CARDIOVASCULAR EFFECTS OF ANTIDIABETIC MEDICATIONS

Ali Gortemoller, PharmD
St. Vincent’s Medical Center
Objectives

• Analyze the pathophysiology behind diabetes mellitus associated macrovascular complications

• Describe the mechanisms of GLP-1 analogs, DPP-4 inhibitors, and SGLT-2 inhibitors

• Assess cardiovascular outcomes associated with antidiabetic medications in type 2 diabetic patients
CARDIOVASCULAR EFFECTS OF DIABETES MELLITUS
Pathophysiology

Diabetes mellitus

Hyperglycemia

Insulin resistance

Dyslipidemia

Increased: AGEs, PKC, platelet and coagulation activation
Decreased: Nitric oxide, PPAR activation

Atherosclerosis

AGE: advanced glycation end product
PKC: protein kinase C
PPAR: peroxisome proliferator activated receptors

JCMS. 2007;2: 108-113
Pathophysiology

AGE activation
- ↑ Vascular permeability
- ↑ Inflammatory cytokines

PKC activation
- ↑ Endothelin 1
- ↑ Vascular permeability

Platelet/coag activation
- ↑ Clotting factors
- ↓ Antithrombin III

AGE: advanced glycation end product
PKC: protein kinase C

JCMS. 2007;2: 108-113
Pathophysiology

Decreased nitric oxide
- ↑ Vasoconstriction
- ↑ Platelet adhesion

Decreased PPAR activity
- ↑ Inflammatory cytokines

PPAR: peroxisome proliferator activated receptors

JCMS. 2007;2: 108-113
Complications

Hyperglycemia

Microvascular
- Nephropathy
- Neuropathy
- Retinopathy

Macrovascular
- CAD
- PVD
- Stroke

CAD: coronary artery disease
PVD: peripheral vascular disease

JCMS. 2007;2: 108-113
CV Disease Risk Management

- American Diabetes Association Guidelines 2017
  - Blood pressure control
  - Lipid management
  - Antiplatelet agents
  - Coronary heart disease
OUTPATIENT LITERATURE REVIEW
### Study Design

**Meta-analysis**

**Criteria for Inclusion**
- Randomized comparator group
- Similar duration of treatment in all groups
- >24 weeks of rosiglitazone exposure

**Inclusion**
- 116 screened: 42 included
  - 5: submitted to FDA for rosiglitazone approval
  - 35: GlaxoSmithKline clinical trial registry
  - 2: DREAM, ADOPT

**Outcomes**
- MI and death from cardiovascular causes

**Results**
- MI: OR 1.43 (95% CI, 1.03 to 1.98; p=0.03)
- Death: OR 1.64 (95% CI, 0.98 to 2.74; p=0.06)
FDA Guidance Document

Large, randomized, placebo-controlled cardiovascular safety trials for all new antihyperglycemic agents

Study drug compared with placebo

- Pre-marketed: non-inferiority margin of 1.8
- Post-marketed: non-inferiority margin of 1.3

Composite cardiovascular outcomes

Outline

- Glucagon like peptide-1 analog
- Dipeptidyl peptidase-4 inhibitor
- Sodium/glucose co-transporter 2 inhibitor
GLP-1 Inhibitors

MOA

- Stimulates insulin release and inhibits glucagon secretion

Cardiovascular effects

- Weight loss promotion
- Reduced blood pressure
- Decreased myocardial and vascular inflammation
- Low platelet aggregation

Trends in Cardiovascular Medicine; 2017 (27): 194-202
# LEADER: Design

## Study Design
- Multicenter, randomized, double blind, placebo controlled trial
- 410 sites in 32 countries

## Inclusion
- Type 2 DM with HgbA1C ≥7%
- ≥50 years old + 1 CV coexisting condition
- ≥60 years old + 1 CV risk factor

## Exclusion
- Type 1 DM, certain DM meds, familial/personal hx of multiple endocrine neoplasia type 2, medullary thyroid cancer, or acute coronary/cerebrovascular event w/in 14 days

LEADER: Procedures

Run –in Phase
• 2 week placebo

Randomization
• Liraglutide 1.8 mg SQ daily + SOC
• Matched placebo SQ daily + SOC

Stratification
• eGFR <30 mL/min
• eGFR ≥30 mL/min

Follow-up
• 1, 3, 6 month and then Q6 months

SOC: standard of care

LEADER: Outcomes

Primary Composite
- Death from CV causes
- Nonfatal MI
- Nonfatal stroke

Exploratory Outcomes
- Expanded CV composite
- Death from any cause
- Composite renal/retinal outcomes
- Neoplasms
- Pancreatitis

