Leveraging the active comparator new user design to identify potential unknown benefits of canagliflozin

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Background

The active comparator new user (ACNU) cohort design has emerged as a best practice for the estimation of drug effects from observational data[1]. However, efforts to leverage such data to identify potential unknown benefits of marketed drugs have largely favored self-controlled methods when generating effect estimates. We describe an attempt to use the ACNU design to screen for potential unknown benefits of the antidiabetic agent canagliflozin and compare our results with those obtained from a self-controlled cohort (SCC) design.

Methods

We generated new user cohorts for canagliflozin (a sodium-glucose transport protein 2 (SGLT2) inhibitor) and two frequently chosen comparators, sitagliptin (a dipeptidyl peptidase-4 [DPP-4] inhibitor) and liraglutide (a glucagon-like peptide 1 [GLP-1] analogue), across five real-world databases[1]. Outcome cohorts were generated based on the first occurrence of each SNOMED condition, but analysis was limited to those with ≥ 300 events to reduce computation time. Large-scale propensity score models were used to match new users of canagliflozin and sitagliptin in a 1:1 manner based on thousands of covariates. For each outcome, Cox proportional hazards models were used to estimate treatment effects conditioned on matched set. Empirical calibration using negative control outcomes[2] was used to account for residual systematic error and objective diagnostics[3] determined whether a result would be eligible for review. The use of the SCC design to identify potential unknown benefits has been previously described[4,5]. In both designs, we used an ad-hoc criteria defining a potential benefit "signal" as an outcome with a hazard ratio (or incidence rate ratio in the SCC design) ≤ 0.7 and p-value ≤ 0.05 after calibration in at least two databases.

Results

1,850 outcomes were assessed in both study designs. Runtime for the ACNU design varied from roughly 1-4 days, depending on database, compared to 1-3 hours for the SCC. Among all outcomes with a potential benefit in at least one database (**Figure 1**), 64 met the ad-hoc signaling criteria in the SCC design vs. 13 in either of the ACNU design. There was no overlap between the SCC and ACNU designs in outcomes that met these criteria. Upon manual review, all outcomes meeting the signaling criteria in the SCC design were deemed to have arisen due to protopathic bias. Of the 13 outcomes that met the signaling criteria in either ACNU design (**Table 1**), clinical concepts related to kidney disease, heart failure, anemia, and vomiting arose.

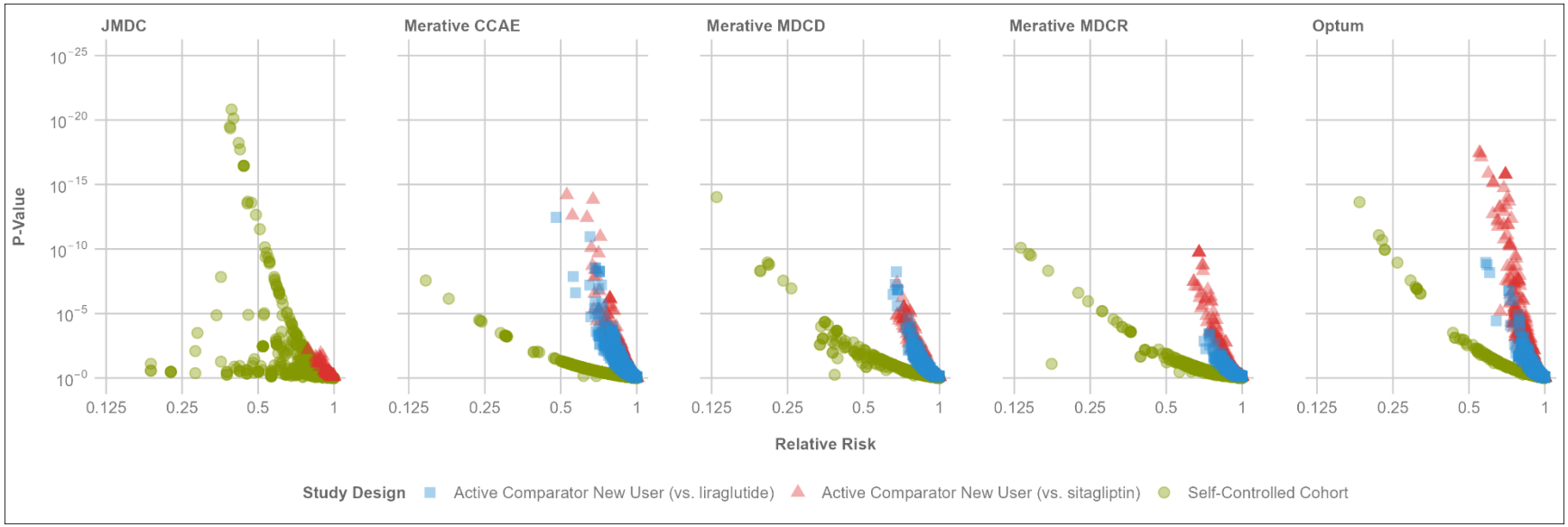
[1] Databases included: Merative™ MarketScan® Commercial Claims and Encounters (CCAE), Merative™ MarketScan® Multi-State Medicaid (MDCD), Merative™ MarketScan®Medicare Supplemental (MDCR); Japan Medical Data Center (JMDC); and Optum© De-Identified Clinformatics© Data Mart.

