How far can we trust "Real World Data"?

Increased use of RWD in regulatory submissions: implications for statisticians

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Acknowledgements, conflicts

- Thanks to Dr Kaspar Rufibach and the organisers of EFSPI for inviting me and funding my travel and stay
- Thanks for comments from Jim Slattery and Andrew Thomson (EMA)

- I teach on pharmaco-epidemiology at LSHTM and they charge fees!
- I have no (other) commercial conflicts

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Regulatory Interests

- European Commission appointed independent Member of Pharmacovigilance & Risk Assessment Committee (PRAC at EMA, 2012-2018)
- Member of CIOMS Working Groups on Meta-analysis for safety, Risk Benefit
- Member of expert working groups at the UK Medicines & Healthcare Products Regulatory Agency (MHRA)
- Consultant to Singapore Health Sciences Authority
- *All remarks are a personal viewpoint and should not be taken as a PRAC or EMA or MHRA viewpoint*

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Outline of talk

- RWD to mean “non-randomised data” (NRD)
- What characteristics of design and analysis of NRD studies make them reliable or unreliable?
- What are the best guidelines, if any?
- Where might they be useful in studies of benefits?
- Where might they be useful in studies of harms?
- Some examples
- Detecting fraud in NRD

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RWD to mean "non-randomised data" (NRD)

- "Real World" is not really what we want to consider.
- All measured data come from the real world
  - As opposed to simulated data
- It presumes that RCTs are an artificial environment and do not reflect subsequent use in clinical practice
- This is not necessarily so, RCTs can reflect practice
  - Pragmatic trials attempt to do this
- The real distinction, leading to analysis and interpretation problems, is between randomized and non-randomised data, in making causal claims

Epidemiologists & Trialists thoughts

Mansournia MA et al Biases in randomized trials: a conversation between trialists and epidemiologists. Epidemiology. 2017; 28: 54–59.

"Being aware of each other's terminologies will enhance communication between trialists and epidemiologists when considering key concepts and methods for causal inference."

"Epidemiologists,… tend to use the categories confounding, selection bias, and measurement (or information) bias.

See also Hernan M & S H-Diaz. Clin Trials. 2012; 9: 48–55.

What characteristics of design and analysis of NRD studies (NRDS) make them reliable or unreliable?

Unreliable

1. Poor choice of controls
2. Confounding (by indication- a form of selection bias)
3. Unmeasured important confounders

Reliable

1. Within person comparisons
2. High dimensional propensity score that replicates randomized results for one outcome, then applied to another

When can NRDS be trusted ?

- Miettinen: Intended v unintended effects
  - (Stat in Med 1983)
- Vandenbroucke: Restrictions in topics; design (e.g. idiopathic& {incident} cases) & analysis
  - (Lancet May 2004 & Int J Epid 2004)
- Risk factors for disease are known, measured well & explain a lot of the variation; if any of these conditions not met, then beware

Comments on non-randomised studies

- Their weaknesses must be acknowledged
  - but they do have strengths
- Better at finding harms than benefits
- Use propensity scores to see if it is worth even starting on an outcome study?
- A large separation of the distribution of PS is a warning that adjustment may not be reliable

Convincing regulators of reliability of epidemiological studies

- There needs to be more work to demonstrate that OS can replicate RCTs
  - (projects by Jessica Franklin & Sebastian Schneeweiss)
  - Schneeweiss S. Clinical Epidemiology 2018:10 771-88
- Methods then applied to questions not answered by RCTs?
  - (Weiner et al; Tannen et al *PDS* 2008)
- Treat OS with appropriate caution

How can we improve the overall approach?

- Epidemiological thinking applied to the whole spectrum from case reports to RCTs
- More use of the self-controlled case series method (Farrington)
  - This deals with unmeasured fixed confounders- very useful with vaccines
  - Not fully appreciated outside the field of vaccines?

