**SUPPLEMENTARY MATERIAL**

**Use of glucagon-like peptide-1-receptor-agonists and risk of serious renal events: Scandinavian cohort study**Pasternak et al.

**Data sources**

Data on filled prescriptions was obtained from the national prescription registers in Sweden,1 Denmark2 and Norway3,4. The registers hold individual-level information on all drug prescriptions filled at all pharmacies in the country since July, 2005, in Sweden, 1995 in Denmark, and 2004 in Norway. The registers provide the anatomical therapeutic chemical (ATC) code of the dispensed drug and information about the amount of drug dispensed, and the date when the prescription was filled.

The national patient register in each of the countries contains individual-level information on outpatient and emergency department visits and inpatient admissions to all public hospitals and private specialist care.5–7 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. Information about outcome events was also obtained from Cause of Death registers in each country which includes data on the date and cause of death based on death certificates.8–10

From each country’s population registers we obtained information on age, sex, country of birth, migration status, civil status (Norway) and vital status of the patients included in the study.11–13 From Statistics Denmark and Statistics Sweden11 we obtained data on patients’ educational level and civil status.

The National Diabetes Register includes data on risk factors in patients with type 1 or type 2 diabetes in Sweden. The data are collected by trained nurses and physicians during patient visits to primary care and outpatient clinics nationwide. The number of patients who have been included in the register has increased over time; at present, over 90% of all patients receiving drugs for diabetes in Sweden are included.14 For patients living in Sweden, we used this register to obtain information on glycated hemoglobin, blood pressure, albuminuria, estimated glomerular filtration rate (eGFR), body-mass index and smoking.

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

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| *Category* | *ATC definition* | *Estimated days of supply Sweden* | *Estimated days of supply Denmark* | *Estimated days of supply Norway* |
| **GLP1-receptor-agonists** | A10BJ01, A10BJ02 (not including saxenda -product no. 131577 or 395175 in Denmark and Norway and 513490 in Sweden), A10BJ03, A10BJ05, A10AE56 | A10BJ01; 5 or 10 microgram = 0.5 per doseA10BJ01; 2 mg = 7.0 per doseA10BJ02 = 5.0 per ml A10BJ03 = 1.0 per doseA10BJ05 = 7.0 per doseA10AE56 = 3.0 per ml  | A10BJ01; 5 or 10 microgram = 0.5 per doseA10BJ01; 2 mg = 7.0 per doseA10BJ02 = 15.0 per pen A10BJ03 = 14.0 per penA10BJ05 = 7.0 per doseA10AE56 = not available | A10BJ01; 5 or 10 microgram = 0.5 per doseA10BJ01; 2 mg = 7.0 per penA10BJ02 = 5.0 per mlA10BJ03 = 1.0 per doseA10BJ05 = 7.0 per penA10AE56 = 3.0 per ml |
| **DPP4 inhibitors** | A10BH01,A10BH02,A10BH03, A10BH04,A10BH05,A10BD07,A10BD08, A10BD09,A10BD10,A10BD11,A10BD13,A10BD19,A10BD21 | All units are days per tabletA10BH01 = 1.0A10BH02 = 0.5A10BH03 = 1.0A10BH04 = 1.0A10BH05 = 1.0A10BD07 = 0.5A10BD08 = 0.5A10BD09 = 1.0A10BD10 = 0.5A10BD11 = 0.5A10BD13 = 0.5A10BD19 = 1.0A10BD21 = 1.0 | As in Sweden | As in Sweden |

**Supplementary Table 1** ATC codes and estimated days of exposure per unit of GLP1-receptor-agonists and DPP4 inhibitors.

**Supplementary Table 2** ICD10 and procedure codes for exclusion criteria.

|  |  |
| --- | --- |
| **Category** | **Codes (ICD-10, procedure, or ATC)** |
| Dialysis or renal transplantation at any time before index datea | ICD-10: Z49, Z94.0, Z99.2Procedure: KASAdditional procedure codes:bSweden: DR012, DR013, DR014, DR015, DR016, DR023, DR024, DR055, DR056, DR060, DR061Denmark: (B)JFD, (B)JFZ |
| Endstage illness (severe malnutrition, cachexia, dementia, coma) at any time before index datea | ICD-10: E40-E43, F00-F03, G30, R40.2b, R64ATC: N06D |
| Drug misuse within last year | ICD-10: F11-F16, F18, F19, R78.1-R78.5b T40b 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 datea) | ICD-10: C25, K86.0, K86.1Procedure: JLC, JLEATC: A09AA02 |
| No specialist care contact or prescription drug in last year prior to the index date | n.a. |
| Hospital admission within 30 days before index date | n.a. |
| Liraglutide with obesity indication (Saxenda) at any time before index date | Drug product number: Denmark: 131577, 395175 Norway: n.a. Sweden: 513490 |

Abbreviations: ICD, International Classification of Diseases; ATC, Anatomical Therapeutic Chemical

a 10-year lookback in Sweden and Denmark; 2 years look-back in Norway
b Not available in the Norwegian dataset.

