Diabetes Cardiovascular Outcome Trials: Implications for Your Practice

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Disclosures

- Janssen Pharmaceuticals
- AstraZeneca
- Sanofi
- Lilly
- Boehringer Ingelheim
- Novo Nordisk
- Dexcom
Objectives

- Review effects of glucose lowering on CVD in T2D
- Review CV outcomes of recent T2D medication trials
- Discuss proposed mechanisms of cardiac benefit observed
- Shifting focus on using medications to lower A1C versus reducing overall CV risk, and discuss implementation of therapy recommendations in practice
Diabetes Increases CV Events

<table>
<thead>
<tr>
<th>Condition</th>
<th>No. of Cases</th>
<th>HR (95% CI)</th>
<th>P (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronary heart disease*</td>
<td>26,505</td>
<td>2.00 (1.83-2.19)</td>
<td>64 (54-71)</td>
</tr>
<tr>
<td>Coronary death</td>
<td>11,556</td>
<td>2.31 (2.05-2.60)</td>
<td>41 (24-54)</td>
</tr>
<tr>
<td>Non-fatal myocardial infarction</td>
<td>14,741</td>
<td>1.82 (1.64-2.03)</td>
<td>37 (19-51)</td>
</tr>
<tr>
<td>Stroke subtypes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischaemic stroke</td>
<td>3,799</td>
<td>2.27 (1.95-2.65)</td>
<td>1 (0-20)</td>
</tr>
<tr>
<td>Haemorrhagic stroke</td>
<td>1,183</td>
<td>1.56 (1.19-2.05)</td>
<td>0 (0-26)</td>
</tr>
<tr>
<td>Unclassified stroke</td>
<td>4,973</td>
<td>1.84 (1.59-2.13)</td>
<td>33 (12-48)</td>
</tr>
<tr>
<td>Other vascular deaths</td>
<td>3,826</td>
<td>1.73 (1.51-1.98)</td>
<td>0 (0-26)</td>
</tr>
</tbody>
</table>

Increased Mortality from CVD in Diabetes

- At least 68% of people age 65 or older with diabetes die from some form of heart disease; and 16% die of stroke.
- Adults with diabetes are 2-4 times more likely to die from heart disease than adults without diabetes.

Contribution of Diabetes to CHD

Impact of Intensive Therapy for T2D

Major Clinical Trials

![Diagram showing impact of intensive therapy on microvascular, CVD, and mortality outcomes in different studies.]

### Intensive Glucose Control and Hospitalization for Heart Failure in Type 2 Diabetes

<table>
<thead>
<tr>
<th>Trials</th>
<th>Number of events (annual event rate, %)</th>
<th>ΔHbA₁c (%)</th>
<th>Favours more intensive</th>
<th>Favours less intensive</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(More intensive)</td>
<td>(Less intensive)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACCORD</td>
<td>152 (0.90)</td>
<td>124 (0.75)</td>
<td>−1.01</td>
<td></td>
<td>1.18 (0.93–1.49)</td>
</tr>
<tr>
<td>ADVANCE</td>
<td>220 (0.83)</td>
<td>231 (0.88)</td>
<td>−0.72</td>
<td></td>
<td>0.95 (0.79–1.14)</td>
</tr>
<tr>
<td>UKPDS</td>
<td>8 (0.06)</td>
<td>6 (0.11)</td>
<td>−0.66</td>
<td></td>
<td>0.55 (0.19–1.60)</td>
</tr>
<tr>
<td>VADT</td>
<td>79 (1.80)</td>
<td>85 (1.94)</td>
<td>−1.16</td>
<td></td>
<td>0.92 (0.68–1.25)</td>
</tr>
<tr>
<td>Overall</td>
<td>459</td>
<td>446</td>
<td>−0.88</td>
<td></td>
<td>1.00 (0.86–1.16)</td>
</tr>
</tbody>
</table>

(Q=3.59, p=0.31, I²=16.4%)

Review of Older Agents

Metformin
- Reduced macrovascular risk in UKPDS in a small number of overweight patients
- Use may decrease mortality among patients with T2D

Sulfonylureas (SFU)
- SFU/insulin reduced macrovascular risk in UKPDS follow-up
- SFU compared to Metformin for initial treatment was associated and increased CV events/death

Pioglitazone
- Do NOT use in CHF (fluid retention)
- May decrease MACE, especially stroke

UKPDS: Risk reduction with Metformin in overweight patients

Pioglitazone stroke outcomes

PROactive trial

IRIS Trial

A1C vs Glycemic Variability

Patterns & Insights (09/20/2016 - 09/27/2016)

