CANADIAN NETWORK FOR OBSERVATIONAL
DRUG EFFECT STUDIES (CNODES)

Methodological Challenges and Design Solutions: An Example from CNODES

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October 23, 2018

JAMA Internal Medicine | Original Investigation

Association Between Incretin-Based Drugs and the Risk of Acute Pancreatitis

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JAMA Intern Med. 2016;176(10):1464-1473. doi:10.1001/jamainternmed.2016.1522
Published online August 1, 2016.

The NEW ENGLAND JOURNAL *of* MEDICINE

ORIGINAL ARTICLE

A Multicenter Observational Study of Incretin-based Drugs and Heart Failure

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RESEARCH 4;12 NEJM.ORG MARCH 24, 2016

OPEN ACCESS

Incretin based drugs and the risk of pancreatic cancer: international multicentre cohort study

Laurent Azoulay,[1,2] Kristian B Filion,[1,3] Robert W Platt,[4] Matthew Dahl,[5] Colin R Dormuth,[6] Kristin K Clemens,[7] Madeleine Durand,[8] David N Juurlink,[9] Laura E Targownik,[5,10] Tanvir C Turin,[11] J Michael Paterson,[9,12] Pierre Ernst[1,3] for the Canadian Network for Observational Drug Effect Studies (CNODES) Investigators

Cite this as: *BMJ* 2016;352:i581
http://dx.doi.org/10.1136/bmj.i581

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Safety of incretins-based drugs

Pancreatic cancer and acute pancreatitis

- Case reports
- Observational studies
  - Conflicting results
  - Many underpowered
  - Many with important methodological limitations

Heart failure (HF)

- RCTs
  - SAVOR-TIMI 53: HR: 1.27, 95% CI: 1.07, 1.51
  - EXAMINE: HR: 1.07, 95% CI: 0.79, 1.46
- Observational studies with conflicting results

Scirica et al. N Engl J Med 2013.
White et al. N Engl J Med 2013.

Objectives

- To determine whether the use of incretin-based drugs, compared to oral hypoglycemic agent (OHA) combinations, is associated with increased risks of hospitalization for acute pancreatitis and for HF.
- To determine whether the use of incretin-based drugs, compared to sulfonylureas, is associated with an increased risk of pancreatic cancer.

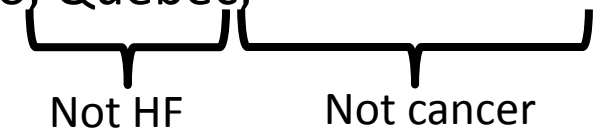
Methodological Challenge:

Treatment is very dynamic, and restricting to new users of both incretin-based drugs and the comparator results in a (overly-) restricted study population.

Study population

7 participating sites

- Alberta, CPRD, MarketScan, Manitoba, Ontario, Quebec, Saskatchewan



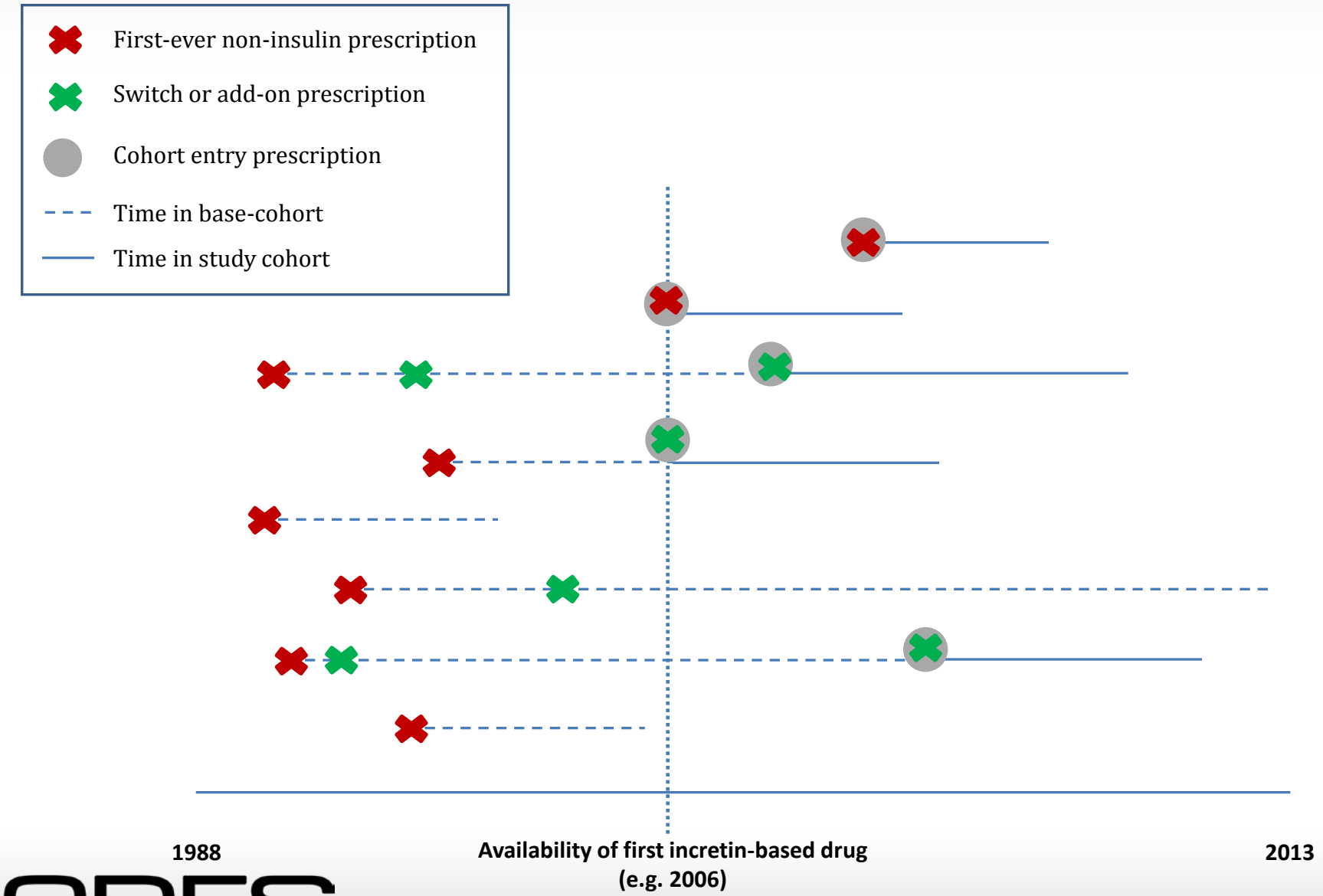
Base cohort

- All patients with a first-ever prescription for a non-insulin anti-diabetic drug from the earliest availability of data in each CNODES site to December 31, 2013

Study cohort

- All patients who initiated a new anti-diabetic drug the year of or any time after incretin-based drugs entered the market in each respective CNODES site up until June 20, 2014
- New users included newly-treated patients and those who added-on/switched to an anti-diabetic drug class not previously used
- Cohort entry: date of prescription for this new drug (pancreatitis and HF) or 1 year later (cancer)

Base-cohort and study cohort



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Rationale for base-study-cohort approach

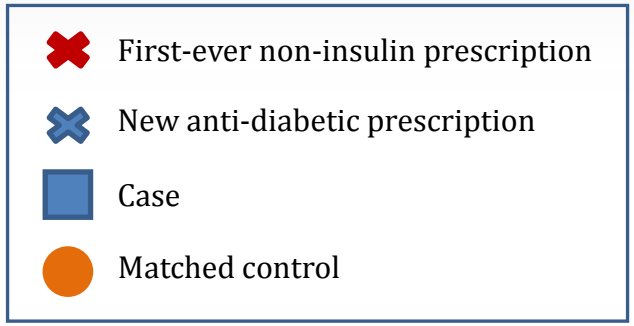
- Traditional new user cohort
  - Large exclusions of patients who used comparator drugs (e.g., ~40% of DPP-4 inhibitor users used sulfonylureas)
  - Decreased generalizability

- Users of anti-diabetic drugs once incretin-based drugs entered market
  - Prevalent users and depletion of susceptibles

- New users of anti-diabetic drugs once incretin-based drugs entered market
  - ↑↑↑ metformin use
  - Insufficient time to progress to incretin-based drugs