**Supplementary Table 3** Propensity score variables and definitions.

|  |  |
| --- | --- |
| **Sociodemographic characteristics** | **ICD/categories** |
| Sex | Women; men  |
| Age  | 5-year categories |
| Educationa | Primary school; high school; vocational or short tertiary education; medium or long tertiary education |
| Place of birth | Scandinaviab; Rest of Europe; Outside Europe, Missing |
| Living with partner | Yes; no |
| **Medical history**c | *ICD-10 codes and procedure codes* |
| Acute coronary syndrome | ICD-10: I200, I21-22 |
| Other ischemic heart disease | ICD-10: I11 (not I110), I20 (not I200), I24, I25 |
| Heart failure/cardiomyopathy | ICD-10: I50, I110, I130, I132, I42, I43, J81  |
| Valve disorders | ICD-10: I34-I37 |
| Stroke | ICD-10: I60-I64 |
| Other cerebrovascular disease | ICD-10: I65-I69, G45 (excl G454), G46 |
| Atrial fibrillation | ICD-10: I48 |
| Other arrhythmia | ICD-10: I44-I47, I49 |
| Arterial disease (including amputation) | ICD-10: I65, I70, I72, I73, I74, I77, K550, K551, E115, E145, E135Procedure: NFQ, NGQ, NHQ |
| Chronic kidney disease | ICD-10: E112, E142, I120, I131, I132, N18, N19 |
| Other renal disease | ICD-10: N00-08, N10-N16, N17, N20-N23, N25-N29 |
| Diabetes complications | ICD-10: E110, E111, E113, E114, E116, E117, E118, E130, E131, E133, E134, E136, E137, E138, E140, E141, E143, E144, E146, E147, E148, E160, E161, E162, G990, G590, G632, H280a, H358, H360, M142, M146, M908, L984Procedure:a CKC10, CKC12, CKC15, CKD65 |
| COPD | ICD-10: J44 |
| Other lung disease | ICD-10: I27, J84, R092, E662, Z99, J40-J43, J45-J47, J60-J69, J70,a J92, J96, J982, J983Procedure: GBB |
| Venous thromboembolism | ICD-10: I26, I80 (except I80.0), I81, I820, I822-I829 |
| Cancer (excl non-melanoma skin cancer) | ICD-10: C00-C43, C45-C97 |
| Liver disease | ICD-10: B18, I850, I859, I982, K70-K77 |
| Rheumatic disease | ICD-10: M05-M09, M30-34, M351, M353, M45 |
| Psychiatric disorder | ICD-10: F04-F10, F20-F99 |
| Coronary revascularization in previous year | Procedure: FNA, FNB, FNC, FND, FNE, FNG, FNP02, FNP12, FNQ05, FNQ12, FNR22 |
| Other cardiac surgery/invasive cardiac procedure in previous year | Procedure: F (except FNA, FNB, FNC, FND, FNE, FNG, FNP02, FNP12, FNQ05, FNQ12, FNR22, FPFE, FPGX), DF020 |
| Fracture in previous year | ICD-10: S02 (except S025), S12, S22, S32, S42, S52, S62, S72, S82, S92, T02, T08, T10, T12, M484, M485, M843 |
| **Prescription-drug use in previous year** | *ATC code* |
| ACE-inhibitor or ARB | C09A-D |
| Calcium channel blocker | C08C, C08D |
| Loop diuretica | C03C, C03EB |
| Other diuretica | 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 |
| **Diabetes drugs in the previous 6 months** |  |
| No diabetes drug | Not any A10 |
| Metformin | A10BA02, A10BD02, A10BD03, A10BD05, A10BD07, A10BD08, A10BD10, A10BD11, A10BD13, A10BD14, A10BD15, A10BD16, A10BD20 |
| Sulfonylureas | A10BB, A10BD01, A10BD02, A10BD04, A10BD06 |
| SGLT2 inhibitors | A10BK01, A10BK02, A10BK03, A10BD15, A10BD16, A10BD19,A10BD20, A10BD21  |
| Insulin  | A10AB, A10AC, A10AD, A10AE |
| Other antidiabetics (glitazones, glinides, acarbose) | A10BF01, A10BG, A10BD03, A10BD04, A10BD05, A10BD06, A10BD09, A10BD14, A10BX |
| **Health care utilization in previous year** |   |
| No. of drugs useda | 1-5, 6-10, 11-15, >15 |
| Hospitalization due to cardiovascular causes  | I00-I99 (primary position) |
| Hospitalization due to type 2 diabetes-related causes  | E11 (primary position) |
| Hospitalization due to non-cardiovascular and non-type 2 diabetes causes  | Not I00-I99, E11 (primary position) |
| Outpatient contact due to cardiovascular causes | I00-I99 (primary position) |
| Outpatient contact due to type 2 diabetes-related causes | E11 (primary position) |
| Outpatient contact due to non-cardiovascular and non-type 2 diabetes causes  | Not I00-I99, E11 (primary position) |

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; SGLT2 sodium-glucose co-transporter 2.

a Not available in Norwegian dataset
b Defined as “Nordic countries” in Norwegian data
c 10-year look-back in Sweden and Denmark; 2-year look-back in Norway.

|  |  |  |
| --- | --- | --- |
| **Outcome** | **ICD 10 or procedure code** | **Type of diagnosis/type of hospital contact (data source)** |
| Dialysis or renal transplantation | *All countries* ICD10: Z49, Z940, Z992*Sweden*Procedure: KAS, DR012, DR013, DR014, DR015, DR016, DR023, DR024, DR055, DR056, DR060, DR061*Denmark* Procedure: KAS, BJFD, BJFZ*Norway*Procedure: KASa | Any position / inpatient admission or outpatient visit (Patient registers) |
| Death from renal causes | ICD10: E112, E132, E142, I120, I131, I132, N00-N08, N10-N16, N17, N18, N19, N20-N23, N25-N29 | Underlying cause of death (Cause of Death registers) |
| Hospitalization for renal events | ICD10: E112, E132, E142, I120, I131, I132, N17, N18, N19 | Primary diagnosis / inpatient admission (Patient registers) |

**Supplementary Table 4** ICD10 and procedure codes used for outcome definitions.

a Extended procedure codes not available in the Norwegian dataset.

