Antihyperglycemic Therapy in Type 2 Diabetes: What's Guiding Pharmacotherapy Choice?
Zach Weber, PharmD, BCPS, BCACP, CDE

Live Activity Handout
2 slides per page
Antihyperglycemic Therapy in Type 2 Diabetes:
What's Guiding Pharmacotherapy Choice?

ACTIVITY DESCRIPTION
Diabetes treatment options continue to expand. While this allows providers to have a larger armamentarium for treatment, questions still remain about the best option(s) to use in certain patients. Clinical inertia related to progressive diabetes management also exists for many patients and providers, making successful glycemic control even more difficult. This program will provide an overview of strategies used for recognizing and overcoming clinical inertia. It will also provide an overview of commonly used diabetes treatment options, and focus on which options are best for certain patients.

30 days following this live webinar, participants will be invited to participate in a 30-minute follow-up home study (0.5 credit hour) that will provide the opportunity to review the main concepts from the webinar and apply what has been learned to patient cases related to diabetes treatment options.

TARGET AUDIENCE
The target audience for this activity is pharmacists, pharmacy technicians, and nurses in hospital, community, and retail pharmacy settings.

LEARNING OBJECTIVES
After completing this activity, the pharmacist will be able to:
- Explain the effect clinical inertia can have on the management of diabetes mellitus
- Identify clinical situations appropriate for early initiation of adjunct diabetes treatment options
- Compare key medication - and disease-specific considerations for selecting adjunct diabetes treatments
- Examine benefits incurred with the early initiation of adjunct diabetes treatments
- Identify patients who could benefit from sodium glucose cotransporter 2 (SGLT2) inhibitors

After completing this activity, the pharmacy technician will be able to:
- Explain the effect clinical inertia can have on the management of diabetes mellitus
- Identify clinical situations appropriate for early initiation of adjunct diabetes treatment options
- Compare key medication - and disease-specific considerations for selecting adjunct diabetes treatments
- Examine benefits incurred with the early initiation of adjunct diabetes treatments
- Identify patients who could benefit from sodium glucose cotransporter 2 (SGLT2) inhibitors

ACREDITATION
Pharmacy
PharmCon, Inc. is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education.

Nursing
PharmCon, Inc. is approved by the California Board of Registered Nursing (Provider Number CEP 13649) and the Florida Board of Nursing (Provider Number 50-3515). Activities approved by the CA BRN and the FL BN are accepted by most State Boards of Nursing.

CE hours provided by PharmCon, Inc. meet the ANCC criteria for formally approved continuing education hours. The ACPE is listed by the AANP as an acceptable, accredited continuing education organization for applicants seeking renewal through continuing education credit. For additional information, please visit: http://www.nursecredentialing.org/RenewalRequirements.aspx

Universal Activity No.: 0798-0000-18-098-L0
Credits: 1.5 contact hour (0.5 CEU)

Release Date: 6/28/2018
freeCE Expiration Date: 6/28/2021
ACPE Expiration Date: 6/28/2021

ACTIVITY TYPE
Knowledge-Based Live Webinar

FINANCIAL SUPPORT BY
Merck & Co., Inc
ABOUT THE AUTHOR
Zach Weber, PharmD, BCPS, BCACP, CDE is a Clinical Associate Professor of Pharmacy Practice for Purdue University College of Pharmacy, an Adjunct Associate Professor of Medicine for Indiana University School of Medicine, and an Ambulatory Care Clinical Pharmacy Specialist for Eskenazi Health in Indianapolis, IN. He received his PharmD degree from Purdue University and completed a PGY1 Pharmacy Practice residency at the Roudebush VA Medical Center in Indianapolis, IN followed by a PGY2 Ambulatory Care Specialty residency at Duke University Hospital in Durham, NC. His practice for Eskenazi Health involves the provision of collaborative drug therapy management services for primary care and endocrinology specialty practices. Dr. Weber’s research interests relate to pharmacist-run chronic disease management services within ambulatory care clinics. His focus is on chronic metabolic and cardiovascular disease, with specific emphasis on expanding ambulatory care pharmacy services.

FACULTY DISCLOSURE
It is the policy of PharmCon, Inc. to require the disclosure of the existence of any significant financial interest or any other relationship a faculty member or a sponsor has with the manufacturer of any commercial product(s) and/or service(s) discussed in an educational activity. Zach Weber reports no actual or potential conflict of interest in relation to this activity.

