Choice of therapy in patients with type 2 diabetes inadequately controlled with metformin and a sulphonylurea: a systematic review and mixed-treatment comparison meta-analysis

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ABSTRACT

Background: Metformin and a sulphonylurea are often used in combination for the treatment of type 2 diabetes mellitus. We conducted a systematic review and meta-analysis to evaluate the comparative safety and efficacy of all available classes of antihyperglycemic therapies in patients with type 2 diabetes inadequately controlled with metformin and sulphonylurea combination therapy.

Methods: MEDLINE, MEDLINE In-Process & Other Non-Indexed Citations, EMBASE, BIOSIS Previews, PubMed and the Cochrane Central Register of Controlled Trials were searched for randomized controlled trials published in English from 1980 to November 2009. Additional citations were obtained from the grey literature and conference proceedings and through stakeholder feedback. Two reviewers independently selected the studies, extracted the data and assessed risk of bias. Key outcomes of interest were hemoglobin A_{1c}, body weight, hypoglycemia, patients' satisfaction with treatment, quality of life, long-term diabetes-related complications, withdrawals due to adverse events, serious adverse events and mortality. Mixed-treatment comparison meta-analyses were conducted to calculate mean differences between drug classes for changes in hemoglobin A_{1c} and body weight. When appropriate, pairwise meta-analyses were used to estimate differences for other outcomes.

Results: We identified 33 randomized controlled trials meeting the inclusion criteria. The methodologic quality of the studies was generally poor. Insulins (basal, biphasic, bolus), dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide-1 (GLP-1) analogues and thiazolidinediones (TZDs) all produced statistically significant reductions in hemoglobin A1c in combination with metformin and a sulphonylurea (−0.89% to −1.17%), whereas meglitinides and alpha-glucosidase inhibitors did not. Biphasic insulin, bolus insulin, and TZDs were associated with weight gain (1.85–5.00 kg), whereas DPP-4 inhibitors and alpha-glucosidase inhibitors were weight-neutral, and GLP-1 analogues were associated with modest weight loss. Treatment regimens containing insulin were associated with increased hypoglycemia relative to comparators, but severe hypoglycemia was rare across all treatments.

Interpretation: Third-line agents for the treatment of type 2 diabetes are similar in terms of glycemic control but differ in their propensity to cause weight gain and hypoglycemia. Longer-term studies with larger sample sizes are required to determine if any of the drug classes are superior with regard to reducing diabetes-related complications.

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➢ Clinical practice guidelines[1–8] recommend metformin as the first-line oral antihyperglycemic drug for most patients with type 2 diabetes mellitus (T2DM) when glycemic control cannot be achieved by dietary and lifestyle interventions. Because T2DM is a progressive disease, metformin alone often does not provide adequate glycemic control over the long term, and many patients need additional therapy. Clinical recommendations from various bodies around the world promote the addition of a sulphonylurea for most patients whose T2DM is inadequately controlled with metformin alone.[2,5,6,8–11] Indeed, when sulphonylureas are used as second-line treatment after failure of metformin, they are associated with reductions in hemoglobin A1c (HbA1c) similar to those achieved with other drug classes, including the dipeptidyl peptidase-4 (DPP-4) inhibitors and glucagon-like peptide-1 (GLP-1) analogues.[12,13] Furthermore, recent Canadian utilization data have revealed that more than 60% of patients with T2DM requiring second-line therapy use a sulphonylurea.[14]

Over time, even dual therapy may not be sufficiently effective, and additional antidiabetes drugs may be required. Considerable uncertainty exists regarding optimal treatment for patients in whom glycemic targets cannot be met with metformin and a sulphonylurea in combination. Various antihyperglycemic drugs are available to such patients, including meglitinides, alpha-glucosidase inhibitors, thiazolidinediones (TZDs), insulins and, more recently, DPP-4 inhibitors and GLP-1 analogues. Many guidelines[4,5,7,8] have recommended that most patients initiate insulin when their diabetes is inadequately controlled with metformin and sulphonylurea combination therapy; however, others have indicated that either insulin or a third oral agent from a different pharmacologic class are suitable options.[1,6] Unlike the relatively consistent use of sulphonylureas as second-line therapy, Canadian utilization data have suggested substantial variability in the agents chosen as third-line therapy.[14]

Given the increasing prevalence of T2DM and the availability of newer, more expensive therapeutic options, there is a need to better understand the relative merits and disadvantages of third-line treatments to allow rational treatment decisions by both clinicians and patients. To address this knowledge gap, we conducted a systematic review and meta-analysis to determine the comparative efficacy and safety of all available antihyperglycemic drug classes for patients with T2DM inadequately controlled with metformin and a sulphonylurea.

Methods

Literature search. This systematic review was conducted according to a protocol prepared in advance. MEDLINE, MEDLINE In-Process & Other Non-Indexed Citations, EMBASE, BIOSIS Previews, PubMed and the Cochrane Central Register of Controlled Trials were searched through the Ovid interface to identify English-language clinical articles published from 1980 to November 2009 (Appendix A, available online). Monthly OVID AutoAlerts were reviewed from December 2009 to October 2010. Additional citations were obtained from the grey literature and conference proceedings and through stakeholder feedback.

