

Leveraging Model-Based Meta-Analysis to Benchmark Chronic Kidney Disease Treatments:

A Focus on Kidney Function and Proteinuria Endpoints

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Objectives

This analysis utilized a model-based meta-analysis (MBMA) approach to develop longitudinal models focusing on the percentage change from baseline (CFB) in glomerular filtration rate (GFR) and urine albumin-to-creatinine ratio (UACR) using summary-level data extracted from chronic kidney disease (CKD) studies conducted worldwide between 1992 and 2022.

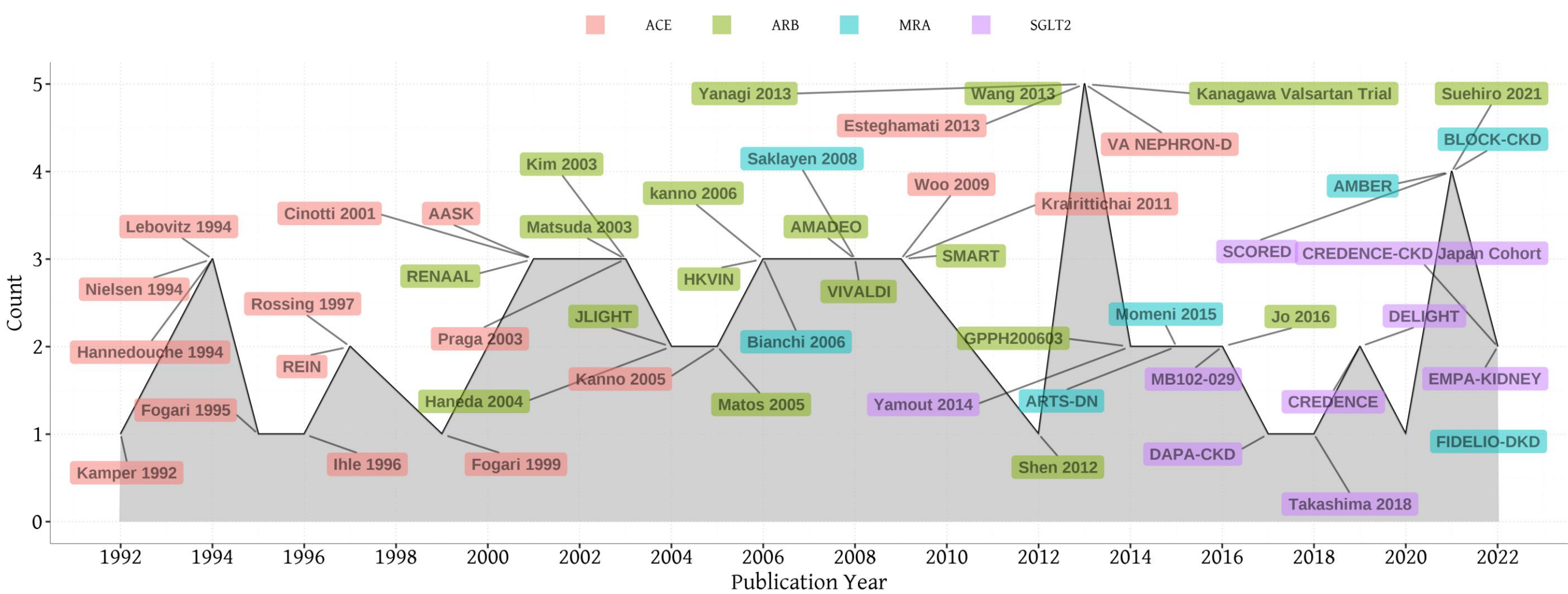
Introduction

- CKD can be treated by non-pharmacological strategies (e.g., dietary and lifestyle adjustments) and pharmacological interventions, including angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), sodium-glucose transport protein 2 (SGLT2) inhibitors and mineralocorticoid receptor antagonists (MRAs).
- eGFR and UACR are commonly used to diagnose and assess CKD.

