Appendix A: Detailed Electronic Database Search Strategies

MEDLINE Strategy

Terms	Returns
((“diabetes mellitus, type 2”[mh] OR “type 2 diabetes”[tiab] OR ((diabetes[tiab] OR diabetics[tiab] OR diabetic[tiab]) AND (“non-insulin dependent”[tiab] OR "type 2"[tiab] or type-2[tiab] OR “type II”[tiab]))) AND ("insulin/analogs and derivatives"[mh] OR "BIAsp 30"[tiab] OR "BIAsp30"[tiab] OR (Humalog[tiab] AND (Mix[tiab] OR 25[tiab] OR 50[tiab])) OR (NovoLog[tiab] AND (Mix[tiab] OR 70[tiab] OR 30[tiab])) OR (insulin[tiab] AND ((biphasic[tiab] OR premixed[tiab] OR "pre-mixed"[tiab] OR protamin*[tiab] OR Mix[tiab] OR mixture[tiab]) OR (aspart[tiab] OR lispro[tiab] OR analogue[tiab] OR analogues[tiab] OR analog[tiab] OR analogs[tiab] OR Humalog[tiab])))) NOT (animals[mh]NOT humans[mh])	1025

EMBASE Strategy

(('non insulin dependent diabetes mellitus'/exp OR 'type 2 diabetes':ti,ab OR ((diabetes:ti,ab OR diabetics:ti,ab OR diabetic:ti,ab) AND ('non-insulin dependent':ti,ab OR 'type 2':ti,ab or type-2:ti,ab OR 'type II':ti,ab))) AND ('biphasic insulin'/exp OR 'BIAsp 30':ti,ab OR 'BIAsp30':ti,ab OR (Humalog:ti,ab AND (Mix:ti,ab OR 25:ti,ab OR 50:ti,ab)) OR (NovoLog:ti,ab AND (Mix:ti,ab OR 70:ti,ab OR 30:ti,ab)) OR ((insulin:ti,ab AND (biphasic:ti,ab OR premixed:ti,ab OR 'pre-mixed':ti,ab OR protamin*:ti,ab OR Mix:ti,ab) OR (aspart:ti,ab OR lispro:ti,ab OR analogue:ti,ab OR analogues:ti,ab OR analog:ti,ab OR analogs:ti,ab OR Humalog:ti,ab)))) NOT ([animals]/lim NOT [humans]/lim)	1265

Cumulative Index to Nursing and Applied Health Literature (CINAHL)

(((MH "Diabetes Mellitus, Non-Insulin-Dependent") OR (TX "type 2 diabetes") OR (((TX "diabetes") OR (TX "diabetics") OR (TX "diabetic")) AND ((TX "non-insulin dependent") OR (TX "type 2") or (TX "type-2") OR (TX "type II")))) AND ((MH "Insulin/AA") OR (TX "BIAsp 30") OR (TX "BIAsp30") OR ((TX "Humalog") AND ((TX "Mix") OR (TX "25") OR (TX "50"))) OR ((TX "NovoLog") AND ((TX "Mix") OR (TX "70") OR (TX "30"))) OR ((TX "insulin") AND (((TX "biphasic") OR (TX "premixed") OR (TX "pre-mixed") OR (TX "protamin*") OR (TX "Mix") OR (TX "mixture")) OR ((TX "aspart") OR (TX "lispro") OR (TX "analogue") OR (TX "analogues") OR (TX "analog") OR (TX "analogs") OR (TX "Humalog"))))))	255

The Cochrane Central Register of Controlled Trials (CENTRAL)

#1	(type 2 diabetes):ti,ab,kw in Clinical Trials	602
#2	(diabetes):ti,ab,kw or (diabetics):ti,ab,kw or (diabetic):ti,ab,kw in Clinical Trials	
#3	(non-insulin dependent):ti,ab,kw or (type 2):ti,ab,kw or (type-2):ti,ab,kw or (type II):ti,ab,kw in Clinical Trials	
#4	(#2 AND #3)	
#5	(#1 OR #4)	
#6	(BIAsp 30):ti,ab,kw or (BIAsp30):ti,ab,kw in Clinical Trials	
#7	(Humalog):ti,ab,kw in Clinical Trials	
#8	(Mix):ti,ab,kw or (25):ti,ab,kw or (50):ti,ab,kw in Clinical Trials	
#9	(#7 AND #8)	
#10	(NovoLog):ti,ab,kw in Clinical Trials	
#11	(Mix):ti,ab,kw or (70):ti,ab,kw or (30):ti,ab,kw in Clinical Trials	
#12	(#10 AND #11)	
#13	(insulin):ti,ab,kw in Clinical Trials	
#14	(biphasic):ti,ab,kw or (premixed):ti,ab,kw or (pre-mixed):ti,ab,kw or (protamin*):ti,ab,kw or (mix):ti,ab,kw in Clinical Trials	
#15	(mixture):ti,ab,kw in Clinical Trials	
#16	(#14 OR #15)	
#17	(aspart):ti,ab,kw or (lispro):ti,ab,kw or (analogue):ti,ab,kw or (analogues):ti,ab,kw or (analog):ti,ab,kw in Clinical Trials	
#18	(analogs):ti,ab,kw or (Humalog):ti,ab,kw in Clinical Trials	
#19	(#17 OR #18)	
#20	(**#16** OR **#19**)	
#21	(**#13** AND **#20**)	
#22	(**#6** OR **#9** OR **#12** OR **#21**)	
#23	(#5 AND #22)	

Appendix B: Hand Searched Journals

All Journals Hand Searched
June 2007 – September 2007

Acta Diabetologica
Annals of Internal Medicine
Clinical Therapeutics
Diabetes Care
Diabetes, Obesity & Metabolism
Diabetic Medicine
Diabetologia
European Journal of Internal Medicine
Experimental and Clinical Endocrinology and Diabetes
Hormone and Metabolic Research
JAMA
Journal of Diabetes and its Complications
New England Journal of Medicine

Appendix C: List of Excluded Articles

1. 1-2-3: study results and clinical application: the "Start & Stay" approach. Journal of Diabetes Nursing 2006;(1):3p.
   No original data

2. The 1-2-3 study: achieving glycaemic goals in type 2 diabetes. Journal of Diabetes Nursing 2006 ;(1):1p.
   No original data

3. Key abstract: the EUROMIX study. Journal of Diabetes Nursing 2005;(3).
   No original data

4. Rapid acting insulin analogue effective in a range of body types launched. Pharm. J. 2005; 275(7369):401.
   No original data

5. DTB questions first-line use of insulin analogues. Pharm. J. 2004;273(7321):552.
   No original data

6. Lispro, a rapid-onset insulin. Med. Lett. Drugs Ther. 96;38(986):97-98.
   No original data

7. The why and how of early intervention with insulin analogs. Diabetes Educator 2007;3352S-75S.
   No original data

8. Abraham M R, Al-Sharafi B A, Saavedra G A et al. Lispro in the treatment of insulin allergy. Diabetes Care 99;22(11):1916-1917.
   No original data

9. Akram J. Prevention of hypoglycaemia in insulin-treated patients during Ramadan: results from a multicentre study: 2. Practical Diabetes International 98;15(1):S19.
   Did not evaluate a premixed insulin analogue

10. Aristides M, Weston A R, FitzGerald P et al. Patient preference and willingness-to-pay for Humalog Mix25 relative to Humulin 30/70: a multicountry application of a discrete choice experiment. Value Health 2004; 7(4):442-54.
    Does not apply to a key question

11. Bain S C, Kamal A D. Safety and side effects of the insulin analogues. Expert Opin. Drug Saf. 2006;5(3):349-350.
    No original data

12. Bell D, Bode B, Clements R S et al. Premixed vs. self-mixed insulin in the treatment of type II diabetes mellitus: A randomized trial. Today's Ther. Trends 91;9(1):63-73.
    Did not evaluate a premixed insulin analogue

13. Bolli G B, Di Marchi R D, Park G D et al. Insulin analogues and their potential in the management of diabetes mellitus. Diabetologia 99;42(10):1151-1167.
    No original data

14. Bullano M F, Fisher M D, Grochulski W D et al. Hypoglycemic events and glycosylated hemoglobin values in patients with type 2 diabetes mellitus newly initiated on insulin glargine or premixed insulin combination products. Am J Health Syst Pharm 2006;63(24):2473-82.

Did not evaluate a premixed insulin analogue

15. Calle-Pascual A L, Bagazgoitia J, Calle J R et al. Use of insulin lispro in pregnancy. Diabetes Nutr Metab 2000;13(3):173-7.
No original data

16. Cappelleri JC, Cefalu WT, Rosenstock J et al. Treatment satisfaction in type 2 diabetes: a comparison between an inhaled insulin regimen and a subcutaneous insulin regimen. Clinical therapeutics 2002;24(4):552-64.
Did not evaluate a premixed insulin analogue

17. Chan W B, Chow C C, Yeung V T F et al. Effect of insulin lispro on glycaemic control in Chinese diabetic patients receiving twice-daily regimens of insulin. Chin. Med. J. 2004;117(9):1404-1407.
Did not evaluate people with type 2 diabetes

18. Cobden D, Lee W C, Balu S et al. Health outcomes and economic impact of therapy conversion to a biphasic insulin analog pen among privately insured patients with type 2 diabetes mellitus. Pharmacotherapy 2007;27(7):948-62.
Did not compare a premixed insulin analogue to another antidiabetic agent

19. Coscelli C, Calabrese G, Fedele D et al. Use of premixed insulin among the elderly. Reduction of errors in patient preparation of mixtures. Diabetes Care 92;15(11):1628-30.
Did not evaluate a premixed insulin analogue

20. Culy C R, Jarvis B. Management of diabetes mellitus: Defining the role of insulin lispro mix75/25 (Humalog(registered trademark) Mix75/25(trademark)). Dis. Manage. Health Outcomes 2001;9(12):711-730.
No original data

21. Currie C J, McEwan P, Poole C et al. Comments on Long-term clinical and cost outcomes of treatment with biphasic insulin aspart 30/70 versus insulin glargine in insulin-naive type 2 diabetes patients: cost-effectiveness analysis in the UK setting. Curr Med Res Opin 2006;22(5):967-9; author reply 968-9.
No original data

22. Davidson M B. Twice-Daily NPH or mixture insulins versus triple therapy: apples versus oranges: response to Poulsen et al. Diabetes Care 2004;27(7):1846; author reply 1847-8.
No original data

23. DeWitt D E. Case study: Treating new-onset catabolic type 2 diabetes with glargine and lispro. Clin. Diabetes 2006;24(4):180-181.
No original data

24. Dunbar JM , Madden PM , Gleeson DT et al. Premixed insulin preparations in pen syringes maintain glycemic control and are preferred by patients. Diabetes care 94;17(8):874-8.
Did not evaluate people with type 2 diabetes

25. Ebeling P, Tuominen J A, Koivisto V A. Insulin analogues and carcinoma of the breast. Diabetologia 96;39(1):124-125.

No original data

26. Edelman S. Does a patient-administered titration algorithm of insulin glargine improve glycemic control? Nat Clin Pract Endocrinol Metab 2006;2(2):78-9.
Did not evaluate a premixed insulin analogue

27. Ejskjaer N, Rasmussen M, Kamp N et al. Comparison of thrice daily 'high' vs. 'medium' premixed insulin aspart with respect to evening and overnight glycaemic control in patients with type 2 diabetes. Diabetes Obes Metab 2003;5(6):438-45.
Did not compare a premixed insulin analogue to another antidiabetic agent

28. Gale E, Del Prato S. Emerging clinical uses for insulin lispro. Practical Diabetes International. 97;14(4 Suppl.):S4-S10.
No original data

29. Garber A J. Assessing the role of biphasic insulin aspart 30 as an effective and tolerable front-line therapy for type 2 diabetes. Clin Ther 2005;27 Suppl 2S39-41.
No original data

30. Garg S K. New insulin analogues. Diabetes Technol Ther 2005;7(5):813-7.
No original data

31. Groop L , Harno K , Tolppanen EM. The combination of insulin and sulphonylurea in the treatment of secondary drug failure in patients with type II diabetes. Acta Endocrinol 84;106(1):97-101.
Did not evaluate a premixed insulin analogue

32. Hamid Z, Simmons D L. Triple therapy in type 2 diabetes: insulin glargine or rosiglitazone added to combination therapy of sulfonylurea plus metformin in insulin-naive patients: response to Rosenstock et al. Diabetes Care 2006;29(10):2331; author reply 2332.
No original data

33. Herz M. Clinical update on Humalog Mix25 a novel pre-mixed formulation of insulin lispro and NPL. Int J Clin Pract Suppl 99;1048-13; discussion 18-20.
No original data

34. Home P D. Comment on: Nauck MA, Duran S, Kim D et al (2007) 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 50:259-267. Diabetologia 2007;50(7):1561-2.
No original data

35. Ishii H, Yamamura A, Malone J K. Quality-of-life (QOL) assessment of type 1 and type 2 diabetes mellitus patients in regard to insulin lispro mixture-25 and mixture-50 twice daily therapy. J. Jpn. Diabetes Soc. 2005;48(8):607-616.
Non-English article

36. Janka H U, Hogy B. Economic evaluation of the treatment of type 2 diabetes with insulin glargine based on the LAPTOP trial. Eur J Health Econ 2007;
Did not evaluate a premixed insulin

analogue

37. JiXiong X, Jianying L, Yulan C et al. The human insulin analog aspart can induce insulin allergy. Diabetes Care 2004;27(8):2084-5.
Does not apply to a key question

38. Jungmann E , Bolle J , Schmitz C et al. Intensified insulin therapy (IIT) in type II Diabetes mellitus: pre- or postprandial injection of aspart insulin? Medizinische Klinik 2004; 99:109.
Non-English article

39. Katahira M, Hara I, Nishizaki T. Insulin allergy decreased by Humulin S (Humulin R) and not by insulin aspart or Actrapid Penfill (Penfill R). Diabetic Med. 2005;22(10):1455-1457.
No original data

40. Kazda C M, Forst T, Gierhake C et al. Improving blood glucose and reducing incidence of hypoglycemia in type 2 diabetics using insulin lispro 25%/NPL 75%: verbesserung der blutglukoseeinstellung und senkung der hypoglykamierate bei typ-2-diabetikern unter insulin lispro 25. Diabetes Stoffwechsel 2003;12(5):233-238.
Non-English article

41. Kitowicz A, Criswell D F. Question: is insulin glargine more effective? J Okla State Med Assoc 2007;100(1):26-7.
No original data

42. Kitzmiller J L, Buchbinder A, Khoury J et al. Insulin lispro and the development of proliferative diabetic retinopathy during pregnancy (multiple letter). Am. J. Obstet. Gynecol. 2001;185(3):774-775.
No original data

43. Kitzmiller J L, Main E, Ward B et al. Insulin lispro and the development of proliferative diabetic retinopathy during pregnancy. Diabetes Care 99;22(5):874-6.
Did not evaluate a premixed insulin analogue

44. Koivisto V A. International experience with insulin lispro. Pract. Diabetes Int. 98;15(1 SUPPL.):S15-S17.
No original data

45. Koivisto V A, Tuominen J A, Ebeling P. Lispro Mix25 insulin as premeal therapy in type 2 diabetic patients. Diabetes Care 99;22(3):459-62.
Does not apply to a key question

46. Lee W C, Balu S, Cobden D et al. Medication adherence and the associated health-economic impact among patients with type 2 diabetes mellitus converting to insulin pen therapy: an analysis of third-party managed care claims data. Clin Ther 2006;28(10):1712-25; discussion 1710-1.
Did not compare a premixed insulin analogue to another antidiabetic agent

47. Levinson P D. Premixed or self-mixed insulin for elderly patients. Ann. Intern. Med. 93;118(Suppl. 3):80.
No original data

48. Lindholm A, Jensen L B, Home P D et al. Immune responses to insulin aspart and biphasic insulin aspart in people with type 1 and type 2 diabetes. Diabetes Care 2002;25(5):876-82.

Does not apply to a key question

49. Luddeke H J. Improving post-prandial control with Humalog and Humalog mixtures. Int J Clin Pract Suppl 2000;(112):23-8.
No original data

50. McCormack J, Bassett K. The evidence for insulin lispro. Canadian Medical Association 98;159(11):1353-5.
No original data

51. Mikhail N. The combined effect of triple therapy with rosiglitazone, metformin, and insulin aspart in type 2 diabetic patients: response to Poulsen et al. Diabetes Care 2004;27(7):1846-7; author reply 1847-8.
No original data

52. Mohn A, Marcovecchio M, Chiarelli F et al. Insulin analogues (multiple letters). New Engl. J. Med. 2005;352(17):1822-1824.
No original data

53. Nathan J P, Rosenberg J M. How are insulin glargine and insulin aspart different from the "older" insulins? Drug Topics 2000;144(22):41.
No original data

54. Nauck M A, Trautman M, Brodows R et al. Response to comment on: Nauck MA, Duran S, Kim D et al (2007) 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 50:259-267. Diabetologia 2007;50(7):1563-4.
No original data

55. Oosthuizen H. Insulin therapy in type 2 diabetes mellitus. J. Endocrinol. Metab. Diabetes S. Afr. 2003;8(3):72-78.
No original data

56. Panczel P, Hosszufalusi N, Horvath M M et al. Advantage of insulin lispro in suspected insulin allergy. Allergy 2000;55(4):409-10.
Exclude other reason

57. Peragallo-Dittko V. Insulin therapy for type 2 diabetes.. Diabetes Self-Management 2003;20(5):17.
No original data

58. Renner R , Vocke K , Hepp KD. Blood Glucose Profiles in Type I and Type II Diabetic Patients under Different Insulin Mixtures of BHI-Regular and BHI-NPH. Munchener Medizinische Wochenschrift 83;125(Suppl 1):57-62.
Non-English article

59. Roach P, Strack T, Arora V et al. Improved glycaemic control with the use of self-prepared mixtures of insulin lispro and insulin lispro protamine suspension in patients with types 1 and 2 diabetes. Int J Clin Pract 2001;55(3):177-82.
Did not evaluate a premixed insulin analogue

60. Robertson D. Achieving fasting and postprandial blood glucose control in type 2 diabetes. Br J Hosp Med (Lond) 2006;67(10):518-22.
No original data

61. Rubin R R, Peyrot M. Quality of life, treatment satisfaction, and treatment preference associated with use of a pen

device delivering a premixed 70/30 insulin aspart suspension (aspart protamine suspension/soluble aspart) versus alternative treatment strategies. Diabetes Care 2004;27(10):2495-7.
Exclude other reason

62. Schmoelzer I, de Campo A, Pressl H et al. Biphasic insulin aspart compared to biphasic human insulin reduces postprandial hyperlipidemia in patients with Type 2 diabetes. Exp Clin Endocrinol Diabetes 2005;113(3):176-81.
Does not apply to a key question

63. Schreiber S A, Russmann A. Insulin glargine and educational intervention in patients with type 2 diabetes in clinical practice: long-term improvement in glycaemic control without weight gain. Exp Clin Endocrinol Diabetes 2006;114(1):41-2.
No original data

64. Shichiri M, Kishikawa H, Ohkubo Y et al. Long-term results of the Kumamoto Study on optimal diabetes control in type 2 diabetic patients. Diabetes Care 2000;23 Suppl 2:B21-9.
Did not evaluate a premixed insulin analogue

65. Sridhar G R. Two regimens of twice-daily premix insulin analogue: an observational study. Diabetes Res Clin Pract 2006;71(1):105-7.
Did not compare a premixed insulin analogue to another antidiabetic agent

66. Swenson K, Brackenridge B. Lispro for type 2?. Diabetes Forecast 2000;53(7):81-83.
No original data

67. Swenson K, Brackenridge B. Lispro insulin for improved glucose control in obese patient with type 2 diabetes.. Diabetes Spectrum 98;11(1):13-15.
No original data

68. Thaware P, Howe J, Lawrence I G et al. Use of the rapid acting insulin analogue lispro and its protamine retarded from (Humalog Mix 25) in a clinical setting. Pract. Diabetes Int. 2004;21(9):329-333.
Did not compare a premixed insulin analogue to another antidiabetic agent

69. Valentine W J, Palmer A J, Lammert M et al. Long-term clinical and cost outcomes of treatment with biphasic insulin aspart 30/70 versus insulin glargine in insulin naive type 2 diabetes patients: cost-effectiveness analysis in the UK setting. Curr Med Res Opin 2005;21(12):2063-71.
No original data

70. Walczak I M. Lantus reduces blood glucose levels, less hypoglycemia in treatment of type 2 diabetes. Diabetes Technol Ther 2002;4(5):735-6.
No original data

71. Warren M L, Conway M J, Klaff L J et al. Postprandial versus preprandial dosing of biphasic insulin aspart in elderly type 2 diabetes patients. Diabetes Res Clin Pract 2004;66(1):23-9.
Did not compare a premixed insulin analogue to another antidiabetic agent

72. White J R. Insulin glargine clinical

trials. Clin Ther 2004;26(7):1179-81; discussion 1182-3.
No original data

73. Yasuda H, Nagata M, Moriyama H et al. Human insulin analog insulin aspart does not cause insulin allergy. Diabetes Care 2001;24(11):2008-9.
Did not evaluate a premixed insulin analogue

74. Zinman B. The pharmacokinetics of insulin analogues and pumps. Pract. Diabetes Int. 2001;18(5 Suppl.):S3-S4.
No original data

Previewing Only: You cannot submit data from this form

Previewing at Level 1

Refid: 1, Devries, J. H., Nattrass, M., and Pieber, T. R., Refining basal insulin therapy: what have we learned in the age of analogues?, *Diabetes Metab Res Rev*, 2007
State: Excluded, Level: 1

Save to finish later | Submit Data

1. Could this article apply to ANY of our key questions?

- Yes--potentially eligible
- No--not eligible

Clear Selection

Save to finish later | Submit Data

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Form Last Modified: Not available

Previewing Only: You cannot submit data from this form

Previewing at Level 2

Refid: 1, Devries, J. H., Nattrass, M., and Pieber, T. R., Refining basal insulin therapy: what have we learned in the age of analogues?, *Diabetes Metab Res Rev*, 2007
State: Excluded, Level: 1

Save to finish later | Submit Data

Premixed Insulin Analogues Abstract Review Form

1. Check box if non-English article

- ☐ **non-English** article

2. Exclude article because... **(check one or more)**

- ☐ no subjects **>=18 years old**
- ☐ no **original data** (e.g., is a review, commentary, etc.)
- ☐ study evaluates outcomes in **animals only** (no humans evaluated)
- ☐ not evaluating any people with **type 2 diabetes**, NIDDM (non-insulin dependent diabetes mellitus), or adult-onset diabetes
- ☐ evaluates none of the **premixed insulin analogues** in our review (insulin aspart 70/30, insulin lispro 75/25, or insulin lispro 50/50)
- ☐ does not **compare an FDA-approved premixed insulin analogue** to another medication or other comparison of interest (see below for acceptable list of comparisons)
- ☐ does not apply to any of the **key questions**
- ☐ other (specify:)

3. Unclear

- ☐ **Unclear or no abstract** (retrieve full article to decide)

This article may apply to at least one of the following key questions: **(check one of the comparisons in Q4 below.)**

KQ1. In adults age >= 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 (see below), compared with insulin regimens including, but not necessarily limited to the following:
1. Premixed human insulin preparations (NPH/Regular 70/30, NPH Regular 50/50)
2. Long acting insulin analogues (insulin detemir, insulin glargine) administered alone
3. Intermediate acting human insulin (NPH insulin) administered alone
4. Short acting human insulin (regular insulin) administered prandially
5. Rapid acting insulin analogues (insulin aspart, insulin glulisine, insulin lispro)

administered separately (prandially) with a long acting insulin analog (insulin detemir, insulin glargine)
KQ2. 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.
KQ3. Does the effectiveness or safety of new premixed insulin analogue regimens differ for the following sub-populations: 1. The elderly (>=65 years), very elderly (>=85 years) 2. Other demographic groups (ethnic or racial groups, sex) 3. Individuals with comorbid medical conditions 4. Individuals with limited life expectancy 5. Individuals with disabilities
KQ4. Does the effectiveness or safety of new premixed insulin analogue regimens differ for individuals on oral 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)?

4. For studies that could apply to a key question, please indicate to what the premixed insulin analogue (insulin aspart 70/30, insulin lispro 75/25, insulin lispro 50/50) is compared:

- ☐ **Premixed human insulin preparations** (NPH/Regular 70/30, NPH Regular 50/50)
- ☐ **Long acting insulin analogues** (insulin detemir, insulin glargine) administered alone
- ☐ **Intermediate acting human insulin** (NPH insulin) administered alone
- ☐ **Short acting human insulin** (regular insulin) administered prandially
- ☐ **Rapid acting insulin analogues** (insulin aspart, insulin glulisine, insulin lispro) administered separately with a long acting insulin analog (insulin detemir, insulin glargine)
- ☐ **Oral hypoglycemic agent** (thiazolidinediones (rosiglitazone and pioglitazone), biguanides (metformin and metformin XR), second generation sulfonylureas (glibenclamide, glipizide, glipizide GITS, glyburide, and glimepiride), meglitinides (nateglinide and repaglinide), and alpha-glucosidase inhibitors (acarbose and miglitol)) Note: we are not including oral hypoglycemic agents that are not approved by the FDA (e.g., gliclazide and voglibose)
- ☐ **Placebo or diet**
- ☐ **Another type of insulin** that is FDA-approved and not specified above (e.g., inhaled insulin)
- ☐ **Another type of antidiabetic medication** that is FDA-approved and not specified above (e.g., exenetide)
- ☐ Some **combination** of antidiabetic medications
- ☐ **Usual care** not otherwise specified

5. Comments

Enlarge Shrink

Save to finish later | Submit Data

Form took 0.109375 seconds to render
Form Creation Date: Not available
Form Last Modified: Not available

Previewing Only: You cannot submit data from this form

Previewing at Level 3

Refid: 1, Devries, J. H., Nattrass, M., and Pieber, T. R., Refining basal insulin therapy: what have we learned in the age of analogues?, *Diabetes Metab Res Rev*, 2007
State: Excluded, Level: 1

Save to finish later | Submit Data

Premixed Insulin Analogues Article Review Form

1. Check box if non-English article

- [ ] **non-English** article

2. Exclude article because... **(check one or more)**

- [ ] no subjects **>=18 years old**
- [ ] no **original data** (e.g., is a review, commentary, etc.)
- [ ] study evaluates outcomes in **animals only** (no humans evaluated)
- [ ] not evaluating any people with **type 2 diabetes**, NIDDM (non-insulin dependent diabetes mellitus), or adult-onset diabetes (Note: Exclude if less than 75% of the total sample has type 2 diabetes AND there is not a separate analysis for type 2 diabetes)
- [ ] evaluates none of the **premixed insulin analogues** in our review (insulin aspart 70/30, insulin lispro 75/25, or insulin lispro 50/50)
- [ ] does not **compare an FDA-approved premixed insulin analogue** to another medication or other comparison of interest (see below for acceptable list of comparisons)
- [ ] does not apply to any of the **key questions**
- [ ] other (specify:)

This article may apply to at least one of the following key questions: **(check one of the comparisons in Q4 below.)**

KQ1. In adults age >= 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 (see below), compared with insulin regimens including, but not necessarily limited to the following:
1. Premixed human insulin preparations (NPH/Regular 70/30, NPH Regular 50/50)
2. Long acting insulin analogues (insulin detemir, insulin glargine) administered alone
3. Intermediate acting human insulin (NPH insulin) administered alone
4. Short acting human insulin (regular insulin) administered prandially
5. Rapid acting insulin analogues (insulin aspart, insulin glulisine, insulin lispro) administered separately (prandially) with a long acting insulin analog (insulin detemir, insulin glargine)

KQ2. 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.

KQ3. Does the effectiveness or safety of new premixed insulin analogue regimens differ for the following sub-populations:
1. The elderly (>=65 years), very elderly (>=85 years)
2. Other demographic groups (ethnic or racial groups, sex)
3. Individuals with comorbid medical conditions
4. Individuals with limited life expectancy
5. Individuals with disabilities

KQ4. Does the effectiveness or safety of new premixed insulin analogue regimens differ for individuals on oral 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)?

Outcomes:

a. Effectiveness in achieving optimal glycemic control as measured by
- Hemoglobin A1c
- Fasting blood glucose
- 2-hour postprandial blood glucose

b. Effectiveness in decreasing complications of type 2 diabetes
- Decrease in renal function as measured by changes in microalbuminuria, development of chronic kidney disease (GFR<60ml/min)
- Development and progression of diabetic retinopathy
- Neuropathy
- Cardiovascular morbidity and mortality
- All-cause mortality

c. Safety and adverse events
- Hypoglycemia
- Weight/BMI change
- Injections site skin reactions
- Other serious adverse events
- Ratio of dropouts in the comparative groups

d. Improvements in quality of life indicators (as measured on a validated scale)

e. Adherence to treatment

3. For studies that could apply to a key question, please indicate to what the premixed insulin analogue (insulin aspart 70/30, insulin lispro 75/25, insulin lispro 50/50) is compared:

- ☐ **Premixed human insulin preparations** (NPH/Regular 70/30, NPH Regular 50/50)
- ☐ **Long acting insulin analogues** (insulin detemir, insulin glargine) administered alone
- ☐ **Intermediate acting human insulin** (NPH insulin) administered alone
- ☐ **Short acting human insulin** (regular insulin) administered prandially
- ☐ **Rapid acting insulin analogues** (insulin aspart, insulin glulisine, insulin lispro) administered separately with a long acting insulin analog (insulin detemir, insulin glargine)
- ☐ **Oral hypoglycemic agent** (thiazolidinediones (rosiglitazone and pioglitazone), biguanides (metformin and metformin XR), second generation sulfonylureas (glibenclamide, glipizide, glipizide GITS, glyburide, and glimepiride), meglitinides (nateglinide and repaglinide), and alpha-glucosidase inhibitors (acarbose and miglitol)) Note: we are not including oral hypoglycemic agents that are not approved by the FDA (e.g., gliclazide and voglibose)
- ☐ **Placebo or diet**
- ☐ **Another type of insulin** that is FDA-approved and not specified above (e.g., inhaled insulin)
- ☐ **Another type of antidiabetic medication** that is FDA-approved and not specified above (e.g., exenetide)
- ☐ Some **combination** of antidiabetic medications
- ☐ **Usual care** not otherwise specified

4. Comments

Enlarge Shrink

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Form Creation Date: Not available
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Previewing at Level 4

Refid: 1, Devries, J. H., Nattrass, M., and Pieber, T. R., Refining basal insulin therapy: what have we learned in the age of analogues?, *Diabetes Metab Res Rev*, 2007
State: Excluded, Level: 1

Save to finish later | Submit Data

Premixed Insulin Analogues

General Form

Study Design Characteristics

Fill out this form for ALL included studies.

1. What was the study question/objective/hypothesis?

Enlarge Shrink

2. In what country does the study occur? **(check all that apply)**

- [ ] United States
- [ ] Canada
- [ ] United Kingdom
- [ ] Other (specify:)

3. What study design is used? **(check only one response)**

- ( ) Randomized controlled trial
- ( ) Non-randomized trial
- ( ) Cross-sectional study
- ( ) Retrospective/non-concurrent case-control
- ( ) Nested case-control (e.g. conducted within a larger cohort study)
- ( ) Other

Clear Selection

4. If this is a trial, then please mark any of the following. **(check all that apply)**

- [ ] Factorial design
- [ ] Parallel arms
- [ ] Cross-over design
- [ ] Placebo-controlled
- [ ] Other (specify:)
- [ ] None of the above apply to the trial/Not applicable (not a trial)

5. If this is a crossover trial, was there a washout period? **(check only one response)**

- ( ) Yes (specify how long in days:)
- ( ) No
- ( ) Not reported
- ( ) NA

Clear Selection

6. Was pharmaceutical company support (funding or drug given for free) received to conduct the study? **(check only one response)**

- Yes
- No
- Not reported

Clear Selection

The mean/median follow-up duration was: (Record your answer in weeks. If reported separately by groups then please list in other by group.)

	Weeks	Other (specify:)	Not reported
7. Mean			
8. Median			
9. Intended duration of followup			

10. Was a subgroup analysis conducted?

- Yes (specify which subgroups were analyzed:)
- No

Clear Selection

11. Please indicate the exclusion criteria. **(If the characteristic is listed as an exclusion criteria, please check the exclusion box. Please list all inclusion criteria as exclusion (i.e., if study includes only patients with coronary artery disease, specify no coronary artery disease in "other" and click exclusion.)**

- Age (specify:)
- Male
- Female
- Any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)
- Any kidney disease (such as microalbuminuria, macroalbuminuria, or elevated creatinine, GFR, or creatinine clearance)
- History of cardiovascular disease (e.g., myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina)
- History of insulin treatment
- History of oral antidiabetic agents
- Neuropathy
- Retinopathy
- HbA1c (specify:)
- Fasting blood glucose (specify:)
- No type 2 diabetes
- Type 1 diabetes
- BMI (specify:)
- Other (specify:)
- Other (specify:)
- Other (specify:)
- Other (specify:)
- Other (specify:)
- Other (specify:)

12. Comments:

Enlarge Shrink

13. References

Enlarge Shrink

Thank you very much!

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Form Last Modified: Nov 9 2007 8:29AM

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Previewing at Level 5

Refid: 1, Devries, J. H., Nattrass, M., and Pieber, T. R., Refining basal insulin therapy: what have we learned in the age of analogues?, *Diabetes Metab Res Rev*, 2007
State: Excluded, Level: 1

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Premixed Insulin Analogues

General Form

Intervention Form

Please fill out this form for all included studies.

In the column "Dosing," if there was no change in dose throughout the study, select"Fixed." If the dose varied, select "Varied."

