LATEST ADVANCES IN THE MANAGEMENT OF DIABETES

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CONFLICT OF INTEREST

- Participated in Research studies funded by the
  - NIH
  - NHLBI
  - VA
  - Kowa Pharmaceuticals

OBJECTIVES

- Describe mechanism, benefits, and side effects of SGLT2 inhibitors, DPP-4 inhibitors, and GLP-1 agonists
- Discuss emerging cardiovascular and renal outcomes associated with SGLT2 inhibitors and GLP-1 agonists
- Practice incorporating novel therapeutics for type-2 diabetes into practice

- You diagnosed a 66 BM with Type 2 DM. He has no other comorbidity with normal exam and labs. His A1c is 8.1. What medicine would you start along with life style modification and physical activities advices?

1. **Glipizide**
2. **Metformin**
3. **Pioglitazone**
4. **Empagliflozin**
5. **Liraglutide**

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PHARMACOLOGIC THERAPY FOR TYPE 2 DIABETES.

- Metformin is the **preferred initial pharmacologic agent** for the treatment of type 2 diabetes.
- Once initiated, metformin **should be continued as long as** it is tolerated and not contraindicated; other agents, including insulin, should be added to metformin.

Pharmacologic Approaches to Glycemic Treatment: *Standards of Medical Care in Diabetes - 2019*. *Diabetes Care* 2019;42(Suppl. 1):S90-S102

- 68 BM with Type 2 DM comes for routine appointment. He is generally well controlled on Metformin for the last 2 years. Only new complaint is burning feet x 3 months. Exams is unchanged except he has sense of vibration impaired in his feet. A1c is 7.1 **What would you do?**

1. Order a Nerve Conduction studies
2. Add gabapentin
3. Order vitamin B12 level
4. Educate about feet care & diabetic complications and increase metformin to get better A1c control
5. Refer to neurologist

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3. **Order vitamin B12 level**
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5. Refer to neurologist

- **Long-term use of metformin can be associated with vitamin B12 deficiency**

- **Periodic measurement of vitamin B12 levels should be considered in metformin-treated patients, especially in those with anemia or peripheral neuropathy.**

American Diabetes Association Standards of Medical Care in Diabetes. Approaches to glycemic treatment. Diabetes Care 2019; 41 (Suppl. 1): S75-S84

Which of the following DM medications have been linked to Bladder cancer?

1. Metformin
2. Glipizide
3. Pioglitazone
4. Canagliflozin
5. Exenitide

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3. **Pioglitazone**
4. Canagliflozin
5. Exenitide

PIOGLITAZONE AND BLADDER CANCER?

- **Pioglitazone, increases the risk of bladder cancer by at least 40% when used for more than a year.**

Cancer Risk for Patients Using Thiazolidinediones for Type 2 Diabetes: A Meta-Analysis *The Oncologist February 1, 2013 18:148-156*

- 66 years old with insulin dependent brittle DM on 4 medications comes for routine appointment for his uncontrolled Diabetes. He read on internet about wearable “Bionic Pancreas” which automatically detect blood sugars levels and adjust insulin. He would like to get that. You will tell him:

1. There is no such device available at the moment
2. Order the Bionic Pancreas
3. Refer him to a research trial for Bionic Pancreas
4. Suggest dietitian consult for better carb counting
5. Add Semaglutide

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4. Suggested dietitian consult for better carb counting
5. Add Semaglutide

HYBRID CLOSED-LOOP INSULIN DELIVERY SYSTEM

- Hailed as the world's first artificial pancreas
- A glucose monitoring device and insulin pump to work together to stabilize blood glucose levels.
- It was approved by the FDA in 2016.

- 58 yo male on atorvastatin, lisinopril and aspirin came to your office worried about the newspaper articles about increase risk of diabetes in patients taking statin medications.
- His HTN and LDL are controlled to goal, his previous glucose readings were normal.
- What would you like to tell him?
  1. Stop atorvastatin
  2. Continue atorvastatin and don't worry
  3. Continue atorvastatin with periodic monitoring of blood sugars
  4. Tell him to not believe in everything he reads in newspaper.
  5. Refer him to endocrinology

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INCREASES IN GLYCOSYLATED HEMOGLOBIN (HBA1C) AND FASTING PLASMA GLUCOSE

- In JUPITER trail, a 27% increase in diabetes mellitus in rosuvastatin-treated patients compared to placebo-treated patients.
- High-dose atorvastatin had also been associated with worsening glycemic control in the PROVE-IT TIMI 22.
- A meta-analysis by Sattar et al. included 13 statin trials with 91,140 participants, reported that statin therapy was associated with a 9% increased risk for incident diabetes (Absolute risk is about 1 in 100-150 patients)

STATIN AND RISK OF HYPERGLYCEMIA

- FDA continues to believe that the cardiovascular benefits of statins outweigh these small increased risks.

- Cause and effect has not been established

WHAT IS THE RECOMMENDED GOAL A1C GOAL?

1. <8
2. <7
3. <6
4. Every patient is different……
5. Whatever patient decides

WHAT IS THE RECOMMENDED GOAL A1C GOAL?

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2. <7
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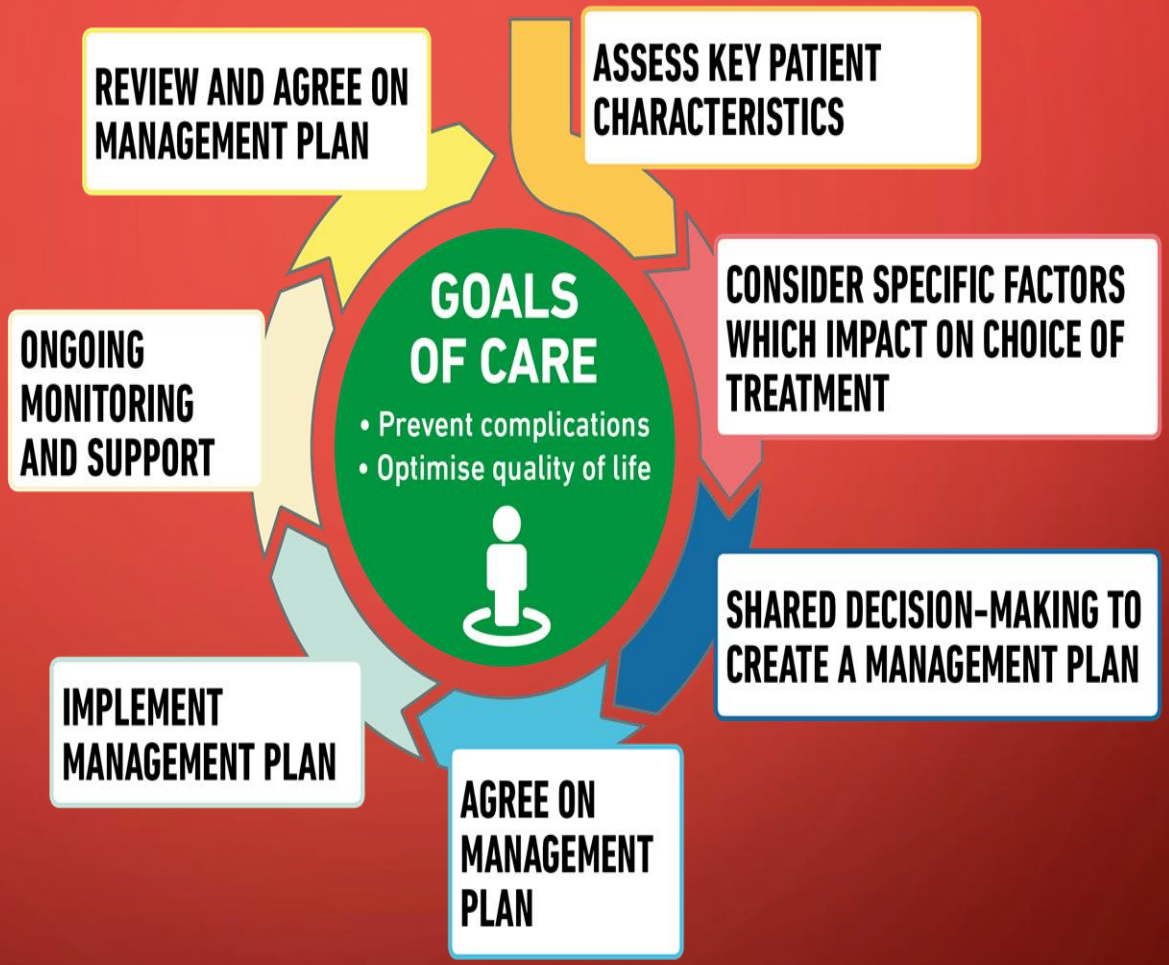
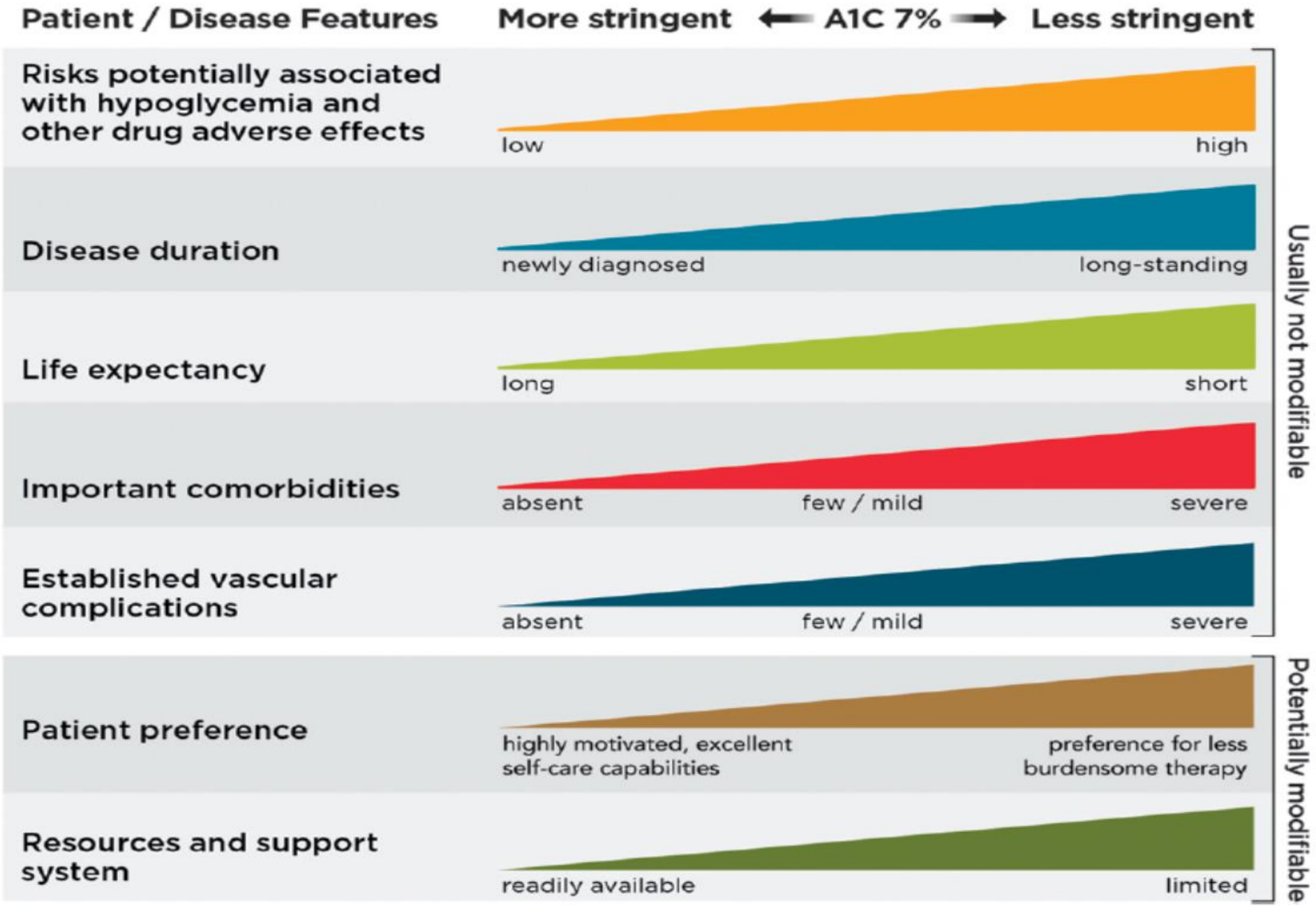
4. **Every patient is different……**
5. Whatever patient decides

