

# **Second-line therapy in patients with type 2 diabetes inadequately controlled with metformin monotherapy: A systematic review and mixed treatment comparisons meta-analysis**

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## **Abstract**

**Background:** While 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-analyses to assess the comparative safety and efficacy of all available classes of antihyperglycemic therapies in patients with type 2 diabetes inadequately controlled on metformin monotherapy.

**Methods:** We identified 49 active and non-active controlled randomized trials that compared two or more of the following classes of antihyperglycemic agents: sulfonylureas, meglitinides, TZDs, DPP-4 inhibitors, GLP-1 analogues, insulins, and alpha-glucosidase inhibitors. The main outcomes of interest were hemoglobin A1c, weight, hypoglycemia, quality-of-life, long-term diabetes-related complications, and mortality. MTC and pairwise meta-analyses were conducted to pool trial results, when appropriate.

**Results:** All classes of second-line antihyperglycemic therapies achieved clinically meaningful reductions in hemoglobin A1c. 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, the exceptions being DPP-4 inhibitors, alpha-glucosidase inhibitors, and GLP-1 analogues.

**Interpretation:** DPP-4 inhibitors and GLP-1 analogues achieved similar improvements in glycemic control compared with established therapies, although they may have modest benefits in terms of 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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## INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a progressive metabolic disease that causes significant morbidity and mortality worldwide. Clinical practice guidelines<sup>1-8</sup> recommend metformin as the first-line oral antihyperglycemic drug (OAD) in most patients with T2DM when glycemic control cannot be achieved by lifestyle interventions. While some guidelines advise sulfonylureas be added as second-line therapy when glycemic control is inadequate with metformin alone,<sup>2,5,6,9</sup> others<sup>3,4,7,10</sup> lack recommendations regarding a preferred agent.

The number of therapies available for T2DM has expanded in recent years to include more expensive drug classes such as thiazolidinediones, glucagon-like peptide (GLP) analogues, and dipeptidyl peptidase-4 (DPP-4) inhibitors. 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.<sup>11</sup> 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 since they did not include newer drug classes, or did not restrict their analyses to patients inadequately controlled with metformin alone.<sup>12-16</sup>

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](http://www.cadth.ca/index.php/en/compus/second-line-therapies-type-2-diabetes)), we

conducted a systematic review of the comparative safety and efficacy of all antihyperglycemic drug classes for patients with T2DM inadequately controlled with metformin monotherapy.

## **METHODS**

This systematic review was conducted according to a protocol

([http://www.cadth.ca/media/pdf/compus\\_2nd\\_line\\_T2DM\\_Protocol\\_e.pdf](http://www.cadth.ca/media/pdf/compus_2nd_line_T2DM_Protocol_e.pdf)) prepared in advance.<sup>17</sup>

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 1). Monthly OVID AutoAlerts were reviewed from June to October 2009. Additional citations were obtained from grey literature, conference proceedings, and through stakeholder feedback.

The population of interest consisted of adults and children with T2DM requiring a second-line antihyperglycemic agent due to inadequate control (HbA1c >6.5%, FPG >7mmol/L, or 2-hour PPG >10mmol/L) on, or intolerance to, metformin monotherapy. 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/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, and severe adverse events. Active and non-active controlled RCTs published in English were included if they were at least four weeks in duration, and compared one or more relevant drugs either: 1) added to metformin due to inadequate glycemic control with metformin alone, or 2) switched from metformin due to intolerance. We included studies regardless of metformin dose or duration at baseline, or treatment history prior to metformin monotherapy.

Study selection, data extraction, and quality assessment were conducted independently by two reviewers. Methodological quality was assessed using the SIGN-50 instrument.<sup>18</sup>

### ***Statistical Methods***

Bayesian MTC meta-analysis was performed for HbA1c, body weight, and overall hypoglycemia, following careful assessment of heterogeneity across trials in terms of subject characteristics, trial methodologies, and treatment protocols. Pairwise meta-analyses were also conducted for these outcomes to enhance acceptability of findings among those unfamiliar with Bayesian meta-analysis, and to assess consistency between direct and indirect evidence. Only pairwise direct comparisons were conducted for the remaining outcomes due to the limited number of available studies, or infrequent events. 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 due to 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/](http://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 (MCMC) 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 based on the proportion of MCMC 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.<sup>19</sup> Model diagnostics including trace plots and the Brooks-Gelman-Rubin statistic<sup>20</sup> were assessed to ensure model convergence. Two chains were fit in WinBUGS for each analysis, each employing  $\geq 20,000$  iterations, with a burn-in of  $\geq 20,000$  iterations.

We conducted meta-regression to adjust for baseline HbA1c, duration of diabetes, and baseline BMI (for body weight only) to test the robustness of our reference case analysis. In other sensitivity analyses, we removed studies from the network that: were of poor methodological quality; employed a cross-over design; were  $< 1$  year in duration; and where baseline metformin dose was  $< 1500$  mg/day.

## RESULTS

### *Study selection*

Of 1946 citations identified in the literature search, 287 were reviewed as full-text articles, and 56<sup>21-76</sup> (representing 49 unique RCTs) were included in this review (figure 1). No evidence was found for children, or individuals experiencing metformin intolerance.

### *Study characteristics and methodological quality*

Most trials were 6-12 months long, although one study was over five years in duration. Mean baseline HbA1c ranged from 6.6%-10% [weighted mean  $\pm$ SD  $8.0 \pm 0.9\%$ ]. The baseline duration of diabetes ranged from 1.8-10.3 years [weighted mean  $\pm$ SD of  $6.1 \pm 5.1$  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  $\geq 1500$  mg for  $\geq 3$  months in many studies. Three scenarios for treatment history prior to 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.<sup>21-29,32,33,36,37,39,40,42-46,48,50-53,55,56,59-62,65-77</sup> In the second scenario, patients using various OADs underwent a run-in period with metformin monotherapy upon trial entry, and were randomized to add-on therapy if glycemic control was inadequate at the end of the run-in.<sup>30,35,38,41,47,49,57,58,63,64</sup> Only one RCT<sup>31</sup> reported inclusion criteria that likely limited the study sample to individuals experiencing inadequate control on initial metformin therapy. Most studies (89%) were industry funded.

About two-thirds of the studies identified were of poor methodological quality; inadequate allocation concealment, failure to use an intention-to-treat analysis, and lack of blinding were common limitations.

### ***Hemoglobin A1C***

Forty RCTs (N = 17795) reported change from baseline in HbA1c (figure 2). All classes of second-line agents added to metformin significantly reduced HbA1c relative to metformin alone (table 1). Effect estimates ranged from -0.65% (95%CI: -1.14,-0.20) for meglitinides to -0.96% (95%CI: -1.57,-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, which was confirmed through formal methods. The results were robust in sensitivity and meta-regression analyses (table 2), and in the dose-stratified analysis (data not reported).

