Comparative Effectiveness Review
Number 14

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

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Preface

The Agency for Healthcare Research and Quality (AHRQ) conducts the Effective Health Care Program as part of its mission to organize knowledge and make it available to inform decisions about health care. As part of the Medicare Prescription Drug, Improvement, and Modernization Act of 2003, Congress directed AHRQ to conduct and support research on the comparative outcomes, clinical effectiveness, and appropriateness of pharmaceuticals, devices, and health care services to meet the needs of Medicare, Medicaid, and the State Children's Health Insurance Program (SCHIP).

AHRQ has an established network of Evidence-based Practice Centers (EPCs) that produce Evidence Reports/Technology Assessments to assist public- and private-sector organizations in their efforts to improve the quality of health care. The EPCs now lend their expertise to the Effective Health Care Program by conducting Comparative Effectiveness Reviews of medications, devices, and other relevant interventions, including strategies for how these items and services can best be organized, managed, and delivered.

Systematic reviews are the building blocks underlying evidence-based practice; they focus attention on the strengths and limits of evidence from research studies about the effectiveness and safety of a clinical intervention. In the context of developing recommendations for practice, systematic reviews are useful because they define the strengths and limits of the evidence, clarifying whether assertions about the value of the intervention are based on strong evidence from clinical studies. For more information about systematic reviews, see http://effectivehealthcare.ahrq.gov/reference/purpose.cfm.

AHRQ expects that Comparative Effectiveness Reviews will be helpful to health plans, providers, purchasers, government programs, and the health care system as a whole. In addition, AHRQ is committed to presenting information in different formats so that consumers who make decisions about their own and their family's health can benefit from the evidence.

Transparency and stakeholder input are essential to the Effective Health Care Program. Please visit the Web site (www.effectivehealthcare.ahrq.gov) to see draft research questions and reports or to join an e-mail list to learn about new program products and opportunities for input. Comparative Effectiveness Reviews will be updated regularly.

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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 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 insuin 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.

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.
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.

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
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 morbidity1	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. 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.

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
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.
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.
Effect of premixed insulin analogues in patients taking oral antidiabetic agents	Low	The evidence was too weak to make a conclusion.

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 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
Hypogly-cemia	IA 70/30	↑	↔*	↓*	↔	↔*	↔*	↑
	IL 75/25	↑*	X	X	↔	X	X	↔
	IL 50/50	↑	↔*	↔*	↔	X	X	X

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

		Long-acting	Rapid-acting	Long + rapid	Premixed human insulin	NPH	NPH + rapid	Noninsulin antidiabetic
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.

Introduction

Background

Optimal control of hyperglycemia in diabetics is of paramount importance for preventing or delaying the occurrence of diabetic complications. The United Kingdom Prospective Diabetes Study (UKPDS) found that intensive control of blood glucose in patients with type 2 diabetes mellitus (type 2 diabetes) resulted in a 10 percent risk reduction in diabetes-related mortality and a 25 percent risk reduction in microvascular complications when compared to conventional control of blood glucose.[1] 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 their diabetes in order to maintain optimal glycemic control. According to the National Health Interview Survey (NHIS), 28 percent of patients with type 2 diabetes are using insulin either alone (16 percent) or in combination with other oral antidiabetic agents (12 percent).[2]

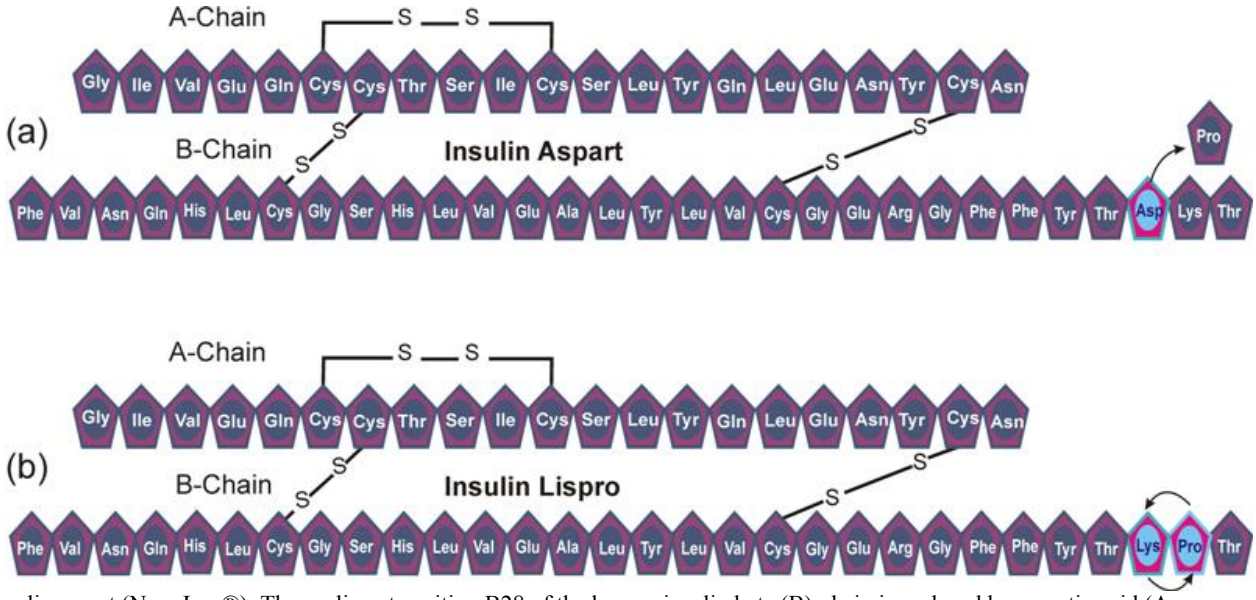
Insulin replacement regimens can be either near-physiologic (prescribed to mimic the natural release of insulin from the beta-cells of the human pancreas) or non-physiologic (all other regimens). Physiologic insulin replacement regimens consist of a bolus of insulin administered at specific times in relation to meals in order to mimic the release of insulin from the beta-cells in response to food intake. In addition, some formulations of longer-acting insulin are prescribed to mimic the constant release of insulin that regulates hepatic gluconeogenesis and lipolysis.[3,4] Although type 2 diabetic patients are reluctant to start insulin therapy,[5] insulin generally improves their quality of life.[6] However, the addition of insulin to their treatment regimen may result in decreased flexibility in the timing of meals and activities, increased frequency of blood glucose monitoring, and increased risk of weight gain and hypoglycemia.[4] Moreover, the need for multiple injections of short-acting (bolus insulin) and long-acting (basal insulin) agents may decrease patients' overall satisfaction with their treatment regimens.

Premixed insulin preparations offer a therapeutic alternative to multiple insulin injections that is also convenient for patients. These preparations are 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 or cannot undertake carbohydrate counting; (4) have a relatively predictable (routine) lifestyle; and (5) consume meals with approximately the same composition of calories, carbohydrates, fats, and fiber at fairly consistent and reproducible times every day.[7,8]

Insulin analogues are related to human insulin and produced using recombinant DNA technology. These analogues have minor changes in their structure that impart pharmacokinetic properties that more closely mimic endogenous insulin secretion. In *premixed insulin analogue* preparations, insulins are mixed with their own protamine suspensions, slowing their release.

Three premixed insulin preparations are available commercially in the United States (see Figure 1). Insulin aspart 70/30, marketed by Novo Nordisk as NovoLog™ Mix 70/30, is an insulin aspart suspension containing 70 percent insulin aspart protamine crystals and 30 percent soluble insulin aspart. Insulin lispro 75/25, marketed by Eli Lilly as Humalog™ 75/25, is a mixture of 75 percent insulin lispro protamine suspension and 25 percent rapid-acting insulin lispro solution. Insulin lispro 50/50, marketed by Eli Lilly as Humalog™ 50/50, is a mixture of 50 percent insulin lispro protamine suspension and 50 percent rapid-acting insulin lispro solution (see Table 1).

Figure 1. Simplified structural diagram of two rapid-acting insulin analogues that are included in premixed insulin analogue preparations



(a) Insulin aspart (NovoLog®): The proline at position B28 of the human insulin beta (B)-chain is replaced by aspartic acid (Asp, circled in red). (b) Insulin lispro (Humalog®): The positions of the lysine at position B29 and the proline at position B28 (circled in red) are reversed when compared to those in the B-chain of human insulin.
Source: Figure derived from information provided in the package insert.[16-18]

Table 1. Pharmacokinetic characteristics of selected insulin preparations

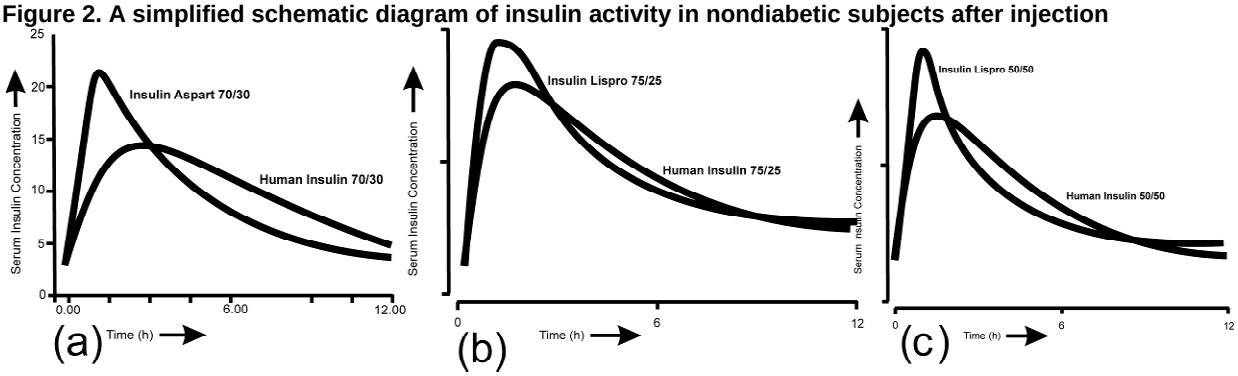
Insulin product	Time to peak activity	Percentage of total activity in first 4 hours	Duration of action (hours)
Insulin glargine	No pronounced peak	NA	24
NPH	6-12 hours	14%	18-24
Insulin detemir	6-8 hours	NA	5.7-23.2*
Insulin lispro	30-90 minutes	70%	3-4
Insulin aspart	60-180 minutes	65%	3-5
Insulin aspart 70/30	60-240 minutes	45%	18-24
Insulin lispro 75/25	2.6 hours	35%	18-24
Insulin lispro 50/50	2.3 hours	45%	18-24
NPH/regular 70/30	4.2 hours	25%	18-24
NPH/regular 50/50	4.0 hours	54%	18-24

Source: Package inserts and UptoDate 15.3 (www.uptodate.com)
*Depends on the dose; shorter duration of action is for smaller doses, longer for larger doses.
NA = not available; NPH = neutral protamine Hagedorn

In the management of type 2 diabetes, the place of premixed insulin analogues in relation to other insulin regimens and noninsulin antidiabetic agents is unclear. They may provide a more physiologic glucose-lowering profile, thus providing better glycemic control (see Figure 2). In addition, as compared to premixed human insulin preparations (such as NPH/regular 70/30), premixed insulin analogues allow patients more flexibility in timing their meals, since these insulin preparations can be administered within 15 minutes before a meal.

Several studies have found that insulin aspart 70/30 and insulin lispro 75/25 lower postprandial glucose levels to a greater degree than does NPH/regular 70/30,[9-12] although the timing of NPH/regular 70/30 may have affected the results in two studies.[11,12] However, the degree of improvement achieved in hemoglobin A1c, however, has been equivalent for the premixed insulin analogues and NPH/regular 70/30, despite improvement in postprandial

Figure 2. A simplified schematic diagram of insulin activity in nondiabetic subjects after injection



(a) Insulin aspart 70/30 and human insulin 70/30, (b) insulin lispro 75/25 and human insulin 75/25, and (c) insulin lispro 50/50 and human insulin 50/50.
Source: Figure derived from information provided in the package insert.[16-18]

glucose in a number of studies.[9,10,13] Similarly, several studies have found that the rate of side-effects, such as hypoglycemia, is similar for premixed insulin analogues and premixed human insulins.[10,14,15]

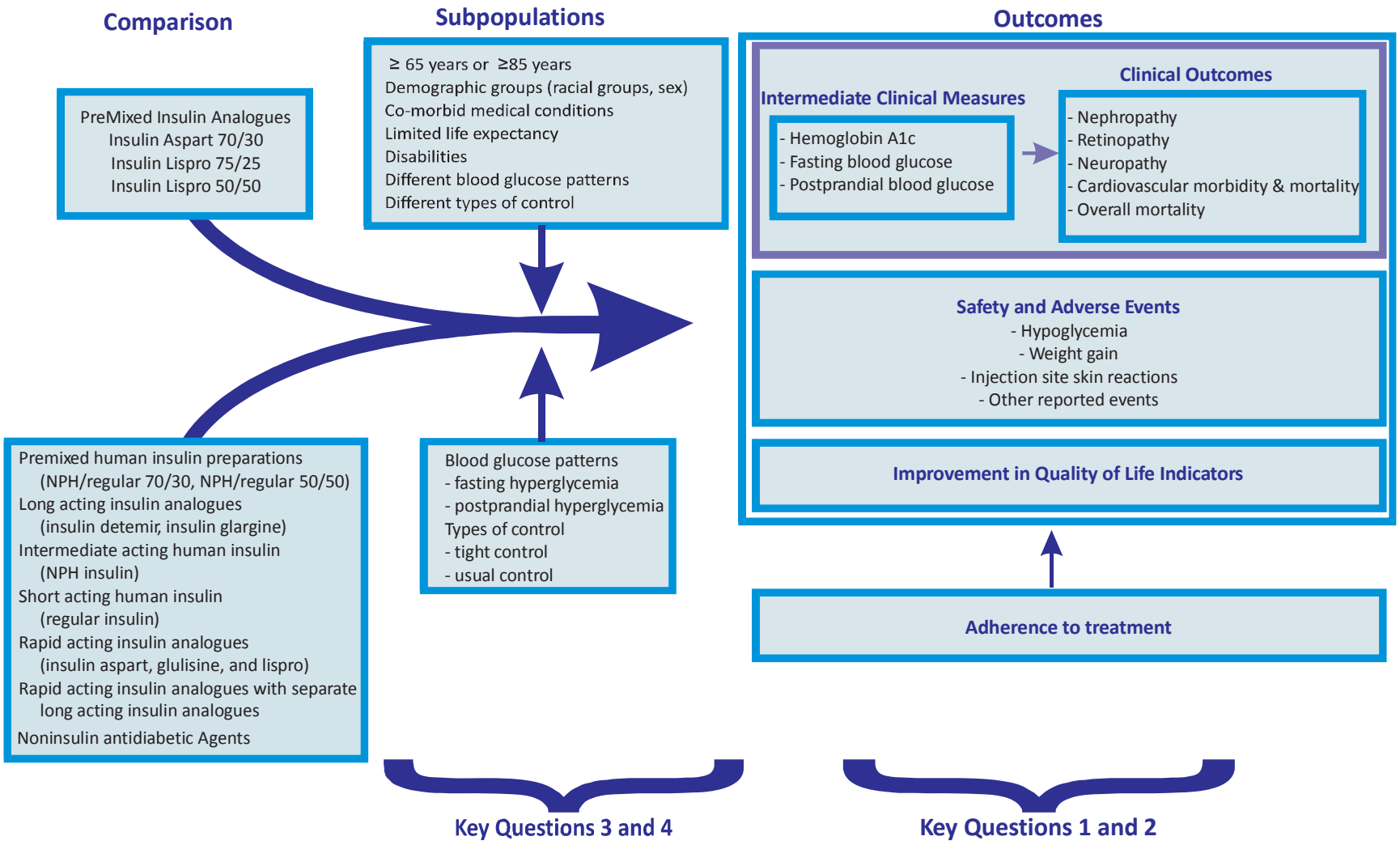
Given the increasing prevalence of type 2 diabetes, the large number of patients who use insulin for glycemic control, and the importance of glycemic control in decreasing mortality and preventing long-term complications, it is important to establish the weight of evidence for the safety and effectiveness of these newer insulin therapies, as compared to those of traditional insulin regimens.

We have therefore performed a systematic review of published studies on the comparative effectiveness and safety of all the premixed insulin analogues that are approved by the Food and Drug Administration (FDA) and available in the United States. A comparison of the intermediate outcomes and clinical outcomes of these analogues to those of other antidiabetic treatments may give clinicians a better sense of how to choose the appropriate treatment for type 2 diabetic patients. In addition, the results presented here may provide policymakers, pharmacy benefit managers, and insurers with useful insights as they consider policies relating to medication coverage.

Conceptual Model

Our conceptual model (see Figure 3) summarizes the premixed insulin analogues, their main comparators, and their effects on intermediate and clinical outcomes, including potential adverse events. Premixed insulin analogues were developed to affect intermediate outcomes such as fasting glucose, postprandial glucose, and A1c. We call these intermediate outcomes and not clinical outcomes, since these are blood tests that are relevant only because of their relationship to clinical outcomes such as mortality. We visualize intermediate outcomes as being connected to metabolic derangements in the body on one hand and to clinical outcomes on the other, thus occupying an intermediate place in the development of diabetic complications.
Premixed insulin analogues and other antidiabetic agents may affect clinical outcomes directly or may do so indirectly by altering intermediate outcomes. Use of these medications may also be associated with adverse effects. These medications can also affect the patients' quality of life in the short-term because of the need for frequent injections and symptoms or because of the anxiety associated with poor glycemic control. The quality of life can also be affected in the

Figure 3. Conceptual framework of premixed insulin analogues



On the left-hand side are the two groups of antidiabetic agents that need to be compared. In the middle are the subpopulations of patients that are also of interest (in addition to all type 2 diabetes patients). On the right, are the outcomes of interest that we aimed to study. The boxes within the larger box represent the relationships between various outcomes as we saw them in our conceptual model for this systematic review.
NPH = neutral protamine Hagedorn

long-term as a result of the effects on overall morbidity and mortality. Adherence to treatment is another important aspect of insulin administration that not only determines intermediate and clinical outcomes but also quality of life. Intermediate and clinical outcomes, safety and adverse events, and quality of life are affected not only by important population variables such as age and comorbid conditions but also by the intensity of intended glucose control and the target chosen for glucose control.

Because this was a comparative effectiveness review, we focused on the outcome measures that are routinely used in clinical practice and are known to help in optimizing glucose control. We did not evaluate outcomes that were not used in clinical practice, such as area under the curve or glucose excursions after premixed insulin analogue injection.

Scope and Key Questions

This systematic review was commissioned by the Agency for Healthcare Research and Quality (AHRQ) to address the following key questions:

5. 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 (neutral protamine Hagedorn [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)

6. 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.

7. 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 is 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)?

Methods

In response to Section 1013 of the Medicare Modernization Act, the AHRQ requested an evidence report to synthesize the evidence on the comparative effectiveness and safety of premixed insulin analogues and other antidiabetic agents. Our Evidence-based Practice Center (EPC) established a team and a work plan to develop the evidence report. The project consisted of formulating and refining the specific questions, performing a comprehensive literature search, summarizing the state of the literature, constructing evidence tables, synthesizing the evidence, and submitting the report for peer review.

Topic Development

The topic for this report was nominated in a public process. With input from technical experts, the Scientific Resource Center for the AHRQ Effective Health Care Program drafted the initial Key Questions and, after approval from the AHRQ, posted them to a public Web site. The public was invited to comment on these questions. After reviewing the public commentary, the Scientific Resource Center drafted final Key Questions and submitted them to the AHRQ for approval.

Search Strategy

We searched the following databases for primary studies during the stipulated periods of time: MEDLINE® (1966 to February 2008), EMBASE® (1974 to February 2008), the Cochrane Central Register of Controlled Trials (CENTRAL; 1966 to February 2008), and the Cumulative Index to Nursing & Allied Health Literature (CINAHL®; 1982 through February 2008). The electronic search was first conducted in August 2007 and then repeated in February 2008. We developed a search strategy for MEDLINE, accessed via PubMed, based on an analysis of the medical subject headings (MeSH) terms and text words of key articles identified a *priori*. Our search strategy combined terms for type 2 diabetes and premixed insulin analogues. The PubMed strategy formed the basis for the strategies developed for the other electronic databases (see Appendix A).

We hand-searched 13 journals that were most likely to publish articles on this topic (see Appendix B), scanning the table of contents of each issue for relevant citations from June through September 2007. We also reviewed the reference lists of included articles.

In addition, we received the following material from the Scientific Resource Center:

- Medical reviews and labels of insulin aspart 70/30, insulin lispro 75/25, and insulin lispro 50/50 obtained from the Web site of the United States FDA.
- Scientific Discussion sections of the European Public Assessment Report obtained from the Web site of the European Medicines Agency (EMEA).
- Public registries of clinical trials, such as the Clinical Study Results Web site (www.clinicalstudyresults.org) and ClinicalTrials.gov (www.clinicaltrials.gov).
- Scientific information packets submitted by Eli Lilly and Company (Indianapolis, IN) and Sanofi-Aventis (Bridgewater, NJ). We requested, but did not receive, a scientific information packet from Novo Nordisk (Bagsværd, Denmark).

The search results were downloaded and imported into ProCite® version 5 (ISI ResearchSoft, Carlsbad, CA). We scanned for exact article duplicates, author/title duplicates, and title duplicates using the duplication check feature. From ProCite®, the articles were uploaded to SRS© 4.0 (TrialStat! Corporation, Ottawa, Ontario, Canada), a Web-based software package developed for systematic review data management. This database was used to track the search results at the title review, abstract review, article inclusion/exclusion, and data abstraction levels. A list of excluded articles is presented in Appendix C.

Study Selection

Study selection proceeded in two phases: title review and abstract review. Two independent reviewers conducted title scans in a parallel fashion. For a title to be eliminated at this level, both reviewers had to indicate that it was ineligible. If the two reviewers did not agree on the eligibility of an article, it was promoted to the next level (see Appendix D). The title review phase was designed to capture as many studies reporting on the efficacy or safety of premixed insulin analogues as possible. All titles that were thought to address efficacy, effectiveness, safety, or quality of life were promoted to the abstract review phase. Titles generally included terms related to type 2 diabetes or insulin treatment.

The abstract review phase was designed to identify studies comparing the effects of premixed insulin analogues and other antidiabetic agents on clinical outcomes, intermediate outcomes, safety and adverse events, quality of life, or adherence. While quality of life was not a specifically stated outcome in the Key Questions, we included these outcomes because they may indirectly affect patient adherence. Abstracts were reviewed independently by two investigators and were excluded if both investigators agreed that the article met one or more of the exclusion criteria (see inclusion and exclusion criteria listed in Table 2 and Appendix D). Differences in opinion regarding abstract inclusion or exclusion were resolved through consensus adjudication.

Full-text articles initially selected on the basis of abstract review underwent another independent parallel review by the investigators to determine whether they should be included in the full data abstraction (see Appendix D). Differences of opinion regarding article inclusion were resolved through consensus adjudication.

Data Abstraction

We used a systematic approach for extracting data to minimize the risk of bias in this process. By creating standardized forms for data extraction, we sought to maximize consistency in identifying all the pertinent data available for synthesis.

Each article underwent double review by the study investigators, at the levels of data abstraction and assessment of study quality. The second reviewer confirmed the first reviewer's data abstraction forms for completeness and accuracy. Reviewer pairs were formed to include personnel with both clinical and methodological expertise. Reviewers were not masked to the articles' authors, institution, or journal.[19] In most instances, data were directly abstracted from the article. If possible, relevant data were also abstracted from figures. Differences in opinion were resolved through consensus adjudication. For assessments of study quality, each reviewer independently judged study quality and rated items on quality assessment forms (see Appendix D).

Table 2. Criteria for inclusion in the reviews

Population and condition of interest	☐	All studies included patients with type 2 diabetes, non-insulin-dependent diabetes mellitus, or adult-onset diabetes. We excluded studies if fewer than 75 percent of the study population had type 2 diabetes and there was no separate analysis for those with type 2 diabetes.
	☐	All studies included human subjects.
	☐	We excluded studies if they included only subjects less than or equal to 18 years of age.
Interventions	☐	All studies must have evaluated a premixed insulin analogue of interest. o We only considered premixed insulin analogues that have been approved by the FDA: insulin aspart 70/30, insulin lispro 75/25, and insulin lispro 50/50.
Comparisons of interest	☐	All studies must have compared a premixed insulin analogue to another antidiabetic agent. Other antidiabetic agents included, but were not limited to: o Long-acting insulin analogues (insulin detemir, insulin glargine) o Rapid-acting insulin analogues (insulin aspart, insulin glulisine, insulin lispro) o Rapid-acting insulin analogues in combination with long-acting insulin analogues o Premixed human insulin (NPH/regular 70/30, NPH/regular 50/50) o Intermediate-acting human insulin (NPH insulin) o Short-acting human insulin (regular insulin) o Noninsulin antidiabetic agents (e.g., oral antidiabetic agents, exenatide) o Placebo, diet, or usual care o Any combination of the above
Outcomes	☐	We excluded studies that did not apply to the key questions.
	☐	We included studies that evaluated at least one of the following outcomes: o Clinical outcomes (mortality, cardiovascular disease mortality and morbidity, nephropathy, retinopathy, and neuropathy) o Intermediate outcomes (A1c, fasting glucose, pre-dinner glucose, and postprandial glucose before and after dinner) o Safety and adverse events (hypoglycemia, weight gain, injection site skin reactions, other and serious adverse events) o Quality of life, or o Adherence.
Type of study	☐	We excluded articles not written in English, editorials, comments, letters, and abstracts.
	☐	We included RCTs, controlled clinical trials, and observational studies with controls.
	☐	Studies were not limited on the basis of their duration or sample size.

A1c = hemoglobin A1c; FDA = Food and Drug Administration; NPH = neutral protamine Hagedorn; RCT = randomized controlled trial; type 2 diabetes = type 2 diabetes mellitus

Reviewers extracted information on general study characteristics (e.g., study design, study period and followup, country, exclusion criteria), study participants (e.g., age, gender, race, weight/body mass index (BMI), A1c levels, duration of diabetes, and previous treatments), interventions (e.g., starting, mean, and range of doses, timing, and duration of use), outcome measures, and the results of each outcome, including measures of variability (see Appendix D).

All information from the article review process was entered into the SRS© 4.0 database by the individual completing the review. Reviewers entered comments into the system whenever applicable.

Quality Assessment

We developed a quality assessment tool for randomized controlled trials (RCTs) and nonrandomized studies based on the Jadad criteria[20] and the Newcastle-Ottawa Scale;[21] this tool was supplemented with additional questions as suggested by the Guide for Conducting Comparative Effectiveness Reviews.[22] The quality of each study was assessed using the following criteria: (1) whether the study question was clearly stated; (2) whether the patients, providers, or outcome assessors were blinded; (3) what method was used to assess the primary outcome; (4) whether the followup was long enough for outcomes to occur; (5) the adequacy of

the followup; (6) whether there was a description of those lost to followup; (7) whether the main conclusions were reflective of the results; (8) what funding source was identified; and (9) whether there was a statement of conflict of interest. In addition, RCTs were evaluated with regard to the appropriateness of their randomization scheme. Nonrandomized studies were also evaluated with regard to the selection of the comparison group, the ascertainment of exposure, the demonstration that the outcome of interest was not present at the start of the study, and the adjustment for key confounders. Reviewers rated the overall quality of each study as:

- **Good (low risk of bias).** These studies had the least bias, and the results were considered valid. These studies adhered to the commonly held concepts of high quality, including the following: a formal randomized controlled design; a clear description of the population, setting, interventions, and comparison groups; appropriate measurement of outcomes; appropriate statistical and analytic methods and reporting; no reporting errors; a low dropout rate; and clear reporting of dropouts.
- **Fair.** These studies were susceptible to some bias, but not enough to invalidate the results. They did not meet all the criteria required for a rating of good quality because they had some deficiencies, but no flaw was likely to cause major bias. The study may have been missing information, making it difficult to assess limitations and potential problems.
- **Poor (high risk of bias).** These studies had significant flaws that imply biases of various types that might have invalidated the results. They had serious errors in design, analysis, or reporting; large amounts of missing information; or discrepancies in reporting.[22]

Applicability

Throughout the report, we discuss the applicability of studies in terms of how well the study population was consistent with the general population of individuals with type 2 diabetes. We evaluated the applicability in terms of (1) the source population from which the subjects were enrolled; (2) the percentage of patients enrolled, as compared to those screened for the trial; (3) the percentage of patients excluded during a run-in period because of poor compliance, poor treatment response, or side-effects; (4) the similarity of the demographic characteristics of the study population to the general U.S. diabetic population;[23] (5) the representativeness of the spectrum of illness severity to all stages of illness; (6) the degree to which the study reflected current clinical practice with regard to the intervention and monitoring; (7) the appropriateness of the comparator; (8) the extent and quality of the reporting on important clinical outcomes and adverse events; and (9) the similarity of the standards of care to that of the U.S.

Data Analysis and Synthesis

For each Key Question, we created a set of detailed evidence tables containing all the information extracted from eligible studies. We conducted meta-analyses for outcomes when there were sufficient data (two or more trials) and studies were homogenous with respect to key variables (population characteristics, study duration, and drug dose).

Data Synthesis for Intermediate Outcomes and Adverse Events

For intermediate outcomes and the adverse outcome of weight change, we recorded the mean difference between groups, along with its measure of dispersion. If this information was not reported, we calculated the point estimate using the mean difference from baseline for each group. If the mean difference from baseline was not reported, we calculated this value from the baseline and final values for each group. If no measure of dispersion was reported for the between-group difference, we calculated this value using the sum of the variances for the mean difference from baseline for each group. If there were no measures of dispersion for the mean difference from baseline for each group, we then calculated the variance using the standard deviation of the baseline and final values, assuming a correlation between baseline and final values of 0.5.[24,25] If data were only presented in graphical form, we abstracted data from the graphs. We pooled the results of the plasma and blood glucose levels from different studies, since blood glucose measurements accurately reflect plasma glucose levels.[26]

For the adverse outcome of hypoglycemia, we used two strategies to synthesize data: If a trial reported the incidence of hypoglycemia (number of patients who developed hypoglycemia), we calculated an odds ratio using the incidence of hypoglycemia in each study group. If a trial reported event rates in episodes per patient per 30 days, we calculated the rate ratio by dividing the event rate in the premixed insulin analogue arm by the event rate in the comparator arm. If a trial reported the number of episodes in each arm or study period or reported an event rate in a form other than episodes per patient per 30 days, we converted this information into episodes per patient per 30 days and used this event rate to calculate the rate ratio in the two arms or study periods of the trial.

Following a qualitative synthesis of the literature, we pooled the results of individual studies within each set of comparisons using Comprehensive Meta-Analysis (version 2.2.046) software. Because we found some clinical heterogeneity within the same-group comparisons, we decided to use a random-effects model. We chose a random-effects model because it assumes that the included studies differ from each other more than would be expected as a result of random error, and it incorporates between-study heterogeneity in pooling study results, thus giving a more conservative estimate of the confidence interval (CI) around the point estimate of the effect size. In contrast, a fixed-effect model assumes that studies differ from each other as a result of random error alone, and it gives narrower CIs around the point estimates of the effect size. Another advantage of using a random-effects model is that if there is no between-study heterogeneity and the studies differ from each other only as a result of random error, the CIs from random-effects and fixed-effects models are similar. Thus, the use of a random-effects model is not over-conservative in the absence of between-study heterogeneity. Although we measured the Q-statistic and I-square index, we did not use these statistics to choose the model for pooling data, since tests for homogeneity are known to have low power for detecting between-study heterogeneity.[27,28] Given the limited number of studies in each comparison group, we did not perform meta-regression to evaluate the effect of study variables on the outcomes. To evaluate excessive influence of a study on the results of meta-analysis, we conducted sensitivity analyses by excluding one study from the meta-analysis at a time and examining the change in the meta-analysis results. We assessed publication bias by visual inspection of the funnel plot and by statistical means using Begg's[29], Egger's[30] and trim-and-fill[31] tests.

Data Synthesis for Clinical Outcomes

We included all studies that reported any information about the clinical outcomes identified in our key questions. If a study reported no cases of specific types of events, we still included the study in its respective section. We abstracted data on events for each arm, and all analyses followed the principle of intention-to-treat. First, we synthesized the data qualitatively. We then conducted meta-analyses when there were sufficient data (two or more studies) and the studies were homogenous with respect to key variables (patient populations, drug comparators such as using one of several accepted comparator drugs, outcome definitions, and study duration). For trials with more than one arm involving premixed insulin analogues, we combined these arms into a premixed insulin analogue group when appropriate. We believed that the results were similar enough for premixed insulin analogues and for "any other" active comparator to allow us to combine the data into these two groups, although we do discuss the studies qualitatively both in combination and separately. In the one study in which there were three arms (premixed insulin analogue versus rapid-acting insulin analogue versus long-acting insulin analogue),[32] we chose what we thought was the most relevant comparison to include in the meta-analyses (premixed insulin analogue versus long-acting insulin analogue). Choosing the other comparator would not have markedly changed the results. We excluded crossover studies from the main meta-analyses, since these studies did not report whether events occurred prior to the first crossover, making it difficult to determine whether the event occurred as a result of the first or second drug given.

Pooled odds ratios and 95 percent CIs were calculated using a Mantel-Haenszel fixed-effects model (with a 0.1 continuity correction) for the main analysis.[33,34] We used a fixed-effects model because there is evidence to suggest that these methods are less biased with rare event data.[35] We also calculated pooled odds ratios and 95 percent CIs using several other well-established methods as a sensitivity analysis, since experts disagree about the best meta-analytic technique for rare event data. These methods included Peto's method, the Mantel-Haenszel fixed-effects model (with a 0.5 and 0.01 continuity correction), and a Bayesian analysis.[36] Heterogeneity among the trials in all the meta-analyses was tested with a standard chi-squared test, using a significance level of alpha less than or equal to 0.10. We also examined inconsistency among studies with an I^2 statistic, which describes the variability in effect estimates that is due to heterogeneity rather than random chance.[37] A value greater than 50 percent may be considered to represent substantial variability. We conducted sensitivity analyses by omitting one study at a time to assess the influence of any one study on the pooled estimate. A sensitivity analysis was conducted in which we included the crossover studies and the unpublished crossover data.

Because statistically significant findings are more likely to be published than are studies without statistically significant results (publication bias), we examined whether there was evidence that smaller, negative studies appeared to be missing from the literature. We therefore conducted formal tests for publication bias using Begg's[29] and Eggers[30] tests, including evaluation of the asymmetry of funnel plots.

Rationale for the Inclusion of Crossover Designs

We decided to include crossover trials because this study design allows comparison of interventions at the individual rather than the group level. In addition, the use of premixed insulin analogues over a short period of time was unlikely to produce long-lasting effects in

study participants, and participants were unlikely to differ systematically between the initial phase of the study and subsequent phases.

However, we used data from crossover studies only for intermediate outcomes, namely A1c, fasting glucose, and postprandial glucose. We excluded crossover trials from the evaluation of outcomes that were either progressive, such as retinopathy, or irreversible, such as mortality. For the evaluation of A1c, we included only those crossover trials that had at least 12 weeks of followup. Crossover clinical trials with a shorter duration of followup were excluded from the analysis of A1c because treatment during an earlier phase, lead-in phase, or pretrial phase could affect the A1c level.[26]

We aimed to use within-individual comparisons data from crossover trials if the trials reported the data in such detail. If results were reported only for each intervention, we ignored the crossover design and used the reported estimates as if they came from a parallel trial. We understand that this is a conservative approach that ignores within-patient correlation and produces wider CIs. If a trial reported a carryover effect, we included only the data from the first period of the crossover trial on the grounds that this period is, in effect, a parallel group trial. Further sensitivity analyses were performed by pooling data without crossover studies and comparing the pooled results from parallel studies alone to the pooled results from combining both study designs.

Data Entry and Quality Control

After a second reviewer reviewed the data that had been entered into SRS© 4.0, adjudicated data were re-entered into Web-based data collection forms by the second reviewer. Second reviewers were generally more experienced members of the research team. If problems were recognized in a reviewer's data abstraction, the problems were discussed at a meeting with the reviewers. In addition, research assistants used a system of random data checks to assure data abstraction accuracy.

Rating the Body of Evidence

At the completion of our review, we graded the quantity, quality and consistency of the best available evidence addressing the Key Questions by adapting an evidence grading scheme recommended by the GRADE Working Group.[38] We applied evidence grades to bodies of evidence on each type of intervention comparison for each major type of outcome. We assessed the strength of the study designs, with RCTs considered best, followed by non-RCTs and observational studies. To assess the quantity of evidence, we focused on the number of studies with the strongest design. We also assessed the quality and consistency of the best available evidence, including assessment of the limitations to individual study quality (using individual quality scores), certainty regarding the directness of the observed effects in the studies, the precision and strength of the findings, and the availability (or lack thereof) of data to answer the Key Question.

We classified evidence bodies pertaining to the Key Questions into three basic categories: (1) "high" grade (indicating confidence that further research is very unlikely to change our confidence in the estimated effect in the abstracted literature), (2) "moderate" grade (indicating that further research is likely to have an important impact on our confidence in the estimates of effects and may change the estimates in the abstracted literature), and (3) "low" grade (indicating

further research is very likely to have an important impact on confidence in the estimates of effects and is likely to change the estimates in the abstracted literature). We graded the body of evidence as “no evidence” if there were no studies evaluating a drug comparison.

Peer Review and Public Commentary

A draft of the completed report was sent to the peer reviewers, the representatives of the AHRQ and the Scientific Resource Center. The draft report was posted to a Web site for public comment. In response to the comments of the peer reviewers and the public, revisions were made to the evidence report, and a summary of the comments and their disposition was submitted to the AHRQ.

Results

Search Results

A summary of the search results for the primary literature review is presented in Figure 4. From the search, we retrieved 2,202 unique citations. After a review of the titles and abstracts, 135 were deemed eligible for further review, and the full articles were retrieved. A total of 50 articles were included in this review. Upon further inspection, we realized that Raskin 2005,[39] Raskin 2007,[40] and Brod 2007;[41] Roach 2001[42] and Tirgoviste 2003;[43] and Malone 2000[44] and Malone 2000[14] were conducted in the same study populations. These articles were abstracted together. Boehm 2004[45] and Boehm 2002[9] had the same study population of type 2 diabetes, but Boehm 2004[45] had the longer followup. We report only the results from Boehm 2004.[45] We used data from Boehm 2002[9] when data were not reported in the second publication of the trial. Therefore, a total of 45 studies, represented in 50 articles, were included.

The bulk of the evidence was for insulin aspart 70/30[9,11,13,15,32,39-41,45-61] and insulin lispro 75/25,[10,12,14,42-44,55,58,62-75] which were evaluated in 22 and 20 studies, respectively. Nine studies evaluated insulin lispro 50/50.[10,62,64,69,76-80]

For insulin aspart 70/30, there were seven studies comparing it to a premixed human insulin,[9,11,15,45,48,53,56,58] six to oral antidiabetic agents,[46,51,54,57,59,60] four to a long-acting insulin analogue,[32,39-41,47,50] two to an intermediate-acting human insulin,[13,15] and one each to a rapid-acting insulin analogue,[32] a rapid-acting insulin analogue with a long-acting insulin analogue,[52] a rapid-acting insulin analogue with an intermediate-acting human insulin,[61] and exenatide.[49] For insulin lispro 75/25, there were ten studies comparing it to a premixed human insulin,[10,12,14,44,58,62,67,70,71,73,75] six to a long-acting insulin analogue,[63-66,74,75] and three to an oral antidiabetic agent.[42,43,68,72] We did not identify any studies comparing insulin lispro 75/25 to a rapid-acting insulin analogue, a rapid-acting insulin analogue with a long-acting insulin analogue, an intermediate-acting human insulin, or exenatide. For insulin lispro 50/50, there were four studies comparing it to a premixed human insulin,[10,62,77,78] three studies comparing it with a long-acting insulin,[64,76,79] one study comparing it to a combination of long-acting insulin analogue and rapid-acting insulin analogue,[80] and one study comparing it to a rapid-acting insulin analogue.[76] We did not indentify any studies comparing insulin lispro 50/50 to an intermediate-acting human insulin or exenatide. Furthermore, we did not identify any studies comparing any of the premixed insulin analogues to regular human insulin or to placebo.

There were four studies with a head-to-head comparison of premixed insulin analogues. Two studies compared insulin aspart 70/30 to insulin lispro 75/25.[55,58] Another two studies compared insulin lispro 75/25 to insulin lispro 50/50.[62,69]

Table 3 shows the number of studies included that evaluated each treatment comparison for each outcome.

