**Supplement**

**Supplement table legends**

**Table S1: Demographics of included studies in the meta-analysis part of Cardiff model**

**Table S2: Baseline demographics in dapagliflozin treatment and metformin treatment as first line therapy, second line therapy and third therapy**

**Table S3: Annual treatment costs for different drugs**

**Table S4: Annual direct medical costs for diabetes-related complications and adverse events**

**Table S5: Body mass index (BMI) associated costs**

**Table S6: Health state utility decrements**

**Table S7: Input data for the univariate sensitivity analyses**

**Table S8: Absolute changes from baseline in dapagliflozin treatment and metformin treatment as first line therapy, second line therapy and third therapy**

**Table S9: Risks of the adverse effects in dapagliflozin treatment and metformin treatment as first line therapy, second line therapy and third therapy**

**Table S10: The results of univariate sensitivity analyses**

**Supplement figure legends**

**Figure S1: Funnel plot of included studies with metfromin treatment**

**Figure S2: Funnel plot of included studies with dapagliflozin treatment**

**Supplement method**

**Supplement references**

**Table S1: Demographics of included studies in the meta-analysis part of Cardiff model**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Author ,**  **year** | **Study duration** | **Treatment group** | **No. of patients** | **Age (years)** | **Men (%)** | **BMI (kg/m2)** | **DM duration**  **(years)** | **Baseline HbA1c (%)** |
| **First line therapy strategy (SGLT-2 inhibitors vs metformin as monotherapy)** | | | | | | | | |
| Henry[1], 2012 | 24weeks | dapagliflozin5mg | 203 | 52.3±10.2 | 45.3 | / | 1.6±3.1 | 9.1±1.4 |
|  |  | MET 2000mg | 201 | 51.8±9.8 | 47.3 | / | 1.6±2.6 | 9.2±1.3 |
|  |  | dapagliflozin10mg | 219 | 51.1±11.5 | 47.9 | / | 2.1±3.8 | 9.1±1.3 |
|  |  | MET 2000mg | 208 | 52.7±10.4 | 46.6 | / | 1.9±4.0 | 9.1±1.3 |
| **Second line therapy strategy (SGLT-2 inhibitors add on SU/TZD/DPP4i versus Placebo)** | | | | | | | | |
| Rosenstock[2], 2012 | 48weeks | dapagliflozin10mg+ pioglitazone | 140 | 53.8±10.4 | 42.1 | / | 5.75±6.44 | 8.37±0.96 |
|  |  | placebo+ pioglitazone | 139 | 53.5±11.4 | 51.1 | / | 5.07±5.05 | 8.34±1 |
| Strojek[3], 2011 | 24weeks | dapagliflozin10mg+  glimepiride4mg | 151 | 58.9±8.32 | 43.7 | / | 7.2±5.5 | 8.07±0.79 |
|  |  | placebo+  glimepiride4mg | 145 | 60.3±10.1 | 49 | / | 7.4±5.7 | 8.15±0.74 |
| **Second line therapy strategy (MET add on SU/TZD/DPP4i versus Placebo)** | | | | | | | | |
| Ahrén[4], 2004 | 12 weeks | LAF237 50mg qd+MET | 56 | 57.9 ± 10.0 | 69.6 | 29.4± 3.6 | 5.6 ± 4.2 | 7.7 ± 0.6 |
|  |  | Placebo+MET | 51 | 55.7 ± 11.0 | 66.7 | 30.2 ± 3.6 | 5.5± 3.7 | 7.8 ± 0.7 |
| Barnett[5], 2013 | 24weeks | Linagliptin 5mg qd+MET/SU | 162 | 74.9±4.4 | 71.6 | 29.6±4.7 | / | 7.8±0.8 |
|  |  | Placebo+MET/SU | 79 | 74.9±4.2 | 62.0 | 29.8±4.5 | / | 7.7±0.7 |
| Bergenstal[6], 2012 | 24weeks | Placebo+MET | 90 | 56.1±10.1 | 52 | 32.5±5.5 | 5.5±3.9 | 8.03±0.83 |
|  |  | Sitagliptin 100mg+MET | 177 | 55.5±9.9 | 59 | 32.4±5 | 6.0±5.0 | 7.94±0.85 |
| Berhanu[7], 2007 | 20 weeks | Pioglitazone 45mg+MET | 110 | 52.9±11.33 | 43.6 | 30.7±6.09 | 7.7±6.15 | 8.4±0.13 |
|  |  | placebo+MET | 112 | 52.5±11.07 | 41.1 | 31.8±6.2 | 8.5±5.43 | 8.6±0.13 |
| Borges[8], 2011 | 80weeks | Rosiglitazone +MET | 344 | 51.5 | 53 | 32.2 | 2.3 | 8.6±0.9 |
|  |  | placebo+MET | 334 | 50.7 | 53 | 33.1 | 2.6 | 8.6±0.9 |
| Bosi[9], 2007 | 24 weeks | vildagliptin50mg+MET | 143 | 54.3±9.7 | 57.3 | 32.1±5.3 | 6.8±5.5 | 8.4±0.9 |
|  |  | Vildagliptin100mg+MET | 143 | 53.9±9.5 | 61.5 | 32.9±5.0 | 5.8±4.7 | 8.4±1.0 |
|  |  | Placebo+MET | 130 | 54.5±10.3 | 53.1 | 33.2±6.1 | 6.2±5.3 | 8.3±0.9 |
| Bosi[10], 2011 | 52weeks | MET+ Pioglitazone 30mg+Alogliptin25mg | 404 | 54.3±9.86 | 52.0 | 31.5±5.25 | 7.5±5.24 | 8.2±0.86 |
|  |  | MET+Pioglitazone45mg | 399 | 55.9±9.94 | 51.1 | 31.6±5.18 | 6.9±4.61 | 8.1±0.83 |
| Brackenridge[11], 2009 | 12weeks | MET+ Rosiglitazone 8mg | 8 | 66.5±2.51 | 50 | 30.0±1.5 | 4.4±1.03 | 6.9±0.3 |
|  |  | MET+ Pioglitazone 30mg | 8 | 61.0±3.93 | 87.5 | 30.8±1.26 | 4.0±0.8 | 7.5±0.21 |
|  |  | placebo+met | 8 | 60.8±3.45 | 87.5 | 32.0±1.56 | 2.9±0.4 | 6.6±0.14 |
| Charbonnel[12], 2006 | 24 weeks | Sitagliptin 100mg qd+MET | 454 | / | / | / | / | 7.96±0.81 |
|  |  | Placebo+MET | 226 | / | / | / | / | 8.03±0.82 |
| Chen[13], 2016 | 24weeks | Saxagliptin+MET | 36 | 63.7±6.3 | 58.1 | 22.9±3.09 | 5.1±5.0 | 8.38±0.69 |
|  |  | Vildagliptin+MET | 37 | 62.1±6.8 | 52.4 | 24.1±4.27 | 5.1±4.0 | 8.33±0.67 |
| Dailey[14], 2004 | 24 weeks | Rosiglitazone＋glyburide/MET | 181 | 57±9 | 58 | 32±5 | 9±7 | 8.1±0.9 |
| placebo＋glyburide/MET | 184 | 57±10 | 61 | 32±5 | 9±6 | 8.1±0.8 |
| DeFronzo[15], 2012 | 26 weeks | placebo+MET | 129 | 55.2±9.9 | 47.3 | 30.6±4.8 | 6.0±5.0 | 8.5±0.6 |
|  |  | Alogliptin 25mg+MET | 129 | 53.7±9.3 | 38.8 | 31.5±5.7 | 5.6±4.9 | 8.6±0.7 |
|  |  | Alogliptin 25mg  +PIO 30mg+MET | 130 | 54.4±9.7 | 42.3 | 31.9±5.6 | 6.6±6.0 | 8.5±0.7 |
| Derosa[16], 2008 | 26weeks | MET2.0g+ rosiglitazone | 56 | 55±4 | 46.4 | 28.6±1.9 | 3±1 | 7.8±0.7 |
|  |  | placebo+MET2.0g | 61 | 54±3 | 47.5 | 28.4±1.7 | 4±1 | 8.0±0.9 |
| Derosa[17], 2012 | 12 months | Sitagliptin 100mg qd+MET | 91 | 55.9±8.8 | 46 | 28.1±1.2 | 5.8±2.6 | 8.1±0.8 |
|  |  | Placebo+MET | 87 | 54.8±7.9 | 51 | 28.9±2.0 | 5.4±2.3 | 8.0±0.7 |