Decision Cycle for Patient-Centered Glycemic Management in Type 2 Diabetes



Comprehensive Medical Evaluation and Assessment of Comorbidities: *Standards of Medical Care in Diabetes - 2019*. *Diabetes Care* 2019;42(Suppl. 1):S34-S45

Approach to Individualization of Glycemic Targets



Glycemic Targets: *Standards of Medical Care in Diabetes - 2019. Diabetes Care* 2019;42(Suppl. 1):S61-S70

GLYCEMIC GOALS IN ADULTS

- A reasonable A1C goal for many nonpregnant adults is <7% (53 mmol/mol).
- Consider more stringent goals (e.g. <6.5%) for select patients if achievable without significant hypos or other adverse effects.
- Consider less stringent goals (e.g. <8%) for patients with a history of severe hypoglycemia, limited life expectancy, or other conditions that make <7% difficult to attain.

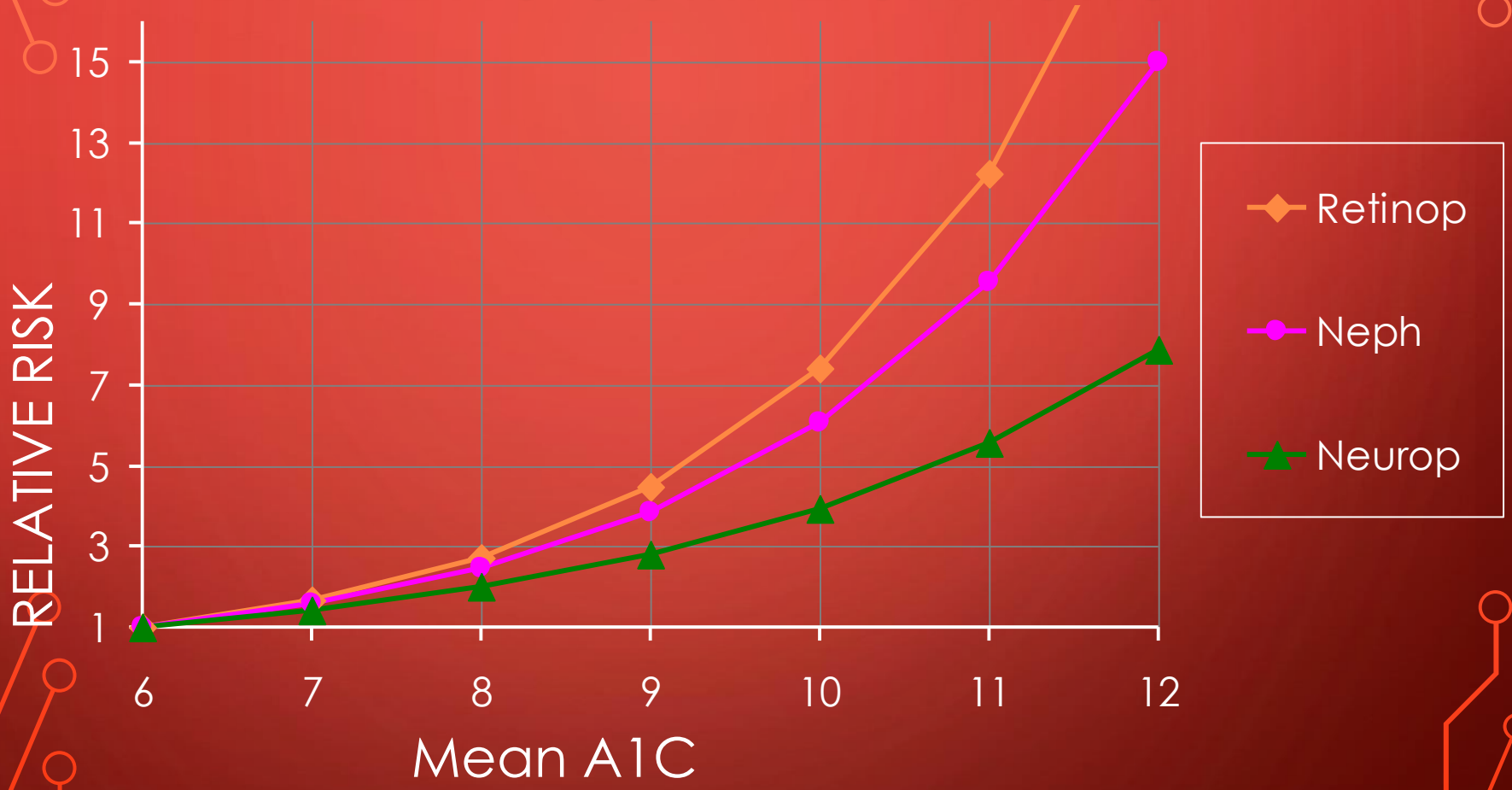
American Diabetes Association. Pharmacologic Approaches to Glycemic Treatment: Standards of Medical Care in Diabetes-2018. Diabetes Care. 2018;41(Suppl 1):S73-S85

ANTI-HYPERGLYCEMIC THERAPY:
GLYCEMIA TARGETS

- HbA1c < 7.0% (MPG ~150 mg/dL)
- Pre-prandial PG 80-130 mg/dL
- Post-prandial PG <180 mg/dL
- Avoidance of hypoglycemia
- Individualization is key:
  - More stringent (6.0-6.5%) - short disease duration, healthier, no CVD
  - Less stringent (7.5-8.0%+) – comorbidities, complications, hypoglycemias, short life expectancy, limited resources, support or motivation

American Diabetes Association. Pharmacologic Approaches to Glycemic Treatment: Standards of Medical Care in Diabetes-2018. Diabetes Care. 2018;41(Suppl 1):S73-S85

RELATIVE RISK OF PROGRESSION OF DIABETIC COMPLICATIONS



DCCT Research Group, *N Engl J Med* 1993, 329:977-986.

DCCT

- 10% reduction in HbA_{1c}
- 43% reduced risk of retinopathy progression
- 18% increased risk of severe hypoglycemia with coma and/or seizure

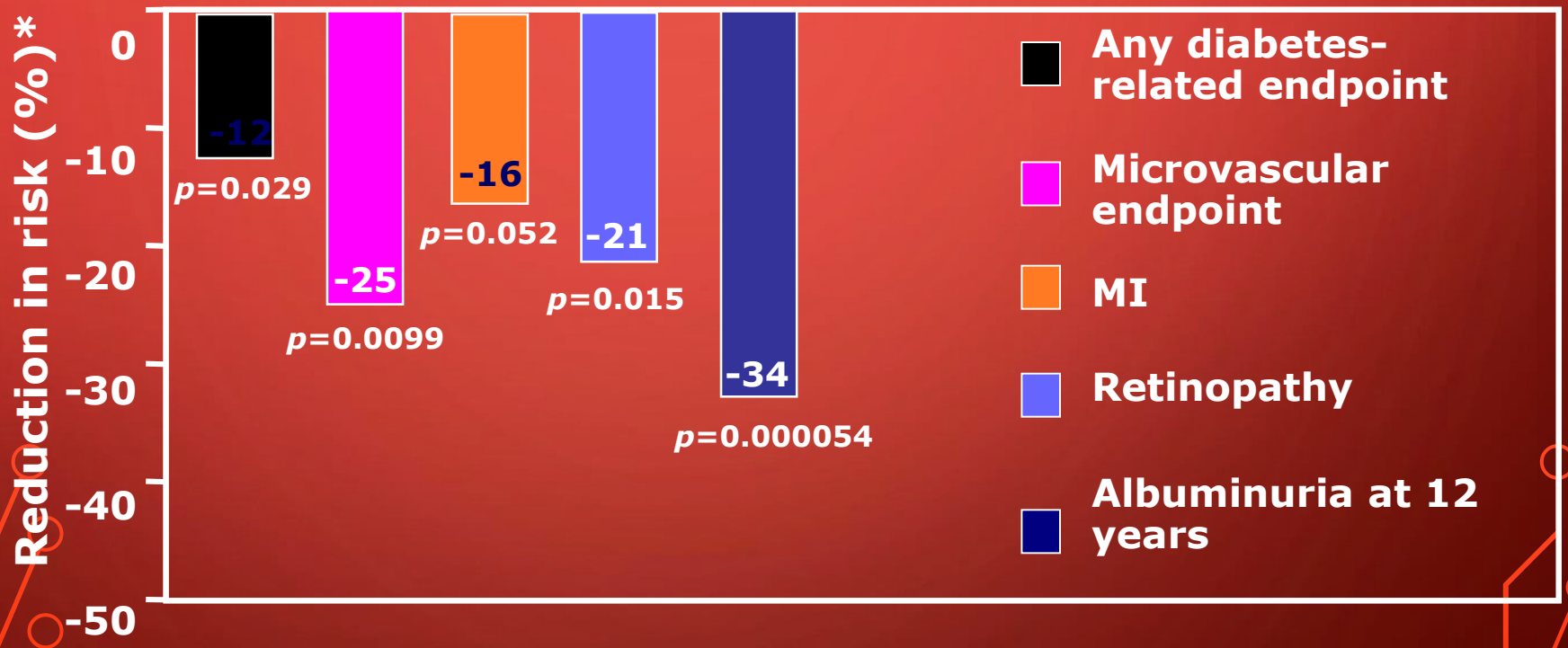
DCCT Research Group, *N Engl J Med* 1993, 329:977-986.

LIFETIME BENEFITS OF INTENSIVE THERAPY (DCCT)

- Gain of **15.3 years** of complication free living compared to conventional therapy
- Gain of **5.1 years** of life compared to conventional therapy

DCCT Study Group, *JAMA* 1996, 276:1409-1415.

United Kingdom Prospective Diabetes Study (UKPDS)



*Percent risk reduction per 0.9% decrease in HbA_{1C}; UKPDS. *Lancet*. 1998;352:837-853.