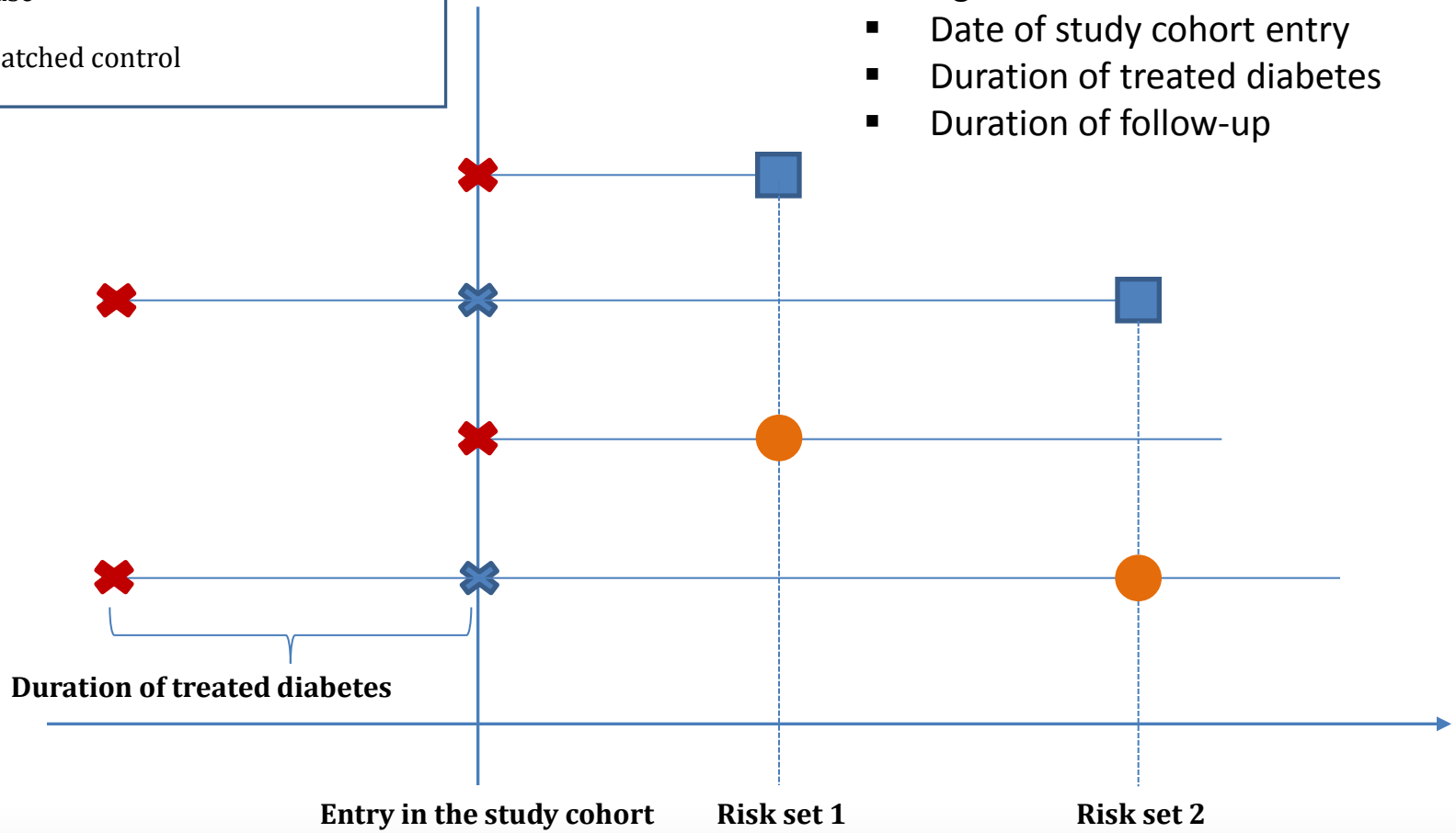
- First ever-users of anti-diabetic drugs (our base cohort)
  - Early risk sets uninformative
  - Comparing new users of incretin-based drugs vs long-time users of reference group (depletion of susceptibles, confounding by indication)

Control selection

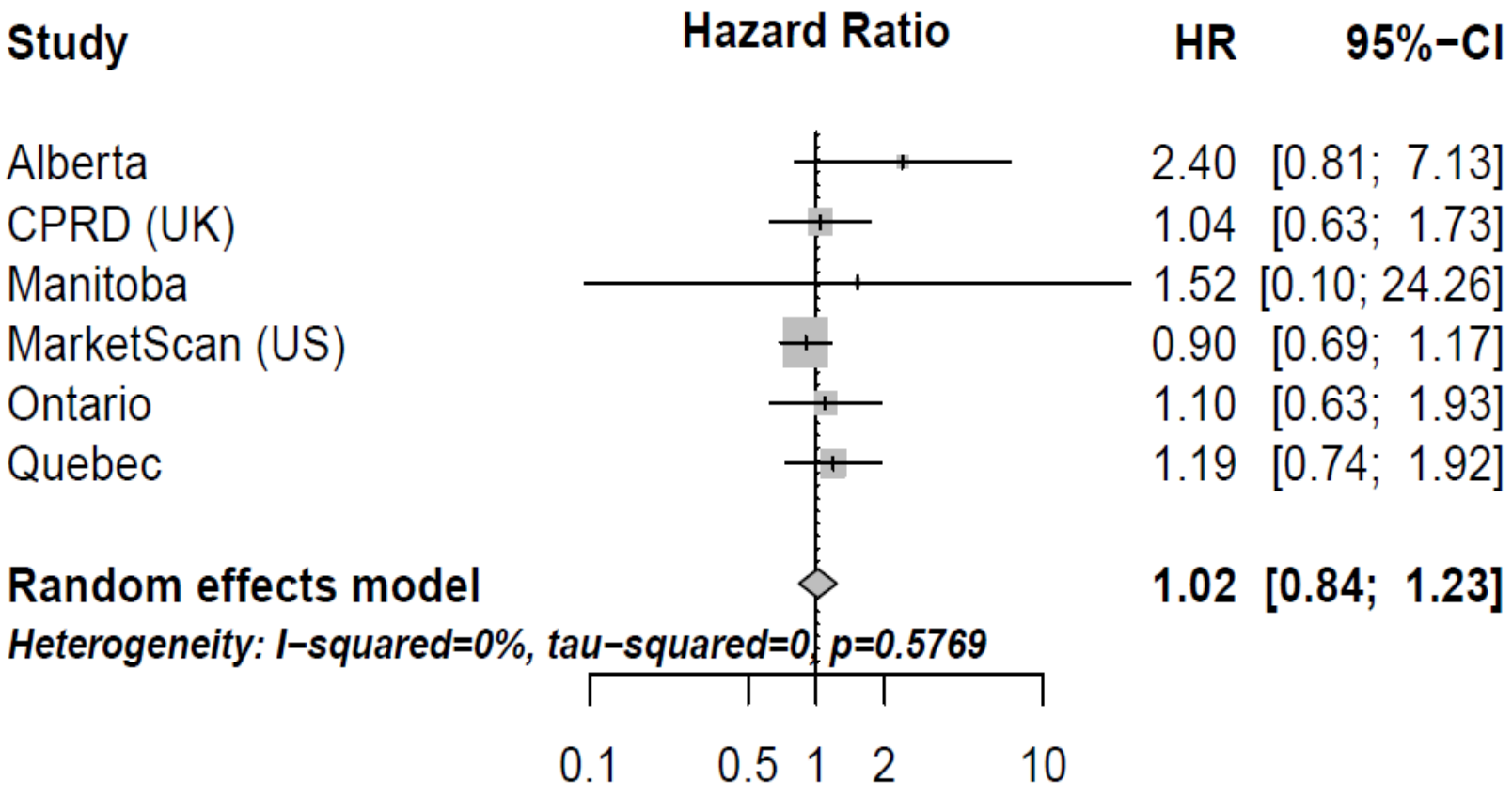


Up to 20 controls randomly selected and matched to each case (hospitalized events) on sex and four time-related variables:

- Age
- Date of study cohort entry
- Duration of treated diabetes
- Duration of follow-up



Pancreatic cancer
(Incretin-based drugs vs sulfonylureas)



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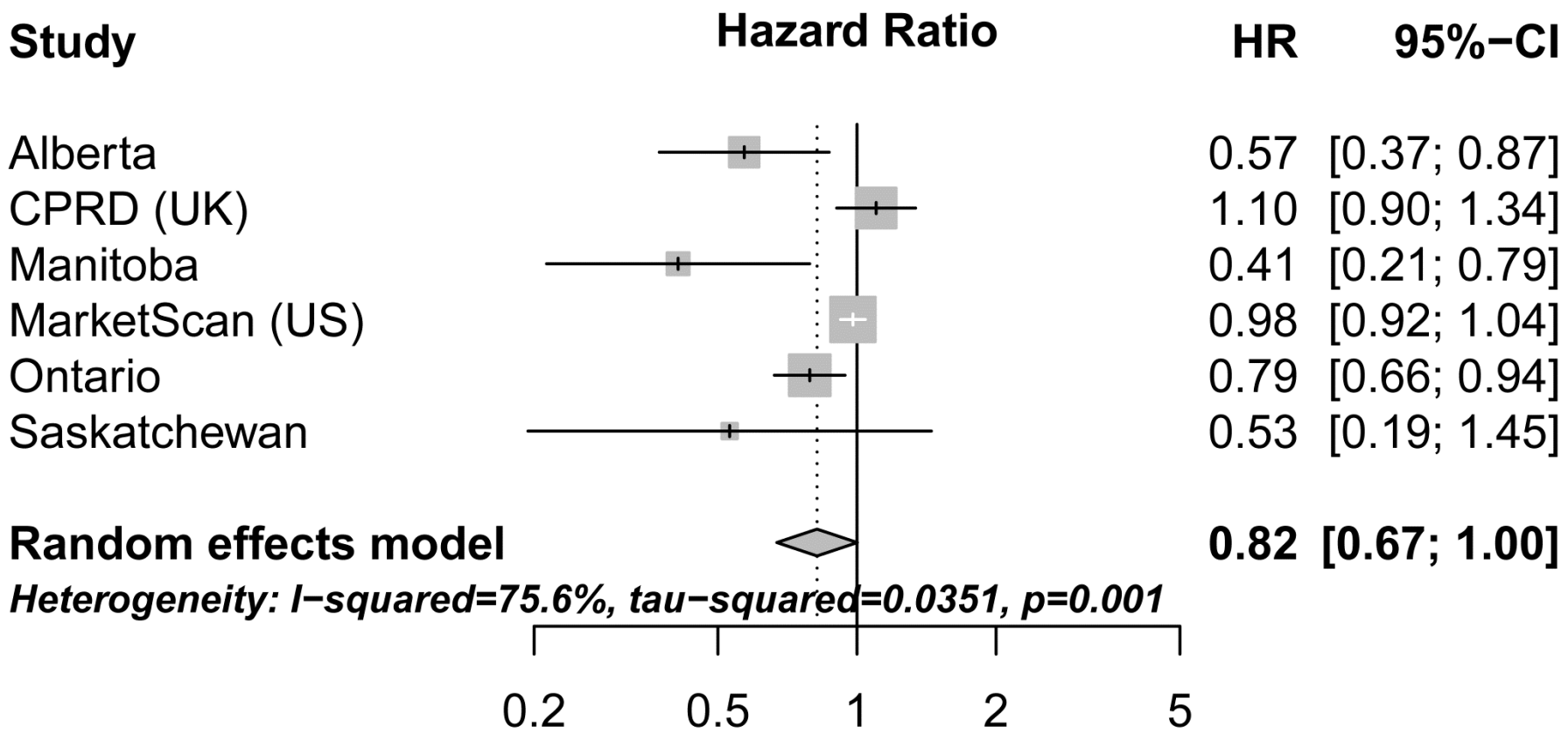
Exposure: Ever use with 1 year lag

