Triple therapy combinations for the treatment of type 2 diabetes – a network meta-analysis

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Abstract

Aim: To estimate and compare the results from all randomized trials of triple combinations of anti-diabetes therapies that reported the reduction of glycated haemoglobin (HbA1c) and associated effects on body weight and hypoglycaemia.

Methods: PubMed and the Cochrane Library were searched for trials with at least one study arm on triple therapy and which reported the differences in mean change in HbA1c between two study arms. These were included in a network meta-analysis.

Results: Altogether, 15182 participants from 40 trials with treatment duration of 6 to 12 months were included. Compared with none/placebo added to dual therapy, the addition of a drug therapy from six of eight drug classes to existing dual therapy resulted in significant additional mean reductions in HbA1c from -0.56% (-6.2 mmol/mol; dipeptidyl peptidase 4 inhibitors) to -0.94% (-10.3 mmol/mol; thiazolidinediones). Of the six drug classes, three were associated with less favourable weight change and two were associated with more favourable weight change when compared with none/placebo added to dual therapy. Furthermore, five drug classes were associated with greater odds of hypoglycaemia. Similar results were observed in analyses of studies with 6 months treatment duration and after excluding study arms that contained insulin.

Conclusions: Overall triple therapy combinations were similar in improving diabetes control although there were some differences in adverse effects. By balancing the risks and benefits of each therapy, the estimates of pairwise comparisons of triple therapies for HbA1c, body weight and hypoglycaemia provided in this study may further inform evidence based practice.

Keywords: type 2 diabetes; treatment; pharmacotherapy.

Introduction

In clinical practice, glucose-lowering pharmacotherapy is prescribed when lifestyle modification is not effective in the management of type 2 diabetes. If glycaemic control becomes inadequate with a single therapy, a second and then a third therapy may be added to the treatment, while reinforcing the importance of lifestyle modification [1]. A network meta-analysis published in 2011 compared the effects of a number of therapies added to metformin (MET) and sulfonylurea (SU) for the treatment of type 2 diabetes [2]. However, triple therapy combinations other than those that include both MET and SU are increasingly used and may result in greater reduction in glycated haemoglobin (HbA1c). A randomised trial that compared the triple combinations MET/SU/DPP-4 (dipeptidyl peptidase 4 inhibitors) and MET/DPP-4/INS (insulin) reported a -0.40% [95% confidence intervals: -0.66, -0.15] (-4.4 [-7.3, -1.7] mmol/mol) greater reduction in HbA1c with MET/DPP-4/INS after a six month treatment period [3]. Moreover, a third therapy is usually added to the existing dual therapy treatment and because of individualized treatment plans, patients may not necessarily be taking the MET/SU dual therapy combination. Therefore, we aimed to estimate and compare the effect of all triple therapy combinations that have been studied in clinical trials on glycaemic control as assessed by HbA1c and to examine the effect on weight changes and hypoglycaemia to further inform evidence based practice in the management of type 2 diabetes.

Materials and methods

We consulted the PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses checklist in preparation of this review [4].

Literature search

We searched PubMed and the Cochrane Library for relevant studies that were published to 8th April 2015, using a combination of key words and MeSH terms: “biguanides”, “metformin”, “sulfonamides”, “sulfonylureas”, “glibenclamide”, “gliclazide”, “glimepiride”, “glipizide”, “glyburide”, “dipeptidyl peptidase 4 inhibitors”, “DPP-4 inhibitors”, “gliptins”, “alogliptin”, “linagliptin”, “saxagliptin”, “sitagliptin”, “vildagliptin”, “GLP-1 receptor agonists”, “incretin analogues”, “albiglutide”, “exenatide”, “liraglutide”, “lixisenatide”, “sodium glucose co-transporter inhibitors”, “SGLT2 inhibitors”, “canagliflozin”, “dapagliflozin”, “empagliflozin”, “alpha glucosidase inhibitors”, “acarbose”, “miglitol”, “voglibose”, “thiazolidinediones”, “TZD”, “glitazones”, “pioglitazone”, “rosiglitazone”, “insulin”, “meglitinide”, “nateglinide”, “repaglinide”, “type 2 diabetes”, and “clinical trial”. The full electronic search strategy is provided in Appendix. References from relevant studies and reviews were inspected to identify other potential studies. No language restriction was applied.

Study selection, data extraction, and quality assessment

Studies were included if they fulfilled the following criteria: randomised trials in adults (aged ≥ 18 years) with type 2 diabetes; at least one study arm involved triple therapy; at least two study arms were on different drug class combinations; and reported the mean change and its variability (i.e. standard deviation, standard error, or 95% confidence interval) in HbA1c from

baseline for each study arm or the difference in mean change and its variability between two study arms. Attempts were made to include studies that did not report the required summary statistics on HbA1c by contacting the corresponding authors of these studies. Drug classes available for the treatment of type 2 diabetes include MET, SU, DPP-4, INS, glucagon-like peptide-1 receptor agonist (GLP-1), sodium-glucose linked transporter protein 2 inhibitors (SGLT2), alpha glucosidase inhibitors (AGI), thiazolidinediones (TZD), and meglitinides (MEG).

Studies were excluded if the treatment period was less than 20 weeks, since adjustments to dosages, such as for INS, may take place in the first few weeks of the treatment period and change in HbA1c may not be noticeable in the first three months due to the 120 day life span of red blood cells. Studies with treatment duration greater than 54 weeks that did not report interim results during the first 6 to 12 months of treatment, sample size less than 30 per study arm, or compared a triple therapy arm with a monotherapy arm were also excluded. Studies that combined participants on different background therapy combinations during the treatment period were excluded unless mean changes in HbA1c were reported for the subgroups that were on the same background therapy combinations.

Literature search and data extraction were conducted by C.M.Y.L in consultation with S.C. Information extracted from each study included study characteristics (name of primary author, year of publication, location of trial, drug class combinations, sample size and details of medications used for each study arm, treatment duration, and analysis set used), baseline characteristics of studied populations (proportion of females, mean age, mean body mass index,

mean duration of diabetes, and mean HbA1c), and study outcomes (change in HbA1c, change in body weight, and number of participants experienced at least mild hypoglycaemia during treatment period). For studies that have multiple follow-up visits, data collected closest to 6 months after the start of treatment were included in the analysis. For multi-arm studies that included study arms that were assigned the same drug class combinations but at different dosages for one of the drugs, the study arm allocated the dosage that was most commonly used in other studies for that drug was included in the analysis. The Jadad Scale was used to assess the quality of the included studies [5].

Data analysis

We estimated the mean difference in HbA1c between each drug class added to an existing dual therapy compared to adding a nothing or adding a placebo (none/placebo) to an existing dual therapy to determine if any of the third therapy added to existing dual therapy is superior in reducing HbA1c.. Since not all triple therapies have been compared in randomised trials, a multivariate network meta-analysis was employed instead of a traditional pairwise meta-analysis. Multivariate network meta-analysis can provide estimates for all pairwise comparisons that are linked to a network of trials through utilising both direct evidence obtained from studies directly comparing drug class combinations and indirect evidence estimated through a common comparator [6]. Furthermore, information from multi-arm studies can be included in the network meta-analysis, thus increasing the number of studies that can be included in the analysis. Estimates of all pairwise comparisons of triple therapies were provided to assist in the selection of the drug class that appears most appropriate as add on to existing dual therapy. In

order to assess the adverse effects of the triple therapy combinations, the analyses were repeated for difference in mean change in body weight reported as kilograms and for difference in the proportion of participants who experienced hypoglycaemia reported as odds ratios. Since the level of HbA1c may be different at 6 months and 12 months after the start of treatment, a sensitivity analysis was conducted restricted to studies with about 6 months (20-30 weeks) treatment duration. Analyses were also repeated after excluding study arms that contained insulin, and after removing studies that were rated "poor" based on the Jadad Scale.

Multiple-outcomes meta-analysis was conducted using *network*, a suite of Stata commands for network meta-analysis within a frequentist framework [7]. A network plot was used to assess the geometry of the network [4]. Each node represents a drug class added to existing dual therapy and direct comparisons between drug classes are represented by connections between the nodes. The number of studies available per direct comparison is provided in the network. The size of the node reflects the number of studies available for the drug class. Estimates derived from consistency models are reported. Overall inconsistency across comparisons between direct and indirect evidence were tested using the design-by-treatment interaction inconsistency model. Relative rankings of the therapy combinations were estimated using the surface under the cumulative ranking curve (SUCRA). SURCA is the cumulative probabilities of a treatment to achieve each of all possible ranks out of all competing treatments [8]. For instance, if three treatments were compared, SUCRA for treatment 1 would be the cumulative probabilities of treatment 1 ranking first out of all three treatments, ranking second out of all

three treatments, and ranking third out of all three treatments. All statistical analyses were performed using Stata/IC 12.0 for Windows (Stata Corp LP., College Station, TX, USA).

Results

A total of 11666 titles and abstracts were screened after duplicates were removed (Supplementary Figure 1). Of these, 137 articles were retrieved to assess their eligibility and 87 articles were removed based on our inclusion and exclusion criteria. Nine authors were contacted for missing data; three authors provided additional information and missing data from two studies were obtained from a published meta-analysis. A further six articles were removed; four trials had sample size less than 30 per arm and two trials were included in other publications. Therefore, 40 studies were included in the network meta-analysis.

