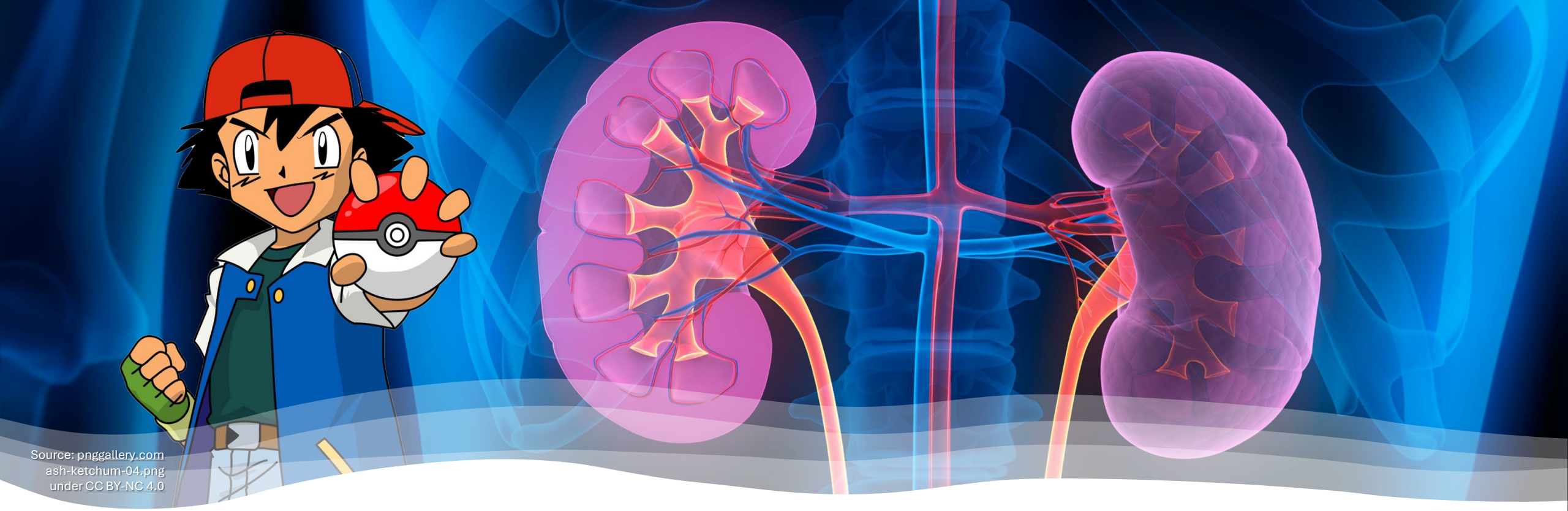

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Gotta Catch ‘Em All
How to Capture All That Matters in CKD Trials?

ASA AMERICAN STATISTICAL ASSOCIATION New Jersey Chapter

Webinar // March 6th 2025

Dr. Patrick Schloemer // Bayer

CKD = Chronic Kidney Disease

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Gotta Catch ‘Em All

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Gotta Catch ‘Em All

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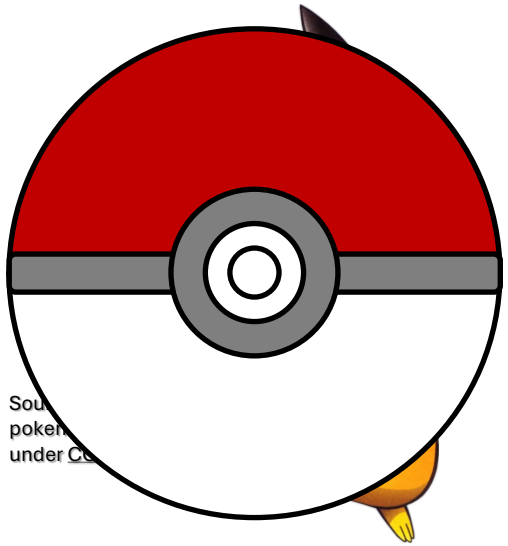

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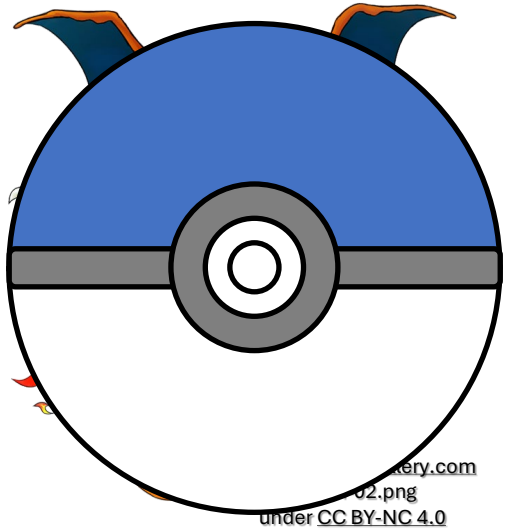

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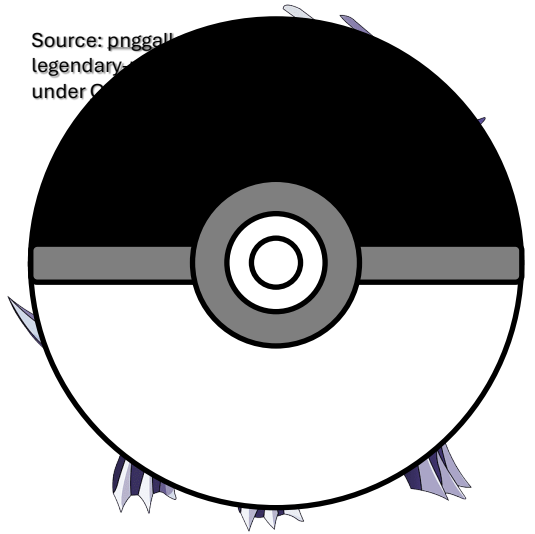

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Gotta Catch 'Em All

Frequent hospitalizations for heart failure (HHF)

Rate of HHF (events/year)

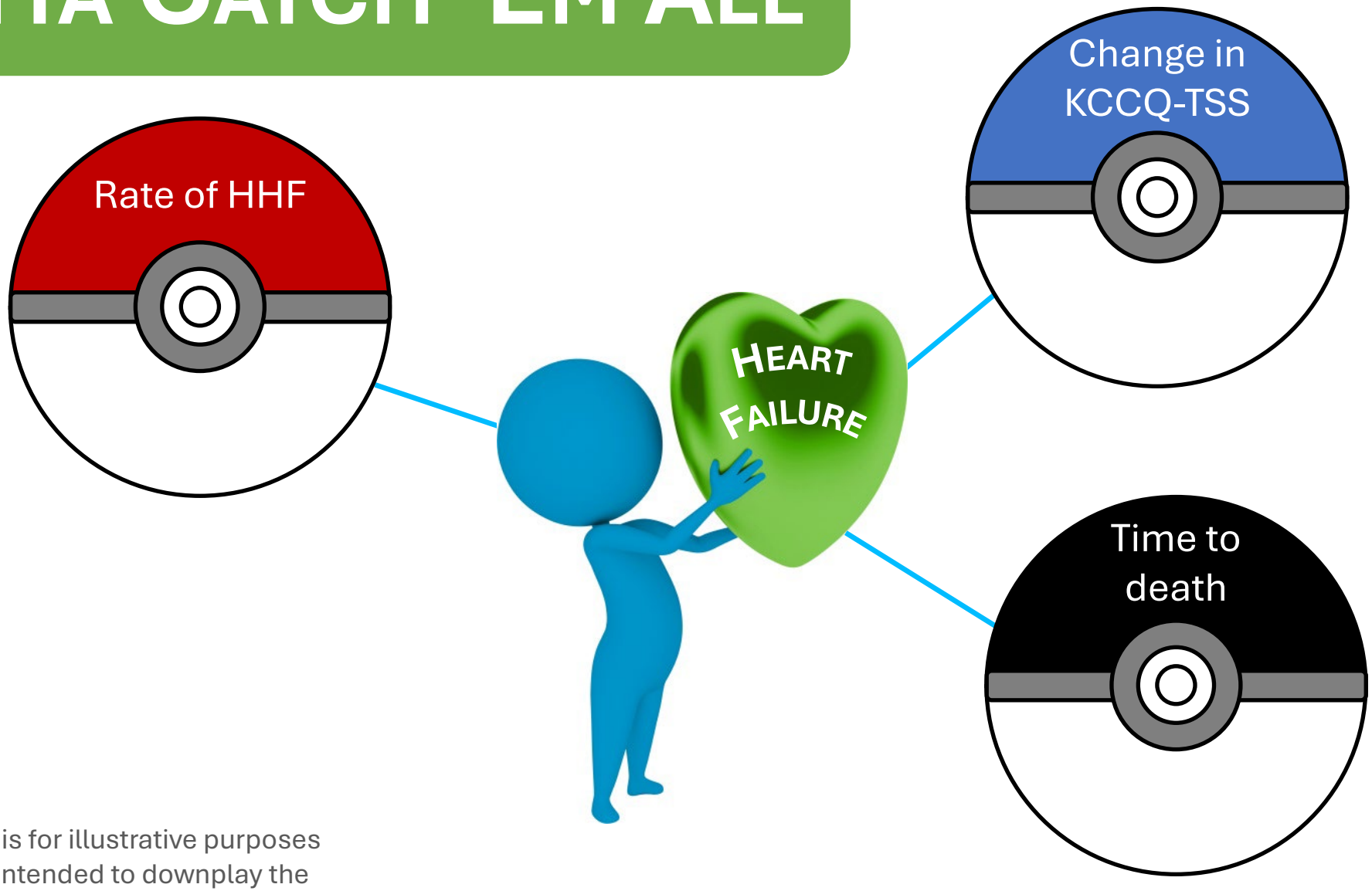
Tiredness, shortness of breath, limited exercise capacity

Change in Kansas City Cardiomyopathy Ques-tionnaire – Total Symptom Score (KCCQ-TSS)

High mortality risk

Time to death

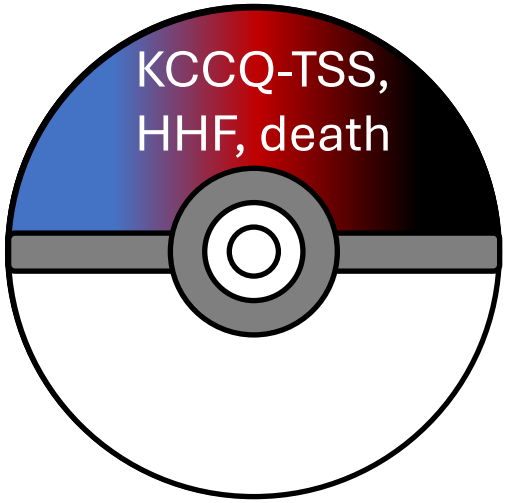
GOTTA CATCH 'EM ALL



Important note: This is for illustrative purposes only and is in no way intended to downplay the seriousness of the diseases discussed here.

