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

Brendan McIntosh, Chris Cameron, Sumeet R. Singh, Changhua Yu, Lisa Dolovich, Robyn Houlden

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 A1c, 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 A1c 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.
Clinical practice guidelines 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. 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. Furthermore, recent Canadian utilization data have revealed that more than 60% of patients with T2DM requiring second-line therapy use a sulphonylurea.

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, GLP-1 analogues. Many guidelines 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. 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.

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 (HbA1c > 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. 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 alphaglucosidase inhibitors. Outcomes of interest were HbA1c, 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)\textsuperscript{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.\textsuperscript{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\textsubscript{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.\textsuperscript{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\textsuperscript{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.\textsuperscript{20} Model diagnostics, including trace plots and the Brooks–Gelman–Rubin statistic,\textsuperscript{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.\textsuperscript{22} We conducted meta-regression to adjust for differences in baseline HbA\textsubscript{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\textsubscript{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\textsuperscript{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\textsubscript{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 enrollment (i.e., baseline). Twenty-eight of the articles reported comparisons of interventions that were added to existing metformin and sulphonylurea combination therapy.\textsuperscript{23–25,27,28,30–35,38–45,47–53,57} In the remaining studies, metformin, the sulphonylurea or both were discontinued upon initiation of the third-line agent. Open-label trials\textsuperscript{23–25,27,30,34,35,40,42–44,46,49,51–54,57,58} were more common than blinded trials,\textsuperscript{28,29,32,33,35,41,47,50,55} and the majority of studies (27 [82%]) were sponsored by the pharmaceutical industry.\textsuperscript{23,24,27,29,32–40,42–44,46–48,50–55,57,58} About two-thirds of the studies were of poor methodologic quality\textsuperscript{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.
Hemoglobin A1C. Thirty RCTs \(^{23–25,27–30,32–44,48–55,57}\) (\(n = 7238\) 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 \(^{23,27,28,32–35,38,40–44,48,50,51,53–55,57}\) 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 \(^{23–25,27–29,32–38,41,44,48–51,53–55,57}\) (\(n = 6717\) patients) reported changes in body weight. As with HbA\(_1c\), 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 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 \( ^{23,24,27–29,33–39,42,44,46–55,57} \) (n = 72,388 patients) reported overall hypoglycemia. Definitions of overall hypoglycemia were reported in 16 RCTs \( ^{23,24,27–29,33–36,39,50–53,55} \) 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 sulpharylurea 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 A1c, change from baseline (%) | Treatment (compared with placebo + Met + SU) | Studies | Direct estimate, WMD (95% CI) | MTC estimate MD (95% CrI) |
|----------------------------------------|---------------------------------------------|---------|-----------------------------|---------------------------|
|                                        | Basal insulin + Met + SU                     | 23,48   | –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                              | 23,35   | –1.16 (–1.36 to –0.96)      | –0.96 (–1.35 to –0.59)    |
|                                        | DPP-4 + Met + SU                            | 13     | –0.89 (–1.11 to –0.66)      | –0.89 (–1.51 to –0.26)    |
|                                        | AG inhibitor + Met + SU                      | 23,24,52| –0.43 (–0.72 to –0.14)      | –0.46 (–0.96 to 0.03)     |
|                                        | GLP-1 + Met + SU                            | 23,48   | –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 \( ^{23,27,28,30,32–35,38,40–44,48,50–53,55} \)

| 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                     | 23,48   | 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                              | 23,35   | 3.54 (2.43 to 4.64)         | 3.10 (1.73 to 4.43)       |
|                                      | DPP-4 + Met + SU                            | 13     | 1.10 (0.28 to 1.92)         | 1.11 (–1.36 to 3.57)      |
|                                      | AG inhibitor + Met + SU                      | 23,34  | –0.88 (–1.63 to –0.14)      | –0.43 (–2.20 to 1.44)     |
|                                      | GLP-1 + Met + SU                            | 23,48  | –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 \( ^{23,27,28,30,32–35,38,40–44,48,50–53,55} \)

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 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. Three RCTs involving exenatide 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 did not report withdrawals due to adverse events. In one 3-arm trial 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 reported total severe, serious or major adverse events; however, only 5 studies provided definitions of these outcomes. Because of the low incidence of such events, our ability to perform statistical comparisons across drug classes was limited.