HF - No history of HF
(Incretin-based drugs vs ≥2 OHAs)



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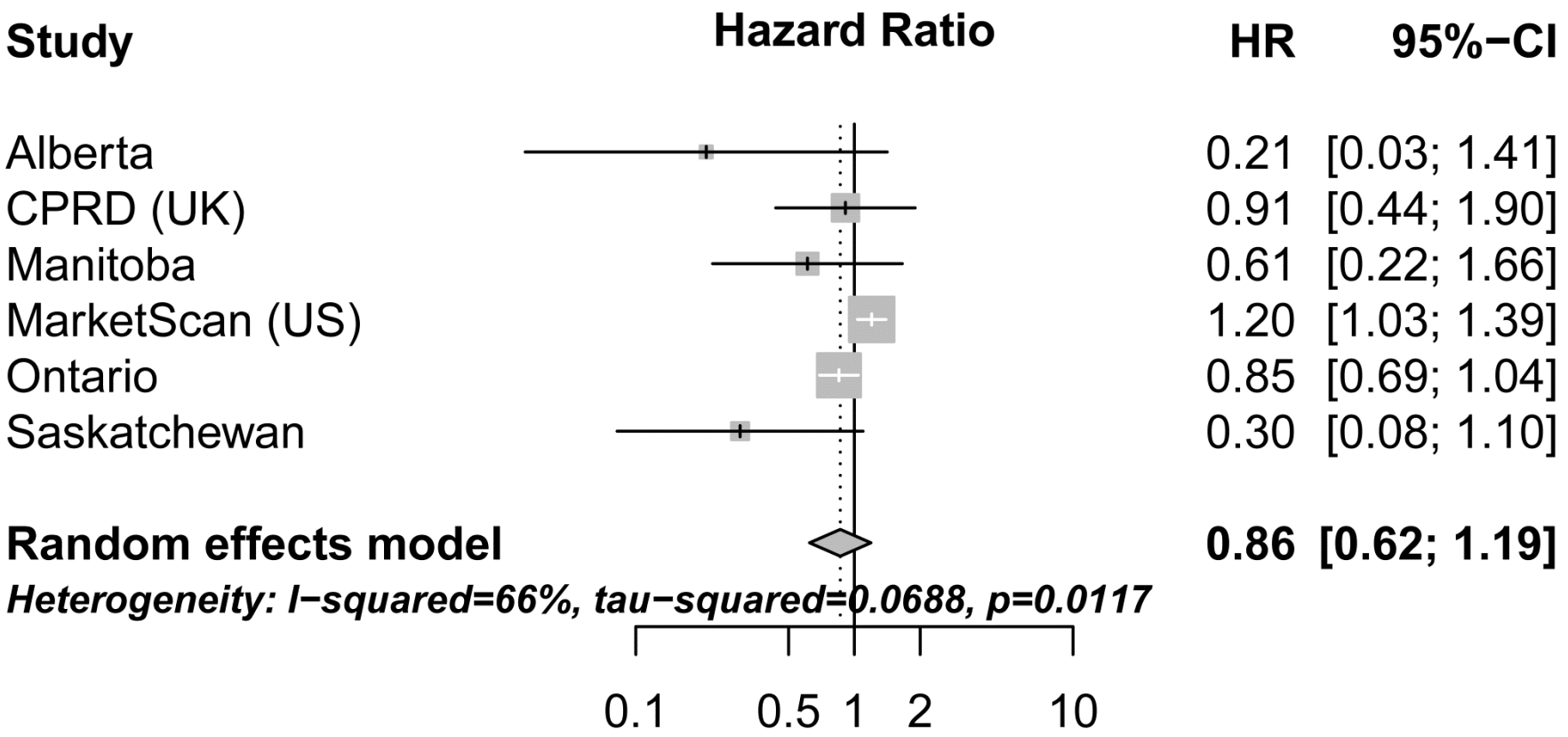
Exposure: current use

HF – History of HF
(Incretin-based drugs vs ≥2 OHAs)



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Exposure: current use

Conclusions

- Careful consideration to cohort construction is needed to:
  - Ensure comparable populations (exposed vs unexposed OR case vs control)
  - Ensure sufficient sample size
  - Account for changes over time in
    - Formulary
    - Prescription patterns
    - Population changes

Conclusions - II

- With its large sample size, CNODES and other multi-database drug safety networks allow for the implementation of unique approaches to addressing some of the methodological challenges present in pharmacoepidemiology.

- The studies presented here highlight the importance of study design, in addition to appropriate statistical methods, in addressing these methodological issues.

Thank you

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CIHR IRSC

COMPETING RISKS ANALYSES IN STUDIES OF DRUG SAFETY AND EFFECTIVENESS: RATIONALE, NEW METHODS AND APPLICATION

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Support : CIHR DSEN CAN-AIM grant

Outline

- Rationale for Competing Risks:

  Drawbacks of Composite Endpoints

- Modeling Cumulative Effects of Drug Use

- New Flexible Method for Competing Risks

- Application:

  comparing Effectiveness of Thiazide Diuretics in reducing the risks of :

  1/ Stroke vs

  2/ Cardiac events

Background

- Most prospective or retrospective Cohort Studies of Drug Safety or Effectiveness rely on multivariable Time-to-Event models such as Cox Proportional Hazards (PH) model
- Such models focus on time to a Single Endpoint
- In practice, both population-based drug studies and RCTs often use *Composite Endpoints* defined as time to the earliest of alternative clinical events (e.g. cancer recurrence or death)

2 MAIN REASONS FOR USING COMPETING RISKS ANALYSES IN STUDIES OF TREATMENT EFFECTS

- 1/ **Drawbacks of (popular) "COMPOSITE ENDPOINTS"**

  [Ferreira-Gonzalez et al, *BMJ* 2007;
  Lim et al, *Annals Internal Medicine* 2008]

- 2/ **Need to Account for Mortality** in any analyses of Non-fatal safety or effectiveness outcomes

  [Allignol et al, *Pharmaceutical Statistics* 2016]