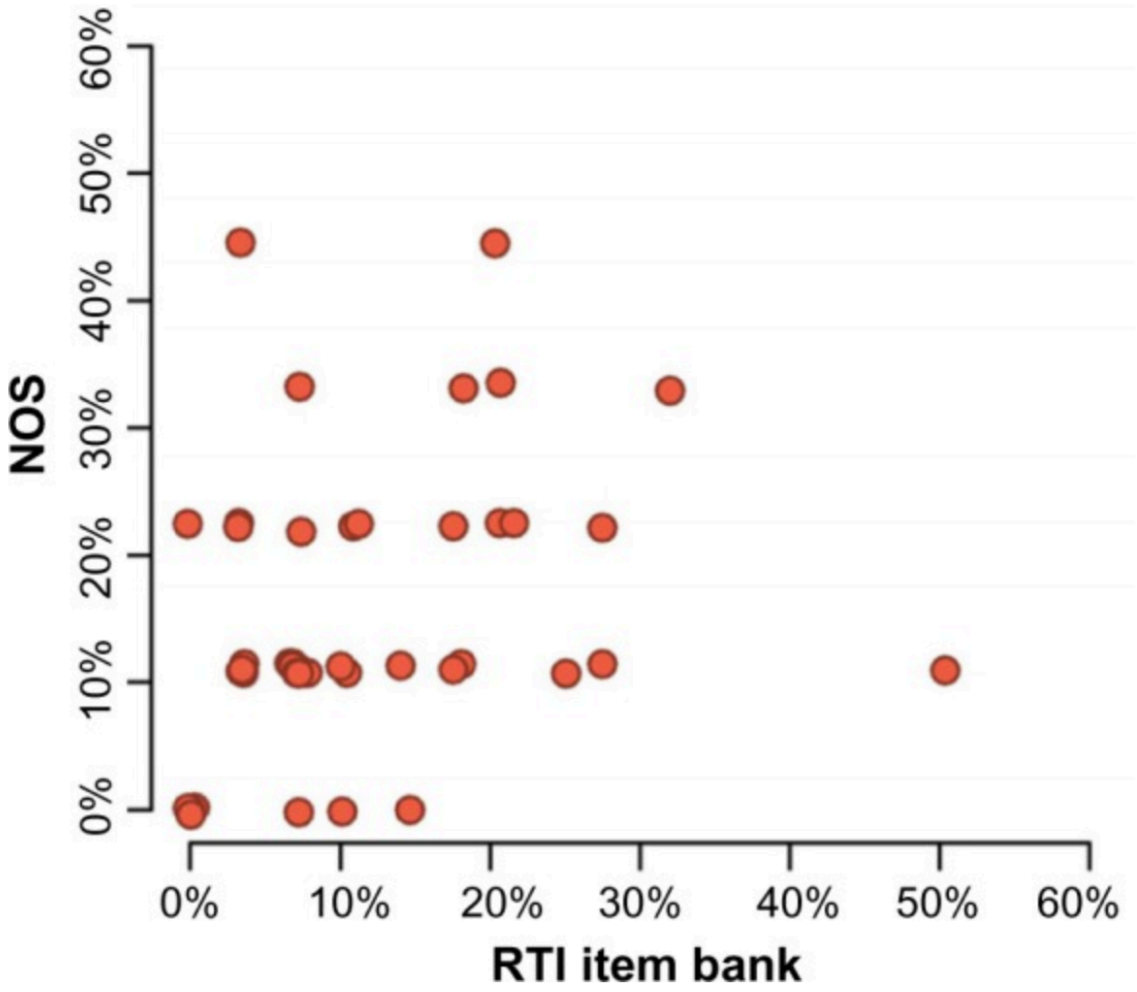
What are the best guidelines, if any?

- Deeks JJ et al. Evaluating non-randomised intervention studies. Health Technol Assess. 2003;7(27):iii–x. 1–173

- Heavily used; The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses
- www.ohri.ca/programs/clinical_epidemiology/oxford.asp

- Easy to use, but neither comprehensive nor reproducible, does not use modern risk of bias approach

Comparison of two tools: the NOS & the RTI item bank. *Clin Epidemiol*. 2014;6:359–368.



Correlation between high risk of bias with the Newcastle–Ottawa Scale and with the RTI item bank.

GRADE-Grading of Recommendations Assessment, Development and Evaluation

Certainty, quality, strength of the evidence, or the confidence in the estimate of effect, is determined for each outcome ***based on a systematic review*** of the evidence for each outcome.

