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Drawing causal inference from observational studies in nephrology

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Disclosure of Interest

Do you have, or have you had during the past 2 years, any formal association with a company or other interested party?

No

Do you have, or have you had during the past 2 years, received any grants from an entity

Yes, grants from the Netherlands Organization for Scientific Research and Dutch Kidney Foundation

Do you have, or have you had during the past 2 years, received any non-financial support from an entity?

No

Are you a member (current) of any kind of committee, board, WG, etc. of another scientific association with similar aims as ERA

No

Content

1. What are causal questions and why do we need observational studies?

2. The importance of target trial emulation

3. Combatting confounding

1. What are causal questions and why do we need observational studies?

Answering **causal questions** using observational data

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

Why do we need observational studies?

- Preferably, each causal question would be answered in large-scale randomized controlled trials
- May not always be feasible, ethical or timely
- Number of clinical questions outpaces the number of trials that can be done

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."

Answering causal questions using **observational data**

- Observational data: data in which persons were not randomized to particular treatments

- Often come from administrative data (e.g. claims), electronic health records, registries…

Routinely collected healthcare data

The patient journey (time)

Healthcare use
- Inpatient
- Outpatient

Diagnoses

Laboratory measurements

Drugs

Adapted from Carrero

2. The importance of target trial emulation

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]