Eligibility criteria. The population of interest consisted of adults with T2DM requiring an antihyperglycemic agent because of inadequate control (HbA_{1c} > 6.5%, fasting plasma glucose > 7 mmol/L or 2-hour postprandial glucose > 10 mmol/L) while receiving metformin and sulphonylurea combination therapy or because of intolerance to such therapy.[1,2,8,15] Agents from the following drug classes marketed in Canada, the United States or the European Union as of December 2009 were assessed: meglitinides, TZDs, DPP-4 inhibitors, GLP-1 analogues, insulins and insulin analogues, and alpha-glucosidase inhibitors. Outcomes of interest were HbA_{1c}, body weight, hypoglycemia, patients' satisfaction with treatment, quality of life, long-term complications of T2DM, withdrawals due to adverse events, severe adverse events and mortality. Active and nonactive randomized controlled trials (RCTs) published in English were included if they were at least 4 weeks in duration and compared one or more relevant drugs in any of the following scenarios: (1) addition of a third agent while the patient continued metformin and sulphonylurea combination therapy (add-on therapy); (2) initiation of third-line therapy with discontinuation of either metformin or sulphonylurea, but not both (partial switch); and (3) initiation of third-line therapy with discontinuation of both metformin and sulphonylurea (full switch). We included studies regardless of the doses of metformin and sulphonylurea used at baseline and regardless of treatment history before metformin and sulphonylurea combination therapy.

Selection of studies, assessment of quality and abstraction of data. Two reviewers (BM, CY) independently selected the studies to be included. They also independently assessed risk of bias for the included RCTs using the 10-item Scottish Intercollegiate Guidelines Network questionnaire

(SIGN-50)[16] and abstracted data using a predesigned form. Disagreements were resolved by consensus. Publication bias could not be formally assessed because of a limited number of RCTs for each pairwise comparison.

Statistical analysis. To compare the various classes of third-line antidiabetes agents, we performed Bayesian mixed-treatment comparison (MTC) meta-analyses, where possible. We selected this type of analysis for 2 reasons: first, many of the available third-line antihyperglycemic agents have not been compared directly with one another, which necessitated indirect comparisons between treatments; and second, the number of individual pairwise comparisons was unwieldy, because of the large number of treatment alternatives, and hence estimates of summary effects against a common comparator were likely to be of greater utility for clinical and policy decisions.[17] Study-level heterogeneity was carefully assessed before the performance of MTC meta-analyses. Because of a paucity of data and heterogeneity in the definition of outcomes, MTC meta-analyses were performed only for HbA_{1c} and body weight. To ensure homogeneity, MTC meta-analysis was restricted to studies in which a third agent was added to metformin and sulphonylurea combination therapy. Reference case analyses were conducted at the drug class level using random-effects models; sensitivity analyses involved fixed-effects models. Conventional insulins were pooled with insulin analogues into groups based on the time–action profile (i.e., basal, biphasic and bolus insulins), and a sensitivity analysis was used to assess the effect on our results of separating insulin analogues from conventional insulins.

We used WinBUGS (Medical Research Council Biostatistics Unit, Cambridge, UK) for the MTC meta-analyses, according to the routine developed at the universities of Bristol and Leicester.[18] Metformin and sulphonylurea combination therapy was the reference category for all MTC meta-analyses. We also performed frequentist, pairwise random-effects meta-analyses for all outcomes using the statistical software package R (www.r-project.org/). Posterior densities for unknown parameters were estimated using Markov chain Monte Carlo methods. Basic parameters were assigned non-informative or vague prior distributions. We assessed consistency between direct and indirect evidence by comparing direct estimates obtained from pairwise meta-analysis with estimates from the MTC meta-analysis. As well, we formally tested for inconsistency using a function[19] that assesses each closed loop of the network (i.e., the body of information considered in the MTC meta-analyses for each outcome) according to the method of Bucher.[20] Model diagnostics, including trace plots and the Brooks–Gelman–Rubin statistic,[21] were assessed to ensure convergence of models. For each analysis, 2 chains were fit in WinBUGS, each employing at least 20 000 iterations, with a burn-in of at least 20 000 iterations. The goodness of fit of the model to the observed data was determined by calculating the posterior mean residual deviance. The deviance information criterion was also calculated to provide a basis for comparing competing models, as reported elsewhere.[22]

We conducted meta-regression to adjust for differences in baseline HbA_{1c}, duration of diabetes and baseline body mass index (for the assessment of body weight) across trials. In other sensitivity analyses, we removed the following studies from the network: studies that employed a crossover design, those for which the inclusion criteria included threshold HbA_{1c} less than 7.0%, those that did not report the dosage of sulphonylurea at baseline and those less than 1 year in duration.

Results

Study selection, study characteristics and methodologic quality. Of 2857 unique citations identified in the literature search, 127 were reviewed as full-text articles, and 37[23–59] (representing 33 unique RCTs) were included in this review (Fig. 1). Most trials were 6 to 12 months long. The mean baseline HbA_{1c} ranged from 8.1% to 11.3%, and the baseline duration of diabetes ranged from 3.5 to 12.7 years. The threshold for baseline HbA1c was typically 7.0% to 10.0%; however, some studies used thresholds as low as 6.5% or as high as 12.0%. No trials shorter than 3 months were included in this review. The duration and dosage of stable metformin and sulphonylurea therapy before the study were inconsistently reported. More specifically, for nearly half of all studies, the authors failed to report mean doses at enrolment (i.e., baseline). Twenty-eight of the articles reported comparisons of interventions that were added to existing metformin and sulphonylurea combination therapy.[23,25,27,28,30–35,38–45,47–51,53–57] In the remaining studies, metformin, the sulphonylurea or both were discontinued upon initiation of the third-line agent. Open-label trials[23-25,27,30,34,36–40,42–46,48,49,51–54,57,58] were more common than blinded trials,[28,29,32,33,35,41,47,50,55] and the majority of studies (27 [82%]) were sponsored by the pharmaceutical industry.[23,24,27,29,32-40,42–44,46–48,50–55,57,58] About two-thirds of the studies were of poor methodologic qual[ty.23,25,27,28,30,32–37,39,40,42–44,46,47,49,50,52,53,58] Inadequate reporting of allocation concealment, failure to report an intention-to-treat analysis and lack of blinding were common limitations.