In the column "Dose," please enter the dose, including the units. If available, enter the mean dose and range of dose.

In the column "Timing," select "Breakfast" if the dose was given with breakfast or in the morning. Select "Lunch" if the dose was given with lunch or around noon. Select "Dinner" if the dose was given with dinner or in the evening. Select "Bedtime" if the dose was given in the late evening. If the article specifies the number of times per day but does not indicate when, select "Other" and enter the number of times per day. Please use QD (once per day), BID (twice per day), TID (three times per day) and QID (four times per day).

In the column "Duration of use," enter the number for days, weeks, months, and years.

If a test meal is given, describe it under comments.

Please indicate the intervention used by Group 1.

Intervention	Dosing	Dose (include units)	Timing	Duration of use
Please Select	Fixed Varied Unclear Clear Selection	Starting dose Mean dose Lower limit of range Upper limit of range	breakfast lunch dinner bedtime other (specify:) not specified	days weeks months years other unclear
Please Select	Fixed Varied Unclear Clear Selection	Starting dose Mean dose Lower limit of range Upper limit of range	breakfast lunch dinner bedtime other (specify:) not specified	days weeks months years other unclear
Diet and/or exercise	NA	NA	NA	days weeks months years other unclear
Usual care	NA	NA	NA	days weeks months years other unclear
Placebo	NA	NA	NA	days weeks months years other unclear

Other (specify:)	Fixed Varied Unclear Clear Selection	Starting dose Mean dose Lower limit of range Upper limit of range	breakfast lunch dinner bedtime other (specify:) not specified	days weeks months years other unclear
Other (specify:)	Fixed Varied Unclear Clear Selection	Starting dose Mean dose Lower limit of range Upper limit of range	breakfast lunch dinner bedtime other (specify:) not specified	days weeks months years other unclear
Other (specify:)	Fixed Varied Unclear Clear Selection	Starting dose Mean dose Lower limit of range Upper limit of range	breakfast lunch dinner bedtime other (specify:) not specified	days weeks months years other unclear

Please indicate the intervention used by Group 2.

Intervention	Dosing	Dose (include units)	Timing	Duration of use
Please Select	Fixed Varied Unclear Clear Selection	Starting dose Mean dose Lower limit of range Upper limit of range	breakfast lunch dinner bedtime other (specify:) not specified	days weeks months years other unclear
Please Select	Fixed Varied Unclear Clear Selection	Starting dose Mean dose Lower limit of range Upper limit of range	breakfast lunch dinner bedtime other (specify:) not specified	days weeks months years other unclear
Diet and/or exercise	NA	NA	NA	days weeks months years other unclear
Usual care	NA	NA	NA	days weeks months years other unclear
Placebo	NA	NA	NA	days weeks months

				years other unclear
Other (specify:)	Fixed Varied Unclear Clear Selection	Starting dose Mean dose Lower limit of range Upper limit of range	breakfast lunch dinner bedtime other (specify:) not specified	days weeks months years other unclear
Other (specify:)	Fixed Varied Unclear Clear Selection	Starting dose Mean dose Lower limit of range Upper limit of range	breakfast lunch dinner bedtime other (specify:) not specified	days weeks months years other unclear
Other (specify:)	Fixed Varied Unclear Clear Selection	Starting dose Mean dose Lower limit of range Upper limit of range	breakfast lunch dinner bedtime other (specify:) not specified	days weeks months years other unclear

Please indicate the intervention used by Group 3.

Intervention	Dosing	Dose (include units)	Timing	Duration of use
Please Select	Fixed Varied Unclear Clear Selection	Starting dose Mean dose Lower limit of range Upper limit of range	breakfast lunch dinner bedtime other (specify:) not specified	days weeks months years other unclear
Please Select	Fixed Varied Unclear Clear Selection	Starting dose Mean dose Lower limit of range Upper limit of range	breakfast lunch dinner bedtime other (specify:) not specified	days weeks months years other unclear
Diet and/or exercise	NA	NA	NA	days weeks months years other unclear
Usual care	NA	NA	NA	days weeks months years other

				unclear
Placebo	NA	NA	NA	days weeks months years other unclear
Other (specify:)	Fixed Varied Unclear Clear Selection	Starting dose Mean dose Lower limit of range Upper limit of range	breakfast lunch dinner bedtime other (specify:) not specified	days weeks months years other unclear
Other (specify:)	Fixed Varied Unclear Clear Selection	Starting dose Mean dose Lower limit of range Upper limit of range	breakfast lunch dinner bedtime other (specify:) not specified	days weeks months years other unclear
Other (specify:)	Fixed Varied Unclear Clear Selection	Starting dose Mean dose Lower limit of range Upper limit of range	breakfast lunch dinner bedtime other (specify:) not specified	days weeks months years other unclear

Please indicate the intervention used by Group 4.

Intervention	Dosing	Dose (include units)	Timing	Duration of use
Please Select	Fixed Varied Unclear Clear Selection	Starting dose Mean dose Lower limit of range Upper limit of range	breakfast lunch dinner bedtime other (specify:) not specified	days weeks months years other unclear
Please Select	Fixed Varied Unclear Clear Selection	Starting dose Mean dose Lower limit of range Upper limit of range	breakfast lunch dinner bedtime other (specify:) not specified	days weeks months years other unclear
Diet and/or exercise	NA	NA	NA	days weeks months years other unclear
	NA	NA	NA	

Usual care				days weeks months years other unclear
Placebo	NA	NA	NA	days weeks months years other unclear
Other (specify:)	Fixed Varied Unclear Clear Selection	Starting dose Mean dose Lower limit of range Upper limit of range	breakfast lunch dinner bedtime other (specify:) not specified	days weeks months years other unclear
Other (specify:)	Fixed Varied Unclear Clear Selection	Starting dose Mean dose Lower limit of range Upper limit of range	breakfast lunch dinner bedtime other (specify:) not specified	days weeks months years other unclear
Other (specify:)	Fixed Varied Unclear Clear Selection	Starting dose Mean dose Lower limit of range Upper limit of range	breakfast lunch dinner bedtime other (specify:) not specified	days weeks months years other unclear

125. If the dose varied, please indicate the target HbA1c or glucose values.

HbA1c

fasting glucose

other glucose measure

126. Comments

Enlarge Shrink

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Form took 0.96875 seconds to render
Form Creation Date: Sep 11 2007 8:30AM
Form Last Modified: Oct 12 2007 3:29PM

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Previewing at Level 6

Refid: 1, Devries, J. H., Nattrass, M., and Pieber, T. R., Refining basal insulin therapy: what have we learned in the age of analogues?, *Diabetes Metab Res Rev*, 2007
State: Excluded, Level: 1

Save to finish later | Submit Data

Premixed Insulin Analogues

General Form

Study Population Characteristics

Fill out this form for ALL included studies.

Please fill in the study population characteristics (age, gender, race/ethnicity, BMI, HgbA1c, and duration of diabetes) below. (NOTE: There are separate lines for recording the N and the percent.)

You do NOT need to record standard errors or standard deviations for these measures.

For crossover studies, record only the first group.

Please record the premixed insulin analogues as Groups 1 and 2; record all other antidiabetic medications as Groups 3 and 4.

Total N at Enrollment

	Group 1	Group 2	Group 3	Group 4	Total
1. Name of group					
2. Total N for **enrollment**					

Age

	Group 1	Group 2	Group 3	Group 4	Total
3. Mean age					
4. Age range					

Specify other age category	Group 1	Group 2	Group 3	Group 4	Total
5. Other age					
6. Other age					
7. Other age					
8. Other age					

Male

	Group 1	Group 2	Group 3	Group 4	Total
9. N					
10. %					

Race/ethnicity

	Group 1	Group 2	Group 3	Group 4	Total
11. African American (N)					
12. African American (%)					
13. Caucasian (N)					
14. Caucasian (%)					
15. Asian or Asian American (N)					
16. Asian or Asian American (%)					
17. Hispanic/Latino (N)					
18. Hispanic/Latino (%)					

Specify other race	Group 1	Group 2	Group 3	Group 4	Total
19. Other race/ethnicity (N)					
20. Other race/ethnicity (%)					
21. Other race/ethnicity (N)					
22. Other race/ethnicity (%)					

BMI/Weight

	Group 1	Group 2	Group 3	Group 4	Total
23. Mean BMI (kg/m2)					
24. Mean weight (kg)					

Specify other weight/BMI category	Group 1	Group 2	Group 3	Group 4	Total
25. Other weight/BMI					
26. Other weight/BMI					

27. Other weight/BMI					
28. Other weight/BMI					

HbA1c

	Group 1	Group 2	Group 3	Group 4	Total
29. Mean HbA1c(%)					
30. Mean HbA1 (%)					

	Specify unit	Group 1	Group 2	Group 3	Group 4	Total
31. Mean fasting plasma glucose						

	Specify other hemoglobin category	Group 1	Group 2	Group 3	Group 4	Total
32. Other hemoglobin						
33. Other hemoglobin						
34. Other hemoglobin						
35. Other hemoglobin						

Duration of Diabetes

	Group 1	Group 2	Group 3	Group 4	Total
36. Mean duration of diabetes (in years)					

	Specify other duration of diabetes	Group 1	Group 2	Group 3	Group 4	Total
37. Other duration of diabetes measures						

Previous treatments used

38. Were patients insulin naive?

- Yes
- No
- Not reported

Clear Selection

	Group 1	Group 2	Group 3	Group 4	Total
39. Previous use of insulin (n)					
40. Previous use of insulin (%)					
41. Previous use of oral antidiabetics (n)					
42. Previous use of oral antidiabetics (%)					
43. Previous use of insulin and oral antidiabetics (n)					
44. Previous use of insulin and oral antidiabetics (%)					

Other key characteristic that was different between randomized groups

	Specify other characteristic	Group 1	Group 2	Group 3	Group 4	Total
45. Other key characteristic						
46. Other key characteristic						
47. Other key characteristic						
48. Other key characteristic						

49. Comments:

Enlarge Shrink

Thank you very much!

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Form Creation Date: Not available
Form Last Modified: Oct 25 2007 10:03AM

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Previewing at Level 7

Refid: 1, Devries, J. H., Nattrass, M., and Pieber, T. R., Refining basal insulin therapy: what have we learned in the age of analogues?, *Diabetes Metab Res Rev*, 2007
State: Excluded, Level: 1

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Premixed Insulin Analogues
Outcomes Form

Fill out this form for ALL included studies.

1. Outcome of interest being reported on this form: **(check only one response)**

- HbA1c
- HbA1
- Total glycated hemoglobin
- 2-hour postprandial glucose - after breakfast
- 2-hour postprandial glucose - after dinner
- Fasting plasma glucose - morning
- Fasting plasma glucose - dinner
- All-cause mortality
- Cardiovascular mortality – fatal MI
- Cardiovascular mortality – fatal stroke
- Cardiovascular mortality – other (specify:)
- Cardiovascular mortality – not specified
- Cardiovascular morbidity – non-fatal myocardial infarction
- Cardiovascular morbidity – non-fatal stroke
- Cardiovascular morbidity – other (specify:)
- Cardiovascular morbidity – not specified
- Diabetic nephropathy (specify definition:)
- Urinary microalbumin
- Diabetic retinopathy (define:)
- Diabetic neuropathy (define:)
- Hypoglycemia – serious (specify definition:)
- Hypoglycemia – moderate (specify definition:)
- Hypoglycemia – mild (specify definition:)
- Hypoglycemia – daytime (specify definition:)
- Hypoglycemia – nighttime (specify definition:)
- Hypoglycemia – other (specify definition:)
- Hypoglycemia – not specified
- Weight/BMI change
- Injection site skin reactions
- Total serious adverse events
- Other serious reported adverse events (specify:)
- Quality of life
- Adherence to treatment
- Other (specify:)

Clear Selection

2. For quality of life outcomes, how was quality of life assessed?

- Insulin Treatment Satisfaction Questionnaire
- Short Form Health Survey (SF-36)
- Euro-QOL (EQ-5D)
- Activities of daily living (ADL)
- Instrumental activities of daily living (IADL)
- World Health Organization Diabetes Treatment Satisfaction Questionnaire (WHO-DTSQ)
- World Health Organization Well-Being Questionnaire (WHO-WBQ)
- Other (specify:)

3. For adherence outcomes, how was adherence to treatment assessed?

- percent patient adherence determined by log/diary
- percent patient adherence determined by questionnaire
- percent patient adherence determined by interview
- percent patient adherence determined by pill count
- percent patient adherence determined by physician rating
- medication self-report inventory
- Medication Prescription Ratio (MPR; sum of total days supply divided by total # days from first prescription fill date to the first day of last prescription fill date)
- % dispensed / % prescribed
- % obtained / % prescribed
- Other (specify:)
- Not specified

4. What units were used? **(check only one response)**

- mmol/L

- umol/L
- mg/dL
- %
- kg
- kg/m2
- mean score
- mean ratio
- Other (specify:)

Clear Selection

5. Were any of the analyses intention-to-treat? **(If an intention-to-treat and other analyses are both reported, report only the intention-to-treat analysis.)**

- Yes
- No
- Not reported

Clear Selection

INCIDENCE

	Number of people in analysis	Numerator	Denominator (if person-time used or # of events in a certain period): enter amount of time below and indicate time period here. days / weeks / months / years / person-years / other (specify:) / not applicable Clear Selection	P-value
Group 1		# with 1 or more events: % with 1 or more events: Specify other numerator type: Specify other numerator value:		
Group 2		# with 1 or more events: % with 1 or more events: Specify other numerator type: Specify other numerator value:		
Group 3		# with 1 or more events: % with 1 or more events: Specify other numerator type: Specify other numerator value:		
Group 4		# with 1 or more events: % with 1 or more events: Specify other numerator type: Specify other numerator value:		

MEASURE OF ASSOCIATION FOR COMPARISON OF OUTCOME BETWEEN STUDY GROUPS

	Point estimate Relative risk / Relative hazard / Odds ratio / Risk difference / Other (specify:) Clear Selection	Measure of variability SE / SD / Other (specify:) Clear Selection	95% CI	N for analysis	P-value
Group 1	mark if reference group		lower limit upper limit		
Group 2	mark if reference group		lower limit upper limit		
Group 3	mark if reference group		lower limit upper limit		
Group 4	mark if reference group		lower limit upper limit		

BASELINE MEASURES OF OUTCOME

	Point Estimate Mean / Median	Measure of Variability SE / SD	95% CI / IQR Clear Selection	N for analysis	P-value

	Other (specify:) Clear Selection	Other (specify:) Clear Selection			
Group 1			lower limit upper limit		
Group 2			lower limit upper limit		
Group 3			lower limit upper limit		
Group 4			lower limit upper limit		

FINAL MEASURES OF OUTCOME

	Point Estimate Mean Median Other (specify:) Clear Selection	Measure of Variability SE SD Other (specify:) Clear Selection	95% CI IQR Clear Selection	N for analysis	P-value
Group 1			lower limit upper limit		
Group 2			lower limit upper limit		
Group 3			lower limit upper limit		
Group 4			lower limit upper limit		

MEAN DIFFERENCE FROM BASELINE MEASURES OF OUTCOME

	Point Estimate Mean Median Other (specify:) Clear Selection	Measure of Variability SE SD Other (specify:) Clear Selection	95% CI IQR Clear Selection	N for analysis	P-value
Group 1			lower limit upper limit		
Group 2			lower limit upper limit		
Group 3			lower limit upper limit		
Group 4			lower limit upper limit		

MEAN DIFFERENCE FROM OTHER GROUP MEASURES OF OUTCOME

	Point Estimate Mean Median Other (specify:) Clear Selection	Measure of Variability SE SD Other (specify:) Clear Selection	95% CI IQR Clear Selection	N for analysis	P-value
Group 1			lower limit upper limit		
Group 2			lower limit upper limit		
Group 3			lower limit upper limit		
Group 4			lower limit upper limit		

OTHER MEASURES

	Other measure	Other measure
Group 1		
Group 2		
Group 3		

Group 4		

147. Are the results adjusted for...?

- [ ] age
- [ ] gender
- [ ] race
- [ ] BMI
- [ ] glycemic control
- [ ] comorbidities
- [ ] duration of diabetes
- [ ] Other
- [ ] Other
- [ ] Other
- [ ] Other
- [ ] Other
- [ ] Other
- [ ] Other
- [ ] Other
- [ ] Results are not adjusted
- [ ] Not applicable (i.e., RCT)

148. Comments:

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Form Creation Date: Sep 17 2007 12:47PM
Form Last Modified: Oct 31 2007 9:47AM

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Previewing at Level 27

Refid: 1, Devries, J. H., Nattrass, M., and Pieber, T. R., Refining basal insulin therapy: what have we learned in the age of analogues?, *Diabetes Metab Res Rev*, 2007
State: Excluded, Level: 1

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Premixed Insulin Analogues
Quality Form

Fill out this form for all studies.

1. Were there clearly stated study questions, objectives, or hypotheses?

- Yes
- No

Clear Selection

Randomization Scheme (Answer Q2 and Q3 if RCT. Otherwise, skip to Q4.)

2. Was the study described as randomized (this includes the use of words such as randomly, random, and randomization)?

- Yes (1)
- No (0)
- Not Reported/Can't Tell (0)

Clear Selection

3. If yes to q2, was the randomization scheme described AND appropriate?

- Yes: (1) appropriate randomization is if each study participant is allowed to have the same chance of receiving each intervention and the investigators could not predict which treatment was next.
- No: (-1) randomization described AND inappropriate (e.g. methods of allocation using date of birth, date of admission, hospital numbers, or alteration should not be regarded as appropriate)
- No: (0) randomization methods not described

Clear Selection

Selection (Answer Q4-Q7 if cohort. Otherwise, skip to Q8.)

4. Selection of the comparison group

- drawn from the same community as the main study group (+1)
- drawn from a different source
- no description of the derivation of the non-exposed cohort

Clear Selection

5. Ascertainment of exposure

- secure record (e.g., medical records) (+1)
- structured interview (+1)
- written self report
- no description
- other

Clear Selection

6. Demonstration that outcome of interest was not present at start of study

- Yes (+1)
- No
- Not applicable

Clear Selection

Comparability

7. Did the study adjust for key confounders (e.g., age, sex, race, comorbidities, glycemic control, and duration of diabetes)?

- ○ study controls for all or most factors (>50%)
- ○ study controls for only a few factors (<50%)
- ○ study does not control for any of these factors

Clear Selection

Blinding

8. Were the following blinded?

- ☐ Patients
- ☐ Providers
- ☐ Outcome assessors

Outcome

9. Assessment of primary outcome(s) **(check all that apply)**

- ☐ independent blind assessment or objective measurement such as HbA1c (+1)
- ☐ medical record review (+1)
- ☐ self report
- ☐ no description

10. Was followup long enough for outcomes to occur

- ○ Yes (e.g., at 1 week for short term outcomes such as FBG or 2-hr PPG; 3 months for intermediate outcomes such as HbA1c; 1 years for clinical/hard outcomes) (+1)
- ○ No

Clear Selection

11. Adequacy of followup of cohorts

- ○ complete followup - all subjects accounted for (+1)
- ○ subjects lost to followup unlikely to introduce bias - small number (< 10%) lost to followup, or description provided of those lost (+1)
- ○ lost to followup rate > 10% and no description of those lost
- ○ no statement

Clear Selection

12. Was there a description of withdrawals and drop-outs?

- ○ Yes: (1) the number and the reasons for withdrawals in each group must be stated or state that there were no withdrawals. If subjects were not included in the analysis, they must state the number and reasons for not including them in the analysis.
- ○ No (0)

Clear Selection

Discussion

13. Are the main conclusions reflective of the results?

- ○ Yes
- ○ Partially
- ○ No

Clear Selection

Funding/Conflict of Interest

14. Indicate the funding source.

- ○ pharmaceutical/industry
- ○ non-pharmaceutical

- not stated

Clear Selection

15. Was there a statement of conflict of interest?

- Yes, authors reported a conflict
- Yes, authors reported **no** conflict
- No description of conflict of interest

Clear Selection

Overall Quality Rating

16. Please rate the overall quality of the study.

- **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 it is not sufficient 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.

Clear Selection

17. Comments

Enlarge Shrink

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Form Last Modified: Nov 7 2007 1:32PM

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Previewing at Level 28

Refid: 1, Devries, J. H., Nattrass, M., and Pieber, T. R., Refining basal insulin therapy: what have we learned in the age of analogues?, *Diabetes Metab Res Rev*, 2007
State: Excluded, Level: 1

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Premixed Insulin Analogues
Applicability Form

Fill out this form for ALL included studies.

Source of population from which subjects were enrolled in the study. (Check all that apply.)

1. Source	2. University affiliation
☐ Inpatient/hospital	☐ University affiliated
☐ Outpatient clinics	☐ Non-university affiliated
☐ Subspecialty clinics	☐ Not reported
☐ Community	
☐ Other _____	
☐ Not reported	

3. Percent of patients enrolled to patients screened for the trial

- ○ Greater than or equal to 50% of the screened patients were enrolled
- ○ Less than 50% of the screened patients were enrolled
- ○ Not reported

Clear Selection

4. Were there any run-in periods in which >10% of patients were excluded based on either poor compliance, poor treatment response, or side effects?

- ○ Yes
- ○ No
- ○ Not applicable (i.e., no run-in period)

Clear Selection

Were the demographic characteristics of patients in the study representative of the general US diabetic population (please use NHANES 6-year survey from 1999-2004 as baseline for general US population [Valdez R, 2007]) (within a 50% change is acceptable).

5. Sex [NHANES survey had 49% males]

- ○ Representative
- ○ Not representative – Specify _____
- ○ Not reported

Clear Selection

6. Age [NHANES survey had 1.4% between the ages of 18 and 34 years; 5.1% between 35 and 44 years; 10.8% between the ages of 45 and 54 years; 16.4% between the ages of 55 and 64 years; and 23.1% were 64+]

- ○ Representative
- ○ Not representative – Specify _____
- ○ Not reported

Clear Selection

7. Race and ethnicity [NHANES survey had 53% whites; 22% blacks; and 25% Mexican Americans]

- Representative
- Not representative – Specify
- Not reported

Clear Selection

8. Was the spectrum of illness severity representative of all stages of illness? (For example, if only newly diagnosed patients were enrolled, the answer would be "no.")

- Yes
- No - Specify
- Not reported

Clear Selection

9. Does the dose, schedule, or the route of administration reflect current clinical practice or can it be easily adopted in current clinical practice?

- Yes for dose, schedule, and route of administration
- Yes for only 2 of the 3
- Yes for only 1 of the 3
- No for all three

Clear Selection

10. If interventions or monitoring were used to promote adherence to the treatment or improve clinical outcomes, did those interventions reflect current clinical practice or can they be easily adopted in current clinical practice? (this includes monitoring of labs, or frequent clinical visits)

- Yes
- No - Specify
- Not applicable

Clear Selection

11. Was the employed alternative therapy (comparator) one of the best alternative therapies available?

- Yes
- No - Specify

Clear Selection

12. Was the comparator used at adequate dose, interval, and schedule?

- Yes
- No - Specify
- Not reported

Clear Selection

13. Did the trial measure any important clinical outcomes (such as mortality, diabetic complications)?

- Yes
- No

Clear Selection

14. Did the trial report on at least a few of the clinically important individual adverse outcomes?

- Yes
- No
- Adverse outcomes not reported

Clear Selection

15. Was the trial performed in a healthcare system where the standards of care differ markedly from US?

- Yes

No

Clear Selection

16. Comments:

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Evidence Table 1. Grading of the body of evidence of the effects of premixed insulin analogues compared to other diabetes medications for each outcome

	Fasting plasma glucose					
	Premixed vs. long-acting insulin analogues	**Premixed vs. rapid-acting insulin analogues**	**Premixed vs. rapid-acting + long-acting insulin analogues**	**Premixed insulin analogues vs. premixed human insulin**	**Premixed insulin analogues vs. NPH**	**Premixed insulin analogues vs. noninsulin antidiabetic agents**
Quantity of evidence: Number of studies	10	2	1	9	2	8
Range of sample sizes	20-469	107-473	145	25-177	93-403	49-597
Quality and consistency of evidence: Were study designs mostly RCTs (high quality), non-RCTs (medium quality), observational studies (low quality), or about a 50:50 mix of experimental and observational (medium quality)?	High	High	Moderate	High	High	High
Did the studies have serious (-1) or very serious (-2) limitations in quality? (Enter 0 if none)	0	0	0	0	0	0
Did the studies have important inconsistency? (-1)	0	-1	0	-1	0	-1
Was there some (-1) or major (-2) uncertainty about the directness (i.e. extent to which the people, interventions and outcomes are similar to those of interest)?	-1	0	0	0	0	-1
Were data imprecise or sparse? (-1) (i.e. lack of data or very wide confidence intervals that may change conclusions)	0	0	0	0	0	0
Did the studies have high probability of reporting bias? (-1)	0	0	-1	0	0	0
Did the studies show strong evidence of association between intervention and outcome? ("strong" if significant relative risk or odds ratio > 2 based on consistent evidence from 2 or more studies with no plausible confounders (+1); "very strong" if significant relative risk or odds ratio > 5 based on direct evidence with no major threats to validity (+2)) - use your clinical judgment for absolute differences.	0	0	0	0	0	0
Did the studies have evidence of a dose-response gradient? (+1)	0	0	0	0	0	0
Did the studies have unmeasured plausible confounders that most likely reduced the magnitude of the observed association? (+1)	0	0	0	0	0	0
Overall grade of evidence (high, moderate, low)	Moderate	Low	Low	Moderate	Low	Moderate

High = further research is very unlikely to change our confidence in the estimates; moderate = further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate; low = further research is likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate; very low = any estimate of effect is very uncertain.

Evidence Table 1. Grading of the body of evidence of the effects of premixed insulin analogues compared to other diabetes medications for each outcome (continued)

	Pre-dinner plasma glucose					
	Premixed vs. long-acting insulin analogues	**Premixed vs. rapid-acting insulin analogues**	**Premixed vs. rapid-acting + long-acting insulin analogues**	**Premixed insulin analogues vs. premixed human insulin**	**Premixed insulin analogues vs. NPH**	**Premixed insulin analogues vs. noninsulin antidiabetic agents**
Quantity of evidence: Number of studies	7	3	0	7	1	6
Range of sample sizes	20-469	106-474	NA	25-187	394	49-501
Quality and consistency of evidence: Were study designs mostly RCTs (high quality), non-RCTs (medium quality), observational studies (low quality), or about a 50:50 mix of experimental and observational (medium quality)?	High	High	NA	High	High	High
Did the studies have serious (-1) or very serious (-2) limitations in quality? (Enter 0 if none)	0	0	NA	0	0	0
Did the studies have important inconsistency? (-1)	0	0	NA	0	0	0
Was there some (-1) or major (-2) uncertainty about the directness (i.e. extent to which the people, interventions and outcomes are similar to those of interest)?	0	0	NA	0	0	0
Were data imprecise or sparse? (-1) (i.e. lack of data or very wide confidence intervals that may change conclusions)	0	0	NA	0	0	0
Did the studies have high probability of reporting bias? (-1)	0	0	NA	0	0	0
Did the studies show strong evidence of association between intervention and outcome? ("strong" if significant relative risk or odds ratio > 2 based on consistent evidence from 2 or more studies with no plausible confounders (+1); "very strong" if significant relative risk or odds ratio > 5 based on direct evidence with no major threats to validity (+2)) - use your clinical judgment for absolute differences.	0	0	NA	0	0	0
Did the studies have evidence of a dose-response gradient? (+1)	0	0	NA	0	0	0
Did the studies have unmeasured plausible confounders that most likely reduced the magnitude of the observed association? (+1)	0	0	NA	0	0	0
Overall grade of evidence (high, moderate, low)	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient

High = further research is very unlikely to change our confidence in the estimates; moderate = further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate; low = further research is likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate; very low = any estimate of effect is very uncertain.

Evidence Table 1. Grading of the body of evidence of the effects of premixed insulin analogues compared to other diabetes medications for each outcome (continued)

	2-hour postprandial glucose after breakfast					
	Premixed vs. long-acting insulin analogues	Premixed vs. rapid-acting insulin analogues	Premixed vs. rapid-acting + long-acting insulin analogues	Premixed insulin analogues vs. premixed human insulin	Premixed insulin analogues vs. NPH	Premixed insulin analogues vs. noninsulin antidiabetic agents
Quantity of evidence: Number of studies	8	1	0	11	2	8
Range of sample sizes	20-255	107	NA	23-177	140-403	143-597
Quality and consistency of evidence: Were study designs mostly RCTs (high quality), non-RCTs (medium quality), observational studies (low quality), or about a 50:50 mix of experimental and observational (medium quality)?	High	High	NA	High	High	High
Did the studies have serious (-1) or very serious (-2) limitations in quality? (Enter 0 if none)	0	0	NA	0	0	0
Did the studies have important inconsistency? (-1)	0	NA	NA	0	NA	0
Was there some (-1) or major (-2) uncertainty about the directness (i.e. extent to which the people, interventions and outcomes are similar to those of interest)?	-1	0	NA	0	0	0
Were data imprecise or sparse? (-1) (i.e. lack of data or very wide confidence intervals that may change conclusions)	0	-1	NA	0	-1	0
Did the studies have high probability of reporting bias? (-1)	0	0	NA	0	0	0
Did the studies show strong evidence of association between intervention and outcome? ("strong" if significant relative risk or odds ratio > 2 based on consistent evidence from 2 or more studies with no plausible confounders (+1); "very strong" if significant relative risk or odds ratio > 5 based on direct evidence with no major threats to validity (+2)) - use your clinical judgment for absolute differences.	1	0	NA	0	0	0
Did the studies have evidence of a dose-response gradient? (+1)	0	0	NA	0	0	0
Did the studies have unmeasured plausible confounders that most likely reduced the magnitude of the observed association? (+1)	0	0	NA	0	0	0
Overall grade of evidence (high, moderate, low)	High	Low	Insufficient	Moderate	Low	Moderate

High = further research is very unlikely to change our confidence in the estimates; moderate = further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate; low = further research is likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate; very low = any estimate of effect is very uncertain.

Evidence Table 1. Grading of the body of evidence of the effects of premixed insulin analogues compared to other diabetes medications for each outcome (continued)

	2-hour postprandial glucose after dinner					
	Premixed vs. long-acting insulin analogues	Premixed vs. rapid-acting insulin analogues	Premixed vs. rapid-acting + long-acting insulin analogues	Premixed insulin analogues vs. premixed human insulin	Premixed insulin analogues vs. NPH	Premixed insulin analogues vs. noninsulin antidiabetic agents
Quantity of evidence: Number of studies	9	2	1	8	2	9
Range of sample sizes	20-469	107-473	145	25-177	140-143	49-597
Quality and consistency of evidence: Were study designs mostly RCTs (high quality), non-RCTs (medium quality), observational studies (low quality), or about a 50:50 mix of experimental and observational (medium quality)?	High	High	Moderate	High	High	high
Did the studies have serious (-1) or very serious (-2) limitations in quality? (Enter 0 if none)	0	0	0	0	0	0
Did the studies have important inconsistency? (-1)	0	0	NA	0	-1	-1
Was there some (-1) or major (-2) uncertainty about the directness (i.e. extent to which the people, interventions and outcomes are similar to those of interest)?	0	0	0	0	0	0
Were data imprecise or sparse? (-1) (i.e. lack of data or very wide confidence intervals that may change conclusions)	0	-1	-1	0	-1	0
Did the studies have high probability of reporting bias? (-1)	0	0	0	0	0	0
Did the studies show strong evidence of association between intervention and outcome? ("strong" if significant relative risk or odds ratio > 2 based on consistent evidence from 2 or more studies with no plausible confounders (+1); "very strong" if significant relative risk or odds ratio > 5 based on direct evidence with no major threats to validity (+2)) - use your clinical judgment for absolute differences.	0	0	0	0	0	0
Did the studies have evidence of a dose-response gradient? (+1)	0	0	0	0	0	0
Did the studies have unmeasured plausible confounders that most likely reduced the magnitude of the observed association? (+1)	0	0	0	0	0	0
Overall grade of evidence (high, moderate, low)	High	Moderate	Low	High	Low	Moderate

High = further research is very unlikely to change our confidence in the estimates; moderate = further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate; low = further research is likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate; very low = any estimate of effect is very uncertain.

Evidence Table 1. Grading of the body of evidence of the effects of premixed insulin analogues compared to other diabetes medications for each outcome (continued)

	HbA1c					
	Premixed vs. long-acting insulin analogues	**Premixed vs. rapid-acting insulin analogues**	**Premixed vs. rapid-acting + long-acting insulin analogues**	**Premixed insulin analogues vs. premixed human insulin**	**Premixed insulin analogues vs. NPH**	**Premixed insulin analogues vs. noninsulin antidiabetic agents**
Quantity of evidence: Number of studies	9	2	1	7	2	6
Range of sample sizes	20-708	159-708	145	40-177	140-403	129-597
Quality and consistency of evidence: Were study designs mostly RCTs (high quality), non-RCTs (medium quality), observational studies (low quality), or about a 50:50 mix of experimental and observational (medium quality)?	High	High	Low	High	High	High
Did the studies have serious (-1) or very serious (-2) limitations in quality? (Enter 0 if none)	0	0	-1	0	0	0
Did the studies have important inconsistency? (-1)	0	0	0	0	0	0
Was there some (-1) or major (-2) uncertainty about the directness (i.e. extent to which the people, interventions and outcomes are similar to those of interest)?	0	0	0	0	0	0
Were data imprecise or sparse? (-1) (i.e. lack of data or very wide confidence intervals that may change conclusions)	0	0	0	0	0	0
Did the studies have high probability of reporting bias? (-1)	0	0	-1	0	0	0
Did the studies show strong evidence of association between intervention and outcome? ("strong" if significant relative risk or odds ratio > 2 based on consistent evidence from 2 or more studies with no plausible confounders (+1); "very strong" if significant relative risk or odds ratio > 5 based on direct evidence with no major threats to validity (+2)) - use your clinical judgment for absolute differences.	+ 1	0	0	+ 1	0	0
Did the studies have evidence of a dose-response gradient? (+1)	+ 1	0	0	+ 1	0	0
Did the studies have unmeasured plausible confounders that most likely reduced the magnitude of the observed association? (+1)	0	0	0	0	0	0
Overall grade of evidence (high, moderate, low)	High	Low	Low	High	Low	Moderate

High = further research is very unlikely to change our confidence in the estimates; moderate = further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate; low = further research is likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate; very low = any estimate of effect is very uncertain.

