Avoiding self-inflicted biases in pharmacoepidemiology: emulate your target trial!

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Division of Pharmacoepidemiology and Pharmacoeconomics
Department of Medicine, Brigham and Women's Hospital and
Harvard Medical School

What will we discuss today?

1. What is pharmacoepidemiology and why do we need it?
2. What is target trial emulation? An example on RASi vs. CCB
3. How to prevent self-inflicted biases: prevalent user bias and immortal time bias
4. How to combat confounding

Main focus of my talk is on how to properly design a pharmacoepidemiology study, not on statistical analysis

What is pharmacoepidemiology?

Pharmacoepidemiology: The study of the therapeutic effect(s), risk(s) and use of drugs, using epidemiological methods and/or reasoning

Examples of pharmacoepidemiology studies

Drug effectiveness

www.kidney-international.org clinical investigation

GLP-1 receptor agonist versus DPP-4 inhibitor and kidney and cardiovascular outcomes in clinical practice in type-2 diabetes

Yang Xu[1,2,6], Edouard L. Fu[2,3,6], Catherine M. Clase[4], Faizan Mazhar[2], Meg J. Jardine[5] and Juan J. Carrero[2]

Drug safety

Original research

Proton pump inhibitors and risk of colorectal cancer

Devin Abrahami,[1,2] Emily Gibson McDonald,[3,4] Mireille E Schnitzer,[1,5] Alan N Barkun ,[1,6] Samy Suissa ,[1,2,7] Laurent Azoulay [1,2,8]

Drug use

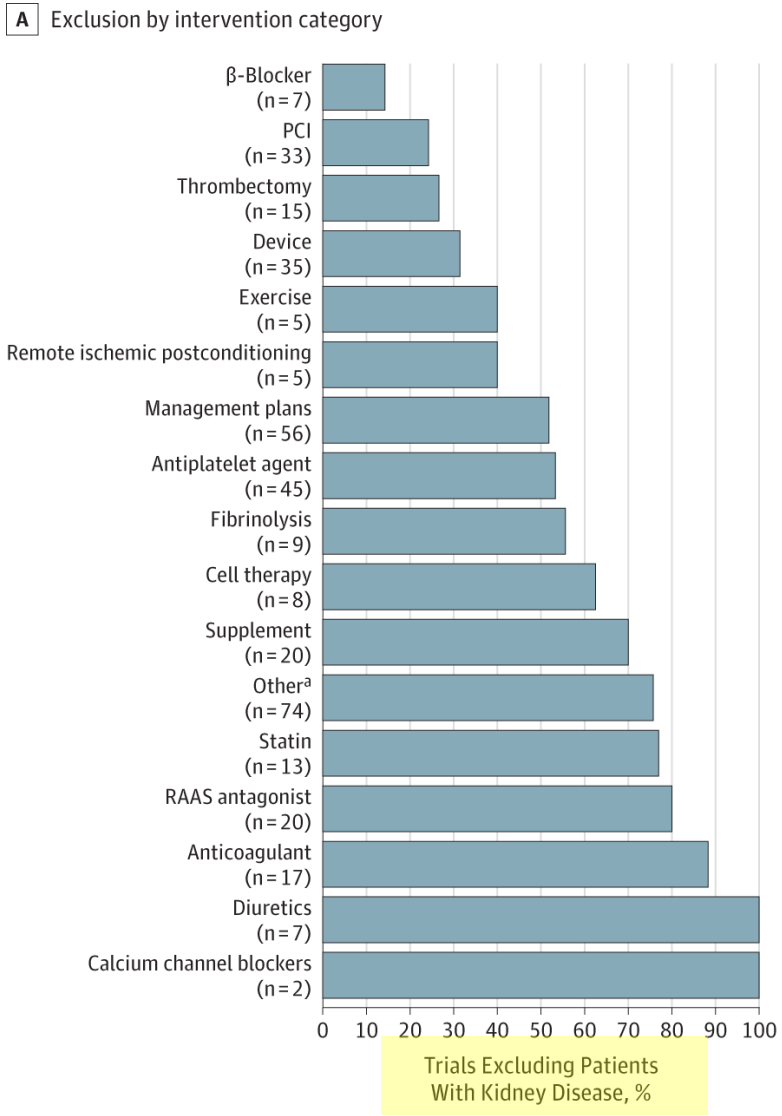
Prescribing Trends of Antidiabetes Medications in Patients With Type 2 Diabetes and Diabetic Kidney Disease: A Cohort Study

Samantha T. Harris,[1,2,3] Elisabetta Patorno,[1,2] Min Zhuo,[1,2,4,5] Seoyoung C. Kim,[1,2] and Julie M. Paik[1,2,4,6]

Diabetes Care 2021;44:2293–2301 | https://doi.org/10.2337/dc21-0529

Why do we need pharmacoepidemiology?

Generalizability (1)



JAMA Intern Med. 2016;176(1):121-124.
doi:10.1001/jamainternmed.2015.6102

Why do we need pharmacoepidemiology?

Generalizability (2)

Research

JAMA Internal Medicine | Original Investigation

Representativeness of Randomized Clinical Trial Cohorts in End-stage Kidney Disease

A Meta-analysis

Brendan Smyth, MBBS; Anna Haber, MBBS; Konlawij Trongtrakul, MD; Carmel Hawley, MMedSci; Vlado Perkovic, PhD; Mark Woodward, PhD; Meg Jardine, PhD

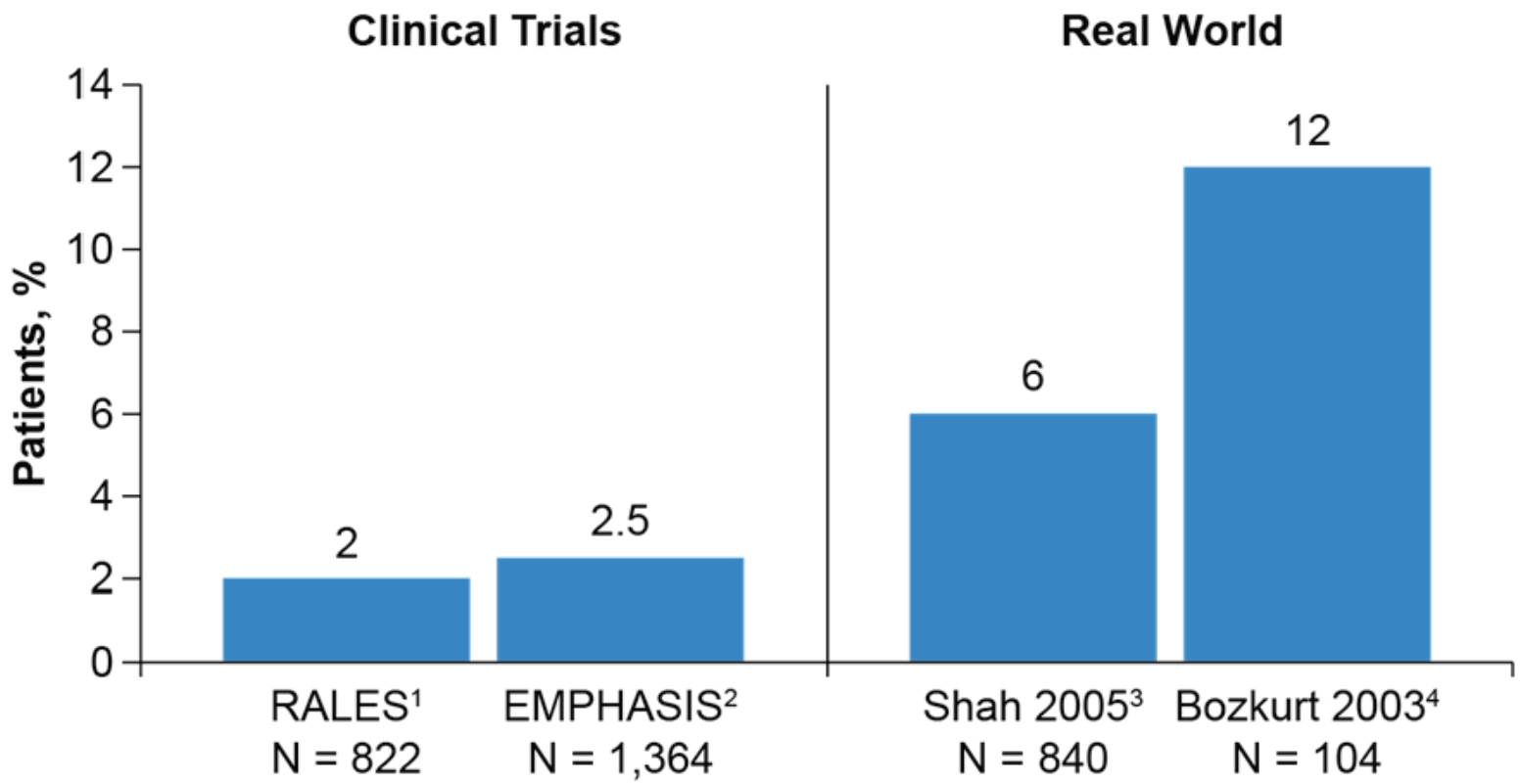
CONCLUSIONS AND RELEVANCE Participants in large, multicenter RCTs of patients with end-stage kidney disease undergoing dialysis are younger, have a different pattern of comorbidities, and have a lower mortality rate than the general population of patients undergoing dialysis. This finding has implications for the generalization of trial results to the broader patient population and for future trial design.

JAMA Intern Med. 2019;179(10):1316-1324. doi:10.1001/jamainternmed.2019.1501
Published online July 8, 2019. Corrected on October 7, 2019.

Why do we need pharmacoepidemiology?

Generalizability (example)

Hyperkalemia risk for mineralocorticoid receptor antagonists



[a] Hyperkalemia defined as $K^+ \geq 6.0$.

