Comparison of glucose-lowering agents following dual therapy failure in type 2 diabetes

Systematic review and network meta–analysis of randomised controlled trials

Short Title: Glucose reduction in dual therapy failure

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ABSTRACT

Aims: To assess the evidence supporting the choice of third–line agents in adults with inadequately controlled type 2 diabetes.

Materials and Methods: We searched RCTs published between Jan 2000 and July 2017 reporting data on cardiometabolic outcomes and hypoglycaemia for glucose–lowering agents added to metformin–based dual treatments. Data were stratified by background therapy and RCT duration and synthesised, when possible, with network meta–analyses.

Results: 43 RCTs (16590 participants) were included, with metformin combined to sulphonylurea (SU) in 20 RCTs; thiazolidinedione (TZD) in 10; basal or rapid acting insulin in 6; DPP–4i in 3; GLP–1RA in 2; and SGLT–2i in 2. When added to metformin and SU, after 24–36 weeks rapid acting insulin resulted in the largest reduction of HbA1c (1.6% vs placebo) followed by GLP–1RA (1.0%), basal insulin (0.8%), and SGLT–2i (0.7%), with no difference between GLP–1RA and SGLT–2i; body weight increased with insulin treatment (about 3 kg vs placebo) while the greatest reduction was observed for SGLT–2i compared to all other therapies. Limited data for hypoglycaemia indicated a similar risk for SGLT–2i and GLP–1RA. Results for third–line agents added to metformin and TZD were comparable, showing similar HbA1c reduction and risk of hypoglycaemia between SGLT–2i and GLP–1RA and a slightly greater reduction of body weight with SGLT–2i vs GLP–1RA. Data for 52–54 weeks were more limited: added to metformin and SU, a TZD, GLP–1RA, or SGLT–2i reduced HbA1c to a similar extent but had different effects on body weight (7kg and 5kg more with TZD vs SGLT–2i and GLP–1RA, respectively; 2kg less comparing SGLT–2i vs GLP–1RA). Formal analyses could not be performed for any other dual failure combinations due to the small number of available RCTs.

Conclusions: Moderate–quality evidence supports the choice of a third–line agent only in patients on metformin combined with SU or TZD, with SGLT–2i performing generally better than other drugs. In suggesting third–line agents, future guidelines should recognise the widely different evidence across possible dual failures.

INTRODUCTION

European and North American consensus guidance for the management of hyperglycaemia in type 2 diabetes increasingly recommend pragmatic use of two or more glucose lowering therapies once pre–set glycosylated haemoglobin thresholds are exceeded. After lifestyle modification and metformin monotherapy, the next step is to add a second and then third agent to achieve glucose control.[1,2] There is an impressive list of available therapeutics for this stepwise approach, including sulphonylureas (SUs), thiazolidinediones (TZDs), dipeptidyl–peptidase–4 inhibitors (DPP–4is), glucagon–like peptide–1 receptor agonists (GLP–1RAs), sodium–glucose co–transporter–2 inhibitors (SGLT–2is), and insulin. In practice, this should involve flexible, individualised patterns of prescribing which are well tolerated and able to compensate adequately for the consequences of progressive beta cell decline.[3]

Pharmacotherapy choices should in principle be based upon effectiveness, safety, tolerability, and cost as well as the patient's individual circumstances and preferences. Shared decision making between patient and health care professional within this precept allows dozens of combinations of currently endorsed therapeutics. Whilst inclusivity and choice over second, third, and fourth line agents after metformin clearly has its advantages, it may also be problematic. It infers equal distribution, availability and affordability of licensed therapies, as well as health care professional awareness and knowledge around latest therapeutic advances. It also assumes that the effectiveness of "add–on" medication is not significantly influenced by background glucose lowering therapy or therapies. This is important because there is unlikely to be extensive and similar evidence supporting the use of multiple permutations and treatment streams arising from these algorithms. For instance, a significant proportion of randomised controlled trials (RCTs) in patients with type 2 diabetes are designed to test the efficacy of a third agent when added to various combinations of "failing" dual therapy. Results of these are commonly not stratified by background medication and assume the effect of the third agent is similar across sub–groups of dual failure. This is unlikely because the pathophysiological determinants of hyperglycaemia could be different, for example comparing patients on metformin and TZD (subjects with high insulin resistance) or on metformin and short-acting insulin (subjects with β-cell failure).[3] Moreover, the benefit/risk profile of a third agent may also differ in relation to background dual therapy (i.e., risk of hypoglycaemia with basal insulin in patients on metformin and SU vs metformin and TZD).

The majority of previous systematic reviews and network meta–analyses undertaken to ascertain the safety and efficacy of a third glucose–lowering agent have focused only on a specific combination of dual therapy, compared only specific agents, evaluated a single or few outcomes, or combined trials with heterogeneous dual "failure".[4-11] We aimed to explore the available evidence when metformin–based dual treatments (i.e. metformin plus SU, TZD, DPP–4i, GLP–1RA,

or SGLT–2i) fail to provide optimal glucose control and, for each combination of dual therapy failure, to compare the efficacy and safety of available glucose–lowering treatments when added as a third–line agent.