Characteristics of included studies

Altogether, 15182 participants with type 2 diabetes from 40 trials with treatment duration ranging from 20 to 54 weeks (90% of trials with treatment duration of 6 months (20-30 weeks)) were available for analysis (Table 1). The characteristics of the studied populations varied with baseline mean values ranging from 52.6 to 65.3 years (median 56.6 years) for age, 7.2 to 10.2% (55 to 88 mmol/mol) (median 8.3% (67 mmol/mol)) for HbA1c, 26.2 to 34.4 kg/m^2 (median 31.2 kg/m^2) for body mass index, and 4.7 to 13.0 years (median 9.0 years) for duration of diabetes. Analyses were conducted on the full analysis set or intention-to-treat in 36 studies, per protocol in 3 studies, and not reported in 1 study. Details of medications used in each study are provided

in supplementary table 1. Of the 33 studies with a dual therapy arm, 27 included a placebo. The quality of studies was rated “good” in 93% of the trials (Supplementary table 2).

HbA1c

A network plot of diabetes treatment combinations for all trials which reported HbA1c and had a treatment duration of 6 to 12 months (20-54 weeks) is presented in Figure 1. Four of the 40 trials included had three arms but two of the trials had two dual therapy arms, hence, 46 direct comparisons were available for comparison among nine therapy combinations (one dual (none/placebo added) and eight triple). Where available, the number of studies per direct comparison between therapy combination pairs ranged from 1 to 13. The triple therapies available for comparison comprised SU, DPP-4, GLP-1, SGLT2, INS, AGI, TZD or MEG added to existing dual therapy.

Compared with none/placebo added to dual therapy, the addition of a third therapy to existing dual therapy resulted in significant additional mean reductions in HbA1c, which ranged from -0.56% [95% confidence intervals: -0.70, -0.42] (-6.2 mmol/mol [-7.7, -4.6]) for DPP-4 to -0.94% [-1.18, -0.70] (-10.3 mmol/mol [-13.0, -7.7]) for TZD (Figure 2). Non-significant mean reductions in HbA1c were observed when AGI or MEG was added to dual therapy. When a third therapy was compared with other third therapies added to existing dual therapy, significant difference was observed between DPP-4 and GLP-1, INS, and TZD (Supplementary table 3). TZD was ranked the most effective in the reduction of HbA1c (SUCRA = 89.6%). There was limited evidence to

suggest inconsistency between studies (p = 0.80). Estimates of all pairwise comparisons of triple therapies for HbA1c are provided in Supplementary table 3.

When study arms containing insulin were excluded, 28 studies with 31 direct comparisons were available for seven therapy combinations (MEG was not studied in these trials). TZD remained the most effective in the reduction of HbA1c (SUCRA = 89.2%). Of note, however, the point estimate of the mean reduction in HbA1c for SU was 0.4% (4.4 mmol/mol) greater than in the analysis of all studies (from -0.59% [-0.90, -0.28] (6.5 mmol/mol [-9.9, 3.1]) to -0.99% [-1.32, -0.66] (-10.9 [-14.5, -7.3])) and its relative ranking improved with SUCRA value increasing from 43.8% to 87.1%.

In the 34 studies with around 6 months treatment duration, 38 direct comparisons were available for nine therapy combinations. The overall conclusion did not differ when compared with the 6 to 12 months results. Removal of three studies that were rated “poor” also did not alter the conclusion.

Body weight

Body weight was reported in 27 two-arm studies and 4 three-arm studies (2 with two dual therapy arms), which resulted in 37 direct comparisons available for eight therapy combinations (data were not available for AGI). Compared with none/placebo added to dual therapy, a more favourable weight difference was observed for GLP-1 (-1.85 kg [-2.81, -0.89]) and SGLT-2 (-1.79

kg [-3.03, -0.55]) (Figure 3). There was, however, evidence of inconsistency between direct and indirect evidence ($p < 0.0001$). According to the SUCRA values for body weight and HbA1c, the two drug classes (TZD, INS) that ranked highest for their effectiveness in the reduction of HbA1c ranked poorly for body weight due to their effect on weight gain (Figure 4). GLP-1 (73.7% and 91.9%) and SGLT-2 (57.3% and 90.6%) have relatively high SUCRA values for both HbA1c and body weight. Estimates of all pairwise comparisons of triple therapies for body weight are provided in Supplementary table 4. Network meta-regression was not performed to investigate whether baseline mean weight was a possible explanation for inconsistency due to the limited studies available for each comparison. However, there was no systematic ordering (higher to lower) of baseline mean weight weighted by sample size according to the order of mean difference in body weight (weight reduction to weight gain) between triple therapy combinations when compared with none/placebo added to dual therapy.

Similar results were obtained when study arms containing insulin were removed from analysis. For sensitivity analysis of studies with about 6 months treatment duration, similar results were observed except that the mean difference in body weight became non-significant for SU (0.90 kg [-0.40, 2.20]) and there was limited evidence to suggest inconsistency ($p = 0.53$).

Hypoglycaemia

Twenty-seven studies reported the number of participants that experienced at least one episode of mild, or worse, hypoglycaemia during the treatment period, which resulted in 33 direct comparisons available for nine therapy combinations. Estimates of all pairwise

comparisons of triple therapies for hypoglycaemia are provided in Supplementary table 5. Compared with none/placebo added to dual therapy, the odds of hypoglycaemia were higher for DPP-4 (1.95 [1.15, 3.29]), SGLT2 (2.27 [1.07, 4.82]), GLP-1 (2.61 [1.42, 4.79]), TZD (2.83 [1.22, 6.57]), and INS (5.94 [2.80, 12.60]). There was limited evidence of inconsistency between studies ($p = 0.61$).

When study arms containing insulin were removed from analysis, the odds of hypoglycaemia also became significantly higher for SU (11.54 [4.75, 27.99]). For studies with about six months treatment duration, only GLP-1 (2.46 [1.24, 4.88]) and INS (3.80 [1.62, 8.89]) were associated with greater odds of hypoglycaemia than none/placebo added to dual therapy.

Discussion

This is the first study which estimated and compared the effectiveness of all triple therapy combinations that have been studied in randomised trials, not limited to those that included both MET and SU [2], on HbA1c and the associated effect on body weight and hypoglycaemia. There is general consensus that additional reduction in HbA1c can be achieved by adding a third therapy to existing dual therapy treatment. Gross et al reported a 0.70% (7.7 mmol/mol; acarbose) to 1.08% (11.9 mmol/mol; INS) additional absolute HbA1c reduction with a third therapy added to MET/SU compared with MET/SU [2] and in the present study we found an additional 0.56% (6.2 mmol/mol; DPP-4) to 0.94% (10.3 mmol/mol; TZD) HbA1c reduction for a third therapy added to an existing dual therapy. This reduction in HbA1c is clinically relevant. The UK Prospective Diabetes Study reported a 37% reduction in the risk of microvascular

complications and 14% reduction in the risk of myocardial infarction for each 1% (11 mmol/mol) reduction in HbA1c [48]. For a difference of 0.8% (9 mmol/mol) in HbA1c, the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) trial reported a 14% reduction in the risk of major microvascular events [49]. A meta-analysis on the effects of glucose lowering and cardiovascular disease, which included ADVANCE, found that a difference of 0.88% (9.7 mmol/mol) in HbA1c was associated with a 9% reduction in the risk of a major cardiovascular event [50].

The specific question addressed by our study was whether there were clinically relevant differences between the various currently available triple therapy combinations. We found no statistical difference in the reduction of HbA1c between six of the drug classes added as a third therapy to existing dual therapy when compared with dual therapy. However, differences were observed between DPP-4 and GLP-1, INS, and TZD when triple therapies were compared.

These changes in HbA1c should be considered in the context of other clinically relevant effects. Estimates of all pairwise comparisons of triple therapies for HbA1c, body weight and hypoglycaemia provided in Supplementary tables 3 to 5 can potentially be used to assist in the selection of drug class as add on to existing dual therapy. For example, compared with DPP-4 (a common first choice added to existing dual therapy), GLP-1 is associated with a 0.25% (2.8 mmol/mol) significantly greater absolute reduction in HbA1c and a 1.9 kg significantly more favourable weight change. In contrast, compared with DPP-4, INS is associated with a 0.35% (3.9 mmol/mol) significantly greater reduction in HbA1c but also a significant 2.3 kg weight gain.

Furthermore, there are also clinically relevant differences in risk of hypoglycaemia between the various therapeutic agents [1,51].

The major strength of this study was that we have compared the relative effects of nine drug classes as add-ons to existing dual therapy on the reduction of HbA1c. However, we were unable to conduct in depth analyses of potential confounders due to the limited number of studies available for each pairwise comparison. For instance, the differences in baseline mean age, body mass index, body weight, HbA1c and duration of diabetes among the 40 trials may have influenced the estimates but we were unable to conduct network meta-regression to explore the effects that these differences may have had on our results. Nevertheless, the baseline mean HbA1c weighted by sample size were similar between drug classes, which ranged from 8.3% (67 mmol/mol) to 8.5% (69 mmol/mol) except for MEG (7.5% (59 mmol/mol)), SGLT2 (8.1% (65 mmol/mol)) and AGI (8.8% (73 mmol/mol)). The lack of direct evidence between drug classes also meant that most comparisons were estimated through direct evidence from one or two studies and indirect evidence. We tested for the overall inconsistency in the network using a global method, yet we were unable to test loop specific inconsistency since most pairwise comparisons only have one study [52]. Furthermore, we have combined study arms that had the same drug class combinations but the drugs used within the same drug class differed among studies, although differences between drugs within the same class are mostly related to adverse effects, rather than in their efficacy in reducing HbA1c. Therefore, it is clinically plausible to combine studies that used different drugs within the same drug class. We have also combined all existing dual therapy combinations since, in clinical practice, a third therapy is only added

when existing dual therapy is no longer effective in controlling blood glucose. The effect of a drug class such as DPP-4 added to any existing dual therapy combinations should result in similar mean difference in HbA1c. We were unable to estimate the odds of severe hypoglycaemia associated with these triple therapy combinations as few studies reported these severe events. Moreover, hypoglycaemia data were the least robust as non-standardised definitions and grading were used.

