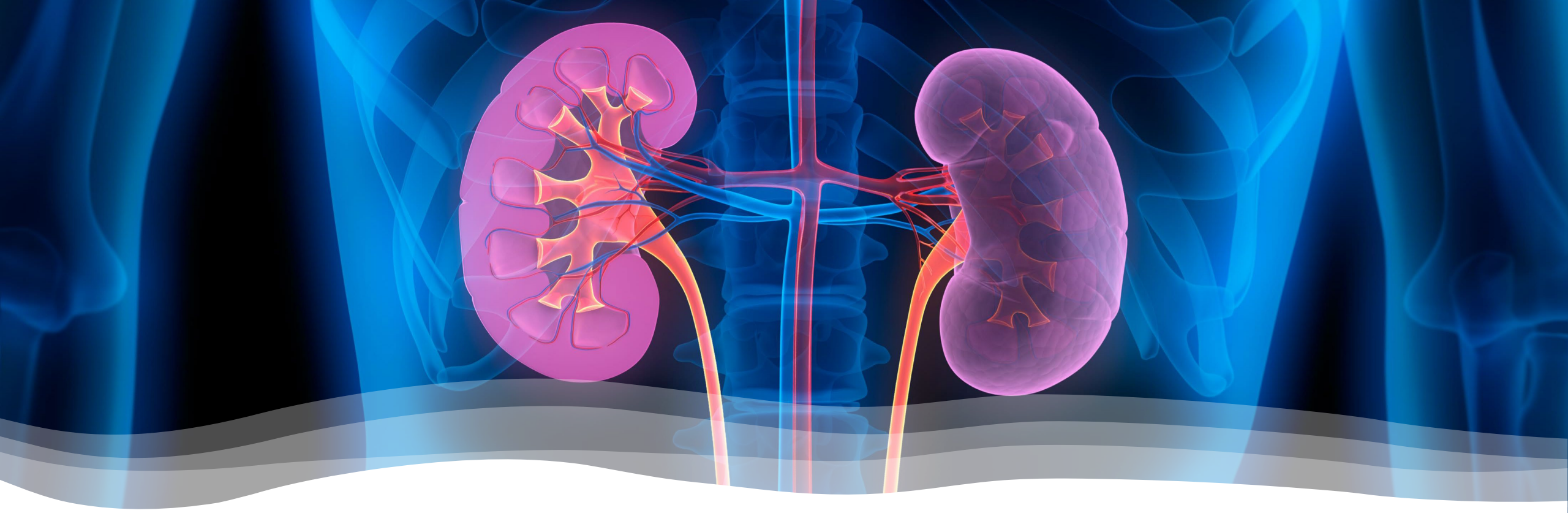

A Holistic Approach to Improve Chronic Kidney Disease Trials – Unlocking the Potential of Hierarchical Composite Endpoints

Kolloquium „Statistische Methoden in der empirischen Forschung“

Patrick Schlömer, Bayer AG // 14. November 2023

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]

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]

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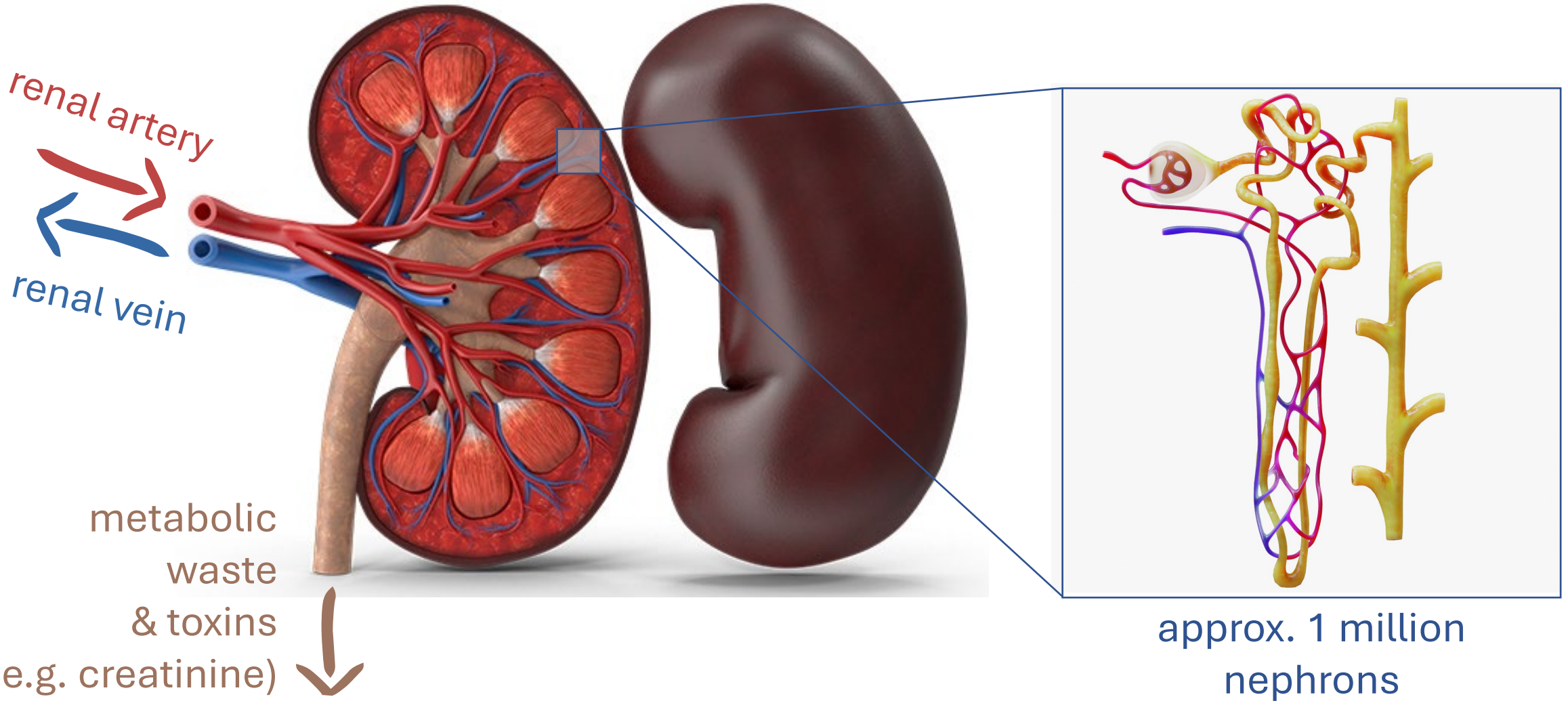
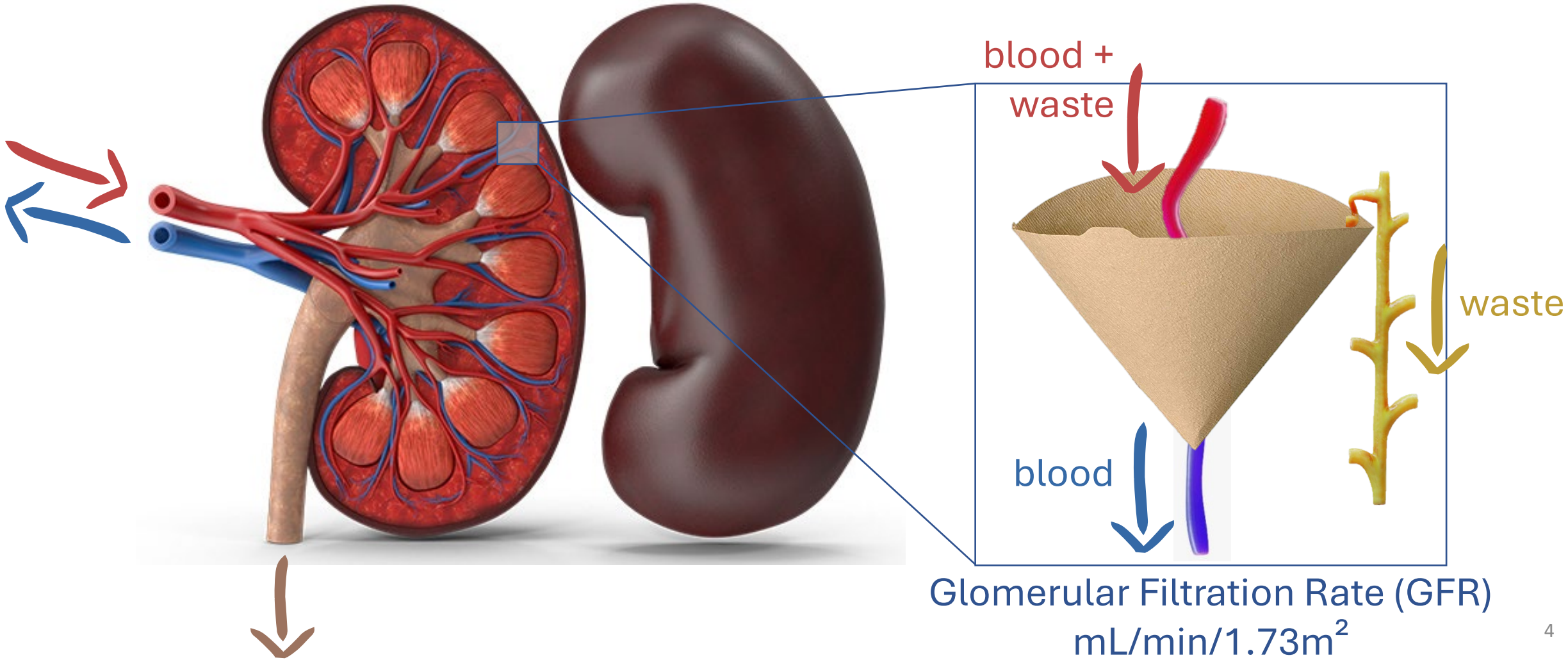
BAYER

Chronic Kidney Disease (CKD) Trials

Chronic Kidney Disease (CKD)

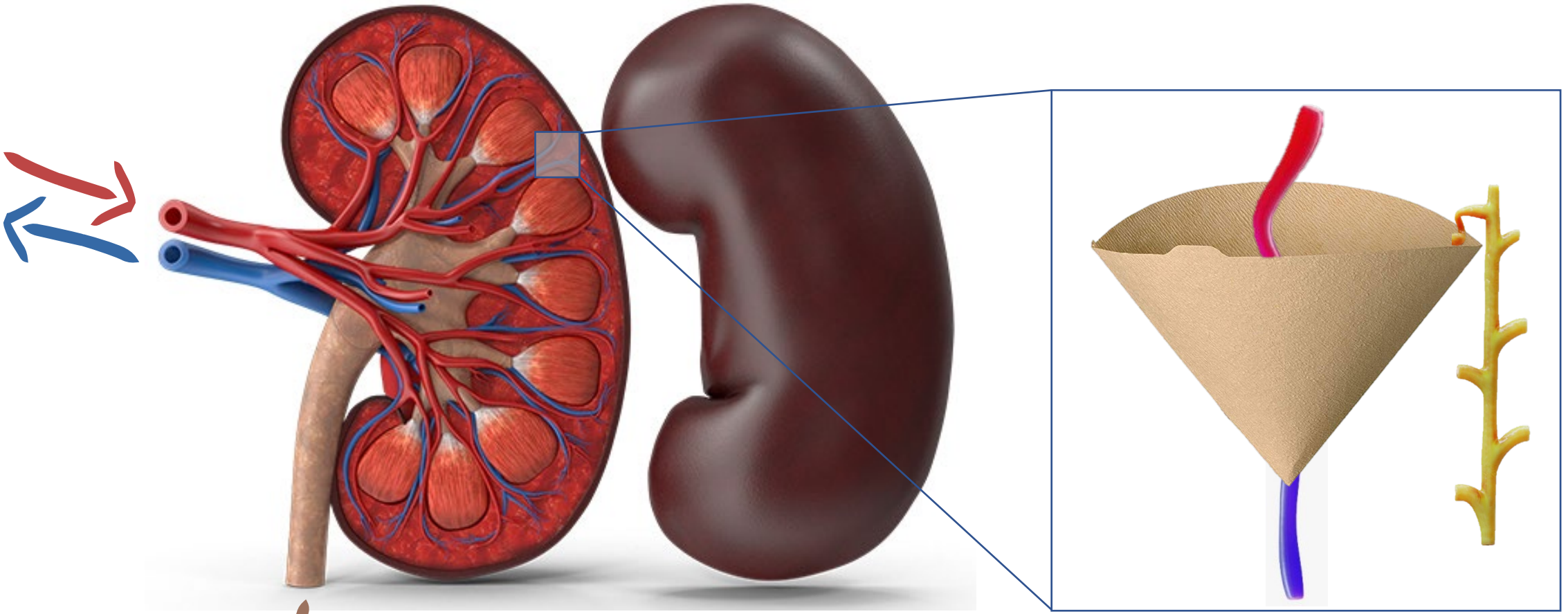


Chronic Kidney Disease (CKD)



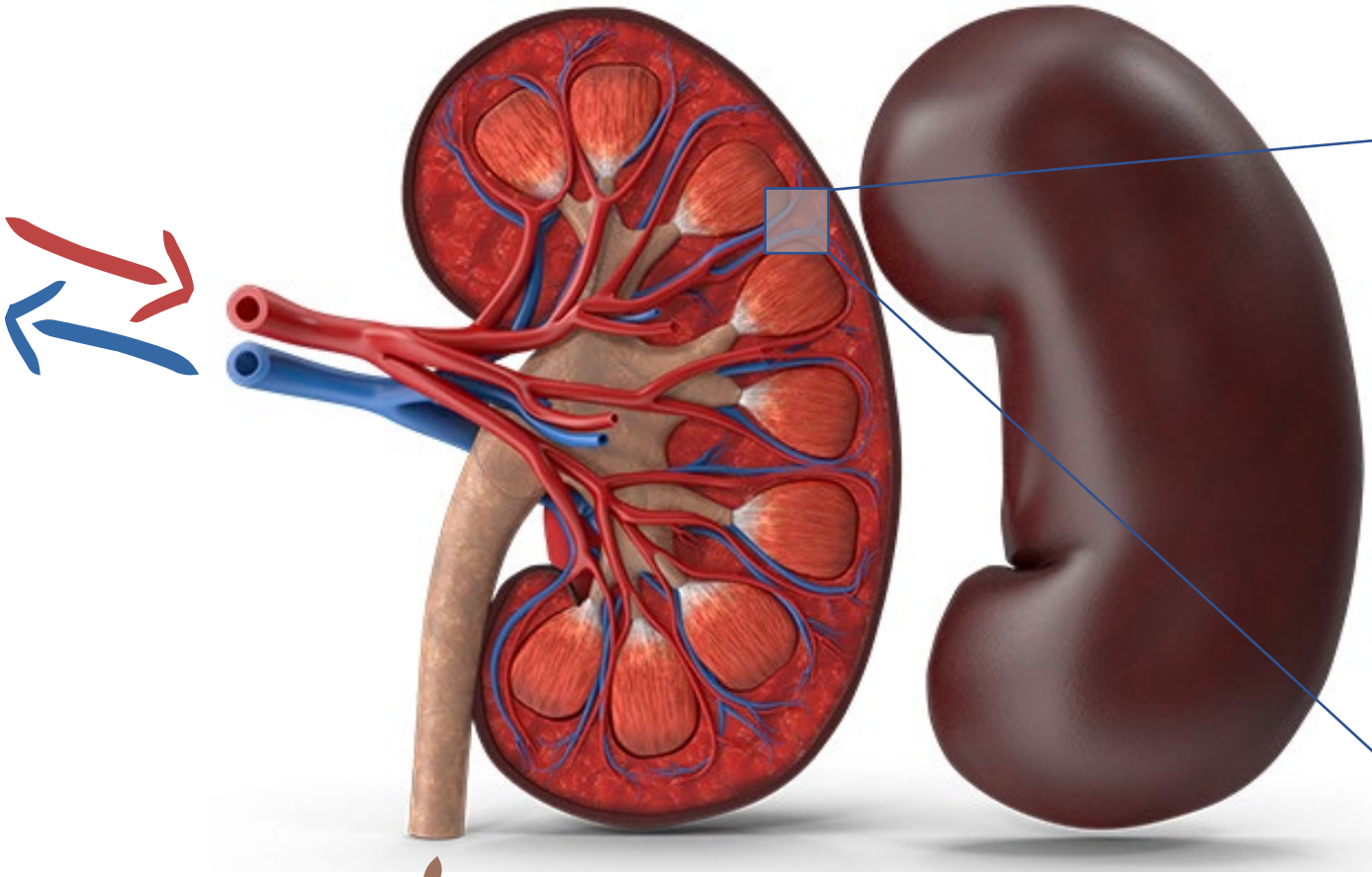
Glomerular Filtration Rate (GFR)
mL/min/1.73m^2

