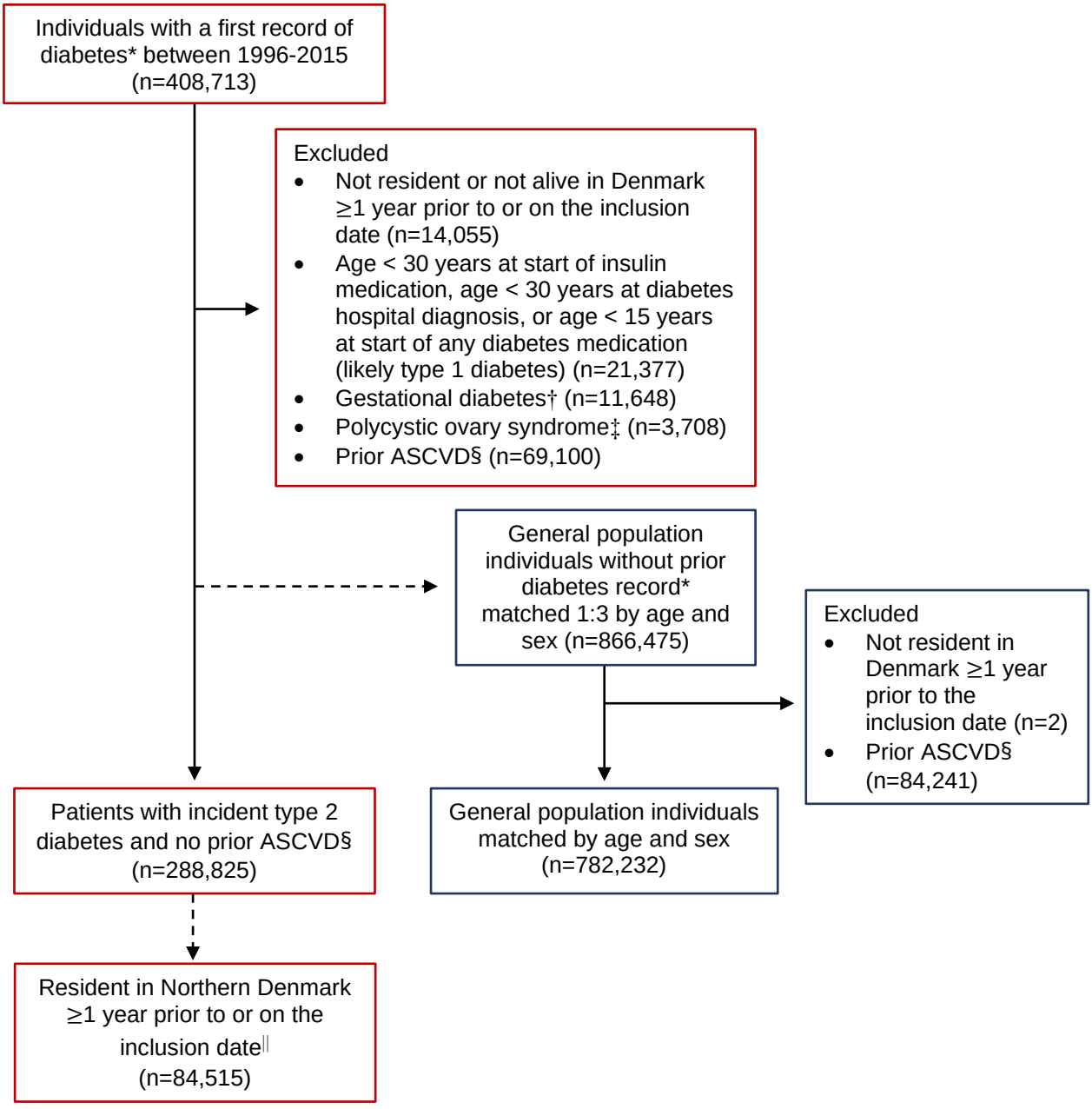
# Online-Only Supplemental Material

Supplementary Fig. 1. Flowchart of selection of study participants.




*The first record of diabetes was defined as either a first-time redemption of a prescription for a glucose-lowering drug (ATC code A10) at any pharmacy in Denmark, or a first-time inpatient hospital admission or outpatient hospital clinic contact at any hospital in Denmark leading to a diabetes diagnosis (ICD-8 codes 249-250, 251.5 and ICD-10 codes E10-E14, O24, E15, E160-E162, DT383A, M142, G590, G632, H280, H334, H450, H360, N083) from January 1, 1996 to December 31, 2015.

