

SUPPLEMENTARY APPENDIX

Use of sodium glucose cotransporter 2 inhibitors and risk of major cardiovascular events and heart failure: Scandinavian register based cohort study

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WebTable 1. Exclusion criteria

Exclusion criterion	Codes (ICD-10, NCSP, or ATC)
Dialysis or renal transplantation at any time before index date ^a	ICD-10: Z49.x, Z94.0, Z99.2 NCSP: KAS (all countries); BJFD, BJFZ (Denmark only); DR012-DR016, DR023, DR024, DR055, DR056, DR060, DR061 (Sweden only)
End-stage illness (severe malnutrition, cachexia, dementia, coma) at any time before index date ^a	ICD-10: E40.x-E43.x, F00.x-F03.x, G30.x, R40.2, R64.x; ATC: N06D
Drug misuse within last year	ICD-10: F11.x-F16.x, F18.x, F19.x, R78.1-R78.5, T40.x; ATC: N07BB, N07BC
Major pancreatic disease (chronic pancreatitis [defined by pancreatic enzyme substitution prescription within last year or diagnosis at any time before index date], pancreatic cancer, major pancreatic surgery at any time before index date ^a)	ICD-10: C25.x, K86.0, K86.1; NCSP: JLC, JLE; ATC: A09AA02
No prescription drug or register entry in the national patient register within 1 year before index date	n.a.
Any-cause hospitalization within 30 days before index date	n.a.
Abbreviations: ATC, Anatomical Therapeutic Chemical; ICD, International Classification of Diseases; NCSP, NOMESCO Classification of Surgical Procedures. ^a 10-year lookback in Danish and Swedish datasets, 5-year lookback in Norwegian dataset	

WebTable 2. Data sources

	Registers	Data
Prescription registers	-Danish National Prescription Registry -Norwegian Prescription Database (NorPD) -Swedish Prescribed Drug Register	Filled prescriptions from all pharmacies in the respective countries; data on specific drug entity, date of dispense, amount of drug
Patient registers	-Danish National Patient Register -Norwegian Patient Registry -Swedish National Patient Register	Diagnoses and procedures from all specialist care (in-hospital and outpatient) in the respective countries; data on ICD-10 codes, procedure codes, date of contact
Population registers Central bureaus of statistics	-Danish Civil Registration System -Statistics Denmark -Norwegian National Registry -Swedish Total Population Register -Statistics Sweden	Nationwide demographic information, vital status, socioeconomic variables
Cause of death registers	-Danish Register of Causes of Death -Norwegian Cause of Death Registry -Swedish Cause of Death Register	Nationwide cause of death data based on death certificates, classified according to ICD-10
Diabetes register	-Swedish National Diabetes Register	Swedish nationwide clinical information regarding patients with type 2 diabetes, e.g. HbA1c, eGFR, albuminuria, smoking

WebTable 3. Variables included in propensity score, with definitions

Variable	Codes
Demographic and socioeconomic characteristics	
Sex	
Age group (5-year age bands)	
Place of birth (Scandinavia, ^a Rest of Europe, Outside Europe)	
Civil status (Married/living with partner, Single)	
Education ^b (Primary-/secondary school/vocational training, Short tertiary education, Medium/long tertiary education)	
Comorbidities	<i>ICD-10/NCSP code</i>
Acute coronary syndrome	I20.0, I21.x, I22.x
Other ischemic heart disease	I11.x (not I11.0), I20.x (not I20.0), I24.x, I25.x
Heart failure/cardiomyopathy	I11.0, I13.0, I13.2, I42.x, I43.x, I50.x, J81.x
Valve disorders	I34.x-I37.x
Stroke	I60.x-I64.x
Other cerebrovascular disease	G45.x (not G45.4), G46.x, I65.x-I69.x
Atrial fibrillation	I48.x
Other arrhythmia	I44.x-I47.x, I49.x
Coronary revascularization in the past year	NCSP: FNA-FNE, FNG, FNP02, FNP12, FNQ05, FNQ12, FNR22
Other cardiac surgery/invasive procedure in the past year	NCSP: DF020, Fxx (not FNA-FNE, FNG, FNP02, FNP12, FNQ05, FNQ12, FNR22)
COPD	J44.x
Other lung disease	E66.2, I27.x, J40.x-J43.x, J45.x-J47.x, J60.x-J70.x, ^c J84.x, J92.x, J96.x, J98.2, J98.3, R09.2, Z99.x; NCSP: GBB
Venous thromboembolism	I26.x, I80.x (not I80.0), I81.x, I82.0, I82.2-I82.9
Cancer	C00.x-C97.x (not C44.x)
Liver disease	B18.x, I85.0, I85.9, I98.2, K70.x-K77.x
Rheumatic disease	M05.x-M09.x, M30.x-M34.x, M35.1, M35.3, M45.x
Psychiatric disorder	F04.x-F10.x, F20.x-F99.x
Fracture in the past year	M48.4, M48.5, M84.3, S02.x (not S02.5), S12.x, S22.x, S32.x, S42.x, S52.x, S62.x, S72.x, S82.x, S92.x, T02.x, T08.x, T10.x, T12.x
Arterial disease (including amputation)	E11.5, E13.5, E14.5, I65.x, I70.x, I72.x-I74.x, I77.x, K55.0, K55.1; NCSP: NFQ, NGQ, NHQ
Renal disease	E11.2, E13.2, E14.2, I12.x, I13.x, N00.x-N08.x, N17.x-N19.x, N25.x- N27.x
Diabetic complications	E11.0, E11.1, E11.3, E11.4, E11.6-E11.8, E13.0, E13.1, E13.3, E13.4, E13.6-E13.8, E14.0, E14.1, E14.3, E14.4, E14.6-E14.8, E16.0-E16.2, G59.0, G63.2, G99.0, H28.0, ^d H35.8, H36.0, L98.4, M14.2, M14.6, M90.8 NCSP: CKC10, CKC12, CKC15, CKD65 ^e

