March 10, 2008

Summary of Revisions:

COMPUS Optimal Therapy Report. *Long-Acting Insulin Analogues for the Treatment of Diabetes Mellitus: Meta-analyses of Clinical Outcomes – Update of CADTH Technology Report No. 92* (originally posted February 21, 2008)

Text Revisions

Page No.	Revision
i	Fifty- eight articles representing 52 unique RCTs were included: seven studies were conducted in pediatric type 1 DM patients, 25 in adult type 1 DM patients, and 20 in adult type 2 DM patients. The number of patients in each study ranged from 14 to 756. Trial duration ranged from four to 52 weeks. The overall quality of most RCTs was low. All studies were of open-label design.
ii	Compared to those in the NPH group, mean body weight at endpoint was statistically significantly lower in patients in the IGlar group [WMD (95%CI) = -0.36kg (-0.67, -0.04)] as well as the IDet group [WMD (95% CI) = -0.73 kg (-1.42, -0.03).
ii	For adult patients with type 2 DM receiving oral antidiabetic agents (OADs), the pooled estimate of difference in mean A1c between treatment groups was not statistically significant for IGlar compared with NPH, and significantly favoured NPH in the comparison with IDet [WMD (95% CI) = 0.13 (0.03, 0.22)].
ii	The frequency of nocturnal hypoglycemia, for patients receiving OADs, was significantly reduced for IGlar versus NPH [rate ratio (95%CI) = 0.41 (0.29, 0.59)], and for IDet versus NPH [rate ratio (95%CI) = 0.48 (0.42, 0.55)].
ii	Conversely, the frequency, but not the risk of overall hypoglycemia, for patients taking OADs, was statistically significantly decreased for the IDet group when compared to the NPH group [rate ratio (95%CI) = 0.59 (0.48, 0.72)]
iii	There was no significant difference in body weight in Type 2 DM patients treated with IGlar as compared to NPH insulin, although there was a significant difference in favour of IGlar in comparison to rosiglitazone [WMD (95% CI) = -1.45 kg (-2.48, -0.42)]. Significant differences in body weight in favour of IDet as compared to NPH insulin were found in patients treated concomitantly with OADs [WMD (95% CI) = -0.96 kg (-1.69, -0.23)], as well as in patients treated with pre-meal IAsp [WMD (95% CI) = -0.80 kg (-1.46, -0.14)]. Furthermore, change in weight from baseline significantly favoured IDet as compared to IGlar ([WMD (95% CI) = -1.50 kg (-2.47, -0.53)] in combination with pre-meal IAsp, and [WMD (95% CI) = -0.80 kg (-1.52, -0.08) in combination with OADs]).
4	There are seven classes of antidiabetic drugs currently available in Canada: And an additional bullet under thiazolidinediones: • Dipeptidyl peptidase 4 (DPP-4) inhibitors (sitagliptin)
11	As well, one additional RCT and an erratum pertaining to one of the selected articles were identified by stakeholders. Therefore, a total of 26 articles were identified during the updating process.... The combined total number of selections from the updating process and studies selected in the technology report[20] was 58. These 58 articles represented 52 unique RCTs.

