Relationship between change in uACR and eGFR-slope, a meta-analysis

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Agenda DSBS/FMS

Introduction

- Urine Albumin-Creatinine Ratio (uACR)
- Estimated Glomerular Filtration Rate (eGFR)
- Analysis
  - Geometric mean ratio (GMR) of change from baseline in uACR on log-scale
  - Mean change from baseline in eGFR
- Idea: Look at link between uACR and eGFR

Short on CKD

- Difficult to detect Chronic Kidney Disease (CKD) early
- No cure
- Important to try to prevent CKD early
- uACR:
  - Indicator that something is probably not right with the renal function
- eGFR-slope:
  - Decline could indicate that kidneys not working fully

Method

- General idea:
  - Look at eGFR-slope as dependent (chronic, 1, 2, 3 or 4 years) with uACR as independent variable (6 or 12 months)
- Subgroups:
  - Baseline disease characteristics, CKD, Diabetes, etc
  - Types of intervention

- Primary analysis: uACR 6 months and 2 year eGFR-slope
- Secondary: uACR 6 months and 1, 3, 4 and chronic eGFR-slope
- Secondary uACR 12 months and 1, 2, 3, 4 and chronic eGFR-slope

Meta-Regression

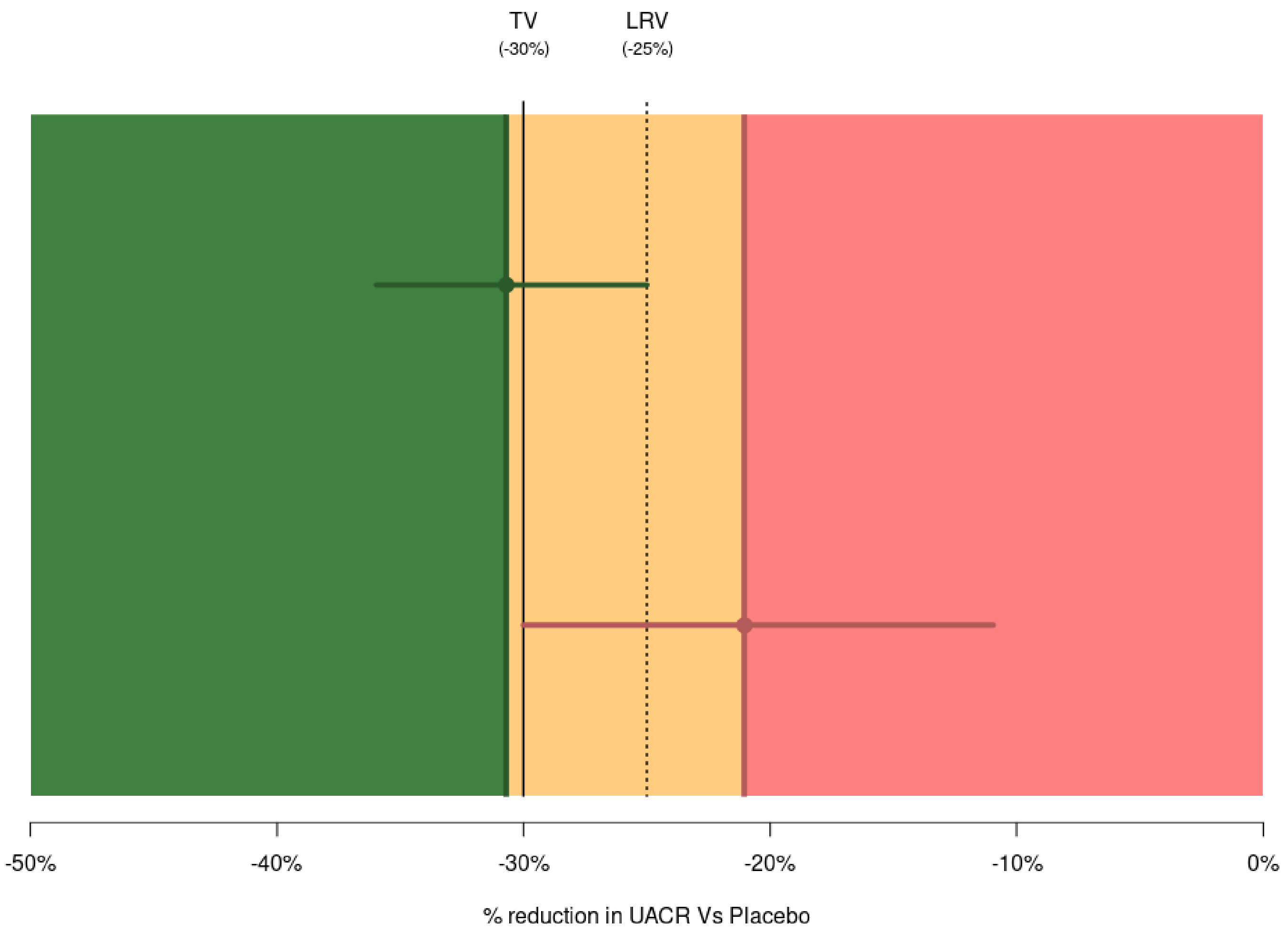
- 46 data points
- Heerspink et al: ”UACR as surrogate”[1]
- Inker et al: ”GFR slope as surrogate”[2]
- Metafor R-package[3]
- Sample variability included in model estimate