Compared to metformin monotherapy, one RCT<sup>23</sup> (n = 69) reported a significant HbA1c reduction in patients treated with metformin plus orlistat [-0.93% (95%CI: -1.58, -0.28)], while a second RCT found no significant difference with sibutramine plus metformin.<sup>55</sup>

### ***Hypoglycemia***

Thirty-four RCTs (n = 16704) reported the numbers of patients experiencing at least one 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 were 5.2-11.0 for insulins, and 8.2 for sulfonylureas) (table 1). 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, an outcome reported in 24 RCTs (n = 8650), was rare for all drug classes including insulins and insulin secretagogues. Most trials reported zero event rates. Based on the limited evidence available, neither sulfonylureas<sup>32,52,58</sup> (n = 501) nor GLP-1 analogues<sup>39,58,72</sup> (n = 389) differed significantly from metformin monotherapy, nor did GLP-1 analogues differ significantly from basal insulin<sup>22,29</sup>. One RCT<sup>37</sup> (n = 2789) reported significantly more events of severe hypoglycemia with sulfonylureas versus DPP-4 inhibitors [OR (95% CI) 21.20 (1.24,362.1)].

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

### ***Body weight***

Thirty RCTs (n = 15265) reported change from baseline body weight (table 1). 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 were weight neutral. The only drug class associated with a significant reduction in body weight versus metformin monotherapy was GLP-1 analogues [-1.77 kg (95%CI: -3.40,-0.15)]. A meta-regression adjusting for differences in baseline BMI



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<sup>55</sup> and orlistat<sup>23</sup> 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. Based on the sparse data available, no significant differences between treatments were found (table 3). 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.<sup>46</sup> Unfortunately, much of these data could not be included in this review since results were not stratified by type of monotherapy at baseline.

Twenty-three RCTs (n = 11933)<sup>24,26,27,29,30,32,37,38,41,42,47,51,52,57,60,61,63,64,66,70-72,77</sup> reported total severe adverse events, however this outcome was rarely defined. Pairwise meta-analysis of three RCTs<sup>24,26,70</sup> (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 (95% CI) = 1.71 (1.06,2.77)]. No significant differences were observed for the other nine pairwise comparisons, although statistical power was limited due to low event rates (data not shown).

### ***Quality-of-life and patient satisfaction***

One RCT<sup>51</sup> 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 three-arm RCT<sup>75</sup> comparing metformin with sulfonylurea, metformin with GLP-1 analogue,

and metformin alone reported statistically significant improvements in favour of liraglutide (a GLP-1 analogue) over the other two arms on the “perceived frequency hyperglycemia” sub-scores of the DTSQ.

## DISCUSSION

We identified 49 RCTs comparing the effects of eight antihyperglycemic drug classes in patients with type 2 diabetes inadequately controlled with metformin monotherapy. To our knowledge, this analysis is the first to synthesize the available efficacy and safety data on 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.<sup>78-81</sup>

Our results for HbA1c, hypoglycemia, and body weight are generally consistent with other systematic reviews of OADs.<sup>12-16,82</sup> All drug classes significantly reduced A1C 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, since 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 *et al* (2010)<sup>82</sup> who recently used MTC meta-analysis to assess the comparative-efficacy of OADs added to metformin. Sulfonylureas, meglitinides, TZDs, and insulins were associated with statistically significant increases in body weight ranging from approximately 2 to 3 kg relative to metformin alone. DPP-4 inhibitors and alpha-glucosidase inhibitors were found to be weight neutral, 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 to 7kg for a 70kg adult) are cited as such in the literature.<sup>83-88</sup> In this context, the differences in body weight that we observed between classes are likely modest for most patients.

Both insulins and insulin secretagogues demonstrated 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 et al. reported 0.90 and 11.8 events that required emergency medical care per 100 patient-years with insulin secretagogues and insulin, respectively,<sup>89</sup> while Bodmer et al. reported rates of 0.06 and 0.24 events that caused either hospitalization or death per 100 patient-years.<sup>90</sup> In comparison, the ADVANCE trialists reported lower incidence rates than Leese et al. (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).<sup>91</sup> 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.<sup>46</sup> 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 likely 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.<sup>46</sup> Although we could not include these results in the review due to 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,<sup>13,92,93</sup> although controversy remains regarding the effects of TZDs

on the risk of ischemic heart disease.<sup>94</sup> 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.<sup>95,96</sup> Advantages of older drug classes such as sulfonylureas and insulin are the availability of trial data regarding long range safety,<sup>97,98</sup> as well as the extensive clinical experience with these agents.

### ***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.<sup>99-102</sup> Second, we did not assess non-serious adverse effects that can impact the tolerability of antihyperglycemic agents. For example, acarbose is commonly associated with gastrointestinal adverse effects that may limit its usefulness.<sup>61</sup> Third, inclusion of insulin in the MTC meta-analysis may be viewed with scepticism since 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 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.

The clinical population of interest with respect to optimal second-line therapy consists of patients 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, since the reference case results were robust to adjustment (through meta-regression) for differences across studies in duration of diabetes and baseline HbA1c. These are likely more important predictors of efficacy than treatment history per se.

## **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 little 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. As well, the cost-effectiveness of newer drugs requires further study in light of their higher cost and modest benefits over older therapies.

**Competing interests:** Marshall Dahl has received an honorarium of less than \$5,000 from Eli Lilly Canada Inc. for his work related to workshops. He has also received an arms-length grant for a diabetes study in coronary artery patients from GlaxoSmithKline Inc. Nicky Welton has received a contribution of £2250 from Pfizer PLC to provide a course on MTC methods.

