Older Diabetes Medications for Type 2 Diabetes

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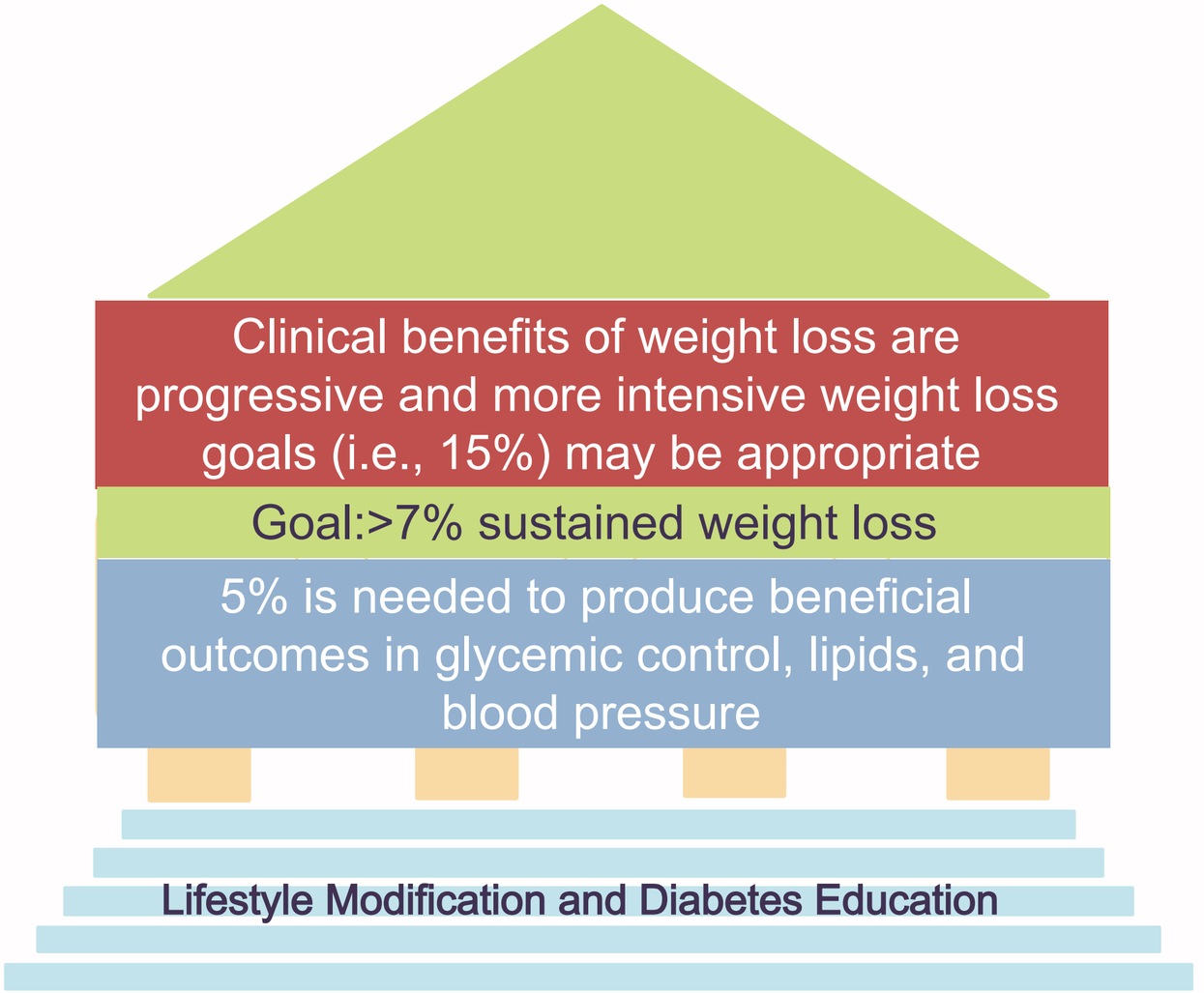
Disclosure

- Dr. Ehrhardt is on an advisory board for Novo Nordisk and Dexcom. She received investigator-initiated grants from Dexcom and educational grants from Merck and Novo Nordisk

Objectives

1. Describe different oral medications available for the treatment of type 2 diabetes
2. Discuss the mechanism of action, efficacy, and side-effects
3. Translate to use in those with CV, renal disease, and liver disease