†Gestational diabetes was defined as women giving birth (ICD-10 code O80-O84) within 9 months after diagnosis.

‡Polycystic ovary syndrome was defined as prior hospital-diagnosed polycystic ovary syndrome (ICD-10 code E28.2) or redemption of any metformin prescription (ATC code A10BA02) in combination with clomifen (ATC code G03GB02) within 12 months following type 2 diabetes diagnosis.

§Prior atherosclerotic cardiovascular disease (ASCVD) was defined as previous diagnoses of ischemic stroke, transient ischemic attack, myocardial infarction, coronary revascularization, peripheral artery disease, peripheral revascularization, and lower-limb amputation.

‖Patients were defined as living in Northern Denmark (*i.e.*, the North and Central Denmark regions, accounting for approximately 30% of Denmark's population or 1.8 million persons) if they had resided in Northern Denmark for at least 1 year prior to or on the inclusion date.

Supplementary Table 1. Codes and definitions used in the study.

| Variable | ICD-8 code | ICD-10 code | Surgical codes / NOMESCO classification | ATC-code |
|---|---|---|---|---|
| Incident diabetes (first-time glucose-lowering drug redemption or first-time hospital diabetes diagnosis) | 249-250, 251.5 | E10-E15, E160-E162, DT383A, G590, G632, H280, H334, H450, H360, M142, N083, O24 | | A10 |
| Gestational diabetes | | Giving birth (O80-O84) within 9 months after diabetes diagnosis | | |
| Polycystic ovary syndrome | | Pre-existing hospital-diagnosed polycystic ovary syndrome (DE28.2) | | A10BA02 (metformin) in combination with G03GB02 (clomifen) within 12 months following diagnosis |
| Ischemic stroke* | 433, 434 | I63, I64 | | |
| Transient ischemic attack | 435 | G45.9 | | |
| Myocardial infarction | 410 | I20-I23 | | |
| Percutaneous coronary intervention | | | KFNG02, KFNG05, KFNG96 | |
| Coronary artery bypass grafting | | | KFNA-KFNE, 30009, 30019, 30029, 30039, 30049, 30059, 30069, 30079, 30089, 30099, 30109, 30119, 30120, 30129, 30139, 30149, 30159, 30169, 30179, 30189, 30199, 30200 | |
| Peripheral artery disease | 440, 443, 444 | I70, I73.9, I74 | KPBE, KPBF, KPBH, KPBQ, KPDE, KPDF, KPDH, KPDQ, KPEE, KPEF, KPEH, KPEQ, KPFE, KPFH, KPFQ, KPDU74, KPDU84, KNFQ, KNGQ, KNHQ | |
| Hypertension (diagnosis code and/or ≥1 antihypertensive drug redemption) | 401-404 | I10-I15 | | C07, C09A, C09B, C09C, C09D, C08C, C08D, C03AA, C03AB |
| Chronic obstructive pulmonary disease | 490-493, 515-518 | J40-J47, J60-J67, J68.4, J70.1, J70.3, J84.1, J92.0, J96.1, J98.2, J98.3 | | |

| | | | | |
|---|---|---|---|---|
| Heart failure | 427.09, 427.10, 427.11, 427.19, 428.99, 782.49 | I50, I110, I130, I132, I420 | | |
| Atrial fibrillation* | 427.93, 427.94 | I48 | | |
| Moderate-severe renal disease | 403, 404, 580-584, 590.09, 593.19, 753.10-753.19, 792 | I12, I13, N00-N05, N07, N11, N14, N17-N19, Q61 | | |
| Moderate-severe liver disease | 070.00, 070.02, 070.04, 070.06, 070.08, 573.00, 456.00-456.09 | B15.0, B16.0, B16.2, B19.0, K70.4, K72, K76.6, I85 | | |
| Connective tissue disease | 712, 716, 734, 446, 135.99 | M05, M06, M08, M09, M30-M36, D86 | | |
| Any malignancy | 140-207, 275.59 | C00-C97 | | |
| Hyperthyroidism (thyrotoxicosis) | 242 | E05 | | |
| Heart valve disease | 394, 395 | I05, I06, I34, I35, I390, I391, I511A | | |
| Venous thromboembolism (deep venous thrombosis or pulmonary embolism) | 45100, 45099 | I801-I803, I26 | | |
| Smoking | 491, 492 | F17, J40-J44, Z72.0, Z71.6 | R03 | |
| Hospital-diagnosed obesity | 277.99 | E65-E68 | A10BJ02 (Saxenda, approved 2014) | |
| Insulin | | | | A10A |
| Biguanides | | | | A10BA, A10BD03, A10BD07, A10BD08, A10BD10, A10BD11, A10BD13, A10BD15, A10BD16, A10BD20, A10BD23 |
| Sulfonylureas | | | | A10BB |
| DPP4i | | | | A10BH, A10BD07, A10BD08, A10BD10, A10BD11, A10BD13, A10BD19, A10BD21, A10BD24 |
| GLP-1 analogues | | | | A10BJ except for A10BJ02 (Saxenda), A10AE54, A10AE56 |
| SGLT-2 inhibitors | | | | A10BK, A10BD15, A10BD16, A10BD19, A10BD20, A10BD21, A10BD23, A10BD24 |
| Statins | | | | C10AA, C10BA |
| High-intensity statins | | | | C10AA05 (Atorvastatin ≥40 mg), C10AA07 (Rosuvastatin ≥20 mg) |
| Other lipid-lowering drugs | | | | C10AX (Ezetimibe, PCSK9-inhibitors) |