Evidence Table 1. Grading of the body of evidence of the effects of premixed insulin analogues compared to other diabetes medications for each outcome (continued)

	Hypoglycemia					
	Premixed vs. long-acting insulin analogues	**Premixed vs. rapid-acting insulin analogues**	**Premixed vs. rapid-acting + long-acting insulin analogues**	**Premixed insulin analogues vs. premixed human insulin**	**Premixed insulin analogues vs. NPH**	**Premixed insulin analogues vs. noninsulin antidiabetic agents**
Quantity of evidence: Number of studies	10	2	1	16	2	8
Range of sample sizes	20-708	159-708	145	13-187	140-403	49-597
Quality and consistency of evidence: Were study designs mostly RCTs (high quality), non-RCTs (medium quality), observational studies (low quality), or about a 50:50 mix of experimental and observational (medium quality)?	High	High	Low	High	High	High
Did the studies have serious (-1) or very serious (-2) limitations in quality? (Enter 0 if none)	0	0	0	0	0	0
Did the studies have important inconsistency? (-1)	0	0	0	0	0	0
Was there some (-1) or major (-2) uncertainty about the directness (i.e. extent to which the people, interventions and outcomes are similar to those of interest)?	0	0	0	0	0	0
Were data imprecise or sparse? (-1) (i.e. lack of data or very wide confidence intervals that may change conclusions)	0	0	0	0	0	0
Did the studies have high probability of reporting bias? (-1)	0	0	0	0	0	0
Did the studies show strong evidence of association between intervention and outcome? ("strong" if significant relative risk or odds ratio > 2 based on consistent evidence from 2 or more studies with no plausible confounders (+1); "very strong" if significant relative risk or odds ratio > 5 based on direct evidence with no major threats to validity (+2)) - use your clinical judgment for absolute differences.	0	0	0	0	0	0
Did the studies have evidence of a dose-response gradient? (+1)	0	0	0	0	0	0
Did the studies have unmeasured plausible confounders that most likely reduced the magnitude of the observed association? (+1)	0	0	+1	0	0	0
Overall grade of evidence (high, moderate, low)	High	Low	Low	High	Low	High

High = further research is very unlikely to change our confidence in the estimates; moderate = further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate; low = further research is likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate; very low = any estimate of effect is very uncertain.

Evidence Table 1. Grading of the body of evidence of the effects of premixed insulin analogues compared to other diabetes medications for each outcome (continued)

	Weight change					
	Premixed vs. long-acting insulin analogues	**Premixed vs. rapid-acting insulin analogues**	**Premixed vs. rapid-acting + long-acting insulin analogues**	**Premixed insulin analogues vs. premixed human insulin**	**Premixed insulin analogues vs. NPH**	**Premixed insulin analogues vs. noninsulin antidiabetic agents**
Quantity of evidence: Number of studies	9	2	1	7	2	8
Total number of patients studied	20-469	98-473	161	30-151	93-403	49-597
Quality and consistency of evidence: Were study designs mostly RCTs (high quality), non-RCTs (medium quality), observational studies (low quality), or about a 50:50 mix of experimental and observational (medium quality)?	High	High	Medium	High	High	High
Did the studies have serious (-1) or very serious (-2) limitations in quality? (Enter 0 if none)	0	0	0	0	0	0
Did the studies have important inconsistency? (-1)	0	0	0	0	0	0
Was there some (-1) or major (-2) uncertainty about the directness (i.e. extent to which the people, interventions and outcomes are similar to those of interest)?	0	0	0	0	0	0
Were data imprecise or sparse? (-1) (i.e. lack of data or very wide confidence intervals that may change conclusions)	0	0	0	0	0	0
Did the studies have high probability of reporting bias? (-1)	0	0	0	0	0	0
Did the studies show strong evidence of association between intervention and outcome? ("strong" if significant relative risk or odds ratio > 2 based on consistent evidence from 2 or more studies with no plausible confounders (+1); "very strong" if significant relative risk or odds ratio > 5 based on direct evidence with no major threats to validity (+2)) - use your clinical judgment for absolute differences.	0	0	0	0	0	0
Did the studies have evidence of a dose-response gradient? (+1)	0	0	0	0	0	0
Did the studies have unmeasured plausible confounders that most likely reduced the magnitude of the observed association? (+1)	0	0	0	0	0	0
Overall grade of evidence (high, moderate, low, very low)	High	Low	Low	High	Low	High

High = further research is very unlikely to change our confidence in the estimates; moderate = further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate; low = further research is likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate; very low = any estimate of effect is very uncertain.

Evidence Table 1. Grading of the body of evidence of the effects of premixed insulin analogues compared to other diabetes medications for each outcome (continued)

	All-cause mortality					
	Premixed vs. long-acting insulin analogues	**Premixed vs. exenatide**	**Premixed vs. another premixed insulin analogue**	**Premixed vs. premixed human insulin**	**Other compari-sons**	**Premixed vs. oral antidiabetic agents**
Quantity of evidence: Number of studies	2	1	1	2	0	2
Total number of patients studied	804	501	133	167	NA	926
Quality and consistency of evidence: Were study designs mostly RCTs (high quality), mostly non-RCTs (medium quality), observational studies (low quality), or about a 50:50 mix of experimental and observational (medium quality)?	High	High	High	High	NA	High
Did the studies have serious (-1) or very serious (-2) limitations in quality? (Enter 0 if none)	0	0	0	0	NA	0
Did the studies have important inconsistency? (-1)	0	0	0	-1	NA	0
Was there some (-1) or major (-2) uncertainty about the directness (i.e. extent to which the people, interventions and outcomes are similar to those of interest)?	0	0	0	0	NA	0
Were data imprecise or sparse? (-1) (i.e. lack of data or very wide confidence intervals that may change conclusions)	-1	-1	-1	-1	NA	-1
Did the studies have high probability of reporting bias? (-1)	-1	-1	-1	-1	NA	-1
Did the studies show strong evidence of association between intervention and outcome? ("strong" if significant relative risk or odds ratio > 2 based on consistent evidence from 2 or more studies with no plausible confounders (+1); "very strong" if significant relative risk or odds ratio > 5 based on direct evidence with no major threats to validity (+2)) - use your clinical judgment for absolute differences.	0	0	0	0	NA	0
Did the studies have evidence of a dose-response gradient? (+1)	0	0	0	0	NA	0
Did the studies have unmeasured plausible confounders that most likely reduced the magnitude of the observed association? (+1)	0	0	0	0	NA	0
Overall grade of evidence (high, moderate, or low)	Low	Low	Low	Low	Insufficient	Low

High = further research is very unlikely to change our confidence in the estimates; moderate = further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate; low = further research is likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate; insufficient = no data.

Evidence Table 1. Grading of the body of evidence of the effects of premixed insulin analogues compared to other diabetes medications for each outcome (continued)

	Cardiovascular mortality			
	Premixed vs. long-acting insulin analogues	**Premixed vs. premixed human insulin**	**Other comparisons**	**Premixed vs. oral antidiabetic agents**
Quantity of evidence: Number of studies	2	1	0	1
Total number of patients studied	804	186	NA	329
Quality and consistency of evidence: Were study designs mostly RCTs (high quality), non-RCTs (medium quality), observational studies (low quality), or about a 50:50 mix of experimental and observational (medium quality)?	High	High	NA	High
Did the studies have serious (-1) or very serious (-2) limitations in quality? (Enter 0 if none)	0	0	NA	0
Did the studies have important inconsistency? (-1)	0	0	NA	0
Was there some (-1) or major (-2) uncertainty about the directness (i.e. extent to which the people, interventions and outcomes are similar to those of interest)?	0	0	NA	0
Were data imprecise or sparse? (-1) (i.e. lack of data or very wide confidence intervals that may change conclusions)	-1	-1	NA	-1
Did the studies have high probability of reporting bias? (-1)	-1	-1	NA	-1
Did the studies show strong evidence of association between intervention and outcome? ("strong" if significant relative risk or odds ratio > 2 based on consistent evidence from 2 or more studies with no plausible confounders (+1); "very strong" if significant relative risk or odds ratio > 5 based on direct evidence with no major threats to validity (+2)) - use your clinical judgment for absolute differences.	0	0	NA	0
Did the studies have evidence of a dose-response gradient? (+1)	0	0	NA	0
Did the studies have unmeasured plausible confounders that most likely reduced the magnitude of the observed association? (+1)	0	0	NA	0
Overall grade of evidence (high, moderate, low, very low)	Low	Low	Insufficient	Low

High = further research is very unlikely to change our confidence in the estimates; moderate = further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate; low = further research is likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate; insufficient = no data.

Evidence Table 1. Grading of the body of evidence of the effects of premixed insulin analogues compared to other diabetes medications for each outcome (continued)

	Cardiovascular morbidity				
	Premixed vs. long-acting insulin analogues	**Premixed vs. exenatide**	**Premixed vs. premixed human insulin**	**Other comparisons**	**Premixed vs. oral antidiabetic agents**
Quantity of evidence: Number of studies	2	1	2	0	2
Total number of patients studied	456	501	368	NA	330
Quality and consistency of evidence: Were study designs mostly RCTs (high quality), non-RCTs (medium quality), observational studies (low quality), or about a 50:50 mix of experimental and observational (medium quality)?	High	High	High	NA	High
Did the studies have serious (-1) or very serious (-2) limitations in quality? (Enter 0 if none)	0	0	0	NA	0
Did the studies have important inconsistency? (-1)	0	0	0	NA	0
Was there some (-1) or major (-2) uncertainty about the directness (i.e. extent to which the people, interventions and outcomes are similar to those of interest)?	0	0	0	NA	0
Were data imprecise or sparse? (-1) (i.e. lack of data or very wide confidence intervals that may change conclusions)	-1	-1	-1	NA	-1
Did the studies have high probability of reporting bias? (-1)	-1	-1	-1	NA	-1
Did the studies show strong evidence of association between intervention and outcome? ("strong" if significant relative risk or odds ratio > 2 based on consistent evidence from 2 or more studies with no plausible confounders (+1); "very strong" if significant relative risk or odds ratio > 5 based on direct evidence with no major threats to validity (+2)) - use your clinical judgment for absolute differences.	0	0	0	NA	0
Did the studies have evidence of a dose-response gradient? (+1)	0	0	0	NA	0
Did the studies have unmeasured plausible confounders that most likely reduced the magnitude of the observed association? (+1)	0	0	0	NA	0
Overall grade of evidence (high, moderate, low, very low)	Low	Low	Low	Insufficient	Low

High = further research is very unlikely to change our confidence in the estimates; moderate = further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate; low = further research is likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate; insufficient = no data.

Evidence Table 1. Grading of the body of evidence of the effects of premixed insulin analogues compared to other diabetes medications for each outcome (continued)

	Nephropathy	
	Premixed vs. long-acting insulin analogues	**Other comparisons**
Quantity of evidence: Number of studies	1	0
Total number of patients studied	708	NA
Quality and consistency of evidence: Were study designs mostly RCTs (high quality), non-RCTs (medium quality), observational studies (low quality), or about a 50:50 mix of experimental and observational (medium quality)?	High	NA
Did the studies have serious (-1) or very serious (-2) limitations in quality? (Enter 0 if none)	0	NA
Did the studies have important inconsistency? (-1)	0	NA
Was there some (-1) or major (-2) uncertainty about the directness (i.e. extent to which the people, interventions and outcomes are similar to those of interest)?	0	NA
Were data imprecise or sparse? (-1) (i.e. lack of data or very wide confidence intervals that may change conclusions)	-1	NA
Did the studies have high probability of reporting bias? (-1)	0	NA
Did the studies show strong evidence of association between intervention and outcome? ("strong" if significant relative risk or odds ratio > 2 based on consistent evidence from 2 or more studies with no plausible confounders (+1); "very strong" if significant relative risk or odds ratio > 5 based on direct evidence with no major threats to validity (+2)) - use your clinical judgment for absolute differences.	0	NA
Did the studies have evidence of a dose-response gradient? (+1)	0	NA
Did the studies have unmeasured plausible confounders that most likely reduced the magnitude of the observed association? (+1)	0	NA
Overall grade of evidence (high, moderate, low, very low)	Low	Insufficient

High = further research is very unlikely to change our confidence in the estimates; moderate = further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate; low = further research is likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate; insufficient = no data.

Evidence Table 1. Grading of the body of evidence of the effects of premixed insulin analogues compared to other diabetes medications for each outcome (continued)

	Quality of life					
	Premixed vs. long-acting insulin analogues	**Premixed vs. rapid-acting insulin analogues**	**Premixed vs. rapid-acting + long-acting insulin analogues**	**Premixed insulin analogues vs. premixed human insulin**	**Premixed insulin analogues vs. NPH**	**Premixed insulin analogues vs. oral antidiabetic agents**
Quantity of evidence: Number of studies	3	1	0	1	0	1
Total range in number of patients studied	45 to 708	159	NA	160	NA	143
Quality and consistency of evidence: Were study designs mostly RCTs (high quality), non-RCTs (medium quality), observational studies (low quality), or about a 50:50 mix of experimental and observational (medium quality)?	High	High	NA	High	NA	High
Did the studies have serious (-1) or very serious (-2) limitations in quality? (Enter 0 if none)	0	-1	NA	0	NA	-1
Did the studies have important inconsistency? (-1)	0	0	NA	0	NA	0
Was there some (-1) or major (-2) uncertainty about the directness (i.e. extent to which the people, interventions and outcomes are similar to those of interest)?	0	-1	NA	0	NA	-1
Were data imprecise or sparse? (-1) (i.e. lack of data or very wide confidence intervals that may change conclusions)	-1	-1	NA	-1	NA	-1
Did the studies have high probability of reporting bias? (-1)	0	-1	NA	0	NA	-1
Did the studies show strong evidence of association between intervention and outcome? ("strong" if significant relative risk or odds ratio > 2 based on consistent evidence from 2 or more studies with no plausible confounders (+1); "very strong" if significant relative risk or odds ratio > 5 based on direct evidence with no major threats to validity (+2)) - use your clinical judgment for absolute differences.	0	0	NA	0	NA	0
Did the studies have evidence of a dose-response gradient? (+1)	0	0	NA	0	NA	0
Did the studies have unmeasured plausible confounders that most likely reduced the magnitude of the observed association? (+1)	0	0	NA	0	NA	0
Overall grade of evidence (high, moderate, low, very low)	Low	Low	Insufficient	Low	Insufficient	Low

High = further research is very unlikely to change our confidence in the estimates; moderate = further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate; low = further research is likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Evidence Table 2. Characteristics of the studies comparing a premixed insulin analogue to other diabetes treatments

Author, year Country	Study Design	Study duration	Exclusion criteria	Target glucose values
Abrahamian, 2005[50] Austria	Parallel-arms, randomized controlled trial	Intended duration: 24 weeks	HbA1c < 7%, no T2DM, BMI > 40 kg/m^2, history of insulin use or OA agent plus insulin and under good control	Target glucose was according to local practice
Bebakar, 2007[43] Western Pacific	Parallel-arms, randomized controlled trial	Intended duration: 24 weeks	Age < 18 years, any liver disease, any kidney disease, HbA1c < 7 and > 12%, no T2DM, BMI < 18 and > 30 kg/m^2, duration of diabetes < 24 and > 60 months, OA agents for < 4 months (SU, biguanide, glinide, alpha-glucosidase inhibitor, or combination (more than two not permissible), CRP < 0.33 nmol/L, TZD therapy in last 6 months	HbA1c ≤ 8.5% FPG ≤ 7 mmol/L
Boehm, 2004[42] Boehm, 2002[10]* United Kingdom, Germany, Ireland	Parallel-arms, randomized controlled trial	Intended duration: 104 weeks	Age < 18 years, HbA1c > 11%, no T2DM, BMI > 35 kg/m^2, duration of diabetes < 2 years	NR
Christiansen, 2003[14] 9 countries	Parallel-arms, randomized controlled trial	Intended duration: 16 weeks	Age < 18 years, HbA1c > 11%, no T2DM, BMI > 35 kg/m^2, insulin doses ≥1.8 IUnits/kg/day, history of serious late diabetic complications or other serious disease	NR
Coscelli, 2003[61] Italy	Cross-over, randomized controlled trial, no washout period	Mean: 24 days Intended duration: 12 weeks	Age < 35 and > 70 years, any liver disease, any kidney disease, history of CVD, HbA1c > 9.5%, no T2DM, BMI < 27 and > 35 kg/m^2, not already taking twice daily premixed insulin (30/70) or NPH insulin therapy for at least 6 months, cancer, drug or alcohol abuse, insulin allergy, recurrent severe hypoglycemia, anemia, hemoglobinopathy, breastfeeding, pregnant, or intending to become pregnant, any treatment with OA agents, systemic glucocorticoids, or insulin doses > 2.0 IU/kg/day	FPG ≤ 7.8 mmol/L (140 mg/dL) 2-hr PPG < 10 mmol/L (180 mg/dL)
Cox, 2007[68] United States	Cross-over, randomized controlled trial, no washout period	Intended duration: 24 weeks	HbA1c < 7 and > 10%, no T2DM, have not used metformin, pregnant, breastfeeding, patients with a previous diagnosis of depression or treated with centrally acting medications (e.g., antidepressants or anxiolytics)	FPG < 6.7 mmol/L (121 mg/dL) 2-hr PPG <8.0 mmol/L (144 mg/dL)
Hermansen, 2002[55] Denmark	Cross-over, randomized controlled trial, washout period: at least 5 days	Intended duration: 1 day	Age < 18 years, any liver disease, any kidney disease, history of CVD, neuropathy, retinopathy, HbA1c ≥ 11%, no T2DM, BMI > 32 kg/m^2, not insulin treated, insulin doses ≥ 1.4 U/kg/day, recurrent severe hypoglycemia, alcohol or drug abuse	NR

Evidence Table 2. Characteristics of the studies comparing a premixed insulin analogue to other diabetes treatments (continued)

Author, year Country	Study Design	Study duration	Exclusion criteria	Target glucose values
Herz, 2002[65] Croatia	Cross-over, randomized controlled trial, no washout period	Intended duration: 4 weeks	Age < 38 and > 69 years, HbA1c ≥ 10%, no T2DM, BMI > 35 kg/m^2, not treated with a fixed mixture of human insulin twice daily for at least 1 month, not capable of exercising for 30 minutes on a cycle ergometer at a heart rate of 120 beats/minute during two exercise sessions separated by 30 minutes on rest, being treated with OA agents, systemic glucocorticoids, or insulin doses > 2.0 U/kg/day	FPG < 7.0 mmol/L 2-hr PPG < 10.0 mmol/L
Herz, 2002[66] Czech Republic, Hungary, Slovenia, Croatia, Poland, Sweden, Australia and New Zealand	Parallel-arms, randomized controlled trial	Intended duration: 16 weeks	Age < 60 and > 80 years, any liver disease, history of CVD, retinopathy, HbA1c < 1.2 fold ULN at visit 1, FBG < 7.8 mmol/L on at least 2 of 3 occasions during 4 week lead-in, no T2DM, BMI > 35 kg/m^2, insulin allergy, treatment with insulin in the last 6 months, taking OA agent other than SU or acarbose, not on maximum dose of SU for at least 1 month, duration of diabetes < 1 year, renal dialysis or renal transplant	FPG < 7 mmol/L (encouraged by the study investigators but targets were at the discretion of the physician) 2 hour PPG < 10 mmol/L
Herz, 2003[13] South Africa	Cross-over, randomized controlled trial, no washout period	Intended duration: 4 weeks	Age < 40 and > 70 years, HbA1c >10%, no T2DM, BMI > 35 kg/m^2, not treated with human insulin 30/70 twice daily, not practiced self-monitoring of BG for at least 3 months, usually injected human insulin 30-45 minutes before meals, being treated with oral antidiabetic agents, systemic glucocorticoids, or insulin doses > 2.0 U/kg/day	FPG < 7.0 mmol/L 2-hr PPG < 10 mmol/L
Holman, 2007[28] United Kingdom, Ireland	Parallel-arms, randomized controlled trial	Mean: 52 weeks Median: 156 weeks, results reported at 52 weeks Intended duration: 156 weeks	Age < 18 years, any liver disease, any kidney disease, history of CVD, history of insulin treatment, retinopathy, HbA1c < 7 and > 10%, no T2DM, BMI > 40 kg/m^2, retinopathy, on less than maximally tolerated doses of metformin and SU for at least 4 months, unawareness of hypoglycemia, pregnant, duration of diabetes < 12 months, TZD treatment or triple OA agents within the previous 6 months, uncontrolled hypertension (SBP > 180 or DBP > 105 mmHg)	HbA1c 6.5% FPG 72 to 99 mg/dL PPG 90 to 126 mg/dL

Evidence Table 2. Characteristics of the studies comparing a premixed insulin analogue to other diabetes treatments (continued)

Author, year Country	Study Design	Study duration	Exclusion criteria	Target glucose values
Jacober, 2006[58] United States	Cross-over, randomized controlled trial, no washout period	Intended duration: 16 weeks	Age < 30 years, any liver disease, any kidney disease, history of CVD, history of insulin treatment, HbA1c < 1.2 - 2 times the ULN reference range as defined by the local laboratory, no T2DM, BMI > 40 kg/m^2, had adequate blood glucose control, as determined by the investigator, while receiving at least 2 OA agents of different classes used in combination for at least 2 months, undergoing treatment for a malignancy other than basal cell or squamous cell skin cancer, insulin allergy, pregnant or intending to become pregnant, history of severe hypoglycemia within 6 months, currently taking rosiglitazone, long term insulin therapy, chronic systemic glucocorticoid therapy, fibric acid derivatives, niacin or a bile acid sequestant to treat hypertriglyceridemia, chronic anemia	FPG <120 mg/dL (6.7 mmol/L) For treatment with insulin lispro mixtures, the target 2-hr PPG was <180 mg/dL (10.00 mmol/L)
Joshi, 2005[49] India	prospective study	Intended duration: 12 weeks	no T2DM	HbA1c < 7% but was up to the individual clinician to titrate
Kann, 2006[47] Austria, Czech Republic, Germany, Hungary, Poland, Slovakia, Slovenia	Parallel-arms, randomized controlled trial	Intended duration: 26 weeks	HbA1c ≤ 7 and > 12%, no T2DM, BMI > 40 kg/m^2, any kidney disease, history of CVD, duration of diabetes < 6 months, not receiving one of the following: SU (at least half maximum dose) with or without metformin, metformin (< 2 g/day), insulin therapy > 7days in last 6 months, alcohol or drug abuse, pregnant, breastfeeding, intending to become pregnant, taking medication interfering with glucose regulation	FPG 5-8mmol/L for both groups 90-min PPG 5-10 mmol/L for BIAsp group
Kapitza, 2004[53] Germany	Cross-over, randomized controlled trial, washout period: 3-21 days	Intended duration: 5 hours	No T2DM, not treated with insulin for the past 6 months	BG < 10 mmol/L
Kazda, 2006[69] Germany	Parallel-arms, randomized controlled trial	Intended duration: 24 weeks	Age < 30 or > 75 years, HbA1c < 6 or > 10.50%, no T2DM, BMI ≥ 40 kg/m^2, duration of diabetes < 1 and > 10 years, insulin treatment during last 3 months	FPG < 7 mmol/L for insulin glargine 2-hr PPG < 10 mmol/L for lispro groups
Kilo, 2003[16] United States	Parallel-arms, randomized controlled trial	Intended duration: 12 weeks	Age < 18 years, any liver disease, any kidney disease, history of CVD, history of insulin treatment, HbA1c < 7.5%, FBG < 126 mg/dL, no T2DM, BMI > 40 kg/m^2, body weight > 100 kg, if significant cardiovascular, liver or kidney disease, NOT on metformin monotherapy or combination with SU or repaglinide for ≥ 3 months, controlled on metformin after 4 week run-in period	FPG 90-126 mg/dL

Evidence Table 2. Characteristics of the studies comparing a premixed insulin analogue to other diabetes treatments (continued)

Author, year Country	Study Design	Study duration	Exclusion criteria	Target glucose values
Kvapil, 2006[48] Croatia, Czech Republic, Denmark, France, Greece, Hungary, Norway, Poland, Portugal, Russia, Spain	Parallel-arms, randomized controlled trial	Intended duration: 16 weeks	Any liver disease, any kidney disease, history of CVD, no T2DM, not on metformin, adequately controlled on metformin monotherapy, significant medical problems (proliferative retinopathy, impaired hepatic or renal function, recurrent severe hypoglycemia, cardiac disease, anemia), change in dose of medications known to interfere with metformin	Breakfast insulin aspart 70/30 dose adjusted to target post-breakfast and pre-dinner glucoses of 5 – 8 mmol/L; evening insulin aspart 70/30 dose adjusted to target post-diner, nighttime, and pre-breakfast blood glucose of 5 – 8 mmol/L
Malone, 2000[41] Malone, 2000[15] Canada	Cross-over, randomized controlled trial, washout period: 3-11 days	Intended duration: 1 day	Age < 38 and > 74 years, HbA1c > 1.5 times ULN, no T2DM, BMI > 35 kg/m^2, not using a manufactured or self-prepared human insulin mixture in the morning, a short-acting insulin at dinner, and a second NPH insulin dose either at dinner or separately at bedtime, total daily insulin dose > 2.0 U/kg, using an OA agent or glucocorticoids within 2 weeks, using Ultralente insulin, pregnant, breastfeeding	NR
Malone, 2003[62] 14 countries	Parallel-arms, randomized controlled trial	Mean: 16 weeks	Age < 35 and > 75 years, HbA1c < 125% of ULN within 4 weeks, no T2DM, BMI > 40 kg/m^2, adequately controlled diabetes, not using a single OA agent, specifically metformin or SU, at a maximally clinically effective dose within last 3 months	FPG and pre-meal BG < 7 mmol/L (126 mg/dL) 2-hr PPG < 10 mmol/L (180 mg/dL)
Malone, 2004[59] United States	Cross-over, randomized controlled trial, no washout period	Intended duration: 16 weeks	Age < 30 and > 80 years, history of insulin treatment, HbA1c < 1.3 and > 2.0 times ULN while using ≥ 1 OA agents without insulin for 30 days before study start, no T2DM, BMI > 40 kg/m^2	FPG 90 to 126 mg/dL 2-hr PPG 144 to 180 mg/dL
Malone, 2005[60] Spain and France	Cross-over, randomized controlled trial, no washout period	Intended duration: 16 weeks	Age < 30 and > 75 years, HbA1c < 1.3 and > 2.0 times ULN by a local laboratory within 30 days, no T2DM, used TZDs within 30 days, not using NPH once or twice daily, alone or in combination with an OA agent, or a once-daily human insulin mixture with an OA agent for at least 30 days	FPG 5 - 7 mmol/L (90 - 126 mg/dL); 8 - 10 mmol/L (144 - 180 mg/dL) for Humalog 75/25 only
Mattoo, 2003[64] India, Pakistan, Malaysia, Singapore, Egypt, Morocco, and South Africa	Cross-over, randomized controlled trial, no washout period	Intended duration: 2 weeks	Any liver disease, any kidney disease, history of CVD, retinopathy, no T2DM, BMI > 35 kg/m^2, not treated with conventional insulin therapy for at least 2 months, not complying with dietary and insulin treatment, not capable or willing to perform self-BG monitoring and use a patient diary, cancer, insulin allergy, drug or alcohol abuse, more than 1 unexplained episode of severe hypoglycemia within 6 months or a history of clinically significant hypoglycemia unawareness, treated with systemic glucocorticoids or insulin doses > 2.0 U/kg	NR

Evidence Table 2. Characteristics of the studies comparing a premixed insulin analogue to other diabetes treatments (continued)

Author, year Country	Study Design	Study duration	Exclusion criteria	Target glucose values
McNally, 2007[45] United Kingdom	Cross-over, randomized controlled trial, no washout period	Intended duration: 16 weeks	HbA1c ≥ 9.5%, no T2DM, BMI ≥ 40 kg/m^2, not treated with insulin for at least 6 months	FPG 5 - 7 mmol/L preprandial glucose 5 - 7 mmol/L
McSorley, 2002[12] NR	Cross-over, randomized controlled trial, no washout period	Intended duration: 2 weeks	Age < 40 and > 75 years, no T2DM, history of type 2 diabetes < 1 year, not using twice-daily BHI 30 for at least 6 months	NR
Nauck, 2007[46] 13 countries	Parallel-arms, randomized controlled trial	Intended duration: 52 weeks	Age < 30 and > 75 years, HbA1c < 7 and > 11%, BMI < 25 and > 40 kg/m^2, not on "optimally effective" metformin and sulfonylurea treatment for at least 3 months, lack of stable body weight (> 10% variation in last 3 months), more than 3 episodes of severe hypoglycemia within 6 months prior to screening, use of a weight loss prescription drug in the last 3 months, treated with insulin, TZDs, alpha-glucosidase inhibitors, or meglitinides for > 2 weeks in last 3 months	FPG < 7 mmol/L (126 mg/dL) 2-hr PPG < 10 mmol/L (180 mg/dL)
Niskanen, 2004[52] United Kingdom, Finland, Norway, Sweden	Cross-over, randomized controlled trial, no washout period	Intended duration: 12 weeks	Age < 18 years, any liver disease, any kidney disease, history of CVD, HbA1c > 12%, no T2DM, BMI > 35 kg/m^2, did not require insulin for the past 6 months, insulin dose ≥ 1.8 IU/kg/day, not eligible for BID mixed insulin treatment, not willing or able to perform self monitoring of BG, previous treatment with insulin analogues or use of OA agents within the last 4 weeks, severe uncontrolled hypertension, known or suspected allergy to trial products, pregnant, alcohol or drug abuse	FPG 5.0 to 8.0 mmol/L postprandial BG (1-3 hours after a meal) 5.0 to 10.0 mmol/L
Raskin, 2005[36] Raskin, 2007[37] Brod, 2007[38] United States	Parallel-arms, randomized controlled trial	Intended duration: 28 weeks	Age < 18 and > 75 years, history of insulin treatment, HbA1c < 8%, no T2DM, BMI > 40 kg/m^2, body weight > 275 lbs, not on metformin > 1000 mg/day as a single agent or as part of combination therapy for at least 3 months, pregnant, breastfeeding, or not practicing contraception	FPG 80-110 mg/dL
Raz, 2003[54] Israel	Parallel-arms, randomized controlled trial	Intended duration: 6 weeks	Age < 30 years, any liver disease, history of CVD, history of insulin treatment, HbA1c ≤ 8 and ≥13%, no T2DM, T1DM, BMI > 35 kg/m^2, alcohol or drug abuse, responding to glibenclamide therapy, not treated with glibenclamide as the only OA agent for at least 4 weeks	FPG 90 to 144 mg/dL PPG (1 – 3 hours after a meal) <180 mg/dL

Evidence Table 2. Characteristics of the studies comparing a premixed insulin analogue to other diabetes treatments (continued)

Author, year Country	Study Design	Study duration	Exclusion criteria	Target glucose values
Raz, 2005[51] Canada, Israel, China, Australia, Croatia, Thailand, South Africa, Poland	Parallel-arms, randomized controlled trial	Intended duration: 18 weeks	Age < 18 years, any liver disease, history of CVD, HbA1c < 7.4 and > 14.7%, no T2DM, BMI > 40kg/m^2, no treatment with SU for within last 3 months, alcohol or drug abuse, any serious disease, pregnant, likely to become pregnant or not using contraception	FPG, preprandial, and nighttime 5-8 mmol/L for insulin aspart 70/30 PPG 5-8 mmol/L for insulin aspart 70/30
Roach, 1999[67] United Kingdom, Spain, South Africa	Cross-over, randomized controlled trial, no washout period	Intended duration: 13 weeks	Age < 18 and > 75 years, any liver disease, any kidney disease, history of CVD, history of OA agents, retinopathy, HbA1c > 9.2%, no T2DM, BMI > 35 kg/m^2, had not received insulin therapy using mixtures of short-acting or rapid-acting insulin and intermediate- or long-acting insulin twice daily for at least 30 days, cancer, anemia, hemoglobinopathy, alcohol or drug abuse, insulin allergy, recurrent severe hypoglycemia, breastfeeding, pregnant, or intending to become pregnant, treated with OA agents, systemic glucocorticoids, or insulin doses > 2.0 U/kg	NR
Roach, 1999[11] United Kingdom, Germany, Hungary, the Netherlands, Switzerland	Cross-over, randomized controlled trial, no washout period	Intended duration: 12 weeks	Age < 18 and > 70 years, any liver disease, any kidney disease, history of CVD, HbA1c > 9.2%, no type 1 or type 2 diabetes, not treated with commercially available insulin for at least 120 days, cancer, drug or alcohol abuse, insulin allergy, recurrent severe hypoglycemia, anemia, or hemoglobinopathy, treated with OA agents, systemic glucocorticoids, or insulin doses > 2.0 U/kg	FPG ≤ 7.8 mmol/L 2-hr PPG ≤ 10 mmol/L
Roach, 2003[63] India	Cross-over, randomized controlled trial, no washout period	Intended duration: 8 weeks	Age < 25 and > 75 years, HbA1c > 12%, no T2DM, BMI > 35 kg/m^2, not taking twice daily insulin therapy with mixtures of short- or rapid-acting and intermediate- or long-acting insulin for at least 6 months, history of recurrent severe hypoglycemia, treated with OA agents, systemic glucocorticoids, or insulin doses > 2.0 U/kg	FPG ≤ 7.8 mmol/L (140 mg/dL) 2-hr PPG ≤ 10 mmol/L (180 mg/dL)
Roach, 2006[57] United States	Cross-over, randomized controlled trial, no washout period	Intended duration: 12 weeks	Age < 21 and > 80 years, any liver disease, any kidney disease, HbA1c < 7 and > 12%, no T2DM, inadequate glycemic control using single or multiple OA agents or once or twice-daily insulin or a combination of OA agents and insulin for at least 3 months, use of a TZD within 3 months, pregnant, evidence of major systemic illness or organ dysfunction	FPG < 6.0 mmol/L
Schernthaner, 2004[70] NR	Cross-over, randomized controlled trial, no washout period	Intended duration: 12 weeks	Diagnosed after 35 years of age, any liver disease, any kidney disease, history of CVD, HbA1c > 11%, no T2DM, BMI > 40 kg/m^2, no severe diabetic complications	NR

Evidence Table 2. Characteristics of the studies comparing a premixed insulin analogue to other diabetes treatments (continued)

Author, year Country	Study Design	Study duration	Exclusion criteria	Target glucose values
Schwartz, 2006[56] United States	Cross-over, randomized controlled trial, washout period: clinic visits were at 3-11 day intervals; last dose of usual insulin taken at least 10 hours before test meal	Intended duration: 1-day 1-dose	Age < 30 years, HbA1c ≥ 2-fold ULN nondiabetic reference range of the local laboratory (4.3% - 6.1%) at screening, no T2DM, BMI > 40 kg/m^2, not using insulin, excluding insulin glargine, for at least 30 days prior to screening, known allergy to trial products, insulin doses > 2.0 U/kg, any condition interfering with the accurate assessment of the glucodynamic and pharmacokinetic properties of insulin, any condition that precluded a patient from following protocol, pregnant or not using contraception	NR
Tamemoto, 2007[44] Japan	Parallel-arms, randomized controlled trial	Intended duration: 24 weeks	Age < 40 or > 75 years, HbA1c < 7.5 or > 12%, FBG < 140 mg/dL, T1DM, duration of diabetes < 1 year, lack of treatment with OA agents (in particular, had to be on a SU--glibenclamide > 5 mg/d or glimepiride > 3 mg/d over 12 weeks), prior use of insulin in last 12 weeks, fasting C-peptide < 0.7 ng/mL	HbA1c < 7% FPG < 120 mg/dL
Tirgoviste, 2003[40] Roach, 2001[39] Romania and Russia	Parallel-arms, randomized controlled trial	Intended duration: 16 weeks	Age < 30 years, any liver disease, any kidney disease, history of CVD, retinopathy, HbA1c ≤ 1.4 times ULN, no T2DM, BMI > 32 kg/m^2, not treated with a 15 mg dose of glibenclamide as their only medication for at least 3 months prior, FBG ≤ 7.8 mmol/L, PPG ≤ 10 mmol/L, adrenal insufficiency, insulin allergy, treated with systemic glucocorticoids, hemoglobinopathy	FPG < 7 mmol/L or 125 mg/dL 2-hr PPG < 10 mmol/L or <180 mg/dL
Yamada, 2007[71] Japan	Parallel-arms, randomized controlled trial	Intended duration: 4 months	Any liver disease, any kidney disease, history of CVD, retinopathy, HbA1c ≤ 6.5%, no T2DM, treatment with a twice-daily injection of 70/30 or 50/50 premixed human insulin for < 3 months, patients who were anti- GAD antibody positive, severe hypertension (SBP/DBP 180/100 mmHg)	Self-monitored FPG < 130 mg/dL Clinic-measured PPG < 180 mg/dL

* The study population for Boehm 2002[10] was patients with either type 1 or type 2 diabetes. The type 2 diabetic population was the same study population used for Boehm 2004.[42] The study duration was 12 weeks.