Hospitalizations and outpatient visits in the past year	
Hospitalization due to cardiovascular causes	
Hospitalization due to type 2 diabetes	
Hospitalization due to other causes	
Outpatient visit due to cardiovascular causes	
Outpatient visit due to type 2 diabetes	
Outpatient visit due to other causes	
Diabetes drugs in the past 6 months	<i>ATC code</i>
Metformin	A10BA02, A10BD02, A10BD03, A10BD05, A10BD07, A10BD08, A10BD10, A10BD11, A10BD13-A10BD16, A10BD20
Sulphonylureas	A10BB, A10BD01, A10BD02, A10BD04, A10BD06
Insulin	A10AB, A10AC, A10AD, A10AE
GLP1 receptor agonists	A10BJ01, A10BJ02, A10BJ03, A10BJ05, A10AE56
Other antidiabetics (glitazones, glinides, acarbose)	A10BG, A10BX, A10BD03-A10BD06, A10BD09, A10BD14, A10BF01
No diabetes drug	
Time since first diabetes drug (<1, 1-2, 3-4, 5-6, ≥7)	
Other drugs in the past year	<i>ATC code</i>
ARB/ACE-I	C09A-C09D
Calcium-channel blocker	C08C, C08D
Loop diuretic ^b	C03C, C03EB
Other diuretic ^b	C03A, C03B, C03D, C03EA
Beta-blocker	C07
Digoxin	C01AA05
Nitrate	C01DA
Platelet inhibitors	B01AC
Anticoagulant	B01AA, B01AF, B01AE07, 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
Opioid	N02A
Number of drugs used in the past year^b (1-5, 6-10, 11-15, ≥16)	
<p>Abbreviations: ACE-I, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; ATC, Anatomical Therapeutic Chemical; COPD, chronic obstructive pulmonary disease; DDP4, dipeptidyl peptidase 4; ICD, International Classification of Diseases; NCSP, NOMESCO Classification of Surgical Procedures; NSAID, non-steroidal anti-inflammatory drug; The look-back for capture of comorbidities was 10 years in Swedish and Danish datasets and 5 years in Norwegian dataset. Diagnoses and procedures in any position and associated with any type of specialist care (inpatient and outpatient) were included.</p> <p>^aDefined as Scandinavian countries in Swedish and Danish datasets, and as Nordic countries in Norwegian dataset. ^bVariable available in Swedish and Danish datasets but not Norwegian dataset. ^cICD-10 code J70.x available in Swedish and Danish datasets but not Norwegian dataset. ^dICD-10 code H28.0 available in Swedish and Danish datasets but not Norwegian dataset. ^eNCSP codes CKC10, CKC12, CKC15, CKD65 available in Swedish and Danish datasets but not Norwegian dataset.</p>	

WebTable 4. Definitions of history of major cardiovascular disease and heart failure

Category	Codes
Major cardiovascular disease (includes acute coronary syndrome, coronary revascularization, stroke, heart failure, and peripheral vascular disease)	ICD-10: E115.x, E135.x, E145.x, I11.0, I13.0, I13.2, I20.0, I21.x, I22.x, I42.x, I43.x, I50.x, I60.x-I65.x, I70.x, I72.x, I73.9, J81.x, K55.0, K55.1; NCSP: FNA-FNE, FNG, FNP02, FNP12, FNQ05, FNQ12, FNR22
Heart failure	ICD-10: I11.0, I13.0, I13.2, I42.x, I43.x, I50.x, J81.x,
Abbreviations: ICD, International Classification of Diseases; NCSP, NOMESCO Classification of Surgical Procedures. The look-back for capture of comorbidities was 10 years in Swedish and Danish datasets and 5 years in Norwegian dataset. Diagnoses and procedures in any position and associated with any type of specialist care (inpatient and outpatient) were included.	

