LATEST ADVANCES IN THE MANAGEMENT OF DIABETES

Shakaib Rehman, MD, SCH, FACP, FAACH

Associate Chief of Staff for Education

Phoenix VA Healthcare Systems

Interim Chair and Professor of Department of Biomedical Informatics

Professor of Medicine

University of Arizona College of Medicine-Phoenix

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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- **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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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

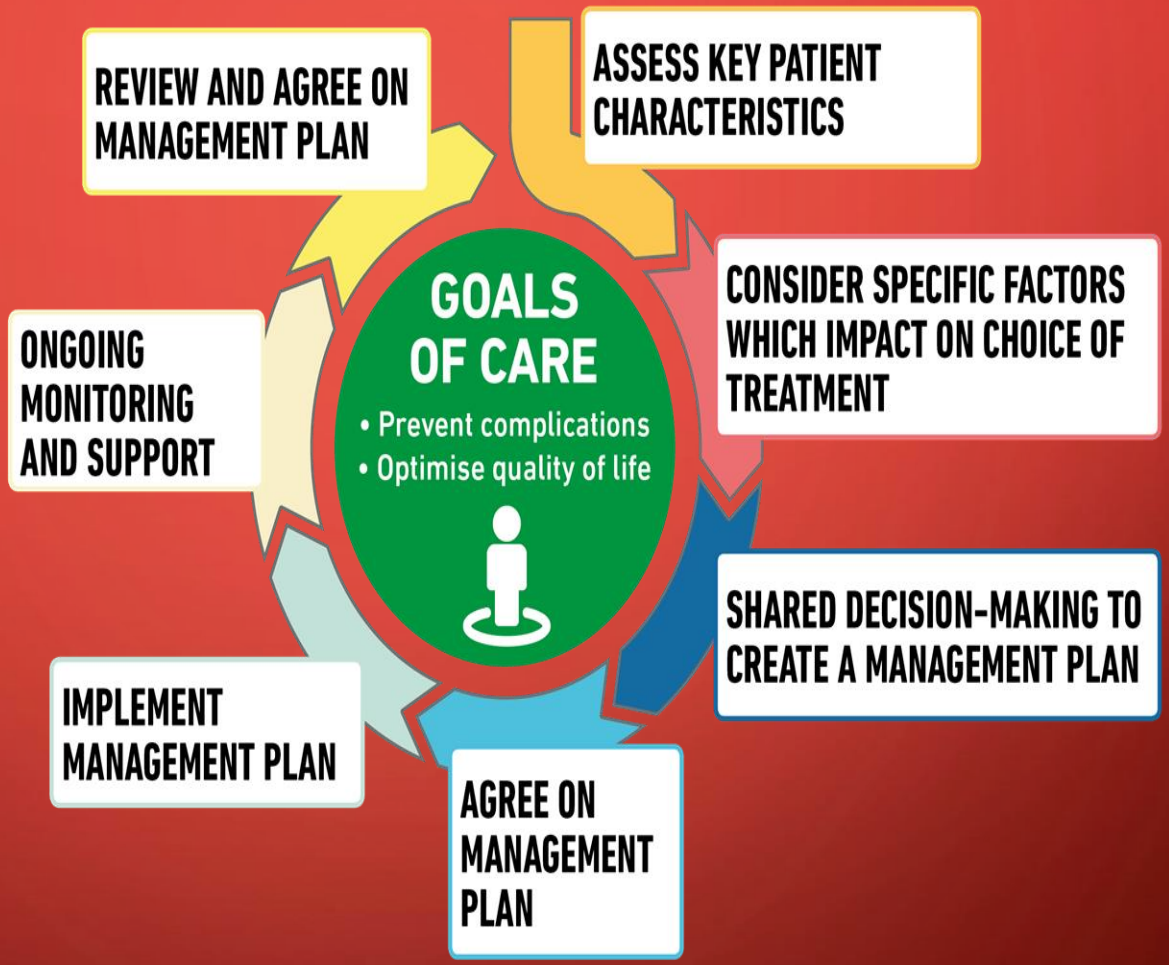
WHAT IS THE RECOMMENDED GOAL A1C GOAL?

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

WHAT IS THE RECOMMENDED GOAL A1C GOAL?

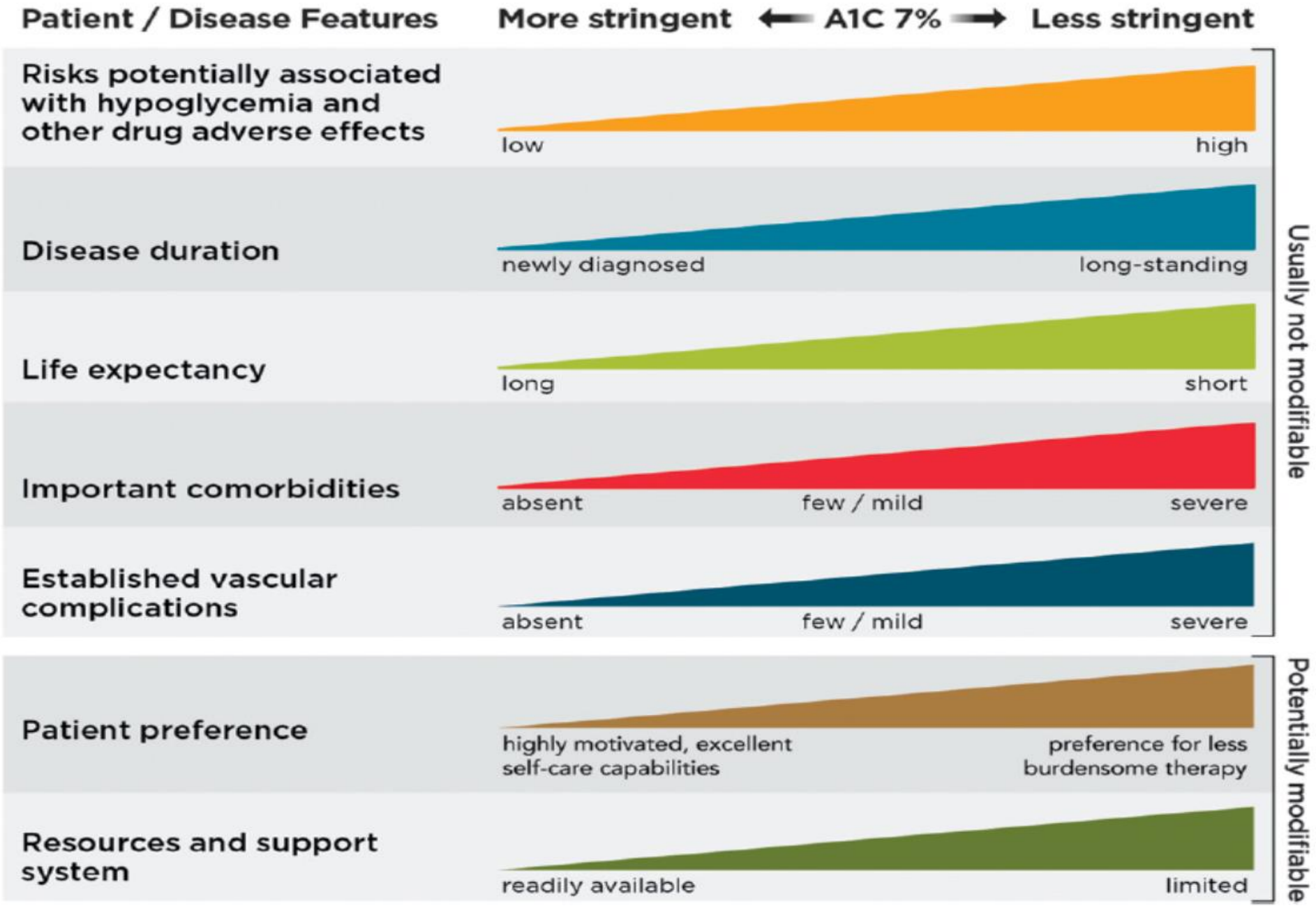
1. <8
2. <7
3. <6
4. **Every patient is different……**
5. Whatever patient decides

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.

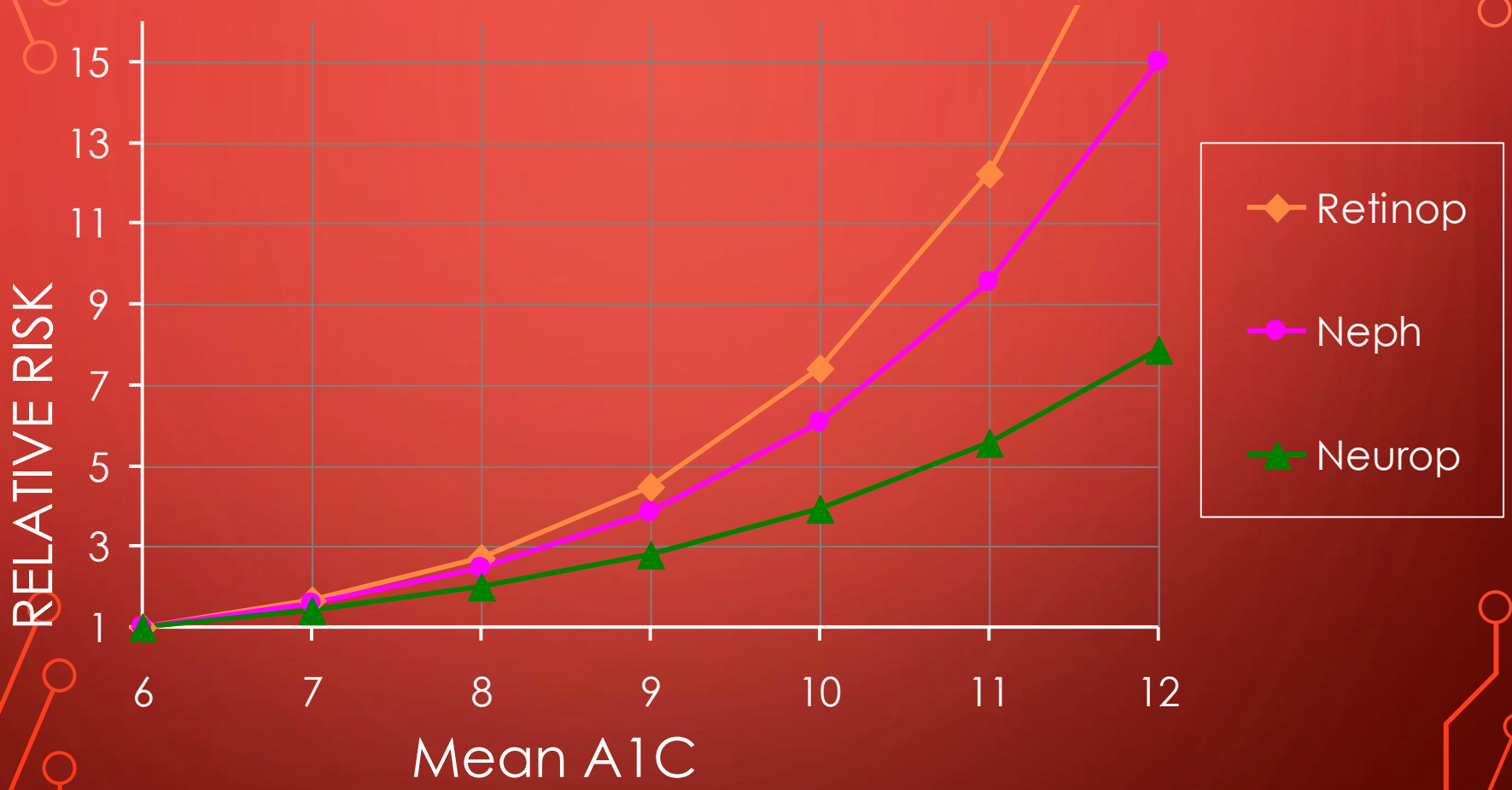
American Diabetes Association. Pharmacologic Approaches to Glycemic Treatment: Standards of Medical Care in Diabetes-2018. Diabetes Care. 2018;41(Suppl 1):S73-S85