1. Pitt B et al. *N Engl J Med*. 1999;341:709-717. 2. Zannad F et al. *N Engl J Med*. 2011;364:11-21.
3. Shah KB et al. *J Am Coll Cardiol*. 2005;46:845-849. 4. Bozkurt B et al. *J Am Coll Cardiol*. 2003;41:211-214.

Why do we need pharmacoepidemiology?

A trial less likely to be sponsored

Comparative Effectiveness and Safety of Sodium–Glucose Cotransporter 2 Inhibitors Versus Glucagon-Like Peptide 1 Receptor Agonists in Older Adults

Diabetes Care 2021;44:826–835 | https://doi.org/10.2337/dc20-1464

Elisabetta Patorno,[1] Ajinkya Pawar,[1] Lily G. Bessette,[1] Dae H. Kim,[1,2,3] Chintan Dave,[1,4] Robert J. Glynn,[1] Medha N. Munshi,[2,5] Sebastian Schneeweiss,[1] Deborah J. Wexler,[6] and Seoyoung C. Kim[1]

	Efficacy (Can it work?)	**Effectiveness** (Does it work in **routine** care?)
Placebo comparison (or usual care)	Most RCTs for drug approval	
Active comparison (head-to-head)		Goal of pharmacoepi

Adapted from Schneeweiss

Why do we need pharmacoepidemiology?

A trial that is not feasible: too many treatment arms

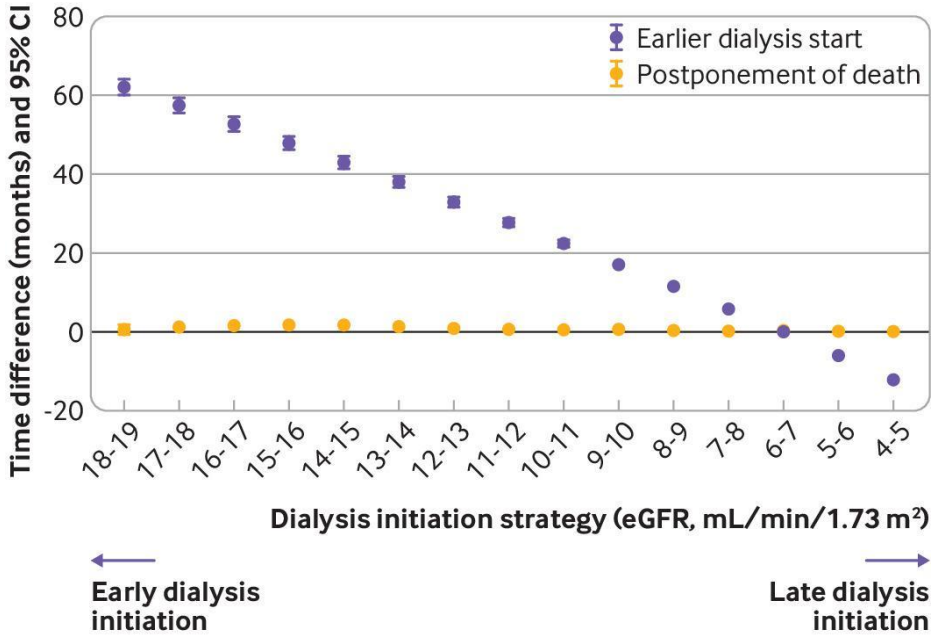
thebmj

Timing of dialysis initiation to reduce mortality and cardiovascular events in advanced chronic kidney disease: nationwide cohort study

Edouard L Fu,[1] Marie Evans,[2] Juan-Jesus Carrero,[3] Hein Putter,[4] Catherine M Clase,[5] Fergus J Caskey,[6] Maciej Szymczak,[7] Claudia Torino,[8] Nicholas C Chesnaye,[9] Kitty J Jager,[9] Christoph Wanner,[10] Friedo W Dekker,[1] Merel van Diepen[1]

MAIN OUTCOME MEASURES

The strict design criteria of a clinical trial were mimicked by using the cloning, censoring, and weighting method to eliminate immortal time bias, lead time bias, and survivor bias. A dynamic marginal structural model was used to estimate adjusted hazard ratios and absolute risks for five year all cause mortality and major adverse cardiovascular events (composite of cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke) for 15 dialysis initiation strategies with eGFR values between 4 and 19 mL/min/1.73 m^2 in increments of 1 mL/min/1.73 m^2. An eGFR between 6 and 7 mL/min/1.73 m^2 ($eGFR_{6-7}$) was taken as the reference.



Why do we need pharmacoepidemiology?

A trial that is not feasible: too few events/too long follow-up needed

ORIGINAL ARTICLE

Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes

Bernard Zinman, M.D., Christoph Wanner, M.D., John M. Lachin, Sc.D., David Fitchett, M.D., Erich Bluhmki, Ph.D., Stefan Hantel, Ph.D., Michaela Mattheus, Dipl. Biomath., Theresa Devins, Dr.P.H., Odd Erik Johansen, M.D., Ph.D., Hans J. Woerle, M.D., Uli C. Broedl, M.D., and Silvio E. Inzucchi, M.D., for the EMPA-REG OUTCOME Investigators

Empagliflozin and risk of DKA

1/2333 vs. 3/2345

HR = 2.9 (0.4-20.0)

CORRESPONDENCE

Risk of Diabetic Ketoacidosis after Initiation of an SGLT2 Inhibitor

Michael Fralick, M.D.
Sebastian Schneeweiss, M.D., Sc.D.
Elisabetta Patorno, M.D., Dr.P.H.

SGLT2i and risk of DKA

26/38,045 vs. 55/38,045

HR = 2.2 (1.4-3.6)

Adapted from Schneeweiss

We have enough observational data to answer these questions!

The patient journey (time)

Healthcare use

- Inpatient
- Outpatient

Diagnoses

Laboratory measurements

Drugs

Specify protocol of the target trial

The hypothetical randomized trial we would have liked to conduct to answer our question (= **target trial**)

Need to specify a **target trial protocol**

- Eligibility criteria
- Treatment strategies
- Randomized assignment
- Start/End follow-up
- Outcomes
- Causal contrast(s) of interest
- Statistical analysis

Observational study needs to emulate

- Eligibility criteria
- Treatment strategies
- Randomized assignment
- Start/End follow-up
- Outcomes
- Causal contrast(s) of interest
- Statistical analysis

Hernán et al. AJE 2016

An example of trial emulation protocol

Original Investigation

AJKD

Comparative Effectiveness of Renin-Angiotensin System Inhibitors and Calcium Channel Blockers in Individuals With Advanced CKD: A Nationwide Observational Cohort Study

Edouard L. Fu, Catherine M. Clase, Marie Evans, Bengt Lindholm, Joris I. Rotmans, Friedo W. Dekker, Merel van Diepen, and Juan-Jesus Carrero

Goal: to study the effect of RASi vs. CCB on kidney replacement therapy, MACE, all-cause death

Rationale: Trials included few patients with advanced CKD, no head-to-head comparisons between different antihypertensive agents

Brief protocol of the target trial and its emulation

Component	Hypothetical target trial	Emulation in Swedish Renal Registry
Eligibility	• ≥18 years • Advanced CKD (i.e. eGFR <30 ml/min/1.73m^2) • No use of either RASi or CCB in previous 6 months • No history of dialysis or kidney transplantation	Same as target trial
Treatment strategies	Initiate RASi vs. initiate CCB	Same as target trial
Treatment assignment	Randomization, no blinding	Randomization is emulated by adjusting for baseline confounders

Fu et al. AJKD 2021

Brief protocol of the target trial and its emulation

Component	Hypothetical target trial	Emulation in Swedish Renal Registry
Follow-up	• Starts at randomization • Ends at endpoint or 5 years	• Starts at treatment initiation • Ends at endpoint, 5 years or administrative censoring
Primary and secondary endpoints	• Kidney replacement therapy • MACE (composite of CV death, MI, stroke) • All-cause mortality	Same as target trial
Causal contrast	Intention-to-treat effect	Same as target trial
Statistical analysis	Cox proportional hazards regression	Same as target trial. Propensity score weighting will be applied to adjust for baseline confounders. Etc etc ….

Fu et al. AJKD 2021

But wait…

- Can observational pharmacoepidemiology studies really give us causal conclusions?
- Don’t we always have unmeasured confounding?
- Well, confounding is often not the biggest problem!
- Currently, biggest problem are self-inflicted biases due to erroneous study design that could be easily prevented by emulating a trial

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 17, 2009 VOL. 361 NO. 12

Dabigatran versus Warfarin in Patients with Atrial Fibrillation

Stuart J. Connolly, M.D., Michael D. Ezekowitz, M.B., Ch.B., D.Phil., Salim Yusuf, F.R.C.P.C., D.Phil., John Eikelboom, M.D., Jonas Oldgren, M.D., Ph.D., Amit Parekh, M.D., Janice Pogue, M.Sc., Paul A. Reilly, Ph.D., Ellison Themeles, B.A., Jeanne Varrone, M.D., Susan Wang, Ph.D., Marco Alings, M.D., Ph.D., Denis Xavier, M.D., Jun Zhu, M.D., Rafael Diaz, M.D., Basil S. Lewis, M.D., Harald Darius, M.D., Hans-Christoph Diener, M.D., Ph.D., Campbell D. Joyner, M.D., Lars Wallentin, M.D., Ph.D., and the RE-LY Steering Committee and Investigators*

Randomized trial:

HR 0.66 (0.53-0.82)

Dabigatran use in Danish atrial fibrillation patients in 2011: a nationwide study