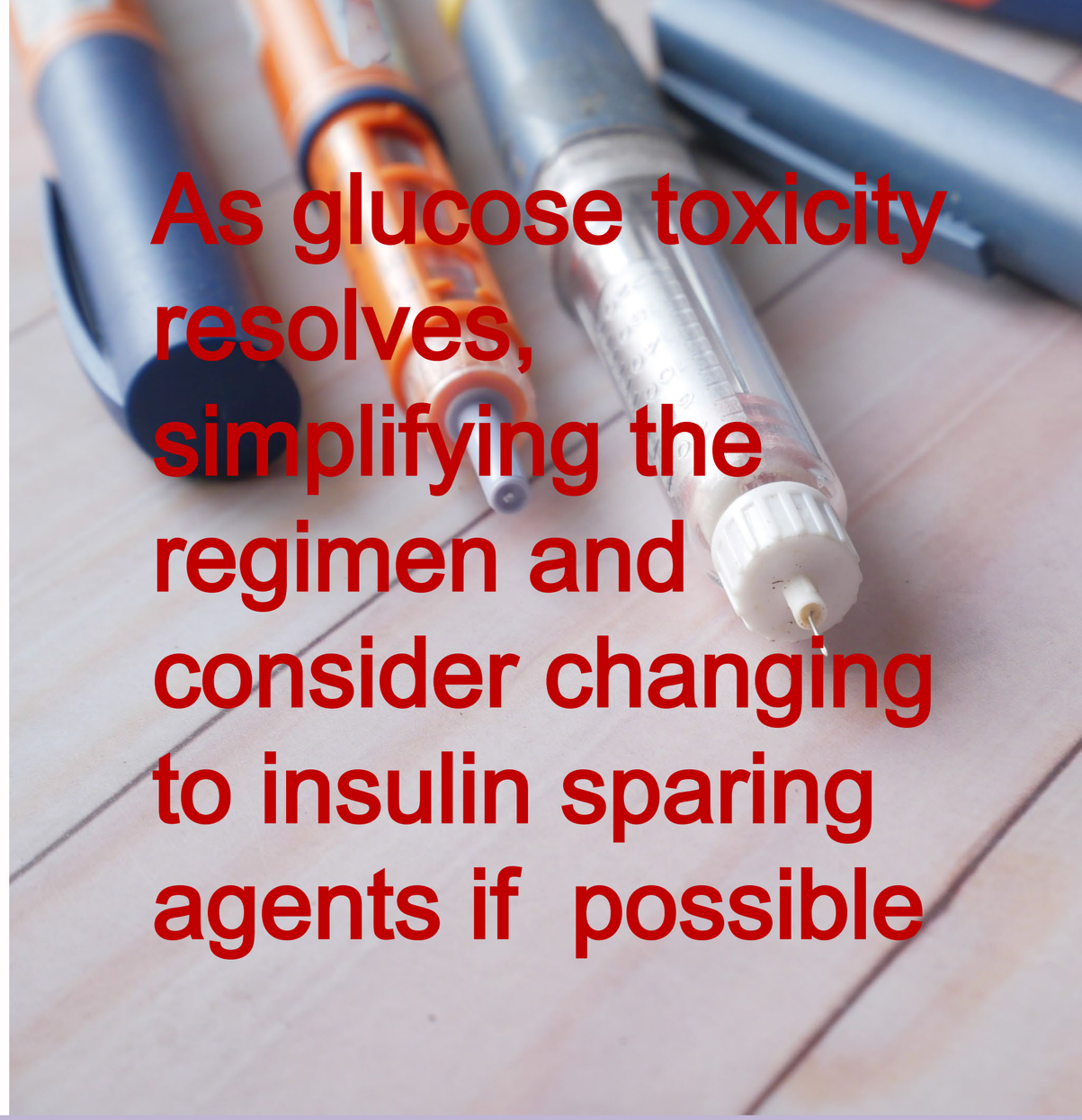
Lifestyle



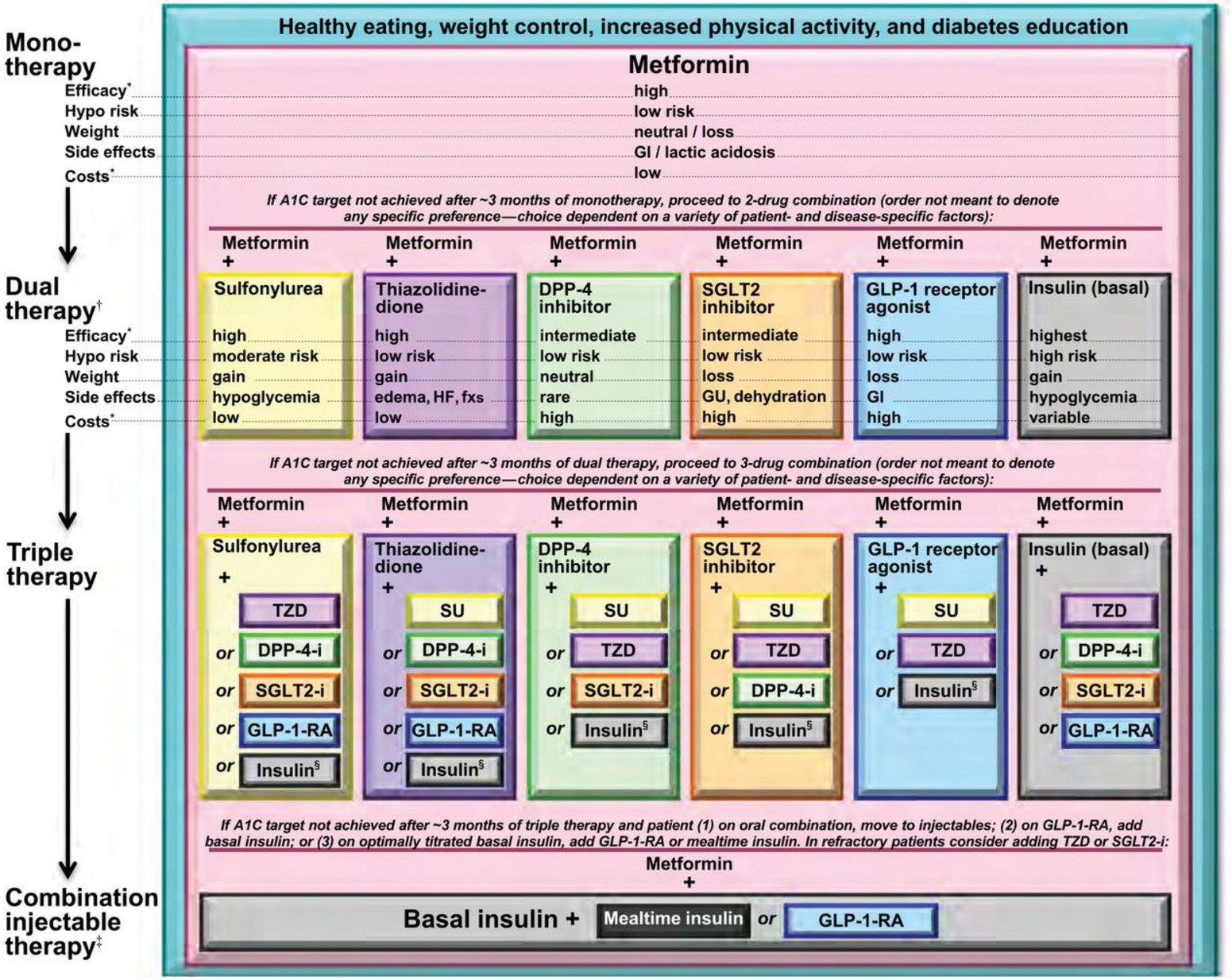
Diabetes Care. 2021;45(Supplement_1):S144 -S174. doi:10.2337/dc22-S010