LEADER: Results

9340 randomized
• 4668: liraglutide
• 4672: placebo

Baseline Characteristics
• Established CV disease: 81.3%
• Mean HgbA1c: 8.7%
• Mean duration of diabetes: 12.8 years
LEADER: Results

Primary Outcome

- HR 0.87 (CI, 0.78-0.97; p<0.001 noninferiority and p=0.01 superiority)
- Death from CV Causes: HR 0.78 (CI, 0.66-0.93; p=0.007)
- Nonfatal MI: HR 0.88 (CI, 0.75-1.03, p=0.11)
- Nonfatal Stroke: HR 0.89 (CI, 0.72-1.11, p=0.30)

Death from any cause

- HR 0.85 (CI, 0.74-0.97; p=0.02)

Adverse effects

- Liraglutide had ↓ episodes of hypoglycemia but ↑ GI effects

Outline

- Glucagon like peptide-1 analog
- Dipeptidyl peptidase-4 inhibitor
- Sodium/glucose co-transporter 2 inhibitor
DPP-4 Inhibitors

- MOA: inhibits degradation of GLP-1 and GIP
Cardiovascular Effect

DPP-4 expression

• Myocardium
• Vascular endothelium
• Myeloid cells

Molecular activity

• Improved endothelial dysfunction
• Increased endothelial nitric oxide synthase
SAVOR-TIMI 53: Design

• Study Design
  • Randomized, double-blind, placebo-controlled, phase 4 trial
  • 788 sites in 26 countries

• Population
  • Inclusion:
    • Type 2 DM and HgbA1c 6.5%-12%
    • ≥ 40 y/o + established CVD
    • ≥55 y/o (M) or ≥60 y/o (F) + risk factor for vascular disease
  • Exclusion
    • Incretin based therapy in last 6 months, renal dysfunction criteria

SAVOR-TIMI 53: Procedures

Stratification
- CV Status
- Renal Function

Randomization
- Saxagliptin
  - 2.5-5 mg
  - Placebo

SAVOR-TIMI 53: Outcomes

Primary Efficacy/Safety
- Composite
  - CV death
  - Nonfatal MI
  - Nonfatal ischemic stroke

Secondary Efficacy
- Composite
  - Primary composite + hospitalization for heart failure
  - Coronary revascularization
  - Unstable angina

SAVOR-TIMI 53: Results

16,492 randomized

Baseline Characteristics

- Established CV disease: 79%
- Median duration of diabetes: 10.3 years
- Mean HgbA1c: 8%

Median follow-up time: 2.1 years

SAVOR-TIMI 53: Results

Primary Outcome

- 7.3% vs 7.2%
- HR 1.00 (95% CI, 0.89 to 1.12; P = 0.99 for superiority and P<0.001 for noninferiority)

Secondary Outcome

- Heart failure hospitalization: 3.5% vs. 2.8%
  - HR 1.27 (95% CI, 1.07 to 1.51; P = 0.007)
TECOS: Design

Study Design

• Randomized, double-blind, placebo-controlled trial
• 673 sites in 38 countries

Population

• Inclusion: Type 2 DM, CV disease, ≥50 years, HgbA1c 6.5-8% on 1 or 2 oral antidiabetic agents or insulin
• Exclusion: DPP-4/GLP-1/TZD in past 3 months, ≥2 episodes of hypoglycemia, eGFR <30 ml/min

TECOS: Procedures/Outcomes

Randomization
- Sitagliptin or placebo + SOC

Primary Outcome
- Composite: cardiovascular death, nonfatal MI, nonfatal stroke, or hospitalization for unstable angina

Secondary Outcome
- Composite: cardiovascular death, nonfatal MI, nonfatal stroke
- Hospitalization from heart failure

TECOS: Results

Randomization: 14,735 patients
• ITT: 14,671 patients
• Sitagliptin: 7332
• Placebo: 7339

Background Characteristics
• HgbA1c: 7.2 ± 0.5%
• Length of DM: 11.6 ± 8.1 years
• Median follow-up: 3 years

TECOS: Results

A. Primary Cardiovascular Outcome

B. Secondary Cardiovascular Outcome

C. Hospitalization for Heart Failure

D. Death from Any Cause

Outline

- Glucagon like peptide-1 analog
- Dipeptidyl peptidase-4 inhibitor
- Sodium/glucose co-transporter 2 inhibitor
SGLT-2 Inhibitors

- MOA: inhibits glucose cotransporter that aids the reabsorption of glucose and sodium in the kidneys

http://www.diabetesincontrol.com
Cardiovascular Effects

SGLT2 transporters in kidney epithelial cells

Cardiovascular benefits

- Glycosuria $\rightarrow$ decreased uric acid levels
- Natriuresis/reduction in arterial stiffness $\rightarrow$ decreased BP
EMPA-REG OUTCOME: Design

