Effect of Exenatide Once-Weekly on Clinical Outcomes in Patients with Type 2 Diabetes Mellitus and Cardiovascular Disease: Insights from the EXSCEL Trial

Discussant

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AHA CSSP 2017 Updates
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Anaheim, CA
Common Endpoints in Diabetes Trials

Examples of Surrogate Outcomes Followed in Diabetes

Hb A1C, blood pressure, LDL, proteinuria, eGFR, neuropathy, retinopathy, LVEF, echocardiographic indices, hemoglobin, exercise parameters, BMI/weight, behavior…
Avandia draws new heart attack claims

Research adds to evidence that GlaxoSmithKline's second-bestselling drug increases the risk of heart attack.

**NEW ENGLAND JOURNAL OF MEDICINE**

**JUNE 14, 2007**

**Vol. 356 No. 24**

**The New York Times**

Heart Attack Risk Seen in Drug for Diabetes

**By STEPHANIE SAUL**

An article in a leading medical journal yesterday raised serious safety questions about the widely used diabetes pill Avandia, and renewed the spotlight on its maker, GlaxoSmithKline. The Food and Drug Administration is considering whether the drug should be linked to heart attacks that may be linked to the pill.

The New York Times

**By STEPHANIE SAUL**

A study found that patients taking Avandia had a higher rate of heart attacks compared to those taking other medications. Avandia, manufactured by GlaxoSmithKline, is one of the most-prescribed drugs for type 2 diabetes.

CONCILIARY

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Guidance for Industry
Diabetes Mellitus — Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes

III. RECOMMENDATIONS

- Sponsors should establish an independent cardiovascular endpoints committee to prospectively adjudicate, in a blinded fashion, cardiovascular events during all phase 2 and phase 3 trials. These events should include cardiovascular mortality, myocardial infarction, and stroke, and can include hospitalization for acute coronary syndrome, urgent revascularization procedures, and possibly other endpoints.
Common Endpoints in Diabetes Trials

POTENTIAL OUTCOMES

Examples of Surrogate Outcomes Followed in Diabetes

Hb A1C, blood pressure, LDL, proteinuria, eGFR, neuropathy, retinopathy, LVEF, echocardiographic indices, hemoglobin, exercise parameters, …
Major Pharmacologic “Glucose Lowering” Treatments for Diabetes

- All classes have been tested/used
- Strategies are changing
- Consider non-glucose lowering mechanisms to improve outcomes?

DM Drugs with MACE Benefits
- Empaglifozin
- Canagliflozin
- Liraglutide
- Semaglutide
Who was enrolled in EXSCEL?

• 14,752 of which 73% had prior CV disease
• Diabetes duration 12 years
• Asian 9.8%, Hispanic 7.7%, Black 6.0%, CAD 70%, CVD 22%, PAD 24%
• HF 16%
• Among 3969 without CV disease (8.1% have HF)

Impact on Outcomes

“...noninferior to placebo with respect to cardiovascular safety but was not superior to placebo with respect to efficacy”.

All-cause death “difference was not considered to be statistically significant on the basis of the hierarchical testing plan”

NNT=125 patients to “prevent” 1 MACE

NNT=100 patients to prevent 1 death

Fixed-Effect Meta-analyses of GLP 1 receptor agonists
All Deaths

<table>
<thead>
<tr>
<th>Trial</th>
<th>Intensive Therapy Events/Patients</th>
<th>Standard Therapy Events/Patients</th>
<th>Hazard Ratio (95% CI)</th>
<th>Study Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>381/4668</td>
<td>447/4672</td>
<td>0.85 (0.74, 0.97)</td>
<td>32.7%</td>
</tr>
<tr>
<td>ELIXA</td>
<td>211/3034</td>
<td>223/3034</td>
<td>0.94 (0.78, 1.13)</td>
<td>17.5%</td>
</tr>
<tr>
<td>SUSTAIN</td>
<td>62/1648</td>
<td>60/1649</td>
<td>1.05 (0.74, 1.50)</td>
<td>4.8%</td>
</tr>
<tr>
<td>EXSCEL</td>
<td>507/7356</td>
<td>584/7396</td>
<td>0.86 (0.77, 0.97)</td>
<td>45.0%</td>
</tr>
<tr>
<td>Overall</td>
<td>1161/16706</td>
<td>1314/16751</td>
<td>0.88 (0.81, 0.95)</td>
<td>100%</td>
</tr>
</tbody>
</table>