Interpretation

Metformin and a sulphonylurea are commonly prescribed in combination to achieve glycaemic 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

| Analysis | Basal insulin | Biphasic insulin | DPP-4 inhibitors | GLP-1 analogues | Other |
|----------|--------------|------------------|------------------|----------------|-------|
| MTC estimate of effect % (95% CrI), compared with placebo + metformin + sulphonylurea +  DPP-4 α−glucosidase inhibitors GLP-1 analogues, mixed-treatment comparison (MTC) | -1.19 (–2.03 to –0.35) | -1.28 (–2.10 to –0.46) | -1.34 (–2.18 to –0.50) | -1.43 (–2.23 to –0.62) |
| Random effects model | -1.20 (–2.00 to –0.40) | -1.29 (–2.09 to –0.49) | -1.37 (–2.17 to –0.57) | -1.46 (–2.25 to –0.66) |
| Fixed effects model | -1.17 (–1.98 to –0.36) | -1.26 (–2.06 to –0.46) | -1.34 (–2.14 to –0.54) | -1.42 (–2.21 to –0.61) |
| Crossover studies | -1.17 (–1.97 to –0.37) | -1.22 (–1.90 to –0.54) | -1.31 (–2.01 to –0.61) | -1.39 (–2.08 to –0.70) |
| NA | -1.18 (–1.98 to –0.37) | -1.26 (–2.05 to –0.45) | -1.33 (–2.12 to –0.54) | -1.41 (–2.20 to –0.60) |
| Sensitivity analyses with removal of: | -1.17 (–1.97 to –0.37) | -1.22 (–1.90 to –0.54) | -1.31 (–2.01 to –0.61) | -1.39 (–2.08 to –0.70) |
| Reference case: fixed effects model | -1.19 (–2.03 to –0.35) | -1.28 (–2.10 to –0.46) | -1.34 (–2.18 to –0.50) | -1.43 (–2.23 to –0.62) |
| Reference case: random effects model | -1.20 (–2.00 to –0.40) | -1.29 (–2.09 to –0.49) | -1.37 (–2.17 to –0.57) | -1.46 (–2.25 to –0.66) |
| Reference case: fixed effects model | -1.17 (–1.98 to –0.36) | -1.26 (–2.06 to –0.46) | -1.34 (–2.14 to –0.54) | -1.42 (–2.21 to –0.61) |
| Reference case: random effects model | -1.18 (–1.98 to –0.37) | -1.26 (–2.05 to –0.45) | -1.33 (–2.12 to –0.54) | -1.41 (–2.20 to –0.60) |
| Reference case: fixed effects model | -1.17 (–1.97 to –0.37) | -1.22 (–1.90 to –0.54) | -1.31 (–2.01 to –0.61) | -1.39 (–2.08 to –0.70) |
| Reference case: random effects model | -1.18 (–1.98 to –0.37) | -1.26 (–2.05 to –0.45) | -1.33 (–2.12 to –0.54) | -1.41 (–2.20 to –0.60) |
| Reference case: fixed effects model | -1.17 (–1.97 to –0.37) | -1.22 (–1.90 to –0.54) | -1.31 (–2.01 to –0.61) | -1.39 (–2.08 to –0.70) |
| Reference case: random effects model | -1.18 (–1.98 to –0.37) | -1.26 (–2.05 to –0.45) | -1.33 (–2.12 to –0.54) | -1.41 (–2.20 to –0.60) |
| Reference case: fixed effects model | -1.17 (–1.97 to –0.37) | -1.22 (–1.90 to –0.54) | -1.31 (–2.01 to –0.61) | -1.39 (–2.08 to –0.70) |
| Reference case: random effects model | -1.18 (–1.98 to –0.37) | -1.26 (–2.05 to –0.45) | -1.33 (–2.12 to –0.54) | -1.41 (–2.20 to –0.60) |
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, as is the propensity of agents to cause weight gain or hypoglycemia. 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. 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. 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 and led to suspension of approval in France and Germany. 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.