MATERIALS AND METHODS

Data Sources and Searches

We conducted this study according to a pre–specified protocol and following the PRISMA guidelines for conducting and reporting systematic reviews and network meta–analysis (Supplementary Appendix).[12] We searched PubMed, ISI Web of Science, the Cochrane Library, Scopus, and ClinicalTrials.gov (https://clinicaltrials.gov/) for RCTs published in English between January 1st, 2000 and July 9th, 2017.

Study Selection

Four authors independently performed the literature search and identified eligible studies. Following the PICO (population, intervention, comparator, outcome) framework, we selected RCTs in adult patients with type 2 diabetes with sub–optimal glucose control on dual therapy with metformin and a second–line agent ("dual therapy failure") (*population*) randomised to a third–line glucose–lowering agent (*interventions and comparators*); details on agents and doses are reported in Supplementary Appendix Table S1. We included RCTs of 24 to 52 weeks duration and reporting data on one or more cardiometabolic (HbA1c, fasting plasma glucose (FPG), body weight, systolic and diastolic blood pressure, total cholesterol, low– and high–density lipoprotein cholesterol, and triglycerides) or safety outcomes (all hypoglycaemic events) (*outcome*). We excluded RCTs that enrolled only specific populations (i.e., all patients with chronic kidney disease) and observational follow-up analyses of RCTs. Reference lists of eligible reports and previous systematic reviews and meta–analyses were scanned for additional relevant studies.

Data Extraction and Quality Assessment

Using standardised pre–defined forms, three authors extracted data which were independently checked by a fourth author. Extracted data included: first author name, PubMed identification number, clinical trial registration number (NCT; https://clinicaltrials.gov/), year of journal article publication, background glucose–lowering therapy, randomisation treatments, duration of follow–up, sample size, gender distribution, baseline age, HbA1c, diabetes duration, and outcome measured. For each RCT, we collected information on third–agent–specific number of participants, mean difference (end of study – baseline), and its standard error (or standard deviation) for continuous outcomes; and total number of participants and participants with event for hypoglycaemia. We extracted data from ClinicalTrials.gov when it was not possible to obtain the relevant information from the published report and assessed study quality with the Cochrane risk of bias tool.[13] Disagreement on study eligibility, data extraction, or study quality was solved by consensus or arbitration.

We graded the quality of evidence using a modified Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework (details are reported in the Supplementary Appendix).[14]

Data Synthesis and Analysis

Stata 14.1 (Stata Corp, College Station, TX, USA) was used to perform DerSimonian and Laird pairwise random-effects meta-analyses and network meta–analyses as multivariate random-effects meta-analysis and meta-regression, assuming that that all treatment contrasts have the same heterogeneity variance.[15-17] We used arm-specific mean difference and odds ratios (ORs) as effect measures for continuous and dichotomous (hypoglycaemia) data, respectively and added 0.5 if studies reported zero participants with hypoglycaemia.[18] For each background dual failure and duration of follow–up, we summarized the available evidence using network diagrams; reported number of participants and events, pairwise and network meta-analyses results, and ranking probabilities in tables; displayed network meta-analysis results against a common comparator (placebo) in forest plots; and assessed small-study effects for active treatments vs placebo using comparison-adjusted funnel plots.[16,19] We evaluated consistency between direct and indirect evidence by using the 'design by treatment' interaction model, estimated the common heterogeneity variance for the network (tau [τ]),[20] and examined with meta-regressions whether patient-level characteristics aggregated at the study level could explain heterogeneity and inconsistency. Results were reported with 95% confidence intervals and $p<0.05$ was deemed as statistically significant.

RESULTS

Study characteristics and available evidence

After duplicates exclusion and selection of articles by title and abstract, 89 reports underwent full–text assessment and 40 were further excluded, leaving 49 reports from 43 unique RCTs for the analyses (Supplementary Appendix Figure S1). We found one RCT with 54 weeks of follow–up (two weeks longer than the inclusion criteria) and opted to include it in the analysis.[21] Table 1 reports the characteristics of the studies: they were published between 2004 and 2017 and enrolled 16590 (range, 106–1055) participants with type 2 diabetes. Baseline HbA1c, age, and disease duration weighted means were 8.0%, 53.7 years, and 8.0 years, respectively and 51.6% were males. 30 RCTs (69.8%) reported data for a follow–up between 24 and 36 weeks (short-term), 4 (9.3%) between 52–54 weeks (long-term), and 9 (20.9%) included both short- and long–term observations. SU was the most common second agent combined with metformin (20 RCTs; 46.5%), followed by TZD (10; 23.2%), basal or rapid acting insulin (6; 13.9%), DPP–4i (3; 7.0%), GLP–1RA (2; 4.6%), or SGLT–2i (2; 4.6%); references of included studies are reported in the Supplementary Appendix.

The overall risk of bias was deemed low, high, and unclear in 31 (63.3%), 3 (6.1%), and 15 (30.6%) studies, respectively (Table S2). High or unclear domain–specific bias was lowest for selective reporting (20.4%) and highest for incomplete outcome data (34.7%) (Figure S2). Almost all studies were supported by one or more pharmaceutical companies (other bias, Table S2).

