Second-line therapy in patients with type 2 diabetes inadequately controlled with metformin monotherapy: a systematic review and mixed-treatment comparison meta-analysis

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ABSTRACT

Background: Although there is general agreement that metformin should be used as first-line pharmacotherapy in patients with type 2 diabetes, uncertainty remains regarding the choice of second-line therapy once metformin is no longer effective. We conducted a systematic review and meta-analysis to assess the comparative safety and efficacy of all available classes of antihyperglycemic therapies in patients with type 2 diabetes inadequately controlled by metformin monotherapy.

Methods: MEDLINE, EMBASE, BIOSIS Previews, PubMed and the Cochrane Central Register of Controlled Trials were searched for randomized controlled trials published in English from 1980 to October 2009. Additional citations were obtained from grey literature and conference proceedings and through stakeholder feedback. Two reviewers independently selected studies, extracted data and assessed risk of bias. Key outcomes of interest were hemoglobin A1c, body weight, hypoglycemia, quality of life, long-term diabetes-related complications, serious adverse drug events and mortality. Mixed-treatment comparison and pairwise meta-analyses were conducted to pool trial results, when appropriate.

Results: We identified 49 active and non-active controlled randomized trials that compared 2 or more of the following classes of antihyperglycemic agents and weight-loss agents: sulfonylureas, meglitinides, thiazolidinediones (TZDs), dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide-1 (GLP-1) analogues, insulins, alpha-glucosidase inhibitors, sibutramine and orlistat. All classes of second-line antihyperglycemic therapies achieved clinically meaningful reductions in hemoglobin A1c (0.6% to 1.0%). No significant differences were found between classes. Insulins and insulin secretagogues were associated with significantly more events of overall hypoglycemia than the other agents, but severe hypoglycemia was rarely observed. An increase in body weight was observed with the majority of second-line therapies (1.8 to 3.0 kg), the exceptions being DPP-4 inhibitors, alpha-glucosidase inhibitors and GLP-1 analogues (0.6 to –1.8 kg). There were insufficient data available for diabetes complications, mortality or quality of life.

Interpretation: DPP-4 inhibitors and GLP-1 analogues achieved improvements in glycemic control similar to those of other second-line therapies, although they may have modest benefits with respect to weight gain and overall hypoglycemia. Further long-term trials of adequate power are required to determine whether newer drug classes differ from older agents in terms of clinically meaningful outcomes.

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The number of therapies available for T2DM has expanded in recent years to include more expensive drug classes such as thiazolidinediones, glucagon-like peptide-1 (GLP-1) analogues and dipeptidyl peptidase-4 (DPP-4) inhibitors (see Appendix 1, available online). Increased use of newer, more expensive drugs, along with the rising incidence of T2DM, has significant budgetary implications for health systems, as evidenced by the growth in the worldwide diabetes pharmaceutical market from US$3.8 billion in 1995 to US$17.8 billion in 2005.[9] Hence, there is a need to determine whether newer agents offer significant advantages over older therapies. The question of optimal second-line pharmacotherapy is particularly relevant given the large number of treatment options available. Existing systematic reviews of treatments for T2DM have limitations in this regard because they did not include newer drug classes or did not restrict their analyses to patients whose T2DM was inadequately controlled with metformin alone.[10–14]

As part of a larger initiative to identify and promote the optimal use of second-line antihyperglycemic agents in type 2 diabetes (www.cadth.ca/index.php/en/compus/second-line-therapies-type-2-diabetes), we conducted a systematic review and meta-analysis to address the following research question: What is the comparative efficacy and safety of available antihyperglycemic drug classes for patients with T2DM inadequately controlled with metformin monotherapy?

Methods

This systematic review was conducted according to a protocol prepared in advance.[15] 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 May 2009 (Appendix 2, available online). Monthly OVID AutoAlerts were reviewed from June to October 2009. Additional citations were obtained from grey literature and conference proceedings and through stakeholder feedback.

The population of interest consisted of adults and children with T2DM requiring a second-line antihyperglycemic agent because of inadequate control (hemoglobin A1c (HbA1c) >6.5%, fasting plasma glucose (FPG) >7 mmol/L or 2-hour postprandial glucose (PPG) >10 mmol/L)[1,2,8,16] on metformin monotherapy or because of intolerance to this therapy. Agents from the following drug classes marketed in Canada, the European Union or the United States as of October 2009 were assessed: sulfonylureas, meglitinides, thiazolidinediones, DPP-4 inhibitors, GLP-1 analogues, insulins and insulin analogues, alpha-glucosidase inhibitors and weight-loss agents (orlistat and sibutramine). Outcomes of interest included HbA1c, hypoglycemia, body weight, quality of life, long-term complications of diabetes, severe adverse events (drug related or otherwise) and mortality. Randomized controlled trials (RCTs) with active-therapy and placebo controls published in English were included if they were at least 4 weeks in duration and compared one or more relevant drugs either (1) added to metformin because of inadequate glycemic control with metformin alone or (2) replacing metformin because of intolerance. We included studies regardless of metformin dose or duration at baseline and regardless of treatment history before metformin monotherapy.