IMPACT OF INTENSIVE THERAPY

Study	Micro		Macro		Mortality	
UKPDS	↓	↓	↔	↓	↔	↓
DCCT / EDIC	↓	↓	↔	↓	↔	↔
ACCORD	↓		↔		↑	
ADVANCE	↓		↔		↔	
VADT	↓		↔		↔	

Initial Trial Long Term Follow-up

Ray KK et al. *Lancet.* 2009; 373:1765–1772.

WHAT HAVE WE LEARNED FROM DIABETES TRIALS?

- **DCCT:** Trend toward lower risk of CVD events with intensive control (T1D)
- **EDIC:** 57% reduction in risk of nonfatal MI, stroke, or CVD death (T1D)
- **UKPDS:** nonsignificant reduction in CVD events (T2D).
- **ACCORD, ADVANCE, VADT** suggested no significant reduction in CVD outcomes with intensive glycemic control. (T2D)

Drake TC, Hire D, Rehman SU, O'Connor P. Factors Associated with Failure to Achieve Hemoglobin A1c <8.0% in the Action to Control Cardiovascular Risk in Diabetes Trial . Diabetes Obes Metab. 2016 Jan;18(1):92-5

67 year old female with T2DM, HTN, osteopenia, idiopathic pancreatitis, and CAD s/p RCA stent in 2015 is seen in clinic today. Her A1c is 8.5%. Current medications include metformin 1000mg BID, ASA 81mg QD, and Lisinopril 40mg QD. BMI is 27.

What would you add?

1. Canagliflozin
2. Empagliflozin
3. Sitagliptin
4. Liraglutide
5. All of above options are reasonable

Case courtesy of Tanya Nikiforova, MD

PHARMACOLOGIC THERAPY FOR TYPE 2 DIABETES

- Consider initiating dual therapy in patients with newly diagnosed type 2 diabetes who have A1C ≥1.5% (12.5 mmol/mol) above their glycemic target.

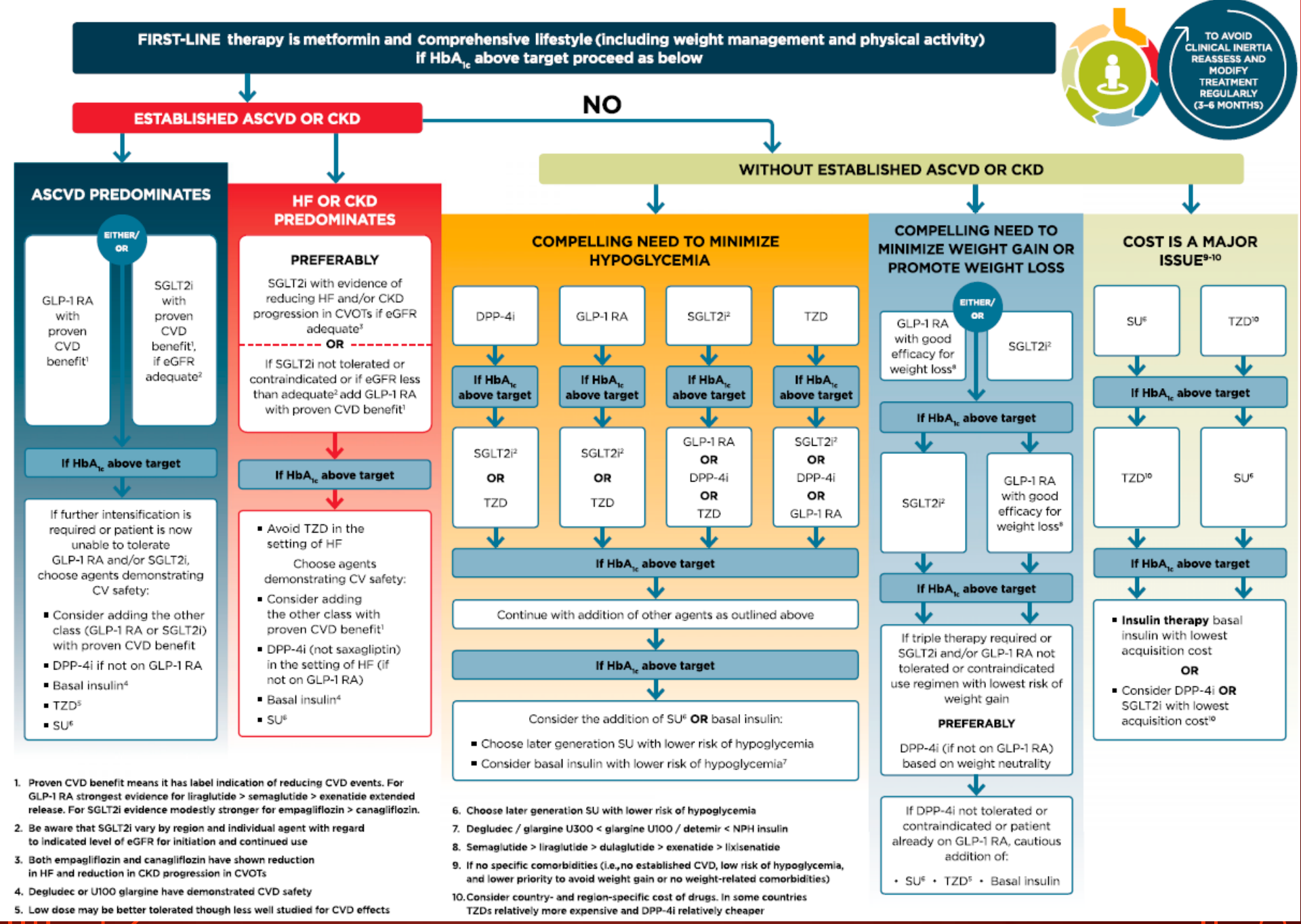
- A patient-centered approach should be used to guide the choice of pharmacologic agents. Considerations include comorbidities (atherosclerotic cardiovascular disease, heart failure, chronic kidney disease), hypoglycemia risk, impact on weight, cost, risk for side effects, and patient preferences.

PHARMACOLOGIC THERAPY FOR TYPE 2 DIABETES

- **The early introduction of insulin should be considered**
  - if there is evidence of ongoing catabolism (weight loss)
  - if symptoms of hyperglycemia are present
  - or when A1C levels (>10% [86 mmol/mol)] or blood glucose levels (≥300 mg/dL [16.7 mmol/L)] are very high.

PHARMACOLOGIC THERAPY FOR TYPE 2 DIABETES

- Among patients with type 2 diabetes who have established atherosclerotic cardiovascular disease, sodium-glucose cotransporter 2 inhibitors, or glucagon-like peptide 1 receptor agonists with demonstrated cardiovascular disease benefit are recommended as part of the antihyperglycemic regimen.
- Among patients with atherosclerotic cardiovascular disease at high risk of heart failure or in whom heart failure coexists, sodium-glucose cotransporter 2 inhibitors are preferred.
- For patients with type 2 diabetes and chronic kidney disease, consider use of a sodium-glucose cotransporter 2 inhibitor or glucagon-like peptide 1 receptor agonist shown to reduce risk of chronic kidney disease progression, cardiovascular events, or both.



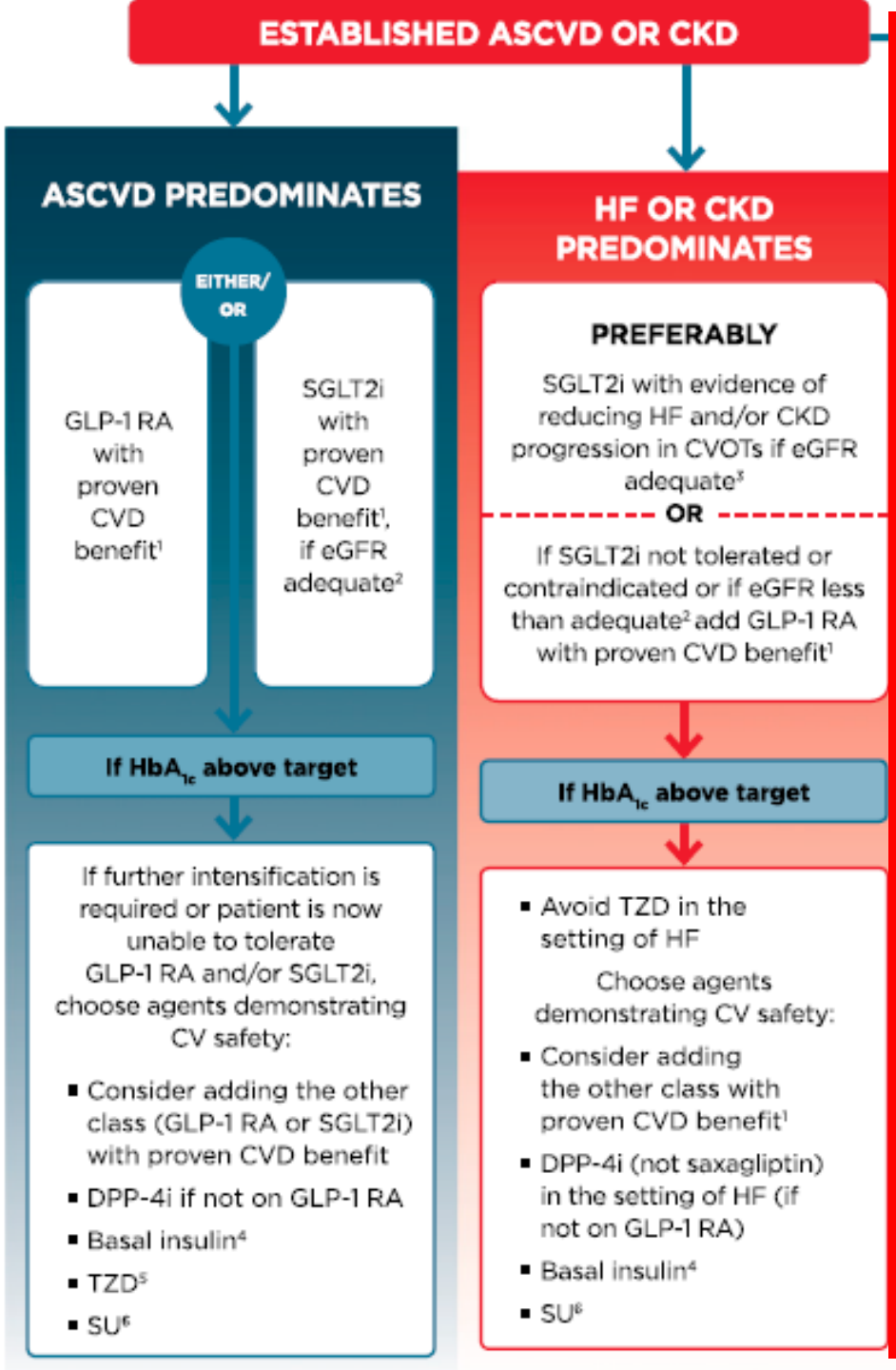
1. Proven CVD benefit means it has label indication of reducing CVD events. For GLP-1 RA strongest evidence for liraglutide > semaglutide > exenatide extended release. For SGLT2i evidence modestly stronger for empagliflozin > canagliflozin.
2. Be aware that SGLT2i vary by region and individual agent with regard to indicated level of eGFR for initiation and continued use
3. Both empagliflozin and canagliflozin have shown reduction in HF and reduction in CKD progression in CVOTs
4. Degludec or U100 glargine have demonstrated CVD safety
5. Low dose may be better tolerated though less well studied for CVD effects
6. Choose later generation SU with lower risk of hypoglycemia
7. Degludec / glargine U300 < glargine U100 / detemir < NPH insulin
8. Semaglutide > liraglutide > dulaglutide > exenatide > lixisenatide
9. 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)
10. Consider country- and region-specific cost of drugs. In some countries TZDs relatively more expensive and DPP-4i relatively cheaper

