Safety of SGLT2 Inhibitors: A Pharmacovigilance Study From 2015 to 2020 Based on FDA Adverse Event Report System Database

Xiang Zhou[1], Xiaofei Ye[2], Yinghong Zhai[1], Fangyuan Hu[2], Yongqing Gao[1], Dongxu Liu[1], Xiao Xu[1], Ziwei Dong[1], and Jia He[1]

[1]Tongji University School of Medicine
[2]Second Military Medical University Department of Health Statistics

May 15, 2021

Abstract

Aim: With the widespread use of SGLT2i, various adverse events (AEs) have been reported. This study aimed to describe the distribution of SGLT2i-related AEs in different systems, quantify the association of important medical events (IMEs) and SGLT2i regimens, and build a signal profile of SGLT2i- induced IMEs. Methods: Data from 2015 Q1 to 2020 Q4 in the FDA Adverse Event Reporting System database (FAERS) were selected to conduct disproportionality analysis. Two signal indicators, the reported odds ratio (ROR) and information component (IC), were used to evaluate the correlation between SGLT2i and IMEs. The lower end of the 95% confidence interval of IC (IC025) exceeding zero was deemed a signal. For ROR, it was defined a signal if ROR025 over one, with at least 3 cases. Results: A total of 45,771,436 records were involved, including 111,564 records related to SGLT2i, with 38,366 records of SGLT2i-induced IMEs. Overall, SGLT2i was significantly associated with IMEs (IC=0.36, 95% CI: 0.35-0.38; ROR=1.44, 95% CI: 1.42-1.46). Most SGLT2i-related adverse events occurred in monotherapy (92.93%). Diabetic ketoacidosis was the most IMEs. Specifically, acute osteomyelitis has the strongest signal of all SGLT2i (IC025=7.83), and it was unique to canagliflozin. Diabetic ketoacidosis, acute kidney injury, ketoacidosis, Fournier's gangrene, and euglycemic diabetic ketoacidosis were common to the four FDA-approved SGLT2i. Conclusion: Our study demonstrated that different SGLT2i regimens lead to different important adverse events, but there are overlapping events. Early identification and management of SGLT2i-associated IMEs are essential for clinical practice.

Hosted file

`Main File.pdf` available at https://authorea.com/users/413950/articles/522128-safety-of-sglt2-inhibitors-a-pharmacovigilance-study-from-2015-to-2020-based-on-fda-adverse-event-report-system-database

Figure 1| Characteristics of patients with SGLT2i-induced AEs and drug distribution.

	Reports	percent(%)
Total SGLT2i	**111564**	
Monotherapy	103673	92.93
*Canagliflozin	50712	48.92
*Empagliflozin	29523	28.48
*Dapagliflozin	21997	21.22
*Ertugliflozin	770	0.74
*Ipragliflozin	407	0.39
*Tofogliflozin	167	0.16
*Luseogliflozin	89	0.09
*Remogliflozin	8	0.01
Polytherapy	7891	7.07
*Canagliflozin+Metformin	3307	41.91
*Empagliflozin+Metformin	2368	30.01
*Empagliflozin+Linagliptin	1883	23.86
*Dapagliflozin+Metformin	109	1.38
*Ertugliflozin+Metformin	81	1.03
*Ertugliflozin+Sitagliptin	96	1.22
*SGLT2i+SGLT1i	47	0.60
Gender		
* Male	53420	47.88
* Female	48569	43.53
* Missing	9575	8.58
Age		
* <18	78	0.07
*18~64	48020	43.04
* >=65	22079	19.79
* Missing	41387	37.10
Weight		
* <=74	7218	6.47
* <=88	7050	6.32
* <=104	7195	6.45
*>104	7035	6.31
* Missing	83066	74.46
Year		
* 2015	16782	15.04
* 2016	13461	12.07
* 2017	15706	14.08
* 2018	25688	23.03
* 2019	21410	19.19
* 2020	18517	16.60
Reporter_Country		
* United States	80939	72.55
* Japan	5558	4.98
* Canada	3863	3.46
* Great Britain	3683	3.30
* Germany	2889	2.59
* Other countries	13509	12.11
* NOT SPECIFIED	1123	1.01
Outcome		
* Death	1865	1.67
* Life-threatening	3026	2.71
* Disability	2807	2.52
* Hospitalization	35064	31.43
* Congenital anomaly	55	0.05
* Other serious	31418	28.16
* Required intervention	133	0.12
* Missing	37196	33.34

