Leiden University
Medical Center

Improving clinical care in cardio-kidney-metabolic diseases with causal inference and big data

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My learning journey in big data & causal inference

PhD LUMC (2018-2021)

- Karolinska Institute: Swedish registries (high quality!)
- Introduced novel causal inference methods in nephrology
- “Optimal cardiovascular treatment strategies in kidney disease: causal inference from observational data”

Postdoc Harvard (2021-2023)

- Further training in causal inference
- Claims datasets (>100 million patients)
- Focus on novel treatments in CKM

Assistant professor & MSc medical student (2023-now)

There is a lot of routine care data

The patient journey (time)

Healthcare use

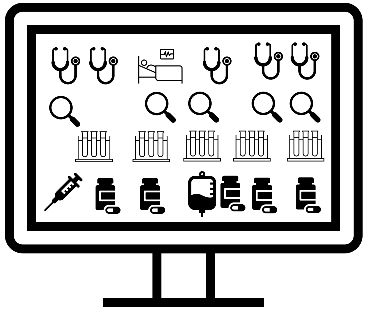
- Inpatient
- Outpatient

Diagnoses

Laboratory measurements

Medications

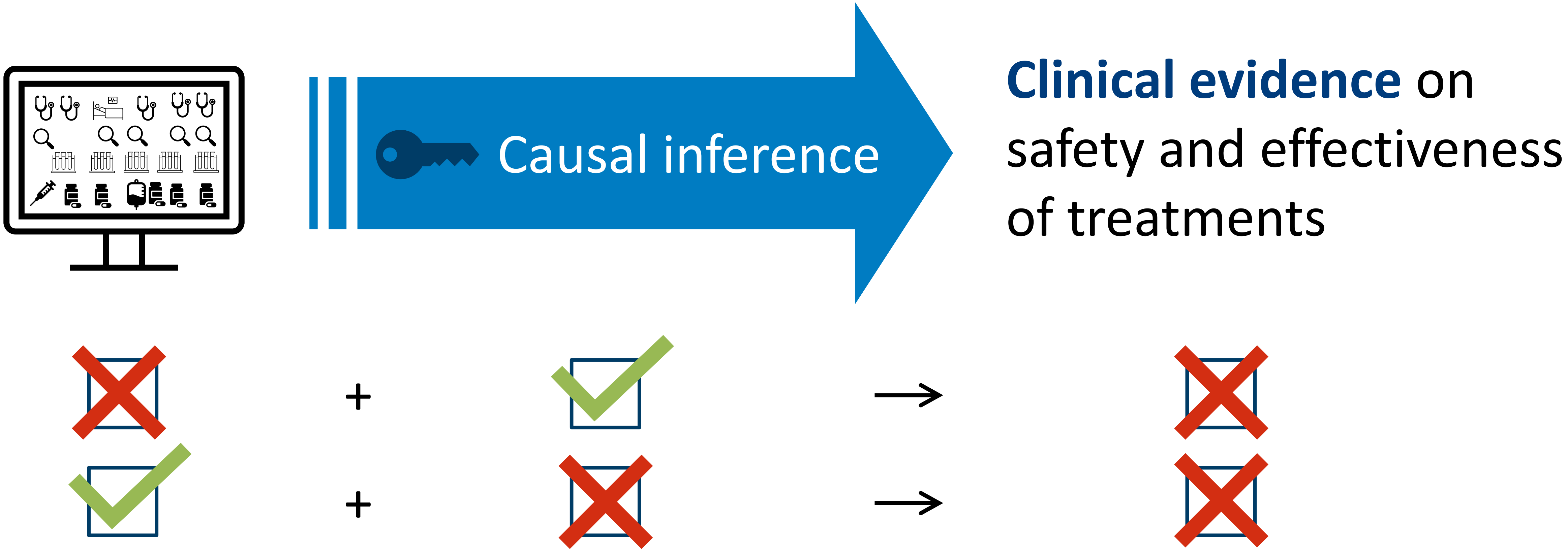
Extracting useful insights from these data is possible