The number of participants for efficacy outcomes and hypoglycaemia is detailed by background therapy, follow–up, trial, and third–line agents in Tables S3–S8. Limited data were available from very few studies for the outcomes blood pressure and lipids across RCTs with different durations or background therapy (Figure 1 and Table S3–S4). Excluding studies with background metformin and sulphonylurea or TZD, data were also limited for HbA1c, FPG, body weight, and hypoglycaemia. Formal network meta–analyses were therefore performed only for studies with background metformin and SU (follow–up 24–36 and 52–54 weeks) or TZD (24–36 weeks).

Efficacy outcomes: HbA1c, fasting plasma glucose, and body weight

Metformin + Sulphonylurea, follow–up 24 to 36 weeks

Data on HbA1c were available from 6244 participants included in 15 RCTs (Figure 1 and Figure S3; Table S7). In direct comparisons, the largest HbA1c reduction was observed for SGLT–2i vs placebo (0.7%; 95% CI: 0.5 to 0.9; Table S9). Results of the network meta-analysis indicated a mean HbA1c reduction vs placebo of 1.6% (0.8 to 2.3) for rapid insulin,

followed by 1.0% (0.7 to 1.2) for GLP–1RA, 0.8% (0.5 to 1.0) for basal insulin, 0.7% (0.5 to 0.9) for SGLT–2i, and 0.7% (0.5 to 0.8) for DPP–4i (Table 2 and Figure 2; differences in mmol/mol are reported in Table S10); no data were available for TZD. Comparisons across third–line agents showed greater HbA1c reductions with GLP–1RA compared to basal insulin (-0.2%; -0.4 to -0.1) and DPP–4i (-0.3%; -0.6 to -0.1); and with rapid insulin compared to basal insulin (-0.8%; -1.5 to -0.1), DPP–4i (-0.9%; -1.6 to -0.2), and SGLT–2i (-0.8%; -1.6 to -0.1); no differences were found comparing GLP–1RA to rapid insulin or SGLT–2i (Table 2).

Values of FPG were available from 4912 participants in 14 RCTs. The largest reduction in direct comparisons was found for SGLT–2i vs placebo (1.7 mmol/l; 1.5 to 1.9; Table S9). In the network meta-analysis, compared to placebo SGLT–2i reduced FPG by 1.8 mmol/l (1.1 to 2.5), basal insulin by 0.9 mmol/l (0.1 to 1.7), and DPP4–i by 0.8 mmol/l (0.3 to 1.4); no differences were found between placebo and TZD, rapid insulin, or GLP–1RA. Comparisons across agents showed a greater FPG reductions with SGLT–2i vs GLP–1RA (-1.5 mmol/l; -2.7 to -0.3), TZD (-1.3 mmol/l; -2.5 to -0.2), and DPP–4i (-0.9 mmol/l; -1.8 to -0.1) (Table 2). No difference was found between SGLT–2i and basal insulin.

Data on body weight were available from 5456 participants in 13 RCTs. Direct comparisons showed the greatest increase in body weight when comparing basal insulin to GLP–1RA (3.5 kg; 2.9 to 4.1; Table S9). In the network meta-analysis, compared to placebo SGLT–2i reduced body weight by 1.9 kg (1.4 to 2.5) and GLP–1RA by 0.8 kg (0.2 to 1.4). Conversely, basal insulin, rapid insulin, and TZD increased body weight by 2.8 kg (2.2 to 3.4), 3.0 kg (1.7 to 4.4), and 4.1 kg (2.7 to 5.5), respectively. No difference was found between DPP–4i and placebo. Comparisons across third–line therapies showed significant reductions of body weight for SGLT–2i vs all other agents, from -1.2 kg (-2.0 to -0.4) vs GLP–1RA to -6.0 kg (-7.6 to -4.5) vs TZD. With the exception of SGLT–2i, GLP–1RA reduced body weight vs all other agents (Table 2).

The highest probabilities of ranking first (i.e., largest reduction) were observed for rapid insulin for HbA1c (93.8%); SGLT–2i for FPG (62.7%); and SGLT–2i for body weight (99.8%) (Table S11).

Metformin + Sulphonylurea, follow–up 52 to 54 weeks

Data on rapid insulin were not available for all three outcomes HbA1c, FPG, and body weight. HbA1c was reported in 6 RCTs including 2781 participants (Figure 1 and S3; Table S7). In direct comparisons, SGLT–2i reduced HbA1c vs placebo by 0.8% (0.6 to 1.1; Table S9). Results of the network meta-analysis indicated a mean HbA1c reduction vs placebo of 1.1% (0.8 to 1.4) for TZD, followed by 0.9% (0.6 to 1.2) for GLP–1RA, 0.8% (0.6 to 1.0) for SGLT–2i, and 0.4% (0.1 to 0.8) for basal insulin (Table 2 and Figure 2). Comparisons of third–line agents showed no significant difference among TZD, GLP–1RA, and SGLT–2i which all reduced HbA1c compared to DPP–4i (-0.7%, -0.5%, and -0.4%, respectively) (Table 2).