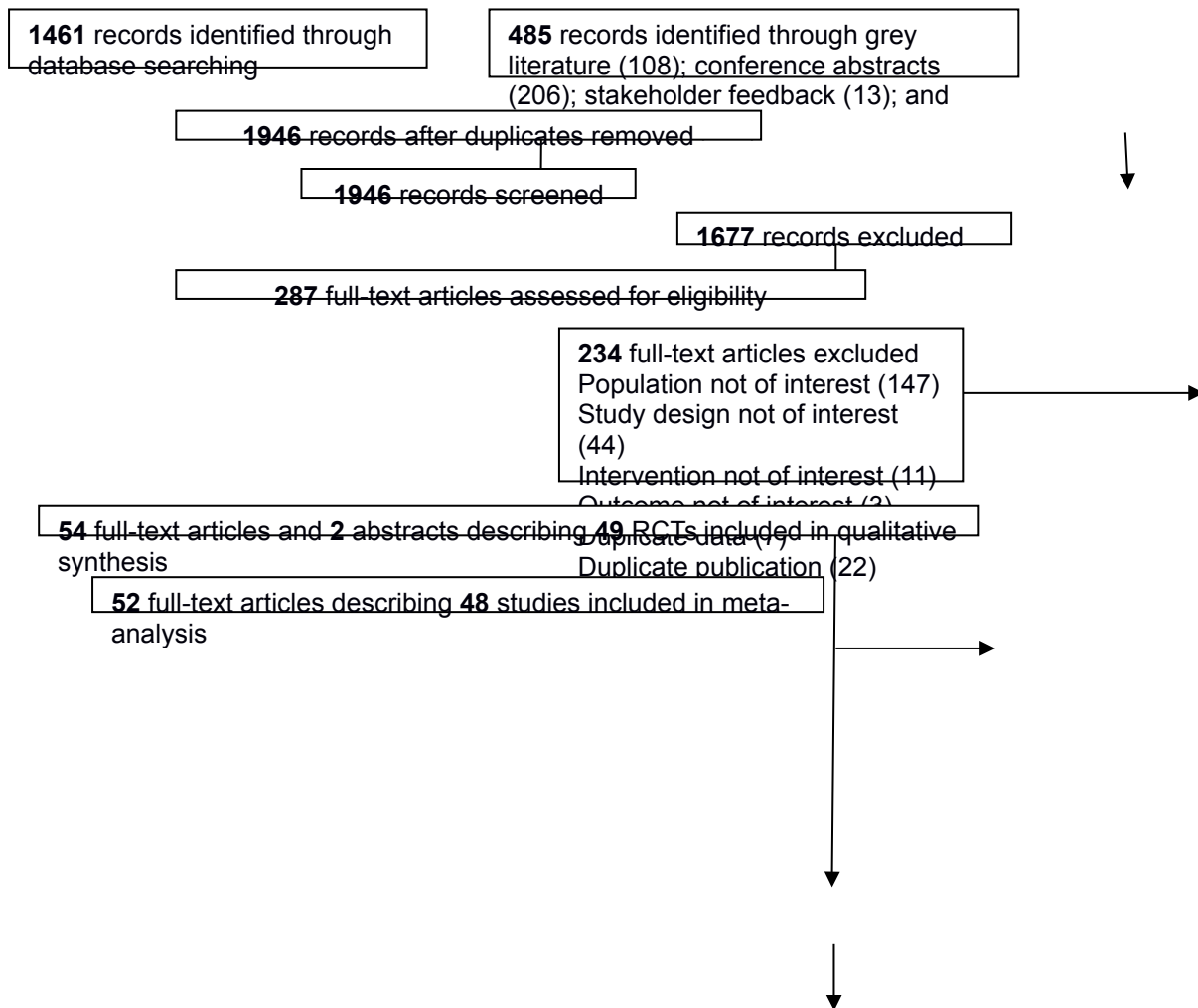
**Contributors:** All of the authors contributed to the conception and design of the study. BM, CY, and TA extracted data from primary studies, CC performed the Bayesian MTC meta-analyses, BM and CY conducted the frequentist pair-wise meta-analyses. CC, NW, BM, SS, and CY interpreted the results. SS and provided oversight for data extraction, analysis and interpretation (with MD). BM with the help of SS, CC, NW, and MD drafted the manuscript. All of the authors critically reviewed the manuscript and approved the final version submitted for publication. SS is the corresponding author and guarantor for the research.

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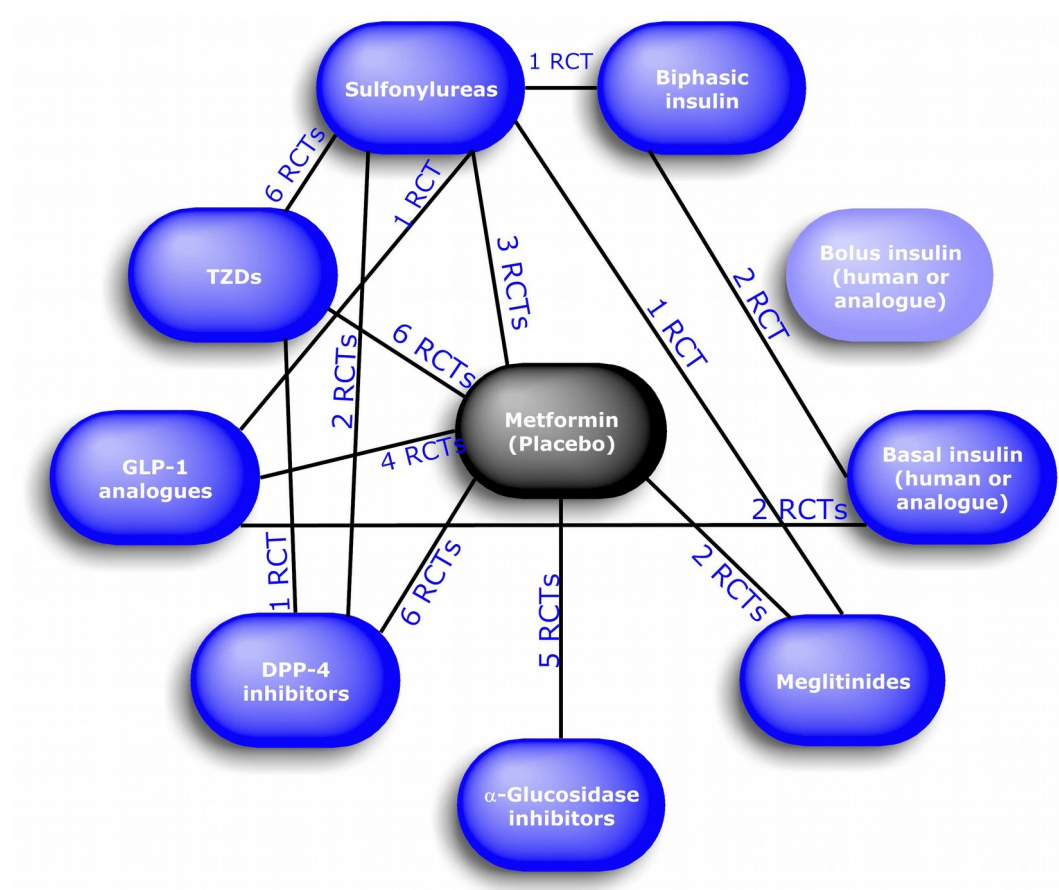
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**Figure 1: PRISMA diagram of study selection results**



