Safety & Effectiveness of Drug Therapies for Type 2 Diabetes: Are pharmacoepi studies part of the problem, or part of the solution?

Jeffrey A. Johnson
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Edmonton, Canada

IDEG Training Workshop
Melbourne, Australia
November 29, 2013
1. Advantages and disadvantages of pharmacoepi (observational) studies and RCT.

2. Discuss major challenges with pharmacoepi studies
   - Time-varying drug exposure
   - Selection Bias
   - Confounding by indication

3. Introduce some potential remedies
• the study of the use and effects of drugs on large groups of people.
  – Borrows from both epidemiology and pharmacology
  – Just as in any form of epidemiology, it helps to have a good understanding of biology/physiology/pharmacology
1. Describing patterns of prescribing/medication use;

2. Policy oriented questions; drug coverage, economic implications of drug use;

3. Quantifying the risks and benefits of drug therapies.
Drug Treatment for Type 1 diabetes

Not all associations need to be tested with RCT.

Insulin in Type 1 DM
Parachute use to prevent death and major trauma related to gravitational challenge: systematic review of randomised controlled trials

Gordon C S Smith and Jill P Pell

BMJ 2003;327;1459-1461

What is already known about this topic

Parachutes are widely used to prevent death and major injury after gravitational challenge

Parachute use is associated with adverse effects due to failure of the intervention and iatrogenic injury

Studies of free fall do not show 100% mortality

What this study adds

No randomised controlled trials of parachute use have been undertaken

The basis for parachute use is purely observational, and its apparent efficacy could potentially be explained by a “healthy cohort” effect

Individuals who insist that all interventions need to be validated by a randomised controlled trial need to come down to earth with a bump

See also Potts, et al., BMJ 2006
Drug Treatment for Type 2 diabetes

- Differences in clinical experience, cost, adverse effects;
- Relatively little evidence of benefit in macrovascular outcomes;
- Main focus of large RCT has been on overall glycemic control;
- Important adverse effects: CVD, HF, cancer, bone health
Phases of drug development

PC: Preclinical studies
1: Dose escalation in healthy patients
2: Dose ranging, first time in patients
3: Pivotal trials for registration (Phase 3 RCTs)
4: Postmarketing – majority of pharmacoepi studies
51% of drugs have label changes due to major safety issues “discovered” after marketing.

20% of drugs get new “black box” warnings after marketing.

4% of drugs are ultimately withdrawn for safety reasons.
Today’s reality…

• The majority of health care evidence is generated from non-experimental approaches

• Fundamental Issue: How to generate valid evidence of the safety and effectiveness of drugs when used in everyday routine clinical care?
How patients are selected may introduce bias.

Random Allocation

This act of choice introduces many potential biases.

Drug exposure and outcomes may be measured poorly.

How patients are retained or removed may introduce bias.

Group of Patients

Drug A

Drug B

Measure Outcomes
Fundamental Weakness of Pharmacoepi studies

**Bias**
Any systematic error in an study that results in an incorrect estimate of the association between exposure and risk of disease.

- Selection bias
- Information bias

**Confoundering**
Exposure → Outcome

Confounding Variable
The best epidemiologic study will be one that captures the causal effect with minimal distortion.
“Hypothesis Generating”

- case reports and case series
- ecologic studies
- cross sectional studies
- case control studies
- hybrid studies
- cohort studies
- intervention studies
- randomized controlled trials

“Vulnerability for bias and confounding”

“Causal Hypothesis screening process”

“Hypothesis Testing”

- retrospective
- prospective
- historical
- prospective
Generating & Testing Hypotheses

20% increased risk of death with intensive glycemic control!

Why?
- Was it TZD use?
- Was it hypoglycemia?

How many hypotheses were generated in ACCORD?

