

## *Comparative Effectiveness Review*

---

Number XX (Provided by AHRQ)

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

**Prepared for:**

Agency for Healthcare Research and Quality  
U.S. Department of Health and Human Services  
540 Gaither Road  
Rockville, MD 20850  
[www.ahrq.gov](http://www.ahrq.gov)

**Contract No. #290-02-0018**

**Prepared by:**

The Johns Hopkins University, Evidence-based Practice Center, Baltimore, MD

*Investigators*

Rehan Qayyum, M.D.  
Lisa M. Wilson, Sc.M.  
Shari Bolen, M.D., M.P.H.  
Nisa Maruther, M.D.  
Spyridon S. Marinopoulos, M.D., M.B.A.  
Leonard Feldman, M.D.  
Padmini Ranasinghe, M.B.B.S., M.P.H.  
Muhammad Amer, M.D.  
Eric B. Bass, M.D., M.P.H.

This draft evidence report/technology assessment is distributed solely for the purpose of pre-release peer review. It has not been otherwise disseminated by AHRQ. It does not represent, and should not be construed to represent, an AHRQ determination or policy.

**This document is in the public domain and may be used and reprinted without permission except those copyrighted materials noted, for which further reproduction is prohibited without the specific permission of copyright holders.**

**Suggested Citation:**

Qayyum R, Wilson LM, Bolen S, Maruther N, Marinopoulos SS, Feldman L, Ranasinghe P, Amer M, Bass EB. Comparative Effectiveness, Safety, and Indications of Insulin Analogues in Premixed Formulations for Adults with Type 2 Diabetes. Comparative Effectiveness Review No. [#]. (Prepared by the Johns Hopkins University Evidence-based Practice Center under Contract No. 290-02-0018.) Rockville, MD: Agency for Healthcare Research and Quality. [Month Year]. Available at: [www.effectivehealthcare.ahrq.gov/reports/final.cfm](http://www.effectivehealthcare.ahrq.gov/reports/final.cfm)

**None of the investigators has any affiliations or financial involvement that conflicts with the material presented in this report.**

DRAFT

DRAFT

This report is based on research conducted by the Johns Hopkins Evidence-based Practice Center (EPC) under contract to the Agency for Healthcare Research and Quality (AHRQ), Rockville, MD (Contract No. 290-02-0018). The findings and conclusions in this document are those of the author(s), who are responsible for its contents; the findings and conclusions do not necessarily represent the views of AHRQ. Therefore, no statement in this report should be construed as an official position of AHRQ or of the U.S. Department of Health and Human Services.

This report is intended as a reference and not as a substitute for clinical judgment. Anyone who makes decisions concerning the provision of clinical care should consider this report in the same way as any medical reference and in conjunction with all other pertinent information.

This report may be used, in whole or in part, as the basis for development of clinical practice guidelines and other quality enhancement tools, or as a basis for reimbursement and coverage policies. AHRQ or U.S. Department of Health and Human Services endorsement of such derivative products may not be stated or implied

## 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 (CERs) 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 strength 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 CERs 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 from are essential to the Effective Health Care Program. Please visit the Web site ([www.effectivehealthcare.ahrq.gov](http://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.

## **Acknowledgments**

The Evidence-based Practice Center thanks Catherine Witkop and Bushra Abid for their assistance with article reviewing and Ritu Sharma for her assistance with final preparations of the report.

### **EPC Program Director**

Beth A. Collins-Sharp, Ph.D.  
Director, EPC Program  
Agency for Healthcare Research and Quality  
Rockville, MD

### **AHRQ Contacts**

Barbara A. Bartman, M.D., M.P.H.  
Task Order Officer  
Agency for Healthcare Research and Quality  
Rockville, MD

DRAFT

# Contents

Executive Summary .....	ES-1
Background and Key Questions.....	ES-1
Conclusions.....	ES-3
Key Questions 1 and 2: Comparative Effectiveness and Safety of Premixed Insulin Analogues .....	ES-3
Key Question 3: Effect of Premixed Insulin Analogues in Certain Subpopulations.....	ES-4
Key Question 4: Effect of Premixed Insulin Analogues Based on Patient Characteristics.....	ES-4
Remaining Issues .....	ES-4
Gaps in Evidence and Future Directions for Research.....	ES-4
Evidence Report.....	1
Introduction.....	1
Background.....	1
Conceptual Model.....	3
Scope and Key Questions .....	5
Methods.....	7
Topic Development.....	7
Search Strategy .....	8
Study Selection .....	8
Data Abstraction .....	8
Quality Assessment.....	9
Applicability .....	10
Data Analysis and Synthesis.....	10
Data Synthesis for Intermediate Outcomes and Adverse Events.....	10
Data Synthesis for Clinical Outcomes .....	11
Rationale for the Inclusion of Crossover Designs .....	12
Data Entry and Quality Control.....	13
Rating the Body of Evidence .....	13
Results.....	15
Search Results.....	15
Key Question 1 .....	20
Key Question 2 .....	20
Intermediate Outcomes and Adverse Events .....	20
Key Messages .....	20
Evidence Grades .....	23
Study Characteristics .....	24
Reporting of Intermediate Outcomes and Adverse Events.....	25
Insulin Aspart 70/30.....	27
Insulin Lispro 75/25.....	42
Insulin Lispro 50/50.....	54

Study Quality Assessment .....	58
Applicability Assessment.....	59
Clinical Outcomes.....	60
Key Messages .....	60
Evidence Grades (see Appendix E, Evidence Table 1) .....	61
Study Characteristics .....	61
Reporting of Clinical Outcomes .....	61
Premixed Insulin Analogues (Insulin Aspart 70/30, Insulin Lispro 50/50, and Insulin Lispro 75/25) Versus Any Other Antidiabetic Agent.....	62
Premixed Insulin Analogue Versus Another Premixed Insulin Analogue (Insulin Aspart 70/30 Versus Insulin Lispro 75/25).....	69
FDA, European Medicines Agency, and Pharmaceutical Industry Data.....	69
Publication Bias .....	70
Study Quality Assessment .....	70
Other Quality Issues.....	70
Applicability Assessment.....	71
Quality of Life.....	71
Key Messages .....	71
Evidence Grades (see Appendix E, Evidence Table 1) .....	71
Study Characteristics .....	71
Reporting of Quality of Life .....	72
Premixed Insulin Analogues Versus Long-Acting Insulin Analogues or Rapid- Acting Insulin Analogues .....	72
Premixed Insulin Analogues Versus Premixed Human Insulin .....	73
Premixed Insulin Analogues Versus Oral Antidiabetic Agents.....	73
FDA, European Medicines Agency, and Pharmaceutical Industry Data.....	73
Study Quality Assessment .....	74
Applicability Assessment.....	74
Key Question 3 .....	74
Key Question 4 .....	75
Effect of Premixed Insulin Analogues in Patients Taking Oral Antidiabetic Agents.....	75
Effect of Premixed Insulin Analogues in Patients With Different Intensity of Glucose Control .....	76
Effect of Premixed Insulin Analogues in Patients With Postprandial Versus Fasting Glucose Control .....	76
Discussion.....	77
Key Findings and Implications .....	77
Fasting Glucose.....	77
Postprandial Glucose .....	77
HgbA1c .....	78
Clinical Outcomes.....	78
Quality of Life.....	79
Hypoglycemia.....	79
Weight Change.....	80
Limitations .....	80

Gaps in the Evidence .....	81
Intermediate Outcomes .....	81
Clinical Outcomes.....	81
Quality of Life.....	81
Hypoglycemia .....	81
Weight Change.....	82
Future Directions for Research.....	82
Conclusion .....	82
References.....	83
List of Abbreviations .....	91

## Figures

Figure 1. Simplified structural diagram of two rapid-acting insulin analogues that are the included in premixed insulin analogue preparations .....	2
Figure 2. A simplified schematic diagram of insulin activity in nondiabetic subjects after injection.....	3
Figure 3. Conceptual framework of premixed insulin analogues.....	4
Figure 4. Summary of literature search for systematic reviews (number of articles).....	10
Figure 5. Meta-analyses of post-treatment difference in fasting glucose between insulin aspart 70/30 and long-acting insulin analogues (with and without Holman et al 2007).....	28
Figure 6. Meta-analyses of post-treatment difference in postprandial glucose between insulin aspart 70/30 and long-acting insulin analogues .....	28
Figure 7. Meta-analyses of post-treatment difference in hemoglobin A1c between insulin aspart 70/30 and long-acting insulin analogues .....	30
Figure 8. Meta-analyses of incidence of mild hypoglycemia between insulin aspart 70/30 and long-acting insulin analogue (glargine) .....	30
Figure 9. Meta-analyses of post-treatment difference in weight change between insulin aspart 70/30 and long-acting insulin analogues.....	31
Figure 10. Meta-analyses of post-treatment difference in fasting glucose between insulin aspart 70/30 and premixed human insulin .....	33
Figure 11. Meta-analyses of post-treatment difference in hemoglobin A1c between insulin aspart 70/30 and premixed human insulin preparations.....	35
Figure 12. Meta-analyses of incidence of mild hypoglycemia between insulin aspart 70/30 and premixed human insulin preparations.....	35
Figure 13. Meta-analyses of post-treatment difference in fasting glucose between insulin aspart 70/30 and noninsulin antidiabetic agents (with and without Nauck et al 2007) .....	38
Figure 14. Meta-analyses of post-treatment difference in postprandial glucose between insulin aspart 70/30 and noninsulin antidiabetic agents .....	39
Figure 15. Meta-analyses of post-treatment difference in hemoglobin A1c between insulin aspart 70/30 and noninsulin antidiabetic agents .....	40
Figure 16. Meta-analyses of incidence of mild hypoglycemia between insulin aspart 70/30 and noninsulin antidiabetic agents.....	41
Figure 17. Meta-analyses of post-treatment difference in weight change between insulin aspart 70/30 and noninsulin antidiabetic agents .....	41

Figure 18. Meta-analyses of post-treatment difference in fasting glucose between insulin lispro 75/25 and long-acting insulin analogues (with and without Jacober et al 2006).....	44
Figure 19. Meta-analyses of post-treatment difference in postprandial glucose between insulin lispro 75/25 and long-acting insulin analogues.....	44
Figure 20. Meta-analyses of post-treatment difference in hemoglobin A1c between insulin lispro 75/25 and long-acting insulin analogues.....	45
Figure 21. Meta-analyses of post-treatment difference in fasting glucose between insulin lispro 75/25 and premixed human insulin.....	49
Figure 22. Meta-analyses of post-treatment difference in postprandial glucose between insulin lispro 75/25 and premixed human insulin preparations.....	49
Figure 23. Meta-analyses of post-treatment difference in fasting glucose between insulin lispro 75/25 and noninsulin antidiabetic agents.....	51
Figure 24. Meta-analyses of post-treatment difference in postprandial glucose between insulin lispro 75/25 and noninsulin antidiabetic agents.....	51
Figure 25. Meta-analyses of post-treatment difference in hemoglobin A1c between insulin lispro 75/25 and noninsulin antidiabetic agents.....	52
Figure 26. Meta-analyses of incidence of mild hypoglycemia between insulin lispro 75/25 and noninsulin antidiabetic agents.....	52
Figure 27. Meta-analyses of post-treatment difference in weight change between insulin lispro 75/25 and noninsulin antidiabetic agents.....	53
Figure 28. Meta-analyses of incidence of mild hypoglycemia between insulin lispro 75/25 and other premixed insulin analogues.....	54
Figure 29. Pooled odds ratios of all-cause mortality comparing premixed insulin analogues with other diabetes medications.....	64
Figure 30. Pooled odds ratios of cardiovascular mortality comparing premixed insulin analogues with other diabetes medications.....	64
Figure 31. Pooled odds ratio of cardiovascular morbidity comparing premixed insulin analogues with other diabetes medications.....	67
Figure 32. Pooled odds ratio of combined outcomes mortality and cardiovascular morbidity comparing premixed insulin analogues with other diabetes medications.....	68
Figure 33. Begg's funnel plots for all-cause mortality and cardiovascular disease mortality.....	70

## Tables

Table A. Summary of the key findings on the comparative effectiveness of premixed insulin analogues and other antidiabetic agents.....	ES-5
Table 1. Pharmacokinetic characteristics of selected insulin preparations.....	2
Table 2. Criteria for inclusion in the reviews.....	9
Table 3. Number of included studies evaluating each treatment comparison for each outcome.....	17
Table 4. List of study funding.....	25
Table 5. Range of risk difference between insulin aspart 70/30 and other antidiabetic agents for selected adverse events.....	32
Table 6. Range of risk difference between insulin lispro 75/25 and other antidiabetic agents for selected adverse events.....	46

Table 7. Range of risk difference between insulin lispro 50/50 and other antidiabetic agents for selected adverse events .....	56
Table 8. Summary of all-cause mortality events in studies comparing a premixed insulin analogue to another antidiabetic agent.....	62
Table 9. Summary of cardiovascular disease mortality events in studies comparing a premixed insulin analogue to another antidiabetic agent.....	62
Table 10. Summary of cardiovascular disease morbidity events in studies comparing a premixed insulin analogue to another antidiabetic agent.....	65
Table 11. Quality of life.....	72

**Appendixes**

- Appendix A: Detailed Electronic Database Search Strategies
- Appendix B: Hand Searched Journals
- Appendix C: List of Excluded Studies
- Appendix D: Data Abstraction Forms
- Appendix E: Evidence Tables

**Appendixes and Evidence Tables for this report are provided electronically at <http://www.ahrq.gov/clinic/epcindex.htm>.**

DRAFT

# Executive Summary

## Background and Key Questions

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

Physiologic insulin replacement regimens consist of a bolus of insulin in relation to meals to mimic the release of insulin from beta-cells in response to food intake. In addition, some formulation of longer-acting insulin is prescribed to mimic the constant release of insulin that regulates hepatic gluconeogenesis and lipolysis. However, the addition of insulin to their treatment regimen usually results in decreased flexibility in timing of meals and activities, increased frequency of blood glucose monitoring, and increased risk of weight gain and hypoglycemia. Moreover, multiple injections of short-acting (bolus insulin) and long-acting insulin (basal insulin) may decrease the overall patient satisfaction with their treatment regimens.

A therapeutic alternative to multiple insulin injections in a physiologic regimen, which is also convenient to patients, is a premixed insulin preparation. Premixed insulin 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 routine life style; (5) consume consistent meals and eat at regular times during each day; and (6) have a hemoglobin A1c (HgbA1c) greater than 8.5% despite maximal therapy with oral antidiabetic agents.

Insulin analogues have been developed by an alteration in one of the two polypeptide chains of human insulin. This alteration alters the pharmacokinetic properties of the insulin analogue, thus imparting it a specific rapidity or duration of action. Premixed insulin analogues are derived from rapid acting insulin analogues and are a mixture of rapid-acting insulin analogues and its intermediate-acting protamine suspension. However, the role of premixed insulin analogues in the management of type 2 diabetes is unclear. Premixed insulin analogues may provide a more physiologic glucose lowering profile, thus providing better glycemic control. In addition, premixed insulin analogues allow patients more flexibility in timing their meals as these insulin preparations can be administered within 15 minutes of a meal.

The effect of premixed insulin analogues on fasting and postprandial glucose and HgbA1c as compared to other antidiabetic medications is not clear. 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, the effectiveness in lowering HgbA1c appears similar. Similarly, premixed insulin analogues appear to be more effective in lowering postprandial blood glucose but less effective in lowering fasting blood glucose than long-acting insulin analogues. Moreover, several studies have found that while the rate of side-effects such as hypoglycemia is similar between premixed insulin analogues and human insulin preparations these side effects are less common with long-acting insulin analogues.

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

To date no one study has compared all premixed insulin analogues with other antidiabetic agents in lowering fasting and postprandial glucose, HgbA1c, microvascular and macrovascular diabetic complications, and side effects of treatments. Clinicians may be better able to choose the most effective therapy for their diabetic patients if they know the comparative effectiveness and safety of different therapeutic options for the treatment of type 2 diabetes. We have therefore preformed a systematic review of published studies on the comparative effectiveness and safety of all premixed insulin analogues that are approved by the Food and Drug Administration (FDA) and available in the US.

This report addresses the following key questions:

1. In adults age  $\geq 18$  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, compared with insulin regimens including, but not necessarily limited to the following:
  - 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 in regard to safety, adverse effects, or adherence compared with other commonly used insulin preparations? 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 new premixed insulin analogue regimens differ for the following sub-populations:
  - a. The elderly ( $\geq 65$  years), very elderly ( $\geq 85$  years)
  - b. Other demographic groups (ethnic or racial groups, sex)
  - c. Individuals with comorbid medical conditions
  - d. Individuals with limited life expectancy
  - e. Individuals with disabilities
4. Does the effectiveness or safety of new premixed insulin analogue regimens differ for 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)?

## Conclusions

### Key Questions 1 and 2: Comparative Effectiveness and Safety of Premixed Insulin Analogues

#### **Premixed insulin analogues versus long-acting insulin analogues (see Table A).**

Premixed insulin analogues were less effective than long-acting insulin analogues alone in lowering fasting glucose. After treatment with premixed insulin analogues, patients had up to 8.5 mg/dL higher fasting glucose levels as compared to long-acting insulin analogues alone. On the other hand, after treatment with premixed insulin analogues, patients had up to 29 mg/dL lower postprandial glucose levels as compared to long-acting insulin analogues alone. Similarly, HgbA1c was also 0.48% lower in patients treated with premixed insulin analogues as compared to long-acting insulin analogues alone. Premixed insulin analogues appear to have a higher risk of hypoglycemia and an increased risk of weight gain although evidence is not very strong.

**Premixed insulin analogues versus rapid-acting insulin analogues (see Table A).** We found only two studies that compared premixed insulin analogues with rapid-acting insulin analogues. Both studies found a different effect of premixed insulin analogues on fasting and postprandial glucose levels as compared to rapid-acting insulin analogues. Premixed insulin analogues were similar to rapid-acting insulin analogues in lowering HgbA1c and incidence of hypoglycemia. Premixed insulin analogues were less likely to result in weight gain when compared to rapid-acting insulin analogues.

**Premixed insulin analogues versus a combination of long-acting and rapid-acting insulin analogues (see Table A).** One nonrandomized prospective trial found that a premixed insulin analogue (insulin aspart 70/30) was similar to the combination therapy in lowering fasting and postprandial glucose levels. Insulin aspart 70/30 was more effective in lowering HgbA1c and had fewer minor hypoglycemic events than a combination of long-acting and rapid-acting insulin analogues. There was no difference between the two treatments in weight gain. However, due to the nonrandomized design, this study is at risk of significant bias.

**Premixed insulin analogues versus premixed human insulin (see Table A).** There is inconclusive evidence that premixed insulin analogues are less effective in lowering fasting glucose levels than premixed human insulin. On the other hand, premixed insulin analogues are more effective in lowering postprandial glucose levels than premixed human insulin. The effect on HgbA1c is inconclusive and there does not appear to be an advantage of premixed insulin analogues over premixed human insulin. Similarly, premixed insulin analogues and premixed human insulin have similar effects on the incidence of hypoglycemia as well as on weight change.

**Premixed insulin analogues versus intermediate-acting insulin (see Table A).** Only two studies evaluated this comparison. Both studies reported similar results and found that premixed insulin analogues are as effective as intermediate-acting insulin (NPH) in lowering fasting and postprandial glucose levels, HgbA1c, and the incidence of hypoglycemia, and in increasing weight.

**Premixed insulin analogues versus noninsulin antidiabetic agents (see Table A).** There is weak evidence that premixed insulin analogues may be better than noninsulin antidiabetic agents in lowering fasting glucose levels, and even weaker evidence for lowering postprandial glucose levels. Premixed insulin analogues are as effective as noninsulin antidiabetic agents in lowering HgbA1c levels. There is weak evidence that premixed insulin analogues may have a higher risk

of hypoglycemia and are associated with more weight gain. However, this effect is likely to differ with the noninsulin antidiabetic agents compared with premixed insulin analogues.

One noninsulin antidiabetic agent, exenatide, needs to be injected. Only one study evaluated exenatide with a premixed insulin analogue (insulin aspart 70/30) and found that premixed insulin analogues are as effective as exenatide in lowering fasting glucose levels but were less effective in lowering postprandial glucose levels. There was no difference in lowering HgbA1c level, although patients on exenatide lost weight in contrast to weight gain in patients on premixed insulin analogues. However, more patients withdrew from the exenatide arm than from the premixed insulin analogue arm.

**Premixed insulin analogues versus premixed insulin analogues (see Table A).** We found only three studies that compared one premixed insulin analogue with the other and we did not find any difference between premixed analogues in lowering fasting and postprandial glucose levels, lowering HgbA1c, incidence of hypoglycemia, and weight change.

### **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 (see Table A).

### **Key Question 4: Effect of Premixed Insulin Analogues Based on Patient Characteristics**

**Effect of premixed insulin analogues in patients taking oral antidiabetic agents (see Table A).** We found two studies that compared premixed insulin analogues alone with a combination of premixed insulin analogue plus an oral antidiabetic agent. These studies found that combination of a premixed insulin analogue and oral antidiabetic agent is more effective than a premixed analogue alone in lowering fasting and postprandial glucose levels and HgbA1c without increasing the risk of hypoglycemia or significant weight gain.

**Effect of premixed insulin analogues in patients with different intensity of glucose control (see Table A).** We did not find any study that evaluated this key question.

**Effect of premixed insulin analogues in patients with postprandial versus fasting blood glucose control (see Table A).** We did not find any study that evaluated this key question.

## **Remaining Issues**

### **Gaps in Evidence and Future Directions for Research**

1. There is very little evidence to compare a regimen of a long-acting insulin analogue as basal insulin with a rapid-acting insulin analogue as bolus insulin. Probably the most important comparative study that needs to be performed should compare premixed insulin analogues and a combination of bolus insulin injections with rapid-acting insulin analogues plus a basal insulin injection with long-acting insulin analogues.

2. All studies were of very short duration. Studies with longer planned duration of followup are needed to study whether the gains in the early part of treatment are sustainable or not and whether differences between the comparators appear later during the treatment.
3. Lack of effectiveness studies limits generalization of results to all diabetic patients in the US. Studies should be planned to examine the effectiveness of premixed insulin analogues with less restrictive inclusion criteria and in a setting that more closely mimics the usual clinical practice.
4. There is no data on the comparative effectiveness of premixed insulin analogues in certain subpopulations. Patients with comorbid conditions, racial minorities, and very elderly patients need to be enrolled in studies to examine the efficacy and effectiveness of premixed insulin analogues in these subpopulations.
5. Clinical outcomes need to be studied to examine the safety of premixed insulin analogues. Sufficiently powered studies need to be planned to study clinical outcomes.
6. As diabetes is a chronic disease, the effect of premixed insulin analogue on quality of life and patient satisfaction need to be studied.

**Table A. Summary of the key findings on the comparative effectiveness of premixed insulin analogues and other antidiabetic agents**

Key question	Strength of evidence	Summary
<b>1a. Fasting glucose</b>		
Long-acting insulin analogues	Moderate	Premixed insulin analogues are less effective than long-acting insulin analogues alone in lowering fasting glucose.
Rapid-acting insulin analogues	Low	Lack of evidence limits our ability to compare premixed insulin analogues with rapid-acting insulin analogues in lowering fasting blood glucose.
Combination of long-acting and rapid-acting insulin analogues	Low	There is not enough evidence to conclusively compare premixed insulin analogues with a combination of long-acting and rapid-acting insulin analogues in lowering fasting glucose.
Premixed human insulin	Moderate	Premixed insulin analogues are not similar to premixed human insulin preparations in lowering fasting glucose.
Intermediate-acting human insulin	Low	Lack of evidence limits our ability to compare premixed insulin analogues with intermediate-acting human insulin preparations in lowering fasting blood glucose.
Noninsulin antidiabetic agents	Moderate	Premixed insulin analogues are more effective than noninsulin antidiabetic agents in lowering fasting glucose.
Premixed insulin analogues	Low	Superiority of one premixed insulin analogue over the other in lowering fasting blood glucose cannot be determined due to a paucity of evidence.
<b>1b. Postprandial glucose</b>		
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	Lack of evidence limits the ability to compare rapid-acting insulin analogues with premixed insulin analogues.
Combination of long-acting and rapid-acting insulin analogues	No evidence	There is no evidence to compare premixed insulin analogues with a combination of rapid-acting insulin and long-acting insulin analogues in lowering postprandial glucose.
Premixed human insulin	High	Premixed insulin analogues are better than NPH/regular 70/30 in lowering postprandial glucose.
Intermediate-acting human insulin	Low	There is very little evidence to compare premixed insulin analogues with intermediate-acting insulin preparations.

**Table A. Summary of the key findings on the comparative effectiveness of premixed insulin analogues and other antidiabetic agents**

<b>Key question</b>	<b>Strength of evidence</b>	<b>Summary</b>
Noninsulin antidiabetic agents	Moderate	Premixed insulin analogues may be better than oral antidiabetic agents in lowering postprandial glucose although the evidence is not strong. There is not enough evidence to conclusively compare the new incretin mimetic agent, exenatide, with premixed insulin analogues in lowering postprandial glucose.
Premixed insulin analogues	Low	Superiority of one premixed insulin analogue over the other cannot be evaluated due to a paucity of evidence.
<b>1c. HgbA1c</b>		
Long-acting insulin analogues	High	Premixed insulin analogues are more effective than long-acting insulin analogues in lowering HgbA1c.
Rapid-acting insulin analogues	Low	Lack of evidence limits our ability to compare intermediate-acting human insulin or rapid-acting insulin analogues with premixed insulin analogues.
Combination of long-acting and rapid-acting insulin analogues	Low	There is not enough evidence to conclusively compare premixed insulin analogues with a combination of rapid-acting insulin and long-acting insulin analogues in lowering HgbA1c.
Premixed human insulin	High	Premixed insulin analogues are as effective as NPH/regular 70/30 in lowering HgbA1c.
Intermediate-acting human insulin	Low	Lack of evidence limits our ability to compare intermediate-acting human insulin or rapid-acting insulin analogues with premixed insulin analogues.
Noninsulin antidiabetic agents	Moderate	Premixed insulin analogues may be better than oral antidiabetic agents in lowering HgbA1c, but the evidence is insufficient. There is not enough evidence to conclusively compare exenatide with premixed insulin analogues.
Premixed insulin analogues	Low	Superiority of one premixed insulin analogue over the other cannot be reliably evaluated due to a paucity of evidence.
1d. All-cause mortality, cardiovascular disease mortality and morbidity	Low	No statistically significant differences in all-cause mortality, cardiovascular mortality, and cardiovascular morbidity between premixed insulin analogues and other diabetes medications were reported in these mainly short duration RCTs. Low absolute events in short duration trials where clinical events were not the primary outcomes made it difficult to draw any firm conclusions regarding any of the clinical outcomes.
1e. Nephropathy	Low	A one-year RCT reported a statistically significant greater increase in plasma creatinine by 0.02 mg/dL in the premixed insulin analogue arm (insulin aspart 70/30) compared with the long-acting insulin analogue arm (insulin detemir insulin); however, the clinical relevance of this mild change is unclear.
1f. Retinopathy and neuropathy	No evidence	No studies evaluated other clinical outcomes such as retinopathy and neuropathy.
2a. Hypoglycemia		Many of the comparisons contain too few studies to draw conclusions. The effect of premixed insulin analogues on the incidence of serious hypoglycemia cannot be conclusively addressed due to very few serious hypoglycemic events in the studies.
Long-acting insulin analogues	High	Premixed insulin analogues are more likely to cause hypoglycemia than long-acting insulin analogues.
Rapid-acting insulin analogues	Low	The body of evidence is not enough to conclusively compare premixed insulin analogues with rapid-acting insulin analogues.
Combination of long-acting and rapid-acting insulin analogues	Low	The body of evidence is not enough to conclusively compare premixed insulin analogues with a combination of rapid-acting insulin analogues and long-acting insulin analogues.

**Table A. Summary of the key findings on the comparative effectiveness of premixed insulin analogues and other antidiabetic agents**

<b>Key question</b>	<b>Strength of evidence</b>	<b>Summary</b>
Premixed human insulin	High	Premixed insulin analogues are similar to premixed human insulin preparations in producing hypoglycemia.
Intermediate-acting human insulin	Low	The body of evidence is not enough to conclusively compare premixed insulin analogues with intermediate-acting human insulin preparations.
Noninsulin antidiabetic agents	High	Premixed insulin analogues cause more hypoglycemic events than oral antidiabetic agents.
Premixed insulin analogues	Low	There is not enough data to conclusively compare one premixed insulin analogue with the other for the incidence of hypoglycemia.
2b. Weight		There is not enough evidence to conclusively compare weight change after treatment with premixed insulin analogues versus other antidiabetic drugs except as noted below.
Long-acting insulin analogues		
Rapid-acting insulin analogues		
Combination of long-acting and rapid-acting insulin analogues		
Premixed human insulin		
Intermediate-acting human insulin		
Noninsulin antidiabetic agents	High	Premixed insulin analogues increase weight as compared to oral antidiabetic agents as a group.
Premixed insulin analogues		
2c. Quality of life	Low	No significant difference was noted in the three 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 due to different outcome definitions, measurement techniques, populations, and comparators.
3. Effect of premixed insulin analogues in certain subpopulations	No evidence	We did not find any study that had specifically explored the effect of premixed insulin analogues in specific subpopulations such as the very elderly, those with comorbid conditions, or minorities.
4a. Effect of premixed insulin analogues in patients taking oral antidiabetic agents		
4b. Effect of premixed insulin analogues in patients with different intensity of glucose control	No evidence	We did not find any study that evaluated this key question.
4c. Effect of premixed insulin analogues in patients with postprandial versus fasting blood glucose control	No evidence	We did not find any study that evaluated this key question.

# Introduction

## Background

Optimal control of hyperglycemia in diabetics is of paramount importance to prevent or delay 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 10% risk reduction in diabetes-related mortality and a 25% risk reduction in microvascular complications as compared to conventional control of blood glucose.<sup>1</sup> Although oral antidiabetic agents are used as first-line agents in patients with type 2 diabetes, insulin is frequently required at some stage during the management of diabetes to maintain optimal glycemic control in a significant number of patients. According to the National Health Interview Survey (NHIS), 28% of patients with type 2 diabetes are using insulin either alone (16%) or in combination with other oral antidiabetic agents (12%).<sup>2</sup>

Insulin replacement regimens can be either physiologic (prescribed to mimic the natural release of insulin from beta-cells of human pancreas) or non-physiologic (all other regimens). Physiologic insulin replacement regimens consist of a bolus of insulin in relation to meals to mimic the release of insulin from beta-cells in response to food intake. In addition, some formulation of longer acting insulin is prescribed to mimic the constant release of insulin that regulates hepatic gluconeogenesis and lipolysis.<sup>3,4</sup> Although type 2 diabetic patients are reluctant to start insulin, insulin therapy improves quality of life in such patients. However, the addition of insulin to their treatment regimen usually results in decreased flexibility in timing of meals and activities, increased frequency of blood glucose monitoring, and increased risk of weight gain and hypoglycemia.<sup>4</sup> Moreover, multiple injections of short-acting (bolus insulin) and long-acting insulin (basal insulin) may decrease the overall patient satisfaction with their treatment regimens.

