

## Supplementary Material

### **Risk of urogenital bacterial infection with sodium-glucose cotransporter-2 inhibitors: A retrospective cohort study using a claims database**

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**Supplementary Table S1.** Outcomes and procedural definitions

**Supplementary Table S2.** Covariates definitions

**Supplementary Table S3.** Additional baseline characteristics

**Supplementary Table S4.** Subgroup analyses of urinary tract infections

**Supplementary Table S5.** Subgroup analyses of genital bacterial infections

**Supplementary Table S6.** Subgroup analyses of perineal soft tissue infections

**Supplementary Table S1.** Outcomes and procedural definitions

Outcome	Definitions
<b>Perineal soft tissue infections</b>	
Necrotizing fasciitis	Japanese electronic claims codes: 8843235, 8846832, or 8848293 PLUS
	Hospitalization PLUS
	Debridement or related surgical procedure
Cellulitis	Japanese electronic claims codes: 8830833, 8836798, or 8837993 PLUS
	Any antibiotics (J01)
Skin abscess	Japanese electronic claims codes: 6164003, 8836796, or 8837992 PLUS
	Any antibiotics (J01)
<b>Genital bacterial infections</b>	
Orchitis, epididymitis	Japanese electronic claims codes: 8831629, 8835905, 8835899, 8835920, 8845529, 6049013, 6049004, 8842191, or 8845610 PLUS
	Any antibiotics (J01)
Balanoposthitis, abscess or cellulitis of corpus cavernosum and penis	Japanese electronic claims codes: 6071004, 6071007, 6071014, 6072002, 6072004, 8831051, or 8831054 PLUS
	Any antibiotics (J01)
Vesiculitis, vasitis, scrotitis, scrotal abscess	Japanese electronic claims codes: 8835946, 6084008, 6084009, 8830679, 8830701, or 8836782 PLUS
	Any antibiotics (J01)

Prostatitis, prostatic abscess	Japanese electronic claims codes: 8845528, 8845611, 8845609, 6011001, or 6012001 PLUS Any antibiotics (J01)
Salpingitis, oophoritis	Japanese electronic claims codes: 8832442, 8832459, 8832460, 6141001, 6141002, 8840408, 6141006, 6142004, 6142005, 6142021, 6142022, 6142027, 6142010, 6142015, 6142011, or 6142017 PLUS Any antibiotics (J01)
Endometritis, metritis, myometritis, pyometra, uterine abscess, cervicitis, endocervicitis, exocervicitis	Japanese electronic claims codes: 6150002, 8847605, 6151003, 8847682, 6159007, 6159011, 6159016, 6160008, 8834208, or 8834210 PLUS Any antibiotics (J01)
Bartholinitis, Bartholin's gland abscess	Japanese electronic claims codes: 6163001, or 6168002 PLUS Any antibiotics (J01)
Vaginitis, vulvitis, abscess of the vagina or vulva	Japanese electronic claims codes: 8832317, 8833940, 8837491, 8837524, 6161027, 8840322, 6164005, 6164008, or 6164009 PLUS Any antibiotics (J01)
<b>Urinary tract infections</b>	
Pyelonephritis, renal and perinephric abscess	Japanese electronic claims codes: 8846554, 5901002, 8846804, 8845884, 8840398, 8839400, 5900001, 8840395, 5908015, 5908007, 8838724, 5902005, 5902002, or 5909001 PLUS Any antibiotics (J01)
Cystitis	Japanese electronic claims codes: 5950003, 5950005, 5952002, 5952008, 5952005, 8843107, 5959003, 8848744, 8845026, 8848787, 8840131, 5959018, 5958007, 5959011, or 5959015 PLUS Any antibiotics (J01)

Urethritis Japanese electronic claims codes: 8831091, 8841329, 8838542, 8838545, 8838549, 8840974, 8839297, 8839424, 5978008, 5978011, 5978015, 8838541, 8838544, 8840142, or 5978028 PLUS  
Any antibiotics (J01)

Urinary tract infection (site not specified) Japanese electronic claims codes: 389011, 8832418, 8842093, 8838561, 8839047, 5990009, or 8840382 PLUS  
Any antibiotics (J01)