Decision framework

1. Effect on eGFR slope, a surrogate endpoint for renal outcomes with increasing regulatory acceptance
2. Effect on renal composite outcomes

- The desicion was to be made via an adapted Lalonde framework[4] where Target Values (TV) and Lower Reference Values (LRV) were prospectively defined together with standard risks for false Stop and Go desicions.

Illustration of LaLonde Decision Framework



A suggested Phase II design with N=145 patients / arm, TV & LRV above and an assumed within subject SD for change from baseline in UACR of 0.8

PTS - Simulation

- N = 10000 of log-GMR of UACR at 6 months, normally distributed with mean -0.31 and sd=0.8
- PTS is then the fraction of studies with predicted eGFR-slope effect ≥ 0.72.

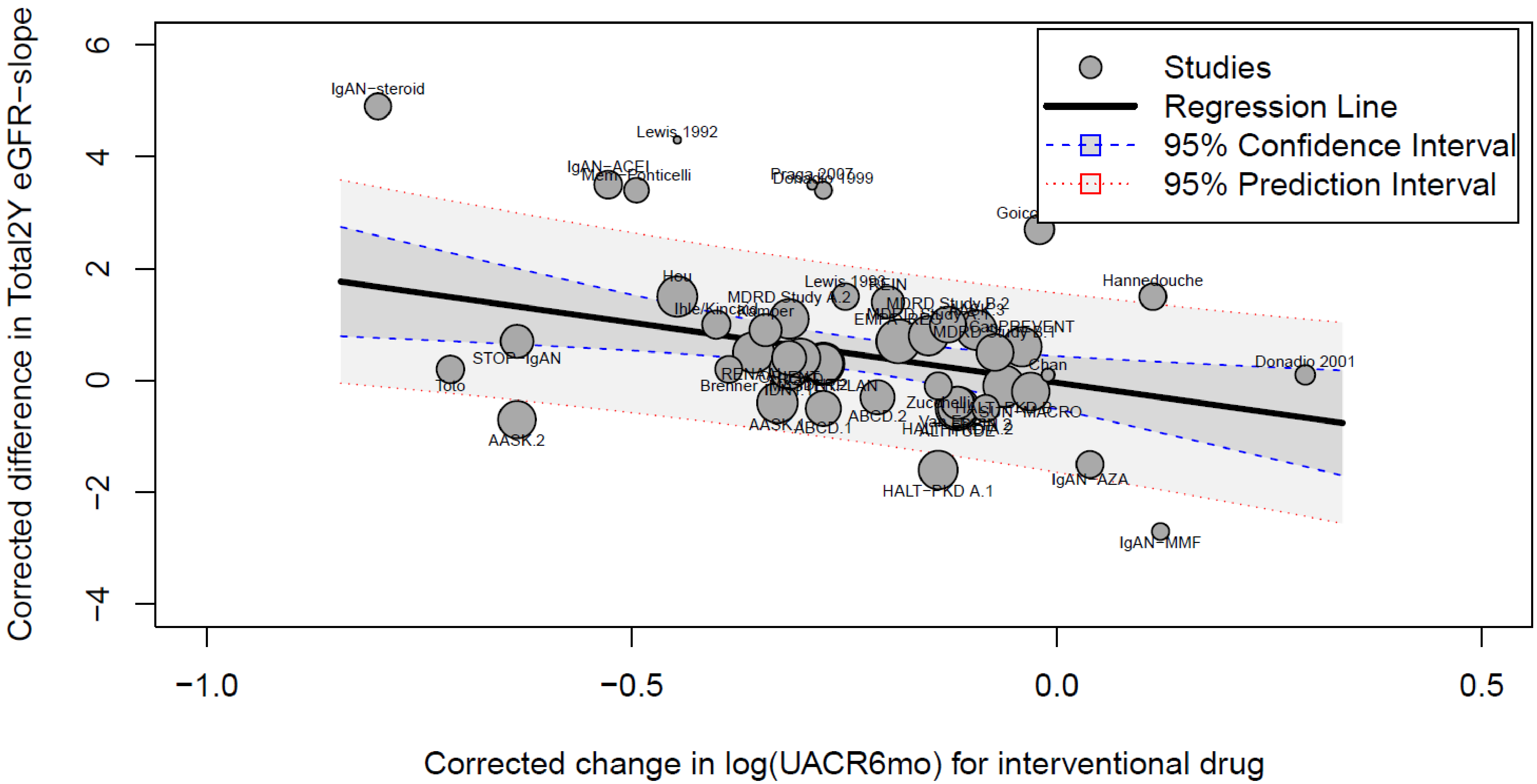
Results

- R^2 of 14.7% for primary analysis
- Possible signal
- uACR significant covariate
- R^2 of 43% for the model with CKD included

