

# Supplementary Appendix

Longitudinal effects of glucose-lowering medications on  $\beta$ -cell function and insulin sensitivity in GRADE

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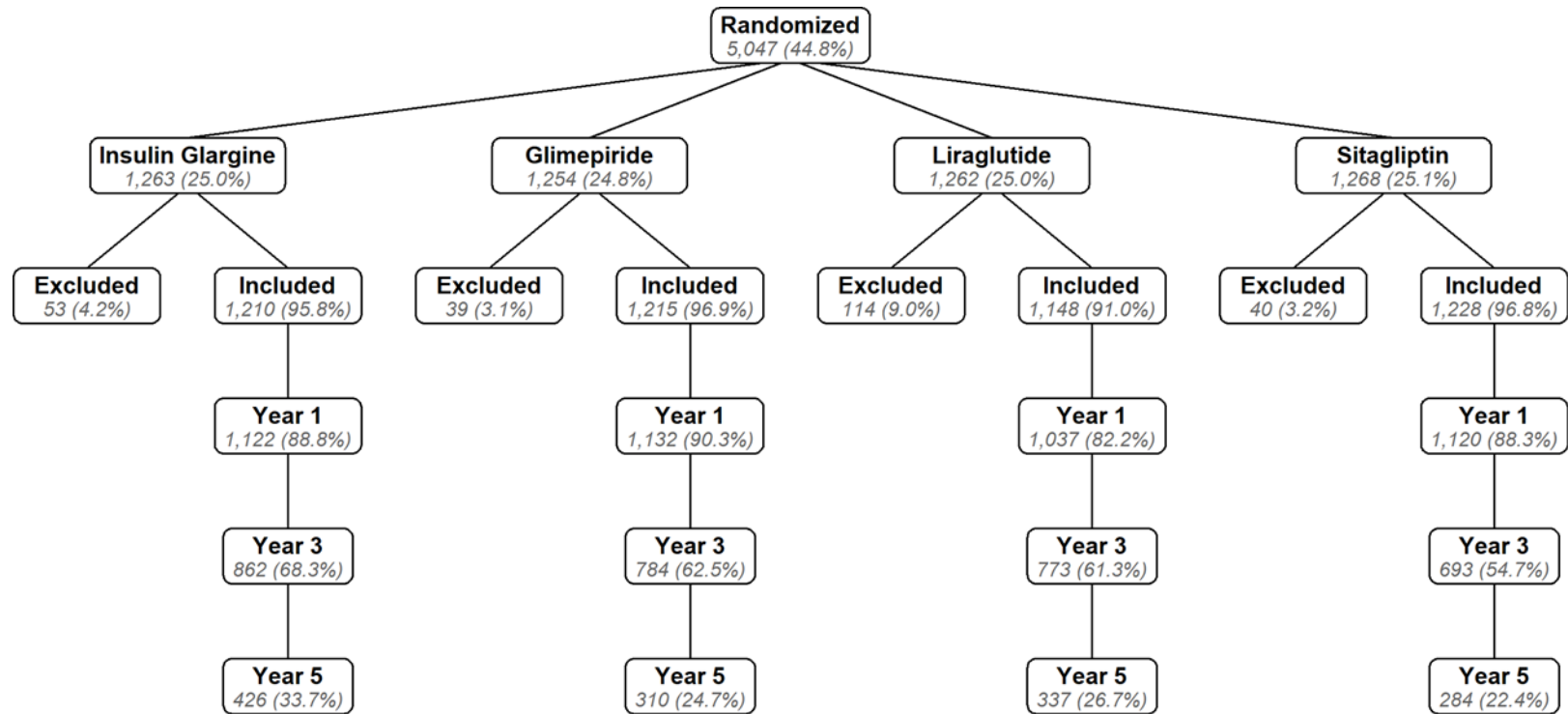
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## Supplemental Figure 1:

### CONSORT Diagram





**Supplemental Table 1:**

HbA1c levels (%) in the different treatment groups at baseline and the follow-up time points.