WebTable 5. ICD-10 codes for outcome definitions

Outcome	ICD-10 codes (sources of data)
Major cardiovascular events	I21.x, I22.x, I60.x, I61.x, I63.x, I64.x (patient registers); I00.x-I99.x, R57.0, R96.0, R96.1 (cause of death register)
Heart failure	ICD-10: I11.0, I13.0, I13.2, I50.x J81.x (patient registers and cause of death registers)
Myocardial infarction	ICD-10: I21.x, I22.x (patient registers and cause of death registers)
Stroke	ICD-10: I60.x, I61.x, I63.x, I64.x (patient registers and cause of death registers)
Cardiovascular death	ICD-10: I00.x-I99.x, R57.0, R96.0, R96.1 (cause of death registers)
Any-cause death	(population registers)
Lower limb amputation (hip to toe level)	Procedure codes: NFQ09, NFQ19, NFQ99, NGQ09, NGQ19, NGQ99, NHQ0, NHQ1, NHQ99 (patient registers)
Diabetic ketoacidosis	ICD-10: Sweden E110A, E111A; Denmark/Norway E111, E131, E141 (patient registers and cause of death registers)
Abbreviation: ICD, International Classification of Diseases	

WebTable 6. Distribution of variables from the Swedish National Diabetes Register in the Swedish part of the matched cohort of SGLT2 inhibitor and DPP4 inhibitor users. All values are n (%).

(the cohort was 1:1 matched on propensity score, age, sex, and history of major cardiovascular disease, but not on the variables from the Swedish National Diabetes Register)

Characteristic	SGLT2 inhibitors (n=9125)	DPP4 inhibitors (n=9125)
HbA1c (%)		
≤ 6.9	450 (5)	581 (6)
7.0-7.8	1239 (14)	1522 (17)
7.9-8.7	1399 (15)	1571 (17)
8.8-9.6	1050 (12)	866 (9)
≥9.7	1206 (13)	936 (10)
Missing	3781 (41)	3649 (40)
Blood pressure (mmHg)		
SBP < 140 and DBP < 90	3945 (43)	4130 (45)
SBP 140-159 or DBP 90-99	2419 (27)	2485 (27)
SBP ≥160 or DBP ≥100	780 (9)	750 (8)
Missing	1981 (22)	1760 (19)
Albuminuria		
Normalalbuminuria	4059 (44)	4163 (46)
Microalbuminuria	1207 (13)	1147 (13)
Macroalbuminuria	310 (3)	372 (4)
Missing	3549 (39)	3443 (38)
eGFR (ml/min)		
≥90	3276 (36)	2969 (33)
≥60 to 89	2843 (31)	2780 (30)
<60	569 (6)	1116 (12)
Missing	2437 (27)	2260 (25)
Body mass index (kg/m²)		
<25	420 (5)	560 (6)
25-29	1901 (21)	2317 (25)
30-34	2430 (27)	2319 (25)
≥35	1884 (21)	1600 (18)
Missing	2490 (27)	2329 (26)
Current smoking		
No	5486 (60)	5667 (62)
Yes	959 (11)	1015 (11)
Missing	2680 (29)	2443 (27)
Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate		

WebTable 7. Baseline characteristics of new users of SGLT2 inhibitors and DPP4 inhibitors in **overall cohort (Denmark, Norway, and Sweden)**, April, 2013, through December, 2016, **before matching**. All values are n (%) unless stated otherwise.

Characteristic	SGLT2 inhibitors (n=25,988)	DPP4 inhibitors (n=94,411)
Male sex	15,748 (61)	57,036 (60)
Age, mean (SD)	61 (10)	64 (11)
Country		
Sweden	10,515 (40)	42,399 (45)
Denmark	8326 (32)	27,084 (29)
Norway	7147 (28)	24,928 (26)
Place of birth		
Scandinavia	22,063 (85)	78,064 (83)
Rest of Europe	1606 (6)	6409 (7)
Outside Europe	2284 (9)	9793 (10)
Missing	35 (0)	145 (0)
Civil status		
Married/living with partner	14,892 (57)	54,254 (57)
Single	11,053 (43)	39,767 (42)
Missing	43 (0)	390 (0)
Education		
Primary-/secondary school/vocational training ^a	14,763 (78)	55,093 (79)
Short tertiary education	1390 (7)	4696 (7)
Medium or long tertiary education	2283 (12)	7614 (11)
Missing	405 (2)	2080 (3)
Year of cohort entry ^b		
2013	1773 (7)	16,155 (17)
2014	5418 (21)	23,490 (25)
2015	7599 (29)	26,701 (28)
2016	11,198 (43)	28,065 (30)
Comorbidities		
Acute coronary syndrome	1959 (8)	6703 (7)
Other ischemic heart disease	4685 (18)	15,654 (17)
Heart failure/cardiomyopathy	1485 (6)	6137 (7)
Valve disorders	548 (2)	2819 (3)
Stroke	919 (4)	4091 (4)
Other cerebrovascular disease	1083 (4)	4612 (5)
Atrial fibrillation	1748 (7)	7800 (8)
Other arrhythmia	1126 (4)	4294 (5)
Coronary revascularization in the past year	338 (1)	1210 (1)
Other cardiac surgery or invasive procedure in the past year	149 (1)	640 (1)
COPD	995 (4)	4089 (4)
Other lung disease	1837 (7)	6403 (7)
Venous thromboembolism	602 (2)	2234 (2)
Cancer	1623 (6)	7977 (8)
Liver disease	531 (2)	1756 (2)
Rheumatic disease	759 (3)	3188 (3)
Psychiatric disorder	2555 (10)	8591 (9)
Fracture in the past year	411 (2)	1637 (2)
Arterial disease (including amputation)	1798 (7)	5721 (6)
Renal disease	1263 (5)	5955 (6)