Study selection, data extraction and quality assessment were conducted independently by 2 reviewers. Risk of bias was assessed using the SIGN-50 instrument.[17]

Statistical methods. Bayesian mixed-treatment comparison (MTC) meta-analysis was conducted for HbA1c, body weight and overall hypoglycemia, after careful assessment of heterogeneity across trials in terms of subject characteristics, trial methodologies and treatment protocols. We elected to perform Bayesian MTC meta-analyses for 2 reasons: (1) many of the available second-line antihyperglycemic agents have not been compared directly with one another, necessitating indirect comparisons between treatments, and (2) the number of individual pairwise comparisons is unwieldy given the large number of treatment alternatives, hence summary effect estimates against a common comparator are likely to be of greater utility for clinical and policy decisions.[18] Pairwise meta-analyses were also conducted for these outcomes to enhance the acceptability of the findings among readers unfamiliar with Bayesian meta-analysis and to assess consistency between direct and indirect effect estimates. Only pairwise direct comparisons were conducted for the remaining outcomes because either a limited number of studies were available or events were infrequent. All analyses were conducted at the drug-class level. Trial

arms in which second-line agents were administered at doses below World Health Organization Defined Daily Doses were excluded from meta-analyses; the robustness of this approach was tested through an alternate, dose-stratified model that included all evidence. All analyses were conducted as random effects models; fixed effects models were tested as sensitivity analyses. Only pairwise comparisons were conducted for orlistat and sibutramine because of their specialized indications.

WinBUGS (MRC Biostatistics Unit, Cambridge, UK) was used for MTC meta-analyses according to the routine developed at the universities of Bristol and Leicester (www.bris.ac.uk/cobm/research/mpes/). Metformin monotherapy was the reference group for all MTC analyses. Posterior densities for unknown parameters were estimated using Markov chain Monte Carlo methods. Basic parameters were assigned non-informative or vague prior distributions. Point estimates and 95% credible intervals were used to summarize all findings. The probability of a drug class being optimal was estimated for each outcome on the basis of the proportion of Markov chain Monte Carlo simulations in which its relative measure of effect was best. We also calculated the mean rank for each drug class. 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 (http://users.uoi.gr/hyepilab/assets/pdfs/help%20on%20MTcoherence.fun.pdf) that assesses each closed loop of the network according to the method of Bucher.[19] Model diagnostics including trace plots and the Brooks-Gelman-Rubin statistic[20] were assessed to ensure model convergence. Two chains were fit in WinBUGS for each analysis, each employing ≥ 20 000 iterations, with a burn-in of ≥ 20 000 iterations.

We conducted meta-regression to adjust for baseline HbA1c, duration of diabetes and baseline body mass index (for body weight only) to test the robustness of our reference case analysis. In other sensitivity analyses, we removed studies of the following types from the network: studies that were of poor methodological quality, studies that

employed a crossover design, studies that were < 1 year in duration and studies in which the baseline metformin dose was < 1500 mg/day.

Results

Study selection. Of 2743 citations identified in the literature search, 288 were reviewed as full-text articles, and 56[21–76] (representing 49 unique RCTs) were included in this review (Fig. 1). All included studies were obtained from peer-reviewed journals, with the exception of 2 conference abstracts.[75,76] No evidence was found for patients switching therapy because of metformin intolerance, nor were there any studies involving children.
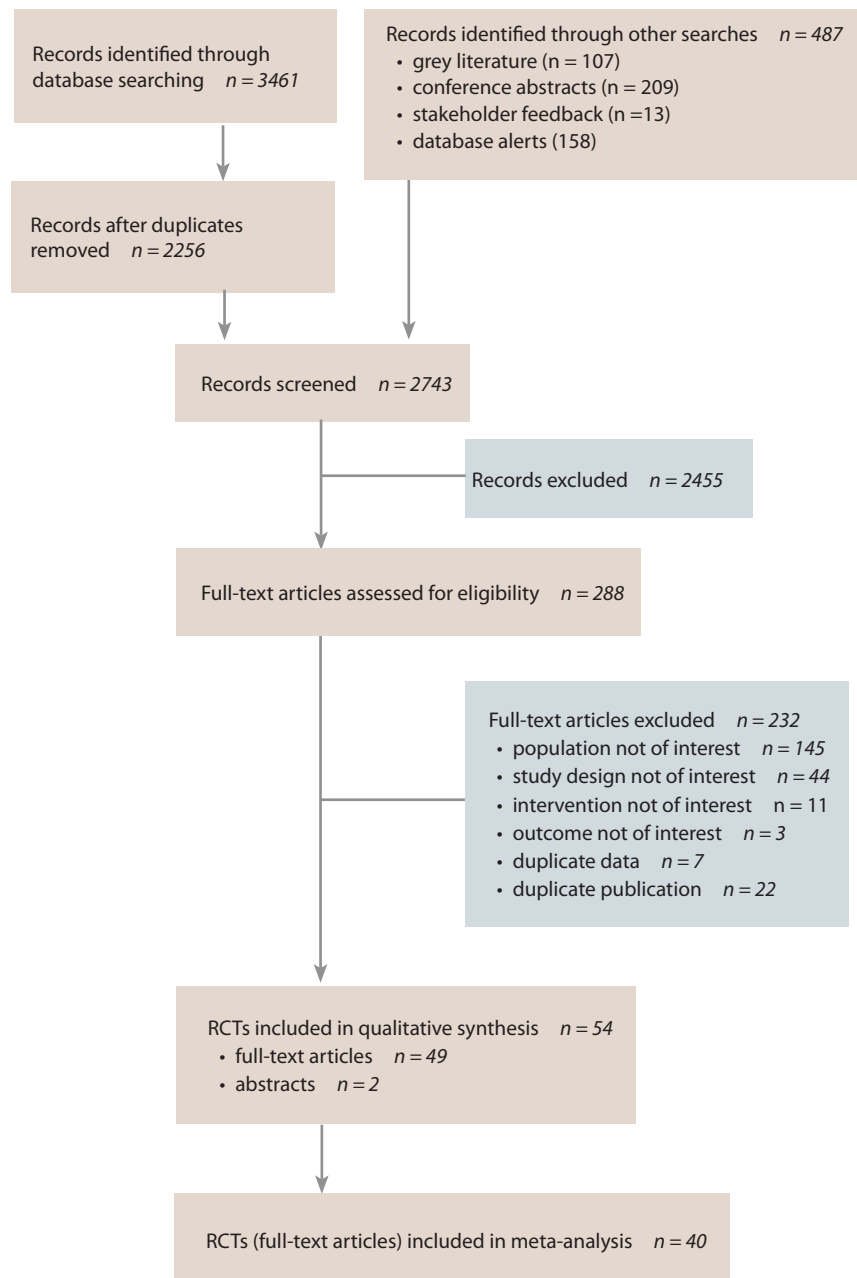

