Type 2 Diabetes: Latest Drug Approvals and Use of the Newer Agents: a 2018 Update

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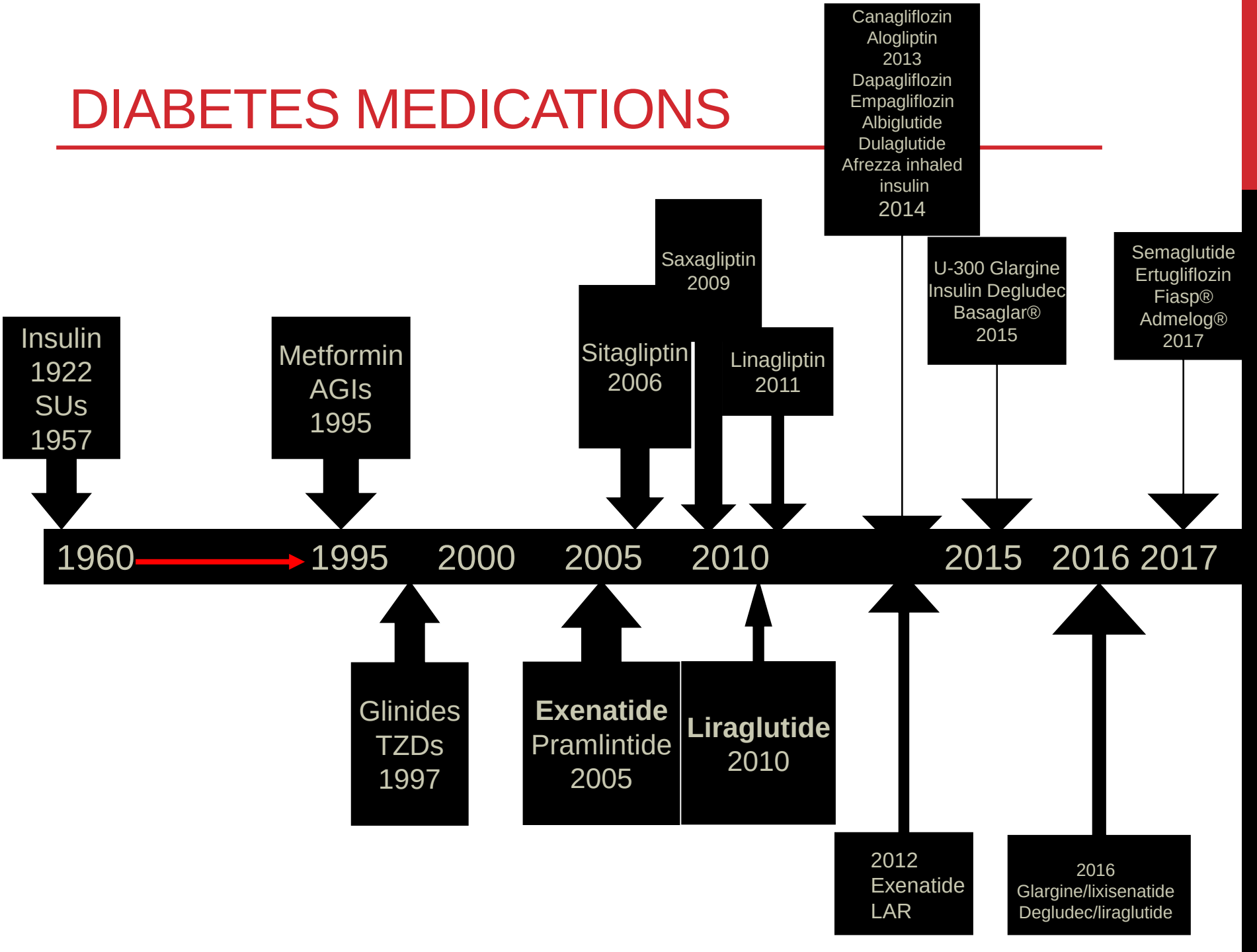
OBJECTIVES

- Describe the most recent drug approvals for type 2 diabetes and the cardiovascular outcome data supporting the newer drug classes
- Describe the 2018 Treatment recommendations from the American Diabetes Association
- Given a patient case, utilize a patient-centered approach when selecting pharmacotherapy options for a patient with type 2 diabetes

UPDATED ADA GUIDELINES

- Standards of Medical Care in Diabetes 2018. *Diabetes Care* 2018;41(Suppl 1)

DIABETES MEDICATIONS



TYPES OF INSULIN

- Rapid Acting
  - Humalog®, **Admelog®** (lispro) (U-100 and U-200-Humalog® only)
  - Novolog ®, **Fiasp®** (aspart)
  - Apidra ® (glulisine)
- Short Acting-Regular Insulin (R)
  - Novolin® R
  - Humulin® R
- Intermediate Acting-NPH (N)
  - Novolin® N
  - Humulin ® N
- Long Acting – Basal Insulin
  - Levemir® (detemir)
  - Lantus®/**Basaglar** ® (U-100 glargine)
  - **Toujeo® (U-300 glargine)**
  - **Tresiba®(Degludec U-100 and U-200)**

INSULIN DEGLUDEC (TRESIBA®)

- Ultra-Long-acting basal insulin
- Duration up to 42 hours
- Injected once a day at any time of day
- U-100 and U-200 strengths
- Available only as a FlexTouch® Pen

Tresiba. Lexi-Drugs. Lexicomp. Wolters Kluwer Health, Inc. Riverwoods, IL. Available at: http://online.lexi.com. Accessed September 12, 2017

DEVOTE: EFFICACY AND SAFETY OF DEGLUDEC VS. GLARGINE IN TYPE 2 DIABETES

- **Primary Outcome:** first occurrence of cardiovascular death, non-fatal MI, or non-fatal stroke
- **Secondary:** number of **severe hypoglycemic episodes**
  - time from randomization to MACE + time to hospitalization for unstable angina pectoris, number of serious adverse events, AEs leading to discontinuation of treatment drug.

Marso SP, et al. NEJM. 2017;377(8):723-32

DEVOTE: EFFICACY AND SAFETY OF DEGLUDEC VS. GLARGINE IN TYPE 2 DIABETES

- Duration of follow-up: 1.99 years
- Mean patient age: 65 years
- Diabetes duration: 16.4 years
- **Key inclusion criteria**:
  - **adult patients with type 2 diabetes, age ≥ 50 years with predefined previous CVD or renal disease**
  - **OR age ≥ 60 years with at least one predefined CV risk factor**
  - A1C ≥ 7.0% or A1C < 7.0% and current insulin treatment corresponding to ≥ 20 units basal insulin per day; and patients on one or more oral or injectable antidiabetic agent(s).

