IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

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Long-acting insulin analogues in the treatment of diabetes mellitus type 2[1]

Executive Summary

[1] Translation of the executive summary of the final report "Langwirksame Insulinanaloga zur Behandlung des Diabetes mellitus Typ 2" (Version 1.1; Status: 26.02.2009). Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

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Long-acting insulin analogues in the treatment of diabetes mellitus type 2

Executive summary

Background

The Federal Joint Committee commissioned the Institute for Quality and Efficiency in Health Care to conduct a benefit assessment of long-acting insulin analogues (LAIAs) in the treatment of diabetes mellitus type 2.

Research question

The aims of this research were:

- the benefit assessment of long-term therapy with an LAIA (insulin glargine or insulin detemir) compared with treatment with a longer-acting insulin based on human insulin;
- the benefit assessment of LAIAs compared with each other,

in each case in patients with diabetes mellitus type 2.

The main focus of the assessment was on patient-relevant therapy goals.

The benefit assessment was based on the comparison of the desired and undesired effects of the individual drugs.

Methods

The assessment was performed on the basis of randomized controlled trials (RCTs) investigating the research questions outlined above. For this purpose, a systematic literature search in the databases MEDLINE, EMBASE, and CENTRAL was performed (coverage up to June 2008). In addition, the reference lists of relevant secondary publications (systematic reviews, HTA reports) were screened, as well as study and study results registries, and publicly accessible drug approval documents. Moreover, the manufacturers of insulin glargine (Sanofi-Aventis) and insulin detemir (Novo Nordisk) were asked to provide information on relevant published or unpublished studies.

The report plan of this benefit assessment plus Amendment 1 to the report plan were published in June 2007; interested persons and parties were invited to submit comments (hearing). Unclear aspects of the written comments were discussed on 30 August 2007 in a scientific debate. The final report plan was subsequently prepared with consideration of the comments received and published in January 2008.

RCTs lasting at least 24 weeks were included, in which one of the 2 LAIAs named above was investigated, either compared with a longer-acting insulin based on human insulin or with the other LAIA. The literature screening was conducted by 2 reviewers independently of one another. After an assessment of study quality, the results of the single trials were collated according to therapy goals and outcomes. IQWiG's preliminary assessment, the preliminary report, was published on the Internet and interested persons and parties were asked to submit comments (hearing).

Unclear aspects of these written comments were discussed in a scientific debate on 17 June 2008. The current final report was subsequently produced considering the comments submitted.

Results

Results of the literature search

A total of 18 studies were considered in the benefit assessment; 13 of these studies had already been published. The bibliographic literature search resulted in a total of 13 publications on 10 relevant studies. In a search update, 2 further relevant studies already published were identified in study registries and were included on the basis of the publication and the study synopsis. The search of study lists provided by the manufacturers resulted in the detection of 6 further relevant studies, of which one had already been published and 5 were still unpublished. The clinical study reports (CSRs) of these studies were requested. As main points in the publications remained unclear, the CSRs of the published studies were also requested. All requested CSRs were provided by the manufacturers.

Interventions

Of the studies included, 15 investigated the comparison between an LAIA and neutral protamine Hagedorn (NPH) insulin, a longer-acting (intermediate-acting) insulin based on human insulin (insulin glargine: 9 studies; insulin detemir: 6 studies). The other 3 studies were direct comparative studies between the 2 LAIAs. In a total of 11 studies, the study drugs were investigated in a treatment scheme with basal insulin in combination with oral antidiabetics (OADs); in 6 studies, patients were treated within the framework of an intensified insulin therapy. In one study insulin glargine and NPH insulin were used in various treatment schemes. Of the 18 studies included, with a treatment period of 5 years only a single study was a long-term study designed to investigate a patient-relevant outcome (changes in the ocular fundus). The other 17 studies were short-term studies with a treatment period of 6 to 12 months.

Study and publication quality

None of the studies included in the benefit assessment was blinded, which would anyway have been very difficult to perform due to the different appearance of the drugs and the different effective concentrations. However, no efforts were undertaken to compensate this, for example, through a blinded assessment of outcomes. Because of this, individual outcomes were subject to a high bias potential. Moreover, it should be emphasized that in 7 of the 9 studies comparing insulin glargine and NPH insulin, the latter was only administered once daily, even though in practice the number of NPH insulin injections per day is often adapted. As a result, the relevance of these studies is generally limited.

Outcomes

The studies included did not contain relevant data on most of the outcomes specified in the report plan, e.g., “late complications of diabetes”, “hyperosmolar and ketoacidotic coma”, and “symptoms caused by chronic hyperglycaemia”.

