

SUPPLEMENTARY MATERIAL

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Sources of Data

We used data on filled prescriptions from the national prescription registers in Sweden¹ and Denmark². These registers hold individual-level information on all drug prescriptions filled at all pharmacies in the country since July, 2005, in Sweden, and 1995 in Denmark. The registers include information on the anatomical therapeutic chemical (ATC) code of the dispensed drug, the amount of drug dispensed, and the date when the prescription was filled.

The national patient register in each of the countries contain individual-level information on outpatient and emergency department visits and inpatient admissions to all hospitals.^{3,4} We used physician-assigned procedure codes, and diagnoses according to the International Classification of Diseases, tenth revision (ICD10), to obtain information about history of disease at cohort entry for each patient and the outcome events during the study period.

We used each country's population registers to obtain information on age, sex, country of birth, migration status, and vital status of the patients included in the study.^{5,6} From Statistics Denmark and Statistics Sweden⁵ we obtained data on patients' educational level and civil status.

The National Diabetes Register includes information on risk factors in patients with type 1 or type 2 diabetes in Sweden. The information is collected by trained nurses and physicians during patient visits to outpatient and primary care clinics nationwide. The number of patients included in the register has increased over time; at present, more than 90% of all patients with drug-treated diabetes in Sweden are included.⁷ From this register, we obtained data on glycated hemoglobin, blood pressure, albuminuria, estimated glomerular filtration rate (eGFR), body-mass index and smoking for patients residing in Sweden.

By the use of the personal identification number assigned to all inhabitants in the two countries, we linked individual-level information between these sources of data.

Supplementary Table 1: ICD10 and procedure codes for exclusion criteria.

Category	Codes
No hospital contact or prescription drug during one year prior to cohort entry	
Dialysis or renal transplantation before cohort entry ^a	<i>ICD10:</i> Z49, Z940, Z992 <i>Procedure code:</i> KAS
End stage illness (severe malnutrition, cachexia, dementia, coma) before cohort entry ^a	<i>ICD10:</i> E40, E41, E42, E43, R402, R64 F00-03, G30 <i>ATC-code:</i> N06D
Drug misuse within one year before cohort entry	<i>ICD10:</i> F11, F12, F13, F14, F15, F16, F18, F19, R781, R782, R783, R784, R785, T40 <i>ATC-code:</i> N07BB, N07BC
Severe pancreatic disorder (chronic pancreatitis [defined by pancreatic enzyme substitution prescription within the past year or diagnosis at any time before cohort entry ^a], pancreatic cancer, major pancreatic surgery) before cohort entry ^a	<i>ICD10:</i> C25, K860, K861 <i>ATC-code:</i> A09AA02 (within the past year) <i>Procedure code:</i> JLC, JLE
Liraglutide with obesity indication (Saxenda) before cohort entry ^b	<i>ATC-code:</i> A10BJ02 with product number 131577 or 395175 in Denmark and 513490 in Sweden.
Any hospitalization within 30 days before cohort entry	

^a 10-year look-back

^b Ever use during time period that the drug has been available

Supplementary Table 2: ATC codes and estimated days of exposure per unit of SGLT2 inhibitors and GLP1-receptor-agonists.

	ATC definition and estimated days of supply	
	SGLT2 inhibitors	GLP1-receptor-agonists
Sweden	All units are days per tablet A10BK01 = 1.0 A10BK02 = 1.0 A10BK03 = 1.0 A10BD15 = 0.5 A10BD16 = 0.5 A10BD19 = 1.0 A10BD20 = 0.5 A10BD21 = 1.0	A10BJ01 (5 or 10 microgram): 0.5 per dose A10BJ01 (2 mg): 7.0 per dose A10BJ02: 5.0 per ml A10BJ03: 1.0 per dose A10BJ05: 7.0 per dose A10AE56: 3.0 per ml
Denmark	As in Sweden	A10BJ01 (5 or 10 microgram): 0.5 per dose A10BJ01 (2 mg): 7.0 per dose A10BJ02: 15.0 per pen A10BJ03: 14.0 per pen A10BJ05: 7.0 per dose A10AE56: not available

Supplementary Table 3: Propensity score variables and definitions.

Sociodemographic characteristics	<i>Categories</i>
Sex	Women; Men
Age	Cubic splines
Place of birth	Scandinavia; Rest of Europe; Outside Europe; Missing
Education	Primary school or high school; Vocational or short tertiary education; Medium or long tertiary education
Married/living with partner ^a	Yes; No
Comorbidities (10 yr look-back unless otherwise specified)	<i>ICD-10 codes and procedure codes</i>
<i>Cardiovascular</i>	
Acute coronary syndrome	I200, I21-22
Other ischemic heart disease	I11 (excl I110), I20 (excl I200), I24, I25
Heart failure/cardiomyopathy	I50, I110, I130, I132, I42, I43, J81
Valve disorders	I34-I37
Stroke	I60-I64
Other cerebrovascular disease	I65-I69, G45 (excl G454), G46
Atrial fibrillation	I48
Other arrhythmia	I44-I47, I49
Coronary revascularization in the past yr	Procedure code: FNA, FNB, FNC, FND, FNE, FNG
Other cardiac surgery/invasive cardiac procedure in the past yr	Procedure code F (except FNA, FNB, FNC, FND, FNE, FNG), DF020
<i>Other organs and psychiatric</i>	
COPD	J44
Other lung disease	I27, J84, R092, E662, Z99, J40-J43, J45-J47, J60-70, J92, J96, J982, J983; surgery code GBB
Venous thromboembolism	I26, I80 (excl I80.0), I81, I820, I822-I829
Cancer (excl non-melanoma skin cancer)	C00-C43, C45-C97
Liver disease	B18, I850, I859, I982, K70-K77
Rheumatic disease	M05-M09, M30-34, M351, M353, M45
Psychiatric disorder	F04-F10, F20-F99