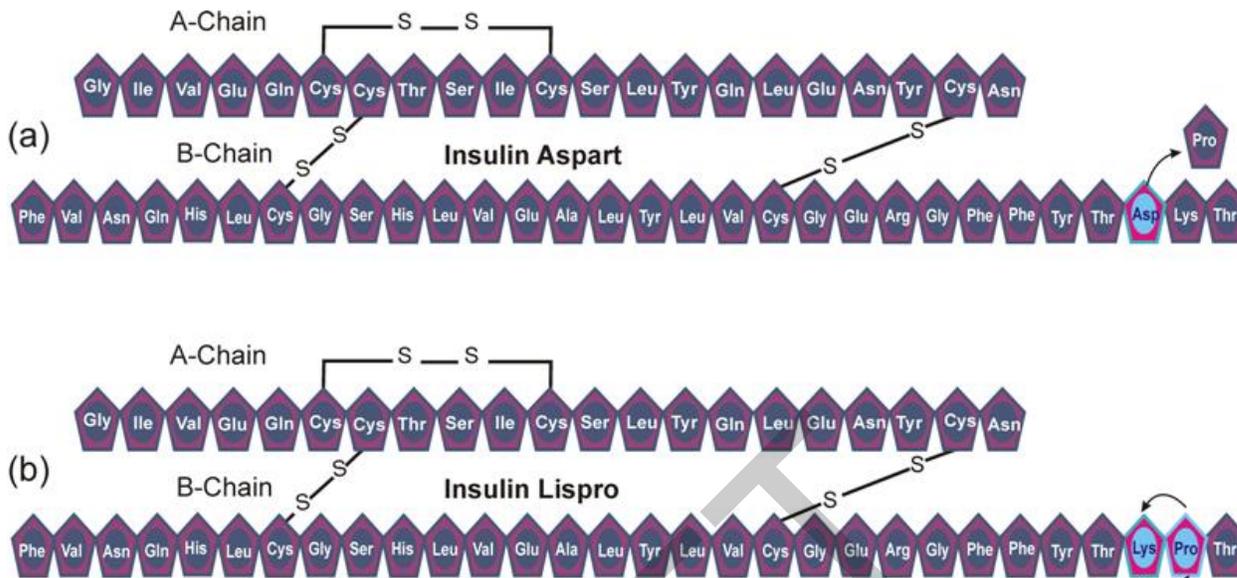
A therapeutic alternative to multiple insulin injections, which is also convenient to patients, is premixed insulin preparations. Premixed insulin preparations are appropriate for patients who: (1) desire a convenient and simple insulin regimen; (2) are unwilling to administer multiple daily injections or use insulin pump; (3) are unwilling or cannot undertake carbohydrate counting; (4) have a routine life style; (5) consume consistent meals and eat at regular times during each day; and (6) have a hemoglobin A1c (HgbA1c) of greater than 8.5% despite maximal therapy with oral antidiabetic agents (ideally, target for each patient should be an HgbA1c of less than 7.0).<sup>5,6</sup>

Three premixed insulin preparations are available commercially in 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% insulin aspart protamine crystals and 30% soluble insulin aspart. Insulin lispro 75/25, marketed by Eli Lilly as Humalog™ 75/25, is a mixture of 75% insulin lispro protamine suspension and 25% rapid-acting insulin lispro solution. Insulin lispro 50/50, marketed by Eli Lilly as Humalog™ 50/50, is a mixture of 50% insulin lispro protamine suspension and 50% rapid-acting insulin lispro solution (see Table 1).

The role of premixed insulin analogues in the management of type 2 diabetes is unclear. Premixed insulin analogues may provide a more physiologic glucose lowering profile, thus providing better glycemic control (see Figure 2). Premixed insulin analogues allow patients more flexibility in timing their meals as these insulin preparations can be administered within 15 minutes of a meal.

Several studies have found that insulin aspart 70/30 and insulin lispro 75/25 lower postprandial glucose levels more than human insulin 70/30.<sup>10-13</sup> Improvement in HgbA1c,

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



(a) Insulin aspart (NovoLog®): proline at position B28 of the human insulin B-chain is replaced by aspartic acid and (b) Insulin lispro (Humalog®): lysine at position B29 on B-chain changes its position with proline at position B28 on B-chain of human insulin

Source: Figure derived from information obtained in package insert.<sup>7-9</sup>

**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

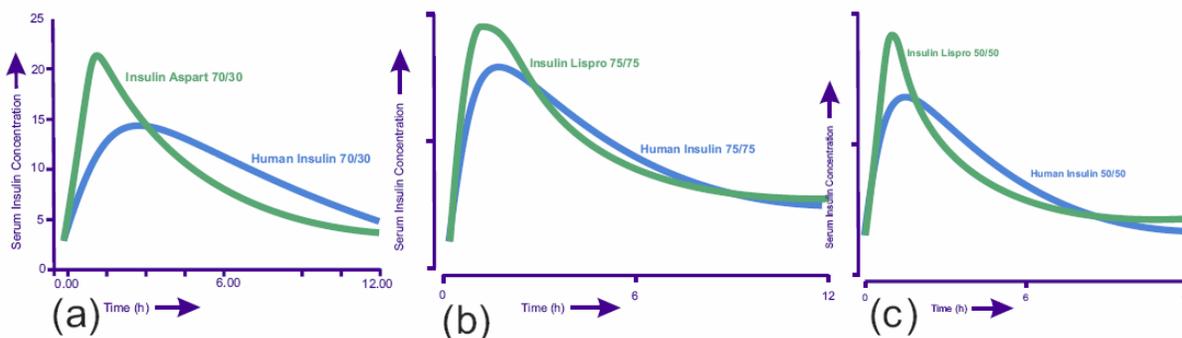
NA = not available; NPH = neutral protamine Hagedorn

however, has been equivalent between the premixed insulin analogues and human insulin 70/30, despite improvement in postprandial glucose in a number of studies.<sup>10 11 14</sup> Similarly, several studies have found that the rate of side-effects such as hypoglycemia is similar between premixed insulin analogues and premixed human insulins.<sup>11 15 16</sup>

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

We have therefore preformed a systematic review of published studies on the comparative effectiveness and safety of all premixed insulin analogues that are approved by the Food and Drug Administration (FDA) and available in the United States. By comparing the intermediate

**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 obtained in package insert.<sup>7-9</sup>

outcomes and clinical outcomes of these analogues in comparison to other antidiabetic treatments, clinicians may get a better sense of how to choose treatment for type 2 diabetic patients. In addition, the results presented here may provide policymakers and insurers with better insight as they consider policies relating to medication coverage.

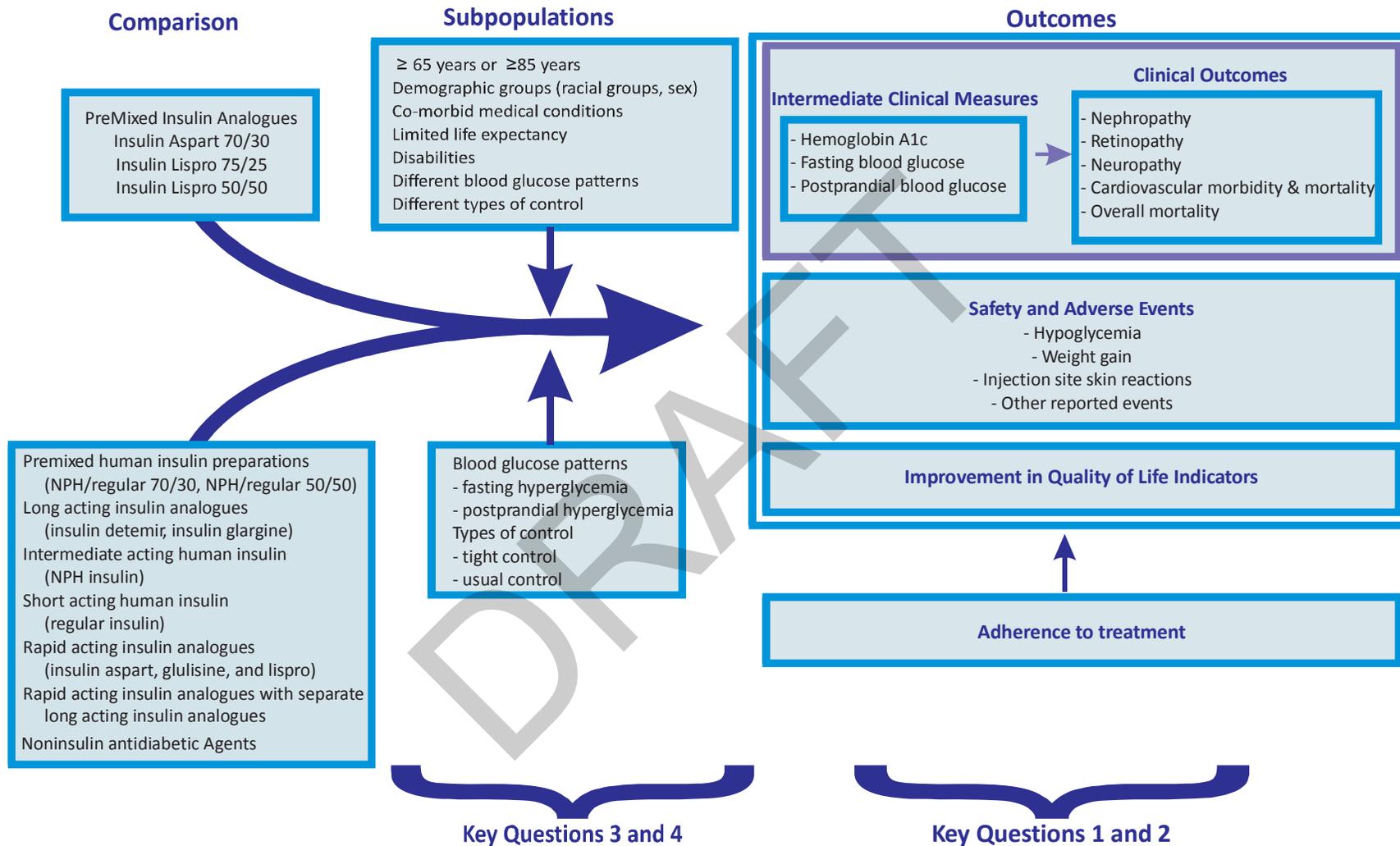
## Conceptual Model

Our conceptual model (see Figure 3) summarizes the premixed insulin analogues, their main comparators, and their effect 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 HgA1c. We call these intermediate outcomes and not clinical outcomes as these are blood tests and are relevant only due to their relationship with clinical outcomes, such as mortality. We visualize intermediate outcomes as 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" through intermediate outcomes. Use of these medications may also be associated with adverse effects. These medications also affect quality of life either in the short-term, due to the need for frequent injections and symptoms, or anxiety associated with poor glycemic control. Quality of life is also affected in the long-term due to the effect on overall morbidity and mortality. Adherence to treatment is another important aspect 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 by important population variables such as age, comorbid conditions, as well as by the intensity of intended glucose control and the target chosen for glucose control.

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

**Figure 3. Conceptual framework of premixed insulin analogues**



NPH = neutral protamine Hagedorn

## Scope and Key Questions

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

1. In adults (age  $\geq 18$  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, compared with insulin regimens including, but not necessarily limited to the following?
  - 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)
- *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 loosely mimic endogenous insulin secretion. In *premixed insulin analogue* preparations, insulins are mixed with their own protamine suspensions that slow their release.
2. For adults with type 2 diabetes, do premixed insulin analogues differ in regard to safety, adverse effects, or adherence compared with other commonly used insulin preparations? 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 new premixed insulin analogue regimens differ for the following subpopulations?
  - a. The elderly ( $\geq 65$  years), very elderly ( $\geq 85$  years)
  - b. Other demographic groups (ethnic or racial groups, sex)
  - c. Individuals with comorbid medical conditions
  - d. Individuals with limited life expectancy
  - e. Individuals with disabilities
4. Does the effectiveness or safety of new premixed insulin analogue regimens differ for 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)?

# Methods

In response to Section 1013 of the Medicare Modernization Act, 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 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 AHRQ for approval.

## Search Strategy

We searched the following databases for primary studies for the periods in parentheses: MEDLINE<sup>®</sup> (1966 to August 2007), EMBASE<sup>®</sup> (1974 to August 2007), the Cochrane Central Register of Controlled Trials (CENTRAL; 1966 to August 2007), and the Cumulative Index to Nursing & Allied Health Literature (CINAHL<sup>®</sup>; 1982 through August 2007). 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 website of the European Medicines Agency (EMA).
- Public registries of clinical trials, such as Clinical Study Results website ([www.clinicalstudyresults.org](http://www.clinicalstudyresults.org)) and ClinicalTrials.gov ([www.clinicaltrials.gov](http://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<sup>®</sup> 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<sup>®</sup>, the articles were uploaded to SRS<sup>®</sup> 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 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, or safety were promoted to the abstract review phase.

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. 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 opinions 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 investigators to determine if they should be included for full data abstraction (see Appendix D). Differences in opinions 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 pertinent data available for synthesis.

Each article underwent double review by study investigators 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.<sup>17</sup> 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).

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), HgbA1c levels, duration of diabetes, and previous treatments),

**Table 2. Criteria for inclusion in the reviews**

<b>Population and condition of interest</b>	<input type="checkbox"/> All studies included patients with type 2 diabetes, non-insulin dependent diabetes mellitus, or adult-onset diabetes. We excluded studies if less than 75 percent of the study population had type 2 diabetes and there was not a separate analysis for those with type 2 diabetes. <input type="checkbox"/> All studies included human subjects. <input type="checkbox"/> We excluded studies if they included only subjects less than or equal to 18 years of age.
<b>Interventions</b>	<input type="checkbox"/> All studies must have evaluated a premixed insulin analogue of interest. <ul style="list-style-type: none"> <li>○ 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.</li> </ul>
<b>Comparisons of interest</b>	<input type="checkbox"/> All studies must have compared a premixed insulin analogue to another antidiabetic agent. Other antidiabetic agents included, but are not limited to: <ul style="list-style-type: none"> <li>○ Long-acting insulin analogues (insulin detemir, insulin glargine)</li> <li>○ Rapid-acting insulin analogues (insulin aspart, insulin glulisine, insulin lispro)</li> <li>○ Rapid-acting insulin analogues in combination with long-acting insulin analogues</li> <li>○ Premixed human insulin (NPH/regular 70/30, NPH/regular 50/50)</li> <li>○ Intermediate-acting human insulin (NPH insulin)</li> <li>○ Short-acting human insulin (regular insulin)</li> <li>○ Noninsulin antidiabetic agents (e.g., oral antidiabetic agents, exenatide)</li> <li>○ Placebo, diet, or usual care</li> <li>○ Any combination of the above</li> </ul>
<b>Outcomes</b>	<input type="checkbox"/> We excluded studies that did not apply to the key questions. <input type="checkbox"/> We included studies that evaluated at least one of the following outcomes: <ul style="list-style-type: none"> <li>○ Clinical outcomes (mortality, cardiovascular disease mortality and morbidity, nephropathy, retinopathy, and neuropathy),</li> <li>○ Intermediate outcomes (HgbA1c, fasting plasma glucose, pre-dinner plasma glucose, and postprandial plasma glucose before and after dinner),</li> <li>○ Safety and adverse events (Hypoglycemia, weight gain, injection site skin reactions, other and serious adverse events),</li> <li>○ Quality of life, or</li> <li>○ Adherence.</li> </ul>
<b>Type of study</b>	<input type="checkbox"/> We excluded articles not written in English, editorials, comments, letters, and abstracts. <input type="checkbox"/> We included RCTs, controlled clinical trials, and observational studies with controls. <input type="checkbox"/> Studies were not limited based on their duration or sample size.

FDA = Food and Drug Administration; HgbA1c = hemoglobin A1c; NPH = neutral protamine Hagedorn; RCT = randomized controlled trial; type 2 diabetes = type 2 diabetes mellitus

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<sup>®</sup> 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<sup>18</sup> and the Newcastle-Ottawa Scale;<sup>19</sup> this tool was supplemented with additional questions as suggested by the Guide for Conducting Comparative Effectiveness Reviews.<sup>20</sup> 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) the method used to assess the primary outcome; (4) whether followup was long enough for outcomes to occur; (5) the adequacy of followup; (6) whether there was a description of those lost to followup; (7) whether the main conclusions were reflective of the results; (8) the funding source; and (9) whether there was a statement of conflict of interest. Additionally, RCTs were evaluated on the appropriateness of their randomization scheme. Nonrandomized studies were also evaluated on 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 have the least bias and results are considered valid. A study that adheres mostly to the commonly held concepts of high quality including the following: a formal randomized controlled study; clear description of the population, setting, interventions, and comparison groups; appropriate measurement of outcomes; appropriate statistical and analytic methods and reporting; no reporting errors; low dropout rate; and clear reporting of dropouts.
- **Fair.** These studies are susceptible to some bias, but not enough to invalidate the results. They do not meet all the criteria required for a rating of good quality because they have some deficiencies, but no flaw is likely to cause major bias. The study may be missing information, making it difficult to assess limitations and potential problems.
- **Poor (high risk of bias).** These studies have significant flaws that imply biases of various types that may invalidate the results. They have serious errors in design, analysis or reporting; large amounts of missing information; or discrepancies in reporting.<sup>20</sup>

## Applicability

Throughout the report, we discuss the applicability of studies in terms of how well the study population was consistent with the type 2 diabetes general population. We evaluated quality in terms of (1) the source population from which subjects were enrolled; (2) the percent of patients enrolled compared to the patients screened for the trial; (3) the percent of patients excluded during a run-in period due to poor compliance, poor treatment response, or side effects; (4) the similarity of the demographic characteristics of the study population to the general US diabetic population;<sup>21</sup> (5) the representativeness of the spectrum of illness severity to all stages of illness; (6) the reflection on current clinical practice of the intervention and monitoring; (7) the appropriateness of the comparator; (8) the reporting on important clinical outcomes and adverse events; and (9) the similarity of the standards of care to that of the US.

## Data Analysis and Synthesis

For each Key Question, we created a set of detailed evidence tables containing all information extracted from eligible studies. We conducted meta-analyses for outcomes when there were sufficient data (2 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 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 from the baseline and final values for each group. If no measure of dispersion was reported for the between-group difference, we then calculated it 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.<sup>22 23</sup> If data were only presented in graphical form, we abstracted data from the graphs.

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 results of individual studies within each set of comparisons using Comprehensive Meta-Analysis (version 2.2.046) software. As we found some clinical heterogeneity within the same group comparisons, we decided to use a random-effects model. We chose a random-effects model as it assumes that the included studies differ from each other more than possible due to random error and 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 due to random error alone and 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 studies differ from each other only due to random error the CIs from random-effects and fixed-effects models are similar. Thus, use of a random-effects model is not over-conservative in the absence of between-study heterogeneity. Although we did measure the Q-statistic and I-square index, we did not use these statistics to choose the model for pooling data as tests for homogeneity are known to have low power for detecting between-study heterogeneity.<sup>24 25</sup> Due to 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 a change in meta-analysis results. We assessed publication bias by visual inspection of the funnel plot and by statistical means with Begg's<sup>26</sup> and Eggers<sup>27</sup> 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 did include such 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 (2 or more studies), and 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 with premixed insulin analogues, we combined these arms into a premixed insulin analogue group when appropriate. We felt that results were similar enough for premixed insulin analogues and for “any other” active comparator to be able to combine the data

into these two groups, although we do discuss the studies qualitatively combined and separated. In the one study where there were three arms (premixed insulin analogue versus rapid-acting insulin analogue versus long-acting insulin analogue),<sup>28</sup> we chose what we felt 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.<sup>29 30</sup> We used a fixed-effects model because there is evidence to suggest that these methods are less biased with rare event data.<sup>31</sup> 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.<sup>32</sup> 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.<sup>33</sup> A value greater than 50% may be considered to have substantial variability. We conducted sensitivity analyses by omitting one study at a time to assess the influence of any single study on the pooled estimate. A sensitivity analysis was conducted where we include the crossover studies, and the unpublished crossover data.

Because statistically significant findings can be more likely to be published than 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<sup>26</sup> and Eggers<sup>27</sup> tests including evaluation of the asymmetry of funnel plots.

## **Rationale for the Inclusion of Crossover Designs**

We decided to include crossover trials as this study design allows comparison of interventions at the individual rather than 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 from the initial phase of the study to subsequent phases.

However, we used data from crossover studies only for intermediate outcomes, namely HgbA1c, fasting blood glucose, and postprandial blood 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 HgbA1c, we only included 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 HgbA1c as the treatment during an earlier phase, lead-in phase, or pretrial phase could affect the HgbA1c level.<sup>34</sup>

We aimed to use within-individual comparisons data from crossover trials if trials had reported data in such detail. If results were reported only for each intervention, we ignored the crossover design and used reported estimates as if they came from a parallel trial. We understand that this is a conservative approach which ignores within-patient correlation and produces wider

CI. If a trial reported a carryover effect, we included only the data from the first period of the crossover trials on the grounds that the first period of a randomized crossover trial is, in effect, a parallel group trial. Further sensitivity analyses was 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 data that had been entered into SRS<sup>®</sup> 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.<sup>35</sup> 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 limitations to individual study quality (using individual quality scores), certainty regarding the directness of the observed effects in studies, precision and strength of findings, and 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).

# Results

## Search Results

A summary of the search results for the primary literature review is presented in Figure 4. From the search, we retrieved 2021 unique citations. After a review of the titles and abstracts, 123 were deemed eligible for further review, and the full articles were retrieved. A total of 46 articles were included in this review. Upon further inspection, we realized that Raskin 2005,<sup>36</sup> Raskin 2007,<sup>37</sup> and Brod 2007;<sup>38</sup> Roach 2001<sup>39</sup> and Tirgoviste 2003;<sup>40</sup> and Malone 2000<sup>41</sup> and Malone 2000<sup>15</sup> were conducted in the same study population. These articles were abstracted together. Boehm 2004<sup>42</sup> and Boehm 2002<sup>10</sup> had the same study population of type 2 diabetes, but Boehm 2004<sup>42</sup> had the longer followup. We report only the results from Boehm 2004.<sup>42</sup> We used data from Boehm 2002<sup>10</sup> when data were not reported in the second publication of the trial.

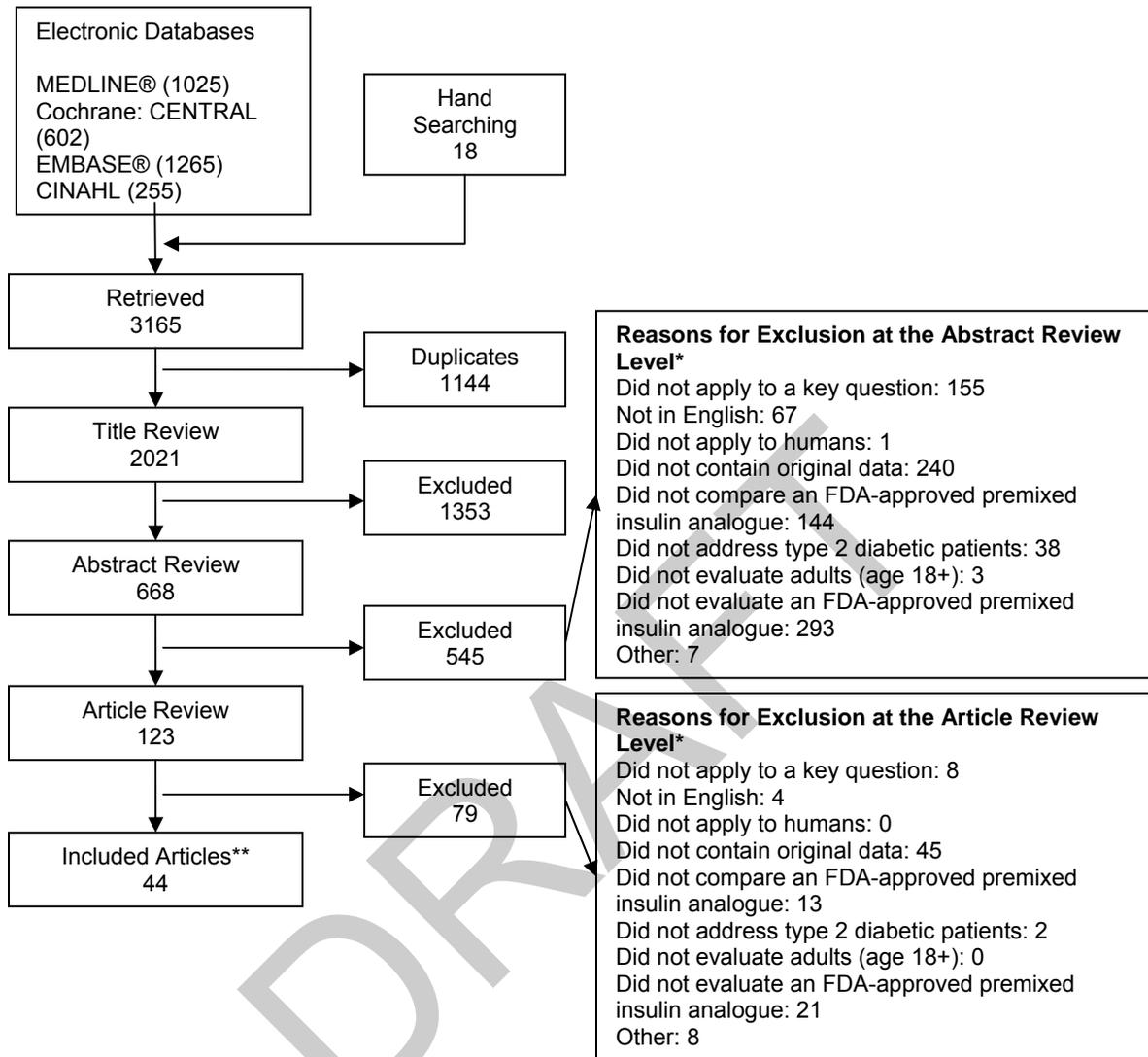
The bulk of the evidence was for insulin aspart 70/30<sup>10 12 14 16 28 36-38 42-55</sup> and insulin lispro 75/25,<sup>11 13 15 39-41 52 55-68</sup> which had 19 studies evaluating each. Seven studies evaluated insulin lispro 50/50.<sup>11 56 58 63 69-71</sup>

For insulin aspart 70/30, there were seven studies comparing it to a premixed human insulin,<sup>10 12 16 42 45 50 53 55</sup> four each to a long-acting insulin analogue<sup>28 36-38 44 47</sup> and to oral antidiabetic agents,<sup>43 48 51 54</sup> two to an intermediate-acting human insulin,<sup>14 16</sup> and one each to a rapid-acting insulin analogue,<sup>28</sup> a rapid-acting insulin analogue with a long-acting insulin analogue,<sup>49</sup> and exenatide.<sup>46</sup> For insulin lispro 75/25, there were nine studies comparing it to a premixed human insulin,<sup>11 13 15 41 55 56 61 64 65 67</sup> five to a long-acting insulin analogue,<sup>57-60 68</sup> and three to an oral antidiabetic agent.<sup>39 40 62 66</sup> 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,<sup>11 56 70 71</sup> two studies comparing it to a long-acting insulin,<sup>58 69</sup> and one study comparing it to a rapid-acting insulin analogue.<sup>69</sup> We did not identify any studies comparing insulin lispro 50/50 to a rapid-acting insulin analogue with a long-acting insulin analogue, an intermediate-acting human insulin, oral antidiabetic agents, 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 with premixed insulin analogues. Two studies compared insulin aspart 70/30 to insulin lispro 75/25.<sup>52 55</sup> Another two studies compared insulin lispro 75/25 to insulin lispro 50/50.<sup>56 63</sup>

Table 3 shows the number of included studies evaluating each treatment comparison for each outcome.<sup>72</sup>

**Figure 4. Summary of literature search for systematic reviews (number of articles)**



\* Total may exceed number in corresponding box, as articles could be excluded for more than one reason at this level.

CENTRAL = Central Register of Controlled Trials; CINAHL = Cumulative Index to Allied Health and Nursing Literature; FDA = U.S. Food and Drug Administration

\*\* 44 articles presented in 39 clinical trials

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

	Insulin aspart 70/30 vs.							
	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
<b>Intermediate outcomes</b>								
HgbA1c	4 <sup>36 44 47 28</sup>	1 <sup>28</sup>	1 <sup>49</sup>	4 <sup>16 42 45 50</sup>	2 <sup>14 16</sup>	3 <sup>43 48 51</sup>	1 <sup>46</sup>	1 <sup>52</sup>
FBG	3 <sup>28 36 47</sup>	1 <sup>28</sup>	1 <sup>49</sup>	2 <sup>16 50</sup>	2 <sup>14 16</sup>	4 <sup>43 48 51 54</sup>	1 <sup>46</sup>	1 <sup>52</sup>
Pre-dinner glucose	3 <sup>28 36 47</sup>	1 <sup>28</sup>	0	1 <sup>50</sup>	0	3 <sup>43 48 54</sup>	1 <sup>46</sup>	1 <sup>52</sup>
PPG after breakfast	2 <sup>36 47</sup>	0	0	4 <sup>16 50 53 55</sup>	1 <sup>16</sup>	3 <sup>43 48 51</sup>	1 <sup>46</sup>	2 <sup>52 55</sup>
PPG after dinner	3 <sup>28 36 47</sup>	1 <sup>28</sup>	1 <sup>49</sup>	2 <sup>16 50</sup>	1 <sup>16</sup>	4 <sup>43 48 51 54</sup>	1 <sup>46</sup>	1 <sup>52</sup>
Quality of life	1 <sup>28</sup>	1 <sup>28</sup>	0	1 <sup>45</sup>	0	0	0	0
<b>Clinical outcomes</b>								
Overall mortality	1 <sup>28</sup>	1 <sup>28</sup>	0	1 <sup>42</sup>	0	1 <sup>48</sup>	1 <sup>46</sup>	1 <sup>52</sup>
CVD mortality	1 <sup>28</sup>	1 <sup>28</sup>	0	1 <sup>42</sup>	0	1 <sup>48</sup>	0	1 <sup>52</sup>
CVD morbidity	1 <sup>47</sup>	0	0	2 <sup>42 55</sup>	0	2 <sup>51 54</sup>	1 <sup>46</sup>	1 <sup>55</sup>
Nephropathy	1 <sup>28</sup>	1 <sup>28</sup>	0	0	0	0	0	0
<b>Safety/Adverse events</b>								
Hypoglycemia	4 <sup>28 36 44 47</sup>	1 <sup>28</sup>	1 <sup>49</sup>	6 <sup>12 16 42 45 50 55</sup>	2 <sup>14 16</sup>	4 <sup>43 48 51 54</sup>	1 <sup>46</sup>	2 <sup>52 55</sup>
Weight/BMI	4 <sup>36 44 47 28</sup>	1 <sup>28</sup>	1 <sup>49</sup>	2 <sup>16 42</sup>	2 <sup>14 16</sup>	4 <sup>43 48 51 54</sup>	1 <sup>46</sup>	0
Injection site reactions	0	0	0	0	0	0	0	1 <sup>52</sup>
Total serious adverse events	3 <sup>28 36 47</sup>	1 <sup>28</sup>	1 <sup>49</sup>	2 <sup>45 50</sup>	1 <sup>14</sup>	3 <sup>43 48 51</sup>	1 <sup>46</sup>	0
Withdrawn due to adverse events	4 <sup>28 36 44 47</sup>	1 <sup>28</sup>	1 <sup>49</sup>	7 <sup>12 16 42 45 50 53 55</sup>	2 <sup>14 16</sup>	4 <sup>43 48 51 54</sup>	1 <sup>46</sup>	2 <sup>52 55</sup>
Other serious adverse events	1 <sup>28</sup>	1 <sup>28</sup>	0	3 <sup>12 16 55</sup>	2 <sup>14 16</sup>	1 <sup>51</sup>	0	2 <sup>52 55</sup>

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

	Insulin lispro 75/25 vs.							
	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
<b>Intermediate outcomes</b>								
HgbA1c	4 <sup>57-60</sup>	0	0	2 <sup>11 67</sup>	0	3 <sup>40 62 66</sup>	0	2 <sup>52 63</sup>
FBG	5 <sup>57-60 68</sup>	0	0	4 <sup>11 13 64 67</sup>	0	3 <sup>40 62 66</sup>	0	2 <sup>52 63</sup>
Pre-dinner glucose	3 <sup>57 58 68</sup>	0	0	4 <sup>11 13 64 67</sup>	0	2 <sup>40 66</sup>	0	1 <sup>52</sup>
PPG after breakfast	5 <sup>57-60 68</sup>	0	0	9 <sup>11 13 41 55 56 61 64 65 67</sup>	0	3 <sup>40 62 66</sup>	0	3 <sup>52 56 63</sup>
PPG after dinner	5 <sup>57-60 68</sup>	0	0	5 <sup>11 13 61 64 67</sup>	0	3 <sup>40 62 66</sup>	0	2 <sup>52 63</sup>
Quality of life	1 <sup>68</sup>	0	0	0	0	1 <sup>66</sup>	0	0
<b>Clinical outcomes</b>								
Overall mortality	1 <sup>60</sup>	0	0	0	0	1 <sup>62</sup>	0	1 <sup>52</sup>
CVD mortality	1 <sup>60</sup>	0	0	0	0	0	0	1 <sup>52</sup>
CVD morbidity	1 <sup>59</sup>	0	0	1 <sup>55</sup>	0	0	0	1 <sup>55</sup>
Nephropathy	0	0	0	0	0	0	0	0
<b>Safety/Adverse events</b>								
Hypoglycemia	5 <sup>57-60 68</sup>	0	0	9 <sup>11 13 41 55 56 61 64 65 67</sup>	0	3 <sup>40 62 66</sup>	0	4 <sup>52 55 56 63</sup>
Weight/BMI	4 <sup>57-60</sup>	0	0	3 <sup>61 64 67</sup>	0	3 <sup>40 62 66</sup>	0	0
Injection site reactions	0	0	0	1 <sup>56</sup>	0	0	0	1 <sup>56</sup>
Total serious adverse events	0	0	0	1 <sup>56</sup>	0	0	0	1 <sup>56</sup>
Withdrawn due to adverse events	5 <sup>57-60 68</sup>	0	0	8 <sup>13 41 55 56 61 64 65 67</sup>	0	2 <sup>62 66</sup>	0	1 <sup>56</sup>
Other serious adverse events	2 <sup>59 60</sup>	0	0	2 <sup>55 61</sup>	0	2 <sup>62 66</sup>	0	0

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

**Insulin lispro 50/50 vs.**

	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
<b>Intermediate outcomes</b>								
HgbA1c	2 <sup>58 69</sup>	1 <sup>69</sup>	0	3 <sup>11 70 71</sup>	0	0	0	1 <sup>63</sup>
FBG	2 <sup>58 69</sup>	1 <sup>69</sup>	0	3 <sup>11 70 71</sup>	0	0	0	1 <sup>63</sup>
Pre-dinner glucose	2 <sup>58 69</sup>	1 <sup>69</sup>	0	2 <sup>11 70</sup>	0	0	0	0
PPG after breakfast	2 <sup>58 69</sup>	1 <sup>69</sup>	0	3 <sup>11 56 70</sup>	0	0	0	1 <sup>63</sup>
PPG after dinner	2 <sup>58 69</sup>	1 <sup>69</sup>	0	2 <sup>11 70</sup>	0	0	0	2 <sup>56 63</sup>
Quality of life	1 <sup>69</sup>	1 <sup>69</sup>	0	0	0	0	0	0
<b>Clinical outcomes</b>								
Overall mortality	0	0	0	1 <sup>70</sup>	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	0	0	0	0	0	0	0	0
<b>Safety/Adverse events</b>								
Hypoglycemia	2 <sup>58 69</sup>	1 <sup>69</sup>	0	4 <sup>11 56 70 71</sup>	0	0	0	2 <sup>56 63</sup>
Weight/BMI	2 <sup>58 69</sup>	1 <sup>69</sup>	0	2 <sup>11 71</sup>	0	0	0	0
Injection site reactions	0	0	0	1 <sup>56</sup>	0	0	0	1 <sup>56</sup>
Total serious adverse events	0	0	0	1 <sup>56</sup>	0	0	0	1 <sup>56</sup>
Withdrawn due to adverse events	2 <sup>58 69</sup>	1 <sup>69</sup>	0	4 <sup>11 56 70 71</sup>	0	0	0	1 <sup>56</sup>
Other serious adverse events	0	0	0	1 <sup>70</sup>	0	0	0	0

BMI = body mass index; CVD = cardiovascular disease; FPG = fasting plasma glucose; HgbA1c = hemoglobin A1c; PPG = postprandial glucose

## Key Question 1

**In adults (age  $\geq$  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, compared with insulin regimens including, but not necessarily limited to the following?**

- 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)

## Key Question 2

**For adults with type 2 diabetes, do premixed insulin analogues differ in regard to safety, adverse effects, or adherence compared with other commonly used insulin preparations? 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 are less effective than long-acting insulin analogues alone in lowering fasting glucose.
- Premixed insulin analogues are similar to premixed human insulin preparations in lowering fasting glucose.
- Premixed insulin analogues are more effective than noninsulin antidiabetic agents (including exenatide) in lowering fasting glucose.
- Not enough evidence exists to conclusively compare premixed insulin analogues with a combination of long-acting and rapid-acting insulin analogues in lowering fasting glucose.

