CADTH

Third-Line Pharmacotherapy for Type 2 Diabetes

Notice of Erratum

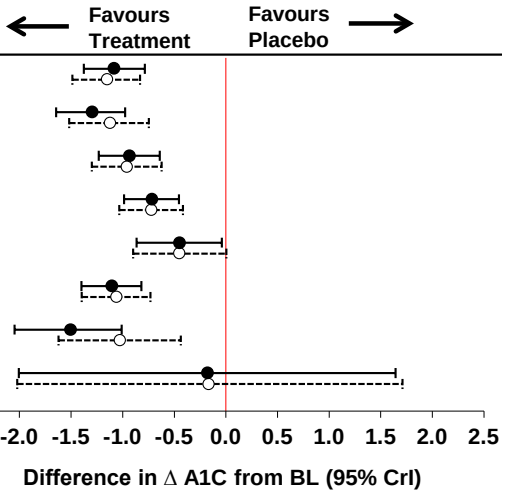
An error was identified in the CADTH report *Third-Line Pharmacotherapy for Type 2 Diabetes —Update* published in July 2013.[1] A data entry error occurred in the conduct of CADTH's network meta-analyses for glycated hemoglobin (A1C) for third-line pharmacotherapy. Specifically, the effect size for basal insulin against biphasic insulin from the 4T trial (Holman et al, 2007)[2] was incorrectly entered as –0.5%, when it should have been entered as 0.5%. This document provides a summary of the corrected results for the network meta-analyses. The correction of this error did not alter the overall conclusions regarding the comparative efficacy of the third-line drugs studied with respect to A1C.

Summary of Revised Network Meta-Analysis

Estimates for basal insulin, thiazolidinediones (TZDs), dipeptidyl-peptidase-4 (DPP-4) inhibitors, alpha-glucosidase inhibitors, glucagon-like peptide-1 (GLP-1) analogues, and meglitinides were largely unchanged in the revised analysis of A1C, with the effect sizes shifting by no more than –0.07% from the original estimates. The result for biphasic insulin changed from –1.12% to –1.29% and the result for bolus insulin changed from –1.02% to –1.51%. The relatively large change in the bolus insulin estimate is not surprising as the 4T study was the only randomized controlled trial (RCT) that investigated this drug class. The revised estimates for the reference case A1C network meta-analysis are shown in Figure 1. Additional details from the reanalysis are provided in Appendices 1 to 3.

Figure 1: Network Meta-Analysis for A1C (%)

Treatment	MTC Estimate (95% CrI) July 2013	MTC Estimate (95% CrI) March 2014
Basal Insulin	–1.15 (–1.49 to –0.83)	–1.08 (–1.38 to –0.81)
Biphasic Insulin	–1.12 (–1.52 to –0.75)	–1.29 (–1.65 to –0.98)
Thiazolidinediones	–0.96 (–1.30 to –0.62)	–0.94 (–1.23 to –0.64)
DPP–4 Inhibitors	–0.72 (–1.03 to –0.42)	–0.72 (–0.99 to –0.45)
AG Inhibitors	–0.45 (–0.90 to –0.01)	–0.45 (–0.86 to –0.04)
GLP–1 Analogues	–1.06 (–1.40 to –0.73)	–1.10 (–1.40 to –0.82)
Bolus Insulin	–1.02 (–1.62 to –0.44)	–1.51 (–2.05 to –1.01)
Meglitinides	–0.17 (–2.02 to 1.71)	–0.17 (–2.01 to 1.64)



Note: Forest plots comparing the results of the correct (●) and original (○) CADTH network meta-analyses for change from baseline in A1C. A1C = glycated hemoglobin; AG = alpha glucosidase; BL = baseline; CrI = credible interval; DPP = dipeptidyl peptidase; GLP = glucagon-like peptide; MTC = mixed-treatment comparison.