ACCORD, NEJM, 2011
Inference: Association
“Hypothesis Generating”

- case reports and case series
- ecologic studies
- cross sectional studies
- case control studies
- cohort studies
- intervention studies
- randomized controlled trials
- hybrid studies
  - retrospective
  - prospective
  - historical
  - prospective

Vulnerability for bias and confounding

Causal Hypothesis screening process

“Hypothesis Testing”
Inference: Causation
Diabetes Pharmacoepi
Special Challenges

- Multiple time scales
  - Age; DM duration; New vs prevalent drug use

- Changing drug exposure
  - Ever/never vs time-varying cumulative exposure
  - Immortal time bias

- Confounding by indication
  - Selection bias
  - Sicker patients more likely to get drug of interest, and more likely to have outcome
drug exposure is time varying
“New Users Design”
• Can better assess time-varying hazard function
• Can better study adverse effects shortly after treatment start
• More appropriate assessment of covariates (not on causal path)
The period of observation or follow-up time during which the outcome of interest (e.g., MACE, death) may not occur.

May be introduced if you don’t consider time before drug starts (even if you use a ‘new users’ design)

This period is immortal because the subject is required to ‘stay alive’ or ‘event free’ to meet the exposure definition.

Exclusion or misclassification of immortal time results in an underestimation of harm, or overestimation of benefit.

Consequently, drugs that have no effect, or worse yet a harmful effect, may falsely appear protective or neutral in effect.
Immortal Time Bias

Immortal time and misclassified

Metformin users

Sulfonylurea users

Time zero: First prescription

● = Cancer death
◊ = Sulfo Rx
♦ = Metformin Rx

Source: Suissa A, Diabetes Care 2012;35:2665
Immortal Time Bias

Do Oscar Winners Live Longer than Less Successful Peers?
A Reanalysis of the Evidence

Marie-Pierre Sylvestre, MSc; Ella Huszti, MSc; and James A. Hanley, PhD

Survival Difference
3.7 years
p=0.006

Relative Reduction Mortality
% (95% CI)

Basic 28 (10-42)
Age, sex, ethnicity 26 (8-40)
Name change 27 (10-42)
Age 1st film 26 (7-40)
Total films 27 (9-42)
All factors 23 (2-38)

Source: Redelmeier & Singh Ann Int Med 2001;134:955
Adjusting for age at time of winning accounted for majority of the difference.

RR 0.85 (0.68-1.05)  
0.7 (0.3-1.6) years

Sylvestre et al., Ann Int Med 2006
Use of insulin was associated with a decreased cancer risk;

HR of insulin users vs. non-users: 0.17 (0.09–0.32)
Associations of Hyperglycemia and Insulin Usage With the Risk of Cancer in Type 2 Diabetes: The Hong Kong Diabetes Registry

Xilin Yang,1 Gary T.C. Ko,2 Wing Yee So,1 Ronald C.W. Ma,1 Linda W.L. Yu,1 Alice P.S. Kong,1 Hailu Zhao,1 Chun-Chung Chow,1 Peter C.Y. Tong,1,2 and Juliana C.N. Chan1,2,3

- Inflated the risk in DM
- Deflated the risk in DM+ins
- Gross under-estimation of RR

Carsetensen, Diabetes 2010;59:e17
This particular relationship is extremely complex;

- Cynicism in observational studies may be justified when poorly conducted or over-interpreted;

- On the other hand, properly conducted and sensibly interpreted observational studies must form the part of any future solution.
Metformin in Type 2 DM

- Proven effectiveness as monotherapy in overweight type 2 DM (UKPDS 34, 1998).
- Metformin SU combination therapy was associated with increased mortality (UKPDS 34; Fisman 1999; Olsson 2000).
- UKPDS 34 was actually a poorly done controlled trial, with small N, but remains the only RCT evidence of clinical benefit of metformin
- Cautious use (esp. in US) due to concern with lactic acidosis
- Contraindicated in patients with heart failure and kidney disease
Metformin & Lactic Acidosis

- Admin data from Saskatchewan Health
- Historical, single group, cohort design
  - 1980 through 1995
- 11,797 residents with metformin prescriptions
  - 22,296 person-years of exposure
- ICD-9 code for acidosis (276.2) in hospital discharge
  - Within 120 days of dispensation
  - Hospital chart abstraction for validation

- 10 cases based on ICD-9 276.2 in admin data
- 2 cases confirmed as LA on chart audit
  - Rate of 9 cases per 100,000 p-yrs (95% CI: 0-21)

Stang et al, Diabetes Care 1999;22:925-927
Metformin in Type 2 Diabetes
Retrospective Cohort Study (N=8,866)
Saskatchewan, Canada, 1991-1999

Johnson et al, Diabetes Care 2002;25:2244-2248

OR: 0.60 (0.49-0.74) 0.64 (0.49-0.84)
Evidence to Reduce Macrovascular Risk?