**Supplementary Table 5** ICD10 and procedure codes used to define history of major cardiovascular disease.

|  |  |
| --- | --- |
| **ICD 10/procedure code**a | **Type of diagnosis / hospital contact** |
| ICD10: I200, I21-22, I60-I64, I110, I130, I132, I42, I43, I50, J81, I65, I70, I72, I73.9, K550, K551, E115, E135, E145Procedure: FNA, FNB, FNC, FND, FNE, FNG, FNP02, FNP12, FNQ05, FNQ12, FNR22 | Any/any |

a 10-year look-back in Sweden and Denmark; 2-year look-back in Norway

**Supplementary Table 6** ICD10 codes used to define history of chronic kidney disease and any renal disease.

|  |  |  |
| --- | --- | --- |
|  | **ICD 10** | **Type of diagnosis / hospital contact** |
| Chronic kidney disease | E112, E132, E142, I120, I131, I132, N18, N19 | Any/any |
| Any renal disease | E112, E132, E142, I120, I131, I132, N18, N19, N00-08, N10-N16, N17, N20-N23, N25-N29 | Any/any |

a10-year look-back in Sweden and Denmark; 2-year look-back in Norway

**Supplementary Table 7** Variable definitions for the analyses using data from the National Diabetes Register in Sweden.

|  |  |  |
| --- | --- | --- |
| **Variable**  | **Categorization** | **Missing values (%)**a |
| HbA1c, % (mmol/L) | ≤6.9 (≤52) ; 7.0-7.8 (53-62); 7.9-8.7 (63-72); 8.8-9.6 (73-82); ≥9.7 (≥83) | 45.6 |
| Blood pressure | *Normotension:* SBP <140 mmHg AND DBP <90 mmHg*Stage 1 hypertension:* SBP ≥140 to <160 mmHg OR DBP: ≥90 to <100mmHg*Stage 2 hypertension:* SBP ≥160 mmHg OR DBP: ≥100 mmHg | 24.2 |
| Albuminuria | Normalbuminuria; microalbuminuria; macroalbuminuria | 39.9 |
| eGFR (ml/min) | ≥90; ≥60 to <90; <60 | 29.0 |
| Body-mass index (kg/m2) | *Normal weight:* <25*Overweight:* ≥25 to <30*Obese class I:* ≥30 to <35*Obese class I/II:* ≥35 | 29.2 |
| Current smoking | Yes/no | 30.2 |

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

a Missing values in the propensity-score-matched cohort of GLP1-receptor-agonist users and DPP4 inhibitor users in Sweden.

**Supplementary Table 8** Baseline characteristics of GLP1-receptor-agonist users and DPP4 inhibitor users in the three-country cohort before propensity score matching. Numbers are shown in n (%) unless otherwise indicated.