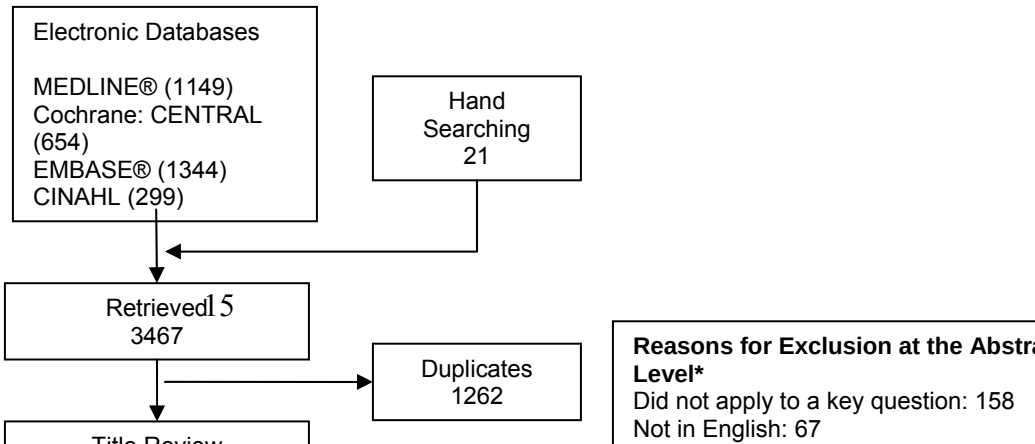


Figure 4. Summary of literature search (number of articles)

Table 3. Number of included studies evaluating each treatment comparison for each outcome

	Insulin aspart 70/30 versus									
	Long-acting insulin analogues	Rapid-acting insulin analogues	Rapid-acting with long-acting insulin analogues	Premixed human insulins	Rapid-acting insulin analogues with inter-acting human insulin	Inter-acting human insulin	Oral antidiabetic agents	Exenatide	Premixed insulin analogues	Premixed insulin analogues with oral antidiabetic agents
Intermediate outcomes										
A1c	4[32,39,47,50]	1[32]	1[52]	4[15,45,48,53]	1[61]	2[13,15]	6[46,51,54,57,59,60]	1[49]	1[55]	3[51,54,59]
Fasting glucose	4[32,39,47,50]	1[32]	1[52]	3[9,15,53]	0	2[13,15]	6[46,51,54,57,59,60]	1[49]	1[55]	3[51,54,59]
Pre-dinner glucose	3[32,39,50]	1[32]	0	1[53]	0	0	6[46,51,54,57,59,60]	1[49]	1[55]	2[51,59]
PPG after breakfast	2[39,50]	0	0	4[9,15,53,58]	0	1[15]	5[46,51,54,59,60]	1[49]	2[55,58]	2[51,54]
PPG after dinner	3[32,39,50]	1[32]	1[52]	3[9,15,53]	0	1[15]	6[46,51,54,57,59,60]	1[49]	1[55]	2[51,54]
Quality of life	1[32]	1[32]	0	1[48]	0	0	1[59]	0	0	1[59]
Clinical outcomes										
Overall mortality	1[32]	1[32]	0	1[45]	0	0	1[51]	1[49]	1[55]	1[51]
CVD mortality	1[32]	1[32]	0	1[45]	0	0	1[51]	0	1[55]	1[51]
CVD morbidity	1[50]	0	0	2[45,58]	0	0	3[54,57,60]	1[49]	1[58]	1[54]
Nephropathy	1[32]	1[32]	0	0	0	0	1[60]	0	0	0
Safety/Adverse events										
Hypoglycemia	4[32,39,47,50]	1[32]	1[52]	6[11,15,45,48,53,58]	1[61]	2[13,15]	5[46,51,54,57,59]	1[49]	2[55,58]	3[51,54,59]
Weight/BMI	4[32,39,47,50]	1[32]	1[52]	2[15,45]	1[61]	2[13,15]	6[46,51,54,57,59,60]	1[49]	0	2[51,54]
Injection site reactions	0	0	0	0	0	0	0	0	1[55]	0
Total serious adverse events	3[32,39,50]	1[32]	1[52]	2[48,53]	0	1[13]	4[46,51,54,59]	1[49]	0	3[51,54,59]
Withdrawn due to adverse events	4[32,39,47,50]	1[32]	1[52]	7[11,15,45,48,53,56,58]	0	2[13,15]	5[46,51,54,57,60]	1[49]	2[55,58]	2[51,54]
Other serious adverse events	1[32]	1[32]	0	3[11,15,58]	0	2[13,15]	2[54,60]	0	2[55,58]	1[54]

Table 3. Number of included studies evaluating each treatment comparison for each outcome (continued)

	Insulin lispro 75/25 versus							
	Long-acting insulin analogues	Rapid-acting insulin analogues	Rapid-acting with long-acting insulin analogues	Premixed human insulins	Intermediate-acting human insulin	Oral antidiabetic agents	Exenatide	Premixed insulin analogues
Intermediate outcomes								
A1c	5[63-66,75]	0	0	3[10,73,75]	0	3[43,68,72]	0	2[55,69]
Fasting glucose	5[63-66,74]	0	0	4[10,12,70,73]	0	3[43,68,72]	0	2[55,69]
Pre-dinner glucose	5[63-66,74]	0	0	4[10,12,70,73]	0	2[43,72]	0	1[55]
PPG after breakfast	5[63-66,74]	0	0	8[12,44,58,62,67,70,71,73]	0	3[43,68,72]	0	3[55,62,69]
PPG after dinner	5[63-66,74]	0	0	4[10,12,70,73]	0	3[43,68,72]	0	2[55,69]
Quality of life	1[74]	0	0	0	0	1[72]	0	0
Clinical outcomes								
Overall mortality	1[66]	0	0	0	0	1[68]	0	1[55]
CVD mortality	1[66]	0	0	0	0	0	0	1[55]
CVD morbidity	1[65]	0	0	1[58]	0	0	0	1[58]
Nephropathy	0	0	0	0	0	0	0	0
Safety/Adverse events								
Hypoglycemia	5[63-66,74]	0	0	9[10,12,44,58,62,67,70,71,73]	0	3[43,68,72]	0	4[55,58,62,69]
Weight/BMI	4[63-66]	0	0	3[67,70,73]	0	3[43,68,72]	0	0
Injection site reactions	0	0	0	1[62]	0	0	0	1[62]
Total serious adverse events	0	0	0	1[62]	0	0	0	1[62]
Withdrawn due to adverse events	5[63-66,74]	0	0	8[12,44,58,62,67,70,71,73]	0	2[68,72]	0	1[62]
Other serious adverse events	2[65,66]	0	0	2[58,67]	0	2[68,72]	0	0

Table 3. Number of included studies evaluating each treatment comparison for each outcome (continued)

	Insulin lispro 50/50 versus							
	Long-acting insulin analogues	Rapid-acting insulin analogues	Rapid-acting with long-acting insulin analogues	Premixed human insulins	Intermediate-acting human insulin	Oral antidiabetic agents	Exenatide	Premixed insulin analogues
Intermediate outcomes								
A1c	3[64,76,79]	1[76]	1[80]	2[77,78]	0	0	0	1[69]
Fasting glucose	2[76,79]	1[76]	1[80]	2[77,78]	0	0	0	1[69]
Pre-dinner glucose	3[64,76,79]	1[76]	1[80]	2[10,77]	0	0	0	0
PPG after breakfast	3[64,76,79]	1[76]	1[80]	3[10,62,77]	0	0	0	1[69]
PPG after dinner	2[64,76]	1[76]	0	2[10,77]	0	0	0	2[62,69]
Quality of life	1[76]	1[76]	0	0	0	0	0	0
Clinical outcomes								
Overall mortality	0	0	0	1[77]	0	0	0	0
CVD mortality	0	0	0	0	0	0	0	0
CVD morbidity	0	0	0	0	0	0	0	0
Nephropathy	1[79]	0	0	0	0	0	0	0
Safety/Adverse events								
Hypoglycemia	3[64,76,79]	1[76]	1[80]	4[10,62,77,78]	0	0	0	2[62,69]
Weight/BMI	3[64,76,79]	1[76]	1[80]	1[78]	0	0	0	0
Injection site reactions	0	0	0	1[62]	0	0	0	1[62]
Total serious adverse events	1[79]	0	1[80]	1[62]	0	0	0	1[62]
Withdrawn due to adverse events	3[64,76,79]	1[76]	0	4[10,62,77,78]	0	0	0	1[62]
Other serious adverse events	0	0	0	1[77]	0	0	0	0

A1c = hemoglobin A1c; BMI = body mass index; CVD = cardiovascular disease; Inter = intermediate; PPG = postprandial glucose

Key Question 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?

f. Premixed human insulin preparations (NPH/regular 70/30, NPH/regular 50/50)
g. Long-acting insulin analogues (insulin detemir, insulin glargine) administered alone
h. Intermediate-acting human insulin (NPH insulin) administered alone
i. Short-acting human insulin (regular insulin) administered prandially
j. Rapid-acting insulin analogues (insulin aspart, insulin glulisine, insulin lispro) administered separately (prandially) with a long-acting insulin analogue (insulin detemir, insulin glargine)

Key Question 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.

Most of the studies that addressed Key Question 1 also addressed Key Question 2. We report both these questions together in one section to avoid repetition. In addition, most studies that reported intermediate outcomes also reported safety and adverse events. To prevent repetition, we discuss intermediate outcomes and adverse events together in one section.

Intermediate Outcomes and Adverse Events

Key Messages

Fasting glucose.

- Premixed insulin analogues may be less effective than long-acting insulin analogues alone in lowering fasting glucose.
    - Insulin aspart 70/30 was similar to long-acting insulin analogues in lowering fasting glucose (pooled mean difference = 6.4 mg/dL; 95 percent CI: -1.5 to 14.2 mg/dL; p = 0.11).

- Insulin lispro 75/25 was less effective than long-acting insulin analogues in lowering fasting glucose (pooled mean difference = 8.5 mg/dL; 95 percent CI: 3.6 to 13.3 mg/dL; $p = 0.001$).
- Insulin lispro 50/50 was less effective than long-acting insulin analogues in lowering fasting glucose (mean difference in 2 studies: (1) -28 mg/dL and (2) -30.6 mg/dL; $p < 0.001$ in both studies).

- Premixed insulin analogues were similarly effective as premixed human insulin preparations in lowering fasting glucose.
  - Insulin aspart 70/30 was less effective than premixed human insulin preparations in lowering fasting glucose (pooled mean difference = 8.3 mg/dL; 95 percent CI: 0.16 to 16.5 mg/dL; $p = 0.04$).
  - Insulin lispro 75/25 was similar to premixed human insulin preparations in lowering fasting glucose (pooled mean difference = 0.12 mg/dL; 95 percent CI: -6.05 to 6.29 mg/dL; $p = 0.97$).
  - Insulin lispro 50/50 may be less effective than premixed human insulin preparations in lowering fasting glucose (effect size in two studies: (1) mean difference = 30.3 mg/dL; $p < 0.001$ and (2) mean difference = 23 mg/dL; p = nonsignificant).

- Premixed insulin analogues were more effective than noninsulin antidiabetic agents in lowering fasting glucose.
  - Insulin aspart 70/30 and insulin lispro 75/25 were more effective than oral antidiabetic agents in lowering fasting glucose (insulin aspart 70/30: pooled mean difference = -13.9 mg/dL; 95 percent CI: -24.4 to -3.4 mg/dL; $p = 0.009$; insulin lispro 75/25: pooled mean difference = -31.4 mg/dL; 95 percent CI: -45.7 to -17.1 mg/dL; $p < 0.001$).
  - A lack of evidence limited our ability to compare insulin lispro 50/50 to oral antidiabetic agents.
  - Limited evidence suggested that insulin aspart 70/30 was similar to exenatide in lowering fasting glucose.
  - A lack of evidence limited our ability to compare insulin lispro 75/25 and 50/50 to exenatide.

- Premixed insulin analogues were less effective than a combination of long-acting insulin analogue and rapid-acting insulin analogue in lowering fasting glucose.
  - Insulin aspart 70/30 may be less effective than a combination of long-acting insulin analogue and rapid-acting insulin analogue in lowering fasting glucose (mean difference in one study = 7.9 mg/dL; $p > 0.05$).
  - A lack of evidence limited our ability to compare insulin lispro 75/25 to a combination of long-acting insulin analogue and rapid-acting insulin analogue in lowering fasting glucose.
  - Insulin lispro 50/50 was less effective than a combination of long-acting insulin analogue and rapid-acting insulin analogue in lowering fasting glucose (mean difference in one study = 12mg/dL; $p = 0.013$).

- Premixed insulin analogues may be at least as effective as rapid-acting insulin analogues in lowering fasting glucose.
    - Insulin aspart 70/30 is more effective than rapid-acting insulin analogues in lowering fasting glucose (mean difference in one study = -22.0 mg/dL; $p < 0.001$).
    - Lack of evidence limits our ability to compare insulin lispro 75/25 to rapid-acting insulin analogues in lowering fasting glucose.
    - Insulin lispro 50/50 may be similar to rapid-acting insulin analogues in lowering fasting glucose (mean difference in one study = 0 mg/dL; $p > 0.05$).

- A lack of evidence limited our ability to compare premixed insulin analogues to intermediate-acting human insulin preparations or to a combination of intermediate-acting human insulin plus rapid-acting insulin analogues in lowering fasting glucose.

- The superiority of one premixed insulin analogue over the other in lowering fasting glucose could not be determined because of the paucity of evidence.

Postprandial glucose.

- Premixed insulin analogues were more effective than long-acting insulin analogues alone in lowering postprandial glucose.
    - Insulin aspart 70/30 was more effective than long-acting insulin analogues in lowering postprandial glucose (pooled mean difference = -22.6 mg/dL; 95 percent CI: -32.1 to -13.2 mg/dL; $p < 0.001$).
    - Insulin lispro 75/25 was more effective than long-acting insulin analogues in lowering postprandial glucose (pooled mean difference = -23.6 mg/dL; 95 percent CI: -30.9 to -16.4 mg/dL; $p < 0.001$).
    - Insulin lispro 50/50 was more effective than long-acting insulin analogues in lowering postprandial glucose (pooled mean difference = -32.7 mg/dL; 95 percent CI: -48.2 to -17.1 mg/dL; $p < 0.001$).

- Premixed insulin analogues were more effective than premixed human insulin preparations in lowering postprandial glucose.
    - Insulin aspart 70/30 was more effective than premixed human insulin preparations in lowering postprandial glucose (pooled mean difference = -18.6 mg/dL; 95 percent CI: -31.1 to -6.0 mg/dL; $p = 0.004$).
    - Insulin lispro 75/25 was more effective than premixed human insulin preparations in lowering postprandial glucose (pooled mean difference = -17.8 mg/dL; 95 percent CI: -27.0 to -8.6 mg/dL; $p < 0.001$).
    - Insulin lispro 50/50 was more effective than premixed human insulin preparations in lowering postprandial glucose (pooled mean difference = -30.3 mg/dL; 95 percent CI: -55.6 to -5.0 mg/dL; $p = 0.02$).

- Two of the three premixed insulin analogues were much more effective than oral antidiabetic agents in lowering postprandial glucose.

- Insulin aspart 70/30 was more effective than oral antidiabetic agents in lowering postprandial glucose (pooled mean difference = -32.8 mg/dL; 95 percent CI: -62.5 to -3.1 mg/dL; $p = 0.03$).
- Insulin lispro 75/25 was more effective than oral antidiabetic agents in lowering postprandial glucose (pooled mean difference = -47.3 mg/dL; 95 percent CI: -63.5 to -31.0 mg/dL; $p < 0.001$).
- A lack of evidence limited our ability to compare insulin lispro 50/50 to oral antidiabetic agents with regard to lowering postprandial glucose.

- Not enough evidence exists to allow us to conclusively compare premixed insulin analogues to a combination of rapid-acting insulin and long-acting insulin analogues in lowering postprandial glucose.
  - Insulin aspart 70/30 may be better than a combination of rapid-acting insulin and long-acting insulin analogues in lowering postprandial glucose (mean difference in one study = -11.8 mg/dL; $p > 0.05$).
  - A lack of evidence limited our ability to compare insulin lispro 75/25 to a combination of rapid-acting insulin and long-acting insulin analogues with regard to lowering postprandial glucose.
  - Insulin lispro 50/50 was less effective than a combination of rapid-acting insulin and long-acting insulin analogues in lowering postprandial glucose (final postprandial glucose values from one study: 174 versus 155 mg/dL; $p = 0.002$).

- Not enough evidence exists to allow us to conclusively compare the new incretin mimetic agent, exenatide, to premixed insulin analogues with regard to lowering postprandial glucose.

- A lack of evidence limited our ability to compare rapid-acting insulin analogues to premixed insulin analogues with regard to lowering postprandial glucose.
  - Insulin aspart 70/30 was less effective than rapid-acting insulin analogues in lowering postprandial glucose (mean difference in one study = 15 mg/dL; $p < 0.001$).
  - A lack of evidence limited our ability to compare insulin lispro 75/25 to rapid-acting insulin analogues with regard to lowering postprandial glucose.
  - Limited evidence suggested that insulin lispro 50/50 was similar to rapid-acting insulin analogues with regard to lowering postprandial glucose (mean difference in one study = 3.6 mg/dL; $p > 0.05$).

- There was very little evidence to allow us to compare premixed insulin analogues to intermediate-acting insulin preparations or to a combination of intermediate-acting human insulin plus rapid-acting insulin analogue.

- The superiority of one premixed insulin analogue over the other could not be determined because of the paucity of evidence.

Hemoglobin A1c.

- Premixed insulin analogues were more effective than long-acting insulin analogues in lowering A1c.
    - Insulin aspart 70/30 was more effective than long-acting insulin analogues in lowering A1c (pooled mean absolute difference = -0.48 percent; 95 percent CI: -0.61 to -0.34 percent; $p < 0.001$).
    - Insulin lispro 75/25 was more effective than long-acting insulin analogues in lowering A1c (pooled mean absolute difference = -0.33 percent; 95 percent CI: -0.48 to -0.17 percent; $p < 0.001$).
    - Insulin lispro 50/50 was more effective than long-acting insulin analogues in lowering A1c (pooled mean absolute difference = -0.40 percent; 95 percent CI: -0.65 to -0.15 percent; $p = 0.001$).

- Premixed insulin analogues were as effective as premixed human insulin in lowering A1c.
    - Insulin aspart 70/30 was similar to premixed human insulin preparations in terms of lowering A1c (pooled mean absolute difference = 0.06 percent; 95 percent CI: -0.04 to 0.16 percent; $p = 0.22$).
    - Insulin lispro 75/25 was similar to premixed human insulin preparations in terms of lowering A1c (absolute mean differences reported in three studies ranged from -0.12 to 0.2 percent; p was not significant in all three studies).
    - Insulin lispro 50/50 was more effective than premixed human insulin preparations in terms of lowering A1c (effect size in two studies: (1) absolute mean difference = -0.5 percent; $p = 0.01$ and (2) absolute mean difference = -0.31 percent; $p < 0.05$).

- Premixed insulin analogues are better than oral antidiabetic agents in lowering A1c.
    - Insulin aspart 70/30 was more effective than oral antidiabetic agents in terms of lowering A1c (pooled mean absolute difference = -0.52 percent; 95 percent CI: -1.0 to -0.04 percent; $p = 0.034$).
    - Insulin lispro 75/25 may be more effective than oral antidiabetic agents in terms of lowering A1c (pooled mean absolute difference = -0.42 percent; 95 percent CI: -1.0 to 0.16 percent; $p = 0.15$).
    - Lack of evidence limited our ability to compare insulin lispro 50/50 to oral antidiabetic agents in terms of lowering A1c.

- Not enough evidence exists to allow us to conclusively compare premixed insulin analogues to a combination of rapid-acting insulin and long-acting insulin analogues in terms of lowering A1c.
    - Insulin aspart 70/30 may be more effective than a combination of rapid-acting insulin and long-acting insulin analogues in lowering A1c, but the quality of the evidence was low (mean difference in one study = -0.42 percent; $p < 0.05$).
    - A lack of evidence limited our ability to compare insulin lispro 75/25 to a combination of rapid-acting insulin and long-acting insulin analogues in terms of lowering A1c.

    - Insulin lispro 50/50 was less effective than a combination of rapid-acting insulin and long-acting insulin analogues in lowering A1c (final A1c values from one study: 6.9 versus 6.8 percent; p = 0.02).

- Not enough evidence exists to allow us to conclusively compare exenatide to premixed insulin analogues.

- A lack of evidence limited our ability to compare intermediate-acting human insulin, rapid-acting insulin analogues, or the combination of the two to premixed insulin analogues.

- The superiority of one premixed insulin analogue over the other could not be reliably evaluated because of the paucity of evidence.

Hypoglycemia.

- Many of the comparisons were represented by too few studies to allow us to draw any conclusions regarding this adverse effect.

- The effect of premixed insulin analogues on the incidence of serious hypoglycemia could not be conclusively addressed because only very few serious hypoglycemic events were reported in the studies.

- Premixed insulin analogues were associated with more hypoglycemic events than were oral antidiabetic agents, but the only study that compared premixed insulin analogues to exenatide found no difference in the incidence of hypoglycemic events.
    - Insulin aspart 70/30 was more likely to be associated with a higher incidence of hypoglycemia than were oral antidiabetic agents (OR for minor hypoglycemia = 3.8; 95 percent CI: 1.7 to 8.5; p = 0.001 and OR for symptom-only hypoglycemia = 3.9; 95 percent CI: 1.2 to 12.4; p = 0.02).
    - Limited evidence suggested that insulin lispro 75/25 may be associated with a higher incidence of overall hypoglycemia than were oral antidiabetic agents (rate ratio = 4.86; 95 percent CI: 0.5 to 49.5; p = 0.18).
    - A lack of evidence limited our ability to compare insulin lispro 50/50 with oral antidiabetic agents in terms of the incidence of hypoglycemia.

- Premixed insulin analogues were more likely to be associated with hypoglycemia than were the long-acting insulin analogues.
    - Insulin aspart 70/30 was more likely to be associated with hypoglycemia than were long-acting insulin analogues (odds ratio (OR) for minor hypoglycemia = 2.8; 95 percent CI: 1.4 to 5.4; p = 0.003).
    - Insulin lispro 75/25 was more likely to be associated with hypoglycemia than were long-acting insulin analogues (p-values for overall hypoglycemia ranged from 0.4 to 0.01).

    - Insulin lispro 50/50 was more likely to be associated with hypoglycemia than were long-acting insulin analogues (p-value for overall hypoglycemia ranged from 0.02 to 0.01).

- Premixed insulin analogues (insulin aspart 70/30, insulin lispro 75/25, and insulin lispro 50/50) were similar to premixed human insulin preparations in terms of the incidence of hypoglycemia.

- There were not enough data to allow us to compare premixed insulin analogues to a combination of intermediate-acting human insulin plus a rapid-acting insulin analogue in terms of the incidence of hypoglycemia.

- There were not enough data to allow us to conclusively compare one premixed insulin analogue with the other in terms of the incidence of hypoglycemia.

Weight change.

- Premixed insulin analogues were associated with weight gain, when compared to oral antidiabetic agents as a group.
    - Insulin aspart 70/30 was associated with weight gain when compared to oral antidiabetic agents (pooled mean difference = 2.8 kg; 95 percent CI: 0.6 to 5.0 kg; $p = 0.01$).
    - Insulin lispro 75/25 was associated with weight gain when compared to oral antidiabetic agents (pooled mean difference = 1.88 kg; 95 percent CI: 1.35 to 2.41 kg; $p < 0.001$).
    - A lack of evidence limited our ability to compare insulin lispro 50/50 to oral antidiabetic agents in terms of weight gain.

- The evidence was conflicting about whether premixed insulin analogues may cause less weight gain than do rapid-acting insulin analogues.
    - Insulin aspart 70/30 was associated with less weight gain than were rapid-acting insulin analogues (mean difference in one study = -1.0 kg; $p = 0.005$).
    - A lack of evidence limited our ability to compare insulin lispro 75/25 to rapid-acting insulin analogues in terms of weight gain.
    - Insulin lispro 50/50 may be associated with more weight gain than are rapid-acting insulin analogues, although the evidence was weak (mean difference in BMI in one study = 0.3 kg/m2; $p = 0.048$).

- Premixed insulin analogues may cause more weight gain than do long-acting insulin analogues.
    - Insulin aspart 70/30 was associated with more weight gain than were long-acting insulin analogues (pooled mean difference = 2.5 kg; 95 percent CI: 1.6 to 3.4 kg; $p < 0.001$).
    - A lack of evidence limited our ability to compare insulin lispro 75/25 and insulin lispro 50/50 to long-acting insulin analogues in terms of weight gain.

- There was not enough evidence to allow us to conclusively compare the weight change after treatment with premixed insulin analogues to that produced by other antidiabetic drugs, except as noted above.

Evidence Grades

Fasting glucose (see Appendix E; Evidence Table 1).

- The strength of evidence was graded as moderate for the following comparisons:
  - Premixed insulin analogues versus long-acting insulin analogues alone
  - Premixed insulin analogues versus premixed human insulin
  - Premixed insulin analogues versus noninsulin antidiabetic agents.

- The strength of evidence was graded as low for the following comparisons:
  - Premixed insulin analogues versus rapid-acting insulin analogues
  - Premixed insulin analogues versus a combination of long-acting and rapid-acting insulin analogues
  - Premixed insulin analogues versus intermediate-acting human insulin.

- There was no evidence for the following comparisons:
  - Premixed insulin analogues versus a combination of intermediate-acting human insulin and rapid-acting insulin analogues.

Postprandial glucose (see Appendix E; Evidence Table 1).

- The strength of evidence was graded as high for the following comparisons:
  - Premixed insulin analogues versus long-acting insulin analogues alone
  - Premixed insulin analogues versus premixed human insulin.

- The strength of evidence was graded as moderate for the following comparison:
  - Premixed insulin analogues versus noninsulin antidiabetic agents.

- The strength of evidence was graded as low for the following comparisons:
  - Premixed insulin analogues versus rapid-acting insulin analogues
  - Premixed insulin analogues versus intermediate-acting human insulin
  - Premixed insulin analogues versus a combination of long-acting and rapid-acting insulin analogues.

- There was no evidence for the following comparisons:
  - Premixed insulin analogues versus a combination of intermediate-acting human insulin and rapid-acting insulin analogue.

Hemoglobin A1c (see Appendix E; Evidence Table 1).

- The evidence was graded as high for the following comparisons:
  - Premixed insulin analogues versus long-acting insulin analogues

- Premixed insulin analogues versus premixed human insulin.

- The evidence was graded as moderate for the following comparison:
  - Premixed insulin analogues versus noninsulin antidiabetic agents.

- The evidence was graded as low for the following comparisons:
  - Premixed insulin analogues versus intermediate-acting human insulin
  - Premixed insulin analogues versus rapid-acting insulin analogues
  - Premixed insulin analogues versus a combination of rapid-acting and long-acting insulin analogues
  - Premixed insulin analogues versus a combination of intermediate-acting human insulin and rapid-acting insulin analogue.

Hypoglycemia (see Appendix E; Evidence Table 1).

- The strength of evidence was graded as high for the following comparisons:
  - Premixed insulin analogues versus long-acting insulin analogues
  - Premixed insulin analogues versus premixed human insulin
  - Premixed insulin analogues versus noninsulin antidiabetic agents.

- The strength of evidence was graded as low for the following comparisons:
  - Premixed insulin analogues versus intermediate-acting human insulin
  - Premixed insulin analogues versus rapid-acting insulin analogues
  - Premixed insulin analogues versus a combination of rapid-acting and long-acting insulin analogues
  - Premixed insulin analogues versus a combination of intermediate-acting human insulin and rapid-acting insulin analogue.

Weight change (see Appendix E; Evidence Table 1).

- The strength of evidence was graded as moderate for the following comparisons:
  - Premixed insulin analogues versus long-acting insulin analogues
  - Premixed insulin analogues versus premixed human insulin
  - Premixed insulin analogues versus noninsulin antidiabetic agents.

- The strength of evidence was graded as low for the following comparisons:
  - Premixed insulin analogues versus intermediate-acting human insulin
  - Premixed insulin analogues versus rapid-acting insulin analogues
  - Premixed insulin analogues versus a combination of rapid-acting and long-acting insulin analogues
  - Premixed insulin analogues versus a combination of intermediate-acting human insulin and rapid-acting insulin analogue.

Study Characteristics

Of the 45 studies included in this review, 43 reported on at least one of the intermediate clinical outcomes, and two did not report any intermediate clinical outcomes.[11,56] Adverse events were reported by 43 studies; two studies did not report any adverse events.[56,75] Of the 45 trials, 16 were conducted in Europe,[10,32,43,45,48,50,51,53,55,56,58,59,66,67,71,76] 11 were conducted in North America,[15,39,44,60,62-65,74,75,80] six were conducted in Asia,[47,52,57,61,69,78] one was conducted in Africa;[12] nine were multinational trials conducted in countries spread across different continents,[13,46,49,54,68,70,72,73,79] and two trials did not report the region from which patients were enrolled (see Appendix E; Evidence Table 2).[11,77] All were RCTs except two.[52,75] In one study,[52] patients were enrolled consecutively and followed prospectively, while in the other study,[75] data were obtained from the medical record database of a large employer. Among the RCTs, 23 were parallel-arm,[13,15,32,39,43,45-47,49-51,53,54,57,59-61,68,72,76,78-80] 16 were crossover without a washout period,[10-12,48,55,63-67,69-71,73,74,77] and four were crossover trials with a washout period.[44,56,58,62] The median duration of followup in these trials was 16 weeks (a range of 1 day to 2 years). The longest study was by Boehm et al.,[45] which first reported results after 3 months[9] and then reported results of the extended followup at 2 years. There were four short studies, each of a single day's duration, in which blood glucose levels were measured after a single dose of study medications.[44,56,58,62]

The trials showed similarities as well as differences in terms of the patient enrollment criteria. All studies except two enrolled type 2 diabetic patients.[10,45] Eight studies limited the age range of their source population to middle age and older.[12,44,47,59,67,71,72,79] One of these studies exclusively enrolled patients between the ages of 60 and 80 years.[72] Eleven studies did not report the age range of the target populations.[48,50-53,61,70,74,75,77,78] Most trials excluded patients with A1c and BMI values above a certain limit (variable between the studies, but ranging from 9.5 to 14.7 percent for A1c and from 30 to 40 kg/m^2 for BMI). Seven studies did not report inclusion criteria for A1c,[11,51,52,56,70,75,77] and 13 studies did not report inclusion criteria for BMI.[10,11,47,51,52,56,61,63,66,74,75,77,78]

Most of these trials proposed to evaluate the comparative efficacy and safety of the study drugs. Three studies also had a stated aim of evaluating intensive blood glucose control as compared to usual control of blood glucose.[63,69,76] Three other studies also specifically aimed to control postprandial blood glucose.[53,64,77]

These trials enrolled a total of 14,603 patients (median number per trial = 93; range: 8 to 8,166 patients). The enrolled populations in the studies had a median age of 59 years (range: 51 to 68 years), and most patients were male (median = 52 percent, range: 16 to 92 percent; see Appendix E, Evidence Table 3). The study populations had a median A1c of 8.7 percent (range: 7.3 to 10.7 percent), a median BMI of 29.4 kg/m^2 (range: 24 to 37 kg/m^2), and a median duration of diabetes of 11 years (range: 4 to 16 years). Eleven trials enrolled insulin-naïve patients,[15,32,39,43,46,59,60,64,65,72,75] nine trials did not specify history of insulin treatment,[47,49-52,54,57,68,74] and the remaining 23 trials enrolled insulin-treated patients.

Source of funding for the included studies. The source of funding was reported by 33 studies; the remaining 12 studies did not clearly state the source of funding.[43,44,47,48,51,60,65,66,70,71,78,79] Of the studies that clearly stated the source of funding, all but two were funded by the pharmaceutical industry: One was jointly funded by the National Institutes of Health (NIH) and the pharmaceutical industry,[74] while the other was funded by the Japan Diabetes Foundation.[61] Of the studies that did not clearly state their source of funding,

employees of the pharmaceutical industry were among the authors in six studies.[48,60,65,66,70,79] Novo Nordisk, the manufacturer of insulin aspart 70/30, funded 16 studies, all using insulin aspart 70/30 (see Table 4). One of the studies funded by Novo Nordisk also used insulin lispro 75/25 and compared it to insulin aspart 70/30.[58] Eli Lilly, the manufacturer of insulin lispro 75/25 and insulin lispro 50/50, funded 16 studies, one of which was also partially funded through the NIH.[74] Only one study funded by Eli Lilly used insulin aspart 70/30; it compared exenatide (manufactured by Eli Lilly) to insulin aspart 70/30.[49]

Table 4. List of study funding

Company	List of funded studies
Eli Lilly	Coscelli 2003,[67] Cox 2007,[74] Hertz 2002,[72] Hertz 2003,[12] Jacober 2006,[64] Kazda 2006,[76] Malone 2003,[68] Nauck 2007,[49] Roach 1999,[73] Roach 1999,[10] Roach 2003,[69] Roach 2006,[63] Rosenstock 2008,[80] Schernthaner 2004,[77] Schwartz 2006,[62] Sun 2007[75]
Novo Nordisk	Abrahamian 2005,[53] Bebakar 2007,[46] Boehm 2004,[45] Christiansen 2003,[13] Hermansen 2002,[58] Holman 2007,[32] Joshi 2005,[52] Kann 2006,[50] Kapitza 2004,[56] Kilo 2003,[15] McSorley 2002,[11] Niskanen 2004,[55] Raj 2003,[57] Raskin 2005,[39] Raz 2005,[54] Ushakova 2007[59]
Other	Cox 2007,[74] Hirao 2008[61]

Reporting of Intermediate Outcomes and Adverse Events

Fasting glucose. The methods of reporting fasting or pre-meal glucose levels were not consistent among all studies. Studies either reported pre-breakfast glucose levels[10,12,13,15,39,43,45,46,49-55,57,63,64,70,72-74,76,77,80] or both pre-breakfast and pre-dinner glucose levels,[10,12,39,43,45,46,49-51,53-55,57,59,63,64,70,72-74,76,77,79] or they simply reported fasting glucose levels without specifying the time of the day at which the glucose was measured.[32,47,60,65,66,68,69,78] Ten studies did not report pre-meal glucose levels.[11,44,48,56,58,61,62,67,71,75] In six of these studies, glucose levels were reported after a single dose of the study drug with a test meal.[44,56,58,62,67,71] As pre-dinner glucose levels are unlikely to be drawn from patients in a fasting state, we evaluated pre-dinner levels separately and combined the fasting and pre-breakfast glucose levels for this review.

Postprandial glucose. In general, studies reported postprandial glucose either 90 min or 2 h after a meal. Postprandial glucose levels were measured at 90 min after meal in 10 studies[13,39,50,51,53-55,57,59,60] and at 2 h after a meal in 25 studies.[10,12,15,43,44,46,49,58,62-74,76,77,79,80] Two studies did not specify the time of the day at which postprandial glucose was tested, or they pooled postprandial values together and reported one value.[32,52] Eight studies did not report postprandial glucose levels.[11,45,47,48,56,61,75,78] All studies that reported 90-min postprandial glucose levels reported results for both after breakfast and after dinner. Eighteen studies reported 2-h postprandial glucose levels after both breakfast and dinner.[10,12,15,43,46,49,63-66,68,70,72-74,76,77,79] Another seven studies reported 2-h postprandial glucose levels after breakfast.[44,58,62,67,69,71,80] Five of these seven studies evaluated postprandial glucose levels after a test meal only, and therefore they were not designed to report after-dinner values.[44,58,62,67,71] Although studies reported other outcomes for postprandial glucose levels, such as glucose excursion or increment in glucose levels, we chose postprandial glucose levels for two reasons. First, postprandial glucose levels were the most frequently reported outcome measures in the trials. Second, postprandial glucose levels are frequently used in clinical practice to direct adjustments in insulin dose.

For the systematic review, we analyzed the 90-min and 2-h studies together as one group. We analyzed the breakfast postprandial glucose levels separately from the dinner postprandial levels.

We analyzed the studies that reported postprandial glucose levels without specifying the time of the day together with the studies that reported dinner postprandial glucose levels.

Hemoglobin A1c. A1c levels were reported by 35 studies;[10,13,15,32,39,43,45-55,57,59-61,63-66,68,69,72,73,75-80] however, we excluded two studies[57,69] from this review because the duration of followup was only 6 or 8 weeks, respectively.

Hypoglycemia. The definitions of severity of hypoglycemia were fairly consistent across studies. The studies defined a major hypoglycemic event as an event that required third-party help for patients who either had a blood glucose value below a pre-defined limit (usually less than 50 to 60 mg/dL) or required food, intravenous glucose, or glucagon to resolve severe central nervous system symptoms. A minor hypoglycemic event was defined as one in which a patient was able to self-treat without third-party intervention. Some studies defined a "symptom only hypoglycemic event" category if the patient felt symptoms of hypoglycemia, did not require third party assistance, and had either no blood glucose measurements or a blood glucose that was above a pre-defined lower limit. The definition of the lower limit of blood glucose varied between studies.

Studies reported hypoglycemic outcomes in different ways. Some studies chose to describe the incidence of hypoglycemia, defined as the number of patients who had at least one hypoglycemic event or the total number of episodes during the treatment period. Studies also often reported the event rate of hypoglycemic episodes, defined as the number of episodes per patients over some unit of time. Authors also commonly chose to report the incidence or event rate of hypoglycemic episodes as a function of the time of day.

Weight or BMI change. Most studies reported a change in weight as one of the adverse effects of the therapy,[13,15,32,39,43,45-47,49-52,57,59,60,63-66,68,70,72,73,79,80,81] except for three studies that reported a change in body mass index.[61,76,78] As noted in the Methods section, we included only parallel-arm studies[13,15,32,39,43,45-47,49-51,54,57,59,60,61,68,72,76,78,79,80] in the evaluation of this outcome because, in the case of crossover studies, there was a high likelihood of a carryover effect in the second period of the study.

Insulin Aspart 70/30

Insulin aspart 70/30 versus long-acting insulin analogues. We identified four randomized parallel-arm studies that compared insulin aspart 70/30, enrolling a total of 453 patients in the insulin aspart 70/30 arm and 458 patients in the long-acting insulin analogue arm.[32,39,47,50] One study used insulin detemir[32] as the long-acting insulin analogue; the remaining three studies used insulin glargine. All studies reported fasting glucose and A1c. One study did not report postprandial glucose levels.[47]

Raskin et al.[39] enrolled 233 subjects in a 28-week trial. Patients received either twice-daily insulin aspart 70/30 or insulin glargine while also receiving metformin and pioglitazone. Both insulin aspart 70/30 and insulin glargine were started at between 10 and 12 units daily, depending on the fasting glucose levels, and the dose was adjusted during followup. At the end of the study, the insulin dose was significantly greater in the insulin aspart 70/30 group than in the insulin glargine group (78.5 units/day versus 51 units/day, or 0.82 units/kg/day versus 0.55 units/kg/day; $p < 0.05$).

Kann et al.[50] enrolled 255 patients to receive either insulin aspart 70/30 in combination with metformin or to receive insulin glargine and glimepiride; these patients were followed for 26 weeks. The insulin dose was adjusted in both treatment arms during the trial, and the mean

insulin doses were 0.4 units/kg/day in the insulin aspart 70/30 arm and 0.39 units/kg/day in the insulin glargine arm. The metformin and glimepiride doses were also adjusted during the study.

The study by Tamemoto et al.[47] was a small study enrolling 30 patients to receive either insulin aspart 70/30 or insulin glargine. Patients were allowed to continue their oral antidiabetic agents, except that the patients in the insulin aspart 70/30 arm were not allowed to take a sulfonylurea. The starting dose was 10 to 16 units/day in the insulin aspart 70/30 arm and 6 to 8 units/day in the insulin glargine arm. The insulin dose was adjusted during the followup period. The mean insulin dose in the insulin aspart 70/30 arm was 26.7 units/day; the mean insulin glargine dose was not reported.

Holman et al.[32] conducted a three-arm study in which two arms compared insulin detemir (n = 234) to insulin aspart 70/30 (n = 235). Patients were followed for 1 year while on treatment. Insulin aspart 70/30 was given twice daily, while insulin detemir was administered once daily; however, insulin detemir could be administered twice daily if the blood glucose was not under control. Patients in both arms continued metformin and sulfonylurea treatment. The insulin doses were similar in the two arms at the end of the study.

