Systematic Review and Meta-analysis
of Short-Acting Insulin Analogues in Patients
With Diabetes Mellitus

Johannes Plank, MD; Andrea Siebenhofer, MD; Andrea Berghold, MsC, PhD; Klaus Jeitler, MD; Karl Horvath, MD; Peter Mrak, MD; Thomas R. Pieber, MD

Background: This article compares the effect of treatment with short-acting insulin (SAI) analogues vs regular insulin on glycemic control, hypoglycemic episodes, quality of life, and diabetes-specific complications.

Methods: Electronic searches (Cochrane Library, MEDLINE, and EMBASE) and additional searching (pharmaceutical companies, experts, approval agencies, abstracts of diabetology meetings) were performed. Two reviewers independently screened randomized controlled trials to determine inclusion.

Results: Forty-two randomized controlled trials that assessed the effect of SAI analogues vs regular insulin in 7933 patients with type 1 diabetes mellitus, type 2 diabetes mellitus, and gestational diabetes mellitus were identified. The weighted mean difference between hemoglobin A1c values obtained using SAI analogues and regular insulin was −0.12% (95% confidence interval [CI], −0.17% to −0.07%) for adult patients with type 1 diabetes mellitus and −0.02% (95% CI, −0.10% to 0.07%) for patients with type 2 diabetes mellitus. The standardized mean difference for overall hypoglycemia (episodes per patient per month) was −0.05 (95% CI, −0.22 to 0.11) and −0.04 (95% CI, −0.12 to 0.04) comparing SAI analogues with regular insulin in adult patients with type 1 and type 2 diabetes mellitus, respectively. No differences between treatments were observed in children with type 1 diabetes, pregnant women with type 1 diabetes mellitus, and women with gestational diabetes. Concerning quality of life, improvement was observed only in open-label studies in patients with type 1 diabetes mellitus. No differences were seen in a double-blinded study of patients with type 1 or in the studies of patients with type 2 diabetes mellitus.

Conclusion: Our analysis suggests only a minor benefit to hemoglobin A1c values in adult patients with type 1 diabetes mellitus but no benefit in the remaining population with type 2 or gestational diabetes from SAI analogue treatment.

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Both the Diabetes Control and Complications Trial (DCCT) and the UK Prospective Diabetes Study confirmed the benefits of improved glycemic control in patients with types 1 and 2 diabetes mellitus. With the strategy of intensive insulin therapy, a physiologic model of insulin replacement is applied in most patients with type 1 diabetes mellitus and in some active patients with type 2 diabetes mellitus. However, metabolic control in many patients is still unsatisfactory, which may in part be due to less than optimal insulin formulations.

With human regular insulin, it is difficult to mimic the physiologic prandial insulin peak of nondiabetic people, because there is a high tendency for regular insulin to associate to hexamers at the injection site. Therefore, considerable attention has been devoted to the development of short-acting insulin (SAI) analogues with fewer tendencies toward self-association, which allows a faster absorption of insulin into the blood and as a consequence a faster onset of action. The 2 currently available SAI analogues, insulin lispro and insulin aspart, achieve plasma peak concentrations about twice as high and within approximately half the time compared with regular insulin. Despite this theoretical superiority of SAI analogues over regular insulin, it is unclear whether the efficacy of SAI analogues in the treatment of diabetic patients is better than with human regular insulin. Treatment with the 2 SAI analogues available on the market is currently promoted with purported advantages with respect to metabolic control, reduced incidence of hypoglycemic episodes, and improved quality of life for patients with diabetes mellitus. We performed a systematic review and meta-analysis according to the
QUOROM statement\textsuperscript{15} of randomized controlled trials with the aim of providing information on glucose control, hypoglycemia, quality of life, and diabetes-specific complications of SAI analogues compared with regular insulin.

## METHODS

### DATA SOURCES

A highly sensitive search for randomized controlled trials combined with keywords (diabetes mellitus, short-acting insulin analogues, lispro, aspart) for identifying studies on SAI analogues vs regular insulin was performed using the Cochrane Library (issue 4 from 2003), MEDLINE (January 1966 to December 2003), and EMBASE (January 1974 to December 2003). We also hand searched reference lists and abstract books from major diabetology meetings from 1992 to 2003, contacted the 3 main insulin-producing pharmaceutical companies (Aventis Pharmaceutica Inc, Bridgewater, NJ, Eli Lilly and Company, Indianapolis, Ind, and Novo Nordisk A/S, Bagsværd, Denmark), and checked bibliographies of textbooks and relevant retrieved articles. Forty-seven authors and experts were contacted for additional (unpublished) data, and 16 (34\%) responded to our queries.

