Canadian Agency for Drugs and Technologies in Health

Agence canadienne des médicaments et des technologies de la santé

CADTH Optimal Use Report

Volume 3, Issue 1C

July 2013

Combination Use of Insulin and Incretins in Type 2 Diabetes

Supporting Informed Decisions

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Cite as: Canadian Agency for Drugs and Technologies in Health. Combination use of insulin and incretins in type 2 diabetes. Ottawa: The Agency; 2013. (CADTH optimal use report; vol.3, no. 1c).

ISSN: 1927-0127

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ABBREVIATIONS

A1C	glycated hemoglobin
CADTH	Canadian Agency for Drugs and Technologies in Health
CI	confidence interval
DPP-4	dipeptidyl peptidase-4
GLP-1	glucagon-like peptide-1
HTA	health technology assessment
ITT	intention-to-treat
MD	mean difference
N	total number of patients
NPH	neutral protamine Hagedorn
OR	odds ratio
RCT	randomized controlled trial
RR	relative risk
SD	standard deviation

1 BACKGROUND

Type 2 diabetes mellitus is a progressive disease and many patients will eventually require treatment with exogenous insulin to maintain glycemic control. Insulin therapy for patients with type 2 diabetes is typically initiated with a basal insulin. Clinical practice guidelines typically recommend intensification of an insulin regimen for most patients inadequately controlled with basal insulin, such as through the use of a biphasic insulin or a basal-bolus insulin regimen. Two dipeptidyl peptidase-4 (DPP-4) inhibitors, saxagliptin (Onglyza) and sitagliptin (Januvia) were recently given approval by Health Canada for use in combination with basal or biphasic insulin when these insulins do not provide adequate glycemic control. In addition, the GLP-1 analogue exenatide (Byetta) has been approved by Health Canada for use in combination with insulin glargine, and liraglutide (Victoza) has Food and Drug Administration approval for use in combination with insulin. The regulatory status of combination use of incretins and insulin is summarized in Table 1.

There is uncertainty regarding the comparative effectiveness of insulin intensification versus the addition of a DPP-4 inhibitor or a glucagon-like peptide-1 (GLP-1) analogue for patients inadequately controlled with basal/biphasic insulin. Therefore, a supplemental review of the evidence for the combination of incretins and insulins was conducted.

Table 1: Regulatory Status of Incretins Combined With Insulin

Class	Drug Name	Approved for T2DM			Approved with Insulin		
		HC	FDA	EMA	HC	FDA	EMA
DPP-4 Inhibitor	Saxagliptin	Yes[1]	Yes[2]	Yes[3]	Yes	Yes	Yes
	Sitagliptin	Yes[4]	Yes[5]	Yes[6]	Yes	Yes	Yes
	Linagliptin	Yes[7]	Yes[8]	Yes[9]	No	No	No
	Vildagliptin	No	No	Yes[10]	–	–	No
	Alogliptin	No	No	No	–	–	–
GLP-1 Analogue	Exenatide	Yes[11]	Yes[12]	Yes[13,14]	Yes	Yes	Yes
	Liraglutide	Yes[15]	Yes[16]	Yes[17]	No	Yes	No

EMA = European Medicines Agency; DPP-4 = dipeptidyl peptidase-4; FDA = Food and Drug Administration; GLP-1 = glucagon-like peptide-1; HC = Health Canada; T2DM = type 2 diabetes mellitus.

1.1 Objective

The objective of this review was to summarize and critically appraise the evidence regarding the clinical effectiveness and harms of combination use of DPP-4 inhibitors or GLP-1 analogues with insulin. The following research questions were assessed:

1. What is the clinical efficacy and safety of DPP-4 inhibitors used in combination with insulin for patients with inadequate glycemic control on a basal or biphasic insulin regimen?
2. What is the clinical efficacy and safety of GLP-1 analogues used in combination with insulin for patients with inadequate glycemic control on a basal or biphasic insulin regimen?

2 METHODS

2.1 Literature Search

The literature search was performed by an information specialist using a peer-reviewed search strategy. Published literature was identified by searching the following bibliographic databases: MEDLINE with In-Process records & daily updates via Ovid; Embase via Ovid; The Cochrane Library via Ovid; and PubMed. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were diabetes, insulin, and DPP-4 inhibitors or GLP-1 analogues.

Methodological filters were applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, and economic studies. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2002, and July 11, 2012. Conference abstracts were excluded from the search results. (See Appendix 1 for the detailed search strategies.) Regular alerts were established to update the search until the publication of the final report. Regular search updates were performed on databases that do not provide alert services.

Grey literature (literature that is not commercially published) was identified by searching keys sections of the Grey Matters checklist (www.cadth.ca/resources/grey-matters), which includes the websites of regulatory agencies, health technology assessment agencies, and professional associations. Google and other Internet search engines were used to search for additional web-based materials. These searches were supplemented by reviewing the bibliographies of key papers, and through contacts with appropriate experts and industry.

2.2 Eligibility Criteria

The eligibility criteria for systematic reviews and randomized controlled trials (RCTs) are summarized in (Table 2). Health technology assessments (HTAs), systematic reviews, and RCTs were eligible for inclusion if they met the following criteria:

- investigated the addition of a GLP-1 analogue or DPP-4 inhibitor compared with an intensified insulin regimen or placebo and with no change to existing insulin
- enrolled patients who were inadequately controlled with a basal, biphasic, or basal/bolus insulin regimen
- reported changes in glycated hemoglobin (A1C), changes in body weight, hypoglycemia, and/or long-term diabetes-related complications.