Peer review of the material in this CE activity was conducted to assess and resolve potential conflict of interest. Reviewers unanimously found that the activity is fair balanced and lacks commercial bias.

Please Note: PharmCon, Inc. does not view the existence of relationships as an implication of bias or that the value of the material is decreased. The content of the activity was planned to be balanced and objective. Occasionally, faculty may express opinions that represent their own viewpoint. Participants have an implied responsibility to use the newly acquired information to enhance patient outcomes and their own professional development. The information presented in this activity is not intended as a substitute for the participant’s own research, or for the participant’s own professional judgement or advice for a specific problem or situation. Conclusions drawn by participants should be derived from objective analysis of scientific data presented from this activity and other unrelated sources.

Neither freeCE/PharmCon nor any content provider intends to or should be considered to be rendering medical, pharmaceutical, or other professional advice. While freeCE/PharmCon and its content providers have exercised care in providing information, no guarantee of its accuracy, timeliness or applicability can be or is made. You assume all risks and responsibilities with respect to any decisions or advice made or given as a result of the use of the content of this activity.
Faculty: Zach Weber, PharmD, BCPS, BCACP, CDE

Antihyperglycemic Therapy in Type 2 Diabetes: What's Guiding Pharmacotherapy Choice?

Learning Objectives

1. Explain the effect clinical inertia can have on the management of diabetes mellitus
2. Identify clinical situations appropriate for early initiation of adjunct diabetes treatment options
3. Compare key medication- and disease-specific considerations for selecting adjunct diabetes treatments
4. Examine benefits incurred with the early initiation of adjunct diabetes treatments
5. Identify patients who could benefit from sodium-glucose cotransporter-2 (SGLT2) inhibitors
Clinical Inertia

“Lack of treatment intensification in a patient not at evidence-based goals of care”

Medical Errors in Chronic Disease Care

Inappropriate use or misuse

Clinical Inertia

“Lack of treatment intensification in a patient not at evidence-based goals of care”

Medical Errors in Chronic Disease Care

Inappropriate use or misuse

Underuse of efficacious therapy

Clinical Inertia

“Lack of treatment intensification in a patient not at evidence-based goals of care”

Medical Errors in Chronic Disease Care

Inappropriate use or misuse

Underuse of efficacious therapy

Adverse Events

Minutes to Hours

Years to Decades

Operationalizing Clinical Inertia

- Requirements
  1. Patient fails to achieve major evidence-based clinical goals
  2. Patient fails to receive appropriate intensification of pharmacotherapy in a defined period of time

- Decisions
  1. Clinical goals selected
  2. Therapy defined (in a way that can be measured)
  3. Time window within which intensification is considered timely
Clinical Inertia Example - Diabetes

Is patient < 80 years old?

- NO
  - Exclude

- YES
  - Is A1c < 7%
    - NO
      - A1c 7-11%
        - Has an appropriate drug move been made within 4 months?
          - YES
            - Adequate Glucose Therapy
          - NO
            - A1c >11%
              - Added insulin, or 2 or more drug moves in the last 4 months?
                - YES
                  - Adequate Glucose Therapy
                - NO
                  - Clinical Inertia

Costs of Clinical Inertia

For Every 20 Adults with Type 2 Diabetes

- A1c 1% over goal of 7%
- LDL 30 mg/dL above goal
- SPB 10 mmHg above 150 mmHg

1 avertable microvascular outcome over 5 years
1 excess myocardial infarction or stroke

AND

1 avertable microvascular outcome over 5 years


Costs of Clinical Inertia

For Every 20 Adults with Type 2 Diabetes

- A1c 1% over goal of 7%
- LDL 30 mg/dL above goal
- SPB 10 mmHg above 150 mmHg

1 avertable microvascular outcome over 5 years
1 excess myocardial infarction or stroke