Claggett B, Seferovic JP, Pfeffer MA
Fixed-Effect Meta-analyses of GLP 1 receptor agonists CV Death

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<th>Study Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV Death</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LEADER</td>
<td>219/4668</td>
<td>278/4672</td>
<td>0.78 (0.66, 0.93)</td>
<td>32.1%</td>
</tr>
<tr>
<td>ELIXA</td>
<td>156/3034</td>
<td>158/3034</td>
<td>0.98 (0.78, 1.22)</td>
<td>18.8%</td>
</tr>
<tr>
<td>SUSTAIN</td>
<td>44/1648</td>
<td>46/1649</td>
<td>0.98 (0.65, 1.48)</td>
<td>5.6%</td>
</tr>
<tr>
<td>EXSCEL</td>
<td>340/7356</td>
<td>383/7396</td>
<td>0.88 (0.76, 1.02)</td>
<td>43.5%</td>
</tr>
<tr>
<td>Overall</td>
<td>759/16706</td>
<td>865/16751</td>
<td>0.87 (0.79, 0.96)</td>
<td>100%</td>
</tr>
</tbody>
</table>

Claggett B, Seferovic JP, Pfeffer MA
<table>
<thead>
<tr>
<th>Decreased Odds</th>
<th>Increased Odds</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women</td>
<td>Older age (per 5 years)</td>
</tr>
<tr>
<td>eGFR (per 10 unit increase)</td>
<td>Prior CV event</td>
</tr>
<tr>
<td></td>
<td>Cerebrovascular disease</td>
</tr>
<tr>
<td></td>
<td>Respiratory disease</td>
</tr>
<tr>
<td></td>
<td>Current smoker</td>
</tr>
<tr>
<td></td>
<td>NYHA II</td>
</tr>
<tr>
<td></td>
<td>Atrial fibrillation</td>
</tr>
<tr>
<td></td>
<td>Diastolic BP (per 10 mm Hg)</td>
</tr>
<tr>
<td></td>
<td>HbA1C (per 1%)</td>
</tr>
</tbody>
</table>
Inconsistent Factors for Mortality and MACE-3

**Death**
- Latin America
- Europe
- Prior Revasc
- Hypertension
- Hyperlipidemia
- SBP (per 10 mm Hg)
- Diabetes Duration

*All-cause death*

**MACE-3**
- Latin America
- Europe
- Prior Revasc
- Hypertension
- Hyperlipidemia
- SBP (per 10 mm Hg)
- Diabetes Duration

*CV death, MI, or stroke*

**Risk Categories**
- **Increased Risk**
- **Neutral Risk**
- **Decreased Risk**
Appraisal of Analysis

**STRENGTHS**

- Sound statistical methods
- Large sample size
- Stratified patients well
- C-statistics
- Did not overstate conclusions
- Pragmatic trial

**WEAKNESSES**

- Primary endpoint of EXSCEL not met
- No validation cohort
- Clinical utility of model
- No interaction between risk factors and treatment
- Potential competing risks
- No information on safety
- Pragmatic trial
Potential Next Steps

- Safety vs. efficacy across quintiles of risk

Reduction in MACE
- Consistency
- Heart failure

Safety and Adherence
- Delivery system
- Drug side-effects
- Pancreatitis/Cancer
Potential Next Steps

• Safety vs. efficacy across quintiles of risk
• Address disparate risk for all-cause mortality and MACE-3
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• Evaluate the third of patients with pre-existing HF to better inform risk given findings of FIGHT

Margulies KB et al JAMA. 2016;316(5):500-508
IMPLICATIONS and FUTURE DIRECTIONS

• No difference across spectrum of CV risk

• Regional differences in risk must be considered and identifications of favorable risk factors can be helpful for patient-centered care

• Trial design with “Enrichment Factors” should take into account population risk for optimal patients to test (Goldilocks)

• Assess glucose lowering effects vs. non-glucose effects