Metformin use

- UKPDS 34 (Lancet 1998;352:854-65) (N=342/921) versus conventional
  - All cause mortality 0.64 (0.45-0.91)
  - Myocardial infarction 0.61 (0.41-0.89)

- Johnson JA, et al. (Diabetes Care 2002;25:2244-8) (N=1150/3033) versus sulfonylurea monotherapy
  - All cause mortality 0.60 (0.49-0.74)
  - Cardiovascular mortality 0.64 (0.49-0.84)

- Evans JM, et al. (Diabetologia 2006;49:930-6) (N=2286/3331) versus sulfonylurea monotherapy
  - All cause mortality 0.70 (0.56-0.87)
  - Cardiovascular mortality 0.59 (0.41-0.85)
Metformin in Diabetes & Heart Failure
Retrospective Cohort Study (N=1,833)
Saskatchewan, Canada, 1991-1999

All-Cause Mortality
- Metformin Monotherapy
- Combination Therapy

All-Cause Hospitalization
- Metformin Monotherapy
- Combination Therapy

Combined Endpoint (Death/Hospitalization)
- Metformin Monotherapy
- Combination Therapy

Hazards Ratio:
- 0.70 (Reduced Risk)
- 0.61
- 0.87
- 0.93
- 0.83
- 0.86

Eurich et al., Diabetes Care 2005
**Metformin in Diabetes & Heart Failure**

**Metformin treatment in diabetes and heart failure: when academic equipoise meets clinical reality**

Dean T Eurich*1, Ross T Tsuyuki2, Sumit R Majumdar1,2, Finlay A McAlister1,2, Richard Lewanczuk2, Marcelo C Shibata2 and Jeffrey A Johnson1


- Pilot study for large RCT
- n=58 patients screened
- None eligible
- No clinical equipoise
- Conclusion:
  No need to do an RCT!!
### Metformin in Diabetes & Heart Failure

**HF contraindication has now been removed from label for metformin (US 2006; Canada 2010)**

- Clinical practice guidelines recommend metformin in patients with DM & HF

**Eurich D T et al. Circ Heart Fail 2013;6:395-402**

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>log[Risk Ratio]</th>
<th>SE</th>
<th>Weight</th>
<th>IV, Random, 95% CI</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evans</td>
<td>-0.5108</td>
<td>0.25</td>
<td>2.6%</td>
<td>0.60 [0.37, 0.98]</td>
<td>2005</td>
</tr>
<tr>
<td>Eurich</td>
<td>-0.4156</td>
<td>0.2</td>
<td>4.1%</td>
<td>0.66 [0.45, 0.98]</td>
<td>2005</td>
</tr>
<tr>
<td>Masoudi</td>
<td>-0.1393</td>
<td>0.06</td>
<td>29.0%</td>
<td>0.87 [0.77, 0.98]</td>
<td>2005</td>
</tr>
<tr>
<td>Inzucchi</td>
<td>-0.0834</td>
<td>0.13</td>
<td>8.9%</td>
<td>0.92 [0.71, 1.19]</td>
<td>2005</td>
</tr>
<tr>
<td>Shah</td>
<td>-0.2357</td>
<td>0.4</td>
<td>1.1%</td>
<td>0.79 [0.36, 1.73]</td>
<td>2010</td>
</tr>
<tr>
<td>MacDonald</td>
<td>-0.4308</td>
<td>0.15</td>
<td>6.9%</td>
<td>0.65 [0.48, 0.87]</td>
<td>2010</td>
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<tr>
<td>Roussel</td>
<td>-0.3711</td>
<td>0.13</td>
<td>8.9%</td>
<td>0.69 [0.53, 0.89]</td>
<td>2010</td>
</tr>
<tr>
<td>Andersson</td>
<td>-0.1625</td>
<td>0.0682</td>
<td>24.6%</td>
<td>0.85 [0.74, 0.97]</td>
<td>2010</td>
</tr>
<tr>
<td>Aguilar</td>
<td>-0.2744</td>
<td>0.1</td>
<td>13.9%</td>
<td>0.76 [0.62, 0.92]</td>
<td>2011</td>
</tr>
</tbody>
</table>

