# SUPPLEMENTAL MATERIAL

**Supplementary Table 1. Baseline and demographic characteristics (overall population)**

| Parameter | Overall – All ages | Age: 40 to <65 y | Age: 65 to <75y | Age: ≥75 y |
|---|---|---|---|---|
| No. of patients | 193,602 | 94,940 | 50,970 | 47,692 |
| Mean (SD) age, years | 64.8 (12.0) | 54.6 (6.6) | 69.4 (2.8) | 80.4 (3.6) |
| Gender, female, n (%) | 96,049 (49.6) | 44,775 (47.2) | 25,223 (49.5) | 26,051 (54.6) |
| Race, n (%) | | | | |
| White | 126,787 (65.5) | 57,407 (60.5) | 34,634 (68.0) | 34,746 (72.9) |
| Black | 17,214 (8.9) | 10,095 (10.6) | 4,119 (8.1) | 3,000 (6.3) |
| Asian | 4,560 (2.4) | 2,802 (3.0) | 960 (1.9) | 798 (1.7) |
| Other/Unknown | 18,590 (9.6) | 9.582 (10.1) | 4,473 (8.8) | 4,535 (9.5) |
| Mean (SD) BMI, kg/m$^2$ | 32.1 (6.9) | 34.0 (7.2) | 31.6 (6.2) | 28.9 (5.6) |
| Mean (SD) HbA$_{1c}$ levels, NGSP % units | 7.47 (1.8) | 7.86 (2.0) | 7.26 (1.6) | 6.99 (1.4) |
| Mean blood pressure (SBP/DBP), mm Hg | 134/77 | 134/81 | 135/76 | 134/72 |
| Mean (SD) eGFR, mL/min/1.73 m$^2$ | 74.9 (22.4) | 82.9 (23.5) | 73.7 (19.0) | 64.4 (19.1) |
| Comorbidities, n (%) | | | | |
| Prior MI | 8,017 (4.1) | 2,457 (2.6) | 2,450 (4.8) | 3,110 (6.5) |
| Prior stroke/TIA | 8,503 (4.4) | 2,038 (2.2) | 2,304 (4.5) | 4,161 (8.7) |
| Prior HF | 8,095 (4.2) | 1,638 (1.7) | 2,046 (4.1) | 4,411 (9.2) |
| Prior dysrhythmia/AF | 19,813 (10.2) | 4,511 (4.8) | 5,374 (10.5) | 9,928 (20.8) |
| Prior PAD | 7,310 (3.8) | 1,550 (1.6) | 2,188 (4.3) | 3,572 (7.5) |
| HTN | 145,874 (75.4) | 65,723 (69.2) | 40,793 (80.0) | 39,358 (82.5) |
| HPLD | 118,244 (61.1) | 53,244 (56.1) | 34,313 (67.3) | 30,687 (64.3) |
| Prior NASH | 989 (0.5) | 518 (0.6) | 286 (0.6) | 185 (0.4) |
| Medication used, n (%) | | | | |
| Glucose-lowering drugs | 58,104 (30.0) | 31,469 (33.2) | 14,839 (29.1) | 11,796 (24.7) |
| Statins | 77,669 (40.1) | 32,33 (34.1) | 24,158 (47.4) | 21,173 (44.4) |
| Anti-hypertensives | 99,413 (51.4) | 40,888 (43.1) | 29,515 (57.9) | 29,010 (60.8) |
| Anti-platelet drugs | 32,242 (16.7) | 8,902 (9.4) | 10,224 (20.1) | 13,116 (27.5) |

Abbreviations: AF, atrial fibrillation; BMI, body mass index; CKD, chronic kidney disease; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HbA$_{1c}$, glycated hemoglobin; HF, heart failure; HPLD, hyperlipidemia; HTN, hypertension; MI, myocardial infarction; NASH, nonalcoholic steatohepatitis; NGSP, National Glycohemoglobin Standardization Program; PAD, peripheral artery disease; SBP, systolic blood pressure; SD, standard deviation; T2DM, type 2 diabetes mellitus; TIA, transient ischemic attack.

