**Pioglitazone and cause specific risk of mortality in patients with type 2 diabetes: extended analysis from a European multi-database cohort study**

**Supplementary appendix**

**Table S1: ICD-10 and ICD-9 Codes for cause-specific deaths of interest as defined in the protocol using Pooled data**

|  |  |
| --- | --- |
| stroke | I63, I64, I69.3, I69.4, I69.0, I69.1, I61, I60, I62 |
| myocardial infarction | I21, I22, I20, I23, I24, I25, 414 |
| sudden death | I46 |
| heart failure | I50, R57.0, I11.0, I42.5, I42.8, I42.6, I42.2, I42.0, I42.9 |
| reno-vascular disease | I70.1, I77.3, I72.2, I82.3, N28.0, I13, I12 |
| peripheral vascular disease | I73.8, I73.9, I71, I80, 441 |
| arrhythmia | I49, I47.2, I49.0, I49.8, I49.9, I48, I44 |
| other CVDs of interest | I10, I51.9, I70.9, I67, I51.1, I51.4, I51.7, I51.6, I69.8, I11.9, I77.2, I77.9, I72.9, I27, I30, I99, I82.9, I51.3, I35, I26, I33, I34, I38, I05, I08, I74, I81, I07 |
| stroke | I63, I64, I69.3, I69.4, I69.0, I69.1, I61, I60, I62 |

**Table 2a: Distribution of exact matching characteristics at cohort entry (Finland)**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **PIO exposed N=15,315 n (%)** | **Non-PIO exposed N=15,315 n (%)** | **Standardised difference** |
| **Type of treatment change at CED** |  |  |  |
| add-on | 8070(52.69) | 8070(52.69) | 0.00 |
| switch | 7245(47.31) | 7245(47.31) | 0.00 |
| **History of TZD at CED** |  |  |  |
| Never | 12659(82.66) | 12659(82.66) | 0.00 |
| Ever | 2656(17.34) | 2656(17.34) | 0.00 |
| **Antidiabetic treatment immediately prior to CED1** |  |  |  |
| Insulin (only or in combination) | 978(6.39) | 978(6.39) | 0.00 |
| Metformin and Sulphonylureas (SU) | 3776(24.66) | 3776(24.66) | 0.00 |
| Metformin only | 5530(36.11) | 5530(36.11) | 0.00 |
| No treatment | 1865(12.18) | 1865(12.18) | 0.00 |
| Other drugs or combination | 1896(12.38) | 1896(12.38) | 0.00 |
| SU only | 1270(8.29) | 1270(8.29) | 0.00 |

1 Treatments initiated at CED are not included

**Table 2b: Distribution of propensity score characteristics at cohort entry (Finland)**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **PIO exposed N=15,315 n (%)** | **Non-PIO exposed N=15,315 n (%)** | **Standardised difference** |
| **Duration of treated diabetes at CED (years)** |  |  |  |
| < 1 | 1722(11.24) | 1814(11.84) | 1.88 |
| 1 - < 2 | 1773(11.58) | 1277(8.34) | 10.83 |
| 2 - < 4 | 2825(18.45) | 2237(14.61) | 10.35 |
| 4 - < 6 | 2800(18.28) | 3372(22.02) | 9.32 |
| ≥ 6 | 6195(40.45) | 6615(43.19) | 5.56 |
| Range (min, max) | (0.00, 12.97) | (0.00, 12.98) |  |
| Mean (+/-SD) | 4.77 (3.43) | 5.11 (3.49) |  |
| Median (Q1,Q3) | 4.47(1.74, 7.36) | 4.88(2.15, 7.57) |  |
| **History of diabetic complications at CED** |  |  |  |
| Diabetic retinopathy or maculopathy | 426(2.78) | 840(5.48) | 13.61 |
| Lower limb severe complications | 176(1.15) | 381(2.49) | 10.03 |
| Diabetic renal complications | 258(1.68) | 412(2.69) | 6.88 |
| Ketoacidosis | 34(0.22) | 64(0.42) | 3.47 |
| Hyperosmolar/ketoacidotic coma | 601(3.92) | 1018(6.65) | 12.19 |
| **Other Comorbidities at CED** |  |  |  |
| Myocardial infarction or stroke | 1066(6.96) | 2137(13.95) | 23.00 |
| Congestive heart failure (CHF) | 438(2.86) | 1457(9.51) | 27.89 |
| **Year at CED** |  |  |  |
| 2000 – 2003 | 451(2.94) | 2532(16.53) | 47.08 |
| 2004 – 2007 | 6254(40.84) | 5302(34.62) | 12.85 |
| 2008 – 2011 | 8610(56.22) | 7481(48.85) | 14.80 |
| **Duration of medication database membership before CED (years)** |  |  |  |
| 1-2 | 0(0.00) | 0(0.00) | - |
| 3-4 | 3(0.02) | 730(4.77) | 31.44 |
| 5-6 | 604(3.94) | 2437(15.91) | 40.85 |
| 7+ | 14708(96.04) | 12148(79.32) | 52.59 |
| Range (min, max) | (4.00, 13.00) | (4.00, 13.00) |  |
| Mean (+/-SD) | 10.05 (2.00) | 9.32 (2.75) |  |
| Median (Q1,Q3) | 10.00(8.00, 12.00) | 10.00(7.00, 12.00) |  |
| **Number of different antidiabetic drug classes ever prior to CED** |  |  |  |
| 0 | 705(4.60) | 668(4.36) | 1.17 |
| 1 | 4872(31.81) | 3483(22.74) | 20.47 |
| 2 | 6359(41.52) | 6253(40.83) | 1.41 |
| 3 | 2565(16.75) | 3714(24.25) | 18.67 |
| >3 | 814(5.32) | 1197(7.82) | 10.11 |