A hierarchical approach was used with respect to study design, such that HTAs/systematic reviews were relied upon wherever possible. These were supplemented with data from individual RCTs not captured in the available HTAs/systematic reviews.

Table 2: Eligibility Criteria for Inclusion in Review	
Criteria	**Description**
Study design	Health technology assessment, systematic review, randomized controlled trial
Population	Inadequately controlled with a basal, biphasic, or basal/bolus insulin regimen
Interventions	Addition of a GLP-1 analogue or DPP-4 inhibitor
Comparators	Intensification of insulin regimen or placebo/no change to existing insulin
Outcomes	A1C, body weight, hypoglycemia, long-term diabetes-related complications, safety

A1C = glycated hemoglobin; DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1; RCT = randomized controlled trial.

3 RESULTS

3.1 Literature Selection

A total of 1,160 citations were reviewed and eight articles were selected for inclusion in this review. There were two systematic reviews[18,19] and six RCTs that investigated the use of incretin agents in patients who were inadequately controlled with an insulin-containing treatment regimen. Neither systematic review performed a meta-analysis; therefore, the individual clinical trials are summarized in this review.

3.2 Study Characteristics

The characteristics of the included RCTs are summarized in Table 3. The six RCTs included five placebo-controlled trials investigating the use of four DPP-4 inhibitors (sitagliptin, saxagliptin, alogliptin, and vildagliptin)[20-23] and one GLP-1 analogue (exenatide).[24] There was one RCT that compared sitagliptin against an increased dosage of insulin.[25] The studies were similar in duration, ranging from 24 to 30 weeks. All of the placebo-controlled trials were double-blind and the active comparison of sitagliptin versus an increase in insulin dose was open-label. Sample sizes ranged from 259 to 641 in the placebo-controlled trials. The active comparison had the smallest sample size with 140 patients.

The trial by Buse et al. (2011)[24] was limited to participants who had been receiving a basal insulin. All of the other studies included a heterogeneous population of patients using basal, biphasic, and basal/bolus insulin regimens. For trials reporting the total insulin dosage at baseline (i.e., regardless of treatment regimen), the dosage ranged from 35 to 82 units per day (Table 4).

Table 3: Summary of Trial and Patient Characteristics						
Incretin	**Author, Year**	**Duration**	**N**	**Comparators**	**Baseline A1C**	**Years with T2DM**
Double-blind placebo-controlled RCTs						
Saxagliptin	Barnett et al. 2012[20]	24 weeks	455	• SAXA + INS ± MET • PLC + INS ± MET	8.7 (0.9) 8.6 (0.9)	11.8 (6.9) 12.2 (7.4)
Sitagliptin	Visbøll et al. 2010[21]	24 weeks	641	• SITA + INS ± MET • PLC + INS ± MET	8.7 (0.9) 8.6 (0.9)	13 (7) 12 (6)
Vildagliptin	Fonseca et al. 2007[22]	24 weeks	296	• VILD + INS • PLC + INS	8.4 (1.0) 8.4 (1.1)	14.4 (8.6) 14.9 (8.4)
Alogliptin	Rosenstock et al. 2009[23]	26 weeks	390	• ALO (12.5) + INS ± MET • ALO (25) + INS ± MET • PLC + INS ± MET	9.3 (1.1) 9.3 (1.1) 9.3 (1.1)	12.2 (7.1) 12.1 (7.2) 13.4 (6.3)
Exenatide	Buse et al. 2011[24]	30 weeks	259	• EXE + INS[a] • PLC + INS[a]	8.3 (0.9) 8.5 (1.0)	12 (7) 12 (7)
Open-label active-controlled RCTs						
Sitagliptin	Hong et al. 2012[25]	24 weeks	140	• SITA + INS + OADs • Intensified INS + OADs	9.2 (1.0) 9.2 (1.1)	15.9 (10.5) 15.8 (9.9)

A1C = glycated hemoglobin; ALO = alogliptin; EXE = exenatide; INS = insulin; MET = metformin; n = total number of patients; OADs = oral antidiabetes drugs; PLC = placebo; RCTs=randomized controlled trials; SITA = sitagliptin; T2DM = type 2 diabetes mellitus; VILD = vildagliptin.
[a]Participants in both groups received "optimized insulin glargine" in addition to the randomized treatment.

Table 4: Insulin Usage at Baseline						
Author (Year)	**Comparators**	**Insulin Type n (%)**	**Insulin Dosage (IU/day) – Mean (SD)**			
			Biphasic	**Basal**	**Bolus**	**Total[a]**
Placebo-controlled RCTs						
Barnett et al. 2012[20]	• SAXA + INS ± MET • PLC + INS ± MET	Biphasic: 271 (60) Basal: 184 (40)	NR NR	NR NR	— —	53.6 55.3
Visboll et al. 2010[21]	• SITA + INS ± MET • PLC + INS ± MET	Biphasic: 169 (26) Basal: 472 (74)	67 (35) 75 (37)	44 (30) 45 (26)	— —	NR NR
Fonseca et al. 2007[22]	• VILD + INS • PLC + INS	NR NR	NR NR	NR NR	NR NR	81 (45) 82 (50)
Rosenstock et al. 2009[23]	• ALO (12.5) + INS ± MET • ALO (25) + INS ± MET • PLC + INS ± MET	Biphasic: 250 (64) Basal: 133 (34)	NR NR NR	NR NR NR	— — —	57 (23) 58 (23) 55 (22)
Buse et al. 2011[24]	• EXE + INS • PLC + INS	Basal: 261 (100)	— —	50 (30) 47 (25)	— —	50 (30) 47 (25)
Active-controlled RCTs						
Hong et al. 2012[25]	• SITA + INS + OADs • Intensified INS + OADs	Basal: 60 (48) Basal/bolus: 64 (52)	NR NR	NR NR	NR NR	40 (19) 35 (16)

ALO = alogliptin; EXE = exenatide; INS = insulin; IU = international units; MET = metformin; NR = not reported; SD = standard deviation; SITA = sitagliptin; OADs = oral antidiabetes drugs; PLC = placebo; VILD = vildagliptin.
[a]These doses apply to trials that did not differentiate between different insulin regimens.