Summary of Revisions to the Pharmacoeconomic Review

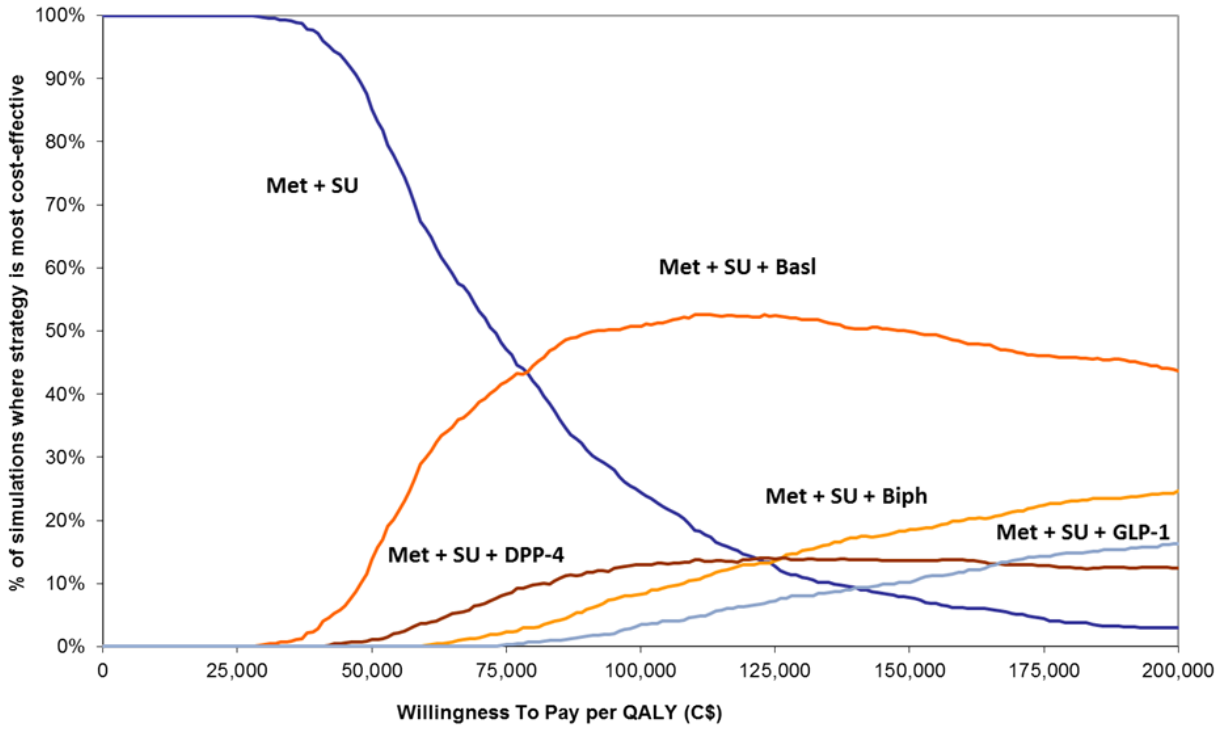
The results of the revised economic analysis, using the updated A1C estimates from the network meta-analysis, showed that basal insulin remained the most cost-effective option relative to treatment with metformin and a sulfonylurea, but at a slightly higher incremental cost-utility ratio (ICUR) of $75,636 per quality-adjusted life-year (QALY) compared with the original ICUR of $68,442 per QALY. The DPP-4 inhibitors continued to be dominated by basal insulin as per the original analysis. However, due to the larger A1C effect of biphasic insulins in the updated analysis, GLP-1 analogues were dominated by biphasic insulin (Table 1) based on small gains in QALY. Results for most one-way sensitivity analyses were not impacted with updated A1C estimates. The one-way sensitivity analysis on the disutilities associated with hypoglycemia (mild, moderate, and severe) were sensitive to the updated A1C estimates: imparting higher disutility for mild to moderate hypoglycemia led to DPP-4 inhibitors being the most cost-effective option with basal insulin ruled out through extended dominance in the revised analysis. Using a higher disutility for severe hypoglycemia resulted in biphasic insulin and DPP-4s to be ruled out through dominance and extended dominance, respectively. This is in contrast to original results showing DPP-4 being cost-effective only when a disutility is applied for mild to moderate hypoglycemia based on a National Institute for Health and Care Excellence (NICE) appraisal. Under the scenario in which insulin is not available as a treatment option, DPP-4 inhibitors remained the more cost-effective option compared with GLP-1 analogues when added to metformin and a sulfonylurea. The revised results and selected one-way sensitivity analyses are shown in Appendix 3. The results of the updated probabilistic sensitivity analysis are presented in Figure 2.