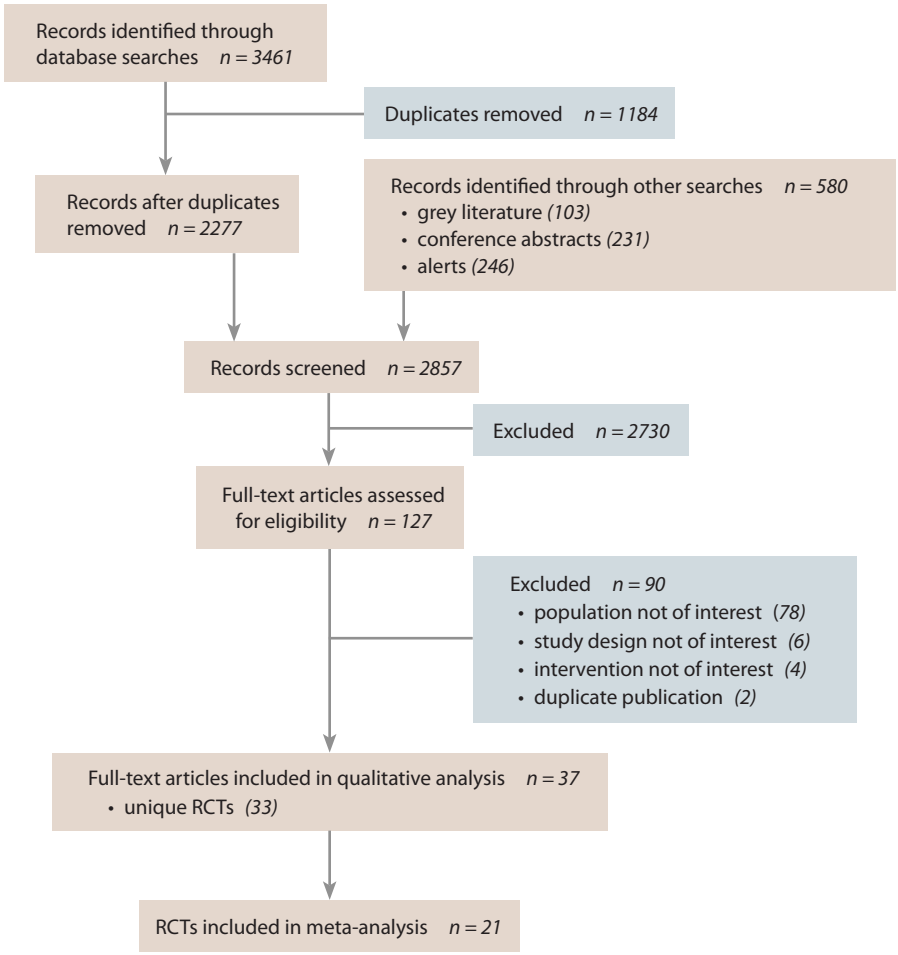

Figure 1
PRISMA diagram showing results of study selection.
(RCT = randomized controlled trial)

Hemoglobin A_{1c}. Thirty RCTs[23–25,27–30,32–44,46,48–55,57] (n = 7238 patients) reported HbA_{1c} in terms of change from baseline. The MTC evidence network, which was restricted to trials of add-on therapy, consisted of 21 RCTs[23,27,28,30,32-35,38,40–44,48,50,51,53–55,57] representing 8 drug classes in addition to placebo (Fig. 2). With the exception of alpha-glucosidase inhibitors and meglitinides, all classes achieved statistically significant reductions in HbA_{1c} (range –0.89% to –1.17%) relative to metformin and sulphonylurea combination therapy (Fig. 3 and Table 1). The addition of a basal or biphasic insulin produced the largest effects, with mean differences of –1.17% (95% credible interval [CrI] –1.57% to –0.81%) and –1.10% (95 % CrI) –1.59% to –0.67%), respectively. However, there were no statistically significant differences between drug classes in terms of reductions in HbA_{1c}. The estimates of effect derived from the frequentist direct pairwise comparisons aligned well with those obtained from the MTC meta-analysis in terms of both direction and magnitude. Differences between treatments in terms of HbA_{1c} were similar across alternative modelling strategies, meta-regression analyses and sensitivity analyses (Table 2).

Body weight. Twenty-three RCTs[23–25,27–29,32–38,41,44,48,49,51–55,57] (n = 6717 patients) reported changes in body weight. As with HbA1c, the MTC meta-analysis was restricted to studies that involved addition of a third-line agent to metformin and sulphonylurea combination therapy. The MTC evidence network consisted of 16 RCTs[23,27,28,32–35,38,41,44,48,51,53–55,57] representing 8 drug classes in addition to placebo (Fig. 2). The estimates of effect derived from the frequentist direct pairwise comparisons aligned well with those obtained from the MTC meta-analysis in terms of both direction and magnitude.

When added to metformin and sulphonylurea combination therapy, basal insulin, biphasic insulin, a rapid-acting insulin analogue or a TZD was associated with a significantly greater increase in body weight than occurred with metformin and sulphonylurea combination therapy alone (range 1.85–5.00 kg). DPP-4 inhibitors and alpha-glucosidase inhibitors were weight-neutral, whereas GLP-1 analogues were associated with statistically significant weight loss (mean difference –1.59 kg, 95% CrI –3.01 to –0.20). The large degree of uncertainty (i.e., very wide confidence interval) for the effect of meglitinides made it difficult to draw conclusions for this drug class; however, there was a trend toward weight gain (mean difference 2.67 kg, 95% CrI –0.94 to 6.32 kg). These results were not significantly altered by alternative modelling approaches, meta-regression analyses or sensitivity analyses.[22]

Hypoglycemia. We identified 21 RCTs[23,27–29,32,35–39,42,44,47–53,55,57] (n = 5899 patients) that reported the number of patients who experienced severe hypoglycemia (i.e., an event requiring third-party assistance) during the trial. Severe hypoglycemic events were rare for all drug classes, including insulins, and no events were reported in 35 of the total 52 treatment arms for these 21 studies. In one RCT,[57] the frequency of severe hypoglycemia was significantly greater with bolus insulin aspart

than with basal insulin detemir (odds ratio [OR] 4.14, 95% CI 1.36–12.59), and there was a trend toward more events with biphasic insulin aspart than with basal insulin detemir (OR 2.82, 95% CI 0.89–9.00). None of the other RCTs included in this analysis reported any significant differences for hypoglycemia.