FPG data were available from 2784 participants in 6 RCTs. In direct comparisons SGLT–2i reduced FPG vs placebo by 1.8 mmol/l (1.5 to 2.1; Table S9). In the network meta-analysis, compared to placebo TZD reduced FPG by 2.4 mmol/l (1.8 to 3.0), followed by SGLT–2i (1.8 mmol/l; 1.5 to 2.1), basal insulin (1.6 mmol/l; 0.8 to 2.4), and GLP–1RA (1.3 mmol/l; 0.7 to 2.0); no difference was found between placebo and DPP–4i. Comparisons across agents showed a greater FPG reduction with TZD vs DPP–4i (-2.0 mmol/l; -2.8 to -1.1), GLP–1RA (-1.1 mmol/l; -1.6 to -0.5), and basal insulin (-0.8 mmol/l; -1.5 to -0.1) and no difference between TZD and SGLT–2i.

Data on body weight were available from 2807 participants in 6 RCTs. Direct comparisons showed a reduction of body weight comparing SGLT–2i to placebo (2.2 kg; 1.6 to 2.4; Table S9). In the network meta-analysis, only SGLT–2i reduced body weight vs placebo (2.0 kg; 1.6 to 2.4), with no difference for GLP–1RA and DPP–4i, and an increase for basal insulin (3.3 kg; 2.2 to 4.4) and TZD (4.8 kg; 4.0 to 5.7). Comparisons across agents evidenced significant reductions for SGLT–2i vs all other agents, from -2.0 kg (-3.0 to -1.0) vs GLP–1RA to -6.8 kg (-7.8 to -5.9) vs TZD.

The highest probabilities of ranking first were observed for TZD about HbA1c (93.3%) and FPG (94.8%) reduction and SGLT–2i (100%) for body weight reduction (Table S11).

Metformin + TZD, follow–up 24 to 36 weeks

Data on rapid and basal insulin were not available for all three outcomes. HbA1c values were available from 2399 participants in 8 RCTs (Figure 1 and S3; Table S7). In direct comparisons, the largest HbA1c reduction was observed for GLP–1RA vs placebo (0.9%; 0.6 to 1.1; Table S9). In the network meta-analysis, compared to placebo SU reduced HbA1c by 1.0% (0.6 to 1.4), followed by GLP–1RA (0.9%; 0.7 to 1.1), and SGLT–2i and DPP–4i (0.7%; 0.4 to 1.0) (Table 2 and Figure 2). No differences were found comparing third-line agents (Table 2).

Values of FPG were available in 1792 participants from 6 RCTs. The largest reduction in direct comparisons was found for GLP–1RA vs placebo (1.6 mmol/l; 0.9 to 2.3; Table S9) while network meta–analysis results showed significant FPG reductions compared to placebo for SGLT–2i (2.0 mmol/l; 1.0 to 2.9), SU (1.9 mmol/l; 0.8 to 2.9), GLP–1RA (1.6 mmol/l; 1.0 to 2.1), and DPP–4i (0.8 mmol/l; 0.1 to 1.5) and a greater reduction for SGLT–2i vs GLP–1RA (-1.2 mmol/l; -2.4 to -0.1).

Data on body weight from 1532 participants in 5 RCTs were limited to GLP–1RA, SGLT–2i, and SU. Direct comparisons showed a reduction of body weight comparing GLP–1RA to placebo (2.4 kg; 2.0 to 2.9; Table S9). In the network meta-analysis, compared to placebo body weight was reduced by SGLT–2i and GLP–1RA (3.7 kg; 2.9 to 4.5, and 2.4 kg; 2.0 to 2.9, respectively) and increased by SU (1.1 kg; 0.7 to 1.5). SGLT–2i reduced body weight compared to GLP–1RA (-1.3 kg; -2.2 to -0.4).

The highest probabilities of ranking first were observed for SU in terms of HbA1c reduction (64.5%) and SGLT–2i for FPG (49.4%) and body weight (99.7%) reduction (Table S11).

Safety outcome: all hypoglycaemic events

Metformin + Sulphonylurea, follow–up 24 to 36 weeks

Data on all hypoglycaemic events were available from 15 RCTs (1334 participants with event in 6330 total participants) and for all agents except rapid insulin (Figure 1 and S3; Table S8). In direct comparisons, the largest increased risk of hypoglycaemia was observed for DPP–4i vs placebo (OR 3.1; 1.5 to 6.1; Table S12). Results of the network meta-analysis showed that all agents except SGLT–2i increased the risk of hypoglycaemia vs placebo, with ORs ranging from 2.3 (1.3 to 4.0) for GLP–1RA to 3.6 (2.1 to 6.3) for basal insulin (Figure 2 and Table 3). No differences were found comparing agents against each other. Excluding placebo, basal insulin (56.4%) and SGLT–2 (52.0%) had the highest probability to be the worst and best treatment, respectively (Table S11).