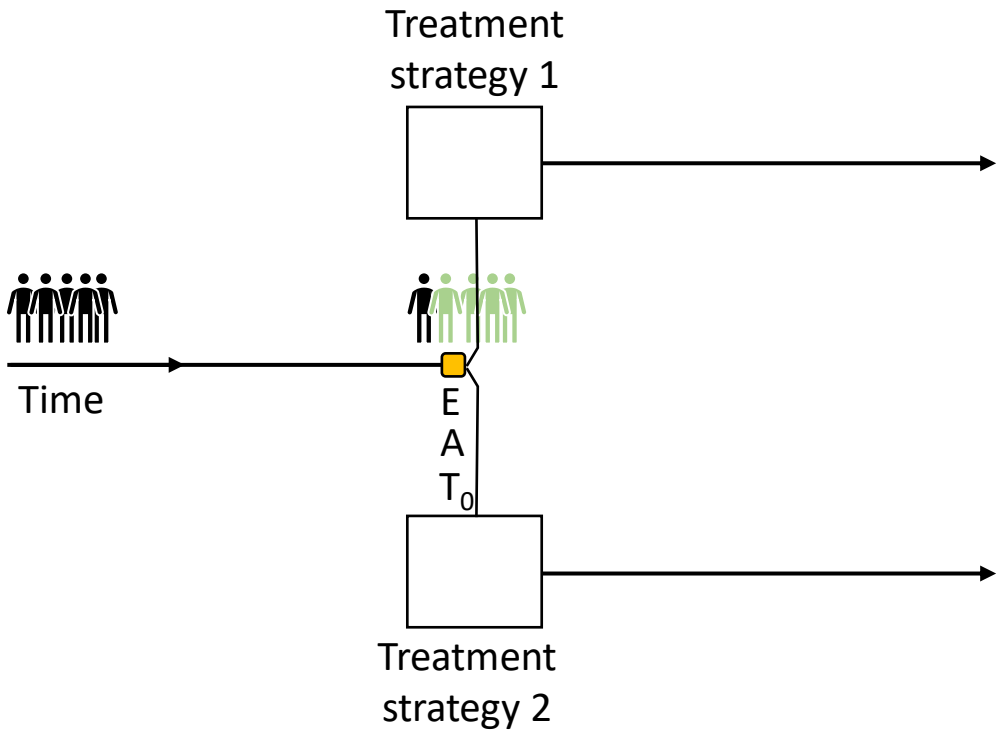
57% suffered from immortal time bias

44% suffered from prevalent user selection

→ These biases are prevented if target trial emulation is used

Target trial emulation: emulate RCT design

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

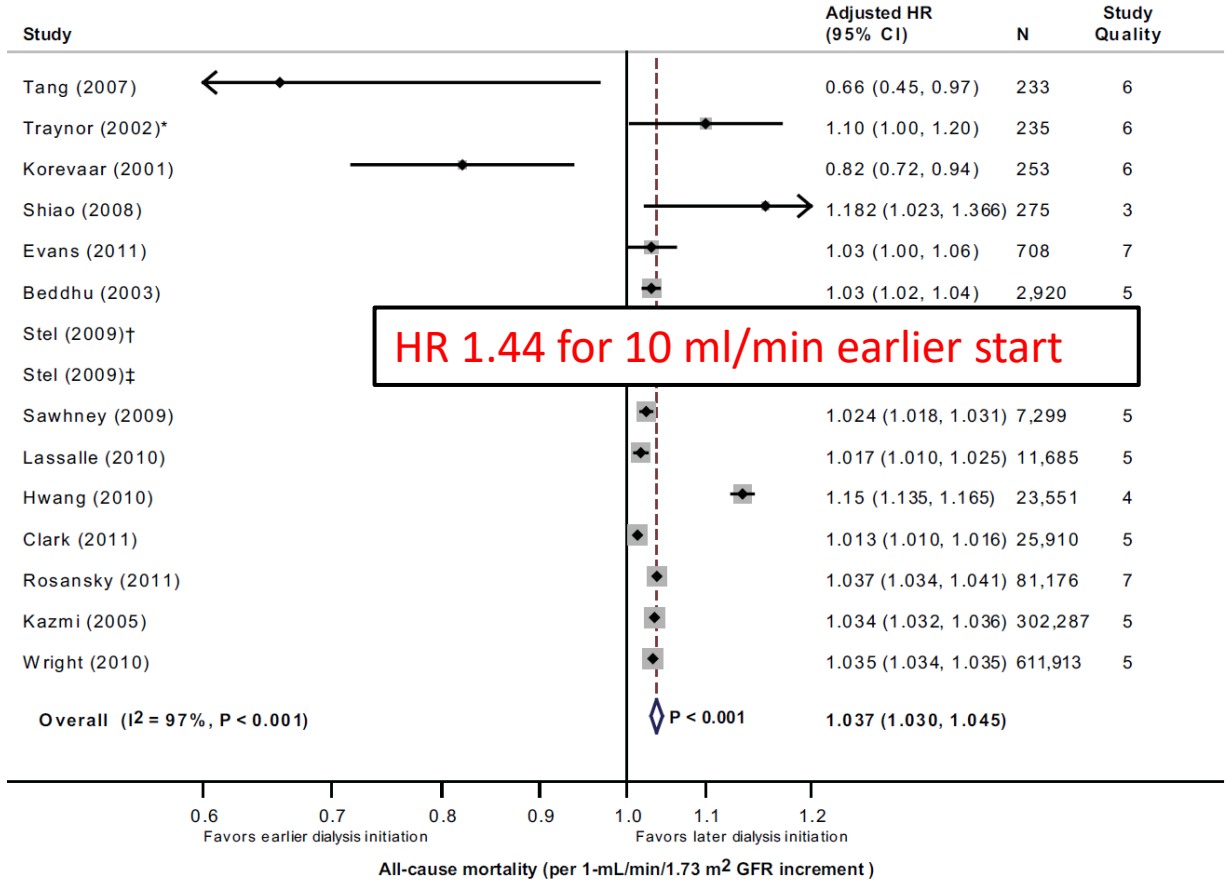
IDEAL trial vs. observational studies

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

thebmj

RESEARCH

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]

Discrepancy due to:

- unnecessary biases which can be prevented by target trial emulation? **or**
- unmeasured confounding?

Target trial emulation helps to estimate causal effects

	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)