A total of 26 RCTs[23,24,27–30,33–39,42,44,46–55,57] (n = 7238 patients) reported overall hypoglycemia. Definitions of overall hypoglycemia were reported in 16 RCTs[23,24,27–29,35,37,38,42,44,46–49,54,57] and were variable with the threshold for blood glucose ranging from 3.1 to 3.9 mmol/L, and 10 RCTs failed to provide a definition.[30,33,34,36,39,50–53,55] Given the large differences across studies in terms of baseline rates of overall hypoglycemia events in the control arms (i.e., with metformin and sulphonylurea combination therapy), we did not conduct MTC meta-analysis for this outcome. The addition of basal insulin,[48] a TZD,[33,35] a DPP-4 inhibitor[55] or a GLP-1 analogue[28,48] to metformin and sulphonylurea combination therapy was associated with a significantly higher risk of overall hypoglycemia than treatment with metformin and a sulphonylurea combination therapy alone (Table 3). Active comparisons demonstrated that the addition of biphasic insulin[54] or bolus insulin[57] to metformin and sulphonylurea combination therapy was associated with a significantly higher risk of hypoglycemia than the addition of basal insulin. There was also a trend toward more hypoglycemia with the bolus insulin aspart than with biphasic insulin, although the difference was not statistically significant.[57] Pooled data from 4 RCTs[23,30,44,51] showed that add-on basal insulin was associated with significantly more hypoglycemia than add-on TZDs.

Long-term complications of diabetes. Most of the RCTs included in this review did not report data for long-term complications or mortality, and those that did were inadequately powered to detect significant differences between treatments for these outcomes.

Table 1

Summary of results from direct pairwise and mixed-treatment comparison (MTC) meta-analyses

Hemoglobin A_{1c}, change from baseline (%)			
Treatment (compared with placebo + Met + SU)	**Studies**	**Direct estimate, WMD (95% CI)**	**MTC estimate MD (95% CrI)**
Basal insulin + Met + SU	2[34,48]	–1.22 (–2.33 to –0.10)	–1.17 (–1.57 to –0.81)
Biphasic insulin + Met + SU	NA	NA	–1.10 (–1.59 to –0.67)
TZD + Met + SU	2[33,35]	–1.16 (–1.36 to –0.96)	–0.96 (–1.35 to –0.59)
DPP-4 + Met + SU	1[51]	–0.89 (–1.11 to –0.66)	–0.89 (–1.51 to –0.26)
AG inhibitor + Met + SU	3[32,34,50]	–0.43 (–0.72 to –0.14)	–0.46 (–0.96 to 0.03)
GLP-1 + Met + SU	2[28,48]	–0.96 (–1.14 to –0.89)	–1.06 (–1.45 to –0.69)
IAsp + Met + SU	NA	NA	–1.01 (–1.71 to –0.35)
Meglitinide + Met + SU	NA	NA	–0.18 (–2.08 to 1.71)
No. of RCTs included in MTC meta-analysis	21 RCTs[23,27,28,30,32–35,38,40–44,48,50,51,53–55,57]		
Body weight, change from baseline (kg)			
Treatment (compared with placebo + Met + SU)	**Studies**	**Direct estimate WMD (95% CI)**	**MTC estimate MD (95% CrI)**
Basal insulin + Met + SU	2[34,48]	0.88 (–1.39 to 3.15)	1.85 (0.54 to 3.09)
Biphasic insulin + Met + SU	NA	NA	3.35 (1.65 to 5.03)
TZD + Met + SU	2[33,35]	3.54 (2.43 to 4.64)	3.10 (1.73 to 4.43)
DPP-4 + Met + SU	1[51]	1.10 (0.28 to 1.29)	1.11 (–1.36 to 3.57)
AG inhibitor + Met + SU	2[32,34]	–0.88 (–1.63 to –0.14)	–0.43 (–2.20 to 1.44)
GLP-1 + Met + SU	2[28,48]	–0.88 (–1.29 to –0.47)	–1.59 (–3.01 to –0.20)
IAsp + Met + SU	NA	NA	5.00 (2.52 to 7.43)
Meglitinide + Met + SU	NA	NA	2.67 (–0.94 to 6.32)
No. of RCTs included in MTC meta-analysis	16 RCTs[23,27,28,32–35,38,41,44,48,51,53–55,57]		

AG = alpha-glucosidase, CI = confidence interval, CrI = credible interval, DPP-4 = dipeptidyl peptidase-4, GLP-1 = glucagon-like peptide-1, IAsp = insulin aspart, MD = mean difference, Met = metformin, NA = not applicable, NPH = neutral protamine Hagedorn, SU = sulphonylurea, TZD = thiazolidinedione, WMD = weighted mean difference.

Patients' satisfaction with treatment. Four RCTs[23,31,49,54] reported no statistically significant differences between treatments in terms of patients' satisfaction with their treatment, as assessed by the Diabetes Treatment Satisfaction Questionnaire.

Adverse events. Withdrawals due to adverse events were reported in 23 RCTs.[23–25,27,29,30,32,33,35–37,41,42,44,45,47,48,50,51,53,55,57,58] Three RCTs involving exenatide[27,47,53] reported significantly more withdrawals due to adverse events among patients receiving the drug than among those receiving placebo, insulin glargine or biphasic insulin aspart, with nausea and vomiting being cited as the primary reasons for withdrawal. The other 2 RCTs involving exenatide[28,38] did not report withdrawals due to adverse events. In one 3-arm trial[48] there were more withdrawals among patients treated with liraglutide (4.7%) than among those receiving insulin glargine (2.1%) or placebo (0.9%). The study also cited nausea as the primary adverse event in the liraglutide treatment arm. There were no statistically significant differences between any other treatment groups with respect to withdrawals due to adverse events.