Metformin + Sulphonylurea, follow–up 52 to 54 weeks

Data were available from all agents except rapid insulin in 5 RCTs, 2483 total participants, and 852 participants with event (Figure 1 and S3; Table S8). SGLT–2i did not significantly increase the risk of hypoglycaemia in direct comparisons (OR 1.6; 0.9 to 3.0; Table S12). Network meta-analyses results showed a higher risk of hypoglycaemia for GLP–1RA (OR 2.1; 1.1 to 4.0), TZD (3.6; 1.9 to 6.7), and basal insulin (3.7; 1.8 to 7.7) and no increased risk for SGLT–2 and DPP–4i when compared to placebo (Figure 2 and Table 3). Comparisons across agents showed no difference between SGLT–2i and DPP–4i and a reduced risk for GLP–1RA vs both basal insulin (0.6; 0.4 to 0.8) and TZD (0.6; 0.4 to 0.9). Amongst active treatments, basal insulin (55.7%) and DPP–4i (48.7%) had the highest probability to be the worst and best treatment, respectively (Table S11).

Metformin + TZD, follow–up 24 to 36 weeks

Data were available from 7 RCTs, 2249 total participants, 207 participants with event, and all agents except rapid and basal insulin (Figure 1 and S3; Table S8). In direct comparisons, the largest increased risk of hypoglycaemia was observed for GLP–1RAs vs placebo (OR 2.9; 1.7 to 4.7; Table S12). Results of the network meta-analysis showed that, compared to placebo, the risk of hypoglycaemia was higher for GLP–1RA (OR 2.9; 1.8 to 4.5) and SU (12.5; 5.0 to 25.0) and not different for SGLT–2i and DPP–4i (Figure 2 and Table 3). No difference was found between SGLT–2i and DPP–4i while SU increased

the risk compared to GLP–1RA (4.2; 1.6 to 11.1). Amongst active treatments, SU (91.8%) and DPP–4i (63.5%) had the highest probability to be the worst and best treatment, respectively (Table S11).

Heterogeneity, inconsistency, publication bias, and overall quality of evidence

Heterogeneity (Table S13) and inconsistency (Tables 2 and 3) were statistically significant for FPG in the analysis of short-term RCTs with background metformin and SU. In meta-regressions, the reduction of FPG was not related to age, sex, diabetes duration, or baseline HbA1c; the only exception was GLP–1RA, whose effect was related to diabetes duration. As some networks had no degrees of freedom, it was not possible to quantify inconsistency for all analyses.

Visual inspection of comparison-adjusted funnel plots did not suggest small-study effects for active treatments vs placebo comparisons (Figure S4).

The overall confidence in the results using the modified GRADE system was deemed high for HbA1c and body weight in short-term RCTs with background metformin and SU and moderate or low in other analyses (Table S14).

DISCUSSION

Existing consensus guidelines advocate flexibility in second- and third-line pharmacotherapy choices as part of a more holistic approach to glucose control in patients with type 2 diabetes.[1,2] This marks a definite move away from the constraints of hierarchy-driven algorithms and offers greater scope for individualised care. Whilst selective glucose lowering therapies have good evidence for efficacy and safety across a range of populations and conditions, it could be argued that the majority of clinical trials are still designed to provide information which relate more to the "traditional" approach of metformin first, SU second, and insulin or another agent third. In this analysis of 43 RCTs published up to July 2017, we showed that 70% of RCTs examined the effects of third–line agents (recognised as particularly important in the stepwise approach to management) added to the combination of metformin and either SU or TZD, corresponding to 67% of all participants included in short–term (24 to 36 weeks) RCTs. Evidence for the effectiveness and safety of a third agent combined for example with metformin and DPP–4i, GLP–1RA, or SGLT–2i is far less clear. In fact, there were not enough short- or longer-term triple therapy studies using any combinations other than metformin and SU or metformin and TZD to allow a formal meta–analysis and draw firm conclusions.

When formal analyses could be performed, high or moderate-quality evidence indicated a larger short–term (24–36 weeks) reduction of HbA1c with rapid acting insulin or GLP–1RA in patients on metformin and SU, and a similar efficacy between SGLT–2i and GLP–1RA; for body weight, however, these two treatments outperformed other drugs and did not increase the risk of hypoglycaemia. These findings, which are different from previous analyses not including RCTs of newer glucose–lowering drugs,[6,9] would suggest SGLT–2i or GLP–1RA as desirable options after metformin and SU, taking into account the slightly greater reduction of body weight for SGLT–2i vs GLP–1RA (1.2kg) and the different safety profile (i.e., genital infections and SGLT–2i and gastrointestinal side effects for GLP–1RA). These are important observations highlighting the novel and particularly useful mechanism of action of these drugs when used in combination with other glucose lowering agents. There were less data from studies of more than 36 weeks duration, highlighting a recognised and largely universal lack of trial evidence in support of long–term durability of glucose–lowering therapies at this stage of disease (low-quality evidence, Table S14).[22-24] Within this limitation, the superior efficacy of SGLT–2i and GLP–1RA in reducing HbA1c was less clear in participants followed up for a year, with numerical greater efficacy for TZD. However, TZD significantly increased body weight compared to both SGLT–2i (6.9kg) and GLP–1RA (4.9kg) while SGLT–2i confirmed the highest efficacy in reducing body weight (2 kg lower vs placebo) and the lowest risk of hypoglycaemia, thus suggesting some stability in the effects of these agents over time.

