Diabetes: Putting it all together to design a high value diabetes regimen for your patient

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Disclosures

- None

Objectives

- Describe the benefits, side effects/risks, and costs of the newer diabetes medications
- Discuss the value of the newer diabetes medications
- Make high-value patient-centered decisions when intensifying diabetes therapy

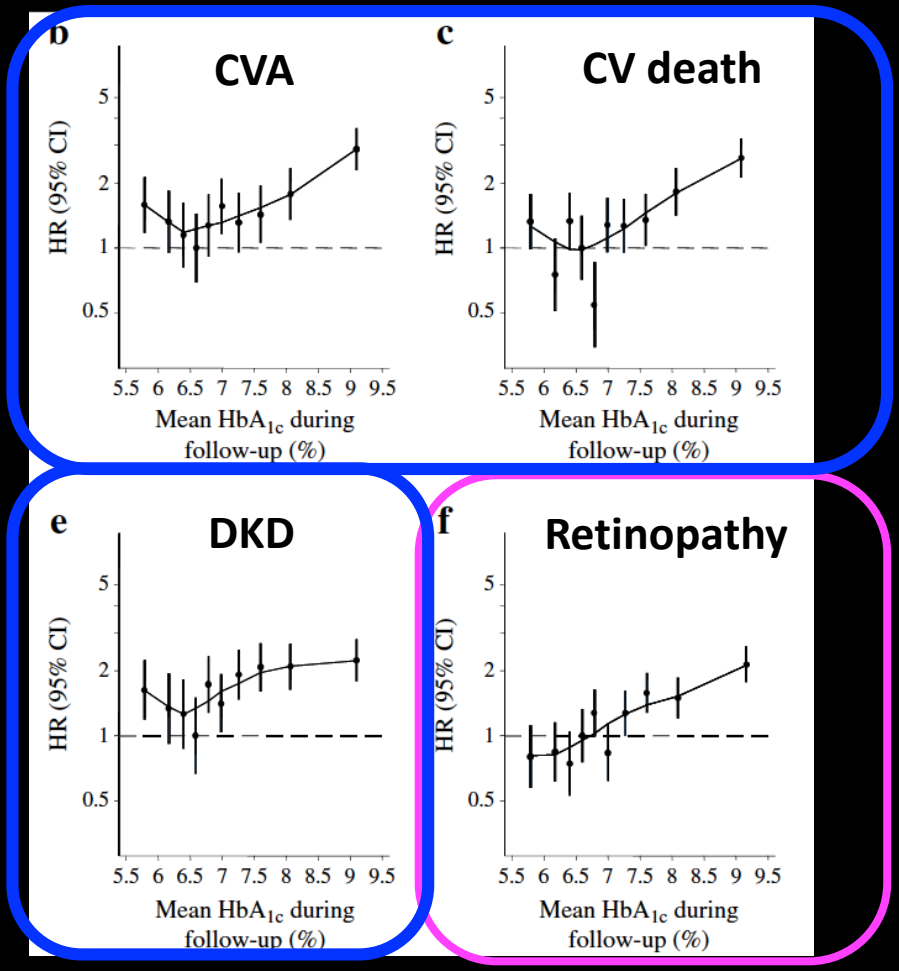
Worsening HbA1c

- Ms L is a 48 year old woman here for routine f/u
- She has Type 2 diabetes (x 5 years; no complications), obesity (BMI 41), chronic knee pain from osteoarthritis, and is postmenopausal s/p TAH 6 yr ago for uterine leiomyomas
- You last saw her 6 months ago. At that time, her A1c was 6.4% on metformin 1000 mg BID
- You see that her A1c is now 8.5%.
- What other information do you need?
- How would you intensify her diabetes treatment?

“New-onset” diabetes

- Mr. B is a 53 year old M hospitalized for NSTEMI and underwent 3v CABG
- He had HTN but no other medical history and was on no medications prior to admission
- Admission point-of-care (POC) glucose: 263 mg/dL
- HbA1c: 11.5%
- He agrees that he needs to be on insulin upon discharge
- Are there any non-insulin medications that should be considered for him?
- How would you design his regimen?

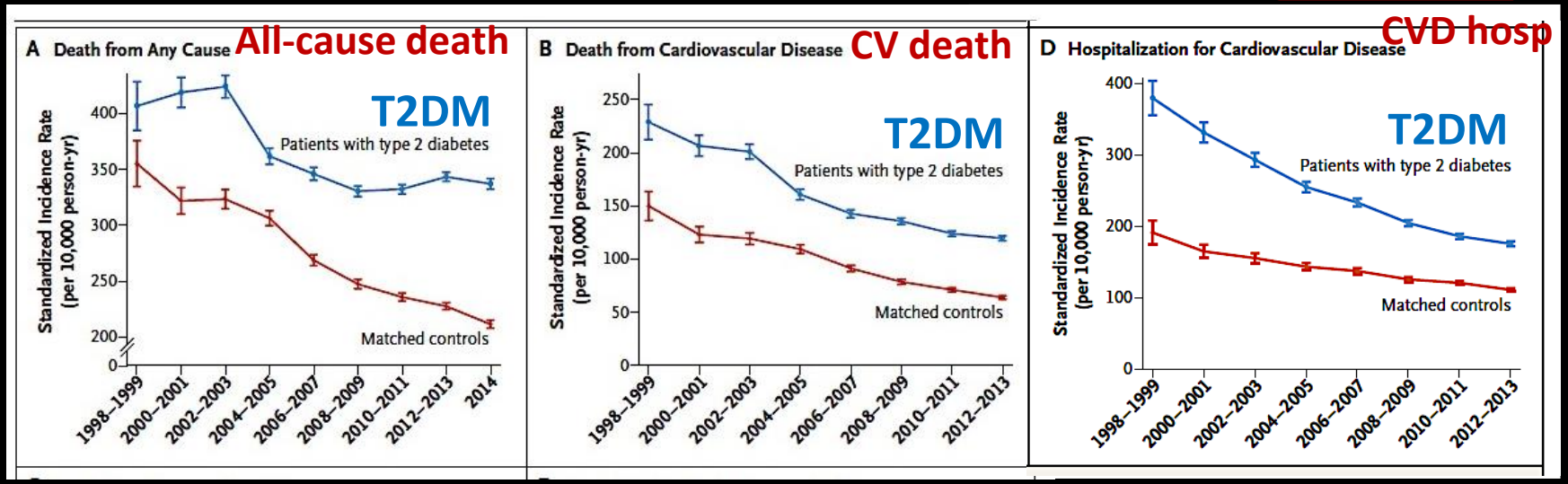
ADVANCE: Diabetes complications and A1c relationship



- Linear relationship (no threshold) for eye complications
- J-curve: Increasing risk with A1c <6.5% for CV and renal complications

Zoungas, et al. *Diabetologia* 2012;55(3):636-643.