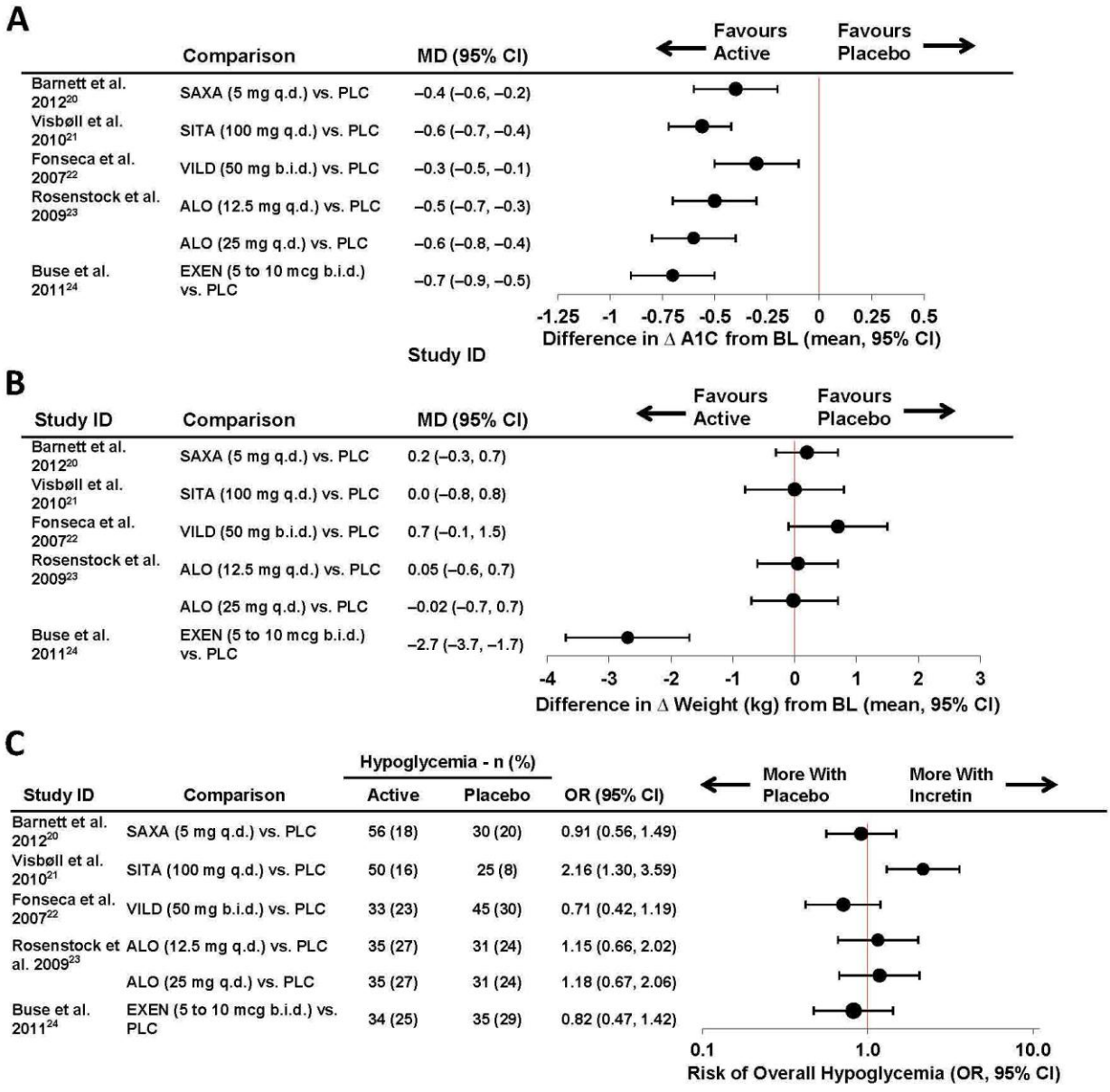
3.3 Addition of an Incretin versus Placebo

Five RCTs[20-24] were identified that compared the addition of a DPP-4 inhibitor to an unchanged insulin regimen[20-23] or a GLP-1 analogue to an insulin regimen adjusted using a standardized algorithm.[24] The results for changes in A1C, changes in body weight, and hypoglycemia are summarized in Figure 2, and detailed results for each end point are summarized in Table 5. Changes from baseline in A1C with the DPP-4 inhibitor groups ranged from –0.5% to –0.7%. All of the DPP-4 inhibitors demonstrated a statistically significant improvement in A1C relative to placebo (range –0.3% to –0.6%). The GLP-1 analogue exenatide also demonstrated a significant improvement compared with placebo (–0.7%). All participants in the exenatide trial received "optimized insulin glargine," which consisted of a standardized titration algorithm based on the Treat-To-Target trial[26] in addition to the randomized treatment; therefore, both the exenatide and placebo groups demonstrated large improvements from baseline (–1.7% and –1.0%, respectively).