Chronic Kidney Disease (CKD)

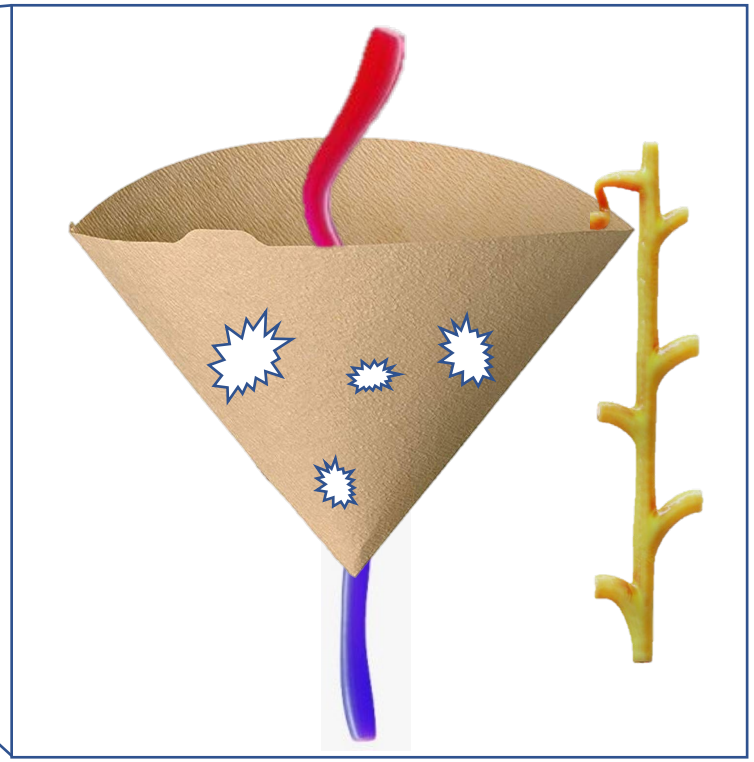


estimated Glomerular Filtration Rate (eGFR)
mL/min/1.73m^2

Chronic Kidney Disease (CKD)



Kidney damage



- GFR ↓
- Urine Albumin ↑
- Urine Albumin-Creatinine Ratio (UACR) ↑[6]

KDIGO Heatmap

GFR categories (ml/min per 1.73 m²) Description and range				Persistent albuminuria categories (UACR) Description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30-300 mg/g 3-30 mg/mmol	>300 mg/g >30 mg/mmol
	G1	Normal or high	≥90	(1 if CKD)	Monitor (1)	Refer* (2)
	G2	Mildly decreased	60-89	(1 if CKD)	Monitor (1)	Refer* (2)
	G3a	Mildly to moderately decreased	45-59	Monitor (1)	Monitor (2)	Refer (3)
	G3b	Moderately to severely decreased	30-44	Monitor (2)	Monitor (3)	Refer (3)
	G4	Severely decreased	15-29	Refer* (3)	Refer* (3)	Refer (4+)
	G5	Kidney failure	<15	Refer (4+)	Refer (4+)	Refer (4+)

- Low Risk
- Moderately increased risk
- High risk
- Very high risk

Main Goals in CKD Management

- Prolong time to **dialysis/kidney transplantation**
- Reduce risk of **cardiovascular (CV) complications**

Efficacy Endpoints for CKD Trials

Time to **dialysis/kidney transplantation**

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

Investigation and validation of **surrogate endpoints**

CVD = Cardiovascular Disease

GFR Decline Endpoints

GFR Decline as Endpoint in CKD Trials

AJKD

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

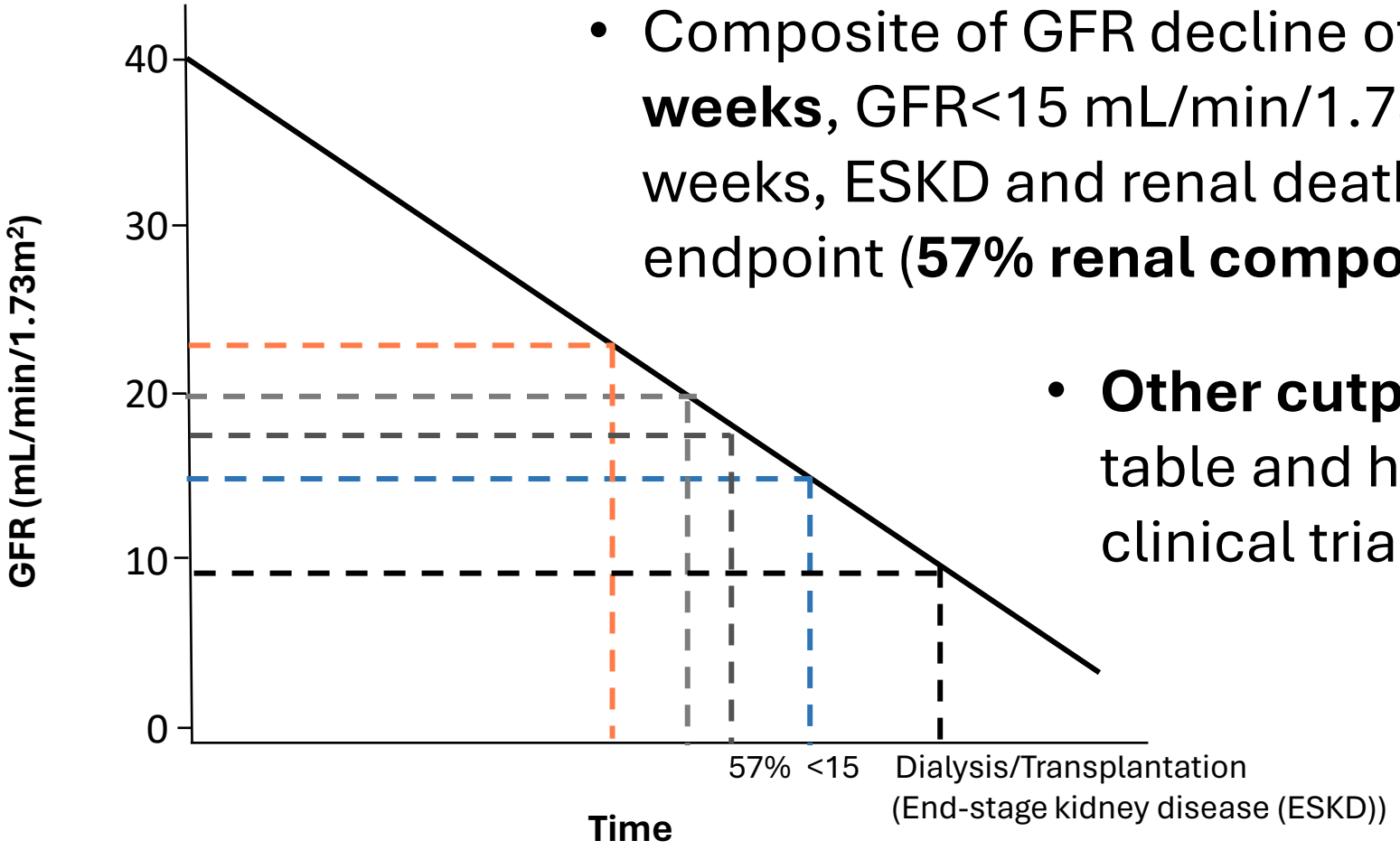
Special Report

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/1.73m^2 sustained over ≥ 4 weeks, ESKD and renal death 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**

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 Decline in Recent CKD Trials

www.kidney-international.org (2023) clinical investigation

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

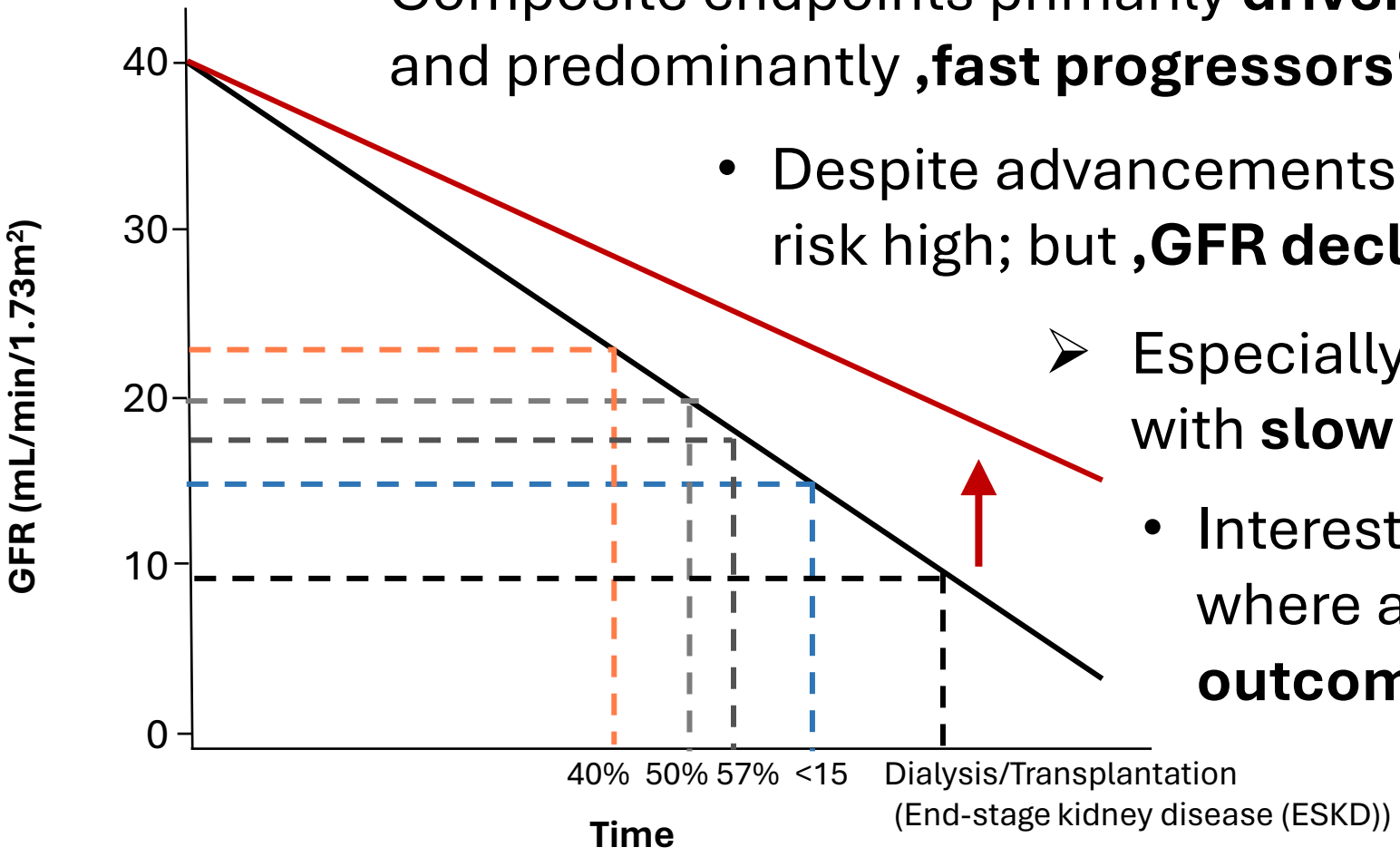
OPEN

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** accross different GFR cutpoints
- 40% vs. 57%: **sample size approx. halved**

