ARTIFICIAL INTELLIGENCE AND DATA ANALYTICS

STATISTICAL LEARNING IN EPIDEMIOLOGY

MAY 29, 2025

HOW TO ANSWER A CAUSAL QUESTION IN EPIDEMIOLOGY – A CASE-STUDY IN THE BIOMEDICAL FIELD

Turoldo Federico MD
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CONTENT

- INTRODUCTION – Causal Questions in the biomedical field
- CASE STUDY - Renal Outcomes in patients with Non Valvular Atrial Fibrillation
  - Biomedical preliminary concepts
  - Observational Data Source
  - Study Design: exposure and outcome definition
  - Statistical Analysis: IPTW and IPCW
- CONCLUSION AND KEY TAKEAWAYS

DISCLAIMER: IT IS AN ONGOING PROJECT!

RESEARCH QUESTIONS IN EPIDEMIOLOGY

Question + Assumptions + Data → Conclusions

- Descriptive
- Causal
- Predictive

Which one is the most popular
In your opinion???

PubMed®

- Search: **(description[Title/Abstract]) OR (descriptive[Title/Abstract])**
- Search: **(prediction[Title/Abstract]) OR (predictive[Title/Abstract])**
- Search: **(causal[Title/Abstract]) OR (cause[Title/Abstract])**

Articles

A Second Chance to Get Causal Inference Right: A Classification of Data Science Tasks

Miguel A. Hernán, John Hsu & Brian Healy

Pages 42-49 | Published online: 14 Mar 2019

Cite this article https://doi.org/10.1080/09332480.2019.1579578 Check for updates

Credits: J.Lebeque, Rotterdam

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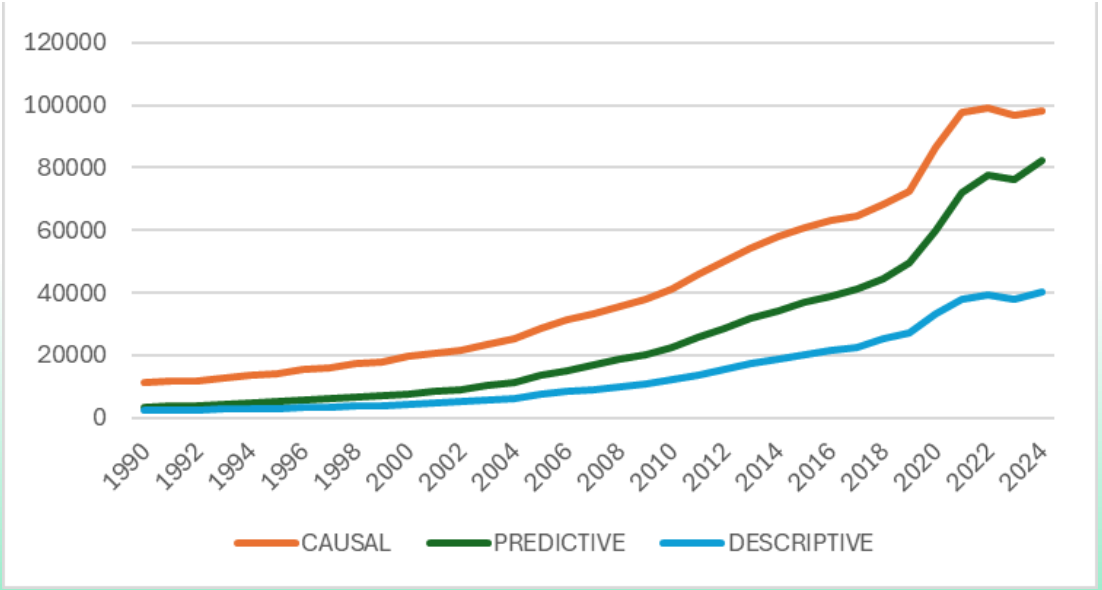

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RESEARCH QUESTIONS IN EPIDEMIOLOGY

Question + Assumptions + Data → Conclusions

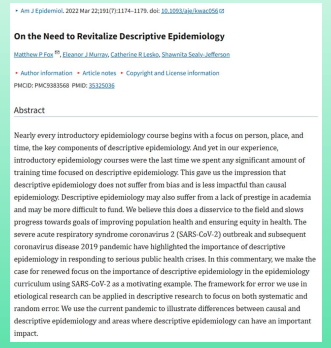
Descriptive: To measure, to give the numeric value of something without any further goal

- Causal
- Predictive

«What percentage of adults aged 15 to 49 is affected by HIV?»

Prevalence, Incidence, Trends,
Groups differences, Clustering …

Pr(HIV | Region)



• Am J Epidemiol. 2022 Mar 22;191(7):1174–1179. doi: 10.1093/aje/kwac056

On the Need to Revitalize Descriptive Epidemiology

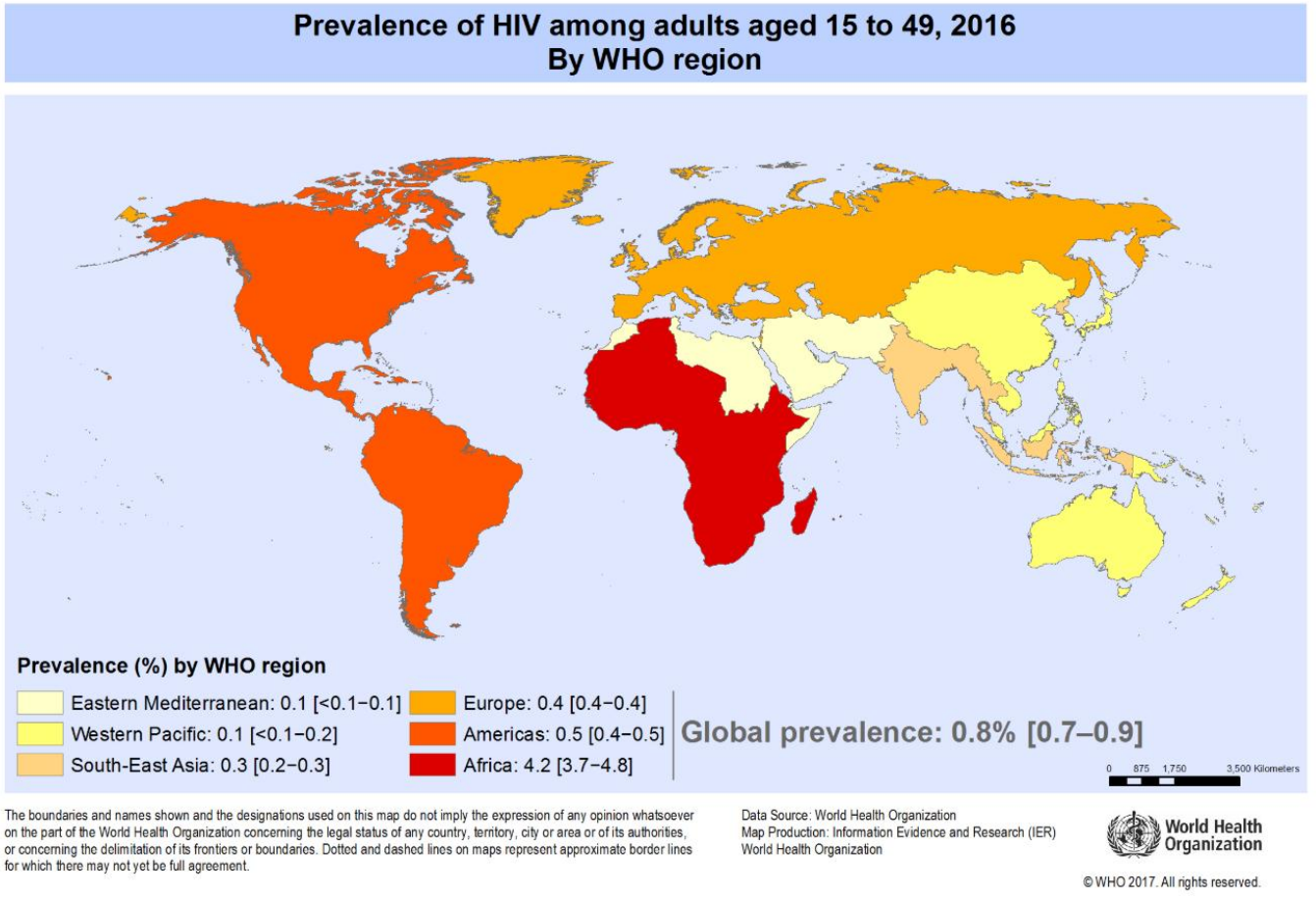
Matthew P Fox, Eleanor J Murray, Catherine R Lesko, Shawnita Sealy-Jefferson

• Author information • Article notes • Copyright and License information

PMCID: PMC9383568 PMID: 35325036

Abstract

Nearly every introductory epidemiology course begins with a focus on person, place, and time, the key components of descriptive epidemiology. And yet in our experience, introductory epidemiology courses were the last time we spent any significant amount of training time focused on descriptive epidemiology. This gave us the impression that descriptive epidemiology does not suffer from bias and is less impactful than causal epidemiology. Descriptive epidemiology may also suffer from a lack of prestige in academia and may be more difficult to fund. We believe this does a disservice to the field and slows progress towards goals of improving population health and ensuring equity in health. The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) outbreak and subsequent coronavirus disease 2019 pandemic have highlighted the importance of descriptive epidemiology in responding to serious public health crises. In this commentary, we make the case for renewed focus on the importance of descriptive epidemiology in the epidemiology curriculum using SARS-CoV-2 as a motivating example. The framework for error we use in etiological research can be applied in descriptive research to focus on both systematic and random error. We use the current pandemic to illustrate differences between causal and descriptive epidemiology and areas where descriptive epidemiology can have an important impact.



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RESEARCH QU

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  - Causal
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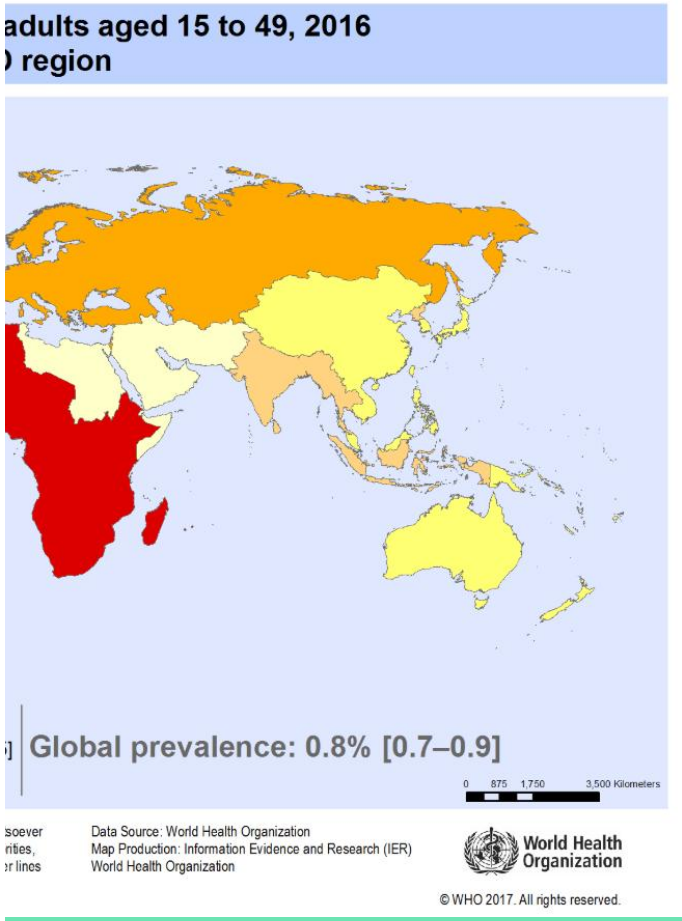

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RESEARCH QUESTIONS IN EPIDEMIOLOGY

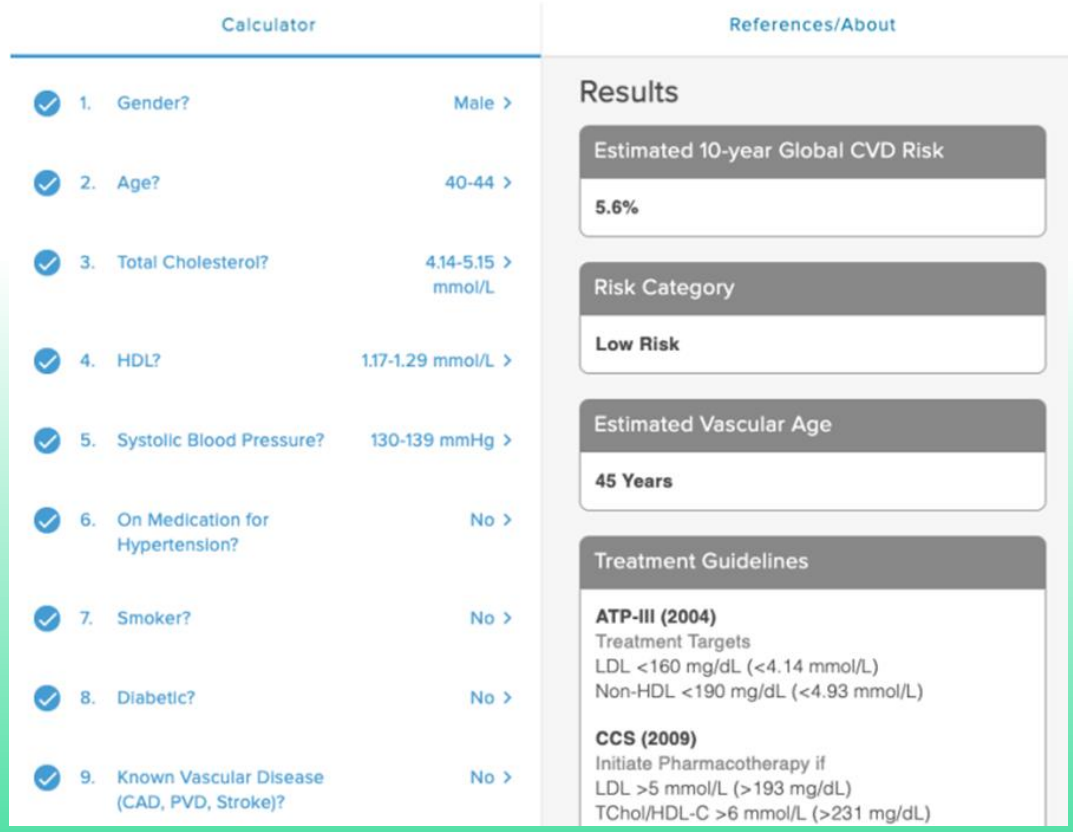
Question + Assumptions + Data → Conclusions

- Descriptive
- Causal
- **Predictive: What is the likely value of something I haven't or can't measure given other information I have?**

«What is the 10 year global CV risk based on sex, age, etc…?»

Pr(CVD10year | Sex=Male, Age=40-44,TChol=4.14-5.15, HDL=1.17-1.29, SBP=135, HTmed=0, Smoke=0, Diabetic=0, VascDis=0)

- Absence of Causal statements
- Absence of Statements involving two variables, we really just want to know the probability (or average) of one variable
- Predictive models require a lot of steps other models don't: Calibration, discrimination, validation
- Adjustment isn't required in predictive models
- Machine learning is useful!



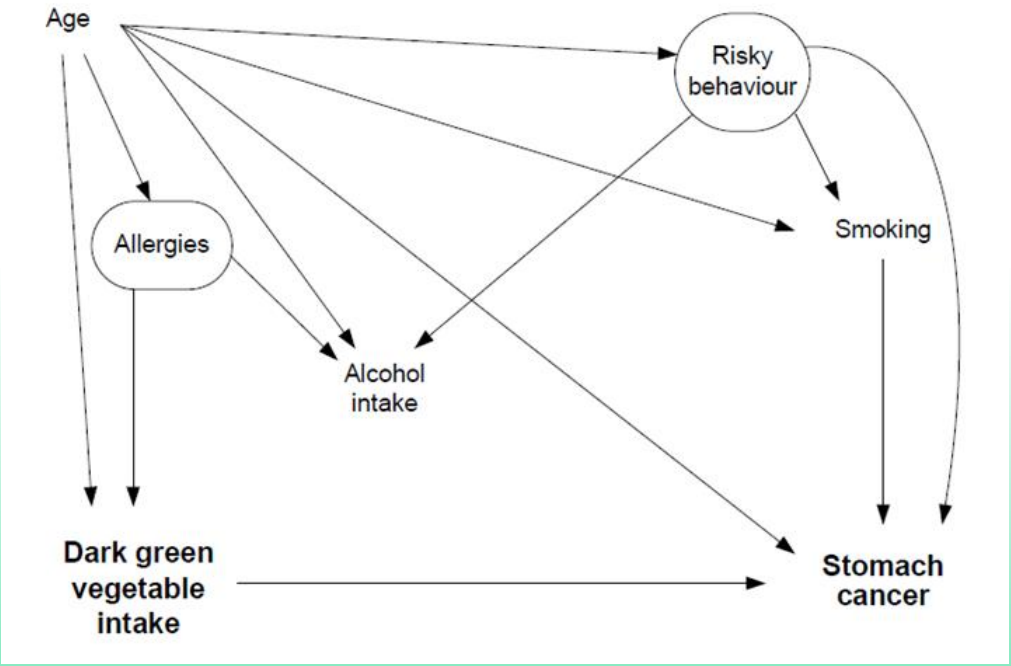
RESEARCH QUESTIONS IN EPIDEMIOLOGY

Question + Assumptions + Data → Conclusions

- Descriptive
- **Causal: To investigate the relationship between variables. What is the effect of A on B?**
- Predictive

«Does a diet rich in vegatables reduce the risk of stomach cancer?»

- Causal Assumption are required
- Adjustment is required to highlight causal pathways
- DAG are useful



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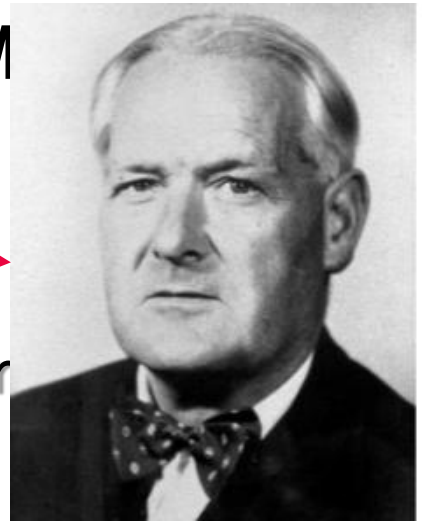


Hill's Criteria

The first complete statement of the epidemiologic criteria of a causality is attributed to Austin Hill (1897-1991). They are:

- Consistency (on replication)
- Strength (of association)
- Specificity
- Dose response relationship
- Temporal relationship (directionality)
- Biological plausibility (evidence)
- Coherence
- Experiment
- Analogy

My estimate is causal if the following assumptions are satisfied:
1) Consistency,
2) Exchangeability,
3) Positivity,
4) No measurement error,
5) Well-specified models

• Good causal inference will convince the reader/reviewer that there is good reason to believe the assumptions above
• Bad causal inference won't mention the assumptions or won't provide arguments for or against them

Biological criteria for causal inference
• Koch's postulates (1884)
• Bradford Hill's criteria (1965)

Modern, structural understanding of causal inference
• Sewall Wright's path diagrams
• Rubin's potential outcomes
• Robins' counterfactual (1932)
• Pearl's do-operator (1995)

Credits: J.Lebeque, Rotterdam

RESEARCH QUESTIONS IN EPIDEMIOLOGY

Question + Assumptions + Data → Conclusions

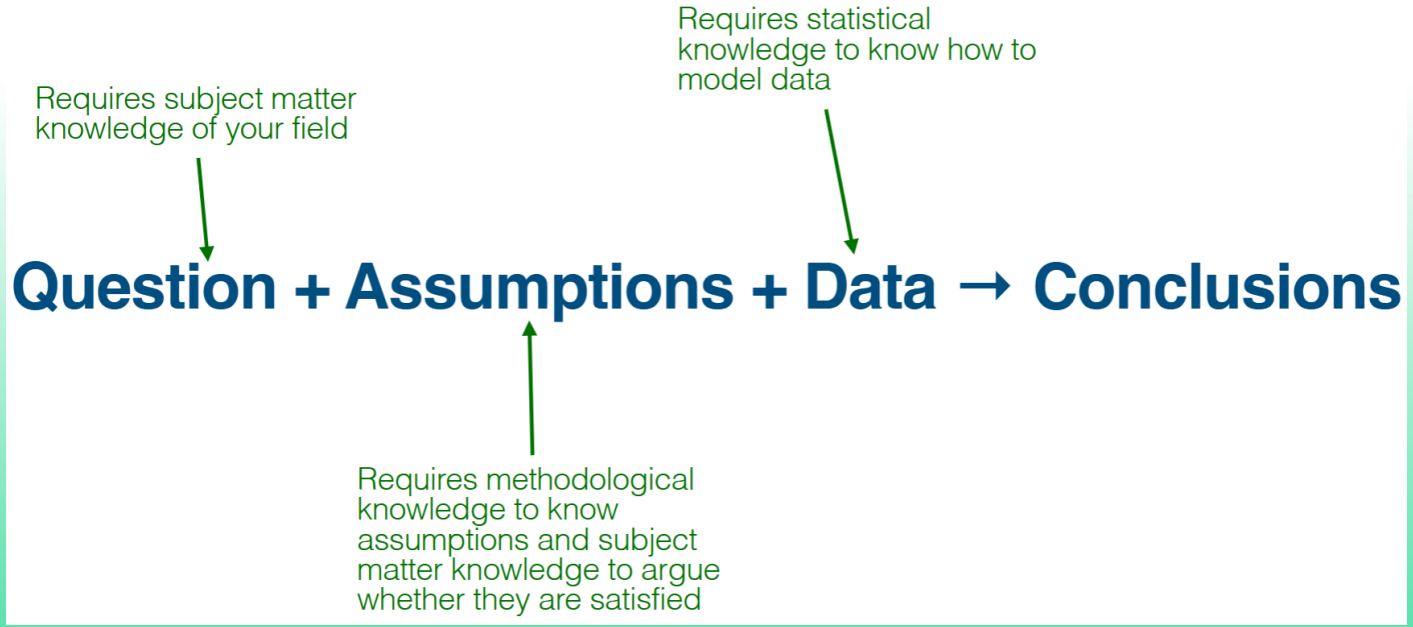
- Descriptive
- Causal
- Predictive

NB: COMBINATION ARE POSSIBLE

"What is the effect on the risk of CVD of free, specially designed exercise classes to people who are at higher risk of CVD?"

"Which patients benefit most from treatment A compared to treatment B in preventing stroke?"

Every Project should begin with some descriptive analysis!



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coffee

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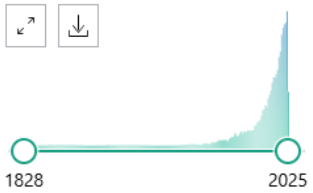
Page 1 of 2,300

RESULTS BY YEAR



PUBLICATION DATE

- 1 year
- 5 years
- 10 years
- Custom Range

1 Cite Share

Coffee and its consumption: benefits and risks.

Butt MS, Sultan MT.

Crit Rev Food Sci Nutr. 2011 Apr;51(4):363-73. doi: 10.1080/10408390903586412.

PMID: 21432699 Review.

Coffee is the leading worldwide beverage after water and its trade exceeds US $10 billion worldwide. ...Caffeine also affects adenosine receptors and its withdrawal is accompanied with muscle fatigue and allied problems in those addicted to **coffee**. An array of evide ...

2 Cite Share

Coffee for Cardioprotection and Longevity.

O'Keefe JH, DiNicolantonio JJ, Lavie CJ.

Prog Cardiovasc Dis. 2018 May-Jun;61(1):38-42. doi: 10.1016/j.pcad.2018.02.002. Epub 2018 Feb 21.

PMID: 29474816 Review.

Habitual **coffee** consumption is also associated with lower risks for cardiovascular (CV) death and a variety of adverse CV outcomes, including coronary heart disease (CHD), congestive heart failure (HF), and stroke; **coffee's** effects on arrhythmias and hyperten ...

WARNING: ANSWERING CAUSAL QUESTIONS IS DIFFICULT!

HARVARD T.H. CHAN SCHOOL OF PUBLIC HEALTH

Home / News / Is coffee good or bad for your health?

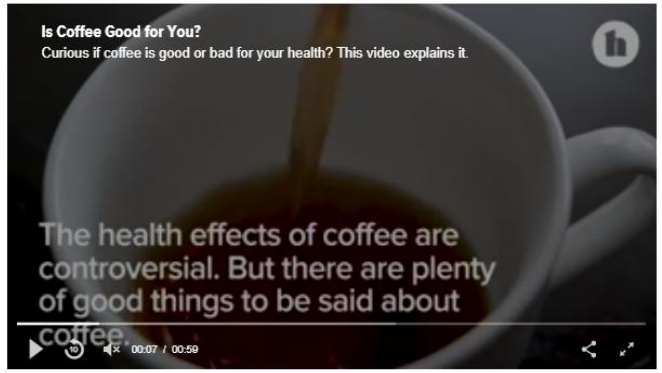
Food, Nutrition, Diet

Is coffee good or bad for your health?

By Staff Writer · April 9, 2021

Coffee — Good or Bad?

Coffee is a popular beverage with many health benefits, including high amounts of antioxidants. That said, its main active ingredient, caffeine, has its downsides.



View video transcript

The health effects of coffee are controversial.

Despite what you may have heard, there are plenty of good things to be said about coffee.

It's high in antioxidants and linked to a reduced risk of many diseases.

However, it also contains caffeine, a stimulant that can cause problems in some people and disrupt sleep.

How Many People Drink Coffee in the World?

Over 1 billion people worldwide drink coffee every day. That's about 12.6% of the world's population.

- Over **1 billion people** worldwide drink coffee every day. That's about 12.6% of the world's population.
- Over **2.25 billion cups** of coffee are consumed in the world daily.

https://www.coffeedasher.com/how-many-people-drink-coffee/

Is drinking coffee healthy?

Drinking coffee can be healthy. For example, studies find that coffee drinkers have a lower risk of death from any cause compared to people who don't drink coffee.

