Model-Based Meta-Analysis (MBMA) to inform Chronic Kidney Disease (CKD) drug development

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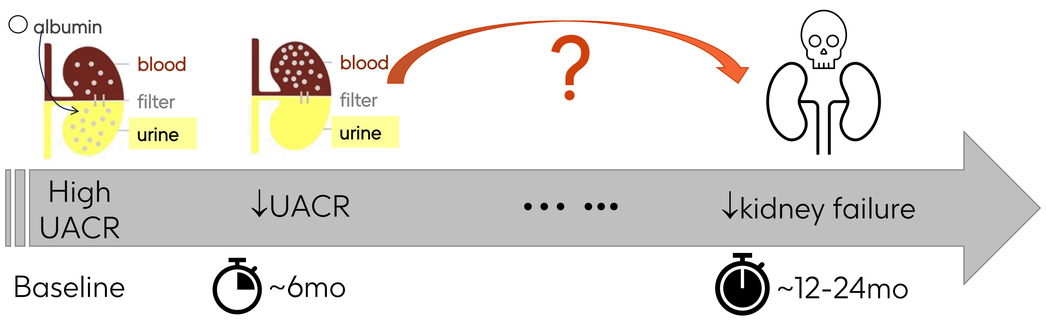
- A challenge of developing new therapies in CKD is relating rapid but variable short-term endpoints to registrational slow-to develop clinical endpoints.
- This MBMA standardizes the heterogeneous surrogate and clinical endpoints reported in different programs and identifies a moderate association between early reductions (~6 mo) in urine albumin-to-creatinine ratio (UACR) and improved clinical outcomes at 1–2 years.
- These results support the use of UACR in futility assessments, adaptive trial designs, and interim Go/No-Go decisions

Background & Aim



- Drug development in CKD is challenging due to disease **heterogeneity** and **long-term clinical outcomes** requiring extended follow-up and large clinical trials[1].
- **Short-term biomarkers** like UACR are used in early-phase studies, but their variability and **uncertain relationship with long-term outcomes** impact confidence in Ph3 efficacy and long-term clinical benefit.
- Heerspink et al[2-3] reinforced UACR role as surrogate endpoint in CKD trials, using individual data to demonstrate the association between treatment effects on UACR at 6 months and clinical endpoint defined as hazard of kidney failure or doubling of serum creatinine concentration at 12 months.
- The validity of their findings when the clinical endpoint is defined differently or measured at different time-points, or using the same drug in different patient populations is unknown.
- The **aim** of this work is to **link short-term biomarker responses to long-term clinical outcomes** in CKD using **aggregate data**[4] from published randomized controlled trials (RCTs) and **MBMA**[5], providing model-informed drug development (MIDD) evidence to support quantitative decision-making, improve trial efficiency and accelerate the development of effective therapies.

Data

- CODEx CKD database[4] (aggregate-level efficacy and safety data).
- Therapeutic interventions: ACE inhibitors, angiotensin II receptor blockers, SGLT2 inhibitors, endothelin receptor antagonists.
- CKD populations: diabetic nephropathy, IgA nephropathy, hypertensive nephrosclerosis, and other proteinuric kidney diseases.
- N = 228 renal endpoints studies, N = 110 clinical endpoints studies, of which 50 studies are retained in this analysis.

Methods

- Treatment effects on UACR expressed as GMR of active treatment versus control, calculated as fold change from baseline.
- Treatment effects on clinical outcomes summarized as HRs of active versus control.
- Different composite endpoints assumed comparable after transformation to HRs.
- To maximize data inclusion, when exact time points were not available, the measurement closest to the desired timepoint was selected.
- The MBMA was conducted at the study arm level using treatment effect estimates derived for each endpoint.
- Linear regression analyses were performed on log-transformed endpoints to account for multiplicative treatment effects.
- Weighting was applied by accounting for study arm size.
- Model parameters including slope, intercept, coefficient of determination (R^2), and statistical significance were estimated.