Diabetic complications	8,715 (34)	21,722 (23)
Hospitalizations and outpatient visits in the past year		
Hospitalization due to cardiovascular causes	1044 (4)	4454 (5)
Hospitalization due to type 2 diabetes	234 (1)	749 (1)
Hospitalization due to other causes	3191 (12)	12,535 (13)
Outpatient visit due to cardiovascular causes	2535 (10)	9500 (10)
Outpatient visit due to type 2 diabetes	6761 (26)	15,474 (16)
Outpatient visit due to other causes	14,808 (57)	51,580 (55)
Diabetes drugs in the past 6 months		
Metformin	20,791 (80)	75,416 (80)
Sulphonylureas	5218 (20)	22,388 (24)
Insulin	9601 (37)	14,645 (16)
GLP1 receptor agonists	6808 (26)	2256 (2)
Other antidiabetics (glitazones, glinides, acarbose)	843 (3)	2593 (3)
No diabetes drug	1687 (6)	9385 (10)
Time since first diabetes drug, years		
<1	2590 (10)	14,538 (15)
1-2	2655 (10)	13,452 (14)
3-4	2828 (11)	14,001 (15)
5-6	3254 (13)	13,191 (14)
≥7	14,661 (56)	39,229 (42)
Other drugs in the past year		
ARB/ACE-I	17,765 (68)	60,281 (64)
Calcium-channel blocker	7925 (30)	28,964 (31)
Loop diuretic ^a	2757 (15)	10,844 (16)
Other diuretic ^a	3481 (18)	12,672 (18)
Beta-blocker	9166 (35)	34,285 (36)
Digoxin	493 (2)	2409 (3)
Nitrate	1871 (7)	6493 (7)
Platelet inhibitors	9811 (38)	33,859 (36)
Anticoagulant	1765 (7)	8128 (9)
Lipid lowering drug	18,137 (70)	62,313 (66)
Antidepressant	4179 (16)	13,492 (14)
Antipsychotic	949 (4)	3570 (4)
Anxiolytic, hypnotic, or sedative	4456 (17)	16,737 (18)
Beta-2 agonist inhalant	2532 (10)	8140 (9)
Anticholinergic inhalant	757 (3)	3290 (3)
Glucocorticoid inhalant	2571 (10)	8658 (9)
Oral glucocorticoid	1810 (7)	7704 (8)
NSAID	6888 (27)	21,139 (22)
Opioid	5213 (20)	16,661 (18)
Number of drugs used in the past year^a		
0-5	3136 (17)	16,625 (24)
6-10	7538 (40)	27,932 (40)
11-15	5100 (27)	15,531 (22)
≥16	3067 (16)	9395 (14)
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; SGLT2 sodium-glucose co-transporter 2.		
^a Variable available in Denmark and Sweden but not Norway. n(%) reported for Denmark and Sweden alone.		
^b Year of cohort entry was not included in the propensity score.		

WebTable 8. Baseline characteristics of new users of SGLT2 inhibitors and DPP4 inhibitors in **Denmark**, April, 2013, through December, 2016, **before matching**. All values are n (%) unless stated otherwise.

Characteristic	SGLT2 inhibitors (n=8326)	DPP4 inhibitors (n=27,084)
Male sex	5,035 (60)	16,495 (61)
Age, mean (SD)	60 (10)	63 (11)
Place of birth		
Scandinavia	7,189 (86)	22,831 (84)
Rest of Europe	509 (6)	1,756 (6)
Outside Europe	593 (7)	2,371 (9)
Missing	35 (0)	126 (0)
Civil status		
Married/living with partner	5,497 (66)	17,481 (65)
Single	2,805 (34)	9,400 (35)
Missing	24 (0)	203 (1)
Education		
Primary-/secondary school/vocational training	6,646 (80)	21,652 (80)
Short tertiary education	302 (4)	830 (3)
Medium or long tertiary education	1,101 (13)	3,415 (13)
Missing	277 (3)	1,187 (4)
Year of cohort entry ^a		
2013	867 (10)	5,122 (19)
2014	1,500 (18)	7,080 (26)
2015	2,197 (26)	7,515 (28)
2016	3,762 (45)	7,367 (27)
Comorbidities		
Acute coronary syndrome	577 (7)	1,771 (7)
Other ischemic heart disease	1,555 (19)	4,478 (17)
Heart failure/cardiomyopathy	517 (6)	1,709 (6)
Valve disorders	148 (2)	727 (3)
Stroke	353 (4)	1,377 (5)
Other cerebrovascular disease	380 (5)	1,406 (5)
Atrial fibrillation	556 (7)	2,201 (8)
Other arrhythmia	364 (4)	1,195 (4)
Coronary revascularization in the past year	73 (1)	309 (1)
Other cardiac surgery or invasive procedure in the past year	17 (0)	85 (0)
COPD	394 (5)	1,438 (5)
Other lung disease	550 (7)	1,714 (6)
Venous thromboembolism	234 (3)	715 (3)
Cancer	518 (6)	2,159 (8)
Liver disease	174 (2)	533 (2)
Rheumatic disease	237 (3)	870 (3)
Psychiatric disorder	495 (6)	1,449 (5)
Fracture in the past year	114 (1)	410 (2)
Arterial disease (including amputation)	850 (10)	2,122 (8)
Renal disease	517 (6)	1,850 (7)
Diabetic complications	3,204 (38)	5,631 (21)
Hospitalizations and outpatient visits in the past year		