**Supplementary Table 2. Patients with CKD at baseline**

| CKD stage | Overall | | | | T2DM + CKD | | | | T2DM + CKD + HTN + HPLD | | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| | Overall n (%) | Age 40 to <65 y, n (%) | Age 65 to <75 y, n (%) | Age ≥75 y, n (%) | Overall n (%) | Age 40 to <65 y, n (%) | Age 65 to <75 y, n (%) | Age ≥75 y, n (%) | Overall n (%) | Age 40 to <65 y, n (%) | Age 65 to <75 y, n (%) | Age ≥75 y, n (%) |
| **Stage 2** | 21,670 (11.2) | 7,202 (7.6) | 7,169 (14.1) | 7,299 (15.3) | 21,670 (54.1) | 7,202 (64.6) | 7,169 (59.4) | 7,299 (43.4) | 13,045 (55.2) | 3,633 (65.9) | 4,630 (61.0) | 4,782 (45.5) |
| **Stage 3** | 14,379 (7.4) | 2,719 (2.9) | 3,878 (7.6) | 7,782 (16.3) | 14,379 (35.9) | 2,719 (24.4) | 3,878 (32.1) | 7,782 (46.2) | 8,572 (36.3) | 1,348 (24.5) | 2,399 (31.6) | 4,825 (45.9) |
| **Stage 4** | 2,500 (1.3) | 589 (0.6) | 629 (1.2) | 1,282 (2.7) | 2,500 (6.2) | 589 (5.3) | 629 (5.2) | 1,282 (7.6) | 1,289 (5.5) | 260 (4.7) | 339 (4.5) | 690 (6.6) |
| **Stage 5** | 1,514 (0.8) | 643 (0.7) | 402 (0.8) | 469 (1.0) | 1,514 (3.8) | 643 (5.8) | 402 (3.3) | 469 (2.8) | 713 (3.0) | 273 (5.0) | 221 (2.9) | 219 (2.1) |

Abbreviations: CKD, chronic kidney disease; HPLD, hyperlipidemia; HTN, hypertension; T2DM, type 2 diabetes mellitus.

**Supplementary Table 3. Combined analyses of US and UK databases: modified MACE, HF, and ACM rates in patients (<u>with no prior ASCVD</u>) with incident T2DM and cardio-renal-metabolic diseases stratified by CKD stages and age**

| Outcome | Comorbid CKD at the time of T2DM diagnosis | Unadjusted event rate, events/100 PY (95% CI) | | | | Adjusted HR (95% CI) |
|---|---|---|---|---|---|---|
| | | Overall | 40 to <65 y | 65 to <75 y | ≥75 y | Overall |
| Modified MACE | T2DM only | 5.60 (5.44, 5.77) | 2.61 (2.47, 2.76) | 7.11 (6.71, 7.52) | 14.13 (13.52, 14.77) | Reference |
| | T2DM + HTN + HPLD | 6.28 (6.16, 6.39) | 3.61 (3.49, 3.73) | 6.71 (6.50, 6.93) | 12.26 (11.91, 12.62) | 1.01 (0.96, 1.06) |
| | T2DM + CKD + HTN + HPLD | 8.64 (8.37, 8.91) | 4.06 (3.71, 4.43) | 6.75 (6.36, 7.16) | 13.66 (13.11, 14.22) | 1.13 (1.03, 1.23)[*] |
| | T2DM + CKD[†] (Stages 2–4) | 8.58 (8.38, 8.79) | 4.13 (3.88, 4.39) | 6.98 (6.67, 7.31) | 14.04 (13.61, 14.49) | 1.25 (1.18, 1.32)[**] |
