Number 14

Effective Health Care

Comparative Effectiveness, Safety, and Indications of Insulin Analogues in Premixed Formulations for Adults With Type 2 Diabetes

Executive Summary

Background and Key Questions

Although oral antidiabetic agents are used as first-line agents in patients with type 2 diabetes, insulin is required in a significant number of patients at some stage during the management of diabetes to maintain optimal glycemic control. Insulin use has been suggested as a first-line therapy in patients with type 2 diabetes, either as an add-on therapy to the existing noninsulin antidiabetic medications or as a replacement for noninsulin medications. According to the National Health Interview Survey, 28 percent of patients with type 2 diabetes are using insulin either alone (16 percent) or in combination with oral antidiabetic agents (12 percent).

To mimic the release of insulin from pancreatic beta-cells in response to food intake, near-physiologic insulin replacement regimens involve giving insulin at specific times in relation to meals. In addition, some formulation of a longer acting insulin is prescribed to mimic the relatively constant and slow release of insulin that regulates hepatic gluconeogenesis and lipolysis. However, the addition of insulin to treatment

Effective Health Care Program

The Effective Health Care Program was initiated in 2005 to provide valid evidence about the comparative effectiveness of different medical interventions. The object is to help consumers, health care providers, and others in making informed choices among treatment alternatives. Through its Comparative Effectiveness Reviews, the program supports systematic appraisals of existing scientific evidence regarding treatments for high-priority health conditions. It also promotes and generates new scientific evidence by identifying gaps in existing scientific evidence and supporting new research. The program puts special emphasis on translating findings into a variety of useful formats for different stakeholders, including consumers.

The full report and this summary are available at **www.effectivehealthcare.ahrq.gov/reports/final.cfm**

Agency for Healthcare Research and Quality
Advancing Excellence in Health Care • www.ahrq.gov

Effective Health Care

regimens may result in decreased flexibility in the timing of meals and activities, increased frequency of blood glucose monitoring, and an increased risk of weight gain and hypoglycemia. Also, the requirement for multiple injections of short-acting insulin (bolus insulin) and long-acting insulin (basal insulin) may affect patients' overall satisfaction with their treatment regimen.

Premixed insulin preparations are a therapeutic alternative to multiple insulin injections in a near-physiologic regimen that is also convenient for patients. A number of patient-related factors have been identified that may help physicians to select patients for therapy with premixed insulin preparations. Such preparations are generally appropriate for patients who: (1) desire a convenient and simple insulin regimen; (2) are unwilling to administer multiple daily injections or use an insulin pump; (3) are unwilling to or cannot undertake carbohydrate counting; (4) have a relatively predictable (routine) life style; and (5) consume meals with approximately the same composition of calories, carbohydrates, fats, and fiber at fairly consistent and reproducible times every day.

Insulin analogues have been developed by altering one of the two polypeptide chains of human insulin. This modification changes the pharmacokinetic and pharmacodynamic properties of the insulin, imparting the desired rapidity or duration of action. Premixed insulin analogues are derived from rapid-acting insulin analogues and consist of a mixture of rapid-acting insulin analogues and an intermediate-acting protamine suspension or protamine alone.

In the management of type 2 diabetes, the place of premixed insulin analogues in relation to other insulin regimens and noninsulin antidiabetic agents is as yet unclear. When compared with premixed human insulin, premixed insulin analogues may provide a glucose-lowering profile that more closely mimics the physiology of a person without diabetes, thus providing better glycemic control. In addition, compared with premixed human insulin preparations, premixed insulin analogues allow patients more flexibility in timing their meals, since premixed insulin analogues can be administered within 15 minutes of a meal.

Despite their advantages, the effect of premixed insulin analogues on fasting and postprandial glucose and hemoglobin A1C (A1c) compared with the effect of other antidiabetic medications has not been clearly established. Although several studies have demonstrated that insulin aspart 70/30 and insulin lispro 75/25 are more effective in lowering postprandial glucose levels than neutral protamine Hagedorn (NPH)/regular 70/30, their effectiveness in lowering A1c appears similar. Similarly, these same two premixed insulin analogues appear to be more effective in lowering postprandial glucose but less effective in lowering fasting glucose than the long-acting insulin analogues are. Moreover, several studies have found that while the rate of side effects (such as hypoglycemia) is similar for premixed insulin analogues and premixed human insulin preparations, these side effects are less common with the long-acting insulin analogues than with premixed insulin analogues.

Given the increasing prevalence of type 2 diabetes, the large number of patients who use insulin for glycemic control, and the well-documented importance of glycemic control in decreasing mortality and preventing long-term complications, it is important to review and evaluate the weight of evidence for the safety and effectiveness of these insulin therapies relative to alternative insulin and noninsulin antidiabetic regimens.

