Industry, Medicine, and Conflict of Interest: The View of a Physician-Epidemiologist

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Disclosures

- Work as expert witness for plaintiffs and companies in 2002 to 2005
- No research, consulting or lecturing for any pharmaceutical company
- Editorialist and commentator on drug-safety issues

Introduction

- Proposition and personal experience
- Brennan's proposal for AMCs
- Pervasiveness and effects of entanglements
- Social science perspective
- Concluding observations

AAUP Statement 1915

"All true universities, whether public or private, are public trusts designed to advance knowledge by safeguarding the free inquiry of impartial teachers and scholars. Their independence is essential because the university provides knowledge not only to its students, but also to the public agency in need of expert guidance and the general society in need of greater knowledge; and … these latter clients have a stake in disinterested professional opinion, stated without fear or favor, which the institution is morally required to respect."

Korn D. JAMA 2000; 284: 2234-7

Definitions

- COI: conflict between the personal interests and the responsibilities of a person in a position of trust
- Hidden curriculum: The culture and the behavior of mentors and colleagues is more powerful than lectures or precepts in establishing norms and expectations

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Proposition

A loose but broad collusion of interests has often developed among industry, academy, professional associations, and funding agencies. Practice, research, and education in medicine best serve the health of the public insofar as they remain independent of industry.

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NIH-funded case-control study

- Use of beta-blockers in hypertensives associated with a lower risk of coronary events than high-dose diuretics
  - OR=0.87, 95% CI = 0.62 to 1.21
- Recently stopping beta-blockers associated with an increased risk of coronary events
  - OR=4.5; 95% CI = 1.1 to 18.5

Psaty BM. JAMA 1989; 261: 2087-94 and 1990; 263: 1653-7. ***CHRU***

Consequences of publication

- One received media attention
- One received pharmaceutical attention
  - Invitation for my family and me to stay at a resort so I could present results
  - Publication of an additional paper in a company-sponsored symposium issue
  - Invitation to work on speakers' slides and to give multiple talks on beta-blockers

Psaty BM. JAMA 2009; 301: 1477-79. ***CHRU***

Social-science insights

"When a gift or gesture of any size is bestowed, it imposes on the recipient a sense of indebtedness. The obligations to directly reciprocate, whether or not the recipient is directly conscious of it, tends to influence behavior…. Feelings of obligation are not related to the size of the gift or favor."

Katz D. Am J Bioeth 2003; 3: 39-46. ***CHRU***

Policy proposal

- Prohibition on all gifts, meals, travel, samples, financial relations for formulary committee, speaker's bureau, publication of ghostwritten articles, or direct support for ACCME-accredited programs
- Central funds for CME, travel, samples
- Transparency for consulting and research

Brennan TA. JAMA 2006; 295: 429-433. ***CHRU***

AAMC Task Force

- "Urges all academic medical centers to accelerate the adoption of policies that better manage, and when necessary, prohibit academic-industry interactions that can inherently create conflicts of interest and undermine standards of professionalism."

AAMC on Industry Funding of Med Education, June 2008. ***CHRU***

AAMC recommendations

- Prohibition on gifts, food, travel, ghostwriting, and non-accredited CME
- Central management of samples & CME funds
- Pharmaceutical representatives only by invitation and in a structured setting
- "Strongly discourage" faculty participation in speaker's bureau, and transparency for all research support

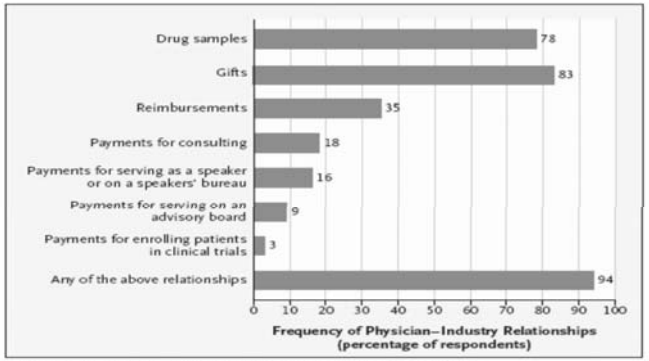
AAMC on Industry Funding of Med Education, June 2008. ***CHRU***

Epidemic of spending

- Prescription drug expenditures increased from $12 billion in 1980 to $250 billion in 2009
- In 2004, $57.5 billion spent on pharmaceutical marketing
  - $4.0 billion on DTCA (7%)
  - $15.9 billion on samples (28%)
  - $20.4 billion on detailing (36%)

