## SUPPLEMENTARY MATERIAL

## Table S1: Criteria for judging risk of bias using the Cochrane Collaboration Risk of Bias Tool [a]

| Bias | Judgment | Criteria |
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| **RANDOM SEQUENCE GENERATION**<br><br>**Selection bias (biased allocation to interventions) due to inadequate generation of a randomised sequence.** | 'Low risk' of bias. | The investigators describe a random component in the sequence generation process such as:<br><br>Referring to a random number table;<br><br>Using a computer random number generator;<br><br>Coin tossing;<br><br>Shuffling cards or envelopes;<br><br>Throwing dice;<br><br>Drawing of lots;<br><br>Minimization*.<br><br>*Minimization may be implemented without a random element, and this is considered to be equivalent to being random. |
| | 'High risk' of bias. | The investigators describe a non-random component in the sequence generation process. Usually, the description would involve some systematic, non-random approach, for example:<br><br>Sequence generated by odd or even date of birth;<br><br>Sequence generated by some rule based on date (or day) of admission;<br><br>Sequence generated by some rule based on hospital or clinic record number.<br><br>Other non-random approaches happen much less frequently than the systematic approaches mentioned above and tend to be obvious. They usually involve judgement or some method of non-random categorization of participants, for example:<br><br>Allocation by judgement of the clinician;<br><br>Allocation by preference of the participant;<br><br>Allocation based on the results of a laboratory test or a series of tests;<br><br>Allocation by availability of the intervention. |
| | 'Unclear risk' of bias. | Insufficient information about the sequence generation process to permit judgement of 'Low risk' or 'High risk'. |
| **ALLOCATION CONCEALMENT**<br><br>**Selection bias (biased allocation to interventions)** | 'Low risk' of bias. | Participants and investigators enrolling participants could not foresee assignment because one of the following, or an equivalent method, was used to conceal allocation:<br><br>Central allocation (including telephone, web-based and pharmacy-controlled randomization); |

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| **due to inadequate concealment of allocations prior to assignment.** | | Sequentially numbered drug containers of identical appearance;<br><br>Sequentially numbered, opaque, sealed envelopes. |
| | 'High risk' of bias. | Participants or investigators enrolling participants could possibly foresee assignments and thus introduce selection bias, such as allocation based on:<br><br>Using an open random allocation schedule (e.g. a list of random numbers);<br><br>Assignment envelopes were used without appropriate safeguards (e.g. if envelopes were unsealed or nonopaque or not sequentially numbered);<br><br>Alternation or rotation;<br><br>Date of birth;<br><br>Case record number;<br><br>Any other explicitly unconcealed procedure. |
| | 'Unclear risk' of bias. | Insufficient information to permit judgement of 'Low risk' or 'High risk'. This is usually the case if the method of concealment is not described or not described in sufficient detail to allow a definite judgement – for example if the use of assignment envelopes is described, but it remains unclear whether envelopes were sequentially numbered, opaque and sealed. |
| **SELECTIVE REPORTING**<br><br>**Reporting bias due to selective outcome reporting.** | 'Low risk' of bias. | Any of the following:<br><br>The study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way;<br><br>The study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified (convincing text of this nature may be uncommon). |
| | 'High risk' of bias. | Any one of the following:<br>Not all of the study's pre-specified primary outcomes have been reported;<br>One or more primary outcomes is reported using measurements, analysis methods or subsets of the data (e.g. subscales) that were not pre-specified;<br>One or more reported primary outcomes were not pre-specified (unless clear justification for their reporting is provided, such as an unexpected adverse effect);<br>One or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis;<br>The study report fails to include results for a key outcome that would be expected to have been reported for such a study. |
| | 'Unclear risk' of bias. | Insufficient information to permit judgement of 'Low risk' or 'High risk'. It is likely that the majority of studies will fall into this category. |
| **OTHER BIAS**<br>**Bias due to problems not covered elsewhere in the table.** | 'Low risk' of bias. | The study appears to be free of other sources of bias. |
| | 'High risk' | There is at least one important risk of bias. For example, the study:<br>Had a potential source of bias related to the specific study design used; |

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| | of bias. | or<br>Has been claimed to have been fraudulent; or<br>Had some other problem. |
| | 'Unclear risk' of bias. | There may be a risk of bias, but there is either:<br>Insufficient information to assess whether an important risk of bias exists; or<br>Insufficient rationale or evidence that an identified problem will introduce bias. |
| **BLINDING OF PARTICIPANTS AND PERSONNEL**<br>**Performance bias due to knowledge of the allocated interventions by participants and personnel during the study.** | 'Low risk' of bias. | Any one of the following:<br>No blinding or incomplete blinding, but the review authors judge that the outcome is not likely to be influenced by lack of blinding;<br>Blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken. |
| | 'High risk' of bias. | Any one of the following:<br>No blinding or incomplete blinding, and the outcome is likely to be influenced by lack of blinding;<br>Blinding of key study participants and personnel attempted, but likely that the blinding could have been broken, and the outcome is likely to be influenced by lack of blinding. |
| | 'Unclear risk' of bias. | Any one of the following:<br>Insufficient information to permit judgment of 'Low risk' or 'High risk';<br>The study did not address this outcome. |
| **BLINDING OF OUTCOME ASSESSMENT**<br>**Detection bias due to knowledge of the allocated interventions by outcome assessors.** | | Any one of the following: |
| | 'Low risk' of bias. | No blinding of outcome assessment, but the review authors judge that the outcome measurement is not likely to be influenced by lack of blinding;<br>Blinding of outcome assessment ensured, and unlikely that the blinding could have been broken. |
| | 'High risk' of bias. | Any one of the following:<br>No blinding of outcome assessment, and the outcome measurement is likely to be influenced by lack of blinding;<br>Blinding of outcome assessment, but likely that the blinding could have been broken and the outcome measurement is likely to be influenced by lack of blinding. |
| | 'Unclear risk' of bias. | Any one of the following:<br>Insufficient information to permit judgment of 'Low risk' or 'High risk';<br>The study did not address this outcome. |
| **INCOMPLETE OUTCOME DATA**<br>**Attrition bias due to amount, nature or handling of incomplete outcome data.** | 'Low risk' of bias. | Any one of the following:<br>No missing outcome data;<br>Reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias);<br>Missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups;<br>For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk not enough to have a clinically relevant impact on the intervention effect estimate;<br>For continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes not enough to have a clinically relevant impact on observed effect size;<br>Missing data have been imputed using appropriate methods. |
| | 'High risk' of bias. | Any one of the following:<br>Reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups;<br>For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate;<br>For continuous outcome data, plausible effect size (difference in means |

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| | or standardized difference in means) among missing outcomes enough to induce clinically relevant bias in observed effect size;<br>'As-treated' analysis done with substantial departure of the intervention received from that assigned at randomization;<br>Potentially inappropriate application of simple imputation. |
| 'Unclear risk' of bias. | Any one of the following:<br>Insufficient reporting of attrition/exclusions to permit judgement of 'Low risk' or 'High risk' (e.g. number randomized not stated, no reasons for missing data provided);<br>The study did not address this outcome. |

**Note:** [a] Adapted from the Cochrane Collaboration Risk of Bias Tool. See Higgins JP, Altman DG, Sterne JA. Chapter 8: Assessing the risk of bias in included studies. In: Higgins JP, Green S, eds. Cochrane handbook for systematic reviews of interventions. The Cochrane Collaboration; 2011.