To date, no one study has compared premixed insulin analogues with other insulin and noninsulin antidiabetic agents in terms of reducing fasting and postprandial glucose, A1c, microvascular and macrovascular diabetic complications and in terms of the side effects of treatment. Clinicians may be better able to choose the most effective therapy for their patients with diabetes if they have the results of an objective, impartial, comprehensive evidence-based review of the comparative effectiveness and safety of different therapeutic options for the treatment of type 2 diabetes. We have therefore performed a systematic review of published studies dealing with the comparative effectiveness and safety of all premixed insulin analogues that are approved by the U.S. Food and Drug Administration (FDA) and available in the United States.

This report addresses the following key questions:

1. In adults (age ≥ 18 years) with type 2 diabetes, what is the effectiveness of premixed insulin analogues (insulin aspart 70/30, insulin lispro 75/25, insulin lispro 50/50) in achieving optimal glycemic control, as compared to insulin regimens including, but not necessarily limited to, the following preparations?
    a. Premixed human insulin preparations (NPH/regular 70/30, NPH/regular 50/50).
    b. Long-acting insulin analogues (insulin detemir, insulin glargine) administered alone.
    c. Intermediate-acting human insulin (NPH insulin) administered alone.
    d. Short-acting human insulin (regular insulin) administered prandially.
    e. Rapid-acting insulin analogues (insulin aspart, insulin glulisine, insulin lispro) administered separately (prandially) with a long-acting insulin analogue (insulin detemir, insulin glargine).
2. For adults with type 2 diabetes, do premixed insulin analogues differ from other commonly used insulin preparations with regard to safety, adverse effects, or adherence? The adverse effects of interest include, but are not limited to, hypoglycemia (nocturnal and daytime), weight gain, and interactions with other medications.
3. Does the effectiveness or safety of the new premixed insulin analogue regimens vary across the following subpopulations of patients with type 2 diabetes?
    a. The elderly (≥ 65 years), very elderly (≥ 85 years).
    b. Other demographic groups (ethnic or racial groups, genders).
    c. Individuals with comorbid medical conditions.
    d. Individuals with limited life expectancy.
    e. Individuals with disabilities.
4. What are the effectiveness and safety of the new premixed insulin analogue regimens in individuals on oral antidiabetic agents and individuals with different blood glucose patterns (such as fasting hyperglycemia or postprandial hyperglycemia) or types of control (such as tight control, usual control, good fasting, or postprandial control)?

Conclusions

The findings in this report are shown in Summary Table A and Summary Figure A.

Key Questions 1 and 2: Comparative effectiveness and safety of premixed insulin analogues

Premixed insulin analogues versus long-acting insulin analogues

Premixed insulin analogues were less effective than long-acting insulin analogues (administered alone) in lowering fasting glucose. Long-acting insulin analogues were more effective than insulin lispro 75/25 in lowering fasting glucose levels (pooled mean difference = 8.5 mg/dL; 95-percent confidence interval [CI]: 3.6 mg/dL to 13.3 mg/dL; $p = 0.001$). Two studies that compared the effect of insulin lispro 50/50 and of long-acting insulin analogues on fasting glucose found the long-acting analogues to be more effective ($p < 0.001$ in both studies). While the difference between insulin aspart 70/30 and long-acting insulin was not statistically significant, the direction of the effect was in favor of the long-acting insulin analogues (pooled mean difference = 6.4 mg/dL; 95-percent CI: -1.5 to 14.2 mg/dL; $p = 0.11$).

In contrast to fasting glucose, premixed analogues were more effective than long-acting insulin analogues in lowering postprandial glucose. When compared with long-acting insulin analogues, insulin aspart 70/30 was significantly more effective in decreasing postprandial

glucose (pooled mean difference = -22.6 mg/dL; 95-percent CI: -32.1 to -13.2 mg/dL; $p < 0.001$), as were insulin lispro 75/25 (pooled mean difference = -23.6 mg/dL; 95-percent CI: -30.9 to -16.4 mg/dL; $p < 0.001$) and insulin lispro 50/50 (pooled mean difference = -32.6 mg/dL; 95-percent CI: -48.2 to -17.1 mg/dL; $p < 0.001$).

As was true for their effect on postprandial glucose, premixed insulin analogues were also more effective than long-acting insulin analogues in lowering A1c levels. Insulin aspart 70/30 produced a 0.48-percent greater decrease in A1c levels than did long-acting insulin analogues (95-percent CI: -0.61 to -0.34 percent; $p < 0.001$). Similarly, compared with long-acting insulin analogues, insulin lispro 75/25 lowered A1c levels by 0.33 percent (95-percent CI: -0.48 to -0.17 percent; $p < 0.001$) and insulin lispro 50/50 lowered A1c levels by 0.40 percent (95-percent CI: -0.65 to -0.15 percent; $p = 0.001$).

