Cost-Effectiveness of Insulin Analogs

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Objective: To examine the cost-effectiveness of analogs versus human insulins, citing primarily studies conducted in the United States.

Study Design: The use of insulin analogs in type 1 and type 2 diabetes mellitus provides a better balance between glycemic control and hypoglycemia compared with human insulins, with the resultant potential to reduce the costs of treatment of hospitalization and chronic complications. The lower incidence of hypoglycemia seen with analogs versus human insulins may help to overcome barriers to insulin acceptance among patients with type 2 diabetes mellitus. In type 2 diabetes mellitus, prompt initiation or intensification of insulin therapy could save costs by delaying the development of complications.

Methods: The cost-effectiveness of analogs was analyzed through a literature review. Searches were conducted in PubMed to identify articles in the past 5 years with the name of any insulin analog plus the word *cost* or *economic* in the title or abstract. American Diabetes Association abstracts for 2005 to 2007 were also searched.

Results: Pharmacoeconomic modeling studies have consistently shown that insulin analogs provide gains in quality-adjusted life-years at costs well below accepted cost-effectiveness limits. In these studies, increased prescription costs were offset by reductions in complications. Retrospective analyses of healthcare databases have also shown cost-effectiveness for analogs versus human insulins, primarily because of lower inpatient care costs.

Conclusion: Treatment with insulin analogs has been demonstrated to be cost-effective versus other options over time and is an appropriate investment of healthcare dollars.

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It is well known that the costs of diabetes mellitus (DM) are high. The American Diabetes Association (ADA)[1] estimated that in the United States the 2007 costs for DM were $174 billion, composed of $116 billion in direct medical expenditure and $58 billion attributed to lost productivity. The ADA also estimated that healthcare costs are more than doubled when DM is present.

Much of this increased expenditure is accounted for by the complications of DM.[2] Landmark clinical trials such as the Diabetes Complications and Control Trial and follow-up studies and the United Kingdom Prospective Diabetes Study have shown that improving glycemic control reduces microvascular and macrovascular complications.[3-6] For example, it is estimated that every 1% decrease in glycosylated hemoglobin (A1C) level is associated with a 37% reduction in microvascular events and a 21% reduction in DM-related mortality ($P < .001$).[6] These are epidemiological associations and not causality studies; nevertheless, on the basis of these and similar studies, leading entities such as the ADA[7] and the American Association of Clinical Endocrinologists[8] have recommended target maximum levels for A1C. However, surveys have shown that in the United States many patients fail to achieve these targets.[9,10]

The costs of DM include direct and indirect costs. Among the direct costs, the cost of the drugs alone is estimated to account for only 10% to 20%, with a much larger proportion of the direct costs being contributed by the costs of healthcare services directly related to DM or associated with complications of DM. For example, a breakdown of DM costs in the United States in 2007 assigned amounts as follows: $27.7 million for outpatient medication and supplies, $65.8 million for institutional care, and $22.7 million for outpatient care.[1]

Indirect costs of DM cover aspects such as lost productivity. Drug treatment that improves glycemic control can reduce the costs of DM, primarily by delaying or preventing the complications of the disease and the associated morbidity and mortality. This was illustrated by a study[11] in which the authors reviewed cost-benefit analyses for 17 DM interventions, with reduction of A1C level shown to be cost-effective. In that study, Klonoff and Schwartz[11] noted that intensive insulin therapy (≥3 insulin injections/d, with dose adjustments based on frequent glucose monitoring) was cost-effective versus conventional therapy (1-2 insulin injections/d, with less stringent glucose goals), based on

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the results of interventional studies[12,13] that used human insulins (analogs were unavailable at the time).

Many patients with type 2 DM will eventually need insulin as their disease progresses and as they become unable to maintain glycemic control using oral antidiabetic drugs (OADs). However, patient acceptance of insulin use is still low, due in part to injection phobias and concerns related to adverse effects such as hypoglycemia or weight gain.[14,15] In recent decades, insulin analogs have been developed with the aim of overcoming some of the disadvantages of conventional human insulins. Analog molecules resemble human insulins except for small changes in amino acid sequence or the addition of a fatty acid chain, which results in different pharmacokinetic and pharmacodynamic profiles. The analogs can be used in regimens that mimic the action of endogenous insulin more closely and provide a less variable and more consistent effect than conventional human insulins. The available insulin analogs are listed in **Table 1**.

Table 1. Available Insulin Analog Preparations in 2007

Generic Name	Trade Names	Manufacturer
Rapid-acting analogs		
Insulin lispro	Humalog	Eli Lilly and Company
Insulin aspart	NovoLog	Novo Nordisk Inc
Insulin glulisine	Apidra	Sanofi Aventis
Basal analogs		
Insulin glargine	Lantus	Sanofi Aventis
Insulin detemir	Levemir	Novo Nordisk Inc
Biphasic premixed analogs		
Biphasic insulin lispro	Humalog Mix 75/25, Humalog Mix 50/50	Eli Lilly and Company
Biphasic insulin aspart 70/30	NovoLog Mix 70/30	Novo Nordisk Inc

In this article, evidence is reviewed about the cost-effectiveness of insulin analogs compared with human insulins, primarily using pharmacoeconomic studies conducted in US settings. Despite the well-established acceptance of insulin analogs by clinicians and patients, such studies are important because the higher initial cost of analogs versus conventional insulins means that their value has to be demonstrated to payers and to authorities. This review presents a brief description of the clinical benefits of insulin analogs and how these may help to overcome barriers to insulin acceptance, followed by an overview of pharmacoeconomic studies that were available as of 2007.

Advantages of Insulin Analogs

Insulin analogs have consistently been shown to improve the balance between glycemic control and tolerability (in terms of hypoglycemia) in type 1 and type 2 DM compared with human insulins. A detailed overview was published by Gough.[16] Some representative studies[17-29] comparing insulin analogs with human insulins are summarized in **Table 2**. These trial durations ranged from 12 to 26 weeks.

In type 1 DM, lower A1C and postprandial glucose levels were achieved with rapid-acting analogs versus human insulins, and hypoglycemia risk was reduced. With basal analogs, A1C levels were generally similar to those achieved with conventional insulins, as the studies were treat-to-target trials in which insulin doses were titrated upward to reach prespecified target glycemic values. However, hypoglycemia risk was reduced by treatment with analogs.