Limitations of GFR Decline Endpoints

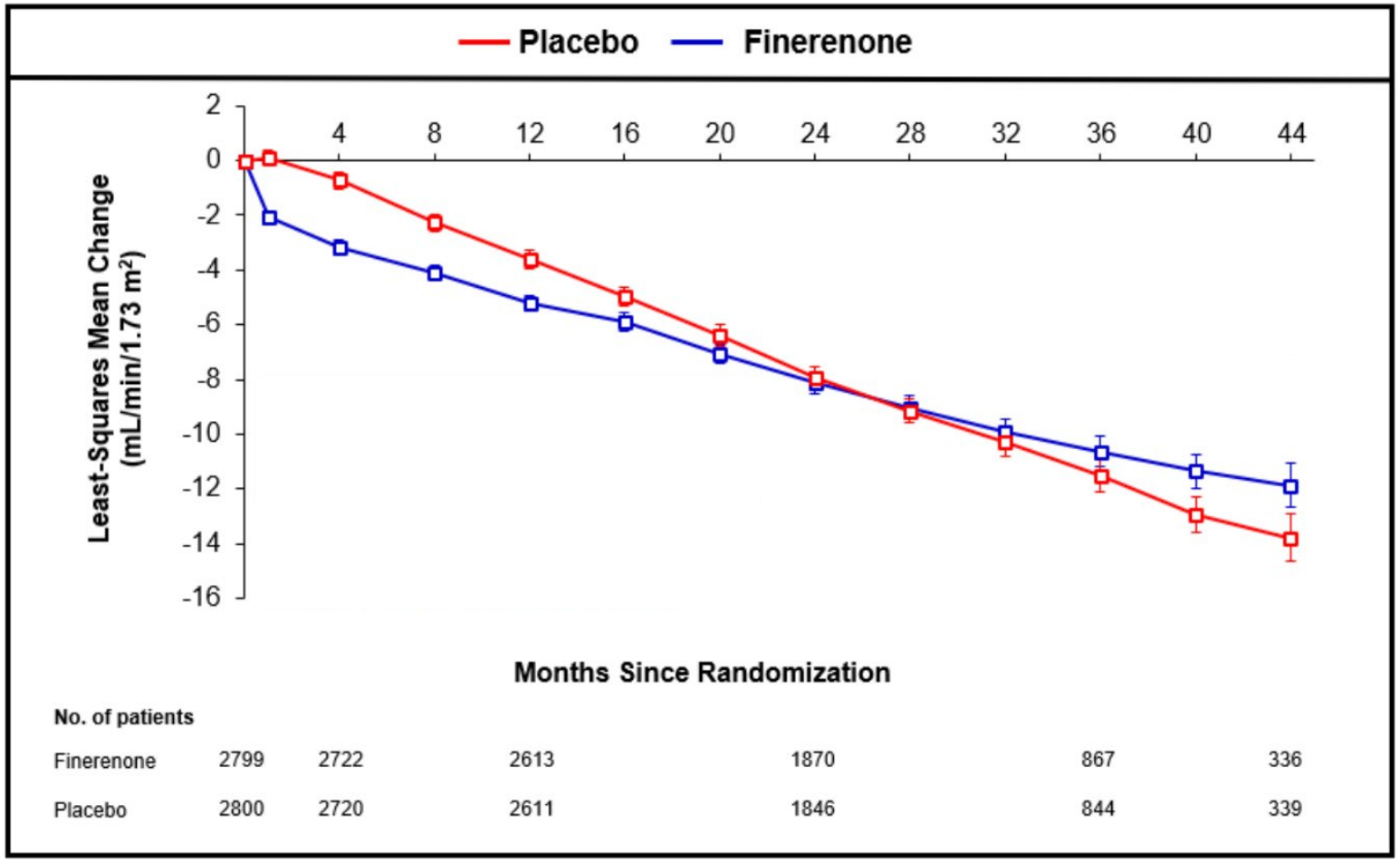
- Composite endpoints primarily **driven by less severe outcomes** and predominantly **‚fast progressors‘ experience events**
- Despite advancements in CKD treatment, residual risk high; but **‚GFR decline‘-based trials large/long**
  - ➢ Especially in **early stage CKD** patients with **slow progression**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



GFR Slope Endpoints

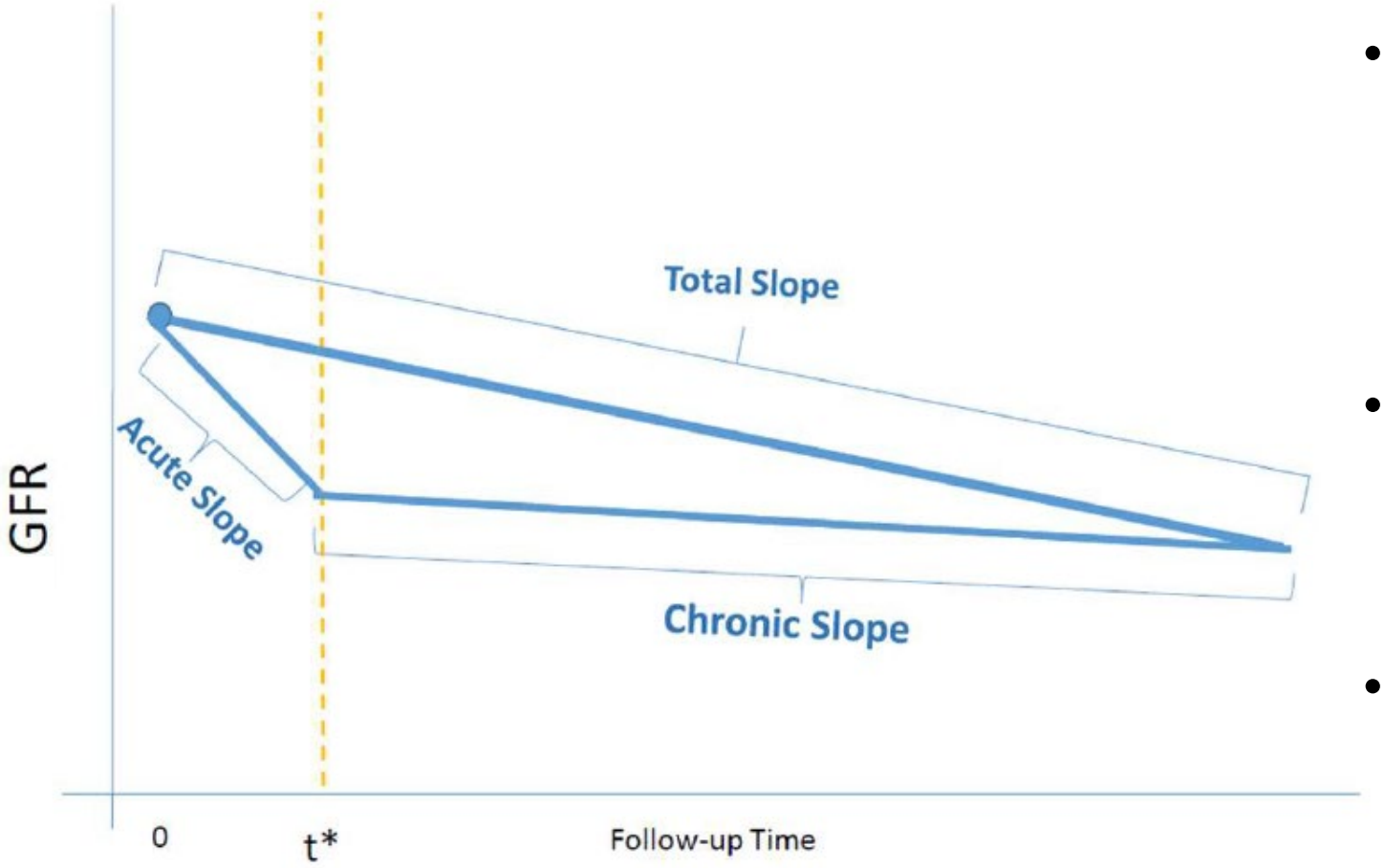
eGFR in FIDELIO-DKD

FInerenone in reducing kiDnEy faiLure and dIsease prOgression in DKD



Source: Bakris GL, Agarwal R, Anker SD, et al. Effect of finerenone on chronic kidney disease outcomes in type 2 diabetes. N Engl J Med 2020; 383:2219-2229.

GFR Slope as Endpoint in CKD Trials



- Most compounds cause short-term **acute drop in GFR** (hemodynamic nature & typically reversible after discontinuation)
- **Two-slope linear spline mixed effect model** typically used to analyse GFR (Vonesh et al. 2019)
- **Total slope more accepted** by health authorities than chronic slope

GFR Slope vs. GFR Decline Endpoints

nature medicine

Analysis

https://doi.org/10.1038/s41591-023-02418-0

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

Received: 31 October 2022

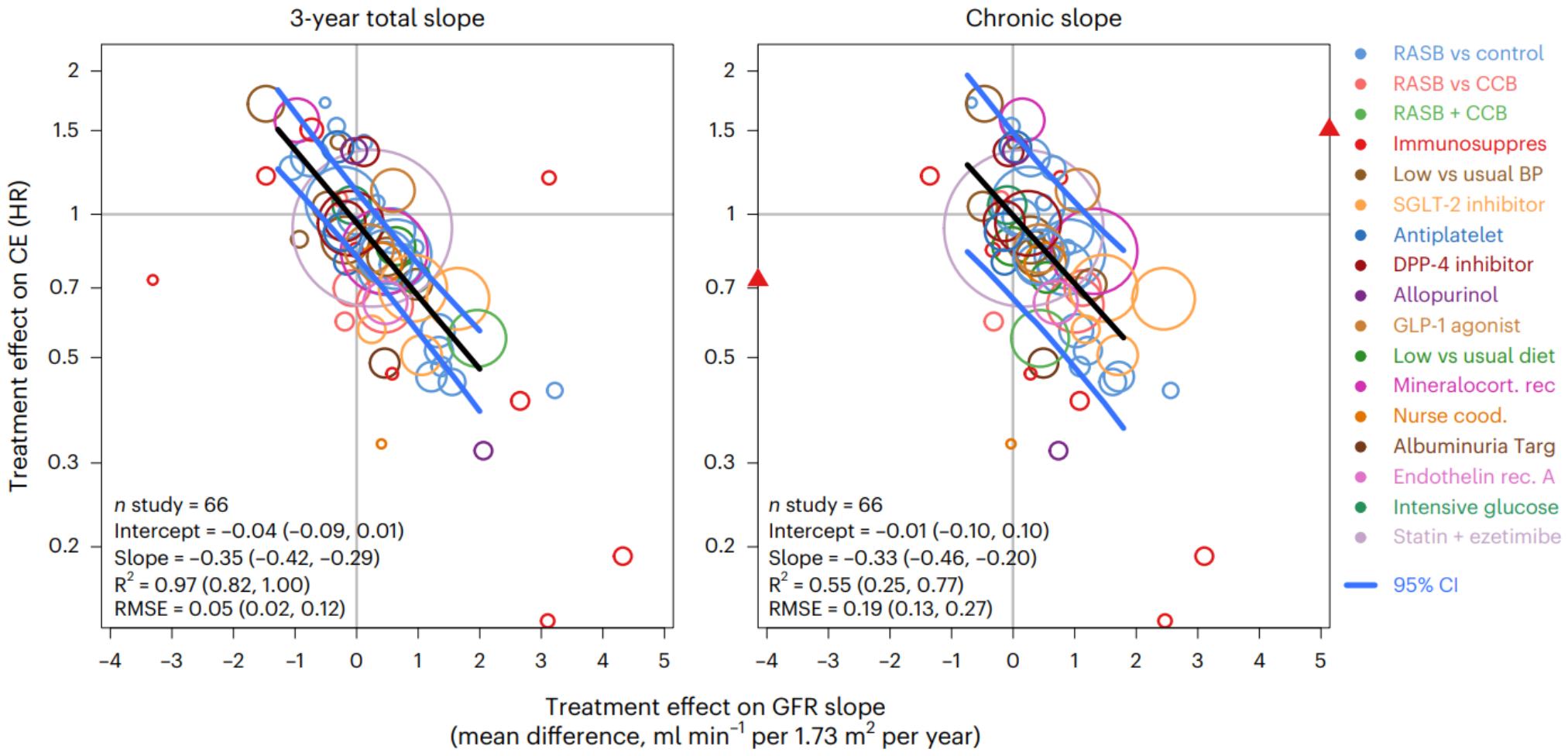
Accepted: 24 May 2023

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



EMA Qualification Opinion (QO)

- **Request for QO** submitted by **CKD-EPI** and **NKF** based on previous work on meta-analyses of GFR slope (August 2022)

CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration, NKF = National Kidney Foundation

EMA Qualification Opinion (QO)

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 over time) can in some trial settings - if properly specified and assessed - serve as a surrogate endpoint for CKD progression in clinical trials for standard marketing authorization and indication extension approvals.

optimised analysis model (e.g., to reflect physiological knowledge) may be preferable. Sponsors should use the estimand framework, justify the selected analysis model and consider how the model-based analysis in a future trial will be impacted by intercurrent events such as treatment discontinuations and missing data due to study drop-outs. Specifically, approaches to handle intercurrent events and

Intercurrent Events – Death & ESKD

- Terminal event **death → No subsequent** GFR values
- Onset of **ESKD** → Subsequent GFR values **not relevant**
- **Strategies for handling death & ESKD** (ICH E9 addendum)
  - **Treatment policy:** Not suitable (events cannot be ignored)
  - **Hypothetical:** Effect if all patients had stayed alive & w/o ESKD (IP weighting; shared parameter model (Vonesh et al. 2019))
  - **Principal stratum:** Effect in patients who would not die or experience ESKD regardless of treatment assignment (of limited clinical relevance)

Intercurrent Events – Death & ESKD

- **While alive:** Effect while alive & w/o ESKD
  (restrict analysis to GFR values prior to death & ESKD)
- **Composite:** Consider death & ESKD as part of endpoint
  - **Attributable estimand** (Darken et al. 2020)
  - **Penalty** after death & ESKD, i.e. **low GFR values**
  - **Interpretability?**

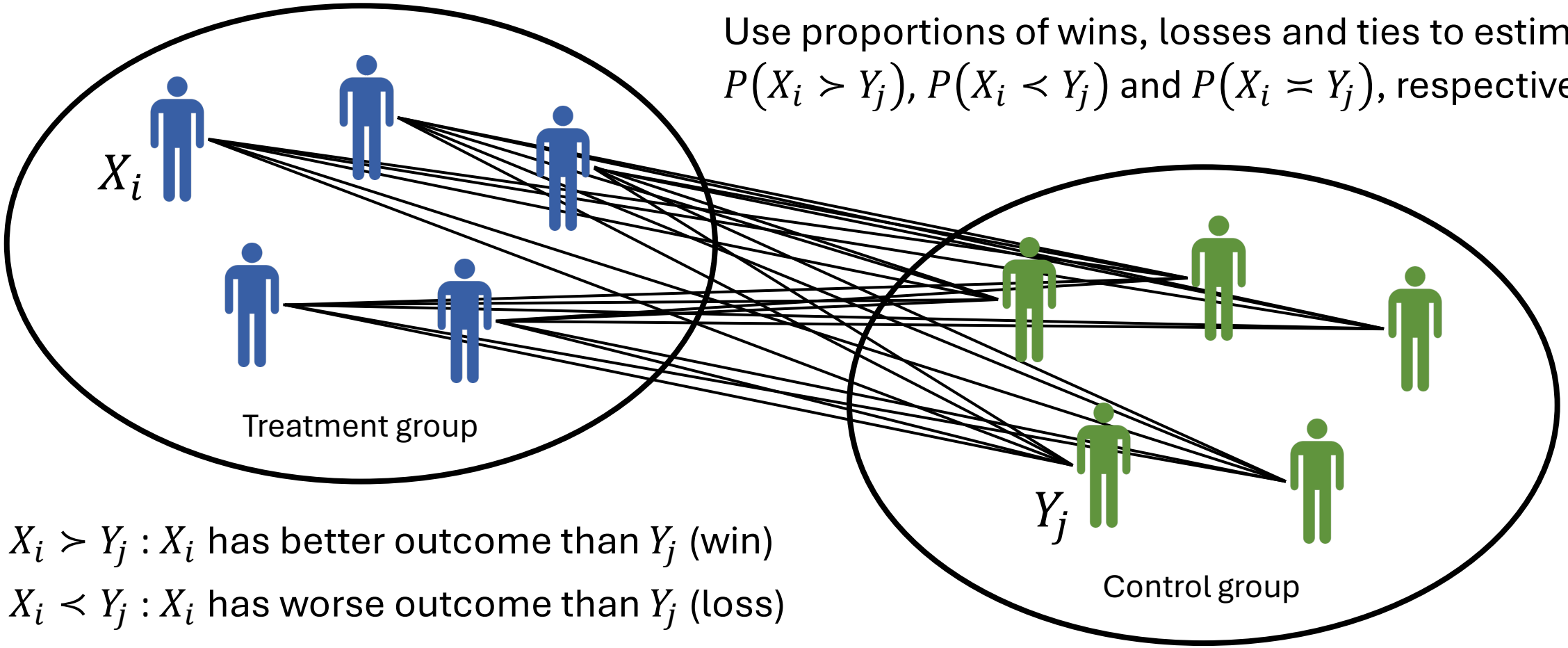
Hierarchical Composite Endpoints (HCEs)