Sixteen RCTs[23,27–29,33,35,37,38,44,45,48,50,55–58] reported total severe, serious or major adverse events; however, only 5 studies[27,44,45,57,58] provided definitions of these outcomes. Because of the low incidence of such events, our ability to perform statistical comparisons across drug classes was limited.

Table 2
Model comparison, meta-regression analyses and sensitivity analyses for hemoglobin A_{1c}

Analysis	MTC estimate of effect, % (95% CrI), compared with placebo + metformin + sulphonylurea							
	Basal insulin	Biphasic insulin	TZDs	DPP-4 inhibitors	α–glucosidase inhibitors	GLP-1 analogues	Bolus insulin	Meglitinides
Random effects model v. fixed effects model								
Reference case: random effects model	−1.17 (−1.57 to −0.81)	−1.10 (−1.59 to −0.67)	−0.96 (−1.35 to −0.59)	−0.89 (−1.51 to −0.26)	−0.46 (−0.96 to 0.03)	−1.06 (−1.45 to −0.69)	−1.01 (−1.71 to −0.35)	−0.18 (−2.08 to 1.71)
Reference case: fixed effects model	−1.07 (−1.20 to −0.95)	−0.94 (−1.09 to −0.78)	−0.99 (−1.14 to −0.85)	−0.89 (−1.09 to −0.69)	−0.42 (−0.71 to −0.14)	−1.01 (−1.14 to −0.88)	−1.04 (−1.29 to −0.79)	−0.12 (−1.87 to 1.64)
Meta-regressions adjusting for:								
Baseline hemoglobin A_{1c}	−1.19 (−1.57 to −0.84)	−1.09 (−1.55 to −0.67)	−0.91 (−1.28 to −0.53)	−0.89 (−1.49 to −0.29)	−0.29 (−0.83 to 0.25)	−1.06 (−1.44 to −0.70)	−0.99 (−1.65 to −0.35)	0.03 (−1.86 to 1.90)
Baseline duration of diabetes	−1.18 (−1.59 to −0.80)	−1.10 (−1.62 to −0.65)	−0.96 (−1.39 to −0.54)	−0.89 (−1.55 to −0.23)	−0.46 (−0.98 to 0.05)	−1.06 (−1.47 to −0.67)	−1.02 (−1.74 to −0.32)	−0.13 (−2.23 to 1.96)
Sensitivity analyses with removal of:								
Crossover studies	−1.13 (−1.51 to −0.76)	−1.07 (−1.55 to −0.61)	−0.94 (−1.33 to −0.56)	−0.89 (−1.52 to −0.26)	−0.45 (−0.97 to 0.06)	−1.03 (−1.42 to −0.64)	−0.98 (−1.66 to −0.30)	NA
Studies using hemoglobin A_{1c} threshold < 7.0% to define inadequate control	−1.19 (−1.60 to −0.83)	−0.98 (−1.54 to −0.51)	−0.99 (−1.37 to −0.61)	−0.89 (−1.52 to −0.27)	−0.46 (−0.95 to 0.04)	−1.02 (−1.43 to −0.64)	−0.96 (−1.67 to −0.29)	NA
Studies without reporting of baseline sulphonylurea dose	−1.31 (−2.03 to −0.69)	−1.16 (−2.18 to −0.26)	−1.09 (−1.83 to −0.43)	−0.89 (−1.87 to 0.11)	−0.58 (−1.51 to 0.37)	−1.03 (−1.90 to −0.20)	−1.10 (−2.26 to −0.02)	NA
Studies < 1 year in duration	−1.19 (−1.59 to −0.84)	−1.00 (−1.54 to −0.54)	−0.98 (−1.36 to −0.61)	−0.89 (−1.51 to −0.26)	−0.46 (−0.95 to 0.03)	−1.03 (−1.42 to −0.66)	−0.97 (−1.67 to −0.31)	−0.17 (−2.10 to 1.73)

AG = alpha-glucosidase, CrI = credible interval, DPP-4 = dipeptidyl peptidase-4, GLP-1 = glucagon-like peptide-1, MTC = mixed-treatment comparison, NA = not applicable, TZD = thiazolidinedione.

Interpretation

Metformin and a sulphonylurea are commonly prescribed in combination to achieve glycemic control in patients with T2DM. Decisions about subsequent treatment are complicated by several factors, including the availability of numerous drug classes, the sometimes conflicting evidence about safety and long-term

effects,[60,61] the preferences and attitudes of the patient and the clinician, clinical factors and cost differences. Negative attitudes toward initiation of insulin, on the part of both patients and clinicians, and a preference for oral therapies are also important determinants in the choice of third-line therapy,[62–64] as is the propensity of agents to cause weight gain or hypoglycemia.[62] Rational decision-making regarding third-line therapy for T2DM, based on individual values and preferences, requires a comprehensive assessment of the relative advantages and disadvantages of the available alternatives. In this systematic review, we simultaneously assessed the relative safety and efficacy of all currently available treatment options for patients whose T2DM is inadequately controlled with metformin and sulphonylurea combination therapy.

None of the RCTs that we identified was adequately powered to detect differences in clinically important long-term complications of diabetes or mortality, a finding consistent with previous systematic reviews.[13,65,66] Since this review was conducted, there have been important regulatory changes to the labelling of both of the TZDs available on the market. Restrictions have been placed on the use of rosiglitazone, and it is now indicated only in patients for whom all other oral antihyperglycemic agents do not result in adequate glycemic control or are inappropriate because of contraindications or intolerance. This regulatory decision was based largely on a potential association between rosiglitazone and increased risk of cardiac ischemia.[61] Concerns over a potential increase in the risk of bladder cancer with pioglitazone prompted the US Food and Drug Administration to include a warning on the label[67] and led to suspension of approval in France and Germany.[68] The safety profile of the newest drug classes (i.e., DPP-4 inhibitors, GLP-1 analogues) requires further study in long-term observational studies and RCTs, although there is some evidence, albeit inconsistent, that they may be associated with pancreatitis.[69,70] The advantages of older drug classes, such as the conventional insulins, are the availability of trial data related to long-term safety[71,72] and extensive clinical experience.