Conclusion

While the ACNU design is far more computationally intensive than the SCC, it is currently tractable for studies of potential unknown benefits of a single target. In this case, adding ACNU-derived evidence led to the identification of several interesting potential signals, some of which had precedent in the literature. For example, results from the CREDENCE trial suggest potential benefits of canagliflozin for heart failure[6], kidney disease[7], and anemia[8], while an apparent decrease in localized edema risk may be related to volume depletion, a known side-effect of canagliflozin's drug class[9]. The apparent decrease in vomiting risk, which only appeared in comparison against liraglutide, likely reflects that drug's tolerability profile and not a potential unknown benefit of canagliflozin, as vomiting is mentioned as an adverse drug reaction identified clinical trial experience in the liraglutide, but not canagliflozin or sitagliptin, label. Further research is needed to fully compare the operating characteristics of the SCC and ACNU designs in the context of identifying potential unknown benefits and to determine how to leverage both methodologies effectively and even how to reconcile potentially different findings. In particular, assessments using alternative target drugs and multiple comparator choices per target are likely to provide additional insights.

Figures

Figure 1: Results for 1,741 outcomes demonstrating a potential unknown benefit of canagliflozin in at least one database using either study design



JMDC: Japan Medical Data Center; CCAE: Commercial Claims and Encounters; MDCD: Multi-State Medicaid; MDCR: Medicare Supplemental and Coordination of Benefits; Optum: Optum© De-Identified Clinformatics© Data Mart. "Relative Risk" refers to hazard ratios in the active comparator new user design and incidence rate ratios in the self-controlled cohort design. Note: 18 points with hazard ratio/incidence rate ratio < 0.125 or p-value < 10^{-25} removed for plotting.

Tables

Table 1: Summary of outcomes that met the ad-hoc signaling criteria for either comparison in the ACNU design