| Derosa[18], 2012 | 12 months | Vildagliptin 50mg bid+MET | 84 | 54.2±8.3 | 50 | 27.9±1.5 | 6.1±3.7 | 8.1±0.6 |
|  |  | Placebo+MET | 83 | 52.4±7.1 | 51.8 | 27.8±1.4 | 6.3±3.9 | 8.2±0.7 |
| Dobs[19], 2013 | 18 weeks | Sitagliptin 100mg qd+MET+rosiglitazone | 170 | 54.4±8.8 | 56 | 30.1±6.2 | 9.3±5.9 | 8.8±1.0 |
|  |  | Placebo+MET+rosiglitazone | 92 | 54.8±9.5 | 60 | 30.8±5.6 | 9.4±6.8 | 8.7±1.0 |
| Einhorn[20], 2000 | 16weeks | MET2.0g+ Pioglitazone 30mg | 168 | 55.5±10.34 | 54.8 | 32.11±5.3 | / | 9.86±1.4 |
|  |  | placebo+MET2.0g | 160 | 55.7±9.92 | 60 | 32.12±5.5 | / | 9.75±1.3 |
| Feinglos[21], 2005 | 16weeks | MET1.0g+  glipizide2.5mg | 61 | 57.7±10.7 | 45.9 | 31.7±4.4 | 6.5 | 7.45 |
|  |  | placebo+MET1.0g | 61 | 58.8±10.0 | 41 | 32.1±4.9 | 4.6 | 7.64 |
| Fonseca[22], 2000 | 26weeks | MET2.5g+ rosiglitazone 4mg | 116 | 57.5±10.5 | 62.1 | 30.2±4.2 | 7.5±6.3 | 8.9±1.3 |
|  |  | MET2.5g+ rosiglitazone 8mg | 110 | 58.3±8.8 | 68.2 | 29.8±3.9 | 8.3±6.3 | 8.9±1.5 |
|  |  | placebo2.5g+MET | 113 | 58.8±9.2 | 74.3 | 30.3±4.4 | 7.3±5.7 | 8.6±1.3 |
| Fonseca[23], 2013 | 26weeks | Sitagliptin100mg+MET+ pioglitazone | 157 | 55.7±8.7 | 61.8 | 29.9±5.2 | 9.4±5.8 | 8.8±1.0 |
|  |  | Placebo+MET+ pioglitazone | 156 | 56.4±9.4 | 62.8 | 30.0±5.2 | 10.2±6.1 | 8.7±1.0 |
| Forst[24], 2010 | 12 weeks | Linagliptin 5mg+MET | 66 | 59.6±9.8 | 56.1 | 31.7±4.5 | 7.3±7.5 | 8.5±0.8 |
|  |  | Glimepiride+MET | 65 | 59.4±9.9 | 63.1 | 31.5±4.2 | 6.7±5.9 | 8.2±0.7 |
|  |  | Placebo+MET | 71 | 60.1±8.1 | 62 | 32.2±4.2 | 6.2±5.1 | 8.4±0.7 |
| Garber[25], 2002 | 20  weeks | glimepiride2.5mg+  MET500mg | 165 | 58.1 | 58.2 | 29.6 | 3.3 | 8.18±1.14 |
|  |  | glimepiride2.5mg | 161 | 56.5 | 50.9 | 30.3 | 2.81 | 8.21±1.09 |
| Garber[26], 2003 | 16  weeks | glimepiride1.25mg+  MET500mg | 171 | 55.6 | 44.4 | 31.4 | 3 | 8.8±1.5 |
|  |  | glimepiride1.25mg | 151 | 55.3 | 43.7 | 31.1 | 3 | 8.7±1.4 |
| Gòmez-Perez[27], 2002 | 26weeks | MET2.5g+RSG4mg | 35 | 54.2±9.3 | 28.6 | 28.0±4.0 | 11.1±7.1 | / |
|  |  | MET2.5g+RSG8mg | 36 | 51.7±8.6 | 19.4 | 27.6±3.2 | 10.7±7.0 | / |
|  |  | placebo+MET2.5g | 34 | 53.4±7.5 | 29.4 | 28.5±3.9 | 9.1±5.6 | / |
| Goodman[28], 2009 | 24 weeks | Vildagliptin 100mg qd+MET | 248 | 54.9±10.8 | 52.8 | 31.4±4.7 | / | 8.5±1 |
|  |  | placebo+MET | 122 | 54.5±9.7 | 67.2 | 31.7±4.3 | / | 8.7±1.1 |
| Haak[29], 2012 | 24 weeks | Placebo+MET500 mg bid | 144 | 52.9±10.4 | 56.9 | 28.9±4.8 | / | 8.7±0.9 |
|  |  | Placebo+MET1000 mg bid | 147 | 55.2±10.6 | 53.1 | 29.5±5.3 | / | 8.5±0.9 |
|  |  | LINA2.5mg+MET500mg | 143 | 55.6±11.2 | 51 | 29.7±5.3 | / | 8.7±1.0 |
|  |  | LINA2.5mg+MET 1000mg bid | 143 | 56.4±10.7 | 53.8 | 28.6±4.8 | / | 8.7±1.0 |
| Hermansen[30], 2007 | 24 weeks | Sitagliptin 100mg qd+Glimepiride±MET | 222 | 55.6±9.6 | 52.7 | 31.2±6.3 | 8.3±5.5 | 8.34±0.76 |
|  |  | Placebo+ Glimepiride±MET | 219 | 56.5±9.6 | 53.4 | 30.7±6.3 | 9.3±6.8 | 8.34±0.74 |
| Jadzinsky[31], 2009 | 24 weeks | Saxagliptin 5mg+MET | 320 | 52.0±10.4 | 51.6 | 29.9±4.5 | 2.0±3.6 | 9.4±1.2 |
|  |  | Saxagliptin 10mg+MET | 323 | 52.1±11.6 | 45.2 | 30.3±5.0 | 1.4±2.5 | 9.5±1.2 |
|  |  | placebo+MET | 328 | 51.8±10.7 | 49.7 | 30.2±4.9 | 1.7±3.1 | 9.4±1.3 |
| Ji[32], 2016 | 24 weeks | Vildagliptin 50mg bid+MET | 2501 | 56.5±10.6 | 54.4 | 25.1±3.2 | 4.3±4.2 | 7.2±0.02 |
|  |  | Placebo+MET | 484 | 56.2±10.8 | 49.6 | 25.1±3.2 | 4.1±4.3 | 7.2±0.04 |
| Kaku[33], 2009 | 28 weeks | pioglitazone 30mg+MET | 83 | 52±8.6 | 66.3 | 25.6±4.2 | 4.5±3.7 | 7.58±1.0 |
|  |  | placebo+MET | 86 | 53±7.5 | 57 | 25.4±3.6 | 5.6±5.0 | 7.55±0.9 |
| Lavalle-González[34], 2013 | 26  weeks | Placebo+MET | 183 | 55.3±9.8 | 51.4 | 31.1±6.1 | 6.8±5.3 | 8.0±0.9 |
| Sitagliptin100mg+MET | 366 | 55.3±9.8 | 47 | 32.0±6.1 | 6.8±5.2 | 7.9±0.9 |
| Lv[35], 2013 | 12 weeks | Saxa+MET | 90 | 44±7 | 51.4 | 30±6 | / | 7.83±0.29 |
|  |  | Acarbose+MET | 90 | 44±7 | 52.6 | 30±4 | / | 7.18±0.27 |
| Lukashevic[36], 2014 | 24  weeks | Vildagliptin 50mg bid+MET+Glimepiride | 158 | 55.3±10.2 | 50.6 | 27.9±4.6 | 7.1±6.2 | 8.7±0.9 |
|  |  | Placebo+MET+Glimepiride | 160 | 55.0±11.1 | 45% | 28.0±4.5 | 7.5±6.1 | 8.8±0.9 |
| Li[37], 2014 | 24weeks | Saxagliptin+MET | 66 | 46.5±10.7 | 59 | 26.9±3.1 | / | 8.86±1.13 |
|  |  | Vildagliptin+MET | 63 | 44.8±8.5 | 59 | 25.3±2.8 | / | 8.75±1.15 |
|  |  | Sitagliptin+MET | 61 | 48.6±11.3 | 54 | 26.6±3.3 | / | 8.54±1.19 |
| Du[38], 2016 | 24weeks | Saxagliptin+MET | 238 | / | / | / | / | / |
|  |  | Acarbose +MET | 243 | / | / | / | / | / |
| Nauck[39], 2009 | 26weeks | MET2.0g+  glimepiride4mg | 244 | 57±9 | 57 | 31.2±4.6 | 8±5 | 8.4±1 |
|  |  | placebo+MET2.0g | 121 | 56±9 | 60 | 31.6±4.4 | 8±6 | 8.4±1.1 |
| Nauck[40], 2009 | 26 weeks | Placebo+MET | 104 | 56±11 | 48 | 32±6 | 6±5 | 8.0±0.9 |
|  |  | Alogliptin 12.5mg+ MET | 213 | 55±11 | 47.4 | 32±5 | 6±5 | 7.9±0.7 |
|  |  | Alogliptin 25mg+ MET | 210 | 54±11 | 54.3 | 32±5 | 6±4 | 7.9±0.8 |
| Negro**[41]**, 2005 | 52weeks | MET2.5g+ rosiglitazone 8mg | 19 | 60.3±6.4 | 52.6 | 28.3±1.7 | 7.1±2.4 | 8.4±0.6 |
|  |  | placebo+MET2.5g | 19 | 59±8 | 63.2 | 28.7±1.9 | 6.6±2.9 | 8.1±0.5 |
| Owens**[42]**, 2011 | 24 weeks | Linagliptin 5 mg+MET+SU | 792 | 58.3±9.9 | 46.8 | 28.4±4.8 | / | 8.15±0.03 |
|  |  | Placebo+MET+SU | 263 | 57.6±9.7 | 48.3 | 28.2±4.5 | / | 8.14±0.05 |
| Pan**[43]**, 2002 | 12 weeks | pioglitazone 30mg  +SU+MET | 141 | / | / | / | / | 8.5±1.34 |
|  |  | PBO+SU+MET | 142 | / | / | / | / | 8.5±1.12 |
| Pan[44], 2012 | 24 weeks | Vildagliptin 50mg bid+ MET | 146 | 54.2±9.62 | 50 | 26.01±3.26 | 4.92±4.8 | 8.09±0.85 |