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

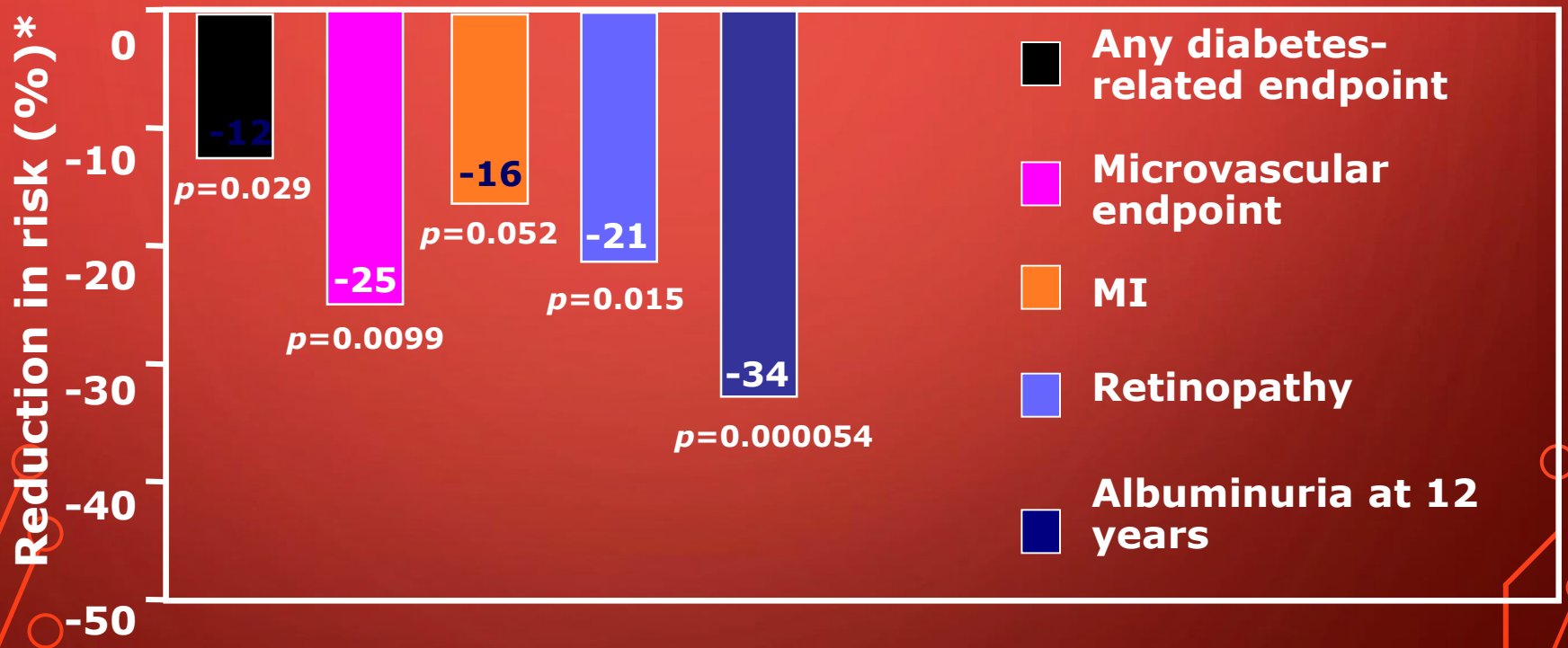
DCCT Research Group, *N Engl J Med* 1993, 329:977-986.

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.

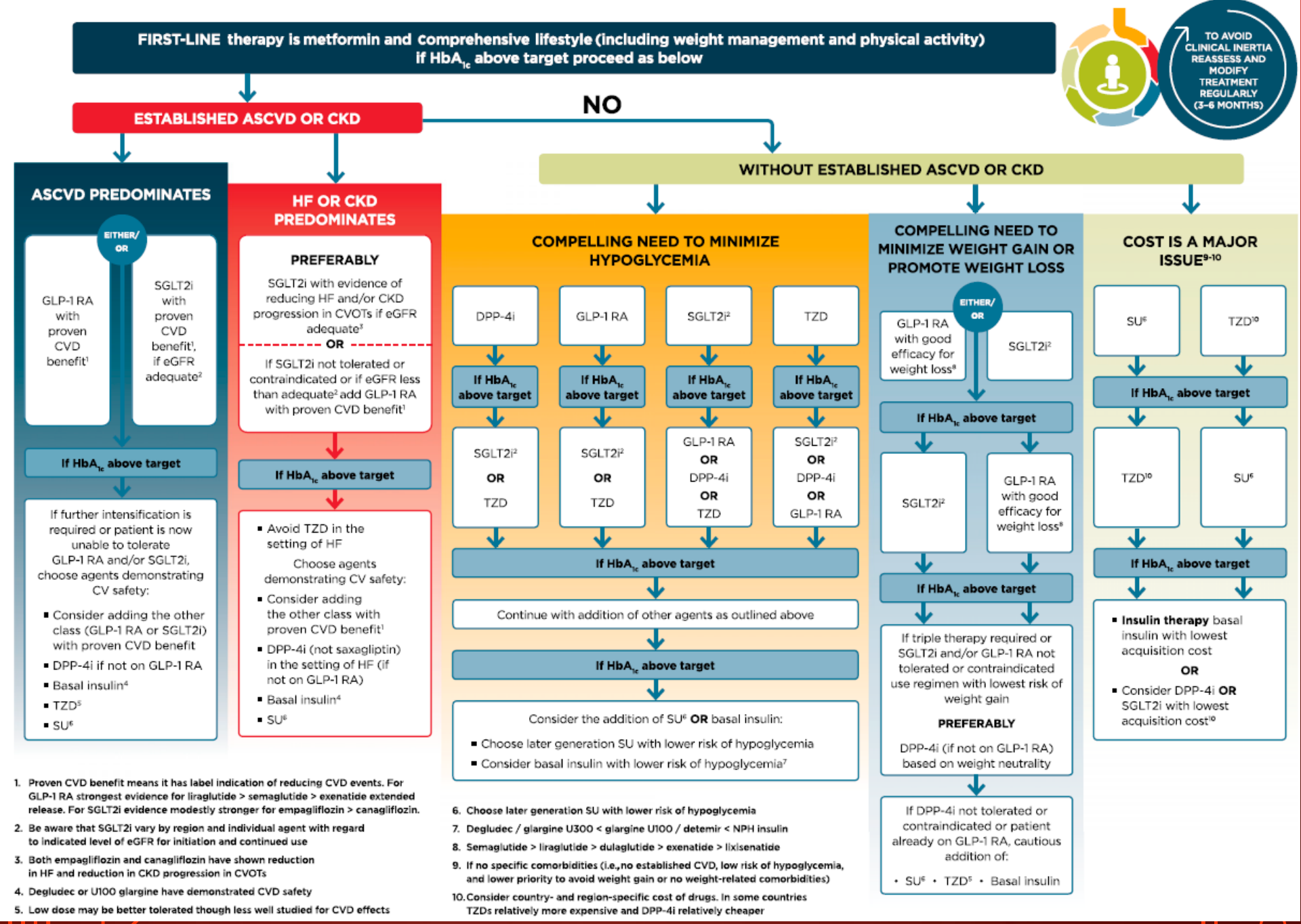
- A patient-centered approach should be used to guide the choice of pharmacologic agents. Considerations include comorbidities (atherosclerotic cardiovascular disease, heart failure, chronic kidney disease), hypoglycemia risk, impact on weight, cost, risk for side effects, and patient preferences.

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.



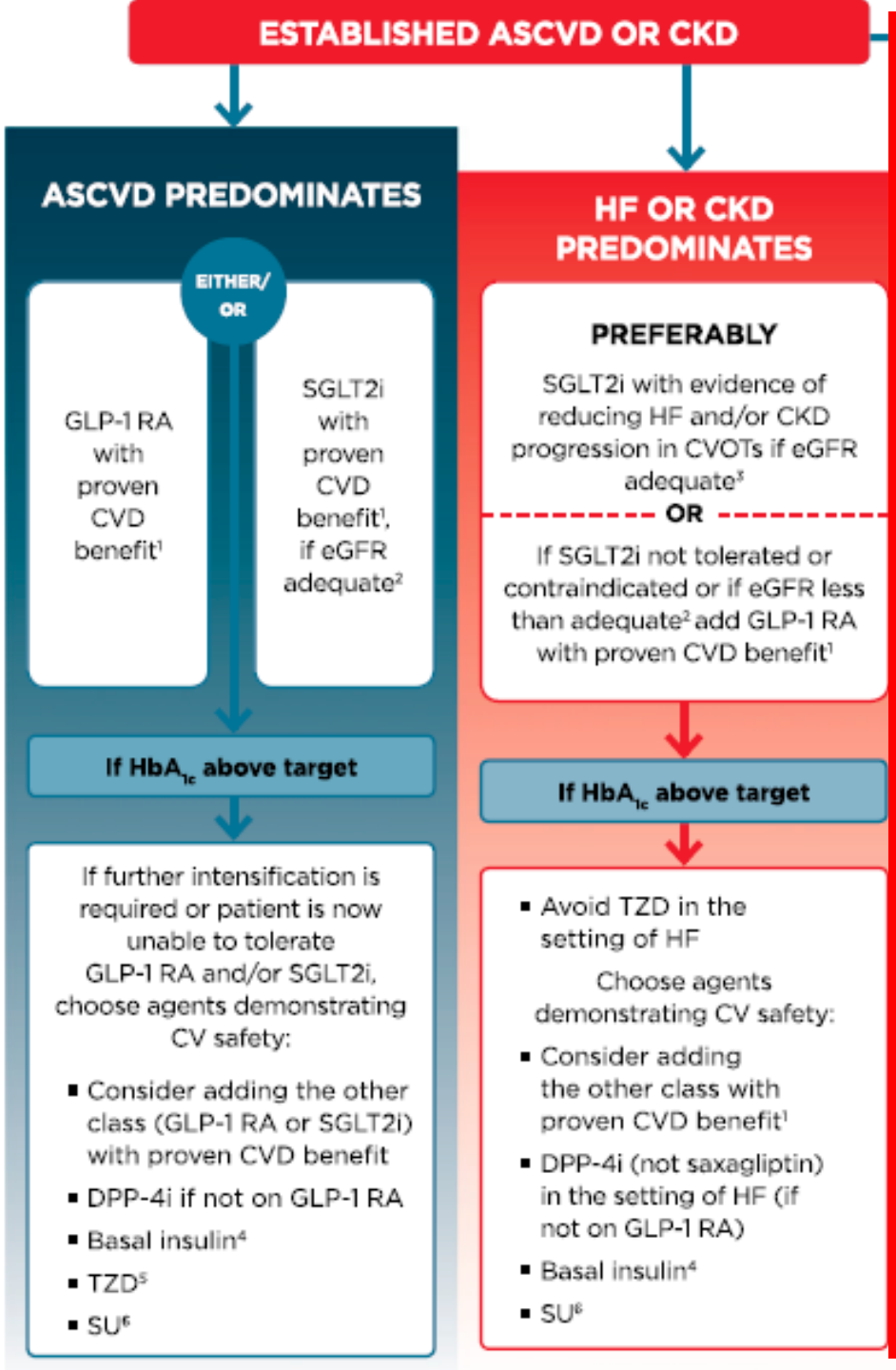
1. Proven CVD benefit means it has label indication of reducing CVD events. For GLP-1 RA strongest evidence for liraglutide > semaglutide > exenatide extended release. For SGLT2i evidence modestly stronger for empagliflozin > canagliflozin.
2. Be aware that SGLT2i vary by region and individual agent 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.