Marso SP, et al. NEJM. 2017;377(8):723-32

DEVOTE: EFFICACY AND SAFETY OF DEGLUDEC VS. GLARGINE IN TYPE 2 DIABETES

Outcome	Degludec (no./100 pt years)	Glargine (no./100 pt year)	Ratio (95% CI), P-value	NNT
Primary Composite	4.29	4.71	HR 0.91(0.78-1.06) P<0.001 for non-inferiority	
Severe Hypoglycemia	3.7	6.25	**RR 0.60(0.48-0.76) p<0.001 for superiority**	**39**

Marso SP, et al. NEJM. 2017;377(8):723-32

INSULIN LISPRO (ADMELOG®): APPROVED DECEMBER 2017

- First **follow-on** insulin lispro
  - Similar to insulin lispro (Humalog®)
- Available in U-100 vials and the Solostar® Pen
- No dose conversions when switching from other rapid acting insulins

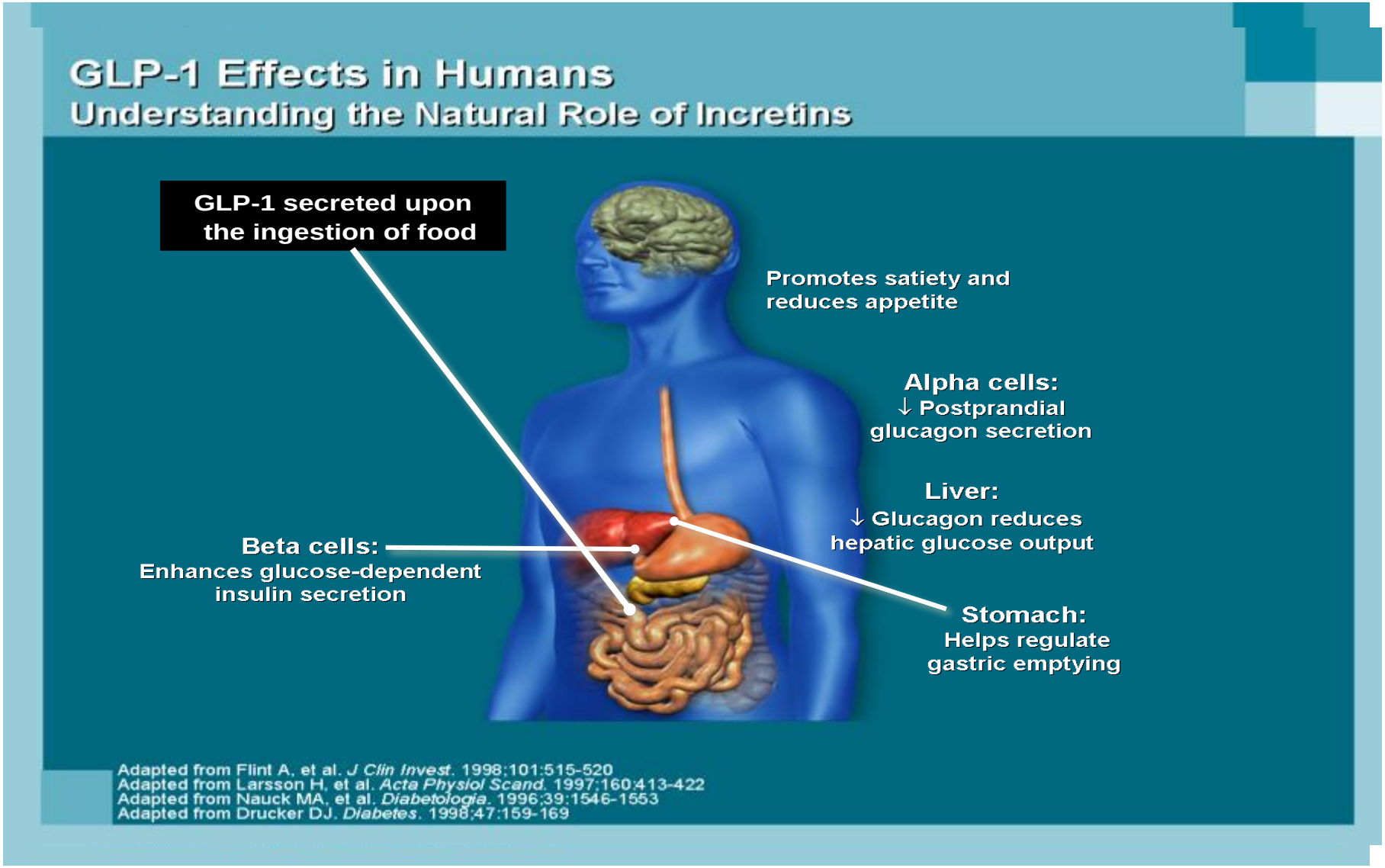
FASTER ACTING INSULIN ASPART (FIASP®): APPROVED 9/2017

- Insulin aspart + added niacinamide to speed absorption + L-arginine as a stabilizing agent
- Faster aspart vs. insulin aspart in type 1 patients pooled analysis[1]
  - 5 min earlier onset of insulin exposure
  - 2 x higher early insulin exposure
  - Offset of exposure and glucose lowering effect 12-14 min earlier with faster aspart
- Inject at **start of meal** or up to 20 minutes after the start of a meal
  - Novolog® approved to inject 5-10 minutes **before** the meal

1. Heise et al. Clin Pharmacokinet 2017;56:551-59

GLP-1 Receptor Agonists

GLP-1 PHYSIOLOGY

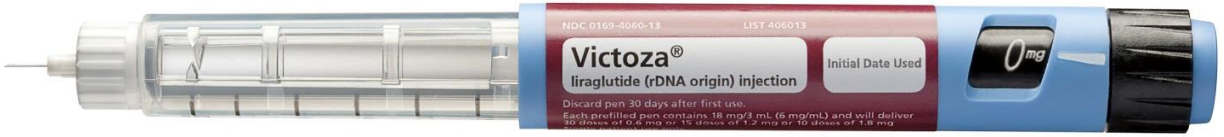


GLP-1 RECEPTOR AGONISTS

- **Exenatide (Byetta®)** BID dosing timed within 1 hour before breakfast and dinner
- **Liraglutide (Victoza®)** Once daily dosing
- **Dulaglutide (Trulicity®)** Once weekly dosing
- **Exenatide Long Acting (Bydureon®)** Once weekly dosing
- **Semaglutide (Ozempic®)** Once weekly dosing-**newly approved December 2017**
- *Lixisenatide (Adlyxin®)- once daily. FDA approved but not yet available in US as monotherapy*
- *Albiglutide (Tanzeum®)- Will be removed from the market in 2018*


Trulicity
dulaglutide
once weekly injection


Byetta
exenatide
5 µg injection
5
µg


NDC 0169-4060-13
LIST 406013
Victoza®
liraglutide (rDNA origin) injection
Initial Date Used
Discard pen 30 days after first use.
0mg


Once weekly
BYDUREON® BCise™
exenatide extended-release
injectable suspension 2 mg
For subcutaneous use only


NDC 0169-4132-11 List: 413211
OZEMPIC®
(semaglutide) injection
For Single Patient Use Only
2 mg/1.5 mL (1.34 mg/mL)
0 mg

GLP-1 AGONIST ADVERSE EFFECTS/PRECAUTIONS

- Adverse Effects
  - Nausea and vomiting – most common AE
  - Cases of acute pancreatitis
- Contraindications/Precautions
  - eGFR <30, do not use exenatide
  - Gastroparesis
  - History of pancreatitis
  - FDA Boxed Warning: History of medullary thyroid carcinoma OR
  - Multiple endocrine neoplasia syndrome 2

GLP-1 AGONIST BENEFITS

- Low risk of hypoglycemia
  - Slightly higher risk when used with sulfonylureas or insulin
- Weight loss!
- Potential for once daily or once weekly dosing
- Studies have shown addition to a basal insulin can be as effective as starting a pre-meal insulin – *see ADA insulin dosing algorithm*

Standards of Medical Care in Diabetes 2018. *Diabetes Care* 2018;41(Suppl 1)

GLP-1 RA CV Safety and Renal Outcome Trials

LEADER: LIRAGLUTIDE EFFECT AND ACTION IN DIABETES: EVALUATION OF CARDIOVASCULAR OUTCOME RESULTS

- Evaluated liraglutide vs. placebo + standard of care in patients with type 2 diabetes and high risk of CV disease or with established CV disease
  - Median follow-up 3.8 years
  - Primary outcome: first occurrence of death from CV cause, non-fatal MI or non-fatal stroke
- **Primary outcome occurred in 13.0% liraglutide vs. 14.9% in placebo group ($p<0.001$ for non-inferiority; $p=0.01$ for superiority)**
  - Granted FDA indication to reduce risk of CV death, nonfatal MI or nonfatal stroke

