Anti-hyperglycemic Agents and Atherosclerotic CV Disease:

A Cardiologist’s Perspective

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University of Texas Southwestern Medical Center

• ICH Guidelines:
  – 1500 patients exposed
  – 300-600 x 6 months
  – 100 x 1 year

• Approval based on as little as 250 patient-years of exposure
Paradigm shift

- Increasing incidence/prevalence of T2DM
  - >10% of US adult population
- Growing awareness of CV impact of T2DM
- Numerous examples of adverse drug effects
  - On target
  - Off target
- Proliferation of medications available
FDA Regulatory Guidance for Drugs for Type 2 Diabetes

FDA NEWS RELEASE
FOR IMMEDIATE RELEASE
December 17, 2008

FDA Announces New Recommendations on Evaluating Cardiovascular Risk in Drugs Intended to Treat Type 2 Diabetes

The U.S. Food and Drug Administration recommended today that manufacturers developing new drugs and biologics for type 2 diabetes provide evidence that the therapy will not increase the risk of such cardiovascular events as a heart attack. The recommendation is part of a new guidance for industry that applies to all diabetes drugs currently under development.

"We need to better understand the safety of new antidiabetic drugs. Therefore, companies should conduct a more thorough examination of their drugs' cardiovascular risks during the product's development stage," said Mary Parks, M.D., director, Division of Metabolism and Endocrinology Products, Center for Drug Evaluation and Research (CDER), FDA. "FDA's guidance outlines the agency's recommendations for doing such an assessment."

"...sponsors should demonstrate that the therapy will not result in an unacceptable increase in cardiovascular risk."

Requires ~15,000 pt-yrs of exposure

http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2008/ucm116994.htm
...it was just an acorn that fell.

SAVOR-TIMI 53 Enrollment

Final Enrollment
n=16,492

1st Patient Enrolled
May 5, 2010

>300/week

Last Patient Enrolled
December 12, 2011

Courtesy of Ben Scirica, MD, TIMI Study Group
The Incretin System: Key Regulator of Post-Prandial Glucose Metabolism

- Insulin secretion
- Glucagon secretion
- Peripheral glucose uptake
- Hepatic glucose production
- Gastric emptying
- Inhibitor
- DPP-4
- GLP-1
- GIP

Courtesy, Silvio Inzucchi, MD
## Incretin Modulators on US Market

<table>
<thead>
<tr>
<th></th>
<th>Generic</th>
<th>Trade Names</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DPP4 inhibitors (tablets)</strong></td>
<td>sitagliptin</td>
<td>Januvia</td>
</tr>
<tr>
<td></td>
<td>saxagliptin</td>
<td>Onglyza</td>
</tr>
<tr>
<td></td>
<td>alogliptin</td>
<td>Nesina</td>
</tr>
<tr>
<td></td>
<td>linagliptin</td>
<td>Tradjenta</td>
</tr>
<tr>
<td><strong>GLP1-Receptor Agonists (injectables)</strong></td>
<td>exenatide</td>
<td>Byetta</td>
</tr>
<tr>
<td></td>
<td>liraglutide</td>
<td>Victoza</td>
</tr>
<tr>
<td></td>
<td>albiglutide</td>
<td>Tanzeum</td>
</tr>
<tr>
<td></td>
<td>exenatide ER</td>
<td>Bydureon</td>
</tr>
<tr>
<td></td>
<td>dulaglutide</td>
<td>Trulicity</td>
</tr>
<tr>
<td></td>
<td>lixisenatide</td>
<td>AdlyxinTM</td>
</tr>
</tbody>
</table>
Phase II / IIIa Pooled Analysis of Effect of Saxagliptin on CV Death/MI/Stroke