While effective in lowering postprandial glucose and A1c, premixed analogues increased the incidence of hypoglycemia and were associated with weight gain to a greater extent than the long-acting insulin analogues were. Use of insulin aspart 70/30 in randomized controlled trials was associated with a higher incidence of overall and minor hypoglycemia. Similarly, weight gain was significantly higher with insulin aspart 70/30 (pooled mean difference = 2.5 kg; 95-percent CI: 1.6 to 3.4 kg; $p < 0.001$). Although the incidence of hypoglycemia was neither consistent nor statistically significant across all trials, the direction of the individual study effect sizes suggested that both insulin lispro 75/25 and insulin lispro 50/50 may increase the incidence of hypoglycemia when compared with long-acting insulin analogues. In two studies, use of insulin lispro 50/50 resulted in a larger weight gain than long-acting insulin analogues did, although this effect reached statistical significance in only one study. None of the studies reported the comparative effects of insulin lispro 75/25 and long-acting insulin analogues on weight change.

Premixed insulin analogues versus rapid-acting insulin analogues

We found only two studies that compared premixed insulin analogues with rapid-acting insulin analogues. In one study, insulin aspart 70/30 was more effective than rapid-acting insulin aspart in decreasing fasting glucose levels (mean difference = -22.0 mg/dL; $p < 0.001$) but less effective in lowering postprandial glucose (mean difference = 15 mg/dL; $p < 0.001$). In contrast, insulin lispro 50/50 and rapid-acting insulin lispro showed similar efficacy in lowering fasting glucose (mean difference = 0 mg/dL; $p > 0.05$) or postprandial glucose (mean difference = 3.6 mg/dL; $p > 0.05$) in another study. The results were identical in both studies in terms of A1c levels and the incidence of hypoglycemia, and there was no difference between insulin aspart 70/30 or insulin lispro 50/50 and rapid-acting insulin analogues. In both studies, rapid-acting insulin analogues were associated with significantly more weight gain than insulin aspart 70/30 (mean weight change = -1.0 kg; $p = 0.005$) or insulin lispro 50/50 (mean change in body mass index = 0.3 kg/m^2; $p = 0.048$).

Premixed insulin analogues versus a combination of long-acting and rapid-acting insulin analogues

We found two parallel-arm trials (one randomized and one nonrandomized) that compared premixed insulin analogues with a combined regimen of long-acting insulin analogue (basal) and rapid-acting insulin analogue (bolus). The randomized trial found that the basal-bolus regimen was more effective than insulin lispro 50/50 in lowering fasting glucose (147 versus 159 mg/dL; $p = 0.013$), 2-hour postbreakfast glucose (155 versus 174 mg/dL; $p = 0.002$), and A1c (6.8 versus 6.9 percent; $p = 0.02$). The incidence of overall, nocturnal, and severe hypoglycemia was similar for the two treatments. The nonrandomized prospective trial found that insulin aspart 70/30 was similar to the basal-bolus regimen in lowering fasting and postprandial glucose levels but was more effective in lowering A1c and was associated with fewer minor hypoglycemic events. Both studies found no difference in weight change between the two treatment regimens.

Premixed insulin analogues versus premixed human insulin

We found 16 studies that compared premixed insulin analogues with premixed human insulin. Premixed insulin analogues and premixed human insulin appeared to be similarly effective in lowering fasting glucose. Premixed insulin analogues were more effective in lowering postprandial glucose. Premixed insulin analogues appeared to be similar to premixed human insulin in lowering A1c levels and the incidence of hypoglycemia.

We found that insulin aspart 70/30 was less effective than premixed human insulin 70/30 in lowering fasting glucose (pooled mean difference = 8.3 mg/dL; 95-percent CI: 0.16 to 16.5 mg/dL; p = 0.04) but was more effective in lowering postprandial glucose (pooled mean difference = -18.5 mg/dL; 95-percent CI: -31.1 to -6.0 mg/dL; p = 0.004). Insulin aspart 70/30 and premixed human insulin were similar in their ability to lower A1c (pooled mean difference = 0.06 percent; 95-percent CI: -0.04 to 0.16 percent; p = 0.22). There was no difference between insulin aspart 70/30 and premixed human insulin in terms of the incidence of major or minor hypoglycemia (odds ratio [OR] = 0.52; 95-percent CI: 0.16 to 1.70; p = 0.28 and OR = 0.98; 95-percent CI: 0.65 to 1.46; p = 0.91, respectively). Similarly, the two treatments were comparable in terms of their effect on weight change.