Table 1: Total Lifetime Costs, QALYs, and ICURs from the Updated Reference Case Analysis

Strategy	Cost	Effectiveness (QALY)	ICUR	
			Incremental vs. Met + SU	Sequential
Met + SU	$46,682	8.2089	NA	
Met + SU + Basal insulin	$52,480	8.2856	$75,636	$75,636
Met + SU + Biphasic insulin	$57,060	8.2972	$117,523	$393,400
Treatments Ruled Out by Dominance or Extended Dominance				
Met + SU + DPP-4 inhibitor	$53,098	8.2662	$112,022	**Dominated by:** Met + SU + Basal insulin
Met + SU + GLP-1 Analogues	$58,253	8.2969	$131,526	**Dominated by:** Met + SU + Biphasic insulin

DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1; ICER = incremental cost-effectiveness ratio; ICUR = incremental cost-utility ratio; Met = metformin; NA = not applicable; QALY = quality-adjusted life-year; SU = sulfonylurea.

Figure 2: Cost-Effectiveness Acceptability Curve for the Reference Case Analysis



Basl = basal insulin; Biph = biphasic insulin; DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1; ICER = incremental cost-effectiveness ratio; ICUR = incremental cost-utility ratio; Met = metformin; QALY = quality-adjusted life-year; SU = sulfonylurea

APPENDIX 1: SENSITIVITY ANALYSES FOR A1C

Table 2: Sensitivity Analyses for Change From Baseline A1C (%) — NMA Estimates vs. Placebo[a]

