Is CVD Outcome for Diabetes Drugs Appropriate?

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Conflicts

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

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

Lancet 1998;352:837-53 and 854-65

ACCORD

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

Diabetes Drugs

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.

Study	Rosiglitazone Group	Control Group	Odds Ratio (95% CI)	P Value
	no. of events/total no. (%)			
Myocardial infarction				
Small trials combined	44/10,285 (0.43)	22/6106 (0.36)	1.45 (0.88–2.39)	0.15
DREAM	15/2,635 (0.57)	9/2634 (0.34)	1.65 (0.74–3.68)	0.22
ADOPT	27/1,456 (1.85)	41/2895 (1.42)	1.33 (0.80–2.21)	0.27
Overall			1.43 (1.03–1.98)	0.03
Death from cardiovascular causes				
Small trials combined	25/6,845 (0.36)	7/3980 (0.18)	2.40 (1.17–4.91)	0.02
DREAM	12/2,635 (0.46)	10/2634 (0.38)	1.20 (0.52–2.78)	0.67
ADOPT	2/1,456 (0.14)	5/2895 (0.17)	0.80 (0.17–3.86)	0.78
Overall			1.64 (0.98–2.74)	0.06

Nissen - NEJM 2007;356:2457-71

2010 Updated Rosiglitazone Meta-analyses

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

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

	Rosiglitazone (N=2220)	Active control (N=2227)	HR	Rate difference per 1000 person-years	p
CV death or CV hospitalisation	321	323	0·99 (0·85 to 1·16)	−0·2 (−4·5 to 4·1)	0·93
All-cause death	136	157	0·86 (0·68 to 1·08)	−1·7 (−4·3 to 0·9)	0·19
CV death	60	71	0·84 (0·59 to 1·18)	−0·9 (−2·7 to 0·9)	0·32
Myocardial infarction*	64	56	1·14 (0·80 to 1·63)	0·6 (−1·1 to 2·4)	0·47
Stroke*	46	63	0·72 (0·49 to 1·06)	−1·4 (−3·1 to 0·2)	0·10
CV death, MI, or stroke	154	165	0·93 (0·74 to 1·15)	−1·0 (−3·9 to 1·9)	0·50
Heart failure*	61	29	2·10 (1·35 to 3·27)	2·6 (1·1 to 4·1)	0·0010

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

FDA 2013 EMDAC Meeting
DCRI Re-adjudication of Record

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

DCRI found more events but overall results unchanged

DCRI did not find any trial misconduct or data integrity concerns

Limitations:

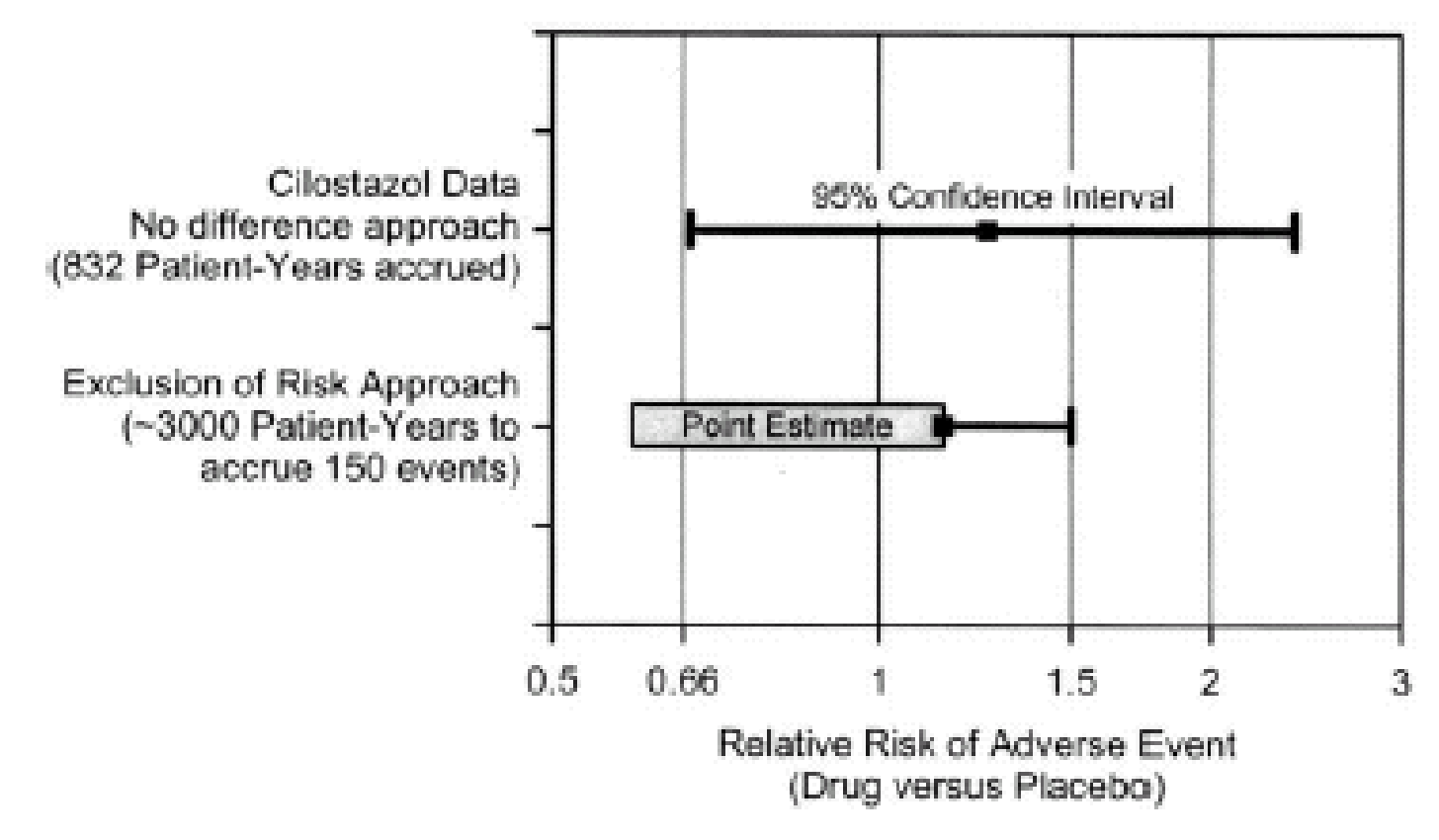
- Reliance on original database and source docs
- Retrospective
- Additional follow up on vital status with limited information on MI or stroke

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)

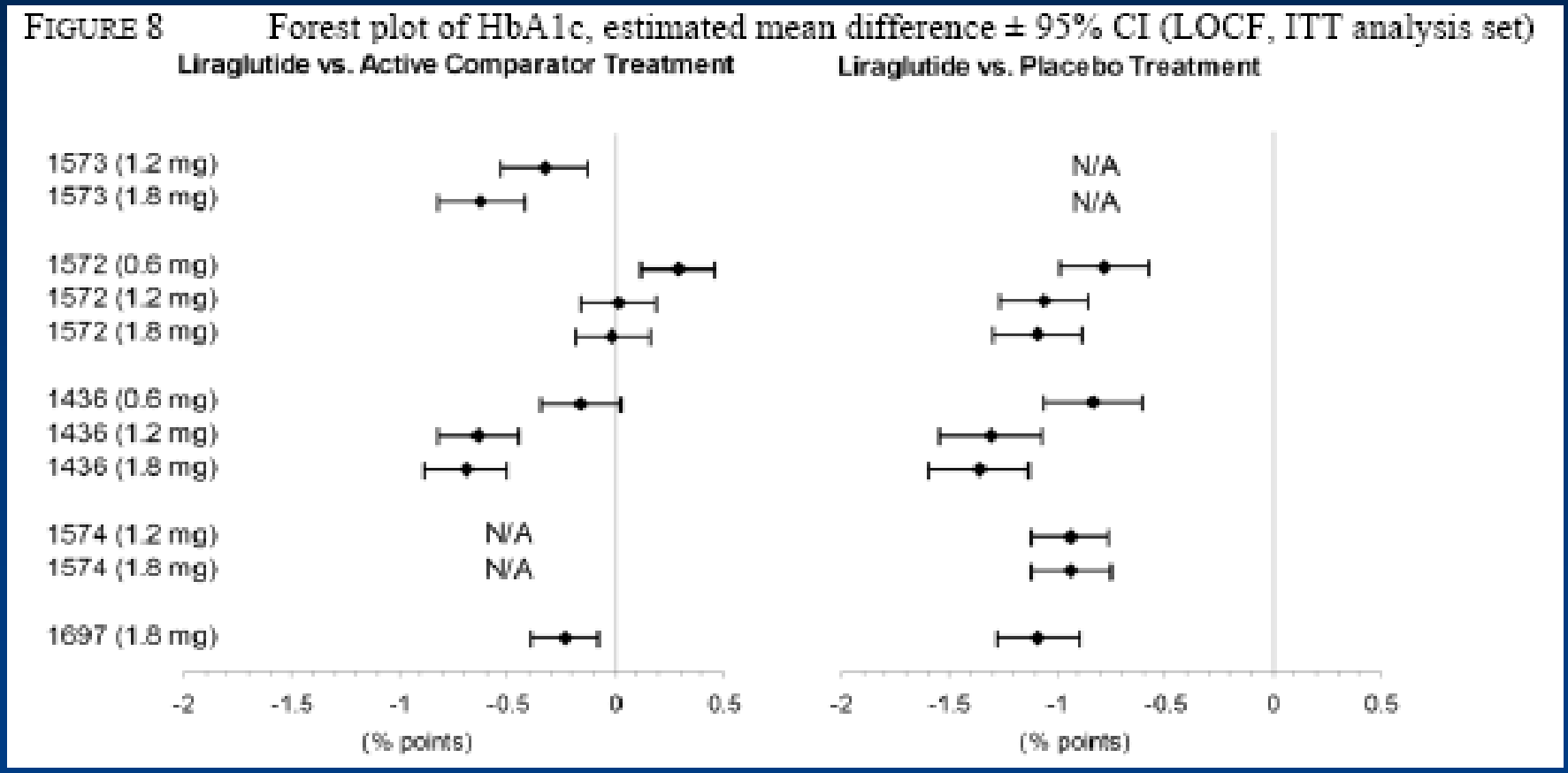
Endocrine Metabolism Advisory Committee voted 8 to 5 that the data ruled out excess CV risk