| | |
|---|---|
| Beta-blockers | C07 |
| ACE inhibitor / angiotensin II-receptor blockers | C09A, C09B, C09C, C09D |
| Calcium channel blockers | C08C, C08D |
| Thiazides | C03AA, C03AB |
| Aspirin | B01AC06, N02BA01 |
| ADP receptor inhibitors | B01AC04, B01AC22, B01AC24, B01AC25 |
| Vitamin K antagonists | B01AA03, B01AA04 |
| Direct oral anticoagulants | B01AF01, B01AF02, B01AF03, B01AE07 |

*Based on primary or secondary hospital discharge diagnoses. The primary discharge diagnosis is the main reason for a hospital contact. Secondary discharge diagnoses can be recorded if they are considered applicable and identify other relevant diseases, *e.g*. underlying chronic diseases, as a supplement to the primary discharge diagnosis.

Supplementary Table 2. Baseline characteristics of individuals in the general population cohort.

| | General population: 1996-2000 | General population: 2001-2005 | General population: 2006-2010 | General population: 2011-2015 | General population: all individuals |
|---|---|---|---|---|---|
| Number of participants | 143,339 | 183,444 | 230,994 | 224,455 | 782,232 |
| Male sex | 76,237 (53.2) | 94,036 (51.3) | 114,271 (49.5) | 113,386 (50.5) | 397,930 (50.9) |
| Age, median ($Q_1$-$Q_3$) | 60 (51-71) | 59 (49-69) | 59 (47-68) | 59 (49-68) | 59 (49-69) |
| Age-group | | | | | |
| <40 years | 12,555 (8.8) | 21,430 (11.7) | 34,097 (14.8) | 28,666 (12.8) | 96,748 (12.4) |
| 40-49 years | 21,185 (14.8) | 27,053 (14.7) | 35,231 (15.3) | 34,819 (15.5) | 118,288 (15.1) |
| 50-59 years | 36,873 (25.7) | 48,171 (26.3) | 54,106 (23.4) | 53,723 (23.9) | 192,874 (24.7) |
| 60-69 years | 33,334 (23.3) | 44,263 (24.1) | 60,890 (26.4) | 60,373 (26.9) | 198,860 (25.4) |
| 70-79 years | 26,154 (18.2) | 28,123 (15.3) | 32,395 (14.0) | 33,794 (15.1) | 120,466 (15.4) |
| ≥80 years | 13,238 (9.2) | 14,403 (7.9) | 14,275 (6.2) | 13,080 (5.8) | 54,996 (7.0) |
| **Comorbidities** | | | | | |
| Hypertension* | 26,998 (18.8) | 39,776 (21.7) | 59,599 (25.8) | 62,733 (27.9) | 189,106 (24.2) |
| COPD | 4,923 (3.4) | 7,888 (4.3) | 11,288 (4.9) | 12,719 (5.7) | 36,818 (4.7) |
| Heart failure | 1,757 (1.2) | 2,358 (1.3) | 2,542 (1.1) | 2,415 (1.1) | 9,072 (1.2) |
| Atrial fibrillation | 2,381 (1.7) | 4,027 (2.2) | 5,927 (2.6) | 6,987 (3.1) | 19,322 (2.5) |
| Moderate-severe renal disease | 771 (0.5) | 1,163 (0.6) | 1,775 (0.8) | 2,390 (1.1) | 6,099 (0.8) |
| Moderate-severe liver disease | 172 (0.1) | 283 (0.2) | 415 (0.2) | 497 (0.2) | 1,367 (0.2) |