HCEs – Background

- **Patient-wise** comparisons with **hierarchically ordered** endpoints
- Idea goes back to **Finkelstein & Schoenfeld (1999)**
- **Buyse (2010)** discussed **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)

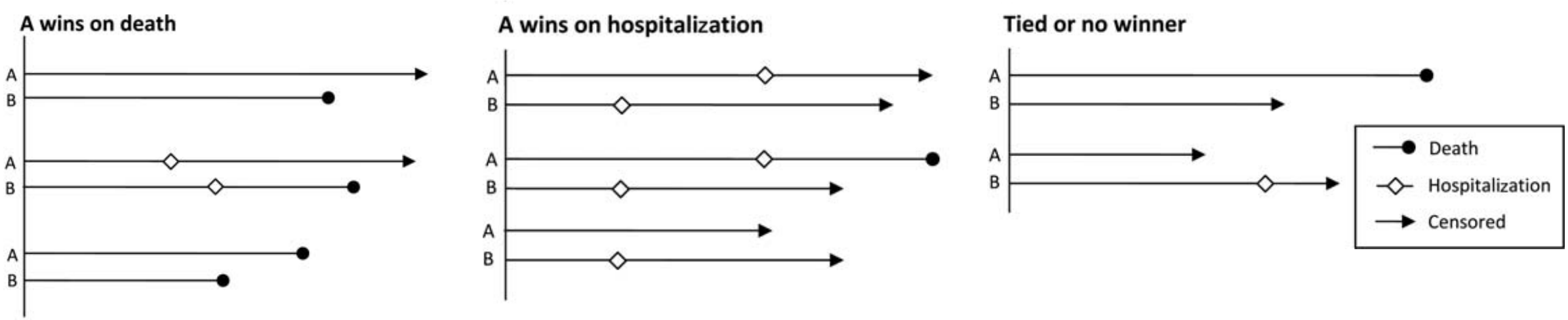
HCEs – Illustration

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



- $X_i \succ Y_j : X_i$ 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)

HCEs – Example & 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)

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

Source: Pocock et al. The win ratio: a new approach to the analysis of composite endpoints in clinical trials based on clinical priorities. EHJ 2012; 33:176-182.

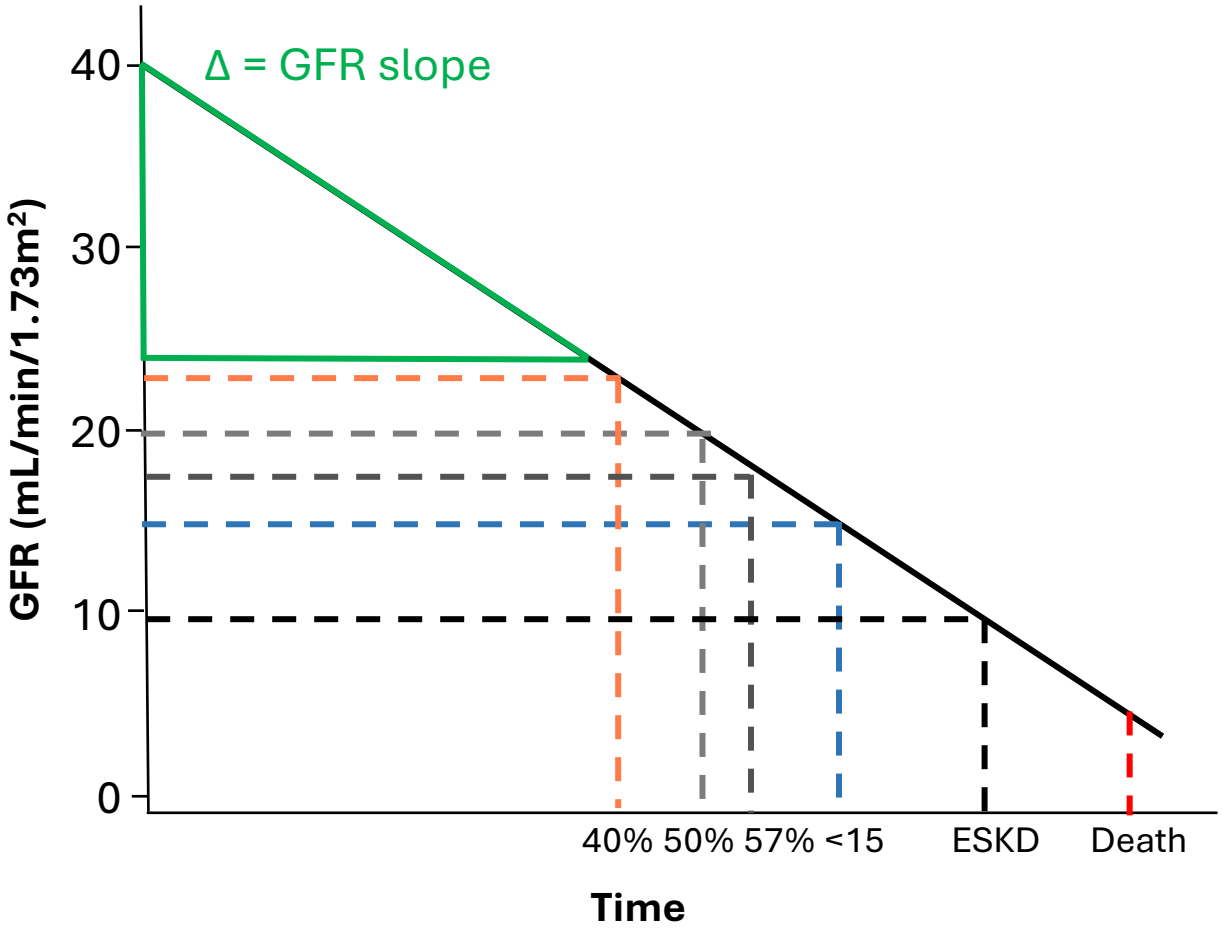
A Novel HCE for CKD Trials

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.



A Holistic Approach to Capture CKD Progression
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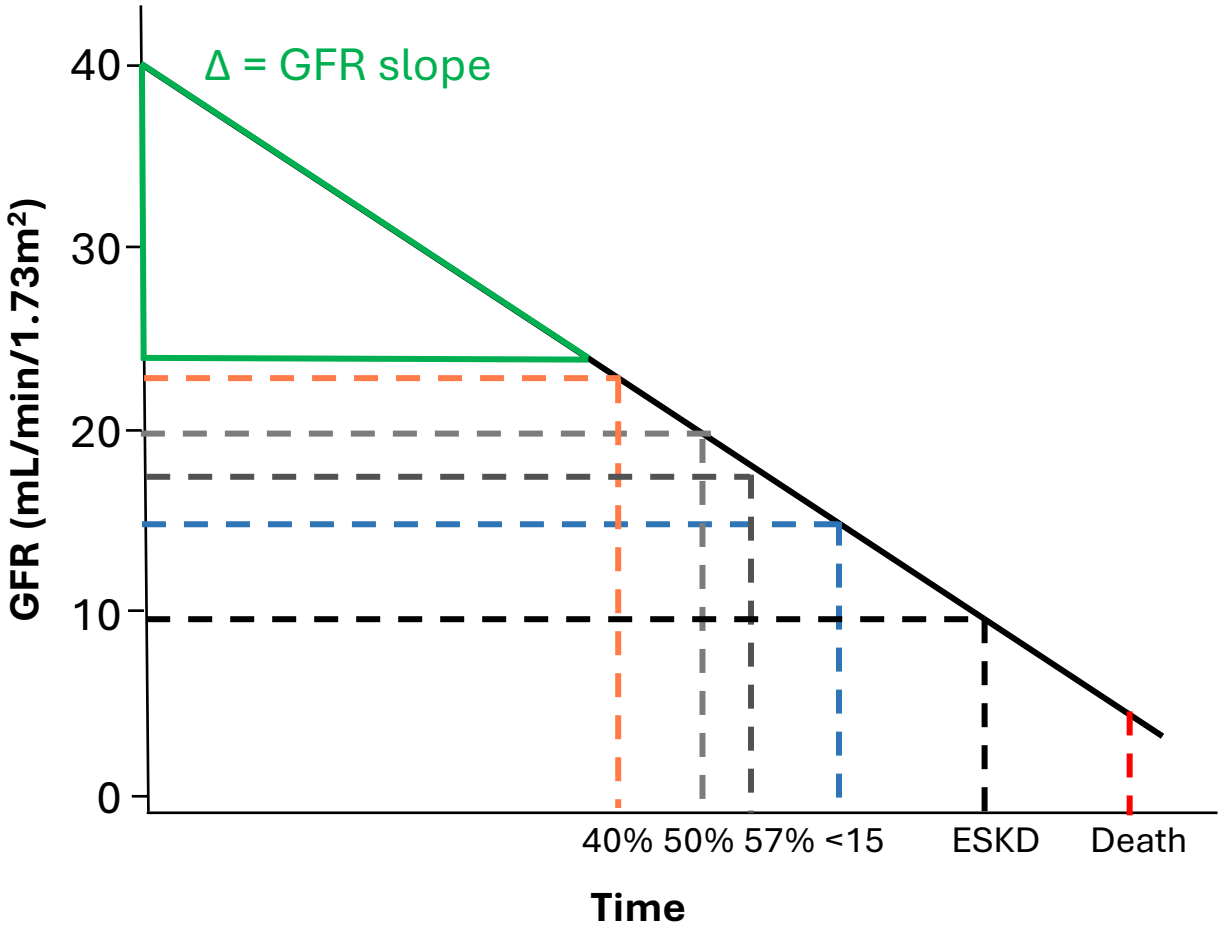
7. Total GFR slope at 3 years

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 **is not an individual causal effect, i.e. the odds that a subject would do better under treatment than under control!** (Fay et al. 2018)



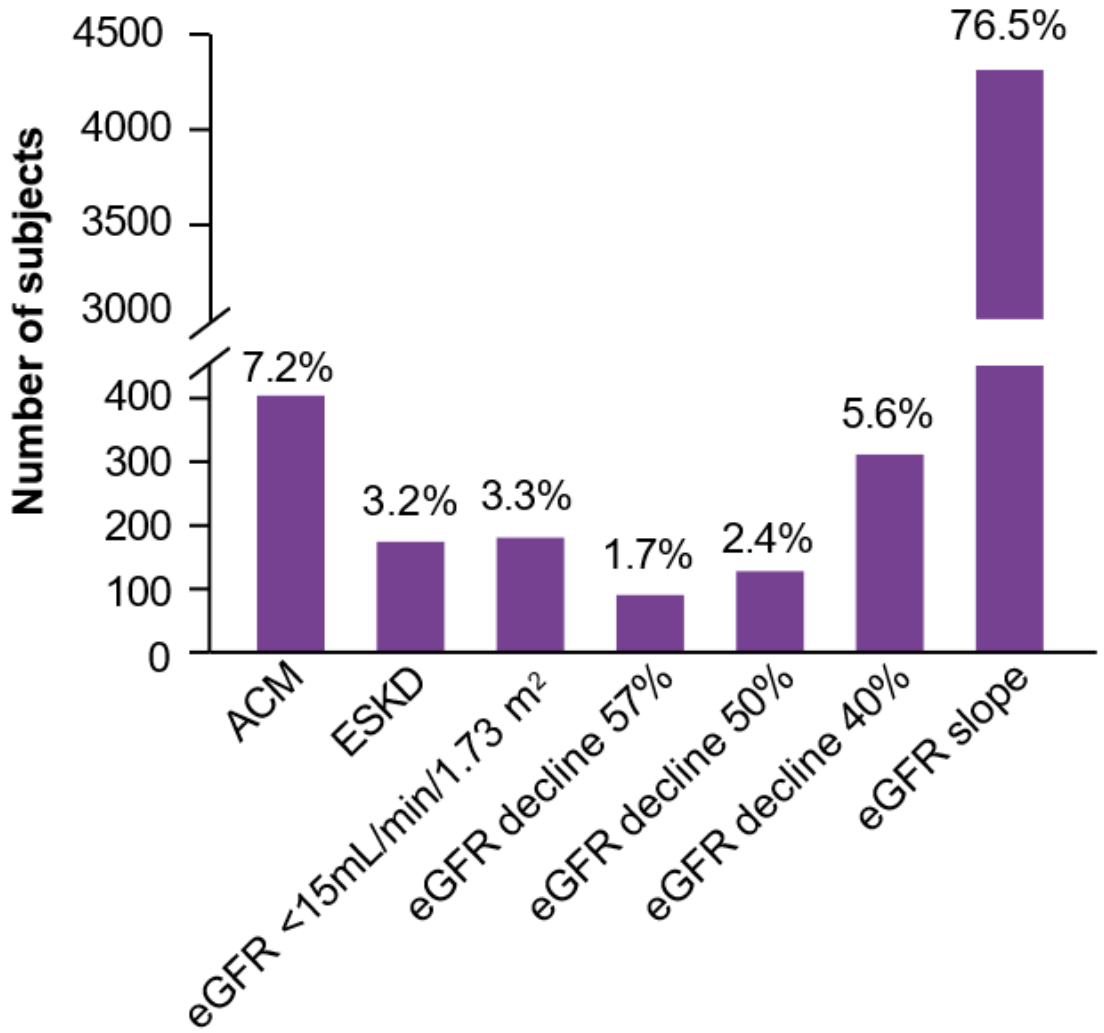
Application of the Kidney HCE in CKD Trials

- 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
- Performed **efficiency comparison** via bootstrap resampling