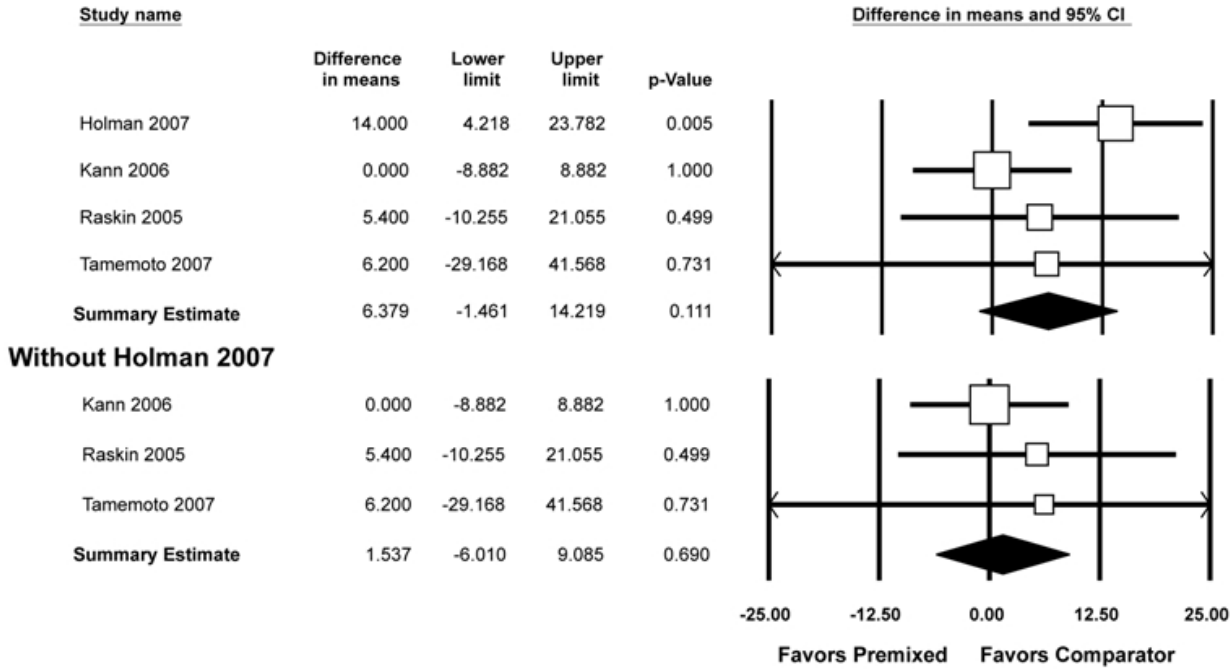
Fasting glucose (see Appendix E, Evidence Table 4). In terms of lowering fasting glucose levels, only one[32] of the four studies found insulin aspart 70/30 to be less effective than long-acting insulin analogues; the other studies did not find any difference. When the results of all four studies were pooled, insulin aspart 70/30 was less effective in lowering fasting glucose than were the long-acting insulin analogues, but the difference did not reach statistical significance (mean difference = 6.4 mg/dL; 95 percent CI: -1.5 to 14.2 mg/dL; $p = 0.11$; see Figure 5). When we excluded the study involving insulin detemir from the pooled analysis, the results did not change (mean difference = 1.5 mg/dL; 95 percent CI: -6.0 to 9.1 mg/dL; $p = 0.69$; see Figure 5). Two studies reported the pre-dinner glucose levels. One study[39] found insulin aspart 70/30 to be more effective than insulin glargine in lowering pre-dinner glucose levels ($p < 0.05$), whereas the second study[50] did not find any difference between the two treatment regimens.

Postprandial glucose (see Appendix E, Evidence Table 4). All three trials found insulin aspart 70/30 to be more effective than long-acting insulin analogues in lowering postprandial glucose levels.[32,39,50] Pooling the results of these studies showed that insulin aspart 70/30 was significantly more effective than long-acting insulin analogues in lowering postprandial glucose levels (mean difference = -22.6 mg/dL; 95 percent CI: -32.1 to -13.2 mg/dL; $p < 0.001$; see Figure 6). Two of the three trials also reported breakfast postprandial levels.[39,50] Insulin aspart 70/30 lowered the breakfast postprandial glucose levels in both studies, but this effect reached statistical significance in only one study.[50]

Hemoglobin A1c (see Appendix E, Evidence Table 4). Insulin aspart 70/30 was found to be significantly more effective than long-acting insulin analogues in lowering A1c in all four studies, except in the study by Tamemoto et al.[47] Tamemoto et al. could have failed to find a difference between the two treatments because of the small sample size (n = 23), giving them a low power to detect a difference. Raskin et al.[39] found that insulin aspart 70/30 lowered A1c to a larger degree in patients with poorer control of diabetes (A1c > 8.5 percent), but no comparative advantage was seen for patients with relatively better control of diabetes (A1c ≤ 8.5 percent). Holman et al.[32] found that not only did patients treated with insulin aspart 70/30 have lower A1c levels ($p < 0.001$), but they were also more likely to reach a target A1c of 6.5 percent or lower than were those in the insulin detemir group ($p = 0.001$). Pooling the study results across the four trials showed that insulin aspart 70/30 was significantly better than long-acting insulin analogues

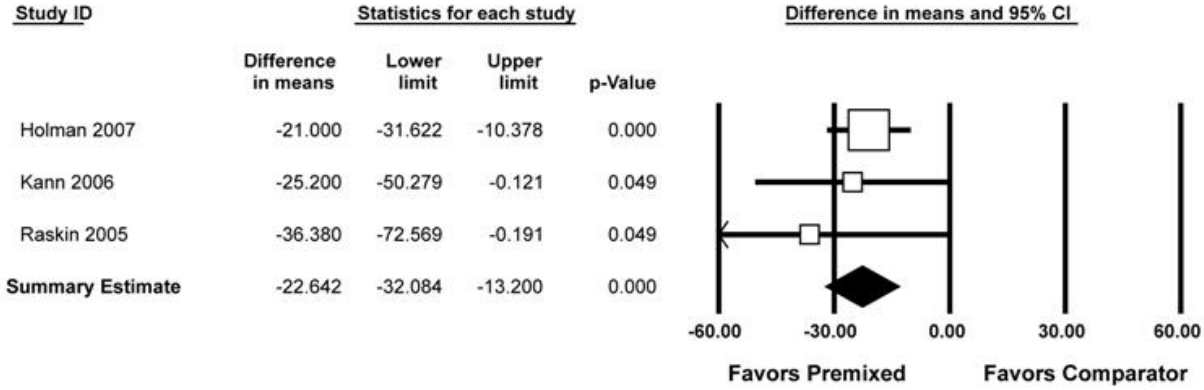
in lowering A1c levels (mean difference = -0.48 percent; 95 percent CI: -0.61 to -0.34 percent; p < 0.001; see Figure 7).

Figure 5. Meta-analyses of post-treatment differences in fasting glucose (mg/dL) between insulin aspart 70/30 and long-acting insulin analogues (with and without Holman et al. 2007)



Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.
Test for heterogeneity: Q = 2.882 with 3 degrees of freedom (p=0.41)
I-squared statistic = 0

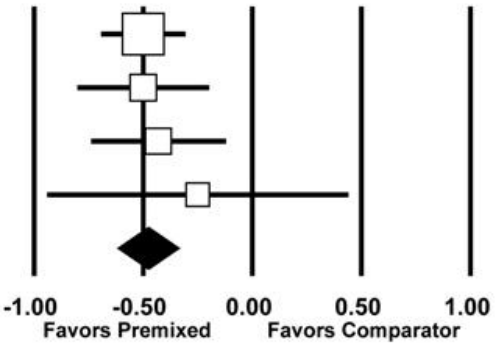
Figure 6. Meta-analyses of post-treatment differences in postprandial glucose (mg/dL) between insulin aspart 70/30 and long-acting insulin analogues



Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.
Test for heterogeneity: Q = 0.685 with 2 degrees of freedom (p = 0.71)
I-squared statistic = 0 percent

Figure 7. Meta-analyses of post-treatment differences in hemoglobin A1c (%) between insulin aspart 70/30 and long-acting insulin analogues

Study name	Difference in means	Lower limit	Upper limit	p-Value
Holman 2007	-0.50	-0.69	-0.31	0.00
Kann 2006	-0.50	-0.80	-0.20	0.00
Raskin 2005	-0.43	-0.74	-0.12	0.01
Tamemoto 2007	-0.25	-0.94	0.44	0.48
Summary Estimate	-0.48	-0.61	-0.34	0.00

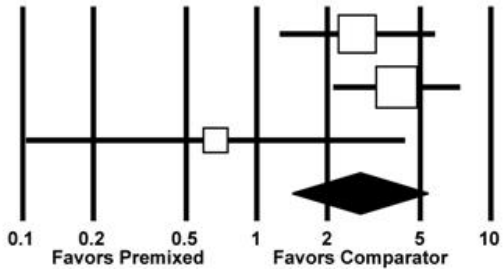


Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.
Test for heterogeneity: Q = 0.589 with 3 degrees of freedom (p =0.899)
I-squared statistic = 0 percent

Hypoglycemia (see Appendix E, Evidence Table 5). The incidence of overall hypoglycemia was reported by Holman et al.[32] and was higher in the insulin aspart 70/30 group than in the insulin detemir group (216 out of 235 versus 173 out of 234 patients; $p < 0.001$). The incidence of minor hypoglycemia was reported by three studies.[39,47,50] In two studies, the incidence of minor hypoglycemia events was significantly higher in the insulin aspart 70/30 group than in the comparison group.[39,50] When the results of these three studies were pooled, the incidence of minor hypoglycemia was found to be significantly higher for insulin aspart 70/30 than for insulin glargine (78 versus 34; odds ratio (OR) = 2.8; 95 percent CI: 1.4 to 5.4; $p = 0.003$; see Figure 8). Two studies[47,50] reported the incidence of symptoms-only hypoglycemia and did not find any difference between the two types of insulin analogues.

Figure 8. Meta-analyses of the incidence of mild hypoglycemia in those receiving insulin aspart 70/30 or a long-acting insulin analogue (glargine)

Study name	Odds ratio	Lower limit	Upper limit	p-Value
Kann 2006	2.688	1.265	5.711	0.010
Raskin 2005	3.961	2.138	7.338	0.000
Tamemoto 2007	0.667	0.104	4.261	0.668
Summary Estimate	2.772	1.419	5.417	0.003

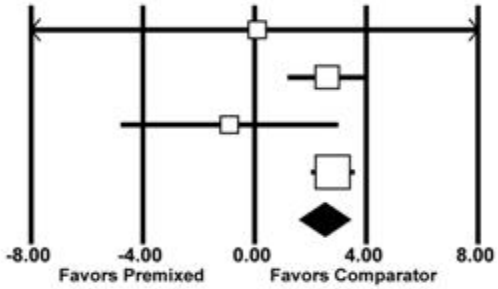


Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.
Test for heterogeneity: Q = 3.378 with 2 degrees of freedom (p =0.185)
I-squared statistic = 41 percent

Weight change (see Appendix E, Evidence Table 6). In two studies,[32,39] patients treated with insulin aspart 70/30 gained significantly more weight than did those receiving a long-acting insulin analogue ($p < 0.001$ in both studies). In the remaining two studies, the weight change was not significant. Pooling the results of these four studies indicated that insulin aspart 70/30 was associated with a much larger weight gain than was insulin glargine (weighted mean difference = 2.5 kg; 95 percent CI: 1.6 to 3.4 kg; $p < 0.001$; see Figure 9).

Figure 9. Meta-analyses of post-treatment differences in weight change (kg) between insulin aspart 70/30 and long-acting insulin analogues

Study name	Statistics for each study			
	Difference in means	Lower limit	Upper limit	p-Value
Tamemoto 2007	0.100	-9.975	10.175	0.984
Raskin 2005	2.600	1.207	3.993	0.000
Kann 2006	-0.900	-4.764	2.964	0.648
Holman 2007	2.800	2.058	3.542	0.000
Summary Estimate	2.529	1.635	3.423	0.000



Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.
Test for heterogeneity: Q = 3.650 with 3 degrees of freedom ($p = 0.302$)
I-squared statistic = 19 percent

Other serious adverse events (see Table 5 and Appendix E, Evidence Table 6). None of the included studies comparing insulin aspart 70/30 to a long-acting insulin analogue reported on injection site reactions. Table 5 shows the range of risk differences between insulin aspart 70/30 and long-acting insulin analogues in terms of total serious adverse events, other serious adverse events, and withdrawals as a result of adverse events.

Insulin aspart 70/30 versus rapid-acting insulin analogues. We identified only one study on this comparison. Holman et al.[32] compared twice-daily insulin aspart 70/30 plus metformin and a sulfonylurea to thrice-daily rapid-acting insulin aspart with meals plus metformin and sulfonylurea. This was a large RCT with 235 patients in the insulin aspart 70/30 arm and 239 patients in the rapid-acting insulin aspart arm. The median starting daily dose of insulin was similar in both groups, and insulin doses were adjusted based on blood glucose levels.

Intermediate outcomes (see Appendix E, Evidence Table 4). Holman et al.[32] found that insulin aspart 70/30 was more effective than rapid-acting insulin aspart in decreasing fasting glucose levels (mean difference = -22.0 mg/dL; $p < 0.001$). On the other hand, rapid-acting insulin aspart was more effective in lowering postprandial blood glucose than was insulin aspart 70/30 (mean difference = -15 mg/dL; $p < 0.001$). Rapid-acting insulin aspart was slightly more effective in lowering A1c than was insulin aspart 70/30, although this difference was not statistically significant (mean difference = -0.1 percent; $p = 0.08$). The percentage of patients who achieved a target A1c of less than or equal to 7.0 percent or 6.5 percent was higher for those receiving rapid-acting insulin aspart than for those receiving insulin aspart 70/30, but this difference was not statistically significant (mean difference = 7.0 percent and 6.9 percent respectively; $p = 0.08$ for both A1c targets).

Adverse events (see Appendix E, Evidence Tables 5 and 6). The incidence of hypoglycemia was not significantly different between the two groups (216 out of 235 patients versus 229 out of 238 patients; p = 0.08).[32] Treatment with insulin aspart 70/30 was associated with less weight gain than was treatment with rapid-acting insulin aspart (mean difference = -1.0 kg; p = 0.005). This study did not report on injection site reactions. Table 5 shows the risk differences between insulin aspart 70/30 and rapid-acting insulin analogues in terms of total serious adverse events, other serious adverse events, and withdrawals due to adverse events.

Insulin aspart 70/30 versus a combination of long-acting and rapid-acting insulin analogues. We identified one nonrandomized prospective trial by Joshi et al. that compared insulin aspart 70/30 to a combination of mealtime insulin aspart and bedtime insulin glargine.[52] Doses of all insulin analogues were adjusted throughout the trial on the basis of glucose levels. At the end of the trial, the total insulin dose was lower in the insulin aspart 70/30 group (40.2 versus 52.8 units/day).

Intermediate outcomes (see Appendix E, Evidence Table 4). After 12 weeks of followup, both treatments were effective in lowering fasting glucose, postprandial glucose, and A1c from baseline levels. When Joshi et al. compared the two treatments, they found insulin aspart 70/30 to be less effective than a combination of mealtime insulin aspart and bedtime insulin glargine in lowering fasting glucose levels, although this difference was not statistically significant (mean difference = 7.9 mg/dL; p > 0.05).[52] On the other hand, insulin aspart 70/30 was more effective than the combination in lowering postprandial glucose levels, although this effect was also not statistically significant (mean difference = -11.8 mg/dL; p > 0.05). Insulin aspart 70/30 was significantly more effective than the combination in lowering A1c (mean difference = -0.42 percent; p < 0.05). Moreover, a larger percentage of patients achieved an A1c of less than 7 percent with insulin aspart 70/30 than with the combination at the end of 12 weeks of followup (risk difference = -14 percent; p-value was not reported).

Adverse events (see Appendix E, Evidence Tables 5 and 6). There were no major hypoglycemic events in this study.[52] Fewer patients in the insulin aspart 70/30 arm had minor hypoglycemic events, as compared to the group that received a combination of insulin glargine and rapid-acting insulin aspart (16.7 versus 58 percent; p < 0.05). There was no significant difference in the body weight in the two groups. This study did not report on injection site reactions. Table 5 shows the risk differences between insulin aspart 70/30 and rapid-acting insulin analogues for total serious adverse events and withdrawals due to adverse events.

Insulin aspart 70/30 versus premixed human insulin. Our search found three parallel-arm trials[15,45,53] and three crossover trials[11,48,58] that compared insulin aspart 70/30 with a premixed human insulin, NPH/regular 70/30.

McNally et al.[48] compared insulin aspart 70/30 with NPH/regular 70/30 (both injected immediately before meals) in a crossover trial enrolling 160 subjects. After a 6-week run-in period, subjects were followed for two treatment periods of 16 weeks each. The insulin dose was adjusted during the followup in order to achieve glucose targets, and the mean insulin dose was similar in both groups.

In a 24-week parallel-arm study by Abrahamian et al.,[53] thrice-daily insulin aspart 70/30 (given with meals) was compared to twice-daily NPH/regular 70/30 (given 30 min before meals). The mean insulin dose was slightly larger in the insulin aspart 70/30 arm than in the premixed human insulin arm (0.61 units/kg/day versus 0.59 units/kg/day, p = nonsignificant).

Table 5. Range of risk differences between insulin aspart 70/30 and other antidiabetic agents for selected adverse events

	Total serious adverse events		Withdrawn due to adverse events		Other serious adverse events	
Comparison	**Number of studies included**	**Range of risk difference* between insulin aspart 70/30 and comparison**	**Number of studies included**	**Range of risk difference* between insulin aspart 70/30 and comparison**	**Number of studies included**	**Range of risk difference* between insulin aspart 70/30 and comparison**
Long-acting insulin analogues	3[32,39,50]	-0.01 – 0.046	4[32,39,47,50]	-0.01 – 0.02	1[32]	0.04 for GI and abdominal pain 0.017 for lower respiratory tract and lung infection
Rapid-acting insulin analogues	1[32]	0.048	1[32]	0.01	1[32]	0.013 for GI and abdominal pain 0.017 for lower respiratory tract and lung infection
Rapid-acting with long-acting insulin analogues	1[52]	0	1[52]	0	0	NA
Premixed human insulins	1**[48]	-0.02	7[11,15,45,48,53,56,58]	0 – 0.04	2†[11,15]	0 – 0.02
Rapid-acting insulin analogues with intermediate-acting human insulin	0	NA	0	NA	0	NA
Intermediate-acting human insulins	1[13]	-0.01	2[13,15]	0 – 0.04	2[13,15]	0 – 0.02
Oral antidiabetic agents	2‡‖[54]¶[59]	0 – 0.02	6[46,51]¶[54]¶[57,59,60]	-0.01 – 0.05	2[54]¶[60]	0 – 0.01 for cellulitis -0.03 – 0.05 for peripheral edema
Exenatide	1[49]	-0.031	1[49]	-0.08	0	NA
Insulin lispro 75/25	0	NA	2[55,58]	0 – 0.02	1§[55]	0.066
Insulin aspart 70/30 + oral antidiabetic agents	2‖[54,59]	0-0.02	3[51,54,59]	-0.01 – 0.02	1[54]	-0.06 for peripheral edema 0.01 for cellulitis

* The risk difference is the proportion having an event in the treatment group minus the proportion having an event in the comparison group. Negative risk differences suggest a protective effect of the treatment, while positive risk differences suggest a harmful effect of the treatment.
** An additional study reported 16 events in the insulin aspart 70/30 arm and 15 events in the premixed human insulin arm.[53]
†An additional study reported 1 event in the insulin aspart 70/30 arm and 0 events in the premixed human insulin arm.[58]
‡An additional study reported 5 events in the insulin aspart 70/30 arm and 0 events in the oral antidiabetic agents arm.[46]
‖An additional study reported a total of 5 events, but did not specify in which arm the events occurred.[51]
¶There were 2 eligible comparisons in this study.
§An additional study reported 1 event in the insulin aspart 70/30 arm and 0 events in the insulin lispro 75/25 arm.[58]
GI = gastrointestinal; NA = not applicable

Boehm at al.[9,45] compared twice-daily insulin aspart 70/30 (given with meals) to twice-daily NPH/regular 70/30 (given 30 min before meals). This was a 3-month trial with an extended followup of 2 years. The initial 3-month period of the trial included both type 1 and type 2 diabetics. The extended followup was limited to type 2 diabetics only. Insulin doses were adjusted throughout the trial. After 2 years, the premixed human insulin group was receiving a significantly larger total insulin dose than the insulin aspart 70/30 group (mean difference = 0.09 units/kg/day; $p < 0.001$).

Kilo et al.[15] conducted a three parallel-arm trial that compared insulin aspart 70/30 (given 10 min before dinner) to NPH/regular 70/30 (given 30 min before dinner) in two of its arms. Metformin was given to patients in both arms. The insulin dose was adjusted throughout the 12-week followup period. The mean insulin dose was slightly higher in the NPH/regular 70/30 group than in the insulin aspart 70/30 group (29 versus 26 units/day).

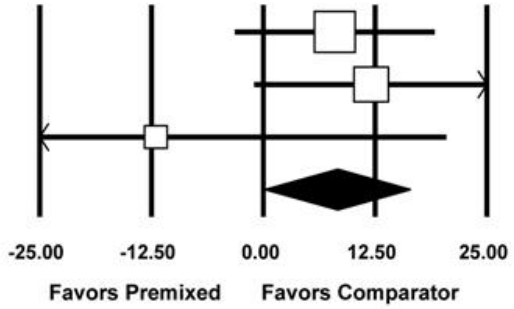
McSorely et al.[11] compared twice-daily insulin aspart 70/30 with twice-daily NPH/regular 70/30 (both given immediately before meals) in a crossover trial over two treatment periods of 2 weeks each. This study did not report on the insulin dose used during the study.

Hermansen et al.[58] conducted a three-arm crossover trial in which study medications were given once only after a test meal in order to study the postprandial serum glucose response. Two arms compared insulin aspart 70/30 (given with the meal) with premixed human insulin 70/30 (given 15 min before the meal). Similar doses were used for both insulins and were based on the weight of the subject (0.4 units/kg).

Fasting glucose (see Appendix E, Evidence Table 4). All three parallel-arm trials reported the change in fasting glucose levels.[15,45,53] Individually, these studies did not report an advantage for one treatment over the other. When the results of the studies were pooled, insulin aspart 70/30 was less effective than premixed human insulin in lowering fasting glucose (mean difference = 8.3 mg/dL; 95 percent CI: 0.16 to 16.5 mg/dL; $p = 0.04$; see Figure 10) although the difference was small.

Figure 10. Meta-analyses of post-treatment differences in fasting glucose (mg/dL) between insulin aspart 70/30 and premixed human insulin

Study name	Statistics for each study			
	Difference in means	Lower limit	Upper limit	p-Value
Abrahamian 2005	8.000	-3.089	19.089	0.157
Boehm 2002	12.060	-0.935	25.055	0.069
Kilo 2003	-12.000	-44.370	20.370	0.467
Summary Estimate	8.330	0.167	16.493	0.045



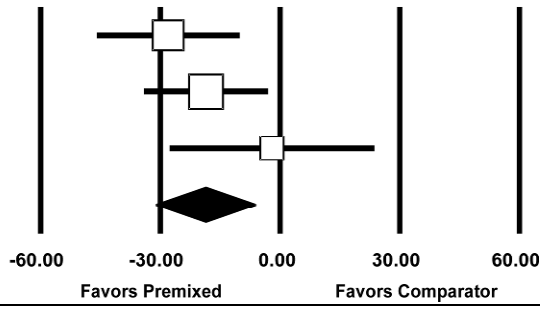
Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.
Test for heterogeneity: Q = 2.065 with 2 degrees of freedom (p = 0.272)
I-squared statistic = 23 percent

Postprandial glucose (see Appendix E, Evidence Table 4). All three parallel-arm trials[15,45,53] and one crossover trial[58] reported changes in postprandial glucose. Boehm et al.[9,45] found a

significant decrease in postprandial glucose levels 90 min after both breakfast ($p < 0.05$) and dinner ($p < 0.02$) after 12 weeks of followup. However, they combined the results from type 2 diabetics (n = 187) with those for type 1 diabetics (n = 104) in reporting changes in postprandial glucose levels, thus making it difficult to extrapolate this finding to type 2 diabetics alone. Abrahamian et al.[53] found a significant decrease in glucose levels 90 minutes after dinner but not after breakfast with insulin aspart 70/30, as compared to a premixed human insulin ($p < 0.002$ and $p > 0.05$, respectively). On the other hand, Kilo et al.[15] did not find a significant difference in glucose levels between insulin aspart 70/30 and premixed human insulin. The difference in the frequency of administration of insulin injection may be responsible for the disparate results in these trials. Kilo et al.[15] also did not find insulin aspart 70/30 to be more effective than premixed human insulin in lowering breakfast postprandial glucose. When the results of these studies were pooled, insulin aspart 70/30 was more effective than premixed human insulin in lowering postprandial glucose (weighted mean difference = -18.6 mg/dL; 95 percent CI: -31.1 to -6.0 mg/dL; $p = 0.004$; see Figure 11). These results were consistent with the results of a single-dose crossover trial[58] that also did not find insulin aspart 70/30 to be more effective than premixed human insulin in lowering breakfast postprandial glucose ($p > 0.05$).

Figure 11. Meta-analyses of post-treatment differences in postprandial glucose (mg/dL) between insulin aspart 70/30 and premixed human insulin

Study name	Statistics for each study			
	Difference in means	Lower limit	Upper limit	p-Value
Abrahamian 2005	-28.000	-45.660	-10.340	0.002
Boehm 2002	-18.540	-33.866	-3.214	0.018
Kilo 2003	-2.000	-27.407	23.407	0.877
Summary Estimate	**-18.557**	**-31.146**	**-5.968**	**0.004**



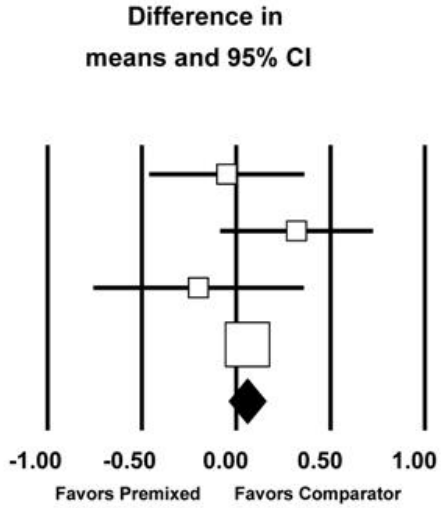
Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.
Test for heterogeneity: Q = 2.721 with 2 degrees of freedom ($p = 0.257$)
I-squared statistic = 26 percent

Hemoglobin A1c (see Appendix E, Evidence Table 4). All three parallel-arm trials[15,45,53] and one crossover trial[48] compared changes in A1c levels with insulin aspart 70/30 and NPH/regular 70/30. Boehm et al.[45] found that the mean A1c increased slightly in both groups after an initial decrease in the first 6 months. There was no statistically significant difference in mean A1c after 24 months (mean difference = 0.03 percent; $p = 0.89$). McNally et al.[48] reported that patients on insulin aspart 70/30 achieved a mean A1c of 7.28 percent, as compared to 7.22 percent after NPH/regular 70/30. The treatment difference of 0.06 percent was not statistically significant ($p = 0.21$). Similar results were reported by Kilo et al.[15] and Abrahamian et al.,[53] who found no significant differences in A1c levels (mean difference = 0.2 percent; $p > 0.05$ and mean difference = 0.1 percent; $p = 0.64$, respectively). When the results of these studies were pooled, there was no indication that one premixed preparation was more effective than the other in

lowering A1c (weighted mean difference = 0.06 percent; 95 percent CI: -0.04 to 0.16 percent; p = 0.22; see Figure 12).

Figure 12. Meta-analyses of post-treatment differences in hemoglobin A1c (%) between insulin aspart 70/30 and premixed human insulin preparations

Study name	Statistics for each study			
	Difference in means	Lower limit	Upper limit	p-Value
Abrahamian 2005	-0.05	-0.46	0.36	0.81
Boehm 2004	0.32	-0.08	0.72	0.12
Kilo 2003	-0.20	-0.75	0.35	0.48
McNally 2007	0.06	-0.04	0.16	0.26
Summary Estimate	0.06	-0.04	0.16	0.22



Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.
Test for heterogeneity: Q = 2.739 with 3 degrees of freedom (p =0.434)
I-squared statistic = 0 percent

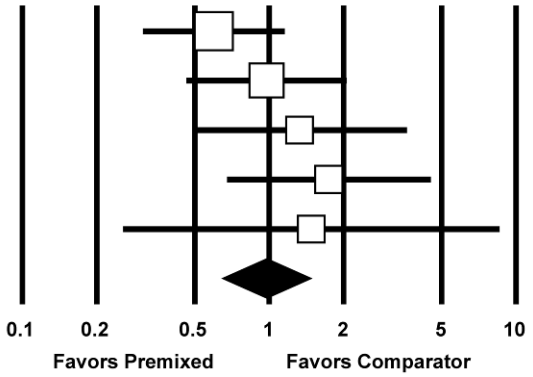
Hypoglycemia (see Appendix E, Evidence Table 5). Two studies reported the incidence of overall hypoglycemia and found no difference between the two premixed preparations.[15,45] Five studies[11,15,45,48,53] reported the incidence of minor hypoglycemia, and none of them found a significant benefit of a particular premixed insulin. Pooling of the study results also revealed no difference (144 out of 284 patients versus 151 out of 293 patients; OR = 0.98; 95 percent CI: 0.65 to 1.46; p = 0.91; see Figure 13). The incidence of major hypoglycemia was reported in four studies,[45,48,53,58] but there was no difference between the treatments in individual studies or when the results of these studies were pooled (9 out of 269 patients versus 16 out of 274 patients; OR = 0.55; 95 percent CI: 0.22 to 1.34; p = 0.19). Only one study reported the incidence of symptom-only hypoglycemia and found no difference between insulin aspart 70/30 and premixed human insulin (13 out of 46 patients versus 11 out of 47 patients; p = 0.59).[15]

Weight change (see Appendix E, Evidence Table 6). Boehm et al.[45] found that premixed human insulin was associated with a higher weight gain than was insulin aspart 70/30, although this difference was not statistically significant (mean difference = -1.5 kg; p = 0.07). Similar results were reported by Kilo et al.,[15] who found that patients on insulin aspart 70/30 gained an average of 0.7 kg, while patients on premixed human insulin gained 1.0 kg (p-value not reported).

Other serious adverse events (see Appendix E, Evidence Table 6). None of the studies comparing insulin aspart 70/30 to a premixed human insulin reported on injection site reactions. Table 5 shows the range of risk differences between insulin aspart 70/30 and premixed human insulins in terms of total serious adverse events, other serious adverse events, and withdrawals due to adverse events.

Figure 13. Meta-analyses of differences in the incidence of mild hypoglycemia between insulin aspart 70/30 and premixed human insulin preparations

Study name	Odds ratio	Lower limit	Upper limit	p-Value
Abrahamian 2005	0.597	0.311	1.146	0.121
Boehm 2004	0.976	0.466	2.043	0.948
Kilo 2003	1.327	0.491	3.583	0.577
McNally 2007	1.746	0.681	4.477	0.246
McSorley 2002	1.481	0.258	8.499	0.659
Summary Estimate	0.978	0.654	1.464	0.915



Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.
Test for heterogeneity: Q = 4.236 with 4 degrees of freedom (p =0.375)
I-squared statistic = 5 percent

Insulin aspart 70/30 versus rapid-acting insulin analogues with intermediate-acting human insulin. One 6-month Japanese randomized parallel-arm trial by Hirao et al. compared insulin aspart 70/30 with three-times-daily injections of insulin aspart with or without an intermediate-acting human insulin (NPH) in insulin-naïve patients with type 2 diabetes.[61]

Intermediate outcomes (see Appendix E, Evidence Table 4). This study did not report changes in fasting or postprandial glucose levels. There was no statistical difference between the two groups in the change in A1c from baseline (2.6 percent in both groups).[61]

Adverse events (see Appendix E, Evidence Tables 5 and 6). There were no major hypoglycemic events observed with either regimen.[61] No other hypoglycemia results were reported. Both arms gained weight, but those in the insulin aspart 70/30 arm gained significantly more weight (p = 0.013) than did those in the multiple daily injection group.[61] The study did not report on injection site reactions.[61] Table 5 shows the range of risk differences between insulin aspart 70/30 and three-times-daily injections of insulin aspart, with or without an intermediate-acting human insulin (NPH), in terms of total serious adverse events, other serious adverse events, and withdrawals due to adverse events. There was one death in the insulin aspart 70/30 arm.

Insulin aspart 70/30 versus intermediate-acting human insulin. Two randomized parallel-arm trials that compared insulin aspart 70/30 to an intermediate-acting human insulin (NPH) met our inclusion criteria.[13,15]

Kilo et al.[15] compared bedtime NPH insulin with insulin aspart 70/30 given 10 min before dinner, while Christiansen et al.[13] compared the two agents when given twice daily (immediately before breakfast and dinner). In both studies, the insulin dose was adjusted during the treatment in order to control glucose levels. The starting insulin dose in Christiansen et al.[13] was similar in the two arms, but the mean dose was not reported in the study. During the study period, oral therapy with metformin was continued with insulin preparations in Kilo et al.,[15] but all oral antidiabetic treatment was discontinued in Christiansen et al.[13]

Fasting glucose (see Appendix E, Evidence Table 4). Both studies did not find any difference between the two treatments in terms of lowering fasting glucose levels.[13,15] Kilo et al. also did not find any advantage of one regimen over the other with regard to lowering pre-dinner glucose levels.[15]

Postprandial glucose (see Appendix E, Evidence Table 4). Kilo et al.[15] reported that 2-h breakfast postprandial glucose levels were lower with NPH insulin, but dinner postprandial levels were lower with insulin aspart 70/30; these differences were not statistically significant (difference between studies were not reported). In contrast, Christiansen et al.[13] found insulin aspart 70/30 to be more effective than NPH insulin in lowering breakfast and dinner postprandial glucose but did not mention whether this difference was statistically significant or due to chance alone (-1.8 and -3.6 mg/dL respectively; p-value not reported).

Hemoglobin A1c (see Appendix E, Evidence Table 4). Both trials found no difference between insulin aspart 70/30 and NPH insulin in terms of lowering A1c. Christiansen et al.[13] found that although A1c decreased in both groups, with reductions of 0.67 and 0.61 percent from baseline in the insulin aspart 70/30 and NPH insulin groups, respectively, there was no difference between the two treatments ($p > 0.05$). Similarly, Kilo et al.[15] found that although A1c decreased from baseline by 1.3 percent in the insulin aspart 70/30 group and by 1.2 percent in the NPH insulin group, the difference between the two treatments was not statistically significant ($p > 0.05$).

Hypoglycemia (see Appendix E, Evidence Table 5). There were no major hypoglycemic events in these studies. Kilo et al.[15] found fewer patients who suffered minor hypoglycemic events (6 out of 47 patients versus 11 out of 46 patients) or symptoms of hypoglycemia (10 out of 47 patients versus 13 out of 46 patients) with NPH insulin than with insulin aspart 70/30. More patients with NPH insulin had nocturnal hypoglycemia, as compared to those taking insulin aspart 70/30 (11 out of 47 patients versus 7 out of 46 patients). Christiansen et al.[13] also found that more patients in the insulin aspart 70/30 group had minor hypoglycemic events than did those in the NPH insulin group (77 out of 201 patients versus 68 out of 202 patients).

Weight change (see Appendix E, Evidence Table 6). In the study by Kilo et al.,[15] insulin aspart 70/30 was associated with more weight gain than was NPH insulin (0.7 kg versus 0.1 kg), although the difference was not statistically significant.

Other serious adverse events (see Appendix E, Evidence Table 6). Neither of these studies comparing insulin aspart 70/30 to an intermediate-acting human insulin reported on injection site reactions. Table 5 shows the range of risk differences between insulin aspart 70/30 and intermediate-acting human insulins in terms of total serious adverse events, other serious adverse events, and withdrawals due to adverse events.

Insulin aspart 70/30 versus noninsulin antidiabetic agents. Of the seven studies identified by our search,[46,49,51,54,57,59,60] two compared insulin aspart 70/30 to a combination of a thiazolidinedione and glibenclamide,[54,57] one to a combination of metformin and glibenclamide,[51] one to either monotherapy or any combination of a sulfonylurea, metformin, or a meglitinide,[46] one to metformin, sulfonylurea, or meglitinide alone or a combination of any two of these drugs,[59] one to metformin plus pioglitazone,[60] and one to exenatide.[49]

Bebakar et al.[46] compared once- or twice-daily insulin aspart 70/30 (n = 128) to oral antidiabetic agents (n = 63) in type 2 diabetics who were poorly controlled with oral antidiabetic agents. The dose of insulin was adjusted based on the basis of glucose level. The dose of oral antidiabetic agents was also adjusted, although addition or substitution of oral antidiabetic agents was not permitted during the study.

Kvapil et al.[51] randomized patients to receive twice-daily insulin aspart 70/30 (n = 107), twice-daily insulin aspart 70/30 in combination with metformin (n = 108), or metformin and glibenclamide (n = 114). In this study, the metformin dose was kept constant, but the doses of insulin aspart 70/30 and glibenclamide were adjusted on the basis of the glucose response.

Raz et al.[54] randomized patients to receive twice-daily insulin aspart 70/30 (n = 97), twice-daily insulin aspart 70/30 with pioglitazone (n = 93), or glibenclamide with pioglitazone (n = 91). The pioglitazone dose was kept fixed throughout the study, while the insulin aspart 70/30 and the glibenclamide doses were adjusted in response to changes in blood glucose. The insulin dose was lower in the insulin aspart 70/30 with pioglitazone group than in the insulin aspart 70/30 alone group (0.2 versus 0.3 units/kg/day).

In another study, Raz et al.[57] compared the efficacy of a combination of insulin aspart 70/30 and rosiglitazone to a combination of glibenclamide and rosiglitazone. In this study, although the dose of insulin aspart 70/30 could be adjusted, doses of rosiglitazone and glibenclamide were kept fixed throughout the study.

Ushakova et al.[59] compared twice-daily insulin aspart 70/30 to oral antidiabetic therapy (metformin, sulfonylurea, or meglitinide or a combination of any two of these drugs). Although the doses of all medications were optimized during the study, there was no dosing protocol.[59]

Raskin et al.[60] enrolled insulin-naïve individuals with poor glycemic control on oral therapy. Before randomization, all participants were given pioglitazone and metformin, and the doses of these medications were optimized over 8 weeks. Participants were then randomized to the combination of twice-daily insulin aspart 70/30, pioglitazone, and metformin or to oral antidiabetic therapy (pioglitazone plus metformin). After randomization, only insulin doses could be titrated, so that the oral antidiabetic agent arm had reached its potential to affect blood glucose measurements by the time of randomization.

Nauck et al.[49] compared twice-daily exenatide (an incretin mimetic) to twice-daily insulin aspart 70/30 in patients with suboptimal diabetes control, with patients being allowed to continue their metformin and sulfonylurea treatments. Insulin aspart 70/30 dose was titrated throughout the study to achieve optimal glucose control. The exenatide dose, on the other hand, was increased only once, at 4 weeks, from 5 micrograms to 10 micrograms twice daily. Since exenatide is the only noninsulin antidiabetic agent that is injectable (all others in this review are oral agents), we pooled these studies with and without the study by Nauck et al.[49]

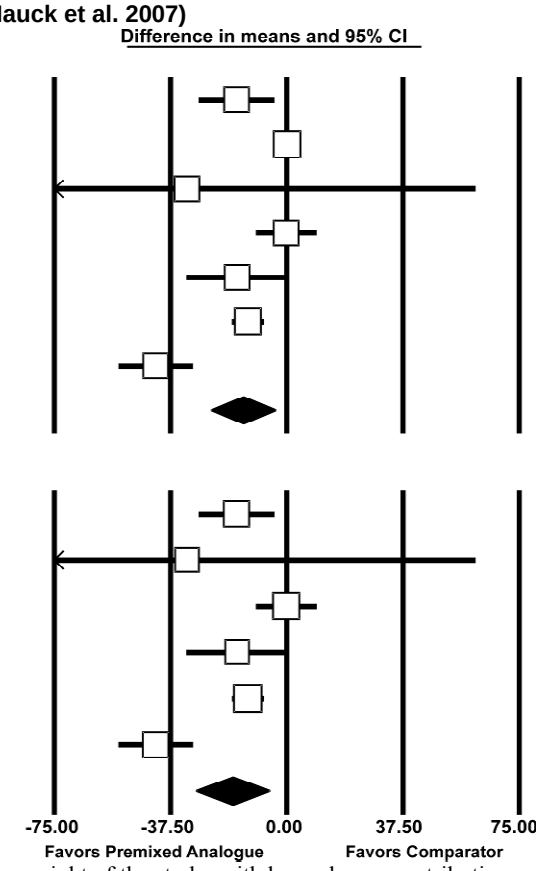
Fasting glucose (see Appendix E, Evidence Table 4). In terms of lowering fasting glucose, insulin aspart 70/30 was found to be more effective than noninsulin antidiabetic agents in all studies except one,[49] but the difference was statistically significant in only three.[46,49,60] When the results of all trials were pooled, insulin aspart 70/30 was found to be more effective than oral antidiabetic agents in lowering fasting glucose (mean difference = -13.9 mg/dL; 95 percent CI: -24.4 to -3.4 mg/dL; p = 0.009; see Figure 14). The funnel plot was asymmetrical, and the trim-and-fill method showed that three studies need to be imputed to make the plot symmetrical. Addition of the imputed studies resulted in a statistically nonsignificant pooled mean difference. When the study by Nauck et al.[49] that compared exenatide with insulin aspart 70/30 was excluded, insulin aspart 70/30 remained significantly different than oral antidiabetic agents in terms of lowering fasting glucose (weighted mean difference = -17.3 mg/dL; 95 percent CI: -29.3 to -5.4 mg/dL; p = 0.009; see Figure 14), and the publication bias disappeared.

All seven studies also reported changes in pre-dinner glucose levels. Insulin aspart 70/30 was significantly more effective in lowering pre-dinner glucose levels than were noninsulin antidiabetic agents in two studies.[46,54] In the study by Raz et al.,[54] insulin aspart 70/30 in

combination with pioglitazone, but not alone, was more effective than the combination of glibenclamide and pioglitazone in lowering pre-dinner glucose levels. When the results of all seven trials were pooled to obtain a summary estimate, insulin aspart 70/30 was found to be similar to noninsulin antidiabetic agents in lowering pre-dinner glucose levels (mean difference = -13.9 mg/dL; 95 percent CI: -30.4 to 2.7 mg/dL; p = 0.1). When we excluded the study by Nauck et al.,[49] insulin aspart 70/30 was more effective than noninsulin antidiabetic agents (mean difference = -18.0 mg/dL; 95 percent CI: -33.1 to -2.7 mg/dL; p = 0.02).