Outcome	# of DBs with Signal Under Design			DB-Specific Estimates				
	A	B	C	JMDC	Merative CCAE	Merative MDCD	Merative MDCR	Optum
Chronic kidney disease due to hypertension	0	4	1	A: n/a B: n/a C: n/a	A: 2.07 (1.03, 4.14) **B: 0.68 (0.59, 0.78)** **C: 0.68 (0.58, 0.80)**	A: 1.78 (1.05, 3.03) **B: 0.69 (0.58, 0.82)** C: 0.80 (0.66, 0.96)	A: 1.78 (1.00, 3.16) **B: 0.70 (0.60, 0.81**) C: 0.84 (0.69, 1.02)	A: n/a **B: 0.69 (0.63, 0.75)** C: 0.82 (0.72, 0.93)
Hydronephrosis	0	2	2	A: 1.02 (0.62, 1.67) B: n/a C: n/a	A: 0.79 (0.39, 1.58) **B: 0.53 (0.45, 0.62)** **C: 0.56 (0.46, 0.68)**	A: 1.39 (0.77, 2.52) B: n/a C: n/a	A: 1.54 (0.80, 2.96) B: n/a C: n/a	A: 0.83 (0.52, 1.31) **B: 0.67 (0.56, 0.79**) **C: 0.64 (0.52, 0.79)**
Hypertensive renal disease	0	3	0	A: 0.42 (0.08, 2.11) B: n/a C: n/a	A: 1.29 (0.65, 2.57) **B: 0.71 (0.63, 0.81)** C: 0.72 (0.61, 0.84)	A: 1.36 (0.81, 2.29) **B: 0.69 (0.59, 0.82)** C: 0.83 (0.69, 1.00)	A: 1.20 (0.69, 2.11) **B: 0.69 (0.60, 0.79)** C: 0.80 (0.66, 0.97)	A: 1.26 (0.82, 1.95) B: 0.70 (0.64, 0.77) C: 0.83 (0.73, 0.94)
Heart failure	0	3	0	A: 0.76 (0.61, 0.94) B: 1.04 (0.94, 1.14) C: n/a	A: 0.81 (0.41, 1.61) B: 0.75 (0.66, 0.86) C: 0.78 (0.67, 0.92)	A: 0.97 (0.58, 1.62) **B: 0.68 (0.57, 0.81)** C: 0.93 (0.77, 1.12)	A: 0.88 (0.50, 1.54) **B: 0.67 (0.58, 0.77)** C: 0.86 (0.70, 1.06)	A: 0.86 (0.55, 1.33) **B: 0.69 (0.62, 0.76)** C: 0.93 (0.81, 1.07)
Localized edema	0	3	0	A: 1.15 (0.77, 1.70) B: n/a C: n/a	A: 1.86 (0.94, 3.71) **B: 0.69 (0.61, 0.78)** C: 0.82 (0.71, 0.95)	A: 1.13 (0.68, 1.87) B: 0.77 (0.67, 0.88) C: 0.93 (0.80, 1.09)	A: 1.60 (0.89, 2.87) **B: 0.69 (0.59, 0.80)** C: n/a	A: n/a **B: 0.69 (0.63, 0.76)** C: 0.89 (0.79, 1.02)
Iron deficiency anemia	0	2	0	A: 1.10 (0.86, 1.40) B: 1.15 (1.02, 1.30) C: n/a	A: 0.85 (0.43, 1.69) B: 0.85 (0.75, 0.95) C: 0.88 (0.76, 1.02)	A: 0.96 (0.57, 1.61) **B: 0.68 (0.57, 0.81)** C: 0.91 (0.75, 1.11)	A: 1.09 (0.61, 1.93) B: n/a C: n/a	A: 1.05 (0.68, 1.63) **B: 0.69 (0.62, 0.77)** C: 0.87 (0.76, 1.01)
Anemia	0	2	0	A: 1.09 (0.87, 1.37) B: 1.03 (0.93, 1.15) C: n/a	A: 0.73 (0.37, 1.43) B: 0.78 (0.71, 0.86) C: 0.80 (0.70, 0.90)	A: 0.82 (0.50, 1.36) B: 0.72 (0.63, 0.83) C: 0.81 (0.70, 0.95)	A: 0.91 (0.52, 1.57) **B: 0.67 (0.60, 0.76)** C: 0.87 (0.74, 1.03)	A: 0.88 (0.57, 1.35) **B: 0.70 (0.64, 0.76)** C: 0.86 (0.76, 0.96)
Vomiting	0	0	2	A: 0.97 (0.78, 1.20) B: 1.06 (0.96, 1.17) C: n/a	A: 1.00 (0.50, 1.96) B: 0.93 (0.84, 1.03) **C: 0.69 (0.61, 0.78)**	A: 1.00 (0.61, 1.65) B: 0.96 (0.84, 1.10) **C: 0.68 (0.59, 0.79)**	A: 1.19 (0.68, 2.09) B: 0.92 (0.78, 1.08) C: 0.79 (0.64, 0.97)	A: 1.04 (0.67, 1.61) B: 0.91 (0.82, 1.00) C: 0.72 (0.64, 0.81)
Chronic heart failure	0	2	0	A: n/a B: n/a C: n/a	A: 0.98 (0.49, 1.98) **B: 0.70 (0.59, 0.83)** C: 0.71 (0.57, 0.88)	A: 1.44 (0.84, 2.45) B: n/a C: n/a	A: 1.12 (0.62, 2.01) B: n/a C: n/a	A: 1.02 (0.65, 1.59) **B: 0.60 (0.53, 0.67)** C: 0.82 (0.70, 0.96)

Design A: self-controlled cohort; Design B: active comparator new user (vs. sitagliptin); Design C: active comparator new user (vs. liraglutide); Results are given as incidence rate ratio (95% CI) for design A or hazard ratio (95% CI) for designs B and C; DB: database; JMDC: Japan Medical Data Center; CCAE: Commercial Claims and Encounters; MDCD: Multi-State Medicaid; MDCR: Medicare Supplemental and Coordination of Benefits; Optum© De-Identified Clinformatics© Data Mart. Note: estimates in bold had HR ≤ 0.7 and p-value ≤ 0.05 after calibration. [1]Four additional outcomes (hemoglobin low, RBC count low, and hemoglobin level outside reference range, finding of vomiting) not included in table due to identical results to related outcomes.

References/Citations

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