

## Supplementary Materials

|   | Overall    | CKD-3A     | CKD-3B      | p-value     |
|---|------------|------------|-------------|-------------|
| N   | 166        | 96         | 70          |             |
| Age (years)   | 72.6±9.5   | 69.5±9.9   | 76.9±7.1    | <0.0001     |
| Sex (%):  |            |            |             | 0.38        |
| Men   | 99 (59.6)  | 60 (62.5)  | 39 (55.7)   |             |
| Women   | 67 (40.4)  | 36 (37.5)  | 31 (44.3)   |             |
| Ethnicity (%):  |            |            |             | 0.39        |
| Caucasian   | 163 (98.2) | 95 (99.0)  | 68 (97.1)   |             |
| Afro-american   | 3 (1.8)    | 1 (1.0)    | 2 (2.9)     |             |
| T2D duration (years)  | 12.1±9.3   | 11.6±10.0  | 12.9±8.1    | 0.35        |
| At least 1 glucose-lowering drug (except empagliflozin) (%)       | 117 (70.5) | 70 (72.9)  | 47 (67.1)   | 0.42        |
| Median [min-max] number of glucose-lowering drugs prescribed (N)  | 1 [0-4]    | 1 [0-3]    | 1 [0-4]     | 0.31        |
| Treated with (%):   |            |            |             |             |
| Diet Only   | 49 (29.5)  | 26 (27.1)  | 23 (32.9)   | 0.18        |
| Oral Agents and/or GLP1   | 84 (50.6)  | 54 (56.3)  | 30 (42.9)   |             |
| Insulin   | 12 (7.2)   | 4 (4.2)    | 8 (11.4)    |             |
| Both  | 21 (12.7)  | 12 (12.5)  | 9 (12.9)    |             |
| Hypertension (%)  | 138 (83.1) | 79 (82.3)  | 59 (84.3)   | 0.73        |
| At least 1 antihypertensive drug (%)                              | 89 (53.6)  | 47 (49.0)  | 42 (60.0)   | 0.16        |
| Median [min-max] number of antihypertensive agents prescribed (N) | 1 [0-5]    | 0 [0-5]    | 2 [0-5]     | 0.07        |
| Treated with (%):   |            |            |             |             |
| ACEi  | 33 (19.9)  | 14 (14.6)  | 19 (27.1)   | <b>0.04</b> |
| ARBs  | 40 (24.1)  | 24 (25.0)  | 16 (22.9)   | 0.75        |
| Beta-blockers   | 37 (22.3)  | 17 (17.7)  | 20 (28.6)   | 0.10        |
| Ca-antagonists  | 38 (22.9)  | 17 (17.7)  | 21 (30.0)   | 0.06        |
| Diuretics   | 49 (29.5)  | 28 (29.2)  | 21 (30.0)   | 0.91        |
| Alpha-blockers  | 5 (3.0)    | 3 (3.1)    | 2 (2.9)     | 0.92        |
| Others  | 16 (9.6)   | 6 (6.3)    | 10 (14.3)   | 0.08        |
| Dyslipidemia (%)  | 107 (64.5) | 64 (66.7)  | 43 (61.4)   | 0.49        |
| Total cholesterol (mg/dl)   | 163.4±41.7 | 162.1±39.6 | 165.1±44.7  | 0.69        |
| LDL-cholesterol (mg/dl)   | 85.2±36.3  | 85.2±37.0  | 85.3±35.8   | 0.99        |
| HDL-cholesterol (mg/dl)   | 47.4±12.1  | 47.2±11.5  | 47.8±12.9   | 0.79        |
| Triglycerides (mg/dl)   | 150.4±90.8 | 145.0±60.7 | 157.7±120.0 | 0.42        |
| Heart failure (%)   | 40 (24.1)  | 19 (19.8)  | 21 (30.0)   | 0.13        |

Supplementary Table 1. Baseline characteristics – population overall and by KDIGO CKD-3 stage. Data are mean and standard deviation, median and min-max values, or frequency and proportion.