Insulin

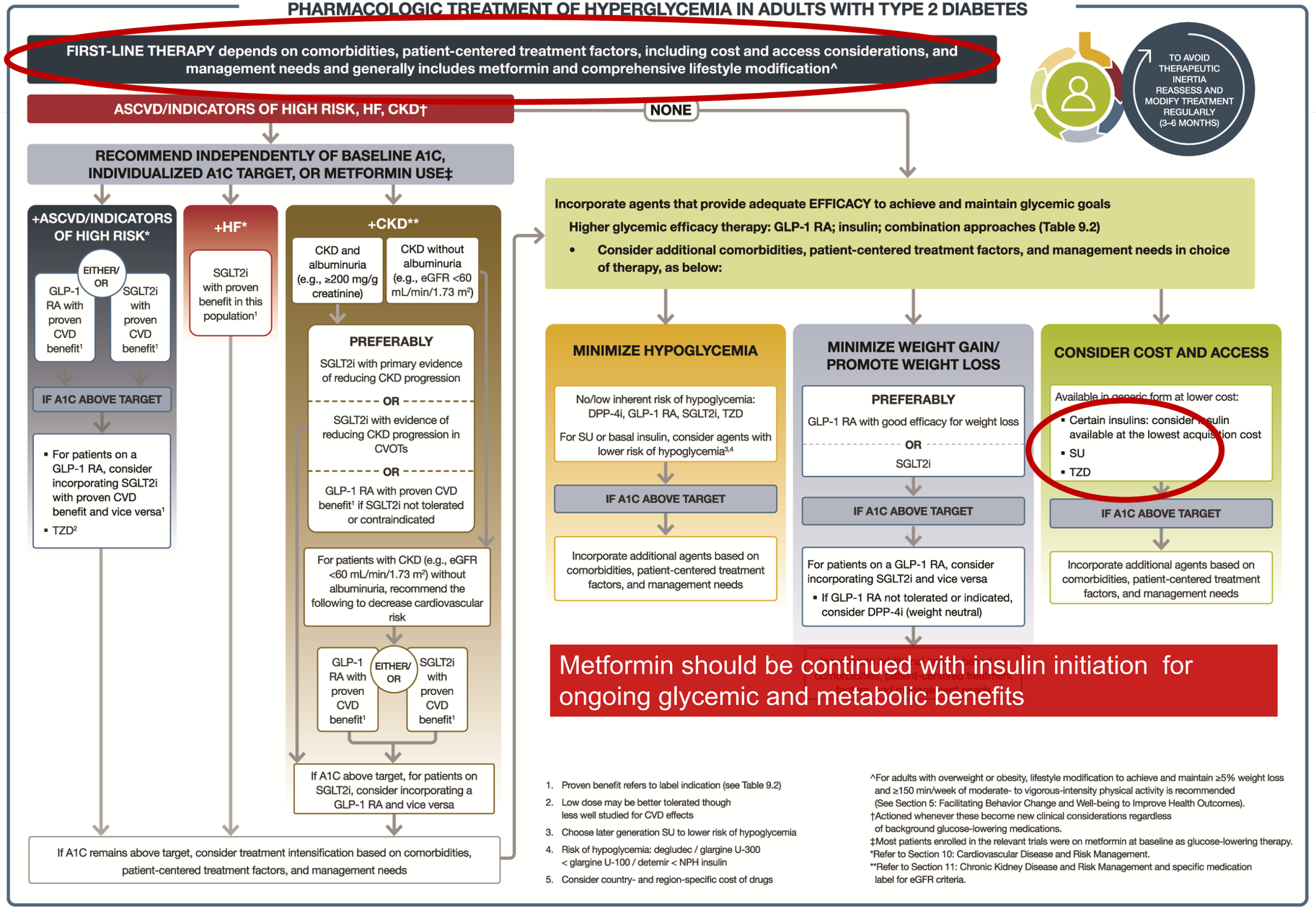
Do not be afraid to use early!