BG = blood glucose; BHI = biphasic human insulin; BIAsp = biphasic insulin aspart; BID = twice daily; BMI = body mass index; CRP = C-reactive protein; CVD = cardiovascular disease; DBP = diastolic blood pressure; dl = deciliter; FPG = fasting plasma glucose; g/day = gram per day; GAD = glutamic acid decarboxylase; HbA1c = Hemoglobin A1c; hr = hours; IU = international unit; kg = kilogram; kg/m2 = kilogram per square meter; L = liter; lbs = pounds; m = meter; mg = milligram; mmHg = millimeter of mercury; mmol = millimole; ng/mL = nanograms per milliliter; nmol = nanomole; NPH = Neutral Protamine Hagedorn; NR = not reported; OA = oral antidiabetic; PPG = postprandial glucose; SBP = systolic blood pressures; SU = sulfonylurea; T1DM = Type 1 diabetes mellitus; T2DM = Type 2 diabetes mellitus; TZD = thiazolidinedione; U = unit; ULN = upper limit of normal

Evidence Table 3. Population characteristics of the studies comparing a premixed insulin analogue to other diabetes treatments

Author, year	Group, N	Mean age (age range) in years	Male, n (%)	Race, n (%)	Mean BMI in kg/m2 Mean weight in kg	Mean HgbA1c in % Mean FBG in mg/dL#	Mean duration of diabetes in years	Previous treatment, n (%)
Abrahamian, 2005[50]	Insulin aspart 70/30, 89	62.6	46* (52)	NR	BMI: 28	HgbA1c: 9.8	12.7	Insulin naive: No
	NPH/regular 70/30, 88	62.3	31* (35)	NR	BMI: 28.3	HgbA1c: 9.85	9.5	Insulin naive: No
Bebakar, 2007[43]	Insulin aspart 70/30 + OAM, 128	55	48 (92)	NR	BMI: 26.2	HgbA1c: 8.6	4.4	Insulin naive: Yes OAM: 128 (100)
	OAM, 63	52.7	41 (69)	NR	BMI: 25.4	HgbA1c: 8.5	4.3	Insulin naive: Yes OAM: 63 (100)
Boehm, 2004[42]	Insulin aspart 70/30, 58	62.8	32 (55*)	NR	BMI: 29.1	HgbA1c: 8.11	15.5	Insulin naive: No
Boehm, 2002[10]†	NPH/regular 70/30, 67	62.6	34 (51*)	NR	BMI: 27.2	HgbA1c: 8.21	12.9	Insulin naive: No
Christiansen, 2003[14]	Insulin aspart 70/30, 201	59.3	94* (47)	NR	BMI: 28 Weight: NR	HgbA1c: 8.8	9.2	Insulin: 66 (33) OAM: 78 (39) Insulin and OAM: 55 (27)
	NPH insulin, 202	59.6	101* (50)	NR	BMI: 28.4 Weight: NR	HgbA1c: 8.8	10.5	Insulin: 66 (33) OAM: 75 (37) Insulin and OAM: 59 (29)
Coscelli, 2003[61]	Insulin lispro 75/25, 18	59.1	7 (39)	NR	BMI: 29.5 Weight: 79	FBG: 154.2	14.9	Insulin naive: No Insulin: 18 (100)
	NPH/regular 70/30, 15	59.2	8 (53)	NR	BMI: 30.1 Weight: 80.2	FBG: 150.9	13.8	Insulin naive: No Insulin: 15 (100)
	Total, 33	59.1	15 (45)	C: 33 (100)	BMI: 29.8 Weight: 79.5	FBG: 152.5	14.4	Insulin naive: No Insulin: 33 (100)
Cox, 2007[68]	Total, 45	52.6	NR	NR	BMI: 35.08	NR	11.9	Insulin naive: NR OAM: 45 (100)
Hermansen, 2002[55]	Total, 61	60.1	40 (66*)	NR	BMI: 27.3	HgbA1c: 8.3	11.6	Insulin naive: No Insulin: 61* (100)
Herz, 2002[65]	Insulin lispro 75/25, 19	56.3	12 (63*)	NR	BMI: 27 Weight: 76	NR	8.9	Insulin naive: No Insulin: 19* (100)
	NPH/regular 70/30, 18	55.3	6 (33*)	NR	BMI: 26.3 Weight: 75.8	NR	7.5	Insulin naive: No Insulin: 18* (100)
Herz, 2002[66]	Insulin lispro 75/25, 71	68.1	37 (52.1)	NR	BMI: 28	HgbA1c: 9.82	11.4	Insulin naive: No
	Glyburide, 72	67.7	32 (44.4)	NR	BMI: 27.8	HgbA1c: 9.9	12.4	Insulin naive: No
Herz, 2003[13]	Insulin lispro 75/25, 13	54.8	10 (77*)	NR	BMI: 29.2	HgbA1c: 7.81	NR	Insulin naive: No Insulin: 13* (100)
	NPH/regular 70/30, 12	53.6	7 (58*)	NR	BMI: 29.3	HgbA1c: 7.6	NR	Insulin naive: No Insulin: 12* (100)

Evidence Table 3. Population characteristics of the studies comparing a premixed insulin analogue to other diabetes treatments (continued)

Author, year	Group, N	Mean age (age range) in years	Male, n (%)	Race, n (%)	Mean BMI in kg/m2 Mean weight in kg	Mean HgbA1c in % Mean FBG in mg/dL#	Mean duration of diabetes in years	Previous treatment, n (%)
Holman, 2007[28]	Insulin aspart 70/30+ usual care, 235	61.7	159 (67.7)	AA: 2 (0.9) C: 221 (94) Asian: 11 (4.7) mixed: 1 (0.4) other: 0 (0)	BMI: 30.2 Weight: 86.9	HgbA1c: 8.6 FBG: 175	9 median (IQR: 6 - 12)	Insulin naive: Yes OAM: 221 (94*)
	Insulin aspart+ usual care, 239	61.6	152 (63.6)	AA: 5 (2.1) C: 214 (89.5) Asian: 15 (6.3) mixed: 4 (1.7) other: 1 (0.4)	BMI: 29.6 Weight: 84.9	HgbA1c: 8.6 FBG: 173	9 median (IQR: 6 - 14)	Insulin naive: Yes OAM: 227 (95*)
	Insulin detemir + usual care, 234	61.9	143 (61.9)	AA: 2 (0.9) C: 218 (93.2) Asian: 9 (3.8) mixed: 2 (0.9) other: 3 (1.3)	BMI: 29.7 Weight: 85.5	HgbA1c: 8.4 FBG: 171	9 median (IQR: 6 - 12)	Insulin naive: Yes OAM: 224 (96*)
	Total, 708	61.7	454 (64.1)	AA: 9 (1.3) C: 653 (92.2) Asian: 35 (4.9) mixed: 7 (1) other: 4 (0.6)	BMI: 29.8 Weight: 85.8	HgbA1c: 8.5 FBG: 173	9 median (IQR: 6 - 13)	Insulin naive: Yes OAM: 672 (95*)
Jacober, 2006[58]	Total, 60	54.9	34 (56.7)	AA: 3 (5) C: 45 (75) Asian: 3 (5) H: 9 (15)	BMI: 32.9 Weight: 95.1	HgbA1c: 9.21	8.4	Insulin naive: Yes OAM: 60 (100)
Joshi, 2005[49]	Insulin aspart 70/30, 114	52.41	76 (67*)	NR	Weight: 70.4	HgbA1c: 8.79 FBG: 186.59	9.53	Insulin naive: NR Insulin: 62 (54.39) OAM: 102 (89.47)
	Insulin aspart + Insulin glargine, 31	51.1	24 (77*)	NR	Weight: 69.63	HgbA1c: 8.53 FBG: 190.23	11.98	Insulin naive: NR Insulin: 21 (67.74) OAM: 25 (80.65)
Kann, 2006[47]	Insulin aspart 70/30 + metformin, 128	61.5	69 (54*)	NR	BMI: 29.9 Weight: 84.2	HgbA1c: 9.21	10.3	Insulin naive: NR
	Insulin glargine + glimepiride, 127	61	62 (49*)	NR	BMI: 30.6 Weight: 86.6	HgbA1c: 8.9	10.2	Insulin naive: NR
Kapitza, 2004[53]	Total, 31	57	21 (68*)	NR	BMI: 29	HgbA1c: 8.7	12	Insulin naive: No Insulin: 31* (100)

Evidence Table 3. Population characteristics of the studies comparing a premixed insulin analogue to other diabetes treatments (continued)

Author, year	Group, N	Mean age (age range) in years	Male, n (%)	Race, n (%)	Mean BMI in kg/m2 Mean weight in kg	Mean HgbA1c in % Mean FBG in mg/dL#	Mean duration of diabetes in years	Previous treatment, n (%)
Kazda, 2006[69]	Insulin lispro 50/50, 54	58.7	32 (59*)	NR	BMI: 31	HgbA1c: 8.1 FBG: 167.4	5.9	Insulin naive: No Insulin: 0 in last 3 months
	Insulin lispro, 52	60.4	32 (62*)	NR	BMI: 31.7	HgbA1c: 8.2 FBG: 176.4	5.3	Insulin naive: No Insulin: 0 in last 3 months
	Insulin glargine, 53	59.1	23 (43*)	NR	BMI: 30.1	HgbA1c: 8.1 FBG: 172.8	5.5	Insulin naive: No Insulin: 0 in last 3 months
Kilo, 2003[16]	Insulin aspart 70/30 + metformin, 46	57.2	25 (54)	AA: 4 (9*) C: 33 (72*) H: 0 (0*) other: 9 (20*)	BMI: 30.4	HgbA1c: 9.5 FBG: 241.8	10.4	Insulin naive: Yes Insulin: 0 (0) OAM: 46 (100) Insulin and OAM: 0 (0)
	NPH insulin + metformin, 47	55.1	19 (40)	AA: 9 (19*) C: 30 (64*) H: 1 (2*) other: 7 (15*)	BMI: 30.4	HgbA1c: 9.5 FBG: 242.7	10.7	Insulin naive: Yes Insulin: 0 (0) OAM: 47 (100) Insulin and OAM: 0 (0)
	NPH/regular 70/30 + metformin, 47	55.4	29 (52)	AA: 6 (13*) C: 35 (74*) H: 1 (2*) other: 5 (11*)	BMI: 30.6	HgbA1c: 9.3 FBG: 227.2	8.4	Insulin naive: Yes Insulin: 0 (0) OAM: 47 (100) Insulin and OAM: 0 (0)
Kvapil, 2006[48]	Insulin aspart 70/30, 107	55.2	50 (47*)	NR	BMI: 30.9 Weight: 87.3	HgbA1c: 9.6	8.2	Insulin naive: NR
	Insulin aspart 70/30 + metformin, 108	56.4	53 (49*)	NR	BMI: 30.4 Weight: 85.1	HgbA1c: 9.3	6.7	Insulin naive: NR
	Metformin + glibenclamide, 114	58.1	52 (46*)	NR	BMI: 30.5 Weight: 84	HgbA1c: 9.4	8.1	Insulin naive: NR
Malone, 2000[41] Malone, 2000[15]	Insulin lispro 75/25, 41	59.2	26 (63*)	NR	BMI: 29.1	NR	14	Insulin naive: No Insulin: 41* (100)
	NPH/regular 70/30, 43	60.5	27 (63*)	NR	BMI: 29.2	NR	16.2	Insulin naive: No Insulin: 43* (100)
	Total, 84	59.9	53 (63*)	NR	BMI: 29.2	NR	15.1	Insulin naive: No Insulin: 84* (100)

Evidence Table 3. Population characteristics of the studies comparing a premixed insulin analogue to other diabetes treatments (continued)

Author, year	Group, N	Mean age (age range) in years	Male, n (%)	Race, n (%)	Mean BMI in kg/m2 Mean weight in kg	Mean HgbA1c in % Mean FBG in mg/dL#	Mean duration of diabetes in years	Previous treatment, n (%)
Malone, 2003[62]	Insulin lispro 75/25 + metformin, 296	58	169 (57)	C: 263 (88.9) H: 22 (7.4) 0ther: 9 (3) African: 2 (0.7)	BMI: 29.8 Weight: 83	HgbA1c: 9.17	8	Insulin naive: NR OAM: 296 (100)
	Glibenclamide + metformin, 301	59	146 (49)	C: 268 (89) H: 18 (6) 0ther: 12 (4) African: 3 (1)	BMI: 29.6 Weight: 81.7	HgbA1c: 9.27	7.4	Insulin naive: NR OAM: 301 (100)
Malone, 2004[59]	Insulin lispro 75/25 + metformin, 52	54.5 (32.3 - 79.1)	33 (63.5)	NR	BMI: 30.1 Weight: 88.5	HgbA1c: 8.7 FBG: 150.2	8.1	Insulin naive: Yes OAM: 52 (100)
	Insulin glargine + metformin, 53	55.3 (35.5 - 75.1)	33 (62.3)	NR	BMI: 31.7 Weight: 94.4	HgbA1c: 8.7 FBG: 155.3	9.8	Insulin naive: Yes OAM: 53 (100)
Malone, 2005[60]	Insulin lispro 75/25 + metformin, 50	59.18	25 (50)	NR	BMI: 29.41 Weight: 77.82	HgbA1c: 8.5 FBG: 529.38	13.52	Insulin naive: No Insulin: 50* (100) OAM: 26 (52*)
	Insulin glargine + metformin, 47	59.63	18 (38)	NR	BMI: 29.64 Weight: 77.21	HgbA1c: 8.48 FBG: 533.52	11.9	Insulin naive: No Insulin: 47* (100) OAM: 28 (60*)
Mattoo, 2003[64]	Insulin lispro 75/25, 72	54 (30-72)	34 (47.2)	NR	BMI: 26.9 (17.8 - 34.6) Weight: 71	NR	13.2	Insulin naive: No Insulin: 72* (100)
	NPH/regular 70/30, 79	52 (32-72)	35 (44.3)	NR	BMI: 26.5 (17.1 - 34.5) Weight: 71	NR	11.8	Insulin naive: No Insulin: 79* (100)
	Total, 151	53 (30-72)	69 (45.7)	NR	BMI: 26.7 (17.1 - 34.6) Weight: 71	NR	12.5	Insulin naive: No Insulin: 151* (100)
McNally, 2007[45]	Insulin aspart 70/30, 80	61.8	49 (61*)	NR	BMI: 29.7 Weight: 83.3	HgbA1c: 7.5	11.5	Insulin naive: No Insulin: 80 (100)
	NPH/regular 70/30, 80	62.7	63 (79*)	NR	BMI: 30.5 Weight: 89.1	HgbA1c: 7.5	12.1	Insulin naive: No Insulin: 80 (100)
	Total, 160	62.3	112 (70*)	NR	BMI: 30.1 Weight: 86.2	HgbA1c: 7.5	11.8	Insulin naive: No Insulin: 160 (100)
McSorley, 2002[12]	Total, 13	64	8 (62*)	NR	BMI: 28.1	HgbA1c: 7.7	13	Insulin naive: No Insulin: 13* (100)

Evidence Table 3. Population characteristics of the studies comparing a premixed insulin analogue to other diabetes treatments (continued)

Author, year	Group, N	Mean age (age range) in years	Male, n (%)	Race, n (%)	Mean BMI in kg/m2 Mean weight in kg	Mean HgbA1c in % Mean FBG in mg/dL#	Mean duration of diabetes in years	Previous treatment, n (%)
Nauck, 2007[46]	Insulin aspart 70/30 + metformin + sulfonylurea, 248	58	126.5 (51)	NR	BMI: 30.2 Weight: 83.4	HgbA1c: 8.6 FBG: 203.4	10	Insulin naive: NR OAM: 248 (100)
	Exenatide + metformin + sulfonylurea, 253	59	118.9 (47)	NR	BMI: 30.6 Weight: 85.5	HgbA1c: 8.6 FBG: 198	9.8	Insulin naive: NR OAM: 253 (100)
Niskanen, 2004[52]	Total, 133	62.3	79 (59*)	NR	BMI: 28.1	HgbA1c: 8.5	12.1	Insulin naive: No Insulin: 133* (100)
Raskin, 2005[36] Brod, 2007[38]	Insulin aspart 70/30 + metformin, 117	52.6	62 (53)	AA: 18 (15) C: 64 (55) Asian: 2 (2) H: 32 (27) Other: 2 (2)	BMI: 31.5 Weight: 90.6	HgbA1c: 9.7 FBG: 252 HgbA1c > 8.5% at baseline, n (%): 10.2 (89)	9.5	Insulin naive: Yes OAM: 117 (100)
	Insulin glargine + metformin, 116	52.3	65 (56)	AA: 20 (17) C: 60 (52) Asian: 5 (4) H: 30 (26) Other: 1 (1)	BMI: 31.4 Weight: 89.9	HgbA1c: 9.8 FBG: 243 HgbA1c>8.5% at baseline (n): 10.1 (99)	8.9	Insulin naive: Yes OAM: 116 (100)
Raskin, 2007[37]‡	Insulin aspart 70/30 + metformin, 79	52	41 (51.9)	AA: 10.3 (13) C: 41.1 (52) Asian: 2.4 (3) H: 25.3 (32) Other: 0.78 (1)	BMI: 31.2 Weight: 88.7	HgbA1c: 9.9 FBG: 255.6	NR	Insulin naive: Yes Insulin: 0 (0) OAM: 79 (100)
	Insulin glargine + metformin, 78	51.7	42 (53.8)	AA: 11.7 (15) C: 36.7 (47) Asian: 3.1 (4) H: 25 (32)	BMI: 30.8 Weight: 86.2	HgbA1c: 9.9 FBG: 239.4	NR	Insulin naive: Yes Insulin: 0 (0) OAM: 78 (100)
Raz, 2003[54]	Insulin aspart 70/30 + rosiglitazone, 26	60.3 (43–77)	19 (73.1)	C: 22 (84.6) Asian: 1 (3.8) Other: 3 (11.5)	BMI: 27.7	HgbA1c: 9.9 FBG: 259.8 Serum fructosamine: 398 µmol/L	10.9	Insulin naive: NR OAM: 26 (100%)
	Glibenclamide + rosiglitazone, 23	57.8 (43–71)	13 (56.5)	C: 19 (82.6) Asian: 2 (8.7) Other: 2 (8.7)	BMI: 27.6	HgbA1c: 10.3 FBG: 265.2 Serum fructosamine: 409.2 µmol/L	10.3	Insulin naive: NR OAM: 23 (100%)

Evidence Table 3. Population characteristics of the studies comparing a premixed insulin analogue to other diabetes treatments (continued)

Author, year	Group, N	Mean age (age range) in years	Male, n (%)	Race, n (%)	Mean BMI in kg/m2 Mean weight in kg	Mean HgbA1c in % Mean FBG in mg/dL#	Mean duration of diabetes in years	Previous treatment, n (%)
Raz, 2005[51]	Insulin aspart 70/30, 97	55.2	63 (65)	NR	BMI: 29.5	HgbA1c: 9.5	10	Insulin naive: NR OAM: 97* (100)
	Insulin aspart 70/30 + pioglitazone, 93	56.7	49 (53)	NR	BMI: 29.4	HgbA1c: 9.6	9.2	Insulin naive: NR OAM: 93* (100)
	Glibenclamide + pioglitazone, 91	55.8	56 (62)	NR	BMI: 29.5	HgbA1c: 9.4	9.9	Insulin naive: NR OAM: 91* (100)
Roach, 1999[67]	Insulin lispro 75/25, 44	56.5	23 (52*)	NR	BMI: 28.3	NR	12.8	Insulin naive: No Insulin: 44* (100)
	NPH/regular 70/30, 45	57.4	19 (42*)	NR	BMI: 29.4	NR	11.5	Insulin naive: No Insulin: 45* (100)
Roach, 1999[11]	Insulin lispro 50/50 + insulin lispro 75/25, 34	58	18 (53*)	NR	BMI: 28.4	NR	12.2	Insulin naive: No Insulin: 34* (100)
	NPH/regular 50/50 + NPH/ regular 70/30, 29	60.2	12 (41*)	NR	BMI: 28.4	NR	13.1	Insulin naive: No Insulin: 29* (100)
Roach, 2003[63]	Insulin lispro 75/25, 57	53.9	21 (40)	Asian: 52 (100)	Weight: 62.8	NR	12.4	Insulin naive: No Insulin: 57* (100)
	Insulin lispro 50/50 + insulin lispro 75/25, 58	54.2	22 (40)	Asian: 55 (100)	Weight: 65.1	NR	13.1	Insulin naive: No Insulin: 58* (100)
Roach, 2006[57]	Total, 20	53.5	10 (50)	AA: 4* (20) C: 16* (80)	BMI: 36.7 Weight: 108	HgbA1c: 8.4	NR	Insulin naive: No
Schernthaner, 2004[70]	Insulin lispro 50/50, 18	66.1	3 (17*)	NR	BMI: 29.5	HgbA1c: 8.3	16.2	Insulin naive: No Insulin: 18* (100)
	NPH/regular 70/30, 17	67.8	5 (29*)	NR	BMI: 28.8	HgbA1c: 8.5	14.2	Insulin naive: No Insulin: 17* (100)
	Total, 35	67	8 (23*)	NR	BMI: 29.2	NR	15.3	Insulin naive: No Insulin: 35* (100)
Schwartz, 2006[56]	Insulin lispro 75/25, 8	NR	NR	NR	NR	NR	NR	Insulin naive: No
	Insulin lispro 50/50, 7	NR	NR	NR	NR	NR	NR	Insulin naive: No
	NPH/regular 70/30, 8	NR	NR	NR	NR	NR	NR	Insulin naive: No
	Total, 23	61.3	17 (73.9)	AA: 2 (8.7) C: 13 (56.5) H: 8 (34.8)	BMI: 33 Weight: 98.5	HgbA1c: 8.1 FBG: 158.7	NR	Insulin naive: No Insulin: 23 (100)
Tamemoto, 2007[44]	Insulin aspart 70/30, 14	55.9	6 (54)	NR	BMI: 23.9	HgbA1c: 9.13 FBG: 183.3	9.8	Insulin naive: NR OAM: 14 (100)
	Insulin glargine, 20	61.7	13 (68)	NR	BMI: 25.5	HgbA1c: 8.45 FBG: 184.1	10.4	Insulin naive: NR OAM: 19 (100)

Evidence Table 3. Population characteristics of the studies comparing a premixed insulin analogue to other diabetes treatments (continued)

Author, year	Group, N	Mean age (age range) in years	Male, n (%)	Race, n (%)	Mean BMI in kg/m2 Mean weight in kg	Mean HgbA1c in % Mean FBG in mg/dL#	Mean duration of diabetes in years	Previous treatment, n (%)
Tirgoviste, 2003[40] Roach, 2001[39]	Insulin lispro 75/25, 85	58.7	30 (35*)	NR	BMI: 26.8 Weight: 74.1	HgbA1c: 9.85 FBG: 11.6 12.2	10.3	Insulin naive: Yes OAM: 85 (100)
	Glibenclamide, 87	60.3	31 (36*)	NR	BMI: 27.6 Weight: 75.8	HgbA1c: 10.07	10.2	Insulin naive: Yes OAM: 87 (100)
	Total, 172	59.5	61 (35*)	NR	Weight: 75	NR	10.2	Insulin naive: Yes OAM: 172 (100)
Yamada, 2007[71]	Insulin lispro 50/50, 15	66	12 (80*)	NR	BMI: 27	HgbA1c: 7.59 FBG: 130.3	13.7	Insulin naive: No Insulin: 15 (100)
	NPH/regular 70/30 + NPH/regular 50/50, 15	66.3	11 (73*)	NR	BMI: 23.8	HgbA1c: 7.33 FBG: 141.8	15.9	Insulin naive: No Insulin: 15 (100)

#All numbers have been converted from mmol/L to mg/dL. To convert from mg/dL to mmol/L, divide by 18.
*Number has been imputed.
†The study population for Boehm 2002[10] was patients with either type 1 or type 2 diabetes. The type 2 diabetic population was the same study population used for Boehm 2004.[42]
‡Raskin 2007[37] was conducted among a subpopulation of Raskin 2005[36] who were not using thiazolidinediones.

µmol/L = micromol per liter; AA = African American; BMI = body mass index; C = Caucasian; dL = deciliter; FPG = fasting blood glucose; H = Hispanic; HgbA1c = hemoglobinA1c; IQR = interquartile range; kg = kilogram; kg/m2 = kilogram per square meter; mg/dL = milligram per deciliter; NPH = neutral protamine Hagedorn; NR = not reported; OAM = oral antidiabetic medication; TZD = thiazolidinedione

Evidence Table 4. Comparative effectiveness of premixed insulin analogues and other diabetes treatments on intermediate outcomes

Author, year	Intervention	Fasting blood glucose in mg/dL#	2-hr PPG in mg/dL after breakfast#	Pre-dinner glucose in mg/dL#	2-hr PPG in mg/dL after dinner#	HgbA1c in %#	Quality of life#
Insulin aspart 70/30 vs. long-acting insulin analogues							
Holman, 2007[28]	GP1: Insulin aspart 70/30 (v) Start: 16 median Range: 10 - 26 T: bid D: 1 year Usual care D: 1 year GP2: Insulin detemir (v) Start: 16 median Range: 10 - 24 T: Bedtime, twice if required D: 1 year Usual care D: 1 year	GP1 F-B: -45 (56) p: <0.001 GP2 F-B: -59 (52) GP1-GP2: 14*	PPG (time not specified) (mg/dL) GP1 F-B: -68 (63) p: <0.001 GP2 F-B: 47 (54) GP1-GP2: -115*	GP1 F: 113.04 Median GP2 F: 115.56 Median		Total glycated hemoglobin GP1 B: 8.6 (0.8) F: 7.3 (0.9) p: <0.001 vs. GP2 F-B: -1.3 (1.1) GP2 B: 8.4 (0.8) F: 7.6 (1) F-B: -0.8 (1) GP1-GP2: 0* Glycated hemoglobin ≤ 7.0%, n (%) GP1 98 (41.7) p: <0.001 vs. GP2 GP2 65 (27.8)	EQ-5D GP1 F: 0.76 (95% CI: 0.73 – 0.8) p: overall 0.48 GP2 F: 0.78 (95% CI: 0.75 – 0.81)

Evidence Table 4. Comparative effectiveness of premixed insulin analogues and other diabetes treatments on intermediate outcomes (continued)

Author, year	Intervention	Fasting blood glucose in mg/dL#	2-hr PPG in mg/dL after breakfast#	Pre-dinner glucose in mg/dL#	2-hr PPG in mg/dL after dinner#	HgbA1c in %#	Quality of life#
Kann, 2006[47]	GP1: Insulin aspart 70/30 (v) Start: 0.1 U/kg bid Mean: 0.4 U/kg T: Breakfast, dinner D: 26 weeks metformin (v) Start: 500 mg bid or current dose T: Breakfast, dinner D: 26 weeks GP2: Insulin glargine (v) Start: 0.2 U/kg qd Mean: 0.39 U/kg T: preferred time (constant through study) D: 26 weeks glimepiride (v) Start: 1 mg daily or current dose T: Breakfast D: 26 weeks	GP1 B: 187.2† F: 136.8 (95% CI: 131.58 – 143.46) F-B: -50.4* GP2 B: 190.8† F: 136.8 (95% CI: 129.6 – 145.26) F-B: -54* GP1-GP2: 3.6* Fasting plasma glucose (time not specified) (mg/dL) GP1 F-B: -46.8 (4.32) p: 0.23 vs. GP2 GP2 F-B: -39.6 (4.5) GP1-GP2: -7*	90-min PPG - after breakfast (mg/dL) GP1 B: 248.4† F: 158.4† F-B: -90* GP2 B: 241.2† F: 187.2† F-B: -54* GP1-GP2: -36*	GP1 B: 187.2† F: 172.8† p: NS F-B: -14.4* GP2 B: 190.8† F: 156.6† F-B: -34.2* GP1-GP2: 19.8	90-min PPG - after dinner (mg/dL) GP1 B: 221.4† F: 156.6† F-B: -66.6* GP2 B: 223.2† F: 183.6† F-B: -39.6* GP1-GP2: -27*	GP1 F: 7.5 (1.1) p: 0.01 GP2 F: 7.9 (1.3) GP1-GP2: -0.5 (95% CI: -0.8 – -0.2) p: 0.0002 HgbA1c < 7%, n (%) GP1 42* (33.1) p: 0.2711 GP2 33* (26.2)	

Evidence Table 4. Comparative effectiveness of premixed insulin analogues and other diabetes treatments on intermediate outcomes (continued)

