Is CVD Outcome for Diabetes Drugs Appropriate?

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CPC Clinical Research (University-based Academic Research Center) receives grant support from numerous industry sponsors.

William Hiatt is a member of the FDA Division of Metabolism and Endocrinology Advisory Committee.

I have no other conflicts and do not receive funds personally from any industry sponsor.
Hemoglobin A1c and Cardiovascular Outcomes

Microvascular disease
• Accepted by FDA and guidelines and acceptable surrogate for treatment benefit
• Provides rationale for target A1c treatment guidelines

Cardiovascular disease (my interpretation of the data)
• Not informative for cardiovascular benefit
  • Pharmacologic lowering not associated with reduced risk of cardiovascular events
• Tight control may increase cardiovascular risk
  • A1c of 6–6.5% is harmful (ACCORD, ADVANCE)
Intensive Glycemic Control

Does intensive glycemic control by any means decrease the risk of cardiovascular events?
UK PROSPECTIVE DIABETES STUDY

## RR REDUCTION

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Intensive</th>
<th>Metformin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any DM endpoint</td>
<td>0.88 (0.79-0.99)*</td>
<td>0.68 (0.53-0.87)*</td>
</tr>
<tr>
<td>Microvascular</td>
<td>0.75 (0.60-0.93)*</td>
<td>0.71 (0.43-1.19)</td>
</tr>
<tr>
<td>Diabetes death</td>
<td>0.90 (0.73-1.11)</td>
<td>0.58 (0.37-0.91)*</td>
</tr>
<tr>
<td>All cause mortality</td>
<td>0.94 (0.80-1.10)</td>
<td>0.64 (0.45-0.91)*</td>
</tr>
<tr>
<td>Myocardial infarct</td>
<td>0.84 (0.71-1.00)</td>
<td>0.61 (0.41-0.89)*</td>
</tr>
<tr>
<td>Stroke</td>
<td>1.11 (0.81-1.51)</td>
<td>0.59 (0.29-1.18)</td>
</tr>
<tr>
<td>PAD death or amp</td>
<td>0.65 (0.36-1.18)</td>
<td>0.74 (0.26-2.09)</td>
</tr>
<tr>
<td>Microvascular</td>
<td>0.75 (0.60-0.93)*</td>
<td>0.71 (0.43-1.19)</td>
</tr>
</tbody>
</table>

No benefit of intensive control on MACE
– but –
suggestion of metformin benefit

Action to Control Cardiovascular Risk in Diabetes

- 10,251 patients median A1c 8.1%
- Randomized to intensive therapy (A1c < 6.0% - median 6.4%) or standard therapy (A1c 7.0–7.9% - median 7.5%)

Results:

- MACE events HR 0.90 (95% CI 0.78-1.04)
- Mortality HR 1.22 (95% CI 1.01-1.46, P=0.04)
- Safety – Intensive therapy associated hypoglycemia and weight gain > 10 kg

Long-term follow up of 5-year outcomes after dropping intensive arm (all patients maintained at A1c of 7.0%-7.9%)

- Mortality HR 1.19 (95% CI 1.03-1.38)
- Nonfatal MI 0.82 (95% CI 0.70-0.96)

NEJM 2008;358:2545–2559
NEJM 2011;364:818-28
ADVANCE

Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation

- 11,140 patients with type 2 diabetes
- Randomized to standard (A1c 7.3%) versus intensive (A1c 6.5%) glycemic control and followed median 5 years
- Primary end points MACE and microvascular (new or worsening nephropathy or retinopathy)

RESULTS:
- Combined macro-micro events HR 0.90 (95% CI 0.82-0.98; P=0.01)
- Microvascular events HR 0.86 (95% CI 0.77-0.97) due to decreased nephropathy
- MACE 0.94 (95% CI 0.84-1.06)
- Safety – severe hypoglycemia HR 1.86 (95% CI 1.42-2.40)

NEJM 2008;358:2560–2572
Do particular drugs or drug classes modulate cardiovascular risk in diabetes?
Rosiglitazone Controversy

Rosiglitazone approved in 1999
Risk concerns: increased LDL cholesterol level, anemia, fluid retention and heart failure

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></td>
<td>no. of events/total no. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<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>

