

# Supplementary Appendix

Impact of Treatment on Health-Related Quality of Life in the Glycemia Reduction Approaches in Diabetes (GRADE) Study: A Comparative Effectiveness Randomized Clinical Trial

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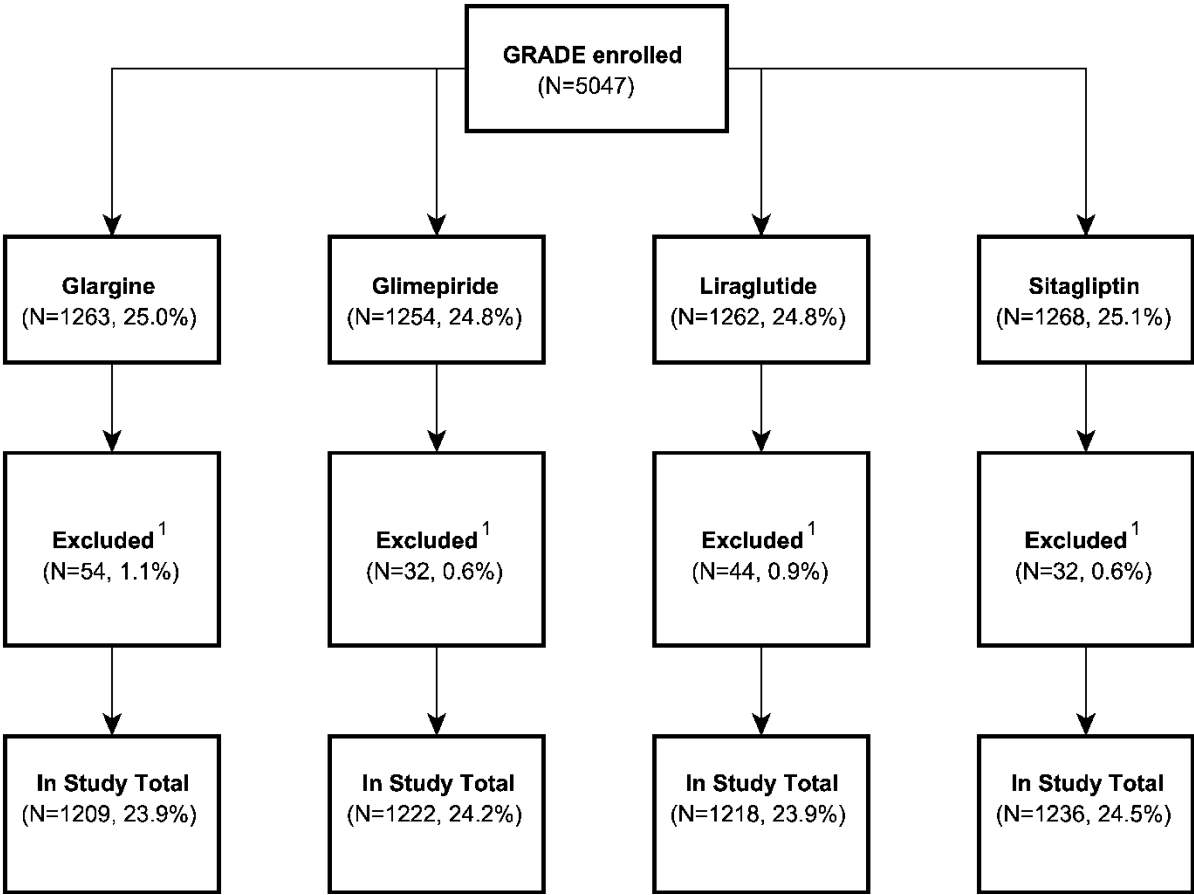
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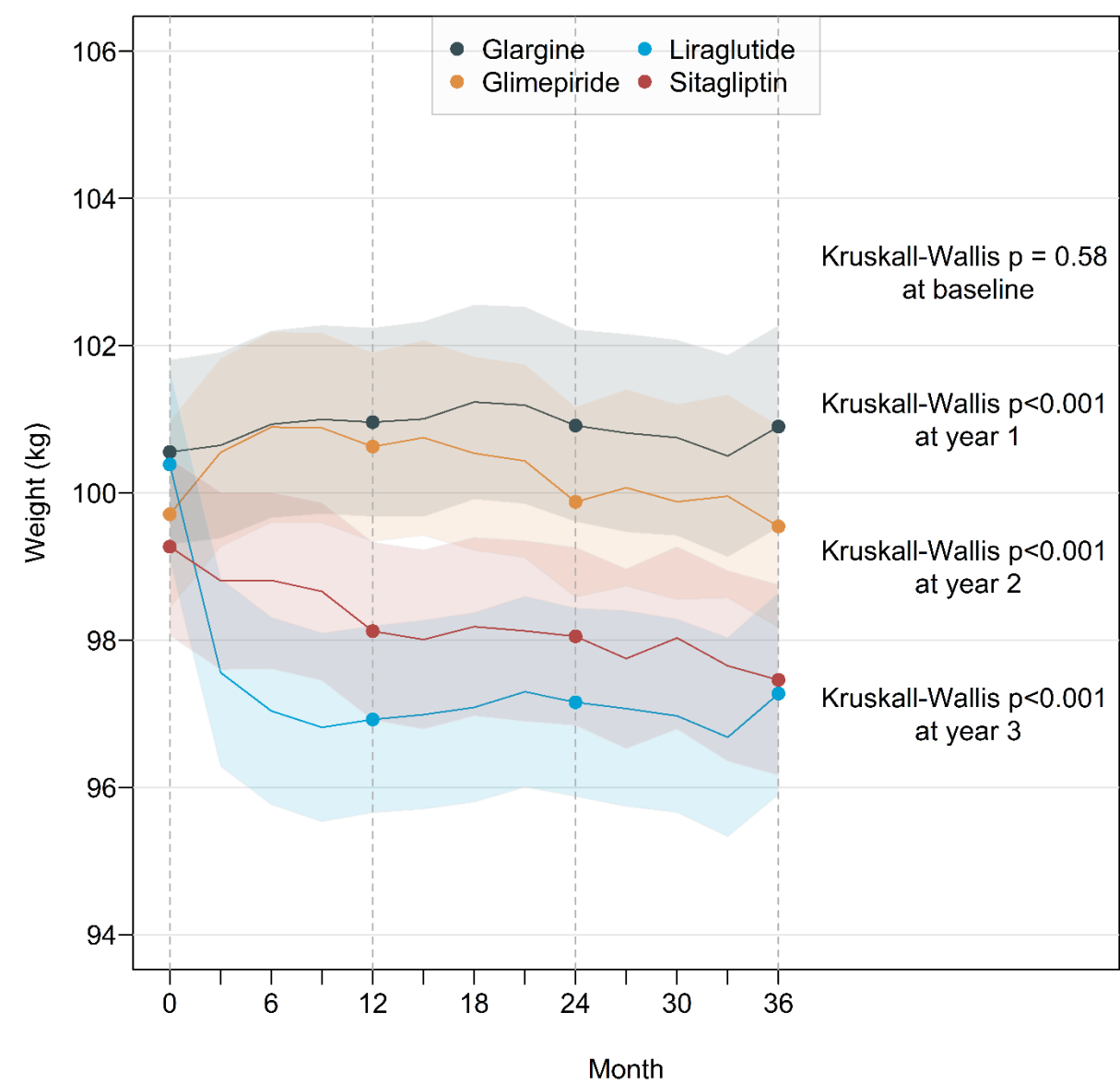
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**Figure S1:** Consort Diagram