In type 2 DM, studies were generally treat-to-target trials, and A1C levels were similar for analogs versus conventional insulins, but hypoglycemia was lower with analogs. Therefore, cost-savings can result if the incidence of hypoglycemia requiring treatment is reduced (discussed herein in the "Retrospective Analyses of Databases" section) and, in the longer term, if preventing complications of DM is obtained through better glycemic control.

In type 2 DM, patients may be unwilling to initiate or intensify insulin therapy, exhibiting so-called psychological insulin resistance. This reluctance to use insulin is based on factors that include a perception of failing in their disease control efforts, fear of hypoglycemia and weight gain, and needle anxiety.[30] However, prompt initiation or intensification of insulin therapy is vital to delay or reduce the development of complications. Analogs may have a role in overcoming psychological insulin resistance, as discussed herein.

The reputed potential for hypoglycemia is widely believed to be a major barrier to insulin acceptance by patients.[30-32] For example, 41% of respondents in a study[33] agreed that possible hypoglycemia might explain the reluctance to begin insulin therapy. However, analogs are associated with less frequent and less severe hypoglycemia,[16,34,35] which may encourage patients to accept and adhere to insulin therapy from an earlier stage. In terms of weight gain, the insulin analog insulin detemir has been associated with slightly less weight gain than conventional insulins. In studies[25,36,37] of patients with type 2 DM, weight gain was slightly but significantly less with detemir than with neutral protamine Hagedorn (NPH) insulin.

Observational studies of insulin analogs reveal an important aspect of treatment outcomes not fully illuminated by

Table 2. Representative Examples of Trials That Have Shown an Improved Balance Between Glycemic Control and Tolerability With Insulin Analogs Relative to Human Insulins

Source	Comparators/Duration of Treatment	No. of Patients	Result
Type 1 Diabetes Mellitus, With Result Expressed for Analogs vs Human Insulins			
Rapid-acting analogs in basal-bolus therapy			
Anderson et al,[17] 1997	Insulin lispro vs human insulin/2 × 3 mo	1008	Similar A1C, PPG lower by 2 mmol/L (P <.001), rate of hypoglycemia 12% lower (P <.001)
Home et al,[18] 2000	Insulin aspart vs human insulin/6 mo	1065	A1C 0.12% lower (P <.02), PPG lower by 0.6-1.2 mmol/L (P <.01), less major nocturnal hypoglycemia (1.3% vs 3.4%, P <.05)
Garg et al,[19] 2005	Insulin glulisine vs human insulin/3 mo	860	A1C 0.13% lower (P = .02), PPG lower by 1.1-1.3 mmol/L (P <.001), hypoglycemia not significantly different
Basal analogs in basal-bolus therapy			
Ratner et al,[20] 2000	Insulin glargine once daily vs NPH insulin once daily or twice daily/≤28 wk	534	Similar A1C, lower FPG (change from baseline, –1.7 vs –0.3 mmol/L; P = .02), less symptomatic (39.2% vs 49.2%, P = .02) and nocturnal (18.2% vs 21.7%, P = .01) hypoglycemia
Russell-Jones et al,[21] 2004	Insulin detemir once daily vs NPH insulin once daily/6 mo	747	Similar A1C, FPG 1.2 mmol/L lower (P = .001), RR of 0.74 for nocturnal hypoglycemia (P = .003)
All-analog vs all-human insulin regimens in basal-bolus therapy			
Hermansen et al,[22] 2004	Aspart at meals plus detemir twice daily vs human insulin at meals plus NPH insulin twice daily/18 wk	595	A1C 0.22% lower (P <.001), PPG lower on 8-point profiles (P <.001), RR of 0.79 for overall and 0.79 for minor hypoglycemia (P <.05), RR of 0.45 for nocturnal hypoglycemia (P <.001)
Ashwell et al,[23] 2006	Lispro at meals plus evening glargine vs human insulin at meals plus NPH insulin once daily or twice daily/2 × 16 wk	56	A1C 0.5% lower (P <.001), FPG 1.5 mmol/L lower (P = .005), PPG area under the curve 15% lower (P = .002), rate of nocturnal hypoglycemia 44% lower (P <.001)
Type 2 Diabetes Mellitus			
Basal analogs in addition to OADs			
Riddle et al,[24] 2003	Glargine once daily vs NPH insulin once daily plus OADs/24 wk	756	Similar A1C, 21% less hypoglycemia (P <.02), 42% less nocturnal hypoglycemia (P <.001)
Hermansen et al,[25] 2006	Detemir twice daily vs NPH insulin twice daily plus OADs/24 wk	476	Similar A1C, RR of 0.53 for overall and 0.45 for nocturnal hypoglycemia (P <.001 for both)
Analogs vs human insulins in basal-bolus therapy			
Anderson et al,[26] 1997	Lispro vs human insulin plus basal insulin/2 × 3 mo	722	Similar A1C, PPG 53% lower (P <.001), overall hypoglycemia 7% lower (P <.02), nocturnal hypoglycemia 36% lower (P <.001)
Raslova et al,[27] 2004	Detemir plus aspart vs NPH insulin plus human insulin/22 wk	395	Similar A1C, less nocturnal hypoglycemia (16.2% vs 22.6% of patients, P = .04)
Premixed insulin analogs in basal-bolus therapy			
Boehm et al,[28] 2002	Biphasic insulin aspart 70/30 twice daily vs biphasic human insulin twice daily/12 wk	187	Similar A1C and hypoglycemia, PPG 0.29 mmol/L lower with biphasic insulin aspart 70/30 (not significant)
Roach et al,[29] 1999	Premixed biphasic insulin lispro twice daily vs biphasic human insulin twice daily/6 mo	89	Similar A1C and hypoglycemia, PPG lower (9.28 vs 10.7 mmol/L, P = .01)

A1C indicates glycosylated hemoglobin; FPG, fasting plasma glucose; NPH, neutral protamine Hagedorn; OADs, oral antidiabetic drugs; PPG, postprandial glucose; RR, relative risk.

controlled clinical trials, namely, adherence to therapy. Adherence to DM therapy has been shown to be cost-saving: a 10% increase in adherence is estimated to be associated with up to a 29% decrease in annual healthcare costs, primarily because better adherence is associated with fewer hospital visits.[38]

Compact, prefilled, disposable pen devices are available for use with all insulin analogs. Human insulins are available in prefilled and refillable pens. These pen devices can help to overcome needle anxiety because they are easier to use, are more discreet than needles and syringes, are typically not painful, and are preferred by patients compared with standard needles.[39] A recent observational study[40] in the United States found that adherence improved and rates of hypoglycemia and total annual costs per patient decreased after patients switched from vial and syringe to an insulin analog pen device. Total annual cost-savings were $1590 per patient, of which $788 were hypoglycemia-related cost-savings and $600 were other DM-related cost-savings (P <.01 for all compared with the use of vials and syringes before the switchover).