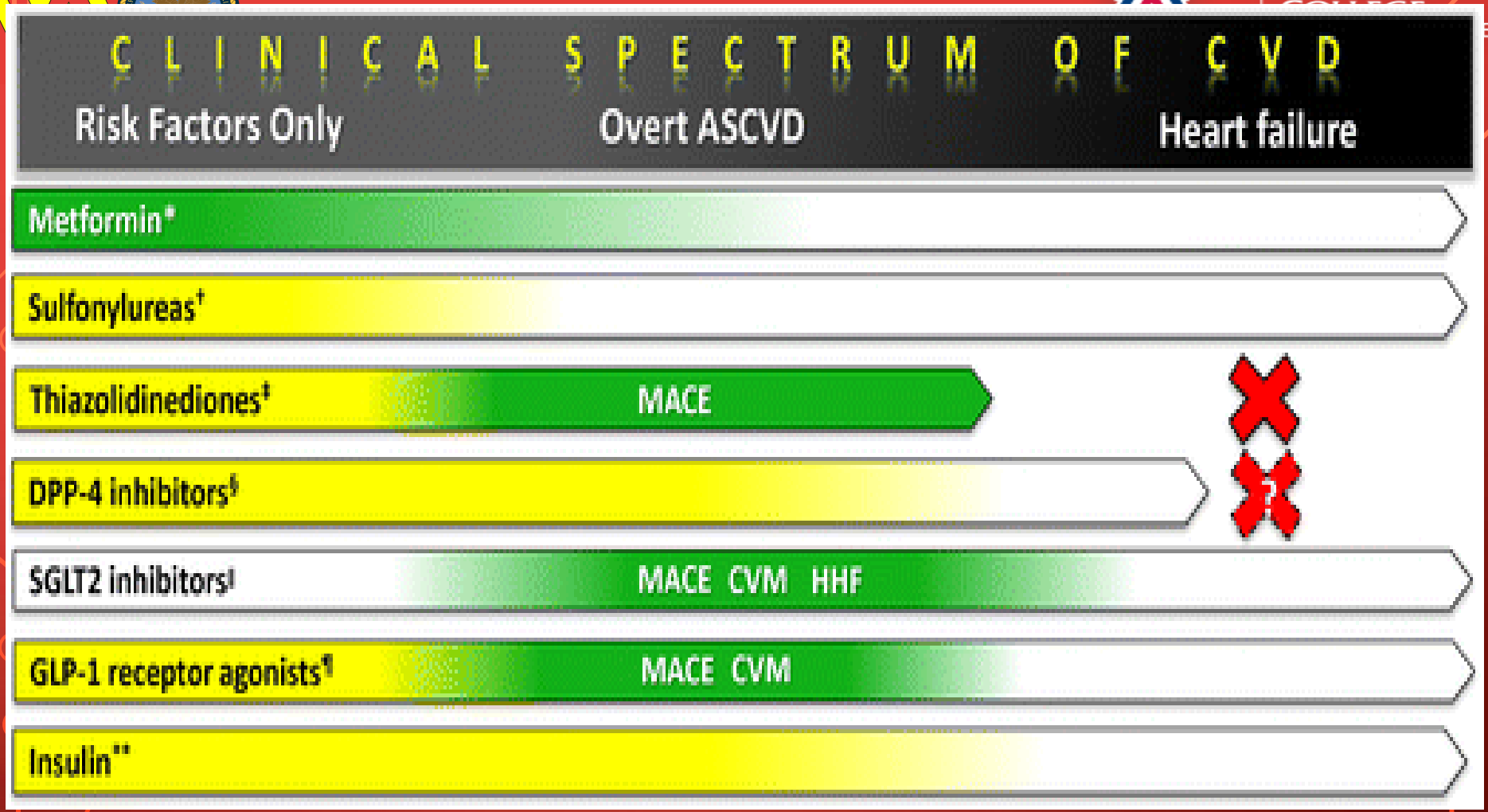


- If A1C is above target despite recommended first-line treatment and the patient has ASCVD or CKD:
  - **ASCVD Predominates:**
    - Add GLP-1 RA with proven CVD benefit, OR
    - Add SGLT-2 inhibitor with proven CVD benefit (if eGFR adequate)
  - **If HF or CKD Predominates:**
    - Add SGLT-2 inhibitor 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

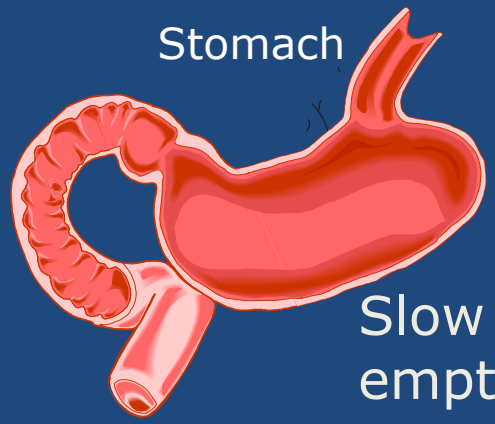
Secretagogues (glucose-independent) SUs

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

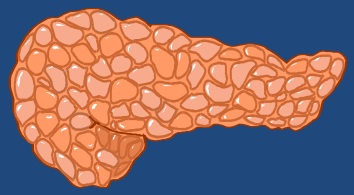
α-Glucosidase inhibitors

Inhibit carbohydrate breakdown

Stomach



Pancreas



Slow gastric emptying

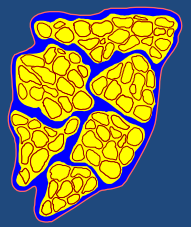
Stimulate insulin secretion

Muscle

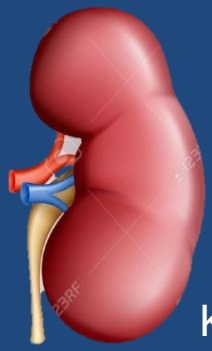
MET
TZDs

↑ Glucose metabolism

TZDs
↑ Glucose intake
↓ FFA output
Adipose tissue



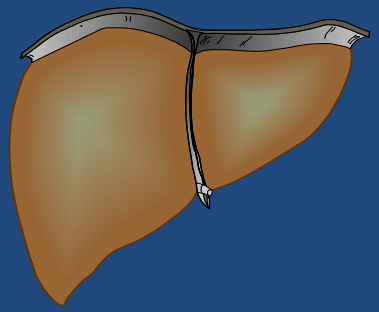
SGLT2 Inhibitors



Increase glucose excretion

Kidney

Liver

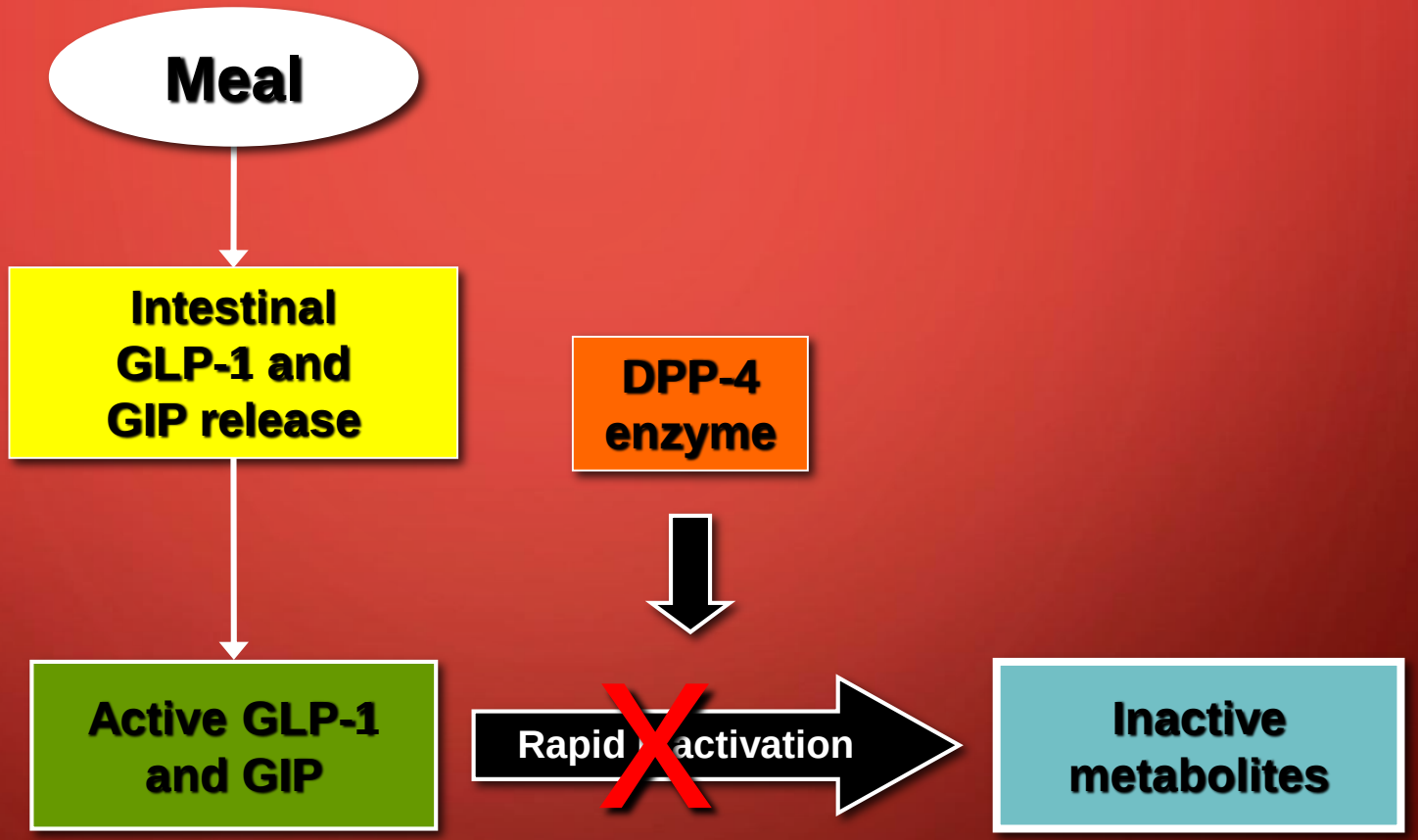


MET
TZDs
DPP-4 inhibitors
Suppress glucose production

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

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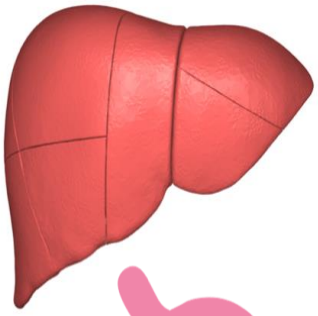
GLP-1

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

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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

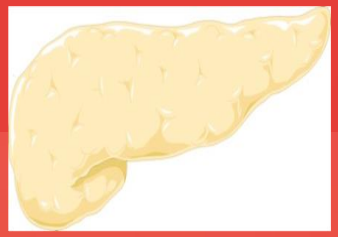
- Most common ADRs: nausea, vomiting, diarrhea, headache, injection site reaction
- Renal impairment
- Severe gastrointestinal disease (gastroparesis)
- Hypoglycemia risk increased when used with insulin or sulfonylurea
- Hypersensitivity reactions
  - angioedema, anaphylaxis, rash, pruritis
- Acute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