Analysis	Basal Insulin	Biphasic Insulin	TZDs	DPP-4 Inhibitors	AGIs	GLP-1 Analogues	Bolus Insulin	Meglitinides
Reference case	−1.1 (−1.4 to −0.8)	−1.3 (−1.6 to −1.0)	−0.9 (−1.2 to −0.6)	−0.7 (−1.0 to −0.5)	−0.5 (−0.9 to 0.0)	−1.1 (−1.4 to −0.8)	−1.5 (−2.0 to −1.0)	−0.2 (−2.0 to 1.6)
Modelling assumption								
Fixed effects (instead of random effects)	−1.0 (−1.1 to −0.9)	−1.2 (−1.3 to −1.1)	−1.0 (−1.1 to −0.8)	−0.7 (−0.8 to −0.6)	−0.4 (−0.7 to −0.1)	−1.1 (−1.2 to −1.0)	−1.3 (−1.5 to −1.1)	−0.1 (−1.9 to 1.6)
Meta–regression adjusting for:								
Baseline A1C	−1.1 (−1.4 to −0.8)	−1.3 −1.7 to −1.0)	−1.0 −1.3 to −0.7)	−0.8 −1.1 to −0.5)	−0.4 −0.8 to 0.1)	−1.2 −1.5 to −0.9)	−1.6 −2.1 to −1.0)	0.0 −1.9 to 1.9)
Baseline duration of diabetes	−1.1 (−1.5 to −0.8)	−1.3 (−1.8 to −0.9)	−0.9 (−1.3 to −0.5)	−0.9 (−1.4 to −0.3)	−0.5 (−0.9 to 0.0)	−1.1 (−1.5 to −0.8)	−1.5 (−2.2 to −1.0)	0.0 (−2.0 to 2.0)
Duration of RCT	−1.1 (−1.5 to −0.7)	−1.3 (−1.8 to −0.9)	−0.9 (−1.4 to −0.5)	−0.9 (−1.5 to −0.3)	−0.4 (−1.0 to 0.1)	−1.1 (−1.5 to −0.7)	−1.5 (−2.2 to −0.9)	−0.2 (−2.1 to 1.7)
Sensitivity analyses with removal of:								
RCTs of rosiglitazone	−1.1 (−1.5 to −0.8)	−1.3 (−1.8 to −0.9)	−0.9 (−1.3 to −0.5)	−0.7 (−1.0 to −0.4)	−0.5 (−0.9 to 0.0)	−1.1 (−1.5 to −0.8)	−1.5 (−2.2 to −0.9)	−0.1 (−2.0 to 1.7)
All TZD RCTs	−0.9 (−1.3 to −0.6)	−1.2 (−1.6 to −0.8)	NA	−0.7 (−1.0 to −0.4)	−0.4 (−0.9 to 0.0)	−1.0 (−1.3 to −0.7)	−1.4 (−2.0 to −0.8)	−0.2 (−2.0 to 1.7)
RCTs with A1C < 7.0% in the inclusion criteria	−1.1 (−1.4 to −0.8)	−1.3 (−1.7 to −1.0)	−0.9 (−1.2 to −0.6)	−0.7 (−1.0 to −0.4)	−0.4 (−0.9 to 0.0)	−1.1 (−1.4 to −0.8)	−1.5 (−2.1 to −1.0)	NA
RCTs not providing SU dosing at baseline	−1.1 (−1.6 to −0.8)	−1.7 (−2.3 to −1.2)	−1.0 (−1.4 to −0.6)	−0.7 (−1.1 to −0.4)	−0.5 (−0.9 to 0.0)	−1.2 (−1.7 to −0.7)	−1.8 (−2.5 to −1.1)	NA
RCTs of drugs not indicated for use with Met + SU in Canada[b]	−1.1 (−1.6 to −0.5)	−1.0 (−1.7 to −0.5)	NA	−0.8 (−1.3 to −0.2)	−0.6 (−1.4 to 0.2)	−1.0 (−1.5 to −0.5)	−0.9 (−1.8 to −0.1)	NA
RCTs from which subgroup data were used	−1.1 (−1.4 to −0.8)	−1.3 (−1.7 to −1.0)	−0.9 (−1.2 to −0.6)	−0.6 (−1.0 to −0.3)	−0.5 (−0.9 to 0.0)	−1.1 (−1.4 to −0.8)	−1.5 (−2.1 to −1.0)	−0.2 (−2.0 to 1.7)
Crossover studies	−1.1 (−1.4 to −0.8)	−1.3 (−1.6 to −0.9)	−0.9 (−1.2 to −0.6)	−0.7 (−1.0 to −0.5)	−0.4 (−0.9 to 0.0)	−1.1 (−1.4 to −0.8)	−1.5 (−2.0 to −1.0)	NA

A1C = glycated hemoglobin; AGI = alpha glucosidase inhibitor; DPP = dipeptidyl peptidase; GLP = glucagon-like peptide; Met=metformin; NMA = network meta-analysis; NOC = Notice of Compliance; RCT = randomized controlled trial; SU=sulfonylurea; TZD = thiazolidinedione.

[a]All active treatments and placebo were provided in combination with metformin and a sulfonylurea.

[b]Includes drugs that do not have a Notice of Compliance for use in Canada.

APPENDIX 2: COMPARISON OF RESULTS FROM NMA AND DIRECT META-ANALYSES FOR A1C (%)