Pharmacologic Approaches to Glycemic Treatment: *Standards of Medical Care in Diabetes - 2019. Diabetes Care* 2019;42(Suppl. 1):S90-S102

Table 9.1—Drug-specific and patient factors to consider when selecting antihyperglycemic treatment in adults with type 2 diabetes

	Efficacy	Hypoglycemia	Weight change	CV effects		Cost	Oral/SQ	Renal effects		Additional considerations
				ASCVD	CHF			Progression of DKD	Dosing/use considerations*	
Metformin	High	No	Neutral (potential for modest loss)	Potential benefit	Neutral	Low	Oral	Neutral	▪ Contraindicated with eGFR <30	▪ Gastrointestinal side effects common (diarrhea, nausea) ▪ Potential for B12 deficiency
SGLT-2 inhibitors	Intermediate	No	Loss	Benefit: empagliflozin†, canagliflozin	Benefit: empagliflozin†, canagliflozin	High	Oral	Benefit: canagliflozin, empagliflozin	▪ Renal dose adjustment required (canagliflozin, dapagliflozin, empagliflozin, ertugliflozin)	▪ **FDA Black Box:** Risk of amputation (**canagliflozin**) ▪ Risk of bone fractures (canagliflozin) ▪ DKA risk (all agents, rare in T2DM) ▪ Genitourinary infections ▪ Risk of volume depletion, hypotension ▪ ↑LDL cholesterol ▪ Risk of Fournier's gangrene
GLP-1 RAs	High	No	Loss	Neutral: lixisenatide Benefit: liraglutide† > semaglutide > exenatide extended release	Neutral	High	SQ	Benefit: liraglutide	▪ Renal dose adjustment required (exenatide, lixisenatide) ▪ Caution when initiating or increasing dose due to potential risk of acute kidney injury	▪ **FDA Black Box:** Risk of thyroid C-cell tumors (**liraglutide, albiglutide, dulaglutide, exenatide extended release**) ▪ Gastrointestinal side effects common (nausea, vomiting, diarrhea) ▪ Injection site reactions ▪ ?Acute pancreatitis risk
DPP-4 inhibitors	Intermediate	No	Neutral	Neutral	Potential risk: saxagliptin, alogliptin	High	Oral	Neutral	▪ Renal dose adjustment required (sitagliptin, saxagliptin, alogliptin); can be used in renal impairment ▪ No dose adjustment required for linagliptin	▪ Potential risk of acute pancreatitis ▪ Joint pain
Thiazolidinediones	High	No	Gain	Potential benefit: pioglitazone	Increased risk	Low	Oral	Neutral	▪ No dose adjustment required ▪ Generally not recommended in renal impairment due to potential for fluid retention	▪ **FDA Black Box:** Congestive heart failure (**pioglitazone, rosiglitazone**) ▪ Fluid retention (edema; heart failure) ▪ Benefit in NASH ▪ Risk of bone fractures ▪ Bladder cancer (pioglitazone) ▪ ↑LDL cholesterol (rosiglitazone)
Sulfonylureas (2nd generation)	High	Yes	Gain	Neutral	Neutral	Low	Oral	Neutral	▪ Glyburide: not recommended ▪ Glipizide and glimepiride: initiate conservatively to avoid hypoglycemia	▪ FDA Special Warning on increased risk of cardiovascular mortality based on studies of an older sulfonylurea (tolbutamide)
Insulin — Human insulin	Highest	Yes	Gain	Neutral	Neutral	Low	SQ	Neutral	▪ Lower insulin doses required with a decrease in eGFR; titrate per clinical response	▪ Injection site reactions ▪ Higher risk of hypoglycemia with human insulin (NPH or premixed formulations) vs. analogs
Insulin — Analogs						High	SQ			

*For agent-specific dosing recommendations, please refer to the manufacturers' prescribing information. †FDA approved for CVD benefit. CHF, congestive heart failure; CV, cardiovascular; DPP-4, dipeptidyl peptidase 4; DKA, diabetic ketoacidosis; DKD, diabetic kidney disease; GLP-1 RAs, glucagon-like peptide 1 receptor agonists; NASH, nonalcoholic steatohepatitis; SGLT2, sodium–glucose cotransporter 2; SQ, subcutaneous; T2DM, type 2 diabetes.

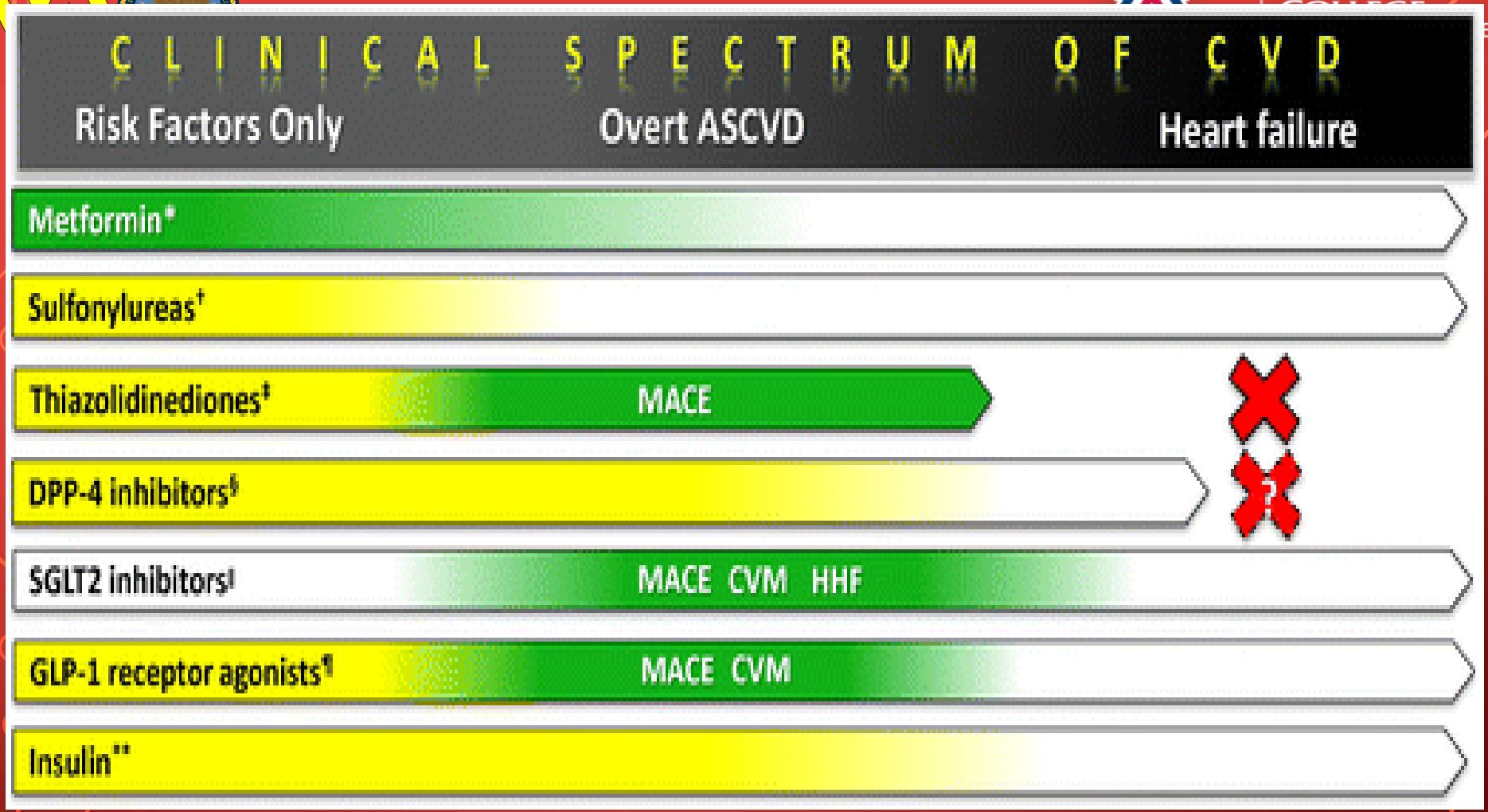


- If A1C is above target despite recommended first-line treatment and the patient has ASCVD or CKD:
  - **ASCVD Predominates:**
    - Add GLP-1 RA with proven CVD benefit, OR
    - Add SGLT-2 inhibitor with proven CVD benefit (if eGFR adequate)
  - **If HF or CKD Predominates:**
    - Add SGLT-2 inhibitor with evidence of benefit
    - If can't take an SGLT-2 inhibitor, use a GLP-1 RA with proven CVD benefit

Agent	MACE*	CVD mortality	All-cause mortality	HF admissions†	Hypoglycemia risk‡	Weight change	Cost
Pioglitazone	↓	↔	↔	↑§	Low	↑	Low
Empagliflozin	↓	↓	↓	↓	Low	↓	High
Liraglutide	↓	↓	↓	↔	Low	↓	High
Semaglutide	↓	↔	↔	↔	Low	↓	High[a]

Risk of CVD outcomes, CVD-related and all-cause mortality, key side effects, and cost associated with use of listed agents. Data are from the following trials: IRIS (pioglitazone), EMPA-REG OUTCOME (empagliflozin), LEADER (liraglutide), and SUSTAIN-6 (semaglutide). Downward arrows (green) indicate a reduction, and upward arrows (red) indicate an increase; horizontal arrows (yellow) indicate neutral effect. *Denotes major adverse cardiovascular events, most commonly a composite of cardiovascular death, nonfatal MI, and nonfatal stroke. †Denotes hospitalization due to heart failure. ‡Risk for severe hypoglycemia is compared to that observed in patients using sulfonylureas or insulin. §Based on several studies using pioglitazone (excluding IRIS). [a]Cost assumed since drug is not yet marketed.

Ismail-Beigi, J GEN INTERN MED (2017) 32: 1044



Indications and CV evidence of glucose-lowering agents in type 2 diabetes. Arrow bar denotes patient category in which the medication class is currently indicated. Green indicates effectiveness (i.e., reduced CV events), yellow indicates CV neutrality, and no color indicates lack of CV data from randomized clinical trials, as interpreted by the authors. For CV effectiveness, the specific types of events reduced are also listed (MACE = major adverse CV events; CVM = CV mortality; HHF = hospitalization for heart failure.) *Metformin effectiveness demonstrated in UKPDS-34 (n = 1704),1 Kooy et al. (n = 390),2 and SPREAD-DIMCAD (n = 304).3 †Sulfonylurea safety demonstrated for glibenclamide and chlorpropamide in UKPDS-33 (n = 3867).6 ‡ For thiazolidinediones, safety shown for rosiglitazone for patients with CV risk factors (RECORD, n = 4447)25 and effectiveness shown for pioglitazone in PROactive (n = 5238)23 and IRIS (insulin-resistant stroke population with no diabetes, n = 3876.).19 Contraindicated in heart failure. § Dipeptidyl peptidase-4 (DPP-4) inhibitor safety shown for saxagliptin (SAVOR-TIMI 53, n = 16,492),14 alogliptin (EXAMINE, n = 5380),15 and sitagliptin (TECOS, n = 14,671).16 SAVOR found an increased HHF with saxagliptin, with a similar trend in EXAMINE; current guidelines caution the use of saxagliptin and alogliptin in heart failure patients. ‖ SGLT2 inhibitor effectiveness demonstrated for empagliflozin in EMPA-REG OUTCOME (n = 7020)18; although HHF was reduced in that study, the drug has not yet been tested in a dedicated heart failure study. ¶ Only GLP-1 receptor agonist effectiveness demonstrated for liraglutide (MACE, CVM) in LEADER (n = 9340)20 and the investigational semaglutide (MACE only) in SUSTAIN-6 (n = 3297).21 ** Insulin safety shown in UKPDS-33 (n = 3867)6 and ORIGIN (n = 12,537).37 Acute in-hospital studies are not considered.