Figure 1: PRISMA diagram of study selection results

Study characteristics and methodological quality.
Most trials were 6–12 months long, although 1 study was over 5 years in duration. Mean baseline HbA1c ranged from 6.6% to 10% (weighted mean ± standard deviation [SD] 8.0% ± 0.9%). The baseline duration of diabetes ranged from 1.8 to 10.3 years (weighted mean ± SD 6.1 ± 5.1 years). The inclusion threshold for baseline HbA1c was typically 7.0%–10%; however, some studies used thresholds as low as 6.5% or as high as 11.5%. There were also differences in the duration and dosage of metformin monotherapy at baseline, although subjects used ≥1500 mg for ≥3 months in many studies. Three scenarios for treatment history before metformin monotherapy failure were identified.

The most common of these was inadequate control with metformin monotherapy under routine clinical care, abstention from use of other antihyperglycemic agents for a certain period (usually 3 months) before screening and an unspecified prior treatment history.[21–29,32,33,36,37,39,40,42–46,48,50–53,55,56,59–62,65–77] In the second scenario, patients using various oral antihyperglycemic drugs underwent a run-in period with metformin monotherapy upon trial entry and were randomly assigned to receive add-on therapy if glycemic control was inadequate at the end of the run-in.[30,35,38,41,47,49,57,58,63,64] Only one RCT[31] reported inclusion criteria that probably limited the study sample to individuals experiencing inadequate control on initial

| Table 1: Summary of results from direct and mixed-treatment comparison (MTC) analyses			
Hemoglobin A1c (change from baseline, %)			
	Direct estimates		**MTC estimates**
Treatment vs. metformin monotherapy	Studies	WMD (95% CI)	MD (95% CrI)
Sulfonylureas	3[32,52,59]	−0.80 (−1.00, −0.59)	−0.79 (−0.95, −0.63)
Meglitinides	2[53,56]	−0.71 (−1.24, −0.18)	−0.64 (−0.93, −0.37)
TZDs	6[35,38,41,47,51,70]	−0.96 (−1.18, −0.75)	−0.82 (−1.00, −0.66)
DPP-4 Inhibitors	6[27,30,42,64,70,77]	−0.78 (−0.96, −0.60)	−0.80 (−0.95, −0.65)
AG inhibitors	5[43,61,67,68,72]	−0.74 (−0.94, −0.53)	−0.74 (−0.98, −0.50)
GLP-1 analogues	4[33,58,59,62]	−0.75 (−0.96, −0.53)	−0.82 (−1.05, −0.59)
Basal insulin	—	—	−0.82 (−1.16, −0.47)
Biphasic insulin	—	—	−0.97 (−1.33, −0.61)
Overall hypoglycemia (odds ratio)			
	Direct estimates		**MTC estimates**
Treatment vs. metformin monotherapy	Studies	WMD (95% CI)	Median OR (95% CrI)
Sulfonylureas	3[32,52,58]	4.64 (1.27, 16.97)	8.22 (4.52, 16.63)
Meglitinides	2[53,56]	6.59 (1.53, 28.29)	8.59 (3.47, 25.20)
TZDs	6[35,38,41,47,51,70]	1.56 (0.56, 4.33)	1.10 (0.54, 2.27)
DPP-4 Inhibitors	7[27,28,30,42,64,70,77]	1.07 (0.59, 1.93)	1.05 (0.56, 2.21)
AG inhibitors	2[68,72]	0.49 (0.04, 5.55)	0.39 (0.01, 6.67)
GLP-1 analogues	1[33]	1.00 (0.31, 3.20)	1.12 (0.33, 3.90)
Basal insulin	—	—	5.20 (1.48, 21.46)
Biphasic insulin	—	—	11.01 (3.48, 40.43)
Body weight (change from baseline, kg)			
	Direct estimates		**MTC estimates**
Treatment vs. metformin monotherapy	Studies	WMD (95% CI)	MD (95% CrI)
Sulfonylureas	3[32,52,58]	1.79 (1.29, 2.28)	2.01 (1.09, 2.94)
Meglitinides	2[53,56]	2.01 (−0.31, 4.32)	1.80 (0.35, 3.29)
TZDs	4[35,41,47,70]	2.30 (1.93, 2.66)	2.59 (1.66, 3.51)
DPP-4 Inhibitors	3[27,42,70]	0.70 (0.20, 1.21)	0.57 (−0.45, 1.60)
AG inhibitors	3[61,68,72]	−0.90 (−1.92, 0.13)	-0.92 (−2.35, 0.51)
GLP-1 analogues	2[33,58]	−1.58 (−3.53, 0.37)	−1.79 (−3.43, −0.14)
Basal insulin	—	—	1.56 (−0.46, 3.63)
Biphasic insulin	—	—	2.96 (0.96, 5.00)

AG = alpha-glucosidase, CI = confidence interval, CrI = credible interval, DPP = dipeptidyl peptidase-4, GLP-1 = glucagon-like peptide-1, OR = odds ratio, TZDs = thiazolidinediones, WMD = weighted mean difference