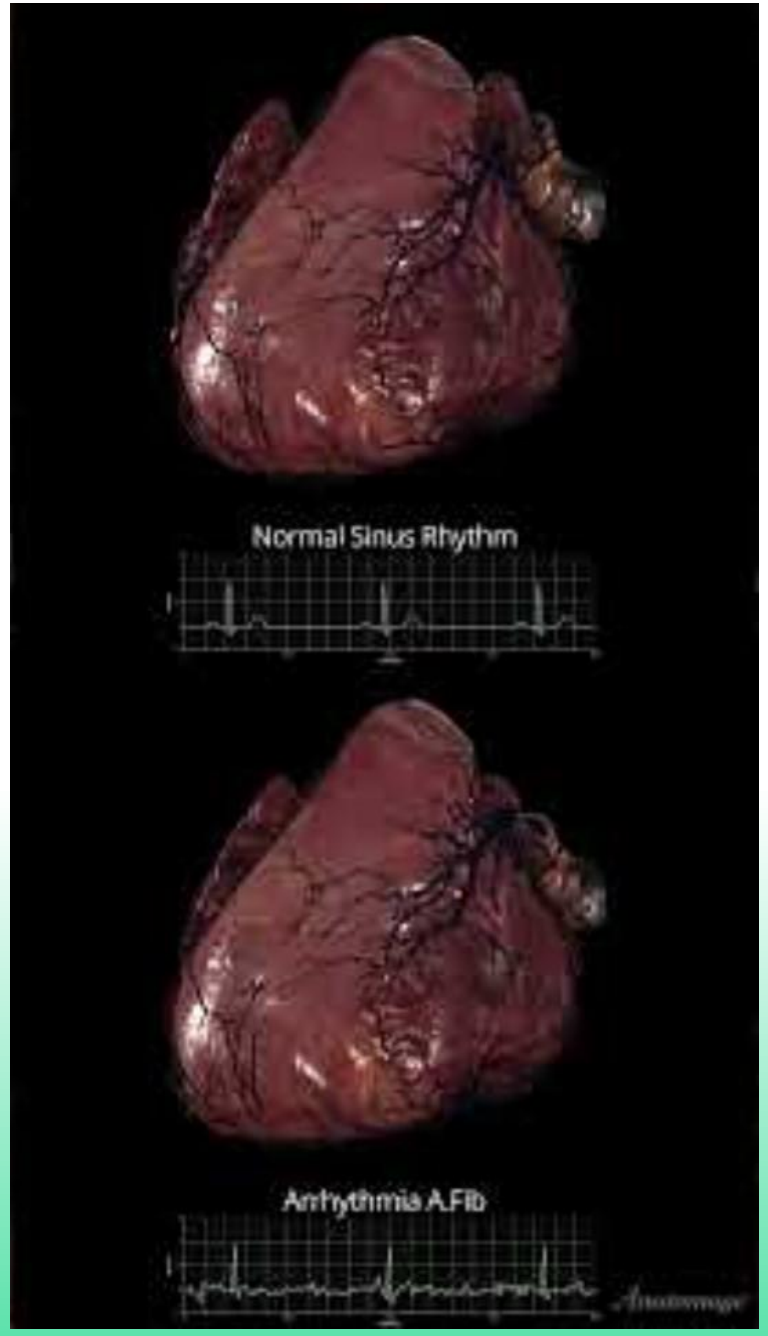
The benefits of coffee depend on things like how much you drink, your age, being biologically male or female, medicine you take, and even your genes.

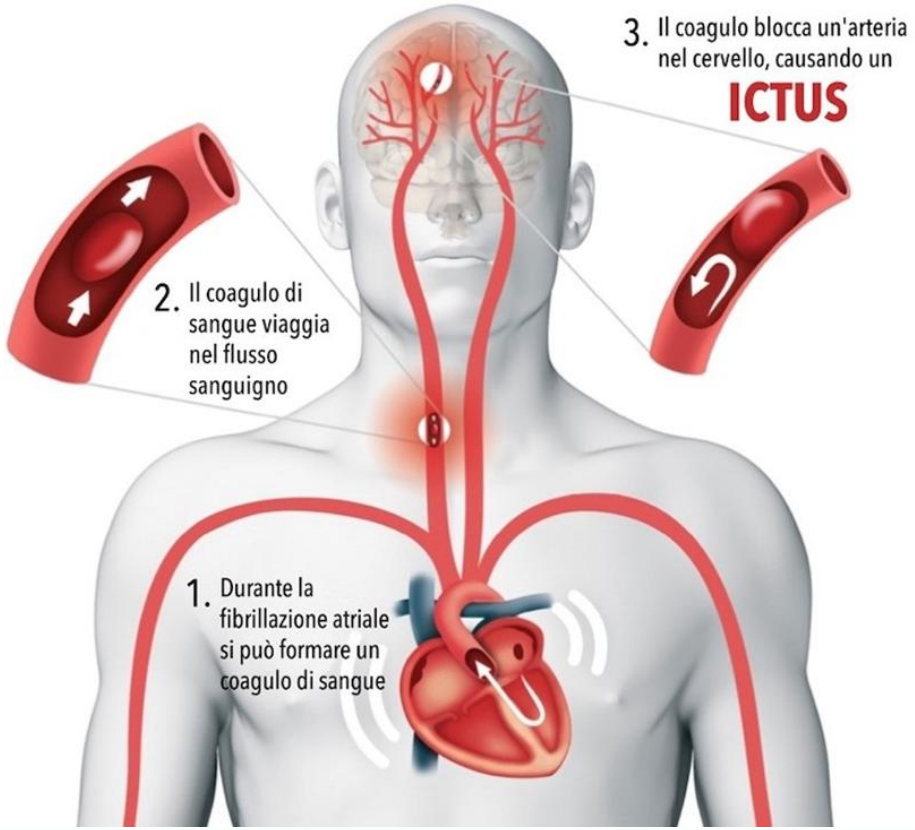
Some benefits are linked to caffeine. Other benefits are related to the other components in coffee. But in general, studies find that coffee is linked to health in many ways. Drinking coffee may be linked to a lower risk of:

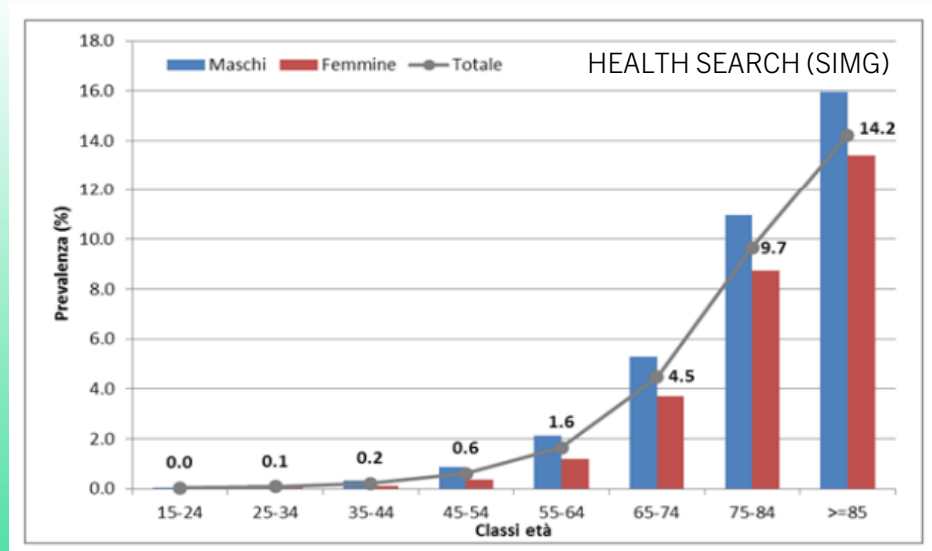
- Parkinson's disease, type 2 diabetes and Alzheimer's disease among some groups of people.
- Metabolic syndrome and chronic kidney disease.
- Liver cancer and liver disease, including cirrhosis.
- Gallstones and kidney stones.

Credits: J.Lebeque, Rotterdam

"Do different anticoagulants in AF lead to different risks of reduced renal function?"







"Do different anticoagulants in AF lead to different risks of reduced renal function?"

DOAC
Direct Oral Anti Coagulant

- Licensed: 2013
- Directly inhibit specific clotting factors:
  - Dabigatran: thrombin (factor IIa)
  - Rivaroxaban, Apixaban, Edoxaban: fact Xa
- No routine monitoring needed

VKA
Vitamin K Antagonist

- Licensed: 1950
- Inhibit Vitamin K epoxide reductase (VKOR) → ↓ synthesis of clotting factors II, VII, IX, X (and proteins C and S)
- Requires regular INR testing (target usually 2.0–3.0)

Before it became a life-saving anticoagulant, what was warfarin originally developed and used for?

A. Sedative for horses
B. A fertilizer for crops
C. A rat poison
D. A food preservative

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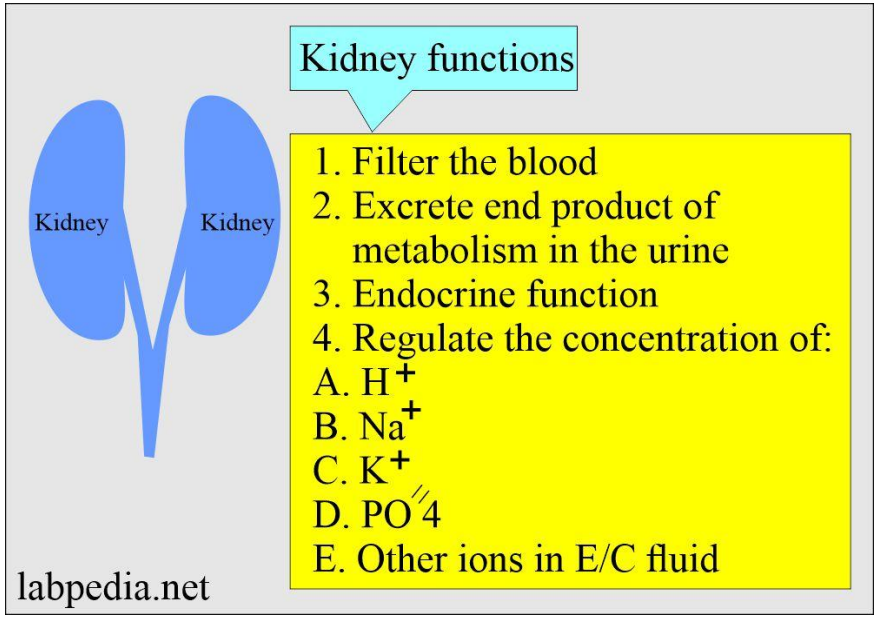
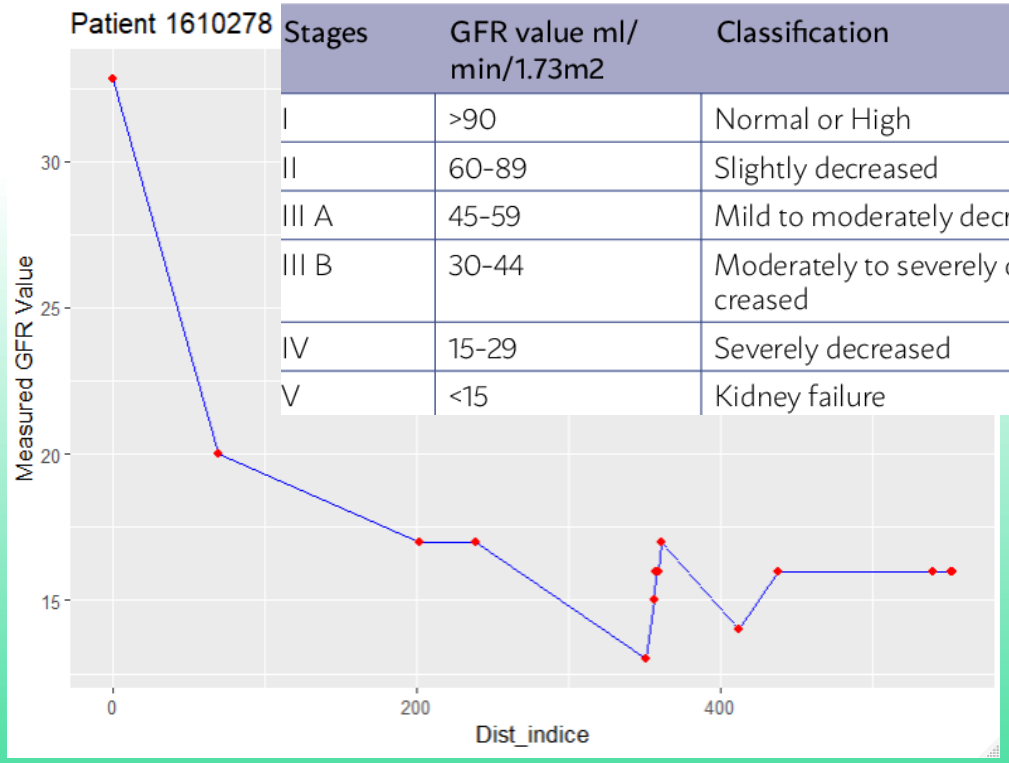




Stages	GFR value ml/ min/1.73m2	Classification
I	>90	Normal or High
II	60-89	Slightly decreased
III A	45-59	Mild to moderately decreased
III B	30-44	Moderately to severely de-creased
IV	15-29	Severely decreased
V	<15	Kidney failure

Cardiorenal Outcomes Among Patients With Atrial Fibrillation Treated With Oral Anticoagulants

Marco Trevisan, Paul Hjemdahl, Catherine M. Clase, Ype de Jong, Marie Evans, Rino Bellocco, Edouard L. and Juan Jesus Carrero

Changes in Renal Function in Patients With Atrial Fibrillation: An Analysis From the RE-LY Trial

Michael Böhm MD *, Michael D. Ezekowitz MD, ChB, DPhil †‡, Stuart J. Connolly MD §, John W. Eikelboom MBBS §, Stefan H. Hohnloser MD ‖, Paul A. Reilly PhD ¶, Helmut Schumacher PhD #, Martina Brueckmann MD #**, Stephan H. Schirmer MD, PhD *, Mario T. Kratz MD *, Salim Yusuf MD, DPhil §, Hans-Christoph Diener MD ††, Ziad Hijazi MD ‡‡, Lars Wallentin MD, PhD ‡‡

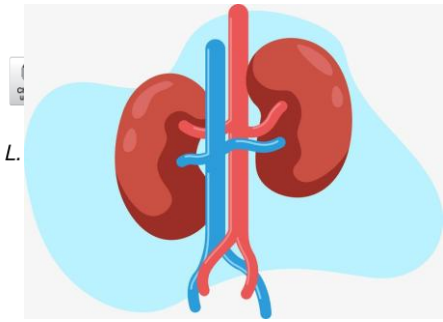
Efficacy and Safety of Apixaban Compared With Warfarin in Patients With Atrial Fibrillation in Relation to Renal Function Over Time

Insights From the ARISTOTLE Randomized Clinical Trial

Ziad Hijazi, MD, PhD[1,2]; Stefan H. Hohnloser, MD[3]; Ulrika Andersson, MSc[2]; et al

» Author Affiliations | Article Information

JAMA Cardiol. 2016;1(4):451-460. doi:10.1001/jamacardio.2016.1170



"Do different anticoagulants in AF lead to different risks of reduced renal function?"

How to get Data?

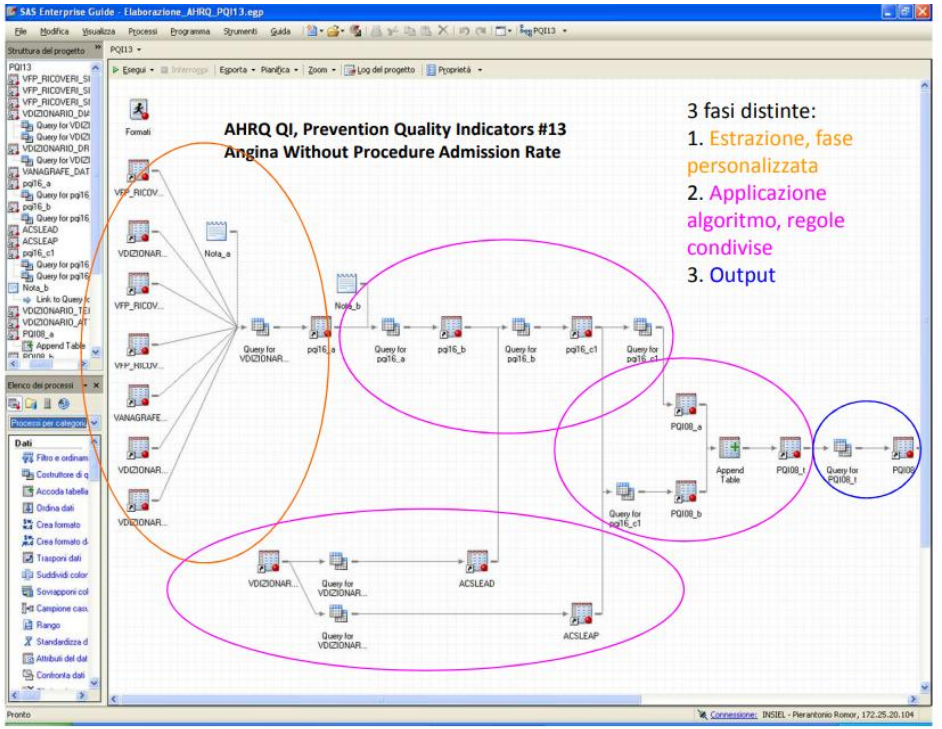
Il **Repository Epidemiologico Regionale (RER)** è un data warehouse gestito da Insiel S.p.A. su mandato dell'ARCSS. Al suo interno non sono presenti dati che consentano l'identificazione diretta degli individui: ogni sei mesi viene generata una nuova "key_anagrafe", una chiave pseudonimizzata che identifica univocamente ciascun soggetto.

Nel RER confluiscono numerose fonti dati, prevalentemente amministrative, ma anche alcune cliniche verticali, attraverso un articolato processo ETL e successivi controlli di consistenza. Un elemento distintivo del sistema del Friuli Venezia Giulia (FVG) è la presenza nel RER dei risultati degli esami di laboratorio eseguiti presso i laboratori pubblici della Regione (DNLAB).

La profondità temporale dei dati varia a seconda del flusso informativo: le SDO risalgono fino al 1985, mentre le anagrafiche contengono dati anche anteriori, relativi a chiunque abbia avuto contatti con il sistema sanitario regionale, indipendentemente dalla residenza. Altri flussi hanno profondità inferiori: i dati di laboratorio sono disponibili dal 2009, quelli relativi alla farmaceutica convenzionata dal 1995, il CUP dal 2013 e il PS dal 2000.

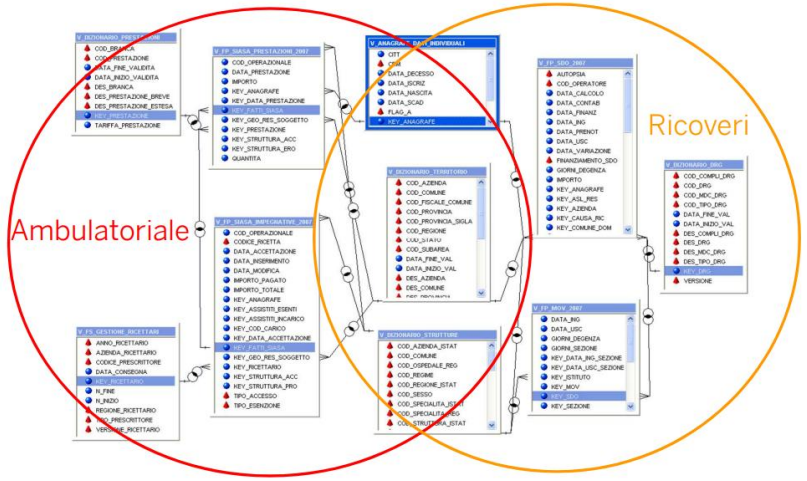
Oltre ai flussi amministrativi, il RER include anche fonti cliniche, come C@rdioNet, un software gestionale verticale che rappresenta la cartella clinica cardiologica, compilata regolarmente da medici cardiologi e personale infermieristico a ogni contatto diretto con il paziente, a partire dal 2010. Fino al 2015, C@rdioNet era accessibile solo tramite un portale regionale basato su Business Object; successivamente è stata integrata completamente nel RER, consentendo così l'accesso ai dati clinici in sinergia con gli altri flussi amministrativi.

Nel RER, la cartella C@rdioNet è suddivisa in 13 tabelle, prive di chiavi esterne di collegamento: tutte sono unite esclusivamente mediante la key_anagrafe. Questo implica che, per caratterizzare un individuo in un determinato momento (es. situazione anamnestica o follow-up), è necessario definire regole temporali per correlare le informazioni provenienti dalle diverse tabelle.



Strutture dati del RER

Esempio di relazioni tra tabelle e fonti a livello di Repository



Linkage basato su nuove chiavi (surrogate) tra cui la key_anagrafe

L0 – dati originari contenuti nel RER.

A questo livello le tabelle sono quelle direttamente accessibili nel RER e derivate dai flussi informativi amministrativi e clinici, dopo un processo ETL in carico a Insiel S.p.A.. L'elenco non esaustivo delle tabelle che rientrano in questo livello include:

- Registry data (general registry, births, deaths, identification of parents, residences, domiciles)
- Hospital admissions (hospital discharge forms)
- ADI (integrated home care)
- PIC (intermediate home services)
- RSA (health care residences)
- Exemptions
- Territorial pharmaceuticals (public drug distribution system)
- Hospital and direct pharmaceuticals
- PS (first aid services)
- Pathological anatomy (SNOMED coded reports)
- CUP (single center bookings)
- Outpatient services
- DNLAB (laboratory tests – FVG public laboratories only)
- C@rdioNet (cardiology ward)

"Do different anticoagulants in AF lead to different risks of reduced renal function?"

Which one would you use??
5 max 🤔

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Which Inclusion and exclusion criteria?

Inclusion
- Age ≥18 years
- Residents in ASUGI for at least 2 years
- Diagnosis of AF in ASUGI in the period 2013-2021
- First purchase of anticoagulant therapy (index date)
- Not purchasing anticoagulants in the 5 years preceding the index date

Exclusion
- Cardiac Valvular Disease
- End stage renal disease (dialysis, Transplant)
- GFR < 15 ml/min/1.73m2
- No GFR measurement available

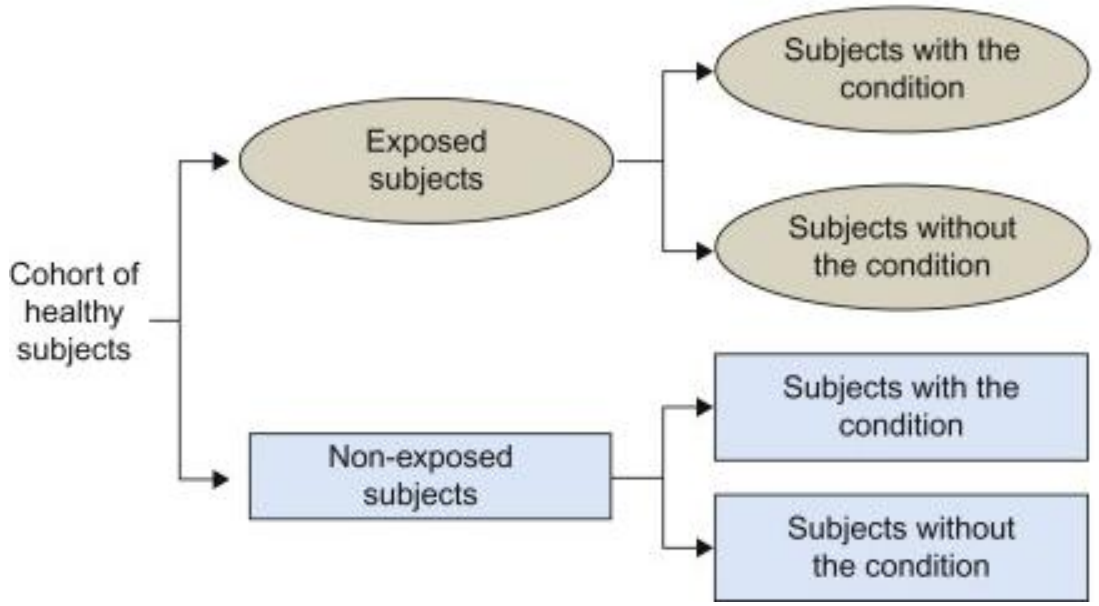
Terapia iniziale VKA 3521

Terapia iniziale NOAC 3352

Follow-up ends: 30-09-2023

Which Study Design would you choose?

Retrospective Cohort Study



"Do different anticoagulants in AF lead to different risks of reduced renal function?"

Table 1. Baseline Characteristics of Patients Initiating Oral Anticoagulants, Overall and Stratified by Initial Treatment Group, included in primary analysis.