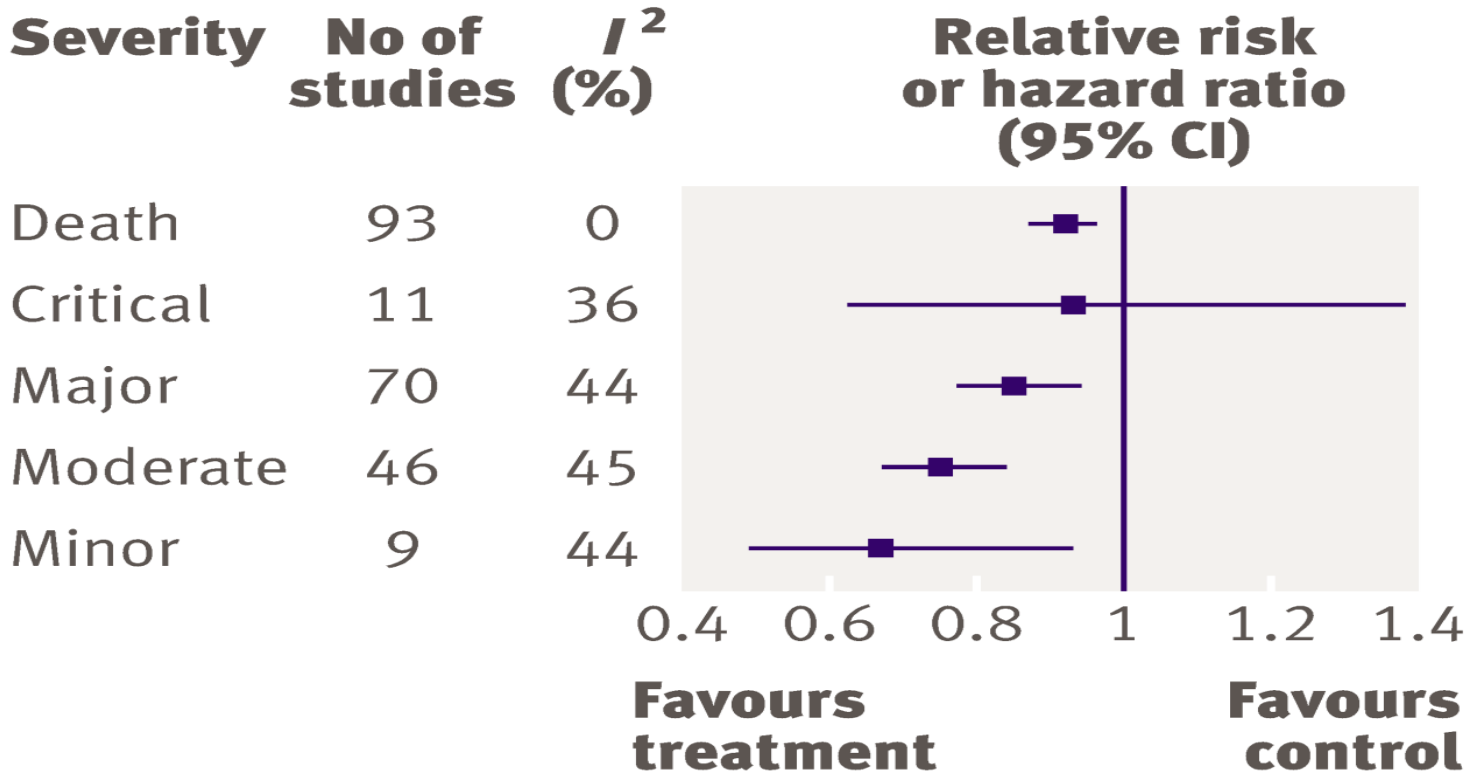
Ferreira-Gonzalez et al, *BMJ* 2007

- **Systematic review of 114 randomised controlled trials (RCTs) with Cardiovascular (CVD) endpoints**, published in top medical journals in 2002-2003
- *Objective*:

  To explore **to what extent Different Components of Composite CVD Endpoints vary** in:

  i. **Importance** to Patients
  ii. **Frequency** of events
  iii. Estimated **Treatment Effects** (relative risks)

FIGURE 2
[FERREIRA-GONZALEZ ET AL, *BMJ* 2007]



Variability in magnitude of the Intervention Effect across Components of Composite Endpoints (categorised according to Importance to Patients)

Example of a study where "Protective" Tx Effect for the "Composite Endpoint" is almost entirely driven by non-fatal outcomes with

No Difference al all in Mortality

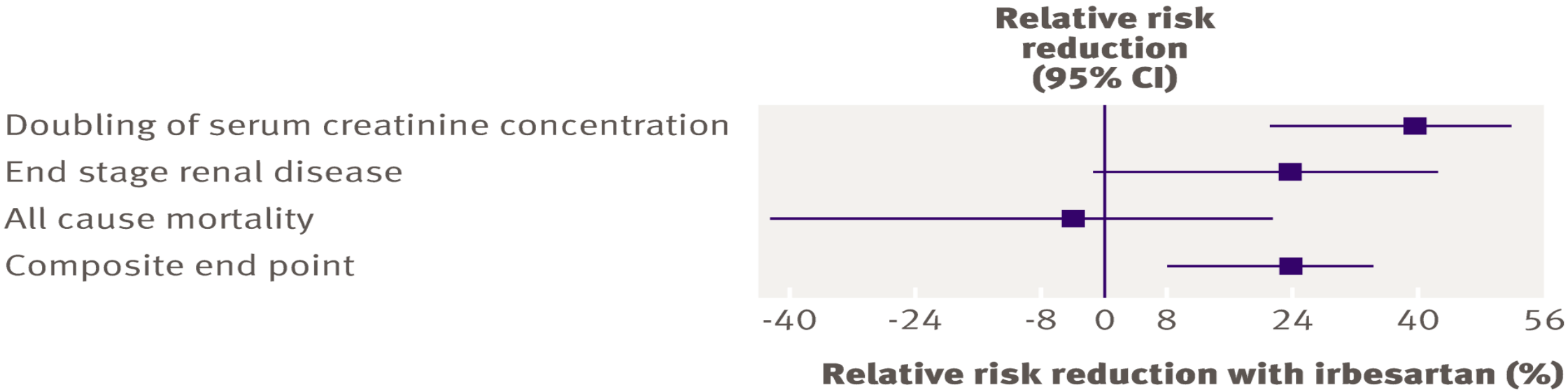


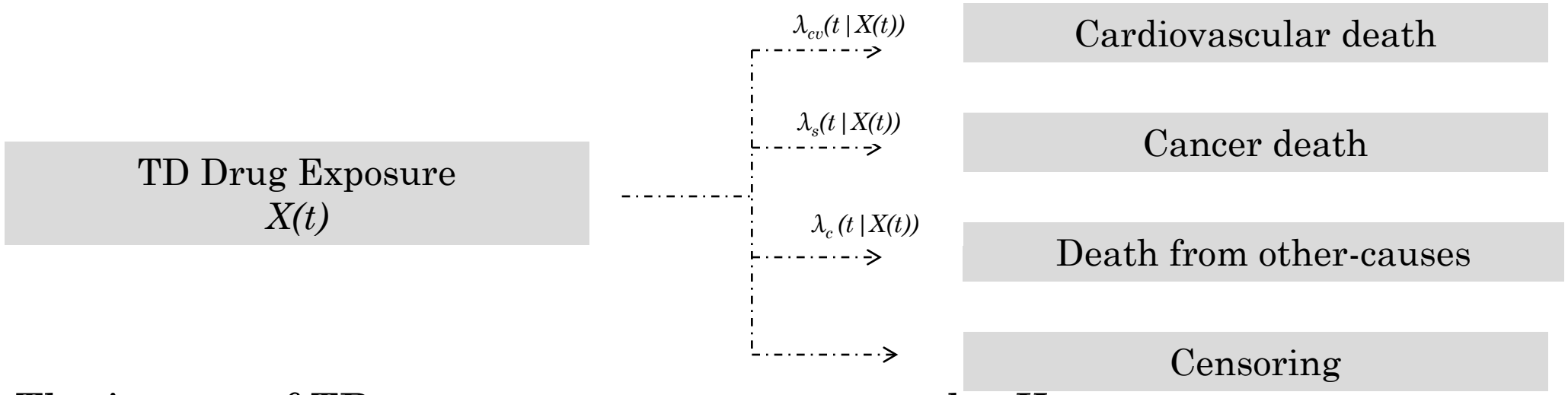
Figure 3: Comparison of irbesartan with amlodipine in the diabetic nephropathy study (1715 hypertensive patients with nephropathy and type 2 diabetes)
[Ferreira-Gonzalez et al, *BMJ* 2007]

Conclusion
[Ferreira-Gonzalez et al, *BMJ* 2007]

- The use of composite end points in cardiovascular trials is frequently complicated by large differences in both importance to patients and in the effect of treatment across component endpoints
- Higher event rates and larger treatment effects are typically associated with less important components of the "composite endpoint",
  which may result in misleading impressions of the "beneficial" effect of treatment

COMPETING RISKS SETTING

- Each subject is followed until the earliest among the $K \geq 2$ different types of mutually exclusive events or until a censoring time



- The impact of TD exposure may vary across the K events

NEW METHOD:
FLEXIBLE WCE MODELING OF CUMULATIVE EFFECTS FOR COMPETING RISKS
[DANIELI & ABRAHAMOWICZ, *SMMR* 2017]

- We have developed a <u>new model that combines:</u>
  - Flexible modeling of the **Cumulative Effects of past drug exposures,** to understand how dosage and timing history affects the current risk of an adverse event (AE)

    Weighted Cumulative Exposure (WCE) model
    [Sylvestre & Abrahamowicz, 2009]

  - Analyses of the separate associations of the same drug with alternative AEs (**Competing risks**)

    Lunn and McNeil data augmentation approach
    [Lunn & McNeil, 1995]

WCE METRIC IN COMPETING RISKS SETTING

- Modeling of the **joint effect of past exposures** on the **hazard of event *k*** at time *u* for patient *i* by the WCE metric [Abrahamowicz & *al.*, 2006; Sylvestre & Abrahamowicz, 2009]:

$$WCE_{k,i}(u) = \sum_{t \le u} w_k(u-t) X_i(t)$$

u : current time (when Risk is being assessed)

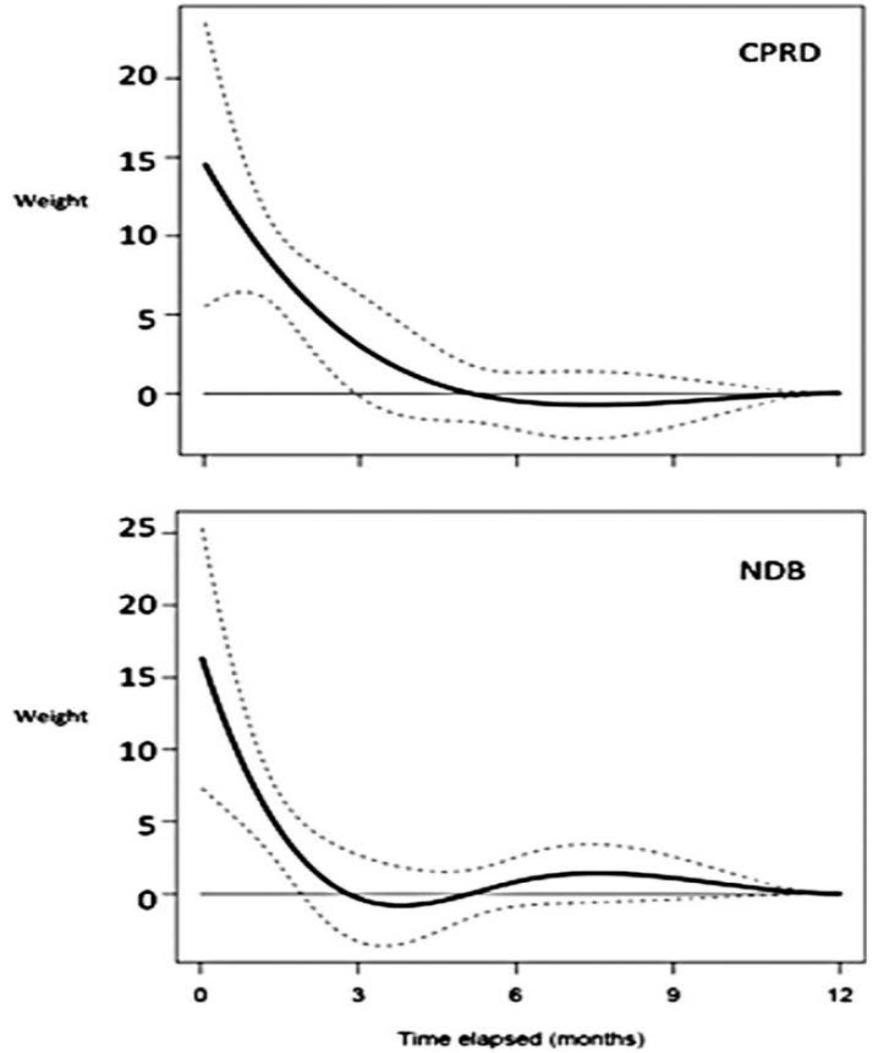
$X_i(t)$: individual exposure intensity (dose) at time t ($t \le u$)