For metformin and TZD dual failure, the evidence is less convincing with only 8 short-term RCTs and none involving insulin as third line option. The addition of SU, GLP–1RA, SGLT–2i or DPP–4i all lowered HbA1c and FPG compared with placebo but there was no difference among agents. Although the limited number of studies incorporating this combination makes it impossible to draw firm comparisons, once again body weight was reduced more by SGLT–2i compared to other treatments, including GLP1–RA (1.3kg), in line with a previous finding.[7] Moreover, treatment with SGLT–2i confirmed the low risk of hypoglycaemia.

To our knowledge, this is the first attempt to systematically compare the totality of evidence for all available agents in patients with type 2 diabetes sub–optimally controlled on dual combination therapy. By deliberately connecting this to current consensus guidance, we hope to provide a highly relevant and thought provoking update for clinicians (and patients) charged with making the right decision at this critical stage of management. We combined clinically meaningful efficacy and safety outcomes to investigate the available data for each dual failure combination, rather than using a generic dual failure term. We did not limit the comparisons to specific drugs and explored all available third line agents in a rapidly expanding field using transparent and reproducible methods. There was a significant amount of new data on GLP–1RA and SGLT–2i, the absence of which may have limited the findings of previous network meta–analyses. We also included both short- and longer-term trials in an attempt to capture all available information, provide an assessment of treatment durability, and reduce the bias of heterogeneous comparisons given the time-dependent efficacy of glucose-lowering drugs.[25] The finding of significant differences in the number of available RCTs by background therapy is relevant and challenges available guidelines which suggest any third–line glucose–lowering drugs can be used, regardless of the specific dual treatment failure. Conversely, our data would rather indicate that for triple therapy the evidence is at best available only in patients on metformin and SU (high– or moderate–quality evidence) or metformin and TZD (moderate quality). Along with qualitative differences, future guidelines should also recognise that there are significant quantitative differences in the evidence supporting the choice of a third agent for different dual therapy failures, and ideally make this clearer adding quantitative indicators (as in Figure 1, for example).

As with all research, there are a number of limitations of the analysis that warrant discussion. One criticism is multiple statistical testing among treatments. Whilst we cannot exclude random chance as a possible explanation for some of our findings, there was clear consistency across and indeed between our networks particularly in the findings with respect to SGLT–2i. We opted to report all results with 95% confidence intervals to facilitate the clinical interpretation of absolute differences rather than focusing only on “statistically significant” differences or ranking probabilities. We characterised groups in a homogeneous way by background dual therapy and duration of follow-up, yet differences are present in study quality and possible in outcomes reporting, mainly for hypoglycaemia. Although TZDs, SUs, and some insulins (Glargine,

Isophane, and Lispro) were approved before 2000, we limited the search to RCTs published after January 2000 because most of the drugs investigated have been developed only in recent years. Of note, the number of three-drug combinations adding TZDs, SUs, or insulin to metformin is very limited (only six) and the choice of a third-line agent has emerged as a clinical question in recent years with the availability of other glucose-lowering drugs. Furthermore, designing, conducting, and reporting of RCTs has significantly improved in the last years (possibly following the introduction of specific guidelines), resulting in more standardised and homogeneous studies. We did not attempt to compare some class–specific side effects because they are systematically reported only for some drugs (i.e., gastrointestinal side effects for GLP–1RA or genitourinary infections for SGLT–2i), limiting the possibility to combine data. The search was confined only to published data in journal articles or available on ClinicalTrials.gov, introducing a possible bias as they are more likely to report 'positive' findings compared to unpublished reports. Moreover, within each dual combination therapy, we assumed that participants could be randomly allocated to any of the treatments being compared (since average baseline characteristics were similar). However, it should be also noted that HbA1c reduction could in part be related to different baseline HbA1c values across RCTs.[26] Lastly, results for FPG in short–term RCTs with background metformin and SU should be interpreted in view of the presence of significant heterogeneity and inconsistency. As age, sex, duration of diabetes, and baseline HbA1c did not explain heterogeneity, it is possible that other factors not captured in this analysis contribute to both heterogeneity and inconsistency.

