Insulin Analogs: Innovation in Biotechnology

New England Healthcare Institute

NEHI Innovation Series

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ABOUT NEHI

Founded in 2002, the New England Healthcare Institute (NEHI) specializes in identifying innovative strategies for improving health care quality and reducing health care costs. NEHI conducts independent, high quality research that supports evidence-based health policy recommendations at the regional and national levels. Member representatives from the academic health center, biotechnology, employer, medical device, payer, pharmaceutical, provider, and research communities bring an unusual diversity of talent to bear on NEHI's work. We collectively address critical health issues through our action-oriented research, education, and policy initiatives.

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Cover Photo: *The photograph of the NovoPen® Junior insulin delivery system (insulin pen), which is used with Novo Nordisk insulin products such as NovoLog® (insulin aspart [rDNA origin] injection), is courtesy of Novo Nordisk Inc.*

Table of Contents

List of Figures ii


Preface 1


Executive Summary 3


Introduction 9


Diabetes Overview 11


Insulin Treatment 15


Insulin Analogs 17


The Value of Insulin Analog Use 19


Conclusions 25

Appendix: Cost-Effectiveness Analysis 28

Endnotes 33

List of Figures

Figure 4-1: Historical Timeline 15

Figure 5-1: Profiles of Bolus Insulins in Type 1 Patients 17

Figure 5-2: Profiles of Basal Insulins in Type 1 Patients 18

Preface

This report is the fourth in the *Innovation Series* published by the New England Healthcare Institute (NEHI). The goal of the *Innovation Series* is to identify opportunities to accelerate the adoption of highly valuable innovations that will benefit patients and help contain U.S. health care costs. Focusing on emerging innovations for the treatment of major diseases, such as cancer, cardiovascular disease and diabetes, these reports analyze specific classes of innovation, identifying their value, drivers and barriers to adoption. Each report closes with recommendations for actions that major stakeholders (e.g., manufacturers, regulatory agencies, payers, patients, providers) can take to help speed an innovation's journey from initial concept to accepted clinical practice. NEHI draws upon its industry-wide membership to guide the development of these recommended actions.

Previous NEHI *Innovation Series* Reports:

Targeting Cancer: Innovation in the Treatment of Chronic Myelogenous Leukemia (March 2004)

Remote Physiological Monitoring: Innovation in the Management of Heart Failure (July 2004)

Continuous Glucose Monitoring: Innovation in the Management of Diabetes (March 2005)

Executive Summary

DIABETES MELLITUS AND GLUCOSE CONTROL

Diabetes is widely acknowledged as an immense and growing public health problem. The disease is associated with increased risk of death, decreased quality of life and costly, dangerous complications. At the root of these problems is the loss of the body's natural ability to produce and use insulin to maintain normal levels of glucose in the blood.

For many patients with diabetes, one of the central means of maintaining blood glucose control is through the external delivery of insulin. For a patient whose body produces little or no insulin, external insulin delivery must simulate two types of internal insulin secretion: a bolus secretion, which is a rapid-onset, high-level secretion of insulin in response to meals, and a basal secretion, which provides a constant, low-level of insulin for the body's between-meal metabolic demands. By delivering insulin at the right time and in the right amount, patients can keep their blood glucose at near normal levels, which will limit the development of serious, long-term complications such as blindness, kidney failure and limb amputation,[1] and subsequently decrease risk of death and increase quality of life.

BIOTECHNOLOGY INNOVATION IN DIABETES: INSULIN ANALOGS

Advances in Insulin Therapy

One of the most significant areas of recent innovation in diabetes treatment has been the development of new forms of insulin, called insulin analogs, which allow the body to more closely mimic the natural regulation of blood glucose that occurs in people without diabetes. Insulin analogs promise improvements in blood glucose control by decreasing the frequency of hypoglycemic (low blood sugar) events and reducing hemoglobin A1C[i] levels. A1C levels are an established proxy for average blood glucose level over time and a strong indicator of long-term complication development. Insulin analogs are also more convenient for patients to take than regular insulin and thus have the potential to improve patient compliance with treatment regimens.

This report analyzes two classes of insulin analogs: rapid-acting insulin analogs and long-acting insulin analogs. Rather than examining the differences among specific products within each class, this analysis focuses on the benefits of each class of insulin analog as a whole:

- Rapid-acting insulin analogs, such as lispro, aspart and glulisine, take effect and lose effect faster than regular insulin (RI), which helps patients

[i] The A1C test measures the percentage of glycated hemoglobin (hemoglobin with glucose bonded to it) in the blood, which in turn corresponds to a patient's average blood glucose over a period of two to three months. An A1C level between 4 percent and 6 percent is considered typical for people without diabetes.

control the rapid change in glucose levels (bolus) that accompanies a meal.

- Long-acting insulin analogs, such as glargine and detemir, improve upon Neutral Protamine Hormone (NPH) by providing the more constant, low-level of insulin (basal) that the body needs between meals.

Insulin analogs can be incorporated into a patient's treatment regimen in a variety of different ways, depending on factors such as the stage of a patient's disease, lifestyle considerations, and the specific times when the patient's blood glucose reaches abnormal levels. For patients who require only bolus or basal insulin, analogs can often replace the patient's traditional insulin. For patients who require both bolus and basal therapy (known as insulin replacement), analogs have been used in two ways. *Independent use* describes the use of a rapid-acting analog to replace RI as the bolus insulin, while maintaining NPH as a basal insulin, **or** the use of a long-acting analog to replace NPH as a basal insulin, while maintaining RI as a bolus insulin. Recently, studies have also explored the use of rapid- and long-acting analogs in *combination use*—a regimen of rapid-acting **and** long-acting insulin replacing a regimen of RI and NPH.[2]

Benefits

In general, the use of rapid- and long-acting insulin analogs is expected to have major benefits in two critical areas of diabetes treatment:

- **Blood Glucose Control:** Landmark clinical trials have shown that intensively managing blood glucose levels to remain within a near-normal range can dramatically decrease the risk of some long-term complications associated with diabetes. Insulin analogs provide benefits in intensive insulin therapy by:

  - Reducing the variability of blood glucose levels over time. When used as independent agents, both rapid- and long-acting analogs have generally been found to be as effective as traditional insulins in controlling blood glucose levels (represented by a reduction in A1C levels). A recent study has also shown that insulin analogs can provide an even greater reduction in A1C than a regimen of traditional insulins when the analogs are used in combination.[2]

  - Reducing the frequency of hypoglycemia. Clinical trials of rapid- and long-acting insulin as independent treatments, and in combination therapy, showed that treatment with analogs generally yields lower rates of hypoglycemia than treatment with traditional insulin.[3]

- **Patient Convenience:** Patient convenience is critical to the self-management of diabetes, as it greatly impacts patients' decisions about how aggressively to manage their conditions. Therefore, the convenience

factor and short-term quality of life improvements will ultimately drive improved health outcomes. Insulin analogs:

- Increase patients' comfort with pursuing tight control of blood glucose by reducing the frequency of hypoglycemia.
- Ease the burden of insulin delivery on patients by allowing them to take rapid-acting insulin with a meal (or in some cases within 20 minutes after starting a meal), rather than 30 to 60 minutes before eating.
- Reduce the number of injections of long-acting insulin, depending on the specific treatment regimen.

Value

This progress in the treatment of diabetes could not be timelier. As innovations, like insulin analogs, deliver better care to patients, it becomes increasingly important to examine the benefits of these innovations relative to their costs. In today's cost-conscious health care environment, there is a growing movement to assess innovations based on value—that is, to determine the benefit of an innovation relative to its cost—rather than to evaluate it on product acquisition cost alone.

In this analysis, NEHI has taken two approaches to examining the value of insulin analogs:

- A traditional cost-effectiveness approach (cost-utility analysis)[4] to determine the value of insulin analog drugs used in combination therapy. Extrapolation of results from the largest randomized trial of combination use in type 1[ii] patients demonstrates that insulin analogs are indeed cost-effective.
- A qualitative review of the benefits of insulin analogs to determine whether increased convenience of drug administration improves the management of diabetes. Patient and clinician experiences suggest that insulin analogs have significant convenience and quality of life benefits that are critical to the long-term management of diabetes. However, these benefits are not quantified fully in NEHI's value analysis because they have not yet been adequately measured in the literature.

Cost Effectiveness

Insulin analogs can be used in a variety of different treatment regimens depending on the stage and type of a patient's disease. A cost-effectiveness evaluation for

[ii] In type 1 diabetes, the pancreas is unable to produce insulin and patients must inject or infuse external insulin in order to live.

each use is beyond the scope of this report.[5] Instead, NEHI's cost-effectiveness analysis examines the specific case of combination insulin analog therapy in type 1 patients. This analysis serves as a case study of the value that insulin analogs can provide. Evaluating the costs and benefits of combination insulin analog therapy in type 1 patients does appear to be cost effective, with a base case cost-effectiveness ratio of $59,001 per Quality-Adjusted Life Year (QALY) (see Appendix for further details). The cost-effectiveness result is sensitive to the cost difference between analogs and traditional insulin, the cost of a hypoglycemic event, and the relative reduction in A1C that can be brought about by analogs. Despite this sensitivity, there are many reasons to believe that the technology may prove to be even more cost effective and valuable over time. For example, there are continual improvements in the clinical understanding and use of the drugs, as well as new findings regarding the additional benefits of blood glucose control in reducing macrovascular complications.[6]

Convenience

One of the major benefits of insulin analog use lies in patients' ability to maintain blood glucose control with fewer restrictions and limitations on their daily lives. There is a growing body of evidence that insulin analogs can significantly improve patients' treatment satisfaction and convenience by improving meal timing and reducing fear of hypoglycemia.[7,8,9] To date, these benefits have not been well quantified in terms of QALYs, and thus cannot be reflected in a cost-utility analysis of insulin analogs.

From Convenience to Compliance

Until a cure is developed, NEHI believes that some of the most significant advances in diabetes care will come in the form of improved management regimens that patients can easily adopt and maintain. Given the poor rate of adherence with management regimens in current diabetes care, innovations that allow a greater number of patients to enter into a treatment regimen may have significant societal value beyond what can be expressed in cost-effectiveness terms. Insulin analogs are extremely important in helping patients achieve higher levels of medication compliance.

Evidence in Practice

NEHI's modeling results suggest that the determination of value is dependent on relatively early assessments of the effectiveness of analog drugs. As such, more work needs to be done to confirm the benefits of combination use observed in initial trials. Despite this uncertainty, the wide adoption of this class of innovation in practice indicates that much of the health care community believes in the use of insulin analogs. Insurers pay for the analogs at the same level as regular insulins and there is evidence of broad adoption among clinicians.[10,11]

SUMMARY

This report examines the value of biotechnology in the treatment of diabetes through a study of one of the most significant advancements in insulin therapy—insulin analogs. Applying cost-effectiveness analysis to the specific case of combination use of insulin analogs in type 1 patients, NEHI determined that insulin analog drugs used in combination therapy are indeed cost effective for type 1 diabetes patients. In addition to quantitative analysis, the qualitative evidence of improved patient convenience and quality of life indicate that insulin analogs offer significant value to patients.

Moving forward, health care decision makers need to find ways to quantitatively evaluate improvements in quality of life and patient convenience. These are critical measures that need to be incorporated in the larger analyses in order to provide a complete picture of the value of an innovation. In particular, health policy researchers need to create a mechanism to test the hypothesis that improved patient convenience leads to increased patient compliance and results in better clinical outcomes.

Introduction

Biotechnology has clearly played a significant role in providing new treatment options for patients with diabetes. Beginning with the first recombinant human insulin in 1982, which virtually eliminated allergic reactions and subcutaneous lipoatrophy[iii] associated with an immune response to animal insulin,[3] biotechnology products have been widely adopted by patients in the United States.[12] Biotechnology is likely to continue to play a large role in improving care in this disease area as more advanced drugs come to market for diabetes and related conditions, such as obesity.

