WHAT IS REAL WORLD EVIDENCE (RWE) AND HOW IT IS USED?

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Real World Evidence (RWE) is defined as …

- … health care–related information that is derived from various sources including electronic health records, claims and billing data, registries, and health applications.

- "… any data regarding the usage, or the potential benefits or risks, of a drug derived from sources other than randomized clinical trials."
  - The 21st Century Cures Act signed by Barack Obama, 2016.

RWD comes from a number of sources

- Electronic medical and health records
- Claim and billing data
- Pharmacy data
- Test results, lab values, pathology results
- Disease and product registries
- Medical births
- Causes of death
- Genomic linked data
- Survey data
- Mobile health and wearable technologies
- Social media

RCT versus RWE

	RCT	RWE
Purpose	Efficacy Can it work?	Effectiveness Does it work?
Patient population	Small highly selected	Big, limited selection
Treatment selection	Controlled by randomization	Uncontrolled
Treatment	Restricted by the protocol	As in clinical practice
Outcome	Directly observed	Often observed indirectly
Study groups	Homogeneous	Heterogeneous
Data quality	High	Variable
Direct comparisons	Valid due to randomization	Invalid due to confounding
Goal	To gain regulatory approval	To influence clinical practice

Mark McClellan former FDA commissioner …

… sees RWE as a way to

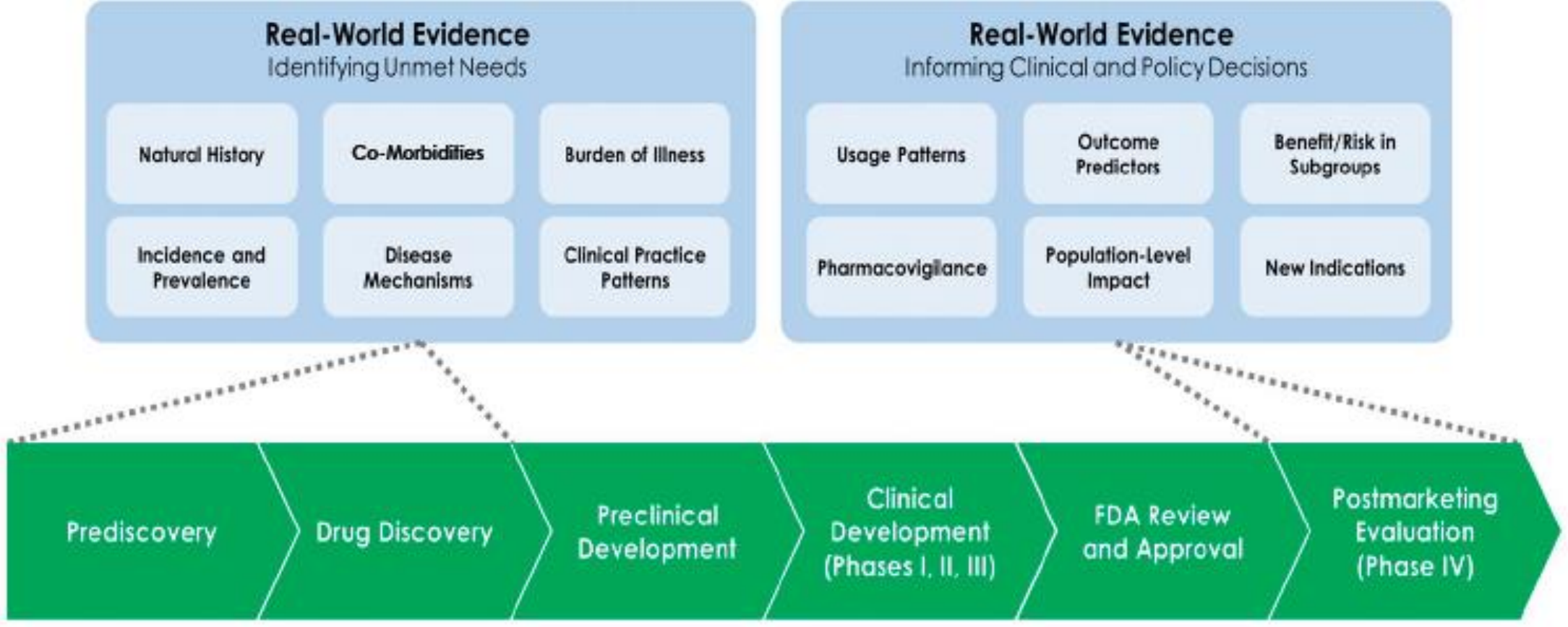
"bridge the knowledge gap between clinical research and clinical practice,"

but stresses that

"more efforts are needed to explore how RWE could be incorporated into the regulatory framework."