\*T-test or Mann-Withney U-test (continuous variables) or chi-square test (categorical variables)

| Endpoints | Visit | OVERALL (N=166)               |  |         | CKD3A (N=96)                  |  |         | CKD3B (N=70)                  |  |         |
|-----------|-------|-------------------------------|--|---------|-------------------------------|--|---------|-------------------------------|--|---------|
|           |       | Estimated mean levels (95%CI) | Estimated mean difference from T0 and 95% CI | p-value | Estimated mean levels (95%CI) | Estimated mean difference from T0 and 95% CI | p-value | Estimated mean levels (95%CI) | Estimated mean difference from T0 and 95% CI | p-value |

|                                      |    |                           |                        |                   |                           |                        |                   |                           |                        |               |
|--------------------------------------|----|---------------------------|------------------------|-------------------|---------------------------|------------------------|-------------------|---------------------------|------------------------|---------------|
| eGFR<br>(ml/min/1.73m <sup>2</sup> ) | T0 | 45.88<br>(44.63;47.14)    | -                      | -                 | 51.73<br>(50.83;52.64)    |                        |                   | 37.86<br>(36.8;38.92)     |                        |               |
|                                      | T1 | 45.49<br>(43.75;47.22)    | -0.4<br>(-1.44;0.64)   | 0.45              | 51.64<br>(49.88;53.41)    | -0.09<br>(-1.46;1.28)  | 0.90              | 37.02<br>(34.95;39.08)    | -0.85<br>(-2.46;0.76)  | 0.30          |
|                                      | T6 | 48.63<br>(46.66;50.6)     | 2.75<br>(1.49;4)       | <b>&lt;0.0001</b> | 55.3<br>(53.25;57.34)     | 3.56<br>(1.94;5.19)    | <b>&lt;0.0001</b> | 39.45<br>(37.04;41.86)    | 1.59<br>(-0.33;3.51)   | 0.10          |
| Creatinine<br>(mg/dl)                | T0 | 1.28<br>(1.21;1.35)       | -                      | -                 | 1.15<br>(1.07;1.23)       |                        |                   | 1.46<br>(1.36;1.56)       |                        |               |
|                                      | T1 | 1.34<br>(1.27;1.41)       | 0.06<br>(0.02;0.1)     | <b>0.006</b>      | 1.18<br>(1.1;1.27)        | 0.03<br>(-0.02;0.09)   | 0.21              | 1.55<br>(1.46;1.65)       | 0.09<br>(0.03;0.15)    | <b>0.06</b>   |
|                                      | T6 | 1.35<br>(1.3;1.4)         | 0.07<br>(0;0.13)       | 0.05              | 1.22<br>(1.16;1.28)       | 0.07<br>(-0.02;0.16)   | 0.13              | 1.53<br>(1.46;1.6)        | 0.07<br>(-0.04;0.17)   | 0.20          |