Endpoints harmonization

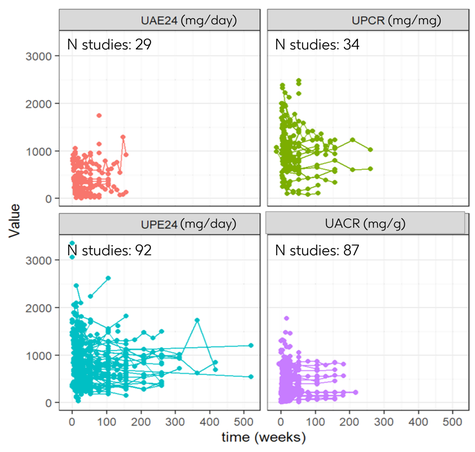
Renal surrogate endpoints

Endpoint	Units	N studies
UPE24	mg/day	102
UACR	mg/g	85
UPCR	mg/mg	56
UAE24	mg/day	39
UACR log10	log10 mg/g	6
UAE24 log10	log10 mg/day	3
UPE24 log10	log10 mg/day	2
UACR ln	ln(mg/g)	2
UAE24 ln	ln(mg/day)	1
UPCR ln	ln(g/g)	1

Conversion to UACR [mg/g] & de-duplication

UACR(mg/g) = 0.6*UAE24(mg/24h)[2-3]
UACR(mg/g) = 0.6*UPE24(mg/24h)[2-3]
UACR (mg/g) = -17+1000*0.78*UPCR (mg/mg)[6]

Endpoint	Units	N studies
UPE24	mg/day	92
UACR	mg/g	87
UPCR	mg/mg	34
UAE24	mg/day	29

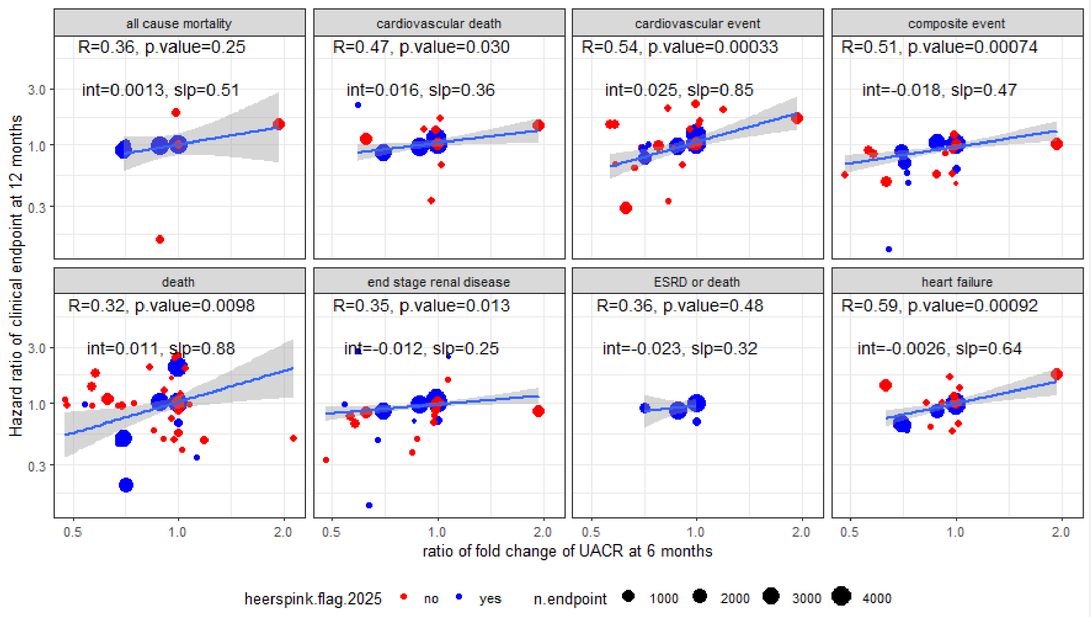


Clinical endpoints (post de-duplication)