Gotta Catch ‘Em All

Any suitable way of combination?



One Option will be discussed in today‘s session!

HCEs = Hierarchical Composite Endpoints

Chronic Kidney Disease (CKD) Trials

Main Goals in CKD Management

- Prolong time to **end-stage kidney disease (ESKD)**

- Reduce risk of **cardiovascular (CV) complications**

ESKD = Dialysis or kidney transplantation

Efficacy Endpoints for CKD Trials

- Too **large & long** trials
- As with CV death in CVD

Investigation and validation of **surrogate endpoints**

CVD = Cardiovascular Disease

GFR Decline Endpoints

GFR = Glomerular Filtration Rate

GFR Decline as Endpoint in CKD Trials

AJKD

Special Section: GFR Decline as an End Point for Clinical Trials in CKD

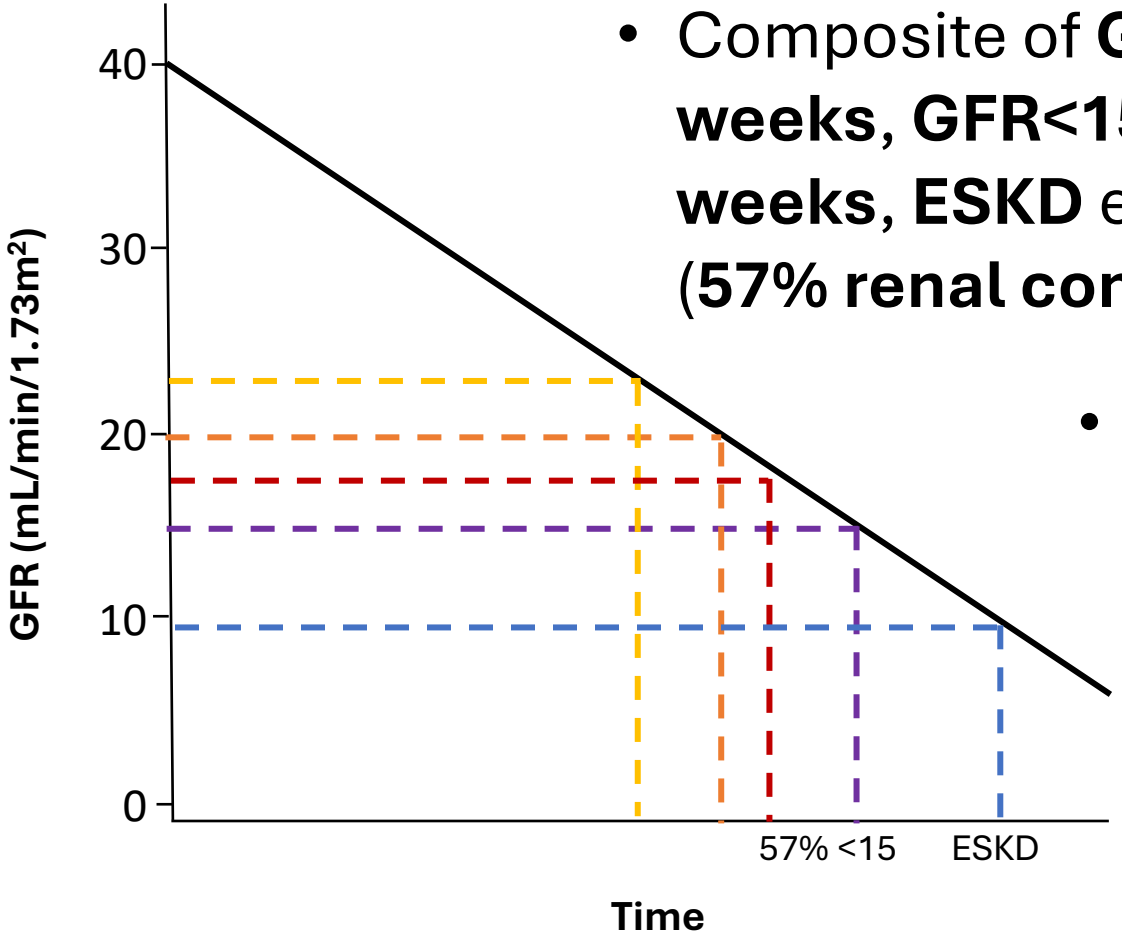
Special Report

2014

GFR Decline as an End Point for Clinical Trials in CKD: A Scientific Workshop Sponsored by the National Kidney Foundation and the US Food and Drug Administration

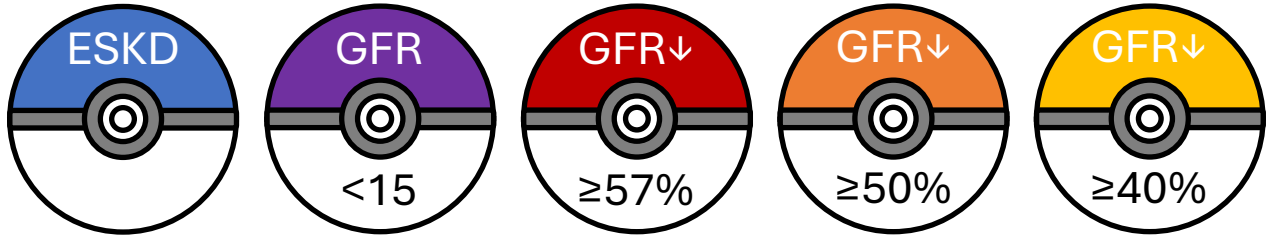
Andrew S. Levey, MD,[1] Lesley A. Inker, MD, MS,[1] Kunihiro Matsushita, MD, PhD,[2] Tom Greene, PhD,[3] Kerry Willis, PhD,[4] Edmund Lewis, MD,[5] Dick de Zeeuw, MD, PhD,[6] Alfred K. Cheung, MD,[7] and Josef Coresh, MD, PhD[2]

GFR Decline as Endpoint in CKD Trials



- Composite of **GFR decline of ≥ 57% sustained over ≥ 4 weeks**, **GFR<15 mL/min/1.73m² sustained over ≥ 4 weeks**, **ESKD** established as standard endpoint (**57% renal composite endpoint**)

- **Other cutpoints** may also be acceptable and have been utilized as well in clinical trials



GFR Decline in Recent CKD Trials

- Different GFR declines used as components of **primary** and/or **secondary endpoints** (besides 

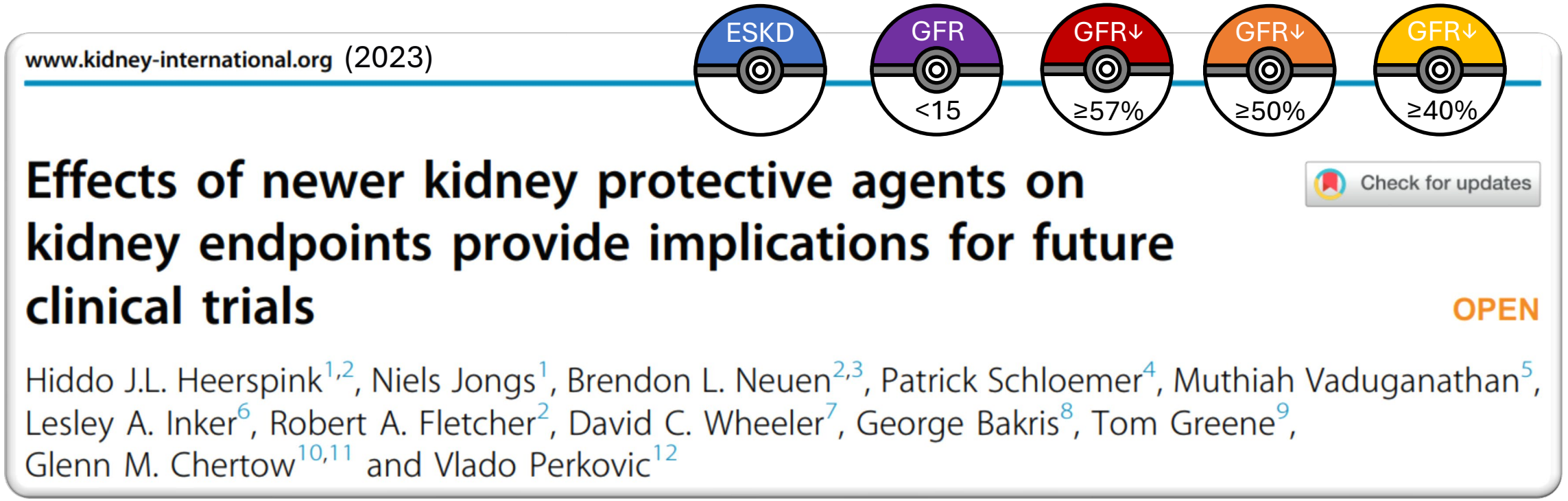
& 

)