Rikke Sørensen,[1,2] Gunnar Gislason,[1,3] Christian Torp-Pedersen,[4] Jonas Bjerring Olesen,[1] Emil L Fosbøl,[5] Morten W Hvidtfeldt,[1] Deniz Karasoy,[1] Morten Lamberts,[1] Mette Charlot,[1,6] Lars Køber,[5] Peter Weeke,[1] Gregory Y H Lip,[7] Morten Lock Hansen[1]

Did not emulate a target trial

Bad observational study:

HR 5.79 (1.81-18.6)

Sequential Monitoring of the Comparative Effectiveness and Safety of Dabigatran in Routine Care

Sebastian Schneeweiss, MD, ScD, Shantha Chandrasekar Gopalakrishnan, MD, MPH, Dorothee B. Bartels, PhD, Jessica M. Franklin, PhD, Kristina Zint, PhD, Martin Kulldorff, PhD, and Krista F. Huybrechts, MS, DPhil

Emulated a target trial

Good observational study:

HR 0.75 (0.58-0.98)

SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials

Thomas A Zelniker, Stephen D Wiviott, Itamar Raz, Kyungah Im, Erica L Goodrich, Marc P Bonaca, Ofri Mosenzon, Eri T Kato, Avivit Cahn, Remo H M Furtado, Deepak L Bhatt, Lawrence A Leiter, Darren K McGuire, John P H Wilding, Marc S Sabatine

Meta-analysis of RCTs:

HR 0.85 (0.78-0.93)

Lower Risk of Heart Failure and Death in Patients Initiated on Sodium-Glucose Cotransporter-2 Inhibitors Versus Other Glucose-Lowering Drugs

The CVD-REAL Study (Comparative Effectiveness of Cardiovascular Outcomes in New Users of Sodium-Glucose Cotransporter-2 Inhibitors)

Did not emulate a target trial

Bad observational study:

HR 0.49 (0.41-0.57)

Use of sodium glucose cotransporter 2 inhibitors and risk of major cardiovascular events and heart failure: Scandinavian register based cohort study

Björn Pasternak,[1,2] Peter Ueda,[1] Lisa Eliasson,[3] Ann-Marie Svensson,[3,4] Stefan Franzén,[4,5] Soffia Gudbjörnsdottir,[3,4] Mette Hviid Hveem,[6,7] Christian Jonasson,[6,7] Viktor Wintzell,[1] Mads Melbye,[1,2] Pontus Svanström[1,2]

Emulated a target trial

Good observational study:

HR 0.80 (0.69-0.92)

Randomized trial:

HR 1.23 (0.99-1.53)

Did not emulate a target trial

Bad observational study:

RR 0.61 (0.52-0.71)

Emulated a target trial

Good observational study:

HR 1.05 (0.82-1.34)

OPEN ACCESS Freely available online

PLoS one

Lack of Effect of Lowering LDL Cholesterol on Cancer: Meta-Analysis of Individual Data from 175,000 People in 27 Randomised Trials of Statin Therapy

Cholesterol Treatment Trialists' (CTT) Collaboration*¶

Meta-analysis of RCTs:

HR 1.00 (0.93-1.08)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Statin Use and Reduced Cancer-Related Mortality

Sune F. Nielsen, Ph.D., Børge G. Nordestgaard, M.D., D.M.Sc.
and Stig E. Bojesen, M.D., Ph.D., D.M.Sc.

Did not emulate a target trial

Bad observational study:

HR 0.85 (0.82-0.87)

JAMA Oncology | Original Investigation

Examining Bias in Studies of Statin Treatment and Survival in Patients With Cancer

Louise Emilsson, MD, PhD; Xabier García-Albéniz, MD, PhD; Roger W. Logan, PhD; Ellen C. Caniglia, ScD;
Mette Kalager, MD, PhD; Miguel A. Hernán, MD, DrPH

Emulated a target trial

Good observational study:

HR 1.00 (0.88-1.15)

We know what went wrong!

- Good observational studies emulated the strict design of a randomized trial

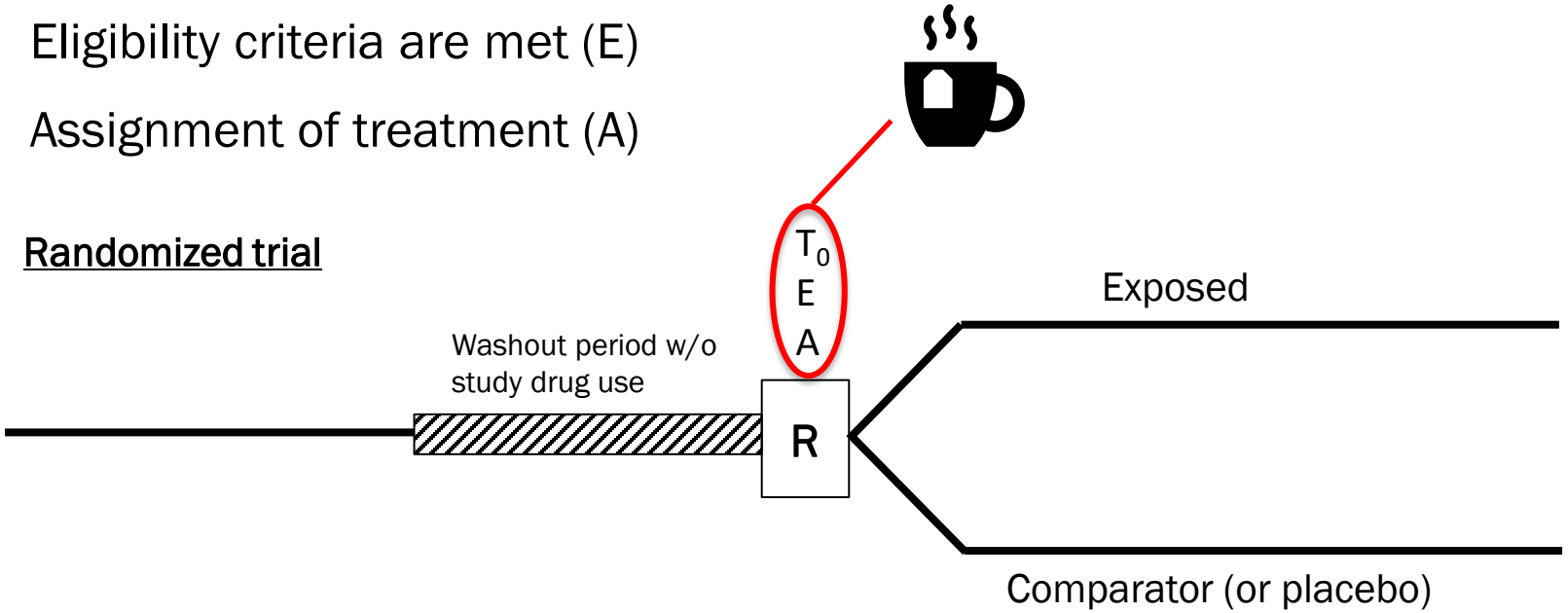
  = target trial emulation

- Bad observational studies did not, which introduced additional “self-inflicted” biases (on top of confounding):
  - Prevalent user bias
  - Immortal time bias

What happens in an RCT?

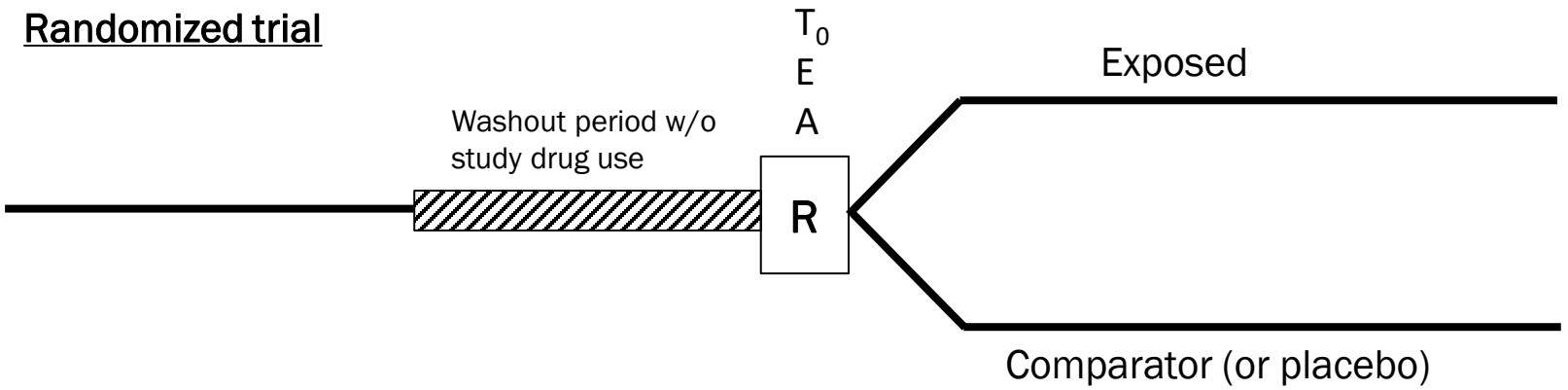
Alignment of 3 components at baseline (=randomization):

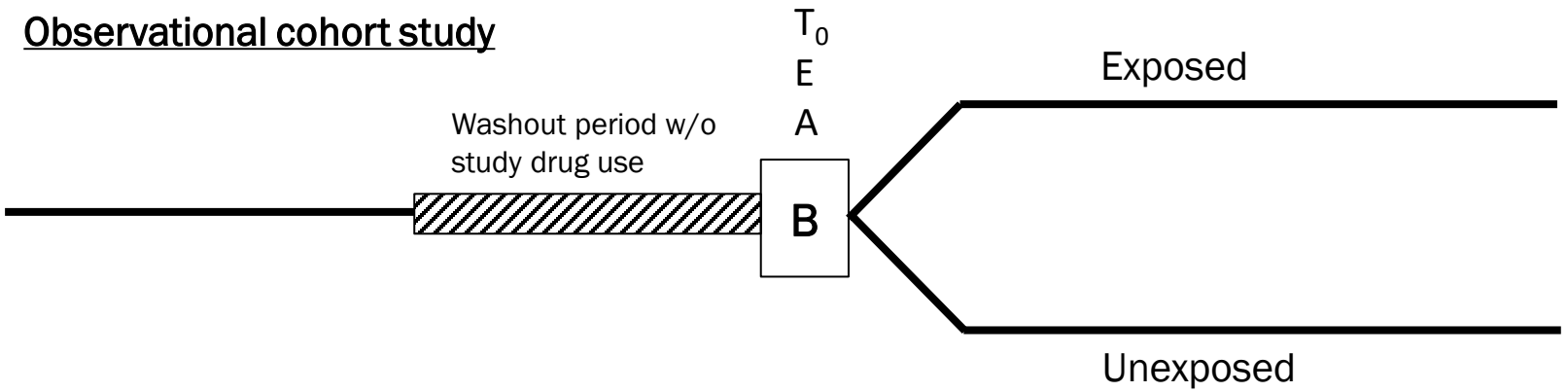
- Start of follow-up (T_0)
- Eligibility criteria are met (E)
- Assignment of treatment (A)



Failure to align these 3 components in observational study introduces bias

What should happen in an observational study?

