Review: Long-acting insulin analogues do not improve glycemic control but do reduce nocturnal hypoglycemia in diabetes

Tran K, Banerjee S, Li H, et al. **Long-acting insulin analogues for diabetes mellitus: meta-analysis of clinical outcomes and assessment of cost-effectiveness.** Technology report #92. Ottawa: Canadian Agency for Drugs and Technologies in Health (CADTH); 2007.

Clinical impact ratings: GIM/FP/GP ★★★★★★☆ Endocrinology ★★★★★★☆ Occup/Envir Health ★★★★☆☆☆

QUESTION

In patients with diabetes mellitus, what is the efficacy of long-acting insulin analogues (LAIAs) compared with human insulin or oral antidiabetic agents?

METHODS

Data sources: MEDLINE, EMBASE/Excerpta Medica, BIOSIS Previews, PASCAL, PubMed, and Cochrane Database of Systematic Reviews (1990 to February 2006); Health Economics Evaluation Database; Web sites of regulatory and health technology assessment agencies and professional associations; and drug manufacturers.

Study selection and assessment: Randomized controlled trials (RCTs) comparing LAIAs (insulin glargine or insulin detemir) with conventional human insulin (including NPH) or oral antidiabetic agents in patients with type 1, type 2, or gestational diabetes. 34 RCTs met efficacy selection criteria: 14 of insulin glargine and 9 of insulin detemir in type 1 diabetes (n = 7142); 9 of insulin glargine and 2 of insulin detemir in type 2 diabetes (n = 4729). 31 trials involved adults only. Average quality of the 28 fully published RCTs was low (mean 2.3 on Jadad scale).

Outcomes: Included glycemic control (hemoglobin A_{1c} [HbA_{1c}] level) and hypoglycemic episodes.

MAIN RESULTS

Meta-analyses showed that LAIAs and NPH did not differ for change in HbA_{1c} levels (Table); results of individual trials varied, but none reported important, large differences (HbA_{1c} reduction ≥ 1%). The range of endpoint HbA_{1c} levels was similar for insulin glargine vs NPH (16 trials, 6.4% to 9.0% vs 7.0% to 9.1%) and insulin detemir vs NPH (10 trials, 6.6% to 8.3% vs 6.5% to 8.4%). Meta-analyses also showed that risk for nocturnal hypoglycemia was reduced by insulin detemir in type 1 diabetes and by insulin glargine in type 2 diabetes compared with NPH (Table); in type 1 diabetes, severe hypoglycemia was reduced with insulin detemir (Table) and with insulin glargine using human insulin as bolus (5 trials, relative risk reduction 27%, 95% CI 5 to 45). Insulin glargine and NPH did not differ for nocturnal hypoglycemia in type 1 diabetes or severe hypoglycemia overall (Table).

CONCLUSION

Long-acting insulin analogues do not reduce HbA_{1c} levels more than NPH insulin but do reduce nocturnal hypoglycemia.

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Long-acting insulin analogues (LAIAs) vs conventional insulin (NPH) in diabetes*

Outcomes	Number of trials (n)	Diabetes type: LAIA	Weighted mean difference (95% CI)†	
Change in HbA_{1c} level‡	8 (2937)	Type 1: detemir	–0.05% (–0.12 to 0.03)	
	2 (980)	Type 2: detemir	0.11% (–0.03 to 0.26)	
	7 (2967)	Type 2: glargine	0.05% (–0.07 to 0.16)	
			RRR/RRI (CI)	NNT/NNH (CI)
Nocturnal hypoglycemia	7 (2590)	Type 1: detemir	RRR 11% (3 to 18)	15 (9 to 34)
	1 (505)	Type 2: detemir	RRR 34% (4 to 54)	13 (7 to 133)
	7 (2826)	Type 1: glargine	RRR 8% (–4 to 19)	Not significant
	5 (2099)	Type 2: glargine	RRR 43% (26 to 56)	9 (7 to 12)
Severe hypoglycemia§	8 (2708)	Type 1: detemir	RRR 25% (5 to 41)	50 (25 to 100)
	6 (2701)	Type 1: glargine	RRR 22% (–5% to 42)	Not significant
	4 (1885)	Type 2: glargine	RRI 9% (–44 to 112)	Not significant

*HbA_{1c} = hemoglobin A_{1c}; NPH = neutral protamine Hagedorn; other abbreviations defined in Glossary. RRR, RRI, NNT, NNH, and CI calculated from data in article; all data combined using a random-effects model.
†Negative values indicate a benefit for insulin glargine or insulin detemir over NPH.
‡Trials of insulin glargine vs NPH in type 1 diabetes were heterogeneous and not pooled.
§Trials of insulin detemir in type 2 diabetes did not report severe hypoglycemia.

COMMENTARY

Tran and colleagues used an appropriate search strategy, bias protection measures, and pooling methods, but did not contact authors of primary studies for unreported data, increasing the risk for reporting bias. They found that LAIAs have minimal impact on glycemic control compared with older agents but reduce the incidence of hypoglycemia, mainly nocturnal. The evidence regarding quality of life, long-term morbidity, death, and cost-effectiveness is limited and inconclusive.

The conclusions of this review should be interpreted with caution considering the potential heterogeneity of included trials in terms of dosing schedules in the control group, targeted level of glycemic control, level of patient training and education for managing insulin therapy, and baseline risk for hypoglycemia. Moreover, in patients at high risk for hypoglycemia, clinicians should consider continuous insulin delivery (insulin pump) as a viable treatment alternative to LAIAs to minimize hypoglycemia.

The review highlights important issues. There is a lack of well-designed trials that demonstrate clinical and economic benefits for some diabetes interventions that have been widely adopted into practice. The extension of trial data, mostly from outpatient settings, to suggest that LAIAs are optimal agents for in-hospital glycemic control (1) is, at best, premature. In addition, diabetes trials need to improve in quality and shift their almost-exclusive focus on HbA_{1c} to include important patient outcomes, such as hypoglycemia, death, vascular events, quality of life, loss of vision, and patient satisfaction. Of note, only 1 in 5 trials published or in progress considered such outcomes as primary endpoints (2).

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References

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