

Supplementary Appendix

Differential Effects of Type 2 Diabetes Treatment Regimen on Diabetes Distress and Depressive Symptoms in GRADE: A Randomized Clinical Trial

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eAppendix 1. GRADE Research Group (April 30, 2021)

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eTable 1. Number of participants with primary EDS outcome data at each visit during study follow-up.

Visit	Baseline	Month 6	Month 12	Month 18	Month 24	Month 30	Month 36
Number	1,739	1,657	1,648	1,559	1,613	1,507	1,536

eTable 2. Differences in diabetes distress and depressive symptoms at one year from baseline across all treatment groups.

	Difference*	LL	UL	p-value
Diabetes Distress	-0.24	-0.28	-0.21	<0.0001
Depressive Symptoms	-0.67	-0.82	-0.51	<0.0001

*Difference in means at one year.

Note: Significant p-values are bolded

eTable3. Differences in diabetes distress and depressive symptoms over the entire 3-year follow-up between insulin glargine vs. the other three groups combined, or between Liraglutide vs. Glargine and between Liraglutide vs. Glimepiride and Sitagliptin combined.

	Glargine vs. the Other Three Groups Combined				Liraglutide vs. Glargine				Liraglutide vs. Glimepiride and Sitagliptin Combined			
	Difference*	LL	UL	p-value	Difference*	LL	UL	p-value	Difference*	LL	UL	p-value
A. Diabetes Distress												
Diabetes Distress Primary	-0.047	-0.098	0.005	0.077	0.023	-0.039	0.084	0.467	-0.041	-0.097	0.014	0.144
Emotional Distress Subscale	-0.031	-0.084	0.023	0.262	0.019	-0.046	0.085	0.560	-0.022	-0.082	0.038	0.476
Regimen Related Distress Subscale	-0.062	-0.122	-0.002	0.042	0.026	-0.045	0.097	0.472	-0.060	-0.124	0.003	0.063
Physician Related Distress Subscale	-0.061	-0.114	-0.008	0.023	0.039	-0.023	0.100	0.217	-0.037	-0.093	0.019	0.197
Interpersonal Distress Subscale	-0.002	-0.066	0.063	0.960	-0.063	-0.136	0.010	0.090	-0.101	-0.167	-0.036	0.003
B. Depressive Symptoms												
Depressive Symptoms Primary	-0.111	-0.350	0.128	0.364	0.245	-0.048	0.538	0.101	0.188	-0.064	0.439	0.144
Somatic Symptoms Score	-0.018	-0.050	0.015	0.278	0.041	0.001	0.080	0.044	0.032	-0.003	0.066	0.071
Cognitive-Affective Symptoms Score	-0.007	-0.041	0.027	0.690	0.014	-0.027	0.056	0.505	0.010	-0.025	0.045	0.576

*Difference in means over the entire follow-up

Note: Significant p-values are bolded.

eTable 4. Pairwise differences in diabetes distress (panel A) and depressive symptoms (panel B) among the treatment groups at one year from baseline or over the entire follow-up.

	Comparisons at One Year From Baseline			Comparisons Over the Entire Follow-Up		
	Difference*	SE	p-value	Difference*	SE	p-value
A. Diabetes Distress Primary						
Glimepiride vs. Glargine	0.151	0.043	0.003	0.069	0.034	0.264
Liraglutide vs. Glargine	0.036	0.040	0.418	0.020	0.032	0.634
Sitagliptin vs. Glargine	0.116	0.039	0.010	0.052	0.033	0.300
Glimepiride vs. Liraglutide	0.115	0.044	0.019	0.049	0.034	0.300
Sitagliptin vs. Liraglutide	0.080	0.041	0.077	0.032	0.033	0.494
Glimepiride vs. Sitagliptin	0.036	0.044	0.418	0.017	0.036	0.634
B. Depressive Symptoms Primary						
Glimepiride vs. GlargineYr1	0.019	0.192	0.920	-0.017	0.151	0.909
Liraglutide vs. GlargineYr1	0.293	0.205	0.458	0.236	0.150	0.346
Sitagliptin vs. GlargineYr1	0.181	0.190	0.539	0.110	0.147	0.546
Glimepiride vs. LiraglutideYr1	-0.273	0.189	0.458	-0.253	0.151	0.346
Sitagliptin vs. LiraglutideYr1	-0.112	0.186	0.656	-0.126	0.146	0.546
Glimepiride vs. SitagliptinYr1	-0.161	0.176	0.539	-0.127	0.150	0.546

*Difference in means

SE=standard error

Note: p-values are adjusted for the six pairwise comparisons using the Holm procedure; significant values are bolded.

eTable 5. Differences in diabetes distress and depressive symptoms between participants in the basal insulin glargine group vs. the other three groups combined without and with adjustment for potential mediators.