Figure 14. Meta-analyses of post-treatment differences in fasting glucose (mg/dL) between insulin aspart 70/30 and noninsulin antidiabetic agents (with and without Nauck et al. 2007)

Study name	Difference in means	Lower limit	Upper limit	p-Value
Bebakar 2007	-16.200	-28.145	-4.255	0.008
Nauck 2007	0.100	-0.399	0.599	0.694
Raz 2003	-32.200	-125.045	60.645	0.497
Kvapil 2006	-0.180	-9.705	9.345	0.970
Raz 2005	-16.000	-32.124	0.124	0.052
Ushakova 2007	-12.530	-17.382	-7.678	0.000
Raskin 2007	-42.300	-54.040	-30.560	0.000
Summary Estimate	**-13.925**	**-24.410**	**-3.441**	**0.009**
Without Nauck 2007				
Bebakar 2007	-16.200	-28.145	-4.255	0.008
Raz 2003	-32.200	-125.045	60.645	0.497
Kvapil 2006	-0.180	-9.705	9.345	0.970
Raz 2005	-16.000	-32.124	0.124	0.052
Ushakova 2007	-12.530	-17.382	-7.678	0.000
Raskin 2007	-42.300	-54.040	-30.560	0.000
Summary Estimate	**-17.313**	**-29.270**	**-5.356**	**0.005**



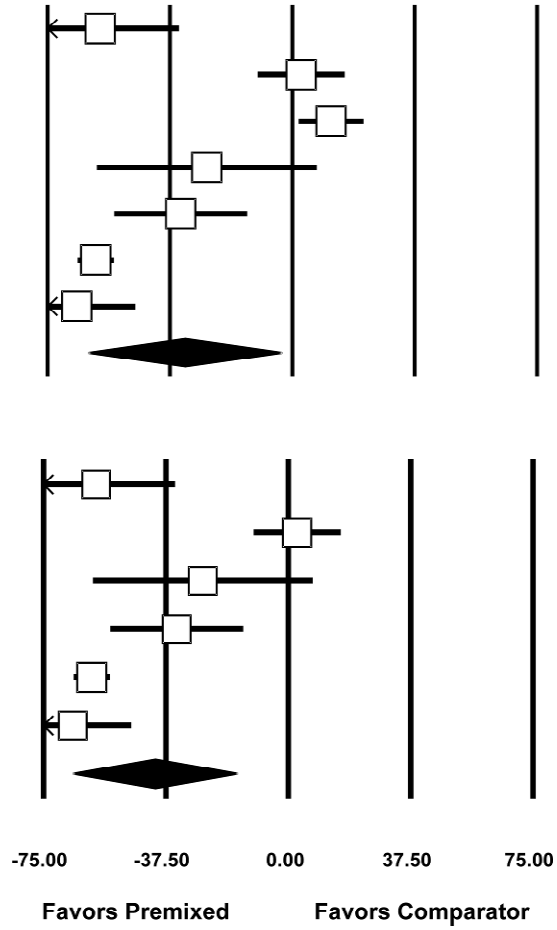
Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.
Test for heterogeneity: Q = 41.86 with 6 degrees of freedom (p < 0.001)
I-squared statistic = 86 percent

Postprandial glucose (see Appendix E, Evidence Table 4). All seven studies also reported changes in postprandial glucose levels. As compared to a combination of a thiazolidinedione and glibenclamide, insulin aspart 70/30 lowered postprandial glucose levels in both studies,[54,57] but the decrease in blood glucose was significant in only one study.[54] Similarly, as compared to a combination of thiazolidinedione and metformin, insulin aspart 70/30 was more effective in lowering postprandial glucose levels in another study.[60] Insulin aspart 70/30 was more effective than either monotherapy or with any combination of a sulfonylurea, metformin, or a meglitinide in lowering dinner postprandial glucose levels in two studies.[46,59] On the other hand, no difference was found between insulin aspart 70/30 and a combination of metformin and glibenclamide in terms of lowering postprandial glucose levels in the study by Kvapil et al.[51]

Nauck et al. found that exenatide was more effective than insulin aspart 70/30 in lowering postprandial glucose levels.[49] Pooling the results of these studies indicated that insulin aspart 70/30 lowered postprandial glucose levels more effectively than did the comparators (mean difference = -32.8 mg/dL; 95 percent CI: -62.5 to -3.1 mg/dL: p = 0.03; see Figure 15). The results did not change even when the study with exenatide[49] was excluded from the meta-analysis (weighted mean difference = -40.7 mg/dL; 95 percent CI: -65.9 to -15.5 mg/dL; p = 0.002; see Figure 15).

Figure 15. Meta-analyses of post-treatment differences in postprandial glucose (mg/dL) between insulin aspart 70/30 and noninsulin antidiabetic agents

Study name	Difference in means	Lower limit	Upper limit	p-Value
Bebakar 2007	-58.860	-82.662	-35.058	0.000
Kvapil 2006	2.700	-10.353	15.753	0.685
Nauck 2007	11.880	2.243	21.517	0.016
Raz 2003	-26.200	-59.589	7.189	0.124
Raz 2005	-34.200	-54.240	-14.160	0.001
Ushakova 2007	-60.219	-65.472	-54.966	0.000
Raskin 2007	-66.048	-83.672	-48.424	0.000
Summary Estimate	**-32.785**	**-62.491**	**-3.079**	**0.031**
Without Nauck 2007				
Bebakar 2007	-58.860	-82.662	-35.058	0.000
Kvapil 2006	2.700	-10.353	15.753	0.685
Raz 2003	-26.200	-59.589	7.189	0.124
Raz 2005	-34.200	-54.240	-14.160	0.001
Ushakova 2007	-60.219	-65.472	-54.966	0.000
Raskin 2007	-66.048	-83.672	-48.424	0.000
Summary Estimate	**-40.716**	**-65.945**	**-15.488**	**0.002**



Boxes indicate individual study point estimates. Box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represent 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates 95 percent confidence interval for the random-effects pooled estimate.
Test for heterogeneity: Q = 221.126 with 6 degrees of freedom (p < 0.001)
I-squared statistic = 97 percent

Six of these seven studies also reported postprandial glucose after breakfast.[46,49,51,54,59,60] Insulin aspart 70/30 performed better than the comparator in four of these studies,[46,54,59,60] was equal to the comparator in one study,[51] and was inferior to the comparator in the sixth study.[49] Pooling the results of these studies pointed to a significant advantage of insulin aspart 70/30 in lowering postprandial glucose after breakfast (weighted mean difference = -24.5 mg/dL; 95

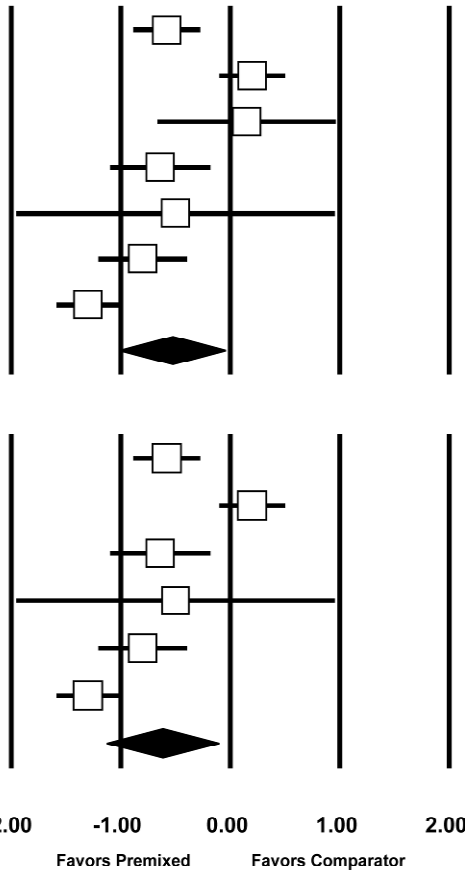
percent CI: -47.1 to -1.8 mg/dL; p = 0.03). When the study by Nauck et al.[49] was excluded from the meta-analysis, the postprandial glucose-lowering effect of insulin aspart 70/30 remained significant (mean difference = -32.0 mg/dL; 95 percent CI: -47.0 to -17.1 mg/dL; p < 0.001).

Hemoglobin A1c (see Appendix E, Evidence Table 4). Changes in A1c in response to treatment were also reported in all seven studies. Bebakar et al.[46] saw a significantly greater reduction in A1c with insulin aspart 70/30 than with oral antidiabetic agents (mean difference = -0.58 percent; p < 0.001). Similarly, Raz et al.[54] reported that HbAlc was significantly lower in the combined insulin aspart 70/30 and pioglitazone group than in the glibenclamide and pioglitazone group (mean change = -0.64 percent; p = 0.005). However, insulin aspart 70/30 alone lowered A1c to a similar extent as did glibenclamide and pioglitazone in this trial (p > 0.05). In another study, Raskin et al.[60] found that a combination of insulin aspart 70/30 plus metformin plus pioglitazone was more effective than metformin plus pioglitazone in lowering A1c (p < 0.001). On the other hand, Raz et al.[57] reported that a combination of insulin aspart 70/30 and rosiglitazone was not more effective than a combination of rosiglitazone and glibenclamide in lowering A1c (mean change = -0.5 percent; p > 0.05); however, this study had a duration of only 6 weeks, and it is quite possible that the A1c levels had not yet reached a steady state with the study medications. Therefore, this study was excluded from the pooled analyses. Somewhat similar results were reported by Kvapil et al.[51] who found that insulin aspart 70/30, whether alone or in combination with metformin, was not more effective than a combination of glibenclamide and metformin in lowering A1c (p > 0.05). Similarly, Ushakova et al.[59]also found that insulin aspart 70/30 alone or in combination with metformin was more effective than oral antidiabetic agents in lowering A1c levels (p < 0.001 for both comparisons). Nauck et al.[49] found that insulin aspart 70/30 was slightly worse than exenatide in lowering A1c although the difference was not statistically significant (mean difference = 0.15 percent; p = 0.07). When the results of all these studies were pooled, insulin aspart 70/30 was found to be more effective than noninsulin antidiabetic agents (weighted mean difference = -0.52 percent; 95 percent CI: -1.0 to -0.04 percent; p = 0.034; see Figure 16). When the study by Nauck et al.[49] was removed from the pooled analysis, the main conclusion of the meta-analysis did not change (weighted mean difference = -0.61 percent; 95 percent CI: -1.13 to - 0.1 percent; p = 0.02; see Figure 16).

Hypoglycemia (see Appendix E, Evidence Table 5). There were no major hypoglycemic events in five studies.[49,51,54,57,59] Bebakar et al.[46] reported one major hypoglycemic event in each arm, while Raskin et al.[60] reported all four major hypoglycemic events in the insulin aspart 70/30 arm. All seven studies reported the incidence of minor hypoglycemic events. Nauck et al.[49] reported the incidence of only nocturnal hypoglycemia, which was significantly lower in the exenatide group (p = 0.038). In all other studies, insulin aspart 70/30 was associated with a greater risk of minor hypoglycemia, reaching statistical significance in three studies.[46,54,60] When the results of these studies were pooled, insulin aspart 70/30 was associated with a higher risk of minor hypoglycemia when compared to noninsulin antidiabetic agents (217 out of 762 patients versus 79 out of 672 patients; OR = 3.8; 95 percent CI: 1.7 to 8.5; p = 0.001; see Figure 17). When the study by Nauck et al.[49] was excluded from the analysis, the results did not change appreciably (155 out of 539 patients versus 35 out of 473 patients; OR = 4.9; 95 percent CI: 1.8 to 13.5; p = 0.002; see Figure 17). Four studies reported the incidence of symptom-only hypoglycemia.[51,54,57,59] Pooling the results of these studies also indicated that insulin aspart 70/30 was associated with a higher risk of symptom-only hypoglycemia than were the noninsulin antidiabetic agents (97 out of 332 patients versus 41 out of 332 patients; OR = 3.9; 95 percent CI: 1.2 to 12.4; p = 0.02; see Figure 18).

Figure 16. Meta-analyses of post-treatment differences in hemoglobin A1c (%) between insulin aspart 70/30 and noninsulin antidiabetic agents

Study name	Statistics for each study			
	Difference in means	Lower limit	Upper limit	p-Value
Bebakar 2007	-0.58	-0.88	-0.28	0.0001
Kvapil 2006	0.20	-0.09	0.49	0.1824
Nauck 2007	0.15	-0.66	0.96	0.7156
Raz 2005	-0.64	-1.09	-0.19	0.0054
Raz 2003	-0.50	-1.95	0.95	0.4984
Ushakova 2007	-0.80	-1.20	-0.40	0.0001
Raskin 2007	-1.30	-1.58	-1.02	0.0000
Summary Estimate	**-0.52**	**-1.01**	**-0.04**	**0.0339**
Without Nauck 2007				
Bebakar 2007	-0.58	-0.88	-0.28	0.0001
Kvapil 2006	0.20	-0.09	0.49	0.1824
Raz 2005	-0.64	-1.09	-0.19	0.0054
Raz 2003	-0.50	-1.95	0.95	0.4984
Ushakova 2007	-0.80	-1.20	-0.40	0.0001
Raskin 2007	-1.30	-1.58	-1.02	0.0000
Summary Estimate	**-0.61**	**-1.13**	**-0.10**	**0.0194**



Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.
Test for heterogeneity: Q = 56.945 with 6 degrees of freedom ($p < 0.001$)
I-squared statistic = 89 percent

Weight change (see Appendix E, Evidence Table 6). All seven studies reported on change in weight, but the data were not sufficiently reported in two studies to be usable in pooling the study results.[54,57] In the five other studies, insulin aspart 70/30 was found to be associated with weight gain when compared to noninsulin antidiabetic agents (weighted mean difference = 2.8 kg; 95 percent CI: 0.6 to 5.0 kg; p = 0.01; see Figure 19).

Other serious adverse events (see Appendix E, Evidence Table 6). None of these studies comparing insulin aspart 70/30 to a noninsulin antidiabetic agent reported on injection site reactions. Table 5 shows the range of risk differences between insulin aspart 70/30 and noninsulin antidiabetic agents in terms of total serious adverse events, other serious adverse events, and withdrawals due to adverse events.

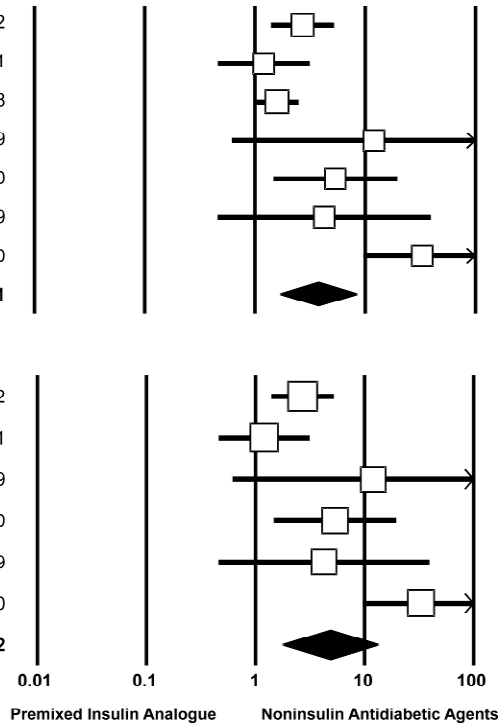
Insulin aspart 70/30 versus other premixed insulin analogues. We found two crossover studies that compared insulin aspart 70/30 to insulin lispro 75/25.[55,58]

Figure 17. Meta-analyses of differences in the incidence of mild hypoglycemia between insulin aspart 70/30 and noninsulin antidiabetic agents

Study name	Odds ratio	Lower limit	Upper limit	p-Value
Bebakar 2007	2.708	1.427	5.139	0.002
Kvapil 2006	1.203	0.469	3.085	0.701
Nauck 2007	1.583	1.026	2.444	0.038
Raz 2003	12.023	0.627	230.535	0.099
Raz 2005	5.366	1.499	19.214	0.010
Ushakova 2007	4.250	0.467	38.701	0.199
Raskin 2007	32.933	9.790	110.785	0.000
Summary Estimate	**3.790**	**1.695**	**8.474**	**0.001**

Without Nauck 2007

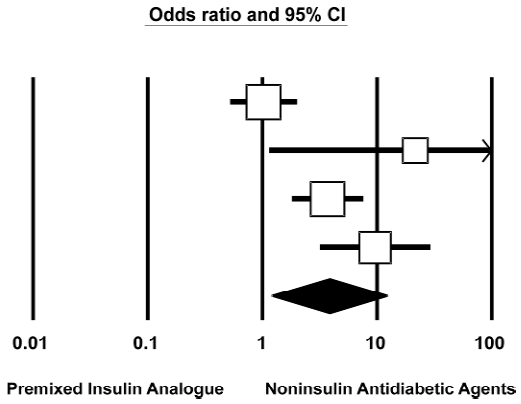
Bebakar 2007	2.708	1.427	5.139	0.002
Kvapil 2006	1.203	0.469	3.085	0.701
Raz 2003	12.023	0.627	230.535	0.099
Raz 2005	5.366	1.499	19.214	0.010
Ushakova 2007	4.250	0.467	38.701	0.199
Raskin 2007	32.933	9.790	110.785	0.000
Summary Estimate	**4.894**	**1.770**	**13.532**	**0.002**



Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.
Test for heterogeneity: Q = 26.562 with 6 degrees of freedom ($p < 0.001$)
I-squared statistic = 77 percent

Figure 18. Meta-analyses of differences in the incidence of symptom-only hypoglycemia between insulin aspart 70/30 and noninsulin antidiabetic agents

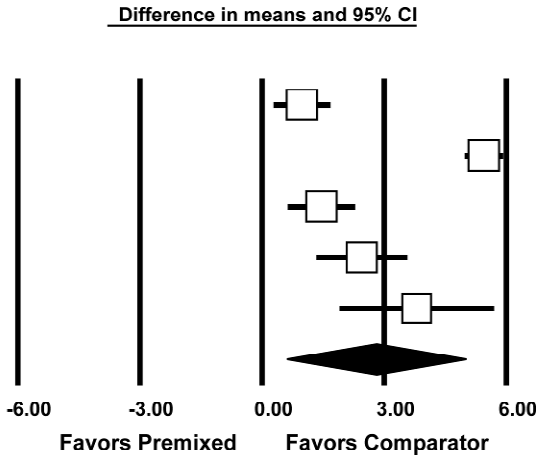
Study name	Odds ratio	Lower limit	Upper limit	p-Value
Kvapil 2006	1.024	0.532	1.971	0.943
Raz 2003	21.595	1.169	398.992	0.039
Raz 2005	3.698	1.838	7.442	0.000
Ushakova 2007	9.625	3.234	28.649	0.000
Summary Estimate	**3.873**	**1.205**	**12.447**	**0.023**



Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.
Test for heterogeneity: Q = 16.296 with 3 degrees of freedom ($p = 0.001$)
I-squared statistic = 82 percent

Figure 19. Meta-analyses of post-treatment differences in weight change (kg) between insulin aspart 70/30 and noninsulin antidiabetic agents

Study name	Statistics for each study: Difference in means	Lower limit	Upper limit	p-Value
Bebakar 2007	0.980	0.302	1.658	0.005
Nauck 2007	5.450	5.001	5.899	0.000
Kvapil 2006	1.460	0.656	2.264	0.000
Ushakova 2007	2.450	1.354	3.546	0.000
Raskin 2007	3.800	1.924	5.676	0.000
Summary Estimate	**2.816**	**0.613**	**5.019**	**0.012**



Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.
Test for heterogeneity: Q = 153.9 with 4 degrees of freedom ($p < 0.001$)
I-squared statistic = 97 percent

Niskanen et al.[55] compared twice-daily insulin aspart 70/30 to twice-daily insulin lispro 75/25 in a crossover study. This study was funded by Novo Nordisk, the manufacturer of insulin aspart 70/30. In both arms, the insulin dose was titrated to obtain optimal blood glucose control. The mean insulin dose was similar for each study drug.

Hermansen et al.[58] compared a single dose of insulin aspart 70/30 to a single dose of insulin lispro 75/25 after a test meal in a crossover study. This study was also funded by Novo Nordisk. In this study, a similar dose of insulin, based on the weight of the patients, was given. As this study was a single-dose study, it was not designed to evaluate either fasting glucose or A1c. In addition, this study reported postprandial glucose excursions only.

Fasting glucose (see Appendix E, Evidence Table 4). Niskanen et al.[55] did not find a significant difference between the two premixed insulin analogues in terms of lowering fasting glucose levels after breakfast ($p = 0.42$).

Postprandial glucose (see Appendix E, Evidence Table 4). Niskanen et al.[55] also did not find a significant difference between the two premixed insulin analogues with regard to lowering 90-min breakfast or dinner postprandial glucose levels ($p = 0.52$ and 0.19, respectively).

Hemoglobin A1c (see Appendix E, Evidence Table 4). Although insulin aspart 70/30 appeared to be less effective than insulin lispro 75/25 in lowering A1c, the difference was not statistically significant (mean difference = 0.14 percent, $p = 0.08$) in the only study that reported this outcome.[55]

Hypoglycemia (see Appendix E, Evidence Table 5). One major hypoglycemic event occurred with each premixed insulin analogue in the trial by Niskanen et al.[55] In Hermansen et al.,[58] there were two major hypoglycemia episodes with insulin aspart 70/30 and five episodes with insulin lispro 75/25. Niskanen et al. reported that 57 out of 132 patients had minor hypoglycemic events with insulin aspart 70/30, as compared to 53 out of 132 patients with insulin lispro 75/25.[55]

Weight change (see Appendix E, Evidence Table 6). Since both studies were crossover studies, treatment-induced changes in weight were not abstracted.

Other serious adverse events (see Appendix E, Evidence Table 6). Niskanen et al.[55] reported

that 1 percent of those in the insulin aspart 70/30 arm and 2 percent in the insulin lispro 75/25 arm experienced injection site reactions. Table 5 shows the range of risk differences between insulin aspart 70/30 and insulin lispro 75/25 for other serious adverse events and withdrawals due to adverse events.

Insulin Lispro 75/25

Insulin lispro 75/25 versus long-acting insulin analogues. We identified five randomized crossover trials[63-66,74] and one observational study[75] that compared insulin lispro 75/25 to a long-acting insulin analogue. Insulin glargine was the comparator agent in all these trials.

Roach et al.[63] compared twice-daily insulin lispro 75/25 plus oral antidiabetic agents to once-daily insulin glargine plus oral antidiabetic agents in a 24-week crossover trial. The insulin dose was allowed to be titrated throughout the study to optimize glucose control. The mean daily dose of insulin lispro 75/25 was larger than the mean daily dose of insulin glargine (60 versus 44 units, respectively). The doses of the oral antidiabetic agents were not reported.

Jacober et al.[64] compared insulin lispro 50/50 before breakfast and lunch plus insulin lispro 75/25 before dinner to once-daily insulin glargine in a crossover trial. The mean insulin dose at the end of therapy was greater for premixed insulin lispro than for insulin glargine ($p = 0.01$).

Malone et al.[65] compared twice-daily insulin lispro 75/25 plus metformin to once-daily insulin glargine plus metformin in a crossover study. In this study, the metformin dose was kept fixed, but the insulin doses were adjusted to optimize glucose control. At the end of the study, the mean daily insulin dose was larger with insulin lispro 75/25, as compared to insulin glargine (0.62 versus 0.57 units/kg; $p < 0.001$).

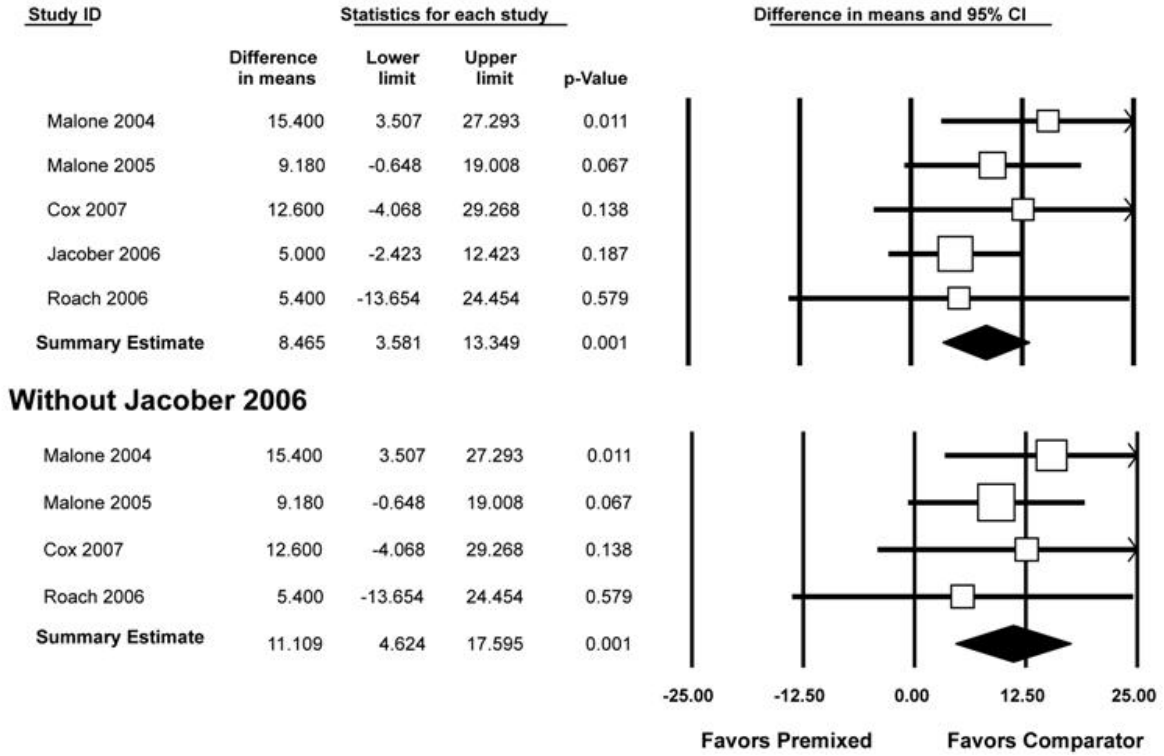
With a similar study design but in a different population, Malone et al.[66] compared twice-daily insulin lispro 75/25 plus metformin to once-daily insulin glargine plus metformin. The metformin dose was similar at the end of treatment; however, as in previous studies the insulin lispro 75/25 dose was significantly larger than the insulin glargine dose (0.42 versus 0.36 units/kg; $p < 0.001$).

Cox et al.[74] compared twice-daily insulin lispro 75/25 with once-daily insulin glargine in poorly controlled type 2 diabetics. Oral antidiabetic agents were discontinued during the study. The doses of both insulin analogues were allowed to be titrated to optimize blood glucose control; however, this study did not report the insulin dose used by each treatment group.

Sun et al.[75] performed a retrospective study by abstracting data on insulin naïve patients with type 2 diabetes from a U.S. national medical records database.

Fasting glucose (see Appendix E, Evidence Table 4). All five randomized trials reported fasting glucose levels. One study by Jacober et al.[64] used insulin lispro 50/50 with breakfast and lunch and insulin lispro 75/25 with dinner. Because the fasting glucose level was likely to have been affected by the evening insulin injection, we included this trial in the current comparison. In all studies, insulin glargine was more effective than insulin lispro 75/25 in lowering fasting glucose, but the difference was significant in only one study.[65] When these study results were pooled, insulin glargine was more effective than insulin lispro 75/25 in lowering fasting glucose levels (mean difference = 8.5 mg/dL; 95 percent CI: 3.6 to 13.3 mg/dL; $p = 0.001$; see Figure 20). Excluding the study by Jacober et al.[64] had no effect on the results of this meta-analysis (weighted mean difference = 11.1 mg/dL; 95 percent CI: 4.6 to 17.6 mg/dL; $p = 0.001$; see Figure 20). We also identified an unpublished trial which found insulin glargine to be more effective than insulin lispro 75/25, but the difference was not statistically significant.[82]

Figure 20. Meta-analyses of post-treatment differences in fasting glucose (mg/dL) between insulin lispro 75/25 and long-acting insulin analogues (with and without Jacober et al. 2006)

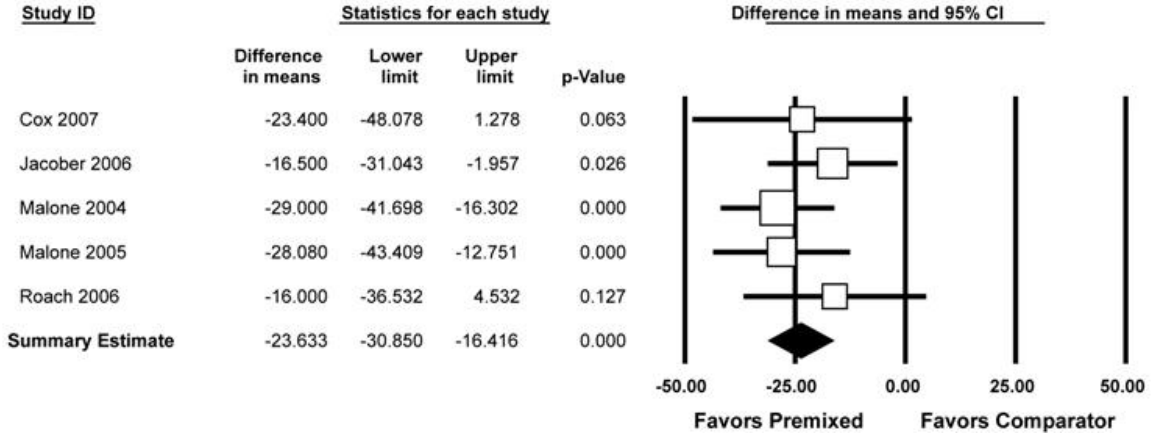


Boxes indcate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.
Test for heterogeneity: Q = 2.499 with 4 degrees of freedom (p = 0.645)
I-squared statistic = 0 percent

Although all five trials reported pre-dinner glucose levels, the study by Jacober et al.[64] was excluded for the reason stated above. The remaining four trials did not find any difference between insulin lispro 75/25 and insulin glargine in terms of lowering pre-dinner glucose levels.[63,65,66,74]

Postprandial glucose (see Appendix E, Evidence Table 4). All randomized trials reported on both dinner and breakfast postprandial glucose levels.[63-66,74] However, as noted above, the trial by Jacober et al.[64] used insulin lispro 50/50 with breakfast and lunch and insulin lispro 75/25 with dinner. For this trial, only dinner postprandial blood glucose values were used for the meta-analysis. Insulin lispro 75/25 was more effective than insulin glargine in lowering dinner postprandial glucose levels in all studies. In two of the four trials, insulin lispro 75/25 was also more effective in lowering breakfast postprandial levels.[65,66] Pooling of the studies identified a significant advantage for insulin lispro 75/25 in lowering dinner postprandial glucose (mean difference = -23.6 mg/dL; 95 percent CI: -30.9 to -16.4 mg/dL; $p < 0.001$; see Figure 21) and a nonsignificant advantage in lowering breakfast postprandial glucose (weighted mean difference = -10.0 mg/dL; 95 percent CI: -23.3 to 3.2 mg/dL; $p = 0.137$). We identified one unpublished trial[82] that found a significant decrease in dinner postprandial glucose with insulin lispro 75/25 but no change in breakfast postprandial glucose levels ($p = 0.04$ and 0.97 respectively).

Figure 21. Meta-analyses of post-treatment differences in postprandial glucose (mg/dL) between insulin lispro 75/25 and long-acting insulin analogues



Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.
Test for heterogeneity: Q = 2.465 with 4 degrees of freedom (p =0.651)
I-squared statistic = 0 percent

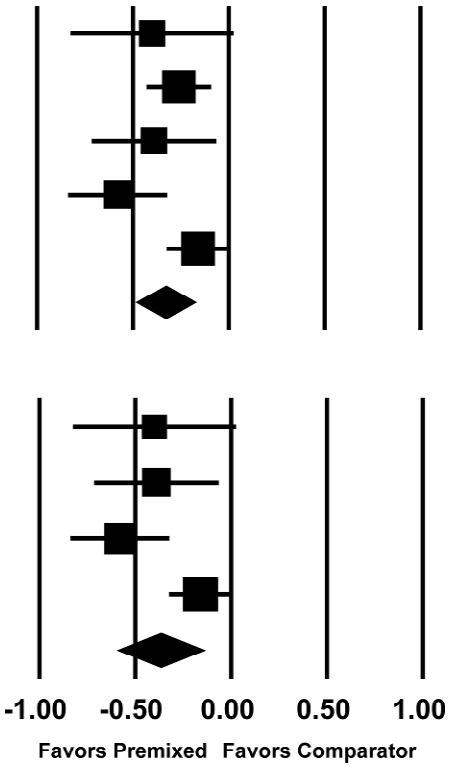
Hemoglobin A1c (see Appendix E, Evidence Table 4). Of the six studies that compared insulin lispro 75/25 to long-acting insulin analogues, five trials reported on the changes in A1c.[63-66,75] As noted above, Jacober et al.[64] administered insulin lispro 50/50 with breakfast and lunch and insulin lispro 75/25 with dinner; therefore, the change in A1c in this study is a reflection of both strengths of insulin. This study found that the premixed insulin lispro based regimen was more effective than insulin glargine in lowering A1c (mean difference = -0.26 percent; p = 0.003). However, there was no significant difference in the percentage of patients who achieved the target A1c of less than or equal to 7 percent (44 versus 31 percent respectively; p = 0.1). On the other hand, in a study by Malone et al.[65] insulin lispro 75/25 was not only able to lower A1c more effectively than was insulin glargine (mean difference = -0.4 percent; p = 0.002), but more patients achieved the target A1c of less than or equal to 7 percent (42 versus 18 percent; p < 0.001). In another study, Malone et al.[66] found a combination of insulin lispro 75/25 and metformin to be more effective than a combination of insulin glargine and metformin in lowering A1c (mean difference = -0.60 percent; p < 0.001). Similar results were obtained by Roach et al.:[63] They found that insulin lispro 75/25 was more effective than insulin glargine in lowering A1c (mean difference = -0.4 percent; p < 0.05). In the retrospective review of medical records, Sun et al.[75] found a significantly larger reduction in A1c with insulin lispro 75/25 than with glargine (-0.10 percent, p < 0.05). When the results of the five trials were pooled, insulin lispro 75/25 was significantly more effective than insulin glargine in lowering A1c (mean difference = -0.33 percent; 95 percent CI: -0.48 to -0.17 percent; p < 0.01; see Figure 22). When the study by Jacober et al.[64] was excluded, there was no change in the results of the meta-analysis (mean difference = -0.36 percent; 95 percent CI: -0.59 to -0.14 percent; p < 0.01; see Figure 22).

Hypoglycemia (see Appendix E, Evidence Table 5). The incidence of all hypoglycemia was reported for three trials.[64-66] Malone et al.[66] found an equal rate of all hypoglycemia with both types of insulins (0.61 versus 0.44 episodes/patient/30 days; p = 0.4). On the other hand, Jacober et al.[64] and Malone et al.[65] found a significantly greater incidence of overall hypoglycemia with insulin lispro than with insulin glargine (48 out of 58 versus 33 out of 54 patients and 57 out of 100 versus 40 out of 101 patients respectively). As Jacober et al.[64] used two different insulin

lispro preparations, it was not possible to identify the hypoglycemic events that were due solely to insulin lispro 75/25. Minor hypoglycemia was reported in two studies.[63,64] In these studies, insulin lispro was associated with a higher risk of minor hypoglycemia, but the difference was statistically significant only in the study by Jacober et al.[64] Cox et al.[74] only reported that there was no difference in the incidence of hypoglycemia in the two groups (data not reported).

Figure 22. Meta-analyses of post-treatment differences in hemoglobin A1c between insulin lispro 75/25 and long-acting insulin analogues

Study name	Statistics for each study: Difference in means	Lower limit	Upper limit	p-Value
Roach 2006	-0.40	-0.82	0.02	0.06
Jacober 2006	-0.26	-0.42	-0.10	0.00
Malone 2004	-0.39	-0.71	-0.07	0.02
Malone 2005	-0.58	-0.83	-0.33	0.00
Sun 2007	-0.16	-0.32	-0.00	0.05
Summary Estimate	**-0.33**	**-0.48**	**-0.17**	**0.00**
Without Jacober 2006				
Roach 2006	-0.40	-0.82	0.02	0.06
Malone 2004	-0.39	-0.71	-0.07	0.02
Malone 2005	-0.58	-0.83	-0.33	0.00
Sun 2007	-0.16	-0.32	-0.00	0.05
Summary Estimate	**-0.36**	**-0.59**	**-0.14**	**0.00**



Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.
Test for heterogeneity: Q = 8.108 with 3 degrees of freedom (p = 0.044)
I-squared statistic = 63 percent

Weight change (see Appendix E, Evidence Table 6). Since all these studies were crossover studies, treatment-induced changes in weight were not abstracted.

Other serious adverse events (see Appendix E, Evidence Table 6). None of these studies reported on injection site skin reactions. Table 6 shows the range of risk differences between insulin lispro 75/25 and long-acting insulin analogues with regard to withdrawals due to adverse events.

Insulin lispro 75/25 versus rapid-acting insulin analogues. We did not find any study that had compared insulin lispro 75/25 to rapid-acting insulin analogues.

Table 6. Range of risk differences between insulin lispro 75/25 and other antidiabetic agents for selected adverse events

	Total serious adverse events		Withdrawn due to adverse events		Other serious adverse events	
Comparison	**Number of studies included**	**Range of risk difference* between insulin lispro 75/25 and comparison**	**Number of studies included**	**Range of risk difference* between insulin lispro 75/25 and comparison**	**Number of studies included**	**Range of risk difference* between insulin lispro 75/25 and comparison**
Long-acting insulin analogues	0	NA	5[63-66,74]	-0.01 – 0.03	2[65,66]	0 – 0.03
Rapid-acting insulin analogues	0	NA	0	NA	0	NA
Rapid-acting with long-acting insulin analogues	0	NA	0	NA	0	NA
Premixed human insulins	1[62]	0	8[12,44,58,62,67,70,71,73]	0	2[58,67]	-0.01 – 0
Intermediate-acting human insulins	0	NA	0	NA	0	NA
Oral antidiabetic agents	0	NA	2[68,72]	-0.01 – 0.02	1**[72]	0.01
Exenatide	0	NA	0	NA	0	NA
Insulin lispro 50/50	1[62]	0	1[62]	0	0	NA

* The risk difference is the proportion having an event in the treatment group minus the proportion having an event in the comparison group. Negative risk differences suggest a protective effect of the treatment, while positive risk differences suggest a harmful effect of the treatment.

** An additional study reported 7 events in the insulin lispro 75/25 arm and 5 events in the oral antidiabetic agents arm.[68]

NA = not applicable

Insulin lispro 75/25 versus a combination of long-acting and rapid-acting insulin analogues. Our search did not find any study that had compared insulin lispro 75/25 to a combination of rapid-acting and long-acting insulin analogues.

Insulin lispro 75/25 versus premixed human insulin. We found nine randomized crossover studies[10,12,44,58,62,67,70,71,73] and one retrospective observational study[75] that compared insulin lispro 75/25 to premixed human insulin preparations. Four studies were one-dose studies and therefore had only one breakfast postprandial value after a test meal.[44,58,62,67] All the studies, except the study by Roach et al.,[10] compared insulin lispro 75/25 to NPH/regular 70/30.

In the study by Roach et al.,[10] patients were randomized to insulin lispro 50/50 before breakfast plus insulin lispro 75/25 before dinner or NPH/regular 50/50 before breakfast plus NPH/regular 70/30 before dinner. This study enrolled both type 1 and type 2 diabetics but reported results for each type of diabetes separately. The doses of all insulin preparations were adjusted to optimize glucose control, and there was no difference in the mean insulin dose at the end of the study.

Mattoo et al.[70] compared twice-daily insulin lispro 75/25 to twice-daily NPH/regular 70/30 in type 2 diabetics who were fasting during the month of Ramadan. Whether the insulin doses were titrated or not was not reported.

In another study, Roach et al.[73] compared twice-daily insulin lispro 75/25 to twice-daily NPH/regular 70/30 in patients with type 2 diabetes. Patients who were taking oral antidiabetic agents were excluded from the study. The insulin dose was titrated to optimize glucose control, and at the end of the study the mean daily insulin doses were similar for both treatment sequences.

Herz et al.[12] compared the effect of insulin lispro 75/25 to that of NPH/regular 70/30 on the 24-h inpatient plasma glucose profile. Insulin doses were adjusted during the trial, and there was no difference in the mean daily insulin dose between the two treatments.

In another study, Herz et al.[71] compared the plasma glucose response with insulin lispro 75/25 to that of a premixed human insulin before and after exercise. The insulin dose was similar in both treatment sequences.

In a three-arm crossover trial, Schwartz et al.[62] compared one dose of insulin lispro 75/25 to one dose of NPH/regular 70/30 before a test meal. Patients were given an insulin dose that was comparable to their regular daily dose.

In another three-arm, crossover trial, Hermansen et al.[58] compared a single dose of insulin lispro 75/25 to a single dose of NPH/regular 70/30 before a test meal. All patients received a fixed dose of insulin based on their body weight.