Insulin analogs have also been shown to improve patients' health-related quality of life (QOL) relative to human insulins.[41,42] Because QOL is an important determinant of adherence,[43] this is another factor that may result in improved adherence to analog use and may lower expenses related to poor compliance with or delayed adoption of insulin therapy. Finally, the rapid-acting insulin analogs are suitable for pump therapy, which allows patients to achieve similar or better glycemic control relative to human insulins.[44,45]

Insulin analogs are more expensive to the payer than human insulins. Although the cost of medication may be higher, there may be reductions in more expensive long-term expenditures such as the costs related to treatment of hypoglycemia or chronic complications of DM.

Selection and Types of Studies

Cost-effectiveness studies for insulin analogs used in the United States were identified by searching PubMed using the name of each available analog preparation (*insulin lispro*, *insulin aspart*, *insulin glulisine*, *insulin glargine*, *insulin detemir*, *premixed insulin lispro* or *Humalog Mix* [separate searches], and *biphasic insulin aspart*) together with the word *cost* or *economic* and the following limits: publication in the past 5 years, studies in humans, English language, and appearance of the terms in the title or abstract. (In the rest of this article, the analog names are used without the "insulin" prefix.) Searches were conducted in June 2007 and were limited to the past 5 years because changing costs mean that older pharmacoeconomic data are of limited value. The ADA Web site was also searched for 2005, 2006, and 2007 abstracts containing the name of each analog; the retrieved abstracts were examined to find any with the word *cost* or *economic* in the title. The decision was made to include abstracts published in the 2 years preceding the search because only a limited number of full published articles dealing specifically with cost-effectiveness of analogs was available. Although abstracts have not undergone the same rigorous review as published articles, they undergo review before being accepted by the ADA.

All identified studies were included in this review if they fulfilled the following criteria: they compared a subcutaneous insulin analog with subcutaneous human insulins or with OADs, they quantified the cost-effectiveness in some form (monetary or by some other measure such as quantified prevention of events), they reported original results, and they were from a US perspective. The numbers of studies that met all these criteria were as follows for the different analogs: 7 studies for glargine, 5 studies for detemir, 2 studies for lispro, and 4 studies for biphasic insulin aspart 70/30.

Results from some non-US studies, chosen where possible to compare similar insulin preparations during similar periods relative to the US studies, are given in Table 3.[46-54] Consequently, the review includes results from 15 pharmacoeconomic modeling studies, 8 retrospective analyses of databases, and 2 studies based on end-of-trial data.

Pharmacoeconomic Modeling

Unlike clinical end points, cost-effectiveness cannot readily be measured using clinical trials because the required time span is too long and there are too many confounding variables that cannot be controlled. Therefore, pharmacoeconomic models are frequently used to compare the effect of 2 or more strategies (eg, drug A vs drug B or drug A vs no intervention) on long-term clinical and cost outcomes. The models may assess direct costs, indirect costs, or both and may calculate costs from different perspectives such as that of the payer (patient, managed care organization, healthcare authority, etc) or of society. The results of models may show that an intervention (drug A) is cost-saving when its use actually results in lower costs than the use of an alternative (drug B or no intervention). Alternatively, the results may suggest that drug A is cost-effective versus drug B or no intervention when its use results in higher costs but in an improved outcome for patients. In the latter case, the number of life-years gained by an intervention is adjusted to allow for QOL and is expressed as quality-adjusted life-years (QALYs). Cost-effectiveness is then expressed as an incremental cost-effectiveness ratio (ICER) (ie, the cost per QALY gained with drug A).

ICERs are relative values and can only be quoted for the intervention of interest (drug A) and not for the reference

Table 3. Results of Pharmacoeconomic Models Comparing Treatment With Insulin Analogs Versus Human Insulins in the United States, Canada, United Kingdom, and Europe

Source	Comparators	Country/Time Horizon	Result[a]
Type 1 Diabetes Mellitus			
Valentine et al,[46] 2006	Insulin detemir, insulin glargine, NPH insulin	US/35 y	Cost per QALY of $14,974 for detemir vs NPH insulin, detemir cost-saving vs glargine
Grima et al,[47] 2007	Glargine vs NPH insulin	Canada/36 y	Cost per QALY of Can$20,799 ($20,701) for glargine vs NPH insulin
McEwan et al,[48] 2007	Glargine vs NPH insulin	UK/40 y	Cost per QALY of £2695-£10,943 ($5262-$21,368) for glargine vs NPH insulin
Palmer et al,[49] 2004	Detemir vs NPH insulin–based basal-bolus therapy	UK/patient lifetimes based on meta-analysis of 4 trials	Cost per QALY of £19,285 ($37,656) for detemir vs NPH insulin
Palmer et al,[50] 2007	Detemir plus insulin aspart vs NPH insulin plus human insulin	UK/patient lifetimes	Cost per QALY of £2500 ($4882) for analogs vs human insulin
Type 2 Diabetes Mellitus			
Palmer et al,[51] 2006	Changing to detemir from NPH insulin or glargine	US/10 y	Costs reduced by $2020-$2416 per patient converted
Valentine et al,[52] 2007	Patients switching to detemir with or without OADs from NPH insulin with or without OADs	US/35 y	Cost per QALY of $6269
Grima et al,[47] 2007	Glargine vs NPH insulin	Canada/36 y	Cost per QALY of Can$8618 ($8578) for glargine vs NPH insulin
McEwan et al,[53] 2007	Glargine vs NPH insulin	UK/40 y	Cost per QALY of <£20,000 (<$39,052) for glargine vs NPH insulin
Lammert et al,[54] 2004	Biphasic insulin aspart 70/30 vs biphasic human insulin	7 European countries/ lifetime	Cost per QALY of €5000-€14,068 ($7694-$21,646)

NPH indicates neutral protamine Hagedorn; OADs, oral antidiabetic drugs; QALY, quality-adjusted life-year.
[a]Results are given in the original reported currency and are converted to US dollars at the following rates obtained in May 2008: Can$1 = $0.995, €1 = $1.54, and £1 = $1.95.

standard (drug B or no intervention) against which it is being measured. The lower the cost per QALY, the more cost-effective the treatment. In the United States, an ICER of $50,000 to $100,000 per QALY is typically deemed as acceptable, although these limits are not fixed and can vary according to many factors such as disease burden and societal expectations. For example, payers may decide that it is acceptable to provide a drug that costs more than $100,000 per QALY if it is effective in a rare disease that affects young patients. For an intervention that will be widely required by older patients, a more stringent ICER cutoff such as $30,000 per QALY may be applied.