Even in 2019, people with diabetes still have more CVD, amputations and death



Age std rate	T2DM	No DM	RR (95% CI)
LE amputations: # of events /10,000 (95% CI)	28.4 (19.4-37.3)	2.7 (1.9-3.5)	10.5 (6.0-15.0)

Rawshani A, et al. *N Engl J Med* 2017;376:1407-1418.
Gregg EW, et al. *N Engl J Med* 2014;370:1514-1523.

Preview of ARS #1

- Which glucose-lowering agent below has NOT been shown to reduce cardiovascular risk?

  A. Liraglutide

  B. Empagliflozin

  C. Linagliptin

  D. Canagliflozin

Diabetes medications with clinical trial evidence for CV risk reduction

Generic	Class	CV benefit	Risk reduction
Empagliflozin	SGLT2i	CV death	↓14%
Canagliflozin	SGLT2i	MACE HF / DKD	↓14% ↓30% /↓30%
Dapagliflozin	SGLT2i	Hosp HF	↓27%
Liraglutide	GLP-1RA	MACE (MI, stroke, CV death)	↓13%
Semaglutide	GLP-1RA	MACE	↓26%
Dulaglutide	GLP-1RA	MACE	↓12%

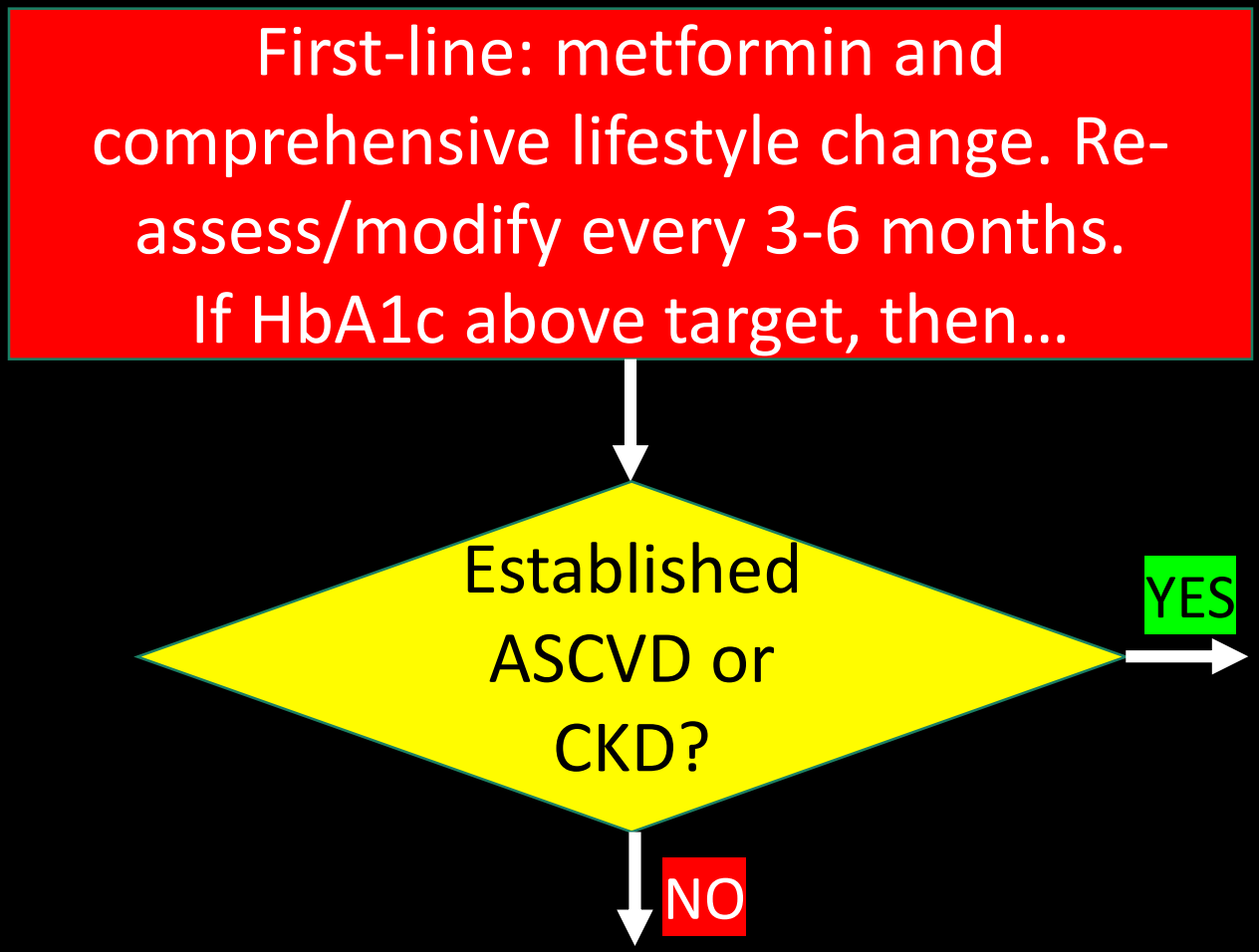
4 of these are now FDA-approved to reduce CV risk in diabetes

Generic	Class	Date	Indication
Empagliflozin	SGLT2i	Dec 2016	CV death
Liraglutide	GLP-1RA	Aug 2017	MACE (MI, stroke, CV death)
Canagliflozin	SGLT2i	Oct 2018 Sep 2019	MACE Hosp HF, DKD
Dapagliflozin	SGLT2i	Oct 2019	Hosp HF

Type 2 diabetes

Established CVD or high CV risk

Overall approach to glucose-lowering in type 2 diabetes



ADA. *Diabetes Care* 2019;42(Suppl 1):S90-S102.

If YES – established ASCVD or CKD

- And ASCVD predominates:
  - GLP-1RA or SGLT-2i (if adequate eGFR) with proven CVD benefit*
- And CHF or CKD predominates:
  - And eGFR adequate, then SGLT-2i with proven CVD or CKD benefit**
  - If SGLT-2i not tolerated, or contraindicated, then GLP-1RA with proven CVD benefit*

***FDA-approved**:
liraglutide
empagliflozin
canagliflozin
Not FDA-approved:
Semaglutide
Dulaglutide

****FDA-approved**:
Canagliflozin
Dapagliflozin
Not FDA-approved:
empagliflozin

ADA. *Diabetes Care* 2019;42(Suppl 1):S90-S102.

Other benefits of diabetes agents

- No hypoglycemia
  - GLP-1RA
  - SGLT-2i
  - DPP-4i
  - Thiazolidinedione (TZD)
- Weight loss
  - GLP-1RA
  - SGLT-2i

How to choose between a GLP-1RA or SGLT2i with CV benefit?

SGLT2i	GLP1-RA
Consider Using an SGLT2 Inhibitor First When Patient and Clinician Priorities Include:	**Consider Using a GLP-1RA First When Patient and Clinician Priorities Include:**
Reducing MACE and CV death	Reducing MACE and CV death
Preventing heart failure hospitalization	Substantial weight loss
Reducing blood pressure	Once weekly (subcutaneous) dosing
Orally administered therapies Exception: oral semaglutide now avail.	Therapy when eGFR consistently <45 ml/min/1.73 m^{2}*

Das SR, Everett BM, et al. *J Am Coll Cardiol* 2018;72(24):3200-3223.