AND

1 avertable microvascular outcome over 5 years

At best: 20% of patients with A1c, SBP, and LDL at goal

- Thousands of ADRs
- Billions in expenditures
- Excess deaths

# Clinical Inertia – Contributing Factors

<table>
<thead>
<tr>
<th>Physician Factors (50%)</th>
<th>Patient Factors (30%)</th>
<th>System Factors (20%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Goal setting pathologies</td>
<td>• Deny having the disease</td>
<td>• No clinical guideline</td>
</tr>
<tr>
<td>• Fail to initiate treatment</td>
<td>• Believe disease is not serious</td>
<td>• No disease registry</td>
</tr>
<tr>
<td>• Fail to titrate treatment until goal is achieved</td>
<td>• Low health literacy</td>
<td>• No visit planning</td>
</tr>
<tr>
<td>• Fail to identify and manage comorbid conditions (e.g. depression)</td>
<td>• Cost of medication</td>
<td>• No active outreach</td>
</tr>
<tr>
<td>• Patient &quot;hijacks&quot; clinical encounter</td>
<td>• Too many medications</td>
<td>• No decision support</td>
</tr>
<tr>
<td>• Insufficient time</td>
<td>• Medication side effects</td>
<td>• No team approach to care</td>
</tr>
<tr>
<td>• Reactive vs. proactive care</td>
<td>• Poor communication with provider</td>
<td>• Poor communication between providers and staff</td>
</tr>
</tbody>
</table>


---

## Determining Diabetes Goals

**Clinical Inertia: Decisions**
1. **Clinical goals selected**
2. Therapy defined (in a way that can be measured)
3. Time window within which intensification is considered timely

**Goals:**
- A1c: < 7%
- Pre-prandial: 80-130 mg/dL
- Post-prandial: < 180 mg/dL

Determining Diabetes Goals

Clinical Inertia: Decisions
1. **Clinical goals selected**
2. Therapy defined (in a way that can be measured)
3. Time window within which intensification is considered timely

Goals:
- A1c: < 7%
- Pre-prandial: 80-130 mg/dL
- Post-prandial: < 180 mg/dL

<table>
<thead>
<tr>
<th>Patient/Disease Feature(s)</th>
<th>More Stringent ( \rightarrow ) A1c 7% ( \rightarrow ) Less Stringent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risks potentially associated with hypoglycemia and other adverse drug effects</td>
<td>Low ( \rightarrow ) High</td>
</tr>
<tr>
<td>Disease duration</td>
<td>Newly diagnosed ( \rightarrow ) Long-standing</td>
</tr>
<tr>
<td>Life expectancy</td>
<td>Long ( \rightarrow ) Short</td>
</tr>
<tr>
<td>Important comorbidities</td>
<td>Absent ( \rightarrow ) Severe</td>
</tr>
<tr>
<td>Established vascular complications</td>
<td>Absent ( \rightarrow ) Severe</td>
</tr>
<tr>
<td>Patient attitude and expected treatment efforts</td>
<td>Highly motivated ( \rightarrow ) High self-care abilities ( \rightarrow ) Less motivated ( \rightarrow ) Poor self-care abilities</td>
</tr>
<tr>
<td>Resources and support system</td>
<td>Readily available ( \rightarrow ) Limited</td>
</tr>
</tbody>
</table>


Evaluating Diabetes Treatments

Monotherapy: Lifestyle Management + Metformin*
- Initiate metformin if no contraindications
  - A1c at target after 3 months?
    - 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 CV events and mortality
  - No: add agent based on drug and patient-specific factors
  - A1c at target after 3 months?
    - 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– and patient-specific factors

*: A1c < 9% at diagnosis – consider monotherapy
^: A1c ≥ 9% at diagnosis – consider dual therapy

Diabetes Care 2018 Jan; 41(Supplement 1)
Diabetes Treatment Options

<table>
<thead>
<tr>
<th>Biguanides</th>
<th>Sulfonylureas (SU)</th>
<th>Meglitinides</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thiazolidinediones (TZDs)</td>
<td>α-glucosidase inhibitors</td>
<td>DPP-4 inhibitors</td>
</tr>
<tr>
<td>Bile acid sequestrants</td>
<td>Dopamine-2 agonists</td>
<td>SGLT2 inhibitors</td>
</tr>
<tr>
<td>GLP-1 receptor agonists</td>
<td>Amylin mimetics</td>
<td>Insulin</td>
</tr>
</tbody>
</table>

DPP-4: dipeptidyl peptidase 4
SGLT2: sodium-glucose co-transporter 2
GLP-1: glucagon-like peptide