**Figure 2:** MTC evidence network for hemoglobin A1C





**Table 1: Summary of results from direct and MTC analyses**

Hemoglobin A1C (change from baseline, %)		
Treatment vs. metformin monotherapy	Direct estimates WMD (95% CI)	MTC estimates (95% CrI)
Sulfonylureas	-0.80 (-1.00, -0.59)	-0.79 (-0.95, -0.63)
Meglitinides	-0.71 (-1.24, -0.18)	-0.64 (-0.93, -0.37)
TZDs	-0.96 (-1.18, -0.75)	-0.82 (-1.00, -0.66)
DPP-4 Inhibitors	-0.78 (-0.96, -0.60)	-0.80 (-0.95, -0.65)
α-glucosidase inhibitors	-0.74 (-0.94, -0.53)	-0.74 (-0.98, -0.50)
GLP-1 analogues	-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)		
Treatment vs. metformin monotherapy	Direct estimates WMD (95% CI)	MTC estimates Median OR (95% CrI)
Sulfonylureas	4.64 (1.27, 16.97)	8.22 (4.52, 16.63)
Meglitinides	6.59 (1.53, 28.29)	8.59 (3.47, 25.20)
TZDs	1.56 (0.56, 4.33)	1.10 (0.54, 2.27)
DPP-4 Inhibitors	1.07 (0.59, 1.93)	1.05 (0.56, 2.21)
α-glucosidase inhibitors	0.49 (0.04, 5.55)	0.39 (0.01, 6.67)
GLP-1 analogues	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)		
Treatment vs. metformin monotherapy	Direct estimates WMD (95% CI)	MTC estimates (95% CrI)
Sulfonylureas	1.79 (1.29, 2.28)	2.01 (1.09, 2.94)
Meglitinides	2.01 (-0.31, 4.32)	1.80 (0.35, 3.29)
TZDs	2.30 (1.93, 2.66)	2.59 (1.66, 3.51)
DPP-4 Inhibitors	0.70 (0.20, 1.21)	0.57 (-0.45, 1.60)
α-glucosidase inhibitors	-0.90 (-1.92, 0.13)	-0.92 (-2.35, 0.51)
GLP-1 analogues	-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)

CI – confidence interval, CrI – credible interval, WMD – weighted mean difference, TZDs – thiazolidinediones, DPP – dipeptidyl peptidase-4, GLP – glucagon-like peptide

**Table 2: Summary of sensitivity analysis results for HbA1c**

Sensitivity analyses for HbA1c – MTC estimate of effect vs. Placebo						
Analysis	Sulfonylureas	Meglitinides	TZDs	DPP-4 Inhibitors	α-glucosidase inhibitors	GLP-1 analogues
<b>Random effects model vs. fixed effects model</b>						
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)
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)
<b>Meta-regressions adjusting for:</b>						
Baseline A1C	-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)
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)
<b>Sensitivity analyses with removal of:</b>						

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)
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)
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)
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)
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)
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)	—

Hb<sub>A1c</sub> – glycosylated hemoglobin, TZD - thiazolidinediones, DPP-4 – dipeptidyl peptidase-4, GLP-1 – glucagon-like peptide-1, N/A – not applicable

**Table 3:** Summary of findings for long-term complications of diabetes

Comparison	No. of trials/total N	OR (95% CI)
<b>Ischemic heart disease</b>		
TZDs vs. Sulfonylureas	1 RCT <sup>54</sup> (N = 630)	2.97 (0.12, 73.22)
α-Glucosidase inhibitors vs. Placebo	1 RCT <sup>72</sup> (N = 153)	0.32 (0.01, 7.89)
Sulfonylureas vs. Meglitinides	1 RCT <sup>66</sup> (N = 213)	0.18 (0.01, 3.73)
Sulfonylureas vs. DPP-4 inhibitors	1 RCT <sup>57</sup> (N = 1135)	0.14 (0.01, 2.68)
DPP-4 inhibitors vs. Placebo	1 RCT <sup>64</sup> (N = 190)	3.10 (0.12, 76.97)
DPP-4 inhibitors vs. TZDs	1 RCT <sup>26</sup> (N = 575)	1.05 (0.07, 16.93)
<b>Congestive heart failure</b>		
TZDs vs. Sulfonylureas	1 RCT <sup>31</sup> (N = 630)	2.49 (0.48, 12.94)
DPP-4 inhibitors vs. Sulfonylureas	1 RCT <sup>37</sup> (N = 2789)	1.00 (0.14, 7.09)
DPP-4 inhibitors vs. TZDs	1 RCT <sup>25</sup> (N = 575)	No events
α-Glucosidase inhibitors vs. Placebo	1 RCT <sup>72</sup> (N = 153)	0.32 (0.01, 7.89)
<b>Macular edema</b>		
TZDs vs. Sulfonylureas	1 RCT <sup>46</sup> (N = 2222)	No events
<b>Mortality</b>		
TZD vs. Sulfonylureas	1 RCT <sup>54</sup> (N = 630)	0.20 (0.01, 4.10)
DPP-4 inhibitors vs. Placebo	3 RCTs <sup>42,64,77</sup> (N= 1117)	0.22 (0.02, 2.16)
DPP-4 inhibitors vs. Sulfonylureas	2 RCTs <sup>37,57</sup> (N = 3924)	0.59 (0.14, 2.50)
TZD vs. Placebo	1 RCT <sup>38</sup> (N = 223)	No events
α-Glucosidase inhibitors vs. Placebo	1 RCT <sup>43</sup> (N = 152)	No events
Meglitinides vs. Sulfonylureas	1 RCT <sup>66</sup> (N = 213)	No events
BiAsp 30 vs. Sulfonylureas	1 RCT <sup>50</sup> (N = 222)	3.20 (0.13, 79.29)
TZD vs. DPP-4 inhibitors	1 RCT <sup>24</sup> (N = 2627)	6.05 (0.25, 148.75)
<b>Neuropathy</b>		
DPP-4 inhibitors vs. Placebo	1 RCT <sup>64</sup> (N = 190)	2.00 (0.36, 11.19)

Comparison	No. of trials/total N	OR (95% CI)
<b>Peripheral vascular disease</b>		
Sulfonylureas vs. DPP-4 inhibitors	1 RCT <sup>37</sup> (N = 2789)	0.33 (0.01, 8.17)
<b>Stroke/transient ischemic attack</b>		
Sulfonylureas vs. DPP-4 inhibitors	1 RCT <sup>37</sup> (N = 2789)	0.07 (0.00, 1.16)
TZDs vs. DPP-4 inhibitors	1 RCT <sup>26</sup> (N = 575)	3.18 (0.33, 30.79)

TZDs - thiazolidinediones, DPP – dipeptidyl peptidase, GLP – glucagon-like peptide, OR – odds ratio, CI – confidence interval, N – total sample size, RCT – randomized controlled trial

## APPENDIX 1: LITERATURE SEARCH STRATEGY

Interface:	OVID
Databases:	BIOSIS Previews <1985 to 2009 Week 21>; EMBASE <1980 to 2009 Week 18>; Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <May 4, 2009>; Ovid MEDLINE(R) <1950 to April Week 4 2009> * Note: Subject headings have been customized for each database.
Date of Search:	May 4, 2009
Alerts:	Monthly search updates began June 2009 and ran to [DATE].
Study Types:	randomized controlled trials
Limits:	Publication years 1980-present English
/	At the end of a phrase, searches the phrase as a subject heading
.sh	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical Subject Heading
fs	Floating subheading
exp	Explode a subject heading
\$	Truncation symbol, or wildcard: retrieves plural or variations of a word
*	Indicates that the marked subject heading is a primary topic
?	Truncation symbol for one or no characters only
ADJ	Requires words are adjacent to each other (in any order)
ADJ#	Adjacency within # number of words (in any order)
.ti	Title