<b>Group</b>	<b>Year</b>	<b>N</b>	<b>HbA1c (%)</b>
Glargine	0	1,210	7.5 (6.5, 8.5)
Glimepiride	0	1,215	7.5 (6.5, 8.5)
Liraglutide	0	1,148	7.5 (6.5, 8.5)
Sitagliptin	0	1,228	7.5 (6.5, 8.5)
Glargine	1	1,122	6.8 (5.2, 8.4)
Glimepiride	1	1,132	6.8 (5.4, 8.2)
Liraglutide	1	1,037	6.6 (5.0, 8.2)
Sitagliptin	1	1,120	6.9 (5.3, 8.5)
Glargine	3	862	6.9 (5.1, 8.7)
Glimepiride	3	784	7.0 (5.2, 8.8)
Liraglutide	3	773	6.8 (4.8, 8.8)
Sitagliptin	3	693	6.8 (5.2, 8.4)
Glargine	5	426	6.9 (4.9, 8.9)
Glimepiride	5	310	7.0 (5.2, 8.8)
Liraglutide	5	337	6.9 (4.9, 8.9)
Sitagliptin	5	284	7.0 (5.2, 8.8)



## Supplemental Table 2:

Estimated glucose levels (mg/dL) in the different treatment groups at baseline and the follow-up time points for participants with complete OGTT profiles, based on GEE models.

Group	Year	N	Fasting	30 minutes	60 minutes	90 minutes	120 minutes
Glargine	0	1,120	152.5 (150.6,154.3)	234.9 (232.2,237.6)	293.4 (290.3,296.4)	305.4 (302.3,308.5)	286.1 (282.9,289.2)
Glimepiride	0	1,089	152.1 (150.3,154.0)	234.9 (232.0,237.7)	294.5 (291.2,297.7)	307.1 (303.8,310.4)	287.0 (283.8,290.3)
Liraglutide	0	1,071	152.0 (150.2,153.9)	236.2 (233.4,239.0)	295.7 (292.6,298.8)	309.9 (306.7,313.0)	290.4 (287.3,293.6)
Sitagliptin	0	1,143	151.7 (150.0,153.4)	234.9 (232.3,237.5)	293.9 (290.8,296.9)	305.9 (302.6,309.1)	285.9 (282.7,289.1)
Glargine	1	1,019	120.9 (119.2,122.7)	205.3 (202.5,208.1)	262.7 (259.4,266.0)	271.5 (268.1,274.9)	248.9 (245.4,252.4)
Glimepiride	1	1,050	132.2 (130.3,134.1)	216.9 (214.1,219.8)	275.2 (271.9,278.5)	285.6 (282.1,289.0)	263.2 (259.8,266.7)
Liraglutide	1	952	124.9 (123.1,126.7)	201.3 (198.2,204.3)	257.5 (253.9,261.2)	255.9 (252.0,259.9)	220.3 (216.0,224.5)
Sitagliptin	1	1,035	138.8 (136.9,140.8)	218.3 (215.4,221.1)	266.0 (262.6,269.4)	274.7 (270.9,278.4)	255.7 (251.8,259.6)
Glargine	3	784	122.5 (120.3,124.7)	209.6 (206.5,212.8)	267.4 (263.7,271.1)	277.3 (273.4,281.2)	255.4 (251.4,259.4)
Glimepiride	3	709	135.7 (133.1,138.3)	222.5 (218.8,226.3)	284.0 (279.7,288.4)	295.0 (290.6,299.5)	274.8 (270.3,279.3)
Liraglutide	3	714	131.8 (129.3,134.3)	213.4 (209.5,217.2)	270.3 (265.7,274.9)	269.2 (264.5,274.0)	234.0 (228.8,239.2)
Sitagliptin	3	627	135.6 (133.2,138.0)	215.4 (211.6,219.1)	260.2 (255.5,264.9)	268.1 (262.9,273.3)	248.7 (243.4,254.1)
Glargine	5	363	125.1 (121.6,128.6)	210.9 (206.0,215.7)	269.0 (263.1,275.0)	282.1 (275.7,288.5)	263.9 (257.3,270.5)
Glimepiride	5	260	133.8 (129.6,138.0)	219.0 (213.0,225.1)	280.0 (273.0,287.1)	296.0 (288.5,303.5)	277.6 (270.1,285.2)
Liraglutide	5	281	131.6 (127.3,136.0)	211.7 (204.9,218.6)	271.2 (263.6,278.8)	271.1 (263.0,279.3)	235.4 (226.6,244.2)
Sitagliptin	5	243	138.9 (134.9,142.8)	214.9 (208.9,220.9)	263.3 (255.8,270.7)	273.7 (265.4,282.0)	257.9 (249.7,266.2)