When to consider an alternative to an SGLT2i or GLP-1RA?

Consider an alternative

to an SGLT2i if:

- Significant CKD*
- History of prior amputation, severe peripheral arterial disease, neuropathy, or diabetic foot ulcers (avoid canagliflozin)
- History of recurrent genital candidiasis
- History of diabetic ketoacidosis
- History of osteoporosis (avoid canagliflozin)

to a GLP-1RA if:

- Persistent nausea, even at low doses
- History of pancreatitis
- History of gastroparesis
- History of MEN2 or medullary thyroid cancer
- History of proliferative retinopathy (semaglutide)

*The SGLT2i effect to lower glucose diminishes with worse CKD, but other benefits for CVD and CKD persist or are greater

Das SR, Everett BM, et al. *J Am Coll Cardiol* 2018;72(24):3200-3223.

ARS #1

- Which glucose-lowering agent below has NOT been shown to reduce cardiovascular risk?

    A. Liraglutide

    B. Empagliflozin

    C. Linagliptin

    D. Canagliflozin

How do the agents compare for glucose-lowering?

- **GLP-1RA > SGLT2i > DPP-4i**
- **GLP-1RA** Semaglutide = dulaglutide = exenatide weekly **>** liraglutide **>** exenatide
- **SGLT2i** Canagliflozin = ertugliflozin **>** empagliflozin = dapagliflozin
- **DPP-4i** Sitagliptin = linagliptin = alogliptin = saxagliptin

Preview of ARS #2

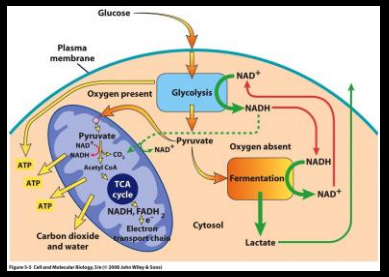
- You are seeing a 76 yr old patient with T2DM, A1c 8.5% on metformin, h/o vertebral fracture and prior toe amputation, with good renal function. What drug class would the best option for A1c lowering?
  - A. Sulfonylurea
  - B. Thiazolidinedione
  - C. SGLT-2 inhibitor
  - D. GLP-1 receptor agonist

What about potential risks and side effects?

Biguanide: Metformin

GI side effects are common:
Diarrhea
Nausea

Vitamin B12 deficiency



Risk for lactic acidosis – Contraindicated if eGR <30 mL/min

Titrate metformin to maximize tolerability – Epic dotphrase

When you start the metformin:

- Take one 500 milligram tablet once a day for one week. THEN
- Take one 500 milligram tablet twice a day for one week. THEN
- Take two 500 milligram tablets in the morning and one 500 milligram tablet in the evening for one week. THEN
- Take two 500 milligram tablets twice a day.
- The final dose is 1000 milligrams twice daily (total 2000 milligrams per day).
- If you develop intolerable symptoms of bloating or diarrhea after you increase the dose, go back to the previous lower dose for an additional week then try increasing it again.

Extended-release formulations tend to be better tolerated

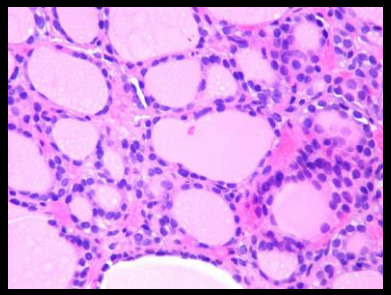
GLP-1 receptor agonists

dulaglutide, semaglutide, exenatide Qwk, liraglutide, exenatide

GI side effects are common: Nausea, vomiting, diarrhea

Injection site reactions

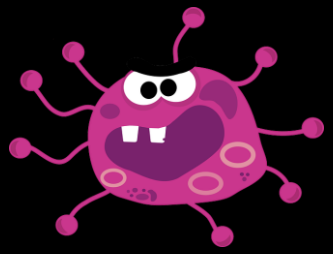
SQ
(with 1 exception)



Risk of thyroid C-cell tumors (liraglutide, dulaglutide, exenatide Qwk)

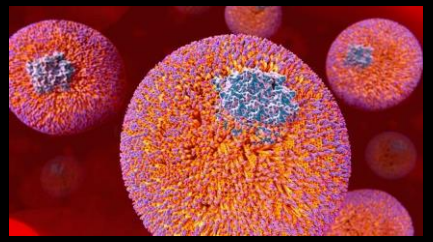
SGLT2-inhibitors

canagliflozin, empagliflozin, dapagliflozin, ertugliflozin

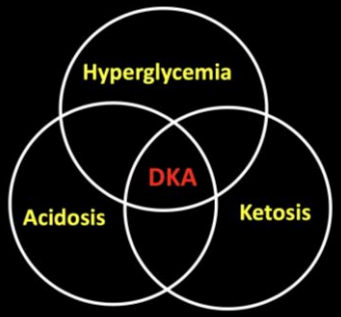


Genitourinary infections. Fournier's gangrene

Risk of hypovolemia, hypotension



↑ LDL-cholesterol



Euglycemic DKA

Canagliflozin

- Amputation
- Fractures

DPP-4 inhibitors

sitagliptin, linagliptin, alogliptin, saxagliptin

Joint pain

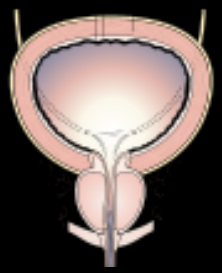
Potential risk of acute pancreatitis

Thiazolidinediones (TZD)

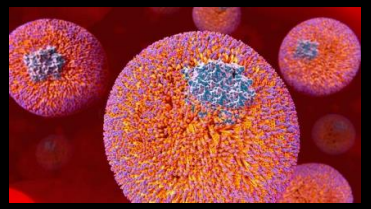
rosiglitazone, pioglitazone

Congestive Heart Failure, Fluid retention/edema

Fractures



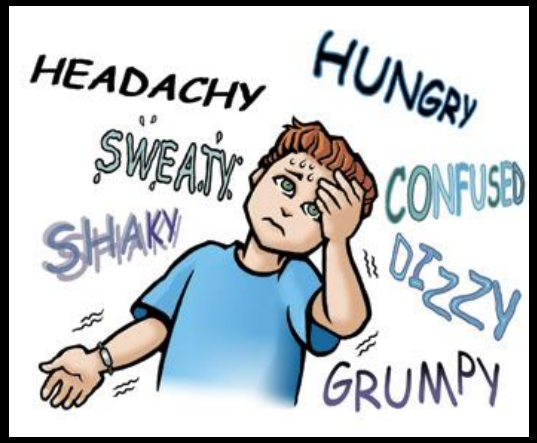
Bladder Cancer (Pioglitazone)



↑ LDL-Cholesterol (rosiglitazone)

Insulin

Glargine U-100 and U-300, detemir, degludec, lispro, aspart, glulisine, NPH, regular, 70/30, 75/25, 50/50