Fracture in the past year	S02 (excl S025), S12, S22, S32, S42, S52, S62, S72, S82, S92, T02, T08, T10, T12, M484, M485, M843
Acute pancreatitis	K85
Serious urinary tract infection	N109, N300, N309, N390 Primary diagnosis / admission, or secondary diagnosis / admission if sepsis code is primary (both countries: A40, A41; Sweden, also: R650, R651)
<i>Diabetes and kidney related comorbidity</i>	
Lower limb amputations	Procedure code: NFQ, NGQ, NHQ
Arterial disease	I65, I70, I72, I73, I74, I77, K550, K551, E115, E145, E135
Renal disease	E112, I12, I13, N00-08, N17, N18, N19, N25-N27, E132, E142
Obesity ^b	E66
Diabetic eye complications	E113, E133, E143, H280, H358, H360 Procedure code: CKC10, CKC12, CKC15, CKD65
Diabetic ketoacidosis	Sweden: E110A, E111A Denmark: E111, E131, E141
Diabetes, other complications	Sweden: E110 (excl E110A), E111 (excl E111A), E130, E131, E140, E141, E160, E161, E162, E116, E117, E118, G990, G590, G632, E114, E134, E136, E137, E138, E144, E146, E147, E148, M142, M146, M908, L984 Denmark: E110, E130, E140, E160, E161, E162, E116, E117, E118, G990, G590, G632, E114, E134, E136, E137, E138, E144, E146, E147, E148, M142, M146, M908, L984
Hospitalizations and outpatient visits in the past year	
Hospitalization due to cardiovascular causes	I00-99
Hospitalization due to type 2 diabetes	E11
Hospitalization due to other causes	
Outpatient contact due to cardiovascular causes	I00-99
Outpatient contact due to type 2 diabetes	E11
Outpatient contact due to other causes	
Diabetes drugs in past 6 months	

Metformin	A10BA02, A10BD02, A10BD03, A10BD05, A10BD07, A10BD08, A10BD10, A10BD11, A10BD13, A10BD14, A10BD15, A10BD16, A10BD20
Sulfonylureas	A10BB, A10BD01, A10BD02, A10BD04, A10BD06
DPP4 inhibitors	A10BH, A10BD07, A10BD08, A10BD09, A10BD10, A10BD11, A10BD13, A10BD19, A10BD21
Insulin, fast-acting	A10AB, A10AD
Insulin, intermediate- and long-acting	A10AC, A10AD, A10AE
Other antidiabetics (glitazones, glinides, acarbose)	A10BF01, A10BG, A10BD03, A10BD04, A10BD05, A10BD06, A10BD09, A10BD14, A10BX
No diabetes drug	Not any A10
Time since first diabetes drug	A10: <1 year, 1-2 years, 3-4 years, 5-6 years, ≥7 years
Other drugs in the past year	<i>ATC code</i>
ACE-inhibitor or ARB	C09A-D
Calcium channel blocker	C08C, C08D
Loop diuretic	C03C, C03EB
Other diuretic	C03A, C03B, C03D, C03EA
Beta-blocker	C07
Digoxin	C01AA05
Nitrates	C01DA
Platelet inhibitor	B01AC
Anticoagulant	B01AA, B01AE07, B01AF, B01AX05
Lipid lowering drug	C10
Antidepressant	N06A
Antipsychotic	N05A
Anxiolytic, hypnotic or sedative	N05B, N05C
Beta-2 agonist inhalant	R03AC
Anticholinergic inhalant	R03BB
Glucocorticoid inhalant	R03BA, R03AK
Oral glucocorticoid	H02AB
NSAID	M01A
Opiate	N02A
Number of drugs used in the past yr	0-4, 5-9, 10-14, ≥15

Abbreviations: ACE-I, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; COPD, chronic obstructive pulmonary disease; DDP4, dipeptidyl peptidase 4; NSAID, non-steroidal anti-inflammatory drug; SD, standard deviation.

^a Including married or living with partner in Denmark and married in Sweden.

^b Diagnosis of obesity in secondary care.

Supplementary Table 4: Outcome definitions for primary and additional outcomes.

Outcome	ICD10 or procedure code	Type of diagnosis (primary, secondary) / type of hospital contact
Lower limb amputation (hip to toe level)	<i>Procedure codes:</i> NFQ09, NFQ19, NFQ99, NGQ09, NGQ19, NGQ99, NHQ0, NHQ1, NHQ99	NA / inpatient or outpatient surgery
Bone fracture	S02 (excl S025), S12, S22, S32, S42, S52, S62, S72, S82, S92, T02, T08, T10, T12, M484, M485, M843	Any / admission or emergency department visit
Diabetic ketoacidosis	<i>Sweden:</i> E110A, E111A <i>Denmark:</i> E111, 131, E141	Any / admission
Acute kidney injury	N17	Any / admission
Serious urinary tract infection	N109, N300, N309, N390	Primary / admission or secondary / admission if sepsis code (both countries: A40, A41; Sweden, also: R650, R651) is primary
Venous thromboembolism	I26, I80 (excl I80.0), I81, I820, I822-I829	Any / admission or emergency department visit
Acute pancreatitis	K85	Any / admission
Toe or metatarsal amputation	<i>Procedure codes:</i> NHQ03, NHQ05, NHQ07, NHQ13, NHQ14, NHQ16, NHQ17	NA / inpatient or outpatient surgery
Major osteoporotic fractures (hip, spine, proximal humerus or forearm)	S720-S722, S120-S127, S129, S220-S221, S320, S327, M484, M485, S422-S423, S52	Any / admission or emergency department visit
Pyelonephritis or urosepsis	N109, N300, N309, N390	Primary / admission (N109) or secondary / admission if sepsis code (both countries: A40, A41; Sweden, also: R650, R651) is primary

Supplementary Table 5 Validation studies for diagnostic codes and procedure codes in the national patient registers of Sweden and Denmark.

