Basal Supplementation of Insulin Lispro Protamine Suspension Versus Insulin Glargine and Detemir for Type 2 Diabetes

Meta-analysis of randomized controlled trials

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OBJECTIVE—We compared the effect of insulin lispro protamine suspension (ILPS) with that of insulin glargine and insulin detemir, all given as basal supplementation, in the treatment of patients with type 2 diabetes.

RESEARCH DESIGN AND METHODS—We conducted an electronic search until February 2012, including online registries of ongoing trials and abstract books. All randomized controlled trials comparing ILPS with insulin glargine or detemir with a duration of ≥12 weeks were included.

RESULTS—We found four trials lasting 24–36 weeks involving 1,336 persons: three studies compared ILPS with glargine, and one trial compared ILPS with detemir. There was no significant difference in change in HbA_{1c} level between ILPS and comparators, in the proportion of patients achieving the HbA_{1c} goals of ≤6.5 or <7%, in weight change, or in daily insulin doses. There was no difference in overall hypoglycemia, but nocturnal hypoglycemia occurred significantly more with ILPS than with comparator insulins (mean difference 0.099 events/patient/30 days [95% CI 0.03–0.17]). In a prespecified sensitivity analysis comparing data obtained in patients who remained on their once-daily insulin regimen, not significantly different event rates for nocturnal hypoglycemia were observed between ILPS and comparator insulins (0.063 [−0.007 to 0.13]), and ILPS was associated with lower insulin dose (0.07 units/kg/day [0.05–0.09]).

CONCLUSIONS—There is no difference between ILPS and insulin glargine or detemir for targeting hyperglycemia, but nocturnal hypoglycemia occurred more frequently with ILPS than with comparator insulins. Nocturnal hypoglycemia was not significantly different in people who injected insulin once daily.

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Diabetes is one of the most common chronic diseases in nearly all countries. In 2011, there were 366 million people with diabetes, and this is expected to rise to 552 million by 2030, rendering previous estimates very conservative (1). Tight glycemic control to maintain an HbA_{1c} concentration of <7% is still recommended for many nonpregnant adults with diabetes to minimize the risk of long-term vascular complications (2). Unfortunately, more than one-half of individuals with type 2 diabetes are still not at goal. Data from the National Committee for Quality Assurance showed that ~40% of diabetic patients (both type 1 and type 2) achieved the HbA_{1c} goal of <7% in 2009 (3), while 43.8% of 415,320 Italian patients with type 2 diabetes met the HbA_{1c} goal in 2010 (4).

The introduction of a basal insulin preparation is advocated when lifestyle interventions and oral therapy with metformin no longer achieve the currently recommended HbA_{1c} goal (5). Because of the pharmacodynamic limitations of NPH insulin, two long-acting insulin analogs are currently available: insulin glargine and insulin detemir (6,7), while a third analog (insuIin lispro protamine suspension [ILPS]) is available in few countries (Italy, Spain, and Japan) (8). In clinical trials in type 2 diabetes, both insulin glargine and insulin detemir have been found to reduce the risks of overall and nocturnal hypoglycemia compared with NPH insulin; moreover, insulin detemir was associated with significantly less weight gain (9). No trial has compared ILPS with NPH insulin. A recent meta-analysis (10) comparing the effects of insulin detemir and insulin glargine in the treatment of patients with type 2 diabetes suggests that there is no overall clinically relevant difference in the efficacy or the safety between the use of these two analogs. However, only two of the four studies included in the meta-analysis (10) did effectively compare detemir and glargine as basal supplementation after failure of oral dugs. We did not identify any reviews that compared ILPS with insulin detemir or glargine in type 2 diabetic patients. Here, we perform a meta-analysis of the randomized controlled trials (RCTs) that assessed the effect of ILPS compared with insulin glargine or insulin detemir, all given as basal insulin supplementation, in the treatment of patients with type 2 diabetes in whom other diabetes medications have failed.

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RESEARCH DESIGN AND METHODS

Data sources

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist for reporting systematic reviews and meta-analyses (11). We searched Medline (until February 2012), Embase (until February 2012), the Cochrane Library, and CINAHL from inception to February 2012. The main search concepts were type 2 diabetes, HbA_{1c}, A1C, long-acting insulin analogs, basal insulin analogs, glargine, detemir, neutral protamine lispro, ILPS, RCTs, and clinical trials. We also reviewed reference lists of included articles, the U.S. Food and Drug Administration, and European Medicines Agency Web sites for the insulin analogs, as well as Web sites of public registries of clinical trials (clinicaltrials.gov, clinicalstudyresults.org, and controlled-trials.com) and abstract books. The electronic database search strategy for Medline is available in Supplementary Table 1.

Study selection

We included all RCTs comparing ILPS with insulin glargine or detemir if *1*) patients aged >18 years with a diagnosis of type 2 diabetes, as defined by criteria current at the time of the trial, were included; 2) RCT duration was ≥12 weeks; 3) basal analogs were given as add-on therapy in patients with suboptimal glycemic control while they were receiving stable doses of noninsulin diabetes medications; and *4*) data on HbA_{1c} change and the proportion of diabetic patients at HbA_{1c} targets at end point were reported. Trials were included irrespective of blinding, number of patients randomized, and language of the publication.

Two authors (D.G. and K.E.) independently screened the title or abstract or both of every record retrieved. All potentially relevant publications were investigated as full text. Returned articles were reviewed against inclusion and exclusion criteria. Risk of bias was assessed using the Cochrane Collaboration's risk of bias tool (12). Two authors (D.G. and K.E.) independently assessed each included trial. Disagreements were resolved by discussion.

