Supplementary Appendix

Importance of insulin sensitivity and β-cell function as predictors of progression of type 2 diabetes in the GRADE Study

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Supplemental Table 1: Risk of reaching the primary and secondary outcomes relative to each insulin sensitivity or β-cell function measure within each treatment group are presented as hazard ratios (HRs). Overall higher insulin sensitivity and CP-responses were associated with a lower risk of primary and secondary outcomes. Treatment group differences (significant heterogeneity) was noted for the primary outcome with HOMA2-%S and the total C-peptide response.

	Overall[2]	Glimepiride[1]	Liraglutide[1]	Sitagliptin[1]	Heterogeneity p-value[1]	Overall p-value[2]	Pairwise p-values[3]
Primary Outcome							
Log HOMA2-%S		0.768 [0.663, 0.889]	0.831 [0.708, 0.977]	0.593 [0.512, 0.687]	0.005	N/A	G – L: 0.755 G – S: 0.037 L – S: 0.006
CPI	0.696 [0.650, 0.746]				0.106	<0.001	
Total C-peptide response		0.614 [0.548, 0.689]	0.692 [0.637, 0.752]	0.578 [0.516, 0.647]	0.025	N/A	G – L: 0.215 G – S: 0.730 L – S: 0.026
Secondary Outcome							
Log HOMA2-%S	0.628 [0.565, 0.698]				0.170	<0.001	
CPI	0.630 [0.579, 0.686]				0.973	<0.001	
Total C-peptide response	0.541 [0.498, 0.587]				0.053	<0.001	

Note: Results in this table are based on Cox regression models with the time-varying metabolic measure as a predictor in the model. All models for β-cell function (CPI, total C-peptide response) are adjusted for insulin sensitivity (HOMA2-%S) as a covariate.

[1] The heterogeneity p-value is from the test of treatment group differences in the association of insulin sensitivity or β-cell function with primary or secondary outcome. If there are significant treatment group differences, then the treatment-specific columns present the risk of outcome as a HR [95% CI] per unit increase in the insulin sensitivity or β-cell function index within that treatment group.

[2] Only if the test of treatment group differences is not significant, then the overall p-value is presented from the test of an overall association (i.e., across all treatment groups) of insulin sensitivity or β-cell function with primary or secondary outcome and the HR is presented in the "Overall" column. If the test of treatment group differences is significant, then the test of an overall association was not conducted, and "N/A" is presented for the overall p-value.

