**SUPPLEMENTARY MATERIAL**

**Supplemental table 1: Literature search strategy:**

|  |  |
| --- | --- |
| **S.No** | **Search terms** |
| 1 | NAFLD |
| 2 | Nonalcoholic fatty liver disease |
| 3 | Non-alcoholic fatty liver disease |
| 4 | Non alcoholic fatty liver disease |
| 5 | NASH |
| 6 | Non-alcoholic steatohepatitis |
| 7 | Nonalcoholic steatohepatitis |
| 8 | Non alcoholic steatohepatitis |
| 9 | Fatty liver |
| 10 | 1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9 |
| 11 | Type 2 diabetes mellitus |
| 12 | Type 2 diabetes |
| 13 | Diabetes mellitus type 2 |
| 14 | Diabetes type 2 |
| 15 | 11 OR 12 OR 13 OR 14 |
| 16 | SGLT-2 inhibitors |
| 17 | Sodium glucose cotransporter-2 inhibitors |
| 18 | SGLT-2 |
| 19 | SGLT2 |
| 20 | SGLT 2 |
| 21 | Canagliflozin |
| 22 | Dapagliflozin |
| 23 | Empagliflozin |
| 24 | Ipragliflozin |
| 25 | Luseogliflozin |
| 26 | Tofogliflozin |
| 27 | Sotagliflozin |
| 28 | Remogliflozin |
| 29 | Ertugliflozin |
| 30 | Sergliflozin |
| 31 | 16 OR 17 OR 18 OR 19 OR 20 OR 21 OR 22 OR 23 OR 24 OR 25 OR 26 OR 27 OR 28 OR 29 OR 30 |
| 32 | 10 AND 15 AND 31 |

**Supplemental table 2 - Assessment of study quality of randomised controlled trials:**

|  |  |  |  |
| --- | --- | --- | --- |
| **Study** | **Criteria** | **Risk of bias** | **Study quality** |
| Kuchay et al | Random sequence generation | Low risk | Good Quality |
| Allocation concealment | Low risk |
| Selective reporting | Low risk |
| Other bias | Low risk |
| Blinding of participants and personnel | Low risk |
| Blinding of outcome assessment | Low risk |
| Incomplete outcome data | Low risk |
| Ito et al | Random sequence generation | Low risk | Fair Quality |
| Allocation concealment | Unclear risk |
| Selective reporting | Low risk |
| Other bias | Low risk |
| Blinding of participants and personnel | Low risk |
| Blinding of outcome assessment | Low risk |
| Incomplete outcome data | Low risk |
| Shibuya et al | Random sequence generation | Unclear risk | Fair Quality |
| Allocation concealment | Unclear risk |
| Selective reporting | Low risk |
| Other bias | Low risk |
| Blinding of participants and personnel | Low risk |
| Blinding of outcome assessment | Low risk |
| Incomplete outcome data | Low risk |
| Eriksson et al | Random sequence generation | Low risk | Good Quality |
| Allocation concealment | Low risk |
| Selective reporting | Low risk |
| Other bias | Low risk |
| Blinding of participants and personnel | Low risk |
| Blinding of outcome assessment | Low risk |
| Incomplete outcome data | Low risk |

**Supplemental table 3 - Assessment of study quality of observational studies:**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **S.No** | **Criteria** | **Ohki et al** | **Seko et al** | **Gautam et al** | **Sumida et al** |
| 1 | A clearly stated aim | 2 | 2 | 2 | 2 |
| 2 | Inclusion of consecutive patients | 0 | 2 | 2 | 1 |
| 3 | Prospective collection of data | 2 | 0 | 2 | 2 |
| 4 | Endpoints appropriate to the aim of the study | 2 | 2 | 2 | 2 |
| 5 | Unbiased assessment of the study endpoint | 0 | 0 | 0 | 0 |
| 6 | Follow-up period appropriate to the aim of the study | 2 | 2 | 2 | 2 |
| 7 | Loss to follow up less than 5% | 2 | 2 | 2 | 2 |
| 8 | Prospective calculation of the study size | 0 | 0 | 0 | 0 |
| 9 | An adequate control group | NA | 0 | NA | NA |
| 10 | Contemporary groups | NA | 2 | NA | NA |
| 11 | Baseline equivalence of groups | NA | 2 | NA | NA |
| 12 | Adequate statistical analyses | NA | 2 | NA | NA |
| 13 | Total score | 10/16 | 16/24 | 12/16 | 11/16 |

