Leiden University
Medical Center

Target trial emulation

Edouard Fu, PhD FERA

Assistant Professor

Department of Clinical Epidemiology, LUMC

Talk based on

REVIEW www.jasn.org

JASN Journal of the American Society of Nephrology

Target Trial Emulation to Improve Causal Inference from Observational Data: What, Why, and How?

Edouard L. Fu

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

What will we discuss this lecture?

1. Why do we need observational studies?
2. What is target trial emulation?
3. Why do we need target trial emulation?
4. Is target trial emulation a magic bullet?

1. Why do we need observational studies?

What are causal questions?

Causal questions:

- Is it better to start an ACEi or calcium channel blocker in CKD?
- Should we start dialysis earlier or later?

Non-causal questions:

- How accurate is CKD-EPI 2021 equation compared with measured GFR?
- Do patients with higher level of biomarker X have a worse prognosis?

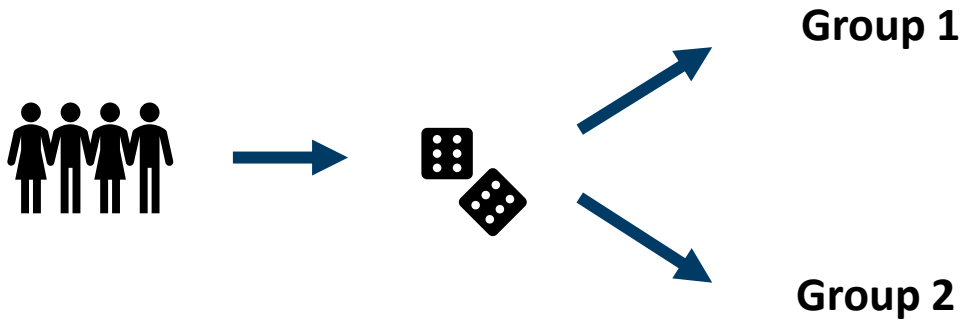
What is the best course of action we could take?

Can be answered with RCT (in theory)

Do not involve interventions

In an ideal world…

For each causal question: perform an RCT



Sometimes we have no trial evidence

CLINICAL EPIDEMIOLOGY www.jasn.org

Stopping Renin-Angiotensin System Inhibitors in Patients with Advanced CKD and Risk of Adverse Outcomes: A Nationwide Study

Edouard L. Fu,[1] Marie Evans,[2] Catherine M. Clase,[3] Laurie A. Tomlinson,[4] Merel van Diepen,[1] Friedo W. Dekker,[1] and Juan J. Carrero[5]

December 2020

The NEW ENGLAND JOURNAL of MEDICINE

Renin–Angiotensin System Inhibition in Advanced Chronic Kidney Disease

Sunil Bhandari, Ph.D., Samir Mehta, M.Sc., Arif Khwaja, Ph.D., John G.F. Cleland, M.D., Natalie Ives, M.Sc., Elizabeth Brettell, B.Sc., Marie Chadburn, Ph.D., and Paul Cockwell, Ph.D., for the STOP ACEi Trial Investigators*

November 2022

Sometimes trial evidence is inconclusive

Circulation

A Randomized Controlled Trial Comparing Apixaban to the Vitamin K-antagonist Phenprocoumon in Patients on Chronic Hemodialysis: The AXADIA-AFNET 8 study

Holger Reinecke, Christiane Engelbertz, Rupert Bauersachs, Günter Breithardt, Hans-Herbert Echterhoff, Joachim Gerβ, Karl Georg Haeusler, Bernd Hewing, Joachim Hoyer, Sabine Juergensmeyer, Thomas Klingenheben, Guido Knapp, Lars Christian Rump, Hans Schmidt-Guertler, Christoph Wanner, Paulus Kirchhof and Dennis Goerlich

44% of intended sample size
HR 0.93 (0.53-1.65)

Circulation

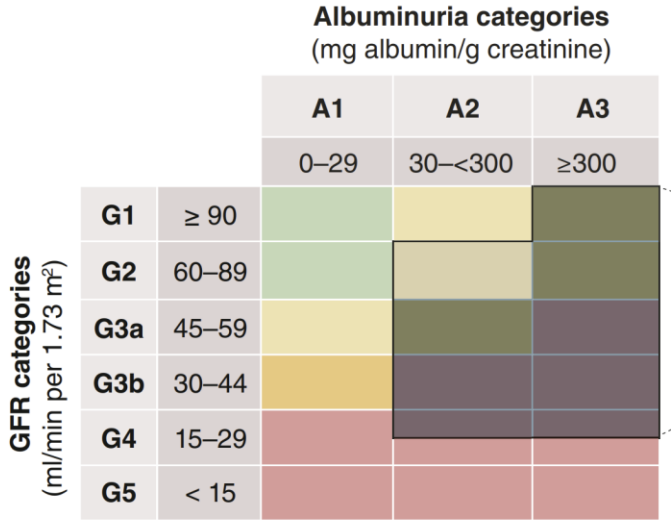
Apixaban for Patients with Atrial Fibrillation on Hemodialysis: A Multicenter Randomized Controlled Trial

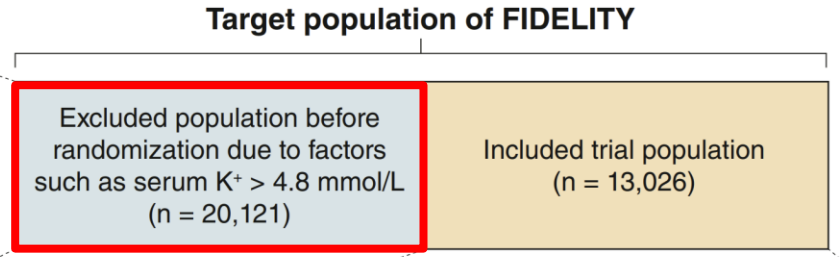
Sean D. Pokorney, Glenn M. Chertow, Hussein R. Al-Khalidi, Dianne Gallup, Pat Dignaco, Kurt Mussina, Nisha Bansal, Crystal A. Gadegbeku, David A. Garcia, Samira Garonzik, Renato D. Lopes, Kenneth W. Mahaffey, Kelly Matsuda, John P. Middleton, Jennifer A. Rymer, George H. Sands, Ravi Thadhani, Kevin L. Thomas, Jeffrey B. Washam, Wolfgang C. Winkelmayer and Christopher B. Granger

20% of intended sample size
HR 1.20 (0.63-2.30)

Conclusion of abstract RENAL-AF: "**There was inadequate power to draw any conclusion** regarding rates of major or clinically relevant non-major bleeding comparing apixaban and warfarin in patients with AF and ESKD on hemodialysis."

Trial populations are highly selected





Risk–benefit profile of finerenone among included patients

	Outcome	Population	HR/RR	3-year risk (%)	NNT/ NNH
Benefit	Kidney composite	Overall	0.77	↓1.7	60
	ESKD (dialysis/transplant)	Overall	0.80	↓0.6*	167*
	Cardiovascular composite	Overall	0.86	↓2.2	46
Risk	Investigated-reported hyperkalemia	eGFR < 60 eGFR ≥ 60	2.2* 1.7*	↑9.8* ↑3.2*	10* 31*
	Permanent discontinuation due to hyperkalemia	eGFR < 60 eGFR ≥ 60	3.0 2.3	↑1.6* ↑0.3*	63* 333*
	Hospitalization due to hyperkalemia	eGFR < 60 eGFR ≥ 60	5.3 9.0	↑1.1* ↑0.3*	91* 333*

