Impact of Regulatory Guidance on Evaluating Cardiovascular Risk of New Glucose-Lowering Therapies to Treat Type 2 Diabetes Mellitus: Lessons Learned and Future Directions

Christopher Granger MD
Duke Clinical Research Institute
Abhinav Sharma MD, PhD
McGill University Health Centre
Disclosures – Christopher Granger

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Agenda

- Diabetes and the scope of the problem
- Outcomes among patients with diabetes
- The need for the 2008 Regulatory Guidance
- Impact of the 2008 Regulatory Guidance
- New updates: 2020 Draft Regulatory Guidance
- Future direction and discussion
Diabetes: An Introduction

http://www.idf.org/about-diabetes
Type 2 Diabetes Mellitus

- **Type 2 diabetes** used to be called non-insulin dependent diabetes or adult-onset diabetes,
- 90% of all cases of diabetes.
- Hallmark is **insulin resistance** and relative insulin deficiency
- The diagnosis of type 2 diabetes can occur at any age
- Associated with overweight or obesity
- People with type 2 diabetes can often initially manage their condition through exercise and diet.
- Over time most people will require oral drugs and or insulin.
Age-Adjusted Prevalence of Obesity and Diagnosed Diabetes Among U.S. Adults

2010

Obesity (BMI ≥ 30 kg/m²)

Diabetes

CDC's Division of Diabetes Translation. National Diabetes Surveillance System
Available at http://www.cdc.gov/diabetes/statistics
Diabetes* is Associated with Significant Loss of Life Years

12.3M patient years follow-up; Mean Age 55; 48% women

On average, a 50-year-old person with diabetes and no history of vascular disease will die 6 years earlier relative to a counterpart without diabetes

* Type 1 or 2 diabetes mellitus
Complications of Diabetes

Diabetic Retinopathy
Leading cause of blindness in adults

Diabetic Nephropathy
Leading cause of end-stage renal disease

Stroke
2- to 4-fold increase in cardiovascular mortality and stroke

Cardiovascular Disease
8/10 individuals with diabetes die from CV events

Diabetic Neuropathy
Leading cause of non-traumatic lower extremity amputations
Scope of the problem

N Engl J Med 2017; 376:1407-1418
Heart Failure and Diabetes: Emerging Epidemic?

Individual non-CV comorbidities

Sharma A et al. Circulation Heart failure; 2018; 11(6)
Scope of the problem

Take away message

- Among patients with diabetes, atherosclerotic disease is the largest driver of morbidity and mortality
- Heart failure is just as common (if not more) in patients with type 2 diabetes
- Diabetes is present in nearly half of patients with heart failure
- Strategies are needed to reduce the burden of cardiovascular outcomes in patients with diabetes
Anti-hyperglycemic Therapies
In Patients with Diabetes
Trigger for the 2008 U.S. FDA Guidance

- Two controversial meta-analyses evaluating MACE risk of 2 classes of T2DM drugs spurred the development of guidance from the FDA and other regulatory agencies.
- Guidance calling for the evaluation of the risk of CV outcomes with glucose-lowering therapies.
Anti-hyperglycemic Therapies and CV Risk

Effect of Rosiglitazone on the Risk of Myocardial Infarction and Death from Cardiovascular Causes

Steven E. Nissen, M.D., and Kathy Wolski, M.P.H.