**Table S2: The standard doses in the clinical practice documented in the included trials**

| Anti-diabetes drugs | Daily dose |
|---|---|
| Metformin | 1500~2000 mg |
| Glyburide | 7.5 mg |
| Nateglinide | 360 mg |
| Rosiglitazone | 8 mg |
| Pioglitazone | 30 mg |
| Sitagliptin | 100 mg |
| Vildagliptin | 100 mg |
| Saxagliptin | 5 mg |
| Alogliptin | 25 mg |
| Linagliptin | 5 mg |
| Tenegliptin | 20 mg |
| Dapagliflozine | 10 mg |
| Canagliflozine | 300 mg |
| Empagliflozine | 25 mg |

**Table S3: Definitions for drug-naïve patients of the studies included in this meta-analysis**

| Author , year | Definitions for drug-naïve patients |
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| **DPP-4 inhibitors + metformin initial combination therapy vs. metformin monotherapy** | |
| Dou, 2017 | Pharmacotherapy-naïve Chinese patients with type 2 diabetes Treatment-naive adults were defined as inadequately controlled by diet and exercise. |
| Jadzinsky, 2009 | Patients had to be treatment naive, defined as never having received medical treatment for diabetes or having received medical treatment for diabetes for a total period of <1 month since original diagnosis and not having received antihyperglycaemic therapy for more than three consecutive days or for a total of seven non-consecutive days during 8 weeks before screening. |
| Bosi, 2009 | 'Treatment naive' was defined as those patients who had never received an antidiabetic agent or had not taken any antidiabetic agent for 12 weeks before screening and for no longer than 3 months at any time. |
| Goldstein, 2007 | Patients with type 2 diabetes, who were either on or not on an OHA at the screening visit were eligible to participate. The percentage of patients absent of OHAs used: 50%, 50.8%, 50%, 49.5%, 53.7%, 48.4% in each group. |
| Ji, 2016 | Patients with type 2 diabetes who had inadequate glycemic control with diet and exercise alone, or while on a single oral AHA other than a thiazolidinedione (HbA1c ≥7.0 and ≤10.5%) or on low dose combination AHA (i.e., ≤50% maximum labeled dose of each agent).<br>The percentage of patients who were drug-naïve, 91.3%, 90%, 91.3%, 87.9%, 88.5%, 88.8% in each group. |
| Olansky, 2011 | Drug-na¨ıve, defined as not on AHA therapy within the 4 months (or longer) preceding the screening visit |
| Reasner, 2011 | Drug-na¨ıve, defined as not on AHA therapy within the 4 months (or longer) preceding the screening visit |
| Williams-Herman, 2009 | Patients with type 2 diabetes who were on or not on an oral AHA at the screening visit were eligible to participate. The percentage of patients absent of OHAs used: 50%, 50.8%, 50%, 49.5%, 53.7%, 48.4% in each group. |
| Pratley, 2014 | Study participants were inadequately controlled T2DM following diet/exercise therapy alone for at least 2 months prior to screening; had taken fewer than 7 days of any antidiabetic medication within 2months of screening. |
| JI, 2017 | Diagnosis of type 2 diabetes for which glycaemic control was inadequate (ie, HbA1c of 7.5%-10.0% after at least 2 months of diet and exercise alone prior to the screening period). |
| Haak,2012 | Patients were either treatment-na¨ıve or had been treated with not more than one OAD (which had to be unchanged for 10 weeks prior to enrolment). |

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| | Of the total study population, 47.5% of patients were treatment-na¨ıve prior to enrolment. |
| Mu, 2016 | Drug-naı ¨ve, defined as patients had never received any antidiabetes drugs (or <30 cumulative days of antidiabetes therapy 12 weeks prior to randomization and no antidiabetes therapy within these 12 weeks) |
| Ji, 2015 | Patients were drug-naı¨ve, defined as an absence of any oral or injectable antihyperglycemic therapies for ≧12 weeks before randomization. |
| Pfutzner, 2011 | Patients also had to be treatment naı¨ve, defined as never having received medical treatment for diabetes or having received medical treatment for diabetes for a total period of <1 month since original diagnosis and not having received antihyperglycaemic therapy for more than three consecutive days or for a total of seven non-consecutive days during 8 weeks before screening. |
| Williams-Herman, 2010 | Patients with type 2 diabetes who were on or not on an oral AHA at the screening visit were eligible to participate. The percentage of patients absent of OHAs used: 50%, 50.8%, 50%, 49.5%, 53.7%, 48.4% in each group. |
| **Sulfonylurea + metformin initial combination therapy vs metformin monotherapy** | |
| Garber, 2002 | Type 2 diabetes and inadequate control (HbA1c>7.0%) with diet and exercise alone |
| Garber, 2003 | Patients with type 2 diabetes who were inadequately controlled (A1C, >7% and ≦12%) with diet and exercise treatment alone |
| **Glinide + metformin initial combination therapy vs metformin monotherapy** | |
| Horton, 2000 | Patients had T2DM diagnosed at least 3 months previously, and were treated with diet and exercise for at least 4 weeks before entering a 4-week. In addition, all oral hypoglycemic agents had to be discontinued for at least 4 weeks before placebo run-in. |
| **TZD + metformin initial combination therapy vs metformin monotherapy** | |
| Rosenstock, 2006 | Patients on diet and exercise alone were screened. Patients were not permitted to take more than a short term course of antidiabetic medication (≦15 days) for 12 weeks prior to screening. |
| Perez, 2009 | Patients were treatment-naı¨ve (had not received treatment with antidiabetic medication in the 12 weeks prior to screening other than short-term use of ≦15 days) |
| Stewart, 2006 | Subjects must have been drug naı¨ve or treated with glucose-lowering monotherapy. Pre-study diabetes treatment: Diet and exercise alone40%, Oral glucose-lowering monotherapy 60% |
| Borges, 2011 | Treatment-naı¨ve was defined as current treatment was to be limited to diet and exercise, and the patient should not have taken more than 2 weeks of an antidiabetic monotherapy or insulin in the past 6 months. |

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| **SGLT2 inhibitors + metformin initial combination therapy vs metformin monotherapy** | |
| Rosenstock, 2016 | Eligible patients were drug-na¨ıve type 2 diabetes patients (i.e., not on AHA therapy or off for ≧12 weeks before screening) inadequately controlled with diet and exercise |
| Henry, 2012-1 | Type 2 diabetes uncontrolled by diet and exercise |
| Henry, 2012-2 | Type 2 diabetes uncontrolled by diet and exercise |
| Hadjadj, 2016 | Drug-na¨ıve (no oral antidiabetes therapy, glucagon-like peptide-1 analog, or insulin for ≧12 weeks before randomization) |
| **DPP-4 inhibitors + TZD initial combination therapy vs TZD monotherapy** | |
| Gomis, 2011 | Study enrolled drug-na¨ıve or previously treated T2DM patients with insufficient glycaemic control |
| | Number of prior antidiabetic drugs, no drugs placebo group (50.8%), initial combine group (49.2%) |
| Henry, 2014 | Either drug-na¨ıve or taking metformin or sulphonylurea monotherapy at screening |
| Rosenstock, 2007 | Patients receiving no pharmacological treatment for at least 12 weeks prior to screening and no OAD for more than three consecutive months at any time in the past. |
| Rosenstock, 2010 | Eligible subjects were drug-naı¨ve (no current antihyperglycemic medication or ≦6 days of any such agent within 3 months of screening) men and women |
| Yoon, 2011 | Patients with type 2 diabetes who were not being treated with an oral antihyperglycemic agent (AHA) prior to screening (and with < 4 weeks cumulative prior treatment with an AHA in the prior 2 years, and none within 4 months of the screening visit) |
| Yoon, 2012 | Patients with T2DM who were not being treated with an AHA prior to screening (and with <4 weeks cumulative prior treatment with an AHA in the prior 2 years, and none within 4 months of the screening visit) |
| **DPP-4 inhibitors + TZD initial combination therapy vs DPP-4 inhibitors monotherapy** | |
| Henry, 2014 | Either drug-na¨ıve or taking metformin or sulphonylurea monotherapy at screening |
| | The percentage of patients who received an oral AHA within 8 weeks prior to screening: 14.5%,15.3%,12.9%,14.4%,14.0%,13.7%,12.1% |
| Rosenstock, 2007 | Patients receiving no pharmacological treatment for at least 12 weeks prior to screening and no OAD for more than three consecutive months at any time in the past. |
| Rosenstock, 2010 | Eligible subjects were drug-naı¨ve (no current antihyperglycemic medication or ≦6 days of any such agent within 3 months of screening) men and |