Insulin lispro 75/25 was similar to premixed human insulin in lowering fasting glucose (pooled mean difference = 0.12 mg/dL; 95-percent CI: -6.05 to 6.29 mg/dL; p = 0.97) but more effective in lowering postprandial glucose (pooled mean difference = -17.8 mg/dL; 95-percent CI: -27.0 to -8.6 mg/dL; p < 0.001). Both treatment regimens were similar in lowering A1c and decreasing the incidence of hypoglycemia.

Insulin lispro 50/50 was less effective than premixed human insulin in lowering fasting glucose in two studies (mean difference = 30.3 mg/dL; p < 0.001 and mean difference = 23 mg/dL; p = nonsignificant) but more effective in lowering postprandial glucose (pooled mean difference = -30.3 mg/dL; 95-percent CI: -55.6 to -5.0 mg/dL; p = 0.02) and A1c (p < 0.05 in both studies). There was no difference in the incidence of hypoglycemia between the two studies.

Premixed insulin analogues versus rapid-acting insulin analogues with intermediate-acting human insulin

We found only one study that evaluated this comparison. This study did not report on the changes in fasting and postprandial glucose. Changes in A1c and the incidence of severe hypoglycemia did not differ between the two treatment regimens. The premixed insulin analogue group experienced significantly more weight gain.

Premixed insulin analogues versus intermediate-acting insulin

Only two studies evaluated this comparison. In one parallel-arm randomized study enrolling 95 patients, NPH was given daily at 10:00 P.M. and insulin aspart 70/30 was given once daily 10 minutes before dinner, with metformin being continued in both arms. In the second parallel-arm randomized study enrolling 403 patients, all oral antidiabetic agents were discontinued, and insulin aspart 70/30 and NPH were given immediately before breakfast and dinner. Both studies reported similar results; premixed insulin analogues were as effective as NPH (an intermediate-acting insulin) in lowering fasting and postprandial glucose levels and A1c, and were similar in terms of the incidence of hypoglycemia and the frequency and magnitude of the weight gain produced. These results are in contrast to what would be expected on the basis of the pharmacokinetic and pharmacodynamic information available for the two agents and may reflect the study design characteristics or a low power of the studies to detect a difference.

Premixed insulin analogues versus noninsulin antidiabetic agents

Ten studies evaluated this comparison. Premixed insulin analogues were more effective than noninsulin antidiabetic agents in terms of glycemic control (lowering fasting glucose, postprandial glucose, and A1c levels) but were also associated with an increased risk of hypoglycemia and weight gain.

Insulin aspart 70/30 was more effective than oral antidiabetic agents in lowering fasting glucose (pooled mean difference = -13.9 mg/dL; 95-percent CI: -24.4 to -3.4 mg/dL; p = 0.009), postprandial glucose (pooled

mean difference = -32.8 mg/dL; 95-percent CI: -62.5 to -3.1 mg/dL; p = 0.03), and A1c (pooled mean difference = -0.52 percent; 95-percent CI: -1.0 to -0.04 percent; p = 0.034). On the other hand, patients on insulin aspart 70/30 had a higher incidence of minor hypoglycemia (OR = 3.79; 95-percent CI: 1.7 to 8.5; p = 0.001) and symptom-only hypoglycemia (OR = 3.9; 95-percent CI: 1.2 to 12.4; p = 0.02) and experienced a larger weight gain (pooled mean difference = 2.8 kg; 95-percent CI: 0.6 kg to 5.0 kg; p = 0.01) than those on oral antihypoglycemic agents did.

One study that compared a premixed insulin analogue (insulin aspart 70/30) to exenatide found that insulin aspart 70/30 was as effective as exenatide in lowering fasting glucose levels but was less effective in lowering postprandial glucose levels. There was no difference in terms of lowering A1c levels. Patients on exenatide lost weight, in contrast to the weight gain experienced by patients on premixed insulin analogues. However, more patients withdrew from the exenatide arm than from the premixed insulin analogue arm of the study.

Insulin lispro 75/25 was also more effective than oral antidiabetic agents in lowering fasting glucose (pooled mean difference = -31.4 mg/dL; 95-percent CI: -45.7 to -17.1 mg/dL; p < 0.001) and postprandial glucose (pooled mean difference = -47.3 mg/dL; 95-percent CI: -63.5 to -31.0 mg/dL; p < 0.001). Insulin lispro 75/25 was again more effective than oral antidiabetic agents in lowering A1c levels, although this effect did not reach statistical significance (pooled mean difference = -0.42 percent; 95-percent CI: -1.0 to 0.16 percent; p = 0.15). Insulin lispro 75/25 was associated with a higher rate of overall hypoglycemia measured as episode/patient/30 -day (rate ratio = 4.86; 95-percent CI: 0.5 to 49.5; p = 0.18) and larger weight gain (pooled mean difference = 1.88 kg; 95-percent CI: 1.35 to 2.41 kg; p < 0.001) when compared with oral antidiabetic agents. No studies compared insulin lispro 50/50 with oral antidiabetic agents.