Primary and secondary outcomes

Glycemic control and hypoglycemia were the primary outcomes. Although no trial included in this analysis considered hypoglycemia as the main outcome, we considered hypoglycemia as a primary end point, as it is associated with vascular events in clinical practice (13). We assessed change in HbA_{1c} level from baseline to study end point, the percentage of participants achieving HbA_{1c} goals of <7 and ≤6.5% at study end point, fasting glucose level at study end point, and rate of overall and nocturnal hypoglycemia. Hypoglycemia was defined as a symptomatic or asymptomatic event with plasma glucose <70–72 mg/dL and was classified as nocturnal if any episode occurred between bedtime and awaking. Secondary end points were weight change and insulin doses.

Data synthesis and analysis

Statistical heterogeneity across trials was tested by Cochran *Q* test. An α value of 0.10 was taken to indicate heterogeneity among trials for each analysis. Degree of heterogeneity for each analysis was presented with I^2 values (14). Fixed-effect models were used in all analyses unless there was evidence of heterogeneity. A random-effects model was used when evidence of heterogeneity was found (15). Risk ratios (RRs) were used as the meta-analytic measure of association for proportion of patients at HbA_{1c} targets (≤6.5 and <7.0%) and were calculated using the number of patients at target and number of patients in each trial group (i.e., 2 × 2 tables).

Changes from baseline in HbA_{1c}, body weight, daily insulin dose, and fasting glucose were analyzed as continuous variables. For these variables, weighted mean differences were used as a summary measure. For hypoglycemic events, we also recorded the mean difference between groups, along with its measure of dispersion. If a trial reported the number of episodes in each group or reported an event rate in a form other than episodes per patient per 30 days, we converted this information into episodes per patients per 30 days. We did not investigate publication bias using graphical or statistical methods owing to the small number of trials; accordingly, the power of these methods is limited and results from such analyses should be treated with considerable caution (16). We planned to perform three sensitivity analyses in order to explore the influence of the following factor on effect size: by repeating the analysis including patients who took a once-daily insulin dose, as in two studies (17,18), an additional daily insulin ILPS injection could be added by the study personnel, excluding the study of Arakaki et al. (19) reported in abstract form and including the three studies comparing ILPS with glargine (17,19,20). *P* values <0.05 were considered significant, and all reported *P* values are two sided. Data were analyzed with STATA, version 11.2 (Stata, College Station, TX).

RESULTS—Our search yielded 1,810 potentially relevant citations after exclusion of duplicate articles. Of these, the vast majority were excluded (non-RCT, mostly review articles, investigation of a nonrelevant question, and use of ILPS in insulin mixtures). Hand searching of the American Diabetes Association's and European Association for the Study of Diabetes' abstract books yielded one potentially relevant publication, resulting in one additional potentially relevant article. We could not identify other relevant studies by searching online registries of ongoing trials. Of the five potentially relevant trials, one was excluded because it compared ILPS with glargine in a basal-bolus insulin regimen. In conclusion, four studies comparing treatment with ILPS with treatment with insulin glargine or detemir in persons with type 2 diabetes were examined as full text (17–20) (Supplementary Fig. 1).

Altogether, 1,336 individuals were randomized and exposed to trial drugs in the included studies (Supplementary Tables 2 and 3). All studies had an open-label, parallel-group design; three were multinational and multicenter (17–19), and one was single center (20). None of the studies were double blinded, due to the visibly different properties of the comparators. One trial was performed in the U.S. and Puerto Rico (19); one in Argentina, Hungary, India, Republic of Korea, Mexico, Poland, Spain, Taiwan, and the U.S. (18); one in Brazil, Canada, India, South Korea, Poland, Russia, Spain, and the U.S. (17); and one in Italy (20). Three trials were sponsored by industry (17–19). All four trials had a so-called treat-to-target design, meaning that the basal insulin dose was systematically titrated according to predefined plasma glucose criteria. In all studies, insulin glargine was dosed once daily in the evening, and the same methodology was used for ILPS in two studies (19,20). Insulin detemir and ILPS were initiated once daily in the evening in two trials (17,18), but the titration algorithm allowed an additional dose in the morning if the predinner plasma

glucose value was above target while the fasting plasma glucose target had been achieved. In two studies (18,19), all previous glucose-lowering drugs were continued unchanged. In one study (20), patients receiving nighttime sulfonylurea before the study were switched to metformin; in the other study (17), patients discontinued rosiglitazone and if taking pioglitazone, reduced it at indicated doses, and all other oral agents were continued unchanged. Trial duration was 24–36 weeks. Two studies recruited people who had type 2 diabetes for at least 1 year (17,18) or >2 years (20), while the other study (19) stated the duration of diabetes (9.9 years). Two studies included patients from the age of 18 years (17,18), one study included persons aged 30–70 years (20), and one study included individuals aged 18–75 years (19). Mean duration of diabetes ranged from 7.8 to 9.9 years and mean age from 53.8 to 58 years. The studies' inclusion ranges for glycemic control were an HbA_{1c} level ≥7.0% or between ≥7.5 and ≤10.0%. Mean HbA_{1c} level at baseline ranged from 8.4 to 8.7%. Two studies included insulin-naive people only, i.e., patients who had not been treated with insulin prior to study participation (17,20). All studies included patients taking oral drugs—mostly metformin plus a sulfonylurea (100% [20], 82.5% [17], and 75.6% [18]); in one study (19), patients were treated with metformin with or without sulfonylurea or pioglitazone and exenatide. In no study were patients being treated with insulin before randomization.