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



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



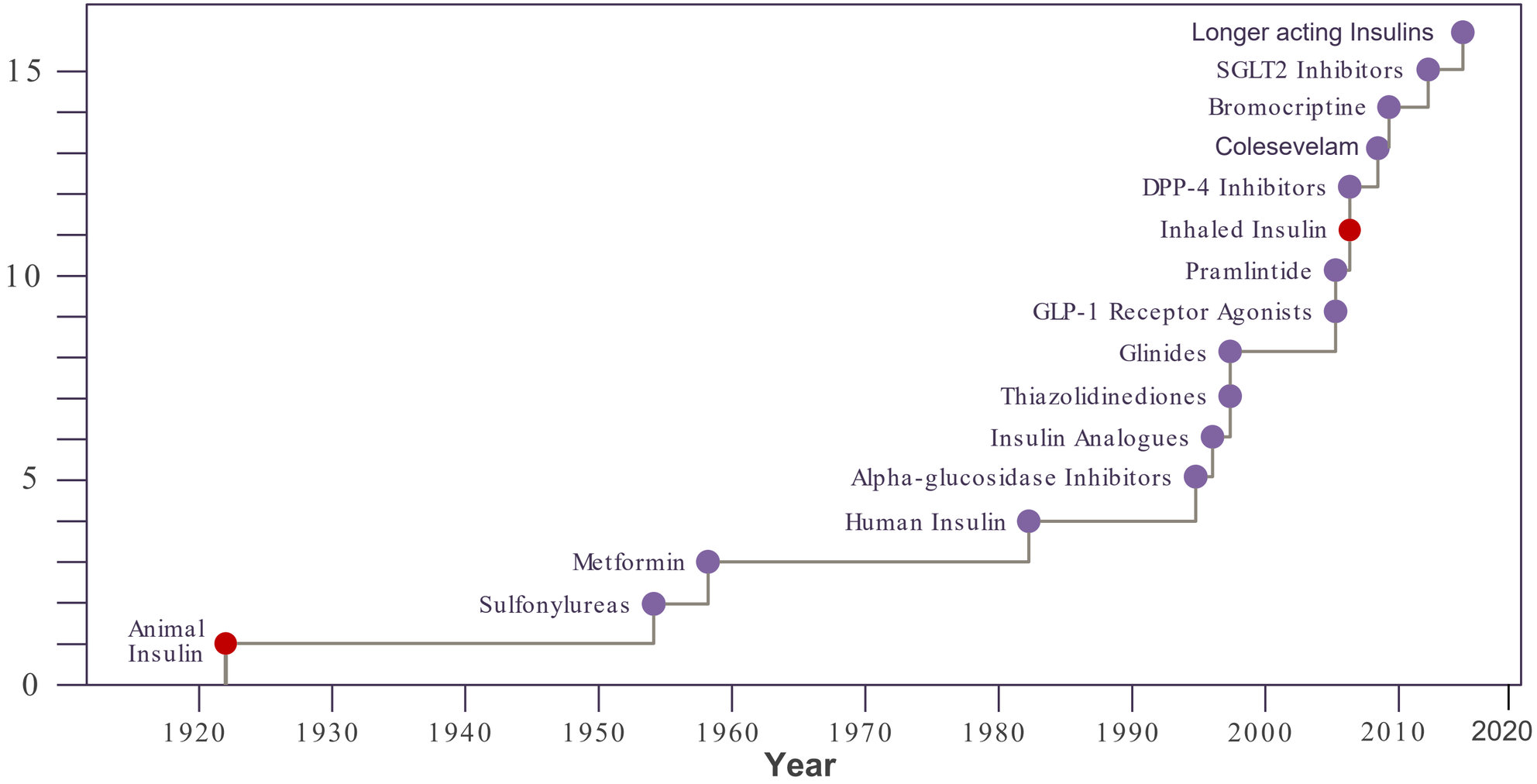
Diabetes Care. 2021;45 (Supplement_1): S125 -S143. doi:10.2337/dc22 -S009

American Diabetes Association.

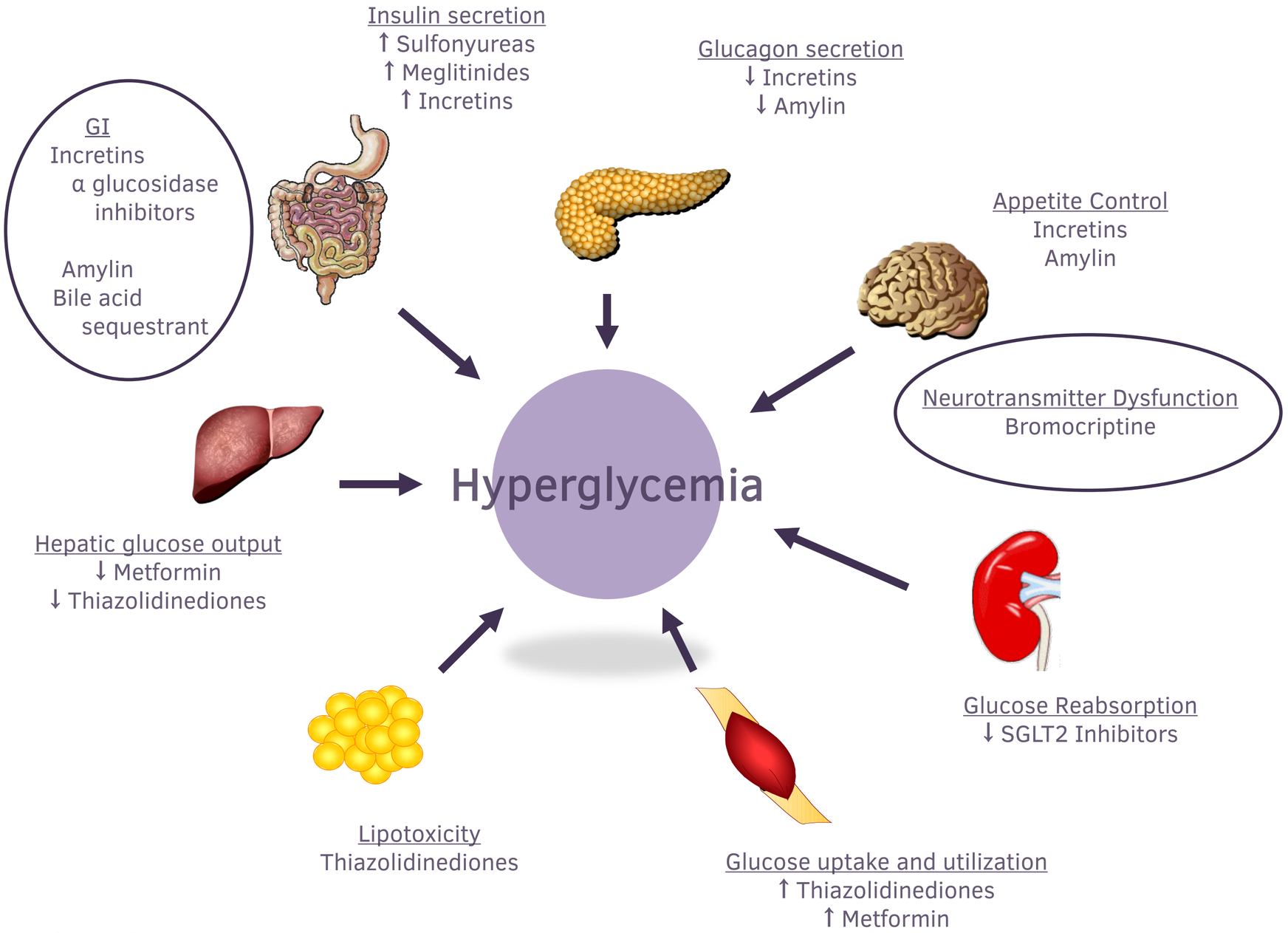
How to Think about Selecting the Appropriate Diabetes Medication(s)