Premixed insulin analogues versus premixed insulin analogues

We found only three studies that compared one premixed insulin analogue with another, and we saw no difference among these premixed insulin analogues (insulin aspart 70/30, insulin lispro 75/25, and insulin lispro 50/50) in terms of lowering fasting or postprandial glucose levels, A1c, or the incidence of hypoglycemia, or in terms of weight change.

Premixed insulin analogues versus other antidiabetic medications: clinical outcomes

We found only 16 studies that evaluated clinical outcomes such as mortality. No statistically significant differences were found between premixed insulin analogues and their comparators in terms of all-cause mortality, cardiovascular mortality, or cardiovascular morbidity. When premixed insulin analogues were compared with other antidiabetic medications, a suggestion of harm was seen in the pooled odds ratios for all-cause mortality, cardiovascular mortality, and the combined outcome of cardiovascular morbidity and mortality, but these point estimates were based on few absolute events in only a few studies, in which clinical outcomes were not the primary end points. Insufficient or no evidence was found with regard to microvascular outcomes.

While the rosiglitazone and pioglitazone labels have warnings concerning increased congestive heart failure events in subjects who use insulin of any type in conjunction with these oral medications (compared with those who use insulin alone), we did not observe any congestive heart failure events in the few available studies, which reported few absolute events. In addition, rosiglitazone labels have warnings regarding the increased ischemic risk in patients who use rosiglitazone with insulin, as compared with insulin alone. The evidence was insufficient to allow us to determine whether this risk applied to premixed insulin analogues specifically. Until more data are available, physicians should be aware of these warnings.

No evidence was found with regard to adherence. Six studies evaluated quality of life. No firm conclusions could be drawn because of the differences between studies in terms of outcome definitions, measurement techniques, populations, and comparators.

Key Question 3: Effect of premixed insulin analogues in certain subpopulations

We did not find any study that specifically explored the effect of premixed insulin analogues in specific subpopulations, such as the very elderly, those with comorbid conditions, or minorities.

Key Question 4: Effect of premixed insulin analogues based on patient characteristics

Comparison of premixed insulin analogues alone with premixed insulin analogues and oral antidiabetic agents

We found three studies that compared using premixed insulin analogues alone with using a combination of a premixed insulin analogue plus an oral antidiabetic agent. These studies found that a combination of premixed insulin analogue and oral antidiabetic agent was probably more effective than a premixed analogue alone in lowering fasting glucose levels (insufficient data to be able to pool studies) and postprandial glucose levels (pooled mean difference = -5.8 mg/dL, 95-percent CI: -15.7 to 4.1 mg/dL; p = 0.25). However, a combination of premixed insulin analogue plus oral antidiabetic agent was more effective than monotherapy with premixed insulin analogue in lowering A1c (pooled mean difference = 0.37 percent; 95-percent CI: 0.12 to 0.62 percent; p = 0.004) without increasing the incidence of minor hypoglycemia (OR = 0.84; 95-percent CI: 0.45 to 1.56; p = 0.6) or symptom-only hypoglycemia (OR = 1.1; 95-percent CI: 0.77 to 1.6; p = 0.6). The effect on weight gain appeared to be related to the type of oral antidiabetic agent used with the premixed insulin analogue. In both studies in which metformin was the oral agent in the combination therapy, monotherapy with premixed insulin analogues resulted in greater weight gain. In one study in which pioglitazone was the oral agent in the combination therapy, monotherapy with premixed analogues was associated with less weight gain (4.0 versus 2.2 kg).

Effect of premixed insulin analogues in patients with different intensities of glucose control

We did not find any study that compared intensive glycemic control with standard glycemic control in patients using premixed insulin analogues.

Effect of premixed insulin analogues in patients with postprandial versus fasting blood glucose control

We did not find any study that evaluated this question.

Applicability

All the identified studies were efficacy trials and not effectiveness trials; thus, the ability to generalize their findings to the U.S. population with diabetes as a whole and to current clinical practice is clearly limited. In general, the study populations reflected the age and sex composition of the U.S. population with diabetes. However, the spectrum of diabetic complications and comorbidities seen in the enrolled participants was limited. Some trials excluded insulin-naïve patients, while others excluded all insulin-treated patients. All trials either excluded patients with cardiac, renal, or hepatic disease or did not report whether or not such patients were included, thus limiting our ability to generalize their results to these subpopulations.