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| | women. |
| **SGLT2 inhibitors + metformin initial combination therapy vs SGLT2 inhibitors monotherapy** | |
| Rosenstock, 2016 | Eligible patients were ≧18 and <75 years of age with drug-na¨ıve type 2 diabetes (i.e., not on AHA therapy or off for ≧12 weeks before screening) that was inadequately controlled with diet and exercise |
| Henry, 2012-1 | Type 2 diabetes uncontrolled by diet and exercise |
| Henry, 2012-2 | Type 2 diabetes uncontrolled by diet and exercise |
| Hadjadj, 2016 | Drug-na¨ıve (no oral antidiabetes therapy, glucagon-like peptide-1 analog, or insulin for ≧12 weeks before randomization) |
| **DPP-4 inhibitors + metformin initial combination therapy vs DPP-4 inhibitors monotherapy** | |
| Dou, 2017 | Pharmacotherapy-naïve Chinese patients with type 2 diabetes Treatment-naive adults were defined as inadequately controlled by diet and exercise. |
| Jadzinsky, 2009 | Patients had to be treatment naı¨ve, defined as never having received medical treatment for diabetes or having received medical treatment for diabetes for a total period of <1 month since original diagnosis and not having received antihyperglycaemic therapy for more than three consecutive days or for a total of seven non-consecutive days during 8 weeks before screening. |
| Bosi, 2009 | 'Treatment naive' was defined as those patients who had never received an antidiabetic agent or had not taken any antidiabetic agent for 12 weeks before screening and for no longer than 3 months at any time. |
| Goldstein, 2007 | Patients with type 2 diabetes, 18–78 years of age, who were either on or not on an OHA at the screening visit were eligible to participate.<br>The percentage of patients absent of OHAs used: 50%, 50.8%, 50%, 49.5%, 53.7%, 48.4% in each group. |
| Ji, 2016 | Patients with type 2 diabetes who had inadequate glycemic control with diet and exercise alone, or while on a single oral AHA other than a thiazolidinedione (HbA1c ≥7.0 and ≤10.5%) or on low dose combination AHA (i.e., ≤50% maximum labeled dose of each agent).<br>The percentage of patients who were drug-naïve, 91.3%, 90%, 91.3%, 87.9%, 88.5%, 88.8% in each group. |
| Williams-Herman, 2009 | Patients with type 2 diabetes, 18–78 years of age, who were either on or not on an OHA at the screening visit were eligible to participate.<br>The percentage of patients absent of OHAs used: 50%, 50.8%, 50%, 49.5%, 53.7%, 48.4% in each group. |
| Pratley, 2014 | Study participants were inadequately controlled T2DM following diet/exercise therapy alone for at least 2 months prior to screening; had taken fewer than 7 days of any antidiabetic medication within 2months of |

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| | screening. |
| JI, 2017 | Diagnosis of type 2 diabetes for which glycaemic control was inadequate (ie, HbA1c of 7.5%-10.0% after at least 2 months of diet and exercise prior to the screening period). |
| Haak,2014 | Patients were either treatment-na¨ıve or had been treated with not more than one OAD (which had to be unchanged for 10 weeks prior to enrolment).<br><br>Of the total study population, 47.5% of patients were treatment-na¨ıve prior to enrolment. |
| Mu, 2016 | Drug-naı ¨ve, defined as patients had never received any antidiabetes drugs (or <30 cumulative days of antidiabetes therapy 12 weeks prior to randomization and no antidiabetes therapy within these 12 weeks) |
| Pfutzner, 2011 | Patients had to be treatment naı¨ve, defined as never having received medical treatment for diabetes or having received medical treatment for diabetes for a total period of <1 month since original diagnosis and not having received antihyperglycaemic therapy for more than three consecutive days or for a total of seven non-consecutive days during 8 weeks before screening. |
| Williams-Herman, 2010 | Patients with type 2 diabetes, 18–78 years of age, who were either on or not on an OHA at the screening visit were eligible to participate.<br><br>The percentage of patients absent of OHAs used: 50%, 50.8%, 50%, 49.5%, 53.7%, 48.4% in each group. |
| Ross, 2015 | Patients had not received any glucose-lowering drug in the previous 12 weeks, |
| **TZD + metformin initial combination therapy vs TZD monotherapy** | |
| Rosenstock, 2006 | Patients on diet and exercise alone were screened, Patients were not permitted to take more than a short term course of antidiabetic medication (≦15 days) for 12 weeks prior to screening. |
| Perez, 2009 | Patients were treatment-naı¨ve (had not received treatment with antidiabetic medication in the 12 weeks prior to screening other than short-term use of ≦15 days) |
| **Sulfonylurea/Glinide + metformin initial combination therapy vs metformin monotherapy** | |
| Garber, 2002 | Type 2 diabetes and inadequate control (HbA1c>7.0%) with diet and exercise |
| Garber, 2003 | Patients with type 2 diabetes who were inadequately controlled (A1C, >7% and ≦12%) with diet and exercise treatment alone |
| Horton, 2004 | Patients had T2DM diagnosed at least 3 months previously, and were treated with diet and exercise for at least 4 weeks before entering a 4-week. In addition, all oral hypoglycemic agents had to be discontinued for at least 4 weeks before placebo run-in. |
| **Sulfonylurea/Glinide + AGI initial combination therapy vs AGI monotherapy** | |

