

Supplementary Appendix

Comparative effects of randomized second-line therapy for type 2 diabetes on a composite outcome incorporating glycemic control, body weight, and hypoglycemia: An analysis of the Glycemia Reduction Approaches in Type 2 Diabetes - A Comparative Effectiveness (GRADE) Study

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Supplementary Table 1. Baseline table of the GRADE participant cohort (n=5,047) by treatment group

	All	Glargine	Glimepiride	Liraglutide	Sitagliptin
N	5,047	1,263	1,254	1,262	1,268
<i>Demographics</i>					
Age (years)	57.7 [50.3, 64.7]	57.3 [50.0, 64.2]	57.7 [50.3, 64.7]	58.1 [50.7, 64.8]	57.3 [50.3, 65.0]
Female	1,837 (36.4%)	452 (35.8%)	476 (38.0%)	439 (34.8%)	470 (37.1%)
Race					
Am Ind/Alaska Native	137 (2.7%)	33 (2.6%)	30 (2.4%)	40 (3.2%)	34 (2.7%)
Asian	182 (3.6%)	34 (2.7%)	47 (3.7%)	47 (3.7%)	54 (4.3%)
Hawaiian/Pacific Isl	28 (0.6%)	5 (0.4%)	7 (0.6%)	8 (0.6%)	8 (0.6%)
Black or African-American	1,000 (19.8%)	253 (20.0%)	271 (21.6%)	251 (19.9%)	225 (17.7%)
White	3,314 (65.7%)	837 (66.3%)	808 (64.4%)	815 (64.6%)	854 (67.4%)
Other/multiple	319 (6.3%)	82 (6.5%)	71 (5.7%)	82 (6.5%)	84 (6.6%)
Unknown/not reported	67 (1.3%)	19 (1.5%)	20 (1.6%)	19 (1.5%)	9 (0.7%)
Hispanic/Latino	929 (18.4%)	220 (17.4%)	234 (18.7%)	234 (18.5%)	241 (19.0%)
Education					
< HS	364 (7.2%)	92 (7.3%)	99 (7.9%)	84 (6.7%)	89 (7.0%)
HS Graduate	1,039 (20.6%)	248 (19.6%)	255 (20.3%)	267 (21.2%)	269 (21.2%)
Some college	1,463 (29.0%)	397 (31.4%)	354 (28.2%)	378 (30.0%)	334 (26.4%)
College degree or greater	2,180 (43.2%)	526 (41.6%)	546 (43.5%)	533 (42.2%)	575 (45.4%)
Current Smoker	695 (13.8%)	158 (12.5%)	183 (14.6%)	170 (13.5%)	184 (14.5%)
Alcohol Use					
Never	1,679 (33.3%)	416 (32.9%)	410 (32.7%)	436 (34.5%)	417 (32.9%)
Occasionally	2,619 (51.9%)	670 (53.0%)	678 (54.1%)	627 (49.7%)	644 (50.8%)
Weekly	563 (11.2%)	142 (11.2%)	129 (10.3%)	148 (11.7%)	144 (11.4%)
Daily	186 (3.7%)	35 (2.8%)	37 (3.0%)	51 (4.0%)	63 (5.0%)
<i>Diabetes Parameters</i>					
Duration (years)	3.8 [1.9, 6.3]	3.8 [1.9, 6.2]	3.9 [1.9, 6.6]	3.9 [1.8, 6.4]	3.8 [1.9, 6.2]
HbA1c (%)	7.4 [7.1, 7.8]	7.4 [7.1, 7.9]	7.4 [7.1, 7.8]	7.4 [7.1, 7.9]	7.4 [7.1, 7.9]
HbA1c (mmol/mol)	57.4 [54.1, 61.8]	57.4 [54.1, 62.8]	57.4 [54.1, 61.8]	57.4 [54.1, 62.8]	57.4 [54.1, 62.8]
<i>Anthropometrics</i>					
Weight (kg)	98.0 [84.4, 112.3]	98.4 [85.7, 112.6]	97.7 [83.5, 112.4]	98.1 [84.5, 113.2]	98.1 [84.1, 111.4]
BMI (kg/m ²)	33.3 [29.5, 38.0]	33.4 [29.5, 38.1]	33.1 [29.3, 38.4]	33.6 [29.7, 37.8]	33.1 [29.1, 37.7]