| | T2DM + CKD[†] (Stage 2) | 6.40 (6.18, 6.63) | 2.92 (2.66, 3.19) | 5.36 (5.02, 5.72) | 11.84 (11.27, 12.42) | 0.89 (0.83, 0.96)[*] |
| | T2DM + CKD[†] (Stage 3) | 10.21 (9.83, 10.61) | 4.58 (4.06, 5.15) | 7.88 (7.27, 8.52) | 14.59 (13.91, 15.28) | 1.23 (1.14, 1.33)[**] |
| | T2DM + CKD[†] (Stage 4) | 18.95 (17.86, 20.10) | 11.84 (10.46, 13.36) | 20.30 (18.13, 22.66) | 25.54 (23.42, 27.80) | 2.44 (2.23, 2.67)[**] |
| HF | T2DM only | 1.70 (1.62, 1.80) | 0.58 (0.52, 0.65) | 2.23 (2.02, 2.45) | 4.68 (4.35, 5.03) | Reference |
| | T2DM + HTN + HPLD | 1.81 (1.75, 1.87) | 0.85 (0.79, 0.91) | 2.0 (1.89, 2.12) | 3.81 (3.63, 4.01) | 0.96 (0.87, 1.05) |
| | T2DM + CKD + HTN + HPLD | 2.69 (2.55, 2.84) | 1.22 (1.03, 1.43) | 2.0 (1.79, 2.22) | 4.33 (4.03, 4.63) | 1.40 (1.20, 1.62)[**] |
| | T2DM + CKD[†] (Stages 2–4) | 2.70 (2.59, 2.81) | 1.24 (1.11, 1.39) | 2.16 (2.00, 2.34) | 4.44 (4.20, 4.68) | 1.45 (1.33, 1.59)[**] |
| | T2DM + CKD[†] (Stage 2) | 1.66 (1.55, 1.78) | 0.59 (0.48, 0.72) | 1.34 (1.17, 1.51) | 3.26 (2.98, 3.56) | 0.70 (0.61 0.81)[**] |
| | T2DM + CKD[†] (Stage 3) | 3.31 (3.10, 3.54) | 1.54 (1.25, 1.88) | 2.54 (2.21, 2.91) | 4.67 (4.31, 5.06) | 1.61 (1.42, 1.82[**] |
| | T2DM + CKD[†] (Stage 4) | 8.40 (7.69, 9.15) | 5.27 (4.37, 6.30) | 9.10 (7.73, 10.65) | 11.08 (9.74, 12.56) | 3.83 (3.33, 4.40)[**] |
| ACM | T2DM only | 2.12 (2.02, 2.22) | 0.80 (0.73, 0.89) | 2.35 (2.14, 2.58) | 5.73 (5.37, 6.10) | Reference |
| | T2DM + HTN + HPLD | 2.31 (2.25, 2.38) | 0.96 (0.90, 1.02) | 2.31 (2.19, 2.43) | 5.31 (5.10, 5.53) | 0.76 (0.70, 0.82)[**] |
| | T2DM + CKD + HTN + HPLD | 4.46 (4.28, 4.65) | 1.53 (1.32, 1.76) | 3.05 (2.80, 3.32) | 7.58 (7.21, 7.97) | 1.21 (1.07, 1.38)[*] |
| | T2DM + CKD[†] (Stage 2–4) | 4.56 (4.42, 4.71) | 1.68 (1.52, 1.84) | 3.22 (3.02, 3.44) | 8.09 (7.79, 8.41) | 1.56 (1.45, 1.69)[**] |
| | T2DM + CKD[†] (Stage 2) | 3.17 (3.02, 3.33) | 1.03 (0.88, 1.19) | 2.27 (2.06, 2.50) | 6.52 (6.13, 6.93) | 1.03 (0.92, 1.15) |
| | T2DM + CKD[†] (Stage 3) | 5.75 (5.48, 6.03) | 1.92 (1.60, 2.29) | 3.94 (3.54, 4.38) | 8.65 (8.17, 9.15) | 1.50 (1.35, 1.67)[**] |
| | T2DM + CKD[†] (Stage 4) | 9.69 (8.99, 10.43) | 5.36 (4.51, 6.33) | 8.83 (7.59, 10.22) | 14.64 (13.21, 16.17) | 3.06 (2.70, 3.48)[**] |