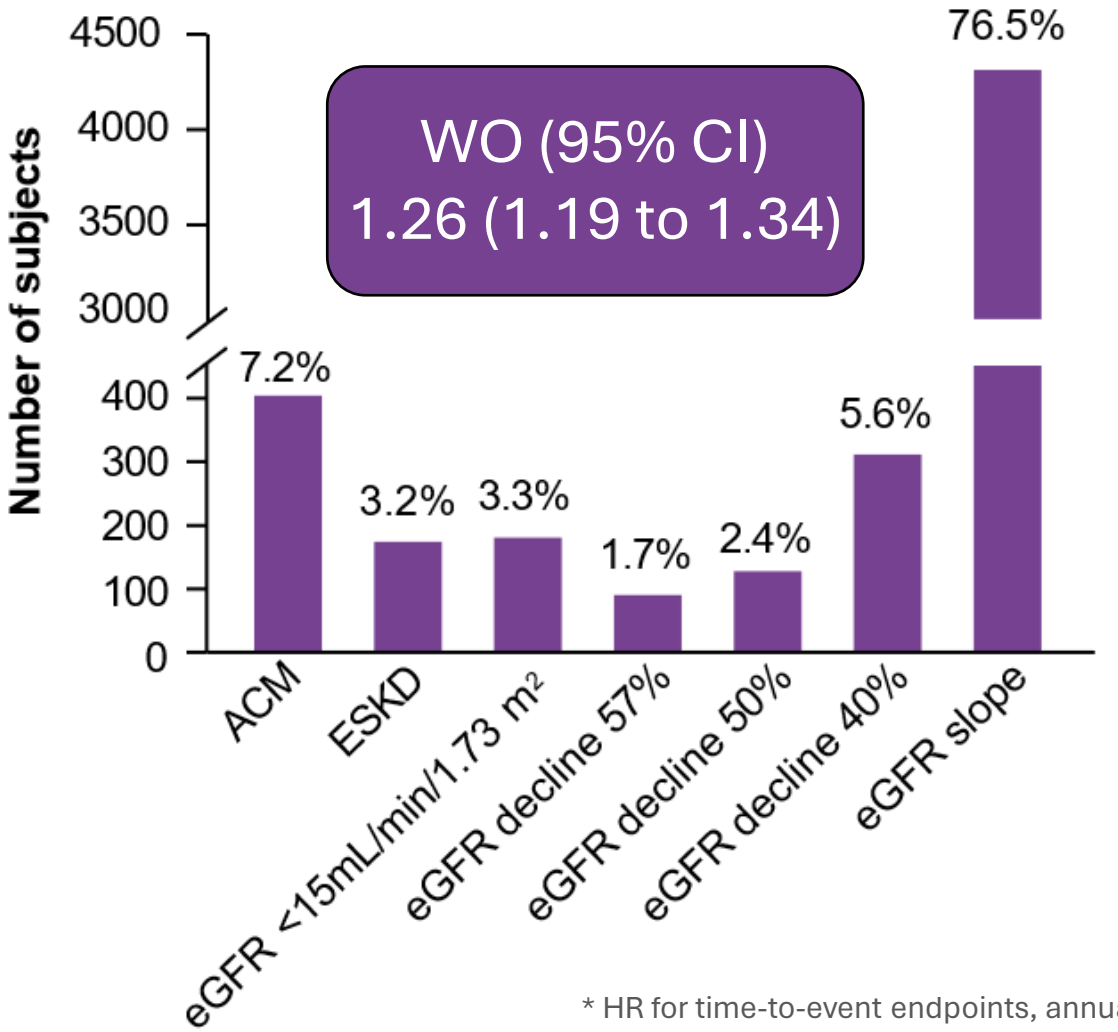
Application in FIDELIO-DKD

- **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 Results in FIDELIO-DKD



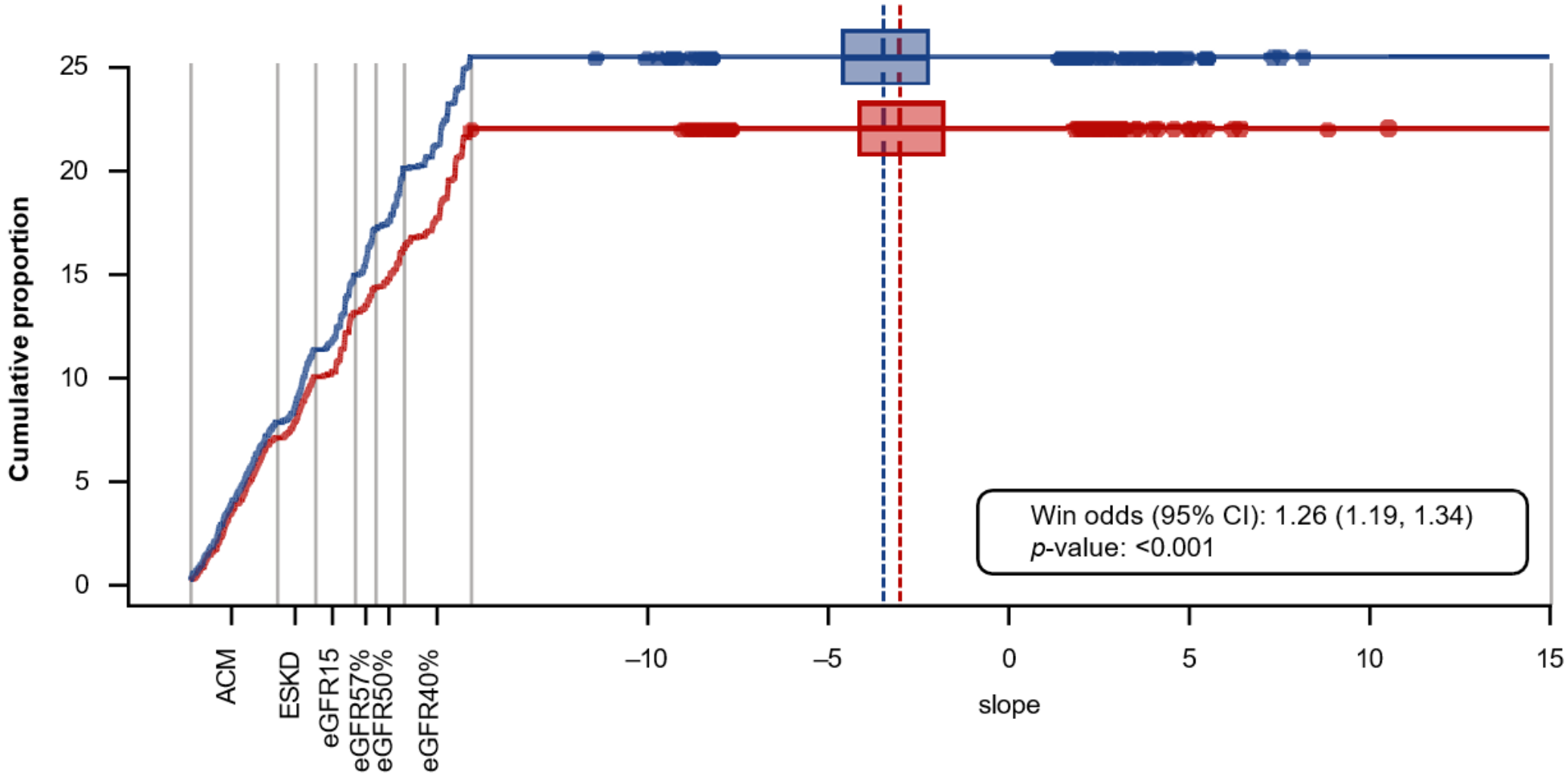
Kidney HCE Results in FIDELIO-DKD



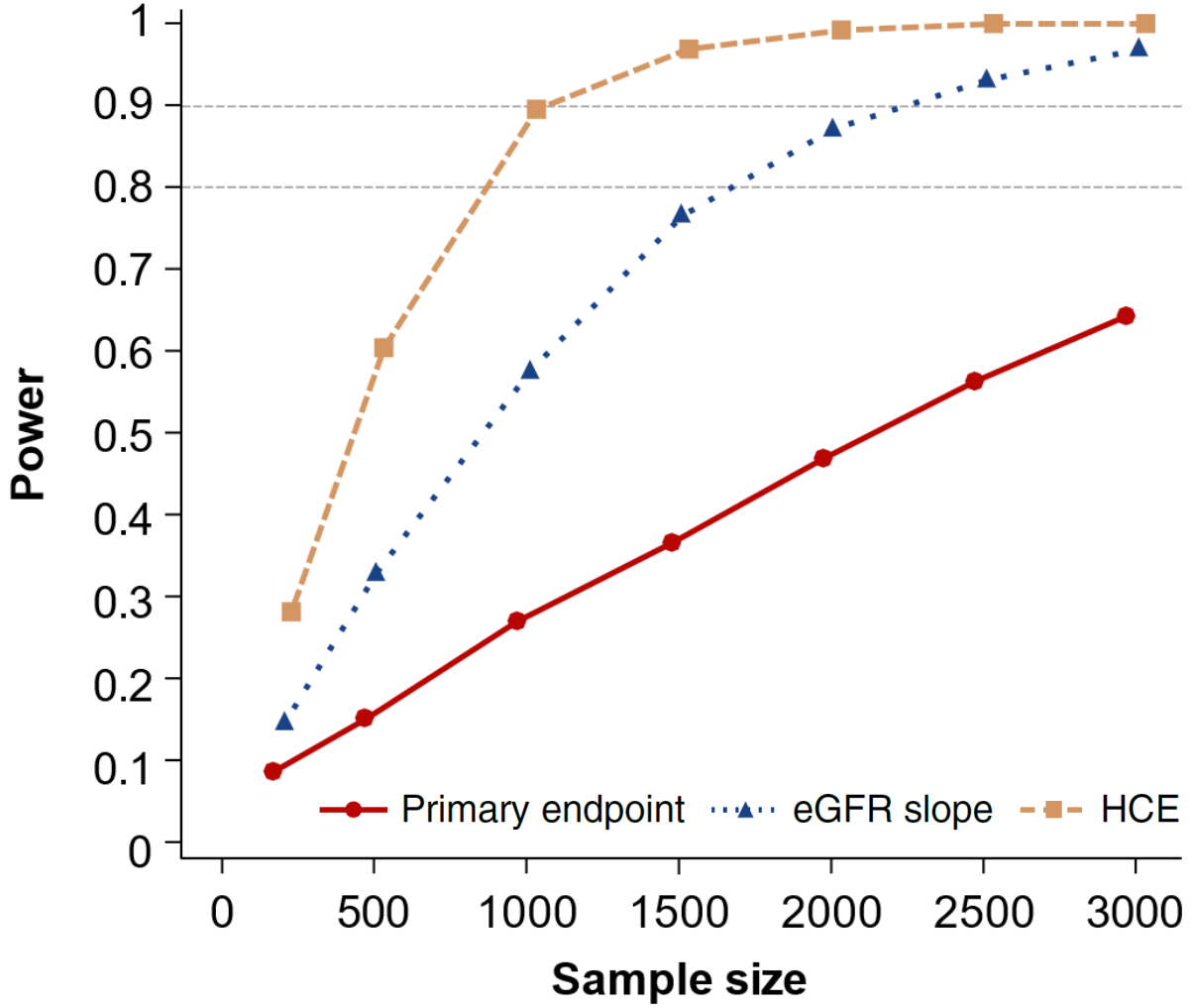
Component	Marginal Effect*
All-cause mortality	0.90 (0.75 to 1.07)
ESKD	0.86 (0.67 to 1.10)
GFR < 15	0.82 (0.67 to 1.01)
57% GFR decline	0.68 (0.55 to 0.82)
50% GFR decline	0.73 (0.62 to 0.85)
40% GFR decline	0.81 (0.72 to 0.92)
GFR slope	0.64 (0.40 to 0.89)