**Table 2c: Distribution of other characteristics at cohort entry (Finland)**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **PIO exposed N=15,315 n (%)** | **Non-PIO exposed N=15,315 n (%)** | **Standardised difference** |
| **Age at CED (years)** |  |  |  |
| 40 – 59 | 6389(41.72) | 4252(27.76) | 29.63 |
| 60 – 69 | 5115(33.40) | 4465(29.15) | 9.16 |
| >= 70 | 3811(24.88) | 6598(43.08) | 39.15 |
| Range (min, max) | (40.00, 98.00) | (40.00, 101.00) |  |
| Mean (+/-SD) | 62.72 (10.45) | 67.43 (11.44) |  |
| Median (Q1,Q3) | 62.00(55.00, 70.00) | 68.00(59.00, 76.00) |  |
| **Sex** |  |  |  |
| Male | 8692(56.75) | 8153(53.24) | 7.08 |
| Female | 6623(43.25) | 7162(46.76) | 7.08 |
| **Number of different antidiabetic drug classes being used at CED2** |  |  |  |
| 1 | 1265(8.26) | 1801(11.76) | 11.68 |
| 2 | 7347(47.97) | 8099(52.88) | 9.83 |
| 3 | 5845(38.17) | 5157(33.67) | 9.37 |
| > 3 | 858(5.60) | 258(1.68) | 21.02 |
| **Antidiabetic treatment at CED2** |  |  |  |
| Insulin (only or in combination) | 1039(6.78) | 6996(45.68) | 98.58 |
| Metformin and SU | 3994(26.08) | 3205(20.93) | 12.17 |
| Metformin only | 5847(38.18) | 1332(8.70) | 74.23 |
| No treatment | 1265(8.26) | 0(0.00) | 42.43 |
| Other drugs or combination | 2011(13.13) | 3556(23.22) | 26.39 |
| SU only | 1159(7.57) | 226(1.48) | 29.64 |
| **Bladder comorbidities at CED** |  |  |  |
| Urinary incontinence | 980(6.40) | 1282(8.37) | 7.55 |
| Urinary tract infection | 158(1.03) | 313(2.04) | 8.23 |
| Pyelonephritis | 274(1.79) | 432(2.82) | 6.88 |
| Urolithiasis | 259(1.69) | 220(1.44) | 2.05 |
| Haematuria | 230(1.50) | 255(1.67) | 1.31 |
| Urinary retention | 128(0.84) | 204(1.33) | 4.79 |
| Neurogenic bladder | 8(0.05) | 7(0.05) | 0.30 |
| Catheterization | 82(0.54) | 134(0.87) | 4.06 |
| **Other comorbidities at CED** |  |  |  |
| Other urinary tract cancer (excl. BC) | 66(0.43) | 75(0.49) | 0.87 |
| Other cancer (excl. urinary tract) | 1367(8.93) | 1817(11.86) | 9.64 |
| COPD | 1158(7.56) | 1293(8.44) | 3.25 |
| **Use of other medications prior to CED** |  |  |  |
| Statins | 10173(66.43) | 9246(60.37) | 12.59 |
| ARB | 5230(34.15) | 4416(28.83) | 11.46 |
| ACE inhibitors | 8155(53.25) | 8479(55.36) | 4.25 |
| BPH | 1703(11.12) | 1971(12.87) | 5.39 |

2 Treatments initiated at CED are included. For the pioglitazone exposed group, the listed treatments are in addition to pioglitazone.