Because of a paucity of data on long-term complications of diabetes, we had to rely on HbA_{1c} to assess relative efficacy across drug classes. The MTC meta-analyses demonstrated that adding a DPP-4 inhibitor, GLP-1 analogue or TZD and all strategies involving the addition of insulin to ongoing therapy with metformin and a

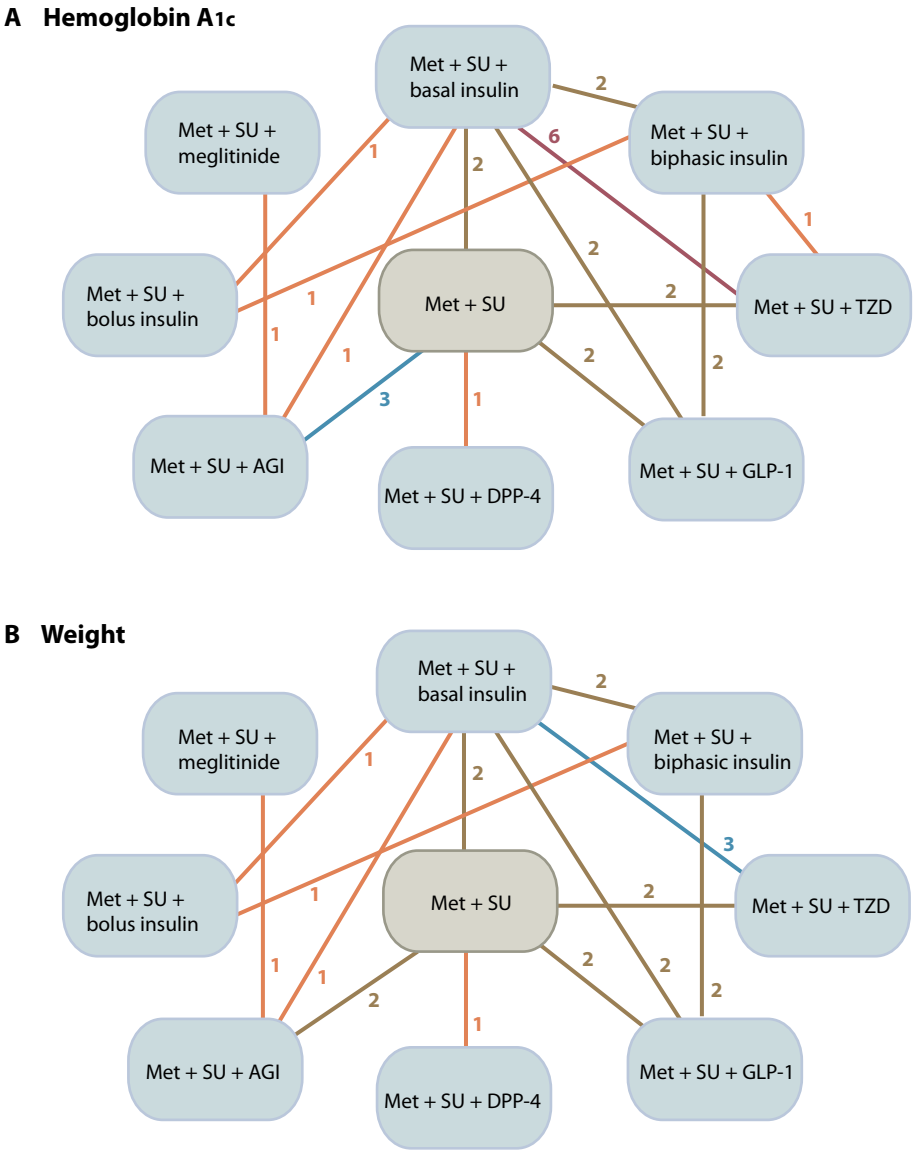

Figure 2
Network diagrams showing the distribution of evidence for each of the mixed-treatment comparison meta-analyses. (A) 21 RCTs reported the change from baseline in hemoglobin A_{1c}. (B) 16 RCTs reported change from baseline in body weight. AGI = alpha glucosidase inhibitor; DPP-4 = dipeptidyl peptidase-4 inhibitor; GLP-1 = glucagon-like peptide-1 analogue; Ins = insulin; Met – metformin; RCT = randomized controlled trial; SU – sulfonylurea; TZD = thiazolidinediones.

sulphonylurea significantly reduced HbA1c relative to placebo (range 0.89%–1.17%), but there were no significant differences between these treatments. Meglitinides and alpha-glucosidase inhibitors did not yield statistically significant reductions in HbA_{1c} relative to metformin and a sulphonylurea alone. The lack of additional benefit observed with meglitinides is consistent with expectations, given that this class has a mechanism of action similar to that of the sulphonylureas. The association between reducing HbA1c and the risk of macrovascular complications in patients with T2DM has been the focus of recent high-profile RCTs,[73,74] meta-analyses[75,76] and observational studies.[77] Despite the ongoing controversy, our results show that there are no important differences between insulins, DPP-4 inhibitors, GLP-analogues and TZDs in terms of antihyperglycemic efficacy as measured by HbA_{1c}. This result is consistent with the findings of Gross et al.,[78] who recently conducted a similar review and meta-analysis.