### STUDY SELECTION CRITERIA

All randomized controlled trials (blinded and open, parallel and crossover design) with a treatment duration of 4 weeks or more designed to compare diabetic patients who were treated with the currently available SAI analogues lispro or aspart vs human regular insulin were included in the review, regardless of dose or schedule and whether insulin was injected subcutaneously via syringe, pen, or pump. Studies were included as long as any additional insulin treatment (basal insulin) was given equally to both groups.

We assessed glycemic control measured by percentage of glycosylated hemoglobin (HbA\textsubscript{1c}) and number of overall hypoglycemic episodes as an adverse effect of insulin therapy. Because of the heterogeneity of labeling hypoglycemic events, only the analysis for overall hypoglycemic episodes, counted as episodes per patient per month, is reported. In addition, we looked for data on quality-of-life assessment, number and severity of adverse events, and diabetes-specific complications (retinopathy, nephropathy, neuropathy, foot complications, cardiovascular events) and mortality.

### DATA EXTRACTION

Two reviewers (J.P. and A.S.) independently screened the title, abstract, and keywords of each reference identified by the search. Where differences in opinion existed, these were resolved by a third party (T.R.P.). Only data from full-length articles that met the inclusion criteria were considered for the systematic review. Data from each study included have been extracted by 2 independent reviewers using a structured data extraction form. The methodologic quality of each trial was assessed using the criteria given in the Cochrane Handbook and the criteria of Jadad et al\textsuperscript{16} and Schulz et al\textsuperscript{17} (minimization of selection bias, performance bias, attrition bias, and detection bias). We used 3 categories: assessment A means that plausible bias is unlikely to seriously affect the results; assessment B, that plausible bias raises some doubt about the results; and assessment C, that plausible bias seriously weakens confidence in the results.

### DATA SYNTHESIS

Weighted mean differences were calculated for the percentage of glycosylated hemoglobin, and a random-effects model was used for the meta-analysis. We tried to incorporate the 2 different study designs used, crossover and parallel studies, into the meta-analysis.\textsuperscript{18,19} To make use of the crossover design, one prerequisite is that the mean difference (or the difference between means) of the treatments is available. In addition, the standard deviation, standard error, or confidence interval (CI) for the within-person differences must be given. In some of the studies, these estimates were provided, whereas for other studies we had to estimate the standard error from the test statistic or from P values. In case no standard error for the within-person differences could be extracted from a trial, the correlation between treatment outcomes was approximated using the lowest observed correlation among the other studies ($r=0.69$). For analysis we used the meta-macro of Stata (Stata Corp, College Station, Tex). The robustness of the results was assessed by repeating the analysis using a fixed-effects model. Heterogeneity between trials was assessed by the $\chi^2$ test. A funnel plot and the Eggers test were used to test for publication bias. The standardized mean difference was calculated for overall hypoglycemic episodes per patient per month using unpaired analysis. This article presents a shortened version of the results of a systematic review entitled “Short Acting Insulin Analogues Versus Regular Human Insulin in Patients With Diabetes Mellitus” by Siebenhofer et al\textsuperscript{10} for the Metabolic and Endocrine Disorders Group of the Cochrane Collaboration, which is published in the Cochrane Library.

### SEARCH RESULTS

The initial search using the search strategy described yielded 1143 studies (Figure 1). After an initial investigation of the abstracts, 1074 articles were excluded. Interobserver agreement was 99.7\% ($k=0.97$; 95\% CI, 0.94-0.99). Another 27 studies were excluded based on review of full-length articles. The main reasons for exclusion were interventions not comparable, duplicate publications of a multicenter study, study duration of less than 4 weeks, or reporting of data of only 1 study period. Therefore, 42 randomized controlled trials were determined to be relevant for inclusion in the meta-analysis.

Table 1 summarizes the characteristics of the trials included in our review.\textsuperscript{21-62} Altogether, 7933 participants took part in the 42 randomized controlled studies. A total of 5925 patients with type 1 diabetes mellitus (weighted mean age, 46 years; diabetes duration, 14 years; and body mass index [calculated as weight in kilograms divided by the square of height in meters], 24.4), 1901 patients with type 2 diabetes mellitus (weighted mean age, 58 years; diabetes duration, 12 years; body mass index, 28.2 kg/m\textsuperscript{2}), and 107 women with gestational diabetes were investigated.