Outcome (ICD 10 codes/procedure codes)	Reference	Country (years)	Type of diagnoses	Comment	Correct diagnoses in the national patient registers (PPV) %
Leg and arm amputations (NR)	Malmstedt ²³	Sweden (NR)	NA	Validation against medical records. Personal communication to Ludvigsson et al. ²³	610/624=98.4%
Minor and major amputations (Procedure codes: NHQ02-08, NHQ12-19, NHQ90-98; NEQ, NEQ19, NEQ99, NFQ, NFQ09, NFQ19, NFQ99, NGQ, NGQ09, NGQ19, NGQ99, NHQ00, NHQ01, NHQ10, NHQ11)	Bruun ²⁵	Denmark (1989-2006)	NA	Analysis of 1381 patients with diabetes included in a cohort study. At 6 and 14 years of follow-up, the general practitioners of the participants indicated in a questionnaire whether amputations had been carried out. All events reported by the general practitioners were recorded in the National Patient Register, and all amputations in the study population recorded in the National Patient Register were also reported by the general practitioner. N=63 events at 19 years of follow-up including events between year 14-19 of follow-up only identified from the National Patient Register. N events at 6 or 14 years of follow-up were not reported.	100%
Hip fracture (NR)	National Board of Health and Welfare ³¹	Sweden (2009)	NR	15,920 cases in the Swedish Hip Fracture Register were compared with registration in the National Patient Register. The proportion of cases identified in the National Patient Register was 95.3%.	NA
Hip fracture (NR)	Nilsson ³²	Sweden (1994)	Primary diagnoses. Hospital admissions.	Validation against medical records.	21/22 = 95%

Hip fracture (NR)	Michaelsson ³ 3	Sweden (1993-1995)	NR	Women aged 50-81 years. Cases identified through procedure codes and diagnostic codes. Validated against medical records.	2556/2597=98.4%
Venous thromboembolism (ICD10: I801-I803, I26)	Sundbøll ²⁴	Denmark (2010-2012)	Position NR. Hospital admission and outpatient visits.	Validation against medical records at 1 university hospital and 2 regional hospitals.	First time venous thromboembolism: 87/99=88% Recurrent venous thromboembolism: 67/93=72%
Venous thromboembolism (ICD-8: 450.99, 451.00, 451.08, 451.09, 451.99 and ICD-10: I26, I80.1-80.9)	Severinsen ³⁴	Denmark (1994-2006)	Primary and secondary position. Hospital admissions and emergency department visits.	First time venous thromboembolism among participants in the cohort study "Diet, Cancer, and Health". Validated against medical records.	643/1100 = 58.5%
Urinary infection (ICD10: N300, N308, N309, N10)	Ingeman ³⁵	Denmark (2003-2006)	Primary and secondary position. Hospital admissions.	Study of stroke patients. Validation against medical records.	30/39 = 76.9%
Infection (ICD8: 000-001,004-006, 008-009, 070, 137, 320, 110-112, 114-117, 040-061, 075, 079, 480-486, 036.1, 038, 680-686, 010-018, 590, 595, ICD10: A00-A01, A03-A04, A06-A09; B15-B19, B20-B24, A39.0, G00-G03, B35-B49 B00-B09, B25- B34, B50-B64, A48.1, J12-J18,	Benfield ³⁶	Denmark (1993-2000)	Primary and secondary position. Hospital admissions.	Admissions to 1 hospital. Validation against medical records.	139/141 = 99%

A32.7, A39.2-4, A40-41, A48.3, A46, L00-L08, A15-A19, B90, N10-12, N30)					
Acute pancreatitis (ICD10: K859)	Munch ³⁷	Sweden, Denmark and Norway (2005-2014)	Primary. Hospital admissions.	Women ≥55 years of age with osteoporosis. Validation against medical records.	113/129 = 87.6%
Acute pancreatitis (ICD10: K859)	Razavi ³⁸	Sweden (1998 and 2007)	Primary (1998), primary and secondary (2007). Hospital admissions.	Random sample of patients with a diagnosis in the National Patient Register. Validation against medical records.	522/530 = 98%
Acute pancreatitis (ICD 8: 577.00-577.09; ICD10: K859)	Floyd ³⁹	Denmark (1981-2000)	Primary and secondary. Hospital admissions.	Random sample of 99 medical records with a diagnosis in the National Patient Register (1981-2000) and 90 women with a diagnosis in 1997 or 1999). Validation against medical records.	163/189 = 86%
Acute pancreatitis (NR)	Lindblad ²³	Sweden (NR)	NR	Validation against medical records. Personal communication to Ludvigsson et al. ²³	695/602 = 98.8%

Abbreviations: PPV: positive predictive value; NR: not reported; NA: not applicable.

Supplementary Table 6: ICD10 and procedure codes used to define history of major cardiovascular disease.

Diagnosis	ICD10/procedure code
Major cardiovascular disease (coronary revascularization, acute coronary syndrome, stroke, heart failure, peripheral artery disease)	Procedure code: FNA, FNB, FNC, FND, FNE, FNG ICD10: I200, I21-22, I60-I64, I110, I130, I132, I50, J81, I65, I70, I72, I73.9, K550, K551, E115, E135, E145

Supplementary Table 7: ICD10 and procedure codes used to define history of lower limb amputation and peripheral artery disease for subgroup analysis.

Diagnosis	ICD10/procedure code
Lower limb amputation and peripheral artery disease	Procedure code: NFQ, NGQ, NHQ ICD10: E115, E135, E145, I70.2, I73.9

Supplementary Table 8: Variable definitions for the analyses using data from the National Diabetes Register in Sweden.

Variable	Categorization	Missing values (%)^a
HbA1c (%)	≤ 6.9; 7.0-7.8; 7.9-8.7; 8.8-9.6; ≥9.7	40
Blood pressure	<i>Normotension:</i> SBP <140 mmHg AND DBP <90 mmHg <i>Stage 1 hypertension:</i> SBP ≥140 to <160 mmHg OR DBP: ≥90 to <100mmHg <i>Stage 2 hypertension:</i> SBP ≥160 mmHg OR DBP: ≥100 mmHg	20
Albuminuria	Normalalbuminuria; microalbuminuria; macroalbuminuria	38
eGFR (ml/min)	≥90; ≥60 to <90; <60	25
Body-mass index (kg/m ²)	<i>Normal weight:</i> <25 <i>Overweight:</i> ≥25 to <30 <i>Obese class I:</i> ≥30 to <35 <i>Obese class I/II:</i> ≥35	26
Current smoking	Yes/no	28

Abbreviations: SBP: systolic blood pressure; DBP: diastolic blood pressure; eGFR: estimated glomerular filtration rate.

^a Missing values in the propensity-score-matched cohort of SGLT2 inhibitor users and GLP1-receptor-agonist users in Sweden as shown in Supplementary Tables 9 and 15

Supplementary Table 9: Baseline characteristics of SGLT2 inhibitor users and GLP1-receptor-agonist users before and after propensity score matching in Sweden. Numbers are shown in n (%) unless otherwise indicated.