Pharmacoeconomic models have several disadvantages. There may be a lack of good-quality clinical data, requiring the use of results from small trials or expert opinion. The observational data used may be biased. Assumptions have to be made, and these may be (intentionally or not) too conservative or too optimistic. Finally, it may be difficult to extrapolate data from one patient population to another. A good model must be transparent (ie, users must have access to how it works and the data sources used, and any assumptions made must be clearly explained). It should also be externally validated (ie, shown to predict accurate results in scenarios in which the real outcomes are known). The uncertainty arising from the need to make assumptions must be explored through sensitivity analyses in which the effect of varying the assumptions is explored.

Many of the modeling studies that were identified for the present analysis examined the cost-effectiveness of different strategies in type 1 and type 2 DM using the CORE Diabetes Model,[55] an interactive Internet-based computer model that allows the calculation of long-term outcomes in different patient populations in realistic clinical settings. Users of the model are able to enter data about the baseline characteristics, history, and future management of the population under study. Development of complications, life expectancy,

Table 4. Pharmacoeconomic Models Comparing Treatment of Type 2 Diabetes With Insulin Analogs Versus Oral Antidiabetic Drugs (OADs) in a US Context

Source	Comparators	Perspective	Cost per Quality-Adjusted Life-Year, $
Palmer et al,[51] 2006	Patients initiating insulin detemir	10 y	657
Valentine et al,[52] 2007	Patients initiating detemir	35 y	7412
Minshall et al,[59] 2005	Biphasic insulin aspart 70/30 plus metformin vs optimal OADs	Lifetime	8487
Nicklasson et al,[60] 2005	Biphasic insulin aspart 70/30 plus thiazolidinedione vs sulfonylurea plus thiazolidinedione	Lifetime	25,400
Valentine et al,[58] 2006	Biphasic insulin aspart 70/30 plus metformin plus pioglitazone hydrochloride vs metformin pioglitazone hydrochloride	35 y	22,209

QALYs, and total costs are then calculated by the model. The key treatment effects included in the model are clinically relevant results seen in trials, primarily reductions in A1C levels and hypoglycemia rates. The CORE Diabetes Model was validated by comparing results from model simulations with observed outcomes from published epidemiological and clinical studies in type 1 and type 2 DM.[56]

It is important to note that model results cannot always be directly extended to other countries because of differences in healthcare systems and costs. Despite these limitations, strong similarities in trends are often mirrored across different countries, as would be expected if one intervention provides real clinical advantages versus another. The results of the pharmacoeconomic modeling studies analyzed in the present review follow.

Analogs Versus Human Insulins. Three pharmacoeconomic modeling studies (1 study[46] of type 1 DM and 2 studies[51,52] of type 2 DM) were identified that compared analogs with human insulins in a US context (Table 3). Representative studies from other countries are also given in Table 3. The data reported for US studies and for non-US studies demonstrate that analog treatment regimens were associated with ICER values that indicate cost-effectiveness.

In type 1 DM, detemir was shown to be cost-effective versus NPH insulin and glargine when considered during a 35-year horizon in the United States.[46] The cost per QALY gained with detemir relative to NPH insulin was $14,974 when direct costs were considered.

In type 2 DM, it was calculated that detemir would reduce costs by $2020 versus NPH insulin during 10 years in a US context, largely through anticipated reductions in complications, notably nephropathy and retinopathy.[51] Projected during a 35-year period, an ICER of $6269 per QALY was calculated for patients switching to detemir (with or without OADs) from NPH insulin (with or without OADs).[52] In these studies, the treatment effects of detemir were based on results from the German cohort of the Predictable Results and Experience in Diabetes Through Intensification and Control to Target: An International Variability Evaluation (PREDICTIVE) study,[57] a large real-life observational trial that included more than 1800 patients with type 2 DM.

Six pharmacoeconomic modeling studies[47-50,53,54] of insulin analogs in type 1 or type 2 DM conducted in Canada, the United Kingdom, or 7 European countries show ICER values associated with cost-effectiveness at levels comparable to those measured in the US studies (Table 3). Because healthcare delivery in those countries is not similar to the US system, the collective pharmacoeconomic modeling data strengthen the point that insulin analogs are cost-effective.

Analogs Versus OADs. The cost-effectiveness of insulin analogs used to replace or enhance OAD regimens in type 2 DM has been examined using pharmacoeconomic modeling in a US context (Table 4).[51,52,58-60] An ICER of $657 per QALY was calculated for patients switching to detemir from OADs during a 10-year period.[51] During a 35-year period, a cost of $7412 per QALY was calculated for patients switching to detemir (with or without OADs) from OADs alone. Similar to the comparisons versus NPH insulin, these models used results from the German arm of the PREDICTIVE observational study,[57] and the low ICERs resulted largely from reductions in DM complications.