The advantages of older drug classes, such as the conventional insulins, are the availability of trial data related to long-term safety and extensive clinical experience. Because of a paucity of data on long-term complications of diabetes, we had to rely on HbA1c 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 A1c. (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 – sulphonylurea; 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 HbA1c 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, meta-analyses and observational studies. 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 HbA1c. This result is consistent with the findings of Gross et al., 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. 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.

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) | I² (%) |
|------------------------------|------------------------------|-------------|----------------|-------------------------------|--------|
| Placebo comparisons (intervention 1 vs. intervention 2) | Placebo + Met + SU | 204          | 432            | 1.88 (1.30–2.69)               | 30     |
| TZD + Met + SU               | Placebo + Met + SU           | 253,35       | 564            | 5.62 (2.81–11.25)             | 33     |
| DPP-4 inhibitor + Met + SU   | Placebo + Met + SU           | 23           | 45             | 2.59 (1.30–5.12)              | 50     |
| GLP-1 + Met + SU             | Placebo + Met + SU           | 286,48       | 1324           | 2.07 (1.54–2.77)              |        |
| Active comparisons (intervention 1 vs. intervention 2) | Biphasic insulin + Met + SU | 127          | 469            | 4.01 (2.31–6.96)              | NA     |
| Biphasic insulin + Met + SU  | Biphasic insulin + Met + SU  | 134          | 469            | 1.29 (0.90–1.86)              | NA     |
| TZD + Met + SU               | Biphasic insulin + Met + SU  | 421,39,41,51 | 413            | 0.40 (0.21–0.75)              | 22     |
| GLP-1 + Met + SU             | Biphasic insulin + Met + SU  | 137          | 462            | 0.93 (0.62–1.39)              | NA     |
| Bolus insulin + Met + SU     | Biphasic insulin + Met + SU  | 137          | 402            | 8.97 (4.34–18.56)             | NA     |
| Biphasic insulin             | Biphasic insulin + Met + SU  | 137          | 236            | 1.32 (0.86–2.03)              | NA     |
| GLP-1 + Met + SU             | Biphasic insulin + Met + SU  | 137          | 105            | 0.33 (0.19–0.55)              | NA     |
| Bolus insulin + Met + SU     | Biphasic insulin + Met + SU  | 137          | 445            | 2.24 (0.99–5.05)              | NA     |
| Biphasic insulin + Met       | Biphasic insulin + Met + SU  | 137          | 248            | 1.26 (0.76–2.09)              | NA     |
| Biphasic insulin + Met       | GLP-1 + Met + SU              | 137          | 112            | 3.87 (2.28–6.58)              | NA     |
| Biphasic insulin + Met       | Basal insulin + Met           | 137          | 56             | 1.32 (0.40–4.33)              | NA     |
| Basal insulin + Meg + Met    | Basal insulin + Met           | 137          | 55             | 0.57 (0.15–2.23)              | NA     |
| Basal insulin + Meg + Met    | Biphasic insulin + Met        | 137          | 53             | 0.43 (0.11–1.66)              | NA     |
| Basal insulin                | Basal insulin + Met           | 132,12       | 174            | 1.08 (0.01–218.9)             | NA     |
| Biphasic insulin             | Basal insulin + Met           | 132,12       | 173            | 1.10 (0.01–115.9)             | NA     |
| CI = confidence interval, DPP-4 = dipeptidyl peptidase-4, GLP-1 = glucagon-like peptide-1, I² = measure of heterogeneity, Meg = meglitinide, Met = metformin, NA = not applicable, OR = odds ratio, RCT = randomized controlled trial, SU = sulphonylurea, TZD = thiazolidinedione.
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. 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. 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, 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.

### Figure 3

**MTC results showing the effect of adding third-line antihyperglycemic agents versus placebo in adults taking metformin and a sulphonylurea.**

**A** Change from baseline in hemoglobin A1c (%; 95% Crl)

| Treatment                        | MTC estimate (95% Crl) | Favours treatment | Favours placebo |
|----------------------------------|------------------------|-------------------|-----------------|
| Basal insulin + Met + SU         | -1.17 (-1.57, -0.81)   | -                  |                 |
| Biphasic insulin + Met + SU      | -1.10 (-1.59, -0.67)   | -                  |                 |
| TZD + Met + SU                   | -0.96 (-1.35, -0.59)   | -                  |                 |
| DPP-4 + Met + SU                 | -0.89 (-1.51, -0.26)   | -                  |                 |
| α-glucosidase + Met + SU         | -0.46 (-0.96, 0.03)    | -                  |                 |
| GLP-1 + Met + SU                 | -1.06 (-1.45, -0.69)   | -                  |                 |
| IAsp + Met + SU                  | -1.01 (-1.71, -0.35)   | -                  |                 |
| Meglitinide + Met SU             | -0.18 (-2.08, 1.71)    | -                  |                 |