One of the most significant areas of biotechnology development in diabetes has been the creation of insulin analogs. Compared with recombinant human insulin, which is identical to the structure of the natural insulin molecule produced by the islet cells in the pancreas, insulin analogs are constructed by altering the amino acid sequences of human insulin and subsequently changing its structure.[13] Given their unique action-profile characteristics, insulin analogs have the potential to help more diabetes patients achieve better control of their blood glucose levels, an important means of preventing diabetes complications. It is this benefit that makes insulin analogs a valuable technology.

Progress in the treatment of diabetes could not be timelier, as the disease continues to grow as a major public health concern in American society.[14] However, as more therapeutic options arise in diabetes care—most often at an increased cost—it becomes increasingly important to examine their benefits relative to their costs. This report looks at the value of biotechnology in diabetes through a study of insulin analogs. In order to understand this value, this report examines:

- The magnitude and complexity of the pubic health problem diabetes poses to society.
- The role insulin analogs have played in improving diabetes care.
- The current evidence of the value insulin analogs can provide.

[iii] Subcutaneous lipoatrophy is the loss of fat under the skin, which can be caused by repeated insulin subcutaneous injection and other conditions.

Diabetes Overview

Policymakers and the public are well aware that diabetes is a significant public health challenge in the United States. Whether it is through knowing a patient or reading the headlines, diabetes has recently moved to the forefront of the public's attention. Despite this broad general awareness of the disease, relatively few people are familiar with the complexity of diabetes and the day-to-day challenges of managing this chronic disease.

THE SOCIETAL IMPACT OF DIABETES

A Growing Epidemic…

Approximately 20.8 million Americans suffer from diabetes.[15] The U.S. Centers for Disease Control and Prevention (CDC) expects this number to more than double by 2050 as 1.5 million new cases are diagnosed each year.[16,17] The CDC's estimates further indicate that about one-third of American children born in 2000 will develop diabetes during their lifetimes.[18]

…With Dangerous Consequences

Not only widespread, the disease is pernicious. Many patients must live with the daily risk of short-term events that can lead to loss of consciousness, seizures and death.[19] In the long term, diabetes contributes to a host of extreme complications, such as blindness, damage to the lower extremities (which leads to amputation), kidney failure, heart disease and stroke.

Diabetes is the sixth leading cause of death in the United States, contributing to over 200,000 deaths per year. Overall, people with diabetes face a risk of death about two times higher than people without diabetes.[20]

…And a High Cost to Society

Diabetes care consumes more than 12 percent of the U.S. health care budget.[21,22] In 2002 diabetes cost the United States over $90 billion in direct medical expenditures—a figure that swells to over $130 billion annually when indirect costs are added. In direct medical costs, nearly $70 billion is spent annually to treat long-term complications, while over $20 billion can be attributed to the cost of daily diabetes care, such as blood glucose monitoring and insulin supplies. The $40 billion in indirect costs are the results of lost workdays, decreased productivity, permanent disability and untimely death. The American Diabetes Association (ADA) estimates that diabetes could cost the United States upward of $192 billion per year by 2020.[21]

THE COMPLEXITY OF DIABETES

The term "diabetes" actually refers to a group of chronic diseases characterized by high levels of glucose in the blood that result from a decrease in the body's ability to produce and use insulin. Insulin plays a central role in regulating the body's blood glucose level. When energy from food is converted to glucose and distributed throughout the body, insulin is required for the uptake of glucose

from the blood and into the cells for use. Without enough insulin, excess glucose accumulates in the blood and can cause damage to blood vessels and result in severe complications. Too much insulin, on the other hand, lowers blood glucose too quickly, which leaves the brain deprived of energy. Such periods of low blood glucose are known as hypoglycemia. Severe cases of hypoglycemia are extremely dangerous, placing a patient at risk for seizures, coma and death.

Types of Diabetes

The various metabolic disorders that are represented by the term "diabetes" are divided into two major classifications—"type 1" and "type 2."[23]

In type 1 diabetes, the pancreas is unable to produce insulin and patients must inject or infuse external insulin in order to live (more details can be found in the chapter "Insulin Treatment"). Typically diagnosed in children and young adults, type 1 diabetes represents only 5 percent to 10 percent of the diabetes population, totaling approximately 1 million individuals.

In type 2 diabetes, the body's ability to use insulin becomes inhibited, and the pancreas is unable to produce enough additional insulin to compensate for this deficiency. Type 2 diabetes represents 90 percent to 95 percent of the diabetes population. The progression of type 2 diabetes is typically more gradual—with insulin production and/or insulin sensitivity decreasing over the course of several years.[24] The onset of type 2 diabetes can typically be prevented, or the progress of the disease delayed, through lifestyle behaviors such as diet, exercise and weight control.[25] As a secondary measure, type 2 patients may use oral medications to enhance the body's use of its own insulin by stimulating more insulin production or by making cells more sensitive to insulin.

For patients with type 2 diabetes whose disease continues to progress, most begin taking insulin, infrequently at first, to augment the body's remaining insulin production capacity. If type 2 diabetes progresses to the point where the body produces only a negligible amount of insulin, external insulin must completely replace the body's insulin production and treatment begins to resemble the regimen for type 1 diabetes.

Control

For all patients, regardless of type, maintaining good blood glucose is essential to the avoidance of long-term complications. During the past 10 years, landmark clinical trials, such as the U.S. Diabetes Complications and Control Trial (DCCT) and the UK Prospective Diabetes Study (UKPDS), have shown that maintaining blood glucose levels within a near-normal range can dramatically decrease the risk of some of the noted long-term microvascular complications associated with diabetes: retinopathy, nephropathy and neuropathy, which, respectively, can cause blindness, kidney failure and lower-extremity amputations. Results from the DCCT, for example, demonstrated that tight control delayed the onset of long-term microvascular complications by 15 years and also extended life expectancy.[26,27] At the 2005 annual scientific meeting of the ADA, a follow-up

study from the DCCT was released which also showed that tight glucose control significantly reduces macrovascular complications by roughly 50 percent, resulting in fewer incidences of heart attack, stroke and angina.[6]