**Total (95% CI)**

100.0% 0.80 [0.74, 0.87]

**Heterogeneity:** $\tau^2 = 0.00$; $\chi^2 = 9.45$, df = 8 (P = 0.31); $I^2 = 15$

**Test for overall effect:** $Z = 5.35$ (P < 0.000001)
Confounding by Indication

• Also referred to as confounding by severity of disease, confounding by reason for drug, channeling, etc.

• Probably the most important bias to keep in mind in clinical epidemiology, including pharmacoepidemiology …

• Result from the conscious choice of different drug treatments (exposure) for patients with different prognosis.

Insulin in T2D \(\rightarrow\) Outcomes

Advanced disease
**Mortality and Other Important Diabetes-Related Outcomes With Insulin vs Other Antihyperglycemic Therapies in Type 2 Diabetes**

Outcome: MACE/Cancer/Death

**Insulin mono**
- N: 58,532
- Age (y): 61
- DM Duration (y): 1.5
- SCr > 130 umol/L: 2.2%

**Metformin mono**
- N: 3,944
- Age (y): 61
- DM Duration (y): 5.2
- SCr > 130 umol/L: 21.1%

\[ \text{aHR} = 1.778 \ (1.575-2.007), \ p < 0.0001 \]

Currie et al., J Clin Endocrinol Met 2013
Dealing with Confounding

Confounding

Measured confounders
- Design
  - Restriction
  - Matching
- Analysis
  - Standardization
  - Stratification
  - Multivariate regression

Unmeasured confounders*
- Unmeasured but measurable in a validation study
  - Two-stage sampling
  - *External adjustment*
- Unmeasurable
  - Design
    - Crossover designs
  - Analysis
    - Instrumental variables
    - Sensitivity analysis

Dealing with Confounding

• Adjusting for many covariates often becomes difficult when:
  – the number of covariates is very large
  – outcome is rare

• One way of handling this is through the use of a summary score
• the propensity score is a type of covariate summary score
• Method to balance confounders b/w treatment groups
• Unmeasured confounders still may be unbalanced
Dealing with Confounding Propensity Score

- PS = p(treatment | pre-treatment covariates)
  - i.e., the conditional probability of receiving a certain treatment given a number of measured covariates
  - each patient receives a score between 0 and 1, representing their ‘propensity’ of getting the drug of interest
Dealing with Confounding Propensity Score

Using Propensity Scores

– Step 1 – estimate the propensity for treatment as a function of the observed covariates

  • Logistic regression: DV observed drug exposure (A or B)
  • IV all your covariates;
  • Predicted value in log regression (b/w 0 and 1) is the patients propensity score (PS)

– Step 2 – Use the estimated PS to adjust drug comparison

  • stratification, matching, or as a covariate
Dealing with Confounding
Propensity Score

Propensity score matching

- Patients never treated with study drug
- Patient always treated with study drug

% of subjects

Exposure propensity score

- = treated with study drug
- = treated with comparison drug
Dealing with Confounding
Propensity Score

PS distributions after matching

- Patients never treated with drug
- Patients always treated with drug

% of subjects vs Exposure propensity score

- Treat with study drug
- Treat with comparison drug
Statins & MI
Results from RCT

Statins and risk of MI

Before Propensity Score Matching

109% Risk Increase (RR= 2.09, 1.58-2.76)