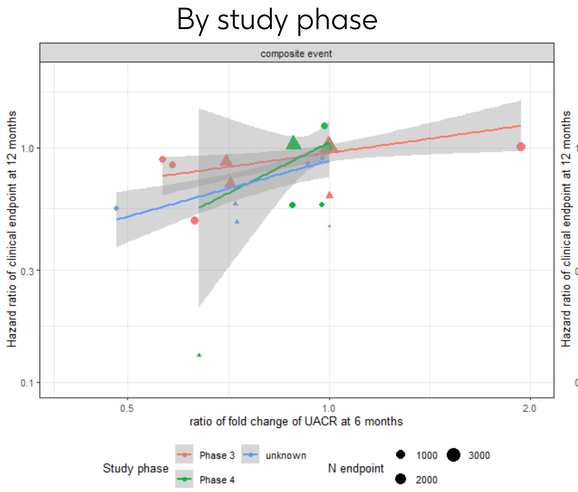
Endpoint	N studies
death	83
ESRD	48
composite event	37
cardiovascular event	33
heart failure	23
cardiovascular death	17
all cause mortality	13
ESRD or death	6
composite event risk decreased	2
ESRD risk decreased	2
death event	1
eGFR responder	1

Results

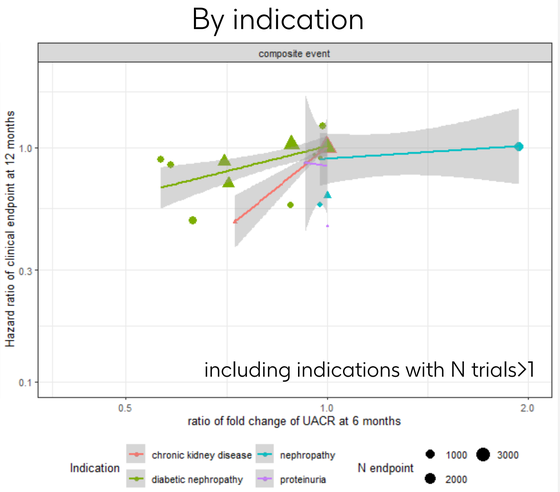
Moderate correlation between ratio of fold change from baseline of UACR at 6 mo and hazard ratio of different clinical endpoints at 12 mo



By study phase

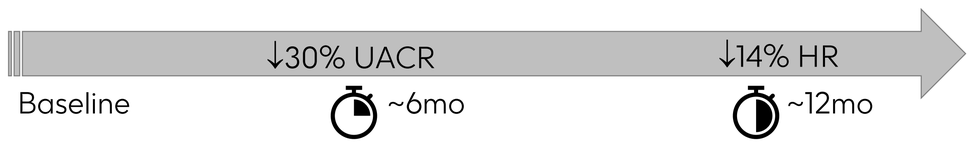


By indication



Due to sparse data, no conclusions can be drawn about the effect of study phase and indication.

↓30% GMR of the fold change of **UACR** (treatment vs control) — MBMA → **↓14%** (95% CI: 6.5–21%) **hazard** of composite endpoint



Conclusions

- This analysis integrates the CODEx CKD database with a rigorous MBMA mathematical framework to characterize the relationship between early surrogate endpoints and long-term clinical outcomes in CKD. Systematic standardization and harmonization of heterogeneous renal and clinical endpoints enabled consistent cross-trial comparisons using aggregate data and addressed limitations of prior analyses.
- Results support a positive association between early reductions in UACR at ~6 months and improved clinical outcomes at 12 months, reinforcing the role of UACR as a meaningful intermediate endpoint in CKD drug development.
- These findings quantitatively support the use of UACR in futility assessments, adaptive trial designs, and interim Go/No-Go decisions.
- Further work will characterize variability across CKD subtypes and severity, drug classes and phases of development and explore longitudinal trajectories of both surrogate and clinical endpoints.

References

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Abbreviations

ACE: angiotensin-converting enzyme; EGFR: estimated glomerular filtration rate; ESRD: end stage renal disease; GMR: geometric mean ratio; HR: Hazard ratio; R: Pearson correlation coefficient; SGLT2: sodium–glucose cotransporter-2; UACR: urine albumin-to-creatinine ratio; UAE24: urinary albumin excretion over 24 hours; UPCR: urine protein-to-creatinine ratio; UPE24: urine protein excretion over 24 hours

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