Budetti PP. JAMA 2008;299:92. Gagnon M. PlosMed 2008:5:e1. ***CHRU***

Doctors and drug companies



Frequency of Various Types of Physician–Industry Relationships.
Percentages were weighted to adjust for the probability of selection within each specialty and for nonresponse. Data are from Campbell et al.[1]

Campbell EG. N Engl J Med 2007: 357: 1796-7. ***CHRU***

Physicians and industry

- Paid trips have long-lasting effect on prescribing of sponsor's product
- Dose-response relationship between industry meals and formulary additions
- Receipt of gifts correlated with the belief that gifts have no effect on prescribing behavior

Wazana A. JAMA 2000; 283: 373-380. ***CHRU***

Drugs reps and MDs in training

- Review of 44 articles
  - 32% changed practice after discussion
  - 40 to 100% accepted lunches or gifts
  - 8 to 50% accepted dinners or trips
  - 91% accept patient education items
- 88 to 96% accepted samples for pts
  - Prescription of 1st line antihypertensives increased from 39 to 72% after samples were eliminated

Zipkin DA. J Gen Intern Med 2005; 20: 777-86. ***CHRU***

Other entanglements

- Clinical practice guidelines
  - 87% of authors had some financial conflict
  - Interactions with mean of 10.5 companies
  - 55% said there was no disclosure process
- Institutional review boards
  - 36% of members had >=1 relationship
  - 23% did not disclose relationship
  - 65% refrained from voting on conflict case

JAMA 2002; 287:612-7. N Engl J Med 2006; 2312-9. ***CHRU***

Continuing medical education

- Income of $2.38 billion in 2006
- Commercial support
  - 76% of income for MECCs
  - 62% of income for medical schools
- New ACCME commitment to assuring validity of CME enterprise
  - "Current situation is at best very troubling"

Steinbrook R. JAMA 2008; 299: 1060-2. ***CHRU***

Scientists' entanglements

- In 2000, 62% of biomedical research privately funded, up from 32% in 1980
- 68% of academic institutions have equity interest in sponsored research performed at the same institutions
- 23 to 28% of academic investigators receive research support from industry

Bekelman JE. JAMA 2003; 289: 454-65. ***CHRU***

Antidepressants: publication bias

- 74 trials of 12 antidepressant
  - 38 viewed by FDA as positive, 37 published
  - 36 viewed by FDA as null or negative
    - 22 (61%) not published
    - 11 (31%) published as positive
- Positive finding for trials
  - 94% of the published literature
  - 51% of the studies seen by the FDA

Turner EH. N Engl J Med 2008; 358: 252-60. ***CHRU***

Effect size in published trials

- Larger in sponsors' publications than in the FDA review of the same trials
  - Range, 11-69% across 12 drugs
  - Mean weighted effect size
    - 0.41 (95% CI, 0.36-0.45) in sponsors'
    - 0.31 (95% CI, 0.27-0.35) in FDA
- By FDA standards, sponsors' results misrepresented in published literature

Turner EH. N Engl J Med 2008; 358: 252-60. ***CHRU***

Clinical trial investigators

- 11 GPs in 10 practices with 26 GPs
  - RCT of budesonide and formoterol
  - Twice daily vs symptom based dosing
- 165 GPs who did not participate
- Sponsor's share of asthma drugs
  - Trial practices: 52.9% to 58.7%
  - Non-trial practices: 52.8% to 51.9%

Anderson M. JAMA 2006; 295: 2759-64. ***CHRU***

Science as marketing

- Seeding trials in the form of RCT
  - Even for large trials, journals are unwitting extension of marketing arm of industry
- Production of scientific articles
  - Support for local investigators, who write articles, give lectures, and teach students
- Consumption of scientific articles
  - Over-value treatments in RCTs

PLOS Med 2005; 2:e138. J Gen Intern Med 2000; 15: 755-6. ***CHRU***

Gabapentin

- Review of documents from litigation
- Comprehensive marketing plan
  - CME events to deliver promotional messages on off-label use
  - Publication of an array of favorable articles
- Sponsor's business plan
  - "Medical education drives the market!! [sic]"