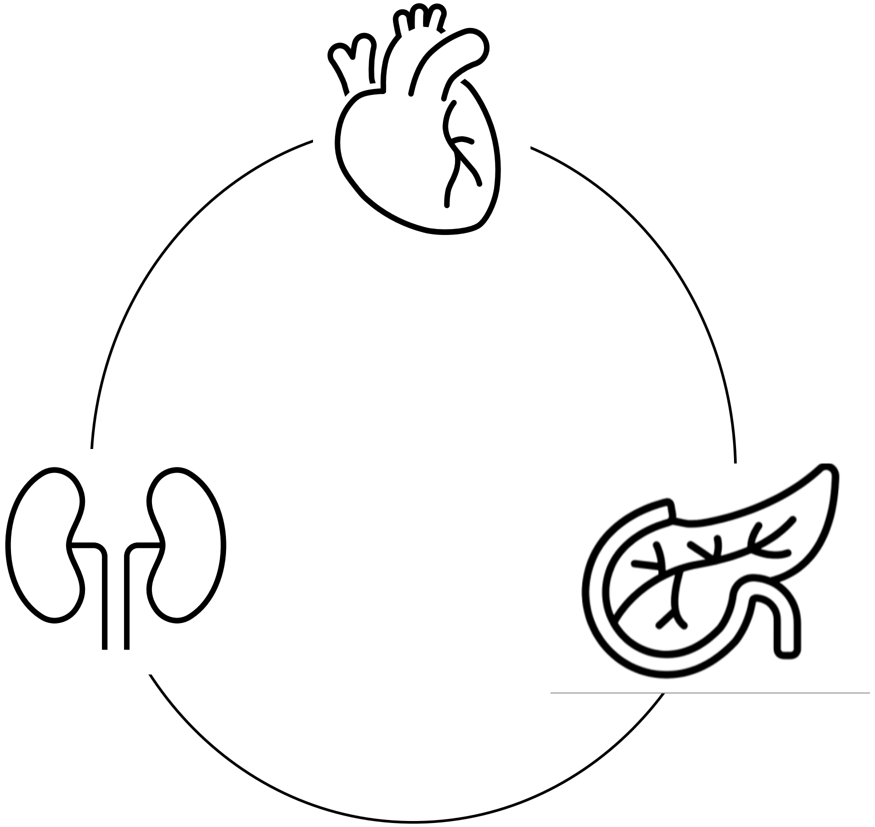
Causal inference

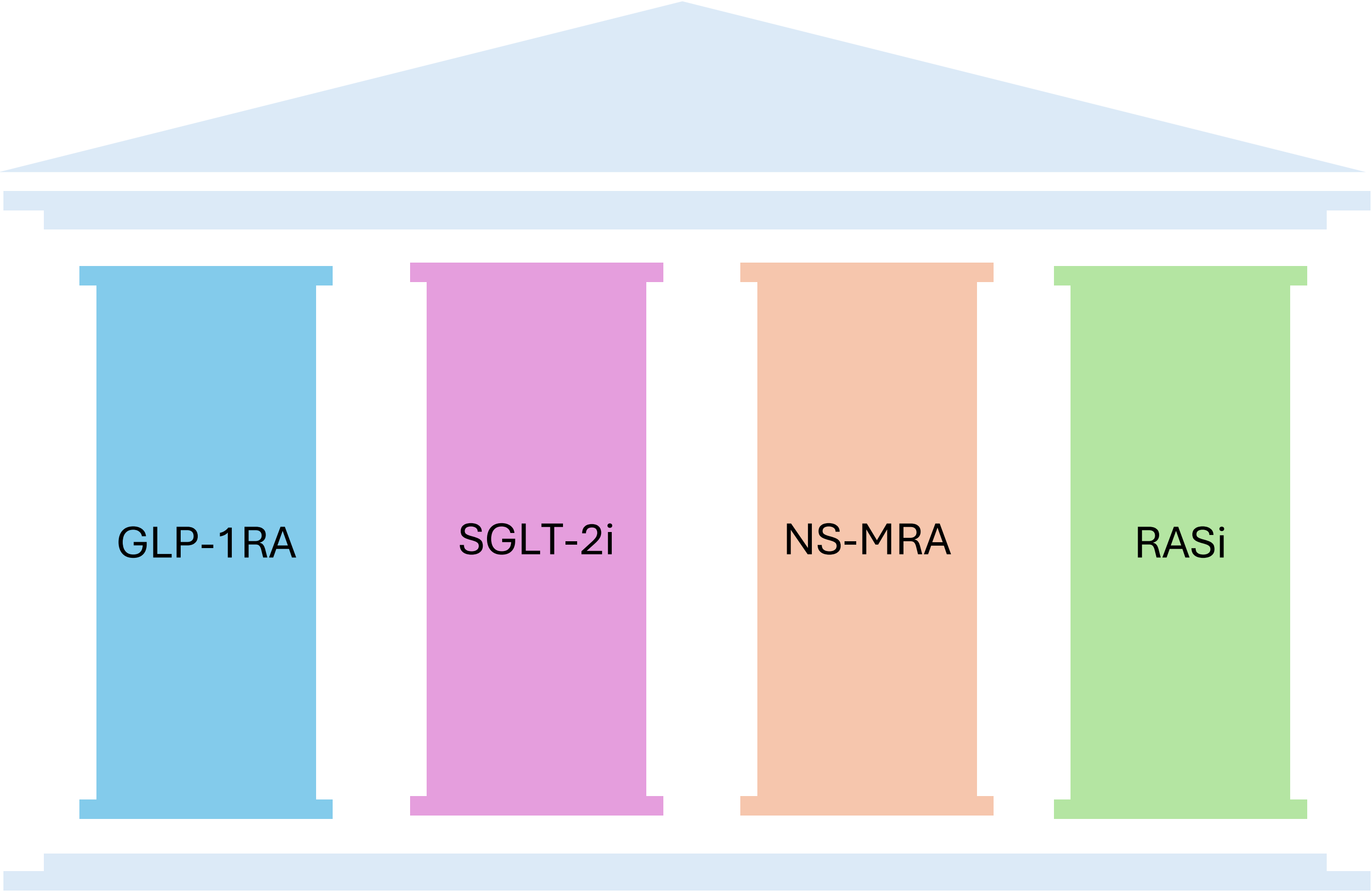
Clinical evidence on safety and effectiveness of treatments

Extracting useful insights from these data is difficult



Clinical research: Cardio-Kidney-Metabolic diseases

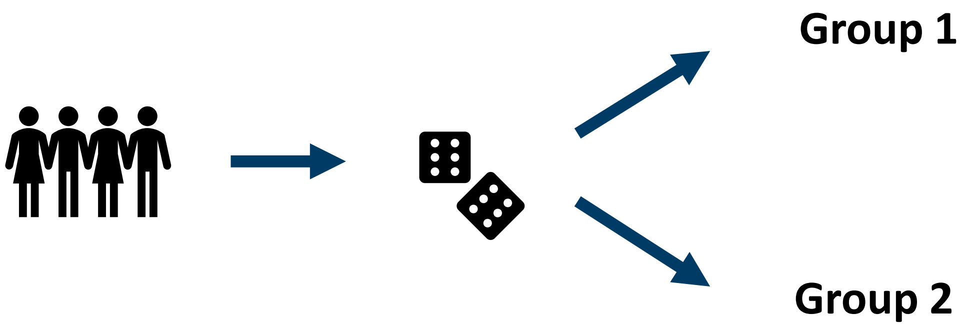




Why do we need routine care data in addition to RCTs?

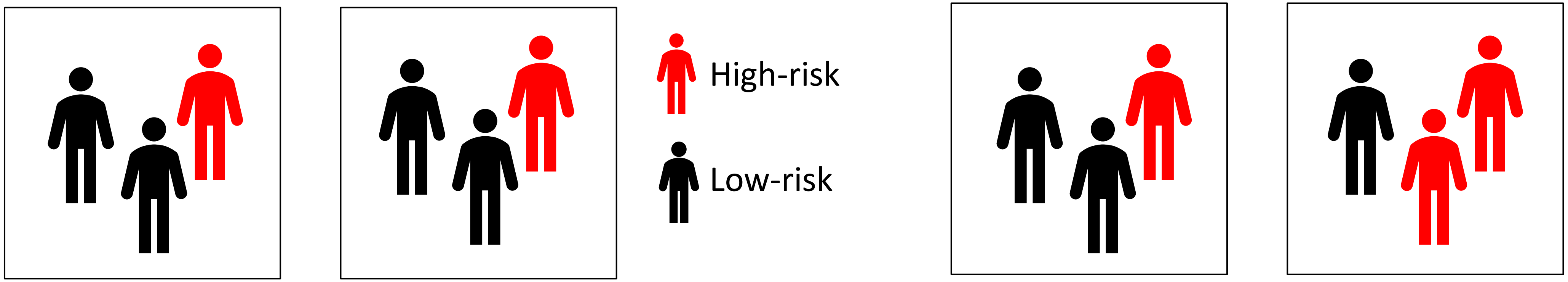
In an ideal world...