## Table 4. Rates of Myocardial Infarction and Death from Cardiovascular Causes.

<table>
<thead>
<tr>
<th>Study</th>
<th>Rosiglitazone Group</th>
<th>Control Group</th>
<th>Odds Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Myocardial infarction</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Small trials combined</td>
<td>44/10,285 (0.43)</td>
<td>22/6106 (0.36)</td>
<td>1.45 (0.88–2.39)</td>
<td>0.15</td>
</tr>
<tr>
<td>DREAM</td>
<td>15/2,635 (0.57)</td>
<td>9/2634 (0.34)</td>
<td>1.65 (0.74–3.68)</td>
<td>0.22</td>
</tr>
<tr>
<td>ADOPT</td>
<td>27/1,456 (1.85)</td>
<td>41/2895 (1.42)</td>
<td>1.33 (0.80–2.21)</td>
<td>0.27</td>
</tr>
<tr>
<td><strong>Overall</strong></td>
<td></td>
<td></td>
<td>1.43 (1.03–1.98)</td>
<td>0.03</td>
</tr>
<tr>
<td><strong>Death from cardiovascular causes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Small trials combined</td>
<td>25/6,845 (0.36)</td>
<td>7/3980 (0.18)</td>
<td>2.40 (1.17–4.91)</td>
<td>0.02</td>
</tr>
<tr>
<td>DREAM</td>
<td>12/2,635 (0.46)</td>
<td>10/2634 (0.38)</td>
<td>1.20 (0.52–2.78)</td>
<td>0.67</td>
</tr>
<tr>
<td>ADOPT</td>
<td>2/1,456 (0.14)</td>
<td>5/2895 (0.17)</td>
<td>0.80 (0.17–3.86)</td>
<td>0.78</td>
</tr>
<tr>
<td><strong>Overall</strong></td>
<td></td>
<td></td>
<td>1.64 (0.98–2.74)</td>
<td>0.06</td>
</tr>
</tbody>
</table>
Effect of Muraglitazar on Death and Major Adverse Cardiovascular Events in Patients With Type 2 Diabetes Mellitus

Steven E Nissen, Kathy Wolski, Eric J Topol

Affiliations + expand

PMID: 16239637 DOI: 10.1001/jama.294.20.joc50147
<table>
<thead>
<tr>
<th>Composite End Points</th>
<th>Muraglitazar (n = 2374)</th>
<th>Control (n = 1351)</th>
<th>Relative Risk (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality plus nonfatal MI or stroke</td>
<td>35 (1.47)</td>
<td>9 (0.67)</td>
<td>2.23 (1.07-4.66)</td>
<td>.03</td>
</tr>
<tr>
<td>All-cause mortality plus nonfatal MI, stroke, CHF, or TIA</td>
<td>50 (2.11)</td>
<td>11 (0.81)</td>
<td>2.62 (1.36-5.05)</td>
<td>.004</td>
</tr>
<tr>
<td>Cardiovascular death plus nonfatal MI or stroke</td>
<td>27 (1.14)</td>
<td>7 (0.52)</td>
<td>2.21 (0.96-5.08)</td>
<td>.06</td>
</tr>
<tr>
<td>Cardiovascular death plus nonfatal MI, stroke, CHF, or TIA</td>
<td>42 (1.77)</td>
<td>9 (0.67)</td>
<td>2.69 (1.30-5.53)</td>
<td>.007</td>
</tr>
<tr>
<td>All-cause mortality or nonfatal MI</td>
<td>27 (1.14)</td>
<td>7 (0.52)</td>
<td>2.21 (0.96-5.08)</td>
<td>.06</td>
</tr>
<tr>
<td>Cardiovascular death or nonfatal MI</td>
<td>19 (0.80)</td>
<td>5 (0.37)</td>
<td>2.17 (0.81-5.83)</td>
<td>.12</td>
</tr>
</tbody>
</table>
In 2008, the US Food and Drug Administration (FDA) put forth guidelines for sponsors to demonstrate that their anti-hyperglycemic medications do not increase the risk of cardiovascular disease.
HISTORICAL CONSIDERATION OF THE 2008 US FDA GUIDANCE

- Approval for T2DM medications indicated to lower blood glucose was previously based primarily on demonstration of reductions in glucose or HbA1c.
- The duration of trials: typically 6 to 12 months or shorter
- Generally requiring only 300 to 600 patients exposed for 6 months and only 100 exposed for a year.
- Patients with existing cardiovascular disease, including HF, were often excluded.
Table 1. Main Components of 2008 FDA Guidance for Sponsors on the Evaluation of Cardiovascular Risk of New Glucose-Lowering Drugs\textsuperscript{13}