Study Design
- Randomized, double blind, placebo controlled trial
- 590 sites in 42 countries

Population
- ≥18 years old, Type 2 DM, BMI ≤45, eGFR ≥30 ml/min
- CVD + no glucose lowering agents x 12 wks + HgA1c 7-9%
- Stable glucose lowering agents x 12 wks + HgA1c 7-10%
EMPA-REG OUTCOME: Procedures

2 week open-label placebo run in period

Empagliflozin 10 mg
Empagliflozin 25 mg
Placebo

HgbA1C
- <8.5%
- ≥8.5%

eGFR
- 30-59 mL/min
- 60-80 mL/min
- ≥90 mL/min

BMI
- <30 kg/m2
- ≥30 kg/m2

Geographic Region
- North America
- Latin America
- Europe
- Africa
- Asia

EMPA-REG OUTCOME: Outcomes

Primary
- Composite
- Death from CV causes, nonfatal MI, nonfatal stroke

Secondary
- Composite
- Primary outcome + hospitalization for unstable angina

Safety
- Confirmed hypoglycemia ≤70 mg/dL, UTI, genital infection, volume depletion, AKI, bone fracture, DKA, thromboembolic event

EMPA-REG OUTCOME: Results

Randomization
- 7028 patients randomized
- Primary analysis: 7020 patients

Background Characteristics
- Established cardiovascular disease: 99%
- HgA1c: 8%
- DM >10 years: 57%
- Median treatment duration: 2.6 years

EMPA-REG OUTCOME: Results

Safety

- Genital infection: higher percentage of patients in pooled empagliflozin
- Similar proportions
  - Hypoglycemia
  - Acute kidney injury
  - Diabetic ketoacidosis
  - Thromboembolic events
  - Bone fracture
  - Volume depletion
  - Urinary tract infection
FDA Expanded Indication

- Risk reduction of CV mortality in adults with Type 2 DM and established CV disease
- First antidiabetic agent approved with additional indication
CVD-REAL: Design/Outcomes

Study Design
- Multinational retrospective observation cohort
- Nationwide registries in Denmark, Norway, Sweden
- New dapagliflozin users and new users of DPP4 inhibitors

Population
- Inclusion
  - ≥18 years old with type 2 DM in database >1 year
  - Newly using dapagliflozin or DPP4-i from 2012-2015
- Exclusion: Type 1 DM, gestational DM, PCOS

Outcomes
- Major adverse cardiovascular event (MACE)
- Heart failure hospitalization
- All cause mortality

CVD-REAL Nordic. doi: 10.1111/dom.13077
### CVD-REAL: Results

#### Patient Groups
- 40,908 new users
  - SGLT2-i: 10,227
  - DPP4-i: 30,681

#### Baseline Characteristics
- Mean age: 61 years
- Women: 40%
- CVD: 23%
- Heart failure: 5%
- Microvascular: 15%
# CVD-REAL: Results

## MACE
- ↓ in dapagliflozin group
  - HR 0.79 (95% CI, 0.67-0.94; p = 0.006)

## Heart Failure Hospitalization
- ↓ in dapagliflozin group
  - HR 0.62 (95% CI, 0.5-0.77; p <0.001)

## All Cause Mortality
- ↓ in dapagliflozin group
  - HR 0.44 (95% CI, 0.33-0.6; p<0.001)
CANVAS Program

CANVAS Program (N=10,142)

CANVAS (N=4330)  CANVAS-R (N=5812)
### CANVAS: Design

#### Study Design
- Randomized, double blind, placebo-controlled trials
- 667 centers in 30 countries

#### Population
- ≥30 years with type 2 diabetes
- HgA1c: ≥7.0% and ≤10.5%
- CV Component
  - Symptomatic atherosclerotic CV disease
  - ≥50 years + 2 or more risk factors for CV disease

*N Engl J Med 2017; 377:644-57*
CANVAS: Procedures/Outcomes

- Primary Composite Outcome
  - Death from CV causes, nonfatal MI, nonfatal stroke

- Secondary Outcomes
  - Death from any cause, death from CV causes, progression from albuminuria, composite of death from CV causes, hospitalization for HF

CANVAS: Results

Baseline characteristics
- CV history: 65.6%
- Mean duration of DM: 13.5 years
- Mean HgA1c: 8.2%
- Mean eGFR: 76.5 mL/min

Follow-up
- Mean: 188.2 weeks
  - CANVAS: 295.9 weeks
  - CANVAS-R: 108 weeks
CANVAS: Results

Primary Outcomes
- Death from CV Causes
  - HR 0.87 (0.72-1.06)
- Nonfatal Stroke
  - HR 0.9 (0.71-1.15)
- Nonfatal MI
  - HR 0.85 (0.69-1.05)