Clinically relevant additional reduction in HbA1c can be achieved with triple therapy. As described above, the estimates provided in this study may be used to guide clinical practice since it is unlikely that a randomised trial will compare all triple therapy combinations included here. Nevertheless, readers should be aware of the limitations in this study and treat these estimates as a general guide rather than precise evidence.

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Conflict of interest

M. Woodward has received payment for consultation from Sanofi-Aventis. S. Colagiuri has served on advisory boards and / or received speaking fees from the following:

Astra Zenica, Bristol-Myers Squibb, Glaxo Smith Kline, Janssen-Cilag, Merck Sharp & Dohme, Medtronics, Novartis, Novo Nordisk, Sanofi-aventis, Servier, and Takeda.

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Figures

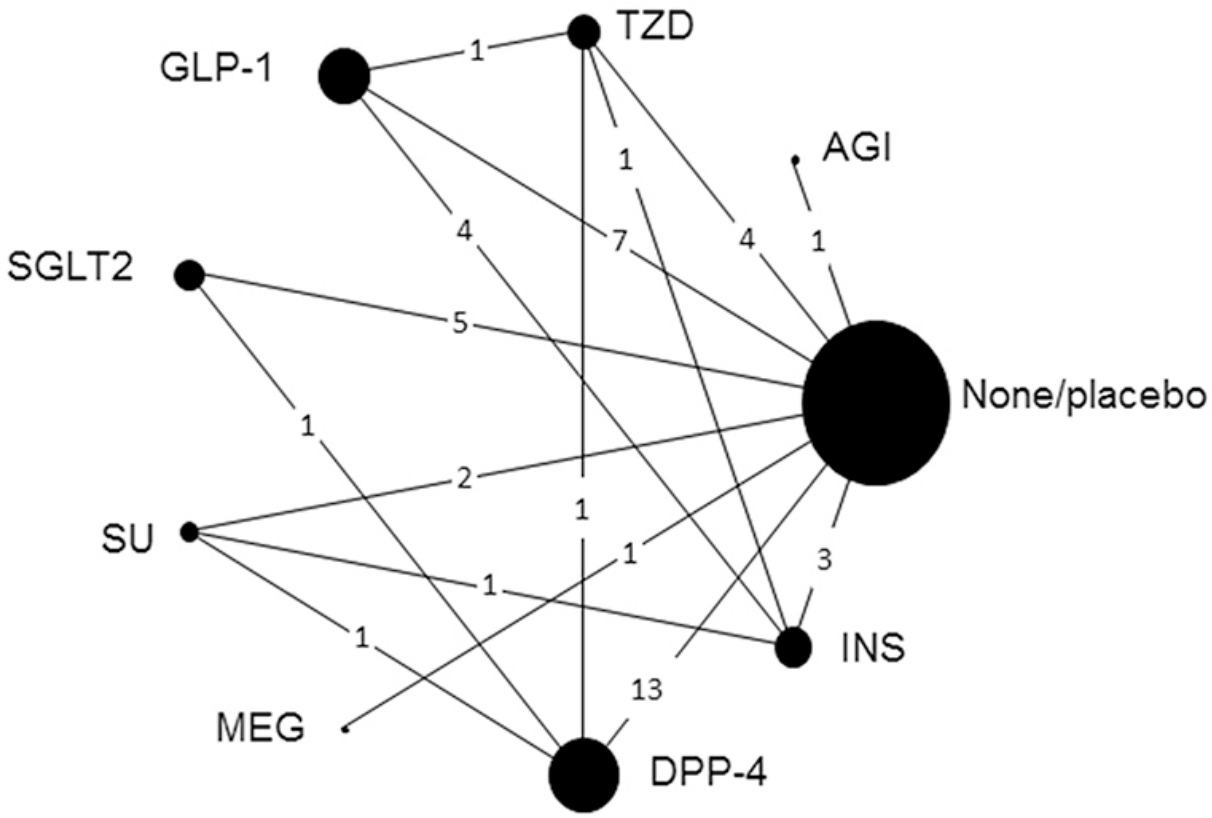

Figure 1: Network plot of available diabetes treatment combinations for studies with a treatment duration of 6 to 12 months (20-54 weeks)

The number of studies available per direct comparison is provided in the network. The size of the node reflects the number of studies available for the therapy combination.

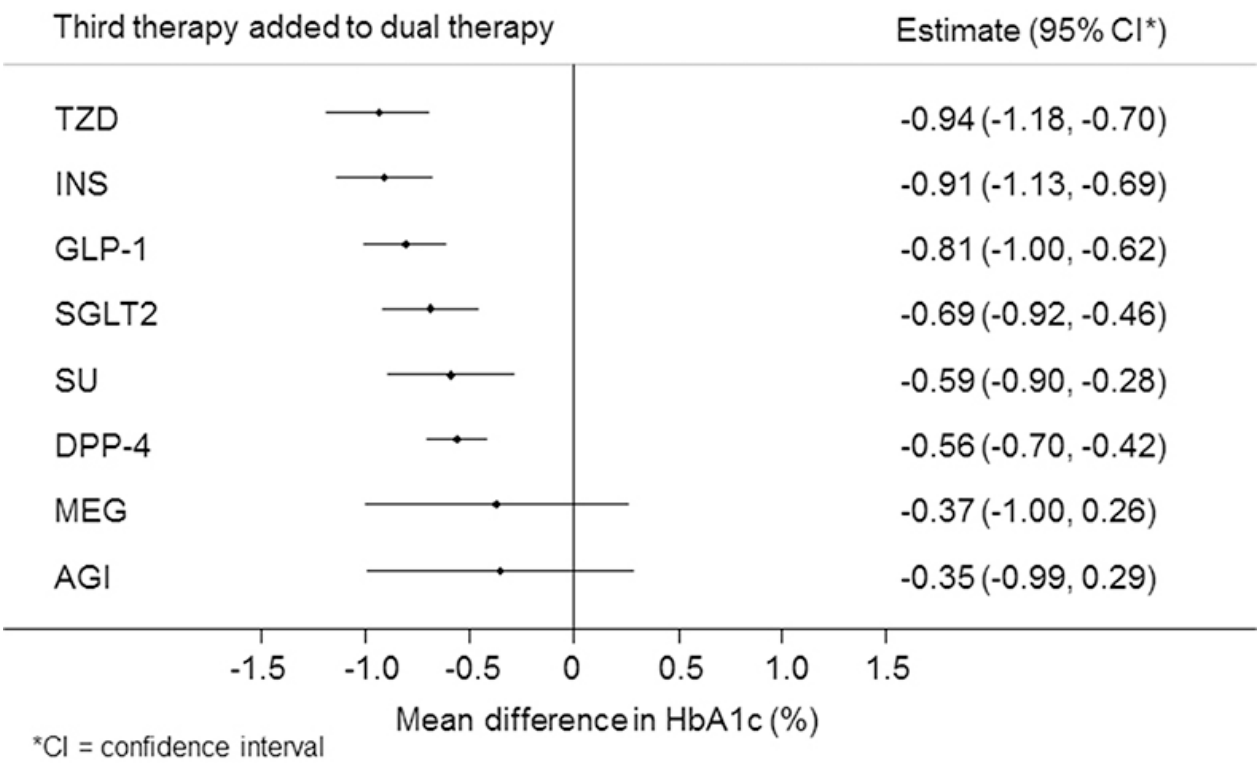

Figure 2: Mean difference in HbA1c (%)* of drug classes added to existing dual therapy compared with placebo/none added to dual therapy for studies with a treatment duration of 6 to 12 months (20-54 weeks)

*Multiply HbA1c values by 11 to convert HbA1c in DCCT (%) to IFCC (mmol/mol)