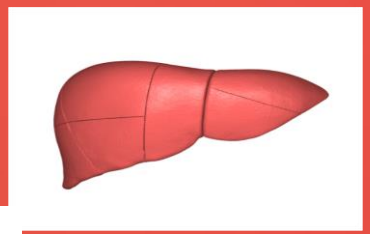
GLP-1 AGONISTS AND THYROID CARCINOMA

- 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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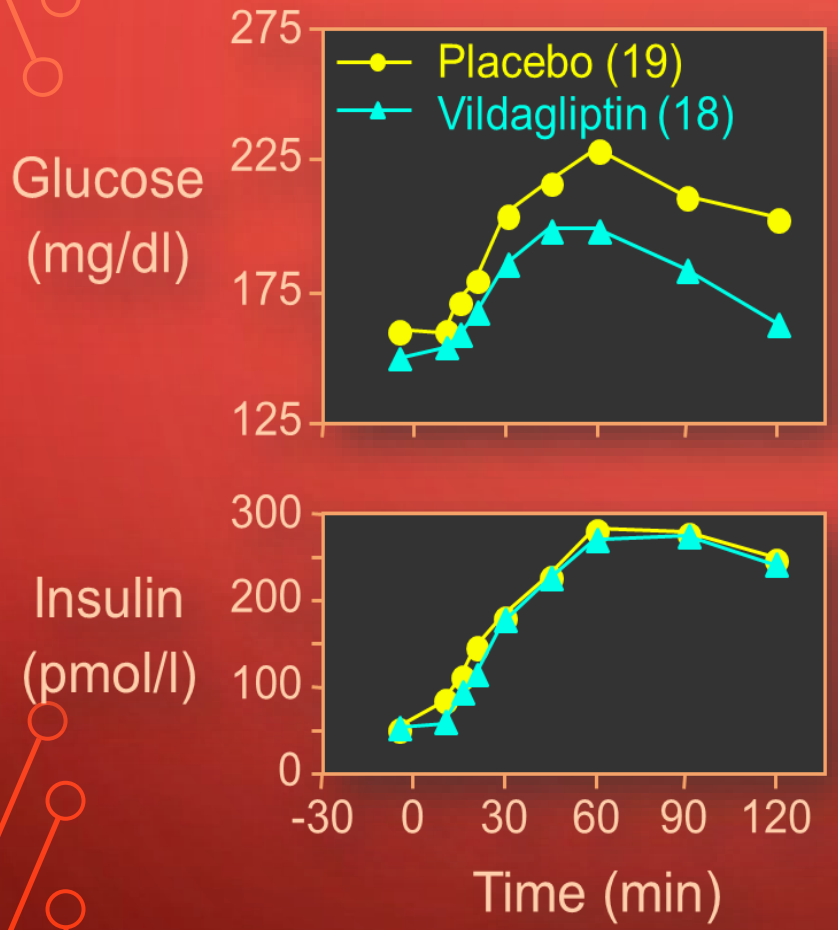
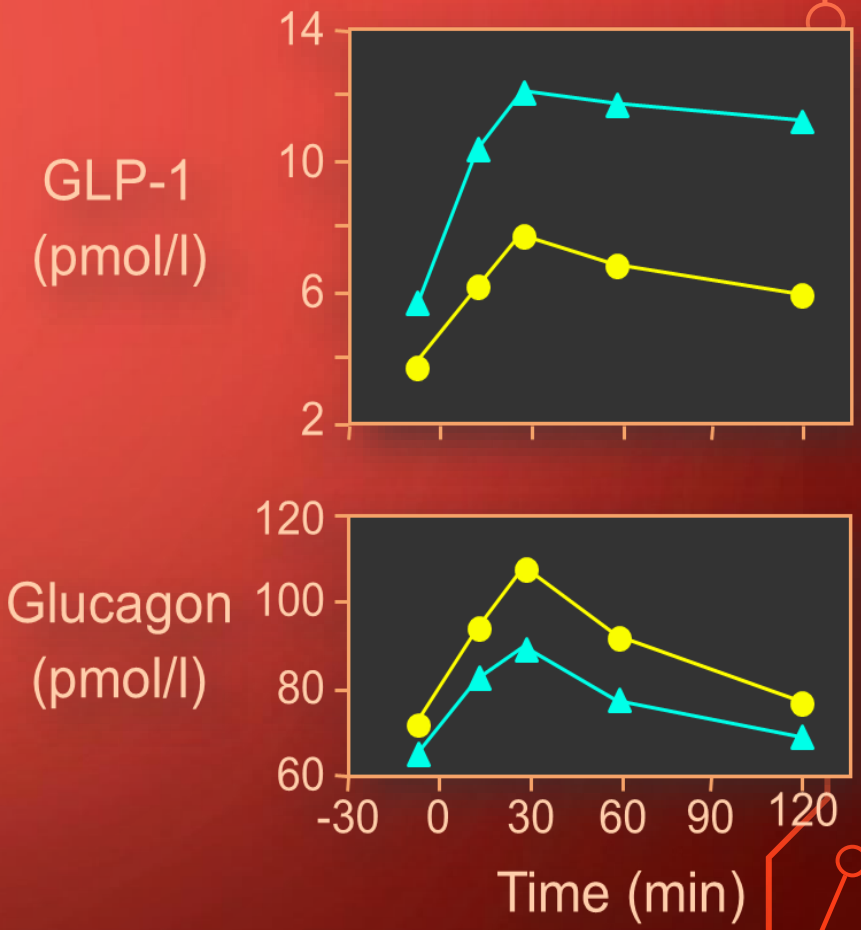
DPP-4 INHIBITORS

• 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

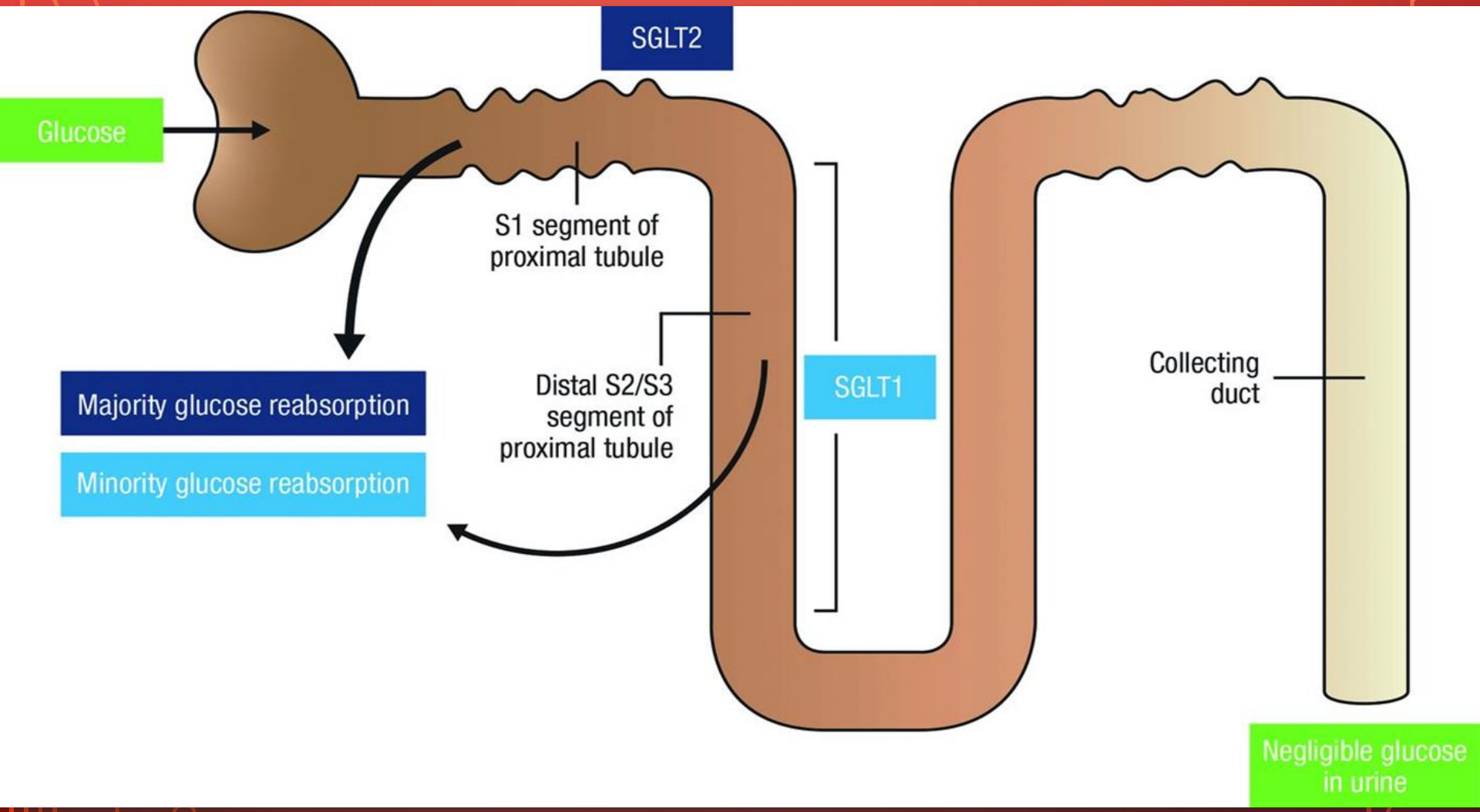
Drucker DJ. *Lancet*. 2006 Nov 11;368(9548):1696-705.
N Engl J Med 2013;369:1327-35.
N Engl J Med 2013;369:1317-26.
N Engl J Med 2015;373: 232-42.

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

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

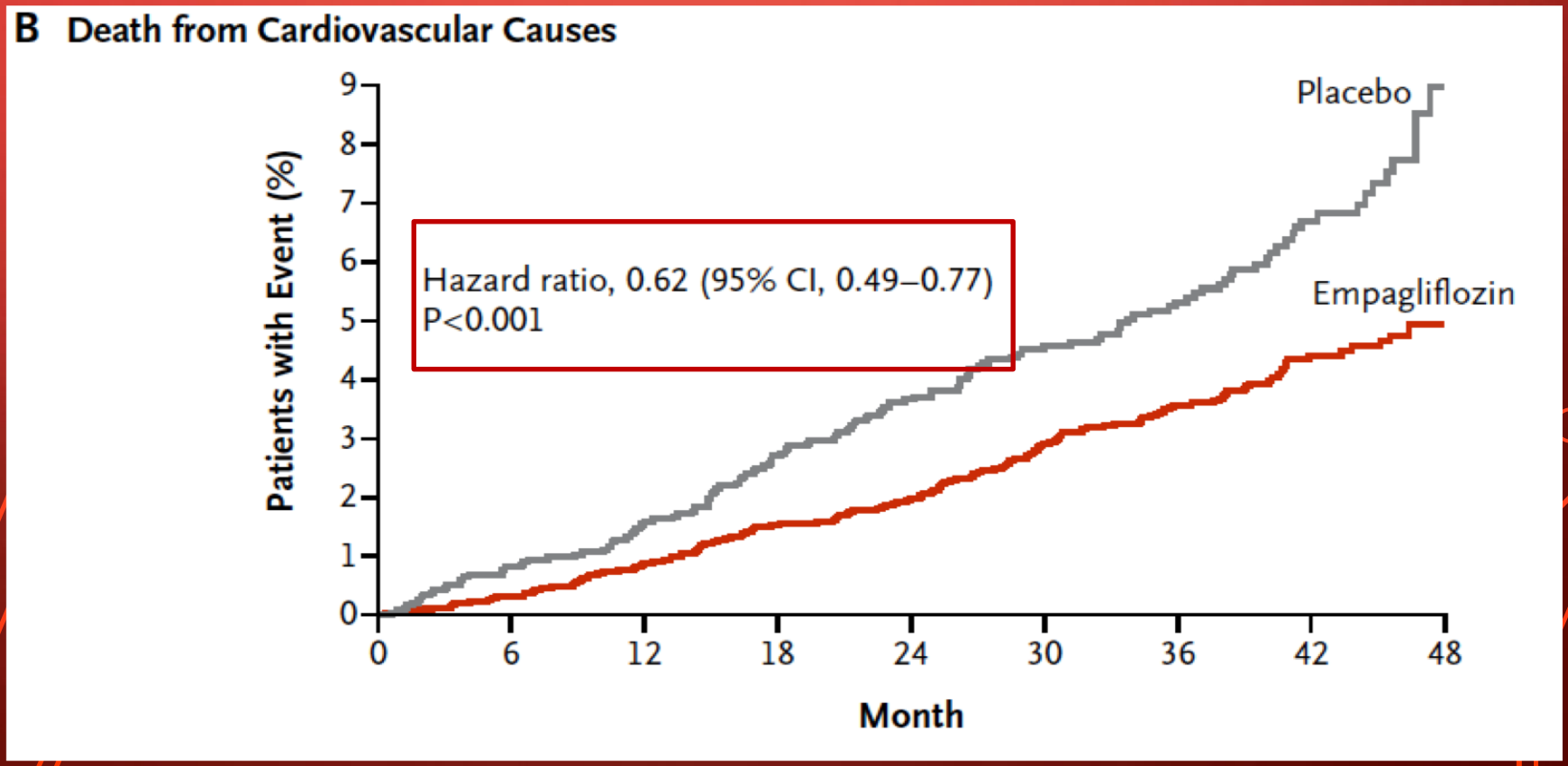
Empagliflozin and CV outcomes

- 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

BLOOD PRESSURE CONTROL & T2DM

Action to Control Cardiovascular Risk in Diabetes (ACCORD):

- Does SBP <120 provide better cardiovascular protection than SBP 130-140? No.