In accordance with the American Diabetes Association and the European Association for the Study of Diabetes position statement, we combined drugs within the same class, although there are some within–class differences.[22-24] Most trials were comparatively small, short-term, and evaluated intermediate biomarkers of uncertain long–term relevance to patients. Recent evidence from much larger cardiovascular outcome trials (i.e., EMPA–REG OUTCOME, LEADER, SUSTAIN–6, CANVAS, EXSCEL, TOSCA) and meta–analyses are now quite correctly influencing treatment decisions in patients with diabetes.[27-34] Whilst recognising this as a limitation of the study, the same could be said of the glucose thresholds used in existing treatment algorithms. From a clinical perspective, we still considered it important to establish relative glucose–lowering efficacy and safety amongst treatment regimes following dual therapy failure. Lastly, this meta–analysis shares the same drawbacks common to other network analyses.[35]

It is not possible to deliver individualised care to patients with type 2 diabetes without a coherent understanding of the relative efficacy and safety of available therapeutic options. Our findings highlighted to clinicians and decision makers the relative lack of evidence for a large number of triple therapy glucose–lowering combinations. All agents in this comprehensive network meta–analysis, whether combined with metformin and SU or metformin and TZD, were effective at lowering blood glucose and HbA1c. There were, however, relative differences in their potential to lower glucose and

influence body weight in this situation. SGLT–2is were found to have similar glucose lowering potential to other classes but appeared to have superior effects on body weight and a lower risk of hypoglycaemia. As the evidence for third glucose–lowering agents in other dual failures is extremely limited, the choice can be based almost exclusively on clinical judgement until new data are available.

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All authors provided final approval of the version to publish. Statistical codes and datasets are available from the corresponding author. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

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MJD has acted as consultant, advisory board member and speaker for Novo Nordisk, Sanofi–Aventis, Lilly, Merck Sharp & Dohme, Boehringer Ingelheim, AstraZeneca and Janssen, an advisory board member for Servier and as a speaker for Mitsubishi Tanabe Pharma Corporation and Takeda Pharmaceuticals International Inc. She has received grants in support of investigator and investigator initiated trials from Novo Nordisk, Sanofi–Aventis, Lilly, Boehringer Ingelheim and Janssen.
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Ethical approval: Not required for this study.

FIGURE LEGENDS

Figure 1: Number of participants by background therapy, outcome, and duration of RCTs

Legend: * Basal/Rapid

Figure 2: Differences vs placebo in efficacy outcomes and hypoglycaemia

Legend: Differences for HbA1c in mmol/mol are reported in Supplementary Appendix Table S10.

Abbreviations | DPP–4i: Dipeptidyl peptidase–4 inhibitor; GLP–1RA: Glucagon–like peptide–1 receptor agonist; SGLT–2i: Sodium–glucose cotransporter–2 inhibitor; SU: Sulphonylurea; TZD: Thiazolidinedione

REFERENCES

1. Inzucchi SE, Bergenstal RM, Buse JB, et al. Management of hyperglycaemia in type 2 diabetes, 2015: a patient-centred approach. Update to a position statement of the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetologia* 2015; **58**(3): 429-42.

2. American Diabetes A. 8. Pharmacologic Approaches to Glycemic Treatment. *Diabetes Care* 2017; **40**(Suppl 1): S64-S74.

3. Zaccardi F, Webb DR, Yates T, Davies MJ. Pathophysiology of type 1 and type 2 diabetes mellitus: a 90-year perspective. *Postgrad Med J* 2016; **92**(1084): 63-9.

4. Gross JL, Kramer CK, Leitao CB, et al. Effect of antihyperglycemic agents added to metformin and a sulfonylurea on glycemic control and weight gain in type 2 diabetes: a network meta-analysis. *Ann Intern Med* 2011; **154**(10): 672-9.

5. Tricco AC, Antony J, Khan PA, et al. Safety and effectiveness of dipeptidyl peptidase-4 inhibitors versus intermediate-acting insulin or placebo for patients with type 2 diabetes failing two oral antihyperglycaemic agents: a systematic review and network meta-analysis. *BMJ Open* 2014; **4**(12): e005752.

6. Mearns ES, Saulsberry WJ, White CM, et al. Efficacy and safety of antihyperglycaemic drug regimens added to metformin and sulphonylurea therapy in Type 2 diabetes: a network meta-analysis. *Diabet Med* 2015; **32**(12): 1530-40.

7. Saulsberry WJ, Coleman CI, Mearns ES, Zaccaro E, Doleh Y, Sobieraj DM. Comparative efficacy and safety of antidiabetic drug regimens added to stable and inadequate metformin and thiazolidinedione therapy in type 2 diabetes. *Int J Clin Pract* 2015; **69**(11): 1221-35.

8. Downes MJ, Bettington EK, Gunton JE, Turkstra E. Triple therapy in type 2 diabetes; a systematic review and network meta-analysis. *PeerJ* 2015; **3**: e1461.

9. Lozano-Ortega G, Goring S, Bennett HA, Bergenheim K, Sternhufvud C, Mukherjee J. Network meta-analysis of treatments for type 2 diabetes mellitus following failure with metformin plus sulfonylurea. *Curr Med Res Opin* 2016; **32**(5): 807-16.

10. Lee CM, Woodward M, Colagiuri S. Triple therapy combinations for the treatment of type 2 diabetes - A network meta-analysis. *Diabetes Res Clin Pract* 2016; **116**: 149-58.

11. Palmer SC, Mavridis D, Nicolucci A, et al. Comparison of Clinical Outcomes and Adverse Events Associated With Glucose-Lowering Drugs in Patients With Type 2 Diabetes: A Meta-analysis. *JAMA* 2016; **316**(3): 313-24.