12	Figure 1: • 1 full-text report from contacted author (in lieu of 1 abstract identified in literature search); 1 RCT and 1 erratum identified by stakeholders • 26 relevant articles • 58 articles included, representing 52 unique RCTs
13	Of the 52 unique RCTs selected for inclusion, 32 were on type 1 DM (including both pediatric and adult populations) and 20 were on adult type 2 DM patients.
13	Seven articles[30-36], each reporting the results of a unique RCT, were on type 1 pediatric patients.
13	Twenty-two articles reported the results of parallel trials[40-42,44-49,51-63] and five those of crossover trials.[39,43,50,64,65]
14	Twenty-four articles[68-91]and one erratum[91] describing 20 RCTs in adult type 2 diabetics were selected. Of the 24 articles,[18 68-71,74-84,88-90] were full-text articles, and six[72,73,85-87,91] were conference abstracts. Three abstracts[85-87] contained data from the same RCT, two full-text articles[88,90] described a single trial, and one article[75] reported a subgroup analysis of another RCT.[74] Therefore, the 24 articles included represented 20 unique RCTs. Eighteen articles[68-71,75-78,80-84,86-90] mentioned industry sponsorship. One RCT[68] compared IDet with NPH in patients also using bolus insulins. Three RCTs[69,70,91] compared IDet with NPH in patients also using OADs. One RCT[71] was on IDet in combination with aspart versus NPH and HI. One RCT compared IDet with IGlar in patients also using bolus insulins. One RCT[56,74] compared IGlar with NPH in patients also using bolus insulins. Nine articles[77-84,92] were on IGlar versus NPH with OAD as co-therapy. Six articles[85-90] describing three RCTs reported the comparison of IGlar with thiazolidinediones (TZDs) as add-on therapy in patients inadequately controlled on sulfonylureas and metformin. All studies were of parallel design. Sample sizes ranged from 20 to 756. Among trials reporting information on centre, only one was of single centre design. Two[83,93] of the 23 trials had a duration of less than three months. Mean age ranged between 53 and 61.3 years. The percentage of females ranged between 33.3% and 57.1%. Three studies did not report this information. The mean duration of diabetes ranged between 8.1 and 14.5 years. Seven articles did not report this information.
14	In terms of ethnic minorities, three studies were conducted in Asian countries (one in China[79], a second in Japan[91], and a third in various countries,[76]). One study was conducted in a Latin American population.[77]
16	(Under IDet vs. NPH) Only one RCT comparing IDet with NPH (and IAsp as bolus insulin in both arms) was identified [mean difference (95% CI)=0.10% (-0.1, 0.3)].
18	(Under IDet vs. NPH) Only one RCT comparing IDet with NPH (and IAsp as bolus insulin in both arms) was identified.
34	(IDet vs. NPH) Six RCTs reported mean body weight at endpoint for this comparison. Overall, IDet was associated with significantly lower body weight than NPH [WMD (95% CI) = -0.73 kg (-1.42, -0.03)].
35	(Under IDet vs. IGlar) In the single RCT reporting the results of this comparison, no statistically significant difference was found in body weight [mean difference (95% CI) = -0.5 kg (-1.21, 0.21)].
38	Nine RCTs[76-84] reported A1c differences for IGlar versus NPH in patients also treated with OADs. The pooled difference in mean A1c was not significant [WMD (95% CI)=-0.05% (-0.13, 0.04)]