**B** Change from baseline in body weight (kg; 95% Crl)

| Treatment                        | MTC estimate (95% Crl) | Favours treatment | Favours placebo |
|----------------------------------|------------------------|-------------------|-----------------|
| Basal insulin + Met + SU         | 1.85 (0.54, 3.09)      | -                  |                 |
| Biphasic insulin + Met + SU      | 3.35 (1.65, 5.03)      | -                  |                 |
| TZD + Met + SU                   | 3.01 (1.73, 4.43)      | -                  |                 |
| DPP-4 + Met + SU                 | 1.11 (-1.36, 3.57)     | -                  |                 |
| α-glucosidase + Met + SU         | -0.43 (-2.20, 1.44)    | -                  |                 |
| GLP-1 + Met + SU                 | -1.59 (-3.01, -0.20)   | -                  |                 |
| IAsp + Met + SU                  | 5.00 (2.52, 7.43)      | -                  |                 |
| Meglitinide + Met SU             | 2.67 (-0.94, 6.32)     | -                  |                 |

### Open Medicine 2012;6(2)e70

Review

McIntosh et al.
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 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.

**Conclusion.** DPP-4 inhibitors, GLP-1 analogues, TZDs and all forms of insulin yielded statistically significant reductions (of a similar magnitude) in HbA1c, 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, conducted the frequentist pairwise meta-analyses. BM, CC and CY performed the Bayesian MTC meta-analyses, and BM and CY interpreted the results. SRS provided oversight for data extraction, conducted the frequentist pairwise meta-analyses. BM, CC and CY performed the Bayesian MTC meta-analyses, and BM and CY interpreted the results.

**Acknowledgements:** We thank Melissa Severn and Amanda Hodgson for developing and implementing the literature search strategies, Wendy Prichett-Pejic and Samantha Verbrugghe for assistance with data management, Carolyn Spry for assistance with referencing, and Denis Bélanger for critical review of the manuscript before submission.

**References**

1. Canadian Diabetes Association. Canadian Diabetes Association 2008 clinical practice guidelines for the prevention and management of diabetes in Canada. *Can J Diabetes* 2008;32(Suppl 1):S1–S201. Available from: www.diabetes.ca/files/cpg2008/cpg-2008.pdf (accessed 2011 Jun 15).

2. National Collaborating Centre for Chronic Conditions. Type 2 diabetes: National clinical guideline for management in primary and secondary care (update). London (UK): Royal College of Physicians; 2008. Available from: www.nice.org.uk/nicemedia/pdf/CG66diabetesfullguideline.pdf (accessed 2008 Dec 19).

3. Standards of medical care in diabetes—2009. *Diabetes Care* 2009;32 Suppl 1:S13–S61.

4. Government of South Australia, Department of Health. Managing type 2 diabetes in South Australia. Adelaide: The Department; 2008. Available from: www.publications.health.sa.gov.au/cgi/viewcontent.cgi?article=1001&context=dis (accessed 2009 Jan 19).

5. New Zealand Guidelines Group. Management of type 2 diabetes, Wellington: The Group; 2003. Available from: www.nzgg.org.nz/resources/102/Diabetes_full_text.pdf (accessed 2009 Jan 19).

6. IDF clinical guidelines task force. Global guideline for type 2 diabetes. Brussels: International Diabetes Federation 2005. Available from: www.idf.org/webdata/docs/IDF%20GT2D.pdf (accessed 2009 Jan 19).

7. American Diabetes Association. Standards of medical care in diabetes—2010. *Diabetes Care* 2010;33(Suppl 1):S11–S61. Available from: http://care.diabetesjournals.org/content/33/Supplement_1/S11.full.pdf+html (accessed 2010 Jan 21).