Statin Initiators

Statin Non-Initiators

## Before Matching

<table>
<thead>
<tr>
<th>Variable</th>
<th>Initiators N=4144</th>
<th>Non-Initiators N=4144</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lipid-related labs</td>
<td>26.04</td>
<td>13.58</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Different Prescription Drugs</td>
<td>5.02</td>
<td>2.88</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LDL level (mg/dl)</td>
<td>180.25</td>
<td>155.08</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Triglyceride level (mg/dl)</td>
<td>202.66</td>
<td>166.91</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Cardiovascular-related Prescription Drugs</td>
<td>0.59</td>
<td>0.26</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Cardiovascular-related visits</td>
<td>1.11</td>
<td>0.27</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Age (years)</td>
<td>62.04</td>
<td>58.02</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Physician Visits</td>
<td>7.69</td>
<td>6.31</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Ischemic Heart Disease</td>
<td>20.27%</td>
<td>5.57%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>HDL level (mg/dl)</td>
<td>43.29</td>
<td>46.60</td>
<td>&lt;0.0001</td>
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<tr>
<td>Cardiovascular-related diagnoses</td>
<td>0.28</td>
<td>0.12</td>
<td>&lt;0.0001</td>
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<td>Cardiovascular-related hospitalizations</td>
<td>0.56</td>
<td>0.13</td>
<td>&lt;0.0001</td>
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<tr>
<td>MI</td>
<td>11.58%</td>
<td>2.92%</td>
<td>&lt;0.0001</td>
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<tr>
<td>Angina</td>
<td>11.92%</td>
<td>3.14%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Unstable Angina</td>
<td>10.59%</td>
<td>2.22%</td>
<td>&lt;0.0001</td>
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<tr>
<td>Smoking</td>
<td>25.80%</td>
<td>18.10%</td>
<td>&lt;0.0001</td>
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<tr>
<td>Hypertension</td>
<td>19.96%</td>
<td>12.96%</td>
<td>&lt;0.0001</td>
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<tr>
<td>Labs</td>
<td>10.48</td>
<td>10.74</td>
<td>0.0074</td>
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<td>Hospitalizations</td>
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<td>0.08</td>
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<tr>
<td>Male</td>
<td>53.14%</td>
<td>47.61%</td>
<td>&lt;0.0001</td>
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</table>
## Balance Achieved

<table>
<thead>
<tr>
<th>Variable</th>
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<th>Non-Initiators N=2901</th>
<th>P-value</th>
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<td>Lipid-related labs</td>
<td>24.90</td>
<td>24.64</td>
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<td>Different Prescription Drugs</td>
<td>4.57</td>
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<td>LDL level (mg/dl)</td>
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<td>0.7837</td>
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<td>Triglyceride level (mg/dl)</td>
<td>200.34</td>
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<td>Cardiovascular-related Prescription Drugs</td>
<td>0.51</td>
<td>0.51</td>
<td>0.9367</td>
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<td>Cardiovascular-related visits</td>
<td>0.74</td>
<td>0.83</td>
<td>0.1249</td>
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<td>Age (years)</td>
<td>61.47</td>
<td>61.68</td>
<td>0.5030</td>
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<tr>
<td>Physician Visits</td>
<td>7.25</td>
<td>7.27</td>
<td>0.8732</td>
</tr>
<tr>
<td>Ischemic Heart Disease</td>
<td>15.13%</td>
<td>15.48%</td>
<td>0.7428</td>
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<td>HDL level (mg/dl)</td>
<td>43.51</td>
<td>43.55</td>
<td>0.9079</td>
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<td>Cardiovascular-related diagnoses</td>
<td>0.21</td>
<td>0.23</td>
<td>0.2145</td>
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<tr>
<td>Cardiovascular-related hospitalizations</td>
<td>0.40</td>
<td>0.39</td>
<td>0.7929</td>
</tr>
<tr>
<td>MI</td>
<td>7.89%</td>
<td>8.69%</td>
<td>0.3169</td>
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<tr>
<td>Angina</td>
<td>8.51%</td>
<td>8.72%</td>
<td>0.8151</td>
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<tr>
<td>Unstable Angina</td>
<td>7.14%</td>
<td>7.31%</td>
<td>0.8393</td>
</tr>
<tr>
<td>Smoking</td>
<td>23.85%</td>
<td>24.27%</td>
<td>0.7355</td>
</tr>
<tr>
<td>Hypertension</td>
<td>16.58%</td>
<td>17.99%</td>
<td>0.1649</td>
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<tr>
<td>Labs</td>
<td>10.45</td>
<td>10.48</td>
<td>0.7874</td>
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<tr>
<td>Hospitalizations</td>
<td>0.16</td>
<td>0.16</td>
<td>0.6915</td>
</tr>
<tr>
<td>Male</td>
<td>52.33%</td>
<td>52.09%</td>
<td>0.8747</td>
</tr>
</tbody>
</table>
Statins and risk of MI