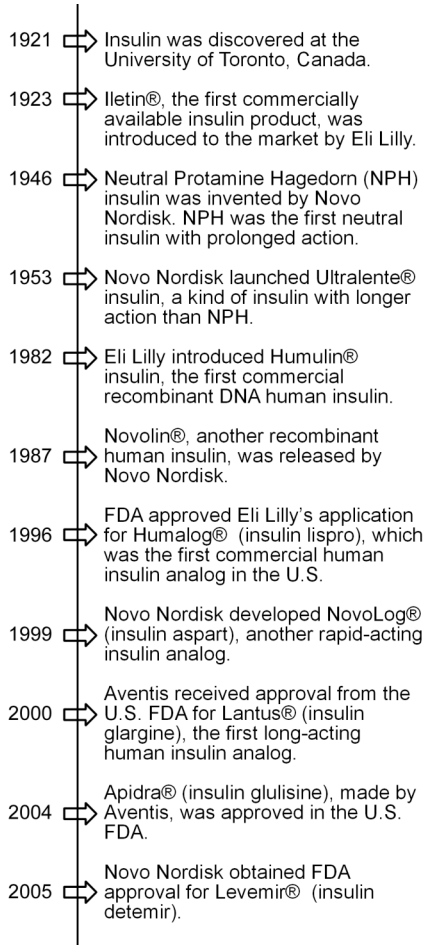
The findings from the DCCT and UKPDS have been incorporated into the clinical guidelines that comprise today's standard of care.[28] Most of these guidelines use the hemoglobin A1C level (commonly referred to as "A1C") as a proxy for the level of blood glucose control a patient has obtained. The A1C level measures the concentration of hemoglobin that binds to glucose, which, in turn, corresponds to a patient's average blood glucose over a period of two to three months. An A1C level between 4 percent and 6 percent is considered normal for people without diabetes.

Insulin Treatment

Insulin is a central tool for obtaining good blood glucose control and has been one of the most important weapons against diabetes worldwide since it was discovered in 1921. Injection or infusion of insulin provides patients with the opportunity to control their blood glucose and reduce the likelihood of developing serious complications. For all patients with type 1 diabetes and those with type 2 diabetes who produce a negligible amount of insulin, frequent external delivery of insulin is essential (insulin replacement). For patients with less advanced type 2 diabetes, insulin is used less frequently as a supplement to their body's compromised level of insulin production (insulin augmentation). While insulin analogs can generally be used in each of these methods of therapy for type 2 diabetes, [29] this report will focus solely on insulin replacement regimens.

Figure 4-1

HISTORICAL TIMELINE



Source: NEHI

BLOOD GLUCOSE REGULATION IN PATIENTS WITHOUT DIABETES

Insulin treatment aims to deliver externally what the non-diabetic body produces on its own. At any given moment, the body's insulin requirements may vary based on a range of factors, such as food intake, physical activity level and stress. In healthy individuals, the body has an uncanny ability to respond quickly to these changing insulin demands. The pancreas is capable of continuously secreting a very low-dosage insulin, known as basal insulin secretion, which can be finely adjusted based on specific metabolic demands on the body. Basal insulin secretion is critical for controlling blood glucose levels between meals and overnight. The pancreas can also produce large amounts of insulin after eating, which is called a bolus insulin secretion.

THE CHALLENGE OF INSULIN DELIVERY

For patients whose bodies produce little or no insulin—all type 1 and a portion of type 2 patients—the goal of insulin replacement therapy is to mimic the

pancreas and deliver the right amount of insulin at the right time to keep blood glucose within a normal range. These patients attempt to do this through a pattern of intensive insulin delivery, which aims to mimic the basal-bolus functions of the pancreas with two types of externally delivered insulin—one that acts quickly to simulate the bolus and one that acts slowly to simulate the basal.

Regrettably, therapeutic technology rarely does as well as the human body in regulating physiological conditions. "Regular insulin" (RI), which is the type traditionally used to provide the bolus dose, acts more slowly and lasts longer than insulin secreted by the pancreas. It takes an average of 45 minutes for RI to have its glucose-lowering effect in the blood, so in order for a dose of insulin to provide an effective bolus for one's meal, it must be injected well in advance. RI also usually lasts longer than what is required to cover the insulin requirements of a meal. The excess insulin that results after a meal can lead to hypoglycemia.

Furthermore, the traditional insulin used for the basal doses, known as Neutral Protamine Hagedorn (NPH), does not replicate the continuous, low secretion of insulin provided by the pancreas. The effectiveness of NPH has a peak, where too much insulin is provided relative to what is required for basal output, and patients are at increased risk of hypoglycemia. NPH also has a relatively short duration of action, sometimes leaving patients without enough insulin between injections and, subsequently, with elevated blood glucose levels. Often, these periods of first insufficient and then excessive insulin occur at night, when patients are less able to take corrective action.

Both of these traditional insulins, RI and NPH, also exhibit a high degree of variability in absorption by the body.[29] The same dose of insulin often provides a different level of glucose lowering effect from patient to patient and from day to day within a single patient. Such inconsistency in glucose regulation effect can frustrate patients' efforts to reliably control their blood glucose.

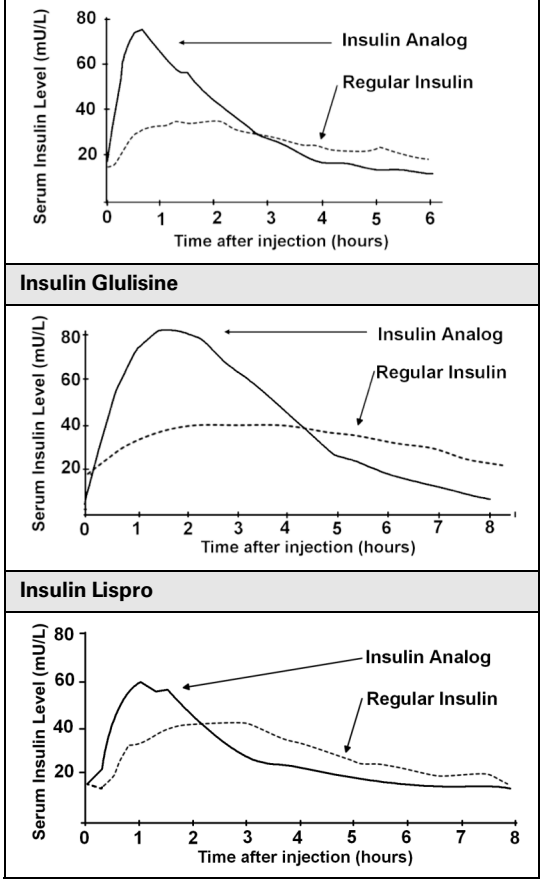
These shortcomings limit the effectiveness of traditional insulin therapy, leading to less-than-optimal blood glucose control and increased frequency of dangerous, acute hypoglycemic events. The benefits and risks of insulin therapy bring to light an important balance that diabetes patients must negotiate. The more one strives for tight control and avoidance of long-term complications, the greater the risk of hypoglycemia and the development of a short-term acute complication.