For recommendations, the overall certainty is determined across outcomes based on the lowest quality outcome among those critical for decision-making for the specific context.

http://www.gradeworkinggroup.org/

It is not generally used for single studies

Series of papers from 2011-19 e.g.-

Schünemann, HJ. et al. J Clin Epidemiology. (2019) 111: 105-114

ROBINS-I (not 1)

- Bristol (UK) based, with website. Looks at individual studies
- https://www.riskofbias.info/welcome/home/current-version-of-robins-i
- ~/robins-i-detailed-guidance-2016
- Published Paper- Sterne JAC et al. *BMJ* 2016; 355; i4919.
- https://www.youtube.com/watch?v=HgZKQo28QSc
  - Has presentation as webinar + experiences of using it

Key ideas: "Target trial" as answering question for the NRD study

"Effect of Interest"

Assignment ("intention to treat")

Starting & adhering ("per protocol")

The "Risk of Bias" is assessed in relation to the hypothetical target trial and is mainly for cohort studies

ROBINS-I 7 Domains

- **Pre-Intervention**
  - Bias due to confounding
  - Bias in selection of participants into the study
- **At Intervention**
  - Bias in classification of interventions
- **Post-Intervention**
  - Bias due to deviations from intended interventions
  - Bias due to missing data
  - Bias in measurement of outcomes
  - Bias in selection of the reported result

Key ideas – not well known

- Beware of using information from the future
  - Very easily done in database studies where the whole time course for each individual is available
  - **adjusting for post-intervention variables is usually not appropriate**
  - Adjusting for **mediating variables** (those on the causal pathway from intervention to outcome) may induce confounding

Where might NRS be useful in studies of benefits?

- When Propensity score methods reproduce RCTs
- Where historical data has very clear results and a single arm study can obtain a good comparison group
- BUT, for regulatory purposes they ought to have the same validity, requiring checks etc, as RCTs {See Jim Slattery's (EMA) presentation at ICPE Philadelphia, 2019}

Where might they be useful in studies of harms?

- They have been used extensively. Possibly more reliable on harms than on benefits
  - E.g. hormone therapy RRs correct for VTE, Cancer, stroke, but not for CHD, until analysed properly by Hernan
- The "unintended effects" are less affected by confounding by indication, but when unexposed are compared with exposed there is still a strong possibility of other confounding
- Active controls, negative control (exposures & outcomes) can be helpful

A 2018 issue at EMA

- Diuretic - hydrochlorothiazide (HCTZ), antihypertensive agent, increases UVA-induced DNA damage: ? Skin/lip cancer ?

- Photosensitisation is listed as rare adverse reaction in the SPC (label), skin-cancer is not listed as an adverse reaction

Pharmacoepidemiological studies in 2017

- Jan 2018 meeting raised as a signal {DK} at PRAC (EMA)

http://www.ema.europa.eu/docs/en_GB/document_library/Minutes/2018/03/WC500244940.pdf

- Pottegård A et al. J Internal Med 2017 and

  Arnspang S et al. J Am Acad Dermatology 2017.

{There had been previous smaller studies as well}

Scanning Study: 22,125 drug–cancer pairs evaluated 344 showed a "signal" of increased risk

Identification of Associations Between Prescribed Medications and Cancer: A Nationwide Screening Study

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ABSTRACT

Purpose: We present a systematic screening for identifying associations between prescribed drugs and cancer risk using the high quality Danish nationwide health registries.
Methods: We identified all patients (cases) with incident cancer in Denmark during 2000–2012 (n = 278,485) and matched each case to 10 controls. Complete prescription histories since 1995 were extracted. Applying a two-phased case–control approach, we first identified drug classes or single drugs associated with an increased or decreased risk of 99 different cancer types, and further evaluated potential associations by examining specificity and dose–response patterns.
Findings: 22,125 drug–cancer pairs underwent evaluation in the first phase. Of 4561 initial signals (i.e., drug–cancer associations), 3541 (78%) failed to meet requirements for dose–response patterns and specificity, leaving 1020 eligible signals. Of these, 510 signals involved the use of single drugs, and 33% (166 signals) and 67% (344 signals) suggested a reduced or an increased cancer risk, respectively. While a large proportion of the signals were attributable to the underlying conditions being treated, our algorithm successfully identified well-established associations, as well as several new signals that deserve further investigation.
Conclusion: Our results provide the basis for future targeted studies of single associations to capture novel carcinogenic or chemopreventive effects of prescription drugs.

JIM Original Article

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Hydrochlorothiazide use is strongly associated with risk of lip cancer

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Abstract. Pottegård A, Hallas J, Olesen M, Svendsen MT, Habel LA, Friedman GD, Friis S (University of Southern Denmark; Odense University Hospital, Odense; Kaiser Permanente Northern California, Oakland, CA, USA; Danish Cancer Society, Copenhagen, Denmark). Hydrochlorothiazide use is strongly associated with risk of lip cancer. *J Intern Med* 2017; **282**: 322–331.