Cardiac morbidity

Due to its length, Study 4016 comparing insulin glargine and NPH insulin was able to supply relevant data on cardiac events recorded within the framework of the safety evaluation. No noticeable differences between treatment groups were shown (serious adverse events [SAEs]: 13.4% [G] vs. 11.7% [NPH]; RR 1.14; 95% CI [0.83; 1.58]).

Mortality

Overall, the data provide no indications of an advantage of any therapy option with regard to mortality.

Changes in the ocular fundus

Overall, no clear statement can be made on the basis of studies with a treatment period of up to a year comparing insulin glargine and NPH insulin, due to scarce and partially heterogeneous data. Overall, the 5-year study (No. 4016) recommended by the FDA, which was designed to investigate this parameter, provides no indications of greater harm caused by insulin glargine compared with NPH insulin. Due to its 5-year treatment period, this study is of higher relevance when compared with the others, and consequently, the overall data provide no indications of a difference between the 2 treatment options for the comparison of insulin glargine and NPH insulin.

Regarding this outcome, no noticeable differences between treatment groups were shown in any of the studies comparing insulin detemir and NPH insulin, or directly comparing the 2 LAIAs with each other.

Hospitalization for any cause

Overall, the data on this outcome were insufficient. Data on such SAEs leading to hospitalization were only found for the comparison of insulin glargine and NPH insulin; no noticeable differences between treatment groups were shown.

Conjoint assessment of severe / serious hypoglycaemia and long-term blood glucose lowering

The conjoint assessment was on the one hand performed on the basis of aggregated data from CSRs and on the other, on the basis of individual patient data (IPD) analyses of hypoglycaemic episodes, adjusted for HbA1c values.

In the 5-year Study 4016 comparing insulin glargine and NPH insulin, a statistically significant difference was shown in favour of insulin glargine regarding severe hypoglycaemic episodes (p=0.0208), with comparable blood glucose (BG) lowering. This was confirmed by the IPD analyses (OR: 0.51; 95% CI [0.27; 0.93]), and resulted in the indication of an advantage for insulin glargine. In the meta-analysis of studies in which insulin glargine and NPH insulin were in each case administered once daily in the evenings in a treatment scheme with basal insulin in combination with OADs, the assessment remained unclear due to conflicting information. For the comparison insulin glargine (once daily, mornings) and NPH insulin (once daily, evenings) in a treatment scheme with basal insulin and OADs, a statistically significant and relevant stronger HbA1c level lowering with insulin glargine was shown (MD glargine vs. NPH: -0.40%; 95% CI: [-0.61; -0.19]). In contrast, in patients

receiving insulin glargine, no noticeable differences with regard to severe hypoglycaemic episodes, as well as statistically significantly fewer severe nocturnal hypoglycaemic episodes were shown (0% [G] vs. 1.8% [NPH]; p=0.0444). In the conjoint assessment, this resulted in a limited indication and an indication of a superiority of insulin glargine with regard to severe hypoglycaemia and nocturnal hypoglycaemia, respectively. The IPD analyses did not deliver additional information. In the other treatment schemes investigated comparing insulin glargine and NPH insulin, no significant differences between treatment groups were shown.

In the comparison of insulin detemir and NPH insulin (in each case administered twice daily in the mornings and evenings in combination with OADs) numerically fewer severe and statistically significantly fewer serious hypoglycaemic episodes occurred with insulin detemir (severe hypoglycaemia: 0.4% [D] vs. 2.5% [NPH]; p=0.069; serious hypoglycaemia: 0% [D] vs. 2.1% [NPH]; p=0.025). However, this result was not confirmed in the IPD analysis. No noticeable differences between treatment groups were shown in the other investigated treatment schemes comparing insulin detemir and NPH insulin.

In the comparison of insulin detemir and insulin glargine, no relevant differences were shown in the conjoint assessment of long-term BG lowering and the occurrence of severe hypoglycaemia, neither on the basis of aggregated data nor IPD analyses.

Conjoint assessment of non-severe hypoglycaemia and long-term blood glucose lowering

For non-severe hypoglycaemic episodes also, the conjoint assessment was undertaken based on aggregated data and on IPD analyses of hypoglycaemic episodes, adjusted for HbA1c values. Only those events that were defined by means of a combination of hypoglycaemic symptoms and a confirming BG measurement below a specified level were considered to have sufficient certainty of measurement and were included in the evaluation. Due to the high bias potential of the outcome “non-severe hypoglycaemia” in the uniformly open-label studies, an adjusted limit was specified for this outcome in order to control for potential bias (upper limit of the 95% CI of the odds ratio < 0.75). Only effects for which the 95% CI lay completely below 0.75 were seen as being large enough not to be accounted for by systematic bias alone.