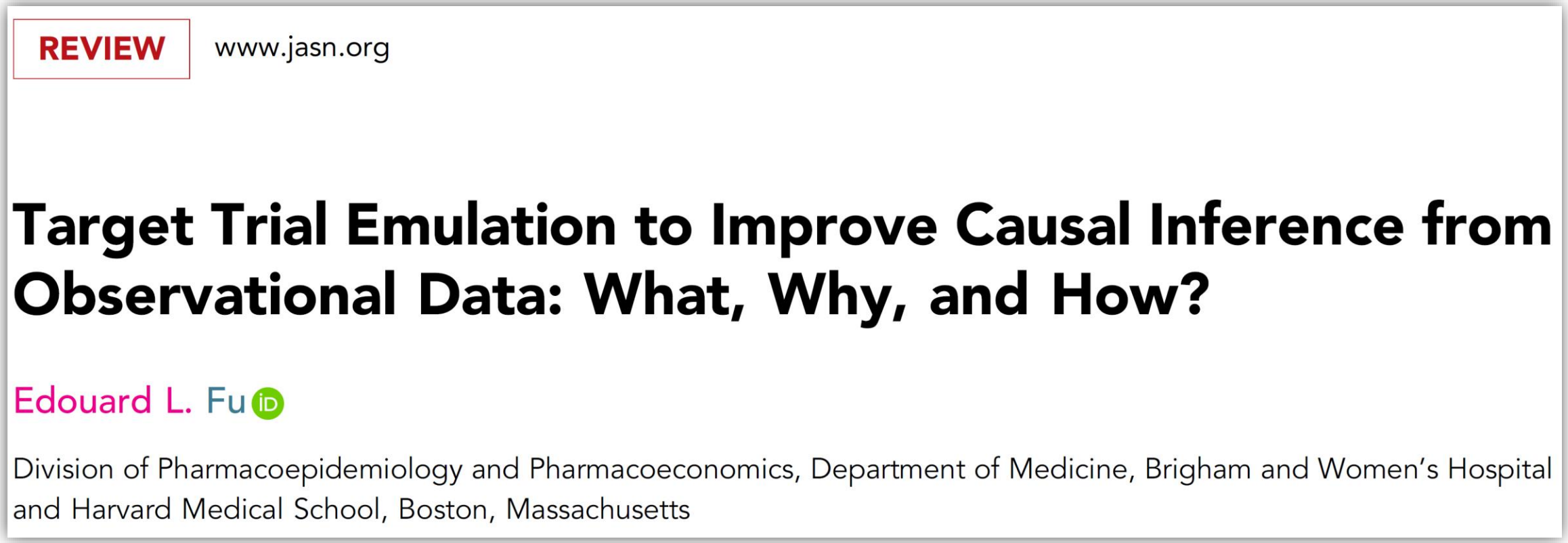
Confounding as the culprit?

- Confounding not the primary reason for discrepancy

- Due to biases introduced by investigator

  → Could have been prevented by target trial emulation

Target trial emulation



REVIEW www.jasn.org

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

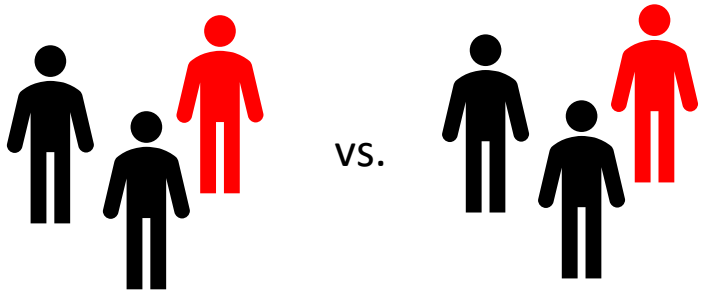
Edouard L. Fu

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

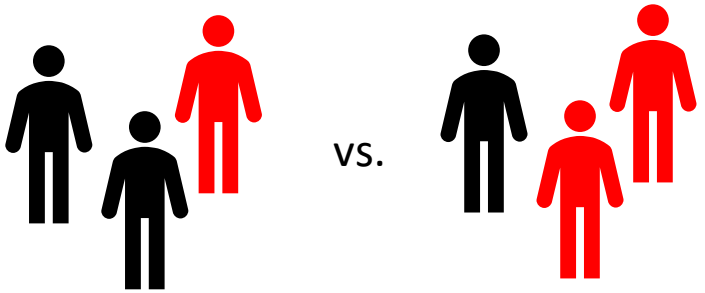
3. Combatting confounding

Difference between RCT and observational studies: confounding

RCT



Observational study



Target trial emulation **does not** solve the problem of unmeasured confounding

- This requires measuring and appropriately adjusting for all confounders

- Target trial emulation only prevents self-inflicted biases (immortal time bias, selection bias, lead time bias)