| Connective tissue disease | 2,573 (1.8) | 3,763 (2.1) | 5,196 (2.2) | 5,964 (2.7) | 17,496 (2.2) |
| Any malignancy | 8,568 (6.0) | 11,607 (6.3) | 16,616 (7.2) | 19,169 (8.5) | 55,960 (7.2) |
| Hyperthyroidism | 1,437 (1.0) | 2,404 (1.3) | 3,526 (1.5) | 3,789 (1.7) | 11,156 (1.4) |
| Heart valve disease | 687 (0.5) | 1,337 (0.7) | 2,085 (0.9) | 2,733 (1.2) | 6,842 (0.9) |
| Prior venous thromboembolism | 1,539 (1.1) | 2,391 (1.3) | 3,466 (1.5) | 4,087 (1.8) | 11,483 (1.5) |
| Smoking (proxy)† | 12,677 (8.8) | 16,004 (8.7) | 21,879 (9.5) | 22,899 (10.2) | 73,459 (9.4) |
| Hospital-diagnosed obesity | 992 (0.7) | 1,936 (1.1) | 4,792 (2.1) | 7,291 (3.2) | 15,011 (1.9) |
| Alcoholism-related disorders | 2,430 (1.7) | 3,972 (2.2) | 6,136 (2.7) | 6,820 (3.0) | 19,358 (2.5) |
| **Medications** | | | | | |
| Statins | 1,403 (1.0) | 5,836 (3.2) | 21,701 (9.4) | 27,148 (12.1) | 56,088 (7.2) |
| High-intensity statins | 7 (0) | 198 (0.1) | 903 (0.4) | 2,311 (1.0) | 3,419 (0.4) |
| Other lipid-lowering drugs | 0 (0) | <5 (0) | 272 (0.1) | 469 (0.2) | 744 (0.1) |
| Beta-blockers | 8,352 (5.8) | 13,700 (7.5) | 18,896 (8.2) | 17,986 (8.0) | 58,934 (7.5) |
| ACE inhibitor/ ARBs | 7,720 (5.4) | 16,658 (9.1) | 32,914 (14.2) | 38,616 (17.2) | 95,908 (12.3) |
| Calcium channel blockers | 8,962 (6.3) | 11,919 (6.5) | 19,588 (8.5) | 22,988 (10.2) | 63,457 (8.1) |
| Thiazides | 11,464 (8.0) | 16,839 (9.2) | 22,244 (9.6) | 18,069 (8.1) | 68,616 (8.8) |
| Aspirin | 8,629 (6.0) | 12,839 (7.0) | 17,204 (7.4) | 14,720 (6.6) | 53,392 (6.8) |
| ADP receptor inhibitors | 7 (0) | 80 (0) | 222 (0.1) | 855 (0.4) | 1,164 (0.1) |

| | | | | | |
|---|---|---|---|---|---|
| Vitamin K antagonists | 1,418 (1.0) | 2,519 (1.4) | 4,346 (1.9) | 4,607 (2.1) | 12,890 (1.6) |
| DOACs | 0 (0) | 0 (0) | 41 (0) | 629 (0.3) | 670 (0.1) |

Numbers are counts (%) unless otherwise indicated.
Abbreviations: ARB, angiotensin II receptor blocker; COPD, chronic obstructive pulmonary disease; DOAC, direct oral anticoagulant; $Q_1$, first quartile; $Q_3$, third quartile.
*Hypertension was defined as ICD-10/8 diagnosis codes for hypertension and/or redemption of ≥1 prescription for antihypertensive treatment.
†Smoking (proxy) was defined by ICD-10/8 diagnosis codes for chronic bronchitis, emphysema, and COPD, and medications used to treat COPD.

Supplementary Table 3. Trends in $HbA_{1c}$ and LDL cholesterol levels in a regional subcohort of patients with incident type 2 diabetes in Northern Denmark.