<sup>1</sup> Excluded because participants had no post baseline QOL assessments

Figure S2: Plot of mean weight over time in study by treatment group



**Table S1:** Baseline characteristics of study population

	All	Glargine	Glimepiride	Liraglutide	Sitagliptin
<i>Demographics</i>					
N	4885	1209	1222	1218	1236
Age at baseline visit (years)	57.2 ±10.0	57.1 ±9.8	57.1 ±10.1	57.4 ±9.9	57.3 ±10.1
Age group (years)					
< 45	593 (12.1%)	142 (11.7%)	157 (12.8%)	150 (12.3%)	144 (11.7%)
45 - <60	2251 (46.1%)	578 (47.8%)	542 (44.4%)	544 (44.7%)	587 (47.5%)
60+	2041 (41.8%)	489 (40.4%)	523 (42.8%)	524 (43.0%)	505 (40.9%)
Female	1777 (36.4%)	435 (36.0%)	464 (38.0%)	417 (34.2%)	461 (37.3%)
Race					
Am Ind/Alaska Native	134 (2.7%)	31 (2.6%)	30 (2.5%)	39 (3.2%)	34 (2.8%)
Asian/Hawaiian/Pacific	203 (4.2%)	37 (3.1%)	53 (4.3%)	55 (4.5%)	58 (4.7%)
Black	957 (19.6%)	240 (19.9%)	262 (21.4%)	242 (19.9%)	213 (17.2%)
Other	370 (7.6%)	97 (8.0%)	88 (7.2%)	94 (7.7%)	91 (7.4%)
White	3221 (65.9%)	804 (66.5%)	789 (64.6%)	788 (64.7%)	840 (68.0%)
Ethnicity					
Non-Hispanic	3965 (81.7%)	994 (82.8%)	984 (81.4%)	994 (81.9%)	993 (80.9%)
Hispanic	886 (18.3%)	207 (17.2%)	225 (18.6%)	220 (18.1%)	234 (19.1%)
Education completed					
Less than high school	342 (7.0%)	87 (7.2%)	96 (7.9%)	74 (6.1%)	85 (6.9%)
High school/GED	999 (20.5%)	234 (19.4%)	248 (20.3%)	257 (21.1%)	260 (21.1%)
Some college	1405 (28.8%)	375 (31.0%)	342 (28.0%)	366 (30.0%)	322 (26.1%)
College	1309 (26.8%)	328 (27.1%)	317 (25.9%)	299 (24.5%)	365 (29.6%)
Graduate school	829 (17.0%)	185 (15.3%)	219 (17.9%)	222 (18.2%)	203 (16.4%)
<i>Diabetes</i>					
BMI (kg/m <sup>2</sup> )	34.3 ± 6.8	34.4 ± 6.8	34.3 ± 6.9	34.3 ± 6.7	34.1 ± 6.7
Duration of diabetes (years)	4.2 ± 2.7	4.2 ± 2.7	4.3 ± 2.8	4.2 ± 2.7	4.2 ± 2.7
HbA1c (%)	7.5 ± 0.5	7.5 ± 0.5	7.5 ± 0.5	7.5 ± 0.5	7.5 ± 0.5
log Fasting insulin (mU/L)	2.9 ± 0.6	3.0 ± 0.6	2.9 ± 0.7	2.8 ± 0.6	2.9 ± 0.6
Insulinogenic Index (μU/mg)	34.6 ± 28.6	37.1 ± 29.7	33.0 ± 27.6	34.3 ± 28.9	34.5 ± 28.3
<i>Quality of Life</i>					
MCS (%)*	52.5 ± 9.0	52.5 ± 8.9	52.6 ± 8.9	52.4 ± 9.1	52.3 ± 8.9
PCS (%)*	46.1 ± 9.5	46.1 ± 9.5	46.4 ± 9.4	45.8 ± 9.9	46.0 ± 9.3
QWB Score*	0.67 ± 0.14	0.67 ± 0.14	0.67 ± 0.13	0.67 ± 0.14	0.67 ± 0.14
Bodily pain (%)	72.9 ± 24.1	73.0 ± 23.7	73.4 ± 23.7	72.3 ± 24.8	72.7 ± 23.9
General health (%)	63.7 ± 18.8	63.8 ± 18.7	64.4 ± 18.5	63.6 ± 19.1	62.9 ± 18.7
Vitality (%)	59.2 ± 20.9	58.6 ± 20.9	59.6 ± 20.8	59.5 ± 21.5	59.1 ± 20.6
Mental health (%)	79.2 ± 16.4	79.3 ± 16.2	79.5 ± 16.2	79.1 ± 16.7	78.7 ± 16.6
Physical functioning (%)	76.4 ± 24.8	76.7 ± 24.7	76.8 ± 24.3	75.9 ± 25.5	76.2 ± 24.8
Role emotional (%)	83.4 ± 31.8	84.0 ± 31.0	83.6 ± 31.4	82.6 ± 32.8	83.2 ± 31.9
Role physical (%)	78.1 ± 35.3	78.4 ± 35.1	79.1 ± 34.6	76.6 ± 36.2	78.1 ± 35.2
Social functioning (%)	84.6 ± 21.7	84.9 ± 21.2	85.6 ± 21.5	83.5 ± 22.1	84.6 ± 22.1