	Before propensity-score-matching		After propensity-score-matching	
	SGLT2 inhibitors (N=11,891)	GLP1-receptor-agonists (N=17,783)	SGLT2 inhibitors (N=10,512)	GLP1-receptor-agonists (N=10,512)
Male sex	7,533 (63)	10,287 (58)	6,493 (62)	6,480 (62)
Mean age (SD), yrs.	63 (10)	61 (10)	62 (10)	62 (10)
Place of birth				
Scandinavia	9,728 (82)	15,219 (86)	8,792 (84)	8,760 (83)
Rest of Europe	995 (8)	1,150 (6)	780 (7)	777 (7)
Outside Europe	1,166 (10)	1,413 (8)	940 (9)	974 (9)
Missing	2 (<1)	1 (<1)	0 (0)	1 (<1)
Civil status				
Married	6,183 (52)	8,995 (51)	5,441 (52)	5,435 (52)
Single	5,683 (48)	8,765 (49)	5,051 (48)	5,056 (48)
Missing	25 (<1)	23 (<1)	20 (<1)	21 (<1)
Education				
Primary-/secondary school/vocational training	9,277 (78)	13,733 (77)	8,181 (78)	8,165 (78)
Short tertiary education	1,158 (10)	1,861 (10)	1,040 (10)	1,074 (10)
Medium or long tertiary education	1,284 (11)	2,001 (11)	1,158 (11)	1,138 (11)
Missing	172 (1)	188 (1)	133 (1)	135 (1)
Year of cohort entry^a				
2013	506 (4)	1,585 (9)	463 (4)	884 (8)
2014	2,094 (18)	3,903 (22)	1,873 (18)	2,235 (21)
2015	3,729 (31)	5,667 (32)	3,304 (31)	3,343 (32)
2016	5,562 (47)	6,628 (37)	4,872 (46)	4,050 (39)
Comorbidities				
Acute coronary syndrome	1,056 (9)	1,429 (8)	878 (8)	889 (8)
Other ischemic heart disease	2,071 (17)	2,855 (16)	1,729 (16)	1,731 (16)
Heart failure/cardiomyopathy	736 (6)	1,253 (7)	648 (6)	679 (6)
Valve disorders	232 (2)	346 (2)	193 (2)	196 (2)
Stroke	460 (4)	685 (4)	390 (4)	383 (4)
Other cerebrovascular disease	525 (4)	843 (5)	461 (4)	457 (4)
Atrial fibrillation	871 (7)	1,356 (8)	754 (7)	762 (7)
Other arrhythmia	475 (4)	690 (4)	394 (4)	403 (4)
Coronary revascularization in the past year	202 (2)	232 (1)	166 (2)	159 (2)
Other cardiac surgery/invasive procedure in the past year	87 (1)	125 (1)	71 (1)	71 (1)

COPD	317 (3)	641 (4)	297 (3)	284 (3)
Other lung disease	815 (7)	1,577 (9)	766 (7)	762 (7)
Venous thromboembolism	302 (3)	533 (3)	277 (3)	289 (3)
Cancer (excluding non-melanoma skin cancer)	829 (7)	1,276 (7)	716 (7)	756 (7)
Liver disease	259 (2)	408 (2)	226 (2)	236 (2)
Rheumatic disease	326 (3)	585 (3)	306 (3)	290 (3)
Psychiatric disorder	1,442 (12)	2,678 (15)	1,339 (13)	1,360 (13)
Fracture in the past year	211 (2)	324 (2)	183 (2)	186 (2)
Acute pancreatitis	120 (1)	185 (1)	107 (1)	100 (1)
Serious urinary tract infection	250 (2)	482 (3)	228 (2)	215 (2)
Lower limb amputation	13 (<1)	16 (<1)	12 (<1)	9 (<1)
Arterial disease	544 (5)	858 (5)	473 (4)	486 (5)
Renal disease	377 (3)	1,038 (6)	369 (4)	388 (4)
Obesity ^b	1,363 (11)	3,709 (21)	1,354 (13)	1,440 (14)
Diabetic eye complications	1,841 (15)	3,349 (19)	1,687 (16)	1,721 (16)
Diabetic ketoacidosis	11 (<1)	27 (<1)	10 (<1)	9 (<1)
Diabetes, other complications	1,942 (16)	3,968 (22)	1,810 (17)	1,820 (17)
Hospitalizations and outpatient visits in the past year				
Hospitalization due to cardiovascular causes	465 (4)	712 (4)	402 (4)	394 (4)
Hospitalization due to type 2 diabetes	63 (1)	203 (1)	60 (1)	58 (1)
Hospitalization due other causes	1,177 (10)	2,062 (12)	1,058 (10)	1,073 (10)
Outpatient visit due to cardiovascular causes	1,084 (9)	1,662 (9)	942 (9)	922 (9)
Outpatient visit due to type 2 diabetes	1,388 (12)	3,188 (18)	1,334 (13)	1,349 (13)
Outpatient visit due to other causes	5,820 (49)	9,601 (54)	5,239 (50)	5,249 (50)
Diabetes drugs in the past 6 months				
Metformin	9,219 (78)	12,815 (72)	8,015 (76)	8,042 (77)
Sulphonylureas	2,691 (23)	3,354 (19)	2,269 (22)	2,280 (22)
DPP4 inhibitors	3,638 (31)	4,228 (24)	2,985 (28)	3,024 (29)
Insulin, fast-acting	2,282 (19)	5,432 (31)	2,268 (22)	2,304 (22)
Insulin, intermediate and long-acting	3,928 (33)	9,102 (51)	3,910 (37)	3,892 (37)
Other antidiabetics (glitazones, glinides, acarbose)	745 (6)	883 (5)	591 (6)	599 (6)
No diabetes drug	644 (5)	1,051 (6)	615 (6)	586 (6)
Time since first diabetes drug (years)				
<1	947 (8)	1,464 (8)	854 (8)	826 (8)
1-2	1,406 (12)	1,892 (11)	1,252 (12)	1,249 (12)
3-4	1,515 (13)	2,166 (12)	1,384 (13)	1,363 (13)
5-6	1,675 (14)	2,334 (13)	1,469 (14)	1,473 (14)