Non-insulin third-line agents providing sustained glycemic control may delay the need to initiate insulin, which may be desirable for some patients and could result in cost savings, given the expense of insulin therapy. Unfortunately, we found insufficient data to assess differences between treatments in the durability of the glycemic response. There is speculation that DPP-4 inhibitors, GLP-1 analogues and TZDs may be associated with prolonged glycemic control because of slowing of the decline of beta-cell function.[79–81] However, recent systematic reviews of DPP-4 inhibitors and GLP-1 analogues have suggested no definitive conclusions regarding the effects of these agents on beta-cell function.[82,83]

Many patients with T2DM are overweight or obese. Therefore, changes in body weight caused by antidiabetes therapy may be important for both patients and clinicians. Our analysis demonstrated that addition of insulin or a TZD to metformin and sulphonylurea resulted in a statistically significant increase in body weight relative to treatment with metformin and sulphonylurea combination therapy alone. By contrast, addition of a DPP-4 inhibitor, alpha-glucosidase inhibitor or GLP-1 analogue was not associated with statistically significant weight gain. There is evidence that the distribution of weight gain observed with antihyperglycemic agents is

Table 3
Summary of results for overall rate of hypoglycemia events

Intervention 1	Intervention 2	No. of RCTs	No. of patients	Direct estimate, OR (95% CI)	I^2 (%)
Placebo comparisons (intervention 1 vs. intervention 2)					
Basal insulin + Met + SU	Placebo + Met + SU	1[48]	346	2.03 (1.15–3.58)	NA
TZD + Met + SU	Placebo + Met + SU	2[33,35]	664	5.62 (2.81–11.25)	33
DPP-4 inhibitor + Met + SU	Placebo + Met + SU	1[55]	229	21.94 (2.88–167)	NA
GLP-1 + Met + SU	Placebo + Met + SU	2[28,48]	1324	2.07 (1.54–2.77)	
Active comparisons (intervention 1 vs. intervention 2)					
Biphasic insulin + Met + SU	Basal insulin + Met + SU	1[57]	469	4.01 (2.31–6.96)	NA
Biphasic insulin + Met + SU	Basal insulin + Met + SU	1[54]	469	1.29 (0.90–1.86)	NA
TZD + Met + SU	Basal insulin + Met + SU	4[23,30,44,51]	413	0.40 (0.21–0.75)	22
GLP-1 + Met + SU	Basal insulin + Met + SU	1[48]	462	0.93 (0.62–1.39)	NA
Bolus insulin + Met + SU	Basal insulin + Met + SU	1[57]	402	8.97 (4.34–18.56)	NA
Biphasic insulin	Basal insulin + Met + SU	1[24]	236	1.32 (0.86–2.03)	NA
GLP-1 + Met + SU	Biphasic insulin + Met + SU	1[27]	105	0.33 (0.19–0.55)	NA
Bolus insulin + Met + SU	Biphasic insulin + Met + SU	1[57]	445	2.24 (0.99–5.05)	NA
Biphasic insulin + Met	Biphasic insulin + Met + SU	1[27]	248	1.26 (0.76–2.09)	NA
Biphasic insulin + Met	GLP-1 + Met + SU	1[27]	112	3.87 (2.28–6.58)	NA
Biphasic insulin + Met	Basal insulin + Met	1[37]	56	1.32 (0.40–4.33)	NA
Basal insulin + Meg + Met	Basal insulin + Met	1[37]	55	0.57 (0.15–2.23)	NA
Basal insulin + Meg + Met	Biphasic insulin + Met	1[37]	53	0.43 (0.11–1.66)	NA
Basal insulin	Basal insulin + Met	1[52]	174	1.08 (0.01–218.9)	NA
Biphasic insulin	Basal insulin + Met	1[52]	173	1.12 (0.01–115.9)	NA
Biphasic insulin	Basal insulin	1[52]	175	1.04 (0.09–12.34)	NA

CI = confidence interval, DPP-4 = dipeptidyl peptidase-4, GLP-1 = glucagon-like peptide-1, I^2 = measure of heterogeneity, Meg = meglitinide, Met = metformin, NA = not applicable, OR = odds ratio, RCT = randomized controlled trial, SU = sulphonylurea, TZD = thiazolidinedione.