After Propensity Score Matching

31% Risk Reduction
(RR= 0.69, 0.52-0.93)

Comparative safety and effectiveness of sitagliptin in patients with type 2 diabetes: retrospective population based cohort study

Eurich et al., *BMJ* 2013;346:f2267

- Used time-varying propensity score in adjustment (60 variables)
- High-dimensional PS (algorithmic based variable selection)
Pioglitazone and risk of bladder cancer among diabetic patients in France: a population-based cohort study

A. Neumann • A. Weill • P. Ricordeau • J. P. Fagot • F. Alla • H. Allemand

Diabetes Pharmacoepi
Pioglitazone and Bladder Ca

Risk of Bladder Cancer Among Diabetic Patients Treated With Pioglitazone

Interim report of a longitudinal cohort study

- Large population-based studies; Incident users
- Used time-varying Cox regression
- Cumulative pioglitazone use (mg and days supply)
- Extensive sensitivity analyses
Pioglitazone & Bladder Cancer

Lewis et al., Diabetes Care 2011
Kaiser Permanente, N~ 193,000
~ 30,000 pio users
~ 880 bladder cancers

Neumann, Diabetologia 2012
France, N~ 1.5 million
~ 155,000 pio users
~ 2000 bladder cancers
Pioglitazone & Bladder Cancer

Cohort studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Exposed n/N</th>
<th>Comparison n/N</th>
<th>Risk ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tseng$^{20}$</td>
<td>10/2 545</td>
<td>155/52 383</td>
<td>1.30 (0.66–2.58)</td>
</tr>
<tr>
<td>Lewis et al.$^{10}$</td>
<td>90/30 173</td>
<td>791/162 926</td>
<td>1.20 (0.93–1.55)</td>
</tr>
<tr>
<td>Neumann et al.$^{19}$</td>
<td>175/155 535</td>
<td>1 841/1 335 525</td>
<td>1.22 (1.05–1.42)</td>
</tr>
</tbody>
</table>

Overall
Heterogeneity: $I^2 = 0$

Randomized controlled trial:
Dormandy et al. (PROactive)
RR: 2.36 (0.91–6.13)

Case-control study:
Piccinni et al.
OR: 4.30 (2.82–6.52)

Colmers et al., CMAJ 2012
Pharmacoepidemiology impacts patients

Pioglitazone suspended in France and Germany

9 June 2011
EMA/278128/2011
Press Office

... based on a cohort study in a French administrative database study that found an association between pioglitazone and bladder cancer
This particular relationship is extremely complex;
- Cynicism in observational studies may be justified when poorly conducted or over-interpreted;
- On the other hand, properly conducted and sensibly interpreted observational studies must form the part of any future solution.
Pharmacoepi Studies
Facing the Challenges

• Advantages
  – Relatively low cost
  – Potential for longer follow-up
  – Larger sample sizes
  – Assessing rare outcomes

• Disadvantages
  – Susceptible to bias & confounding
Pharmacoepi Studies
Facing the Challenges

• Address all relevant time scales
  – Incident diabetes
  – Incident drug use “New user design”

• Address time-varying exposure
  – Immortal time
  – Cumulative exposure (vs ever/never)

• Address time-varying risk

• Address assumptions in exposure and outcome with sensitivity analyses
If you have been...,

Thanks for listening

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