Insulin Analogs—Are They Worth It? Yes!

George Grunberger

Diabetes Care 2014;37:1767–1770 | DOI: 10.2337/dc14-0031

The availability of insulin analogs has offered insulin replacement strategies that are proposed to more closely mimic normal human physiology. Specifically, there are a considerable number of reports demonstrating that prandial insulin analogs (lispro, aspart, glulisine) have pharmacokinetic and pharmacodynamic profiles closer to normal, with resulting faster onset and offset of insulin effect when compared with regular human insulin. In addition, basal insulin analogs (glargine, detemir) have been reported to offer longer duration of action, less variability, more predictability, less hypoglycemia (especially nocturnal), and a favorable effect on weight. However, an argument against use of analog insulins as compared with use of regular or NPH insulin is one that states that the effectiveness and risk of hypoglycemia are the only two valid clinical outcomes that should be used to compare the analog and human insulins. Thus, there remains a debate in some circles that analog insulins are no more effective than human insulins, yet at a much higher financial cost. To provide an in-depth understanding of both sides of the argument, we provide a discussion of this topic as part of this two-part point-counterpoint narrative. In the counterpoint narrative, Dr. Davidson provides his argument and defends his opinion that outside of a few exceptions, analog insulins provide no clinical benefit compared with human insulins but cost much more. In the point narrative presented here, Dr. Grunberger provides a defense of analog insulins and their value in clinical management and suggests that when evaluating the "cost" of therapy, a much more global assessment is needed.

—William T. Cefalu
Editor in Chief, *Diabetes Care*

Insulin analogs offer insulin replacement strategy that results in a situation closer to normal human physiology (traditionally assumed as ~50% basal insulin secretion throughout the day and ~50% prandial secretion in response to meals). These insulin preparations started becoming available on the U.S. market with the approval of lispro in 1996. Hundreds of registration trials and postmarketing studies have been conducted and representative results for each analog are listed in references 1–12. Specifically, prandial insulin analogs (lispro, aspart, glulisine) have pharmacokinetic and pharmacodynamic profiles closer to normal; i.e., more rapid rise after subcutaneous injections to higher insulin levels and then more rapid fall than regular human insulin, with resulting faster onset and offset of insulin effect (1–3). Basal insulin analogs (glargine, detemir) offer longer duration of action, less variability, more predictability, less hypoglycemia (especially nocturnal), and, in case of detemir, more favorable weight profile (4–11). Thus, fewer injections are necessary to achieve their purpose (which is suppression of glucose production between meals and overnight). The clinical advantages of analog insulin use are apparent from results of the numerous trials. As the registration trials were designed to achieve equivalent A1C lowering in the subjects treated with human versus respective

Grunberger Diabetes Institute, Bloomfield Hills, MI; Internal Medicine and Molecular Medicine and Genetics, Wayne State University School of Medicine, Detroit, MI; and Oakland University William Beaumont School of Medicine, Rochester, MI

Corresponding author: George Grunberger, grunberger@comcast.net.

See accompanying article, p. 1771.

analog insulin, those advantages could be summarized as decreased incidence of hypoglycemia and weight gain, the two major fears both patients and physicians have when intensifying diabetes therapy. Indeed, glargine insulin, the first basal insulin analog, was approved based on the significant decline of nocturnal hypoglycemia (by 42–48%) when tested against NPH (8). Similar, significant reduction was seen in a study of detemir versus NPH (reduction of nocturnal hypoglycemia by 34%) (11). The Cochrane review of data with rapid-acting analogs concluded there was likewise a significant reduction of severe hypoglycemic reactions (21.8 vs. 46.1 per 100 person-years) compared with regular insulin (12). The weight advantage of insulin detemir versus NPH has been shown in every study, in both type 1 and type 2 diabetes (range 1–2 kg over 16–52-week duration of studies), exemplified in Raslová et al. (9) and Hermansen et al. (10).