Steinman MA. Ann Intern Med 2006; 145: 284-93. ***CHRU***

Rofecoxib trials

- Many trial reports and reviews ghost authored
  - Academic authors often recruited and paid to be "guest" authors
  - Sponsor funding disclosed for 92% of trials but only 50% of reviews
- Three "guest" authors added their names to protocol 078

Ross JS. JAMA 2008; 299: 1800-12. ***CHRU***

Rofecoxib Alzheimer trials

- Intention to treat analyses of two trials showed increase in total mortality
  - No DSMB to protect patients
- ITT analyses and data not made public or submitted to FDA in a timely fashion
  - Sponsor dismissed FDA questions as a matter of "chance fluctuations"
  - Marketing, not science, dominates

Psaty BM. JAMA 2008; 299: 1813-7. ***CHRU***

Ghost management

- Systematic effort to control and shape multiple steps in research, analysis, composition, and dissemination
- Medical education and communication companies used to orchestrate plans
- Up to 40% of articles on sertraline, 1998-2000, managed by one company

Sismondo S. PLOS Med 2007; 4: e286. ***CHRU***

Concealed consulting

- Promotion of atypicals for bipolar
  - 40 fold increase in use, 1994-2003
- Failure to report income, 2000-7
  - Biederman, MGH, $1.4 of 1.6 million
  - Nemeroff, Emory, $1.2 of 2.8 million
  - Goodwin, NPR, $1.3 million
- MGH center's goal was "to move forward the commercial goals of J&J"

Harris G. NY Times, 11/22/08, 11/25/08. ***CHRU***

Tradition of enforced ignorance

- Enormous energy to show efficacy
- Studied inattention to risk, active effort to minimize chance of finding harm, and non-publication of unfavorable findings
- Well-studied benefits and ill-defined risks
  - Produces distorted knowledge base
  - Undermines validity of risk-benefit

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Editorial

"The profession of medicine, in every aspect—clinical, education, and research—has been inundated with profound influence from the pharmaceutical and medical device industries. This has occurred because physicians have allowed it to happened, and it is time to stop."

DeAngelis CD. JAMA 2008; 299: 1833-5.

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Survey of medical residents

- 61% were confident that drug-company promotions did not influence their practice
- 16% were equally confident that their colleagues were not influenced by those same drug-company promotions
- Self-interest simply distorts the way that individuals render judgments

Steinman MA. Am J Med 2001; 110: 551-557.

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Academic-industry relations

- Survey of dept chairs at 125 schools
  - 60% had some relationship with industry
    - 27% consultants, 14% paid speaker
    - 27% member of advisory board
- 72% view > 1 activity as having negative impact on independent research
- 70% report that relationship had no effect on personal activities

Campbell EG. JAMA 2007; 298: 1779-86.

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Professional syllogism

- Professionals are not biased or influenced by commercial forces
- I am a professional
- I am not biased or influenced by commercial forces
- Logic of self-serving bias

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Diagnostic models

- Deliberate choice model
  - Small gifts not enough to affect behavior
  - Trade cost of bias vs benefit of reward
- If individuals are unaware of self-serving bias, it cannot be remedied by training
- Narrative-based professionalism
  - Dialectic between culture and narrative

Dana J. JAMA 2003;290:252; Coulehan J. Acad Med 2005;80:892.***CHRU***

Cheating experiment

- Write down 10 commandments or 10 books and solve math problems
- Subjects paid for the number of correct answers and cheating was possible
- Subjects listing books cheated by 1 question, none for those who listed commandments

Ariely D. Symposium on influence and reciprocity, 2007. ***CHRU***

Series of experiments

- People cheat when they have a chance but only a “little bit”
- Magnitude of dishonesty is not monotonic in relation to rewards
- People know they are overclaiming
- Cheating “a bit” does not cause people to think of themselves as dishonest

Ariely D. Symposium on influence and reciprocity, 2007. ***CHRU***

Study of readers' perceptions

- Used a paper concluding that zoster pain is substantial
- Same paper, same authors, two different disclosures—none vs employees of fictional CT company
- Rated by 300 BMJ readers on 1-5 scale (proportion rated high, 4-5)

Chaudhry S. BMJ 2002; 325: 1391-2. ***CHRU***

Perception of competing interests

Question	Present	None
Interest	15%	33%
Importance	16%	31%
Relevance	27%	42%
Validity	21%	41%
Believability	31%	51%