ADVANCE-BP:

- Significant risk reduction

American Diabetes Association Standards of Medical Care in Diabetes. Cardiovascular disease and risk management. Diabetes Care 2017; 40 (Suppl. 1): S75-S87

BLOOD PRESSURE CONTROL & T2DM

Systolic Targets:

- People with diabetes and hypertension should be treated to a systolic blood pressure goal of <140 mmHg. A
- Lower systolic targets, such as <130 mmHg, may be appropriate for certain individuals at high risk of CVD, if they can be achieved without undue treatment burden. C

American Diabetes Association Standards of Medical Care in Diabetes.
Cardiovascular disease and risk management. Diabetes Care 2017; 40 (Suppl. 1): S75-S87

BLOOD PRESSURE CONTROL & T2DM

Diastolic Targets:

- Patients with diabetes should be treated to a diastolic blood pressure <90 mmHg. A
- Lower diastolic targets, such as <80 mmHg, may be appropriate for certain individuals at high risk for CVD if they can be achieved without undue treatment burden. C

American Diabetes Association Standards of Medical Care in Diabetes.
Cardiovascular disease and risk management. Diabetes Care 2017; 40 (Suppl. 1): S75-S87

BLOOD PRESSURE CONTROL & T2DM

Pregnant patients:

- **In pregnant patients with diabetes and chronic hypertension, blood pressure targets of 120–160/80–105 mmHg are suggested in the interest of optimizing long-term maternal health and minimizing impaired fetal growth. E**

American Diabetes Association Standards of Medical Care in Diabetes.
Cardiovascular disease and risk management. Diabetes Care 2017; 40 (Suppl. 1): S75-S87

BLOOD PRESSURE CONTROL & T2DM

- An ACE inhibitor or angiotensin receptor blocker, at the maximum tolerated dose indicated for blood pressure treatment, is the recommended first-line treatment for hypertension in patients with diabetes and urinary albumin–to– creatinine ratio ≥300 mg/g creatinine (A) or 30–299 mg/g creatinine (B).

- If one class is not tolerated, the other should be substituted. B

- Serum creatinine/eGFR and K monitoring

American Diabetes Association Standards of Medical Care in Diabetes.
Cardiovascular disease and risk management. Diabetes Care 2017; 40 (Suppl. 1): S75-S87

ANTIPLATELET AGENTS

Consider aspirin therapy (75–162 mg/day) C

- **As a primary prevention strategy in those with type 1 or type 2 diabetes at increased cardiovascular risk**

- **Includes most men or women with diabetes age ≥50 years who have at least one additional major risk factor, including:**

  - **Family history of premature ASCVD**
  - **Hypertension**
  - **Smoking**
  - **Dyslipidemia**
  - **Albuminuria**

American Diabetes Association Standards of Medical Care in Diabetes. Cardiovascular disease and risk management. Diabetes Care 2017; 40 (Suppl. 1): S75-S87

ANTIPLATELET AGENTS

- Aspirin is not recommended for ASCVD prevention for adults with DM at low ASCVD risk, since potential adverse effects from bleeding likely offset potential benefits. C

- In patients with diabetes <50 years of age with multiple other risk factors (e.g., 10-year risk 5–10%), clinical judgment is required. E

American Diabetes Association Standards of Medical Care in Diabetes. Cardiovascular disease and risk management. Diabetes Care 2017; 40 (Suppl. 1): S75-S87

Recommendations for statin and combination treatment in adults with diabetes

Age	ASCVD	Recommended statin intensity and combination treatment
<40 years	No	None
	Yes	•High LDL cholesterol ≥70 mg/dL despite maximally tolerated statin dose, consider adding additional LDL-lowering therapy (such as ezetimibe or PCSK9 inhibitor)
≥40 years	No	Moderate
	Yes	•High LDL cholesterol ≥70 mg/dL despite maximally tolerated statin dose, consider adding additional LDL-lowering therapy (such as ezetimibe or PCSK9 inhibitor)

DIABETES CARE IN THE HOSPITAL

- Perform an A1C for all patients with diabetes or hyperglycemia admitted to the hospital if not performed in the prior 3 months. B
- Insulin therapy for should be initiated for treatment of persistent hyperglycemia starting at a threshold ≥180 mg/dL. Then a target glucose of 140–180 mg/dL is recommended for the majority of critically ill A and noncritically ill patients. C

American Diabetes Association. Standards of Medical Care in Diabetes. Diabetes care in the hospital. *Diabetes Care* 2017;40(Suppl. 1):S120–S127

DIABETES CARE IN THE HOSPITAL

- More stringent goals, such as <140 mg/dL mmol/L) may be appropriate for selected critically ill patients, if achievable without significant hypoglycemia. C
- Intravenous insulin infusions should be administered using validated written or computerized protocols that allow for predefined adjustments in the infusion rate based on glycemic fluctuations and insulin dose. E

American Diabetes Association. Standards of Medical Care in Diabetes. Diabetes care in the hospital. *Diabetes Care* 2017;40(Suppl. 1):S120–S127

DIABETES CARE IN THE HOSPITAL

- **Basal insulin or basal + bolus correction regimen is the preferred treatment for noncritically ill patients with poor oral intake or those who are taking nothing by mouth. An insulin regimen with basal, nutritional & correction components is the preferred treatment for noncritically ill patients with good nutritional intake. A**
- **The sole use of sliding scale insulin in the inpatient hospital setting is strongly discouraged. A**

American Diabetes Association. Standards of Medical Care in Diabetes. Diabetes care in the hospital. *Diabetes Care* 2017;40(Suppl. 1):S120–S127

DIABETES CARE IN THE HOSPITAL

- A hypoglycemia management protocol should be adopted and implemented by each hospital or hospital system. E
- A plan for preventing and treating hypoglycemia should be established for each patient. E
- Episodes of hypoglycemia in the hospital should be documented in the medical record and tracked. E

American Diabetes Association. Standards of Medical Care in Diabetes. Diabetes care in the hospital. *Diabetes Care* 2017;40(Suppl. 1):S120–S127

DIABETES CARE IN THE HOSPITAL

- A hypoglycemia management protocol should be adopted and implemented by each hospital or hospital system. A plan for preventing and treating hypoglycemia should be established for each patient. Episodes of hypoglycemia in the hospital should be documented in the medical record and tracked. E

American Diabetes Association. Standards of Medical Care in Diabetes. Diabetes care in the hospital. *Diabetes Care* 2017;40(Suppl. 1):S120–S127

DIABETES CARE IN THE HOSPITAL

- The treatment regimen should be reviewed and changed if necessary to prevent further hypoglycemia when a blood glucose value is <70 mg/dL (3.9 mmol/L). C
- There should be a structured discharge plan tailored to the individual patient. B

American Diabetes Association. Standards of Medical Care in Diabetes. Diabetes care in the hospital. *Diabetes Care* 2017;40(Suppl. 1):S120–S127

Antihyperglycemic Therapy in Adults with Type 2 Diabetes

At diagnosis, initiate lifestyle management, set A1C target, and initiate pharmacologic therapy based on A1C:

A1C is less than 9%, **consider Monotherapy.**

A1C is greater than or equal to 9%, **consider Dual Therapy.**

A1C is greater than or equal to 10%, blood glucose is greater than or equal to 300 mg/dL, or patient is markedly symptomatic, **consider Combination Injectable Therapy** (See Figure 8.2).

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

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)

A1C at target after 3 months of dual therapy?

Yes: - Monitor A1C every 3–6 months

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

Triple Therapy — Lifestyle Management + Metformin + Two Additional Agents

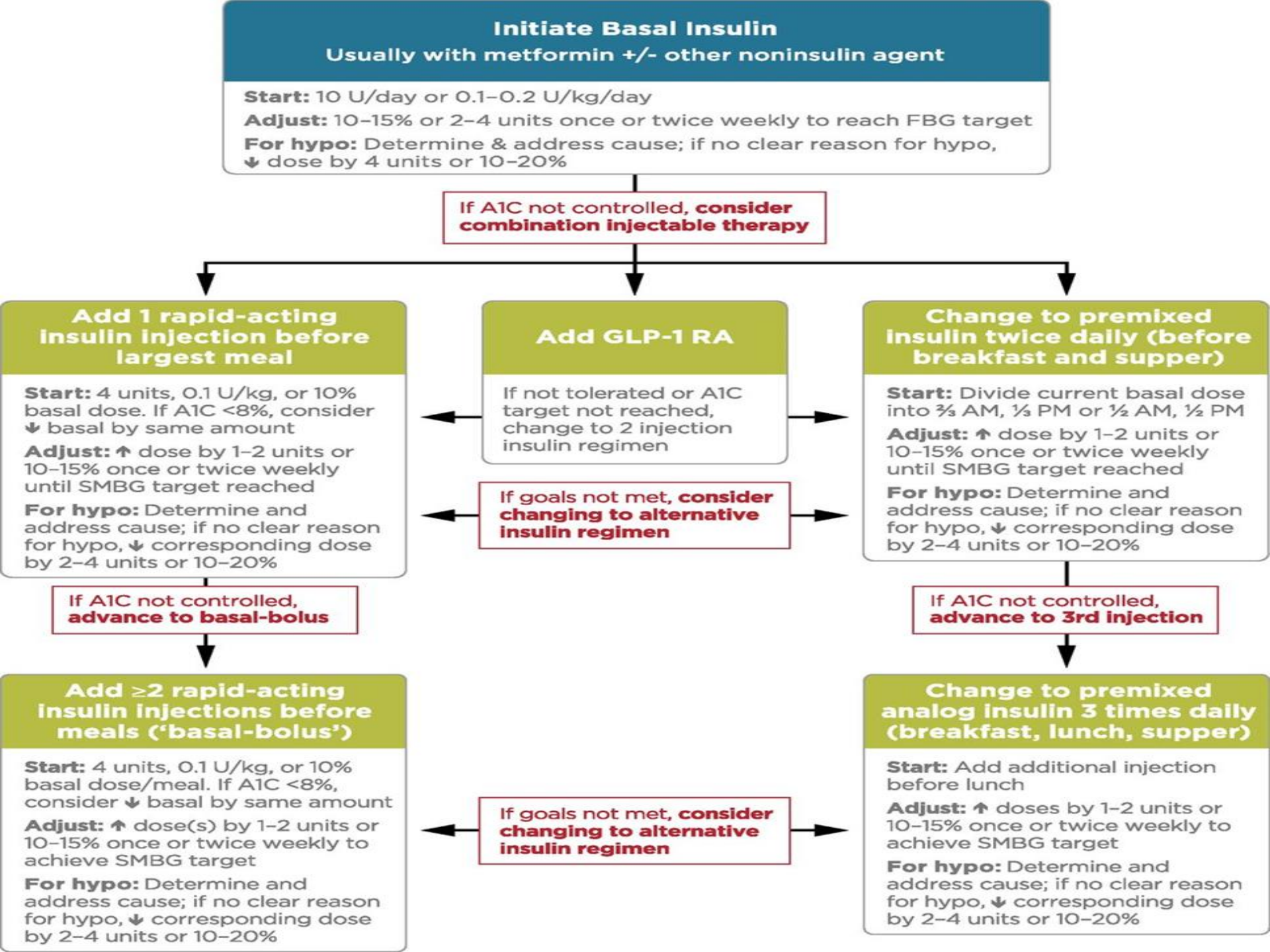
Add third agent based on drug-specific effects and patient factors# (See Table 8.1)

A1C at target after 3 months of triple therapy?