Analog insulins have several additional advantages over human insulins: Their use has been shown to improve treatment adherence and treatment satisfaction due to fewer injections, flexibility of timing of basal analogs, less fear of dose adjustments, mealtime administration of prandial analogs, as well as user-friendly injection devices. In spite of prevailing opinions, there is also evidence of a pharmacoeconomic advantage with insulin analogs mainly due to reduction in hypoglycemia-related claims and lower inpatient hospital costs.

For a patient on an intensive insulin injection regimen, these are the choices in 2014: *1*) inject a basal insulin once a day regardless of the time of the day and inject prandial insulin just before (or even immediately after) each meal based on the carbohydrate or calorie content of the meal or *2*) inject an intermediate-acting insulin at least twice a day and regular insulin 30–45 min before a meal, while constantly fearing late postprandial and nocturnal hypoglycemia and having to eat a bedtime snack to prevent the latter (not exactly physiologic and not helpful with the ongoing obesity epidemic). One would think this would represent an easy choice. Distilled to the bottom line, this point-counterpoint debate revolves around a single question: Is the putative higher "cost" of insulin analogs "worth" it?

We need to wade into the pool of the "cost" of the therapy. How does one truly evaluate the question? We are dealing with the cost to individuals, their families, employers, insurance companies, and society as a whole over a lifetime (as one can safely assume most of these patients will need insulin for the rest of their lives). Thus, one has to focus not on the grossly inflated retail cost of the next insulin prescription in the local pharmacy, but on the big picture. That picture, of necessity, needs to include the overall cost of medical care, rate of absenteeism, loss of productivity, as well as adherence, treatment satisfaction, and satisfaction with lifestyle imposed on an individual by demands of this complex disease. Because the big picture is so difficult to study and get one's arms around, most pundits zero in on the retail price difference between human and analog insulins and conclude that the extra expenditure is "not worth it" as no data exist yet that individuals on analog insulins lead less expensive, longer, and happier lives!

Futility of debating "costs" on the pages of a medical journal was documented in a study by Health Action International (13), assessing the retail price for a 10-mL vial of regular human insulin on the same day (11 May 2010) in 60 different countries: patients in Iran paid $1.55 while those in Austria paid $76.69! The situation is no different with analog insulins: a vial of glargine in Malaysia is currently $14.83, while in India a 10-mL vial of Basalog (generic glargine made by Biocon [Bangalore, India]) is $23.88 and a vial of authentic Lantus (Sanofi, Bridgewater, NJ) is $41.08 (14); in the U.S., the same vial retails for $180–200 (13). For insulin pens, 5 aspart FlexPens (Novo Nordisk, Plainsboro, NJ) are $26.52 and 5 lispro KwikPens (Eli Lilly, Indianapolis, IN) are $40.48 in India (14); in the U.S., they are $310 and $391, respectively (14). Clearly, patients are paying for the gamesmanship between the government regulatory bodies and big pharma politics.

The political nature of the "cost" debate was exemplified by the situation on the German insulin market. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWiG) considered only seven small randomized controlled trials (15). In five of the studies, lispro insulin was compared with human insulin; in the other two, the comparison was with glulisine insulin. In all cases, short-acting insulin was added to basal long-acting insulin. All the clinical trials that met the inclusion criteria were over a short period (5.5–12 months), which meant that they could not consider the effect of rapid-acting insulin analogs on diabetes complications or overall mortality. The analysis was limited to assessments of hypoglycemic rate and stability of the blood glucose level. There were only limited measurements of illness-related quality of life and none of patient satisfaction. Not surprisingly, no differences were found. However, based on the report, the rapid-acting insulin analogs aspart, glulisine, and lispro were excluded from reimbursement by the Federal Joint Committee (G-BA) for patients with type 2 diabetes as long as cost of treatment with a rapid-acting insulin analog was more "expensive" than the cost of treatment with human insulin. Manufacturers reacted by offering large rebates to the sickness funds, while keeping the retail prices above the threshold. When G-BA issued an edict to similarly exclude insulin analogs from treatment of type 1 diabetes, a worldwide storm of protest ensued in 2008 (16). For example, the International Diabetes Federation expressed "major concern about the potential discontinuation of reimbursement for short-acting insulin analogues to people with type 1 diabetes in Germany, which would result in many patients being excluded from this type of therapy" (17). This decision was eventually withdrawn but the situation demonstrated the difficulty in objectively assessing the cost of the analog versus human insulin therapy.