Lipska KJ, Krumholz HM. Is hemoglobin A1c the right outcome for studies of diabetes? JAMA 2017;317:1017–18.

GLYCEMIC CONTROL ALGORITHM

LIFESTYLE THERAPY
(Including Medically Assisted Weight Loss)

Entry A1C < 7.5%

MONOTHERAPY*

- ✓ Metformin
- ✓ GLP-1 RA
- ✓ SGLT-2i
- ✓ DPP-4i
- ! TZD
- ✓ AGi
- ! SU/GLN

If not at goal in 3 months proceed to Dual Therapy

Entry A1C ≥ 7.5%

DUAL THERAPY*

MET or other 1st-line agent +

- ✓ GLP-1 RA
- ✓ SGLT-2i
- ✓ DPP-4i
- ! TZD
- ! Basal Insulin
- ✓ Colesevelam
- ✓ Bromocriptine QR
- ✓ AGi
- ! SU/GLN

If not at goal in 3 months proceed to Triple Therapy

TRIPLE THERAPY*

MET or other 1st-line agent + 2nd-line agent +

- ✓ GLP-1 RA
- ✓ SGLT-2i
- ! TZD
- ! Basal insulin
- ✓ DPP-4i
- ✓ Colesevelam
- ✓ Bromocriptine QR
- ✓ AGi
- ! SU/GLN

If not at goal in 3 months proceed to or intensify insulin therapy

Entry A1C > 9.0%

SYMPTOMS

NO	YES
DUAL Therapy OR TRIPLE Therapy	INSULIN ± Other Agents

ADD OR INTENSIFY INSULIN

Refer to Insulin Algorithm

LEGEND

- ✓ Few adverse events and/or possible benefits
- ! Use with caution

* Order of medications represents a suggested hierarchy of usage; length of line reflects strength of recommendation

PROGRESSION OF DISEASE

NEW RECOMMENDATION: PHARMACOLOGIC THERAPY FOR T2DM

- In patients with long-standing suboptimally controlled type 2 diabetes and established atherosclerotic cardiovascular disease, empagliflozin or canagliflozin or liraglutide should be considered

- These agents have been shown to reduce cardiovascular and all-cause mortality when added to standard care.

American Diabetes Association Standards of Medical Care in Diabetes. Diabetes Care 2019; 41 (Suppl. 1): S74-S85

Medication	Population studied	Primary outcome	MACE	CHF Hospitalization	All-cause mortality
Empagliflozin (EMPA-REG OUTCOME trial, NEJM 2015)	Known CV disease or at high risk	MACE: CV mortality, nonfatal MI, nonfatal stroke	↓	↓	↓
Canagliflozin (CANVAS trial, NEJM 2017)			↓	↓	
Liraglutide (LEADER trial, NEJM 2016)			↓		↓
Semaglutide (SUSTAIN-6 trial, NEJM 2016)			↓		

ANTI-HYPERGLYCEMIC THERAPY: ORAL AGENTS & NON-INSULIN INJECTABLES

- Biguanides
- Sulfonylureas
- Thiazolidinediones
- Meglitinides
- Alpha-glucosidase inhibitors
- DPP-4 inhibitors
- SGLT-2 inhibitors
- Dopamine-2 agonists
- Bile acid sequestrants
- GLP-1 receptor agonists
- Amylinomimetics

Diabetes Care, *Diabetologia.* 19 April 2012.
www.diabetes.org/living-with-diabetes/treatment-and-care/medication/oral-medications/what-are-my-options.html.

EFFICACY

Drug	A1c Reduction (%)
Metformin	1.5–2.0
Secretagogue (SFU/Glinide)	1.5–2.0
GLP1RA	1.0-1.5
TZD	1.0–1.5
SGLT2i[1]	0.8-1.5
DPP4i[1]	0.5–1.5
α–GI	0.5–1.0
Bromocriptine IR[2]	0.6-0.9
Amylin[2]	0.4-0.7
Colesevelam[2]	0.3-0.5

Not head to head. Baselines and background therapies differ. Information derived from multiple studies.

Oral Therapy for Type 2 Diabetes: Sites of Action

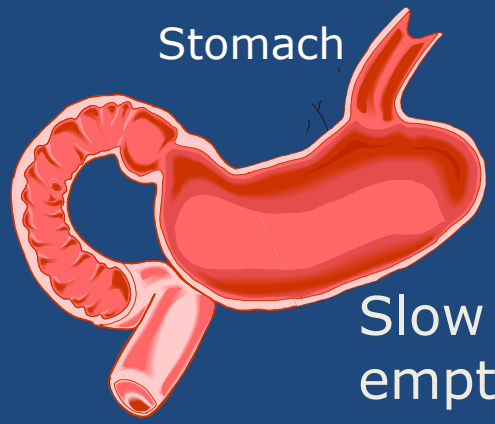
Secretagogues (glucose-independent) SUs

DPP-4 inhibitors /GLP-1Ra (glucose-dependent)

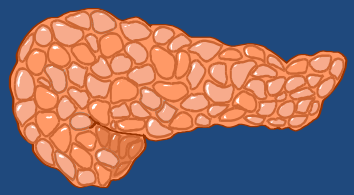
α-Glucosidase inhibitors

Inhibit carbohydrate breakdown

Stomach



Pancreas



Slow gastric emptying

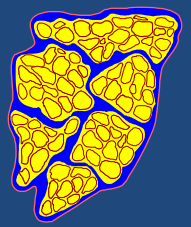
Stimulate insulin secretion

Muscle

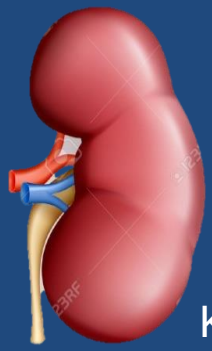
MET
TZDs

↑ Glucose metabolism

TZDs
↑ Glucose intake
↓ FFA output
Adipose tissue



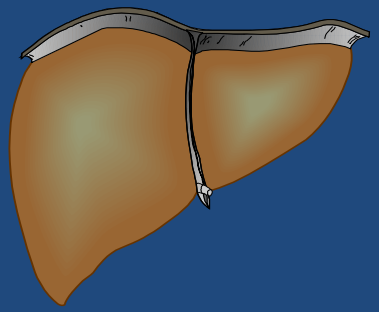
SGLT2 Inhibitors



Increase glucose excretion

Kidney

Liver

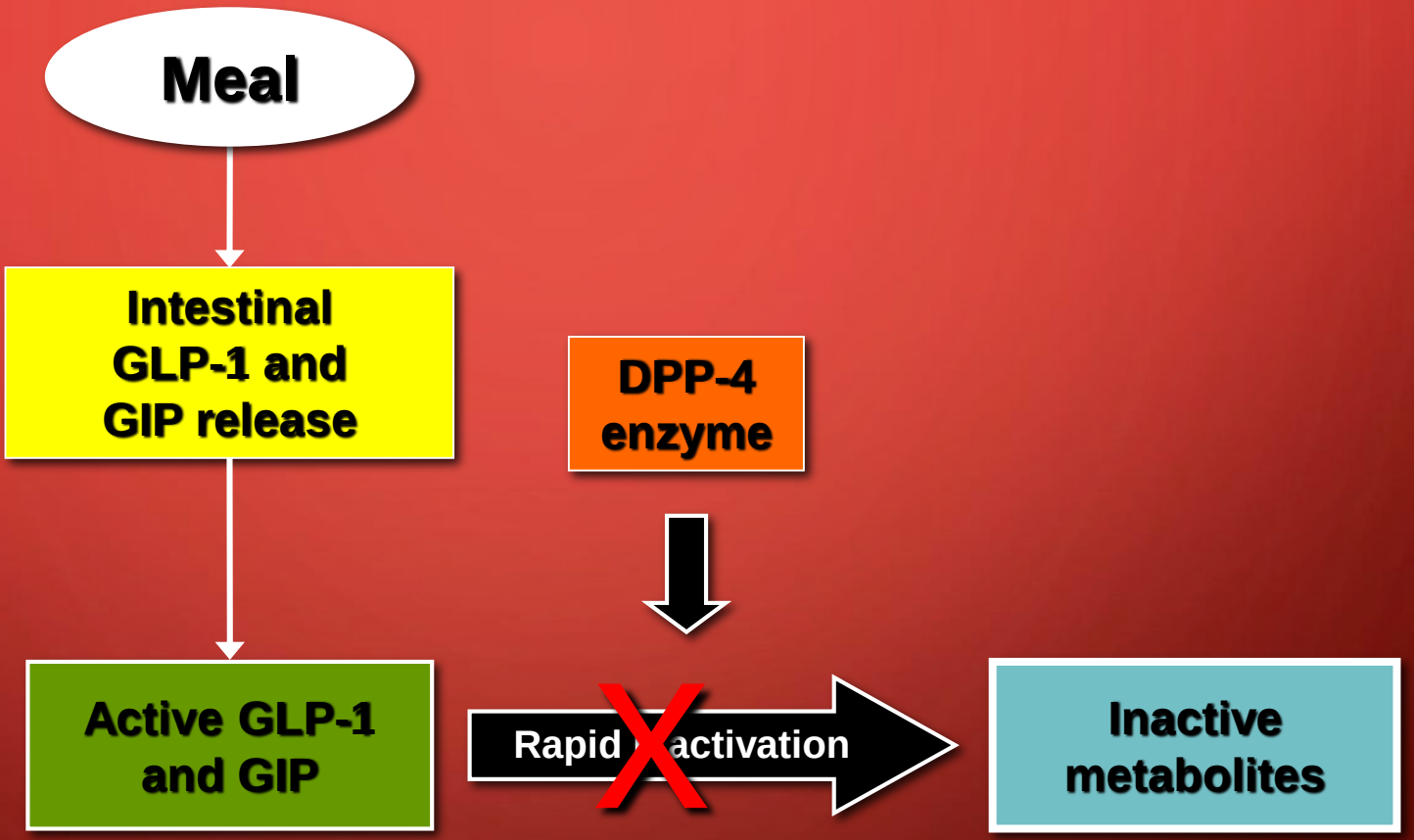


MET
TZDs
DPP-4 inhibitors
Suppress glucose production

MET=metformin; TZD=thiazolidinedione; FFA=free fatty acid

Saltiel AR, et al. *Diabetes.* 1996;45:1661-1669. Drucker DJ. *Mol Endocrinol.* 2003;17:161-171.