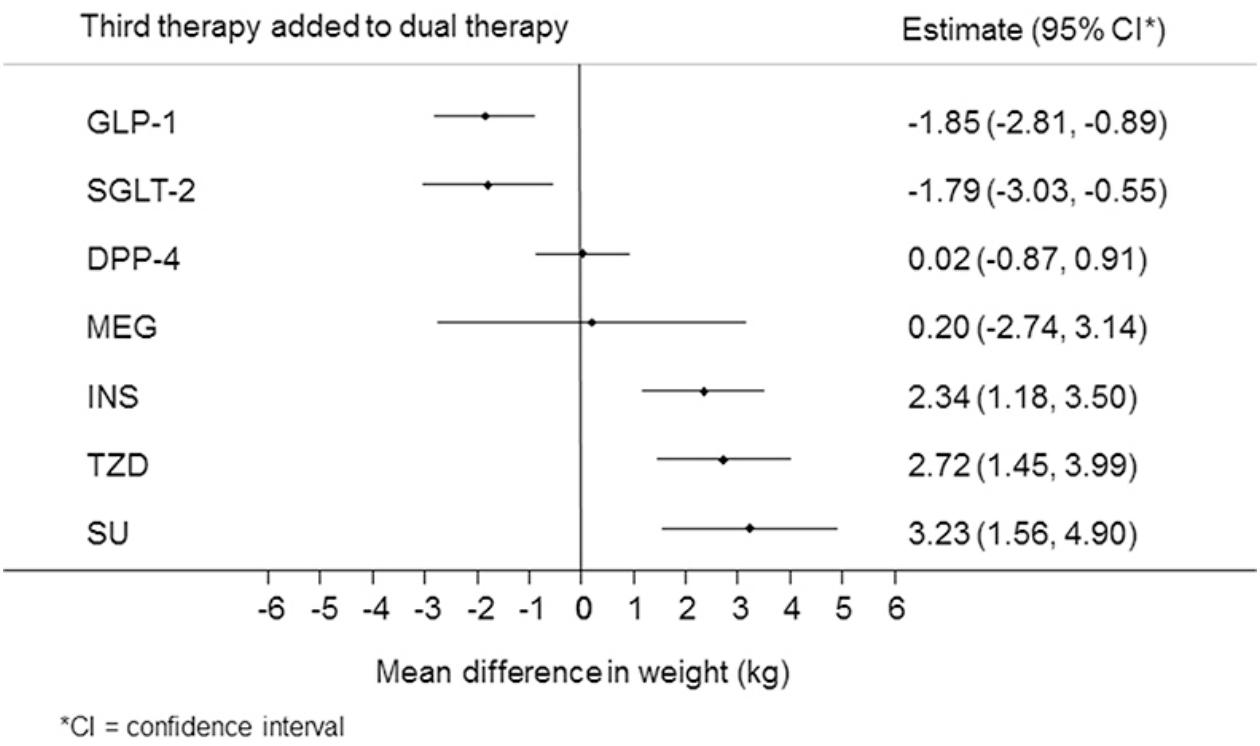

Figure 3: Mean difference in body weight (kg) of drug classes added to existing dual therapy compared with placebo/none added to dual therapy for studies with a treatment duration of 6 to 12 months (20-54 weeks)

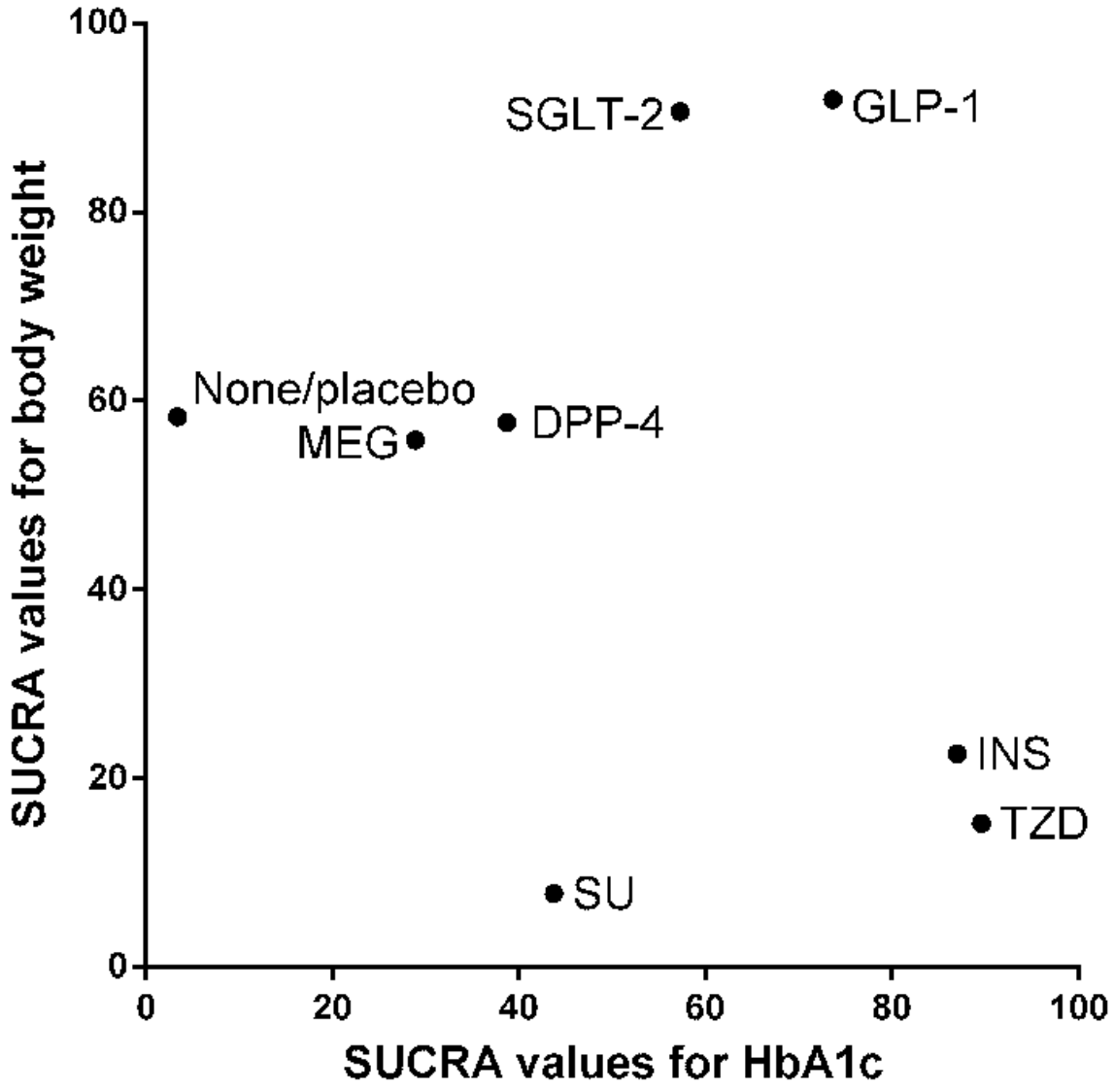

Figure 4: Surface under the cumulative ranking curve (SUCRA) values of HbA1c by body weight for all triple therapies with data for HbA1c and body weight for studies with a treatment duration of 6 to 12 months (20-54 weeks)

Higher SUCRA values for HbA1c indicate greater effectiveness in the reduction of HbA1c. Likewise, higher SUCRA values for body weight indicate greater effectiveness in the reduction of body weight.

Table 1: Characteristics of included studies

Study	Country	Study arms included in analysis (Combinations by drug class)	Sample size	Treatment duration	Female (%)	Mean diabetes duration (years)	Baseline mean			Analysis set used in study
							Age (years)	HbA1c (%) (mmol/mol)	BMI (kg/m^2)	
Standl et al, 2001 [9]	4 countries	**MET/SU/AGI** **MET/SU**	n_1= 65 n_2= 68	24 weeks	47	8.5	61.5	8.8 (73)	27.8	PP
Yale et al, 2001 [10]	Canada	**MET/SU/TZD** **MET/SU**	n_1= 101 n_2= 99	24 weeks	44	11.4	59.0	9.6 (81)	30.1	FAS/ITT
Heine et al, 2005 [11]	13 countries	**MET/SU/GLP-1** **MET/SU/INS**	n_1= 282 n_2= 267	26 weeks	44	9.6	58.9	8.2 (66)	31.4	FAS/ITT and PP
Kendall et al, 2005 [12]	USA	**MET/SU/GLP-1** **MET/SU**	n_1= 241 n_2= 247	30 weeks	42	9.1	55.5	8.5 (69)	34	FAS/ITT
Roberts et al, 2005 [13]	USA	**MET/SU/TZD** **MET/TZD**	n_1= 82 n_2= 77	26 weeks	38	8.3	56.5	8.2 (66)	33.4	FAS/ITT
Rosenstock et al, 2006 [14]	USA	**MET/SU/TZD** **MET/SU/INS**	n_1= 112 n_2= 104	24 weeks	48	8.3	55.6	8.7 (72)	34.1	FAS/ITT
Hermansen et al, 2007 [15]	Multi-national	**MET/SU/DPP-4** **MET/SU**	n_1= 116 n_2= 113 (52% of entire cohort)	24 weeks	48	9.9	57.1	8.3 (67)	31.0	FAS/ITT
Nauck et al, 2007 [16]	13 countries	**MET/SU/GLP-1** **MET/SU/INS**	n_1= 253 n_2= 248	52 weeks	49	9.9	58.5	8.6 (71)	30.4	FAS/ITT and PP
Kadoglou et al, 2008 [17]	-	**MET/SU/TZD** **MET/SU**	n_1= 35 n_2= 35	26 weeks	57	8.0	65.3	8.1 (65)	29.7	-
Bergenstal et al, 2009 [18]	USA	**MET/SU/GLP-1** **MET/SU/INS** **MET/INS**	n_1= 124 n_2= 124 n_3= 124	24 weeks	52	9.0	52.6	10.2 (88)	33.8	FAS/ITT
Juurinen et al, 2009 [19]	Finland	**MET/INS/MEG** **MET/INS**	n_1= 40 n_2= 41	24 weeks	45	9.4	56.0	7.4 (57)	32.8	FAS/ITT
Raskin et al, 2009 [20]	USA	**MET/INS/TZD** **MET/TZD**	n_1= 102 n_2= 98	34 weeks	58	8.8	53.8	8.1 (65)	32.9	FAS/ITT
Russell-Jones et al,	17	**MET/SU/GLP-1**	n_1= 230	26 weeks	43	9.4	57.5	8.3	30.5	FAS/ITT