THIS IS FINE, I CAN SEE ALL THE EVIDENCE I NEED FROM HERE
COST-EFFECTIVENESS
EFFECTIVENESS
EFFICACY
COCHRANE LADDER of EVIDENCE
willett

What do we use RWE for?



https://nam.edu/real-world-evidence-to-guide-the-approval-and-use-of-new-treatments/

Nordic registries

Register	Finland	Sweden	Norway	Denmark
Prescriptions	1994	2005	2004	1994
Hospital care	1967 1998[1]	1964 1987[2] 2001	2008	1969 1977[2]
Causes of death	1969	1952	1951	1970
Cancer	1953	1958	1952	1943
Medical births	1987	1973	1967	1973

Key benefits

- Nationwide data
- Good coverage
- Long history
- Data linkage between registers

Potential barriers of accessing the right data for RWE

- *The enormous volume of RWD*
  - A file larger than 20% of Random Access Memory (RAM)
    - You will get into problems
  - Parallel programming
  - Execution of code across multiple processors
  - Better usage of computers memory capacity

- *Data Quality*
  - Lack of a common data infrastructure and consistent terminology
  - Most of it is not collected for research purposes
  - Text-mining technics
  - Time for data cleaning, integration and standardization

Potential barriers of accessing the right data for RWE

- *Limited access to data*
  - Legal frameworks that legally restrict data sharing and access to patient identifiable information
- *Data linkage restrictions*
  - The current data vendor landscape can make it difficult to bring data assets together
- *Data mining*
  - is not inherently bad, and can be used to generate useful information
  - Need for well-defined research questions, strict protocols, and analysis plans

Challenges associated with the use of RWD

- *Selection bias*
  - E.g. therapies may be differently prescribed depending upon patient and disease characteristics
  - Good news:
    - Usually well defined from previous research and literature
    - Use statistical methods to reduce its effects

- *Incomplete data*
  - Databases are vulnerable to systematic omissions or misclassification
    - Continuous validation and ambition to have high coverage
  - Gaps in the data
    - The ability to link datasets to one another would also be a useful way of not only filling in the gaps but also validating the data

Propensity score (PS) matching

- *Goal*
  - To estimate the average casual effect of treatment
- *Problem*
  - Selection bias
- *Concept behind PS*
  - to balance the distributions of covariates between the treatment and control groups
- *Condition*
  - *Ignorability assumption* - the choice to assign a subject to the control or treatment group is effectively random when conditioned on observable characteristics
- *Calculation of the PS*
  - Logistic regression
  - Generalized boosted modeling - use decision trees
- *Matching methods*
  - Nearest available matching (greedy matching), caliper matching or optimal matching

ADVANTAGES AND DISADVANTAGES

CENTRAL ILLUSTRATION: Comparison of Propensity Score Methods and Covariate Adjustment

Primary study analysis method	Pros	Cons
Traditional covariate adjustment	• Performed well • Provides prognostic model for outcome of interest	• May not be suitable with many covariates in smaller studies
Propensity score (PS) stratification	• Retains data from all study participants • Opportunity to explore interactions between treatment and PS on outcome risk • Provides effect estimates for every stratum	• Performs less well in datasets with few outcomes, particularly when the number of strata is large • May not account for strong confounding
PS matching	• Reliable; provides excellent covariate balance in most circumstances • Simple to analyze, present and interpret	• Some patients are unmatched leading to information excluded from the analysis • Less precise
PS inverse probability weighting	• Retains data from all study participants • Easy to implement • Creates a pseudo population with perfect covariate balance	• Can be unstable when extreme weights occur
PS covariate adjustment (use of PS as a covariate)	• Performed well	• Adding the PS as an additional covariate produced results very similar (and not necessarily superior) to traditional covariate adjustment

Elze, M.C. et al. J Am Coll Cardiol. 2017;69(3):345-57.