|  |  | Vildagliptin 50 mg qd+ MET | 146 | 53.7±10.0 | 44.6 | 25.03±3.09 | 5.02±4.42 | 8.05±0.84 |
|  |  | Placebo+MET | 144 | 54.5±9.68 | 45.8 | 25.46±3.09 | 5.15±4.58 | 8.01±0.82 |
| Pan[45], 2015 | 16 weeks | Alo+MET | 91 | 52.6±9.8 | 53.3 | 25.7±3.1 | 5.3±4.2 | 8.05±0.83 |
|  |  | Placebo+MET | 93 | 53.4±9.4 | 48.9 | 25.5±3.9 | 5.5±3.9 | 7.98±0.75 |
| Perez[46], 2009 | 24weeks | pioglitazone15mg+MET | 201 | 54.7 | 44.8 | 30.8 |  | 8.89±0.07 |
|  |  | Placebo+MET | 210 | 53.7 | 46.7 | 30.8 |  | 8.65±0.07 |
| Raz[47], 2008 | 18 weeks | Sitagliptin 100mg qd+MET | 96 | 53.6±9.5 | 51 | 30.1±4.4 | 8.4±6.5 | 9.3±0.9 |
|  |  | placebo+MET | 94 | 56.1±9.5 | 41.5 | 30.4±5.3 | 7.3±5.3 | 9.1±0.8 |
| Roberts[48], 2005 | 26 weeks | glimepiride8mg+  MET+SU | 82 | 56.5±9.8 | 61 | 33.98±5.15 | 8.7±6.8 | 8.15±0.76 |
|  |  | PBO+MET+SU | 77 | 56.4±10.0 | 62.3 | 32.76±5.11 | 7.9±4.9 | 8.15±0.65 |
| Rosenstock[49], 2006 | 32weeks | rosiglitazone +MET | 155 | 50.1 | 57 | 33.2 | 2.3 | 8.9±1.1 |
|  |  | placebo+MET | 154 | 51.5 | 56 | 32.5 | 2.9 | 8.8±1 |
| Rosenstock[50], 2012 | 12 weeks | sitagliptin 100mg Qd+MET | 65 | 51.7±8.1 | 58 | 31.6±5.0 | 5.6±4.7 | 7.64±0.95 |
|  |  | PBO+MET | 65 | 53.3±7.8 | 48 | 30.6±4.6 | 6.4±5.0 | 7.75±0.83 |
| Ross[51], 2012 | 12 weeks | Linagliptin 2.5mg+ MET | 214 | 58.7±9.9 | 61.9 | 29.8±5.2 | / | 7.96±0.78 |
|  |  | Linagliptin 5mg+ MET | 221 | 58.4±10.6 | 54 | 29.6±5.0 | / | 7.98±0.72 |
|  |  | Placebo+ MET | 43 | 59.9±10.7 | 47.7 | 28.7±5.5 | / | 7.92±0.74 |
| Scheen[52],2009 | 155weeks | MET2.5g+ pioglitazone 45mg | 253 | 60.8±7.6 | 70 | 31.9±4.7 | 5.1±5.1 | 7.6±1.3 |
|  |  | placebo+MET2.5g | 261 | 60.3±7.9 | 67 | 32.0±5.3 | 5.6±5.4 | 7.6±1.2 |
| Scott[53], 2008 | 18 weeks | Sitagliptin 100mg qd+MET | 94 | 55.2±9.8 | 55 | 30.3±4.7 | 4.9±3.5 | 7.8±1.0 |
|  |  | placebo+MET | 92 | 55.3±9.3 | 59 | 30.0±4.5 | 5.4±3.7 | 7.7±0.9 |
|  |  | Rosiglitazone+MET | 87 | 54.8±10.5 | 63 | 30.4±5.5 | 4.6±4 | 7.7±0.8 |
| Seino[54], 2012 | 24 weeks | Alogliptin 12.5 mg od +MET | 92 | 53.4 ±8.80 | 65.2 | 25.63 ±4.10 | 6.34 ±5.39 | 7.89 ±0.82 |
|  |  | Alogliptin 25 mg od +MET | 96 | 52.3 ±8.02 | 68.8 | 25.79 ±3.70 | 6.62 ±4.80 | 8.02 ±0.73 |
|  |  | Placebo + MET | 100 | 52.1 ±8.05 | 72 | 26.14 ±4.58 | 6.04 ±4.36 | 8.00 ±0.86 |
| Sridhar[55], 2013 | 24 weeks | pioglitazone 30mg  +glimepide+MET | 25 | 47.9±5.8 | 100 | 25.3±2.7 | 2.2±1.7 | 6.8±0.4 |
|  |  | placebo+glimepide+MET | 25 | 44.0±7.2 | 100 | 25.1±3.2 | 2.9±2.1 | 6.8±0.4 |
| Stewart[56], 2006 | 32weeks | rosiglitazone +MET | 254 | 58.9 | 55 | 30.9 | 3.7 | 7.2±0.6 |
|  |  | placebo+MET | 272 | 59 | 56 | 30.6 | 3.7 | 7.2±0.6 |
| Taskinen[57], 2011 | 24 weeks | Placebo+MET | 177 | 56.6±10.9 | 57 | 30.05±5.01 | / | 8.02±0.88 |
|  |  | Linagliptin 5mg qd+MET | 523 | 56.5±10.1 | 53 | 29.85±4.84 | / | 8.09±0.86 |
| Wang[58], 2015 | 24 weeks | Linagliptin+MET | 184 | 55.1±10.7 | 49.8 | 25.5±3.9 | / | 7.99±0.83 |
|  |  | Placebo+MET | 80 | 56.5±8.7 | 50 | 25.8±4.0 | / | 8.00±0.80 |
| Yale[59], 2001 | 24 weeks | troglitazone400mg+MET+SU | 101 | 58±0.9 | 55 | 30.1±0.5 | 11.9±0.8 | 9.6±0.1 |
|  |  | placebo+MET+SU | 99 | 60±0.9 | 58 | 30.0±0.4 | 10.8±0.6 | 9.7±0.1 |
| Yang[60], 2011 | 24 weeks | Saxagliptin 5mg qd+MET | 283 | 53.8 ±10.4 | 48.1 | 26.3 ±3.6 | 5.1 ±5.0 | 7.9 ±0.8 |
|  |  | Placebo+MET | 287 | 54.4 ±10.1 | 48.7 | 26.1 ±3.5 | 5.1 ±4.0 | 7.9±0.8 |
| Yang[61], 2012 | 24 weeks | Sitagliptin 100mg qd+MET | 197 | 54.1±9.0 | 47 | 25.3±3.1 | 6.4±4.4 | 8.5±0.9 |
|  |  | Placebo+MET | 198 | 55.1±9.8 | 55 | 25.3±3.6 | 7.3±4.6 | 8.5±0.9 |
| **Third line therapy strategy (SGLT-2 addon INS versus Placebo)** | | | | | | | | |
| Araki[62], 2016 | 16weeks | dapagliflozin5mg+ins | 122 | 58.3 | 73 | 26.89 | 15.32 | 8.26±0.79 |
|  |  | placebo+ins | 60 | 57.6 | 66.7 | 26.12 | 14.24 | 8.52±0.94 |
| Cefalu[63], 2015 | 52weeks | dapagliflozin10mg+  OAD/ins | 455 | 62.8±7.0 | 67.9 | 32.6±5.9 | 12.6±8.7 | 8.18±0.84 |
|  |  | placebo+OAD/ins | 459 | 63.0±7.7 | 68.6 | 32.9±6.1 | 12.3±8.2 | 8.08±0.8 |
| Wilding[64], 2009 | 12weeks | dapagliflozin10mg+ins | 24 | 55.7±9.2 | 54.2 | 35.5±3.6 | 11.8±5.8 | 8.4±0.7 |
|  |  | placebo+ins | 23 | 58.4±6.5 | 69.6 | 34.8±4.6 | 13.8±7.3 | 8.4±0.9 |
| Wilding[65], 2012 | 48weeks | dapagliflozin10mg+ins | 194 | 59.3±8.8 | 44.8 | 33.4±5.1 | 14.2±7.3 | 8.57±0.82 |
|  |  | palcebo+ins | 193 | 58.8±8.6 | 49.2 | 33.1±5.9 | 13.5±7.3 | 8.47±0.77 |
| **Third line therapy strategy (MET addon INS versus Placebo)** | | | | | | | | |
| Avilés-Santa[66], 1999 | 24 weeks | MET2.5g+ins | 21 | 53.1±9.4 | 28.6 | / | 9.2±6.4 | 9.0±1.4 |
| placebo+ins | 22 | 54.6±7.8 | 45.5 | / | 10.1±4.7 | 9.1±1.5 |
| Douek[67], 2005 | 52weeks | MET2.0g+ins | 92 | 58±8.9 | 67.4 | 30.9±4.5 | 9±5.2 | 9.7±1.3 |
| placebo+ins | 91 | 58±7.7 | 62.6 | 31.5±4.3 | 10±5.2 | 10.0±1.5 |
| Gram[68], 2011 | 104weeks | MET2.0g+NPH | 45 | 55.4 | 57.8 | 35.4 | 8.2 | 8.9±1.2 |
| placebo+NPH | 46 | 55.8 | 71.7 | 34 | 7.3 | 8.7±1.3 |
| Gram-2[68], 2011 | 104weeks | MET2.0g+ASP | 45 | 56.1 | 62.2 | 33.7 | 8.7 | 8.5±1.2 |
| placebo+ASP | 48 | 57.1 | 47.9 | 33.7 | 9.1 | 8.5±1.2 |
| Hermann[69], 2001 | 52 weeks | MET1.7g+ins | 16 | 56.9±10.2 | 43.8 | 33.6±3.5 | 13 | 9.1±1.3 |
| placebo+ins | 19 | 58.1±9.7 | 63.2 | 32.6±3.8 | 13 | 8.7±1.0 |
| Kooy[70], 2009 | 224weeks | MET2.55g+ins | 196 | 64±10 | 41.3 | 30±5 | 14±9 | 7.9±1.2 |
| placebo+ins | 194 | 59±11 | 50 | 30±5 | 12±8 | 7.9±1.2 |

