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Real-world Effectiveness of SGLT2 Inhibitors vs Metformin as First-line Therapy in Type 2 Diabetes

Patricia J Rodriguez, PhD MPH[1], Samuel Gratzl, PhD[1], Ryan Lee, MD[1], Sarah Gilson, MD[1], Peter Smits, PhD[1], Nicholas Stucky, MD PhD[1,2], Ty J. Gluckman, MD, MHA[3]

[1]Truveta Inc, Seattle, WA ; [2]Providence St Joseph Health, Portland, OR ;[3]Center for Cardiovascular Analytics, Research and Data Science (CARDS), Providence Heart Institute, Providence St Joseph Health, Portland, OR

BACKGROUND

EXISTING KNOWLEDGE

- In Type II Diabetes Mellitus (T2DM), sodium glucose cotransporter-2 inhibitors (SGLT2i) have demonstrated protection against adverse cardiovascular outcomes for individuals at elevated cardiovascular risk in clinical trials[1-3] and real-world evidence,[4,5] but metformin remains the standard of care for first-line treatment for most patients with Type II Diabetes Mellitus (T2DM)
- It remains unclear whether an all-comer population initiating treatment with SGLT2i in real-world clinical practice experience similar benefits

OBJECTIVE

- To evaluate differences in cardiovascular and A1c outcomes associated with initiation of SGLT2i vs. metformin in an all-comer population

METHODS

DATA

- A subset of real-world EHR data from the Truveta platform, which aggregates and normalizes de-identified EHR data from >25 US health care systems (HCSs) comprising >20,000 clinics and 700 hospitals..
- Data included conditions, medications requests (e.g., prescriptions), laboratory values, and demographics.

POPULATION

- New-user study of treatment-naïve adult patients with T2DM, newly prescribed SGLT2i or metformin as monotherapy between 2016 and 2022 and who received regular care at a Truveta HCS
- Excluded patients with history of gestational diabetes, organ transplant, ESRD, or HIV and those missing age or gender

OUTCOMES

- Patients were followed over time for clinical and biomarker (A1c) outcomes:
  1. Time to composite cardiovascular event (myocardial infarction, ischemic stroke, hospitalization for heart failure)
  2. Time to normal (<7) A1C [among those with elevated A1C at baseline]
  3. Change in 12-month A1c
- Patients censored at the first of: 5 years, administrative end of data (12/31/22), discontinuation, or initiation of the comparator treatment.

TREATMENT EFFECT ESTIMATION

- 1:1 nearest neighbors propensity score matching to balance populations on baseline characteristics
- Matched Cox proportional hazards model, adjusted for residual confounding, for time to event outcomes
- Matched linear regression to compare changes 12-month A1c

TRUVETA

Disclosures: PJR, SG, RL, SG, PS, and NS are employees of Truveta Inc.

In a large and diverse real-world EHR dataset, we found no significant difference in time to composite MI, stroke, or hospitalization for heart failure between patients with T2DM first initiated on treatment with SGLT2i vs. metformin.

However, those initiated on SGLT2i were less likely to achieve normal A1c and experienced smaller A1c reductions by 12 months.

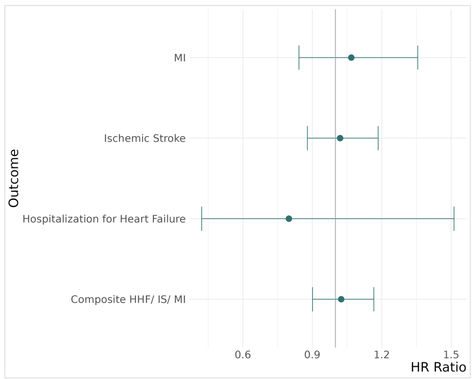

Figure 1: Hazard of cardiovascular event associated with SGLT2i (vs. metformin)

RESULTS

POPULATION CHARACTERISTICS

- N = 135,729 patients met our study criteria – 129,305 initiated on metformin and 6,424 initiated on SGLT2i.
- A higher proportion of those initiated on SGLT2i were male (55% on SGLT2i vs. 48% on metformin), white (69% on SGLT2i vs. 66% on metformin), initiated in 2020 or later (58% on SGLT2i vs. 32% on metformin), and had more comorbidities
- N = 12,848 remained after 1:1 propensity score matching. PS matching achieved good balance, with all standardized mean differences < 0.1.

CARDIOVASCULAR OUTCOMES

- Composite cardiovascular outcomes did not differ significantly between those on an SGLT2i and metformin (hazard ratio: 1.025 [95% CI: 0.901, 1.166])
- Individual cardiovascular endpoints did not differ significantly between those on an SGLT2i vs. metformin

A1C OUTCOMES

- Among those with elevated baseline A1c (>7), those initiating SGLT2i (vs metformin) were less likely to achieve normal A1c (hazard ratio: 0.68 [95% CI: 0.64, 0.72])
- Among those with baseline and 12-month A1c values available (n = 5,472), SGLT2i use was associated with a smaller absolute decrease in A1c by 0.25% (0.19% - 0.32%).