Coscelli et al.[67] compared twice-daily insulin lispro 75/25 to NPH/regular 70/30 in diabetic patients with Italian dietary habits. However, they evaluated changes in blood glucose after a test meal. The mean daily insulin dose was similar in the two treatment groups.

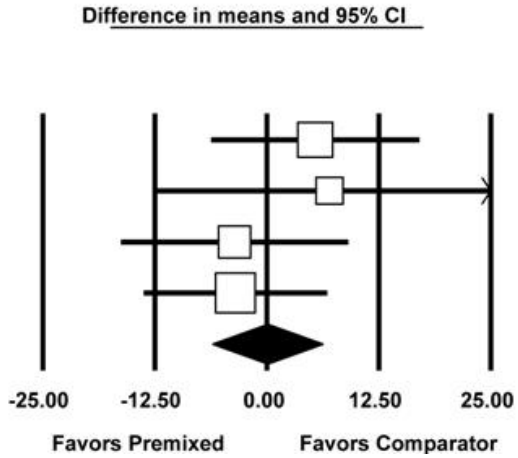
Malone et al.[44] compared a single dose of insulin lispro 75/25 to a single dose of a premixed human insulin before a test meal. Oral antidiabetic agents were discontinued for this study. All study participants received a fixed dose of insulin based on their body weight.

Fasting glucose (see Appendix E, Evidence Table 4). We identified four studies that reported on fasting blood glucose.[10,12,70,73] All four studies were randomized crossover trials and compared insulin lispro 75/25 to NPH/regular 70/30, except for the study by Roach et al.,[10] in which subjects were given NPH/regular 50/50 before breakfast and NPH/regular 70/30 before dinner. As noted above, insulin lispro 50/50 was given before breakfast and insulin lispro 75/25 was given before dinner in this study. Since the fasting glucose levels are likely to be affected by

dinner-time insulin, this study was included in this subsection. All four studies found a decrease in fasting glucose with insulin lispro 75/25, but the decrease was not statistically significant. One study[12] did not report numerical values for the fasting glucose levels and therefore could not be included in meta-analysis. When the results of these studies were pooled, there was no difference between the two treatments in terms of lowering fasting glucose (weighted mean difference = 0.12 mg/dL; 95 percent CI: -6.05 to 6.29 mg/dL; p = 0.97; see Figure 23).

Figure 23. Meta-analyses of post-treatment differences in fasting glucose (mg/dL) between insulin lispro 75/25 and premixed human insulin

Study name	Statistics for each study			
	Difference in means	Lower limit	Upper limit	p-Value
Malone 2000	5.400	-6.138	16.938	0.359
Schwartz 2006	7.000	-12.110	26.110	0.473
Mattoo 2003	-3.600	-16.193	8.993	0.575
Roach 1999b	-3.500	-13.647	6.647	0.499
Summary Estimate	0.116	-6.054	6.286	0.971



Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.
Test for heterogeneity: Q = 2.126 with 3 degrees of freedom (p = 0.547)
I-squared statistic = 0 percent

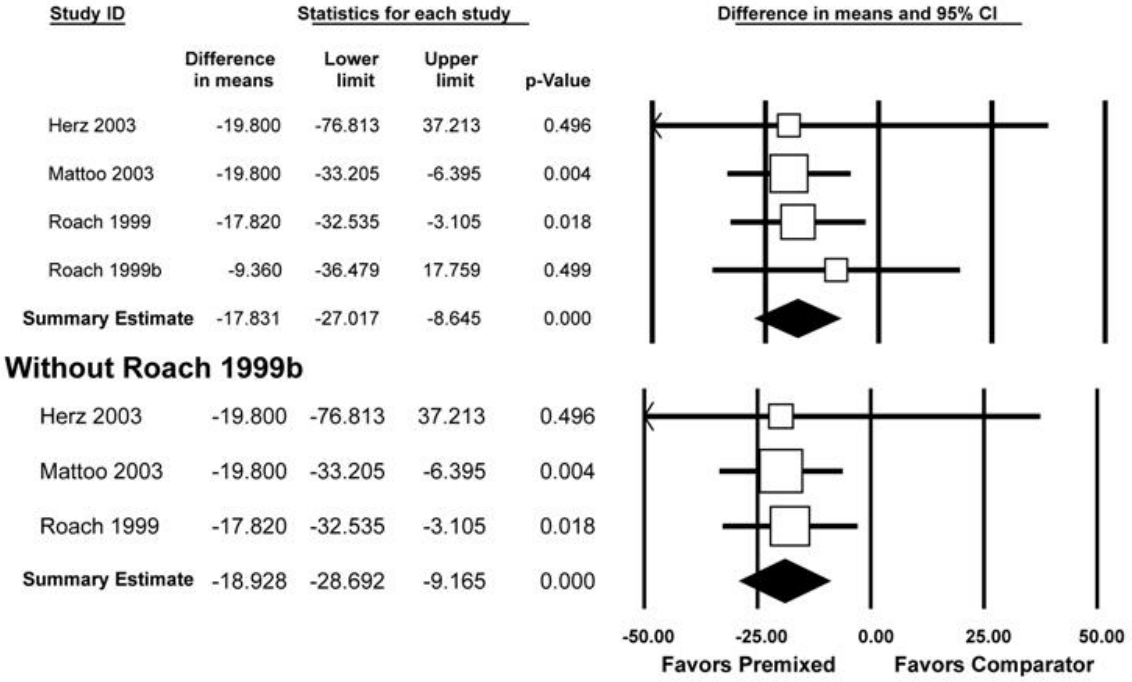
Three studies reported pre-dinner blood glucose levels.[12,70,73] Of the three studies, one[70] found insulin lispro 75/25 to be more effective than the premixed human insulin (mean difference = -7.2 mg/dL; p = 0.34). One study only mentioned that there was no difference in pre-dinner glucose between the two treatments during inpatient monitoring of the patients,[12] and the second study reported pre-dinner glucose as a figure with a large overlap between the standard error of the mean error bars.[73]

Postprandial glucose (see Appendix E, Evidence Table 4). Four studies reported treatment-related changes in dinner postprandial glucose levels.[10,12,70,73] As noted above, we used the data from Roach et al.[10] only for dinner postprandial values. Insulin lispro 75/25 lowered the dinner postprandial blood glucose in all studies, but the decrease was statistically significant in only two of the four studies.[70,73] When we pooled the study results, insulin lispro 75/25 was more effective than the premixed human insulin in lowering dinner postprandial glucose (mean difference = -17.8 mg/dL; 95 percent CI: -27.0 to -8.6 mg/dL; p < 0.001; see Figure 24). When we excluded the study by Roach et al.,[10] the pooled result remained significant (weighted mean difference = -18.9 mg/dL; 95 percent CI: -28.7 to -9.2 mg/dL; p < 0.001; see Figure 24).

Breakfast postprandial glucose levels were reported in eight studies.[12,44,58,62,67,70,71,73] As noted above, in four of these studies, one dose of the study drugs was given with a test meal.[44,58,62,67] All studies found insulin lispro 75/25 to be more effective than the premixed human insulin in lowering breakfast postprandial glucose levels, but the difference was statistically significant in only three of the eight studies.[67,71,73] In the pooled analysis, insulin lispro 75/25 was more effective than premixed human insulin in lowering breakfast postprandial

glucose levels (weighted mean difference = -14.9 mg/dL; 95 percent CI: -21.4 to -8.4 mg/dL; p < 0.001).

Figure 24. Meta-analyses of post-treatment differences in postprandial glucose (mg/dL) between insulin lispro 75/25 and premixed human insulin preparations



Boxes indcate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.
Test for heterogeneity: Q = 0.462 with 3 degrees of freedom (p =0.927)
I-squared statistic = 0 percent

Hemoglobin A1c (see Appendix E, Evidence Table 4). Three of nine studies reported changes in A1c levels.[10,73,75] Roach et al.[73] did not find any significant difference between insulin lispro 75/25 and the premixed human insulin in terms of decreasing A1c levels after 6 months of followup (mean difference = 0.2 percent; p = 0.41). Similar results were reported in the second study by Roach et al.,[10] which used two different insulin lispro preparations (insulin lispro 75/25 and insulin lispro 50/50) and did not find any difference between the two treatment regimens in terms of lowering A1c levels (mean difference = 0.07 percent; p = 0.37). The retrospective chart review found insulin lispro 75/25 to be more effective than premixed human insulin in lowering A1c (-0.12 percent; statistical significance not reported), but it did not provide enough data for a meta-analysis.

Hypoglycemia (see Appendix E, Evidence Table 5). Schwartz et al.[62] reported one episode of minor hypoglycemia in which a patient received a premixed human insulin before the test meal but received insulin lispro at lunch, making it difficult to attribute this event to a premixed formulation. Roach et al.[73] did not find a difference in the incidence of all hypoglycemia between insulin lispro 75/25 and a premixed human insulin (42 versus 35 percent respectively; p = 0.4). Similarly, Herz et al.[12] and Mattoo et al.[70] also reported a similar hypoglycemia rate for the two treatment regimens (p = 0.59 and 0.72, respectively). Hermansen et al.[58] reported fewer hypoglycemic events with a premixed human insulin than with insulin lispro 75/25 (11 versus 19 events among 44 and 42 patients, respectively), although they did not report whether the

difference was significant. Malone et al.[44] reported that the distribution of hypoglycemic episodes was similar for the two premixed insulin preparations. Coscelli et al.[67] reported a total of 11 hypoglycemic episodes during the study, but the difference between the two treatments was not statistically significant.

Weight change (see Appendix E, Evidence Table 6). Since all these studies were crossover studies, treatment-induced changes in weight were not abstracted.

Other serious adverse events (see Appendix E, Evidence Table 6). In the study by Schwartz et al.,[62] one patient (5 percent) in the insulin lispro 75/25 arm, but none in the NPH/regular 70/30 arm, experienced an injection site reaction. Table 6 shows the range of risk differences between insulin lispro 75/25 and premixed human insulins in terms of total serious adverse events, withdrawals due to adverse events, and other serious adverse events.

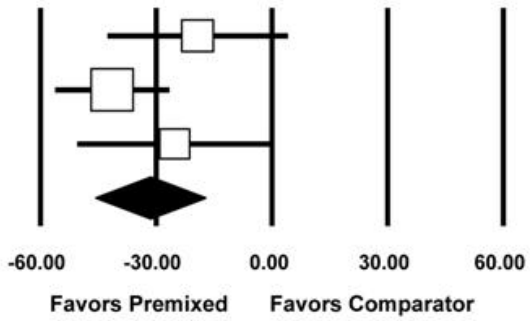
Insulin lispro 75/25 versus intermediate-acting human insulin. We did not find any study that compared insulin lispro 75/25 to an intermediate-acting human insulin.

Insulin lispro 75/25 versus noninsulin antidiabetic agents. We found three randomized parallel-arm studies that compared insulin lispro 75/25 to noninsulin antidiabetic agents.[43,68,72] Tirgoviste et al.[43] compared insulin lispro 75/25 to a fixed dose of glibenclamide. Malone et al.[68] compared a combination of insulin lispro 75/25 and metformin to a combination of glibenclamide and metformin. Herz et al.[72] compared insulin lispro 75/25 to a fixed dose of glyburide. All trials were 16 weeks in duration and reported on all intermediate outcomes. The insulin lispro 75/25 dose was titrated in order to optimize glucose control. Oral antidiabetic agents' doses were adjusted to optimize glucose control in only one study.[68]

Fasting glucose (see Appendix E, Evidence Table 4). In terms of fasting glucose, all three trials individually found insulin lispro 75/25 to be more effective than noninsulin antidiabetic agents in lowering fasting glucose, but this difference was not significant in one study.[68] Pooling the results of all three studies indicated that insulin lispro 75/25 was more effective than noninsulin antidiabetic agents in lowering fasting glucose levels (weighted mean difference = -31.4 mg/dL; 95 percent CI: -45.7 to -17.1 mg/dL; $p < 0.001$; see Figure 25).

Figure 25. Meta-analyses of post-treatment differences in fasting glucose (mg/dL) between insulin lispro 75/25 and noninsulin antidiabetic agents

Study name	Statistics for each study			
	Difference in means	Lower limit	Upper limit	p-Value
Malone 2003	-19.260	-42.433	3.913	0.103
Herz 2002	-41.400	-55.997	-26.803	0.000
Tirgoviste 2003	-25.200	-50.222	-0.178	0.048
Summary Estimate	-31.388	-45.690	-17.085	0.000



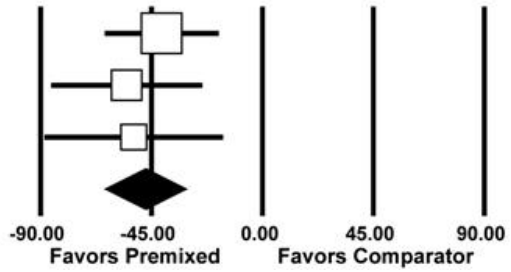
Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.
Test for heterogeneity: Q = 2.995 with 2 degrees of freedom (p = 0.224)
I-squared statistic = 33 percent

Insulin lispro 75/25 was also significantly more effective in reducing pre-dinner glucose levels in all three studies. When the results of these studies were pooled, insulin lispro 75/25 remained more effective than noninsulin antidiabetic agents in terms of lowering pre-dinner glucose levels (weighted mean difference = -25.0 mg/dL; 95 percent CI: -37.0 to -13.1 mg/dL; p < 0.001).

Postprandial glucose (see Appendix E, Evidence Table 4). With regard to postprandial glucose levels, insulin lispro 75/25 was more effective than oral antidiabetic agents in all three trials. When the results of these studies were pooled, insulin lispro 75/25 remained more effective than its comparator in lowering postprandial glucose levels after dinner (weighted mean difference = -47.3 mg/dL; 95 percent CI: -63.5 to -31.0 mg/dL; p < 0.001; see Figure 26) and after breakfast (weighted mean difference = -54.2 mg/dL; 95 percent CI: -70.7 to -37.7 mg/dL; p < 0.001).

Figure 26. Meta-analyses of post-treatment differences in postprandial glucose (mg/dL) between insulin lispro 75/25 and noninsulin antidiabetic agents

Study name	Statistics for each study			
	Difference in means	Lower limit	Upper limit	p-Value
Herz 2002b	-40.860	-63.663	-18.057	0.000
Malone 2003	-55.080	-85.386	-24.774	0.000
Tirgoviste 2003	-52.200	-88.034	-16.366	0.004
Summary Estimate	-47.274	-63.516	-31.032	0.000

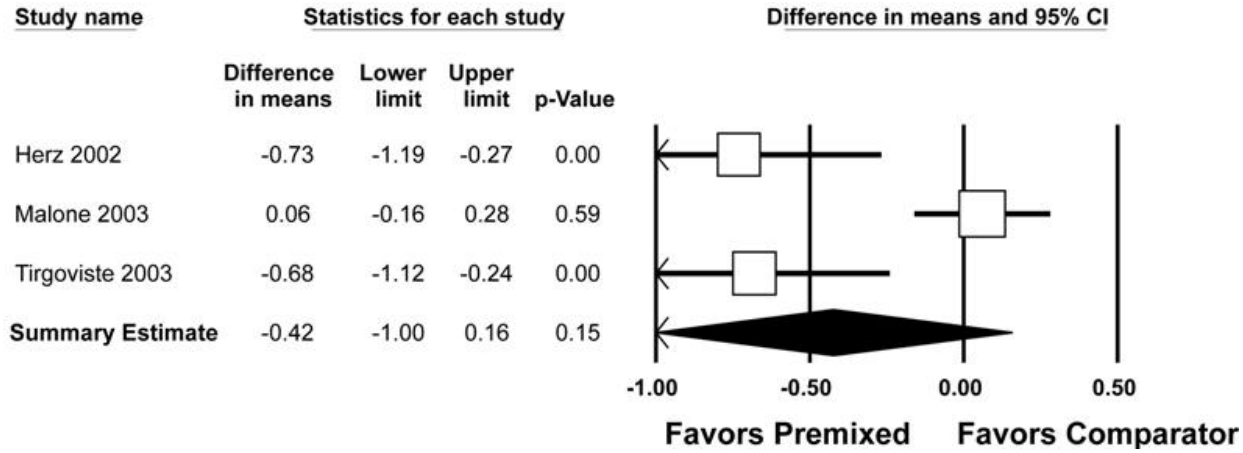


Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.
Test for heterogeneity: Q = 0.631 with 2 degrees of freedom (p =0.729)
I-squared statistic = 0 percent

Hemoglobin A1c (see Appendix E, Evidence Table 4). In two trials,[43,72] insulin lispro 75/25 was more effective than noninsulin antidiabetic agents in lowering A1c, but the difference was not statistically significant in the third trial.[68] Pooling the study results indicated that insulin lispro 75/25 was not significantly more effective than oral antidiabetic agents in lowering A1c levels (weighted mean difference = -0.42 percent; 95 percent CI: -1.00 to 0.16 percent; p = 0.15; see Figure 27).

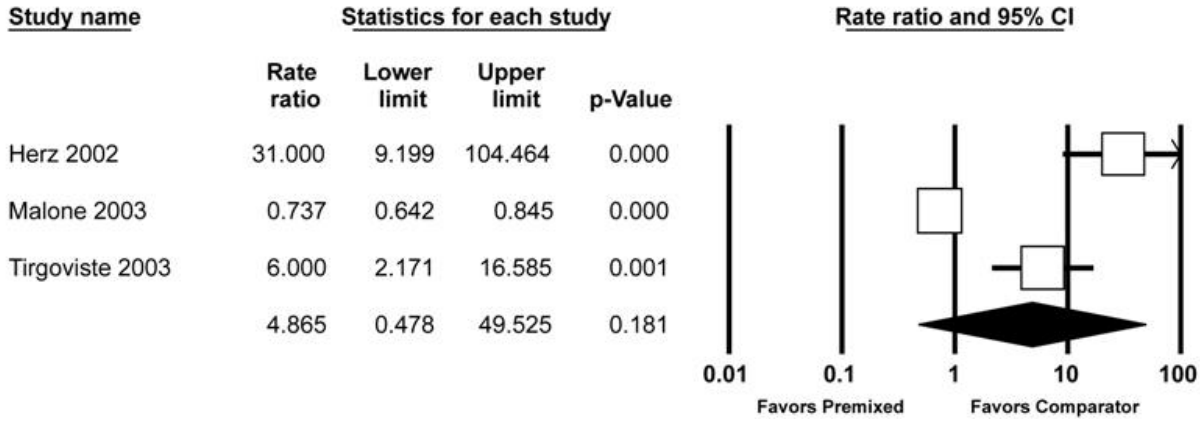
Hypoglycemia (see Appendix E, Evidence Table 5). In the study by Tirgoviste et al.,[43] the incidence of hypoglycemia was higher in patients treated with insulin lispro 75/25 than in those treated with glibenclamide (44.7 versus 10.3 percent; p = 0.001). Similar results were reported by Herz et al.,[72] who found a lower rate of hypoglycemia in patients treated with glibenclamide. In contrast, Malone et al.[68] found a higher rate of overall hypoglycemia in the oral antidiabetic treatment arm, although the difference did not reach statistical significance (p = 0.07). Pooling the results of these three studies indicated no difference in the overall hypoglycemia rate (hypoglycemia incidence not reported by all trials) measured as episodes per patient per 30 days (rate ratio = 4.86; 95 percent CI: 0.48 to 49.52; p = 0.18; see Figure 28).

Figure 27. Meta-analyses of post-treatment differences in hemoglobin A1c (%) between insulin lispro 75/25 and noninsulin antidiabetic agents



Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.
Test for heterogeneity: Q = 2.995 with 2 degrees of freedom (p = 0.224)
I-squared statistic = 33 percent

Figure 28. Meta-analyses of differences in the incidence of mild hypoglycemia between insulin lispro 75/25 and noninsulin antidiabetic agents

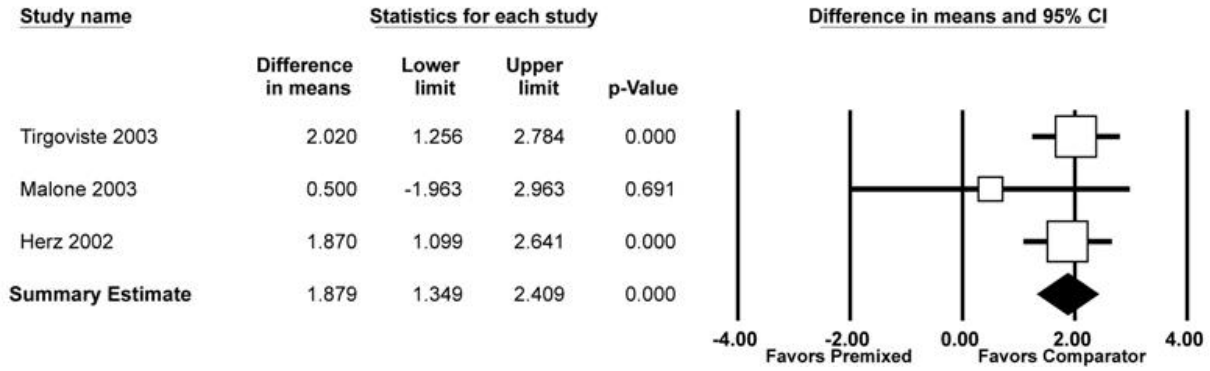


Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.
Test for heterogeneity: Q = 51.295 with 2 degrees of freedom (p < 0.001)
I-squared statistic = 96 percent

Weight change (see Appendix E, Evidence Table 6). Insulin lispro 75/25 was associated with weight gain in all three studies, and this effect was significant in two studies.[43,72] When the results of these studies were pooled, insulin lispro 75/25 was associated with a larger weight increase than were oral antidiabetic agents (weighted mean difference = 1.88 kg; 95 percent CI: 1.35 to 2.41 kg; p < 0.001; see Figure 29).

Other serious adverse events (see Appendix E, Evidence Table 6). Injection site reactions were not evaluated in any of these studies. Table 6 shows the range of risk differences between insulin lispro 75/25 and oral antidiabetic agents in terms of withdrawals due to adverse events and other serious adverse events.

Figure 29. Meta-analyses of post-treatment differences in weight change (kg) between insulin lispro 75/25 and noninsulin antidiabetic agents



Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.
Test for heterogeneity: Q = 1.335 with 2 degrees of freedom (p = 0.513)
I-squared statistic = 0 percent

Insulin lispro 75/25 versus other premixed insulin analogues. We identified four randomized crossover studies: two comparing insulin lispro 75/25 to insulin aspart 70/30,[55,58] one to insulin lispro 50/50,[62] and one to a combination of morning insulin lispro 50/50 and dinner insulin lispro 75/25.[69]

Details of the comparison in two studies have been reviewed above in the insulin aspart 70/30 section.[55,58] In the third study, Schwartz et al.[62] compared insulin lispro 75/25 and insulin lispro 50/50 in a single-dose, three-way crossover trial. The doses of both insulin preparations were comparable and fixed in this study. Roach et al.[69] compared a regimen of insulin lispro 50/50 before breakfast plus insulin lispro 75/25 before dinner to twice-daily insulin lispro 75/25. There was no difference in the morning or evening mean insulin dose between the two treatments in this study (p = 0.85 and 0.88 respectively).

Fasting glucose (see Appendix E, Evidence Table 4). Fasting glucose levels were reported in only one study,[55] which did not find a significant difference between the two premixed insulin analogues. In the second study, one dose of the study medication was given with a test meal and blood glucose levels were measured,[62] and therefore fasting glucose levels from this study were not available. In the third study,[69] insulin lispro 75/25 was given at dinner to both arms, and therefore fasting glucose levels were likely to reflect insulin lispro 75/25 in both arms.

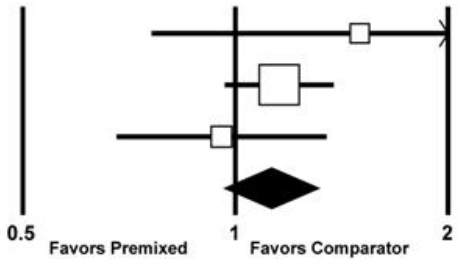
Postprandial glucose (see Appendix E, Evidence Table 4). With regard to postprandial glucose, the comparison between insulin aspart 70/30 and insulin lispro 75/25 did not find a significant advantage of one premixed insulin analogue over the other in terms of lowering dinner or breakfast postprandial glucose levels.[55] In the second study,[62] insulin lispro 50/50 was more effective than insulin lispro 75/25 in lowering postprandial glucose levels after a test-meal ($p < 0.05$). In the third study,[69] insulin lispro 75/25 was inferior to insulin lispro 50/50 in terms of lowering postprandial glucose levels after breakfast (p = 0.001). Dinner postprandial glucose levels were not compared in the third study, since both treatment arms received the same insulin formulation. The fourth study did not report postprandial glucose levels after 2 h or 90 min of the test meal.[58]

Hemoglobin A1c (see Appendix E, Evidence Table 4). Only one study reported changes in A1c levels and did not find a significant difference between insulin lispro 75/25 and insulin aspart 70/30 in terms of lowering A1c levels (mean difference = 0.14 percent, p = 0.08).[69]

Hypoglycemia (see Appendix E, Evidence Table 5). In one study,[62] it was not possible to discern which insulin preparation was responsible for the hypoglycemic events. In the other three studies, the overall hypoglycemia event rates did not differ.[55,58,69] When the results of these studies were combined, there was no difference between insulin lispro 75/25 and the other premixed insulin analogues (rate ratio = 1.13; 95 percent CI: 0.97 to 1.31; p = 0.12; see Figure 30).

Figure 30. Meta-analyses of differences in the incidence of mild hypoglycemia between insulin lispro 75/25 and other premixed insulin analogues

Study name	Statistics for each study			
	Rate ratio	Lower limit	Upper limit	p-Value
Hermansen 2002	1.500	0.763	2.950	0.240
Niskanen 2004	1.154	0.969	1.375	0.109
Roach 2003	0.956	0.680	1.343	0.795
Summary Estimate	1.126	0.968	1.311	0.125



Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.
Test for heterogeneity: Q = 1.657 with 2 degrees of freedom (p =0.437)
I-squared statistic = 0 percent

Weight change (see Appendix E, Evidence Table 6). Because all the trials had a crossover design, we did not abstract weight change data.

Other serious adverse events (see Appendix E, Evidence Table 6). Schwartz et al.[62] reported one injection site reaction in each of the premixed insulin analogue arms. Table 6 shows the range of risk differences between insulin lispro 75/25 and other premixed insulin analogues in terms of total serious adverse events and withdrawals due to adverse events.

Insulin Lispro 50/50

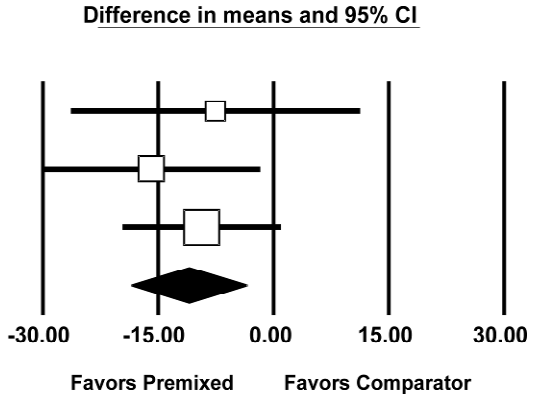
Insulin lispro 50/50 versus long-acting insulin analogues. Our search identified three randomized trials[64,76,79] that compared insulin lispro 50/50 to a long-acting insulin analogue, insulin glargine in all three cases. The study by Jacober et al.[64] compared a regimen of insulin lispro 50/50 before breakfast and lunch and insulin lispro 75/25 before dinner to a once-daily insulin glargine injection over a 16-week period, while the study by Kazda et al.[76] was a parallel-arm trial that compared insulin lispro 50/50 to insulin glargine over a followup of 24 weeks. A third study, the parallel-arm trial,[79] compared thrice-daily insulin lispro 50/50 plus metformin twice-daily to daily insulin glargine plus metformin twice-daily. The insulin dose was significantly higher in the premixed insulin analogue arm than in the insulin glargine arm in all three studies.

Fasting glucose (see Appendix E, Evidence Table 4). Fasting glucose was reported in two studies.[76,79] Kazda et al.[76] reported that insulin glargine was more effective than insulin lispro 50/50 in lowering fasting glucose (mean difference = -30.6 mg/dL; p < 0.001). Similarly, Robbins et al.[79] found that glargine plus metformin was more effective than insulin lispro 50/50

plus metformin in lowering fasting glucose (mean difference = -28 mg/dL; p < 0.001). Pre-dinner glucose levels were reported in three trials.[64,76,79] Pooling the results of these trials indicated that insulin lispro 50/50 was more effective in lowering pre-dinner fasting glucose than was insulin glargine (mean difference = -10.9 mg/dL, 95 percent CI: -18.5 to -3.4 mg/dL; p = 0.004; see Figure 31).

Figure 31. Meta-analyses of post-treatment differences in fasting glucose (mg/dL) between insulin lispro 50/50 and long-acting insulin analogues

Study name	Statistics for each study: Difference in means	Lower limit	Upper limit	p-Value
Kazda 2006	-7.560	-26.256	11.136	0.428
Jacober 2006	-15.900	-29.945	-1.855	0.026
Robbins 2008	-9.344	-19.537	0.849	0.072
Summary Estimate	**-10.947**	**-18.494**	**-3.399**	**0.004**



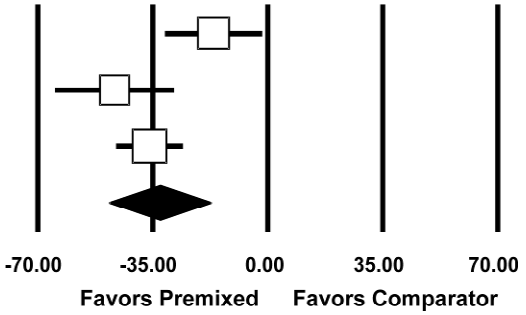
Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.
Test for heterogeneity: Q = 0.699 with 2 degrees of freedom (p = 0.705)
I-squared statistic = 0 percent

Postprandial glucose (see Appendix E, Evidence Table 4). Postprandial glucose was reported in all three trials.[64,76,79] Jacober et al.[64] found a significant decrease in postprandial glucose levels after breakfast (p < 0.003) with insulin lispro 50/50, as compared to insulin glargine. Similarly, Robbins et al.[79] found insulin lispro 50/50 to be more effective than insulin glargine in reducing 2-h postprandial glucose after breakfast (-10 mg/dL; p = 0.03) and after dinner (36 mg/dL; p < 0.001). Kazda et al.[76] found insulin lispro 50/50 to be more effective than insulin glargine in lowering postprandial glucose levels after dinner but not after breakfast (p-value not reported). When the results from these trials were pooled, insulin lispro 50/50 was found to be more effective than insulin glargine in lowering postprandial glucose levels (mean difference = -32.7 mg/dL; 95 percent CI: -48.2 to -17.1 mg/dL; p < 0.001; see Figure 32).

Hemoglobin A1c (see Appendix E, Evidence Table 4). Changes in A1c in response to treatment were reported in the three studies.[64,76,79] Jacober et al. found a greater decrease in A1c with insulin lispro 50/50 given with breakfast and lunch and insulin lispro 75/25 given with dinner than with insulin glargine (mean difference = -0.26 percent; p = 0.007). However, this result reflects combined treatment with two premixed preparations of insulin lispro and cannot be attributed to a single preparation. In the second study by Kazda et al.,[76] thrice-daily insulin lispro 50/50 was more effective than once-daily insulin glargine in lowering A1c (-0.9 percent; p < 0.001). Robbins et al.[79] found insulin lispro 50/50 plus metformin to be more effective than insulin glargine plus metformin in reducing A1c levels (mean difference = -0.4; p < 0.001). Pooling the results of these studies also indicated that insulin lispro 50/50 was more effective than insulin glargine in lowering A1c (mean difference = -0.4 percent; 95 percent CI: -0.65 to -0.15 percent; p = 0.002; see Figure 33).

Figure 32. Meta-analyses of post-treatment differences in postprandial glucose (mg/dL) between insulin lispro 50/50 and long-acting insulin analogues

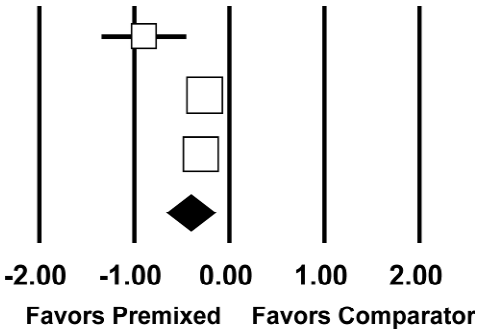
Study name	Statistics for each study: Difference in means	Lower limit	Upper limit	p-Value
Jacober 2006	-16.500	-31.043	-1.957	0.026
Kazda 2006	-46.620	-64.482	-28.758	0.000
Robbins 2007	-36.000	-45.889	-26.111	0.000
Summary Estimate	**-32.651**	**-48.177**	**-17.124**	**0.000**



Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.
Test for heterogeneity: Q = 7.527 with 2 degrees of freedom (p = 0.023)
I-squared statistic = 73 percent

Figure 33. Meta-analyses of post-treatment differences in hemoglobin A1c (%) between insulin lispro 50/50 and long-acting insulin analogues

Study name	Statistics for each study: Difference in means	Lower limit	Upper limit	p-Value
Kazda 2006	-0.90	-1.34	-0.46	0.0001
Jacober 2006	-0.26	-0.42	-0.10	0.0019
Robbins 2007	-0.30	-0.48	-0.12	0.0009
Summary Estimate	**-0.40**	**-0.65**	**-0.15**	**0.0017**



Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.
Test for heterogeneity: Q = 7.3 with 2 degrees of freedom (p = 0.026)
I-squared statistic = 73 percent

Hypoglycemia (see Appendix E, Evidence Table 5). Insulin glargine was associated with a lower risk of hypoglycemia in the three studies.[64,76,79] Jacober et al.[64] reported that a significantly larger number of patients receiving premixed insulin analogues had at least one episode of hypoglycemia when compared with those receiving insulin glargine (48 out of 58 patients versus 33 out of 54 patients; p = 0.01). In Kazda et al.,[76] 44.4 percent of the patients treated with insulin lispro 50/50 had at least one episode of hypoglycemia, as compared to 32.1 percent of those treated with insulin glargine (p-value not reported). In Robbins et al.,[79] both arms had a similar incidence of severe hypoglycemia and nocturnal hypoglycemia (3 versus 2 and 17 versus 19 among 157 and 158 patients respectively; p = nonsignificant for both); however, the overall

hypoglycemia incidence was higher in the insulin lispro 50/50 group (45 versus 28 among 157 and 158 patients; p = 0.02).

Weight change (see Appendix E, Evidence Table 6). Robbins et al.[79] reported a significant weight gain in the insulin lispro 50/50 arm as compared to the insulin glargine arm (mean difference = 1.7 kg; p < 0.001). Similarly, Kazda et al.[76] reported a larger increase in BMI with insulin lispro 50/50 than with insulin glargine, although this difference did not reach statistical significance (mean difference = 0.4 kg/m2; p = 0.19).

Other serious adverse events (see Appendix E, Evidence Table 6). None of the studies reported on injection site reactions. Table 7 shows the range of risk differences between insulin lispro 50/50 and long-acting insulin analogues with regard to withdrawals due to adverse events.

Insulin lispro 50/50 versus rapid-acting insulin analogues. We found only one study that compared insulin lispro 50/50 to rapid-acting prandial insulin lispro.[76] In this study, Kazda et al. compared insulin lispro 50/50 thrice-daily before meals to rapid-acting insulin lispro three times before meals over a period of 24 weeks. The insulin dose was allowed to be titrated to achieve optimal glucose control. All oral antidiabetic agents were discontinued. At the end of the study, the mean daily insulin dose was lower in the rapid-acting insulin lispro group than in the insulin lispro 50/50 group (0.50 versus 0.59 units/kg; p-value not reported).

Intermediate outcomes (see Appendix E, Evidence Table 4). This study did not find any difference between insulin lispro 50/50 and rapid-acting insulin lispro in terms of lowering fasting glucose (mean difference = 0 mg/dL; p > 0.05) or postprandial glucose (mean difference = 3.6 mg/dL; p > 0.05). Similarly, there was no difference between insulin lispro 50/50 and rapid-acting insulin lispro in terms of lowering A1c levels (mean difference = -0.1 percent; p = 0.57).

Adverse events (see Appendix E, Evidence Tables 5 and 6). The incidence of hypoglycemia was greater with rapid-acting insulin lispro than with insulin lispro 50/50 (53.8 percent versus 44.4 percent; p-value not reported). Similarly, there was a larger increase in BMI with rapid-acting insulin lispro than with insulin lispro 50/50 (mean difference = 0.3 kg/m2; p = 0.048). This study did not report on injection site reactions. Table 7 shows the risk difference between insulin lispro 50/50 and rapid-acting insulin lispro in terms of withdrawals due to adverse events.

Insulin lispro 50/50 versus a combination of long-acting and rapid-acting insulin analogues. We identified one parallel-arm study by Rosenstock et al.[80] that evaluated thrice-daily insulin lispro 50/50 against an insulin glargine at bedtime plus mealtime rapid-acting insulin lispro regimen. This randomized open-label trial did allow investigators to replace the evening meal insulin lispro 50/50 with insulin lispro 75/25. At the end of the study, the mean insulin dose was higher for the insulin glargine arm than for the insulin lispro 50/50 arm (147 versus 159 units, p = 0.002).

Intermediate outcomes (see Appendix E, Evidence Table 4). In this study, insulin glargine plus rapid-acting insulin lispro combination was more effective than insulin lispro 50/50 in lowering fasting glucose (147 versus 159 mg/dL; p = 0.013) and 2-h postbreakfast glucose (155 versus 174 mg/dL; p = 0.002).[80] Similarly, the insulin glargine plus rapid-acting insulin lispro combination was more effective in lowering A1c (6.8 versus 6.9 percent; p = 0.02) and in increasing the number of patients who achieved the target A1c of less than 7.0 percent (69 versus 54 percent, p = 0.009).

Table 7. Range of risk differences between insulin lispro 50/50 and other antidiabetic agents for selected adverse events

	Total serious adverse events		Withdrawn due to adverse events		Other serious adverse events	
Comparison	**Number of studies included**	**Range of risk difference* between insulin lispro 50/50 and comparison**	**Number of studies included**	**Range of risk difference* between insulin lispro 50/50 and comparison**	**Number of studies included**	**Range of risk difference* between insulin lispro 50/50 and comparison**
Long-acting insulin analogues	1[79]	0.04	3[64,76,79]	0 – 0.03	0	NA
Rapid-acting insulin analogues	0	NA	1[76]	0	0	NA
Rapid-acting with long-acting insulin analogues	1[80]	-0.02	0	NA	0	NA
Premixed human insulins	1[62]	0	4[10,62,77,78]	0	1[77]	-0.12
Intermediate-acting human insulins	0	NA	0	NA	0	NA
Oral antidiabetic agents	0	NA	0	NA	0	NA
Exenatide	0	NA	0	NA	0	NA

* The risk difference is the proportion having an event in the treatment group minus the proportion having an event in the comparison group. Negative risk differences suggest a protective effect of the treatment, while positive risk differences suggest a harmful effect of the treatment.

NA = not applicable

Adverse events (see Appendix E, Evidence Table 5 and 6). The incidence of overall, nocturnal, and severe hypoglycemia was similar between the two arms (169 out of 187 patients versus 166 out of 187 patients, p = 0.7; 109 versus 110, p = 1.0; 6 versus 4, p = 0.7 respectively). Similarly, there was no difference in the amount of weight gain (4.0 kg vs. 4.5 kg; p = 0.2). This study reported a total of 22 serious adverse events, nine of which were in the premixed insulin lispro group and 13 in the insulin glargine plus rapid-acting group. Table 7 shows the range of risk differences between insulin lispro 50/50 and long-acting insulin analogues plus a rapid-acting insulin analogue in terms of withdrawals due to adverse events.

Insulin lispro 50/50 versus premixed human insulin. We identified three randomized crossover studies[10,62,77] and one parallel-arm study[78] that compared insulin lispro 50/50 to premixed human insulin preparations. In the first crossover study,[62] only one fixed dose of the study medication was given with a test meal, and glucose levels were measured. In the second study,[10] insulin lispro 50/50 with the morning meal and insulin lispro 75/25 with evening meal was compared to NPH/regular 50/50 with breakfast and NPH/regular 70/30 with dinner. Both these studies have been discussed in the preceding sections.

Schernthaner et al.[77] compared thrice-daily insulin lispro 50/50 before each meal to twice-daily NPH/regular 70/30 in type 2 diabetic patients who had previously been treated with other insulin preparations. The insulin dose was adjusted throughout the study to optimize glucose control. There was no difference in the total daily dose at the end of the study between the two treatments.

Yamada et al.[78] compared twice-daily insulin lispro 50/50 with twice-daily premixed human insulin preparations. The insulin dose was adjusted during the study in order to optimize glucose control, and there was no difference in the total daily insulin dose between the two arms at the end of the study ($p > 0.05$).

Fasting glucose (see Appendix E, Evidence Table 4). Of the four studies, two evaluated changes in fasting glucose levels. In one trial, there was no difference between insulin lispro 50/50 and a premixed human insulin in terms of lowering fasting glucose.[78] In the second trial,[77] the premixed human insulin was more effective than insulin lispro 50/50 in lowering fasting glucose ($p < 0.001$).

