June 2020

Pharmacy Pearls

GLP-1 Receptor Agonists: Comparison of CV Outcomes

AHP Contact: AHPPharmacist@URMC.Rochester.edu

In 2008, the FDA issued a *Guidance for Industry* to conduct post-marketing trials to demonstrate cardiovascular (CV) safety for antihyperglycemic therapies due to a history of CV safety concerns with previously approved agents such as rosiglitazone (Avandia®). Since then a number of new antihyperglycemic classes have come to market, including glucagon-like peptide-1 receptor agonists (GLP-1 RA). The table below presents the study characteristics and results for each GLP-1 RA currently on the market. **The green boxes in the results represent statistically significant results for superiority.**

Trial Characteristic	Soliqua® (lixisenatide)	Bydureon® (exenatide ER)	Trulicity® (dulaglutide)	Victoza® (liraglutide)	Ozempic® (SQ semaglutide)	Rybelsus® (PO semaglutide)
BASELINE CHARACTERISTICS						
Trial Name	ELIXA[1]	EXSCEL	REWIND	LEADER	SUSTAIN-6	PIONEER 6
Participants Enrolled	6,068	14,752	9,901	9,340	3,297	3,183
Follow-up (years)	2.1	3.2	5.4	3.8	2.1	1.3
Baseline A1c (%)	7.7	8	7.4	8.7	8.7	8.2
Duration of DM (years)	9.3	12	10.5	12.8	13.9	14.9
Baseline metformin use (%)	66	77	81	76	73	77
Baseline statin use (%)	93	74	66	72	73	85
Baseline prevalence of CVD (%)	100	73.1	31	81	72	85
Baseline prevalence of HF (%)	22	16.2	8.5	18	24	11.8
RESULTS						
Primary composite outcome[2]	1.02 (0.89-1.17)	0.91 (0.83-1.00)	0.88 (0.79-0.99)	0.87 (0.78-0.97)	0.74 (0.58-0.95)	0.79 (0.57-1.11)
Cardiovascular death	0.98 (0.78-1.22)	0.88 (0.76-1.02)	0.91 (0.78-1.06)	0.78 (0.66-0.93)	0.98 (0.65-1.48)	0.49 (0.27-0.92)
Fatal or non-fatal MI	1.03 (0.87-1.22)	0.97 (0.85-1.10)	0.96 (0.79-1.16)	0.86 (0.73-1.00)	0.74 (0.51-1.08)	1.18 (0.73-1.90)
Fatal or non-fatal stroke	1.12 (0.79-1.58)	0.85 (0.70-1.03)	0.76 (0.61-0.95)	0.86 (0.71-1.06)	0.61 (0.38-0.99)	0.74 (0.35-1.57)
All-cause mortality	0.94 (0.78-1.13)	0.86 (0.77-0.97)	0.90 (0.80-1.01)	0.86 (0.74-0.97)	1.05 (0.74-1.50)	0.51 (0.31-0.84)
Heart failure hospitalization	0.96 (0.75-1.23)	0.94 (0.78-1.13)	0.93 (0.77-1.12)	0.87 (0.73-1.05)	1.11 (0.77-1.61)	0.86 (0.48-1.55)

[1]Acute coronary syndrome patients. Only a composite of CV death and hospital admission for heart failure was reported (HR 0.85, 0.70-1.04). [2] 3-point MACE is defined as a composite of cardiovascular death, non-fatal myocardial infarction and non-fatal stroke.

Oral Semaglutide: Key Points

- Dosing: Start with 3mg once daily x 30 days, then increase to 7mg. If additional glycemic control is needed after at least 30 days on the 7mg dose, can increase to 14mg.
- Administration: **MUST** be taken in the morning with no more than 4 oz. of water, in a fasting state AND at least 30 minutes before eating, drinking or taking any other oral medication
- Adverse Reactions: At 14mg dose, incidence of adverse reactions is similar to 1mg SQ semaglutide except with greater incidence of abdominal pain
- CV Outcomes: Did not reach superiority in 3-point MACE, fatal or non-fatal MI or stroke
- Cost: $915 per 30-day supply

