

ONLINE-ONLY SUPPLEMENTAL APPENDIX

Supplemental Table 1. Systematic Review Search Terms

Search strategy for OVID MEDLINE

1. glucagon like peptide*.mp.
2. Receptors, Glucagon/ag [Agonists]
3. exenatide.af.
4. liraglutide.af.
5. albiglutide.af.
6. taspoglutide.af.
7. lixisenatide.af.
8. dulaglutide.af.
9. semaglutide.af.
10. ZP10A peptide*.af.
11. GLP 1 Receptor Agonist*.af.
12. GLP 1 RA*.af.
13. GLP 1RA*.af.
14. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13
15. randomized controlled trial.pt.
16. controlled clinical trial.pt.
17. randomi*.tw.
18. randomly.ab.
19. trial.mp.
20. 15 or 16 or 17 or 18 or 19
21. Diabetes Mellitus/ or Diabetes Mellitus, Type 2/
22. diabet*.mp.
23. 21 or 22
24. 14 and 20 and 23
25. animals/ not (humans/ and animals/)
26. 24 not 25
27. remove duplicates from 26
28. limit 27 to yr="2018 -Current"

Supplemental Table 2. Average Reduction in HbA1c from Each CVOT

Trial	Total Follow-up (month)	Baseline HbA1c	Average Reduction Weighted by Follow- up (%)			AUC Relative difference (%)		
			Difference at 3 Months	Year 1 Follow-up	Overall Follow-up	3 Month Follow-up	Year 1 Follow-up	Overall Follow-up
LEADER	54	8.7	1.05	0.79	0.41	6.2	9.3	6.3
SUSTAIN-6	24	8.7	1.11	1.16	0.99	7.5	12.9	12.3
EXSCEL	60	8.1	0.37	0.61	0.31	2.3	5.3	4.4
HARMONY	28	8.7	0.57	0.61	0.42	3.1	6.4	5.6
REWIND	60	7.3	0.83	0.74	0.60	5.6	9.3	8.5
PIONEER-6	14.3	8.2	0.82	0.75	0.74	5.4	9.2	9.2

Data are weighted by follow-up time. AUC for HbA1c was calculated for treatment and placebo-controlled arm by trapezoidal integration from the published digitized curves. Then, the relative treatment differences were calculated. The average reduction was calculated as the average of the differences between groups, weighted by time (years). Abbreviations: AUC = area under the curve; CVOT = cardiovascular outcome trial; HbA1c = glycated hemoglobin.

Supplemental Table 3. Average Reduction in Systolic Blood Pressure from Each CVOT

Trial	Total Follow-up (month)	Baseline SBP	Average Reduction Weighted by Follow-up (mmHg)			AUC Relative difference (%)		
			Difference at 3 Months	Year 1 Follow-up	Overall Follow-up	3 Month Follow-up	Year 1 Follow-up	Overall Follow-up
LEADER	54	136.0	0.98	1.98	1.22	0.3	1.1	1.0
SUSTAIN-6	24	135.6	3.82	3.55	3.20	1.9	2.6	2.5
EXSCel	60	135.5	0.92	1.95	1.50	0.4	1.1	1.2
HARMONY	28	134.8	2.20	0.68	0.33	0.8	0.9	0.6
REWIND	60	137.2	0.74	2.34	1.45	0.3	0.9	1.1
PIONEER-6	14.3	136.0	N/A	N/A	N/A	N/A	N/A	N/A

Data are weighted by follow-up time. AUC for SBP was calculated for treatment and placebo-controlled arm by trapezoidal integration from the published digitized curves. Then, the relative treatment differences were calculated. The average reduction was calculated as the average of the differences between groups, weighted by time (years). Abbreviations: AUC = area under the curve; CVOT = cardiovascular outcome trial; SBP = systolic blood pressure.