2009 [21]	countries	**MET/SU/INS** **MET/SU**	n_2= 232 n_3= 114					(67)		
Zinman et al, 2009 [22]	2 countries	**MET/GLP-1/TZD** **MET/TZD**	n_1= 178 n_2= 177	26 weeks	44	9	55	8.5 (69)	33.7	FAS/ITT
DeFronzo et al, 2010 [23]	USA	**MET/GLP-1/TZD** **MET/GLP-1** **MET/TZD**	n_1= 47 n_2= 45 n_3= 45	20 weeks	49	4.7	56	7.8 (62)	32.5	FAS/ITT
Liutkus et al, 2010 [24]	5 countries	**MET/GLP-1/TZD** **MET/TZD**	n_1= 105 n_2= 52 (95% of entire cohort)	26 weeks	41	6.3	54.7	8.2 (66)	33.7	FAS/ITT
Vilsboll et al, 2010 [25]	23 countries	**MET/DPP-4/INS** **MET/INS**	n_1= 229 n_2= 233 (72% of entire cohort)	24 weeks	49	12.5	57.7	8.6 (71)	31	FAS/ITT
Bosi et al, 2011 [26]	Multi-national	**MET/DPP-4/TZD** **MET/TZD**	n_1= 404 n_2= 399	52 weeks (interim data for 26 weeks)	48	7.2	55.1	8.2 (66)	31.5	PP
Hollander et al, 2011 [3]	8 countries	**MET/DPP-4/INS** **MET/SU/DPP-4**	n_1= 80 n_2= 85 (76% of entire cohort)	26 weeks	46	9.8	56.9	8.5 (69)	31.9	FAS/ITT
Owens et al, 2011 [27]	11 countries	**MET/SU/DPP-4** **MET/SU**	n_1= 792 n_2= 263	24 weeks	53	73% >5 years	58.1	8.1 (65)	28.3	FAS/ITT
Barnett et al, 2012 [28]	10 countries	**MET/DDP-4/INS** **Met/INS**	n_1= 209 n_2= 105 (69% of entire cohort)	24 weeks	59	11.9	57.2	8.7 (72)	32.3	FAS/ITT
DeFronzo et al, 2012 [29]	20 countries	**MET/DPP-4/TZD** **MET/TZD**	n_1= 780 n_2= 388 (75% of entire cohort)	26 weeks	56	6.4	54.5	8.5 (69)	31.2	FAS/ITT
DeVries et al, 2012 [30]	9 countries	**MET/GLP-1/INS** **MET/GLP-1**	n_1= 162 n_2= 161	26 weeks	45	8.6	57.0	7.6 (60)	34.4	FAS/ITT
Violante et al, 2012 [31]	7 countries	**MET/DPP-4/GLP-1** **MET/GLP-1**	n_1= 128 n_2= 127	20 weeks	50	8	56	7.9 (63)	31.2	PP
Derosa et al, 2013 [32]	Italy	**MET/DPP-4/TZD** **MET/SU/TZD**	n_1= 228 n_2= 225	52 weeks	50	-	-	7.2 (55)	27.5	FAS/ITT
Dobs et al, 2013 [33]	Multi-national	**MET/DPP-4/TZD** **MET/TZD**	n_1= 170 n_2= 92	54 weeks	43	9.3	54.5	8.8 (73)	30.3	FAS/ITT
Fonseca et al, 2013	12	**MET/DPP-4/TZD**	n_1= 157	26 weeks	38	9.8	56.0	8.8	29.9	FAS/ITT

[34]	countries	**MET/TZD**	n_2= 156					(73)		
Haring et al, 2013 [35]	12 countries	**MET/SU/SGLT2** **MET/SU**	n_1= 216 n_2= 225	24 weeks	49	80% >5 years	57.1	8.1 (65)	28.1	FAS/ITT
Kothny et al, 2013 [36]	11 countries	**MET/DPP-4/INS** **MET/INS**	n_1= 139 n_2= 137 (62% of entire cohort)	24 weeks	50	13.0	59.2	8.8 (73)	28.9	FAS/ITT
Liu et al, 2013 [37]	Taiwan	**MET/SU/TZD** **MET/SU/DPP-4**	n_1= 60 n_2= 60	24 weeks	63	7.8	59.1	8.4 (68)	26.2	FAS/ITT
Schernthaner et al, 2013 [38]	17 countries	**MET/SU/SGLT2** **MET/SU/DPP-4**	n_1= 377 n_2= 378	52 weeks	44	9.6	56.7	8.1 (65)	31.6	FAS/ITT
Wilding et al, 2013 [39]	11 countries	**MET/SU/SGLT2** **MET/SU**	n_1= 156 n_2= 156	52 weeks (interim data for 26 weeks)	50	9.9	56.5	8.1 (65)	33.0	FAS/ITT
Yki-Jarvinen et al, 2013 [40]	19 countries	**MET/DPP-4/INS** **MET/INS**	n_1= 470 n_2= 464 (74% of entire cohort)	24 weeks	48	86% >5 years	60.0	8.3 (67)	31.0	FAS/ITT
Jabbour et al, 2014 [41]	6 countries	**MET/DPP-4/SGLT2** **MET/DPP-4**	n_1= 113 n_2= 113 (51% of entire cohort)	24 weeks	41	6.6	56.7	7.9 (63)	-	FAS/ITT
Kovacs et al, 2014 [42]	8 countries	**MET/SGLT2/TZD** **MET/TZD**	n_1= 127 n_2= 124 (75% of entire cohort)	24 weeks	47	43% >5 years	54.4	8.1 (65)	29.2	FAS/ITT
Lukashevich et al, 2014 [43]	11 countries	**MET/SU/DPP-4** **MET/SU**	n_1= 158 n_2= 160	24 weeks	52	7.3	55.1	8.8 (73)	28.0	FAS/ITT
Moses et al, 2014 [44]	6 countries	**MET/SU/DPP-4** **MET/SU**	n_1= 129 n_2= 128	24 weeks	40	-	57.0	8.3 (67)	29.3	FAS/ITT
Wysham et al, 2014 [45]	3 countries	**MET/GLP-1/TZD** **MET/TZD**	n_1= 276 n_2= 141	52 weeks (Placebo only included in first 26 weeks)	43	9	55	8.1 (65)	33.7	FAS/ITT
Home et al, 2015 [46]	9 countries	**MET/SU/GLP-1** **MET/SU/TZD** **MET/SU**	n_1= 271 n_2= 277 n_3= 115	52 weeks	47	8.9	55.2	8.2 (66)	32.2	FAS/ITT
Matthaei et al, 2015 [47]	6 countries	**MET/SU/SGLT2** **MET/SU**	n_1= 108 n_2= 108	24 weeks	51	9.5	61.0	8.2 (66)	32.0	FAS/ITT

AGI=alpha glucosidase inhibitor; BMI=body mass index; DPP-4=dipeptidyl peptidase 4 inhibitor; FAS/ITT=full analysis set or intention-to-treat; FBG=fasting blood glucose; FPG=fasting plasma glucose; GLP-1=Glucagon-like peptide-1 receptor agonist; HbA1c=glycated haemoglobin; INS=insulin; MEG=meglitinide; MET=metformin; PP=per protocol; SGLT2=sodium-glucose linked transporter protein 2 inhibitor; SU=sulfonylurea; TZD=thiazolidinedione;

Appendix

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Supplementary table 1: Description of medications used in each study arm

Study	Study arms		
	1	2	3 or more
Standl et al, 2001 [9]	Metformin At least one 500-850 mg per tablet daily Glibenclamide 2-4 tablets (3.5 or 5 mg per tablet) Miglitol 25 mg tid for 4 weeks, 50 mg tid for 4 weeks, then 50 or 100 mg tid	Metformin At least one 500-850 mg per tablet daily Glibenclamide 2-4 tablets (3.5 or 5 mg per tablet) Placebo	
Yale et al, 2001 [10]	Metformin Prestudy level Sulfonylurea Prestudy level Troglitazone 400 mg/day	Metformin Prestudy level Sulfonylurea Prestudy level Placebo	
Heine et al, 2005 [11]	Metformin Prestudy level Sulfonylurea Prestudy level Exenatide 5 µg bid for 4 weeks, then 10 µg bid	Metformin Prestudy level Sulfonylurea Prestudy level Insulin glargine 10 U/d then titrated to achieve FBG<5.6 mmol/L on daily glucose monitoring	
Kendall et al, 2005 [12]	Metformin Prestudy level Sulfonylurea Randomized to either maximally effective or minimum recommended dose Exenatide 10 µg bid	Metformin Prestudy level Sulfonylurea Randomized to either maximally effective or minimum recommended dose Placebo	**(Not included)** As for arm 1 with Exenatide in 5 µg dosage
Roberts et al, 2005 [13]	Metformin Prestudy level Thiazolidinedione Prestudy level Glimepiride 2 mg/day	Metformin Prestudy level Thiazolidinedione Prestudy level Placebo	
Rosenstock et al, 2006 [14]	Metformin 2000 mg/day Sulfonylurea Prestudy level Rosiglitazone 4 mg/day for 6 weeks, then 4-8 mg/day	Metformin 2000 mg/day Sulfonylurea Prestudy level Insulin glargine 10 IU/day for 7 days, then titrated to achieve FPG <5.5-6.7 mmol/L	
Hermansen et al, 2007 [15]	Metformin 1500-3000 mg/day Glimepiride 4-8 mg/day Sitagliptin 100 mg qd	Metformin 1500-3000 mg/day Glimepiride 4-8 mg/day Placebo	
Nauck et al, 2007 [16]	Metformin Prestudy level Sulfonylurea Prestudy level Exenatide 5 µg bid for 4 weeks, then 10 µg bid	Metformin Prestudy level Sulfonylurea Prestudy level Premixed insulin bid	
Kadoglou et al, 2008 [17]	Metformin Prestudy level Gliclazide Prestudy level Rosiglitazone 8 mg/day	Metformin Prestudy level Gliclazide Prestudy level	
Bergenstal et al,	Metformin Prestudy level	Metformin Prestudy level	Metformin Prestudy level