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| Tatsumi, 2013 | Patients undergoing dietary/exercise therapy with or without metformin |
| **Sulfonylurea/Glinide + AGI initial combination therapy vs Sulfonylurea/Glinide monotherapy** | |
| Tatsumi, 2013 | Patients undergoing dietary/exercise therapy with or without metformin |
| **Sulfonylurea/Glinide + TZD initial combination therapy vs TZD monotherapy** | |
| Chou,2008 | Patients who had been treated with diet and/or exercise alone or who had not taken oral antidiabetic medication or insulin for >15 days in the preceding 4 months. |
| **Sulfonylurea/Glinide + TZD initial combination therapy vs Sulfonylurea/Glinide monotherapy** | |
| Chou,2008 | Patients who had been treated with diet and/or exercise alone or who had not taken oral antidiabetic medication or insulin for >15 days in the preceding 4 months. |
| **DPP-4 inhibitors + metformin initial combination therapy vs TZD monotherapy** | |
| Wainstein,2012 | Patients were not to have been on an AHA in the 3 months prior to the screening visit and were to have had less than 4 weeks of cumulative duration of treatment with an AHA over the 3 years prior to the screening visit. |
| **DPP-4 inhibitors + metformin initial combination therapy vs SU monotherapy** | |
| Amblee, 2016 | Patients with new-onset T2DM (≦1 y duration), either drug naïve or no diabetes medications taken longer than 2 weeks |
| **Colesvelam + metformin initial combination therapy vs metformin monotherapy** | |
| Rosenstock, 2010 | All patients were drug-naïve, defined as never having received antidiabetes treatment or not having received treatment for ≥3 months before screening. |
| **DPP-4 inhibitors + AGI initial combination therapy vs AGI monotherapy** | |
| Mikada, 2014 | Patients undergoing diet and exercise therapies with or without one of the following medications: metformin at a dose of 2250 mg daily or less; low-dose sulfonylurea (glimepiride 2 mg daily or less, glibenclamide 1.25 mg daily or less, gliclazide 40 mg daily or less) with an HbA1c ≧ 7.4%. Switching from therapy including other drugs mentioned above was allowed after the sufficient washout period (at least 2 months). |
| **DPP-4 inhibitors + AGI initial combination therapy vs DPP4i monotherapy** | |
| Mikada, 2014 | Patients undergoing diet and exercise therapies with or without one of the following medications: metformin at a dose of 2250 mg daily or less; low-dose sulfonylurea (glimepiride 2 mg daily or less, glibenclamide 1.25 mg daily or less, gliclazide 40 mg daily or less) with an HbA1c ≧ 7.4%. Switching from therapy including other drugs mentioned above was allowed after the sufficient washout period (at least 2 months). |
| **SGLT2 inhibitors + DPP4 inhibitors initial combination therapy vs SGLT2 inhibitors monotherapy** | |

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| Lewin 2015 | Patients at screening despite a diet and exercise regimen had not received treatment with oral antidiabetes therapy, GLP-1 analog, or insulin for >12 weeks prior to randomization. |
| **SGLT2 inhibitors + DPP4 inhibitors initial combination therapy vs DPP4 inhibitors monotherapy** | |
| Lewin 2015 | Patients at screening despite a diet and exercise regimen had not received treatment with oral antidiabetes therapy, GLP-1 analog, or insulin for >12 weeks prior to randomization. |
| **Triple initial combination therapy vs convention therapy** | |
| Abdul-Ghani, 2015 | drug-naïve patients and recently diagnosed (<2 years) according to ADA criteria |

**Table S4: Meta-regression analysis of the association between baseline HbA1c and HbA1c changes of initial combination therapy compared with monotherapy**

| Treatment group | coefficient | 95%CI | p |
|---|---|---|---|
| DPP-4 inhibitors + MET vs MET | -0.41 | -3.54, 2.73 | 0.774 |
| DPP-4 inhibitors + MET vs DPP-4 inhibitors | -0.76 | -7.89, 6.37 | 0.782 |
| SU/Glinide + MET vs MET | -1.63 | -55.04, 51.78 | 0.764 |
| SU/Glinide + MET vs SU/Glinide | 2.64 | -90.13, 95.41 | 0.779 |
| TZD + MET vs MET | -0.40 | -3.00, 2.19 | 0.575 |
| TZD + MET vs TZD | / | / | / |
| SGLT2 inhibitors + MET vs MET | -2.65 | -28.81, 23.50 | 0.705 |
| SGLT2 inhibitors + MET vs SGLT2 inhibitors | 0.99 | -10.29, 8.31 | 0.693 |
| DPP-4 inhibitors + TZD vs TZD | 2.57 | -4.67, 9.81 | 0.341 |
| DPP-4 inhibitors + TZD vs DPP-4 inhibitors | / | / | / |
| Total | -2.98 | -5.32, -0.63 | 0.014 |

Meta-regression analysis was made to evaluate whether the baseline HbA1c was associated with HbA1c changes of initial combination therapy corrected by monotherapy. If the coefficient was positive, that means the baseline HbA1c was positively associated with HbA1c changes. P value less than 0.05 was considered to be with significance.

**Table S5: Comparisons of HbA1c changes between initial combination therapy and monotherapy stratified by study time periods**

| Comparison group | Included studies | No. of patients | WMD | 95% CI |
|---|---|---|---|---|
| **DPP-4 inhibitors + MET vs DPP-4 inhibitors** | | | | |
| Total | 10 | 1967/1951 | -0.88 | -0.99,-0.78 |
| 24 weeks | 10 | 1967/1951 | -0.88 | -0.99,-0.78 |
| **DPP-4 inhibitors + MET vs MET** | | | | |
| Total | 11 | 3379/3375 | -0.44 | -0.57, -0.31 |
| 24 weeks | 10 | 2754/2754 | -0.43 | -0.56,-0.29 |
| **SU/Glinide + MET vs MET** | | | | |
| Total | 3 | 425/429 | -0.68 | -0.86, -0.50 |
| 24 weeks | 1 | 89/104 | -0.80 | -0.83, -0.77 |
| **SU/Glinide + MET vs SU/Glinide** | | | | |
| Total | 3 | 425/416 | -0.49 | -0.77,-0.20 |
| 24 weeks | 1 | 89/104 | -0.80 | -0.83, -0.77 |
| **TZD + MET vs MET** | | | | |
| Total | 4 | 954/970 | -0.44 | -0.68, -0.19 |
| 24 weeks | 1 | 201/210 | -0.84 | -0.92, -0.76 |
| **TZD + MET vs TZD** | | | | |
| Total | 2 | 356/348 | -0.83 | -0.97,-0.68 |
| 24 weeks | 1 | 201/189 | -0.87 | -0.95, -0.79 |
| **SGLT2 inhibitors + MET vs MET** | | | | |
| Total | 3 | 978/974 | -0.47 | -0.58, -0.37 |
| 24 weeks | 3 | 978/974 | -0.47 | -0.58, -0.37 |
| **SGLT2 inhibitors + MET vs SGLT2 inhibitors** | | | | |
| Total | 3 | 978/989 | -0.64 | -0.84,-0.43 |
| 24 weeks | 3 | 978/989 | -0.64 | -0.84,-0.43 |
| **DPP-4 inhibitors + TZD vs TZD** | | | | |
| Total | 6 | 1577/1431 | -0.54 | -0.65,-0.44 |
| 24 weeks | 4 | 832/713 | -0.56 | -0.75, -0.38 |
| **DPP-4 inhibitors + TZD vs DPP-4 inhibitors** | | | | |
| Total | 3 | 502/504 | -0.62 | -0.75,-0.48 |
| 24 weeks | 2 | 312/318 | -0.68 | -0.82, -0.53 |