N Engl J Med 2016;375:311-22

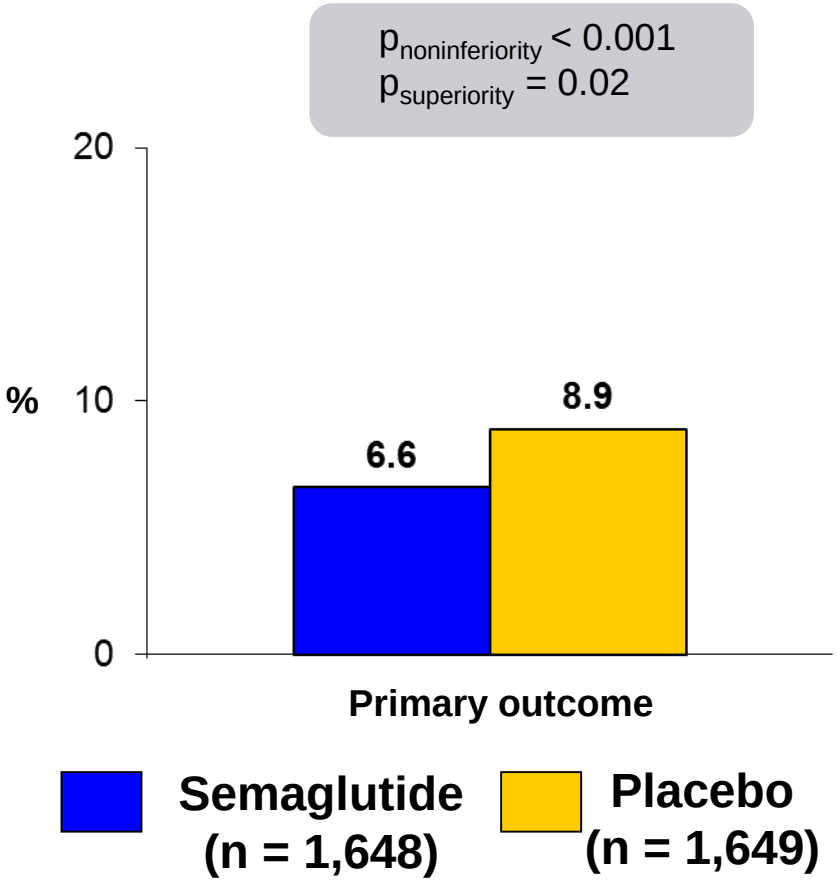
LEADER: LIRAGLUTIDE EFFECT AND ACTION IN DIABETES: EVALUATION OF CARDIOVASCULAR OUTCOME RESULTS

- **Secondary Analysis of Renal Outcomes**
  - Composite of new onset persistent macroalbuminurea, persistent doubling of SCr level, end-state renal disease, or death due to renal disease
  - Renal outcome occurred in fewer patients in liraglutide group (5.7% vs. 7.2% HR, 0.78; p=0.003)

NEJM 2017;377(9):839-48

SUSTAIN-6: SEMAGLUTIDE CV SAFETY TRIAL

Trial design: Patients with DM2 at high risk for CV events were randomized in a 1:1:1:1 fashion to either semaglutide 0.5 mg, semaglutide 1 mg, or matching placebo. They were followed for a median of 2.1 years.



Results

- Primary outcome- **CV death/MI/stroke: semaglutide vs. placebo: 6.6% vs. 8.9%, HR 0.74, 95% CI 0.58-0.95, p < 0.001 for noninferiority; p = 0.02 for superiority**
- CV death: 2.7% vs. 2.8%, p = 0.92; all MI: 2.9% vs. 3.9%, p = 0.12; all stroke: 1.6% vs. 2.7%, p = 0.04
- HbA1c at week 104: 7.6% vs. 7.3% vs. 8.3%

Conclusions

- **Injectable once a week semaglutide (GLP-1 agonist) was superior to placebo in improving glycemic control and ↓ CV events in high-risk patients with diabetes**

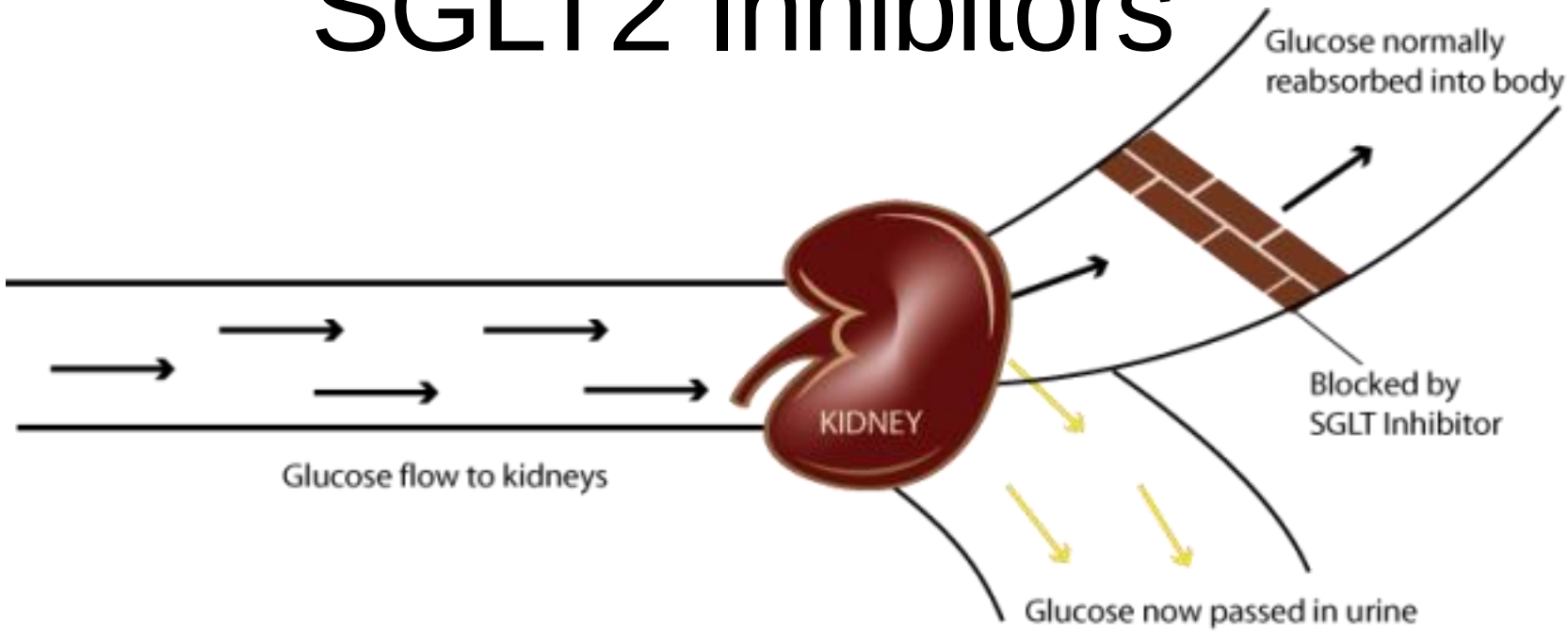
Marso SP, et al. N Engl J Med 2016;375:1834-44