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**Procedures**

Debridement or related surgical procedures Japanese electronic claims codes: 150001570, 150001810, 150001910, 150002010, 150002210, 150002310, 150002410, 150342970, 150368370, 150423370, 150186510, 150187110, 150187210, 150245410, 150297510, 150325210, 150337810, 150337910, 150402470, 150402570, 150407210, 150407310, 150407410, 150420610, 150189810, 150202410, 150206410, 150206510, 150207310, 150207510, 150207910, 150208810, 150209510, 150212410, or 140012950

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**Supplementary Table S2.** Covariates definitions

Covariates	Definition
<b>Diabetic complications</b>	<b>ICD-10 codes</b>
Nephropathy	E11.2, E14.2
Retinopathy	E11.3, E14.3
Neuropathy	E11.4, E14.4
Peripheral vascular disease	E11.5, E14.5
<b>Comorbidities</b>	<b>ICD-10 codes</b>
Hypertension	I10-I15
Ischemic heart disease	I20-I25
Heart failure	I50
Chronic kidney disease	N18
Liver disease	K70-K77
Cerebrovascular disease	I60-I69
Peripheral artery disease	I70, I73, I74
COPD	J43
Autoimmune disease	M05-M14, M30-M36
Cancer	C00-C97
HIV infection	B20-B24
Urinary tract infection	Japanese electronic claims codes: 389011, 8832418, 8842093, 8838561, 8839047, 5990009, 8840382

Neurogenic bladder	N31
Spinal cord injury	S14, S24, S34, T09.3, T91.3
Intestinal tract infection	A00-A09
Sexually transmitted disease	A50-A64
Asthma	J45
Atrial fibrillation	I48
Psychiatric disease	F20-F48, F50-F89
Prostatic hypertrophy	N40
Nephrolithiasis	N20-N23
Trauma	S30-S99, T00-T07

<b>Diabetic medications</b>	<b>ATC classification</b>
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$\alpha$ -Glucosidase inhibitors	A10BF
Meglitinides	A10BX02, A10BX03, A10BX08
Sulfonylureas	A10BB
Biguanides	A10BA
Thiazolidinediones	A10BG
GLP-1 receptor agonists	A10BJ
Insulin	A10A

<b>Comedications</b>	<b>ATC classification</b>
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Immunosuppressants	L04A
Oral corticosteroids	H02AB



β-blockers	C07A
Calcium channel blockers	C08C, C08D, C08E
RAAS inhibitors	C09A, C09C
Antithrombotics	B01AA, B01AB, B01AE, B01AF, B01AC04, B01AC05, B01AC06, B01AC22, B01AC23, B01AC24, B01AC25
Antilipidemics	C10A
Nitrates	C01D
Loop diuretics	C03CA
Antibiotics	J01

<b>Procedures</b>	<b>Japanese electronic claims codes or ICD-10 codes</b>
Irregular outpatient visits	112006470, 112006570, 112006670, 112006770, 111000570, 111000870, 111000110, 111015370, 111012510, 111014210, 111014310, 111015470, 111012710, 111013850, 111011810, 111012610, 111012810, 111014510
Colonoscopy	D313
PCI, CABG	K546-K552, Z95.1 (ICD-10), Z95.5 (ICD-10)
Urinary devices	K783-2, K783-3, J06.3 (ICD-10), Z96.0 (ICD-10)

Abbreviations: ICD-10, 10<sup>th</sup> edition of the International Classification of Diseases; ATC, Anatomical Therapeutic Chemical; COPD, chronic obstructive pulmonary disease; HIV, human immunodeficiency virus; GLP-1, glucagon-like peptide-1; RAAS, renin-angiotensin-aldosterone system; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting.