In general, the quality of the evidence was low owing to low number of events, lack of hard end points, and lack of blinding. The overall risk of bias was high, as no studies were blinded; moreover, three studies did not describe random sequence generation or allocation concealment (17–19).

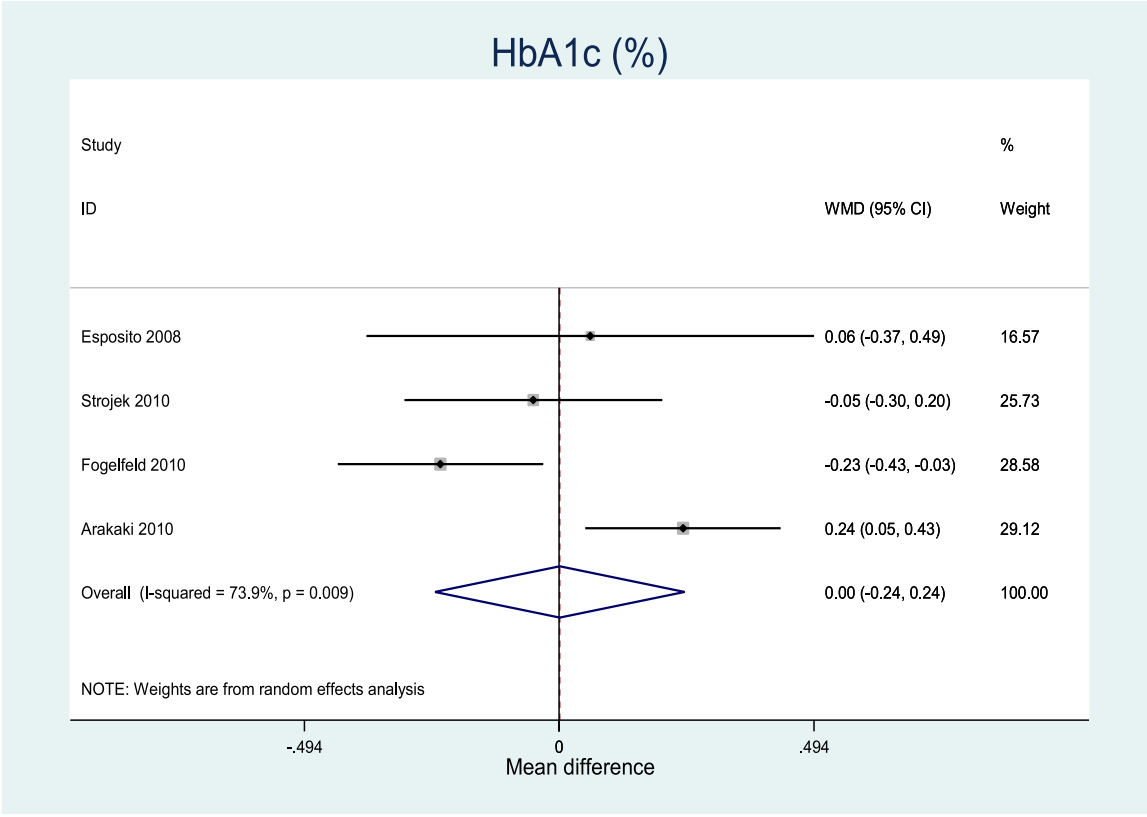
Meta-analysis of change in HbA_{1c} level between ILPS and comparators resulted in a null difference (0.00% [95% CI −0.24 to 0.24], $P = 0.99$), with substantial heterogeneity between studies ($I^2 = 74\%$, $P = 0.009$) (Fig. 1 and Table 1). There was no significant difference in mean HbA_{1c} change between ILPS and comparators when once-daily dosing of insulin was considered (0.08% [−0.04 to 0.20], with low heterogeneity: $I^2 = 37\%$, $P = 0.188$) or when the study reported in abstract form (19) was excluded (−0.135% [−0.28 to 0.01], $P = 0.071$) (Fig. 1 and Table 1). In the three studies comparing ILPS with glargine, there also was no significant difference in HbA_{1c} change (Table 2). The percentage of patients achieving HbA_{1c} target <7% at study end point was similar between ILPS and comparators in full studies (RR 0.99 [95% CI 0.87–1.12], no heterogeneity: $I^2 = 0\%$), in studies using once-daily insulin dosing (0.96 [0.84–1.08], $I^2 = 0\%$), and in the analysis excluding the abstract (1.065 [0.90–1.25], $I^2 = 0\%$). Similar results were obtained for the percentage of patients achieving the HbA_{1c} target ≤6.5% (Table 1). Similarly, the percentages of patients achieving the HbA_{1c} targets of ≤6.5 or <7% at study end point were similar between ILPS and glargine (Table 2). There was no statistical significant difference in fasting glucose at study end point between ILPS and comparators (mean difference of 2.05 mg/dL [95% CI −0.301 to 4.4], $P = 0.087$), with no significant heterogeneity ($P = 0.116$, $I^2 = 49\%$) (Table 1). Similarly, there was no difference in end point glucose between ILPS and glargine (Table 2).