Chaudhry S. BMJ 2002; 325: 1391-2. ***CHRU***

Study of effects of disclosure

- Task—to estimate the amount of money in a large jar full of coins
- Estimators rewarded for accuracy
- Advisors rewarded according to
  - estimator's accuracy
  - size of estimator's guess without disclosure
  - size of estimator's guess with disclosure

Cain DM. J Legal Studies 2005; 34; 1-26. ***CHRU***

Effects of disclosure

Experiment	First	Second	Third
Advisor paid for	accurate	high	
Conflict	none	undisclosed	
Advisor suggests	16.48		
Estimator guesses	14.21		

Cain DM. J Legal Studies 2005; 34; 1-26. ***CHRU***

Effects of disclosure

Experiment	First	Second	Third
Advisor paid for	accurate	high	high
Conflict	none	undisclosed	disclosed
Advisor suggests	16.48	20.16	
Estimator guesses	14.21	16.81	

Cain DM. J Legal Studies 2005; 34; 1-26.

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Effects of disclosure

Experiment	First	Second	Third
Advisor paid for	accurate	high	high
Conflict	none	undisclosed	disclosed
Advisor suggests	16.48	20.16	24.16
Estimator guesses	14.21	16.81	18.14

Cain DM. J Legal Studies 2005; 34; 1-26.

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Sole function of disclosure

"To maintain credibility with the public, disclosure is essential for authors of guidelines…. It is a preventive measure: full disclosure simply precludes the possibility that some potential conflict may eventually be revealed and discredit the profession."

Psaty BM. BMJ 1999; 319: 589-90.

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COI bias as behavioral

- Transparency
- Trial design
- Trial conduct
- Trial Interpretation

Psaty BM. JAMA 2009; 301: 1477-79.

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IOM report: conflict of interest

- "The committee recommends that medical institutions establish conflict of interest policies that require disclosure and management of both individual and institutional financial ties to industry"
- Support for Sunshine law proposed by Grassley and Kohl

IOM Conflict of interest report, April 28, 2009.

Institutional responses

- Conduct of clinical trials
  - Mandatory education and certification
- Relations with pharmaceutical companies
  - Prohibited gifts and meals
  - Curtailed CME and formulary associations
- Clinical and teaching environment
  - Role models of professionalism

Wasserstein AG. Acad Med 2007; 82: 1049-56.

Concluding observations

- Academic-industry collaborations
- Foundation of system of medical education and research is trust
  - Protected by few safeguards
  - Assailed by unrelenting commercialization
- Transparency and distance as remedies
  - Limited utility associated with disclosure
  - Independence and "managed" distance

Extras follow

Rosiglitazone: what did we know, when did we know it, and how long did it take to do something once we knew?

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Cardiovascular Health Research Unit, Seattle, WA

Introduction

- Natural history of approved drugs
  - Timely risk identification and action
- Outcomes used for drug approval
  - Importance of large long-term trials of health outcomes rather than surrogate endpoints
- Studies of rosiglitazone
  - Phase III and IV trials
  - Meta-analyses and observational studies

Rosiglitazone timeline

May 1999	Approved by the FDA, ADOPT as Phase IV trial
July 2000	Approved by European Commission, RECORD as Phase IV
Jan 2004	WHO signal document on TZDs and cardiac disease
Apr 2004	Sponsor forms working group on analysis of CV events
Oct 2005	Summary of first meta-analysis (n=37) submitted to FDA
Aug 2006	Final report of 2nd meta-analysis (n=42) submitted to FDA
Oct 2006	European product label incorporates meta-analysis results
Dec 2006	ADOPT trial published
May 2007	Nissen meta-analysis published (OR=1.43)
June 2007	Sponsor publishes interim data from RECORD trial
Nov 2007	FDA adds boxed warning on myocardial ischemia
July 2010	Completed results from RECORD trial published
Sept 2010	EMA suspends sales; FDA announces REMS restrictions

Nissen S. N Engl J Med 2007; 356: 2457-2471.

Surrogates in drug approval

- The use of linear "logical" extrapolations
  - Drug → surrogate marker → disease
- Evaluation of drug effects on glucose rather than on major health outcomes
  - Partial evaluation of the hypothesis
- Small short-term trials possible
  - Reduced costs and time to approval
  - Incomplete answer about risks and benefits

Psaty BM. JAMA 1999; 282: 786-790

Uneasy history of type-2 trials

- UGDP trial launched in 1960, early CER
  - Tolbutamide arm stopped for cardiac mortality
  - Precipitated contentious debate
  - Ended large trials in diabetes for years
- Metformin approved in 1957
  - Health benefits not identified until 1998
- What are the expected and observed CV benefits and risks of tight glucose control?