| | Diabetes: 1996-2000 (n=15,510) | Diabetes: 2001-2005 (n=19,418) | Diabetes: 2006-2010 (n=26,492) | Diabetes: 2011-2015 (n=27,013) |
|---|---|---|---|---|
| **Pre-diagnosis measurement*** | | | | |
| Missing $HbA_{1c}$ | 10,838 (70) | 9,846 (51) | 7,444 (28) | 3,152 (12) |
| Median $HbA_{1c}$, mmol/mol ($Q_1$-$Q_3$) | 77 (58-98) (9.2% [7.5%-11.1%]) | 64 (51-87) (8.0% [6.8%-10.1%]) | 56 (48-75) (7.3% [6.5%-9.0%]) | 52 (47-65) (6.9% [6.5%-8.1%]) |
| Missing LDL cholesterol | 13,774 (89) | 12,600 (65) | 9,181 (35) | 5,671 (21) |
| Median LDL cholesterol, mmol/L ($Q_1$-$Q_3$) | 3.6 (3.0-4.3) | 3.3 (2.7-4.0) | 2.9 (2.3-3.6) | 2.9 (2.2-3.6) |
| Missing eGFR | 9,085 (59) | 7,391 (38) | 4,346 (16) | 1,642 (6) |
| Median eGFR, ml/min/1.73m$^2$, ($Q_1$-$Q_3$) | 83 (71-97) | 81 (69-94) | 71 (61-83) | 72 (61-84) |
| **Post-diagnosis measurement**† | | | | |
| Missing $HbA_{1c}$ | 9,302 (60) | 8,352 (43) | 6,880 (26) | 4,249 (16) |
| Median $HbA_{1c}$, mmol/mol ($Q_1$-$Q_3$) | 51 (43-62) (6.8% [6.1%-7.8%]) | 49 (42-55) (6.6% [6.0%-7.2%]) | 46 (42-53) (6.4% [6.0%-7.0%]) | 45 (42-50) (6.3% [6.0%-6.7%]) |
| Missing LDL cholesterol | 12,948 (83) | 10,987 (57) | 8,590 (32) | 6,424 (24) |
| Median LDL cholesterol, mmol/L ($Q_1$-$Q_3$) | 3.3 (2.7-4.0) | 2.6 (2.1-3.3) | 2.3 (1.8-2.8) | 2.2 (1.8-2.9) |
| Missing eGFR | 9,292 (60) | 7,951 (41) | 5,715 (22) | 3,722 (14) |
| Median eGFR, ml/min/1.73m$^2$, ($Q_1$-$Q_3$) | 82 (71-96) | 79 (67-92) | 72 (61-84) | 73 (63-86) |

Numbers are counts (%) unless otherwise indicated.
Abbreviation: eGFR, estimated glomerular filtration rate.
*Pre-diagnosis measurement was defined as the latest measurement within 12 months before the diabetes diagnosis date.
†Post-diagnosis measurement was defined as the latest measurement 6-18 months following the diabetes diagnosis date.

Supplementary Table 4. Interaction effect between type 2 diabetes and atrial fibrillation on five-year risk of ischemic stroke.

| | Individuals (events) | 5-year cumulative incidence* (95% CI) | Crude hazard ratio (95% CI) | Adjusted hazard ratio† (95% CI) | Interaction contrast (95% CI) |
|---|---|---|---|---|---|
| Ischemic stroke | | | | | |
| -T2DM, -AF | 771,347 (16,419) | 2.2% (2.2-2.2) | reference | reference | |
| -T2DM, +AF | 10,885 (661) | 6.2% (5.8-6.7) | 3.31 (3.06-3.58) | 1.76 (1.63-1.91) | |
| +T2DM, -AF | 280,151 (8,945) | 3.3% (3.2-3.3) | 1.58 (1.54-1.62) | 1.53 (1.49-1.57) | |
| +T2DM, +AF | 8,674 (656) | 7.7% (7.1-8.3) | 4.72 (4.36-5.10) | 2.44 (2.25-2.64) | 0.4 (-0.3-1.1) |

The interaction contrast is calculated as $R_{AB}$-$R_A$-$R_B$+$R_U$, i.e., $risk_{+DM+AF} - risk_{+DM-AF} - risk_{-DM+AF} + risk_{-DM-AF}$.
Abbreviations: AF, atrial fibrillation; T2DM, type 2 diabetes.
*Accounting for the competing risk of death.
†Adjusted for sex and age.