**Table S2: Baseline demographics in dapagliflozin treatment and metformin treatment as first line therapy, second line therapy and third therapy**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | **First line therapy** | | **Second line therapy** | | **Third line therapy** | |
| **Variables** | **Dapagliflozin monotherapy** | **Metformin monotherapy** | **Dapagliflozin add on SU/TZD** | **Metformin add on SU/TZD** | **Dapagliflozin add on insulin** | **Metformin add on insulin** |
| n. | 219 | 208 | 291 | 3127 | 795 | 415 |
| Age (year) | 51.5±11.5 | 52.7±10.4 | 56.50±3.54 | 56.25±3.95 | 59.00±2.94 | 57.17±3.76 |
| Gender (female percent) | 52.1% | 53.4% | 43.0% | 57.9% | 60.00% | 50.17% |
| BMI(kg/m2) | / | / | / | 30.08±2.33 | 32.25±3.78 | 33.00±2.45 |
| Diabetes duration(year) | 2.1±3.8 | 1.9±4.0 | 6.50±0.71 | 6.05±3.18 | 13.50±1.29 | 10.33±2.50 |
| HbA1c(%) | 9.1±1.3 | 9.1±1.3 | 8.00±0.00 | 8.26±0.86 | 8.25±0.50 | 8.83±0.75 |
| Weight(kg) | 88.5±19.3 | 87.2±19.4 | 83.00±2.83 | 88.75±7.62 | 91.00±12.19 | 96.33±8.31 |
| SBP(mmHg) | 127.8±13.7 | 130.6±15.2 | 132.00 | 132.75±1.50 | 135.33±5.13 | 153.67±7.10 |
| DBP(mmHg) | 80.1±8.0 | 80.7±8.2 | 79.00 | 81.25±3.50 | 78.67±1.53 | 84.67±1.16 |
| TCHO(mmol/l) | / | / | 5.00 | 5.05±0.21 | 4.00 | 5.65±0.47 |
| TG(mmol/l) | / | / | 2.00 | 2.30±0.84 | 2.00 | 2.42±0.68 |
| LDLC(mmol/l) | / | / | 3.00 | 2.89±0.29 | 2.00 | 3.53±0.50 |
| HDLC(mmol/l) | / | / | 1.00 | 1.12±0.13 | 1.00 | 1.07±0.15 |
| SUA(umol/l) | 302.2±85.7 | 302.8±77.3 | 301.00±82.4 | / | 325.00 | / |