Hospitalization due to cardiovascular causes	324 (4)	1,324 (5)
Hospitalization due to type 2 diabetes	109 (1)	275 (1)
Hospitalization due to other causes	1,270 (15)	4,356 (16)
Outpatient visit due to cardiovascular causes	626 (8)	2,137 (8)
Outpatient visit due to type 2 diabetes	2,229 (27)	3,312 (12)
Outpatient visit due to other causes	4,941 (59)	14,979 (55)
Diabetes drugs in the past 6 months		
Metformin	7,184 (86)	23,615 (87)
Sulphonylureas	1,535 (18)	5,937 (22)
Insulin	3,163 (38)	2,350 (9)
GLP1 receptor agonists	3,452 (41)	942 (3)
Other antidiabetics (glitazones, glinides, acarbose)	65 (1)	170 (1)
No diabetes drug	334 (4)	1,855 (7)
Time since first diabetes drug, years		
<1	580 (7)	4,104 (15)
1-2	690 (8)	4,057 (15)
3-4	925 (11)	4,604 (17)
5-6	1,161 (14)	4,135 (15)
≥7	4,970 (60)	10,184 (38)
Other drugs in the past year		
ARB/ACE-I	5,996 (72)	17,591 (65)
Calcium-channel blocker	2,751 (33)	8,547 (32)
Loop diuretic	1,220 (15)	4,129 (15)
Other diuretic	1,830 (22)	5,761 (21)
Beta-blocker	2,334 (28)	7,632 (28)
Digoxin	200 (2)	998 (4)
Nitrate	428 (5)	1,260 (5)
Platelet inhibitors	3,413 (41)	9,823 (36)
Anticoagulant	554 (7)	2,319 (9)
Lipid lowering drug	6,384 (77)	19,678 (73)
Antidepressant	1,342 (16)	3,822 (14)
Antipsychotic	345 (4)	1,166 (4)
Anxiolytic, hypnotic, or sedative	868 (10)	3,120 (12)
Beta-2 agonist inhalant	744 (9)	2,271 (8)
Anticholinergic inhalant	217 (3)	936 (3)
Glucocorticoid inhalant	683 (8)	2,177 (8)
Oral glucocorticoid	405 (5)	1,770 (7)
NSAID	2,341 (28)	6,490 (24)
Opioid	1,618 (19)	4,590 (17)
Number of drugs used in the past year		
0-5	1,497 (18)	7,717 (28)
6-10	3,589 (43)	11,487 (42)
11-15	2,207 (27)	5,381 (20)
≥16	1,033 (12)	2,499 (9)
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; SGLT2 sodium-glucose co-transporter 2.		
ªYear of cohort entry was not included in the propensity score.		

WebTable 9. Baseline characteristics of new users of SGLT2 inhibitors and DPP4 inhibitors in **Norway**, April, 2013, through December, 2016, **before matching**. All values are n (%) unless stated otherwise.

Characteristic	SGLT2 inhibitors (n=7147)	DPP4 inhibitors (n=24,928)
Male sex	4,118 (58)	15,333 (62)
Age, mean (SD)	60 (11)	63 (11)
Place of birth		
Scandinavia	5,993 (84)	20,984 (84)
Rest of Europe	344 (5)	1,069 (4)
Outside Europe	810 (11)	2,875 (12)
Missing	0 (0)	0 (0)
Civil status		
Married/living with partner	4,055 (57)	13,988 (56)
Single	3,092 (43)	10,940 (44)
Missing	0 (0)	0 (0)
Education		
Primary-/secondary school/vocational training ^a	-	-
Short tertiary education	-	-
Medium or long tertiary education	-	-
Missing	-	-
Year of cohort entry ^b		
2013	458 (6)	5,059 (20)
2014	1,960 (27)	6,970 (28)
2015	2,055 (29)	6,585 (26)
2016	2,674 (37)	6,314 (25)
Comorbidities		
Acute coronary syndrome	437 (6)	1,474 (6)
Other ischemic heart disease	1,232 (17)	4,066 (16)
Heart failure/cardiomyopathy	277 (4)	1,328 (5)
Valve disorders	200 (3)	1,011 (4)
Stroke	157 (2)	693 (3)
Other cerebrovascular disease	228 (3)	1,007 (4)
Atrial fibrillation	396 (6)	1,744 (7)
Other arrhythmia	321 (4)	1,280 (5)
Coronary revascularization in the past year	84 (1)	332 (1)
Other cardiac surgery or invasive procedure in the past year	39 (1)	192 (1)
COPD	301 (4)	1,179 (5)
Other lung disease	451 (6)	1,598 (6)
Venous thromboembolism	88 (1)	341 (1)
Cancer	400 (6)	1,899 (8)
Liver disease	116 (2)	410 (2)
Rheumatic disease	223 (3)	870 (3)
Psychiatric disorder	701 (10)	2,023 (8)
Fracture in the past year	103 (1)	465 (2)
Arterial disease (including amputation)	420 (6)	1,553 (6)
Renal disease	270 (4)	1,822 (7)
Diabetic complications	2,133 (30)	6,187 (25)
Hospitalizations and outpatient visits in the past year		