In the meta-analysis of the 8 studies in which insulin glargine and NPH insulin were used (in each case once daily in the evenings in combination with OADs), on the basis of aggregated data a sufficiently large difference was shown in favour of insulin glargine with regard to non-severe nocturnal hypoglycaemia (OR: 0.56; 95% CI [0.46; 0.69]), with comparable HbA1c lowering. This result was confirmed by IPD analyses (OR: 0.52; 95% CI [0.43; 0.62]). In the one study comparing insulin glargine (once daily, mornings) and NPH insulin (once daily, evenings), a sufficiently large effect was shown with regard to non-severe nocturnal hypoglycaemia, both on the basis of aggregated data and of IPD analyses (aggregated data: 8.0% [G] vs. 27.9% [NPH], OR: 0.23; 95% CI [0.13; 0.39]; IPD analyses: OR: 0.20; 95% CI [0.11; 0.34]). However, none of these studies included therapy optimization for NPH insulin, so that one cannot assume a fair comparison of the treatments. For the other treatment schemes investigated, no significant differences were shown between treatment groups.

In the only study comparing insulin detemir and NPH insulin (in each case twice daily in a treatment scheme with basal insulin in combination with OADs), on the basis of aggregated

data a sufficiently large effect in favour of insulin detemir was shown both for overall non-severe hypoglycaemia and for non-severe nocturnal hypoglycaemia (overall non-severe hypoglycaemia: 57.0% [D] vs. 78.2% [NPH], OR: 0.37, 95% CI [0.25; 0.55]; non-severe nocturnal hypoglycaemia: 26.2% [D] vs. 44.1% [NPH], OR: 0.45, 95% CI [0.31; 0.67]). In each case, these results were confirmed in the IPD analyses (overall non-severe hypoglycaemia – OR: 0.35; 95% CI [0.23; 0.53]; non-severe nocturnal hypoglycaemia – OR: 0.45; 95% CI [0.31; 0.67]). In the comparison between insulin detemir and NPH insulin (in each case once daily in the evenings in a treatment scheme with basal insulin in combination with OADs), in one of the 2 studies (No. 1337) a superiority of insulin detemir with regard to non-severe nocturnal hypoglycaemia was shown based on sufficiently large effects in the IPD analysis (OR: 0.32; 95% CI [0.17; 0.61]). This result was not questioned by the result of the second study (No. 1477) on this treatment scheme. Regarding the overall rate of non-severe hypoglycaemia, the IPD analyses in Study 1337 also showed a sufficiently large effect in favour of insulin detemir (OR: 0.38; 95% CI [0.23; 0.61]). However, this result was questioned by the results of Study 1477, in which no noticeable differences between treatment groups were shown. Because of this, proof of an advantage of one of the 2 therapy options was not shown with regard to this outcome. For intensified insulin therapy, no relevant differences between treatment groups were shown with regard to non-severe hypoglycaemia.

In the comparison of insulin detemir and insulin glargine, no relevant differences were shown in the conjoint assessment of long-term BG lowering and the occurrence of non-severe hypoglycaemic episodes, neither on the basis of aggregated data nor on the basis of IPD analyses.

Health-related quality of life

Overall, only 4 studies reported data on the outcome “health-related quality of life” (QoL) and in most cases, the instruments applied (W-BQ[2], DHP-18[3]) only covered some sections of QoL. Only the questionnaire SF-36v2,[4] which was used in one study, reflected all sections of QoL.

A statistically significant difference between treatment groups was only shown in one of the 4 studies. In this study comparing insulin detemir and NPH insulin (in each case within the framework of intensified insulin therapy), the SF-36v2 was used. A statistically significant difference in favour of insulin detemir was only shown for the dimension “mental health” (group difference of the change from baseline to end of study: 5.32; 95% CI [0.48; 10.15]). Due to the very wide CI, about half of which lay below the minimal important difference (MID), the relevance of this difference is unclear. This result was not assessed as an indication of an advantage of insulin detemir. No noticeable differences between treatment groups were shown in other studies.