2009 [18]	Sulfonylurea Prestudy level Exenatide 5 µg bid for 4 weeks, then 10 µg bid	Sulfonylurea Prestudy level Biphasic insulin 12 U qd	Biphasic insulin 6 U bid
Juurinen et al, 2009 [19]	Metformin 500 mg/day Basal insulin Titrated to achieve FPG 4-5.5 mmol/L Nateglinide 120 mg tid	Metformin 500 mg/day Basal insulin Titrated to achieve FPG 4-5.5 mmol/L Placebo	
Raskin et al, 2009 [20]	Metformin 2500 mg/day Pioglitazone 30 or 45 mg/day BIAsp 30 6 units bid titrated every 3-4 days to achieve FPG and pre-evening meal PG 4.4-6.1 mmol/L	Metformin 2500 mg/day Pioglitazone 30 or 45 mg/day	
Russell-Jones et al, 2009 [21]	Metformin 2000 mg/day Glimepiride 4 mg/day Liraglutide 0.6 mg qd with weekly increments of 0.6 mg reaching final daily dose of 1.8 mg	Metformin 2000 mg/day Glimepiride 4 mg/day Insulin glargine Titrated twice weekly to achieve FPG≤5.5 mmol/L	Metformin 2 g/day Glimepiride 4 mg/day Placebo
Zinman et al, 2009 [22]	Metformin 1000 mg bid Rosiglitazone 4 mg bid Liraglutide 1.8 mg qd	Metformin 1000 mg bid Rosiglitazone 4 mg bid Placebo	**(Not included)** As for arm 1 with Liraglutide in 1.2 mg dosage
DeFronzo et al, 2010 [23]	Metformin Prestudy level Exenatide 5 µg bid for 4 weeks, then 10 µg bid Rosiglitazone 2 mg bid 4 weeks, then 4 mg bid	Metformin Prestudy level Exenatide 5 µg bid for 4 weeks, then 10 µg bid	Metformin Prestudy level Rosiglitazone 2 mg bid 4 weeks, then 4 mg bid
Liutkus et al, 2010 [24]	Metformin Prestudy level Thiazolidinedione Prestudy level Exenatide 5 µg bid for 4 weeks, then 10 µg bid	Metformin Prestudy level Thiazolidinedione Prestudy level Placebo	
Vilsboll et al, 2010 [25]	Metformin Prestudy level Insulin Prestudy level Sitagliptin 100 mg qd	Metformin Prestudy level Insulin Prestudy level Placebo	
Bosi et al, 2011 [26]	Metformin ≥1500 mg/day Pioglitazone 30 mg/day Alogliptin 25 mg/day	Metformin ≥1500 mg/day Pioglitazone 45 mg/day Placebo	
Hollander et al, 2011 [3]	Metformin Prestudy level Sitagliptin 100 mg/day Insulin detemir Titrated weekly to achieve pre-breakfast PG 4.0-6.0 mmol/L	Metformin Prestudy level Sulfonylurea Prestudy level Sitagliptin 100 mg/day	
Owens et al, 2011 [27]	Metformin Prestudy level Sulfonylurea Prestudy level Linagliptin 5 mg qd	Metformin Prestudy level Sulfonylurea Prestudy level Placebo	
Barnett et al, 2012	Metformin Prestudy level	Metformin Prestudy level	

[28]	Insulin Prestudy level Saxagliptin 5 mg/day	Insulin Prestudy level Placebo	
DeFronzo et al, 2012 [29]	Metformin ≤1500 mg/day Pioglitazone 15, 30 or 45 mg/day Alogliptin 12.5 or 25 mg/day	Metformin ≤1500 mg/day Pioglitazone 15, 30 or 45 mg/day	**(Not included)** Arm 3 Metformin + Alogliptin Arm 4 Metformin + placebo
DeVries et al, 2012 [30]	Metformin Prestudy level Liraglutide 1.8 mg/day Insulin detemir 10 U titrated weekly to achieve FPG 4.1-6.0 mmol/L	Metformin Prestudy level Liraglutide 1.8 mg/day	
Violante et al, 2012 [31]	Metformin Prestudy level Exenatide 5 µg bid for 4 weeks, then 10 µg bid Sitagliptin 100 mg qd	Metformin Prestudy level Exenatide 5 µg bid for 4 weeks, then 10 µg bid Placebo	
Derosa et al, 2013 [32]	Metformin 2200 mg/day Pioglitazone 30 mg/day Sitagliptin 100 mg/day	Metformin 2200 mg/day Pioglitazone 30 mg/day Glibenclamide 5 mg tid	
Dobs et al, 2013 [33]	Metformin 1500-2550 mg/day Rosiglitazone 4-8 mg/day Sitagliptin 100 mg/day	Metformin 1500-2550 mg/day Rosiglitazone 4-8 mg/day Placebo	
Fonseca et al, 2013 [34]	Metformin 1500-2550 mg/day Pioglitazone 30-45 mg/day Sitagliptin 100 mg/day	Metformin 1500-2550 mg/day Pioglitazone 30-45 mg/day Placebo	
Haring et al, 2013 [35]	Metformin ≥1500 mg/day Sulfonylurea Maximum recommended or tolerated dose Empagliflozin 25 mg/day	Metformin ≥1500 mg/day Sulfonylurea Maximum recommended or tolerated dose Placebo	**(Not included)** As for arm 1 with Empagliflozin in 10 mg dosage
Kothny et al, 2013 [36]	Metformin ≥1500 mg Insulin ≤1 U/kg/day Vildagliptin 50 mg bid	Metformin ≥1500 mg Insulin ≤1 U/kg/day Placebo	
Liu et al, 2013 [37]	Metformin Prestudy level Sulfonylurea Prestudy level Pioglitazone 30 mg/day	Metformin Prestudy level Sulfonylurea Prestudy level Sitagliptin 100 mg/day	
Schernthaner et al, 2013 [38]	Metformin Prestudy level Sulfonylurea Prestudy level Canagliflozin 300 mg qd	Metformin Prestudy level Sulfonylurea Prestudy level Sitagliptin 100 mg qd	
Wilding et al, 2013 [39]	Metformin Prestudy level Sulfonylurea Prestudy level	Metformin Prestudy level Sulfonylurea Prestudy level	**(Not included)** As for arm 1 with canagliflozin

	Canagliflozin 300 mg/day	Placebo	in 100 mg dosage
Yki-Jarvinen et al, 2013 [40]	Metformin Prestudy level Basal insulin Prestudy level Linagliptin 5 mg/day	Metformin Prestudy level Basal insulin Prestudy level Placebo	
Jabbour et al, 2014 [41]	Metformin ≥1500 mg/day Sitagliptin 100 mg/day Dapagliflozin 10 mg	Metformin ≥1500 mg/day Sitagliptin 100 mg/day Placebo	
Kovacs et al, 2014 [42]	Metformin Prestudy level Pioglitazone Prestudy level Empagliflozin 25 mg qd	Metformin Prestudy level Pioglitazone Prestudy level Placebo	**(Not included)** As for arm 1 with empagliflozin in 10 mg dosage
Lukashevich et al, 2014 [43]	Metformin ≥1500 mg/day Glimepiride ≥4 mg/day Vildagliptin 50 mg bid	Metformin ≥1500 mg/day Glimepiride ≥4 mg/day Placebo	
Moses et al, 2014 [44]	Metformin Prestudy level Sulfonylurea Prestudy level Saxagliptin 5 mg qd	Metformin Prestudy level Sulfonylurea Prestudy level Placebo	
Wysham et al, 2014 [45]	Metformin 1500-3000 mg/day Pioglitazone 30-45 mg/day Exenatide 5 µg bid for 4 weeks, then 10 µg bid	Metformin 1500-3000 mg/day Pioglitazone 30-45 mg/day Placebo Once weekly	**(Not included)** Arm 3 as for arm 2 replacing placebo with dulaglutide 1.5 mg once weekly Arm 4 as for arm 3 with dulaglutide in 0.75 mg dosage
Home et al, 2015 [46]	Metformin Prestudy level Glimepiride 4 mg/day Albiglutide 30 mg/week	Metformin Prestudy level Glimepiride 4 mg/day Pioglitazone 30 mg/day	Metformin Prestudy level Glimepiride 4 mg/day Placebo
Matthaei et al, 2015 [47]	Metformin Prestudy level Sulfonylurea Prestudy level Dapagliflozin 10 mg qd	Metformin Prestudy level Sulfonylurea Prestudy level Placebo	

