GLP-1 RAs AND CARDIOVASCULAR OUTCOMES IN TYPE 2 DIABETES

2008 — **FDA guidance to industry on CVOT**

2015 — **ELIXA**[1] (Lixisenatide) n=6068; follow-up 2.1 yrs.

2016 — **LEADER**[1] (Liraglutide) n=9340; duration 3.8 yrs.

2016 — **SUSTAIN 6**[1] (Semaglutide) n=3297; duration 2.1 yrs.

2017 — **EXSCEL**[1] (Exenatide ER) n=14752; follow-up 3.2 yrs.

2019 — **REWIND**[1] (Dulaglutide) n=9901; duration 5.4 yrs.

2019 — **HARMONY**[1] (Albiglutide) n=9463; duration 1.6 yrs.

2019 — **PIONEER 6**[1] (Oral semaglutide) n=3183; duration 1.3 yrs.

2021 — **AMPLITUDE-O**[1] (Efpeglenatide) n=4076; duration 1.8 yrs.

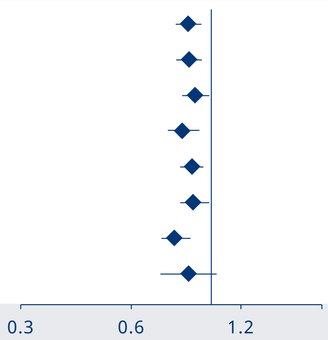
2024 — **SOUL**[2] (Oral semaglutide) n=9650; duration 5.2 yrs.

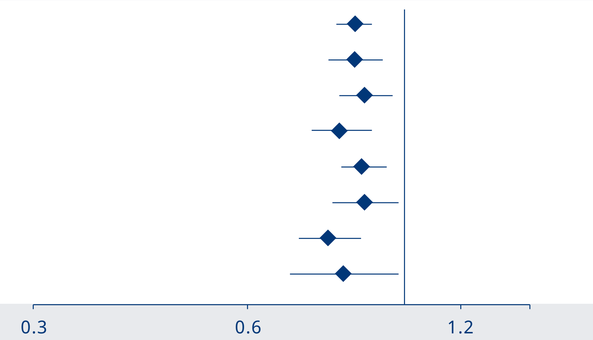
Baseline Characteristics and Use of Glucose-Lowering Agents Across Trials[1]

Drug	ELIXA (n=6068)	LEADER (n=9340)	SUSTAIN 6 (n=3297)	EXSCEL (n=14752)	HARMONY OUTCOMES (n=9463)	REWIND (n=9901)	PIONEER-6 (n=3183)	AMPLITUDE-O (n=4076)
	Lixisenatide	Liraglutide	Semaglutide	Exenatide	Albiglutide	Dulaglutide	Semaglutide	Efpeglenatide
Administration route	Subcutaneous	Subcutaneous	Subcutaneous	Subcutaneous	Subcutaneous	Subcutaneous	Oral	Subcutaneous
Target dose	10 µg/d or 20 µg/d	1.8 mg/d	0.5 mg/wk or 1 mg/wk	2 mg/wk	30 mg/wk or 50 mg/wk	1.5 mg/wk	14 mg/d	4 mg/wk or 6 mg/wk
Age, yrs.	60±10	64±7	65±7	62±9	64±7	66±7	66±7	65±8
Female	31%	36%	39%	38%	31%	46%	32%	33%
Male	69%	64%	61%	62%	69%	54%	68%	67%
BMI kg/m²	30.1±5.6	32.5±6.3	32.8±6.2	32.7±6.4	32.3±5.9	32.3±5.7	32.3±6.5	32.7±6.2
Diabetes duration, yrs.	9.2±8.2	12.8±8.0	13.9±8.1	13.1±8.3	14.2±8.8	10.5±7.2	14.9±8.5	15.4±8.8
HbA_{1c} %	7.7±1.3	8.7±1.6	8.7±1.5	8.1±1.0	8.7±1.5	7.3±1.1	8.2±1.6	8.9±1.5
Established cardiovascular disease	100%	81%	83%	73%	100%	31%	85%	90%
History of heart failure	22%	18%	24%	16%	20%	9%	12%	18%
Systolic blood pressure (mm Hg)	129±17	136±18	136±17	135±17	135±17	137±17	136±18	135±16
eGFR, mL/min per 1.73 m²*	78±21	80 (NR)	80 (61–92)	77 (61–92)	79±25	77±23	74±21	72±22

Summary Results of Meta-Analysis for MACE and Its Components[1]

	Main analysis with all 8 CVOTs (HR; I-squared)	Sensitivity analyses minus ELIXA (HR; I-squared)
MACE	0.86 (0.80 to 0.93)	0.85 (0.80 to 0.90)
CV death	0.87 (0.80 to 0.94)	0.85 (0.78 to 0.93)
Fatal or non fatal MI	0.90 (0.83 to 0.98)	0.88 (0.81 to 0.96)
Fatal or non fatal stroke	0·83 (0·76 to 0·92)	0.81 (0.74 to 0.90)
All-cause mortality	0.88 (0.82 to 0.94)	0.87 (0.81 to 0.94)
Incident HHF	0.89 (0.82 to 0.98)	0.88 (0.79 to 0.98)
Kidney composite (+ macroalbuminuria)	0.79 (0.73 to 0.87)	0.78 (0.71 to 0.87)
Worsening kidney function (eGFR)	0.86 (0.72 to 1.02)	0.82 (0.69 to 0.98)





***eGFR data are median (interquartile range) for SUSTAIN 6 and EXSCEL*
ASCVD, atherosclerotic cardiovascular disease; BMI, body mass index; CV, cardiovascular; CVOT, cardiovascular outcomes trial; ER extended release, EOT, end of treatment , eGFR, estimated glomerular filtration rate; FDA, food and drug administration; GLP-1RA, glucagon like peptide 1 receptor agonist; HHF, hospitalization due to heart failure; I, interval; HbA_{1c}, glycated hemoglobin; HR, hazard ratio; MACE, major adverse cardiovascular events; MI, myocardial infarction; NR, not reported; SGLT2i, Sodium-glucose cotransporter 2 inhibitors; SoC, standard of care; T2D, type 2 diabetes

1. Sattar N et al. Lancet Diabetes Endocrinol. 2021; S2213-8587(21)00203-5, 2. https://clinicaltrials.gov/study/NCT03914326