[2] Well-being Questionnaire
[3] Diabetes Health Profile
[4] Short-Form Health Survey Version 2.0

Treatment satisfaction

Treatment satisfaction was investigated in 5 studies comparing insulin glargine and NPH insulin and in 3 studies comparing insulin detemir and NPH insulin; the instruments applied were the DTSQs,[5] DTSQc,[6] and the ITSQ-J.[7] In 2 studies comparing insulin glargine and insulin detemir, treatment satisfaction was investigated by means of the ITSQ.

In the studies comparing insulin glargine and NPH insulin, a statistically significant difference in favour of insulin glargine was only shown in the meta-analysis of studies in which a treatment scheme with basal insulin in combination with OADs was used (SMD with Cohen's d -0.11; 95% CI [-0.20; -0.02]). However, the relevance of this effect was questionable. In addition, due to the high bias potential, the effect was regarded as too small not to be accounted for by bias alone. For these reasons, no indication of an advantage of one the 2 treatment options could be inferred. The study on intensified insulin therapy did not show any noticeable differences between insulin glargine and NPH insulin.

Only one study comparing insulin detemir and NPH insulin within the framework of intensified insulin therapy showed a statistically significant difference in favour of insulin detemir (SMD with Cohen's d: 0.31; 95% CI [0.05; 0.58]). Here too, the relevance of the effect was unclear. Likewise, due to the high bias potential, the effect was regarded as too small not to be accounted for by bias alone. Regarding treatment satisfaction, no other study showed noticeable differences between treatment groups.

No study comparing insulin detemir and insulin glargine showed statistically significant differences between treatment groups with regard to the total score of the ITSQ. In Study 1431, a statistically significant difference in favour of insulin detemir was shown after 52 weeks for the dimension "glycaemic control" (p=0.0262). The relevance of the effect was questionable. Moreover, due to the high bias potential, the effect cannot be regarded as large enough that it could not be based on systematic bias alone.

Adverse drug effects

Only one study was identified that aimed to demonstrate long-term safety. However, the study was only designed to investigate one selected outcome. Data on non-hypoglycaemic adverse events (AEs) were available for every study, but for some studies they were only available in the CSR provided.

In the comparison of insulin glargine and NPH insulin, within the framework of the safety evaluation no noticeable differences were shown with regard to SAEs or study discontinuations due to AEs. In the meta-analysis of all studies high heterogeneity was shown with regard to weight development; this was caused by one study on intensified insulin therapy. The meta-analysis of studies in which OADs were used as an additional BG-lowering treatment showed a statistically significant difference to the disadvantage of insulin glargine (WMD of the meta-analysis: 0.30 kg; 95% CI [0.06; 0.54]). The relevance of this effect is

[5] Diabetes Treatment Satisfaction Questionnaire, status version (DTSQs)
[6] Diabetes Treatment Satisfaction Questionnaire, change version (DTSQc)
[7] Insulin Treatment Satisfaction Questionnaire - (Japan)

unclear. Regarding the occurrence of tumours, a numerically noticeable difference to the disadvantage of NPH insulin was shown in the 5-year study; however, the sample size of this study was insufficient to draw any reliable conclusions.

The meta-analysis of all studies comparing insulin detemir and NPH insulin showed no noticeable differences regarding SAEs or study discontinuations due to AEs. Likewise, no indication of an advantage of either treatment option was shown for the outcome "reaction at the injection site". Regarding weight development, the meta-analysis of all studies showed a statistically significantly smaller increase in weight with insulin detemir (WMD of the meta-analysis: 0.92 kg; 95% CI [0.49; 1.35]). The relevance of this effect is unclear.

In the comparison of insulin detemir and insulin glargine, no indication of an advantage of either treatment option was shown regarding SAEs, with great heterogeneity between studies. On the other hand, noticeably more (and in the meta-analysis statistically significantly more) study discontinuations due to AEs and more reactions at the injection site were reported with insulin detemir (discontinuations: RR: 1.99; 95% CI [1.15; 3.45]; reactions at the injection site: RR: 1.90; 95 % CI [1.02; 3.52]). This resulted in proof of a greater potential to cause harm of insulin detemir. With regard to weight development, a statistically significant difference in favour of insulin detemir was shown (WMD 1.11 kg; 95% CI [0.54; 1.69]); the relevance of this finding is unclear.

Subgroup analyses

Data on the subgroup "gender" were only found in 3 studies, in each case for the comparison of insulin glargine and NPH insulin. The data provide no indications of differing results between men and women with regard to the change in HbA1c values throughout the course of the study. No information on statistical interaction tests were found for the occurrence of severe hypoglycaemic episodes. Overall, the data provide no indications of gender-specific effects of either treatment option.