GLP-1 RA CV STUDIES DEMONSTRATING NON-INFERIORITY

- ELIXA[1]-lixisenatide
- EXSCEL[2]- exenatide LAR

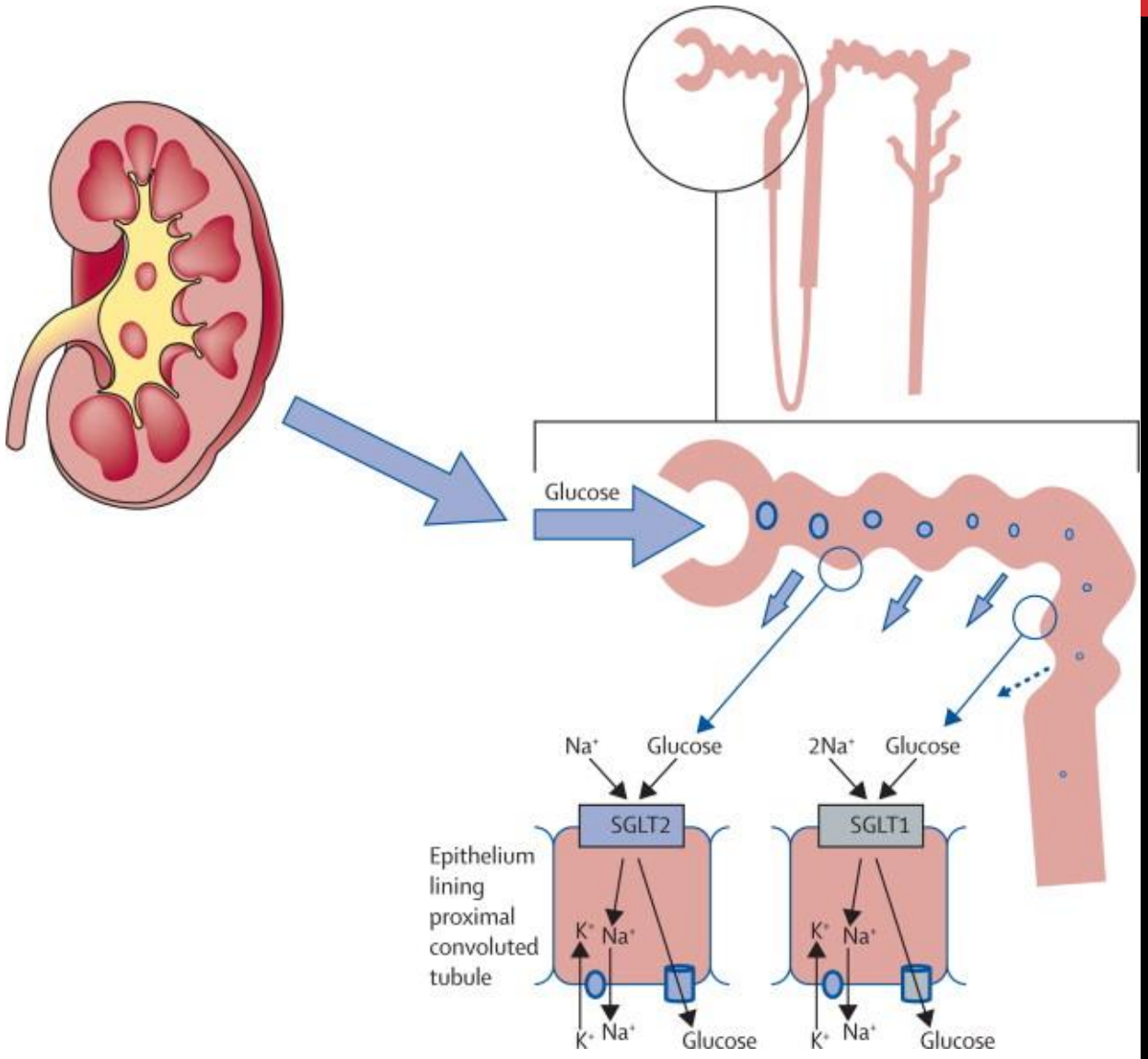
1. Pfeffer MA, et al. NEJM. 2015;373(23):2247-57
2. Holman RR, et al. NEJM. 2017 Sept 14; epub ahead of print

SGLT2 Inhibitors



SGLT2 INHIBITORS

- Sodium-glucose co-transporter inhibitors (SGLT2)
- Increase urinary glucose excretion



SGLT2 INHIBITORS

Canagliflozin
(Invokana™)

Dapagliflozin
(Farxiga™)

Empagliflozin
(Jardiance™)

Ertugliflozin
(Steglatro™)-
Newly approved 12-2017

SGLT2 INHIBITORS

Side Effects/Precautions

- Genital mycotic infections
- UTI
- Increased urination
- Hypotension due to volume depletion
- Hyperkalemia
- Euglycemic ketoacidosis
  - Rare but recent FDA warning
- Possible fracture risk- Canagliflozin
- Amputation risk with canagliflozin

Benefits

- Once daily oral agents
- Insulin independent action
- Small weight loss in studies
- Low risk of hypoglycemia

