Comment Letter

Comment on Garvey *et al.* Association of Baseline Factors With Glycemic Outcomes in GRADE: A Comparative Effectiveness Randomized Clinical Trial. Diabetes Care 25 March 2024; 47 (4): 562–570

Running title: Comment:treatment effect heterogeneity in GRADE

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To the Editor:

The recent analysis of treatment effect heterogeneity for glycemic response in the GRADE RCT by Garvey *et al*. [1] represents a major advance in type 2 diabetes precision medicine. The authors provide important new evidence of differential glycemic outcomes in a systematic direct comparison of 4 widely used drug classes: sulfonylureas [glimepiride], DPP4-inhibitors [sitagliptin], GLP1-receptor agonists [liraglutide], and insulin.

Encouragingly for the field, findings add to the growing evidence of clinically relevant treatment effect heterogeneity for non-insulin type 2 diabetes therapies, including the recent TRIMASTER 3-drug crossover trial [2-5]. Concordant with these studies, sex is identified as a key treatment effect modifier for both GLP-1RA, with greater short-term glycemic efficacy in females compared to males [2], and SU, with greater efficacy in males [3]. DPP4-inhibitors demonstrated reduced efficacy relative to other agents, most marked at higher HbA_{1c} levels [3]. Although older age is consistently associated with greater efficacy for all agents in GRADE, this may differ for SGLT2i, the major drug class omitted, for which reduced renal function (negatively correlated with age) has been robustly associated with lesser efficacy in trial data [4]. Importantly, these studies demonstrate the precision medicine approaches will have greatest utility if based on combining multiple clinical features in models to predict individual-level treatment efficacy [2-3], an approach that was not tested in the GRADE analysis.

Beyond these notable findings, two points should be clarified. In our opinion, the general lack of evidence for treatment effect heterogeneity at 4-years should be interpreted with caution. These findings may reflect the choice of a tight HbA_{1c} <7% binary efficacy endpoint, which meant most individuals demonstrated a lack of efficacy by four years. The likely impact is a reduction in statistical power compared to analysis of a continuous glycemic outcome incorporating repeated HbA_{1c} measures over time, which would be possible in GRADE.

Therefore, the lack of statistical significance may reflect low statistical power rather than the absence of heterogeneous treatment effects.

As a second point, the article suggests that the lack of association found between insulin secretion (measured using the insulinogenic index) and GLP-1RA response in GRADE is not consistent with previous evidence that measures of reduced insulin secretion are associated with substantially reduced glycemic response. In our understanding, this is not correct. The previous studies demonstrated reduced response with low insulin secretion in insulin-treated participants, with the association driven by severe endogenous insulin deficiency that will be rare in those non-insulin-treated. The largest study (Predicting Response to Incretin Based Agents [PRIBA]) demonstrated markedly reduced glycemic response to GLP-1RA in insulin-treated participants diagnosed with type 2 diabetes who had developed C-peptide in the range associated with type 1 diabetes and insulin requirement [5]. Research in people with insulin-treated type 1 diabetes has demonstrated a similar relationship, with markedly better HbA_{1c} response and less adverse outcomes, in those with very modest levels of retained C-peptide. In contrast, GRADE participants were non-insulin-treated, effectively excluding severe insulin deficiency. Consistent with GRADE, in those non-insulin-treated in PRIBA, we reported no relationship between HbA_{1c} response to GLP-1RA and markers of β-cell function (plasma C-peptide, UCPCR and HOMA2%B) [5]. Therefore, while GRADE provides further evidence that measures of β-cell function should not be used to guide the selection of GLP-1RA therapy in those non-insulin-treated, these findings are not contradictory to previous research suggesting the utility of C-peptide testing for this purpose in those with insulin-treated diabetes.

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Conflict of Interest. All authors declare that there are no relationships or activities that might bias, or be perceived to bias, their work.

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