Risk of Cardiovascular Events in Type 2 Diabetes Patients Initiating Second Line Therapy with Glucose Lowering Drugs: A Population-Based Analysis

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Conflict of interest: None. Funded by CIHR through the Drug Safety and Effectiveness Network

Background

Type 2 diabetes (T2D) patients are at high risk of cardiovascular events. Recent trials have described a protective cardiovascular effect of new oral antidiabetic drugs (OAD), including sodium-glucose cotransporter-2 (SGLT-2) inhibitors, but whether these findings hold true in the general population remains uncertain.

Objective

To compare the risk of cardiovascular and cerebrovascular events among patients initiating SGLT-2 or other OAD as second line therapy after metformin.

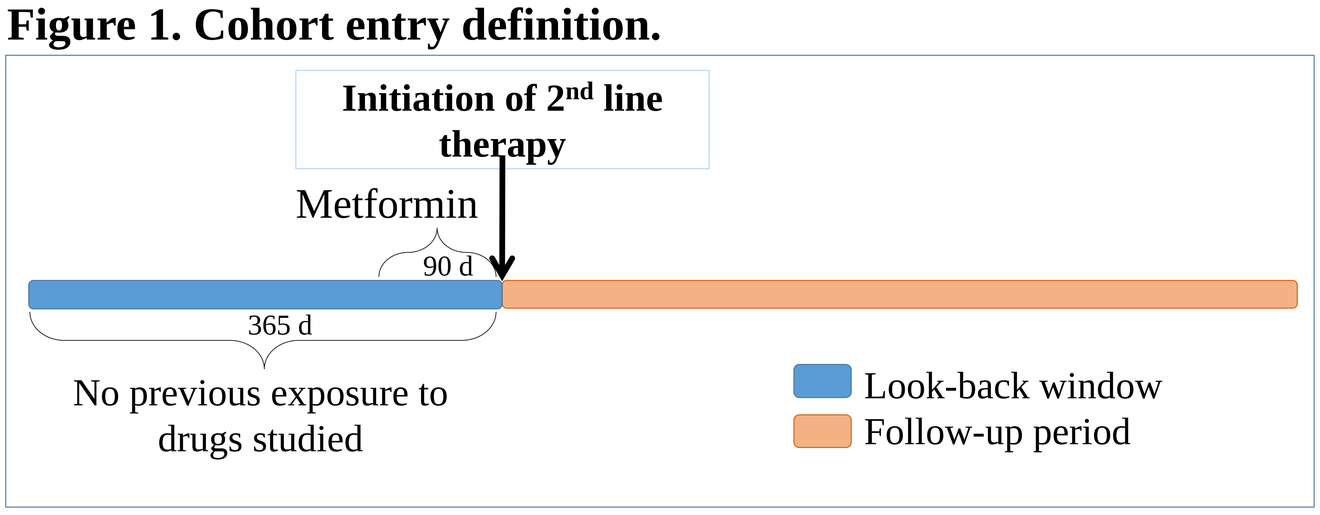
Methods

Study design: The MarketScan database (2011-2015) was used to create a cohort of patients initiating second-line T2D therapy after metformin (see Figure 1).

Exposure: i) sulfonylureas (SU); ii) SGLT-2; iii) Dipeptidyl peptidase-4 inhibitor (DPP-4); or iv) Glucagon-like peptide-1 (GLP-1) agonists.

Outcomes: Cardiovascular and cerebrovascular events after cohort entry: i) acute myocardial infarction (AMI), ii) unstable angina, and iii) ischemic or hemorrhagic stroke.

Figure 1. Cohort entry definition.



Follow-up: Cohort entry was defined by date of first prescription of second-line agent. Patients were censored at death, loss of insurance coverage, discontinuation/switching initial therapy, or end of study period (Dec. 31, 2015).

Statistical analysis: Cox regression models adjusted for baseline age, sex, year of cohort entry, employment status, place of residence, and comorbidities.

Results

Table 1. Selected baseline characteristics of T2D patients included in the cohort.

Characteristics	All patients (N=118,774)	Sulfonylurea (N=57,293)	DPP-4i (N=41,045)	GLP-1a (N=13,104)	SGLT-2i (N=7332)
Female sex, n (%)	54,578 (46)	25,058 (44)	18,541 (45)	7845 (60)	3494 (48)
Age at entry, mean (SD)	56 (11)	57 (12)	56 (11)	52 (10)	54 (9)
Co-morbidities, n (%)					
Cerebrovascular disease	6496 (5.5)	3302 (5.8)	2330 (5.7)	560 (4.3)	304 (4.2)
Myocardial Infarction	2516 (2.1)	1341 (2.3)	835 (2.0)	213 (1.6)	126 (1.7)
Congestive heart failure	4302 (3.5)	2295 (4.0)	1377 (3.4)	375 (2.9)	155 (2.1)
Peripheral Vascular Disease	3912 (3.3)	2007 (3.5)	1353 (3.3)	364 (2.8)	188 (2.6)
Any renal disease	4289 (3.6)	2250 (3.9)	1510 (3.7)	390 (3.0)	139 (1.9)

- We studied 118,774 T2D individuals (Table 1); most patients were sulfonylurea initiators (48%), 35% were on DPP-4, 11% on GLP-1, and 6% on SGLT-2.
- Overall, this cohort represents patients at low risk of cardiovascular events
- Cardiovascular and cerebrovascular events were higher in sulfonylurea initiators than in other groups (Table 2).
- After adjusting for potential confounders, the risk of cardiovascular events was 55% lower in users of GLP-1a and 58% in the SGLT-2i (compared with sulfonylurea users - Table 3).

Table 2. Number of events, incidence, and time to event for cardiovascular and cerebrovascular outcomes .

	All patients	Sulfonylurea	DPP-4	GLP-1A	SGLT-2I
No. of events	1078	694	317	46	21
Incidence per 1000 person years (95% CI)	10.7 (10.1-11.3)	12.7 (11.8-13.6)	9.2 (8.3-10.2)	5.8 (4.3-7.7)	5.7 (3.8-8.8)
Time to event (years)	0.85	0.96	0.84	0.61	0.5

Table 3. Cox regression analysis for cardiovascular and cerebrovascular outcomes.

	Unadjusted		Adjusted*	
	HR	95% CI	HR	95% CI
DPP-4i	0.72	0.63, 0.82	0.79	0.69, 0.91
GLP-1	0.45	0.33, 0.60	0.65	0.48, 0.89
SGLT-2	0.42	0.27, 0.66	0.61	0.39, 0.96

Reference: Sulfonylurea

*Adjusted for sex, age at entry, cardiovascular disease, severe renal disease, urban residency, medication use, employment history, and year of cohort entry

Conclusions

This real-world analysis of second-line agents in T2D suggests that compared to sulfonylureas, newer agents are associated with lower cardiovascular events. Our results are consistent with findings of recent trials although residual confounding including channelling may partially explain our findings.