Author, year	Intervention	Fasting blood glucose in mg/dL#	2-hr PPG in mg/dL after breakfast#	Pre-dinner glucose in mg/dL#	2-hr PPG in mg/dL after dinner#	HgbA1c in %#	Quality of life#
Raskin, 2005[36 37]	GP1: Insulin aspart 70/30 (v) Start: 10 or 12 units T: Breakfast, dinner D: Unclear metformin (v) Range: 1500 – 2550 mg/day T: NR D: Unclear GP2: Insulin glargine (v) Start: 10-12 units/day T: Bedtime D: Unclear metformin (v) Range: 1500 - 2550 mg/day T: NR D: Unclear	GP1 F: 118.75† p: <0.05 GP2 F: 112.5† GP1‖ F: 122.4† p: NS GP2‖ F: 117† Fasting plasma glucose (time not specified) (mg/dL) GP1 B: 252 (67.4) F: 127 (40.6) p: NS F-B: 125 (72.9) GP2 B: 243 (68.8) F: 117 (44.3) F-B: 125 (74.4) GP1-GP2: 0* GP1‖ F-B: -128.88 (75.06) p: 0.11 GP2‖ F-B: -126 (79.02) GP1-GP2: -3*	90-min PPG - after breakfast (mg/dL) GP1 F: 153.125† p: NS GP2 F: 168.75† GP1‖ F: 154.8† p: NS GP2‖ F: 172.8†	GP1 F: 120.31† p: <0.05 GP2 F: 134.38† GP1‖ F: 129.6† p: NS GP2‖ F: 131.4†	90-min PPG - after dinner (mg/dL) GP1 F: 135.5† p: <0.05 GP2 F: 171.88† GP1‖ F: 127.62 (40.68) p: 0.0008 GP2‖ F: 176.22 (59.04) Dinner postprandial glucose increment (mg/dL) GP1-GP2‖: 19.386† p: 0.003	GP1 B: 10* F: 6.91 (1.17) p: <0.01 F-B: -2.79 (0.11) p: <0.01 GP2 B: 9* F: 7.41 (1.24) F-B: -2.36 (0.11) GP1-GP2: -1* GP1‖ F: 7 (1.3) p: 0.035 F-B: -2.89 (1.6) p: 0.035 GP2‖ F: 7.4 (1.3) F-B: -2.46 (1.6) HgbA1c < 7.0% GP1 71.3* (66†) p: <0.001 GP2 45.6* (40†) GP1‖ (65) p: 0.003 GP2‖ (41) HgbA1c ≤ 6.5% GP1 43.2* (40†) p: 0.036 GP2 31.9* (28†) GP1‖ (40) p: 0.17 GP2‖ (29)	

Evidence Table 4. Comparative effectiveness of premixed insulin analogues and other diabetes treatments on intermediate outcomes (continued)

Author, year	Intervention	Fasting blood glucose in mg/dL#	2-hr PPG in mg/dL after breakfast#	Pre-dinner glucose in mg/dL#	2-hr PPG in mg/dL after dinner#	HgbA1c in %#	Quality of life#
Tame-moto, 2007[44]	GP1: Insulin aspart 70/30 (v) Start: 10-16 units/day Mean: 26.7 units T: Breakfast, dinner D: 6 months continued ODM (unclear) T: NR D: 6 months GP2: Insulin glargine (v) Start: 6-8 units/day T: NR D: 6 months continued ODM (unclear) T: NR D: 6 months	GP1 B: 183.3 (54.6) p: 0.90 F: 141.4 (59.8) p: 0.79 vs. GP2; <0.01 vs. baseline F-B: -41.9* GP2 B: 184.1 (42.1) F: 136.0 (40.3) F-B: -48.1* GP1-GP2: 6.2				GP1 F-B: -1.2 (1.06) p: 0.49 GP2 F-B: -0.95 (0.84) GP1-GP2: 0* HgbA1c < 7%, n (%) GP1 1 (9.1) p: NS GP2 6 (31.6)	
Insulin aspart 70/30 vs. rapid-acting insulin analogues							
Holman, 2007[28]	GP1: Insulin aspart 70/30 (v) Start: 16 median Range: 10 - 26 T: bid D: 1 year Usual care D: 1 year GP2: Insulin aspart (v) Start: 18 median Range: 9 - 24 T: Breakfast, lunch, dinner D: 1 year Usual care D: 1 year	GP1 F-B: -45 (56) p: <0.001 vs. GP2 GP2 F-B: -23 (49) GP1-GP2: -22*	PPG (time not specified) (mg/dL) GP1 F-B: -68 (63) p: <0.001 vs. GP2 GP2 F-B: -83 (54) GP1-GP2: 15*	GP1 F: 113.04 Median GP2 F: 128.52 Median		Total glycated hemoglobin GP1 B: 8.6 (0.8) F: 7.3 (0.9) p: 0.08 vs. GP2 F-B: -1.3 (1.1) GP2 B: 8.6 (0.8) F: 7.2 (0.9) F-B: -1.4 (1) GP1-GP2: 0* Glycated hemoglobin ≤ 7.0% GP1 98 (41.7) p: 0.08 vs. GP2 GP2 116 (48.7)	EQ-5D GP1 F: 0.76 (95% CI: 0.73 – 0.8) p: overall 0.48 GP2 F: 0.76 (95% CI: 0.73 – 0.79)

Evidence Table 4. Comparative effectiveness of premixed insulin analogues and other diabetes treatments on intermediate outcomes (continued)

Author, year	Intervention	Fasting blood glucose in mg/dL#	2-hr PPG in mg/dL after breakfast#	Pre-dinner glucose in mg/dL#	2-hr PPG in mg/dL after dinner#	HgbA1c in %#	Quality of life#
Insulin aspart 70/30 vs. rapid-acting with long-acting insulin analogues							
Joshi, 2005[49]	GP1: Insulin aspart 70/30 (v) Mean: 40.19 U/day T: twice daily D: 12 weeks GP2: Insulin aspart (v) Mean: 28.26 U/day T: before every meal D: 12 weeks Insulin glargine (v) Mean: 24.52 U/day T: Bedtime D: 12 weeks	GP1 B: 186.59 (47.35) F: 114.83 (18.68) F-B: -72* p: <0.0001 GP2 B: 190.23 (55.63) F: 110.61 (16.79) F-B: -79* p: <0.0001 GP1-GP2: 7*	PPG (time not specified) (mg/dL) GP1 B: 287.29 (58.4) F: 171.54 (28.75) F-B: -115* p: <0.0001 GP2 B: 281.42 (68.76) F: 177.52 (24.72) F-B: -103* p: <0.0001 GP1-GP2: -12*			GP1 B: 8.79 (1.13) F: 7.2 (0.83) F-B: -1.58 p: <0.0001 GP2 B: 8.53 (1.22) F: 7.37 (0.83) F-B: -1.16 p: <0.0001 GP1-GP2: -1* p: <0.05 HgbA1c < 7%, n (%) GP1 52* (45.61) GP2 10* (32.26)	
Insulin aspart 70/30 vs. premixed human insulins							
Abraha-mian, 2005[50]	GP1: Insulin aspart 70/30 (v) Mean: 0.49 U/kg (start) and 0.61 U/kg (end) T: Breakfast, lunch, dinner D: 24 weeks GP2: NPH/regular 70/30 (v) Mean: 0.46 U/kg (start) and 0.59 U/kg (end) T: Breakfast, dinner D: 24 weeks	GP1 F: 151† (SEM 4†) GP2 F: 143† (SEM 4†)	90-min PPG - after breakfast (mg/dL) GP1 F: 175† (SEM 10†) GP2 F: 189† (SEM 20†) 90-min PPG increment - after breakfast (mg/dL) F: p: 0.0572 vs. GP2 (favoring GP1)	GP1 F: 142 (SEM 7†) p: 0.0069 vs GP2 GP2 F: 166 (SEM 15†)	90-min PPG - after dinner (mg/dL) GP1 F: 154 (SEM 15†) p: 0.0022 vs GP2 GP2 F: 182 (SEM 7†) 90-min PPG increment - after dinner (mg/dL) F: p: 0.4096	GP1 B: 9.8 (1.55) F: 7.6 (1.1) F-B: -2* p: <0.0001 GP2 B: 9.85 (1.55) F: 7.7 (1.1) F-B: -2* p: <0.0001 GP1-GP2: 0* p: 0.641 vs GP2	

Evidence Table 4. Comparative effectiveness of premixed insulin analogues and other diabetes treatments on intermediate outcomes (continued)

Author, year	Intervention	Fasting blood glucose in mg/dL#	2-hr PPG in mg/dL after breakfast#	Pre-dinner glucose in mg/dL#	2-hr PPG in mg/dL after dinner#	HgbA1c in %#	Quality of life#
Boehm, 2004[10] [42]‡	GP1: Insulin aspart 70/30 (v) Start: 0.57 U/kg T: Breakfast, dinner D: 24 months GP2: NPH/regular 70/30 (v) Start: 0.57 U/Kg T: Breakfast, dinner D: 24 months					GP1 F: 8.35 (0.2) GP2 F: 8.13 (0.16) GP1-GP2: 0.03 (90% CI: -0.29 – 0.34) p: 0.89	
Herman-sen, 2002[55]	GP1: Insulin aspart 70/30 (fix) Start: 0.4 units/kg T: Breakfast D: 1 day GP2: NPH/regular 70/30 (fix) Start: 0.4 units/kg T: Breakfast D: 1 day		GP1 F: 13.9† GP2 F: 15.0† 2-hr PPG excursion GP1 F: 7.7 (2.7) p: <0.01 Ratio between treatments = 0.81 (95% CI: 0.71 - 0.93) p: <0.01			
Kapitza, 2004[53]	GP1: Insulin aspart 70/30 (NA) T: Breakfast (15 min after) D: 1 day GP2: NPH/regular 70/30 (NA) T: Breakfast (15 min before) D: 1 day		2-hr PPG increment - after breakfast (mg/dL) GP1 F: 52.2† GP2 F: 91.8†				

Evidence Table 4. Comparative effectiveness of premixed insulin analogues and other diabetes treatments on intermediate outcomes (continued)

Author, year	Intervention	Fasting blood glucose in mg/dL#	2-hr PPG in mg/dL after breakfast#	Pre-dinner glucose in mg/dL#	2-hr PPG in mg/dL after dinner#	HgbA1c in %#	Quality of life#
Kapitza, 2004[53]	GP1: Insulin aspart 70/30 (NA) T: Breakfast (15 min after) D: 1 day GP2: NPH/regular 70/30 (NA) T: Breakfast (right before) D: 1 day		2-hr PPG increment - after breakfast (mg/dL) GP1 F: 52.2† GP2 F: 81†				
Kapitza, 2004[53]	GP1: Insulin aspart 70/30 (NA) T: Breakfast (right before) D: 1 day GP2: NPH/regular 70/30 (NA) T: Breakfast (15 min before) D: 1 day		2-hr PPG increment - after breakfast (mg/dL) GP1 F: 81† GP2 F: 91.8†				
Kapitza, 2004[53]	GP1: Insulin aspart 70/30 (NA) T: Breakfast (right before) D: 1 day GP2: NPH/regular 70/30 (NA) T: Breakfast (right before) D: 1 day		2-hr PPG increment - after breakfast (mg/dL) GP1 F: 81† GP2 F: 81†				

Evidence Table 4. Comparative effectiveness of premixed insulin analogues and other diabetes treatments on intermediate outcomes (continued)

Author, year	Intervention	Fasting blood glucose in mg/dL#	2-hr PPG in mg/dL after breakfast#	Pre-dinner glucose in mg/dL#	2-hr PPG in mg/dL after dinner#	HgbA1c in %#	Quality of life#
Kilo, 2003[16]	GP1: Insulin aspart 70/30 (v) Start: 0.16 Units/day Mean: 26 U/day T: Dinner D: 12 weeks metformin (fix) Mean: about 2200 mg Range: 500 - 2550 mg T: 1-3 times/day D: 4 weeks run-in, then 12 weeks GP2: NPH/regular 70/30 (v) Start: 0.16 Units/day Mean: 29 U/day T: Dinner D: 12 weeks metformin (fix) Mean: about 2200 mg Range: 500 - 2550 mg T: 1-3 times/day D: 4 weeks run-in, then 12 weeks	GP1 F-B: -75 (72.3) GP2 F-B: -63 (86.2) GP1-GP2: -12*	GP1 B: 265† (±SE 5-10†) F: 190† (±SE 5-10†) F-B: -75 GP2 B: 266† (±SE 5-10†) F: 180† (±SE 5-10†) F-B: -86 GP1-GP2: 11		GP1 B: 250† (±SE 5-10†) F: 165† (±SE 5-10†) F-B: -85 GP2 B: 235† (±SE 5-10†) F: 168† (±SE 5-10†) F-B: -67 GP1-GP2: -18	GP1 F-B: -1.3 (SE 0.2†) GP2 F-B: -1.1 (SE 0.2†) GP1-GP2: 0*	
McNally, 2007[45]	GP1: Insulin aspart 70/30 (v) Start: 100 units/mL Mean: 68.8 units Range: 6 - 238.7 T: Breakfast, dinner D: 16 weeks GP2: NPH/regular 70/30 (v) Start: 100 units/mL Mean: 66.6 units Range: 11.3 - 240 T: Breakfast, dinner D: 16 weeks					GP1 F: 7.28 GP2 F: 7.22 GP1-GP2: 0.06 (95% CI: -0.04 – 0.17) p: 0.21	WHO-DTSQ GP1 F: 30.6 (5.84) GP2 F: 30.95 (5.01) GP1-GP2: -0.46 p: 0.25

Evidence Table 4. Comparative effectiveness of premixed insulin analogues and other diabetes treatments on intermediate outcomes (continued)

Author, year	Intervention	Fasting blood glucose in mg/dL#	2-hr PPG in mg/dL after breakfast#	Pre-dinner glucose in mg/dL#	2-hr PPG in mg/dL after dinner#	HgbA1c in %#	Quality of life#
Insulin aspart 70/30 vs. intermediate-acting human insulins							
Christ-iansen, 2003[14]	GP1: Insulin aspart 70/30 (v) Start: insulin naïve: 8 - 16 units/day; taking NPH prior to trial: pretrial dose T: Breakfast, dinner D: 16 weeks GP2: NPH insulin (v) Start: insulin naïve: 8 - 16 units/day; taking NPH prior to trial: pretrial dose T: Breakfast, dinner D: 16 weeks	GP1 F-B: -25.2 GP2 F-B: -27 GP1-GP2: 2*				GP1 F-B: 0.67 p: <0.0001 vs. baseline GP2 F-B: 0.61 p: <0.0001 vs. baseline GP1-GP2: 0*	
Kilo, 2003[16]	GP1: Insulin aspart 70/30 (v) Start: 0.16 Units/day Mean: 26 U/day T: Dinner D: 12 weeks metformin (fix) Mean: about 2200 mg Range: 500 - 2550 mg T: 1-3 times/day D: 4 weeks run-in, then 12 weeks GP2: NPH insulin (v) Start: 0.16 Units/day Mean: 28 U/day T: Bedtime D: 12 weeks metformin (fix) Mean: about 2200 mg Range: 500 - 2550 mg T: 1-3 times/day D: 4 weeks run-in, then 12 weeks	GP1 F-B: -75 (72.3) GP2 F-B: -91 (72) GP1-GP2: 16*	GP1 B: 265† (±SE 5-10†) F: 190† (±SE 5-10†) F-B: -75 GP2 B: 266† (±SE 5-10†) F: 180† (±SE 5-10†) F-B: -86 GP1-GP2: 11		GP1 B: 250† (±SE 5-10†) F: 165† (±SE 5-10†) F-B: -85 GP2 B: 240† (±SE 5-10†) F: 190† (±SE 5-10†) F-B: -50 GP1-GP2: -35	GP1 F-B: -1.3 (SE 0.2†) GP2 F-B: -1.2 (SE 0.2†) GP1-GP2: 0*	

Evidence Table 4. Comparative effectiveness of premixed insulin analogues and other diabetes treatments on intermediate outcomes (continued)

Author, year	Intervention	Fasting blood glucose in mg/dL#	2-hr PPG in mg/dL after breakfast#	Pre-dinner glucose in mg/dL#	2-hr PPG in mg/dL after dinner#	HgbA1c in %#	Quality of life#
Insulin aspart 70/30 vs. oral antidiabetic agents							
Bebakar, 2007[43]	GP1: Insulin aspart 70/30 (v) Start: 0.2 U/kg/day Range: 0.16 U/kg (qd group) - 0.43 U/kg (bid group) T: once or twice daily D: 24 weeks GP2: ODM (v) T: NR D: 24 weeks	GP1 F-B: -39.6 (54) p: <0.005 vs. GP2 GP2 F-B: -9 (48.24) GP1-GP2: -31* Fasting plasma glucose (time not specified) (mg/dL) GP1 F-B: -34.38 (39.96) p: <0.05 vs. GP2 GP2 F-B: -18.18 (39.6) GP1-GP2: -16*	90-min PPG - after breakfast (mg/dL) GP1 F-B: -43.38 (84.24) p: <0.05 vs. GP2 GP2 F-B: -14.04 (71.46) GP1-GP2: -18*	GP1 F-B: -36.72 (69.66) p: <0.005 vs. GP2 GP2 F-B: 1.44 (61.92) GP1-GP2: -38*	90-min PPG - after dinner (mg/dL) GP1 F-B: -68.22 (80.64) p: <0.005 vs. GP2 GP2 F-B: -9.36 (75.24) GP1-GP2: -59*	GP1 F-B: -1.16 (1.01) p: <0.005 vs. GP2 GP2 F-B: -0.58 (0.95) GP1-GP2: 0* HgbA1c < 7%, n (%) GP1 32* (25) GP2 8* (12)	
Kvapil, 2006[48]	GP1: Insulin aspart 70/30 (v) Start: 0.3 U/kg/day Mean: 0.51 U/kg/day T: Breakfast, dinner D: 16 weeks GP2: metformin (fix) Mean: 1660 mg daily Range: 500 - 3000 mg T: NR D: 16 weeks glibencamide (v) Start: 1.75 mg Mean: 2.33 (start) and 6.58 mg daily (end) T: once or twice daily D: 16 weeks	GP1-GP2: -0.18 (SE 4.86) p: NS	90-min PPG - after breakfast (mg/dL) GP1-GP2: -5.22 (SE 7.2) p: NS	GP1-GP2: 10.26 (SE 6.12) p: NS	90-min PPG - after dinner (mg/dL) GP1-GP2: 2.7 (SE 6.66) p: NS	GP1-GP2: 0.2 (SE 0.15) p: NS	

Evidence Table 4. Comparative effectiveness of premixed insulin analogues and other diabetes treatments on intermediate outcomes (continued)

Author, year	Intervention	Fasting blood glucose in mg/dL#	2-hr PPG in mg/dL after breakfast#	Pre-dinner glucose in mg/dL#	2-hr PPG in mg/dL after dinner#	HgbA1c in %#	Quality of life#
Kvapil, 2006[48]	GP1: Insulin aspart 70/30 (v) Start: 0.2 U/kg/day Mean: 0.3 U/kg/day T: Breakfast, dinner D: 16 weeks metformin (fix) Mean: 1660 mg daily Range: 500 - 3000 mg T: NR D: 16 weeks GP2: metformin (fix) Mean: 1660 mg daily Range: 500 - 3000 mg T: NR D: 16 weeks glibencamide (v) Start: 1.75 mg Mean: 2.33 (start) and 6.58 mg daily (end) T: once or twice daily D: 16 weeks	GP1-GP2: -1.26 (SE 4.86) p: NS	90-min PPG - after breakfast (mg/dL) GP1-GP2: -5.22 (SE 7.2) p: NS	GP1-GP2: 9.18 (SE 6.12) p: NS	90-min PPG - after dinner (mg/dL) GP1-GP2: -0.36 (SE 6.66) p: NS	GP1-GP2: -0.20 (SE 0.15) p: NS	
Raz, 2003[54]	GP1: Insulin aspart 70/30 (v) Start: 6 - 8 U bid T: Breakfast, dinner D: 6 weeks rosiglitazone (fix) Start: 4 mg T: Breakfast D: 6 weeks GP2: glibenclamide (fix) Range: 7.5 – 15 mg T: Dinner D: 6 weeks rosiglitazone (fix) Start: 4 mg T: Breakfast D: 6 weeks	GP1 F-B: 58 p: NS vs. GP2 GP2 F-B: 34.2 GP1-GP2: 24*	PPG (time not specified) (mg/dL) GP1 F-B: 80.6 GP2 F-B: 52.9 GP1-GP2: 28*	GP1 F-B: 36.2 p: NS vs. GP2 GP2 F-B: 43.3 GP1-GP2: -7*	GP1 F-B: 72.8 p: NS vs. GP2 GP2 F-B: 47 GP1-GP2: 26*	GP1 B: 9.9 F: 9.4 F-B: 0.7 p: NS vs. GP2 GP2 B: 10.3 F: 10.1 F-B: 0.2 GP1-GP2: 1*	

Evidence Table 4. Comparative effectiveness of premixed insulin analogues and other diabetes treatments on intermediate outcomes (continued)

Author, year	Intervention	Fasting blood glucose in mg/dL#	2-hr PPG in mg/dL after breakfast#	Pre-dinner glucose in mg/dL#	2-hr PPG in mg/dL after dinner#	HgbA1c in %#	Quality of life#
Raz, 2005[51]	GP1: Insulin aspart 70/30 (v) Start: 0.3 U/kg/day Mean: 0.7 U/kg/day T: Breakfast, dinner D: 18 weeks GP2: Glibenclamide (v) Start: 5 to 10 mg Mean: 14 mg T: Breakfast D: 18 weeks Pioglitazone (fix) Start: 30 mg Mean: 30 mg T: Breakfast D: 18 weeks	GP1 B: 178* F: 162† F-B: -16 p: NS GP2 B: 171* F: 169 (65) F-B: -2 p: NS GP1-GP2: -14*	90-min PPG - after breakfast (mg/dL) GP1 F: 196.2† GP2 F: 223.2†		90-min PPG - after dinner (mg/dL) GP1 F: 199.8† GP2 F: 212.4† 90-min PPG increment - after dinner (mg/dL) GP1-GP2: -8.1 (8.46) p: NS	GP1 B: 9.5 (1.3) F: 9 (1.3) F-B: -0.5 p: NS GP2 B: 9.4 (1.4) F: 9 (2.1) F-B: -0.4 p: NS GP1-GP2: -0.9*	
Raz, 2005[51]	GP1: Insulin aspart 70/30 (v) Start: 0.2 U/kg/day Mean: 0.5 U/kg/day T: Breakfast, dinner D: 18 weeks Pioglitazone (fix) Start: 30 mg Mean: 30 mg T: Breakfast D: 18 weeks GP2: Glibenclamide (v) Start: 5 to 10 mg Mean: 14 mg T: Breakfast D: 18 weeks Pioglitazone (fix) Start: 30 mg Mean: 30 mg T: Breakfast D: 18 weeks	GP1 B: 184* F: 153 (45) p: 0.012 vs GP2 F-B: -31 p: NS GP2 B: 171* F: 169 (65) F-B: -2 p: NS GP1-GP2: -29*	90-min PPG - after breakfast (mg/dL) GP1 F: 178.2† GP2 F: 223.2†		90-min PPG increment - after dinner (mg/dL) F: 178.2† GP2 F: 212.4† GP1-GP2: -12.96 (8.64) p: NS	GP1 B: 9.6 (1.3) F: 8.4 (1.2) F-B: -1.2 p: NS GP2 B: 9.4 (1.4) F: 9 (2.1) F-B: -0.4 p: NS GP1-GP2: -0.64 (0.23) p: 0.005	

Evidence Table 4. Comparative effectiveness of premixed insulin analogues and other diabetes treatments on intermediate outcomes (continued)

Author, year	Intervention	Fasting blood glucose in mg/dL#	2-hr PPG in mg/dL after breakfast#	Pre-dinner glucose in mg/dL#	2-hr PPG in mg/dL after dinner#	HgbA1c in %#	Quality of life#
Insulin aspart 70/30 vs. exenatide							
Nauck, 2007[46]	GP1: Insulin aspart 70/30 (v) Start: 15.7 U/day Mean: 24.4 U/day T: Breakfast, dinner D: 52 weeks 'optimally' effective metformin and sulfonylurea therapy (v) T: NR D: 52 weeks GP2: exenatide (v) Start: 5 µg bid Range: 5 - 10 µg bid T: Breakfast D: 52 weeks 'optimally' effective metformin and sulfonylurea (v) T: NR D: 52 weeks	GP1 B: 177.12† (SE 3.006†) F: 147.06† (SE 1.512†) p: 0.037 F-B: -30.06* p: <0.001 GP2 B: 173.34† (SE 2.16†) F: 153† (SE 2.16†) F-B: -20.34* p: <0.001 Fasting plasma glucose (time not specified) (mg/dL) GP1 F-B: -30.6 p: <0.001 GP2 F-B: -32.4 p: <0.001 GP1-GP2: 1.8 (95% CI: -7.2 – 10.8) p: 0.689	GP1 B: 229.5† (SE 3.6†) F: 171† (SE 3.06†) F-B: -58.5* p: <0.001 GP2 B: 222.84† (SE 3.06†) F: 153† (SE 2.16†) p: <0.001 F-B: -69.84* p: <0.001 GP1-GP2: 11.34* PPG excursion - after breakfast (NA) GP1 p: <0.001	GP1 B: 171.72† (SE 3.42†) F: 141.12† (SE 3.06†) p: <0.001 vs. baseline F-B: -30.6* GP2 B: 168.84† (SE 3.78†) F: 147.24† (SE 3.06†) p: <0.001 vs. baseline F-B: -21.6* GP1-GP2: -9*	GP1 B: 210.06† (SE 3.78†) F: 165.06† (SE 3.06†) p: <0.001 F-B: -45 GP2 B: 203.94† (SE 3.06†) F: 147.06† (SE 3.78†) p: <0.001 F-B: -57.6 p: <0.001 GP1-GP2: 13* PPG excursion after dinner (NA) GP1 p: <0.001	GP1 F-B: -0.89 p: <0.001 GP2 F-B: -1.04 p: <0.001 GP1-GP2: 0.15 (95% CI: -0.01 – 0.32) p: 0.067 HgbA1c ≤ 7.0%, n (%) GP1 57 (24) p: 0.038 GP2 72 (32)	

Evidence Table 4. Comparative effectiveness of premixed insulin analogues and other diabetes treatments on intermediate outcomes (continued)

Author, year	Intervention	Fasting blood glucose in mg/dL#	2-hr PPG in mg/dL after breakfast#	Pre-dinner glucose in mg/dL#	2-hr PPG in mg/dL after dinner#	HgbA1c in %#	Quality of life#
Insulin aspart 70/30 vs. insulin lispro 75/25							
Hermansen, 2002[55]	GP1: Insulin aspart 70/30 (fix) Start: 0.4 units/kg T: Breakfast D: 1 day GP2: Insulin lispro 75/25 (fix) Start: 0.4 units/kg T: Breakfast D: 1 day		GP1 F: 13.9† GP2 F: 14.5† 2-hr PPG excursion GP1 F: 7.7 (2.7) p: NS vs. GP2 Ratio between treatments = 0.97 (95% CI: 0.85 - 1.11) p: NS				
Niskanen, 2004[52]	GP1: Insulin aspart 70/30 (v) Mean: 0.65 U/kg to 0.67 U/kg T: Breakfast, dinner D: 12 weeks GP2: Insulin lispro 75/25 (v) Mean: 0.67 U/kg to 0.71 U/kg T: Breakfast, dinner D: 12 weeks	GP1 F: 136.8 GP2 F: 135 GP1-GP2: 3.6 (95% CI: -0.54 – 10.8) p: 0.422	90-min PPG after breakfast (mg/dL) GP1 F: 171 GP2 F: 174.6 GP1-GP2: -3.6 (95% CI: -18 – 9) p: 0.524	GP1 F: 8.7 GP2 F: 8.6 GP1-GP2: 0.1 (95% CI: -0.5 – 0.7) p: 0.824	90-min PPG after dinner (mg/dL) GP1 F: 172.8 GP2 F: 180 GP1-GP2: -7.2 (95% CI: -19.8 – 3.6) p: 0.186	GP1 F: 8.15 GP2 F: 8.01 GP1-GP2: 0.14 (90% CI: 0.008 – 0.275) p: 0.082	

Evidence Table 4. Comparative effectiveness of premixed insulin analogues and other diabetes treatments on intermediate outcomes (continued)

Author, year	Intervention	Fasting blood glucose in mg/dL#	2-hr PPG in mg/dL after breakfast#	Pre-dinner glucose in mg/dL#	2-hr PPG in mg/dL after dinner#	HgbA1c in %#	Quality of life#
Insulin aspart 70/30 vs. insulin aspart 70/30 + oral antidiabetic agents							
Kvapil, 2006[48]	GP1: Insulin aspart 70/30 (v) Start: 0.3 U/kg/day Mean: 0.51 U/kg/day T: Breakfast, dinner D: 16 weeks GP2: Insulin aspart 70/30 (v) Start: 0.2 U/kg/day Mean: 0.3 U/kg/day T: Breakfast, dinner D: 16 weeks metformin (fix) Mean: 1660 mg daily Range: 500 - 3000 mg T: NR D: 16 weeks	GP1-GP2: 0.9 (SE 4.86) p: NS	90-min PPG - after breakfast (mg/dL) GP1-GP2: 0 (SE 7.38) p: NS	GP1-GP2: 1.08 (SE 6.3) p: NS	90-min PPG - after dinner (mg/dL) GP1-GP2: 3.06 (SE 6.66) p: NS	GP1-GP2: 0.39 (SE 0.15) p: <0.01	
Raz, 2005[51]	GP1: Insulin aspart 70/30 (v) Start: 0.3 U/kg/day Mean: 0.7 U/kg/day T: Breakfast, dinner D: 18 weeks GP2: Insulin aspart 70/30 (v) Start: 0.2 U/kg/day Mean: 0.5 U/kg/day T: Breakfast, dinner D: 18 weeks Pioglitazone (fix) Start: 30 mg Mean: 30 mg T: Breakfast D: 18 weeks	GP1 B: 178* F: 162† F-B: -16 p: NS GP2 B: 184* F: 153 (45) F-B: -31 p: NS GP1-GP2: 15*	90-min PPG - after breakfast (mg/dL) GP1 F: 196.2† GP2 F: 178.2†		90-min PPG - after dinner (mg/dL) GP1 F: 199.8† GP2 F: 178.2† 90-min PPG increment - after dinner (mg/dL) GP1-GP2: 4.86 (8.46) p: NS	GP1 B: 9.5 (1.3) F: 9 (1.3) F-B: -0.5 p: NS GP2 B: 9.6 (1.3) F: 8.4 (1.2) F-B: -1.2 p: NS GP1-GP2: 0.60 (0.22) p: 0.008	

Evidence Table 4. Comparative effectiveness of premixed insulin analogues and other diabetes treatments on intermediate outcomes (continued)

Author, year	Intervention	Fasting blood glucose in mg/dL#	2-hr PPG in mg/dL after breakfast#	Pre-dinner glucose in mg/dL#	2-hr PPG in mg/dL after dinner#	HgbA1c in %#	Quality of life#
Insulin lispro 75/25 vs. long-acting insulin analogues							
Cox, 2007[68]	GP1: Insulin lispro 75/25 (v) T: Breakfast, dinner D: 12 weeks metformin (unclear) T: NR D: 12 weeks GP2: Insulin glargine (v) T: Bedtime D: 12 weeks metformin (unclear) T: NR D: 12 weeks	GP1 F: 8.5 (1.5) p: 0.056 GP2 F: 7.8 (2)	GP1 F: 11 (1.9) p: 0.642 GP2 F: 10.9 (2.1) GP1-GP2: 2.2 (0.7) p: NS	GP1 F: 176.4 (45) p: 0.076 GP2 F: 192.6 (54)	GP1 F: 198 (41.4) p: 0.001 GP2 F: 221.4 (52.2) GP1-GP2: 55.8 (23.4) p: NS		BDI-II GP1 B: 8.2 (6) p: NS F: 5.5 (3.8) p: 0.115 F-B: -2* p: 0.018 GP2 B: 8.2 (6) F: 6.8 (5.9) F-B: -1* p: NS GP1-GP2: -1*

Evidence Table 4. Comparative effectiveness of premixed insulin analogues and other diabetes treatments on intermediate outcomes (continued)

Author, year	Intervention	Fasting blood glucose in mg/dL#	2-hr PPG in mg/dL after breakfast#	Pre-dinner glucose in mg/dL#	2-hr PPG in mg/dL after dinner#	HgbA1c in %#	Quality of life#
Jacober, 2006[58]	GP1: Insulin lispro 50/50 (v) Mean: 0.353 IU/kg; 36.73 IU T: Breakfast, lunch D: 4 months Insulin lispro 75/25 (v) T: Dinner D: 4 months existing ODM (NR) T: NR D: 4 months GP2: Insulin glargine (v) Mean: 0.276 IU/kg; 27.98 IU T: Bedtime D: 4 months existing ODM (NR) T: NR D: 4 months	GP1 F: 130† (25†) p: NS GP2 F: 125† (15†)	GP1 F: 153.5 (35.6) p: 0.0034 GP2 F: 172.1 (35)	GP1 F: 123.1 (36.1) p: 0.0205 GP2 F: 139 (41.9)	GP1 F: 145.4 (38.2) p: 0.0066 GP2 F: 161.9 (42.3)	Overall results GP1 B: 8* F: 7.08 (0.11) p: 0.003 F-B: -1.01 (0.1) p: 0.0068 vs. GP2 GP2 B: 8* F: 7.34 (0.11) F-B: -0.75 (0.1) GP1-GP2: 0* 1st per. results GP1 F: 6.97 (0.62†) GP2 F: 7.32 (0.93†) 2nd per. results GP1 F: 7.22 (0.77†) GP2 F: 7.33 (0.92†) HgbA1c ≤ 7%, n (%) GP1 26* (44) p: 0.1026 GP2 18* (31)	

Evidence Table 4. Comparative effectiveness of premixed insulin analogues and other diabetes treatments on intermediate outcomes (continued)