<table>
<thead>
<tr>
<th>Requirement</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Outcome trial must exclude</td>
<td>HR 1.8 (preapproval) and 1.3 (postapproval)</td>
</tr>
<tr>
<td>Patient selection should include</td>
<td>high-risk population, including the elderly and those with advanced cardiovascular disease, and some degree of renal impairment</td>
</tr>
<tr>
<td>Duration must be at least 2 y</td>
<td></td>
</tr>
<tr>
<td>Required cardiovascular events:</td>
<td>cardiovascular mortality, myocardial infarction, stroke</td>
</tr>
<tr>
<td>Optional cardiovascular events:</td>
<td>hospitalization for acute coronary syndrome or urgent revascularization procedures</td>
</tr>
<tr>
<td>Cardiovascular events must be adjudicated in a blinded, independent process</td>
<td></td>
</tr>
</tbody>
</table>

FDA indicates US Food and Drug Administration; and HR, hazard ratio.
Impact of the 2008 FDA Guidance

Figure 1. Timeline of cardiovascular outcome trials since the 2008 US Food and Drug Administration guidance.
Impact of the 2008 FDA Guidance

- Most studies conducted after the establishment of the guidelines were enriched for participants with CV disease or additional CV risk factors.
- The recruitment of these patients satisfied the guidance requirement that the safety of studied drugs in the treatment of patients at high CV risk.
- Helped in the accrual of adequate numbers of events to be able to rule out the upper bounds of risk.

Circulation. 2020;141:843–862
Characteristics of the CVOT

- Typically, trials were conducted to demonstrate cardiovascular safety with a noninferiority margin of <1.3

- Because no previous glucose-lowering drug has a claim or indication of CV efficacy, CVOTs used a placebo control arm as the comparator group

- An exception to the placebo control design is the recently completed CAROLINA trial (Cardiovascular Outcome Study of Linagliptin Versus Glimepiride in Patients With Type 2 Diabetes), which compared linagliptin with glimepiride
Characteristics of the CVOT

- Most of the CVOTs had the 3-point MACE outcome (CV death, nonfatal MI, or nonfatal stroke) as the primary outcome.

- Three trials added hospitalization for unstable angina to create a 4-point MACE outcome as the primary outcome.
Results of the CVOT

- To date, the completed CVOTs have all demonstrated noninferiority

- i.e. no trial demonstrated an increase in the risk of 3-point or 4-point MACE associated with the antihyperglycemic agent compared to placebo

- Several trials have demonstrated superiority in 3-point MACE outcomes and other outcomes include HF and renal endpoints

Circulation. 2020;141:843–862
Results of the CVOT

- Some molecules within two classes of anti-hyperglycemic therapies have demonstrated efficacy in reducing the risk of CV outcomes
  
