Insulin Analogs—Is There a Compelling Case to Use Them? No!

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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 presented here, 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 preceding point narrative, 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.

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In 2011, global insulin sales cost $16.7 billion, of which $8.3 billion was spent in the U.S. (1). Some of this high cost, of course, is due the increasing number of people with diabetes. However, the unit cost of insulin is increasing at a rate far outstripping the rate of inflation, which was 17.5% over the 7 years from 2005 to 2011 (2). For instance, the increases over that period of time in the price per vial of Humulin R (Eli Lilly, Indianapolis, IN) and Novolin N (Novo Nordisk, Plainsboro, NJ) were 114%, 134% for lispro insulin, 116% for glargine insulin, and 117% for aspart insulin FlexPens (2). The wholesale prices for insulin in the past 2 years from 2011 to 2013 have increased on average by 43% (3).

In 2011, the cost per unit of insulin was twice as much for an analog compared with a generic preparation (2). In 2013, the wholesale cost of a vial of rapid-acting insulin was 81% more expensive than regular insulin, a vial of analog basal insulin (glargine, detemir) was 126% more expensive than NPH insulin, and a vial of analog premixed insulin 92% was more expensive than premixed NPH/regular insulin (3).

Given the high and increasing costs of insulin, it behooves us to examine whether analog preparations are worth their extra costs. What should be the outcomes used to compare analog insulins with human insulins? Pharmacokinetic and pharmacodynamic

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data are generated in acute studies and do not speak to clinical outcomes. For instance, both show that the rapid-acting analogs have significantly different pharmacokinetic and pharmacodynamic dynamics than human insulin. Based on these results, it is widely believed that regular insulin should be injected 20–30 min before a meal to yield lower postprandial glucose concentrations than if injected just prior to eating. Yet a recent study by Müller et al. (4) showed that both preprandial and postprandial glucose values measured at home were the same whether regular insulin was injected 20 min before or just prior to meals. This may not be too surprising given that the absorption and action of regular insulin varies over 20% in the same individual from day to day (5,6). There is little evidence that variability of glucose levels per se affects clinical outcomes (7,8). On the other hand, there is good evidence that lower overall glycemia, as reflected in A1C levels, leads to less microvascular diabetes complications (9–11). Therefore, changes in A1C levels and hypoglycemia should be the basis upon which analog and human insulins are compared.

The outcomes in 60 randomized control trials comparing analog and human insulins are summarized in Table 1. As there is little difference among the three rapid-acting insulins (lispro, aspart, glulisine) and the two basal insulins (glargine, detemir) regarding these outcomes, the results in each class of analog insulins are combined. Studies in type 1 and type 2 diabetic patients are presented separately. It is important to realize that a negative value for ΔA1C means a better response for the analog insulins. Also, note that regarding the ratios in Table 1, the numerator is the number of studies in which the outcome for the analog insulins was statistically significant compared with human insulins with the arrow signifying the direction of the difference and the denominator is the number of studies in which the outcome was measured. Regarding efficacy, across evaluations of all comparisons, only 15 of 64 (23%) showed a significant increase in the lowering of A1C levels with analog insulins compared with human insulins. The weighted mean difference between the change in A1C levels between analog and human insulins across all comparisons ranged from –0.01 to −0.23%, with an average difference of −0.09%—hardly of clinical importance in my opinion.

Regarding hypoglycemia, overall hypoglycemia was evaluated in 62 comparisons. In 17 of them, hypoglycemia was significantly less with analog insulins, while in 3 it was significantly increased. The most striking difference occurred in nocturnal hypoglycemia; in the 43 comparisons in which it was evaluated, it was significantly decreased in 27. In the 45 comparisons in which severe hypoglycemia was evaluated, it was significantly decreased by analog insulins in only 6. Thus, hypoglycemia occurred less often in patients receiving analog insulins, especially overnight. However, in none of the 60 studies was a bedtime snack recommended. In our practice, we insist that patients taking insulin eat a small bedtime snack and very few experience nocturnal hypoglycemia. As the vast majority of people with type 2 diabetes are overweight or obese, we instruct them to switch some calories from their largest meal to their bedtime snack.

Patients taking detemir insulin gained significantly less weight than those taking either NPH or glargine insulin in a number of studies (12–17). However, the differences were only 0.4–1.3 kg, which are not clinically significant.

Some would argue that treatment satisfaction and cost-effectiveness should play a role in the decision to consider using analog insulins. At least six studies have evaluated treatment satisfaction. Treatment satisfaction was assessed in three studies utilizing the Diabetes Treatment Satisfaction Questionnaire (18), which is an eight-item questionnaire with six questions evaluating treatment satisfaction and two questions related to perceived hyperglycemia and hypoglycemia. The maximum score for all eight questions is 48. One found no difference between glargine and NPH insulin (19). In a comparison between lispro and regular insulin in pump patients evaluating all eight questions, lispro insulin users scored 35.2 ± 4.2 versus 32.4 ± 5.9 for regular insulin users, which apparently was statistically significant ($P < 0.001$) by the nonparametric Friedman rank sum test (20). In a comparison between glargine and NPH insulins in which the two questions related to the perception of hyperglycemia and hypoglycemia were not reported, treatment satisfaction rose from 12.6 at baseline to 16.6 in the analog group versus 12.5 to 16.0 in those using NPH, which apparently also was statistically significant ($P < 0.02$) by pairwise ANCOVA (21). In a comparison between lispro and regular insulin, it was simply stated that there were no differences in the domains of energy/fatigue, health distress, or treatment flexibility but significant improvement was seen in the treatment satisfaction domain (no data were provided) (22). Two studies comparing lispro (14) or aspart (23) to regular insulin found the analogs provided significantly more flexibility than the human insulin, but this might be expected given that patients were instructed to take regular insulin 30 min before eating versus immediately before eating for the analogs. This difference in timing may not be considered important in the future given the results of Müller et al. (4), which showed that home glucose levels were the same whether regular insulin was injected 20 min before or just prior to a meal. These data on treatment satisfaction between analog and human insulins do not present a strong argument favoring the analogs.