Trial	Year	Sample Size	GFR decline used
CREDENCE	2014 – 2019	4401	57%
SONAR	2013 – 2019	2648	57%
FIDELIO-DKD	2015 – 2020	5674	40%, 57%
DAPA-CKD	2017 – 2020	4304	50%
FIGARO-DKD	2015 – 2021	7352	40%, 57%
EMPA-KIDNEY*	2019 – 2023	6609	40%
FLOW	2019 – 2023	3534	50%

* GFR<10 mL/min/1.73m^2 used instead of GFR<15 mL/min/1.73m^2

GFR Decline in Recent CKD Trials



www.kidney-international.org (2023)

Effects of newer kidney protective agents on kidney endpoints provide implications for future clinical trials

Check for updates

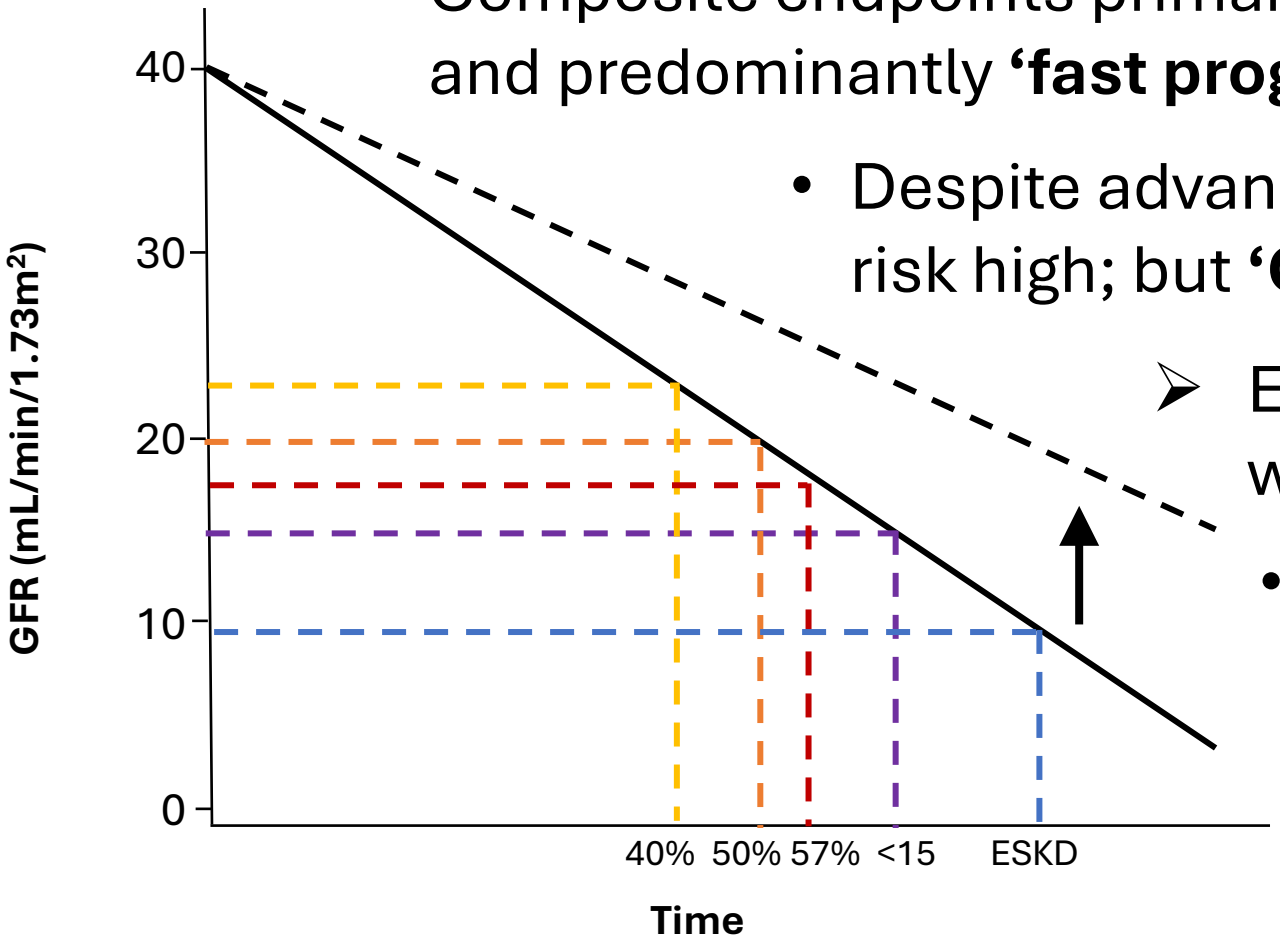
OPEN

Hiddo J.L. Heerspink[1,2], Niels Jongs[1], Brendon L. Neuen[2,3], Patrick Schloemer[4], Muthiah Vaduganathan[5], Lesley A. Inker[6], Robert A. Fletcher[2], David C. Wheeler[7], George Bakris[8], Tom Greene[9], Glenn M. Chertow[10,11] and Vlado Perkovic[12]

- **Effects generally consistent** across different GFR cutpoints
- GFR↓ ≥40% vs. GFR↓ ≥57%: **sample size approx. halved**

Limitations of GFR Decline Endpoints

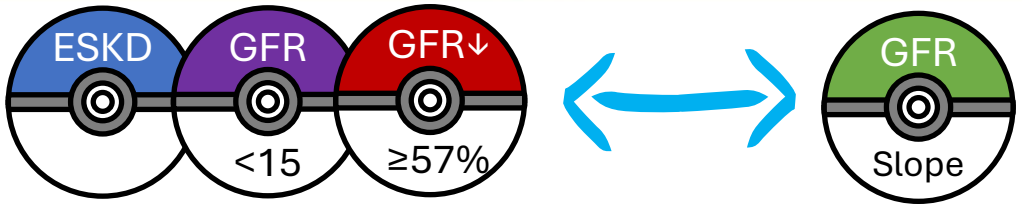
- Composite endpoints primarily **driven by less severe outcomes** and predominantly **‘fast progressors‘ experience events**
- Despite advancements in CKD treatment, residual risk high; but **‘GFR decline‘-based trials large/long**
  - ➢ Especially in **early stage CKD** patients with **slow progression**
  - Interest in **more efficient** endpoints where all patients **contribute an outcome → Continuous GFR analysis**