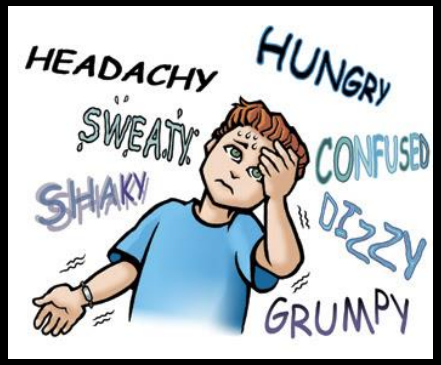


Hypoglycemia
More so
with NPH,
regular, 70/30

Injection
site
reactions

Weight
gain

Sulfonylureas (SU)
glipizide, glyburide, glimepiride



Hypoglycemia

Increased risk of CV death based on studies of older SU tolbutamide

Weight gain

ARS #2

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  A. Sulfonylurea

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  C. SGLT-2 inhibitor

  D. GLP-1 receptor agonist

"New-onset" diabetes

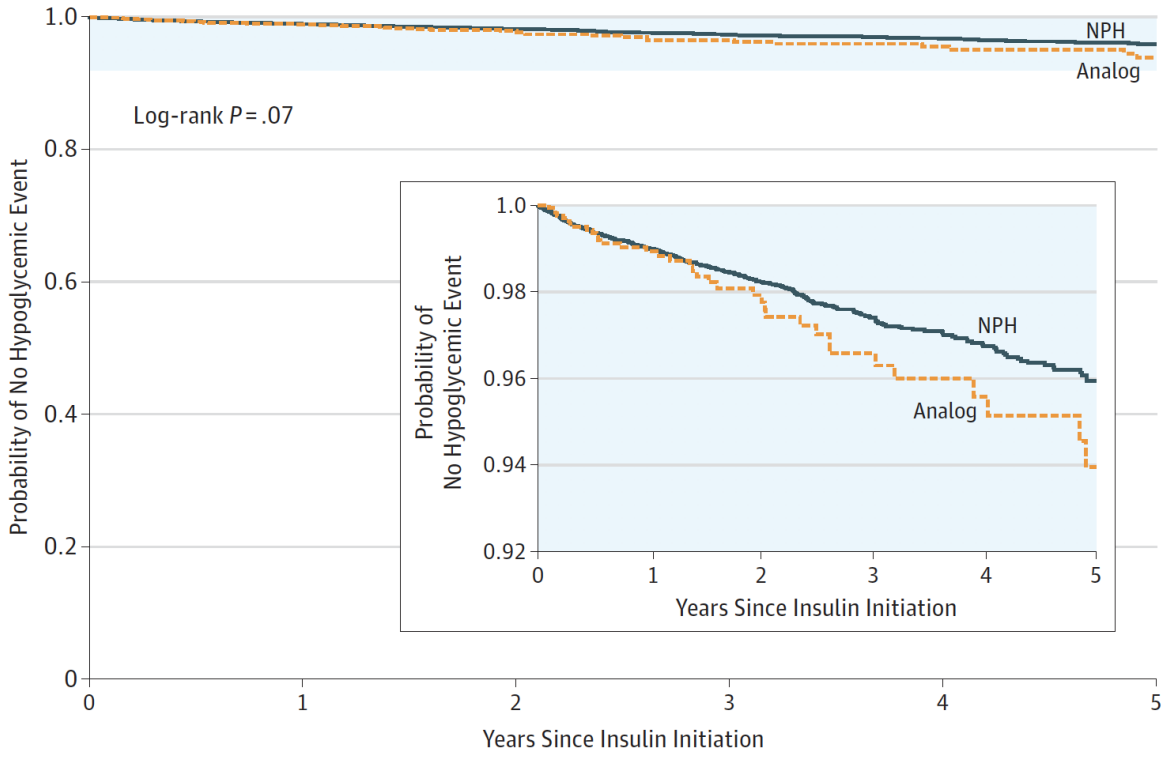
- Mr. B is a 53 year old M hospitalized for NSTEMI and underwent 3v CABG
- He had HTN but no other medical history and was on no medications prior to admission
- Admission point-of-care (POC) glucose: 263 mg/dL
- HbA1c: 11.5%
- He agrees that he needs to be on insulin upon discharge
- Which insulin is safe?
- Are there any non-insulin medications that should be considered for him?

No HF

eGFR 89

Is it safe to use NPH instead of a basal insulin analog? Maybe.

Figure 2. Time to First Hypoglycemia-Related Emergency Department Visit or Hospital Admission Among Patients With Type 2 Diabetes



Type of insulin						
NPH	23 561	12 474	7247	4217	2478	1480
Analog	1928	985	597	353	219	149

Lipska KJ, et al. *JAMA* 2018;320:53-62.

Is it safe to use NPH instead of a basal insulin analog?

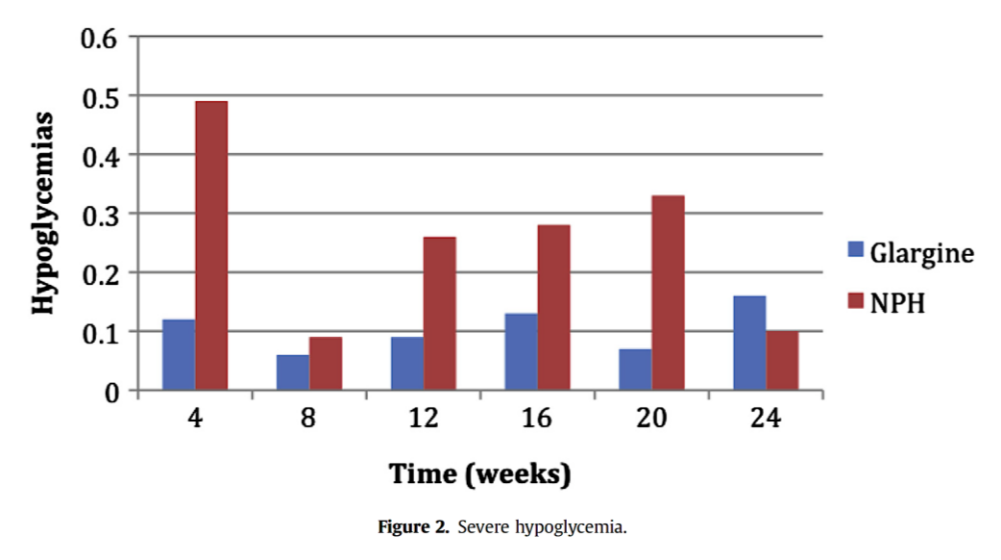


Figure 2. Severe hypoglycemia.

In the ACCORD population, NO

Switching from Glargine to NPH in a subpopulation of ACCORD caused more episodes of severe hypoglycemia but no difference in nocturnal hypoglycemia or health care resource utilization.

Berard L, et al. *Can J Diab* 2015:39(296-301).