The addition of a DPP-4 inhibitor did not result in significant changes in body weight relative to placebo, and the GLP-analogue resulted in statistically significant weight loss (–2.7 kg). Trials involving saxagliptin, vildagliptin, alogliptin, and exenatide demonstrated no significant increase in risk of overall hypoglycemia relative to placebo; however, a single trial involving sitagliptin showed a significantly increased risk of hypoglycemia compared with placebo (odds ratio [95% CI] = 2.16 [1.30 to 3.59]). Events of severe hypoglycemia were rare in the included trials, making it difficult to conduct meaningful comparisons.

Total adverse events, serious adverse events, and withdrawals due to adverse events are summarized in Table 6. A larger proportion of sitagliptin-treated patients reported at least one adverse event compared with placebo (52% versus 43%).[21] With the exception of hypoglycemia (15% versus 8%), there were no specific categories of adverse events responsible for the increase in the sitagliptin group.[27] Exenatide was associated with a greater proportion of patients with at least one adverse event (79% versus 70%), largely due to an increase in gastrointestinal adverse events (i.e., nausea, vomiting, diarrhea, and constipation).[24] Sitagliptin was the only treatment associated with a larger proportion of patients that reported at least one serious adverse event relative to placebo (6.2% versus 3.5%). The serious adverse events reported in this trial represented a wide range of categories, with few events occurring in a single category. Two DPP-4 inhibitors, vildagliptin (50 mg twice daily) and sitagliptin (100 mg once a day), were associated with more withdrawals due to adverse events than placebo (6% versus 0.7% and 3% versus 1%, respectively). Exenatide (10 mcg twice daily) was also associated with more withdrawals due to adverse events than placebo (9% versus 1%); however, the reasons for withdrawal were not reported for this trial.

Figure 1: Results for Hemoglobin A1C (%) (A), Body Weight (kg) (B), Hypoglycemia (C)



Δ = change; A1C = glycated hemoglobin; ALO = alogliptin; BID = twice daily; BL = baseline; CI = confidence interval; EXEN = exenatide; MD = mean difference; OR = odds ratio; PLC = placebo; QD = once daily; SAXA = saxagliptin; SITA = sitagliptin; VILD = Vildagliptin; vs. = versus.

Table 5: Detailed Results for Hemoglobin A1C, Body Weight, and Hypoglycemia

Hemoglobin A1C

Study	Treatment	Δ BL in A1C (%)		Incretin vs. Placebo	
		Incretin	Placebo	MD (95% CI)	*P* value
Barnett et al. 2012[20]	SAXA (5 mg q.d.)	–0.7 (0.1)	–0.3 (0.1)	-0.4 (–0.6, –0.2)	<0.0001
Visbøll et al. 2010[21]	SITA (100 mg q.d.)	–0.6 (–0.7, –0.5)	0.0 (–0.1, 0.1)	–0.6 (–0.7, –0.4)	<0.001
Fonseca et al. 2007[22]	VILD (50 mg b.i.d.)	–0.5 (0.1)	–0.2 (0.1)	–0.3 (–0.5, –0.1)	0.010
Rosenstock et al. 2009[23]	ALO (12.5 mg q.d.)	–0.6 (0.1)	–0.1 (0.1)	–0.5 (–0.7, –0.3)	<0.001
	ALO (25 mg q.d.)	–0.7 (0.1)	–0.1 (0.1)	–0.6 (–0.8, –0.4)	<0.001
Buse 2011[24]	EXEN (5 to10 mcg b.i.d.)	–1.7 (0.1)	–1.0 (0.1)	–0.7 (–0.9, –0.5)	<0.001

Body Weight

Study	Treatment	Δ BL in Weight (kg)		Incretin vs. Placebo	
		Incretin	Placebo	MD (95% CI)	*P* value
Barnett et al. 2012[20]	SAXA (5 mg q.d.)	0.4 (0.2)	0.2 (0.2)	0.2 (–0.3, 0.7)	NR
Visbøll et al. 2010[21]	SITA (100 mg q.d.)	0.1 (0.3)	0.1 (0.3)	0.0 (–0.8, 0.8)	NR
Fonseca et al. 2007[22]	VILD (50 mg b.i.d.)	1.3 (0.3)	0.6 (0.3)	0.7 (–0.1, 1.5)	0.067
Rosenstock et al. 2009[23]	ALO (12.5 mg q.d.)	0.7 (0.2)	0.6 (0.2)	0.05 (–0.6, 0.7)	0.874
	ALO (25 mg q.d.)	0.6 (0.2)	0.6 (0.2)	–0.02 (–0.7, 0.7)	0.948
Buse et al. 2011[24]	EXEN (5 to10 mcg b.i.d.)	–1.8 (–2.5, –1.1)	1.0 (0.2, 1.7)	–2.7 (–3.7, –1.7)	<0.001

Overall Hypoglycemia

Study	Treatment	Incretin		Placebo		Incretin vs. Placebo OR (95% CI)
		n (%)	Events	n (%)	Events	
Barnett et al. 2012[20]	SAXA (5 mg q.d.)	56 (18)	NR	30 (20)	NR	0.91 (0.56, 1.49)
Visbøll et al. 2010[21]	SITA (100 mg q.d.)	60 (16)	155	25 (8)	76	2.16 (1.30, 3.59)
Fonseca et al. 2007[22]	VILD (50 mg b.i.d.)	33 (23)	115	45 (30)	185	0.71 (0.42, 1.19)
Rosenstock et al. 2009[23]	ALO (12.5 mg q.d.)	35 (27)	NR	31 (24)	NR	1.15 (0.66, 2.02)
	ALO (25 mg q.d.)	35 (27)	NR	31 (24)	NR	1.18 (0.67, 2.06)
Buse et al. 2011[24]	EXEN (5–10 mcg b.i.d.)	34 (25)	NR	35 (29)	NR	0.82 (0.47, 1.42)