**Table S3: Annual treatment costs for different drugs.**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Drug Type** | **Size (tablets/capsules)** | **Price per package** | **Annual Utilization (tablets per patient)** | **Annual Cost** |
| Metformin | 20 | 25.0 | 1277.5 | 1596.0 |
| Dapagliflozin | 14 | 229.6 | 365 | 5985.8 |
| SU/TZD/DPP4 inhibitors |  |  |  | 2818.4 |
| Gliclazide | 30 | 57.7 | 1095 | 2106.4 |
| Glimepiride | 15 | 66.8 | 730 | 3251.4 |
| Glipizide | 30 | 32.3 | 912.5 | 982.7 |
| Pioglitazone | 7 | 43.9 | 365 | 2287.2 |
| Rosiglitazone | 7 | 65.6 | 365 | 3419.0 |
| Saxagliptin | 7 | 59.2 | 365 | 3085.6 |
| Sitagliptin | 7 | 73.4 | 365 | 3825.3 |
| Linagliptin | 7 | 61.2 | 365 | 3193.7 |
| Vildagliptin | 14 | 61.6 | 730 | 3214.4 |

SU: sulfonylurea; TZD: thiazolidinedione; DPP4: Dipeptidyl peptidase-4

\* Annual cost for SU/TZD/DPP4 inhibitors was calculated as (¥2106.4 + ¥3251.4 + ¥982.7 + ¥2287.2 + ¥3419.0+ ¥3085.6+ ¥3825.3+ ¥3193.7+ ¥3214.4)/5 = ¥2818.4, due to the lack of utilization pattern of these drugs.