Observational data: All-cause mortality on insulin vs novel oral agents

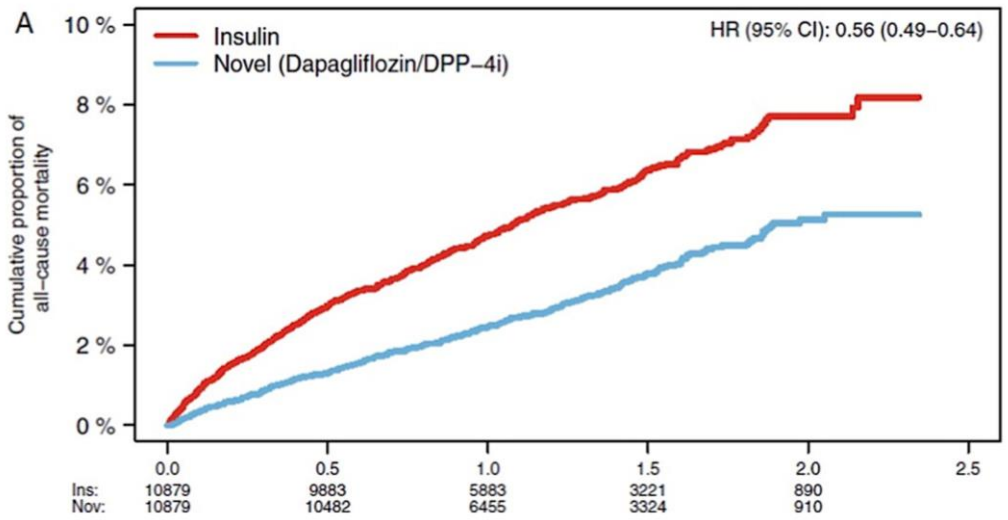


Fig 3 – Kaplan–Meier curves for all-cause mortality comparing propensity score-matched groups treated with novel drugs (SGLT-2 inhibitor and DPP-4 inhibitor) versus insulin.[53]

- Lower all-cause mortality with novel agents in propensity score-matched groups treated with SGLT-2i and DPP-4i vs insulin

Herman M, et al. *Prog Cardiovasc Dis* 2017;60:422-434.

"New-onset" diabetes
Key aspects to consider

- Established ASCVD
- No heart failure or CKD
- Very high A1c of 11.5%
- Goals: improve/lower A1c, avoid hypoglycemia

- Basal insulin analog preferred over NPH
- Liraglutide (or dulaglutide or semaglutide)
- Canagliflozin (more glucose-lowering) or empagliflozin

Median monthly cost of max approved daily dose of non-insulin DM medications in US*

*Actual out of pocket cost is usually different

Class	Compound	Form/product	Max daily dose	Median Avg Wholesale Price
Sulfonylurea	Glipizide	10 mg XL	20 mg (XL)	$75
Thiazolidinedione	Pioglitazone Rosiglitazone	45 mg 4 mg	45 mg 8 mg	$348 $407
DPP-4i	Alogliptin Saxagliptin Linagliptin Sitagliptin	25 mg 5 mg 5 mg 100 mg	25 mg 5 mg 5 mg 100 mg	$234-516
SGLT2i	Ertugliflozin Dapagliflozin Canagliflozin Empagliflozin	15 mg 10 mg 300 mg 25 mg	15 mg 10 mg 300 mg 25 mg	$322-558
GLP-1RA	Exenatide Qwk Exenatide Dulaglutide Semaglutide Liraglutide	2 mg suspension/pen 10 mcg pen 1.5/0.5 mL pen 1 mg pen 18 mg/3 mL pen	2 mg 20 mcg 1.5 mg 1 mg 1.8 mg	$792-1044 $1044

Adapted from ADA. 9. Pharmacologic approaches to glycemic treatment – Standards of Medical Care in Diabetes. *Diabetes Care* 2019;42(Supp. 1):S90-S102.

Median cost of insulin (US) per 1000 units*

*Actual out of pocket cost is usually different - Does not take into account discounts, rebates, other price adjustments

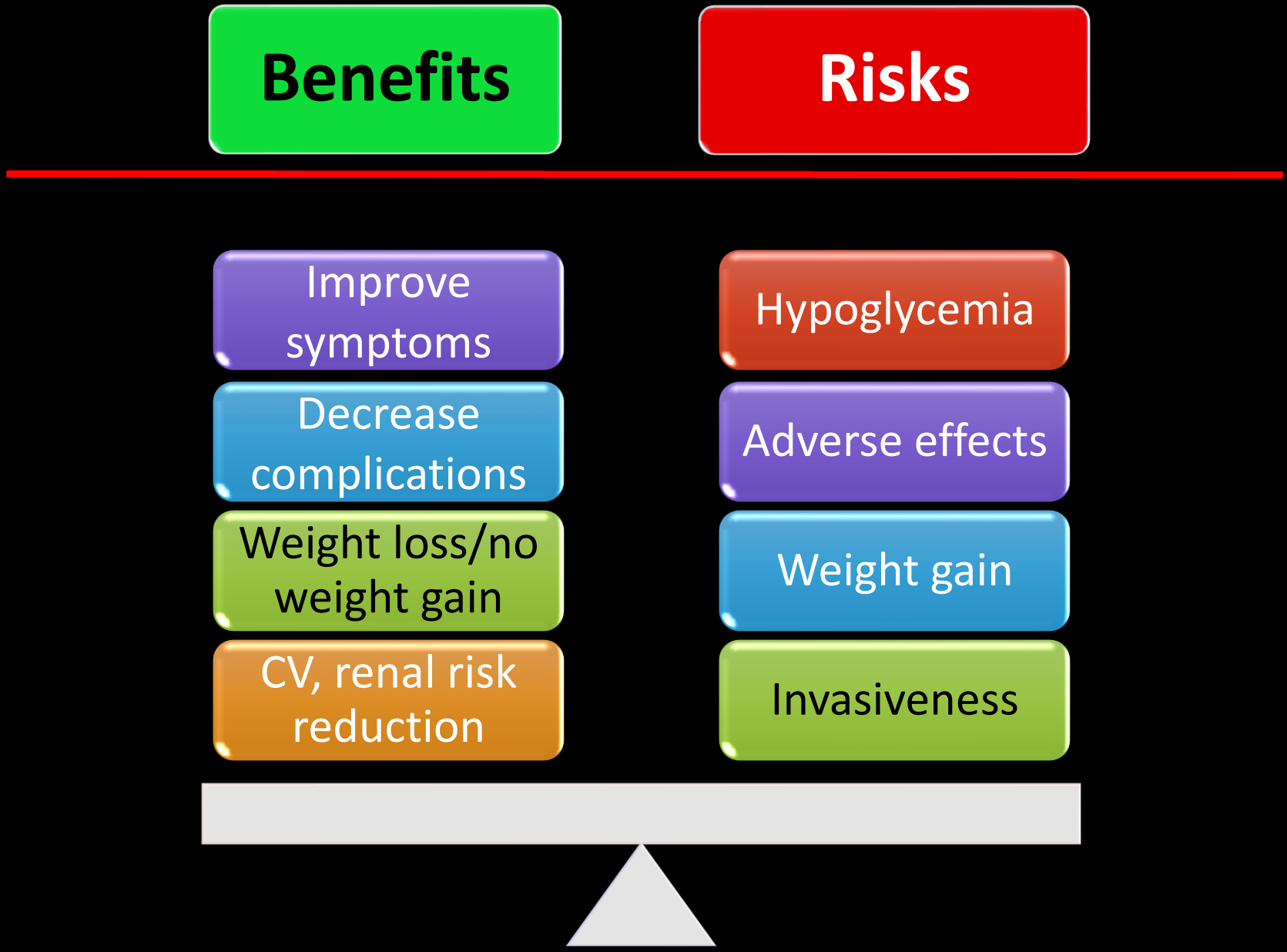
Insulin	Compound	Form/product	Median Avg Wholesale Price	Walmart Price ("Reli-On")
Basal analog	Glargine (Lantus)	U-100 vial U-100 prefilled pen	$323 $331	
Concentrated Human Regular	U-500 Human Regular	U-500 vial U-500 prefilled pen	$178 $230	
Intermediate-acting	Human NPH	U-100 vial U-100 prefilled pen	$165 $377	**$25**
Short-acting	Human Regular	U-100 vial	$165	**$25**
Rapid-acting	Lispro (Humalog)	U-100 vial U-100 3 mL cartridge U-100 or U-200 prefilled pen	$330 $408 $424	
Pre-mixed	NPH/Regular 70/30	U-100 vial U-100 prefilled pen	$165 $377	**$25**
Pre-mixed analog	Lispro 75/25	U-100 vial U-100 prefilled pen	$342 $424	