Remaining Issues

Gaps in evidence and future directions for research are outlined below.

- There was only limited evidence to allow us to compare premixed insulin analogues with a regimen consisting of a long-acting insulin analogue (basal insulin) plus a rapid-acting insulin analogue (bolus insulin). Probably the most important comparative study that needs to be performed is to compare premixed insulin analogues with a basal-bolus regimen.
- All the studies identified were of very short duration. Studies with a longer planned duration of followup are needed to allow us to ascertain whether the gains achieved early in treatment are sustainable in the long term and whether differences between the comparators appear later during the treatment.

- The lack of effectiveness studies limited our ability to make generalizations from the reported results to all patients with diabetes in the United States. Studies designed to examine the effectiveness of premixed insulin analogues should be conducted with less restrictive inclusion criteria and in a setting that more closely mimics the usual clinical practice.
- There were no, or only very limited, data specifically related to the comparative effectiveness of premixed insulin analogues and other antidiabetic agents in certain subpopulations. Patients with comorbid conditions, racial minorities, and very elderly patients need to be enrolled in studies examining the efficacy and effectiveness of premixed insulin analogues in these subpopulations.
- Clinical outcomes need to be studied in order to better evaluate the safety of premixed insulin analogues, especially given the suggestion of increased mortality and cardiovascular morbidity seen in the pooled estimates from the available short-duration trials. Studies need to be sufficiently powered to make it possible to assess clinical outcomes.
- Because diabetes is a chronic disease that requires different injection patterns and glucose testing depending on the type of medication regimen prescribed, evaluating patient adherence and quality of life for users of premixed insulin analogues compared with those on other diabetes regimens is critical.

Full Report

This executive summary is part of the following document: Qayyum R, Wilson LM, Bolen S, Maruthur N, Marinopoulos SS, Feldman L, Ranasinghe P, Amer M, Bass EB. Comparative Effectiveness, Safety, and Indications of Insulin Analogues in Premixed Formulations for Adults With Type 2 Diabetes. Comparative Effectiveness Review No. 14. (Prepared by the Johns Hopkins University Evidence-based Practice Center under Contract No. 290-02-0018.) Rockville, MD: Agency for Healthcare Research and Quality. September 2008. Available at: www.effectivehealthcare.ahrq.gov/reports/final.cfm.

For More Copies

For more copies of Comparative Effectiveness, Safety, and Indications of Insulin Analogues in Premixed Formulations for Adults With Type 2 Diabetes: Executive Summary No. 14 (AHRQ Pub. No. 08-EHC017-1), please call the AHRQ Clearinghouse at 1-800-358-9295.

Summary Table A. Summary of key findings on comparative effectiveness of premixed insulin analogues and other antidiabetic agents		
Outcome and comparison agent	**Strength of evidence**	**Summary**
Fasting glucose		
Long-acting insulin analogues	Moderate	Premixed insulin analogues are similarly effective as long-acting insulin analogues alone in lowering fasting glucose.
Rapid-acting insulin analogues	Low	The evidence was too weak to make a conclusion.
Combination of long-acting and rapid-acting insulin analogues (basal-bolus regimen)	Low	The evidence was too weak to make a conclusion.
Premixed human insulin	Moderate	Premixed insulin analogues are similarly effective as premixed human insulin preparations in lowering fasting glucose.
Intermediate-acting human insulin	Low	The evidence was too weak to make a conclusion.
Combination of intermediate-acting human insulin and rapid-acting insulin analogue	No evidence	There is no evidence for this comparison.
Noninsulin antidiabetic agents	Moderate	Premixed insulin analogues are more effective than noninsulin antidiabetic agents in lowering fasting glucose.
Premixed insulin analogues	Low	The evidence was too weak to make a conclusion.
Postprandial glucose		
Long-acting insulin analogues	High	Premixed insulin analogues are better than long-acting insulin analogues alone in lowering postprandial glucose.
Rapid-acting insulin analogues	Low	The evidence was too weak to make a conclusion.
Combination of long-acting and rapid-acting insulin analogues (basal-bolus regimen)	Low	The evidence was too weak to make a conclusion.
Premixed human insulin	High	Premixed insulin analogues are better than NPH/regular 70/30 in lowering postprandial glucose.
Intermediate-acting human insulin	Low	The evidence was too weak to make a conclusion.
Combination of intermediate-acting human insulin and rapid-acting insulin analogue	No evidence	There is no evidence for this comparison.