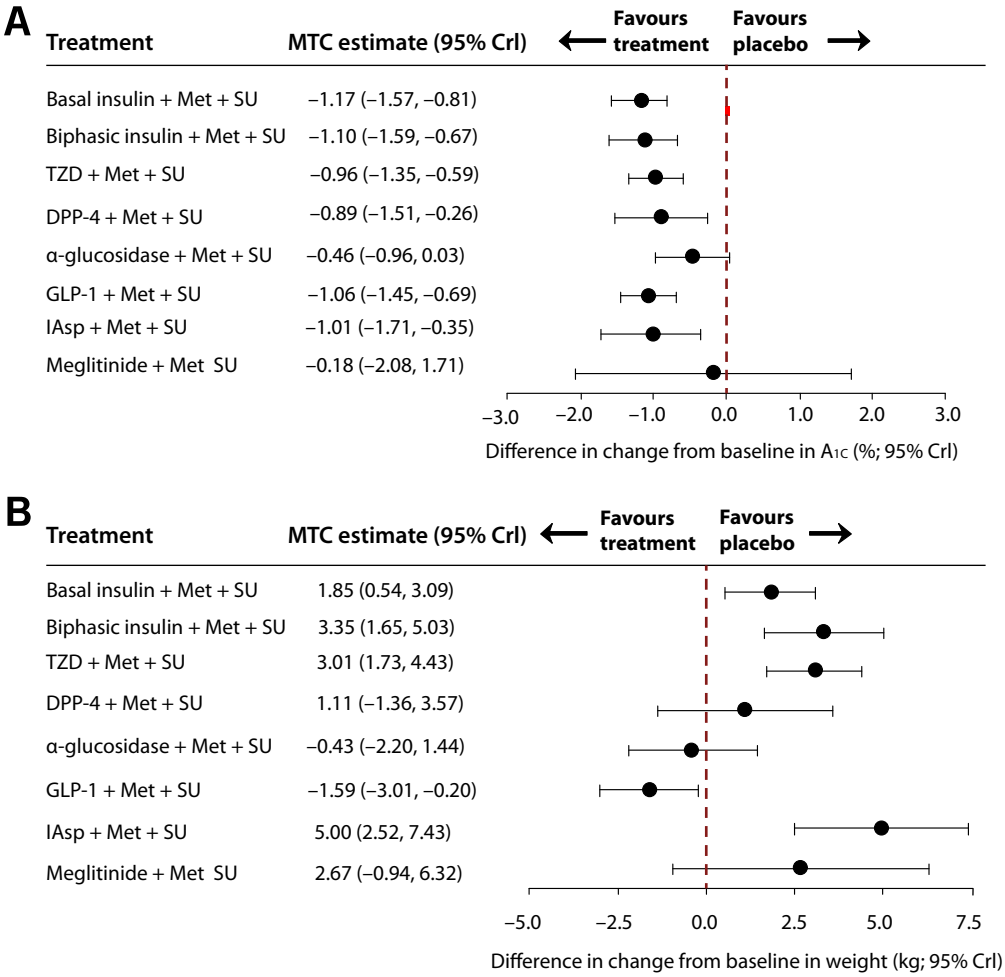

Figure 3

MTC results showing the effect of adding third-line antihyperglycemic agents versus placebo in adults taking metformin and a sulfonylurea. (A) change from baseline in hemoglobin A1c. (B) change from baseline in body weight. Abbreviations: CrI = credible interval; DPP = dipeptidyl peptidase; GLP = glucagon-like peptide; IAsp – insulin aspart; MET = metformin; MTC = mixed treatment comparison; SU = sulfonylurea; TZD = thiazolidinediones.

not identical among drug classes, with TZDs being associated with subcutaneous fat deposition and insulins with visceral fat deposition.[84–86] The latter is thought to be more metabolically detrimental.[87] Because of the possibility of distinct pathophysiologic consequences, absolute differences in weight gain between different drug classes should be interpreted with caution. Furthermore, there is no universally accepted minimal clinically important difference for body weight, although 5% is the smallest change cited as being of clinical importance in the literature.[88–90] On the basis of estimated average weight of the patients included in the MTC analysis reported here (weighted mean 87.0 kg), only bolus insulins were associated with a weight increase exceeding 5% relative to placebo. Differences in weight change between GLP-1 analogues and TZDs or biphasic insulins also exceeded the 5% threshold.

The definitions of hypoglycemia were variable and often not reported in the included clinical trials, which made it difficult to accurately compare the risk of hypoglycemia across drug classes.[91] Treatment strategies involving insulin were typically associated with a greater risk of hypoglycemia relative to other active comparators. Biphasic and bolus insulins were associated with a significantly greater risk of hypoglycemia than basal insulin. DPP-4 inhibitors, GLP-1 analogues and TZDs are typically thought to be associated with a minimal risk of hypoglycemia; however, in combination with metformin and sulphonylureas, these classes were associated with a significantly greater number of patients experiencing hypoglycemia than placebo. In contrast, in our prior analysis of second-line therapy, we found no increased risk of hypoglycemia when these agents were administered in combination with metformin alone, which suggests that combined use with a sulphonylurea may potentiate risk through an as-yet-unknown mechanism.[13] Events of severe hypoglycemia were infrequent in most trials, which limited the statistical power to compare drug classes.

Strengths and limitations. Unlike previous systematic reviews of therapies for T2DM,[65,66,82,92,93] this review included newer drug classes available for the treatment of T2DM in patients with inadequate control with metformin and sulphonylurea combination therapy. The results from our MTC meta-analyses were consistent with those from direct pairwise comparisons across all outcomes, which adds validity to the analysis. Finally, the results of a variety of alternative modelling approaches, meta-regressions and sensitivity analyses were aligned with the reference case, which demonstrates the robustness of the analysis.

In addition to the short duration of the trials and the lack of adequate data on diabetes-related complications, a number of other limitations of the available evidence warrant discussion. A majority of the RCTs were assessed as having significant methodologic limitations. There was significant variability in the reporting of metformin and sulphonylurea dosing at baseline, with most RCTs failing to report this information. Furthermore, several studies required only half-maximal dosing of sulphonylureas before therapy was considered to have failed. This approach may not reflect clinical practice, given that higher doses may be tried before third-line therapy is added. The data were pooled at the drug class level, although it is possible that there were differences between individual drugs within a class. Finally, the glycemic targets used in individual trial protocols varied somewhat between RCTs. It is possible that trials with more aggressive glycemic targets achieved larger effect sizes than those with more modest glycemic targets.

Conclusion. DPP-4 inhibitors, GLP-1 analogues, TZDs and all forms of insulin yielded statistically significant reductions (of a similar magnitude) in HbA_{1c} when added to metformin and sulphonylurea combination therapy, whereas alpha-glucosidase inhibitors and meglitinides did not produce as large a reduction in HbA1c. Key features distinguishing among the treatments were weight gain and risk of hypoglycemia. Insulins and TZDs were associated with a statistically significant increase in body weight, whereas DPP-4 inhibitors, alpha-glucosidase inhibitors and GLP-1 analogues were not. Treatment regimens incorporating insulin were associated with increased hypoglycemia relative to other active comparators, although severe hypoglycemic events were rare for all treatments. Longer-term studies, with adequate power to measure possible differences in macrovascular and microvascular complications, are required.

Contributors: All of the authors contributed to the conception and design of the study. BM and CY extracted data from the primary studies, CC performed the Bayesian MTC meta-analyses, and BM and CY conducted the frequentist pairwise meta-analyses. BM, CC and CY interpreted the results. SRS provided oversight for data extraction, analysis and interpretation. BM, with the help of CC, SRS, LD, and RH, drafted the manuscript. All of the authors critically reviewed the manuscript and approved the final version submitted for publication.

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