**Table 3a: Distribution of exact matching characteristics at cohort entry (Sweden)**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **PIO exposed N=3,712 n (%)** | **Non-PIO exposed N=3,712**  **n (%)** | **Standardised difference** |
| **Type of treatment change at CED** |  |  |  |
| add-on | 2454(66.11) | 2454(66.11) | 0.00 |
| switch | 1258(33.89) | 1258(33.89) | 0.00 |
| **History of TZD at CED** |  |  |  |
| Never | 2298(61.91) | 2298(61.91) | 0.00 |
| Ever | 1414(38.09) | 1414(38.09) | 0.00 |
| **Antidiabetic treatment immediately prior to CED1** |  |  |  |
| Insulin (only or in combination) | 230(6.20) | 230(6.20) | 0.00 |
| Metformin and Sulphonylureas (SU) | 407(10.96) | 407(10.96) | 0.00 |
| Metformin only | 1225(33.00) | 1225(33.00) | 0.00 |
| No treatment | 609(16.41) | 609(16.41) | 0.00 |
| Other drugs or combination | 1023(27.56) | 1023(27.56) | 0.00 |
| SU only | 218(5.87) | 218(5.87) | 0.00 |

1 Treatments initiated at CED are not included

**Table 3b: Distribution of propensity score characteristics at cohort entry (Sweden)**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **PIO exposed N=3,712 n (%)** | **Non-PIO exposed N=3,712**  **n (%)** | **Standardised difference** |
| **Duration of treated diabetes at CED (years)** |  |  |  |
| < 1 | 699(18.83) | 695(18.72) | 0.28 |
| 1 - < 2 | 693(18.67) | 697(18.78) | 0.28 |
| 2 - < 4 | 894(24.08) | 896(24.14) | 0.13 |
| 4 - < 6 | 1426(38.42) | 1424(38.36) | 0.11 |
| ≥ 6 | 0(0.00) | 0(0.00) | - |
| Range (min, max) | (0.00, 5.95) | (0.00, 5.99) |  |
| Mean (+/-SD) | 3.02 (1.94) | 2.99 (1.92) |  |
| Median (Q1,Q3) | 2.90 (1.32, 5.16) | 2.98 (1.30, 4.91) |  |
| **History of diabetic complications at CED** |  |  |  |
| Diabetic retinopathy or maculopathy | 312(8.41) | 309(8.32) | 0.29 |
| Lower limb severe complications | 33(0.89) | 25(0.67) | 2.45 |
| Diabetic renal complications | 85(2.29) | 69(1.86) | 3.02 |
| Ketoacidosis | 7(0.19) | 6(0.16) | 0.64 |
| Hyperosmolar/ketoacidotic coma | 32(0.86) | 37(1.00) | 1.40 |
| **Other Comorbidities at CED** |  |  |  |
| Myocardial infarction or stroke | 235(6.33) | 228(6.14) | 0.78 |
| Congestive heart failure (CHF) | 101(2.72) | 107(2.88) | 0.98 |
| **Year at CED** |  |  |  |
| 2000 – 2003 | 0(0.00) | 0(0.00) | - |
| 2004 – 2007 | 979(26.37) | 989(26.64) | 0.61 |
| 2008 – 2011 | 2733(73.63) | 2723(73.36) | 0.61 |
| **Duration of medication database membership before CED (years)** |  |  |  |
| 1-2 | 1000(26.94) | 1007(27.13) | 0.42 |
| 3-4 | 895(24.11) | 904(24.35) | 0.57 |
| 5-6 | 1817(48.95) | 1801(48.52) | 0.86 |
| 7+ | 0(0.00) | 0(0.00) | - |
| Range (min, max) | (1.00, 6.00) | (1.00, 6.00) |  |
| Mean (+/-SD) | 3.89 (1.66) | 3.88 (1.66) |  |
| Median (Q1,Q3) | 4.00 (2.00, 5.00) | 4.00 (2.00, 5.00) |  |
| **Number of different antidiabetic drug classes ever prior to CED** |  |  |  |
| 0 | 209(5.63) | 207(5.58) | 0.23 |
| 1 | 1084(29.20) | 1089(29.34) | 0.30 |
| 2 | 1503(40.49) | 1504(40.52) | 0.05 |
| 3 | 666(17.94) | 664(17.89) | 0.14 |
| >3 | 250(6.73) | 248(6.68) | 0.22 |