	Overall (100%) 6873	DOAC (48.77 %) 3352	VKA (51.23 %) 3521	SMD
Gender (n, %)				0.075
Male	3544 (51.56)	1664 (49.6)	1880 (53.4)	
Female	3329 (48.44)	1688 (50.36)	1641 (46.61)	
Year of enrolment (n, %)				1.242
2013-2015	2106 (30.64)	340 (10.1)	1766 (50.2)	
2016-2018	2504 (36.43)	1153 (34.4)	1351 (38.4)	
2019-2021	2263 (32.93)	1859 (55.5)	404 (11.5)	
Province of residence (n, %)				0.287
Gorizia	2335 (33.97)	1370 (40.9)	965 (27.4)	
Trieste	4538 (66.03)	1982 (59.1)	2556 (72.6)	
Age, y (median [Q1-Q3])	79 [73-84]	79 [73-85]	78 [73- 84]	0.053
Baseline GFR (median [Q1-Q3])	68 [54-81]	69 [56- 81]	67 [52-80]	0.149
Baseline GFR class (n, %)				0.227
15-29	212 (3.08)	42 (1.3)	170 (4.8)	
30-45	768 (11.17)	341 (10.2)	427 (12.1)	
46-60	1446 (21.04)	701 (20.9)	745 (21.2)	
61-90	3837 (55.83)	1961 (58.5)	1876 (53.3)	
>90	610 (8.88)	307 (9.2)	303 (8.6)	
Other conditions (n, %)				
Microalbuminuria	794 (11.55)	398 (11.9)	396 (11.2)	0.02
COPD	1542 (22.44)	732 (21.8)	810 (23.0)	0.028
Diabetes	1976 (28.75)	941 (28.1)	1035 (29.4)	0.029
Anemia	3023 (43.98)	1468 (43.8)	1555 (44.2)	0.007
Dislipidemia	6454 (93.9)	3164 (94.4)	3290 (93.4)	0.04
Hypertension	5906 (85.93)	2846 (84.9)	3060 (86.9)	0.058
CKD	2042 (29.71)	919 (27.4)	1123 (31.9)	0.098
Obesity	1986 (28.9)	932 (27.8)	1054 (29.9)	0.047
CHF	2257 (32.84)	1038 (31.0)	1219 (34.6)	0.078

	Overall (100%) 6873	DOAC (48.77 %) 3352	VKA (51.23 %) 3521	SMD
Concomitant medications (n,%)				
ACE-Inhibitors	3229 (46.98)	1535 (45.8)	1694 (48.1)	0.046
Antiplatelets	3377 (49.13)	1602 (47.8)	1775 (50.4)	0.052
Antiarrhythmic	2324 (33.81)	1176 (35.1)	1148 (32.6)	0.052
Antidiabetics	1536 (22.35)	725 (21.6)	811 (23.0)	0.034
Antihypertensives	6427 (93.51)	3113 (92.9)	3314 (94.1)	0.051
ASA (Aspirin)	2859 (41.6)	1300 (38.8)	1559 (44.3)	0.112
Beta-blockers	5193 (75.56)	2533 (75.6)	2660 (75.5)	<0.001
Total diuretics	1361 (19.8)	608 (18.1)	753 (21.4)	0.082
Lipid-lowering agents	3207 (46.66)	1642 (49.0)	1565 (44.4)	0.091
Metformin	1233 (17.94)	605 (18.0)	628 (17.8)	0.006
Renin-angiotensin system inhibitor (RASi)	4884 (71.06)	2375 (70.9)	2509 (71.3)	0.009
Statins	3099 (45.09)	1588 (47.4)	1511 (42.9)	0.09
Diuretics	3433 (49.95)	1591 (47.5)	1842 (52.3)	0.097
SGLT2 inhibitors	125 (1.82)	98 (2.9)	27 (0.8)	0.161
Sartans (ARBs)	2057 (29.93)	1001 (29.9)	1056 (30.0)	0.003
Sulfonylureas	342 (4.98)	143 (4.3)	199 (5.7)	0.064
Vasodilators	877 (12.76)	367 (10.9)	510 (14.5)	0.106
Insulin	374 (5.44)	160 (4.8)	214 (6.1)	0.058
Other antiplatelets	828 (12.05)	456 (13.6)	372 (10.6)	0.093
Ezetimibe	383 (5.57)	230 (6.9)	153 (4.3)	0.11
Glitazones	59 (0.86)	19 (0.6)	40 (1.1)	0.062
DPP-4 inhibitors	175 (2.55)	83 (2.5)	92 (2.6)	0.009
GLP-1 receptor agonists	61 (0.89)	44 (1.3)	17 (0.5)	0.088
ARNI (Angiotensin receptor-neprilysin inhibitors)	41 (0.6)	34 (1.0)	7 (0.2)	0.105
Repaglinide	198 (2.88)	69 (2.1)	129 (3.7)	0.096
Scores				
CHARLSON (median [Q1-Q3])	1 [0-3]	1 [0-3]	1 [0-3]	0.017
CHARLSON AGE (median [Q1-Q	5 [3-6]	5 [4-6]	5 [3-6]	
CHAD VASC (median [Q1-Q3])	4 [3-5]	4 [3-5]	4 [3-5]	0.084
CHADS (median [Q1-Q3])	2 [2-3]	2 [2-3]	2 [2-3]	0.117
ATRIA (median [Q1-Q3])	3 [2-6]	3 [2-6]	3 [2-6]	0.045
ORBIT (median [Q1-Q3])	2 [1-4]	2 [1-4]	2 [1-4]	0.030
CV risk score (%)				0.068
– Low or Moderate	1339 (19.5)	625 (18.6)	714 (20.3)	
– High	672 (9.78)	304 (9.1)	368 (10.5)	
– Very High	4862 (70.74)	2423 (72.3)	2439 (69.3)	

Anything wrong? 🤔

Table 1. Baseline Characteristics of Patients Initiating Oral Anticoagulants, Overall and Stratified by Initial Treatment Group, included in primary analysis.

	SMD	Overall (100%) 6873	DOAC (48.77 %) 3352	VKA (51.23 %) 3521	SMD
	>0.1				
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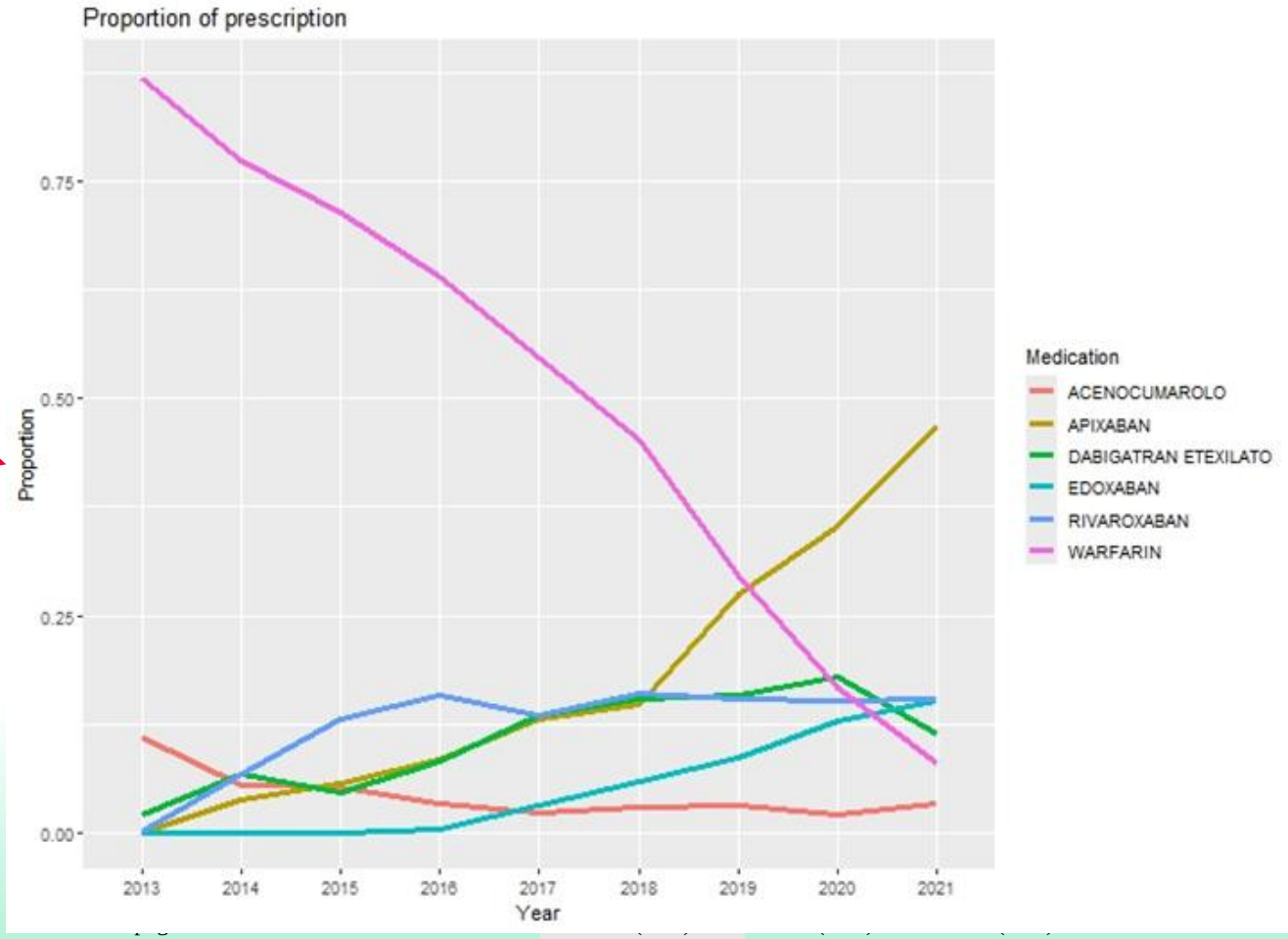
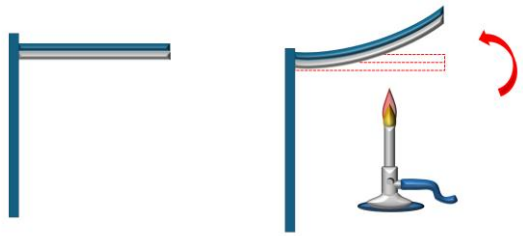
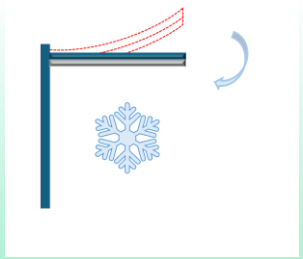


Anything wrong? 🤔

Scores					
CHARLSON (median [Q1-Q3])		1 [0-3]	1 [0-3]	1 [0-3]	0.017
CHARLSON AGE (median [Q1-Q3])		5 [3-6]	5 [4-6]	5 [3-6]	
CHAD VASC (median [Q1-Q3])		4 [3-5]	4 [3-5]	4 [3-5]	0.084
CHADS (median [Q1-Q3])	*	2 [2-3]	2 [2-3]	2 [2-3]	0.117
ATRIA (median [Q1-Q3])		3 [2-6]	3 [2-6]	3 [2-6]	0.045
ORBIT (median [Q1-Q3])		2 [1-4]	2 [1-4]	2 [1-4]	0.030
CV risk score (%)					0.068
– Low or Moderate		1339 (19.5)	625 (18.6)	714 (20.3)	
– High		672 (9.78)	304 (9.1)	368 (10.5)	
– Very High		4862 (70.74)	2423 (72.3)	2439 (69.3)	

CAUSALITY
In physics and epidemiology



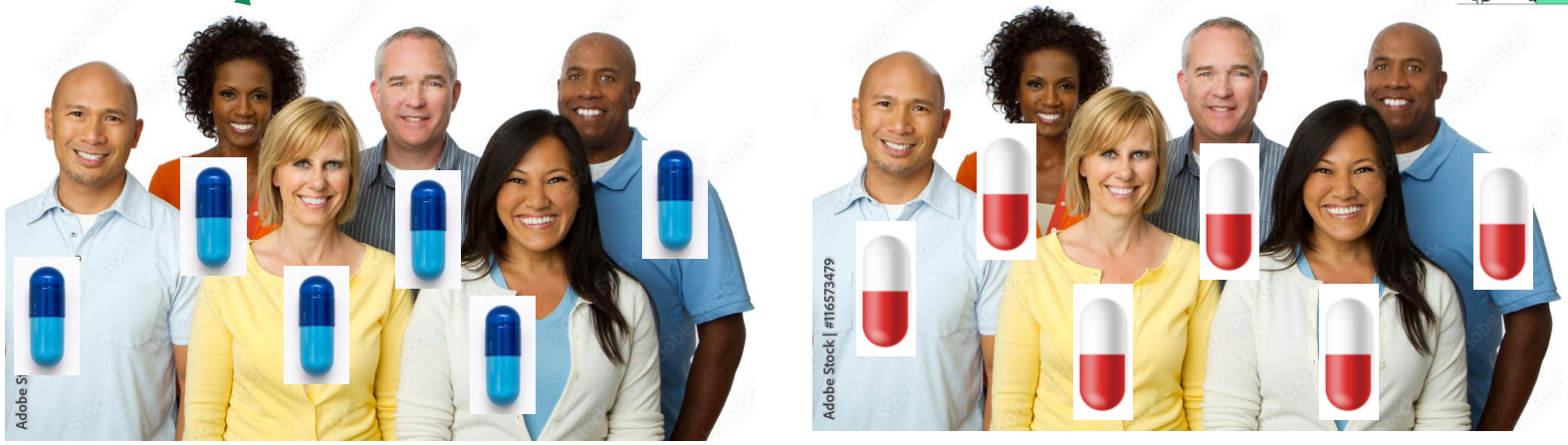


$$\Delta l = \lambda \cdot l_0 \cdot \Delta T$$

dove Δl indica la variazione di lunghezza del corpo, λ indica il coefficiente di dilatazione lineare, l_0 indica la lunghezza originaria del corpo.

Causal questions require comparing the same group of people under two different conditions

$$Pr(M^{T=1}) - Pr(M^{T=0})$$

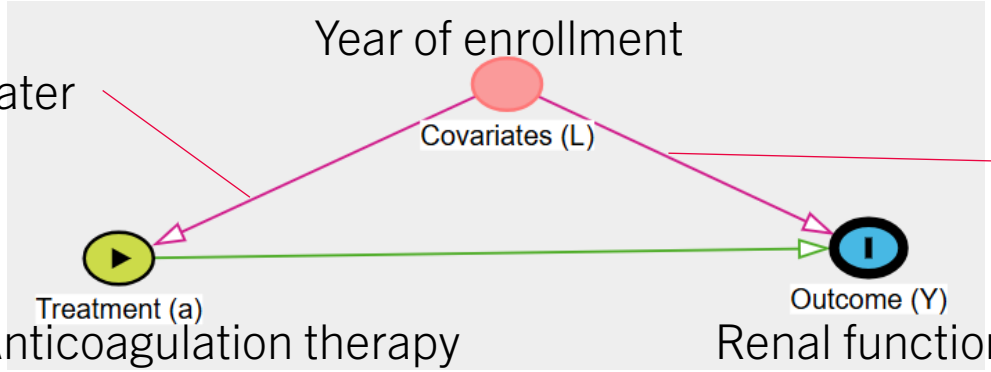


...we compare different groups of people because, practically, it's the only thing we can do

- Irreversibility of some biomedical phenomena
- Logistic difficulties
- Complex and multiple variables involved

$$Pr(M \mid T = 1) - Pr(M \mid T = 0)$$

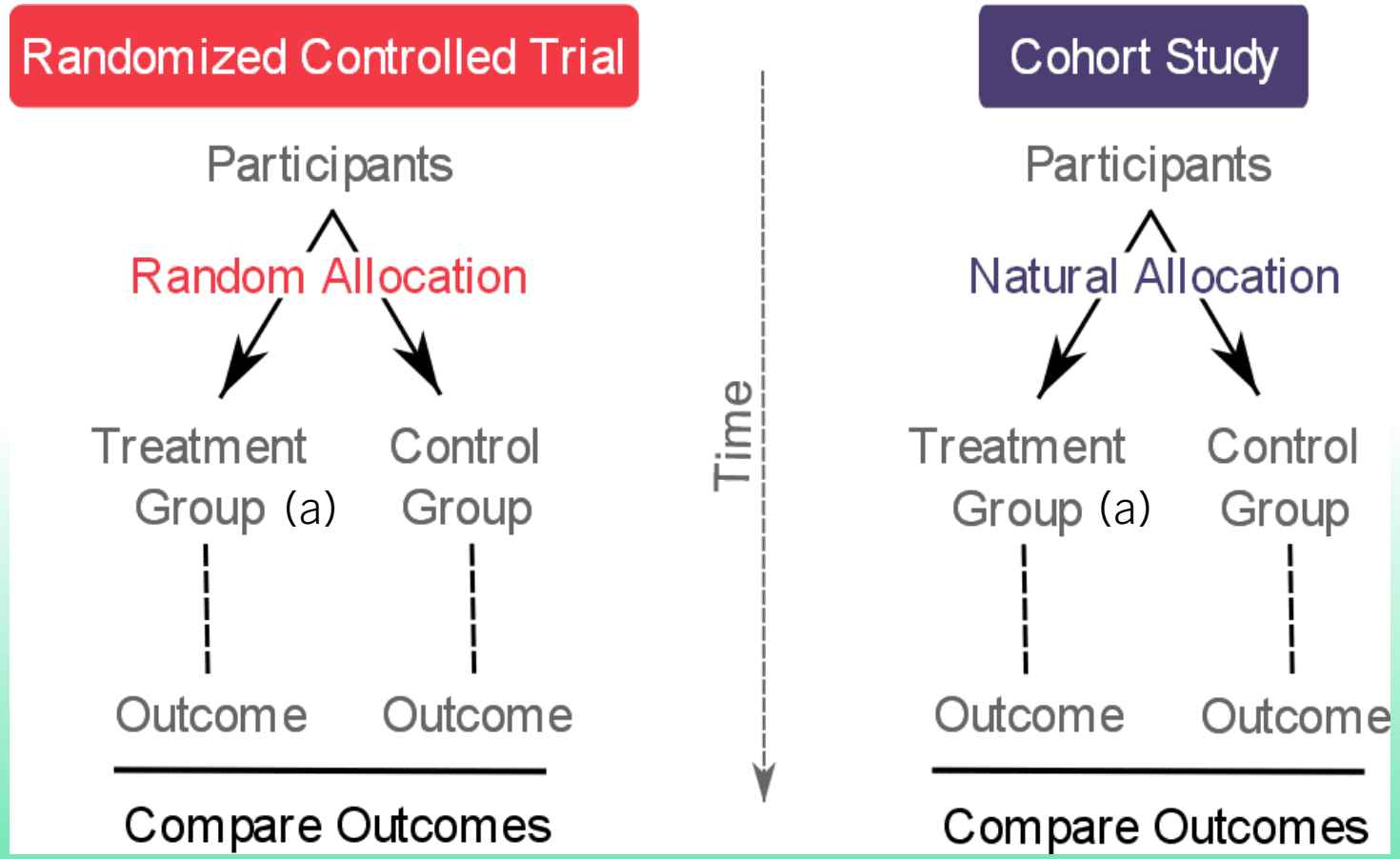
DOAC were developed later



In 2013 doctors could have had less medication to prevent renal function decline overall compared to 2021. Or they could have been worse at diagnosing the condition

Anticoagulation therapy

Renal function decline



Excheangability: $Y^a \perp A$

$P(Y^a \mid A) = P(Y^a)$

The distribution of the potential outcome under treatment a is the same regardless of whether or not they actually received treatment a.

Conditional Excheangeability: $Y^a \perp A \mid L$

The potential outcome under treatment a is independent of the actual treatment assignment A, conditional on covariates L.

Exchangeability is the assumption of being able to exchange groups without changing the outcome of the study.

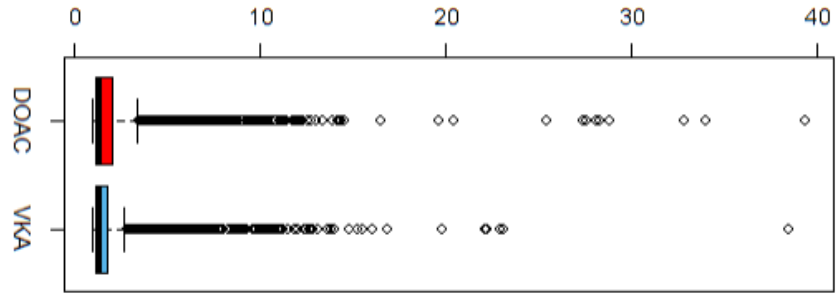
$P(A=a|L)=P(A=a)$

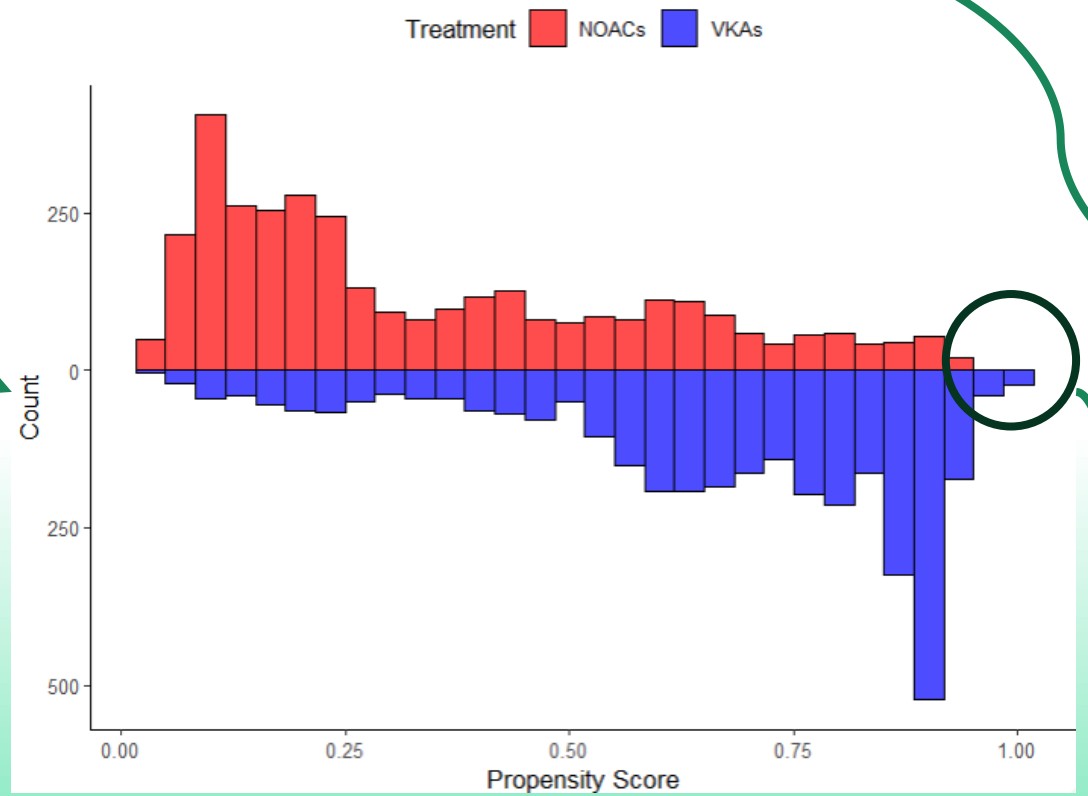
~~$P(A=a|L)=P(A=a)$~~

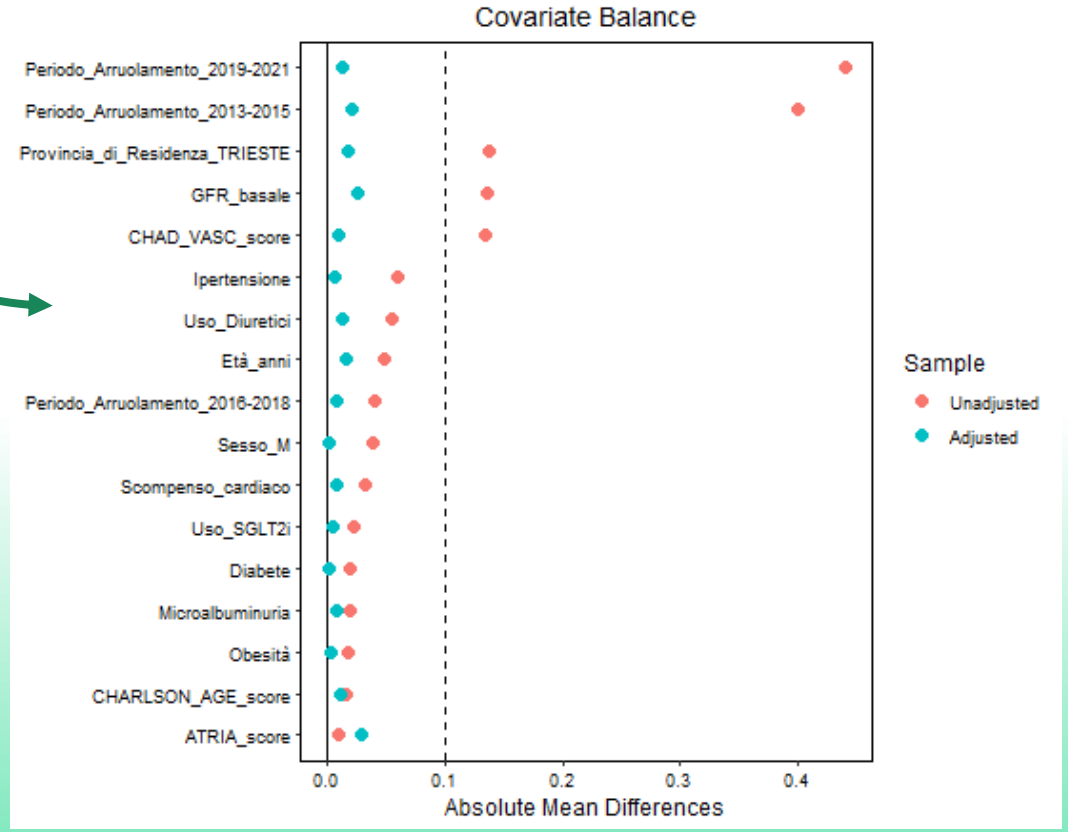
```r
# Step 1: Calculate Propensity Scores
ps_model <- glm(drug_group ~ epoch + gender + age_indice + classe_GFR + integrata_diabete +
                  integrata_ipertensione + INTEGRATA_OBESITA + integrata_scc + integrata_microalbuminuria +
                  DIURETICITOT2_af + SGLT2I_af + resid_provincia +
                  integrata_rcvma + CHARLSON_AGE_score + CHAD_VASC_score + ATRIA_score ,
                data = test, family = binomial)

test$propensity_score <- predict(ps_model, type = "response")
summary(test$propensity_score)
test$iptw1 <-(test$drug_group==1)/test$propensity_score+(test$drug_group==0)/(1-test$propensity_score)
```

How to adjust? Inverse Probability of Treatment Weighting (IPTW) is an option!





