The Latest in Anti-Diabetes Medications and Cardiovascular Disease:

The Good, the Bad and the Ugly

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Objectives

- 1)Recognize the two classes of medications that have indications for CV benefit in patients with diabetes
- 2)Discuss the outcomes of recent CV trials for 2 classes of anti-diabetes medications (SGLT2 inhibitors and GLP 1 mimetics)
- 3)Discuss the risks and benefits of SGLT2 inhibitors and GLP1 mimetics, and identify appropriate patients for each

Disclosures

- Nothing to Disclose

Current Stats

From the American Diabetes Association Website there are:

- **30.3 million Americans (9.4% of total population) have diabetes**
- **About 95% with type 2 diabetes**
- **7.2 million people undiagnosed**
- **25% over the age of 65 with diabetes**
- **84.1 million Americans over 18 with prediabetes**
- **1.5 million Americans diagnosed with diabetes every year**

Impact

- **Cardiovascular disease is the leading cause of morbidity and mortality in patients with diabetes**
- **$327 billion: Total costs of diagnosed diabetes in the United States in 2017**
- **$237 billion for direct medical costs**
- **$90 billion in reduced productivity**
- **After adjusting for population age and sex differences, average medical expenditures among people with diagnosed diabetes were 2.3 times higher than what expenditures would be in the absence of diabetes.**

American Diabetes Association. Economic Costs of Diabetes in the U.S. in 2017. *Diabetes Care 2018, May;*41(5): 917-928

A Little History…

- Historically, little was known about the impact of anti-hyperglycemic medications (if any) on cardiovascular health
- Unfortunately, some seemed to show data in retrospect that they may, in fact, cause harm- controversial
- In 2008, amid the concerns of increased CV risk, the FDA required that glucose lowering medications undergo CV outcomes trials to prove there was not a negative impact on cardiovascular health. Already approved medications did not have to undergo testing

Cardiovascular Outcomes Trials Showing Benefit

- SGLT2 inhibitors:

  Empa-Reg: Empagliflozin (Jardiance)

  Canvas and Canvas-R: Canagliflozin (Invokana)

- GLP1 receptor agonist:

  LEADER: liraglitude (Victoza)

EMPA-REG OUTCOME

- A breakthrough in the diabetes world
- For the first time, there was an anti-diabetes medication that showed not only *lack of cardiovascular harm*, but showed *cardiovascular benefit*
- First announced in September 2015 at the European Association for the Study of Diabetes- highly anticipated
- Published in The New England Journal of Medicine in November 2015

EMPA- REG OUTCOME
Study Design and Procedures

- Randomized, double blind, placebo-controlled trial
- Assessed the effect of the SGLT2 inhibitor empagliflozin v. placebo on cardiovascular outcomes
- 7020 patients with T2DM and established cardiovascular disease
- 590 sites in 42 countries
- Randomly assigned 1:1:1 to receive 10 mg or 25 mg empagliflozin or placebo
- Primary outcome was defined as composite of death from cardiovascular causes, nonfatal MI (excluding silent MI), or nonfatal stroke
- Median follow up of 3.1 years

Zinman, B., Wanner, C., Lachin, J., et al. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. *New England Journal of Medicine 2015;* 373:2117-2128

DOI:10.1056/NEJMoal1504720

American Diabetes Association. Standards of Medical Care in Diabetes-2019. *Diabetes Care 2019.*42:s115.

EMPA-REG OUTCOME
Results

- 14% Reduction in composite outcome of fatal and nonfatal MI, and nonfatal stroke
- 38% Reduction in cardiovascular death
- 32% reduction in all-cause mortality
- 35% reduction in hospitalizations from heart failure
- No significant difference in nonfatal MI or stroke when those outcomes looked at individually

Zinman, B., Wanner, C., Lachin, J., et al. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. *New England Journal of Medicine 2015;* 373:2117-2128

DOI:10.1056/NEJMoal1504720

American Diabetes Association. Standards of Medical Care in Diabetes-2019. *Diabetes Care 2019.*42:s115.