≥7	6,348 (53)	9,927 (56)	5,553 (53)	5,601 (53)
Other drugs in the past year				
ARB/ACE-I	8,245 (69)	12,502 (70)	7,338 (70)	7,354 (70)
Calcium-channel blocker	3,945 (33)	6,190 (35)	3,531 (34)	3,525 (34)
Loop diuretic	1,497 (13)	3,091 (17)	1,394 (13)	1,460 (14)
Other diuretic	1,753 (15)	2,989 (17)	1,614 (15)	1,624 (15)
Beta-blocker	5,037 (42)	7,453 (42)	4,404 (42)	4,389 (42)
Digoxin	234 (2)	341 (2)	200 (2)	201 (2)
Nitrate	1,127 (9)	1,476 (8)	932 (9)	932 (9)
Platelet inhibitors	4,219 (35)	5,844 (33)	3,562 (34)	3,563 (34)
Anticoagulant	850 (7)	1,391 (8)	748 (7)	767 (7)
Lipid lowering drug	8,229 (69)	12,257 (69)	7,250 (69)	7,199 (68)
Antidepressant	1,915 (16)	3,469 (20)	1,782 (17)	1,816 (17)
Antipsychotic	318 (3)	532 (3)	297 (3)	294 (3)
Anxiolytic, hypnotic, or sedative	2,274 (19)	3,566 (20)	2,018 (19)	2,040 (19)
Beta-2 agonist inhalant	1,034 (9)	1,945 (11)	965 (9)	960 (9)
Anticholinergic inhalant	311 (3)	546 (3)	285 (3)	281 (3)
Glucocorticoid inhalant	1,144 (10)	2,052 (12)	1,060 (10)	1,049 (10)
Oral glucocorticoid	887 (7)	1,487 (8)	796 (8)	786 (7)
NSAID	2,541 (21)	3,953 (22)	2,284 (22)	2,281 (22)
Opioid	1,995 (17)	3,566 (20)	1,838 (17)	1,833 (17)
Number of drugs used in the past year				
0-4	1,281 (11)	1,427 (8)	1,072 (10)	1,057 (10)
5-9	4,575 (38)	5,978 (34)	3,940 (37)	3,979 (38)
10-14	3,585 (30)	5,569 (31)	3,217 (31)	3,184 (30)
≥15	2,450 (21)	4,809 (27)	2,283 (22)	2,292 (22)

Abbreviations: ACE-I, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; COPD, chronic obstructive pulmonary disease; DDP4, dipeptidyl peptidase 4; NSAID, non-steroidal anti-inflammatory drug; SD, standard deviation.

^a Year of cohort entry was not included in propensity score.

^b Diagnosis of obesity in secondary care.

Supplementary Table 10: Baseline characteristics of SGLT2 inhibitor users and GLP1-receptor-agonist users before and after propensity score matching in Denmark. Numbers are shown in n (%) unless otherwise indicated.

	Before propensity-score-matching		After propensity-score-matching	
	SGLT2 inhibitors (N=9,117)	GLP1-receptor-agonists (N=9,495)	SGLT2 inhibitors (N=6,701)	GLP1-receptor-agonists (N=6,701)
Male sex	5,580 (61)	5,425 (57)	3,989 (60)	3,969 (59)
Mean age (SD), yrs.	62 (11)	60 (11)	61 (11)	61 (11)
Place of birth				
Scandinavia	7,514 (82)	8,395 (88)	5,815 (87)	5,796 (86)
Rest of Europe	676 (7)	527 (6)	404 (6)	428 (6)
Outside Europe	886 (10)	537 (6)	459 (7)	452 (7)
Missing	41 (<1)	36 (<1)	23 (<1)	25 (<1)
Civil status				
Married/living with partner	5,989 (66)	6,135 (65)	4,378 (65)	4,388 (65)
Single	3,095 (34)	3,323 (35)	2,297 (34)	2,287 (34)
Missing	33 (<1)	37 (<1)	26 (<1)	26 (<1)
Education				
Primary-/secondary school/vocational training	7,241 (79)	7,531 (79)	5,328 (80)	5,335 (80)
Short tertiary education	289 (3)	296 (3)	213 (3)	204 (3)
Medium or long tertiary education	1,211 (13)	1,325 (14)	906 (14)	910 (14)
Missing	376 (4)	343 (4)	254 (4)	252 (4)
Year of cohort entry^a				
2013	499 (5)	1,260 (13)	370 (6)	862 (13)
2014	1,554 (17)	2,531 (27)	1,161 (17)	1,774 (26)
2015	2,539 (28)	2,877 (30)	1,857 (28)	2,044 (31)
2016	4,525 (50)	2,827 (30)	3,313 (49)	2,021 (30)
Comorbidities				
Acute coronary syndrome	552 (6)	641 (7)	422 (6)	427 (6)
Other ischemic heart disease	1,397 (15)	1,623 (17)	1,057 (16)	1,063 (16)
Heart failure/cardiomyopathy	459 (5)	628 (7)	378 (6)	379 (6)
Valve disorders	170 (2)	217 (2)	133 (2)	136 (2)
Stroke	376 (4)	429 (5)	289 (4)	272 (4)
Other cerebrovascular disease	393 (4)	431 (5)	296 (4)	276 (4)
Atrial fibrillation	591 (6)	687 (7)	468 (7)	445 (7)
Other arrhythmia	359 (4)	419 (4)	279 (4)	284 (4)
Coronary revascularization in the past year	80 (1)	102 (1)	64 (1)	60 (1)
Other cardiac surgery/invasive procedure in the past year	20 (<1)	26 (<1)	15 (<1)	14 (<1)