*Calculated from reported absolute risks

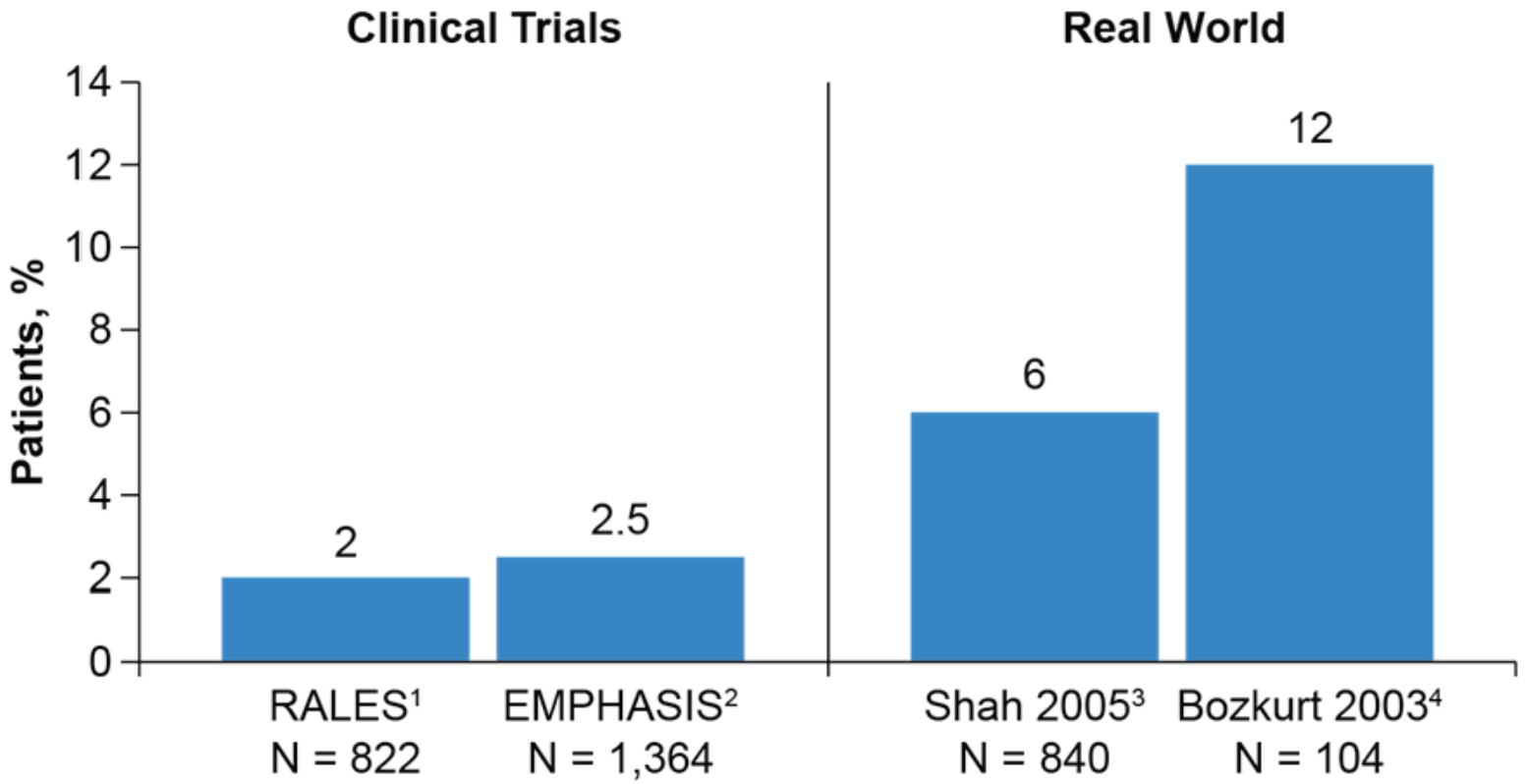
Finerenone in chronic kidney disease and type 2 diabetes: the known and the unknown

Edouard L. Fu[1], Alexander Kutz[1] and Rishi J. Desai[1]

Kidney International (2023) **103,** 30–33

Consequences of highly selected populations

Hyperkalemia risk for mineralocorticoid receptor antagonists



[a] Hyperkalemia defined as K^+ ≥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.

Routinely collected healthcare data to the rescue!

The patient journey (time)

Healthcare use

- Inpatient
- Outpatient

Diagnoses

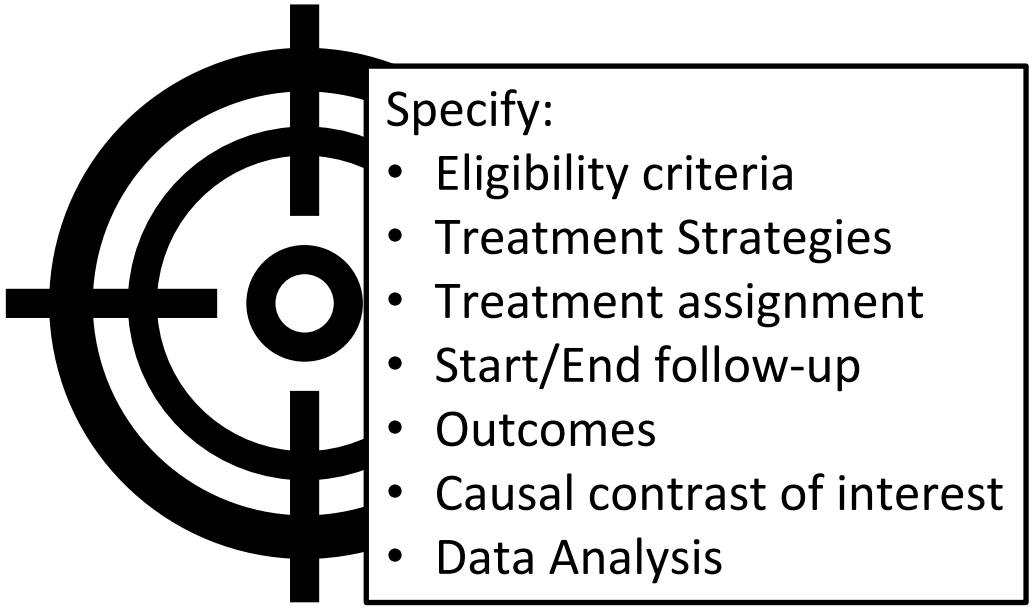
Laboratory measurements

Drugs

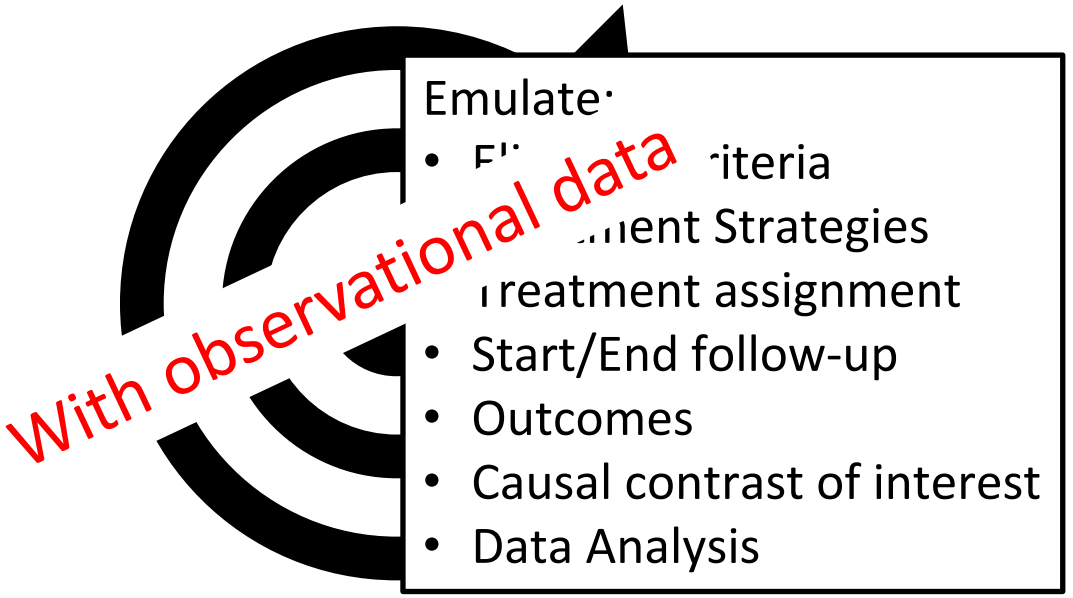
Adapted from Carrero

2. What is target trial emulation?

Target trial emulation framework



Target trial specification



Target trial emulation

Hernán et al. AJE 2016

An example of specified target trial 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 causal effect of RASi (ACEi or ARB) vs. CCB on kidney replacement therapy, MACE, all-cause death in advanced CKD

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

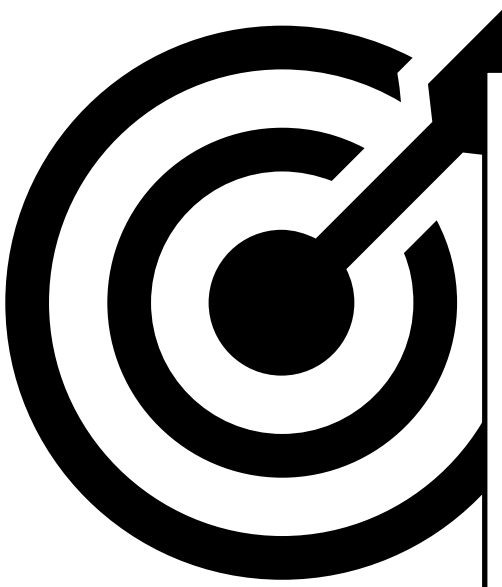
Brief protocol of the target trial

Hypothetical target trial we would ideally conduct:

Component	Hypothetical target trial specification
Eligibility	Adult patients with CKD G4 (i.e. eGFR <30 ml/min/1.73m^2), no history of kidney transplantation and no use of RASi or CCB in previous 180 days
Treatment strategies	1. Initiate RASi (ACEi or ARB) and always use during follow-up 2. Initiate CCB and always use during follow-up
Treatment assignment	Randomization, no blinding
Outcome	Kidney replacement therapy, all-cause mortality, major adverse cardiovascular events
Follow-up	Starts at randomization and ends at occurrence of endpoint, death or 5 years
Causal contrast	Intention-to-treat effect, per protocol effect
Analysis plan	Cox proportional hazards regression, propensity score weighting, … etc

Fu et al. AJKD 2021

Target trial emulation



Emulate:

- Eligibility criteria
- Treatment Strategies
- Treatment assignment
- Start/End follow-up
- Outcomes
- Causal contrast of interest
- Data Analysis

1. Make treatment groups correctly
2. Adjust for baseline (and time-varying) confounding
3. Estimate your treatment effect of interest

Target trial **emulation**

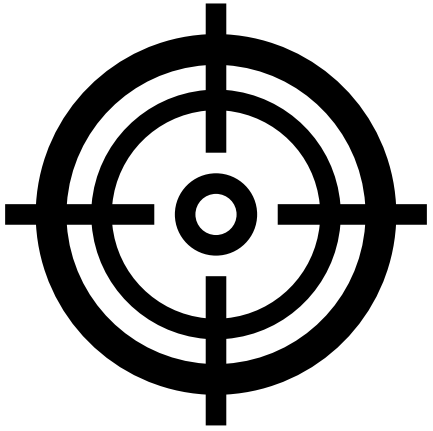
What target trial emulation is and what it is not

- Framework for designing & analyzing observational studies
- Specification step & emulation step
- Can be applied to every causal question on interventions

- A specific design (“sequential trials”, “clone-censor-weight”)

3. Why do we need target trial emulation?

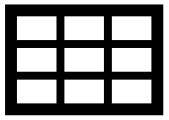
Many observational studies don’t specify the target…



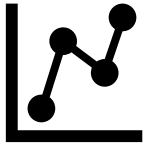
“Causal estimand”

“We investigated the association between metformin and major adverse cardiovascular events”

1. Start metformin *vs*. Do not start metformin
2. Start metformin and always use *vs*. Never start metformin
3. Start metformin and use for 6 months *vs*. Start metformin and use for 12 months
4. Start treatment metformin when event Y occurs *vs*. Start metformin when event Z occurs

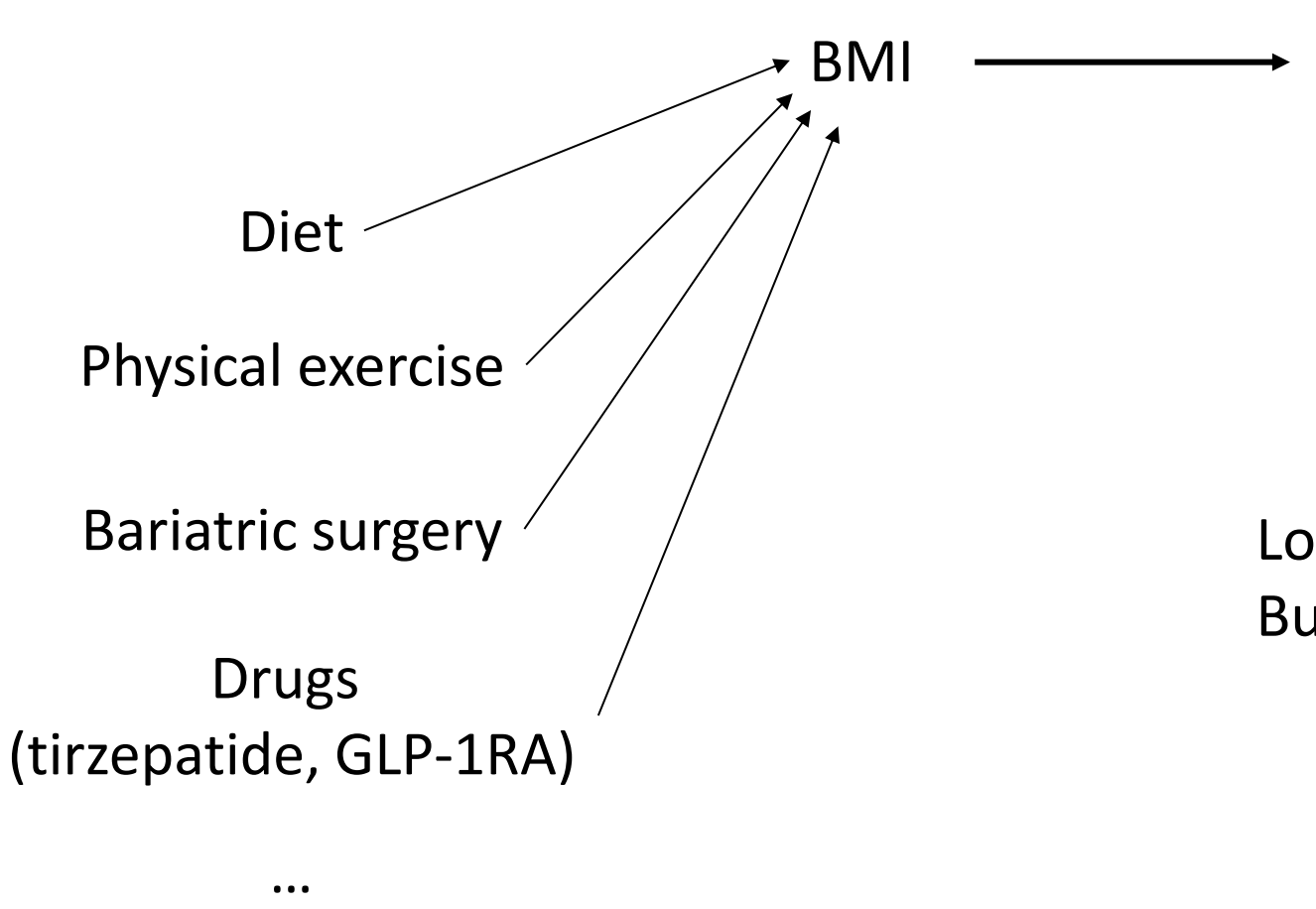


Different data



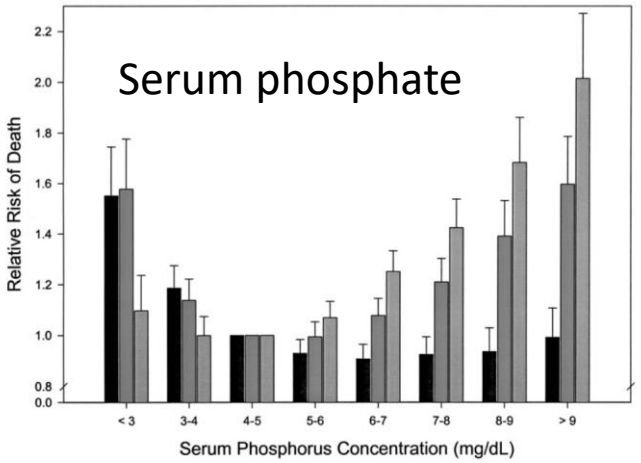
Different statistical analysis

TTE forces investigators to ask questions about interventions



Lowering BMI from 30 to 25
But how? Through which intervention?

What would the target trial look like?

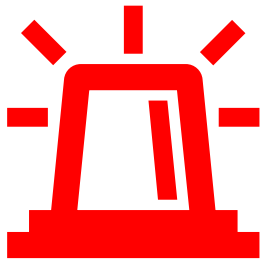


Design and Rationale of HiLo: A Pragmatic, Randomized Trial of Phosphate Management for Patients Receiving Maintenance Hemodialysis

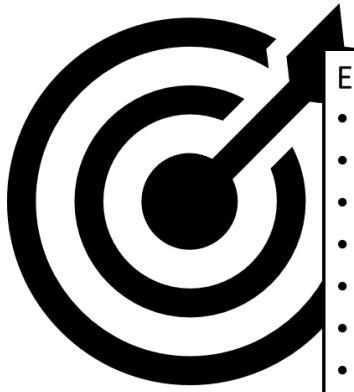
Daniel L. Edmonston, Tamara Isakova, Laura M. Dember, Steven Brunelli, Amy Young, Rebecca Brosch, Srinivasan Beddhu, Hrishikesh Chakraborty, and Myles Wolf

Intervention: Phosphate binder prescriptions and dietary recommendations to achieve the "Hi" serum phosphate target (≥6.5 mg/dL) or the "Lo" serum phosphate target (<5.5 mg/dL).