Pioglitazone use and risk of bladder cancer in patients with type 2 diabetes: retrospective cohort study using datasets from four European countries

Pasi Korhonen,[1] Edith M Heintjes,[2] Rachael Williams,[3] Fabian Hoti,[1] Solomon Christopher,[1] Maila Majak,[1] Leanne Kool-Houweling,[2] Helen Strongman,[3] Marie Linder,[4] Paul Dolin,[5] Shahram Bahmanyar[4]

WHAT IS ALREADY KNOWN ON THIS TOPIC

Many earlier epidemiological studies have reported an increased bladder cancer risk in patients with type 2 diabetes using pioglitazone

However, several of these early studies had little control of treatment allocation bias or had no information on known risk factors of bladder cancer

Recent large studies with longer follow-up have reported no association between pioglitazone exposure and bladder cancer risk

WHAT THIS STUDY ADDS

This analysis of datasets from Finland, Sweden, the Netherlands, and the UK shows no evidence of an association between ever use of pioglitazone and risk of bladder cancer, compared with never use

Results indicate that longer duration of pioglitazone use does not increase the risk of bladder cancer

These results provide additional important information on the safety of pioglitazone use in Europe

ABSTRACT

OBJECTIVE

To evaluate the association between pioglitazone use and bladder cancer risk in patients with type 2 diabetes.

DESIGN

Retrospective cohort study using propensity score matched cohorts.

SETTINGS

Healthcare databases from Finland, the Netherlands, Sweden, and the United Kingdom. Data comprised country specific datasets of linked records on prescriptions, hospitals, general practitioners, cancer, and deaths.

PARTICIPANTS

Patients with type 2 diabetes who initiated pioglitazone (n=56 337) matched with patients with type 2 diabetes in the same country exposed to diabetes drug treatments other than pioglitazone (n=317 109). Two matched cohorts were created, using a 1:1 fixed ratio (nearest match cohort) and a 1:10 variable ratio (multiple match cohort). Patients were matched on treatment history and propensity scores accounting for several variables associated with pioglitazone initiation.

MAIN OUTCOME MEASURES

Hazard ratios and 95% confidence intervals were estimated by Cox's proportional hazards model with adjustments for relevant confounders. To assess the robustness of the findings, several sensitivity and stratified analyses were performed.

RESULTS

In the cohort exposed to pioglitazone treatment, 130 bladder cancers occurred over a mean follow-up time of 2.9 years. In the nearest match and multiple match cohorts not exposed to pioglitazone treatment, 153 and 970 bladder cancers were recorded, with a mean follow-up time of 2.8 and 2.9 years, respectively. With regards to bladder cancer risk, the adjusted hazard ratio for patients ever exposed versus never exposed to pioglitazone was 0.99 (95% confidence interval 0.75 to 1.30) and 1.00 (0.83 to 1.21) in the nearest and multiple match cohorts, respectively. Increasing duration of pioglitazone use and increasing cumulative dose were not associated with risk of bladder cancer (>48 months of pioglitazone use, adjusted hazard ratio 0.86 (0.44 to 1.66); >40 000 mg cumulative dose, 0.65 (0.33 to 1.26) in the nearest match cohort).

CONCLUSIONS

This study shows no evidence of an association between ever use of pioglitzone and risk of bladder cancer compared with never use, which is consistent with results from other recent studies that also included a long follow-up period.