There was no statistically significant difference in the event rate for overall hypoglycemia: mean difference was 0.17 events/patient/30 days (95% CI −0.14 to 0.48, heterogeneity: $I^2 = 56\%$, $P = 0.076$) (Table 1). There also was no statistically significant difference in the event rate of overall hypoglycemia between ILPS and comparators in once-daily dosing analysis (−0.01 events/patient/30 days [95% CI −0.20 to 0.19], with no heterogeneity: $I^2 = 23\%$, $P = 0.270$) (Table 1) or between ILPS and glargine (Table 2). There was a significant difference in overall hypoglycemia (higher in ILPS users) in the analysis excluding the abstract (mean difference 0.23 events/patient/30 days [95% CI 0.02–0.45], with moderate heterogeneity: $I^2 = 53\%$) (Table 1). Nocturnal hypoglycemia occurred significantly more with ILPS in the full studies analysis (mean difference 0.10 events/patient/30 days [0.03–0.17]), but similar event rates were observed in both once-daily dosing analysis between ILPS and comparator insulins (0.063 events/patient/30 days [−0.007 to 0.13], with no heterogeneity: $I^2 = 0\%$, $P = 0.403$) (Fig. 2 and Table 2) and the analysis excluding the abstract (0.079 events/patient/30 days [−0.00 to 0.158], $I^2 = 36\%$) (Table 1). Compared with glargine groups, nocturnal hypoglycemia occurred more frequently in ILPS groups in full studies analysis (0.085 events/patient/30 days, $P = 0.022$) but not in once-daily dosing analysis (0.06 events/patient/30 days, $P = 0.095$) (Table 2 and Supplementary Fig. 2).

There was no statistically significant difference in weight change between ILPS and comparators in the full analysis (0.223 kg [95% CI −0.81 to 1.26]), in analysis of studies using once-daily insulin dosing (−0.34 kg [−1.21 to 0.56]), or in the analysis excluding the abstract (0.431 kg [−0.81 to 1.67]) (Table 1). Weight gain was greater in glargine than in ILPS groups and reached a statistically significant difference in analysis of studies using once-daily insulin dosing (−0.76 kg [−1.27 to −0.26], $P = 0.003$) (Table 2).

There was no statistically significant difference in daily insulin dose between ILPS and comparators either in the full analysis (−0.04 units/kg [95% CI −0.09 to 0.01]) or in the analysis excluding the abstract (−0.03 units/kg [−0.09 to 0.04]) (Table 1). In the analysis of studies using once-daily dosing, the mean difference in daily basal insulin dose was 0.067 units/kg (95% CI 0.05–0.09) ($P < 0.001$) in favor of insulin ILPS, with low heterogeneity ($I^2 = 21\%$). Daily insulin dose was lower with ILPS than with glargine, with significant difference in analysis of studies using once-daily insulin dosing (−0.076 units/kg, $P < 0.0001$) (Table 2 and Supplementary Fig. 3).

CONCLUSIONS—This meta-analysis included four RCTs comparing the effects of ILPS to insulin glargine or detemir in patients with type 2 diabetes who had failed on previous anti–diabetes medications. Overall, pooling all four studies resulted in a not statistically significant difference in glycemic control between the two treatment groups, as detailed by HbA_{1c} change, the percentage of patients achieving the HbA_{1c} goals (<7 and ≤6.5%), and end-point fasting glucose. The results also showed a not statistically significant difference in overall hypoglycemia, although nocturnal hypoglycemia was less frequent in association with comparator insulins than ILPS: this translates to 1.2 fewer nocturnal glycemia episodes/patient/year with glargine or detemir therapy compared with ILPS. There was no difference in weight change or daily insulin dose between the two treatment groups. The results of the meta-analysis excluding the study of Arakaki et al. (19) reported in abstract form showed similar results, except for overall hypoglycemia (significantly higher with ILPS than comparators) and nocturnal hypoglycemia