For each causal question: perform an RCT



RCT vs. observational studies: confounding

RCT **Observational study**



Observational studies need to measure and appropriately adjust for all confounders

Trials may not be timely

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

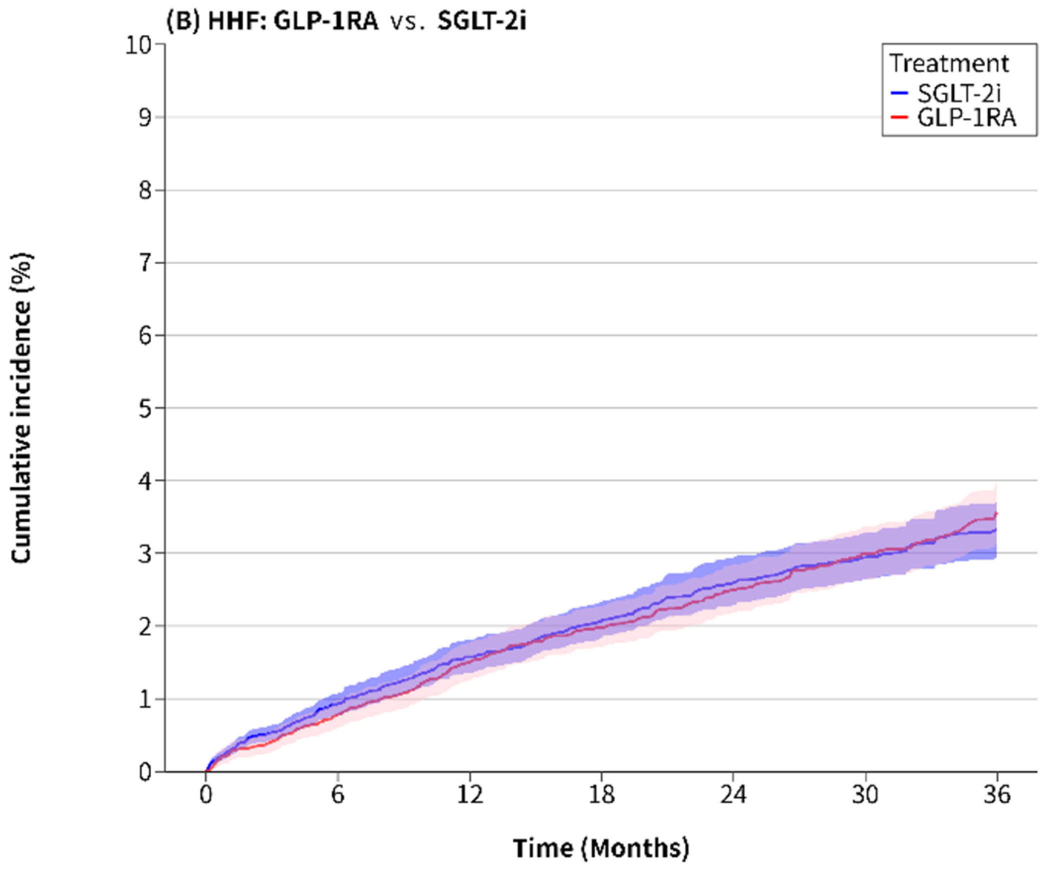
The NEW ENGLAND JOURNAL of MEDICINE

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

Trials unlikely to be conducted

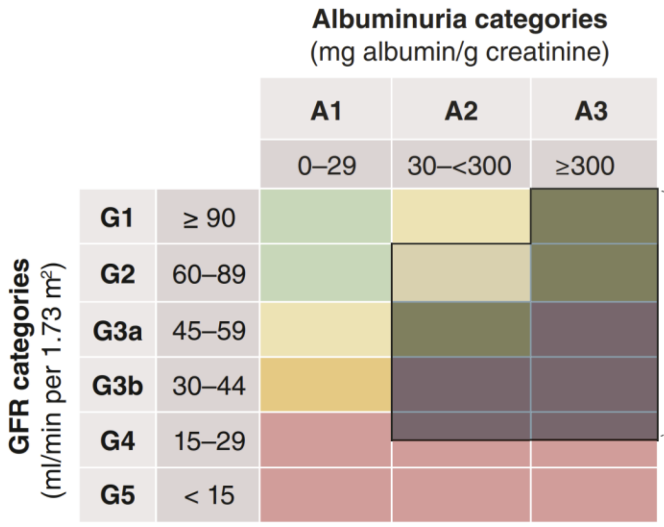


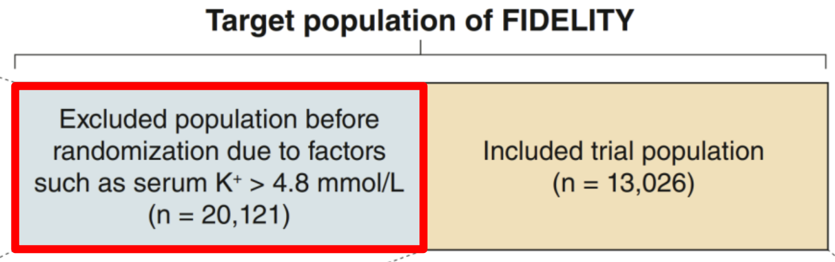
No. at risk

SGLT-2i	15229	12260	9961	8372	6767	5562	4327
GLP-1RA	14875	12681	10704	9264	7917	6759	5564

Risk of heart failure hospitalization for GLP-1 receptor agonists vs. DPP-4 inhibitors or SGLT-2 inhibitors in patients with type 2 diabetes: a target trial emulation. Xu Y, … EL Fu. *Circulation 2025 (resubmitted)*