39	Three RCTs[69,70,91] reported A1c differences for IDet versus NPH in patients also treated with OADs (Figure 24). The pooled result significantly favoured NPH insulin [WMD (95% CI) = 0.13% (0.03, 0.22)]. All three studies used various OADs, therefore subgroup analysis was not possible. One study[69] also reported the number of patients who reached A1c• 7%; no significant difference was found between groups.
41	Three studies[69,70,91] reported FPG data for this comparison in patients also treated with OADs. There was no significant difference between treatments (Figure 27). However, there was a high degree of heterogeneity (I2=69.0%). One of the three studies found a statistically significant benefit in favour of IDet,[70] while the other two found a non-significant benefit in favour of NPH.[69,91] One possible cause for the observed heterogeneity may be that both insulins were administered once daily in the former study, and twice daily in the latter studies.
47	Subgroup analysis by OAD was not possible, since all three studies used various OADs.
49	There was a high degree of heterogeneity in all three meta-analyses of RR (I2=68.8%, 51.6% and 82.1% for severe, nocturnal, and overall hypoglycemia, respectively), as well as in the meta-analysis of overall hypoglycemia rate ratio (I2=86.9%). A possible cause for heterogeneity in RRs may lie in the fact that one study administered both IDet and NPH once daily,[70] while the other administered them twice daily.[69] The RRs observed in the former study for both nocturnal and overall hypoglycemia were smaller than those reported in the latter.
53	Three RCTs[69,70,91] reported weight change from baseline for the comparison of IDet with NPH in patients also using OADs. The pooled estimate revealed that there was significantly less weight gain in the IDet arm [WMD (95% CI) = -0.96 kg (-1.69, -0.23)] (Figure 43, Table 24). There was a high degree of heterogeneity in this analysis (I2= 82.0%). The main difference between the RCTs was that insulins were administered twice daily in one study[69] and once daily in the other two studies.[70,91] Subgroup analysis by OAD was not possible since various agents were allowed in all three studies.
63	Only three studies with OAD co-therapy[69,70,91] and one study with bolus insulin (IAsp) therapy[68] were identified.... In the OAD studies, glycemic control as measured by A1c significantly favoured NPH, although the observed difference was unlikely to be clinically significant. FPG did not differ significantly between groups. Heterogeneity was evident in that one of the three studies reported significantly higher mean A1c at endpoint in the IDet arm with no significant difference in FPG,[69] another reported no difference in A1c with a significant improvement in FPG,[70] and the third reported no significant difference between groups for either measure.[91] These differences may have been due to the fact that two studies administered both IDet and NPH once daily,[70,91] while the third study administered them twice daily.[69] The overall relative risks for severe and overall hypoglycemia were not statistically significant, while the rate ratios for each outcome significantly favoured IDet. Of note is the high degree of imprecision caused by the low number of severe hypoglycemia events. As well, each of the two studies that comprised the overall RR estimate reported statistically significant reductions in favour of IDet; the lack of statistical significance of the pooled estimate resulted from heterogeneity in the two individual estimates. Both the RR and rate ratio for nocturnal hypoglycemia significantly favoured IDet. Mean body weight was also significantly lower in detemir-treated subjects as compared with NPH. No studies assessed HRQoL, patient satisfaction, or long-term complications.
64	One additional study compared IDet with NPH, with IAsp used as bolus insulin with IDet, and HI with NPH. No significant differences were reported for A1c or severe hypoglycemia, although the relative risk and rate ratio for nocturnal hypoglycemia significantly favoured IDet. As well, change in body weight from baseline significantly favoured the analogue arm.

64	Both studies were reported in abstract form. In the former study, the IGlar arm was found to have a small but statistically significant advantage over detemir in terms of A1c, although there was no difference in terms of FPG. This study did not report hypoglycemia data, although the authors noted that there was no significant difference in the risk of hypoglycemia.
64	In contrast to IGlar, IDet demonstrated small but statistically significant benefits in terms of body weight in comparison to NPH insulin. In head-to-head studies, there was no evidence that one long-acting analogue is superior to the other, although IDet produced significantly lower increases in body weight as compared to IGlar.

Table Revisions

Page No.	Table
15	Table 1 (last row)
17	Table 4 (RR for severe hypoglycemia)
33	Table 14 (IDet vs. NPH)
37	Table 15 (IDet vs. NPH with various OADs)
47	Table 19 (Rate Ratio side only: Nocturnal hypoglycemia; Overall hypoglycemia)
54	Table 24)IDet vs. NPH with various OADs)

Figure Revisions

Page No.	Figure Replaced
21	Figure 5
34	Figure 20
39	Figure 24
41	Figure 27
48	Figure 37
49	Figure 38
53	Figure 43

Appendices Revised to include additional abstract

(Tajima N, Iwamoto Y, Kaku K, Kawamori R, Nishida T, Kobayashi M. Once-daily insulin detemir added to oral antidiabetic drugs results in less weight gain and a trend for reduced hypoglycaemia in comparison to NPH insulin in Japanese patients with type 2 diabetes [abstract]. *Diabetologia* 2006;49(Suppl 1):609.)

APPENDIX 7B: STUDY CHARACTERISTICS OF RCTS IN ADULT TYPE 2 DM
APPENDIX 8: PATIENT INCLUSION AND EXCLUSION CRITERIA OF SELECTED RCTS
APPENDIX 10B: HYPOGLYCEMIA DATA ON TYPE 2 DM PATIENTS
APPENDIX 11A: MEAN HBA1C AND FPG LEVELS AT ENDPOINT IN RCTS OF TYPE 1 DM
APPENDIX 12B: STUDY-LEVEL BODY WEIGHT AND BMI DATA FROM RCTS IN TYPE 2 DM
APPENDIX 13B: ADVERSE EVENTS DATA (EXCLUDING HYPOGLYCEMIA) FOR RCTS IN TYPE 2 DM