|  |  |  |  |
| --- | --- | --- | --- |
| *Country* | **GLP1-receptor-agonists**(n=45880) | **DPP4 inhibitors**(n=153853) | **Standardized mean difference** **(%)** |
|    Sweden | 21097 (46.0) | 59638 (38.8) | - |
|    Denmark | 18467 (40.3) | 45591 (29.6) | - |
|    Norway | 6316 (13.8) | 48624 (31.6) | - |
| Male | 25789 (56.2) | 93420 (60.7) | 9.2 |
| Age, mean (SD) | 58.8 (10.4) | 63.1 (10.8) | - |
| *Age, years* |  |  |  |
|    35-39 | 1912 (4.2) | 3019 (2.0) | 12.8 |
|    40-44 | 3204 (7.0) | 6392 (4.2) | 12.4 |
|    45-49 | 4960 (10.8) | 11172 (7.3) | 12.4 |
|    50-54 | 6253 (13.6) | 16098 (10.5) | 9.7 |
|    55-59 | 7364 (16.1) | 20497 (13.3) | 7.7 |
|    60-64 | 8127 (17.7) | 24899 (16.2) | 4.1 |
|    65-69 | 7439 (16.2) | 27473 (17.9) | 4.4 |
|    70-74 | 4330 (9.4) | 22000 (14.3) | 15.1 |
|    75-79 | 1825 (4.0) | 14786 (9.6) | 22.5 |
|    80-84 | 466 (1.0) | 7517 (4.9) | 23 |
| *Place of Birth* |  |  |  |
|    Scandinavia | 40685 (88.7) | 128434 (83.5) | 15.1 |
|    Rest of Europe | 2324 (5.1) | 10024 (6.5) | 6.2 |
|    Outside Europe | 2806 (6.1) | 15134 (9.8) | 13.8 |
|    Missing | 65 (0.1) | 261 (0.2) | 0.7 |
| *Civil status* |  |  |  |
|    Married/living with partner | 26237 (57.2) | 89436 (58.1) | 1.9 |
|    Single | 19533 (42.6) | 63833 (41.5) | 2.2 |
|    Missing | 110 (0.2) | 584 (0.4) | 2.5 |
| *Educationa* |  |  |  |
|    Primary-/Secondary school, vocational training | 31065 (78.5) | 83506 (79.4) | 2.1 |
|    Short tertiary education | 2778 (7.0) | 6837 (6.5) | 2.1 |
|    Medium or long tertiary education | 4948 (12.5) | 11661 (11.1) | 4.4 |
|    Missing | 773 (2.0) | 3225 (3.1) | 7.1 |
| *Calendar yearb* |  |  |  |
|    2010-2011 | 14668 (32.0) | 41909 (27.2) | - |
|    2012-2014 | 17504 (38.2) | 60212 (39.1) | - |
|    2015-2016 | 13708 (29.9) | 51732 (33.6) | - |
| *Medical history* |  |  |  |
| Acute coronary syndrome | 3325 (7.2) | 8937 (5.8) | 5.8 |
| Other ischemic heart disease | 7428 (16.2) | 21311 (13.9) | 6.5 |
| Heart failure/cardiomyopathy | 2908 (6.3) | 7941 (5.2) | 5.1 |
| Valve disorders | 845 (1.8) | 3576 (2.3) | 3.4 |
| Stroke | 1628 (3.5) | 5425 (3.5) | 0.1 |
| Other cerebrovascular disease | 1803 (3.9) | 5903 (3.8) | 0.5 |
| Atrial fibrillation | 2891 (6.3) | 10264 (6.7) | 1.5 |
| Other arrythmia | 1652 (3.6) | 5249 (3.4) | 1.0 |
| Coronary revascularization in the previous year | 613 (1.3) | 1892 (1.2) | 0.9 |
| Other cardiac surgery/invasive procedure in the previous year | 213 (0.5) | 932 (0.6) | 1.9 |
| Arterial disease | 3047 (6.6) | 7556 (4.9) | 7.4 |
| Chronic kidney disease | 2336 (5.1) | 5856 (3.8) | 6.2 |
| Other renal disease | 2797 (6.1) | 7802 (5.1) | 4.5 |
| Diabetic complications | 15510 (33.8) | 31551 (20.5) | 30.2 |
| COPD | 1939 (4.2) | 5449 (3.5) | 3.5 |
| Other lung disease | 3609 (7.9) | 8354 (5.4) | 9.8 |
| Venous thromboembolism | 1230 (2.7) | 2958 (1.9) | 5.1 |
| Cancer | 2602 (5.7) | 10665 (6.9) | 5.2 |
| Liver disease | 892 (1.9) | 2307 (1.5) | 3.4 |
| Rheumatic disease | 1341 (2.9) | 4189 (2.7) | 1.2 |
| Psychiatric disorder | 4538 (9.9) | 11324 (7.4) | 9 |
| Fracture in the previous year | 787 (1.7) | 2629 (1.7) | 0.1 |
| *Hospitalizations in previous year* |  |  |  |
| Cardiovascular causes | 2178 (4.7) | 6811 (4.4) | 1.5 |
| Type 2 diabetes-related causes | 744 (1.6) | 1177 (0.8) | 7.9 |
| Non-cardiovascular/type 2 diabetes-related causes | 6567 (14.3) | 19299 (12.5) | 5.2 |
| *Outpatient contacts in previous year* |  |  |  |
| Cardiovascular causes | 4436 (9.7) | 14953 (9.7) | 0.2 |
| Type 2 diabetes-related causes | 12467 (27.2) | 26047 (16.9) | 24.9 |
| Non-cardiovascular/type 2 diabetes-related causes | 27019 (58.9) | 81255 (52.8) | 12.3 |
| *Diabetes drugs in previous 6 months* |  |  |  |
| None | 3299 (7.2) | 13543 (8.8) | 5.9 |
| Metformin | 35275 (76.9) | 125491 (81.6) | 11.6 |
| Sulphonylureas | 10234 (22.3) | 45481 (29.6) | 16.6 |
| SGLT2 inhibitors | 782 (1.7) | 1513 (1.0) | 6.3 |
| Insulin | 20968 (45.7) | 19682 (12.8) | 77.6 |
| Other antidiabetics (glitazones, glinides, acarbose) | 1911 (4.2) | 9222 (6.0) | 8.3 |
| *Prescription drugs in previous year* |  |  |  |
| ACEi/ARB | 31619 (68.9) | 97597 (63.4) | 11.6 |
| Calcium channel blocker | 14710 (32.1) | 45155 (29.3) | 5.9 |
| Loop diuretica | 7702 (19.5) | 15505 (14.7) | 12.6 |
| Other diuretica | 8701 (22.0) | 19767 (18.8) | 8.0 |
| Beta-blocker | 16153 (35.2) | 53765 (34.9) | 0.5 |
| Digoxin | 949 (2.1) | 3444 (2.2) | 1.2 |
| Nitrate | 3199 (7.0) | 10457 (6.8) | 0.7 |
| Platelet inhibitor | 17785 (38.8) | 58058 (37.7) | 2.1 |
| Anticoagulant | 3032 (6.6) | 11477 (7.5) | 3.3 |
| Lipid lowering drug | 31860 (69.4) | 101813 (66.2) | 7.0 |
| Antidepressant | 8571 (18.7) | 21668 (14.1) | 12.4 |
| Antipsychotic | 1775 (3.9) | 5986 (3.9) | 0.1 |
| Anxiolytic hypnotic or sedative | 8053 (17.6) | 27609 (17.9) | 1.0 |
| Beta-2 agonist inhalant | 5017 (10.9) | 12688 (8.2) | 9.1 |
| Anticholinergic inhalant | 1546 (3.4) | 5072 (3.3) | 0.4 |
| Glucocorticoid inhalant | 5146 (11.2) | 13934 (9.1) | 7.2 |
| Oral glucocorticoid | 3511 (7.7) | 11783 (7.7) | 0 |
| NSAID | 13158 (28.7) | 37778 (24.6) | 9.3 |
| Opioid | 9878 (21.5) | 26934 (17.5) | 10.2 |
| *No. of prescription drugs in last yeara* |  |  |  |
|    0-5 | 6403 (16.2) | 25394 (24.1) | 19.9 |
|    6-10 | 15154 (38.3) | 43117 (41.0) | 5.5 |
|    11-15 | 10602 (26.8) | 23293 (22.1) | 10.9 |
|    >15 | 7405 (18.7) | 13425 (12.8) | 16.4 |

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 Not available in Norwegian dataset; numbers are for patients in Sweden and Denmark.
b Year of cohort entry was not included in propensity score.

**Supplementary Table 9** Follow-up time according to individual GLP1-receptor-agonist initiated at cohort entry in the matched cohort.

|  |  |  |
| --- | --- | --- |
|  |  | Follow-up time, years |
|  | n(%)a | Mean (SD) | Total | Overall %  |
| Liraglutide | 34582 (89.3) | 3.2 (1.7) | 110736 | 92.5% |
| Exenatide | 2311 (6.0) | 3.2 (1.6) | 7450 | 6.2% |
| Lixisenatide | 641 (1.7) | 1.3 (0.8) | 860 | 0.7% |
| Dulaglutide | 1202 (3.1) | 0.6 (0.4) | 739 | 0.6% |

a Patients could initiate more than one drug at cohort entry.