**Figure S1: Risk of bias evaluation of included studies (Criteria for judging risk of bias was explained in Table S1)**

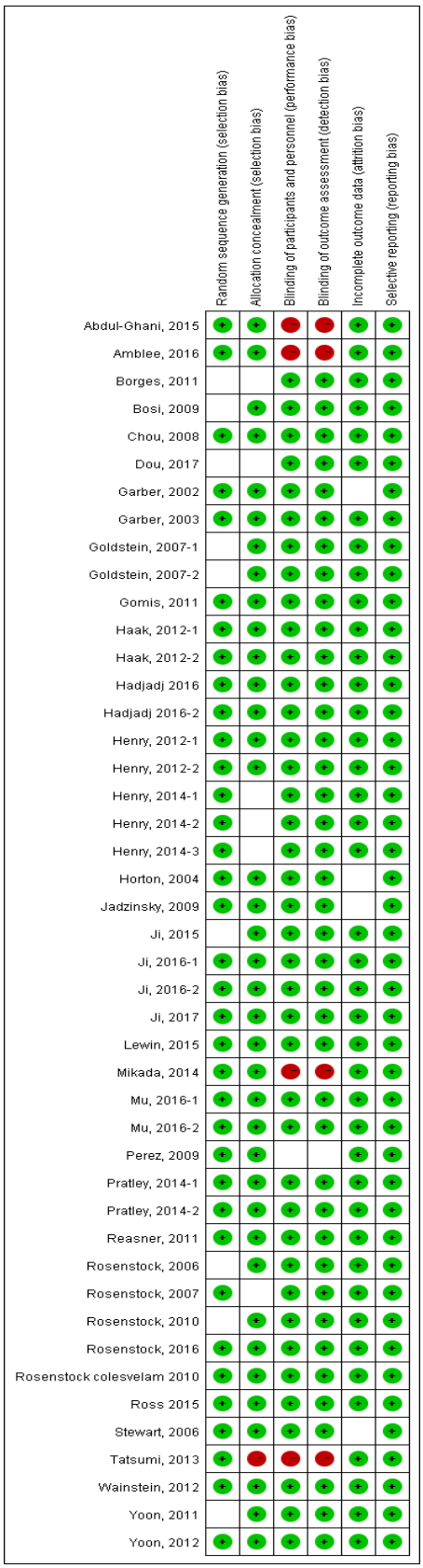


**Figure S2：Funnel plots**

**Figure S2-A: DPP-4 inhibitors + metformin initial combination therapy vs metformin monotherapy; Figure S2-B: DPP-4 inhibitors + metformin initial combination therapy vs DPP-4 inhibitors monotherapy; Figure S2-C: Sulfonylurea /Glinide + metformin initial combination therapy vs metformin monotherapy; Figure S2-D: Sulfonylurea/Glinide + metformin initial combination therapy vs Sulfonylurea /Glinide monotherapy; Figure S2-E：TZD + metformin initial combination therapy vs metformin monotherapy; Figure S2-F：TZD + metformin initial combination therapy vs TZD monotherapy; Figure S2-G：SGLT2 inhibitors + metformin initial combination therapy vs metformin monotherapy; Figure S2-H：SGLT2 inhibitors + metformin initial combination therapy vs SGLT2 inhibitors monotherapy; Figure S2-I：DPP-4 inhibitors + TZD initial combination therapy vs TZD monotherapy; Figure S2-J：DPP-4 inhibitors + TZD initial combination therapy vs DPP-4 inhibitors monotherapy.**

**Explanation for a funnel plot**

A funnel plot is a scatter plot of individual studies, their precision and results. Each dot represents a single study. Larger studies with higher power are placed towards the top. Lower powered studies are placed towards the bottom. The plot should ideally resemble a pyramid or inverted funnel, with scatter due to sampling variation. The shape is expected because the studies have a wide range of standard errors. If the standard errors were the same size, the studies would all fall on a horizontal line. (**Reference:** Sedgwick, P. Meta-analyses: how to read a funnel plot. BMJ 2013; 346: f1342.)