  - GLP-1 receptor agonists and SGLT-2 inhibitors
# GLP-1 Receptor Agonists

## Three-component MACE

<table>
<thead>
<tr>
<th>GLP-1 receptor agonist n/N (%)</th>
<th>Placebo n/N (%)</th>
<th>Hazard ratio (95% CI)</th>
<th>NNT (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ELIXA 400/3034 (13%)</td>
<td>392/3034 (13%)</td>
<td>1.02 (0.89-1.17)</td>
<td></td>
<td>0.78</td>
</tr>
<tr>
<td>LEADER 608/4668 (13%)</td>
<td>694/4672 (15%)</td>
<td>0.87 (0.78-0.97)</td>
<td></td>
<td>0.015</td>
</tr>
<tr>
<td>SUSTAIN-6 108/1648 (7%)</td>
<td>146/1649 (9%)</td>
<td>0.74 (0.58-0.95)</td>
<td></td>
<td>0.016</td>
</tr>
<tr>
<td>EXSCEL 839/7356 (11%)</td>
<td>905/7396 (12%)</td>
<td>0.91 (0.82-1.00)</td>
<td></td>
<td>0.061</td>
</tr>
<tr>
<td>Harmony Outcomes 338/4731 (7%)</td>
<td>428/4732 (9%)</td>
<td>0.78 (0.68-0.90)</td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>REWIND 594/4949 (12%)</td>
<td>663/4952 (13%)</td>
<td>0.88 (0.79-0.99)</td>
<td></td>
<td>0.026</td>
</tr>
<tr>
<td>PIONEER 6 61/1591 (4%)</td>
<td>76/1592 (5%)</td>
<td>0.79 (0.57-1.11)</td>
<td></td>
<td>0.17</td>
</tr>
<tr>
<td>Overall 2948/27977 (11%)</td>
<td>3304/28027 (12%)</td>
<td>0.88 (0.82-0.94)</td>
<td>75 (50-151)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

* I²=40.9%, p=0.118

## Cardiovascular death

<table>
<thead>
<tr>
<th>GLP-1 receptor agonist n/N (%)</th>
<th>Placebo n/N (%)</th>
<th>Hazard ratio (95% CI)</th>
<th>NNT (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ELIXA 156/3034 (5%)</td>
<td>158/3034 (5%)</td>
<td>0.98 (0.78-1.22)</td>
<td></td>
<td>0.85</td>
</tr>
<tr>
<td>LEADER 219/4668 (5%)</td>
<td>278/4672 (6%)</td>
<td>0.78 (0.66-0.93)</td>
<td></td>
<td>0.007</td>
</tr>
<tr>
<td>SUSTAIN-6 44/1648 (3%)</td>
<td>46/1649 (3%)</td>
<td>0.98 (0.65-1.48)</td>
<td></td>
<td>0.92</td>
</tr>
<tr>
<td>EXSCEL 340/7356 (5%)</td>
<td>383/7396 (5%)</td>
<td>0.88 (0.76-1.02)</td>
<td></td>
<td>0.096</td>
</tr>
<tr>
<td>Harmony Outcomes 122/4731 (3%)</td>
<td>130/4732 (3%)</td>
<td>0.93 (0.73-1.19)</td>
<td></td>
<td>0.58</td>
</tr>
<tr>
<td>REWIND 317/4949 (6%)</td>
<td>346/4952 (7%)</td>
<td>0.91 (0.78-1.06)</td>
<td></td>
<td>0.18</td>
</tr>
<tr>
<td>PIONEER 6 15/1591 (1%)</td>
<td>30/1592 (2%)</td>
<td>0.49 (0.27-0.92)</td>
<td></td>
<td>0.021</td>
</tr>
<tr>
<td>Overall 1213/27977 (4%)</td>
<td>1371/28027 (5%)</td>
<td>0.88 (0.81-0.96)</td>
<td>175 (110-524)</td>
<td>0.003</td>
</tr>
</tbody>
</table>

* I²=13.5%, p=0.327

# SGLT-2 Inhibitors

**Figure 1:** Meta-analysis of SGLT2i trials on the composite of myocardial infarction, stroke, and cardiovascular death (major adverse cardiovascular events) stratified by the presence of established atherosclerotic cardiovascular disease.

Lancet 2019; 393: 31–39

<table>
<thead>
<tr>
<th>Patients with atherosclerotic cardiovascular disease</th>
<th>Patients (n)</th>
<th>Events</th>
<th>Events per 1000 patient-years</th>
<th>Weight (%)</th>
<th>HR</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EMPA-REG OUTCOME</td>
<td>4687</td>
<td>2333</td>
<td>772</td>
<td>37.4</td>
<td>43.9</td>
<td>29.4</td>
</tr>
<tr>
<td>CANVAS Program</td>
<td>3756</td>
<td>2900</td>
<td>796</td>
<td>34.1</td>
<td>41.3</td>
<td>32.4</td>
</tr>
<tr>
<td>DECLARE-TIMI 58</td>
<td>3474</td>
<td>3500</td>
<td>1020</td>
<td>36.8</td>
<td>41.0</td>
<td>38.2</td>
</tr>
</tbody>
</table>