Adapted from ADA. 9. Pharmacologic approaches to glycemic treatment – Standards of Medical Care in Diabetes. *Diabetes Care* 2019;42(Supp. 1):S90-S102.

Inexpensive NPH, regular, or 70/30 insulin (no Rx needed) and supplies

Walmart

Item	Unit cost
Reli-On NPH insulin	$25 / vial
Reli-On Regular insulin	$25 / vial
Reli-On 70/30 insulin	$25 / vial
Reli-On Insulin syringes	$15.58 / box of 100
Reli-On Prime Glucose Monitor	$9
Reli-On Prime Test Strips	$17.88/100 strips
Reli-On Lancets	$1.58 for 100 lancets


Benefits
Risks
Improve symptoms
Decrease complications
Weight loss/no weight gain
CV, renal risk reduction
Hypoglycemia
Adverse effects
Weight gain
Invasiveness

What is high value diabetes care?

Value takes into account

net clinical benefit, cost, and likelihood of patient adherence

Drugs don’t work in patients who don’t take them.

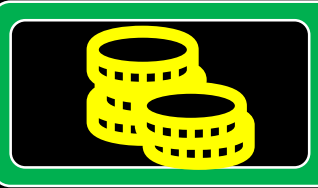
- *C. Everett Koop* (US Surgeon General, 1982-1989)

Strategies to increase adherence

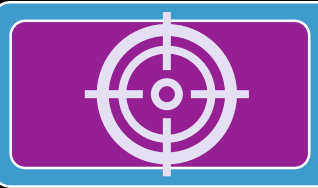
- **U**seful (demonstrate value) - educate about harms, benefits
- **U**seable (fits into real-life workflow)
  - lower cost
  - easy to take
  - minimize side effects
- **U** establish trust (and respect)
  - Show outcomes/effectiveness
  - Show that you are monitoring med adherence

Larry Garber – American Diabetes Association Scientific Sessions 2019.

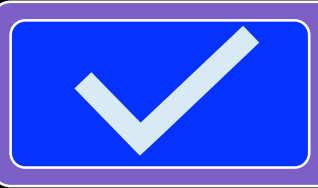
Is it more cost-effective to start an SGLT-2i or NPH insulin as a 3rd agent?



Cost-effectiveness analysis in U.K. from a payer perspective



Type 2 DM not at A1c goal on metformin and DPP-4i



Well-established, validated model, over a patient's lifetime; conservative assumptions

- Conclusion: Treatment intensification with an SGLT2i prior to NPH was cost-effective or cost-neutral compared with immediately starting NPH. Higher drug costs offset by lower incidence of complications

Pawaskar M, et al. *Diab Obes Metab* 2019;21:1010-1017.

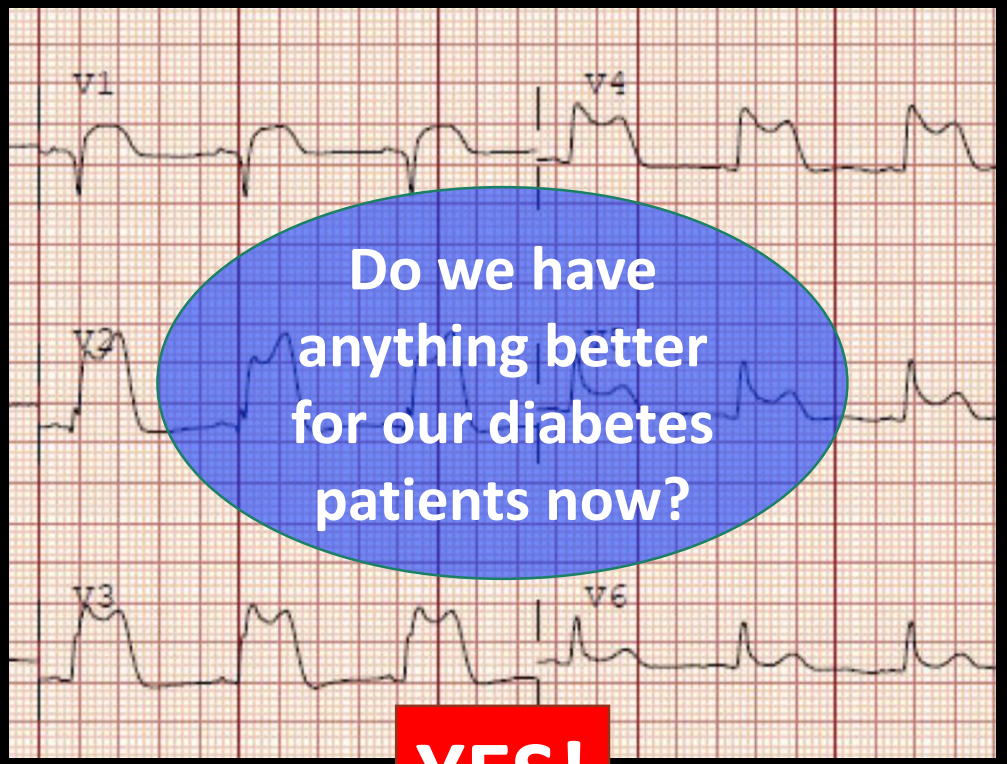
Patient EV: 62 yr old F

- CC: shortness of breath x 2 days, fatigue x 1 month
- No fever, chest pain, cough, edema or weight change
- No other symptoms
- T2DM x 10 years, HTN
- Metformin XR 2000 mg QD, Glyburide 10 mg BID, enalapril 40 mg QD, NPH insulin 20 units QHS