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

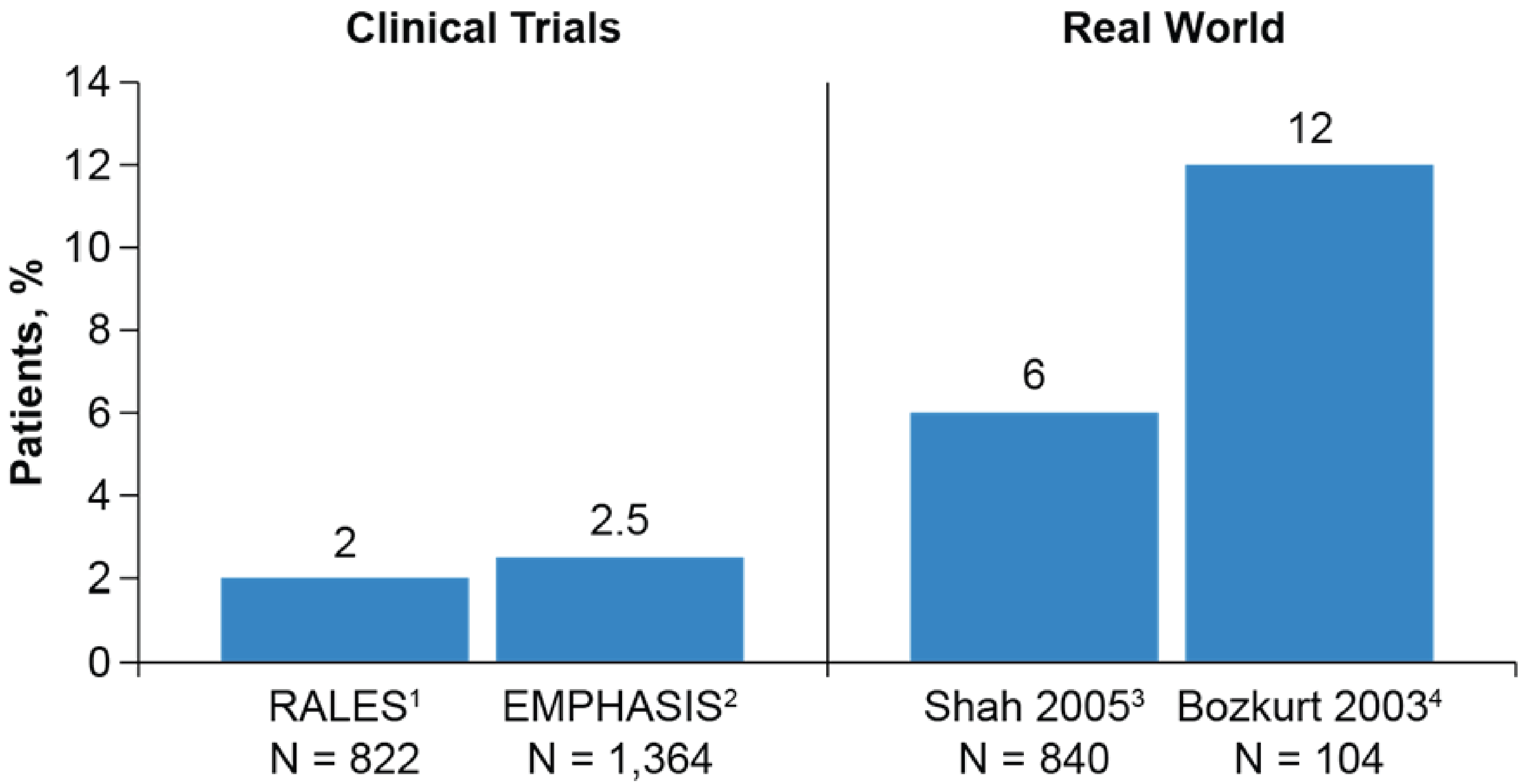
Finerenone in chronic kidney disease and type 2 diabetes: the known and the unknown

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

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

Consequences of highly selected populations

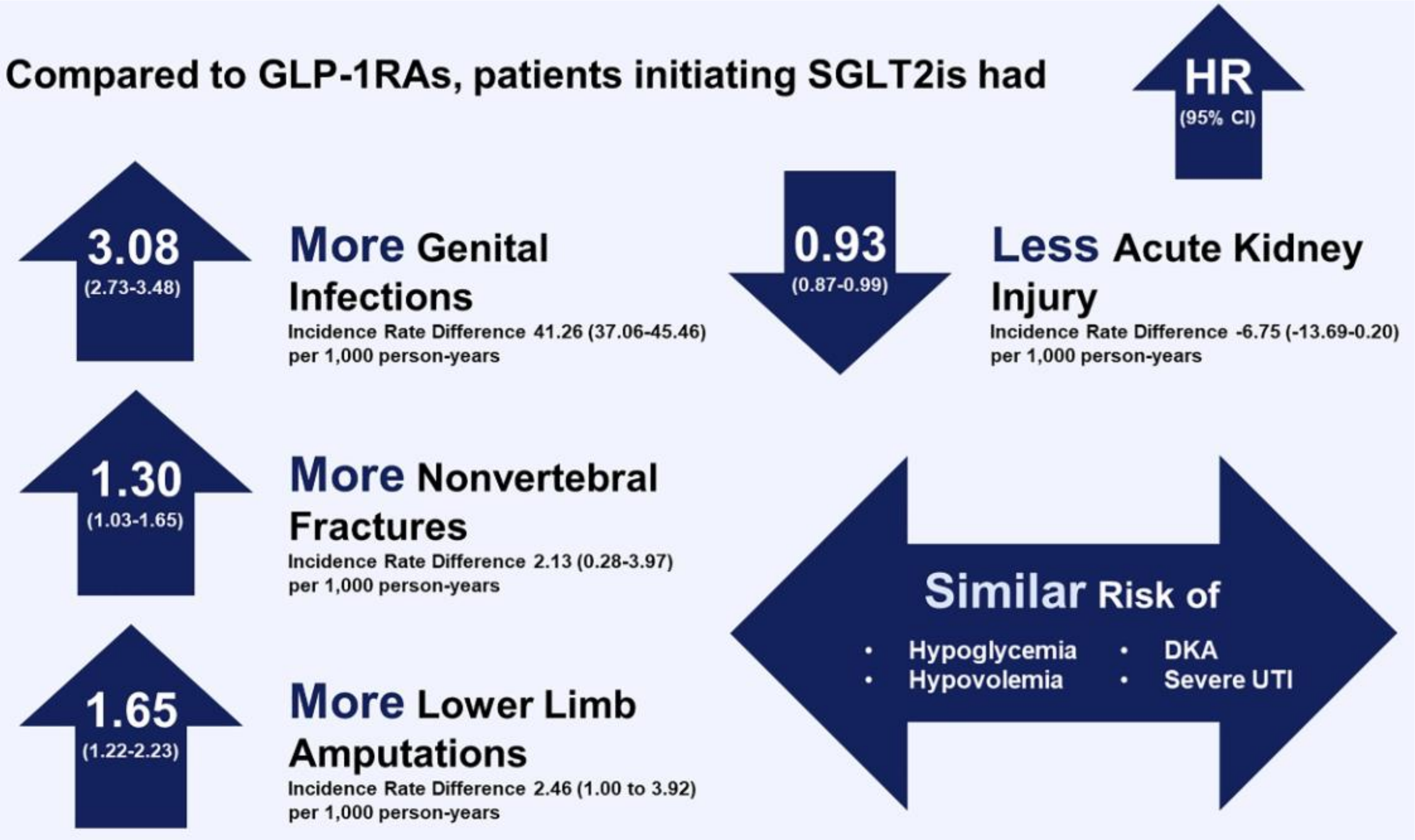
Hyperkalemia risk for mineralocorticoid receptor antagonists



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

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.