**Supplementary Table 10** Follow-up time according to individual DPP4 inhibitors initiated at cohort entry in the matched cohort.

|  |  |  |
| --- | --- | --- |
|  |  | Follow-up time, years |
|  | n (%)a | Mean (SD) | Total | Overall % |
| Sitagliptin | 28223 (72.9) | 2.9 (1.7) | 83019 | 71.8% |
| Vildagliptin | 5803 (15.0) | 3.6 (1.5) | 20706 | 17.9% |
| Saxagliptin | 1992 (5.1) | 3.9 (1.4) | 7671 | 6.6% |
| Linagliptin | 2402 (6.2) | 1.6 (1.2) | 3802 | 3.3% |
| Alogliptin | 314 (0.8) | 1.4 (0.7) | 443 | 0.4% |

a Patients could initiate more than one drug at cohort entry.

**Supplementary Table 11** Analyses of the primary outcome by country.

|  |  |  |  |
| --- | --- | --- | --- |
|  | GLP1-receptor-agonists | DPP4 inhibitors | HR (95% CI) |
|  | Patients | Events | Events per 1000 person-years | Patients | Events | Events per 1000 person-years |  |
| Denmark | 13286 | 255 | 5.2 | 13286 | 288 | 6.9 | 0.76 (0.64 to 0.90) |
| Sweden | 19214 | 225 | 4.4 | 19214 | 307 | 5.9 | 0.75 (0.63 to 0.89) |
| Norway | 6231 | 90 | 4.7 | 6231 | 127 | 6.2 | 0.75 (0.57 to 0.98) |

**Supplementary Table 12** Distribution of variables from the Swedish National Diabetes Register in the propensity-score-matched cohort of GLP1-receptor-agonist users and DPP4 inhibitor users in Sweden. Numbers are shown in n (%).

|  |  |  |
| --- | --- | --- |
| **--** | **GLP1-receptor-agonists**(n=19214) | **DPP4 inhibitors**(n=19214) |
| Blood pressure, mmHg |  |  |
|    SBP <150 and DBP <90 | 7959 (41.4) | 8140 (42.4) |
|    SBP: 140-159 or DBP: 90-99 | 5108 (26.6) | 4805 (25.0) |
|    SBP≥160 or DBP ≥100 | 1567 (8.2) | 1559 (8.1) |
|    Missing | 4580 (23.8) | 4710 (24.5) |
| Glycated hemoglobin (HbA1c), % (mmol/mol) |  |  |
|    ≤6.9 (≤52) | 1067 (5.6) | 1103 (5.7) |
|    7.0-7.8 (53-62) | 2274 (11.8) | 2808 (14.6) |
|    7.9-8.7 (63-72) | 2804 (14.6) | 2725 (14.2) |
|    8.8-9.6 (73-82) | 2083 (10.8) | 1857 (9.7) |
|    ≥9.7 (≥83) | 2329 (12.1) | 1841 (9.6) |
|    Missing | 8657 (45.1) | 8880 (46.2) |
| BMI, kg/m2 |  |  |
|    <25 | 261 (1.4) | 1020 (5.3) |
|    25-29 | 2427 (12.6) | 4160 (21.7) |
|    30-34 | 5077 (26.4) | 4686 (24.4) |
|    ≥35 | 5977 (31.1) | 3589 (18.7) |
|    Missing | 5472 (28.5) | 5759 (30.0) |
| Albuminuria |  |  |
|    Normalbuminuria | 8189 (42.6) | 8023 (41.8) |
|    Microalbuminuria | 2575 (13.4) | 2357 (12.3) |
|    Macroalbuminuria | 964 (5.0) | 981 (5.1) |
|    Missing | 7486 (39.0) | 7853 (40.9) |
| eGFR, ml/min/1,73 m2 |  |  |
|    ≥90 | 6351 (33.1) | 6129 (31.9) |
|    60-89 | 5597 (29.1) | 5292 (27.5) |
|    <60 | 1829 (9.5) | 2097 (10.9) |
|    Missing | 5437 (28.3) | 5696 (29.6) |
| Current smoking |  |  |
|    No | 11642 (60.6) | 11167 (58.1) |
|    Yes | 1925 (10.0) | 2105 (11.0) |
|    Missing | 5647 (29.4) | 5942 (30.9) |

Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; eGFR, estimated glomerular filtration rate.

**Supplementary Table 13** Baseline characteristics of liraglutide users and DPP4 inhibitor users in the three-country cohort before and after propensity score matching. Numbers are shown in n (%) unless otherwise indicated.