- Exam: 128/64. HR 72. T 98.2 BMI 31
- Total Chol 199. LDL 126. HDL 37. TG 179.
- HbA1c 8.3% Creatinine 0.9

EV: 62 yo F, T2DM x 10 yr on metformin, no CAD, A1c 8.3%, dyspnea x 2 days

- After workup, found to have CHF (EF 30%) and suspected to have had an MI in the past month
- Transferred out of ICU to step-down unit
- Paged by nurse: Unable to obtain blood pressure
- New STEMI



Key aspects to consider

- Established ASCVD
  - Heart failure (HFrEF)
- No CKD (creatinine 0.9 → eGFR 69 mL/min
- A1c 8.3% - not at goal
  - How much lowering does she need?
  - Avoiding hypoglycemia is a priority

ARS #4 – 62 yo F with T2D x 10 yr on metformin, A1c 8.3%, established ASCVD and CHF, no CKD

- What class of diabetes agents would you add to her regimen of max dose metformin?
  - A. DPP-4i
  - B. GLP-1RA
  - C. SGLT2i
  - D. Sulfonylurea

62 yo F with T2D x 10 yr on metformin, A1c 8.3%, established ASCVD and CHF, no CKD

- Which SGLT2i would you select?
  - Empagliflozin or canagliflozin
    - FDA indications for lowering risk in ASCVD
    - Trial evidence to lower hospitalization for heart failure
  - Alternative agents but lower on list: dapagliflozin, ertugliflozin
- Stop glipizide
- Later, consider adding liraglutide if not at A1c goal or for further CV risk reduction

What if these are not "preferred" by her insurance company, or her out of pocket expense is too high?

- Discount/savings/copay cards?
- Are there any alternatives (without the FDA indication for lowering CV risk)?
  - Dapagliflozin (CV death, heart failure), ertugliflozin
  - GLP-1RA not as preferred since SGLT2i's greatly benefit in HF, but data for CV risk reduction are available for: semaglutide, dulaglutide

Patient EV: 3 years later - CKD

- Age 65
- T2DM x 13 yr, HTN
- CAD with silent MI, HFrEF
- Creatinine 1.3 → eGFR 43 (CKD stage 3b)
- Metformin XR 2000 mg QD, empagliflozin 25 mg QD, liraglutide 1.8 mg QD
- A1c 7.9%
- How would you change her regimen?

Key aspects to consider

- Established ASCVD
- Heart failure
- CKD
- Goals: maintain A1c, avoid hypoglycemia

- Reduce metformin to 500 mg BID
- Continue SGLT-2i
- Certain GLP-1RA ok (semaglutide; liraglutide, lixisenatide)
  - Post marketing reports of AKI and worsening renal function requiring HD
  - Caution if severe GI side effects (monitor renal function, avoid uptitrating dose, consider stopping)
- Start insulin therapy with a basal analog

Metformin use

- CKD Stage 3a (45-59 mL/min): 500 mg QAM, 1000 mg QPM
- CKD Stage 3b (30-44 mL/min): 500 mg BID
- Monitor eGFR every 6 months
- Stop metformin if AKI likely or if eGFR <30
- D/C metformin if eGFR 30-60 mL/min and undergoing iodinated contrast study, liver disease, alcoholism, heart failure. Re-eval 48 hr after contrast study and restart if stable.

Lalau J-D, et al. *Diabetes Care* 2018;41:547-553.
https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-fda-revises-warnings-regarding-use-diabetes-medicine-metformin-certain

If your patient with T2DM and ASCVD has CKD

	Data available?	Renal dosing
Empagliflozin	>1800 pts studied with eGFR <60; small CKD study (30-60)	Sparse data for eGFR <60. D/C if eGFR <45.
Canagliflozin	Small CKD study (30-50)	*Ok for eGFR 30-45 if albuminuria >300 mg/day; contraindicated for eGFR <30
Dapagliflozin	Small CKD study (45-60)	FDA: Avoid if eGFR <45
Liraglutide*	>3000 pts studied with eGFR <60 but not ESRD	No dose adjustment. Avoid in ESRD
Dulaglutide	No data in eGFR <30	GI side effects, renal fxn
Semaglutide*		No dose adjustment
Exenatide QW	Increased exposure with ↓eGFR	Avoid if eGFR <45
Lixisenatide	655 pts studied with eGFR 30-59	*Avoid if eGFR <30

Sources: Prescribing information for each drug listed above

No ASCVD, but with CKD

- LS is a 49 yr old woman with CKD
- T2DM x 10 yr, longstanding HTN
- Renal cell ca s/p nephrectomy
- Creatinine 2.2 → eGFR 44 (CKD stage 3b)
- Metformin XR 2000 mg QD, empagliflozin 25 mg QD, liraglutide 1.8 mg QD
- A1c 7.9%
- How would you change her regimen?

Key aspects to consider

- No known ASCVD
  - Any suspicion? Careful HPI/ROS for clues
- CKD (creatinine 2.2 → eGFR 44 mL/min)

Evidence for CV risk reduction by the new therapies is weaker without established ASCVD, but there is some evidence for renal benefits

- Reduce metformin to 500 mg BID. Stop empa
- Consider: reducing risk of nephropathy progression, cost, preference (route, dosing), comorbidities, potential side effects
- Limited options: GLP-1RA, linagliptin/other DPP4i, insulin

What to do with DPP-4i dosing if renal function decreases

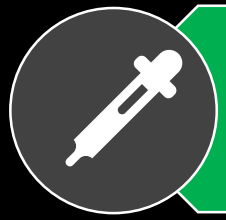
- Renal dysfunction:
  - Linagliptin ok to use at the same dose no matter what renal function

If eGFR ↓ below…	Reduce:
60 mL/min	Alogliptin to 12.5
50 mL/min	Sitagliptin to 50, Saxagliptin to 2.5
30 mL/min	Sitagliptin to 25, Alogliptin to 6.25

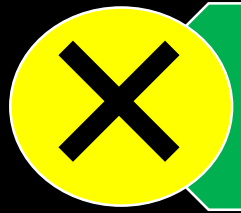
Final thoughts (1)

The newer DM medications do not cause hypoglycemia or weight gain but are costly

Continue metformin for as long as possible. Uptitrate for adherence



NPH insulin can be safely used in many/most pts with type 2 DM

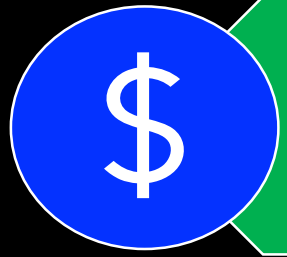


DO NOT prescribe a GLP-1RA with a DPP-4i

Final thoughts (2)

All of the SGLT2i reduce CV, HF and/or CKD risk

Some of the GLP-1RA reduce CV and/or CKD risk

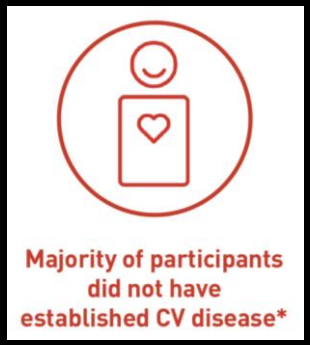


SGLT2i and GLP-1RA are high value therapies in patients with ASCVD, HF and/or CKD

On the near horizon

REWIND
Dulaglutide CV Outcomes Trial

- Dulaglutide (GLP-1RA) reduced risk of MACE by 12%. Also renal, microvascular (eye or kidney)
- ?FDA approval for broader patient population?