GFR Slope Endpoints

GFR Slope vs. GFR Decline Endpoints

nature medicine



Analysis

A meta-analysis of GFR slope as a surrogate endpoint for kidney failure

Received: 31 October 2022

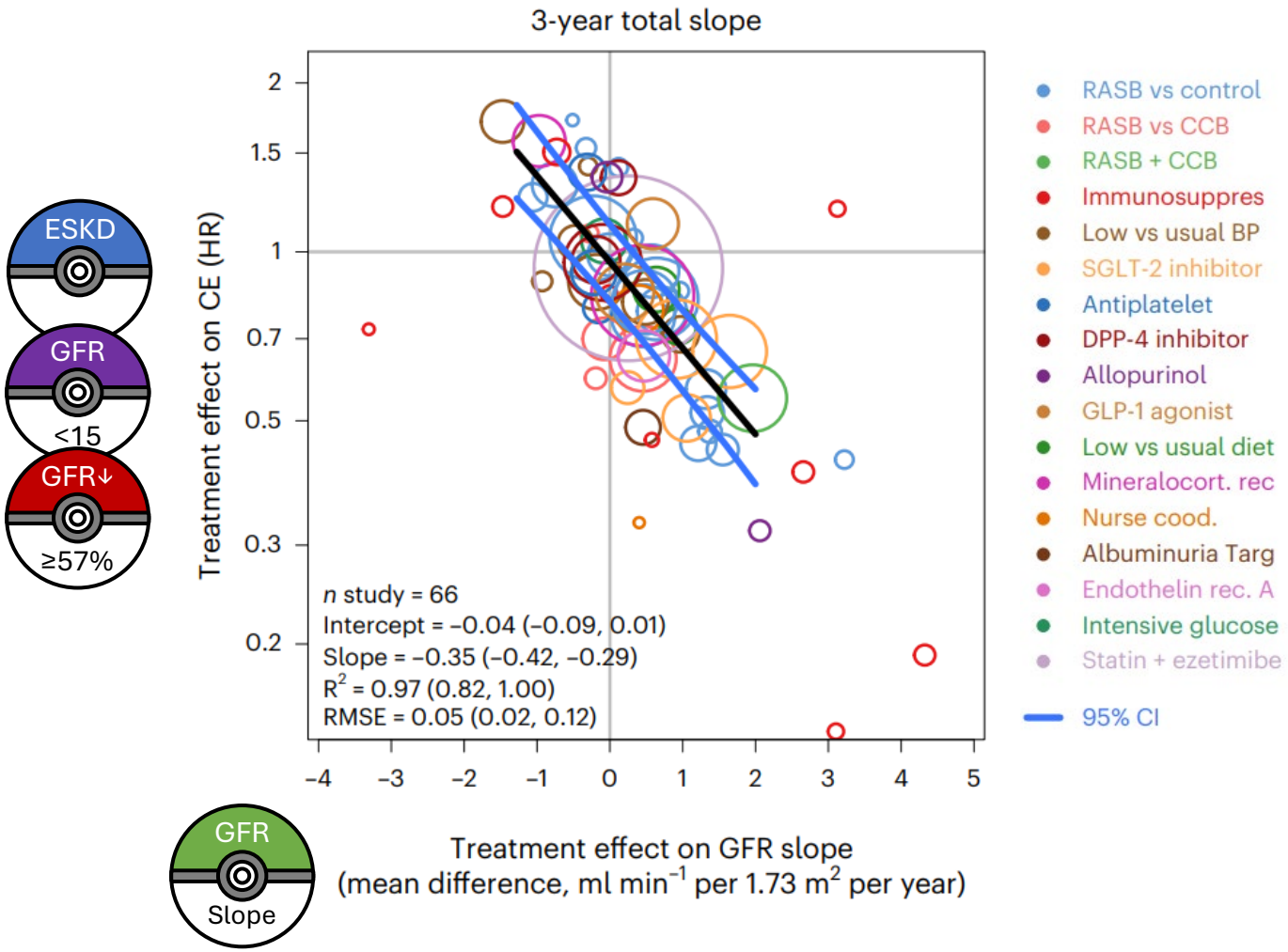
Accepted: 24 May 2023

Published online: 17 June 2023

Check for updates

Lesley A. Inker[1], Willem Collier[2], Tom Greene[2], Shiyuan Miao[1], Juhi Chaudhari[1], Gerald B. Appel[3], Sunil V. Badve[4], Fernando Caravaca-Fontán[5], Lucia Del Vecchio[6], Jürgen Floege[7], Marian Goicoechea[8], Benjamin Haaland[2], William G. Herrington[9], Enyu Imai[10], Tazeen H. Jafar[11], Julia B. Lewis[12], Philip K. T. Li[13], Bart D. Maes[14], Brendon L. Neuen[4], Ronald D. Perrone[1], Giuseppe Remuzzi[15], Francesco P. Schena[16], Christoph Wanner[17], Jack F. M. Wetzels[18], Mark Woodward[4,19], Hiddo J. L. Heerspink[20] & the CKD-EPI Clinical Trials Consortium*

GFR Slope vs. GFR Decline Endpoints



Qualification Opinion for GFR slope as a Validated Surrogate Endpoint for RCT in CKD

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Qualification Opinion as agreed by CHMP

Based on the evidence presented in the qualification opinion request and in a discussion meeting, CHMP considers that GFR slope (i.e., the mean rate of change in GFR) can in some trial settings - if adequately specified and assessed - serve as a surrogate endpoint for CKD in clinical trials for standard marketing authorisation and extension of indication approvals.

Agreed Context of Use (CoU):

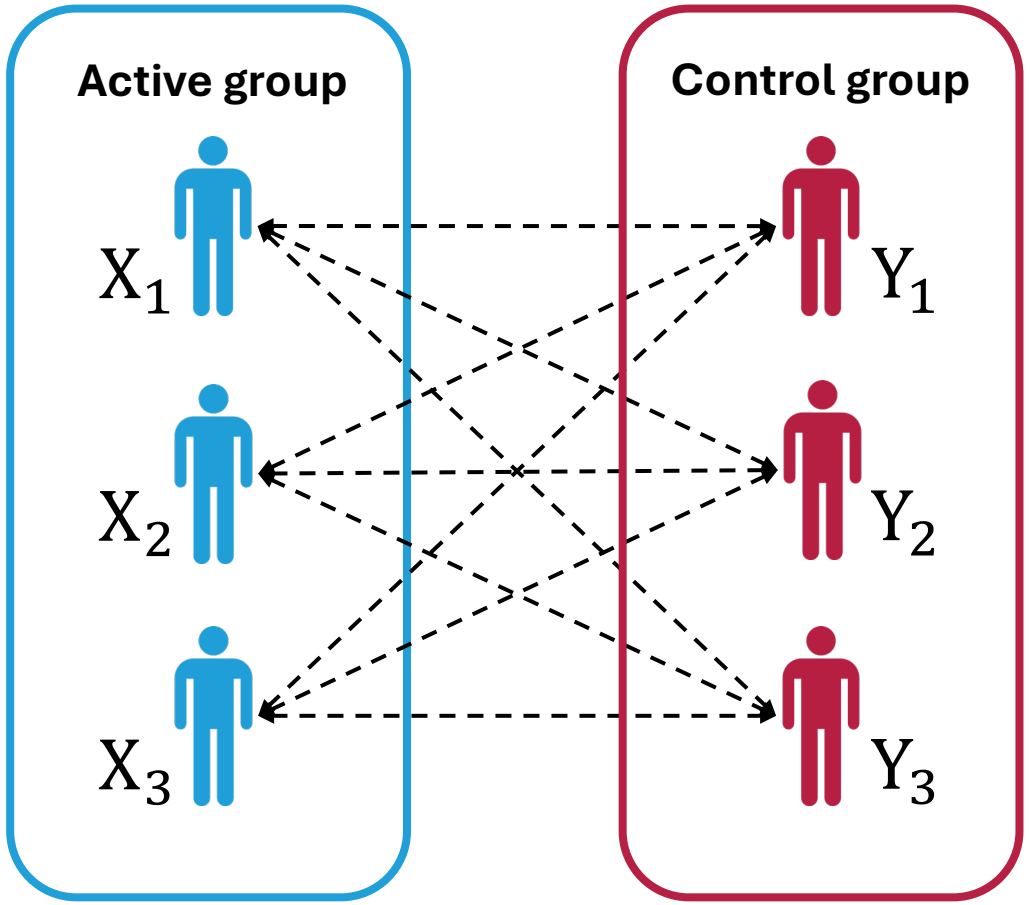
The proposed novel method, GFR slope, is qualified to be used as a validated surrogate endpoint for CKD progression in randomised controlled clinical trials to support marketing authorisation and extension of indication approvals when the use of clinical endpoints is not feasible due to rarity of the disease or need for a very long study period.

Hierarchical Composite Endpoints (HCEs)

HCEs – Background

- **Patient-wise** comparisons with **hierarchically ordered** endpoints
- Idea goes back to **Finkelstein & Schoenfeld (1999)**
- **Buyse (2010)** introduced **Generalized Pairwise Comparison (GPC)**
- **Pocock et al. (2012)** introduced **Win Ratio**
  - ➢ **Increasing application** in **CV trials**
- Methodology based on **Wilcoxon-Mann-Whitney U statistic** (Wilcoxon 1945, Mann & Whitney 1947)

HCEs – Illustration



- $X_i \succ Y_j : X_i$ has better outcome than Y_j (win)
- $X_i \prec Y_j : X_i$ has worse outcome than Y_j (loss)
- $X_i \asymp Y_j : X_i$ and Y_j have similar outcomes (tie)

Use proportions of wins, losses and ties to estimate $P(X_i \succ Y_j)$, $P(X_i \prec Y_j)$ and $P(X_i \asymp Y_j)$

HCEs – Summary Measures

Net Benefit

(Buyse 2010)

$$P\left(X_i \succ Y_j\right) - P\left(X_i \prec Y_j\right)$$

Win Ratio (WR)

(Pocock et al. 2012)

$$\frac{P\left(X_i \succ Y_j\right)}{P\left(X_i \prec Y_j\right)}$$

Win Odds (WO)

(Dong et al. 2020; Brunner et al. 2021)

$$\frac{P\left(X_i \succ Y_j\right) + \frac{1}{2} P\left(X_i \asymp Y_j\right)}{P\left(X_i \prec Y_j\right) + \frac{1}{2} P\left(X_i \asymp Y_j\right)}$$

A Novel HCE for CKD Trials

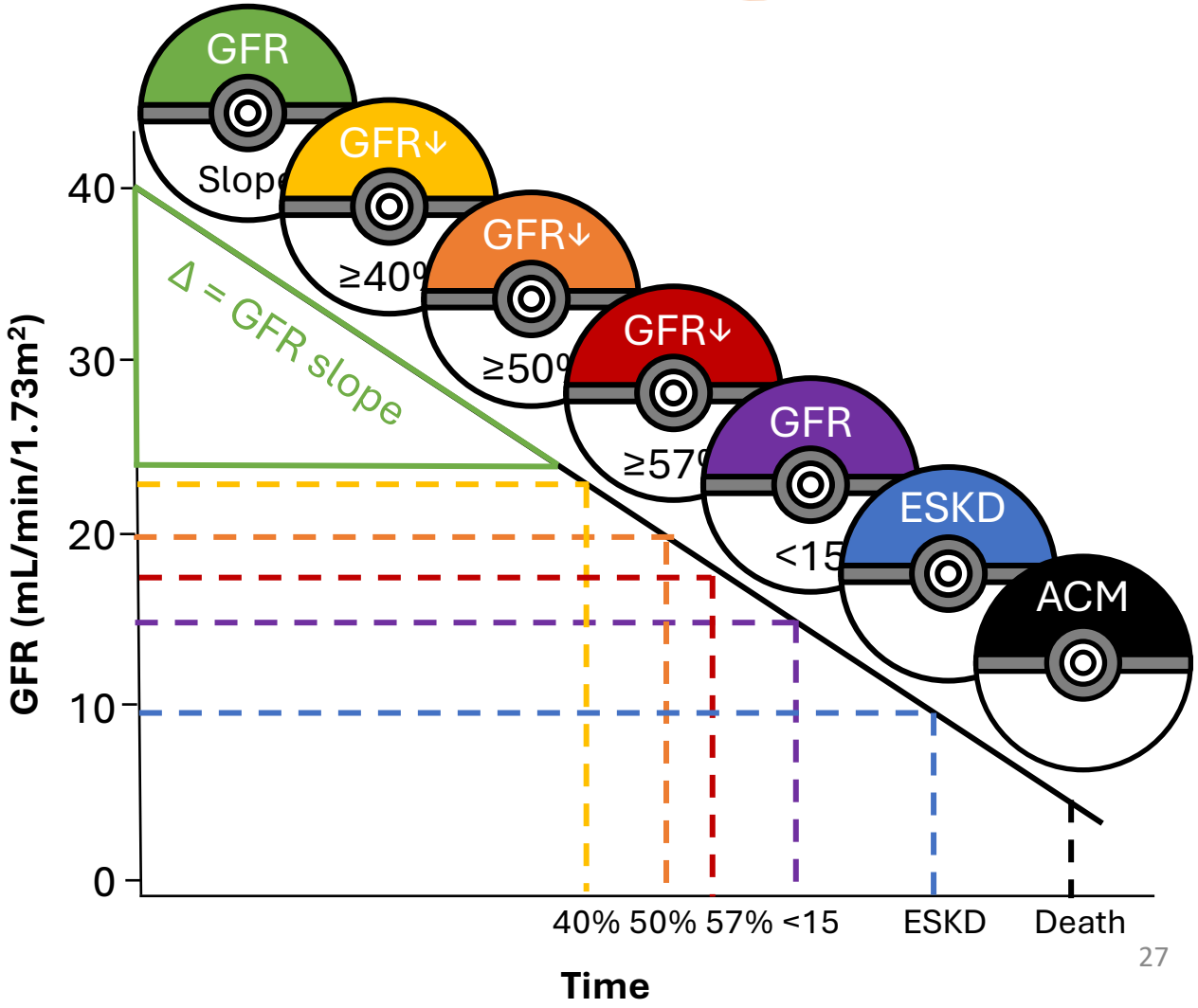
A Holistic Approach to Capture CKD Progression
The **Kidney Hierarchical Composite Endpoint** (HCE)