Severe Hypoglycemia

Study	Treatment	Incretin		Placebo	
		n (%)	Events	n (%)	Events
Barnett et al. 2012[20]	SAXA (5 mg q.d.)	3 (1.0)	NR	2 (1.3)	NR
Visbøll et al. 2010[21]	SITA (100 mg q.d.)	2 (0.6)	2	1 (0.3)	1
Fonseca et al. 2007[22]	VILD (50 mg b.i.d.)	0 (0)	0	NR	6
Rosenstock et al. 2009[23]	ALO (12.5 mg q.d.)	0 (0)	0	2 (1.5)	2
	ALO (25 mg q.d.)	1 (0.8)	1	2 (1.5)	2
Buse et al. 2011[24]	EXEN (5–10 mcg b.i.d.)	0 (0)	0	1 (1)	2

Δ = change; A1C = glycated hemoglobin; ALO = alogliptin; b.i.d. = twice daily; BL = baseline; CI = confidence interval; EXEN = exenatide; n = number of patients; NR = not reported; OR = odds ratio; q.d. = once daily; SAXA = saxagliptin; SITA = sitagliptin; VILD = Vildagliptin; vs. = versus.

Table 6: Summary of Adverse Events							
Study	**Incretin**	**Total AEs — n (%)**		**SAEs — n (%)**		**WDAEs — n (%)**	
		Incretin	**Placebo**	**Incretin**	**Placebo**	**Incretin**	**Placebo**
Barnett et al. 2012[20]	Saxagliptin	202 (67)	108 (72)	25 (8)	13 (9)	9 (3)	3 (2)
Visbøll et al. 2010[21]	Sitagliptin	168 (52)	137 (43)	20 (6)	11 (3)	11 (3)	4 (1)
Fonseca et al. 2007[22]	Vildagliptin	117 (81)	126 (83)	12 (8)	14 (9)	9 (6)	1 (0.7)
Rosenstock et al. 2009[23]	Alogliptin 25 Alogliptin 12.5	86 (67) 89 (68)	95 (74) 95 (74)	7 (5) 8 (6)	6 (5) 6 (5)	6 (5) 1 (0.8)	6 (5) 6 (5)
Buse et al. 2011[24]	Exenatide	109 (79)	86 (70)	8 (6)	11 (9)	13 (9)	1 (1)

AEs = adverse events; SAEs = serious adverse events; WDAE = withdrawals due to adverse events.

3.4 Addition of DPP-4 Inhibitor versus Intensified Insulin

Only a single RCT was identified that compared the addition of an incretin against an intensified insulin regimen for patients who were inadequately controlled on their existing insulin therapy. Hong et al., 2012 compared the addition of sitagliptin (100 mg once daily) against an increase in insulin dosage in 140 Korean patients.[25] Patients allocated to the increased insulin dosage group were instructed to increase their daily dosage of insulin as follows:

- ≥ 10% at randomization
- ≥ 10% at the 12-week follow-up, if their A1C was not within the target level (i.e., ≤ 7.0%)
- an additional 2 U every week, based on the self-monitoring of their blood glucose.

Eligible patients were required to have an A1C of between 7.5% and 11.0%, and to have received insulin injections for at least three months at a dose of at least 10 U/day for a minimum of four weeks. Forty-eight per cent of participants were using insulin glargine only, 20% were using insulin glargine and a rapid-acting insulin, and 31% were insulin NPH and regular insulin.

Compared with an increased insulin dosage, the addition of sitagliptin (100 mg once daily) was associated with statistically significant improvements in A1C (MD [95% CI] = –0.42% (–0.91 to –0.11]) and body weight (MD [95% CI] = –1.7 kg [–2.5 to –0.5]) (Table 7). The mean dosage of insulin at baseline was numerically greater in the sitagliptin group (39.6 ± 19.1) compared with the intensified insulin group (35.4 ± 16.3). After 24 weeks, the mean insulin dosage in the intensified insulin group had increased by 10.1 U per day and had decreased in the sitagliptin group by 2.5 U per day ($P < 0.05$). There was also a lower rate of overall and severe hypoglycemia with sitagliptin compared with the increased insulin dosage (both $P < 0.01$).

Table 7: Summary of Results for Intensified Insulin Versus Addition of an Incretin

Results for Hemoglobin A1C, Body Weight, Insulin Dosage				
End Point	**Change from Baseline**		**Incretin vs. Intensified INS**	
	SITA + INS	**Intensified INS**	**MD (95% CI)**	***P* value**
Hemoglobin A1C (%)	−0.63 (−0.93, −0.38)	−0.22 (−0.55, 0.31)	−0.42 (−0.91, −0.11)	0.01
Body weight (kg)	−0.7 (−1.4, −0.1)	1.1 (0.2, 1.8)	−1.7 (−2.5, −0.5)	NS
Insulin dose (U/day)	−2.5 (−4.5, −1.3)	10.1 (4.5, 14.9)	−12.8 (−19.7, −5.6)	<0.05

Results for Hypoglycemia and Adverse Events					
End Point	**Sitagliptin**		**Intensified Insulin**		***P* value**
	n (%)	**Evt/Pt/Yr**	**n (%)**	**Evt/Pt/Yr**	
Overall hypoglycemia	5 (8.2)	7.02	11 (17.5)	14.29	<0.01
Severe hypoglycemia	1 (1.6)	0.88	3 (4.8)	2.81	<0.01
Total adverse events	21 (34.4)	NR	23 (36.5)	NR	NR
Serious adverse events	3 (4.9)	NR	4 (6.3)	NR	NR
Withdrawal due to AE	6 (9.8)	NR	6 (9.5)	NR	NR

A1C = glycated hemoglobin; AE = adverse event; BL = baseline; CI = confidence interval; Evt/Pt/Yr = events per patient year; INS = insulin; MD = Mean Difference; NR = not reported; NS = non-significant; SITA = sitagliptin; vs. = versus.