Models	Estimate of model parameter (p value)	CI	R^2 (%)
6 Months uACR and 1 Year eGFR-slope	-1.7689 (0.1550)	(-4.2066, 0.6689)	0.50
6 Months uACR and 2 Years eGFR-slope	-2.1439 (0.0065*)	(-3.6876, -0.6001)	14.74
6 Months uACR and 3 Years eGFR-slope	-2.1926 (0.0009***)	(-3.4863, -0.8989)	25.68
6 Months uACR and 4 Years eGFR-slope	-2.2133 (0.0002***)	(-3.3976, -1.0290)	31.37
6 Months uACR and chronic eGFR-slope	-2.1560 (<0.0001***)	(-3.2044, -1.1076)	34.84
12 Months uACR and 1 Year eGFR-slope	-1.7948 (0.2545)	(-4.8817, 1.2920)	0.00
12 Months uACR and 2 Years eGFR-slope	-2.2776 (0.0149*)	(-4.1104, -0.4448)	12.94
12 Months uACR and 3 Years eGFR-slope	-2.3500 (0.0023**)	(-3.8612, -0.8388)	27.10
12 Months uACR and 4 Years eGFR-slope	-2.2880 (0.0011**)	(-3.6580, -0.9180)	30.92
12 Months uACR and chronic eGFR-slope	-2.3111 (0.0003***)	(-3.5710, -1.0513)	36.37

*: <0.05, **: <0.01, ***: <0.001

Meta Regression: eGFR SlopeTotal2Y vs log(UACR6mo)