Trials may be too small for severe, rare safety signals



Fu EL, et al. Safety of SGLT-2 Inhibitors in Patients with CKD and Type 2 Diabetes: Population-Based US Cohort Study. CJASN. 2023

High quality causal inference methods

A 20-year old open problem…

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]

Due to confounding (the usually culprit we point to)? Or something else…

IDEAL trial vs. observational studies

The NEW ENGLAND JOURNAL of MEDICINE

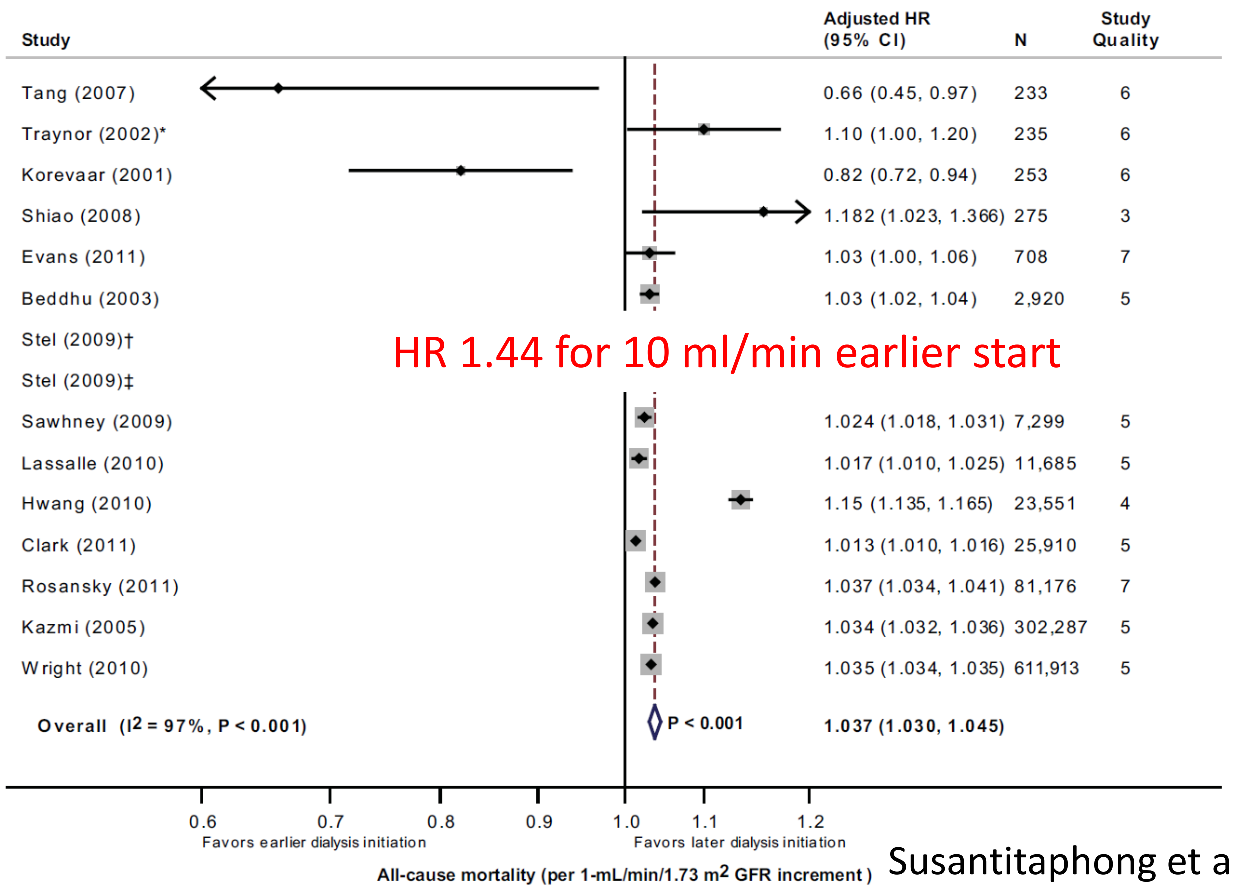
ESTABLISHED IN 1812 AUGUST 12, 2010 VOL. 363 NO. 7

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

Randomized IDEAL trial :

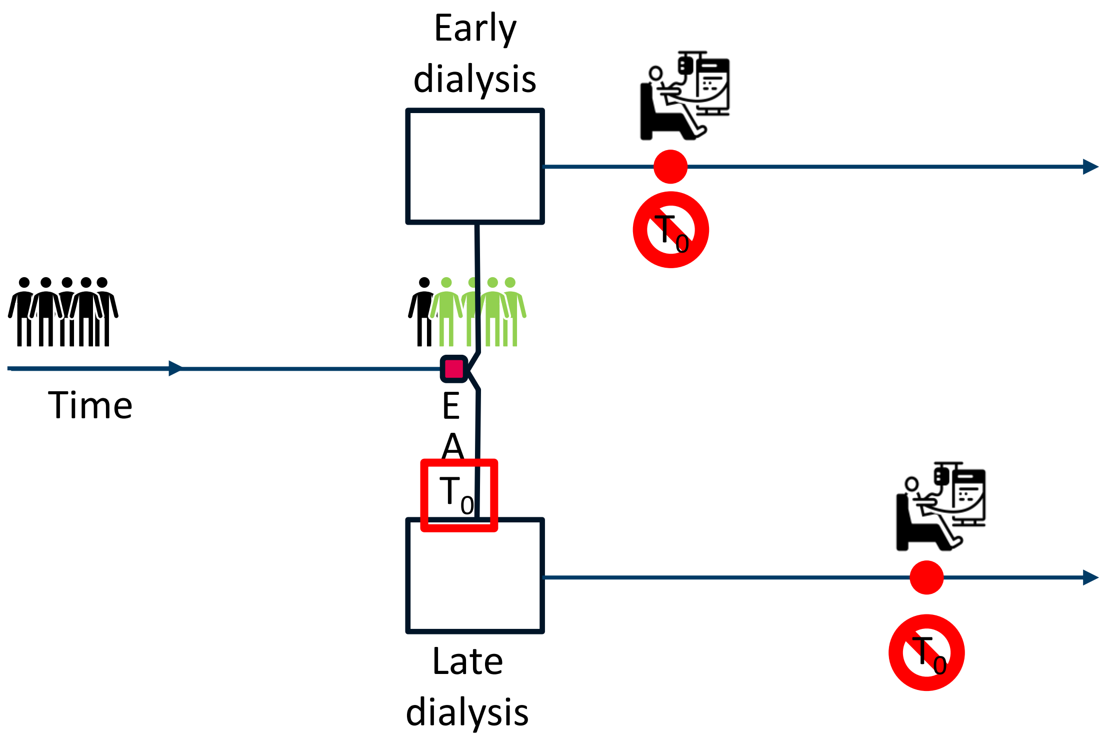
No mortality difference between early vs. late dialysis start: HR 1.04 (0.83-1.30)

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



Susantitaphong et al. AJKD 2012

What would the RCT look like?



3 components aligned at randomization:

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

None of the ~20 studies did this!

Misaligning these 3 components

introduces bias in an observational study

Framework for designing and analyzing studies

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

Impact of incorrect methods

Fu et al. BMJ 2021

	Correct study design	Biases due to misalignment	Confounding adjustment necessary	Hazard ratio (95% CI) early vs. late
Randomized IDEAL trial	✓	-	No	1.04 (0.83-1.30)
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)
Trial emulation analysis	✓	-	Yes	0.96 (0.94-0.99)

HR of 1.46 and 1.58 similar in magnitude to previous biased observational studies (n= 21)
→ able to replicate previous biased results

But… can we replicate IDEAL findings when using a proper design?

Looks simple, but is it implemented?

