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Review Article

Efficacy and safety of antihyperglycaemic drug regimens added to metformin and sulphonylurea therapy in Type 2 diabetes: a network meta-analysis

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What's new?

- This network meta-analysis is the first to assess the comparative efficacy and safety of all 13 currently approved antihyperglycaemic agents (including sodium glucose cotransporter-2 inhibitors) as third-line therapy in people with uncontrolled Type 2 diabetes despite stable, optimized metformin and sulphonylurea therapy.
- Based on HbA_{1c}, weight gain, systolic blood pressure, confirmed hypoglycaemia, urinary tract infections and genital tract infections, we found differences between agents that could help in patient-specific drug selection.
- Our network meta-analysis results support the American Diabetes Association/European Association for the Study of Diabetes pharmacological treatment guididelines regarding the addition of adjunctive antihyperglycaemic agents to existing therapy, including the newer sodium glucose cotransporter-2 inhibitors.

Abstract

Aim To assess the efficacy and safety of third-line adjuvant antihyperglycaemic agents in people with Type 2 diabetes mellitus failing metformin and sulphonylurea combination therapy.

Methods We searched MEDLINE, CENTRAL, clinicaltrials.gov and regulatory websites, and conducted a manual search of references in the identified studies. Randomized trials evaluating antihyperglycaemic agents in adults with Type 2 diabetes experiencing poor glycaemic control despite optimized metformin and sulphonylurea therapy (≥1500 mg metformin or maximum tolerated dose; ≥50% of maximum sulphonylurea dose for ≥3 weeks) were included. Data extraction included: study characteristics; change in HbA_{1c} concentration; weight; systolic blood pressure; and relative risk of hypoglycaemia, urinary tract infections; and genital tract infections. A network meta-analysis was performed.

Results A total of 20 trials evaluating 13 antihyperglycaemic agents were included. Compared with placebo/control, all antihyperglycaemic agents reduced HbA_{1c} levels, albeit by differing magnitudes [range 7 mmol/mol (0.6%) for acarbose to 13 mmol/mol (1.20%) for liraglutide]. Sodium glucose cotransporter-2 inhibitors reduced weight (1.43–2.07 kg) whereas thiazolidinediones, glargine and sitagliptin caused weight gain (1.48–3.62 kg) compared with placebo/control. Sodium glucose cotransporter-2 inhibitors, rosiglitazone and liraglutide decreased systolic blood pressure compared with

placebo/control, pioglitazone, glargine and sitagliptin (2.41–8.88). Glargine, thiazolidinediones, liraglutide, sitagliptin and canagliflozin increased hypoglycaemia risk compared with placebo/control (relative risk 1.92–7.47), while glargine and rosiglitazone increased hypoglycaemia compared with most antihyperglycaemic agents (relative risk 2.81–7.47). No antihyperglycaemic agent increased the risk of urinary tract infection, but canagliflozin increased the risk of genital tract infection by 3.9-fold compared with placebo/control.

Conclusions When added to metformin and a sulphonylurea, antihyperglycaemic agents had varying effects on efficacy and safety endpoints. These conclusions should be considered when clinicians choose between possible adjunctive agents.

Introduction

Type 2 diabetes mellitus is a chronic progressive disease [1] and, despite lifestyle modification and metformin monotherapy, most people experience deterioration in β-cell function and increased insulin resistance, necessitating the use of combination therapies [2–4]. Long-term follow-up of the UK Prospective Diabetes Study showed that people with Type 2 diabetes fail oral therapy at a rate of 5–10% per year, with about half requiring a second agent after 3 years and at least 75% requiring multiple medications by 9 years after diagnosis [5]. Sulphonylureas (SUs) are frequently used as second-line agents but even this combination is inadequate in many people and triple therapy is used [6]. Numerous antihyperglycaemic agents (AHAs) are available for adjunctive third-line therapy, including a new class of sodium glucose cotransporter-2 (SGLT2) inhibitors. A third-line adjuvant agent should be one that is effective in reducing HbA_{1c} levels with a low risk or magnitude of adverse events. With the aim of helping clinicians to choose the optimum therapy, we performed a network meta-analysis (NMA) to assess the comparative efficacy and safety of third-line adjunctive AHAs in people with Type 2 diabetes not adequately controlled on a stable, optimized combination of metformin and SU.

Methods

Data sources and searches

We performed a systematic literature search for all relevant articles from the earliest possible date up to May 2014 in MEDLINE and Cochrane CENTRAL bibliographic databases. Our search strategy combined the medical subject heading terms and keywords for 'metformin', Type 2 diabetes and HbA_{1c} (Appendix S1). In addition, we performed a manual search of references from reports of randomized

controlled trials (RCTs), previous meta-analyses and review articles to identify additional relevant studies. The results of identified studies were supplemented with data identified through the grey literature, including regulatory agency reports and www.clinicaltrials.gov, and through contacting investigators for clarification or additional data. Two investigators reviewed all potentially relevant citations independently.