\*\* Annual cost for “metformin add on SU/TZD/DPP4 inhibitors” was ¥1596 + ¥2818.4 = ¥4414.4, and that for “dapagliflozin add on SU/TZD/DPP4 inhibitors” was ¥5985.8 + ¥2818.4 = ¥8804.2 in 2016.

**Table S4: Annual direct medical costs for diabetes-related complications and adverse events**

|  |  |  |  |
| --- | --- | --- | --- |
| **Event** | **Fatal** | **Non-fatal** | **Maintenance** |
| Ischemic heart disease | \ | 38660.37 | 6901.83 |
| Myocardial infarction | 46092.75 | 46092.75 | 10588.1 |
| Congestive heart failure | 15328.57 | 15328.57 | 9317.53 |
| Stroke | 13922.2 | 17964.09 | 8089.54 |
| Blind | \ | 11930.02 | 9207.04 |
| End stage renal disease | \ | 113521.66 | 91084.11 |
| Amputation | 18055.01 | 18055.01 | 14391.76 |
| Ulcer | \ | 14190.51 | 4994.42 |
| Severe hypoglycemia | \ | 3787.91 | \ |
| Genital infection | \ | 201.7 | \ |
| Urinary infection | \ | 201.7 | \ |

**Table S5: Body mass index (BMI) associated costs**

|  |  |
| --- | --- |
| **BMI (kg/m2)** | **Annual Cost (Chinese Yuan)** |
| 20 | 0 |
| 21 | 0 |
| 22 | 0 |
| 23 | 0 |
| 24 | 1574.4 |
| 25 | 3877.9 |
| 26 | 6181.4 |
| 27 | 8484.9 |
| 28 | 10788.4 |
| 29 | 13091.9 |
| 30 | 15395.4 |
| 31 | 17698.9 |
| 32 | 20002.4 |
| 33 | 22305.9 |
| 34 | 24609.4 |
| 35 | 26912.9 |
| 36 | 29216.4 |
| 37 | 31519.9 |
| 38 | 33823.4 |
| 39 | 36126.9 |
| 40+ | 38430.40 |

**Table S6: Health state utility decrements**

|  |  |
| --- | --- |
| **Event** | **Utility Decrement** |
| Ischemic heart disease | 0.09 |
| Myocardial infarction | 0.055 |
| Congestive heart failure | 0.108 |
| Stroke | 0.164 |
| Blind | 0.074 |
| End-stage renal disease | 0.263 |
| Amputation | 0.28 |
| Ulcer | 0.059 |
| Symptomatic hypoglycemia | 0.0142 |
| Severe hypoglycemia | 0.047 |
| Urinary tract infection | 0.003 |
| Genital infection | 0.003 |
| Gastrointestinal side effects | 0.04 |
| Per unit decrease in BMI | 0.0171 |
| Per unit increase in BMI | 0.0472 |

**Table S7: Input data for the univariate sensitivity analyses**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Parameter Group | Parameter | Upper Value | Lower Value | Variation Type |
| Model Settings | Discounting (%) | 0 | 0.06 | Absolute |
| Time horizon (years) | 20 | 5 | Absolute |
| Patient Demographics | Age (years) | 60 | 30 | Absolute |
| Proportion female (%) | 1 | 0 | Absolute |
| Current smoker (%) | 1 | 0 | Absolute |
| Patient Clinical  Risk Factors | HbA1c (%) | 25 | 25 | Percentage |
| Total cholesterol (%) | 25 | 25 | Percentage |
| HDL cholesterol (%) | 25 | 25 | Percentage |
| Systolic blood pressure (mmHg) | 25 | 25 | Percentage |
| Weight (kg) | 25 | 25 | Percentage |
| Treatment | HbA1c treatment effect (%) | 25 | 25 | Percentage |
| Weight treatment effect (kg) | 25 | 25 | Percentage |
| Non-severe hypoglycemia rates | 25 | 25 | Percentage |
| Severe hypoglycemia rates | 25 | 25 | Percentage |
| Adverse event rates | 25 | 25 | Percentage |
| Costs | Event costs | 25 | 25 | Percentage |
| BMI costs | 25 | 25 | Percentage |
| Health Utility | Baseline utility | 25 | 25 | Percentage |
| Event disutility | 25 | 25 | Percentage |
| BMI-related utility | 25 | 25 | Percentage |