	Diabetes Distress Primary				PHQ-8 Total			
	Difference*	LL	UL	p-value	Difference*	LL	UL	p-value
No Mediator	-0.101	-0.164	-0.037	0.002	-0.165	-	0.158	0.316
Mediator								
DTSQ	-0.114	-0.177	-0.051	<0.001	-0.221	-	0.102	0.179
Side Effects†	-0.100	-0.163	-0.037	0.002	-0.145	-	0.176	0.377
Rapid Acting Insulin Aspart	-0.095	-0.159	-0.032	0.003	-0.151	-	0.167	0.353
Hypoglycemia	-0.101	-0.164	-0.038	0.002	-0.169	-	0.153	0.303
BMI	-0.103	-0.165	-0.040	0.001	-0.171	-	0.153	0.300
HbA1c	-0.108	-0.170	-0.046	0.001	-0.177	-	0.145	0.281

*Difference in means at one year

†Defined as weekly or daily occurrences of at least one of nausea, vomiting, bloating or diarrhea over the last 30 days.

DDS=Diabetes Distress Scale

PHQ-8=Patient Health Questionnaire

DTSQ=Diabetes Treatment Satisfaction Questionnaire

BMI=Body Mass Index

Note: Significant p-values are bolded.

eTable 6. Differences at one year in diabetes distress and depressive symptoms between participants in the liraglutide group vs. glimepiride and sitagliptin groups combined without and with adjustment for potential mediators.

	Diabetes Distress Primary				Depressive Symptoms Primary			
	Difference*	LL	UL	p-value	Difference*	LL	UL	p-value
No Mediator	-0.097	-0.169	-0.026	0.008	0.189	-0.135	0.513	0.252
Mediator	-0.096	-0.167	-0.025	0.008	0.188	-0.134	0.509	0.253
DTSQ	-0.104	-0.176	-0.033	0.004	0.181	-0.141	0.502	0.271
Side Effects†	-0.100	-0.172	-0.028	0.006	0.141	-0.179	0.460	0.388
Rapid Acting Insulin Aspart	-0.096	-0.168	-0.024	0.009	0.210	-0.121	0.541	0.215
Hypoglycemia	-0.098	-0.170	-0.026	0.008	0.182	-0.142	0.505	0.272
BMI	-0.075	-0.147	-0.003	0.043	0.243	-0.093	0.578	0.157
HbA1c	-0.097	-0.169	-0.026	0.008	0.189	-0.135	0.513	0.252

*Difference in means at one year

†Defined as weekly or daily occurrences of at least one of nausea, vomiting, bloating or diarrhea over the last 30 days.

LL=Lower Limit of confidence interval

UL=Upper Limit of confidence interval

DTSQ=Diabetes Treatment Satisfaction Questionnaire

BMI=Body Mass Index

Note: Significant p-values are bolded.

eTable 7. Difference in Diabetes Distress Primary (panel A) and Depressive Symptoms Primary (panel B) outcomes at one year predicted by baseline age, and across sex, race/ethnicity, and income, first in the Glargine group (left columns), and then in the Liraglutide, Glimepiride and Sitagliptin groups combined (the right columns).

	Glargine Group				Liraglutide, Glimepiride and Sitagliptin Combined			
A. Diabetes Distress Primary								
	Difference*	LL	UL	p-value	Difference*	LL	UL	p-value
Age (per 1 year older age)	-0.006	-0.010	-0.003	0.001	-0.010	-0.012	-0.007	<0.001
Sex (vs. Male)								
Female	0.026	-0.056	0.109	0.531	0.067	0.015	0.119	0.011
Race/Ethnicity (vs. NHW)								
Hispanic	0.237	0.105	0.369	<0.001	0.146	0.072	0.221	<0.001
NHB	0.005	-0.104	0.115	0.926	0.105	0.036	0.173	0.003
NH Other	0.087	-0.021	0.196	0.114	0.155	0.068	0.242	0.001
Income (vs. <10K)								
10-20k	0.045	-0.291	0.381	0.793	0.029	-0.124	0.183	0.708
20-50k	-0.079	-0.403	0.245	0.631	-0.046	-0.174	0.082	0.485
>50k	-0.077	-0.392	0.239	0.633	-0.123	-0.247	0.001	0.052
B. Depressive Symptoms Primary								
Age (per 1 year older age)	-0.018	-0.035	-0.001	0.042	-0.017	-0.028	-0.006	0.002
Sex (vs. Male)								
Female	0.103	-0.223	0.428	0.536	0.217	-0.008	0.441	0.058
Race/Ethnicity (vs. NHW)								
Hispanic	-0.071	-0.525	0.383	0.760	0.080	-0.207	0.368	0.584
NHB	-0.200	-0.680	0.279	0.413	-0.101	-0.394	0.193	0.502
NH Other	0.591	-0.024	1.206	0.060	0.373	-0.029	0.774	0.069
Income (vs. <10K)								
10-20k	0.165	-1.108	1.439	0.799	-0.029	-0.709	0.651	0.933
20-50k	-0.230	-1.305	0.844	0.674	0.049	-0.524	0.623	0.866
>50k	-0.457	-1.517	0.603	0.398	-0.083	-0.641	0.474	0.770

*Difference in means at one year

NHW=Non-Hispanic White

NHB=Non-Hispanic Black

NH Other=Non-Hispanic Other

Note: Significant p-values are bolded