Impact of early initiation of SGLT2 inhibitor on cardiovascular outcomes in diabetic patients with known atherosclerotic cardiovascular disease or risk factors: propensity score matched analysis

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Purpose: Sodium-glucose cotransporter 2 (SGLT2) inhibitors have demonstrated cardiovascular benefits in patients with diabetes and atherosclerotic cardiovascular disease (ASCVD). We aimed to evaluate the impact of early initiation of SGLT2 inhibitor on cardiovascular outcomes in diabetic patients with known and at risk of ASCVD.

Methods: We retrospectively analyzed 29,309 consecutive patients with type 2 diabetes prescribed empagliflozin (N=18,979, 64.8%) and dapagliflozin (N=10,330, 35.2%) between August 2015 and August 2020 in 16 public hospitals in Hong Kong. Patients with diagnosis of diabetes to first prescription of SGLT2 inhibitors (Dx-to-Rx time) $\leq$12 months were matched with $>$12 months using propensity score derived from logistic regression. 3,370 matched patients were divided into 4 groups: (i) patients with known ASCVD involving 1 territory (coronary artery, peripheral artery or cerebrovascular disease); (ii) known ASCVD involving $>$1 territories; (iii) CV risk factor(s) other than diabetes and (iv) no known ASCVD or additional CV risk factors. Incidence rates of 3-point major adverse cardiovascular events (MACE, including non-fatal stroke, non-fatal myocardial infarction and cardiovascular death) were compared between Dx-to-Rx time $\leq$12 months and $>$12 months across 4 subgroups during a median follow-up of 2.8 years (IQR 2.2 to 3.4).

Results: Of 29,309 patients (mean age 54.9±11.6 years, female 41.0%), 22.9% had single territory and 6.1% multi-territories ASCVD, 53.3% with additional CV risk factors and 17.7% neither risk factor nor ASCVD. Overall, 19.0% of patients had Dx-to-Rx time $\leq$12 month; 19.3%, 15.7%, 17.6% and 30.0% in each group, respectively. Overall, Dx-to-Rx time $\leq$12 months was associated with lower rates of MACE (hazard ratio (HR) =0.27, 95% CI: 0.17–0.42). Subgroup analysis showed similar results in patients with CV risk factors of or known ASCVD but not in patients with neither risk factor nor ASCVD (P for interaction=0.001, Table 1).

Conclusion: Early initiation of SGLT2 inhibitor was associated with significant lower MACE rates in diabetic patients with known ASCVD or additional CV risk factors. The impact was more marked in patients with additional CV risk factors. Our findings suggested early initiation in diabetic patients with known ASCVD and additional CV risk factors.

Table 1. MACE with Dx-to-Rx time $\leq$12 months versus $>$12 months in subgroups stratified by presence or absence of known ASCVD or risk factors.

	Dx-to-Rx time $\leq$12 months			Dx-to-Rx time $>$12 months			Hazard ratio (95%CI)	P for interaction
MACE	n/N	%	Rate/1000 person-years	n/N	%	Rate/1000 person-years		
All patients	30/1,685	1.8	6.0	71/1,685	4.2	14.2	0.27 (0.17-0.42)	
Neither ASCVD nor CV risk factor	1/317	0.3	1.1	1/280	0.4	1.3	0.52 (0.03-8.27)	0.001
CV Risk factor only	4/932	0.4	1.4	14/864	1.6	5.3	0.11(0.03-0.42)	
Single ASCVD	21/364	5.8	20.2	39/408	9.6	32.3	0.54(0.31-0.94)	
Multiple ASCVD	4/72	5.6	19.42	17/133	12.8	45.03	0.24(0.06-0.93)	