|  |  |  |
| --- | --- | --- |
|  | Before matching | After matching |
| -- | Liraglutide  (N=41394) | DPP4 inhibitors (N=153853) | Liraglutide(N=35081) | DPP4 inhibitors (N=35081) | Standardized mean difference (%) |
| *Countrya* |  |  |  |  |  |
|    Sweden | 18247 (44.1) | 59638 (38.8) | 17000 (48.5) | 17000 (48.5) | - |
|    Denmark | 18179 (43.9) | 45591 (29.6) | 13138 (37.5) | 13138 (37.5) | - |
|    Norway | 4968 (12.0) | 48624 (31.6) | 4943 (14.1) | 4943 (14.1) | - |
| Male | 23180 (56.0) | 93420 (60.7) | 19872 (56.6) | 19872 (56.6) | 0 |
| Age, mean (SD) | 58.8 (10.4) | 63.1 (10.8) | 59.3 (10.4) | 59.4 (10.5) | - |
| *Age, years* |  |  |  |  |  |
|    35-39 | 1714 (4.1) | 3019 (2.0) | 1291 (3.7) | 1291 (3.7) | 0 |
|    40-44  | 2903 (7.0) | 6392 (4.2) | 2332 (6.6) | 2332 (6.6) | 0 |
|    45-49  | 4436 (10.7) | 11172 (7.3) | 3635 (10.4) | 3635 (10.4) | 0 |
|    50-54  | 5619 (13.6) | 16098 (10.5) | 4765 (13.6) | 4765 (13.6) | 0 |
|    55-59  | 6629 (16.0) | 20497 (13.3) | 5548 (15.8) | 5548 (15.8) | 0 |
|    60-64  | 7386 (17.8) | 24899 (16.2) | 6099 (17.4) | 6099 (17.4) | 0 |
|    65-69  | 6778 (16.4) | 27473 (17.9) | 5832 (16.6) | 5832 (16.6) | 0 |
|    70-74  | 3863 (9.3) | 22000 (14.3) | 3542 (10.1) | 3542 (10.1) | 0 |
|    75-79 | 1652 (4.0) | 14786 (9.6) | 1625 (4.6) | 1625 (4.6) | 0 |
|    80-84 | 414 (1.0) | 7517 (4.9) | 412 (1.2) | 412 (1.2) | 0 |
| *Place of Birth* |  |  |  |  |  |
|    Scandinavia | 36798 (88.9) | 128434 (83.5) | 30941 (88.2) | 31116 (88.7) | 1.6 |
|    Rest of Europe | 2054 (5.0) | 10024 (6.5) | 1844 (5.3) | 1768 (5.0) | 1 |
|    Outside Europe | 2479 (6.0) | 15134 (9.8) | 2246 (6.4) | 2147 (6.1) | 1.2 |
|    Missing | 63 (0.2) | 261 (0.2) | 50 (0.1) | 50 (0.1) | 0 |
| *Civil status* |  |  |  |  |  |
|    Married/living with partner | 24010 (58.0) | 89436 (58.1) | 20002 (57.0) | 20037 (57.1) | 0.2 |
|    Single | 17282 (41.8) | 63833 (41.5) | 14986 (42.7) | 14961 (42.6) | 0.1 |
|    Missing | 102 (0.2) | 584 (0.4) | 93 (0.3) | 83 (0.2) | 0.6 |
| *Educationb* |  |  |  |  |  |
|    Primary-/Secondary school, vocational training | 28675 (78.7) | 83506 (79.4) | 23661 (78.5) | 23655 (78.5) | 0 |
|    Short tertiary education | 2429 (6.7) | 6837 (6.5) | 2159 (7.2) | 2192 (7.3) | 0.4 |
|    Medium or long tertiary education | 4600 (12.6) | 11661 (11.1) | 3725 (12.4) | 3714 (12.3) | 0.1 |
|    Missing | 722 (2.0) | 3225 (3.1) | 593 (2.0) | 577 (1.9) | 0.4 |
| *Calendar yearc* |  |  |  |  |  |
|    2010-2011 | 14020 (33.9) | 41909 (27.2) | 10851 (30.9) | 9864 (28.1) | - |
|    2012-2014 | 16168 (39.1) | 60212 (39.1) | 14084 (40.1) | 13993 (39.9) | - |
|    2015-2016 | 11206 (27.1) | 51732 (33.6) | 10146 (28.9) | 11224 (32.0) | - |
| *Medical history* |  |  |  |  |  |
| Acute coronary syndrome | 3037 (7.3) | 8937 (5.8) | 2488 (7.1) | 2477 (7.1) | 0.1 |
| Other ischemic heart disease | 6749 (16.3) | 21311 (13.9) | 5467 (15.6) | 5486 (15.6) | 0.1 |
| Heart failure/cardiomyopathy | 2665 (6.4) | 7941 (5.2) | 2174 (6.2) | 2197 (6.3) | 0.3 |
| Valve disorders | 749 (1.8) | 3576 (2.3) | 651 (1.9) | 675 (1.9) | 0.5 |
| Stroke | 1488 (3.6) | 5425 (3.5) | 1202 (3.4) | 1221 (3.5) | 0.3 |
| Other cerebrovascular disease | 1633 (3.9) | 5903 (3.8) | 1351 (3.9) | 1402 (4.0) | 0.7 |
| Atrial fibrillation | 2635 (6.4) | 10264 (6.7) | 2264 (6.5) | 2233 (6.4) | 0.4 |
| Other arrythmia | 1501 (3.6) | 5249 (3.4) | 1271 (3.6) | 1274 (3.6) | 0 |
| Coronary revascularization in the previous year | 543 (1.3) | 1892 (1.2) | 462 (1.3) | 459 (1.3) | 0.1 |
| Other cardiac surgery/invasive procedure in the previous year | 190 (0.5) | 932 (0.6) | 175 (0.5) | 189 (0.5) | 0.6 |
| Arterial disease | 2812 (6.8) | 7556 (4.9) | 2082 (5.9) | 2103 (6.0) | 0.3 |
| Chronic kidney disease | 2140 (5.2) | 5856 (3.8) | 1646 (4.7) | 1708 (4.9) | 0.8 |
| Other renal disease | 2496 (6.0) | 7802 (5.1) | 2115 (6.0) | 2110 (6.0) | 0.1 |