Placebo ← Vs.								
-1.1 (-1.4 to -0.8) *-1.2 (-2.3 to -0.1)*	**Basal Insulin**							
-1.3 (-1.6 to -1.0) *NA*	-0.2 (-0.4 to 0.0) *-0.3 (-0.7 to 0.0)*	**Biphasic Insulin**						
-0.9 (-1.2 to -0.6) *-1.2 (-1.4 to -1.0)*	0.1 (-0.1 to 0.4) *0.2 (0.04 to 0.4)*	0.4 (0.0 to 0.7) *0.3 (-1.0 to 1.6)*	**TZDs**					
-0.7 (-1.0 to -0.5) *-0.7 (-0.9 to -0.6)*	0.4 (0.0 to 0.8) *NA*	0.6 (0.2 to 1.0) *NA*	0.2 (-0.2 to 0.6) *NA*	**DPP-4 Inhibitors**				
-0.5 (-0.9 to 0.0) *-0.4 (-0.7 to -0.1)*	0.6 (0.1 to 1.1) *1.5 (-1.5 to 3.5)*	0.8 (0.3 to 1.4) *NA*	0.5 (0.0 to 1.0) *NA*	0.3 (-0.2 to 0.8) *NA*	**AG Inhibitors**			
-1.1 (-1.4 to -0.8) *-1.0 (-1.1 to -0.9)*	0.0 (-0.3 to 0.2) *-0.1 (-0.4 to 0.2)*	0.2 (-0.1 to 0.5) *0.2 (-0.5 to 0.9)*	-0.2 (-0.5 to 0.2) *NA*	-0.4 (-0.8 to 0.0) *NA*	-0.7 (-1.2 to -0.1) *NA*	**GLP-1 Analogues**		
-1.5 (-2.0 to -1.0) *NA*	-0.4 (-0.9 to 0.0) *-0.6 (-0.8 to -0.4)*	-0.2 (-0.7 to 0.2) *-0.1 (-0.3 to 0.1)*	-0.6 (-1.1 to -0.1) *NA*	-0.8 (-1.4 to -0.2) *NA*	-1.1 (-1.7 to -0.4) *NA*	-0.4 (-0.9 to 0.1) *NA*	**Bolus Insulin**	
-0.2 (-2.0 to 1.6) *NA*	0.9 (-0.9 to 2.7) *NA*	1.1 (-0.7 to 3.0) *NA*	0.8 (-1.1 to 2.6) *NA*	0.5 (-1.3 to 2.4) *NA*	0.3 (-1.5 to 2.0) *0.3 (-1.4 to 2.0)*	0.9 (-0.9 to 2.8) *NA*	1.3 (-0.6 to 3.2) *NA*	**Meglitinides**

Note: Table shows the results of direct and mixed-treatment comparison network meta-analyses for A1C. Results of the network meta-analyses are shown in black, non-italicized text and the direct estimates are shown in blue, italicized text.
A1C = glycated hemoglobin; AG = alpha glucosidase; DPP = dipeptidyl peptidase; GLP = glucagon-like peptide; NA = not applicable; TZD = thiazolidinedione.

APPENDIX 3: SUMMARY OF MODEL-FIT PARAMETERS AND RANKINGS

Table 3: Model-Fit Parameters for All Network Meta-Analyses			
Analysis	**Mean Residual Deviance**	**Unconstrained Data Points**	**DIC**
Random effects	24.11	28	5.046
Fixed effects	53.87	28	25.178
Remove RCTs with drugs not indicated for use with metformin and a sulfonylurea	15.31	16	–2.143
Remove crossover RCTs	21.64	24	–3.137
Remove RCTs with A1C < 7.0% in the inclusion criteria	21.76	24	1.207
Remove RCTs with TZDs	18.9	18	–0.130
Remove RCTs with rosiglitazone	21.74	22	2.750
Remove RCTs not providing sulfonylurea dosage at baseline	14.56	17	2.828
Drug level network meta-analysis	25.82	27	10.909

A1C = glycated hemoglobin; DIC = deviance information criterion; RCT = randomized controlled trial; TZD = thiazolidinedione.

Table 4: Probability Best and Ranking from Reference Case for A1C		
Treatment	**Probability and Ranks — Mean (SD)**	
	Probability Best	**Ranking**
Placebo	0.00 (0.00)	8.6 (0.5)
Basal insulin	0.00 (0.04)	3.9 (0.8)
Biphasic insulin	0.13 (0.33)	2.1 (0.7)
TZD	0.00 (0.04)	5.1 (0.9)
DPP-4 inhibitors	0.00 (0.03)	6.2 (0.8)
AG inhibitors	0.00 (0.02)	7.2 (0.7)
GLP-1 analogues	0.01 (0.10)	3.7 (1.0)
Bolus insulin	0.78 (0.42)	1.3 (0.7)
Meglitinides	0.08 (0.27)	7.0 (2.6)

A1C = glycated hemoglobin; AG = alpha glucosidase; DPP = dipeptidyl peptidase; GLP = glucagon-like peptide; SD = standard deviation; TZD = thiazolidinedione.