Hospitalization due to cardiovascular causes	269 (4)	1,165 (5)
Hospitalization due to type 2 diabetes	56 (1)	170 (1)
Hospitalization due to other causes	811 (11)	3,255 (13)
Outpatient visit due to cardiovascular causes	870 (12)	3,218 (13)
Outpatient visit due to type 2 diabetes	2,770 (39)	8,029 (32)
Outpatient visit due to other causes	4,567 (64)	15,201 (61)
Diabetes drugs in the past 6 months		
Metformin	5,542 (78)	19,767 (79)
Sulphonylureas	1,720 (24)	6,962 (28)
Insulin	1,729 (24)	2,636 (11)
GLP1 receptor agonists	1,229 (17)	485 (2)
Other antidiabetics (glitazones, glinides, acarbose)	155 (2)	325 (1)
No diabetes drug	768 (11)	2,972 (12)
Time since first diabetes drug, years		
<1	1,158 (16)	4,914 (20)
1-2	882 (12)	3,588 (14)
3-4	736 (10)	3,254 (13)
5-6	804 (11)	3,123 (13)
≥7	3,567 (50)	10,049 (40)
Other drugs in the past year		
ARB/ACE-I	4,321 (60)	14,277 (57)
Calcium-channel blocker	1,607 (22)	5,985 (24)
Loop diuretic ^a	-	-
Other diuretic ^a	-	-
Beta-blocker	2,295 (32)	8,372 (34)
Digoxin	75 (1)	399 (2)
Nitrate	419 (6)	1,564 (6)
Platelet inhibitors	2,644 (37)	9,305 (37)
Anticoagulant	437 (6)	1,898 (8)
Lipid lowering drug	4,395 (61)	14,542 (58)
Antidepressant	1,022 (14)	3,235 (13)
Antipsychotic	343 (5)	1,151 (5)
Anxiolytic, hypnotic, or sedative	1,526 (21)	5,172 (21)
Beta-2 agonist inhalant	761 (11)	2,309 (9)
Anticholinergic inhalant	267 (4)	989 (4)
Glucocorticoid inhalant	785 (11)	2,427 (10)
Oral glucocorticoid	607 (8)	2,338 (9)
NSAID	2,224 (31)	6,751 (27)
Opioid	1,663 (23)	5,341 (21)
Number of drugs used in the past year^a		
0-5	-	-
6-10	-	-
11-15	-	-
≥16	-	-
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; SGLT2 sodium-glucose co-transporter 2.		
^a Variable not available in Norway.		
^b Year of cohort entry was not included in the propensity score.		

WebTable 10. Baseline characteristics of new users of SGLT2 inhibitors and DPP4 inhibitors in **Sweden**, April, 2013, through December, 2016, **before matching**. All values are n (%) unless stated otherwise.

Characteristic	SGLT2 inhibitors (n=10,515)	DPP4 inhibitors (n=42,399)
Male sex	6,595 (63)	25,208 (59)
Age, mean (SD)	62 (10)	65 (11)
Place of birth		
Scandinavia	8,881 (84)	34,249 (81)
Rest of Europe	753 (7)	3,584 (8)
Outside Europe	881 (8)	4,547 (11)
Missing	0 (0)	19 (0)
Civil status		
Married/living with partner	5,340 (51)	22,785 (54)
Single	5,156 (49)	19,427 (46)
Missing	19 (0)	187 (0)
Education		
Primary-/secondary school/vocational training	8,117 (77)	33,441 (79)
Short tertiary education	1,088 (10)	3,866 (9)
Medium or long tertiary education	1,182 (11)	4,199 (10)
Missing	128 (1)	893 (2)
Year of cohort entry ^a		
2013	448 (4)	5,974 (14)
2014	1,958 (19)	9,440 (22)
2015	3,347 (32)	12,601 (30)
2016	4,762 (45)	14,384 (34)
Comorbidities		
Acute coronary syndrome	945 (9)	3,458 (8)
Other ischemic heart disease	1,898 (18)	7,110 (17)
Heart failure/cardiomyopathy	691 (7)	3,100 (7)
Valve disorders	200 (2)	1,081 (3)
Stroke	409 (4)	2,021 (5)
Other cerebrovascular disease	475 (5)	2,199 (5)
Atrial fibrillation	796 (8)	3,855 (9)
Other arrhythmia	441 (4)	1,819 (4)
Coronary revascularization in the past year	181 (2)	569 (1)
Other cardiac surgery or invasive procedure in the past year	93 (1)	363 (1)
COPD	300 (3)	1,472 (3)
Other lung disease	836 (8)	3,091 (7)
Venous thromboembolism	280 (3)	1,178 (3)
Cancer	705 (7)	3,919 (9)
Liver disease	241 (2)	813 (2)
Rheumatic disease	299 (3)	1,448 (3)
Psychiatric disorder	1,359 (13)	5,119 (12)
Fracture in the past year	194 (2)	762 (2)
Arterial disease (including amputation)	528 (5)	2,046 (5)
Renal disease	476 (5)	2,283 (5)
Diabetic complications	3,378 (32)	9,904 (23)
Hospitalizations and outpatient visits in the past year		