- Lack of evidence limits our ability to compare premixed insulin analogues with rapid-acting insulin analogues or intermediate-acting human insulin preparations in lowering fasting blood glucose.
- Superiority of one premixed insulin analogue over the other in lowering fasting blood glucose cannot be determined due to a paucity of evidence.

### **Postprandial glucose.**

- Premixed insulin analogues are better than long-acting insulin analogues alone in lowering postprandial glucose.
- Premixed insulin analogues are better than premixed human insulin preparations in lowering postprandial glucose.
- Premixed insulin analogues may be better than oral antidiabetic agents in lowering postprandial glucose although the evidence is not strong.
- Not enough evidence exists to conclusively compare premixed insulin analogues with a combination of rapid-acting insulin and long-acting insulin analogues in lowering postprandial glucose.
- Not enough evidence exists to conclusively compare the new incretin mimetic agent, exenatide, with premixed insulin analogues in lowering postprandial glucose.
- Lack of evidence limits the ability to compare rapid-acting insulin analogues with premixed insulin analogues.
- There is very little evidence to compare premixed insulin analogues with intermediate-acting insulin preparations.
- Superiority of one premixed insulin analogue over the other cannot be determined due to a paucity of evidence.

### **HgbA1c.**

- Premixed insulin analogues are more effective than long-acting insulin analogues in lowering HgbA1c.
- Premixed insulin analogues are as effective as premixed human insulin in lowering HgbA1c.
- Premixed insulin analogues may be better than oral antidiabetic agents in lowering HgbA1c, but the evidence is insufficient.

- Not enough evidence exists to conclusively compare premixed insulin analogues with a combination of rapid-acting insulin and long-acting insulin analogues in lowering HgbA1c.
- Not enough evidence exists to conclusively compare exenatide with premixed insulin analogues.
- Lack of evidence limits our ability to compare intermediate-acting human insulin or rapid-acting insulin analogues with premixed insulin analogues.
- Superiority of one premixed insulin analogue over the other cannot be reliably evaluated due to a paucity of evidence.

### **Hypoglycemia.**

- Many of the comparisons contain too few studies to draw conclusions regarding this adverse effect.
- The effect of premixed insulin analogues on the incidence of serious hypoglycemia cannot be conclusively addressed due to very few serious hypoglycemic events in the studies.
- Premixed insulin analogues cause more hypoglycemic events than oral antidiabetic agents, although the only study that compared premixed insulin analogues with exenatide found no difference in rate of hypoglycemic events.
- Premixed insulin analogues are more likely to cause hypoglycemia than long-acting insulin analogues.
- Premixed insulin analogues are similar to premixed human insulin preparations in producing hypoglycemia.
- There is not enough data to conclusively compare one premixed insulin analogue with the other for the incidence of hypoglycemia.

### **Weight change.**

- Premixed insulin analogues increase weight as compared to oral antidiabetic agents as a group.
- There is not enough evidence to conclusively compare weight change after treatment with premixed insulin analogues versus other antidiabetic drugs except as noted above.

## Evidence Grades

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

- The body 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 body 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.

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

- The body 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 body of evidence was graded as moderate for the following comparison:
  - Premixed insulin analogues versus noninsulin antidiabetic agents.
- The body of evidence was considered low for the following comparisons:
  - Premixed insulin analogues versus rapid-acting insulin analogues
  - Premixed insulin analogues versus intermediate-acting human insulin.
- There was no evidence for the following comparison:
  - Premixed insulin analogues versus a combination of long-acting and rapid-acting insulin analogues.

### HgbA1c (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 analogue versus rapid-acting and long-acting insulin analogues.

### **Hypoglycemia (see Appendix E; Evidence Table 1).**

- The body 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 body 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 rapid-acting and long-acting insulin analogues.

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

- The body 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 body 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 rapid-acting and long-acting insulin analogues.

## **Study Characteristics**

Our search identified 37 trials that had reported on at least one of the intermediate clinical outcomes (see Figure 4). Two studies did not report any intermediate clinical outcomes.<sup>12 53</sup> Adverse events were reported by 38 studies; one study did not report any adverse events.<sup>53</sup> Of the 39 trials, 15 were conducted in Europe,<sup>11 28 40 42 45 47 48 50 52 53 55 60 61 65 69</sup> eight were conducted in North America,<sup>16 36 41 56-59 68</sup> five were conducted in Asia,<sup>44 49 54 63 71</sup> one was conducted in Africa,<sup>13</sup> eight were multinational trials conducted in countries spread across different continents,<sup>14 43 46 51 62 64 66 67</sup> and two trials did not report the region from which patients were enrolled (see Appendix E; Evidence Table 2).<sup>12 70</sup> All were RCTs except one<sup>49</sup> in which patients were enrolled consecutively and followed prospectively. We did not find any observational study that fulfilled our inclusion criteria. Among the RCTs, 18 were parallel-arm,<sup>14 16 28 36 40 42-44 46-48 50 51 54 62 66 69 71</sup> 16 were crossover without washout period,<sup>11-13 45 52 57-61 63-65 67 68 70</sup> and four were crossover trials with a washout period.<sup>41 53 55 56</sup> Median duration of followup in these trials was 16 weeks (range of one-dose 1-day to 2 years). The longest study was by Boehm et al.<sup>42</sup> which had first reported results after 3 months<sup>10</sup> and then reported results of the extended followup at 2 years. There were four short studies, each of 1-day duration, in which blood glucose levels were measured after a single dose of study medications.<sup>41 53 55 56</sup>

Trials had similarities as well as differences in the patient enrollment criteria. All studies enrolled type 2 diabetic patients except two studies.<sup>11 42</sup> Six studies limited the age range of their source population to middle age and older patients.<sup>13 41 44 61 65 66</sup> One of these studies exclusively enrolled older patients between the ages of 60 and 80 years.<sup>66</sup> Nine studies did not report the age

range of the target populations for these studies.<sup>45 47-50 64 68 70 71</sup> Most trials excluded patients with HgbA1c and BMI above a certain limit (variable between the studies, but ranged from 9.5% to 14.7 % for HgbA1c and from 30 to 40 kg/m<sup>2</sup> for BMI). Six studies did not report inclusion criteria for HgbA1c<sup>12 48 49 53 64 70</sup> and 11 studies did not report inclusion criteria for BMI.<sup>11 12 44 48 49 53 57 60 68 70 71</sup>

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 with usual control of blood glucose.<sup>57 63 69</sup> Three other studies also specifically aimed to control postprandial blood glucose.<sup>50 58 70</sup>

These trials enrolled a total of 6051 patients (median number per trial = 115; range: 13 to 708 patients). Enrolled populations in the studies had a median age of 59 years (range: 51 to 68 years) and most patients were male (median = 55%, range: 23% to 92%; see Appendix E, Evidence Table 3). Study populations had a median HgbA1c of 8.7% (range: 7.3 to 10.3%), a median BMI of 29.5 kg/m<sup>2</sup> (range: 24 to 37 kg/m<sup>2</sup>), and a median duration of diabetes of 11 years (range: 4 to 16 years). Eight trials enrolled insulin-naïve patients,<sup>16 28 36 40 43 58 59 66</sup> nine trials did not specify history of insulin treatment,<sup>44 46-49 51 54 62 68</sup> and the remaining 20 trials enrolled insulin-treated patients.

**Source of funding for included studies.** The source of funding was reported by 29 studies; the remaining 10 studies did not clearly state the source of funding.<sup>40 41 44 45 48 59 60 64 65 71</sup> Of the studies that clearly stated source of funding, all were funded by the pharmaceutical industry except one study which was jointly funded by the National Institute of Health (NIH) and the pharmaceutical industry.<sup>68</sup> Of the studies that did not clearly state their source of funding, employees of pharmaceutical industry were among the authors in four studies.<sup>45 59 60 64</sup> Novo Nordisk, the manufacturer of insulin aspart 70/30, funded 15 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 with insulin aspart 70/30.<sup>55</sup> Eli Lilly, the manufacturer of insulin lispro 75/25 and insulin lispro 50/50, funded 14 studies, one of which was also partially funded through the NIH.<sup>68</sup> Only one study funded by Eli Lilly used insulin aspart 70/30; it compared exenatide (manufactured by Eli Lilly) with insulin aspart 70/30.<sup>46</sup>

**Table 4. List of study funding**

Company	List of studies funded
Eli Lilly	Coscelli 2003, <sup>61</sup> Cox 2007, <sup>68</sup> Hertz 2002, <sup>66</sup> Hertz 2003, <sup>13</sup> Jacober 2006, <sup>58</sup> Kazda 2006, <sup>69</sup> Malone 2003, <sup>62</sup> Nauck 2007, <sup>46</sup> Roach 1999, <sup>67</sup> Roach 1999, <sup>11</sup> Roach 2003, <sup>63</sup> Roach 2006, <sup>57</sup> Scherthaner 2004, <sup>70</sup> Schwartz 2006 <sup>56</sup>
Novo Nordisk	Abrahamian 2005, <sup>50</sup> Bebakar 2007, <sup>43</sup> Boehm 2004, <sup>42</sup> Christiansen 2003, <sup>14</sup> Hermansen 2002, <sup>55</sup> Holman 2007, <sup>28</sup> Joshi 2005, <sup>49</sup> Kann 2006, <sup>47</sup> Kapitza 2004, <sup>53</sup> Kilo 2003, <sup>16</sup> McSorley 2002, <sup>12</sup> Niskanen 2004, <sup>52</sup> Raj 2003, <sup>54</sup> Raskin 2005, <sup>36</sup> Raz 2005 <sup>51</sup>
Other	Cox 2007, <sup>68</sup> Mattoo 2003 <sup>73</sup>

## Reporting of Intermediate Outcomes and Adverse Events

**Fasting glucose.** The methods of reporting fasting or pre-meal blood glucose levels were not consistent among all studies. Studies either reported pre-breakfast blood glucose levels<sup>11 13 14 16 36 40 42 43 46-52 54 57 58 64 66-70</sup> both pre-breakfast and pre-dinner blood glucose levels,<sup>11 13 36 40 42 43 46-48 50-52 54 57 58 64 66-70</sup> or simply reported fasting blood glucose levels without specifying the time of the day when blood glucose was measured.<sup>28 44 59 60 62 63 71</sup> Eight studies did not report on pre-meal blood glucose level.<sup>12 41 45 53 55 56 61 65</sup> In six of these studies, blood glucose levels were reported after a single dose of the study drug with a test meal.<sup>41 53 55 56 61 65</sup> As pre-dinner blood

glucose levels are unlikely to be drawn in a fasting state, we evaluated pre-dinner levels separately and combined the fasting and pre-breakfast blood glucose levels for this review.

**Postprandial glucose.** In general, studies reported postprandial blood glucose either 90 minutes or 2 hours after a meal. Postprandial blood glucose levels were measured at 90 minutes after meal in eight studies<sup>14 36 47 48 50-52 54</sup> and at 2 hours after meal in 23 studies.<sup>11 13 16 40 41 43 46 55-70</sup>

Two studies did not specify what time of the day postprandial blood glucose was tested or pooled postprandial values together and reported one value.<sup>28 49</sup> Six studies did not report postprandial blood glucose levels.<sup>12 42 44 45 53 71</sup> All studies that reported 90-minute postprandial blood glucose levels reported results for both after breakfast and after dinner. Seventeen studies reported 2-hour postprandial blood glucose levels after both breakfast and dinner.<sup>11 13 16 40 43 46 57-60 62 64 66-70</sup>

Six additional studies reported 2-hour postprandial blood glucose levels after breakfast.<sup>41 55 56 61 63 65</sup> Five of these six studies evaluated postprandial blood glucose levels after a test-meal only and thus were not designed to report after-dinner values.<sup>41 55 56 61 65</sup> Although studies reported other outcomes for postprandial blood glucose levels such as blood glucose excursion or increment in blood glucose levels, we chose postprandial blood glucose levels for two reasons. First, postprandial blood glucose levels were the most frequently reported outcome measures in the trials. Second, postprandial blood glucose levels are frequently used in clinical practice to direct adjustments in insulin dose.

For the systematic review, we analyzed the 90-minute and 2-hour studies together as one group. We separately analyzed the breakfast postprandial blood glucose levels from the dinner postprandial levels. We analyzed studies that reported postprandial blood glucose levels without specifying the time of the day with studies that reported dinner postprandial glucose levels.

**HgbA1c.** HgbA1c levels were reported by 29 studies,<sup>11 14 16 28 36 40 42-52 54 57-60 62 63 66 67 69-71</sup> however we excluded two studies<sup>54 63</sup> from this review as the duration of followup in these two studies was only 6 and 8 weeks respectively.

**Hypoglycemia.** 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 change in weight as one of the adverse effects of the therapy,<sup>14 16 28 36 40 42-44 46-49 54 57-60 62 64 66 67 74</sup> except two studies that reported change in body mass index.<sup>69 71</sup> As noted in the Methods section, we included only parallel-arm studies<sup>14 16 28 36 40 42-44 46-48 51 54 62 66 69 71</sup> for the evaluation of this outcome as there is a high likelihood of a carryover effect in crossover studies 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 453 patients in the insulin aspart 70/30 arm and 458 patients in the long-acting insulin analogue arm.<sup>28 36 44 47</sup> One study used insulin detemir<sup>28</sup> as the long-acting insulin analogue; the remaining four studies used insulin glargine. All studies reported fasting blood glucose and HgbA1c. One study did not report postprandial blood glucose levels.<sup>44</sup>

Raskin et al.<sup>36</sup> enrolled 233 subjects for a 28-week trial. Patients either received 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 between 10 to 12 units daily depending on the fasting glucose levels and the dose was adjusted during followup.

Kann et al.<sup>47</sup> enrolled 255 patients to either insulin aspart 70/30 in combination with metformin or to insulin glargine and glimepiride and followed these patients for 26 weeks. Insulin dose was adjusted in both treatment arms during the trial and 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.

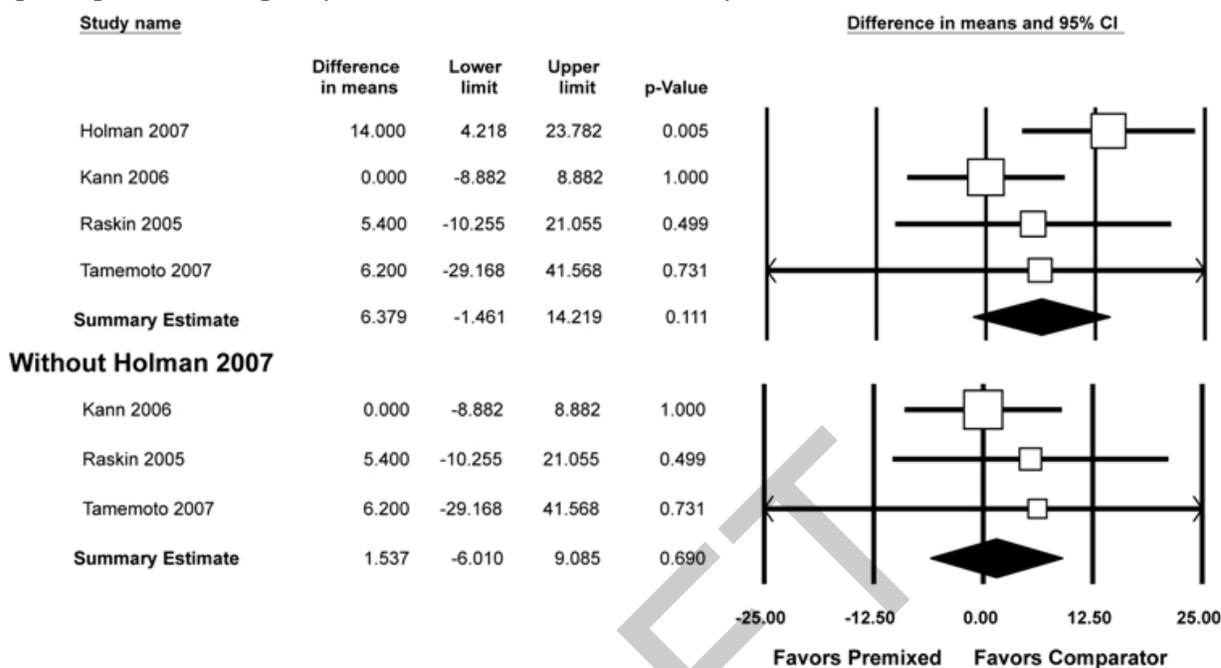
The study by Tamemoto et al.<sup>44</sup> was a small study enrolling 34 patients to either insulin aspart 70/30 or to insulin glargine. Patients were allowed to continue their oral antidiabetic agents except that patients in the insulin aspart 70/30 arm were not allowed to take a sulfonylurea. The starting dose was 10 to 16 units/day in the insulin aspart 70/30 arm and 6 to 8 units/day in insulin glargine arm. Insulin dose was adjusted during the followup period. Mean insulin dose in the insulin aspart 70/30 arm was 26.7 units/day; mean insulin glargine dose was not reported.

Holman et al.<sup>28</sup> conducted a three-arm study in which two arms compared insulin detemir (n = 234) with insulin aspart 70/30 (n = 235). Patients were followed for one 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. This study was funded by Novo Nordisk, manufacturer of insulin aspart 70/30.

Fasting glucose (see Appendix E, Evidence Table 4). For lowering fasting blood glucose levels, only one<sup>28</sup> of the four studies found insulin aspart 70/30 less effective than long-acting insulin analogues; other studies did not find any difference. When the results of all studies were pooled, insulin aspart 70/30 was less effective in lowering fasting blood glucose than long-acting insulin analogues, but this difference did not reach statistical significance (mean weighted difference = 6.4 mg/dL; 95% CI: -1.5 to 14.2 mg/dL; p = 0.11; see Figure 5). When we excluded the study with insulin detemir from the pooled analysis, the results did not change (weighted mean difference = 1.5 mg/dL; 95% CI: -6.0 to 9.1 mg/dL; p = 0.69; see Figure 5). Two studies reported on the pre-dinner blood glucose levels. One study<sup>36</sup> found insulin aspart 70/30 more effective than insulin glargine in lowering pre-dinner blood glucose levels (p < 0.05) while the second study<sup>47</sup> 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 more effective than long-acting insulin analogues in lowering postprandial glucose levels.<sup>28 36 47</sup> Pooling the results of these studies found insulin aspart 70/30 significantly better than long-acting insulin analogues in lowering postprandial blood glucose levels (weighted mean difference = -22.6 mg/dL; 95% CI: -32.1 to -13.2 mg/dL; p < 0.001; see Figure 6). Two of the

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

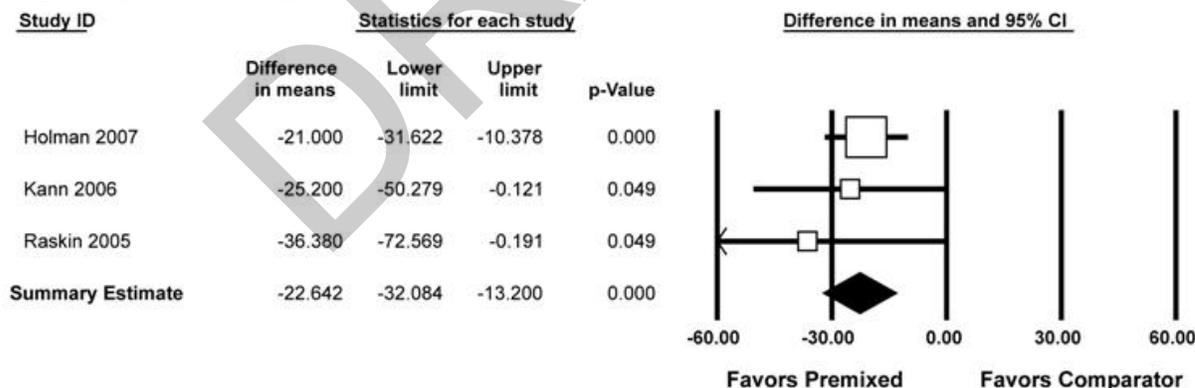


Boxes indicate individual study point estimates. Box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represent 95% confidence intervals for each study. The diamond at the bottom of the graph indicates 95% confidence interval 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 difference in postprandial glucose between insulin aspart 70/30 and long-acting insulin analogues**



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% confidence intervals for each study. The diamond at the bottom of the graph indicates 95% 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%

three trials also reported breakfast postprandial levels.<sup>36 47</sup> Insulin aspart 70/30 lowered breakfast postprandial blood glucose levels in both studies, but this effect reached statistical significance in one study only.<sup>47</sup>

HgbA1c (see Appendix E, Evidence Table 4). Insulin aspart 70/30 was significantly more effective than long-acting insulin analogues for lowering HgbA1c in all studies except in one

study by Tamemoto et al.<sup>44</sup> Tamemoto et al. could have failed to find a difference between the two treatments due to a small sample size (n = 23) resulting in low power to detect a difference. Raskin et al.<sup>36</sup> found that insulin aspart 70/30 lowered HgbA1c to a larger degree in patients with poorer control of diabetes (HgbA1c > 8.4%). Holman et al.<sup>28</sup> found that not only patients treated with insulin aspart 70/30 had lower HgbA1c levels (p < 0.001), they also were more likely to reach a target HgbA1c of 6.5 or less in the insulin aspart 70/30 group than in the insulin detemir group (p = 0.001). Pooling the study results across the four trials found that insulin aspart 70/30 was significantly better than long-acting insulin analogues in lowering HgbA1c levels (weighted mean difference = -0.48%; 95% CI: -0.61 to -0.34%; p < 0.001; see Figure 7).

Hypoglycemia (see Appendix E, Evidence Table 5). The incidence of overall hypoglycemia was reported by Holman et al.<sup>28</sup> and was higher in the insulin aspart 70/30 group than in the insulin detemir group (216 patients versus 173 patients; p < 0.001). Incidence of minor hypoglycemia was reported by three studies.<sup>36 44 47</sup> In two studies, minor hypoglycemia incidence was significantly higher in the insulin aspart 70/30 group than in the comparison group.<sup>36 47</sup> When the results of these three studies were pooled, the incidence of minor hypoglycemia was significantly higher with insulin aspart 70/30 as compared to insulin glargine (odds ratio (OR) = 2.8; 95% CI: 1.4 to 5.4; p = 0.003; see Figure 8). Two studies<sup>44 47</sup> reported the incidence of symptoms only and did not find any difference between the two types of insulin analogues.

Weight change (see Appendix E, Evidence Table 6). In two studies,<sup>28 36</sup> patients gained significantly more weight with insulin aspart 70/30 as compared to a long-acting insulin analogue (p < 0.001 in both studies). In the remaining two studies, weight change was not significant. Pooling the results of these four studies found that insulin aspart 70/30 was associated with a much larger weight gain than insulin glargine (weighted mean difference = 2.5 kg; 95% CI: 1.6 to 3.4 kg; p < 0.001; see Figure 9).

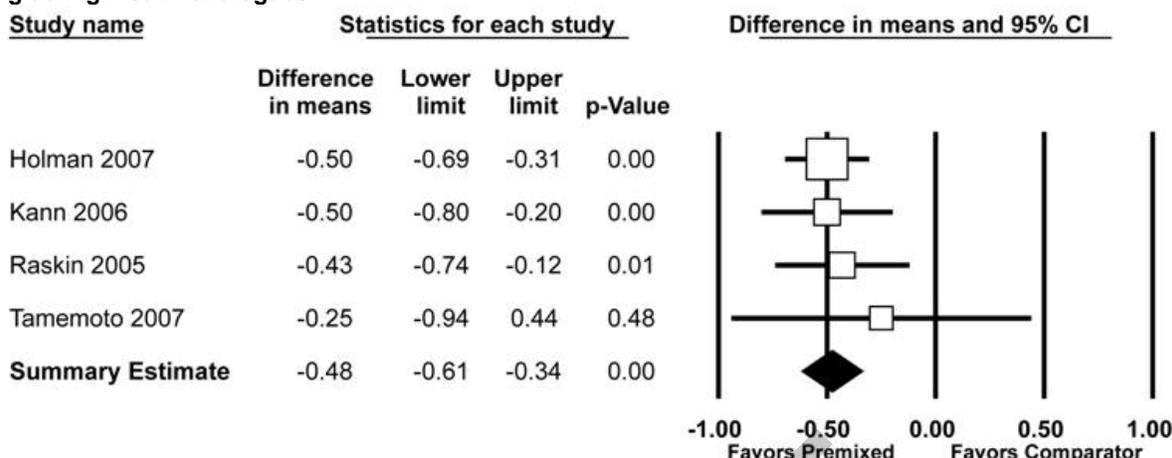
Other serious adverse events (see Table 5 and Appendix E, Evidence Table 6). No included studies comparing insulin aspart 70/30 to a long-acting insulin analogue reported on injection site reactions. Table 5 shows the range of risk differences between insulin aspart 70/30 and long-acting insulin analogues for total serious adverse events, other serious adverse events, and withdrawals due to adverse events.

**Insulin aspart 70/30 versus rapid-acting insulin analogues.** We identified only one study by Holman et al.<sup>28</sup> that compared twice-daily insulin aspart 70/30 with three-times daily rapid-acting insulin aspart with meals. This was a large RCT with 235 patients in the insulin aspart 70/30 arm and 238 patients in the rapid-acting insulin aspart arm. 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.<sup>28</sup> found that insulin aspart 70/30 was more effective than rapid-acting insulin aspart in decreasing fasting blood 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 as compared to insulin aspart 70/30 (mean difference = -15 mg/dL; p < 0.001). Rapid-acting insulin aspart was slightly more effective in lowering HgbA1c than insulin aspart 70/30 although this difference did not reach statistical significance (mean difference = -0.1%; p = 0.08). The percentage of patients who achieved a target HgbA1c of less than or equal to 7.0% and 6.5% was higher with rapid-acting insulin aspart as compared to insulin aspart 70/30 but this difference was not statistically significant (mean difference = 7.0% and 6.9% respectively; p = 0.08 for both HgbA1c targets).

Adverse events (see Appendix E, Evidence Tables 5 and 6). The incidence of hypoglycemia was not significantly different between the two groups (216 patients versus 229 patients; p =

**Figure 7. Meta-analyses of post-treatment difference in hemoglobin A1c between insulin aspart 70/30 and long-acting insulin analogues**

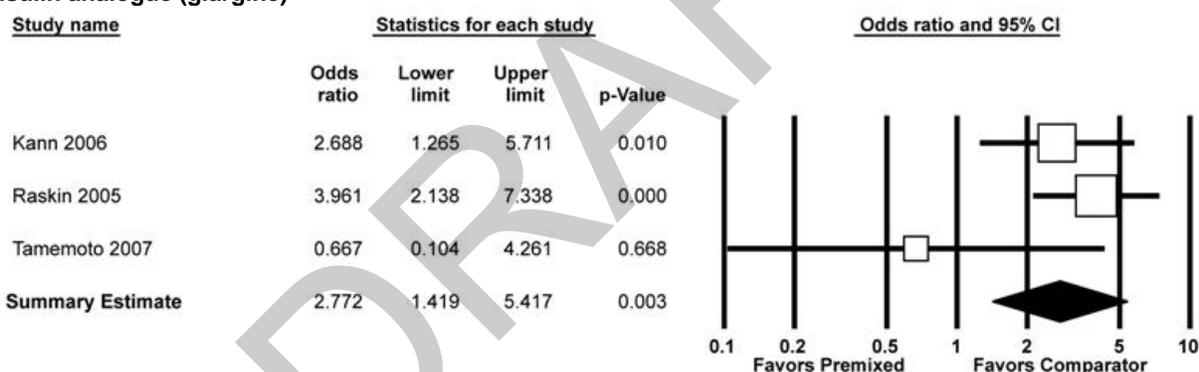


Boxes indicate individual study point estimates. Box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represent 95% confidence intervals for each study. The diamond at the bottom of the graph indicates 95% confidence interval for the random-effects pooled estimate.

Test for heterogeneity:  $Q = 0.589$  with 3 degrees of freedom ( $p = 0.899$ )

I-squared statistic = 0%

**Figure 8. Meta-analyses of incidence of mild hypoglycemia between insulin aspart 70/30 and long-acting insulin analogue (glargine)**



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 represents 95% confidence intervals for each study. The diamond at the bottom of the graph indicates 95% confidence interval for the random-effects pooled estimate.