### Supplemental Table 3:

Estimated C-peptide levels (nmol/L) during the OGTT in the different treatment groups at baseline and the follow-up time points for participants with complete OGTT profiles, based on GEE models.

Group	Year	N	Fasting	30 minutes	60 minutes	90 minutes	120 minutes
Glargine	0	1,117	1.33 (1.30,1.36)	1.94 (1.89,1.98)	2.60 (2.54,2.66)	2.98 (2.91,3.04)	3.07 (3.00,3.14)
Glimepiride	0	1,080	1.36 (1.32,1.39)	1.95 (1.91,2.00)	2.63 (2.57,2.69)	3.04 (2.97,3.11)	3.15 (3.07,3.22)
Liraglutide	0	1,068	1.34 (1.31,1.38)	1.94 (1.90,1.99)	2.60 (2.54,2.66)	3.01 (2.94,3.08)	3.14 (3.07,3.21)
Sitagliptin	0	1,132	1.34 (1.31,1.38)	1.95 (1.91,2.00)	2.62 (2.56,2.68)	3.00 (2.94,3.07)	3.10 (3.04,3.17)
Glargine	1	1,016	0.94 (0.92,0.97)	1.66 (1.61,1.70)	2.40 (2.34,2.46)	2.84 (2.77,2.91)	2.97 (2.89,3.04)
Glimepiride	1	1,045	1.40 (1.37,1.44)	2.07 (2.02,2.11)	2.78 (2.72,2.84)	3.22 (3.15,3.29)	3.39 (3.31,3.47)
Liraglutide	1	949	1.34 (1.31,1.38)	2.06 (2.01,2.11)	3.22 (3.13,3.30)	4.12 (4.00,4.23)	4.49 (4.37,4.62)
Sitagliptin	1	1,032	1.29 (1.26,1.33)	2.05 (1.99,2.10)	2.86 (2.79,2.93)	3.33 (3.25,3.40)	3.44 (3.36,3.52)
Glargine	3	773	0.87 (0.84,0.90)	1.52 (1.47,1.56)	2.20 (2.14,2.27)	2.60 (2.53,2.67)	2.72 (2.64,2.80)
Glimepiride	3	699	1.31 (1.27,1.35)	1.91 (1.85,1.96)	2.55 (2.48,2.62)	2.92 (2.84,3.01)	3.05 (2.97,3.14)
Liraglutide	3	705	1.27 (1.23,1.31)	1.94 (1.89,2.00)	2.94 (2.85,3.03)	3.74 (3.63,3.86)	3.99 (3.87,4.12)
Sitagliptin	3	616	1.21 (1.17,1.25)	1.98 (1.91,2.04)	2.74 (2.66,2.83)	3.20 (3.10,3.29)	3.30 (3.21,3.40)
Glargine	5	357	0.82 (0.78,0.87)	1.46 (1.39,1.53)	2.09 (1.99,2.19)	2.46 (2.35,2.57)	2.56 (2.45,2.68)
Glimepiride	5	253	1.25 (1.19,1.31)	1.80 (1.72,1.89)	2.41 (2.30,2.52)	2.79 (2.66,2.91)	2.90 (2.77,3.02)
Liraglutide	5	278	1.23 (1.17,1.29)	1.87 (1.77,1.96)	2.92 (2.78,3.07)	3.69 (3.51,3.88)	3.99 (3.79,4.19)
Sitagliptin	5	237	1.15 (1.08,1.22)	1.81 (1.72,1.90)	2.54 (2.41,2.67)	3.02 (2.87,3.18)	3.20 (3.04,3.36)



**Supplemental Table 4:**

Estimated HOMA2-%S in the different treatment groups at baseline and the follow-up time points for participants with complete OGTT profiles, based on GEE models.