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

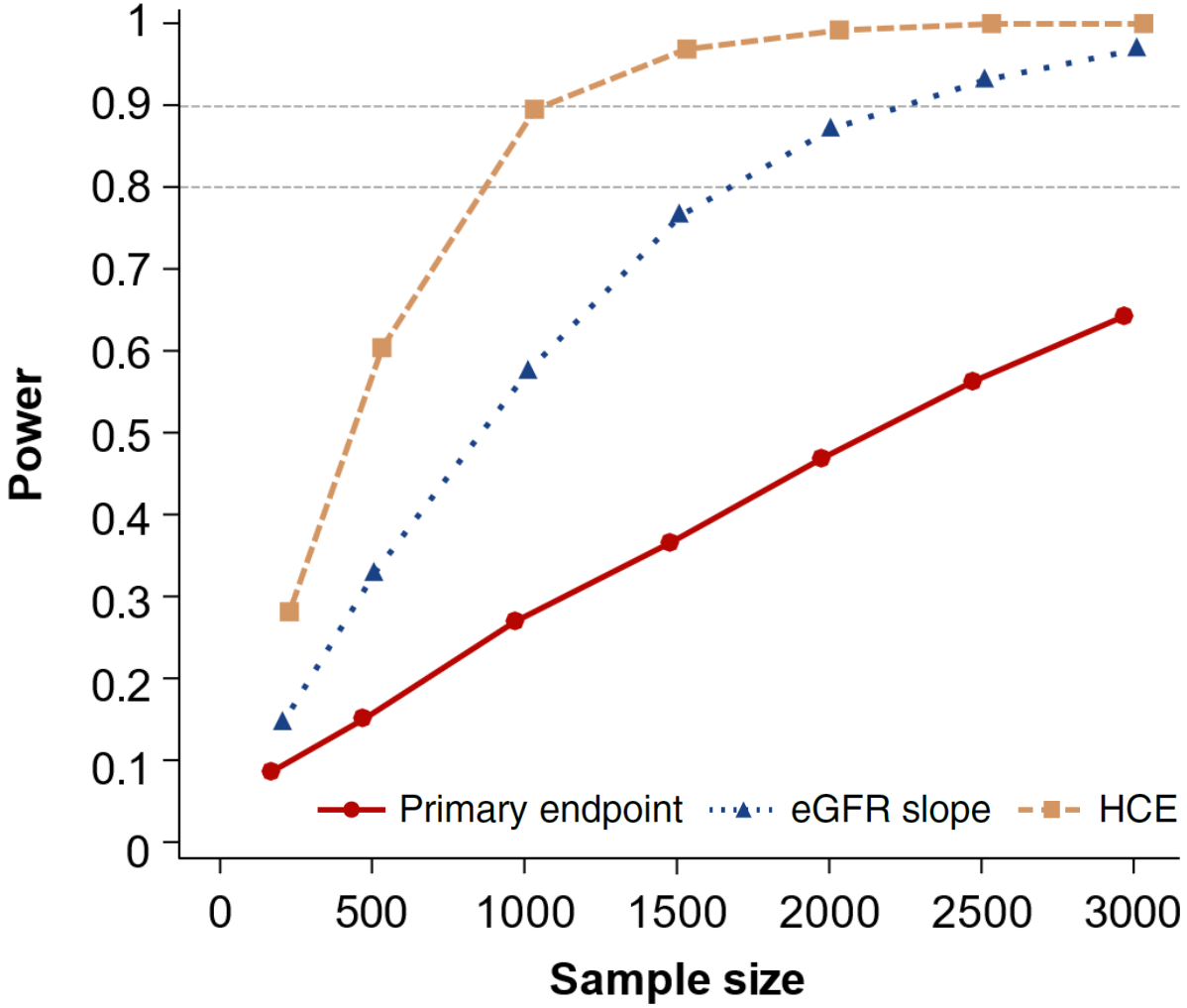
Maraca Plot for FIDELIO-DKD



Bootstrap-Based Power for FIDELIO-DKD



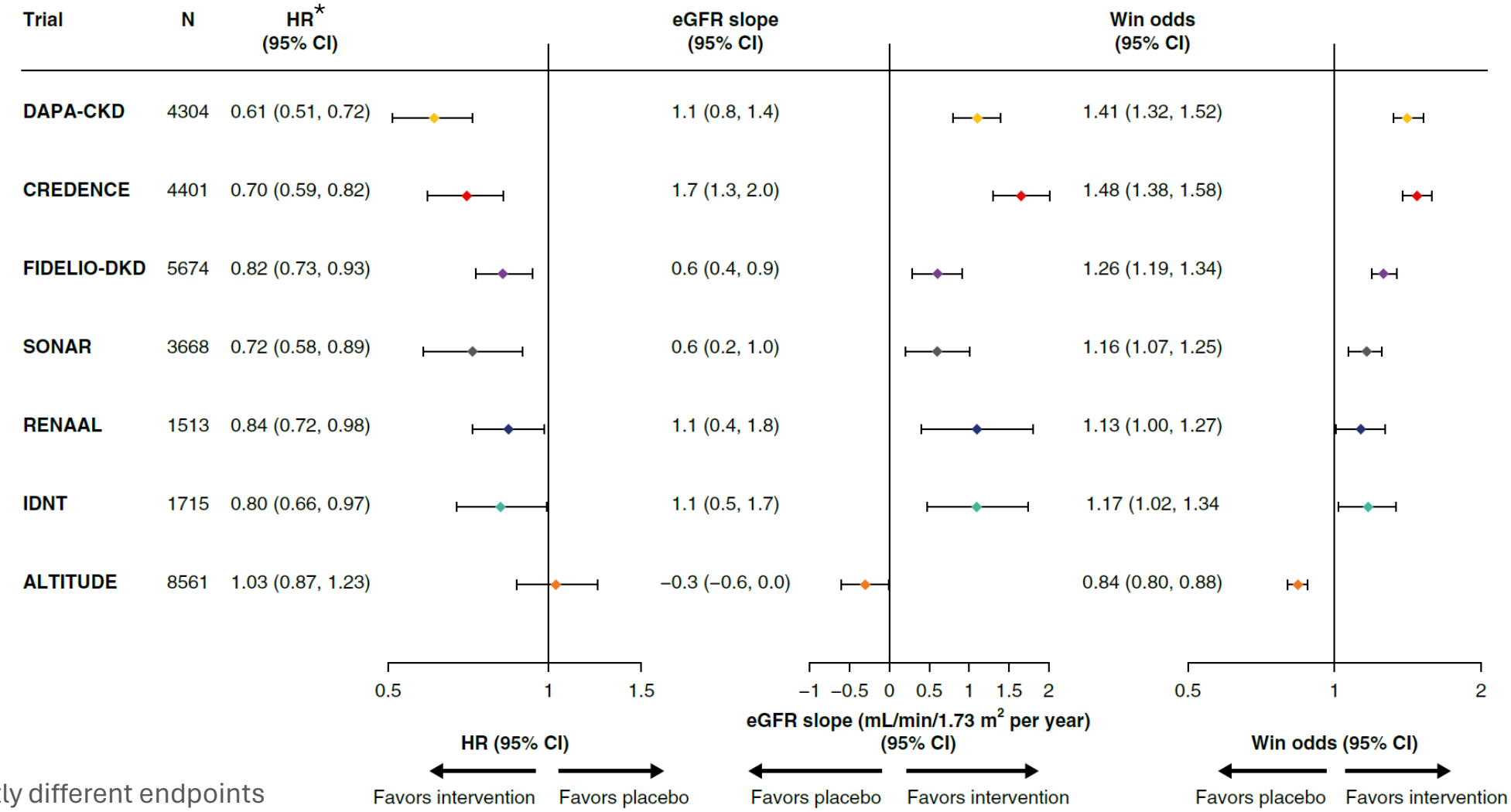
Bootstrap-Based Power for FIDELIO-DKD



Win odds	Power = 80%	Power = 90%
1.10	4616	6179
1.15	2151	2879
1.20	1267	1696
1.25	848	1135
1.30	616	824
1.35	472	632
1.40	377	505
1.45	311	416
1.50	262	351

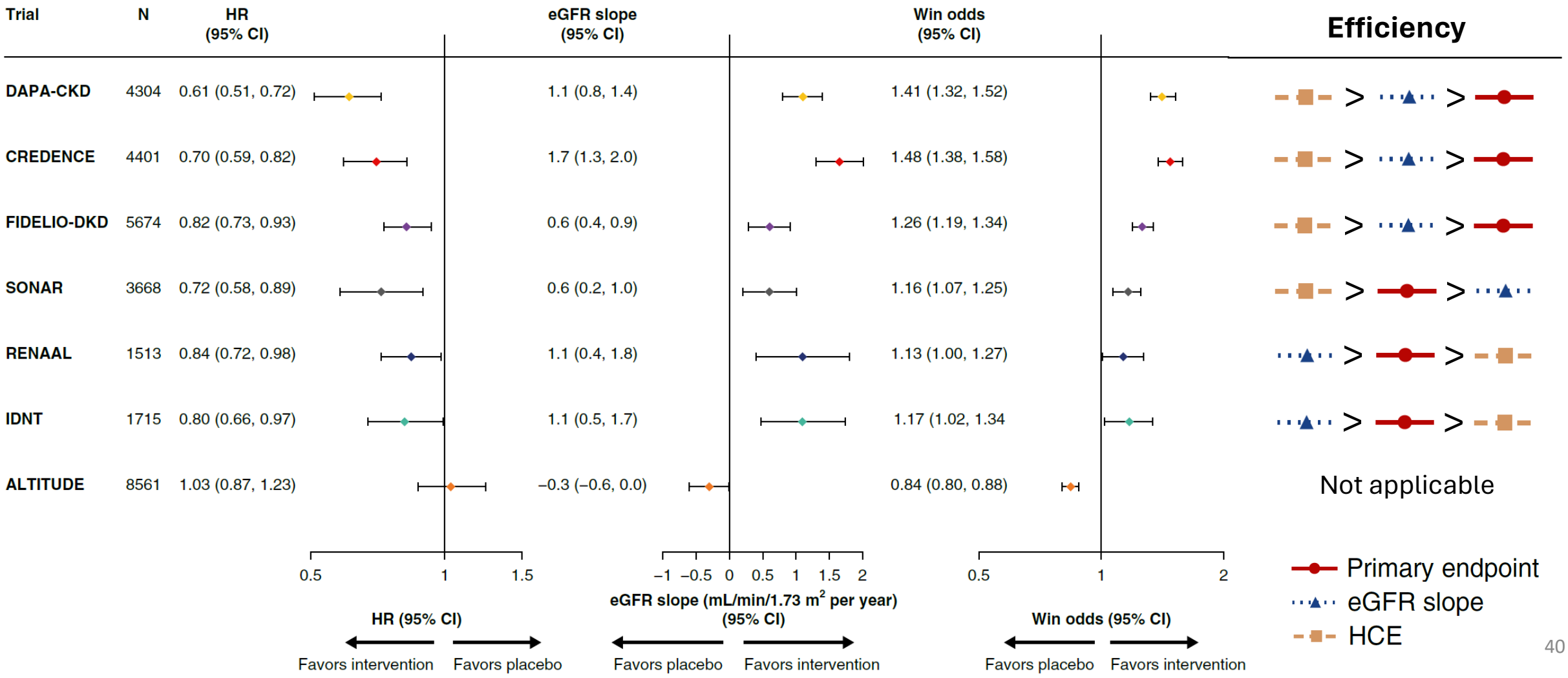
Resampling results in line with **sample size formula** derived in Gasparyan et al. (2021)

Results Across Trials



* Based on slightly different endpoints

Results Across Trials



Summary & Conclusions

- 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**)
- **R implementation** of Kidney HCE incl. **synthetic dataset** available in **Supplemental Appendix** of **Heerspink et al. (2023)**

References 1/3

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.

Little DJ, Gasparyan SB, Schloemer P, Jongs N, Brinker M, Karpefors M, Tasto C, Rethemeier N, Frison L, Nkulikiyinka R, Rossert J, Heerspink HL. Validity and Utility of a Hierarchical Composite End Point for Clinical Trials of Kidney Disease Progression: A Review. J Am Soc Nephrol. 2023 Oct 9.

Levey A. S., Inker L. A., Matsushita K., Greene T., Willis K., Lewis E., de Zeeuw D., Cheung A. K. and Coresh J.. 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. Am J Kidney Dis. 2014; 64(4): 821-35.

Heerspink H. J. L., Jongs N., Neuen B. L., Schloemer P., Vaduganathan M., Inker L. A., Fletcher R. A., Wheeler D. C., Bakris G., Greene T., Chertow G. M. and Perkovic V. Effects of newer kidney protective agents on kidney endpoints provide implications for future clinical trials. Kidney Int. 2023; 104(1): 181-188.

Vonesh E, Tighiouart H, Ying J, Heerspink HL, Lewis J, Staplin N, Inker L, Greene T. Mixed-effects models for slope-based endpoints in clinical trials of chronic kidney disease. Stat Med. 2019 Sep 30;38(22):4218-4239.

Inker LA, Collier W, Greene T, Miao S, Chaudhari J, Appel GB, Badve SV, Caravaca-Fontán F, Del Vecchio L, Floege J, Goicoechea M, Haaland B, Herrington WG, Imai E, Jafar TH, Lewis JB, Li PKT, Maes BD, Neuen BL, Perrone RD, Remuzzi G, Schena FP, Wanner C, Wetzels JFM, Woodward M, Heerspink HJL; CKD-EPI Clinical Trials Consortium. A meta-analysis of GFR slope as a surrogate endpoint for kidney failure. Nat Med. 2023 Jul;29(7):1867-1876.

Darken P., Nyberg J., Ballal S. and Wright D. The attributable estimand: A new approach to account for intercurrent events. Pharm Stat. 2020; 19(5): 626-635.

European Medicines Agency. DRAFT Qualification Opinion for GFR slope as a Surrogate Endpoint in RCT for CKD. 04 Sep 2023.

ICH E9 (R1) addendum on estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials. Step 5, 17 Feb 2020.

Finkelstein DM, Schoenfeld DA. Combining mortality and longitudinal measures in clinical trials. Stat Med. 1999 Jun 15;18(11):1341-54.

References 2/3

Buyse M. Generalized pairwise comparisons of prioritized outcomes in the two-sample problem. Stat Med. 2010 Dec 30;29(30):3245-57.

Pocock S. J., Ariti C. A., Collier T. J. and Wand D. The win ratio: a new approach to the analysis of composite endpoints in clinical trials based on clinical priorities. European Heart Journal. 2012; 33: 176-182.

Wilcoxon F. Individual Comparisons by Ranking Methods. Biometrics Bulletin. 1945; vol. 1, no. 6, pp. 80–83.

Mann, H. B., and Whitney D. R. On a Test of Whether One of Two Random Variables Is Stochastically Larger than the Other. The Annals of Mathematical Statistics. 1947; vol. 18, no. 1, pp. 50–60.

Gaohong Dong, David C. Hoaglin, Junshan Qiu, Roland A. Matsouaka, Yu-Wei Chang, Jiuzhou Wang & Marc Vandemeulebroecke. The Win Ratio: On Interpretation and Handling of Ties, Statistics in Biopharmaceutical Research. 2020; 12:1, 99-106

Brunner E, Vandemeulebroecke M, Mütze T. Win odds: An adaptation of the win ratio to include ties. Stat Med. 2021 Jun 30;40(14):3367-3384.

Fay MP, Brittain EH, Shih JH, Follmann DA, Gabriel EE. Causal estimands and confidence intervals associated with Wilcoxon-Mann-Whitney tests in randomized experiments. Stat Med. 2018 Sep 10;37(20):2923-2937.

Heerspink HJL, Stefánsson BV, Correa-Rotter R, Chertow GM, Greene T, Hou FF, Mann JFE, McMurray JJV, Lindberg M, Rossing P, Sjöström CD, Toto RD, Langkilde AM, Wheeler DC; DAPA-CKD Trial Committees and Investigators. Dapagliflozin in Patients with Chronic Kidney Disease. N Engl J Med. 2020 Oct 8;383(15):1436-1446.

Perkovic V, Jardine MJ, Neal B, Bompoint S, Heerspink HJL, Charytan DM, Edwards R, Agarwal R, Bakris G, Bull S, Cannon CP, Capuano G, Chu PL, de Zeeuw D, Greene T, Levin A, Pollock C, Wheeler DC, Yavin Y, Zhang H, Zinman B, Meininger G, Brenner BM, Mahaffey KW; CREDENCE Trial Investigators. Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy. N Engl J Med. 2019 Jun 13;380(24):2295-2306.

References 3/3

Bakris GL, Agarwal R, Anker SD, Pitt B, Ruilope LM, Rossing P, Kolkhof P, Nowack C, Schloemer P, Joseph A, Filippatos G; FIDELIO-DKD Investigators. Effect of Finerenone on Chronic Kidney Disease Outcomes in Type 2 Diabetes. N Engl J Med. 2020 Dec 3;383(23):2219-2229.

Heerspink HJL, Parving HH, Andress DL, Bakris G, Correa-Rotter R, Hou FF, Kitzman DW, Kohan D, Makino H, McMurray JJV, Melnick JZ, Miller MG, Pergola PE, Perkovic V, Tobe S, Yi T, Wigderson M, de Zeeuw D; SONAR Committees and Investigators. Atrasentan and renal events in patients with type 2 diabetes and chronic kidney disease (SONAR): a double-blind, randomised, placebo-controlled trial. Lancet. 2019 May 11;393(10184):1937-1947.

Brenner BM, Cooper ME, de Zeeuw D, Keane WF, Mitch WE, Parving HH, Remuzzi G, Snapinn SM, Zhang Z, Shahinfar S; RENAAL Study Investigators. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. N Engl J Med. 2001 Sep 20;345(12):861-9.

Lewis EJ, Hunsicker LG, Clarke WR, Berl T, Pohl MA, Lewis JB, Ritz E, Atkins RC, Rohde R, Raz I; Collaborative Study Group. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. N Engl J Med. 2001 Sep 20;345(12):851-60.