Choosing Diabetes Treatment – MOA

<table>
<thead>
<tr>
<th>Biguanides:</th>
<th>Sulfonylureas (SU):</th>
<th>Meglitinides:</th>
</tr>
</thead>
<tbody>
<tr>
<td>↓ hepatic glucose production</td>
<td>↑ insulin secretion</td>
<td>↑ insulin secretion</td>
</tr>
<tr>
<td>Thiazolidinediones (TZDs):</td>
<td>α-glucosidase inhibitors:</td>
<td>DPP-4 inhibitors:</td>
</tr>
<tr>
<td>↓ insulin sensitivity</td>
<td>slow carbohydrate absorption/digestion</td>
<td>↑ insulin secretion ↓ glucagon secretion Delay gastric emptying Promote satiety</td>
</tr>
<tr>
<td>Bile acid sequestrants: unclear MOA</td>
<td>Dopamine-2 agonists: modulate hypothalamic metabolism</td>
<td>SGLT2 inhibitors: block glucose reabsorption</td>
</tr>
<tr>
<td>GLP-1 receptor agonists: same as DPP-4 inhibitors</td>
<td>Amylin mimetics:</td>
<td>Insulin:</td>
</tr>
<tr>
<td></td>
<td>↓ glucagon secretion Delay gastric emptying Promote satiety</td>
<td>↑ glucose disposal ↓ hepatic glucose production</td>
</tr>
</tbody>
</table>
Choosing Diabetes Treatment – Hierarchy

- Metformin
- Sulfonylurea
- TZD
- DPP-4 Inhibitor
- SGLT-2 Inhibitor
- GLP-1 Agonist
- Basal Insulin
- Combination of Above Options

Choosing Diabetes Treatment – Comparing Key Properties

- Metformin
- Sulfonylurea
- TZD
- DPP-4 Inhibitor
- SGLT-2 Inhibitor
- GLP-1 Agonist
- Basal Insulin

- Efficacy
- Hypo risk
- Weight
Choosing Diabetes Treatment – Comparing Key Properties

Metformin

- Sulfonylurea
  - Efficacy: High
  - Hypo risk: Moderate
  - Weight: High

- TZD
  - Efficacy: High
  - Hypo risk: Moderate
  - Weight: Low

- DPP-4 Inhibitor
  - Efficacy: Moderate
  - Hypo risk: Low
  - Weight: Low

- SGLT-2 Inhibitor
  - Efficacy: Moderate
  - Hypo risk: Low
  - Weight: Low

- GLP-1 Agonist
  - Efficacy: High
  - Hypo risk: High
  - Weight: High

- Basal Insulin
  - Efficacy: Highest
  - Hypo risk: High
  - Weight: High

Diabetes Care 2015 Jan; 38(1): 140-149
Choosing Diabetes Treatment – Comparing Key Properties

- **Metformin**
  - **Sulfonylurea**
    - Efficacy: High
      - Hypo risk: Moderate
      - Weight: Gain
    - Hypoglycemia
    - Weight gain

- **TZD**
  - Efficacy: High
    - Hypo risk: Low
    - Weight: Gain

- **DPP-4 Inhibitor**
  - Efficacy: Moderate
    - Hypo risk: Low
    - Weight: Neutral

- **SGLT-2 Inhibitor**
  - Efficacy: Moderate
    - Hypo risk: Low
    - Weight: Loss

- **GLP-1 Agonist**
  - Efficacy: High
    - Hypo risk: Low
    - Weight: Loss

- **Basal Insulin**
  - Efficacy: Highest
    - Hypo risk: High
    - Weight: Gain

Choosing Diabetes Treatment – Notable Side Effects

- **Metformin**
  - Hypoglycemia
  - Nausea
  - B12 deficiency

- **Sulfonylurea**
  - Hypoglycemia
  - Weight gain

- **TZD**
  - Edema/fluid
  - Osteoporosis
  - Bladder ca. (Pio)
  - ↑ LDL (Rosi)

- **DPP-4 Inhibitor**
  - Pancreatitis
  - Joint pain

- **SGLT-2 Inhibitor**
  - UTI
  - ↓ volume
  - Hypotension
  - DKA
  - Bone fx. (Can)

- **GLP-1 Agonist**
  - GI SE
  - Injection site
  - Hypoglycemia
  - Injection site

- **Basal Insulin**
  - Hypoglycemia
  - Injection site
Choosing Diabetes Treatment – Significant Warnings

**Metformin**

- **Sulfonylurea**
  - Tolbutamide: ↑ CV risk

- **TZD**
  - BBW: CHF

- **DPP-4 Inhibitor**
  - BBW: amputation (Canagliflozin - Invokana)

- **SGLT-2 Inhibitor**
  - BBW: thyroid c-cell tumors (NOT exenatide BID - Byetta)

