

Precision medicine in T2DM: Harnessing individual-level trial data alongside routine care records to identify predictors of response to SGLT2 inhibitors and DPP4 inhibitors

Authors: John Dennis^{1,2}, William Henley¹, Angus Jones², Ewan Pearson³, Andrew Hattersley², Beverley Shields² on behalf of the MASTERMIND Consortium

¹Health Statistics Group, University of Exeter Medical School; ²National Institute for Health Research Exeter Clinical Research Facility, University of Exeter Medical School ³University of Dundee

Background: Individual participant data from randomised trials are increasingly available for researchers to answer secondary research questions. Online repositories include The Yale University Open Data Access (YODA) and Clinical Study Data Request. There may be great potential to harness these datasets to evaluate potential precision medicine approaches to target specific medications at individuals most likely to benefit. We propose a framework involving discovery analysis in routine clinical data followed by validation in trial data, and apply this to identify and evaluate clinical features associated with greater response to SGLT2-inhibitor and DPP4-inhibitor therapy.

Methods: Discovery analysis: We studied 30,511 patients with type 2 diabetes starting either SGLT-2 inhibitor (SGLT2i) or DPP4-inhibitor (DPP4i) therapy for the first time in routine clinical data from the UK (CPRD). Associations between standardised baseline clinical features and reduction in HbA1c at 6 months (6 month HbA1c–baseline HbA1c) to each drug were evaluated using linear regression. Validation analysis: We pooled individual-level data from 9 randomised drug efficacy trials of the SGLT2i's Canagliflozin and Empagliflozin, 3 of which had DPP4i (Sitagliptin) comparator arms (n=5,653), accessed through YODA. We then tested whether the associations between clinical features and response observed in CPRD were replicated in the trials, using multivariable three-level (nested trial-patient-study visit) linear mixed-effects models.

Results: In CPRD, we identified simple clinical features associated with differential response to the two drugs. Greater SGLT2i response was associated with higher eGFR (reduction in HbA1c (β) per standard deviation (SD) higher GFR -1.1 mmol/mol (95% confidence interval (CI) -1.6;-0.7), $P<0.0001$), lower HDL (β per SD increase in HDL 1.2 mmol/mol (95% CI 0.7;1.7), $P<0.0001$), but not higher BMI (β per SD greater HDL 0.3 mmol/mol (95% CI -0.1;0.7), $P=0.17$). With DPP4i's, higher BMI and higher eGFR were associated with lesser response (β per SD increase in BMI 1.0 mmol/mol (95% CI 0.7;1.2), $P<0.0001$; β per SD increase in eGFR 0.8 mmol/mol (95% CI 0.6;1.0), $P<0.0001$), but there was no association for HDL (β per SD increase in HDL -0.1 mmol/mol (95% CI -0.3;0.1), $P=0.52$). All associations were replicated when tested in trial data: DPP4i β 0.6 mmol/mol (95%CI 0.3;1.2) for BMI, β 0.7 mmol/mol (95% CI 0.3;1.1) for eGFR, β 0.1 mmol/mol (95% CI -0.7;0.9) for HDL; SGLT2i β 0.2 mmol/mol (95%CI 0.0;0.4) for BMI, β -1.0 mmol/mol (95%CI -1.3;-0.7) for eGFR, β 0.7 mmol/mol (95% CI 0.4;1.0) for HDL.

Conclusion: The availability of individual-level trial data from repositories such as YODA and Clinical Study Data Request provides a tremendous opportunity to evaluate precision medicine in type 2 diabetes. Discovery in routine data followed by validation in trial data provides a principled framework to utilise trial data without data-mining. Our findings using this framework suggest there may be potential to use simple clinical features to target SGLT2-inhibitor and DPP4-inhibitor therapy at individuals most likely to benefit.