**HR 0.44**
*(95% CI 0.24-0.82)*

41 total events

Proposed Pleiotropic CV Effects of DPP4 Inhibition and GLP1-RA

- Myocardial infarct size\(^1,2\)
- Triglycerides\(^8\)
- Left ventricular function\(^6,7\)
- Endothelial function\(^3\)
- Inflammation and oxidative stress\(^4\)
- Atherosclerotic plaque volume\(^5\)

Saxagliptin and Cardiovascular Outcomes in Patients with Type 2 Diabetes Mellitus


Alogliptin after Acute Coronary Syndrome in Patients with Type 2 Diabetes

William B. White, M.D., Christopher P. Cannon, M.D., Simon R. Lim, M.D., Steven E. Nissen, M.D., Richard M. Bergenstal, M.D., George L. Borch-Johnsen, M.D., Alfonso T. Perez, M.D., Penny R. Fleck, M.B.A., Cyrus R. Mehta, Stuart Kufner, M.D., Craig Wilson, Ph.D., William C. Cushman, and Fazli Zannad, M.D., Ph.D., for the EXAMINE Investigators.

Effect of Sitagliptin on Cardiovascular Outcomes in Type 2 Diabetes

SAVOR-TIMI 53, EXAMINE, and TECOS: MACE Events

<table>
<thead>
<tr>
<th>Study Drug</th>
<th>Drug n/N (%)</th>
<th>Placebo n/N (%)</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SAVOR-TIMI (saxagliptin vs. placebo)</td>
<td>613/8280 (7.4%)</td>
<td>609/8212 (7.4%)</td>
<td>1.00</td>
<td>0.89, 1.12</td>
<td>0.99</td>
</tr>
<tr>
<td>EXAMINE (alogliptin vs. placebo)</td>
<td>305/2701 (11.3%)</td>
<td>316/2679 (11.8%)</td>
<td>0.96</td>
<td>NA, 1.16</td>
<td>0.315</td>
</tr>
<tr>
<td>TECOS (sitagliptin vs. placebo)</td>
<td>745/7332 (10.2%)</td>
<td>746/7339 (10.2%)</td>
<td>0.99</td>
<td>0.89, 1.10</td>
<td>0.844</td>
</tr>
<tr>
<td>SAVOR + EXAMINE + TECOS</td>
<td>1663/18313 (9.1%)</td>
<td>1671/18230 (9.2%)</td>
<td>0.99</td>
<td>0.92, 1.06</td>
<td></td>
</tr>
</tbody>
</table>

ELIXA: CV Effects of Lixisenatide vs Placebo

1° Outcome: CV Death, MI, Stroke, or UA

HR 1.02  
(95% CI, 0.89-1.17)

Lixisenatide: 406/3034 (13.4%)
Placebo: 399/3034 (13.2%)

No. at risk:
Placebo 3034  
Lixisenatide 3034
2759  
2785  
1566  
1558  
476  
484

There’s got to be a better way…

**ON MY MIND**

Randomized Trials to Evaluate Cardiovascular Safety of Antihyperglycemic Medications

A Worthwhile Effort?


Evaluating the Cardiovascular Safety of New Medications for Type 2 Diabetes: Time to Reassess?

Rare but serious adverse drug reactions require large exposure…

- **Taspoglutide (~600 pt years)**
  - Nausea
  - Vomiting
  - Antibody formation
  - Anaphylactoid reactions

- **Aleglitazar (>14,000 patient years)**
  - HF
  - Decline in eGFR
  - Bone fracture
  - GI Bleeds

- **Fasiglifam (~2000 patient years)**
  - Drug-associated liver injury (10-fold increase in elevated LFTs)