GRADE
Glycemia Reduction Approaches in Diabetes: A Comparative Effectiveness Study (GRADE)

- Comparative effectiveness trial of sulfonylurea (glimepiride) vs DPP-4i (sitagliptin) vs GLP-1RA (liraglutide) vs insulin (glargine)
- Estimated completion: July 2021

Resources

- ADA. Pharmacologic approaches to glycemic treatment: Standards of Medical Care in Diabetes – 2020. *Diabetes Care* 2020;43(Suppl. 1).
- ADA. Cardiovascular disease and risk management: Standards of Medical Care in Diabetes – 2020. *Diabetes Care* 2020;43(Suppl. 1).
- Das SR, Everett BM, et al. 2018 ACC Expert consensus decision pathway on novel therapies for cardiovascular risk reduction in patients with type 2 diabetes and atherosclerotic cardiovascular disease. *J Am Coll Cardiol* 2018;72(24):3200-3223.

What is one thing you will do differently when you see your next diabetes patient?

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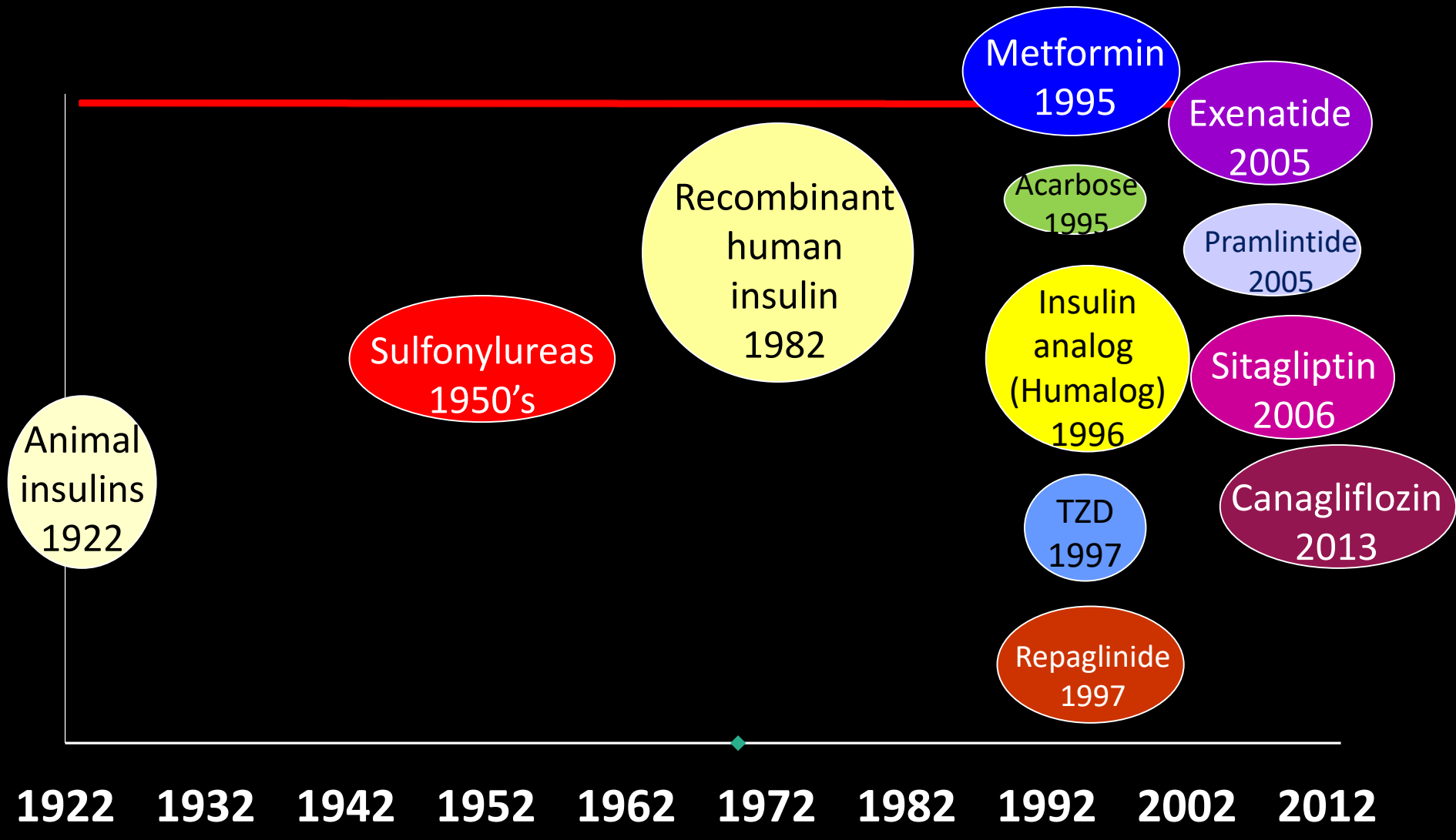
Reinforce lifestyle recommendations for type 2 DM

- Lifestyle changes
  - Less calorie-dense foods
  - Emphasis on:
    - Complex carbohydrates higher in fiber
    - Lean/plant proteins
    - Smaller portions
  - Increase physical activity
  - Weight loss if overweight
    - Mediterranean or DASH diet
    - Meal replacement shakes (1-2 meals/day)

Classes of diabetes therapies



The most commonly-used diabetes medications

Biguanide	metformin
Glucagon-like peptide-1 receptor agonist	exena**tide**, exena**tide** QW, liraglu**tide**, dulaglu**tide**, lixisenatide, semaglutide (& PO)
Sodium glucose co-transport-2 inhibitor	cana**gliflozin**, dapa**gliflozin**, empa**gliflozin**, ertu**gliflozin**
Dipeptidyl peptidase-4 inhibitor	sita**gliptin**, saxa**gliptin**, lina**gliptin**, alo**gliptin**
Insulin Insulin analogs	NPH, Regular, 70/30 Lispro, Aspart, Glulisine, Glargine, Detemir, Degludec, inhaled
Sulfonylurea	glimepiride, glyburide, glipizide
Thiazolidinedione	pioglitazone, rosiglitazone

Insulin	Onset	Peak (hr)	Duration (hr)
inhaled	<5-10 min	0.5-1.5	2.5
rapid acting*	5-15 min	1-2	3-5
regular	30-60 min	2	6-8
NPH	1-2 hr	4-8	10-18
U500	1-2 hr	4-8	10-18
detemir	1-2 hr	-	12-20
glargine U100	1-2 hr	-	24
glargine U300	6 hr	-	≥30
degludec	1-2 hr	-	42

*lispro U100, U200; aspart, FiAsp, glulisine