TRIAL REGISTRATION

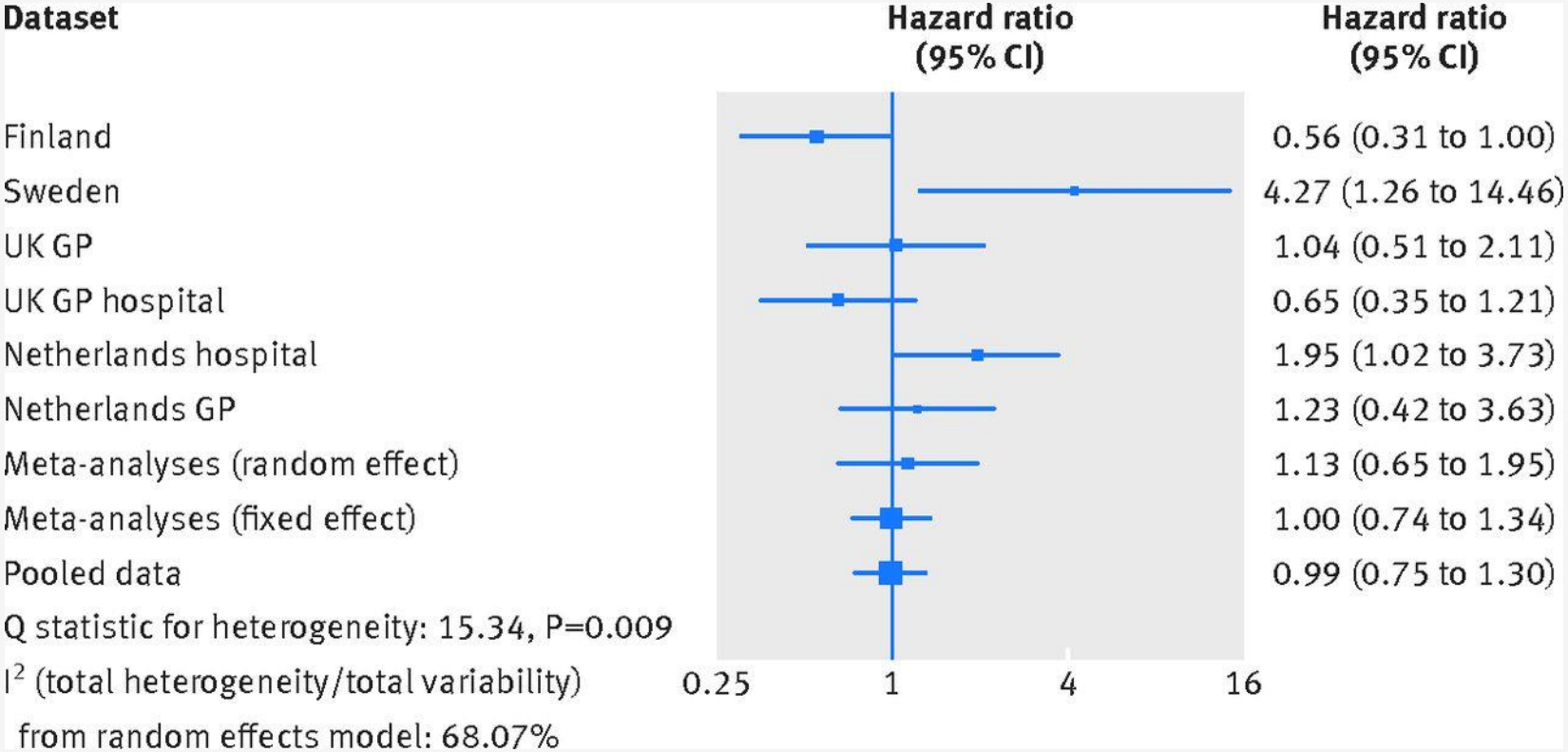
Registered to the European Union electronic register of post-authorisation studies (EU PAS register no EUPAS3626).

Introduction

Pioglitazone is a drug from the thiazolidinediones class that is used for the treatment of type 2 diabetes mellitus. Whether pioglitazone use causes an increased risk