This target trial can be emulated!



Most observational studies do not make treatment groups correctly, and use flawed designs introducing bias



Emulate:
- Eligibility criteria
- Treatment Strategies
- Treatment assignment
- Start/End follow-up
- Outcomes
- Causal contrast of interest
- Data Analysis

1. Make treatment groups correctly
2. Adjust for baseline confounding
3. Estimate your treatment effect of interest

Target trial **emulation**

Most studies use flawed designs

Prevalence of Avoidable and Bias-Inflicting Methodological Pitfalls in Real-World Studies of Medication Safety and Effectiveness

Katsiaryna Bykov[1,*], Elisabetta Patorno[1], Elvira D'Andrea[1], Mengdong He[1], Hemin Lee[1], Jennifer S. Graff[2] and Jessica M. Franklin[1]

57% suffered from immortal person-time (→ immortal time bias)

44% suffered from prevalent user selection (→ depletion of susceptibles bias)

These would have been prevented if TTE was applied

Bykov et al. CPT 2022

Early vs. late dialysis initiation in ESKD

Timing of Dialysis Initiation and Survival in ESRD

Nephrol Dial Transplant (2010) 25: 2616–2624
doi: 10.1093/ndt/gfq308
Advance Access publication 2 June 2010

Original Articles

NDT Nephrology Dialysis Transplantation

...oi: 10.2215/CJN.06230909

Dovepress
open access to scientific and medical research

ORIGINAL RESEARCH

...rate at dialysis initiation on survival in patients with advanced chronic kidney disease: what is the effect of lead-time bias?

...mpact of the clinical conditions at dialysis initiation on mortality in incident haemodialysis patients: a national cohort study in Taiwan

...Early Initiation of Dialysis

Kidney Disease... Vol 46, No 5 (November), 2005: pp 887-896

Association between estimated glomerular filtration rate a...

Hemodialysis International 2021; 25:188–197

...ephrol Dial Transplant (2009) 24: 3186–3192
...oi: 10.1093/ndt/gfp189
...dvance Access publication 23 April 2009

ORIGINAL ARTICLE

Adequacy

Association of early initiation of dialysis with all-cause and cardiovascular mortality: A propensity score weighted analysis of the United States...

...urvival and dialysis initiation: comparing British Columbia and ...cotland registries

...505–2512, 2003

...is May Be Harmful

Impact of Timing of Initiation of Dialysis on Mortality

...lues in New End-Stage ...ients

Estimated GFR at Dialysis Initiation and Mortality in Children and Adolescents

Check for updates

...seases, Vol 34, No 4 (October), 1999: pp 694-701

Immortal time bias

Lead time bias

Depletion of susceptibles bias

IDEAL trial vs. observational studies

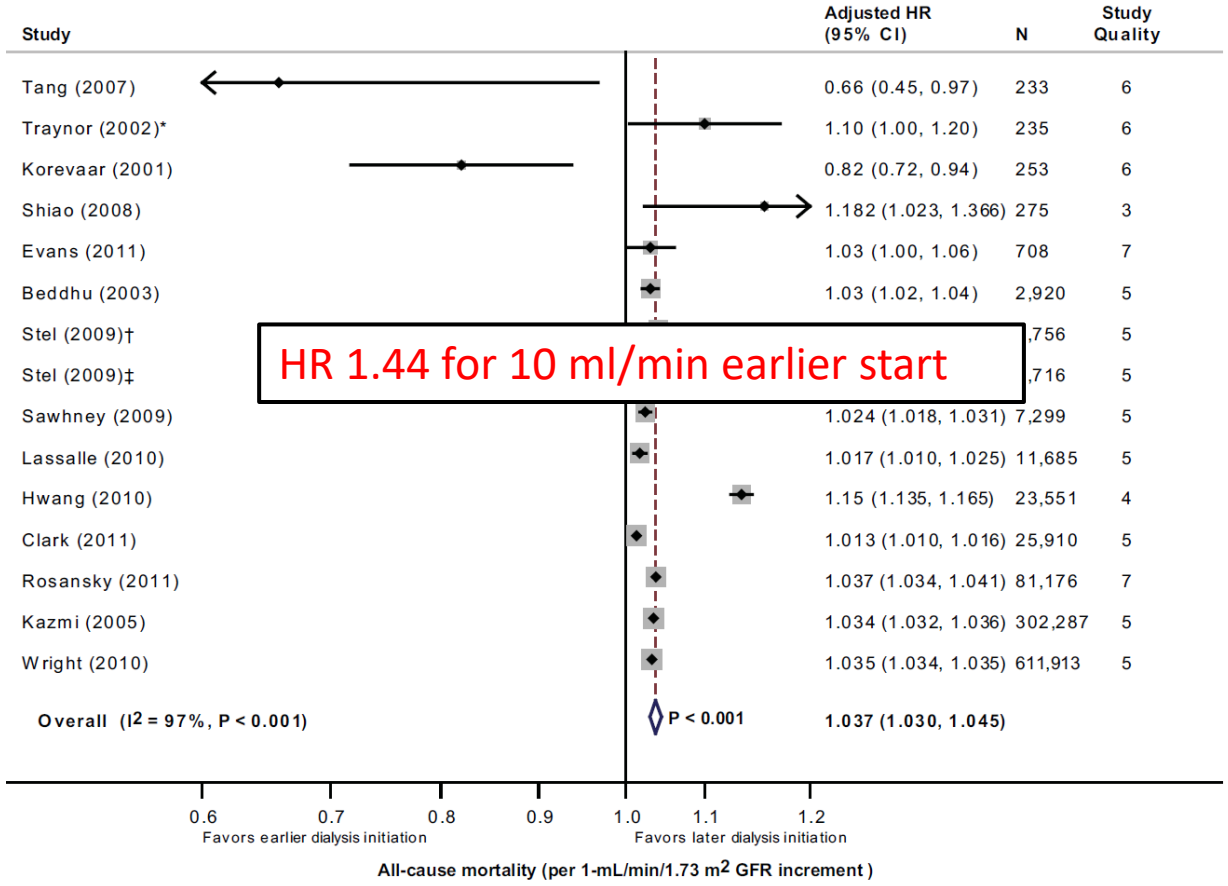
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 AUGUST 12, 2010 VOL. 363 NO. 7

A Randomized, Controlled Trial of Early versus Late Initiation of Dialysis

Randomized IDEAL trial (NEJM, 2010) showed no difference for all-cause mortality between early vs. late dialysis initiation: HR 1.04 (0.83-1.30)

Meta-analysis of observational studies showed strong survival disadvantage for early dialysis start



Susantitaphong et al. AJKD 2012

These biases can be prevented!

	Correct study design	Biases introduced	Confounding adjustment necessary	Hazard ratio (95% CI) early vs. late
Randomized IDEAL trial	☑	-	No	1.04 (0.83-1.30)
Trial emulation analysis	☑	-	Yes	0.96 (0.94-0.99)
Biased method #1	⊘	Immortal time bias	Yes	1.46 (1.19-1.78)
Biased method #2	⊘	Lead time bias, Depl. suscept. bias	Yes	1.58 (1.37-1.83)

HR of 1.46 and 1.58 very similar in magnitude to previous biased observational studies (n = 21)

BMJ 2021. Fu et al.