Parving HH, Brenner BM, McMurray JJ, de Zeeuw D, Haffner SM, Solomon SD, Chaturvedi N, Persson F, Desai AS, Nicolaides M, Richard A, Xiang Z, Brunel P, Pfeffer MA; ALTITUDE Investigators. Cardiorenal end points in a trial of aliskiren for type 2 diabetes. N Engl J Med. 2012 Dec 6;367(23):2204-13.

Karpefors M, Lindholm D, Gasparyan SB. The maraca plot: A novel visualization of hierarchical composite endpoints. Clin Trials. 2023 Feb;20(1):84-88.

Gasparyan SB, Kowalewski EK, Folkvaljon F, Bengtsson O, Buenconsejo J, Adler J, Koch GG. Power and sample size calculation for the win odds test: application to an ordinal endpoint in COVID-19 trials. J Biopharm Stat. 2021 Nov 2;31(6):765-787.

Questions?

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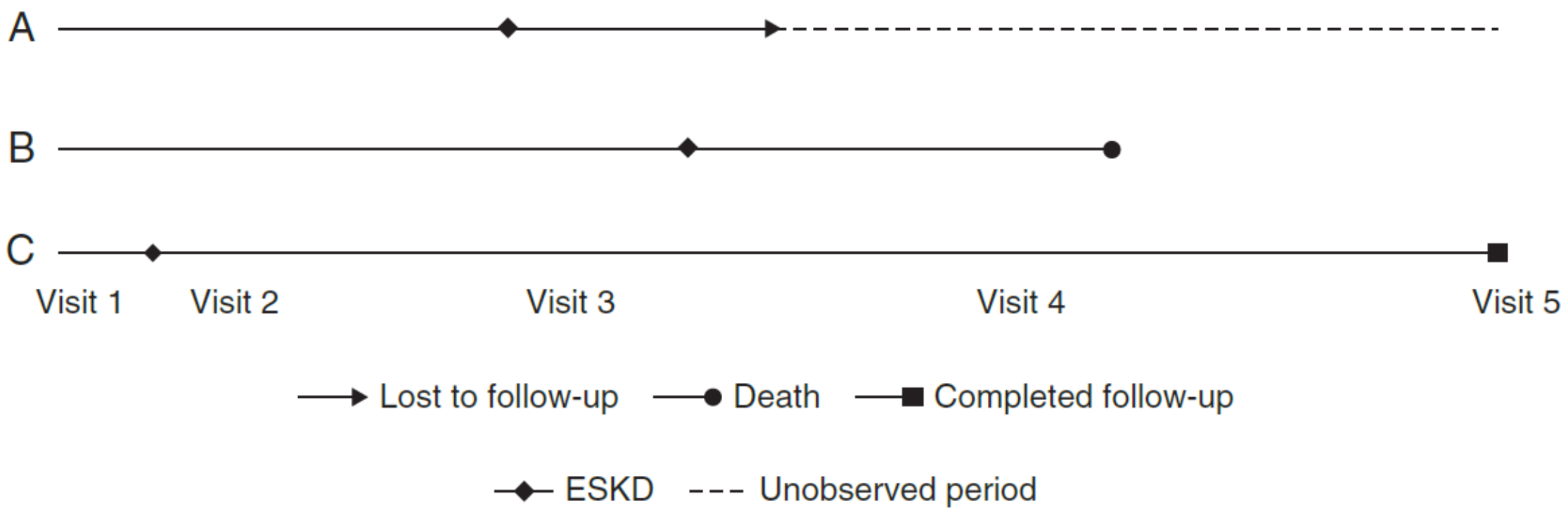
Back-up

HCEs – Lack of Transitivity



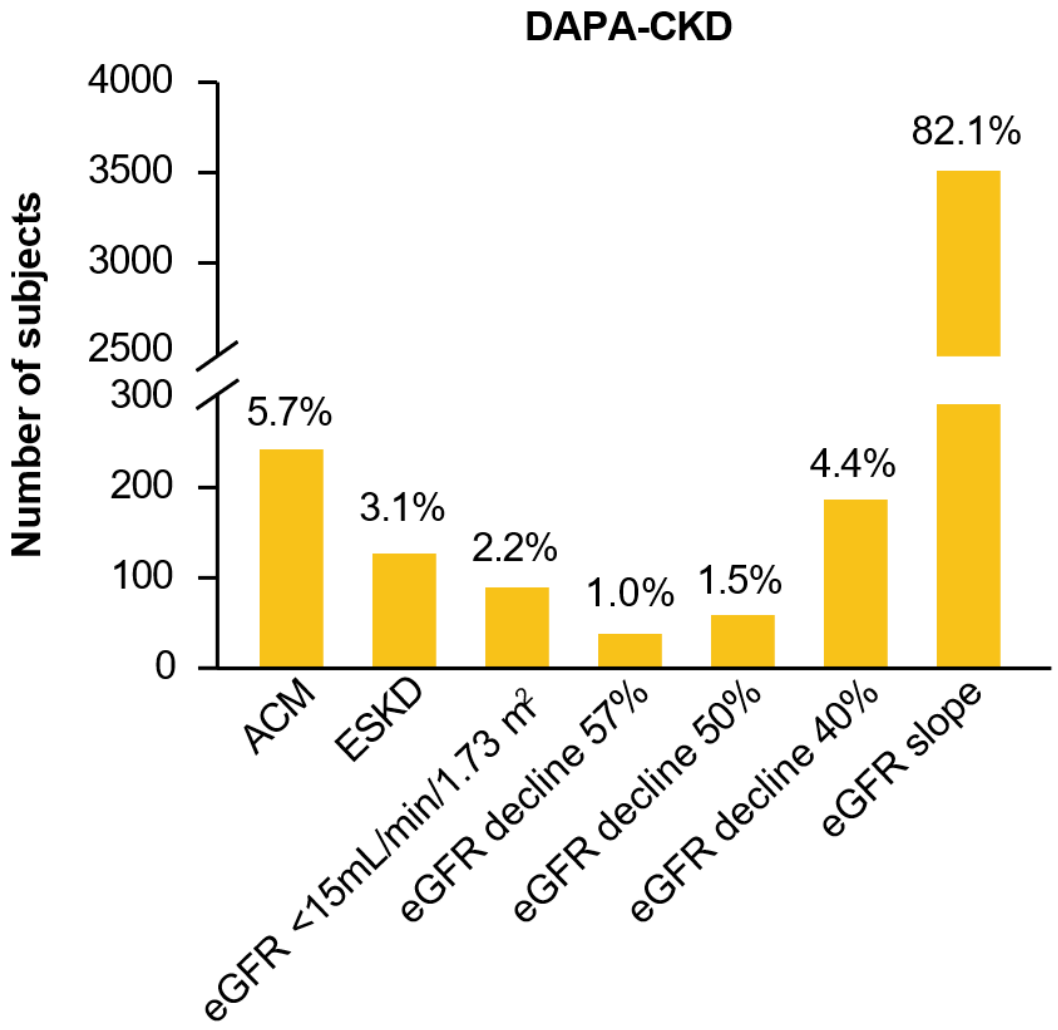
$A \prec B$ and $B \prec C$, **but** $C \prec A$!

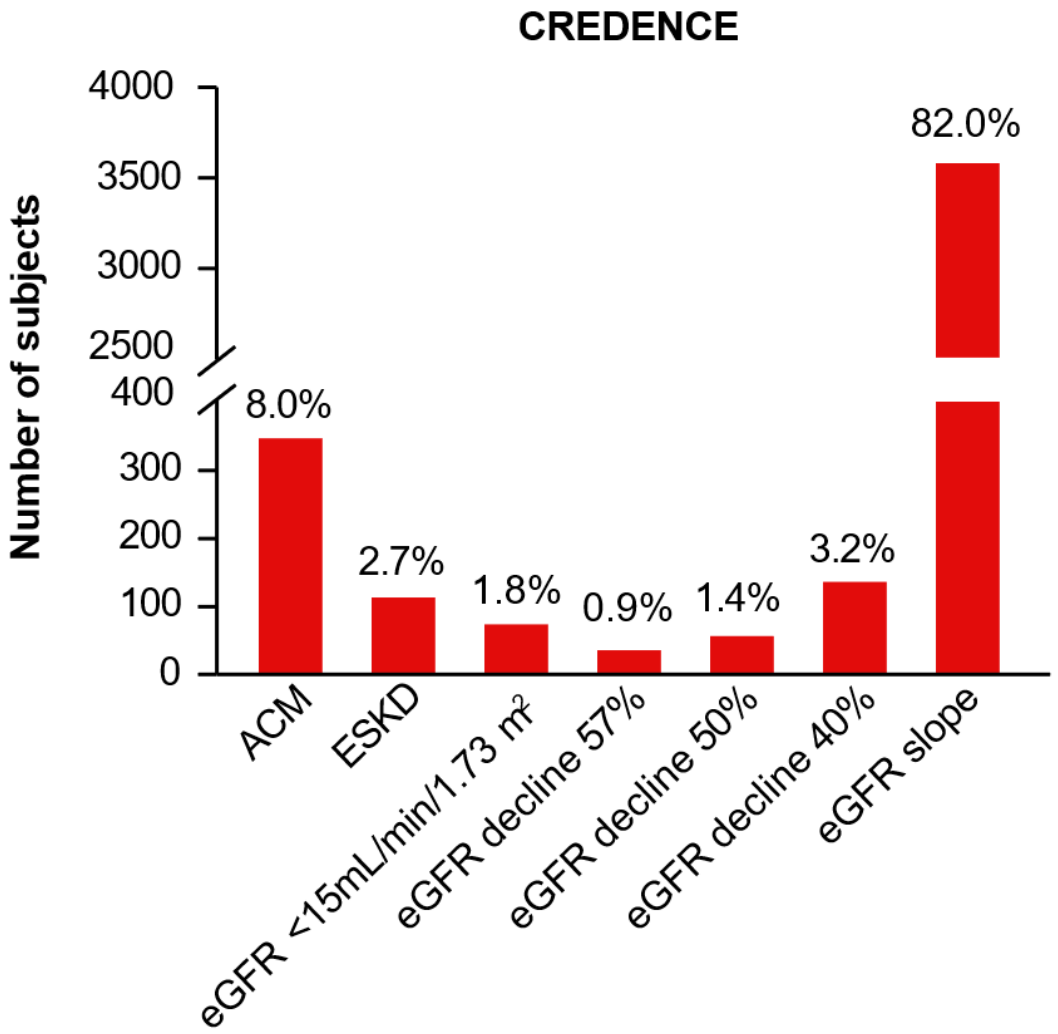
Primary Kidney Endpoint of Trials

Clinical trial	Endpoint definition
DAPA-CKD	Sustained 50% eGFR decline, kidney failure, renal or cardiovascular death
CREDENCE	Sustained 57% eGFR decline, kidney failure, renal or cardiovascular death
FIDELIO-DKD	Sustained 40% eGFR decline, kidney failure, renal death
SONAR	Sustained 57% eGFR decline, kidney failure, renal death
RENAAL	Sustained 57% eGFR decline, kidney failure**, all cause mortality
IDNT	Sustained 57% eGFR decline, kidney failure‡, all cause mortality
ALTITUDE	Sustained 57% eGFR decline, kidney failure, all cause mortality

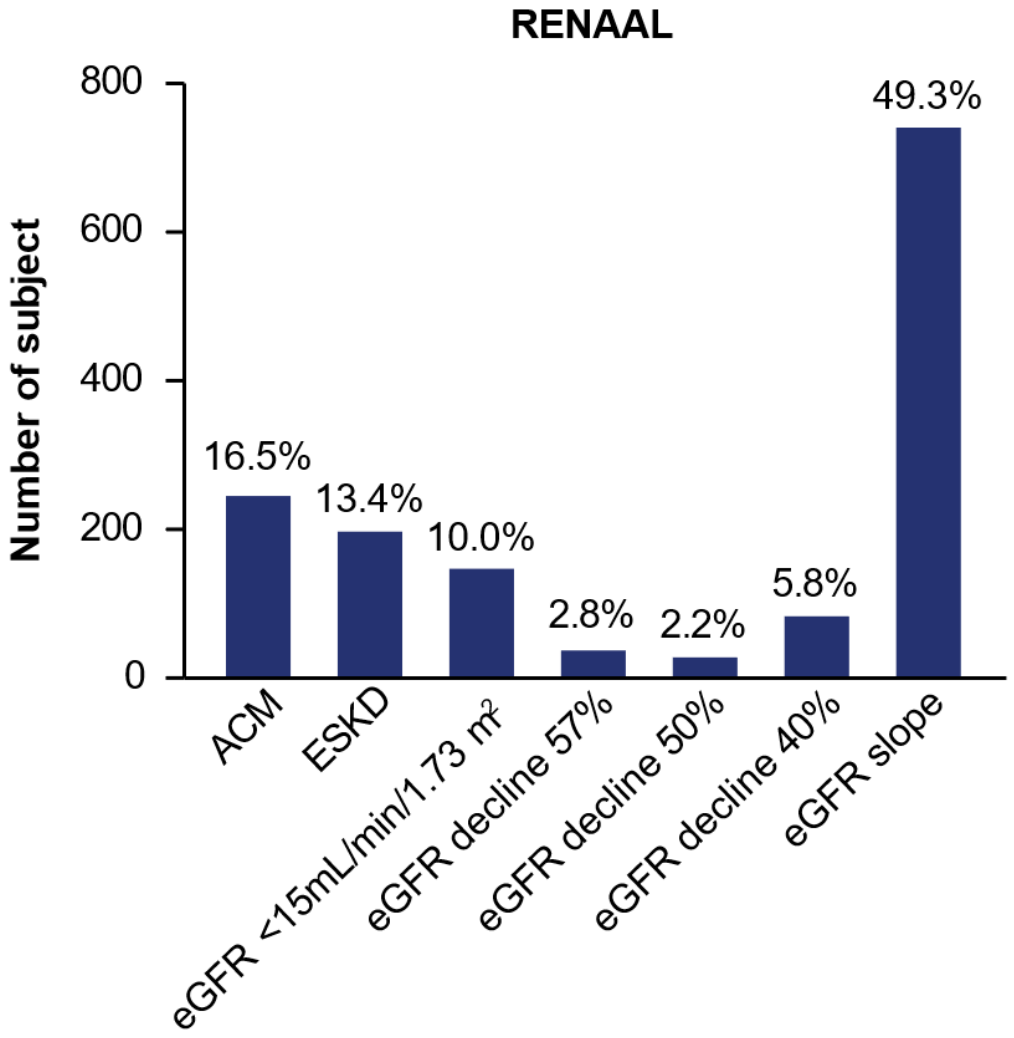
*kidney failure defined as chronic dialysis, kidney transplantation or sustained GFR<15 mL/min/1.73m^2
** kidney failure defined as chronic dialysis, kidney transplantation
‡ kidney failure defined as chronic dialysis, kidney transplantation or sustained serum creatinine >6 mg/dL