- **GLP-1 Agonist**
- **Basal Insulin**

BBW: Black Box Warning

Choosing Diabetes Treatment – Renal Considerations

**DKD: Diabetic Kidney Disease**

<table>
<thead>
<tr>
<th>Drug/Class</th>
<th>Progression of DKD</th>
<th>Dosing Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin</td>
<td>Neutral</td>
<td>CI: eGFR &lt; 30 mL/min</td>
</tr>
<tr>
<td>Sulfonylureas</td>
<td>Neutral</td>
<td>Glyburide: NOT recommended Others: initiate conservatively</td>
</tr>
<tr>
<td>TZDs</td>
<td>Neutral</td>
<td>No dose adjustment NOT recommended in dysfunction (risk of fluid accumulation)</td>
</tr>
<tr>
<td>DPP-4 Inhibitors</td>
<td>Neutral</td>
<td>Renal dose adjustment required (NOT Linagliptin- Tradjenta)</td>
</tr>
<tr>
<td>SGLT2 Inhibitors</td>
<td>Benefit: canagliflozin (Invokana), empagliflozin (Jardiance)</td>
<td>Not recommended eGFR &lt; 30-60 mL/min (depending on agent)</td>
</tr>
<tr>
<td>GLP-1 Agonists</td>
<td>Benefit: Liraglutide (Victoza)</td>
<td>Avoid eGFR &lt; 30 mL/min exenatide- (Byetta, Bydureon) and lixisenatide (Adlyxin) Increased SE risk in patients with renal impairment</td>
</tr>
<tr>
<td>Insulin</td>
<td>Neutral</td>
<td>Lower initial doses with reduced eGFR (accumulation risk)</td>
</tr>
</tbody>
</table>
Choosing Diabetes Treatment – Cardiovascular Considerations

<table>
<thead>
<tr>
<th>Drug/Class</th>
<th>ASCVD</th>
<th>CHF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin</td>
<td>Potential benefit</td>
<td>Neutral</td>
</tr>
<tr>
<td>Sulfonlureas</td>
<td>Neutral</td>
<td>Neutral</td>
</tr>
<tr>
<td>TZDs</td>
<td>Potential benefit: Pioglitazone (Actos)</td>
<td>Increased risk</td>
</tr>
<tr>
<td>DPP-4 Inhibitors</td>
<td>Neutral</td>
<td>Potential risk: saxagliptin (Onglyza), alogliptin (Nesina)</td>
</tr>
<tr>
<td>SGLT2 Inhibitors</td>
<td>Benefit: canagliflozin (Invokana), empagliflozin (Jardiance)</td>
<td>Benefit: canagliflozin (Invokana), empagliflozin (Jardiance)</td>
</tr>
<tr>
<td>GLP-1 Agonists</td>
<td>Neutral: lixisenatide (Adlyxin), exenatide ER (Bydureon) Benefit: liraglutide</td>
<td>Neutral</td>
</tr>
<tr>
<td>Insulin</td>
<td>Neutral</td>
<td>Neutral</td>
</tr>
</tbody>
</table>

ASCVD: atherosclerotic cardiovascular disease  
CHF: congestive heart failure

Cardiovascular Considerations – Pioglitazone (Actos)

- Metanalysis from 1966 – 2016: 12,026 patients across 9 trials
- Lower risk:
  - MACE in patients with pre-diabetes or insulin resistance (RR 0.77, 95% CI 0.64 to 0.93)
  - MACE if patients with diabetes (RR 0.83, 95% CI 0.72 to 0.97)
- Increased risk:
  - Heart failure (RR 1.32; CI 1.14 to 1.54)
  - Bone fracture (RR 1.52, 95% CI 1.17 to 1.99)
  - Edema (RR, 1.63; CI 1.52 to 1.75)
  - Weight gain (RR 1.60; CI 1.50 to 1.72)

MACE: major adverse cardiovascular event (composite of non-fatal MI, non-fatal stroke, and CV death)