Statistics

- Average Glucose: 171 mg/dL
- Sensor Usage: 8 of 6 Days
- Calibrations / Day: 2.8
- Standard Deviation: ± 85 mg/dL
- Target Range: 80 - 130 mg/dL
- Nighttime: 10:00 PM - 6:00 AM

Target Range Percentages:
- 64% High
- 20% Target
- 16% Low

---|---|---|---
BP - Systolic | 118 | 1
BP - Diastolic | 62 | 1
Height | 5 ft 3 in | 1
Weight | 140 lb | 1
BMI Calculated | 24.8 kg/m² | 1
HbA1C | 7.1% | 1
## Glucose Variability and Association with Complications

<table>
<thead>
<tr>
<th>Study</th>
<th>EndPoint</th>
<th>Finding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gimeno-Orna</td>
<td>Diabetic retinopathy</td>
<td>CV-FPG predicted development of retinopathy independent of A1C</td>
</tr>
<tr>
<td>(N=130)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zoppini</td>
<td>Diabetic retinopathy</td>
<td>No association</td>
</tr>
<tr>
<td>(N=746)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Xu (N=90)</td>
<td>Peripheral neuropathy</td>
<td>Glucose Variability found to be the most significant independent risk</td>
</tr>
<tr>
<td></td>
<td></td>
<td>factor for diabetic peripheral neuropathy</td>
</tr>
<tr>
<td>Muggeo</td>
<td>CV-related mortality</td>
<td>Glucose Variability was a predictor of CVD-related mortality in elderly</td>
</tr>
<tr>
<td></td>
<td></td>
<td>patients &gt; 75 years old</td>
</tr>
<tr>
<td>Stahn</td>
<td>Ventricular Arrhythmias</td>
<td>Positive Association between high glucose variability and severe</td>
</tr>
<tr>
<td></td>
<td></td>
<td>hypoglycemia episodes with incidence of ventricular extrasystoles</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(P=0.008)</td>
</tr>
<tr>
<td>Pochinka</td>
<td>Ventricular Arrhythmias</td>
<td>Positive correlation between high glucose variability and ventricular</td>
</tr>
<tr>
<td></td>
<td></td>
<td>arrhythmias (P=0.02)</td>
</tr>
<tr>
<td>Rizzo</td>
<td>Mini-Mental Status Exam</td>
<td>Higher glucose variability was associated with lower cognition,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>independent of mean glucose levels</td>
</tr>
</tbody>
</table>

5) Pochinka, StronigiL, StruchkoI. Glycaemic variability and ventricular cardiac arrhythmias in type 2 diabetic
Patients with hypoglycemia had **significantly higher risks of CV events** (HR 2.0 [95% CI 1.6–2.4]) and **microvascular complications** (1.76 [1.46–2.11]).

FDA Requirements

- Phase 2 and 3 development programs will need to be larger and more comprehensive and will include high-risk patients.
- In addition, it is likely that most (if not all) newly approved drugs will be required to conduct post-approval CV safety outcome studies.

CVD remains major cause of mortality and morbidity in patients with diabetes

Large trials of intensive glucose control have failed to reduce adverse CV events, despite dramatic improvement in HbA1C

How glycemic control is achieved is important, and may guide therapy decisions
# Overview of CV Outcome Trials

<table>
<thead>
<tr>
<th>Category</th>
<th>Trial</th>
<th>Duration of Trial</th>
<th>Risk of CV Death and/or Composite Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DPP-4i</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alogliptin</td>
<td>EXAMINE</td>
<td>1.5 years</td>
<td>Neutral</td>
</tr>
<tr>
<td>Saxagliptin</td>
<td>SAVOR-TIMI</td>
<td>2.1 years</td>
<td>Neutral</td>
</tr>
<tr>
<td>Sitagliptin</td>
<td>TECOS</td>
<td>3 years</td>
<td>Neutral</td>
</tr>
<tr>
<td><strong>GLP-1 RA</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lixisenatide</td>
<td>ELIXA</td>
<td>2 years</td>
<td>Neutral</td>
</tr>
<tr>
<td>Liraglutide</td>
<td>LEADER</td>
<td>5 years</td>
<td>Positive (+)</td>
</tr>
<tr>
<td>Semaglutide</td>
<td>SUSTAIN 6</td>
<td>2 years</td>
<td>Positive (+)</td>
</tr>
<tr>
<td>Exenatide LR</td>
<td>EXSCEL</td>
<td>4.4 years</td>
<td>Neutral</td>
</tr>
<tr>
<td><strong>SGLT-2i</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Empagliflozin</td>
<td>EMPA-REG</td>
<td>3.1 years</td>
<td>Positive (+)</td>
</tr>
<tr>
<td>Canaglglizin</td>
<td>CANVAS</td>
<td>6.5 years</td>
<td>Positive (+)</td>
</tr>
</tbody>
</table>
LEADER (liraglutide, Victoza®)