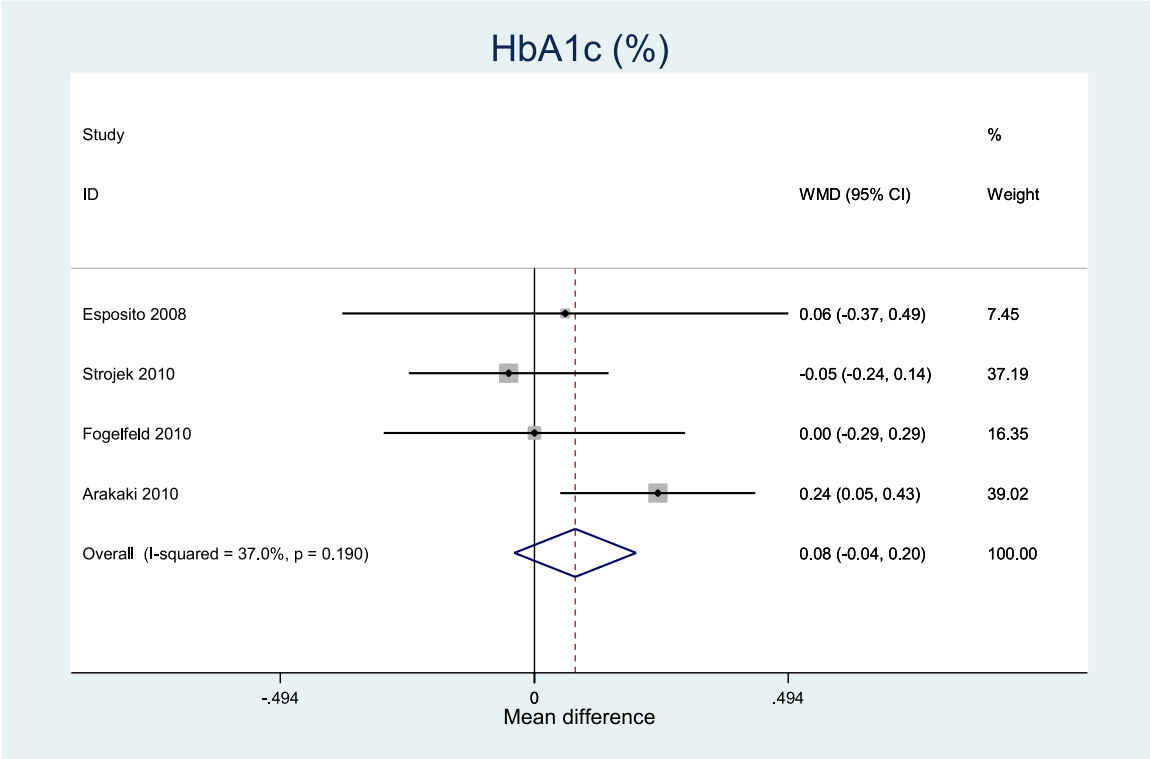


Figure 1—*Change in HbA$_{1c}$ level from baseline was not different between ILPS and comparators (glargine or detemir) either in full analysis* (top panel) *or in sensitivity analysis comparing patients who remained on their once-daily insulin regimen* (bottom panel). *Comparator insulins better on the right and ILPS better on the left. WMD, weighted mean difference. (A high-quality color representation of this figure is available in the online issue.)*

Table 1—*Comparison of ILPS with comparator insulins (glargine and detemir): full analysis, once-daily dose,* and analysis excluding the abstract of Arakaki (ref. 19)§*

Variable	Summary measure	Type	*P* heterogeneity test (I^2)	Estimate	95% CI	*P*
HbA_{1c} change from baseline (%)	MD	RE	0.009 (74%)	0.001	−0.240 to 0.243	0.992
HbA_{1c} <7.0%	RR	FE	0.403 (0%)	0.987	0.873–1.116	0.837
HbA_{1c} ≤6.5%	RR	FE	0.721 (0%)	1.049	0.849–1.296	0.660
Fasting glucose at end point (mg/dL)	MD	FE	0.116 (49%)	2.050	−0.301 to 4.402	0.087
All hypoglycemia (events/pt/30d)	MD	RE	0.076 (56%)	0.172	−0.138 to 0.482	0.276
Nocturnal hypoglycemia (events/pt/30d)	MD	FE	0.248 (27%)	0.100	0.031–0.168	0.005
Weight change (kg)	MD	RE	<0.001 (85%)	0.223	−0.814 to 1.259	0.674
Insulin dose (units/kg)	MD	RE	0.006 (76%)	−0.041	−0.092 to 0.010	0.114
HbA_{1c} change from baseline (%)*	MD	FE	0.190 (37%)	0.080	−0.039 to 0.198	0.188
HbA_{1c} <7.0%*	RR	FE	0.542 (0%)	0.958	0.845–1.087	0.507
HbA_{1c} ≤6.5%*	RR	FE	0.486 (0%)	1.080	0.869–1.342	0.487
All hypoglycemia (events/pt/30d)*	MD	FE	0.270 (23%)	−0.010	−0.208 to 0.189	0.926
Nocturnal hypoglycemia (events/pt/30d)*	MD	FE	0.403 (0%)	0.063	−0.007 to 0.134	0.079
Weight change (kg)*	MD	RE	0.010 (73%)	−0.343	−1.215 to 0.529	0.441
Insulin dose (units/kg)*	MD	FE	0.282 (21%)	−0.067	−0.088 to −0.046	<0.001
HbA_{1c} change from baseline (%)§	MD	FE	0.351 (4.6%)	−0.135	−0.281 to 0.012	0.071
HbA_{1c} <7%§	RR	FE	0.793 (0%)	1.065	0.905–1.253	0.451
HbA_{1c} ≤6.5%§	RR	FE	0.867 (0%)	1.137	0.873–1.481	0.341
All hypoglycemia (events/pt/30d)§	MD	FE	0.119 (53%)	0.236	0.022–0.450	0.031
Nocturnal hypoglycemia (events/pt/30d)§	MD	FE	0.211 (36%)	0.079	−0.000 to 0.158	0.051
Weight change (kg)§	MD	RE	0.001 (85%)	0.431	−0.817 to 1.679	0.499
Insulin dose (units/kg)§	MD	RE	0.008 (79%)	−0.030	−0.099 to 0.040	0.407

events/pt/30d, events/patient/30 days; FE, fixed effect; MD, mean difference; RE, random effect. *Four studies (refs. 17–20). §Three studies (refs. 17,18,20).