4 CRITICAL APPRAISAL

The primary limitation of the available evidence is the absence of well-designed trials comparing the addition of an incretin with intensified insulin for patients inadequately controlled on their existing insulin regimen. The only trial[25] that directly compared the addition of a DPP-4 inhibitor against an intensified insulin regimen was conducted exclusively in Korea, had a small sample size (N = 124), and used an open-label design. As well, the rate and extent of insulin titration may have been somewhat conservative in this trial than in clinical practice, potentially biasing results in favour of sitagliptin. All of the placebo-controlled trials were double-blind, with well-reported methodology. Sample sizes were appropriate for assessing the primary end point (i.e., hemoglobin A1C); however, the persistence of efficacy cannot be accurately assessed beyond six months in the included studies, as all of the trials were relatively short in duration (range 24 to 30 weeks).

5 DISCUSSION

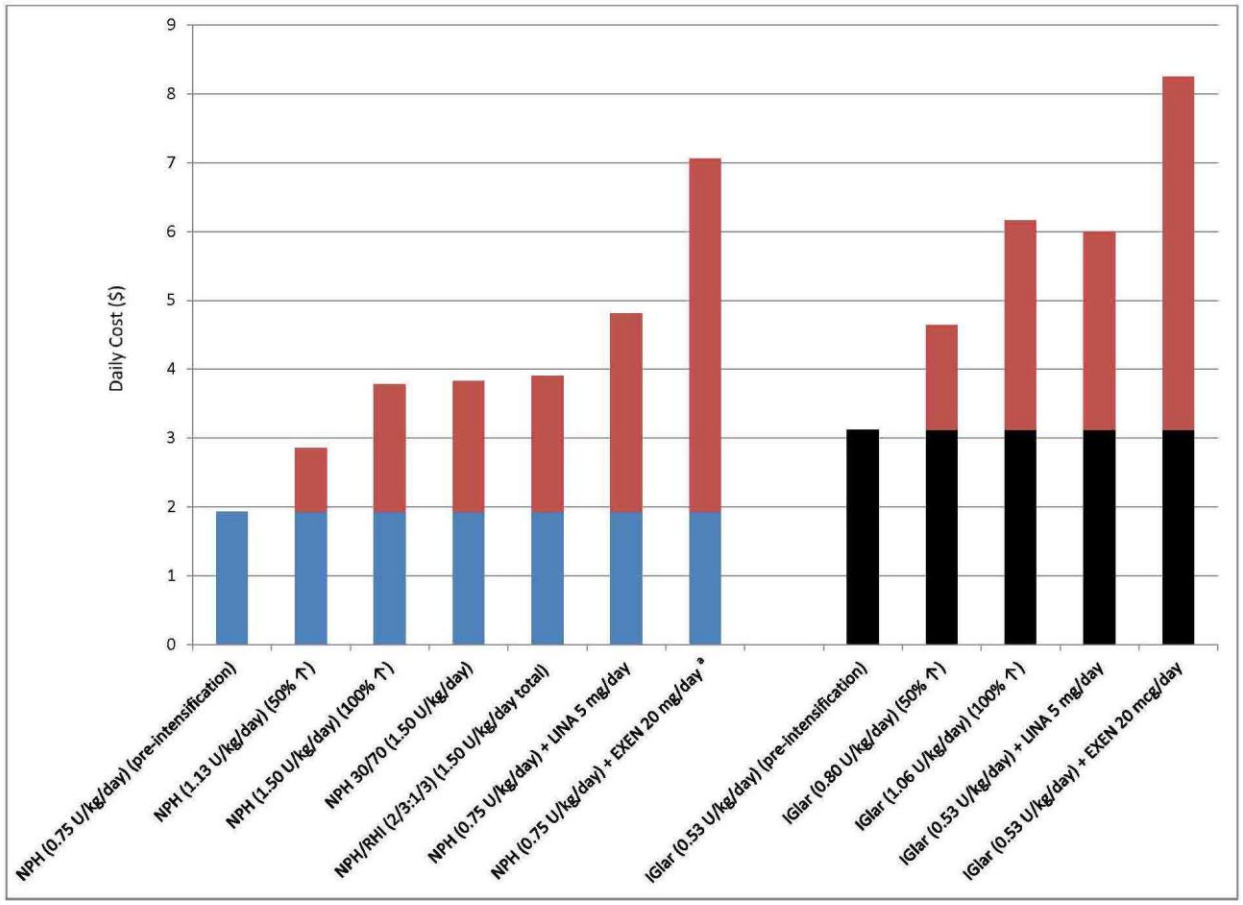
For patients who are inadequately controlled with insulin, the included RCTs demonstrated that the addition of a DPP-4 inhibitor results in an improvement in A1C of approximately 0.5% relative to placebo (range 0.3% to 0.6%). One study demonstrated an improvement of 0.7% with a GLP-analogue compared with placebo. A single trial directly comparing the addition of a DPP-4 inhibitor against intensification of insulin (i.e., increased dose) found a larger benefit on A1C with the former strategy, although this study was associated with a number of limitations. Overall, there was insufficient RCT evidence to accurately compare the addition of an incretin agent versus intensification of insulin for patients who are inadequately controlled with their existing insulin regimen.