- 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)



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

Advances in Health Technology, Policy, and 10 Drug Classes and New Therapies Have NOT Translated to Improvements in Diabetes Care Quality

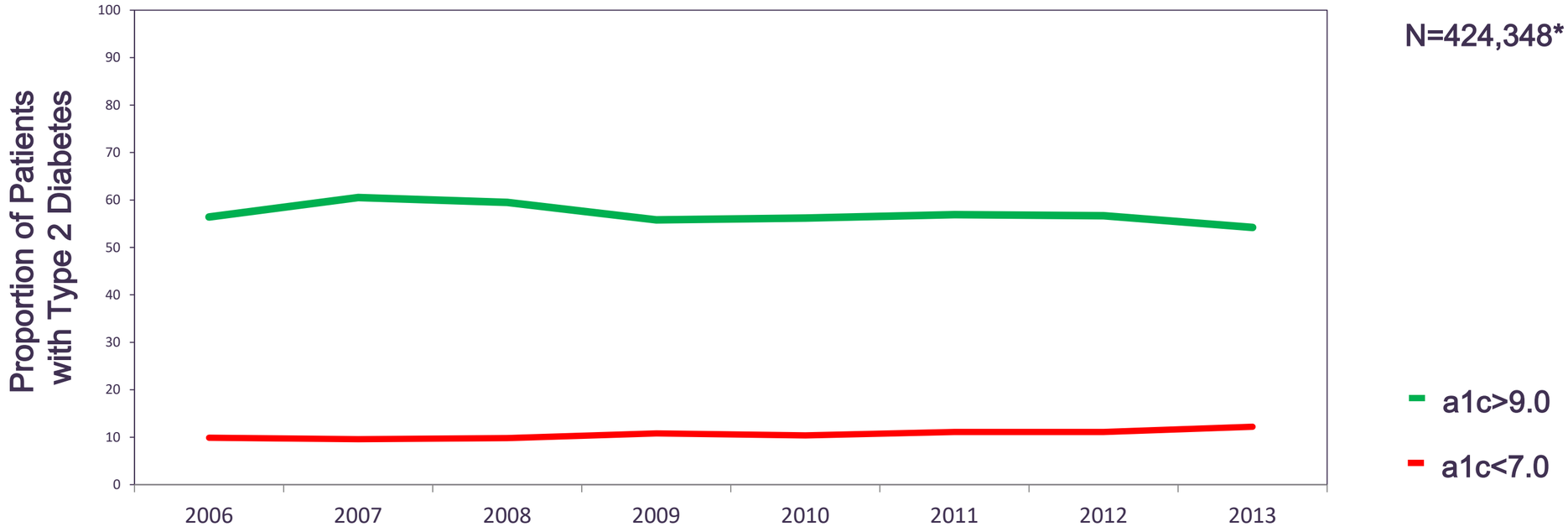
DPP-4i and GLP-1 RA approved

Increased adoption of EHRs, HITECH Act, iPhone and apps introduced

Affordable Care Act becomes law, proliferation of “personal tech”

Meaningful Use Implementation, PCMH, ACO formations

SGLT2 inhibitor Rx approved



Courtesy of Robert Gabbay MD, PhD from Tackling Therapeutic Inertia: American Diabetes Association Standard of Care Updates.

*Subset of 1.66M patients with an HbA1c available.

Adapted from: Lipska KJ, et al. Diabetes Care. 2017;40:468-475.

Biguanides/Metformin

Biguanides/Metformin

Class / Main Action	Names(s)	Daily Dose Range	Considerations
Biguanides • Decreases hepatic glucose output • First-line med at diagnosis type 2	Metformin (Glucophage) Riomet (Liquid Metformin)	500 – 2500mg (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 is stable **Benefits**: lowers cholesterol, no hypo or weight gain, cheap. Approved for pediatrics, 10 yrs + Lowers A1c 1.0% - 2%
	Extended Release XR (Glucophage XR) (Glumetza) (Fortamet)	(1x daily w/dinner) 500 – 2000mg 500 – 2000mg 500 – 2500mg	

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		
2	60-<90	2	
3A	45-<60	2000	Avoid if kidney function is or expected to become unstable. Consider more cautious follow-up of kidney function
3B	3--<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	

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

3 per 100,000 person -years to 10 per 100,000 person -years

Indistinguishable from the background rate in the overall population with diabetes.