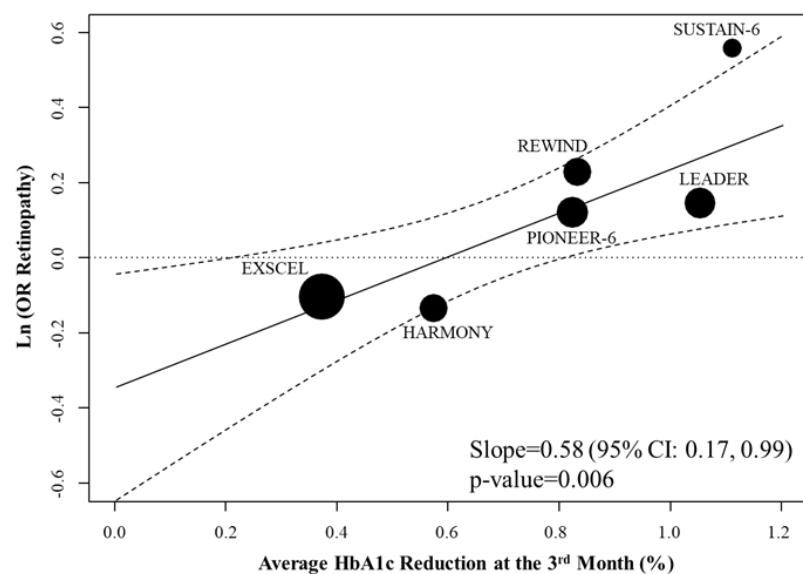
Supplemental Table 4. Average Reduction in Body Weight from Each CVOT

Trial	Total Follow-up (month)	Baseline Body Weight	Average Reduction Weighted by Follow- up (kg)			AUC Relative difference (%)		
			Difference at 3 Months	Year 1 Follow-up	Overall Follow-up	3 Month Follow-up	Year 1 Follow-up	Overall Follow-up
LEADER	54	91.7	1.04	2.31	2.28	0.5	1.8	2.3
SUSTAIN-6	24	91.8	2.25	3.45	3.61	1.3	3.1	3.6
EXSCEL	60	92.1	0.64	1.26	1.09	0.4	1.0	1.1
HARMONY	28	92.1	-1.13	0.44	0.55	-0.8	-0.2	0.5
REWIND	60	88.7	0.71	1.56	1.57	0.6	1.1	1.7
PIONEER-6	14.3	90.9	2.71	4.30	4.49	3.5	3.8	4.0

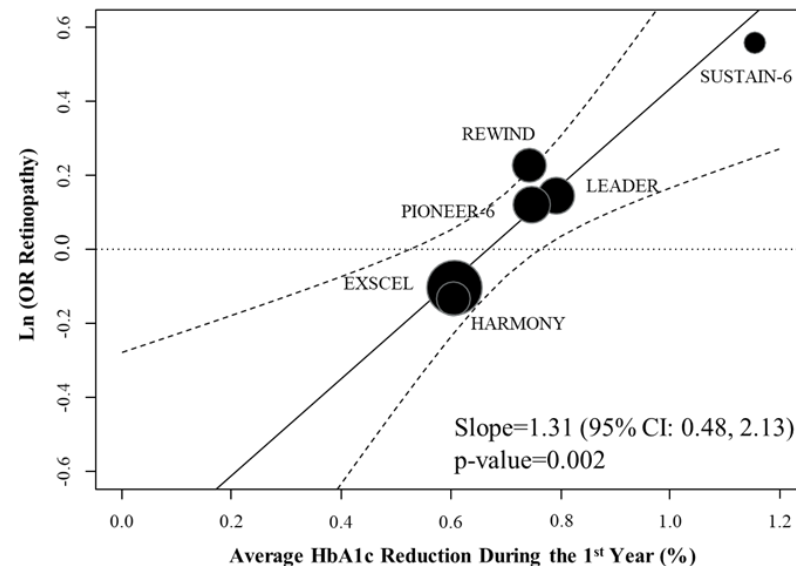
Data are weighted by follow-up time. AUC for body weight was calculated for treatment and placebo-controlled arm by trapezoidal integration from the published digitized curves. Then, the relative treatment differences were calculated. The average reduction was calculated as the average of the differences between groups, weighted by time (years). Abbreviations: AUC = area under the curve; CVOT = cardiovascular outcome trial.