Asche et al. (2012)[28] conducted a systematic review to assess the clinical benefits of insulin intensification. The authors did not pool the 14 included studies that reported mean change from baseline in A1C; however, they noted that the mean reduction in A1C with intensified insulin therapy exceeded 1% in seven studies and 2% in three studies. The majority of studies included in the review by Asche have limited generalizability to the current CADTH review, due to the following: involved patients

who were insulin-naïve; included patients with type 1 diabetes; investigated a treatment that may not be clinically relevant in the setting of interest for this review (i.e., continuous subcutaneous insulin infusion); involved patients who were "relatively well-controlled"; very limited sample size (i.e., less than 20 patients); and one study was a subgroup of an observational study. Of the studies included in the Asche review, only a single RCT reported patient and trial characteristics that were similar to those reported in the studies investigating combination use of insulin and incretins. Rosenstock et al., 2008[29] conducted an open-label, 24-week, non-inferiority RCT in patients (N = 374) with inadequate glycemic control despite using at least 30 U per day of insulin glargine for a minimum of 90 days. The study compared a basal-bolus regimen (i.e., the addition of prandial insulin lispro three times daily to ongoing insulin glargine at bedtime) against switching to a biphasic insulin (i.e., 50% insulin lispro and 50% insulin lispro protamine three times dialy). Hemoglobin A1C was reduced from 8.8% to 6.9% (–1.9%) in the biphasic insulin group and from 8.9% to 6.8% (–2.1%) in the basal-bolus group — an effect size greater than the change from baseline reported in the DPP-4 inhibitor trials (range –0.5% to –0.7%). The lack of a common comparative group precludes conducting a formal indirect comparison of the addition of an incretin versus intensification of insulin; therefore, comparisons of changes from baseline across trials are of limited interpretability and, at best, hypothesis-generating. Also, intensification of an insulin regimen would likely result in additional weight gain and hypoglycemia than would be expected in patients adding an incretin to their insulin-containing regimen.

The placebo-controlled trials included in this review demonstrated the efficacy of adding an incretin to insulin; however, the available data is too limited to determine how long the improvement in glycemic control obtained with the addition of an incretin would last. Although these patients may demonstrate improvements in glycemic control upon the addition of an incretin, they may eventually require intensification of insulin in order maintain control in the longer term. It is possible that incretins initiated in response to an initial insulin failure may be continued when subsequent insulin intensification is required. Such treatment regimens could be associated with significant costs (see Figure 2) and uncertain clinical and economic benefits. Ascertainment of the cost-effectiveness of incretin/insulin combination regimens requires well-designed trials to compare the safety and efficacy of these strategies, particularly against insulin intensification.

Figure 2: Examples of Incremental Costs (Red Bars) Associated with Various Intensification Strategies after Insulin NPH (Blue Bars) and Insulin Glargine (Black Bars)



EXEN = exenatide; IGlar = insulin glargine; LINA = linagliptin; NPH = insulin neutral protamine Hagedorn; RHI = regular human insulin; U = units.
[a] Exenatide is only indicated in Canada for use with insulin glargine.[11]
Note: Costs include 10% markup and $7.00 dispensing fee per 90-day supply. Assumed body weight = 87 kg.

6 REFERENCES

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APPENDIX 1: LITERATURE SEARCH STRATEGY

OVERVIEW	
Interface:	Ovid
Databases:	EMBASE Ovid MEDLINE Ovid MEDLINE In-Process & Other Non-Indexed Citations **Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	July 11, 2012
Alerts:	Monthly search updates ran until publication of the final report.
Study Types:	Systematic reviews; meta-analyses; technology assessments; randomized controlled trials; and economic literature.
Limits:	Publication years January 1, 2002 onwards English language

SYNTAX GUIDE	
/	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
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
#	Truncation symbol for one character
?	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

Ovid MEDLINE & Embase Strategy	
#	**Searches**
1	exp insulin/ use pmez
2	*biphasic insulin/ or *human insulin/ or *insulin/ or *insulin aspart/ or *insulin detemir/ or *insulin 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/ use emef
3	(long acting insulin* or long acting analog* or slow* acting insulin* or slow* acting analog*).ti,ab.
4	(glargine or Lantus or Optisulin or hoe 901 or 160337-95-1).ti,ab,rn.
5	(detemir or determir or Levemir or nn 304 or 169148-63-4).ti,ab,rn.
6	(nph insulin or humulin or novolin).ti,ab.
7	11061-68-0.rn.
8	(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.
9	(Lispro or Lyspro or Humalog or Liprolog or 133107-64-9).ti,ab,rn.
10	(Insulin Aspart or 116094-23-6 or NovoLog or NovoRapid or NovoMix).ti,ab,rn.
11	(Glulisine or 207748-29-6 or Apidra).ti,ab,rn.
12	or/1-11
13	Dipeptidyl-Peptidase IV Inhibitors/ use pmez
14	exp *Dipeptidyl Peptidase IV Inhibitor/ use emef
15	*albiglutide/ or *liraglutide/ or *lixisenatide/ or *taspoglutide/ use emef
16	*exendin 4/ use emef
17	Glucagon-Like Peptide 1/aa [Analogs & Derivatives]
18	(dpp adj IV adj inhibitor*).ti,ab.
19	(dipeptidyl-Peptidase adj IV adj inhibitor*).ti,ab.
20	DPP-4 inhibitors.ti,ab.
21	dipeptidyl peptidase-4 inhibitors.ti,ab.
22	gliptins.ti,ab.
23	((GLP-1 or glucagon-like peptide*) adj2 analog*).ti,ab.
24	(sitagliptin or Januvia or Janumet or vildagliptin or Galvus or gliptin or incretin agent* or exenatide or Byetta or Bydureon or Exendin-4 or liraglutide or Victoza).ti,ab.
25	(486460-32-6 or 274901-16-5 or 141758-74-9 or 204656-20-2).rn.
26	(taspoglutide or R-1583 or R1583 or BIM51077 or BIM-51077 or lixisenatide or AVE0010 or AVE-0010 or albiglutide).ti,ab,rn.
27	275371-94-3.rn.
28	(saxagliptin or Onglyza or bms 477118 or bms-477118 or bms477118 or 3-hydroxyadamantylglycine-4,5-methanoprolinenitrile).ti,ab,rn.
29	(361442-04-811 or 945667-22-111 or 361442-04-8 or 945667-22-1).rn.
30	(linagliptin or Tradjenta or Trajenta or BI-1356 or alogliptin or SYR-322 or SYR322 or Nesina or dutogliptin).ti,ab,rn.
31	(668270-12-0 or 850649-62-6 or 852329-66-9).rn.
32	or/13-31
33	12 and 32
34	exp Diabetes Mellitus, Type 2/ use pmez
35	Diabetes mellitus/ use pmez