**Table 3c: Distribution of other characteristics at cohort entry (Sweden)**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **PIO exposed N=3,712 n (%)** | **Non-PIO exposed N=3,712**  **n (%)** | **Standardised difference** |
| **Age at CED (years)** |  |  |  |
| 40 – 59 | 1263(34.02) | 1152(31.03) | 6.39 |
| 60 – 69 | 1402(37.77) | 1308(35.24) | 5.26 |
| >= 70 | 1047(28.21) | 1252(33.73) | 11.97 |
| Range (min, max) | (40.04, 95.28) | (40.08, 100.62) |  |
| Mean (+/-SD) | 63.96 (10.23) | 65.48 (11.21) |  |
| Median (Q1,Q3) | 63.99 (56.98, 71.09) | 64.98 (57.86, 73.39) |  |
| **Sex** |  |  |  |
| Male | 2264(60.99) | 2130(57.38) | 7.35 |
| Female | 1448(39.01) | 1582(42.62) | 7.35 |
| **Number of different antidiabetic drug classes being used at CED2** |  |  |  |
| 1 | 464(12.50) | 568(15.30) | 8.11 |
| 2 | 1737(46.79) | 1957(52.72) | 11.87 |
| 3 | 1228(33.08) | 1092(29.42) | 7.91 |
| > 3 | 283(7.62) | 95(2.56) | 23.19 |
| **Antidiabetic treatment at CED2** |  |  |  |
| Insulin (only or in combination) | 244(6.57) | 1389(37.42) | 80.24 |
| Metformin and SU | 447(12.04) | 697(18.78) | 18.74 |
| Metformin only | 1310(35.29) | 365(9.83) | 63.94 |
| No treatment | 464(12.50) | 0(0.00) | 53.45 |
| Other drugs or combination | 1025(27.61) | 1160(31.25) | 7.99 |
| SU only | 222(5.98) | 101(2.72) | 16.03 |
| **Bladder comorbidities at CED** |  |  |  |
| Urinary incontinence | 219(5.90) | 243(6.55) | 2.68 |
| Urinary tract infection | 130(3.50) | 117(3.15) | 1.95 |
| Pyelonephritis | 42(1.13) | 37(1.00) | 1.31 |
| Urolithiasis | 149(4.01) | 136(3.66) | 1.82 |
| Haematuria | 83(2.24) | 82(2.21) | 0.18 |
| Urinary retention | 33(0.89) | 57(1.54) | 5.91 |
| Neurogenic bladder | 18(0.48) | 20(0.54) | 0.76 |
| Catheterization | 17(0.46) | 16(0.43) | 0.40 |
| **Other comorbidities at CED** |  |  |  |
| Other urinary tract cancer (excl. BC) | 14(0.38) | 10(0.27) | 1.90 |
| Other cancer (excl. urinary tract) | 439(11.83) | 469(12.63) | 2.47 |
| COPD | 138(3.72) | 147(3.96) | 1.26 |
| **Use of other medications prior to CED** |  |  |  |
| Statins | 2588(69.72) | 2477(66.73) | 6.43 |
| ARB | 1372(36.96) | 1165(31.38) | 11.78 |
| ACE inhibitors | 1649(44.42) | 1756(47.31) | 5.79 |
| BPH | 233(6.28) | 192(5.17) | 4.76 |

2 Treatments initiated at CED are included. For the pioglitazone exposed group, the listed treatments are in addition to pioglitazone.

**Table 4a: Distribution of exact matching characteristics at cohort entry (United Kingdom)**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **PIO exposed N=12,106 n (%)** | **Non-PIO exposed N=12,106 n (%)** | **Standardised difference** |
| **Type of treatment change at CED** |  |  |  |
| add-on | 8250(68.15) | 8250(68.15) | 0.00 |
| switch | 3856(31.85) | 3856(31.85) | 0.00 |
| **History of TZD at CED** |  |  |  |
| Never |  |  |  |
| Ever | 8304(68.59) | 8304(68.59) | 0.00 |
| **Antidiabetic treatment immediately prior to CED1** | 3802(31.41) | 3802(31.41) | 0.00 |
| Insulin (only or in combination) | 248(2.05) | 248(2.05) | 0.00 |
| Metformin and Sulphonylureas (SU) | 3488(28.81) | 3488(28.81) | 0.00 |
| Metformin only | 3281(27.10) | 3281(27.10) | 0.00 |
| No treatment | 1162(9.60) | 1162(9.60) | 0.00 |
| Other drugs or combination | 2486(20.54) | 2486(20.54) | 0.00 |
| SU only | 1441(11.90%) | 1441(11.90%) | 0.00 |