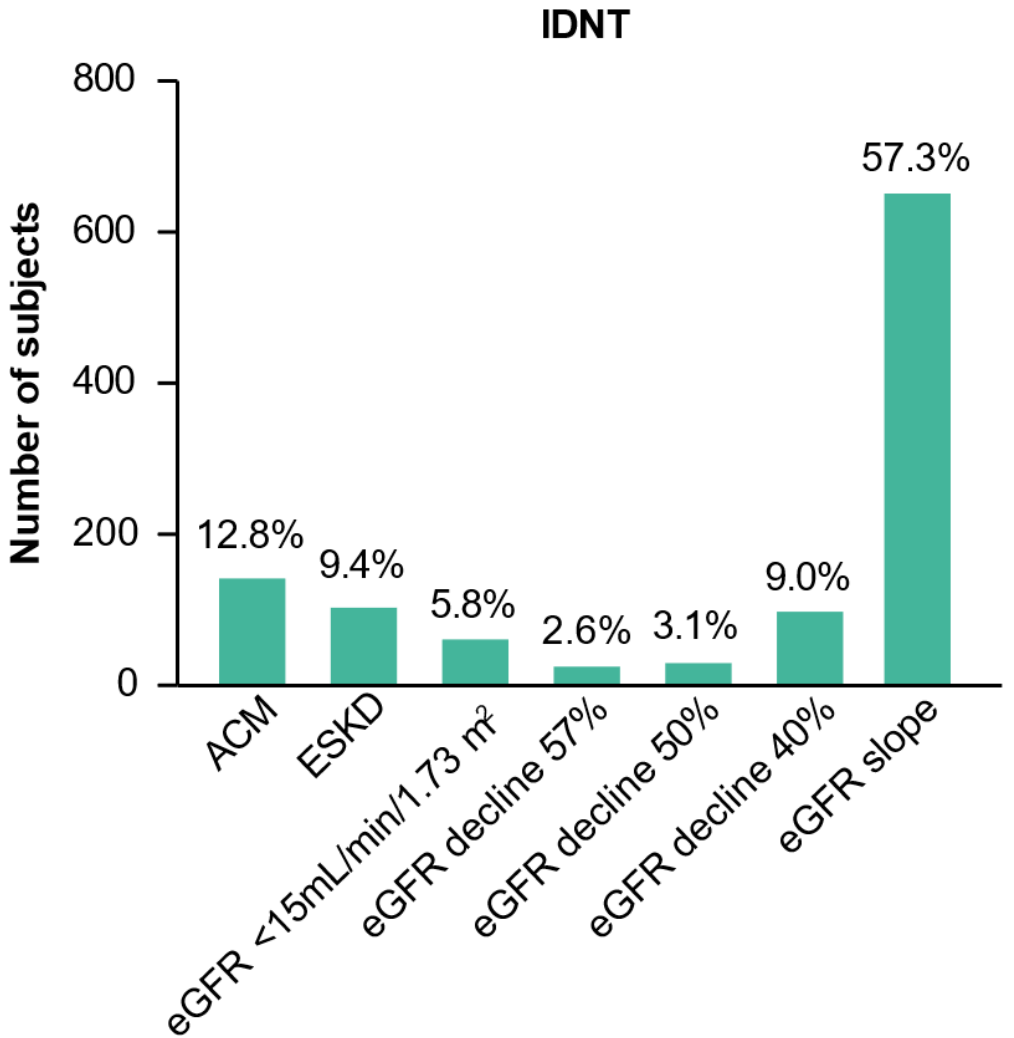
Contribution of Components to Kidney HCE Across Trials 1/3



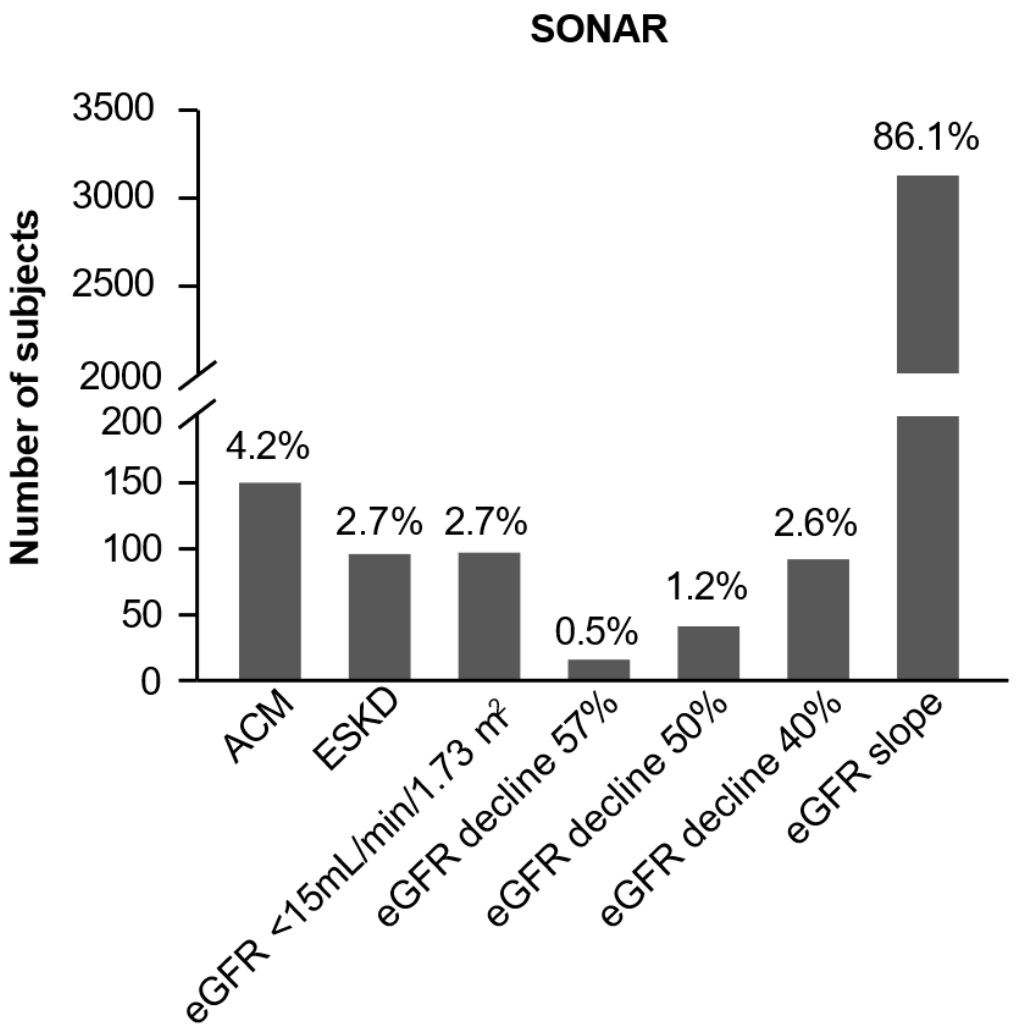


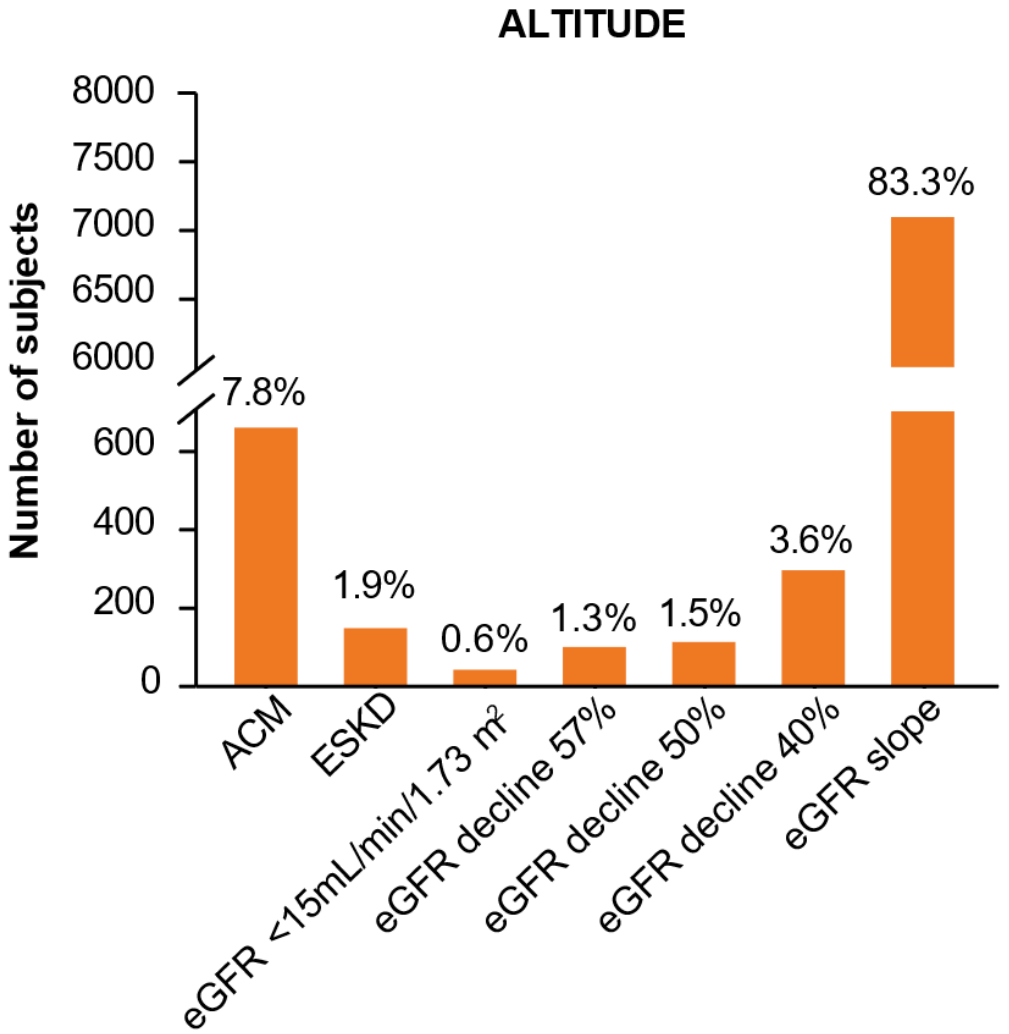
Contribution of Components to Kidney HCE Across Trials 2/3





Contribution of Components to Kidney HCE Across Trials 3/3





Detailed Results Across Trials 1/2

Treatment Comparisons	DAPA-CKD		CREDENCE		FIDELIO-DKD	
	Dapagliflozin versus Placebo		Canagliflozin versus Placebo		Finerenone versus Placebo	
	n	HR (95% CI)	*n*	HR (95% CI)	*n*	HR (95% CI)
Event						
All-cause mortality	247	0.69 (0.53 to 0.88)	369	0.83 (0.68 to 1.02)	463	0.90 (0.75 to 1.07)
Kidney replacement	174	0.66 (0.49 to 0.90)	176	0.74 (0.55 to 1.00)	258	0.86 (0.67 to 1.10)
GFR <15 ml/min per 1.73 m^2	204	0.67 (0.51 to 0.88)	203	0.60 (0.45 to 0.80)	366	0.82 (0.67 to 1.01)
57% GFR decline	201	0.61 (0.46 to 0.82)	156	0.41 (0.29 to 0.57)	412	0.68 (0.55 to 0.82)
50% GFR decline	313	0.53 (0.42 to 0.67)	262	0.53 (0.41 to 0.69)	638	0.73 (0.62 to 0.85)
40% GFR decline	538	0.63 (0.53 to 0.74)	454	0.59 (0.48 to 0.71)	1056	0.81 (0.72 to 0.92)
GFR slope[a]		1.12 (0.80,1.43)		1.66 (1.30,2.00)		0.64 (0.40 to 0.89)
Treatment effect composite end point						
HR (Cox)		0.61 (0.51 to 0.73)		0.70 (0.59 to 0.82)		0.82 (0.73 to 0.93)
WOs[b]		1.41 (1.32 to 1.52)		1.48 (1.38 to 1.58)		1.26 (1.19 to 1.34)

Detailed Results Across Trials 2/2

Treatment Comparisons	SONAR		RENAAL		IDNT		ALTITUDE	
	Atrasentan versus Placebo		Losartan versus Placebo		Irbesartan versus Placebo		Aliskiren versus Placebo	
	n	HR (95% CI)	*n*	HR (95% CI)	*n*	HR (95% CI)	*n*	HR (95% CI)
Event								
All-cause mortality	162	0.80 (0.67 to 0.96)	313	1.02 (0.81 to 1.27)	180	0.92 (0.69 to 1.23)	734	1.07 (0.92 to 1.23)
Kidney replacement	287	0.70 (0.55 to 0.88)	341	0.71 (0.58 to 0.88)	183	0.77 (0.57 to 1.03)	229	1.09 (0.84 to 1.41)
GFR <15 ml/min per 1.73 m^2	114	0.76 (0.52 to 1.10)	409	0.76 (0.62 to 0.91)	196	0.61 (0.46 to 0.81)	175	1.12 (0.83 to 1.51)
57% GFR decline	103	0.62 (0.42 to 0.92)	359	0.74 (0.60 to 0.92)	166	0.65 (0.48 to 0.89)	304	1.10 (0.88 to 1.37)
50% GFR decline	193	0.58 (0.44 to 0.78)	443	0.80 (0.67 to 0.97)	248	0.61 (0.47 to 0.79)	468	1.08 (0.90 to 1.30)
40% GFR decline	329	0.81 (0.65 to 1.01)	598	0.88 (0.75 to 1.04)	400	0.83 (0.68 to 1.01)	832	1.12 (0.98 to 1.28)
GFR slope[a]		0.60 (0.23 to 0.97)		1.08 (0.40 to 1.76)		1.10 (0.47 to 1.74)		-0.30 (-0.6 to 0.01)
Treatment effect composite end point								
HR (Cox)		0.71 (0.58 to 0.88)		0.79 (0.66 to 0.94)		0.74 (0.59 to 0.94)		1.08 (0.95 to 1.23)
WOs[b]		1.16 (1.07 to 1.25)		1.13 (1.00 to 1.27)		1.17 (1.02 to 1.34)		0.84 (0.80 to 0.88)

Non-Shared vs. Shared Follow-Up

Trial acronym	Win odds non-shared follow-up	Win odds shared follow-up
DAPA-CKD	1.41 (1.32, 1.52)	1.42 (1.32, 1.52)
CREDENCE	1.48 (1.38, 1.58)	1.49 (1.39, 1.59)
FIDELIO-DKD	1.26 (1.19, 1.34)	1.28 (1.21, 1.36)
SONAR	1.16 (1.07, 1.25)	1.16 (1.08, 1.25)
RENAAL	1.13 (1.00, 1.27)	1.13 (1.01, 1.27)
IDNT	1.17 (1.02, 1.34)	1.16 (1.02, 1.33)
ALTITUDE	0.84 (0.80, 0.88)	0.84 (0.80, 0.88)

Kidney HCE without Death