Background. The diuretic hydrochlorothiazide is amongst the most frequently prescribed drugs in the United States and Western Europe, but there is suggestive evidence that hydrochlorothiazide use increases the risk of lip cancer.

Objectives. To study the association between use of hydrochlorothiazide and squamous cell carcinoma of the lip.

Methods. We conducted a case–control study using Danish nationwide registry data. From the Cancer Registry (2004–2012), we identified 633 case patients with squamous cell carcinoma (SCC) of the lip and matched them to 63 067 population controls using a risk-set sampling strategy. Hydrochlorothiazide use (1995–2012) was obtained from the Prescription Registry and defined according to cumulative use. Applying conditional logistic regression, we calculated odds ratios (ORs) for SCC lip cancer associated with hydrochlorothiazide use, adjusting for predefined potential confounders obtained from demographic, prescription and patient registries.

Results. Ever-use of hydrochlorothiazide was associated with an adjusted OR for SCC lip cancer of 2.1 (95% confidence interval (CI): 1.7–2.6), increasing to 3.9 (95%CI: 3.0–4.9) for high use (≥25 000 mg). There was a clear dose–response effect ($P < 0.001$), with the highest cumulative dose category of hydrochlorothiazide (≥100 000 mg) presenting an OR of 7.7 (95%CI: 5.7–10.5). No association with lip cancer was seen with use of other diuretics or nondiuretic antihypertensives. Assuming causality, we estimated that 11% of the SCC lip cancer cases could be attributed to hydrochlorothiazide use.

Conclusions. Hydrochlorothiazide use is strongly associated with an increased risk of lip cancer.

Keywords: cancer, epidemiology, hydrochlorothiazide, pharmacology.

First study (Pottegard)

- 633 cases of lip-cancer were matched with 63,067 population controls
- Nested case-control study
- Looked at other BP lowering drugs and Bendroflumethiazide
- HCTZ in high cumulative dose,

  OR 3.9 (3.0-4.9) & “dose-response”

Other drugs -no notable association

Hydrochlorothiazide use and risk of nonmelanoma skin cancer: A nationwide case-control study from Denmark

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Background: Hydrochlorothiazide, one of the most frequently used diuretic and antihypertensive drugs in the United States and Western Europe, is photosensitizing and has previously been linked to lip cancer.

Objective: To examine the association between hydrochlorothiazide use and the risk of basal cell carcinoma (BCC) and squamous cell carcinoma (SCC).

Methods: From the Danish Cancer Registry, we identified patients (cases) with nonmelanoma skin cancer (NMSC) during 2004-2012. Controls were matched 1:20 by age and sex. Cumulative hydrochlorothiazide use (in 1995-2012) was assessed from the Danish Prescription Registry. Using conditional logistic regression, we calculated odds ratios (ORs) for BCC and SCC associated with hydrochlorothiazide use.

Results: High use of hydrochlorothiazide (≥50,000 mg) was associated with ORs of 1.29 (95% confidence interval [CI], 1.23-1.35) for BCC and 3.98 (95% CI, 3.68-4.31) for SCC. We found clear dose-response relationships between hydrochlorothiazide use and both BCC and SCC; the highest cumulative dose category (≥200,000 mg of HCTZ) had ORs of 1.54 (95% CI, 1.38-1.71) and 7.38 (95% CI, 6.32-8.60) for BCC and SCC, respectively. Use of other diuretics and antihypertensives was not associated with NMSC.

Limitations: No data on sun exposure were available.

Conclusions: Hydrochlorothiazide use is associated with a substantially increased risk of NMSC, especially SCC. (J Am Acad Dermatol 2018;78:673-81.)

Second study (Arnspang)

- HCTZ and different types of non-melanoma skin cancer [NMSC]

  (i.e. Basal Cell Carcinoma [BCC]and squamous cell carcinoma [SCC] independent of location – excluding lip-cancer)

  "We found a dose-dependent increased risk of non-melanoma skin cancer, particularly squamous cell carcinoma, among users of hydrochlorothiazide."