A Holistic Approach to Capture CKD Progression
The **Kidney Hierarchical Composite Endpoint** (HCE)

1. All-cause mortality
2. Dialysis/transplantation (ESKD)
3. Sustained GFR <15mL/min/1.73m^2
4. Sustained GFR decline from baseline of ≥57%
5. Sustained GFR decline from baseline of ≥50%
6. Sustained GFR decline from baseline of ≥40%
7. Total GFR slope at 3 years

Variable (patient-level): Time to the most severe of the first six components within 3 years. If none of the time-to-event components occurred within 3 years, total GFR slope at 3 years is considered.

Population-Level Summary: Win Odds, i.e. the odds that a random subject in the treatment group has a better outcome than a random subject in the control group.



Application of the Kidney HCE in CKD Trials

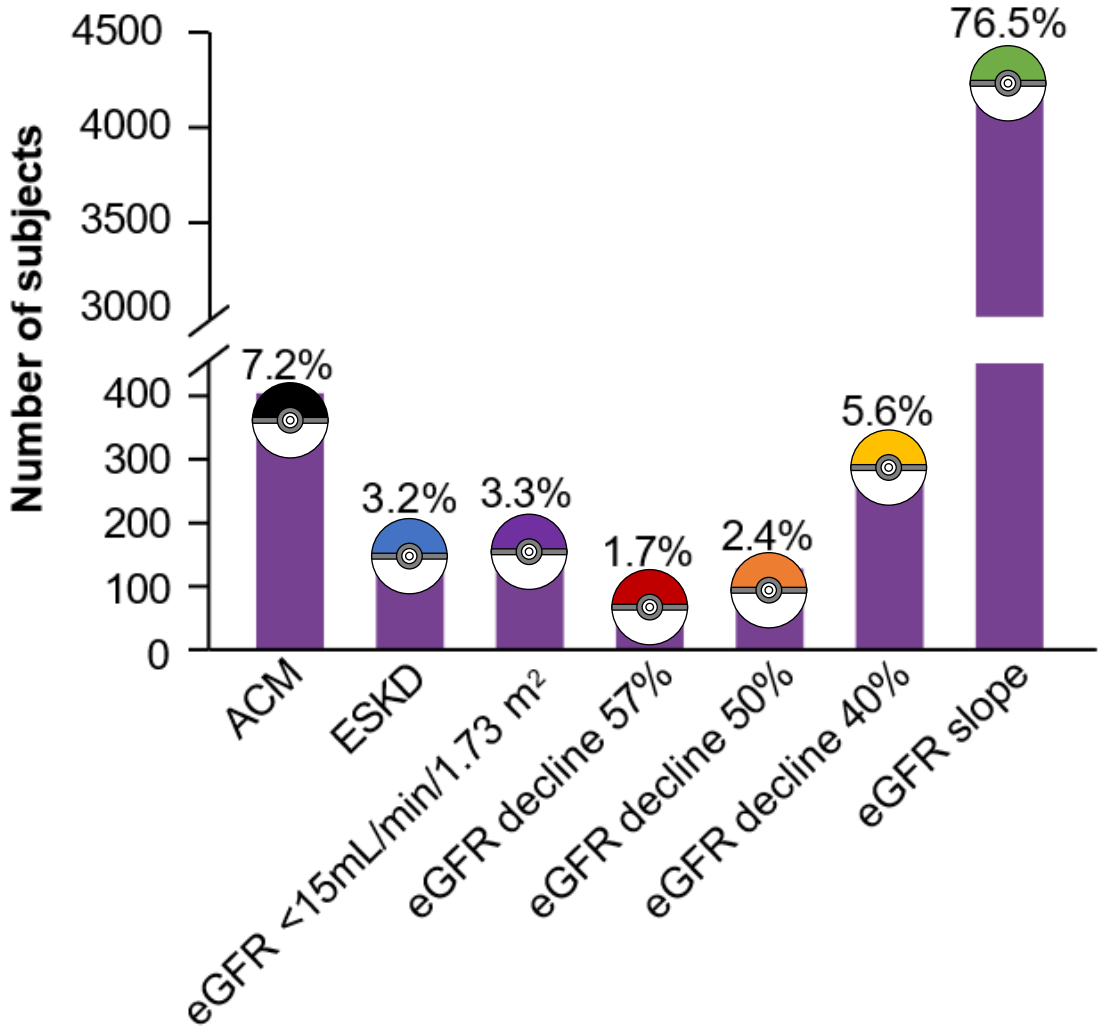
- Applied the Kidney HCE in **seven major Phase III CKD trials** (DAPA-CKD, CREDENCE, FIDELIO-DKD, SONAR, RENAAL, IDNT and ALTITUDE)
- Calculated and compared:
  - **Win Odds** for Kidney HCE over 3 years
  - **Hazard Ratio** for original primary kidney outcome in each trial
  - **Total GFR slope** at 3 years

Application in FIDELIO-DKD

- **FI**nerenone in reducing ki**D**n**E**y fai**L**ure and d**I**sease pr**O**gression in **D**iabetic **K**idney **D**isease (**FIDELIO-DKD**) trial
- Randomized, double-blind, placebo-controlled Phase III study
- **N=5,674** randomly assigned to finerenone or placebo (**1:1**)
- Primary endpoint result: **40% renal composite endpoint** with **HR = 0.82** (95% CI: 0.73 to 0.93, p=0.001)
- **Total GFR slope difference at 3 years** of **0.64 mL/min/1.73m^2/year** (95% CI: 0.40 to 0.89 mL/min/1.73m^2)