Two studies[59,60] considered the use of biphasic insulin aspart 70/30. Regimens of biphasic insulin aspart 70/30 plus an OAD were compared with OAD regimens over a lifetime perspective. In the first study,[59] total lifetime direct costs were higher with biphasic insulin aspart 70/30 plus metformin than with an optimized OAD regimen. However, the use of biphasic insulin aspart 70/30 was projected to result in reduced complications, particularly nephropathy (one of the costliest DM-related complications); this resulted in an ICER of $8487 per QALY gained for biphasic

Table 5. Retrospective Cost Analyses Comparing Treatment With Insulin Analogs Versus Human Insulins in a US Context

Source	Comparators	Data Source/Enrollment Dates/Duration of Follow-up[a]	Result
Bullano et al,[61] 2005 (mainly type 2 DM, 5% type 1 DM)	Patients newly initiated on insulin glargine (n = 310) vs NPH insulin (n = 1124)	Southeastern US managed care plan/July 2000 to August 2002/≥4 mo (mean treatment period, 8.6 mo)	Cost per hypoglycemic event of $1087; glargine cost $47 more per patient than NPH insulin; need to treat 9 patients to avoid 1 hypoglycemia event per year with glargine (cost, 9 × $47 = $423); therefore, glargine is cost-saving
Bullano et al,[62] 2006 (type 2 DM)	Patients newly initiated on glargine (n = 1212) vs premixed human insulin (n = 1103)	Southeastern US managed care plan/June 2001 to February 2004/≥4 mo (mean treatment period, 13.4-14 mo)	Cost per hypoglycemic event of $1049; glargine cost $46 more per patient than premixed human insulin; need to treat 15 patients to avoid 1 hypoglycemia event per year with glargine (cost, 15 × $46 = $690); therefore, glargine is cost-saving
Zhang and Menditto,[63] 2005 (DM type not specified)	Glargine (n = 267) vs other insulins (n = 534)	Medi-Cal (Medicaid program in California)/November 2000 to September 2002/cost of care was compared for the 6 mo before and 6 mo after glargine index date	Glargine was associated with a reduction in hypoglycemia-related claims; extra cost of glargine was offset by reduced cost of inpatient care
Orsini and Huse,[64] 2005 (DM type not specified)	Glargine (n = 1268) vs NPH insulin or Lente (n = 10,441)	Medicaid in 4 states/July 2001 to 2003 (month not specified)/12 mo	Diabetes-related claims per patient per year were similar for both groups; total healthcare costs were lower for glargine ($22,086) than for NPH insulin/Lente ($24,225) ($P < .001$)
Miller et al,[65] 2005 (DM type not specified)	Glargine (n = 5057) vs other insulins (n = 69,940)	Veterans Administration/ patients initiated in 2001 to 2002/12 mo	Medication cost for patients taking glargine was on average $347 more; patients taking glargine had more outpatient care (+$229) but fewer inpatient days (–$820)
Ory et al,[66] 2005 (DM type not specified)	Glargine vs other insulins (n = 27,157) (treatment group totals not given)	Pharmacy and medical claims (no further details)/April 2001 to June 2002/6 mo	For patients receiving insulin only, total healthcare costs were lower with glargine ($12,367 vs $15,772, $P = .02$); for patients receiving insulin plus OADs, total healthcare costs were similar for glargine and other insulins ($14,290 vs $13,179)
Hall et al,[67] 2003 (type 1 and type 2 DM)	Insulin lispro (n = 3341) vs human insulin (n = 8102)	14 US healthcare plans/ January 1998 to December 1999/12 mo	Users of lispro had higher pharmacy costs vs users of human insulin ($2244 vs $1797) and higher office visit costs ($822 vs $716) but lower inpatient hospital costs ($1741 vs $2519); total costs similar between groups ($519 vs $543 per patient per month)
Chen et al,[68] 2005 (type 1 and type 2 DM)	Lispro (n = 1972) vs human insulin (n = 4464)	Western US managed care plan/March 2000 to February 2001/12 mo	Users of lispro had higher pharmacy costs (+$212 vs human insulin) but similar total medical costs (–$2327 vs human insulin, not significant)

DM indicates diabetes mellitus; NPH, neutral protamine Hagedorn; OADs, oral antidiabetic drugs.
[a]Enrollment dates are the period during which patients were enrolled or had to be continuously enrolled (this differed by study). Glargine was introduced to the US market in May 2001. In most studies, the duration of follow-up was measured from an "index date," defined as the date on which a prescription for the relevant insulin was first filled.

insulin aspart 70/30 plus metformin versus the optimized OAD regimen.

When a regimen of biphasic insulin aspart 70/30 plus a thiazolidinedione was compared with a sulfonylurea plus a thiazolidinedione, the cost per QALY was $25,400.[60] In another study,[58] the addition of biphasic insulin aspart 70/30 to metformin plus pioglitazone hydrochloride was cost-effective versus metformin plus pioglitazone hydrochloride during a

35-year period, with a projected cost per QALY of $22,209.

In all of these studies versus OADs, the use of an insulin analog resulted in increased prescription costs, but these were offset by reductions in complications. This finding underlines the importance of achieving effective glycemic control as early as possible.

Take-away Points

Treatment of type 1 and type 2 diabetes mellitus with insulin analogs is cost-effective versus other options over time.

- Insulin analogs versus conventional human insulins improve the balance between glycemic control and hypoglycemia.
- In type 2 diabetes mellitus, the use of analogs can help to overcome some of the barriers to insulin use. Prompt initiation or intensification of insulin therapy and adherence to an insulin regimen will delay or prevent the development of diabetes complications.
- Pharmacoeconomic models and retrospective analyses of healthcare databases have demonstrated the cost-effectiveness of analogs.

Retrospective Analyses of Databases

For assessing the cost-effectiveness of interventions, an alternative to modeling studies is retrospective analyses of data held in computerized databases such as those maintained by managed healthcare organizations, major hospitals, or the Veterans Administration. A weakness of this method is that it assumes that there are no systematic differences between the groups being compared. For example, in groups that received human insulins or analogs, analogs may systematically have been prescribed to patients with more advanced disease. Multivariate analyses are used to control for some demographic differences such as age, but these analyses cannot be applied to data that are unavailable in the database. In addition, retrospective analyses typically consider 6 to 12 months of an intervention because of the practical difficulties of maintaining patient cohorts and complete records during longer periods; therefore, differences arising from the slower development of chronic complications are unlikely to be revealed in such analyses.

Retrospective cost analyses comparing analogs with human insulins are summarized in Table 5. In general, these studies[61-68] analyzed information from databases that recorded all patients' healthcare costs whether or not they were related to DM. Follow-up ranged from 4 to 14 months.

