Association between Diabetes Treatment and Urinary Tract Infections: An Analysis Using Data from the JMDC Claims Database

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OBJECTIVE

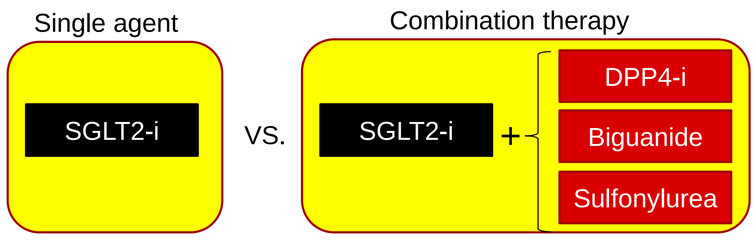
The sodium-glucose cotransporter-2 (SGLT2) inhibitors are glucose-lowering drugs which inhibit glucose reabsorption from the early proximal tubule whereas there is also potential risk for urinary tract infections (UTIs).

We analyzed the occurrence of UTIs among diabetic patients with single agent of SGLT2 inhibitor (SGLT2-i) and with combination therapy (SGLT2-i+), which is also commonly administered, by using data from the Japan Medical Data Center (JMDC) Claims Database.

METHODS

Data Source: The claims data from April 2015 to March 2017

Exposure/Control:



Outcome: Urinary Tract Infections (UTIs) defined by International Classification of Diseases 10th revision (ICD-10)

Exception:
- Diagnosed as UTIs in 3 months before the study period
- Prescribed SGLT2-i once in the study period

Statistical Analysis: Cox proportional hazards model analysis was performed (covariates: age, gender, and diabetes severity) and the incidence rate was calculated

Code Definition

Table 1 UTIs

ICD-10	ICD-10 Description
N300	Acute cystitis
N308	Other cystitis
N309	Cystitis, unspecified
N390	Urinary tract infection, site not specified
B373	Candidiasis of vulva and vagina

Table 2 Diabetes Severity

Type	ICD-10	ICD-10 Description
Diabetic retinopathy	E113	Type 2 diabetes mellitus with ophthalmic complications
	E143	Unspecified diabetes mellitus with ophthalmic complications
Diabetic nephropathy	E112	Type 2 diabetes mellitus with kidney complications
	E142	Unspecified diabetes mellitus with renal complications
Diabetic neuropathy	E114	Type 2 diabetes mellitus with neurological complications
	E144	Unspecified diabetes mellitus with neurological complications
	E115	Type 2 diabetes mellitus with circulatory complications
	E145	Unspecified diabetes mellitus with peripheral circulatory complications