COPD	345 (4)	495 (5)	289 (4)	275 (4)
Other lung disease	483 (5)	680 (7)	409 (6)	398 (6)
Venous thromboembolism	193 (2)	276 (3)	163 (2)	156 (2)
Cancer (excluding non-melanoma skin cancer)	604 (7)	608 (6)	436 (7)	419 (6)
Liver disease	161 (2)	201 (2)	123 (2)	140 (2)
Rheumatic disease	272 (3)	285 (3)	193 (3)	208 (3)
Psychiatric disorder	472 (5)	601 (6)	366 (5)	369 (6)
Fracture in the past year	115 (1)	125 (1)	84 (1)	82 (1)
Acute pancreatitis	78 (1)	49 (1)	49 (1)	42 (1)
Serious urinary tract infection	155 (2)	234 (2)	133 (2)	126 (2)
Lower limb amputation	21 (<1)	18 (<1)	15 (<1)	14 (<1)
Arterial disease	700 (8)	904 (10)	562 (8)	563 (8)
Renal disease	378 (4)	688 (7)	339 (5)	347 (5)
Obesity ^b	1,379 (15)	2,488 (26)	1,280 (19)	1,286 (19)
Diabetic eye complications	764 (8)	1,054 (11)	587 (9)	594 (9)
Diabetic ketoacidosis	23 (<1)	41 (<1)	19 (<1)	21 (<1)
Diabetes, other complications	1,835 (20)	2,398 (25)	1,442 (22)	1,431 (21)
Hospitalizations and outpatient visits in the past year				
Hospitalization due to cardiovascular causes	344 (4)	448 (5)	280 (4)	278 (4)
Hospitalization due to type 2 diabetes	100 (1)	166 (2)	85 (1)	76 (1)
Hospitalization due to other causes	1,195 (13)	1,534 (16)	943 (14)	947 (14)
Outpatient visit due to cardiovascular causes	617 (7)	767 (8)	491 (7)	473 (7)
Outpatient visit due to type 2 diabetes	1,976 (22)	3,047 (32)	1,720 (26)	1,755 (26)
Outpatient visit due to other causes	5,038 (55)	5,709 (60)	3,852 (57)	3,828 (57)
Diabetes drugs in the past 6 months				
Metformin	7,984 (88)	7,975 (84)	5,778 (86)	5,788 (86)
Sulphonylureas	2,266 (25)	2,159 (23)	1,668 (25)	1,675 (25)
DPP4 inhibitors	4,677 (51)	3,453 (36)	2,963 (44)	2,983 (45)
Insulin, fast-acting	514 (6)	1,392 (15)	506 (8)	532 (8)
Insulin, intermediate and long-acting	1,177 (13)	2,716 (29)	1,153 (17)	1,158 (17)
Other antidiabetics (glitazones, glinides, acarbose)	80 (1)	62 (1)	55 (1)	54 (1)
No diabetes drug	394 (4)	471 (5)	327 (5)	319 (5)
Time since first diabetes drug (years)				
<1	701 (8)	941 (10)	626 (9)	601 (9)
1-2	1,057 (12)	1,177 (12)	865 (13)	825 (12)
3-4	1,428 (16)	1,433 (15)	1,089 (16)	1,085 (16)
5-6	1,498 (16)	1,431 (15)	1,060 (16)	1,109 (17)

≥7	4,433 (49)	4,513 (48)	3,061 (46)	3,081 (46)
Other drugs in the past year				
ARB/ACE-I	6,157 (68)	6,557 (69)	4,590 (68)	4,590 (68)
Calcium-channel blocker	2,784 (31)	3,072 (32)	2,088 (31)	2,086 (31)
Loop diuretic	966 (11)	1,631 (17)	870 (13)	848 (13)
Other diuretic	1,805 (20)	2,242 (24)	1,444 (22)	1,419 (21)
Beta-blocker	2,377 (26)	2,743 (29)	1,827 (27)	1,835 (27)
Digoxin	220 (2)	278 (3)	181 (3)	176 (3)
Nitrate	378 (4)	463 (5)	280 (4)	279 (4)
Platelet inhibitors	3,228 (35)	3,509 (37)	2,375 (35)	2,401 (36)
Anticoagulant	620 (7)	741 (8)	489 (7)	473 (7)
Lipid lowering drug	6,817 (75)	7,117 (75)	5,023 (75)	5,062 (76)
Antidepressant	1,224 (13)	1,737 (18)	1,059 (16)	1,039 (16)
Antipsychotic	383 (4)	457 (5)	312 (5)	290 (4)
Anxiolytic, hypnotic, or sedative	880 (10)	1,052 (11)	693 (10)	688 (10)
Beta-2 agonist inhalant	691 (8)	942 (10)	573 (9)	562 (8)
Anticholinergic inhalant	227 (2)	308 (3)	188 (3)	188 (3)
Glucocorticoid inhalant	675 (7)	912 (10)	558 (8)	553 (8)
Oral glucocorticoid	478 (5)	552 (6)	374 (6)	337 (5)
NSAID	2,287 (25)	2,591 (27)	1,745 (26)	1,775 (26)
Opioid	1,479 (16)	1,818 (19)	1,144 (17)	1,156 (17)
Number of drugs used in the past year				
0-4	1,339 (15)	1,088 (11)	872 (13)	875 (13)
5-9	4,397 (48)	4,068 (43)	3,106 (46)	3,117 (47)
10-14	2,410 (26)	2,791 (29)	1,885 (28)	1,906 (28)
≥15	971 (11)	1,548 (16)	838 (13)	803 (12)

Abbreviations: ACE-I, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; COPD, chronic obstructive pulmonary disease; DDP4, dipeptidyl peptidase 4; NSAID, non-steroidal anti-inflammatory drug; SD, standard deviation.

^a Year of cohort entry was not included in propensity score.

^b Diagnosis of obesity in secondary care.

Supplementary Table 11. Median (interquartile range) follow-up time for primary outcomes and additional outcomes.

Outcome	Median (interquartile range) follow-up time in days		
	Total cohort	SGLT2 inhibitors	GLP1-receptor-agonists
Lower limb amputation	274 (135-516)	237 (118-431)	319 (146-599)
Bone fracture	270 (132-508)	235 (118-426)	314 (144-591)
Diabetic ketoacidosis	274 (135-517)	238 (118-431)	319 (147-599)
Acute kidney injury	274 (135-516)	237 (118-431)	319 (146-598)
Serious urinary tract infection	272 (135-514)	237 (118-430)	318 (146-595)
Venous thromboembolism	273 (135-514)	237 (118-430)	318 (146-597)
Acute pancreatitis	274 (135-516)	237 (118-431)	319 (147-599)

The most common reason for censoring was end of study period (31-32% among SGLT2 inhibitor users and 30-31% among GLP1-receptor-agonist users).

Supplementary Table 12: Association between use of SGLT2 inhibitors vs. GLP1-receptor-agonists and risk of additional outcomes.