8. National Collaborating Centre for Chronic Conditions. Type 2 diabetes: the management of type 2 diabetes. London: National Institute for Health and Clinical Excellence; 2009. (NICE clinical guideline 87). Available from: www.nice.org.uk/nicemedia/pdf/CG87NICEGuideline.pdf (accessed 2010 Jan 21).

9. Canadian Agency for Drugs and Technologies in Health. Optimal therapy recommendations for the prescribing and use of second-line therapy for patients with type 2 diabetes inadequately controlled on metformin. Ottawa: The Agency; 2010. (CADTH optimal therapy report; vol 4 no. 5). Available from: www.cadth.ca/media/pdf/C1110_OT_Recommendations_final_e.pdf (accessed 2011 Jun 15).

10. Colagiuri S, Dickinson S, Girgis S, Colagiuri R. National evidence based guideline for blood glucose control in type 2 diabetes. Canberra: Diabetes Australia and NHMRC; 2009. Available from: www.nhmrc.gov.au/_files_nhmrc/file/publications/synopses/di19-diabetes-blood-glucose-control.pdf (accessed 2010 Feb 17).

11. Scotish Intercollegiate Guidelines Network. *Management of diabetes: a national clinical guideline*. Edinburgh: The Network; 2010. (Guideline no 116). Available from: www.sign.ac.uk/pdf/sign116.pdf (accessed 2010 Mar 25).

12. Phung OJ, Scholle JM, Talwar M, Coleman CL. Effect of noninsulin antidiabetic drugs added to metformin therapy on glycemic control, weight gain, and hypoglycemia in type 2 diabetes. *JAMA* 2010;303(14):1410–1418.

13. Canadian Agency for Drugs and Technologies in Health. Second-line therapy for patients with type 2 diabetes inadequately controlled on metformin: a systematic review and cost-effectiveness analysis. (Optimal therapy report; vol 4 no. 2). Ottawa: The Agency; 2010.

14. Canadian Agency for Drugs and Technologies in Health. Current utilization of second- and third-line therapies in patients with type 2 diabetes. (Optimal therapy report; vol 4 no. 3). Ottawa: The Agency; 2010. Available from: www.cadth.ca/media/pdf/C1110-CU-Report-2nd-3rd-Line-Agents-final-e.pdf (accessed 2010 Sep 11).

15. Rodbard HW, Jellinger PS, Davidson JA, Einhorn D, Garber AJ, Grunberger G, et al. Statement by an American Association of Clinical Endocrinologists/American College of Endocrinology consensus panel on type 2 diabetes mellitus: an algorithm for glycemic control.

Open Medicine 2012;6(2) e71
Bergenstal R, Lewin A, Bailey T, Chang D, Gylvin T, Roberts V, et al. Effect of two starting insulin regimens in patients with type II diabetes not controlled on a combination of oral antihyperglycemic medications. Exp Clin Endocrinol Diabetes 2009;117(5):223–229.

Milecic Z, Hancu N, Car N, Ivanji T, Schwarzenhofer M, Jeremdij M. Effect of two starting insulin regimens in patients with type II diabetes not controlled on a combination of oral antihyperglycemic medications. Exp Clin Endocrinol Diabetes 2009;117(5):223–229.

Davies MJ, Thawere PK, Tringham JR, Lowe J, Jarvis J, Johnston V, et al. A randomized controlled trial examining combinations of repaglinide, metformin and NPH insulin. Diabet Med 2007;24(7):714–719.

Nauck MA, Duran S, Kim D, Johns D, Northrup J, Festa A, et al. A comparison of twice-daily exenatide and biphasic insulin aspart in patients with type 2 diabetes who were suboptimally controlled with sulfonylurea and metformin: a non-inferiority study. Diabetologia 2007;50(2):259–267.

De Mattia G, Laurenti O, Moretti A. Comparison of glycaemic control in patients with Type 2 diabetes on basal insulin and fixed combination oral antidiabetic treatment: results of a pilot study. Acta Diabetol 2009;46(1):67–73.

Ovalle F, Bell DS. Effect of rosiglitazone versus insulin on the pancreatic beta-cell function of subjects with type 2 diabetes. Diabetes Care 2004;27(11):2585–2589.