12. Hutton B, Salanti G, Caldwell DM, et al. The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: checklist and explanations. *Ann Intern Med* 2015; **162**(11): 777-84.

13. Higgins JP, Altman DG, Gotzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011; **343**: d5928.

14. Salanti G, Del Giovane C, Chaimani A, Caldwell DM, Higgins JP. Evaluating the quality of evidence from a network meta-analysis. *PLoS One* 2014; **9**(7): e99682.

15. White IR. Network meta-analysis. *Stata J* 2015; (15): 951-85.

16. Chaimani A, Higgins JP, Mavridis D, Spyridonos P, Salanti G. Graphical tools for network meta-analysis in STATA. *PLoS One* 2013; **8**(10): e76654.

17. White IR, Barrett JK, Jackson D, Higgins JP. Consistency and inconsistency in network meta-analysis: model estimation using multivariate meta-regression. *Res Synth Methods* 2012; **3**(2): 111-25.

18. Sweeting MJ, Sutton AJ, Lambert PC. What to add to nothing? Use and avoidance of continuity corrections in meta-analysis of sparse data. *Stat Med* 2004; **23**(9): 1351-75.

19. Salanti G, Ades AE, Ioannidis JP. Graphical methods and numerical summaries for presenting results from multiple-treatment meta-analysis: an overview and tutorial. *J Clin Epidemiol* 2011; **64**(2): 163-71.

20. Jackson D, Barrett JK, Rice S, White IR, Higgins JP. A design-by-treatment interaction model for network meta-analysis with random inconsistency effects. *Stat Med* 2014; **33**(21): 3639-54.

21. Dobs AS, Goldstein BJ, Aschner P, et al. Efficacy and safety of sitagliptin added to ongoing metformin and rosiglitazone combination therapy in a randomized placebo-controlled 54-week trial in patients with type 2 diabetes. *J Diabetes* 2013; **5**(1): 68-79.

22. Zaccardi F, Htike ZZ, Webb DR, Khunti K, Davies MJ. Benefits and Harms of Once-Weekly Glucagon-like Peptide-1 Receptor Agonist Treatments: A Systematic Review and Network Meta-analysis. *Ann Intern Med* 2016; **164**(2): 102-13.

23. Zaccardi F, Webb DR, Htike ZZ, Youssef D, Khunti K, Davies MJ. Efficacy and safety of sodium-glucose co-transporter-2 inhibitors in type 2 diabetes mellitus: systematic review and network meta-analysis. *Diabetes Obes Metab* 2016; **18**(8): 783-94.

24. Htike ZZ, Zaccardi F, Papamargaritis D, Webb DR, Khunti K, Davies MJ. Efficacy and safety of glucagon-like peptide-1 receptor agonists in type 2 diabetes: A systematic review and mixed-treatment comparison analysis. *Diabetes Obes Metab* 2017; **19**(4): 524-36.

25. Kahn SE, Haffner SM, Heise MA, et al. Glycemic durability of rosiglitazone, metformin, or glyburide monotherapy. *N Engl J Med* 2006; **355**(23): 2427-43.

26. DeFronzo RA, Stonehouse AH, Han J, Wintle ME. Relationship of baseline HbA1c and efficacy of current glucose-lowering therapies: a meta-analysis of randomized clinical trials. *Diabet Med* 2010; **27**(3): 309-17.

27. Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. *N Engl J Med* 2015; **373**(22): 2117-28.

28. Varvaki Rados D, Catani Pinto L, Reck Remonti L, Bauermann Leitao C, Gross JL. The Association between Sulfonylurea Use and All-Cause and Cardiovascular Mortality: A Meta-Analysis with Trial Sequential Analysis of Randomized Clinical Trials. *PLoS Med* 2016; **13**(4): e1001992.

29. Marso SP, Daniels GH, Brown-Frandsen K, et al. Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes. *N Engl J Med* 2016; **375**(4): 311-22.

30. Neal B, Perkovic V, Mahaffey KW, et al. Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes. *N Engl J Med* 2017; **377**(7): 644-57.

31. Avogaro A, Fadini GP, Sesti G, Bonora E, Del Prato S. Continued efforts to translate diabetes cardiovascular outcome trials into clinical practice. *Cardiovasc Diabetol* 2016; **15**(1): 111.

32. Marso SP, Bain SC, Consoli A, et al. Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes. *N Engl J Med* 2016; **375**(19): 1834-44.

33. Vaccaro O, Masulli M, Nicolucci A, et al. Effects on the incidence of cardiovascular events of the addition of pioglitazone versus sulfonylureas in patients with type 2 diabetes inadequately controlled with metformin (TOSCA.IT): a randomised, multicentre trial. *Lancet Diabetes Endocrinol* 2017.

34. Holman RR, Bethel MA, Mentz RJ, et al. Effects of Once-Weekly Exenatide on Cardiovascular Outcomes in Type 2 Diabetes. *N Engl J Med* 2017; **377**(13): 1228-39.

35. Cipriani A, Higgins JP, Geddes JR, Salanti G. Conceptual and technical challenges in network meta-analysis. *Ann Intern Med* 2013; **159**(2): 130-7.