### METHODOLOGIC QUALITY

Seven studies were of higher quality (category B) and described methodologic issues in some detail (for example, randomization method, flow of participants, and blinding of outcome assessment). Interobserver calculation of the key elements of study quality revealed an observed agreement of 90\%×7\% ($k=0.69$; 95\% CI, 0.41 to 0.97).
META-ANALYSIS AND SUBGROUP ANALYSIS

Glycemic Control

HbA1c Levels in Patients With Type 1 Diabetes Mellitus. In 20 studies of patients with type 1 diabetes mellitus, data on posttreatment HbA1c levels could be extracted (Figure 2A). The weighted mean difference of HbA1c values was estimated to be −0.12% (95% CI, −0.17% to −0.07%) in favor of insulin analogues compared with regular insulin. The test of heterogeneity gave a P value of .06. An application of the fixed-effects model showed similar results (weighted mean difference, −0.12%; 95% CI, −0.15% to −0.08%). The funnel plot did not indicate publication bias with the Eggers test, yielding nonsignificant results (P = .41). Results from subgroup analyses in patients with type 1 diabetes mellitus are given in Table 2.

HbA1c Levels in Patients With Type 2 Diabetes Mellitus. In 4 studies HbA1c was mentioned in patients with type 2 diabetes mellitus (Figure 2B). The weighted mean difference of HbA1c values was estimated to be −0.02% (95% CI, −0.10% to 0.07%). None of the 4 studies included showed any significant difference of HbA1c values between insulin analogues and regular insulin.

HbA1c Levels in Children, Adolescents, Pregnant Patients With Type 1 Diabetes Mellitus, and Patients With Gestational Diabetes. The 3 existing studies in prepubertal children35-37 and the study with adolescents54 with type 1 diabetes mellitus did not show any significant reduction in HbA1c levels. In pregnant women with type 1 diabetes mellitus, the reduction in HbA1c levels obtained in the analogue and regular groups was similar.58 No significant difference was found in patients with gestational diabetes.59,60

Hypoglycemic Episodes

Overall, hypoglycemic episodes were mentioned in most studies. Various studies reported different intervals of hypoglycemic events, and the episodes were counted per patient per month, overall, and sometimes as a percentage per patient. Furthermore, different definitions of hypoglycemic episodes were chosen: some used glucose levels of between less than 36 mg/dL (<2 mmol/L) or less than 70 mg/dL (<3.9 mmol/L); others used symptoms of different severity from sickness to coma.

Overall Hypoglycemic Episodes in Patients With Type 1 Diabetes Mellitus. Nine studies25,26,28-30,40,44-45 mentioned mean episodes per patient per month (Figure 3A). The standardized mean difference of the overall mean hypoglycemic episodes per patient per month was −0.05 (95% CI, −0.22 to 0.11) for analogues compared with regular insulin. In these selected 9 studies, distinct heterogeneity was observed (P < .001). Excluding small studies (fewer than 30 participants)50,51 did not change the result, but heterogeneity was then nonsignificant (P = .13).

Overall Hypoglycemic Episodes in Children, Adolescents, Pregnant Patients With Type 1 Diabetes Mellitus, Patients With Gestational Diabetes, and Patients With Type 1 Diabetes Mellitus and Hypoglycemia Unawareness. The overall rate of hypoglycemic episodes per patient per month did not significantly differ in prepubertal children in either of the studies.35,36 In the study with adolescents,54 the event rate of overall hypoglycemia per patient per month was significantly reduced with the insulin analogue (P = .02). In pregnant women,60 the event rate regarding biochemical hypoglycemia was significantly higher in the analogue group compared with the regular group (P < .05). In one study,60 of women with gestational diabetes, the total number of hypoglycemic events did not differ between the groups, whereas another trial60 did not report data on hypoglycemic episodes. The study that investigated effects of analogues on those who were unaware of hypoglycemia31 found no significant difference of the overall hypoglycemic rates.
**Table 1. Characteristics of Trials Included**

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<th>Source</th>
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<th>No. of Participants</th>
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<th>Additional Data</th>
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<th>Mean Age, y</th>
<th>Mean Duration of Diabetes Treatment</th>
<th>Regimen/Type of Insulin</th>
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</tbody>
</table>

Abbreviations: B, plausible bias raises some doubt about the results; C, plausible bias seriously weakens confidence in the results; CSII, continuous subcutaneous insulin infusion; 1/pre, type 1 diabetes and pregnant; d, delivery; gw, gestational week; HbA1c, glycosylated hemoglobin A1c; hypo, hypoglycemic; MIT, multiple injection therapy; NA, not available; QoL, quality of life.