GLP-1 AND GIP ARE DEGRADED BY THE DPP-4 ENZYME

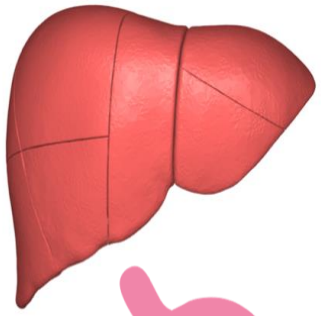


Deacon CF et al. *Diabetes*. 1995;44:1126–1131. Meier JJ et al. *Diabetes*. 2004;53:654–662.

Glucagon-Like Peptide-1 Agonists

GLP-1 Agonists	
Daily or BID Injection	**Weekly Injection**
Liraglutide	Dulaglutide
Exenatide	Exenatide ER
Lixisenatide	Albiglutide
	Semaglutide

GLP-1



Insulin Secretion

Glucagon

Gastric Emptying

Appetite

GLP-1 AGONISTS: HOW DO THEY WORK?

Remember **TIDE**
TAMES gastric emptying
INCREASES insulin secretion
DECREASES glucagon
EATING effects

Case courtesy of Tanya Nikiforova, MD

GLP-1 AGONISTS

THE UNIVERSITY OF ARIZONA COLLEGE OF MEDICINE PHOENIX

Advantages

- High efficacy: A1c reduction 1-1.5%
- Weight reduction: approved at higher doses to treat obesity
- Rare hypoglycemia
- Liraglutide (Victoza): CV benefits in high-risk patients, less progression of nephropathy

Disadvantages

- Injectable medication: injection site reactions
- Pancreatitis: potential risk
- GI side effects common: nausea, vomiting, diarrhea in 10-50%
- Risk of medullary thyroid cancer (FDA black box warning)
- Limited experience with ESRD: CAN be used by increased risk of side effects

SUMMARY OF GLP-1 AGONIST HEAD-TO-HEAD TRIALS

TRIAL	TREATMENT	A1c △ (%)	WT △ (Kg)
HARMONY 7	Albiglutide 30 mg, up to 50 mg weekly Liraglutide 1.8 mg daily	Albiglutide: -0.78 Liraglutide: -0.99*	Albiglutide: -0.6 Liraglutide: -2.2*
AWARD-1	Dulaglutide 0.75 mg weekly Dulaglutide 1.5 mg weekly Exenatide 10 mcg BID	Dulaglutide 0.75 mg: -1.3 Dulaglutide 1.5 mg: -1.5 Exenatide: -0.99	Dulaglutide 0.75 mg: 0.2 Dulaglutide 1.5 mg: -1.3 Exenatide: -1.07
AWARD-6	Dulaglutide 1.5 mg weekly Liraglutide 1.8 mg daily	Dulaglutide:-1.42 Liraglutide: -1.36	Dulaglutide: - 2.9 Liraglutide: -3.61
LEAD-6	Liraglutide 1.8 mg daily Exenatide 10 mcg BID	Liraglutide: -1.12* Exenatide: -0.79	Liraglutide: -3.24 Exenatide: -2.87
DURATION-1	Exenatide ER 2 mg weekly Exenatide 10 mcg BID	Exenatide ER: -1.9* Exenatide: -1.5	Exenatide ER:-3.6 Exenatide: -3.7
DURATION-5	Exenatide ER 2 mg weekly Exenatide 10 mcg BID	Exenatide ER: -1.6* Exenatide: -0.9	Exenatide ER: -2.3 Exenatide: -1.4
DURATION-6	Exenatide ER 2 mg weekly Liraglutide 1.8 mg daily	Exenatide ER: -1.28 Liraglutide: –1.48*	Exenatide: -2.68 Liraglutide: -3.57*

*Statistically significant

SAFETY CONCERNS FOR GLP-1 AGONIST

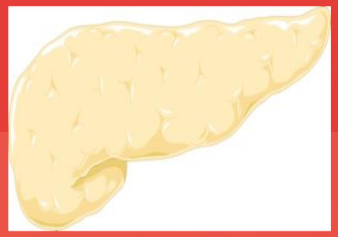
- Most common ADRs: nausea, vomiting, diarrhea, headache, injection site reaction
- Renal impairment
- Severe gastrointestinal disease (gastroparesis)
- Hypoglycemia risk increased when used with insulin or sulfonylurea
- Hypersensitivity reactions
  - angioedema, anaphylaxis, rash, pruritis
- Acute pancreatitis

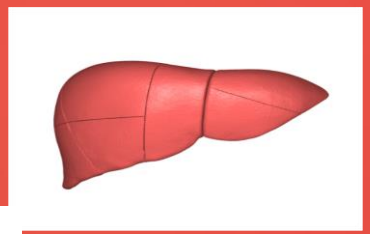
GLP-1 AGONISTS AND THYROID CARCINOMA

- GLP-1 agonists except exenatide IR/lixisenatide have black box warning for thyroid carcinoma
- Contraindicated with a personal or family history of medullary thyroid cancer or multiple endocrine neoplasia syndrome type 2
- Thyroid C-cell tumors observed in animal studies
- Cases of MTC in humans treated with liraglutide have been reported in post marketing period

U.S. Food and Drug Administration Website. http://www.fda.gov/safety/medwatch/safetyinformation/ucm400570.htm

DPP-4 Inhibitors
Sitagliptin
Linagliptin
Saxagliptin
Alogliptin





GLP-1

DPP-4

Insulin Secretion

Glucagon

Gastric Emptying

Appetite

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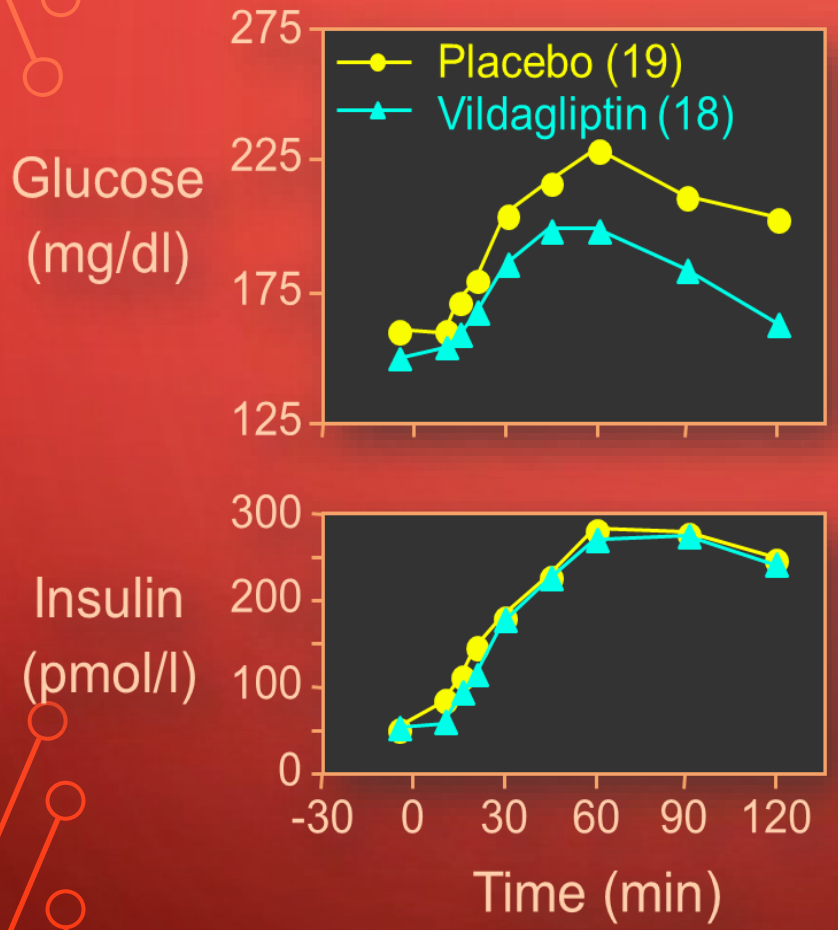
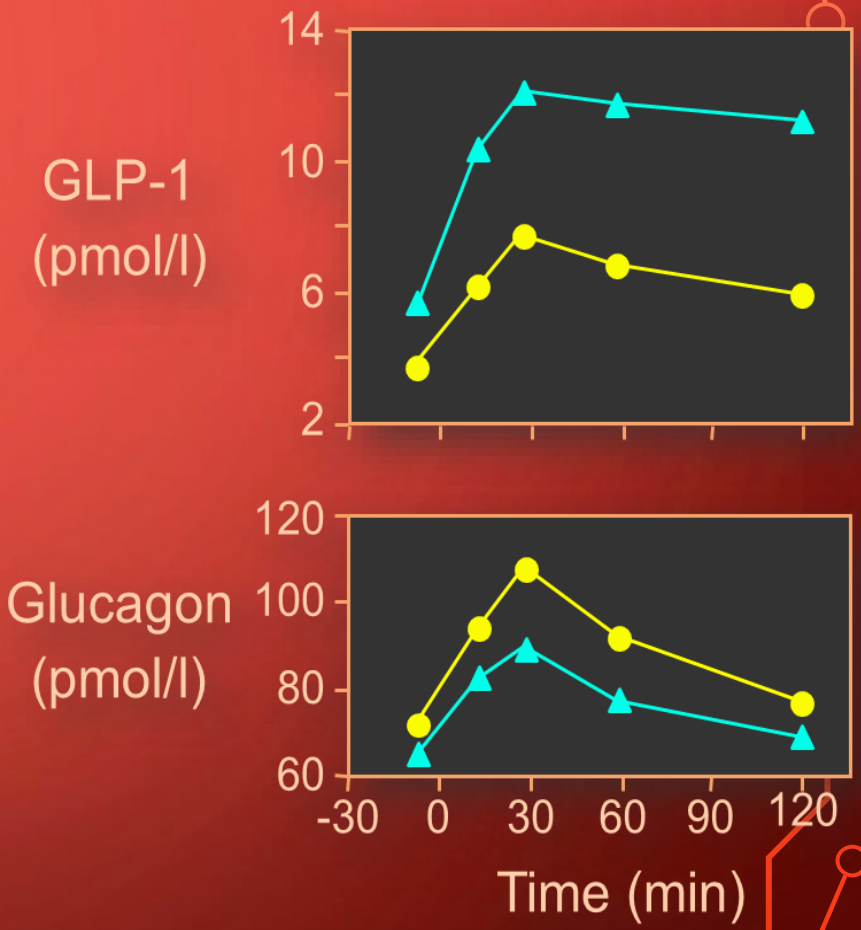
DPP-4 INHIBITORS

• Advantages	Disadvantages
• Daily dosing; pill form • Weight neutral • Rare hypoglycemia • Overall well tolerated • Can be used in CKD/ESRD • – Linagliptin – no dose adjustment needed due to hepatic clearance • – Sitagliptin – can be dose adjusted	• Efficacy: Lower than GLP-1 agonists (A1c reduction 0.4-0.8%) • Pancreatitis: Potential risk • Skin reactions: Urticaria, angioedema • Musculoskeletal: joint pain, muscles aches

DPP4 INHIBITORS





Ahrén B et al. J Clin Endocrinol Metab 89:2078-2084; 2004.