Kidney HCE in FIDELIO-DKD

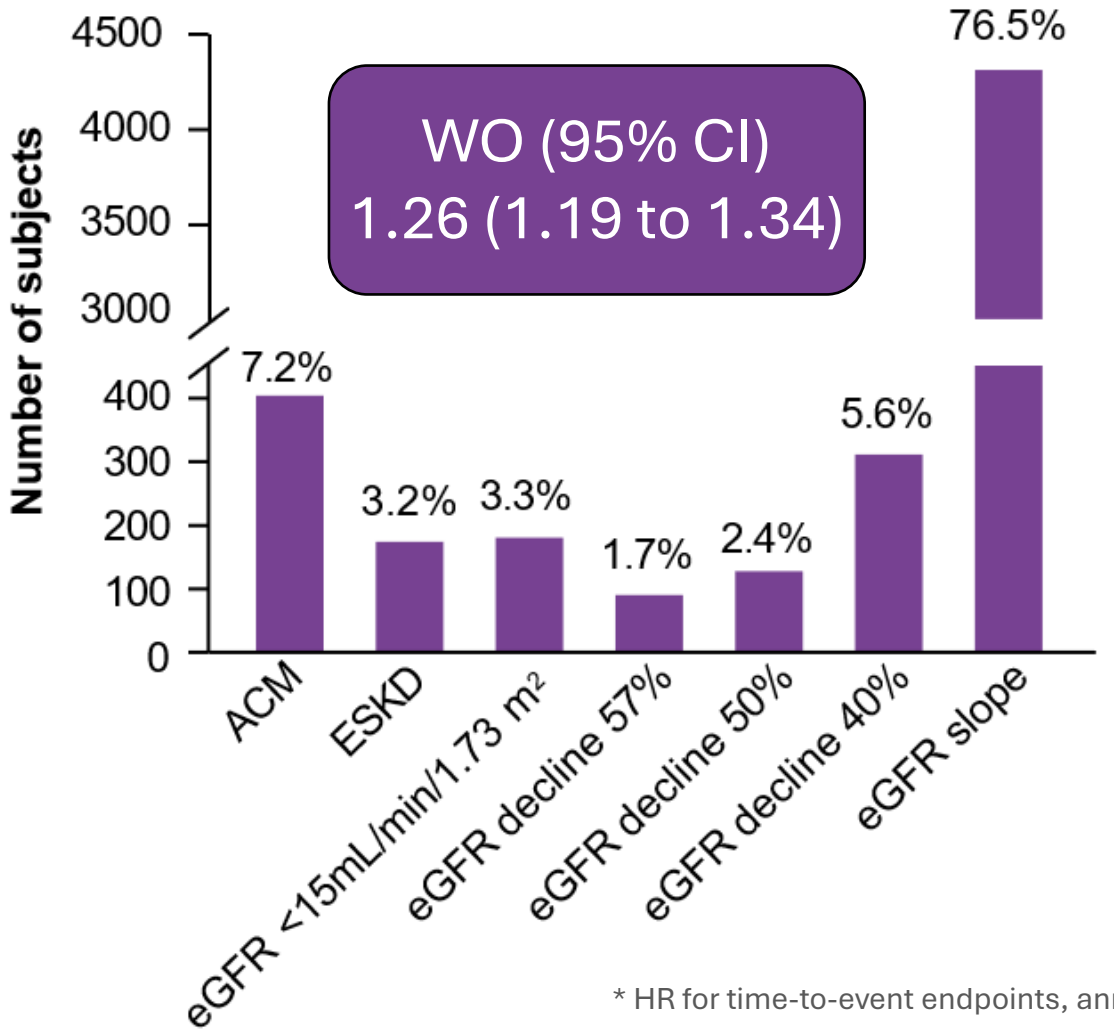
Contribution of individual components



ACM = All-cause mortality

Kidney HCE in FIDELIO-DKD

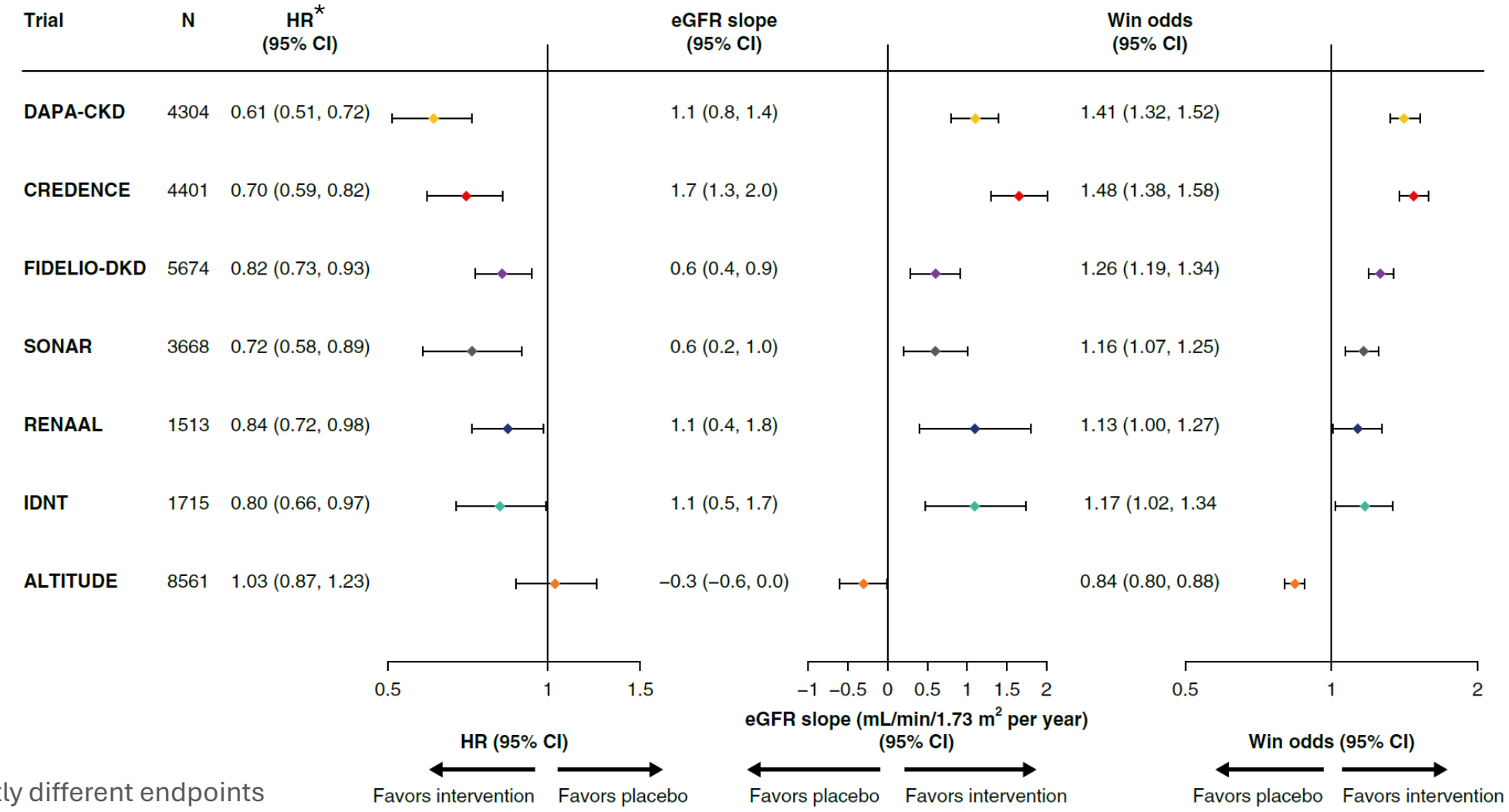
Overall results and for each individual component



Component	Marginal Effect*
All-cause mortality	0.90 (0.75 to 1.07)
ESKD	0.86 (0.67 to 1.10)
GFR < 15	0.82 (0.67 to 1.01)
57% GFR decline	0.68 (0.55 to 0.82)
50% GFR decline	0.73 (0.62 to 0.85)
40% GFR decline	0.81 (0.72 to 0.92)
GFR slope	0.64 (0.40 to 0.89)

* HR for time-to-event endpoints, annualized total slope difference at 3 years for GFR slope. 95% CI are given in parentheses.

Results Across Trials



* Based on slightly different endpoints

Conclusion

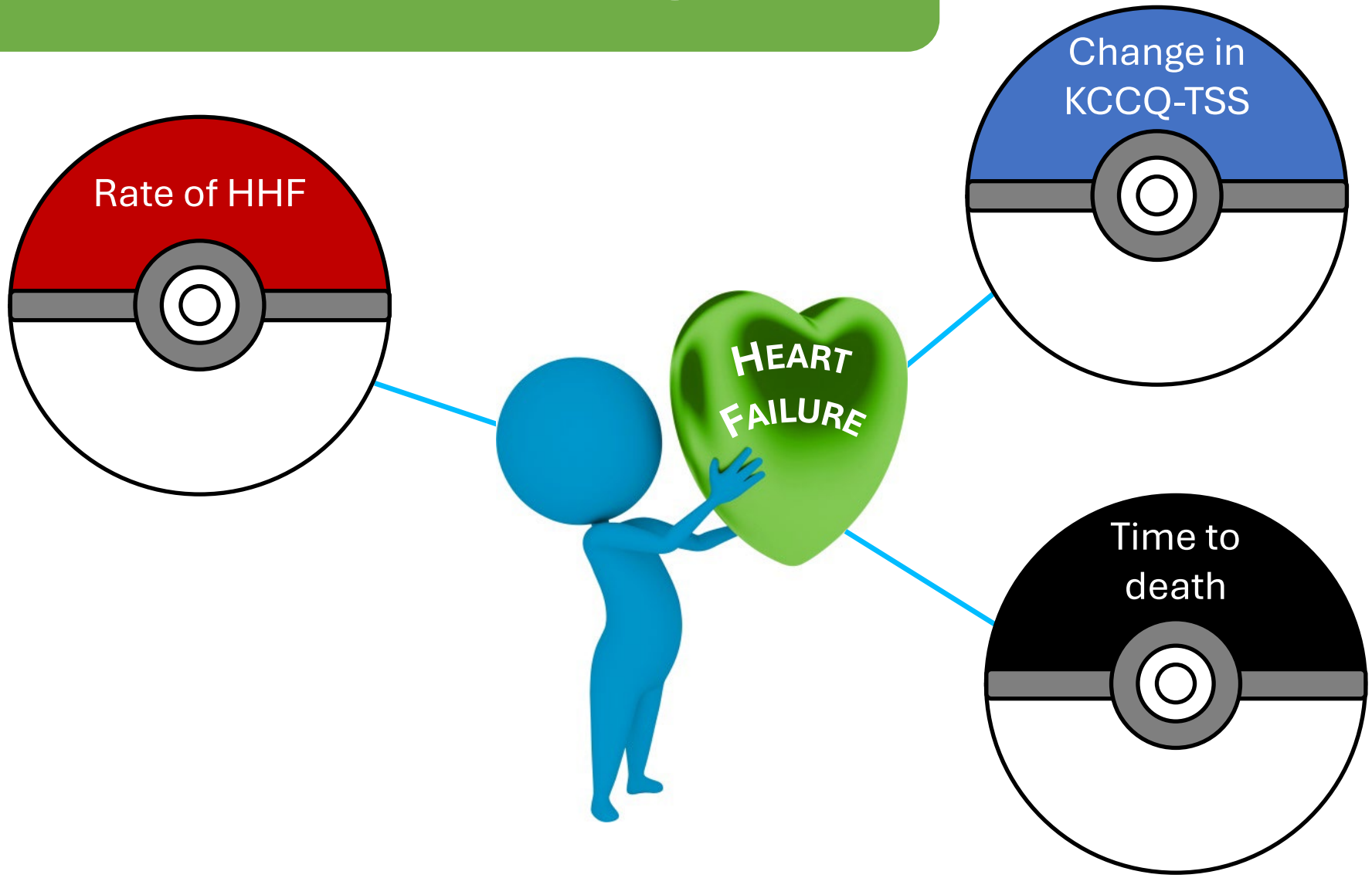
- Kidney HCE enables **prioritization of outcomes** & **combination of clinical events and GFR slope**
- Kidney HCE **well aligned with traditional endpoints** in 7 CKD RCTs
- **Potential for efficiency gains** compared to traditional endpoints
- **Design considerations** for **Kidney HCE trials** are discussed in **Little et al. (2023)** (e.g. how to avoid **transitivity issues**)
- **Basic data structure for HCEs** described in **Gasparyan et al. (2024)**