*Data not shown for the study by Kotsanos et al. Bott et al reported QoL data of trials; no data were available for statistical analyses.
†These trials included patients with both type 1 and type 2 diabetes mellitus.
between the analogue and regular insulin groups.

Quality of Life

Eleven trials reported data on quality of life. Various instruments and open study design hardly allow an objective interpretation of the data reported. With the most used instrument in patients with type 1 diabetes mellitus, the Diabetes Treatment Satisfaction Questionnaire (DTSQ), 63 3 studies (1 double-blind32 and 2 open design23,31) found no significant difference between the treatment arms, whereas 4 studies25,36,41,62 observed improvement in the analogue group. Detailed information on DTSQ domains in these trials is given in Table 3. In the 2 open-label studies that assessed quality of life in patients with type 2 diabetes mellitus,53,61 no difference was observed between the treatments.

Pregnancy Outcome

No significant differences in fetal or maternal outcome between patient groups using analogue and regular insulin were described in articles, including those reporting on pregnant women with type 1 diabetes mellitus58 and women with gestational diabetes.39,60 However, in all

<table>
<thead>
<tr>
<th>Variable</th>
<th>WMD, % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Publication date</td>
<td></td>
</tr>
<tr>
<td>Before 2000</td>
<td>–0.09 (–0.19 to 0.02)</td>
</tr>
<tr>
<td>After 2000</td>
<td>–0.14 (–0.20 to –0.09)</td>
</tr>
<tr>
<td>Intervention time</td>
<td></td>
</tr>
<tr>
<td>≤3 mo</td>
<td>–0.09 (–0.18 to 0.00)</td>
</tr>
<tr>
<td>&gt;3 mo</td>
<td>–0.15 (–0.21 to –0.10)</td>
</tr>
<tr>
<td>Type of insulin</td>
<td></td>
</tr>
<tr>
<td>Lispro</td>
<td>–0.11 (–0.18 to 0.04)</td>
</tr>
<tr>
<td>Aspart</td>
<td>–0.15 (–0.22 to –0.07)</td>
</tr>
<tr>
<td>Injection regimen</td>
<td></td>
</tr>
<tr>
<td>CSII</td>
<td>–0.19 (–0.27 to –0.12)</td>
</tr>
<tr>
<td>MIT</td>
<td>–0.08 (–0.15 to –0.02)</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; CSII, continuous subcutaneous insulin infusion; MIT, multiple injection therapy; WMD, weighted mean difference.
of these trials, allocation to trial treatment was performed after the embryonic phase.

**Adverse Events, Diabetes-Specific Complications, and Mortality**

A total of 60% of the studies provided at least some information on adverse events. Overall, the reported frequency and type of adverse events (local site reactions, ketoadiabetes) and discontinuation rate were comparable for the 2 treatment groups. Studies were not planned to investigate mortality, effect of insulin analogues on pre-existing late complications, or eventual development of these complications under trial drug treatment.

**COMMENT**

In adults with type 1 diabetes mellitus, our analysis resulted in a small (Δ HbA1c, −0.12%) but statistically significant decrease in HbA1c values using SAI analogues. In patients with type 2 diabetes mellitus, no superiority in HbA1c values was observed. In terms of overall hypoglycemia, the results obtained with SAI analogues and regular insulin were comparable for patients with both types 1 and 2 diabetes mellitus.

In a subgroup analysis of patients with type 1 diabetes mellitus, we found a statistically significant improvement in HbA1c values in favor of insulin aspart and a trend for improvement in HbA1c values for insulin lispro. However, no clinically significant difference between the 2 SAI analogues was observed in the only direct clinical comparison. This seems to be in accordance with controlled clinical clamp studies, which demonstrated identical pharmacokinetic and pharmacodynamic properties. The use of SAI analogues in continuous subcutaneous insulin infusion therapy results in improved glycemic control compared with multiple injection therapy. Throughout our extensive literature search, we did not identify any trials using long-acting insulin analogues, insulin glargine or insulin detemir, for comparison of SAI analogues to regular insulin. Therefore, it remains an open question whether the use of SAI analogues in combination with long-acting analogues will attain results comparable to continuous subcutaneous insulin infusion.