Supplementary table 2: Quality of included studies

Study	**Jadad Scale [5]**								
	Was the study described as randomized (this includes the use of words such as randomly, random, and randomization)? *Yes=1, No=0*	Was the method used to generate the sequence of randomization described and appropriate (table of random numbers, computer generated, etc.)? *Yes=1, No=0*	Deduct one point if the method used to generate the sequence of randomization was described and it was inappropriate (patients were allocated alternately, or according to date of birth, hospital number, etc.). *Described but inappropriate=-1, Described and appropriate=0*	Was the study described as double blind? *Yes=1, No=0*	Was the method of double blinding described and appropriate (identical placebo, active placebo, dummy, etc.)? *Yes=1, No=0*	Deduct one point if the study was described as double blind but the method of blinding was inappropriate (e.g. comparison of tablet vs. injection with no double dummy). *Described but inappropriate=-1, described and appropriate=0*	Was there a description of withdrawals and dropouts? *Yes=1, No=0*	Total score	Quality *Score 0-2= Poor quality, Score 3-5= Good quality*
Standl et al, 2001 [9]	1	0	N/A	1	1	0	1	4	Good
Yale et al, 2001 [10]	1	1	0	1	1	0	1	5	Good
Heine et al, 2005 [11]	1	1	0	0	0	N/A	1	3	Good
Kendall et al, 2005 [12]	1	0	N/A	1	1	0	1	4	Good
Roberts et al, 2005 [13]	1	1	-1	1	1	0	1	4	Good
Rosenstock et al, 2006 [14]	1	0	N/A	0	0	N/A	1	2	Poor
Hermansen et al, 2007 [15]	1	1	0	1	1	0	1	5	Good
Nauck et al, 2007 [16]	1	1	0	0	0	N/A	1	3	Good
Kadoglou et al, 2008 [17]	1	0	N/A	0	0	N/A	1	2	Poor
Bergenstal et al, 2009 [18]	1	1	0	0	0	N/A	1	3	Good
Juurinen et al, 2009 [19]	1	1	0	1	1	0	1	5	Good
Raskin et al, 2009 [20]	1	0	N/A	0	0	N/A	1	2	Poor
Russell-Jones et al, 2009 [21]	1	1	0	1	1	-1	1	4	Good

Zinman et al, 2009 [22]	1	1	0	1	1	0	1	5	Good
DeFronzo et al, 2010 [23]	1	1	0	0	0	N/A	1	3	Good
Liutkus et al, 2010 [24]	1	1	-1	1	1	0	1	4	Good
Vilsboll et al, 2010 [25]	1	1	0	1	1	0	1	5	Good
Bosi et al, 2011 [26]	1	0	N/A	1	1	0	1	4	Good
Hollander et al, 2011 [3]	1	1	0	0	0	N/A	1	3	Good
Owens et al, 2011 [27]	1	0	N/A	1	1	0	1	4	Good
Barnett et al, 2012 [28]	1	1	0	1	1	0	1	5	Good
DeFronzo et al, 2012[29]	1	0	N/A	1	1	0	1	4	Good
DeVries et al, 2012 [30]	1	1	0	0	0	N/A	1	3	Good
Violante et al, 2012 [31]	1	0	N/A	1	1	0	1	4	Good
Derosa et al, 2013 [32]	1	1	0	1	1	0	1	5	Good
Dobs et al, 2013 [33]	1	1	0	1	1	0	1	5	Good
Fonseca et al, 2013 [34]	1	0	N/A	1	1	0	1	4	Good
Haring et al, 2013 [35]	1	1	0	1	1	0	1	5	Good
Kothny et al, 2013 [36]	1	1	0	1	1	0	1	5	Good
Liu et al, 2013 [37]	1	1	0	0	0	N/A	1	3	Good
Schernthaner et al, 2013 [38]	1	1	0	1	1	0	1	5	Good
Wilding et al, 2013 [39]	1	1	0	1	1	0	1	5	Good
Yki-Jarvinen et al, 2013 [40]	1	1	0	1	1	0	1	5	Good
Jabbour et al, 2014 [41]	1	0	N/A	1	1	0	1	4	Good
Kovacs et al, 2014 [42]	1	1	0	1	1	0	1	5	Good
Lukashevich et al, 2014 [43]	1	0	N/A	1	1	0	1	4	Good
Moses et al, 2014 [44]	1	1	-1	1	1	0	1	4	Good
Wysham et al, 2014 [45]	1	1	0	0	1	-1	1	3	Good
Home et al, 2015 [46]	1	1	0	1	1	0	1	5	Good
Matthaei et al, 2015 [47]	1	1	0	1	1	0	1	5	Good

Supplementary table 3: Estimated mean difference (95% confidence intervals) in HbA1c* (%) for all pairwise therapy combinations obtained from consistency model

Third therapy added	None/placebo	SU	DPP-4	GLP-1	SGLT2
None/placebo	**None/placebo**	-0.59 (-0.90,-0.28)	-0.56 (-0.71,-0.42)	-0.81 (-1.01,-0.62)	-0.69 (-0.92,-0.46)
SU	0.59 (0.28,0.90)	**SU**	0.03 (-0.29,0.35)	-0.23 (-0.57,0.12)	-0.10 (-0.48,0.28)
DPP-4	0.56 (0.42,0.71)	-0.03 (-0.35,0.29)	**DPP-4**	-0.25 (-0.49,-0.01)	-0.13 (-0.39,0.13)
GLP-1	0.81 (0.62,1.01)	0.23 (-0.12,0.57)	0.25 (0.01,0.49)	**GLP-1**	0.12 (-0.18,0.43)
SGLT2	0.69 (0.46,0.92)	0.10 (-0.28,0.48)	0.13 (-0.13,0.39)	-0.12 (-0.43,0.18)	**SGLT2**
INS	0.91 (0.68,1.13)	0.32 (-0.03,0.66)	0.35 (0.08,0.61)	0.09 (-0.14,0.32)	0.22 (-0.11,0.54)
AGI	0.35 (-0.29,0.99)	-0.24 (-0.95,0.47)	-0.21 (-0.87,0.45)	-0.46 (-1.14,0.21)	-0.34 (-1.02,0.34)
TZD	0.94 (0.69,1.18)	0.35 (-0.03,0.73)	0.38 (0.10,0.65)	0.12 (-0.16,0.41)	0.25 (-0.09,0.58)
MEG	0.37 (-0.26,1.00)	-0.22 (-0.92,0.48)	-0.19 (-0.84,0.45)	-0.44 (-1.10,0.21)	-0.32 (-0.99,0.35)

Third therapy added	INS	AGI	TZD	MEG
None/placebo	-0.91 (-1.13,-0.68)	-0.35 (-0.99,0.29)	-0.94 (-1.18,-0.69)	-0.37 (-1.00,0.26)
SU	-0.32 (-0.66,0.03)	0.24 (-0.47,0.95)	-0.35 (-0.73,0.03)	0.22 (-0.48,0.92)
DPP-4	-0.35 (-0.61,-0.08)	0.21 (-0.45,0.87)	-0.38 (-0.65,-0.10)	0.19 (-0.45,0.84)
GLP-1	-0.09 (-0.32,0.14)	0.46 (-0.21,1.14)	-0.12 (-0.41,0.16)	0.44 (-0.21,1.10)
SGLT2	-0.22 (-0.54,0.11)	0.34 (-0.34,1.02)	-0.25 (-0.58,0.09)	0.32 (-0.35,0.99)
INS	**INS**	0.56 (-0.12,1.24)	-0.03 (-0.33,0.27)	0.54 (-0.13,1.21)
AGI	-0.56 (-1.24,0.12)	**AGI**	-0.59 (-1.28,0.10)	-0.02 (-0.92,0.88)
TZD	0.03 (-0.27,0.33)	0.59 (-0.10,1.28)	**TZD**	0.57 (-0.11,1.24)
MEG	-0.54 (-1.21,0.13)	0.02 (-0.88,0.92)	-0.57 (-1.24,0.11)	**MEG**

*Multiply HbA1c values by 11 to convert HbA1c in DCCT (%) to IFCC (mmol/mol)

AGI=alpha glucosidase inhibitor; DPP-4=dipeptidyl peptidase 4 inhibitor; GLP-1=Glucagon-like peptide-1 receptor agonist; INS=insulin; SGLT2=sodium-glucose linked transporter protein 2 inhibitor; SU=sulfonylurea; TZD= thiazolidinedione;

A positive value suggests that the reduction in HbA1c is worse with the column therapy combination in comparison to the row therapy combination. Likewise, a negative value suggests that the reduction in HbA1c is better with the column therapy combination in comparison to the row therapy combination.