Derosa G, Salvadeo SA, D’Angelo A, Ferrari I, Mereu R, Palumbo I, et al. Metabolic effect of repaglinide or acarbose when added to a double oral antidiabetic treatment with sulfonylureas and metformin: a double-blind, cross-over, clinical trial. Curr Med Res Opin 2009;25(3):607–615.

Reynolds LR, Kingsley FJ, Karounos DG, Tannock LR. Differential effects of rosiglitazone and insulin glargine on inflammatory markers, glycemic control, and lipids in type 2 diabetes. Diabetes Res Clin Pract 2007;77(2):180–187.

Dorkhan M, Dencker M, Stagmo M, Groop L. Effect of pioglitazone versus insulin glargine on cardiac size, function, and measures of fluid retention in patients with type 2 diabetes. Cardiovasc Diabetol 2009;8(15). Available from: www.cardiab.com/content/pdf/1475-2840-8-15.pdf (accessed 2009 Dec 4)

Rosenstock J, Sugimoto D, Strange P, Stewart JA, Soltes-Rak E, Dailey G. Triple therapy in type 2 diabetes: insulin glargine or rosiglitazone added to combination therapy of sulfonylurea plus metformin in insulin-naive patients. Diabetes Care 2006;29(3):554–559. Available from: http://care.diabetesjournals.org/cgi/reprint/29/3/554 (accessed 2009 Dec 4).

Esposito K, Ciottola M, Maiorino MI, Guaidello R, Schisano B, Ceriello A, et al. Addition of neutral protamine lispro insulin or insulin glargine to oral type 2 diabetes regimens for patients with suboptimal glycemic control: a randomized trial. Ann Intern Med 2008;149(8):531–539.

Ross SA, Zinman B, Campos RV, Strack T, Canadian Lispro Study Group. A comparative study of insulin lispro and human regular insulin in patients with type 2 diabetes mellitus and secondary failure of oral hypoglycemic agents. Clin Invest Med 2001;24(6):292–298.

Gao Y, Yoon KH, Chuang LM, Mohan V, Ning G, Shah S, et al. Efficacy and safety of exenatide in patients of Asian descent with type 2 dia-
butes inadequately controlled with metformin or metformin and a sulphonylurea. Diabetes Res Clin Pract 2009;83(1):69–76.

58. Yki-Järvinen H, Kauppinen-Mäkelin R, Tiikkainen M, Vähätalo M, al. Three-year efficacy of complex insulin regimens in type 2 diabetes. Diabetologia 2007;50(3):442–451.

59. Herrmens K, Kipnes M, Luo E, Fanurik D, Khatri M, Stein P, et al. Efﬁcacy and safety of the dipeptidyl peptidase-4 inhibitor, sitagliptin, in patients with type 2 diabetes mellitus inadequately controlled on glimepiride alone or on glimepiride and metformin. Diabetes Obes Metab 2007;9(5):733–745.

60. Binik AI, Zhang Q. Adding insulin glargine versus rosiglitazone: a randomised controlled trial in primary care. J Fam Pract 2004;53(5):393–399. Available from: www.jfponline.com/Pages.asp?AID=1703 (accessed 2009 Dec 4).

61. Stehouwer MH, DeVries JH, Lumeij JA, Adèr HJ, Engbers AM, Iperen al. Rosiglitazone evaluated for cardiovascular outcomes in oral agent combination therapy for type 2 diabetes (RECORD): a multicentre, randomised, open-label trial. Lancet 2009;373(9681):2125–2135.

62. Canadian Agency for Drugs and Technologies in Health. Current practice analysis: insulin analogues. A qualitative analysis of Canadian physician perceptions and use of insulin analogues. Ottawa: The Agency; 2008. (Optimal therapy report; vol. 2 no. 6). Available from: http://cadth.ca/media/compus/compus_Insulin-Analogues-Curr-Practice-Analysis.pdf (accessed 2008 Apr 11).

63. Canadian Agency for Drugs and Technologies in Health. Current practice analysis: sulphonylureas. A qualitative analysis of Canadian physician perceptions and use of sulphonylureas. Ottawa: The Agency; 2008. (Optimal therapy report; vol. 2 no. 6). Available from: www.cadth.ca/media/compus/compus_Sulphonylureas-Curr-Practice-Analysis.pdf (accessed 2010 Jun 29).