u-t : time elapsed since exposure $X_i(t)$

w(u-t) : **weight function** that quantifies the relative importance of past exposures or drug doses $X_i(t)$ as a function of Time-since-Exposure *(u-t)*

Risk of Incident Diabetes Associated with Oral Glucocorticoid Therapy in Patients With Rheumatoid Arthritis

[Movahedi et al., *Arthritis Rheumatol* 2016]



Estimated weight functions (solid curve), with 95% confidence limits (dashed curves), in the Clinical Practice Research Datalink (CPRD) and the National Data Bank for Rheumatic Diseases (NDB).

Application: Competing risks WCE
[Danieli & Abrahamowicz, 2017]

- Objective:

  To assess and compare potential **separate associations of**

  Thiazide Diuretics (TD), popular antihypertensive drugs, with each of the **2 "competing" CVD Events:** (**)

  - **Coronary Heart Disease (CHD)** events
    (acute myocardial infarction, unstable angina, congestive heart failure)
  - **Stroke**

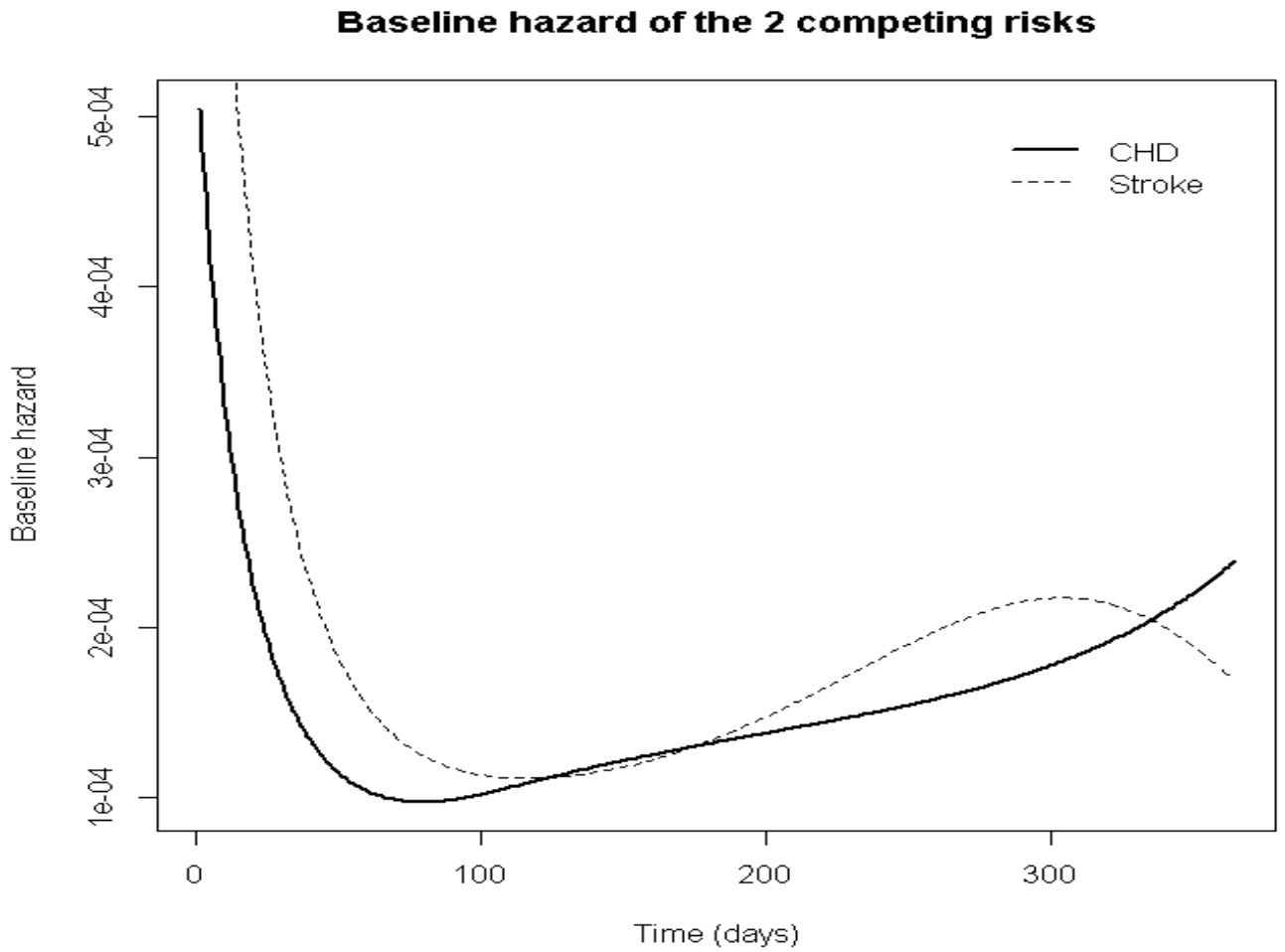
(**) Most studies use the Composite CVD Endpoint of "CHD and/or Stroke" but recent Cochrane meta-analysis suggested TD effects may differ between the 2 events

Data Source

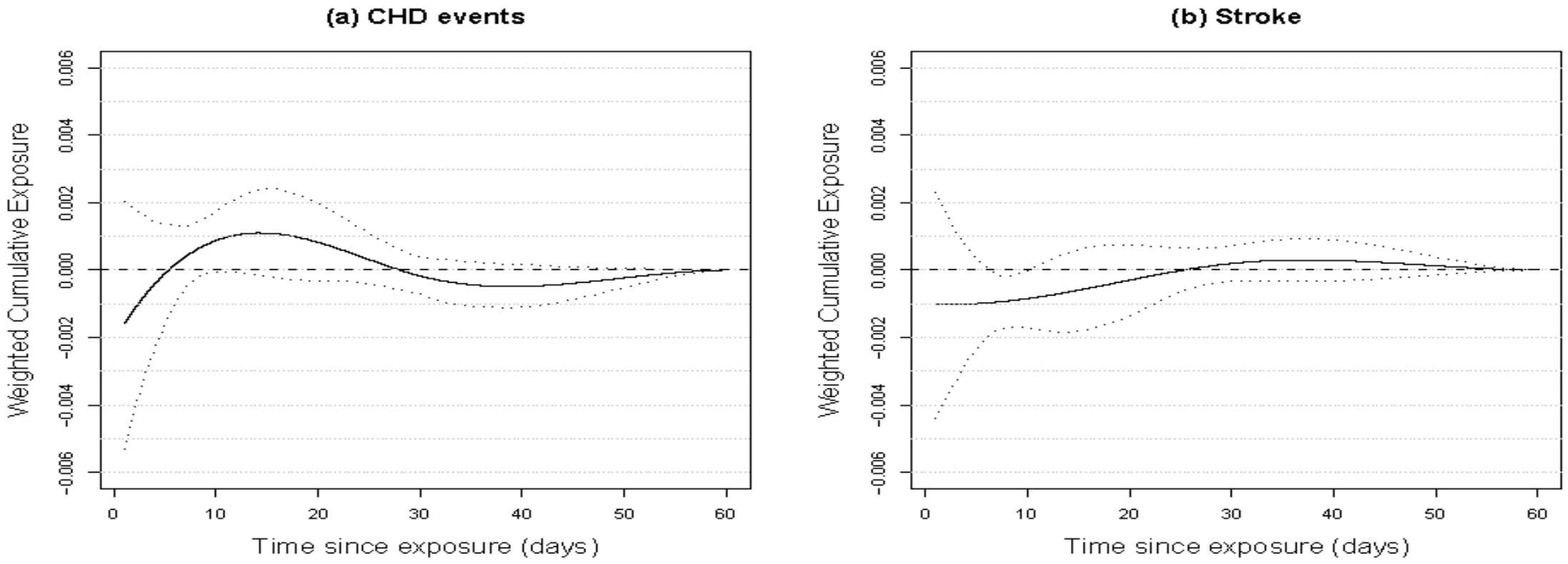
- US Marketscan Data (2011-2014):
  Random sample of 10,000 incident male TD users
- Time 0 = start of 1st TD Rx
- Each subject followed until the earliest dates among:
  - Either event of primary interest
  - Administrative censoring on December 31, 2014
  - Loss of coverage
  - Switch to another anti-hypertensive drug
- Followed for up to 4 years
- 979 subjects (9.8%) had an event during follow-up:
  - **440 CHD events** (Incidence rate = 4.0/100 py)
  - **539 Strokes** (Incidence rate = 4.9/100 py)
- Covariates: age and binary indicator of combination with another treatment