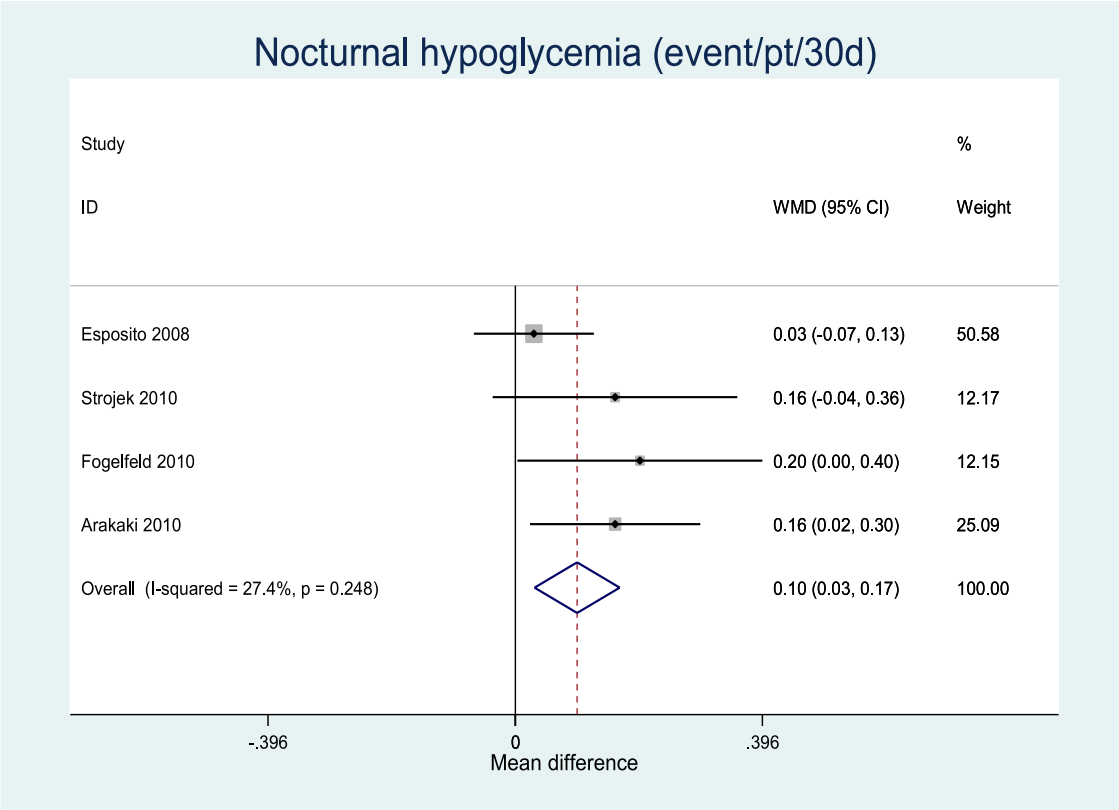
(not significantly different between ILPS and comparators).

The results of the meta-analysis comparing ILPS with glargine (three studies) yielded similar results, with no statistically significant differences in overall glycemic control (HbA_{1c} change, HbA_{1c} targets, and fasting glucose at end point), overall hypoglycemia, weight change, or daily insulin dose. Nocturnal hypoglycemia also occurred less frequently with glargine compared with ILPS, with a difference of 0.085 episodes/patient/30 days, which translates to a difference of approximately one episode per patient per year. In all four studies, insulin glargine was dosed once daily in the evening. In two studies, insulin ILPS was initiated once daily in the evening with the option of an additional dose in the morning based on failure to achieve a prespecified predinner plasma glucose target. However, the differences between ILPS and the other two basal insulin analogs should be defined on the basis of a similar insulin administration regimen. This problem was addressed by the sensitivity analysis comparing data obtained in patients who remained on their once-daily insulin regimen: no statistically significant difference between

Table 2—*Comparison of ILPS with glargine: full analysis and once-daily dose**

Variable	Summary measure	Type	*P* of heterogeneity test (I^2)	Estimate	95% CI	*P*
HbA_{1c} change from baseline (%)	MD	FE	0.184 (41%)	0.126	−0.017 to 0.269	0.083
HbA_{1c} <7.0%	RR	FE	0.419 (0%)	0.947	0.828–1.084	0.433
HbA_{1c} ≤6.5%	RR	FE	0.736 (0%)	0.987	0.771–1.265	0.920
Fasting glucose at end point (mg/dL)	MD	RE	0.052 (66.2%)	1.75	−2.87 to 6.36	0.458
All hypoglycemia (events/pt/30d)	MD	RE	0.554 (0%)	0.049	−0.161 to 0.258	0.648
Nocturnal hypoglycemia (events/pt/30d)	MD	FE	0.226 (32.8%)	0.085	0.012–0.158	0.022
Weight change (kg)	MD	FE	0.788 (0%)	−0.244	−0.751 to 0.263	0.346
Insulin dose (units/kg)	MD	RE	0.003 (83%)	−0.032	−0.098 to 0.035	0.354
HbA_{1c} change from baseline (%)*	MD	FE	0.110 (54.8%)	0.095	−0.034 to 0.224	0.153
HbA_{1c} <7.0%*	RR	FE	0.348 (5.3%)	0.954	0.834–1.092	0.497
HbA_{1c} ≤6.5%*	RR	FE	0.309 (14.8%)	1.062	0.835–1.350	0.624
All hypoglycemia (events/pt/30d)*	MD	FE	0.177 (42%)	−0.029	−0.236 to 0.179	0.782
Nocturnal hypoglycemia (events/pt/30d)*	MD	FE	0.239 (30%)	0.061	−0.011 to 0.133	0.095
Weight change (kg)*	MD	FE	0.236 (30.7%)	−0.762	−1.266 to −0.257	0.003
Insulin dose (units/kg)*	MD	FE	0.614 (0%)	−0.076	−0.099 to −0.052	<0.0001

events/pt/30d, events/patient/30 days; FE, fixed effect; MD, mean difference; RE, random effect. *Three studies (refs. 17,19,20).



