Cardiovascular Benefits of Diabetes Medications

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Learning Objectives

- 1. Examine the link between diabetes and cardiovascular disease
- 2. Identify the classes of diabetes medications that offer cardiovascular benefits
- 3. Determine the mechanism of action of medications that reduce cardiovascular risk

"My cardiologist said to me, diabetes is heart disease"

Larry King

Diagnosed with Type 2 Diabetes in 1995

Introduction & History

- Early 2008 and before
  - Primary focus was glycemic control
  - Concerns were growing regarding Cardiovascular safety of the (then) newer diabetes medications
    - Rosiglitazone → → → Pioglitazone

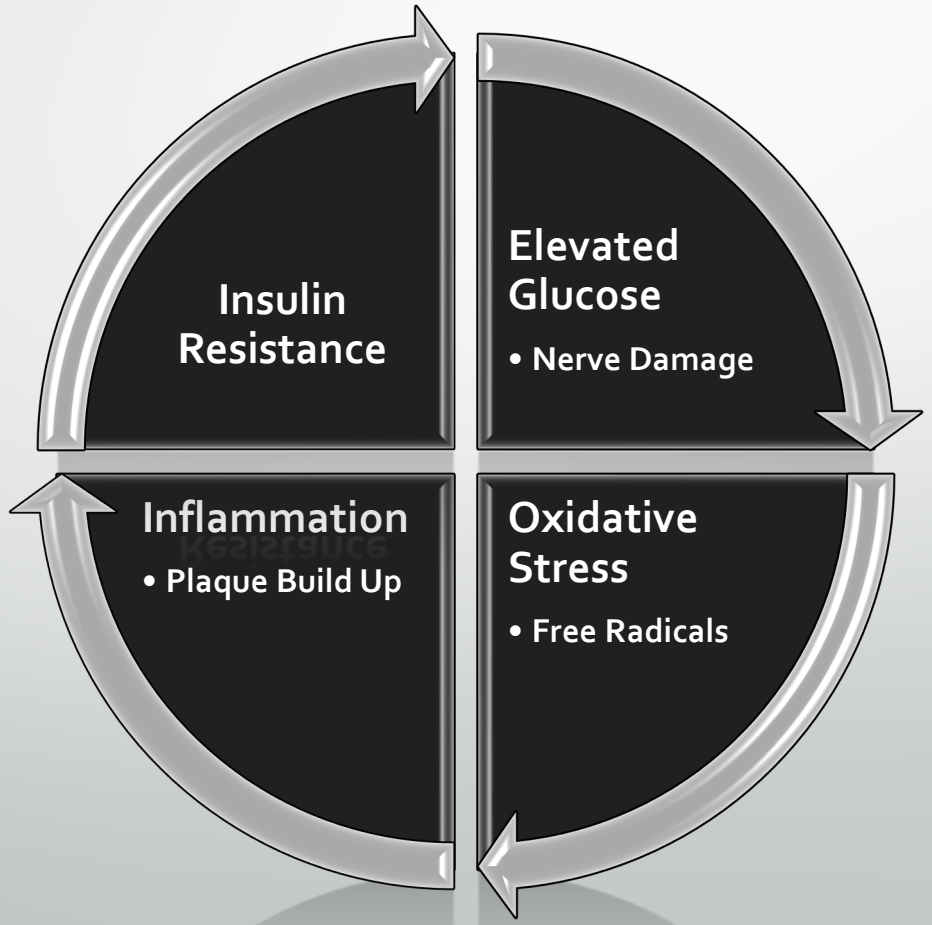
Introduction & History

- Late 2008
  - FDA mandated Cardiovascular Outcome Trials (CVOTs) for any new medication for Type 2 diabetes
- Discovery
  - 2 novel drug classes were found not only to be safe but provided cardiovascular and renal protection

The Cardiovascular-(renal)-Diabetes Connection

- Cardiovascular disease is main cause of mortality and morbidity in people with diabetes
  - Vascular damage → Atherosclerosis
  - Blood Pressure
  - Cholesterol
  - Nerve Damage
  - Kidney Disease