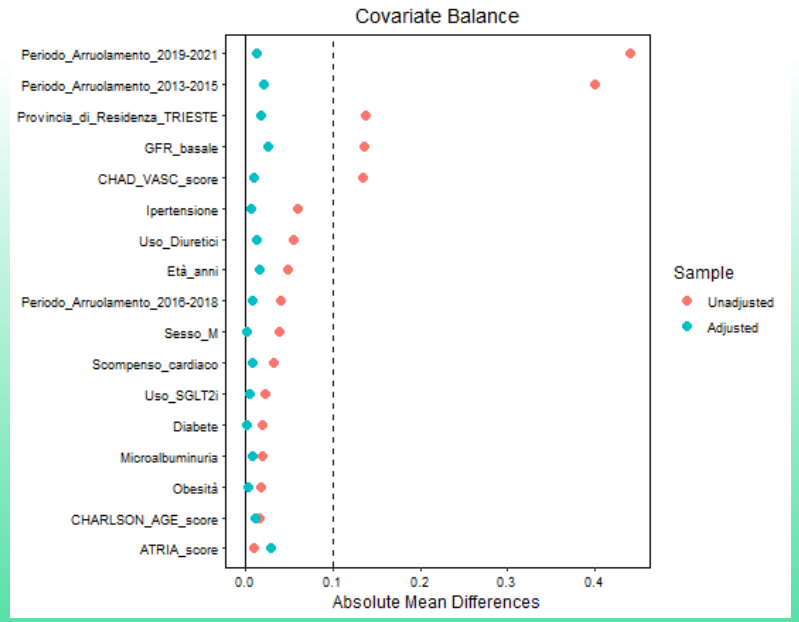


Why remove patient without PS overlap?

overlap	drug_group 0	1
0	0	21
1	3370	3499

The positivity assumption states that there must be a non-zero probability of receiving any level of treatment or exposure for every individual or unit, regardless of their observed characteristics.

	SMD	DOAC	VKA	SMD
	>0.1			
Gender (n, %)				
Male		3581.9 (50.9)	3540.1 (51.4)	0.009
Year of enrolment (n, %)				0.046
2013-2015		2296.3 (32.7)	2101.5 (30.5)	
2016-2018		2477.4 (35.2)	2491.9 (36.2)	
2019-2021		2258.7 (32.1)	2292.9 (33.3)	
Province of residence (n, %)				
Trieste		4739.6 (67.4)	4522.2 (65.7)	0.037
Age, y (mean (SD))		78.19 (9.59)	77.95 (8.96)	0.025
Baseline GFR (mean (SD))		65.60 (19.05)	66.45 (18.61)	0.045
Baseline GFR class (n, %)				0.097
15-29		338.8 (4.8)	207.1 (3.0)	
30-45		820.4 (11.7)	785.2 (11.4)	
46-60		1485.7 (21.1)	1438.2 (20.9)	
61-90		3819.3 (54.3)	3897.1 (56.6)	
>90		568.2 (8.1)	558.6 (8.1)	
Other conditions (n, %)				
Microalbuminuria		968.9 (13.8)	800.9 (11.6)	0.065
COPD		1618.0 (23.0)	1582.5 (23.0)	0.001
Diabetes		2001.0 (28.5)	1985.9 (28.8)	0.008
Anemia	*	3060.5 (43.5)	3390.5 (49.2)	0.115
Dislipidemia		6640.0 (94.4)	6461.8 (93.8)	0.025
Hypertension		6075.8 (86.4)	5888.2 (85.5)	0.026
CKD		2250.5 (32.0)	2062.3 (29.9)	0.044
Obesity		1941.9 (27.6)	1914.3 (27.8)	0.004
CHF		2322.7 (33.0)	2264.2 (32.9)	0.003



Concomitant medications (n, %)			
ACE-Inhibitors	3093.2 (44.0)	3236.3 (47.0)	0.061
Antiplatelets	3560.2 (50.6)	3594.4 (52.2)	0.031
Antiarrhythmic	2500.8 (35.6)	2173.7 (31.6)	0.085
Antidiabetics	1492.7 (21.2)	1557.0 (22.6)	0.033
Antihypertensives	6537.0 (93.0)	6439.1 (93.5)	0.022
ASA (Aspirin)	2906.9 (41.3)	3108.8 (45.1)	0.077
Beta-blockers	5160.1 (73.4)	5287.1 (76.8)	0.079
Total diuretics	1321.7 (18.8)	1394.3 (20.2)	0.037
Lipid-lowering agents	3298.5 (46.9)	3248.2 (47.2)	0.005
Metformin	1223.0 (17.4)	1237.2 (18.0)	0.015
Renin-angiotensin system inhibitors (RASi)	5033.7 (71.6)	4872.6 (70.8)	0.018
Statins	3177.2 (45.2)	3148.5 (45.7)	0.011
Diuretics	3551.1 (50.5)	3463.9 (50.3)	0.004
Aldosterone antagonists	1491.0 (21.2)	1571.4 (22.8)	0.039
Calcium channel blockers	2613.6 (37.2)	2513.2 (36.5)	0.014
Vitamins/Supplements	1500.5 (21.3)	1511.6 (22.0)	0.015
Alpha-blockers	1299.8 (18.5)	1173.8 (17.0)	0.038
Other cardiac preparations	1118.7 (15.9)	1141.9 (16.6)	0.018
Anti-ischemic agents	129.5 (1.8)	126.7 (1.8)	<0.001
SGLT2 inhibitors	124.4 (1.8)	130.5 (1.9)	0.009
Sartans (ARBs)	2271.7 (32.3)	2092.9 (30.4)	0.041
Sulfonylureas	292.3 (4.2)	418.1 (6.1)	0.087
Vasodilators	889.2 (12.6)	898.7 (13.1)	0.012
Insulin	332.7 (4.7)	422.6 (6.1)	0.062
Other antiplatelets	908.1 (12.9)	810.2 (11.8)	0.035
Ezetimibe	476.2 (6.8)	389.9 (5.7)	0.046
Glitazones	25.3 (0.4)	74.4 (1.1)	0.085
DPP-4 inhibitors	168.8 (2.4)	259.7 (3.8)	0.079
GLP-1 receptor agonists	58.0 (0.8)	42.7 (0.6)	0.024
ARNI (Angiotensin receptor-neprilysin inhibitors)	43.4 (0.6)	30.2 (0.4)	0.025
Repaglinide	168.5 (2.4)	195.1 (2.8)	0.027
Scores			
CHARLSON (mean (SD))	1.94 (2.12)	1.91 (2.08)	0.017
CHARLSON_AGE (mean (SD))	5.21 (2.44)	5.16 (2.32)	0.02
CHAD_VASC (mean (SD))	4.21 (1.64)	4.08 (1.55)	0.08
CHADS (mean (SD))	2.51 (1.29)	2.40 (1.22)	0.08
ATRIA (mean (SD))	3.69 (2.12)	3.82 (2.07)	0.063
ORBIT (mean (SD))	2.54 (1.63)	2.61 (1.54)	0.040
CV risk score (n, %)			0.077
– Low or Moderate	1194.9 (17.0)	1358.7 (19.7)	
– High	736.5 (10.5)	637.3 (9.3)	
– Very High	5100.9 (72.5)	4890.2 (71.0)	

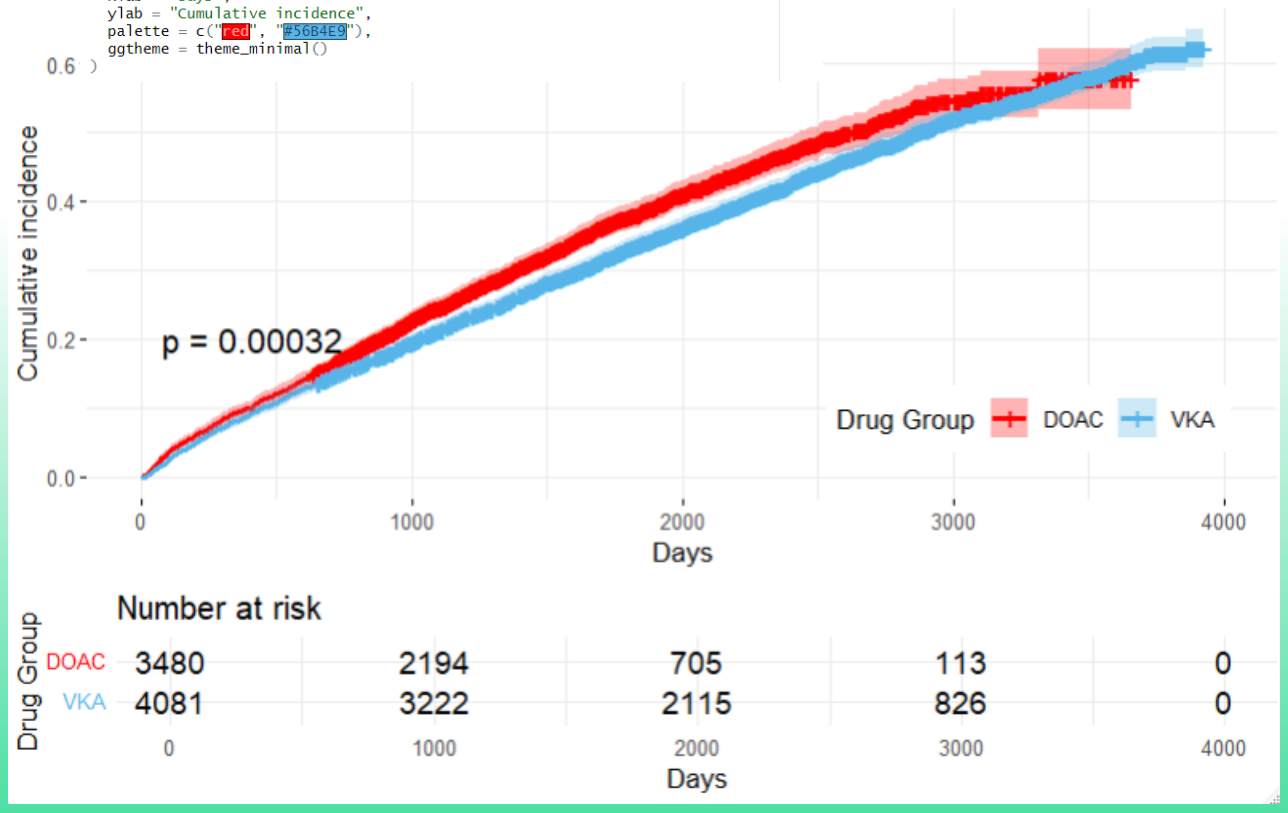
LET'S START SIMPLE...

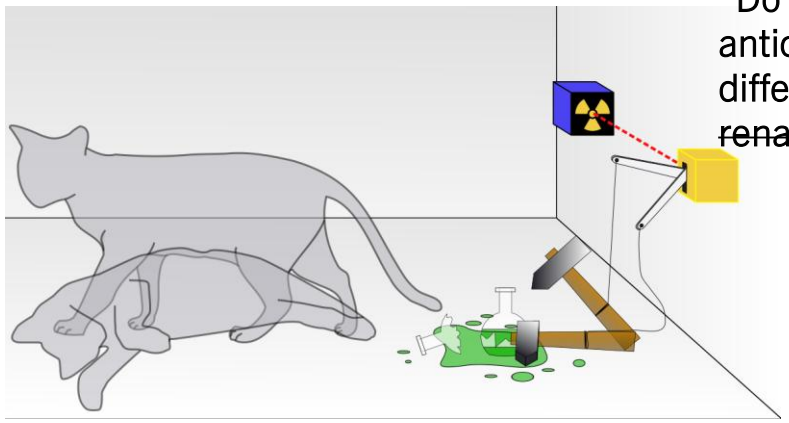
New Use of Anticoagulants

Death

End of Follow up (31-09-2023)

```
cumincPP.ev1 <- survfit(Surv(timing_decesso_comp,decesso_comp) ~ drug_group, data)
ggsurvplot(
  cumincPP.ev1,
  data = data,
  fun = "event",              # This shows cumulative incidence (1 - S(t))
  conf.int = TRUE,            # Show 95% CI
  risk.table = TRUE,          # Add number at risk below plot
  pval = FALSE,                # Add log-rank test p-value
  legend.title = "Drug Group",
  legend.labs = c("DOAC", "VKA"),
  xlab = "Days",
  ylab = "Cumulative incidence",
  palette = c("red", "#5GB4E9"),
  ggtheme = theme_minimal()
)
```

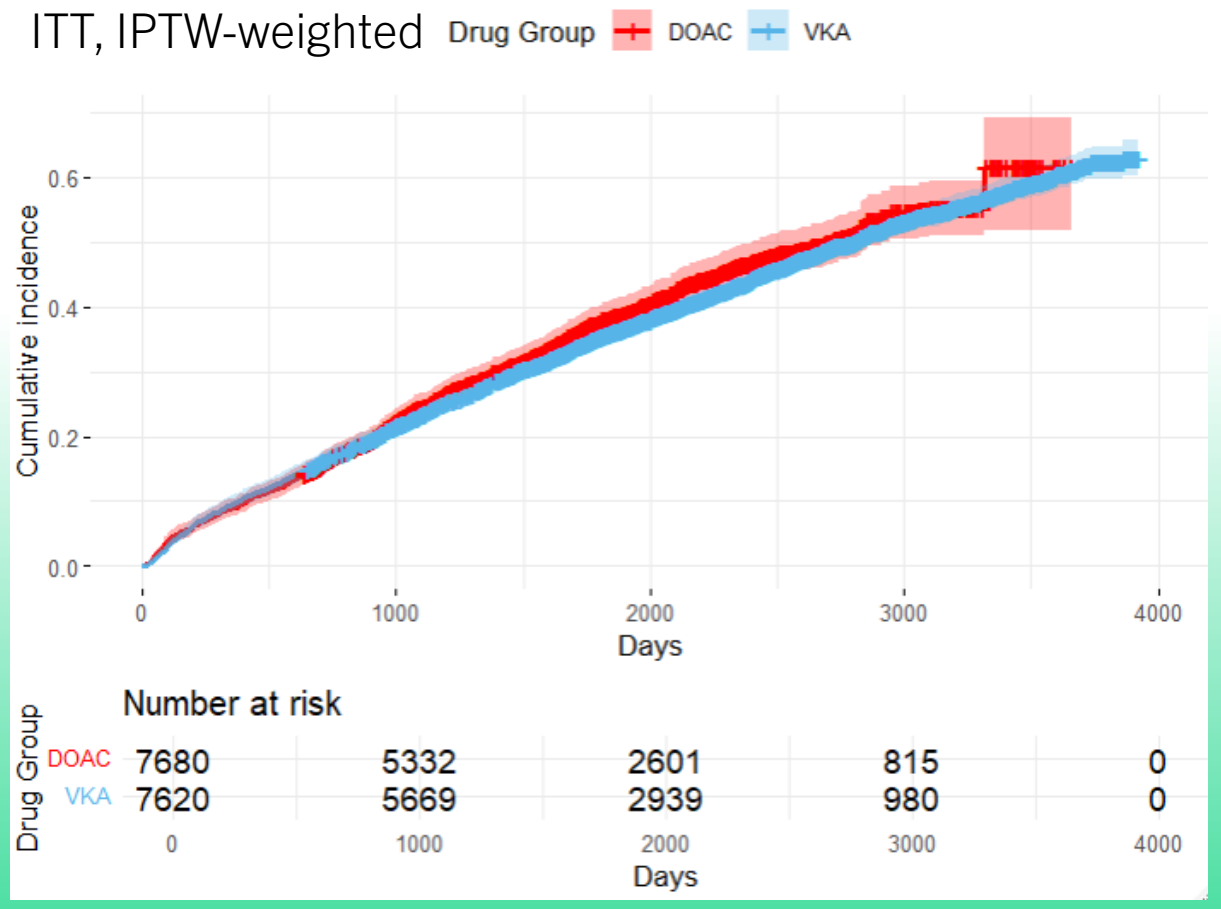




"Do different anticoagulants in AF lead to different risks of ~~reduced renal function?~~ Death?"

```
cumincPP.ev1 <- survfit(Surv(timing_decesso_comp,decesso_comp) ~ drug_group, weights= iptw1 , data)
```

ITT, IPTW-weighted



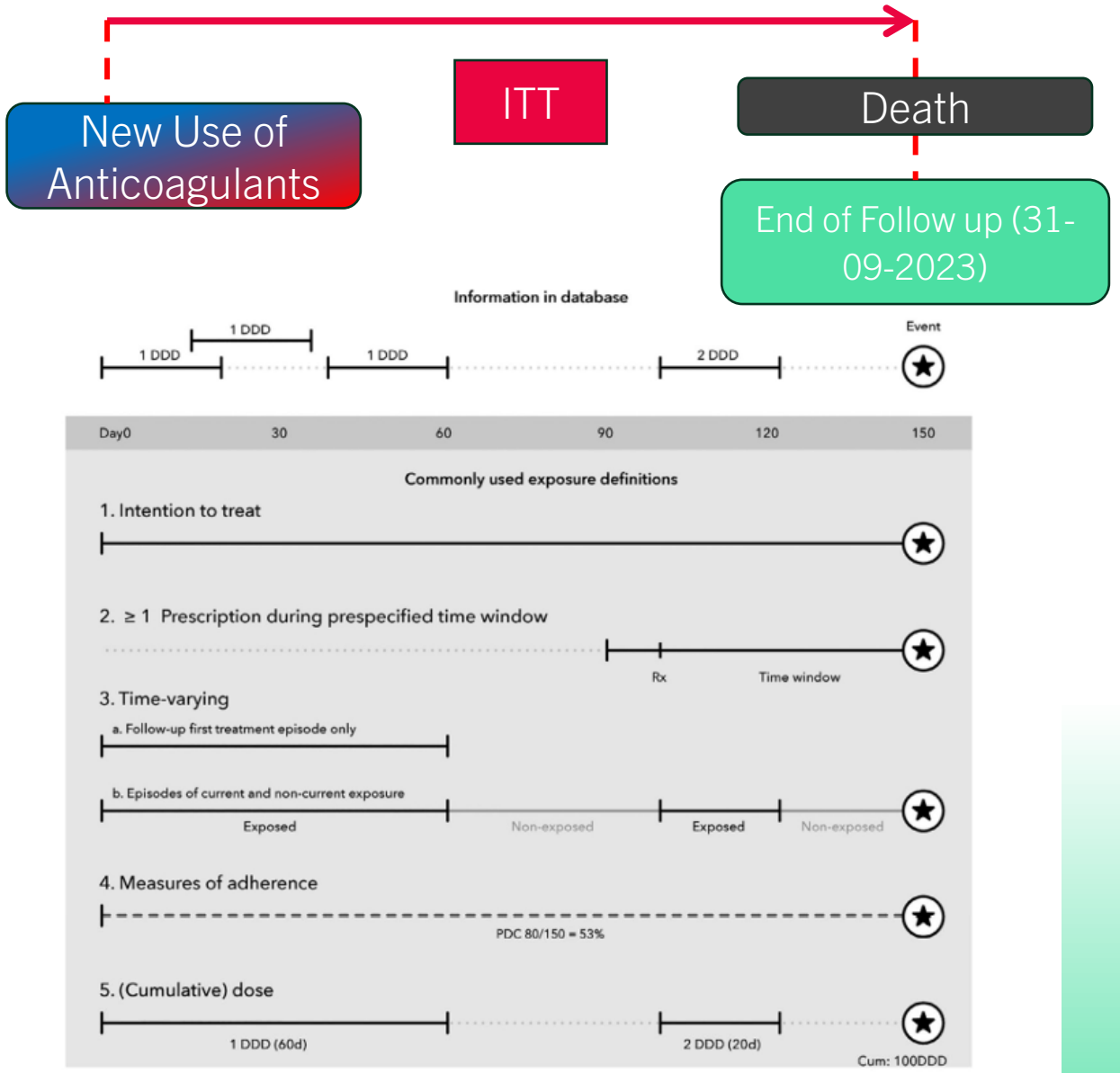


FIGURE 1 Categorization of commonly used exposure definitions in pharmacoepidemiological studies. Different types of exposure definition are applied in pharmacoepidemiological research. We divided these in five categories for further analysis: 1. intention to treat: exposure at baseline is included as a time-fixed variable in the model; 2. the presence of ≥1 prescriptions during a certain time period, for example during pregnancy or during the last 12 months prior to the event; 3. time-varying: episodes of (non)exposure are constructed based on duration of each prescription; 4. measures of adherence: for example, level of exposure is measured as proportion of days covered and 5. dose and cumulative dose: exposure is modeled as a continuous or ordinal variable and the effects of different dosages are compared (time-fixed or time-varying). DDD, daily defined dose; PDC, percentage of days covered; Rx, prescription

...TOO SIMPLE?

What could be wrong about this first ITT (intention-to-treat) analysis? 🤔

Therapy Discontinuation (last purchase + extension + 90 days)

Therapy Switch

PP

New Use of Anticoagulants

Death

End of Follow up (31-09-2023)

Received: 18 June 2021 | Accepted: 12 October 2021
DOI: 10.1002/pds.5372

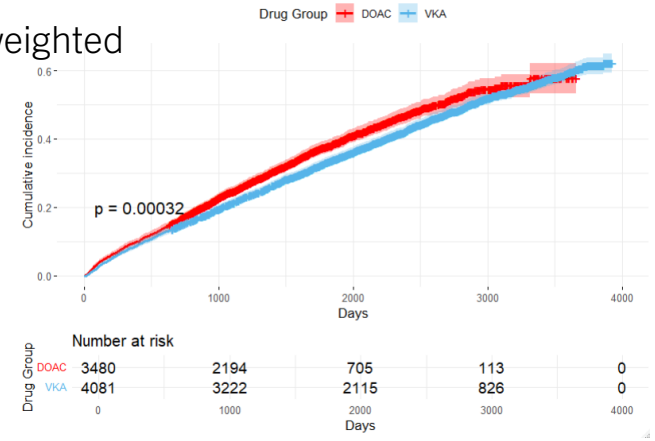
REVIEW

WILEY

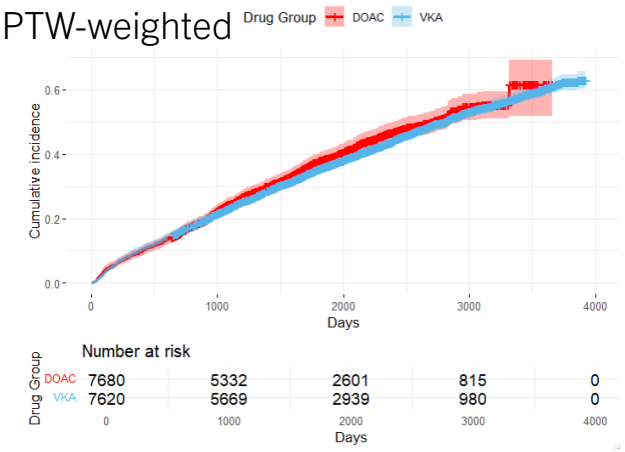
A systematic, concept-based method of developing the exposure measure for drug safety and effectiveness studies

Lisa K. Kuramoto[1] | Boris G. Sobolev[1,2] | Jan Rosner[3,4] | Penelope M. A. Brasher[1] | Laurent Azoulay[5] | Jacquelyn J. Cragg[3,6]

ITT, unweighted

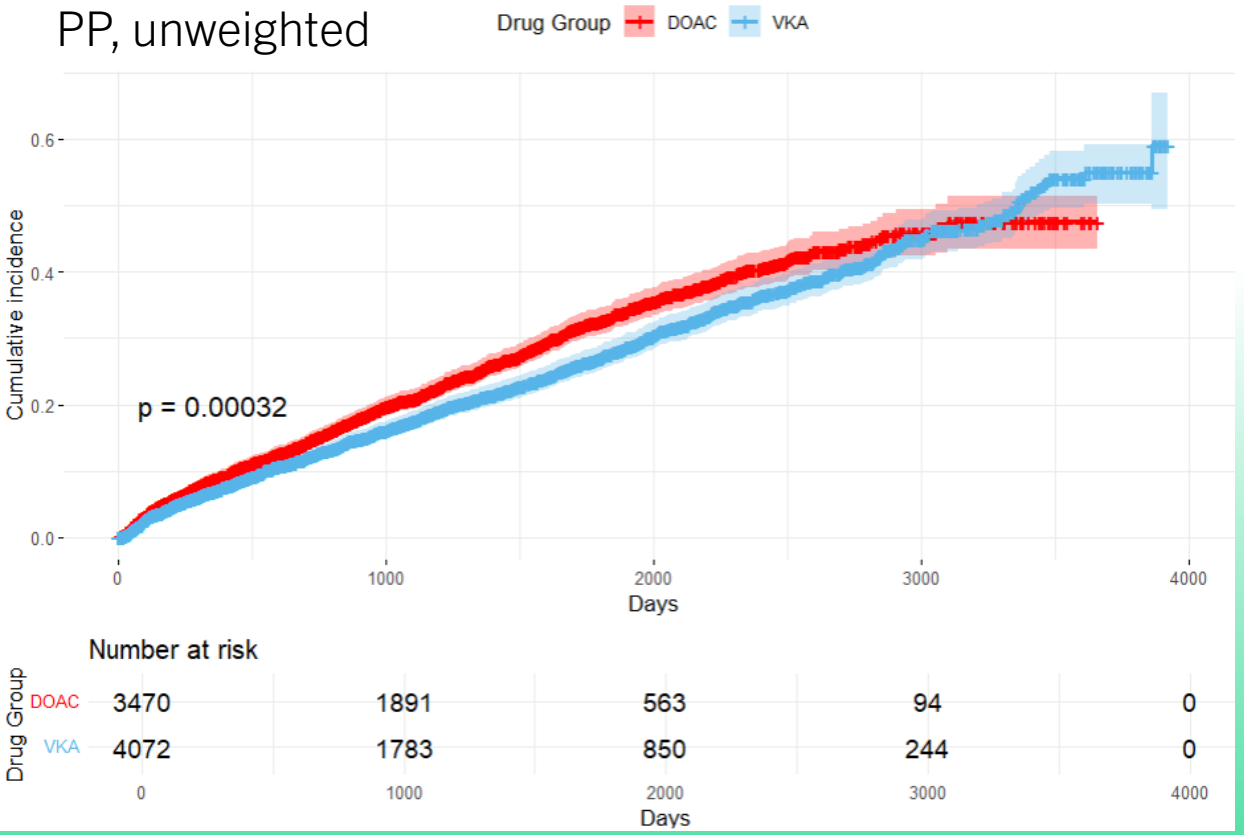


ITT, IPTW-weighted

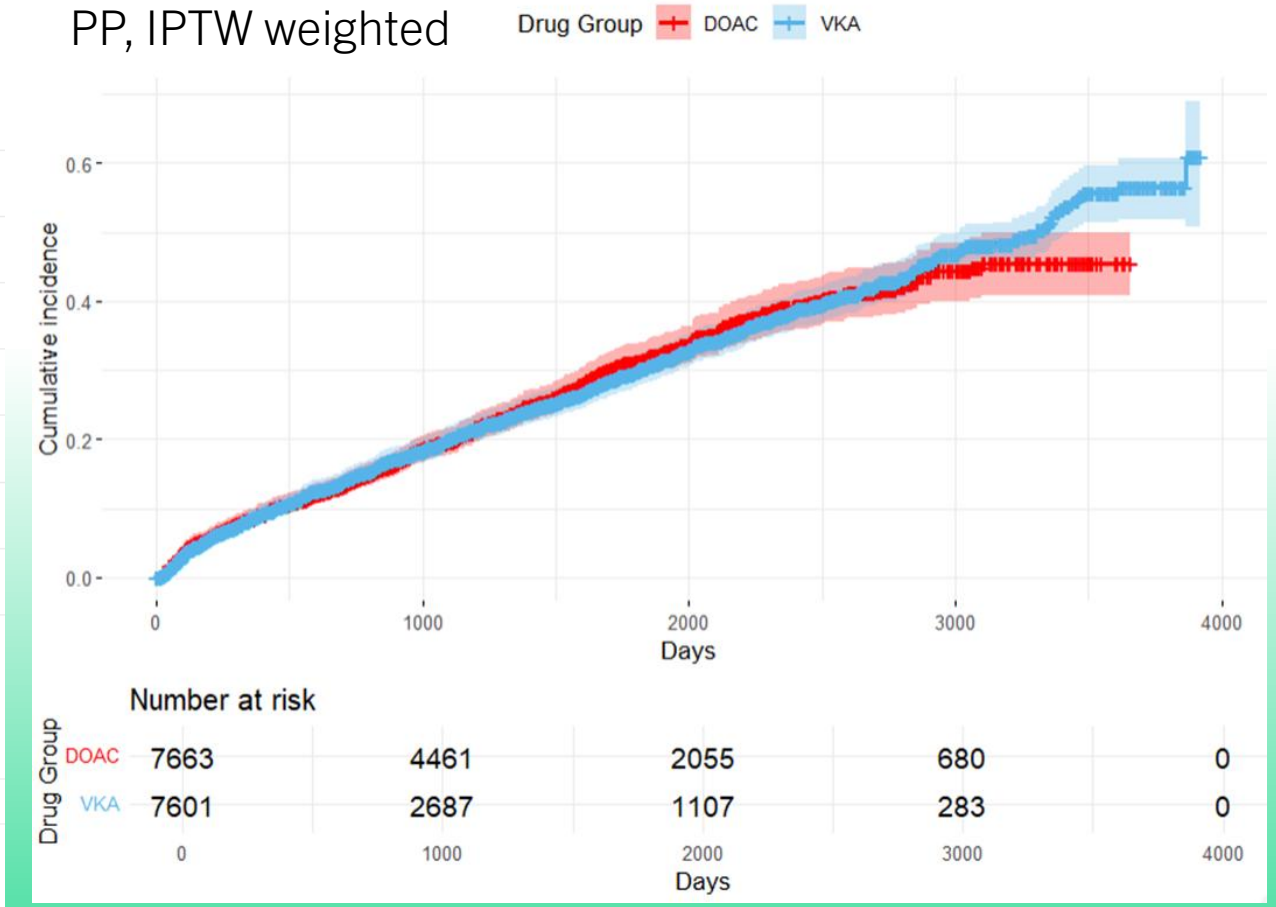


"Do different anticoagulants in AF lead to different risks of ~~reduced renal function?~~ Death?"