Hospitalization due to cardiovascular causes	451 (4)	1,965 (5)
Hospitalization due to type 2 diabetes	69 (1)	304 (1)
Hospitalization due to other causes	1,110 (11)	4,924 (12)
Outpatient visit due to cardiovascular causes	1,039 (10)	4,145 (10)
Outpatient visit due to type 2 diabetes	1,762 (17)	4,133 (10)
Outpatient visit due to other causes	5,300 (50)	21,400 (50)
Diabetes drugs in the past 6 months		
Metformin	8,065 (77)	32,034 (76)
Sulphonylureas	1,963 (19)	9,489 (22)
Insulin	4,709 (45)	9,659 (23)
GLP1 receptor agonists	2,127 (20)	829 (2)
Other antidiabetics (glitazones, glinides, acarbose)	623 (6)	2,098 (5)
No diabetes drug	585 (6)	4,558 (11)
Time since first diabetes drug, years		
<1	852 (8)	5,520 (13)
1-2	1,083 (10)	5,807 (14)
3-4	1,167 (11)	6,143 (14)
5-6	1,289 (12)	5,933 (14)
≥7	6,124 (58)	18,996 (45)
Other drugs in the past year		
ARB/ACE-I	7,448 (71)	28,413 (67)
Calcium-channel blocker	3,567 (34)	14,432 (34)
Loop diuretic	1,537 (15)	6,715 (16)
Other diuretic	1,651 (16)	6,911 (16)
Beta-blocker	4,537 (43)	18,281 (43)
Digoxin	218 (2)	1,012 (2)
Nitrate	1,024 (10)	3,669 (9)
Platelet inhibitors	3,754 (36)	14,731 (35)
Anticoagulant	774 (7)	3,911 (9)
Lipid lowering drug	7,358 (70)	28,093 (66)
Antidepressant	1,815 (17)	6,435 (15)
Antipsychotic	261 (2)	1,253 (3)
Anxiolytic, hypnotic, or sedative	2,062 (20)	8,445 (20)
Beta-2 agonist inhalant	1,027 (10)	3,560 (8)
Anticholinergic inhalant	273 (3)	1,365 (3)
Glucocorticoid inhalant	1,103 (10)	4,054 (10)
Oral glucocorticoid	798 (8)	3,596 (8)
NSAID	2,323 (22)	7,898 (19)
Opioid	1,932 (18)	6,730 (16)
Number of drugs used in the past year		
0-5	1,639 (16)	8,908 (21)
6-10	3,949 (38)	16,445 (39)
11-15	2,893 (28)	10,150 (24)
≥16	2,034 (19)	6,896 (16)
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; SGLT2 sodium-glucose co-transporter 2.		
ªYear of cohort entry was not included in the propensity score.		

WebTable 11. Distribution of person-years of follow-up by individual DPP4 inhibitors.

DPP4 inhibitor	Person-years, n (%)
Any	36,793 (100)
Saxagliptin	24,869 (68)
Vildagliptin	6735 (18)
Linagliptin	3537 (10)
Saxagliptin	1323 (4)
Alogliptin	329 (1)

WebTable 12. Reasons for censoring in analyses of co-primary outcomes. All values are n (%)

Reason for censoring	SGLT2 inhibitor (n=20,983)	DPP inhibitor (n=20,983)
Primary analyses (intention-to-treat exposure definition)		
<i>Major cardiovascular events</i>		
End of study period	20,215 (96.3)	19,853 (94.6)
Outcome event	467 (2.2)	662 (3.2)
Death	175 (0.8)	307 (1.5)
Age 85 years	91 (0.4)	122 (0.6)
Emigration	35 (0.2)	39 (0.2)
<i>Heart failure</i>		
End of study period	20,462 (97.5)	20,122 (95.9)
Outcome event	130 (0.6)	265 (1.3)
Death	265 (1.3)	435 (2.1)
Age 85 years	92 (0.4)	122 (0.6)
Emigration	34 (0.2)	39 (0.2)
Additional analyses (as-treated exposure definition)		
<i>Major cardiovascular events</i>		
End of study period	12,568 (59.9)	11,154 (53.2)
Outcome event	281 (1.3)	433 (2.1)
Death	95 (0.5)	151 (0.7)
Age 85 years	50 (0.2)	88 (0.4)
Emigration	17 (0.1)	21 (0.1)
End of treatment	6253 (29.8)	7156 (34.1)
Cross-over to the other study drug ^a	1719 (8.2)	1980 (9.4)
<i>Heart failure</i>		
End of study period	12,671 (60.4)	11,246 (53.6)
Outcome event	73 (0.3)	172 (0.8)
Death	150 (0.7)	248 (1.2)
Age 85 years	51 (0.2)	87 (0.4)
Emigration	17 (0.1)	21 (0.1)
End of treatment	6298 (30.0)	7218 (34.4)
Cross-over to the other study drug ^a	1723 (8.2)	1991 (9.5)

^aInitiation of DPP4 inhibitor among SGLT2 inhibitor users and vice versa (may represent treatment switch or add-on).