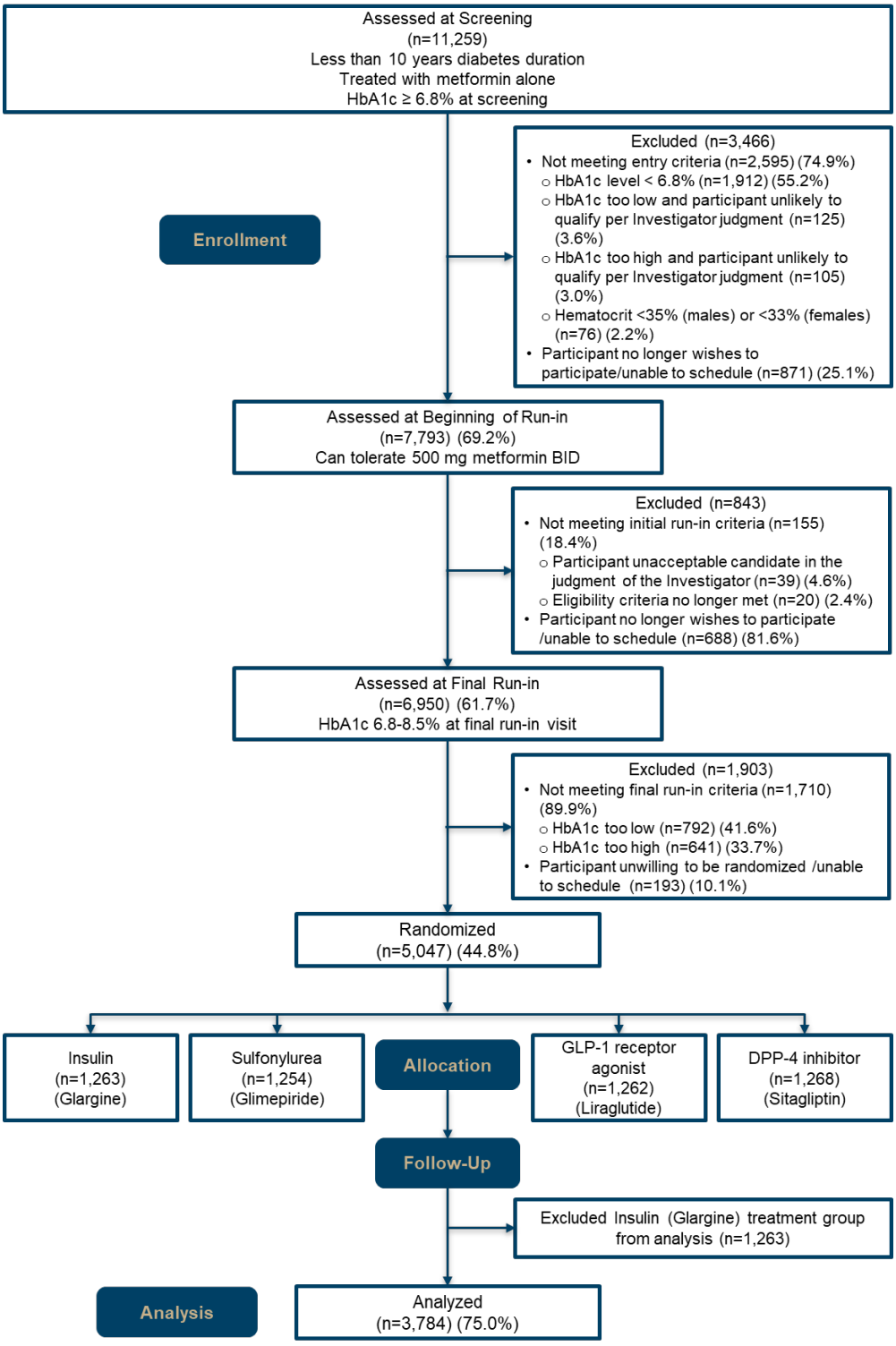
[3] If there are significant treatment group differences, then pairwise comparisons of the treatment groups are tested. "G – L" indicates the p-value testing the comparison of glimepiride vs. liraglutide. "G – S" indicates the p-value testing the comparison of glimepiride vs. sitagliptin. "L – S" indicates the p-value testing the comparison of liraglutide vs. sitagliptin. If the test of heterogeneity across treatment groups is not significant, then tests of pairwise comparisons were not conducted, and "N/A" is presented in the pairwise p-values column.

Supplemental Table 2: Subgroup analyses to assess whether the effect of each metabolic variable on reaching the primary and secondary outcome by treatment group varied by age, sex, BMI, race, ethnicity, and diabetes duration (p-values for 3-way interaction term among the metabolic variable, treatment group, and the subgroup factor)

	Age	Sex	BMI	Race	Ethnicity	Diabetes Duration
Primary Outcome						
HOMA2-%S	0.838	0.728	0.849	0.808	0.166	0.752
CPI	0.781	0.924	0.814	0.612	0.092	0.413
Total CP response	0.152	0.358	0.028	0.855	0.807	0.360
Secondary Outcome						
HOMA2-%S	0.925	0.089	0.349	0.955	0.366	0.602
CPI	0.607	0.110	0.467	0.427	0.168	0.232
Total CP response	0.073	0.454	0.563	0.746	0.948	0.674

Note: Results in this table are based on Cox regression models with interactions between the subgroup variable (age, sex, BMI, diabetes duration, race, ethnicity), treatment group and the time-varying metabolic measure on risk of reaching the primary or secondary outcome. All models for β-cell function (CPI, total C-peptide response) are adjusted for insulin sensitivity (HOMA2-%S) as a covariate. A significant p-value indicates that the three-way interaction between the subgroup variable, treatment group and the metabolic measure is significant, and therefore the effect of a unit increase in the insulin sensitivity or β-cell function index on the risk of the outcome within treatment groups differs from one level of the subgroup variable to the next (e.g., from one age group to the next).

Supplemental Figure 1: CONSORT Diagram



Supplemental Figure 2: The effect of baseline insulin sensitivity and C-peptide responses (CPI, total C-peptide response) by tertiles on time to reach secondary outcome is depicted by Kaplan-Meier plots for each treatment group (glimepiride (orange), liraglutide (blue), sitagliptin (red)). There were no significant treatment group differences in this association by Cox regression analysis (CP indices adjusted for HOMA2-%S).