Common Questions

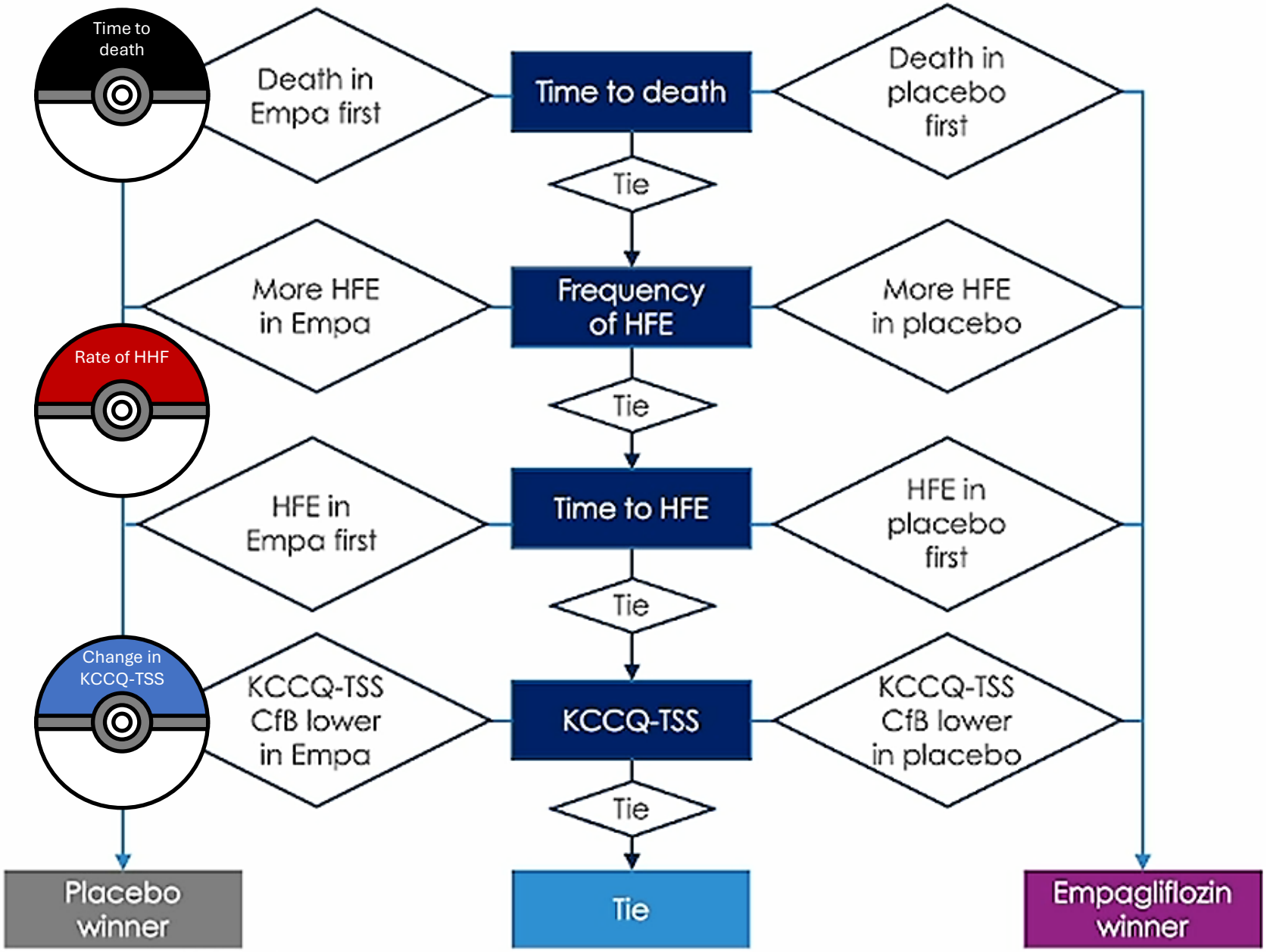
- Isn't this just a **GFR slope 2.0**? → Depends on **individual contributions!**
- Can we include **CV events**? → Yes, but which **order**?
- What about **thresholds** for **GFR slope**?
  - GFR slope difference of **0.5 ml/min/1.73m^2/year** ↔ **HR=0.80** for clinical outcomes[1]
  - **No direct patient-level interpretation** (like for KCCQ)
- **Future use** of **Kidney HCE**
  - **Secondary endpoint** in one **ongoing Phase III CKD trial**[2]
  - **Close dialogue** with **ISN**[3] and **NKF**[4]**/FDA** about **HCEs in CKD trials**
  - **Ongoing evaluation** of the **Kidney HCE**

[1] Inker et al. (2023), [2] https://clinicaltrials.gov/study/NCT06268873, [3] International Society of Nephrology, [4] National Kidney Foundation

HF Example Revisited

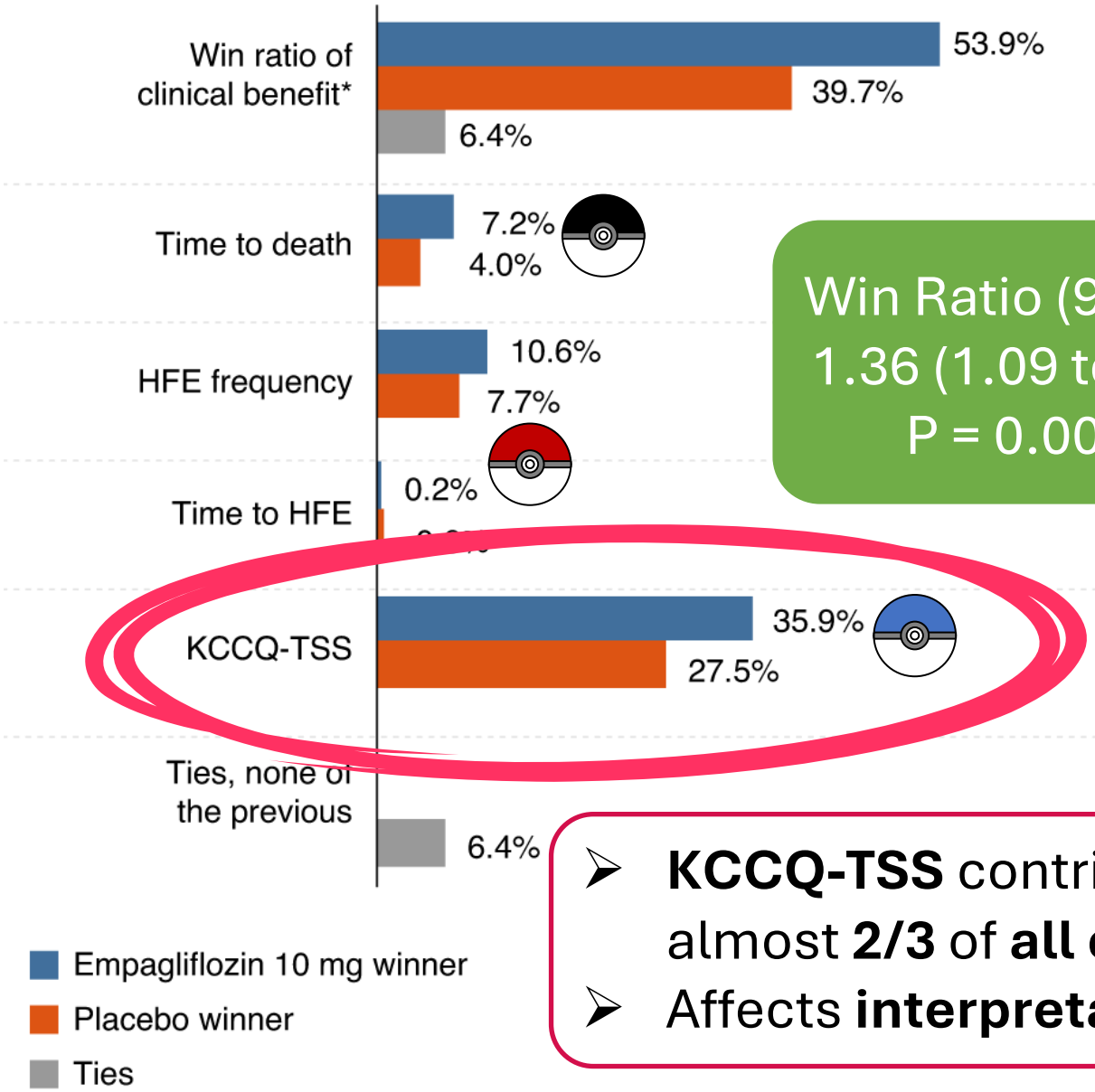


EMPULSE TRIAL



Source: Voors et al. The SGLT2 inhibitor empagliflozin in patients hospitalized for acute heart failure: a multinational randomized trial. Nature Medicine. 28: 568-574.

EMPULSE TRIAL



Win Ratio (95% CI)
1.36 (1.09 to 1.68)
P = 0.0054

- **KCCQ-TSS** contributes to almost **2/3** of **all comparisons**
- Affects **interpretation** of HCE

Source: Voors et al. The SGLT2 inhibitor empagliflozin in patients hospitalized for acute heart failure: a multinational randomized trial. Nature Medicine. 28: 568-574.

WITH GREAT POWER COMES GREAT RESPONSIBILITY

If overall effect is **primarily driven** by outcome with **lesser or questionable clinical importance**, "*a positive result represents* ***only a technical success*** *that does* ***not provide any actionable information***"

Circulation

PERSPECTIVE

Win Ratio: A Seductive But Potentially Misleading Method for Evaluating Evidence from Clinical Trials

Javed Butler, MD, MPH, MBA; Norman Stockbridge, MD, PhD; Milton Packer, MD

Other Challenges with the Win Ratio

Causal Interpretation

Population-Level Summary:
Win Odds, i.e. the odds that **a random subject** in the treatment group has a better outcome than **a random subject** in the control group.