| HbA1c<br>(mmol/mol)                  | T0 | 55.56<br>(53.73;57.4)     | -                      | -                 | 54.89<br>(52.48;57.3)     |                        |                   | 56.49<br>(53.66;59.31)    |                        |               |
|                                      | T6 | 51.4<br>(50.09;52.71)     | -4.17<br>(-5.57;-2.77) | <b>&lt;0.0001</b> | 50.55<br>(48.85;52.25)    | -4.34<br>(-6.17;-2.51) | <b>&lt;0.0001</b> | 52.63<br>(50.59;54.67)    | -3.86<br>(-6.05;-1.67) | <b>0.0001</b> |
| BMI<br>(Kg/m <sup>2</sup> )          | T0 | 28.78<br>(28.04;29.52)    | -                      | -                 | 29.2<br>(28.23;30.17)     |                        |                   | 28.19<br>(27.06;29.33)    |                        |               |
|                                      | T6 | 28.17<br>(27.43;28.92)    | -0.6<br>(-0.96;-0.25)  | <b>0.001</b>      | 28.24<br>(27.26;29.23)    | -0.96<br>(-1.42;-0.5)  | <b>&lt;0.0001</b> | 28.09<br>(26.94;29.25)    | -0.1<br>(-0.65;0.45)   | 0.72          |
| Body weight<br>(kg)                  | T0 | 79.54<br>(76.97;82.1)     | -                      | -                 | 81.69<br>(78.35;85.03)    |                        |                   | 76.58<br>(72.67;80.5)     |                        |               |
|                                      | T6 | 77.42<br>(75.02;79.81)    | -2.12<br>(-2.73;-1.51) | <b>&lt;0.0001</b> | 78.92<br>(75.78;82.05)    | -2.77<br>(-3.56;-1.98) | <b>&lt;0.0001</b> | 75.37<br>(71.7;79.04)     | -1.21<br>(-2.14;-0.28) | <b>0.0001</b> |
| SBP<br>(mmHg)                        | T0 | 134.57<br>(132.1;137.05)  | -                      | -                 | 136.55<br>(133.32;139.78) |                        |                   | 131.86<br>(128.07;135.64) |                        |               |
|                                      | T6 | 130.62<br>(128.32;132.92) | -3.95<br>(-6.59;-1.32) | <b>0.003</b>      | 131.23<br>(128.21;134.25) | -5.32<br>(-8.77;-1.86) | <b>0.003</b>      | 129.78<br>(126.22;133.34) | -2.08<br>(-6.15;1.99)  | 0.31          |
| DBP<br>(mmHg)                        | T0 | 78.01<br>(76.64;79.37)    | -                      | -                 | 78.27<br>(76.47;80.07)    |                        |                   | 77.64<br>(75.54;79.75)    |                        |               |
|                                      | T6 | 76.16<br>(74.66;77.66)    | -1.85<br>(-3.61;-0.09) | <b>0.04</b>       | 76.09<br>(74.11;78.06)    | -2.19<br>(-4.5;0.13)   | 0.06              | 76.26<br>(73.93;78.59)    | -1.38<br>(-4.1;1.35)   | 0.32          |