Author, year	Intervention	Fasting blood glucose in mg/dL#	2-hr PPG in mg/dL after breakfast#	Pre-dinner glucose in mg/dL#	2-hr PPG in mg/dL after dinner#	HgbA1c in %#	Quality of life#
Malone, 2004[59]	GP1: Insulin lispro 75/25 (v) Mean: 0.62 U/kg T: Breakfast, dinner D: 16 weeks Metformin (NR) Mean: 1945 mg Range: 1500 - 2550 mg T: NR D: 16 weeks GP2: Insulin glargine (v) Mean: 0.57 U/kg T: Bedtime D: 16 weeks Metformin (NR) Mean: 1997 mg Range: 1500 - 2550 mg T: NR D: 16 weeks	GP1 B: 150* F: 139.3 (36.6) p: <0.001 F-B: -11.3 (44.5) p: 0.001 vs. GP2 GP2 B: 153* F: 123.9 (34.9) F-B: -29 (47.4) GP1-GP2: 18* Met target FBG of 90 to 126 mg/dL, n (%) GP1 31 (45) p: 0.019 GP2 44 (65)	GP1 F: 156.4 (43.6) p: 0.012 GP2 F: 171.1 (44.9) Met target 2-hr PPG of 144 to 180 mg/dL, n (%) GP1 55 (80) p: 0.036 GP2 43 (63)		GP1 F: 164.8 (42.5) p: <0.001 GP2 F: 193.8 (51) Met target 2-hr PPG of 144 to 180 mg/dL, n (%) GP1 50 (72) p: <0.001 GP2 29 (43)	GP1 B: 8.7 (1.3) F: 7.4 (1.1) p: 0.002 F-B: -1.32 (1.01) p: 0.003 vs. GP2; <0.001 vs. baseline GP2 B: 8.7 (1.3) F: 7.8 (1.1) F-B: -0.93 (0.89) p: <0.001 vs. baseline GP1-GP2: 0* HgbA1c ≤ 7.0%, n (%) GP1 30 (42) p: <0.001 GP2 13 (18)	

Evidence Table 4. Comparative effectiveness of premixed insulin analogues and other diabetes treatments on intermediate outcomes (continued)

Author, year	Intervention	Fasting blood glucose in mg/dL#	2-hr PPG in mg/dL after breakfast#	Pre-dinner glucose in mg/dL#	2-hr PPG in mg/dL after dinner#	HgbA1c in %#	Quality of life#
Malone, 2005[60]	GP1: Insulin lispro 75/25 (v) Mean: 0.42 U/kg T: Breakfast, dinner D: 16 weeks Metformin (fix) Mean: 2128 mg Range: 1500 - 2550 mg T: NR D: 16 weeks GP2: Insulin glargine (v) Mean: 0.36 U/kg T: Bedtime D: 16 weeks Metformin (fix) Mean: 2146 mg Range: 1500 - 2550 mg T: NR D: 16 weeks	GP1 F: 142.2 (34.56) p: 0.007 GP2 F: 133.02 (35.28) Met target FBG of < 126 mg/dL (7.0 mmol/L), n (%) GP1 33* (34) p: 0.01 GP2 49* (51)	GP1 F: 169.92 (46.08) p: <0.001 GP2 F: 194.94 (49.32) Met target 2-hr PPG of < 180 mg/dL (10 mmol/L), n (%) GP1 64* (66) p: <0.001 GP2 41* (42)		GP1 F: 172.62 (45) p: <0.001 GP2 F: 200.7 (45.36) Met target 2-hr PPG of < 180 mg/dL (10 mmol/L), n (%) GP1 62* (64) p: <0.001 GP2 39* (40)	GP1 B: 9* F: 7.54 (0.87) p: <0.001 F-B: -1 (0.85) p: <0.001 vs. GP2 GP2 B: 8* F: 8.14 (1.03) F-B: -0.42 (0.92) GP1-GP2: -1* HgbA1c ≤ 7.0%, n (%) GP1 (30) p: 0.002 GP2 (12) HgbA1c ≤ 6.5%, n (%) GP1 p: 0.1	

Evidence Table 4. Comparative effectiveness of premixed insulin analogues and other diabetes treatments on intermediate outcomes (continued)

Author, year	Intervention	Fasting blood glucose in mg/dL#	2-hr PPG in mg/dL after breakfast#	Pre-dinner glucose in mg/dL#	2-hr PPG in mg/dL after dinner#	HgbA1c in %#	Quality of life#
Roach, 2006[57]	GP1: Insulin lispro 75/25 (v) Mean: 23 U (morning) and 37 U (evening) Range: 0 – 72 U (morning); 11 – 88 U (evening) T: Breakfast, dinner D: 12 weeks ODM (NR) Start: current dose T: NR D: 12 weeks Metformin (v) Start: 500 mg qd T: NR D: 12 weeks GP2: Insulin glargine (v) Mean: 44 U Range: 14 - 100 U T: Breakfast D: 12 weeks ODM (NR) Start: current dose T: NR D: 12 weeks Metformin (v) Start: 500 mg qd T: NR D: 12 weeks	GP1 F: 104.4 (20.16) p: 0.649 GP2 F: 99 (38.52)	GP1 F: 187.2 (43.2) p: 0.551 GP2 F: 180 (37.8)	GP1 F: 91.8 (17.1) p: 0.141 GP2 F: 100.8 (25.38)	GP1 F: 144 (39.24) p: 0.005 GP2 F: 176.4 (36)	GP1 F: 6.9 (0.52) p: 0.035 GP2 F: 7.3 (0.81)	

Evidence Table 4. Comparative effectiveness of premixed insulin analogues and other diabetes treatments on intermediate outcomes (continued)

Author, year	Intervention	Fasting blood glucose in mg/dL#	2-hr PPG in mg/dL after breakfast#	Pre-dinner glucose in mg/dL#	2-hr PPG in mg/dL after dinner#	HgbA1c in %#	Quality of life#
Insulin lispro 75/25 vs. premixed human insulins							
Coscelli, 2003[61]	GP1: Insulin lispro 75/25 (v) Mean: 38.1 Range: 12 - 72 T: Breakfast, dinner D: 12 days diet/exercise D: 12 days GP2: NPH/regular 70/30 (v) Mean: 37.3 Range: 10 - 72 T: Breakfast, dinner D: 12 days diet/exercise D: 12 days		GP1 F: 157 (43.2) p: <0.05 GP2 F: 180 (43.2) 2-hr PPG excursion GP1 F: 2.4 (48.9) p: 0.08 GP2 F: 17.9 (41.43)		2-hr PPG excursion GP1 F: 12.2 (48.01) p: <0.05 GP2 F: 35.5 (36.92)		
Herman-sen, 2002[55]	GP1: Insulin lispro 75/25 (fix) Start: 0.4 units/kg T: Breakfast D: 1 day GP2: NPH/regular 70/30 (fix) Start: 0.4 units/kg T: Breakfast D: 1 day		GP1 F: 14.5† GP2 F: 15.0† 2-hr PPG excursion GP1 F: 8.5 (3.3) Ratio between treatments = 0.81 (95% CI: 0.72 – 0.94) p: <0.01 GP2 F: 9.4 (2.7) Ratio between treatments = ref				

Evidence Table 4. Comparative effectiveness of premixed insulin analogues and other diabetes treatments on intermediate outcomes (continued)

Author, year	Intervention	Fasting blood glucose in mg/dL#	2-hr PPG in mg/dL after breakfast#	Pre-dinner glucose in mg/dL#	2-hr PPG in mg/dL after dinner#	HgbA1c in %#	Quality of life#
Herz, 2002[65]	GP1: Insulin lispro 75/25 (v) Mean: 26.1 U T: Breakfast, dinner D: 4 weeks GP2: NPH/regular 70/30 (v) Mean: 26.2 U T: Breakfast, dinner D: 4 weeks		GP1 F: 189 (SE 7.2) p: 0.016 GP2 F: 208.8 (SE 7.2)				
Herz, 2003[13]	GP1: Insulin lispro 75/25 (v) Mean: 31.6¶ (morning) and 26.8¶ units (evening) and 32.4§ (morning) and 27.6§ units (evening) T: Breakfast, dinner D: 4 weeks GP2: NPH/regular 70/30 (v) Mean: 32.3¶ (morning) and 26.4¶ units (evening) and 33.3§ (morning) and 27.5§ units (evening) T: Breakfast, dinner D: 4 weeks	GP1 F: 117† GP2 F: 117†	GP1 F: 223.2† GP2 F: 259.2† 2-hr PPG excursion GP1 F: 99 (SE 6.12) p: 0.002 GP2 F: 129.6 (SE 6.12)	GP1 F: 135† GP2 F: 135†	GP1 F: 181.8† GP2 F: 201.6† 2-hr PPG excursion GP1 F: 43.2 (SE 4.86) p: 0.018 GP2 F: 61.2 (SE 4.86)		
Malone, 2000[41]	GP1: Insulin lispro 75/25 (fix) Mean: 35.4 U (0.43 U/kg) T: Breakfast D: 2 days GP2: NPH/regular 70/30 (fix) Mean: 35.4 U (0.43 U/kg) T: Breakfast D: 2 days		GP1 F: 221.4 (52.2) p: 0.066 GP2 F: 230.4 (54) 2-hr PPG excursion GP1 F: 60.3 (41.04) p: <0.001 GP2 F: 74.34 (40.68)				

Evidence Table 4. Comparative effectiveness of premixed insulin analogues and other diabetes treatments on intermediate outcomes (continued)

Author, year	Intervention	Fasting blood glucose in mg/dL#	2-hr PPG in mg/dL after breakfast#	Pre-dinner glucose in mg/dL#	2-hr PPG in mg/dL after dinner#	HgbA1c in %#	Quality of life#
Mattoo, 2003[64]	GP1: Insulin lispro 75/25 (unclear) Mean: 20 U (morning), 32 U (evening) T: Breakfast, dinner D: 2 weeks GP2: NPH/regular 70/30 (unclear) Mean: 20 U (morning), 32 U (evening) T: Breakfast, dinner D: 2 weeks	GP1 F: 160.2 (54) p: 0.393 GP2 F: 163.8 (57.6)	GP1 F: 208.8 (66.6) p: 0.104 GP2 F: 216 (64.8) 2-hr PPG excursion GP1 F: 48.6 (57.6) p: 0.397 GP2 F: 54 (55.8)	GP1 F: 127.8 (39.6) p: 0.034 GP2 F: 135 (46.8)	GP1 F: 189 (57.6) p: 0.001 GP2 F: 208.8 (61.2) 2-hr PPG excursion GP1 F: 61.2 (52.2) p: 0.007 GP2 F: 72 (57.6)		
Roach, 1999[67]	GP1: Insulin lispro 75/25 (v) Mean: 0.37 (morning) and 0.28 (evening) T: Breakfast, dinner D: 13 weeks GP2: NPH/regular 70/30 (v) Mean: 0.36 (morning) and 0.27 (evening) T: Breakfast, dinner D: 13 weeks	GP1 F: 154.8† p: NS GP2 F: 157.5†	GP1 F: 161.1 (39.06) p: 0.017 GP2 F: 180 (41.04)	GP1 F: 170.1† p: NS GP2 F: 169.2†	GP1 F: 167.04 (45.18) p: 0.014 GP2 F: 184.86 (49.68)	GP1 F: 7.8 p: 0.408 GP2 F: 8.1	
Schwartz, 2006[56]	GP1: Insulin lispro 75/25 (fix) Start: 2/3 of patient's usual daily dose Mean: 44.1 U T: Breakfast D: 1 day GP2: NPH/regular 70/30 (fix) Start: 2/3 of patient's usual daily dose Mean: 44.1 U T: Breakfast D: 1 day		GP1 F: 198 (67.5) p: <0.05 GP2 F: 213 (47) p: <0.05				

Evidence Table 4. Comparative effectiveness of premixed insulin analogues and other diabetes treatments on intermediate outcomes (continued)

Author, year	Intervention	Fasting blood glucose in mg/dL#	2-hr PPG in mg/dL after breakfast#	Pre-dinner glucose in mg/dL#	2-hr PPG in mg/dL after dinner#	HgbA1c in %#	Quality of life#
Insulin lispro 75/25 vs. oral antidiabetic agents							
Herz, 2002[66]	GP1: Insulin lispro 75/25 (v) Start: 0.3 - 0.5 U/kg Mean: 0.46 U/kg T: Breakfast, dinner D: 16 weeks GP2: Glyburide (fix) Start: 15 mg/day T: Breakfast, dinner D: 16 weeks	GP1 B: 199.44 (SE 6.3) p: 0.139 vs. GP2 F: 147.06 (SE 4.14) p: <0.001 vs. GP2 F-B: -52.74 (SE 5.94) p: <0.001 vs. GP2 GP2 B: 187.74 (SE 4.68) F: 176.76 (SE 5.22) F-B: -8.82 (SE 5.04) GP1-GP2: -44*	GP1 B: 255.6 (SE 9) p: 0.621 vs. GP2 F: 174.96 (SE 6.66) p: <0.001 vs. GP2 F-B: -80.82 (SE 9) p: <0.001 vs. GP2 GP2 B: 261.18 (SE 7.02) F: 236.52 (SE 7.02) F-B: -22.5 (SE 7.02) GP1-GP2: -59*	GP1 B: 222.48 (SE 8.82) p: 0.216 vs. GP2 F: 175.68 (SE 5.94) p: 0.120 vs. GP2 F-B: -47.34 (SE 7.92) p: 0.002 vs. GP2 GP2 B: 207.18 (SE 8.64) F: 189.9 (SE 7.02) F-B: -14.76 (SE 6.48) GP1-GP2: -32*	GP1 B: 241.2 (SE 9.54) p: 0.711 vs. GP2 F: 181.98 (SE 6.84) p: <0.001 vs. GP2 F-B: -58.86 (SE 8.82) p: <0.001 vs. GP2 GP2 B: 245.88 (SE 8.28) F: 227.52 (SE 7.56) F-B: -14.94 (SE 7.56) GP1-GP2: -44*	GP1 B: 9.82 (1.51) F: 8.64 (SE 0.17) p: <0.001 vs. GP2 F-B: -1.14 (SE 0.18) p: 0.001 vs. GP2 GP2 B: 9.9 (1.3) F: 9.45 (SE 0.16) F-B: -0.36 (SE 0.15) GP1-GP2: -1*	Treatment acceptance questionnaire (satisfaction rated from 1 (very low) to 5 (very high) GP1 F: 4.35 p: 0.014 vs. GP2 GP2 F: 3.98 Willingness to continue treatment GP1 (92) p: 0.041 GP2 (79)

Evidence Table 4. Comparative effectiveness of premixed insulin analogues and other diabetes treatments on intermediate outcomes (continued)

Author, year	Intervention	Fasting blood glucose in mg/dL#	2-hr PPG in mg/dL after breakfast#	Pre-dinner glucose in mg/dL#	2-hr PPG in mg/dL after dinner#	HgbA1c in %#	Quality of life#
Malone, 2003[62]	GP1: Insulin lispro 75/25 (v) Mean: 0.19 U/kg (morning) and 0.14 U/kg (evening) T: Breakfast, dinner D: 16 weeks Metformin (v) Mean: 1813 mg/day Range: 1500 – 2550 mg/day T: 2 to 3 times/day D: 16 weeks GP2: Metformin (v) Mean: 1968 mg/day Range: 1500 - 2550 mg/day T: 2 to 3 times/day D: 16 weeks Glibenclamide (v) Mean: 14.2 mg/day T: NR D: 16 weeks	GP1 B: 239.4 (68.22) F: 156.06 Median (60.48) F-B: -83* GP2 B: 233.82 (68.04) F: 169.74 Median (61.02) F-B: -64* GP1-GP2: -19* p: 0.173	GP1 B: 252 (+/- SE 246.6 - 257.4) F: 147.6 (+/- SE 145.8 - 151.2) F-B: -104* GP2 B: 259.2 (+/- SE 252 - 273.6) F: 190.8 (+/- SE 185.4 - 199.8) F-B: -68* GP1-GP2: -36* 2-hr PPG (time not specified) (mg/dL) GP1 F-B: -124.02 (84.42) p: 0.007 GP2 F-B: -68.94 (84.96) GP1-GP2: -55* 2-hr PPG excursion (time not specified) (mg/dL) GP1 F-B: -40.86 (69.66) p: 0.009 GP2 F-B: -3.96 (35.82) GP1-GP2: -37*			Test meal patients GP1 B: 9.64 (1.6) F: 7.29 (1.12) p: 0.192 vs. GP2 F-B: -3* GP2 B: 9.78 (1.83) F: 7.53 (1.27) F-B: -2* GP1-GP2: -1* All patients GP1 B: 9.17 (1.5) F: 7.29 (1.00) p: 0.661 vs. GP2 F-B: -1.87 (1.35) p: <0.001 GP2 B: 9.27 (1.55) F: 7.33 (1.14) F-B: -1.98 (1.28) p: <0.001 GP1-GP2: 0* HgbA1c < 7.0%, (%) GP1 (40) GP2 (41) HgbA1c < 6.5%, (%) GP1 (18) GP2 (19)	

Evidence Table 4. Comparative effectiveness of premixed insulin analogues and other diabetes treatments on intermediate outcomes (continued)

Author, year	Intervention	Fasting blood glucose in mg/dL#	2-hr PPG in mg/dL after breakfast#	Pre-dinner glucose in mg/dL#	2-hr PPG in mg/dL after dinner#	HgbA1c in %#	Quality of life#
Tirgo-viste, 2003[40]	GP1: Insulin lispro 75/25 (v) Start: 0.3 - 0.5 U/kg T: Breakfast, dinner D: 16 weeks GP2: glibenclamide (v) Start: 15 mg T: Breakfast, dinner D: 16 weeks	GP1 B: 221* F: 171 F-B: -50.4 p: <0.01 GP2 B: 209* F: 189 F-B: -19.8 GP1-GP2: -30*	GP1 B: 279* F: 187.2 F-B: -91.8 p: <0.001 GP2 B: 265* F: 234 F-B: -30.6 GP1-GP2: -61*	GP1 B: 233* F: 192.6 F-B: -39.6 p: <0.05 GP2 B: 219* F: 205.2 F-B: -14.4 GP1-GP2: -26*	GP1 B: 272* F: 192.6 F-B: -79.2 p: <0.001 GP2 B: 261* F: 234 F-B: -27 GP1-GP2: -52*	GP1 B: 9* F: 8.5 (1.3) p: 0.001 F-B: -1.4 p: 0.004 GP2 B: 10* F: 9.4 (1.8) F-B: -0.7 GP1-GP2: 0*	
Insulin lispro 75/25 vs. insulin lispro 50/50							
Roach, 2003[63]	GP1: Insulin lispro 75/25 (v) Mean: 31.3 (morning) and 27.6 U (evening) T: Breakfast, dinner D: 8 weeks GP2: Insulin lispro 50/50 (v) Mean: 31.5 U T: Breakfast D: 8 weeks Insulin lispro 75/25 (v) Mean: 27.9 U T: Dinner D: 8 weeks	GP1 F: 160.2 (SE 5.4) p: 0.129 GP2 F: 171 (SE 5.4)	GP1 F: 223.2 (SE 5.94) p: 0.0012 GP2 F: 196.2 (SE 5.04) 2-hr PPG excursion GP1 F: 63 (SE 5.04) p: <0.001 GP2 F: 25.2 (SE 5.04)			GP1 F: 8.14 (SE 1.07) p: 0.919 GP2 F: 8.14 (SE 1.14)	
Schwartz, 2006[56]	GP1: Insulin lispro 75/25 (fix) Start: 2/3 of patient's usual daily dose Mean: 44.1 U T: Breakfast D: 1 day GP2: Insulin lispro 50/50 (fix) Start: 2/3 of patient's usual daily dose Mean: 43.8 U T: Breakfast D: 1 day		GP1 F: 198 (67.5) p: <0.05 GP2 F: 159 (52.3) p: <0.05				

Evidence Table 4. Comparative effectiveness of premixed insulin analogues and other diabetes treatments on intermediate outcomes (continued)

Author, year	Intervention	Fasting blood glucose in mg/dL#	2-hr PPG in mg/dL after breakfast#	Pre-dinner glucose in mg/dL#	2-hr PPG in mg/dL after dinner#	HgbA1c in %#	Quality of life#
Insulin lispro 50/50 vs. long-acting insulin analogues							
Kazda, 2006[69]	GP1: Insulin lispro 50/50 (v) Start: 0.30 IU/kg mean Mean: 0.59 IU/kg T: Breakfast, lunch, dinner D: 24 weeks GP2: Insulin glargine (v) Start: 0.16 IU/kg/day mean Mean: 0.43 IU/kg/day T: Bedtime D: 24 weeks	GP1 B: 167.4 (37.8) F: 151* F-B: -16.2 (32.4) p: <0.001 vs. GP2 GP2 B: 172.8 (43.2) F: 126* F-B: -46.8 (43.2) GP1-GP2: 31*	GP1 B: 214.2 (50.4) F: 164* F-B: -50.4 (52.2) p: 0.43 vs. GP2 GP2 B: 219.6 (55.8) F: 173* F-B: -46.8 (59.4) GP1-GP2: -3* 2-hr PPG excursion GP1 B: 48.6 (32.4) F: 17* F-B: -32.4 (43.2) p: <0.001 vs. GP2 GP2 B: 45 (39.6) F: 43* F-B: -1.8 (39.6) GP1-GP2: -30*	GP1 B: 166.5† (SE 5.4†) F: 144† (SE 7.56†) F-B: -22.5* GP2 B: 174.06† (SE 5.4†) F: 159.12† (SE 7.56†) F-B: -14.94* GP1-GP2: -7.56*	GP1 B: 198† (SE 5.94†) F: 149.94† (SE 5.94†) F-B: -48.06* GP2 B: 208.44† (SE 7.38†) F: 207† (SE 7.38†) F-B: -1.44* GP1-GP2: -46.62*	GP1 B: 8.1 (1.2) F: 7* F-B: -1.2 (1.1) p: <0.001 vs. GP2 GP2 B: 8.1 (1.3) F: 8* F-B: -0.3 (1.1) GP1-GP2: -1* HgbA1c < 7%, n (%) GP1 29* (59.3) GP2 12* (24.5)	Willing to continue current treatment at end of study GP1 F: 83.3% GP2 F: 77.4% Overall satisfaction based on 5-point Likert scale (nonvalidated): proportion with high or very high treatment satisfaction GP1 B: 18.5% F: 63% GP2 B: 26.4% F: 50.9%

Evidence Table 4. Comparative effectiveness of premixed insulin analogues and other diabetes treatments on intermediate outcomes (continued)

Author, year	Intervention	Fasting blood glucose in mg/dL#	2-hr PPG in mg/dL after breakfast#	Pre-dinner glucose in mg/dL#	2-hr PPG in mg/dL after dinner#	HgbA1c in %#	Quality of life#
Insulin lispro 50/50 vs. rapid-acting insulin analogues							
Kazda, 2006[69]	GP1: Insulin lispro 50/50 (v) Start: 0.30 IU/kg/day mean Mean: 0.59 IU/kg/day T: Breakfast, lunch, dinner D: 24 weeks GP2: Insulin lispro (v) Start: 0.25 IU/kg/day mean Mean: 0.50 IU/kg/day T: Breakfast, lunch, dinner D: 24 weeks	GP1 B: 167.4 (37.8) F: 151* F-B: -16.2 (32.4) GP2 B: 176.4 (50.4) F: 160* F-B: -16.2 (39.6) GP1-GP2: 0*	GP1 B: 214.2 (50.4) F: 164* F-B: -50.4 (52.2) GP2 B: 205.2 (61.2) F: 151* F-B: -54 (63) GP1-GP2: 4* 2-hr PPG excursion GP1 B: 48.6 (32.4) F: 17* F-B: -32.4 (43.2) GP2 B: 28.8 (43.2) F: -9* F-B: -37.8 (52.2) GP1-GP2: 6*	GP1 B: 166.5† (SE 5.4†) F: 144† (SE 7.56†) F-B: -22.5* GP2 B: 169.38† (SE 5.4†) F: 145.44† (SE 7.56†) F-B: -23.94* GP1-GP2: -1.44	GP1 B: 198† (SE 5.94†) F: 149.94† (SE 5.94†) F-B: -48.06* GP2 B: 205.38† (SE 4.5†) F: 141.12† (SE 4.5†) F-B: -64.26* GP1-GP2: 16.2	GP1 B: 8.1 (1.2) F: 7* F-B: -1.2 (1.1) GP2 B: 8.2 (1.2) F: 7* F-B: -1.1 (1.1) GP1-GP2: 0* HgbA1c < 7%, n (%) GP1 29* (59.3) GP2 20* (40.4)	Willing to continue current treatment at end of study GP1 F: 83.3% GP2 F: 88.5% Overall satisfaction based on 5-point Likert scale (nonvalidated): proportion with high or very high treatment satisfaction GP1 B: 18.5% F: 63% GP2 B: 21.2% F: 65.4%

Evidence Table 4. Comparative effectiveness of premixed insulin analogues and other diabetes treatments on intermediate outcomes (continued)

Author, year	Intervention	Fasting blood glucose in mg/dL#	2-hr PPG in mg/dL after breakfast#	Pre-dinner glucose in mg/dL#	2-hr PPG in mg/dL after dinner#	HgbA1c in %#	Quality of life#
Insulin lispro 50/50 vs. premixed human insulins							
Roach, 1999[11]	GP1: Insulin lispro 50/50 (v) Mean: 0.31 U/kg T: Breakfast D: 3 months Insulin lispro 75/25 (v) Mean: 0.26 U/kg T: Dinner D: 3 months GP2: NPH/regular 50/50 (v) Mean: 0.32 U/kg T: Breakfast D: 3 months NPH/regular 70/30 (v) Mean: 0.26 U/kg T: Dinner D: 3 months	GP1 F: 160.38 p: NS GP2 F: 162.18	GP1 F: 150.3 p: <0.001 GP2 F: 182.16 2-hr PPG excursion GP1 F: -10.44 p: <0.001 GP2 F: 21.42	GP1 F: 171 p: 0.01 GP2 F: 166.68	GP1 F: 179.28 p: NS GP2 F: 188.64 2-hr PPG excursion GP1 F: 6.48 p: NS GP2 F: 21.96	GP1 F: 7.73 p: 0.371 GP2 F: 7.66	

Evidence Table 4. Comparative effectiveness of premixed insulin analogues and other diabetes treatments on intermediate outcomes (continued)

Author, year	Intervention	Fasting blood glucose in mg/dL#	2-hr PPG in mg/dL after breakfast#	Pre-dinner glucose in mg/dL#	2-hr PPG in mg/dL after dinner#	HgbA1c in %#	Quality of life#
Schern-thaner, 2004[70]	GP1: Insulin lispro 50/50 (v) Mean: 64.6 IU T: Breakfast, lunch, dinner D: 12 weeks diet/exercise D: 12 weeks GP2: NPH/regular 70/30 (v) Mean: 61.8 IU T: Breakfast, dinner D: 12 weeks diet/exercise D: 12 weeks	GP1 B: 155* F: 177.7 (SE 9.6) F-B: 23.3 (SE 7.8) p: 0.005 vs. baseline GP2 B: 154* F: 147.4 (SE 6.3) F-B: -7 (SE 8) p: 0.387 vs. baseline GP1-GP2: 30* p: <0.001	GP1 B: 198* F: 189.8 (SE 10.2) F-B: -8.3 (SE 11) p: 0.456 vs. baseline GP2 B: 198* F: 191.3 (SE 10.5) F-B: -6.9 (SE 7.8) p: 0.384 vs. baseline GP1-GP2: -1* p: 0.836 2-hr PPG increment GP1 F-B: -32.3 (SE 9.7) p: 0.002 vs. baseline GP2 F-B: 1 (SE 7.3) p: NS vs. baseline GP1-GP2: -33* p: <0.001	GP1 B: 192* F: 174.8 (SE 7.3) F-B: -17.3 (SE 9.6) p: 0.079 vs. baseline GP2 B: 192* F: 187.8 (SE 9.5) F-B: -4.3 (SE 8.5) p: 0.614 vs. baseline GP1-GP2: -13* p: 0.064	GP1 B: 209* F: 166.3 (SE 7.2) F-B: -42.8 (SE 10) p: <0.001 vs. baseline GP2 B: 209* F: 198.2 (SE 10) F-B: -10.9 (SE 9.7) p: 0.268 vs. baseline GP1-GP2: -32* p: <0.001 2-hr PPG increment GP1 F-B: -21 (SE 9.7) p: 0.037 vs. baseline GP2 F-B: -4.6 (SE 8.2) p: NS vs. baseline GP1-GP2: -16* p: 0.055	GP1 B: 9* F: 7.6 (SE 1.1) F-B: -0.8 (SE 1.1) p: <0.001 vs. baseline GP2 B: 8* F: 8.1 (SE 1.4) F-B: -0.3 (SE 1.1) p: 0.034 vs. baseline GP1-GP2: -1* p: 0.021	
Schwartz, 2006[56]	GP1: Insulin lispro 50/50 (fix) Start: 2/3 of patient's usual daily dose Mean: 43.8 U T: Breakfast D: 1 day GP2: NPH/regular 70/30 (fix) Start: 2/3 of patient's usual daily dose Mean: 44.1 U T: Breakfast D: 1 day		GP1 F: 159 (52.3) p: <0.05 GP2 F: 213 (47) p: <0.05				

Evidence Table 4. Comparative effectiveness of premixed insulin analogues and other diabetes treatments on intermediate outcomes (continued)

Author, year	Intervention	Fasting blood glucose in mg/dL#	2-hr PPG in mg/dL after breakfast#	Pre-dinner glucose in mg/dL#	2-hr PPG in mg/dL after dinner#	HgbA1c in %#	Quality of life#
Yamada, 2007[71]	GP1: Insulin lispro 50/50 (v) Start: current dose Mean: 0.37 U/kg (start) and 0.38 U/kg (end) T: twice daily D: 4 months GP2: NPH/regular 70/30 (v) Start: current dose Mean: 0.34 U/kg (start) and 0.37 U/kg (end) T: twice daily D: 4 months NPH/regular 50/50 (v) Start: current dose Mean: 0.34 U/kg (start) and 0.37 U/kg (end) T: twice daily D: 4 months	GP1 B: 130.3 (50.7) F: 158.5 (63.4) F-B: 28* p: NS vs. baseline GP2 B: 141.8 (51.9) F: 136.4 (47.2) F-B: -6* p: NS vs. baseline GP1-GP2: 34* p: NS				GP1 B: 7.59 (0.44) F: 7.24 (0.49) F-B: -1* p: <0.05 vs. baseline GP2 B: 7.33 (0.58) F: 7.29 (0.65) F-B: 0* p: NS vs. baseline GP1-GP2: -1* p: <0.05	

Numbers are mean (SD) unless otherwise specified.
* Number has been imputed.
† Number has been estimated from a figure.
‡ One-hundred and four (36%) of the 291 participants of this trial are patients with type 1 diabetes. The remaining population has type 2 diabetes and is the same study population as Boehm 2004.[42] Only data for the Boehm 2004 study is presented because it has the longest followup.
¶ Dosing during the outpatient phase.
§ Dosing during the inpatient phase.
‖ Among those who were not using thiazolidinediones.