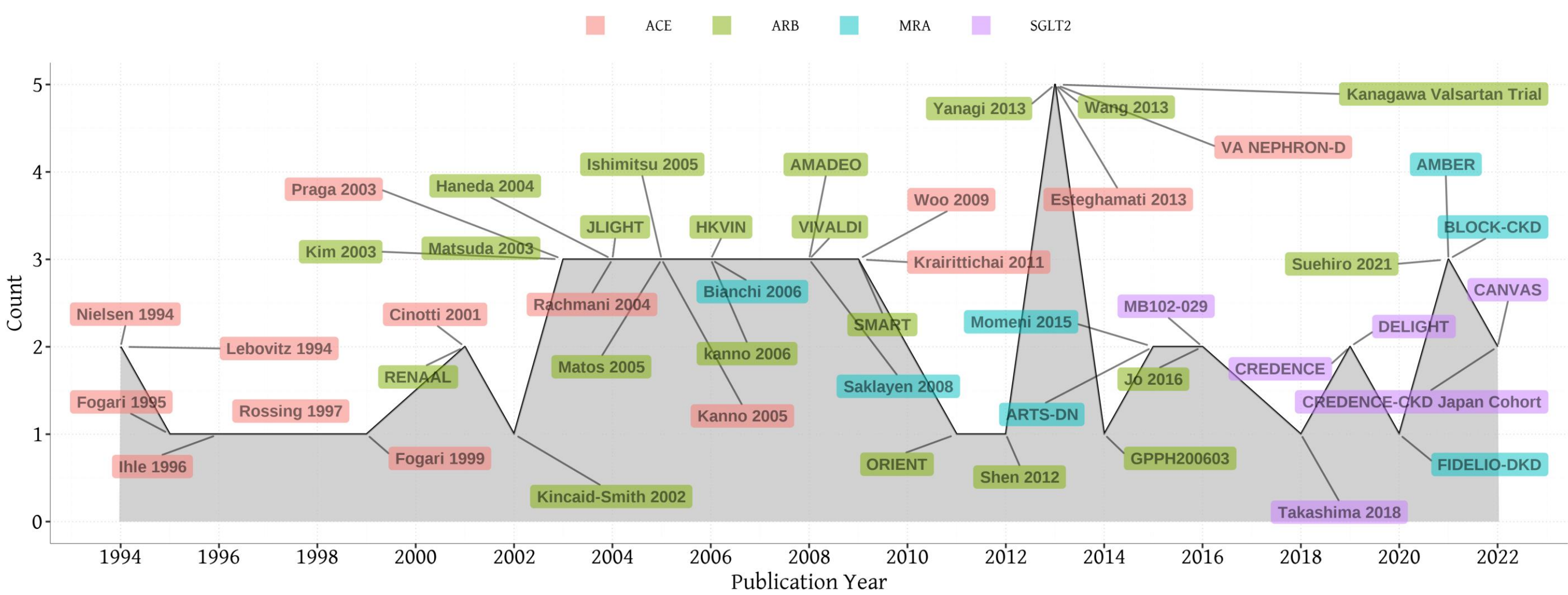
Data

- Two distinct analysis datasets containing summary level study, clinical endpoint, and demographic data were created from a licensed CKD database (CODEX) augmented by newer studies:
 - kidney function endpoints (eGFR, GFR, CRCL): 52 studies, 112 treatment arms
 - proteinuria endpoints (UACR, UAE24, UPCR, UPE24): 48 studies, 103 treatment arms
- Efforts were dedicated to standardizing units and summary metrics:
- For UACR, conversion of UPCR to UACR values was implemented following the equation published by Sumida et al. [1].
- Multiple endpoint metrics and various reported summary statistics were assumed comparable and compatible when modeling percentage CFB.

Overview of studies included in GFR analysis by publication year



Overview of studies included in UACR analysis by publication year



Methods

- Different structural longitudinal models were tested in NONMEM.
- A nested study and arm variability structure was introduced via super ID, and \$LEVEL functionality to acknowledge that variability between treatment arms within a study is likely less than across different studies.
- Residual unexplained variability (RUV) and inter-arm variability were weighted by the (time-varying) treatment arm sample size.
- Many covariates were not available for the majority of studies and stepwise covariate modeling was limited to only those covariates available in ≥80% of the studies.