| Diabetic complications | 14140 (34.2) | 31551 (20.5) | 10609 (30.2) | 10540 (30.0) | 0.4 |
| COPD | 1780 (4.3) | 5449 (3.5) | 1408 (4.0) | 1420 (4.0) | 0.2 |
| Other lung disease | 3291 (8.0) | 8354 (5.4) | 2631 (7.5) | 2673 (7.6) | 0.5 |
| Venous thromboembolism | 1127 (2.7) | 2958 (1.9) | 903 (2.6) | 900 (2.6) | 0.1 |
| Cancer | 2349 (5.7) | 10665 (6.9) | 2066 (5.9) | 2072 (5.9) | 0.1 |
| Liver disease | 812 (2.0) | 2307 (1.5) | 671 (1.9) | 657 (1.9) | 0.3 |
| Rheumatic disease | 1192 (2.9) | 4189 (2.7) | 985 (2.8) | 966 (2.8) | 0.3 |
| Psychiatric disorder | 4004 (9.7) | 11324 (7.4) | 3438 (9.8) | 3409 (9.7) | 0.3 |
| Fracture in the previous year | 705 (1.7) | 2629 (1.7) | 584 (1.7) | 550 (1.6) | 0.8 |
| *Hospitalization in previous year* |  |  |  |  |  |
| Cardiovascular causes | 1980 (4.8) | 6811 (4.4) | 1603 (4.6) | 1693 (4.8) | 1.2 |
| Type 2 diabetes-related causes | 677 (1.6) | 1177 (0.8) | 499 (1.4) | 482 (1.4) | 0.4 |
| Non-cardiovascular/type 2 diabetes-related causes | 5979 (14.4) | 19299 (12.5) | 4772 (13.6) | 4720 (13.5) | 0.4 |
| *Outpatient contacts in previous year* |  |  |  |  |  |
| Cardiovascular causes | 3968 (9.6) | 14953 (9.7) | 3346 (9.5) | 3380 (9.6) | 0.3 |
| Type 2 diabetes-related causes | 11159 (27.0) | 26047 (16.9) | 8444 (24.1) | 8315 (23.7) | 0.9 |
| Non-cardiovascular/type 2 diabetes-related causes | 24408 (59.0) | 81255 (52.8) | 20093 (57.3) | 19921 (56.8) | 1.0 |
| *Diabetes drugs in previous 6 months* |  |  |  |  |  |
| None | 2945 (7.1) | 13543 (8.8) | 2856 (8.1) | 2823 (8.0) | 0.3 |
| Metformin | 31896 (77.1) | 125491 (81.6) | 27211 (77.6) | 27165 (77.4) | 0.3 |
| Sulphonylureas | 9342 (22.6) | 45481 (29.6) | 8638 (24.6) | 9028 (25.7) | 2.6 |
| SGLT2 inhibitors | 523 (1.3) | 1513 (1.0) | 446 (1.3) | 461 (1.3) | 0.4 |
| Insulin | 18988 (45.9) | 19682 (12.8) | 13034 (37.2) | 12884 (36.7) | 0.9 |
| Other antidiabetics (glitazones, glinides, acarbose) | 1667 (4.0) | 9222 (6.0) | 1559 (4.4) | 1559 (4.4) | 0 |
| *Prescription drugs in previous year* |  |  |  |  |  |
| ACEi/ARB | 28620 (69.1) | 97597 (63.4) | 23798 (67.8) | 23765 (67.7) | 0.2 |
| Calcium channel blocker | 13307 (32.1) | 45155 (29.3) | 11026 (31.4) | 10979 (31.3) | 0.3 |
| Loop diureticb | 7178 (19.7) | 15505 (14.7) | 5485 (18.2) | 5506 (18.3) | 0.2 |
| Other diureticb | 8152 (22.4) | 19767 (18.8) | 6275 (20.8) | 6373 (21.1) | 0.8 |
| Beta-blocker | 14489 (35.0) | 53765 (34.9) | 12402 (35.4) | 12495 (35.6) | 0.6 |
| Digoxin | 882 (2.1) | 3444 (2.2) | 735 (2.1) | 768 (2.2) | 0.6 |
| Nitrate | 2880 (7.0) | 10457 (6.8) | 2415 (6.9) | 2416 (6.9) | 0 |
| Platelet inhibitor | 16240 (39.2) | 58058 (37.7) | 13270 (37.8) | 13327 (38.0) | 0.3 |
| Anticoagulant | 2729 (6.6) | 11477 (7.5) | 2333 (6.7) | 2359 (6.7) | 0.3 |
| Lipid lowering drug | 28905 (69.8) | 101813 (66.2) | 23989 (68.4) | 23881 (68.1) | 0.7 |
| Antidepressant | 7731 (18.7) | 21668 (14.1) | 6290 (17.9) | 6315 (18.0) | 0.2 |
| Antipsychotic | 1567 (3.8) | 5986 (3.9) | 1316 (3.8) | 1304 (3.7) | 0.2 |
| Anxiolytic hypnotic or sedative | 7205 (17.4) | 27609 (17.9) | 6234 (17.8) | 6180 (17.6) | 0.4 |
| Beta-2 agonist inhalant | 4523 (10.9) | 12688 (8.2) | 3718 (10.6) | 3700 (10.5) | 0.2 |
| Anticholinergic inhalant | 1382 (3.3) | 5072 (3.3) | 1157 (3.3) | 1175 (3.3) | 0.3 |
| Glucocorticoid inhalant | 4631 (11.2) | 13934 (9.1) | 3841 (10.9) | 3804 (10.8) | 0.3 |
| Oral glucocorticoid | 3163 (7.6) | 11783 (7.7) | 2669 (7.6) | 2644 (7.5) | 0.3 |
| NSAID | 12008 (29.0) | 37778 (24.6) | 9697 (27.6) | 9654 (27.5) | 0.3 |
| Opioid | 8907 (21.5) | 26934 (17.5) | 7211 (20.6) | 7055 (20.1) | 1.1 |
| *No. of prescription drugs in previous yearb* |  |  |  |  |  |
|    0-5 | 5860 (16.1) | 25394 (24.1) | 5362 (17.8) | 5324 (17.7) | 0.3 |
|    6-10 | 13994 (38.4) | 43117 (41.0) | 11748 (39.0) | 11847 (39.3) | 0.7 |
|    11-15 | 9755 (26.8) | 23293 (22.1) | 7733 (25.7) | 7744 (25.7) | 0.1 |
|    >15 | 6817 (18.7) | 13425 (12.8) | 5295 (17.6) | 5223 (17.3) | 0.6 |