	SGLT2 inhibitors (n=17,213)		GLP1-receptor-agonists (n=17,213)		Hazard ratio (95% CI)	Absolute risk difference (95% CI) ^a
	n events	n events per 1000 person-years	n events	n events per 1000 person-years		
Toe or metatarsal amputation	26	1.7	21	1.1	1.55 (0.87-2.77)	0.6 (-0.1-1.9)
Major osteoporotic bone fracture ^b	93	6.2	113	5.9	1.05 (0.80-1.39)	0.3 (-1.2-2.3)

^a n events per 1000 patient years. Calculated as (Hazard ratio-1) x rate of the comparator.

^b Major osteoporotic fracture (hip, spine, proximal humerus or forearm) as defined in Supplementary Table 4.

Supplemental Table 13 P-values for homogeneity of associations in subgroup analyses.

	Country	Sex	Age	CVD	PAD/LLA	Insulin use
Lower limb amputation	0.70	0.27	0.48	0.71	0.78	
Bone fracture	0.51	0.47	0.65	0.35		
Diabetic ketoacidosis	0.80	0.23	0.19	0.74		0.65
Acute kidney injury	0.46	0.99	0.70	0.19		
Serious urinary tract infection	0.08	0.94	0.13	0.91		
Venous thromboembolism	0.95	0.31	0.21	0.85		
Acute pancreatitis	0.32	0.08	0.22	0.69		

Subgroups were: country (Sweden/Denmark); sex (men/women); age (<65/≥65 years); history of cardiovascular disease (yes/no); history of peripheral artery disease or lower limb amputation (yes/no); insulin use at cohort entry (yes/no)
 Abbreviations: CVD, cardiovascular disease; PAD, peripheral artery disease; LLA, lower limb amputation.

Supplementary Table 14: Association between use of SGLT2 inhibitors vs. GLP1-receptor-agonists and risk of diabetic ketoacidosis, and acute kidney injury in additional analyses with follow-up time limited to 6 months after treatment initiation.

	SGLT2 inhibitors (n=17,213)		GLP1-receptor-agonists (n=17,213)		Hazard ratio (95% CI)
	n events	n events per 1000 person- years	n events	n events per 1000 person- years	
Diabetic ketoacidosis	12	1.7	5	0.7	2.50 (0.88-7.10)
Acute kidney injury	21	3.0	24	3.3	0.93 (0.52-1.67)

Supplementary Table 15: Distribution of variables from the National Diabetes Register in Sweden among SGLT2 inhibitor users^a and GLP1-receptor-agonist users, before and after propensity-score-matching. Numbers are shown in n (%).

	Before propensity-score matching		Propensity-score-matched cohort	
	SGLT2 inhibitors (n=11,891)	GLP1-receptor-agonists (n=17,783)	SGLT2 inhibitors (n=10,512)	GLP1-receptor-agonists (n=10,512)
HbA1c (%)				
≤ 6.9	540 (5)	893 (5)	490 (5)	505 (5)
7.0-7.8	1,823 (15)	2,306 (13)	1,560 (15)	1,490 (14)
7.9-8.7	1,945 (16)	2,913 (16)	1,693 (16)	1,770 (17)
8.8-9.6	1,329 (11)	2,223 (13)	1,192 (11)	1,291 (12)
≥9.7	1,357 (11)	2,421 (14)	1,224 (12)	1,348 (13)
Missing	4,897 (41)	7,027 (40)	4,353 (41)	4,108 (39)
Blood pressure (mmHg)				
SBP < 140 and DBP < 90	5,271 (44)	7,882 (44)	4,656 (44)	4,643 (44)
SBP 140-159 OR DBP 90-99	3,135 (26)	4,931 (28)	2,755 (26)	2,950 (28)
SBP ≥160 OR DBP ≥100	972 (8)	1,477 (8)	875 (8)	883 (8)
Missing	2,513 (21)	3,493 (20)	2,226 (21)	2,036 (19)
Albuminuria				
Normalalbuminuria	5,329 (45)	7,917 (45)	4,718 (45)	4,719 (45)
Microalbuminuria	1,502 (13)	2,447 (14)	1,327 (13)	1,423 (14)
Macroalbuminuria	393 (3)	880 (5)	358 (3)	470 (4)
Missing	4,667 (39)	6,539 (37)	4,109 (39)	3,900 (37)
eGFR (ml/min)				
≥90	4,175 (35)	6,050 (34)	3,721 (35)	3,533 (34)
≥60 to 89	3,826 (32)	5,359 (30)	3,366 (32)	3,284 (31)
<60	772 (6)	2,009 (11)	683 (6)	1,111 (11)
Missing	3,118 (26)	4,365 (25)	2,742 (26)	2,584 (25)
Body mass index (kg/m²)				
<25	683 (6)	314 (2)	550 (5)	230 (2)
25-29	2,875 (24)	2,655 (15)	2,450 (23)	1,710 (16)
30-34	3,010 (25)	5,026 (28)	2,700 (26)	3,074 (29)
≥35	2,063 (17)	5,310 (30)	1,946 (19)	2,862 (27)
Missing	3,260 (27)	4,478 (25)	2,866 (27)	2,636 (25)
Current smoking				
No	7,145 (60)	11,151 (63)	6,348 (60)	6,655 (63)
Yes	1,257 (11)	1,845 (10)	1,115 (11)	1,063 (10)
Missing	3,489 (29)	4,787 (27)	3,049 (29)	2,794 (27)