  ORs 1.29 (1.23-1.35) for BCC &

  3.98 (3.68-4.31) for SCC

June 2018 Meeting

http://www.ema.europa.eu/ema/index.jsp?curl=pages/about_us/document_listing/document_listing_000353.jsp&mid=WC0b01ac05805a21cf

- The study authors replied to the request for information
- Responses assessed by the Rapporteur (50 page report + appendices).
- EMA replicated results in a UK database & obtained absolute risks
- Based on the assessment of all available data,
- "PRAC considered there was a biologically plausible mechanistic model supporting the increased risk of non-melanoma skin cancer (NMSC) following higher cumulative dose of hydrochlorothiazide (HCTZ), and therefore that an update of the product information of HCTZ-containing products was warranted."

My comments

- A really careful assessment of the strengths & weaknesses of the totality of the evidence
- Useful interaction with the Danish authors
- Some concerns over most of the evidence being based on a single data source, but EMA study helped Interpretation following the scanning study?
- Pharmacoepidemiology taken very seriously, and mechanisms also explored

Second example

- Glitazone antidiabetics and fractures
- Clinical trials consistently show an increased risk
  - Limited to women?
  - Limited to arm, wrist, hands and feet?
- Trials not powered to address this
- Further characterisation needed
- Could we use a self-controlled case-series (SCCS)?

rosiglitazone label in US