PCS = Physical Component Summary score derived from the 8 subscales of the SF-36 questionnaire

MCS = Mental Component Summary score derived from the 8 subscales of the SF-36 questionnaire

QWB = Summary score from the Quality of Well-Being self-administered questionnaire

GED = General equivalency diploma

\*The QWB summary score (QWB-SA Form) ranges between 0 and 1 with higher scores indicating better quality of life. The MCS and PCS summary scores (SF-36 Form) both range between 0-100%, with higher scores indicating better function.

**Table S2:** Mean change from baseline for all component outcomes of the SF-36

Time	Outcome	Glargine	Glimepiride	Liraglutide	Sitagliptin
Year 1	Bodily pain (%)	0.92 (-0.14,1.97)	1.43 (0.37,2.48) <sup>‡</sup>	3.17 (2.12,4.22) <sup>§</sup>	2.53 (1.48,3.58) <sup>§</sup>
(N=4820)	General health (%)	2.31 (1.53,3.10) <sup>§</sup>	2.08 (1.30,2.87) <sup>§</sup>	3.59 (2.81,4.37) <sup>§</sup>	2.15 (1.37,2.93) <sup>§</sup>
	Vitality (%)	1.55 (0.67,2.42) <sup>§</sup>	1.60 (0.73,2.48) <sup>§</sup>	2.90 (2.02,3.77) <sup>§</sup>	1.58 (0.71,2.45) <sup>§</sup>
	Mental health (%)	1.19 (0.45,1.93) <sup>‡</sup>	1.33 (0.60,2.07) <sup>§</sup>	1.77 (1.04,2.51) <sup>§</sup>	1.68 (0.95,2.42) <sup>§</sup>
	Physical functioning (%)	1.78 (0.68,2.88) <sup>‡</sup>	1.34 (0.24,2.44) <sup>‡</sup>	2.65 (1.54,3.75) <sup>§</sup>	1.92 (0.82,3.02) <sup>§</sup>
	Role emotional (%)	1.65 (0.08,3.22) <sup>‡</sup>	1.43 (-0.13,3.00)	1.17 (-0.40,2.73)	2.10 (0.54,3.66) <sup>‡</sup>
	Role physical (%)	1.09 (-0.58,2.76)	1.64 (-0.03,3.31)	3.72 (2.05,5.39) <sup>§</sup>	2.20 (0.54,3.86) <sup>‡</sup>
	Social functioning (%)	0.65 (-0.40,1.71)	0.21 (-0.84,1.27)	0.66 (-0.39,1.72)	1.08 (0.03,2.13) <sup>‡</sup>
Year 2	Bodily pain (%)	0.34 (-0.79,1.47)	1.55 (0.43,2.67) <sup>‡</sup>	1.53 (0.41,2.65) <sup>‡</sup>	1.35 (0.23,2.46) <sup>‡</sup>
(N=4726)	General health (%)	1.93 (1.12,2.74) <sup>§</sup>	1.84 (1.04,2.64) <sup>§</sup>	2.89 (2.09,3.69) <sup>§</sup>	2.42 (1.62,3.22) <sup>§</sup>