Fixed effects model for atherosclerotic cardiovascular disease (p=0.0002)

<table>
<thead>
<tr>
<th>Patients with multiple risk factors</th>
<th>Patients (n)</th>
<th>Events</th>
<th>Events per 1000 patient-years</th>
<th>Weight (%)</th>
<th>HR</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CANVAS Program</td>
<td>2039</td>
<td>1447</td>
<td>215</td>
<td>15.8</td>
<td>15.5</td>
<td>25.9</td>
</tr>
<tr>
<td>DECLARE-TIMI 58</td>
<td>5108</td>
<td>5078</td>
<td>539</td>
<td>13.4</td>
<td>13.3</td>
<td>74.1</td>
</tr>
</tbody>
</table>

Fixed effects model for multiple risk factors (p=0.98)
# SGLT-2 Inhibitors

![Figure 3: Meta-analysis of SGLT2i trials on hospitalisation for heart failure and cardiovascular death stratified by history of heart failure](image)

<table>
<thead>
<tr>
<th>Patients with history of heart failure</th>
<th>Patients</th>
<th>Events</th>
<th>Events per 1000 patient-years</th>
<th>Weight (%)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Treatment (n)</td>
<td>Placebo (n)</td>
<td>Treatment</td>
<td>Placebo</td>
<td></td>
</tr>
<tr>
<td>HPV-REG OUTCOME</td>
<td>462</td>
<td>244</td>
<td>124</td>
<td>63.6</td>
<td>85.5</td>
</tr>
<tr>
<td>CANVAS Program</td>
<td>803</td>
<td>658</td>
<td>203</td>
<td>35.4</td>
<td>56.8</td>
</tr>
<tr>
<td>DECLARE-TIMI 58</td>
<td>852</td>
<td>872</td>
<td>314</td>
<td>45.1</td>
<td>55.5</td>
</tr>
</tbody>
</table>

Fixed effects model for history of heart failure (p<0.0001)

<table>
<thead>
<tr>
<th>Patients with no history of heart failure</th>
<th>Patients</th>
<th>Events</th>
<th>Events per 1000 patient-years</th>
<th>Weight (%)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Treatment (n)</td>
<td>Placebo (n)</td>
<td>Treatment</td>
<td>Placebo</td>
<td></td>
</tr>
<tr>
<td>HPV-REG OUTCOME</td>
<td>4225</td>
<td>2089</td>
<td>339</td>
<td>15.5</td>
<td>24.9</td>
</tr>
<tr>
<td>CANVAS Program</td>
<td>4992</td>
<td>3689</td>
<td>449</td>
<td>13.6</td>
<td>15.2</td>
</tr>
<tr>
<td>DECLARE-TIMI 58</td>
<td>7730</td>
<td>7706</td>
<td>599</td>
<td>8.9</td>
<td>10.5</td>
</tr>
</tbody>
</table>

Fixed effects model for no history of heart failure (p<0.0001)
Adverse Safety Issues in CVOT

▪ In SAVOR-TIMI 53, saxagliptin was, compared to placebo was associated with an increased risk of HF (HR, 1.27; 95% CI 1.07–1.51)

▪ In EXAMINE, alogliptin was associated with a trend to increased HF risk (HR, 1.19 95% CI 0.90–1.58)

▪ There is now a black-box warning for the risk of HF among DPP-4 inhibitors due to data from the SAVOR-TIMI 53 trial and EXAMINE trial
Adverse Safety Issues in CVOT

- In the CANVAS trials an unexpected finding was an increased risk of extremity amputation with canagliflozin (HR, 1.97 [95% CI, 1.41–2.75])

- liraglutide and semaglutide were associated with a numerical increase in the risk of diabetic retinopathy complications compared with placebo
Overall Summary

- Explosion of CVOT since in the 2008 FDA guidance
- Significant costs to conducting these trials – estimated at $2 billion from discovery to FDA approval
- Affirmed the 3-point MACE safety of newer anti-hyperglycemic drugs
- Identified CV benefit with regards to CV death, HF and renal outcomes for various agents
- Identified safety issues with various agents
In October 2018, the FDA’s Endocrinologic and Metabolic Drugs Advisory Committee met to discuss the 2008 guidance.