.ab	Abstract
.hw	Heading Word; usually includes subject headings and controlled vocabulary
.pt	Publication type
.rn	CAS registry number

## Line # Searches

### MEDLINE / BIOSIS

- 1 Hypoglycemic drugs/  
((Antidiabetic or anti diabetic or antihyperglycemic or anti-hyperglycemic or oral hypoglycemic or
- 2 anti-diabetes or antidiabetes) adj (agent or agents or drug or drugs or compound or  
compounds)).ti,ab.
- 3 Thiazolidinediones/  
(glitazone\* or thiazolidinedione\* or pioglitazone\* or rosiglitazone\* or actos or avandia or avandamet
- 4 or avandaryl).ti,ab.
- 5 (122320-73-4 or 155141-29-0).rn.
- 6 Dipeptidyl-Peptidase IV Inhibitors/  
(Sitagliptin or januvia or Vildagliptin or galvus or gliptin or incretin agent\* or Exenatide or byetta
- 7 or Liraglutide or victoza).ti,ab.
- 8 (486460-32-6 or 274901-16-5 or 141758-74-9 or 204656-20-2).rn.
- 9 (dpp adj IV adj inhibitor\*).ti,ab.
- 10 (Dipeptidyl-Peptidase adj IV adj inhibitor\*).ti,ab.
- 11 DPP-4 inhibitors.ti,ab.
- 12 dipeptidyl peptidase-4 inhibitors.ti,ab.
- 13 exp Sulfonylurea Compounds/  
(sulfonylurea\* or tolbutamide or Orinase or glyconon or tolazamide or Tolinase or chlorpropamide
- 14 or Diabinese or glymese or glipizide or Glucotrol or glyburide or glibenclamide or glybenclamide or  
Diabeta or Micronase or Glynase or gen-glybe or euglucon or glimepiride or Amaryl or gliclazide or  
Diamicon or diaglyk or glibenese or minodiab or gen-gliclazide).ti,ab.
- 15 (64-77-7 or 1156-19-0 or 94-20-2 or 29094-61-9 or 10238-21-8 or 93479-97-1 or 21187-98-4).rn.
- 16 alpha-Glucosidases/ai [Antagonists & Inhibitors]  
(acarbose or glucobay or precose or prandase or akarbose or miglitol\* or glyset or diastabol or
- 17 voglibose).ti,ab.
- 18 (56180-94-0 or 72432-03-2 or 83480-29-9).rn.
- 19 ((alph\* adj glucos\* adj inhibit\*) or (alf\* adj glucos\* adj inhibit\*)).ti,ab.
- 20 acarbose/ [mesh]
- 21 Lipase/ai [Antagonists & Inhibitors]  
(Orlistat or Xenical or Tetrahydrolipstatin or Sibutramine or meridia).ti,ab.
- 22 (96829-58-2 or 106650-56-0).rn.
- 23 (lipase adj inhibit\*).ti,ab.
- 24 (repaglinide or nateglinide or Meglitinide\* or prandin or gluconorm or starlix or novonorm).ti,ab.
- 25 (135062-02-1 or 105816-04-4).rn.
- 27 Amyloid/  
(Pramlintide or symlin).ti,ab.
- 29 (amylin adj analog\*).ti,ab.
- 30 151126-32-8.rn.
- 31 exp insulin/  
(long acting insulin\* or long acting analog\* or slow\* acting insulin\* or slow\* acting analog\*).ti,ab.
- 32 (glargine or Lantus or Optisulin or hoe 901 or 160337-95-1).ti,ab,rn.
- 34 (detemir or determir or Levemir or nn 304 or 169148-63-4).ti,ab,rn.
- 35 (nph insulin or humulin or novolin).ti,ab.
- 36 11061-68-0.rn.
- 37 (short acting insulin\* or quick acting insulin\* or rapid acting insulin\* or rapidly acting insulin\* or fast

acting insulin\* or quick acting analog\* or rapid acting analog\* or rapidly acting analog\* or short  
 acting analog\* or fast acting analog\*).ti,ab.  
 38 (Lispro or Lyspro or Humalog or Liprolog or 133107-64-9).ti,ab,rn.  
 39 (Insulin Aspart or 116094-23-6 or NovoLog or NovoRapid or NovoMix).ti,ab,rn.  
 40 (Glulisine or 207748-29-6 or Apidra).ti,ab,rn.  
 41 or/1-40  
 42 ((adult or ketosis-resistant or matur\* or late or non-insulin depend\* or noninsulin depend\* or slow  
 or stable or type 2 or type II or lipoatrophic) adj3 diabet\$).ti,ab.  
 43 exp Diabetes Mellitus, Type 2/  
 44 (Mody or niddm or t2dm).ti,ab.  
 45 diabetes mellitus/  
 46 or/42-45  
 47 41 and 46  
 48 Randomized Controlled Trial.pt.  
 49 Randomized Controlled Trials as Topic/  
 50 Randomized Controlled Trial/  
 51 Randomization/  
 52 Random Allocation/  
 53 Double-Blind Method/  
 54 Double Blind Procedure/  
 55 Double-Blind Studies/  
 56 Single-Blind Method/  
 57 Single Blind Procedure/  
 58 Single-Blind Studies/  
 59 Placebos/  
 60 Placebo/  
 61 (random\* or sham or placebo\*).ti,ab,hw.  
 62 ((singl\* or doubl\*) adj (blind\* or dumm\* or mask\*)).ti,ab,hw.  
 63 ((tripl\* or trebl\*) adj (blind\* or dumm\* or mask\*)).ti,ab,hw.  
 64 or/48-63  
 65 Metformin/  
 66 Metformin.ti,ab.  
 67 (dimethylguanylguanidine or dimethylbiguanidine or glucophage).ti,ab.  
 68 (657-24-9 or 1115-70-4).rn.  
 (Glycon or Fortamet or Riomet or Venez or Diaformina or Dimefor or Glaformil or Glucaminol or  
 69 Glucofage or Diabex or Diaformin or Glucohexal or Glucomet or Novomet or Metomin or Glucamet  
 or Metsol or Orabet).ti,ab.  
 (apo-metformin or apotex or genmetformin or glucophage or glumetza or novo-metformin or nu-  
 70 metformin or pms-metformin or ran-metformin or ratio-metformin or rhoxal-metformin or sandoz  
 metformin).ti,ab.  
 (Aron or Diabetosan or Diabex or Diformin or Diformin Retard or Dimethylbiguanide or Dmgg or  
 71 Fluamine or Fortamet or Gliguanid or Glucoformin or Haurymellin or La 6023 or La6023 or Meguan  
 or Mellittin or Metaformin or Methformin or Metiguamide or Metphormin or Dimethylguanylguanide  
 or Nndg or Dimethylbiguanide or Dimethyl Biguanidine or Dimethylbiguanidine or  
 Dimethyldiguanide).ti,ab.  
 72 or/65-71  
 73 47 and 64 and 72  
 74 limit 73 to yr="1980 -Current"  
 75 limit 74 to english language