Study selection

To be included in this meta-analysis, studies had to: (1) be published in English; (2) use a parallel-RCT design (any phase) in adult subjects with Type 2 diabetes; (3) compare US Food and Drug Administration or European Union-approved Type 2 diabetes drug therapy including non-insulin and long-acting, once-daily basal insulin agents (as a single or combination therapy) with another Type 2 diabetes drug therapy or placebo/control (in addition to metformin and an SU); (4) include only patients who showed inadequate response [defined as a having an HbA_{1c} concentration >53 mmol/mol (7%)] to stable, optimum metformin and SU combination therapy at randomization; (5) treat subjects for 12–52 weeks after randomization; and (6) report change in HbA_{1c} concentration from baseline. The criterion of stable therapy was considered to be met if an RCT included participants who received ≥1500mg/day (or maximum tolerated dose) of metformin (or 1000 mg/day as long as the mean dose in the study was ≥1500 mg/day) and ≥50% of the maximum daily dose of SU (glipizide 20 mg; glyburide/glibenclamide 10 mg; glimepiride 4 mg; gliclazide 160 mg) [7]. In addition, patients had to be on metformin and SU combination therapy for at least 3 weeks before randomization, or the study had to explicitly state that patients failed stable therapy [8].

Data extraction and quality assessment

Two independent investigators assessed the quality of each included RCT using the Cochrane Risk of Bias tool [9,10]. This checklist includes seven quality questions covering the following domains: random sequence generation, allocation concealment, blinding, blinding of outcome assessment, incomplete data reporting, and selective reporting. Each item was scored as a low, unclear or high risk of bias as described in Appendix S2.

Two investigators used a standardized tool to extract all data independently, with disagreements resolved by discussion or by a third investigator. The following data were extracted for each RCT: (1) author identifier and year of publication; (2) study design and methodological quality information needed to complete validity assessment; (3) sample size; (4) inclusion/exclusion criteria; (5) duration of follow-up; (6) metformin, SU and other AHA doses and schedules; and (7) baseline characteristics (age, gender, anthropometrics, baseline HbA_{1c} and duration of Type 2 diabetes). Our primary endpoint for this network

meta-analysis was the mean change from baseline in HbA_{1c}. If a study did not report the change in HbA_{1c} from baseline for each agent, we calculated the change using accepted methods [9]. Secondary endpoints included the mean change from baseline in body weight and systolic blood pressure (SBP), and the proportion of participants experiencing confirmed hypoglycaemia, urinary tract infections (UTIs) and genital tract infections (GTIs).

Data synthesis and analysis

We performed traditional meta-analyses, analysing changes in HbA_{1c}, body weight and SBP as continuous variables using STATSDIRECT version 2.7.8 (StatsDirect Ltd, Altrincham, UK) with a *P* value <0.05 taken to indicate statistical significance. We did not pool agents within the same class so as to allow for evaluation of intraclass differences in efficacy and safety endpoints. Pairwise meta-analyses were performed for each AHA, combining data from approved doses of the same therapies using accepted methods [9]. In all cases, weighted (absolute) mean differences and associated 95% CIs were calculated using a random-effects approach to account for between-study heterogeneity. Net changes in each of the endpoints were calculated as the difference between treatment groups in the changes (baseline to follow-up). The risk of participants experiencing confirmed hypoglycaemia, UTI and GTI on each drug therapy (combining data from approved doses of the same therapies) was meta-analysed using a random-effects model and weighted averages were reported as relative risks and 95% CIs. When at least three studies making the same direct comparison were available, the likelihood of statistical heterogeneity (using the I^2 statistic, with a value >50% representing important statistical heterogeneity) and publication bias (using the Egger's weighted regression statistic, with a *P* value <0.05 suggesting a higher likelihood of publication bias) were assessed.

We then performed a network meta-analysis which, in addition to analysing direct within-trial comparisons between two treatments, enables incorporation of indirect comparisons constructed from two trials that have one treatment in common [9,11]. This type of analysis safeguards the within-trial randomized treatment comparison of each trial while combining all available comparisons between treatments. We used the package 'NETMETA' (version 0.5-0) in R (version 3.0.2, The R Foundation for Statistical Computing) to perform the network meta-analysis [12]. The package constructs a Frequentist network meta-analysis model accounting for the correlated treatment effects in multi-arm trials [13]. A random-effects model assuming common heterogeneity across all comparisons was implemented. We assessed inconsistency in our network meta-analysis using a 'loop-specific' approach [14,15]. We evaluated inconsistency in all closed loops of evidence formed by three treatments (triangle loops) within each network. This was carried out by statistically comparing direct with indirect estimates of a specific

treatment effect. We used the loop-specific approach because it is simple, easily applied without specialized software, and the most frequently applied approach in network meta-analysiss.