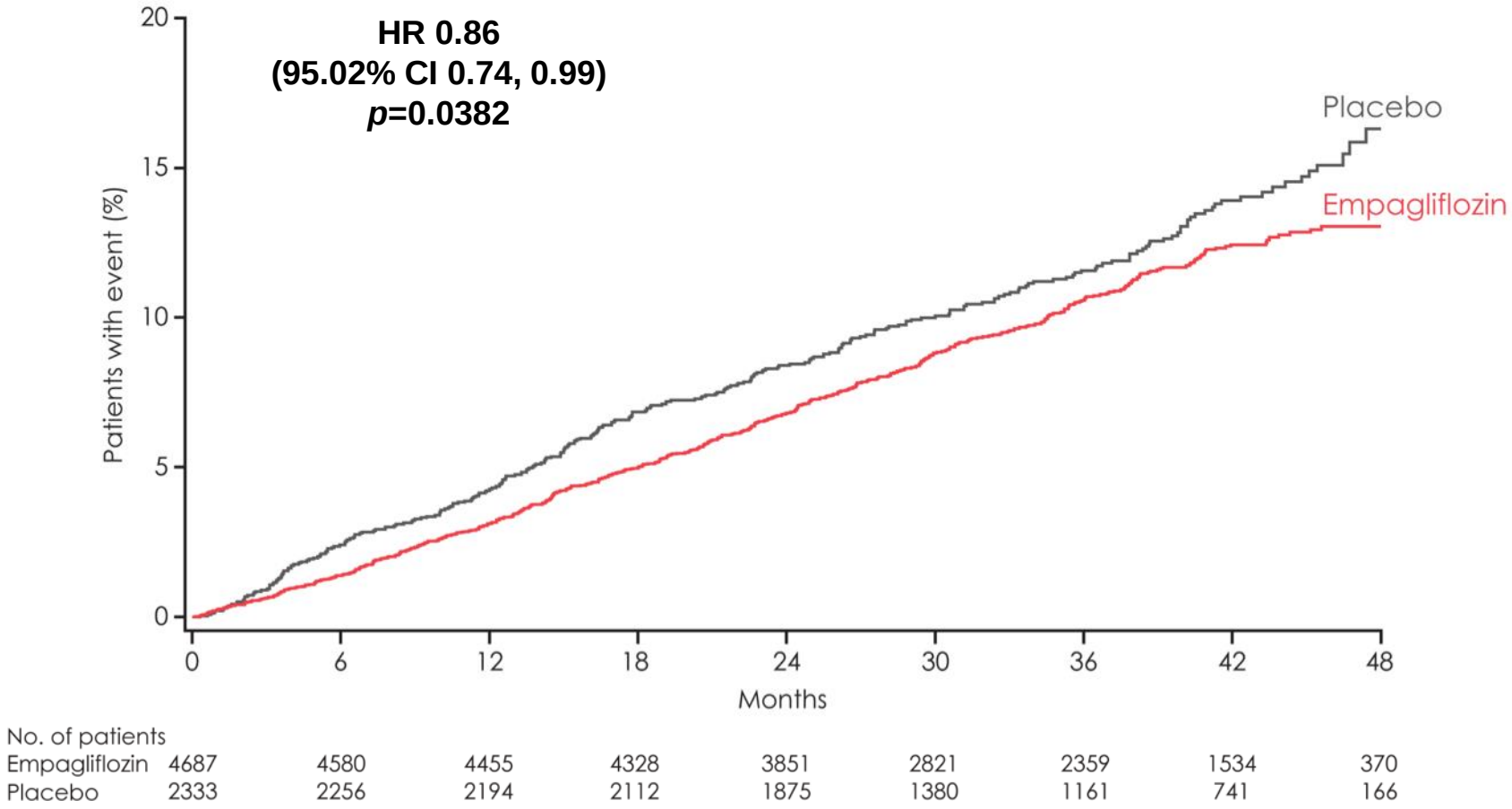
SGLT2 Inhibitor CV Safety Trials

EMPA-REG OUTCOME STUDY

- 7020 patients with **established CVD** randomized to empagliflozin or placebo
  - Primary composite outcome: death from CV cause, nonfatal MI, or nonfatal stroke
  - **10.5% in empagliflozin group vs. 12.1% placebo p=0.04 for superiority**
  - Death from CV causes:
    - 3.7% empagliflozin 5.9% in placebo
      - 38% relative risk reduction
  - **Granted FDA indication for reduction of CV mortality in adults with Type 2 DM and established CV Disease**

Zinman B, et al. NEJM 2015. 373 (22):2117-28

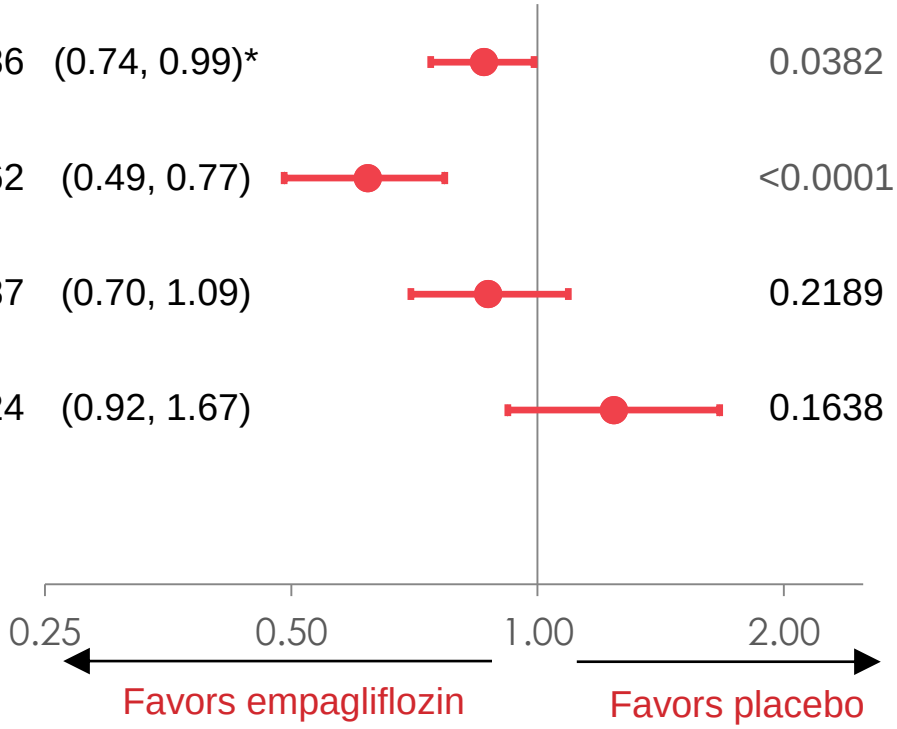
EMPA-REG: PRIMARY OUTCOME:3-POINT MACE



Zinman B, et al. NEJM 2015. 373 (22):2117-28

EMPA-REG:CV DEATH, MI AND STROKE

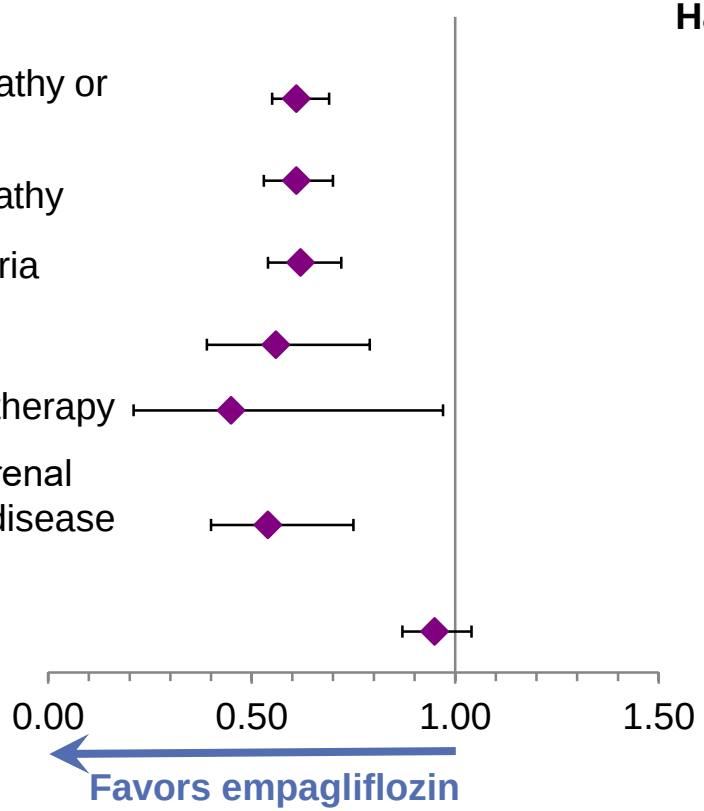
	Patients with event/analyzed Empagliflozin	Placebo	HR	(95% CI)	*p*-value
3-point MACE	490/4687	282/2333	0.86	(0.74, 0.99)*	0.0382
CV death	172/4687	137/2333	0.62	(0.49, 0.77)	<0.0001
Non-fatal MI	213/4687	121/2333	0.87	(0.70, 1.09)	0.2189
Non-fatal stroke	150/4687	60/2333	1.24	(0.92, 1.67)	0.1638



Zinman B, et al. NEJM 2015. 373 (22):2117-28

RENAL OUTCOMES WITH EMPAGLIFLOZIN OVER 3.2 YEARS

EMPA-REG RENAL (N=7020)



	Hazard ratio (95% CI)	*P* value
Incident or worsening nephropathy or CV death	0.61 (0.55-0.69)	<0.001
Incident or worsening nephropathy	0.61 (0.53-0.70)	<0.001
Progression to macroalbuminuria	0.62 (0.54-0.72)	<0.001
Doubling of SCr + eGFR ≤45	0.56 (0.39-0.79)	<0.001
Initiation of renal replacement therapy	0.45 (0.21-0.97)	0.04
Doubling of SCr + eGFR ≤45, renal replacement therapy, or renal disease death	0.54 (0.40-0.75)	<0.001
Incident albuminuria*	0.95 (0.87-1.04)	0.25

*In patients with normal albuminuria at baseline.