Insulin Analogs

Innovation in insulin development has focused on creating new insulins that are better able to mimic the basal-bolus functions of the pancreas. This has been made possible through biotechnology techniques that allow for the alteration of the amino acid sequences that comprise a molecule of insulin. Two types of biotechnology insulin analogs have been created: insulin that acts faster than RI and better mimics the pancreatic bolus secretion (rapid-acting insulin) and insulin that has a prolonged, steady effect to better mimic basal secretion (long-acting insulin). A third classification of insulin analogs is premixed insulin, which combines a rapid-acting analog with a component that is functionally identical to NPH. This analysis will focus on rapid- and long-acting analogs.[33]

Figure 5-1

PROFILES OF BOLUS INSULINS IN TYPE 1 PATIENTS



Source: Novo Nordisk;[30] Sanofi-Aventis;[31] Eli Lilly and Co.[32] Charts adjusted to scale from prescribing information. Glucose infusion rate is a measure of the amount of exogenous glucose required to maintain a constant blood glucose level when a patient is given an insulin dose. The measure can provide a parallel indication of insulin action profile.

RAPID-ACTING ANALOGS

Three rapid-acting insulins have been approved for sale by the FDA: insulin lispro, approved in 1996; insulin aspart, approved in 1999; and insulin glulisine, approved in 2004. These three rapid-acting insulins have similar profiles and effects on patients.[34] Rapid-acting insulin starts working faster than RI, so it can control the short period of rise in blood glucose that occurs immediately after meals better than RI.

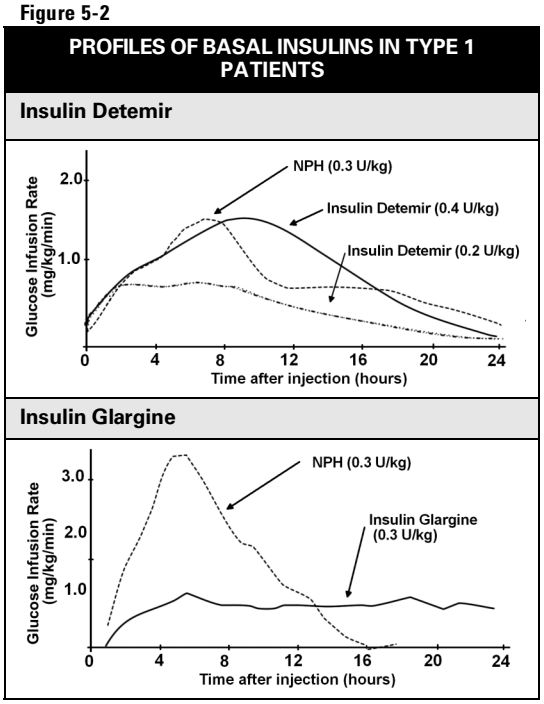
A further benefit is the short action profile of rapid-acting insulins relative to RI. A shorter period of insulin action means a lower likelihood of excess insulin after a meal (post-prandial) and, thus, a lower likelihood of hypoglycemia.

LONG-ACTING ANALOGS

Newer long-acting insulins are capable of providing an insulin action profile that more closely resembles the low basal output of the pancreas. The development of long-acting insulins has lagged relative to rapid-acting insulins—insulin glargine was approved in 2000 and insulin detemir was approved in 2005. While NPH has a peak effect and a shorter duration of action, both of these newer long-acting insulin analogs have a relatively constant blood concentration and can provide a longer period of glucose-lowering activity than NPH. By providing basal insulin with little or no peak and a longer duration of action, hypoglycemia can be reduced.

Figure 5-2

PROFILES OF BASAL INSULINS IN TYPE 1 PATIENTS



Source: FDA;[35] Sanofi-Aventis.[36] Charts adjusted to scale from prescribing information.

RAPID- AND LONG-ACTING ANALOGS: INDEPENDENT VERSUS COMBINATION USE

Early trials of replacement therapy with insulin analogs focused on independent use—identifying the separate and independent effects of either:

- Rapid-acting insulin used with NPH, compared to RI with NPH, **or**
- RI used with long-acting insulin, compared to RI with NPH.

Large clinical trials of independent insulin analog use have shown that analogs are as effective in reducing A1C levels as traditional insulins. Independent use, however, has not been shown to consistently reduce A1C levels any more than traditional insulins.[3,37] Some researchers have hypothesized that the full benefits of insulin analogs cannot be realized when they are used in concert with traditional insulins (RI or NPH), as the benefits of the insulin analog are masked by the shortcomings of the accompanying traditional insulin.[2,38] Recent trials have focused on comparing the combination of rapid- and long-acting insulin analogs with the combination of RI and NPH. One key trial, conducted in 2004, demonstrated that combination use of insulin analogs resulted in a 3 percent relative reduction in A1C levels compared with those obtained with traditional insulins. Combination analog therapy also resulted in an 83 percent reduction in severe nocturnal hypoglycemia when compared with traditional insulins.[2,38]

The Value of Insulin Analog Use

COST-EFFECTIVENESS ANALYSIS

As innovations emerge, evidence of value (the cost is worth the benefit) is required more and more frequently by health care decision makers. As a result, stakeholders increasingly rely on cost-effectiveness analysis as an important tool for assessing the value of these innovations.