A Hemoglobin A1c
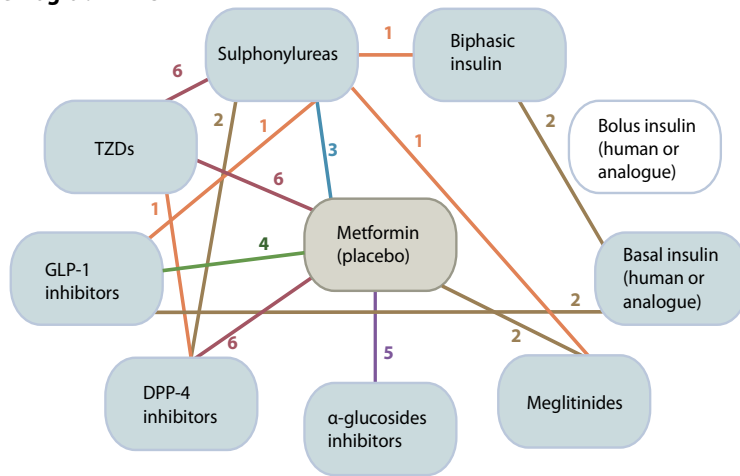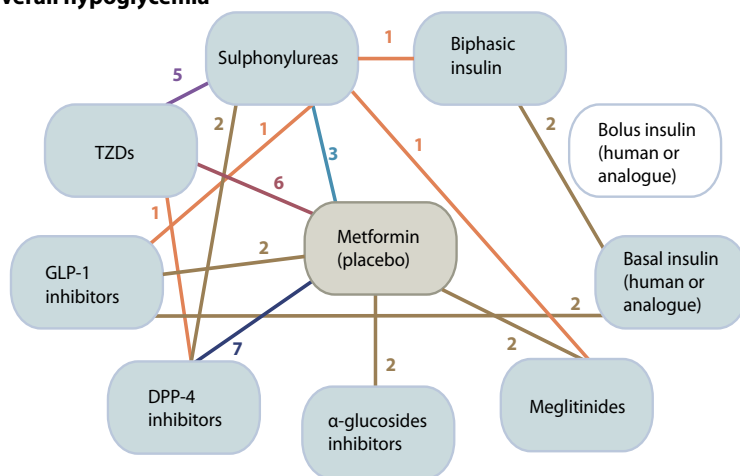

B Body weight
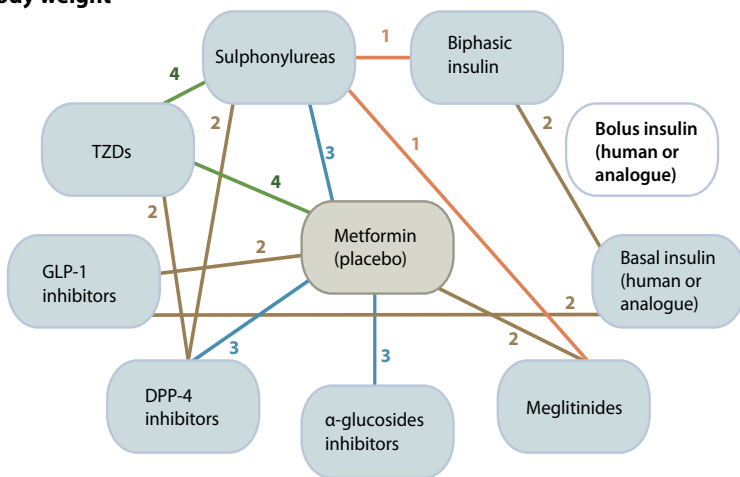
C Overall hypoglycemia

Figure 2: Network diagrams showing the distribution of evidence for each of the mixed-treatment comparison meta-analyses. Numbers denote number of randomized controlled trials (RCTs). (A) 40 RCTs (n = 17 795) reported change from baseline in hemoglobin A1c. (B) 30 RCTs (n = 15 265) reported change from baseline in body weight. (C) 34 RCTs (n = 16 704) reported the numbers of patients experiencing at least one event of overall hypoglycemia.

metformin therapy. Most studies (89%) were industry funded. Complete trial and subject characteristics are presented in Appendices 3 and 4 (available online).

About two-thirds of the studies identified were of poor methodological quality (see Appendix 5, available online); inadequate allocation concealment, failure to use an intention-to-treat analysis and lack of blinding were common limitations. Publication bias was not assessed because of a limited number of studies for each pairwise comparison.

Heterogeneity. We identified a number of areas where there was clinical and methodological heterogeneity (Appendix 6, available online). Nearly all of the issues were identified in advance and were specified in our review protocol.[15] Overall, meta-regression and sensitivity analyses yielded minimal differences from the reference case. Therefore, any differences across studies in the patient and trial characteristics assessed had little impact on the results of the analysis.

Hemoglobin AIC. Forty RCTs (n = 17 795) reported change from baseline in HbA1c (Fig. 2). All classes of second-line agents added to metformin significantly reduced HbA1c relative to metformin alone (Table 1, Fig. 3A). Effect estimates ranged from –0.65% (95% confidence interval [CI] –1.14 to –0.20) for meglitinides to –0.96% (95% CI –1.57 to –0.38) for biphasic insulins; there were no statistically significant differences between drug classes. There was good agreement between direct pairwise estimates and MTC estimates; this finding was confirmed through formal methods. The results were robust in sensitivity and meta-regression analyses (Table 2) and in the dose-stratified analysis.[78] In addition to grouping second-line agents by drug class, we constructed an additional MTC evidence network that separated the thiazolidinedione (TZD) and sulfonylurea classes into their respective individual agents. Specifically, the TZD class was split into pioglitazone and rosiglitazone, and the sulfonylurea class was split into glyburide, gliclazide, glipizide and glimepiride. All agents resulted in a statistically significant reduction in HbA1c relative to placebo,

with no statistically significant differences between individual agents in each class.[78]

Two studies investigated the addition of weight-loss agents to metformin. One RCT[23] (n = 69) reported a significant HbA1c reduction in patients treated with metformin plus orlistat relative to metformin monotherapy (−0.93%, 95% CI −1.58 to −0.28), whereas a second RCT found no significant difference with sibutramine plus metformin.[55]