When more educated attempts were made to assess these costs, a different picture emerged. Palmer et al. (18) used a published and validated computer simulation model and found that treatment with analog insulin (detemir + aspart) was associated with decreased incidence of long-term diabetes complications, improved quality-adjusted life expectancy, and only slightly higher cost ($2,713 over lifetime) than human insulin–based regimen (NPH + regular). Brixner et al. (19) published an analysis

of cost-effectiveness of insulin analogs versus human insulins. In their retrospective cost analysis using computerized databases (from the Veterans Health Administration, Medicaid, Medi-Cal, and a variety of U.S. health plans and regional U.S. managed care plans), the cost-effectiveness of analogs was shown, predominantly due to the lower costs of treating hypoglycemia and in several instances to lower inpatient costs. Meece (20) similarly concluded a pharmacoeconomic advantage of insulin analogs due to improved glycemic control, improved adherence to therapy (less fear of hypoglycemia and weight gain), and lower rates of hypoglycemia.

The annual costs of diabetes care among 1,024 patients (512 on glargine, 512 on NPH) with type 2 diabetes in Germany were lower by $495 (361 euro) ($P = 0.0004$) for those on glargine-based therapy, mainly due to fewer glucose measurements and diabetes-related materials (21). The complexity of dealing with overall cost issues was shown in an analysis that found only 6 studies (out of 382 publications between 2000 and 2009) offered data on both the acquisition costs of glargine versus NPH in patients with type 1 diabetes but also on clinical effects, diabetes complications, quality of life, fear of hypoglycemia, etc. (22). In one study, glargine was less expensive and in four additional studies use of glargine was deemed "good value" (i.e., cost $4,420–$17,946; 3,227–13,100 euro per quality-adjusted life-years gained) (23). In another large-scale real-life study of cost comparison among patients with type 2 diabetes in Germany, glargine-based regimens (annual cost $1,635 [1,194 euro]) cost the same as NPH-based treatments ($1,652 [1,206 euro]) (24). The slightly higher cost of the analog insulin was more than offset by smaller use of test strips. Detemir-based regimens cost more, mainly due to higher cost of the bolus component. That survey was based on the IMS LRx database (a longitudinal history of de-identified but unique patients collected by IMS Health worldwide of virtually all dispensed prescriptions; it accesses nationwide pharmacy data centers processing prescription data) of 542,438 patients between 2009 and 2011.

In Spain, average overall cost of an episode of severe hypoglycemia was $494 (361 euro). With the reported reduction of anywhere between 14 and 43 such episodes per 100 patients per year among those on lispro versus regular insulin, Reviriego et al. (25) calculated that use of lispro can be considered cost-effective.

In a different take on the issue, Chen et al. (26) compared cost among 6,436 users of regular and lispro insulins in a managed care setting in California. Due to fewer hospitalizations for lispro users and thus less expensive nondiabetes-related medical costs, total costs were similar for the human and analog insulin users.

There are few studies of adherence, but in two examples the lower perceived fear of nocturnal hypoglycemia was less with glargine than with NPH insulin and patients were more willing to adjust insulin to titrate their fasting glucose levels (27,28). Treatment satisfaction was increased while being treated with insulin analogs among teens and adults on lispro who found coping with diabetes less difficult than on regular insulin. Less negative effect on quality of life and fewer worries about diabetes were reported with lispro than with regular insulin (29–32). The same observation was reported among 944 Japanese children and adolescents with type 1 diabetes where rapid-acting analog therapy was associated with more flexibility and improved quality of life (33). Health-related quality-of-life scores increased significantly in patients administering any insulin analog regimen (whether starting or switching to) in a 24-week prospective study among 66,726 patients across India (34).