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)

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,[3] Pär Eliasson,[3] Ann-Marie Svensson,[3,4] Stefan Franzén,[4,5] Soffia Gudbjörnsdottir,[3,4] Jan Hveem,[6,7] Christian Jonasson,[6,7] Viktor Wintzell,[1] Mads Melbye,[1,2] Anders Svanström[1,2]

Emulated a target trial

Good observational study:

HR 0.80 (0.69-0.92)

Confounding as the culprit

- In many examples, confounding not primary reason for discrepancy between trials and observational studies

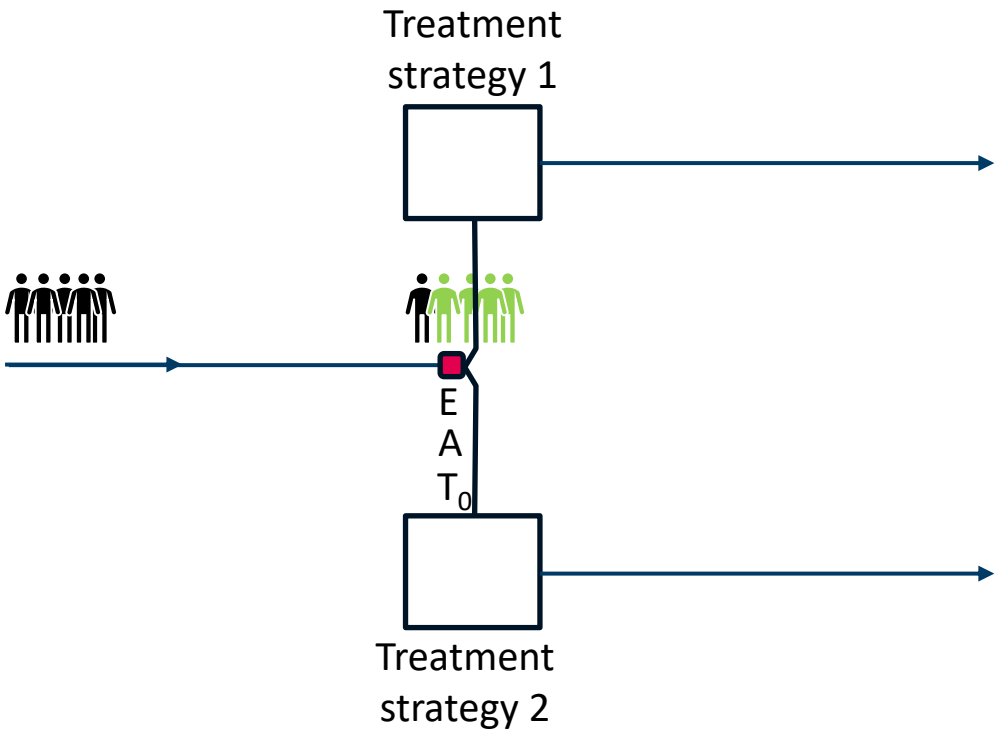
- Due to biases introduced by investigator

  → Could have been prevented by target trial emulation

- To make treatment groups correctly, need to adhere to fundamental design principle

Fundamental design principle

What happens in an RCT?



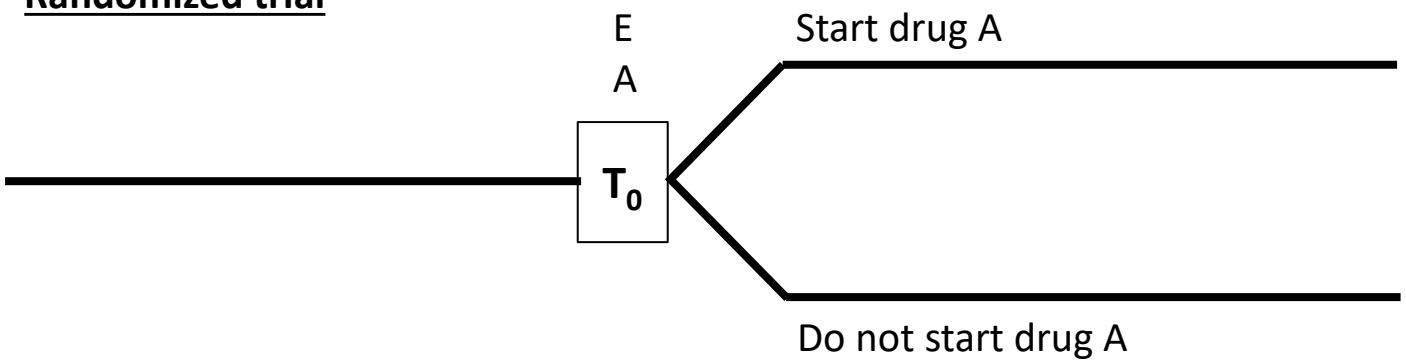
3 components aligned at randomization:

- Eligibility criteria are met (E)
- Assignment of treatment strategy (A)
- Start of follow-up (= **time zero**, T_0)

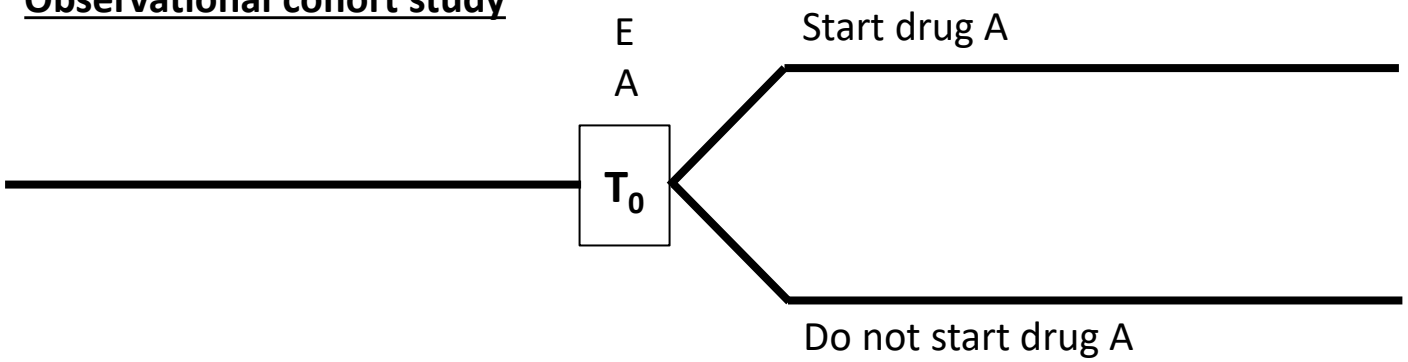
Aligning these 3 components in observational study prevents bias

What should happen in an observational study?

