Assessing Cardiovascular Risk of Non-Cardiac Drugs

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William R. Hiatt Conflicts

- Peripheral artery disease research grants: AstraZeneca, CSI, DNAVEC, Kyushu University, NIH, Pluristem, ReNeuron, Rigel
- Obesity drugs: None
- Diabetes drugs: None
- Lipid drugs: None
Evaluation of Cardiovascular Risk
Assessment of New Drugs

All case examples taken from FDA Advisory Committee deliberations over past 10+ years
All case examples met primary endpoints but had uncertainty regarding cardiac safety
Primary endpoints included:
• Cilostazol – treat claudication symptoms, improve exercise performance
• Obesity drugs – Induce weight loss
• Diabetes drugs – lower hemoglobin A1c

Why Should You Care What Regulators (FDA) Think?

Food and Drug Administration:
• Authority derived from US Congress
• Role to approve new drugs, expand indications of marketed drugs, withdraw unsafe drugs
• Control points include approvals, labeling and marketing with a standard of safe and effective
• Employs rigorous interpretation of data as a standard for evidence-based decision making
• Emphasizes importance of trial design and biostatistics
Advisory Committees mandatory for drug review

- Center for Drug Evaluation and Research (CDER)
  - Cardiovascular & Renal Drugs Advisory Committee (CRAC)
  - Endocrinologic and Metabolic Drugs Advisory Committee (EMDAC)
- Advisory to FDA, n=6-10 voting
- Conflicts reviewed prior to meeting
- Composition:
  - Disease expertise, trialists, biostatisticians, drug safety
  - Patient and industry rep (non-voting)
- Review process: Includes presentations from sponsor, FDA, and open public forum, pre-defined questions
- Discussions transparent and public

Cilostazol Clinical Experience

Typical clinical scenario
- Dr. Parnes sees 10 patients with claudication
- He follows these patients approximately 1 year
- 1 patient experiences a myocardial infarction
- Patients with PAD have underlying cardiovascular disease
- Are you concerned?
- Did cilostazol cause the MI or did the underlying CAD?
Cilostazol Clinical Experience

- PAD CV event rate (myocardial infarction, ischemic stroke or vascular death
  - 4%/year (4 events/100 patient years)
- Therefore 1 event/10 patient years extrapolates to 10%/year (10 events/100 patient years)
- Illustrates challenge in determining CV risk with sparse data

Vasc Med 2006;11:141-45

Cilostazol
PDE-3 Inhibitor for Claudication

Efficacy well established

Vasc Med 2010;15:181-8
Cilostazol
PDE-3 Inhibitor for Claudication

Cardio-Renal Advisory Committee review 1998

- History of excess mortality with Milrinone (PDE-3 inhibitor) in heart failure
- Cilostazol development in 2702 patients with 4-6 month trials exposure and exercise performance as primary endpoint
- 20 deaths total (MACE not assessed), point estimate 1.3, broad confidence intervals

NEJM 1991;325:1468-75

Exclusion of Risk Approach

Table 1. Number of total adverse events required to demonstrate no greater risk (exclusion-of-risk approach)

<table>
<thead>
<tr>
<th>Relative risk to be excluded (% increase)</th>
<th>1.10 (10%)</th>
<th>1.25 (25%)</th>
<th>1.50 (50%)</th>
<th>1.75 (75%)</th>
<th>2.00 (100%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total No. of events required in both groups</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>80% Power</td>
<td>2722</td>
<td>497</td>
<td>159</td>
<td>79</td>
<td>51</td>
</tr>
<tr>
<td>90% Power</td>
<td>3771</td>
<td>688</td>
<td>208</td>
<td>109</td>
<td>71</td>
</tr>
<tr>
<td>95% Power</td>
<td>4765</td>
<td>869</td>
<td>263</td>
<td>138</td>
<td>90</td>
</tr>
</tbody>
</table>

Clin Pharmacol Ther 2006;79:165-72
CASTLE safety study of cilostazol

- 1435 patients followed out to 36 months
- Mortality event rate lower than expected, early drug discontinuation higher than expected
- 37 deaths on treatment
  - HR 0.99 (95% CI 0.52-1.88)
- 101 deaths ITT
  - HR 0.94 (95% CI 0.64-1.39)


Obesity Epidemic

NHANES 2012 obesity data

- Men obesity prevalence = 35.5%
- Women obesity prevalence = 35.8%
- Children prevalence of obesity = 16.9%

JAMA 2012;307(5):491-7
JAMA 2012;307:483-90
What are the Treatment Goals for Obesity?