No study designed to investigate possible long-term effects was found. It seems unlikely that the effect of improved glycemic control, which was observed in analogue treatment (overall, −0.1% HbA1c), will prevent the development and progression of microvascular complications. Assuming that a reduction in HbA1c values with insulin analogues would result in a similar relative benefit compared with regular insulin treatment in the DCCT during a period of 6.5 years, the number needed to treat to prevent a single case of microvascular progression is estimated to be approximately 650 compared with regular insulin use. The homologous structure of insulin analogues and insulin-like growth factor I has caused concern regarding the progression of late diabetic complications and potential mitogenic effects, especially with the long-term use of insulin analogues. Insulin-like growth factor I may affect the progression of retinopathy, and certain modified insulin analogues have shown a carcinogenic effect in the mammary glands in female rats or in the mitogenic potency in osteosarcoma cells. Despite these potentially adverse properties of insulin analogues, we did not find data concerning long-term safety. Moreover, patients with clinically advanced microvascular complications have been excluded from most clinical studies.

Data on SAI analogue use in pregnancy is limited. We did not identify a single randomized controlled trial that follows the entire course of pregnancy in insulin-dependent pregnant women. Since insulin analogues are becoming more popular among young women with type 1 diabetes mellitus, well-designed studies in pregnant women to determine the safety profile for both the mother and the unborn child are urgently needed.

Analysis of overall hypoglycemic episodes in patients with type 1 diabetes mellitus revealed a small non-significant reduction for analogue treatment, which is in accordance with previous findings and clinically negligible considering that an average patient with type 1 diabetes mellitus experiences 6 to 8 mild episodes of hypoglycemia per month.
It has been argued that treatment with SAI analogues is associated with increased quality of life. When the most frequently used instrument, the DTSQ, showed significant improvement for analogues, it was mainly due to changes in the convenience, flexibility, and continuity of treatment. According to the study protocols in the open-label studies, patients were advised to inject regular insulin on average 30 minutes before mealtime. One may hypothesize that the difference in injection time (immediately vs regular: approximately 30 minutes before meals) is a major underlying reason for treatment satisfaction improvements reported by patients who use analogues. However, this interval has never been established on the basis of controlled trials, and most patients do not use a fixed injection-meal interval of 30 minutes. The only study that used a double-blind design did not find an improvement in any quality-of-life item, metabolic control, or overall hypoglycemia.

Some limitations of our review must be addressed. For several trials that met the inclusion criteria, outcome data from the original publication could not be included in the analysis for methodologic reasons (eg, no separate analysis for types 1 and 2 diabetes mellitus provided). Unfortunately, the communication process with the authors did not substantially improve the data quality. Few authors submitted the original data we requested. However, findings from these trials do not contradict the results of our meta-analysis.

In the main analysis, we incorporated the studies with parallel and crossover design. Crossover trials have the particular strength that treatments are evaluated on the same patients, allowing for comparison at the individual rather than the group level and requiring fewer patients to get the same precision as a parallel group trial. However, there are also limitations of crossover trials, such as problems with patient withdrawal, unstable disease, period effects, carryover effects, or other interaction between treatment and period. When interpreting the results of our analysis these limitations should be considered.

In conclusion, our analysis suggests only a minor benefit in terms of HbA1c, values in adult patients with type 1 diabetes mellitus but no benefit in the remaining population of patients with type 2 or gestational diabetes from SAI analogue treatment. For safety purposes, we need a long-term follow-up of large numbers of patients who use SAI analogues. Furthermore, we need well-designed studies in pregnant women to determine the safety profile for both the mother and the unborn child.

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Author Affiliations: Department of Internal Medicine, Division of Diabetes and Metabolism (Drs Plank, Siebenhofer, Jeitler, Horvath, and Pieber), and Institute for Medical Informatics, Statistics and Documentation (Dr Berghold), Medical University, Graz, Department of Internal Medicine, Landeskranankenanstalt, Horgas (Dr Mrak), and Joanneum Research, Institute of Medical Technologies and Health Management, Graz (Drs Jeitler and Pieber), Austria.

Correspondence: Johannes Plank, MD, Department of Internal Medicine, Division of Diabetes and Metabolism, Medical University Hospital, Auenbruggerplatz 15, A-8036 Graz, Austria (johannes.plank@klinikum-graz.at).

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REFERENCES


4. DAfNE Study Group. Training in flexible, intensive insulin management to enable dietary free eating in people with type 1 diabetes: dose adjustment for normal eating (DAfNE) randomised controlled trial. BMJ. 2002;325:746-751.