APPENDIX 4: UPDATED RESULTS OF SENSITIVITY ANALYSES

Scenario	Incremental Cost-Effectiveness Ratio ($/QALY)[a]
Reference case analysis	Met + SU + Basl vs. Met + SU: $75,636 Met + SU + Biph vs. Met + SU + Basl: $393,400 Met + SU + DPP-4 is dominated by Met + SU + Basl Met + SU + GLP-1 is dominated by Met + SU + Biph
Patients add-on insulin NPH (0.75 U/kg/day) added to non-insulin groups when A1C ≥ 9%	Met + SU + Basl vs. Met + SU : $84,118 Met + SU + Biph vs Met + SU + Basl: $358,783 Met + SU + DPP-4 is dominated by Met + SU + Basl Met + SU + GLP-1[b] is dominated by Met + SU + Biph
Insulins are removed as treatment options	Met + SU + DPP-4 vs. Met + SU : $112,022 Met + SU + GLP1 vs. Met + SU + DPP-4: $167,907
Higher disutility associated with severe hypoglycemia (from Currie et al.)[3]	Met + SU + DPP-4 vs. Met + SU: $112,022 Met + SU + Basl vs. Met + SU + DPP-4: $108,785 Met + SU + GLP-1 vs. Met + SU + Basl: $187,053 Met + SU + Biph is dominated by Met + SU + GLP-1 DPP + SU + DPP-4 is ruled out through extended dominance
Higher disutility associated with mild to moderate hypoglycemia (from Levy et al.)[4]	Met + SU + DPP-4 vs. Met + SU: $124,671 Met + SU + GLP-1 vs. Met + SU + DPP-4 : $167,999 Met + SU + Biph is dominated by Met + SU + DPP-4 Met + SU + Basl ruled out through extended dominance
Higher disutility associated with mild to moderate hypoglycemia [0.0052] (from NICE study)[5]	Met + SU + DPP-4 vs. Met + SU: $133,353 Met + SU + GLP-1 vs. Met + SU + DPP-4: $168,053 Met + SU + Biph is dominated by Met + SU + DPP-4 Met + SU + Basl ruled out through extended dominance
Disutility of 0.030 associated with insulin use in year one (rather than no disutility)	Met + SU + Basl vs. Met + SU : $84,939 Met + SU + GLP-1 vs. Met + SU + Basl : $292,872 Met + SU + DPP-4 is dominated by Met + SU + Basl Met + SU + Biph is ruled out by extended dominance
Disutility of 0.060 associated with insulin use in year one (rather than no disutility)	Met + SU + Basl vs. Met + SU : $96,852 Met + SU + GLP-1 vs. Met + SU + Basl : $205,382 Met + SU + DPP-4 is dominated by Met + SU + Basl Met + SU + Biph is ruled out by extended dominance
Model incorporates reduced quality of life associated with weight gain (NICE Guidelines)[6]	Met + SU + Basl vs. Met + SU: $102,650 Met + SU + GLP-1 vs. Met + SU + Basl: $145,534 Met + SU + DPP-4 is dominated by Met + SU + Basl Met + SU + Biph is ruled out by extended dominance

A1C = glycated hemoglobin; Basl = basal insulin; Biph = biphasic insulin; DPP = dipeptidyl peptidase; GLP = glucagon-like peptide; Met= metformin; NICE = National Institute for Health and Care Excellence; NPH = neutral protamine Hagedorn; QALY = quality-adjusted life-year; SU = sulfonylurea.

[a]Treatment strategies that cost more, but provide less QALYs compared with another treatment strategy are considered "dominated" by the less costly strategy.

[b]Byetta (exenatide) is indicated in combination with insulin glargine (with or without metformin) to improve glycemic control in patients with type 2 diabetes mellitus when insulin glargine (with or without metformin), in addition to diet and exercise, does not provide adequate glycemic control.

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