Combatting confounding

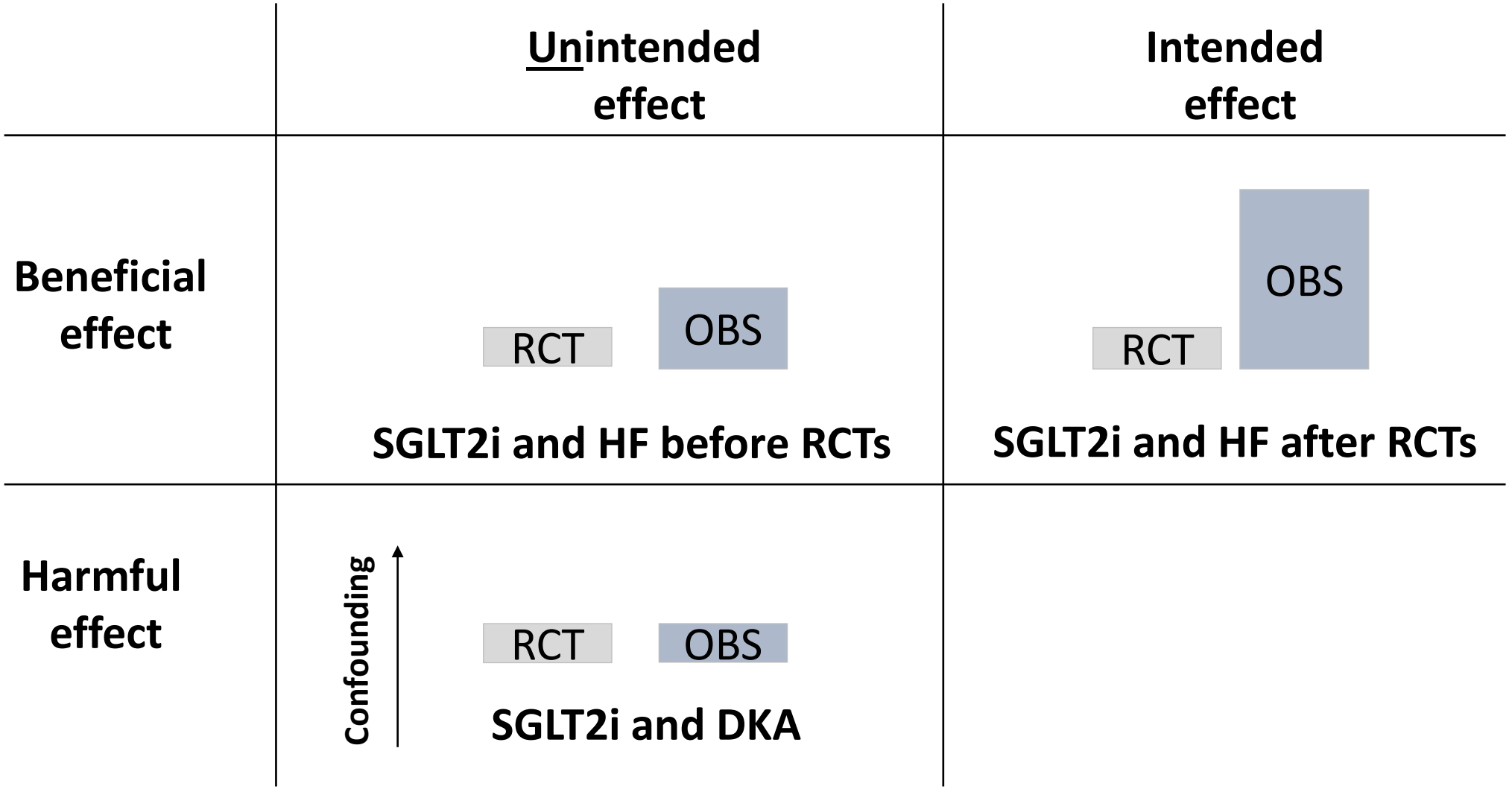
Study question

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

Statistical analysis

Checks

Not all questions equally susceptible to confounding



Adapted from Schneeweiss

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

Combatting confounding

Study question

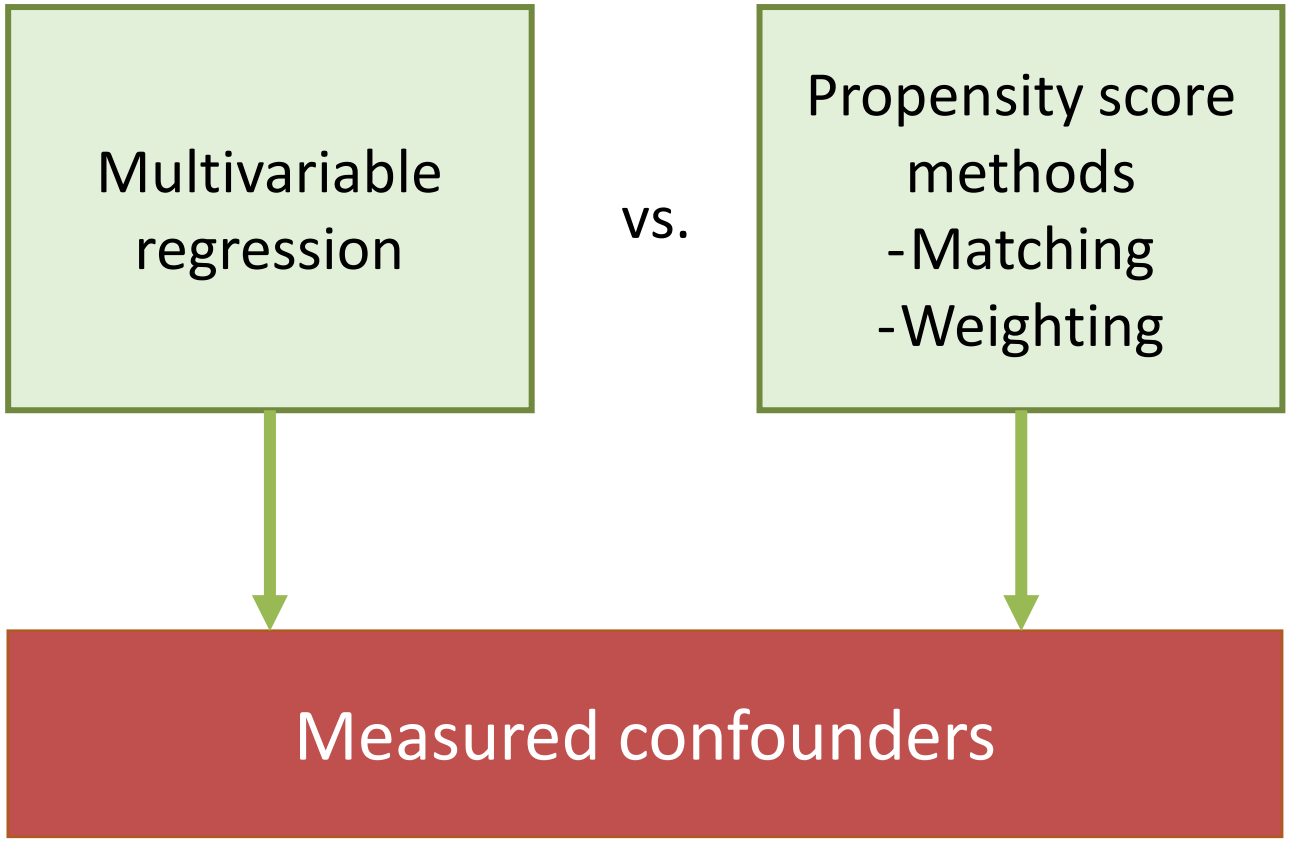
- Intended/unintended, beneficial/harmful effects
- Active comparators

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
- Active comparators

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)	0.65 (0.51-0.80)	-
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)	0.94 (0.75-1.12)	-

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

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]

Study question

- P: HF, type 2 diabetes, ≥65 years
- I: SGLT-2i
- C: Sitagliptin (DPP-4i)
- O: All-cause death, heart failure hospitalization

Data source: Medicare claims data

Active-comparator new-user design, adjusting for >100 potential confounders (demographics, comorbidities, medications, healthcare utilization, healthy behavior markers)

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)

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

How to improve causal inference from observational data?

1. Apply target trial emulation!
   - Emulate the design of an RCT by aligning E/A/T0