Year	Group	N	Mean (95% CI)	p vs. Glim	p vs. Lira	p vs. Sita
0	Glargine	1,210	34.39 (34.34, 34.44)			
	Glimepiride	1,215	34.41 (34.36, 34.46)			
	Liraglutide	1,147	34.40 (34.35, 34.46)			
	Sitagliptin	1,228	34.41 (34.37, 34.46)			
1	Glargine	1,122	57.71 (56.06, 59.37)	<0.001	<0.001	<0.001
	Glimepiride	1,132	34.46 (33.84, 35.08)			
	Liraglutide	1,036	37.27 (36.54, 38.01)		<0.001	0.751
	Sitagliptin	1,120	37.00 (36.27, 37.72)			
3	Glargine	862	62.36 (60.21, 64.51)	<0.001	<0.001	<0.001
	Glimepiride	784	35.58 (34.78, 36.38)			
	Liraglutide	772	37.83 (36.97, 38.69)		<0.001	0.606
	Sitagliptin	693	38.39 (37.39, 39.38)			
5	Glargine	425	65.18 (61.80, 68.56)	<0.001	<0.001	<0.001
	Glimepiride	310	36.21 (34.99, 37.43)			
	Liraglutide	337	38.84 (37.54, 40.15)		0.007	0.009
	Sitagliptin	284	38.98 (37.45, 40.51)			



**Supplemental Table 5:**

Estimated HOMA2-%B in the different treatment groups at baseline and the follow-up time points for participants with complete OGTT profiles, based on GEE models.

Year	Group	N	Mean (95% CI)	p vs. Glim	p vs. Lira	p vs. Sita
0	Glargine	1,210	85.69 (85.41, 85.98)			
	Glimepiride	1,215	85.89 (85.59, 86.19)			
	Liraglutide	1,147	85.86 (85.57, 86.14)			
	Sitagliptin	1,228	85.92 (85.62, 86.21)			
1	Glargine	1,122	95.76 (94.16, 97.36)	<0.001	<0.001	0.199
	Glimepiride	1,132	115.73 (113.16, 118.31)			
	Liraglutide	1,036	120.81 (118.60, 123.02)			
	Sitagliptin	1,120	97.56 (95.90, 99.22)			
3	Glargine	862	89.86 (88.03, 91.69)	<0.001	<0.001	0.035
	Glimepiride	784	105.50 (102.36, 108.63)			
	Liraglutide	772	105.77 (103.14, 108.40)			
	Sitagliptin	693	93.28 (91.04, 95.52)			
5	Glargine	425	85.36 (83.00, 87.72)	<0.001	<0.001	0.456
	Glimepiride	310	103.52 (98.53, 108.52)			
	Liraglutide	337	103.63 (99.90, 107.36)			
	Sitagliptin	284	87.51 (83.95, 91.07)			



**Supplemental Table 6:**

Estimated C-peptide index [(nmol/L)/(mg/dL)\*100] in the different treatment groups at baseline and the follow-up time points for participants with complete OGTT profiles, based on GEE models.

Year	Group	N	Mean (95% CI)	p vs. Glim	p vs. Lira	p vs. Sita
0	Glargine	1,145	0.77 (0.76, 0.78)			
	Glimepiride	1,116	0.76 (0.75, 0.77)			
	Liraglutide	1,092	0.76 (0.75, 0.77)			
	Sitagliptin	1,166	0.77 (0.76, 0.78)			
1	Glargine	996	0.89 (0.85, 0.92)	0.223	<0.001	<0.001
	Glimepiride	1,005	0.85 (0.82, 0.89)			
	Liraglutide	942	1.03 (0.99, 1.08)			
	Sitagliptin	1,022	1.00 (0.97, 1.04)			
3	Glargine	765	0.75 (0.72, 0.79)	0.262	<0.001	<0.001
	Glimepiride	662	0.72 (0.68, 0.76)			
	Liraglutide	698	0.87 (0.82, 0.92)			
	Sitagliptin	609	0.96 (0.91, 1.01)			
5	Glargine	347	0.74 (0.69, 0.79)	0.026	0.201	0.012
	Glimepiride	245	0.64 (0.59, 0.70)			
	Liraglutide	269	0.80 (0.74, 0.87)			
	Sitagliptin	237	0.87 (0.79, 0.95)			