Separate Estimates of Baseline hazards for each event

[Danieli & Abrahamowicz 2017]

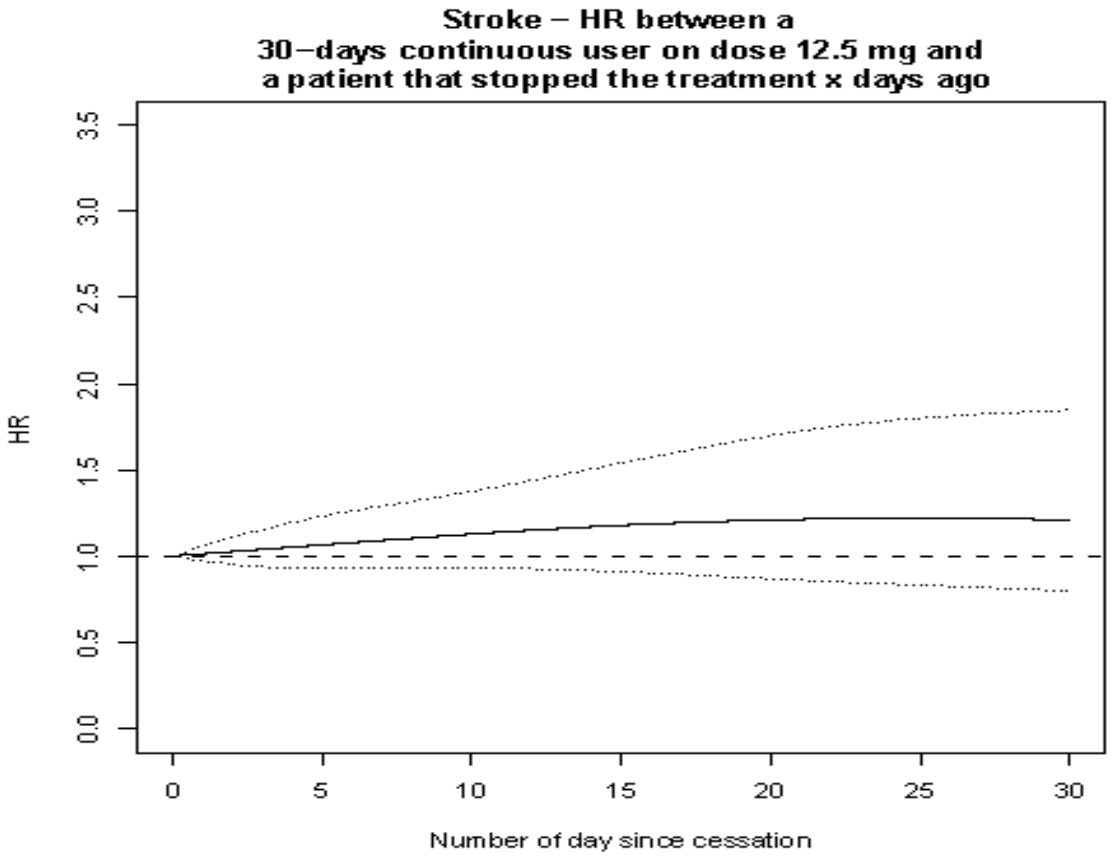


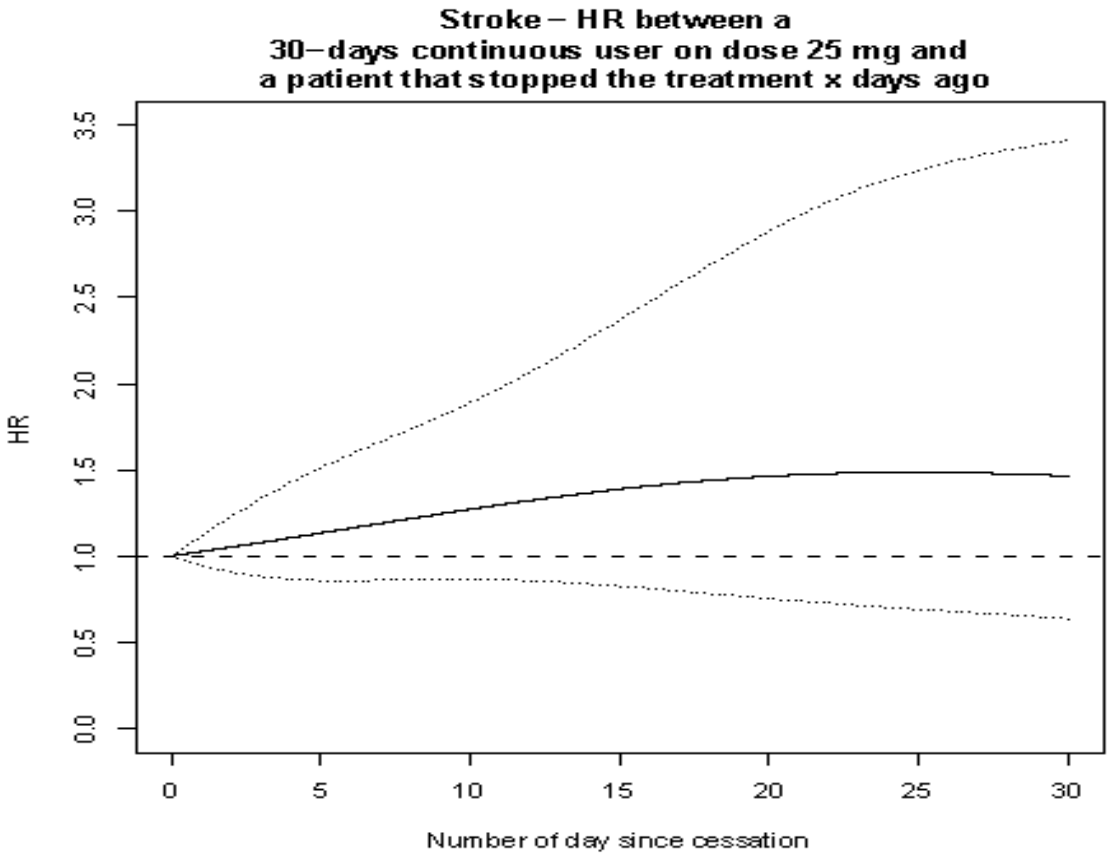
Event-specific Weight functions



- **Stroke: Significant Protective effect of recent TD exposures (test of No Association: p = 0.05)**
- CHD: No evidence of any effects (p>0.3)

Estimated Impact of Recent Interruption of the TD treatment on the hazard of Stroke





HR increases gradually in the first 2 weeks after TD discontinuation but then stabilizes

Insights from Competing Risks WCE analyses
[Danieli & Abrahamowicz, 2017]

- Competing Risks analyses revealed that
  recent TD use is Protective against Stroke but has No effect on CHD risks
  [differences in the effects of TD exposure on the hazards of the events are significant ($p<0.05$)] *

  (* this difference would be masked while using a popular "Composite CVD Endpoint")

- <u>Impact of TD treatment cessation on Stroke risk:</u>
  - Risk increases in the 2 weeks after cessation **
  - Impact of Tx cessation stronger for recent users of higher TD doses

** <u>Implication:</u>
to maintain protection against stroke, TD users need to be treated continuously, without interruptions

CONCLUSIONS

- Competing Risks analyses help avoiding the limitations of *Composite Endpoints* and ensures a more accurate estimation of the (potentially different) associations with each of the clinically different endpoints
- Flexible modeling of the Cumulative Effects of past drug use yields additional insights and helps assessing the impact of treatment interruptions

THANK YOU - MERCI

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Integration of individual level patient data into network meta-analysis

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LEARNING OBJECTIVES

LEARNING OBJECTIVES

I. To Define Individual Patient Data and Network Meta-Analysis

II. To Explain How To Retrieve Individual Patient Data

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OBJECTIVE 1: Individual Patient Data and Network Meta Analysis

AGGREGATE DATA (AD) VS. INDIVIDUAL PATIENT DATA (IPD)

AD		IPD	
What is it?	Data from entire group of patients enrolled in each included trial	**What is it?**	Data from each individual patient enrolled in each included trial
Use in MA + NMA	Summary point estimates for all patients	**Use in MA + NMA**	Individual patient point estimates
Limitations	May suffer from low statistical power	**Strengths**	Allows investigation of patient-level moderators
	Challenging to harmonize variable definitions		Allows similar analysis across all trials
	Challenging to harmonize inclusion and exclusion criteria		
	Challenging to adjust for study-specific biases (e.g. aggregation bias)		
	Challenging to explore sources of between-study heterogeneity (e.g. due to treatment-covariate interactions)		