EMPA-REG OUTCOME
Renal Effects

Though not a primary outcome of the study, and study population not selected for CKD, there were large numbers of participants with kidney disease. There was an examination of renal effects as secondary outcomes:

- **39% reduction in worsening nephropathy (defined as composite of progression to UACR >300 mg/g Cr, doubling of serum Cr, ESRD, or death from ESRD)**
- **44% reduction in the risk of doubling of serum Cr accompanied by eGFR $\leq$ 45ml/min/1.73 m^2**

Zinman, B., Wanner, C., Lachin, J., et al. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. *New England Journal of Medicine 2015;* 373:2117-2128

DOI:10.1056/NEJMoal1504720

American Diabetes Association. Standards of Medical Care in Diabetes-2019. *Diabetes Care 2019.*42:s128.

CANVAS TRIALS

- Another SGLT2 inhibitor (canagliflozin) cardiovascular outcomes trial
- Published in The New England Journal of Medicine in August of 2017
- Integrated data from two trials: CANVAS trial that started in 2009 before FDA approval of canagliflozin, and CANVAS-Renal trial that began in 2014 after approval of canagliflozin

CANVAS Trial
Study Design and Procedures

- Randomized, double blind, placebo-controlled trial (though the original CANVAS was partially unblinded early to file interim CV data for regulatory approval of the drug)
- Assessed the effect of the SGLT2 inhibitor canagliflozin v. placebo on cardiovascular outcomes
- 10,142 patients with type 2 diabetes, two thirds of which had established cardiovascular disease
- 667 centers in 30 countries
- Randomly assigned 1:1:1 to receive 100 mg or 300 mg canagliflozin or placebo
- Primary outcome was defined as composite of death from cardiovascular causes, nonfatal MI, and nonfatal stroke; several secondary outcomes including renal outcomes and CHF hospitalizations were planned as well
- Mean follow up was 3.6 years

Neal, B., Perkovic, V., Mahaffey, K.W., et al. Canagliflozin and Cardiovascular and Renal events in type 2 Diabetes. *New England Journal of Medicine 2017.* 377:644-657

DOI: 10.1056/NEJMoa1611925

American Diabetes Association. Standards of Medical Care in Diabetes-2019. *Diabetes Care 2019.*42:s128.

CANVAS TRIAL
Results

- 14% reduction in cardiovascular events
- 40% decrease in risk of reduction in eGFR, ESRD, or death from ESRD
- 27% reduction in risk of progression of albuminuria
- 33% risk in reduction of hospitalization for heart failure

Neal, B., Perkovic, V., Mahaffey, K.W., et al. Canagliflozin and Cardiovascular and Renal events in type 2 Diabetes. *New England Journal of Medicine 2017.* 377:644-657

DOI: 10.1056/NEJMoa1611925

American Diabetes Association. Standards of Medical Care in Diabetes-2019. *Diabetes Care 2019.*42:s116-119,128

LEADER Trial

- Cardiovascular outcomes trial for liraglutide, a GLP-1 receptor agonist
- Published in the New England Journal of Medicine in 2016, in between the 2 major SGLT2 trials

LEADER trial
Study Design and Procedures

- Randomized, double blind, placebo controlled trial
- Assessed liraglutide v. placebo on cardiovascular outcomes
- 9,340 patients with type 2 diabetes with, at high risk for cardiovascular disease
- 410 sites in 32 countries
- Randomly assigned 1:1 to receive 1.8 mg of liraglutide (or the maximum tolerated dose) v. placebo once daily
- Primary outcome was composite of cardiovascular death, nonfatal MI, and nonfatal stroke
- Median follow up 3.8 years

Marso, S., Daniels, G.H., Brown-Frandensen, K., et al. Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes. *The New England Journal of Medicine 2016.* 375:311-322
DOI:10.1056/NEJMoal603827

American Diabetes Association. Standards of Medical Care in Diabetes-2019. *Diabetes Care 2019.*42:s116.