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

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

Liver Disease and Metformin

Reduction in HCC risk, mortality and need for transplant

Reduce the incidence of overt hepatic encephalopathy by 8 folds through inhibition of glutaminase activity

Metformin is often held due to concern for metformin -associated lactic acidosis

Consider discontinuation Child B and C

Ampuero J et al. PLoSOne. 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
Yip TC et l.. Health Sci Rep. 2021 Aug 11;4(3):e352. doi: 10.1002/hsr2.352

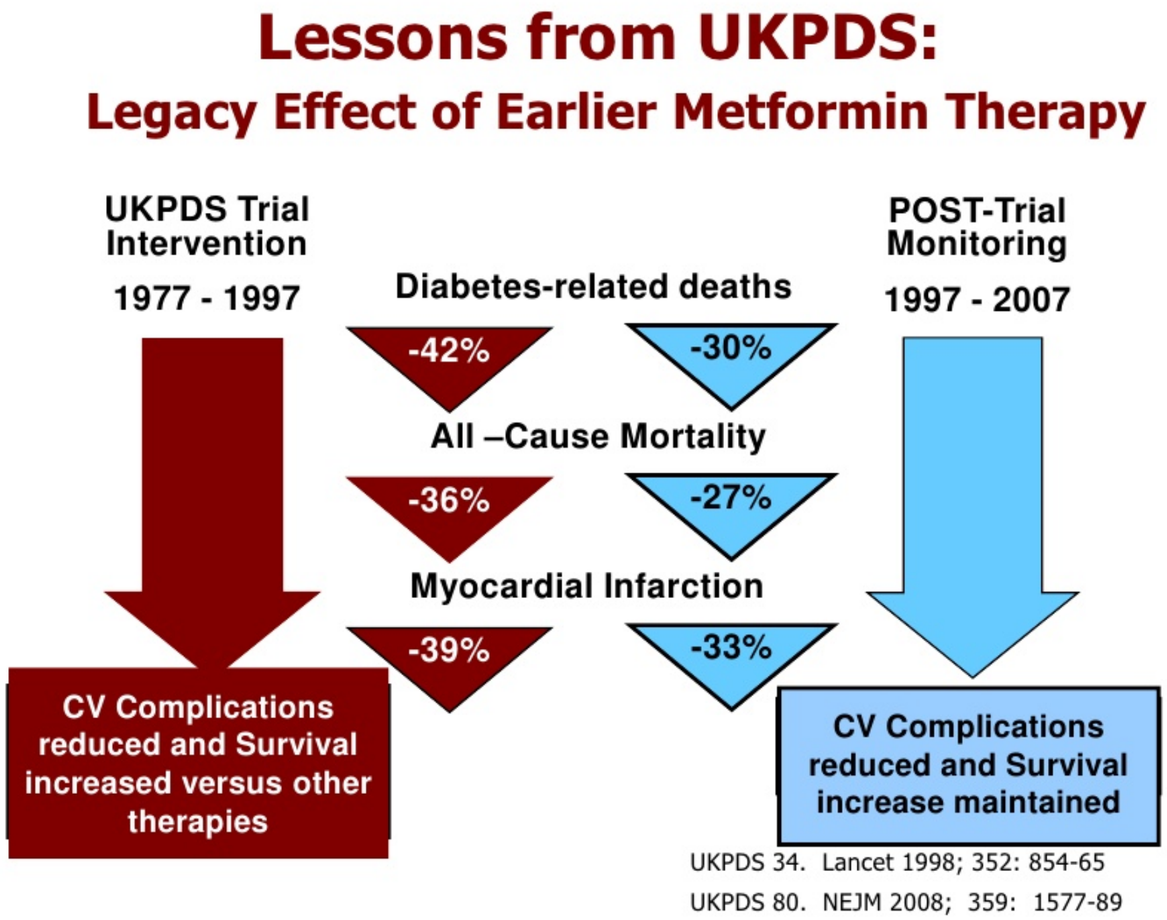
2 Minute Medicine®	**Child-Pugh Score**		2minutemedicine.com
Factor	**1 point**	**2 points**	**3 points**
Total bilirubin (µmol/L)	<34	34-50	>50
Serum albumin (g/L)	>35	28-35	<28
PT INR	<1.7	1.71-2.30	>2.30
Ascites	None	Mild	Moderate to Severe
Hepatic encephalopathy	None	Grade I-II (or suppressed with medication)	Grade III-IV (or refractory)

	Class A	**Class B**	**Class C**
Total points	5-6	7-9	10-15
1-year survival	100%	80%	45%

Table I. Child-Pugh score.

Figure from: 2 Minute Medicine's The Classics in Medicine: Summaries of the Landmark Trials, 1e (The Classics Series).

UKPDS: CV risk reduction



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

Holman R et al. 10-year follow-up of intensive glucose control in type 2 diabetes *N Engl J Med* 2008 ;359:1577 –1589

Summary: Metformin

- Try again low dose with Extended Release (XR) in those with hx of GI intolerance
- Do not stop if eGFR > 30 and can start eGFR> 45
- Cheap, low risk hypoglycemia, causes slight weight loss
- Continue use if insulin is initiated
- May have CV benefits
- Consider use in prediabetes (hx of GDM, BMI >30, Age <60)