Nissen - NEJM 2007;356:2457-71
2010 Updated Rosiglitazone Meta-analyses

<table>
<thead>
<tr>
<th></th>
<th>Nissen/Wolski</th>
<th>FDA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of trials</td>
<td>56</td>
<td>52</td>
</tr>
<tr>
<td>Type analysis</td>
<td>Study level</td>
<td>Patient level</td>
</tr>
<tr>
<td>MI</td>
<td>OR 1.28 (1.01-1.62)</td>
<td>1.80 (1.03-3.25)</td>
</tr>
<tr>
<td>CV death</td>
<td>OR 1.03 (0.78-1.36)</td>
<td>1.46 (0.60-3.77)</td>
</tr>
<tr>
<td>MACE</td>
<td></td>
<td>1.44 (0.95-2.20)</td>
</tr>
</tbody>
</table>

2013 FDA update on meta analysis separated placebo from active controls and supports 2010 observations

Arch Intern Med 2010;170:1191-1201
FDA briefing document 2010 and 2013
RECORD Trial
Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes

RCT in 4447 patients with diabetes
Rosiglitazone plus metformin or rosiglitazone plus sulfonylurea versus combination MET/SU

Limitations:
• Open label, non-inferiority design
• Primary endpoint CV hospitalization or CV death
• Active control not established as safe
• Low adherence, high crossover
• Imbalance in statin and diuretic use
• FDA reviewer allegations of data mishandling and trial misconduct

Lancet 2009;373:2125-35
# RECORD Results

<table>
<thead>
<tr>
<th>Event</th>
<th>Rosiglitazone (N=2220)</th>
<th>Active control (N=2227)</th>
<th>HR (95% CI)</th>
<th>Rate difference per 1000 person-years (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV death or CV hospitalisation</td>
<td>321</td>
<td>323</td>
<td>0.99 (0.85 to 1.16)</td>
<td>-0.2 (-4.5 to 4.1)</td>
<td>0.93</td>
</tr>
<tr>
<td>All-cause death</td>
<td>136</td>
<td>157</td>
<td>0.86 (0.68 to 1.08)</td>
<td>-1.7 (-4.3 to 0.9)</td>
<td>0.19</td>
</tr>
<tr>
<td>CV death</td>
<td>60</td>
<td>71</td>
<td>0.84 (0.59 to 1.18)</td>
<td>-0.9 (-2.7 to 0.9)</td>
<td>0.32</td>
</tr>
<tr>
<td>Myocardial infarction*</td>
<td>64</td>
<td>56</td>
<td>1.14 (0.80 to 1.63)</td>
<td>0.6 (-1.1 to 2.4)</td>
<td>0.47</td>
</tr>
<tr>
<td>Stroke*</td>
<td>46</td>
<td>63</td>
<td>0.72 (0.49 to 1.06)</td>
<td>-1.4 (-3.1 to 0.2)</td>
<td>0.10</td>
</tr>
<tr>
<td>CV death, MI, or stroke</td>
<td>154</td>
<td>165</td>
<td>0.93 (0.74 to 1.15)</td>
<td>-1.0 (-3.9 to 1.9)</td>
<td>0.50</td>
</tr>
<tr>
<td>Heart failure*</td>
<td>61</td>
<td>29</td>
<td>2.10 (1.35 to 3.27)</td>
<td>2.6 (1.1 to 4.1)</td>
<td>0.0010</td>
</tr>
</tbody>
</table>

*Lancet 2009;373:2125-35*
Janet Woodcock acknowledged “multiple and conflicting signals of CV risk associated with rosiglitazone” and:

1. Put the drug on restricted distribution
2. Stopped the TIDE trial
   -11,680 event-driven trial evaluating MACE
   -Non-inferiority comparison of rosiglitazone versus pioglitazone and superiority of TZD versus placebo
3. Ordered a re-adjudication of RECORD –by DCRI
FDA 2013 EMDAC Meeting
DCRI Re-adjudication of Record

<table>
<thead>
<tr>
<th>Event</th>
<th>RSG N=2220</th>
<th>MET/SU N=2227</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV death, MI, CVA</td>
<td>181 (8.3%)</td>
<td>188 (8.4%)</td>
<td>0.95 (0.78-1.17)</td>
</tr>
<tr>
<td>CV death</td>
<td>88 (4.0%)</td>
<td>96 (4.3%)</td>
<td>0.90 (0.68-1.21)</td>
</tr>
<tr>
<td>MI</td>
<td>68 (3.1%)</td>
<td>60 (2.7%)</td>
<td>1.13 (0.80-1.59)</td>
</tr>
<tr>
<td>Stroke</td>
<td>50 (2.3%)</td>
<td>63 (2.8%)</td>
<td>0.79 (0.54-1.14)</td>
</tr>
<tr>
<td>All cause mortality</td>
<td>139 (6.3%)</td>
<td>160 (7.2%)</td>
<td>0.86 (0.68-1.08)</td>
</tr>
</tbody>
</table>