"An increased incidence of bone fracture has been observed in female patients taking AVANDIA in a long-term trial. The majority of the fractures in the women who received AVANDIA were reported in the upper arm, hand, and foot. These sites of fracture are different from those associated with post-menopausal osteoporosis (e.g., hip or spine). The risk of fracture should be considered in the care of patients, especially female patients, treated with AVANDIA & attention given to assessing & maintaining bone health according to current standards of care"

Simpler message for pioglitazone in US but EU SPC "Some epidemiological studies have suggested a similarly increased risk of fracture in both men and women."

Glitazones and fractures

- Exposure well defined – measurable by prescriptions, daily dosing
- Outcome well defined and likely to result in a clinical consultation – accurate dating
- SCCS assumptions fulfilled
  - Having a fracture unlikely to alter the possibility of receiving a glitazone
  - Most fractures don't lead to death or otherwise censor observation time

Glitazones and fractures

- CPRD (was GPRD in 2009)
- 1,819 patients prescribed thiazolidinedione antidiabetic agents and with a fracture in their medical record
- 720 fractures during treatment

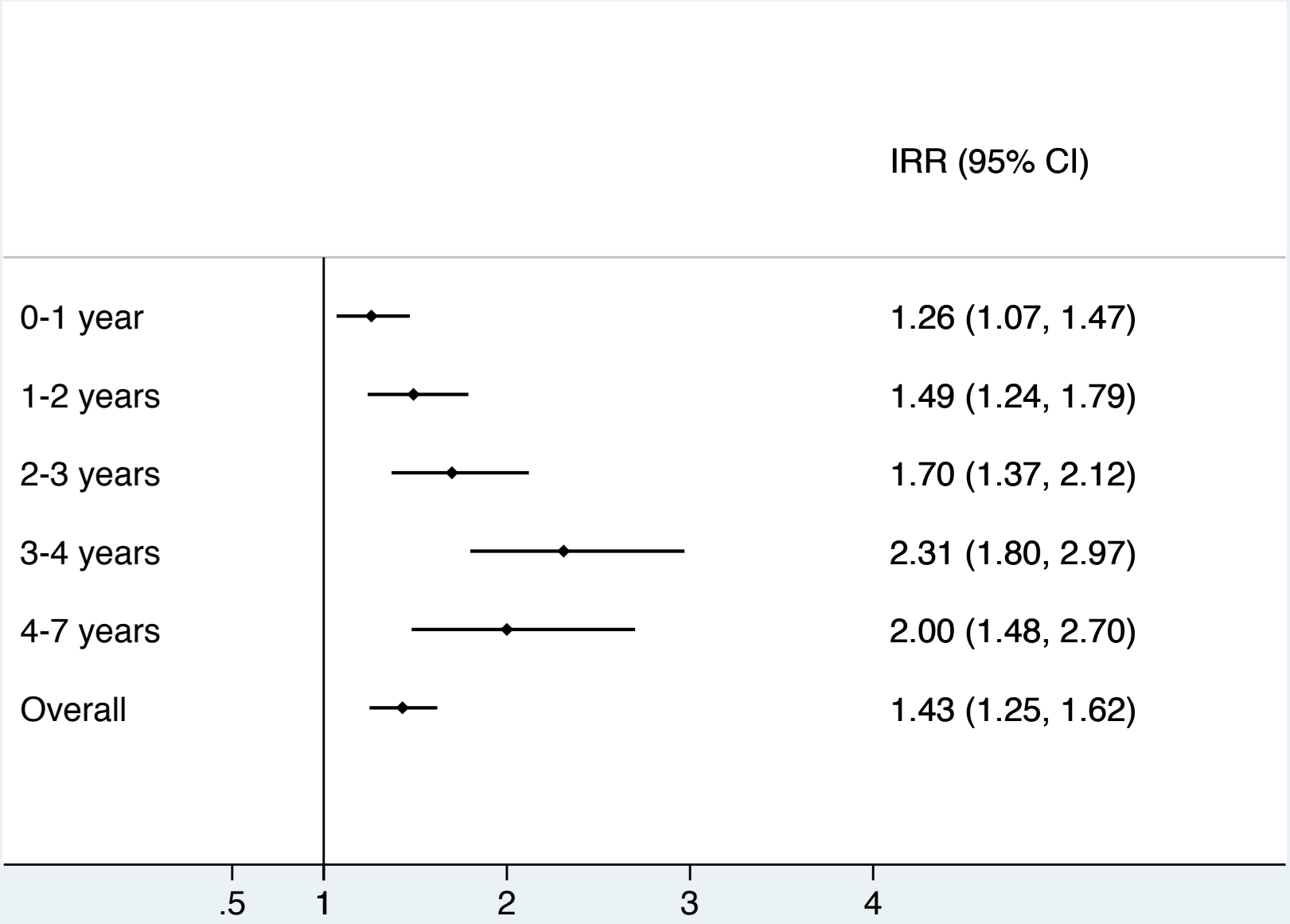
Douglas IJ, Evans SJ, Pocock S, Smeeth L (2009) The Risk of Fractures Associated with Thiazolidinediones: A Self-controlled Case-Series Study. PLoS Med 6(9): e1000154.