PP, unweighted



PP, IPTW weighted



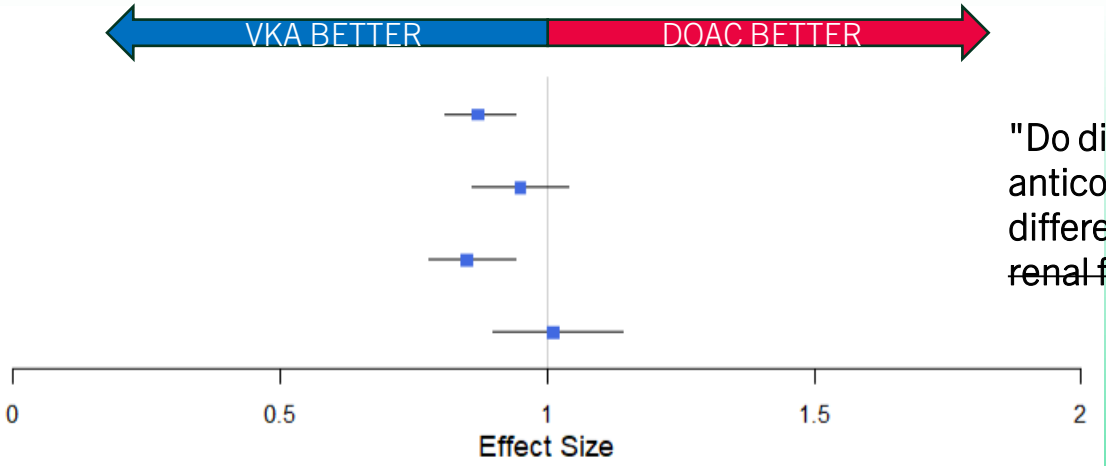
Incidence Rates (per 1000 person-years)

	Overall			DOAC			VKA		
	N events	IR / 1000py	S.E.	N events	IR / 1000py	S.E.	N events	IR / 1000py	S.E.
Death – ITT unweighted	3155	**89.29**	*1.58*	1233	**95.14**	*2.71*	1922	**85.91**	*1.92*
Death – ITT IPTW	3155	**92.42**	*2.22*	1233	**94.87**	*3.76*	1922	**90.14**	*2.5*
Death – PP unweighted	1757	**74.14**	*1.78*	911	**79.44**	*2.66*	846	**69.17**	*2.35*
Death – PP IPTW	1757	**75.41**	*2.5*	911	**74.41**	*3.57*	846	**77**	*3.15*

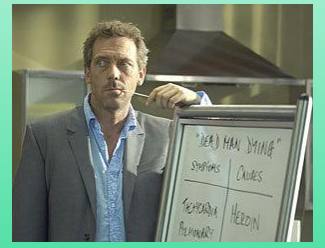
Hazard Ratio

```
#coxmodel
cox.wt <- coxph(Surv(timing_decesso_comp,decesso_comp) ~ drug_group, weights=data.overlap_PP3A$iptw1 ,data.overlap_PP3A)
```

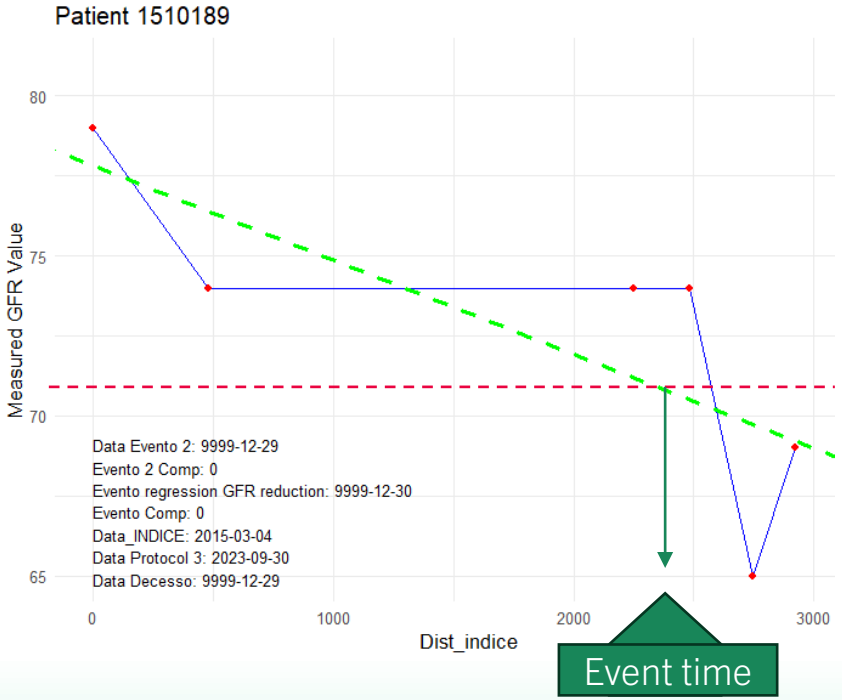
Death Hazard Ratio - VKA vs DOAC	[HR, 95%CI]
- ITT-Unweighted	0.87 (0.81-0.94)
- ITT-IPTW	0.95 (0.86-1.04)
- PP-Unweighted	0.85 (0.78-0.94)
- PP-IPTW	1.01 (0.90-1.14)

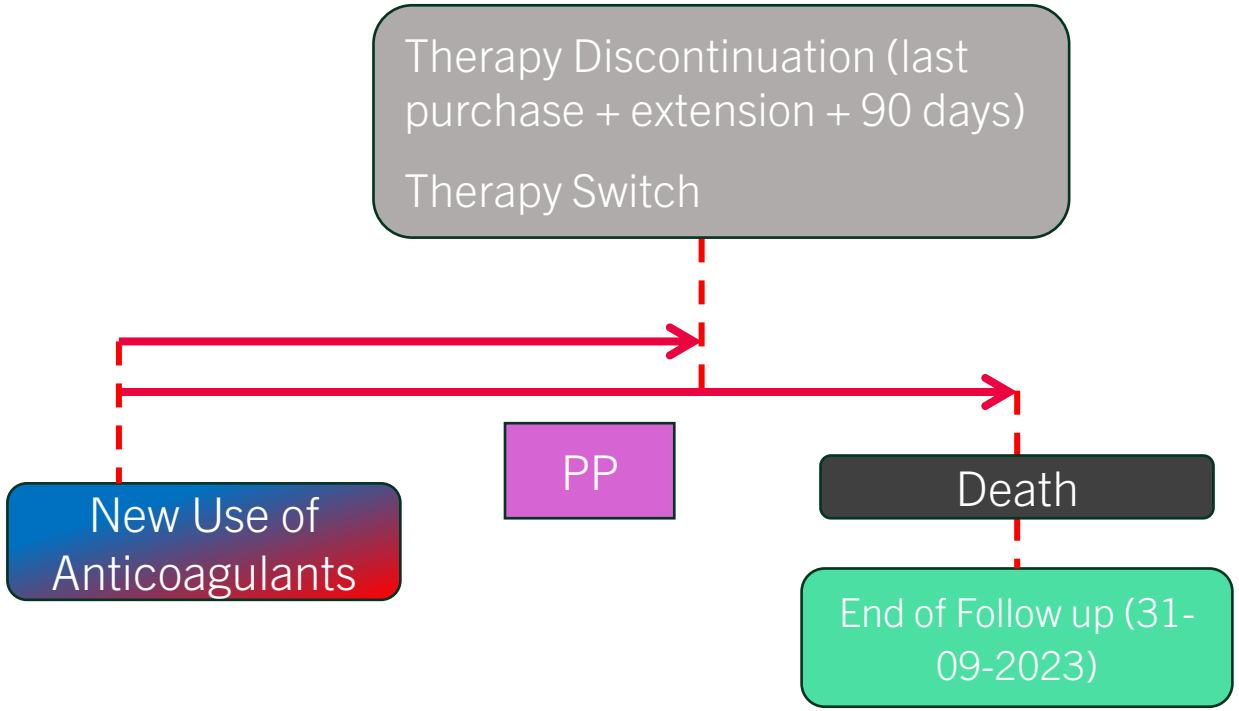


"Do different anticoagulants in AF lead to different risks of ~~reduced renal function?~~ Death?"



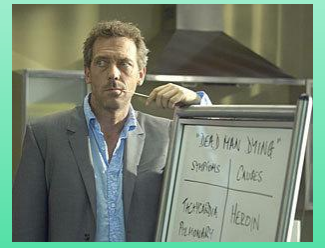
RENAL OUTCOMES



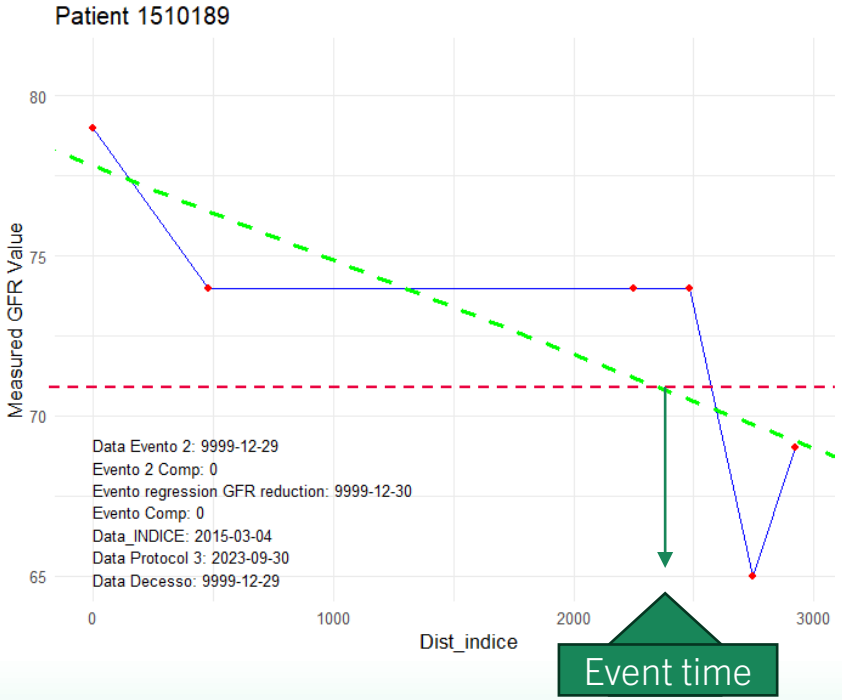


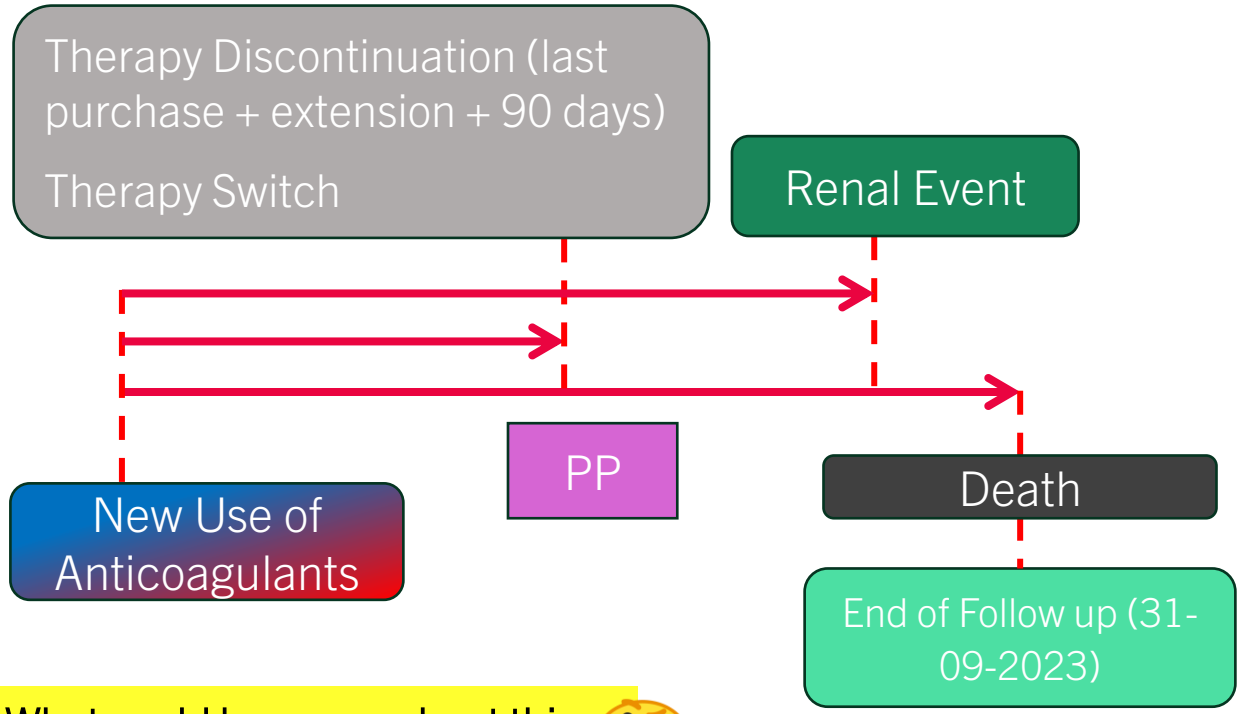
Composite Outcome	Specific Events	Data source	Method
CKD progression	Sustained 30% eGFR Decline	eGFR measurements	Regression interpolation*
	Kidney Failure	eGFR measurements	Regression interpolation**
		Hospital Discharge data	Admission to the hospital for renal transplant or hemodialysis or peritoneal dialysis (ICD9CM: V420, V451, V56)
AKI (Acute Kidney Injury)	Elevation of creatinine	Creatinine measurements	Creatinine elevation 2 times higher than baseline during an hospital admission
	Hospitalization for AKI	Hospital Discharge data	Admission to the hospital (ICD9CM: 593.9x or 584.x)

"Do different anticoagulants in AF lead to different risks of reduced renal function?"



RENAL OUTCOMES





What could be wrong about this PP analysis of renal outcomes? 🤔

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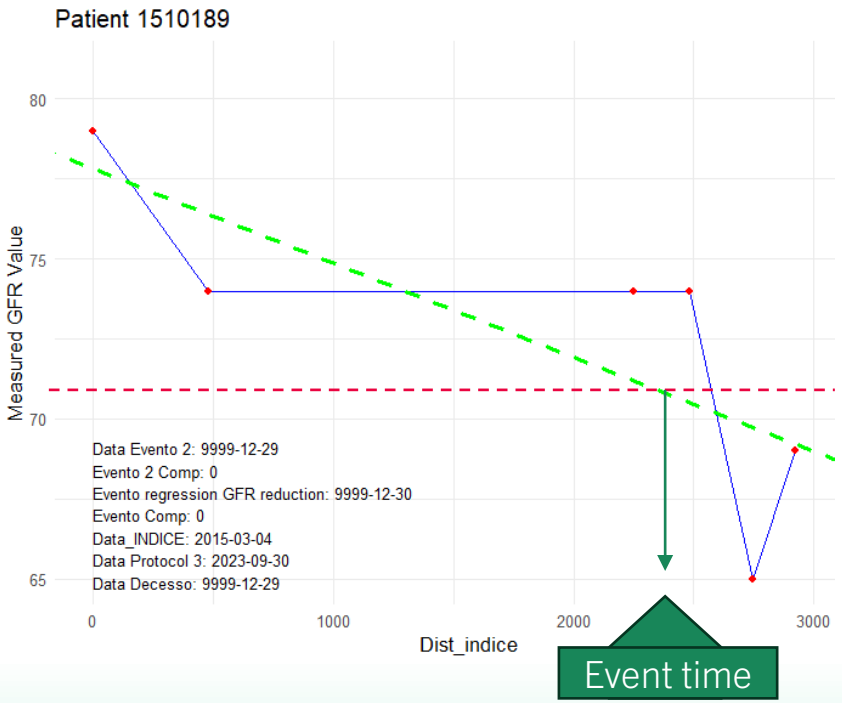
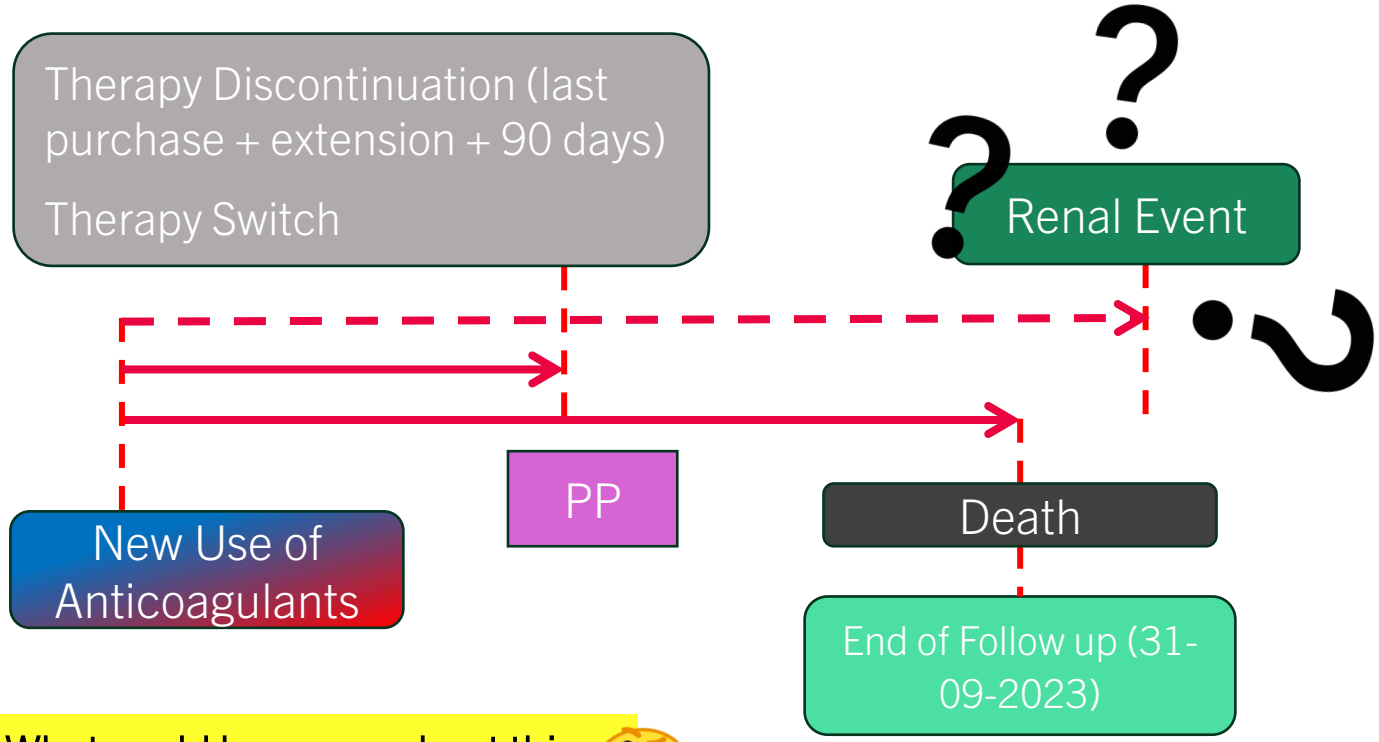
"Do different anticoagulants in AF lead to different risks of reduced renal function?"

RENAL OUTCOMES





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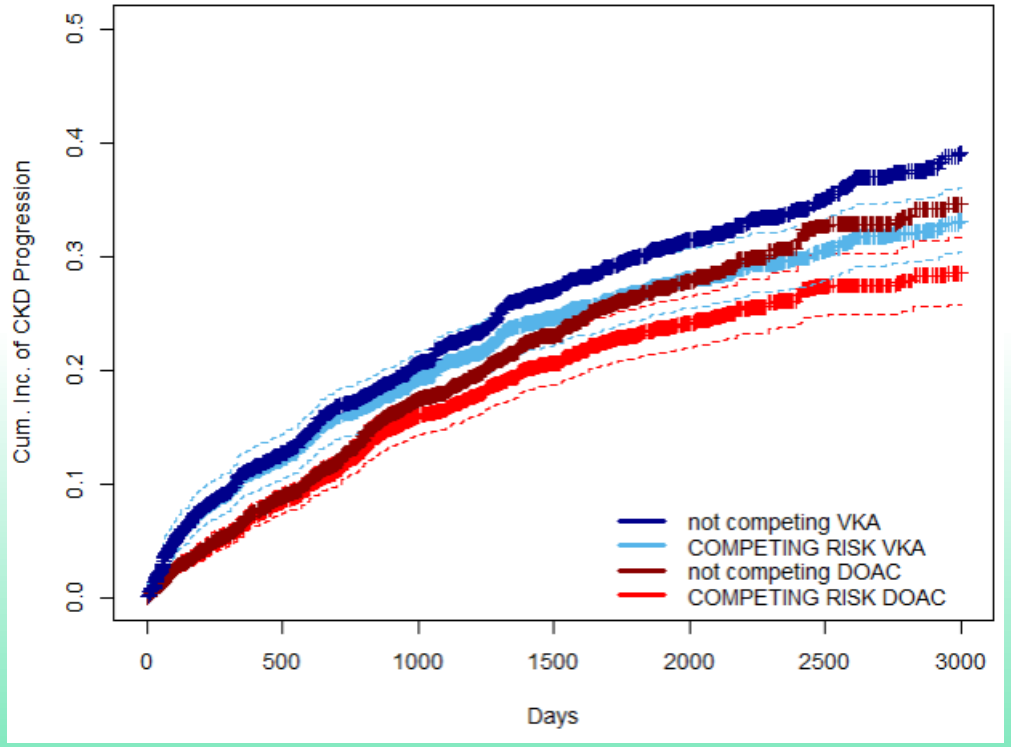
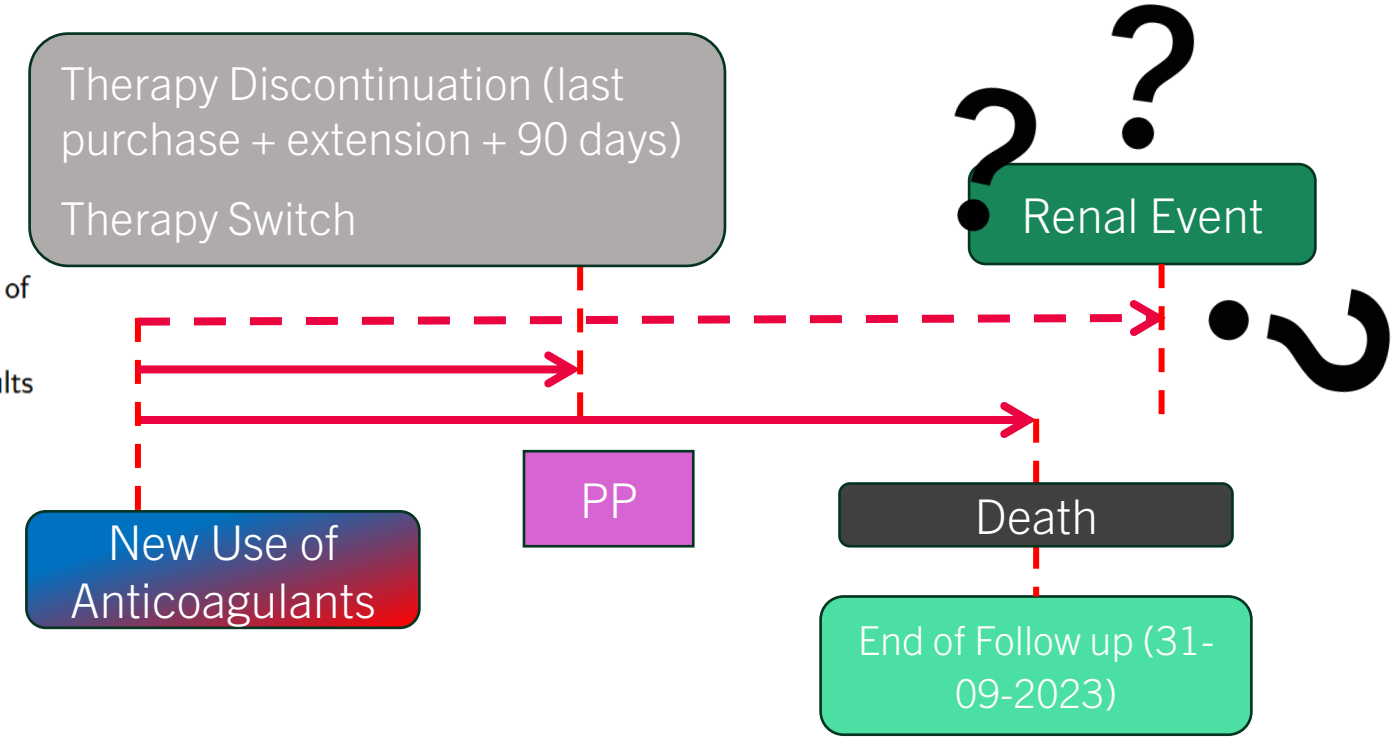
"Do different anticoagulants in AF lead to different risks of reduced renal function?"