**Supplemental Table 7:**

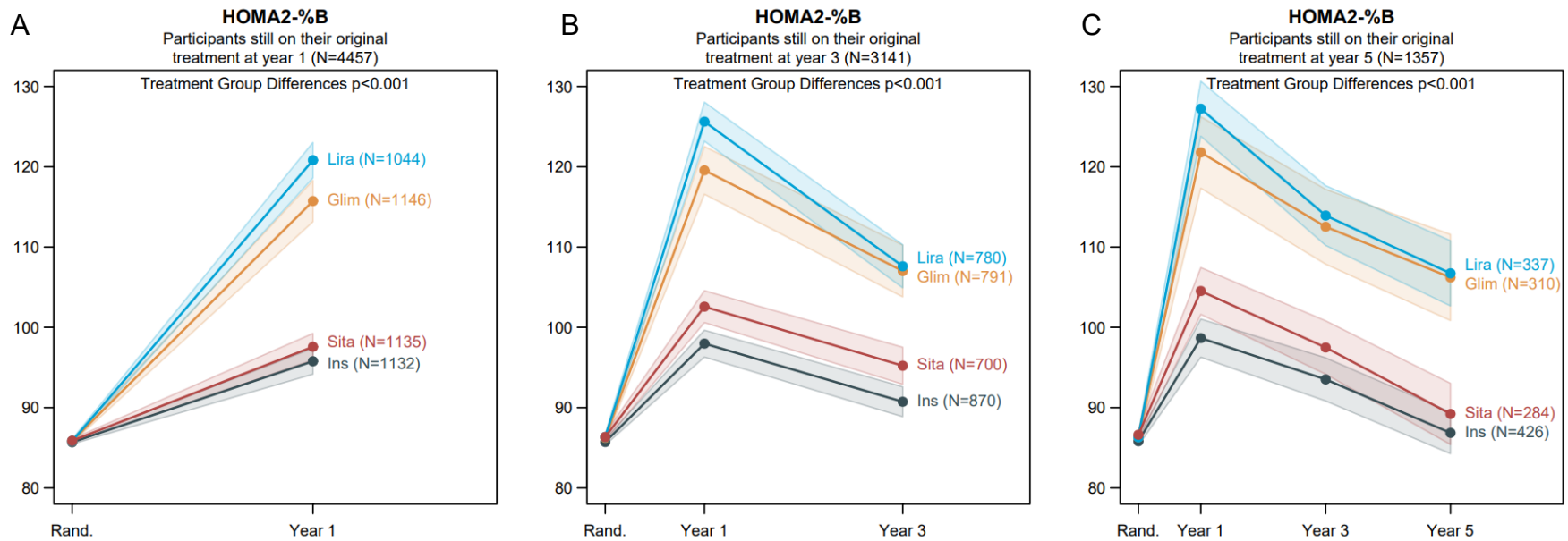
Estimated total C-peptide response [Incremental mean AUC C-peptide/Glucose (nmol/L)/(mg/dL)\*100] in the different treatment groups at baseline and the follow-up time points for participants with complete OGTT profiles, based on GEE models.