9,340 adults
Followed over an average of 3.8 years

- ↓ 3-point MACE by 13%
- ↓ all-cause death by 15%
- ↓ cardiovascular death by 22%

LEADER (liraglutide)

SUSTAIN – 6 (Semaglutide, Ozempic®)

↓ CV risk was principally driven by:

- 39% ↓ nonfatal stroke (significant)
- 26% ↓ nonfatal MI (nonsignificant)
- No difference in cardiovascular deaths
- NNT = 45 over 2 years
- Higher rates of retinopathy complications
  - Occurring in 3% of patients on the active drug compared with 1.8% of the placebo group, a 76% increase ($P = .02$).

Marso, S. “Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes”. NEJM. September 16, 2016 DOI: 10.1056/NEJMoa1607141
SUSTAIN - 6

Marso, S. “Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes”. NEJM. September 16, 2016DOI: 10.1056/NEJMoa1607141
EXSCEL (exenatide, Bydureon®)

14,752 adults
Followed over an average of 3.3 years

- ↓ 3-point MACE by 9% (p-value = 0.061 not statistically significant)
- ↓ non-fatal stroke by 14%
- ↓ cardiovascular death by 12%
- no differences in pancreatic or medullary thyroid cancer

EXSCEL (exenatide, Bydureon®)

ELIXA (lixisenatide)

- Contained in Adlyxin (not marketed in US), Soliqua (insulin glargine/lixisenatide)
- Short-acting GLP1 agonist
- Trial included high-risk patient population (recent ACS)
- Demonstrated CV safety, did not show significant CV benefit
- Reduction in all-cause mortality in patients aged 65 years and older
- No risk of pancreatic cancer or pancreatitis
So... is it a “class effect?!?
# Meta-analysis: MACE-3 endpoint

<table>
<thead>
<tr>
<th>Study name</th>
<th>GLP-1 Group</th>
<th>Placebo Group</th>
<th>Hazard ratio and 95% CI</th>
<th>Hazard ratio</th>
<th>Lower limit</th>
<th>Upper limit</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>EUXA</td>
<td>400/3034 (13.2%)</td>
<td>392/3034 (12.9%)</td>
<td>1.02</td>
<td>0.89</td>
<td>1.17</td>
<td>0.776</td>
<td></td>
</tr>
<tr>
<td>LEADER</td>
<td>608/4668 (13.0%)</td>
<td>694/4672 (14.9%)</td>
<td>0.87</td>
<td>0.78</td>
<td>0.97</td>
<td>0.015</td>
<td></td>
</tr>
<tr>
<td>SUSTAIN-6</td>
<td>108/1648 (6.6%)</td>
<td>146/1649 (8.9%)</td>
<td>0.74</td>
<td>0.58</td>
<td>0.95</td>
<td>0.016</td>
<td></td>
</tr>
<tr>
<td>EXSCHEL</td>
<td>839/7356 (11.4%)</td>
<td>905/7396 (12.2%)</td>
<td>0.91</td>
<td>0.83</td>
<td>1.00</td>
<td>0.061</td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td></td>
<td>0.90</td>
<td>0.82</td>
<td>0.99</td>
<td>0.033</td>
<td></td>
</tr>
</tbody>
</table>

Test for heterogeneity
Q-test p value = 0.11
\( P = 50\% \)

Bethel et al. TLDE 2017; in press.
Proposed mechanisms of CV Benefit with GLP1 RA

Effects on reducing atherosclerosis ...