# Cardiovascular Considerations – DPP-4 Inhibitors

<table>
<thead>
<tr>
<th></th>
<th>Saxagliptin (Onglyza)</th>
<th>Alogliptin (Nesina)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Intervention</strong></td>
<td>vs. placebo</td>
<td>vs. placebo</td>
</tr>
<tr>
<td><strong>Main Inclusion Criteria</strong></td>
<td>Type 2 diabetes and history of, or multiple risk factors for, CVD</td>
<td>Type 2 diabetes and ACS within 15–90 days before randomization</td>
</tr>
<tr>
<td><strong>A1c Inclusion</strong></td>
<td>≥ 6.5%</td>
<td>6.5 – 11%</td>
</tr>
<tr>
<td><strong>Average Patient</strong></td>
<td>65 YO, A1c 8.0%, DM x 10 years, CVD (78%), metformin (70%)</td>
<td>61 YO, A1c 8%, DM x 7 years, CVD (100%), metformin (66%)</td>
</tr>
<tr>
<td><strong>Primary Outcome</strong></td>
<td>MACE: 1.00 (0.89-1.12)</td>
<td>MACE: 0.96 (95% UL &lt; 1.16)</td>
</tr>
<tr>
<td><strong>Key Secondary Outcomes</strong></td>
<td>HF hospitalization: 1.27 (1.07-1.51)</td>
<td>HF hospitalization: 1.19 (0.9-1.58)</td>
</tr>
</tbody>
</table>

MACE: major adverse cardiovascular event (composite of non-fatal MI, non-fatal stroke, and CV death)

---

# Cardiovascular Considerations – SGLT2 Inhibitors - MACE

MACE: major adverse cardiovascular event (composite of non-fatal MI, non-fatal stroke, and CV death)

<table>
<thead>
<tr>
<th></th>
<th>Empagliflozin (Jardiance)</th>
<th>Canagliflozin (Invokana)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Intervention</strong></td>
<td>vs. placebo</td>
<td>vs. placebo</td>
</tr>
<tr>
<td><strong>Main Inclusion Criteria</strong></td>
<td>Type 2 diabetes and preexisting CVD with BMI ≤45 kg/m² and eGFR ≥30 mL/min</td>
<td>Type 2 diabetes and pre-existing CVD at ≥30 years of age or ≥2 cardiovascular risk factors at ≥50 years of age</td>
</tr>
<tr>
<td><strong>A1c Inclusion</strong></td>
<td>7 – 10%</td>
<td>7 – 10.5%</td>
</tr>
<tr>
<td><strong>Average Patient</strong></td>
<td>63 YO, A1c 8.1%, DM &gt; 10 years, CVD (99%), metformin (74%)</td>
<td>63 YO, A1c 8.2%, DM &gt; 13.5 years, CVD (65.5%), metformin (77%)</td>
</tr>
<tr>
<td><strong>Primary Outcome</strong></td>
<td>3-point MACE: 0.86 (0.74-0.99)</td>
<td>3-point MACE: 0.86 (0.75-0.97)</td>
</tr>
<tr>
<td></td>
<td>CV mortality: 0.62 (0.49-0.77)</td>
<td>Albuminuria 0.73 (0.47-0.77)</td>
</tr>
<tr>
<td><strong>Key Secondary Outcomes</strong></td>
<td>All-cause mortality: 0.86 (0.77-0.97)</td>
<td>Composite: eGFR, renal replacement, renal death 0.60 (0.47-0.77)</td>
</tr>
</tbody>
</table>

---

N Engl J Med 2015; 373:2117-2128
N Engl J Med 2017; 377:446-457
### Cardiovascular Considerations – SGLT2 Inhibitors - HF

<table>
<thead>
<tr>
<th></th>
<th>Empagliflozin (Jardiance) EMPA-REG OUTCOME n=7,020</th>
<th>Canagliflozin (Invokana) CANVAS / CANVAS-R n=4,330 / 5,812</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention</td>
<td>vs. placebo</td>
<td>vs. placebo</td>
</tr>
<tr>
<td>Main Inclusion Criteria</td>
<td>Type 2 diabetes and preexisting CVD with BMI ≤45 kg/m² and eGFR ≥30 mL/min</td>
<td>Type 2 diabetes and pre-existing CVD at ≥30 years of age or ≥2 cardiovascular risk factors at ≥50 years of age</td>
</tr>
<tr>
<td>A1c Inclusion</td>
<td>7 – 10%</td>
<td>7 – 10.5%</td>
</tr>
<tr>
<td>Average Patient</td>
<td>63 YO, A1c 8.1%, DM &gt; 10 years, CVD (99%), metformin (74%)</td>
<td>63 YO, A1c 8.2%, DM x 13.5 years, CVD (65.5%), metformin (77%)</td>
</tr>
<tr>
<td>HF Hospitalizations</td>
<td>0.65 (0.50-0.85)</td>
<td>0.77 (0.55-1.08)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.56 (0.38-0.83)</td>
</tr>
</tbody>
</table>