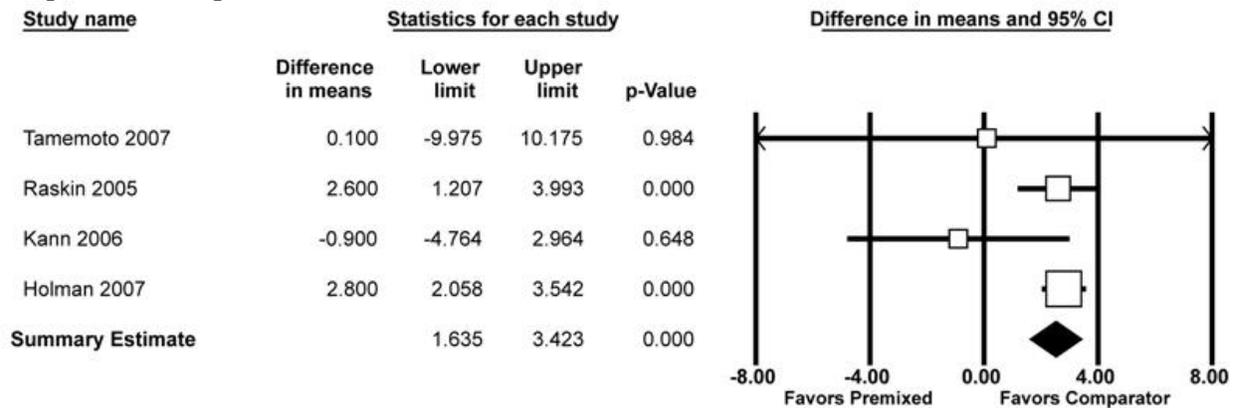
Test for heterogeneity:  $Q = 3.378$  with 2 degrees of freedom ( $p = 0.185$ )

I-squared statistic = 41%

0.08).<sup>28</sup> Treatment with insulin aspart 70/30 was associated with less weight gain than 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 for 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 with a combination of mealtime insulin aspart and bedtime insulin glargine.<sup>49</sup> Doses of all insulin analogues were adjusted throughout the trial based on glucose levels. At the end of the trial, total insulin dose was lower in the insulin aspart 70/30 group (40.2 units/day versus 52.8 units/day).

**Figure 9. Meta-analyses of post-treatment difference in weight change between insulin aspart 70/30 and long-acting insulin analogues**



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 represents 95% confidence intervals for each study. The diamond at the bottom of the graph indicates 95% 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%

Intermediate outcomes (see Appendix E, Evidence Table 4). After 12 weeks of followup, both treatments were effective in lowering fasting blood glucose, postprandial blood glucose, and HgbA1c from baseline levels. When both treatments were compared to one another, Joshi et al. found insulin aspart 70/30 less effective than a combination of mealtime insulin aspart and bedtime insulin glargine in lowering fasting blood glucose levels although this difference was not statistically significant (mean difference = 7.9 mg/dL;  $p > 0.05$ ).<sup>49</sup> On the other hand, insulin aspart 70/30 was more effective than the combination in lowering postprandial blood glucose levels although this effect was 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 HgbA1c (mean difference = -0.42%;  $p < 0.05$ ). Moreover, a larger percentage of patients achieved HgbA1c of less than 7% with insulin aspart 70/30 than with the combination at the end of 12 weeks of followup (mean difference = -14%; p-value was not reported).

Adverse events (see Appendix E, Evidence Tables 5 and 6). There were no major hypoglycemic events in this study.<sup>49</sup> 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%;  $p < 0.05$ ). There was no significant difference in the body weight in both 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<sup>16 42 50</sup> and three crossover trials<sup>12 45 55</sup> that compared insulin aspart 70/30 with a premixed human insulin, NPH/regular 70/30.

McNally et al.<sup>45</sup> compared insulin aspart 70/30 with NPH/regular 70/30 in a crossover trial enrolling 160 subjects. After a 6-week run in period, subjects were followed for two treatment periods each of 16 weeks duration. Insulin dose was adjusted during the followup 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.,<sup>50</sup> three-times daily insulin aspart 70/30 ( $n = 89$ ) was compared with twice-daily NPH/regular 70/30 ( $n = 88$ ). Mean insulin dose

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

Comparison	Total serious adverse events		Withdrawn due to adverse events		Other serious adverse events	
	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 <sup>28 36 47</sup>	-0.01 – 0.046	4 <sup>28 36 44 47</sup>	-0.01 – 0.02	1 <sup>28</sup>	0.04 for GI and abdominal pain 0.017 for lower respiratory tract and lung infection
Rapid-acting insulin analogues	1 <sup>28</sup>	0.048	1 <sup>28</sup>	0.01	1 <sup>28</sup>	0.013 for GI and abdominal pain 0.017 for lower respiratory tract and lung infection
Rapid-acting with long-acting insulin analogues	1 <sup>49</sup>	0	1 <sup>49</sup>	0	0	NA
Premixed human insulins	1 <sup>*45</sup>	-0.02	7 <sup>12 16 42 45 50 53 55</sup>	0 – 0.04	2 <sup>†12 16</sup>	0 – 0.02
Intermediate-acting human insulins	1 <sup>14</sup>	-0.01	2 <sup>14 16</sup>	0 – 0.04	2 <sup>14 16</sup>	0 – 0.02
Oral antidiabetic agents	1 <sup>‡  <sup>51</sup>¶</sup>	0 – 0.02	4 <sup>43 48 ¶<sup>51</sup>¶<sup>54</sup></sup>	-0.01 – 0.05	1 <sup>51 ¶</sup>	0 – 0.01 for cellulitis -0.01 – 0.05 for peripheral edema
Exenatide	1 <sup>46</sup>	-0.031	1 <sup>46</sup>	-0.08	0	NA
Insulin lispro 75/25	0	NA	2 <sup>§2 55</sup>	0 – 0.02	1 <sup>§52</sup>	0.066
Insulin aspart 70/30 + oral antidiabetic agents	1 <sup>  <sup>51</sup></sup>	0.02	2 <sup>48 51</sup>	-0.01 – 0.02	1 <sup>51</sup>	-0.06 for peripheral edema 0.01 for cellulitis

# The risk difference is the risk in the treatment group minus the risk 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.<sup>50</sup>

† An additional study reported 1 event in the insulin aspart 70/30 arm and 0 events in the premixed human insulin arm.<sup>55</sup>

‡ An additional study reported 5 events in the insulin aspart 70/30 arm and 0 events in the oral antidiabetic agents arm.<sup>43</sup>

|| An additional study reported a total of 5 events, but did not specify in which arm the events occurred.<sup>48</sup>

¶ 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.<sup>55</sup>

GI = gastrointestinal; NA = not applicable

was slightly larger in the insulin aspart 70/30 arm as compared to the premixed human insulin arm (0.61 units/kg/day versus 0.59 units/kg/day).

Boehm et al.<sup>10,42</sup> compared twice-daily insulin aspart 70/30 with twice-daily premixed human insulin 70/30. This was a 3-month trial with an extended followup of 2 years. The initial three 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.<sup>16</sup> conducted a three parallel-arm trial which compared insulin aspart 70/30 (given 10 minutes before dinner) with NPH/regular 70/30 (given 30 minutes before dinner) in two of its arms. Metformin was given to patients in both arms. Insulin dose was adjusted throughout the 12-week followup period. Mean insulin dose was slightly higher in the NPH/regular 70/30 group as compared to the insulin aspart 70/30 group (29 units/day versus 26 units/day).

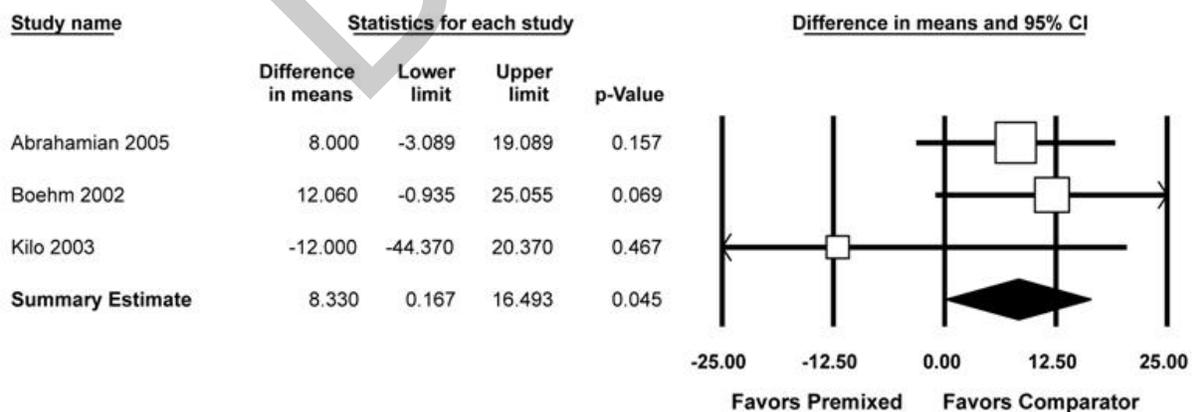
McSorely et al.<sup>12</sup> compared twice-daily insulin aspart 70/30 with twice-daily premixed human insulin 70/30 in a crossover trial over two treatment periods of 2 weeks each. This study did not report on the insulin dose used during the study.

Hermansen et al.<sup>55</sup> conducted a three-arm crossover trial in which study medications were given once only after a test meal to study the response of postprandial serum glucose. Two arms compared insulin aspart 70/30 with NPH/regular 70/30. Similar doses were used for both insulins based on weight of the subject (0.4 units/kg).

**Fasting glucose (see Appendix E, Evidence Table 4).** All three parallel-arm trials reported change in fasting blood glucose levels.<sup>16,42,50</sup> Individually, these studies did not find an advantage of one treatment over the other. When results of these studies were pooled, NPH/regular 70/30 was more effective than insulin aspart 70/30 in lowering fasting blood glucose (weighted mean difference = 8.3 mg/dL; 95% CI: 0.16 to 16.5 mg/dL;  $p = 0.04$ ; see Figure 10) although the difference was small.

**Postprandial glucose (see Appendix E, Evidence Table 4).** All three parallel-arm trials<sup>16,42,50</sup> and one crossover trial<sup>55</sup> reported changes in postprandial glucose. Boehm et al.<sup>10,42</sup> found a

**Figure 10. Meta-analyses of post-treatment difference in fasting glucose between insulin aspart 70/30 and premixed human insulin**



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% confidence intervals for each study. The diamond at the bottom of the graph indicates 95% 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%

significant decrease in postprandial blood glucose levels 90 minutes after breakfast ( $p < 0.05$ ) and after dinner ( $p < 0.02$ ) after 12 weeks of followup. However, Boehm et al. combined the results from type 2 diabetics ( $n = 187$ ) with type 1 diabetics ( $n = 104$ ) in reporting changes in postprandial blood glucose levels, thus making it difficult to extrapolate this finding to type 2 diabetics alone. Abrahamian et al.<sup>50</sup> found a significant decrease in blood glucose 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.<sup>16</sup> did not find a significant difference in blood 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.<sup>16</sup> also did not find insulin aspart 70/30 better than premixed human insulin in lowering breakfast postprandial blood glucose. These results were consistent with the results of a crossover trial.<sup>55</sup> that also did not find insulin aspart 70/30 better than premixed human insulin in lowering breakfast postprandial blood glucose after a single-dose of experimental drugs with a test-meal ( $p > 0.05$ ).

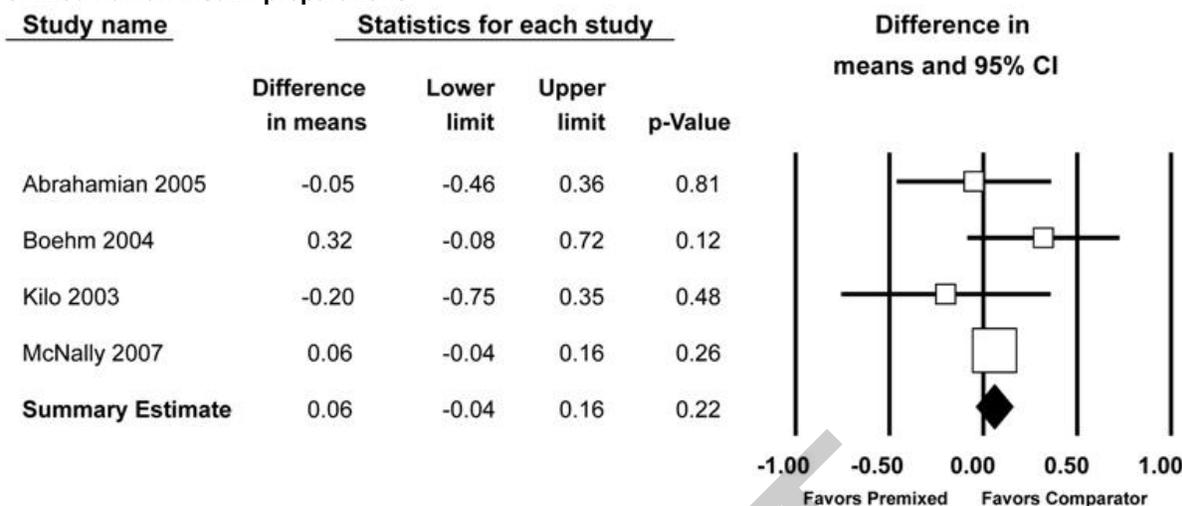
HgbA1c (see Appendix E, Evidence Table 4). All three parallel-arm trials<sup>16 42 50</sup> and one crossover trial<sup>45</sup> compared changes in HgbA1c levels with insulin aspart 70/30 and NPH/regular 70/30. Boehm et al.<sup>42</sup> found that mean HgbA1c increased slightly in both groups after an initial decrease in the first 6 months. There was no statistically significant difference in mean HgbA1c after 24 months (mean difference = 0.03%;  $p = 0.89$ ). McNally et al.<sup>45</sup> reported that patients on insulin aspart 70/30 achieved a mean HgbA1c of 7.28% compared with 7.22% after NPH/regular 70/30. The treatment difference of 0.06% was not statistically significant ( $p = 0.21$ ). Similar results were reported by Kilo et al.<sup>16</sup> and Abrahamian et al.<sup>50</sup> who found no significant differences in HgbA1c levels (mean difference = 0.2%;  $p > 0.05$  and mean difference = 0.1%;  $p = 0.64$  respectively). Pooling the results of these studies did not find one premixed preparation better than the other in lowering HgbA1c (weighted mean difference = 0.06%; 95% CI: -0.04 to 0.16%;  $p = 0.22$ ; see Figure 11).

Hypoglycemia (see Appendix E, Evidence Table 5). Two studies reported the incidence of hypoglycemia in general and found no difference between the two premixed preparations.<sup>16 42</sup> Five studies<sup>12 16 42 45 50</sup> reported the incidence of mild hypoglycemia, and none of them found a significant benefit of a particular premixed insulin. Pooling of the study results also did not change the results (OR = 0.98; 95% CI: 0.65 to 1.46;  $p = 0.91$ ; see Figure 12). The incidence of major hypoglycemia was reported in three studies,<sup>42 45 50</sup> but there was no difference between the treatments in individual studies nor upon pooling the results of these studies (OR = 0.52; 95% CI: 0.16 to 1.70;  $p = 0.28$ ). Only one study reported the incidence of symptoms only and found no difference between insulin aspart 70/30 and premixed human insulin (13 versus 11;  $p = 0.59$ ).<sup>16</sup>

Weight change (see Appendix E, Evidence Table 6). Boehm et al.<sup>42</sup> found that premixed human insulin was associated with higher weight gain than 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.<sup>16</sup> 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).

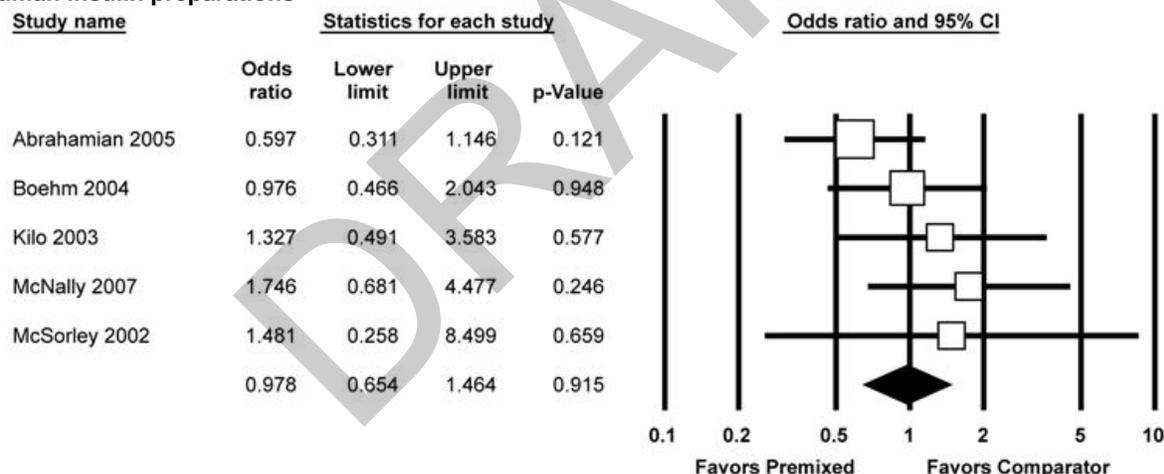
Other serious adverse events (see Appendix E, Evidence Table 6). None of these studies comparing insulin aspart 70/30 to a premixed human insulin reported on injection site reactions. Table 5 shows the range of risk differences between insulin aspart 70/30 and premixed human insulins for total serious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

**Figure 11. Meta-analyses of post-treatment difference in hemoglobin A1c between insulin aspart 70/30 and premixed human insulin preparations**



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% confidence intervals for each study. The diamond at the bottom of the graph indicates 95% 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%

**Figure 12. Meta-analyses of incidence of mild hypoglycemia between insulin aspart 70/30 and premixed human insulin preparations**



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 represents 95% confidence intervals for each study. The diamond at the bottom of the graph indicates 95% 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%

**Insulin aspart 70/30 versus intermediate-acting human insulin.** Two randomized parallel-arm trials that compared insulin aspart 70/30 with an intermediate-acting human insulin (NPH) met our inclusion criteria.<sup>14 16</sup>

Kilo et al.<sup>16</sup> compared bedtime NPH insulin with insulin aspart 70/30 given 10 minutes before meals, while Christiansen et al.<sup>14</sup> compared the two agents when given twice-daily (immediately before breakfast and dinner). In both studies insulin dose was adjusted during the

treatment to control blood glucose levels. The starting insulin dose in Christiansen et al.<sup>14</sup> was similar between the two arms but the mean dose was not reported in this study.

Fasting glucose (see Appendix E, Evidence Table 4). Both studies did not find any difference between the two treatments in lowering fasting blood glucose levels.<sup>14 16</sup> Kilo et al. also did not find any advantage of one regimen over the other in lowering pre-dinner blood glucose levels.<sup>16</sup>

Postprandial glucose (see Appendix E, Evidence Table 4). Kilo et al.<sup>16</sup> reported that 2-hour breakfast postprandial blood 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). On the other hand, Christiansen et al.<sup>14</sup> found insulin aspart 70/30 more effective than NPH insulin in lowering breakfast and dinner postprandial blood 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).

HgbA1c (see Appendix E, Evidence Table 4). Both trials found no difference between insulin aspart 70/30 and NPH insulin in lowering HgbA1c. Christiansen et al.<sup>14</sup> found that although HgbA1c decreased in both groups with reductions of 0.67% and 0.61% from baseline in the aspart 70/30 and NPH insulin groups respectively, there was no difference between the two treatments ( $p > 0.05$ ). Similarly, Kilo et al.<sup>16</sup> found that although HgbA1c decreased from baseline by 1.3% in the insulin aspart 70/30 group and by 1.2% 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.<sup>16</sup> found fewer patients who suffered minor hypoglycemia (6 versus 11) or symptoms of hypoglycemia (10 versus 13) with NPH insulin as compared to insulin aspart 70/30. More patients with NPH insulin had nocturnal hypoglycemia as compared to insulin aspart 70/30 (11 versus 7). Christiansen et al.<sup>14</sup> also found that more patients in the insulin aspart 70/30 group had minor hypoglycemia than the NPH insulin group (77 versus 68).

Weight change (see Appendix E, Evidence Table 6). In the study by Kilo et al.<sup>16</sup> insulin aspart 70/30 was associated with more weight gain as compared to 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 for total serious adverse events, other serious adverse events, and withdrawals due to adverse events.

**Insulin aspart 70/30 versus noninsulin antidiabetic agents.** Of the five studies identified by our search,<sup>43 46 48 51 54</sup> two studies compared insulin aspart 70/30 to a combination of a thiazolidinedione and glibenclamide,<sup>51 54</sup> one to a combination of metformin and glibenclamide,<sup>48</sup> one to either monotherapy or any combination of a sulfonylurea, metformin, or a meglitinide,<sup>43</sup> and one to exenatide.<sup>46</sup>

Bebakar et al.<sup>43</sup> evaluated once- or twice-daily insulin aspart 70/30 (n = 128) with 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 blood 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.<sup>48</sup> 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 while the doses of insulin aspart 70/30 and glibenclamide were adjusted based on glucose response.

Raz et al.<sup>51</sup> randomized patients to 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. Insulin dose was lower in the insulin aspart 70/30 with pioglitazone group as compared to insulin aspart 70/30 alone group (0.2 units/kg/day versus 0.3 units/kg/day).

In another study, Raz et al.<sup>54</sup> 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 was allowed to be adjusted, doses of rosiglitazone and glibenclamide were kept fixed throughout the study.

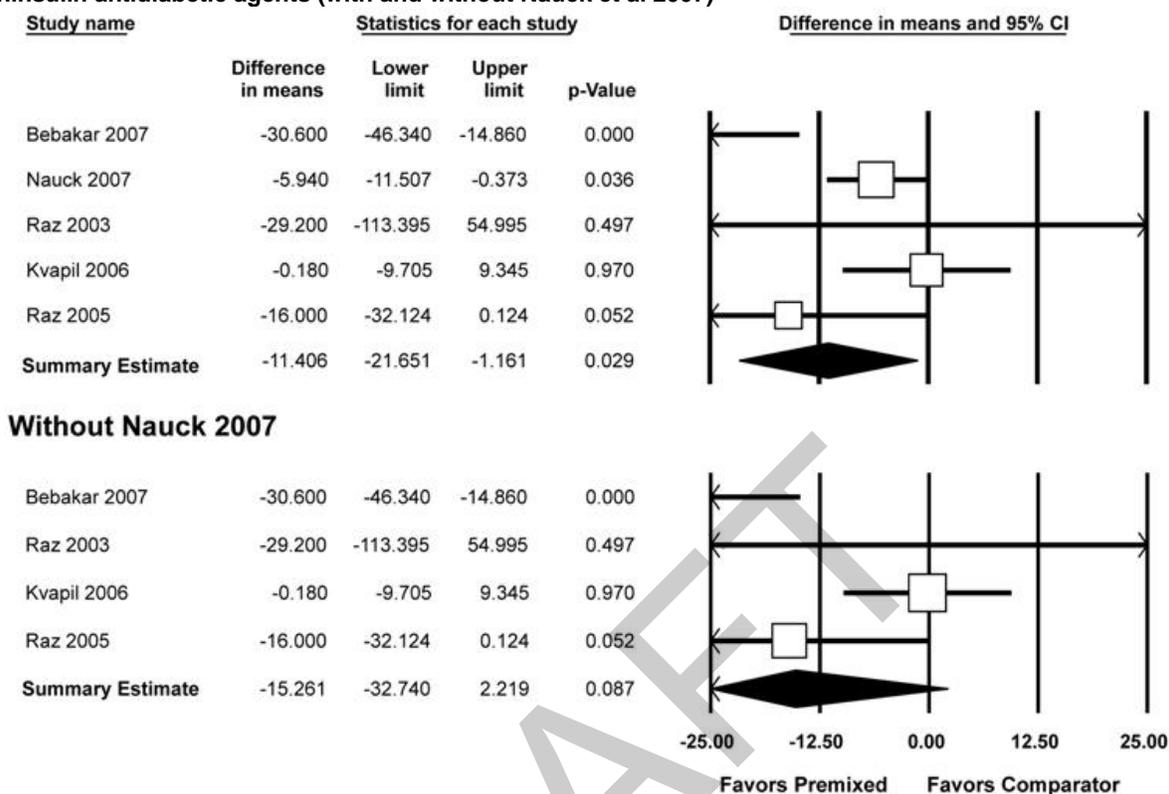
Nauck et al.<sup>46</sup> compared twice-daily exenatide (an incretin mimetic) to twice-daily insulin aspart 70/30 in patients with suboptimal diabetes control while patients were allowed to continue their metformin and sulfonylurea treatments. Insulin aspart 70/30 dose was titrated throughout the study to achieve optimal glucose control. Exenatide dose, on the other hand, was increased only once at 4 weeks from 5 micrograms to 10 micrograms twice daily.

Fasting glucose (see Appendix E, Evidence Table 4). For lowering fasting blood glucose, insulin aspart 70/30 was more effective than noninsulin antidiabetic agents in all studies but the difference was statistically significant in only two studies.<sup>43 46</sup> When the results of all trials were pooled, insulin aspart 70/30 was more effective than oral antidiabetic agents in lowering fasting blood glucose (weighted mean difference = -11.4 mg/dL; 95% CI: -21.6 to -1.2 mg/dL; p = 0.03; see Figure 13). When the study by Nauck et al.<sup>46</sup> that compared exenatide with insulin aspart 70/30 was excluded, insulin aspart 70/30 was no longer significantly different than oral antidiabetic agents in lowering fasting blood glucose (weighted mean difference = -15.3 mg/dL; 95% CI: -32.7 to 2.2 mg/dL; p = 0.09; see Figure 13).

All studies also reported changes in pre-dinner blood glucose levels. Insulin aspart 70/30 was significantly more effective in lowering pre-dinner blood glucose levels than noninsulin antidiabetic agents in two studies.<sup>43 51</sup> In the study by Raz et al.,<sup>51</sup> insulin aspart 70/30 in combination with pioglitazone but not alone was better than the combination of glibenclamide and pioglitazone in lowering pre-dinner blood glucose levels. When the results of all five 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 blood glucose levels (weighted mean difference = -7.1 mg/dL; 95% CI: -23.3 to 9.1 mg/dL; p = 0.39). When we excluded the study by Nauck et al.,<sup>46</sup> there was no change in the direction of the summary estimate or the results of the meta-analysis (weighted mean difference = -12.1 mg/dL; 95% CI: -33.1 to 8.8 mg/dL; p = 0.26).

Postprandial glucose (see Appendix E, Evidence Table 4). All five studies also reported changes in postprandial glucose levels. As compared to a combination of a thiazolidinedione and metformin, insulin aspart 70/30 lowered postprandial blood glucose levels in both studies<sup>51 54</sup> but the decrease in blood glucose was significant only in one study.<sup>51</sup> Insulin aspart 70/30 was better than either monotherapy or with any combination of a sulfonylurea, metformin, or a meglitinide in lowering dinner postprandial blood glucose levels in one study.<sup>43</sup> On the other hand, insulin aspart 70/30 was not different than a combination of metformin and glibenclamide in lowering postprandial blood glucose levels in the study by Kvapil et al.<sup>48</sup> Nauck et al. found that exenatide was better than insulin aspart 70/30 in lowering postprandial blood glucose levels.<sup>46</sup> Pooling the results of these studies found that insulin aspart 70/30 lowers postprandial blood glucose levels

**Figure 13. Meta-analyses of post-treatment difference in fasting glucose between insulin aspart 70/30 and noninsulin antidiabetic agents (with and without Nauck et al 2007)**



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% confidence intervals for each study. The diamond at the bottom of the graph indicates 95% confidence interval for the random-effects pooled estimate.

Test for heterogeneity:  $Q = 12.167$  with 4 degrees of freedom ( $p = 0.016$ )

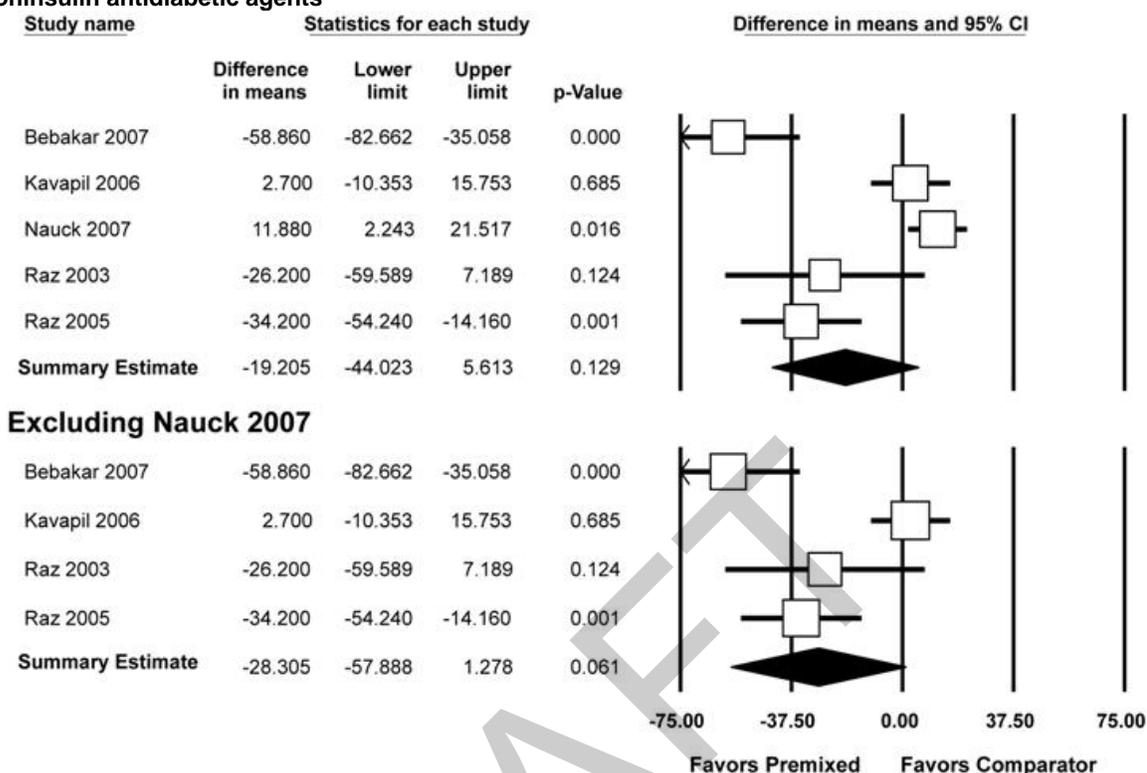
I-squared statistic = 67%

but the lowering was not statistically significant (weighted mean difference = -19.2 mg/dL; 95% CI: -44.0 to 5.6 mg/dL;  $p = 0.13$ ; see Figure 14). The results did not change even when the study with exenatide<sup>46</sup> was excluded from the meta-analysis (weighted mean difference = -28.3 mg/dL; 95% CI: -57.9 to 1.3 mg/dL;  $p = 0.06$ ; see Figure 14).

Four of these five studies also reported postprandial blood glucose after breakfast.<sup>43 46 48 51</sup> Insulin aspart 70/30 was better than the comparator in two of these studies,<sup>43 51</sup> was equal to the comparator in one study,<sup>48</sup> and inferior to the comparator in the fourth study.<sup>46</sup> Pooling the results of these studies found a nonsignificant advantage of insulin aspart 70/30 in lowering postprandial blood glucose after breakfast (weighted mean difference = -14.4 mg/dL; 95% CI: -37.7 to 8.96 mg/dL;  $p = 0.23$ ). When the study by Nauck et al.<sup>46</sup> was excluded from the meta-analysis, the postprandial blood glucose lowering effect of insulin aspart 70/30 almost reached statistical significance (weighted mean difference = -24.5 mg/dL; 95% CI: -49.1 to 0.05 mg/dL;  $p = 0.05$ ).