Results

Study characteristics

The literature search yielded 1014 citations with nine additional RCTs identified through other sources (Fig. 1). After removal of duplicates and title/abstract screening, 318 articles were eligible for full-text screening, resulting in the inclusion of 20 RCTs in the network meta-analysis [8,16–34]. Thirteen treatments, as well as placebo/control, were analysed including an α-glucosidase inhibitor (acarbose), dipeptidyl peptidase-4 (DPP-4) inhibitors (linagliptin, saxagliptin, sitagliptin and vildagliptin), glucagon-like peptide-1 (GLP-1) analogues (exenatide and liraglutide), a long-acting once-daily basal insulin (insulin glargine), SGLT2 inhibitors (canagliflozin, dapagliflozin and empagliflozin) and thiazolidinediones (TZDs; rosiglitazone and pioglitazone).

Characteristics of the included trials are described in Table S1. The trial duration range was 16–52 weeks; mean age 41–67 years; BMI 24–35 kg/m^2; weight 65–99 kg; SBP 127–146 mmHg; and baseline HbA_{1c} 64–80 mmol/mol (8.0–9.5%). Figure 2 shows the network of RCTs with available direct comparisons for the HbA_{1c} endpoint, and individual RCT endpoint data are shown in Table 1 [8,16–34]. The quality of RCTs for each of the seven bias domains is shown in Fig. S1.

Main network meta-analysis endpoint comparisons

Table 2 shows the results of traditional meta-analysis and network meta-analysis for comparators that were directly compared with placebo/control or were directly compared with another active therapy. The main results are summarized in the text below and full network meta-analysis comparisons are included in the supplemental figures.

Change in HbA_{1c}

All AHAs assessed in the network meta-analysis significantly lowered HbA_{1c} from baseline but by different magnitudes [ranging from 7 mmol/mol (0.6%) for acarbose and linagliptin to 13 mmol/mol (1.20%) for liraglutide] when compared with placebo/control**.** Canagliflozin, GLP-1 analogues, insulin glargine and TZDs all reduced HbA_{1c} by ~11 mmol/mol (1%) [11–13 mmol/mol (0.98–1.2%)]; whereas acarbose, dapagliflozin, empagliflozin and DPP-4 inhibitors reduced HbA_{1c} by 7–8 mmol/mol (0.60–0.76%) when compared with placebo/control. When comparing active drugs, liraglutide, insulin glargine

and TZDs significantly reduced HbA_{1c} compared with empagliflozin and DPP-4 inhibitors (with the exception of vildagliptin; Fig. S2). Among the SGLT2 inhibitors, canagliflozin was the only therapy for which statistically significant reductions in HbA_{1c} were observed when compared with other active therapies, while dapagliflozin was inferior to liraglutide and rosiglitazone.

Body weight

The SGLT2 inhibitors were the only agents that showed statistically significant weight loss compared with placebo/control (1.43–2.07 kg) while the TZDs, glargine and sitagliptin resulted in significant weight gain compared with placebo/control (1.48–3.62 kg). GLP-1 agonists, acarbose, linagliptin and saxagliptin were weight-neutral compared with placebo/control. When comparing active drugs, pioglitazone resulted in statistically significant weight gain compared with all other therapies except rosiglitazone and insulin glargine (2.14–5.69 kg). All SGLT-2 inhibitors, acarbose and GLP-1 analogues were associated with statistically greater weight loss compared with insulin glargine and TZDs (2.98–5.69 kg; Fig. S3). Data for vildagliptin was not available for this endpoint.

Systolic blood pressure

Rosiglitazone, liraglutide and all SGLT2 inhibitors, significantly decreased SBP compared with placebo/control (2.93–6.83 mmHg). Pioglitazone, sitagliptin and insulin glargine had a neutral effect on SBP. In active drug comparisons, rosiglitazone significantly reduced SBP when compared with all other therapies analysed (3.43–9.38 mmHg) except dapagliflozin where SBP reductions were similar. All SLGT2 inhibitors and liraglutide were associated with a significant decrease in SBP compared with pioglitazone, insulin glargine and sitagliptin (Fig. S4). No data were available to assess the impact of acarbose, exenatide, linagliptin, saxagliptin or vildagliptin on SBP.

Confirmed hypoglycaemia

The TZDs, glargine, sitagliptin, liraglutide, and canagliflozin were associated with significantly higher rates of confirmed hypoglycaemia compared with placebo/control (relative risk 1.92–7.47). In contrast, empagliflozin, exenatide and DPP-4 inhibitors (with the exception of sitagliptin) were not. In active drug comparisons, glargine and rosiglitazone were associated with significantly higher rates of confirmed hypoglycaemia compared with the SGLT-2 inhibitors, exenatide, linagliptin and sitagliptin (Fig. S5). There were no data assessing the impact of acarbose and dapagliflozin on hypoglycaemia.

Urinary and genital tract infections

There were no data evaluating three of the agents (acarbose, pioglitazone and rosiglitazone) for the UTI endpoint and only four of the 13 agents (all SGLT2 inhibitors and sitagliptin) reported on GTI. No evaluable therapy was associated with an increased risk of UTI when compared with placebo/control and only canagliflozin was associated with a greater risk of GTI compared with placebo/control (relative risk 3.9, 95% CI 1.58--9.6) and sitagliptin (relative risk 5.64, 95% CI 2.68–11.88; Figs S6 and S7).