Glitazones and fractures

	Fractures during treatment	Age adj Rate ratio	95% CI
Any glitazone, all fractures			
Overall	720	1.43	1.25-1.62
Glitazone duration			
0-1 year	235	1.26	1.07-1.47
1-2 years	179	1.49	1.24-1.79
2-3 years	127	1.70	1.37-2.12
3-4 years	104	2.31	1.80-2.97
4-7 years	75	2.00	1.48-2.70

Incidence rate ratios for fractures

Duration of treatment

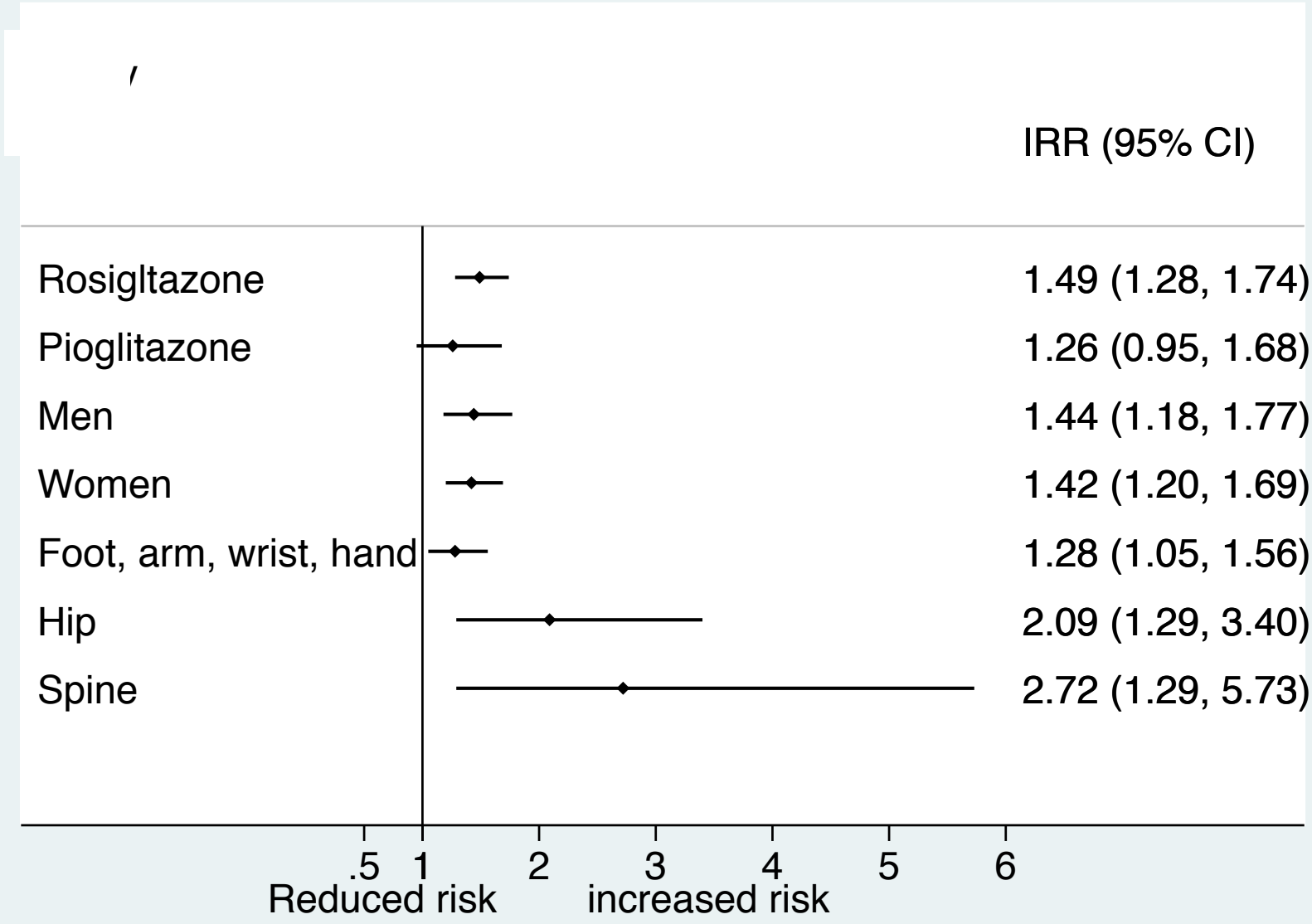


Glitazones and fractures

	Fractures	Rate ratio	95% CI
All fractures			
Men	274	1.44	1.18-1.77
Women	446	1.42	1.20-1.69
Specific glitazones			
Rosiglitazone only	543	1.49	1.28-1.74
Pioglitazone only	149	1.26	0.95-1.68
Specific fracture sites			
Foot, arm, wrist, hand	735	1.28	1.05-1.56
Hip	71	2.09	1.29-3.40
Spine	41	2.72	1.29-5.73

Incidence rate ratios for fractures

Rosi/Pio Men/Women Site



Glitazones and fractures

- How do we know the results are not biased?
- Case series takes care of fixed confounders – what about confounders that change with time? Did we adjust well enough for age?
- Can we ever really know???
- Select another drug as a possible “negative control exposure”

Sulphonylureas and fractures

	Fractures during treatment	Rate ratio	95% CI
Any sulph. any fracture			
Overall	348	0.84	0.66-1.08
Sulphonylurea duration			
0-1 year	102	0.89	0.69-1.16
1-2 years	61	0.77	0.56-1.05
2-3 years	53	0.94	0.67-1.31
3-4 years	43	1.09	0.76-1.59
4-7 years	62	1.01	0.71-1.43

Glitazone and fracture conclusions

- Results confirm an association between glitazones and fractures
- Study design gives us confidence the results are not due to confounding by indication
- High study power allows further characterisation of this association:
  - Applies to both women and men
  - Appears to involve fractures at all sites
  - Risk seems to increase with duration of treatment

Case series conclusions

- The self-controlled case series makes comparisons within individuals
- Therefore can overcome between person confounding
- Time-varying confounding factors may remain a problem – can adjust for these
- Can be statistically very efficient