Summary Table A. Summary of key findings on comparative effectiveness of premixed insulin analogues and other antidiabetic agents		
Outcome and comparison agent	**Strength of evidence**	**Summary**
Postprandial glucose (continued)		
Noninsulin antidiabetic agents	Moderate	Premixed insulin analogues are better than oral antidiabetic agents in lowering postprandial glucose, although there is no evidence available for insulin lispro 50/50. There is not enough evidence to conclusively compare the new incretin mimetic agent exenatide to premixed insulin analogues in terms of lowering postprandial glucose.
Premixed insulin analogues	Low	The evidence was too weak to make a conclusion.
A1c		
Long-acting insulin analogues	High	Premixed insulin analogues are more effective than long-acting insulin analogues in lowering A1c.
Rapid-acting insulin analogues alone or intermediate-acting insulin analogues alone	Low	The evidence was too weak to make a conclusion.
Combination of long-acting and rapid-acting insulin analogues (basal-bolus regimen)	Low	The evidence was too weak to make a conclusion.
Premixed human insulin	High	Premixed insulin analogues are as effective as NPH/regular 70/30 in lowering A1c.
Intermediate-acting human insulin (used alone)	Low	The evidence was too weak to make a conclusion.
Combination of intermediate-acting human insulin and rapid-acting insulin analogue	Low	The evidence was too weak to make a conclusion.
Noninsulin antidiabetic agents	Moderate	Premixed insulin analogues are more effective than oral antidiabetic agents in lowering A1c. There is not enough evidence to allow us to conclusively compare exenatide to premixed insulin analogues.
Premixed insulin analogues	Low	The evidence was too weak to make a conclusion.
All-cause mortality, cardiovascular disease mortality and morbidity[1]	Low	No statistically significant differences in all-cause mortality (OR = 2.93; 95% CI: 0.95 to 9.05), cardiovascular mortality (OR = 6.80; 95% CI: 0.87 to 53.12), cardiovascular morbidity (OR = 0.86; 95% CI: 0.49 to 1.52), or the combined outcome of all-cause mortality and cardiovascular morbidity (OR = 2.10; 95% CI: 0.87 to 5.10) were found between premixed insulin analogues and other diabetes medications in these short-duration randomized controlled trials.

Summary Table A. Summary of key findings on comparative effectiveness of premixed insulin analogues and other antidiabetic agents (continued)		
Outcome and comparison agent	**Strength of evidence**	**Summary**
All-cause mortality, cardiovascular disease mortality and morbidity[1] (continued)		Low absolute numbers of events in short-duration trials in which clinical events were not the primary outcomes made it difficult to draw any firm conclusions regarding clinical outcomes.
Nephropathy	Low	The evidence was too weak to make a conclusion.
Retinopathy and neuropathy	No evidence	No studies evaluated other clinical outcomes, such as retinopathy and neuropathy.
Hypoglycemia		Many of the comparisons were made in too few studies to allow us to draw any conclusions. The effect of premixed insulin analogues on the incidence of serious hypoglycemia cannot be conclusively addressed because of the very small numbers of serious hypoglycemic events reported in the studies.
Long-acting insulin analogues	High	Premixed insulin analogues are more likely to be associated with hypoglycemia than long-acting insulin analogues are.
Rapid-acting insulin analogues	Low	The evidence was too weak to make a conclusion.
Combination of long-acting and rapid-acting insulin analogues (basal-bolus regimen)	Low	The evidence was too weak to make a conclusion.
Premixed human insulin	High	Premixed insulin analogues are similar to premixed human insulin preparations in terms of the frequency of hypoglycemia reported.
Intermediate-acting human insulin (used alone)	Low	The evidence was too weak to make a conclusion.
Combination of intermediate-acting human insulin and rapid-acting insulin analogue	Low	The evidence was too weak to make a conclusion.
Noninsulin antidiabetic agents	High	Premixed insulin analogues are associated with a higher frequency of hypoglycemic events than oral antidiabetic agents are.
Premixed insulin analogues	Low	The evidence was too weak to make a conclusion.
Weight change		There is not enough evidence to allow us to conclusively compare the weight change after treatment with premixed insulin analogues versus the change after treatment with other antidiabetic drugs, except as noted below.