Direct and indirect meta-analysis coherence

The results of the direct (pairwise) meta-analysis are reported in Tables S2–S7. When comparing the results of the 36 possible direct and indirect effect estimates across all six endpoints, we found evidence of incoherence for only two comparisons; both for the body weight endpoint (canagliflozin–sitagliptin–placebo and pioglitazone–sitagliptin–placebo).

Discussion

In our network meta-analysis of 20 RCTs conducted from the earliest date up to May 2014, we found all AHAs significantly reduced HbA_{1c} as compared with placebo/control when added to metformin and SU therapy. Evaluated AHAs could generally be broken into two broad groups, those that lower HbA_{1c} by 7–8 mmol/mol (0.60–0.76%) and those that lower HbA_{1c} by ≥11 mmol/mol (1%). The American Diabetes Association/European Association for the Study of Diabetes guidelines state that with regard to triple therapy, the new SGLT2 inhibitors are a reasonable option [1] and the results of our network meta-analysis support this recommendation. Despite the potent HbA_{1c}-lowering effects of injectables such as insulin glargine and GLP-1 analogues, many peoples' strong apprehension about needles and self-injections may still make oral agents, such as SGLT2 inhibitors, a better choice for them [17]. Importantly, our meta-analysis suggests patients can be prescribed many oral agents with minimal sacrifice of glycaemic efficacy.

While glycaemic efficacy is an important consideration, an agent with the best balance of HbA_{1c} reduction to adverse effects will be the optimum third-line choice. In our network meta-analysis, we selected change in body weight, SBP and risk of confirmed hypoglycaemia as endpoints because they encompass the most common and troubling adverse events and comorbidities for people with Type 2 diabetes. In particular, hypoglycaemia is a critical safety characteristic of AHAs, with ramifications ranging from excessive sweating, tachycardia and dizziness to cardiac arrhythmias, coma or even death [35]. Glargine, rosiglitazone, pioglitazone and sitagliptin were found to increase the risk of hypoglycaemic events compared with placebo/control. Among the new SGLT2 agents, canagliflozin

showed a twofold increased risk of hypoglycaemia; whereas empagliflozin showed no difference compared with placebo/control (no data were available to assess dapagliflozin). Glargine was found to lead to a significantly elevated risk of hypoglycaemia compared with both cangliflozin and empagliflozin (relative risk 3.73–4.58).

Many people with Type 2 diabetes are overweight or obese [35] and even modest weight loss can reduce the incidence of diabetes-related cardiovascular complications [36]. In our network meta-analysis, glargine as well as the TZDs and sitagliptin were associated with increases in body weight, which may offset at least some of their beneficial effects on the cardiovascular system gained through good glycaemic control [37]. Unlike SUs and insulins, which increase weight gain by enhancing adiposity and accelerating atherosclerosis, TZDs increase body weight by causing fluid retention which can exacerbate heart failure in some people. In our analysis, only the SGLT2 inhibitors significantly reduced body weight when compared with placebo/control; probably as a result of their novel mechanism of urinary glucose excretion and resulting caloric losses [38]. When compared with other active agents (such as glargine and TZDs), the SGLT2 inhibitors, GLP-1 analogues and acarbose showed dramatic reductions in body weight ranging between 3 and 5.5 kg.

There is a direct correlation between increased blood pressure and the development of albuminuria, a marker of glomerular nephropathy [39]. People with Type 2 diabetes are already at an elevated risk of nephropathy from both diabetes and associated obesity [40]. Moreover, evidence suggests blood pressure control reduces the risk of micro- and macrovascular disease related to diabetes [41]; therefore, blood pressure regulation is a very important endpoint to assess when selecting an AHA. The SGLT2 inhibitors, rosiglitazone and liraglutide were associated with significant decreases in SBP compared with placebo/control and most other agents analysed in our network meta-analysis.

People with Type 2 diabetes, especially women, have an increased risk of developing UTIs and GTIs from a variety of bacterial and fungal species, and initial trials suggest SGLT2 inhibitors may further increase this risk [42,43]. In addition to the above-mentioned adverse effect endpoints, therefore, we evaluated the risk of UTI and GTI in our network meta-analysis. Although SGLT2 inhibitors act by inducing glycosuria and predispose patients to bacterial and mycotic growth, we did not find a greater risk of UTIs for this drug class or any other evaluable agent compared with placebo/control. Canagliflozin increased the risk of GTI compared with placebo/control and sitagliptin. Nevertheless, it is important to counsel people with Type 2 diabetes on signs and symptoms of both UTIs and GTIs.