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

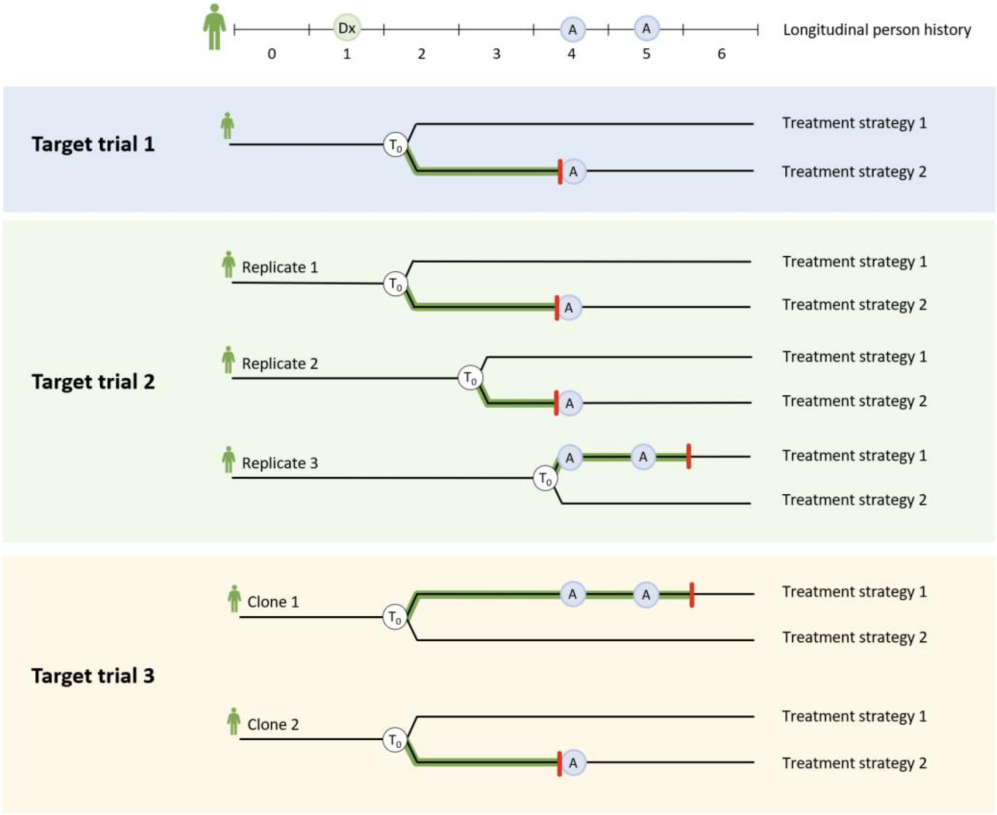
44% suffered from prevalent user selection

→ These biases are prevented if target trial emulation is used

Preprint

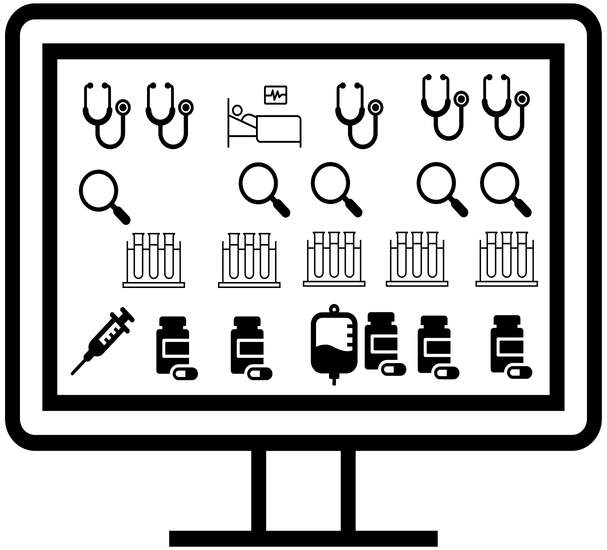
Starting right: aligning eligibility and treatment assignment at time zero when emulating a target trial

EL Fu, … MA Hernan. *BMJ 2025 (resubmitted). Preprint online at SSRN*



High data quality

Data quality



Treatments

Confounders

Outcomes

Data quality vs. data quantity

EHR, tumor registries, genomic databases, and claims linked and harmonized to common terminologies for in-depth analysis

275M+ patient lives

120+
healthcare organizations providing continuous, comprehensive, up-to-the month data

19
countries in North and South America, EMEA, and Asia-Pacific, including Japan

122
lab results in the typical record of U.S. and EMEA patients

70B+
date- and patient-indexed clinical observations available for download

TriNetX

Treatment

A ALIMENTARY TRACT AND METABOLISM
A10 DRUGS USED IN DIABETES
A10B BLOOD GLUCOSE LOWERING DRUGS, EXCL. INSULINS
A10BJ Glucagon-like peptide-1 (GLP-1) analogues

ATC code	Name	DDD	U	Adm.R	Note
A10BJ01	exenatide	0.286	mg	P	depot inj
		15	mcg	P	
A10BJ02	liraglutide	1.5	mg	P	
A10BJ03	lixisenatide	20	mcg	P	
A10BJ04	albiglutide	5.7	mg	P	
A10BJ05	dulaglutide	0.16	mg	P	
A10BJ06	semaglutide	10.5	mg	O	
		0.11	mg	P	
A10BJ07	beinaglutide				

Prescription vs. filled prescription (and adherence)

vs.

Outcomes

Electronic health records

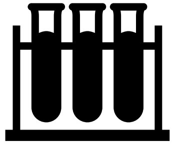
Hospital A

Hospital B

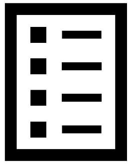
Identifying Patients With High Data Completeness to Improve Validity of Comparative Effectiveness Research in Electronic Health Records Data

Kueiyu Joshua Lin[1,2,3], Daniel E. Singer[2,3], Robert J. Glynn[1,3], Shawn N. Murphy[4], Joyce Lii[1] and Sebastian Schneeweiss[1,3]

Outcome definition



Lab



ICD-10

www.kidney-international.org review

Defining measures of kidney function in observational studies using routine health care data: methodological and reporting considerations

Check for updates

OPEN

Juan Jesus Carrero[1,24], Edouard L. Fu[1,2,3,24], Søren V. Vestergaard[4,5], Simon Kok Jensen[4,5], Alessandro Gasparini[1], Viyaasan Mahalingasivam[6], Samira Bell[7], Henrik Birn[5,8,9], Uffe Heide-Jørgensen[4,5], Catherine M. Clase[10,11], Faye Cleary[6], Josef Coresh[12], Friedo W. Dekker[3], Ron T. Gansevoort[13], Brenda R. Hemmelgarn[14], Kitty J. Jager[15,16], Tazeen H. Jafar[17], Csaba P. Kovesdy[18], Manish M. Sood[19], Bénédicte Stengel[20], Christian F. Christiansen[4,5], Masao Iwagami[6,21,25] and Dorothea Nitsch[6,22,23,25]