HgbA1c (see Appendix E, Evidence Table 4). Changes in HgbA1c in response to treatment were also reported by all five studies. Bebakar et al.<sup>43</sup> found a significantly greater reduction in HgbA1c with insulin aspart 70/30 versus oral antidiabetic agents (difference = -0.58%;  $p < 0.001$ ). Similarly, Raz et al.<sup>51</sup> reported that HbA1c was significantly lower in the combined insulin aspart 70/30 and pioglitazone group compared to the glibenclamide and pioglitazone group (mean change -0.64%;  $p = 0.005$ ). However, insulin aspart 70/30 alone lowered HgbA1c

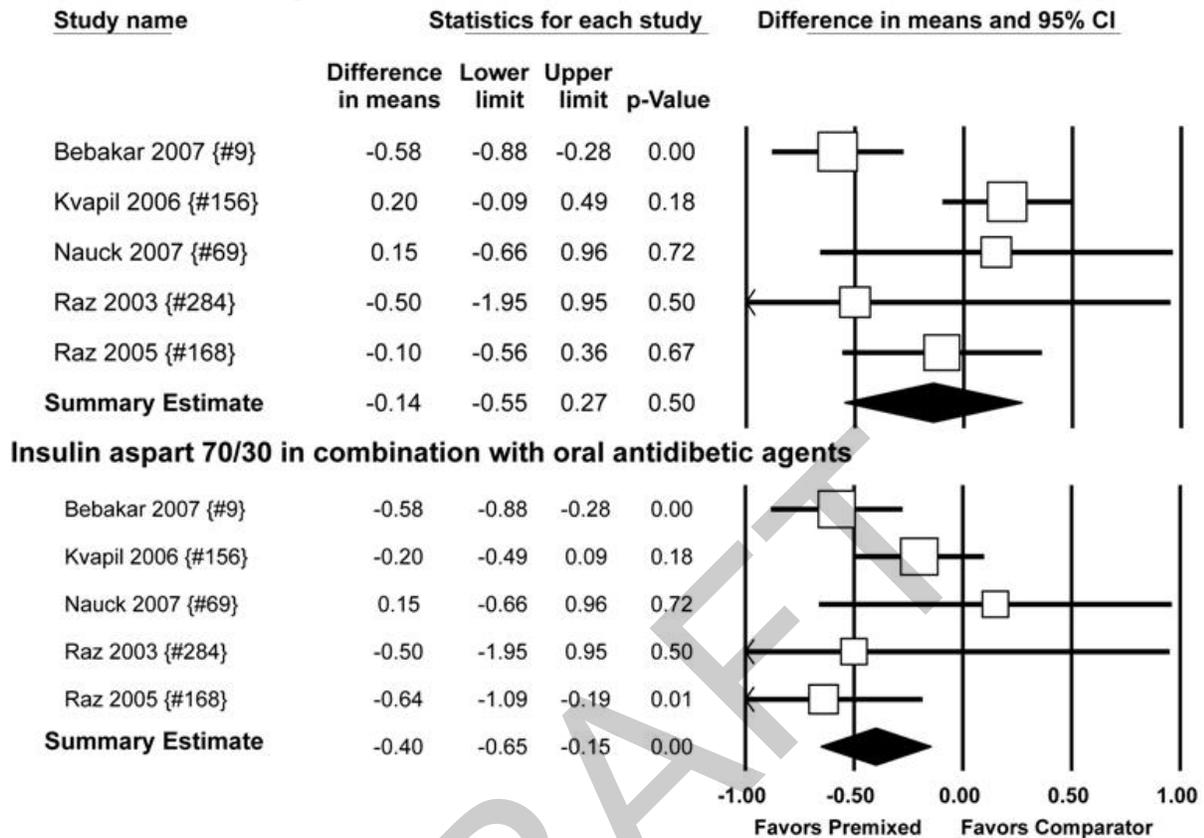
**Figure 14. Meta-analyses of post-treatment difference in postprandial glucose between insulin aspart 70/30 and noninsulin antidiabetic agents**



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% confidence intervals for each study. The diamond at the bottom of the graph indicates 95% confidence interval for the random-effects pooled estimate. Test for heterogeneity:  $Q = 42.212$  with 4 degrees of freedom ( $p < 0.001$ )  
I-squared statistic = 90%

to a similar extent as that of glibenclamide and pioglitazone in this trial ( $p > 0.05$ ). On the other hand, in another study by Raz et al.<sup>54</sup> a combination of insulin aspart 70/30 and rosiglitazone was not more effective than a combination of rosiglitazone and glibenclamide in lowering HgbA1c (mean change = -0.5%;  $p > 0.05$ ). This study was only 6 weeks in duration and it is quite possible that the HgbA1c levels may not have reached a steady state with the study medications and, therefore, was excluded from the pooled analyses. Somewhat similar results were reported by Kvapil et al.<sup>48</sup> 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 HgbA1c ( $p > 0.05$ ). Nauck et al.<sup>46</sup> found that exenatide was slightly better than insulin aspart 70/30 in lowering HgbA1c although the difference was not statistically significant (mean difference = -0.15%;  $p = 0.07$ ). When the results of all these studies were pooled together, insulin aspart 70/30 was slightly better than noninsulin antidiabetic agents although this difference was not statistically significant (weighted mean difference = -0.14%; 95% CI: -0.55 to 0.27%;  $p = 0.50$ ; see Figure 15). When the insulin aspart 70/30 only arms in two trials<sup>48 51</sup> were replaced by the combination arms of insulin aspart 70/30 with oral antidiabetic agents, insulin aspart 70/30 was more effective than noninsulin antidiabetic agents in lowering HgbA1c levels (weighted mean difference = -0.40%; 95% CI: -0.65 to -0.15%;  $p < 0.01$ ; see Figure 15). When the study by Nauck et al.<sup>46</sup> was removed from the pooled analysis, the main conclusion of the meta-analysis did not change (weighted mean difference = -0.16%; 95% CI: -0.67 to 0.35%;  $p =$

Figure 15. Meta-analyses of post-treatment difference in hemoglobin A1c between insulin aspart 70/30 and noninsulin antidiabetic agents



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% confidence intervals for each study. The diamond at the bottom of the graph indicates 95% confidence interval for the random-effects pooled estimate.

Test for heterogeneity:  $Q = 14.193$  with 4 degrees of freedom ( $p = 0.007$ )

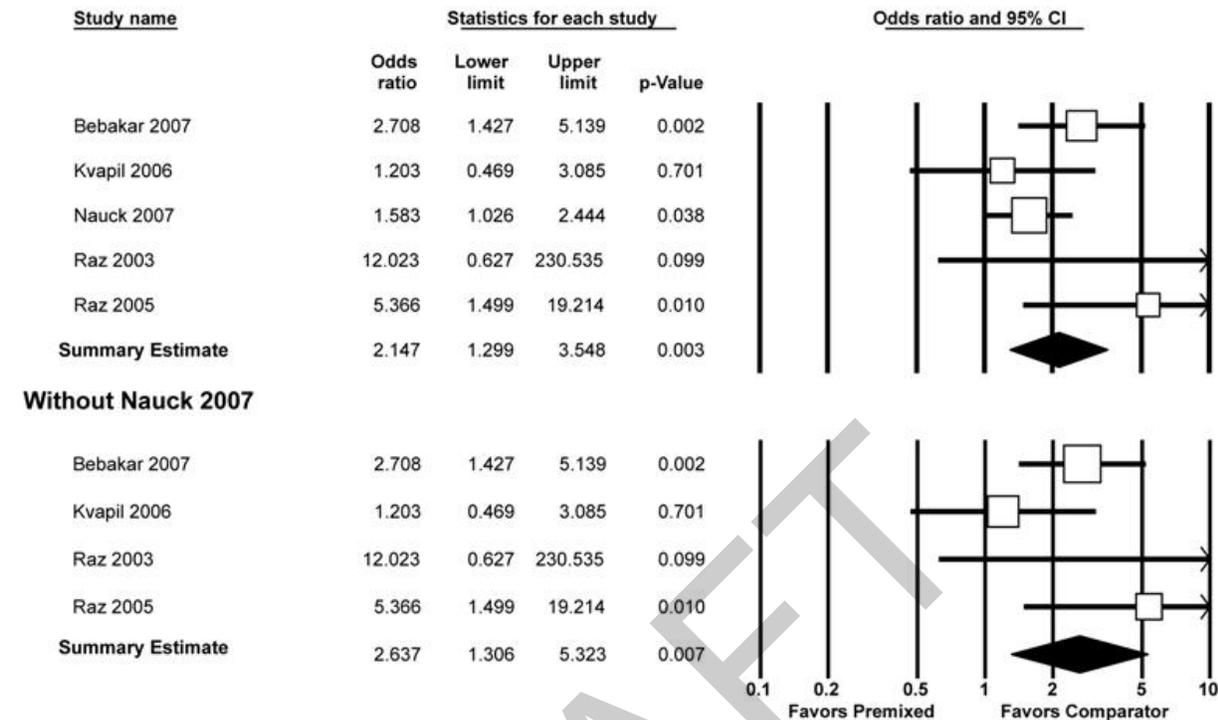
I-squared statistic = 72%

0.53).

**Hypoglycemia** (see Appendix E, Evidence Table 5). There were no major hypoglycemic events in four studies.<sup>46 48 51 54</sup> Bebakar et al.<sup>43</sup> reported one major hypoglycemic event in each arm. All five studies reported the incidence of minor hypoglycemic events. Nauck et al.<sup>46</sup> 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, although it reached statistical significance in only two studies.<sup>43 51</sup> When the results of these studies were pooled together, insulin aspart 70/30 was associated with a higher risk of minor hypoglycemia as compared to noninsulin antidiabetic agents (OR = 2.1; 95% CI: 1.3 to 3.5;  $p = 0.003$ ; see Figure 16). When the study by Nauck et al.<sup>46</sup> was excluded from the analysis, the results did not change very much (OR = 2.6; 95% CI: 1.3 to 5.3;  $p = 0.007$ ; see Figure 16).

**Weight change** (see Appendix E, Evidence Table 6). All five studies reported on change in weight, but the data was not sufficiently reported in two studies to be used in pooling the study results.<sup>51 54</sup> In the three other studies, insulin aspart 70/30 was associated with weight gain as compared to noninsulin antidiabetic agents (weighted mean difference = 2.6 kg; 95% CI: -0.5 to 5.8 kg;  $p = 0.1$ ; see Figure 17).

**Figure 16. Meta-analyses of incidence of mild hypoglycemia between insulin aspart 70/30 and noninsulin antidiabetic agents**

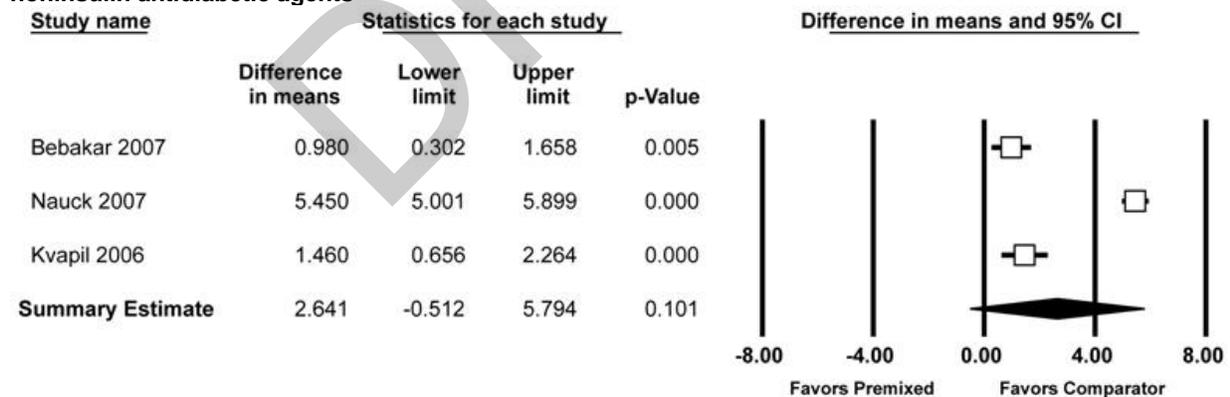


Boxes indicate individual study point estimates. Box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents 95% confidence intervals for each study. The diamond at the bottom of the graph indicates 95% confidence interval for the random-effects pooled estimate.

Test for heterogeneity:  $Q = 6.783$  with 4 degrees of freedom ( $p = 0.148$ )

I-squared statistic = 41%

**Figure 17. Meta-analyses of post-treatment difference in weight change between insulin aspart 70/30 and noninsulin antidiabetic agents**



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 represents 95% confidence intervals for each study. The diamond at the bottom of the graph indicates 95% confidence interval for the random-effects pooled estimate.

Test for heterogeneity:  $Q = 149.811$  with 2 degrees of freedom ( $p < 0.001$ )

I-squared statistic = 99%

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 for 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.<sup>52 55</sup>

Niskanen et al.<sup>52</sup> compared twice-daily insulin aspart 70/30 with twice-daily insulin lispro 75/25 in a crossover study. This study was funded by Novo Nordisk, 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 with each study drug.

Hermansen et al.<sup>55</sup> compared a single dose of insulin aspart 70/30 with 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, this study was not designed to evaluate either fasting blood glucose or HgbA1c. In addition, this study reported postprandial blood glucose excursions only.

Fasting glucose (see Appendix E, Evidence Table 4). Niskanen et al.<sup>52</sup> did not find a significant difference between the two premixed insulin analogues in lowering fasting blood glucose levels after breakfast ( $p = 0.42$ ).

Postprandial glucose (see Appendix E, Evidence Table 4). Niskanen et al.<sup>52</sup> also did not find a significant difference between the two premixed insulin analogues in lowering 90-minute breakfast or dinner postprandial blood glucose levels ( $p = 0.52$  and  $0.19$  respectively).

HgbA1c (see Appendix E, Evidence Table 4). Although insulin aspart 70/30 appeared less effective than insulin lispro 75/25 in lowering HgbA1c, the difference was not statistically significant (mean difference =  $0.14\%$ ,  $p = 0.08$ ) in the only study which reported this outcome.<sup>52</sup>

Hypoglycemia (see Appendix E, Evidence Table 5). One major hypoglycemic event occurred with each premixed insulin analogue in the trial by Niskanen et al.<sup>52</sup> In Hermansen et al.,<sup>55</sup> 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 patients had minor hypoglycemic events with insulin aspart 70/30 as compared to 53 patients with insulin lispro 75/25.<sup>52</sup>

Weight change (see Appendix E, Evidence Table 6). As 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.<sup>52</sup> reported that 1% of the insulin aspart 70/30 arm and 2% of 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<sup>57-60 68</sup> that compared insulin lispro 75/25 with a long-acting insulin analogue. Insulin glargine was the comparator agent in all these trials.

Roach et al.<sup>57</sup> compared twice-daily insulin lispro 75/25 plus oral antidiabetic agents with 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. Mean daily dose of insulin lispro 75/25 was larger as compared to the mean daily dose of insulin glargine (60 units versus 44 units respectively). Doses of oral antidiabetic agents were not reported.

Jacober et al.<sup>58</sup> compared insulin lispro 50/50 before breakfast and lunch plus insulin lispro 75/25 before dinner with 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.<sup>59</sup> compared twice-daily insulin lispro 75/25 plus metformin with once-daily insulin glargine plus metformin in a crossover study. In this study, the metformin dose was kept fixed but the insulin doses were allowed to be changed 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 units/kg versus 0.57 units/kg;  $p < 0.001$ ).

With a similar study design but in a different population, Malone et al.<sup>60</sup> compared twice-daily insulin lispro 75/25 plus metformin with once-daily insulin glargine plus metformin. The metformin dose was similar at the end of treatment, but the insulin lispro 75/25 dose was significantly larger than the insulin glargine dose (0.42 units/kg versus 0.36 units/kg;  $p < 0.001$ ).

Cox et al.<sup>68</sup> 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. 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.

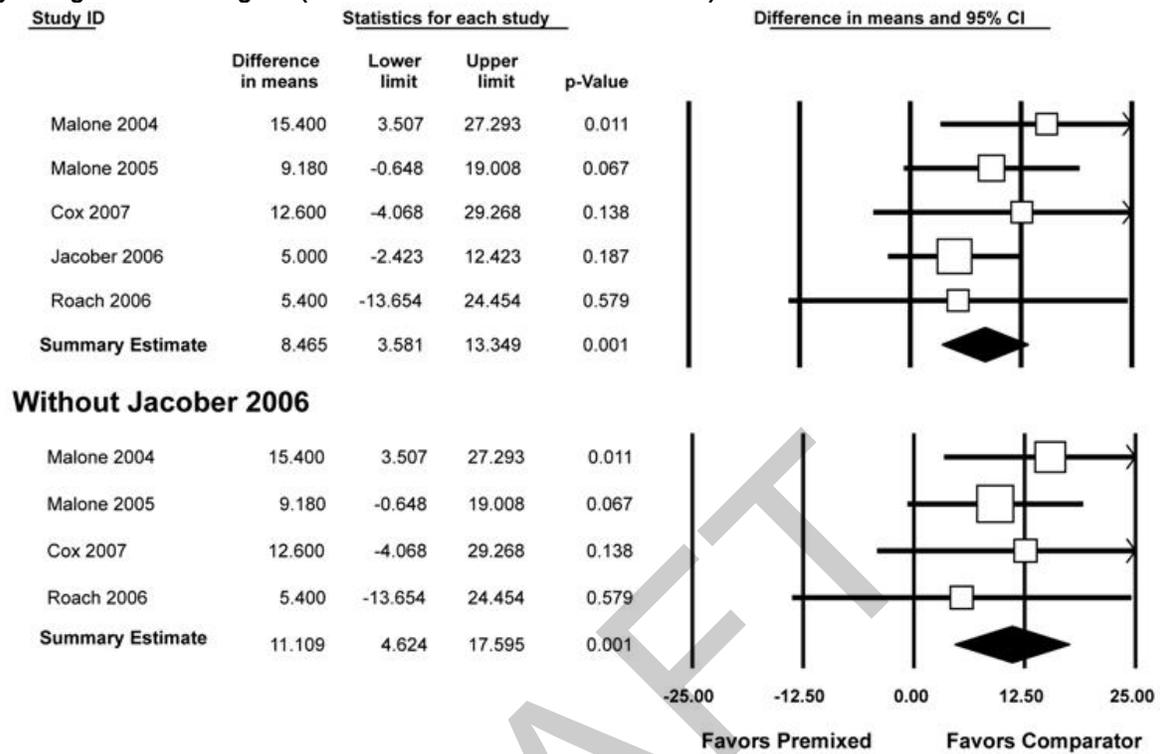
Fasting glucose (see Appendix E, Evidence Table 4). All five trials reported fasting blood glucose levels. One study by Jacober et al.<sup>58</sup> used insulin lispro 50/50 with breakfast and lunch and insulin lispro 75/25 with dinner. As the fasting blood glucose level was likely to be affected by 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 blood glucose but the difference was significant in only one study.<sup>59</sup> When these study results were pooled, insulin glargine was more effective than insulin lispro 75/25 in lowering fasting blood glucose levels (weighted mean difference = 8.5 mg/dL; 95% CI: 3.6 to 13.3 mg/dL;  $p = 0.001$ ; see Figure 18). Excluding the study by Jacober et al.<sup>58</sup> had no effect on the results of this meta-analysis (weighted mean difference = 11.1 mg/dL; 95% CI: 4.6 to 17.6 mg/dL;  $p = 0.001$ ; see Figure 18). We also identified an unpublished trial which found insulin glargine more effective than insulin lispro 75/25 but the difference was not statistically significant.<sup>75</sup>

Although all five trials reported pre-dinner blood glucose levels, one study by Jacober et al.<sup>58</sup> was excluded due to the above stated reason. The remaining four trials did not find any difference between insulin lispro 75/25 and insulin glargine in lowering pre-dinner blood glucose levels.<sup>57 59 60 68</sup>

Postprandial glucose (see Appendix E, Evidence Table 4). These trials reported on both dinner and breakfast postprandial blood glucose levels.<sup>57-60 68</sup> However, as noted above, one trial by Jacober et al.<sup>58</sup> 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 better than insulin glargine in lowering dinner postprandial blood glucose levels in all except one study.<sup>68</sup> In two of the four trials, insulin lispro 75/25 was also better in lowering breakfast postprandial levels.<sup>59 60</sup> Pooling of the studies found a significant advantage of insulin lispro 75/25 in lowering dinner postprandial blood glucose (weighted mean difference = -23.6 mg/dL; 95% CI: -30.9 to -16.4 mg/dL;  $p < 0.001$ ; see Figure 19) and a nonsignificant advantage in lowering breakfast postprandial glucose (weighted mean difference = -10.0 mg/dL; 95% CI: -23.3 to 3.2 mg/dL;  $p = 0.137$ ). We identified one unpublished trial<sup>75</sup> which found a significant decrease in dinner postprandial glucose with insulin lispro 75/25 but no change in breakfast postprandial blood glucose levels ( $p = 0.04$  and  $0.97$  respectively).

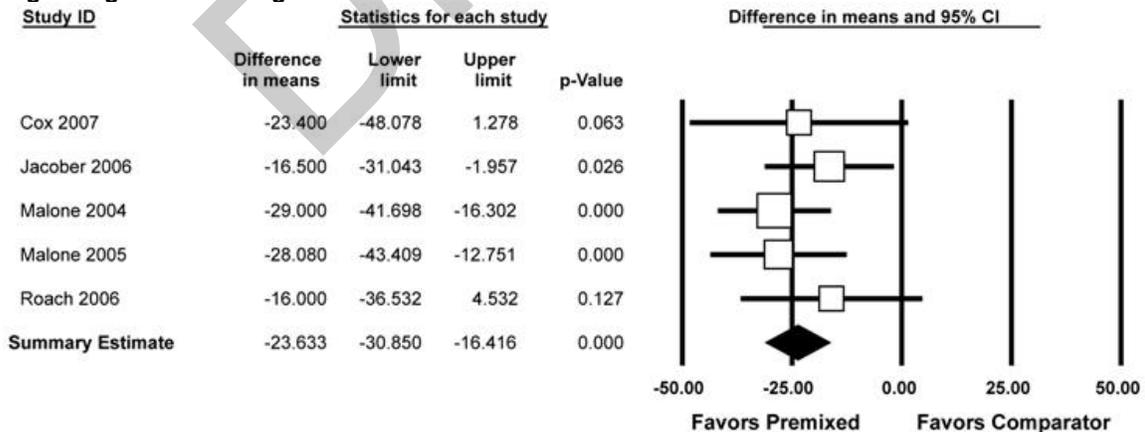
HgbA1c (see Appendix E, Evidence Table 4). Of the five trials that compared insulin lispro 75/25 to long-acting insulin analogues, four trials reported on the changes in HgbA1c.<sup>57-60</sup> As noted above, Jacober et al.<sup>58</sup> administered insulin lispro 50/50 with breakfast and lunch and

**Figure 18. Meta-analyses of post-treatment difference in fasting glucose between insulin lispro 75/25 and long-acting insulin analogues (with and without Jacober et al 2006)**



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% confidence intervals for each study. The diamond at the bottom of the graph indicates 95% 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%

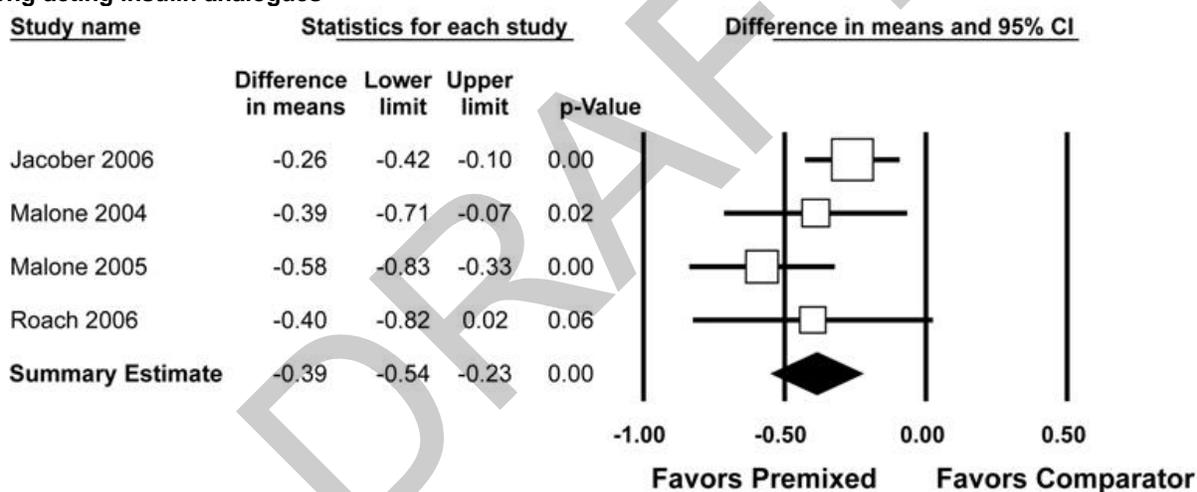
**Figure 19. Meta-analyses of post-treatment difference in postprandial glucose between insulin lispro 75/25 and long-acting insulin analogues**



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% confidence intervals for each study. The diamond at the bottom of the graph indicates 95% 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%

insulin lispro 75/25 with dinner; therefore, the change in HgbA1c in this study is a reflection of both strengths of insulin. This study found that the premixed insulin lispro based regimen was better in lowering HgbA1c than insulin glargine (mean difference = -0.26%; p = 0.003). However, there was no significant difference in the percentage of patients who achieved target HgbA1c less than or equal to 7% (44% versus 31% respective; p = 0.1). On the other hand, in a study by Malone et al.<sup>59</sup> insulin lispro 75/25 was not only able to lower HgbA1c more than insulin glargine (mean difference = -0.4%; p = 0.002), but more patients achieved target HgbA1c less than or equal to 7% (42% versus 18%; p < 0.001). In another study, Malone et al.<sup>60</sup> found a combination of insulin lispro 75/25 and metformin better than a combination of insulin glargine and metformin in lowering HgbA1c (mean difference = -0.60%; p < 0.001). Similar results were obtained by Roach et al.:<sup>57</sup> insulin lispro 75/25 was more effective than insulin glargine in lowering HgbA1c (mean difference = -0.4%; p < 0.05). When the results of these trials were pooled, insulin lispro 75/25 was significantly more effective than insulin glargine in lowering HgbA1c (weighted mean difference = -0.39%; 95% CI: -0.54 to -0.23%; p < 0.001; see Figure 20). When the study by Jacober et al.<sup>58</sup> was excluded, there was no change in the results of the meta-analysis (weighted mean difference = -0.49%; 95% CI: -0.67 to -0.31%; p < 0.001).

**Figure 20. Meta-analyses of post-treatment difference in hemoglobin A1c between insulin lispro 75/25 and long-acting insulin analogues**



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 represents 95% confidence intervals for each study. The diamond at the bottom of the graph indicates 95% confidence interval for the random-effects pooled estimate.

Test for heterogeneity:  $Q = 4.354$  with 3 degrees of freedom ( $p = 0.226$ )

I-squared statistic = 31%

Hypoglycemia (see Appendix E, Evidence Table 5). Incidence of all hypoglycemia was reported by two trials.<sup>58 60</sup> Malone et al.<sup>60</sup> found an equal incidence of all hypoglycemia with both types of insulins. On the other hand, Jacober et al.<sup>58</sup> found a significantly greater risk of all hypoglycemia with insulin lispro than with insulin glargine. As Jacober et al.<sup>58</sup> used two different insulin lispro preparations, it is not possible to separate hypoglycemic events due to insulin lispro 75/25. Minor hypoglycemia was reported in three studies.<sup>57-59</sup> In all 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.<sup>58</sup> Cox et al.<sup>68</sup> only reported that there was no difference in the incidence of hypoglycemia in the two groups.

Weight change (see Appendix E, Evidence Table 6). As all studies were crossover studies,

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

Comparison	Total serious adverse events		Withdrawn due to adverse events		Other serious adverse events	
	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 <sup>57-60 68</sup>	-0.01 – 0.03	2 <sup>59 60</sup>	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 <sup>56</sup>	0	8 <sup>13 41 55 56 61 64 65 67</sup>	0	2 <sup>55 61</sup>	-0.01 – 0
Intermediate-acting human insulins	0	NA	0	NA	0	NA
Oral antidiabetic agents	0	NA	2 <sup>62 66</sup>	-0.01 – 0.02	1 <sup>*66</sup>	0.01
Exenatide	0	NA	0	NA	0	NA
Insulin lispro 50/50	1 <sup>56</sup>	0	1 <sup>56</sup>	0	0	NA

# The risk difference is the risk in the treatment group minus the risk 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.<sup>62</sup>

NA = not applicable

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 for withdrawals due to adverse events.

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

**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 with a combination of rapid-acting and long-acting insulin analogues.

**Insulin lispro 75/25 versus premixed human insulin.** We found nine randomized crossover studies that compared insulin lispro 75/25 with premixed human insulin preparations.<sup>11 13 41 55 56 61 64 65 67</sup> Four studies were one-dose studies and thus had only one breakfast postprandial value after a test meal.<sup>41 55 56 61</sup> All trials compared insulin lispro 75/25 with NPH/regular 70/30 except the study by Roach et al.<sup>11</sup>

In the study by Roach et al.<sup>11</sup> 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.<sup>64</sup> compared twice-daily insulin lispro 75/25 with 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.<sup>67</sup> compared twice-daily insulin lispro 75/25 with 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 mean daily insulin doses were similar with both treatment sequences.

Herz et al.<sup>13</sup> compared the effect of insulin lispro 75/25 with NPH/regular 70/30 on the 24-hour 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.<sup>65</sup> compared the plasma glucose response with insulin lispro 75/25 versus a premixed human insulin before and after exercise. Insulin dose was similar in both treatment sequences.

In a three-arm crossover trial, Schwartz et al.<sup>56</sup> compared one dose of insulin lispro 75/25 with 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.<sup>55</sup> compared a single dose of insulin lispro 75/25 with 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.<sup>61</sup> compared twice-daily insulin lispro 75/25 with NPH/regular 70/30 in diabetic patients with Italian dietary habits. However, they evaluated changes in blood glucose after a test meal. Mean daily insulin dose was similar between the two treatment groups.

Malone et al.<sup>41</sup> compared a single dose of insulin lispro 75/25 with 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.<sup>11 13 64 67</sup> All four studies were randomized crossover trials and compared insulin lispro 75/25 with NPH/regular 70/30 except the study by Roach et al.<sup>11</sup> 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. As the fasting blood glucose levels are likely to be affected by dinner-time insulin, this study was included in this subsection. All studies found a decrease in fasting blood glucose with insulin lispro 75/25 but the decrease was not statistically significant. One study<sup>13</sup> did not report numerical values of the fasting blood glucose 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 lowering fasting blood glucose (weighted mean difference = 0.12 mg/dL; 95% CI: -6.05 to 6.29 mg/dL;  $p = 0.97$ ; see Figure 21).

Three studies reported pre-dinner blood glucose levels.<sup>13 64 67</sup> Of the three studies, one study<sup>64</sup> found insulin lispro 75/25 better 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 blood glucose between the two treatments during inpatient monitoring of the patients<sup>13</sup> and the second study reported pre-dinner blood glucose in a figure with a large overlap between the standard error of mean error bars.<sup>67</sup>

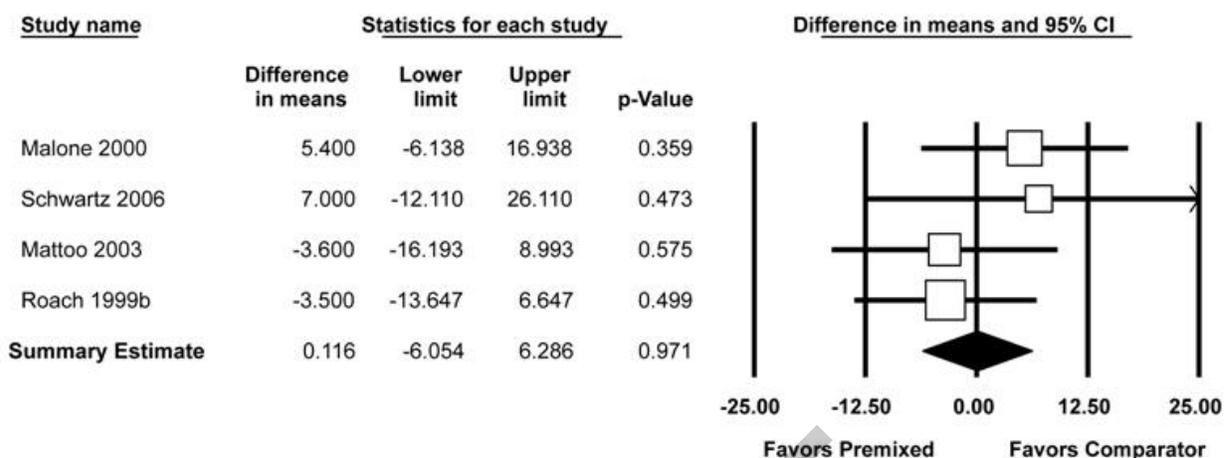
Postprandial glucose (see Appendix E, Evidence Table 4). Four studies reported treatment-related changes in dinner postprandial blood glucose levels.<sup>11 13 64 67</sup> As noted above, we used data from Roach et al.<sup>11</sup> for only dinner postprandial values. Insulin lispro 75/25 lowered dinner postprandial blood glucose in all studies but the decrease was statistically significant in two of the four studies.<sup>64 67</sup> When we pooled the study results, insulin lispro 75/25 was better than the premixed human insulin in lowering dinner postprandial blood glucose (weighted mean difference = -17.8 mg/dL; 95% CI: -27.0 to -8.6 mg/dL;  $p < 0.001$ ; see Figure 22). When we excluded the study by Roach et al.,<sup>11</sup> the pooled result remained significant (weighted mean difference = -18.9 mg/dL; 95% CI: -28.7 to -9.2 mg/dL;  $p < 0.001$ ; see Figure 22).