WebTable 13. Risk of co-primary outcomes associated with use of SGLT2 inhibitors, compared with DPP4 inhibitors, according to study country

	SGLT2 inhibitors (n=20,983)		DPP4 inhibitors (n=20,983)		Hazard ratio (95% CI)
	Events	Incidence rate, events per 1000 person- years	Events	Incidence rate, events per 1000 person- years	
Major cardiovascular events					
Denmark	91	12.7	163	15.8	0.80 (0.62-1.04)
Norway	153	16.8	215	18.2	0.93 (0.75-1.15)
Sweden	223	20.0	284	19.3	1.01 (0.85-1.21)
Heart failure					
Denmark	30	4.2	66	6.4	0.68 (0.44-1.05)
Norway	30	3.3	79	6.6	0.48 (0.31-0.73)
Sweden	70	6.2	120	8.1	0.77 (0.57-1.04)

WebTable 14. Multiple imputation estimates of hazard ratios for major cardiovascular events and heart failure associated with use of SGLT2 inhibitors, HbA1c, blood pressure, eGFR, albuminuria, body mass index, and smoking. The analysis was carried out as a multivariable model in the matched cohort in Sweden.

	Major cardiovascular events	Heart failure
	Hazard ratio (95% CI)	Hazard ratio (95% CI)
Treatment		
DPP4 inhibitors	1.00 (ref.)	1.00 (ref.)
SGLT2 inhibitors	1.04 (0.87-1.24)	0.83 (0.61-1.12)
HbA1c (%)		
≤ 6.9	1.00 (ref.)	1.00 (ref.)
7.0-7.8	0.89 (0.55-1.44)	0.70 (0.32-1.54)
7.9-8.7	1.10 (0.73-1.66)	0.90 (0.46-1.76)
8.8-9.6	1.36 (0.87-2.12)	1.10 (0.54-2.24)
≥9.7	1.52 (1.00-2.30)	1.53 (0.74-3.16)
Blood pressure (mmHg)		
SBP < 140 and DBP < 90	1.00 (ref.)	1.00 (ref.)
SBP 140-159 OR DBP 90-99	1.06 (0.85-1.32)	0.97 (0.67-1.40)
SBP ≥160 OR DBP ≥100	1.11 (0.81-1.53)	1.28 (0.78-2.11)
Albuminuria		
Normalalbuminuria	1.00 (ref.)	1.00 (ref.)
Microalbuminuria	1.12 (0.89-1.41)	1.63 (1.12-2.38)
Macroalbuminuria	2.07 (1.50-2.86)	2.36 (1.44-3.87)
eGFR (ml/min)		
≥90	1.00 (ref.)	1.00 (ref.)
≥60 to 89	1.41 (1.13-1.77)	2.43 (1.57-3.77)
<60	2.37 (1.77-3.16)	6.63 (4.24-10.35)
Body mass index (kg/m²)		
<25	1.00 (ref.)	1.00 (ref.)
25-29	0.87 (0.58-1.31)	1.40 (0.47-4.18)
30-34	0.90 (0.61-1.32)	1.75 (0.54-5.66)
≥35	0.90 (0.59-1.37)	2.41 (0.83-7.02)
Current smoking		
No	1.00 (ref.)	1.00 (ref.)
Yes	1.46 (1.12-1.90)	1.41 (0.95-2.09)

WebTable 15. Post-hoc sensitivity analyses

	SGLT2 inhibitors (n=20,983)		DPP4 inhibitors (n=20,983)		Hazard ratio (95% CI)
	Events	Incidence rate, events per 1000 person- years	Events	Incidence rate, events per 1000 person- years	
Additional adjustment for country (primary analyses with intention-to-treat exposure definition)					
Major cardiovascular events	467	17.0	662	18.0	0.94 (0.83 to 1.06)
Heart failure	130	4.7	265	7.1	0.66 (0.53 to 0.81)
Gap period 30 days (additional analyses with as-treated exposure definition)					
Major cardiovascular events	208	14.5	299	16.7	0.85 (0.71 to 1.02)
Heart failure	46	3.2	133	7.4	0.43 (0.31 to 0.60)
Gap period 60 days (additional analyses with as-treated exposure definition)					
Major cardiovascular events	250	14.5	384	17.1	0.83 (0.71 to 0.98)
Heart failure	63	3.6	156	6.9	0.51 (0.38 to 0.69)

WebTable 16. Supplementary serious adverse event outcomes

	SGLT2 inhibitors (n=20,983)		DPP4 inhibitors (n=20,983)		Hazard ratio (95% CI)
	Events	Incidence rate, events per 1000 person- years	Events	Incidence rate, events per 1000 person- years	
Lower limb amputation	59	3.1	64	2.6	1.26 (0.88 to 1.81)
Diabetic ketoacidosis	27	1.4	16	0.6	2.14 (1.17 to 4.09)