# **Line # Searches**

## **EMBASE**

- 1 \*Diabetes Mellitus/
- 2 \*Maturity Onset Diabetes Mellitus/
- 3 \*Non Insulin Dependent Diabetes Mellitus/

4 \*Lipoatrophic Diabetes Mellitus/  
 5 ((adult or ketosis-resistant or matur\* or late or non-insulin depend\* or noninsulin depend\* or slow  
 or stable or type 2 or type II or lipoatrophic) adj3 diabet\$).ti,ab.  
 6 (Mody or niddm or t2dm).ti,ab.  
 7 or/1-6  
 8 Metformin/  
 9 Metformin.ti,ab.  
 10 (dimethylguanylguanidine or dimethylbiguanidine or glucophage).ti,ab.  
 11 (657-24-9 or 1115-70-4).rn.  
 (apo-metformin or apotex or genmetformin or glucophage or glumetza or novo-metformin or nu-  
 12 metformin or pms-metformin or ran-metformin or ratio-metformin or rhoxal-metformin or sandoz  
 metformin).ti,ab.  
 (Glycon or Fortamet or Riomet or Venez or Diaformina or Dimefor or Glafornil or Glucaminol or  
 13 Glucofage or Diabex or Diaformin or Glucohexal or Glucomet or Novomet or Metomin or Glucamet  
 or Metsol or Orabet).ti,ab.  
 (Aron or Diabetosan or Diabex or Diformin or Diformin Retard or Dimethylbiguanide or Dmgg or  
 Fluamine or Fortamet or Gliguanid or Glucoformin or Haurymellin or La 6023 or La6023 or Meguan  
 14 or Mellittin or Metaformin or Methformin or Metiguanide or Metphormin or Dimethylguanylguanide  
 or Nndg or Dimethylbiguanide or Dimethyl Biguanidine or Dimethylbiguanidine or  
 Dimethyldiguanide).ti,ab.  
 15 or/8-14  
 16 Antidiabetic agent/  
 17 Oral Antidiabetic agent/  
 ((Antidiabetic or anti diabetic or antihyperglycemic or anti-hyperglycemic or oral hypoglycemic or  
 18 anti-diabetes or antidiabetes) adj (agent or agents or drug or drugs or compound or  
 compounds)).ti,ab.  
 19 exp \*glitazone derivative/  
 20 (glitazone\* or thiazolidinedione\* or pioglitazone or rosiglitazone or actos or avandia or avandamet  
 or avandaryl).ti,ab.  
 21 (122320-73-4 or 155141-29-0).rn.  
 22 exp \*Dipeptidyl Peptidase IV Inhibitor/  
 23 (Sitagliptin or januvia or Vildagliptin or galvus or gliptin or incretin agent\* or Exenatide or byetta  
 or Liraglutide or victoza).ti,ab.  
 24 (486460-32-6 or 274901-16-5 or 141758-74-9 or 204656-20-2).rn.  
 25 (dpp adj IV adj inhibitor\*).ti,ab.  
 26 (Dipeptidyl-Peptidase adj IV adj inhibitor\*).ti,ab.  
 27 DPP-4 inhibitors.ti,ab.  
 28 dipeptidyl peptidase-4 inhibitors.ti,ab.  
 29 exp \*sulfonylurea derivative/  
 (sulfonylurea\* or tolbutamide or Orinase or glyconon or tolazamide or Tolinase or chlorpropamide  
 30 or Diabinese or glymese or glipizide or Glucotrol or glyburide or glibenclamide or glybenclamide or  
 Diabeta or Micronase or Glynase or gen-glybe or euglucon or glimepiride or Amaryl or gliclazide or  
 Diamicron or diaglyk or glibenese or minodiab or gen-gliclazide).ti,ab.  
 31 (64-77-7 or 1156-19-0 or 94-20-2 or 29094-61-9 or 10238-21-8 or 93479-97-1 or 21187-98-4).rn.  
 32 exp \*"Alpha Glucosidase Inhibitor"/  
 33 (acarbose or glucobay or precose or prandase or akarbose or miglitol\* or glyset or diastabol or  
 voglibose).ti,ab.  
 34 (56180-94-0 or 72432-03-2 or 83480-29-9).rn.  
 35 ((alph\* adj glucos\* adj inhibit\*) or (alf\* adj glucos\* adj inhibit\*)).ti,ab.  
 36 Lipase inhibitor/  
 37 \*Tetrahydrolipstatin/  
 38 \*Sibutramine/  
 39 (Orlistat or Xenical or Tetrahydrolipstatin or Sibutramine or meridia).ti,ab.  
 40 (96829-58-2 or 106650-56-0).rn.  
 41 (lipase adj inhibit\*).ti,ab.  
 42 \*Meglitinide/

43 \*Repaglinide/  
 44 \*Nateglinide/  
 45 (repaglinide or nateglinide or Meglitinide\* or prandin or gluconorm or starlix or novonorm).ti,ab.  
 46 (135062-02-1 or 105816-04-4).rn.  
 47 \*Pramlintide/  
 48 (Pramlintide or symlin).ti,ab.  
 49 (amylin adj analog\*).ti,ab.  
 50 151126-32-8.rn.  
 \*biphasic insulin/ or \*human insulin/ or \*insulin/ or \*insulin aspart/ or \*insulin detemir/ or \*insulin  
 51 glargine/ or \*insulin glulisine/ or \*insulin lispro/ or \*isophane insulin/ or \*long acting insulin/ or  
 \*monocomponent insulin/ or \*neutral insulin/ or \*recombinant human insulin/ or \*synthetic insulin/  
 52 (long acting insulin\* or long acting analog\* or slow\* acting insulin\* or slow\* acting analog\*).ti,ab.  
 53 (glargine or Lantus or Optisulin or hoe 901 or 160337-95-1).ti,ab,rn.  
 54 (detemir or determir or Levemir or nn 304 or 169148-63-4).ti,ab,rn.  
 55 (nph insulin or humulin or novolin).ti,ab.  
 56 11061-68-0.rn.  
 (short acting insulin\* or quick acting insulin\* or rapid acting insulin\* or rapidly acting insulin\* or fast  
 57 acting insulin\* or quick acting analog\* or rapid acting analog\* or rapidly acting analog\* or short  
 acting analog\* or fast acting analog\*).ti,ab.  
 58 (Lispro or Lyspro or Humalog or Liprolog or 133107-64-9).ti,ab,rn.  
 59 (Insulin Aspart or 116094-23-6 or NovoLog or NovoRapid or NovoMix).ti,ab,rn.  
 60 (Glulisine or 207748-29-6 or Apidra).ti,ab,rn.  
 61 or/16-60  
 62 7 and 15 and 61  
 63 Randomized Controlled Trial.pt.  
 64 Randomized Controlled Trials as Topic/  
 65 Randomized Controlled Trial/  
 66 Randomization/  
 67 Random Allocation/  
 68 Double-Blind Method/  
 69 Double Blind Procedure/  
 70 Double-Blind Studies/  
 71 Single-Blind Method/  
 72 Single Blind Procedure/  
 73 Single-Blind Studies/  
 74 Placebos/  
 75 Placebo/  
 76 (random\* or sham or placebo\*).ti,ab,hw.  
 77 ((singl\* or doubl\*) adj (blind\* or dumm\* or mask\*)).ti,ab,hw.  
 78 ((tripl\* or trebl\*) adj (blind\* or dumm\* or mask\*)).ti,ab,hw.  
 79 or/63-78  
 80 62 and 79  
 81 limit 80 to english language