Several studies[61-63] showed that glargine was cost-effective versus human insulins because hypoglycemia-related costs were reduced. For example, Bullano et al[61] showed that treating 9 patients with glargine for 1 year would prevent 1 hypoglycemic event. The mean annualized cost of medication per patient was $47 more for glargine than for NPH insulin. Because the additional cost of this treatment (9 × $47 = $423) is less than the mean total attributable cost per hypoglycemic event ($1087), the use of glargine would be cost-saving.

In other studies,[64-66] the total costs for glargine were lower than or similar to those for human insulins. One glargine group had higher 12-month drug costs (mean, $347 more per patient) and outpatient care costs (mean, $229 more), but these were more than offset by decreased inpatient costs ($820 less), giving a net saving of $244 per patient.[65] Additional comparisons are summarized in Table 5. Two other studies[67,68] found that the total medical costs for insulin lispro were similar to those for human insulins.

Analyses Based on End-of-Trial Data

Two studies[69,70] compared an analog with OADs in type 2 DM using a different approach. Direct drug costs were calculated based on the mean daily doses of the different drugs at the end of a clinical trial.

The first of these was a 24-week study[69] evaluating the efficacy and safety of add-on glargine versus rosiglitazone maleate in insulin-naive patients with type 2 DM inadequately controlled on therapy with a sulfonylurea plus metformin. The improvements in A1C level from baseline were similar in both groups, but there was less weight gain with glargine (P = .02). The mean cost of all antihyperglycemic medications and resources during the 24 weeks was $1368 with glargine and $1603 with rosiglitazone; therefore, the mean cost of glycemic control was $235 lower with glargine.

In the second study,[70] costs were estimated based on drug dosages at the end of a 16-week clinical trial of patients receiving biphasic insulin aspart 70/30 plus metformin versus patients receiving 1 or more OADs titrated by their clinicians to optimize glycemic control.[71] Direct pharmacy costs were higher for the biphasic insulin aspart 70/30 group. With the biphasic insulin aspart 70/30 regimen, significantly more patients achieved an A1C level of 7.0% or less (P <.02). These patients were considered successfully treated; the mean annual cost for each successfully treated patient was $896 lower with biphasic insulin aspart 70/30.[70]

CONCLUSIONS

Insulin analogs offer an improved balance between glycemic control and the risk of hypoglycemia, with the resultant potential to reduce the costs of treatment of hypoglycemia, hospitalization, and chronic complications. This better tolerability of analogs and the ease of administration offered by insulin pen devices can help to overcome some of the barriers to insulin use

in patients with type 2 DM. Prompt initiation or intensification of insulin therapy in type 2 DM and adherence to an insulin regimen will save costs by delaying or preventing DM complications. Pharmacoeconomic models and retrospective analyses of healthcare databases have consistently shown that treatment with insulin analogs is cost-effective versus other options in the long run. Therefore, the use of insulin analogs in type 1 and type 2 DM is an appropriate investment of healthcare dollars. This review shows that validation of these potential benefits through real-world data analysis is warranted.

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REFERENCES

1. American Diabetes Association. Economic costs of diabetes in the US in 2007. *Diabetes Care.* 2008;31(3):596-615.

2. Caro JJ, Ward AJ, O'Brien JA. Lifetime costs of complications resulting from type 2 diabetes in the US. *Diabetes Care.* 2002;25(3):476-481.

3. Writing Team for the DCCT/EDIC Research Group. Effect of intensive therapy on the microvascular complications of type 1 diabetes mellitus. *JAMA.* 2002;287(19):2563-2569.

4. Writing Team for the DCCT/EDIC Research Group. Sustained effect of intensive treatment of type 1 diabetes mellitus on development and progression of diabetic nephropathy: the Epidemiology of Diabetes Interventions and Complications (EDIC) study. *JAMA.* 2003;290(16):2159-2167.

5. United Kingdom Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33) [published correction appears in *Lancet.* 1999;354(9178):602]. *Lancet.* 1998;352(9131):837-853.

6. Stratton IM, Adler AI, Neil HA, et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. *BMJ.* 2000;321(7258):405-412.

7. American Diabetes Association. Standards of medical care in diabetes. *Diabetes Care.* 2007;30(suppl 1):S4-S41.

8. AACE Diabetes Mellitus Clinical Practice Guidelines Task Force. American Association of Clinical Endocrinologists medical guidelines for clinical practice for the management of diabetes mellitus. *Endocr Pract.* 2007;13(suppl 1):1-68.

9. Koro CE, Bowlin SJ, Bourgeois N, Fedder DO. Glycemic control from 1988 to 2000 among U.S. adults diagnosed with type 2 diabetes: a preliminary report. *Diabetes Care.* 2004;27(1):17-20.

10. Greisinger AJ, Balkrishnan R, Shenolikar RA, Wehmanen OA, Muhammad S, Champion PK. Diabetes care management participation in a primary care setting and subsequent hospitalization risk. *Dis Manag.* 2004;7(4):325-332.

11. Klonoff DC, Schwartz DM. An economic analysis of interventions for diabetes. *Diabetes Care.* 2000;23(3):390-404.

12. Diabetes Control and Complications Trial Research Group. Lifetime benefits and costs of intensive therapy as practiced in the Diabetes Control and Complications Trial [published correction appears in *JAMA.* 1997;278(1):25]. *JAMA.* 1996;276(17):1409-1415.

13. Eastman RC, Javitt JC, Herman WH, et al. Model of complications of NIDDM, II: analysis of the health benefits and cost-effectiveness of treating NIDDM with the goal of normoglycemia. *Diabetes Care.* 1997;20(5):735-744.

14. Mollema ED, Snoek FJ, Pouwer F, Heine RJ, van der Ploeg HM. Diabetes Fear of Injecting and Self-Testing Questionnaire: a psychometric evaluation. *Diabetes Care.* 2000;23(6):765-769.

15. Peyrot M, Rubin RR, Lauritzen T, et al; the international DAWN advisory panel. Resistance to insulin therapy among patients and providers. *Diabetes Care.* 2005;28(11):2673-2679.

16. Gough SC. A review of human and analogue insulin trials. *Diabetes Res Clin Pract.* 2007;77(1):1-15.

17. Anderson JH Jr, Brunelle RL, Koivisto VA, et al; Multicenter Insulin Lispro Study Group. Reduction of postprandial hyperglycaemia and frequency of hypoglycaemia in IDDM patients on insulin-analog treatment. *Diabetes.* 1997;46(2):265-270.