The Cardiovascular-(renal)-Diabetes Connection



The Cardiovascular-(renal)-Diabetes Connection

- A complicated relationship that is intermingled with one another
- Combined risk factor management may be a better option than traditional individual risk factor management
  - BP
  - Lipids
  - Blood Glucose
  - Renal Function

The Main Characters

- Sodium-glucose cotransporter 2 (SGLT2) inhibitors
  - Empagliflozin, dapagliflozin, canagliflozin, etc…
- Block the SGLT-2 transporter in the kidneys
  - Reduces glucose and sodium reabsorption in the proximal tubule
    - Glucosuria, weight loss, blood pressure reduction
- Reduction in heart failure hospitalization and CV death regardless of diabetes status
- Slow the progression of chronic kidney disease

The Main Characters

- SGLT2i effects
  - Hemodynamic
    - Diuresis/natriuresis reduce plasma volume and blood pressure
      - Lower cardiac pre/after load
  - Cardiac
    - Inhibits sodium/hydrogen exchanger which lower intracellular calcium
      - Prevents calcium overload → which can lead to arrhythmias
    - Heart Failure
      - Major reduction in hospitalizations

The Main Characters

- SGLT2i effects
  - Renal
    - Lower intraglomerular pressure via complex tubuloglomerular feedback system
  - Inflammation
    - Reduce inflammation and slow atherosclerosis
    - Reduce oxidative stress (free radicals)

The Main Characters (example)

- Empagliflozin
  - 10 mg daily
    - Myocardial infarction, CKD, Heart Failure, T2DM
  - 25 mg daily
    - T2DM – after starting the 10 mg tablet

The Main Characters (example)

- Empagliflozin
  - Adjustments
    - Glucose lowering decreases as renal function declines
      - ~GFR 30
    - Cardio and Renal protection remain with declining GFR
    - Currently no hepatic adjustments needed
      - Caution with severe hepatic impairment

The Main Characters (example)

- Empagliflozin
  - Clinical Pearls
    - Volume Depletion
    - Ketoacidosis
    - Genitourinary Infections

The Main Characters

- Glucagon-like peptide-1 (GLP-1) Receptor Agonists
  - Liraglutide, semaglutide, dulaglutide
- Mimics a gut hormone that enhances glucose dependent insulin secretion
  - Suppresses glucagon & slows gastric emptying
- Reduction in major adverse cardiovascular events
  - Reduction in ischemic events

The Main Characters

- GLP-1 Receptor Agonists effects
  - Metabolic
    - Weight loss through appetite suppression and delayed gastric emptying
    - Improved glycemic control
  - Renal
    - Slow decline of renal function in CKD

The Main Characters

- GLP-1 Receptor Agonists effects
  - Heart Failure (HFpEF) in obesity
    - Reduced hospitalization
    - Reduced all-cause mortality
    - Linked to reduced loop diuretics and improved walking distance

The Main Characters (example)

- Semaglutide
  - 0.25 mg – 2.4 mg subcutaneous titration
    - CKD, CVD, Obesity, T2DM, MASH, MASLD
  - Adjustments
    - No renal or hepatic adjustments

The Main Characters (example)

- Semaglutide
  - Clinical Pearls
    - Hypoglycemia: higher risk when used in combination with insulin or a sulfonylurea
    - Pancreatitis
    - Gastrointestinal (GI) Side Effects
      - Nausea, vomiting, diarrhea, constipation

The Main Characters (example)

- Semaglutide
  - Managing GI effects
    - Smaller meals, stop eating sooner, digestive enzymes
    - Microdosing

The Data (overview)

SGLT2 Inhibitor	
Major Adverse CV Events	↓
CV Death	↓↓
HF Hospitalizations	↓↓↓
Stroke	↔
Renal Composite	↓↓↓

