**Clinical risk scores for predicting benefit and harm from intensive glycemic control and the influence of haptoglobin phenotype: the ACCORD study**

**Background & Aim:** Recent research reported that people with type 2 diabetes mellitus (T2DM) and the haptoglobin (Hp) 2-2 phenotype had reduced coronary artery disease (CAD) risk from intensive glycemic control, while those without the Hp2-2 phenotype did not and actually faced increased mortality risk. This suggests that Hp phenotype may help predict benefit and harm from intensive glycemic control. Currently, there are no risk calculators available to personalize glycemic control based on combinations of individual characteristics, including Hp phenotype. We aimed todevelop and internally validate clinical risk scores for predicting individual patients living with T2DM’s chances of (a) benefit (CAD prevention) and (b) harm (total mortality) from intensive glycemic control, determining whether Hp phenotype contributes to score predictability.

**Method:** We used elastic net regularization to select Cox models for CAD and total mortality using data from 8,547 ACCORD trial participants with complete covariable data. The models were then used to estimate the absolute risk reduction in CAD events and absolute risk increase in total mortality for each participant from intensive glycemic control over 7 years. Model performance was assessed by calculating discrimination and calibration.

**Results:** The selected models for CAD and total mortality included demographic characteristics, clinical variables, comorbidities, medications, and biomarkers. The selected model for total mortality included an interaction term between Hp phenotype and treatment arm (intensive or standard glycemic control), suggesting possible heterogeneous treatment effects. Both models showed acceptable discrimination (Harrell’s C-index: CAD 0.704; total mortality 0.720) and good calibration during internal validation (Brier score: CAD 0.088, 95% confidence interval (CI) 0.081-0.095; total mortality 0.057, 95% CI 0.051-0.063).

**Conclusion:** Hp phenotype may contribute to score predictability for harm from intensive glycemic control, but not benefit. The models we developed could potentially help guide treatment decisions regarding the intensity of glycemic control for individuals with T2DM.