DIPEPTIDYL PEPTIDASE-4 INHIBITORS - DPP4 INHIBITORS

- No significant hypoglycemia or weight gain
- Most common ADRs: URI, nasopharyngitis, headache
- No head-to-head trials
- No clear concern regarding CV outcomes/CHF (saxagliptin)
- Can be used in CKD/ESRD

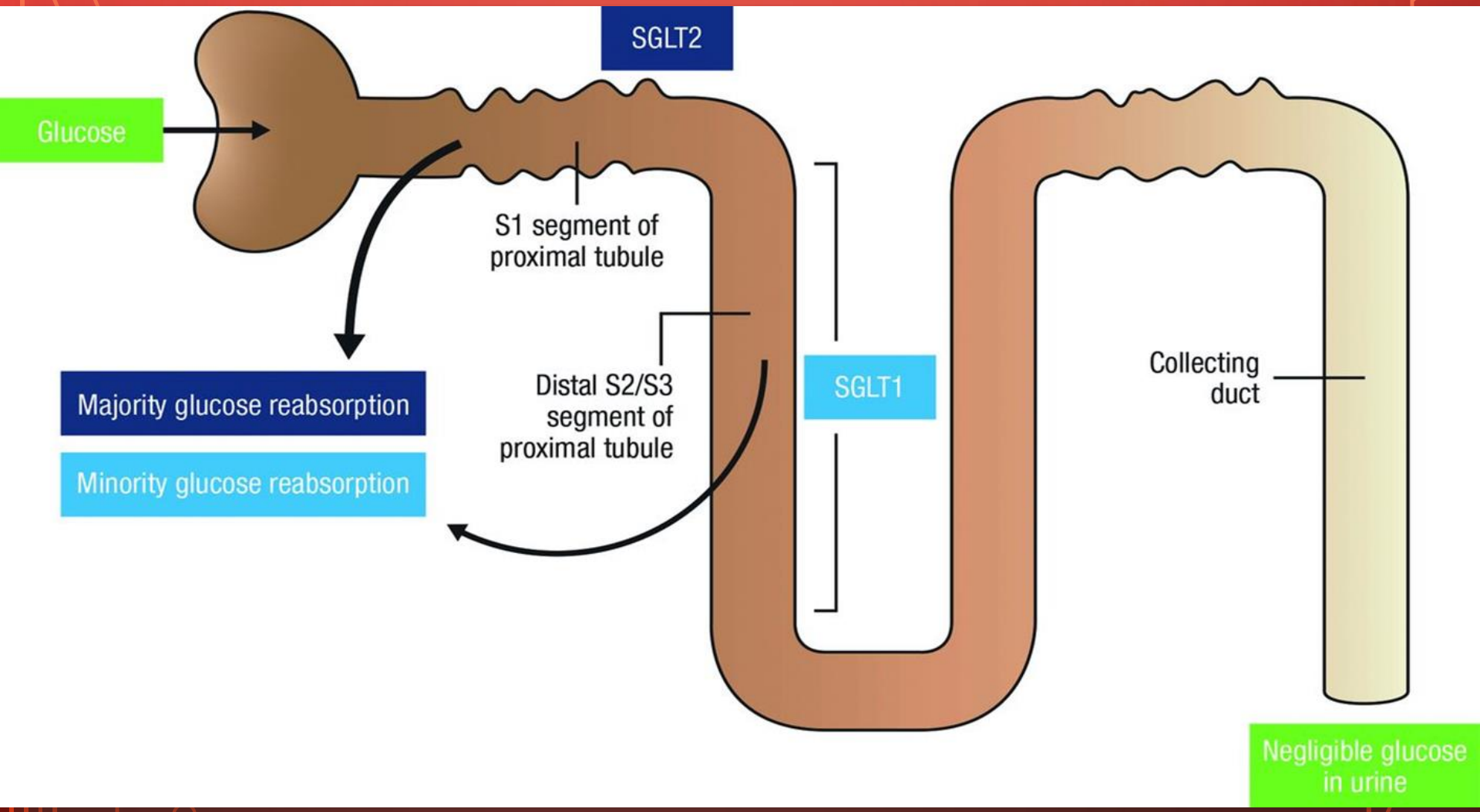
Drucker DJ. *Lancet*. 2006 Nov 11;368(9548):1696-705.
N Engl J Med 2013;369:1327-35.
N Engl J Med 2013;369:1317-26.
N Engl J Med 2015;373: 232-42.

DPP4 INHIBITORS

- Pancreatitis reports, although no causal relationship has been established
- FDA concluded these drugs may not cause or contribute to the development of pancreatic cancer.”
- Extensive review by FDA (>80,000 patients) has not uncovered reliable evidence of increased pancreatic cancer risk with incretins vs other agents.

www.fda.gov/drugs/drugsafety/ucm343187.htm. www.diabetes.org/newsroom/press-releases/2013/recommendations-for.html.
Buse JB. *Diabetes Care* Feb 2017;40(2) 164-170.

SGLT-2 INHIBITORS



Valentine V. *Clin Diabetes* 2015;33:5-13.

SODIUM-GLUCOSE CO-TRANSPORTER 2 (SGLT-2) INHIBITOR

- Mechanism is not insulin-dependent
- Reduction of weight and BP
- Increased genital mycotic infections
- Cannot be used with reduced eGFR
- Hyperkalemia, renal insufficiency, hypotension and LDL elevation

Clar C et al. BMJ Open. 2012;2(5).

Sodium-Glucose Cotransporter-2 Inhibitors

SGLT-2 Inhibitors
Empagliflozin
Canagliflozin
Dapagliflozin
Ertugliflozin

SGLT-2 INHIBITORS

- Euglycemic diabetic ketoacidosis
- Bladder cancer incidence higher with dapagliflozin
- Amputations higher with canagliflozin
- Non significant incidence of bone fx
- CV benefits with empagliflozin in patients with established cv disease

Peters AL et al. Diabetes Care. 2015;38(9):1687.
Watts NB et al. J Clin Endocrinol Metab. 2016 Jan;101(1):157-66.
Zinman B et al. Engl J Med. 2015;373(22):2117.

Monotherapy

Lifestyle Management + Metformin

Initiate metformin therapy if no contraindications* (See Table 8.1)

A1C at target after 3 months of monotherapy?

Yes: - Monitor A1C every 3–6 months

No: - Assess medication-taking behavior
- Consider Dual Therapy

ADA 2019 Guidelines

COLLEGE OF MEDICINE PHOENIX

Dual Therapy **Metformin +** **Lifestyle Management**

	Sulfonylurea	Thiazolidinedione	DPP-4 inhibitor	SGLT2 inhibitor	GLP-1 receptor agonist	Insulin (basal)
EFFICACY*	high	high	intermediate	intermediate	high	highest
HYPO RISK	moderate risk	low risk	low risk	low risk	low risk	high risk
WEIGHT	gain	gain	neutral	loss	loss	gain
SIDE EFFECTS	hypoglycemia	edema, HF, fxs	rare	GU, dehydration, fxs	GI	hypoglycemia
COSTS*	low	low	high	high	high	high

If A1C target not achieved after approximately 3 months of dual therapy, proceed to 3-drug combination (order not meant to denote any specific preference – choice dependent on a variety of patient- & disease-specific factors):

ADA 2019 Guidelines

Dual Therapy

Lifestyle Management + Metformin + Additional Agent

ASCVD?

Yes: - Add agent proven to reduce major adverse cardiovascular events and/or cardiovascular mortality (see recommendations with * on p. S75 and **Table 8.1**)

No: - Add second agent after consideration of drug-specific effects and patient factors (See Table 8.1)

ADA 2019 Guidelines

CV outcomes

Composite of major adverse cardiac events (MACE), including CV death, nonfatal MI, nonfatal stroke

- Heart failure
- All-cause mortality

- Several medications were found to reduce cardiovascular risk

SGLT-2 inhibitors = Empagliflozin, Canagliflozin

GLP-1 agonists = Liraglutide, Semaglutide

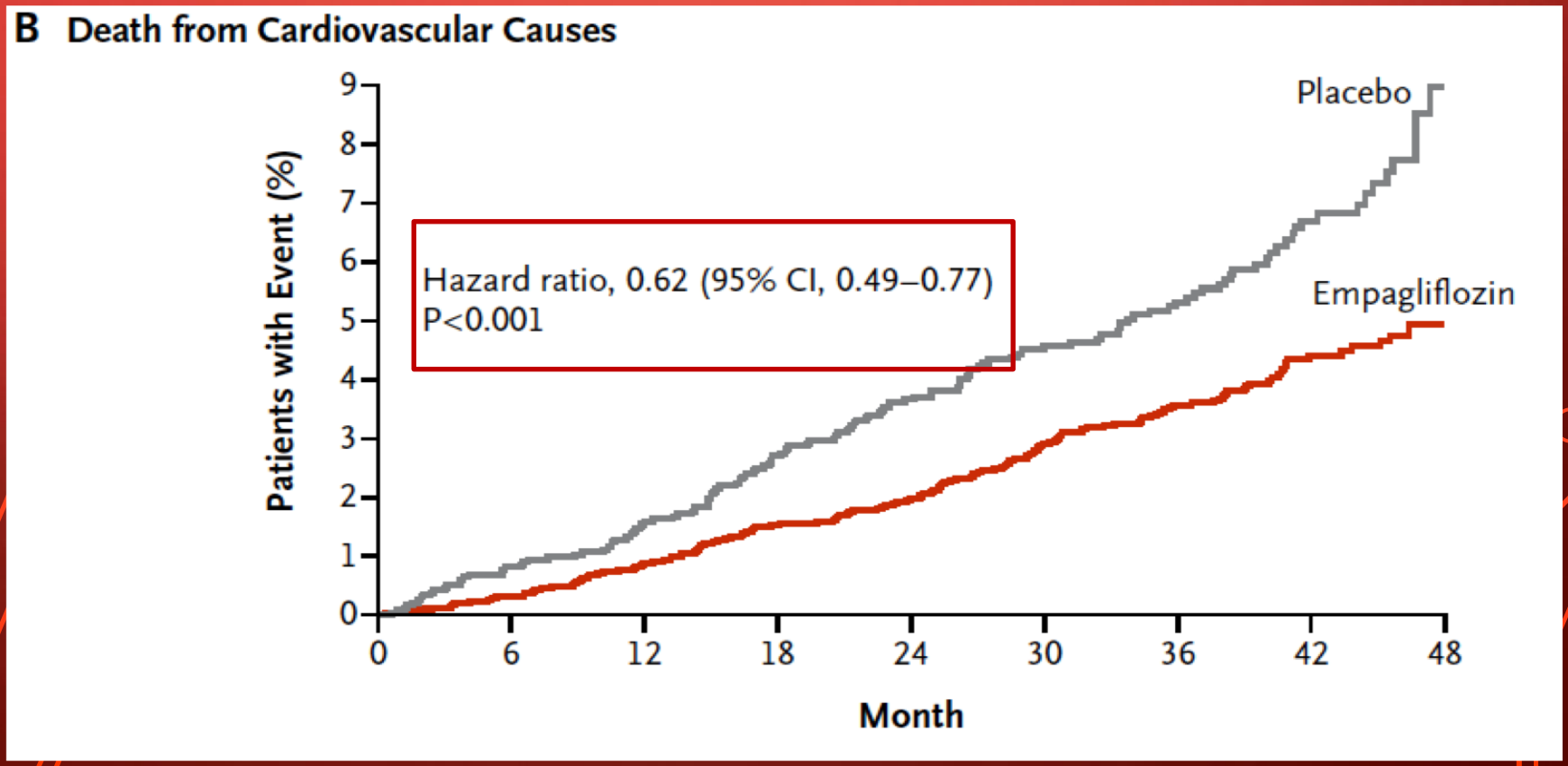
Empagliflozin and CV outcomes

- 7020 patients assigned to receive 10mg/25mg of empagliflozin vs placebo
- All patients had established CV disease
  - history of CAD, prior MI, prior stroke, or PVD
- • Most were white men (72%) with mean age 63, BMI 31, A1c 8%

Zinmanet al, NEJM, 2015

Empagliflozin and CV outcomes

- Difference in MACE driven by reduced mortality from CV causes
- Fewer hospitalizations for heart failure
- Decreased all-cause mortality



CANAGLIFLOZIN COMPARED TO SITAGLIPTIN, BOTH AS ADD-ON COMBINATION WITH METFORMIN AND SULFONYLUREA

- Canagliflozin 300 mg provided greater HbA1C reduction compared to sitagliptin 100 mg when added to metformin and sulfonylurea ($p<0.05$).
- Canagliflozin 300 mg resulted in a mean percent change in body weight from baseline of -2.5% compared to +0.3% with sitagliptin 100 mg.
- A mean change in systolic blood pressure from baseline of -5.06 mmHg was observed with Invokana 300 mg compared to +0.85 mmHg with sitagliptin 100 mg.