Despite some differences in inclusion/exclusion criteria (including our exclusion of non-US Food and Drug Administration- or European Union-approved agents, inclusion of only long-acting, once-daily

basal insulins, and a more stringent definition of maximum metformin dosing), our HbA_{1c} results are similar to those of a previous network meta-analysis by Gross *et al.* [44]. The authors of that meta-analysis reported a reduction in HbA_{1c} levels ranging from 8 to 12 mmol/mol (0.70 to 1.08%) when a third AHA was added to metformin and SU therapy. The present analysis is unique, however, in that: it included eight additional trials not available at the time the previous network meta-analysis was published; additional drug classes were assessed including the SGLT-2 inhibitors; other endpoints pertinent to people with Type 2 diabetes (SBP, confirmed hypoglycaemia, UTI and GTI) were included; and we only assessed long-acting once-daily basal insulins rather than allowing all insulin agents (including short-acting and mixed) to be pooled together [44,45]. Additionally, our network meta-analysis used strict inclusion criteria and included only trials that required stable and optimized metformin therapy before randomization; unlike a previous analysis by McIntosh *et al*. [45], which disregarded current or previous metformin therapy duration and dose. This latter criterion is important as guidelines recommend a stepwise approach to treatment as a way to optimize glycaemic control [1].

Our network meta-analysis has several limitations. First, we did not assess other agent-specific endpoints (e.g. pancreatitis, gastrointestinal effects and cardiovascular events) because of a lack of data and short follow-up of included trials. Secondly, many AHAs were only compared in one or two trials and certain endpoints were sparsely reported (UTI and GTI), which makes it difficult to draw concrete conclusions (potential for type 2 error). At the same time, we either directly and/or indirectly compared 13 AHAs plus placebo/control on six different endpoints; thus there is the possibility of erred conclusions of statistical differences between therapies (type 1 error) because of multiple hypothesis testing. Thirdly, most trials only followed patients for 24 weeks, which is not sufficient to assess the long-term durability of medications. Next, we saw little evidence of incoherence in our network (as evidenced by finding only two out of 36 possible direct vs. indirect evidence comparisons statistically significant). While, we cannot entirely exclude the presence of incoherence in our network, the two statistically significant findings stemming from 36 statistical tests are consistent with what would be expected due to chance (the probability of observing one significant result just due to chance in our analysis = $1-(1-0.05)^{36}$ or 84%). Finally, the quality of trial reporting and conduct varied between studies, with seven out of 20 trials being open-label, and incomplete outcomes data and selective reporting being somewhat common sources of potential bias. Despite these limitations, however, in the absence of head-to-head trials addressing every endpoint for all AHAs, our network meta-analysis provides the most comprehensive and current evidence available to help clinicians choose an appropriate individualized agent for third-line adjunctive therapy.

Understanding the comparative efficacy and safety of available agents is critical to individualizing therapy for patients with Type 2 diabetes. When selecting an add-on agent to metformin and an SU,

improving glycaemic control must be balanced with the risks of unwanted adverse effects (or the potential for other beneficial effects). Using important health outcomes, such as HbA_{1c}, weight gain, SBP, confirmed hypoglycaemia, UTIs and GTIs, we found differences between agents that can help in patient-specific drug selection. Taken as a whole, our network meta-analysis results support the American Diabetes Association/European Association for the Study of Diabetes pharmacological treatment guidelines which recommend TZDs, DPP-4 inhibitors, GLP-1 analogues, SGLT2 inhibitors or basal insulin for third-line add-on treatments to metformin and SUs [1].

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Competing interests

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Supporting information

Additional Supporting Information may be found in the online version of this article:

Appendix S1. Medline search strategy.

Appendix S2. Grading parameters for the Cochrane Risk of Bias tool.

Table S1. Baseline characteristics of randomized controlled trials evaluating antihyperglycaemic agents in addition to metformin and a sulphonylurea in adults with Type 2 diabetes.

Table S2. Results of traditional meta-analysis comparing effect of antihyperglycaemic agents on HbA_{1c}.

Table S3. Results of traditional meta-analysis comparing effect of antihyperglycaemic agents on body weight.

Table S4. Results of traditional meta-analysis comparing effect of antihyperglycaemic agents on systolic blood pressure.

Table S5. Results of traditional meta-analysis comparing effect of antihyperglycaemic agents on experiencing confirmed hypoglycemia

Table S6. Results of traditional meta-analysis effect of antihyperglycaemic agents on experiencing urinary tract infections

Table S7. Results of traditional meta-analysis comparing effect of antihyperglycaemic agents on experiencing genital tract infections.

Figure S1. Risk of Bias Assessment of Randomized Controlled Trials

Figure S2. Network meta-analysis results of the effect of antihyperglycemic agents on change in HbA_{1c} from baseline.

Figure S3. Network meta-analysis results of the effect of antihyperglycemic agents on change in body weight from baseline.

Figure S4. Network meta-analysis results of the effect of antihyperglycaemic agents on change in systolic blood pressure from baseline.

Figure S5. Network meta-analysis results of the effect of antihyperglycaemic agents on risk of confirmed hypoglycaemia.

Figure S6. Network meta-analysis results of the effect of antihyperglycaemic agents on risk of urinary tract infections.

Figure S7. Network meta-analysis results of the effect of antihyperglycaemic agents on risk of genital tract infections.

FIGURE 1 Results of the literature search. CCTR, Cochrane Controlled Trials Register; EU, European Union; FDA, US Food and Drug Administration; SU, sulphonylurea.