µg = microgram; B = baseline; BDI-II = Beck Depression Inventory – Revised; B-F = mean difference from baseline; bid = twice daily; CI = confidence interval; D = duration; dl = deciliter; DM = diabetes mellitus; EQ-5D = EuroQol-5D; F = final; FBG = fasting blood glucose; fix = fixed dosing; GP = group; GP1-GP2 = mean difference between the difference from baseline; HgbA1c = Hemoglobin A1c; hr = hour; IU = international unit; kg = kilogram; l = liter; mg = milligrams; min = minutes; ml = milliliter; mmol = millimole; NA = not applicable; NPH = neutral protamine Hagedorn; NR = not reported; NS = not significant; ODM = oral diabetes medicine; p = p-value; per = period; PPG = postprandial glucose; qd = once daily; ref = reference group; SE = standard error; SEM = standard error of the mean; T = time of day when insulin taken; U = units; v = dose varied; WHO-DTSQ = World Health Organization-Diabetes Treatment Satisfaction Questionnaire

Evidence Table 5. Comparative safety of premixed insulin analogues and other diabetes treatments on hypoglycemia

Author, year	Intervention	Mild hypoglycemia, n (%)	Moderate hypoglycemia, n (%)	Serious hypoglycemia, n (%)	Daytime hypoglycemia, n (%)	Nighttime hypoglycemia, n (%)	Other hypoglycemia, n (%)
Insulin aspart 70/30 vs. long-acting insulin analogues							
Holman, 2007[28]	GP1: Insulin aspart 70/30 (v) Start: 16 median Range: 10 - 26 T: bid D: 1 year Usual care D: 1 year GP2: Insulin detemir (v) Start: 16 median Range: 10 - 24 T: Bedtime, twice if required D: 1 year Usual care D: 1 year		Grade 2: symptoms and BG < 56 mg/dL GP1 Median number of events per patient-year: 3.9 (IQR 1.0 - 9.0) p: 0.01 GP2 Median number of events per patient-year: 0 (IQR 0 - 2.0)	Grade 3: third party assistance required GP1 11 (4.7) p: overall 0.20 Median number of events per patient-year: 0 p: overall 0.10 GP2 4 (1.7) Median number of events per patient-year: 0			Grades 1, 2, or 3 GP1 216 (91.9) p: overall < 0.001 GP2 173 (73.9)
Kann, 2006[47]	GP1: Insulin aspart 70/30 (v) Start: 0.1 U/kg bid Mean: 0.4 U/kg T: Breakfast, dinner D: 26 weeks metformin (v) Start: 500mg bid or current dose T: Breakfast, dinner D: 26 weeks GP2: Insulin glargine (v) Start: 0.2 U/kg qd Mean: 0.3 U/kg T: preferred time (constant thru study) D: glimepiride (v) Start: 1mg daily or current dose T: Breakfast D: 26 weeks	Treat self, PG < 55.8 mg/dL (3.1 mmol/L) GP1 26* (20.3) p: 0.0124 GP2 11* (9)		Unable to treat self GP1 1 (1*) GP2 1 (1*) Hypoglycemic coma GP1 2 (1.6) GP2 0 (0)	% mild episodes that occurred in daytime GP1 number (%) of events: 61 (77) GP2 number (%) of events: 25 (71)		Symptoms only GP1 14* (10.6) GP2 9* (6.6)

Evidence Table 5. Comparative safety of premixed insulin analogues and other diabetes treatments on hypoglycemia (continued)

Author, year	Intervention	Mild hypoglycemia, n (%)	Moderate hypoglycemia, n (%)	Serious hypoglycemia, n (%)	Daytime hypoglycemia, n (%)	Nighttime hypoglycemia, n (%)	Other hypoglycemia, n (%)
Raskin, 2005[36 37]	GP1: Insulin aspart 70/30 (v) Start: 10 or 12 units T: Breakfast, dinner D: Unclear metformin (v) Range: 1500 – 2550 mg/day T: NR D: Unclear GP2: Insulin glargine (v) Start: 10-12 units/day T: Bedtime D: Unclear metformin (v) Range: 1500 – 2550 mg/day T: NR D: Unclear	PG < 56 mg/dL with or without symptoms, self-treated GP1 46.4* (43) event rate: 3.4/patient-year p: < 0.05 GP2 18.2* (16) event rate: 0.7/patient-year GP1‖ 33 (41.8*) number of events: 121 GP2 ‖ 11 (14.1*) number of events: 23		Neurological symptoms, required assistance, PG < 56 mg/dL or reversal with treatment GP1 0 (0) GP2 1 (0.88) GP1‖ 0 (0) GP2‖ 0 (0)		Mild or serious between 11pm and 8am GP1‖ 19.8* (25) p: 0.021 GP2‖ 7.8* (10)	Symptoms but PG >= 56 mg/dL GP1 event rate: 9.8/patient-year p: < 0.05 GP2 event rate: 4.7/patient-year Reported hypoglycemic event GP1‖ 54 (68) p: 0.0013 GP2‖ 33 (42)
Tame-moto, 2007[44]	GP1: Insulin aspart 70/30 (v) Start: 10 - 16 units/day Mean: 26.7 units T: Breakfast, dinner D: 6 months continued ODM (unclear) T: NR D: 6 months GP2: Insulin glargine (v) Start: 6 - 8 units/day T: NR D: 6 months continued ODM (unclear) T: NR D: 6 months						From self-monitored blood glucose data, < 70 mg/dL GP1 2 (50*) number of events: 11 GP2 4 (57*) number of events: 43 Self-reported events GP1 4 (80*) GP2 6 (55*)

Evidence Table 5. Comparative safety of premixed insulin analogues and other diabetes treatments on hypoglycemia (continued)

Author, year	Intervention	Mild hypoglycemia, n (%)	Moderate hypoglycemia, n (%)	Serious hypoglycemia, n (%)	Daytime hypoglycemia, n (%)	Nighttime hypoglycemia, n (%)	Other hypoglycemia, n (%)
Insulin aspart 70/30 vs. rapid-acting insulin analogues							
Holman, 2007[28]	GP1: Insulin aspart 70/30 (v) Start: 16 median Range: 10 - 26 T: bid D: 1 year Usual care D: 1 year GP2: Insulin aspart (v) Start: 18 median Range: 9 - 24 T: Breakfast, lunch, dinner, D: 1 year Usual care D: 1 year		Grade 2: symptoms and BG < 56 mg/dL GP1 Median number of events per patient-year: 3.9 (IQR 1.0-9.0) p: 0.002 GP2 Median number of events per patient-year: 8.0 (IQR 2.9-17.7)	Grade 3: third party assistance required GP1 11 (4.7) p: overall 0.20 Median number of events per patient-year: 0 p: overall 0.10 GP2 16 (6.7) Median number of events per patient-year: 0			Grades 1, 2, or 3 GP1 216 (91.9) p: 0.08 GP2 229 (96.2)
Insulin aspart 70/30 vs. rapid-acting with long-acting insulin analogues							
Joshi, 2005[49]	GP1: Insulin aspart 70/30 (v) Mean: 40.19 U/day T: twice daily D: 12 weeks GP2: Insulin aspart (v) Mean: 28.26 U/day at 12 weeks T: before every meal D: 12 weeks Insulin glargine (v) Mean: 24.52 U/day T: Bedtime D: 12 weeks	BS < 50 mg/dL but self managed GP1 19* (16.7) p: <0.05 vs GP2 GP2 18* (58.06)		Requiring 3rd party assistance GP1 0 (0) GP2 0 (0)			

Evidence Table 5. Comparative safety of premixed insulin analogues and other diabetes treatments on hypoglycemia (continued)

Author, year	Intervention	Mild hypoglycemia, n (%)	Moderate hypoglycemia, n (%)	Serious hypoglycemia, n (%)	Daytime hypoglycemia, n (%)	Nighttime hypoglycemia, n (%)	Other hypoglycemia, n (%)
Insulin aspart 70/30 vs. premixed human insulins							
Abra-hamian, 2005[50]	GP1: Insulin aspart 70/30 (v) Mean: 0.49 U/kg (start) and 0.61 U/kg (end) T: Breakfast, lunch, dinner D: 24 weeks GP2: NPH/regular 70/30 (v) Mean: 0.46 U/kg (start) and 0.59 U/kg (end) T: Breakfast, dinner D: 24 weeks	Not defined GP1 number of events: 130 GP2 number of events: 185		Major GP1 number of events: 2 GP2 number of events: 0		Not defined GP1 p: NS	
Boehm, 2004[42] Boehm, 2002[10]‡	GP1: Insulin aspart 70/30 (v) Start: 0.57 U/kg T: Breakfast, dinner D: 24 months GP2: NPH/regular 70/30 (v) Start: 0.57 U/Kg T: Breakfast, dinner D: 24 months	GP1 35 (63) number of events: 398 p: 1 GP2 41 (63) number of events: 555		Major hypoglycemia GP1 3 (5) number of events: 3 p: 0.14 GP2 9 (14) number of events: 19			
Herman-sen, 2002[55]	GP1: Insulin aspart 70/30 (fix) Start: 0.4 units/kg T: Breakfast D: 1 day GP2: NPH/regular 70/30 (fix) Start: 0.4 units/kg T: Breakfast D: 1 day			Requiring third-party assistance GP1 number of events: 2 GP2 number of events: 2			Overall hypoglycemia rates (not specified) GP1 number of events: 23 GP2 number of events: 11

Evidence Table 5. Comparative safety of premixed insulin analogues and other diabetes treatments on hypoglycemia (continued)

Author, year	Intervention	Mild hypoglycemia, n (%)	Moderate hypoglycemia, n (%)	Serious hypoglycemia, n (%)	Daytime hypoglycemia, n (%)	Nighttime hypoglycemia, n (%)	Other hypoglycemia, n (%)
Kilo, 2003[16]	GP1: Insulin aspart 70/30 (v) Start: 0.16 Units/day Mean: 26 U/day T: Dinner D: 12 weeks metformin (fix) Mean: about 2200 mg Range: 500 - 2550 mg T: 1-3 times/day D: 4 weeks run-in, then 12 weeks GP2: NPH/regular 70/30 (v) Start: 0.16 Units/day Mean: 29 U/day T: Dinner D: 12 weeks metformin (fix) Mean: about 2200 mg Range: 500 - 2550 mg T: 1-3 times/day D: 4 weeks run-in, then 12 weeks	Symptoms with BS < 50 mg/dL but not requiring third party assistance GP1 11 (24) GP2 9 (19)		BS < 50 mg/dL with severe CNS symptoms and required third party assistance GP1 0 (0*) GP2 0 (0*)		Between midnight and 6 am GP1 7 (15) GP2 11 (23)	Symptoms only GP1 13 (28) GP2 11 (23) Any (reported symptoms or BS < 50 mg/dL) GP1 20 (43) p: overall 0.245 GP2 15 (32)

Evidence Table 5. Comparative safety of premixed insulin analogues and other diabetes treatments on hypoglycemia (continued)

Author, year	Intervention	Mild hypoglycemia, n (%)	Moderate hypoglycemia, n (%)	Serious hypoglycemia, n (%)	Daytime hypoglycemia, n (%)	Nighttime hypoglycemia, n (%)	Other hypoglycemia, n (%)
McNally, 2007[45]	GP1: Insulin aspart 70/30 (v) Start: 100 units/mL Mean: 68.8 units Range: 6 - 238.7 units T: Breakfast, dinner D: 16 weeks GP2: NPH/regular 70/30 (v) Start: 100 units/mL Mean: 66.6 units Range: 11.3 - 240 units T: Breakfast, dinner D: 16 weeks	Self reported minor hypoglycemia (patient able to self-treat and blood glucose < 50.4 mg/dL (2.8 mmol/L)) GP1 63* (90) GP2 65* (84)		Patients unable to self-treat GP1 2 (3*) number of events: 2 GP2 5 (6*) number of events: 7	< 45 mg/dL (2.5 mmol/L) recorded by CGMS between 0600 - 0000 h GP1 29* (41) p: 0.1 GP2 31* (41) < 63 mg/dL (3.5 mmol/L) recorded by CGMS between 0600 - 0000 h GP1 51* (73) p: 0.6 event rate: 2.58/patient-week p: 0.32 GP2 52* (70) event rate: 2.36/patient-week Daytime self-reported rates GP1 p: NS	< 45 mg/dL (2.5 mmol/L) recorded by CGMS between 0000 - 0600 h GP1 18* (25) p: 0.039 GP2 28* (37) < 63 mg/dL (3.5 mmol/L) recorded by CGMS between 0000 - 0600 h GP1 36* (51) p: 0.015 event rate: 1.18/patient-week p: 0.011 GP2 50* (66) event rate: 1.62/patient-week Nighttime self-reported rates GP1 event rate: 1.5/patient-year (SD = 4.54) p: 0.002 GP2 event rate: 3.8/patient-year (SD = 8)	< 45 mg/dL (2.5 mmol/L) recorded by CGMS at any time GP1 32* (46) p: 0.28 GP2 40* (54) < 63 mg/dL (3.5 mmol/L) recorded by CGMS at any time GP1 57* (82) p: 1 event rate: 3.76/patient-week p: 0.62 GP2 62* (82) event rate: 3.93/patient-week Total self-reported rates GP1 p: NS

Evidence Table 5. Comparative safety of premixed insulin analogues and other diabetes treatments on hypoglycemia (continued)

Author, year	Intervention	Mild hypoglycemia, n (%)	Moderate hypoglycemia, n (%)	Serious hypoglycemia, n (%)	Daytime hypoglycemia, n (%)	Nighttime hypoglycemia, n (%)	Other hypoglycemia, n (%)
McSorley, 2002[12]	GP1: Insulin aspart 70/30 (unclear) T: Breakfast, dinner D: 2 weeks GP2: NPH/regular 70/30 (unclear) T: Breakfast, dinner D: 2 weeks			Required third party assistance or injection of glucose or glucagon GP1 0 (0*) GP2 0 (0*)			Experienced symptoms, but did not require assistance GP1 4 (31*) number of events: 7 GP2 3 (23*) number of events: 5
Insulin aspart 70/30 vs. intermediate-acting human insulins							
Christiansen, 2003[14]	GP1: Insulin aspart 70/30 (v) Start: insulin naive = 8 - 16 units/day; taking NPH prior to trial = started at pretrial dose T: Breakfast, dinner D: 16 weeks GP2: NPH insulin (v) Start: insulin naive = 8 - 16 units/day; taking NPH prior to trial = started at pretrial dose T: Breakfast, dinner D: 16 weeks	Not requiring third party assistance or glucagon injection GP1 77 (38*) number of events: 341 RR = 1.21 (95% CI: 0.77 - 1.9) p: 0.4 GP2 68 (34*) number of events: 285		Requiring third party assistance or use of glucagon GP1 NR (<2) GP2 NR (<2)		Minor (not requiring assistance) and nocturnal (midnight to 6 am) GP1 22* (10.9) p: NS GP2 22* (11.4) p: NS	

Evidence Table 5. Comparative safety of premixed insulin analogues and other diabetes treatments on hypoglycemia (continued)

Author, year	Intervention	Mild hypoglycemia, n (%)	Moderate hypoglycemia, n (%)	Serious hypoglycemia, n (%)	Daytime hypoglycemia, n (%)	Nighttime hypoglycemia, n (%)	Other hypoglycemia, n (%)
Kilo, 2003[16]	GP1: Insulin aspart 70/30 (v) Start: 0.16 Units/day Mean: 26 U/day T: Dinner D: 12 weeks metformin (fix) Mean: about 2200 mg Range: 500 - 2550 mg T: 1-3 times/day D: 4 weeks run-in, then 12 weeks GP2: NPH insulin (v) Start: 0.16 Units/day Mean: 28 U/day T: Bedtime D: 12 weeks metformin (fix) Mean: about 2200 mg Range: 500 mg - 2550 mg T: 1-3 times/day D: 4 weeks run-in, then 12 weeks	Symptoms with BS < 50 mg/dL but not requiring third party assistance GP1 11 (24) GP2 6 (13)		BS < 50 mg/dL with severe CNS symptoms and required third party assistance GP1 0 (0*) GP2 0 (0*)		Between midnight and 6 am GP1 7 (15) GP2 11 (23)	Symptoms only GP1 13 (28) GP2 10 (21) Any (reported symptoms or BS < 50 mg/dL) GP1 20 (43) p: overall 0.245 GP2 13 (28)
Insulin aspart 70/30 vs. oral antidiabetic agents							
Bebakar, 2007[43]	GP1: Insulin aspart 70/30 (v) Start: 0.2 U/kg/day Range: 0.16U/kg (for qday group) - 0.43U/kg (for bid group) T: once or twice daily D: 24 weeks GP2: ODM (v) T: NR D: 24 weeks	Symptoms and PG < 56 mg/dL and handled by self or PG < 56 mg/dL GP1 number of events: 177 GP2 number of events: 45		Severe CNS symptoms and unable to treat self + PG < 56 mg/dL or reversal of symptoms with treatment GP1 number of events: 1 GP2 number of events: 1			Mild and severe GP1 178 (54) p: < 0.005 GP2 46 (30)

Evidence Table 5. Comparative safety of premixed insulin analogues and other diabetes treatments on hypoglycemia (continued)

Author, year	Intervention	Mild hypoglycemia, n (%)	Moderate hypoglycemia, n (%)	Serious hypoglycemia, n (%)	Daytime hypoglycemia, n (%)	Nighttime hypoglycemia, n (%)	Other hypoglycemia, n (%)
Kvapil, 2006[48]	GP1: Insulin aspart 70/30 (v) Start: 0.3 U/kg/day Mean: 0.51 U/kg/day T: Breakfast, dinner D: 16 weeks GP2: metformin (fix) Mean: 1660 mg daily Range: 500 - 3000 mg qd T: NR D: 16 weeks glibencamide (v) Start: 1.75 mg Mean: 2.33 (start) and 6.58 mg daily (end) T: once or twice daily	Symptoms confirmed by BG < 50.4 mg/dL (2.8 mmol/l), handled by patient; asymptomatic BG < 50.4 mg/dL GP1 10 (9*) number of events: 20 GP2 9 (8*) number of events: 28		Required assistance, BG < 50.4 mg/dL (2.8 mmol/)l, need for food or IV glucose GP1 0 (0*) GP2 0 (0*)			Total hypoglycemic events (includes minor and symptomatic only) GP1 event rate: 0.037/patient-week GP2 event rate: 0.04/patient-week Symptoms without confirmatory BG GP1 22 (21*) number of events: 44 GP2 23 (20*) number of events: 43

Evidence Table 5. Comparative safety of premixed insulin analogues and other diabetes treatments on hypoglycemia (continued)

Author, year	Intervention	Mild hypoglycemia, n (%)	Moderate hypoglycemia, n (%)	Serious hypoglycemia, n (%)	Daytime hypoglycemia, n (%)	Nighttime hypoglycemia, n (%)	Other hypoglycemia, n (%)
Kvapil, 2006[48]	GP1: Insulin aspart 70/30 (v) Start: 0.2 U/kg/day Mean: 0.3 U/kg/day T: Breakfast, dinner D: 16 weeks metformin (fix) Mean: 1660 mg daily Range: 500 - 3000 mg qd T: NR D: 16 weeks GP2: metformin (fix) Mean: 1660 mg daily Range: 500 - 3000 mg qd T: NR D: 16 weeks glibencamide (v) Start: 1.75 mg Mean: 2.33 (start) and 6.58 mg daily (end) T: once or twice daily D: 16 weeks	Symptoms confirmed by BG < 50.4 mg/dL (2.8 mmol/l), handled by patient; asymptomatic BG < 50.4 mg/dL GP1 13 (12*) number of events: 23 GP2 9 (8*) number of events: 28		Required assistance, BG < 50.4 mg/dL (2.8 mmol/)l, need for food or IV glucose GP1 0 (0*) GP2 0 (0*)			Symptoms without confirmatory BG GP1 22 (20*) number of events: 44 GP2 23 (20*) number of events: 43 Total hypoglycemic events (includes minor and symptomatic only) GP1 event rate: 0.039/patient-week GP2 event rate: 0.04/patient-week
Raz, 2003[54]	GP1: Insulin aspart 70/30 (v) Start: 6-8 U BID T: Breakfast, dinner D: 6 weeks rosiglitazone (fix) Start: 4 mg T: Breakfast D: 6 weeks GP2: glibenclamide (fix) Range: 7.5 – 15 mg T: Dinner D: 6 weeks rosiglitazone (fix) Start: 4 mg T: Breakfast D: 6 weeks	BG < 50 mg/dL handled by self GP1 event rate: 1.8/year p: 0.03 GP2 event rate: 0/year					Minor episodes with symptoms but no blood sugars GP1 event rate: 5.3/year p: <0.01 vs. GP2 GP2 event rate: 0/year

Evidence Table 5. Comparative safety of premixed insulin analogues and other diabetes treatments on hypoglycemia (continued)

Author, year	Intervention	Mild hypoglycemia, n (%)	Moderate hypoglycemia, n (%)	Serious hypoglycemia, n (%)	Daytime hypoglycemia, n (%)	Nighttime hypoglycemia, n (%)	Other hypoglycemia, n (%)
Raz, 2005[51]	GP1: Insulin aspart 70/30 (v) Start: 0.3 U/kg/day Mean: 0.7 U/kg/day T: Breakfast, dinner D: 18 weeks GP2: Glibenclamide (v) Start: 5 to 10 mg Mean: 14 mg T: Breakfast D: 18 weeks Pioglitazone (fix) Start: 30 mg Mean: 30 mg T: Breakfast D: 18 weeks	BG < 50 mg/dL but did not require third party assistance GP1 15 (15) number of events: 47 GP2 3 (3) number of events: 3		BG < 50 mg/dL or requiring third party assistance GP1 0 (0*) GP2 0 (0*)		Midnight to 6 am GP1 number of events: 8 GP2 number of events: 0	All hypoglycemic episodes - symptoms or BG < 50 mg/dL GP1 event rate: 0.132/patient-week GP2 event rate: 0.032/patient-week
Raz, 2005[51]	GP1: Insulin aspart 70/30 (v) Start: 0.2 U/kg per day Mean: 0.5 U/kg/day T: Breakfast, dinner D: 18 weeks Pioglitazone (fix) Start: 30 mg Mean: 30 mg T: Breakfast D: 18 weeks GP2: Glibenclamide (v) Start: 5 to 10 mg Mean: 14 mg T: Breakfast D: 18 weeks Pioglitazone (fix) Start: 30 mg Mean: 30 mg T: Breakfast D: 18 weeks	BG < 50 mg/dL but did not require third party assistance GP1 11 (12) number of events: 15 GP2 3 (3) number of events: 3		BG < 50 mg/dL or requiring third party assistance GP1 0 (0*) GP2 0 (0*)		Midnight to 6 am GP1 number of events: 0 GP2 number of events: 0	All hypoglycemic episodes - symptoms or BG < 50 mg/dL GP1 event rate: 0.083/patient-week GP2 event rate: 0.032/patient-week

Evidence Table 5. Comparative safety of premixed insulin analogues and other diabetes treatments on hypoglycemia (continued)

Author, year	Intervention	Mild hypoglycemia, n (%)	Moderate hypoglycemia, n (%)	Serious hypoglycemia, n (%)	Daytime hypoglycemia, n (%)	Nighttime hypoglycemia, n (%)	Other hypoglycemia, n (%)
Insulin aspart 70/30 vs. exenatide							
Nauck, 2007[46]	GP1: Insulin aspart 70/30 (v) Start: 15.7 U/day Mean: 24.4 U/day T: Breakfast, dinner D: 52 weeks 'optimally' effective metformin and sulfonylurea therapy (v) T: NR D: 52 weeks GP2: exenatide (v) Start: 5 µg bid Range: 5 - 10 µg bid T: Breakfast D: 52 weeks 'optimally' effective metformin and sulfonylurea therapy (v) T: NR D: 52 weeks			Severe, not further defined GP1 0 (0) GP2 0 (0)	Not further defined GP1 event rate: 4.4/patient-year p: NS GP2 event rate: 4.1/patient-year	Nocturnal, not further defined GP1 25 (62) event rate: 1.1/patient-year p: NS GP2 44 (17) event rate: 0.6/patient-year	Symptoms or PG < 61.2 mg/dL (3.4 mmol/L) GP1 event rate: 5.6/patient-year p: NS GP2 event rate: 4.7/patient-year
Insulin aspart 70/30 vs. insulin lispro 75/25							
Herman-sen, 2002[55]	GP1: Insulin aspart 70/30 (fix) Start: 0.4 units/kg T: Breakfast D: 1 day GP2: Insulin lispro 75/25 (fix) Start: 0.4 units/kg T: Breakfast D: 1 day			Requiring third-party assistance GP1 number of events: 2 GP2 number of events: 5			Overall hypoglycemia rates (not specified) GP1 number of events: 23 GP2 number of events: 19

Evidence Table 5. Comparative safety of premixed insulin analogues and other diabetes treatments on hypoglycemia (continued)

Author, year	Intervention	Mild hypoglycemia, n (%)	Moderate hypoglycemia, n (%)	Serious hypoglycemia, n (%)	Daytime hypoglycemia, n (%)	Nighttime hypoglycemia, n (%)	Other hypoglycemia, n (%)
Niska-nen, 2004[52]	GP1: Insulin aspart 70/30 (v) Mean: 0.65 to 0.67 U/kg T: Breakfast, dinner D: 12 weeks GP2: Insulin lispro 75/25 (v) Mean: 0.67 to 0.71 U/kg T: Breakfast, dinner D: 12 weeks	BG < 50.4 mg/dL (2.8 mmol/L) with or without symptoms or symptoms not confirmed by BG reading GP1 57 (43*) number of events: 269 GP2 53 (40*) number of events: 233		Required third party assistance GP1 1 (1*) GP2 1 (1*)			
Insulin aspart 70/30 vs. insulin aspart 70/30 + oral antidiabetic agents							
Kvapil, 2006[48]	GP1: Insulin aspart 70/30 (v) Start: 0.3 U/kg/day Mean: 0.51 U/kg/day T: Breakfast, dinner D: 16 weeks GP2: Insulin aspart 70/30 (v) Start: 0.2 U/kg/day Mean: 0.3 U/kg/day T: Breakfast, dinner D: 16 weeks metformin (fix) Mean: 1660 mg daily Range: 500 - 3000 mg qd T: NR D: 16 weeks	Symptoms confirmed by BG < 50.4 mg/dL (2.8 mmol/l), handled by patient; asymptomatic BG < 50.4 mg/dL GP1 10 (9*) number of events: 20 GP2 13 (12*) number of events: 23		Required assistance, BG < 50.4 mg/dL (2.8 mmol/)l, need for food or IV glucose GP1 0 (0*) GP2 0 (0*)			Symptoms without confirmatory BG GP1 22 (21*) number of events: 44 GP2 22 (20*) number of events: 44 Total hypoglycemic events (includes minor and symptomatic only) GP1 event rate: 0.037/patient-week GP2 event rate: 0.039/patient-week

Evidence Table 5. Comparative safety of premixed insulin analogues and other diabetes treatments on hypoglycemia (continued)

Author, year	Intervention	Mild hypoglycemia, n (%)	Moderate hypoglycemia, n (%)	Serious hypoglycemia, n (%)	Daytime hypoglycemia, n (%)	Nighttime hypoglycemia, n (%)	Other hypoglycemia, n (%)
Raz, 2005[51]	GP1: Insulin aspart 70/30 (v) Start: 0.3 U/kg/day Mean: 0.7 U/kg/day T: Breakfast, dinner D: 18 weeks GP2: Insulin aspart 70/30 (v) Start: 0.2 U/kg/day Mean: 0.5 U/kg/day T: Breakfast, dinner D: 18 weeks Pioglitazone (fix) Start: 30 mg Mean: 30 mg T: Breakfast D: 18 weeks	BG < 50 mg/dL but did not require third party assistance GP1 15 (15) number of events: 47 GP2 11 (12) number of events: 15		BG < 50 mg/dL or requiring third party assistance GP1 0 (0*) GP2 0 (0*)		Midnight to 6 am GP1 number of events: 8 GP2 number of events: 0	All hypoglycemic episodes - symptoms or BG < 50 mg/dL GP1 event rate: 0.132/patient-week GP2 event rate: 0.083/patient-week
Insulin lispro 75/25 vs. long-acting insulin analogues							
Cox, 2007[68]	GP1: Insulin lispro 75/25 (v) T: Breakfast, dinner D: 12 weeks metformin (unclear) T: NR D: 12 weeks GP2: Insulin glargine (v) T: Bedtime D: 12 weeks metformin (unclear) T: NR D: 12 weeks			Severe, not defined GP1 0 (0*) GP2 0 (0*)			Symptoms or BG < 63 md/dL (3.5 mmol/L) GP1 p: NS

Evidence Table 5. Comparative safety of premixed insulin analogues and other diabetes treatments on hypoglycemia (continued)

Author, year	Intervention	Mild hypoglycemia, n (%)	Moderate hypoglycemia, n (%)	Serious hypoglycemia, n (%)	Daytime hypoglycemia, n (%)	Nighttime hypoglycemia, n (%)	Other hypoglycemia, n (%)
Jacober, 2006[58]	GP1: Insulin lispro 50/50 (v) Mean: 0.353 IU/kg; 36.73 IU T: Breakfast, lunch D: 4 months Insulin lispro 75/25 (v) T: Dinner D: 4 months existing oral therapy (NR) T: NR D: 4 months GP2: Insulin glargine (v) Mean: 0.276 IU/kg; 27.98 IU T: Bedtime D: 4 months existing oral therapy (NR) T: NR D: 4 months			Self reported GP1 0 (0) GP2 0 (0)		Self reported symptoms or PG <= 72 mg/dL GP1 event rate: 0.8/patient/30 days (SD: 2.12) p: 0.3604 GP2 event rate: 1.05/patient/30 days (SD: 1.59)	Self reported symptoms or PG <= 72 mg/dL GP1 event rate: 3.98/patient/30 days (SD: 4.74) p: 0.0013 GP2 event rate: 2.57/patient/30 days (SD: 3.22) Self reported symptoms or PG <= 72 mg/dL GP1 42* (72.2) p: 0.033 GP2 56* (94.8)
Malone, 2004[59]	GP1: Insulin lispro 75/25 (v) Mean: 0.62 U/kg T: Breakfast, dinner D: 16 weeks Metformin (NR) Mean: 1945 mg Range: 1500 - 2550 mg T: NR D: 16 weeks GP2: Insulin glargine (v) Mean: 0.57 U/kg T: Bedtime D: 16 weeks Metformin (NR) Mean: 1997 mg Range: 1500 - 2550 mg T: NR D: 16 weeks			Requiring third-party assistance due to disabling hypoglycemia GP1 0 (0) GP2 0 (0)		BG < 63 mg/dL or symptoms occurring between bedtime and before breakfast GP1 30 (30) number of events: 39 GP2 28 (28) number of events: 63	BG < 63 mg/dL or symptoms GP1 57 (57) number of events: 181 event rate: 0.68/patient/30 days (SD: 1.38) p: 0.041 GP2 40 (40) number of events: 87 event rate: 0.39/patient/30 days (SD: 1.24)

Evidence Table 5. Comparative safety of premixed insulin analogues and other diabetes treatments on hypoglycemia (continued)

Author, year	Intervention	Mild hypoglycemia, n (%)	Moderate hypoglycemia, n (%)	Serious hypoglycemia, n (%)	Daytime hypoglycemia, n (%)	Nighttime hypoglycemia, n (%)	Other hypoglycemia, n (%)
Malone, 2005[60]	GP1: Insulin lispro 75/25 (v) Mean: 0.42 U/kg T: Breakfast, dinner D: 16 weeks Metformin (fix) Mean: 2128 mg Range: 1500 - 2550 mg T: NR D: 16 weeks GP2: Insulin glargine (v) Mean: 0.36 U/kg T: Bedtime D: 16 weeks Metformin (fix) Mean: 2146 mg Range: 1500 - 2550 mg T: NR D: 16 weeks			Not defined GP1 0 (0*) GP2 0 (0*)	BG < 63 mg/dL (3.5 mmol/L) or symptoms GP1 event rate: 0.46/patient/30 days (SD: 1.28) p: 0.003 GP2 event rate: 0.1/patient/30 days (SD: 0.51)	BG < 63 mg/dL (3.5 mmol/L) or symptoms occurring between bedtime and breakfast for the patient GP1 event rate: 0.14//patient/30 days (SD: 0.49) p: 0.002 GP2 event rate: 0.34/patient/30 days (SD: 0.85)	Overall rate of BG < 63 mg/dL (3.5 mmol/L) or symptoms GP1 event rate: 0.61/patient/30 days (SD: 1.41) p: 0.477 GP2 event rate: 0.44/patient/30 days (SD: 1.07)

Evidence Table 5. Comparative safety of premixed insulin analogues and other diabetes treatments on hypoglycemia (continued)

Author, year	Intervention	Mild hypoglycemia, n (%)	Moderate hypoglycemia, n (%)	Serious hypoglycemia, n (%)	Daytime hypoglycemia, n (%)	Nighttime hypoglycemia, n (%)	Other hypoglycemia, n (%)
Roach, 2006[57]	GP1: Insulin lispro 75/25 (v) Mean: 23 U (morning) and 37 U (evening) Range: 0 – 72 U (morning); 11 – 88 U (evening) T: Breakfast, dinner D: 12 weeks ODM (NR) Start: current dose T: NR D: 12 weeks Metformin (v) Start: 500 mg qd T: NR D: 12 weeks GP2: Insulin glargine (v) Mean: 44 U Range: 14 U - 100 U T: Breakfast D: 12 weeks ODM (NR) Start: current dose T: NR D: 12 weeks Metformin (v) Start: 500 mg qd T: NR D: 12 weeks	Self reported blood glucose < 63 mg/dL (3.5 mmol/L) or symptoms GP1 3 (15*) GP2 2 (10*)		Not defined GP1 0 (0*) GP2 0 (0*)	PG < 63 mg/dL (3.5 mmol/L) GP1 0 (0*) GP2 1 (5*)	PG < 63 mg/dL (3.5 mmol/L) GP1 8 (40*) GP2 2 (10*)	PG < 63 mg/dL (3.5 mmol/L) GP1 8 (40*) GP2 3 (15*)

Evidence Table 5. Comparative safety of premixed insulin analogues and other diabetes treatments on hypoglycemia (continued)

Author, year	Intervention	Mild hypoglycemia, n (%)	Moderate hypoglycemia, n (%)	Serious hypoglycemia, n (%)	Daytime hypoglycemia, n (%)	Nighttime hypoglycemia, n (%)	Other hypoglycemia, n (%)
Insulin lispro 75/25 vs. premixed human insulins							
Coscelli, 2003[61]	GP1: Insulin lispro 75/25 (v) Mean: 38.1 Range: 12 - 72 T: Breakfast, dinner D: 12 days diet/exercise D: 12 days GP2: NPH/regular 70/30 (v) Mean: 37.3 Range: 10 - 72 T: Breakfast, dinner D: 12 days diet/exercise D: 12 days						Not defined GP1 p: NS vs. GP2
Herman-sen, 2002[55]	GP1: Insulin lispro 75/25 (fix) Start: 0.4 units/kg T: Breakfast D: 1 day GP2: NPH/regular 70/30 (fix) Start: 0.4 units/kg T: Breakfast D: 1 day			Requiring third-party assistance GP1 number of events: 5 GP2 number of events: 2			Overall hypoglycemia (not specified) GP1 number of events: 19 GP2 number of events: 11

Evidence Table 5. Comparative safety of premixed insulin analogues and other diabetes treatments on hypoglycemia (continued)

Author, year	Intervention	Mild hypoglycemia, n (%)	Moderate hypoglycemia, n (%)	Serious hypoglycemia, n (%)	Daytime hypoglycemia, n (%)	Nighttime hypoglycemia, n (%)	Other hypoglycemia, n (%)
Herz, 2002[65]	GP1: Insulin lispro 75/25 (v) Mean: 26.1 U T: Breakfast, dinner D: 4 weeks GP2: NPH/regular 70/30 (v) Mean: 26.2 U T: Breakfast, dinner D: 4 weeks						Symptoms or BG < 54 mg/dL (3.0 mmol/L)¶ GP1 event rate: 0.7/patient/30 days (SE = 0.2) p: 0.042 GP2 event rate: 1.2/patient/30 days (SE = 0.3) Symptoms or BG < 54 mg/dL (3.0 mmol/L)§ GP1 event rate: 0.9/patient/30 days (SE = 0.2) p: 0.569 GP2 event rate: 0.9/patient/30 days (SE = 0.1)