Summary

- Victoza®, Ozempic® and Trulicity® are the only GLP-1 RAs that reached superiority in 3-point MACE
- Rybelsus® is the first oral GLP-1 RA to market. It has strict administration criteria that must be followed and did not reach superiority in 3-point MACE.
- First line approach to the treatment of type 2 diabetes is still metformin + lifestyle. If your patient has ASCVD or CKD with predominant ASCVD, GLP-1 RAs are recommended.
- Note that DPP-4s lack positive CV outcomes; Onglyza® (saxagliptin) and Nesina® (alogliptin) are associated with a modest increased risk of hospitalization for heart failure

See AHP's Best Practices for Management of T2DM here

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SGLT2 Inhibitors: Comparison of CV Outcomes

AHP Contact: AHPPharmacist@URMC.Rochester.edu

The table below presents the study characteristics and results for the CV outcomes trials for the sodium glucose cotransporter 2 (SGLT2) inhibitor class of medications. We are still awaiting CV outcomes for Steglatro® (ertugliflozin). **The green boxes in the results represent statistically significant results for superiority.** The FDA recently advised a label change that canagliflozin, dapagliflozin and empagliflozin should be discontinued 3 days before scheduled surgery and ertugliflozin 4 days before due to higher risk of ketoacidosis. Monitor BGs after discontinuation and appropriately manage before surgery.

Trial Characteristic	Jardiance® (empagliflozin 10mg, 25mg)	Invokana® (canagliflozin 100mg, 300mg)	Farxiga® (dapagliflozin 10mg)
BASELINE CHARACTERISTICS			
Trial Name	EMPA-REG	CANVAS/CANVAS-R	DECLARE-TIMI 58
Participants Enrolled	7,020	10,142	17,160
Median Follow-up (years)	3.1	2.4	4.2
Baseline A1c (%)	8.1	8.2	8.3
Duration of DM (years)	10+	13.5	11
Baseline metformin use (%)	74	77	82
Baseline statin use (%)	77	75	75
Baseline prevalence of CVD (%)	99.4	66	41
Baseline prevalence of HF (%)	10	14	10
Baseline eGFR (mL/min/1.73m^2)	74.2	76.5	85.2
RESULTS			
Primary composite outcome[1]	0.86 (0.74-0.99)	0.86 (0.75-0.97)	0.93[2] (0.84-1.03)
Cardiovascular death	0.62 (0.49-0.77)	0.87 (0.72-1.06)	0.98 (0.82-1.17)
Fatal or non-fatal MI	0.87 (0.70-1.09)	0.89 (0.73-1.09)	0.89 (0.77-1.01)
Fatal or non-fatal stroke	1.18 (0.89-1.56)	0.87 (0.69-1.09)	1.01 (0.84-1.21)
All-cause mortality	0.68 (0.57-0.82)	0.87 (0.74-1.01)	0.93 (0.82-1.04)
Heart failure hospitalization	0.65 (0.50-0.85)	0.67 (0.52-0.87)	0.73 (0.61-0.88)
40% reduction in eGFR, renal-replacement therapy or renal death	Not studied	0.60 (0.47-.077)	0.53 (0.43-0.66)
A1c reduction (%)	-0.8%	-0.94	-2.0%

[1] 3-point MACE is defined as a composite of cardiovascular death, non-fatal myocardial infarction and non-fatal stroke [2] Co-primary outcome: cardiovascular death and hospitalization for heart failure = HR 0.83 (0.73-0.95)

Expanded Indications

Jardiance®	○ To reduce the risk of **CV death** in adult patients with type 2 diabetes *and established CVD*
Invokana®	○ To reduce the risk of **major adverse CV events** in adults with type 2 diabetes *and established CVD* ○ To reduce the risk of **ESRD, doubling of serum creatinine, CV death and hospitalization for heart failure** in adults with type 2 diabetes *and diabetic nephropathy with albuminuria*
Farxiga®	○ To reduce the risk of **cardiovascular death and hospitalization** in NYHA class II to IV HFrEF

Summary

- Jardiance® and Invokana® reached superiority in 3-point MACE
- Invokana® and Farxiga® reached superiority in the reduction of poor renal outcomes
- All SGLT2 inhibitors reached superiority in the reduction of heart failure hospitalization
- First line approach to the treatment of type 2 diabetes is still metformin + lifestyle. If your patient has ASCVD and CKD with predominant CHF or CKD, SGLT2 inhibitors are recommended.

See AHP's Best Practices for Management of T2DM here