Donegan et al Stat Med 2012, 2013

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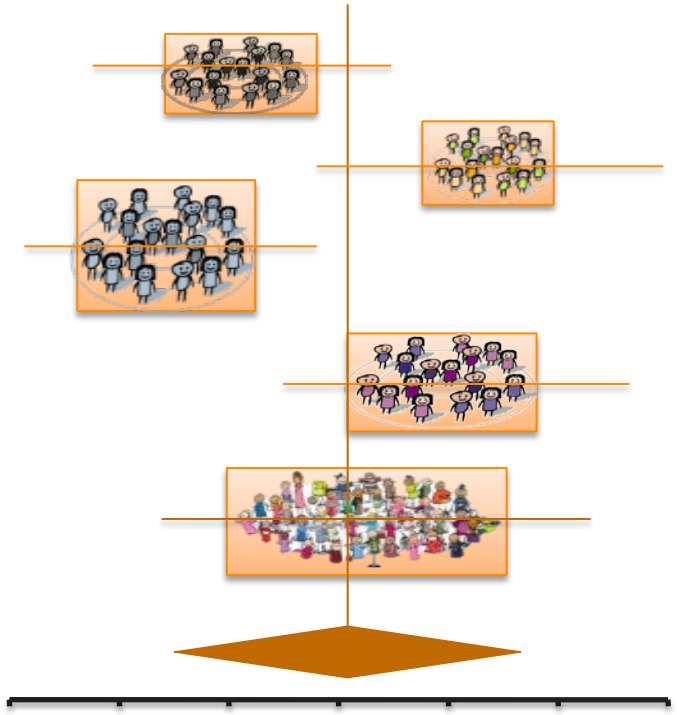
AD VS. IPD IN NETWORK META-ANALYSIS (NMA)



- AD and IPD models can be equivalent if data & effect size are equivalent
  - ❑ *Discrepancies arise because IPD data sets include different data than AD (e.g. may reinstate patients originally excluded, additional follow-up data)*
- IPD meta-analysis in soft tissue sarcoma:
  - ❑ 24% of patients were excluded in the treatment arm compared with 20% in the control arm – 99% of excluded patients were recovered
    - *Meta-analysis with exclusions: HR=0.85 (p=0.06)*
    - *Meta-analysis reinstating all exclusions: HR=0.90 (p=0.16)*

Tierney and Stewart Int J Epidemiol 2005

- Empirical evidence suggests AD models might be misleading for the evaluation of the consistency assumption, and might suggest different ranking due to differences in a patient-level covariate distribution within and across studies

Donegan et al Stat Med 2012, 2013

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IPD ADDRESSES THE SHORTCOMINGS OF AD

- IPD meta-analysis is the **gold standard** for synthesizing evidence across clinical trials, as it can:
  - ✓ Increase precision
  - ✓ Explore the patient-level treatment effects
  - ✓ Tailor results to the patient characteristics
  - ✓ Use consistent inclusion/exclusion criteria across studies

	A	B	C	D	E	F	G
1	Study	StudyID	ParticipantID	InterventionCode	BinaryOutcome	age	gender
2	CAR001	1	1	Granisetron	Vomit	23	woman
3	CAR001	1	2	Placebo	No Vomit	24	woman
4	CAR001	1	3	Granisetron	No Vomit	43	man
5	CAR001	1	4	Granisetron	No Vomit	22	man
6	CAR001	1	5	Granisetron	No Vomit	39	man
7	CAR001	1	6	Granisetron	No Vomit	21	man
8	CAR001	1	7	Granisetron	No Vomit	37	man
9	CAR001	1	8	Granisetron	No Vomit	37	man
10	CAR001	1	9	Granisetron	No Vomit	19	man
11	CAR001	1	10	Placebo	Vomit	39	man
12	CAR001	1	11	Placebo	Vomit	23	woman
13	CAR001	1	12	Placebo	Vomit	22	woman
14	CAR001	1	13	Placebo	No Vomit	43	woman
15	CAR001	1	14	Placebo	No Vomit	28	woman

Stewart and Tierney Eval Health Prof 2002

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USING IPD IN NMA: ADVANTAGES & DISADVANTAGES

ADVANTAGES	DISADVANTAGES
Includes checks to ensure homogeneity, quality of randomization, and follow-up analysis	Time-consuming and costly
Overcomes outcome reporting bias	May not be able to obtain all IPD = ***retrieval bias***
Allows participant-level covariates to be directly modeled, increasing statistical power and detects participant-treatment relationships if they are present. • Answers what interventions are most effective in (for example): o men versus women o older people versus younger people	"…the balance of gains and losses of the approach will vary according to the disease, treatment, and therapeutic questions explored"

Stewart and Tierney Eval Health Prof 2002

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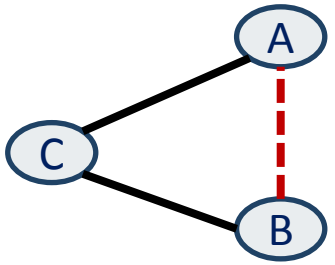
WHEN TO USE IPD IN NMA



When Individual Patient Data May Be Beneficial	*When Individual Patient Data May Not Be Beneficial*
Poor reporting of trials: Information inadequate, selective, or ambiguous	Detailed and clear reporting of trials (CONSORT quality)
Long-term outcomes	Short-term outcomes
Time-to-event outcome measures	Binary outcome measures
Multivariate or other complex analyses	Univariate or simple analyses
Differently defined outcome measures	Outcome measures defined uniformly across trials
Subgroup analyses of patient-level characteristics important	Patient subgroups not important
Individual patient data available for high proportion of trials/individuals	Individual patient data available for only a limited number of trials

Stewart and Tierney Eval Health Prof 2002

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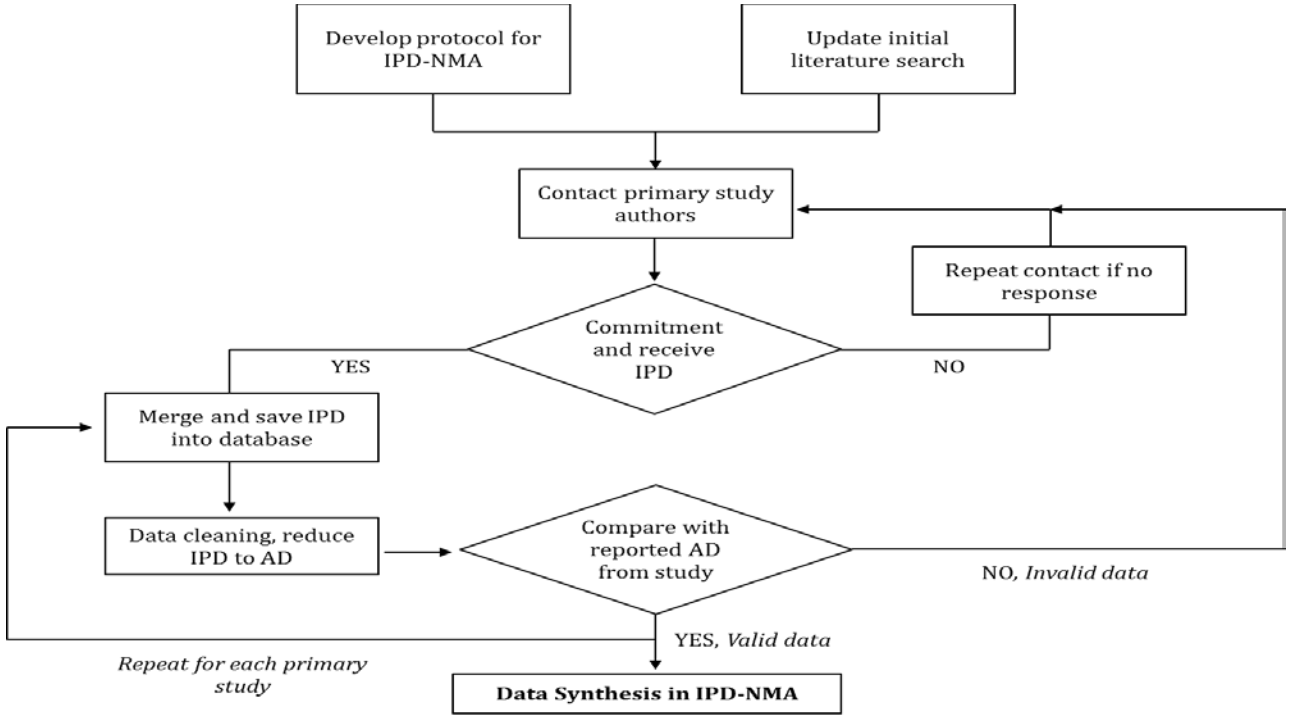
OBJECTIVE 2: Retrieving Individual Patient Data

PROCESS FOR AN IPD-NMA

- Eligible trials identified by search as in an AD review
- Identify contact information for authors published each eligible study



- Response to request may vary (e.g., no reply, no with reason provided, yes - will send the data, yes – here is the data)
- Data format and supporting material may vary per IPD received

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HOW TO OBTAIN IPD: CONTACT AUTHOR AND/OR SPONSOR

Choice of authors (no duplicates allowed – no author was contacted more than once for each study during the RCT process):

- Corresponding authors
- If a corresponding author comes up for more than one study, the next available author was used (first author, if not corresponding)
  - ❑ This step was repeated if the first author also appears more than once (move onto second author, third author, etc.).
- Final list of authors to be contacted did not have any duplicates

We specified data we were requesting and provided a summary/protocol of our study

---

General email/phone inquiry sent to all sponsors to achieve the following:

- Confirm what their process is, and ask if there are any 'special' steps we need to be aware of
- Ask whether they are able to provide their signatory and contact info of their 'point-person' to facilitate our data sharing agreements (DSA)
- Ask if the DSA is available in WORD format, in case we need to make any changes

All sponsors require the following:

- ❑ ***Research application/proposal***
- ❑ ***Statistical analysis plan (SAP), including Clinical Trials requested and Publication Plan***
- ❑ ***Data sharing agreement***
- ❑ ***Conflict of Interests for primary investigators***