Hypoglycemia. Thirty-four RCTs (n = 16 704) reported the numbers of patients experiencing at least 1 event of overall hypoglycemia, an outcome that was variably defined across trials. Relative to metformin monotherapy, risk was significantly elevated with insulins, sulfonylureas and meglitinides (odds ratios [ORs] were 5.2–11.0 for insulins and 8.2 for sulfonylureas) (Table 1, Fig. 3B). There were no significant differences between these classes. By contrast, there was no significant increase in hypoglycemia risk with TZDs, alpha-glucosidase inhibitors, DPP-4 inhibitors or GLP-1 analogues. There was good agreement between direct pairwise estimates and MTC estimates. Results from meta-regression and sensitivity analyses were similar to the reference case (data not reported).

Severe hypoglycemia was typically defined in the included trials as a hypoglycemic episode requiring the assistance of a third party. This outcome, reported in 24 RCTs (n = 8650), was rare for all drug classes, including insulins and insulin secretagogues. Most trials reported zero event rates. On the basis of the limited evidence available, neither sulfonylureas[32,52,58] (n = 501) nor GLP-1 analogues[39,58,72] (n = 389) differed significantly from metformin monotherapy, nor did GLP-1 analogues differ significantly from basal insulin.[22,29] One RCT[37] (n = 2789) reported significantly more events of severe hypoglycemia with sulfonylureas than with DPP-4 inhibitors (OR 21.20, 95% CI 1.24–362.1).

Nocturnal hypoglycemia was reported in 6 RCTs (n = 805), most of which reported zero events. No significant differences between agents were observed.

Body weight. Thirty RCTs (n = 15 265) reported change from baseline body weight (Table 1, Fig. 3C). Treatment with sulfonylureas, meglitinides, TZDs and biphasic insulin resulted in significantly greater increases in body weight than metformin monotherapy (range 1.8–3.0 kg), with no significant differences between these classes. DPP-4 inhibitors and alpha-glucosidase inhibitors did not affect body weight. The only drug class associated

Table 2: Sensitivity analyses for HbA1c — MTC estimate of effect versus placebo								
Analysis	Sulfonylureas	Meglitinides	TZDs	DPP−4 inhibitors	α−glucosidase inhibitors	GLP−1 analogues	Basal insulin	Biphasic insulin
Random effects model v. fixed effects model								
Reference case: random effects model	−0.80 (−0.96, −0.65)	−0.64 (−0.92, −0.38)	−0.85 (−1.02, −0.69)	−0.77 (−0.92, −0.64)	−0.75 (−0.98, −0.51)	−0.82 (−1.05, −0.60)	−0.82 (−1.16, −0.48)	−0.97 (−1.33, −0.62)
Reference case: fixed effects model	−0.79 (−0.87, −0.70)	−0.60 (−0.78, −0.43)	−0.85 (−0.94, −0.76)	−0.74 (−0.82, −0.66)	−0.73 (−0.92, −0.54)	−0.83 (−0.99, −0.68)	−0.84 (−1.09, −0.60)	−0.96 (−1.20, −0.72)
Meta-regressions adjusting for:								
Baseline HbA1c	−0.82 (−0.99, −0.65)	−0.64 (−0.93, −0.36)	−0.83 (−1.00, −0.66)	−0.80 (−0.95, −0.66)	−0.75 (−0.99, −0.51)	−0.84 (−1.07, −0.61)	−0.89 (−1.26, −0.52)	−1.00 (−1.36, −0.63)
Baseline duration of diabetes	−0.81 (−0.98, −0.64)	−0.65 (−0.95, −0.37)	−0.81 (−0.99, −0.64)	−0.80 (−0.95, −0.65)	−0.72 (−0.97, −0.47)	−0.86 (−1.11, −0.61)	−0.87 (−1.26, −0.49)	−0.97 (−1.34, −0.60)
Sensitivity analyses with removal of:								
Poor quality studies	−0.87 (−1.35, −0.43)	−0.71 (−1.24, −0.24)	−0.83 (−1.46, −0.27)	−0.78 (−1.54, −0.02)	−0.73 (−1.23, −0.24)	−0.90 (−1.67, −0.14)	−0.95 (−2.05, 0.15)	−1.07 (−1.99, −0.20)
Cross−over studies	−0.79 (−0.96, −0.63)	−0.65 (−0.94, −0.37)	−0.82 (−1.00, −0.65)	−0.80 (−0.95, −0.65)	−0.75 (−0.99, −0.51)	−0.83 (−1.07, −0.59)	−0.79 (−1.21, −0.36)	−0.95 (−1.35, −0.56)
Studies < 1 year in duration	−0.82 (−1.02, −0.61)	−0.64 (−1.02, −0.30)	−0.78 (−0.98, −0.60)	−0.80 (−0.97, −0.64)	−0.74 (−1.00, −0.48)	−0.82 (−1.06, −0.58)	−0.87 (−1.28, −0.46)	−1.02 (−1.42, −0.62)
Studies with < 1500 mg/day of metformin at baseline	−0.83 (−1.04, −0.63)	−0.67 (−0.99, −0.36)	−0.86 (−1.13, −0.60)	−0.79 (−0.97, −0.62)	−0.74 (−1.02, −0.46)	−0.90 (−1.27, −0.52)	−0.88 (−1.31, −0.44)	−1.03 (−1.45, −0.61)
Studies < 3 months in duration	−0.83 (−1.00, −0.67)	−0.66 (−0.95, −0.38)	−0.85 (−1.03, −0.68)	−0.81 (−0.96, −0.67)	−0.74 (−0.99, −0.50)	−0.90 (−1.25, −0.56)	−0.89 (−1.28, −0.50)	−1.02 (−1.40, −0.65)
Studies with agents not sold in Canada	−0.82 (−1.04, −0.61)	−0.67 (−0.99, −0.37)	−0.88 (−1.11, −0.67)	−0.73 (−0.97, −0.51)	−0.85 (−1.14, −0.55)	—	−0.87 (−1.52, −0.23)	−1.02 (−1.55, −0.50)