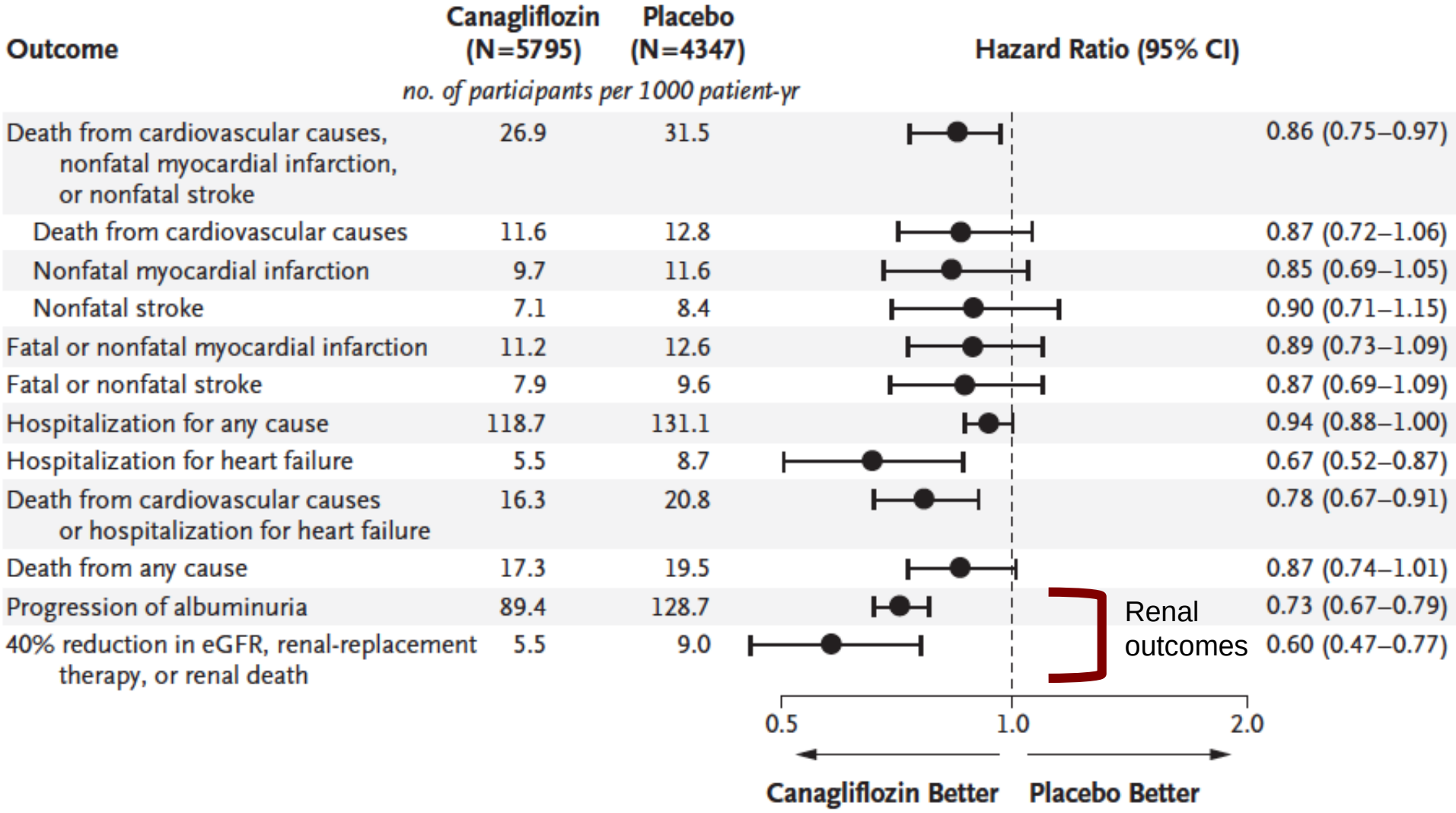
Wanner C, et al. *N Engl J Med*. 2016:375(4):323-34

CANVAS AND CANVAS-R

- Canagliflozin CV safety and renal outcome study
- Included patients >30 years with established ASCVD or >50 years with 2 or more risk factors
- Primary outcome: composite of death from CV cause, non-fatal MI or non-fatal stroke

Neil B, et al. NEJM 2017;377(7):644-657

CANVAS AND CANVAS-R



Neil B, et al. NEJM 2017;377(7):644-657

CANVAS AND CANVAS-R SAFETY ENDPOINTS

- Newly identified amputation risk in the canagliflozin group
  - 6.3 vs. 3.4 events/1000 pt years (HR 1.97 [CI 1.41-2.75])
    - Mechanism unknown
- Possible increased risk of fracture
- Other side effects were similar to other SGLT2 inhibitor trials

Neil B, et al. NEJM 2017;377(7):644-657

SGLT2-I CV SAFETY TRIALS IN PROGRESS

- Dapagliflozin: DECLARE-TIMI58
  - Estimated completion July 2018
- Ertuglifozin: Vertis CV Study
  - Estimated completion October 2019

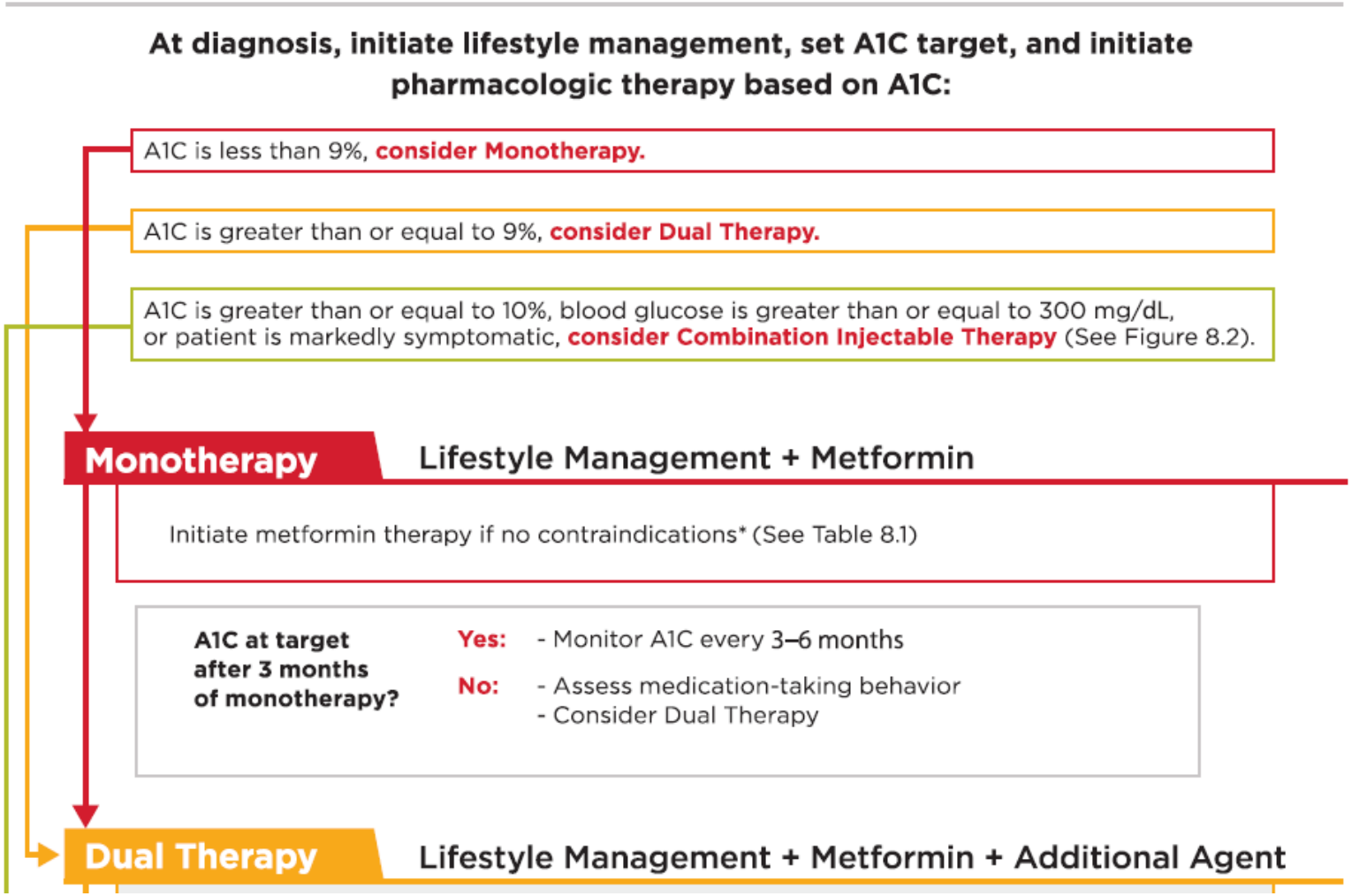
ADA Management of Hyperglycemia in Type 2 Diabetes

