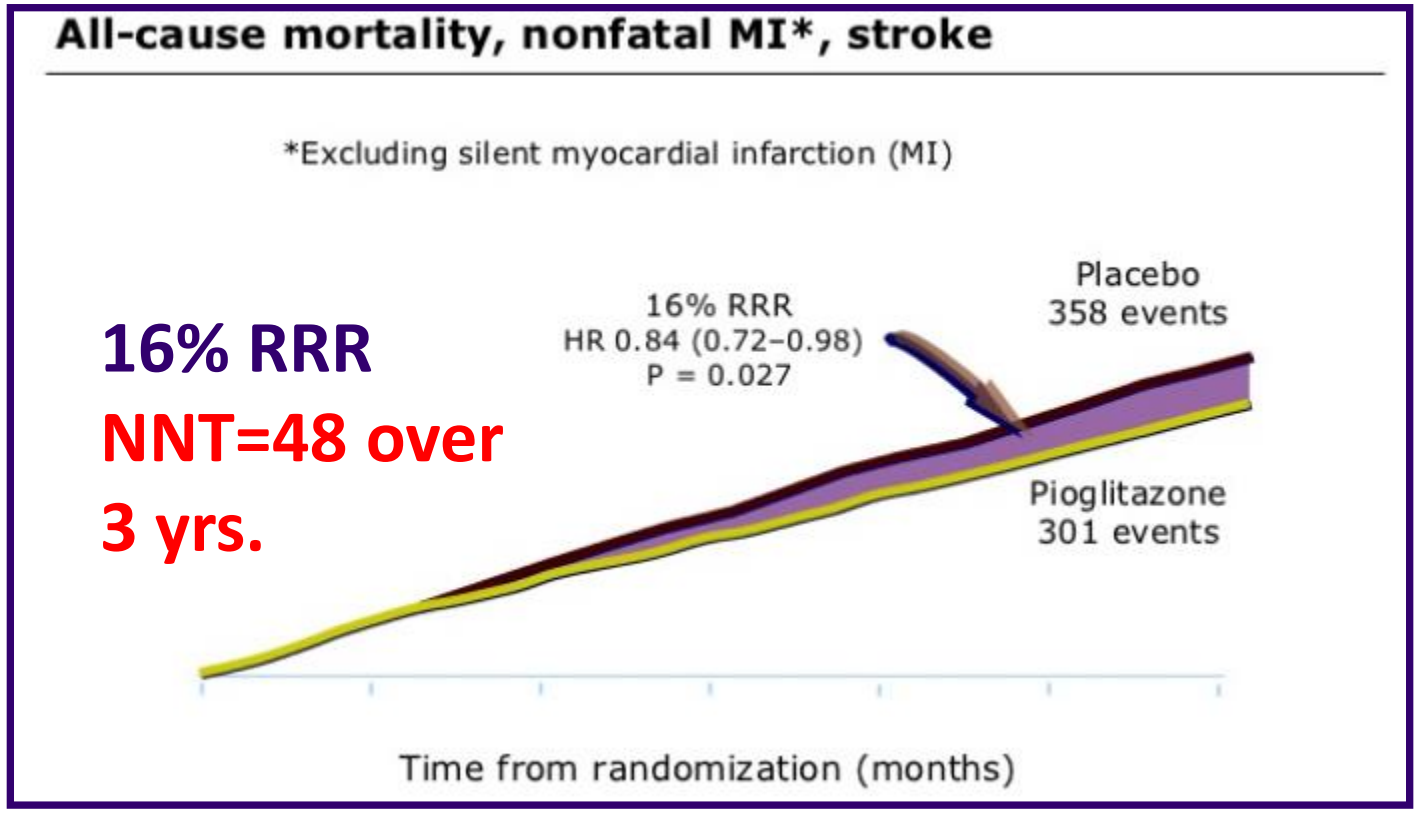
- 70 y/o female with DM for 8 yrs. on metformin. HbA1c is 8.2%.
  - **Next step?**

What questions should you ask?

  - A1c goal is 7.5% given age
- GFR is 40
- Insurance

Glimiperide 1mg or
Glipizide 5mg XR
vs.
Sitagliptin 50mg or
Linagliptin 5mg

Secondary Prevention of Macrovascular Events in Patients with T2DM: PROactive Study



Dormandy et al. *The Lancet* 2005 366, 1279-1289