64. Canadian Agency for Drugs and Technologies in Health. Current practice analysis: metformin. A qualitative analysis of Canadian physician perceptions and use of metformin. Ottawa: The Agency; 2008. (Optimal therapy report; vol. 2 no. 6). Available from: www.cadth.ca/media/compus/compus_Metformin-Curr-Practice-Analysis.pdf (accessed 2010 Jun 29).

65. Bolen S, Feldman L, Vassy J, Wilson L, Yeh HC, Marinosopouls S, et al. Systematic review: comparative effectiveness and safety of oral medications for type 2 diabetes mellitus. Ann Intern Med 2007;147(6):386-399. Available from: www.annals.org/cgi/reprint/147/6/386.pdf (accessed 2010 May 14).

66. Selvin E, Bolen S, Yeh HC, Wiley C, Wilson LM, Marinosopouls SS, et al. Cardiovascular outcomes in trials of oral diabetes medications: a systematic review. Arch Intern Med 2008;168(19):2070–2080.

67. Hormans K, Chalmers J, Neal B, Billot L, Woodward M, et al. Effects of intensive control of glucose on cardiovascular and health-related quality-of-life outcomes in type 2 diabetes (UKPDS 33): a run-in phase and 3-year randomised controlled trial. Lancet 2008;372(9626):2235–2242.

68. Patel A, MacMahon S, Chalmers J, Neal B, Billot L, Woodward M, et al. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. Lancet 1998;352(9131):853–863.

69. Gerstein HC, Miller ME, Byington RP, Goff DC, Jr., Buse JB, Wasser WC, et al. Intensive glucose control and macrovascular outcomes in type 2 diabetes. N Engl J Med 2008;359(15):1577–1589.

70. Dore DD, Seeger JD, Chan KA. Use of a claims-based active drug safety surveillance system to assess the risk of acute pancreatitis with exenatide or sitagliptin compared to metformin or glyburide. Curr Med Res Opin 2009;25(4):2867–2894.

71. Patel A, MacMahon S, Chalmers J, Neal B, Billot L, Woodward M, et al. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33): a run-in phase and 3-year randomised controlled trial. Lancet 2008;372(9626):2235–2242.

72. Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA. 10-year follow-up of intensive glucose control in type 2 diabetes. N Engl J Med 2008;359(15):1577–1589.

73. Gerstein HC, Miller ME, Byington RP, Goff DC, Jr., Buse JB, Wasser WC, et al. Intensive glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. Lancet 1998;352(9131):853–863.

74. Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA. 10-year follow-up of intensive glucose control in type 2 diabetes. N Engl J Med 2008;359(15):1577–1589.

75. Gerstein HC, Miller ME, Byington RP, Goff DC, Jr., Buse JB, Wasser WC, et al. Intensive glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33): a run-in phase and 3-year randomised controlled trial. Lancet 2008;359(15):1577–1589.

76. Patel A, MacMahon S, Chalmers J, Neal B, Billot L, Woodward M, et al. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33): a run-in phase and 3-year randomised controlled trial. Lancet 2008;359(15):1577–1589.

77. Currie CJ, Peters JR, Tynan A, Evans M, Heine RJ, Bracco OL, et al. Survival as a function of HbA(1c) in people with type 2 diabetes: a retrospective cohort study. Lancet 2010;375(9713):481–489.
78. Gross JL, Kramer CK, Leitão CB, Hawkins N, Viana LV, Schaan BD, 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):672–679.

79. Perfetti R, Merkel P. Glucagon-like peptide-1: a major regulator of pancreatic beta-cell function. Eur J Endocrinol 2000;143(6):717–725.

80. Yeom JA, Kim ES, Park HS, Ham DS, Sun C, Kim JW, et al. Both sitagliptin analogue & pioglitazone preserve the Beta-cell proportion in the islets with different mechanism in non-obese and obese diabetic mice. BMB Rep 2011;44(11):713–718.

81. Kanda Y, Shimoda M, Hamamoto S, Tawaramoto K, Kawasaki F, Hashiramoto M, et al. Molecular mechanism by which pioglitazone preserves pancreatic beta-cells in obese diabetic mice: evidence for acute and chronic actions as a PPARgamma agonist. Am J Physiol Endocrinol Metab 2010;298(2):E278–E286 (accessed 2012 Mar 22). Available from: www.ncbi.nlm.nih.gov/pmc/articles/PMC2822485.