**Figure S2-A: DPP-4 inhibitors + metformin initial combination therapy vs metformin monotherapy**

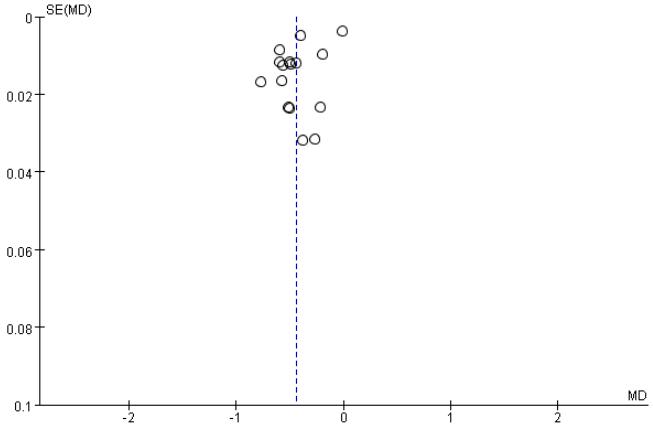



**Figure S2-B: DPP-4 inhibitors + metformin initial combination therapy vs DPP-4 inhibitors monotherapy**

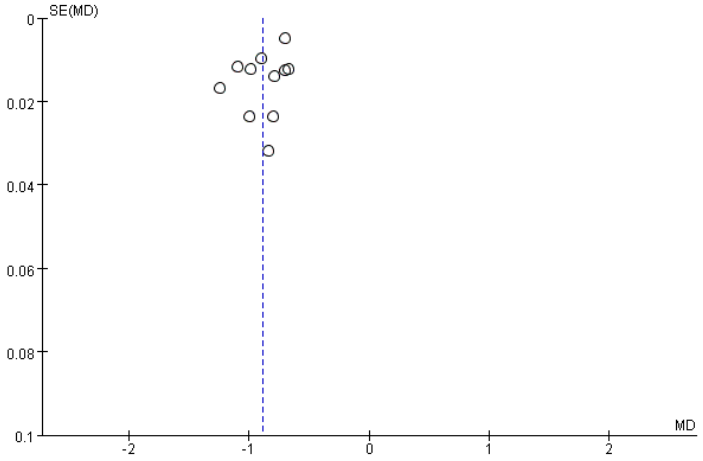



**Figure S2-C: Sulfonylurea /Glinide + metformin initial combination therapy vs metformin monotherapy**

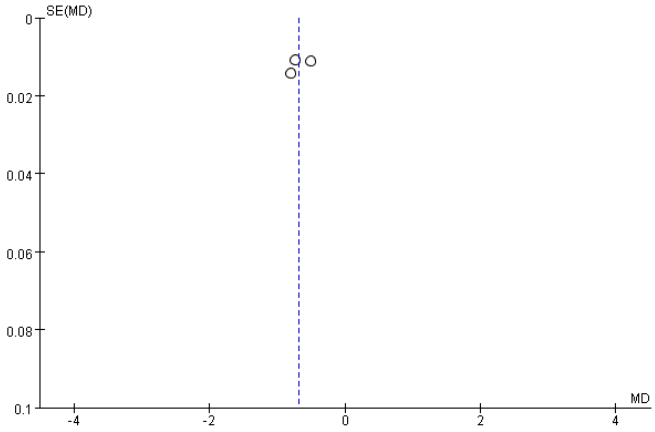



**Figure S2-D: Sulfonylurea/Glinide + metformin initial combination therapy vs Sulfonylurea /Glinide monotherapy**

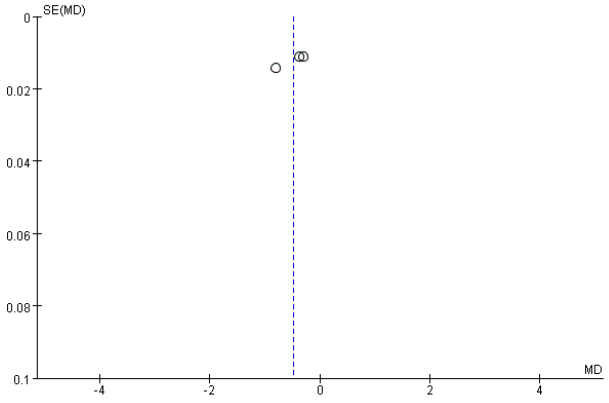



**Figure S2-E: TZD + metformin initial combination therapy vs metformin monotherapy**

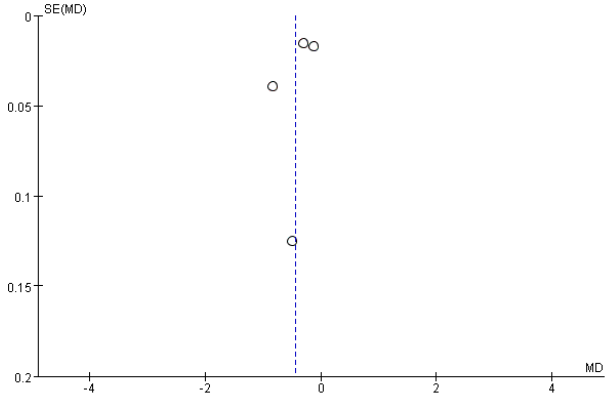



**Figure S2-F: TZD + metformin initial combination therapy vs TZD monotherapy**

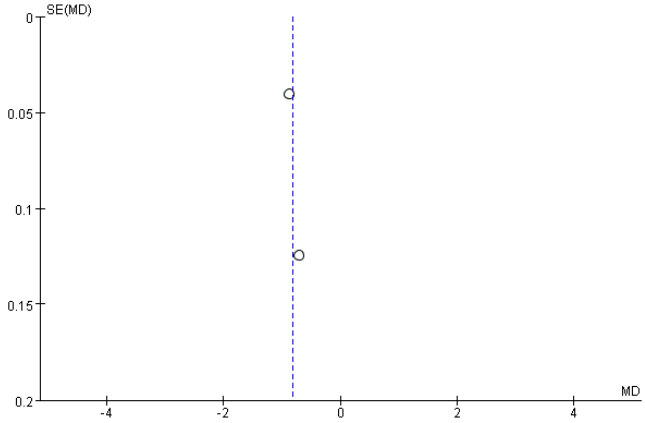



**Figure S2-G: SGLT2 inhibitors + metformin initial combination therapy vs metformin monotherapy**

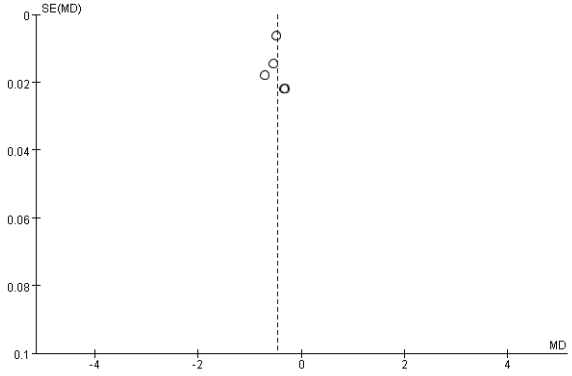



**Figure S2-H: SGLT2 inhibitors + metformin initial combination therapy vs SGLT2 inhibitors monotherapy**

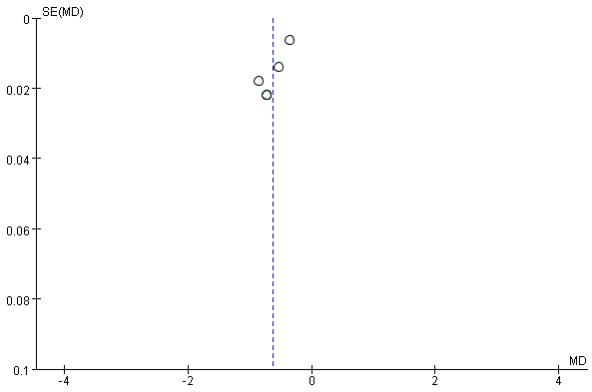



**Figure S2-I: DPP-4 inhibitors + TZD initial combination therapy vs TZD monotherapy**

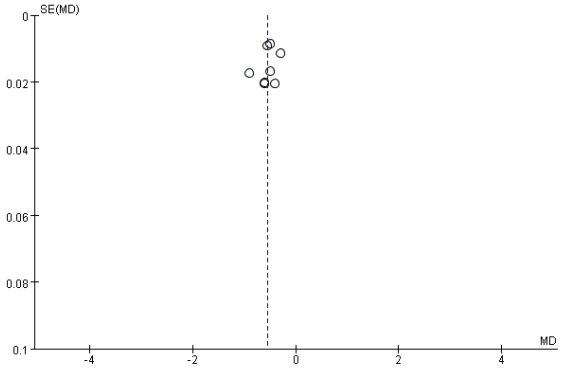



**Figure S2-J: DPP-4 inhibitors + TZD initial combination therapy vs DPP-4 inhibitors monotherapy**

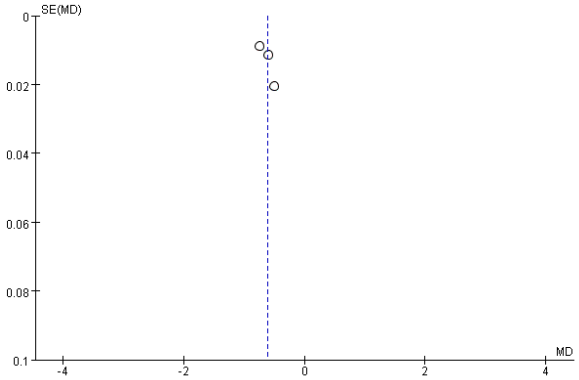
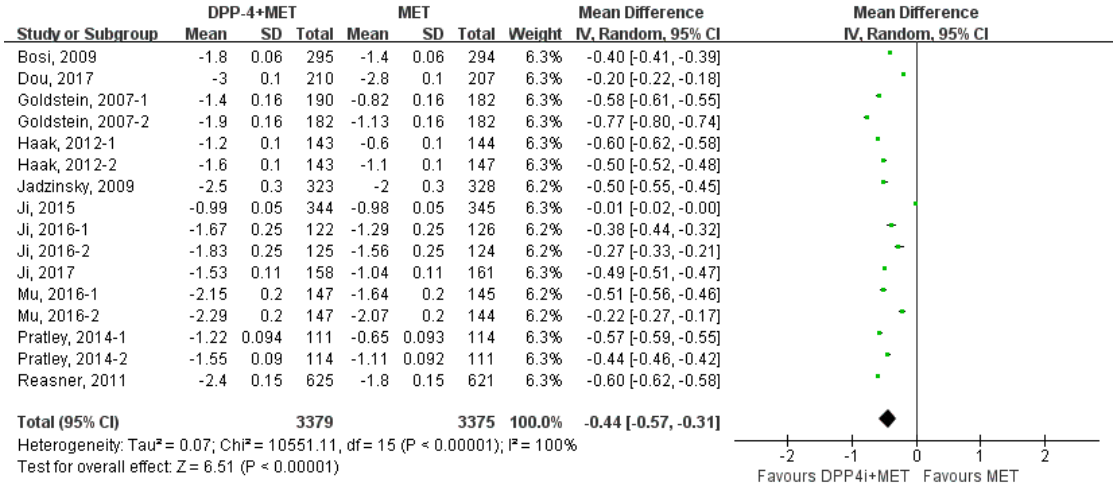


**Figure S3：Forest plots of comparisons of HbA1c changes between initial combination therapy and monotherapy**

**Figure S3-A: DPP-4 inhibitors + metformin initial combination therapy vs metformin monotherapy; Figure S3-B: DPP-4 inhibitors + metformin initial combination therapy vs DPP-4 inhibitors monotherapy; Figure S3-C: Sulfonylurea /Glinide + metformin initial combination therapy vs metformin monotherapy; Figure S3-D: Sulfonylurea/Glinide + metformin initial combination therapy vs Sulfonylurea /Glinide monotherapy; Figure S3-E: TZD + metformin initial combination therapy vs metformin monotherapy; Figure S3-F: TZD + metformin initial combination therapy vs TZD monotherapy; Figure S3-G: SGLT2 inhibitors + metformin initial combination therapy vs metformin monotherapy; Figure S3-H: SGLT2 inhibitors + metformin initial combination therapy vs SGLT2 inhibitors monotherapy; Figure S3-I: DPP-4 inhibitors + TZD initial combination therapy vs TZD monotherapy; Figure S3-J: DPP-4 inhibitors + TZD initial combination therapy vs DPP-4 inhibitors monotherapy**