1 Treatments initiated at CED are not included

**Table 4b: Distribution of propensity score characteristics at cohort entry (United Kingdom)**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **PIO exposed N=12,106 n (%)** | **Non-PIO exposed N=12,106 n (%)** | **Standardised difference** |
| **Duration of treated diabetes at CED (years)** |  |  |  |
| < 1 | 1412(11.66) | 1361(11.24) | 1.32 |
| 1 - < 2 | 1457(12.04) | 1597(13.19) | 3.48 |
| 2 - < 4 | 2614(21.59) | 2824(23.33) | 4.16 |
| 4 - < 6 | 2153(17.78) | 2221(18.35) | 1.46 |
| ≥ 6 | 4470(36.92) | 4103(33.89) | 6.34 |
| Range (min, max) | (0.00, 34.18) | (0.00, 22.67) |  |
| Mean (+/-SD) | 5.30(4.03) | 5.12(3.98) |  |
| Median (Q1,Q3) | 4.47(2.13, 7.62) | 4.22(2.05, 7.35) |  |
| **History of diabetic complications at CED** |  |  |  |
| Diabetic retinopathy or maculopathy | 2451(20.25) | 2311(19.09) | 2.91 |
| Lower limb severe complications | 541(4.47) | 552(4.56) | 0.44 |
| Diabetic renal complications | 2008(16.59) | 1971(16.28) | 0.82 |
| Ketoacidosis | 33(0.27) | 46(0.38) | 1.88 |
| Hyperosmolar/ketoacidotic coma | 28(0.23) | 42(0.35) | 2.15 |
| **Other Comorbidities at CED** |  |  |  |
| Myocardial infarction or stroke | 1386(11.45) | 1488(12.29) | 2.61 |
| Congestive heart failure (CHF) | 530(4.38) | 649(5.36) | 4.57 |
| **Year at CED** |  |  |  |
| 2000 – 2003 | 1221(10.09) | 1571(12.98) | 9.06 |
| 2004 – 2007 | 3981(32.88) | 4282(35.37) | 5.25 |
| 2008 – 2011 | 6904(57.03) | 6253(51.65) | 10.81 |
| **Duration of medication database membership before CED (years)** |  |  |  |
| 1-2 | 1538(12.70) | 1521(12.56) | 0.42 |
| 3-4 | 1455(12.02) | 1550(12.80) | 2.38 |
| 5-6 | 1509(12.46) | 1674(13.83) | 4.03 |
| 7+ | 7604(62.81) | 7361(60.80) | 4.13 |
| Range (min, max) | (1.00, 22.00) | (1.00, 22.00) |  |
| Mean (+/-SD) | 8.87(5.36) | 8.55(5.10) |  |
| Median (Q1,Q3) | 8.00(5.00, 12.00) | 8.00(4.00, 12.00) |  |
| **Number of different antidiabetic drug classes ever prior to CED** |  |  |  |
| 0 | 183(1.51) | 186(1.54) | 0.20 |
| 1 | 2972(24.55) | 3261(26.94) | 5.46 |
| 2 | 5892(48.67) | 5075(41.92) | 13.59 |
| 3 | 2602(21.49) | 2826(23.34) | 4.44 |
| >3 | 457(3.77) | 758(6.26) | 11.41 |

**Table 4c: Distribution of other characteristics at cohort entry (United Kingdom)**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **PIO exposed N=12,106 n (%)** | **Non-PIO exposed N=12,106 n (%)** | **Standardised difference** |
| **Age at CED (years)** |  |  |  |
| 40 – 59 | 4421(36.52) | 4299(35.51%) | 2.10 |
| 60 – 69 | 3838(31.70) | 3733(30.84%) | 1.87 |
| >= 70 | 3847(31.78) | 4074(33.65%) | 4.00 |
| Range (min, max) | (40.00, 97.00) | (40.00, 97.00) |  |
| Mean (+/-SD) | 63.50(11.07) | 64.08(11.48) |  |
| Median (Q1,Q3) | 63.00(55.00, 72.00) | 64.00(56.00, 73.00) |  |
| **Sex** |  |  |  |
| Male | 7033(58.10) | 6844(56.53) | 3.16 |
| Female | 5073(41.90) | 5262(43.47) | 3.16 |
| **Number of different antidiabetic drug classes being used at CED2** |  |  |  |
| 1 | 1513(12.50) | 2358(19.48) | 19.13 |
| 2 | 6692(55.28) | 6426(53.08) | 4.41 |
| 3 | 3789(31.30) | 3245(26.80) | 9.91 |
| > 3 | 112(0.93) | 77(0.64) | 3.29 |
| **Antidiabetic treatment at CED2** |  |  |  |
| Insulin (only or in combination) | 179(1.48) | 3277(27.07) | 78.60 |
| Metformin and SU | 3484(28.78) | 2970(24.53) | 9.61 |
| Metformin only | 4282(35.37) | 310(2.56) | 92.15 |
| No treatment | 1513(12.50) | 0(0.00) | 53.45 |
| Other drugs or combination | 794(6.56) | 4855(40.10) | 86.40 |
| SU only | 1854(15.31) | 694(5.73) | 31.61 |
| **Bladder comorbidities at CED** |  |  |  |
| Urinary incontinence | 742(6.13) | 811(6.70) | 2.33 |
| Urinary tract infection | 2170(17.92) | 2388(19.73) | 4.61 |
| Pyelonephritis | 142(1.17) | 135(1.12) | 0.54 |
| Urolithiasis | 401(3.31) | 367(3.03) | 1.60 |
| Haematuria | 805(6.65) | 855(7.06) | 1.63 |
| Urinary retention | 208(1.72) | 269(2.22) | 3.63 |
| Neurogenic bladder | 14(0.12) | 23(0.19) | 1.90 |
| Catheterization | 222(1.83) | 300(2.48) | 4.44 |
| **Other comorbidities at CED** |  |  |  |
| Other urinary tract cancer (excl. BC) | 16(0.13) | 20(0.17) | 0.86 |
| Other cancer (excl. urinary tract) | 1609(13.29) | 1792(14.80) | 4.35 |
| COPD | 1433(11.84) | 1519(12.55) | 2.17 |
| **Use of other medications prior to CED** |  |  |  |
| Statins | 2172(17.94) | 2109(17.42) | 1.36 |
| ARB | 2464(20.35) | 2275(18.79) | 3.94 |
| ACE inhibitors | 7958(65.74) | 7769(64.17) | 3.27 |
| BPH | 2172(17.94) | 2109(17.42) | 1.36 |