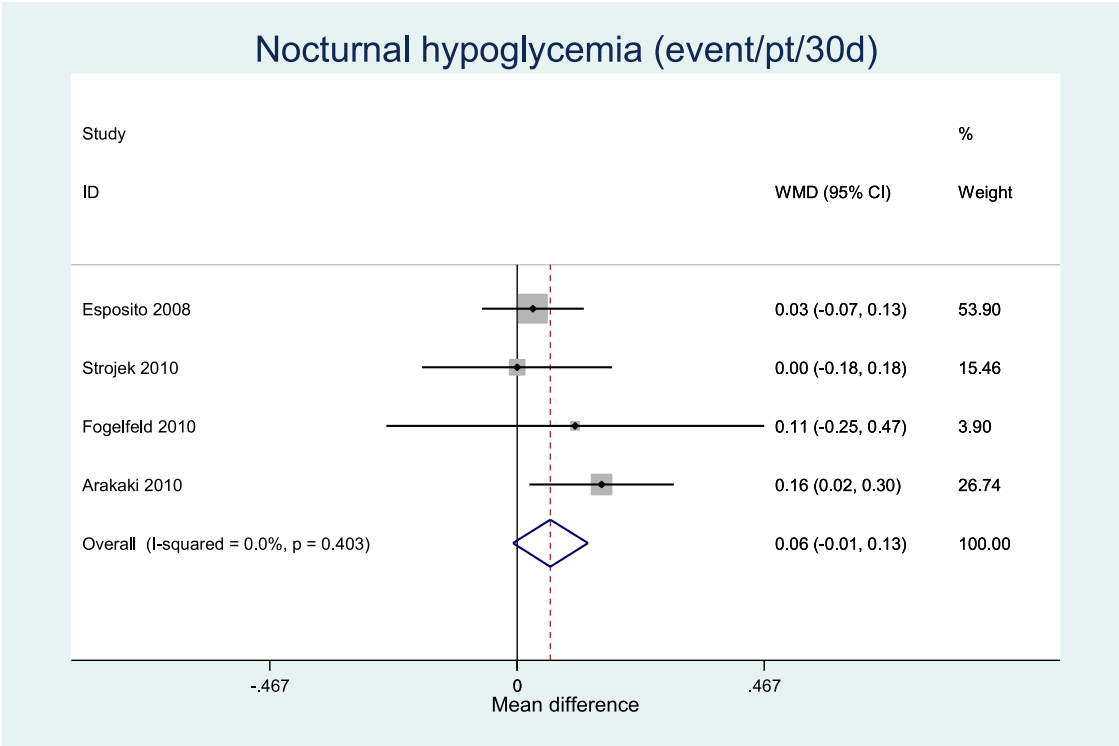


Figure 2—*Nocturnal hypoglycemia was significantly more frequent in patients assigned to ILPS than comparators (glargine or detemir) in full analysis* (top panel) *but not in sensitivity analysis comparing patients who remained on their once-daily insulin regimen* (bottom panel). *Comparator insulins better on the right and ILPS better on the left. WMD, weighted mean difference. (A high-quality color representation of this figure is available in the online issue.)*

ILPS or comparator insulins in any of the efficacy and safety parameters was found, including nocturnal hypoglycemia. On the other hand, patients who remained on their once-daily ILPS insulin, compared with those assigned to once-daily glargine or detemir, presented a lower daily insulin dose of 0.067 units/kg. The difference in required insulin dose was slightly greater when ILPS was compared with glargine (three studies) and averaged 0.076 units/kg; this was also associated with significantly less weight gain of 0.76 kg with ILPS. So, when data were analyzed from a patient perspective, which should preferably be once daily (21), ILPS was associated with reduction of daily insulin dose compared with glargine and detemir and also with reduced weight gain compared with glargine.

Patients with type 2 diabetes are typically treated initially with oral anti–diabetes agents; however, given the chronic and progressive nature of type 2 diabetes, ultimately most patients will require insulin therapy to maintain glycemic control. Although insulin has traditionally been used as a final treatment option, the introduction of insulin is advocated as a second-line treatment after lifestyle changes and metformin fail to reach or maintain an HbA_{1c} of <7% in type 2 diabetes (5). There are still many uncertainties about the optimal insulin treatment regimens for type 2 diabetes (22), but the long-acting insulin analogs seem promising. Even today, there are barriers to initiation of insulin therapy in type 2 diabetes, as many patients who could benefit from insulin therapy do not receive it in a timely manner (23,24). Therefore, type 2 diabetic patients should be offered the least intrusive insulin regimen with the least number of side effects. According to the most recent Position Statement of the American Diabetes Association and the European Association for the Study of Diabetic recommendations (21), the most convenient strategy for starting insulin therapy in type 2 diabetic patients is with a single injection of basal insulin.

The main limitation of all four RCTs was lack of blinding. Although all trials were adequately powered and had acceptable attrition rates and although most of the prespecified outcomes have been reported, all studies were open label, which implies that the risk of bias was considered high. In addition, outcome measures did not include health-related quality of life, treatment satisfaction, or costs. Owing to the short study durations (<1 year), no study was designed or adequately powered to investigate mortality or vascular complications. Finally, three of the four studies were sponsored by the manufacturer of ILPS.

In conclusion, our analyses suggest that there is no clinically relevant difference in the efficacy of ILPS versus insulin glargine or detemir for targeting hyperglycemia, but ILPS was associated with more nocturnal hypoglycemia than comparators. The comparison of ILPS with insulin glargine or detemir using a once-daily dosing regimen shows a nonsignificant difference in HbA_{1c} change from baseline and hypoglycemia.