LEADER Trial
Results

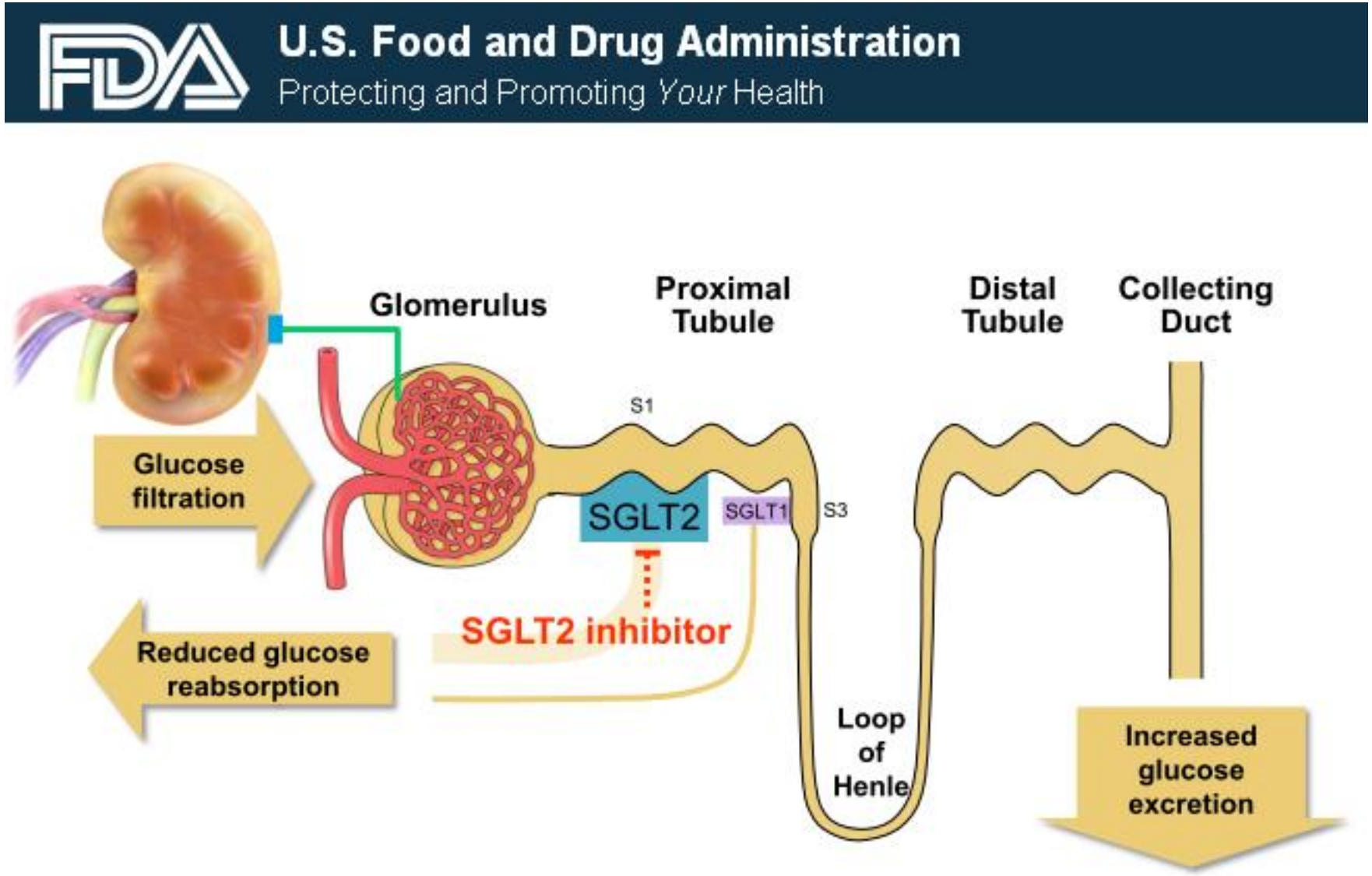
- **Primary outcome (composite of CV death, nonfatal MI and stroke) occurred in fewer patients taking liraglutide than placebo (13% v. 14.9%)**
- **Cardiovascular death was reduced (4.7% liraglutide v. 6 % placebo)**
- **Reduced death from any cause in liraglutide group (8.2% liraglutide v. 9.6% placebo)**
- **Non-statistically significant reduction in rates of nonfatal MI, stroke and CHF hospitalization**
- **22% reduction in risk of new or worsening nephropathy (defined as a composite of persistent macroalbuminuria, doubling of serum Cr, ESRD or death from ESRD)**