Supplementary Table 2. Continuous endpoints – Results of longitudinal linear mixed models for repeated measurements - population overall and by KDIGO CKD-3 stage. p-values = paired t-test derived from linear mixed models for repeated measurements. Statistically significant p-values (p<0.05) are in bold.

| Endpoint  | Visit | OVERALL (N=166)                  |                  |         | DIPPERS (N=35)                   |                  |         | NON DIPPERS (N=127)              |                  |         | CKD3A (N=96)                     |                  |         | CKD3B (N=70)                     |                  |         |
|---|-------|----------------------------------|------------------|---------|----------------------------------|------------------|---------|----------------------------------|------------------|---------|----------------------------------|------------------|---------|----------------------------------|------------------|---------|
|   |       | Probability estimates and 95% CI | OR and 95% CI    | p-value | Probability estimates and 95% CI | OR and 95% CI    | p-value | Probability estimates and 95% CI | OR and 95% CI    | p-value | Probability estimates and 95% CI | OR and 95% CI    | p-value | Probability estimates and 95% CI | OR and 95% CI    | p-value |
| At least 1 glucose-lowering drug (except empagliflozin) | T     | 84.94 (78.59;89.66)              | -                | -       | 100                              |                  |         | 80.31 (72.37;86.41)              | -                | -       | 86.46 (77.88;92.05)              |                  |         | 82.86 (71.88;90.14)              |                  |         |
|   | 0     | 70.48 (63.03;76.98)              | 0.42 (0.29;0.63) | <0.0001 | 85.71 (73.52;97.91)              | -                | -       | 65.35 (56.57;73.21)              | 0.46 (0.31;0.69) | 0.0003  | 72.92 (63;80.98)                 | 0.42 (0.24;0.74) | 0.0003  | 67.14 (55.07;77.31)              | 0.42 (0.25;0.73) | 0.0002  |
| Metformin   | T     | 61.45 (53.75;68.61)              | -                | -       | 62.86 (45.14;77.68)              | -                | -       | 60.63 (51.77;68.84)              | -                | -       | 75.00 (65.21;82.76)              |                  |         | 42.86 (31.58;54.92)              |                  |         |
|   | 0     | 51.20 (43.55;58.80)              | 0.66 (0.51;0.85) | 0.0005  | 51.43 (34.52;68.02)              | 0.63 (0.4;0.99)  | 0.005   | 51.18 (42.42;59.87)              | 0.68 (0.50;0.93) | 0.0001  | 63.54 (53.3;72.69)               | 0.58 (0.38;0.88) | 0.0001  | 34.29 (23.93;46.39)              | 0.70 (0.48;1.01) | 0.0006  |
| Sulphonylureas  | T     | 13.25 (8.85;19.38)               | -                | -       | -                                | -                | -       | 14.17 (9.06;21.49)               | -                | -       | 10.42 (5.63;18.47)               |                  |         | 17.14 (9.86;28.12)               |                  |         |
|   | 0     | 4.82 (2.41;9.4)                  | 0.33 (0.18;0.62) | 0.0007  | -                                | -                | -       | 5.51 (2.62;11.21)                | 0.35 (0.19;0.66) | 0.0001  | 4.17 (1.55;10.75)                | 0.37 (0.15;0.96) | 0.0004  | 5.71 (2.11;14.57)                | 0.29 (0.12;0.7)  | 0.0006  |
| Pioglitazone  | T     | 9.04 (5.49;14.52)                | -                | -       | 2.86 (0.36;19.24)                | -                | -       | 10.24 (5.99;16.94)               | -                | -       | 7.29 (3.47;14.69)                |                  |         | 11.43 (5.72;21.54)               |                  |         |
|   | 0     | 8.43 (5.03;13.8)                 | 0.93 (0.66;1.3)  | 0.66    | 5.71 (1.33;21.39)                | 2.06 (0.46;9.25) | 0.0033  | 9.45 (5.4;16.01)                 | 0.92 (0.67;1.24) | 0.057   | 7.29 (3.47;14.69)                | 1.00 (0.54;1.85) | 1.000   | 10.00 (4.75;19.83)               | 0.86 (0.64;1.16) | 0.0032  |
| DPP-IVi   | T     | 19.88 (14.44;26.72)              | -                | -       | 20.00 (9.47;37.4)                | -                | -       | 19.69 (13.59;27.63)              |                  |         | 15.62 (9.56;24.5)                |                  |         | 25.71 (16.65;37.49)              |                  |         |
|   | 0     | 15.06 (10.34;21.41)              | 0.72 (0.47;1.09) | 0.12    | 20.00 (9.47;37.4)                | 1.00 (0.48;2.09) | 1.000   | 13.39 (8.43;20.6)                | 0.63 (0.37;1.08) | 0.009   | 12.5 (7.16;20.92)                | 0.77 (0.43;1.37) | 0.0037  | 18.57 (10.95;29.72)              | 0.66 (0.35;1.26) | 0.0020  |
| GLP-1RA   | T     | 16.87 (11.86;23.42)              | -                | -       | 17.14 (7.58;34.28)               |                  |         | 16.54 (10.97;24.15)              |                  |         | 17.71 (11.21;26.84)              |                  |         | 15.71 (8.79;26.51)               |                  |         |
|   | 0     | 16.27 (11.35;22.5)               | 0.96 (0.67;1.37) | 0.81    | 20.00 (9.47;37.4)                | 1.21 (0.82;1.82) | 0.0032  | 14.17 (9.06;21.49)               | 0.83 (0.52;1.34) | 0.044   | 17.71 (11.21;26.84)              | 1.00 (0.64;1.56) | 1.000   | 14.29 (7.74;24.87)               | 0.89 (0.49;1.62) | 0.0071  |