GLP-1 Receptor Agonist	
Major Adverse CV Events	↓↓
CV Death	↓↓
HF Hospitalizations	↓
Stroke	↓↓
Renal Composite	↔

EMPA-REG, DAPA-HF, LEADER, SUSTAIN-6, SELECT, FLOW

Precautions

- SLGT2 inhibitor
  - Genital mycotic infections
    - glucosuria
  - Volume depletion
    - Hypotension
  - Euglycemic Diabetic Ketoacidosis
- Glp-1 Receptor Agonist
  - GI effects
    - Nausea, Vomiting, Diarrhea
  - Weight Loss
    - Appetite suppression
  - Delayed Gastric Emptying

What about the supporting cast?

Metformin

Sulfonylureas

Thiazolidinedione

Dipeptidyl Peptidase-4 Inhibitors

Supporting Cast

Thiazolidinediones

- Pioglitzaone/Rosiglitazone
  - Specific benefits but significant risks
  - Anti-atherosclerotic effects
  - Improved lipid profile
  - Fluid retention can exacerbate/precipitate heart failure

Sulfonylureas

- Neutral or increased risk for cardiovascular effects
- Risk of hypoglycemia
  - Which can lead to adverse cardiovascular events
- Some agents may interfere with the body's protective mechanisms during ischemia

Supporting Cast

Metformin

- Mixed results regarding cardiovascular benefit
- Workhorse of diabetes management for decades
- Its pleotropic effects were thought to drive its CV benefit
  - Improved lipids, anti-inflammation, etc…
- It is still considered to have a favorable cardiovascular profile

Dipeptidyl Peptidase-4 Inhibitors

- Neutral for cardiovascular effects
  - Saxagliptin may have an increased risk
- Alternative for those who can't tolerate newer agents
- Add on agent to metformin gives a better safety profile vs other agents

Metformin + GLP-1 Agonist

Journal of Diabetes, Obesity, and Metabolism

Synergistic associations of metformin and GLP-1 receptor agonist use with adiposity-related cancer incidence in people living with type 2 diabetes

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Abstract

Background: Metformin and glucagon-like peptide-1 receptor agonists (GLP-1 RAs) may reduce the risk of adiposity-related cancers in patients with type 2 diabetes (T2D). The potential synergistic effects of these treatments on cancer incidence remain unclear, considering their distinct biological mechanisms and their associated effects on body weight.

Methods: A retrospective cohort analysis was conducted using a large global database (TriNetX) of patients with T2D. Three cohorts: single agent use with metformin or GLP-1 RAs, and dual/combination metformin/GLP-1 RA use, were compared with a reference group treated with DPP4 inhibitors (DPP4i). Propensity score matching (1:1) was applied to control for confounders. Cancer incidence and all cause mortality were assessed over 5 years of follow up.

Results: After matching, metformin and GLP-1 RA treatment were both associated with a lower risk of all adiposity-related cancers and all-cause mortality; the latter was associated with greater reductions in both. Cancer rates were (hazard ratio) 0.96 [95% CI 0.92, 0.99] and 0.86 [0.82, 0.89], while mortality rates were 0.78 [0.76, 0.80] and 0.61 [0.59, 0.63] for metformin and GLP-1 RA, respectively. Dual therapy showed the strongest association with lower cancer incidence (0.61 [0.57, 0.65]) and mortality (0.33 [0.32, 0.35]). Results were more significant in younger, male patients with obesity.

Conclusion: In patients with T2D, dual metformin and GLP-1 RA treatment was associated with a 39% lower incidence of adiposity-related cancers and a 67% lower mortality, with a striking impact on cancer-related outcomes.