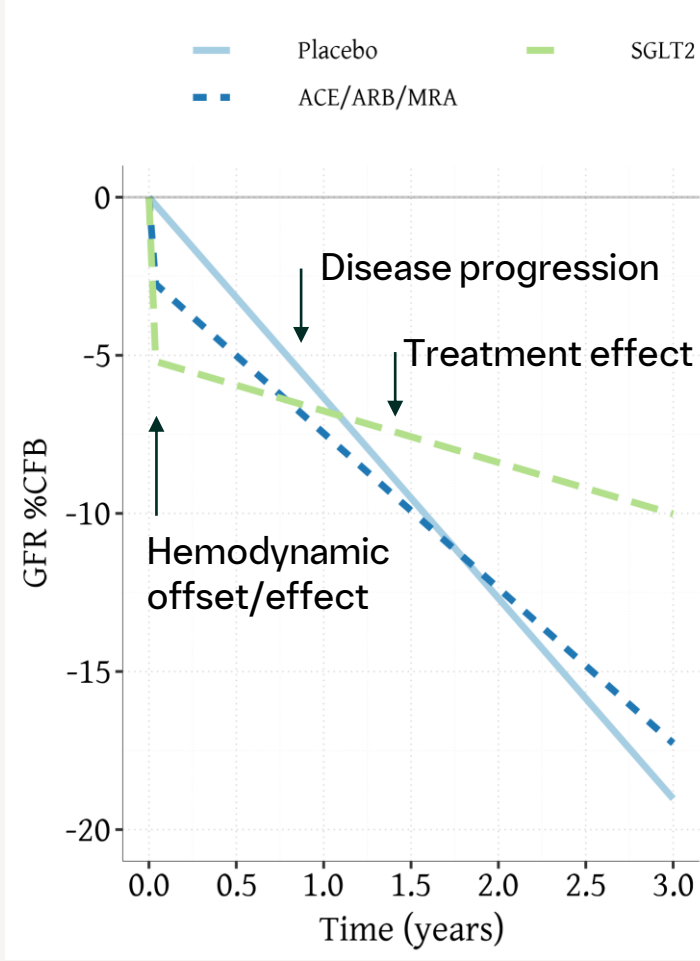
Abbreviations
ACE, Angiotensin-Converting Enzyme; ARB, Angiotensin Receptor Blocker; CI, confidence interval; CKD, Chronic kidney disease; eGFR, Estimated glomerular filtration rate; MBMA, Model-based Meta-Analysis; MRA, Mineralocorticoid Receptor Antagonist; RUV, Residual Unexplained Variability; SGLT2, Sodium-Glucose Transport Protein 2; UACR, Urine Albumin-to-Creatinine Ratio; UAE24, 24-hour Urinary Albumin Excretion; UPCR, Urine Protein-to-Creatinine Ratio; UPE24, 24-hour Urinary Protein Excretion; VPC, Visual predictive check; w, week

References
1. Sumida et al. Ann Intern Med, 173(6):426-435 (2020.)