Juliann Horne, PharmD, PhC, BCACP

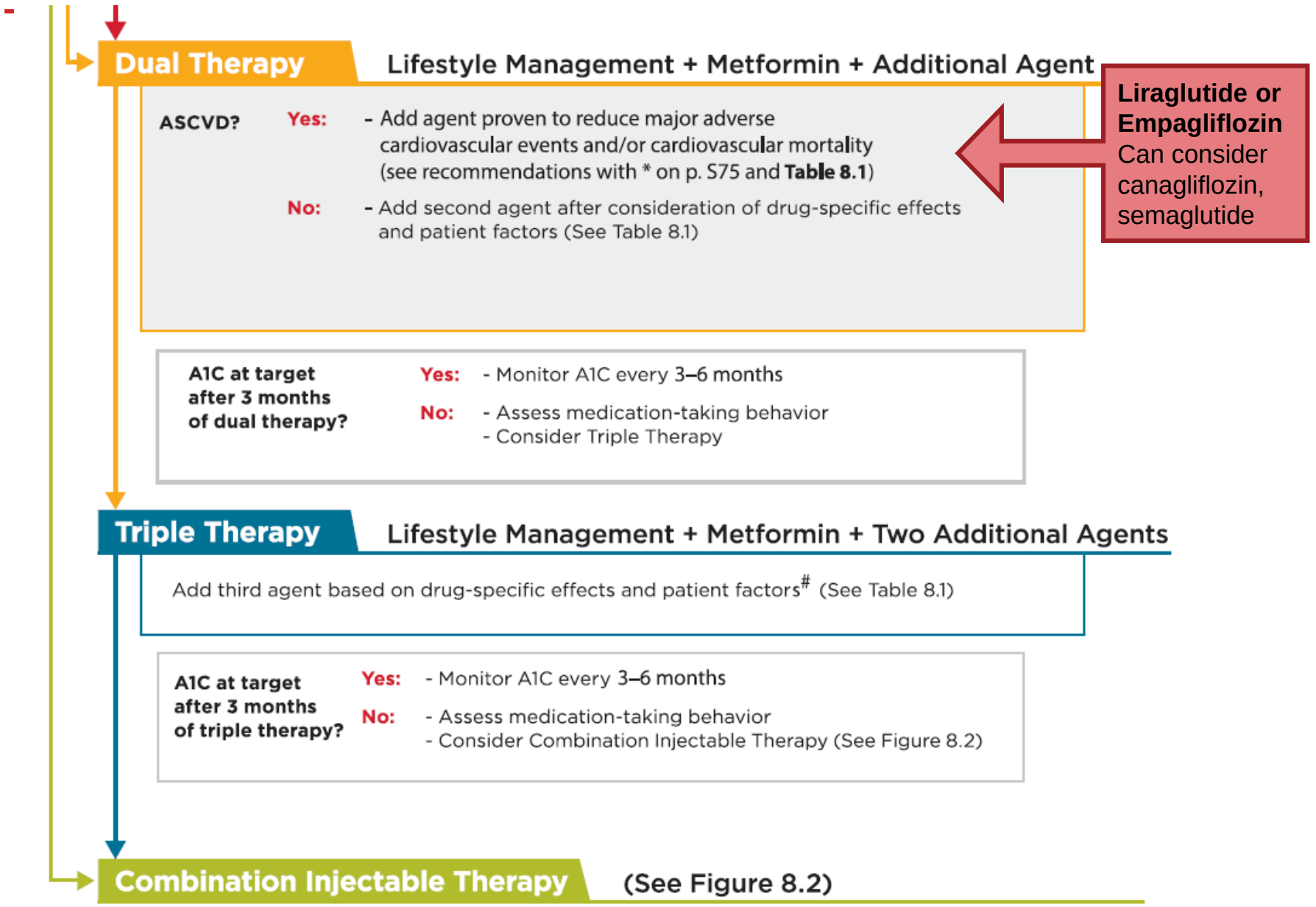
UNM North Valley Center for Family & Community Medicine