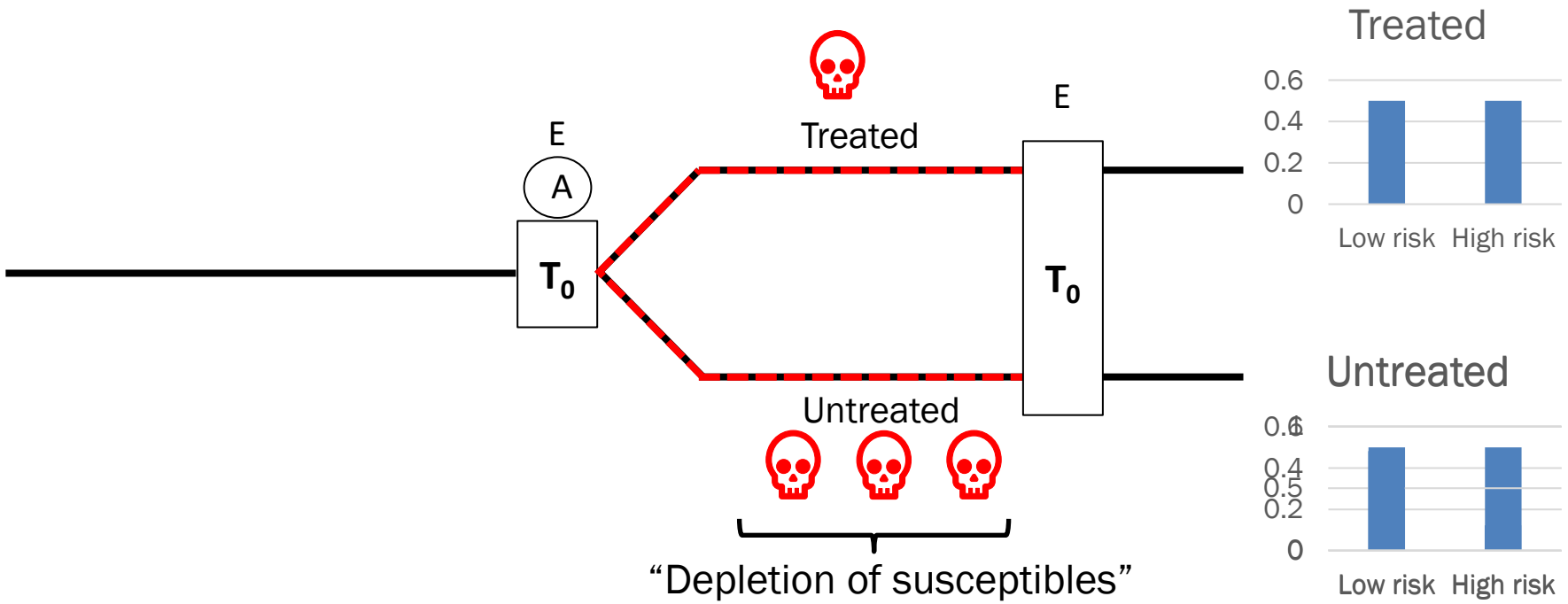
Randomized trial



Observational cohort study



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

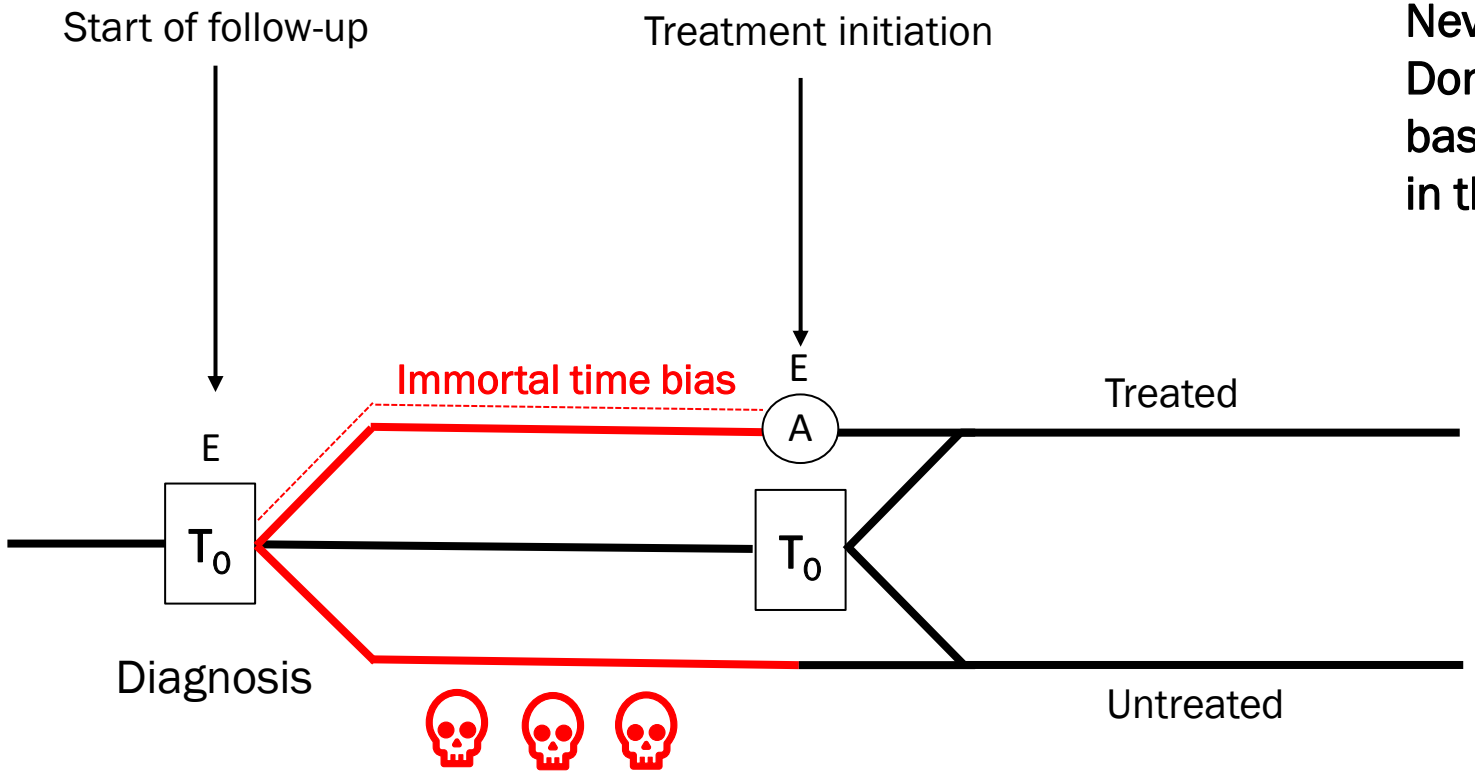


If treatment is truly protective…

<u>"Depletion of susceptibles bias"</u> occurs whenever the start of follow-up is *after* treatment initiation (medication studies use "prevalent user bias"), and is a form of selection bias

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

Observational cohort study

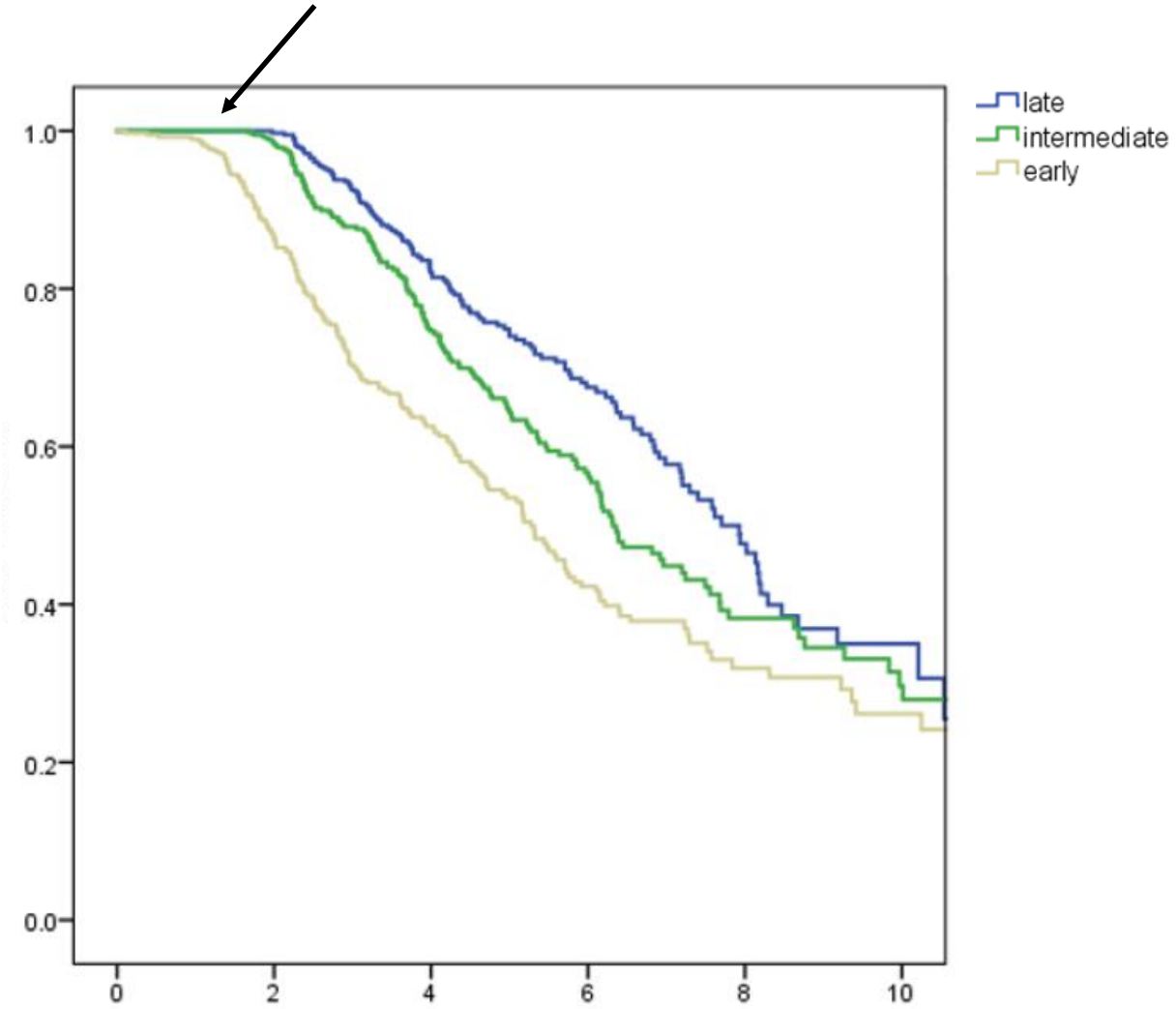


Never "peek into the future":
Don't classify patients into treatment arms based on treatment they receive in the future!

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

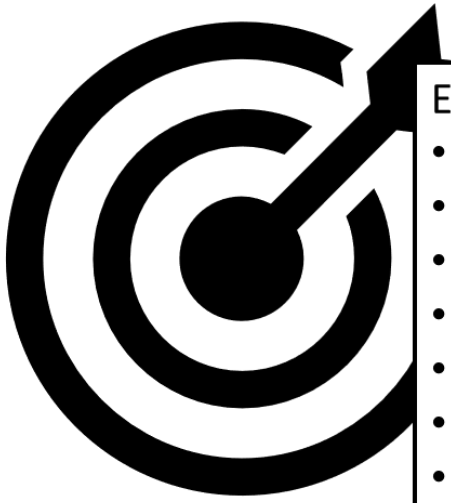
How to spot immortal time bias: suspicious survival curves

Advanced CKD population, yet nobody dies…….



