COMPARISON OF CLINICAL EFFICACY OF INSULIN GLARGINE ADDED TO ORAL ANTIDIABETIC DRUGS VS PREMIXED INSULIN ALONE IN THE TREATEMENT OF TYPE 2 DIABETES MELLITUS

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*A study conducted by **HTA Consulting** **www.hta.pl***

Objective

The aim of this analysis was to compare efficacy and safety of insulin glargine (IGlar) when added to oral antidiabetic drugs (OADs) with premixed human insulin alone in type 2 diabetes mellitus (T2DM).

Introduction

Diabetes mellitus comprises a group of common metabolic disorders characterized by elevated blood glucose level. Type 2 diabetes mellitus is a chronic condition in which insulin is produced but not utilized properly. Without adequate control of blood glucose, the disease leads to vascular and non-vascular complications. The prevalence of all types of diabetes worldwide estimated by the WHO for the year 2000 was 2.8%.

Insulin glargine (Lantus®) is a long-acting human insulin analogue, produced using recombinant DNA technology in E. coli K12 strain. In T2DM, when a combination of 2 or 3 OADs becomes ineffective, it is possible to introduce a basal + OADs treatment regimen or therapy with premixed insulin. In a basal + OADs regimen patients receive basal insulin added to oral medications (except glitazones). Basal insulin is administered once daily (in the evening if morning hypoglycaemia is observed or in the morning in the case of normoglycaemia), while during the day the patient receives oral medications.

Premixed insulin is a mixture of a rapid-acting insulin analogue with protamin suspension of this analogue or a mixture of a short-acting human insulin with an intermediate-acting human isophane insulin. Usually mixtures are administered twice daily, although other dosage regimens are used.

Methodology

The comparison was based on randomized controlled trials (RCTs) identified by means of a systematic review, carried out according to the Cochrane Collaboration and the Agency for Health Technology Assessment in Poland guidelines. The most important medical databases (EMBASE, MEDLINE and CENTRAL) were searched in October 2008. Two reviewers independently selected trials, assessed their quality and extracted data. Meta-analysis of head-to-head trials was performed in order to compare IGlar added to OADs with premixed insulin alone (without OADs).

Table 1. Inclusion and exclusion criteria

Target population	Type 2 diabetes mellitus
Evaluated intervention	Insulin glargine when added to oral antidiabetic agents
Evaluated comparator	Premixed human insulin alone (without OADs)
Design of clinical trials	Randomized controlled trials
Other inclusion criteria	Studies published in English, French or German Studies published in full text Head to head comparisons
Exclusion criteria	Studies, in which oral antidiabetic agents were not added to insulin glargine or studies where OADs were administrated in both arms

Characeristics of clinical trials

The search in medical databases resulted in a total number of 2,289 identified publications (including repeated titles). Finally 3 trials met the inclusion criteria and were qualified for further analysis. All included studies had parallel design and their methodological credibility was assessed as medium.