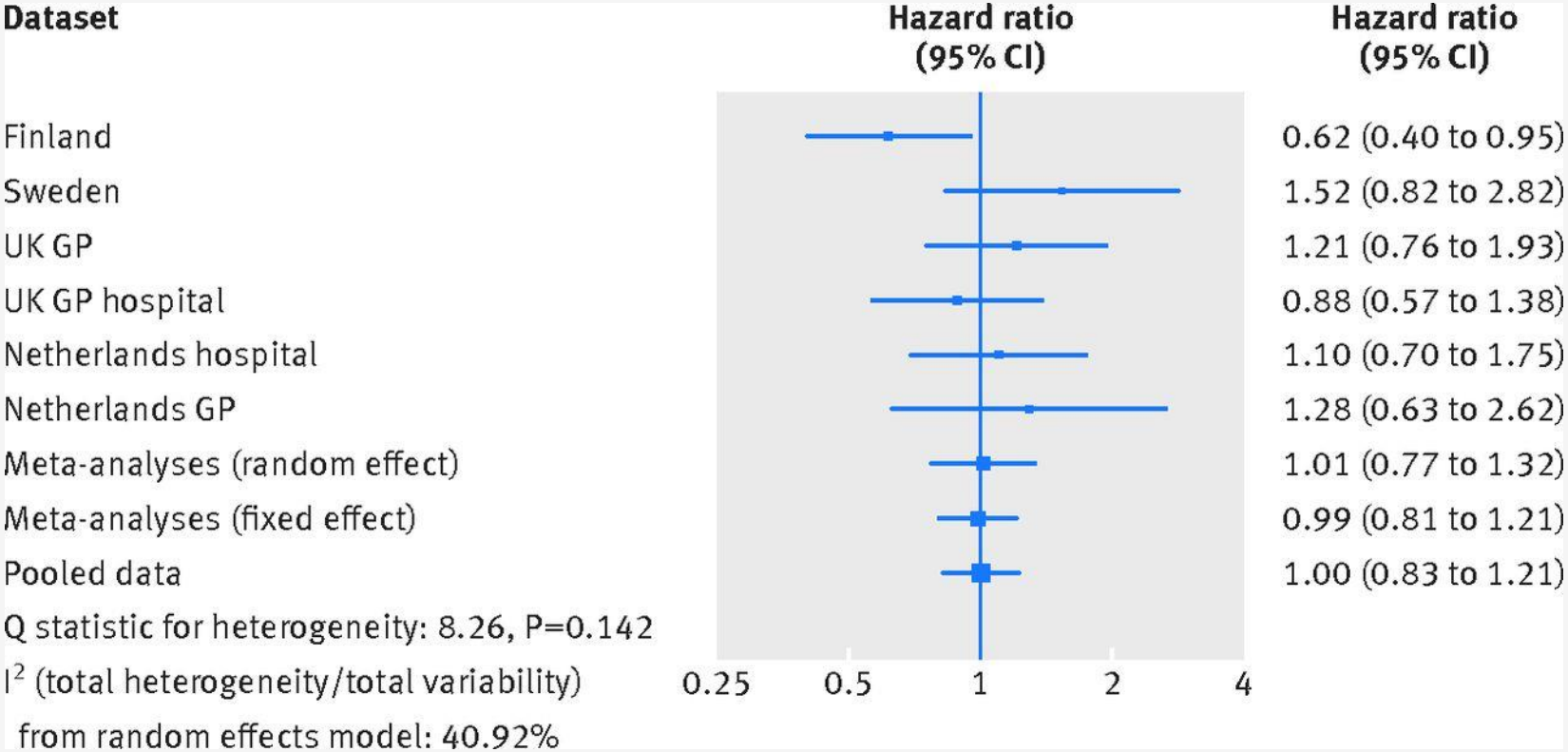
Pasi Korhonen et al. BMJ 2016;354:bmj.i3903

Fig 3 Adjusted hazard ratio estimates for bladder cancer in patients ever exposed to pioglitazone in the nearest matched cohort .



Pasi Korhonen et al. BMJ 2016;354:bmj.i3903

Fig 4 Adjusted hazard ratio estimates for bladder cancer in patients ever exposed to pioglitazone in the multiple matched cohort .



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Who needs RWE and what are the questions?

Regulators	Does the treatment work? How safe is it?
Payers	How much does this treatment cost? Is it worth it?
Providers	How are other healthcare professionals using this treatment? What are the results they are seeing?
Patients	Is this the best treatment for me?

What works best for whom,
in what context,
and at what price?

The final goal is to answer the hard question of …