**Figure S3-A: DPP-4 inhibitors + metformin initial combination therapy vs metformin monotherapy;**

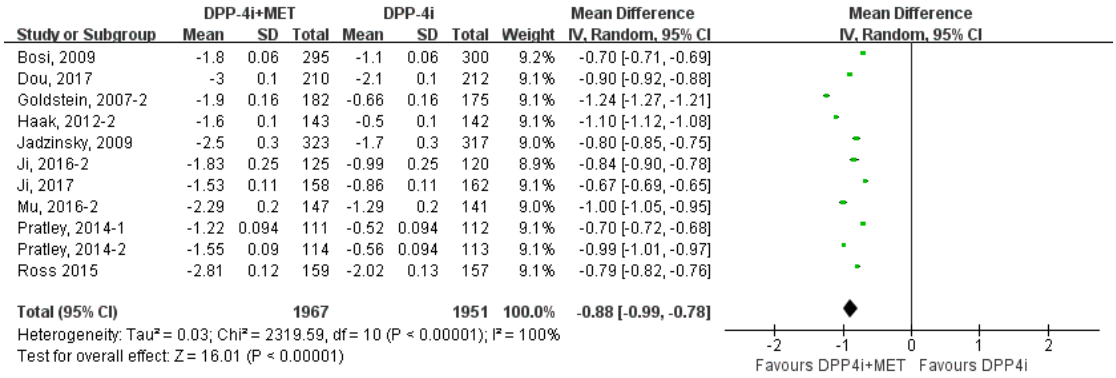


| | DPP-4+MET | | | MET | | | | Mean Difference | Mean Difference |
|---|---|---|---|---|---|---|---|---|---|
| Study or Subgroup | Mean | SD | Total | Mean | SD | Total | Weight | IV, Random, 95% CI | IV, Random, 95% CI |
| Bosi, 2009 | -1.8 | 0.06 | 295 | -1.4 | 0.06 | 294 | 6.3% | -0.40 [-0.41, -0.39] | |
| Dou, 2017 | -3 | 0.1 | 210 | -2.8 | 0.1 | 207 | 6.3% | -0.20 [-0.22, -0.18] | |
| Goldstein, 2007-1 | -1.4 | 0.16 | 190 | -0.82 | 0.16 | 182 | 6.3% | -0.58 [-0.61, -0.55] | |
| Goldstein, 2007-2 | -1.9 | 0.16 | 182 | -1.13 | 0.16 | 182 | 6.3% | -0.77 [-0.80, -0.74] | |
| Haak, 2012-1 | -1.2 | 0.1 | 143 | -0.6 | 0.1 | 144 | 6.3% | -0.60 [-0.62, -0.58] | |
| Haak, 2012-2 | -1.6 | 0.1 | 143 | -1.1 | 0.1 | 147 | 6.3% | -0.50 [-0.52, -0.48] | |
| Jadzinsky, 2009 | -2.5 | 0.3 | 323 | -2 | 0.3 | 328 | 6.2% | -0.50 [-0.55, -0.45] | |
| Ji, 2015 | -0.99 | 0.05 | 344 | -0.98 | 0.05 | 345 | 6.3% | -0.01 [-0.02, -0.00] | |
| Ji, 2016-1 | -1.67 | 0.25 | 122 | -1.29 | 0.25 | 126 | 6.2% | -0.38 [-0.44, -0.32] | |
| Ji, 2016-2 | -1.83 | 0.25 | 125 | -1.56 | 0.25 | 124 | 6.2% | -0.27 [-0.33, -0.21] | |
| Ji, 2017 | -1.53 | 0.11 | 158 | -1.04 | 0.11 | 161 | 6.3% | -0.49 [-0.51, -0.47] | |
| Mu, 2016-1 | -2.15 | 0.2 | 147 | -1.64 | 0.2 | 145 | 6.2% | -0.51 [-0.56, -0.46] | |
| Mu, 2016-2 | -2.29 | 0.2 | 147 | -2.07 | 0.2 | 144 | 6.2% | -0.22 [-0.27, -0.17] | |
| Pratley, 2014-1 | -1.22 | 0.094 | 111 | -0.65 | 0.093 | 114 | 6.3% | -0.57 [-0.59, -0.55] | |
| Pratley, 2014-2 | -1.55 | 0.09 | 114 | -1.11 | 0.092 | 111 | 6.3% | -0.44 [-0.46, -0.42] | |
| Reasner, 2011 | -2.4 | 0.15 | 625 | -1.8 | 0.15 | 621 | 6.3% | -0.60 [-0.62, -0.58] | |
| **Total (95% CI)** | | | **3379** | | | **3375** | **100.0%** | **-0.44 [-0.57, -0.31]** | |

Heterogeneity: Tau² = 0.07; Chi² = 10551.11, df = 15 (P < 0.00001); I² = 100%
Test for overall effect: Z = 6.51 (P < 0.00001)



**Figure S3-B: DPP-4 inhibitors + metformin initial combination therapy vs DPP-4 inhibitors monotherapy;**



| | DPP-4i+MET | | | DPP-4i | | | | Mean Difference | Mean Difference |
|---|---|---|---|---|---|---|---|---|---|
| Study or Subgroup | Mean | SD | Total | Mean | SD | Total | Weight | IV, Random, 95% CI | IV, Random, 95% CI |
| Bosi, 2009 | -1.8 | 0.06 | 295 | -1.1 | 0.06 | 300 | 9.2% | -0.70 [-0.71, -0.69] | |
| Dou, 2017 | -3 | 0.1 | 210 | -2.1 | 0.1 | 212 | 9.1% | -0.90 [-0.92, -0.88] | |
| Goldstein, 2007-2 | -1.9 | 0.16 | 182 | -0.66 | 0.16 | 175 | 9.1% | -1.24 [-1.27, -1.21] | |
| Haak, 2012-2 | -1.6 | 0.1 | 143 | -0.5 | 0.1 | 142 | 9.1% | -1.10 [-1.12, -1.08] | |
| Jadzinsky, 2009 | -2.5 | 0.3 | 323 | -1.7 | 0.3 | 317 | 9.0% | -0.80 [-0.85, -0.75] | |
| Ji, 2016-2 | -1.83 | 0.25 | 125 | -0.99 | 0.25 | 120 | 8.9% | -0.84 [-0.90, -0.78] | |
| Ji, 2017 | -1.53 | 0.11 | 158 | -0.86 | 0.11 | 162 | 9.1% | -0.67 [-0.69, -0.65] | |
| Mu, 2016-2 | -2.29 | 0.2 | 147 | -1.29 | 0.2 | 141 | 9.0% | -1.00 [-1.05, -0.95] | |
| Pratley, 2014-1 | -1.22 | 0.094 | 111 | -0.52 | 0.094 | 112 | 9.1% | -0.70 [-0.72, -0.68] | |
| Pratley, 2014-2 | -1.55 | 0.09 | 114 | -0.56 | 0.094 | 113 | 9.1% | -0.99 [-1.01, -0.97] | |
| Ross 2015 | -2.81 | 0.12 | 159 | -2.02 | 0.13 | 157 | 9.1% | -0.79 [-0.82, -0.76] | |
| **Total (95% CI)** | | | **1967** | | | **1951** | **100.0%** | **-0.88 [-0.99, -0.78]** | |