**Supplementary Table S3.** Additional baseline characteristics

	Before propensity score matching			After propensity score matching		
	SGLT2 inhibitors (n = 34,897)	DPP-4 inhibitors (n = 135,311)	SMD	SGLT2 inhibitors (n = 31,659)	DPP-4 inhibitors (n = 31,659)	SMD
<b>Characteristics</b>						
Cohort entry						
April 2014–March 2016	3399 (9.7)	37989 (28.1)	0.482	3105 (9.8)	2933 (9.3)	0.018
April 2016–March 2018	10603 (30.4)	49067 (36.3)	0.125	9681 (30.6)	9763 (30.8)	0.006
April 2018–February 2020	16202 (46.4)	38926 (28.8)	0.371	14722 (46.5)	14864 (46.9)	0.009
<b>Diabetic complications</b>						
Peripheral vascular disease, n (%)	154 (0.4)	458 (0.3)	0.016	118 (0.4)	120 (0.4)	0.001
<b>Comorbidities</b>						
HIV infection, n (%)	20 (0.1)	72 (0.1)	0.002	18 (0.1)	12 (0.0)	0.009
Urinary tract infection, n (%)	933 (2.7)	3923 (2.9)	0.014	839 (2.6)	875 (2.8)	0.007
Neurogenic bladder, n (%)	152 (0.4)	964 (0.7)	0.037	132 (0.4)	128 (0.4)	0.002
Urinary devices, n (%)	208 (0.6)	1168 (0.9)	0.031	198 (0.6)	209 (0.7)	0.004
Spinal cord injury, n (%)	26 (0.1)	130 (0.1)	0.007	23 (0.1)	14 (0.0)	0.012
Intestinal tract infection, n (%)	1962 (5.6)	6271 (4.6)	0.045	1735 (5.5)	1789 (5.6)	0.007
Sexually transmitted diseases, n (%)	129 (0.4)	357 (0.3)	0.019	116 (0.4)	112 (0.4)	0.002
Prostatic hypertrophy, n (%)	775 (2.2)	4243 (3.1)	0.057	714 (2.3)	728 (2.3)	0.003
Nephrolithiasis, n (%)	799 (2.3)	3207 (2.4)	0.005	719 (2.3)	701 (2.2)	0.004
<b>Comedications</b>						

Nitrates, n (%)	998 (2.9)	3651 (2.7)	0.010	895 (2.8)	875 (2.8)	0.004
Loop diuretics, n (%)	913 (2.6)	3465 (2.6)	0.003	781 (2.5)	723 (2.3)	0.012
<b>Healthcare utilization</b>						
Hospitalizations, n (%)	2371 (6.8)	9155 (6.8)	0.001	2140 (6.8)	2085 (6.6)	0.007
Irregular outpatient visits 0, n (%)	17996 (51.6)	79734 (58.9)	0.148	15998 (50.5)	15751 (49.7)	0.016
Irregular outpatient visits 1, n (%)	7601 (21.8)	26944 (19.9)	0.046	6998 (22.1)	7114 (22.5)	0.009
Irregular outpatient visits >1, n (%)	9300 (26.6)	28633 (21.2)	0.129	8669 (27.4)	8800 (27.8)	0.009
Colonoscopy, n (%)	438 (1.3)	1744 (1.3)	0.003	405 (1.3)	421 (1.3)	0.004
PCI or CABG, n (%)	689 (2.0)	2350 (1.7)	0.018	609 (1.9)	613 (1.9)	0.001

Abbreviations: PS, propensity score; SMD, standardized mean difference; COPD, chronic obstructive pulmonary disease; HIV, human immunodeficiency virus; GLP-1, glucagon-like peptide-1; RAAS, renin-angiotensin-aldosterone system; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting.

**Supplementary Table S4.** Subgroup analyses of urinary tract infections

	Urinary tract infection				HR (95% CI)
	Number of events		Incidence rate†		
	SGLT2	DPP-4	SGLT2	DPP-4	
	inhibitors	inhibitors	inhibitors	inhibitors	
	(n = 31,665)	(n = 31,665)	(n = 31,665)	(n = 31,665)	
Male	463	416	13.41	15.32	0.91 (0.79–1.04)
Female	667	622	50.93	58.36	0.91 (0.81–1.02)
Age					
<40 years	110	75	25.37	26.17	1.05 (0.78–1.42)
40–64 years	924	850	22.92	26.39	0.90 (0.82–0.99)
≥65 years	96	113	32.44	41.23	0.79 (0.60–1.04)
Ischemic heart disease					
yes	101	99	19.99	24.72	0.84 (0.64–1.11)
no	1029	939	24.18	27.77	0.91 (0.83–0.99)
Cerebrovascular disease					
yes	78	87	20.69	31.64	0.69 (0.50–0.93)
no	1052	951	23.99	27.12	0.92 (0.84–1.01)
Biguanides					
yes	455	375	23.96	28.21	0.90 (0.79–1.04)
no	675	663	23.58	27.03	0.90 (0.81–1.00)
Insulin					
yes	148	103	28.34	30.39	1.01 (0.79–1.31)
no	982	935	23.16	27.15	0.88 (0.81–0.97)
Sulfonylureas					
yes	126	115	24.16	30.5	0.86 (0.66–1.10)
no	1004	923	23.68	27.11	0.91 (0.83–0.99)

Abbreviations: SGLT2, sodium glucose cotransporter 2; DPP-4, dipeptidyl peptidase-4; HR, hazard ratio; CI, confidence interval.