Patients often want *cosmetic benefit* defined as weight loss per se, look better, feel better

Providers want *clinical benefit* defined as:
- Reduce mortality
- Prevent and treat diabetes
- Prevent and treat cardiovascular disease
  - Blood pressure, lipids and insulin sensitivity
- Treat sleep apnea and lower blood pressure
- Treat degenerative arthritis
- Improve physical functioning

FDA Criteria for Weight Loss Drugs

Weight loss of 5% (mean or categorical)
And…FDA obesity drug guidance 2007 links a reduction in fat mass to clinical benefit:
- Reduced morbidity and mortality
- “through quantifiable improvements in biomarkers, such as blood pressure, lipids and HbA1c”
- Therefore weight loss alone not sufficient

FDA Weight Management Guidance 2007
Current Weight Loss Drugs

Sibutramine (approved 1997) – sympathomimetic with effects on NE, serotonin and B₃ receptors

Phentermine/Topiramate (Qnexa) - Phentermine is sympathomimetic to reduce food intake and increase thermogenesis. Topiramate treats seizures and migraines with unclear weight loss mechanism

Naltrexone/Bupropion (Contrave) – is an opioid receptor antagonist with a NE and dopamine receptor inhibitor

Lorcaserin (Lorcess) – activates 5-hydroxytryptamine 2c receptors

CV Risk of Weight Loss Drugs

Sympathomimetic drugs have a mechanism of CV risk

- Sibutramine
- Phentermine/topiramate
- Naltrexone SR/Bupropion SR

5-hydroxytryptamine drugs have valvulopathy and pulmonary hypertension risks

- Fenfluramine
- Lorcaserine

Cardiac events low frequency but devastating
What Works?  
(what has proven clinical benefit)

My bias is to challenge the role of pharmacotherapy

• Lifestyle (diet and exercise) works
• Bariatric surgery works
• Drugs?

Circulation 2012;125:1171-7
JAMA 2012;308:1099-1100

Look AHEAD

ILS=Intensive Lifestyle Intervention
DSE=diabetes support and education
Arch Intern Med 2010;170:1566-75
Bariatric Surgery and Mortality

Sibutramine NDA
FDA Review 1997

Efficacy included 26 studies < 24 weeks, 20 long-term, patients low risk for CV events

Efficacy = 4% mean placebo-adjusted weight loss

<table>
<thead>
<tr>
<th></th>
<th>Sibutramine</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV events</td>
<td>0.5%</td>
<td>0.6%</td>
</tr>
<tr>
<td>Death</td>
<td>4</td>
<td>4</td>
</tr>
</tbody>
</table>

Therefore no hint of safety concern and FDA agreed

Post approval excess CV events reported in Europe
European regulators mandated phase IV safety study
SCOUT
Sibutramine Cardiovascular Outcomes Trial

Enrolled 10,744 patients at increased CV risk
- Diabetes with additional CV risk factor (n=2385)
- H/O cardiovascular disease (n=1552)
- Diabetes + CV disease (n=5807)
- Duration 3.4 years, but only 58% completed on Rx
- Primary endpoint = MI, CVA, vascular death, resuscitated cardiac arrest with 1051 total events

Sibutramine Hemodynamics
Pulse

Cardiovascular Risk by Subgroup

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>1.16</td>
<td>1.03-1.31</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.01</td>
<td>0.74-1.38</td>
</tr>
<tr>
<td>CV disease</td>
<td>1.28</td>
<td>0.92-1.78</td>
</tr>
<tr>
<td>DM &amp; CV disease</td>
<td>1.18</td>
<td>1.02-1.37</td>
</tr>
</tbody>
</table>

- P for interaction 0.56 so risk similar across subgroups
- Sponsor argued to keep drug on market for low risk subjects
- Drug subsequently withdrawn from market

Obesity Drug Cardiac Risks

Table. Weight Loss and MACEs Associated With Weight-Loss Drugs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mean Weight Loss from Baseline, %</th>
<th>MACEs, No. (%)</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Topiramate/Phentermine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No diabetes</td>
<td>-10.9</td>
<td>5/10.5</td>
<td>0.84 (0.76-0.94)</td>
</tr>
<tr>
<td>10% Diabetes</td>
<td>-0.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Naltrexone/Bupropion</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No diabetes, study No. 1</td>
<td>-4.6</td>
<td>3/10.5</td>
<td>1.0</td>
</tr>
<tr>
<td>No diabetes, study No. 2</td>
<td>-4.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>-5.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lorcaserin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study No. 1, no diabetes, BLOOM</td>
<td>-5.8</td>
<td>1/0.93</td>
<td>1.04 (0.93-1.18)</td>
</tr>
<tr>
<td>Study No. 2, no diabetes, BLOOM</td>
<td>-5.8</td>
<td>4/0.93</td>
<td>1.0 (0.93-5.37)</td>
</tr>
<tr>
<td>Diabetes, BLOOM</td>
<td>-4.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sibutramine²</td>
<td>-6.4 kg</td>
<td>0/0.10</td>
<td>1.16 (1.03-1.31)</td>
</tr>
</tbody>
</table>