In summary, for patients on intensive insulin regimens, analog insulins are "worth it."

Duality of Interest. G.G. has received research funding from and has served on speakers' bureaus of Eli Lilly, Novo Nordisk, and Sanofi. No other potential conflicts of interest relevant to this article were reported.

References

1. Becker RH, Frick AD. Clinical pharmacokinetics and pharmacodynamics of insulin glulisine. Clin Pharmacokinet 2008;47:7–20
2. Lindholm A, Jacobsen LV. Clinical pharmacokinetics and pharmacodynamics of insulin aspart. Clin Pharmacokinet 2001;40:641–659
3. Holleman F, Hoekstra JB. Insulin lispro. N Engl J Med 1997;337:176–183
4. 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
5. 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
6. Heise T, Nosek L, Rønn BB, et al. Lower within-subject variability of insulin detemir in comparison to NPH insulin and insulin glargine in people with type 1 diabetes. Diabetes 2004; 53:1614–1620
7. 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
8. Riddle MC, Rosenstock J, Gerich J; Insulin Glargine 4002 Study Investigators. The treat-to-target trial: randomized addition of glargine or human NPH insulin to oral therapy of type 2 diabetic patients. Diabetes Care 2003;26:3080–3086
9. Raslová K, Bogoev M, Raz I, Leth G, Gall MA, Hâncu N. Insulin detemir and insulin aspart: a promising basal-bolus regimen for type 2 diabetes. Diabetes Res Clin Pract 2004;66:193–201
10. Hermansen K, Davies M, Derezinski T, Martinez Ravn G, Clauson P, Home P. A 26-week, randomized, parallel, treat-to-target trial comparing insulin detemir with NPH insulin as add-on therapy to oral glucose-lowering drugs in insulin-naive people with type 2 diabetes. Diabetes Care 2006;29:1269–1274
11. Vague P, Selam J-L, Skeie S, et al. Insulin detemir is associated with more predictable glycemic control and reduced risk of hypoglycemia than NPH insulin in patients with type 1 diabetes on basal-bolus regimen with pre meal insulin aspart. Diabetes Care 2003;36:590–596
12. Siebenhofer A, Plank J, Berghold A, et al. Short acting insulin analogues versus regular human insulin in patients with diabetes mellitus. Cochrane Database Syst Rev 2006; 2: CD003287
13. Health Action International. Life-saving insulin largely unaffordable—A one day snapshot of the price of insulin across 60 countries [article online], 2010. Available from www.haiweb.org/medicineprices/07072010/Global_briefing_note_FINAL.pdf. Accessed 24 December 2013
14. DrugsUpdate. Available from www.drugsupdate.com/brand/search. Accessed 24 December 2013
15. IQWiG Reports–Commission No. A05-04. Rapid-acting insulin analogues for the treatment of diabetes mellitus type 2 [article online], 2006. Available from www.iqwig.de/download/A05-04_Final_Report_Rapid-acting_insulin_analogues_for_the_treatment_of_diabetes_mellitus_type_2.pdf. Accessed 24 December 2013
16. IQWiG Reports–Commission No. A05-02. Rapid-acting insulin analogues in the treatment of diabetes mellitus type 1 [article online], 2007. Available from www.iqwig.de/download/A05-02_Abschlussbericht_Kurzwirksame_Insulinanaloga_