FIGURE 2 Network diagram of randomized controlled trials evaluating antihyperglycaemic agents in addition to metformin and a sulphonylurea in Type 2 diabetes. All therapies are in combination with metformin and a sulphonylurea. Lines represent the presence of direct comparison trial(s). All direct comparisons were based upon a single study; except where otherwise indicated.

Table 1 Outcomes reported in randomized controlled trials evaluating antihyperglycaemic agents added to metformin and a sulphonylurea in adult patients with Type 2 diabetes

Author, Year	**Interventions evaluated**	***N****	**Change in HbA_{1c}, mean, mmol/mol (SE)**	**Change in HbA_{1c}, mean, % (SE)**	**Change in body weight, mean, kg (SE)**	**Change in SBP, mean, mmHg (SE)**	**Confirmed hypoglycaemia (*n*/*N*)**	**UTI (*n*/*N*)**	**GTI (*n*/*N*)**
Moses 2014 [16]	Saxagliptin 5 mg once daily	127	-8 (1)	-0.74 (0.07)	0.2 (0.19)	NR	2/129	4/129	NR
	Placebo	127	-1 (1)	-0.08 (0.08)	-0.6 (0.19)	NR	0/128	8/129	NR
Lukashevich 2014 [17]	Vildagliptin 50 mg twice daily	158	-11 (1)	-1.01 (0.10)	0.5 (NR)	NR	8/157	10/158	NR
	Placebo	160	-3 (1)	-0.25 (0.10)	-0.1 (NR)	NR	3/160	13/160	NR
NCT01392677/ D1693C0005 [18]	Dapagliflozin 10 mg once daily	108	-9 (1)	-0.86 (0.07)	-2.65 (0.26)	-4.04 (1.18)	NR	5/109	6/109
	Placebo	108	-2 (1)	-0.17 (0.10)	-0.58 (0.26)	-0.27 (1.19)	NR	7/109	0/109
NCT01076075/ MK-0431-229 [19]	Sitagliptin 100 mg once daily	203	-9 (1)	-0.84 (0.07)	NR	NR	38/210	NR	NR
	Placebo	202	-2 (1)	-0.16 (0.06)	NR	NR	31/212	NR	NR
Liu 2013 [20]	Sitagliptin 100 mg once daily	60	-8 (1)	-0.71 (0.12)	-0.26 (0.32)	0 (0.9)	6/60	NR	NR
	Pioglitazone 30 mg once daily	59	-10 (1)	-0.94 (0.12)	1.34 (0.32)	-0.5 (0.9)	5/60	NR	NR
Häring 2013 [21]	Empagliflozin 10 mg once daily	225	-9 (1)	-0.82 (0.05)	-2.16 (0.15)	-4.1 (0.7)	36/224	23/225	6/225
	Empagliflozin 25	216	-8 (1)	-0.77	-2.39	-3.5 (0.7)	25/217	18/216	5/216

	mg once daily			(0.05)	(0.16)				
	Placebo	225	-2 (1)	-0.17 (0.05)	-0.39 (0.15)	-1.4 (0.7)	19/225	18/225	2/225
Wilding 2013 [8]	Canagliflozin 100 mg once daily	157	-8 (1)	-0.75 (0.10)	-1.0 (0.41)	-3.7 (1.0)	53/157	13/157	21/157
	Canagliflozin 300 mg once daily	156	-11 (1)	-0.97 (0.10)	-2.1 (0.43)	-2.9 (1.0)	57/156	13/156	18/156
	Placebo	156	Referent	Referent	Referent	0.1 (1.0)	28/156	12/156	5/156
Schernthaner 2013 [22]	Canagliflozin 300 mg once daily	377	-4 (1)	-0.37 (0.06)	-2.5 (0.2)	-5.1 (0.66)	163/377	15/377	45/377
	Sitagliptin 100 mg once daily	378	Referent	Referent	0.3 (0.2)	0.85 (0.67)	154/378	21/378	8/378
Owens 2011 [23]	Linagliptin 5 mg once daily	778	-8 (0)	-0.7 (0.03)	0.27 (0.09)	-0.31 (NR)	132/792	26/792	NR
	Placebo	262	-1 (1)	-0.1 (0.05)	-0.06 (0.16)	0.63 (NR)	27/263	14/263	NR
Kadoglou 2010 [24]	Maintenance of habitual activities	21	6 (1)	0.51 (0.13)	NR	0.79 (0.55)	NR	NR	NR
	Rosiglitazone 8 mg once daily	23	-9 (2)	-0.83 (0.19)	NR	-6.38 (0.67)	NR	NR	NR
	Exercise alone	22	-3 (1)	-0.29 (0.12)	NR	-6.29 (0.90)	NR	NR	NR
	Rosiglitazone 8 mg once daily plus exercise	23	-16 (2)	-1.42 (0.19)	NR	-13.08 (1.31)	NR	NR	NR
Russell-Jones 2009 [25]	Liraglutide 1.8 mg once daily	230	-15 (1)	-1.33 (0.09)	-1.8 (0.33)	-4.0 (1.3)	73/230†	3/230	NR
	Insulin glargine, dose algorithm	114	-12 (1)	-1.09 (0.09)	1.6 (0.33)	0.5 (1.3)	67/114	3/114	NR
	Placebo	232	-3 (1)	-0.24 (0.11)	-0.42 (0.39)	-1.4 (1.6)	19/232	2/232	NR
Charpentier 2009 [26]	Pioglitazone 30-45 mg once daily (>90% at 45 mg)	142	-13 (1)	-1.18 (0.11)	3.9 (0.25)	NR	35/145	NR	NR
	Placebo	147	Referent	Referent	-0.2 (0.25)	NR	11/154	NR	NR
Kadoglou 2008 [27]	Rosiglitazone 8 mg once daily	35	-10 (1)	-0.9 (0.07)	NR	-7 (2.89)	NR	NR	NR
	Control	35	3 (1)	0.3 (0.10)	NR	-2 (3.06)	NR	NR	NR
Hermansen 2007 [28]	Sitagliptin 100 mg once daily	116	-6 (1)	-0.59 (0.08)	0.40 (0.26)	NR	19/116	NR	NR