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



CDER April 2009

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

Liraglutide vs. Placebo	5 of 12	0.80 (0.23, 2.83)
Liraglutide vs. Active	7 of 9	0.68 (0.28, 1.66)
Liraglutide vs. Total Comparator	8 of 15	0.72 (0.32, 1.61)

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

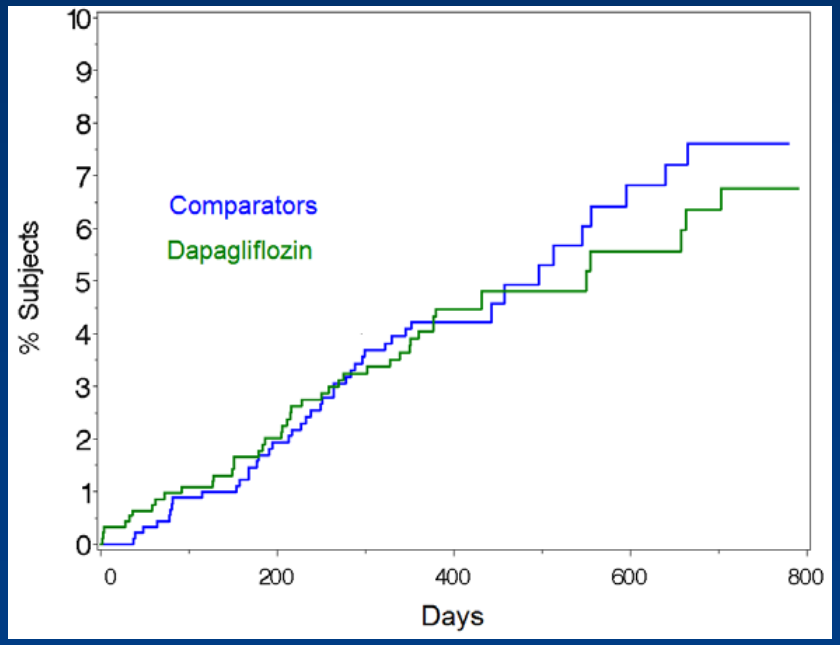
- Reduced HgbA1c -0.3%
- 1222 primary events of MI, Stroke, CV death
- MACE HR 1.00 (0.89-1.12)
- All cause mortality HR 1.11 (95% CI 0.96-1.27)
- Hospitalize for heart failure HR 1.27 (1.07-1.51)

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