- Improved endothelial function
- Increased vasodilation
- Increased peripheral and coronary flow
- Increased ventricular function
# SGLT-2i CV Trials

<table>
<thead>
<tr>
<th>Study Design</th>
<th>CANVAS/CANVAS-R Canagliflozin INVOKANA®</th>
<th>EMPA-REG Empagliflozin JARDIANCE®</th>
<th>DECLARE Dapagliflozin FARXIGA®</th>
</tr>
</thead>
<tbody>
<tr>
<td># Patients</td>
<td>10,039</td>
<td>7034</td>
<td>17,150</td>
</tr>
<tr>
<td>Primary Prevention</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Secondary Prevention</td>
<td>Yes</td>
<td>Yes (99%)</td>
<td>Yes</td>
</tr>
<tr>
<td>Outcomes</td>
<td>3-Point MACE</td>
<td>HR 0.86, (p=0.02)</td>
<td>HR 0.86, (p=0.04) ↓ CV Death by 38%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PENDING 2018</td>
<td>**Primary outcome also includes composite endpoint of CV death or hospitalization due to heart failure</td>
</tr>
</tbody>
</table>

**Primary outcome also includes composite endpoint of CV death or hospitalization due to heart failure.**
Empagliflozin CV Outcomes

A. Primary Outcome

- Hazard rate: 0.88 (95% CI: 0.74–0.98)
- P=0.04 for superiority

B. Death from Cardiovascular Causes

- Hazard rate: 0.62 (95% CI: 0.49–0.77)
- P=0.001

C. Death from Any Cause

- Hazard rate: 0.61 (95% CI: 0.53–0.69)
- P<0.001

D. Hospitalization for Heart Failure

- Hazard rate: 0.63 (95% CI: 0.50–0.80)
- P=0.003

EMP A-REG CV Outcomes

- FIRST study to show a T2M medication can reduce CV events

- Disconnect observed between the three MACE endpoints...
  - Non-fatal MI ↓ slightly (not significant, HR = 0.87, p = 0.22)
  - Stroke modestly ↑ (not significant, HR = 1.24, p = 0.22)
  - CV death ↓ 38% (significant, HR = 0.62), Largely driven by a reduction of CHF (↓ 35%)

**EMPA-REG Background Therapies**

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetylsalicylic acid</td>
<td>5990 (85)</td>
</tr>
<tr>
<td>Statins</td>
<td>5387 (77)</td>
</tr>
<tr>
<td>Fibrates</td>
<td>630 (9)</td>
</tr>
<tr>
<td>Any antihypertensive therapy (n, %)</td>
<td>6641 (94)</td>
</tr>
<tr>
<td>Blockers of the renin-angiotensin system</td>
<td>5651 (80)</td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>4537 (64)</td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td>2114 (30)</td>
</tr>
</tbody>
</table>

[Link](https://cardiab.biomedcentral.com/articles/10.1186/1475-2840-13-102)
CANVAS CV Outcomes

*Decreased hospitalization for HF by 33%*
CANVAS - Background Therapies

## EMPA-REG Renal Outcomes

**Table 2: EMPA-REG OUTCOME Trial: Renal Outcomes (Pre-Specified & Post-Hoc Analysis)**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Empagliflozin</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. with event/analyzed (%)</td>
<td>Rate/1000 patient-yr</td>
</tr>
<tr>
<td>Incident or worsening nephropathy*</td>
<td>525/4124 (12.7)</td>
<td>47.8</td>
</tr>
<tr>
<td>Progression to macroalbuminuria*</td>
<td>459/4091 (11.2)</td>
<td>41.8</td>
</tr>
<tr>
<td>Doubling of serum creatinine (accompanied by eGFR [MDRD] ≤ 45ml/min/1.73m²*)</td>
<td>70/4645 (1.5)</td>
<td>5.5</td>
</tr>
</tbody>
</table>

EMPA-REG Renal Outcomes

CANVAS Observed Renal Effects

- Progression of albuminuria occurred less frequently (27% reduction)
- Regression of albuminuria also occurred more frequently (hazard ratio=1.70)
- Worsening renal outcomes occurred less frequently (40% reduction)

CANVAS Renal Outcomes

CVD REAL Study

- Retrospective, observational study – collected data from health records
- 39% relative risk reduction for hospitalization for HF
- 51% relative risk reduction for all-cause death

(1) https://www.cvdreal.com
CVD Real Study
Contribution of SGLT2 inhibitors

https://www.medscape.org/viewarticle/877494_2
Observations…

- Reduction was observed early
  - Within 2-3 months of starting therapy
  - Clearly established at 6 months

- A1C reduction was modest
  - 0.3-0.45% (empa-reg), 0.58% (canvas)

- Changed in lipid levels were small/insignificant

Haemodynamic Mechanism?

- **Blood pressure reduction**
  - 5/2.5 mmHg (empa-reg), 3.93/1.39 mmHg (canvas)
  - Significantly reduced at 1 month, maximum at 4 months

- **SGTL2 inhibition**
  - Modest ↓ in *intravascular volume depletion*
  - ↓ body weight (fluid loss AND fat/muscle mass) max at 4 months with empa-reg

- Combined afterload and preload reduction
- No increased heart rate


Other considerations...