Marso, S., Daniels, G.H., Brown-Frandensen, K., et al. Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes. *The New England Journal of Medicine 2016.* 375:311-322
DOI:10.1056/NEJMoal603827

American Diabetes Association. Standards of Medical Care in Diabetes-2019. *Diabetes Care 2019.*42:s116

SGLT2 Inhibitors: Mechanism of Action

- Sodium glucose co-transporter 2 in the proximal tubules, is responsible for the majority of the reabsorption of filtered glucose from the tubular lumen.
- Inhibition therefore reduces reabsorption of filtered glucose, and increases urinary glucose excretion.
- This in turn lowers blood glucose levels and Hg A1c levels


U.S. Food and Drug Administration
Protecting and Promoting Your Health
Glomerulus
Proximal Tubule
Distal Tubule
Collecting Duct
S1
S3
SGLT2
SGLT1
Glucose filtration
Reduced glucose reabsorption
SGLT2 inhibitor
Loop of Henle
Increased glucose excretion

SGLT2 Inhibitors: Benefits/ Indications for Use

- Lower BG and HgA1c levels
- Improved Cardiovascular outcomes
- Reduced progression in chronic kidney disease
- Lower blood pressure
- Potential for weight loss

SGLT2 Inhibitors: Potential Adverse Reactions

- Hypotension
- Dehydration
- Acute Kidney Injury
- Ketoacidosis (even with normal blood glucose)
- UTI
- Genital Mycotic Infections
- Necrotizing Fasciitis
- Increased LDL
- Bone Fracture
- Hypersensitivity
- Hypoglycemia with insulin or insulin secretagogues

Canagliflozin: Amputations

- In the CANVAS trials, canagliflozin showed an approximately twofold increase in lower limb amputations compared with placebo (3.3% v. 1.5%)
- Most frequently involved toe and midfoot, however, BKA and AKA also both observed
- Occurred with both the 100 mg dose and the 300 mg dose
- Lower limb infections, gangrene, diabetic foot ulcers were the most common precipitating events
- Risk of amputation was the highest in prior amputees, those with peripheral vascular disease, and those with diabetic peripheral neuropathy
- Mechanism currently unknown