Breakfast postprandial blood glucose levels were reported by eight studies.<sup>13 41 55 56 61 64 65 67</sup> As noted above, in four of these studies, one dose of the study drugs was given with a test meal.<sup>41 55 56 61</sup> All studies found insulin lispro 75/25 better than the premixed human insulin in lowering breakfast postprandial blood glucose levels, but the difference was statistically significant in only three of the eight studies.<sup>61 65 67</sup> In the pooled analysis, insulin lispro was more effective than premixed human insulin in lowering breakfast postprandial blood glucose levels (weighted mean difference = -14.9 mg/dL; 95% CI: -21.4 to -8.4 mg/dL;  $p < 0.001$ ).

HgbA1c (see Appendix E, Evidence Table 4). Two of nine studies reported changes in HgbA1c levels.<sup>11 67</sup> Roach et al.<sup>67</sup> did not find any significant difference between insulin lispro 75/25 and the premixed human insulin in decreasing HgbA1c levels after 6 months of followup (mean difference = 0.2%;  $p = 0.41$ ). Similar results were reported in the second study by Roach et al.<sup>11</sup> 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 lowering HgbA1c levels (mean difference = 0.07%;  $p = 0.37$ ).

Hypoglycemia (see Appendix E, Evidence Table 5). Schwartz et al.<sup>56</sup> 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.<sup>67</sup> did not find a difference in the incidence of all hypoglycemia between insulin lispro 75/25 and a premixed human insulin (42% versus 35% respectively;  $p = 0.4$ ). Similarly, Herz et al.<sup>13</sup> and Mattoo et al.<sup>64</sup> also reported a similar hypoglycemia rate with the two

**Figure 21. Meta-analyses of post-treatment difference in fasting glucose between insulin lispro 75/25 and premixed human insulin**

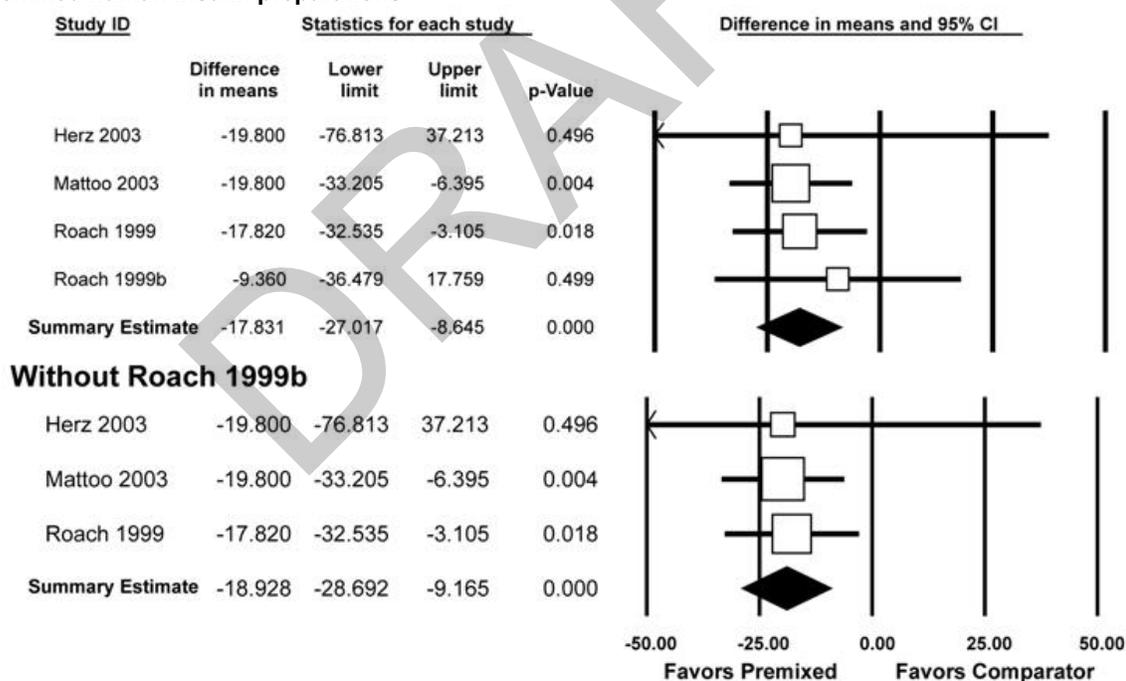


Boxes indicate individual study point estimates. Box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represent 95% confidence intervals for each study. The diamond at the bottom of the graph indicates 95% confidence interval for the random-effects pooled estimate.

Test for heterogeneity:  $Q = 2.126$  with 3 degrees of freedom ( $p = 0.547$ )

I-squared statistic = 0%

**Figure 22. Meta-analyses of post-treatment difference in postprandial glucose between insulin lispro 75/25 and premixed human insulin preparations**



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% confidence intervals for each study. The diamond at the bottom of the graph indicates 95% 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%

treatment regimens ( $p = 0.59$  and  $0.72$  respectively). Hermansen et al.<sup>55</sup> reported fewer hypoglycemic events with a premixed human insulin than with insulin lispro 75/25 (11 versus 19 events respectively) although they did not report whether the difference was significant. Malone

et al.<sup>41</sup> reported that the distribution of hypoglycemic episodes was similar between the two premixed insulin preparations. Coscelli et al.<sup>61</sup> 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). As all 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.,<sup>56</sup> one patient (5%) in the insulin lispro 75/25 arm and no patients 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 for 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 with 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 with noninsulin antidiabetic agents.<sup>40 62 66</sup> Tirgoviste et al.<sup>40</sup> compared insulin lispro 75/25 with a fixed-dose of glibenclamide. Malone et al.<sup>62</sup> compared a combination of insulin lispro 75/25 and metformin with a combination of glibenclamide and metformin. Herz et al.<sup>66</sup> compared insulin lispro 75/25 with a fixed dose of glyburide. All trials were 16 weeks in duration and reported on all intermediate outcomes. Insulin lispro dose was titrated to optimize glucose control. Oral antidiabetic agents' doses were adjusted to optimize glucose control in only one study.<sup>62</sup>

Fasting glucose (see Appendix E, Evidence Table 4). For fasting blood glucose, all three trials individually found insulin lispro 75/25 more effective than noninsulin antidiabetic agents in lowering fasting blood glucose but this difference was not significant in one study.<sup>62</sup> Pooling the results of all three studies found insulin lispro 75/25 more effective than noninsulin antidiabetic agents in lowering fasting blood glucose levels (weighted mean difference = -31.4 mg/dL; 95% CI: -45.7 to -17.1 mg/dL;  $p < 0.001$ ; see Figure 23).

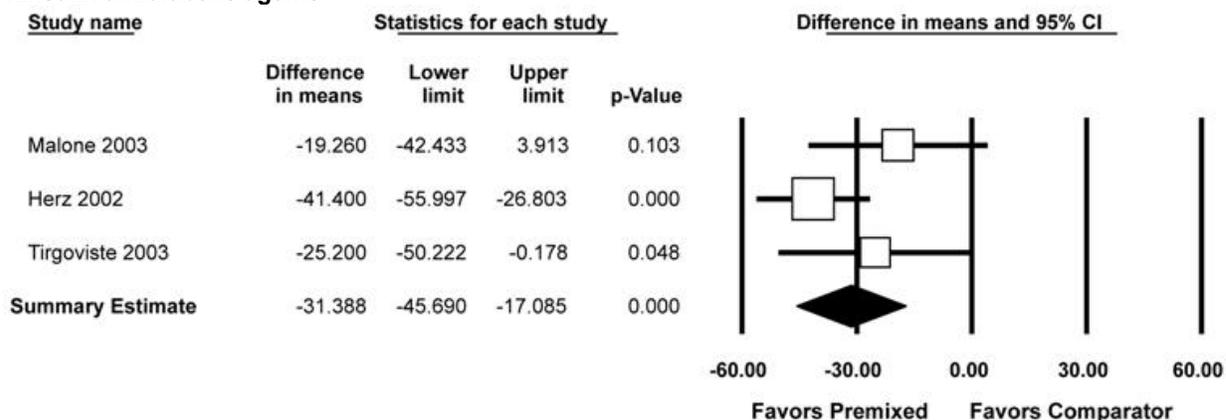
Insulin lispro 75/25 was also significantly more effective in reducing pre-dinner blood glucose levels in all three studies. When the results of these studies were pooled, insulin lispro 75/25 remained more effective than noninsulin antidiabetic agents in lowering pre-dinner blood glucose levels (weighted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

Postprandial glucose (see Appendix E, Evidence Table 4). For postprandial blood glucose levels, insulin lispro 75/25 was better than oral diabetic 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 blood glucose levels after dinner (weighted mean difference = -47.3 mg/dL; 95% CI: -63.5 to -31.0 mg/dL;  $p < 0.001$ ; see Figure 24) and after breakfast (weighted mean difference = -54.2 mg/dL; 95% CI: -70.7 to -37.7 mg/dL;  $p < 0.001$ ).

HgbA1c (see Appendix E, Evidence Table 4). In two trials,<sup>40 66</sup> insulin lispro 75/25 was better than noninsulin antidiabetic agents in lowering HgbA1c while the difference was not statistically significant in the third trial.<sup>62</sup> Pooling the study results found that insulin lispro 75/25 was not significantly better than oral antidiabetic agents in lowering HgbA1c levels (weighted mean difference = -0.42%; 95% CI: -1.00 to 0.16%;  $p = 0.15$ ; see Figure 25).

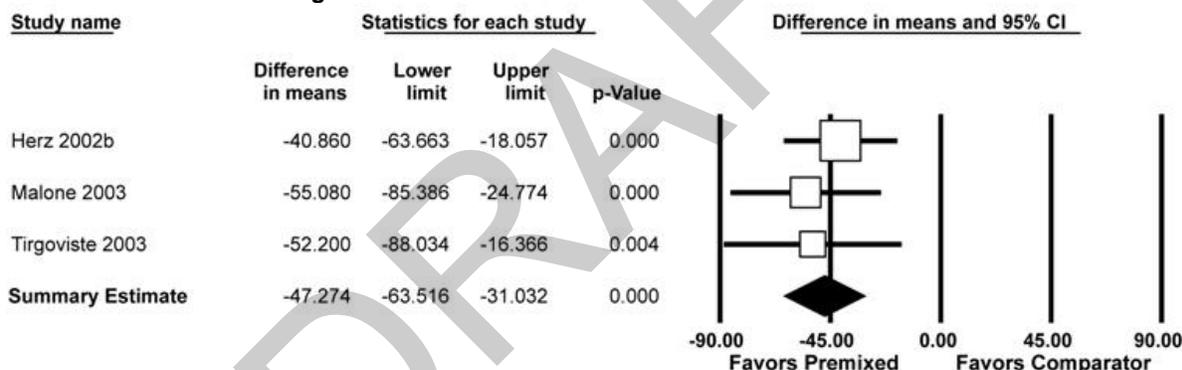
Hypoglycemia (see Appendix E, Evidence Table 5). In the study by Tirgoviste et al.,<sup>40</sup> the incidence of hypoglycemia was higher in patients treated with insulin lispro 75/25 as compared to those treated with glibenclamide (44.7% versus 10.3%;  $p = 0.001$ ). Similar results were reported by Herz et al.<sup>66</sup> who found a lower rate of hypoglycemia in patients treated with

**Figure 23. Meta-analyses of post-treatment difference in fasting glucose between insulin lispro 75/25 and noninsulin antidiabetic agents**



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% confidence intervals for each study. The diamond at the bottom of the graph indicates 95% 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%

**Figure 24. Meta-analyses of post-treatment difference in postprandial glucose between insulin lispro 75/25 and noninsulin antidiabetic agents**



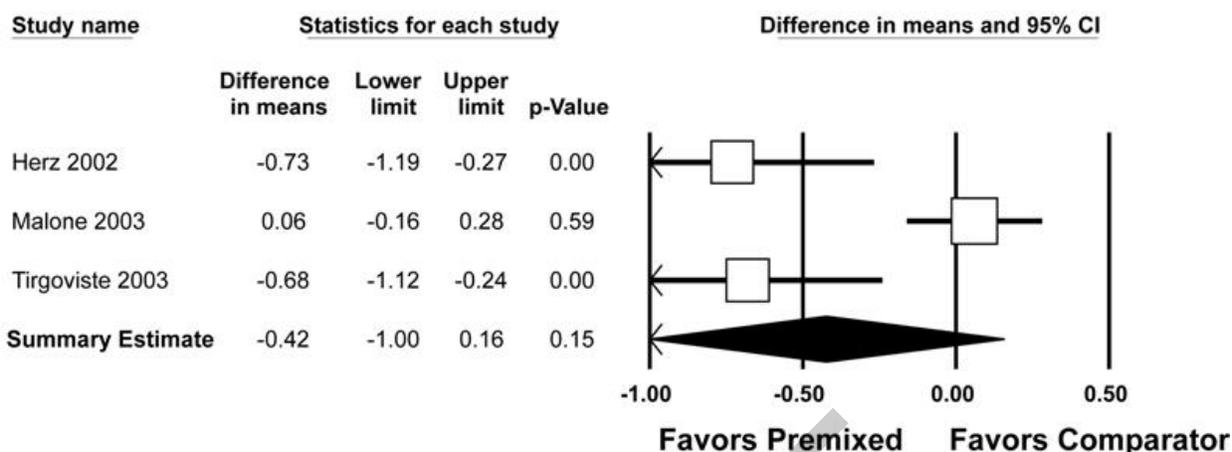
Boxes indicate individual study point estimates. Box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represent 95% confidence intervals for each study. The diamond at the bottom of the graph indicates 95% confidence interval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

glibenclamide. In contrast, Malone et al.<sup>62</sup> found a higher rate of overall hypoglycemia although the difference did not reach statistical significance ( $p = 0.07$ ). Pooling the results of these three studies found no difference in the overall hypoglycemia rate measured as episodes per patient per 30 days (rate ratio = 4.86; 95% CI: 0.48 to 49.52;  $p = 0.18$ ; see Figure 26).

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.<sup>40 66</sup> When the results of these studies were pooled together, insulin lispro 75/25 was associated with a larger weight increase than oral antidiabetic agents (weighted mean difference = 1.88 kg; 95% CI: 1.35 to 2.41 kg;  $p < 0.001$ ; see Figure 27).

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 for withdrawals due to adverse events and other

**Figure 25. Meta-analyses of post-treatment difference in hemoglobin A1c between insulin lispro 75/25 and noninsulin antidiabetic agents**

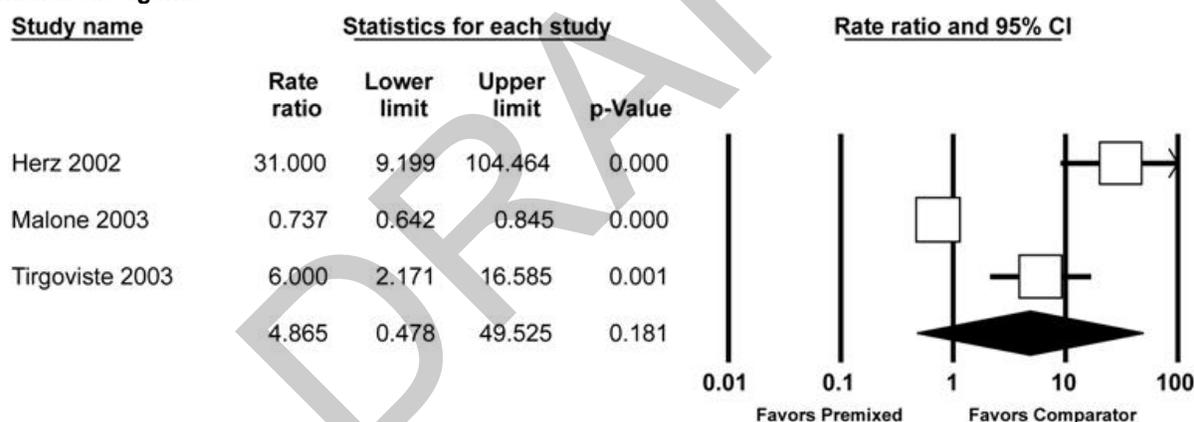


Boxes indicate individual study point estimates. Box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents 95% confidence intervals for each study. The diamond at the bottom of the graph indicates 95% confidence 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%

**Figure 26. Meta-analyses of incidence of mild hypoglycemia between insulin lispro 75/25 and noninsulin antidiabetic agents**



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 represents 95% confidence intervals for each study. The diamond at the bottom of the graph indicates 95% confidence interval for the random-effects pooled estimate.

Test for heterogeneity:  $Q = 51.295$  with 2 degrees of freedom ( $p < 0.001$ )

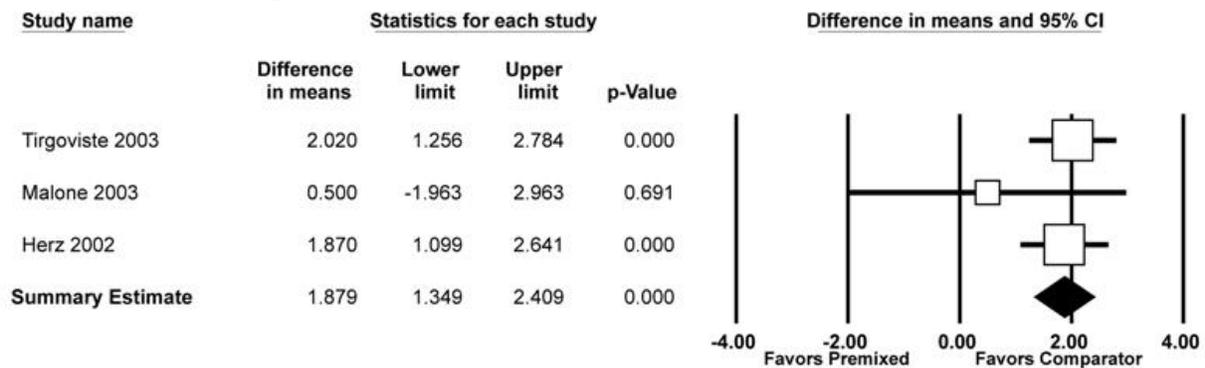
I-squared statistic = 96%

serious adverse events.

**Insulin lispro 75/25 versus other premixed insulin analogues.** We identified four randomized crossover studies: two comparing insulin lispro 75/25 with insulin aspart 70/30,<sup>52 55</sup> one with insulin lispro 50/50,<sup>56</sup> and one with a combination of morning insulin lispro 50/50 and dinner insulin lispro 75/25.<sup>63</sup>

Details of the comparison in two studies have been reviewed above in the insulin aspart 70/30 section.<sup>52 55</sup> In the third study, Schwartz et al.<sup>56</sup> 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.<sup>63</sup> compared a regimen of insulin lispro 50/50 before breakfast plus insulin lispro 75/25 before dinner with twice-daily insulin lispro

**Figure 27. Meta-analyses of post-treatment difference in weight change between insulin lispro 75/25 and noninsulin antidiabetic agents**



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 represents 95% confidence intervals for each study. The diamond at the bottom of the graph indicates 95% 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%

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 blood glucose levels were reported in one study only,<sup>52</sup> 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<sup>56</sup> and therefore fasting blood glucose levels from this study were not available. In the third study,<sup>63</sup> insulin lispro 75/25 was given at dinner to both arms and thus fasting blood glucose levels were likely to reflect insulin lispro 75/25 in both arms.

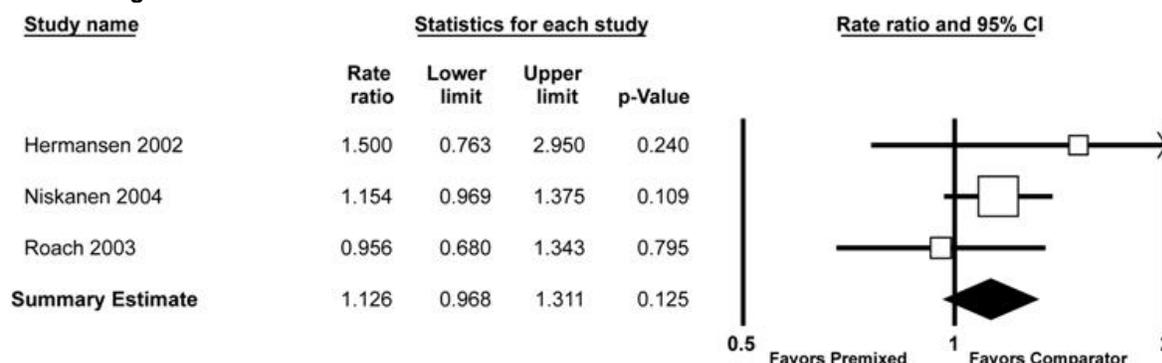
Postprandial glucose (see Appendix E, Evidence Table 4). For postprandial blood glucose, comparison between insulin aspart 70/30 and insulin lispro 75/25 did not find a significant advantage of one premixed insulin analogue in lowering dinner or breakfast postprandial blood glucose levels.<sup>52</sup> In the second study,<sup>56</sup> insulin lispro 50/50 was more effective in lowering postprandial blood glucose levels after a test-meal than insulin lispro 75/25 ( $p < 0.05$ ). In the third study,<sup>63</sup> insulin lispro 75/25 was inferior to insulin lispro 50/50 in lowering postprandial blood glucose levels after breakfast ( $p = 0.001$ ). Dinner postprandial blood glucose levels were not compared in the third study as both treatment arms received the same insulin formulation. The fourth study did not report postprandial blood glucose levels after 2 hours or 90 minutes of the test-meal.<sup>55</sup>

HgbA1c (see Appendix E, Evidence Table 4). Only one study reported changes in HgbA1c levels and did not find a significant difference between insulin lispro 75/25 and insulin aspart 70/30 in lowering HgbA1c levels (mean difference =  $0.14\%$ ,  $p = 0.08$ ).<sup>63</sup>

Hypoglycemia (see Appendix E, Evidence Table 5). In one study,<sup>56</sup> it was not possible to discern which insulin preparation was responsible for hypoglycemic events. In the other three studies, the overall hypoglycemia event rate was not different.<sup>52 55 63</sup> 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% CI:  $0.97$  to  $1.31$ ;  $p = 0.12$ ; see Figure 28).

Weight change (see Appendix E, Evidence Table 6). As all trials were crossover, we did not abstract weight change data.

**Figure 28. Meta-analyses of incidence of mild hypoglycemia between insulin lispro 75/25 and other premixed insulin analogues**



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 represents 95% confidence intervals for each study. The diamond at the bottom of the graph indicates 95% 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%

Other serious adverse events (see Appendix E, Evidence Table 6). Schwartz et al.<sup>56</sup> 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 for 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 two randomized trials<sup>58 69</sup> that compared insulin lispro 50/50 with a long-acting insulin analogue, insulin glargine in both studies. The study by Jacober et al.<sup>58</sup> compared a regimen of insulin lispro 50/50 before breakfast and lunch and insulin lispro 75/25 before dinner with an once-daily insulin glargine injection over a 16-week period while the study by Kazda et al.<sup>69</sup> was a parallel-arm trial which compared insulin lispro 50/50 with insulin glargine over a followup of 24 weeks. As noted in an earlier section, the insulin dose was higher in the premixed insulin analogue arm than in the insulin glargine arm ( $p = 0.01$ ).<sup>58</sup> Insulin glargine was also given at a lower mean daily dose in the study by Kazda et al.<sup>69</sup> (0.43 units/kg versus 0.59 units/kg;  $p < 0.005$ ).

Fasting glucose (see Appendix E, Evidence Table 4). Fasting blood glucose was reported by one study<sup>69</sup> which found insulin glargine more effective than insulin lispro 50/50 in lowering fasting blood glucose (mean difference = -1.7 mg/dL;  $p < 0.001$ ). Pre-dinner blood glucose levels were reported by both trials. Jacober et al.<sup>58</sup> found insulin lispro 50/50 more effective than insulin glargine in lowering pre-dinner blood glucose levels (-15.9 mg/dL;  $p = 0.02$ ) while Kazda et al.<sup>69</sup> did not find any difference between the two treatments ( $p > 0.05$ ).

Postprandial glucose (see Appendix E, Evidence Table 4). Postprandial blood glucose was reported by both trials.<sup>58 69</sup> Jacober et al.<sup>58</sup> found a significant decrease in postprandial glucose levels after breakfast ( $p < 0.003$ ) with insulin lispro 50/50 as compared to insulin glargine. Similarly, Kazda et al.<sup>69</sup> found insulin lispro 50/50 more effective in lowering postprandial blood glucose levels than insulin glargine after dinner but not after breakfast ( $p$ -value not reported).

HgbA1c (see Appendix E, Evidence Table 4). Changes in HgbA1c in response to treatment were reported in both studies.<sup>58 69</sup> Jacober et al. found a greater decrease in HgbA1c with insulin lispro 50/50 with breakfast and lunch and insulin lispro 75/25 with dinner as compared to insulin

glargine (mean difference = -0.26%;  $p = 0.007$ ). However, this result reflects the 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.,<sup>69</sup> three-times daily insulin lispro 50/50 was more effective in lowering HgbA1c than once-daily insulin glargine (-0.9%;  $p < 0.001$ ).

Hypoglycemia (see Appendix E, Evidence Table 5). Insulin glargine was associated with a lower risk of hypoglycemia in both studies.<sup>58,69</sup> Jacober et al.<sup>58</sup> reported that a significantly larger number of patients had at least one episode of hypoglycemia with premixed insulin analogues as compared with insulin glargine (48 versus 33;  $p = 0.01$ ). In Kazda et al.,<sup>69</sup> 44.4% of patients treated with insulin lispro 50/50 had at least one episode of hypoglycemia as compared to 32.1% of patients treated with insulin glargine ( $p$ -value not reported).

Weight change (see Appendix E, Evidence Table 6). Kazda et al.<sup>69</sup> reported a larger increase in BMI with insulin lispro 50/50 as compared to insulin glargine, although this difference did not reach statistical significance (mean difference =  $0.4 \text{ kg/m}^2$ ;  $p = 0.19$ ).

Other serious adverse events (see Appendix E, Evidence Table 6). Neither of these two studies reported on injection site reactions. Table 7 shows the range of risk differences between insulin lispro 50/50 and long-acting insulin analogues for 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 with rapid-acting prandial insulin lispro.<sup>69</sup> In this study, Kazda et al. compared insulin lispro 50/50 three-times daily before meals with rapid-acting insulin lispro three times before meals over a period of 24 weeks. The insulin dose was allowed to be titrated to have optimal glucose control. At the end of the study, mean daily insulin dose was lower in the rapid-acting insulin lispro group than in the insulin lispro 50/50 group (0.50 units/kg 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 lowering fasting blood glucose (mean difference =  $0 \text{ mg/dL}$ ;  $p > 0.05$ ) or postprandial blood glucose (mean difference =  $3.6 \text{ mg/dL}$ ;  $p > 0.05$ ). Similarly, there was no difference between insulin lispro 50/50 and rapid-acting insulin lispro in lowering HgbA1c levels (mean difference =  $-0.1\%$ ;  $p = 0.57$ ).

Adverse events (see Appendix E, Evidence Tables 5 and 6). Incidence of hypoglycemia was greater with rapid-acting insulin lispro as compared to insulin lispro 50/50 (53.8% versus 44.4%;  $p$ -value not reported). Similarly, there was a larger increase in BMI with rapid-acting than with premixed insulin lispro (mean difference =  $0.3 \text{ kg/m}^2$ ;  $p = 0.048$ ). 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 for withdrawals due to adverse events.

**Insulin lispro 50/50 versus a combination of long-acting and rapid-acting insulin analogues.** Our search did not find any study that looked at this comparison.

**Insulin lispro 50/50 versus premixed human insulin.** We identified three randomized crossover studies<sup>11,56,70</sup> and one parallel-arm study<sup>71</sup> that compared insulin lispro 50/50 with premixed human insulin preparations. In the first crossover study,<sup>56</sup> only one fixed dose of the study medication was given with a test meal and blood glucose levels were measured. In the second study,<sup>11</sup> 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 noted in the preceding sections.

Schernthaner et al.<sup>70</sup> compared three-times daily insulin lispro 50/50 before each meal with twice-daily NPH/regular 70/30 in type 2 diabetic patients who were previously treated with other insulin preparations. The insulin dose was adjusted throughout the study to optimize glucose

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

Comparison	Total serious adverse events		Withdrawn due to adverse events		Other serious adverse events	
	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	0	NA	2 <sup>58 69</sup>	0	0	NA
Rapid-acting insulin analogues	0	NA	1 <sup>69</sup>	0	0	NA
Rapid-acting with long-acting insulin analogues	0	NA	0	NA	0	NA
Premixed human insulins	1 <sup>56</sup>	0	4 <sup>11 56 70 71</sup>	0	1 <sup>70</sup>	-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 risk in the treatment group minus the risk 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

control. There was no difference in the total daily dose at the end of the study between the two treatments.

Yamada et al.<sup>71</sup> compared twice-daily insulin lispro 50/50 with twice-daily premixed human insulin preparations. Insulin dose was adjusted during the study 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 blood glucose levels. In one trial, there was no difference between insulin lispro 50/50 and a premixed human insulin in lowering fasting blood glucose.<sup>71</sup> In the second trial,<sup>70</sup> the premixed human insulin was more effective than insulin lispro 50/50 in lowering fasting blood glucose ( $p < 0.001$ ).

Changes in pre-dinner blood glucose levels were evaluated in two studies.<sup>11 70</sup> Roach et al.<sup>11</sup> found insulin lispro 50/50 less effective in lowering pre-dinner blood glucose levels than premixed human insulin 50/50 (mean difference = 4.32 mg/dL;  $p = 0.01$ ). On the other hand, Scherthner et al.<sup>70</sup> found insulin lispro 50/50 more effective than NPH/regular 70/30 in lowering pre-dinner blood 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 blood glucose levels were reported by two and three studies respectively. Insulin lispro 50/50 was better than premixed human insulin in lowering dinner postprandial blood glucose in one of the two studies<sup>70</sup> and in lowering breakfast postprandial glucose levels in two of the three studies.<sup>11 56</sup> In a pooled analysis, insulin lispro 50/50 was more effective in lowering breakfast postprandial blood glucose levels (weighted mean difference = -30.3 mg/dL; 95% CI: -55.6 to -5.0 mg/dL;  $p = 0.02$ ).

HgbA1c (see Appendix E, Evidence Table 4). Two<sup>70 71</sup> of the four trials reported treatment-related changes in HgbA1c. Scherthner et al.<sup>70</sup> found that although HgbA1c decreased from baseline in both treatment arms, the decrease was significantly greater with insulin lispro 50/50 as compared to NPH/regular 70/30 (mean difference = -0.5%;  $p = 0.01$ ). Similarly, Yamada<sup>71</sup> also found insulin lispro 50/50 more effective than the premixed human insulin preparations in lowering HgbA1c (mean difference = -0.31%;  $p < 0.05$ ).

