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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 randomised 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, 15,182 participants from 40 trials with treatment duration of 6–12 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 a 6 month 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.

1. 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

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meta-analysis published in 2011 compared the effects of a number of therapies added to metformin (MET) and sulphonylurea (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 individualised 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.

2. 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].

2.1. 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.

2.2. 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 6–12 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].

2.3. Data analysis

We estimated the mean difference in HbA1c between each drug class added to an existing dual therapy compared to adding 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