2 Treatments initiated at CED are included. For the pioglitazone exposed group, the listed treatments are in addition to pioglitazone.

Table S5a Sensitivity analysis (#1) to assess the impact of smoking, BMI, and HbA1c for CV, non-CV and all-cause mortality (Sweden and UK data only)

| Analysis | **CV  HR (95%CI)** | **Non-CV  HR (95%CI)** | **All-cause  HR (95%CI)** |
| --- | --- | --- | --- |
| Sensitivity #1  Not Adjusted for smoking, HbA1c, and BMI | 0.80  (0.69, 0.93) | 0.81  (0.72, 0.91) | 0.81  (0.74, 0.89) |
| Sensitivity #1  Adjusted for smoking, HbA1c, and BMI | 0.85  (0.72, 1.01) | 0.85  (0.74, 0.97) | 0.85  (0.77, 0.95) |
| Percentage (%) change in HR | 6.0 | 5.0 | 5.4 |

Table S5b Sensitivity analysis (#2-#6) for CV, non-CV and all-cause mortality (Finland, Sweden and UK)

| Sensitivity analysis | **CV  HR (95%CI)** | **Non-CV  HR (95%CI)** | **All-cause  HR (95%CI)** |
| --- | --- | --- | --- |
| Original model | 0.58  (0.52, 0.63) | 0.63  (0.58, 0.68) | 0.60  (0.57, 0.64) |
| Sensitivity #2 Incident | 0.57  (0.49, 0.65) | 0.62  (0.55, 0.70) | 0.60  (0.54, 0.65) |
| Sensitivity #2 Prevalent | 0.57  (0.50, 0.64) | 0.63  (0.57, 0.70) | 0.60  (0.55, 0.65) |
| Sensitivity #3 2 purchases within 6 months | 0.63  (0.56, 0.70) | 0.65  (0.59, 0.71) | 0.64  (0.59, 0.69) |
| Sensitivity #4 log(age) at CED | 0.62  (0.57, 0.69) | 0.66  (0.61, 0.71) | 0.64  (0.60, 0.68) |
| Sensitivity #5 Exclude CV events at CED | 0.58  (0.51, 0.66) | 0.58  (0.52, 0.64) | 0.58  (0.53, 0.63) |
| Sensitivity #6 FIN | 0.46  (0.41, 0.53) | 0.49  (0.44, 0.55) | 0.48  (0.44, 0.52) |
| Sensitivity #6 SWE | 0.35  (0.22, 0.56) | 0.83  (0.62, 1.10) | 0.63  (0.49, 0.80) |
| Sensitivity #6 UK | 0.93  (0.79, 1.09) | 0.82  (0.72, 0.94) | 0.86  (0.78, 0.95) |

Table S6 Adjusted Hazard ratios for cause specific CV mortality for different exposure definitions.