The primary question: whether an unacceptable increase in CV risk needed to be excluded for all new antihyperglycemics in patients with T2DM, regardless of the presence or absence of a signal for CV risk in the development program.

The advisory committee narrowly voted 10 to 9 in favor of continuing to exclude unacceptable increases in CV risk for all new glucose-lowering therapies.
A think tank with representatives from academia, industry, government, private payers, and regulatory agencies convened to review the impact of the FDA guidance since 2008.

The aims of this meeting were to review the experience of CVOTs conducted since the guidance was issued and future directions.
Impact of Regulatory Guidance on Evaluating Cardiovascular Risk of New Glucose-Lowering Therapies to Treat Type 2 Diabetes Mellitus

Lessons Learned and Future Directions
2020 Draft FDA Guidance

- FDA recently updated the 2008 FDA Guidance and released a new draft version
- Removed the recommendation for the demonstration of a 1:3 non-inferiority margin
- Instead, focused on three features:
  1. Size and exposure duration of the Safety Database
  2. Patient Characteristics in the Development Program
  3. Other Considerations
Size of the Safety Database:

- At least 4,000 patient-years of exposure to the new drug in phase 3 clinical trials. (This exposure includes all dosage strengths studied in the phase 3 clinical trials.)
- At least 1,500 patients exposed to the new drug for at least 1 year
- At least 500 patients exposed to the new drug for at least 2 years
Patient Characteristics in the Development Program:

- At least 500 patients with stage 3/4 chronic kidney disease exposed to the new drug.
- At least 600 patients with established CV disease (e.g., previous myocardial infarction, documented coronary artery disease, previous stroke, peripheral vascular disease) exposed to the new drug
- At least 600 patients older than 65 years of age exposed to the new drug
Other Considerations:

- Sponsors should use rigorous methods for the collection of adverse CV events and assess them by adjudication.
- In some cases, the evaluation of a premarket safety concern may require that a drug development program accrue a minimum number of relevant adverse events to exclude a meaningful degree of risk. Adjudication of these adverse events may also be needed. The Agency expects that situations where the collection of these additional safety data is necessary will be identified and discussed before phase 3 trials are initiated.
- Sponsors should include DSMB or committees to provide independent oversight.
Future Directions

Issues to Re-evaluate

- Relatively short study duration
- Metformin as first-line therapy
- Limited scope of MACE outcomes
- 1.8 safety margin for initial approval

Recommendations

- Longer study duration
- Consider study drug as monotherapy
- Expand to include heart failure and renal outcomes
- Require 1.3 non-inferiority margin only
Future Directions

- Placebo comparator vs. Traditional RCT Design
- Homogenous study population vs. Low usage rates of study drugs in real world
- Active comparator (head-to-head comparison) vs. Pragmatic design (streamline safety reporting and clinical event adjudication)
- Diverse study population (women, minorities, elderly) vs. Implementation programs to improve care broadly
Questions

- When there is substantial evidence of efficacy and safety in a drug class, should the regulatory requirements for approval of a new drug be different?
- Is the cardiovascular protection of some of the antihyperglycemic drugs independent of effect on blood glucose?
- How should we consider varying effects on ischemic events, heart failure and kidney disease?
- How can regulators, industry, academia, payers, patient advocacy groups assure that evidence generation to improve care is incentivized without undue regulatory burdens?
Thank you for your time!