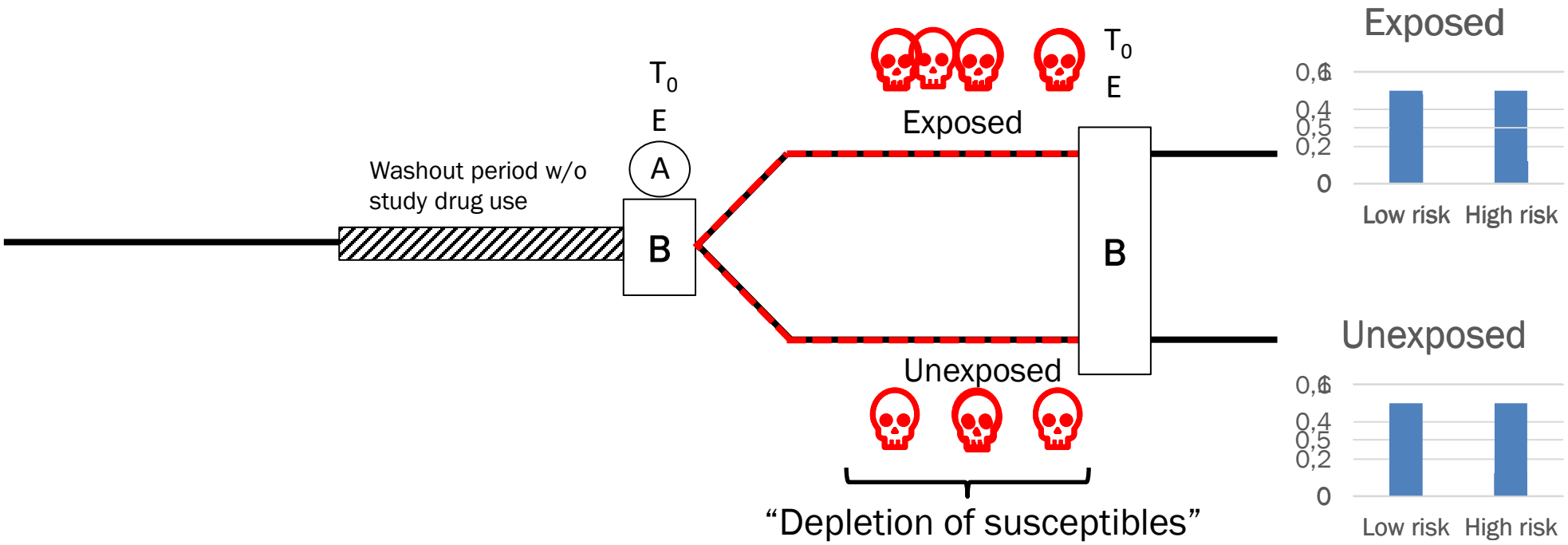




B = baseline

What happens if we start follow-up after treatment initiation?

Observational cohort study

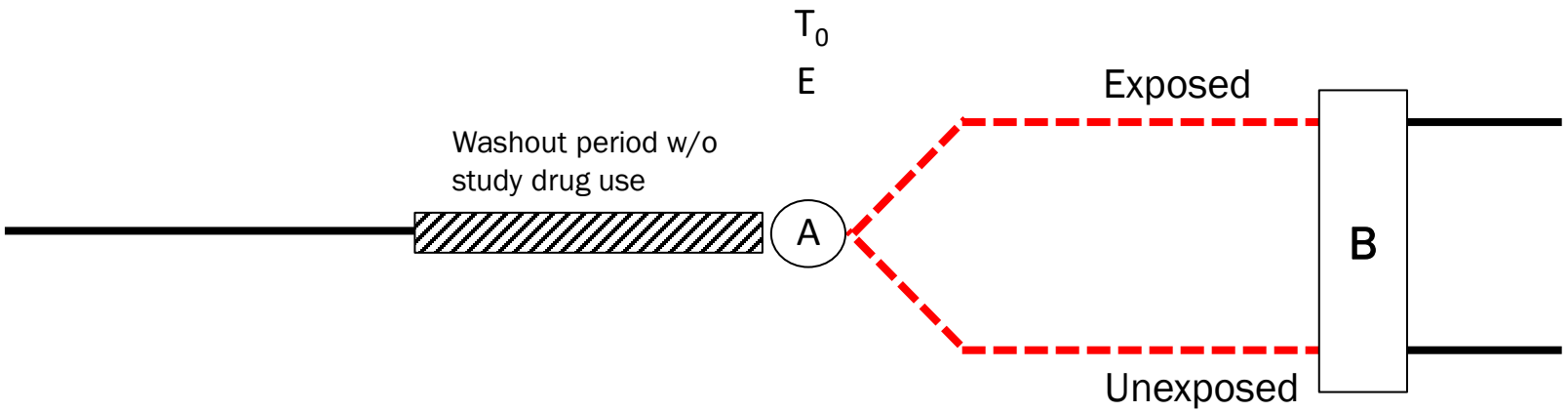


If treatment is truly protective…
If treatment is truly harmful…
If treatment truly has NO effect…

Prevalent user bias occurs whenever the start of follow-up is *after* treatment initiation

Prevalent vs. new users

Prevalent user bias occurs whenever we are looking at prevalent users, instead of new users



Additional problems:

1) This study design does not give an answer to our question of interest
2) Adjusting in the causal pathway

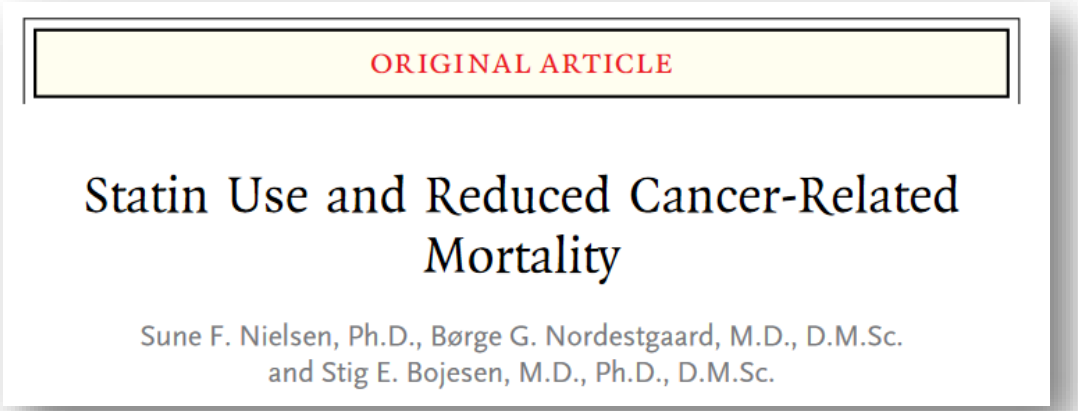
Prevalent user bias happens fairly commonly…

BMJ Open. 2013 May 3;3(5):e002758.

Dabigatran use in Danish atrial fibrillation patients in 2011: a nationwide study

Rikke Sørensen,[1,2] Gunnar Gislason,[1,3] Christian Torp-Pedersen,[4] Jonas Bjerring Olesen,[1] Emil L Fosbøl,[5] Morten W Hvidtfeldt,[1] Deniz Karasoy,[1] Morten Lamberts,[1] Mette Charlot,[1,6] Lars Køber,[5] Peter Weeke,[1] Gregory Y H Lip,[7] Morten Lock Hansen[1]

N Engl J Med. 2012 Nov 8;367(19):1792-802.

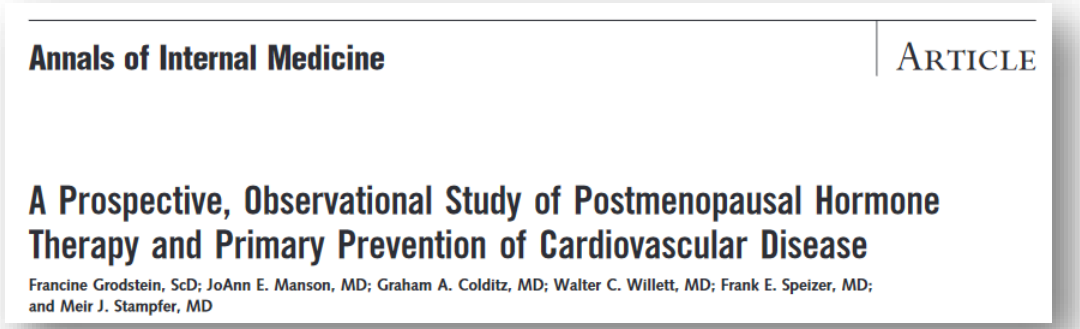


ORIGINAL ARTICLE

Statin Use and Reduced Cancer-Related Mortality

Sune F. Nielsen, Ph.D., Børge G. Nordestgaard, M.D., D.M.Sc. and Stig E. Bojesen, M.D., Ph.D., D.M.Sc.