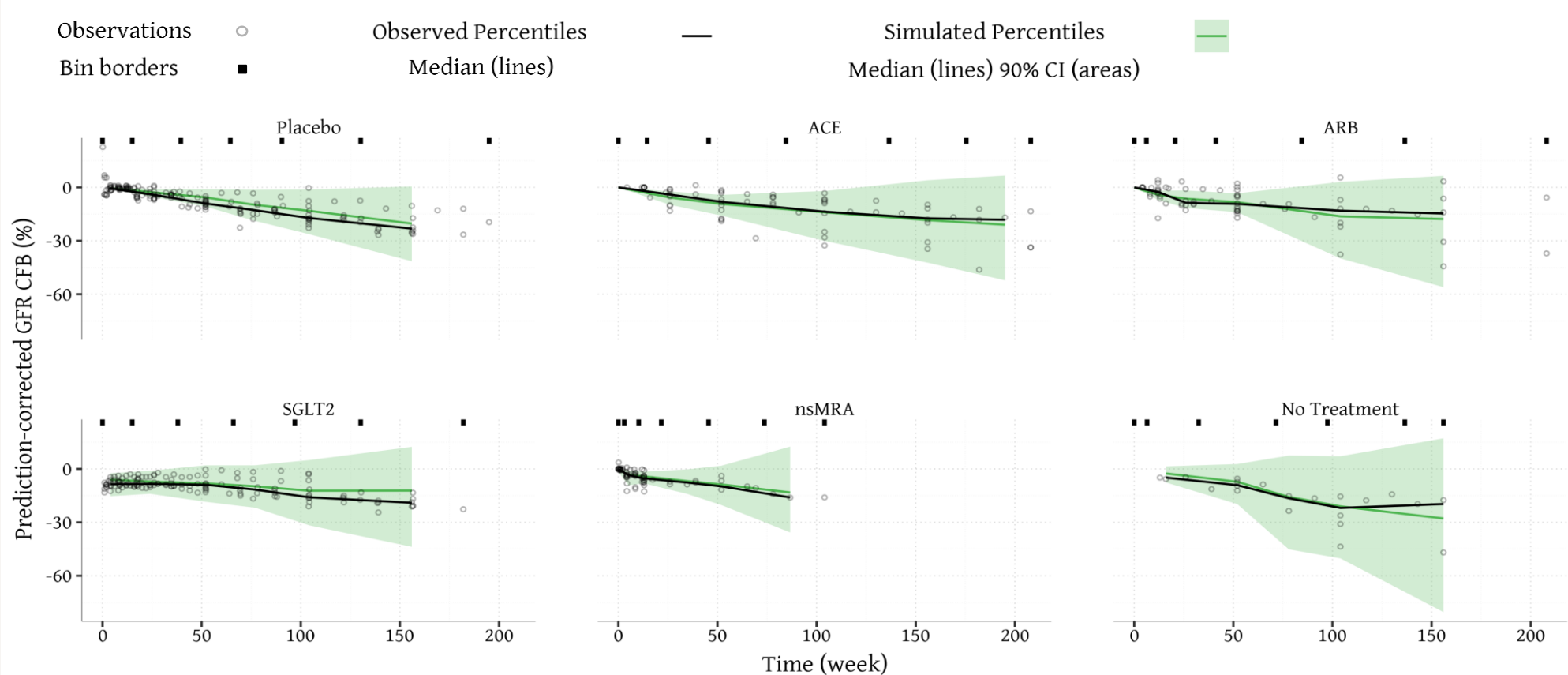
Results

GFR Model

Parameter	Unit	Estimate (95% CI)
Disease Progression	%/w	-0.122 (-0.136- -0.108)
Hemodynamic Effect ACEi/ARB/MRA	%	-2.56 (-2.16- -3.03)
Hemodynamic Effect SGLT2	%	-5.13 (-3.46- -7.55)
Treatment Effect - ACEi/ARB/MRA	%/w	0.028 (0.011-0.044)
Treatment Effect SGLT2	%/w	0.091 (0.074-0.107)
Finerenone Dose on Hemodynamic Effect	-	0.061 (0.041-0.081)
Baseline GFR on Disease Progression	-	-0.391 (-0.621- -0.161)

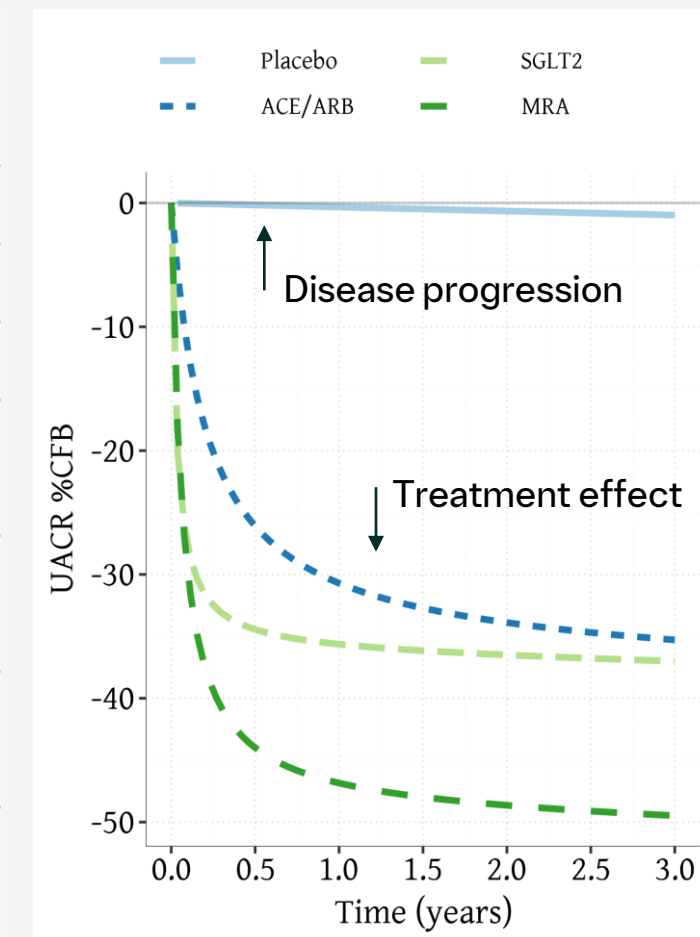


Visual predictive check of GFR versus time, stratified by mode of action.