Cost-effectiveness analysis is a standardized method of evaluating health care interventions by comparing the costs and benefits of competing treatment strategies. It may be true, for example, that the cost of using a new treatment is several thousand dollars per year more than the current treatment, but without knowing what one is getting in return (e.g., how many lives are saved, how many complications are prevented), one cannot know if this additional money is well spent.

The most common form of cost-effectiveness analysis, cost-utility analysis, compares the costs and quantified quality of life effects (represented by Quality Adjusted Life Years, or QALYs) for the use of a new treatment relative to the previous standard of care. The resulting measure of value is most commonly expressed in the form of a cost-utility ratio, with units of dollars per QALY.

QALYs provide a global quality of life measurement through a single number that is intended to represent the overall health status of an individual over time, ranging from 1.0 for a year's worth of perfect health to 0.0 for a year in which an individual is dead. For example, if an individual lived for one year at a quality of life that is measured at only three-fourths of a year in perfect health, he will have lived 0.75 QALYs. This standardized measure of health allows for the expression of value (cost versus benefit), as a ratio of dollars per QALY.

However, it is important to note that such measures of cost effectiveness are only able to capture the treatment effects that can be well-quantified by the QALY metric, such as averted costs or well-documented quality of life changes for debilitating conditions such as blindness. When quality of life effects are not well-quantified, the dollars per QALY measure becomes only a partial picture of value.

In the case of insulin analogs, an improvement in A1C levels and the concomitant reduction in long-term complications is a central benefit that lends itself to a cost-utility analysis. Early evidence of this benefit has been demonstrated in the use of two insulin analogs in combination with each other. NEHI modeled the benefits and costs of combination insulin analog use with a base-case scenario where analog use yields a 3 percent relative reduction in A1C and an 83 percent reduction in severe nocturnal hypoglycemia.[2] The model assumed an annual insulin cost increase of $716 for the use of analogs and a cost per hypoglycemic event of $640. This base-case analysis results in a favorable cost-effectiveness outcome, with a specific cost-effectiveness ratio of $59,001 per QALY. Sensitivity

analysis showed that the conclusion of cost effectiveness is sensitive to the cost difference between analogs and traditional insulins, the cost of a hypoglycemic event and the A1C reductions brought about by insulin analogs. Details of NEHI's cost-utility analysis are contained in the Appendix of this report.

CONVENIENCE TO THE PATIENT

A review of the patient's perspective on the clinical benefits of insulin analogs can provide an even more complete view of the innovation's value, as benefits such as patient convenience are not reflected in the cost-effectiveness measure. The convenience benefit from insulin analogs is multi-faceted. Common sense dictates that a treatment that allows for fewer scheduling constraints and reduced risk of dangerous acute events would lead to direct improvements in the lives of patients. Although such improvements have been observed in several clinical trials of insulin analogs, they have only been documented on an anecdotal level. Clinical experience and patient opinion have identified three main outcomes that result from increased patient convenience: improved meal timing, reduced number of injections and fewer hypoglycemic events.

Meal Timing

When one of the leading diabetes patient Web sites, childrenwithdiabetes.com, asked its audience in December 2003, "What do you think is the hardest part of diabetes?," 18 percent of respondents cited meal planning.[39]

The 30- to 60-minute delay in insulin action seen with RI requires patients to rigorously plan their meals around insulin delivery—a missed bolus before a meal or a bolus that is not followed by a meal can lead to dangerously high blood glucose levels. Further, a patient's meal regimen must not only be timed correctly, but the meal content must be estimated in advance in order to provide the right amount of insulin in the pre-meal bolus. This opportunity to take rapid-acting insulin analogs immediately before a meal allows the insulin dose to be more closely matched with meal contents, as patients are not forced to estimate the time and content of their meal well in advance.

Insulin analogs have the added benefit of eliminating what is commonly referred to as the "snack effect." With the prolonged duration of RI, patients who take a bolus injection to account for dinner must also eat a late-night snack that will balance the insulin that remains in their system. Such a requirement adds a further burden to the lives of diabetes patients.

Frequency of Injections

Another benefit of insulin analog use is that patients who are exclusively using long-acting analogs can get through a day with fewer injections. With a 24-hour period of action in an insulin like glargine, patients are able to go from two injections of NPH per day to a single injection of a long-acting insulin. This reduction in the number of injections can be an important benefit for patients, as they are able to avoid the discomfort of a daily injection and reduce the scheduling restraints of their treatment regimen.

Hypoglycemia Reduction

In their milder manifestations, hypoglycemic events result in anxiety, trembling, heart palpitations, sweating and hunger. If uncorrected, these symptoms can quickly worsen to include confusion, behavioral changes, mood swings, seizures, loss of consciousness and—in extreme cases—death.

Consistent reductions in nocturnal hypoglycemia were observed in the use of rapid- and long-acting insulin analogs both as individual agents and when used in combination. Early results from trials of combination use show substantial reductions across all other types of hypoglycemia as well. Unfortunately, it is difficult to translate these reductions in hypoglycemic events into measurable cost-savings or quantifiable measures of quality of life. While less severe hypoglycemic events can still be difficult and burdensome for patients, they are generally short-term events and do not translate well into a quantifiable decrease in the measure of quality of life.[40]

The most significant effect of hypoglycemia reduction may be found in the reduction of stress and fear associated with a patient anticipating a severe hypoglycemic event. In the patient group poll referenced above, the number one difficulty cited by patients (38 percent of respondents) was "hypoglycemia and the fear of going low." Clinician experience also supports these findings. As Dr. Robert Sherwin, director of the Juvenile Diabetes Research Foundation's Center for the Study of Hypoglycemia, has noted, "We asked parents of children with diabetes what they fear most, and at the top of the list was hypoglycemia. Even if you ask most of the adults I treat, their fear is hypoglycemia."[19]