N Engl J Med 2015; 373:2117-2128  

### Cardiovascular Considerations – SGLT2 Inhibitors – Class Effect?

<table>
<thead>
<tr>
<th></th>
<th>Dapagliflozin (Farxiga) DECLARE-TIMI58 n=17,276</th>
<th>Ertugliflozin (Steglatro) VERTIS CV Study n=8,000</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention</td>
<td>vs. placebo</td>
<td>vs. placebo</td>
</tr>
<tr>
<td>Main Inclusion Criteria</td>
<td>Type 2 diabetes, age &gt; 40 years, high risk for CV events</td>
<td>Type 2 diabetes (A1c 7-10.5%), BMI ≥ 18 kg/m², h/o atherosclerosis or established vascular disease</td>
</tr>
<tr>
<td>Primary Outcomes</td>
<td>Time to first event (composite CV death, MI, or ischemic stroke)</td>
<td>Time to first occurrence of MACE</td>
</tr>
<tr>
<td>Follow up</td>
<td>Up to 6 years</td>
<td>Up to 6.1 years</td>
</tr>
<tr>
<td>Expected Completion</td>
<td>July 2018</td>
<td>September 2019</td>
</tr>
</tbody>
</table>

MACE: major adverse cardiovascular event (composite of non-fatal MI, non-fatal stroke, and CV death)

https://clinicaltrials.gov/ct2/show/NCT01730534  
https://clinicaltrials.gov/ct2/show/NCT01986881
Cardiovascular Considerations – SGLT2 Inhibitors – Class Effect?

- Noninferiority Cardiovascular Outcome Trials are required by the FDA for all US-marketed diabetes medications
- Class effect MUST be demonstrated – CANNOT be assumed
  - Current benefits only shown with empagliflozin and canagliflozin

- GLP-1 Agonist Example: lixisenatide and liraglutide
  - ELIXA (lixisenatide): neutral results towards CVD
  - LEADER (liraglutide): positive results towards CVD

Cardiovascular Considerations – GLP-1 Agonists

<table>
<thead>
<tr>
<th></th>
<th>Liraglutide (Victoza)</th>
<th>LEADER n=9,340</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention</td>
<td>vs. placebo</td>
<td></td>
</tr>
<tr>
<td>Main Inclusion Criteria</td>
<td>Type 2 diabetes and preexisting CVD, kidney disease, or HF at ≥50 years of age or cardiovascular risk at ≥60 years of age</td>
<td></td>
</tr>
<tr>
<td>A1c Inclusion</td>
<td>≥ 7.0%</td>
<td></td>
</tr>
<tr>
<td>Average Patient</td>
<td>64 YO, A1c 8.7%, DM x 12.8 years, CVD (81%), metformin (76%)</td>
<td></td>
</tr>
<tr>
<td>Primary Outcome</td>
<td>MACE: 0.87 (0.78-0.97)</td>
<td></td>
</tr>
<tr>
<td>Key Secondary Outcomes</td>
<td>Expanded MACE: 0.88 (0.81-0.96)</td>
<td></td>
</tr>
</tbody>
</table>

MACE: major adverse cardiovascular event (composite of non-fatal MI, non-fatal stroke, and CV death)
Expanded MACE: death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, or hospitalization for unstable angina pectoris or heart failure
Choosing Diabetes Treatment – Comorbid Conditions (HTN)

<table>
<thead>
<tr>
<th>Clinical Trial</th>
<th>Population</th>
<th>Outcome</th>
</tr>
</thead>
</table>
| ACCORD BP        | 4,733 participants with T2D, aged 40–79 years, with prior evidence of CVD or multiple cardiovascular risk factors | - Stroke risk reduced 41% with intensive control (not sustained through follow-up beyond the period of active treatment)  
- Adverse events more common in intensive group |
| ADVANCE BP       | 11,140 participants with T2D, aged 55 years and older, with prior evidence of CVD or multiple cardiovascular risk factors | - Intervention reduced risk of primary composite end point of major macrovascular and microvascular events (9%), death from any cause (14%), and death from CVD (18%)  
- 6-year observational follow-up found reduction in risk of death in intervention group attenuated, but still significant |
| HOT              | 18,790 participants, including 1,501 with diabetes                           | - In the subpopulation with diabetes, an intensive diastolic target was associated with a significantly reduced risk (51%) of CVD events |

Choosing Diabetes Treatment – Comorbid Conditions (Dyslipidemia)