Hypoglycemia (see Appendix E, Evidence Table 5). In one study,<sup>56</sup> the insulin preparation which was responsible for 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 the incidence or rate of hypoglycemia.<sup>11 70 71</sup>

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

Other serious adverse events (see Appendix E, Evidence Table 6). One study reported one (4%) injection site reaction in the insulin lispro 50/50 arm and no reactions in the premixed human insulin arm.<sup>56</sup> Table 6 shows the range of risk differences between insulin lispro 50/50 and premixed human insulins for 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 performed this comparison.

**Insulin lispro 50/50 versus other premixed insulin analogues.** We found one study comparing insulin lispro 50/50 with insulin lispro 75/25<sup>56</sup> and another study comparing a

regimen of insulin lispro 50/50 in the morning and insulin lispro 75/25 in the evening with twice-daily insulin lispro 75/25.<sup>63</sup> 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 blood glucose levels or pre-dinner blood glucose levels after treatment with insulin lispro 50/50. Both studies reported postprandial blood glucose levels after breakfast and found insulin lispro 50/50 more effective than insulin lispro 75/25 in lowering blood glucose levels ( $p < 0.05$  in both studies). Although HgbA1c was reported in one crossover study,<sup>63</sup> the duration of followup was only 8 weeks in each study period without a 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.<sup>63</sup> 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% versus 26.1%;  $p = 0.08$ ).

## Study Quality Assessment

The overall quality of included studies was fair to good (see Appendix E, Evidence Table 7). All trials except one<sup>49</sup> were RCTs. Randomization methods were described in 14 studies<sup>28 36 40 42 44-48 52 54 55 59 71</sup> and were adequate in all these studies except one.<sup>44</sup> The remaining RCTs did not describe randomization methods in sufficient detail.

Only seven trials used blinding of the treatment at some stage of the trial. Five trials used blinding for patients and providers,<sup>14 41 45 56 63</sup> while the remaining two trials used blinding for outcome assessors.<sup>28 42</sup> 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, outcome assessment is unlikely to be biased by the lack of blinding. However, the assessment of other outcomes could be biased. Several studies asked patients to maintain a diary of their blood glucose levels. This self-monitoring of blood glucose may have affected an 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 HgbA1c levels.<sup>54 63</sup> Four studies had complete followup with no study participant lost during followup,<sup>11 40 49 62</sup> while five studies lost more than 10% of the enrolled participants during followup.<sup>13 51 57 58 68</sup> In all the remaining studies, the percentage of patients who were lost to followup was less than 10%. Of the studies in which some patients withdrew, five studies<sup>13 50 61 64 68</sup> 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 all trials except one which was funded jointly by the NIH and Eli Lilly.<sup>68</sup> Five trials did not report their source of funding.<sup>40 41 59 60 65</sup> A statement on the conflicts of interest by authors was not reported by 19 studies.<sup>11 13 16 40 41 43 48 52 54 55 58 59 61-65 68 70</sup>

Study conclusions were reflective of the study results in most studies except five studies in which conclusions were partially supported by the results.<sup>14 49 50 58 66</sup>

## Applicability Assessment

All identified studies were efficacy trials and not effectiveness trials, thus limiting their generalization to the U.S. diabetic population and current clinical practice (see Appendix E, Evidence Table 8). Participants were recruited from outpatient clinics in three trials,<sup>44 46 54</sup> from subspecialty clinics in three additional trials,<sup>56 61 66</sup> from both outpatient and subspecialty clinics in one trial,<sup>49</sup> and from clinical centers without specifying further details in one trial.<sup>28</sup> The remaining trials did not mention the population source from which participants were enrolled. The ratio of enrolled patients to the screened population was not reported in 20 studies;<sup>11-14 36 40 41 44 47 53 54 57 60 61 63-65 67 70 71</sup> in all other studies, this ratio was more than 50%. In three trials, more than 10% of the participants were excluded during the lead-in period.<sup>36 43 60</sup>

Most studies enrolled patients that were similar in age to the general US diabetic population except five studies.<sup>44 45 56 66 70</sup> Women were underrepresented in five trials<sup>43 49 54 56 71</sup> and in one trial there were more women than men.<sup>36</sup> One study did not report on the sex ratio.<sup>68</sup> In two trials, the proportion of enrolled racial and ethnic groups was reflective of the general population in the U.S.<sup>16 36</sup> Twenty trials did not report on the race/ethnicity admixture of the enrolled population<sup>11-13 40-42 45-47 51-53 55 59 60 64-67 70</sup> and the remaining trials did not have the racial and ethnicity admixture reflective of the U.S. population.

In most trials, the spectrum of diabetic complications and comorbidities in 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 the generalization of results to these subpopulations.

The dose of insulin, route of administration, and schedule of administration was reflective of clinical practice or was easy to replicate in clinical practice in all trials except in one<sup>64</sup> 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.<sup>13 14 16 40 41 50 65</sup> In one trial,<sup>40</sup> adjustments to insulin dose were made every few days and patients had frequent visits during the study period. In another study, investigators telephoned patients at least once weekly,<sup>13</sup> while in three studies monitoring of blood glucose was too frequent to be implemented in clinical practice.<sup>14 16 50</sup> In two studies, patients were hospitalized or closely monitored throughout the duration of the study, which cannot be applied in clinical practice.<sup>41 65</sup> Premixed insulin analogues were compared with adequate dosing and schedule of medicines in all but four studies.<sup>40 46 54 66</sup> In these studies, the dose of the comparator was held constant while the premixed insulin dose was increased based on blood glucose levels.

Overall applicability of the studies to the diabetic population of the U.S. for fasting glucose outcomes was fair. In most studies, self-monitoring of fasting blood glucose was reported, and this reflects 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 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. for postprandial blood glucose was also graded as fair. As for fasting blood glucose, most studies used self-monitoring of blood glucose by patients, which is reflective of clinical practice. Four one-dose

studies<sup>41 53 55 56</sup> were not reflective of clinical practice and as insulin preparations had not achieved steady state in plasma, it is possible that the results from these trials may not be reproducible in practice. The calculation of 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 HgbA1c was graded as fair and is limited due to the aforementioned reasons for fasting and postprandial glucose.

The overall applicability of the studies to the diabetic population of U.S. for the adverse event of hypoglycemia was fair. As 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, monitoring of the patient population was not feasible as compared to usual clinical practice.

The overall applicability of the studies to the U.S. diabetic population for the adverse outcome of weight gain was graded as fair. Most studies were of relatively shorter duration except two studies,<sup>28 42</sup> which followed patients for 1 year and 2 years respectively. As weight gain is a relatively slower process, it is difficult to draw conclusions from the short-term studies. In addition, many studies with premixed insulin lispro preparations were crossover studies which were excluded from the analysis for weight gain thus limiting the amount of evidence available from which conclusions need to be drawn.

## Clinical Outcomes

### Key Messages

- No statistically significant differences in all-cause mortality, cardiovascular mortality, and cardiovascular morbidity between premixed insulin analogues and other diabetes medications were reported in these mainly short duration RCTs.
- Low absolute events in short duration trials where clinical events were not the primary outcomes made it difficult to draw any firm conclusions regarding any of the clinical outcomes.
- A one-year RCT reported a statistically significant greater increase in plasma creatinine by 0.02 mg/dL in the premixed insulin analogue arm (insulin aspart 70/30) compared with the long-acting insulin analogue arm (insulin detemir); however, the clinical relevance of this mild change is unclear.
- 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 even did not 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 morbidity 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 mortality 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.
- The quantity, quality, and consistency of the evidence was graded as insufficient for all other clinical outcomes.

## Study Characteristics

Out of 39 included studies, only 13 studies reported on a clinical outcome.<sup>28 42 46-48 51 52 54 55 59</sup> Eight studies reported on all-cause mortality,<sup>60 62 70 28 42 46 48 52 60 62 70</sup> four reported on cardiovascular mortality,<sup>28 42 48 60 42 46 47 51 54 55 59</sup> seven reported on cardiovascular morbidity,<sup>42 46 47 51 54 55 59</sup> and one reported on nephropathy.<sup>28</sup> All the studies except one<sup>42</sup> were short duration RCTs lasting less than or equal to one year where the clinical outcome (such as mortality) was not the primary outcome (see Appendix E, Evidence Table 2). Most studies (n = 8) were parallel-arm RCTs,<sup>28 42 46-48 51 54 62</sup> and the remaining were crossover RCTs. Most parallel-arm RCTs were moderately-sized (range in number of subjects from 255 to 708),<sup>28 46-48 51 62</sup> except for two smaller studies (number of subjects from 49 to 125).<sup>42 54</sup> The crossover studies were mainly small-size (range in number of subjects from 35 to 133).<sup>52 55 59 60 70</sup> Most studies were multicenter trials occurring in multiple countries,<sup>42 46-48 51 52 62</sup> while the remaining studies occurred in one or two countries in Europe,<sup>28 55 60</sup> the United States,<sup>59</sup> the Middle East,<sup>54</sup> or did not report on geographic location.<sup>70</sup> Most studies (n = 7) excluded subjects with significant comorbidity such as a history of cardiovascular disease or complications from type 2 diabetes,<sup>28 48 51 52 54 55 70</sup> and most studies (n = 11) excluded moderate to severely obese subjects with BMI greater than 35 or 40 kg/m<sup>2</sup>.<sup>28 42 46 47 51 52 54 55 59 62 70</sup>

Subjects were mainly middle-aged to older, overweight to mildly obese adults with moderate glycemia (range in mean HgbA1c from 8.1 to 10.3 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 were not as diverse in racial mix. Of the three studies reporting race, all reported greater than 80% Caucasian subjects.<sup>28 54 62</sup> Six studies<sup>42 46 52 55 60 70</sup> included insulin-treated patients and the remaining seven studies included insulin-naïve patients.<sup>28 42 52 55 59 60 70</sup>

## Reporting of Clinical Outcomes

Death from any cause and cardiovascular death were 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 deaths occurred, then we recorded that as 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 no events.

## 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. Eight RCTs of shorter duration reported few absolute deaths from any cause (n = 8 studies) in each study arm, with a range of 0 to 3 deaths for the premixed insulin analogues versus 0 to 2 deaths for the other diabetes agents (less than 5 percent for each arm; see Table 8 and Appendix E, Evidence Table 9).<sup>28 42 46 48 52 60 62 70</sup> Four RCTs reported 1 to 2 cardiovascular deaths in the premixed insulin analogue arms and no cardiovascular deaths in the other arms (see Table 9).<sup>28 42 48 60</sup> 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.<sup>42</sup> 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, then 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, then 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 with long-acting insulin analogues, reporting similar percentage of death in each arm (less than 1% versus 0% and 2% versus 2%).<sup>28</sup>  
<sup>60</sup> One of these studies also compared a premixed insulin analogue with a rapid-acting insulin

analogue, and showed similar deaths and cardiovascular deaths in both groups (1% versus less than 1% respectively for both outcomes).<sup>28</sup> 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).<sup>28</sup> That study reported similar percent events among the groups (0.6% in the premixed insulin analogue arm versus 0% 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 ischemic heart disease case, and one fatal congestive heart failure case in the insulin aspart 70/30 twice-daily arm; one fatal myocardial infarction in the insulin aspart three-times daily arm; and no deaths in the long-acting insulin detemir arm. The insulin detemir arm had no deaths despite having a slightly higher HgbA1c than the other two insulin analogue arms, although the insulin analogue arms were associated with slightly greater weight gain over one year. The smaller 16-week crossover study comparing insulin lispro 75/25 plus metformin to glargine plus metformin also showed similar percent events in each arm (2% versus 2% or 1 death from any cause in each study arm).<sup>60</sup> The death in the premixed insulin analogue arm was from a myocardial infarction whereas the etiology of the death in the glargine arm was not described.

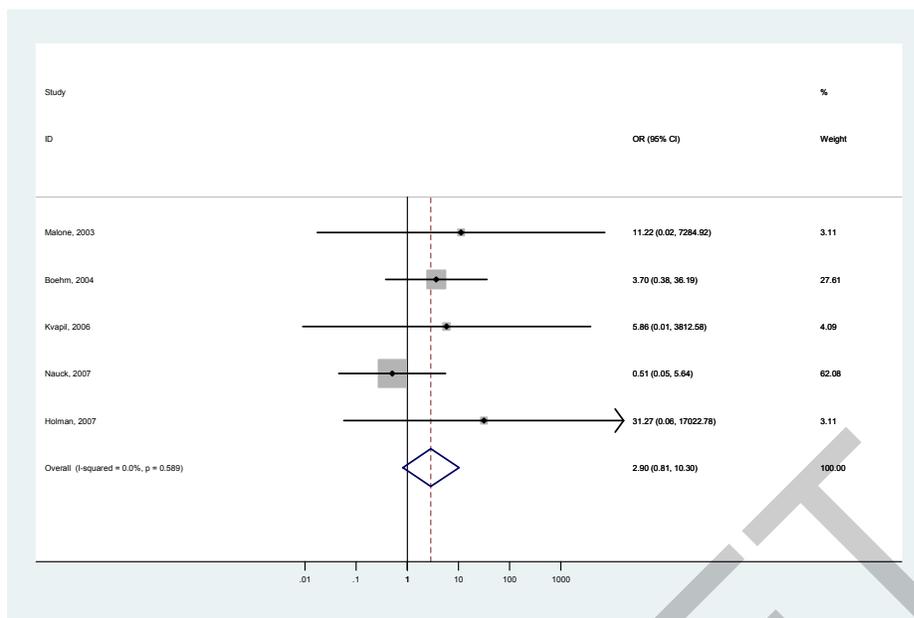
*Premixed insulin analogues versus premixed human insulin.* Two small RCTs (one parallel-arm and one crossover) compared a premixed insulin analogue with a premixed human insulin, and reported similar deaths from any cause in each arm (4 versus 1% and 0 versus 3%).<sup>42 70</sup> The longest 2-year multicenter, multinational RCT that specifically set out to evaluate safety (hypoglycemia and adverse events) was one of these two studies.<sup>42</sup> This study compared insulin aspart 70/30 with NPH/regular 70/30 in subjects previously on insulin regimens, and reported 3 deaths (4%) in the premixed insulin analogue arm versus 1 death (1%) in the premixed human insulin arm. Of these deaths, one was due to a myocardial infarction in the premixed insulin analogue arm compared with no cardiovascular causes of death in the premixed human insulin arm. The smaller 12-week crossover study compared insulin lispro 50/50 with NPH/regular 70/30 showing similarly low events in the two groups, 0 versus 1 death respectively.<sup>70</sup>

*Premixed insulin analogues versus noninsulin antidiabetic agents.* Two parallel arm moderate-size RCTs of short duration compared premixed insulin analogues with oral antidiabetic agents, reporting a small number of deaths in the premixed insulin analogue arms versus no deaths in the oral diabetes medication arms (less than 1% versus 0% for each study).<sup>48</sup> <sup>62</sup> 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).<sup>48</sup> The study reported one fatal myocardial infarction in the insulin aspart 70/30 plus fixed metformin arm compared with no deaths in the other two arms. The other 16-week RCT compared insulin lispro 75/25 plus metformin with glibenclamide plus metformin in subjects previously taking metformin or a sulfonylurea.<sup>62</sup> The study reported one death with no description of etiology in the premixed insulin analogue arm compared with no deaths in the oral diabetes medication 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 with addition of exenatide twice-daily. The total number of deaths in each group was not statistically different (1 (0.4%) versus 2 (0.8%) deaths respectively), yet did not describe the etiology of these deaths.<sup>46</sup>

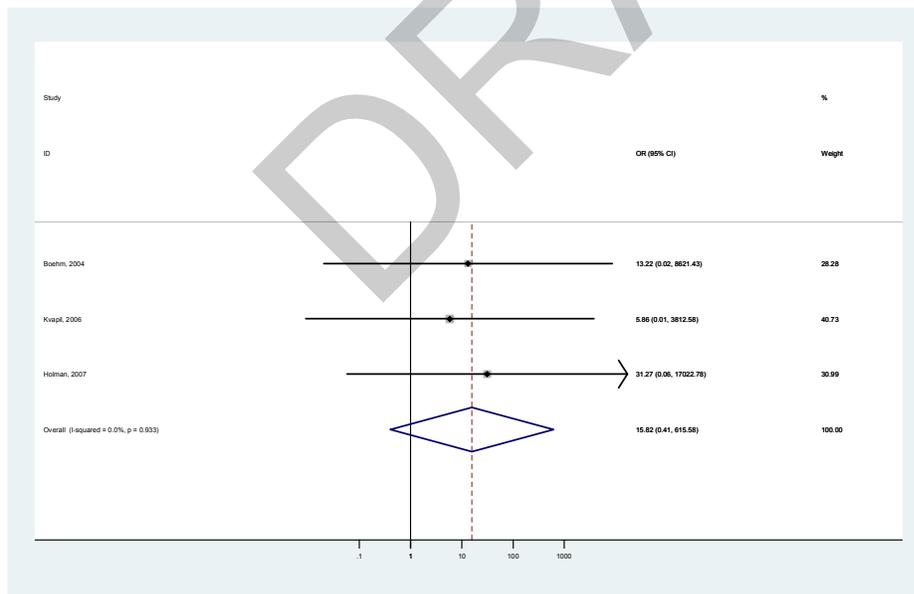
Quantitative assessment. We found no statistically significant differences in all-cause mortality between the premixed insulin analogue arms compared with any other active

**Figure 29. Pooled odds ratios of all-cause mortality comparing premixed insulin analogues with other diabetes medications**



Subscript: 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% confidence intervals for each study. The diamond at the bottom of the graph indicates 95% confidence interval for the random-effects pooled estimate. Test for heterogeneity:  $Q = 2.81$  with 4 degrees of freedom ( $p = 0.589$ )  
I-squared statistic = 0%

**Figure 30. Pooled odds ratios of cardiovascular mortality comparing premixed insulin analogues with other diabetes medications**



Subscript: 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% confidence intervals for each study. The diamond at the bottom of the graph indicates 95% confidence interval for the random-effects pooled estimate. Test for heterogeneity:  $Q = 0.14$  with 2 degrees of freedom ( $p = 0.933$ )  
I-squared statistic = 0%

comparator in the five parallel-arm RCTs (OR = 2.90; 95% CI: 0.81 to 10.30; p = 0.10; see Figure 29). The inclusion of the three crossover studies in the meta-analysis did not markedly influence these results (OR = 1.94; 95% CI: 0.68 to 5.53; p = 0.22). We also found no statistically significant differences in cardiovascular disease mortality between the premixed insulin analogue arms compared with any other active comparator (OR = 15.82; 95% CI: 0.41 to 615.58; p = 0.14; see Figure 30). The inclusion of the one crossover study in the meta-analysis did not markedly influence these results (OR = 14.55; 95% CI: 0.60 to 351.89; p = 0.10). No one study strongly influenced either of the mortality results. While point estimates and confidence intervals varied somewhat depending on the meta-analytic technique used, the overall direction of the point estimates and conclusions of no statistically significant difference did not change (see Appendix E, Evidence Table 10). While the pooled odds ratios suggest an increased risk of all-cause and cardiovascular disease mortality with use of premixed insulin analogues versus other diabetes drug comparators, the wide 95% CI confirms our qualitative assessment of no difference between groups and lack of reliability of the point estimate due to few absolute events in few studies. No statistically significant heterogeneity was found in these studies with I-squared statistics less than 50 percent for all analyses; therefore, no further analyses were done to evaluate sources of potential heterogeneity.

### Cardiovascular disease morbidity.

**Qualitative assessment.** Seven studies compared premixed insulin analogues with another diabetes medication, reporting cardiovascular morbidity between groups (see Table 10 and Appendix E, Evidence Table 9).<sup>42 46 47 51 54 55 59</sup> The articles compared premixed insulin analogues with premixed human insulin in two studies,<sup>42 55</sup> oral medications in two studies,<sup>51 54</sup> long-acting insulin in two studies,<sup>47 59</sup> or exenatide in one study.<sup>46</sup> The seven articles had a diverse set of cardiovascular morbidity outcomes, including non-fatal myocardial infarction,<sup>51 54 59</sup> transient ischemic attack,<sup>55</sup> peripheral vascular disease,<sup>47</sup> congestive heart failure,<sup>47 59</sup> chest pain,<sup>59</sup> and unspecified total cardiac adverse events.<sup>42 46</sup>

**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	2	330	Study 1: <1% Study 2: <1%	Study 1: 0% Study 2: 0%
Premixed insulin analogue vs exenatide	1	501	2%	4%

\*If a study had more than one arm with premixed insulin analogues, then 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 two-years of followup.<sup>42</sup> This and another one-year study had larger numbers of cardiac adverse events largely due to a more vague definition of unspecified cardiac disorders which could include less serious cardiac events such as palpitations.<sup>42 46</sup> Although the absolute numbers of events were greater in these two studies than the other five studies, no major differences in cardiovascular morbidity were noted between groups (18% versus 17% and 2% versus 4%). Neither study broke down these cardiac disorders into more serious versus less serious events. The rest were mainly short

duration studies with few absolute events which occurred mainly in the premixed insulin analogue arms (range of 1 for the premixed insulin analogues versus 0 to 1 for the other diabetes agents; less than 1 percent for each arm). Two of these shorter duration studies were crossover studies,<sup>55 59</sup> which 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 with long-acting insulin analogues, and reported no differences in cardiovascular morbidity in each arm (less than 1% versus 0% and 0.8% versus 0.8%).<sup>47 59</sup> The 28-week parallel-arm RCT of 255 insulin-naïve patients compared insulin aspart 70/30 plus metformin with insulin glargine plus glimepiride.<sup>47</sup> The oral antidiabetic agents could have been in place prior to study start or added after the study started. 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 with insulin glargine plus metformin, and reported similarly low absolute events and no major differences between arms.<sup>59</sup> 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 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 with premixed human insulin reporting similar percent cardiovascular events between groups (18% versus 17% and less than 1% versus 0%).<sup>42 55</sup> The longest 2-year multicenter, multinational RCT that specifically evaluated safety (hypoglycemia and adverse events) was one of these two studies.<sup>42</sup> This study compared insulin aspart 70/30 with NPH/regular 70/30 in subjects previously on insulin regimens, and reported 15 unspecified cardiac disorders (18%) in the premixed insulin analogue arm versus 17 unspecified cardiac disorders (17%) 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 lower absolute events due to the higher specificity of the cardiac adverse event and the 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.

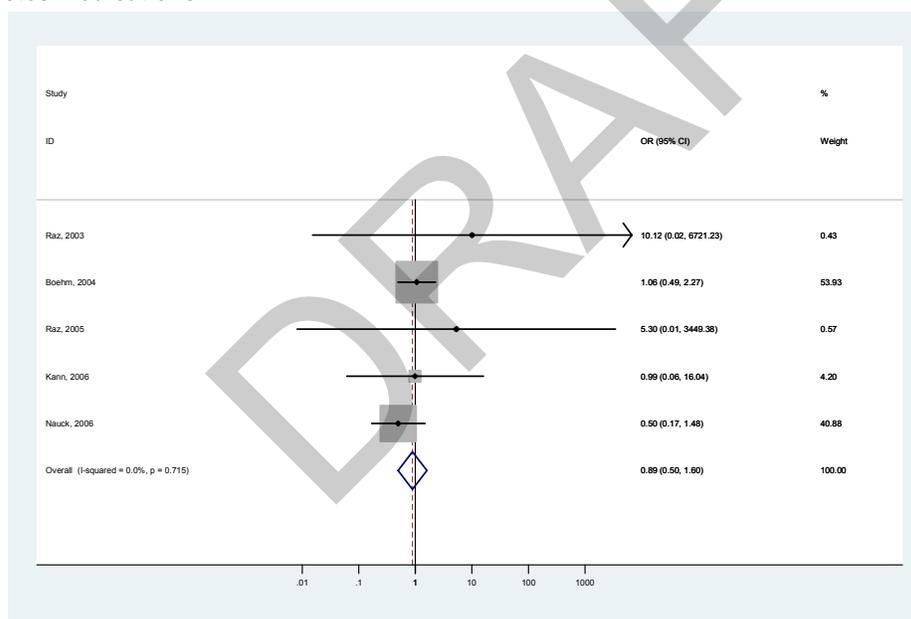
*Premixed insulin analogues versus noninsulin antidiabetic agents.* Two RCTs compared premixed insulin analogues with oral antidiabetic agents, reporting few absolute cardiovascular morbidity events in the premixed insulin analogue groups compared with no events in the oral medication groups (less than 1% versus 0% respectively for both studies).<sup>51 54</sup> Both 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 study also had a third arm of insulin aspart 70/30 monotherapy.<sup>51</sup> The thiazolidinedione was pioglitazone<sup>51</sup> in one study and rosiglitazone in the other study.<sup>54</sup> 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).

A relatively large-size 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.<sup>46</sup> The study reported slightly higher absolute nonspecific cardiac disorders in the exenatide arm compared with the insulin aspart 70/30 arm (10 (4%) versus 5

(2%) cardiac adverse events respectively). They did not further elaborate 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 compared with any other active comparator in the five parallel-arm RCTs (OR = 0.89; 95% CI: 0.50 to 1.60; p = 0.80; see Figure 31). The inclusion of the two crossover studies in the meta-analysis did not markedly influence these results (OR = 0.96; 95% CI: 0.54 to 1.70). No one study strongly influenced these results. Despite different definitions of cardiovascular morbidity, we decided to combine these trials in a meta-analysis due to the underlying shared pathophysiology of 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 two RCTs which lumped less serious and more serious cardiac disorders.<sup>42 46</sup> While 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% 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.

**Figure 31. Pooled odds ratio of cardiovascular morbidity comparing premixed insulin analogues with other diabetes medications**



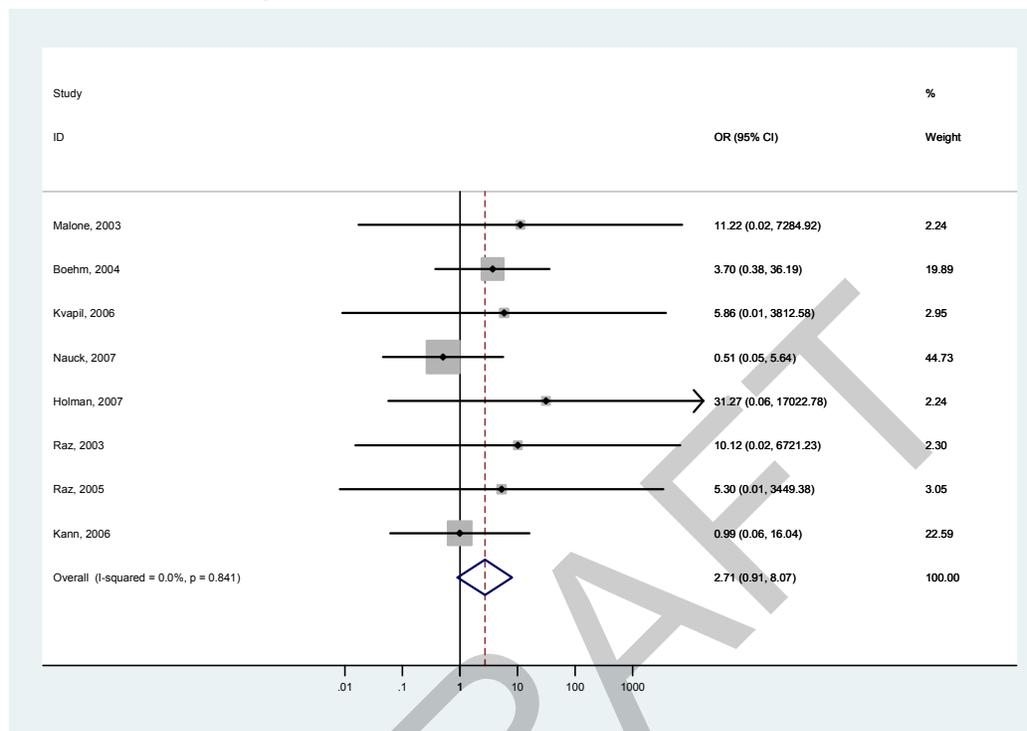
Subscript: Boxes indicate individual study point estimates. Box Size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represent 95% confidence intervals for each study. The diamond at the bottom of the graph indicates 95% confidence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

### **Combined mortality and cardiovascular disease morbidity.**

**Quantitative assessment.** We decided to combine eight parallel-arm RCTs evaluating mortality and cardiovascular disease morbidity in one meta-analysis as the current understanding of these outcomes propose a shared pathophysiology of these outcomes, using the mortality results for the two studies that reported both outcomes.<sup>42 46</sup> We found no statistically significant

differences between premixed insulin analogues and any other active diabetes medication comparator (OR = 2.71; 95% CI: 0.98 to 8.07; p = 0.07; see Figure 32). No one study markedly influenced these results. We did not identify any statistically significant heterogeneity.

**Figure 32. Pooled odds ratio of combined outcomes mortality and cardiovascular morbidity comparing premixed insulin analogues with other diabetes medications**



Subscript: 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% confidence intervals for each study. The diamond at the bottom of the graph indicates 95% confidence interval for the random-effects pooled estimate. Test for heterogeneity:  $Q = 3.45$  with 7 degrees of freedom ( $p = 0.841$ )  
I-squared statistic = 0%

## Nephropathy.

Premixed insulin analogues versus long-acting insulin analogues. Only one study reported nephropathy as an outcome.<sup>28</sup> This 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 three-times a day, and long-acting insulin detemir at bedtime or twice-daily if required).<sup>28</sup> 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). Additionally, the study 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 differences among the three groups). This potential difference in albumin-to-creatinine ratio may be responsible for the mild yet statistically significant differences in plasma creatinine. The long-term clinical impact of these mild absolute differences in plasma creatinine is uncertain.

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

## **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 with insulin lispro 75/25, and reported one death from myocardial infarction in the insulin lispro 75/25 arm which occurred after patient had withdrawn from the study due to the diagnosis of malignant neoplasm compared with no deaths in the insulin aspart 70/30 arm.<sup>52</sup>

**Other clinical outcomes.** No study reported any other clinical outcomes such as cardiovascular morbidity or microvascular disease between one premixed insulin analogue versus another premixed insulin analogue.

### **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 was no report of death or other clinical outcomes.<sup>76</sup> 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 this data since the documentation only stated the deaths but not the total number of subjects. Additionally, no descriptions were given on 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% type 1 diabetes subjects.<sup>77</sup> 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 a reporting of presence of absence of clinical outcomes in these documents.<sup>78</sup>

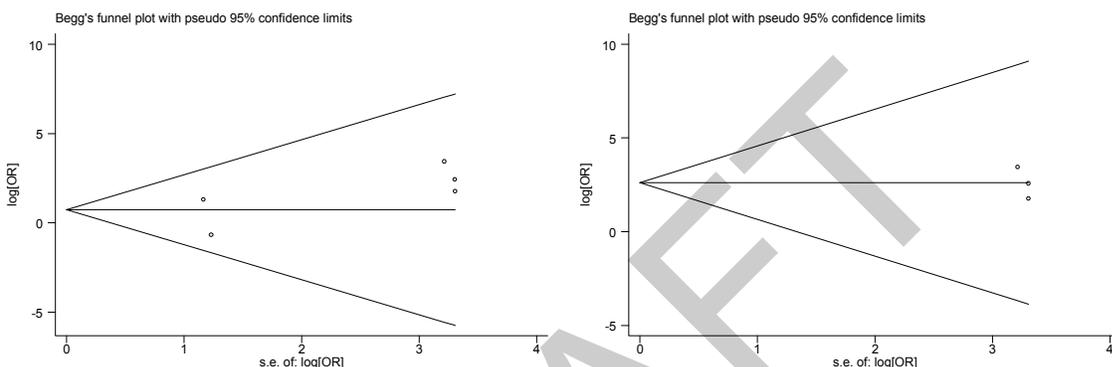
Lastly, we evaluated product labels and data provided by several pharmaceutical industries (Eli Lilly and Company and sanofi-aventis). We identified three crossover studies that reported data on clinical outcomes. Although all three studies were included in our overall review as they were peer-reviewed publications,<sup>58-60</sup> we found additional data from 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,<sup>79</sup> yet did not state this in the peer-reviewed publications.<sup>58 59</sup> Furthermore, the pharmaceutical information reported one person with chest pain, one with cardiac disorder (tachycardia and palpitations), and one with peripheral vascular disorder in the 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).<sup>80</sup> The peer-reviewed publication however did not report on these cardiovascular events.<sup>58</sup> In the third study, the peer-reviewed publication<sup>60</sup> reported one death from fatal myocardial infarction in the premixed insulin analogue arm and one death in the glargine arm; however, the pharmaceutical information reported only the event in the premixed insulin analogue arm.<sup>81</sup> No new information relevant to these clinical outcomes was reported in the data sent by sanofi-aventis or in any of the product labels.