**Supplemental table 4– Change in serum aspartate aminotransferase (AST) levels in individual studies**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Study** | **Serum aspartate aminotransferase (AST) levels ( U/L)** | | | **P value** | **P value between groups** |
| **Group** | **Baseline** | **Study completion** |
| Kuchay et al | Empagliflozin | 44.6(23.5) | 36.2 (9) | 0.04 | 0.212 |
| Control | 45.3(24.3) | 44.6(23.8) | 0.931 |
| Ito et al | Ipragliflozin | 39.7(16.7) | 27.3(8.9) | < 0.05 | 0.802 |
| Pioglitazone | 43.3(20.5) | 32.4(15.4) | < 0.05 |
| Eriksson et al | Placebo | 29.4(13.2) | -1.2(7.2)1 | - | Non-significant |
| Omega-3 CAa | 30.6(10.2) | +4.8(9)1 | - | Non-significant2 |
| Dapagliflozin | 31.2(11.4) | -4.2(5.4)1 | - | < 0.052 |
| O+Db | 30(10.2) | +1.2(5.4)1 | - | Non-significant2 |
| Ohki et al | Ipragliflozin | 37(29-52) | 28(23-31) | 0.03 | - |
| Seko et al | SGLT-2c inhibitor | 54.4(5.6) | 38(3.1) | 0.001 | - |
| Sitagliptin | 67(7.7) | 52.5(7.7) | 0.016 |  |
| Gautam et al | Canagliflozin | 72(16.7) | 53(10.3) | 0.00001 | - |
| Sumida et al | Luseogliflozin | 40.7(22.2) | 31.9(18.2) | < 0.001 | - |

1Change from baseline; 2Compared to placebo; a carboxylic acid; b Omega-3 carboxylic acid + Dapagliflozin; c SGLT-2 - Sodium glucose cotransporter-2

**Supplemental table 5 – Change in serum gamma-glutamyl transferase (GGT) levels in individual studies**:

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Study** | **Serum gamma-glutamyl transferase (GGT) ( IU/L )** | | | **P value** | **P value between groups** |
| **Group** | **Baseline** | **Study completion** |
| Kuchay et al | Empagliflozin | 65.8(36.1) | 50.9(24.6) | 0.002 | 0.057 |
| Control | 63.9(45.3) | 60(39) | 0.421 |
| Ito et al | Ipragliflozin | 62.8(58.3) | 44(38.3) | < 0.05 | 0.642 |
| Pioglitazone | 71.6(54.1) | 48.8(61.2) | < 0.05 |
| Eriksson et al | Placebo | 32.39(17.4) | +2.4(9.6)1 | - | Non-significant |
| Omega-3 CAa | 53.99(57.59) | +2.4(12)1 | - | Non-significant2 |
| Dapagliflozin | 58.19(43.19) | -4.8(13.8)1 | - | < 0.052 |
| O+Db | 40.19(14.4) | -0.6(13.8)1 | - | Non-significant2 |
| Ohki et al | Ipragliflozin | 75(47-105) | 60(40-101) | 0.03 | - |
| Seko et al | SGLT-2c inhibitor | 61.7(9.1) | 58.7(11.5) | 0.051 | - |
| Sitagliptin | 89.2 (11.8) | 82.4(11.9) | 0.36 |
| Gautam et al | Canagliflozin | 75.06(31.8) | 69.19(26.2) | 0.003 | - |
| Sumida et al | Luseogliflozin | 62.4(77.1) | 48.2(56.3) | 0.003 | - |

1Change from baseline; 2Compared to placebo; a carboxylic acid; b Omega-3 carboxylic acid + Dapagliflozin; c SGLT-2 - Sodium glucose cotransporter-2