Selection process according to QUOROM

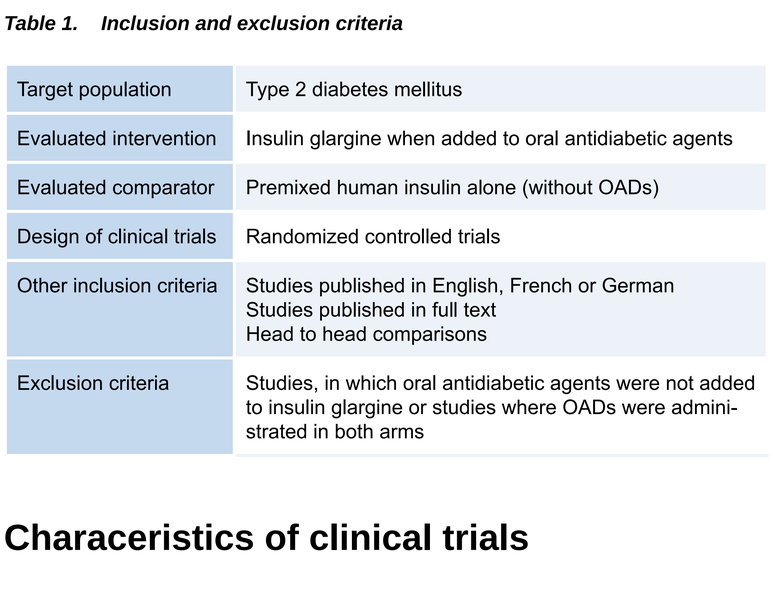


Table 2. Qualified trials

Author, Yr	Comparison	OADs	No. of subjects	Follow-up	Jadad score
Al-Shaikh 2006	IGlar + OADs	MET + SU	111	24 weeks	2/5
	IMT 30/70	x	110		
Janka 2005	IGlar + OADs	GLIM + MET	177	24 weeks	3/5
	IMT 30/70	x	187		
Schiel 2007	IGlar + OADs	GLIM	17	16 weeks	3/5
	IGlar + OADs	GLIM + MET	18		
	IMT 75/25 or 70/30	x	17		

Results

Efficacy

HbA1c and FPG level

Pooled data for HbA1c demonstrated a lower level in the IGlar group than in the premixed insulin group (WMD = -0.33% [-0.50; -0.16]). In addition meta-analysis for FPG level also revealed statistically significant differences in favour of IGlar (WMD = -0.87 mmol/l [-1,.21; -0.53]). No statistically significant heterogeneity between the studies was found (Figure 1 and 2).

Figure 1. Weighted mean difference in the HbA1c level

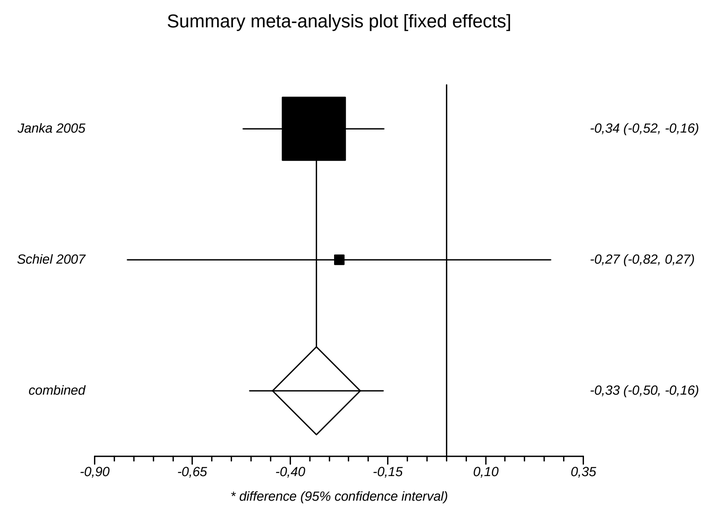
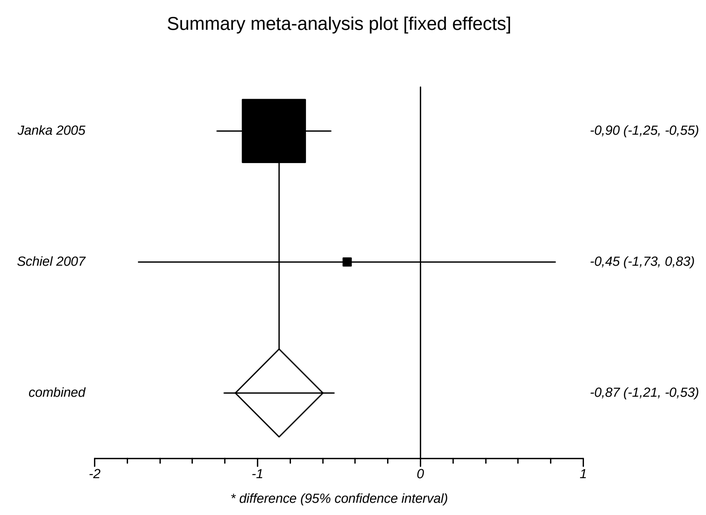


Figure 2. Weighted mean difference in the FPG level



Target HbA1c and FPG levels

More patients in the IGlar group achieved HbA1c ≤7%, although the difference was on the border of statistical significance (RB=1.26 [1.00; 1.59]). The proportion of patients achieving a FPG level ≤ 5.6 mmol/l was higher in the IGlar group and the difference was statistically significant (RB=2.11 [1.41; 3.17], NNT= 6.00 [3.97; 12.32]).

Weight gain

Weight gain was observed in both groups with no statistically significant differences between them (MD= -0.70 kg [-1.48; 0.08]).

Treatment satisfaction

In one identified study there was no statistically significant difference between treatment groups in the treatment satisfaction measured using the DTSQ.