| Exposure definitions | **Stroke  HR (95%CI)** | **Myocardial infarction  HR (95%CI)** | **Heart failure  HR (95%CI)** | **Renovascular disease** **HR (95%CI)** | **Peripheral vascular disease** **HR (95%CI)** | **Arrhythmia  HR (95%CI)** | **Other CV HR (95%CI)** |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Pioglitazone exposure |  |  |  |  |  |  |  |
| Never | reference | reference | reference | reference | reference | reference | reference |
| Ever | 0.48  (0.38, 0.62) | 0.61  (0.55, 0.69) | 0.60  (0.42, 0.86) | 0.12  (0.01, 1.03) | 0.56  (0.28, 1.10) | 0.37  (0.17, 0.80) | 0.54  (0.39, 0.74) |
| Pioglitazone current exposure |  |  |  |  |  |  |  |
| No | reference | reference | reference | reference | reference | reference | reference |
| Yes | 0.30  (0.20, 0.44) | 0.45  (0.38, 0.54) | 0.43  (0.25, 0.74) | 0.00  (0.00, Inf) | 0.20  (0.07, 0.58) | 0.16  (0.04, 0.69) | 0.42  (0.27, 0.66) |
| Duration of pioglitazone exposure (months) |  |  |  |  |  |  |  |
| Never | reference | reference | reference | reference | reference | reference | reference |
| <12 | 0.51  (0.37, 0.71) | 0.58  (0.50, 0.67) | 0.59  (0.37, 0.94) | 0.26  (0.03, 2.13) | 0.62  (0.28, 1.38) | 0.37  (0.14, 0.98) | 0.57  (0.38, 0.85) |
| 12-24 | 0.56  (0.36, 0.86) | 0.70  (0.58, 0.86) | 0.63  (0.33, 1.20) | 0.00  (0.00, Inf) | 0.74  (0.24, 2.32) | 0.00  (0.00, Inf) | 0.53  (0.28, 0.98) |
| 24-48 | 0.37  (0.22, 0.64) | 0.68  (0.55, 0.85) | 0.49  (0.23, 1.04) | 0.00  (0.00, Inf) | 0.21  (0.03, 1.69) | 0.90  (0.29, 2.83) | 0.51  (0.27, 0.95) |
| >48 | 0.35  (0.14, 0.86) | 0.44  (0.29, 0.66) | 0.86  (0.33, 2.25) | 0.00  (0.00, Inf) | 0.39  (0.05, 3.23) | 0.00  (0.00, Inf) | 0.43  (0.15, 1.21) |
| Cumulative pioglitazone dose (mg) |  |  |  |  |  |  |  |
| Never | reference | reference | reference | reference | reference | reference | reference |
| 1-10,500 | 0.52  (0.39, 0.70) | 0.60  (0.52, 0.69) | 0.61  (0.40, 0.94) | 0.23  (0.03, 1.88) | 0.55  (0.25, 1.23) | 0.32  (0.12, 0.84) | 0.51  (0.34, 0.76) |
| 10,501-28,000 | 0.56  (0.38, 0.82) | 0.65  (0.54, 0.79) | 0.52  (0.27, 0.98) | 0.00  (0.00, Inf) | 0.80  (0.29, 2.21) | 0.53  (0.15, 1.82) | 0.68  (0.41, 1.12) |
| 28,001-40,000 | 0.13  (0.03, 0.53) | 0.67  (0.48, 0.94) | 0.48  (0.15, 1.55) | 0.00  (0.00, Inf) | 0.52  (0.07, 4.11) | 0.62  (0.08, 4.76) | 0.47  (0.17, 1.29) |
| >40,000 | 0.31  (0.13, 0.77) | 0.53  (0.37, 0.77) | 0.92  (0.38, 2.19) | 0.00  (0.00, Inf) | 0.00  (0.00, Inf) | 0.00  (0.00, Inf) | 0.40  (0.14, 1.11) |
| Time since last exposure (years) |  |  |  |  |  |  |  |
| Never | reference | reference | reference | reference | reference | reference | reference |
| Current use | 0.27  (0.18, 0.40) | 0.43  (0.36, 0.51) | 0.40  (0.23, 0.70) | 0.00  (0.00, Inf) | 0.20  (0.07, 0.60) | 0.15  (0.03, 0.64) | 0.39  (0.25, 0.62) |
| < 1 | 0.77  (0.51, 1.17) | 0.99  (0.82, 1.19) | 0.86  (0.46, 1.62) | 0.00  (0.00, Inf) | 0.61  (0.18, 2.05) | 1.16  (0.44, 3.06) | 1.13  (0.70, 1.81) |
| 1-2 | 0.58  (0.33, 0.99) | 0.63  (0.48, 0.81) | 0.59  (0.26, 1.35) | 1.10  (0.13, 9.33) | 2.57  (0.94, 7.05) | 0.00  (0.00, Inf) | 0.35  (0.13, 0.96) |
| 2-4 | 0.66  (0.40, 1.10) | 0.68  (0.53, 0.87) | 0.77  (0.38, 1.54) | 0.00  (0.00, Inf) | 1.39  (0.40, 4.87) | 0.28  (0.04, 2.11) | 0.39  (0.16, 0.97) |
| >4 | 0.79  (0.37, 1.72) | 0.78  (0.54, 1.12) | 0.91  (0.32, 2.57) | 0.00  (0.00, Inf) | 0.00  (0.00, Inf) | 1.76  (0.21, 14.71) | 0.72  (0.26, 2.01) |