**Supplemental table 6- Change in hepatic fat in individual studies**:

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Study** | **Parameter** | **Group** | **Baseline** | **Study completion** | **P value** | **P value between groups** |
| Kuchay et al | MRI-PDFFa | Empagliflozin | 16.2(7) | 11.3(5.3) | < 0.0001 | <0.0001 |
| Control | 16.4(7.3) | 15.5(6.7) | 0.054 |
| Ito et al | L/S ratiob | Ipragliflozin | 0.8(0.24) | 1(0.18) | < 0.05 | 0.90 |
| Pioglitazone | 0.78(0.26) | 0.98(0.16) | < 0.05 |
| Shibuya et al | L/S ratiob | Luseogliflozin | 0.907(0.637-1.036) | 1.033(0.798-1.199) | 0.0008 | 0.00002 |
| Metformin | 0.991(0.813-1.118) | 0.851(0.675-1.001) | 0.017 |
| Eriksson et al | MRI-PDFFa | Placebo | 15.1(6.5) | -0.59(1.86)1 | - | Non-significant |
| Omega-3 CAd | 22.2(11) | -3.15(2.88)1 | - | Non-significant2 |
| Dapagliflozin | 17.3(9.1) | -2.23(3.3)1 | - | Non-significant2 |
| O+De | 17.8(9.2) | -3.15(3.49)1 | - | < 0.052 |
| Sumida et al | MRI-HFFc | Luseogliflozin | 21.46(7.17) | 15.66(6.82) | < 0.001 | - |

a Magnetic resonance imaging- derived proton density fat fraction; b Liver/Spleen attenuation ratio; c Magnetic resonance imaging-hepatic fat fraction; d Carboxylic acid; e Omega-3 CA + Dapagliflozin arm

1Change from baseline; 2 Compared to placebo

**Supplemental table 7 - Assessment of liver fibrosis in individual studies**:

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Study | Parameter | Group | Baseline | Study completion | P value | P value between groups |
| Ito et al | FIBa-4 index | Ipragliflozin | 1.44(0.64) | 1.22(0.55) | < 0.05 | 0.596 |
| Pioglitazone | 1.84(1.13) | 1.71(1.19) | Non-significant |
| Ohki et al | FIBa-4 index | Ipragliflozin | 1.75(0.82-1.93) | 1.39(0.77-1.99) | 0.04 | - |
| Sumida et al | FIBa-4 index | Luseogliflozin | 1.63(1.19) | 1.52(0.92) | 0.17 | - |
| NAFLDb fibrosis score | Luseogliflozin | 1.61(0.71) | 1.62(0.88) | 0.86 | - |

a Fibrosis 4; b Non-alcoholic fatty liver disease

**Supplemental table 8– Change in fasting plasma glucose in individual studies:**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Study** | **Fasting plasma glucose ( mg/dl )** | | | **P value** | **P value between groups** |
| Group | Baseline | Study completion |
| Kuchay et al | Empagliflozin | 173(44) | 124(17) | < 0.001 | 0.85 |
| Control | 176(57) | 120(19) | < 0.0001 |
| Ito et al | Ipragliflozin | 160.1(38.7) | 136.5(26.7) | < 0.05 | 0.785 |
| Pioglitazone | 169.4(50.9) | 139(26.6) | < 0.05 |
| Shibuya et al | Luseogliflozin | 127(116,136) | 125(113,138) | 0.87 | 0.583 |
| Metformin | 147(126,161) | 134(122,145) | 0.32 |
| Eriksson et al | Placebo | 169.2(29.7) | +6.66(14.76)1 | - | Non-significant |
| Omega-3 CAa | 162.36(26.64) | +3.78(19.26)1 | - | Non-significant2 |
| Dapagliflozin | 161.82(33.3) | -17.64(26.82)1 | - | < 0.052 |
| O+Db | 168.84(35.46) | -16.38(36)1 | - | < 0.052 |
| Ohki et al | Ipragliflozin | 162(135-189) | 135(120-166) | 0.3 | - |
| Seko et al | SGLT-2c inhibitor | 125(6) | 116.6(4.2) | 0.07 | Non-significant |
| Sitagliptin | 114.6(7) | 134(10.5) | 0.067 |
| Sumida et al | Luseogliflozin | 142(30.3) | 135.4(25.6) | 0.009 | - |

1Change from baseline; 2 Compared to placebo a carboxylic acid; b Omega-3 carboxylic acid + Dapagliflozin; c SGLT-2 - Sodium glucose cotransporter-2