|   |             |                              |                             |          |                               |                             |              |                              |                             |          |                               |                             |              |                               |                              |              |
|---|-------------|------------------------------|-----------------------------|----------|-------------------------------|-----------------------------|--------------|------------------------------|-----------------------------|----------|-------------------------------|-----------------------------|--------------|-------------------------------|------------------------------|--------------|
|   |             | 76)                          | 37)                         |          |                               | 78)                         |              | )                            | 33)                         |          | 84)                           | 57)                         |              | )                             | )                            |              |
| Fixed ratio combination of basal insulin and GLP 1 RA | T<br>-<br>1 | 1.81<br>(0.58;<br>5.51)      | -                           | -        | -                             | -                           | -            | 2.36<br>(0.75;<br>7.17)      | -                           | -        | 2.08<br>(0.51;<br>8.14)       |                             |              | 1.43<br>(0.19;<br>9.88)       |                              |              |
|   | T<br>0      | 4.22<br>(2.01;<br>8.64)      | 2.39<br>(0.6<br>8;8.<br>37) | 0.1<br>7 | -                             | -                           | -            | 2.36<br>(0.75;<br>7.17)      | 1.00<br>(0.2<br>6;3.<br>88) | 1.<br>00 | 3.13<br>(0.99;<br>9.42)       | 1.52<br>(0.2<br>3;9.<br>82) | 0.<br>6<br>6 | 5.71<br>(2.11;<br>14.57<br>)  | 4.18<br>(0.72<br>;24.4<br>5) | 0.<br>1<br>1 |
| Basal insulin   | T<br>-<br>1 | 12.65<br>(8.36;<br>18.7)     | -                           | -        | 11.43<br>(4.14;<br>27.84<br>) | -                           | -            | 11.81<br>(7.2;1<br>8.78)     | -                           | -        | 10.42<br>(5.63;<br>18.47<br>) |                             |              | 15.71<br>(8.79;<br>26.51<br>) |                              |              |
|   | T<br>0      | 9.64<br>(5.96;<br>15.22<br>) | 0.74<br>(0.5<br>1;1.<br>06) | 0.1<br>0 | 8.57<br>(2.63;<br>24.56<br>)  | 0.73<br>(0.3<br>8;1.<br>39) | 0.<br>3<br>3 | 9.45<br>(5.40;<br>16.01<br>) | 0.78<br>(0.5<br>0;1.<br>21) | 0.<br>26 | 8.33<br>(4.17;<br>15.96<br>)  | 0.78<br>(0.4<br>3;1.<br>43) | 0.<br>4<br>2 | 11.43<br>(5.72;<br>21.54<br>) | 0.69<br>(0.46<br>;1.05<br>)  | 0.<br>0<br>8 |
| Short-acting insulin                                  | T<br>-<br>1 | 7.23<br>(4.13;<br>12.36<br>) | -                           | -        | 14.29<br>(5.8;3<br>1.09)      | -                           | -            | 4.72<br>(2.11;<br>10.22<br>) | -                           | -        | 5.21<br>(2.15;<br>12.08<br>)  |                             |              | 10.00<br>(4.75;<br>19.83<br>) |                              |              |
|   | T<br>0      | 6.02<br>(3.25;<br>10.9)      | 0.82<br>(0.5<br>1;1.<br>32) | 0.4<br>2 | 11.43<br>(4.14;<br>27.84<br>) | 0.77<br>(0.4<br>6;1.<br>3)  | 0.<br>3<br>2 | 4.72<br>(2.11;<br>10.22<br>) | 1.00<br>(0.5<br>0;2.<br>00) | 1.<br>00 | 5.21<br>(2.15;<br>12.08<br>)  | 1.00<br>(0.5<br>5;1.<br>81) | 1.<br>0<br>0 | 7.14<br>(2.94;<br>16.35<br>)  | 0.69<br>(0.33<br>;1.45<br>)  | 0.<br>3<br>2 |

Supplementary Table 3. Changes in the likelihood of being treated with the different classes of glucose lowering agents before and after empagliflozin initiation. T1 = before starting empagliflozin; T0 = at the first prescription of empagliflozin

Results from mixed effects models for repeated measurements. OR: odds ratio, 95%CI: confidence intervals. \*Statistically significant p-values ( $p < 0.05$ ) are in bold.