Supplemental Figure 1. HbA1c Reduction Versus Retinopathy OR (Natural Log) at (A) 3 Months and (B) 1 Year

A.

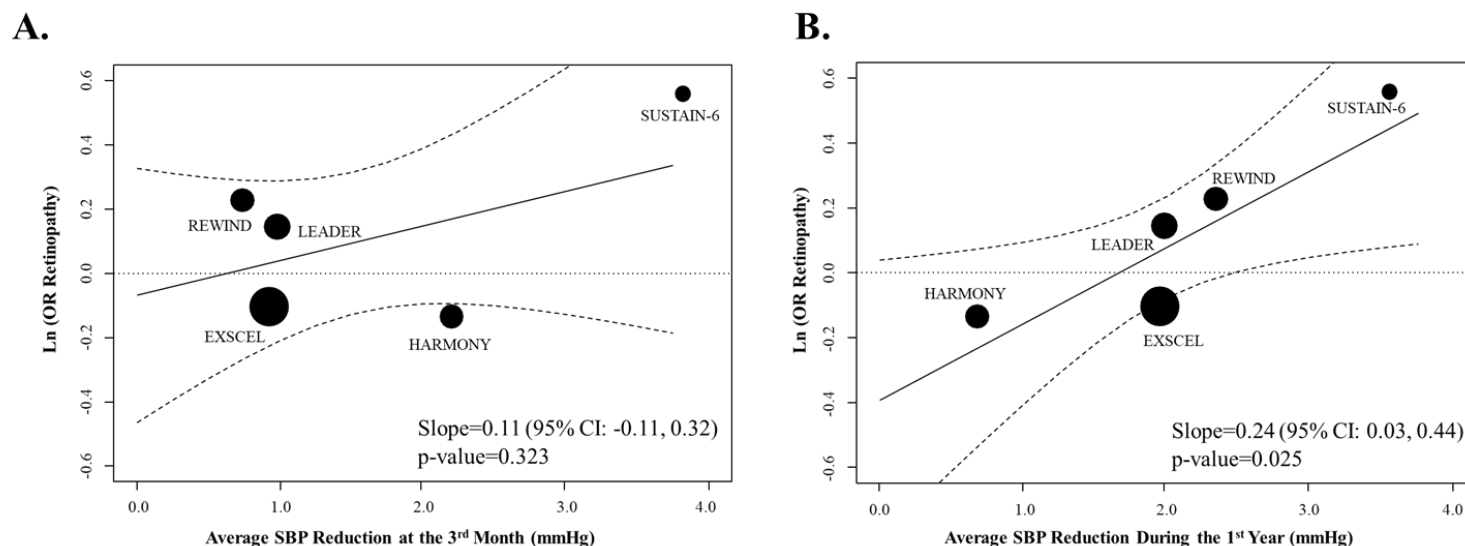


B.