DCRI found more events but overall results unchanged
DCRI did not find any trial misconduct or data integrity concerns

Limitations:
- Reliance on original database and source docs
- Retrospective
- Additional follow up on vital status with limited information on MI or stroke
FDA Guidance Evaluating CV Risk

- Establish independent CV endpoints committee
- Adjudicate all CV events from all phase 2 and 3 trials
- Meta-analysis and prospective analysis plan
- Pre-approval, upper boundary of 2-sided 95% CI of risk must be < 1.8. If between 1.3-1.8 then:
  - Post marketing a CVOT must demonstrate < 1.3.
- New development programs may be subject to greater scrutiny

CDER Guidance Dec 2008
Exclusion of Risk Approach
Cilostazol as a Symptomatic Rx for PAD

Brass and Hiatt, Clin Pharmacol Ther 2006;79:165-72
Liraglutide Safety

Safety evaluated in all phase 2 & 3 RCT’s included 6638 patients, 2926 patient years (1880 on Liraglutide)

114 events acquired as possible MACE with RR of:

- Lira v placebo  0.80 (0.23-2.83)
- Lira v active  0.68 (0.28-1.66)
- Lira v all  0.72 (0.32-1.61)

Endocrine Metabolism Advisory Committee voted 8 to 5 that the data ruled out excess CV risk

CDER April 2009
Liraglutide

Glucagon-like peptide-1 indicated as an adjunct to diet and exercise to improve glycemic control in type 2 DM

5 phase 3 trials in 4655 subjects, 2412 for 24 weeks
Liraglutide Safety

Safety evaluated in all phase 2-3 RCT’s included 6638 patients, 2926 patient years (1880 on Liraglutide)

Broad MACE = 114 events

Upper 95% CI bound estimates 2.83 versus placebo

Versus active was 1.66 suggesting active may have risk

<table>
<thead>
<tr>
<th></th>
<th>Liraglutide vs. Placebo</th>
<th>Liraglutide vs. Active</th>
<th>Liraglutide vs. Total Comparator</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>5 of 12</td>
<td>7 of 9</td>
<td>8 of 15</td>
</tr>
<tr>
<td></td>
<td>0.80 (0.23, 2.83)</td>
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<td>0.72 (0.32, 1.61)</td>
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Endocrine Metabolism Advisory Committee agreed (8 to 5) data ruled out excess CV risk

CDER April 2009
Alogliptin in Diabetes + ACS

DPP-4 inhibitor studied in 5380 patients with prior ACS
Hypothesized drug non-inferior to placebo on MACE
- Reduced HgbA1c -0.36%
- 621 primary events of MI, Stroke, CV death
- MACE HR 0.96 (upper bound CI ≤ 1.16)
- All cause mortality HR 0.88 (95% CI 0.71-1.09)

NEJM 2013;369:1327-35
Saxagliptin in diabetes with CV risk

DPP-4 inhibitor in 16,492 patients with diabetes with history of or at risk for CV disease
Hypothesized drug non-inferior to placebo
• Reduced HgbA1c -0.3%
• 1222 primary events of MI, Stroke, CV death
• MACE HR 1.00 (0.89-1.12)
• All cause mortality HR 1.11 (95% CI 0.96-1.27)
• Hospitalize for heart failure HR 1.27 (1.07-1.51)

NEJM 2013;369:1327-35
SGLT-2 Drugs – A New Mechanism

Dapagliflozin increases urine excretion of glucose and net caloric loss. Placebo-adjusted results CV risk factors:

- A1c -0.5% (95% CI -0.6 to -0.3)
- Weight -2.3 kg (95% CI, -2.6 to -1.9)
- Systolic BP -2.0 mmHg (95% CI -3.6 to -0.3)
- Cardiovascular risk HR 0.98 (95% CI 0.64-1.49)

CV risk HR 0.98 (95% CI 0.64-1.49)

EMDAC December 2013
Glycemic Control and Cardiovascular Disease in Diabetes

Strategy of lowering A1c < 6.5% associated with cardiovascular harm
CV risk of ‘old’ diabetes drugs not known (making them poor active comparators)
Metformin may have CV benefit but not proven
Rosiglitazone (and pioglitazone), alogliptin, saxagliptin likely do not pose increase CV risk
Potential CV benefit of SGLT-2 drugs but this is theory until tested in CVOT