4. Is target trial emulation a magic bullet?

Target trial emulation does not solve the problem of unmeasured confounding



Emulate:
- Eligibility criteria
- Treatment Strategies
- Treatment assignment
- Start/End follow-up
- Outcomes
- Causal contrast of interest
- Data Analysis

1. Make treatment groups correctly
2. Adjust for baseline confounding
3. Estimate your treatment effect of interest

Prevents immortal time & selection bias

Getting step 2 right requires measuring and appropriately adjusting for all confounders

Target trial **emulation**

ESC European Society of Cardiology

European Heart Journal (2023) **00**, 1–16
https://doi.org/10.1093/eurheartj/ehad273

CLINICAL RESEARCH
Heart failure and cardiomyopathies

Sodium–glucose cotransporter 2 inhibitors vs. sitagliptin in heart failure and type 2 diabetes: an observational cohort study

Edouard L. Fu [1]*, Elisabetta Patorno [1], Brendan M. Everett[2,3], Muthiah Vaduganathan [2], Scott D. Solomon [2], Raisa Levin[1], Sebastian Schneeweiss [1], and Rishi J. Desai [1]

Our study with clear residual confounding

PICO:

P: HFpEF, type 2 diabetes, ≥65 years

I: SGLT2i

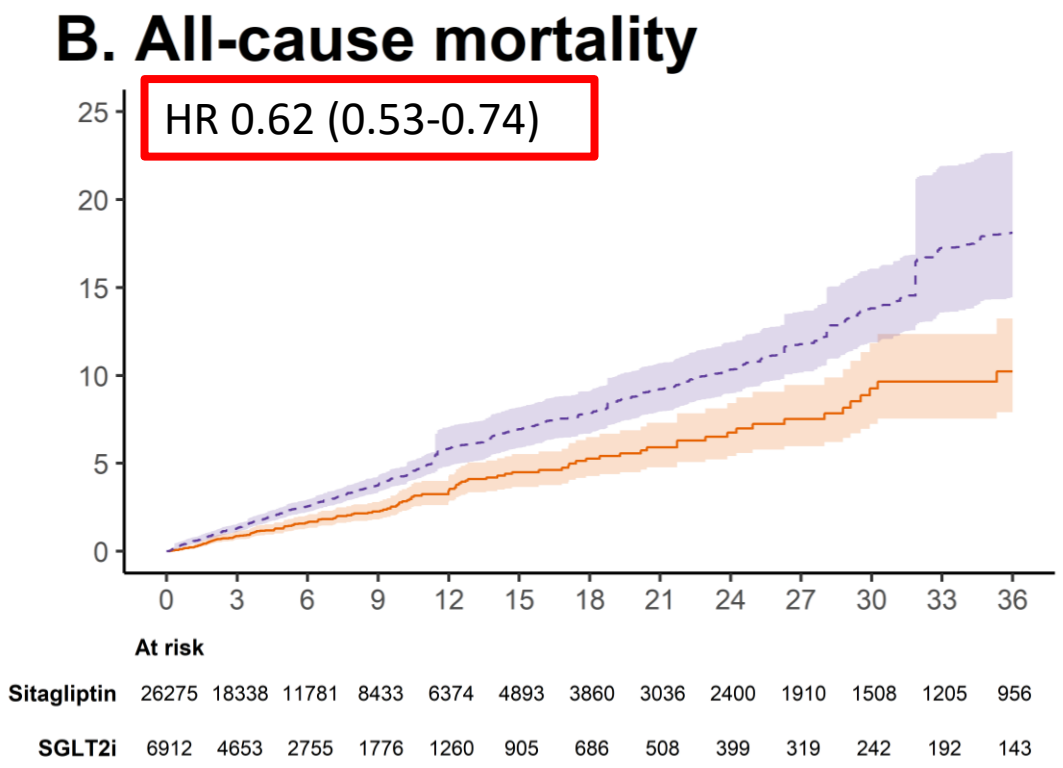
C: Sitagliptin (DPP4i)

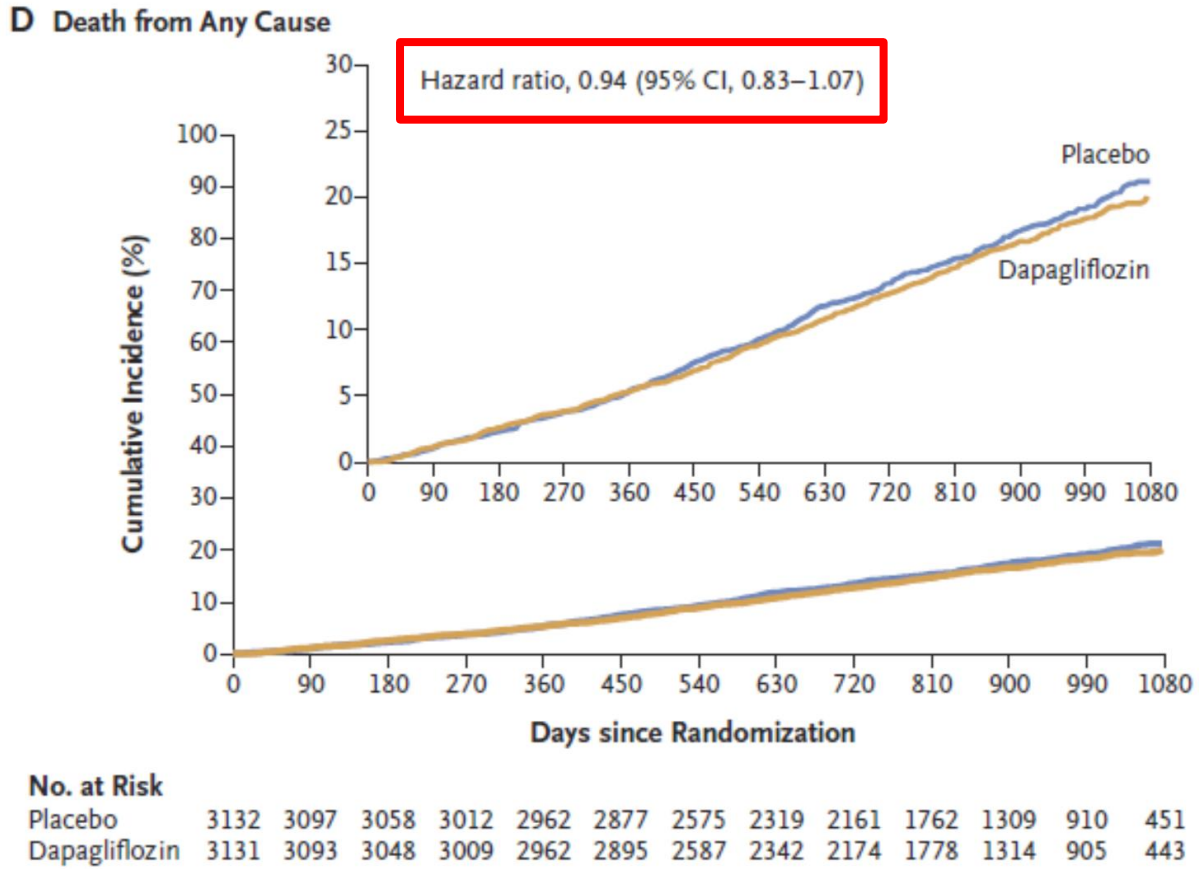
O: All-cause death, heart failure hospitalization

Data source: Medicare claims data

Active-comparator new-user design [no self-inflicted biases], adjusting for >100 potential confounders (demographics, comorbidities, medications, healthcare utilization, healthy behavior markers)