Diabetes 1970; 19(suppl I): 789. Lancet 1998; 352: 854.

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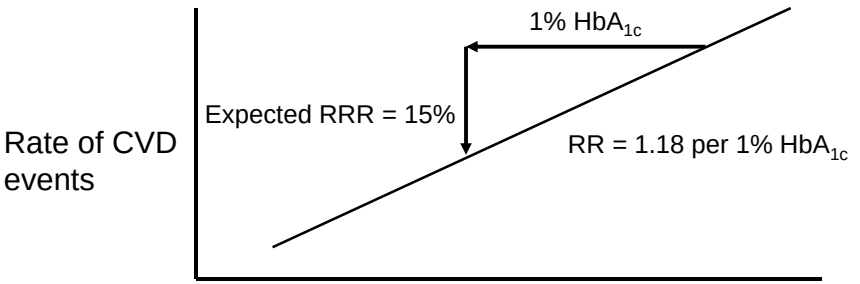
Type 2 diabetes: HbA_{1C} & CVD



Selvin E. Ann Intern Med 2004; 141: 421-31.

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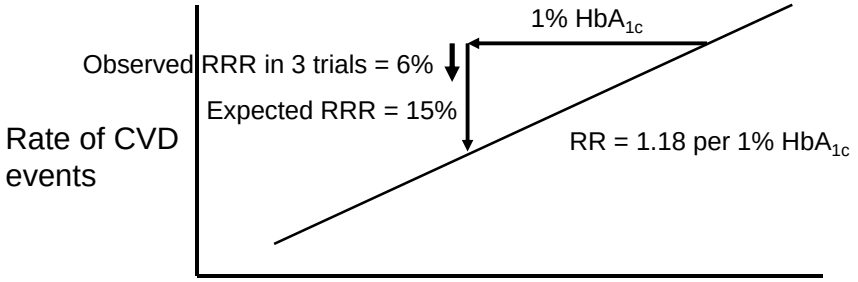
Type 2 diabetes: trial results



Kelly T. Ann Intern Med 2009; 151: 394-403.

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Findings from ACCORD

- Trial of intensive glucose control
  - Failed to prevent coronary events or microvascular composite outcome
  - Increased weight, low-glucose episodes
  - Increased mortality by 22% (CI,1 to 46%)
  - Unconfirmed hypotheses plus unanticipated off-target effects
- Highlights importance of evaluating actual health risks and benefits in large RCTs

ACCORD. NEJM 2008; 358: 2545; Lancet 2010; 376: 419.

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Rosiglitazone phase III results

Outcome	Placebo	RSG 4	RSG 8
Fasting glucose	233	204	186
HbA1c	9.7	8.9	8.6
LDL cholesterol	130	145	148
Weight change	0	4.2	8.8

US product label for rosiglitazone, June 2007.

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FDA medical review

"Whether RSG favorably affects the natural history of type 2 diabetes is an open question. However, **the increase in body weight and undesirable effects on serum lipids is a cause for concern…. Heart disease … is a major cause of morbidity and mortality … and it cannot be assumed that RSG will decrease the [CVD] risk…. My concern about deleterious long term effects on the heart should be addressed**…. A postmarketing study to address these issues needs to be a condition of approval."

Misbin RI. CDER, 21-071 (rosiglitazone), Apr 1999.

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Phase IV trial: ADOPT

- Design: n=4360, new onset diabetes
  - Randomized to glyburide, metformin, or rosiglitazone and followed for 4 years
  - Duration of one-drug control of glucose
- Failure rates for control with one drug
  - 15% for rosiglitazone, 21% for metformin, and 34% for glyburide
- MI & stroke events not assessed

Kahn SE. N Engl J Med 2006; 355: 2427-43.

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Phase IV trial: RECORD

- Design, open-label non-inferiority, n=4447
  - Randomized to RSG+(Met or Slf) or Met+Slf
  - CV deaths or hospitalizations as outcome
- Results: CVD HR = 0.99 (0.85-1.16)
  - Only one third of expected events identified
  - Increased HF risk: RR=2.1(1.4-3.3)
  - Increased fracture risk: RR = 1.6 (1.3-2.0)
  - MI risk: RR = 1.14 (0.80-1.63)
  - Sponsor interfered with SC and DSMB

Lancet 2009; 373: 2125-35; N Engl J Med 2010; 365: 477-8.