[†] This is T2DM plus CKD with or without HTN and/or HPLD. [*]$p < 0.05$. [**]$p < 0.001$.

Abbreviations: ACM, all-cause mortality (mortality from any cause in the patient population, taken directly from the deceased flag on the patient's record); ASCVD, atherosclerotic cardiovascular disease; CI, confidence interval; CKD, chronic kidney disease; HF, heart failure; HPLD, hyperlipidemia; HR, hazard ratio; HTN, hypertension; MACE, major adverse cardiovascular events; PY, person-years; T2DM, type 2 diabetes mellitus; UK, United Kingdom; US, United States.

**Supplementary Table 4. Combined analyses of US and UK databases: modified MACE, HF, and ACM rates in patients (<u>with prior ASCVD</u>) with incident T2DM and cardio-renal-metabolic diseases stratified by CKD stages and age**

| Outcome | Comorbid CKD at the time of T2DM diagnosis | Unadjusted event rate, events/100 PY (95% CI) | | | | Adjusted HR (95% CI) |
|---|---|---|---|---|---|---|
| | | Overall | 40 to <65 y | 65 to <75 y | ≥75 y | Overall |
| **Modified MACE** | T2DM only | 22.76 (21.48, 24.10) | 17.18 (15.10, 19.48) | 21.86 (19.42, 24.53) | 26.54 (24.52, 28.67) | Reference |
| | T2DM + HTN + HPLD | 17.90 (17.42, 18.39) | 12.16 (11.46, 12.89) | 15.92 (15.13, 16.74) | 24.90 (23.95, 25.88) | 1.05 (0.97, 1.14) |
| | T2DM + CKD + HTN + HPLD | 29.98 (29.08, 30.91) | 26.91 (24.46, 29.55) | 22.52 (21.08, 24.03) | 34.36 (33.09, 35.66) | 1.11 (1.00, 1.24) |
| | T2DM + CKD[†] (Stages 2–4) | 29.81 (29.09, 30.54) | 23.55 (21.9, 25.3) | 23.40 (22.19, 24.65) | 34.50 (33.48, 35.54) | 1.14 (1.05, 1.24)[*] |
| | T2DM + CKD[†] (Stage 2) | 27.69 (26.67, 28.75) | 21.01 (18.96, 23.22) | 20.70 (19.14, 22.35) | 34.72 (33.08, 36.41) | 0.97 (0.87, 1.08) |
| | T2DM + CKD[†] (Stage 3) | 28.40 (27.34, 29.48) | 21.59 (18.73, 24.77) | 22.17 (20.28, 24.18) | 31.64 (30.28, 33.06) | 1.12 (1.01, 1.25)[*] |
| | T2DM + CKD[†] (Stage 4) | 44.73 (42.04, 47.54) | 37.61 (32.23, 43.63) | 43.29 (38.06, 49.04) | 47.96 (44.23, 51.92) | 1.58 (1.38, 1.81)[**] |
| **HF** | T2DM only | 10.20 (9.41, 11.04) | 5.35 (4.33, 6.55) | 9.90 (8.42, 11.57) | 13.51 (12.17, 14.97) | Reference |
| | T2DM + HTN + HPLD | 6.61 (6.34, 6.89) | 3.84 (3.48, 4.23) | 5.77 (5.33, 6.24) | 9.85 (9.30, 10.43) | 0.86 (0.76, 0.97)[*] |
| | T2DM + CKD + HTN + HPLD | 10.66 (10.17, 11.16) | 7.11 (6.05, 8.31) | 7.94 (7.17, 8.77) | 12.85 (12.15, 13.59) | 1.09 (0.93, 1.28) |
| | T2DM + CKD[†] (Stages 2–4) | 11.64 (11.23, 12.07) | 7.78 (6.94, 8.68) | 9.07 (8.38, 9.79) | 14.0 (13.40, 14.63) | 1.20 (1.08, 1.35)[*] |
| | T2DM + CKD[†] (Stage 2) | 8.60 (8.10, 9.13) | 4.69 (3.87, 5.64) | 6.51 (5.74, 7.36) | 11.44 (10.62, 12.31) | 0.89 (0.75, 1.04) |
| | T2DM + CKD[†] (Stage 3) | 12.51 (11.84, 13.20) | 8.99 (7.30, 10.96) | 9.33 (8.19, 10.58) | 14.28 (13.40, 15.20) | 1.29 (1.12, 1.49)[**] |
| | T2DM + CKD[†] (Stage 4) | 23.44 (21.57, 25.43) | 19.68 (16.05, 23.89) | 24.08 (20.38, 28.26) | 24.60 (22.01, 27.42) | 1.86 (1.57, 2.21)[**] |
| **ACM** | T2DM only | 6.51 (5.94, 7.11) | 2.83 (2.14, 3.67) | 3.92 (3.09, 4.90) | 10.02 (9.00, 11.12) | Reference |
| | T2DM + HTN + HPLD | 6.13 (5.89, 6.38) | 2.31 (2.06, 2.61) | 4.77 (4.40, 5.17) | 10.42 (9.90, 10.96) | 0.73 (0.62, 0.84)[**] |
| | T2DM + CKD + HTN + HPLD | 11.43 (10.96, 11.90) | 4.65 (3.85, 5.56) | 7.31 (6.62, 8.04) | 14.87 (14.19, 15.58) | 1.39 (1.19, 1.64)[**] |
| | T2DM + CKD[†] (Stages 2–4) | 12.34 (11.95, 12.74) | 5.17 (4.54, 5.86) | 8.15 (7.55, 8.79) | 16.19 (15.61, 16.79) | 1.66 (1.47, 1.87)[**] |
| | T2DM + CKD[†] (Stage 2) | 8.90 (8.43, 9.40) | 2.93 (2.31, 3.66) | 5.71 (5.03, 6.46) | 12.92 (12.12, 13.76) | 1.34 (1.14, 1.57)[**] |
| | T2DM + CKD[†] (Stage 3) | 13.89 (13.26, 14.55) | 6.23 (4.94, 7.75) | 8.88 (7.87, 9.99) | 16.86 (16.00, 17.75) | 1.62 (1.40, 1.88)[**] |
| | T2DM + CKD[†] (Stage 4) | 21.06 (19.55, 22.65) | 11.46 (9.14, 14.19) | 17.84 (15.16, 20.86) | 26.49 (24.18, 28.97) | 2.54 (2.12, 3.04)[**] |

[†] Refers to T2DM plus CKD with or without HTN and/or HPLD. [*]p < 0.05. [**]p < 0.001.

Abbreviations: ACM, all-cause mortality (mortality from any cause in the patient population, taken directly from the deceased flag on the patient's record); ASCVD, atherosclerotic cardiovascular disease; CI, confidence interval; CKD, chronic kidney disease; HF, heart failure; HPLD, hyperlipidemia; HR, hazard ratio; HTN, hypertension; MACE, major adverse cardiovascular events; PY, person-years; T2DM, type 2 diabetes mellitus; UK, United Kingdom; US, United States.