Sulfonylureas

Sulfonylureas

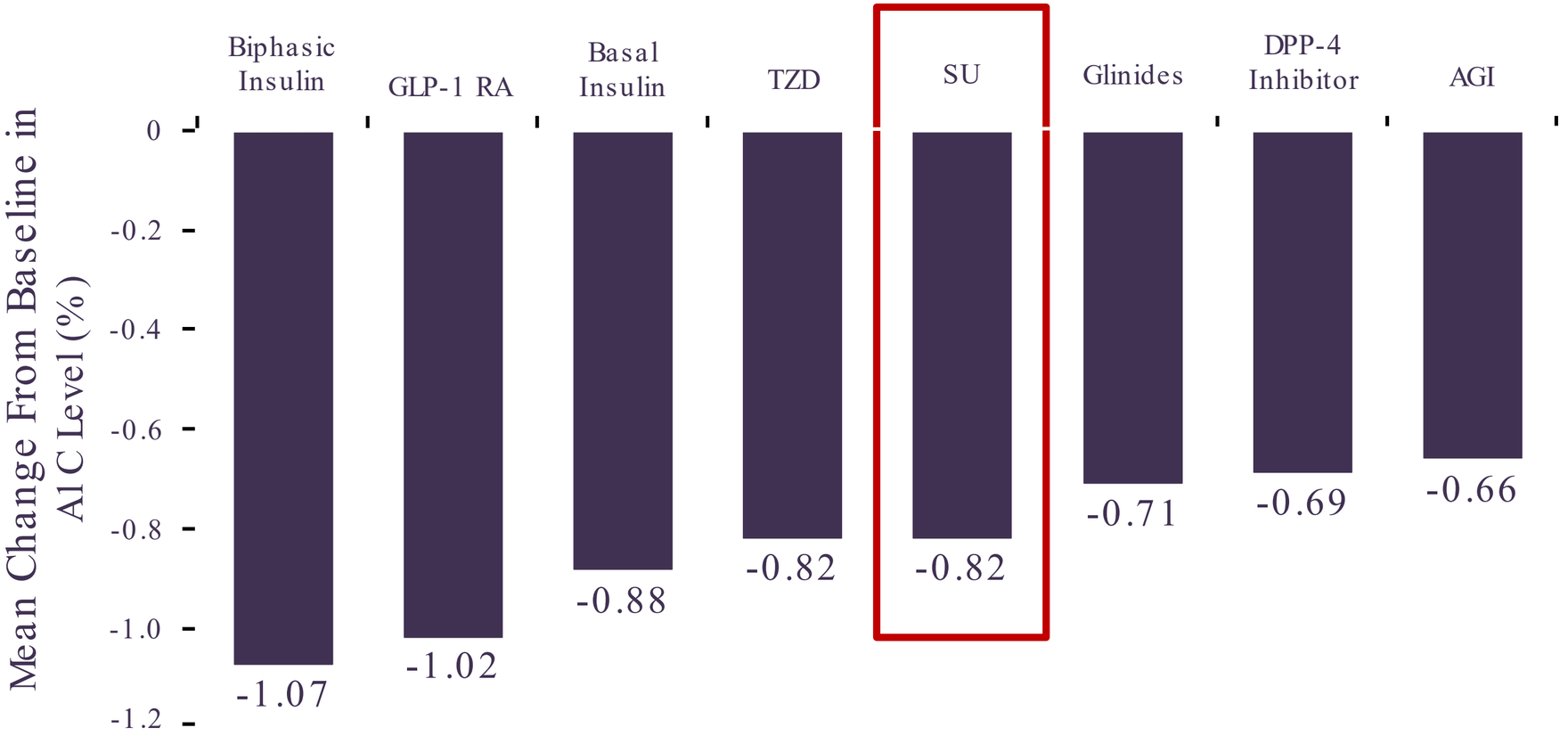
- Glimepiride and glipizide associated with a reduced likelihood of hypoglycemia
- Glimepiride also improves first-phase insulin secretion
  - Reducing postprandial hyperglycemia.
- Glyburide more associated with hypoglycemia

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 (eGRF59-30):

- 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.

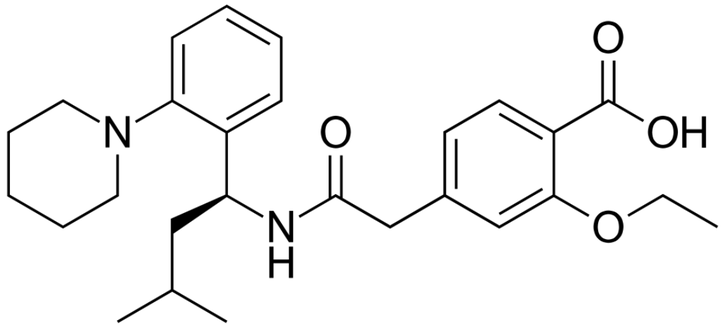
Stage 4 CKD (eGFR <30)

*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 Action 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

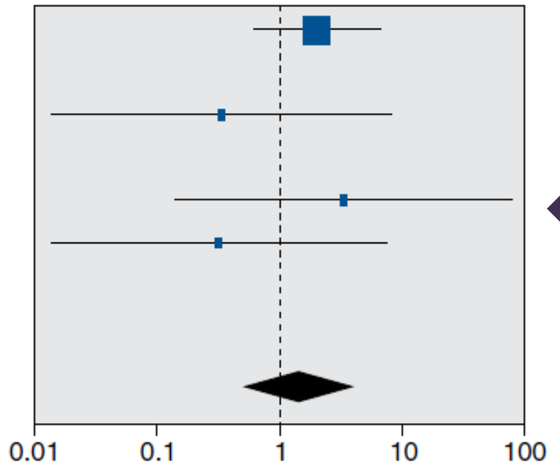
Second and Third Generation Sulfonylurea vs. Metformin Monotherapy in Patients with Type 2 Diabetes

B: Cardiovascular mortality

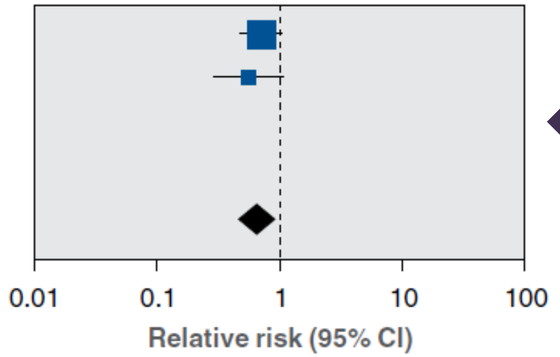
ADOPT 2006[20–26]	8/1447	4/1455	2.01 (0.61–6.66)
Campbell et al., 1994[27]	0/24	0/24	Not estimable
DeFronzo et al., 1995[29]	0/209	1/210	0.33 (0.01–8.17)
Derosa et al., 2004[42]	0/81	0/83	Not estimable
Hermann et al., 1991b[31–34]	1/34	0/38	3.34 (0.14–79.42)
Lawrence et al., 2004[36]	0/22	1/21	0.32 (0.01–7.42)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