Our study with clear residual confounding





Combatting confounding

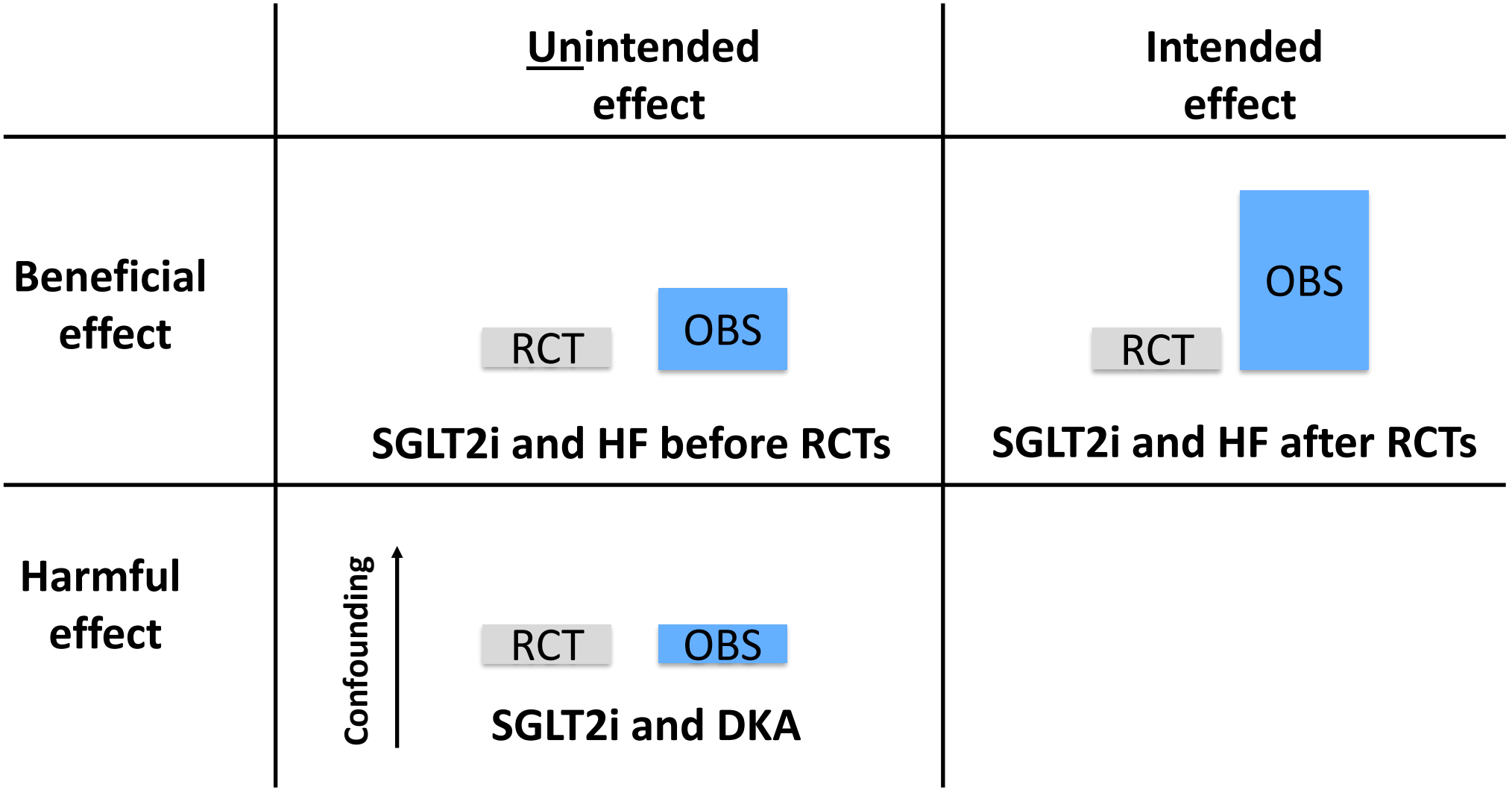
Study question

- Intended/unintended, beneficial/harmful effects
- Active comparators

Statistical analysis

Checks

Not all questions equally susceptible to confounding



Adapted from Schneeweiss

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

Combatting confounding

Study question

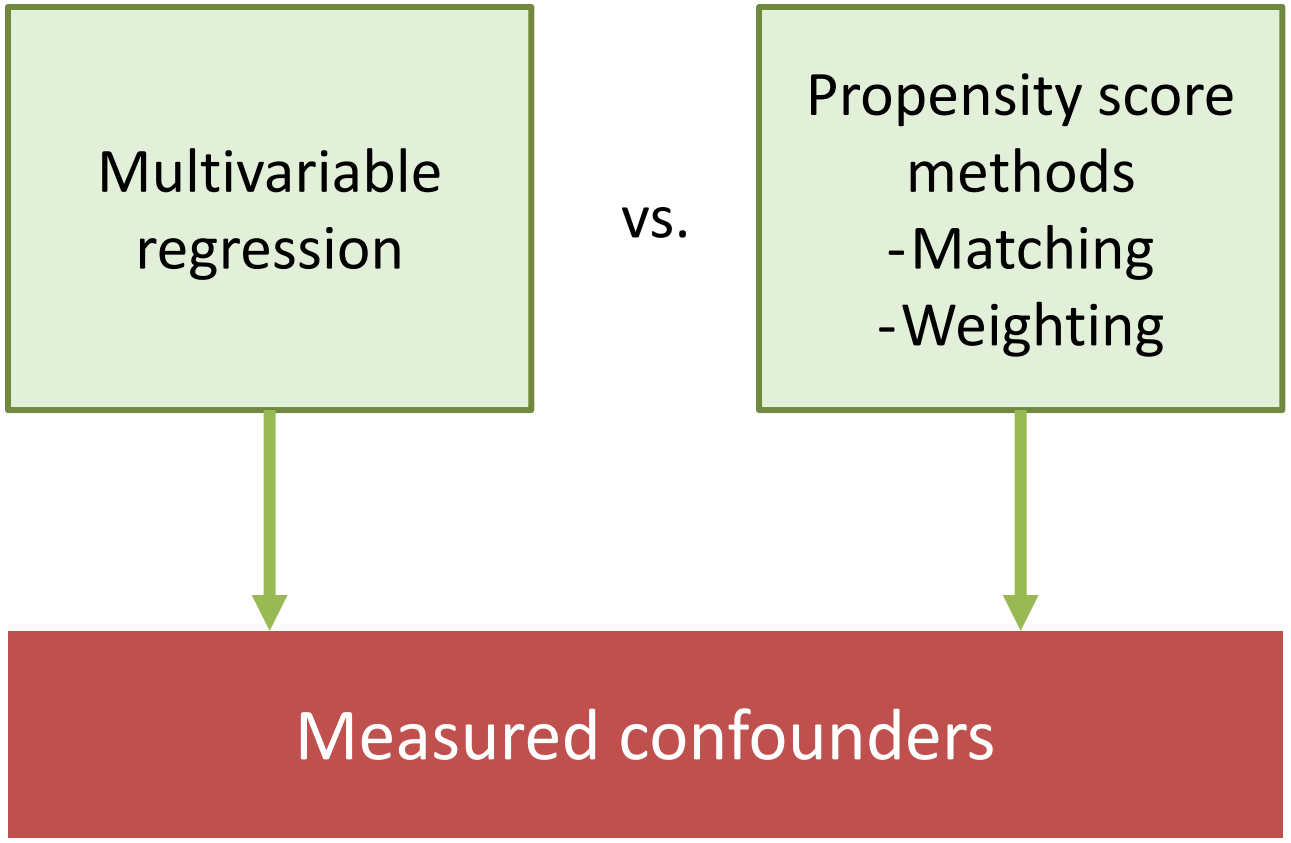
- Intended/unintended, beneficial/harmful effects
- Active comparators

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/harmful effects
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Statistical analysis

Adjustment for measured confounders

Checks

- Benchmark against trial results
- Negative control outcomes

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

Using negative control outcomes to correct for residual confounding

				Primary composite	All-cause death	Hospitalization for Heart Failure
				0.72 (0.67-0.77)	0.70 (0.63-0.78)	0.64 (0.58-0.70)
Negative control outcome	**Assumed true HR**	**Observed HR (95% CI)**	**Estimated bias on log scale**	**Corrected HR's for residual confounding**		
Non-CV death	1.00	0.81 (0.65-1.01)	0.21	0.89 (0.72-1.11)	0.87 (0.71-1.10)	0.78 (0.62-0.99)
Ischemic stroke	1.00	0.83 (0.65-1.06)	0.18	0.86 (0.67-1.10)	0.84 (0.65-1.09)	0.77 (0.60-0.99)

Is there residual confounding?

Whether there is residual confounding (& more importantly, its magnitude) is a nuanced discussion

Depends e.g. on **study question** and **data quality**

- Generally, unintended-harmful effects (SGLT2i→DKA) often have less confounding than intended-beneficial effects (SGLT2i→HHF)
- Active comparators (SGLT2i vs. GLP-1RA) often have less confounding than. nonactive comparators (SGLT2i vs. no SGLT2i)
- Some data sources have richer information (ejection fraction, lab data)

Benchmarking & negative control outcomes can increase confidence

Take home points

1. TTE is a framework for designing and analyzing observational studies

2. Involves specifying the target trial protocol and then emulating it with observational data

3. The design of RCTs should be explicitly emulated by carefully aligning eligibility criteria, treatment assignment and start of follow-up; This prevents unnecessary biases (immortal time, depletion of susceptibles)

4. Trial emulation does not solve the problem of confounding, but confounding is nuanced, and there are some tricks

5. For each causal question you have: Think about the target trial

Leiden University
Medical Center

Questions

e.l.fu@lumc.nl