Age-group specific results were reported in 3 studies, in each case for the comparison of insulin glargine and NPH insulin. Only 2 of these data provide information on a statistical interaction test with regard to changes in HbA1c values; these tests were not statistically significant. The few data available do not provide indications of age-specific effects of either treatment option.

No study reported subgroup results for concomitant diseases, the definition of diabetes, and additional BG-lowering therapy.

Conclusion

Insulin glargine vs. NPH insulin

For treatment within the framework of intensified insulin therapy, there is no proof of an additional benefit of insulin glargine vs. NPH insulin.

For treatment within the framework of a treatment scheme with basal insulin in combination with OADs, there is also no proof of an additional benefit of insulin glargine vs. NPH insulin when the use of NPH insulin is optimized. In studies investigating a treatment scheme with basal insulin in combination with OADs, the required adaptation of the frequency of NPH

insulin injections to individual circumstances, which is performed in clinical practice, was not possible. Differences were shown in studies in which NPH insulin was injected once daily in the evenings. In these studies, in the conjoint assessment of non-severe nocturnal hypoglycaemia and long-term BG lowering, the data provide proof of the superiority of insulin glargine vs. NPH insulin (both injected in the evenings), and also provide an indication of the superiority of insulin glargine (mornings) vs. NPH insulin (evenings). Furthermore, in the conjoint assessment of long-term BG lowering and severe hypoglycaemia (nocturnal and overall), the data provide an indication of the superiority of insulin glargine (mornings) vs. NPH insulin (evenings).

A long-term study in which insulin glargine (once daily) and NPH insulin (twice daily) were administered within the framework of different treatment schemes does not prove an additional benefit, either. However, this study provides an indication of an additional benefit of insulin glargine with regard to the conjoint assessment of severe hypoglycaemia and long-term BG lowering.

For treatment within the framework of conventional insulin therapy, there is no proof of an additional benefit of insulin glargine vs. NPH insulin, due to a lack of data.

In general, the long-term benefits and harms of insulin glargine vs. NPH insulin with regard to diabetic late complications have not been investigated sufficiently. Concerning the aspect “changes in the ocular fundus with insulin glargine therapy”, with consideration of the long-term study conducted on this question, the data do not provide indications of harm caused by insulin glargine.

Insulin detemir vs. NPH insulin

For treatment within the framework of intensified insulin therapy, the data do not provide proof of an additional benefit of insulin detemir vs. NPH insulin.

For treatment within the framework of a treatment scheme with basal insulin in combination with OADs, there is no proof of an additional benefit of insulin detemir compared with NPH insulin. For both the once-daily and twice-daily administration, in each case the data provide an indication of an additional benefit of insulin detemir vs. NPH insulin with regard to the conjoint assessment of non-severe nocturnal hypoglycaemia and long-term BG lowering. For the comparison of twice-daily administration of insulin detemir and NPH insulin, the data also provide an indication of an additional benefit of insulin detemir with regard to the conjoint assessment of the overall rate of non-severe hypoglycaemia and long-term BG lowering.

For treatment within the framework of conventional insulin therapy, there is no proof of an additional benefit of insulin detemir vs. NPH insulin, due to a lack of data.

There is proof of a lower increase in weight with insulin detemir compared with NPH insulin. After 6 months of treatment, the mean difference between groups was approx. 0.4 kg to 1.6 kg. The relevance of this difference is unclear. It is also unclear whether this effect is long-term, as only studies with a maximum duration of 11 months were available.

In general, the long-term benefits and harms of insulin detemir vs. NPH insulin regarding diabetic late complications have not been sufficiently investigated.

Insulin detemir vs. insulin glargine

The data do not provide proof of an additional benefit of one LAIA over the other, neither for treatment in a scheme with basal insulin therapy in combination with OADs, nor for intensified insulin therapy.

Likewise, for the treatment within the framework of conventional insulin therapy, there is also no proof of an additional benefit of either LAIA, due to a lack of data.

Regarding study discontinuation due to adverse events and reactions at the injection site, the data provide proof of greater harm caused by insulin detemir. There is also proof of a smaller increase in weight in patients using insulin detemir compared with those using insulin glargine. The mean difference between groups after 6 to 12 months of treatment was approx. 0.9 kg to 1.3 kg. The relevance of the difference is unclear. It is also unclear whether this effect is long-term, as only studies with a maximum duration of 12 months were available.

In general, the long-term benefits and harms of insulin detemir versus insulin glargine with regard to diabetic late complications have not been sufficiently investigated.

Key words: insulin analogues, insulin glargine, insulin detemir, NPH insulin, diabetes mellitus type 2