<table>
<thead>
<tr>
<th>Age</th>
<th>ASCVD</th>
<th>Recommended statin intensity and combination treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 40 years</td>
<td>No</td>
<td>None</td>
</tr>
</tbody>
</table>
|                  | Yes   | High  
- If LDL cholesterol ≥70 mg/dL despite maximally tolerated statin dose, consider adding additional LDL-lowering therapy (such as ezetimibe (Zetia) or PCSK9 inhibitor |
| ≥ 40 years       | No    | Moderate                                                                       |
|                  | Yes   | High  
- If LDL cholesterol ≥70 mg/dL despite maximally tolerated statin dose, consider adding additional LDL-lowering therapy (such as ezetimibe (Zetia) or PCSK9 inhibitor |
Diabetes Considerations

• 30.3 million people (9.4%) have diabetes
• 6.7 new cases/1000 persons > 18 years old
• 7.2 million hospital discharges reported with diabetes as any listed diagnosis
  • 245,000 ED visits for hypoglycemia (11.2 per 1,000 persons with diabetes)
  • 207,000 ED for hyperglycemic crisis (9.5 per 1,000 persons with diabetes)
• $245 billion in direct and indirect costs
  • $13,700/person/year ($7,900 of this attributed to DM)
• 7th leading cause of death


Diabetes Complications

• Hospitalizations:
  • All CV Disease: 70.4/1000 persons
  • Ischemic heart disease: 18.3/1000 persons
  • Stroke: 11.5/1000 persons
  • Amputation: 5/1000 persons
• Leading cause of kidney disease
  • Chronic Kidney Disease (stages 1-4): 36.5% of DM patients
  • ESRD: 154.4 cases/1 million persons annually
• Leading cause of new-onset blindness
• Leading cause of non-traumatic amputations

Diabetes and Microvascular Events

DCCT:
- After 6.5 years, intensive control reduced retinopathy, nephropathy, and neuropathy in T1DM
- Additional 4 years follow up, initial A1c control reduced retinopathy and nephropathy, despite narrowing of A1c control

Kumamoto Trial:
- Multiple daily injections reduced A1c 9.4% to 7.1%, retinopathy by 69%, and nephropathy by 70% (compared to once or twice daily injections)

UKPDS:
- Intensive treatment reduced A1c 7% vs. 7.9%, retinal photo coagulation by 27%, microalbuminuria by 33%, and doubling of SCr levels by 74%

HTN and DM Study (part of UKPDS):
- Intensive BP control after 9 years reduced retinal photo coagulation by 35%. Retinopathy by 34%, and risk of visual acuity reduction by 47%

ACE Inhibitor Reductions:
- Progression of retinopathy by up to 50%
- Development of nephropathy by up to 62%
Diabetes and Macrovascular Events

- Risk of acute MI, stroke, or death compared to A1c of < 6.5% over 2.6 years
  - 6.5-6.99%: HR 1.18 (95% CI 1.07-1.30)
  - 7.0-7.49%: HR 1.23 (1.09-1.40)
  - 7.5-7.99%: HR 1.34 (1.14-1.57)
  - ≥ 8%: HR 1.59 (CI 1.37-1.84)
- Reduction is risk of acute MI, stroke, or death per reduction in A1c over first 6 months
  - Δ -4%: HR 0.80 (0.65-0.97)
  - Δ -3%: HR 0.98 (0.80-1.20)
  - Δ -2%: HR 0.92 (0.78-1.08)
  - Δ -1%: HR 0.99 (0.89-1.10)

Summary – Clinical Inertia

Requirements
1. Patient fails to achieve major evidence-based clinical goals
2. Patient fails to receive appropriate intensification of pharmacotherapy in a defined period of time

Decisions
1. Clinical goals selected
2. Therapy defined (in a way that can be measured)
3. Time window within which intensification is considered timely
Summary - Overcoming Clinical Inertia in Diabetes

• Consider
  • Medication mechanism of action
  • Key comparative characteristics (i.e. efficacy, hypoglycemia risk, and risk of weight gain)
  • Notable side effects and warnings
  • Benefits and risks in kidney disease and heart disease
    • Canagliflozin and empagliflozin: shown most benefit in delaying diabetic kidney disease, reducing outcomes related to ASCVD, and reducing risk of HF hospitalizations

Antihyperglycemic Therapy in Type 2 Diabetes: What's Guiding Pharmacotherapy Choice?

Zach Weber, PharmD, BCPS, BCACP, CDE
Director of Interprofessional Education
Clinical Associate Professor of Pharmacy Practice
Purdue College of Pharmacy
Clinical Pharmacy Specialist, Ambulatory Care
Eskenazi Health