Table S7a Pre-planned stratified analysis for pioglitazone use and MI mortality

| **Strata (category A, Category B)** | **Category A**  **HR (95%CI)** | **Category B**  **HR (95%CI)** | **P-value for interaction test** |
| --- | --- | --- | --- |
| Duration of treated diabetes (<4, ≥4) | 0.67 (0.55,0.82) | 0.56 (0.48,0.64) | 0.238 |
| Use of other TZDs (Never, Ever) | 0.61 (0.54,0.69) | 0.7 (0.49,0.99) | 0.771 |
| History of diabetic complications (No, Yes) | 0.56 (0.48,0.66) | 0.65 (0.55,0.77) | 0.049 |
| History of macrovascular disease (No, Yes) | 0.54 (0.44,0.66) | 0.68 (0.59,0.78) | 0.006 |
| History of Chronic Kidney disease or renal impairment (No, Yes) | 0.56 (0.5,0.64) | 0.75 (0.6,0.95)) | 0.089 |

Table S7b Pre-planned stratified analysis for pioglitazone use and Stroke mortality

| **Strata (category A, Category B)** | **Category A**  **HR (95%CI)** | **Category B**  **HR (95%CI)** | **P-value for interaction test** |
| --- | --- | --- | --- |
| Duration of treated diabetes (<4, ≥4) | 0.38 (0.24,0.6) | 0.51 (0.38,0.69) | 0.157 |
| Use of other TZDs (Never, Ever) | 0.48 (0.37,0.62) | 0.43 (0.2,0.94) | 0.603 |
| History of diabetic complications (No, Yes) | 0.42 (0.3,0.59) | 0.55 (0.38,0.79) | 0.059 |
| History of macrovascular disease (No, Yes) | 0.55 (0.35,0.87) | 0.46 (0.34,0.62) | 0.814 |
| History of Chronic Kidney disease or renal impairment (No, Yes) | 0.42 (0.32,0.57) | 0.66 (0.39,1.09) | 0.087 |

Table S8a Sensitivity analysis (#1) to assess the impact of smoking, BMI, and HbA1c.

| Analysis | **Stroke  HR (95%CI)** | **Myocardial infarction  HR (95%CI)** | **Heart failure  HR (95%CI)** |
| --- | --- | --- | --- |
| Sensitivity #1  Not Adjusted for smoking, HbA1c, and BMI | 0.75  (0.52, 1.10) | 0.92  (0.76, 1.11) | 0.74  (0.42, 1.29) |
| Sensitivity #1  Adjusted for smoking, HbA1c, and BMI | 0.80  (0.53, 1.22) | 0.94  (0.75, 1.16) | 0.84  (0.45, 1.58) |
| Percentage (%) change in HR | 6.0 | 2.2 | 13.7 |

Table S8b Sensitivity analysis (#2-#6)

| Sensitivity analysis | **Stroke  HR (95%CI)** | **Myocardial infarction  HR (95%CI)** | **Heart failure  HR (95%CI)** |
| --- | --- | --- | --- |
| Original model | 0.48  (0.38, 0.62) | 0.61  (0.55, 0.69) | 0.60  (0.42, 0.86) |
| Sensitivity #2 Incident | 0.42  (0.28, 0.64) | 0.60  (0.50, 0.71) | 0.72  (0.44, 1.19) |
| Sensitivity #2 Prevalent | 0.51  (0.37, 0.69) | 0.61  (0.53, 0.71) | 0.47  (0.28, 0.79) |
| Sensitivity #3 2 purchases within 6 months | 0.53  (0.39, 0.70) | 0.68  (0.59, 0.78) | 0.69  (0.45, 1.05) |
| Sensitivity #4 log(age) at CED | 0.54  (0.42, 0.69) | 0.67  (0.59, 0.75) | 0.65  (0.45, 0.93) |
| Sensitivity #5 Exclude CV events at CED | 0.62  (0.45, 0.85) | 0.64  (0.54, 0.75) | 0.49  (0.29, 0.83) |
| Sensitivity #6 FIN | 0.32  (0.22, 0.46) | 0.50  (0.44, 0.58) | NA |
| Sensitivity #6 SWE | 0.65  (0.25, 1.68) | 0.34  (0.17, 0.68) | NA |
| Sensitivity #6 UK | 0.78  (0.52, 1.17) | 1.05  (0.86, 1.28) | NA |