   - This prevents immortal time and selection bias
2. Address confounding in various steps throughout your study
   - Start with the question (unintended/intended? Active comparator?)
   - Use appropriate methods for time-varying confounding
   - Use negative controls or benchmarking when possible

Useful references

- Target Trial Emulation to Improve Causal Inference from Observational Data: What, Why, and How? JASN 2023. (introduction to target trial emulation)
- Pharmacoepidemiology for nephrologists (part 2): potential biases and how to overcome them. CKJ 2020. Fu et al. (immortal/prevalent user bias)
- Timing of dialysis initiation to reduce mortality and cardiovascular events in advanced chronic kidney disease: nationwide cohort study. BMJ 2021. Fu et al. (application of TTE)
- Stopping Renin-Angiotensin System Inhibitors in Patients with Advanced CKD and Risk of Adverse Outcomes: A Nationwide Study. JASN 2021. Fu et al. (application of TTE)
- Sodium-glucose cotransporter 2 inhibitors vs. sitagliptin in heart failure and type 2 diabetes: an observational cohort study. European Heart Journal 2023. Fu et al. (& negative control outcomes)
- Comparative Effectiveness of Renin-Angiotensin System Inhibitors and Calcium Channel Blockers in Individuals With Advanced CKD: A Nationwide Observational Cohort Study. AJKD 2021. (benchmarking against trial findings)