Standards of Medical Care in Diabetes.
***Diabetes Care* 2018;41(Suppl 1)**

ANTIHYPERGLYCEMIC THERAPY IN ADULTS WITH T2DM



ANTIHYPERGLYCEMIC THERAPY IN ADULTS WITH T2DM



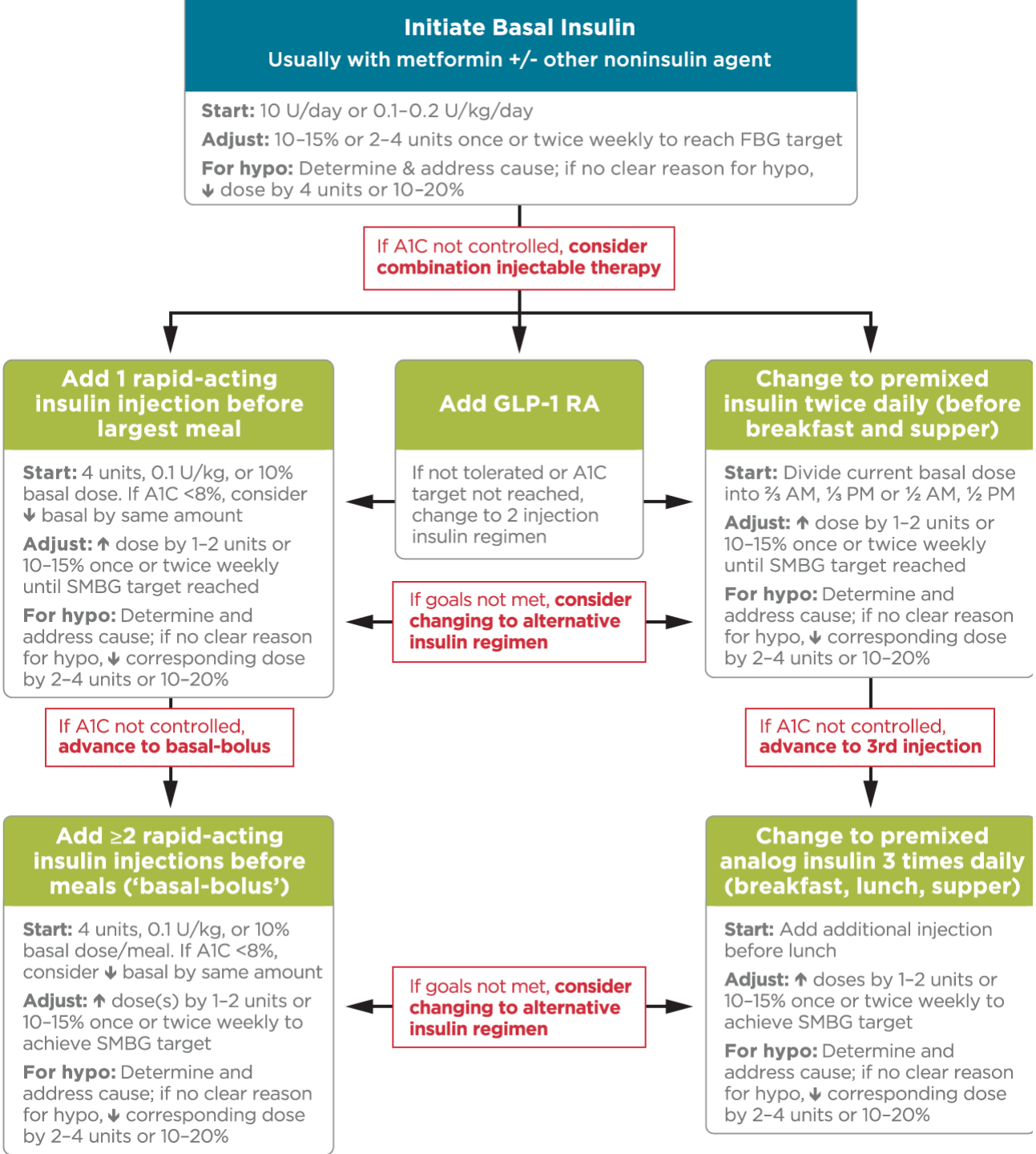
DRUG FACTORS TO CONSIDER

	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: canagliflozin, empagliflozin†	Benefit: canagliflozin, empagliflozin	High	Oral	Benefit: canagliflozin, empagliflozin	▪ Canagliflozin: not recommended with eGFR <45 ▪ Dapagliflozin: not recommended with eGFR <60; contraindicated with eGFR <30 ▪ Empagliflozin: contraindicated with eGFR <30	▪ **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
GLP-1 RAs	High	No	Loss	Neutral: lixisenatide, exenatide extended release Benefit: liraglutide†	Neutral	High	SQ	Benefit: liraglutide	▪ Exenatide: not indicated with eGFR <30 ▪ Lixisenatide: caution with eGFR <30 ▪ Increased risk of side effects in patients with renal impairment	▪ **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; can be used in renal impairment	▪ 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 & 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			

DRUG FACTORS TO CONSIDER

Class	Effect on A1c	Hypo	Weight	CV Events		Cost	Oral/ SQ	Renal Effects		Other considerations
				ASCVD	CHF			CKD	Dosing/ use	
SGLT-2 Inh.	Med	no	loss	Benefit: cana **empa**	Benefit: cana empa	high	oral	Benefit: cana empa	GFR adjustments for all agents	• GU infection • Volume depletion • Hypotension • **Cana** risk of amputation & bone fx
GLP-1 RA	High	no	loss	Benefit: **lira** *sema*	neutral	high	SQ	Benefit: lira *sema*	Exenatide C.I. if GFR<30	• **FDA Box warning:** thyroid C-cell tumors • GI side effects • Injection site reaction • Pancreatitis?

Standards of Medical Care in Diabetes. *Diabetes Care* 2018;41(Suppl 1)


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%

INSURANCE ISSUES

- Commercial
  - SGLT2s $0 copay card
  - GLP1s $25 per month copay card
- Medicaid
  - Most plans cover ONE formulary SGLT2 inhibitor and GLP1 agonist
  - Prior auths may work for patients with CAD (liraglutide, empagliflozin)
- Medicare
  - Dual Medicare/Medicaid: usually covered with low copay
  - Medicare patients: could be considered as an alternative to prandial insulin, but otherwise not generally affordable due to coverage gap

Case Scenarios

CASE 1: ASCVD RISK REDUCTION

62 year old male

PMH: DM, history of MI (2 years ago), hypertension

Point of care A1c 8.5%, not having any hypoglycemia

DM Meds: Metformin 1000 mg BID, Lantus® 20 units QHS

He has commercial insurance

What would you add (all on his insurance formulary)?

A. Glipizide (sulfonylurea)
B. Sitagliptin (DPP4 inhibitor)
C. Empagliflozin (SGLT2 inhibitor)
D. Insulin aspart (rapid-acting insulin)
E. Dulaglutide (once weekly GLP1 agonist)

CASE 1 CONTINUED

You decide to start him on empagliflozin (Jardiance™). On lisinopril 40 mg, carvedilol 12.5 mg BID and HCTZ 12.5 mg, his clinic blood pressures typically run 110s/60s.

How would you dose empagliflozin and would you adjust any of his other medications?

- Empagliflozin 10 mg once a day (may increase to 25 mg if 10 mg well-tolerated)
- Discontinue HCTZ, encourage fluids
- Continue same dose Lantus® 20 units

CASE 2: FACILITATING WEIGHT LOSS

55 year old female

PMH: Diabetes x 3 years, dyslipidemia, recurrent UTI, knee pain

Meds: Metformin 1000 mg BID, Levemir® (insulin detemir) 45 units BID, atorvastatin 10 mg daily, aspirin 81 mg daily

Recent A1c 7.2%. She has mild hypoglycemia (60s-70s) twice a month.

BMI 41kg/m^2.

She wants to lose weight and is exercising and trying to reduce her portions. What would you recommend? She has a Medicaid plan that covers the following options:

A. Pioglitazone (TZD)
B. Alogliptin (DPP4 inhibitor)
C. Canagliflozin (SGLT2 inhibitor)
D. Liraglutide (once daily GLP1 agonist)

CASE 2 CONTINUED

- How would you start liraglutide (Victoza®) and would you adjust any of her other medications?

- Victoza® 0.6 mg daily for 1 week. Increase after 1 week if tolerated to 1.2 mg daily.
- Reduce portion sizes!
- Decrease insulin detemir from 45 to 40 units twice a day (10%).
- Will likely need further reductions of insulin as liraglutide is increased to 1.8 mg and as she successfully loses weight.

CASE 2 CONTINUED

She returns to your clinic stating that is very pleased with the liraglutide. She has lost 4 kg in the last month! When you ask about nausea, she states she is vomiting almost every day in the mornings after taking liraglutide. She is using 1.2 mg on most days, but admits she sometimes forgets for a few days in a row.

What would you tell her?

- Important to take the medicine consistently to avoid nausea/vomiting.
- Try backing down to 0.6 mg until well tolerated.

CASE 3: INCONSISTENT INSULIN TIMING

67 year old female

PMH: T2DM, CKD, neuropathy, gastroparesis

A1c 8.7%, eGFR 29 ml/min

Meds: Glipizide 10 mg BID, Lantus® 45 units once a day

Silverscript Medicare

She often forgets her medicine. She gets busy taking care of grandkids and remembers later in the day but skips the dose.

Silverscript no longer covers Lantus. Which of these Tier 2 formulary options would you choose?

- Basaglar® (insulin glargine)
- Levemir® (insulin detemir)
- Tresiba® (insulin degludec)

CASE 4: PRANDIAL INSULIN ADHERENCE

- 68 year old female
- PMH: DM2, HTN, neuropathy, CKD
- A1c 8.5%, eGFR 32
- DM Meds: Lantus® 60 units QAM, Humalog® 10-20 units with meals. Trouble remembering mealtime insulin despite multiple attempts at strategies. As a result, glucose levels are sometimes at goal and sometimes 300s.
- Coverage: Medicare Part D
- What would you do?

- D/C Humalog®
- Start GLP1 receptor agonist once daily or once weekly
- Titrate basal insulin as needed

Questions