Waist (cm)	111.3 [101.2, 121.8]	111.3 [101.3, 121.8]	111.5 [100.5, 122.5]	111.2 [101.5, 122.2]	111.3 [101.2, 121.0]
<i>Blood Pressure (BP)</i>					
Systolic BP (mmHg)	127.5 [118.0, 137.5]	128.0 [118.0, 137.5]	127.5 [118.5, 138.0]	127.0 [118.0, 137.5]	127.5 [117.5, 137.5]
Diastolic BP (mmHg)	77.0 [70.5, 83.5]	77.0 [70.5, 84.0]	77.0 [70.5, 83.0]	77.5 [71.0, 84.0]	77.0 [70.5, 83.5]
ACEi/ARB use	2,933 (58.1%)	724 (57.3%)	742 (59.2%)	738 (58.5%)	729 (57.5%)
Any antihypertensive use	3,496 (69.3%)	882 (69.8%)	865 (69.0%)	890 (70.5%)	859 (67.7%)
Hypertension History	3,339 (66.2%)	845 (66.9%)	834 (66.5%)	843 (66.8%)	817 (64.4%)
<i>Lipids</i>					
Total Cholesterol (mg/dL)	160.0 [137.0, 186.0]	162.0 [137.0, 187.0]	158.0 [136.0, 186.0]	161.0 [137.8, 187.0]	160.0 [136.0, 185.0]
HDL (mg/dL)	41.0 [36.0, 49.0]	41.0 [36.0, 48.0]	42.0 [36.0, 49.0]	41.0 [36.0, 49.0]	41.0 [36.0, 49.0]
LDL (mg/dL)	87.0 [68.0, 109.0]	88.0 [69.0, 112.0]	86.0 [67.0, 107.0]	89.0 [68.0, 111.0]	86.0 [68.0, 107.0]
Triglycerides (mg/dL)	87.0 [68.0, 109.0]	88.0 [69.0, 112.0]	86.0 [67.0, 107.0]	89.0 [68.0, 111.0]	86.0 [68.0, 107.0]
Lipid lowering medication	3,321 (65.8%)	825 (65.3%)	857 (68.3%)	795 (63.0%)	844 (66.6%)
<i>DTSQ with metformin only</i>					
DTSQ summary score	33.0 [29.0, 36.0]	33.0 [29.0, 36.0]	33.0 [29.5, 36.0]	33.0 [29.0, 36.0]	33.0 [30.0, 36.0]

Continuous variables (e.g., HbA1c) are described using median (with 1st and 3rd quartiles), while categorical variables (e.g., sex) are described using as counts (with percent).

Supplementary Table 2. The percent change¹ in treatment effect on the risk of the composite outcome after adjustment for potential mediators.

Mediators	Pairwise Treatment Group Comparisons					
	Glimepiride vs Glargine	Liraglutide vs Glargine	Sitagliptin vs Glargine	Liraglutide vs Glimepiride	Sitagliptin vs Glimepiride	Sitagliptin vs Liraglutide
Metformin Adherence	0.71 (-1.47, 2.89)	-0.97 (-3.00, 1.06)	-5.52 (-18.97, 7.92)	-0.29 (-1.22, 0.63)	-0.94 (-2.64, 0.75)	0.71 (-1.51, 2.93)
Randomized Medication Adherence	-0.43 (-1.76, 0.91)	0.96 (-0.16, 2.08)	-3.91 (-13.01, 5.18)	0.35 (-0.06, 0.77)	-1.07 (-2.34, 0.20)	3.53 (-0.42, 7.48)
Smoking status	1.00 (-1.11, 3.11)	-0.77 (-2.37, 0.83)	1.50 (-2.42, 5.42)	-0.12 (-0.48, 0.23)	0.86 (-0.36, 2.08)	-2.22 (-6.18, 1.74)
Alcohol use	1.23 (-1.43, 3.91)	0.22 (-0.57, 1.01)	4.68 (-5.79, 15.16)	0.42 (-0.37, 1.22)	1.72 (-0.66, 4.11)	-1.74 (-4.33, 0.85)