**Table S8: Absolute changes from baseline in dapagliflozin treatment and metformin treatment as first line therapy, second line therapy and third line therapy**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Variables** | **dapagliflozin** | | | **metformin** | | |
|  | **change from baseline** | **95%CI** | **P** | **change from baseline** | **95%CI** | **P** |
| **First line therapy (monotherapy)** | | | | | | |
| HbA1c (%) | -1.45 | -1.59, -1.31 | 0.00 | -1.44 | -1.59, -1.29 | 0.00 |
| Weight (kg) | -2.73 | -3.19, -2.27 | 0.00 | -1.36 | -1.83, -0.89 | 0.00 |
| SBP (mmHg) | -4.01 | 0.9**\*** | / | -1.2 | 1.0**\*** | / |
| DBP (mmHg) | -1.9 | 0.5**\*** | / | 0 | 0.6**\*** | / |
| TCHO(mmol/l) | / | / | / | / | / | / |
| TG(mmol/l) | / | / | / | / | / | / |
| LDLC(mmol/l) | / | / | / | / | / | / |
| HDLC(mmol/l) | / | / | / | / | / | / |
| SUA(umol/l) | -33.3 | 3.6**\*** | / | 18.4 | 3.6**\*** | / |
| **Second line therapy (add on SU/TZD/DPP4i)** | | | | | | |
| HbA1c (%) | -1.008 | -1.723,-0.293 | 0.006 | -1.222 | -1.545, -0.898 | 0.00 |
| Weight (kg) | -0.841 | -1.584, -0.098 | 0.027 | 1.442 | 0.931, 1.953 | 0.00 |
| SBP (mmHg) | -2.2 | -4.552, 0.152 | / | -2.842 | -4.193, -1.491 | 0.00 |
| DBP (mmHg) | -2.4 | -3.772, -1.028 | 0.00 | / | / | / |
| TCHO(mmol/l) | / | / | / | 1.807 | 1.528, 2.086 | 0.00 |
| TG(mmol/l) | / | / | / | -0.089 | -0.477, 0.299 | 0.653 |
| LDLC(mmol/l) | / | / | / | 0.139 | -0.100, 0.379 | 0.255 |
| HDLC(mmol/l) | / | / | / | 0.113 | -0.058, 0.285 | 0.195 |
| SUA(umol/l) | -26.17 | -35.77, -16.57 | / | / | / | / |
| **Third line therapy (add on insulin)** | | | | | | |
| HbA1c (%) | -0.61 | -1.089, -0.132 | 0.012 | -0.752 | -2.008, 0.504 | 0.24 |
| Weight (kg) | -2.578 | -3.23, -1.927 | 0.00 | 3.05 | -14.01,20.11 | 0.726 |
| SBP (mmHg) | -3.734 | -5.747, -1.722 | 0.00 | -12.931 | -27.666,1.804 | 0.085 |
| DBP (mmHg) | -2.668 | -4.733, -0.604 | 0.011 | -6.444 | -21.179, 8.291 | 0.391 |
| TCHO(mmol/l) | -0.09 | -0.698, 0.518 | 0.772 | -0.982 | -2.357, 0.392 | 0.161 |
| TG(mmol/l) | -0.06 | -0.746, 0.626 | 0.864 | -0.31 | -1.684, 1.063 | 0.658 |
| LDLC(mmol/l) | -0.100 | -0.649, 0.449 | 0.721 | -1.311 | -2.962, 0.340 | 0.120 |
| HDLC(mmol/l) | -0.020 | -0.118,0.078 | 0.689 | 0.055 | -0.084, 0.193 | 0.438 |
| SUA(umol/l) | -14.28 | -137.66,109.1 | 0.821 | / | / | / |

\*: standard deviation (SD)

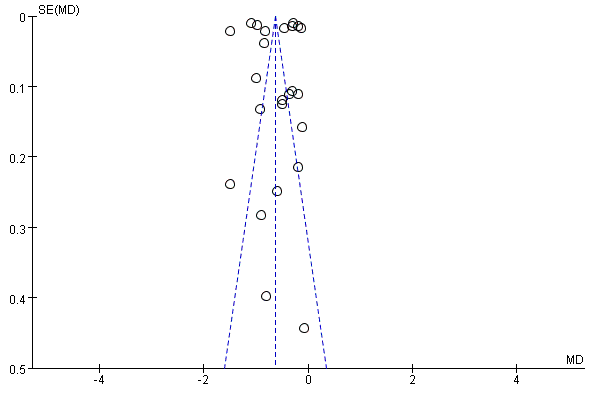
SU: sulfonylurea; TZD: thiazolidinedione; DPP4: Dipeptidyl peptidase-4; SBP: systolic blood pressure; DBP: diastolic blood pressure; TCHO: total cholesterol; TG: triglyceride; LDLC: low-density lipoprotein cholesterol; HDLC: high-density lipoprotein cholesterol; SUA: serum uric acd;

**Table S9: Risks of the adverse effects in dapagliflozin treatment and metformin treatment as first line therapy, second line therapy and third line therapy**

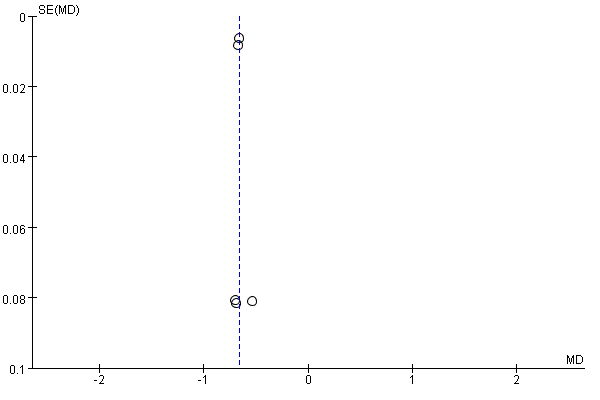
|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Variables** | **dapagliflozin** | | | **metformin** |  |
| **N** | **Total number** |  | **N** | **Total number** |
| **First line therapy (monotherapy)** |  |  |  |  |  |
| **hypoglycemia** | 2 | 219 |  | 6 | 208 |
| **Genital infection** | 28 | 219 |  | 5 | 208 |
| **Urinary infection** | 24 | 219 |  | 9 | 208 |
| **GI side effects** | 14 | 219 |  | 25 | 208 |
| **Serious side effects** | 5 | 219 |  | 4 | 208 |
| **Therapy discontinuation** | 9 | 219 |  | 8 | 208 |
| **Second line therapy (add on SU/TZD/DPP4i)** | | | | | |
| **hypoglycemia** | 12 | 291 |  | 319 | 3011 |
| **Genital infection** | 22 | 291 |  | / | / |
| **Urinary infection** | 15 | 291 |  | 6 | 201 |
| **GI side effects** | 113 | 291 |  | 1056 | 3036 |
| **Serious side effects** | 11 | 291 |  | 62 | 1923 |
| **Therapy discontinuation** | 7 | 291 |  | 303 | 2606 |
| **Third line therapy (add on insulin)** |  |  |  |  |  |
| **hypoglycemia** | 252 | 795 |  | 10 | 325 |
| **Genital infection** | 50 | 795 |  | / | / |
| **Urinary infection** | 49 | 795 |  | / | / |
| **GI side effects** | 236 | 795 |  | 69 | 415 |
| **Serious side effects** | 88 | 795 |  | / | / |
| **Therapy discontinuation** | 70 | 795 |  | 95 | 399 |