Year	Group	N	Mean (95% CI)	p vs. Glim	p vs. Lira	p vs. Sita
0	Glargine	1,115	1.05 (1.05, 1.06)			
	Glimepiride	1,079	1.05 (1.05, 1.06)			
	Liraglutide	1,065	1.05 (1.04, 1.05)			
	Sitagliptin	1,131	1.05 (1.05, 1.06)			
1	Glargine	954	1.24 (1.20, 1.27)	0.024	<0.001	<0.001
	Glimepiride	952	1.17 (1.13, 1.21)		<0.001	<0.001
	Liraglutide	900	1.99 (1.92, 2.05)			<0.001
	Sitagliptin	974	1.50 (1.45, 1.55)			
3	Glargine	727	1.06 (1.02, 1.10)	0.005	<0.001	<0.001
	Glimepiride	630	0.97 (0.92, 1.01)		<0.001	<0.001
	Liraglutide	661	1.62 (1.55, 1.69)			0.002
	Sitagliptin	584	1.45 (1.38, 1.52)			
5	Glargine	330	1.02 (0.96, 1.08)	0.003	<0.001	<0.001
	Glimepiride	221	0.87 (0.81, 0.94)		<0.001	<0.001
	Liraglutide	256	1.54 (1.44, 1.64)			<0.001
	Sitagliptin	222	1.25 (1.15, 1.34)			



## Supplemental Figure 2:

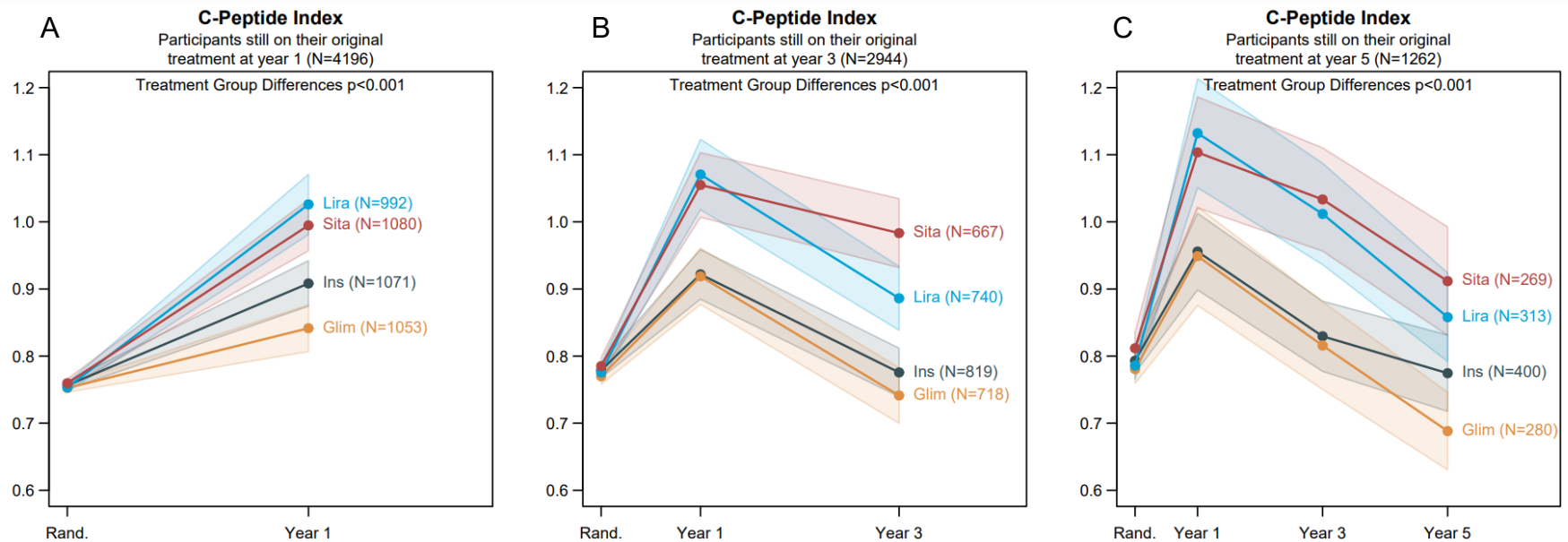
Effects of the four different glucose-lowering medications on HOMA2-%B in participants on their assigned dual therapy at year 1 (A), year 3 (B) and year 5 (C).





### Supplemental Figure 3:

Effects of the four different glucose-lowering medications on CPI in participants on their originally assigned dual therapy at year 1 (A), year 3 (B) and year 5 (C).





## Supplemental Figure 4:

Effects of the four different glucose-lowering medications on total C-peptide response in participants on their originally assigned dual therapy at year 1 (A), year 3 (B) and year 5 (C).