Supplementary Table 5. Proportion of patients with type 2 diabetes who redeemed ≥ 1 prescription(s) for prophylactic cardiovascular medications within 12 months after diabetes diagnosis.

| | Diabetes: 1996-2000 | Diabetes: 2001-2005 | Diabetes: 2006-2010 | Diabetes: 2011-2015 |
|---|---|---|---|---|
| All patients with type 2 diabetes | | | | |
| Number of patients | 52,463 | 67,693 | 85,426 | 83,243 |
| Statins | 5.2 (5.0-5.4) | 28.7 (28.4-29.0) | 49.4 (49.1-49.7) | 50.4 (50.0-50.7) |
| High-intensity statins | 0.1 (0.0-0.1) | 0.8 (0.7-0.8) | 2.3 (2.2-2.4) | 7.4 (7.2-7.6) |
| Other lipid-lowering drugs | - | - | 0.6 (0.6-0.7) | 0.8 (0.7-0.8) |
| Beta-blockers | 12.6 (12.3-12.8) | 18.1 (17.8-18.4) | 19.3 (19.1-19.6) | 19.3 (19.0-19.5) |
| ACE inhibitor/ARBs | 22.4 (22.0-22.7) | 36.9 (36.6-37.3) | 45.9 (45.5-46.2) | 46.9 (46.6-47.3) |
| Calcium channel blockers | 15.2 (14.9-15.5) | 16.3 (16.0-16.6) | 21.4 (21.1-21.7) | 22.6 (22.3-22.8) |
| Thiazides | 14.7 (14.4-15.0) | 19.0 (18.7-19.3) | 18.5 (18.2-18.7) | 14.9 (14.6-15.1) |
| Aspirin | 15.6 (15.3-15.9) | 23.7 (23.4-24.1) | 25.5 (25.2-25.8) | 16.2 (16.0-16.5) |
| ADP receptor inhibitors | 0.2 (0.1-0.2) | 0.9 (0.9-1.0) | 1.1 (1.0-1.1) | 1.9 (1.8-2.0) |
| Vitamin K antagonists | 3.5 (3.3-3.6) | 4.5 (4.4-4.6) | 5.1 (4.9-5.2) | 5.1 (5.0-5.3) |
| DOACs | - | - | - | 1.0 (0.9-1.1) |
| Antihypertensive drugs used | | | | |
| 0 | 57.5 (57.1-57.9) | 46.6 (46.3-47.0) | 40.5 (40.2-40.8) | 39.9 (39.6-40.3) |
| 1 | 25.0 (24.6-25.4) | 25.7 (25.4-26.0) | 26.1 (25.8-26.4) | 27.6 (27.3-27.9) |
| 2 | 12.6 (12.3-12.9) | 18.0 (17.7-18.3) | 20.5 (20.3-20.8) | 21.3 (21.0-21.6) |
| ≥3 | 4.9 (4.7-5.1) | 9.6 (9.4-9.9) | 12.8 (12.6-13.1) | 11.2 (11.0-11.4) |
| Patients with type 2 diabetes and atrial fibrillation | | | | |
| Number of patients | 2,555 | 3,750 | 4,892 | 5,456 |
| Vitamin K antagonists | 34.6 (32.8-36.5) | 47.1 (45.5-48.7) | 54.7 (53.3-56.1) | 50.2 (48.9-51.5) |
| DOACs | - | - | - | 8.0 (7.3-8.7) |

Numbers are percentages (95% CI) unless otherwise indicated.
Abbreviations: ARB, angiotensin II receptor blocker; DOAC, direct oral anticoagulant.

Supplementary Table 6. Five-year risk of ischemic stroke in patients with incident type 2 diabetes stratified by age category and sex.