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Events rates in diabetes trials

Study name Study type	ARIC cohort	RECORD trial	ACCORD trial	VADT trial
Age, years	59	58	62	60
Sex, % male	47	51	62	97
Diabetes, %	8	100	100	100
Heart disease, %	0	31	35	40
Body mass index	27	31	32	31
Systolic presure	118	139	137	132
LDL cholesterol	140	127	104	108
Heart attack rate	**4.3**	**5.2**	**13.8**	**15.9**

Psaty BM. JAMA 2009; 302: 1698-1700.

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Marciniak's review of outcomes

Outcome	RSG	Control	Total
Number reviewed	278	271	549
With problems	45	25	70
Favors rosiglitazone	44	13	57
Favors control	1	12	13

Psaty BM. JAMA 2010; 304: 793-4

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Rosiglitazone summary

- Heavily advertised and promoted
  - 2000-06, 58 million prescriptions
    - 4.8 million person years of use
  - In 2010, sponsor's trials leave unanswered CV risk-benefit question posed by Misbin
- "System" for drug evaluation sometimes provides incomplete patchwork of evidence about risks and benefits

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Nissen's meta-analyses

- In 2007, meta-analyses by Nissen, FDA and sponsor all produced similar results
- Updated version including data from 56 trials with 35531 patients
  - MI risk: OR = 1.28 (95% CI =1.02-1.63)
  - Without RECORD: OR = 1.39 (1.02-1.89)
  - Similar results from 2010 FDA meta-analysis (n=52): OR = 1.80 (1.03-3.25)

Nissen S. Arch Intern Med 2010; 170: 1191-1201.

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Observational studies

- Meta-analyses as observational studies
  - Cumulative evidence about risk
- Often a limited role for case series, case-control and cohort studies
  - Most valuable for identifying safety signals
- Unique opportunity to compare MI risk
  - New users: rosiglitazone vs pioglitazone
  - Absence of "anchor" data on comparator

Vandenbrouck J. JAMA 2008; 300: 2417-9.

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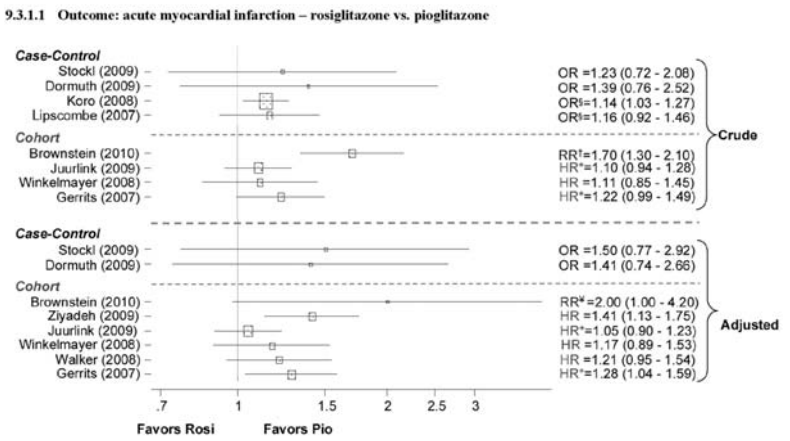
Rosiglitazone vs pioglitazone



Gelperin K, FDA OSE Review, June 15, 2010.

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Rosiglitazone: risks & benefits

- Reduces HbA1C and glucose
  - Presumed micro-vascular benefit
- Increases weight, LDL cholesterol, and fluid retention
- Increases risks of fracture, heart failure, and (probably) myocardial infarction
  - Lower 95% CI excludes reduced MI risk

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Concluding observations

- Surrogates in RCTs unreliable Rx guide
  - Large RCTs to establish risk-benefit profile
- Asymmetric interest in efficacy and safety
  - Marketing trials as notoriously "safe"
  - Evidence of bias in open-label trial
  - Sponsor's interference with trial conduct
- Importance of observational studies
  - Meta-analysis of small trials
  - New user cohort designs

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A new first rule of medicine?

ante omnia, iuvare amplius quam nocere.

(Above all, do more good than harm.)

Senior JR. Toxicol Pathol 2010; 38: 142-7.

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