Secondary Outcomes
- Hospitalization for HF
  - HR 0.67 (0.52-0.87)

CANVAS: Results

Significantly greater in canagliflozin group

- All serious adverse events
- Adverse events leading to discontinuation
- Amputation
- All fractures
- Infection of male genitalia
- Mycotic genital infection in women
- Osmotic diuresis

INPATIENT EVIDENCE
Inpatient Management

• Goals
  • Prevent hyper/hypoglycemia
    • Hyperglycemia: blood glucose >140 mg/dL
    • Hypoglycemia: blood glucose <54 mg/dL

• Preferred treatment: insulin

• Protocol for resuming oral antihyperglycemic medications 1-2 days prior to discharge

ADA 2017 Standards of Medical Care in Diabetes
Sitagliptin

Multicenter, open-label, randomized study

n = 90

18-80 y/o, type 2 DM >3 months, admission BG 140-400 mg/dL

Sitagliptin daily

Sitagliptin + glargine

Basal bolus insulin/glargine

Diabetes Care 2013; 36: 3430-3435
## Sitagliptin

- **Primary Outcome**
  - Difference in mean daily BG concentration

<table>
<thead>
<tr>
<th>Results</th>
<th>No Significant Difference</th>
<th>Significantly Less in Sitagliptin Groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>BG: blood glucose</td>
<td>• Mean daily BG</td>
<td>• Total daily insulin doses</td>
</tr>
<tr>
<td></td>
<td>• BG reading w/in target</td>
<td>• Number of insulin injections</td>
</tr>
<tr>
<td></td>
<td>• Treatment failures</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Hospital length of stay</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Hypoglycemic events</td>
<td></td>
</tr>
</tbody>
</table>

Diabetes Care 2013; 36: 3430-3435
SGLT-2 Inhibitors: Benefits

- Selective for SGLT-2
  - Insulin independent mechanism

- Low risk of hypoglycemia
  - Unless given with insulin/sulfonylurea

- Synergistic effect
  - Beta-blockers, calcium channel blockers, RAAS blockers
SGLT-2 Inhibitors: Risks

- No published trials examining risks in inpatient setting
- Euglycemic diabetic ketoacidosis
- Renal dysfunction
- Urinary tract infections
- Postural hypotension
FUTURE DIRECTIONS
## Future Trials

<table>
<thead>
<tr>
<th></th>
<th>DPP4-i</th>
<th>GLP-1</th>
<th>SGLT2-i</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CARMELINA</strong></td>
<td>Linagliptin</td>
<td>Exenatide</td>
<td>DECLARE-TIMI</td>
</tr>
<tr>
<td></td>
<td>January 2018</td>
<td>April 2018</td>
<td>April 2019</td>
</tr>
<tr>
<td><strong>CAROLINA</strong></td>
<td>Linagliptin vs Glimepiride</td>
<td>Dulaglutide</td>
<td>VERTIS-CV</td>
</tr>
<tr>
<td></td>
<td>September 2018</td>
<td>April 2019</td>
<td>Ertugliflozin</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>June 2019</td>
</tr>
<tr>
<td><strong>HARMONY</strong></td>
<td></td>
<td>Albiglutide</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>May 2019</td>
<td></td>
</tr>
</tbody>
</table>
Assessment Question

GLP-1 agonists have all of the following effects on the cardiovascular system except:

A. Promote weight loss
B. Increase blood pressure
C. Decrease myocardial and vascular inflammation
D. Decrease platelet aggregation
Assessment Question

GLP-1 agonists have all of the following effects on the cardiovascular system except:

A. Promote weight loss
B. Increase blood pressure
C. Decrease myocardial and vascular inflammation
D. Decrease platelet aggregation
Assessment Question

Which of the following statements regarding the results of EMPA-REG OUTCOME trial is true?

A. Empagliflozin reduced death from CV causes, nonfatal MI, and nonfatal stroke
B. Empagliflozin reduced death from any cause
C. Empagliflozin increased hospitalization from heart failure
D. A and B
E. All of the above
Assessment Question

Which of the following statements regarding the results of EMPA-REG OUTCOME trial is true?

A. Empagliflozin reduced death from CV causes, nonfatal MI, and nonfatal stroke
B. Empagliflozin reduced death from any cause
C. Empagliflozin increased hospitalization from heart failure
D. A and B
E. All of the above
Conclusion

• Liraglutide decreased death from CV causes/any cause

• Conflicting evidence of CV effects of DPP4 inhibitors

• SGLT2-i show beneficial CV outcomes in outpatient setting

• Growing evidence for inpatient oral antidiabetic agents, but insulin is still preferred
CARDIOVASCULAR EFFECTS OF ANTIDIABETIC MEDICATIONS

Ali Gortemoller, PharmD
St. Vincent's Medical Center