18. 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. *Diabetic Med.* 2000;17(11):762-770.

19. Garg SK, Rosenstock J, Ways K. Optimized basal-bolus insulin regimens in type 1 diabetes: insulin glulisine versus regular human insulin in combination with basal insulin glargine [published correction appears in *Endocr Pract.* 2005;11(2):145]. *Endocr Pract.* 2005;11(1):11-17.

20. Ratner RE, Hirsch IB, Neifing JL, Garg SK, Mecca TE, Wilson CA; U.S. Study Group of Insulin Glargine in Type 1 Diabetes. Less hypoglycaemia with insulin glargine in intensive insulin therapy for type 1 diabetes. *Diabetes Care.* 2000;23(5):639-643.

21. Russell-Jones D, Simpson R, Hylleberg B, Draeger E, Bolinder J. Effects of QD insulin detemir or neutral protamine Hagedorn on blood glucose control in patients with type I diabetes mellitus using a basal-bolus regimen. *Clin Ther.* 2004;26(5):724-736.

22. Hermansen K, Fontaine P, Kukolja K, Peterkova V, Leth G, Gall MA. Insulin analogues (insulin detemir and insulin aspart) versus traditional human insulins (NPH insulin and regular human insulin) in basal-bolus therapy for patients with type 1 diabetes. *Diabetologia.* 2004;47(4):622-629.

23. Ashwell SG, Amiel SA, Bilous RW, et al. Improved glycaemic control with insulin glargine plus insulin lispro: a multicentre, randomized, cross-over trial in people with type 1 diabetes. *Diabet Med.* 2006;23(3):285-292.

24. Riddle M, 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(11):3080-3086.

25. 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 [published correction appears in *Diabetes Care.* 2007;30(4):1035]. *Diabetes Care.* 2006;29(6):1269-1274.

26. Anderson JH Jr, Brunelle RL, Keohane P, et al; Multicenter Insulin Lispro Study Group. Mealtime treatment with insulin analog improves postprandial hyperglycemia and hypoglycemia in patients with non–insulin-dependent diabetes mellitus. *Arch Intern Med.* 1997;157(11):1249-1255.

27. Raslova K, Bogoev M, Raz I, Leth G, Gall MA, Hancu M. Insulin detemir and insulin aspart: a promising basal-bolus regimen for type 2 diabetes [published correction appears in *Diabetes Res Clin Pract.* 2006;72:112]. *Diabetes Res Clin Pract.* 2004;66(2):193-201.

28. Boehm BO, Home PD, Behrend C, Kamp NM, Lindholm A. Premixed insulin aspart 30 vs. premixed human insulin 30/70 twice daily: a randomized trial in type 1 and type 2 diabetic patients [published correction appears in *Diabet Med.* 2002;19(9):797]. *Diabet Med.* 2002;19(5):393-399.

29. Roach P, Yue L, Arora V; Humalog Mix25 Study Group. Improved postprandial glycemic control during treatment with Humalog Mix25, a novel protamine-based insulin lispro formulation. *Diabetes Care.* 1999;22(8):1258-1261.

30. Korytkowski M. When oral agents fail: practical barriers to starting insulin. *Int J Obes Relat Metab Disord.* 2002;26(suppl 3):S18-S24.

31. Hunt LM, Valenzuela M, Pugh J. NIDDM patients' fears and hopes about insulin therapy. *Diabetes Care.* 1997;20(3):292-298.

32. Leiter LA, Yale JF, Chiasson JL, Harris SB, Kleinstiver P, Sauriol L. Assessment of the impact of fear of hypoglycemic episodes on glycemic and hypoglycemia management. *Can J Diabetes.* 2005;29(3):186-192.

33. Polonsky WH, Fisher L, Guzman S, Villa-Caballero L, Edelman SV. Psychological insulin resistance in patients with type 2 diabetes: the scope of the problem. *Diabetes Care.* 2005;28(10):2543-2545.

34. 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.

35. 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.

36. Haak T, Tiengo A, Draeger E, Suntum M, Waldhäusl W. Lower within-subject variability of fasting blood glucose and reduced weight gain with insulin detemir compared to NPH insulin in patients with type 2 diabetes. *Diabetes Obes Metab.* 2005;7(1):56-64.

37. Hermansen K, Davies M. Does insulin detemir have a role in reducing risk of insulin-associated weight gain? *Diabetes Obes Metab.* 2007;9(3):209-217.

38. Lee WC, Balu S, Cobden D, Joshi AV, Pashos CL. Prevalence and economic consequences of medication adherence in diabetes: a systematic literature review. *Manag Care Interface.* 2006;19(7):31-41.

39. Korytkowski M, Bell D, Jacobsen C, Suwannasari R; FlexPen Study Team. A multicenter, randomized, open-label, comparative, two-period crossover trial of preference, efficacy, and safety profiles of a prefilled, disposable pen and conventional vial/syringe for insulin injection in patients with type 1 or 2 diabetes mellitus. *Clin Ther.* 2003;25(11):2836-2848.

40. Lee WC, Balu S, Cobden D, Joshi AV, Pashos CL. Medication adherence and the associated health-economic impact among patients with type 2 diabetes mellitus converting to insulin pen therapy: an analysis of third-party managed care claims data [published correction appears in *Clin Ther.* 2006;28(11):1968-1969]. *Clin Ther.* 2006;28(10):1712-1725.

41. Bott U, Ebrahim S, Hirschberger S, Skovlund SE. Effect of the insulin analogue insulin aspart on quality-of-life and treatment satisfaction in type 1 diabetic patients. *Diabet Med.* 2003;20(8):626-634.

42. 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(7):493-498.

43. Hanestad BR, Albrektsen G. Quality of life, perceived difficulties in adherence to a diabetes regimen, and blood glucose control. *Diabet Med.* 1991;8(8):759-764.

44. Bode B, Weinstein R, Bell D, et al. Comparison of insulin aspart to buffered regular insulin and insulin lispro in continuous subcutaneous insulin infusion: a randomized study in type 1 diabetes. *Diabetes Care.* 2002;25(3):439-444.

45. Raskin P, Holcombe JH, Tamborlane WV, et al. A comparison of insulin lispro and buffered regular human insulin administered via continuous subcutaneous insulin infusion pump. *J Diabetes Complications.* 2001;15(6):295-300.