COMPETING RISKS

- **Crucial distinction:** are the competing risks independent?
  - ▷ if yes, then treating all events from all other causes (except from the one of interest) as censored will produce valid results
  - ▷ if not, then treating all other events as censored will produce **biased** results





Statistical Primer for Cardiovascular Research

OPEN

Introduction to the Analysis of Survival Data in the Presence of Competing Risks

Peter C. Austin, PhD; Douglas S. Lee, MD, PhD; Jason P. Fine, PhD

A Class of K-Sample Tests for Comparing the Cumulative Incidence of a Competing Risk

Robert J. Gray

The Annals of Statistics, Vol. 16, No. 3. (Sep., 1988), pp. 1141-1154.

Credits: D. Rizoupoulous, Eramus University

ITT - IPTW

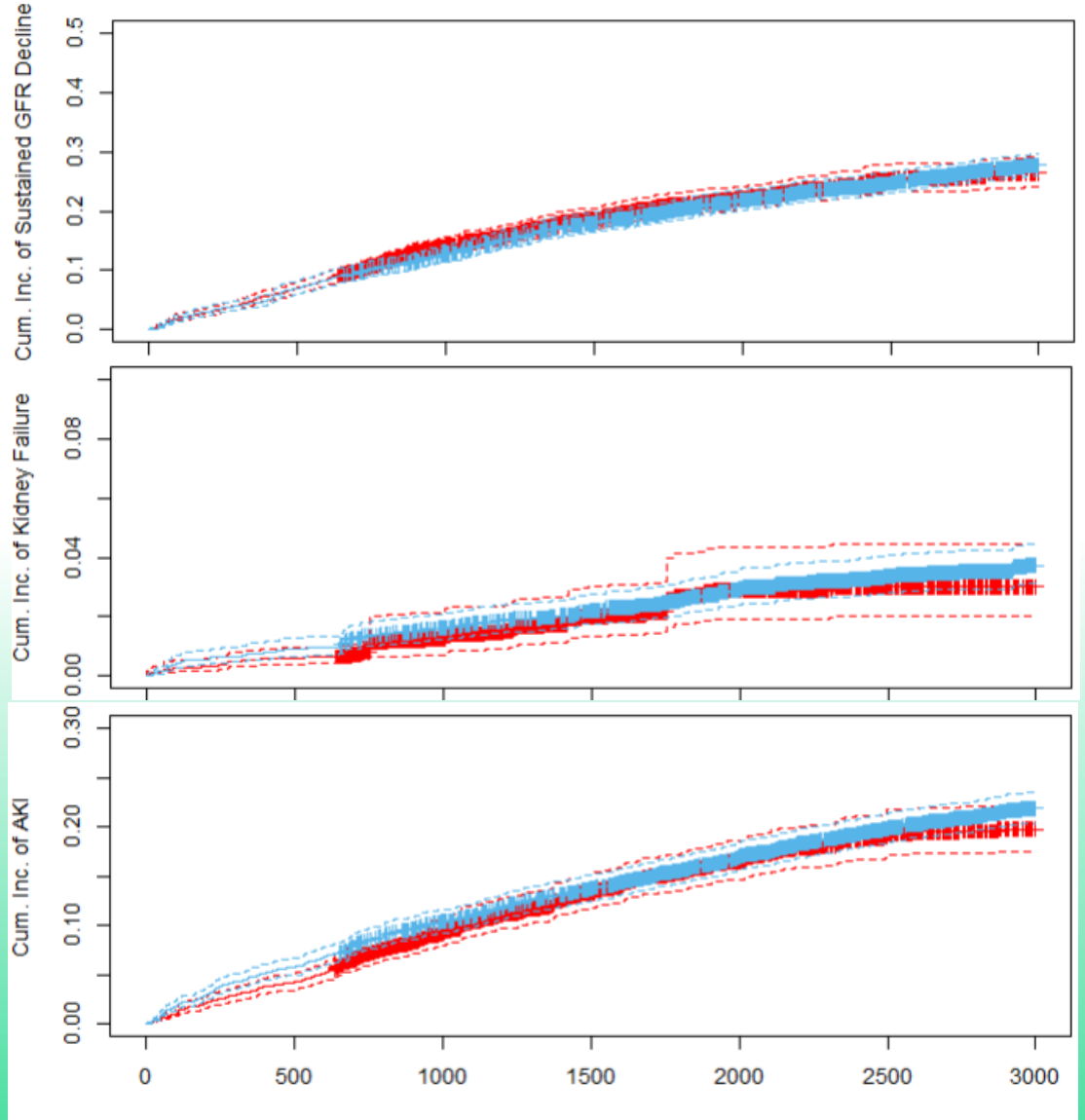
	HR (95%CI) VKA vs DOAC
Primary Outcomes	
Sustained GFR Decline	0.98 (0.87-1.12)
Kidney Failure	1.08 (0.70-1.64)
AKI	1.09 (0.94-1-29)

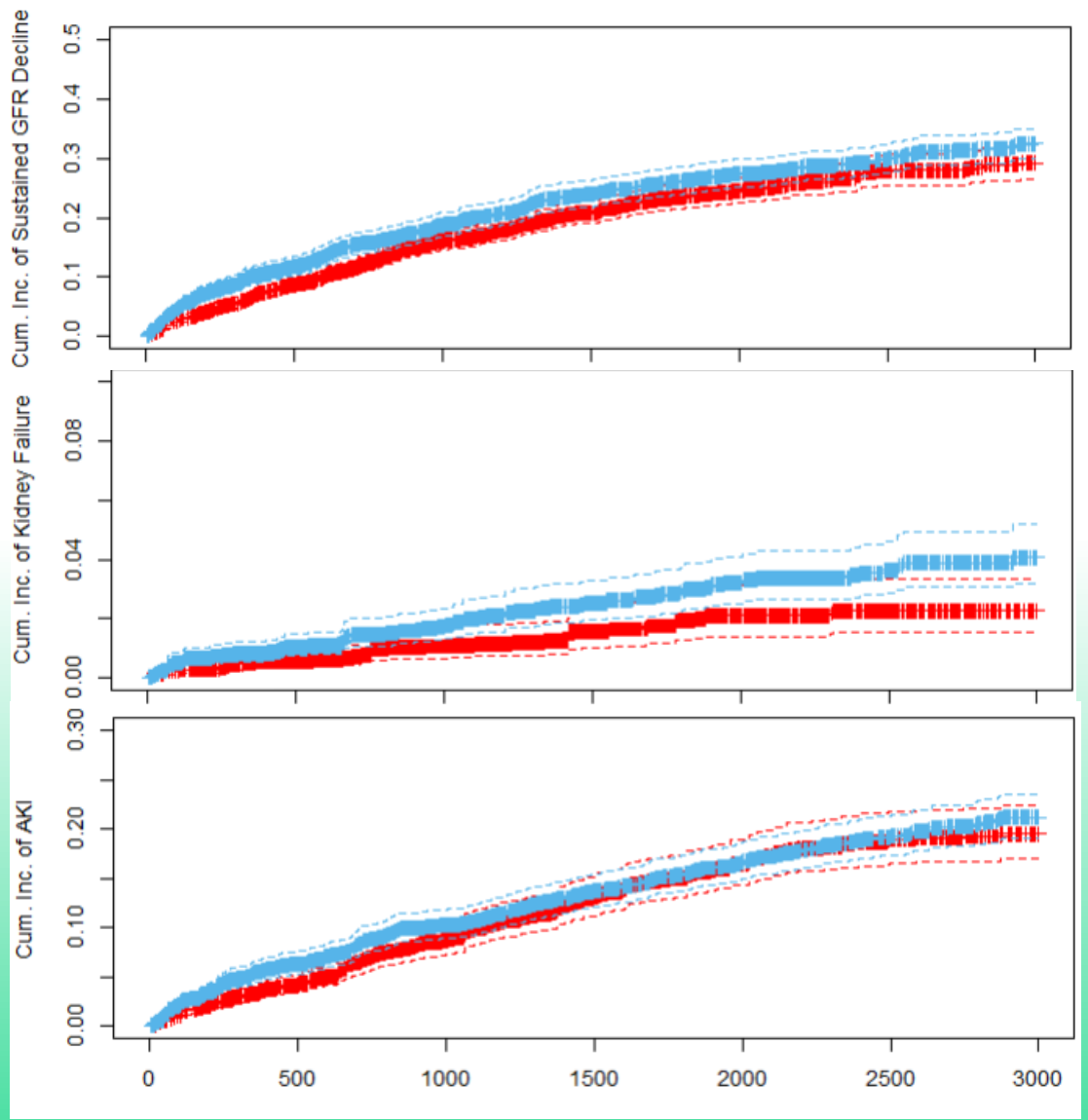
VKA

DOAC

PP - IPTW

	HR (95%CI) VKA vs DOAC
Primary Outcomes	
Sustained GFR Decline	**1.18 (1.03-1.35)**
Kidney Failure	**1.69 (1.10-2.60)**
AKI	1.13 (0.95-1.34)





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ITT - IPTW

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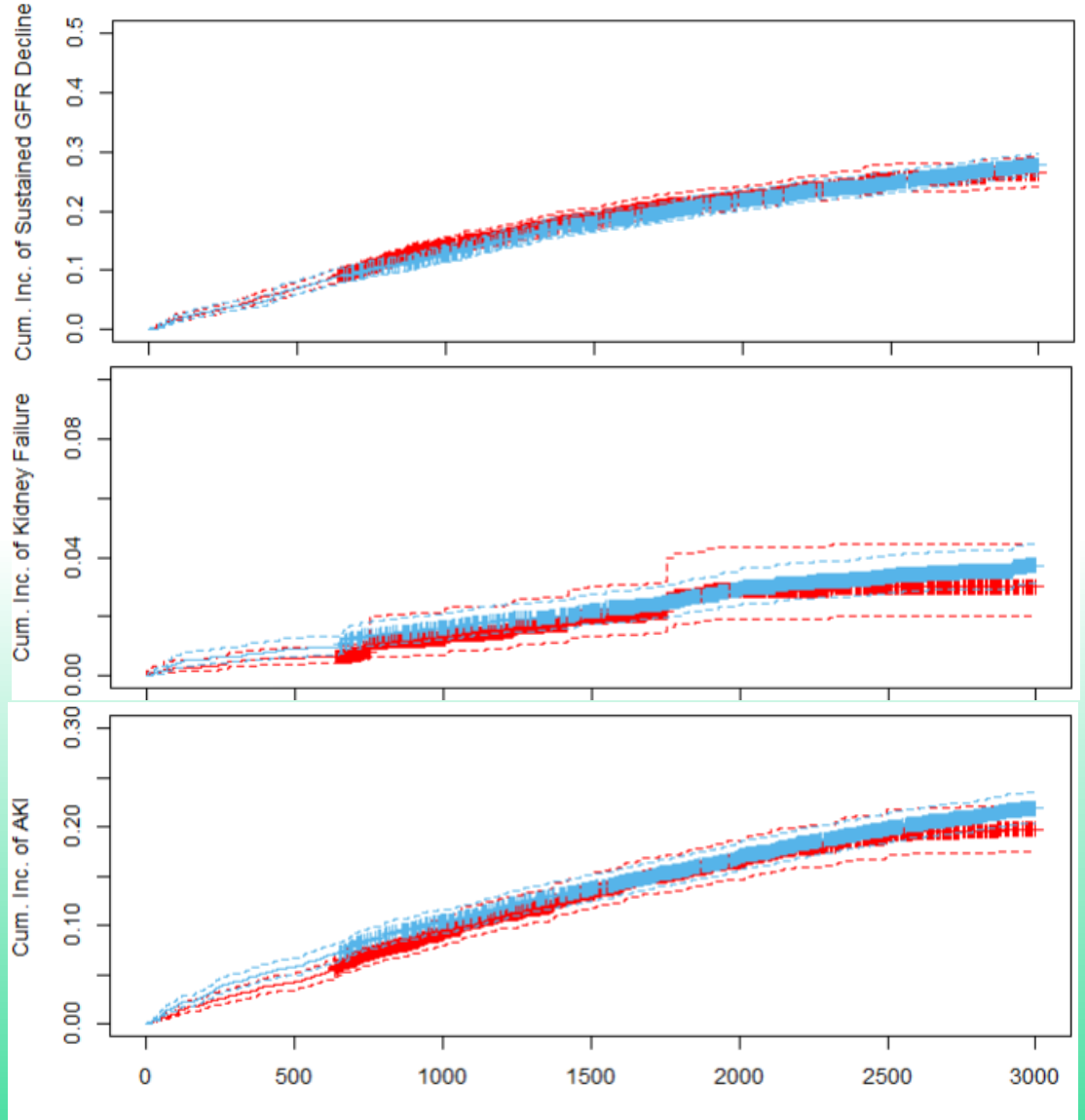
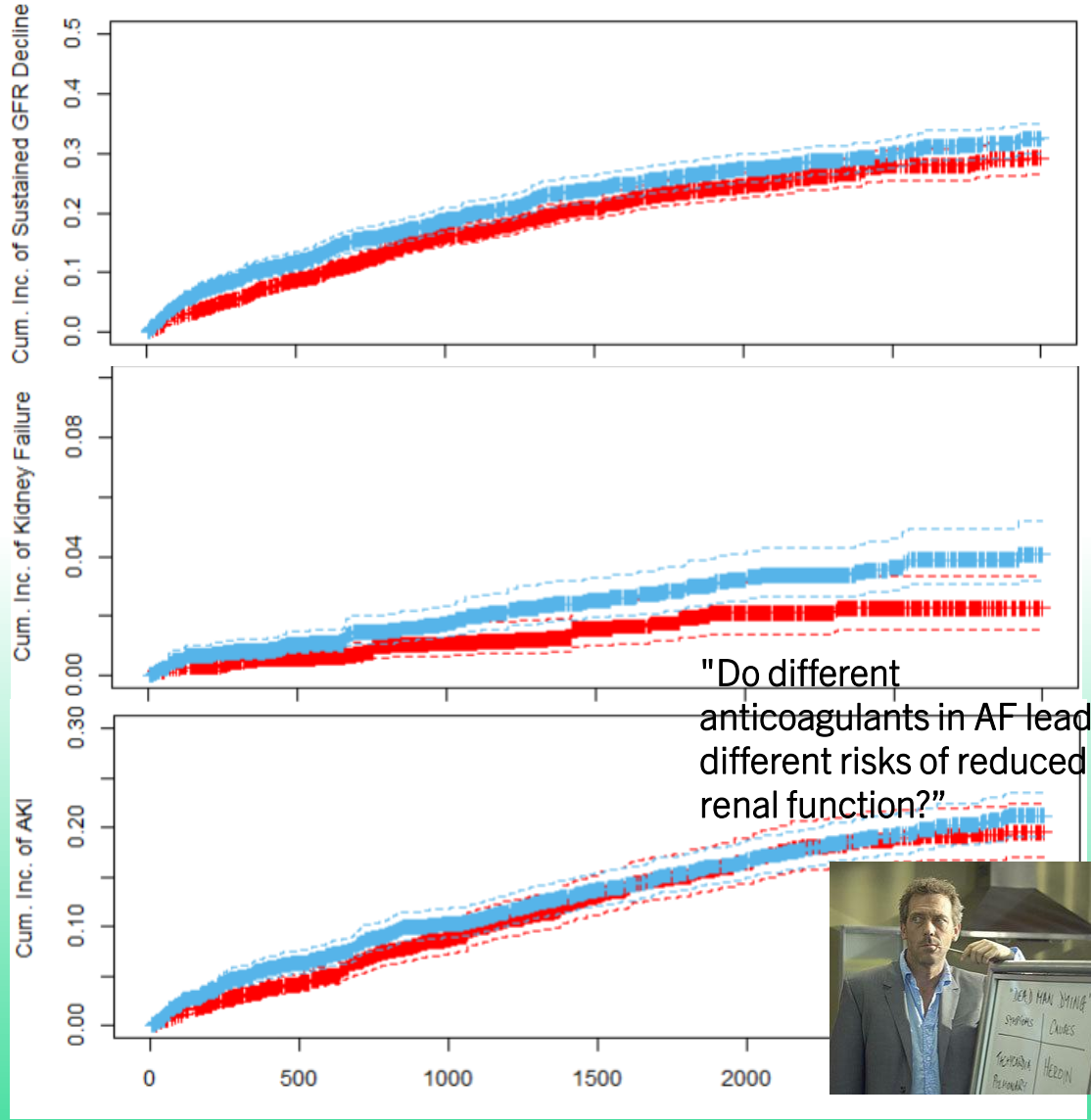
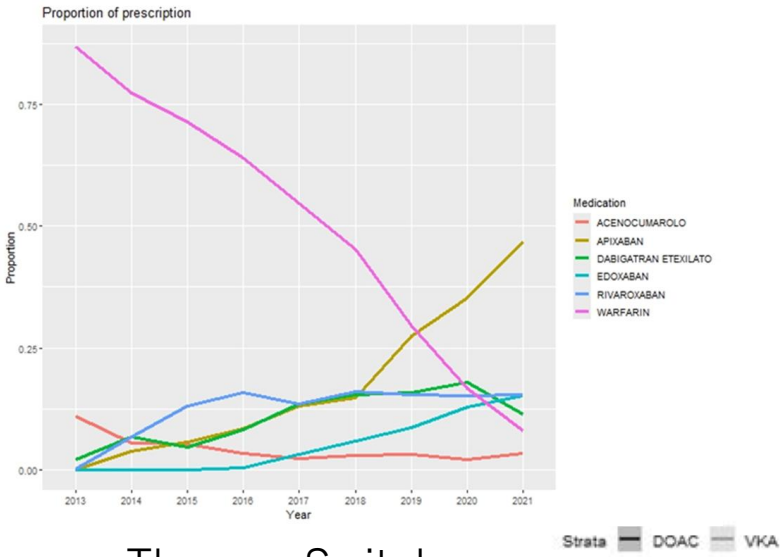
PP - IPTW



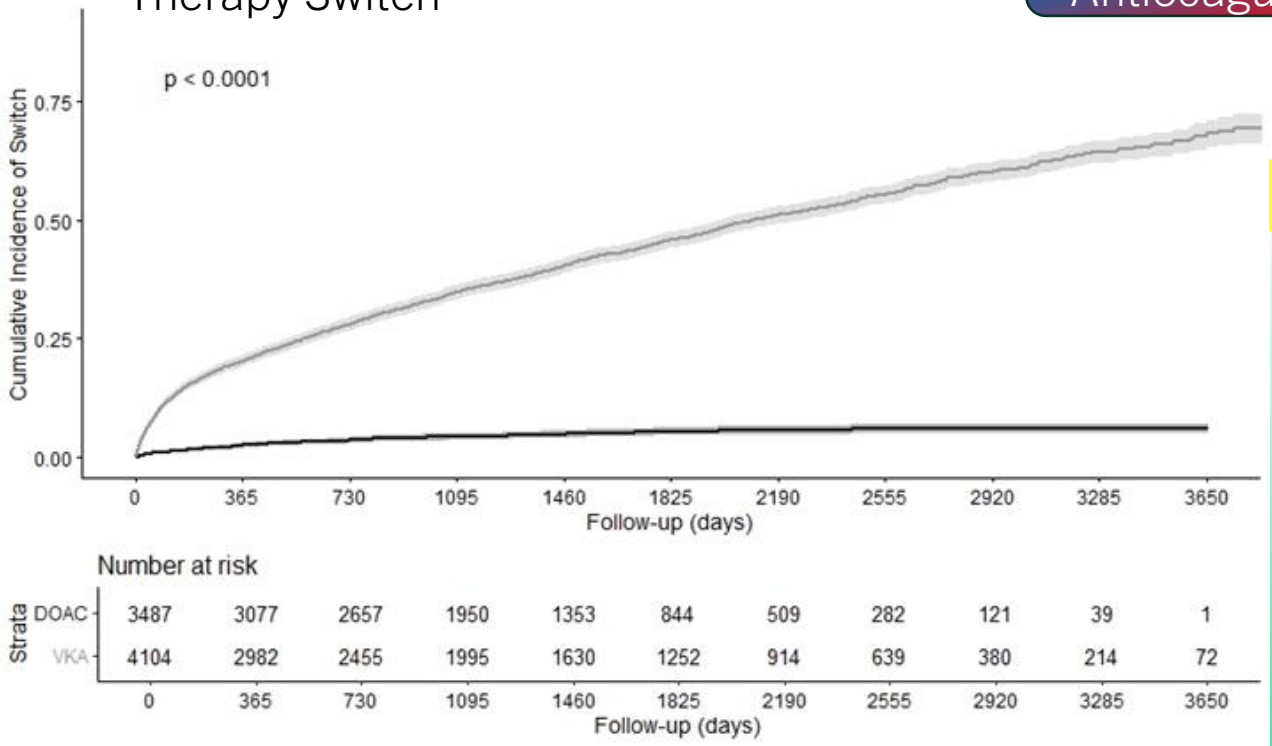


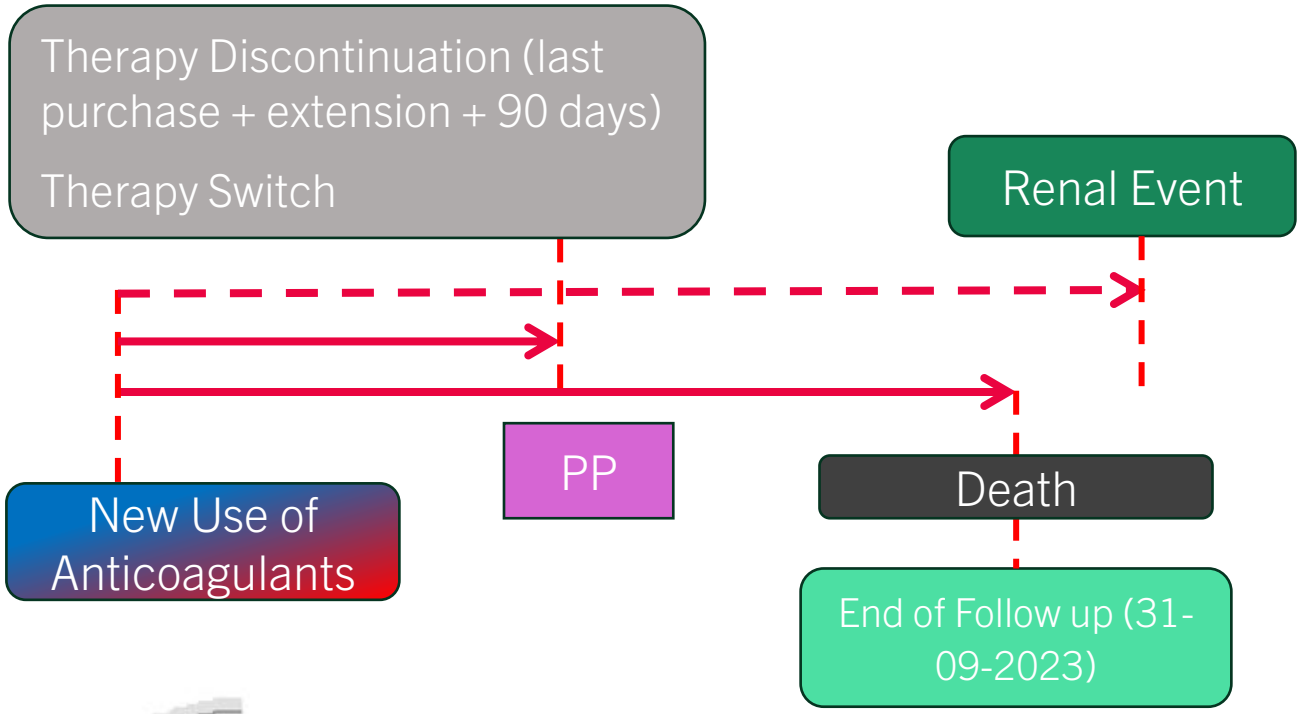
"Do different anticoagulants in AF lead to different risks of reduced renal function?"

Therapy Initiation



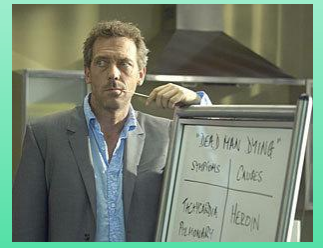
Therapy Switch





What could be wrong here? 🤔

"Do different anticoagulants in AF lead to different risks of reduced renal function?"