Case series conclusions

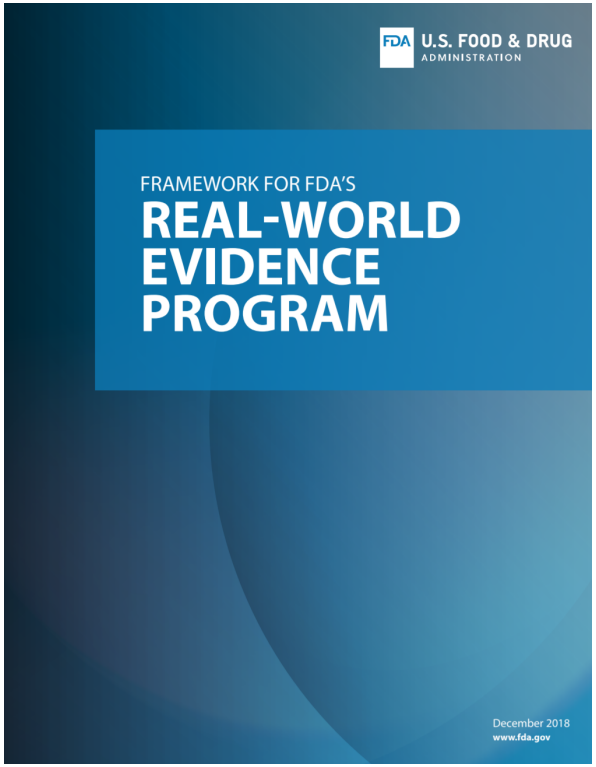
- Works best for:
  - Well defined risk periods (e.g. drug exposure periods)
  - Outcomes with a well defined onset
- Some strong assumptions need to be met
- Powerful, but under used, study design
- More information

http://statistics.open.ac.uk/sccs

Learning points

- RCTs will detect effects in high risk participants but absence of “significant” risk in other groups is not evidence of absence of risk
- OS may have power to detect a wider range of effects. More confidence in results if a) compatible with RCTs and b) a negative control is convincing
- Incorporation into patient information dependent both on company & regulator

21st Century Cures – A Path forward for RWE(from presentation at ICPE 2019)



Scope of RWE Program Under 21st Century Cures Act

Under the Cures Act, FDA's RWE Program must evaluate the potential use of RWD to generate RWE of product effectiveness to help support approval of new indications for drugs approved under FD&C Act Section 505(c) or to help to support or satisfy postapproval study requirements. FDA's RWE Program will also apply to biological products licensed under section 351 of the Public Health Service Act.

https://www.fda.gov/downloads/ScienceResearch/SpecialTopics/RealWorldEvidence/UCM627769.pdf

Recent FDA Guidance

Interacting with the FDA on Complex Innovative Trial Designs for Drugs and Biological Products

Draft Guidance for Industry

20 September 2019

"….. trial designs that might be considered novel or CID are those that formally borrow external or historical information or borrow control arm data from previous studies to expand upon concurrent controls (Section IV of this guidance) "

EU Examples

- Cave A et al(2019). "Real-World Data for Regulatory Decision Making: Challenges and Possible Solutions for Europe." Clinical Pharmacology & Therapeutics **106**: 36-39.

- https://ascpt.onlinelibrary.wiley.com/action/downloadSupplement?doi=10.1002%2Fcpt.1426&file=cpt1426-sup-0001-TableS1.pdf

EU Examples of 6 drugs

Axicabtagene ciloleucel	A retrospective patient level pooled analysis of two Phase III RCTs and two observational studies
Tisagenlecleucel	Efficacy results compared against three external data sets
Zalmoxis	Patient registry
Strimvelis	survival compared to historical data
Nusinersen	Long term results from registries
Eculizumab	Extension of Indication to paroxysmal nocturnal haemoglobinuria disease registry used

Detecting fraud in NRD

- Randomisation can make detecting fraud in baseline variables relatively easy
- Fabrication and falsification is slightly less likely in clinical data where there is no motive
- Misconduct much more likely in selection of data from the real data
- The scandal of Sudbø- total invention of 900
- https://en.wikipedia.org/wiki/Jon_Sudbø

Techniques from RCTs

- Distribution of last, next to last,…first digits
  - Compare with known genuine data
  - Last digits uniform? First digits **not** Benford's law
- Patterns of correlations
- Mahalanobis distances from mean & adjacent observations
- Days of week in records (meta data)

Additional SCCS References

- Glanz JM et al. Four different study designs to evaluate vaccine safety were equally validated with contrasting limitations. *J Clin Epidem* 2006; **59**: 808-818.
- Whitaker HJ et al. The methodology of self-controlled case series studies. *Stat Meth in Medical Research*, 2009, **18**(1): 7-26.
- Farrington CP, Hocine MN. Within-individual dependence in self-controlled case series models for recurrent events. *Journal of the Royal Statistical Society series C,* 2010, **59**:457-475.

Thank you

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