Supplementary table 4: Estimated mean difference (95% confidence intervals) in body weight (kg) for all pairwise therapy combinations obtained from consistency model

Third therapy added	None/placebo	SU	DPP-4	GLP-1	SGLT2
None/placebo	**None/placebo**	3.23 (1.56,4.90)	0.02 (-0.87,0.92)	-1.85 (-2.81,-0.89)	-1.79 (-3.03,-0.55)
SU	-3.23 (-4.90,-1.56)	**SU**	-3.21 (-4.94,-1.48)	-5.08 (-7.00,-3.16)	-5.02 (-7.10,-2.94)
DPP-4	-0.02 (-0.92,0.87)	3.21 (1.48,4.94)	**DPP-4**	-1.88 (-3.17,-0.58)	-1.81 (-3.34,-0.29)
GLP-1	1.85 (0.89,2.81)	5.08 (3.16,7.00)	1.88 (0.58,3.17)	**GLP-1**	0.06 (-1.50,1.63)
SGLT2	1.79 (0.55,3.03)	5.02 (2.94,7.10)	1.81 (0.29,3.34)	-0.06 (-1.63,1.50)	**SGLT2**
INS	-2.34 (-3.51,-1.18)	0.89 (-1.14,2.92)	-2.32 (-3.77,-0.87)	-4.19 (-5.32,-3.07)	-4.13 (-5.83,-2.43)
TZD	-2.72 (-3.99,-1.45)	0.51 (-1.56,2.58)	-2.70 (-4.15,-1.25)	-4.57 (-6.02,-3.13)	-4.51 (-6.29,-2.74)
MEG	-0.20 (-3.14,2.74)	3.03 (-0.35,6.41)	-0.18 (-3.25,2.90)	-2.05 (-5.14,1.04)	-1.99 (-5.18,1.20)

Third therapy added	INS	TZD	MEG
None/placebo	2.34 (1.18,3.51)	2.72 (1.45,3.99)	0.20 (-2.74,3.14)
SU	-0.89 (-2.92,1.14)	-0.51 (-2.58,1.56)	-3.03 (-6.41,0.35)
DPP-4	2.32 (0.87,3.77)	2.70 (1.25,4.15)	0.18 (-2.90,3.25)
GLP-1	4.19 (3.07,5.32)	4.57 (3.13,6.02)	2.05 (-1.04,5.14)
SGLT2	4.13 (2.43,5.83)	4.51 (2.74,6.29)	1.99 (-1.20,5.18)
INS	**INS**	0.38 (-1.15,1.91)	-2.14 (-5.31,1.02)
TZD	-0.38 (-1.91,1.15)	**TZD**	-2.52 (-5.73,0.68)
MEG	2.14 (-1.02,5.31)	2.52 (-0.68,5.73)	**MEG**

AGI=alpha glucosidase inhibitor; DPP-4=dipeptidyl peptidase 4 inhibitor; GLP-1=Glucagon-like peptide-1 receptor agonist; INS=insulin; SGLT2=sodium-glucose linked transporter protein 2 inhibitor; SU=sulfonylurea; TZD= thiazolidinedione;

A positive value indicates that the body weight outcome is worse with the column therapy combination in comparison to the row therapy combination. Likewise, a negative value indicates that the body weight outcome is better with the column therapy combination in comparison to the row therapy combination.

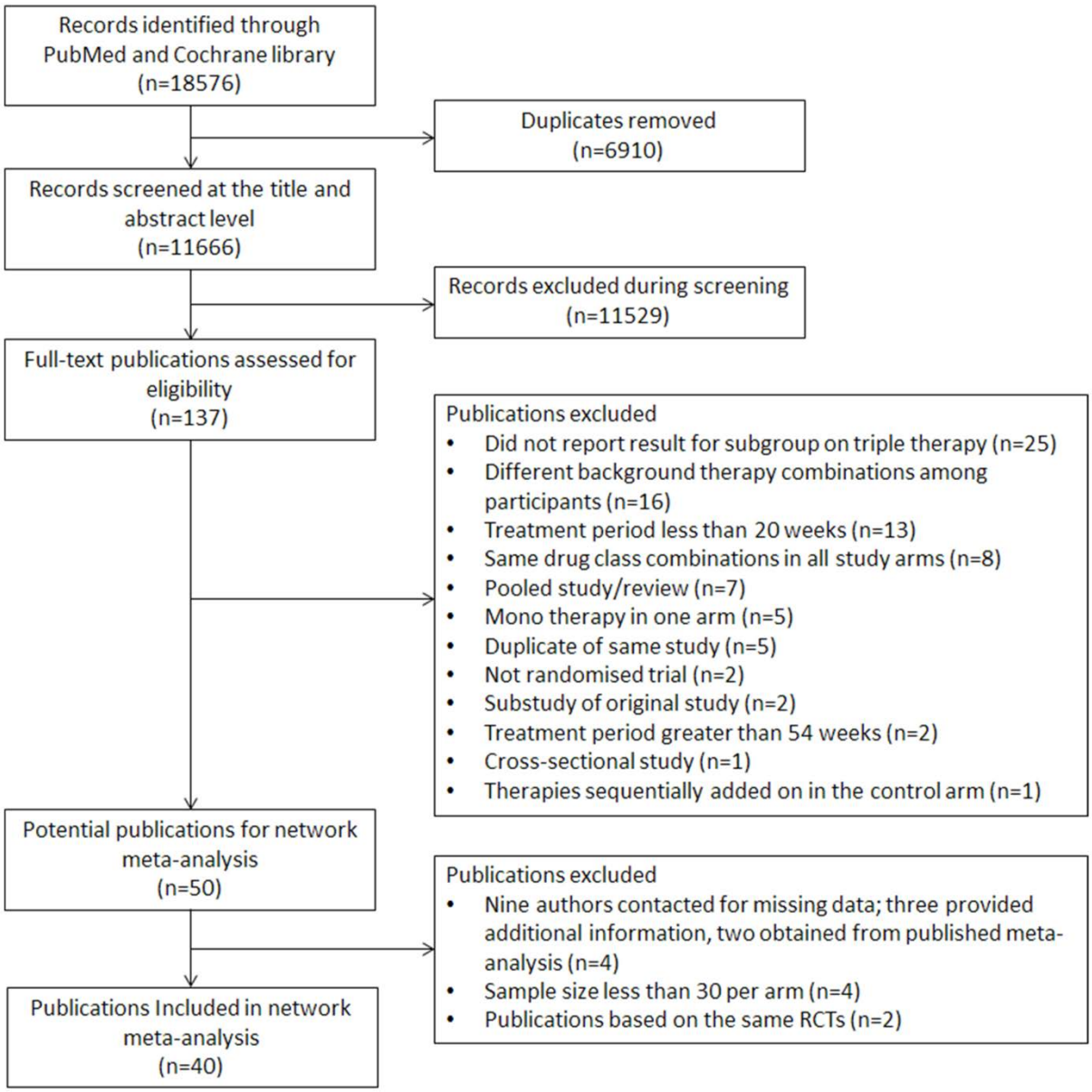
Supplementary table 5: Estimated odds ratios (95% confidence intervals) of hypoglycaemia for all pairwise therapy combinations obtained from consistency mode

Third therapy added	None/placebo	SU	DPP-4	GLP-1	SGLT2
None/placebo	**None/placebo**	2.59 (0.90,7.45)	1.95 (1.15,3.29)	2.61 (1.42,4.79)	2.27 (1.07,4.82)
SU	0.39 (0.13,1.11)	**SU**	0.75 (0.23,2.44)	1.01 (0.30,3.41)	0.88 (0.24,3.21)
DPP-4	0.51 (0.30,0.87)	1.33 (0.41,4.30)	**DPP-4**	1.34 (0.61,2.94)	1.17 (0.51,2.65)
GLP-1	0.38 (0.21,0.71)	0.99 (0.29,3.36)	0.75 (0.34,1.64)	**GLP-1**	0.87 (0.33,2.28)
SGLT2	0.44 (0.21,0.93)	1.14 (0.31,4.16)	0.86 (0.38,1.95)	1.15 (0.44,3.01)	**SGLT2**
INS	0.17 (0.08,0.36)	0.44 (0.12,1.58)	0.33 (0.13,0.80)	0.44 (0.20,0.94)	0.38 (0.13,1.10)
AGI	0.96 (0.02,60.55)	2.47 (0.03,178.76)	1.86 (0.03,121.88)	2.49 (0.04,164.93)	2.17 (0.03,147.07)
TZD	0.35 (0.15,0.82)	0.91 (0.24,3.55)	0.69 (0.27,1.76)	0.92 (0.38,2.26)	0.80 (0.26,2.45)
MEG	0.45 (0.09,2.33)	1.17 (0.17,8.22)	0.88 (0.16,4.92)	1.18 (0.21,6.76)	1.03 (0.17,6.23)

Third therapy added	INS	AGI	TZD	MEG
None/placebo	5.94 (2.80,12.60)	1.05 (0.02,66.23)	2.83 (1.22,6.57)	2.20 (0.43,11.30)
SU	2.30 (0.63,8.35)	0.40 (0.01,29.26)	1.09 (0.28,4.25)	0.85 (0.12,5.98)
DPP-4	3.05 (1.25,7.44)	0.54 (0.01,35.14)	1.45 (0.57,3.70)	1.13 (0.20,6.30)
GLP-1	2.28 (1.06,4.89)	0.40 (0.01,26.58)	1.09 (0.44,2.67)	0.85 (0.15,4.84)
SGLT2	2.61 (0.91,7.52)	0.46 (0.01,31.21)	1.25 (0.41,3.80)	0.97 (0.16,5.87)
INS	**INS**	0.18 (0.00,11.94)	0.48 (0.19,1.21)	0.37 (0.06,2.25)
AGI	5.68 (0.08,384.58)	**AGI**	2.70 (0.04,186.44)	2.11 (0.02,182.08)
TZD	2.10 (0.83,5.32)	0.37 (0.01,25.49)	**TZD**	0.78 (0.12,4.90)
MEG	2.69 (0.45,16.28)	0.47 (0.01,40.98)	1.28 (0.20,8.07)	**MEG**

AGI=alpha glucosidase inhibitor; DPP-4=dipeptidyl peptidase 4 inhibitor; GLP-1=Glucagon-like peptide-1 receptor agonist; INS=insulin; SGLT2=sodium-glucose linked transporter protein 2 inhibitor; SU=sulfonylurea; TZD= thiazolidinedione;

A value greater than one indicates that the column therapy combination is associated with greater odds of hypoglycaemia than the row therapy combination. A value less than one indicates that the column therapy combination is associated with lower odds of hypoglycaemia than the row therapy combination.



Supplementary figure 1: Flow diagram for identifying eligible studies