- ↑ hematocrit = ↓ preload to the heart
- Metabolic change
  - Moderate ↑ ketonemia
  - Beta-hydroxybutyrate to heart and kidney, a more effective fuel source?
- Decreased markers of arterial stiffness (direct effects on vessel wall?)
- Normalization of low magnesium levels
- Slowed progression of renal disease


Normalization of Serum Mg Observed with Canagliflozin

Figure 2. Percent change from baseline in serum Mg at Week 26.

<table>
<thead>
<tr>
<th>Baseline serum Mg &lt;1.8 mg/dL</th>
<th>Baseline serum Mg ≥1.8 mg/dL</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>n</td>
</tr>
<tr>
<td>111</td>
<td>517</td>
</tr>
<tr>
<td>166</td>
<td>658</td>
</tr>
<tr>
<td>134</td>
<td>683</td>
</tr>
<tr>
<td>1.6</td>
<td>2.0</td>
</tr>
<tr>
<td>1.6</td>
<td>2.0</td>
</tr>
<tr>
<td>1.6</td>
<td>2.0</td>
</tr>
</tbody>
</table>

15.1% (95% CI: 12.4, 17.7)
13.0% (95% CI: 10.5, 15.6)
8.4% (95% CI: 7.6, 9.2)
6.3% (95% CI: 5.5, 7.2)

LS mean % change from baseline

PBO  CANA 100 mg  CANA 300 mg
CV risk in CKD

- Impaired kidney function and raised concentrations of albumin in urine increase the risk of CVD by 2-4 times
- Strong causal association between CKD and CV risk implies that to prevent progression of CKD is, by definition, to prevent CVD

CV risk in CKD
Ongoing SGLT2 inhibitor in CHF trials

**EMPEROR-HF**
- Evaluate the efficacy and safety of empagliflozin in patients with CHF, including those with and without type 2 diabetes
- Estimated completion 2020

**DAPA-HF**
- Evaluate the effect of dapagliflozin on time to first worsening heart failure event or CV death in patients with CHF and reduced ejection fraction, irrespective of glycaemic status
- Estimated completion of Dec 2019

Patient Case

History of Type 2 Db for 6.5 years
A1C = 6.8%, Weight = 235 lbs, BMI = ?, Hispanic
History of MI 2 years ago

Current meds:
- Metformin 500 mg once daily, sitagliptin (Januvia®) 100 mg daily

Other pertinent info:
Would consider injectable therapy
Has a high deductible plan
eGFR = 80 mL/min
Meeting LDL goals on high-intensity statin, meeting BP goals on ARB, using daily aspirin 81 mg, non-smoker. Microalbuminuria present.
Medication Decisions – Scenarios

- Even though Db is “Stable”, would you consider changing her therapies?
- What if background therapy was Glipizide?
- What if her CVD history was a stroke instead of MI?
- What if she did not have CVD history?
- What if her A1C was 7.7% and you wanted to start one medication only?
- What if her A1C was 9.5%?
“But these new drugs are too expensive!”
## Break down of the costs of diabetes

<table>
<thead>
<tr>
<th>Cost Component</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospital stays</td>
<td>43%</td>
</tr>
<tr>
<td>Prescriptions for diabetes complications</td>
<td>18%</td>
</tr>
<tr>
<td>Anti-diabetic agents and diabetes supplies</td>
<td>12%</td>
</tr>
<tr>
<td>Doctor’s visits</td>
<td>9%</td>
</tr>
<tr>
<td>Nursing/residential facility stays</td>
<td>8%</td>
</tr>
</tbody>
</table>

How to Approach Cost Concerns

- High Deductible (use copay cards)
- Medicare (Deductible, Donut Hole)
- Generic options (SFU, pioglitazone)
- Formulary look-up apps (MMIT)
- Setting patient expectations, sampling
- Replacement with more effective therapies
Summary

- Intensive glucose control has not demonstrated reduced CV death or HF
- Pioglitazone can increase risk of CHF, but can decreased stroke risk
- GLP1 RA
  - In patients with T2D and high CV risk, various GLP1 RA & SGLT2i trials have shown reduction in 3-point MACE
    - GLP1 RA associated with reduced CV death and slowing of atherosclerosis
    - SGLT2i associated with HF hospitalization and cardiac death
- SGLT2i therapy been associated with improved renal outcomes
- Treatment recommendations should consider overall CV risk reduction versus an isolated goal of HbA1C reduction
Questions?

it's about the journey
not the destination.