¹The percent change in the treatment effect (unadjusted for the mediator – adjusted for the mediator) with Holm corrected 95% confidence intervals in parentheses. Note, negative change indicates that the magnitude of the treatment effect was increased by including the mediator in the model. Asterisk superscripts indicate the p-value for the test of percent change equal to zero. The levels of significance are: *: p<0.05, **: p<0.01, ***: p<0.001. The p-values are Holm corrected for 6- pairwise treatment group comparisons. If no asterisk superscripts appear then the percent change in the treatment effect is not significantly different from zero.

Supplementary Table 3. Treatment group comparisons of outcomes by rescue insulin status (addition of mealtime insulin for group randomized to glargine and addition of glargine for those randomized to other therapies) among participants who initiated rescue insulin at some point during follow-up (n=1577).

Outcomes ¹	Treatment Group			
	Glargine	Glimepiride	Liraglutide	Sitagliptin
HbA1c %				
<i>Number of participants⁵</i>	222	411	399	545
<i>Mean (SE)⁴</i>				
Before insulin	8.30 (0.06)	8.10 (0.05)	8.12 (0.05)	8.23 (0.04)
After insulin	7.89 (0.07)	7.55 (0.05)	7.37 (0.06)	7.32 (0.05)
Difference (before – after)	0.41 (0.07) ^{***}	0.56 (0.05) ^{***}	0.75 (0.06) ^{***}	0.91 (0.05) ^{***}
Difference (CI) pairwise treatment after rescue insulin initiated				
vs. Glimepiride	0.35 (0.13, 0.57) ^{***}			
vs. Liraglutide	0.52 (0.28, 0.76) ^{***}	0.17 (0.01, 0.34) [*]		
vs. Sitagliptin	0.58 (0.35, 0.81) ^{***}	0.23 (0.07, 0.39) ^{**}	0.06 (-0.09, 0.20)	
Weight gain ≥ 5%				
<i>Number of participants⁵</i>	222	411	398	544
<i>Number of cases (%)</i>				
Before rescue insulin	121 (54.5%)	187 (45.5%)	82 (20.6%)	123 (22.6%)
After rescue insulin	31 (14.0%)	53 (12.9%)	79 (19.9%)	129 (23.7%)
<i>Patient years²</i>				
Before rescue insulin	426.32	831.94	1012.82	1173.87
After rescue insulin	184.44	411.84	593.44	813.69
<i>Event Rate/100yrs(SE)</i>				
Before rescue insulin	28.4 (2.6)	22.5 (1.8)	8.1 (0.8)	10.5 (1.0)
After rescue insulin	16.8 (3.1)	12.9 (1.8)	13.3 (1.6)	15.9 (1.5)
<i>RR (SE) before vs after rescue insulin³</i>	1.69 (0.35) [*]	1.75 (0.29) ^{**}	0.61 (0.10) ^{**}	0.66 (0.09) ^{**}
RR (SE) pairwise treatment comparison after rescue insulin initiated				
vs. Glimepiride	1.31 (0.70, 2.42)			
vs. Liraglutide	1.26 (0.71, 2.25)	0.97 (0.59, 1.57)		
vs. Sitagliptin	1.06 (0.61, 1.83)	0.81 (0.52, 1.27)	0.84 (0.57, 1.24)	
Any Hypoglycemia				
<i>Number of participants⁵</i>	221	409	392	542
<i>Number of cases (%)</i>				
Before rescue insulin	64 (29.0%)	150 (36.7%)	57 (14.5%)	57 (10.5%)
After rescue insulin	55 (24.9%)	118 (28.9%)	91 (23.2%)	145 (26.8%)
<i>Patient years²</i>				
Before rescue insulin	570.86	905.66	1014.84	1260.90
After rescue insulin	303.42	514.65	711.37	1134.18
<i>Event Rate/100yrs(SE)</i>				
Before rescue insulin	11.2 (1.3)	16.6 (1.3)	5.6 (0.7)	4.5 (0.6)
After rescue insulin	18.1 (2.5)	22.9 (2.2)	12.8 (1.3)	12.8 (1.1)
<i>RR (SE) before vs after insulin³</i>	0.62 (0.11) [*]	0.72 (0.09) [*]	0.44 (0.07) ^{***}	0.35 (0.06) ^{***}
RR (CI) pairwise treatment after rescue insulin initiated ⁴				

vs. Glimepiride	0.79 (0.51, 1.23)			
vs. Liraglutide	1.42 (0.90, 2.24)	1.79 (1.23, 2.62)***		
vs. Sitagliptin	1.42 (0.93, 2.17)	1.79 (1.28, 2.52)***	1.00 (0.70, 1.43)	

