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Real World Evidence and Model-Informed Drug Development – an antidiabetic drug cardiovascular outcome case study

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INTRODUCTION

- Cardiovascular (CV) safety outcome study is routinely required in type II diabetes (T2DM) drug approval.
- Empagliflozin (Sodium-glucose cotransporter 2 Inhibitors (SGLT2i))approval for CV indication provides an additional risk reduction option for T2DM patients with high CV risks [1],
- Presents a confounding in the CV effect assessment for future studies.
  - ✓ Patients might already take SGLT2i at the study start or initiate it during the study
  - ✓ Concomitant administration of SGLT2i increases the CV effect assessment uncertainty, especially when there is imbalanced SGLT2i addition between treatments during the study
- A glucagon-like peptide-1 receptor agonists (GLP-1ra) class drug CV outcome study as a case study to understand the impact of this co-administration
  - ✓ Historical GLP-1ra CV outcome studies (LEADER [2] and SUSTAIN 6 [3]) can provide assumptions for GLP-1ra CV effect compared to standard of care (SOC),
  - ✓ Currently, there is no clinical study available to assess the CV effect of concomitant administration of SGLT-2i and GLP-1ra.
- AstraZeneca's CVD-REAL study [4] used real world data (RWD) assessing SGLT-2i, as a class, significantly reduced CV risks versus other T2DM medicines

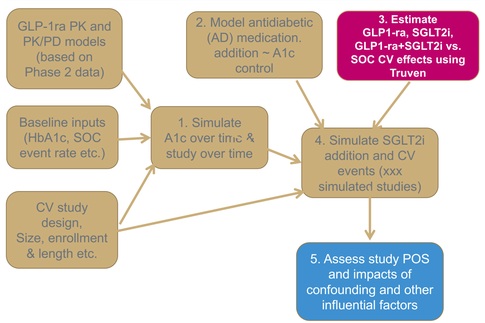
OBJECTIVES

- To estimate GLP-1ra, SGLT2i, GLP-1ra + SGLT2i CV effects relative to SOC using RWD
- To assess the impact of this confounding and other influential factors on the study probability of success (POS) of a GLP-1ra drug CV outcome study

METHODS

1. Simulate patients' HbA1c over time for GLP-1ra and SOC using PopPK and PK/HbA1c exposure-response models and planned study design
2. Model antidiabetic medication addition, especially imbalanced addition between treatments due to differential HbA1c control using literature and internal CV outcome studies
3. Estimate relative CV effects of GLP-1ra, SGLT2i, GLP-1ra+SGLT2i vs SOC using Truven database
   - ✓ Assume all SGLT2i with similar CV effects → empa can be assessed separately if desired (not done)
   - ✓ *See left for details*
4. Simulate the study and CV events with SGLT2i addition at baseline & during the study
   - ✓ Integrate PK, PK/PD, conmed models, study design and assumptions etc.
   - ✓ % SGLT2i patients at baseline and addition during the study based on SGLT2i utilization market prediction
5. Analyze each simulated study as if observed and summarize study POS (over 1000 simulated studies)
   - ✓ To explore and identify influential factor(s) such as SGLT2i patient%, study sample size, enrollment rate, event rates and study dropout rates, etc.

Clinical Trial Simulation Schema



Estimate GLP-1ra, SGLT2i, GLP-1ra + SGLT2i CV effects relative to SOC using Truven database

Data sources Truven:

- Patients market scan claims (insurance) data from year 2008 to 2017 in US
- Inpatient/outpatient services and facility settings documenting patient's demographics, diagnosis, limited labs, procedures

Patient selection

- T2DM patients started on 1st GLP-1ra on 2014 or later (see Figure 1) → GLP1 arm
- T2DM patients never used GLP-1ra and started on new antidiabetic med. other than GLP-1ra or SGLT2i on 2014 or later – non-GLP1 arm (SOC arm)
  - ✓ 1st GLP1 or non-GLP date as the start date
  - ✓ event date or last enrollment date (whichever earlier) as the end date
- With/without SGLT2i status at baseline determined
  - ✓ Patients adding SGLT2i during the study excluded
- All and high CV risk populations assessed
  - ✓ High CV risk: with at least one prior CV event including cerebrovascular disease (CD), coronary artery disease (CAD), peripheral vascular disease (PVD), stroke, MI, HF → ICD9/10 codes & medical review
  - ✓ Patients with stroke in 6M prior to the start excluded