Yes: - Monitor A1C every 3–6 months

No: - Assess medication-taking behavior
- Consider Combination Injectable Therapy (See Figure 8.2)

Combination Injectable Therapy (See Figure 8.2)

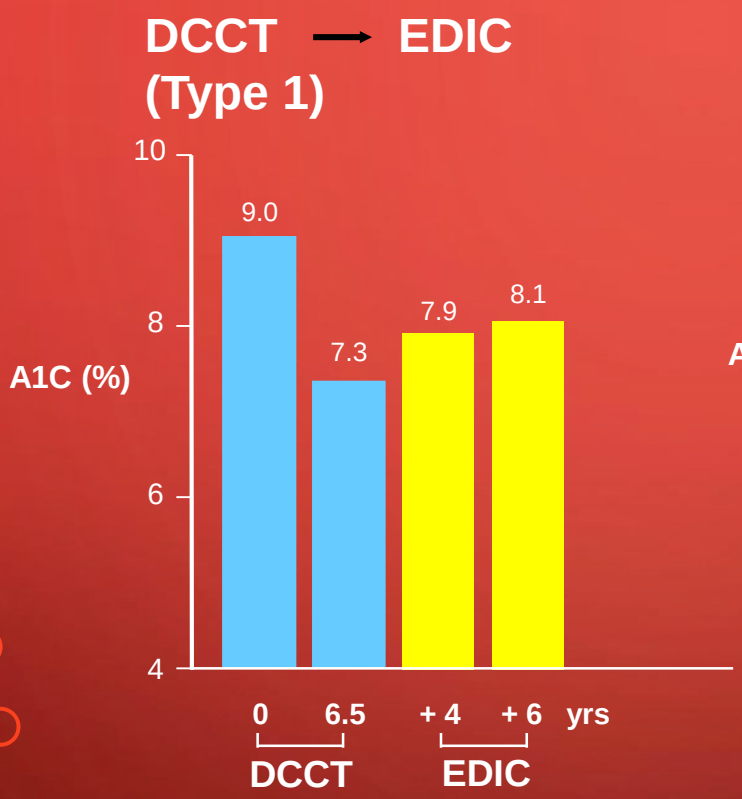

Initiate Basal Insulin
Usually with metformin +/- other noninsulin agent
Start: 10 U/day or 0.1–0.2 U/kg/day
Adjust: 10–15% or 2–4 units once or twice weekly to reach FBG target
For hypo: Determine & address cause; if no clear reason for hypo, ↓ dose by 4 units or 10–20%
If A1C not controlled, consider combination injectable therapy
Add 1 rapid-acting insulin injection before largest meal
Start: 4 units, 0.1 U/kg, or 10% basal dose. If A1C <8%, consider ↓ basal by same amount
Adjust: ↑ dose by 1–2 units or 10–15% once or twice weekly until SMBG target reached
For hypo: Determine and address cause; if no clear reason for hypo, ↓ corresponding dose by 2–4 units or 10–20%
If A1C not controlled, advance to basal-bolus
Add ≥2 rapid-acting insulin injections before meals ('basal-bolus')
Start: 4 units, 0.1 U/kg, or 10% basal dose/meal. If A1C <8%, consider ↓ basal by same amount
Adjust: ↑ dose(s) by 1–2 units or 10–15% once or twice weekly to achieve SMBG target
For hypo: Determine and address cause; if no clear reason for hypo, ↓ corresponding dose by 2–4 units or 10–20%
Add GLP-1 RA
If not tolerated or A1C target not reached, change to 2 injection insulin regimen
If goals not met, consider changing to alternative insulin regimen
If goals not met, consider changing to alternative insulin regimen
Change to premixed insulin twice daily (before breakfast and supper)
Start: Divide current basal dose into ⅔ AM, ⅓ PM or ½ AM, ½ PM
Adjust: ↑ dose by 1–2 units or 10–15% once or twice weekly until SMBG target reached
For hypo: Determine and address cause; if no clear reason for hypo, ↓ corresponding dose by 2–4 units or 10–20%
If A1C not controlled, advance to 3rd injection
Change to premixed analog insulin 3 times daily (breakfast, lunch, supper)
Start: Add additional injection before lunch
Adjust: ↑ doses by 1–2 units or 10–15% once or twice weekly to achieve SMBG target
For hypo: Determine and address cause; if no clear reason for hypo, ↓ corresponding dose by 2–4 units or 10–20%

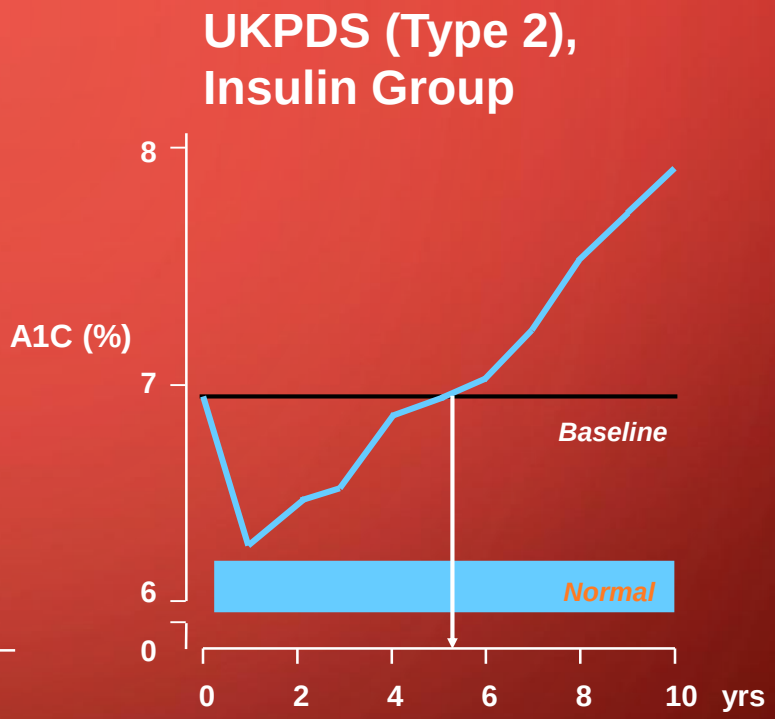
NEW RECOMMENDATION: PHARMACOLOGIC THERAPY FOR T2DM

- **Long-term use of metformin may be associated with biochemical vitamin B12 deficiency, and periodic measurement of vitamin B12 levels should be considered in metformin-treated patients, especially in those with anemia or peripheral neuropathy. B**

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

LESSONS FROM THE DCCT AND UKPDS: SUSTAINED INTENSIFICATION OF THERAPY IS DIFFICULT





DCCT/EDIC Research Group. *New Engl J Med* 2000; 342:381-389
Steffes M et al. *Diabetes* 2001; 50 (suppl 2):A63
UK Prospective Diabetes Study Group (UKPDS) 33
Lancet 1998; 352:837-853

PHARMACOLOGIC THERAPY FOR T2DM

- **Metformin, if not contraindicated and if tolerated, is the preferred initial pharmacologic agent for T2DM. A**
- **Consider insulin therapy (with or without additional agents) in patients with newly dx'd T2DM who are markedly symptomatic and/or have elevated blood glucose levels (≥300 mg/dL) or A1C (≥10%). E**

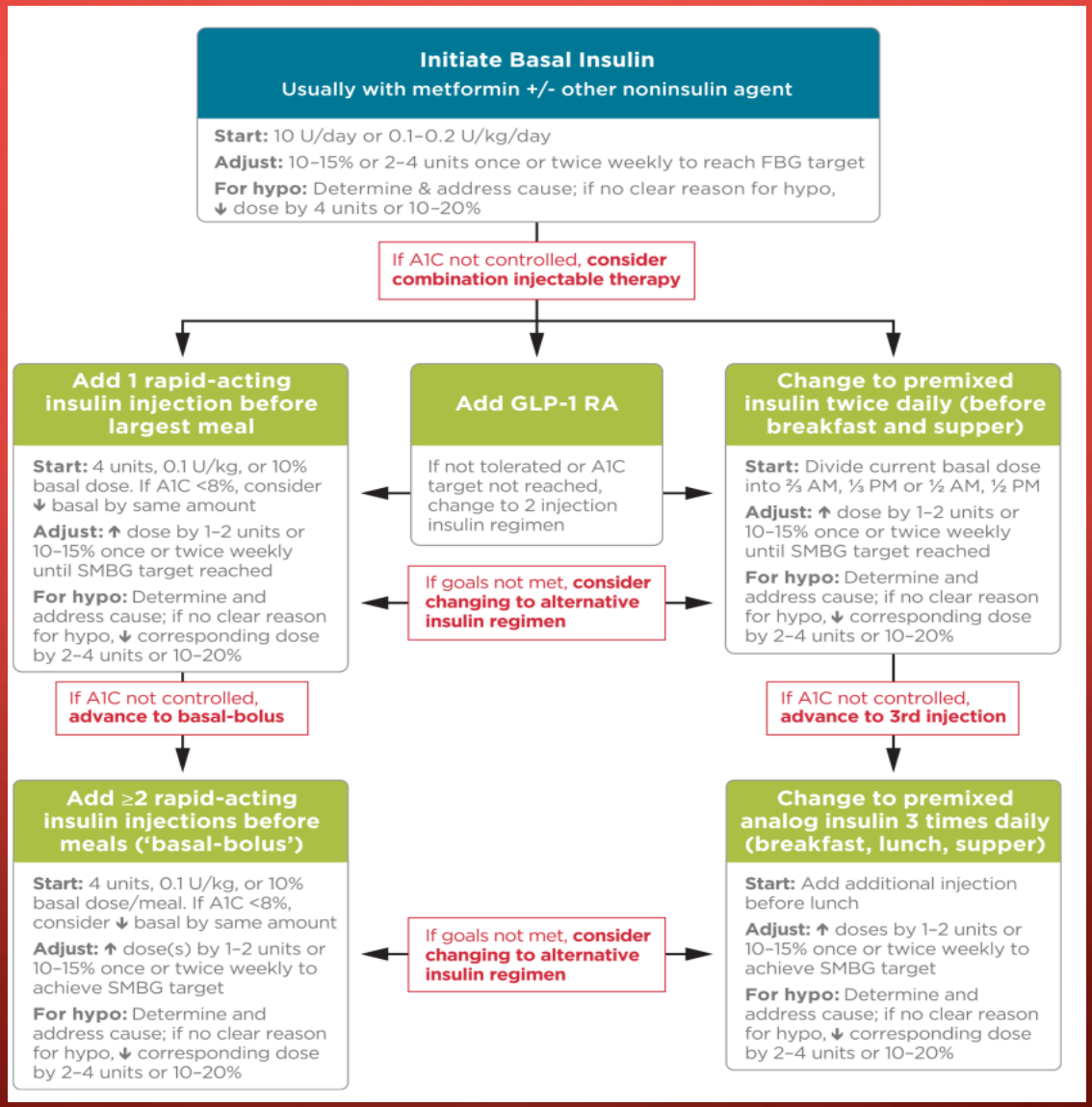
American Diabetes Association. Pharmacologic Approaches to Glycemic Treatment: Standards of Medical Care in Diabetes-2018. Diabetes Care. 2018;41(Suppl 1):S73-S85

PHARMACOLOGICAL THERAPY FOR T2DM

- If noninsulin monotherapy at maximal tolerated dose does not achieve or maintain the A1C target over 3 months, add a second oral agent, a GLP-1 receptor agonist, or basal insulin. A
- Use a patient-centered approach to guide choice of pharmacologic agents. E
- Don’t delay insulin initiation in patients not achieving glycemic goals. B

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

COMBINATION INJECTABLE THERAPY



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

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

LATEST PREVALENCE OF DIABETES IN THE US

- 29.1 million people or 9.3% of the US population
  - Diagnosed: 21 million
  - Undiagnosed: 8.1 million/27.8%
- Leading cause of kidney failure, nontraumatic lower-limb amputation, new cases of adult blindness
- Major cause of CVD and stroke
- 7th leading cause of death in US

www.cdc.gov/diabetes/data/statistics/2014StatisticsReport.html.
www.phdmc.org/images/uploads/CHA_ID_final.pdf --1/2014.