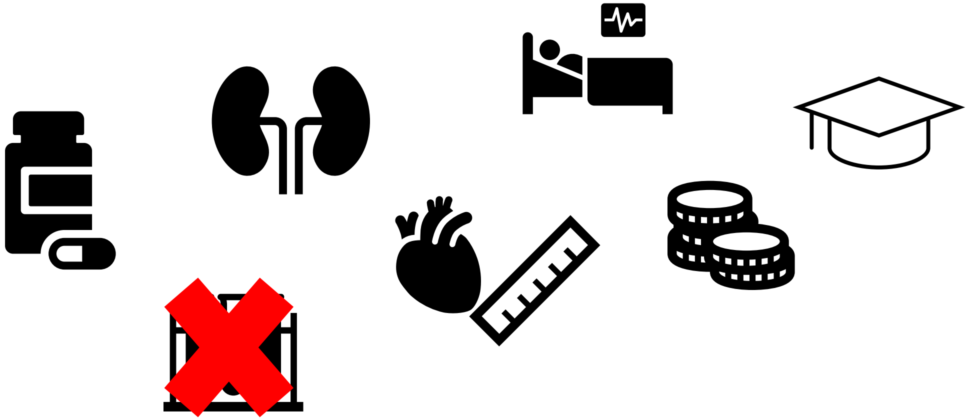
Confounders: measurement and adjustment

Measurement

RESEARCH

SGLT-2 inhibitors, GLP-1 receptor agonists, and DPP-4 inhibitors and risk of hyperkalemia among people with type 2 diabetes in clinical practice: population based cohort study

Edouard L Fu,[1,2] Deborah J Wexler,[3,4] Sara J Cromer,[3,4] Katsiaryna Bykov,[1] Julie M Paik,[1,5,6] Elisabetta Patorno[1]



unmeasured confounding

Some questions require longitudinal data on and adjustment for **time-varying** confounders with complex methods:

- Inverse probability weighting
- Marginal structural models

How do we handle missing data?

Benchmarking against trial findings

Original Investigation AJKD

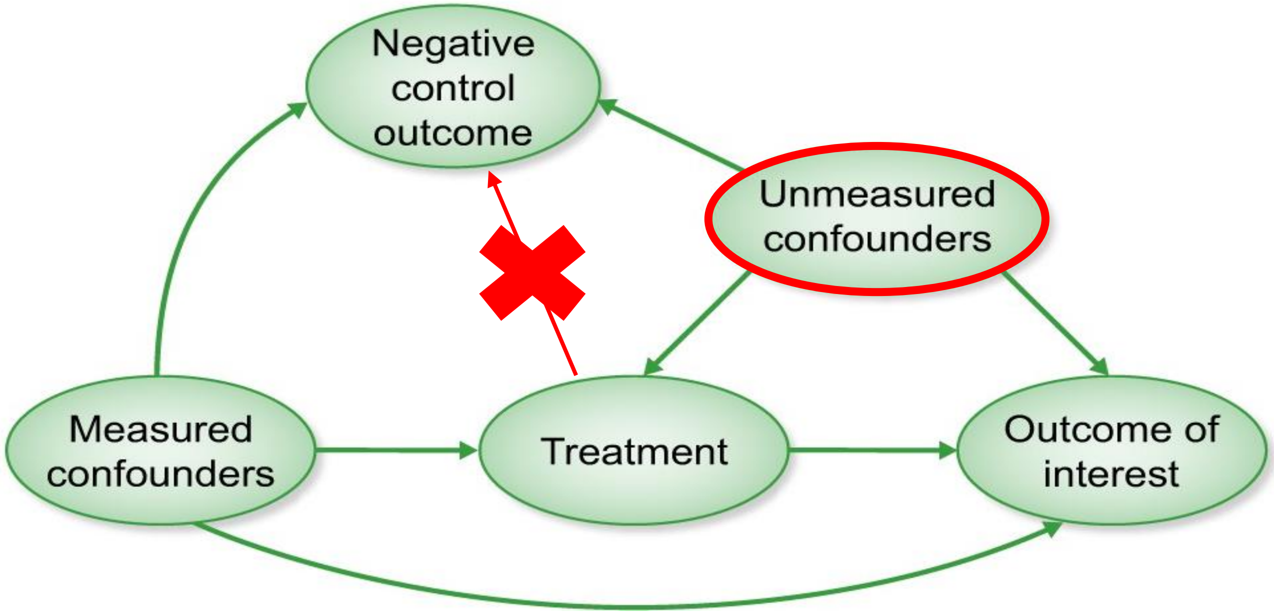
Comparative Effectiveness of Renin-Angiotensin System Inhibitors and Calcium Channel Blockers in Individuals With Advanced CKD: A Nationwide Observational Cohort Study

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

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

KRT = kidney replacement therapy; MACE = major adverse cardiovascular events

Negative control outcomes



CKJ REVIEW

Pharmacoepidemiology for nephrologists (part 2): potential biases and how to overcome them

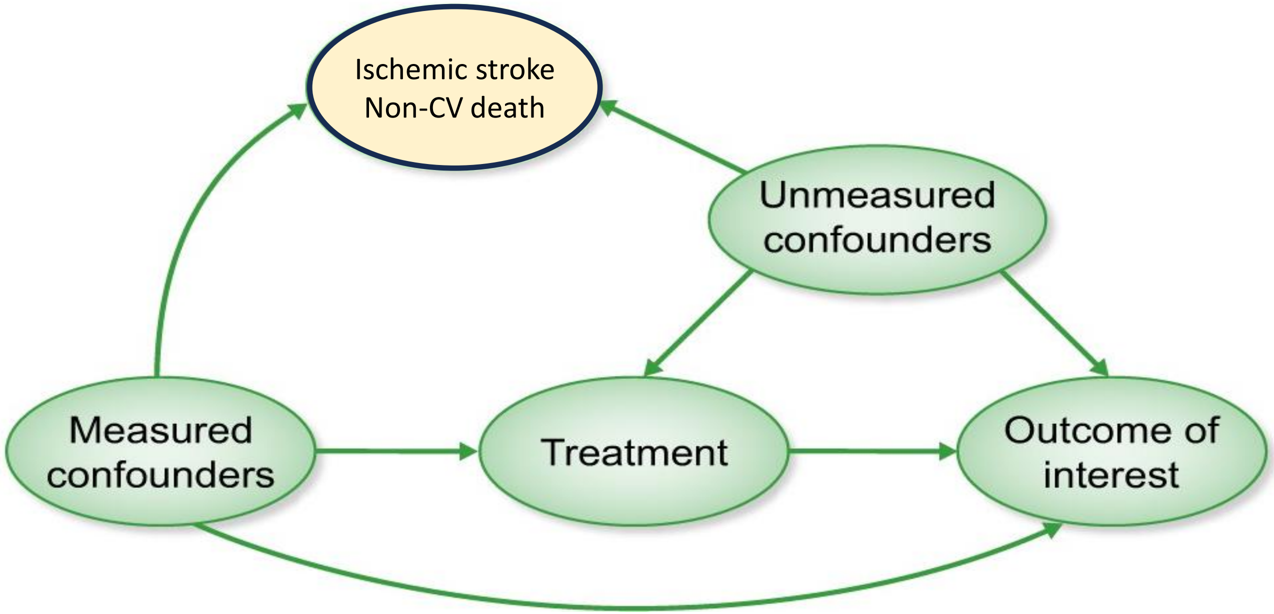
Edouard L. Fu [1], Merel van Diepen[1], Yang Xu[2], Marco Trevisan[2], Friedo W. Dekker[1], Carmine Zoccali[3], Kitty Jager[4] and Juan Jesus Carrero [2]