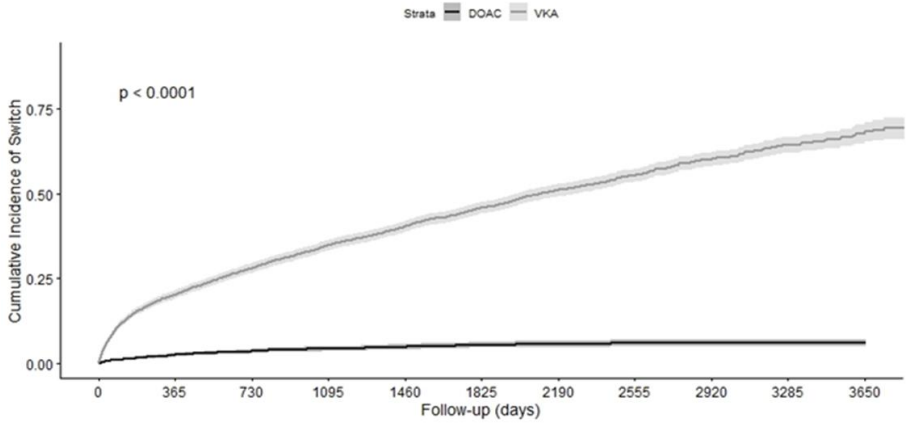
6.2.2. Vitamin K antagonists

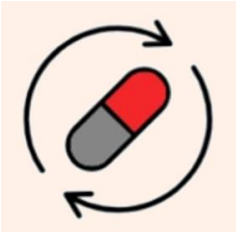
Vitamin K antagonist therapy reduces stroke risk by 64% and mortality by 26% in patients with AF at elevated thromboembolic risk (mostly warfarin in trials, compared with placebo or no treatment).[239] Vitamin K antagonists are still used in many patients worldwide, but prescriptions have declined sharply since the introduction of DOACs.[340,341] Vitamin K antagonists are currently the only treatment option in AF patients with mechanical heart valves or moderate-to-severe mitral valve stenosis.[294,331] The use of VKAs is not only limited by numerous drug and food interactions (*Figure 9*), but also a narrow therapeutic range. This requires frequent monitoring and dose adjustment according to the prothrombin time expressed as the international normalized ratio (INR).[342] If the time in therapeutic range (TTR) is maintained for long periods (e.g. >70% with INR 2.0–3.0), then VKA can be effective for thromboembolic protection with an acceptable safety profile.[295–297,343] However, VKAs are associated with higher rates of intracranial bleeding,[299,300] and also higher rates of other types of bleeding compared with DOACs.[83]

In view of the potential safety benefits, switching from VKAs to a DOAC is justified where there are concerns about intracranial bleeding or for patient-choice reasons, and a switch is recommended where patients have failed to maintain an adequate TTR (<70%). This depends on patients fulfilling eligibility criteria for DOACs and should take into account other correctable reasons for poor INR control. There is limited data on switching OAC in older patients (≥75 years) with polypharmacy or other markers of frailty. A recent trial in this patient group prematurely stopped for futility showed that switching from VKAs to DOACs led to a higher primary outcome rate of major or clinically relevant non-major bleeding events compared with continuing with INR-guided VKA (17.8 vs. 10.5 per 100 patient-years, driven by non-major bleeds).[309] Hence, in such patients who are clinically stable with good TTR, VKAs may be continued rather than switching to a DOAC after an open discussion with the patient and shared decision-making.

6.2.3. Clinical vs. device-detected subclinical AF

The known benefit of anticoagulation applies to clinical AF. Two RCTs have been published assessing the value of DOAC therapy in device-detected subclinical AF. The ARTESiA trial (Apixaban for the Reduction of Thromboembolism in Patients With Device-Detected Sub-Clinical Atrial Fibrillation) was completed with 4012 patients with device-detected subclinical AF and a mean follow-up of 3.5 years.[282] The primary efficacy outcome of stroke or systemic embolism was significantly less in those randomized to apixaban compared with aspirin (HR, 0.63; 95% CI, 0.45–0.88; $P = .007$). In the intention-to-treat analysis, the primary safety outcome of major bleeding was higher with apixaban (HR, 1.36; 95% CI, 1.01–1.82; $P = .04$). The NOAH trial (Non-vitamin K Antagonist Oral Anticoagulants in Patients With Atrial High Rate Episodes) was stopped prematurely due to safety concerns and futility for the efficacy of edoxaban, and hence provides limited information.[281] The analysis of 2536 patients with device-detected atrial high-rate episodes and a median follow-up of 21 months identified no difference in a composite of cardiovascular death, stroke, or embolism comparing edoxaban and placebo (HR, 0.81; 95% CI, 0.60–1.08; $P = .15$). Those randomized to edoxaban had a higher rate of the composite of death or major bleeding than placebo (HR, 1.31; 95% CI, 1.02–1.67; $P = .03$). Patients had a low burden of device-detected subclinical AF in both trials (median duration 1.5 h and





(risk ratio, 0.42; 95% CI, 0.21–0.86; $P = .017$), with no heterogeneity between trials and no significant difference in major bleeding.[293]

Specific patient subgroups show consistent benefit with DOACs vs. VKAs. For heart failure, major thromboembolic events were lower in DOAC-treated patients vs. warfarin in subgroup analysis of landmark RCTs,[322] confirmed in large-scale real-world data.[323] In a retrospective cohort of patients aged over 80 years, DOAC use was associated with a lower risk of ischaemic stroke, dementia, mortality, and major bleeding than warfarin,[324] but this may be confounded by prescription bias.

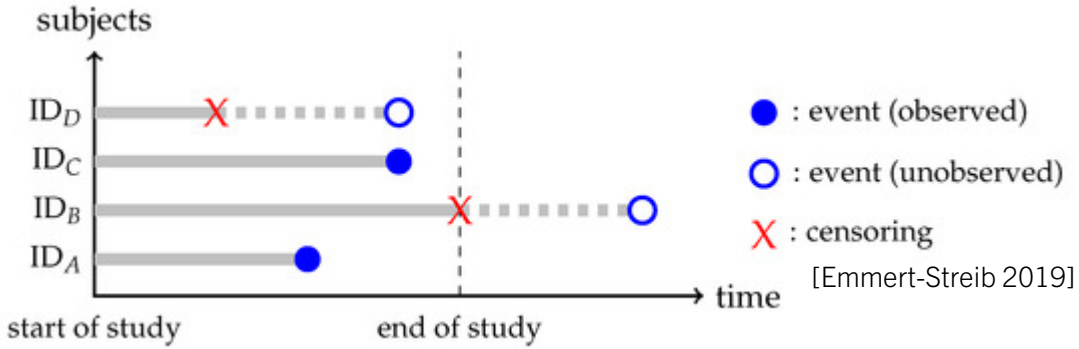
Direct oral anticoagulants retain their efficacy and safety over VKAs in patients with mild-to-moderate CKD (creatinine clearance [CrCl] >30 mL/min),[325] although specific dosing adjustments apply.[25–28,326] In Europe, reduced doses of rivaroxaban, apixaban, and edoxaban are approved in patients with severe CKD (CrCl 15–29 mL/min), although limited numbers of patients were included in the major RCTs against VKA.[327] Dabigatran is more dependent on renal elimination and so is contraindicated with an estimated glomerular filtration rate <30 mL/min/1.73 m^2. Small trials have been performed in patients on haemodialysis, with two finding no difference between apixaban 2.5 mg twice daily and VKA for efficacy or safety outcomes,[328,329] and one trial showing that rivaroxaban 10 mg led to significantly lower rates of cardiovascular events and major bleeding compared with VKA.[330] Careful institution and regular follow-up are advised when instituting anticoagulants in any patient with impaired renal function (See Supplementary data online, *Additional Evidence Table 8*).[326]

Direct oral anticoagulants as a class should be avoided in specific patient groups, such as those with mechanical heart valves or moderate-to-severe mitral stenosis. In patients with mechanical heart

Recommendations	Class[a]	Level[b]
Direct oral anticoagulants are recommended in preference to VKAs to prevent ischaemic stroke and thromboembolism, except in patients with mechanical heart valves or moderate-to-severe mitral stenosis.[25–28,292–294]	I	A
A target INR of 2.0–3.0 is recommended for patients with AF prescribed a VKA for stroke prevention to ensure safety and effectiveness.[295–298]	I	B
Switching to a DOAC is recommended for eligible patients that have failed to maintain an adequate time in therapeutic range on a VKA (TTR <70%) to prevent thromboembolism and intracranial haemorrhage.[299–303]	I	B
Keeping the time in therapeutic range above 70% should be considered in patients taking a VKA to ensure safety and effectiveness, with INR checks at appropriate frequency and patient-directed education and counselling.[304–308]	IIa	A
Maintaining VKA treatment rather than switching to a DOAC may be considered in patients aged ≥75 years on clinically stable therapeutic VKA with polypharmacy to prevent excess bleeding risk.[309]	IIb	B
A reduced dose of DOAC therapy is not recommended, unless patients meet DOAC-specific criteria,[c] to prevent underdosing and avoidable thromboembolic events.[310–312]	III	B

[2024 ESC Guidelines for the management of atrial fibrillation]

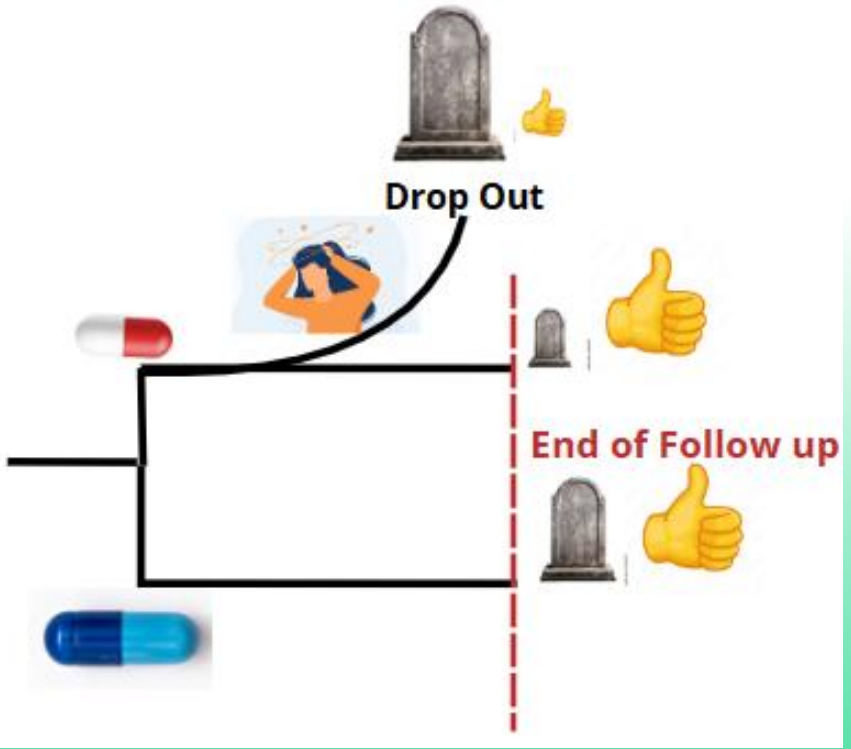
INFORMATIVE CENSORING

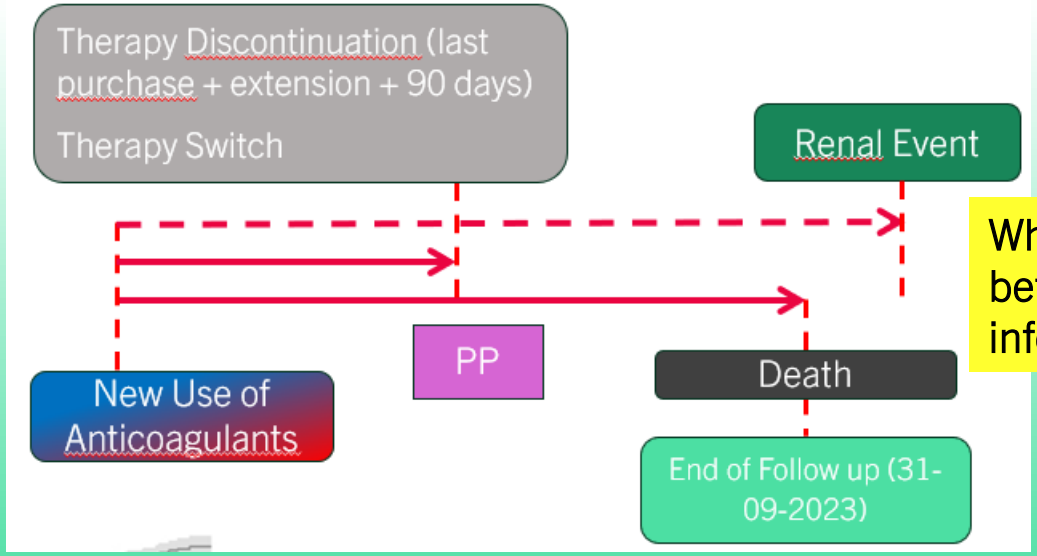


[Emmert-Streib 2019]

In the analysis of survival data, the time to an event of interest is modelled with the possibility to take predictive variables into account. Given the longitudinal aspect of survival data, the actual event time is not observed for all subjects and one of the reasons for this is censoring. In order to incorporate censored observations in the analysis, the assumption of (conditional) non-informative censoring is omnipresent in many survival techniques. This assumption implies that the censoring time and the true survival time are (conditionally) independent. Stated otherwise, it is assumed that an individual that is censored at a given time point t, is equally likely to experience an event as a subject who remains uncensored. This assumption can be weakened by making it conditional on a set of covariates. [H. Dehaene 2020]

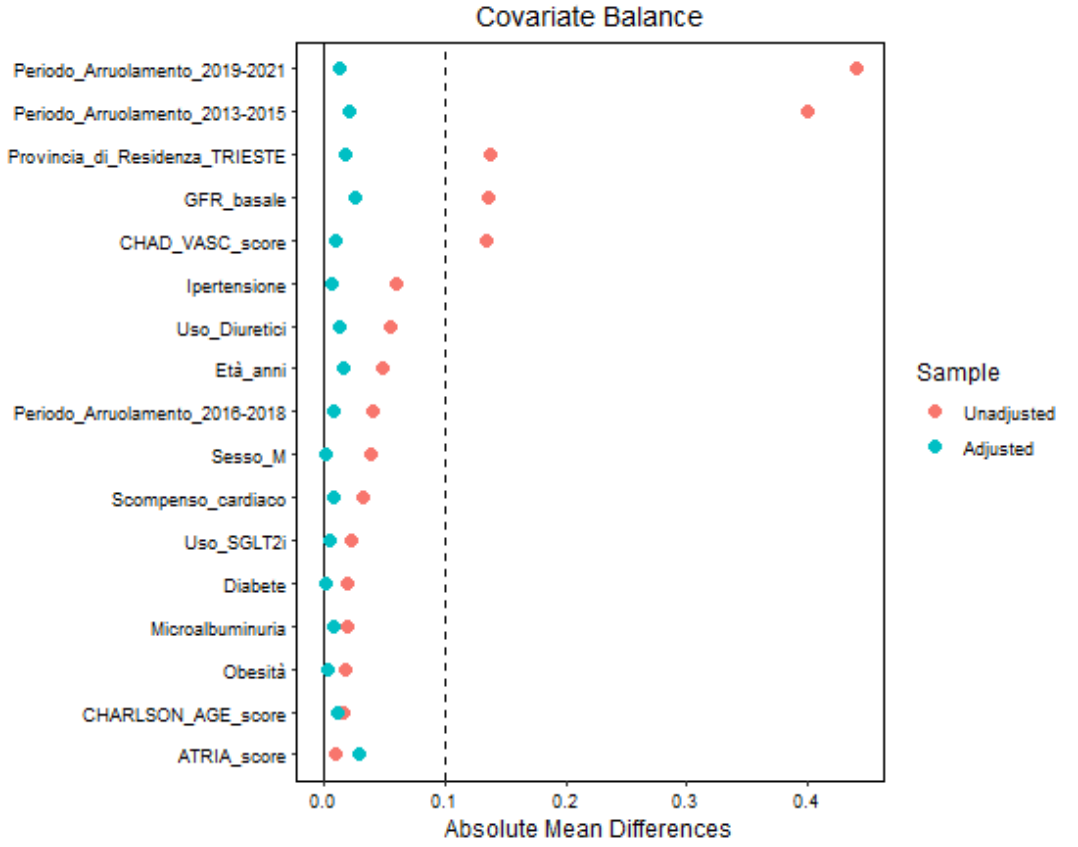
- If the probability of censoring depends on factors associated with the outcome (e.g., high-risk individuals are censored more often), the survival estimate may be biased.
- If censoring is also related to the exposure/treatment, and thus occurs differently between the two groups, the estimated treatment effect may be erroneously attenuated or amplified.



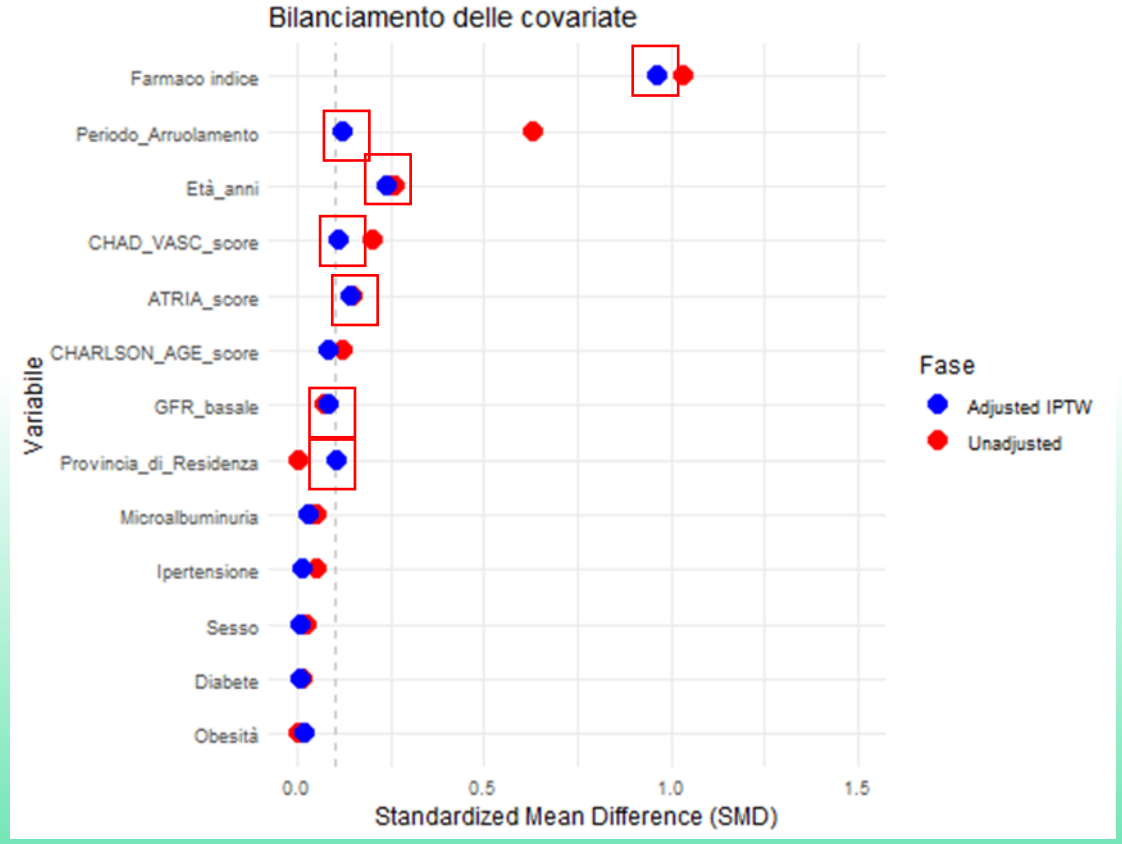


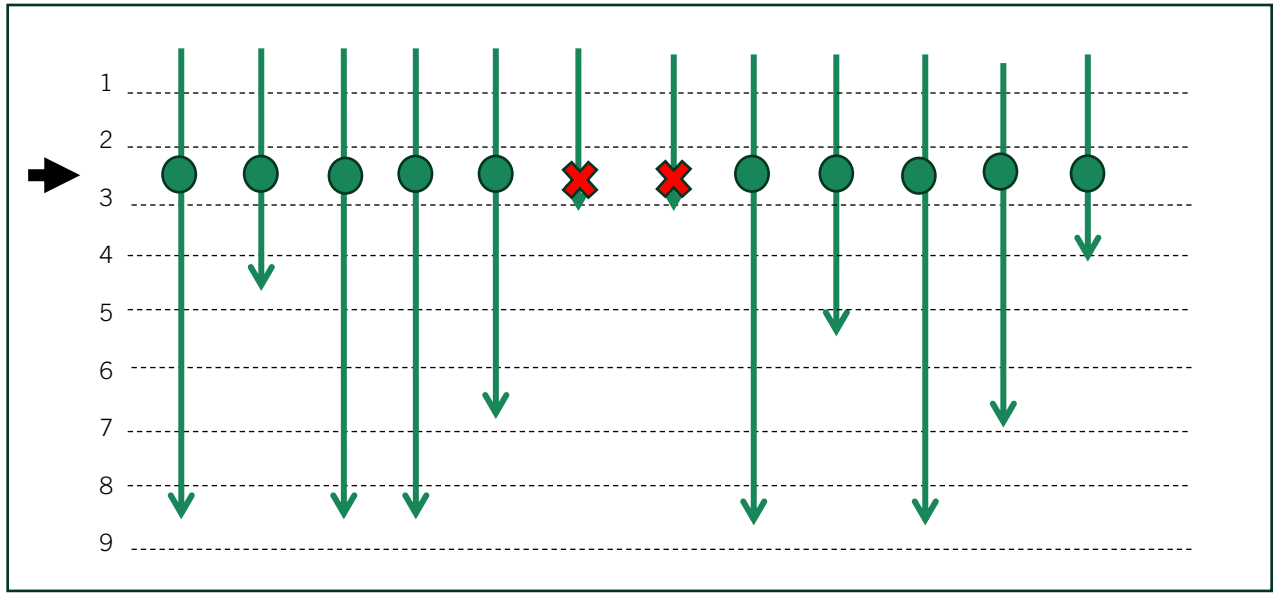
What is the relationship between competing risk and informative censoring? 🤔

Treatment group (VKA vs NOAC)



Censoring (Switch vs Fine follow-up)



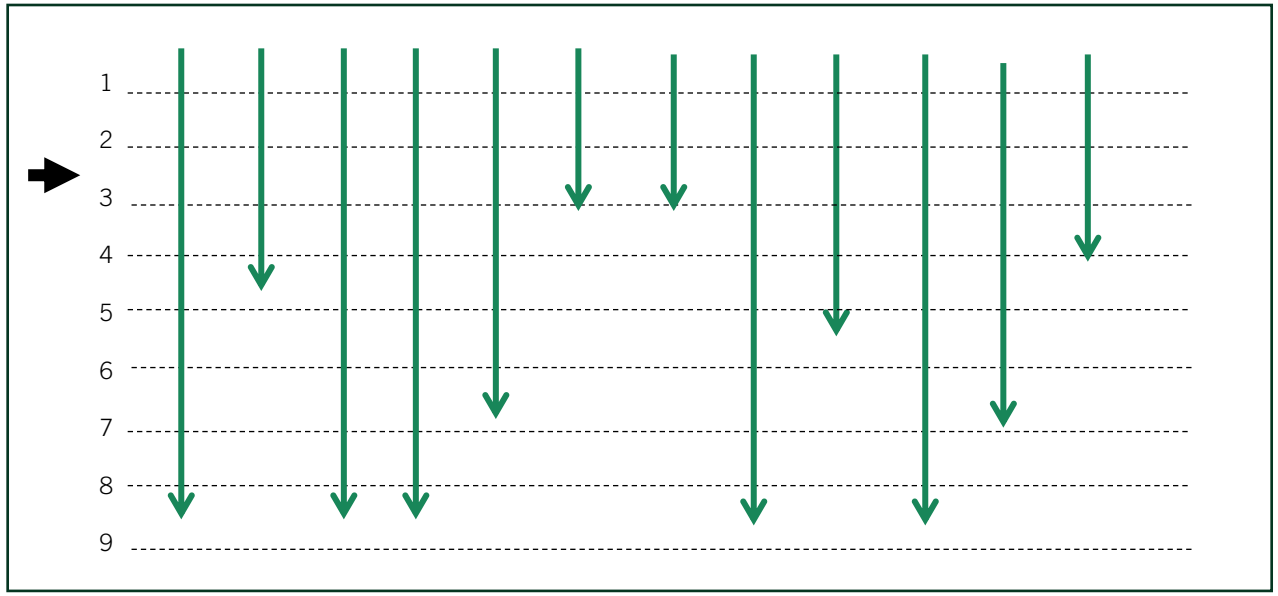


Censura Informativa?

MEASURES OF COVARIATE BALANCE FOR (IN)DEPENDENT CENSORING

The definitions outlined above have direct implications for using covariate balance to describe (in)dependent censoring and the nature of its associated selection bias. The general approach is, for each censoring mechanism, to compare at each time the distribution of covariate history among those who become censored versus those who do not, among those following the same treatment protocol who have not yet been censored by any

[JW Jackson, 2018]



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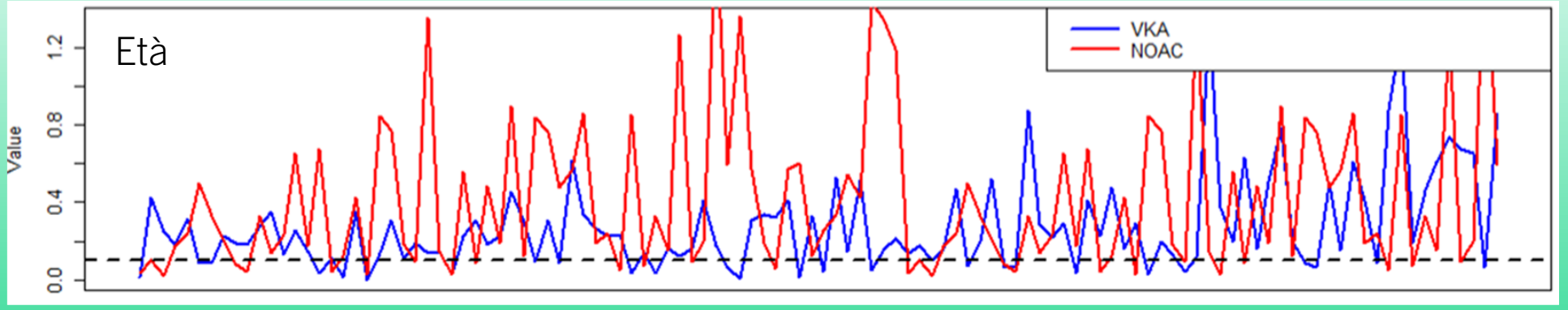


IPCW: Inverse Probability of Censoring Weighting

ID	sivstand18	sivstand19	sivstand20	lavv18	lavv19	lavv20	kjavn
1	1	1	2	120000	150000	180000	1
2	1	1	1	300000	340000	360000	2
3	2	2	2	400000	600000	630000	1
4	2	4	4	160000	170000	175000	2

ID	date@panel	sivstand	lavv	kjavn
1	18	1	120000	1
2	18	1	300000	2
3	18	2	400000	1
4	18	2	160000	2
1	19	1	150000	1
2	19	1	340000	2
3	19	2	600000	1
4	19	4	170000	2
1	20	2	180000	1
2	20	1	360000	2
3	20	2	630000	1
4	20	4	175000	2

IPCW to correct for dependent censoring

Step 1: Fit a model for the censoring mechanism that incorporates covariates associated with event and censoring time.