Abbreviations: ACE-I, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; COPD, chronic obstructive pulmonary disease; DDP4, dipeptidyl peptidase 4; GLP1, glucagon-like peptide 1; NSAID, non-steroidal anti-inflammatory drug; SD, standard deviation; SGLT2, sodium-glucose co-transporter 2.

a Propensity score matching was performed separately by country. Additional matching criteria included sex and age (5-year intervals). b Not available in Norwegian dataset; numbers are shown for patients in Sweden and Denmark.
c Year of cohort entry was not included in propensity score.

**Supplementary Table 14** Primary and secondary outcome analyses of association between use of liraglutide vs. DPP4 inhibitors and risk of serious renal events.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | Liraglutide (n=35081) | DPP4 inhibitors (n=35081) | HR (95% CI) | Absolute difference, events (95% CI) per 1000 person-years |
|  | Events | Events per 1000 person-years | Events | Events per 1000 person-years |  |  |
| Primary outcomea | 528 | 4.7 | 683 | 6.5 | 0.72 (0.64 to 0.81) | -1.8 (-2.4 to -1.2) |
| *Secondary outcomes* |  |  |  |  |  |  |
| Renal replacement therapy | 213 | 1.9 | 272 | 2.6 | 0.73 (0.61 to 0.87) | -0.7 (-1.1 to -0.3) |
| Death from renal causes | 38 | 0.3 | 51 | 0.5 | 0.68 (0.45 to 1.04) | -0.1 (-0.3 to 0.0) |
| Hospitalization for renal events | 408 | 3.7 | 554 | 5.3 | 0.69 (0.61 to 0.78) | -1.6 (-2.2 to -1.1) |

 a Serious renal events, a composite of renal replacement therapy, death from renal causes and hospitalization for renal events.

**Supplementary Table 15** Subgroup analyses of serious renal events among liraglutide users vs. DPP4 inhibitor users

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | Liraglutide | DPP4 inhibitors | HR (95% CI) | p value for interaction |
|  | Patients (%) | Events | Events per 1000 person-years | Patients (%) | Events | Events per 1000 person-years |  |  |
| **Sex** |  |  |  |  |  |  |  |  |
| Men | 19872 (57) | 334 | 5.3 | 19872 (57) | 428 | 7.3 | 0.72 (0.62 to 0.83) |  |
| Women | 15209 (43) | 194 | 4.0 | 15209 (43) | 255 | 5.5 | 0.72 (0.60 to 0.87) | 0.986 |
| **Age** |   |   |   |  |   |   |   |  |
| 35-64 years | 23670 (67) | 272 | 3.5 | 23670 (67) | 337 | 4.6 | 0.77 (0.65 to 0.90) |  |
| 65-84 years | 11411 (33) | 256 | 7.5 | 11411 (33) | 346 | 11.2 | 0.66 (0.56 to 0.77) | 0.182 |
| **Major cardiovascular disease** |   |   |   |  |   |   |   |  |
| Yes | 6546 (19) | 206 | 10.1 | 6490 (19) | 261 | 14.3 | 0.70 (0.58 to 0.84) |  |
| No | 28535 (81) | 322 | 3.5 | 28591 (81) | 422 | 4.9 | 0.72 (0.62 to 0.83) | 0.809 |
| **Chronic kidney disease** |   |   |   |  |   |   |   |  |
| Yes | 1646 (5) | 119 | 23.2 | 1708 (5) | 194 | 45.8 | 0.50 (0.40 to 0.63) |  |
| No | 33435 (95) | 409 | 3.8 | 33373 (95) | 489 | 4.9 | 0.78 (0.69 to 0.89) | 0.001 |

**Supplementary Figure 1** Schoenfeld residuals for the primary outcome analysis.



Schoenfeld residual

Days of follow-up

**Supplementary Figure 2** Schoenfeld residuals for the primary outcome analysis using an as-treated exposure definition.



Days of follow-up

Schoenfeld residual

**Supplementary Figure 3** Flow chart of patient inclusion in the study cohort (liraglutide users and DPP4 inhibitor users), Sweden, Denmark and Norway, January, 2010, through December, 2016



**References**

1. Wettermark B, Hammar N, Fored M, et al. The new Swedish Prescribed Drug Register—Opportunities for pharmacoepidemiological research and experience from the first six months. Pharmacoepidemiol Drug Saf 2007;16(7):726–35.

2. Pottegård A, Schmidt SAJ, Wallach-Kildemoes H, Sørensen HT, Hallas J, Schmidt M. Data Resource Profile: The Danish National Prescription Registry. Int J Epidemiol 2016;46(3):dyw213.

3. Norwegian Institute of Public Health. Norwegian Prescription Database [Internet]. [cited 2018 Jan 16];Available from: https://www.fhi.no/en/hn/health-registries/norpd/norwegian-prescription-database/

4. Furu K, Wettermark B, Andersen M, Martikainen JE, Almarsdottir AB, SÃ¸rensen HT. The Nordic Countries as a Cohort for Pharmacoepidemiological Research. Basic Clin Pharmacol Toxicol 2010;106(2):86–94.

5. Ludvigsson JF, Andersson E, Ekbom A, et al. External review and validation of the Swedish national inpatient register. BMC Public Health 2011;11(1):450.

6. Schmidt M, Schmidt SAJ, Sandegaard JL, Ehrenstein V, Pedersen L, Sørensen HT. The Danish National Patient Registry: a review of content, data quality, and research potential. Clin Epidemiol 2015;7:449.

7. Norwegian Institute of Public Health. Overview of the national health registries [Internet]. 2016 [cited 2019 Feb 19];Available from: https://www.fhi.no/en/more/access-to-data/about-the-national-health-registries2/

8. Norwegian Institute of Public Health. Norwegian Cause of Death Registry [Internet]. [cited 2019 Feb 19];Available from: https://www.fhi.no/en/hn/health-registries/cause-of-death-registry/

9. Brooke HL, Talbäck M, Hörnblad J, et al. The Swedish cause of death register. Eur J Epidemiol 2017;32(9):765–73.

10. Helweg-Larsen K. The Danish Register of Causes of Death. Scand J Public Health 2011;39(7\_suppl):26–9.

11. Ludvigsson JF, Almqvist C, Bonamy A-KE, et al. Registers of the Swedish total population and their use in medical research. Eur J Epidemiol 2016;31(2):125–36.

12. Schmidt M, Pedersen L, Sørensen HT. The Danish Civil Registration System as a tool in epidemiology. Eur J Epidemiol 2014;29(8):541–9.

13. National Registry. The Norwegian Tax Administration. [Internet]. Available from: https://www.skatteetaten.no/en/person/national-registry/

14. Gudbjörnsdottir S, Svensson A-M, Eliasson B, et al. National Diabetes Register. Annual Report 2016. 2017.