ANTI-HYPERGLYCEMIC THERAPY

Class	Primary Mechanism of Action	Agent(s)	Available as
α-Glucosidase inhibitors	• Delay carbohydrate absorption from intestine	Acarbose Miglitol	Precose or generic Glyset
Amylin analogue	• Decrease glucagon secretion • Slow gastric emptying • Increase satiety	Pramlintide	Symlin
Biguanide	• Decrease HGP • Increase glucose uptake in muscle	Metformin	Glucophage or generic
Bile acid sequestrant	• Decrease HGP? • Increase incretin levels?	Colesevelam	WelChol
DPP-4 inhibitors	• Increase glucose-dependent insulin secretion • Decrease glucagon secretion	Alogliptin Linagliptin Saxagliptin Sitagliptin	Nesina Tradjenta Onglyza Januvia
Dopamine-2 agonist	• Activates dopaminergic receptors	Bromocriptine	Cycloset
Glinides	• Increase insulin secretion	Nateglinide Repaglinide	Starlix or generic Prandin

DPP-4 = dipeptidyl peptidase; HGP = hepatic glucose production

Garber AJ, et al. *Endocr Pract*. 2013;19(suppl 2):1-48. Inzucchi SE, et al. *Diabetes Care*. 2012;35:1364-1379

ANTI-HYPERGLYCEMIC THERAPY

THE UNIVERSITY OF ARIZONA COLLEGE OF MEDICINE PHOENIX

Class	Primary Mechanism of Action	Agent(s)	Available as
GLP-1 receptor agonists	• Increase glucose-dependent insulin secretion • Decrease glucagon secretion • Slow gastric emptying • Increase satiety	Albiglutide Dulaglutide Exenatide Exenatide XR Liraglutide	Tanzeum Trulicity Byetta Bydureon Victoza
SGLT2 inhibitors	• Increase urinary excretion of glucose	Canagliflozin Dapagliflozin Empagliflozin	Invokana Farxiga Jardiance
Sulfonylureas	• Increase insulin secretion	Glimepiride Glipizide Glyburide	Amaryl or generic Glucotrol or generic Diaβeta, Glynase, Micronase, or generic
Thiazolidinediones	• Increase glucose uptake in muscle and fat • Decrease HGP	Pioglitazone Rosiglitazone	Actos Avandia

GLP-1 = glucagon-like peptide; HGP = hepatic glucose production; SGLT2 = sodium glucose cotransporter 2

Garber AJ, et al. *Endocr Pract*. 2013;19(suppl 2):1-48. Inzucchi SE, et al. *Diabetes Care*. 2012;35:1364-1379

METFORMIN

- Weight neutral
- Low cost
- GI side effects common (~30%/5%)
  - Slow titration and administration with meals
  - Consider extended release
- Vitamin B12 malabsorption
- Cardioprotective?

UKPDS (34). *Lancet*. 1998;352:854-65.
Johnson JA. *Diabetes Care. 2002;*25:2244–2248.
Tomkin GH. *Br Med J* 1973;3:673–675.
Bell DS. *South Med J.* 2010;103(3):265-267.
Dujic T. *Diabetes Care* Nov 2016,39 (11) 1896-1901.

Use of Metformin in CKD Patients

- Contraindicated eGFR < 30
- Starting with eGFR 30-45 is not recommended
- Obtain eGFR at least annually
  - More often if at risk to develop of renal impairment
- If eGFR later falls below 45 assess risks vs benefits
- Discontinue if eGFR later falls below 30
-

eGFR=estimated glomerular filtration rate (units=mL/minute/1.73 m^2).
http://www.fda.gov/Drugs/DrugSafety/ucm493244.htm.
https://www.kidney.org/professionals/KDOQI/gfr_calculator.

METFORMIN AND IODINATED CONTRAST

- Discontinue at the time of or before an iodinated contrast imaging procedure if eGFR between 30 and 60; in patients with a history of liver disease, alcoholism, or heart failure; or in patients who will be administered intra-arterial iodinated contrast
- Re-evaluate eGFR 48 hours after procedure; restart metformin if renal function is stable

eGFR=estimated glomerular filtration rate (units=mL/minute/1.73 m^2).
http://www.fda.gov/Drugs/DrugSafety/ucm493244.htm.
https://www.kidney.org/professionals/KDOQI/gfr_calculator.

SULFONYLUREAS

- 1st Generation
  - Chlorpropamide, tolazamide, acetohexamide or tolbutamide
- 2nd Generation
  - Glyburide, glipizide or glimepiride
- Can target fasting hyperglycemia/postprandial
  - Enhance insulin secretion

DeFronzo RA. *Ann Intern Med*. 1999 Aug 17;131(4):281-303.

SULFONYLUREAS

- Secondary failure rate
- Hypoglycemia
  - Elderly
  - Impaired renal function
  - Irregular meal schedule
- Weight gain
- Low cost
- Increase cardiovascular events?

DeFronzo RA. *Ann Intern Med*. 1999 Aug 17;131(4):281-303.
Monami M. *Diabetes Obes Metab*. 2013; Oct;15(10):938-53.

THIAZOLIDINEDIONES

- Directly reduce insulin resistance
  - Targets fasting and postprandial hyperglycemia
- No hypoglycemia
- No renal metabolism
- Indirect markers of CVD
- β-cell preservation

DeFronzo RA. *Ann Intern Med*. 1999 Aug 17;131(4):281-303.

THIAZOLIDINEDIONES

- Weight gain
- Edema
- Anemia
- Bone fractures
- Bladder cancer
- Cardiovascular affects
- Max dose with strong inhibitors of CYP2C8 (gemfibrozil) pioglitazone 15 mg

DeFronzo RA. *Ann Intern Med*. 1999 Aug 17;131(4):281-303.
Lancet. 2009, Volume 373, Issue 9681, 2125-2135.
Lewis JD et al. *Diabetes Care*. April 2011 vol. 34 no. 4 916-922.
Lewis JD et al. JAMA. 2015 Jul;314(3):265-77.
Kaul S et al. Circulation. 2010;121(16):1868.
http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm.

MEGLITINIDES: REPAGLINIDE AND NATEGLINIDE

- Targets postprandial hyperglycemia
  - Stimulates insulin secretion
  - Rapid onset; short acting
- No dose adjustment in renal insufficiency
- Less hypoglycemia than sulfonylureas
- No sulfa moiety

DeFronzo RA. *Ann Intern Med*. 1999 Aug 17;131(4):281-303.

α-GLUCOSIDASE INHIBITORS: ACARBOSE AND MIGLITOL

- Target postprandial hyperglycemia
- Inhibit saccharidases of small intestine
  - Delay glucose entry into the circulation
- Flatulence (80%), diarrhea (27%), n/v (8%)
- No hypoglycemia or weight gain
  - Treatment of hypoglycemia in combination treated patients may be affected. Use simple sugars

DeFronzo RA. *Annals of Internal Medicine* 1999;131:281-303.

CENTRALLY ACTING DOPAMINE AGONIST (BROMOCRIPTINE IR)

- Increases CNS dopaminergic activity
  - Diabetes patients may have low morning levels of hypothalamic dopamine, which is thought to lead to hyperglycemia and dyslipidemia
- PPG reductions, without increasing plasma insulin concentrations
  - Not prone to hypoglycemia or weight gain
- Side effects-nausea, dizziness, fatigue, HA

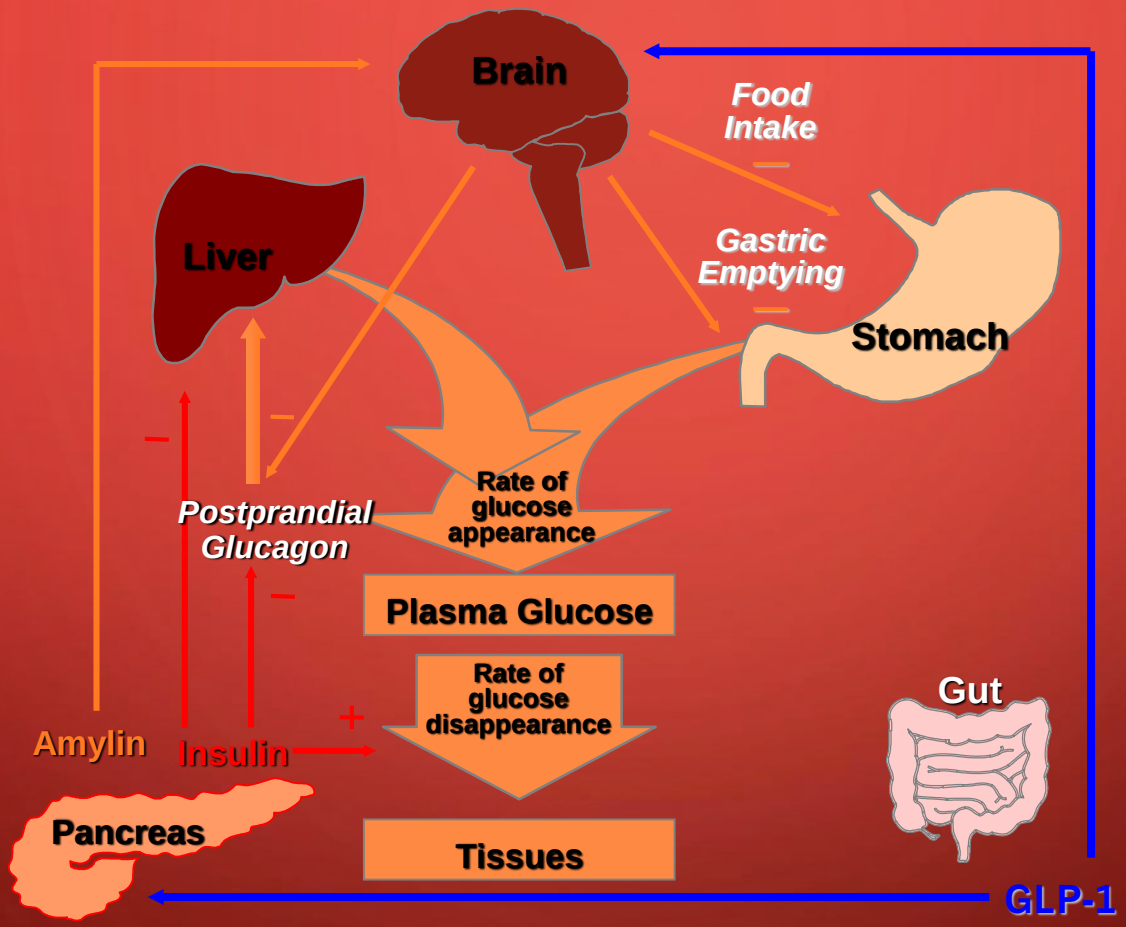
Med Lett Drugs Ther. 2010;52:97.