Addition of extra data into the meta-analyses that included crossover studies did not markedly change any of our conclusions (OR for all-cause mortality = 2.37; 95% CI 0.78 to 7.22 and OR for cardiovascular morbidity = 0.96; 95% CI: 0.56 to 1.65).

## Publication Bias

Overall, we did not find strong evidence for publication bias in this literature on clinical outcomes. Across all analyses, there were no statistically significant publication bias ( $p < 0.05$ ) 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 plots for all-cause mortality and cardiovascular morbidity was suggestive that some small studies with protective effects of premixed insulin analogues may have been missing (see Figure 33).

**Figure 33. Begg's funnel plots for all-cause mortality and cardiovascular disease mortality**



## Study Quality Assessment

Most of the thirteen studies ( $n = 11$ ) were rated as of good or fair quality. These were randomized with few losses to followup, and described dropouts and withdrawals.<sup>28 42 46 48 52 54 55 60 62 70 82</sup> One randomized study was rated as poor quality since they excluded one-third of the subjects from the efficacy analysis due to receipt of expired drug.<sup>59</sup> Another study had greater than 10 percent patients who were lost during followup, but they did report on reasons for withdrawals and losses to followup.<sup>51</sup> All studies were unblinded except for one,<sup>28</sup> and most studies ( $n = 11$ ) reported receiving pharmaceutical industry funding. Source of funding has a potential to induce reporting bias, especially for outcomes such as cardiovascular morbidity which involves more subjectivity in outcome ascertainment than mortality.

## Other Quality Issues

Only one RCT evaluated safety outcomes for longer than one year.<sup>42</sup> Followup was sufficient in the remaining RCTs for the primary outcome but not for assessment of clinical outcomes which are relatively rare, especially mortality. Even the one RCT with two-year data had extremely few mortality events.<sup>42</sup> While four studies did not report on whether the analysis for adverse events was intention to treat,<sup>28 42 52 62</sup> this would not affect our results since we abstracted data as if it were intention to treat. Several studies reported on serious adverse events, but did not give specific mention to 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.<sup>40 63</sup> While elimination of the two studies did not affect our results, elimination of many studies due to lack of reporting by authors could bias these results in either direction.

## Applicability Assessment

Although the evidence is insufficient to conclude an effect of premixed insulin analogues on clinical outcomes, the applicability of this scarce data is 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 in the ones that did report race.<sup>28 48 54 62</sup> Studies had diverse inclusion and exclusion criteria which excluded selected populations in most of the studies. Three studies excluded subjects with major complications from type 2 diabetes.<sup>51 55 70</sup> Others excluded insulin-naïve subjects,<sup>48</sup> subjects with suboptimal glucose control,<sup>46</sup> and insulin-treated subjects.<sup>28 47 55 59</sup> Outpatient clinics were the population source in the few studies reporting this data.<sup>28 46 54</sup> Comparator medications were considered a good alternative in most studies,<sup>28 42 47 48 51 52 55 59 60 62 70</sup> and dose schedule and route 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 US standards in most studies.<sup>28 42 48 51 52 54 55 59 60 62 70</sup> The percentage of subjects enrolled versus screened were greater than 50 percent for most studies, although four studies did not report this data.<sup>47 54 60 70</sup> All except one study<sup>60</sup> had less than 10 percent of subjects excluded during run-in or no run-in period existed.

## Quality of Life

### Key Messages

- No significant difference was noted in the three 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 due to different outcome definitions, measurement techniques, populations, and comparators.

### 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.
- The quantity, quality, and consistency of the body of evidence was graded as insufficient for the following comparisons:
  - Premixed insulin analogues versus any other comparison not listed above.

### Study Characteristics

Of the 39 studies, only five reported on the quality of life.<sup>28 45 66 68 69</sup> Three studies were moderate-size parallel-arm RCTs (number of subjects ranged from 143 to 708),<sup>28 66 69</sup> while the other two were small to moderate-sized crossover studies with no washout period (number of subjects ranged from 49 to 160).<sup>45 68</sup> Most studies had short-duration of followup lasting 4 to 6 months,<sup>45 66 68 69</sup> with one study lasting 1 year.<sup>28</sup> Three studies were conducted in one or two

mainly European countries,<sup>28 45 69</sup> while the rest of the studies were conducted in the U.S.<sup>28</sup> or multiple countries.<sup>66</sup> Exclusion criteria varied depending on the study. Most studies (n = 4) excluded moderate to severely obese subjects with a BMI over 35 or 40 kg/m<sup>2</sup>,<sup>28 45 66 69</sup> and/or subjects with severe hyperglycemia (i.e. HgbA1c  $\geq$  9.5, 10, or 10.5%).<sup>28 45 68 69</sup> Most studies reported either excluding subjects who used insulin in the last 3 to 6 months,<sup>45 66 69</sup> or excluding prior insulin users.<sup>28</sup> Two studies excluded subjects with significant comorbidity such as a history of cardiovascular disease or complications from type 2 diabetes.<sup>28 66</sup>

Subjects were mainly middle-age or older, overweight to mildly obese adults with mild to moderate hyperglycemia (mean HgbA1c range from 7.5% to 9.9%). 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 racial mix. One study that reported race had mainly Caucasian subjects.<sup>28</sup>

## Reporting of Quality of Life

We used the definitions for quality of life outcome as reported by authors, which could include 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<sup>28 68 69</sup> evaluated four different quality of life outcomes (quality of life, treatment satisfaction, willingness to continue treatment, and depression) and compared premixed insulin analogues with long-acting insulin analogues or rapid-acting insulin analogues (see Table 11 and Appendix E, Evidence Table 4).

**Table 11. Quality of life**

Comparisons	N of studies	N of total participants	Outcomes measured	Number of studies using validated instruments
Premixed insulin analogues versus long-acting insulins	3 <sup>28 68 69</sup>	912	Quality of life, depression/mood, treatment satisfaction, or willingness to continue treatment	2
Premixed insulin analogues versus premixed human insulin	1 <sup>45</sup>	160	Treatment satisfaction	1
Premixed insulin analogues versus oral medications	1 <sup>66</sup>	143	Treatment satisfaction and willingness to continue treatment	0
Premixed insulin analogues versus rapid-acting insulin analogue	2 <sup>28 69</sup>	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 did report a qualitative difference between groups when comparing the premixed insulin analogue with the long-acting insulin analogue arm only.

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 three-times a day, and long-acting insulin detemir at bedtime or twice-daily if required). This study did not find a statistically significant difference between groups in self-reported quality of life using the Euro-QoL validated questionnaire (winsorized means 0.76, 0.76, and 0.78 respectively).<sup>28</sup>

The second study was a crossover RCT comparing insulin lispro 75/25 with insulin glargine for 12 weeks on each treatment, and 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).<sup>68</sup>

The third and relatively lower quality parallel-arm RCT compared three-times daily insulin lispro 50/50 with three-times daily insulin lispro or once-daily insulin glargine. Study participants who were already on oral antidiabetic agents were advised to stop their medications.<sup>69</sup> They reported an increased proportion of subjects with treatment satisfaction in all three arms at the end of the study 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%) than the other two arms (44.2% and 44.5%) and had a lower proportion of subjects willing to continue treatment (77.4% versus 88.5% and 83.3%), the authors did not analyze whether these small differences were statistically significant. The glargine comparator arm was not given with oral agents as is typical in clinical practice; therefore, the glargine arm had a higher fasting blood glucose and lower decreases in HgbA1c than the other two arms, which 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 with 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).<sup>45</sup>

### **Premixed Insulin Analogues Versus Oral Antidiabetic Agents**

One 16-week parallel-arm RCT compared overall treatment satisfaction among insulin lispro 75/25 preprandial injections, insulin lispro 75/25 postprandial injections, or glyburide in subjects 60 to 80 years of age, and reported a slightly lower overall treatment satisfaction score with glyburide compared with insulin lispro 75/25 (mean score 3.98 versus 4.35 respectively, p = 0.014) using a nonvalidated questionnaire (see Table 11 and Appendix E, Evidence Table 4).<sup>66</sup> The clinical importance of this minor difference in scores was unclear. Additionally, they reported a higher willingness to continue treatment in the insulin lispro arms compared with the glyburide arm (92% versus 79% 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, subjects may have been less satisfied with their treatment since they were not receiving optimal

treatment for their hyperglycemia. As one might expect, the insulin lispro 75/25 arms had greater reductions in HbA1c than glyburide in this trial.

## **FDA, European Medicines Agency, and Pharmaceutical Industry Data**

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

### **Study Quality Assessment**

Most of the studies (n = 4) were rated as good or fair quality,<sup>28 45 68 69</sup> were randomized with few losses to followup,<sup>28 45 66 69</sup> and described dropouts and withdrawals (see Appendix E, Evidence Table 7).<sup>28 45 66 69</sup> 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.<sup>66</sup> This would potentially affect glycemic control outcomes and thereby patient satisfaction with treatment. Another study had greater than 10 percent loss to followup, and they did not report reasons for withdrawals and participant loss during followup.<sup>68</sup> The majority of studies were unblinded except two,<sup>28 45</sup> and most studies (n = 4) received funding from the pharmaceutical industry.

### **Applicability Assessment**

We concluded that the body of evidence of quality of life outcomes had fair applicability to the U.S. population of people with type 2 diabetes (see Appendix E, Evidence Table 8). These studies were mainly representative of the general population of type 2 diabetes, with the exception of race and severity/spectrum of illness. Additionally, drug comparators were only considered the best alternatives in three<sup>28 45 68</sup> of the five studies. Race was not reported in two studies,<sup>45 66</sup> and was deemed not representative in the ones that did report race.<sup>28 68 69</sup> The studies had diverse eligibility criteria which excluded selected populations in most of the studies. Studies excluded subjects with a new diagnosis of type 2 diabetes,<sup>66</sup> or subjects taking insulin already.<sup>28 69</sup> One study excluded subjects less than 60 years old and greater than 80 years old.<sup>66</sup> Outpatient clinics were the population source in the two studies reporting this data,<sup>28 66</sup> and one of these occurred in subspecialty clinics.<sup>66</sup> Dose schedule and route 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 the U.S. in all the studies. The percent of subjects enrolled versus screened were greater than 50 percent for all the studies, and all had less than 10 percent of subjects excluded during run-in or no run-in period existed.<sup>28 45 66 68 69</sup>

## **Key Question 3**

**Does the effectiveness or safety of new premixed insulin analogue regimens differ for the following sub-populations?**

- a. The elderly ( $\geq 65$  years), very elderly ( $\geq 85$  years)**
- b. Other demographic groups (ethnic or racial groups, sex)**
- 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 in the very elderly, minorities, or with patients with comorbid conditions. Only one study enrolled somewhat older patients (between 60 and 80 years) and compared insulin lispro 75/25 with glyburide.<sup>66</sup> This study found a significant decrease in fasting blood glucose as well as pre-dinner blood glucose levels with insulin lispro 75/25 as compared to glyburide (mean difference = -43.9 mg/dL and -32.6 mg/dL respectively;  $p < 0.01$  for both). In addition, there was a significant decrease in postprandial blood glucose after breakfast and dinner with insulin lispro 75/25 in this relatively older population (mean difference = -58.3 mg/dL and -43.9 mg/dL respectively;  $p < 0.01$  for both). This study also found a significant decrease in HgbA1c with insulin lispro 75/25 as compared to glyburide (mean difference = -0.78%;  $p < 0.01$ ).

## Key Question 4

**Does the effectiveness or safety of new premixed insulin analogue regimens differ for 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)?**

### **Effect of Premixed Insulin Analogues in Patients Taking Oral Antidiabetic Agents**

We identified two studies that compared premixed insulin analogues monotherapy with a combination of oral antidiabetic agents and premixed insulin analogues.<sup>48,51</sup> In the study by Kvapil et al., insulin aspart 70/30 was compared with a combination of insulin aspart 70/30 and metformin.<sup>48</sup> 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 0.30 units/kg/day;  $p$ -value not reported).

Raz et al.<sup>51</sup> compared insulin aspart 70/30 monotherapy with 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 the combination arm (0.4 units/kg versus 0.3 units/kg;  $p = 0.002$ ).

**Fasting glucose (see Appendix E, Evidence Table 4).** Both 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 it did not reach statistical significance in either study. Similarly, pre-dinner glucose levels were lower in both studies with the combination therapy but reached statistical significance in only one study ( $p < 0.05$ ).<sup>51</sup>

**Postprandial glucose (see Appendix E, Evidence Table 4).** Both studies also reported breakfast and dinner postprandial glucose levels and found postprandial glucose levels lower with the combination therapy as compared to the monotherapy. However, this difference reached statistical difference in only one study.<sup>51</sup>

**HgbA1c (see Appendix E, Evidence Table 4).** Raz et al.<sup>51</sup> found that combination therapy was associated with lower HgbA1c levels than monotherapy with insulin aspart 70/30 alone

(mean difference = -0.6%;  $p = 0.008$ ). Similarly, Kvapil et al.<sup>48</sup> also reported a significant decrease in HgbA1c with combination therapy as compared to monotherapy (mean difference = -0.39%;  $p < 0.01$ ).

**Hypoglycemia (see Appendix E, Evidence Table 5).** There were no major hypoglycemic events in both studies.<sup>48 51</sup> The incidence of minor hypoglycemic and symptoms of hypoglycemia was smaller in the combination arm in both studies as compared to the insulin aspart 70/30 monotherapy arm.

**Weight change (see Appendix E, Evidence Table 6).** Patients on combination therapy with insulin aspart 70/30 plus metformin gained less weight than patients who were on monotherapy,<sup>48</sup> 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 patients on monotherapy; the difference between the two groups in this trial was also not significant.<sup>51</sup>

### **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 intensity 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 HgbA1c. Among adverse events, hypoglycemia was the most frequently reported outcome. Although premixed insulin analogues appear promising agents in treating hyperglycemia in type 2 diabetics, their comparative effectiveness to other several antidiabetic agents is not fully studied.

The Diabetes Control and Complication Trial (DCCT) and the UKPDS have highlighted the importance of achieving tighter glycaemic control with an aim to achieve an HgbA1c of less than 7% or 6.5% (depending on the organization issuing the guidelines).<sup>83 84</sup> To achieve this HgbA1c target, both fasting and postprandial glucose need to be controlled.<sup>85</sup> Current evidence suggests that in patients with higher HgbA1c levels, targeting fasting glucose is more beneficial in bringing HgbA1c closer to the desired target. However, as HgbA1c gets closer to 7%, controlling postprandial glucose becomes more important to achieve the target HgbA1c.<sup>85-87</sup> The American Diabetic Association guidelines recommend a target fasting glucose between 70-130 mg/dL and a postprandial glucose less than 180 mg/dL.<sup>88</sup>

A physiologic insulin replacement regimen generally requires four daily injections of insulin which may affect overall patient satisfaction. Premixed insulin analogues can be a convenient and effective alternative to a physiologic insulin replacement regimen by providing bolus insulin with meals through their rapid-acting component and by fulfilling basal insulin requirements through the protaminated slower release component.

## Key Findings and Implications

### Fasting Glucose

In this systematic review we found that premixed insulin analogues were either less effective or not effective in lowering fasting glucose when compared to all other insulin preparations except rapid-acting insulin analogues. However, when compared to oral antidiabetic agents, premixed insulin analogues appear to be more effective in lowering fasting glucose. This finding has important clinical implications as control of fasting blood glucose is more effective in bringing a relatively high HgbA1c closer to the target range. It is possible that patients with very poor fasting blood glucose control may not get as much benefit from these premixed insulin analogues. Most studies included in this systematic review excluded patients with relatively higher HgbA1c levels. Findings of this systematic review cannot be extrapolated to the subpopulation of diabetic patients with relatively poor blood glucose control.

### Postprandial Glucose

In contrast to our above findings, we found that premixed insulin analogues are more effective in lowering postprandial glucose levels when compared to long-acting insulin analogues or premixed human insulin preparations. Controlling postprandial glucose is important as cardiovascular complications of diabetes, such as coronary heart disease, stroke, cardiovascular mortality, sudden cardiac death, and all cause mortality are closely related to

postprandial glucose levels in epidemiological studies.<sup>89-92</sup> Better control of postprandial hyperglycemia may result in decreased cardiovascular complications.<sup>93-96</sup> However, whether the effectiveness of premixed insulin analogues in lowering postprandial hyperglycemia translates into lower cardiovascular diseases is not known as very few studies reported any hard clinical outcomes.

## HgbA1c

We found premixed insulin analogues to be more effective than long-acting insulin analogues in lowering HgbA1c probably due to the ability of premixed insulin analogues to control postprandial hyperglycemia. We did not find convincing evidence that premixed insulin analogues as a group lower HgbA1c more than other antidiabetic agents. HgbA1c is the standard of care for monitoring long-term glycemic control and reflects both fasting and postprandial glucose control.<sup>88</sup> A decrease in HgbA1c is associated with decreased diabetic complications such as retinopathy, nephropathy, and neuropathy.<sup>197</sup> Of these microvascular complications, only one study evaluated diabetic nephropathy and 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, although in this study the premixed insulin analogue was more effective than the long-acting insulin analogue in lowering HgbA1c.<sup>28</sup>

## Clinical Outcomes

Clinical outcomes (such as all-cause mortality, cardiovascular mortality, and morbidity) were reported by only 13 RCTs. No statistically significant differences were found between premixed insulin analogues and their comparators for all-cause mortality, cardiovascular mortality, and cardiovascular morbidity. While a suggestion of harm was seen in the pooled odds ratios for all-cause mortality and cardiovascular morbidity, the 95% CIs were wide (crossing one), indicating the lack of reliability of these point estimates based on few absolute events in studies where clinical outcomes were not the primary outcomes. Reporting bias may exist since we noted that the majority of trials did not report on clinical outcomes and if there were no clinical outcomes they did not report that no events occurred. Also, two studies from the pharmaceutical industry reported no deaths in either arm, but this data was not in the peer-reviewed publications. Cardiovascular morbidity was reported in the pharmaceutical data for one study that did not report on this information in the peer-reviewed publication. The addition of this data did not significantly change our results. However, if further data were missing from the other studies where we did not have industry data, this could have impacted our results in either direction.

Cardiovascular morbidity definitions were varied. Two studies<sup>46 98</sup> lumped serious and less serious events together which may mask any potential differences in serious cardiovascular morbidity between drugs.

One study evaluated change in plasma creatinine showing a 0.02 mg/dL difference between groups favoring insulin detemir (a long-acting insulin analogue). The clinical importance of this small difference is unclear.

No studies were identified that evaluated any critical subgroups such as the elderly, those with significant comorbidity, such as a history of cardiovascular disease, race, or the impact of drug-drug interactions.

No systematic review has synthesized clinical outcomes comparing premixed insulin analogues to their comparators. These outcomes are the most clinically relevant, yet require studies with long-term followup where the clinical outcomes are the primary outcome. While glycemic control has been associated with improved microvascular and potentially macrovascular outcomes in subjects with type 2 diabetes,<sup>99-103</sup> diabetes drugs which lower glycemic control have been potentially associated with cardiovascular harm (i.e., muraglitazar and rosiglitazone).<sup>104 105</sup> This demonstrates the importance of evaluating potential clinical harms in all diabetes drugs. An ongoing retrospective observational study funded by sanofi-aventis comparing cardiovascular outcomes in initiators of insulin glargine with initiators of premixed insulin analogues using the Integrated HealthCare Information Services (IHCIS) databases will be finished in January 2008. That study will give us further information in this important area.

## Quality of Life

Only five RCTs reported on quality of life measures.<sup>28 45 66 68 69</sup> In the three studies<sup>28 45 68</sup> using validated instruments to measure quality of life outcomes, no statistically significant differences were seen between the groups. In the two studies that showed potential differences between groups favoring the premixed insulin analogues, the active comparator arms were not the best alternative comparators to use which may have influenced patient satisfaction and willingness to continue treatment.<sup>66 69</sup>

No systematic review has synthesized quality of life outcomes comparing premixed insulin analogues to their comparators. While quality of life may directly impact adherence to a medication and thereby indirectly impact intermediate and clinical outcomes, they are rarely reported. Two industry-sponsored studies are currently underway to evaluate quality of life and treatment satisfaction between premixed insulin analogues and the long-acting insulin glargine. Data is expected to be available later in 2008 or 2009. If validated measures are used, then this will be a helpful start in amassing data on this important outcome.

## Hypoglycemia

A relatively common side-effect of treatment of diabetes, hypoglycemia is the major limiting factor in the management of hyperglycemia.<sup>106</sup> As compared to long-acting insulin analogues, premixed insulin analogues are more likely to cause hypoglycemia. Evidence was lacking to conclusively compare premixed insulin analogues with other diabetic treatments for hypoglycemia incidence or hypoglycemic events. As 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 due to the difference in glycemic control. Davidson et al.<sup>107</sup> reviewed the incidence of hypoglycemia with insulin aspart 70/30 and found that the risk of major hypoglycemia was less with insulin aspart 70/30 as compared to premixed human insulin but there was no difference in the incidence of minor hypoglycemia. Our findings are only partially consistent with their findings. There are two reasons why we reached a different conclusion. One is that we have included additional studies that have been published since their review, and second is that Davidson et al. included trials without a comparator in their review while we did not.

## Weight Change

Weight gain is a common side-effect of insulin replacement therapy.<sup>108</sup> According to one estimate, each 5 kg weight gain is associated with a 30% increase in risk of coronary heart disease.<sup>108</sup> Due to a paucity of data, we could evaluate change in weight with 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 HgbA1c. Weight gain with insulin aspart 70/30 was also evaluated in a systematic review by Davidson et al.<sup>107</sup> who reported weight gain with insulin aspart 70/30 monotherapy as well as when 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.<sup>109</sup> evaluated efficacy and safety of insulin aspart 70/30. They reached results similar to ours except that hypoglycemia and weight gain with insulin aspart 70/30 were similar to the long-acting insulin analogue. As our systematic review includes more recently published trials and we compare the effect across all premixed insulin analogues, our results are more reflective of current state of knowledge.

## Limitations

There are several potential limitations of this systematic review. All studies did not report on all outcomes included in this systematic review. In addition, studies varied in the manner the findings were reported. Several studies presented data on changes in blood glucose in the figure and only commented on significant findings in the text forcing us to abstract data from figures whenever possible. Some studies reported point estimates but did not report dispersion around the point estimates. Some reported enough data to impute standard error of means. Almost half of the studies were crossover studies and data was not reported in a manner that can be used in a quantitative synthesis without making some assumptions. These assumptions may have affected the quantitative synthesis of the evidence. Due to the smaller number of studies for each comparison, a full analysis and exploration for heterogeneity could not be done. We addressed this limitation by using random-effects models for all analyses regardless of the presence or absence of statistical heterogeneity. Similarly, a smaller number of studies also precluded our ability to evaluate for publication bias.

The methodological quality of studies was good but the applicability was poor. The main reason for poor applicability is that these were efficacy studies and therefore designed to study premixed insulin analogues in a limited subgroup of patients. Therefore, most studies excluded patients with diabetic complications, other comorbid conditions, or in certain other subpopulations. Another factor that limits the applicability of these trials is the limited duration of followup of patients while on treatment. This is in contrast to the real-world situation where once diabetic patients require insulin, they have to continue taking it for rest of their lives. Thus, whether the relative effectiveness of premixed insulin analogues on some outcome measures persist over a longer duration cannot be extrapolated from these studies.

Almost all studies were funded by the pharmaceutical industry, when investigators reported their source of funding, raising the possibility of publication bias. However, in searching the FDA scientific review, we did not find any additional studies that have not yet been reported. We

found only one relevant unpublished study at [www.clinicalstudyresults.org](http://www.clinicalstudyresults.org), which was completed recently and may have been going through peer-review process prior to publication.

Only for some comparisons and a few outcomes we found sufficient evidence to comment on the effectiveness of premixed insulin analogues. For several other comparisons and outcomes, we either found insufficient evidence or did not find any evidence on 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 determine adherence to therapy and should be addressed for patients with chronic diseases. However, we found very few studies that have looked at this outcome. Moreover, studies that reported quality of life sometimes did not use validated scales.

## **Gaps in the Evidence**

### **Intermediate Outcomes**

The lack of effectiveness studies limits the generalization of the results to all U.S. diabetic patients as well as to current clinical practice. Not all comparisons have enough data to compare premixed insulin analogues with other antidiabetic treatments.

### **Clinical Outcomes**

Scant data exist to assess clinical outcomes when premixed insulin analogues are compared with other antidiabetic treatments. Not only were the few studies that reported clinical outcomes of shorter duration, these trials were neither designed nor powered to assess clinical outcomes.

### **Quality of Life**

Few studies have compared the effectiveness of premixed insulin analogues with other antidiabetic treatments in improving quality of life. In addition, two of the studies that did evaluate quality of life used non-validated scales.<sup>66 69</sup> As diabetes is a chronic disease, longer duration studies are needed to assess the effect of premixed insulin analogues on quality of life.

### **Hypoglycemia**

Several comparisons between premixed insulin analogues and other antidiabetic treatments either have very few studies or no study at all. Shorter duration of followup limits our ability to comment on the incidence of hypoglycemia over a longer duration of time. Only one study that compared hypoglycemia incidence at one year and at 2 years found a lower incidence during the second year.<sup>42</sup> Patients with comorbid conditions need to be included in future studies. Patients with comorbid conditions were excluded from trials which may be at a different risk of developing hypoglycemia from these medications. Thus, the results of these trials cannot be extrapolated to patients with comorbid conditions. Definitions for minor hypoglycemia and symptoms of hypoglycemia were variable between the studies.

## Weight Change

The main gap in the evidence on weight change is the shorter duration of studies. A process such as weight gain is a relatively slow progressing outcome and therefore studies with 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. Probably the most important comparative study that needs to be performed should compare premixed insulin analogues and a combination of bolus insulin injections with rapid-acting insulin analogues plus basal insulin injections with long-acting insulin analogues.
2. Studies with longer followup are needed to study whether the gains in the early part of treatment are sustainable or not and whether differences between the comparators appear later during the treatment.
3. Studies should be planned to examine the effectiveness of premixed insulin analogues with less restrictive inclusion criteria and in a setting that more closely mimics the usual clinical practice.
4. Patients with comorbid conditions, racial minorities, and very elderly patients need to be enrolled in studies to examine the efficacy and effectiveness of premixed insulin analogues in these subpopulations.
5. Clinical outcomes need to be studied to examine the safety of premixed insulin analogues. Sufficiently powered studies need to be planned to study clinical outcomes.
6. As diabetes is a chronic disease, the effect of premixed insulin analogues on quality of life and patient satisfaction needs to be studied.

## Conclusion

In summary, premixed insulin analogues are more effective than long-acting insulin analogues alone in lowering postprandial glucose and HgbA1c. Premixed insulin analogues are also more effective than premixed human insulin preparations in lowering postprandial glucose but not HgbA1c. Studies had several limitations so that the results of these studies cannot be extrapolated to a wider diabetic population of the U.S. Longer duration of studies with sufficient power to examine clinical outcomes 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. 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.
6. Garber AJ. Premixed insulin analogues for the treatment of diabetes mellitus. *Drugs* 2006; 66(1):31-49.
7. Novo Nordisk. NovoLog Mix 70/30 Package Insert. [Web Page]. Available at [http://www.novologmix70-30.com/NovoLogMix7030\\_PI.pdf](http://www.novologmix70-30.com/NovoLogMix7030_PI.pdf). (Accessed 2 February 2008).
8. Eli Lilly and Company. Humalog Mix75/25 Patient Information. [Web Page]. Available at <http://www.humalog.com/index.jsp>. (Accessed 2 February 2008).
9. Eli Lilly and Company. Humalog Mix50/50 Patient Information. [Web Page]. Available at <http://www.humalog.com/index.jsp>. (Accessed 2 February 2008).
10. 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.
11. 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.
12. 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.
13. 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.
14. 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.
15. 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.
16. 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.
17. 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.
18. 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.

19. Wells, GA, Shea, B, O'Connell, D *et al.* The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses [Web Page]. (Accessed 20 September 2007).
20. Guide for Conducting Comparative Effectiveness Reviews. Rockville, MD: Agency for Healthcare Research and Quality, 2007.
21. 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.
22. 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.
23. Robertson C, Idris NR, Boyle P. Beyond classical meta-analysis: can inadequately reported studies be included? *Drug Discov Today* 2004; 9(21):924-31.
24. Thompson SG, Pocock SJ. Can meta-analyses be trusted? *Lancet* 1991; 338(8775):1127-30.
25. Whitehead A, Whitehead J. A general parametric approach to the meta-analysis of randomized clinical trials. *Stat Med* 1991; 10(11):1665-77.
26. Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. *Biometrics* 1994; 50(4):1088-101.
27. 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.
28. 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.
29. 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.
30. 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.
31. 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.
32. 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.
33. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003; 327(7414):557-60.
34. Saudek CD, Derr RL, Kalyani RR. Assessing glycemia in diabetes using self-monitoring blood glucose and hemoglobin A1c. *JAMA* 2006; 295(14):1688-97.
35. Atkins D, Best D, Briss PA *et al.* Grading quality of evidence and strength of recommendations. *BMJ* 2004; 328(7454):1490.
36. 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.
37. 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.
38. 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.
39. 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.

40. 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.
41. 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.
42. 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.
43. 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.
44. 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.
45. 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.
46. 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.
47. 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.
48. 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.
49. 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.
50. 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.
51. 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.
52. 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.
53. 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.
54. 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.

55. 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.
56. 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.
57. 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.
58. 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.
59. 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.
60. 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.
61. 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.
62. 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.
63. 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.
64. 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.
65. 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.
66. 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.
67. 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.
68. 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.
69. 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.

70. 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.
71. 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.
72. Holst JJ. Glucagon-like peptide-1: from extract to agent. The Claude Bernard Lecture, 2005. *Diabetologia* 2006; 49(2):253-60.
73. Takei I, Kasatani T. Future therapy of diabetes mellitus. *Biomed. Pharmacother.* 2004; 58(10):578-81.
74. 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.
75. 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.
76. 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](http://www.fda.gov/cder/foi/nda/99/21017_Humalog_medr.pdf). (Accessed 30 August 2007).
77. 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).
78. 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).
79. 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](http://www.clinicalstudyresults.org/documents/company-study_1045_0.pdf). (Accessed 30 August 2007).
80. 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](http://www.clinicalstudyresults.org/documents/company-study_1048_0.pdf).
81. 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 Diabetes 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](http://www.clinicalstudyresults.org/documents/company-study_2418_0.pdf). (Accessed 30 August 2007).
82. 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.
83. Clinical Practice Recommendations 2005. *Diabetes Care* 2005; 28 Suppl 1:S1-79.
84. 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.
85. Abrahamson MJ. Optimal glycemic control in type 2 diabetes mellitus: fasting and postprandial glucose in context. *Arch Intern Med* 2004; 164(5):486-91.

86. 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.
87. 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.
88. Standards of medical care in diabetes--2008. *Diabetes Care* 2008; 31 Suppl 1:S12-54.
89. 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.
90. Orenca AJ, Daviglius 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.
91. 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.
92. 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.
93. 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.
94. 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.
95. 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.
96. 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.
97. 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.
98. Bethel MA, Feinglos MN. Insulin analogues: new therapies for type 2 diabetes mellitus. *Curr Diab Rep* 2002; 2(5):403-8.
99. Schellhase KG, Koepsell TD, Weiss NS. Glycemic control and the risk of multiple microvascular diabetic complications. *Fam Med* 2005; 37(2):125-30.
100. 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.
101. 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.
102. 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.
103. 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.
104. 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.

105. 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.
106. Cryer PE. Hypoglycaemia: the limiting factor in the glycaemic management of Type I and Type II diabetes. *Diabetologia* 2002; 45(7):937-48.
107. 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.
108. Hermansen K, Mortensen LS. Bodyweight changes associated with antihyperglycaemic agents in type 2 diabetes mellitus. *Drug Saf* 2007; 30(12):1127-42.
109. 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.

DRAFT

## 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
EMA	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/m <sup>2</sup>	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

DRAFT