Step 2: Estimate the probability of remaining uncensored at each observed time point t for all subjects at risk at that time point. Denote this estimated probability for subject j at time t as $\widehat{K}_j^{\mathbf{Z}}(t)$.

Step 3: Compute the IPCW weights as $\widehat{W}_j(t) = 1/\widehat{K}_j^{\mathbf{Z}}(t)$.

Step 4: Estimate the survival probabilities $\hat{S}_{IPCW}(t_\tau)$ for time to event in the absence of censoring with subjects weighted according to the IPCW methodology at each observed time point t_τ of interest.

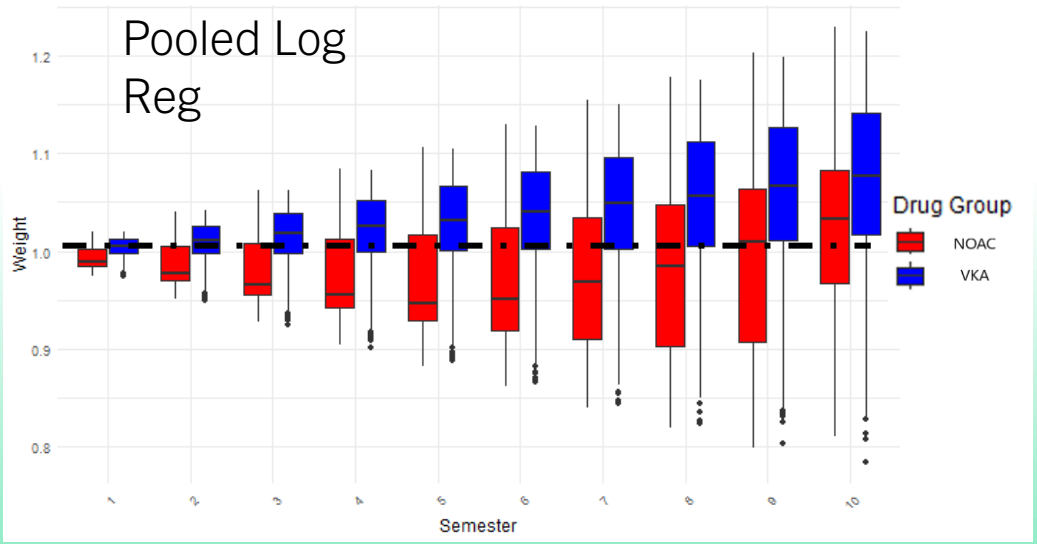
[SJW Willems & al. 2018]

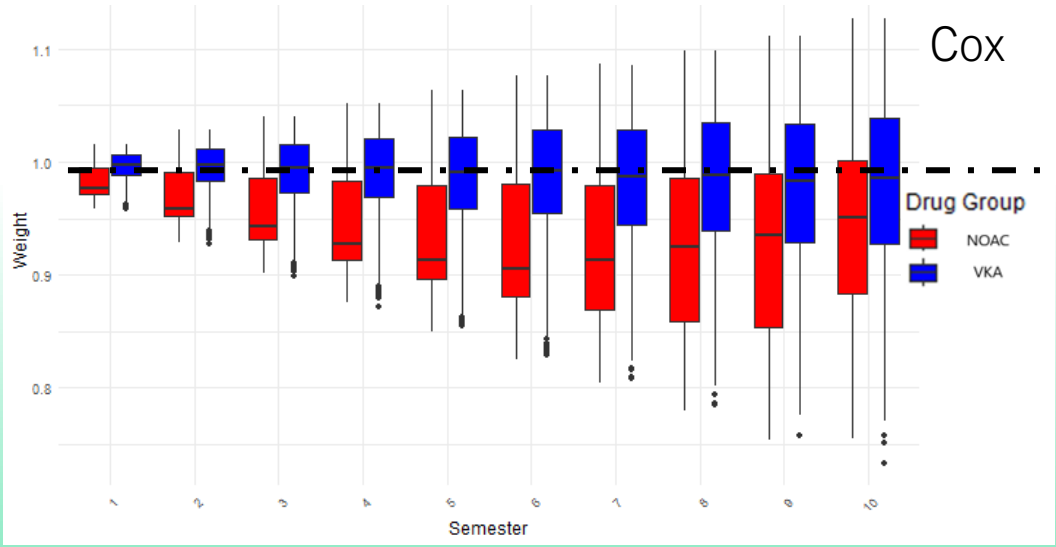
This method is based on the idea of compensating for censored subjects by giving extra weight to subjects who are not censored. More specific, IPCW assigns extra weight to subjects with similar characteristics to the ones that are censored

1. Variabile censura
2. Intervallo temporale
3. Scelta modello
4. Scelta covariate

Evento AKI

Covariate: Periodo di Arruolamento, Età_anni, GFR_basale, CHARLSON_AGE_score,



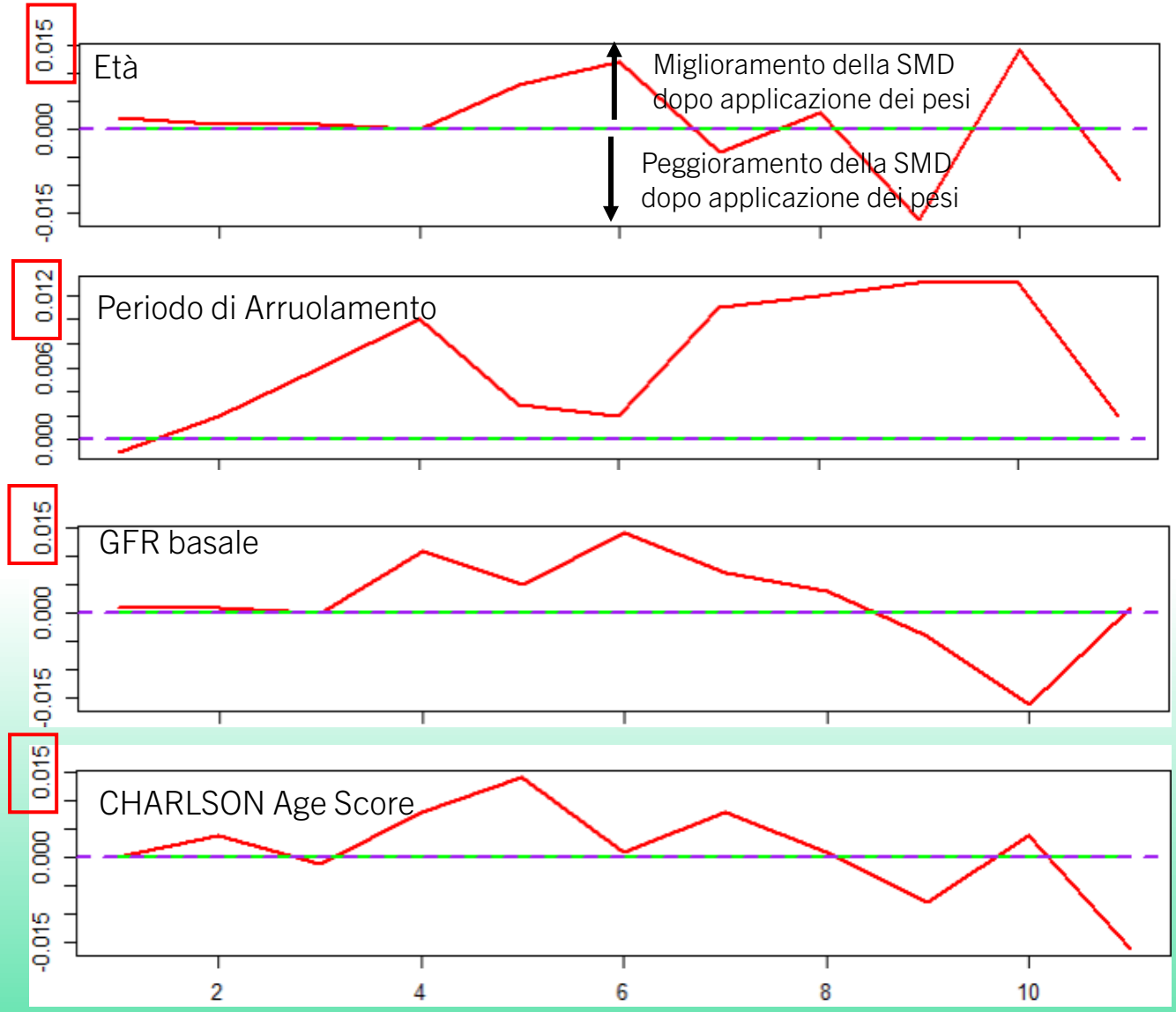


cation are met (7). Estimated weights that are extreme in value or that in aggregate do not have a mean close to 1 indicate model misspecification or nonpositivity. In turn, an

[Howe 2010]

Differenza tra le SMD prima e dopo applicazione di IPCW, ad ogni semestre t di follow-up (VKA)

Evento AKI



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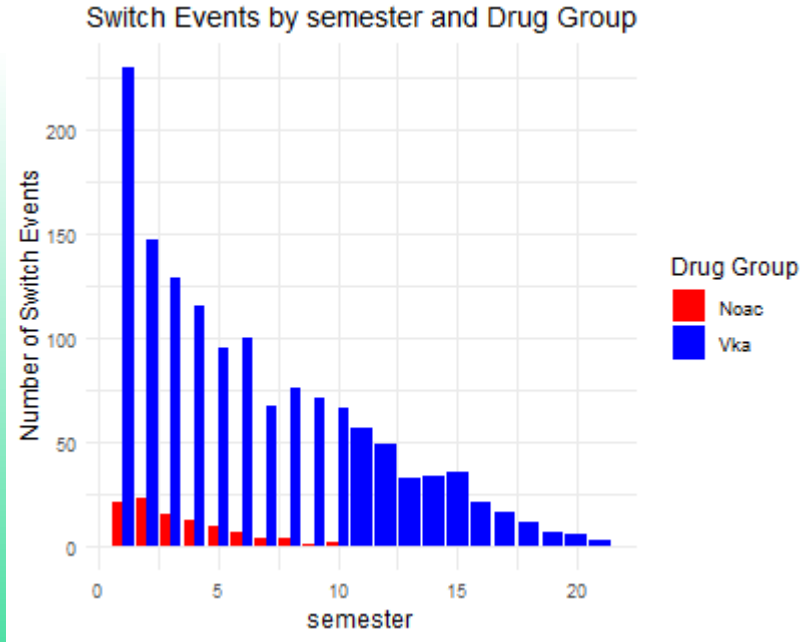

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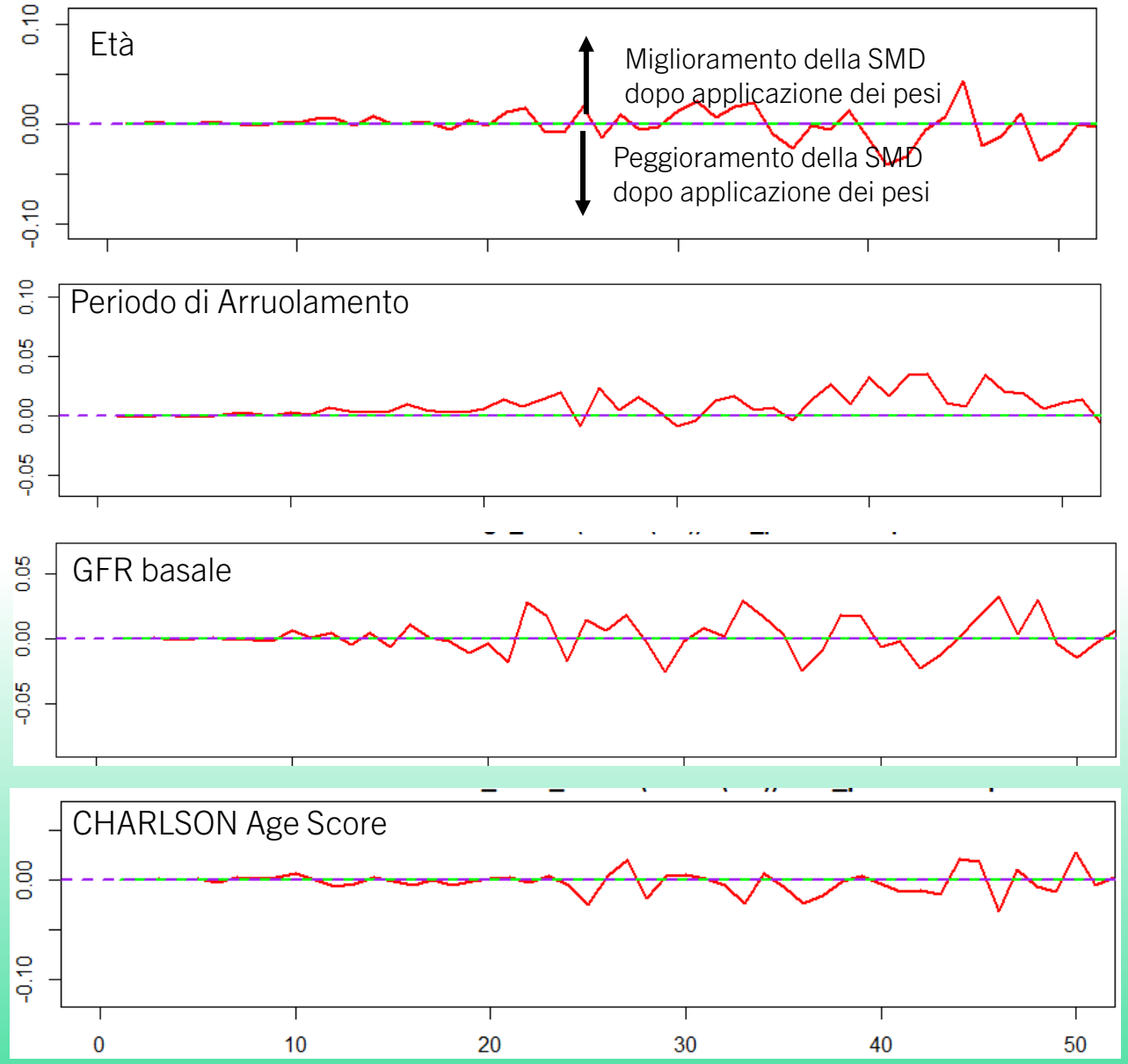

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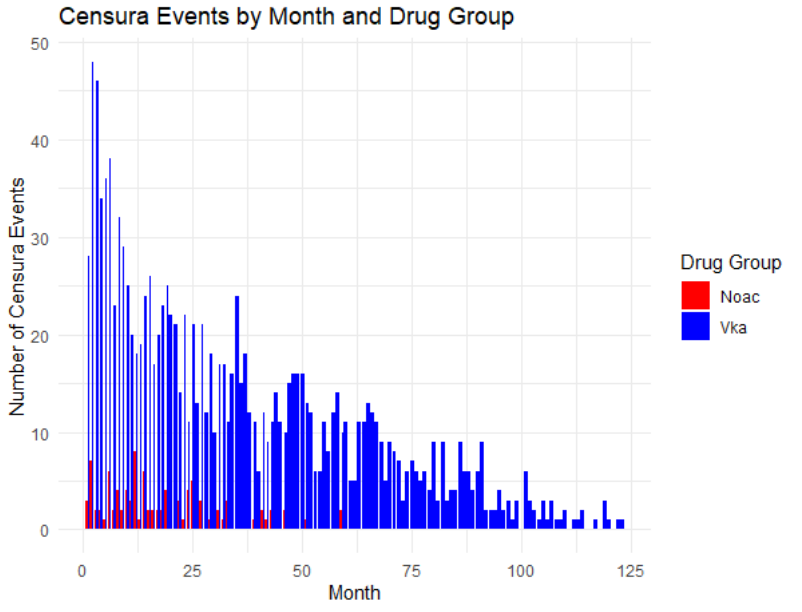
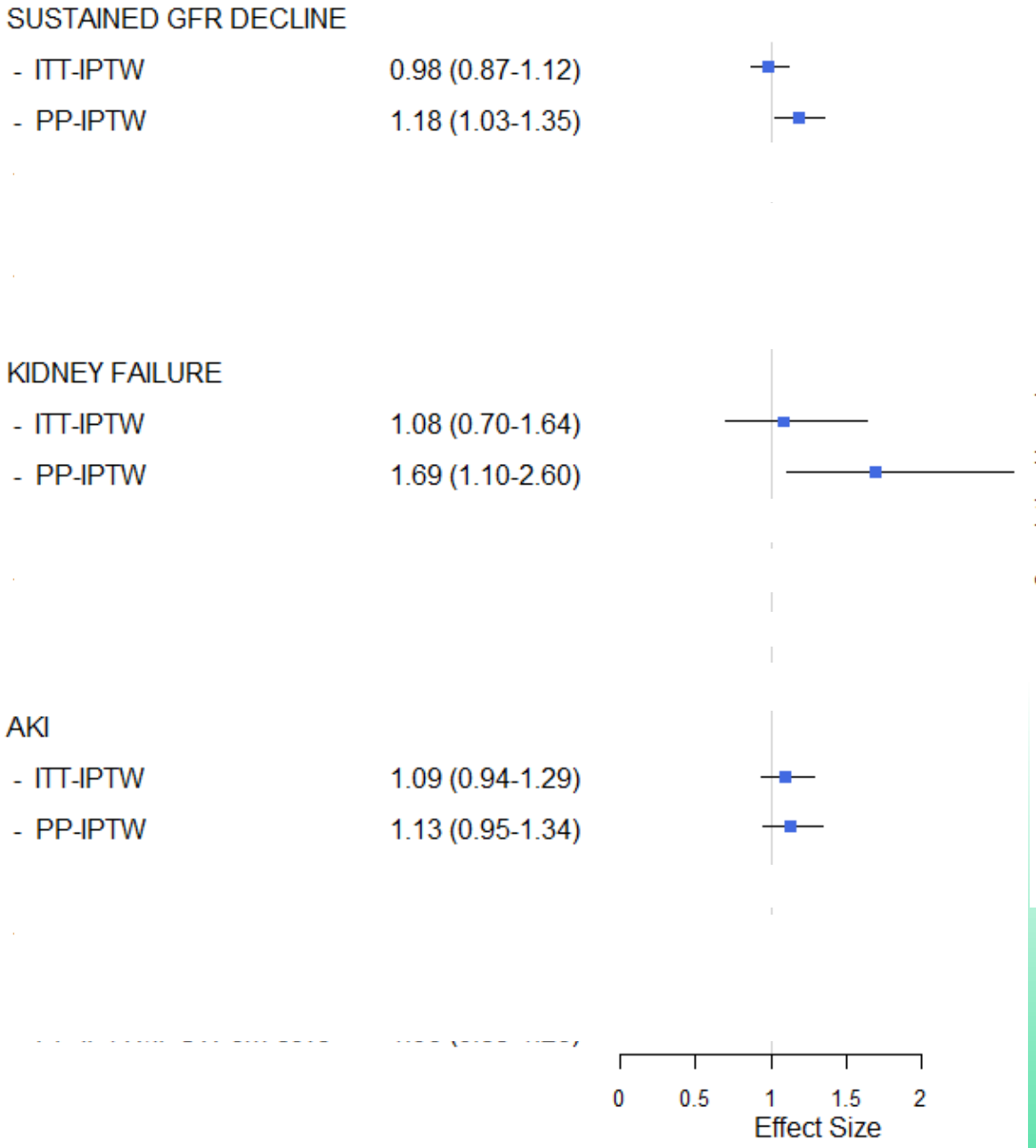
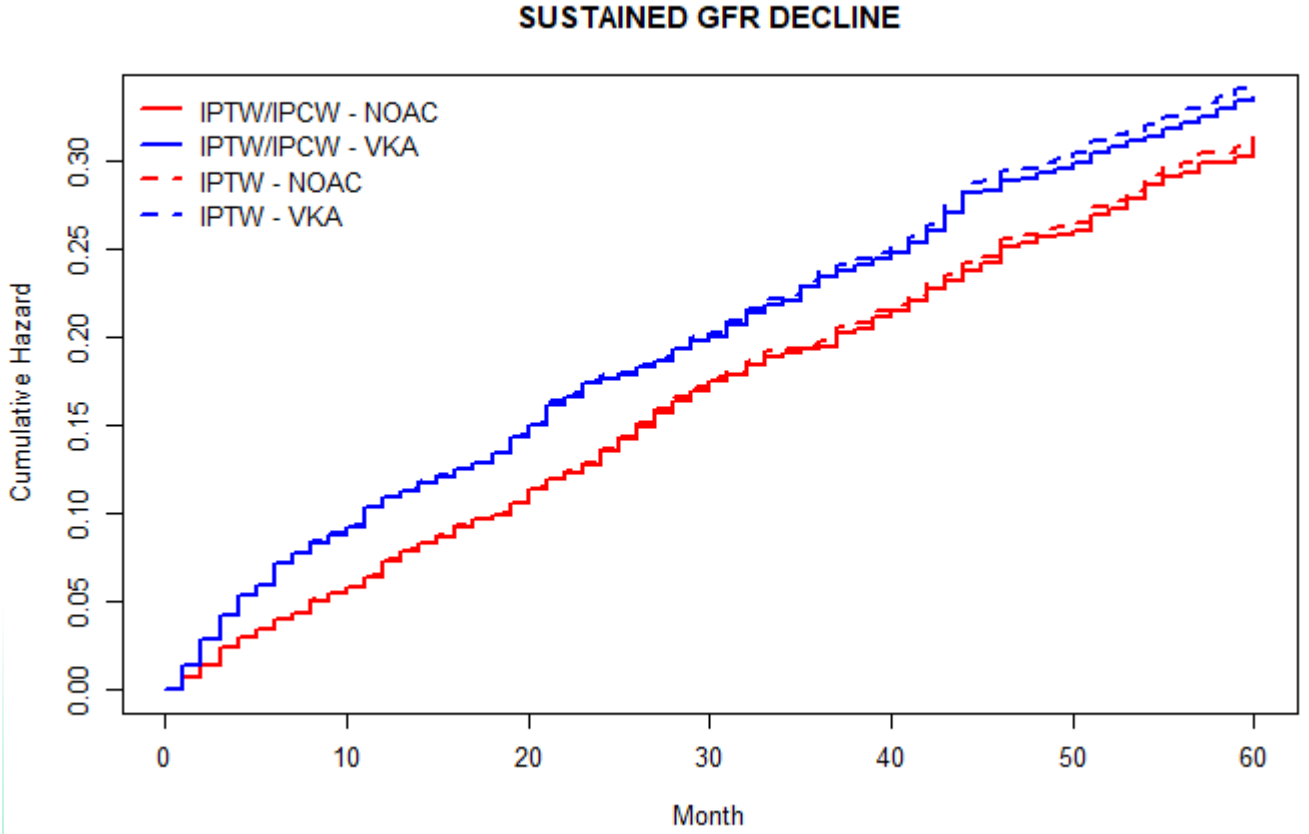


*Set Covariate 2: Periodo di Arruolamento, Farmaco Indice, Sesso, Età (anni), Diabete, GFR basale, Ipertensione, Obesità, Microalbuminuria, Scompenso cardiaco, Uso Diuretici, Uso SGLT2i, Provincia di Residenza, CHARLSON_AGE score, CHAD_VASC score, ATRIA score

**Set Covariate 3: Farmaco Indice * (Periodo di Arruolamento, Età (anni), GFR basale, CHARLSON_AGE score)





"Do different anticoagulants in AF lead to different risks of reduced renal function????????"

Our result suggest that VKA lead to an higher risk of Sustained GFR Decline (HR 1.17 [1.03-1.34]) and Kidney Failure 1.71 (HR: 1.71 [1.11-2.63]) compared to DOAC, with similar risk of AKI (HR: 1.13 [0.95-1.34]) and Death (HR: 1.01 [0.90-1.14]), even after accounting for differences in baseline covariates, informative censoring and competing risks.

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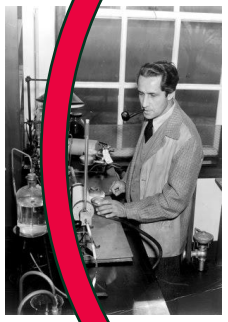
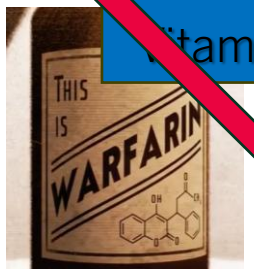
That's it? 🤔





VKA
Vitamin K Antagonist

DOAC
Direct Oral Anti Coagulant

Replication studies

Literature Review and meta-analysis

Biological mechanism

Clinical Significance

Risk vs Benefits

Cost-Effectiveness

Dose – Response Analysis

Subgroup and Effect Modification Analyses

Prospective Studies / Registry

Patient Preferences & Decision-Making

Policy or Guideline Impact

CONCLUSION AND KEY TAKEAWAYS

- The biomedical field calls for rigorous, collaborative, and intellectually engaging research.
- Causal inference is a cornerstone of meaningful findings.
- Interdisciplinary collaboration is vital — statisticians and data analysts should actively engage with clinicians, biologists, and other experts.
- Begin with a thorough literature review — it shapes your question, avoids redundancy, and identifies gaps.
- Be mindful of methodological limitations and the assumptions behind your tools: ackowledge them
- Ask questions freely — whether to your supervisor or colleagues from other fields. Curiosity is a strength!

Thanks for Listening!