Analysis setup

- GLP1 and non-GLP arms by 1-1 propensity score matching within SGLT-2i baseline usage (Y/N) groups
  - ✓ By age, gender, T2DM duration, prior CV events
- CV endpoint: MI, stoke, CV death*
  - ✓ Fist event
  - ✓ Approximated by death/expired discharged status and Hospice codes in blood circulation related category

RESULTS

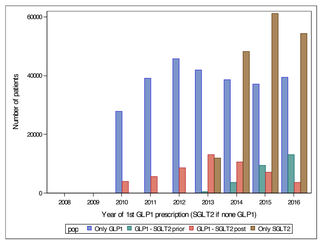
Table 1: LEADER[2] antidiabetic medication addition during the study

Table S4. Cardiovascular and anti-diabetes medications at baseline and during trial.

	Baseline			Introduced during trial		
	Liraglutide (N=4668)	Placebo (N=4672)	p-value	Liraglutide (N=4668)	Placebo (N=4672)	p-value
Antihyperglycemic medication	4113 (88.1)	4129 (88.4)	0.69	1012 (21.7)	3242 (29.1)	<.001

- Imbalanced ~20% and ~30% concomitant antidiabetic med. observed for GLP-1ra and SOC arms in historical GLP-1ra CV outcome studies (Table 1)
- An empirical concomitant med. addition model during the blinded study phase under differential HbA1c control of SOC and GLP-1ra arms was established using an internal historical CV outcome study (not shown)

Figure 1: First GLP1-ra & first SGLT2i Patient Counts in Truven



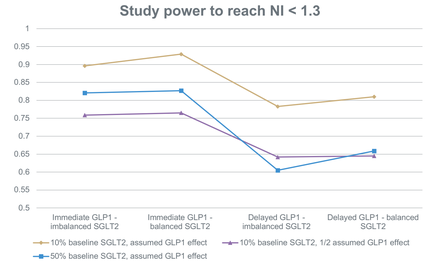
SGLT2 prior or post: SGLT2i started before or after GLP-1ra start

Table 2: MACE: GLP1 vs. non-GLP1 CV effect by SGLT2i use subgroup

Population	glp1: n/N(%)	Non-glp1:n/N(%)	HR (95% CI)
All Patients			
All	1858/115152(1.61%)	2091/115152(1.82%)	0.947 (0.889,1.008)
No SGLT2i	1537/93091 (1.65%)	1792/93091(1.92%)	0.928 (0.866,0.993)
Prior SGLT2i	321/22061 (1.46%)	299/22061 (1.36%)	1.056(0.902,1.236)
High CV risk Patients			
All	796/18853 (4.22%)	909/18853 (4.82%)	0.926 (0.842,1.109)
No SGLT2i	649/15124 (4.29%)	774/15124 (5.12%)	0.890 (0.802,0.988)
Prior SGLT2i	147/3729 (3.94%)	134/3729 (3.59%)	1.129 (0.893,1.427)

- RWD estimated a GLP-1ra vs. SOC CV benefit ~10% reduction and smaller GLP-1ra+SGLT-2i vs. SGLT-2i CV benefit in high CV risk population

Figure 2: Simulated Power assuming no additional GLP-1ra CV benefit when on top of SGLT2i



- Design: 4000 patients with ~300 events to non inferiority with margin 1.3 (safety)
- The simulation indicated a small impact of differential SGLT-2i addition during the blinded study phase unless there was a fairly large % SGLT-2i patient usage.
- The percentage of patients on SGLT-2i can be monitored during the study to mitigate the risk.

CONCLUSIONS:
Real world data was used to estimate the concomitant CV effects with/without empagliflozin and inform the CTS and study POS assessment.

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