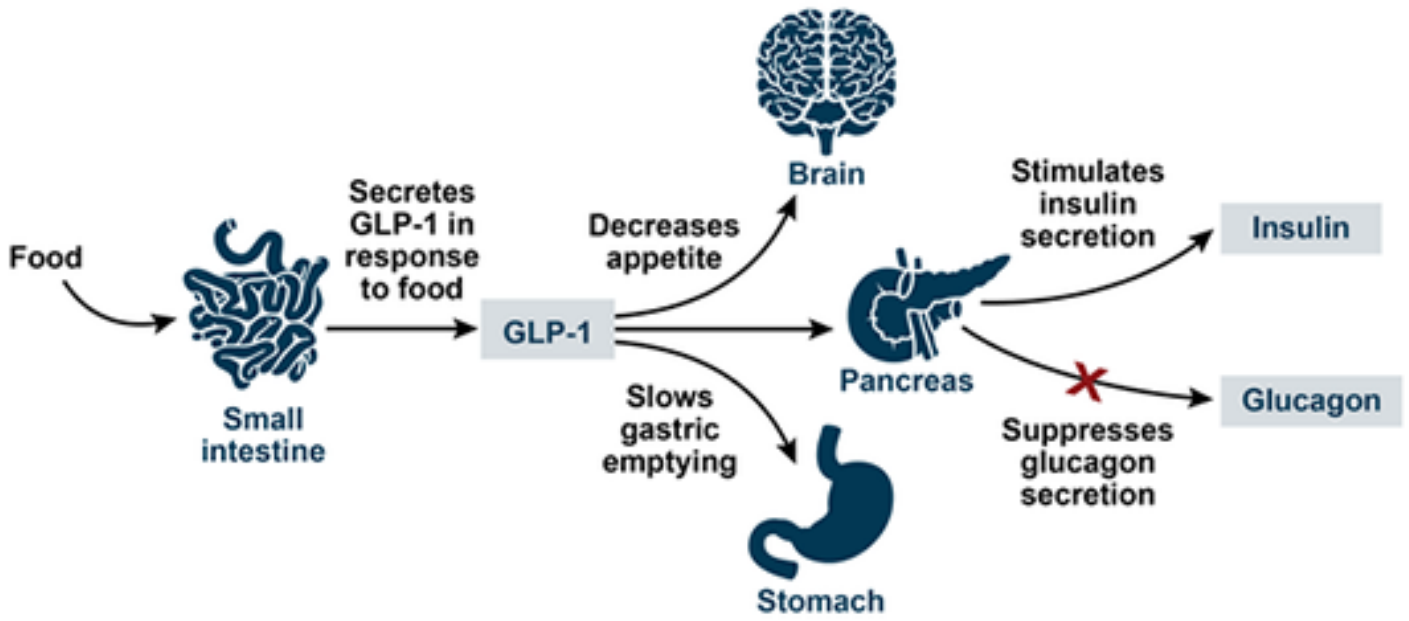
SGLT2 Inhibitors: Summary

- Positive Impact to HgA1c as well as positive effect on major cardiovascular events
- Potential for BP lowering and weight loss
- Positive effect on progression of nephropathy
- Fewer CHF hospitalizations
- Consider use in patients with T2DM with known cardiovascular disease or at high risk for cardiovascular disease, those who want to lose weight, and those who could benefit from lowered intravascular volume (HTN, CHF)
- Assess volume and renal status before beginning
- Use with caution in those with history of frequent mycotic infections or UTI's and assess symptoms frequently
- Consider baseline amputation risk factors before initiating canagliflozin in particular. Stress the importance of routine preventive foot care

Liraglutide: Mechanism of Action

- Glucagon-Like Peptide-1 activates the GLP-1 receptor on the surface membrane of pancreatic beta cells
- This leads to an increase in intracellular cAMP and leads to insulin release in the presence of elevated glucose concentrations
- Also decreases glucagon secretion in a glucose- dependent manner
- Slows gastric emptying
- Liraglutide is a receptor agonist or mimetic of Glucagon-Like Peptide-1

GLP-1 RAs
Mechanism of Action



Meier JJ. *Nat Rev Endocrinol*. 2012;8:728-742.

Liraglutide:
Benefits/ Indications for Use

- Lower BG and HgA1c levels
- Improved Cardiovascular outcomes
- Reduction in risk of progression of nephropathy
- Potential for weight loss

Liraglutide: Potential Adverse Reactions

- GI symptoms including nausea, vomiting, diarrhea, dyspepsia, and decreased appetite
- Acute gallbladder disease
- Hypoglycemia with insulin or insulin secretagogues
- Injection site reactions
- Hypersensitivity
- Potential for malignant thyroid c-cell tumors (seen in rats and mice).

  Contraindicated in patients with personal history of medullary thyroid carcinoma or in patients with a personal or family history of MEN 2
- Potential for Pancreatitis, including fatal and nonfatal hemorrhagic and necrotizing pancreatitis

Liraglutide: Summary

- Positive impact on blood glucose and HgA1c levels
- Positive cardiovascular impact
- Potential for decreased risk of nephropathy progression
- Potential for weight loss
- Consider use in patients with T2DM that have, or are at high risk for cardiovascular disease, and those that may want to lose weight, and do not mind/ are capable of giving self injections
- Contraindicated in patients with personal or family history of medullary thyroid cancer or MEN 2
- Use with caution in patients with history of, or at risk for pancreatitis or biliary disease
- Use with caution in patients with known gastroparesis


"We combined all your medications into ONE convenient dose."
NICKEL