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 Heterogeneity: I^2 = 0%	50/1540	76/1554	0.67 (0.48–0.93)



No increased risk with Sulfonylurea use



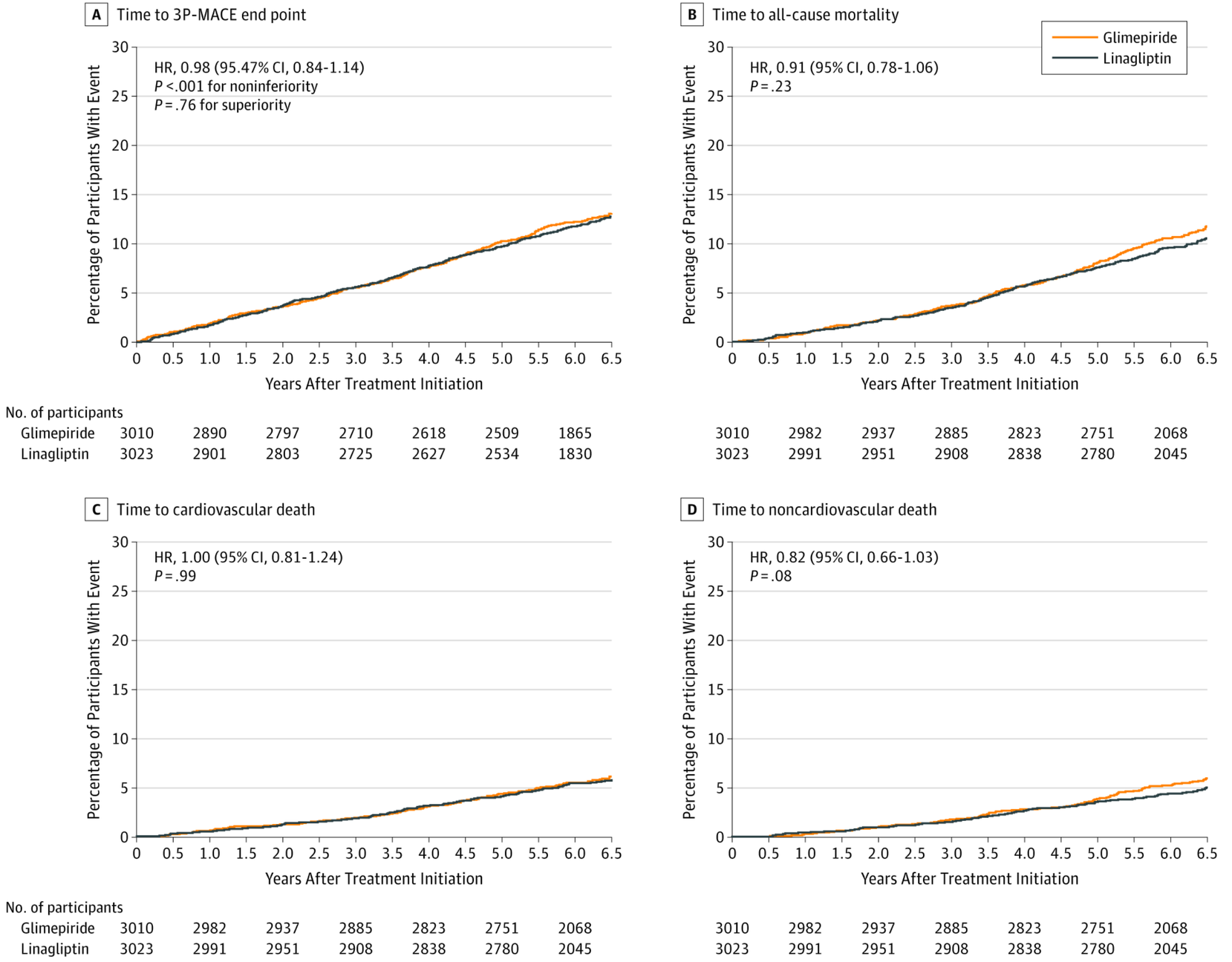
Favors Sulfonylurea use

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

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

- Can use both metformin and sulfonylureas(glimepiride) 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

Questions?

University of Washington
Cardiometabolic
ECHO

Cardiometabolic teleECHO™ Clinic

Patient Recommendation Form

Presentation Date: May 4th, 2022 **Presenter name:** Tom Chin, MD

Presenter Facility: Healthpoint Community Health Clinic

Case Report Recap: 57 year old male, Mexican heritage, type 2 diabetes (BMI 24) diagnosed age 50 – A1C range 10-12% without microvascular complications. Also with controlled HTN and HLD and Hx of previous smoker. He works as a roofer and uninsured. Diabetes medications include liraglutide (0.6 with back pain from higher dose), metformin 1g bid, empagliflozin 10mg and detemir 16 units.

Case Recommendations:

1. In a non-judgement way continue to assess if able to take all medications or any barriers
2. Appears sig improvement from CGM use. Share with patient options for acquiring freestyle CGM at $30 per sensor. If needed, consider cyclical use of CGM sensor 2 weeks on and 2 weeks off.
3. Maximize insulin sparing medications: increase Empagliflozin to 25mg daily and retrial of liraglutide at 1.2 or do it by 5 additional "clicks" from 0.6 for "micro-dosing" to enhance the patient's confidence and slower increase.
4. Reduce detemir by 2 units and simple instruction of if 2 or more am sugars < 100 or any less than 70mg/dl reduce by 2 more insulin as able with goal off insulin. However, if sugars higher once on max dose of tolerate liraglutide increase by 2 units detemir every 4-5 days for am sugars >140mg/dl
5. Consider Atorvastatin for moderate intensity statin to replace pravastatin as low intensity statin

Nicole Ehrhardt, MD

_____Nicole Ehrhardt____

Physician Signature Nicole Ehrhardt
Represent case July 2022