SAVOR TIMI 53-Hospitalization for Heart Failure

Time to the 1st occurrence of any hospitalization for heart failure; 517 events

HR 1.27
P=0.007

Saxagliptin: 3.5%
Placebo: 2.8%

SAVOR-TIMI 53, EXAMINE, and TECOS*: Hospitalization for Heart Failure

<table>
<thead>
<tr>
<th>Trial</th>
<th>HR (95% CI)</th>
<th>P-Value</th>
<th>Events (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SAVOR-TIMI 53</td>
<td>1.27 (1.07–1.51)</td>
<td>0.007</td>
<td>517</td>
</tr>
<tr>
<td>EXAMINE</td>
<td>1.19 (0.89–1.59)</td>
<td>0.235</td>
<td>195</td>
</tr>
<tr>
<td>TECOS</td>
<td>1.00 (0.84–1.20)</td>
<td>1.000</td>
<td>457</td>
</tr>
<tr>
<td>SAVOR-TIMI + EXAMINE + TECOS</td>
<td>1.14 (0.97–1.34)</td>
<td>0.102</td>
<td>1169</td>
</tr>
</tbody>
</table>

Test for heterogeneity for 3 trials: p=0.16, I²=44.9

Normal Kidney Glucose Handling

Majority of glucose is reabsorbed by SGLT2 (90%)\(^1,2\)

Remaining glucose is reabsorbed by SGLT1 (10%)\(^1,2\)

Glucose filtration ≈ 180 g/day\(^1,2\)

Proximal tubule

Remaining glucose is reabsorbed by SGLT1 (10%)\(^1,2\)

Minimal to no glucose excretion\(^3\)

### SGLT2 Antagonists on US Market

<table>
<thead>
<tr>
<th>Generic</th>
<th>Trade Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>canagliflozin</td>
<td>Invokana</td>
</tr>
<tr>
<td>dapagliflozin</td>
<td>Forxiga</td>
</tr>
<tr>
<td>empagliflozin</td>
<td>Jardiance</td>
</tr>
</tbody>
</table>
EMPA REG OUCTOME: Effect of empagliflozin on CV Death/MI/Stroke

HR 0.86
(95.02% CI 0.74, 0.99)
p = 0.0382*

# EMPA-REG OUTCOME: CV outcomes

<table>
<thead>
<tr>
<th>Event</th>
<th>HR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>3P-MACE</td>
<td>0.86 (0.74, 0.99)</td>
<td>0.04</td>
</tr>
<tr>
<td>CV death</td>
<td>0.62 (0.49, 0.77)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Non-fatal MI</td>
<td>0.87 (0.70, 1.09)</td>
<td>0.22</td>
</tr>
<tr>
<td>Non-fatal stroke</td>
<td>1.24 (0.92, 1.67)</td>
<td>0.16</td>
</tr>
<tr>
<td>HHF</td>
<td>0.65 (0.50, 0.85)</td>
<td>0.002</td>
</tr>
</tbody>
</table>

The chart shows the hazard ratios (HR) with 95% confidence intervals (CI) for each event. The difference in outcomes favors empagliflozin over placebo. Zinman B et al. N Engl J Med 2015; 373: 2117-28
EMPA REG OUTCOME: Effect of empagliflozin on CV Death

HR 0.62
(95% CI 0.49, 0.77)
p<0.0001

First Ever Clinical Outcome Indication for a Type 2 Diabetes Medication

FDA News Release

FDA approves Jardiance to reduce cardiovascular death in adults with type 2 diabetes

Study links Jardiance to improved survival in patients with type 2 diabetes with cardiovascular disease

For Immediate Release

December 2, 2016
Hospitalization for heart failure

HR 0.65
(95% CI 0.50, 0.85)
\( p = 0.0017 \)

### Adjusted mean systolic blood pressure

<table>
<thead>
<tr>
<th>Week</th>
<th>Placebo</th>
<th>Empagliflozin 10 mg</th>
<th>Empagliflozin 25 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>127</td>
<td>125</td>
<td>123</td>
</tr>
<tr>
<td>16</td>
<td>136</td>
<td>133</td>
<td>131</td>
</tr>
<tr>
<td>28</td>
<td>141</td>
<td>137</td>
<td>135</td>
</tr>
<tr>
<td>52</td>
<td>143</td>
<td>139</td>
<td>137</td>
</tr>
<tr>
<td>88</td>
<td>146</td>
<td>142</td>
<td>140</td>
</tr>
<tr>
<td>133</td>
<td>150</td>
<td>146</td>
<td>143</td>
</tr>
<tr>
<td>178</td>
<td>156</td>
<td>152</td>
<td>150</td>
</tr>
<tr>
<td>206</td>
<td>164</td>
<td>160</td>
<td>158</td>
</tr>
</tbody>
</table>