KEYWORDS
cohort study, GLP-1 analogue, metformin, real-world evidence, type 2 diabetes

Overview

- Newer class of medications provide their own unique cardiovascular benefits
- Patient characteristics may determine using one over another
  - However you may choose to use together
- Older classes of medication use may wane as we move forward into the future

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Renal Composite	↔

Future Considerations

- GLP-1/Gastric Inhibitory polypeptide (GIP) agonist
  - 2025 Scientific Sessions (vs semaglutide in patients with CKD and HF)
    - Greater weight loss and improvement in insulin sensitivity
    - Greater reduction in all-cause mortality, ischemic stroke, and myocardial infarction
  - Long-term data is still coming as these are newer agents

Future Considerations

- Triple agonist
  - GLP-1/GIP/Glucagon
    - TRIUMPH-4 clinical trials
      - Weight loss of greater than 30%
      - Reduction in pain with osteoarthritis
      - Reduced Non-HDL cholesterol, Triglycerides, and Blood Pressure

Future Considerations

- With new agents on the horizon, guidelines may shift in their recommendations
- Focus may shift to a Cardiovascular-Kidney-Metabolic (CKM) approach vs a fragmented approach to each disease state

Case Study 1

- AB is a 68 year-old male with Type 2 diabetes mellitus, hypertension, and HFrEF. He is currently taking metformin 1000mg twice daily, lisinopril 20mg daily, and metoprolol succinate 100mg daily. His A1c is 7.5% with normal renal function.
- What class of medication should be added? Why?

Case Study 1

- SGLT2 Inhibitor
  - Major reduction in heart failure hospitalizations

Case Study 2

- CD is a 55 year-old female with Type 2 diabetes mellitus, obesity, history of a myocardial infarction (10 months ago), and an A1c 9%.
- What class of medication should be added? Why?

Case Study 2

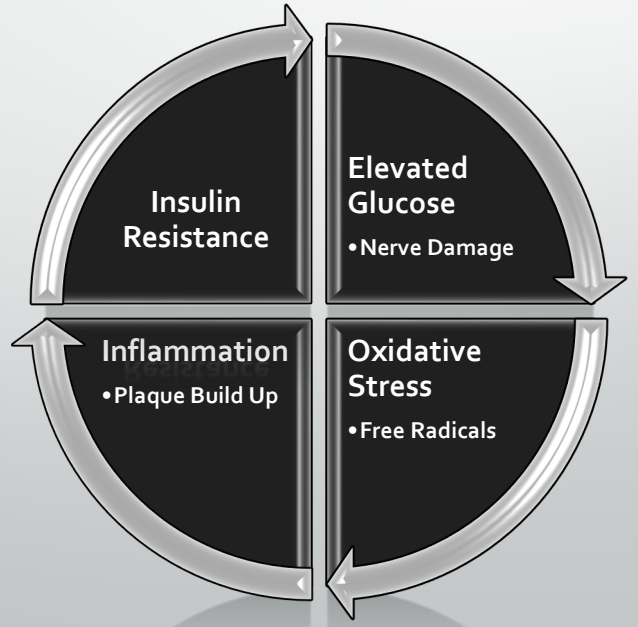
- GLP-1 Receptor Agonist
  - MACE reduction, weight loss

Clinical Pearls

- SGLT2 Inhibitor
  - Dose adjustment with reduced renal function
    - ~20-30 GFR
  - Reduction in BP may require adjustments with concurrent BP medications
  - Don't discredit s/sx of DKA even if lab values show normal glycemia
- GLP-1 Receptor Agonist
  - Weight loss can have huge implications on other disease states
  - Closer follow up of other co-morbidities is warranted if greater than 10% weight loss is achieved
  - Consider digestive enzymes to help mitigate GI side effects

Learning Objectives

- 1. Examine the link between diabetes and cardiovascular disease



Learning Objectives

- 1. Identify the classes of diabetes medications that offer cardiovascular benefits
  - SGLT2 Inhibitors
  - GLP-1 Receptor Agonist

Learning Objectives

- 3. Determine the mechanism of action of medications that reduce cardiovascular risk
  - SGLT2 Inhibitor
    - Reduces glucose and sodium reabsorption in the proximal tubule
  - GLP-1 Receptor Agonist
    - Mimics a gut hormone that enhances glucose dependent insulin secretion

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