**Supplemental table 9- Change in glycosylated hemoglobin (HbA1c) in individual studies:**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Study | Glycosylated hemoglobin (%) | | | P value | P value between groups |
| Group | Baseline | Study completion |
| Kuchay et al | Empagliflozin | 9(1) | 7.2(0.6) | < 0.001 | 0.88 |
| Control | 9.1(1.4) | 7.1(0.9) | < 0.0001 |
| Ito et al | Ipragliflozin | 8.52(1.46) | 7.57(1.02) | < 0.05 | 0.522 |
| Pioglitazone | 8.28(1.38) | 7.07(0.89) | < 0.05 |
| Shibuya et al | Luseogliflozin | 7.8(7.2,7.9) | 6.5(6.4,7) | 0.002 | 0.023 |
| Metformin | 7.4(6.9,7.7) | 7.3(6.7,7.6) | 0.362 |
| Eriksson et al | Placebo | 7.44(0.8) | -0.09(0.35)1 | - | Non-significant |
| Omega-3 CAa | 7.38(0.68) | +0.13(0.40)1 | - | Non-significant2 |
| Dapagliflozin | 7.38(0.56) | -0.63(0.66)1 | - | < 0.052 |
| O+Db | 7.50(0.76) | -0.45(0.48)1 | - | Non-significant2 |
| Ohki et al | Ipragliflozin | 8.4(7.8-8.9) | 7.6(6.9-8.2) | < 0.01 | - |
| Seko et al | SGLT-2c inhibitor | 6.7(0.1) | 6.5(0.1) | 0.055 | Non-significant |
| Sitagliptin | 7(0.3) | 6.9(0.3) | 0.331 |
| Sumida et al | Luseogliflozin | 7.29(0.65) | 7(0.67) | 0.002 | - |

1Change from baseline; 2 Compared to placebo a carboxylic acid; b Omega-3 carboxylic acid + Dapagliflozin; c SGLT-2 - Sodium glucose cotransporter-2

**Supplemental table 10– Change in homeostasis model assessment-estimated insulin resistance (HOMA-IR) in individual studies**:

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Study** | **HOMA-IR** | | | **P value** | **P value between groups** |
| **Group** | **Baseline** | **Study completion** |
| Ito et al | Ipragliflozin | 5.16(2.51) | 4.82(5.45) | Non-significant | 0.401 |
| Pioglitazone | 5.69(3.42) | 4.45(2.7) | < 0.05 |
| Eriksson et al | Placebo | 4.2(2.4) | -0.19(1.44)1 | - | Non-significant |
| Omega 3-CAa | 5.4(2.9) | +0.31(2.39)1 | - | Non-significant2 |
| Dapagliflozin | 4.3(1.9) | -1.08(1.38)1 | - | < 0.052 |
| O+Db | 4.4(1.7) | -0.86(1.58)1 | - | < 0.052 |
| Seko et al | SGLT-2c inhibitor | 4.5(0.5) | 7.9(2.3) | 0.955 | - |
| Sitagliptin | 4.4(0.5) | 6.5(0.8) | 0.163 |

1Change from baseline; 2 Compared to placebo a carboxylic acid; b Omega-3 carboxylic acid + Dapagliflozin; c SGLT-2 - Sodium glucose cotransporter-2

**Supplemental table 11- Change in serum triglycerides in individual studies**:

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Study** | **Serum triglycerides ( mg/dl)** | | | **P value** | **P value between groups** |
| **Group** | **Baseline** | **Study completion** |
| Kuchay et al | Empagliflozin | 201(124) | 155(52) | 0.01 | 0.678 |
| Control | 212(115) | 175(43) | 0.019 |
| Ito et al | Ipragliflozin | 166.9(76.4) | 143.4(81.4) | < 0.05 | 0.938 |
| Pioglitazone | 188.4(148.8) | 169.3(131.3) | Non-significant |
| Eriksson et al | Placebo | 169.17(84.14) | -11.51(45.61)1 | - | Non-significant |
| Omega-3 CAa | 186.88(81.48) | -15.94(47.38)1 | - | Non-significant2 |
| Dapagliflozin | 178.03(103.62) | +14.17(40.48)1 | - | Non-significant2 |
| O+Db | 168.28(72.63) | -25.69(57.13)1 | - | Non-significant2 |
| Ohki et al | Ipragliflozin | 148(107,222) | 145(114,172) | 0.75 | - |
| Seko et al | SGLT-2c inhibitor | 153.8(15.9) | 137.8(10.5) | 0.236 | - |
| Sitagliptin | 193.4(25.2) | 191.1(23.8) | 0.986 |
| Sumida et al | Luseogliflozin | 158.1(110.5) | 129.4(59.5) | 0.062 | - |

1Change from baseline; 2 Compared to placebo a carboxylic acid; b Omega-3 carboxylic acid + Dapagliflozin; c SGLT-2 - Sodium glucose cotransporter-2