82. Richter B, Bandeira-Echtler E, Bergerhoff K, Lerch CL. Dipeptidyl peptidase-4 (DPP-4) inhibitors for type 2 diabetes mellitus. Cochrane Database Syst Rev 2008;(2):CD006739.

83. Shyangdan DS, Royle PL, Clar C, Sharma P, Waugh NR. Glucagon-like peptide analogues for type 2 diabetes mellitus: systematic review and meta-analysis. BMC Endocr Disord 2010;10:20. Available from: www.ncbi.nlm.nih.gov/pmc/articles/PMC3017518 (accessed 2011 Aug 11).

84. Nakamura T, Funahashi T, Yamashita S, Nishida M, Nishida Y, Takahashi M, et al. Thiazolidinedione derivative improves fat distribution and multiple risk factors in subjects with visceral fat accumulation–double-blind placebo-controlled trial. Diabetes Res Clin Pract 2001;54(3):181–190.

85. Nesto RW, Bell D, Bonow RO, Fonseca V, Grundy SM, Horton ES, et al. Thiazolidinedione use, fluid retention, and congestive heart failure: a consensus statement from the American Heart Association and American Diabetes Association. October 7, 2003. Circulation 2003;108(23):2941–2948. Available from: www.circ.ahajournals.org/cgi/reprint/108/23/2941 (accessed 2007 Nov 20).

86. Fonseca V. Effect of thiazolidinediones on body weight in patients with diabetes mellitus. Am J Med 2003;115 Suppl 8A:425–485.

87. Wajchenberg BL. Subcutaneous and visceral adipose tissue: their relation to the metabolic syndrome. Endocr Rev 2000;21(6):697–738.

88. WHO Consultation on Obesity (1999: Geneva, Switzerland). Obesity: preventing and managing the global epidemic: report of a WHO consultation. (WHO technical report series; 894). Geneva: World Health Organization (WHO); 2000. Available from: http://whqlibdoc.who.int/trs/WHO_TRS_894.pdf (accessed 2009 Nov 29).

89. Wing RR, Koeske R, Epstein LH, Nowalk MP, Gooding W, Becker D. Long-term effects of modest weight loss in type II diabetic patients. Arch Intern Med 1987;147(10):1749–1753.

90. Fujikoa K, Seaton TB, Rowe E, Jelinek CA, Raskin P, Lebovitz HE, et al. Weight loss with sibutramine improves glycaemic control and other metabolic parameters in obese patients with type 2 diabetes mellitus. Diabetes Obes Metab 2000;2(3):175–187.

91. Amiel SA, Dixon T, Mann R, Jameson K. Hypoglycaemia in Type 2 diabetes. Diabet Med 2008;25(3):245–254. Available from: www.ncbi.nlm.nih.gov/pmc/articles/PMC2322721. (accessed 2010 Jan 22).

92. Edwards KL, Alvarez C, Irons BK, Fields J. Third-line agent selection for patients with type 2 diabetes mellitus uncontrolled with sulfonylureas and metformin. Pharmacotherapy 2008;28(4):506–521.

93. Black C, Donnelly P, McIntyre L, Royle PL, Shepherd JP, Thomas S. Meglitinide analogues for type 2 diabetes mellitus. Cochrane Database Syst Rev 2007;(2):CD004654.

Published: 31 May 2012

Citation: McIntosh B, Cameron C, Singh SR, Yu C, Dolovich L, Houlden R. Choice of therapy in patients with type 2 diabetes inadequately controlled with metformin and α sulphonylurea: a systematic review and mixed-treatment comparison meta-analysis. Open Med 2012;6(2):e62–e74.

Copyright: Open Medicine applies the Creative Commons Attribution Share Alike License, which means that anyone is able to freely copy, download, reprint, reuse, distribute, display or perform this work and that authors retain copyright of their work. Any derivative use of this work must be distributed only under a license identical to this one and must be attributed to the authors. Any of these conditions can be waived with permission from the copyright holder. These conditions do not negate or supersede Fair Use laws in any country. For more information, please see http://creativecommons.org/licenses/by-sa/2.5/ca/.