Changes in pre-dinner glucose levels were evaluated in two studies.[10,77] Roach et al.[10] found insulin lispro 50/50 to be less effective than NPH/regular 50/50 in lowering pre-dinner glucose levels (mean difference = 4.32 mg/dL; p = 0.01). On the other hand, Schernthaner et al.[77] found insulin lispro 50/50 to be more effective than NPH/regular 70/30 in lowering pre-dinner glucose levels, although this difference was not statistically significant (mean difference = -13.0 mg/dL, p = 0.06).

Postprandial glucose (see Appendix E, Evidence Table 4). Dinner and breakfast postprandial glucose levels were reported by two and three studies, respectively. Insulin lispro 50/50 was more effective than premixed human insulin in lowering dinner postprandial glucose in one of the two studies[77] and in lowering breakfast postprandial glucose levels in two of the three studies.[10,62] In a pooled analysis, insulin lispro 50/50 was more effective in lowering breakfast postprandial glucose levels (weighted mean difference = -30.3 mg/dL; 95 percent CI: -55.6 to -5.0 mg/dL; p = 0.02).

Hemoglobin A1c (see Appendix E, Evidence Table 4). Two[77,78] of the four trials reported treatment-related changes in A1c. Schernthaner et al.[77] found that although A1c decreased from baseline in both treatment arms, the decrease was significantly greater with insulin lispro 50/50 than with NPH/regular 70/30 (mean difference = -0.5 percent; p = 0.01). Similarly, Yamada et

al.[78] also found insulin lispro 50/50 to be more effective than the premixed human insulin preparations in lowering A1c (mean difference = -0.31 percent; $p < 0.05$).

Hypoglycemia (see Appendix E, Evidence Table 5). In one study,[62] the insulin preparation that was responsible for the hypoglycemia was not clear. In the other three studies, there was no difference between the insulin lispro 50/50 and the premixed human insulin in terms of the incidence or rate of hypoglycemia.[10,77,78]

Weight change (see Appendix E, Evidence Table 7). The only parallel-arm study did not report on the weight change during the trial with study drugs.

Other serious adverse events (see Appendix E, Evidence Table 6). One study reported one (4 percent) injection site reaction in the insulin lispro 50/50 arm and no reactions in the premixed human insulin arm.[62] Table 6 shows the range of risk differences between insulin lispro 50/50 and premixed human insulins in terms of withdrawals due to adverse events.

Insulin lispro 50/50 versus intermediate-acting human insulin. We could not identify any study that had performed this comparison.

Insulin lispro 50/50 versus noninsulin antidiabetic agents. Our search did not find any study that had performed this comparison.

Insulin lispro 50/50 versus other premixed insulin analogues. We found one study comparing insulin lispro 50/50 to insulin lispro 75/25,[62] and one study comparing a regimen of insulin lispro 50/50 in the morning and insulin lispro 75/25 in the evening to twice-daily insulin lispro 75/25.[69] Both these studies have been noted in the preceding sections.

Intermediate outcomes (see Appendix E, Evidence Table 4). These studies did not report changes in either fasting glucose levels or pre-dinner glucose levels after treatment with insulin lispro 50/50. Both studies reported postprandial glucose levels after breakfast and found insulin lispro 50/50 to be more effective than insulin lispro 75/25 in lowering glucose levels ($p < 0.05$ in both studies). Although A1c was reported in one crossover study,[69] the duration of followup was only 8 weeks in each study period, with no washout period, raising the possibility of a carryover effect from the previous treatment period.

Adverse events (see Appendix E, Evidence Tables 5 and 6). Roach et al.[69] found a higher incidence of overall hypoglycemia with insulin lispro 50/50 than with insulin lispro 75/25, although this difference was not statistically significant (32.4 percent versus 26.1 percent; $p = 0.08$).

Publication Bias

For the body of literature on fasting glucose values comparing for insulin aspart 70/30 with noninsulin antidiabetic agents, we found strong evidence of publication bias. As mentioned earlier, the funnel plot was asymmetrical and the trim-and-fill method showed that three studies need to be imputed to make the plot symmetrical. We did not find strong evidence of publication bias for all other comparisons for intermediate outcomes.

Study Quality Assessment

The overall quality of the included studies was fair to good (see Appendix E, Evidence Table 7). All the trials except two[52,75] were RCTs. Randomization methods were described in 17 studies[32,39,43,45,47-51,55,57-59,65,78-80] and were adequate in all these studies except one.[47] The remaining RCTs did not describe their randomization methods is sufficient detail.

Only seven trials used blinding of the treatment at some stage of the trial. Five trials used blinding for patients and providers,[13,44,48,62,69] while the remaining two trials used blinding for outcome assessors.[32,45] It is difficult to achieve blinding of patients and providers because premixed insulin analogues need to be given with meals, while the other insulin preparations are generally given at other times, with different frequency, or with a different route of administration.

For outcomes based on blood tests, the outcome assessment was unlikely to have been biased by the lack of blinding. However, the assessment of other outcomes could have been biased. Several studies asked patients to maintain a diary of their blood glucose levels. This self-monitoring of blood glucose may have affected the accurate and precise measurement of fasting and postprandial blood glucose.

In two studies, followup was inadequate to fully assess the effectiveness of premixed insulin analogues in lowering A1c levels.[57,69] Four studies had complete followup, with no study participant lost during followup,[10,43,52,68] while eight studies lost more than 10 percent of the enrolled participants during followup.[12,54,61,63,64,74,75,80] In all the remaining studies, the percentage of patients who were lost to followup was less than 10 percent. Of the studies in which some patients withdrew, six studies[12,53,67,70,74,75] either did not provide a description of withdrawals or the withdrawals were described inadequately; the remaining studies had an adequate description of withdrawals.

As mentioned earlier, the source of funding was the pharmaceutical industry in the case of all trials except two; one was funded jointly by the NIH and Eli Lilly,[74] and the other was funded by the Japan Diabetes Foundation.[61] Six trials did not report their source of funding.[43,44,60,65,66,71] A statement regarding conflict of interest was not included in 27 studies.[10-12,15,43,44,46,47,51,55-61,64,65,67-71,74,77,78,83]

The study conclusions were reflective of the study results in most cases, except for five studies in which the conclusions were only partially supported by the results.[13,52,53,64,72]

Applicability Assessment

Generalization of these results to the U.S. diabetic population and current clinical practice was limited by the fact that all the identified studies were efficacy trials and not effectiveness trials (see Appendix E, Evidence Table 8). Participants were recruited from outpatient clinics in three trials,[47,49,57] from subspecialty clinics in three additional trials,[62,67,72] from both outpatient and subspecialty clinics in one trial,[52] from clinics and hospitals in one trial,[61] and from clinical centers (without further details being specified) in one trial.[32] The remaining trials did not mention the population source from which the participants were enrolled. The ratio of enrolled patients to the screened population was not reported in 22 studies;[10-13,39,43,44,47,50,56,57,61,63,66,67,69-71,73,75,77,78] in all the other studies, this ratio was higher than 50 percent. In four trials, more than 10 percent of the participants were excluded during the lead-in period.[39,46,60,66]

Most studies enrolled patients similar in age to the general U.S. diabetic population, except for the case of five studies.[47,48,62,72,77] Women were underrepresented in five trials,[46,52,57,62,78] and in two trials there were more women than men.[39,59] One study did not report on the sex ratio.[74] In five trials, the proportion of enrolled racial and ethnic groups was reflective of the general population in the U.S.[15,39,60,75,80] Twenty-one trials did not report on the race/ethnicity admixture of the enrolled population,[10-12,43-45,48-50,54-56,58,59,65,66,70-73,77] and the remaining trials did not have a racial and ethnicity admixture reflective of the U.S. population.

In most trials, the spectrum of diabetic complications and comorbidities among the enrolled participants was limited. Some trials excluded insulin-naïve patients, while other trials 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 the results to these subpopulations.

The dose of insulin, route of administration, and schedule of administration were reflective of clinical practice or were easy to replicate in clinical practice in all trials except in one,[70] in which patients who wished to fast were given insulin during the month of Ramadan. The monitoring of the treatment was reflective of general clinical practice in most studies except seven.[12,13,15,43,44,53,71] In one trial,[43] adjustments to the insulin dose were made every few days, and the patients had frequent visits during the study period. In another study, investigators telephoned patients at least once weekly,[12] while in three studies monitoring of blood glucose was too frequent to be implemented in clinical practice.[13,15,53] In two studies, patients were hospitalized or closely monitored throughout the duration of the study, a situation that cannot be applied in clinical practice.[44,71] Premixed insulin analogues were compared with adequate dosing and schedule of medicines in all but six studies.[43,49,57,59,60,72] In these studies, the dose of the comparator was held constant, while the premixed insulin dose was increased on the basis of glucose levels. Holding the dose of comparator may have biased the results of these studies in favor of premixed insulin analogues.

Overall, the applicability of the studies to the diabetic population of the U.S. in terms of fasting glucose outcomes was fair. In most studies, self-monitoring of fasting blood glucose was reported, reflecting current clinical practice in which a patient maintains a blood glucose diary and the physician adjusts the insulin dose to optimize glucose control. When premixed insulin analogues were compared to or used in combination with oral antidiabetic agents, the dose of these antidiabetic agents was held constant in most studies. This situation is in contrast to usual clinical practice, in which the dose of oral antidiabetic agents is either titrated to reflect glucose control, or the antidiabetic agent is changed to a different class or discontinued all together.

The overall applicability of the studies to the diabetic population of the U.S. with regard to postprandial glucose levels was also graded as fair. In terms of fasting glucose, most studies used self-monitoring of glucose by patients, an approach that is reflective of clinical practice. Four one-dose studies[44,56,58,62] were not reflective of clinical practice, and because the insulin preparations had not achieved a steady state in plasma, it is possible that the results from these trials might not be reproducible in practice. Calculation of the insulin dose and a test meal also cannot be reproduced in clinical practice.

The overall applicability of the studies to the U.S. diabetic population for A1c was graded as fair and was limited because of the aforementioned reasons related to fasting and postprandial glucose.

The overall applicability of the studies to the diabetic population of U.S. in terms of the adverse event of hypoglycemia was also fair. Since most studies excluded patients with significant comorbidity, severe obesity, and very poorly controlled diabetes, it is not possible to generalize the results of these studies to the patient population in clinical practice. In some studies, the monitoring of the patient population as conducted would not be feasible in usual clinical practice.

The overall applicability of the studies to the U.S. diabetic population with regard to the adverse outcome of weight gain was graded as fair. Most studies were of relatively short duration except for two studies[32,45] that followed patients for 1 year and 2 years, respectively. Because

weight gain is a relatively slow process, it is difficult to draw relevant conclusions from short-term studies. In addition, many studies using premixed insulin lispro preparations were crossover studies that were excluded from the analysis of weight gain, thus limiting the amount of evidence from which conclusions could be drawn.

Clinical Outcomes

Key Messages

- No statistically significant differences in all-cause mortality (OR = 2.93; 95 percent CI: 0.95 to 9.05), cardiovascular mortality (OR = 6.80; 95 percent CI: 0.87 to 53.12), cardiovascular morbidity (OR = 0.86; 95 percent CI: 0.49 to 1.52), or the combined outcome of all-cause mortality and cardiovascular morbidity (OR = 2.10; 95 percent CI: 0.87 to 5.10) between premixed insulin analogues and other diabetes medications were reported in these mainly short-duration RCTs.

- The low absolute number of events in these short duration trials in which clinical events were not the primary outcomes made it difficult to draw any firm conclusions regarding any of the clinical outcomes.

- Insufficient evidence existed with regard to nephropathy outcomes to allow us to draw any conclusions.

- No studies evaluated other clinical outcomes, such as retinopathy and neuropathy.

- Many of the studies in this overall review did not report on any of the clinically relevant outcomes (some did not even state whether any deaths or events occurred), introducing the possibility of publication bias.

Evidence Grades (see Appendix E, Evidence Table 1)

- The quantity, quality, and consistency of the body of evidence was graded as low for all-cause mortality and cardiovascular mortality for the following comparisons:
    - Premixed insulin analogues versus other insulin or noninsulin antidiabetic agents.

- The quantity, quality, and consistency of the evidence was graded as low for cardiovascular morbidity for the following comparisons:
    - Premixed insulin analogues versus other insulin or noninsulin antidiabetic agents.

- The quantity, quality, and consistency of the body of evidence was graded as low for nephropathy for the following comparisons:
    - Premixed insulin analogues versus other insulin or noninsulin antidiabetic agents.

- There was no evidence to assess the quantity, quality, and consistency for all other clinical outcomes.

Study Characteristics

Out of 45 included studies, only 16 studies reported on a clinical outcome.[32,45,49-51,54,55,57,58,60,61,65,66,68,77,79] Nine studies reported on all-cause mortality,[32,45,49,51,55,61,66,68,77] four reported on cardiovascular mortality,[32,45,51,66] eight reported on cardiovascular morbidity,[45,49,50,54,57,58,60,65] and three reported on nephropathy.[32,60,79] All the studies except one[45]were short-duration RCTs lasting 1 year or less, in which the clinical outcome (such as mortality) was not the primary outcome (see Appendix E, Evidence Table 2). Most studies (n = 11) were parallel-arm RCTs,[32,45,49-51,54,57,60,61,68,79] and the remaining studies were crossover RCTs. Most parallel-arm RCTs were moderately-sized (range: 160 to 708 subjects),[32,49-51,54,60,61,68,79] except for two smaller studies (125 and 49 subjects).[45,57] The crossover studies were mainly small-sized (range: 35 to 133 subjects).[55,58,65,66,77] Half of the studies were multicenter trials occurring in multiple countries,[45,49-51,54,55,68,79] while the other half of the studies occurred in one or two countries in Europe,[32,58,66] the United States,[60,65] the Middle East,[57] or Japan,[61] or the geographic location was not reported.[77] Half of the studies (n = 8) reported excluding subjects with significant comorbidity, such as a history of cardiovascular disease or complications from type 2 diabetes,[32,51,54,55,57,58,77,79] and most studies (n = 12) excluded moderate to severely obese subjects with BMI greater than 35 or 40 kg/m^2.[32,45,49,50,54,55,57,58,60,65,68,77]

Subjects were mainly middle-aged to older, overweight to mildly obese adults with moderate glycemia (range in mean A1c from 7.8 to 10.7 absolute percentage points; see Appendix E, Evidence Table 3). The average or median duration of diabetes for these subjects was moderate ranging from 7 to 16 years. The studies had a diverse gender ratio, yet they were less diverse in terms of racial mix. Of the five studies reporting race, three reported greater than 80 percent Caucasian subjects,[32,57,68] while two studies reported a more diverse racial mix.[60,79] Half of the studies[45,49,55,58,61,66,77,79] included insulin-treated patients, and the other half included insulin-naïve patients.[32,45,55,58,60,65,66,77]

Reporting of Clinical Outcomes

Death from any cause and cardiovascular death was abstracted from all articles. Cardiovascular morbidity could be any cardiovascular event, including myocardial infarction or stroke. If the article specified no clinical outcomes such as death, we recorded it as having zero events in each arm. If an article did not report that no events such as deaths occurred, we did not include that article in this section, since we did not want to assume that no events had occurred.

Premixed Insulin Analogues (Insulin Aspart 70/30, Insulin Lispro 50/50, and Insulin Lispro 75/25) Versus Any Other Antidiabetic Agent

All-cause and cardiovascular disease mortality.

Qualitative assessment. Nine RCTs of short duration reported few absolute deaths from any cause in each study arm, with zero to three deaths for the premixed insulin analogues, versus zero to two deaths for the other diabetes agents (less than 5 percent for each arm; see Table 8 and Appendix E, Evidence Table 9).[32,45,49,51,55,61,66,68,77] Four RCTs reported one to two cardiovascular deaths in the premixed insulin analogue arms and no cardiovascular deaths in the

other arms (see Table 9).[32,45,51,66] Even the 2-year parallel-arm RCT, which did not exclude subjects with a prior history of cardiovascular disease and whose primary objective was to evaluate safety, had very few events, making it difficult to determine differences between groups.[45] We further describe these trials qualitatively below.

Table 8. Summary of all-cause mortality events in studies comparing a premixed insulin analogue to another antidiabetic agent

Main comparison (drug 1 vs drug 2)	N of studies	N of total participants	Percent events drug 1	Percent events drug 2
Premixed insulin analogue vs long-acting insulin analogue	2	804	Study 1: 1% Study 2: 2%	Study 1: 0% Study 2: 2%
Premixed insulin analogue vs rapid-acting insulin analogue	1	708	1%	<1%
Premixed insulin analogue vs premixed human insulin	2	167	Study 1: 0% Study 2: 4%	Study 1: 3% Study 2: 1%
Premixed insulin analogue vs oral antidiabetic agents	2	926	Study 1: <1% Study 2: <1%	Study 1: 0% Study 2: 0%
Premixed insulin analogue vs exenatide	1	501	<1%	<1%
Premixed insulin analogue vs premixed insulin analogue	1	133	<1%	0%

*If a study had more than one arm with premixed insulin analogues, we combined the two arms into one arm in order to summarize the results.
N = number; vs = versus

Table 9. Summary of cardiovascular disease mortality events in studies comparing a premixed insulin analogue to another antidiabetic agent

Main comparison (drug 1 vs drug 2)	N of studies	N of total participants	Percent events drug 1	Percent events drug 2
Premixed insulin analogue vs long-acting insulin analogue	2	804	Study 1: 2% Study 2: <1%	Study 1: 0% Study 2: 0%
Premixed insulin analogue vs rapid-acting insulin analogue	1	708	1%	<1%
Premixed insulin analogue vs premixed human insulin	1	186	1%	0%
Premixed insulin analogue vs oral antidiabetic agents	1	329	<1%	0%

*If a study had more than one arm with premixed insulin analogues, we combined the two arms into one arm in order to summarize the results.
N = number; vs = versus

Premixed insulin analogues versus long-acting insulin analogues or rapid-acting insulin analogues. Two RCTs compared premixed insulin analogues to long-acting insulin analogues, reporting similar percentages of death in each arm (less than 1 versus 0 percent and 2 versus 2 percent).[32,66] One of these studies also compared a premixed insulin analogue to a rapid-acting insulin analogue and found similar percentages of death and cardiovascular death in both groups (1 versus less than 1 percent, respectively, for both outcomes).[32] The largest 1-year parallel-arm RCT of patients already taking metformin plus a sulfonylurea (n = 708) compared three arms (insulin aspart 70/30 twice-daily, insulin aspart three times a day, and long-acting insulin detemir at bedtime or twice-daily if required).[32] That study reported similar percentages of events among the groups (0.6 percent in the premixed insulin analogue arm versus 0 percent in the long-acting insulin arm), but the insulin aspart 70/30 group had a higher absolute number of deaths. The study reported one fatal myocardial infarction, one fatal case of ischemic heart disease, and one fatal case of congestive heart failure in the insulin aspart 70/30 twice-daily arm; one fatal

myocardial infarction in the insulin aspart thrice-daily arm; and no deaths in the long-acting insulin detemir arm. The insulin detemir arm had no deaths, despite having a slightly higher A1c than the other two insulin analogue arms, although the insulin analogue arms were associated with slightly greater weight gain over 1 year. The smaller 16-week crossover study comparing insulin lispro 75/25 plus metformin to insulin glargine plus metformin also showed similar percentages of events in each arm (2 versus 2 percent, or one death from any cause in each study arm).[66] The death in the premixed insulin analogue arm was from a myocardial infarction, whereas the etiology of the death in the insulin glargine arm was not described.

Premixed insulin analogues versus premixed human insulin. Two small RCTs (one parallel-arm and one crossover) compared a premixed insulin analogue to a premixed human insulin and reported similar percentages of death from any cause in each arm (4 versus 1 percent and 0 versus 3 percent).[45,77] The longest 2-year multicenter, multinational RCT that specifically set out to evaluate safety (hypoglycemia and adverse events) was one of these two studies.[45] This study compared insulin aspart 70/30 to NPH/regular 70/30 in subjects previously on insulin regimens and reported three deaths (4 percent) in the premixed insulin analogue arm versus one death (1 percent) in the premixed human insulin arm. Of these deaths, one was due to a myocardial infarction in the premixed insulin analogue arm, as compared to no cardiovascular causes of death in the premixed human insulin arm. The smaller 12-week crossover study compared insulin lispro 50/50 to NPH/regular 70/30 and showed similarly low numbers of events in the two groups, none versus one death, respectively.[77]

Premixed insulin analogues versus a rapid-acting insulin analogue, with or without an intermediate-acting insulin. One parallel-arm 6-month RCT compared a premixed insulin analogue (insulin aspart 70/30) to a rapid-acting insulin analogue (insulin aspart), with or without an intermediate-acting insulin (NPH insulin), and reported one death of unspecified etiology in the premixed insulin analogue arm, as compared to no deaths in the other arm.[61]

Premixed insulin analogues versus noninsulin antidiabetic agents. Two parallel-arm moderate-size RCTs of short duration compared premixed insulin analogues to oral antidiabetic agents, reporting a small number of deaths in the premixed insulin analogue arms, versus no deaths in the oral antidiabetic agent arms (less than 1 percent versus 0 percent for each study).[51,68] The 16-week RCT compared three arms (insulin aspart 70/30 twice-daily alone, insulin aspart 70/30 twice-daily plus fixed metformin, and fixed metformin plus variably dosed glibenclamide).[51] This study reported one fatal myocardial infarction in the insulin aspart 70/30 plus fixed metformin arm, as compared to no deaths in the other two arms. The other 16-week RCT compared insulin lispro 75/25 plus metformin to glibenclamide plus metformin in subjects previously taking metformin or a sulfonylurea.[68] The study reported one death with no description of etiology in the premixed insulin analogue arm, as compared to no deaths in the oral antidiabetic agent arm.

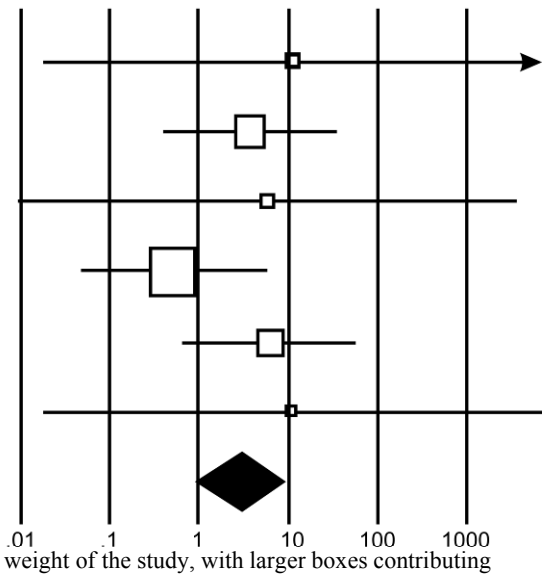
A moderately-sized 1-year parallel-arm RCT of subjects already taking metformin plus a sulfonylurea (n = 501) compared the addition of insulin aspart 70/30 twice daily to the addition of exenatide twice daily. The total number of deaths in each group was not statistically different (one (0.4 percent) versus two (0.8 percent) deaths, respectively), but the etiology of these deaths was not described.[49]

Quantitative assessment. We found a statistically insignificant trend towards increased risk of all-cause mortality with premixed insulin analogues as compared to all other comparators combined in the six parallel-arm RCTs (OR = 2.93; 95 percent CI: 0.95 to 9.05; p = 0.06; see Figure 34). The inclusion of the two crossover studies in the meta-analysis did not markedly

influence these results (OR = 2.06; 95 percent CI: 0.79 to 5.42; p = 0.14). When the study by Nauck et al. was removed from the meta-analysis,[49] the results reached statistical significance (OR = 5.49; 95 percent CI: 1.25 to 24.08). Their study was the only study with the active comparator of exenatide, and they reported slightly more deaths in the exenatide arm than in the premixed insulin analogue arm.[49] No other single study markedly influenced the all-cause mortality results. We also found a statistically insignificant trend towards increased cardiovascular mortality with the premixed insulin analogues as compared to all other active comparator combined (OR = 6.80; 95 percent CI: 0.87 to 53.12; p = 0.07; see Figure 35). No single parallel-arm RCT strongly influenced the cardiovascular disease mortality results, although the study by Holman et al. had the largest study population and contributed the most to the pooled estimate.[32] The inclusion of the one crossover study in the meta-analysis did not markedly influence the point estimate, but it did cause the results to reach borderline statistical significance (OR = 7.19; 95 percent CI: 1.01 to 51.11; p = 0.049). While point estimates and confidence intervals varied somewhat depending on the meta-analytic technique used, the overall direction of the point estimates did not change (see Appendix E, Evidence Table 10). The pooled odds ratios suggested an increased risk of all-cause and cardiovascular disease mortality with the use of premixed insulin analogues versus other diabetes drug comparators, yet the wide 95 percent CI confirmed our conclusion regarding a lack of reliability in the point estimate because of the small number of absolute events in few studies. No statistically significant heterogeneity was found in these studies, with I-squared statistics of less than 50 percent for all analyses; therefore, no further analyses were done to evaluate sources of potential heterogeneity.

Figure 34. Pooled odds ratios for all-cause mortality, comparing premixed insulin analogues to other diabetes medications

Study ID	Odds ratio	Lower limit	Upper limit
Malone, 2003	11.22	0.02	7284.92
Boehm, 2004	3.70	0.38	36.19
Kvapil, 2006	5.86	0.01	3812.58
Nauck, 2007	0.51	0.05	5.64
Holman, 2007	6.10	0.63	59.00
Hirao, 2008	11.14	0.02	7269.60
Summary Estimate (p = 0.723)	**2.93**	**0.95**	**9.05**

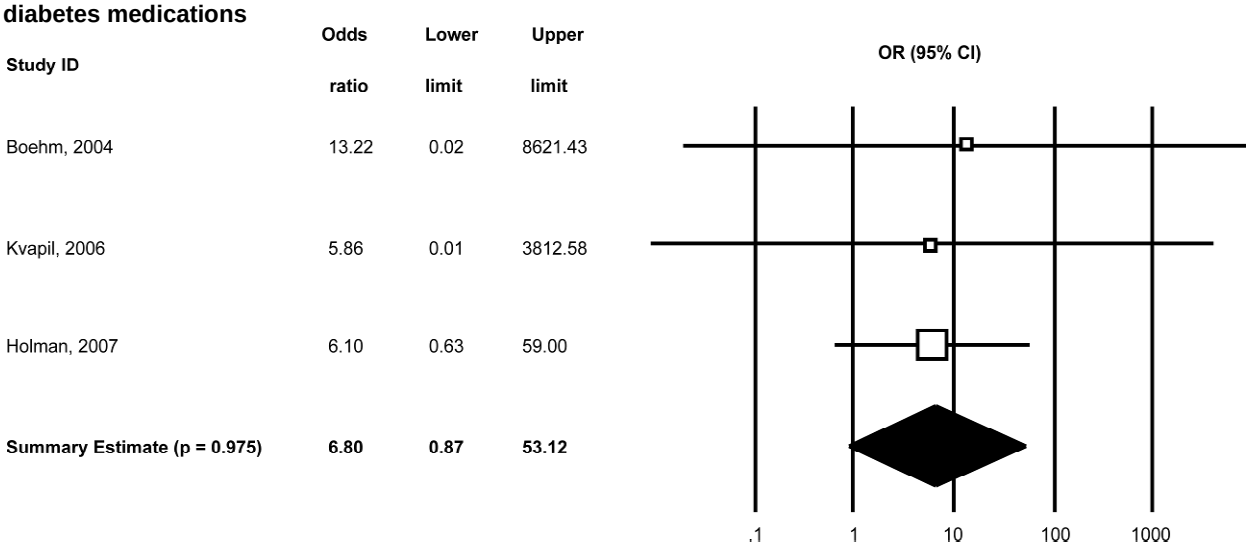


Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.
Test for heterogeniety: Q = 2.81 with 4 degrees of freedom (p =0.589)
I-squared statistic = 0 percent

Cardiovascular disease morbidity.

Qualitative assessment. Eight studies compared premixed insulin analogues to another diabetes medication, reporting cardiovascular morbidity between groups (see Table 10 and Appendix E, Evidence Table 9).[45,49,50,54,57,58,60,65] The articles compared premixed insulin analogues to premixed human insulin in the case of two studies,[45,58] oral antidiabetic agents in three studies,[54,57,60] long-acting insulin analogues in two studies,[50,65] and exenatide in one study.[49] The eight articles reported a diverse set of cardiovascular morbidity outcomes, including non-fatal myocardial infarction,[54,57,65] transient ischemic attack,[58] peripheral vascular disease,[50] congestive heart failure,[50,65] angina,[60] arrhythmia,[60] coronary artery disease,[60] chest pain,[65] and unspecified total cardiac adverse events.[45,49]

Figure 35. Pooled odds ratios for cardiovascular mortality, comparing premixed insulin analogues to other diabetes medications



Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.
Test for heterogeniety: Q = 0.14 with 2 degrees of freedom (p =0.933)
I-squared statistic = 0 percent

Table 10. Summary of cardiovascular disease morbidity events in studies comparing a premixed insulin analogue to another antidiabetic agent

Main comparison (drug 1 vs drug 2)	N of studies	N of total participants	Percent events drug 1	Percent events drug 2
Premixed insulin analogue vs premixed human insulin	2	368	Study 1: <1% Study 2: 18%	Study 1: 0% Study 2: 17%
Premixed insulin analogue vs long-acting insulin	2	456	Study 1: 1% Study 2: <1%	Study 1: 0% Study 2: <1%
Premixed insulin analogue vs oral medications	3	530	Study 1: <1% Study 2: <1% Study 3: 1%	Study 1: 0% Study 2: 0% Study 3: 2%
Premixed insulin analogue vs exenatide	1	501	2%	4%

*If a study had more than one arm with premixed insulin analogues, we combined the two arms into one arm in order to summarize the results.
N = number; vs = versus

Only one of these studies specifically set out to evaluate safety over 2 years of followup.[45] This and another 1-year study had larger numbers of cardiac adverse events, largely because of their vaguer definition of unspecified cardiac disorders, which could include less serious cardiac events such as palpitations.[45,49] Although the absolute numbers of events were greater in these two studies than in the other six studies, no major differences in cardiovascular morbidity were noted between groups (18 versus 17 percent and 2 versus 4 percent). Neither study broke these cardiac disorders down into more serious versus less serious events. The rest of the studies were mainly short-duration studies with few absolute events, which occurred mainly in the premixed insulin analogue arms (one event for the premixed insulin analogues versus none to two for the other antidiabetic agents; less than 2 percent for each arm). Two of these shorter-duration studies were crossover studies[58,65] that did not report whether the events occurred prior to the first crossover. We describe these studies qualitatively in more depth below.

Premixed insulin analogues versus long-acting insulin analogues. Two RCTs compared premixed insulin analogues to long-acting insulin analogues and reported no differences in cardiovascular morbidity between arms (less than 1 versus 0 percent and 0.8 versus 0.8 percent).[50,65] The 28-week parallel-arm RCT of 255 insulin-naïve patients compared insulin aspart 70/30 plus metformin to insulin glargine plus glimepiride.[50] The oral antidiabetic agents could have been in place before the beginning of the study or could have been added after the study began. This study reported one congestive heart failure event in the insulin glargine arm and one peripheral vascular disorder event in the insulin aspart 70/30 arm. The 32-week crossover RCT (including an 8-week run-in period on NPH insulin plus metformin) compared insulin lispro 75/25 plus metformin to insulin glargine plus metformin and reported similarly low absolute events and no major differences between arms.[65] The study reported one subject with congestive heart failure and one subject with chest pain in the insulin lispro 75/25 arm, a nonfatal myocardial infarction during the lead-in period when the subjects were using NPH insulin plus metformin, and no events in the insulin glargine arm.

Premixed insulin analogues versus premixed human insulin. Two studies compared premixed insulin analogues to premixed human insulin, reporting similar percentages of cardiovascular events between groups (18 versus 17 percent and less than 1 versus 0 percent).[45,58] The longest 2-year multicenter, multinational RCT that specifically evaluated safety (hypoglycemia and adverse events) was one of these two studies.[45] This study compared insulin aspart 70/30 to NPH/regular 70/30 in subjects previously on insulin regimens, and reported 15 unspecified cardiac disorders (18 percent) in the premixed insulin analogue arm versus 17 unspecified cardiac disorders (17 percent) in the premixed human insulin arm. This study did not further elaborate on the severity of these cardiac disorders. Similarly, the one three-way crossover study compared insulin aspart 70/30, insulin lispro 75/25, and NPH/regular 70/30 and reported no major differences between groups. This study had a lower absolute number of events because of its higher specificity in defining the cardiac adverse event and because of its short 3-day study period. A transient ischemic attack was reported in the insulin aspart 70/30 arm, versus no events in the insulin lispro 75/25 or premixed human insulin arms.

Premixed insulin analogues versus noninsulin antidiabetic agents. Three RCTs compared premixed insulin analogues to oral antidiabetic agents, reporting few absolute cardiovascular morbidity events in the premixed insulin analogue groups ($\leq$1 percent) compared with none or few events (0 to 2 percent) in the oral antidiabetic agent groups.[54,57,60] Two were short duration (6-week and 18-week) parallel-arm RCTs comparing insulin aspart 70/30 plus a thiazolidinedione to a sulfonylurea plus a thiazolidinedione. One of these studies also had a third

arm, insulin aspart 70/30 monotherapy.[54] The thiazolidinedione was pioglitazone[54] in one study and rosiglitazone in the other study.[57] In both studies, one subject experienced a nonfatal myocardial infarction in the premixed insulin analogue arm (monotherapy insulin aspart 70/30 arm in one study and insulin aspart 70/30 plus rosiglitazone arm in the second study). The third short-duration 34-week parallel-arm RCT compared premixed insulin aspart 70/30 plus the combination of metformin and pioglitazone to the combination of metformin plus pioglitazone, reporting slightly lower withdrawals due to cardiac morbidity in the premixed insulin analogue plus oral antidiabetic agent arm (1 percent), as compared to oral antidiabetic agents alone (2 percent).[60] These three studies were the only studies with thiazolidinediones in any of the arms. 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 antidiabetic agents (versus insulin alone),[84,85] we did not observe any congestive heart failure events in these few studies, which reported few absolute events. In addition, rosiglitazone labels have warnings regarding increased ischemic risk in patients who use rosiglitazone with insulin, as compared to insulin alone. We had insufficient evidence to determine whether this risk might be increased in the presence of premixed insulin analogues, as compared to other insulins used alone.

A relatively large 1-year parallel-arm RCT of subjects already taking metformin plus a sulfonylurea (n = 501) compared the addition of insulin aspart 70/30 twice-daily to the addition of exenatide twice daily.[49] The study reported slightly higher absolute nonspecific cardiac disorders in the exenatide arm, as compared to the insulin aspart 70/30 arm (10 (4 percent) versus 5 (2 percent) cardiac adverse events, respectively). They did not elaborate further on the proportion of serious and less serious events.

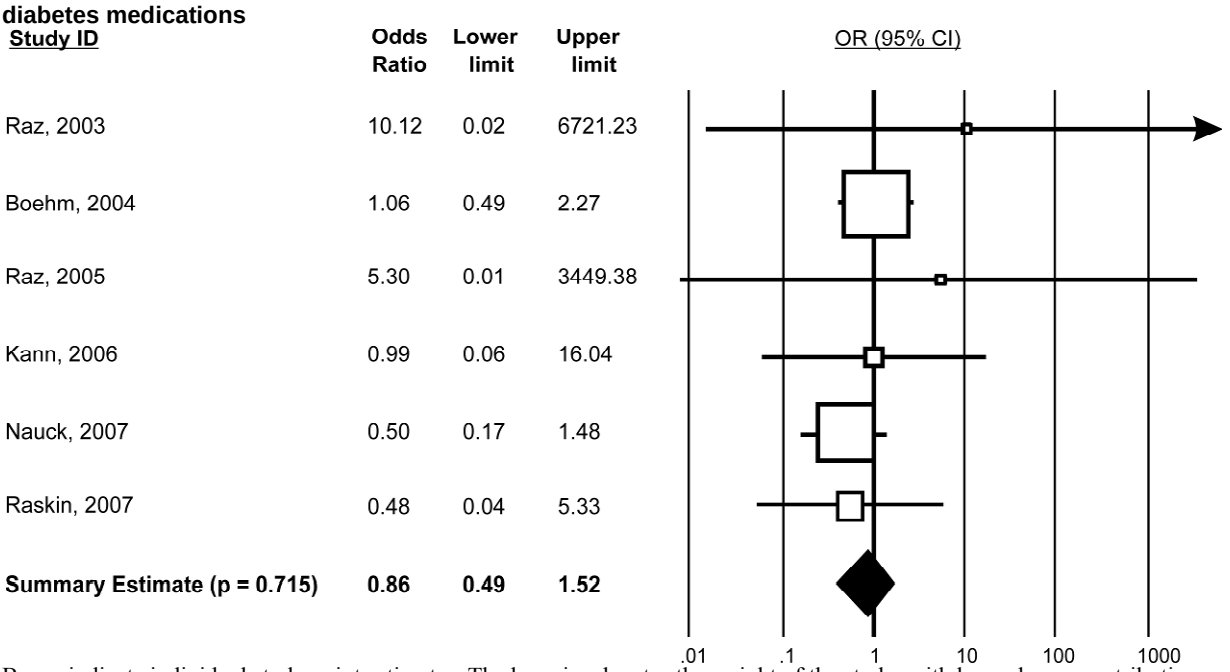
Quantitative assessment. We found no statistically significant differences in cardiovascular morbidity between the premixed insulin analogue arms and with any other active comparator in the six parallel-arm RCTs (OR = 0.86; 95 percent CI: 0.49 to 1.52; p = 0.60; see Figure 36). The inclusion of the two crossover studies in the meta-analysis did not markedly alter these results (OR = 0.92; 95 percent CI: 0.53 to 1.61). No one study strongly influenced these results. Despite their different definitions of cardiovascular morbidity, we decided to combine these trials in a meta-analysis because of the underlying shared pathophysiology of the cardiovascular disease outcomes. We conducted a separate meta-analysis using the three parallel-arm RCTs with serious cardiac events (i.e., nonfatal myocardial infarction or transient ischemic attack), and excluded the three RCTs that combined less serious and more serious cardiac disorders or reported more nonspecific cardiac morbidity such as arrhythmia.[45,49,60] Although the conclusions of no significant difference did not change, the point estimate, which initially suggested a protective benefit of the premixed insulin analogues, now suggested potential harm (OR = 2.22; 95 percent CI: 0.26 to 19.12). No statistically significant heterogeneity was found in these studies, with an I-squared statistic less than 50 percent; therefore, no further analyses were performed to evaluate the sources of potential heterogeneity.

Combined mortality and cardiovascular disease morbidity.

Quantitative and quantitative assessment. We decided to combine ten parallel-arm RCTs evaluating mortality and cardiovascular disease morbidity in one meta-analysis (since the current understanding of these outcomes proposes a shared pathophysiology), using the mortality results for the two studies that reported both outcomes.[45,49] We found no statistically significant

differences between premixed insulin analogues and any other active diabetes medication comparator (OR = 2.10; 95 percent CI: 0.87 to 5.10; p = 0.10; see Figure 37). While no single study markedly changed the point estimate, removal of the Nauck et al.[49] or Raskin et al.[60]studies individually brought the results to borderline statistical significance. There were no clear differences between these two studies and the other included studies. Given the small number of events in a small number of studies and the lack of statistically significant heterogeneity, we were unable to explore potential differences between studies.

Figure 36. Pooled odds ratio of cardiovascular morbidity, comparing premixed insulin analogues to other diabetes medications

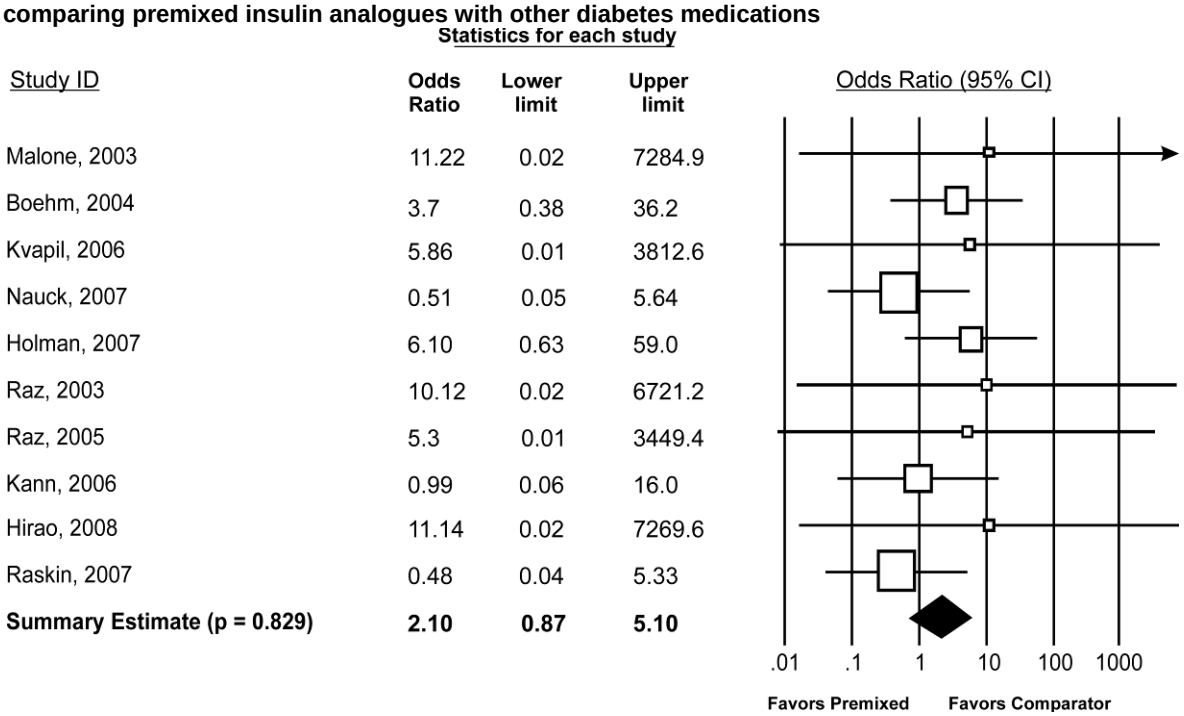


Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.
Test for heterogeniety: Q = 2.11 with 4 degrees of freedom (p =0.715)
I-squared statistic = 0 percent

Nephropathy.