HbA1c – glycosylated hemoglobin, TZD – thiazolidinediones, DPP−4 – dipeptidyl peptidase−4, GLP−1 – glucagon−like peptide−1

A

Treatment	MTC estimate (95% CrI)
Sulfonylureas	−0.79 (−0.95, −0.63)
Meglitinides	−0.64 (−0.93, −0.37)
Thiazolidinediones	−0.82 (−1.00, −0.66)
DPP-4 inhibitors	−0.80 (−0.95, −0.65)
α-glucosidase inhibitors	−0.74 (−0.98, −0.50)
GLP-1 analogues	−0.82 (−1.05, −0.59)
Basal insulin	−0.82 (−1.16, −0.47)
Biphasic insulin	−0.97 (−1.33, −0.61)

Difference in change from baseline in HbA1c (%, 95% CI)

B

Treatment	MTC estimate (95% CrI)
Sulfonylureas	8.22 (4.5,16.63)
Meglitinides	8.59 (3.34, 25.20)
Thiazolidinediones	1.10 (0.54, 2.27)
DPP-4 inhibitors	1.05 (0.56, 2.21)
α-glucosidase inhibitors	0.39 (0.01, 6.67)
GLP-1 analogues	1.12 (0.33, 3.90)
Basal insulin	5.20 (1.48, 21.46)
Biphasic insulin	11.02 (3.48, 40.43)

Log median odds ratio (95% CI)

C

Treatment	MTC estimate (95% CI)
Sulfonylureas	2.01 (1.09, 2.94)
Meglitinides	1.80 (0.35, 3.29)
Thiazolidinediones	2.59 (1.66, 3.51)
DPP-4 inhibitors	0.57 (−0.45 to 1.60)
α-glucosidase inhibitors	−0.92 (−2.35, 0.51)
GLP-1 analogues	−1.79 (−3.43, −0.14)
Basal insulin	1.56 (−046, 3.63)
Biphasic insulin	2.96 (0.96, 5.00)

Difference in change from baseline in body weight kg (95% CI)
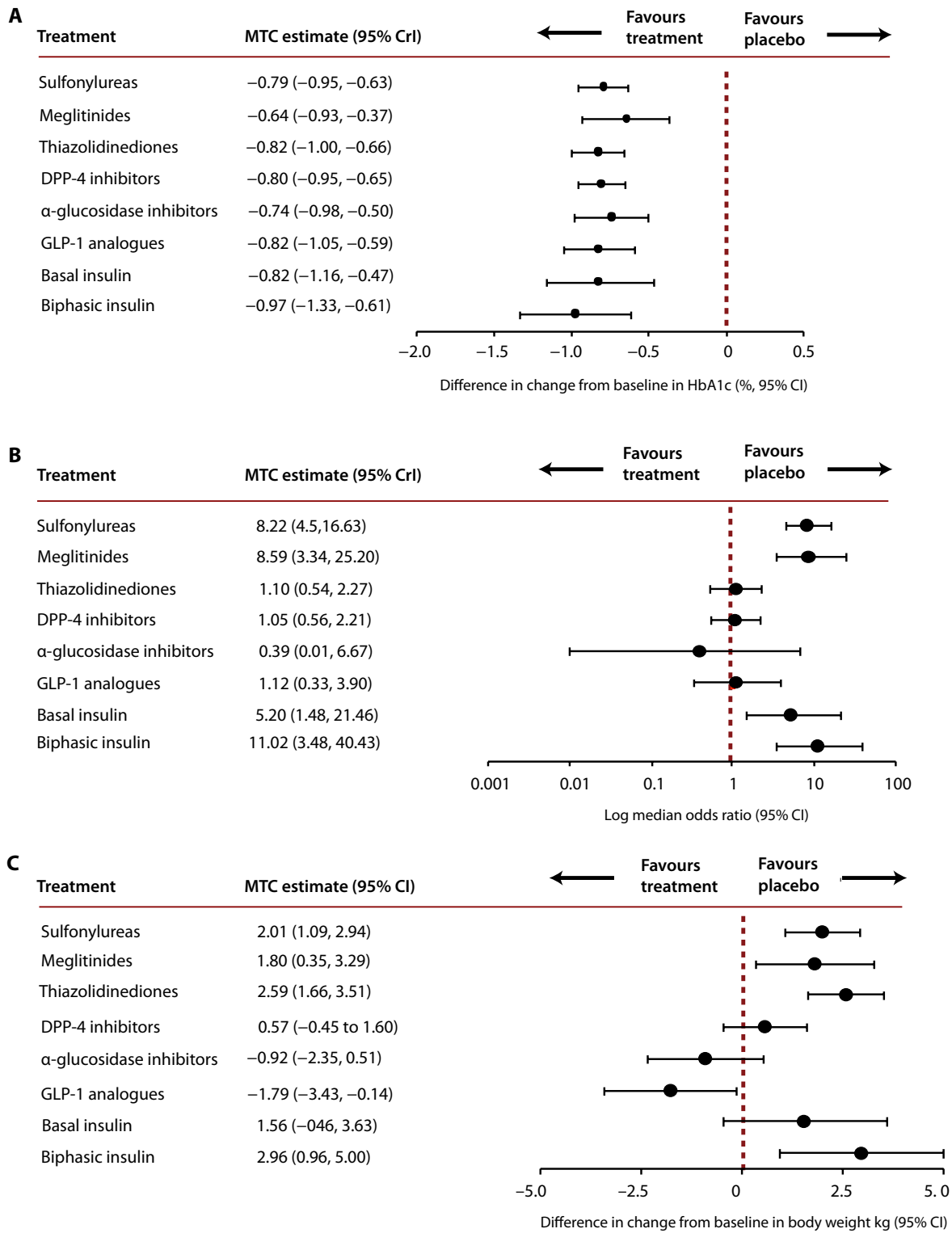