Heterogeneity: Tau² = 0.03; Chi² = 2319.59, df = 10 (P < 0.00001); I² = 100%
Test for overall effect: Z = 16.01 (P < 0.00001)



**Figure S3-C: Sulfonylurea /Glinide + metformin initial combination therapy vs metformin monotherapy;**

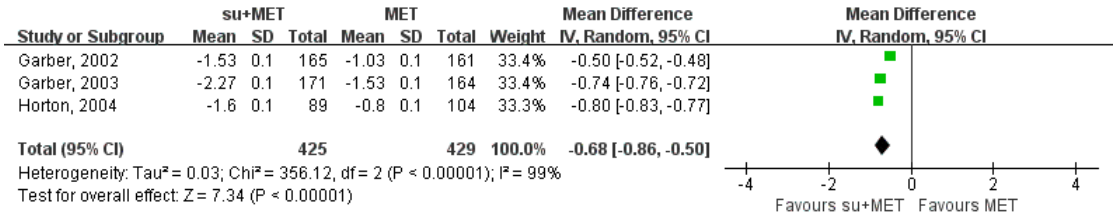



**Figure S3-D: Sulfonylurea/Glinide + metformin initial combination therapy vs Sulfonylurea /Glinide monotherapy;**

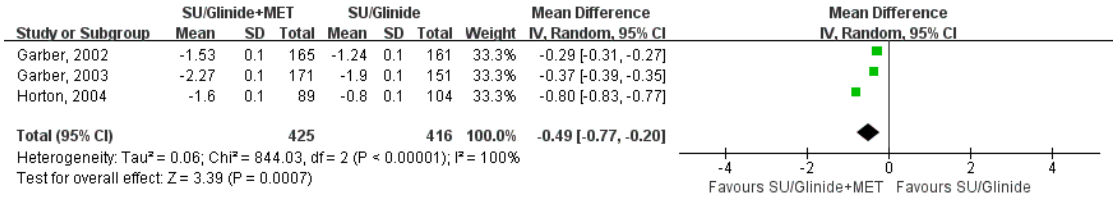



**Figure S3-E: TZD + metformin initial combination therapy vs metformin monotherapy;**

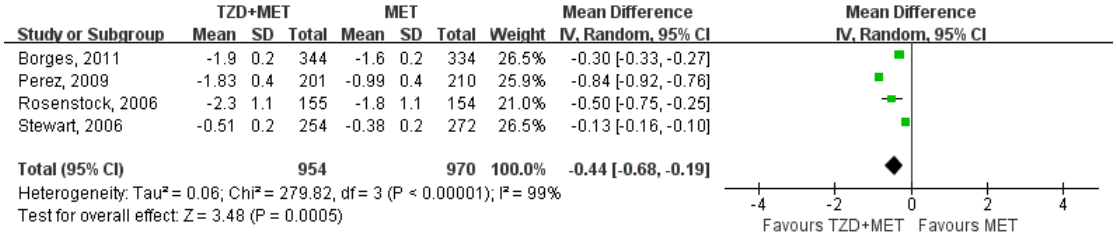



**Figure S3-F: TZD + metformin initial combination therapy vs TZD monotherapy;**

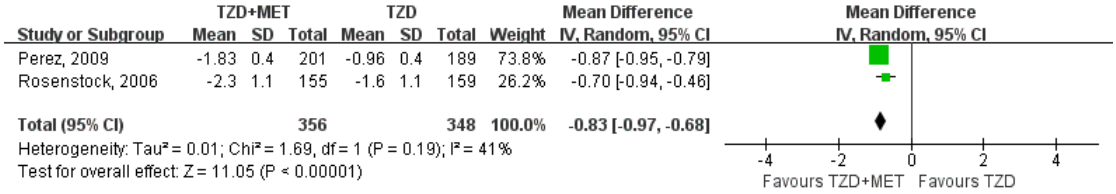



**Figure S3-G: SGLT2 inhibitors + metformin initial combination therapy vs metformin monotherapy;**

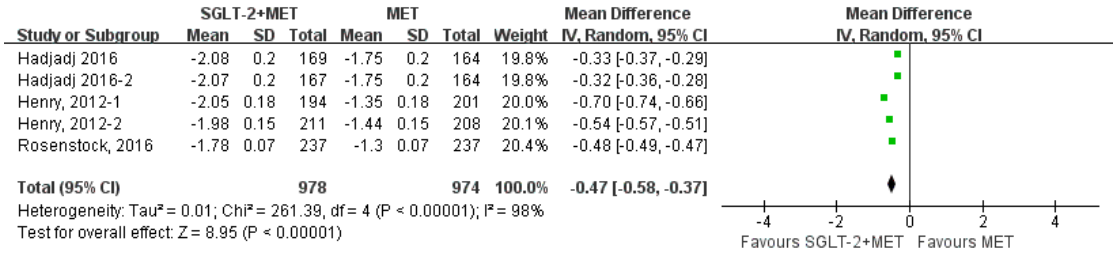



**Figure S3-H: SGLT2 inhibitors + metformin initial combination therapy vs SGLT2 inhibitors monotherapy;**

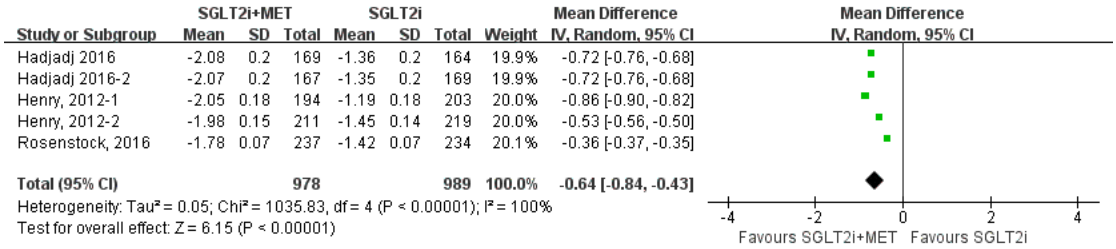



**Figure S3-I: DPP-4 inhibitors + TZD initial combination therapy vs TZD monotherapy;**

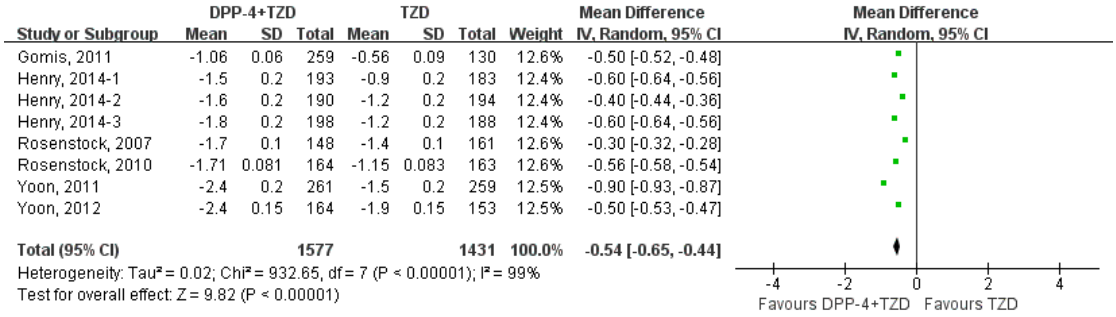



**Figure S3-J: DPP-4 inhibitors + TZD initial combination therapy vs DPP-4 inhibitors monotherapy**