	Placebo	113	3 (1)	0.30 (0.08)	-0.7 (0.33)	NR	1/113	NR	NR
Triplitt 2006 [29]	Insulin glargine dose algorithm	10	-16 (2)	-1.5 (0.2)	4.7 (1.0)	-2 (4.58)	0/10	NR	NR
	Rosiglitazone 4 mg twice daily	10	-20 (4)	-1.8 (0.4)	2.3 (1.0)	2 (4.00)	1/10	NR	NR
Rosenstock 2006 [30]	Insulin glargine dose algorithm	104	-2 (1)	-0.15 (0.10)	1.7 (0.4)	NR	57/104	NR	NR
	Rosiglitazone 4-8 mg once daily (mean dose=7.1 mg once daily)	112	Referent	Referent	3.0 (0.4)	NR	47/112	NR	NR
Heine 2005 [31]	Exenatide 10 µg twice daily	282	0 (1)	0 (0.07)	-2.32 (0.21)	NR	NR	7/282	NR
	Insulin glargine dose algorithm	267	Referent	Referent	1.75 (0.21)	NR	NR	3/267	NR
Kendall 2005‡ [32]	Exenatide 5 µg twice daily	NR	-8 (1)	-0.7 (0.1)	NR	NR	27/123	NR	NR
	Exenatide 10 µg twice daily	NR	-10 (1)	-0.9 (0.1)	NR	NR	42/121	NR	NR
	Placebo	NR	2 (1)	0.2 (0.1)	NR	NR	19/124	NR	NR
Dailey 2004 [33]	Rosiglitazone 4-8 mg once daily (mean dose=7.4mg once daily)	181	-10 (1)	-0.9 (0.09)	3.0 (NR)	NR	40/181	NR	NR
	Placebo	184	1 (1)	0.1 (0.07)	0.03 (NR)	NR	6/184	NR	NR
Lam 1998 [34]	Acarbose 100 mg three times daily	41	-6 (2)	-0.5 (0.2)	-0.54 (0.32)	NR	NR	NR	NR
	Placebo	40	1 (2)	0.1 (0.2)	0.42 (0.29)	NR	NR	NR	NR

GTI, genital tract infection; NR, not reported; SBP, systolic blood pressure; SU, sulphonylurea; UTI, urinary tract infection.

*Number of study participants evaluated for change in HbA_{1c} from baseline (sample size may vary for other endpoints).

† Determined by adding both minor and severe hypoglycaemic events together.

‡Includes only those participants randomized to receive double-blind study treatment along with a maximum dose of sulphonylurea.

Table 2 Results of direct placebo and active comparisons of network meta-analysis and traditional meta-analysis on change in HbA_{1c}, body weight and systolic blood pressure