bei_Diabetes_mellitus_Typ_1.pdf. Accessed 24 December 2013
17. International Diabetes Federation. German analogue insulin issue. Available from http://www.idf.org/german-analogue-insulin-issue. Accessed 24 December 2013
18. Palmer AJ, Valentine WJ, Ray JA, et al. An economic assessment of analogue basal-bolus insulin versus human basal-bolus insulin in subjects with type 1 diabetes in the UK. Curr Med Res Opin 2007;23:895–901
19. Brixner DI, McAdam-Marx C. Cost-effectiveness of insulin analogs. Am J Manag Care 2008;14:766–775
20. Meece J. Pharmacoeconomic advantages of insulin analogs. US Pharm 2006:HS42–HS50
21. Schöffski O, Breitscheidel L, Benter U, et al. Resource utilisation and costs in patients with type 2 diabetes mellitus treated with insulin glargine or conventional basal insulin under real-world condition in Germany: LIVE-SPP study. J Med Econ 2008;11:695–712
22. Hagenmeyer EG, Koltermann KC, Dippel FW, Schädlich PK. Health economic evaluations comparing insulin glargine with NPH insulin in patients with type 1 diabetes: a systematic review. Cost Eff Resour Alloc 2011;9:15
23. McEwan P, Poole CD, Tetlow T, Holmes P, Currie CJ. Evaluation of the cost-effectiveness of insulin glargine versus NPH insulin for the treatment of type 1 diabetes in the UK. Curr Medical Res Opin2007;23(Supp. 1):S7–S19
24. Dippel FW, Schneider T. Cost-comparison between different treatment regimens in diabetes mellitus in Germany based on long acting insulins. Diabetologie und Stoffwechsel 2013; 8:168
25. Reviriego J, Gomis R, Marañés JP, Ricart W, Hudson P, Sacristán JA. Cost of severe hypoglycaemia in patients with type 1 diabetes in Spain and the cost-effectiveness of insulin lispro compared with regular human insulin in preventing severe hypoglycaemia. Int J Clin Pract 2008;62: 1026–1032
26. Chen K, Chang EY, Summers KH, Obenchain RL, Yu-Isenberg KS, Sun P. Comparison of costs and utilization between users of insulin lispro versus users of regular insulin in a managed care setting. J Manag Care Pharm 2005;11: 376–382
27. Fritsche A, Schweitzer MA, Häring HU; 4001 Study Group. Glimepiride combined with morning insulin glargine, bedtime neutral protamine Hagedorn insulin, or bedtime insulin glargine in patients with type 2 diabetes. A randomized, controlled trial. Ann Intern Med 2003;138: 952–959
28. Manini R, Forlani G, Moscatiello S, Zannoni C, Marzocchi R, Marchesini G. Insulin glargine improves glycemic control and health-related quality of life in type 1 diabetes. Nutr Metab Cardiovasc Dis 2007;17:493–498
29. Tamás G, Marre M, Astorga R, Dedov I, Jacobsen J, Lindholm A; Insulin Aspart Study Group. Glycaemic control in type 1 diabetic patients using optimised insulin aspart or human insulin in a randomised multinational study. Diabetes Res Clin Pract 2001;54:105–114
30. Home PD, Lindholm A, Riis A; European Insulin Aspart Study Group. Insulin aspart vs. human insulin in the management of long-term blood glucose control in type 1 diabetes mellitus: a randomized controlled trial. Diabet Med 2000;17:762–770
31. Kotsanos JG, Vignati L, Huster W, et al. Health-related quality-of-life results from multinational clinical trials of insulin lispro. Assessing benefits of a new diabetes therapy. Diabetes Care 1997;20:948–958
32. Grey M, Boland EA, Tamborlane WV. Use of lispro insulin and quality of life in adolescents on intensive insulin therapy. Diabetes Educ 1999; 25:934–941
33. Urakami T, Kawamura T, Sugihara S, et al.; Japanese Study Group of Insulin Therapy for Childhood and Adolescent Diabetes. A questionnaire survey on the use of quick-acting insulin analog in Japanese children and adolescents with type 1 diabetes. Pediatr Int 2004;46: 285–290
34. Shah S, Zilov A, Malek R, Soewondo P, Bech O, Litwak L. Improvements in quality of life associated with insulin analogue therapies in people with type 2 diabetes: results from the A1chieve observational study. Diabetes Res Clin Pract 2011;94:364–370