Summary Table A. Summary of key findings on comparative effectiveness of premixed insulin analogues and other antidiabetic agents (continued)		
Outcome and comparison agent	**Strength of evidence**	**Summary**
Weight change (continued)		
Long-acting insulin analogues	Moderate	Premixed insulin analogues may cause more weight gain than long-acting insulin analogues do.
Rapid-acting insulin analogues	Low	Premixed insulin analogues may cause less weight gain than rapid-acting insulin analogues do.
Combination of long-acting and rapid-acting insulin analogues (basal-bolus regimen).	Low	The evidence was too weak to make a conclusion.
Premixed human insulin	Moderate	Premixed insulin analogues may be similar to premixed human insulin preparations in their effect on weight change.
Intermediate-acting human insulin	Low	The evidence was too weak to make a conclusion.
Combination of intermediate-acting human insulin and rapid-acting insulin analogue	Low	Premixed insulin analogues may be associated with weight gain compared with a combination of intermediate-acting human insulin and rapid-acting insulin analogue.
Noninsulin antidiabetic agents	Moderate	Premixed insulin analogues cause weight gain compared with oral antidiabetic agents considered as a group.
Premixed insulin analogues	No evidence	There is no evidence for this comparison.
Adherence	No evidence	There is no evidence for adherence in terms of the comparisons of interest.
Quality of life	Low	No significant difference was noted in the 3 studies that compared premixed insulin analogues with other antidiabetic agents and used a validated quality-of-life instrument. No firm conclusions can be drawn regarding quality-of-life outcomes because of the differences between studies in outcome definitions, measurement techniques, populations, and comparators.
Effect of premixed insulin analogues in certain subpopulations	No evidence	We did not find any study that specifically explored the effect of premixed insulin analogues in specific subpopulations, such as the very elderly, those with comorbid conditions, or minorities.

Summary Table A. Summary of key findings on comparative effectiveness of premixed insulin analogues and other antidiabetic agents (continued)		
Outcome and comparison agent	**Strength of evidence**	**Summary**
Effect of premixed insulin analogues in patients taking oral antidiabetic agents	Low	The evidence was too weak to make a conclusion.
Effect of premixed insulin analogues in patients with different intensities of glucose control	No evidence	We did not find any study that evaluated this question.
Effect of premixed insulin analogues in patients requiring postprandial versus fasting blood glucose control	No evidence	We did not find any study that evaluated this question.

[1]While the rosiglitazone and pioglitazone labels have warnings concerning increased congestive heart failure events in subjects who use insulin of any type in conjunction with these oral medications (versus insulin alone), we did not observe any congestive heart failure events in these few studies, which reported only very few absolute events. In addition, rosiglitazone labels have warnings regarding increased ischemic risk in patients who use rosiglitazone with insulin compared to those who use insulin alone. There was insufficient evidence to allow us to determine whether this risk applies to premixed insulin analogues specifically. Until more data are available, physicians should be aware of these warnings.

Abbreviations: A1c = hemoglobin A1c; CI = confidence interval; NPH = neutral protamine Hagedorn (an intermediate-acting insulin); OR = odds ratio.

Summary Figure A. Key findings on comparative effectiveness of individual premixed insulin analogues and other antidiabetic agents

		Long-acting	Rapid acting	Long + rapid	Premixed human insulin	NPH	NPH + rapid	Noninsulin antidiabetic
FG	IA 70/30	↔	↓*	↔*	↑	↔*	X	↓
	IL 75/25	↑	X*	X	↔	X	X	↓
	IL 50/50	↑	↔*	↑*	↑	X	X	X
PPG	IA 70/30	↓	↑*	↔*	↓	↔*	X	↓
	IL 75/25	↓	X	X	↓	X	X	↓
	IL 50/50	↓	↔*	↑*	↓	X	X	X
A1c	IA 70/30	↓	↔§*	↓*	↔	↔*	↔*	↓
	IL 75/25	↓	X	X	↔	X	X	↔
	IL 50/50	↓	↔*	↑*	↓	X	X	X
Hypoglycemia	IA 70/30	↑	↔*	↓*	↔	↔*	↔*	↑
	IL 75/25	↑*	X	X	↔	X	X	↔
	IL 50/50	↑	↔*	↔*	↔	X	X	X
Weight change	IA 70/30	↑	↓*	↔*	↔	↔*	↑*	↑
	IL 75/25	X	X	X	↔	X	X	↑
	IL 50/50	↑*	↑*	↔*	↔	X	X	X

↑ = variable increases with premixed analogue versus comparator

↓ = variable decreases with premixed analogue versus comparator

↔ = premixed analogue and comparator have same effect on variable

X = no studies have looked at the comparison

* = overall evidence is not of sufficient strength

§ = benefit with premixed insulin analogue almost reached statistical significance

Note: A1c = hemoglobin A1c; FG = fasting glucose; IA 70/30 = insulin aspart 70/30; IL 75/25 = insulin lispro 75/25; IL 50/50 = insulin lispro 50/50; long + rapid = combination of long-acting and rapid-acting insulin analogues; long-acting = long-acting insulin analogues; NPH + rapid = combination of intermediate-acting human insulin and rapid-acting insulin analogue; NPH = neutral protamine Hagedorn (an intermediate-acting insulin); PPG = postprandial glucose; rapid-acting = rapid-acting insulin analogues.

AHRQ Pub. No. 08-EHC017-1
September 2008