Empagliflozin lowers intraglomerular pressure

Empagliflozin blocks SGLT2

Favorably affecting:
RAAS
Sympathetic tone

Adapted from Cherney D et al. Circulation 2014;129:587
Empagliflozin slowed decline in kidney function (eGFR) over time compared with placebo

**eGFR (CKD-EPI formula) over 192 weeks**

- **Placebo**
- **Empagliflozin 10 mg**
- **Empagliflozin 25 mg**

**Adjusted mean (SE) eGFR (ml/min/1.73 m²)**

<table>
<thead>
<tr>
<th>Week</th>
<th>Placebo</th>
<th>Empagliflozin 10 mg</th>
<th>Empagliflozin 25 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td>80</td>
<td>80</td>
<td>80</td>
</tr>
<tr>
<td>28</td>
<td>122</td>
<td>122</td>
<td>122</td>
</tr>
<tr>
<td>52</td>
<td>136</td>
<td>136</td>
<td>136</td>
</tr>
<tr>
<td>94</td>
<td>150</td>
<td>150</td>
<td>150</td>
</tr>
<tr>
<td>164</td>
<td>164</td>
<td>164</td>
<td>164</td>
</tr>
<tr>
<td>192</td>
<td>164</td>
<td>164</td>
<td>164</td>
</tr>
</tbody>
</table>

**No. analysed**

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Empagliflozin 10 mg</th>
<th>Empagliflozin 25 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>7020</td>
<td>7020</td>
<td>6996</td>
</tr>
<tr>
<td>No. in follow-up for adverse/outcome events</td>
<td>6864</td>
<td>6765</td>
<td>6696</td>
</tr>
</tbody>
</table>

Empagliflozin elevates ketone bodies – especially in the fasted state

T2D (n=66)

Ferrannini et al, Diabetes 2016;65:1190–1195
Hematocrit increased with empagliflozin: hemoconcentration and/or RBC expansion

Hematopoietic effects of dapagliflozin

The CANVAS Program consists of two randomised, double-blind, placebo-controlled trials.

### CANVAS Program (N=10,142)

|------|------|------|------|------|------|------|------|------|------|

#### CANVAS (n=4330)

- **CV safety study**
- Primary endpoint: 3P-MACE\(^1\)
- Follow-up: 296 weeks\(^2\)

#### CANVAS-R (n=5812)

- **Safety and albuminuria study**
- Primary endpoint: progression of albuminuria\(^1\)
- Follow-up: 108 weeks\(^2\)

\(^1\) End point 3P-MACE: All-cause mortality, non-fatal MI, non-fatal stroke

\(^2\) Follow-up time in weeks.
CANVAS Program: primary endpoint 3P-MACE

CV death, non-fatal MI or non-fatal stroke

![Graph showing the comparison between placebos and Canagliflozin over weeks.]

- **HR 0.86 (95% CI 0.75, 0.97)**
- *p* < 0.001 for noninferiority
- *p* = 0.02 for superiority

**No. at risk**
- Canagliflozin: 5795, 5672, 5566, 5447, 4343, 2984, 2555, 2513, 24
- Placebo: 4347, 4239, 4153, 4061, 2942, 1626, 1240, 1217, 11

**Patients with an event (%)**

- Weeks since randomisation: 0, 26, 52, 78, 104, 130, 156, 182, 208, 234, 260, 286, 312, 338
- Placebo
- Canagliflozin

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## CANVAS Program: components of 3P-MACE