**Supplemental table 12 – Change in serum low-density lipoprotein cholesterol in individual studies**:

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Study** | **Serum low-density lipoprotein cholesterol (mg/dl)** | | | **P value** | **P value between groups** |
| **Group** | **Baseline** | **Study completion** |
| Kuchay et al | Empagliflozin | 112(35) | 95(22) | 0.018 | 0.512 |
| Control | 114(30) | 96(17) | 0.001 |
| Ito et al | Ipragliflozin | 108.3(36.2) | 110.7(40.1) | Non-significant | 0.057 |
| Pioglitazone | 104(27.9) | 114.6(29.5) | < 0.05 |
| Eriksson et al | Placebo | 98.22(34.42) | +1.55(15.47)1 | - | Non-significant |
| Omega-3 CAa | 111.76(34.42) | +2.32(17.4)1 | - | Non-significant2 |
| Dapagliflozin | 109.44(34.8) | +7.73(20.5)1 | - | Non-significant2 |
| O+Db | 88.94(23.2) | +5.8(21.66)1 | - | Non-significant2 |
| Ohki et al | Ipragliflozin | 113(89-142) | 103(92-122) | 0.08 | - |
| Seko et al | SGLT-2c inhibitor | 119.2(5.8) | 119.8(5.7) | 0.943 | - |
| Sitagliptin | 112.9(4.9) | 127.1(8.8) | 0.063 |
| Sumida et al | Luseogliflozin | 101(22.4) | 105(24.4) | 0.11 | - |

1Change from baseline; 2 Compared to placebo a carboxylic acid; b Omega-3 carboxylic acid + Dapagliflozin; c SGLT-2 - Sodium glucose cotransporter-2

**Supplemental table 13 – Change in serum high-density lipoprotein cholesterol in individual studies:**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Study** | **Serum high-density lipoprotein cholesterol (mg/dl)** | | | **P value** | **P value between groups** |
| **Group** | **Baseline** | **Study completion** |
| Kuchay et al | Empagliflozin | 42(12) | 45(12) | 0.087 | 0.752 |
| Control | 45(15) | 47(12) | 0.097 |
| Ito et al | Ipragliflozin | 48.9(9.3) | 54.7(10.4) | < 0.05 | 0.82 |
| Pioglitazone | 47.4(11.6) | 52.7(13.5) | < 0.05 |
| Eriksson et al | Placebo | 51.43(14.85) | -0.39(5.03)1 | - | Non-significant |
| Omega-3 CAa | 49.88(14.11) | +0.39(3.17)1 | - | Non-significant2 |
| Dapagliflozin | 49.88(9.51) | +0.39(4.8)1 | - | Non-significant2 |
| O+Db | 51.43(10.2) | +1.55(4.99)1 | - | Non-significant2 |
| Ohki et al | Ipragliflozin | 42(40-50) | 44(42-59) | 0.01 | - |
| Seko et al | SGLT-2c inhibitor | 53.9(2.5) | 55.4(2.6) | 0.043 | - |
| Sitagliptin | 54.8(3.3) | 55.6(2.3) | 0.531 |
| Sumida et al | Luseogliflozin | 55.6(11.7) | 57.5(13.4) | 0.062 | - |

1Change from baseline; 2 Compared to placebo a carboxylic acid; b Omega-3 carboxylic acid + Dapagliflozin; c SGLT-2 - Sodium glucose cotransporter-2

**Supplemental table 14– Change in body mass index in individual studies**:

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Study** | **Body mass index ( kg/m2)** | | | **P value** | **P value between groups** |
| **Group** | **Baseline** | **Study completion** |
| Kuchay et al | Empagliflozin | 30(3.8) | 28.7(3.5) | 0.001 | 0.124 |
| Control | 29.4(3.1) | 28.8(2.8) | 0.019 |
| Shibuya et al | Luseogliflozin | 27.9(26.2,28.7) | 27(25.6,28.3) | 0.002 | 0.031 |
| Metformin | 27.2(24.8,32.1) | 27.3(24.3,31.6) | 0.646 |
| Ohki et al | Ipragliflozin | 30.1(26.1-31.4) | 27.6(25.3-30.2) | < 0.01 | - |
| Seko et al | SGLT-2a inhibitor | 29.6(0.7) | 28.3(0.7) | < 0.001 | - |
| Sitagliptin | 29.2 (1.5) | 28.9(1.4) | 0.295 |
| Sumida et al | Luseogliflozin | 27.76(3.62) | 27.164(1.01) | < 0.001 | - |

a SGLT-2 - Sodium glucose cotransporter-2