Obesity Drug Outcomes

Sibutramine - withdrawn

Phentermine/Topramate (Qnexa) – Approved with post approval commitment for large CV outcomes trial

Naltrexone/Bupropion (Contrave) – Denied with pre-approval CV outcomes trial requirement

Lorcaserin (Lorqess) – Approved with post approval CV outcomes trial commitment

Real risk is valvular heart disease not ischemic
Trials can use HbA1c as an acceptable surrogate of glycemic control for approval

Guidance on how to demonstrate a new antidiabetic therapy is not associated with unacceptable CV risk

Individual trial designs typically under-powered to demonstrate CV benefit or harm

Use of the exclusion of risk approach to rule out an unacceptable level of safety concern

FDA Guidance Evaluating CV Risk Trials Developing New Antidiabetic Rx

- Establish independent CV endpoints committee
- Adjudicate all CV events from all phase 2 and 3 trials
- Meta-analysis and prospective analysis plan
- Upper boundary of 2-sided 95% CI of risk < 1.8
- Risk ratio < 1.3. If 1.3-1.8 then additional safety study (phase 4) required
- New development programs may be subject to greater scrutiny

CDER Guidance Dec 2008
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

Endocrine Metabolism Advisory Committee agreed
(8 to 5) data ruled out excess CV risk

CDER April 2009
Rosiglitazone Controversy

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

<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>Small trials</td>
<td>44/10,285 (0.43)</td>
<td>22/6386 (0.34)</td>
<td>1.45 (0.88-2.39)</td>
<td>0.15</td>
</tr>
<tr>
<td>DREAM</td>
<td>25/2,635 (0.97)</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>13/2,465 (0.53)</td>
<td>14/2,895 (0.49)</td>
<td>1.35 (0.80-2.23)</td>
<td>0.27</td>
</tr>
<tr>
<td>Overall</td>
<td>57/10,520 (0.5)</td>
<td>36/6,521 (0.54)</td>
<td>1.43 (1.03-1.98)</td>
<td>0.03</td>
</tr>
</tbody>
</table>

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>1.44 (0.95-2.20)</td>
<td></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</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>0.85 (0.68 to 1.08)</td>
<td>-17 (-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 1.61)</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>2.5 (1.1 to 4.1)</td>
<td>0.0010</td>
</tr>
</tbody>
</table>

Lancet 2009;373:2125-35
FDA Decisions on Rosiglitazone
2010

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

DCRI Re-adjudication

<table>
<thead>
<tr>
<th></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
**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

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**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
Summary of MACE Events

Cilostazol (approved)
• 20 deaths in development, 37 deaths post market

Obesity drugs
• Topiramate/phentermine 12 MACE (approved)
• Naltrexone/bupropion 4 MACE (not approved)
• Lorcaserin 11 MACE (approved)
• Sibutramine 1051 (withdrawn)

Diabetes drugs
• Liraglutide 114 broad MACE (approved)
• Rosiglitazone 319 MACE (restrictions lifted)
• Alogliptin 621 MACE (approved)
• Saxagliptin 1222 MACE (approved)

Summary
Evaluating Cardiovascular Safety

• Many drugs treat symptoms or surrogates
• Those development programs are generally inadequate to evaluate cardiovascular safety
• Assessing CV safety dependent on acquiring CV events which often requires a large, expensive CVOT
• When to trigger a CVOT?
  • Mechanistic concerns of CV risk (obesity drugs)
  • Meta analyses suggesting CV risk (Rosiglitazone)
  • But – all drugs to treat symptoms and surrogates do not need a CVOT
Summary
Cardiovascular Safety Diabetes Drugs

- Hemoglobin A1c an inadequate surrogate to evaluate cardiovascular benefit or cardiovascular risk
- CV risk of ‘old’ diabetes drugs not known (making them poor active comparators)
- Rosiglitazone (and pioglitazone), alogliptin, saxagliptin all likely do not pose an increased CV risk