Ann Intern Med. 2000 Dec 19;133(12):933-41.

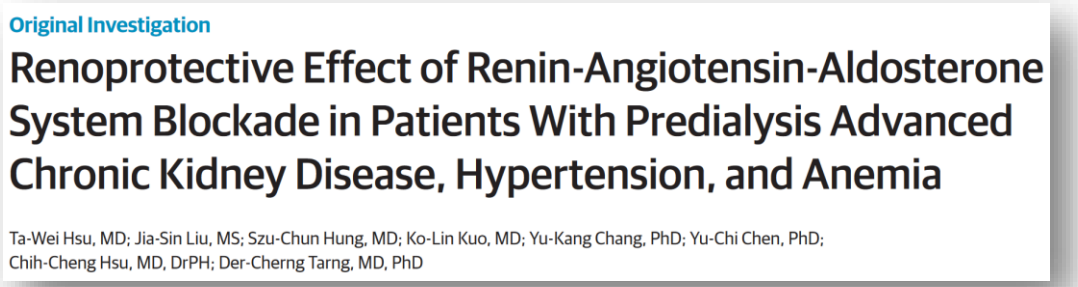


Annals of Internal Medicine | ARTICLE

A Prospective, Observational Study of Postmenopausal Hormone Therapy and Primary Prevention of Cardiovascular Disease

Francine Grodstein, ScD; JoAnn E. Manson, MD; Graham A. Colditz, MD; Walter C. Willett, MD; Frank E. Speizer, MD; and Meir J. Stampfer, MD

JAMA Intern Med. 2014 Mar;174(3):347-54.



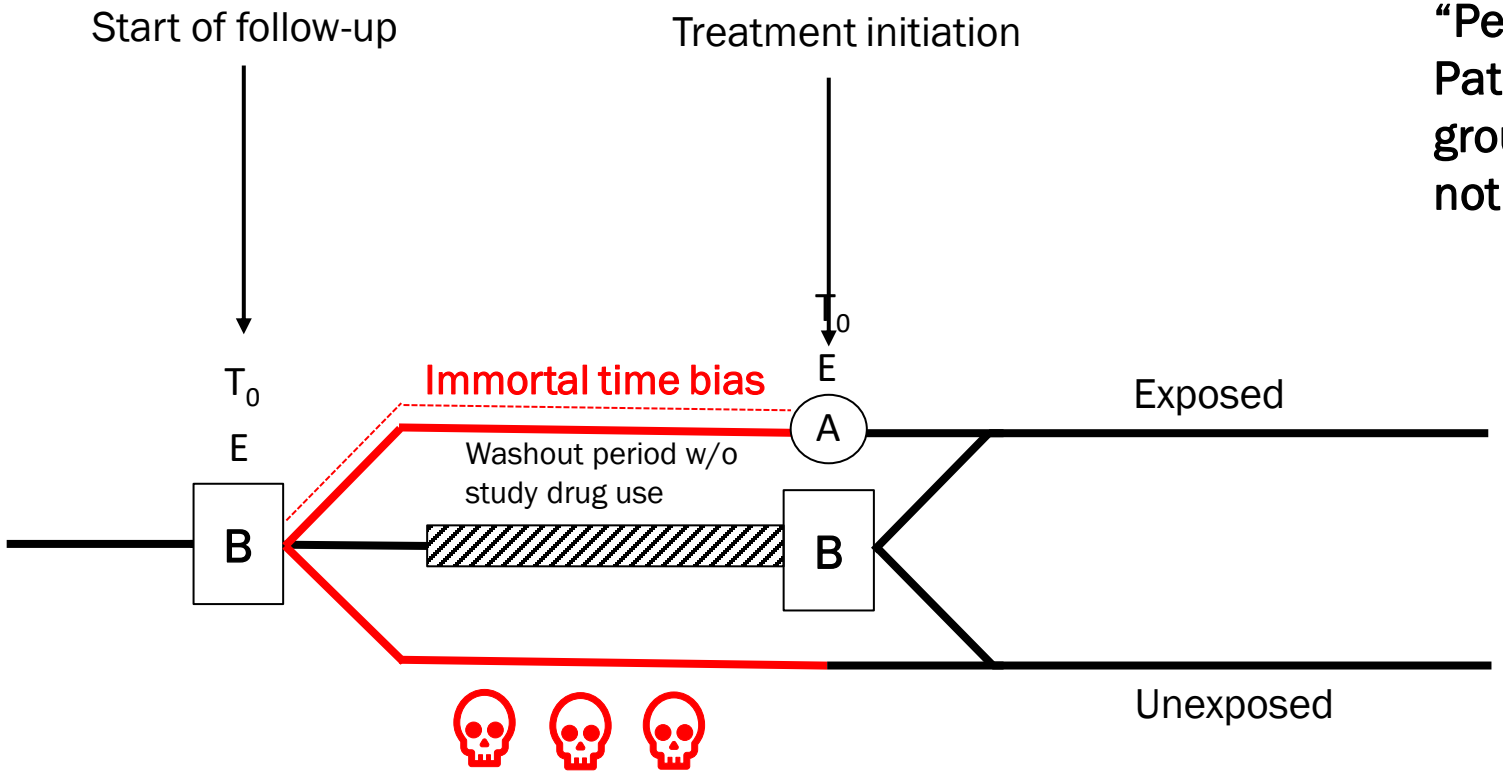
Original Investigation

Renoprotective Effect of Renin-Angiotensin-Aldosterone System Blockade in Patients With Predialysis Advanced Chronic Kidney Disease, Hypertension, and Anemia

Ta-Wei Hsu, MD; Jia-Sin Liu, MS; Szu-Chun Hung, MD; Ko-Lin Kuo, MD; Yu-Kang Chang, PhD; Yu-Chi Chen, PhD; Chih-Cheng Hsu, MD, DrPH; Der-Cherng Tarng, MD, PhD

What happens if we start follow-up *before* treatment initiation?

Observational cohort study

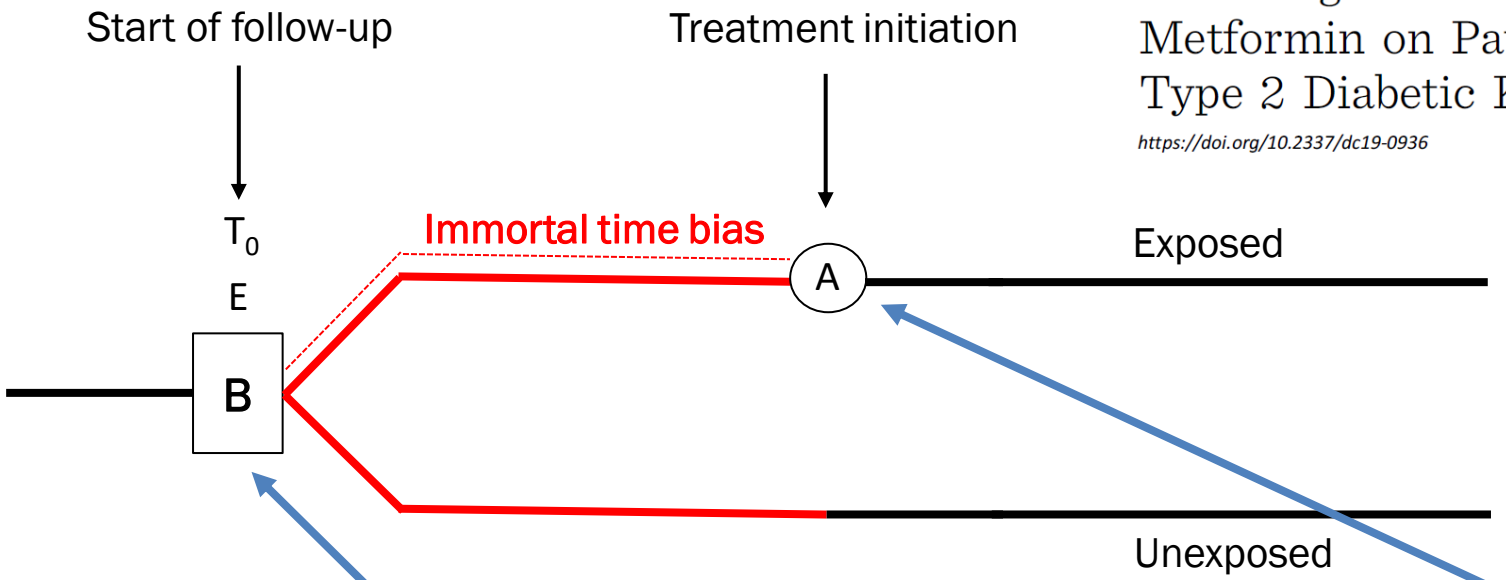


"Peeking into the future":
Patients are classified into exposure groups based on treatment they have not yet received

T_0 = start of follow-up
E = meeting all eligibility criteria
A = treatment initiation

Immortal time bias occurs whenever the start of follow-up is *before* treatment initiation

Immortal time bias example



Diabetes Care 1

The Long-term Effects of Metformin on Patients With Type 2 Diabetic Kidney Disease

Soie Kwon,[1,2] Yong Chul Kim,[1] Jae Yoon Park,[3] Jeonghwan Lee,[2] Jung Nam An,[4] Clara Tammy Kim,[5] Sohee Oh,[6] Seokwoo Park,[7,8] Dong Ki Kim,[1,8] Yun Kyu Oh,[2,8] Yon Su Kim,[1] Chun Soo Lim,[2,8] and Jung Pyo Lee[2,8]

https://doi.org/10.2337/dc19-0936

"The follow-up period for each patient was defined as the interval between the first and last dates of creatinine measurements."