CANAGLIFLOZIN COMPARED TO GLIMEPIRIDE, BOTH AS ADD-ON COMBINATION WITH METFORMIN

- Canagliflozin 300 mg provided a greater reduction from baseline in HbA1C compared to glimepiride

- Treatment with Canagliflozin 100 mg and 300 mg daily provided greater improvements in percent body weight change, relative to glimepiride.

CANAGLIFLOZIN

- Canagliflozin is a sodium-glucose co-transporter 2 (SGLT2) inhibitor

- Reduce blood glucose levels by increasing the amount of glucose excreted in the urine.

- Monotherapy or added to Metformin

- A greater proportion of patients achieving
  - an HbA1C less than 7%,
  - significant reduction in fasting plasma glucose (FPG),
  - improved postprandial glucose (PPG),
  - Percent body weight reduction compared to placebo.

Stenlöf K, Cefalu WT, Kim KA, Alba M, Usiskin K, Tong C, Canovatchel W, Meininger G Efficacy and safety of canagliflozin monotherapy in subjects with type 2 diabetes mellitus inadequately controlled with diet and exercise. *Diabetes, Obesity and Metabolism* 2013 Apr;15(4):372-82

CANAGLIFLOZIN

- The recommended starting dose of Canagliflozin is 100 mg once daily, taken before the first meal of the day.

- If the eGFR of 60 mL/min/1.73 m2 or greater and require additional glycemic control, the dose can be increased to 300 mg once daily.

CANAGLIFLOZIN SIDE EFFECTS

- Female genital mycotic infections
- Urinary tract infection
- Increased urination

Stenlöf K, Cefalu WT, Kim KA, Alba M, Usiskin K, Tong C, Canovatchel W, Meininger G Efficacy and safety of canagliflozin monotherapy in subjects with type 2 diabetes mellitus inadequately controlled with diet and exercise. *Diabetes, Obesity and Metabolism* 2013 Apr;15(4):372-82

ERTUGLIFLOZIN

- 5mg QAM w/o regards to meals up to 15mg/day
- Sodium-Glucose Cotransporter 2 (SGLT2) Inhibitor
- Renal impairment: Not recommended if eGFR persistently 30-60 as decreased efficacy & contraindicated if <30

Dual Therapy

Lifestyle Management + Metformin + Additional Agent

ASCVD?

Yes: – Add agent proven to reduce major adverse cardiovascular events and/or cardiovascular mortality (see recommendations with * on p. S75 and **Table 8.1**)

No: – Add second agent after consideration of drug-specific effects and patient factors (See Table 8.1)

Semaglutide – FDA approved 12/2017

Grade A recommendation:
Empagliflozin
Liraglutide

Grade C recommendation:
Canagliflozin

67 year old female with T2DM, HTN, osteopenia, idiopathic pancreatitis, and CAD s/p RCA stent in 2015 is seen in clinic today. Her A1c is 8.5%. Current medications include metformin 1000mg BID, ASA 81mg QD, and Lisinopril 40mg QD. BMI is 27.

What would you add?

A. Canagliflozin
B. Empagliflozin
C. Sitagliptin
D. Liraglutide
E. All of above options are reasonable

Case courtesy of Tanya Nikiforova, MD

67 year old female an with T2DM, HTN, osteopenia, idiopathic pancreatitis, and CAD s/p RCA stent in 2015 is seen in clinic today. Her A1c is 8.5%. Current medications include metformin 1000mg BID, ASA 81mg QD, and Lisinopril 40mg QD. BMI is 27.
What would you add?

A. Canagliflozin (Bone Fracture Risk)

B. Empagliflozin

C. Sitagliptin (No CV benefit)

D. Liraglutide (Pancreatitis Risk)

E. All of these options are reasonable (Pt has known CAD)

Case courtesy of Tanya Nikiforova, MD

- **Individualization of goals and therapy** should continue to play a central role in decision-making.
- In choosing a therapeutic regimen, we should continue to **consider**, in addition to prevalent CVD, each patient's capabilities, finances, living situation, support systems, cognitive status, other comorbidities, and life expectancy, while implementing shared decision-making.

Ismail-Beigi F. Individualizing glycemic targets in type 2 diabetes mellitus: implications of recent clinical trials. Ann Intern Med 2011;154:554–9.

- Cardiovascular disease (CVD) is the main cause of excess mortality in diabetic patients.

- More intensive glycemic control improves certain microvascular outcomes but has not substantially reduced the risk of cardiovascular (CV) mortality and other adverse CV events such as myocardial infarction and stroke.

- Based on the results of recent trials, the use of medications now proven to reduce CV complications should be prioritized in patients with established CVD, while continuing a multifaceted approach for controlling hypertension and dyslipidemia.

- We anticipate future trials using SGLT2 inhibitors or GLP-1 receptor agonists at earlier stages of type 2 diabetes, especially in those without prevalent CVD.

- Current algorithms for the management of type 2 diabetes based primarily on HbA1c values ought to shift towards a new paradigm that incorporates patients' CV risk and their likelihood of realizing a CVD benefit into the glucose-lowering drug selection process.

78 year old male with PMHxof obesity, HTN, hyperlipidemia, CKD, and DM2. He had been on glipizide 2.5mg and metformin 500mg bid for years. Six months ago, glipizide was stopped due to frequent hypoglycemia. On return, he has mild leg edema. His creatinine is 2.2, eGFRis 28, and microalbuminto creatinine ratio is 1500. He doesn't want insulin. A1C is 8.8%.

After stopping metformin, what medication do you start?

1. Add glipizide back at the lowest dose
2. Start pioglitazone
3. Start dapagliflozin
4. Start linagliptin
5. Start insulin

Case courtesy of Tanya Nikiforova, MD

78 year old male with PMHxof obesity, HTN, hyperlipidemia, CKD, and DM2. He had been on glipizide 2.5mg and metformin 500mg bid for years. Six months ago, glipizide was stopped due to frequent hypoglycemia. On return, he has mild leg edema. His creatinine is 2.2, eGFRis 28, and microalbuminto creatinine ratio is 1500. He doesn't want insulin. A1C is 8.8%.

After stopping metformin, what medication do you start?

1. Add glipizide back at the lowest dose (He has hx of hypoglycemia)
2. Start pioglitazone (Could worsen his edema)
3. Start dapagliflozin (eGRR is too low)
4. **Start linagliptin**
5. Start insulin (Pt does not want)

Case courtesy of Tanya Nikiforova, MD

A 42 year old woman with hypertension, hyperlipidemia, obesity, and recent diagnosis of DM2 presents for follow-up after taking metformin for 4 months. She has been compliant with the medication and been doing her best to exercise and eat well but has not lost any weight. You check her hemoglobin A1c and find that it remains elevated at 7.5. On exam her BP is 135/80 and BMI is 40.

What is the most appropriate next step?

A. Start liraglutide
B. Start linagliptin
C. Start glipizide
D. Start insulin
E. No change in medications

Case courtesy of Tanya Nikiforova, MD

A 42 year old woman with hypertension, hyperlipidemia, obesity, and recent diagnosis of DM2 presents for follow-up after taking metformin for 4 months. She has been compliant with the medication and been doing her best to exercise and eat well but has not lost any weight. You check her hemoglobin A1c and find that it remains elevated at 7.5. On exam her BP is 135/80 and BMI is 40.

What is the most appropriate next step?

A. **Start liraglutide** (Weight loss + CVD Benefits)

B. Start linagliptin (Weight neutral)

C. Start glipizide (Weight gain)

D. Start insulin (Weight gain)

E. No change in medications (DM uncontrolled)

Case courtesy of Tanya Nikiforova, MD

- 58 yo overweight men with diabetes on maximum doses of Metformin, Glipizide and Canagliflozin. Hga1c is 8 now, still refusing insulin but receptive to injectables if he does not have to inject a lot. He is still trying to loose weight.
- Which of the following injectable would you recommend?

1. Daily Liraglutide (Victoza)
2. Weekly Liraglutide (Victoza)
3. Weekly Pramlintide (Symlin)
4. Weekly Semaglutide (Ozempic)
5. Daily Semaglutide

- 58 yo overweight men with diabetes on maximum doses of Metformin, Glipizide and Canagliflozin. Hga1c is 8 now, still refusing insulin but receptive to injectables if he does not have to inject a lot. He is still trying to loose weight.
- Which of the following injectable would you recommend?

1. Daily Liraglutide (Victoza)
2. Weekly Liraglutide (Victoza)
3. Weekly Pramlintide (Symlin)
4. **Weekly Semaglutide (Ozempic)**
5. Daily Semaglutide

Semaglutide

- FDA approval in Nov, 2016.
- Longer-acting version of L**iraglutide** which is once daily.
- Semaglutide once per week.

SEMAGLUTIDE

- Convenience
- Excellent efficacy in reducing blood sugar levels
- Helping patients lose weight

SEMAGLUTIDE

- Glucagon-Like Peptide (GLP-1) receptor agonist
- Acting on the same receptor as the endogenous hormone incretin
  - increases glucose-dependent insulin secretion
  - decreases inappropriate glucagon secretion
  - slows gastric emptying.
  - Increases first- and second-phase insulin secretion

Semaglutide

- Initial 0.25mg SQ Qwk
- → 0.5mg → 1mg SQ Qwk
- 0.25mg is only for initiation & not therapeutic

SUMMARY

- Glucose goals & therapies must be individualized
- Diet, exercise & education
- Unless contraindicated, metformin 1st-line drug
- After metformin, data are limited
  - Combination therapy with oral and/or injectables is reasonable
  - Minimize side effects and address patient specific characteristics
- Many patients will require insulin therapy

DM ABC…