† Per 1000 person-years of follow-up.

**Supplementary Table S5.** Subgroup analyses of genital bacterial infections

	Genital bacterial infection				HR (95% CI)
	Number of events		Incidence rate†		
	SGLT2	DPP-4	SGLT2	DPP-4	
	inhibitors (n = 31,665)	inhibitors (n = 31,665)	inhibitors (n = 31,665)	inhibitors (n = 31,665)	
Male	246	141	7.07	5.13	1.43 (1.16–1.76)
Female	75	75	5.39	6.62	0.84 (0.61–1.16)
Age					
<40 years	53	30	12.05	10.35	1.23 (0.78–1.93)
40–64 years	249	167	6.04	5.05	1.24 (1.02–1.51)
≥65 years	19	19	6.22	6.63	0.93 (0.49–1.77)
Ischemic heart disease					
yes	43	17	8.40	4.15	2.08 (1.19–3.65)
no	278	199	6.38	5.73	1.15 (0.96–1.39)
Cerebrovascular disease					
yes	17	10	4.41	3.54	1.27 (0.58–2.78)
no	304	206	6.78	5.72	1.23 (1.03–1.47)
Biguanides					
yes	125	63	6.43	4.61	1.46 (1.08–1.98)
no	196	153	6.70	6.08	1.13 (0.91–1.40)
Insulin					
yes	33	17	6.12	4.86	1.32 (0.73–2.37)
no	288	199	6.65	5.63	1.22 (1.02–1.46)
Sulfonylureas					
yes	28	16	5.22	4.12	1.32 (0.71–2.44)
no	293	200	6.76	5.72	1.22 (1.02–1.46)

Abbreviations: SGLT2, sodium glucose cotransporter 2; DPP-4, dipeptidyl peptidase-4; HR, hazard ratio; CI, confidence interval.

† Per 1000 person-years of follow-up.

**Supplementary Table S6.** Subgroup analyses of perineal soft tissue infections

	Perineal soft tissue infection				HR (95% CI)
	Number of events		Incidence rate†		
	SGLT2	DPP-4	SGLT2	DPP-4	
	inhibitors (n = 31,665)	inhibitors (n = 31,665)	inhibitors (n = 31,665)	inhibitors (n = 31,665)	
Male	24	20	0.68	0.72	0.97 (0.53–1.75)
Female	6	3	0.43	0.26	1.6 (0.40–6.51)
Age					
<40 years	2	4	0.45	1.37	0.32 (0.06–1.77)
40–64 years	26	18	0.63	0.54	1.17 (0.64–2.14)
≥65 years	2	1	0.65	0.34	1.86 (0.17–20.53)
Ischemic heart disease					
yes	6	1	1.16	0.24	3.92 (0.47–32.57)
no	24	22	0.55	0.63	0.91 (0.51–1.62)
Cerebrovascular disease					
yes	2	3	0.52	1.06	0.60 (0.10–3.60)
no	28	20	0.62	0.55	1.12 (0.63–1.99)
Biguanides					
yes	10	8	0.51	0.58	0.88 (0.35–2.26)
no	20	15	0.68	0.59	1.16 (0.59–2.27)
Insulin					
yes	3	8	0.55	2.28	0.28 (0.07–1.06)
no	27	15	0.62	0.42	1.46 (0.78–2.75)
Sulfonylureas					
yes	2	5	0.37	1.28	0.33 (0.06–1.71)
no	28	18	0.64	0.52	1.26 (0.69–2.28)

Abbreviations: SGLT2, sodium glucose cotransporter 2; DPP-4, dipeptidyl peptidase-4; HR, hazard ratio; CI, confidence interval.

† Per 1000 person-years of follow-up.