| | Patients | Events | 5-year cumulative incidence* (95% CI) | Crude hazard ratio (95% CI) | Adjusted hazard ratio† (95% CI) |
|---|---|---|---|---|---|
| Age <60 years | | | | | |
| 1996-2000 | 24,410 | 571 | 2.3% (2.2-2.5) | reference | reference |
| 2001-2005 | 33,378 | 589 | 1.8% (1.6-1.9) | 0.75 (0.67-0.84) | 0.77 (0.69-0.86) |
| 2006-2010 | 42,519 | 525 | 1.2% (1.1-1.4) | 0.52 (0.46-0.59) | 0.55 (0.48-0.61) |
| 2011-2015 | 40,413 | 440 | 1.2% (1.1-1.3) | 0.50 (0.44-0.56) | 0.51 (0.45-0.58) |
| Age 60-69 years | | | | | |
| 1996-2000 | 12,330 | 695 | 5.6% (5.2-6.1) | reference | reference |
| 2001-2005 | 16,580 | 666 | 4.0% (3.7-4.3) | 0.70 (0.63-0.77) | 0.69 (0.62-0.77) |
| 2006-2010 | 22,918 | 586 | 2.6% (2.4-2.8) | 0.43 (0.39-0.49) | 0.43 (0.39-0.48) |
| 2011-2015 | 22,717 | 622 | 3.0% (2.7-3.2) | 0.50 (0.45-0.55) | 0.49 (0.44-0.55) |
| Age 70-79 years | | | | | |
| 1996-2000 | 10,327 | 943 | 9.1% (8.6-9.7) | reference | reference |
| 2001-2005 | 11,456 | 815 | 7.1% (6.7-7.6) | 0.75 (0.69-0.83) | 0.75 (0.69-0.83) |
| 2006-2010 | 13,496 | 641 | 4.8% (4.4-5.1) | 0.49 (0.44-0.54) | 0.48 (0.44-0.53) |
| 2011-2015 | 13,961 | 599 | 4.6% (4.3-5.0) | 0.46 (0.41-0.51) | 0.45 (0.41-0.50) |
| Age ≥80 years | | | | | |
| 1996-2000 | 5,396 | 521 | 9.7% (8.9-10.5) | reference | reference |
| 2001-2005 | 6,279 | 552 | 8.8% (8.1-9.5) | 0.89 (0.79-1.00) | 0.89 (0.79-1.00) |
| 2006-2010 | 6,493 | 441 | 6.8% (6.2-7.4) | 0.67 (0.59-0.76) | 0.67 (0.59-0.76) |
| 2011-2015 | 6,152 | 395 | 6.8% (6.2-7.5) | 0.65 (0.57-0.74) | 0.65 (0.57-0.74) |
| Male patients | | | | | |
| 1996-2000 | 28,228 | 1,502 | 5.3% (5.1-5.6) | reference | reference |
| 2001-2005 | 35,289 | 1,449 | 4.1% (3.9-4.3) | 0.76 (0.70-0.81) | 0.76 (0.71-0.82) |
| 2006-2010 | 43,208 | 1,188 | 2.8% (2.6-2.9) | 0.50 (0.46-0.54) | 0.50 (0.46-0.54) |
| 2011-2015 | 43,037 | 1,145 | 2.9% (2.7-3.1) | 0.51 (0.47-0.55) | 0.50 (0.46-0.54) |
| Female patients | | | | | |
| 1996-2000 | 24,235 | 1,228 | 5.1% (4.8-5.4) | reference | reference |
| 2001-2005 | 32,404 | 1,173 | 3.6% (3.4-3.8) | 0.70 (0.64-0.76) | 0.78 (0.72-0.85) |
| 2006-2010 | 42,218 | 1,005 | 2.4% (2.2-2.5) | 0.45 (0.41-0.49) | 0.56 (0.52-0.61) |
| 2011-2015 | 40,206 | 911 | 2.5% (2.3-2.6) | 0.45 (0.42-0.49) | 0.55 (0.50-0.60) |

*Accounting for the competing risk of death.
†Adjusted for sex in the analysis stratified by age and adjusted for age in the analysis stratified by sex.

Supplementary Table 7. Five-year risk of ischemic stroke in patients with incident type 2 diabetes and matched individuals from the general population. Matched individuals were censored if they developed type 2 diabetes during follow-up.

| | General population individuals | | Type 2 diabetes vs. general population | |
|---|---|---|---|---|
| | Individuals (events) | 5-year cumulative incidence* (95% CI) | Risk difference*,† (95% CI) | Sex- and age-matched hazard ratio† (95% CI) |
| 1996-2000 | 143,339 (4,009) | 2.8% (2.8-2.9) | 2.4% (2.2-2.6) | 1.97 (1.89-2.06) |
| 2001-2005 | 183,444 (4,400) | 2.4% (2.4-2.5) | 1.4% (1.3-1.6) | 1.66 (1.59-1.73) |
| 2006-2010 | 230,994 (4,259) | 1.9% (1.8-1.9) | 0.7% (0.6-0.8) | 1.37 (1.31-1.43) |
| 2011-2015 | 224,455 (3,982) | 2.0% (1.9-2.0) | 0.7% (0.6-0.8) | 1.40 (1.33-1.46) |

*Accounting for the competing risk of death.
†Matched individuals from same calendar period were used as reference.