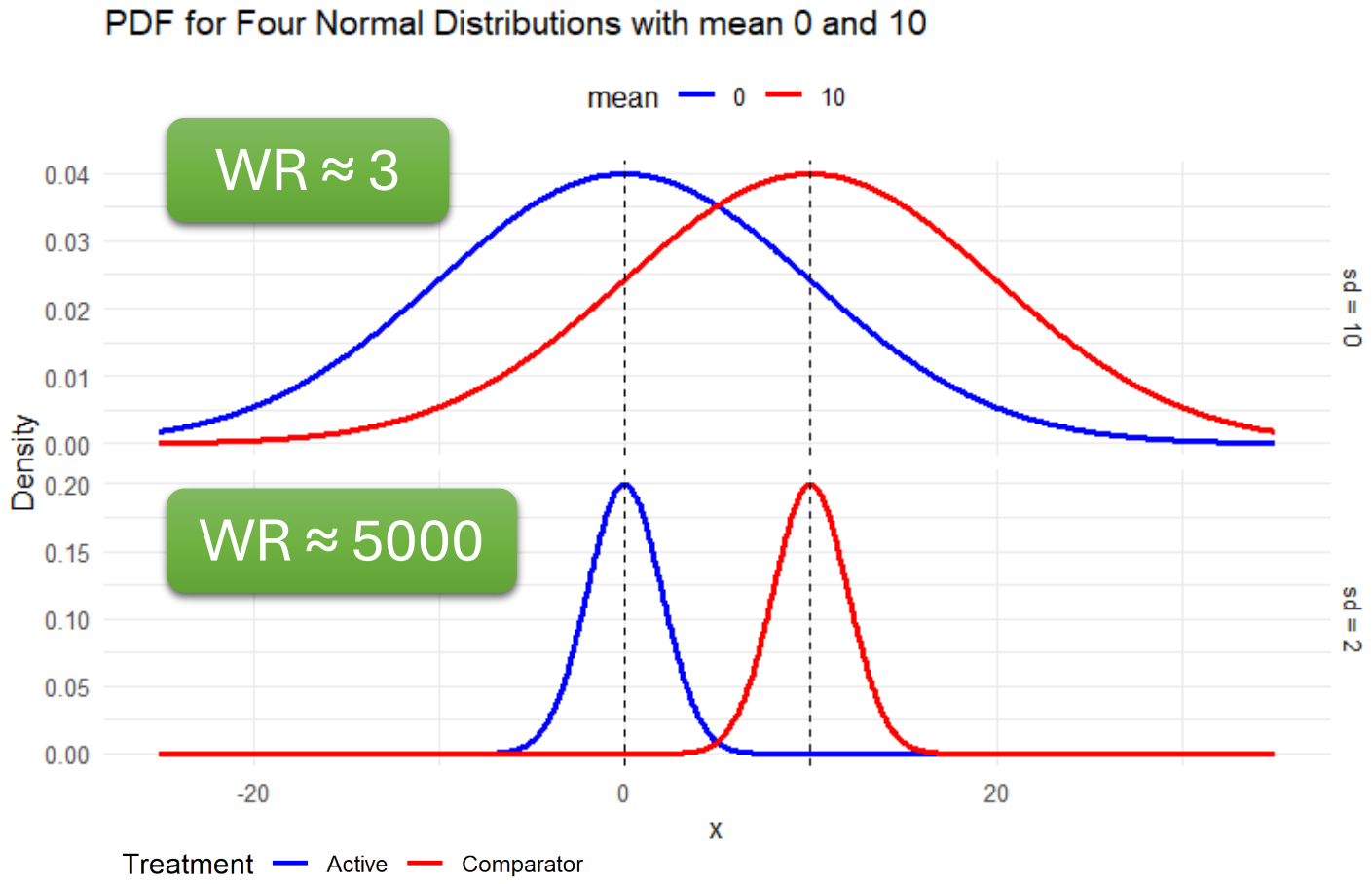
Hand's Paradox[1,2]

$$\mathrm{WR} = \frac{\sum_{i,j} P\left[Y_i(1) \succ Y_j(0)\right]}{\sum_{i,j} P\left[Y_i(1) \prec Y_j(0)\right]} \neq \widetilde{\mathrm{WR}} = \frac{\sum_{i} P\left[Y_i(1) \succ Y_i(0)\right]}{\sum_{i} P\left[Y_i(1) \prec Y_i(0)\right]}$$

[1] Hand (1992), [2] Fay et al. (2018)

Other Challenges with the Win Ratio

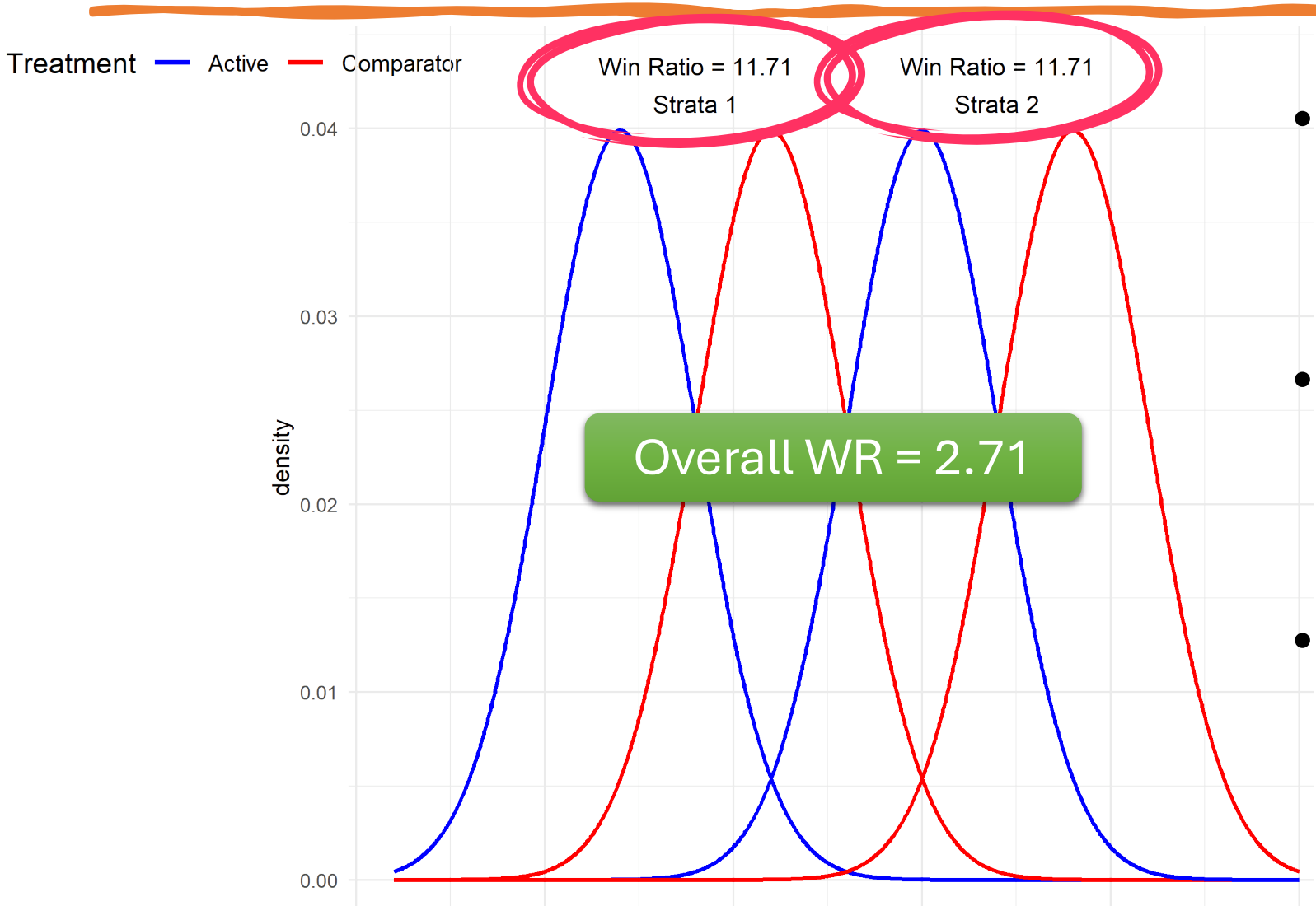
Variance Dependence



- Win Ratio is a **measure of discrimination**
- **Measurement method** affects Win Ratio
- **Between-trial comparisons** difficult
- Highlights importance of **individual component analyses**

Other Challenges with the Win Ratio

Non-Collapsibility



- Win Ratio is **non-collapsable** similar to e.g. the Odds Ratio
- Complicates **transportability** between different populations
- Particularly pronounced in **meta-analyses**

JASN Journal of the American Society of Nephrology

Development and Validation of a New Hierarchical Composite End Point for Clinical Trials of Kidney Disease Progression

Hiddo L. Heerspink,[1,2] Niels Jongs,[1] Patrick Schloemer,[3] Dustin J. Little,[4] Meike Brinker,[5] Christoph Tasto,[5] Martin Karpefors,[6] David C. Wheeler,[2,7] George Bakris,[8] Vlado Perkovic,[2,9] Richard Nkulikiyinka,[3] Jerome Rossert,[4] and Samvel B. Gasparyan[6]

umcg

university of groningen

Validity and Utility of a Hierarchical Composite End Point for Clinical Trials of Kidney Disease Progression: A Review

Dustin J. Little,[1] Samvel B. Gasparyan,[2] Patrick Schloemer,[3] Niels Jongs,[4] Meike Brinker,[5] Martin Karpefors,[2] Christoph Tasto,[5] Nicole Rethemeier,[5] Lars Frison,[2] Richard Nkulikiyinka,[3] Jerome Rossert,[1] and Hiddo L Heerspink[4,6]

AstraZeneca

BAYER

References 1/4

Heerspink HL, Jongs N, Schloemer P, Little DJ, Brinker M, Tasto C, Karpefors M, Wheeler DC, Bakris G, Perkovic V, Nkulikiyinka R, Rossert J, Gasparyan SB. Development and Validation of a New Hierarchical Composite End Point for Clinical Trials of Kidney Disease Progression. J Am Soc Nephrol. 2023 Oct 24.

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Questions?

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