	Before Matching			After Matching		
Variable (Mean (SD))	Metformin (N=129,305)	SGLT2i (N=6,424)	Overall (N=135,729)	Metformin (N=6424)	SGLT2i (N=6,424)	Overall (N=12,848)
Age	62.2 (13.0)	63.4 (12.7)	62.3 (13.0)	63.5 (13.6)	63.4 (12.7)	63.5 (13.2)
Sex: Female	66,927 (51.8%)	2,877 (44.8%)	69,804 (51.4%)	2874 (44.7%)	2877 (44.8%)	5751 (44.8%)
Race						
American Indian or Alaska Native	720 (0.6%)	32 (0.5%)	752 (0.6%)	38 (0.6%)	32 (0.5%)	70 (0.5%)
Asian	9,087 (7.0%)	260 (4.0%)	9,347 (6.9%)	251 (3.9%)	260 (4.0%)	511 (4.0%)
Black	21,903 (16.9%)	1,190 (18.5%)	23,093 (17.0%)	1144 (17.8%)	1190 (18.5%)	2334 (18.2%)
Native Hawaiian or Other Pacific Islander	803 (0.6%)	34 (0.5%)	837 (0.6%)	39 (0.6%)	34 (0.5%)	73 (0.6%)
White	85,378 (66.0%)	4,420 (68.8%)	89,798 (66.2%)	4475 (69.7%)	4420 (68.8%)	8895 (69.2%)
Unknown	5,162 (4.0%)	278 (4.3%)	5,440 (4.0%)	288 (4.5%)	278 (4.3%)	566 (4.4%)
Other Race	6,252 (4.8%)	210 (3.3%)	6,462 (4.8%)	189 (2.9%)	210 (3.3%)	399 (3.1%)
Initiation Year						
2016	23,274 (18.0%)	801 (12.5%)	24,075 (17.7%)	876 (13.6%)	801 (12.5%)	1677 (13.1%)
2017	22,155 (17.1%)	531 (8.3%)	22,686 (16.7%)	571 (8.9%)	531 (8.3%)	1102 (8.6%)
2018	19,175 (14.8%)	588 (9.2%)	19,763 (14.6%)	667 (10.4%)	588 (9.2%)	1255 (9.8%)
2019	23,451 (18.1%)	754 (11.7%)	24,205 (17.8%)	834 (13.0%)	754 (11.7%)	1588 (12.4%)
2020	13,236 (10.2%)	546 (8.5%)	13,782 (10.2%)	599 (9.3%)	546 (8.5%)	1145 (8.9%)
2021	15,078 (11.7%)	1,199 (18.7%)	16,277 (12.0%)	1121 (17.5%)	1199 (18.7%)	2320 (18.1%)
2022	12,936 (10.0%)	2,005 (31.2%)	14,941 (11.0%)	1756 (27.3%)	2005 (31.2%)	3761 (29.3%)
T2DM Severity						
Time (days) since First T2D Diagnosis	691 (842)	813 (941)	696 (847)	822 (1030)	813 (941)	818 (985)
Diabetic Nephropathy	10,518 (8.1%)	1,008 (15.7%)	11,526 (8.5%)	1028 (16.0%)	1008 (15.7%)	2036 (15.8%)
Diabetic Retinopathy	2,546 (2.0%)	159 (2.5%)	2,705 (2.0%)	166 (2.6%)	159 (2.5%)	325 (2.5%)
Baseline A1c	7.50 (1.62)	7.61 (1.60)	7.51 (1.62)	7.56 (1.67)	7.61 (1.60)	7.58 (1.64)
Missing	24,032 (18.6%)	1,755 (27.3%)	25,787 (19.0%)	1275 (19.8%)	1755 (27.3%)	3030 (23.6%)
Risk Factors and Comorbidities						
History of Smoking	18,532 (14.3%)	1,184 (18.4%)	19,716 (14.5%)	1131 (17.6%)	1184 (18.4%)	2315 (18.0%)
ASCVD	19,149 (14.8%)	1,798 (28.0%)	20,947 (15.4%)	1777 (27.7%)	1798 (28.0%)	3575 (27.8%)
Heart Failure	5,830 (4.5%)	1,330 (20.7%)	7,160 (5.3%)	1456 (22.7%)	1330 (20.7%)	2786 (21.7%)
Ischemic Stroke	3,030 (2.3%)	181 (2.8%)	3,211 (2.4%)	146 (2.3%)	181 (2.8%)	327 (2.5%)
Myocardial Infarction	3,291 (2.5%)	539 (8.4%)	3,830 (2.8%)	540 (8.4%)	539 (8.4%)	1079 (8.4%)
Hyperlipidemia	77,031 (59.6%)	3,888 (60.5%)	80,919 (59.6%)	3893 (60.6%)	3888 (60.5%)	7781 (60.6%)
Hypertension	76,823 (59.4%)	4,047 (63.0%)	80,870 (59.6%)	4068 (63.3%)	4047 (63.0%)	8115 (63.2%)
Chronic Kidney Disease	8,538 (6.6%)	1,158 (18.0%)	9,696 (7.1%)	1180 (18.4%)	1158 (18.0%)	2338 (18.2%)
Cancer	12,463 (9.6%)	627 (9.8%)	13,090 (9.6%)	606 (9.4%)	627 (9.8%)	1233 (9.6%)
Utilization in Previous Year						
Inpatient Encounters	0.0562 (0.349)	0.150 (0.698)	0.0607 (0.373)	0.144 (0.791)	0.150 (0.698)	0.147 (0.746)
Emergency Department Encounters	0.261 (0.870)	0.379 (1.12)	0.267 (0.884)	0.347 (1.11)	0.379 (1.12)	0.363 (1.12)

CONCLUSIONS

Patients initiated on an SGLT2i had similar risk of cardiovascular events to those initiated on metformin, but experienced a smaller 12-month reduction in A1c and were less likely to achieve normal A1c.

Future work is needed to compare the relative benefits among those with vs. without an indication for initiation with SGLT2i.

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