Comparison	_____Change in HbA_{1c}, mmol/mol [%]_____			_____Change in body weight, kg_____			_Change in SBP, mmHg_		
	No. of trials, n*	Direct estimate, WMD (95% CI)	Network meta-analysis Estimate, WMD (95% CI)	No. of trials, n*	Direct estimate, WMD (95% CI)	Network meta-analysis estimate, WMD (95% CI)	No. of trials, n*	Direct estimate, WMD (95% CI)	Network meta-analysis estimate, WMD (95% CI)
Direct placebo comparisons									
Acarbose	1	-7 (-13, -1) [-0.60 (-1.15, -0.05)]	-7 (-13, 0) [-0.60 (-1.19, -0.01)]	1	-0.96 (-1.8, -0.12)	-0.96 (-2.52, 0.6)	0	–	–
Canagliflozin	1	-9 (-11,-8) [-0.86 (-1.00, -0.72)]	-11 (-13, -9) [-0.98 (-1.18, -0.78)]	1	-1.55 (-2.16, -0.94)	-1.40 (-2.58, 0.28)	1	-3.40 (-5.81, -0.99)	-3.40 (-5.97, -0.83)
Dapagliflozin	1	-8 (-10, -5) [-0.69 (-0.93, -0.45)]	-8 (-11, -4) [-0.69 (-1.01, -0.37)]	1	-2.07 (-2.80, -1.34)	-2.07 (-3.57, -0.57)	1	-3.77 (-7.06, -0.48)	-3.77 (-7.28, -0.26)
Empagliflozin	1	-7 (-8, -5) [-0.63 (-0.77, -0.49)]	-7 (-10, -4) [-0.63 (-0.88, -0.38)]	1	-1.88 (-2.25, -1.51)	-1.88 (-3.25, -0.51)	1	-2.41 (-4.08, -0.74)	-2.41 (-4.19, -0.63)
Exenatide	1	-11 (-14, -8) [-1.00 (-1.24, -0.76)]	-11 (-14, -8) [-1.01 (-1.25, -0.77)]	0	–	-2.05 (-4.33, 0.23)	0	–	–
Insulin glargine	1	-9 (-13, -6) [-0.85 (-1.18, -0.52)]	-12 (-14, -9) [-1.07 (-1.29, -0.85)]	1	2.02 (0.84, 3.20)	2.02 (0.26, 3.78))	1	1.90 (-2.92, 6.72)	1.31 (-1.59, 4.22)
Linagliptin	1	-7 (-8, -5) [-0.60 (-0.72, -0.48)]	-7 (-9, -4) [-0.60 (-0.84, -0.36)]	1	0.33 (-0.02, 0.68)	0.33 (-1.03, 1.69)	0	–	–
Liraglutide	1	-12 (-15, -9) [-1.09 (-1.36, -0.82)]	-13 (-17, -10) [-1.20 (-1.51, -0.89)]	1	-1.38 (-2.38, -0.38)	-1.38 (-3.03, 0.27)	1	-2.53 (-5.35, 0.29)	-2.93 (-5.51, -0.35)
Pioglitazone	1	-13 (-15, -10) [-1.17 (-1.39, -0.95)]	-12 (-15, -9) [-1.09 (-1.34, -0.84)]	1	4.10 (3.41, 4.79)	3.62 (2.43, 4.82)	0	–	2.05 (-2.13, 6.23)

Rosiglitazone	4	-12 (-14, -11) [-1.12 (-1.26, -0.98)]	-12 (-14, -10) [-1.08 (-1.25, -0.91)]	0	–	2.43 (0.11, 4.74)	3	-7.01 (-8.50, -5.53)	-6.83 (-8.40, -5.25)
Saxagliptin	1	-7 (-10, -5) [-0.66 (-0.88, -0.44)]	-7 (-11, -4) [-0.66 (-0.96, -0.36)]	1	0.80 (0.27, 1.33)	0.80 (-0.62, 2.22)	0	–	–
Sitagliptin	2	-9 (-11, -6) [-0.78 (-0.98, -0.57)]	-8 (-10, -6) [-0.7 (-0.9, -0.56)]	1	1.10 (0.28, 1.92)	1.48 (0.41, 2.56)	0	–	2.55 (-0.68, 5.78)
Vildagliptin	1	-8 (-11, -5) [-0.76 (-1.03, -0.49)]	-8 (-12, -5) [-0.76 (-1.11, -0.41)]	0	–	–	0	–	–
Direct active comparisons									
Canagliflozin vs. sitagliptin	1	-4 (-6, -3) [-0.37 (-0.51, -0.23)]	-3 (-5, -1) [-0.25 (-0.45, -0.05)]	1	-2.80 (-3.35, -2.25)	2.44 (1.88, 3)	1	-5.95 (-7.79, -4.11)	-5.95 (-7.91, -3.99)
Exenatide vs. insulin glargine	1	1 (-1, 2) [0.05 (-0.11, 0.21)]	1 (-2, 3) [0.06 (-0.16, 0.28)]	1	-4.07 (-4.66, -3.48)	-2.91 (-4.06, -1.77)	0	–	–
Insulin glargine vs. rosiglitazone	2	-1 (-4, 1) [-0.13 (-0.32, 0.06)]	1 (-2, 4) [0.07 (-0.19, 0.33)]	2	0.33 (-3.27, 3.92)	-0.41 (-1.91, 1.09)	1	-4.00 (-15.92, 7.92)	8.14 (4.87, 11.40)
Liraglutide vs. insulin glargine	1	-3 (-6, 0) [-0.24 (-0.51, 0.03)]	-1 (-5, 2) [-0.13 (-0.44, 0.18)]	1	-3.40 (-4.42, -2.38)	-3.4 (-5.06, -1.74)	1	-4.51 (-6.82, -2.20)	-4.24 (-6.48,-2.01)
Sitagliptin vs. pioglitazone	1	3 (-1, 6) [0.23 (-0.10, 0.56)]	4 (1, 7) [0.36 (0.1, 0.62)]	1	-1.60 (-2.48, -0.72)	-2.14 (-3.36, -0.92)	1	0.50 (-1.99, 2.99)	0.50 (-2.15, 3.15)

SBP, systolic blood pressure; WMD, weighted mean difference

*Number of trials with direct comparisons.

†I^2 >50%.

‡Egger's P value <0.05.