Nocturnal hypoglycemia can be an even more threatening risk for patients, as patients fear having an extremely low blood glucose level that they are unable to address during their sleep. Anxiety surrounding nocturnal hypoglycemia results in sleepless nights, especially for parents of children with diabetes. JoAnn Ahern, coordinator of the Yale Program for Children with Diabetes, notes, "Some parents are up all night, checking their kids' blood sugar, and I don't think that's good for anybody. I think it makes the kids afraid."[19]

The Magnitude of Convenience Improvements

While common sense and patient experience dictate that reducing these factors would improve patient quality of life, this improvement has yet to be sufficiently quantified in a manner that can be incorporated into cost-effectiveness calculations. In the United Kingdom, there have been attempts to estimate the QALY benefit of reduced fear of hypoglycemia; however, the data behind these attempts have not been released and the regulatory body that evaluated the estimate was highly critical of the result.[40] Another approach that has been attempted outside the United States is the Willingness-To-Pay (WTP) analysis. Such studies have tried to quantify convenience by laying out the consequences of a disease and the benefit of treatment, and then asking individuals how much they would be willing to pay for the treatment. As of 2004, the only WTP studies conducted on insulin analogs were completed outside the United States;

the results, therefore, cannot be extrapolated to the American market due to cultural and health care system differences.[41,42]

FROM CONVENIENCE TO COMPLIANCE

Until the development of a cure for diabetes, one of the most significant improvements in diabetes care will be the creation of management regimens that patients can easily adopt and maintain. Insulin analogs are an important step in that direction, as they provide improved convenience and a likely reduction in hypoglycemic events.

Only 37 percent of people with diabetes are achieving the ADA's goal for blood glucose level with an A1C score of less than 7 percent,[43] and compliance with an effective management regimen is likely at the heart of this poor outcome. Although several clinical trials of insulin analog use have tracked some measures of patient compliance, most have not done so as a primary area of interest. That said, at least four major trials of insulin analogs have observed increased compliance in the analog group over the traditional insulin control group.[44,45,46,47]

Given the significant challenge of motivating patients to adhere to treatment regimens in diabetes, insulin analogs have an important value to patients in helping them achieve effective treatment levels.

IMPROVING THE USE OF INSULIN ANALOGS

Clinical use of insulin analogs is in its early stages and there is some sentiment among experts in the area that these drugs will demonstrate their ability to reduce long-term complications over time. One hypothesis is that rapid-acting analogs require improved fine-tuning of basal insulin delivery in ways that are just beginning to be understood by physicians. Further study may lead to improved coordination of basal and bolus insulin delivery and, consequently, improved glycemic control.[48,49,50]

Ongoing clinical research may also demonstrate improvements in blood glucose control when the therapy is targeted toward particular subgroups of patients who are most likely to benefit. Such subgroups may include patients with an atypical eating pattern or hypoglycemia unawareness.[iv,51]

EVIDENCE IN PRACTICE

In the absence of hard data that quantify the magnitude of benefits gained from convenience and the potential for improved compliance, the best indicators of value come from the real-world experience of clinical practice and reimbursement.

NEHI's survey of regional and national insurers revealed broad coverage of insulin analogs at the same benefit level as RI. While the inclusion of specific

[iv] Patients with hypoglycemia unawareness are unable to feel or recognize the symptoms of hypoglycemia, which may impair their ability to detect and treat low blood glucose levels before they become severe.

drugs in Medicare formularies under the new law will be done by pharmaceutical benefits managers and health plans that will administer the benefit, insulin analogs are currently included in the legislatively mandated model guidelines for drug benefits produced by the United States Pharmacopeia.[52]

There is also anecdotal evidence of broad adoption among clinicians. According to a Novo Nordisk 2003 quarterly report, 27 percent of the market for insulin is now comprised of insulin analogs.[53] Growth of the overall insulin market in the United States is between 5 percent to 10 percent per year. This increase is believed to be fueled largely by the introduction of additional insulin analogs.[37]

Conclusions

Landmark clinical trials have shown that intensively managing blood glucose levels to remain within a near-normal range can dramatically decrease the risk of some of the long-term, costly complications associated with diabetes. Insulin analogs provide significant benefits in intensive insulin therapy by reducing the frequency of hypoglycemia and, as early trials of combination use suggest, bringing about a greater decrease in A1C levels than traditional insulins. Extrapolation of the benefits of blood glucose control through cost-utility analysis indicates positive value for the use of insulin analogs in combination therapies.

Beyond this cost-effectiveness analysis, insulin analogs also present significant convenience and short-term quality of life benefits to patients. While there is little research that quantifies the value of these benefits, the wide coverage and use of insulin analogs suggest that these convenience factors carry significant weight with patients and physicians. The reduction in patients' fear of a hypoglycemic event may also allow more patients to aggressively pursue recommended A1C goals. The balance of blood glucose control and patient convenience benefits suggests that insulin analogs present significant overall value in diabetes care.

Moving forward, it is important for health care decision makers to better quantify improvements in quality of life and patient convenience and evaluate whether or not this convenience leads to improved patient compliance and better clinical outcomes.

Appendix: Cost-Effectiveness Analysis

NEHI has modeled combination insulin analog use in type 1 patients as a case study of the value this class of drugs can provide. The model is based on the results of a trial conducted by Hermansen, et al.—the first large randomized clinical trial comparing a combination of rapid- and long-acting insulin analogs with a combination of RI and NPH.[2]

According to the literature on cost-effectiveness analysis, treatments with a cost effectiveness ratio above $100,000 per QALY are generally not considered cost effective, those between $50,000 and $100,000 are marginally cost effective, and those below $50,000 per QALY are the most cost effective.[54]

MODEL STRUCTURE

To extrapolate the costs and benefits of new interventions from clinical trial data to the lifetime of a population of patients, NEHI applied an existing Monte Carlo simulation of the progression of diabetes, using Excel (Microsoft Corporation, Redmond, WA) and @Risk (Palisade Corporation, Ithaca, NY).[27,55]

- The model structure was based on an analysis that has been previously described and validated in the literature. Details on the basic structure of the model can be found in the original DCCT Research Group cost-effectiveness publication and relevant subsequent analyses.[27,55] The model used for this analysis adds a field for average annual cost of hypoglycemia.