Supplementary Table 8. Five-year risk of any type of stroke (ICD-10 codes I60-I64) in patients with incident type 2 diabetes and matched individuals from the general population.

| | Type 2 diabetes | | | | General population | | Type 2 diabetes vs. general population |
|---|---|---|---|---|---|---|---|
| | Individuals (events) | 5-year cumulative incidence* (95% CI) | Crude HR (95% CI) | Adjusted HR† (95% CI) | Individuals (events) | 5-year cumulative incidence* (95% CI) | Sex- and age-matched HR‡ (95% CI) |
| 1996-2000 | 52,463 (2,920) | 5.6% (5.4-5.8) | reference | reference | 143,339 (4,573) | 3.2% (3.1-3.3) | 1.88 (1.80-1.96) |
| 2001-2005 | 67,693 (2,884) | 4.3% (4.1-4.4) | 0.75 (0.71-0.79) | 0.79 (0.75-0.84) | 183,444 (5,082) | 2.8% (2.7-2.9) | 1.62 (1.55-1.68) |
| 2006-2010 | 85,426 (2,522) | 3.0% (2.9-3.1) | 0.51 (0.48-0.54) | 0.57 (0.54-0.60) | 230,994 (5,192) | 2.3% (2.2-2.3) | 1.32 (1.27-1.38) |
| 2011-2015 | 83,243 (2,204) | 2.8% (2.7-3.0) | 0.48 (0.46-0.51) | 0.52 (0.49-0.55) | 224,455 (4,487) | 2.2% (2.1-2.2) | 1.33 (1.27-1.39) |

Abbreviations: HR, hazard ratio.
*Accounting for the competing risk of death. †Comparing patients with type 2 diabetes by calendar period, adjusted for sex and age. ‡Comparing patients with type 2 diabetes with matched individuals from the same calendar period as reference.

Supplementary Table 9. Treatment goals for patients with type 2 diabetes in Denmark, 1988-2021.

| | 1988-1999[1,2] | 2000-2003[3,4] | 2004[5] | 2008[6] | 2011[7] | 2012[8] | 2018, 2019, 2021[9,10,11] |
|---|---|---|---|---|---|---|---|
| **Systolic blood pressure (mm Hg)** | <160 | <135 | <130<br><br><125 (patients with albuminuria) | <130<br><br><125 (patients with micro-albuminuria and renal disease) | <130 | <130 | <130 |
| **Diastolic blood pressure (mm Hg)** | <95 | <85 | <80 | <80<br><br><75 (patients with micro-albuminuria and renal disease) | <80 | <80 | <80 |
| **Glycosylated hemoglobin** | <7.5% (58 mmol/mol) | <6.5% (48 mmol/mol) | ≤6.1% | <6.5% | <6.5% in the first years after diagnosis; later <7%, <7.5%, and <7.5-9.0%* | ≤48 mmol/mol (6.5%) in the first years after diagnosis, later 48-58 mmol/mol (6.5-7.5%)* | <48 mmol/mol (6.5%) in the first years after diagnosis, later < 53 mmol/mol (7%), < 58 mmol/mol (7.5%), 58-75 mmol/mol (7.5-9%)* |
| **Fasting serum total cholesterol (mmol/L)** | <6.5 | <5 | <4.5 | <4.5 | - | - | - |
| **LDL cholesterol (mmol/L)** | - | - | <2.5 | <2.5<br><br><2.0 (patients with CVD or at high risk†) | <2.5 (patients without CVD)<br><br><2.0 (patients with CVD or at high risk†) | <2.5 (patients without CVD)<br><br><1.8 or at least 50% reduction (patients with CVD or at high risk†) | <2.6 or at least 50% reduction at LDL 2.6-5.2 (patients without CVD and age<40)<br><br><1.8 or at least 50% reduction at LDL 1.8-3.5 (patients with CVD or at high risk†)<br><br><1.4 (should be considered for patients at very high CVD risk) |
| **Fasting serum triglycerides (mmol/L)** | <2.2 | <2 | <1.7 | <1.7 | - | - | - |
| **Treatment with ACE inhibitor irrespective of blood pressure** | No | Yes | Yes, in presence of macro- or microalbuminuria | Yes, in presence of macro- or microalbuminuria | Yes, in presence of macro- or microalbuminuria | Yes, in presence of macro- or microalbuminuria | Should be considered in presence of macro- or microalbuminuria |
| **Aspirin therapy** | | | | | | | |
| **Patients with CVD** | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| **Patients without CVD** | No | No | Unclear, individual risk assessment (risk of CVD vs. GI side effects) | Yes, for high-risk patients† | Should be considered for high-risk patients† | Should be considered for high-risk patients† | Should be considered for high-risk patients† |

Abbreviations: CVD, cardiovascular disease; GI, gastrointestinal; LDL, low density lipoprotein.

*Treatment goals depend on diabetes duration, risk of hypoglycaemia, and risk of micro- and macro-vascular complications.

†High-risk: microalbuminuria or several risk factors such as hypertension, smoking, and family history of CVD.

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