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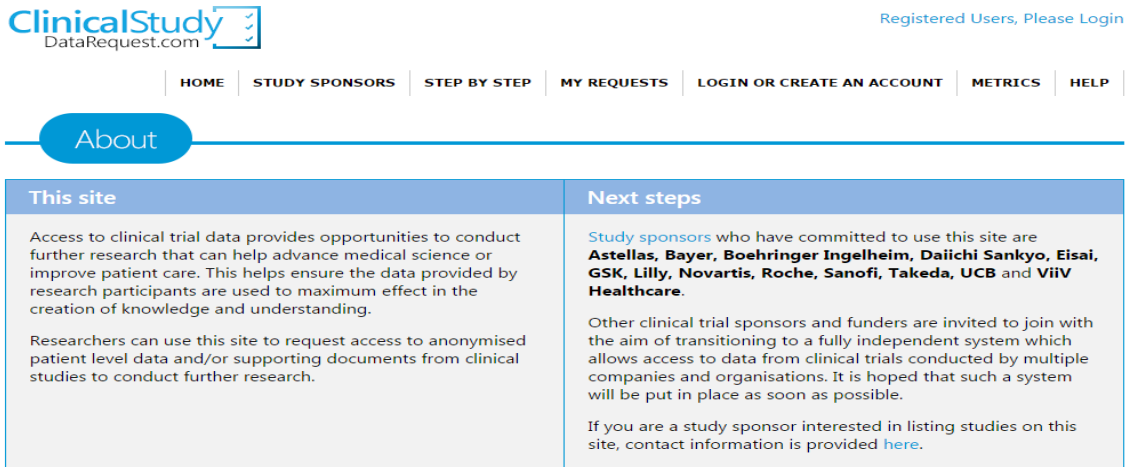
Veroniki et al Trials 2016

HOW TO OBTAIN IPD: IPD DATABASES

Initiatives to encourage data sharing and clinical transparency

- The Clinical Study Data Request System:
  https://www.clinicalstudydatarequest.com/



- The Yale University Open Data Access Project:
  http://yoda.yale.edu/

Important consideration:
protect the privacy and confidentiality of research participants
(anonymised data sharing)

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AFTER IPD HAS BEEN OBTAINED…

- Understand the data (check the protocol and decipher the variable codes)
- Reproduce published results
- Check the data (e.g. missing participants, chronological randomization sequence)
- Raise queries and discuss them with original authors
- Clean and prepare data in a common format across all studies
- Recode data to a consistent format
- Define outcomes of interest consistently across trials
- Perform analysis of the data
- Share results with data providers for discussion (if needed)
- Report findings according to the Preferred Reporting Items for a Systematic Review and Meta-analysis of Individual Participant Data (PRISMA-IPD) guidelines

Stewart et al JAMA 2015

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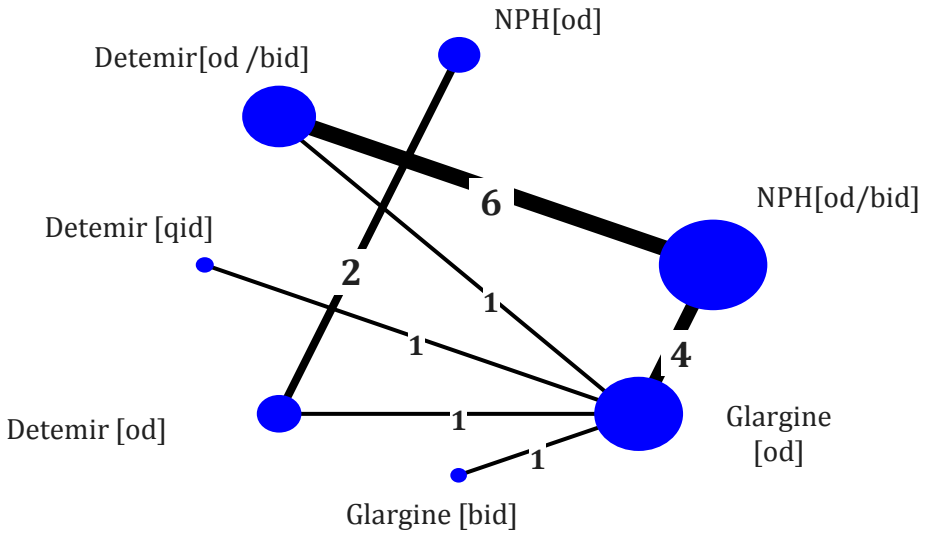
NMA USING IPD: AN EXAMPLE

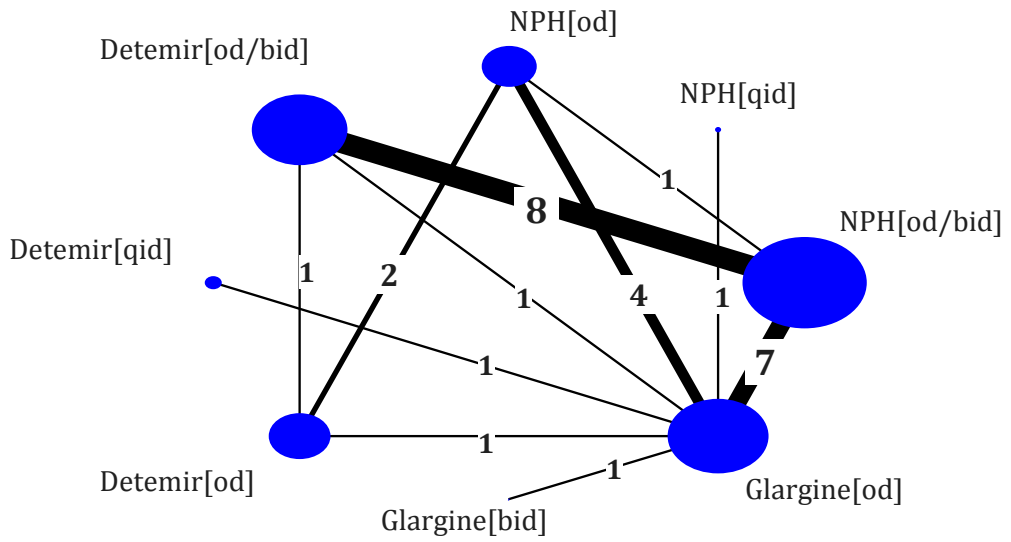
Safety and effectiveness of long-acting versus intermediate-acting insulin for patients with type 1 diabetes mellitus (T1DM)

Tricco et al BMJ 2014;349:g5459

Severe Hypoglycemia



Baseline glycosylated hemoglobin (A1C)



Veroniki et al BMJ Open 2015;5:e010160

Aim:

To update our previous systematic review and perform an IPD-NMA to evaluate the comparative safety and effectiveness of long- vs. intermediate-acting insulin in different subgroups of patients with T1DM.

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NMA USING IPD: AN EXAMPLE (2)

Safety and effectiveness of long-acting versus intermediate-acting insulin for patients with type 1 diabetes mellitus (T1DM)

Tricco et al BMJ 2014;349:g5459

Intended Impact:

- To explore relationships at the study level which may not be true at the individual level
  - In typical AD-NMAs, we use summary point estimates for each patients and lack information on these important patient-level modifiers
  - **EXAMPLE:** Patients with a longer duration of T1DM, e.g. older patients, may have better control of $A1_C$
- To inform the tailoring of evidence to individual patient characteristics, e.g. the tailoring of insulin regimens to specific patients
  - Our previous NMA assessed the impact of different insulin regimens on outcomes such as $A1_C$, quality of life, but could not assess the impact of these regimens on individual patient characteristics (e.g. baseline $A1_C$ levels, gender, age) due to the use of AD vs IPD

Veroniki et al BMJ Open 2015;5:e010160

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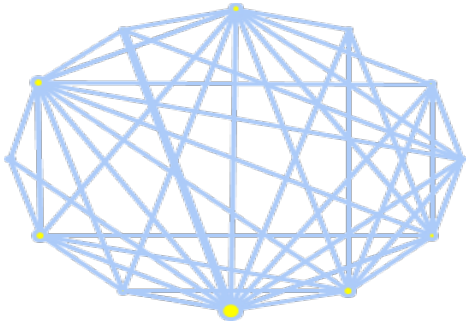
SUMMARY

IN SUMMARY…



Why apply an IPD-NMA?

- Individual study results do not answer all potentially relevant clinical questions
- Previous NMAs based on AD may have limitations
- Enables further research to benefit medical research and patient care
- Enables tailoring results to patient characteristics, and hence improving existing guideline recommendations
- Enables the validation of individual study results
- Avoids duplication of research, unnecessarily enrolling patients into clinical trials and exposing them to possible risks (e.g., serious adverse events)
- Increases transparency

But…

- Further studies are needed to evaluate the assumptions and the properties of an IPD-NMA in complex networks of interventions
- Process of obtaining IPD (i.e. costs and time) must be weighed against the benefits

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ACKNOWLEDGEMENTS

Knowledge Synthesis Team, Knowledge Translation Program, St. Michael's Hospital:

Dr. Areti Angeliki Veroniki

Dr. Sharon Straus

Huda Ashoor

Myanca Rodrigues

Funding from:

Drug Safety and Effectiveness Network (Canadian Institutes of Health Research), Canada Research Chair, Ontario Ministry of Research, Innovation, and Science

For more details on our work please visit http://knowledgetranslation.net/

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QUESTIONS?

Do you have any questions about today's presentation?

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Thank you for your attention!

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LEARNING OBJECTIVES