<table>
<thead>
<tr>
<th>Patients with event/analyzed</th>
<th>Canagliflozin</th>
<th>Placebo</th>
<th>HR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>3P-MACE</td>
<td>585/5795</td>
<td>426/4347</td>
<td>0.86 (0.75, 0.97)</td>
<td>&lt;0.001 (non-inferiority) 0.02 (superiority)</td>
</tr>
<tr>
<td>CV death</td>
<td>268/5795</td>
<td>185/4347</td>
<td>0.87 (0.72, 1.06)</td>
<td>NR*</td>
</tr>
<tr>
<td>Non-fatal MI</td>
<td>215/5795</td>
<td>159/4347</td>
<td>0.85 (0.69, 1.05)</td>
<td>NR*</td>
</tr>
<tr>
<td>Non-fatal stroke</td>
<td>158/5795</td>
<td>116/4347</td>
<td>0.90 (0.71, 1.15)</td>
<td>NR*</td>
</tr>
</tbody>
</table>

*NR* indicates not reported.
EMPA REG versus CANVAS key outcomes

<table>
<thead>
<tr>
<th>Event</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV death, nonfatal myocardial infarction, or nonfatal stroke</td>
<td>CANVAS Program</td>
</tr>
<tr>
<td>CV death</td>
<td></td>
</tr>
<tr>
<td>Nonfatal myocardial infarction</td>
<td>EMPA-REG OUTCOME</td>
</tr>
<tr>
<td>Nonfatal stroke</td>
<td></td>
</tr>
<tr>
<td>Hospitalization for heart failure</td>
<td></td>
</tr>
<tr>
<td>CV death or hospitalization for heart failure</td>
<td></td>
</tr>
<tr>
<td>All-cause mortality</td>
<td></td>
</tr>
<tr>
<td>Progression to macroalbuminuria*</td>
<td></td>
</tr>
<tr>
<td>Renal composite*</td>
<td></td>
</tr>
</tbody>
</table>

*CANVAS Program endpoints comparable with

Effects of Canagliflozin and Empagliflozin on eGFR

Presented at EASD September 2017, Lisbon Portugal
**CANVAS Program: lower-limb amputations**

<table>
<thead>
<tr>
<th>Event rate per 1000 patient-years</th>
<th>Canagliflozin</th>
<th>Placebo</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All amputations (n=187)</strong></td>
<td>6.30</td>
<td>3.37</td>
<td>1.97 (1.41, 2.75)</td>
</tr>
<tr>
<td><strong>Minor amputations (71%)</strong></td>
<td>4.48</td>
<td>2.44</td>
<td>1.94 (1.31, 2.88)</td>
</tr>
<tr>
<td>Toe</td>
<td>3.44</td>
<td>2.16</td>
<td></td>
</tr>
<tr>
<td>Transmetatarsal</td>
<td>1.03</td>
<td>0.29</td>
<td></td>
</tr>
<tr>
<td><strong>Major amputations (29%)</strong></td>
<td>1.82</td>
<td>0.93</td>
<td>2.03 (1.08, 3.82)</td>
</tr>
<tr>
<td>Ankle</td>
<td>0.04</td>
<td>0.07</td>
<td></td>
</tr>
<tr>
<td>Below-knee</td>
<td>1.16</td>
<td>0.64</td>
<td></td>
</tr>
<tr>
<td>Above-knee</td>
<td>0.62</td>
<td>0.21</td>
<td></td>
</tr>
</tbody>
</table>

Favours canagliflozin
Favours placebo
## Amputation

<table>
<thead>
<tr>
<th></th>
<th>Per 1000 patient-years</th>
<th>Relative risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Active</td>
<td>Control</td>
</tr>
<tr>
<td>Canagliflozin</td>
<td>6.3</td>
<td>3.4</td>
</tr>
<tr>
<td>Empagliflozin</td>
<td>6.3</td>
<td>6.3</td>
</tr>
<tr>
<td><strong>Subtotal</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\( I^2 = 86\%; p = 0.01 \)

