GLP-1 RAs and Cardiovascular Outcomes

2008

FDA guidance to industry on CVOT

2015

ELIXA[1]
(Lixisenatide)
n=6068; follow-up ~2 yrs.

GLP-1 and inflammation discussed

2016

LEADER[2]
(Liraglutide)
n=9340; duration 3.5–5 yrs.

SUSTAIN 6[3]
(Semaglutide)
n=3297; duration ~2.8 yrs.

2017

EXSCEL[4]
(Exenatide ER)
n=14752; follow-up ~3 yrs.

2019

A novel endocrine-immune axis regulating inflammation

REWIND[5]
(Dulaglutide)
n=9622; duration ~6.5 yrs.

HARMONY[6]
(Albiglutide)
n=9463; duration ~2.6 yrs.

PIONEER 6[7]
(Oral semaglutide)
n=3176; duration ~2 yrs.

2020

- Cardioprotective GLP-1 metabolite
- GLP-1 on endothelial function
- GLP-1 on coronary atherosclerosis progression

2021

AMPLITUDE-O[8]
(Efpeglenatide)
n=4076; duration ~2 .5 yrs.

2023

STEP HFpEF[9]
(Semaglutide)
n=529; duration ~2 yrs.

SELECT[10]
(Semaglutide)
n=17609; duration ~5 yrs.

Semaglutide CV MoA trial[11]
n=100; duration ~1 yr.

2024

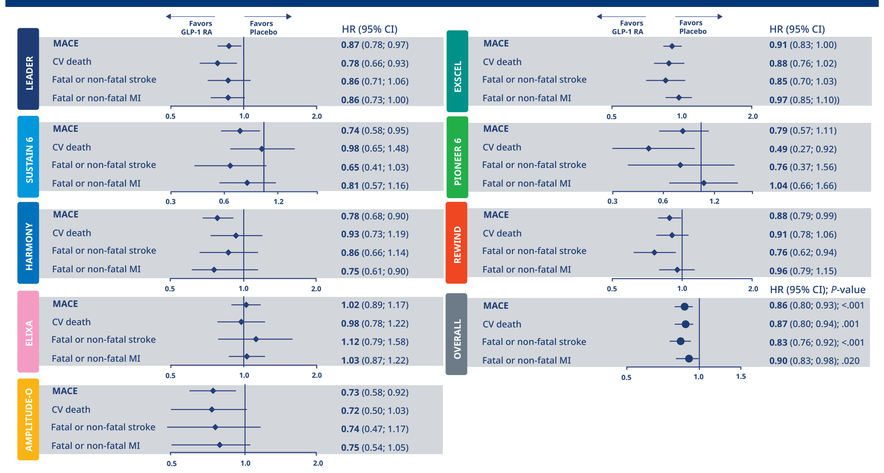
Ongoing Trials
STEP HFpEF DM[11]
(EOT: 2024)

SOUL trial[11] (A heart disease study of semaglutide in people with T2D; EOT: 2024)

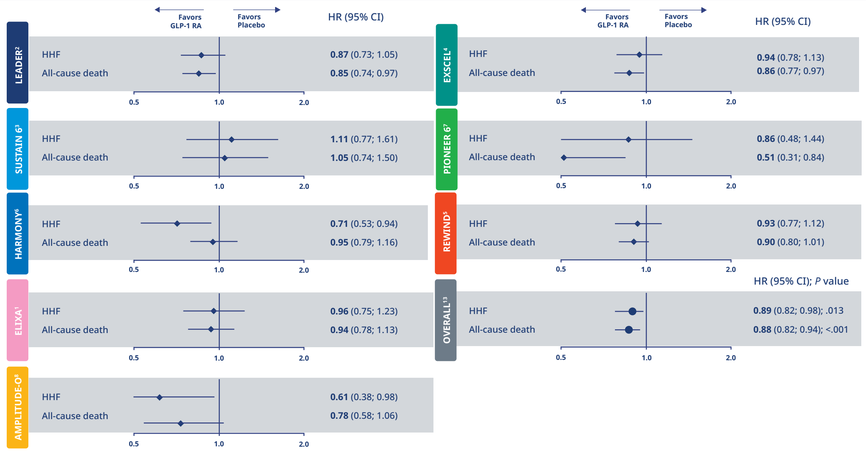
ACC Expert Consensus Recommendations on Considerations for Drug Initiation and Monitoring in Patients Starting a GLP-1 RA with CV Benefit[12]

- If HbA_{1c} is well-controlled at baseline or known history of frequent hypoglycemic events, wean or stop sulfonylurea and consider reducing total daily insulin dose by ~20% when starting therapy.
- Instruct patients to more closely monitor glucose at home for the first 4 weeks of therapy. Consider discontinuing any sulfonylurea or glinide. For patients taking insulin, consider modestly reducing total daily insulin dose (by up to 20%).
- Discontinue DPP-4 inhibitor before starting.
- To mitigate nausea, recommend small portion sizes for meals, start at the lowest dose, and up-titrate as tolerated toward the goal doses used in CV outcome trials.
- Advise patients to undergo appropriate, guideline-recommended eye examinations before starting therapy if not done within the last 12 months.
- Discuss potential risk of diabetic retinopathy complications (for dulaglutide or injectable semaglutide).
- Avoid in patients with diabetic gastroparesis or active gallbladder disease.