Table 4. Abbreviations

CI	Confidence Interval
DTSQ	Diabetes Treatment Satisfaction Questionnaire
FPG	Fasting Plasma Glucose
GLIM	Glimepiride
HbA1c	Glycated hemoglobin
IGlar	Insulin Glargine
IMT	Insulin Mixed Therapy
MD	Mean Difference
MET	Metformin
NNT	Number Needed to Treat
NS	Not Statistically Significant
OADs	Oral Antidiabetic Drugs
p	p-value
Pts.	Patients
RB	Relative Benefit
RCT	Randomized Controlled Trial
RR	Relative Risk
SU	Sulphonylourea
T2DM	Type 2 Diabetes Mellitus
WMD	Weighted Mean Difference

Safety

No statistically significant differences were found in the percentage of patients experiencing any hypoglycaemic episodes: RR=0.90 [0.78; 1.04]. The number of hypoglycemic episodes per patient per month was significantly lower in the IGlar group as compared with the premixed insulin group (0.3 vs 0.8; p<0.001). The number of nocturnal hypoglycemic episodes per patient per month was significantly lower in the IGlar group as compared with the premixed insulin group (0.04 vs 0.09; p=0.0449). Severe hypoglycaemia was investigated in one study but no patient experienced this event.

Figure 3. Relative risk of occurrence of a hypoglycaemic episode

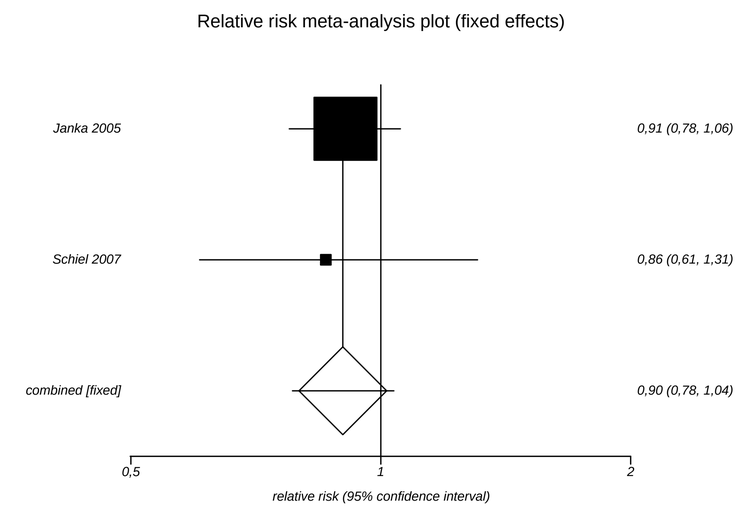


Table3. Summary of the results of comparison of efficacy of insulin glargine vs premixed insulin – continuous outcomes

Endpoint [parameter]	No. of studies	No. of subjects		WMD or RR or RB [95% CI]	Statistical significance
		IGlar	IMT		
HbA1c level [%]	2	202	204	WMD= -0.33% [-0.50; -0.16]	In favour of IGlar
FPG level [mmol/l]	2	212	204	WMD= -0.87 mmol/l [-1.21; -0.53]	In favour of IGlar
Weight gain [kg]	1	177	187	WMD= -0.70 kg [-1.48; 0.08]	NS
Percentage of pts. with HbA1c level ≤ 7%	1	177	187	RB=1.26 [1.00; 1.59]	NS
Percentage of pts. with FPG level ≤ 5.6 mmol/l	1	177	187	RB=2.11 [1.41; 3.17]	In favour of IGlar NNT= 6.00 [3.97; 12.32]
Hypoglycaemic episodes	2	212	204	RR=0.90 [0.78; 1.04]	NS
Number of hypoglycaemic episodes per patient per month [mean]	1	177	187	x	In favour of IGlar 0.3 vs 0.8 p<0.001
Number of nocturnal hypoglycaemic episodes per patient per month [mean]	1	177	187	x	In favour of IGlar 0.04 vs 0.09 p=0.0449
Severe hypoglycaemia	1	35	17	x	No patient experienced this event

Conclusions

IGlar combined with OADs is associated with better glycemic control than premixed human insulin alone. The risk of hypoglycaemia or weight gain is comparable between both arms.

Limitations

We found only 3 studies which met the inclusion criteria. In all of them surrogate endpoints were assessed. There were no trials with clinically important endpoints, such as mortality or morbidity.