- The model utilizes the relationship observed between A1C levels and the development and progression of microvascular diabetic complications (nephropathy, retinopathy and neuropathy) to predict the health outcomes of patients.[26] The benefits of reducing macrovascular complications are not included.

- The model simulates the lifetimes of two 10,000-patient cohorts and tracks the costs and benefits that accrue over time.

- The model estimated the complication cost, total cost and total QALYs for the cohort of 10,000 patients utilizing standard care and insulin analogs, respectively.

- The time horizon of the model is 100 years, which captures costs and benefits throughout a reasonable expected patient lifetime. Simulated outcomes, costs and benefits are tracked annually. All costs are expressed in 2004 U.S. dollars. Costs and QALYs are discounted at 3 percent annually.

COMPARISON

The model compares two groups of patients: a standard care group and an intervention group. Patients in the standard care group are treated with a

combination of RI and NPH, while patients in the intervention group receive a combination of rapid- and long-acting insulin analogs.

COST AND QUALITY OF LIFE INPUTS

Based on trial data for combination insulin analog use, NEHI modeled a 3.0 percent relative reduction in A1C for patients (i.e. a patient with an initial A1C of 8.00 would have his/her A1C reduced to 7.76) and an 83 percent reduction in nocturnal hypoglycemic events.[56] Costs and quality of life effects for long-term complications were taken from the values used in the original DCCT cost-effectiveness model. Costs were updated from the most recent published application of the model.[55]

Reduction in hypoglycemia was represented by the 83 percent reduction in severe nocturnal hypoglycemic events observed in the Hermansen trial, with "severe" events being defined as those which require the assistance of another individual to treat.[2] A range of estimates exists for hypoglycemic event cost (from $188 per episode,[57] $397 per episode,[58] $640 per episode,[59] to $1,186 per episode).[60] Lower estimates frequently include the cost of patients who are able to successfully treat themselves, while higher cost estimates tend to be derived from medical claims data that do not account for situations when patients are adequately treated by another individual without utilizing formal medical care. NEHI chose a mid-range estimate of $640 for hypoglycemia cost[60] and explored variation in sensitivity analyses.

In the base-case, quality of life is conservatively incorporated into the model by assigning decreased health-related utility value only to end-stage diabetes complications, such as blindness, end-stage renal disease, and amputation. The model incorporated utility data used in the original DCCT cost-effectiveness model. Daily quality-of-life difference was not assumed for patients using insulin analogs compared with a traditional insulin regimen. Nor were any quality-of-life reductions included to account for hypoglycemia reduction. Costs and utility associated with complications included in the model are listed below:

COST AND QUALITY OF LIFE ASSIGNMENTS FOR LONG-TERM COMPLICATIONS

Disease State	One-Time Cost ($)	Annual Cost ($)	Utility
Proliferative Diabetic Retinopathy	3,602	57	1.00
Blindness	0	2,655	0.69
Severe Nephropathy	1,470	976	1.00
End-Stage Renal Disease	0	88,725	0.61
Severe Neuropathy	300	1	1.00
Amputation	40,540	135	0.80
Hypoglycemia	0	640/episode	1.00

Source: Eastman et al. 2003; DCCT Study Group 1996.

The costs of treatment for both groups were based on the mean daily insulin doses used in the Hermansen trial (32.1 U, 28.2 U, 26.4 U and 26.3 U of detemir, NPH, aspart and RI, respectively).[2] NEHI estimated insulin price based

on the average wholesale price.[61] Prices were averaged across brand names of each type of insulin, as price differences between brands were minimal. While all patients in the Hermansen trial utilized pen delivery systems, NEHI based the cost of insulin therapy on syringe delivery. This allows broader applicability of the base-case scenario given the lack of evidence that pen delivery provides an independent A1C benefit over syringe delivery. The cost differences that would result from pen delivery were explored in sensitivity analyses. Consistent with the trial, insulin was the primary driver of cost differences between the insulin analog and traditional insulin groups:

ANNUAL INSULIN COST	
Insulin Analogs	$1,557.02
Traditional Insulins	$840.89
Difference	$716.13

Source: 2004 Red Book; Hermansen K, et al.

RESULTS

Base-case analyses suggest that insulin analog combination therapy would result in a lifetime increase of 0.12 QALYs per patient. The lifetime discounted cost increase from the use of therapy (after including the increased cost of treatment and the decreased cost of hypoglycemia and microvascular complications) is $6,839 per patient. These results yield a base-case cost-effectiveness ratio of $59,001 per QALY.

One-way sensitivity analyses were performed on A1C reduction, hypoglycemic event cost and insulin cost, and the conclusion of cost effectiveness was sensitive to reasonable changes in these inputs.

A1C Reduction. The difference in A1C was varied between 1.5 percent and 6.0 percent (half and double the base case, respectively). This caused the cost-effectiveness ratio to vary from $205,154 per QALY at a 1.5 percent A1C reduction to $21,920 per QALY at a 6.0 percent reduction. The cost-effectiveness ratio crossed the $100,000 per QALY mark when the relative A1C reduction was moved from 3.0 percent to 2.1 percent.

Hypoglycemic Event Cost. Hypoglycemic event cost was varied between 0, in the most conservative scenario, and $1,186 per event, and the resulting cost effectiveness ratios ranged from $89,583 per QALY to $32,911 per QALY, respectively.

Insulin Cost. The annual cost difference between combination insulin analog treatment and traditional insulin treatment was varied between a minimum of $331 and a maximum of $1,693 per year, based on the estimated cost differences of having all patients use pre-filled disposable pen delivery systems ($331) or having the insulin analog group use non-disposable pen delivery and the traditional insulin group use syringe delivery ($1,693). The cost-effectiveness ratios varied between $209,594 when the high-cost difference was used and a finding of slight cost savings when the low-cost difference value was used. The

cost-effectiveness ratio crossed the $100,000 per QALY mark when the difference in annual insulin cost was moved from $716 to $1,000.

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Advanced Medical Technology Association
Alkermes, Inc.
American Hospital Association
Amgen, Inc.
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Anthem Blue Cross and Blue Shield East
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