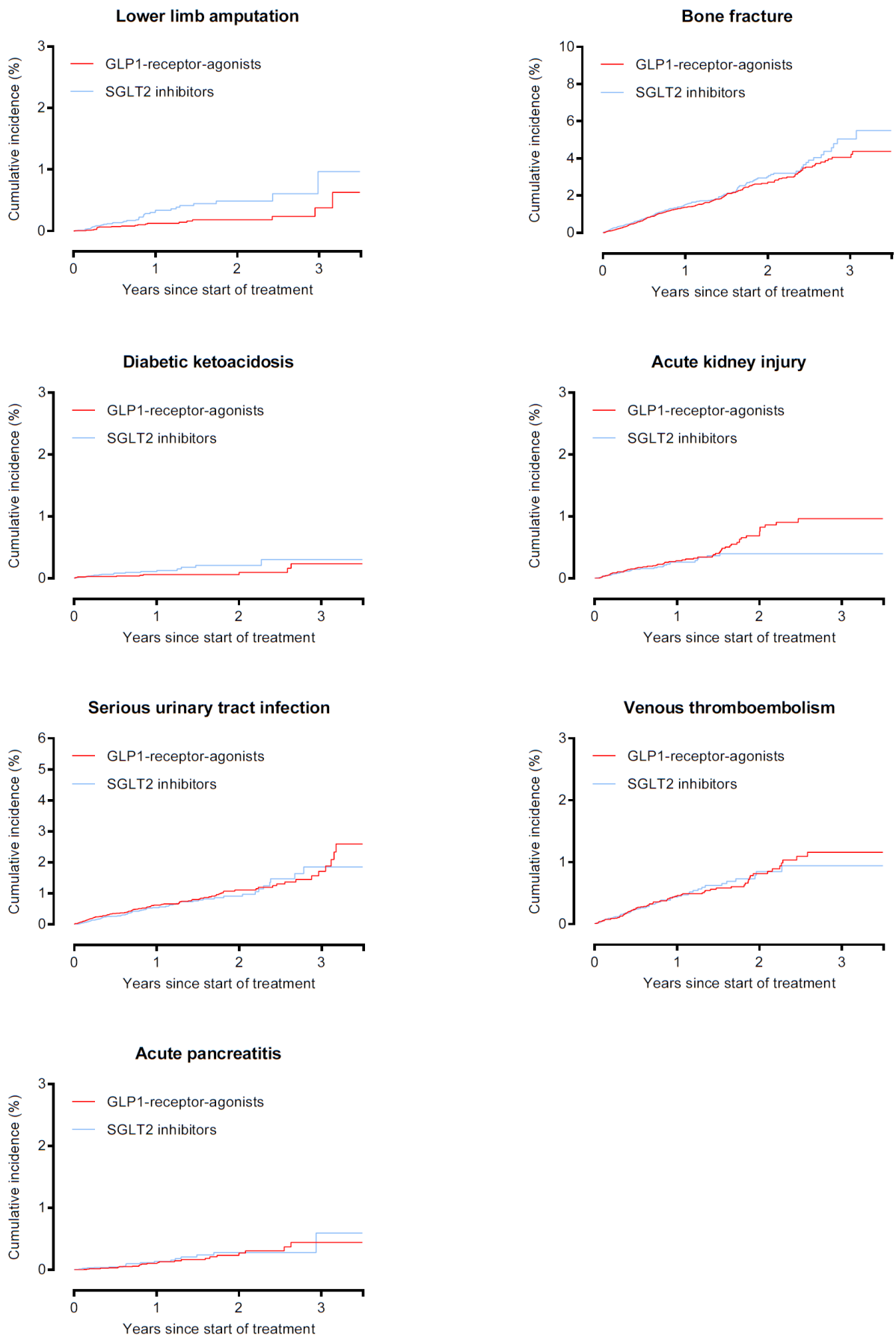
Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate

^a The propensity-score-matched cohort in Sweden, as presented in Supplementary Table 9. The variables in this table were adjusted for in the Cox regressions and were not used for propensity-score-matching.

Supplementary Table 16 Hazard ratios (95% CI) for use of SGLT2 inhibitors vs GLP1-receptor-agonists for each imputation in the analysis in the propensity-score-matched cohort in Sweden, adjusting for glycated hemoglobin level, blood pressure, eGFR, albuminuria, body-mass index and smoking, using multiple imputation for missing values.^{8,9}

Imputation	Lower limb amputation	Bone fracture	Diabetic ketoacidosis	Acute kidney injury	Serious urinary tract infection	Venous thromboembolism	Acute pancreatitis
1	2.86 (1.22-6.68)	1.10 (0.87-1.40)	2.14 (0.79-5.78)	0.72 (0.44-1.18)	0.84 (0.57-1.23)	1.10 (0.72-1.70)	1.50 (0.71-3.20)
2	2.72 (1.16-6.40)	1.09 (0.85-1.38)	2.11 (0.78-5.71)	0.70 (0.43-1.15)	0.81 (0.55-1.20)	1.09 (0.71-1.68)	1.49 (0.70-3.18)
3	2.76 (1.18-6.46)	1.10 (0.87-1.40)	2.20 (0.81-5.98)	0.73 (0.44-1.19)	0.81 (0.55-1.19)	1.11 (0.72-1.70)	1.36 (0.64-2.90)
4	2.77 (1.19-6.48)	1.09 (0.86-1.38)	2.04 (0.76-5.51)	0.71 (0.44-1.17)	0.82 (0.55-1.20)	1.11 (0.72-1.70)	1.41 (0.66-3.00)
5	2.83 (1.21-6.61)	1.10 (0.86-1.39)	2.03 (0.75-5.49)	0.74 (0.45-1.20)	0.82 (0.56-1.22)	1.11 (0.72-1.72)	1.49 (0.70-3.18)
6	2.98 (1.28-6.98)	1.11 (0.88-1.41)	2.18 (0.81-5.90)	0.73 (0.44-1.19)	0.80 (0.54-1.18)	1.13 (0.73-1.74)	1.53 (0.72-3.26)
7	2.80 (1.20-6.52)	1.09 (0.86-1.38)	2.22 (0.82-6.00)	0.72 (0.44-1.17)	0.78 (0.53-1.16)	1.10 (0.71-1.69)	1.45 (0.68-3.09)
8	2.88 (1.23-6.74)	1.09 (0.86-1.39)	2.24 (0.83-6.05)	0.73 (0.44-1.19)	0.83 (0.56-1.22)	1.15 (0.74-1.76)	1.52 (0.72-3.25)
9	2.65 (1.14-6.20)	1.09 (0.86-1.39)	2.15 (0.79-5.82)	0.72 (0.44-1.18)	0.81 (0.55-1.20)	1.07 (0.69-1.64)	1.40 (0.66-2.97)
10	2.71 (1.16-6.32)	1.07 (0.84-1.35)	2.01 (0.75-5.42)	0.73 (0.44-1.19)	0.80 (0.54-1.18)	1.12 (0.73-1.73)	1.51 (0.71-3.21)
Combined	2.79 (1.19-6.55)	1.09 (0.86-1.39)	2.13 (0.79-5.78)	0.72 (0.44-1.18)	0.81 (0.55-1.20)	1.11 (0.72-1.71)	1.47 (0.69-3.14)

Supplementary Figure 1 Cumulative incidence of primary outcome serious adverse events.



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