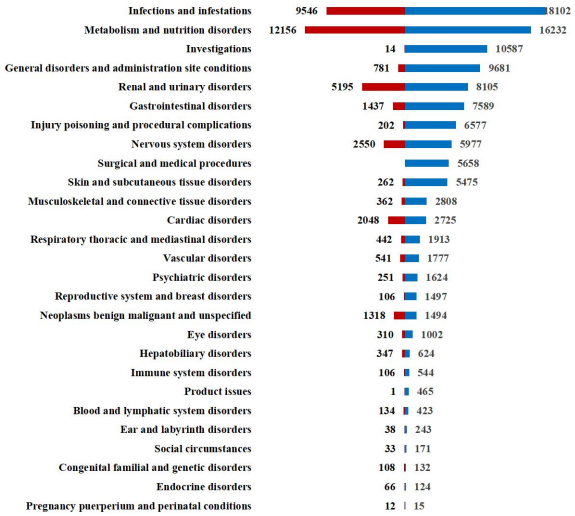

Figure 2 | Reports of SGLT2i-induced AEs and IMEs in different SOCs*.

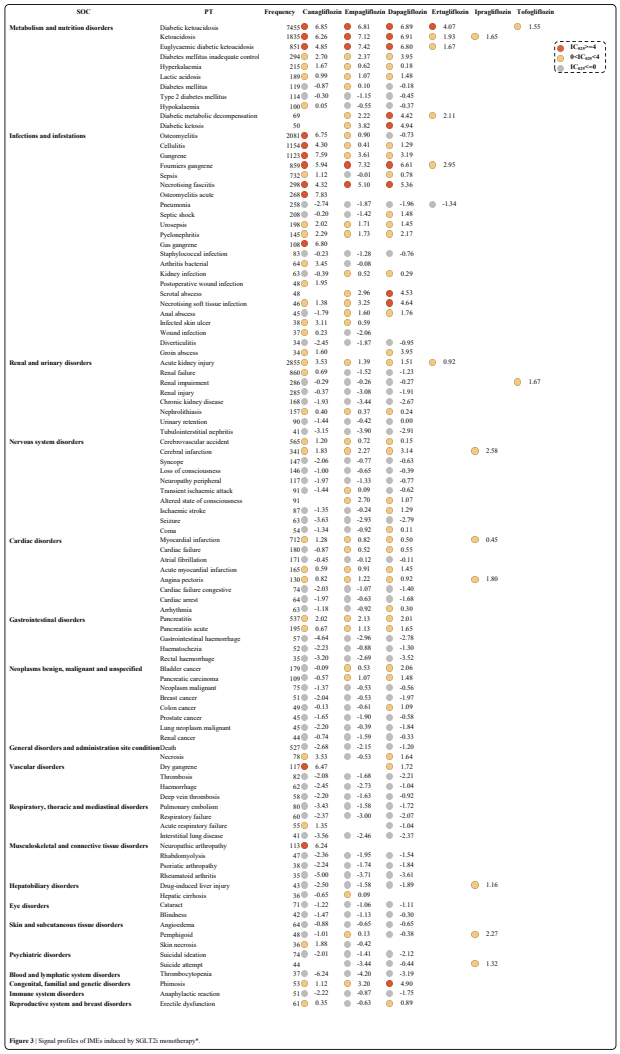

Figure 3 | Signal profiles of IMEs induced by SGLT2i monotherapy*.