Ovid MEDLINE & Embase Strategy	
#	**Searches**
36	*Diabetes Mellitus/ use emef
37	*Maturity Onset Diabetes Mellitus/ use emef
38	*Non Insulin Dependent Diabetes Mellitus/ use emef
39	*Lipoatrophic Diabetes Mellitus/ use emef
40	((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.
41	(mody or niddm or t2dm).ti,ab.
42	or/34-41
43	33 and 42
44	remove duplicates from 43
45	limit 44 to english language
46	meta-analysis.pt.
47	meta-analysis/ or systematic review/ or meta-analysis as topic/ or "meta analysis (topic)"/ or "systematic review (topic)"/ or exp technology assessment, biomedical/
48	((systematic* adj3 (review* or overview*)) or (methodologic* adj3 (review* or overview*))).ti,ab.
49	((quantitative adj3 (review* or overview* or synthes*)) or (research adj3 (integrati* or overview*))).ti,ab.
50	((integrative adj3 (review* or overview*)) or (collaborative adj3 (review* or overview*)) or (pool* adj3 analy*)).ti,ab.
51	(data synthes* or data extraction* or data abstraction*).ti,ab.
52	(handsearch* or hand search*).ti,ab.
53	(mantel haenszel or peto or der simonian or dersimonian or fixed effect* or latin square*).ti,ab.
54	(met analy* or metanaly* or health technology assessment* or HTA or HTAs).ti,ab.
55	(meta regression* or metaregression* or mega regression*).ti,ab.
56	(meta-analy* or metaanaly* or systematic review* or biomedical technology assessment* or bio-medical technology assessment*).mp,hw.
57	(medline or Cochrane or pubmed or medlars).ti,ab,hw.
58	(cochrane or (health adj2 technology assessment) or evidence report).jw.
59	(meta-analysis or systematic review).md.
60	or/46-59
61	Randomized Controlled Trial.pt.
62	Randomized Controlled Trials as Topic/
63	"Randomized Controlled Trial (topic)"/
64	Randomized Controlled Trial/
65	Randomization/
66	Random Allocation/
67	Double-Blind Method/
68	Double Blind Procedure/
69	Double-Blind Studies/
70	Single-Blind Method/
71	Single Blind Procedure/
72	Single-Blind Studies/
73	Placebos/
74	Placebo/

Ovid MEDLINE & Embase Strategy	
#	**Searches**
75	(random* or sham or placebo*).ti,ab,hw.
76	((singl* or doubl*) adj (blind* or dumm* or mask*)).ti,ab,hw.
77	((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti,ab,hw.
78	or/61-77
79	(economic adj2 model*).mp.
80	(cost minimi* or cost-utilit* or health utilit* or economic evaluation* or economic review* or cost outcome or cost analys?s or economic analys?s or budget* impact analys?s).ti,ab.
81	(cost-effective* or pharmacoeconomic* or pharmaco-economic* or cost-benefit).ti.
82	(life year or life years or qaly* or cost-benefit analys?s or cost-effectiveness analys?s).ab.
83	(cost or costs or economic*).ti. and (costs or cost-effectiveness or markov).ab.
84	or/79-83
85	45 and 60
86	limit 85 to english language
87	86 not CONFERENCE ABSTRACT.pt.
88	limit 87 to yr="2002 -Current"
89	45 and 78
90	limit 89 to english language
91	90 not CONFERENCE ABSTRACT.pt.
92	limit 91 to yr="2002 -Current"
93	45 and 84
94	limit 93 to english language
95	94 not CONFERENCE ABSTRACT.pt.
96	limit 95 to yr="2002 -Current"

OTHER DATABASES	
PubMed	Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used.
Cochrane Library, 2012 Issue 7 (Wiley)	Same MeSH, keywords, and date limits used as per MEDLINE search, with appropriate syntax used.

Grey Literature

Dates for Search:	May 7 to 15, 2012
Keywords:	Included terms for diabetes, insulin, and second- and third-line antidiabetes drugs including DPP-4 inhibitors or GLP-1 analogues.
Limits:	Publication years 2009 to 2012

The following sections of the CADTH grey literature checklist *Grey Matters: A Practical Search Tool for Evidence-Based Medicine* (www.cadth.ca/resources/grey-matters) were searched:

- Health Technology Assessment Agencies
- Health Economics
- Internet Search
- Open Access Journals.
- Clinical Practice Guidelines
- Databases (free)