"A metformin user was defined as a patient who was prescribed metformin for longer than 90 days during the follow-up period."

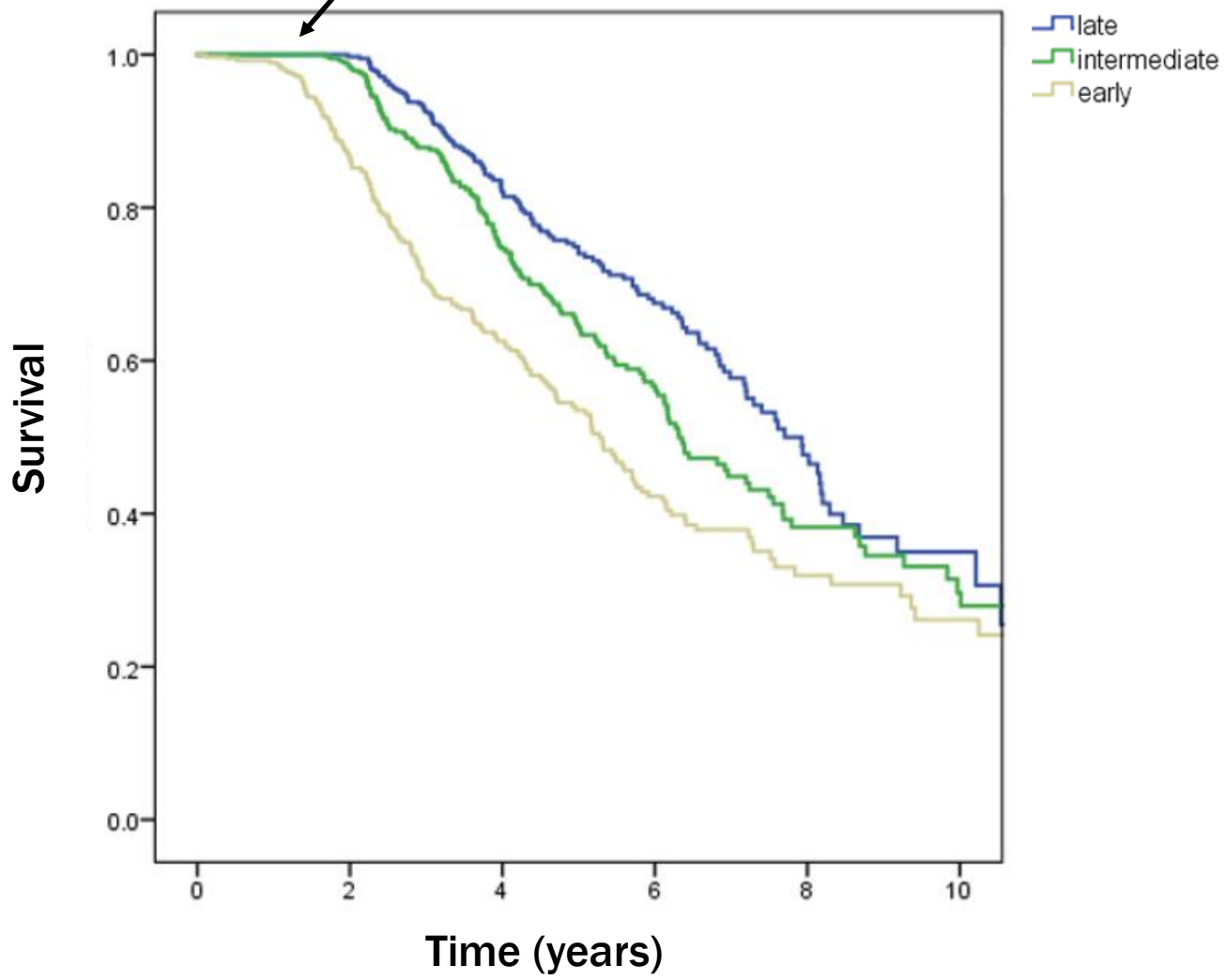
How to spot immortal time bias: implausibly large effects

RESULTS

All-cause mortality and incident ESRD were lower in the metformin group according to the multivariate Cox analysis. Because the two groups had significantly different baseline characteristics, PSM was performed. After matching, metformin usage was still associated with lower all-cause mortality (adjusted hazard ratio [aHR] 0.65; 95% CI 0.57–0.73; $P < 0.001$) and ESRD progression (aHR 0.67; 95% CI 0.58–0.77; $P < 0.001$). Only one event of metformin-associated lactic acidosis was recorded. In both the original and PSM groups, metformin usage did not increase the risk of lactic acidosis events from all causes (aHR 0.92; 95% CI 0.668–1.276; $P = 0.629$).

How to spot immortal time bias: suspicious KM curves

Advanced CKD population, yet nobody dies.....



Recap: target trial emulation and aligning TEA at baseline

How

Make target trial protocol

In the hypothetical RCT, TEA would be aligned at baseline, so in your observational emulation as well!

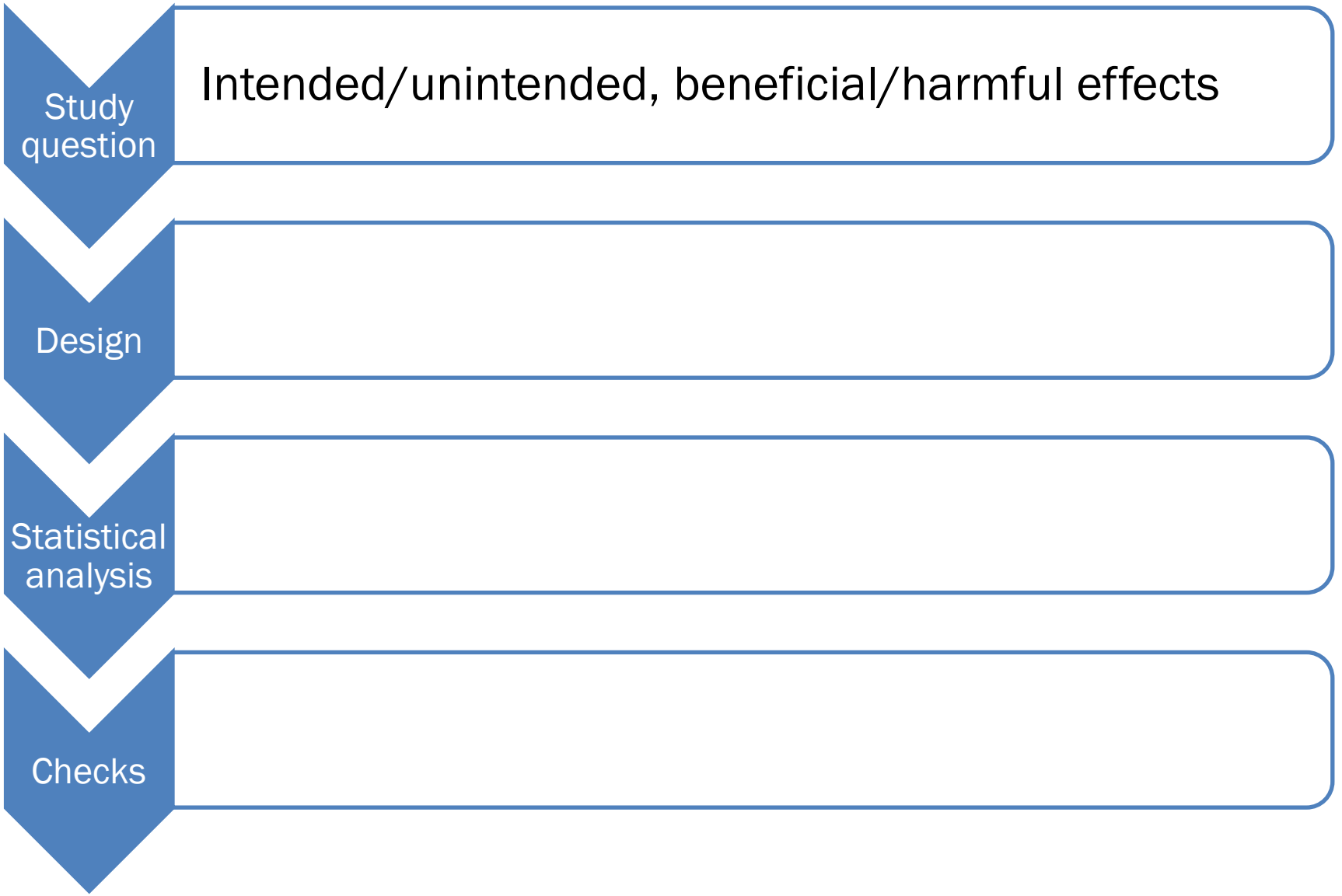
Why

Avoid self-inflicted biases!