## Line # Searches

**Cochrane Central Register of Controlled Trials**  
 1 Hypoglycemic drugs/  
 ((Antidiabetic or anti diabetic or antihyperglycemic or anti-hyperglycemic or oral hypoglycemic or  
 2 anti-diabetes or antidiabetes) adj (agent or agents or drug or drugs or compound or  
 compounds)).ti,ab.  
 3 Thiazolidinediones/  
 (glitazone\* or thiazolidinedione\* or pioglitazone\* or rosiglitazone\* or actos or avandia or avandamet  
 4 or avandaryl).ti,ab.  
 5 [(122320-73-4 or 155141-29-0).rn.]  
 6 Dipeptidyl-Peptidase IV Inhibitors/



7 (Sitagliptin or januvia or Vildagliptin or galvus or gliptin or incretin agent\* or Exenatide or byetta  
 or Liraglutide or victoza).ti,ab.  
 8 [(486460-32-6 or 274901-16-5 or 141758-74-9 or 204656-20-2).rn.]  
 9 (dpp adj IV adj inhibitor\*).ti,ab.  
 10 (Dipeptidyl-Peptidase adj IV adj inhibitor\*).ti,ab.  
 11 DPP-4 inhibitors.ti,ab.  
 12 dipeptidyl peptidase-4 inhibitors.ti,ab.  
 13 exp Sulfonylurea Compounds/  
 (sulfonylurea\* or tolbutamide or Orinase or glyconon or tolazamide or Tolinase or chlorpropamide  
 14 or Diabinese or glymese or glipizide or Glucotrol or glyburide or glibenclamide or glybenclamide or  
 Diabeta or Micronase or Glynase or gen-glybe or euglucon or glimepiride or Amaryl or gliclazide or  
 Diamicron or diaglyk or glibenese or minodiab or gen-gliclazide).ti,ab.  
 15 [(64-77-7 or 1156-19-0 or 94-20-2 or 29094-61-9 or 10238-21-8 or 93479-97-1 or 21187-98-4).rn.]  
 16 alpha-Glucosidases/ai [Antagonists & Inhibitors]  
 (acarbose or glucobay or precose or prandase or akarbose or miglitol\* or glyset or diastabol or  
 17 voglibose).ti,ab.  
 18 [(56180-94-0 or 72432-03-2 or 83480-29-9).rn.]  
 19 ((alph\* adj glucos\* adj inhibit\*) or (alf\* adj glucos\* adj inhibit\*)).ti,ab.  
 20 acarbose/ [mesh]  
 21 Lipase/ai [Antagonists & Inhibitors]  
 (Orlistat or Xenical or Tetrahydrolipstatin or Sibutramine or meridia).ti,ab.  
 22 [(96829-58-2 or 106650-56-0).rn.]  
 23 (lipase adj inhibit\*).ti,ab.  
 24 (repaglinide or nateglinide or Meglitinide\* or prandin or gluconorm or starlix or novonorm).ti,ab.  
 25 [(135062-02-1 or 105816-04-4).rn.]  
 26 Amyloid/  
 27 (Pramlintide or symlin).ti,ab.  
 28 (amylin adj analog\*).ti,ab.  
 29 [151126-32-8.rn.]  
 30 exp insulin/  
 31 (long acting insulin\* or long acting analog\* or slow\* acting insulin\* or slow\* acting analog\*).ti,ab.  
 32 (glargine or Lantus or Optisulin or hoe 901 or 160337-95-1).ti,ab,rn.  
 33 (detemir or determir or Levemir or nn 304 or 169148-63-4).ti,ab,rn.  
 34 (nph insulin or humulin or novolin).ti,ab.  
 35 [11061-68-0.rn.]  
 36 (short acting insulin\* or quick acting insulin\* or rapid acting insulin\* or rapidly acting insulin\* or fast  
 37 acting insulin\* or quick acting analog\* or rapid acting analog\* or rapidly acting analog\* or short  
 acting analog\* or fast acting analog\*).ti,ab.  
 38 (Lispro or Lyspro or Humalog or Liprolog or 133107-64-9).ti,ab,rn.  
 39 (Insulin Aspart or 116094-23-6 or NovoLog or NovoRapid or NovoMix).ti,ab,rn.  
 40 (Glulisine or 207748-29-6 or Apidra).ti,ab,rn.  
 41 or/1-40  
 42 ((adult or ketosis-resistant or matur\* or late or non-insulin depend\* or noninsulin depend\* or slow  
 or stable or type 2 or type II or lipoatrophic) adj3 diabet\$).ti,ab.  
 43 exp Diabetes Mellitus, Type 2/  
 44 (Mody or niddm or t2dm).ti,ab.  
 45 or/42-44  
 46 41 and 45  
 47 Metformin/  
 48 Metformin.ti,ab.  
 49 (dimethylguanylguanidine or dimethylbiguanidine or glucophage).ti,ab.  
 (apo-metformin or apotex or genmetformin or glucophage or glumetza or novo-metformin or nu-  
 50 metformin or pms-metformin or ran-metformin or ratio-metformin or rhoxal-metformin or sandoz  
 metformin).ti,ab.  
 51 (Glycon or Fortamet or Riomet or Venez or Diaformina or Dimefor or Glafornil or Glucaminol or

Glucophage or Diabex or Diaformin or Glucohexal or Glucomet or Novomet or Metomin or Glucamet or Metsol or Orabet).ti,ab.