Premixed insulin analogues versus other diabetes medications. One study reported nephropathy as an outcome,[32] and two studies reported it as an adverse event.[60,79] A 1-year parallel-arm RCT of patients already taking metformin plus a sulfonylurea (n = 708) had three arms (insulin aspart 70/30 twice daily, insulin aspart thrice daily, and long-acting insulin detemir at bedtime or twice daily if required) and reported nephropathy as an outcome.[32] This study reported a statistically significant increase in plasma creatinine in the premixed and rapid-acting insulin analogue groups (0.05 mg/dL in both) after 1-year of followup, as compared to the long-acting insulin analogue group (0.02 mg/dL). The study also reported a decrease in the absolute albumin-to-creatinine ratio in the long-acting insulin group (-1.8), as compared to the other two groups (-0.9), although this difference was not statistically significant (p-value = 0.08 for the differences among the three groups). This potential difference in albumin-to-creatinine ratio may be responsible for the small yet statistically significant differences in plasma creatinine. The long-term clinical impact of these small absolute differences in plasma creatinine is uncertain.

Figure 37. Pooled odds ratio of combined outcomes including mortality and cardiovascular morbidity, comparing premixed insulin analogues with other diabetes medications



Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.
Test for heterogeniety: Q = 3.45 with 7 degrees of freedom (p =0.841)
I-squared statistic = 0 percent

Two short duration parallel-arm RCTs reported on withdrawals because of kidney problems but showed no consistent patterns. They reported a withdrawal due to increased creatinine in the premixed insulin analogue arm (insulin aspart 70/30 in combination with metformin plus pioglitazone), as compared with no events in the active comparator arm (metformin plus pioglitazone) in one study,[60] and one withdrawal due to renal insufficiency in the active comparator arm (insulin glargine plus metformin), as compared with no events in the premixed insulin arm (insulin lispro 50/50 plus metformin) in the second study.[79]

Other clinical outcomes. We did not find any study that reported other clinical outcomes, such as neuropathy or retinopathy, while comparing premixed insulin analogues to other antidiabetic agents.

One Premixed Insulin Analogue Versus Another Premixed Insulin Analogue (Insulin Aspart 70/30 Versus Insulin Lispro 75/25)

All-cause and cardiovascular disease mortality. One small crossover RCT of 24-week duration compared insulin aspart 70/30 to insulin lispro 75/25 and reported one death from myocardial infarction in the insulin lispro 75/25 arm; this death occurred after the patient had withdrawn from the study following a diagnosis of malignant neoplasm; there were no deaths in the insulin aspart 70/30 arm.[55]

Other clinical outcomes. No study comparing one premixed insulin analogue to another reported any other clinical outcomes, such as cardiovascular morbidity or microvascular disease.

FDA, European Medicines Agency, and Pharmaceutical Industry Data

In the FDA medical reviews on insulin lispro 50/50 and insulin lispro 75/25 that evaluated three studies (study numbers IODK, IODM, IODN), there were no reports of death or other clinical outcomes.[86] However, the FDA review mentioned 17 deaths that occurred in the related studies using insulin analogues in premixed and in non-premixed formulations. We were unable to synthesize these data, since the documentation stated the number of deaths but not the total number of subjects. Also, there was no information about whether there were comparator arms with any deaths.

The FDA medical reviews on insulin aspart 70/30 reported a few clinical events in a study with 35 percent type 1 diabetes subjects.[87] They did not break down the events by type of diabetes; therefore, we did not include this study in our review.

We also evaluated documents from the EMEA for insulin aspart 70/30 and did not find any reports of the presence or absence of clinical outcomes in these documents.[88]

Finally, we evaluated product labels and data provided by several pharmaceutical companies (Eli Lilly and Company and Sanofi-Aventis). We identified three crossover studies that reported data on clinical outcomes. Although all three studies were included in our overall review because they were peer-reviewed publications,[64-66] we found additional data in the information supplied by Eli Lilly and Company. For instance, the pharmaceutical information reported no deaths in either arm in two of the three studies,[89] yet this result was not stated in the peer-reviewed publications.[64,65] Furthermore, the pharmaceutical information listed one person with chest pain, one with cardiac disorder (tachycardia and palpitations), and one with peripheral vascular disorder in the insulin glargine arm, versus no subjects with chest pain, two with cardiac disorders, and one with a peripheral vascular disorder in the premixed insulin analogue arm (insulin lispro 50/50 with breakfast/lunch and insulin lispro 75/25 with dinner).[90] The peer-reviewed publication, however, did not report on these cardiovascular events.[64] In the third study, the peer-reviewed publication[66] reported one death from fatal myocardial infarction in the premixed insulin analogue arm and one death in the insulin glargine arm; however, the pharmaceutical information reported only the event in the premixed insulin analogue arm.[91] No new information relevant to these clinical outcomes was reported in the data sent by Sanofi-Aventis or in any of the product labels.

The incorporation of these extra data into the meta-analyses that included crossover studies did not markedly change any of our conclusions (OR for all-cause mortality = 2.46; 95 percent CI: 0.89 to 6.80 and OR for cardiovascular morbidity = 0.93; 95 percent CI: 0.55 to 1.57).

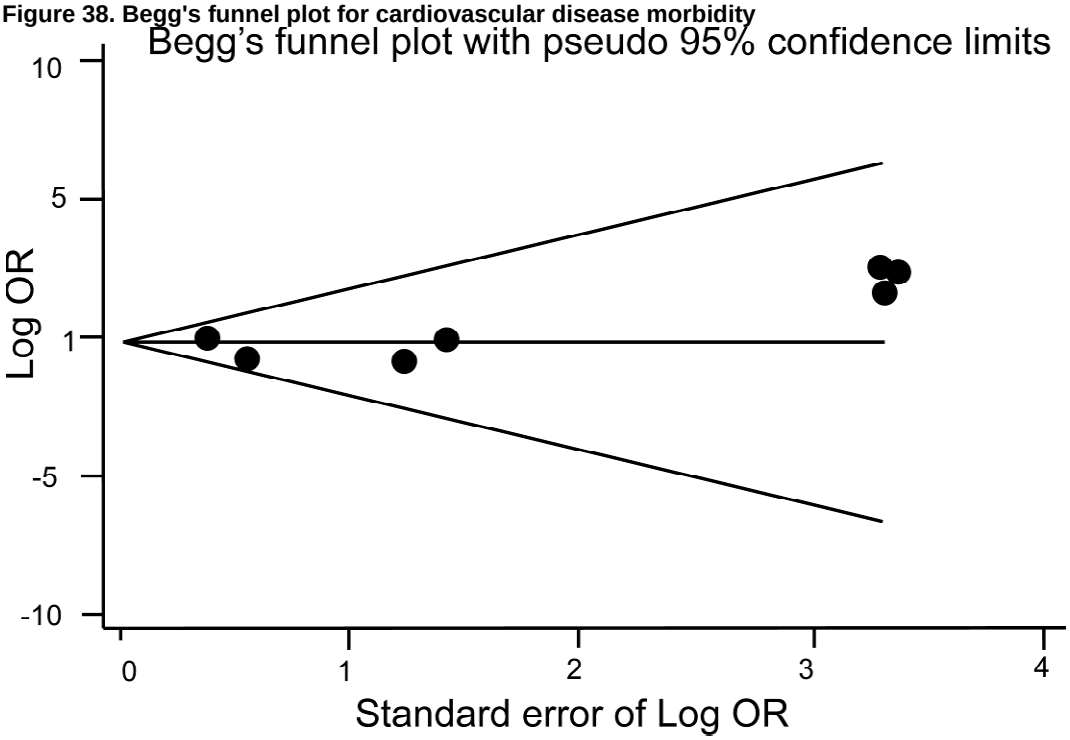
Publication Bias

Overall, we did not find strong evidence for publication bias in this literature on clinical outcomes. Across all analyses, there was no statistically significant publication bias ($p < 0.05$), as assessed by the less-conservative Eggers test. It is important to note that in most cases the number of studies in each comparison was small and was unlikely to have had high power to detect moderate publication bias. Visual examination of the funnel plot for cardiovascular morbidity was suggestive that some small studies with protective effects of premixed insulin analogues may have been missing (see Figure 38).

Study Quality Assessment

Most of the 16 studies (n = 14) were rated as being of good or fair quality.[32,45,49,51,55,57,58,60,61,66,68,77,79,83] Thirteen of these were randomized with few losses to followup, and they described dropouts and withdrawals.[32,45,49,51,55,57,58,60,66,68,77,79,83] One randomized study was rated as poor quality since it excluded one-third of the subjects from the efficacy analysis due to receipt of expired drug.[65] Two studies had greater than 10 percent patients who were lost during followup,[54,61] but one of these did report on reasons for withdrawals and losses to followup.[54] All studies were unblinded except for one,[32] and most studies (n = 12) reported receiving pharmaceutical industry funding. The source of funding has the potential to induce reporting bias, especially for outcomes such as cardiovascular morbidity, which involves more subjectivity in outcome ascertainment than does mortality.

Figure 38. Begg's funnel plot for cardiovascular disease morbidity



Other Quality Issues

Only one RCT evaluated safety outcomes for longer than 1 year.[45] Followup was sufficient in the remaining RCTs for intermediate outcomes but not for assessment of clinical outcomes, which were relatively rare, especially mortality. Even the one RCT with 2-year data had extremely few mortality events.[45] While four studies did not report on whether the analysis for adverse events was intention-to-treat,[32,45,55,68] this information would not have affected our results, since we abstracted data assuming intention-to-treat. Several studies reported on serious adverse events but did not specifically mention clinical outcomes or did not define what was meant by serious events. Two studies reported one death but did not state in which arm the event occurred,[43,69] Although the elimination of the two studies did not affect our results, elimination

of many studies as a result of a lack of reporting by authors could bias these results in either direction.

Applicability Assessment

Although the evidence was insufficient to allow us to conclusively identify an effect of premixed insulin analogues on clinical outcomes, the applicability of these scanty data was fair, with some limitations as noted below. We found that the studies were mainly representative of the general population of type 2 diabetes, with the exception of race and severity/spectrum of illness. Race was not reported in most of the studies and was deemed not representative or only partially representative in the majority of studies that did report race.[32,51,57,68,79] Studies had diverse inclusion and exclusion criteria that excluded selected populations in the case of most studies. Four studies excluded subjects with major complications from type 2 diabetes.[54,58,77,79] Others excluded insulin-naïve subjects,[51,80] subjects with suboptimal glucose control,[49] and/or insulin-treated subjects.[32,50,58,65] Outpatient clinics were the population source in the few studies supplying this information.[32,49,57,61] Comparator medications were considered a good alternative in most studies,[32,45,50,51,54,55,58,61,65,66,68,77,79] and the dose schedules and routes of administration of these medications were reflective of current clinical practice in all the studies. Standards of care for subjects with diabetes were similar to the U.S. standards in most studies.[32,45,51,54,55,57,58,60,65,66,68,77,79] The percentage of subjects enrolled versus those screened was greater than 50 percent for most studies, although five studies did not report this information.[50,57,61,66,77] All except two studies[60,66] had fewer than 10 percent of subjects excluded during run-in, or no run-in period existed.

Adherence

Key Messages

- No evidence was found in any studies regarding the outcome of patient adherence. We therefore evaluated quality of life outcomes, since these outcomes may affect patient adherence.

Quality of Life

Key Messages

- In the four studies using validated measurement tools, only one of six quality of life outcomes (psychological distress) showed a statistically significant difference, favoring the premixed insulin analogues over other antidiabetic agents.

- No firm conclusions could be drawn regarding quality of life outcomes for any comparisons because of the differences in outcome definitions, measurement techniques, populations, and comparators between studies.

Evidence Grades (see Appendix E, Evidence Table 1)

- The quantity, quality, and consistency of the body of evidence was graded as low for the following comparison:
    - Premixed insulin analogues versus other antidiabetic agents.

- There was no evidence to assess the quantity, quality, and consistency of the body of evidence or the following comparisons:
    - Premixed insulin analogues versus any other comparison evaluated in this report but not listed above.

Study Characteristics

Of the 45 studies, only six reported on quality of life.[32,48,59,72,74,76] Four studies were moderate-size parallel-arm RCTs (143 to 708 subjects),[32,59,72,76] while the other two were small- to moderate-sized crossover studies with no washout period (49 to 160 subjects).[48,74] Most studies had a short duration of followup, lasting 4 to 6 months,[48,59,72,74,76] with one study lasting 1 year.[32] Four studies were conducted in one or two mainly European countries[32,48,76] or Russia,[59] while the rest of the studies were conducted in the U.S.[32] or multiple countries.[72] Exclusion criteria varied depending on the study. Most studies (n = 5) excluded moderate to severely obese subjects with a BMI over 35 or 40 kg/m^2,[32,48,59,72,76] and/or subjects with severe hyperglycemia (i.e., A1c greater than or equal to 9.5, 10, or 10.5 percent).[32,48,74,76] Most studies reported either excluding subjects who used insulin during the past 3 to 6 months,[48,72,76] or excluding prior insulin users.[32,59] Half of the studies excluded subjects with significant comorbidity, such as a history of cardiovascular disease or complications from type 2 diabetes.[32,59,72]

Subjects were mainly middle-aged or older, overweight to mildly obese adults with mild to moderate hyperglycemia (mean A1c range from 7.5 percent to 10.4 percent). The average or median duration of diabetes for these subjects ranged from 5 to 12 years. The studies had a diverse gender ratio but were not as diverse in terms of racial mix. One study that reported race had mainly Caucasian subjects.[32]

Reporting of Quality of Life

We used the definitions for the quality of life outcome that were reported by the authors; these definitions included a variety of outcomes, such as treatment satisfaction or depression.

Premixed Insulin Analogues Versus Long-Acting Insulin Analogues or Rapid-Acting Insulin Analogues

Three studies[32,74,76] evaluated four different quality of life outcomes (quality of life, treatment satisfaction, willingness to continue treatment, and depression) and compared premixed insulin analogues to long-acting insulin analogues or rapid-acting insulin analogues (see Table 11 and Appendix E, Evidence Table 4).

The largest and longest 1-year parallel-arm RCT of patients already taking metformin plus a sulfonylurea (n = 708) compared three treatments (insulin aspart 70/30 twice daily, insulin aspart

thrice daily, and long-acting insulin detemir at bedtime or twice-daily if required). This study did not find a statistically significant difference between groups in terms of self-reported quality of life using the Euro-QoL validated questionnaire (winsorized means 0.76, 0.76, and 0.78, respectively).[32]

The second study was a crossover RCT comparing insulin lispro 75/25 to insulin glargine for 12 weeks on each treatment. It reported no statistically significant differences in depression using the Beck Depression Inventory II, which is a validated questionnaire (mean scores of 5.5 and 6.8, respectively).[74]

Table 11. Summary of quality of life measures in studies comparing a premixed insulin analogue to another antidiabetic agent

Comparisons	N of studies	N of total participants	Outcomes measured	Number of studies using validated instruments
Premixed insulin analogues versus long-acting insulins	3[32,76*,74]	912	Quality of life, depression/mood, treatment satisfaction, or willingness to continue treatment	2
Premixed insulin analogues versus premixed human insulin	1[48]	160	Treatment satisfaction	1
Premixed insulin analogues versus oral medications	2[59,72]	451	Treatment satisfaction, barriers to activity, psychological distress, disinhibited eating, or willingness to continue treatment	1
Premixed insulin analogues versus rapid-acting insulin analogue	2[76*,32]	867	Quality of life, treatment satisfaction, or willingness to continue treatment	1

* The one study using a nonvalidated instrument to measure treatment satisfaction and willingness to continue treatment did not do a statistical analysis to compare groups, yet it reported a qualitative difference between groups when comparing the premixed insulin analogue to the long-acting insulin analogue arm only.

The third, and relatively lower-quality, parallel-arm RCT compared thrice-daily insulin lispro 50/50 to thrice-daily insulin lispro or once-daily insulin glargine. Study participants who were already on oral antidiabetic agents were advised to stop their medications.[76] The authors reported an increased proportion of subjects with treatment satisfaction in all three arms at the end of the study, as compared with baseline, and a high willingness to continue treatment in all three arms when measured using nonvalidated questionnaires. While the long-acting insulin arm had a smaller increase in treatment satisfaction (24.5 percent) than the other two arms (44.2 percent and 44.5 percent) and had a lower proportion of subjects willing to continue treatment (77.4 percent versus 88.5 percent and 83.3 percent), the authors did not analyze whether these small differences were statistically significant. The insulin glargine comparator arm was not given with oral antidiabetic agents as is typical in clinical practice; therefore, those in the insulin glargine arm had a higher fasting glucose and lower decreases in A1c than did those in the other two arms, a result that may have caused patients to be less satisfied with their overall treatment.

Premixed Insulin Analogues Versus Premixed Human Insulin

One double-blinded crossover RCT compared treatment satisfaction after 16 weeks in subjects taking insulin aspart 70/30 to the subjects taking NPH/regular insulin 70/30 and reported no statistically significant difference between groups (mean difference = -0.46) using the validated Diabetes Treatment Satisfaction Questionnaire (DTSQ; see Table 11 and Appendix E, Evidence Table 4).[48]

Premixed Insulin Analogues Versus Oral Antidiabetic Agents

Two short duration parallel-arm RCTs evaluated five different quality of life outcomes (treatment satisfaction, barriers to activity, willingness to continue treatment, disinhibitory eating, or psychological distress), comparing premixed insulin analogues to oral antidiabetic agents (see Table 11 and Appendix E, Evidence Table 4).[59,72] Only one of these studies used validated questionnaires (the DTSQ for treatment satisfaction and the Diabetes Health Profile for disinhibitory eating, barriers to activity, and psychological distress).[59] This 16 week parallel-arm RCT compared these quality of life measures among three arms: thrice-daily insulin aspart 70/30, thrice-daily insulin aspart 70/30 plus metformin, and continuation of oral antidiabetic agents. They reported no statistically significant differences between groups in any of the validated measures, except for a lower psychological distress score in the insulin aspart 70/30 arm than in the continued oral antidiabetic agent arm. They did not report any quantitative results beyond a p-value of 0.026; therefore, we were unable to determine the clinical relevance of these data.

Another 16-week parallel-arm RCT compared overall treatment satisfaction among subjects 60 to 80 years of age who received insulin lispro 75/25 preprandial injections, insulin lispro 75/25 postprandial injections, or glyburide. The authors reported a slightly lower overall treatment satisfaction score with glyburide than with insulin lispro 75/25 (mean score 3.98 versus 4.35, respectively, p = 0.014) using a nonvalidated questionnaire.[72] The clinical importance of this minor difference in scores was unclear. They also reported a higher willingness to continue treatment in the insulin lispro arms than in the glyburide arm (92 percent versus 79 percent, respectively, p = 0.041). The glyburide active comparator arm was not the best comparator for the premixed insulin analogues, since all subjects were hyperglycemic on maximum dose sulfonylureas prior to study randomization. Therefore, the subjects may have been less satisfied with their treatment because they were not receiving optimal treatment for their hyperglycemia. As one might expect, the insulin lispro 75/25 arm showed a greater reduction in HbA1c than did glyburide in this trial.

FDA, European Medicines Agency, and Pharmaceutical Industry Data

No additional data on quality of life outcomes were identified from these sources.

Study Quality Assessment

Most of the studies (n = 5) were rated as being of good or fair quality,[32,48,59,74,76] were randomized with few losses to followup,[32,48,59,72,76] and described dropouts and withdrawals (see Appendix E, Evidence Table 7).[32,48,59,72,76] One randomized study was rated as poor quality since

the comparator, glyburide, was maintained at pretrial doses while the premixed insulin analogue dose was adjusted to obtain optimal glucose control.[72] This difference could potentially have affected glycemic control outcomes and thereby affected patients' satisfaction with their treatment. Another study had a greater than 10 percent loss to followup, and the reasons for withdrawals and participant loss during followup were not reported.[74] The majority of these studies were unblended, with the exception of two,[32,48] and most studies (n = 5) received funding from the pharmaceutical industry.

Applicability Assessment

We concluded that the body of evidence regarding quality of life outcomes had fair applicability to the U.S. population with type 2 diabetes (see Appendix E, Evidence Table 8). These studies were mainly representative of the general population with type 2 diabetes, with the exception of race and severity/spectrum of illness. Drug comparators were only considered the best alternatives in four[32,48,59,74] of the six studies. Race was not reported in half of the studies[48,59,72] and was deemed non-representative in the ones that did report race.[32,74,76] The studies had diverse eligibility criteria that excluded selected populations from most of the studies. They excluded subjects with a new diagnosis of type 2 diabetes[72] or subjects taking insulin already.[32,59,76] One study excluded subjects under 60 years of age or greater than 80 years of age.[72] Outpatient clinics were the population source in the two studies reporting these data,[32,72] and one of these trials occurred in subspecialty clinics.[72] The dose schedules and routes of administration of the comparator medications were reflective of current clinical practice in all the studies. Standards of care for subjects with diabetes were similar to those in the U.S. in all of the studies except one.[59] The percent of subjects enrolled versus screened were greater than 50 percent for all the studies, and all had fewer than 10 percent of subjects excluded during the run-in, or no run-in period existed.[32,48,59,72,74,76]

Key Question 3

Does the effectiveness or safety of the new premixed insulin analogue regimens differ in the following sub-populations from that of diabetes patients as a whole?

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

We could not find any studies that had specifically explored the effect of premixed insulin analogues on specific subpopulations such as the very elderly, minorities, or patients with comorbid conditions. Only one study enrolled somewhat older patients (between 60 and 80 years of age) and compared insulin lispro 75/25 to glyburide.[72] This study found a significant decrease in fasting glucose as well as pre-dinner glucose levels with insulin lispro 75/25 as compared to glyburide (mean difference = -43.9 and -32.6 mg/dL, respectively; $p < 0.01$ for both). In addition, there was a significant decrease in postprandial glucose after breakfast and dinner with

insulin lispro 75/25 in this relatively older population (mean difference = -58.3 and -43.9 mg/dL, respectively; $p < 0.01$ for both). This study also found a significant decrease in A1c with insulin lispro 75/25, as compared to glyburide (mean difference = -0.78 percent; $p < 0.01$).

Key Question 4

Does the effectiveness or safety of the new premixed insulin analogue regimens differ in individuals on oral antidiabetic agents and 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) from that of diabetes patients as a whole?

Effect of Premixed Insulin Analogues in Patients Taking Oral Antidiabetic Agents

We identified three published studies[51,54,59] and two unpublished studies[92,93] that compared premixed insulin analogue monotherapy to a combination of oral antidiabetic agents and premixed insulin analogues. In the study by Kvapil et al., insulin aspart 70/30 was compared to a combination of insulin aspart 70/30 and metformin.[51] The insulin aspart 70/30 dose was adjusted in both arms throughout the trial to optimize glucose control, while the metformin dose was fixed throughout the trial. At the end of the trial, the daily insulin dose was higher in the insulin aspart 70/30 monotherapy group than in the combination group (0.51 units/kg/day versus 0.30units/kg/day; p-value not reported).

Raz et al.[54] compared insulin aspart 70/30 monotherapy to a combination of insulin aspart 70/30 and pioglitazone over 18 weeks. The insulin dose was adjusted to optimize glucose control, while the pioglitazone dose was kept fixed at 30 mg daily. At the end of the trial, the insulin dose in the monotherapy arm was significantly larger than that in the combination arm (0.4 units/kg versus 0.3 units/kg; $p = 0.002$).

Ushakova et al.[59] compared thrice-daily insulin aspart 70/30 to twice-daily insulin aspart 70/30 plus metformin over a 16-week period. Insulin aspart and metformin doses were adjusted to optimize glycemic control. At the end of the trial, the total daily insulin dose was higher in the insulin aspart 70/30 monotherapy arm (55.5 versus 44.8 units).

In one unpublished study, insulin aspart 70/30 twice daily was compared to insulin aspart 70/30 once daily plus metformin over a 24-week period.[92] In the second unpublished study, insulin aspart 70/30 twice daily was compared with aspart 70/30 twice daily plus metformin over a 24-week period.[93]

Fasting glucose (see Appendix E, Evidences Table 4 and 11). All studies found that the combination of insulin aspart 70/30 with oral antidiabetic agents was more effective than monotherapy with insulin aspart 70/30 in lowering fasting glucose, although the differences did not reach statistical significance in any study. Similarly, pre-dinner glucose levels were lower in two studies with the combination therapy, but the reduction did not reach statistical significance in one study,[51] and statistical significance was not reported in the second study.[54] In contrast, monotherapy with insulin aspart 70/30 three times daily was more effective in lowering pre-

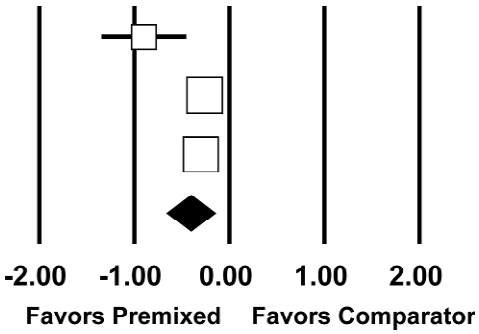
dinner glucose levels than was combination therapy in the third study, although this difference also did not reach statistical significance.[59] In one unpublished study, combination therapy with insulin aspart 70/30 once daily plus metformin was significantly more effective than twice-daily monotherapy in lowering fasting glucose (-18 mg/dL, p = 0.01).[92] In contrast, a second unpublished study found twice-daily monotherapy to be more effective than combination therapy with twice-daily insulin aspart 70/30 plus metformin in lowering fasting glucose levels (-18 mg/dL, p = nonsignificant).[93]

Postprandial glucose (see Appendix E, Evidences Table 4 and 11). All three studies reported breakfast and dinner postprandial glucose levels and found postprandial glucose levels to be lower with the combination therapy than with the monotherapy. However, this difference reached statistical difference in only one study.[59] When the results of these three studies were pooled, there was no beneficial effect of either of the two therapies on breakfast (mean difference = 5.8 mg/dL, 95 percent CI: -4.1 to 15.7 mg/dL; p = 0.25) or dinner postprandial glucose levels (mean difference = 1.2 mg/dL; 95 percent CI: -1.7 to 1.0 mg/dL; p = 0.42).

Hemoglobin A1c (see Appendix E, Evidence Tables 4 and 11). In all three studies combination therapy with insulin aspart 70/30 plus an oral antidiabetic agent was more effective than monotherapy with insulin aspart 70/30 in lowering A1c levels. When the results of the three trials were pooled, the A1c-lowering effect of combination therapy remained significant (mean difference = 0.37 percent; 95 percent CI: 0.12 to 0.62 percent; p = 0.004; see Figure 39). In both unpublished studies, combination therapy was more effective than insulin aspart 70/30 monotherapy in lowering A1c levels, although the difference was statistically nonsignificant in one study,[92] and the other study did not report statistical significance.[93]

Figure 39. Meta-analyses of post-treatment differences in hemoglobin A1c between insulin aspart 70/30 and insulin aspart 70/30 plus oral antidiabetic agents

Study name	Statistics for each study			
	Difference in means	Lower limit	Upper limit	p-Value
Kazda 2006	-0.90	-1.34	-0.46	0.0001
Jacober 2006	-0.26	-0.42	-0.10	0.0019
Robbins 2007	-0.30	-0.48	-0.12	0.0009
Summary Estimate	**-0.40**	**-0.65**	**-0.15**	**0.0017**



Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.
Test for heterogeneity: Q = 2.626 with 2 degrees of freedom (p = 0.269)
I-squared statistic = 24 percent

Hypoglycemia (see Appendix E, Evidence Tables 5 and 11). There were no major hypoglycemic events in the three studies.[51,54,59] The incidence of minor hypoglycemic events was greater in the combination arm in the two studies than in the insulin aspart 70/30 monotherapy arm,[51,59] but it was lower in the third study.[54] On the other hand, all three studies found a statistically nonsignificant increase in the incidence of symptom-only hypoglycemia with insulin

aspart 70/30 monotherapy. Pooling the results of these studies indicated that the incidence of minor hypoglycemic events (29 versus 33; OR = 0.84; 95 percent CI: 0.45 to 1.56; p = 0.6) and symptom-only hypoglycemia (89 versus 82; OR = 1.1; 95 percent CI: 0.77 to 1.6; p = 0.6) was similar for both therapies. One unpublished study reported a single major hypoglycemic event in the combination therapy arm,[92] while there were no major events in the second unpublished study.[93] In an unpublished study,[92] there were more minor or symptom-only hypoglycemic events in the monotherapy arm (43 percent vs. 40 percent; p = not reported), while the second study[93] had more events in the combination therapy arm (40 percent vs. 29 percent, p = not reported).

Weight change (see Appendix E, Evidence Tables 6 and 11). Patients on combination therapy with insulin aspart 70/30 plus metformin gained less weight than did patients who were on monotherapy,[51,59] although the difference was not statistically significant. On the other hand, patients on the combination therapy with insulin aspart 70/30 plus pioglitazone gained more weight than did patients on monotherapy (4.0 vs. 2.2 kg); the difference between the two groups in this trial was also not significant.[54] In both unpublished studies, patients on insulin aspart 70/30 plus metformin gained less weight than did those on monotherapy.[92,93]

Quality of life (See Appendix E, Evidence Tables 6 and 11). One study[59] reported this outcome and found no difference between insulin aspart 70/30 monotherapy and insulin aspart 70/30 plus oral antidiabetic agents.

Adherence. No study evaluated this outcome.

Clinical outcomes (See Appendix E, Evidence Tables 6 and 11). One study reported a death due to myocardial infarction in the combination therapy arm.[51] Another study reported one incidence of myocardial infarction in a patient assigned to the monotherapy group.[54]

Effect of Premixed Insulin Analogues in Patients With Different Intensity of Glucose Control

We did not find any trials that specifically studied the use of premixed insulin analogues in patients with different intensities of glucose control.

Effect of Premixed Insulin Analogues in Patients With Postprandial Versus Fasting Glucose Control

We did not find any study that studied premixed insulin analogues and compared targeting control of fasting glucose with targeting control of postprandial glucose.

Discussion

This report addresses the comparative effectiveness and safety of premixed insulin analogues that are available in the U.S. Changes in blood glucose before or after a meal were the most frequently reported outcomes, followed by changes in A1c. Among adverse events, hypoglycemia was the most frequently reported outcome. Although premixed insulin analogues appear to be promising agents for treating hyperglycemia in type 2 diabetics, their effectiveness when compared to that of other antidiabetic agents has not yet been fully studied.

The Diabetes Control and Complication Trial (DCCT) and the UKPDS have highlighted the importance of achieving tighter glycemic control, with an aim of achieving an A1c of less than 7 percent or 6.5 percent (depending on the organization issuing the guidelines).[94,95] To achieve either of these targets, both fasting and postprandial glucose levels need to be controlled.[96] Current evidence suggests that in patients with higher A1c levels, targeting fasting glucose is more beneficial in bringing A1c closer to the desired target; however, as the A1c approaches 7 percent, controlling postprandial glucose becomes more important for achieving the target A1c.[96-98] The American Diabetic Association guidelines recommend a target fasting glucose of 70 to130 mg/dL and a postprandial glucose under 180 mg/dL.[99]

A near-physiologic insulin replacement regimen generally requires four daily injections of insulin, a requirement that may affect overall patient satisfaction. Premixed insulin analogues can provide a convenient and effective alternative to a near-physiologic insulin replacement regimen by providing bolus insulin with meals through a rapid-acting component and by fulfilling basal insulin requirements through a protaminated slower-release component. A major caveat of premixed insulin preparations, however, is the assumption that a particular proportion of rapid- and intermediate-acting components will be suitable for all patients; thus, they offer only limited opportunity for individualizing glycemic control.

Key Findings and Implications

Fasting Glucose

In this systematic review, we found that as compared to long-acting insulin analogues and premixed human insulin preparations, premixed insulin analogues were either less effective or similar in lowering fasting glucose. Premixed insulin analogues may be better than rapid-acting insulin analogues in lowering fasting glucose. When compared to oral antidiabetic agents, premixed insulin analogues appeared to be more effective in lowering fasting glucose. This finding has important clinical implications, since controlling fasting glucose is more effective than controlling postprandial glucose in bringing a relatively high A1c closer to the target range.[100] Most studies included in this systematic review excluded patients with very high A1c levels. Thus, the findings of this systematic review should not be extrapolated to the subpopulation of diabetic patients with uncontrolled diabetes.

Postprandial Glucose

In contrast to our findings with regard to fasting glucose (discussed above), we found that premixed insulin analogues were more effective than the long-acting insulin analogues or

premixed human insulin preparations in lowering postprandial glucose levels. However, the injections were given at the recommended time before meals in only eight studies[10,15,45,53,67,70,77,101] that compared premixed insulin analogues to premixed human insulin. Administration of premixed human insulin injections immediately before meals may have been responsible for the observed benefit of the premixed insulin analogues. Controlling postprandial glucose is important, because cardiovascular complications of diabetes, such as coronary heart disease, stroke, cardiovascular mortality, sudden cardiac death, and all-cause mortality, have been found to be closely related to postprandial glucose levels in epidemiological studies.[102-105] Better control of postprandial hyperglycemia may reduce cardiovascular complications.[106-109] However, whether the effectiveness of premixed insulin analogues in lowering postprandial hyperglycemia translates into lower incidence of cardiovascular disease is not known, since very few studies reported any measurable clinical outcomes.

Hemoglobin A1c

We found premixed insulin analogues to be more effective than long-acting insulin analogues in lowering A1c, probably because of the ability of premixed insulin analogues to control postprandial hyperglycemia. However, this finding may also reflect the fact that the total daily dose of the long-acting insulin analogue was lower than that for the daily premixed insulin analogue in several studies. We found premixed insulin analogues to be more effective than oral antidiabetic agents in lowering A1c. A1c is the standard of care for monitoring long-term glycemic control and reflects both fasting and postprandial glucose control.[99] A decrease in A1c is associated with a decrease in diabetic complications, such as retinopathy, nephropathy, and neuropathy.[1,110] Only one of these microvascular complications, diabetic nephropathy, was evaluated, and in only one study.[32] This study found no difference between premixed insulin analogues (insulin aspart 70/30), long-acting insulin analogues (insulin detemir), and rapid-acting insulin analogues (insulin aspart) in decreasing the albumin–to-creatinine ratio, even though the premixed insulin analogue was found to be more effective than the long-acting insulin analogue in lowering A1c.[32]

Clinical Outcomes

Clinical outcomes (such as all-cause mortality, cardiovascular mortality, and morbidity) were reported in only 16 RCTs. No statistically significant differences were found between premixed insulin analogues and their comparators in terms of all-cause mortality, cardiovascular mortality, or cardiovascular morbidity. While a suggestion of harm was seen in the pooled odds ratios for all-cause mortality, cardiovascular mortality, and the combined outcome for cardiovascular morbidity and mortality, these point estimates were based on few absolute events in only a few studies, in which clinical outcomes were not the primary outcomes.

Reporting bias may also be a concern, since we noted that the majority of the trials did not report on clinical outcomes; if there were no clinical outcomes, they did not report the absence of any adverse clinical effects. Also, three studies from the pharmaceutical industry reported no deaths in either arm, but these studies were not published in the peer-reviewed literature. Cardiovascular morbidity was reported in the pharmaceutical data for one study that was not peer-reviewed. The addition of these data did not significantly change our results. However, if

further data were missing from the other studies for which we did not have industry data, our results could have been shifted in either direction.

The definitions of cardiovascular morbidity varied from one study to another. Two studies[49,111] combined serious and less serious events together, potentially masking any real differences in serious cardiovascular morbidity between drugs. When we considered studies that separated more serious from less serious cardiovascular morbidity, the pooled odds ratio for the more serious cardiovascular morbidity indicated a potentially harmful effect of the premixed insulin analogues, although the results were not statistically significant in the case of either more or less serious mortality. While the rosiglitazone and pioglitazone labels have warnings about increased congestive heart failure events in subjects who use insulin of any type in conjunction with these oral medications (versus insulin alone),[84,85] we did not observe any congestive heart failure events in the few available studies, which reported only very few absolute events. In addition, rosiglitazone labels have warnings regarding the increased ischemic risk in patients who use rosiglitazone with insulin, as compared to insulin alone. The evidence was insufficient to allow us to determine whether this risk might be increased in the presence of premixed insulin analogues, as compared to other insulins used alone.

There was also insufficient evidence to allow us to draw conclusions about nephropathy outcomes. One study evaluated changes in plasma creatinine and reported a 0.02-mg/dL difference between groups, favoring insulin detemir (a long-acting insulin analogue). The clinical importance of this small difference is, however, unclear. Two other studies reported one withdrawal as a result of renal insufficiency, yet no consistent results were seen according to drug arm.

No studies were identified that evaluated any other clinical outcomes. Also, evidence is lacking on potential differences in the efficacy and safety of these medications by age, gender, race, or any comorbidity, such as a history of cardiovascular disease. We also found no evidence on the impact of potential interactions between premixed insulin analogues and other medications.

No previous systematic review has synthesized clinical outcomes comparing premixed insulin analogues to their comparators. These outcomes are the most clinically relevant, yet they require studies with long-term followup in which the clinical outcomes are the primary outcomes. While glycemic control has been associated with improved microvascular, and potentially macrovascular, outcomes in subjects with type 2 diabetes,[112-116] diabetes drugs that lower glycemic control (i.e., muraglitazar and rosiglitazone) have been potentially associated with cardiovascular harm.[117,118] This finding demonstrates the importance of evaluating potential clinical harms in all evaluations of diabetes drugs. We found no study that compared intensive control to standard glycemic control, compared premixed insulin analogues to other comparators, and reported clinical outcomes. This aspect is especially important in light of the recent early termination of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial,[119] which found higher mortality in patients randomized to the intensive therapy arm. An ongoing retrospective observational study funded by Sanofi-Aventis comparing cardiovascular outcomes in those initiating insulin glargine to those initiating premixed insulin analogues using the Integrated HealthCare Information Services (IHCIS) databases was completed in January 2008. The results of this study will give us further information regarding this important area of study.

Adherence

No evidence was found with regard to patient adherence outcomes; therefore, we decided to review studies reporting on quality of life, since such factors may affect patient adherence.

Quality of Life

Only six RCTs reported on quality of life measures.[32,48,59,72,74,76] No firm conclusions could be drawn because of the differences between studies in terms of outcome definitions, measurement techniques, populations, and comparators. In the four studies[32,48,59,74] using validated measurement tools, only one of six quality of life outcomes (psychological distress) showed a statistically significant difference, favoring the premixed insulin analogues over other antidiabetic agents In the other two studies that showed potential differences between groups that favored the premixed insulin analogues, the active comparator arms were not the best alternative comparators to use, and this choice may have influenced patient satisfaction and willingness to continue treatment.[72,76]

No systematic review has synthesized quality of life outcomes comparing premixed insulin analogues to their comparators. While quality of life may affect adherence to a medication and thereby indirectly affect intermediate and clinical outcomes, outcomes related to quality of life were rarely reported. Two industry-sponsored studies are currently underway to evaluate quality of life and treatment satisfaction with regard to premixed insulin analogues and the long-acting insulin glargine, with or without rapid-acting glulisine. The data are expected to be available later in 2008 or 2009.[120,121] If validated measures are used, then this study will constitute a helpful step toward amassing data on this important outcome.

Hypoglycemia

A relatively common side-effect of the treatment of diabetes, hypoglycemia is the major limiting factor in the management of hyperglycemia.[122] As compared to long-acting insulin analogues, premixed insulin analogues are more likely to cause hypoglycemia. This increased risk of hypoglycemia needs to be weighed against the better glycemic control obtained with premixed insulin analogues. Evidence was lacking to allow us to conclusively compare premixed insulin analogues with other antidiabetic treatments in terms of hypoglycemia incidence or hypoglycemic events. Since tighter glycemic control is associated with higher risk of hypoglycemia, it is possible that the difference in hypoglycemia between premixed insulin analogues and long-acting insulin analogues is a result of the difference in glycemic control. Davidson et al.[123] reviewed the incidence of hypoglycemia with insulin aspart 70/30 treatment and found that the risk of major hypoglycemia was lower for insulin aspart 70/30 than for premixed human insulin, but there was no difference in the incidence of minor hypoglycemia. Our conclusions are only partially consistent with theirs, for two reasons: First, we have included additional studies that have been published since their review, and, second, they included trials without a comparator in their review, whereas we did not.