Figure 3: Mixed-treatment comparison results showing the effect of adding second-line antihyperglycemic agents versus placebo in adults taking metformin on (A) change from baseline in hemoglobin A1c; (B) odds of at least 1 event of overall hypoglycemia; (C) change from baseline in body weight.

with a significant reduction in body weight versus metformin monotherapy was GLP-1 analogues (–1.77 kg, 95% CI –3.40 to –0.15). A meta-regression adjusting for differences in baseline body mass index and other sensitivity analyses generated results that were similar to the reference case (data not shown). There was excellent alignment between the direct pairwise estimates and the MTC results, which was confirmed through formal methods.

Both sibutramine[55] and orlistat[23] combined with metformin were associated with significant reductions in body weight of 4 to 5 kg versus metformin alone.

Long-term complications and severe adverse events.
Most RCTs included in this review were of inadequate size or duration to detect differences in the occurrence of long-term complications of diabetes. On the basis of the sparse data available, no significant differences between treatments were found (Appendix 7, available online). The RECORD trial, which compared metformin and rosiglitazone versus metformin and sulfonylurea, is noteworthy as the only RCT powered to detect differences in macrovascular complications.[46] Unfortunately, much of these data could not be included in this review because the results were not stratified by type of monotherapy at baseline.

Twenty-three RCTs (n = 11 933)[24,26,27,29,30,32,37,38,41,42,] [47,51,52,57,60,61,63,64,66,70–72,77] reported total severe adverse events; however, this outcome was rarely defined. Pairwise meta-analysis of 3 RCTs[24,26,70] (n = 3383) demonstrated a statistically significant increase in the number of severe adverse events for patients treated with TZDs in comparison with DPP-4 inhibitors (OR 1.71, 95% CI 1.06–2.77). No significant differences were observed for the other 9 pairwise comparisons, although statistical power was limited because of low event rates (data not shown).

Quality of life and patient satisfaction.
One RCT[51] comparing TZDs with placebo reported no significant differences in either the physical or mental components of the SF-36 questionnaire or Diabetes Treatment Satisfaction Questionnaire (DTSQ) scores. A 3-arm RCT[75] comparing metformin with sulfonylurea, metformin with GLP-1 analogue, and metformin alone reported statistically significant improvements in favour of metformin with liraglutide (a GLP-1 analogue) over the other 2 arms on the "perceived frequency hyperglycemia" sub-scores of the DTSQ.

Discussion

We identified 49 RCTs comparing the effects of 8 antihyperglycemic drug classes in patients with T2DM inadequately controlled with metformin monotherapy. To our knowledge, this analysis is the first to synthesize the available efficacy and safety data on all therapies for T2DM through Bayesian MTC meta-analysis. This approach combines direct and indirect evidence in a single analysis that enables simultaneous comparison of multiple treatment interventions in a clinically interpretable manner.[18,79–81]

Our results for HbA1c, hypoglycemia and body weight are generally consistent with other systematic reviews of oral antihyperglycemic drugs.[10–14,82] All drug classes significantly reduced HbA1c relative to placebo to a similar degree. In some instances, our estimates of effect on HbA1c are somewhat lower than in other reviews. This may be due to our restricted focus on efficacy in the context of second-line therapy, because patients requiring second-line therapy may have more advanced diabetes and experience smaller treatment effects than treatment-naïve patients. However, our findings are similar to those reported by Phung and colleagues,[82] who recently used MTC meta-analysis to assess the comparative efficacy of oral antihyperglycemic drugs added to metformin. Sulfonylureas, meglitinides, TZDs and insulins were associated with statistically significant increases in body weight ranging from approximately 2 kg to 3 kg relative to metformin alone. DPP-4 inhibitors and alpha-glucosidase inhibitors were found to not affect body weight, and GLP-1 analogues were associated with a statistically significant reduction in body weight of just under 2 kg. There are no well-accepted thresholds for the minimal weight change considered clinically significant, although weight reductions of 5%–10% (i.e., 3.5–7 kg for a 70-kg adult) are cited as such in the literature.[83–88] In this context, the differences in body weight that we observed between classes are probably modest for most patients.

Both insulins and insulin secretagogues produced significantly increased hypoglycemia relative to placebo, whereas the TZDs, DPP-4 inhibitors, GLP-1 analogues and alpha-glucosidase inhibitors did not. Severe hypoglycemia events were rarely reported for all drug classes, including the insulins and insulin secretagogues. Large observational studies and long-term RCTs provide further insight into the risk of severe hypoglycemia among individuals with T2DM, although estimates vary considerably. Leese and colleagues reported 0.90 and 11.8 events that required emergency medical care per 100 patient-years with insulin secretagogues and insulin, respectively,[89] whereas Bodmer and colleagues reported rates of 0.06 and 0.24 events that caused either hospitalization or death per 100 patient-years.[90] In comparison,

the ADVANCE trialists reported lower incidence rates than Leese and colleagues (0.7 per 100 patient-years in the intensive glycemic control arm versus 0.4 per 100 patient-years in the standard control arm), even though they defined severe hypoglycemia more liberally (i.e., medical resource use was not required).[91] In the RECORD study, only 0.3% of subjects in the control arm (all of whom used metformin and a sulfonylurea) experienced a severe hypoglycemic event over the 5.5-year mean follow-up of the study.[46] Overall, it appears that the risk of severe hypoglycemia with insulin secretagogues is quite low; therefore, any advantages of TZDs, GLP-1 analogues and DPP-4 inhibitors are probably modest in absolute terms. Further research is required to determine whether these agents provide greater benefits in patient groups at higher risk of severe hypoglycemia or its consequences.