BILE ACID SEQUESTRANT COLESEVELAM

- Lowers LDL cholesterol
- Mechanism to improve glycemic control is uncertain
  - May act in the gastrointestinal tract to reduce glucose absorption
- Side effects constipation, nausea, dyspepsia and increase TG ~20%

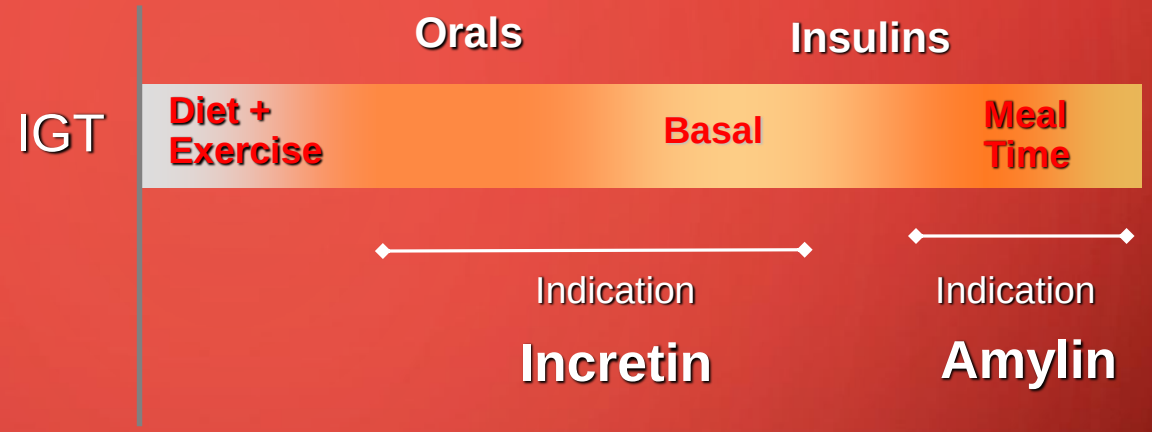
Med Lett Drugs Ther. 2008; 50:33.

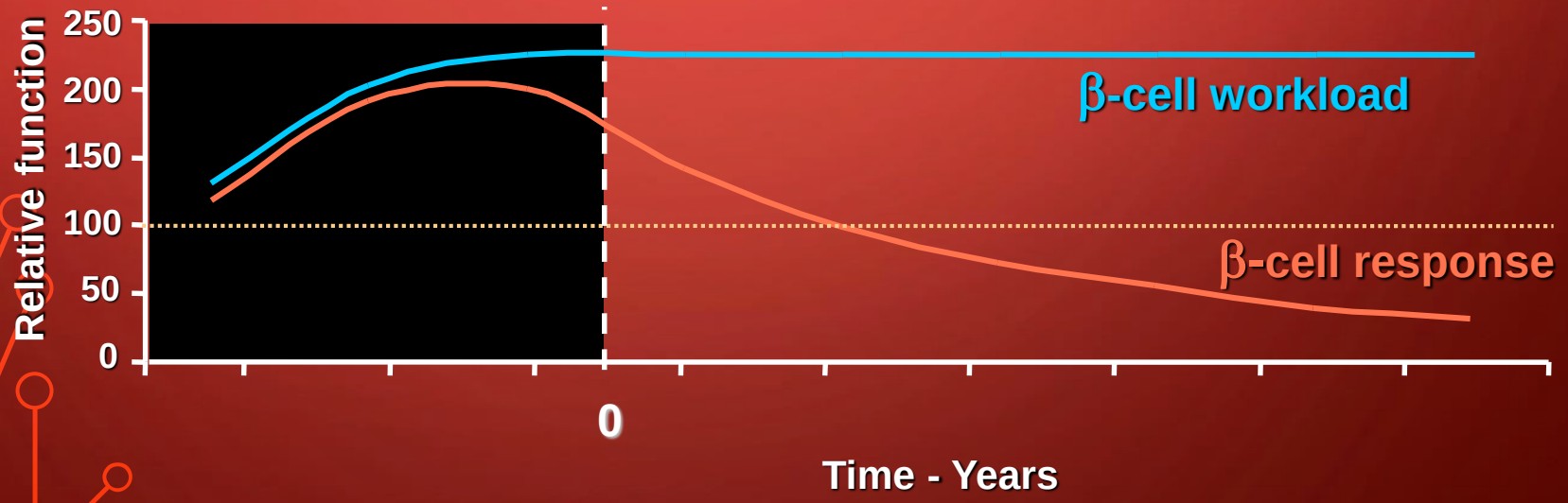
MULTIHORMONAL REGULATION OF GLUCOSE: INSULIN, GLUCAGON, GLP1 AND AMYLIN



Edelman S et al. *Diabetes Technol Ther* 2002; 4:175-189.

INCRETINS AND AMYLIN: THE DIABETES TREATMENT CONTINUUM





PRAMLINTIDE

- Synthetic amylin
- Inhibits post prandial glucagon secretion
- Slows gastric emptying
- Promotes satiety
- Contraindicated with high A1c, gastroparesis, hypoglycemia unawareness
- Dosed qAC tid
- ADR: hypoglycemia, n/v, ha, dizziness

Diabetes Care. 2016; 32(S1): S1-S112.

INSULIN THERAPY

- Regular
- Neutral protamine Hagedorn (NPH)
- Rapid analogues (aspart, glulisine, lispro)
- Basal analogues (detemir, glargine, degludec)
- Pre-mixed varieties and incretin mixes
  - Glargine/lixisenatide, degludec/liraglutide
- Inhaled insulin

Differences related to PK, not efficacy/A1c

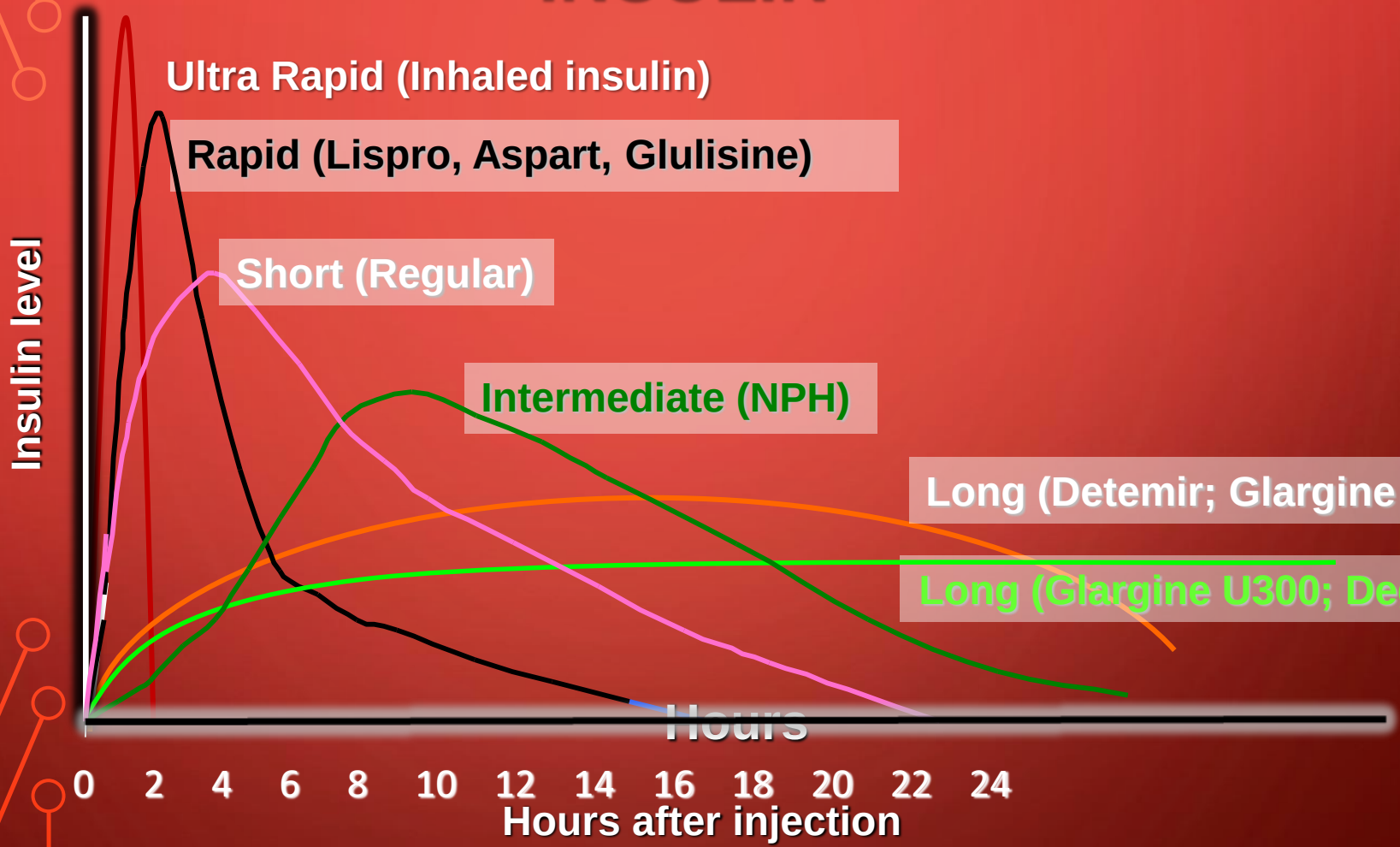
Hirsch IB. *N Engl J Med* 2005; 352:174-183.

INSULIN THERAPY IN DM2: INDICATIONS

- Significant hyperglycemia at presentation
- Hyperglycemia on effective doses of oral agents
- Intolerance of orals
- Need more flexibility
- Renal or hepatic disease
- Surgery
- Pregnancy
- Unable to afford orals
- Decompensation
  - Acute injury, stress, infection, myocardial ischemia, stroke
  - Hyperglycemia with ketones, weight loss
  - Use of diabetogenic medications

Hirsch IB. *N Engl J Med* 2005; 352:174-183.

ANTI-HYPERGLYCEMIC THERAPY: INSULIN



Hirsch IB. *N Engl J Med*. 2005;352(2):177.

Afrezza (insulin human) inhalation powder PI. MannKind Corporation; 2014.

Riddle MC et al. Diabetes Care. 2014 Oct;37(10):2755-62.

Zinman B et al. Diabetes Care. 2012 Dec;35(12):2464-71.

INHALED INSULIN

- Ultra rapid-acting insulin
  - Peak levels achieved in ~15 minutes
- Less weight gain/hypos than others
- Address issues of dexterity and phobia
- Contraindicated in chronic lung diseases
- Spirometry-baseline, 6 months and then annual
- Cough/throat irritation
- Do not use in patients with active lung cancer; use with caution in patients with h/o lung cancer or at risk for lung cancer

Afrezza (insulin human) inhalation powder PI. MannKind Corporation; 2014.
Rosenstock J, et al. Lancet. 2010 Jun 26;375(9733):2244-53.

SPECTRUM OF OPTIONS

Conventional Insulin Therapy

Intensive Insulin Therapy

Insulin Pump Therapy

Sensor Augmented Pumps

Artificial Pancreas Technology