	Vitality (%)	2.02 (1.09,2.94) <sup>§</sup>	2.11 (1.20,3.03) <sup>§</sup>	2.90 (1.99,3.81) <sup>§</sup>	2.48 (1.57,3.40) <sup>§</sup>
	Mental health (%)	1.72 (0.95,2.48) <sup>§</sup>	1.91 (1.15,2.67) <sup>§</sup>	1.63 (0.87,2.39) <sup>§</sup>	1.93 (1.17,2.69) <sup>§</sup>
	Physical functioning (%)	0.11 (-1.08,1.29)	1.03 (-0.14,2.21)	1.86 (0.68,3.03) <sup>‡</sup>	1.78 (0.61,2.96) <sup>‡</sup>
	Role emotional (%)	0.01 (-1.63,1.66)	1.63 (-0.01,3.26)	0.47 (-1.16,2.10)	0.90 (-0.73,2.54)
	Role physical (%)	-0.25 (-2.03,1.53)	1.10 (-0.67,2.86)	-0.08 (-1.85,1.68)	0.35 (-1.41,2.11)
	Social functioning (%)	0.40 (-0.69,1.50)	1.01 (-0.07,2.10)	-0.32 (-1.41,0.76)	1.48 (0.39,2.56) <sup>‡</sup>
Year 3	Bodily pain (%)	0.81 (-0.33,1.94)	2.13 (1.00,3.26) <sup>§</sup>	1.88 (0.75,3.01) <sup>‡</sup>	0.88 (-0.25,2.00)
(N=4604)	General health (%)	0.62 (-0.23,1.46)	0.75 (-0.09,1.59)	1.74 (0.91,2.58) <sup>§</sup>	1.64 (0.81,2.48) <sup>§</sup>
	Vitality (%)	1.47 (0.51,2.44) <sup>‡</sup>	1.89 (0.93,2.84) <sup>§</sup>	1.79 (0.84,2.74) <sup>§</sup>	1.92 (0.97,2.88) <sup>§</sup>
	Mental health (%)	1.38 (0.58,2.17) <sup>§</sup>	1.74 (0.95,2.53) <sup>§</sup>	1.31 (0.52,2.09) <sup>‡</sup>	1.94 (1.16,2.73) <sup>§</sup>
	Physical functioning (%)	0.33 (-0.86,1.52)	1.05 (-0.14,2.23)	1.17 (-0.01,2.36)	0.94 (-0.24,2.12)
	Role emotional (%)	-0.06 (-1.76,1.64)	0.64 (-1.05,2.33)	0.99 (-0.69,2.67)	0.05 (-1.63,1.73)
	Role physical (%)	-0.92 (-2.76,0.92)	0.94 (-0.89,2.77)	-0.14 (-1.96,1.69)	0.38 (-1.44,2.20)
	Social functioning (%)	-0.39 (-1.54,0.76)	0.96 (-0.18,2.10)	-0.11 (-1.25,1.03)	-0.02 (-1.16,1.11)

Statistics reported in the table cells are mean change from baseline (95% confidence interval).

Superscripts in each cell of the table give the unadjusted significance level of the test of the mean change equal to zero (†:  $p < 0.05$ , ‡:  $p < 0.01$ , §:  $p < 0.001$ ).