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]



Negative control outcome	Assumed true HR	Observed HR (95% CI)
Non-CV death	1.00	0.81 (0.65-1.01)
Ischemic stroke	1.00	0.83 (0.65-1.06)

Bias correction

Primary outcome
0.72 (0.67-0.77)

Non-CV death:
0.89 (0.72-1.11)

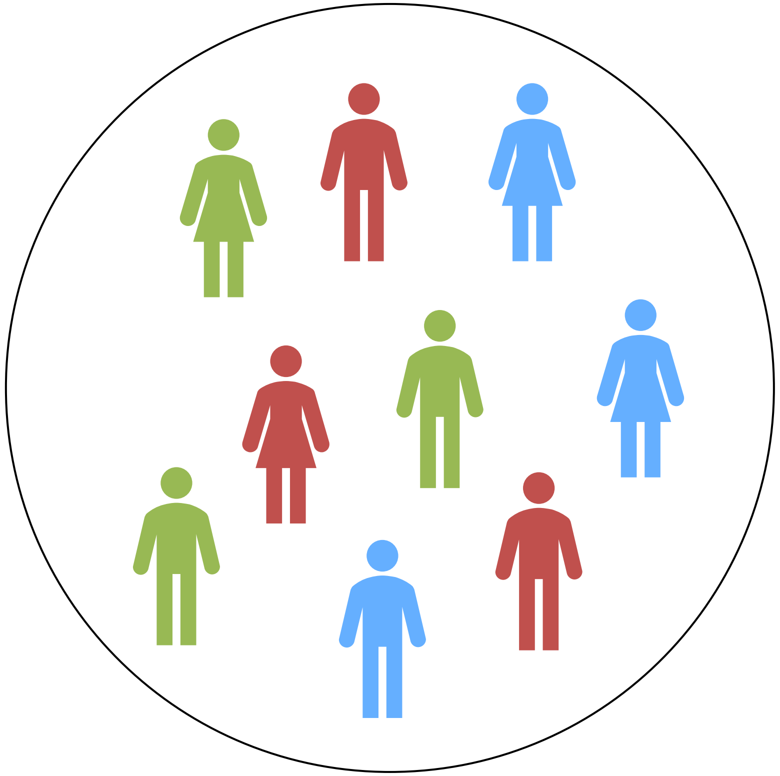
Ischemic stroke:
0.86 (0.67-1.10)

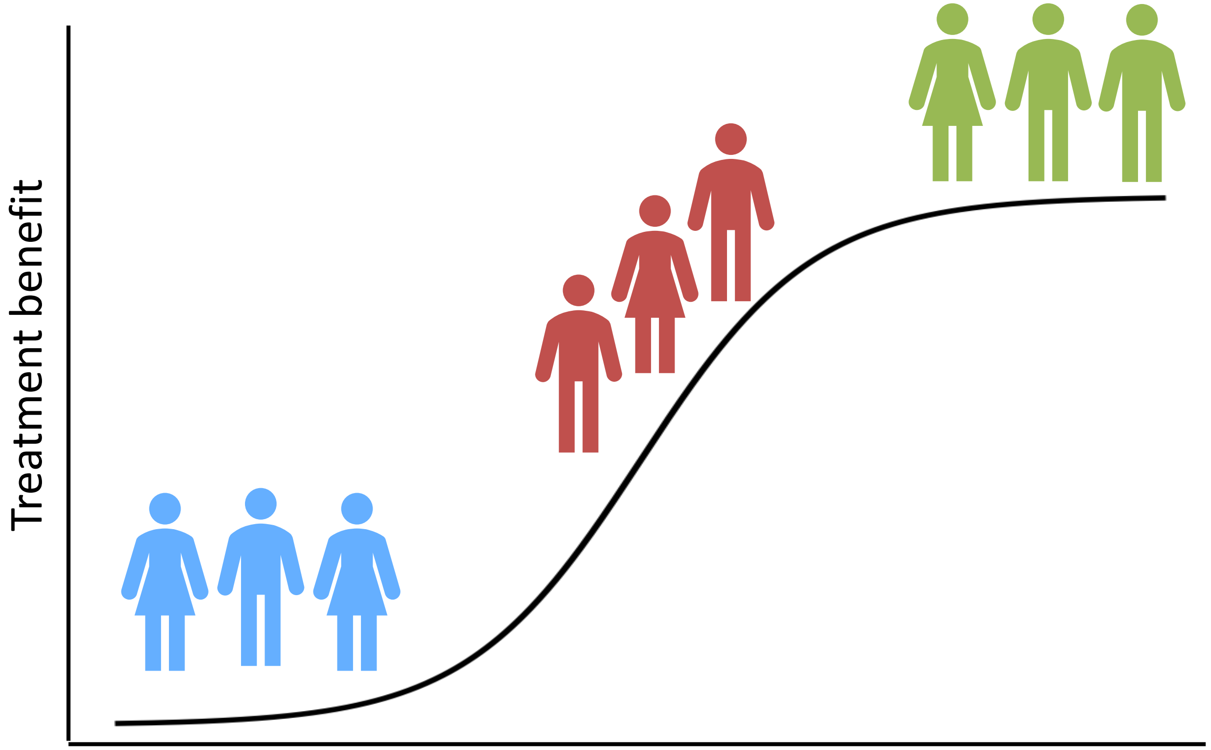
Combatting confounding

Study question	•Intended/unintended, beneficial/harmful effects •Active comparators
Data quality	• Granularity of confounders (e.g. presence of laboratory measurements, ejection fraction etc)
Statistical analysis	Adjustment for measured confounders
Checks	•Benchmark against trial results •Negative control outcomes

What’s next?

From average treatment effects to personalized medicine





Useful references

- Starting right: aligning eligibility and treatment assignment at time zero when emulating a target. trial Fu et al. *BMJ 2025 (resubmitted). Preprint online at SSRN* (algorithm to ensure correct alignment)
- 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 target trial emulation)
- 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 target trial emulation)
- 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. Fu et al. (benchmarking against trial findings)

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NIER STICHTING