- (Aron or Diabetosan or Diabex or Diformin or Diformin Retard or Dimethylbiguanide or Dmagg or Fluamine or Fortamet or Gliguanid or Glucoformin or Haurymellin or La 6023 or La6023 or Meguan or Mellittin or Metaformin or Methformin or Metiguanide or Metphormin or Dimethylguanylguanide or Nndg or Dimethylbiguanide or Dimethyl Biguanidine or Dimethylbiguanidine or Dimethyldiguanide).ti,ab.
- 52 or/47-52
- 53 46 and 53
- 54 limit 54 to yr="1980 -Current"
- 55 limit 55 to randomized controlled trial

## SUPPLEMENTAL SEARCH, SAXAGLIPTIN

Interface:	OVID
Databases:	EMBASE <1980 to 2009 Week 31>; Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <August 5, 2009>; Ovid MEDLINE(R) <1950 to July Week 4 2009> * Note: Subject headings have been customized for each database.
Date of Search:	August 5, 2009
Alerts:	Monthly search updates began August 5, 2009 and ran to [DATE].
Study Types:	No limits
Limits:	Publication years 1980-present English
/	At the end of a phrase, searches the phrase as a subject heading
.sh	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical Subject Heading
fs	Floating subheading
exp	Explode a subject heading
\$	Truncation symbol, or wildcard: retrieves plural or variations of a word
*	Indicates that the marked subject heading is a primary topic
?	Truncation symbol for one or no characters only
ADJ	Requires words are adjacent to each other (in any order)
ADJ#	Adjacency within # number of words (in any order)
.ti	Title
.ab	Abstract
.hw	Heading Word; usually includes subject headings and controlled vocabulary

.pt	Publication type
.rn	CAS registry number

Line #	Searches
	<b>MEDLINE</b>
1	(saxagliptin or onglyza or bms 477118 or bms-477118 or bms477118 or 3-hydroxyadamantylglycine-4,5-methanoprolinenitrile).ti,ab,rn.
2	(361442-04-811 or 945667-22-111).rn.
3	or/1-2
4	from 3 keep 1-19
5	limit 4 to (english language and yr="1980 -Current")

Line #	Searches
	<b>EMBASE</b>
1	(saxagliptin or onglyza or bms 477118 or bms-477118 or bms477118 or 3-hydroxyadamantylglycine-4,5-methanoprolinenitrile).ti,ab,rn.
2	(361442-04-811 or 945667-22-111).rn.
3	saxagliptin/
4	or/1-3
5	limit 4 to english language

Line #	Searches
	<b>Cochrane Central Register of Controlled Trials</b>
1	(saxagliptin or onglyza or bms 477118 or bms-477118 or bms477118 or 3-hydroxyadamantylglycine-4,5-methanoprolinenitrile).ti,ab,rn.
2	[(361442-04-811 or 945667-22-111).rn.]
3	saxagliptin/
4	or/1-3

PubMed	Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used.
Cochrane Library Issue 4,	Same MeSH, keywords, and date limits used as per MEDLINE search, excluding study types. Syntax adjusted for Cochrane Library databases.

#### Grey Literature and Hand Searches

Dates for Search:	May 2009
Keywords:	metformin, second line therapy, oral anti diabetes agents, anti diabetic agents, type 2 diabetes. All keywords associated with each included drug
Limits:	Publication years 1980-present

This section lists the main agencies, organizations, and websites searched; it is not a complete list.

Institute of Health Economics

<http://www.ihe.ca/>

Agence d'Evaluation des Technologies et des Modes d'Intervention en Santé (AETMIS).

[http://www.aetmis.gouv.qc.ca/site/en\\_publications\\_liste.phtml](http://www.aetmis.gouv.qc.ca/site/en_publications_liste.phtml)

Canadian Agency for Drugs and Technologies in Health

<http://www.cadth.ca/index.php/en/hta/reports-publications>

Ontario Ministry of Health and Long Term Care. Health Technology Reviews

[http://www.health.gov.on.ca/english/providers/program/ohnac/tech/techlist\\_mn.html](http://www.health.gov.on.ca/english/providers/program/ohnac/tech/techlist_mn.html)

Institute for Clinical Evaluative Sciences (ICES). Ontario.

<http://www.ices.on.ca/>

The Technology Assessment Unit of the McGill University Health Centre

[http://www.mcgill.ca/tau/publications/publications\\_by\\_subject/](http://www.mcgill.ca/tau/publications/publications_by_subject/)

The Therapeutics Initiative. Evidence-Based Drug Therapy. University of British Columbia.

<http://www.ti.ubc.ca>

Health Quality Council. Saskatchewan.

<http://www.hqc.sk.ca/>

International Network for Agencies for Health Technology Assessment

<http://www.inahta.org>

NPS RADAR (National Prescribing Service Ltd)

[http://www.npsradar.org.au/site.php?page=1&content=/npsradar%2Fcontent%2Farchive\\_alpha.html](http://www.npsradar.org.au/site.php?page=1&content=/npsradar%2Fcontent%2Farchive_alpha.html)

Centre for Reviews and Dissemination

[www.york.ac.uk/inst/crd/crddatabases.htm](http://www.york.ac.uk/inst/crd/crddatabases.htm)

NHS Health Technology Assessment /National Coordinating Centre for Health Technology Assessment (NCCHTA).

<http://www.hta.ac.uk/> (E)

NHS National Institute for Clinical Excellence (NICE)

<http://www.nice.org.uk>

Agency for Healthcare Research and Quality (AHRQ)

<http://www.ahrq.gov/clinic/techix.htm>

AHRQ. Effective Health Care Program. Reports. <http://effectivehealthcare.ahrq.gov/index.cfm>

ECRI

<http://www.ecri.org/>

Evidence Based Information on Prescription Drugs for Consumers and Health Care Providers

[http://www.oregon.gov/DAS/OHPPR/ORRX/HRC/evidence\\_based\\_reports.shtml#Prescription\\_Drugs](http://www.oregon.gov/DAS/OHPPR/ORRX/HRC/evidence_based_reports.shtml#Prescription_Drugs)

DERP

<http://www.ohsu.edu/ohsuedu/research/policycenter/DERP/products.cfm>

Veterans Affairs. Drug Class Reviews (U.S.)

<http://www.pbm.va.gov/DrugClassReviews.aspx>

Saskatoon Health Regions

<http://www.rxfiles.ca/rxfiles/modules/druginfoindex/druginfo.aspx>

Clinical Trials Database (U.S. National Institutes of Health)

<http://clinicaltrials.gov/ct/gui>

Current Controlled Trials

<http://www.controlled-trials.com/>

National Research Register. U.K. Dept. of Health.

<http://www.update-software.com/national/>

WHO - International Clinical Trials Registry Platform  
Search Portal

<http://www.who.int/trialsearch>

## **Conferences**

### **Societies/Organizations/Associations**

Canadian Diabetes Association (CDA)

<http://www.diabetes.ca>

European Society of Endocrinology

<http://www.euro-endo.org/>

Society for Endocrinology

<http://www.endocrinology.org/>

European Society for Paediatric Endocrinology

<http://www.eurospe.org/>

Endocrine Society (US)

<http://www.endo-society.org/>

American Association of Clinical Endocrinologists Annual Meeting and Clinical Congress (AACE)

<http://www.aace.com>

American Diabetes Association (ADA) Scientific Sessions

<http://www.diabetes.org/home.jsp>

European Association for the Study of Diabetes (EASD)

<http://www.easd.org/>

Association of British Clinical Diabetologists

[www.diabetologists.org.uk](http://www.diabetologists.org.uk)

Primary Care Diabetes Europe (PCDE)

<http://www.pcdeurope.org>

International Diabetes Federation

[www.idf.org/home](http://www.idf.org/home)

## **Search Engines**

Google

<http://www.google.ca/>