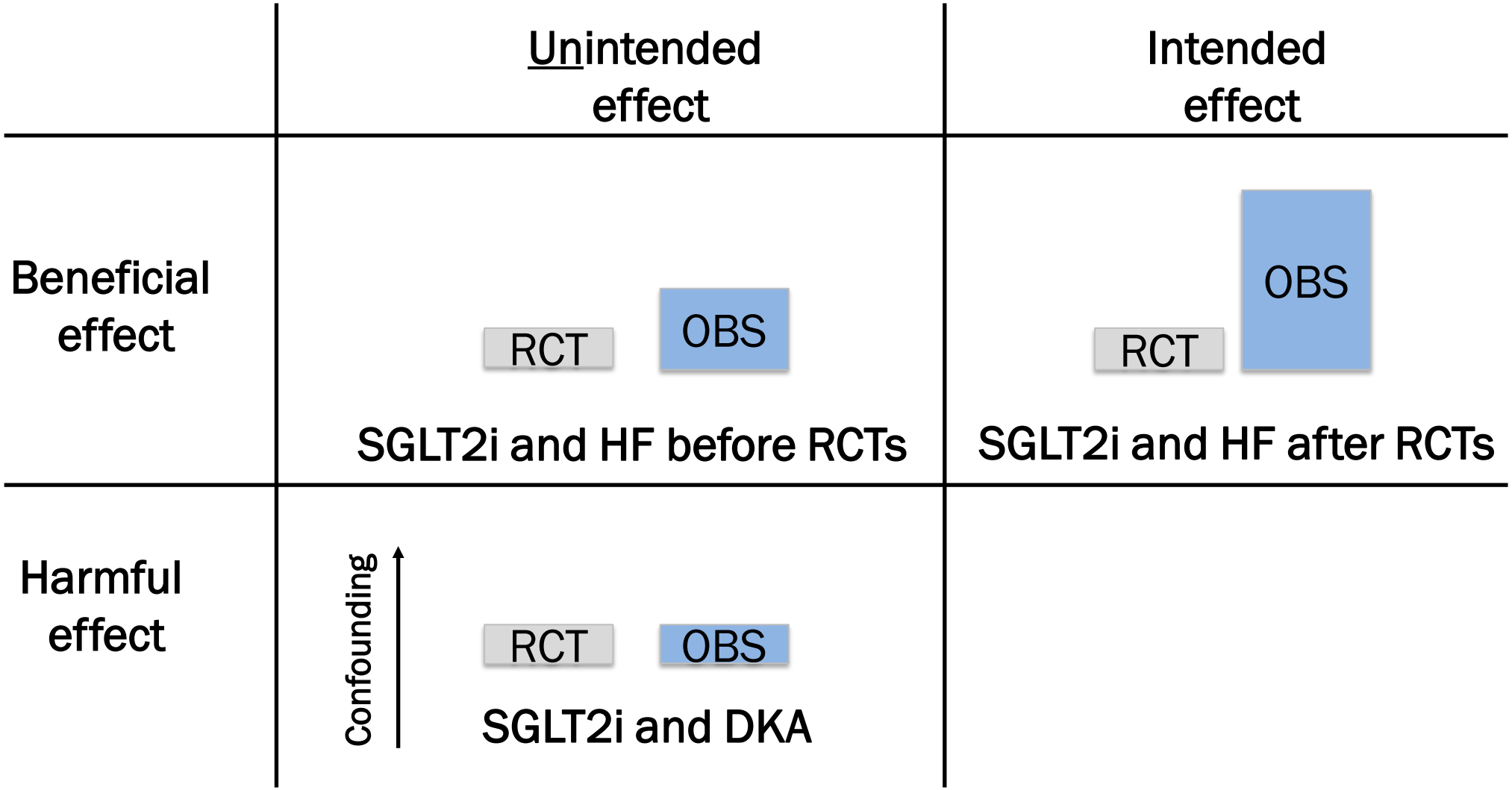
- Prevalent user
- Immortal time

Influence of these biases often much bigger than (residual) confounding

Combatting confounding



Not all questions are equally susceptible to confounding



Adapted from Schneeweiss

Combatting confounding

Study question	Intended/unintended, beneficial/non-beneficial effects
Design	Active comparator design
Statistical analysis	
Checks	

Active comparators help

Table 1. Baseline Characteristics of the Study Populations

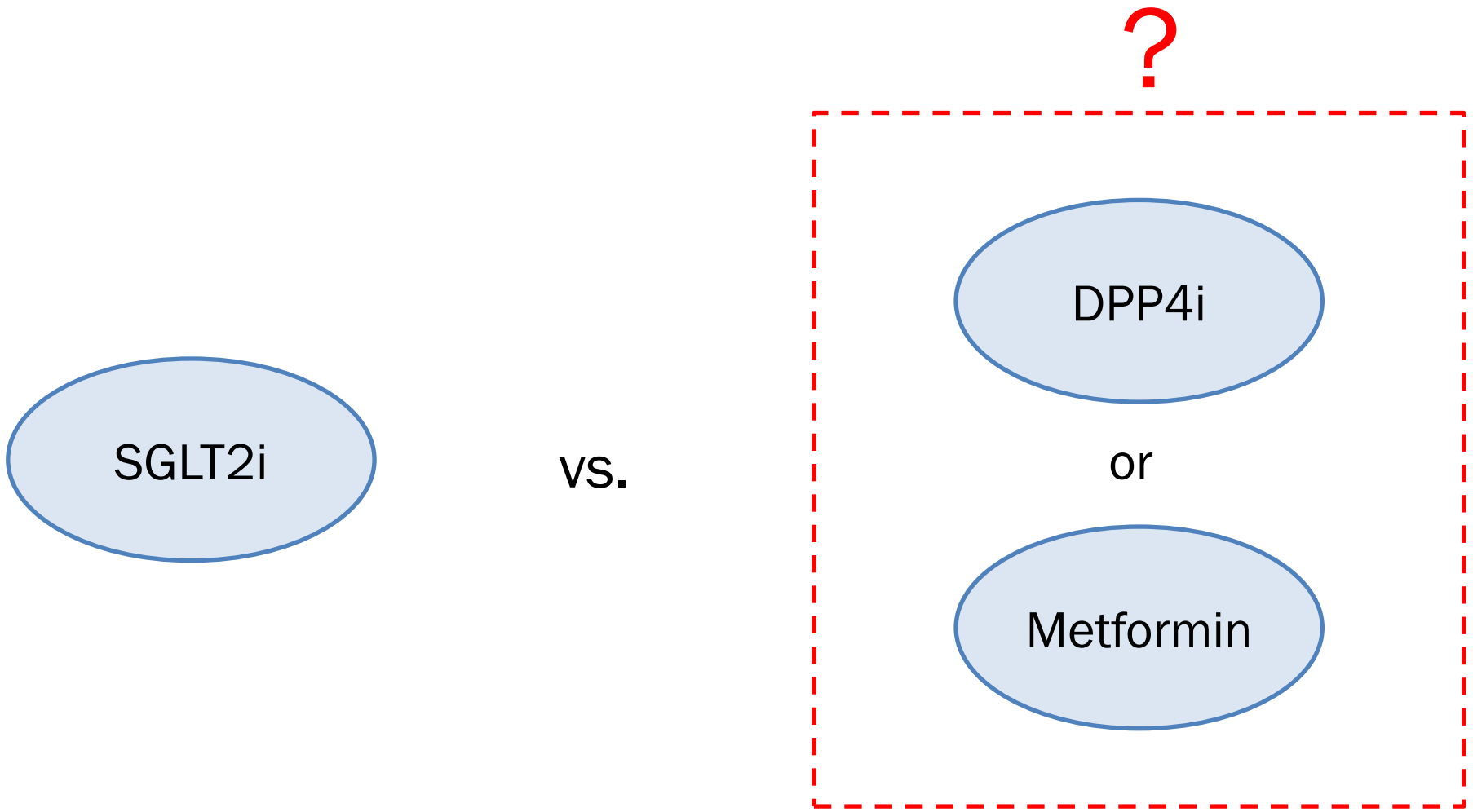
Variable	Atherosclerosis Risk in Communities Study		
	PPI Users (n = 322)	H_2 Receptor Antagonist Users[a] (n = 956)	Nonusers (n = 9204)
Age, mean (SD), y	62.8 (5.5)	63.1 (5.5)	62.5 (5.6)
Male sex, %	42.5	39.3	44.4
Prevalent medical condition, %			
Hypertension	54.3	50.0	44.8
Diabetes mellitus	14.9	18.0	15.6
Cardiovascular disease	13.7	14.1	10.8
Concomitant medication use, %			
Antihypertensive	55.3	48.5	39.9
ACE-I/ARB	16.8	13.4	12.9
Diuretic	16.1	12.1	9.6
Aspirin	64.9	67.6	54.9
Nonsteroidal anti-inflammatory drug	27.6	32.8	33.2
Statin	20.2	13.6	10.3
Anticoagulant	1.9	2.8	1.7