**Table S10: The results of univariate sensitivity analyses**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Parameter | Variation | Incremental | | ICER (¥/QALY) |
|  |  | Costs | QALYs |  |
| Baseline |  | 8626 | 0.80 | 10729 |
| Discounting = 0% | Upper | 2047 | 1.30 | 1575 |
| Discounting = 6% | Lower | 3610 | 0.01 | 344903 |
| Time horizon =20 years | Upper | 14639 | 0.58 | 25447 |
| Time horizon =5 years | Lower | 9683 | 0.77 | 12581 |
| Age =60 years | Upper | 11705 | 0.70 | 16765 |
| Age =30 years | Lower | -19709 | 1.64 | -12007 |
| Proportion Female (%)=1 | Upper | 5424 | 0.86 | 6297 |
| Proportion Female (%)=0 | Lower | 12925 | 0.73 | 17673 |
| Current Smoker (%)=1 | Upper | 10641 | 0.80 | 13382 |
| Current Smoker (%)=0 | Lower | 6674 | 0.20 | 34014 |
| HbA1c +25% | Upper | -20563 | 1.04 | -19772 |
| HbA1c -25% | Lower | 32246 | 0.52 | 61672 |
| Total Cholesterol (%) +25% | Upper | 9637 | 0.80 | 12096 |
| Total Cholesterol (%) -25% | Lower | 7568 | 0.81 | 9331 |
| HDL Cholesterol (%) +25% | Upper | 7957 | 0.82 | 9761 |
| HDL Cholesterol (%) -25% | Lower | 9658 | 0.78 | 12307 |
| SBP (mmHg) +25% | Upper | 10820 | 0.77 | 14096 |
| SBP (mmHg) -25% | Lower | 6734 | 0.83 | 8087 |
| Weight (kg) +25% | Upper | -20563 | 1.04 | -19772 |
| Weight (kg) -25% | Lower | 68437 | 0.85 | 80188 |
| HbA1c Treatment Effect (%) +25% | Upper | 10882 | 0.76 | 14321 |
| HbA1c Treatment Effect (%) -25% | Lower | 8933 | 0.80 | 11099 |
| Weight Treatment Effect (kg) +25% | Upper | 53621 | 2.92 | 18379 |
| Weight Treatment Effect (kg) -25% | Lower | 27679 | 1.77 | 15614 |
| Non-severe Hypoglycemia Rate +25% | Upper | 8626 | 0.81 | 10692 |
| Non-severe Hypoglycemia Rate -25% | Lower | 8626 | 0.80 | 10766 |
| Severe Hypoglycaemia Rates +25% | Upper | 8461 | 0.81 | 10499 |
| Severe Hypoglycaemia Rates -25% | Lower | 8790 | 0.80 | 10960 |
| Adverse Event Rates +25% | Upper | 8722 | 0.79 | 10975 |
| Adverse Event Rates -25% | Lower | 8529 | 0.81 | 10489 |
| Event Costs +25% | Upper | 9333 | 0.80 | 11608 |
| Event Costs -25% | Lower | 7919 | 0.80 | 9849 |
| BMI Costs +25% | Upper | -5653 | 0.80 | -7032 |
| BMI Costs -25% | Lower | 22905 | 0.80 | 28489 |
| Baseline Utility +25% | Upper | 8626 | 0.82 | 10472 |
| Baseline Utility -25% | Lower | 8626 | 0.78 | 10998 |
| Event Disutility +25% | Upper | 8626 | 0.80 | 10803 |
| Event Disutility -25% | Lower | 8626 | 0.81 | 10656 |
| BMI Utility +25% (0.0214; 0.059) | Upper | 8626 | 1.00 | 8625 |
| BMI Utility -25% (0.0128; 0.0354) | Lower | 8626 | 0.62 | 14022 |
| Scenario analysis: |  | Costs | QALYs | ICER (¥/QALY) |
| BMI utility=0.0061; 0.0061 |  | 8626 | 0.19 | 45548 |
| Base case analysis | Utility Decrement | +25% | -25% |  |
| Per unit decrease in BMI | 0.0171 | 0.0214 | 0.0128 |  |
| Per unit increase in BMI | 0.0472 | 0.059 | 0.0354 |  |
|  |  |  |  |  |

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**Figure S1: Funnel plot of included studies with metformin treatment**

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**Figure S2: Funnel plot of included studies with dapagliflozin treatment**

**Supplement Methods:**

***1. Search Strategy and Inclusion Criteria***

The databases of the MEDLINE and the Cochrane Library Central Register of Controlled Trials were searched in December 2016 and updated in July 2017. Randomized clinical trials publicly available before July 2017, comparing dapagliflozin treatment with placebo or active anti-diabetes drugs as monotherapy or add-on therapy as well as metformin treatment with placebo or active anti-diabetes drugs as monotherapy or add-on therapy in type 2 diabetes patients were identified. The search terms were: type 2 diabetes, sodium-glucose cotransporter 2 inhibitors, dapagliflozin, biguides, metformin, and randomized controlled trials.

The inclusion criteria were as follows: (1) placebo-controlled or active anti-diabetes drugs controlled trial of dapagliflozin treatment, (2) placebo-controlled or active anti-diabetes drugs controlled trial of metformin treatment, (3) type 2 diabetes participants, (4) the efficacy of glucose control was the primary outcome of the study, and (5) randomized controlled trials.

The exclusion criteria were as follows: (1) nonrandomized trial or observational study, (2) trials in type 1 diabetes, (3) the efficacy of glucose control was not the primary endpoint of the trial.

Two investigators (XYG and WJY) screened the titles and abstracts independently to identify potentially eligible trials. Then, relevant citation was evaluated in full-text. The two investigators independently reviewed the main reports and supplementary materials, and extracted study and patient characteristics and treatment strategies. The quality of each study and the risk of bias were evaluated using the Cochrane instrument.

***2. Endpoints***

The primary endpoint of this meta-analysis was absolute HbA1c change from baseline after dapagliflozin treatment and metformin treatment in type 2 diabetes patients.

The secondary endpoints were (1) absolute weight changes from baseline after dapagliflozin treatment and after metformin treatment; (2) absolute systolic blood pressure (SBP) changes from baseline after dapagliflozin treatment and after metformin treatment; (3) absolute total cholesterol (TCHO) changes from baseline after dapagliflozin treatment and after metformin treatment; (4) the risks of adverse effects including hypoglycemia, genital infection, urinary infection, gastrointestinal side effects and therapy discontinuation after dapagliflozin treatment and after metformin treatment.

***3 Statistical Analysis***

Treatment effects were estimated by random-effects or fixed-effects pairwise meta-analysis. The results were shown in the weighted mean difference (WMD) for HbA1c level, blood pressure level, lipid profile levels and body weight, and in the odds ratios (ORs) for all the adverse events and hypoglycemia, together with 95% confidence intervals (95% CI). Higgins *I*2 statistics were used to quantify the percentage of the total variance in the summary estimate due to between-study heterogeneity. Publication bias was assessed via a funnel plot vision. Statistical testing was two-sided, with P<0.05 considered statistically significant. Statistical analyses were performed with the STATA statistical software package (Version 11.0). This meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for conducting and reporting meta-analyses of randomized controlled trials (RCTs).

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