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K.E. participated in the conception and design of the study; analyzed and interpreted data; drafted the manuscript; critically revised the manuscript for important intellectual content; had final approval of the manuscript; provided study materials; obtained funding; provided administrative, technical, or logistical support; and collected and assembled data. P.C. analyzed and interpreted data, critically revised the manuscript for important intellectual content, provided statistical expertise, and collected and assembled data. A.C. analyzed and interpreted data, critically revised the manuscript for important intellectual content, and had final approval of the manuscript. M.P. and M.R.I. analyzed and interpreted data, critically revised the manuscript for important intellectual content, had final approval of the manuscript, and provided administrative, technical, or logistical support. D.G. participated in the conception and design of the study; analyzed and interpreted data; drafted the manuscript; critically revised the manuscript for important intellectual content; had final approval of the manuscript; provided study materials; provided statistical expertise; obtained funding; provided administrative, technical, or logistical support; and collected and assembled data.

D.G. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

References

1. Whiting DR, Guariguata L, Weil C, Shaw J. IDF diabetes atlas: global estimates of the prevalence of diabetes for 2011 and 2030. Diabetes Res Clin Pract 2011;94:311–321
2. American Diabetes Association. Standards of medical care in diabetes—2012. Diabetes Care 2012;35(Suppl. 1):S11–S63
3. National Committee for Quality Assurance. The state of health care quality [article online], 2010. Washington, DC, National Committee for Quality Assurance. Available from http://www.ncqa.org/portals/0/state%20of%20health%20care/2010/sohc%202010%20-%20full2.pdf. Accessed 14 February 2012
4. Cimino A, Fava D, Giorda C, et al. AMD annals 2010: quality indicators of diabetes care in Italy [article online], 2010. Available from http://www.infodiabetes.it/files/Annali_2010_inglese_II.pdf. Accessed 29 February 2012
5. Nathan DM, Buse JB, Davidson MB, et al.; American Diabetes Association; European Association for Study of Diabetes. Medical management of hyperglycemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy: a consensus statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care 2009;32:193–203
6. Heinemann L, Linkeschova R, Rave K, Hompesch B, Sedlak M, Heise T. Time-action profile of the long-acting insulin analog insulin glargine (HOE901) in comparison with those of NPH insulin and placebo. Diabetes Care 2000;23:644–649
7. Plank J, Bodenlenz M, Sinner F, et al. A double-blind, randomized, dose-response study investigating the pharmacodynamic and pharmacokinetic properties of the long-acting insulin analog detemir. Diabetes Care 2005;28:1107–1112
8. Hompesch M, Ocheltree SM, Wondmagegnehu ET, et al. Pharmacokinetics and pharmacodynamics of insulin lispro protamine suspension compared with insulin glargine and insulin detemir in type 2 diabetes. Curr Med Res Opin 2009;25:2679–2687
9. Horvath K, Jeitler K, Berghold A, et al. Long-acting insulin analogues versus NPH insulin (human isophane insulin) for type 2 diabetes mellitus. Cochrane Database Syst Rev 2007;2:CD005613
10. Swinnen SG, Simon AC, Holleman F, Hoekstra JB, Devries JH. Insulin detemir versus insulin glargine for type 2 diabetes mellitus. Cochrane Database Syst Rev 2011;7:CD006383
11. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. Ann Intern Med 2009;151:W65–W94
12. Higgins JPT, Green S, Eds. Cochrane handbook for systematic reviews of interventions version 5.0.0 [Internet], 2008. Available from www.cochrane-handbook.org. Accessed 14 February 2012
13. Zhao Y, Campbell CR, Fonseca V, Shi L. Impact of hypoglycemia associated with antihyperglycemic medications on vascular risks in veterans with type 2 diabetes. Diabetes Care 2012;35:1126–1132

14. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med 2002;21:1539–1558
15. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986;7: 177–188
16. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997;315: 629–634
17. Strojek K, Shi C, Carey MA, Jacober SJ. Addition of insulin lispro protamine suspension or insulin glargine to oral type 2 diabetes regimens: a randomized trial. Diabetes Obes Metab 2010;12:916–922
18. Fogelfeld L, Dharmalingam M, Robling K, Jones C, Swanson D, Jacober SA. A randomized, treat-to-target trial comparing insulin lispro protamine suspension and insulin detemir in insulin-naive patients with Type 2 diabetes. Diabet Med 2010;27: 181–188
19. Arakaki RF, Blevins TC, Liljenquist DR, et al. Efficacy and safety of insulin lispro protamine suspension versus insulin glargine added to oral antihyperglycemic medications and exenatide in patients with type 2 diabetes (abstract). Diabetologia 2010; 53(Suppl. 1):S-390
20. Esposito K, Ciotola M, Maiorino MI, et al. Addition of neutral protamine lispro insulin or insulin glargine to oral type 2 diabetes regimens for patients with suboptimal glycemic control: a randomized trial. Ann Intern Med 2008;149:531–539
21. Inzucchi SE, Bergenstal RM, Buse JB, et al. Management of hyperglycemia in type 2 diabetes: a patient-centered approach: Position Statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care 2012;35:1364–1379
22. Giugliano D, Maiorino MI, Bellastella G, Chiodini P, Ceriello A, Esposito K. Efficacy of insulin analogs in achieving the hemoglobin A1c target of <7% in type 2 diabetes: meta-analysis of randomized controlled trials. Diabetes Care 2011;34:510–517
23. Peyrot M, Rubin RR, Lauritzen T, et al.; International DAWN Advisory Panel. Resistance to insulin therapy among patients and providers: results of the cross-national Diabetes Attitudes, Wishes, and Needs (DAWN) study. Diabetes Care 2005;28:2673–2679
24. Karter AJ, Subramanian U, Saha C, et al. Barriers to insulin initiation: the translating research into action for diabetes insulin starts project. Diabetes Care 2010; 33:733–735