Defining “SEVERE” if patients were recorded any of above diagnoses at baseline

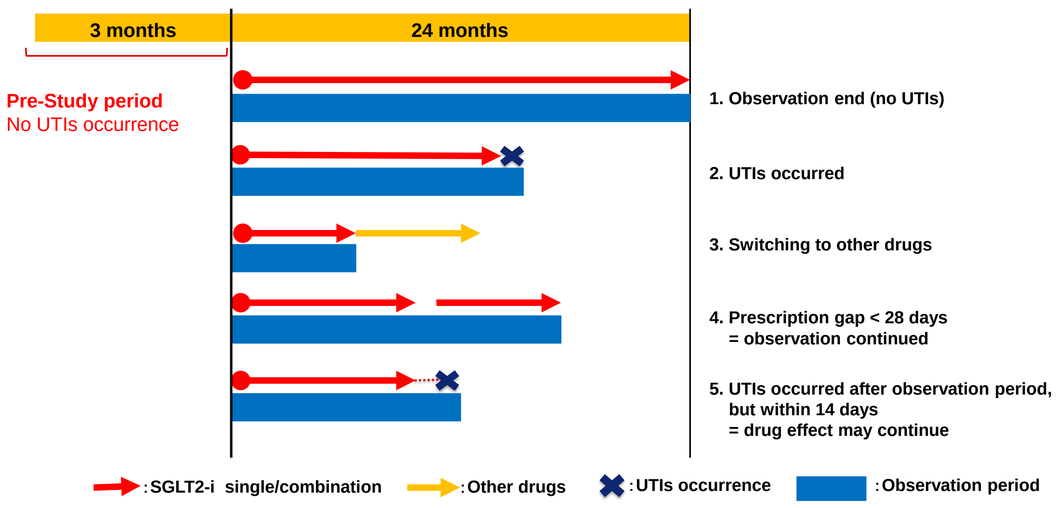


Fig. 1 Study Period

RESULTS

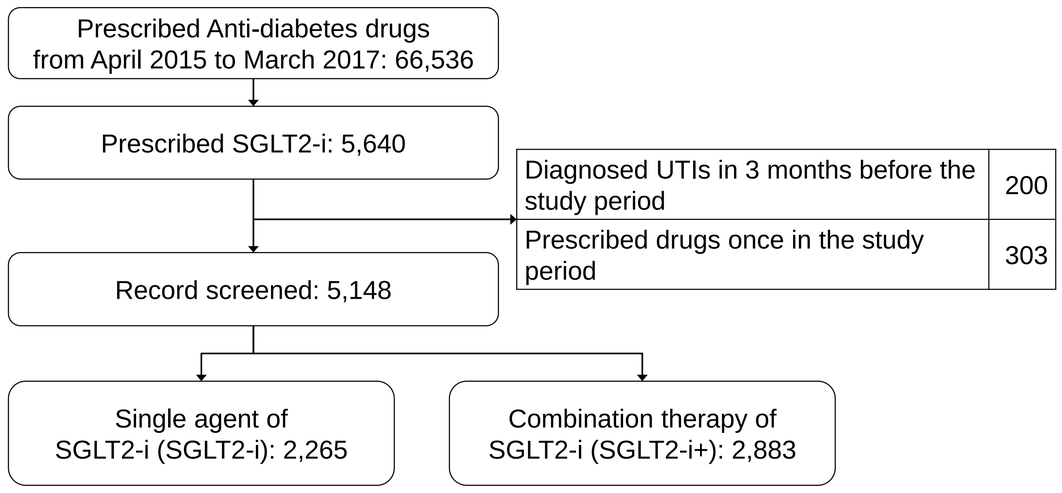


Fig. 2 Cohort creation diagram

Table 3 Patient baseline characteristics (%), $p < 0.05$

		All	SGLT2-i	SGLT2-i+
Overall		5,148	2,265	2,883
Gender	**Male**	3,603 (70.0)	1,587 (70.1)	2,016 (69.9)
	Female	1,545 (30.0)	678 (29.9)	867 (30.1)
Age [years]	**<15**	0 (0.0)	0 (0.0)	0 (0.0)
	15-65	4,872 (94.6)	2,133 (94.2)	2,739 (95.0)
	65<	276 (5.4)	132 (5.8)	144 (5.0)
	Mean±SD	50.6±9.21	50.2±9.45	50.7±9.02
HbA1c [percent]	**<8.4**	2,410(46.8)	1,211 (53.5)	1,199 (41.6)
	8.4<	807 (15.7)	261 (11.5)	546 (18.9)
	Unknown	1,931 (37.5)	793 (35.0)	1,138 (39.5)
	Mean±SD	7.7±1.6	7.3±1.55	8.0±1.56
Diabetes Severity	**Severe**	2,563 (49.8)	914 (40.4)	1,649 (57.2)
	Not Severe	2,585 (50.2)	1,351 (59.6)	1,234 (42.8)

Table 4 Incidence rate [95% CI], $p < 0.05$

	Overall	Person-year	Average Person-year	UTIs Cases	Incidence rate (per 100 person-year)
All	5,148	3750.7	0.729	573	15.28 [14.05 – 16.58]
SGLT2-i	2,265	1371.7	0.606	247	18.01 [15.83 – 20.40]
SGLT2-i+	2,883	2379.0	0.825	326	13.70 [12.26 – 15.27]

No difference in the given dose of SGLT2-i

Table 5 Multivariate Cox proportional hazard analysis [95% CI]

		Overall	UTIs Cases	Prevalence Proportion (%)	Adjusted Hazard Ratio	p-value
All		5,148	573	11.1		
Drugs	**SGLT2-i**	2,265	247	10.9		
	SGLT2-i+	2,883	326	11.3	0.77 [0.65 – 0.91]	p < 0.01
Gender	**Male**	3,603	255	7.1		
	Female	1,545	318	20.6	3.04 [2.57 – 3.59]	p < 0.01
Age (years)		5,148	573	11.1	0.99 [0.98 – 1.00]	p = 0.100
Diabetes Severity	**Severe**	1,620	190	11.7		
	Not Severe	3,528	383	10.9	1.18 [0.99 – 1.40]	p = 0.064

JMDC Claims Database

- One of the largest claims database in Japan.
- The health insurance societies are composed with employees and their families, so that the most of data is about less than 65 years old
- Eligibility information, claims(in-patient, out-patient, pharmacy) received from payers (health insurance societies), as well as annual health checkups data
- Cumulative observed population of 5,600,000 with data from 2005 (at June 2018)
- Being population based with eligibility information, JMDC Claims Database permits to assess the prevalence and/or incidence of disease
- The ability to grant insured individuals a unique ID and track their movement and treatment across medical facilities

※ Annual health checkups available data is limited.

DISCUSSION

The dosing period of SGLT2-i was shorter than SGLT2-i+. and there was no difference in the given dose of SGLT2-i between single agent and combination therapy.
Nevertheless, SGLT2-i had an increased risk and hazard ratio of UTIs relative to SGLT2-i+.
This result suggests that SGLT2-i is more likely to cause UTIs because SGLT2-i increase urinary glucose based on mechanism action whereas other antidiabetics included in SGLT2-i+ help control blood glucose.

Limitation of study

This result may not be generalized in elderly population (over 65 years old) due to the composition of JMDC.
There may be unmeasured confounding factors and biases.
We have to analyze and discuss the results with these limitations in mind.
It is useful to compare some different kind of databases like this study.

Conflict of Interest (COI) Disclosure
Akiko Tamon, Makoto Goto, Shinichi Yamaguchi, Toshio Yoshii
The authors have no financial conflicts of interest to disclose concerning the presentation.