¹The weight and hypoglycemia components of the composite outcome are presented along with mean HbA1c. The HbA1c component of the composite outcome (time to A1c > 7.5%, confirmed) cannot be included in this analysis because insulin status is based on it.

²Patient years for the weight and hypoglycemia outcomes represent the total follow-up time at risk for the specific outcome.

³RR is the rate ratio (SE) in the period before vs after rescue insulin.

⁴RR is the rate ratio (95% CI) between pairwise treatment groups (column group vs row group) in the period after rescue insulin is initiated.

⁵The number of participants vary depending on availability of post-randomization data for the specific outcome.

The following superscripts are used to denote statistical significance: * $0.01 < p \leq 0.05$, ** $0.001 < p \leq 0.01$, *** $p \leq 0.001$. The p-values from the 4 tests (one for each of the four treatment groups) of the rate ratios before vs after rescue insulin are Holm adjusted for 4 tests. The p-values from the tests of pairwise treatment group rate ratios in the period after initiation of rescue insulin are Holm adjusted for 6 pairwise comparisons.

Supplementary Table 4. Mean and standard deviation of DTSQ Scores at 12 months after randomization separately by treatment group, along with pairwise group comparisons.

	Treatment Group			
	Glargine	Glimepiride	Liraglutide	Sitagliptin
Number of Participants	1188	1197	1203	1205
DTSQ Score	32.69 (0.11)	32.93 (0.11)	33.15 (0.11)	33.05 (0.11)
Pairwise Comparisons ¹				
vs. Glimepiride	-0.25 (-0.64, 0.15)			
vs. Liraglutide	-0.46 (-0.86, -0.06)*	-0.21 (-0.61, 0.18)		
vs. Sitagliptin	-0.37 (-0.76, 0.03)	-0.12 (-0.52, 0.28)	0.09 (-0.30, 0.49)	

Results based on a linear model of DTSQ at 12 months adjusted for baseline DTSQ.

¹The following superscripts are used to denote statistical significance for pairwise comparisons: * $0.01 < p \leq 0.05$;

** $0.001 < p \leq 0.01$; *** $p \leq 0.001$. Note that p-values and 95% confidence intervals are Holm adjusted for the 6 pairwise treatment comparisons of mean DTSQ score at 1-year.

Supplementary Table 5. DTSQ scores for participants with outcomes present vs. not by month 12 from randomization.

	Number of participants (n = 4793)	DTSQ Score Mean (SE)	Difference (95% CI)
Composite Outcome			
Yes	1186	32.52 (0.11)	Yes - No
No	3607	33.10 (0.06)	-0.59 (-0.83, -0.34) ^{***}
HbA1c >7.5%			
Yes	518	31.96 (0.16)	Yes - No
No	4275	33.08 (0.06)	-1.12 (-1.45, -0.78) ^{***}
Weight gain ≥ 5%			
Yes	523	32.82 (0.16)	Yes - No
No	4270	32.97 (0.06)	-0.15 (-0.49, 0.19)
Hypoglycemia			
Yes	301	32.90 (0.21)	Yes - No
No	4492	32.96 (0.05)	-0.06 (-0.50, 0.37)

The following superscripts are used to denote statistical significance: * $0.01 < p \leq 0.05$; ** $0.001 < p \leq 0.01$; *** $p \leq 0.001$.

Means (SE) are estimated from a linear model of DTSQ at 12 months adjusted for treatment group and baseline DTSQ score. The exposure variable is an indicator (no vs yes) for having reached the various outcomes prior to 1-year post-randomization.