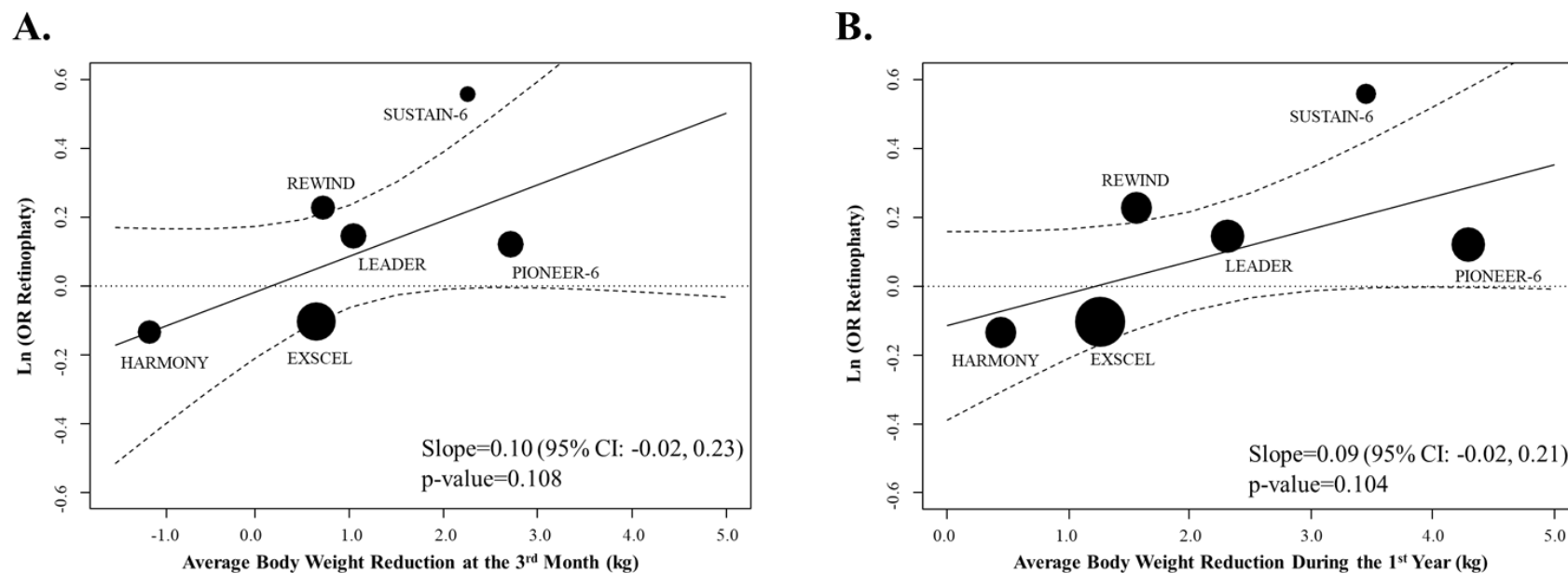
Data are meta-regression estimations and 95% CI (represented by the dotted lines). (A) HbA1c (%) mean difference at 3rd month between the two treatment groups (GLP-1RA or placebo). (B) Average of the differences of HbA1c (%) during the first year between the two treatment groups weighted by follow-up (years). The area of each circle is proportional to the study's variance. Abbreviations: CI = confidence interval; HbA1c = glycated hemoglobin; Ln = natural logarithm; OR = odds ratio.

Supplemental Figure 2. Systolic Blood Pressure Reduction Versus Retinopathy OR (Natural Log) at (A) 3 Months and (B) 1 Year



Data are meta-regression estimations and 95% CI (represented by the dotted lines). (A) Systolic blood pressure (mmHg) mean difference at 3rd month between the two treatment groups (GLP-1RA or placebo). (B) Average of the differences of systolic blood pressure (mmHg) during the first year between the two treatment groups weighted by follow-up (years). The area of each circle is proportional to the study's variance. Abbreviations: CI = confidence interval; Ln = natural logarithm; OR = odds ratio; SBP = systolic blood pressure.

Supplemental Figure 3. Body Weight Reduction Versus Retinopathy OR (Natural Log) at (A) 3 Months and (B) 1 Year.



Data are meta-regression estimations and 95% CI (represented by the dotted lines). (A) Body weight (kg) mean difference at 3rd month between the two treatment groups (GLP-1RA or placebo). (B) Average of the differences of body weight (kg) during the first year between the two treatment groups weighted by follow-up (years). The area of each circle is proportional to the study's variance. Abbreviations: CI = confidence interval; Ln = natural logarithm; OR = odds ratio.