Weight Change

Weight gain is a common side-effect of insulin replacement therapy.[124] According to one estimate, each 5-kg weight gain is associated with a 30 percent increase in the risk of coronary heart disease.[124] Given the paucity of data, we were able to evaluate the change in weight in the case of only one premixed insulin analogue, insulin aspart 70/30. As compared to long-acting insulin analogues, insulin aspart 70/30 was associated with greater weight gain. However, this finding is difficult to interpret, in light of the fact that long-acting insulin analogues were less effective in controlling hyperglycemia and lowering A1c. Weight gain with insulin aspart 70/30 was also evaluated in the review by Davidson et al.,[123] who reported that the weight gain seen with insulin aspart 70/30 monotherapy also occurred when this drug was used in combination with oral antidiabetic agents. Our systematic review adds to this knowledge by including more recently published trials. A recent systematic review by Gough and Tibaldi[125] evaluated the efficacy and safety of insulin aspart 70/30. Their results were similar to ours, except that they found that the degree of hypoglycemia and weight gain associated with insulin aspart 70/30 were similar to that seen with the long-acting insulin analogue. Since our systematic review includes more recently published trials and we have compared the effect across all premixed insulin analogues, we suggest that our results are more reflective of the current state of knowledge.

Limitations

There are several potential limitations to this systematic review. No studies reported on all the outcomes included in this review. In addition, the studies varied in terms of the manner in which the findings were reported. Several studies presented data on changes in blood glucose in a figure and only commented on the significant findings in the text, forcing us to abstract data from figures when possible. Some studies reported point estimates but did not report dispersion around the point estimates. Some studies did report enough data to make it possible to impute standard error of the means. Almost half of the studies were crossover studies, and the data were not reported in a manner that could be used in a quantitative synthesis without some assumptions being made. These assumptions may have affected the quantitative synthesis of the evidence. Because of the relatively small number of studies available for each comparison, a full analysis and exploration for heterogeneity could not be done. We addressed this limitation by using a random-effects model for all analyses, regardless of the presence or absence of statistical heterogeneity. The small number of studies also precluded our ability to fully assess the potential for publication bias. In addition, the small number of trials in each comparison limited our ability to analyze noninferiority and superiority trials separately.

Management of the control group was not optimal in several studies. For example, in several studies the dose of premixed insulin analogues was titrated to achieve optimal glycemic control, while the dose of oral antidiabetic agents was kept constant.[51,57,59,60,72] Also, the studies used different targets for fasting glucose to guide the titration of insulin. In cases in which a relatively less aggressive target for fasting glucose (<120 mg/dL) was applied, the trial may not have used the optimal dose of long-acting insulin analogues, resulting in a bias in favor of the premixed analogues. However, in light of the results of the ACCORD trial,[119] which reported increased mortality in patients randomized to intensive glycemic control as compared to patients randomized to standard glycemic control, it is difficult to determine the ideal target for fasting glucose.

The methodological quality of the studies evaluated was good, but the applicability was fair to good. The main reason for this limited applicability was that these were efficacy studies, which were designed to evaluate premixed insulin analogues in a limited subgroup of patients. Thus, most of the studies excluded patients with diabetic complications, other comorbid conditions, or certain subpopulations. Another factor that limited the applicability of these trials was the relatively short duration of followup of patients while on treatment. This limited followup fails to mirror the real-world situation: Once diabetic patients require insulin, they usually continue to take it for rest of their lives. Thus, whether the relative effectiveness of premixed insulin analogues with regard to some outcome measures would persist over a longer period of administration cannot be extrapolated from these studies.

Almost all of the studies that reported their source of funding were funded by the pharmaceutical industry, raising the possibility of publication bias. However, our search of the FDA scientific review did not reveal any additional studies that had not yet been reported. We found only one relevant unpublished study at www.clinicalstudyresults.org, which was completed recently.

Only in the case of some comparisons and a few outcomes were we able to find sufficient evidence to allow us to comment on the effectiveness of premixed insulin analogues. For several other comparisons and outcomes, the evidence was insufficient regarding the effectiveness of premixed insulin analogues. We found very few studies that commented on clinical outcomes.

The quality of life associated with choosing a particular treatment may influence adherence to therapy and should be addressed in the case of patients with chronic diseases. However, we found very few studies that looked at quality of life, and none addressed adherence. Moreover, those that reported quality of life did not use validated scales in some cases.

This systematic review examines the effectiveness of premixed insulin analogues compared with other antidiabetic agents (insulin or noninsulin) alone or in combination. This systematic review does not specifically examine the comparative effectiveness of different insulin regimens (such as those that vary by the frequency of premixed insulin injections in a day) for the treatment of type 2 diabetes.

Gaps in the Evidence

Intermediate Outcomes

Because of the current lack of effectiveness studies, the results of the research analyzed here should be applied with caution to individual patients with type 2 diabetes. Not all comparisons provided enough data to allow us to compare premixed insulin analogues with other antidiabetic treatments. However, several ongoing studies may provide valuable additional data to bridge the gap in the current evidence.[120,121,126]

Clinical Outcomes

Scant data exist for use in assessing clinical outcomes when premixed insulin analogues are compared with other antidiabetic treatments. The few studies that reported clinical outcomes were of relatively short duration and were neither designed nor powered to assess clinical outcomes.

Adherence and Quality of Life

No studies evaluated patient adherence. Few studies have compared the effectiveness of premixed insulin analogues to that of other antidiabetic treatments in terms of improving quality of life. In addition, two of the studies that did evaluate quality of life used non-validated scales.[72,76] Since diabetes is a chronic disease that requires different injection patterns and glucose testing depending on type of insulin regimen prescribed, longer-duration studies are needed to assess the effect of premixed insulin analogues on adherence and quality of life.

Hypoglycemia

Very few studies (or, in some cases, no studies) were available that included comparisons between certain combinations of premixed insulin analogues and other antidiabetic treatments. The relatively short duration of followup in the available studies limited our ability to draw conclusions about the incidence of hypoglycemia over a longer duration of time. Only one study that compared hypoglycemia incidence at 1 year and 2 years found a lower incidence during the second year.[45] Patients with comorbid conditions need to be included in future studies. Patients with comorbid conditions, who may be at a different risk of developing hypoglycemia from these medications, were excluded from the available trials. Thus, the results of these trials cannot be extrapolated to patients with comorbid conditions. Furthermore, definitions of minor hypoglycemia and symptoms of hypoglycemia differed among the studies.

Weight Change

The main gap in the evidence on weight change was related to the short duration of the studies. Weight gain is a relatively slowly progressing outcome, and therefore studies with a longer duration of followup can provide better insight into the extent to which premixed insulin analogues can cause weight gain.

Future Directions for Research

1. Very few studies compared a premixed insulin analogue with another premixed analogue in patients with type 2 diabetes. As premixed insulin analogues vary in their insulin structure and the ratio of rapid-acting and long-acting components, future comparative research is needed to study whether one premixed analogue is better than the other. Future research should also focus on the type of patients and/or type of glycemic controls in which a particular premixed analogue preparation is better than the other. Such studies should not only aim to evaluate intermediate clinical outcomes (such as A1c) but should also evaluate clinical outcomes.
2. We also found very few studies comparing a near-physiologic regimen (consisting of prandial rapid-acting insulin analogue injections and long-acting insulin analogues) with a relatively convenient regimen consisting of premixed insulin analogues in type 2 diabetic pateints. Such studies should not only evaluate the intermediate outcomes, clinical outcomes, and safety, but should also evaluate patient adherence to insulin treatment and quality of life.

3. Most of the studies included in this systematic review had a short followup duration. Studies with longer followup are needed to determine whether the effects observed early in treatment are sustainable and whether differences between the comparators appear later in treatment.
4. All studies had inclusion criteria that excluded certain type 2 diabetic subpopulations (such as morbidly obese, or with very poor glycemic control). These inclusion criteria limit the generalizability of these findings to all type 2 diabetic patients. Studies designed to examine the effectiveness and safety of premixed insulin analogues in type 2 diabetic patients should be conducted with less restrictive inclusion criteria. In addition, research should be conducted in representative primary care settings to assess the effectiveness and safety of premixed insulin analogues.
5. Patients with comorbid conditions, racial minorities, and very elderly patients were either excluded from the studies or were under-represented in the study populations. Such subpopulations of diabetic patients need to be included in studies examining the effectiveness and safety of premixed insulin analogues.
6. Most studies were relatively small and could not evaluate the effect of patient characteristics on study outcomes. Studies of the effectiveness and safety of premixed insulin analogues should be large enough to permit analysis of how effects may vary by patient characteristics, such as age, gender, race/ethnicity, socioeconomic status, and comorbidity.
7. We did not find any study which was specifically designed to compare the effect of premixed insulin analogues with comparators on clinical outcomes (such as cardiovascular morbidity and/or mortality). As improvement in intermediate outcomes may not always result in improvement in clinical outcomes, studies specifically designed to evaluate clinical outcomes are needed. Thus, we believe that studies should compare the potential benefits and harms of premixed insulin analogues, compared to other diabetes medications, especially in light of the wide confidence intervals we found for the risk of cardiovascular morbidity and mortality associated with premixed insulin analogues. Studies need to be sufficiently powered to make it possible to assess clinical outcomes.
8. Quality of life and adherence to treatment were evaluated in very few studies. Because diabetes is a chronic disease, the effects of premixed insulin analogues on quality of life and patient satisfaction need to be examined.
9. Another area of research that was not addressed by any study in this systematic review but needs to explored is how type 2 diabetic patients' preferences regarding the use of different insulin regimens depend on the convenience of dosing as well as the expected effects on mortality, morbidity, glycemic control, hypoglycemia, and body weight.

Conclusion

In summary, premixed insulin analogues are more effective than long-acting insulin analogues administered alone in terms of lowering postprandial glucose and A1c. Premixed insulin analogues are also more effective than premixed human insulin preparations in lowering postprandial glucose, but not A1c. The studies analyzed had several limitations that call for caution in applying the results to individual patients with type 2 diabetes. These results can only be extended to a larger population of patients with type 2 diabetes if we assume that the

unstudied subpopulations of patients will respond similarly to the patients in these studies. Individual patient factors should continue to play an important role in the selection of a particular type of insulin. Moreover, studies with a longer duration and sufficient power to allow assessment of clinical outcomes still need to be performed.

References

1. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. Lancet 1998; 352(9131):837-53.

2. Centers for Disease Control and Prevention. National diabetes fact sheet: general information and national estimates on diabetes in the United States, 2005. Atlanta, GA: U.S.: Department of Health and Human Services, Centers for Disease Control and Prevention, 2005.

3. Hirsch IB. Insulin analogues. N Engl J Med 2005; 352(2):174-83.

4. DeWitt DE, Hirsch IB. Outpatient insulin therapy in type 1 and type 2 diabetes mellitus: scientific review. JAMA 2003; 289(17):2254-64.

5. Marrero DG. Overcoming patient barriers to initiating insulin therapy in type 2 diabetes mellitus. Clin Cornerstone 2007; 8(2):33-40; discussion 41-3.

6. Hendra TJ, Taylor CD. A randomised trial of insulin on well-being and carer strain in elderly type 2 diabetic subjects. J Diabetes Complications 2004; 18(3):148-54.

7. Rolla AR, Rakel RE. Practical approaches to insulin therapy for type 2 diabetes mellitus with premixed insulin analogues. Clin Ther 2005; 27(8):1113-25.

8. Garber AJ. Premixed insulin analogues for the treatment of diabetes mellitus. Drugs 2006; 66(1):31-49.

9. 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. Diabet Med 2002; 19(5):393-9.

10. Roach P, Trautmann M, Arora V, Sun B, Anderson JH Jr. Improved postprandial blood glucose control and reduced nocturnal hypoglycemia during treatment with two novel insulin lispro-protamine formulations, insulin lispro mix25 and insulin lispro mix50. Mix50 Study Group. Clin Ther 1999; 21(3):523-34.

11. McSorley PT, Bell PM, Jacobsen LV, Kristensen A, Lindholm A. Twice-daily biphasic insulin aspart 30 versus biphasic human insulin 30: a double-blind crossover study in adults with type 2 diabetes mellitus. Clin Ther 2002; 24(4):530-9.

12. Herz M, Arora V, Campaigne BN, Scholtz HE, Potgieter MA, Mollentze W. Humalog Mix25 improves 24-hour plasma glucose profiles compared with the human insulin mixture 30/70 in patients with type 2 diabetes mellitus. S Afr Med J 2003; 93(3):219-23.

13. Christiansen JS, Vaz JA, Metelko Z, Bogoev M, Dedov I. Twice daily biphasic insulin aspart improves postprandial glycaemic control more effectively than twice daily NPH insulin, with low risk of hypoglycaemia, in patients with type 2 diabetes. Diabetes Obes Metab 2003; 5(6):446-54.

14. Malone JK, Yang H, Woodworth JR *et al*. Humalog Mix25 offers better mealtime glycemic control in patients with type 1 or type 2 diabetes. Diabetes Metab 2000; 26(6):481-7.

15. Kilo C, Mezitis N, Jain R, Mersey J, McGill J, Raskin P. Starting patients with type 2 diabetes on insulin therapy using once-daily injections of biphasic insulin aspart 70/30, biphasic human insulin 70/30, or NPH insulin in combination with metformin. J Diabetes Complications 2003; 17(6):307-13.

16. Novo Nordisk. NovoLog Mix 70/30 Package Insert. [Web Page]. Available at http://www.novologmix70-30.com/NovoLogMix7030_PI.pdf. (Accessed 2 February 2008).

17. Eli Lilly and Company. Humalog Mix75/25 Patient Information. [Web Page]. Available at http://www.humalog.com/index.jsp. (Accessed 2 February 2008).

18. Eli Lilly and Company. Humalog Mix50/50 Patient Information. [Web Page]. Available at http://www.humalog.com/index.jsp. (Accessed 2 February 2008).

19. Berlin JA. Does blinding of readers affect the results of meta-analyses? University of Pennsylvania Meta-analysis Blinding Study Group. Lancet 1997; 350(9072):185-6.

20. Jadad AR, Moore RA, Carroll D *et al*. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Control Clin Trials 1996; 17(1):1-12.

21. Wells, GA, Shea, B, O'Connel, D *et al*. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses [Web Page]. (Accessed 20 September 2007).

22. Guide for Conducting Comparative Effectiveness Reviews. Rockville, MD: Agency for Healthcare Research and Quality, 2007.

23. Valdez R, Yoon PW, Liu T, Khoury MJ. Family history and prevalence of diabetes in the US population: 6-year results from the National Health and Nutrition Examination Survey (NHANES, 1999 2004). Diabetes 2007.

24. Follmann D, Elliott P, Suh I, Cutler J. Variance imputation for overviews of clinical trials with continuous response. J Clin Epidemiol 1992; 45(7):769-73.

25. Robertson C, Idris NR, Boyle P. Beyond classical meta-analysis: can inadequately reported studies be included? Drug Discov Today 2004; 9(21):924-31.

26. Saudek CD, Derr RL, Kalyani RR. Assessing glycemia in diabetes using self-monitoring blood glucose and hemoglobin A1c. JAMA 2006; 295(14):1688-97.

27. Thompson SG, Pocock SJ. Can meta-analyses be trusted? Lancet 1991; 338(8775):1127-30.

28. Whitehead A, Whitehead J. A general parametric approach to the meta-analysis of randomized clinical trials. Stat Med 1991; 10(11):1665-77.

29. Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. Biometrics 1994; 50(4):1088-101.

30. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997; 315(7109):629-34.

31. Duval S, Tweedie R. Trim and fill: A simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. Biometrics 2000; 56(2):455-63.

32. Holman RR, Thorne KI, Farmer AJ *et al*. Addition of Biphasic, Prandial, or Basal Insulin to Oral Therapy in Type 2 Diabetes. N Engl J Med 2007; 357(17):1716-30.

33. Mantel N, Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. J Natl Cancer Inst 1959; 22(4):719-48.

34. Robins J, Greenland S, Breslow NE. A general estimator for the variance of the Mantel-Haenszel odds ratio. Am J Epidemiol 1986; 124(5):719-23.

35. Bradburn MJ, Deeks JJ, Berlin JA, Russell Localio A. Much ado about nothing: a comparison of the performance of meta-analytical methods with rare events. Stat Med 2007; 26(1):53-77.

36. Yusuf S, Peto R, Lewis J, Collins R, Sleight P. Beta blockade during and after myocardial infarction: an overview of the randomized trials. Prog Cardiovasc Dis 1985; 27(5):335-71.

37. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003; 327(7414):557-60.

38. Atkins D, Best D, Briss PA *et al*. Grading quality of evidence and strength of recommendations. BMJ 2004; 328(7454):1490.

39. Raskin P, Allen E, Hollander P *et al*. Initiating insulin therapy in type 2 Diabetes: a comparison of biphasic and basal insulin analogs. Diabetes Care 2005; 28(2):260-5.

40. Raskin PR, Hollander PA, Lewin A, Gabbay RA, Bode B, Garber AJ. Basal insulin or premix analogue therapy in type 2 diabetes patients. Eur J Intern Med 2007; 18(1):56-62.

41. Brod M, Cobden D, Lammert M, Bushnell D, Raskin P. Examining correlates of treatment satisfaction for injectable insulin in type 2 diabetes: lessons learned from a clinical trial comparing biphasic and basal analogues. Health Qual Life Outcomes 2007; 5:8.

42. Roach, Koledova E, Metcalfe S, Hultman C, Milicevic Z. Glycemic control with Humalog Mix25 in type 2 diabetes inadequately controlled with glyburide. Clin Ther 2001; 23(10):1732-44.

43. Tirgoviste CI, Strachinariu R, Farcasiu E, Milicevic Z, Teodorescu G. Humalog Mix 25 in patients with type 2 diabetes which do not achieve acceptable glycemic control with oral agents: results from a phase III, randomized, parallel study. Rom J Intern Med 2003; 41(2):153-62.

44. Malone JK, Woodworth JR, Arora V *et al*. Improved postprandial glycemic control with Humalog Mix75/25 after a standard test meal in patients with type 2 diabetes mellitus. Clin Ther 2000; 22(2):222-30.

45. Boehm BO, Vaz JA, Brondsted L, Home PD. Long-term efficacy and safety of biphasic insulin aspart in patients with type 2 diabetes. Eur J Intern Med 2004; 15(8):496-502.

46. Bebakar WM, Chow CC, Kadir KA, Suwanwalaikorn S, Vaz JA, Bech OM. Adding biphasic insulin aspart 30 once or twice daily is more efficacious than optimizing oral antidiabetic treatment in patients with type 2 diabetes. Diabetes Obes Metab 2007; 9(5):724-32.

47. Tamemoto H, Ikoma A, Saitoh T, Ishikawa SE, Kawakami M. Comparison of once-daily glargine plus sulfonylurea with twice-daily 70/30 aspart premix in insulin-naive Japanese patients with diabetes. Diabetes Technol Ther 2007; 9(3):246-53.

48. McNally PG, Dean JD, Morris AD, Wilkinson PD, Compion G, Heller SR. Using continuous glucose monitoring to measure the frequency of low glucose values when using biphasic insulin aspart 30 compared with biphasic human insulin 30: a double-blind crossover study in individuals with type 2 diabetes. Diabetes Care 2007; 30(5):1044-8.

49. Nauck MA, Duran S, Kim D *et al*. A comparison of twice-daily exenatide and biphasic insulin aspart in patients with type 2 diabetes who were suboptimally controlled with sulfonylurea and metformin: a non-inferiority study. Diabetologia 2007; 50(2):259-67.

50. Kann PH, Wascher T, Zackova V *et al*. Starting insulin therapy in type 2 diabetes: twice-daily biphasic insulin Aspart 30 plus metformin versus once-daily insulin glargine plus glimepiride. Exp Clin Endocrinol Diabetes 2006; 114(9):527-32.

51. Kvapil M, Swatko A, Hilberg C, Shestakova M. Biphasic insulin aspart 30 plus metformin: an effective combination in type 2 diabetes. Diabetes Obes Metab 2006; 8(1):39-48.

52. Joshi SR, Kalra S, Badgandi M, Rao YS, Chawla M. Designer insulins regimens in clinical practice--pilot multicenter Indian study. J Assoc Physicians India 2005; 53:775-9.

53. Abrahamian H, Ludvik B, Schernthaner G *et al*. Improvement of glucose tolerance in type 2 diabetic patients: traditional vs. modern insulin regimens (results from the Austrian Biaspart Study). Horm Metab Res 2005; 37(11):684-9.

54. Raz I, Stranks S, Filipczak R *et al*. Efficacy and safety of biphasic insulin aspart 30 combined with pioglitazone in type 2 diabetes poorly controlled on glibenclamide (glyburide) monotherapy or combination therapy: an 18-week, randomized, open-label study. Clin Ther 2005; 27(9):1432-43.

55. Niskanen L, Jensen LE, Rastam J, Nygaard-Pedersen L, Erichsen K, Vora JP. Randomized, multinational, open-label, 2-period, crossover comparison of biphasic insulin aspart 30 and biphasic insulin lispro 25 and pen devices in adult patients with type 2 diabetes mellitus. Clin Ther 2004; 26(4):531-40.

56. Kapitza C, Rave K, Ostrowski K, Heise T, Heinemann L. Reduced postprandial glycaemic excursion with biphasic insulin Aspart 30 injected immediately before a meal. Diabet Med 2004; 21(5):500-1.

57. Raz I, Mouritzen U, Vaz J, Hershkovitz T, Wainstein J, Harman-Boehm I. Addition of biphasic insulin aspart 30 to rosiglitazone in type 2 diabetes mellitus that is poorly controlled with glibenclamide monotherapy. Clin Ther 2003; 25(12):3109-23.

58. Hermansen K, Colombo M, Storgaard H, OStergaard A, Kolendorf K, Madsbad S. Improved postprandial glycemic control with biphasic insulin aspart relative to biphasic insulin lispro and biphasic human insulin in patients with type 2 diabetes. Diabetes Care 2002; 25(5):883-8.

59. Ushakova O, Sokolovskaya V, Morozova A *et al*. Comparison of biphasic insulin aspart 30 given three times daily or twice daily in combination with metformin versus oral antidiabetic drugs alone in patients with poorly controlled type 2 diabetes: a 16-week, randomized, open-label, parallel-group trial conducted in russia. Clin Ther 2007; 29(11):2374-84.

60. Raskin P, Matfin G, Schwartz SL *et al*. Addition of biphasic insulin aspart 30 to optimized metformin and pioglitazone treatment of type 2 diabetes mellitus: The ACTION Study (Achieving Control Through Insulin plus Oral ageNts). Diabetes Obes Metab 2007.

61. Hirao K, Arai K, Yamauchi M, Takagi H, Kobayashi M. Six-month multicentric, open-label, randomized trial of twice-daily injections of biphasic insulin aspart 30 versus multiple daily injections of insulin aspart in Japanese type 2 diabetic patients (JDDM 11). Diabetes Res Clin Pract 2008; 79(1):171-6.

62. Schwartz S, Zagar AJ, Althouse SK, Pinaire JA, Holcombe JH. A single-center, randomized, double-blind, three-way crossover study examining postchallenge glucose responses to human insulin 70/30 and insulin lispro fixed mixtures 75/25 and 50/50 in patients with type 2 diabetes mellitus. Clin Ther 2006; 28(10):1649-57.

63. Roach P, Malone JK. Comparison of insulin lispro mixture 25/75 with insulin glargine during a 24-h standardized test-meal period in patients with Type 2 diabetes. Diabet Med 2006; 23(7):743-9.

64. Jacober SJ, Scism-Bacon JL, Zagar AJ. A comparison of intensive mixture therapy with basal insulin therapy in insulin-naive patients with type 2 diabetes receiving oral antidiabetes agents. Diabetes Obes Metab 2006; 8(4):448-55.

65. Malone JK, Kerr LF, Campaigne BN, Sachson RA, Holcombe JH. Combined therapy with insulin lispro Mix 75/25 plus metformin or insulin glargine plus metformin: a 16-week, randomized, open-label, crossover study in patients with type 2 diabetes beginning insulin therapy. Clin Ther 2004; 26(12):2034-44.

66. Malone JK, Bai S, Campaigne BN, Reviriego J, Augendre-Ferrante B. Twice-daily pre-mixed insulin rather than basal insulin therapy alone results in better overall glycaemic control in patients with Type 2 diabetes. Diabet Med 2005; 22(4):374-81.

67. Coscelli C, Iacobellis G, Calderini C *et al*. Importance of premeal injection time in insulin therapy: Humalog Mix25 is convenient for improved post-prandial glycemic control in type 2 diabetic patients with Italian dietary habits. Acta Diabetol 2003; 40(4):187-92.

68. Malone JK, Beattie SD, Campaigne BN, Johnson PA, Howard AS, Milicevic Z. Therapy after single oral agent failure: adding a second oral agent or an insulin mixture? Diabetes Res Clin Pract 2003; 62(3):187-95.

69. Roach P, Arora V, Campaigne BN, Mattoo V, Rangwala S. Humalog Mix50 before carbohydrate-rich meals in type 2 diabetes mellitus. Diabetes Obes Metab 2003; 5(5):311-6.

70. Mattoo V, Milicevic Z, Malone JK *et al*. A comparison of insulin lispro Mix25 and human insulin 30/70 in the treatment of type 2 diabetes during Ramadan. Diabetes Res Clin Pract 2003; 59(2):137-43.

71. Herz M, Profozic V, Arora V *et al*. Effects of a fixed mixture of 25% insulin lispro and 75% NPL on plasma glucose during and after moderate physical exercise in patients with type 2 diabetes. Curr Med Res Opin 2002; 18(4):188-93.

72. Herz M, Sun B, Milicevic Z *et al*. Comparative efficacy of preprandial or postprandial Humalog Mix75/25 versus glyburide in patients 60 to 80 years of age with type 2 diabetes mellitus. Clin Ther 2002; 24(1):73-86.

73. Roach P, Yue L, Arora V. Improved postprandial glycemic control during treatment with Humalog Mix25, a novel protamine-based insulin lispro formulation. Humalog Mix25 Study Group. Diabetes Care 1999; 22(8):1258-61.

74. Cox DJ, McCall A, Kovatchev B, Sarwat S, Ilag LL, Tan MH. Effects of blood glucose rate of changes on perceived mood and cognitive symptoms in insulin-treated type 2 diabetes. Diabetes Care 2007; 30(8):2001-2.

75. Sun P, Wang R, Jacober S. The effectiveness of insulin initiation regimens in patients with type 2 diabetes mellitus: a large national medical records review study comparing a basal insulin analogue to premixed insulin. Curr Med Res Opin 2007; 23(12):3017-23.

76. Kazda C, Hulstrunk H, Helsberg K, Langer F, Forst T, Hanefeld M. Prandial insulin substitution with insulin lispro or insulin lispro mid mixture vs. basal therapy with insulin glargine: a randomized controlled trial in patients with type 2 diabetes beginning insulin therapy. J Diabetes Complications 2006; 20(3):145-52.

77. Schernthaner G, Kopp HP, Ristic S, Muzyka B, Peter L, Mitteregger G. Metabolic control in patients with type 2 diabetes using Humalog Mix50 injected three times daily: crossover comparison with human insulin 30/70. Horm Metab Res 2004; 36(3):188-93.

78. Yamada S, Watanabe M, Kitaoka A *et al*. Switching from premixed human insulin to premixed insulin lispro: a prospective study comparing the effects on glucose control and quality of life. Intern Med 2007; 46(18):1513-7.

79. Robbins DC, Beisswenger PJ, Ceriello A *et al*. Mealtime 50/50 basal + prandial insulin analogue mixture with a basal insulin analogue, both plus metformin, in the achievement of target HbA1c and pre- and postprandial blood glucose levels in patients with type 2 diabetes: a multinational, 24-week, randomized, open-label, parallel-group comparison. Clin Ther 2007; 29(11):2349-64.

80. Rosenstock J, Ahmann AJ, Colon G, Scism-Bacon J, Jiang H, Martin S. Advancing insulin therapy in type 2 diabetes previously treated with glargine plus oral agents: prandial premixed (insulin lispro protamine suspension/lispro) versus basal/bolus (glargine/lispro) therapy. Diabetes Care 2008; 31(1):20-5.

81. Korytkowski M, Bell D, Jacobsen C, Suwannasari R. 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):2836-48.

82. Eli Lilly. Trial 4957 Pilot Study Investigating the Effects of Insulin Lispro Low Mixture Compared with Insulin Glargine on Perceived Mood Symptoms in Patients with Type 2 Diabetes Mellitus. 2006.

83. Ligthelm RJ, Mouritzen U, Lynggaard H *et al*. Biphasic insulin aspart given thrice daily is as efficacious as a basal-bolus insulin regimen with four daily injections: a randomised open-label parallel group four months comparison in patients with type 2 diabetes. Exp Clin Endocrinol Diabetes 2006; 114(9):511-9.

84. Takeda Pharmaceuticals North America, I. ACTOS, A Type 2 Diabetes Treatment: Prescribing Information [Web Page]. September 2007; Available at http://www.actos.com/actos/prescribinginfo.aspx. (Accessed 1 May 2008).

85. GlaxoSmithKline. AVANDIA (rosiglitazone maleate) Tablets. Highlights of Prescribing Information [Web Page]. March 2008; Available at http://us.gsk.com/products/assets/us_avandia.pdf. (Accessed 1 May 2008).

86. Center for Drug Evaluation and Research. Medical Review(s). Application Number: 21-017, 21-018 [Web Page]. Available at http://www.fda.gov/cder/foi/nda/99/21017_Humalog_medr.pdf. (Accessed 30 August 2007).

87. Center for Drug Evaluation and Research. Medical Review(s). Approval Package for: NovoLog Mix 70-30. Application Number: 21-172 [Web Page]. (Accessed 30 August 2007).

88. European Medicine Agency. European Public Assessment Report for NovoRapid. Scientific Discussion. [Web Page]. Available at http://www.emea.europa.eu/humandocs/PDFs/EPAR/Novorapid/272799en6.pdf. (Accessed 30 August 2007).

89. Eli Lilly and Company. Summary ID #4050. Clinical Study Summary: Study F3Z-MC-IOND. Efficacy and Safety of Twice-Daily Insulin Lispro Low Mixture Compared to Once-Daily Insulin Glargine in Patients Who Have Been Using One or More Oral Antihyperglycemic Agents Without Insulin [Web Page]. Available at http://www.clinicalstudyresults.org/documents/company-study_1045_0.pdf. (Accessed 30 August 2007).

90. Eli Lilly and Company. Summary ID #5881. Clinical Study Summary: Study F3Z-US-IONW. Comparison of Intensive Mixture Therapy vs. Basal Insulin Therapy in Patients with Type 2 Diabetes Receiving Oral Antidiabetes Agents [Web Page]. Available at http://www.clinicalstudyresults.org/documents/company-study_1048_0.pdf.

91. Eli Lilly and Company. Summary ID #4011. Clinical Study Summary: Study F3Z-MC-IOMX. Efficacy and Safety of Twice-Daily Insulin Lispro Low Mixture Compared to Once-Daily Insulin Glargine in Patients With Type 2 Diabets on NPH Alone or Combination Therapy of Insulin and Oral Agents [Web Page]. Available at http://www.clinicalstudyresults.org/documents/company-study_2418_0.pdf. (Accessed 30 August 2007).

92. Novo Nordisk . Biphasic insulin aspart. Trial ID: BIAsp-1579. Integrated Clinical Trial Report. Report Body and Synopsis [Web Page]. 29 June 2006; Available at http://www.novonordisk-trials.com/website/pdf/registry/bin_20070903-125523-991.pdf. (Accessed 30 April 2008).

93. Novo Nordisk . Biphasic insulin aspart 30. Trial ID: BIAsp-1594. Clinical Trial Report. Report Synopsis [Web Page]. 20 July 2007; Available at http://www.novonordisk-trials.com/website/pdf/registry/bin_20071204-125712-724.pdf. (Accessed 30 April 2008).

94. Clinical Practice Recommendations 2005. Diabetes Care 2005; 28 Suppl 1:S1-79.

95. The American Association of Clinical Endocrinologists Medical Guidelines for the Management of Diabetes Mellitus: the AACE system of intensive diabetes self-management--2000 update. Endocr Pract 2000; 6(1):43-84.

96. Abrahamson MJ. Optimal glycemic control in type 2 diabetes mellitus: fasting and postprandial glucose in context. Arch Intern Med 2004; 164(5):486-91.

97. Monnier L, Lapinski H, Colette C. Contributions of fasting and postprandial plasma glucose increments to the overall diurnal hyperglycemia of type 2 diabetic patients: variations with increasing levels of HbA(1c). Diabetes Care 2003; 26(3):881-5.

98. Woerle HJ, Neumann C, Zschau S *et al*. Impact of fasting and postprandial glycemia on overall glycemic control in type 2 diabetes Importance of postprandial glycemia to achieve target HbA1c levels. Diabetes Res Clin Pract 2007; 77(2):280-5.

99. Standards of medical care in diabetes--2008. Diabetes Care 2008; 31 Suppl 1:S12-54.

100. Monnier L, Colette C, Monnier L, Colette C. Contributions of fasting and postprandial glucose to hemoglobin A1c. Endocr Pract 2006; 12 Suppl 1:42-6.

101. White JR Jr. Insulin glargine clinical trials. Clin Ther 2004; 26(7):1179-81; discussion 1182-3.

102. Lowe LP, Liu K, Greenland P, Metzger BE, Dyer AR, Stamler J. Diabetes, asymptomatic hyperglycemia, and 22-year mortality in black and white men. The Chicago Heart Association Detection Project in Industry Study. Diabetes Care 1997; 20(2):163-9.

103. Orencia AJ, Daviglus ML, Dyer AR, Walsh M, Greenland P, Stamler J. One-hour postload plasma glucose and risks of fatal coronary heart disease and stroke among nondiabetic men and women: the Chicago Heart Association Detection Project in Industry (CHA) Study. J Clin Epidemiol 1997; 50(12):1369-76.

104. de Vegt F, Dekker JM, Ruhe HG *et al*. Hyperglycaemia is associated with all-cause and cardiovascular mortality in the Hoorn population: the Hoorn Study. Diabetologia 1999; 42(8):926-31.

105. Curb JD, Rodriguez BL, Burchfiel CM, Abbott RD, Chiu D, Yano K. Sudden death, impaired glucose tolerance, and diabetes in Japanese American men. Circulation 1995; 91(10):2591-5.

106. Shichiri M, Kishikawa H, Ohkubo Y, Wake N. Long-term results of the Kumamoto Study on optimal diabetes control in type 2 diabetic patients. Diabetes Care 2000; 23 Suppl 2:B21-9.

107. Wake N, Hisashige A, Katayama T *et al*. Cost-effectiveness of intensive insulin therapy for type 2 diabetes: a 10-year follow-up of the Kumamoto study. Diabetes Res Clin Pract 2000; 48(3):201-10.

108. Chiasson JL, Josse RG, Gomis R, Hanefeld M, Karasik A, Laakso M. Acarbose treatment and the risk of cardiovascular disease and hypertension in patients with impaired glucose tolerance: the STOP-NIDDM trial. JAMA 2003; 290(4):486-94.

109. Esposito K, Giugliano D, Nappo F, Marfella R. Regression of carotid atherosclerosis by control of postprandial hyperglycemia in type 2 diabetes mellitus. Circulation 2004; 110(2):214-9.

110. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). UK Prospective Diabetes Study (UKPDS) Group. Lancet 1998; 352(9131):854-65.

111. Bethel MA, Feinglos MN. Insulin analogues: new therapies for type 2 diabetes mellitus. Curr Diab Rep 2002; 2(5):403-8.

112. Schellhase KG, Koepsell TD, Weiss NS. Glycemic control and the risk of multiple microvascular diabetic complications. Fam Med 2005; 37(2):125-30.

113. Vijan S, Hofer TP, Hayward RA. Estimated benefits of glycemic control in microvascular complications in type 2 diabetes. Ann Intern Med 1997; 127(9):788-95.

114. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. Lancet 1998; 352(9131):837-53.

115. The relationship of glycemic exposure (HbA1c) to the risk of development and progression of retinopathy in the diabetes control and complications trial. Diabetes 1995; 44(8):968-83.

116. Selvin E, Marinopoulos S, Berkenblit G *et al*. Meta-analysis: glycosylated hemoglobin and cardiovascular disease in diabetes mellitus. Ann Intern Med 2004; 141(6):421-31.

117. Nissen SE, Wolski K, Topol EJ. Effect of muraglitazar on death and major adverse cardiovascular events in patients with type 2 diabetes mellitus. JAMA 2005; 294(20):2581-6.

118. Kahn SE, Haffner SM, Heise MA *et al*. Glycemic durability of rosiglitazone, metformin, or glyburide monotherapy. N Engl J Med 2006; 355(23):2427-43.

119. National Heart Lung and Blood Institute. ACCORD, Questions and Answers, NHLBI [Web Page]. 13 February 2008; Available at http://www.nhlbi.nih.gov/health/prof/heart/other/accord/q_a.htm. (Accessed 3 May 2008).

120. sanofi-aventis. Insulin Glargine Plus Insulin Glulisine Multiple Daily Injections (MDI) Versus Premix Insulin Treatment in Subjects with With Diabetes Mellitus (Type 1 or Type 2) [Web Page]. 1 May 2008; Available at http://www.clinicaltrials.gov/ct2/show/NCT00135941. (Accessed 2 May 2008).

121. sanofi-aventis. Insulin Glargine "All to Target" Trial [Web Page]. 1 May 2008; Available at http://www.clinicaltrials.gov/ct2/show/NCT00384085. (Accessed 2 May 2008).

122. Cryer PE. Hypoglycaemia: the limiting factor in the glycaemic management of Type I and Type II diabetes. Diabetologia 2002; 45(7):937-48.

123. Davidson J, Vexiau P, Cucinotta D, Vaz J, Kawamori R. Biphasic insulin aspart 30: literature review of adverse events associated with treatment. Clin Ther 2005; 27 Suppl B:S75-88.

124. Hermansen K, Mortensen LS. Bodyweight changes associated with antihyperglycaemic agents in type 2 diabetes mellitus. Drug Saf 2007; 30(12):1127-42.

125. Gough SC, Tibaldi J. Biphasic insulin aspart in type 2 diabetes mellitus: an evidence-based medicine review. Clin Drug Investig 2007; 27(5):299-324.

126. Sanofi-aventis Groupe. GINGER: Insulin Glulisine in Diabetes Mellitus, Type 2 [Web Page]. 1 May 2008; Available at http://www.clinicaltrials.gov/ct2/show/NCT00174668. (Accessed 2 May 2008).

List of Abbreviations

µg	Microgram
µmol/L	Micromol per liter
AA	African American
AHRQ	Agency for Healthcare Research and Quality
B	Baseline
BDI-II	Beck Depression Inventory – revised
B-F	Mean difference from baseline
BG	Blood glucose
BHI	Biphasic human insulin
BIAsp	Biphasic insulin aspart
BID	Twice daily
BMI	Body mass index
BS	Blood sugar
C	Caucasian
CGMS	Continuous glucose monitoring system
CI	Confidence interval
CINAHL	Cumulative Index to Nursing & Allied Health Literature
CNS	Central nervous system
CRP	C-reactive protein
CVD	Cardiovascular disease
D	Duration
DBP	Diastolic blood pressure
DCCT	Diabetes Control and Complications Trial
dl	Deciliter
DM	Diabetes mellitus
DTSQ	Diabetes Treatment Satisfaction Questionnaire
EMEA	European Medicines Agency
EPC	Evidence-based Practice Centers
EQ-5D	Euroqol-5D
F	Final
F-B	Mean difference from baseline
FBG	Fasting blood glucose
FDA	Food and Drug Administration
FPG	Fasting plasma glucose
g/day	Gram per day
GAD	Glutamic acid decarboxylase
GP	Group
GP1-GP2	Mean difference between the difference from baseline
h	Hour
H	Hispanic
HgbA1c	Hemoglobin A1c
IHCIS	Integrated healthcare information services

IQR	Interquartile range
IU	International unit
kg	Kilogram
mg	Milligram
kg/m2	Kilogram per square meter
L	Liter
lbs	Pounds
m	Meter
mg	Milligram
mg/dL	Milligram per deciliter
min	Minute
ml	Milliliter
mmHg	Millimeter of mercury
mmol	Millimole
NA	Not applicable
ng/mL	Nanograms per milliliter
NHIS	National health interview survey
NIH	National Institutes of Health
nmol	Nanomole
NPH	Neutral protamine hagedorn
NR	Not reported
NS	Not significant
OA	Oral antidiabetic
OAM	Oral antidiabetic medication
ODM	Oral diabetes medicine
OR	Odds ratio
p	P-value
PG	Plasma glucose
PPG	Postprandial glucose
qd	Once daily
RCTs	Randomized controlled trial
ref	Reference group
RR	Relative risk
SBP	Systolic blood pressures
SD	Standard deviation
SE	Standard error
SEM	Standard error of the mean
SU	Sulfonylurea
T	Time of day when insulin taken
T1DM	Type 1 diabetes mellitus
T2DM	Type 2 diabetes mellitus
TZD	Thiazolidinedione
U	Unit
UKPDS	United Kingdom Prospective Diabetes Study
ULN	Upper limit of normal

US	United States
v	Dosing varied
WHO-DTSQ	World Health Organization-Diabetes Treatment Satisfaction Questionnaire