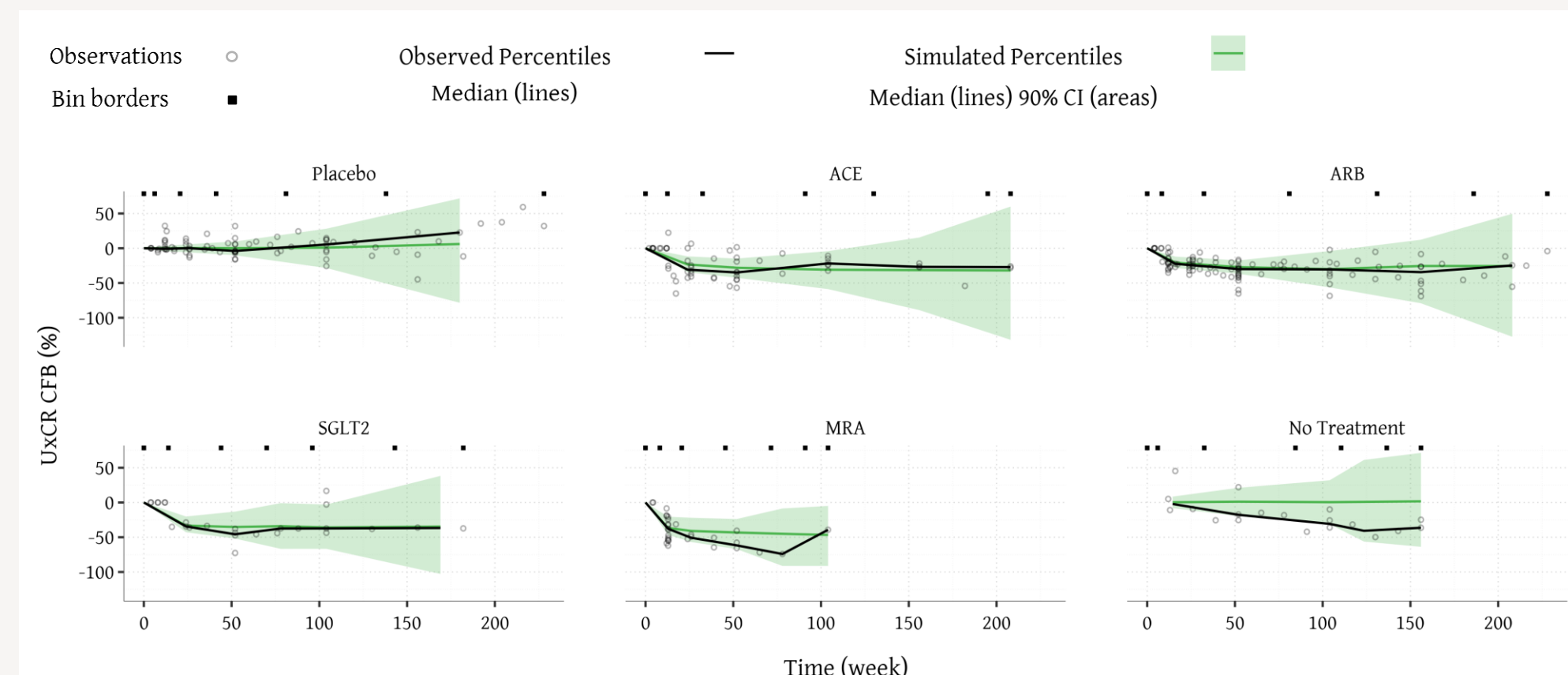


UACR Model

Parameter	Unit	Estimate (95% CI)
Disease Progression	%/w	-0.006 (-0.061- 0.048)
Max. Effect ACEi/ARB	%	-36.7 (30.0- -43.9)
Max. Effect SGLT2	%	-36.4 (-32.0- -41.1)
Max. Effect MRA	%	-49.6 (-49.1- -50.1)
Drug Effect Time50 ACEi/ARB	w	10.8 (5.48- 21.2)
Drug Effect Time50 SGLT2	w	1.61 (0.383-6.76)
Drug Effect Time50 MRA	w	3.40 (1.69-6.83)
Finerenone Dose Effect on Emax	-	-6.28 (-10.7- -1.87)



Visual predictive check of UACR versus time, stratified by mode of action.



- Clinical trial simulations, employing the developed models, offered valuable insights into the impact of different drug classes on kidney function and proteinuria outcomes in CKD patients, paving the way for benchmarking of emerging treatments.

Conclusions

- Summary-level literature data were used to successfully develop longitudinal models for GFR and UACR percentage change from baseline.
- This model-based meta-analysis will facilitate the future benchmarking of novel CKD treatments against existing drugs.