We can reduce confounding by applying an active comparator design

JAMA Intern Med. 2016;176(2):238-46

But they are not a golden bullet

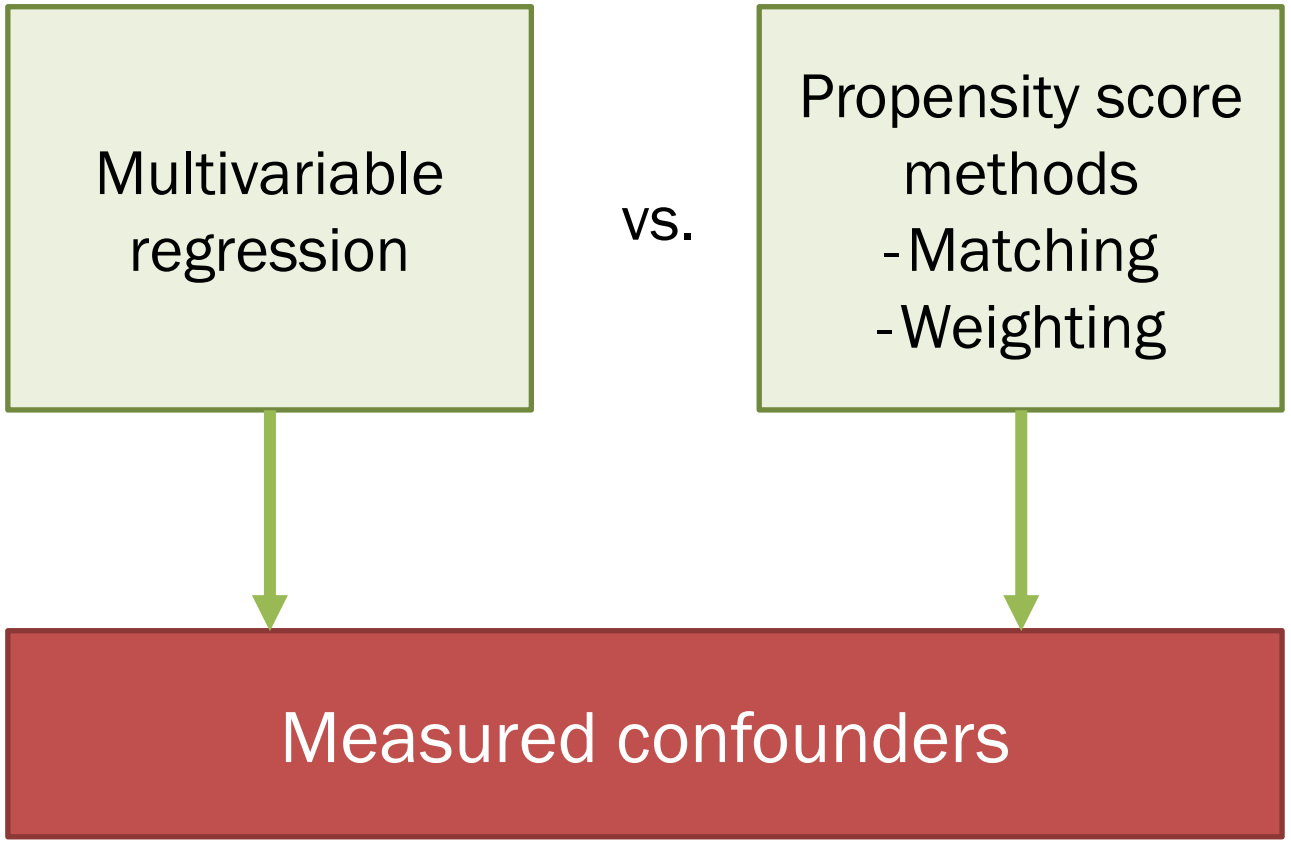
Some active comparators are better than others



Combatting confounding

Study question	Intended/unintended, beneficial/non-beneficial effects
Design	Active comparator design
Statistical analysis	Adjustment for measured confounders
Checks	

Adjusting for measured confounders



- In general, similar results
- In setting of time-varying confounding, methods such as weighting are required

Combatting confounding

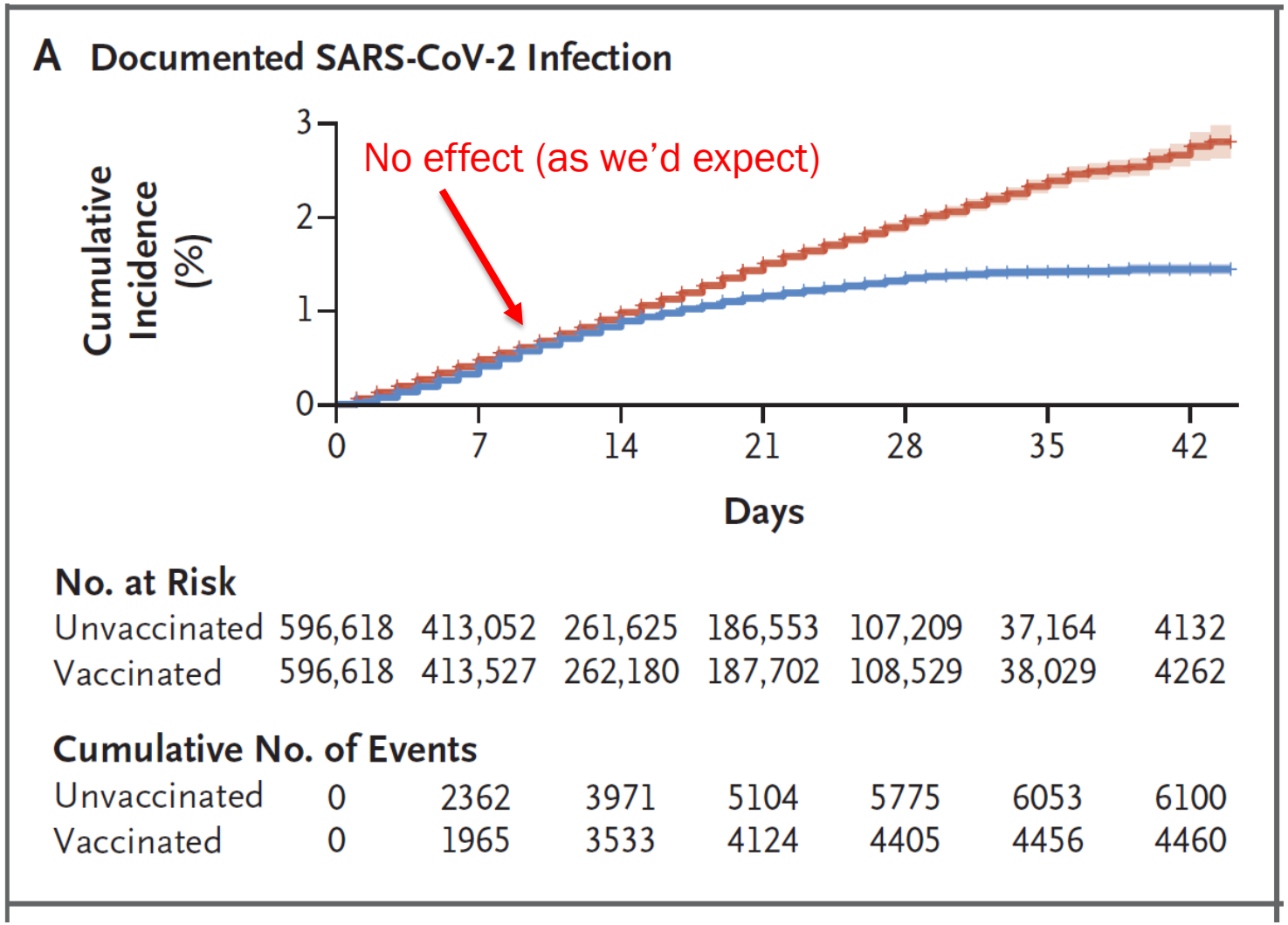
Study question	Intended/unintended, beneficial/non-beneficial effects
Design	Active comparator design
Statistical analysis	Adjustment for measured confounders
Checks	Benchmark against trial results, positive/negative controls

Benchmarking against trial findings

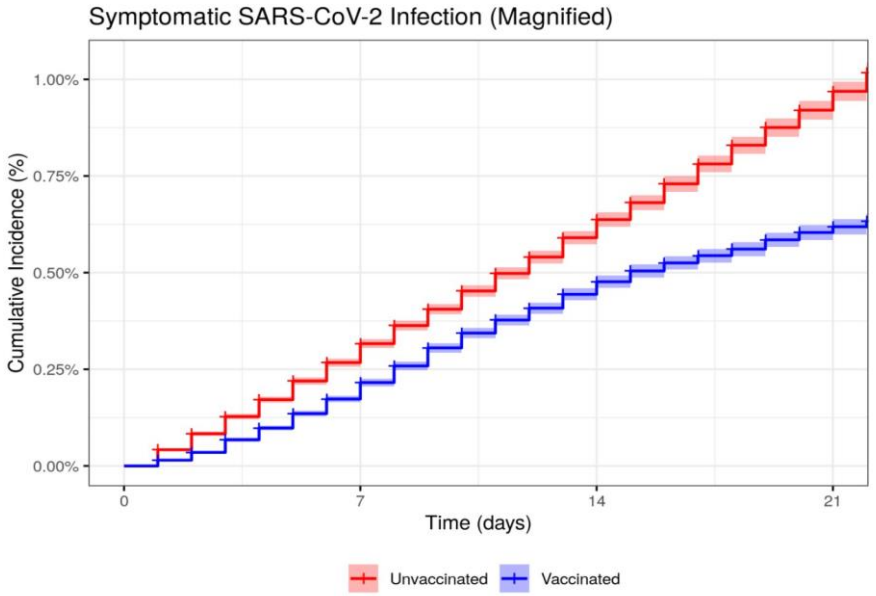
	CKD G4-5	CKD G3	CKD G3	CKD G3
	Observational estimates, HR (95% CI)	Observational estimates, HR (95% CI)	Network meta-analysis Xie et al. AJKD 2016, OR (95% CI)	Meta-analysis Ninomiya et al. BMJ 2013, HR (95% CI)
KRT	0.79 (0.69-0.89)	0.68 (0.48-0.98)	ACE: 0.65 (0.51-0.80) ARB: 0.75 (0.54-0.97)	-
Death	0.97 (0.88-1.07)	0.97 (0.81-1.17)	-	1.00 (0.89-1.13)
MACE	1.00 (0.88-1.15)	1.09 (0.85-1.40)	ACE: 0.94 (0.75-1.12) ARB: 0.86 (0.70-1.03)	-

Fu et al. AJKD. 2021;77(5):719-29

Negative control



Without sufficient confounder adjustment, we'd see this:



Dagan et al. NEJM. 2021;384:1412-23

Confounding and residual confounding

- The discussion whether there is residual confounding (and more importantly, how big it is), is nuanced

- Influenced by many things:
  - Study question, design, statistical analysis
  - Data (which variables are present in dataset?)

- Not all observational studies are the same

- **Not all observational studies are biased!**

Take home points

1. Baseline: think about TEA 
2. Prevalent user bias and immortal time bias arise because of not following the design of a trial
3. Target trial emulation ensures aligning TEA at baseline
4. Confounding in observational studies is not black-and-white and can be addressed in various steps throughout your study

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