Diabetes and CV outcome trials: Selected Lessons Learned thus Far

Darren K. McGuire, MD, MHSc
Professor of Medicine
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 underpinning regulatory change

- Increasing incidence/prevalence of T2DM
  - >10% of US adult population
- Growing awareness of CV impact of T2DM
- Proliferation of medications available
- Numerous examples of adverse drug effects
  - On target
  - Off target
Present 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 risk 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

The sky is falling...
...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

Incretin Modulators on US Market

<table>
<thead>
<tr>
<th></th>
<th>Generic</th>
<th>Trade Names</th>
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<tbody>
<tr>
<td>DPP4 inhibitors</td>
<td>sitagliptin</td>
<td>Januvia</td>
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<td>saxagliptin</td>
<td>Onglyza</td>
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<td></td>
<td>alogliptin</td>
<td>Nesina</td>
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<td>linagliptin</td>
<td>Tradjenta</td>
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<td>GLP1-Receptor Agonists</td>
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<td>Byetta</td>
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<td></td>
<td>liraglutide</td>
<td>Victoza</td>
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<td>dulaglutide</td>
<td>Trulicity</td>
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Time to Onset of First Primary MACE in Prior Pooled Analysis

Patients at Risk

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Saxagliptin Controlled Phase 2b/3 Pooled Population

HR 0.44 (95% CI 0.24-0.82)
41 total events

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Proposed Pleiotropic CV Effects of DPP4 Inhibition and GLP1-RA

SAVOR TIMI 53-Primary Endpoint

N = 16,492
1222 Primary MACE Events

CV Death, MI or Ischemic CVA (%)

Months

2y KM

Saxagliptin 7.3%

Placebo 7.2%

HR 1.00
95% CI 0.89-1.12
p<0.001 (non-inferiority)

N = 16,492
1222 Primary MACE Events

Primary end point

N = 5380

Hazard ratio, 0.96 (* one-sided repeated CI bound, 1.16)

Events, No. (%) Placebo: 316 (11.8) Alogliptin: 305 (11.3)

Cumulative Incidence of the Primary End Point (%)

Placebo (n): 2679 2299 1891 1375 805 286
Alogliptin (n): 2701 2316 1899 1394 821 296

Primary Composite Cardiovascular Outcome*
Per Protocol Analysis for Noninferiority

Green JB et al. NEJM 2015;373: 232-42

ELIXA: Lixisenatide vs. Placebo
Effects on CV Outcomes

Pfeffer MA et al. NEJM 2015; 373: 2247-57.
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)

Gastrointestinal Bleeding Associated with Aleglitazar: ALECARDIO Trial


SAVOR TIMI 53-Hospitalization for Heart Failure

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

Saxagliptin Placebo

HR 1.80 P=0.001
HR 1.46 P=0.002
HR 1.27 P=0.007

0.6% 1.1% 1.9% 2.8%

1.3%

Landmark Analysis at 12m
1.7% vs. 1.5% - HR 1.09, p=0.51
Time-varying interaction p value = 0.017

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>
</tr>
</thead>
<tbody>
<tr>
<td>SAVOR-TIMI</td>
<td>1.27 (1.07–1.51)</td>
<td>0.007</td>
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<tr>
<td>EXAMINE</td>
<td>1.19 (0.89–1.59)</td>
<td>0.235</td>
</tr>
<tr>
<td>TECOS</td>
<td>1.00 (0.84–1.20)</td>
<td>1.000</td>
</tr>
<tr>
<td>SAVOR-TIMI + EXAMINE + TECOS</td>
<td>1.14 (0.97–1.34)</td>
<td>0.102</td>
</tr>
</tbody>
</table>

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

McGuire DK, et al. ESC 2015

Annualized Rates of CV Death/MI/Stroke in Recent Outcomes Trials

### PROactive Primary Endpoint

**Kaplan-Meier Event Rate**

- **Time From Randomization (mo)**:
  - 5238
  - 5018
  - 4786
  - 4619
  - 4433
  - 4268
  - 4268
  - 693 (228)

- **Risk**:
  - Placebo (572 events)
  - Pioglitazone (514 events)

- **HR**: 0.90
- **P**: 0.095
- **95% CI**: 0.80-1.02

**Death, MI, CVA, ACS, Leg Revascularization or Amputation, PCI, or CABG**


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### PROactive Prioritized Secondary Endpoint

**Kaplan-Meier Event Rate**

- **Time From Randomization (mo)**:
  - 5238
  - 5012
  - 4991
  - 4877
  - 4752
  - 4651
  - 786 (256)

- **Risk**:
  - Placebo (358 events)
  - Pioglitazone (301 events)

- **HR**: 0.84
- **P**: 0.027
- **95% CI**: 0.72-0.98

**Death, MI, CVA**

Normal renal glucose handling

Majority of glucose is reabsorbed by SGLT2 (90%)

Proximal tubule

Remaining glucose is reabsorbed by SGLT1 (10%)

Minimal to no glucose excretion

Glucose Filtration ~180g/day

SGLT2 Antagonists on US Market

<table>
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<tr>
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<tr>
<td>canagliflozin</td>
<td>Invokana</td>
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<tr>
<td>dapagliflozin</td>
<td>Farxiga</td>
</tr>
<tr>
<td>empagliflozin</td>
<td>Jardiance</td>
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</tbody>
</table>
Primary outcome:
3-point MACE

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


CV death

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

CV death

Empagliflozin 10 mg
HR 0.65
(95% CI 0.50, 0.85)
p = 0.0016

Empagliflozin 25 mg
HR 0.59
(95% CI 0.45, 0.77)
p = 0.0001

Hospitalization for heart failure

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

**IRIS Primary Outcome**

![Graph showing cumulative event-free survival probability over months in trial for Pioglitazone and Placebo, with HR 0.76 (95% CI 0.62 to 0.93) and P=0.007.]


*Cumulative event rates

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**Hot of the Press…**

*company announcement*

**Victoza® significantly reduces the risk of major adverse cardiovascular events in the LEADER trial**

*Bagsværden, Denmark, 4 March 2016* - Novo Nordisk today announced the top-line results from the LEADER trial, which investigated the cardiovascular safety of Victoza® (liraglutide) over a period of up to 5 years in more than 9,000 adults with type 2 diabetes at high risk of major adverse cardiovascular events. The trial compared the addition of either Victoza® or placebo to standard of care and met the primary endpoint of showing non-inferiority as well as demonstrating superiority, with a statistically significant reduction in cardiovascular risk. The primary endpoint of the study was defined as the composite outcome of the first occurrence of cardiovascular death, non-fatal myocardial infarction or non-fatal stroke. The superior reduction of major adverse cardiovascular events demonstrated by Victoza® was derived from all three components of the endpoint.*
Conclusions

• Diabetes is common and increasing, with significant associated CV morbidity and mortality

• Role of glucose control in CVD risk mitigation remains uncertain
  • What drugs/strategies; what intensity; what timing
  • Side effects-both on- and off-target
  • Imperative to at a minimum establish CV safety

• Evolution of regulatory guidance has dramatically altered the trial landscape of drug development for type 2 diabetes mellitus
  • >200,000 patients enrolled/planned in CV outcomes trials
  • 4 trials now reported demonstrating CV safety
  • EMPA REG outcome has reported CV efficacy with empagliflozin