CV Outcomes of GLP-1 RAs on MACE Endpoints[13]



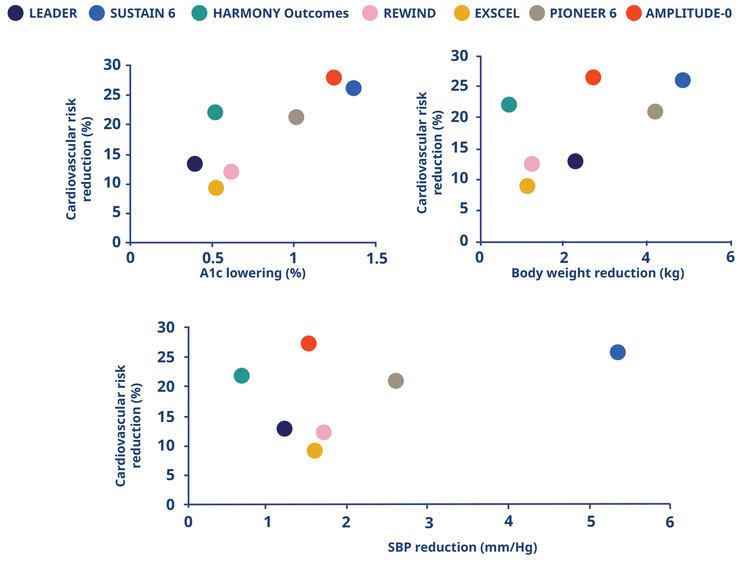
Key Outcomes of GLP-1 RAs on HF and all-cause Mortality



Effect of GLP-1 RAs on CV Risk Factors in CVOTs

Characteristic	LEADER[2]	REWIND[5]	SUSTAIN 6[3]		PIONEER 6[7]	HARMONY[6]	ELIXA[1]	EXSCEL[4]	AMPLITUDE-O[8]
Dose	1.8 mg/day	1.5 mg/week	0.5 mg/week	1.0 mg/week	14 mg/day	30 or 50 mg/week	20 µg/day	2 mg/week	4 or 6 mg/week
Median follow-up (years)	3.8	5.4	2.1	2.1	1.3	1.6	2.1	3.2	1.8
A1c (%)	-0.40	-0.61	-1.1	-1.4	-1.0	-0.52	-0.27*	-0.53*	-1.24
Weight (kg)	-2.3	-1.46	-3.6	-4.9	-4.2	-0.83	-0.7*	-1.27*	-2.6
SBP (mmHG)	-1.2	-1.70	-3.4	-5.4	-2.6	-0.67	-0.8	-1.57	-1.5
HR (bpm)	3.0	1.9	2.1	2.4	3.9	1.3	0.4	2.51	3.9
LDL (mg/dL)	0.98 (ETR)	0.9 (ETR)	0.96 (ETR)	0.99 (ETR)	0.96 (ETR)	-	-	-1.5 (ETD)	-2.7 (ETD)

*Placebo subtracted difference at EOT
ETD: estimated treatment difference; ETR: estimated treatment ratio; EOT: end of treatment



References: (**1**) Pfeffer MA et al. *N Engl J Med* 2015;373(23):2247-2257; (**2**) Marso SP et al. *N Engl J Med* 2016;375:311–322; (**3**) Marso SP et al. *N Engl J Med* 2016;375:1834–1844; (**4**) Holman RR et al. *N Engl J Med* 2017;377:1228-39; (**5**) Gerstein HC et al. *Lancet* 2019. 394:121–30; (**6**) Hernandez AF et al. *Lancet* 2018;392:1519–1529; (**7**) Husain M et al. *N Engl J Med* 2019;381:841-51; (**8**) Gerstein HC et al. *N Engl J Med* 2021;385:896-907; (**9**) Kosiborod MN et al. *JACC Heart Fail* 2023;11(8 Pt 1):1000-1010; (**10**) Data on file. Novo Nordisk Inc; Plainsboro, NJ. www.clinicaltrials.gov.; (**11**) www.clinicaltrials.gov.; (**12**) Das SR et al. *J Am Coll Cardiol*. 2020;76 (9):1117-1145; (**13**) Yoshiji S et al. *Diabetes Obes Metab* 2022;24:1029–1037.