Favours SGLT2i    Favours placebo

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*Presented at the 63rd Annual Meeting of the European Association for the Study of Diabetes; 16 September 2017; Lisbon, Portugal.*

*Rådholm K, et al. 2017, submitted for publication*
• 2016 ESC HF Guidelines
  – Empagliflozin should be considered in patients with type 2 diabetes in order to prevent or delay the onset of HF and prolong life
  
  European Heart Journal 2016; 37, 2129–2200

• 2016 ESC CVD Prevention Guidelines
  – In patients with type 2 DM and CVD, the use of an SGLT2 inhibitor should be considered early on the course of the disease to reduce CV and total mortality.
  
  European Heart Journal 2016; 37, 2315-2381

• 2017 ADA Standards of Medical Care
  – Empagliflozin should be considered in patients with long-standing suboptimally controlled T2D and established atherosclerotic cardiovascular disease (ASCVD) to reduce the risk of mortality.
  
  Diabetes Care 2017; 40 (Suppl 1): S1-S135
SGLT2 Inhibitors:
Practical considerations for their prescription

- Consider altering background blood pressure medications if intensively controlled
- Consider stopping/reducing background diuretics
- If on insulin and/or sulfonylurea, consider dose reducing each of those
- Counsel re: urinary hygiene
- “Sick Day” medication concept-hold on days with reduced PO intake
LEADER
Primary Outcome and CV Death

Primary Outcome

Death From Cardiovascular Causes

HR, 0.87 (95% CI, 0.78-0.97)
*P* < .001 (noninferiority)
P < .01 (superiority)

No. at Risk

Liraglutide | Placebo
---|---
4668 | 4593
4599 | 4476
4400 | 4350
4280 | 4230
4172 | 4123
4072 | 4013
3982 | 3913
1582 | 1543
424 | 407

SUSTAIN-6
Primary Outcome

HR, 0.74 (95% CI, 0.58-0.95)
\( P < .001 \) (noninferiority)
\( P = .02 \) (superiority)

GLP-1 RA Studies
Primary Outcome & its individual components

<table>
<thead>
<tr>
<th>Drug</th>
<th>ELIXA</th>
<th>LEADER</th>
<th>SUSTAIN-6</th>
<th>EXSCEL</th>
</tr>
</thead>
<tbody>
<tr>
<td>lixisenatide</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>liraglutide</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>semaglutide</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exenatide ER</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- **Primary composite MACE**
  - lixisenatide: $P = 0.81$
  - liraglutide: $P = 0.01$
  - semaglutide: $P = 0.02$
  - Exenatide ER: $P = 0.06$

- **Cardiovascular mortality**
  - liraglutide: $P = 0.007$
  - Exenatide ER: ns

- **Myocardial infarction**
  - semaglutide: $P = 0.046$
  - Exenatide ER: ns

- **Stroke**
  - Exenatide ER: ns

- **Unstable angina**
  - Exenatide ER: ns

Cl: confidence interval; MACE: major adverse cardiovascular event; ns, not significant.

Conclusions

• Regulatory requirements have dramatically altered the trial landscape of drug development for T2DM
  – > 240,000 patients enrolled/planned in CV outcomes trials

• 5 completed trials demonstrating CV safety
  – SAVOR TIMI 53: saxagliptin
  – EXAMINE: alogliptin
  – TECOS: sitagliptin
    ▪ Labeled caution for HF for all DPP4i’s based on alogliptin and saxagliptin data
  – ELIXA: lixisenatide
  – EXCSEL: exenatide ER

• 4 trials/programs have reported CV benefit
  – EMPA-REG: empagliflozin
  – CANVAS Program: canagliflozin
  – LEADER: liraglutide
  – SUSTAIN-6: semaglutide
    ▪ The mechanisms for these favorable results are not fully understood