Evidence regarding long-term diabetes-related complications and severe adverse events was inconclusive. The RECORD trial was the only included study powered to detect differences in long-term complications.[46] Although we could not include these results in the review because of the lack of subgroup data for subjects initially taking metformin monotherapy, the overall results from RECORD are nevertheless noteworthy. Rosiglitazone was found to be non-inferior to the control treatment with respect to the primary macrovascular outcome of cardiovascular death or hospitalization, but the drug was associated with a significantly higher risk of heart failure and fractures. The data on fractures and heart failure were consistent with past studies,[11,92,93] although controversy remains regarding the effects of TZDs on the risk of ischemic heart disease.[94] 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 evidence, albeit inconsistent, that they may be associated with pancreatitis.[95,96] Advantages of older drug classes such as sulfonylureas and insulin are the availability of trial data regarding long-range safety[97,98] and the extensive clinical experience with these agents.

Long-term studies such as the United Kingdom Prospective Diabetes Study (UKPDS) have convincingly demonstrated a progressive time-dependent increase in the HbA1c levels of patients with T2DM.[99,100] This gradual loss of glycemic control is primarily attributable to a corresponding decrease in pancreatic beta-cell function. There is speculation that newer agents such as DPP-4 inhibitors, GLP-1 analogues and TZDs can offer the benefit of prolonged glycemic control by slowing the decline of beta-cell function; however, the evidence is limited and inconclusive. A recent systematic review of DPP-4 inhibitors reported that no definite conclusions can be made regarding their effects on beta-cell function.[12] In contrast, A Diabetes Outcome Progression Trial (ADOPT) reported a statistically significant difference in the number of patients experiencing monotherapy failure, with a lower failure rate for TZDs than for sulfonylureas and metformin.[101] The progressive nature of T2DM means that many patients will eventually require insulin therapy to maintain glycemic control. In this context, oral agents that are capable of producing longer periods of sustained glycemic control could delay initiation of insulin initiation, which may be desirable for some patients and could result in cost savings, given the expense of insulin therapy. We could find no conclusive evidence that TZDs and incretin mimetics have more durable effects on glycemia than sulfonylureas. Further long-term studies are needed to explore differences in glycemic durability between agents over time, especially for the newer, more expensive oral antidiabetes drugs.

Strengths and limitations. The strengths of our analysis were its comprehensiveness in terms of the drug classes considered, the number of outcomes assessed and the use of MTC meta-analyses incorporating both direct and indirect evidence in a clinically interpretable manner. However, certain limitations also deserve mention. First, potentially relevant non-English studies may have been excluded, although restriction to English-language studies has been reported to have minimal impact on systematic review results.[102–105] Second, we did not assess non-serious adverse effects that can affect the tolerability of antihyperglycemic agents. For example, acarbose is commonly associated with gastrointestinal adverse effects that may limit its usefulness.[61] Third, inclusion of insulin in the MTC meta-analysis may be viewed with scepticism because it is not commonly considered as second-line therapy after metformin in clinical practice and because trials of insulin may have enrolled patients with more advanced or severe disease than trials of oral agents. However, we believed it important to quantify the effects of insulin relative to other antihyperglycemic agents so that patients and clinicians can make informed choices regarding all available treatment options. Furthermore, scrutiny of subject characteristics revealed no major differences between the subjects enrolled in insulin trials and trials of other agents. Meta-regression analyses to adjust for differences in baseline HbA1c and duration of diabetes produced results that were similar to the reference case; therefore, any differences in these parameters

between insulin and non-insulin studies were of little consequence.

Possible limitations concerning the internal validity and generalizability of the included studies should be noted. A majority of the RCTs in our analysis, including the largest trials, received a poor rating upon assessment for risk of bias. In addition, the majority of the trials failed to address 2 or more of the major sources of bias, that is, proper allocation concealment, use of intention-to-treat analysis and equal treatment of patients in each trial arm except for study medications. The clinical population of interest with respect to optimal second-line therapy consists of patients whose T2DM is inadequately controlled with metformin alone, the first-line treatment recommended by most guidelines. However, the available RCTs typically included patients with various treatment histories, such that metformin monotherapy failure did not necessarily occur in the context of first-line therapy. Nevertheless, we believe the relative treatment effects we report are transferable to patients treated with initial metformin monotherapy, because the reference case results were robust to adjustment (through meta-regression) for differences across studies in duration of T2DM and baseline HbA1c. These factors are probably more important predictors of treatment efficacy than treatment history per se. Although meta-regression analyses are limited by an inherent lack of statistical power, the fact that adjusted and unadjusted effect estimates were similar in nearly all analyses supports the generalizability of our results to a broad population of patients with T2DM inadequately controlled with metformin monotherapy.

Conclusion

When added to metformin, all classes of second-line antihyperglycemic drugs achieved clinically meaningful reductions in HbA1c in patients with T2DM inadequately controlled with metformin monotherapy. Events of severe hypoglycemia were rare for all agents. A modest increase in body weight was observed with most second-line therapies, the exceptions being DPP-4 inhibitors, alpha-glucosidase inhibitors and GLP-1 analogues. There were few data on diabetes complications, mortality or quality of life.

Optimal use of treatments for T2DM is of paramount importance to the sustainability of health care systems given the rising global burden of this condition. Further research is therefore required to determine whether agents differ in terms of long-term complications of diabetes and mortality. As well, the cost-effectiveness of newer drugs requires further study in light of their higher cost and modest benefits over older therapies.

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