Cardiovascular Risk Management in Diabetes: Role of the Cardiovascular Clinician

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Disclosures

- Advisory board participation
  - Akcea, Amgen, Sanofi Regeneron
Objectives

- Implement the changing paradigm for CV clinicians in risk reduction in patients with ASCVD and diabetes
- Understand the approach to selection of new therapies with proven CV outcomes benefits
- Consider practical strategies for collaborative and multidisciplinary management of patients with diabetes
The Changing Paradigm

• Evidence of significant reduction in major adverse CV events with SGLT2 inhibitors and GLP1-RAs has triggered a major paradigm shift

Glucose Control → Comprehensive CV Risk Reduction

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SGLT2i and GLP1-RA in CV Risk Reduction

**Primary Endpoints**

**CVD/HHF**
- 4.9% vs 5.8%
- HR 0.83 (0.73-0.95)
- P(Superiority) 0.005

**MACE**
- 8.8% vs 9.4%
- HR 0.93 (0.84-1.03)
- P(Noninferiority) <0.001
- P(Superiority) 0.17

**Table 1** Summary of Key Findings of the 3 Positive CVOTs Implicated in CV Benefits

<table>
<thead>
<tr>
<th><strong>EMPA-REG OUTCOME</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Agent</strong></td>
</tr>
<tr>
<td><strong>Inclusion criteria</strong></td>
</tr>
<tr>
<td><strong>Duration of trial</strong></td>
</tr>
<tr>
<td><strong>Baseline HbA1c</strong></td>
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<tr>
<td><strong>Primary endpoint</strong></td>
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<tr>
<td><strong>CV death</strong></td>
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<tr>
<td><strong>MI</strong></td>
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<tr>
<td><strong>Stroke</strong></td>
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<tr>
<td><strong>HF hospitalization</strong></td>
</tr>
<tr>
<td><strong>Noteworthy adverse effects</strong></td>
</tr>
<tr>
<td><strong>Likely broad mechanisms of benefit</strong></td>
</tr>
</tbody>
</table>

**Graphs**

- **CVD/HHF**
- **MACE**

**Legend**
- Dapagliflozin
- Placebo

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Changing paradigm and role of CV clinicians

• Scientific evidence of CV outcomes benefits
  – SGLT2 inhibitors and GLP1-RAs

• Principles for selection, dosing, titration, potential adverse effects, and monitoring of therapy

• Care model that works best within the context of clinician’s practice

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SGLT2 INHIBITORS IN CV RISK REDUCTION
SGLT2 Inhibitors: Mechanism and Effects

- Inhibition of sodium-glucose transporter in proximal tubule
  - Responsible for 90% of urinary glucose reabsorption
  - Glucosuria
    - More pronounced in hyperglycemia
    - Diminishes as blood glucose normalizes
    - Risk of hypoglycemia is low
  - Modest diuretic and natriuretic effects
  - Weight loss
  - Lowering of systolic blood pressure

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SGLT2 Inhibitors: FDA Approved indications in the U.S.

- **Empagliflozin**
  - To reduce the risk of cardiovascular *death* in adult patients with type 2 diabetes mellitus and established cardiovascular disease

- **Canagliflozin**
  - To reduce the risk of major adverse cardiovascular events in adults with type 2 diabetes mellitus and established cardiovascular disease

- **Dapagliflozin, ertugliflozin** indicated only for glycemic control
  - DECLARE trial results presented at AHA

https://docs.boehringer-ingelheim.com/Prescribing%20Information/PIs/Jardiance/jardiance.pdf
SGLT2 Inhibitors: Dosing

• Empagliflozin
  – 10 or 25 mg daily orally
  – Avoid in severe renal impairment

• Canagliflozin
  – 100 to 300 mg daily orally
  – Dose adjust or avoid with moderate to severe renal impairment

• For both agents
  – CV outcomes benefits similar for CV event reduction
  – Dose titration is not indicated for CV event reduction

https://docs.boehringer-ingelheim.com/Prescribing%20Information/PIs/Jardiance/jardiance.pdf
SGLT2 Inhibitors: Adverse Effects

- May cause intravascular volume contraction
- Hypoglycemia risk with insulin or insulin secretagogues (SUs)
  - Reduce dose of insulin, insulin secretagogues
- Genital infections (treatable, seldom recur)
- Euglycemic ketoacidosis in vulnerable patients

- Canagliflozin
  - Increased incidence of bone fractures
  - BLACK BOX WARNING:

  **WARNING: LOWER LIMB AMPUTATION**
  See full prescribing information for complete boxed warning.
  - In patients with type 2 diabetes who have established cardiovascular disease (CVD) or at risk for CVD, INVOKANA has been associated with lower limb amputations, most frequently of the toe and midfoot; some also involved the leg. (5.1)
  - Before initiating, consider factors that may increase the risk of amputation. Monitor patients receiving INVOKANA for infections or ulcers of the lower limbs, and discontinue if these occur. (5.1)

- DECLARE trial: no signal for limb ischemia/amputation

GLP2-RAs IN CV RISK REDUCTION
GLP1-RAs: Mechanism and Effects

- GLP1 is a peptide hormone released from the small intestine after oral nutrient intake
  - Increases insulin secretion
  - Decreases glucagon
  - Slows gastric emptying
- Lead to satiety, weight loss
- Longer acting agents (liraglutide, semaglutide) appear more likely to have ASCVD benefit

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GLP1-RAs: FDA Approved Indications in U.S.

• Liraglutide
  – To reduce the risk of major adverse cardiovascular events in adults with type 2 diabetes mellitus and established cardiovascular disease

• Semaglutide, lixisenatide, exenatide, dulaglutide
  – Do not have CV reduction indication
  – Glycemic control only

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GLP1-RA: Dosing

- Liraglutide
  - Initiate 0.6 mg subcutaneously daily in arm, thigh, abdomen
  - Uptitrate slowly to prevent nausea, vomiting
  - No dose adjustment with renal or hepatic impairment
GLP1-RAs: Adverse Effects

- Injection site reactions
- Nausea and vomiting
  - Transient, mitigate by gradual dose escalation, reduced meal size
- Gall bladder disease, cholecystitis
- Risk of hypoglycemia if used with insulin or insulin secretagogues
- Avoid in ESRD
- Semaglutide: higher risk of progression of proliferative retinopathy

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CONSIDERATIONS IN SELECTION OF AGENTS FOR CV RISK REDUCTION IN DIABETES
**CENTRAL ILLUSTRATION:** Novel Paradigm for Care of the Patient With CV Disease and T2DM

Patient with established cardiovascular (CV) disease but **no prior** Type 2 diabetes mellitus (T2DM): Cardiologist to perform routine, systematic measurement of HbA1c to evaluate presence of T2DM

And/or

Eligible patients with CV disease **and prior** T2DM

Consider recommending treatments if no contraindication:

- **SGLT2 inhibitor:** empagliflozin
  - Decreased CV mortality and decreased heart failure hospitalizations
  - Decreased blood glucose
  - Promotes weight loss
  - Renal benefits

- **GLP-1 receptor agonist:** liraglutide
  - Decreased CV mortality
  - Decreased blood glucose
  - Promotes weight loss
  - Potential renal benefits

Refer to primary care physician or endocrinologist
Follow CV and T2DM progress in tandem

Considerations in Selection of SGLT2i or GLP1-RA for CV Risk Reduction in ASCVD/diabetes

• SGLT2i
  – Consider alternate agent if:
    • eGFR <45 ml/min/1.73 m²
    • History of amputation, severe PAD, foot ulcers, severe neuropathy (canagliflozin only)
    • History of recurrent genital fungal infections
    • History of DKA

• GLP1-RA
  – Consider alternate agent if:
    • Uncontrollable nausea at low doses
    • Unwilling to discontinue DPP4 inhibitor
    • History of pancreatitis
    • History of gastroparesis
    • History of MEN2 or medullary thyroid cancer
    • Proliferative retinopathy (semaglutide only)

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Systems of Care in ASCVD and Diabetes for Optimal CV Risk Reduction

- CV specialists take ownership of therapies with CV outcomes benefits
- Requires a shift in focus for CV clinicians from glycemic control to CV risk reduction
Systems of Care in ASCVD and Diabetes for Optimal CV Risk Reduction

• Consultative Approach
• Comprehensive Team Approach
  – Similar to organ transplant or HIV care team models
Summary

• Current evidence demands a change in paradigm for how CV clinicians approach care of patients with ASCVD and diabetes
• Benefits of SGLT2i and GLP1-RAs are independent of effects on A1c
• Stay tuned for 2018 ACC Expert Consensus Decision Pathway on Novel Therapies for CV Risk Reduction in Patients with Type 2 Diabetes!
  • Practical guidance for CV clinicians
  • Publication date: November 26th
THANK YOU!