46. Valentine WJ, Palmer AJ, Erny-Albrecht KM, et al. Cost-effectiveness of basal insulin from a US health system perspective: comparative analyses of detemir, glargine, and NPH. *Adv Ther.* 2006;23(2):191-207.

47. Grima DT, Thompson MF, Sauriol L. Modelling cost effectiveness of insulin glargine for the treatment of type 1 and 2 diabetes in Canada. *Pharmacoeconomics.* 2007;25(3):253-266.

48. 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 Med Res Opin.* 2007;23(suppl 1):7-19.

49. Palmer AJ, Roze S, Valentine WJ, Smith I, Wittrup-Jensen KU. Cost-effectiveness of detemir-based basal/bolus therapy versus NPH-based basal/bolus therapy for type 1 diabetes in a UK setting: an economic analysis based on meta-analysis results of four clinical trials. *Curr Med Res Opin.* 2004;20(11):1729-1746.

50. 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(4):895-901.

51. Palmer AJ, Cobden D, Koenen C, et al. Projecting the economic and health outcome effects of basal insulin among type 2 patients in clinical practice settings [abstract]. *Diabet Med.* 2006;23(suppl 4):368.

52. Valentine WJ, Erny-Albrecht KM, Ray JA, Roze S, Cobden D, Palmer AJ. Therapy conversion to insulin detemir among patients with type 2 diabetes treated with oral agents: a modeling study of cost-effectiveness in the United States. *Adv Ther.* 2007;24(2):273-290.

53. 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 2 diabetes in the UK. *Curr Med Res Opin.* 2007;23(suppl 1):21-31.

54. Lammert M, Palmer AJ, Roze S, et al. Decreased rates of major hypoglycemic events lead to improved long-term cost-effectiveness of biphasic insulin aspart 30/70 versus biphasic human insulin 30 in type 2 diabetic subjects in Danish, Finnish, German, Norwegian, Spanish, Swedish and UK settings [abstract]. *Value Health.* 2004;7(6):736.

55. Palmer AJ, Roze S, Valentine WJ, et al. The CORE Diabetes Model: projecting long-term clinical outcomes, costs and cost-effectiveness of interventions in diabetes mellitus (types 1 and 2) to support clinical and reimbursement decision-making. *Curr Med Res Opin.* 2004;20(suppl 1):S5-S26.

56. Palmer AJ, Roze S, Valentine WJ, et al. Validation of the CORE Diabetes Model against epidemiological and clinical studies. *Curr Med Res Opin.* 2004;20(suppl 1):S27-S40.

57. Meneghini CF, Rosenberg KH, Koenen C, Merilainen MJ, Lilddeke HJ. Insulin detemir improves glycaemic control with less hypoglycaemia and no weight gain in patients with type 2 diabetes who were insulin naive or treated with NPH or insulin glargine: clinical practice experience from a German subgroup of the PREDICTIVE study. *Diabetes Obes Metab.* 2007;9(3):418-427.

58. Valentine W, Cobden D, Braceras R, et al. Health economic evaluation of improved glycemic control: initiating biphasic analog insulin [abstract]. *Diabet Med.* 2006;23(suppl 4):367.

59. Minshall M, Ray J, Lammert M, et al. Estimating the long-term cost-effectiveness of biphasic insulin aspart plus metformin versus optimization of oral hypoglycemic agents in insulin-naive patients with type 2 diabetes in a US cost setting [poster]. *Diabetologia.* 2005;48(suppl 1):A335.

60. Nicklasson L, Palmer AJ, Cobden D, et al. Long-term cost-effectiveness analysis of patients with type 2 diabetes mellitus inadequately controlled on thiazolidinedione therapy and either biphasic insulin aspart 30 or sulfonylurea [poster]. *Diabetologia.* 2005;48(suppl 1):A334.

61. Bullano MF, Al-Zakwani IS, Fisher MD, Menditto L, Willey VJ. Differences in hypoglycemia event rates and associated cost-consequence in patients initiated on long-acting and intermediate-acting insulin products. *Curr Med Res Opin.* 2005;21(2):291-298.

62. Bullano MF, Fisher MD, Grochulski WD, Menditto L, Willey VJ. Hypoglycemic events and glycosylated hemoglobin values in patients with type 2 diabetes mellitus newly initiated on insulin glargine or premixed insulin combination products. *Am J Health Syst Pharm.* 2006;63(24):2473-2482.

63. Zhang Q, Menditto L. Incremental cost savings 6 months following initiation of insulin glargine in a Medicaid fee-for-service sample. *Am J Ther.* 2005;12(4):337-343.

64. Orsini L, Huse DM. Total health care costs in Medicaid patients receiving NPH, Lente, or insulin glargine [abstract]. *Diabetes.* 2005;54(suppl 1):A144.

65. Miller DM, Gardner J, Hendricks A, Fincke G, Zhang Q. Changes in health care utilization and expenditures associated with insulin glargine use [abstract]. *Diabetes.* 2005;54(suppl 1):A302.

66. Ory C, Cyprien L, Menditto LA, Chang E. Health economic outcomes associated with insulin therapies: an evaluation of insulin glargine [abstract]. *Diabetes.* 2005;54(suppl 1):A612.

67. Hall JA, Summers KH, Obenchain RL. Cost and utilization comparisons among propensity score–matched insulin lispro and regular insulin users. *J Manag Care Pharm.* 2003;9(3):263-268.

68. 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(5):376-382.

69. Rosenstock J, Sugimoto D, Strange P, Stewart JA, Soltes-Rak E, Dailey G. Triple therapy in type 2 diabetes: insulin glargine or rosiglitazone added to combination therapy of sulfonylurea plus metformin in insulin-naive patients. *Diabetes Care.* 2006;29(3):554-559.

70. Botteman M, Cobden D, Nicklasson L. Cost to reach target HbA1c in poorly controlled patients with type 2 diabetes mellitus on either biphasic insulin aspart 30 and metformin or a maximized oral hypoglycemic regimen [poster]. *Diabetologia.* 2005;48(suppl 1):A334.

71. Ushakova O, Sokolovskaya V, Morozova A, et al. Biphasic insulin aspart 30 (NovoLog Mix 70/30), a premix analogue, is an effective and well tolerated starter insulin in type 2 diabetes [abstract]. *Diabetes.* 2005;54(suppl 1):A502. ■