There are reports based on modeling studies that analog insulins are more cost-effective than human insulin (24,25). Cost-effectiveness was defined as an incremental value of less than $50,000 per quality-adjusted life-year. The time horizon for the models ranged from 10 to 60 years and some for the lifetime of the patient. The various analyses use three major inputs: changes in A1C levels (affecting future diabetes complications that are the major drivers of costs for diabetes), costs for hypoglycemia (emergency room/hospital), and fear of hypoglycemia. The latter is considered important because with less analog-induced hypoglycemia, there would presumably be better adherence to insulin therapy; in the general population, better adherence to medications is associated with less medical care costs. It is difficult, of course, to project costs and complications for 10–60 years because of potential changes in the natural history of diabetes as well as non-insulin changes in treatments affecting diabetes complications. The data in Table 1 do not support assumptions that there are meaningful clinical changes in A1C levels between analog and human insulins. Although there are statistically

Table 1—A1C and hypoglycemia outcomes in 64 comparisons between analog and human insulins in randomized control trials

Comparison	No. of studies	No. of subjects	ΔA1C (%) [mmol/mol] analog minus regular or NPH			Hypoglycemia*		
			Range	No. of significant studies*	Weighted mean	Overall	Nocturnal	Severe†
Type 1 diabetes								
Analog vs. regular‡[a]	17	6,002	(−0.50 to +0.51) [−5.5 to +5.6]	↑4/17	(−0.03) [−0.3]	↓3/16 ↑2/16	↓6/7	↓2/15
Basal vs. NPH§[b]	12	4,770	(−0.40 to +0.05) [−4.4 to +0.5]	↑2/12	(−0.08) [−0.9]	↓4/12	↓6/12	↓2/8
Both analogs vs. NPH/regular‖[c]	3	674	(−0.50 to +0.10) [−5.5 to +1.1]	↑1/3	(−0.23) [−2.5]	↓1/3	↓2/3	↓1/3
Analog vs. regular¶ in pumps[d]	7	445	(−0.53 to +0.03) [−5.8 to +0.3]	↑5/8	(−0.16) [−1.7]	↓2/7	↓1/2	0/5
Type 2 diabetes								
Analog vs. regular#[e]	9	3,507	(−0.52 to +0.03) [−5.7 to +0.3]	↑2/9	(−0.08) [−0.9]	↓1/9 ↑1/9	↓2/4	0/4
Basal vs. NPH**[f]	14	5,742	(−0.34 to +0.21) [−3.7 to +2.3]	↑1/14	(−0.01) [−0.1]	↓6/14	↓10/14	↓1/9
Both analogs vs. NPH/regular††[g]	1	394	Only 1 study	0/1	(−0.07) [−0.8]	0/1	0/1	0/1

*Number of studies in which ΔA1C or hypoglycemia were statistically significantly different (numerator)/number of studies in which outcome was evaluated (denominator). †Very few severe hypoglycemic events occurred. ‡Fourteen lispro and three aspart studies. §Five glargine and seven detemir studies. ‖One detemir/aspart and two glargine/lispro studies. ¶Six lispro and two aspart studies. #Six lispro, one aspart, and two glulisine studies. **Eleven glargine and three detemir studies. ††One detemir/aspart study. [a]Refs. 1–17; [b]refs. 18–29; [c]refs. 30–32; [d]refs. 33–39; [e]refs. 4,5,16,40–45; [f]refs. 46–59; and [g]ref. 60 in Supplementary Data.

significant reported differences in hypoglycemia between analogs and human insulin, these mainly occur overnight and bedtime snacks minimize this difference. Fear of hypoglycemia and its effect on adherence to insulin therapy is based on assumptions that are difficult to quantitate. In my view, these data on cost-effectiveness are not a strong argument for preferring the more expensive analog insulins.

In conclusion, regular insulin is just as effective as the rapid-acting insulin analogs (lispro, aspart, glulisine). Similarly, NPH insulin is just as effective as the basal insulin analogs (glargine, detemir). Without a bedtime snack, overnight hypoglycemia may be more common with regular insulin taken before supper and NPH insulin taken at bedtime than their corresponding analogs. In general, analog insulins are twice as expensive as human insulins. For those who wish to use a much less expensive, evidence-based approach to insulin therapy, analog insulins are not preferred with two important exceptions. Type 1 diabetic patients require basal analog insulin because they produce no endogenous insulin and need 24-h coverage. In the unusual occurrence of overnight hypoglycemia in type 2 diabetic patients who ingest a bedtime snack, it may be helpful to prescribe an analog rapid-acting insulin before supper (and presumably before the other meals to simplify the regimen) if the hypoglycemia occurs early overnight, and a basal analog insulin if it occurs toward morning. With these two exceptions, analog insulins provide no clinical benefit compared with human insulins, but cost much more.

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