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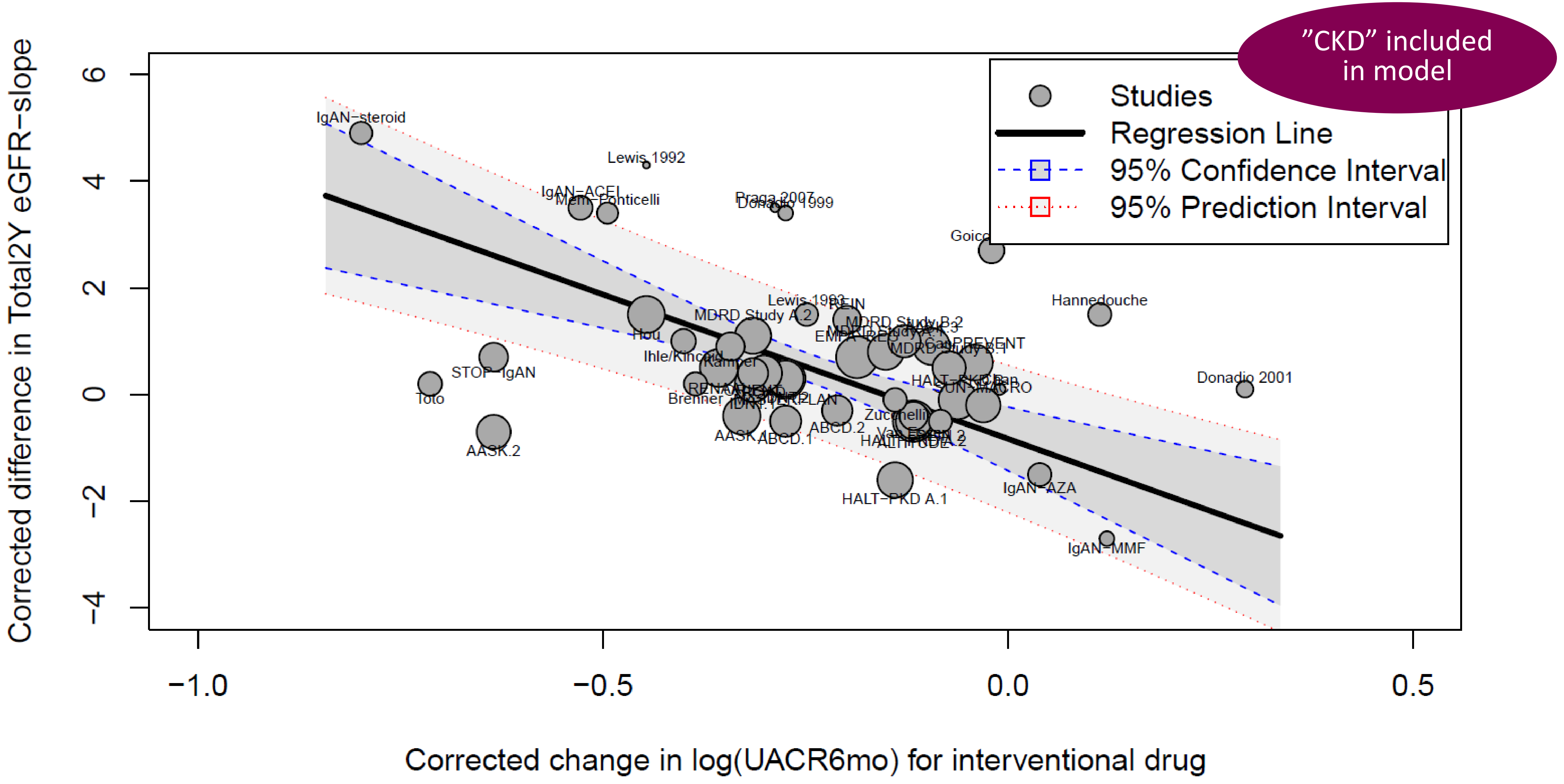

Probability of Technical Success

Models	PTS
6 Months uACR and 1 Year eGFR-slope	48%
6 Months uACR and 2 Years eGFR-slope	51%
6 Months uACR and 3 Years eGFR-slope	51%
6 Months uACR and 4 Years eGFR-slope	51%
6 Months uACR and chronic eGFR-slope	52%
12 Months uACR and 1 Year eGFR-slope	43%
12 Months uACR and 2 Years eGFR-slope	47%
12 Months uACR and 3 Years eGFR-slope	48%
12 Months uACR and 4 Years eGFR-slope	49%
12 Months uACR and chronic eGFR-slope	50%

Summary of results and Conclusions

- 12 months not necessarily better
  - Both regarding R^2 and PTS
- Higher R^2 with longer eGFR measurement, regardless of uACR measurement
- PTS estimated to around 50%.
  - Based on the previous data we are looking at a coin-flip.

Project's Future

- Possible Bayesian approach, similarly to Inker et al. & Heerspink et al.
- Look at uACR -> eGFR -> renal outcomes

Thank you for listening!

- [1] Heerspink, H. J., Greene, T., Tighiouart, H., Gansevoort, R. T., Coresh, J., Simon, A. L., ... & Keane, W. (2019). Change in albuminuria as a surrogate endpoint for progression of kidney disease: a meta-analysis of treatment effects in randomised clinical trials. The lancet Diabetes & endocrinology, 7(2), 128-139.
- [2] Inker, L. A., Heerspink, H. J., Tighiouart, H., Levey, A. S., Coresh, J., Gansevoort, R. T., ... & Greene, T. (2019). GFR slope as a surrogate end point for kidney disease progression in clinical trials: a meta-analysis of treatment effects of randomized controlled trials.
- [3] Viechtbauer, W. (2010). Conducting Meta-Analyses in r with the Metafor Package. Journal of Statistical Software 36 (3): 1–48.
- [4] Lalonde, R. L., Kowalski, K. G., Hutmacher, M. M., Ewy, W., Nichols, D. J., Milligan, P. A., ... & Miller, R. (2007). Model-based drug development. Clinical Pharmacology & Therapeutics, 82(1), 21-32.

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