Note that ANOVA tests of any group differences were performed for each outcome at each timepoint and none were significantly different from zero after FDR adjusting for 8 tests at each timepoint.



**Table S3:** Number of participants initiating rescue insulin by study year.

<b>Landmark Time point</b>	<b>Glargine (N=1263)</b>	<b>Glimepiride (N=1254)</b>	<b>Liraglutide (N=1262)</b>	<b>Sitagliptin (N=1268)</b>
<i>1-year</i>				
Participants	1199	1207	1208	1167
No. Initiating Insulin (%) <sup>*</sup>	10 (0.8%)	16 (1.3%)	29 (2.4%)	53 (4.5%)
Time (yrs) <sup>†</sup>	0.97	0.89	0.76	0.79
<i>2-year</i>				
Participants	1171	1190	1192	1193
No. Initiating Insulin (%)	70 (6.0%)	138 (11.6%)	132 (11.1%)	249 (20.9%)
Time (yrs)	1.41	1.41	1.30	1.29
<i>3-year</i>				
Participants	1156	1166	1165	1171
No. Initiating Insulin (%)	119 (10.3%)	235 (20.2%)	215 (18.5%)	363 (31.0%)
Time (yrs)	1.87	1.89	1.77	1.67

<sup>\*</sup>Denominator is the number of participants who attended the landmark visit

Numerator is the number of participants initiating rescue insulin prior to the landmark time point

<sup>†</sup>Mean time in years from randomization until rescue insulin initiation for those initiating rescue insulin prior to the landmark time point

**Table S4:** Mediation Analysis of 1-year PCS change scores

Mediator Variable	Treatment Effects	
	Liraglutide vs Glargine	Liraglutide vs Glimepiride
HbA1c %	5.0 (-0.4, 10.4)	5.8 (-0.3, 12.0)
Weight	52.8 (14.7, 90.9)	56.7 (15.9, 97.5)
Non-Severe Hypoglycemia	1.0 (-1.8, 3.9)	4.6 (-3.7, 12.9)
Gastrointestinal Symptoms	-6.8 (-16.9, 3.4)	-12.7 (-25.7, 0.3)
Number of SAEs	5.8 (-2.3, 13.8)	8.2 (-0.7, 17.2)

The percent of the treatment effects mediated by each mediator is presented with 95% confidence intervals in parentheses.

Mediation is tested for the LvI and LvG comparisons because these treatment comparisons were significantly different in the ITT analysis (Table 1)

**Table S5:** Subgroup analysis of the PCS change at annual visits by baseline body mass index (BMI) tertiles\*

Time point (p) <sup>†</sup>	BMI (kg/m <sup>2</sup> )	Change in PCS from baseline			
		Glargine (I)	Glimepiride (G)	Liraglutide (L)	Sitagliptin (S)
<b>Year 1</b> (p=0.03)	18.2 to 30.7	0.01	0.71	0.91	0.77
	30.8 to 36.2	0.96	0.82	0.96	1.08
	<b>36.3 to 74.3<sup>*</sup></b>	<b>0.92</b>	<b>0.32</b>	<b>2.75</b>	<b>0.70</b>
<b>Year 2</b> (p=0.96)	18.2 to 30.7	-0.41	0.41	0.60	0.36
	30.8 to 36.2	0.03	0.49	0.69	0.74
	36.3 to 74.3	0.72	0.28	0.99	0.64
<b>Year 3</b> (p=0.87)	18.2 to 30.7	-0.40	0.57	0.31	0.44
	30.8 to 36.2	-0.08	0.63	0.39	0.33
	36.3 to 74.3	0.59	0.02	0.98	0.30

\*Bolded rows indicate that there are significant pairwise treatment differences between groups.

<sup>†</sup>p = p-value from the 6 degree of freedom chi-square test of global homogeneity after adjustment for all 11 subgroups tested using the false discovery rate (FDR) method of adjustment