Evidence Table 5. Comparative safety of premixed insulin analogues and other diabetes treatments on hypoglycemia (continued)

Author, year	Intervention	Mild hypoglycemia, n (%)	Moderate hypoglycemia, n (%)	Serious hypoglycemia, n (%)	Daytime hypoglycemia, n (%)	Nighttime hypoglycemia, n (%)	Other hypoglycemia, n (%)
Herz, 2003[13]	GP1: Insulin lispro 75/25 (v) Mean: 31.6 (morning)¶ and 26.8 units (evening)¶ and 32.4 (morning)§ and 27.6 units (evening)§ T: Breakfast, dinner D: 4 weeks GP2: NPH/regular 70/30 (v) Mean: 32.3 (morning)¶ and 26.4 units (evening)¶ and 33.3 (morning)§ and 27.5 units (evening)§ T: Breakfast, dinner D: 4 weeks						Symptoms or any spontaneous BG < 54 mg/dL (3.0 mmol/L)¶ GP1 event rate: 0.049/patient/30 days (SE = 0.018) p: 0.586 GP2 event rate: 0.1/patient/30 days (SE = 0.018) Symptoms or any spontaneous BG < 54 mg/dL (3.0 mmol/L)§ GP1 event rate: 0.241/patient/30 days (SE = 0.053) p: 0.524 GP2 event rate: 0.222/patient/30 days (SE = 0.053)

Evidence Table 5. Comparative safety of premixed insulin analogues and other diabetes treatments on hypoglycemia (continued)

Author, year	Intervention	Mild hypoglycemia, n (%)	Moderate hypoglycemia, n (%)	Serious hypoglycemia, n (%)	Daytime hypoglycemia, n (%)	Nighttime hypoglycemia, n (%)	Other hypoglycemia, n (%)
Malone, 2000[41]	GP1: Insulin lispro 75/25 (fix) Mean: 35.4 U (0.43U/kg) T: Breakfast D: 2 days GP2: NPH/regular 70/30 (fix) Mean: 35.4 U (0.43U/kg) T: Breakfast D: 2 days						BG < 63 mg/dL (3.5 mmol/L) or symptoms occurring between lunch and dinner GP1 number of events: 3 GP2 number of events: 5 BG < 63 mg/dL (3.5 mmol/L) or symptoms GP1 number of events: 7 GP2 number of events: 10 BG < 63 mg/dL (3.5 mmol/L) or symptoms occurring within 4 hours of test meal GP1 number of events: 5 GP2 number of events: 8

Evidence Table 5. Comparative safety of premixed insulin analogues and other diabetes treatments on hypoglycemia (continued)

Author, year	Intervention	Mild hypoglycemia, n (%)	Moderate hypoglycemia, n (%)	Serious hypoglycemia, n (%)	Daytime hypoglycemia, n (%)	Nighttime hypoglycemia, n (%)	Other hypoglycemia, n (%)
Mattoo, 2003[64]	GP1: Insulin lispro 75/25 (unclear) Mean: 20 U (morning), 32 U (evening) T: Breakfast, dinner D: 2 weeks GP2: NPH/regular 70/30 (unclear) Mean: 20 U (morning), 32 U (evening) T: Breakfast, dinner D: 2 weeks						Symptoms or BG < 63 mg/dL (3.5 mmol/L) GP1 event rate: 0.4/patient/14 days (SD = 0.9) p: 0.725 GP2 event rate: 0.4/patient/14 days (SD = 0.8)
Roach, 1999[67]	GP1: Insulin lispro 75/25 (v) Mean: 0.37 (morning) and 0.28 (evening) T: Breakfast, dinner D: 13 weeks GP2: NPH/regular 70/30 (v) Mean: 0.36 (morning) and 0.27 (evening) T: Breakfast, dinner D: 13 weeks			Required third party assistance GP1 1 (1*) GP2 1 (1*)		Symptoms or BG < 54 mg/dL (3.0 mmol/L) occurring between mean reported bedtime and mean reported breakfast time for each country GP1 13 (15) p: 0.266 GP2 8 (9)	Symptoms or BG < 54 mg/dL (3.0 mmol/L) GP1 34* (42) p: 0.398 GP2 28* (35)
Schwartz, 2006[56]	GP1: Insulin lispro 75/25 (fix) Start: 2/3 of patient's usual daily dose Mean: 44.1 U T: Breakfast D: 1 day GP2: NPH/regular 70/30 (fix) Start: 2/3 of patient's usual daily dose Mean: 44.1 U T: Breakfast D: 1 day	GP1 0 (0*) GP2 1 (5*)					

Evidence Table 5. Comparative safety of premixed insulin analogues and other diabetes treatments on hypoglycemia (continued)

Author, year	Intervention	Mild hypoglycemia, n (%)	Moderate hypoglycemia, n (%)	Serious hypoglycemia, n (%)	Daytime hypoglycemia, n (%)	Nighttime hypoglycemia, n (%)	Other hypoglycemia, n (%)
Insulin lispro 75/25 vs. oral antidiabetic agents							
Herz, 2002[66]	GP1: Insulin lispro 75/25 (v) Start: 0.3-0.5 U/kg Mean: 0.46 U/kg T: Breakfast, dinner D: 16 weeks GP2: Glyburide (fix) Start: 15 mg/day T: Breakfast, dinner D: 16 weeks			Requiring assistance of third party GP1 0 (0*) GP2 0 (0*)			Any (BG < 54 mg/dL (3 mmol/L) or symptoms) GP1 B: 0.14 episodes/ patient/30 days (SE 0.14) p: 0.361 vs GP2 F: 0.31 episodes/ patient/30 days (SE 0.21) p: 0.028 vs GP2 F-B: 0.17episodes/ patient/30 days (SE 0.02) p: 0.077 vs GP2

Evidence Table 5. Comparative safety of premixed insulin analogues and other diabetes treatments on hypoglycemia (continued)

Author, year	Intervention	Mild hypoglycemia, n (%)	Moderate hypoglycemia, n (%)	Serious hypoglycemia, n (%)	Daytime hypoglycemia, n (%)	Nighttime hypoglycemia, n (%)	Other hypoglycemia, n (%)
Malone, 2003[62]	GP1: Insulin lispro 75/25 (v) Mean: 0.19 U/kg (morning) and 0.14 U/kg (evening) T: Breakfast, dinner D: 16 weeks Metformin (v) Mean: 1813 mg/day Range: 1500 – 2550 mg/day T: 2 to 3 times/day D: 16 weeks GP2: Metformin (v) Mean: 1968 mg/day Range: 1500 - 2550 mg/day T: 2 to 3 times/day D: 16 weeks Glibenclamide (v) Mean: 14.2 mg/day T: NR D: 16 weeks			Unable to treat self or BG < 36 mg/dL (2.0 mmol/L) (events/patient/30 days) GP1 B: 0.01 Median (0.09) F: 0.01 Median (0.11) F-B: 0* (1) GP2 B: 0 Median (0) F: 0.02 Median (0.15) F-B: 0* (1.3) GP1-GP2: 0*		Symptoms or BG < 63 mg/dL (3.5 mmol/L) occurring after bedtime (events/patient/30 days) GP1 B: 0.03 (0.23) F: 0.01 (0.11) F-B: 0* GP2 B: 0 (0) F: 0.08 (0.4) F-B: 0* GP1-GP2: 0* Symptoms or BG < 63 mg/dL (3.5 mmol/L) occurring after bedtime GP1 (1) GP2 (5)	Overall events/ patient/30 days GP1 B: 0.08 (0.59) F: 0.31 (1.07) F-B: 0* GP2 B: 0.07 (0.57) F: 0.48 (1.17) F-B: 0* GP1-GP2: 0*
Tirgo-viste, 2003[40]	GP1: Insulin lispro 75/25 (v) Start: 0.3-0.5 U/kg T: Breakfast, dinner D: 16 weeks GP2: glibenclamide (v) Start: 15 mg T: Breakfast, dinner D: 16 weeks						Symptoms and/or BG < 54 mg/dL (3.0 mmol/L) GP1 38 (44.7) p: 0.001 GP2 9 (10.3)

Evidence Table 5. Comparative safety of premixed insulin analogues and other diabetes treatments on hypoglycemia (continued)

Author, year	Intervention	Mild hypoglycemia, n (%)	Moderate hypoglycemia, n (%)	Serious hypoglycemia, n (%)	Daytime hypoglycemia, n (%)	Nighttime hypoglycemia, n (%)	Other hypoglycemia, n (%)
Insulin lispro 75/25 vs. insulin lispro 50/50							
Roach, 2003[63]	GP1: Insulin lispro 75/25 (v) Mean: 31.3 (morning) and 27.6 units (evening) T: Breakfast, dinner D: 8 weeks GP2: Insulin lispro 50/50 (v) Mean: 31.5 units T: Breakfast D: 8 weeks Insulin lispro 75/25 (v) Mean: 27.9 units T: Dinner D: 8 weeks			Required third party assistance GP1 0* (0) GP2 0* (0)			Symptoms GP1 28* (26.1) p: 0.078 number of events: 65 p: 0.681 GP2 34* (32.4) number of events: 68
Schwartz, 2006[56]	GP1: Insulin lispro 75/25 (fix) Start: 2/3 of patient's usual daily dose Mean: 44.1 U T: Breakfast D: 1 day GP2: Insulin lispro 50/50 (fix) Start: 2/3 of patient's usual daily dose Mean: 43.8 U T: Breakfast D: 1 day	GP1 0 (0*) GP2 0 (0*)					

Evidence Table 5. Comparative safety of premixed insulin analogues and other diabetes treatments on hypoglycemia (continued)

Author, year	Intervention	Mild hypoglycemia, n (%)	Moderate hypoglycemia, n (%)	Serious hypoglycemia, n (%)	Daytime hypoglycemia, n (%)	Nighttime hypoglycemia, n (%)	Other hypoglycemia, n (%)
Insulin lispro 50/50 vs. long-acting insulin analogues							
Kazda, 2006[69]	GP1: Insulin lispro 50/50 (v) Start: 0.30 IU/kg mean Mean: 0.59 IU/kg T: Breakfast, lunch, dinner D: 24 weeks GP2: Insulin glargine (v) Start: 0.16 IU/kg mean Mean: 0.43 IU/kg T: Bedtime D: 24 weeks			Not defined GP1 0 (0) GP2 0 (0)			Patient felt or was observed to have symptoms or PG < 54 mg/dL (3.0 mmol/L) GP1 24* (44.4) event rate: 1.5/ 100 patient-days GP2 17* (32.1) event rate: 1/ 100 patient-days
Insulin lispro 50/50 vs. rapid-acting insulin analogues							
Kazda, 2006[69]	GP1: Insulin lispro 50/50 (v) Start: 0.30 IU/kg mean Mean: 0.59 IU/kg T: Breakfast, lunch, dinner D: 24 weeks GP2: Insulin lispro (v) Start: 0.25 IU/kg mean Mean: 0.50 IU/kg T: Breakfast, lunch, dinner D: 24 weeks			Not defined GP1 0 (0) GP2 0 (0)			Patient felt or was observed to have symptoms or PG < 54 mg/dL (3.0 mmol/L) GP1 24* (44.4) event rate: 1.5/ 100 patient-days GP2 28* (53.8) event rate: 1.4/ 100 patient-days

Evidence Table 5. Comparative safety of premixed insulin analogues and other diabetes treatments on hypoglycemia (continued)

Author, year	Intervention	Mild hypoglycemia, n (%)	Moderate hypoglycemia, n (%)	Serious hypoglycemia, n (%)	Daytime hypoglycemia, n (%)	Nighttime hypoglycemia, n (%)	Other hypoglycemia, n (%)
Insulin lispro 50/50 vs. premixed human insulins							
Roach, 1999[11]	GP1: Insulin lispro 50/50 (v) Mean: 0.31 U/kg T: Breakfast D: 3 months Insulin lispro 75/25 (v) Mean: 0.26 U/kg T: Dinner D: 3 months GP2: NPH/regular 50/50 (v) Mean: 0.32 U/kg T: Breakfast D: 3 months NPH/regular 70/30 (v) Mean: 0.26 U/kg T: Dinner D: 3 months			Occurrence of coma or requirement for intravenous glucose, glucagon, or both GP1 0 (0*) GP2 0 (0*)		Symptoms or BG < 54 mg/dL (3.0 mmol/L) occurring between median bedtime (10:30pm) and median breakfast (7:45am) GP1 mean number of events/patient/3 months: 0.3 (SD: 1.0) p: 0.199 GP2 mean number of events/patient/3 months: 0.6 (SD: 1.4)	Symptoms or BG < 54 mg/dL (3.0 mmol/L) GP1 25* (40) p: NS GP2 23* (37)
Schern-thaner, 2004[70]	GP1: Insulin lispro 50/50 (v) Mean: 64.6 IU T: Breakfast, lunch, dinner D: 12 weeks diet/exercise D: 12 weeks GP2: NPH/regular 70/30 (v) Mean: 61.8 IU T: Breakfast, dinner D: 12 weeks diet/exercise D: 12 weeks			BG < 36 mg/dL, coma, or treatment with glucagon or intravenous glucose GP1 0 GP2 1			BG < 65 mg/dL or symptoms GP1 14 (41.2) p: NS GP2 10 (29.4)

Evidence Table 5. Comparative safety of premixed insulin analogues and other diabetes treatments on hypoglycemia (continued)

Author, year	Intervention	Mild hypoglycemia, n (%)	Moderate hypoglycemia, n (%)	Serious hypoglycemia, n (%)	Daytime hypoglycemia, n (%)	Nighttime hypoglycemia, n (%)	Other hypoglycemia, n (%)
Schwartz, 2006[56]	GP1: Insulin lispro 50/50 (fix) Start: 2/3 of usual daily dose Mean: 43.8 U T: Breakfast D: 1 day GP2: NPH/regular 70/30 (fix) Start: 2/3 of usual daily dose Mean: 44.1 U T: Breakfast D: 1 day	GP1 0 (0*) GP2 1 (5*)					

Evidence Table 5. Comparative safety of premixed insulin analogues and other diabetes treatments on hypoglycemia (continued)

Author, year	Intervention	Mild hypoglycemia, n (%)	Moderate hypoglycemia, n (%)	Serious hypoglycemia, n (%)	Daytime hypoglycemia, n (%)	Nighttime hypoglycemia, n (%)	Other hypoglycemia, n (%)
Yamada, 2007[71]	GP1: Insulin lispro 50/50 (v) Start: current dose Mean: 0.37 U/kg (start) and 0.38 U/kg (end) T: twice daily D: 4 months GP2: NPH/regular 70/30 (v) Start: current dose Mean: 0.34 U/kg (start) and 0.37 U/kg (end) T: twice daily D: 4 months NPH/regular 50/50 (v) Start: current dose Mean: 0.34 U/kg (start) and 0.37 U/kg (end) T: twice daily D: 4 months			Requiring third party assistance GP1 0 (0*) GP2 0 (0*)			

* Number has been imputed.
‖ Among those not using thiazolidinediones.
‡ One-hundred and four (36%) of the 291 participants of this trial are patients with type 1 diabetes. The remaining population has type 2 diabetes and is the same study population as Boehm 2004.[42] Only data for the Boehm 2004 study is presented because it has the longest followup.
¶ Results occurring during the outpatient phase.
§ Results occurring during the inpatient phase.

µg = microgram; B = baseline; BG = blood glucose; bid = twice daily ; BS = blood sugar; CGMS = Continuous Glucose Monitoring System; CI = confidence interval; CNS = central nervous system; D = duration; dl = deciliter; F = final; F-B = mean difference from baseline; fix = fixed dosing; GP = group; GP1-GP2 = mean difference between the difference from baseline; h = hour; IQR = interquartile range; IU = international unit; kg = kilogram; L = liter; mg = milligram; ml = milliliter; mmol = millimole; NPH = neutral protamine Hagedorn; NR = not reported; NS = not significant; ODM = oral diabetes medicine; p = p-value; PG = plasma glucose; qd = once daily; RR = relative risk; SD = standard deviation; SE = standard error; T = time of day when insulin taken; U = unit; v = dosing varied

Evidence Table 6. Comparative effectiveness of premixed insulin analogues and other diabetes treatments on adverse events

Author, year	Intervention	Weight in kg, mean (SD)	Injection Site Reaction, n (%)	Total serious adverse events, n (%)	Withdrawn due to adverse events, n (%)	Other serious adverse events, n (%)
Insulin aspart 70/30 vs. long-acting insulin analogues						
Holman, 2007[28]	GP1: Insulin aspart 70/30 (v) Start: 16 median Range: 10 - 26 T: bid D: 1 year Usual care D: 1 year GP2: Insulin detemir (v) Start: 16 median Range: 10 - 24 T: Bedtime, twice if required D: 1 year Usual care D: 1 year	GP1 F-B: 4.7 (4) p: <0.001 GP2 F-B: 1.9 (4.2) GP1-GP2: 3*		GP1 41 (17.4) p: overall 0.25 GP2 30 (12.8)	GP1 2 (1*) GP2 4 (2*)	Gastrointestinal and abdominal pain GP1 3 (1.3) p: overall 0.21 GP2 2 (0.9) Lower respiratory tract and lung infection GP1 4 (1.7) p: overall 0.02 GP2 0 (0)
Kann, 2006[47]	GP1: Insulin aspart 70/30 (v) Start: 0.1 U/kg bid Mean: 0.4 U/kg T: Breakfast, dinner D: 26 weeks metformin (v) Start: 500 mg bid or current dose T: Breakfast, dinner D: 26 weeks GP2: Insulin glargine (v) Start: 0.2 U/kg qd Mean: 0.39 U/kg T: preferred time (constant through study) D: 26 weeks glimepiride (v) Start: 1 mg daily or current dose T: Breakfast D: 26 weeks	GP1 B: 84* F: 84.8 (17.2) F-B: 0.7 p: NS vs. baseline GP2 B: 86* F: 88.1 (14.6) F-B: 1.5 (95% CI: 0.84 – 2.19) p: <0.0001 vs. baseline GP1-GP2: -1*		GP1 10 (7.8) GP2 11 (8.7)	GP1 5 (4*) GP2 2 (2*)	

Evidence Table 6. Comparative effectiveness of premixed insulin analogues and other diabetes treatments on adverse events (continued)

Author, year	Intervention	Weight in kg, mean (SD)	Injection Site Reaction, n (%)	Total serious adverse events, n (%)	Withdrawn due to adverse events, n (%)	Other serious adverse events, n (%)
Raskin, 2005[36] Raskin, 2007[37]	GP1: Insulin aspart 70/30 (v) Start: 10 or 12 units T: Breakfast, dinner D: Unclear metformin (v) Range: 1500 – 2550 mg/day T: NR D: Unclear GP2: Insulin glargine (v) Start: 10-12 units/day T: Bedtime D: Unclear metformin (v) Range: 1500 - 2550 mg/day T: NR D: Unclear	GP1 F-B: 5.4 (4.8) p: <0.01 GP2 F-B: 3.5 (4.5) GP1-GP2: 1* GP1‖ F-B: 5.6 (4.6) p: 0.0004 GP2‖ F-B: 3 (4.3) GP1-GP2: 3*		GP1‖ 4 (5) GP2‖ 5 (6)	GP1 4 (3*) GP2 1 (1*) GP1‖ 3 (4*) GP2‖ 0 (0*)	
Tamemoto, 2007[44]	GP1: Insulin aspart 70/30 (v) Start: 10 - 16 units/day Mean: 26.7 units T: Breakfast, dinner D: 6 months continued ODM (unclear) T: NR D: 6 months GP2: Insulin glargine (v) Start: 6 - 8 units/day T: NR D: 6 (expected) months continued ODM (unclear) T: NR D: 6 months	GP1 F-B: 0.42 p: NS GP2 F-B: 0.51 GP1-GP2: -1*			GP1 0 (0*) GP2 0 (0*)	

Evidence Table 6. Comparative effectiveness of premixed insulin analogues and other diabetes treatments on adverse events (continued)

Author, year	Intervention	Weight in kg, mean (SD)	Injection Site Reaction, n (%)	Total serious adverse events, n (%)	Withdrawn due to adverse events, n (%)	Other serious adverse events, n (%)
Insulin aspart 70/30 vs. rapid-acting insulin analogues						
Holman, 2007[28]	GP1: Insulin aspart 70/30 (v) Start: 16 median Range: 10 - 26 T: bid D: 1 year Usual care D: 1 year GP2: Insulin aspart (v) Start: 18 median Range: 9 - 24 T: Breakfast, lunch, dinner D: 1 year Usual care D: 1 year	GP1 F-B: 4.7 (4) p: 0.005 vs. GP2 GP2 F-B: 5.7 (4.6) GP1-GP2: -1*		GP1 41 (17.4) p: overall 0.25 GP2 30 (12.6)	GP1 2 (1*) GP2 0 (0*)	Gastrointestinal and abdominal pain GP1 3 (1.3) p: overall 0.21 GP2 0 (0) Lower respiratory tract and lung infection GP1 4 (1.7) p: overall 0.02 GP2 0 (0)
Insulin aspart 70/30 vs. rapid-acting with long-acting insulin analogues						
Joshi, 2005[49]	GP1: Insulin aspart 70/30 (v) Mean: 40.19 U/day T: twice daily D: 12 weeks GP2: Insulin aspart (v) Mean: 28.26 U/day T: before every meal D: 12 weeks Insulin glargine (v) Mean: 24.52 U/day T: Bedtime D: 12 weeks	GP1 B: 70.4 (12.18) F: 70.61 (11.23) F-B: 1* p: NS vs. baseline GP2 B: 69.63 (10.31) F: 69.68 (9.58) F-B: 0* p: NS vs. baseline GP1-GP2: 1*		GP1 0 (0*) GP2 0 (0*)	GP1 0 (0*) GP2 0 (0*)	

Evidence Table 6. Comparative effectiveness of premixed insulin analogues and other diabetes treatments on adverse events (continued)

Author, year	Intervention	Weight in kg, mean (SD)	Injection Site Reaction, n (%)	Total serious adverse events, n (%)	Withdrawn due to adverse events, n (%)	Other serious adverse events, n (%)
Insulin aspart 70/30 vs. premixed human insulins						
Abrahamian, 2005[50]	GP1: Insulin aspart 70/30 (v) Mean: 0.49 U/kg (start) and 0.61 (end) T: Breakfast, lunch, dinner D: 24 weeks GP2: NPH/regular 70/30 (v) Mean: 0.46 U/kg (start) and 0.59 U/kg (end) T: Breakfast, dinner D: 24 weeks			GP1 number of events: 16 GP2 number of events: 15	GP1 3 (3*) GP2 0 (0*)	
Boehm, 2004[42] Boehm, 2002[10]‡	GP1: Insulin aspart 70/30 (v) Start: 0.57 U/kg T: Breakfast, dinner D: 24 months GP2: NPH/regular 70/30 (v) Start: 0.57 U/Kg T: Breakfast, dinner D: 24 months	GP1 F-B: 0.05 (SE 0.81) p: 0.07 vs. GP2 GP2 F-B: 2 (SE 0.69) GP1-GP2: -2*			GP1 5 (6*) GP2 6 (6*)	
Hermansen, 2002[55]	GP1: Insulin aspart 70/30 (fix) Start: 0.4 units/kg body weight T: Breakfast D: 1 day GP2: NPH/regular 70/30 (fix) Start: 0.4 units/kg body weight T: Breakfast D: 1 day				GP1 1 (2*) GP2 0 (0*)	GP1 number of events: 1 GP2 number of events: 0
Kapitza, 2004[53]	GP1: Insulin aspart 70/30 (NA) T: Breakfast D: 1 day GP2: NPH/regular 70/30 (NA) T: Breakfast D: 1 day				GP1 0 (0*) GP2 0 (0*)	

Evidence Table 6. Comparative effectiveness of premixed insulin analogues and other diabetes treatments on adverse events (continued)

Author, year	Intervention	Weight in kg, mean (SD)	Injection Site Reaction, n (%)	Total serious adverse events, n (%)	Withdrawn due to adverse events, n (%)	Other serious adverse events, n (%)
Kilo, 2003[16]	GP1: Insulin aspart 70/30 (v) Start: 0.16 Units/day Mean: 26 U/day T: Dinner D: 12 weeks metformin (fix) Mean: about 2200 mg Range: 500 - 2550 mg T: 1-3 times/day D: 4 weeks run-in, then 12 weeks GP2: NPH/regular 70/30 (v) Start: 0.16 Units/day Mean: 29 U/day T: Dinner D: 12 weeks metformin (fix) Mean: about 2200 mg Range: 500 - 2550 mg T: 1-3 times/day D: 4 weeks run-in, then 12 weeks	GP1 F-B: 0.7 p: 0.251 vs. GP2 GP2 F-B: 1 GP1-GP2: 0*			GP1 2 (4*) GP2 0 (0*)	Blurred vision and pain in the extremities GP1 1 (2*) GP2 0 (0*)
McNally, 2007[45]	GP1: Insulin aspart 70/30 (v) Start: 100 units/mL Mean: 68.8 units Range: 6 - 238.7 T: Breakfast, dinner D: 16 weeks GP2: NPH/regular 70/30 (v) Start: 100 units/mL Mean: 66.6 units Range: 11.3 - 240 T: Breakfast, dinner D: 16 weeks			Resulted in death, was life-threatening or caused (or prolonged) hospitalization GP1 3* (4) GP2 5* (6)	GP1 2 (1*) GP2 1 (1*)	

Evidence Table 6. Comparative effectiveness of premixed insulin analogues and other diabetes treatments on adverse events (continued)

Author, year	Intervention	Weight in kg, mean (SD)	Injection Site Reaction, n (%)	Total serious adverse events, n (%)	Withdrawn due to adverse events, n (%)	Other serious adverse events, n (%)
McSorley, 2002[12]	GP1: Insulin aspart 70/30 (unclear) T: Breakfast, dinner D: 2 weeks GP2: NPH/regular 70/30 (unclear) T: Breakfast, dinner D: 2 weeks				GP1 0 (0*) GP2 0 (0*)	GP1 0 (0*) GP2 0 (0*)
Insulin aspart 70/30 vs. intermediate-acting human insulin						
Christiansen, 2003[14]	GP1: Insulin aspart 70/30 (v) Start: insulin naïve: 8 - 16 units/day; taking NPH prior to trial: pretrial dose T: Breakfast, dinner D: 16 weeks GP2: NPH insulin (v) Start: insulin naïve: 8 - 16 units/day; taking NPH prior to trial: pretrial dose T: Breakfast, dinner D: 16 weeks	GP1 1 (0*) GP2 1 (0*)		GP1 5 (2*) number of events: 5 GP2 7 (3*) number of events: 8	GP1 2 (1*) GP2 2 (1*)	Allergic reaction to protamine GP1 1 (0*) GP2 0 (0*)

Evidence Table 6. Comparative effectiveness of premixed insulin analogues and other diabetes treatments on adverse events (continued)

Author, year	Intervention	Weight in kg, mean (SD)	Injection Site Reaction, n (%)	Total serious adverse events, n (%)	Withdrawn due to adverse events, n (%)	Other serious adverse events, n (%)
Kilo, 2003[16]	GP1: Insulin aspart 70/30 (v) Start: 0.16 Units/day Mean: 26 U/day T: Dinner D: 12 weeks metformin (fix) Mean: about 2200 mg Range: 500 - 2550 mg T: 1-3 times/day D: 4 weeks run-in, then 12 weeks GP2: NPH insulin (v) Start: 0.16 Units/day Mean: 28 U/day T: Bedtime D: 12 weeks metformin (fix) Mean: about 2200 mg Range: 500 - 2550 mg T: 1-3 times/day D: 4 weeks run-in, then 12 weeks	GP1 F-B: 0.7 p: 0.251 between treatments GP2 F-B: 0.1 GP1-GP2: 1*			GP1 2 (4*) GP2 0 (0*)	Blurred vision and pain in the extremities GP1 1 (2*) GP2 0 (0*)
Insulin aspart 70/30 vs. oral antidiabetic agents						
Bebakar, 2007[43]	GP1: Insulin aspart 70/30 (v) Start: 0.2 U/kg/day Range: 0.16U/kg (qd group) - 0.43U/kg (bid group) T: once or twice daily D: 24 weeks GP2: ODM (v) T: NR D: 24 weeks	GP1 F-B: 0.98 p: <0.005 vs. GP2 GP2 F-B: 0 GP1-GP2: 1*		GP1 number of events: 5 GP2 number of events: 0	GP1 6 (5*) GP2 0 (0*)	

Evidence Table 6. Comparative effectiveness of premixed insulin analogues and other diabetes treatments on adverse events (continued)

Author, year	Intervention	Weight in kg, mean (SD)	Injection Site Reaction, n (%)	Total serious adverse events, n (%)	Withdrawn due to adverse events, n (%)	Other serious adverse events, n (%)
Kvapil, 2006[48]	GP1: Insulin aspart 70/30 (v) Start: 0.3U/kg/day Mean: 0.51 U/kg/day T: Breakfast, dinner D: 16 weeks GP2: metformin (fix) Mean: 1660 mg Range: 500 - 3000 mg qd T: NR D: 16 weeks glibencamide (v) Start: 1.75 mg Mean: 2.33 (start), 6.58 mg (end) T: once or twice daily	GP1 F-B: 1.6 GP2 F-B: 0.1 GP1-GP2: 1.46 (SE 00.41) p: <0.001		GP1 total events for all groups: 5 GP2 total events for all groups: 5	GP1 1 (1*) GP2 0 (0*)	
Kvapil, 2006[48]	GP1: Insulin aspart 70/30 (v) Start: 0.2 U/kg/day Mean: 0.3 U/kg/day T: Breakfast, dinner D: 16 weeks metformin (fix) Mean: 1660 mg daily Range: 500 - 3000 mg qd T: NR D: 16 weeks GP2: metformin (fix) Mean: 1660 mg daily Range: 500 - 3000 mg qd T: NR D: 16 weeks glibencamide (v) Start: 1.75 mg Mean: 2.33 (start), 6.58 mg (end) T: once or twice daily	GP1 F-B: 0.8 GP2 F-B: 0.1 GP1-GP2: 0.66 (SE 0.41) p: NS		GP1 total events for all groups: 5 GP2 total events for all groups: 5	GP1 2 (2*) GP2 0 (0*)	

Evidence Table 6. Comparative effectiveness of premixed insulin analogues and other diabetes treatments on adverse events (continued)

Author, year	Intervention	Weight in kg, mean (SD)	Injection Site Reaction, n (%)	Total serious adverse events, n (%)	Withdrawn due to adverse events, n (%)	Other serious adverse events, n (%)
Raz, 2003[54]	GP1: Insulin aspart 70/30 (v) Start: 6-8 U bid T: Breakfast, dinner D: 6 weeks rosiglitazone (fix) Start: 4 mg T: Breakfast D: 6 weeks GP2: glibenclamide (fix) Range: 7.5 – 15 mg T: Dinner D: 6 weeks rosiglitazone (fix) Start: 4 mg T: Breakfast D: 6 weeks	GP1 F-B: 0.23 p: NS vs. GP2 GP2 F-B: 0.03 GP1-GP2: 0*			GP1 0 (0*) GP2 0 (0*)	
Raz, 2005[51]	GP1: Insulin aspart 70/30 (v) Start: 0.3 U/kg/day Mean: 0.7 U/kg/day T: Breakfast, dinner D: 18 weeks GP2: Glibenclamide (v) Start: 5 to 10 mg Mean: 14 mg T: Breakfast D: 18 weeks Pioglitazone (fix) Start: 30 mg Mean: 30 mg T: Breakfast D: 18 weeks	GP1 F-B: 2.2 GP2 F-B: 2.2 GP1-GP2: 0* Experienced weight gain GP1 3* (3) p: <0.05 overall GP2 2* (2)		GP1 2 (2*) GP2 0 (0*)	GP1 3 (3*) GP2 2 (2*)	Cellulitis GP1 1 (1*) GP2 0 (0*) Peripheral edema GP1 0* (0) GP2 1* (1)

Evidence Table 6. Comparative effectiveness of premixed insulin analogues and other diabetes treatments on adverse events (continued)

Author, year	Intervention	Weight in kg, mean (SD)	Injection Site Reaction, n (%)	Total serious adverse events, n (%)	Withdrawn due to adverse events, n (%)	Other serious adverse events, n (%)
Raz, 2005[51]	GP1: Insulin aspart 70/30 (v) Start: 0.2 U/kg/day Mean: 0.5 U/kg/day T: Breakfast, dinner D: 18 weeks Pioglitazone (fix) Start: 30 mg Mean: 30 mg T: Breakfast D: 18 weeks GP2: Glibenclamide (v) Start: 5 to 10 mg Mean: 14 mg T: Breakfast D: 18 weeks Pioglitazone (fix) Start: 30 mg Mean: 30 mg T: Breakfast D: 18 weeks	GP1 F-B: 4 GP2 F-B: 2.2 GP1-GP2: 2* Experienced weight gain GP1 7* (8) p: <0.05 overall GP2 2* (2)		GP1 0 (0*) GP2 0 (0*)	GP1 1 (1*) GP2 2 (2*)	Cellulitis GP1 0 (0*) GP2 0 (0*) Peripheral edema GP1 6* (6) GP2 1* (1)

Evidence Table 6. Comparative effectiveness of premixed insulin analogues and other diabetes treatments on adverse events (continued)

Author, year	Intervention	Weight in kg, mean (SD)	Injection Site Reaction, n (%)	Total serious adverse events, n (%)	Withdrawn due to adverse events, n (%)	Other serious adverse events, n (%)
Insulin aspart 70/30 vs. exenatide						
Nauck, 2007[46]	GP1: Insulin aspart 70/30 (v) Start: 15.7 U/day Mean: 24.4 U/day T: Breakfast, dinner D: 52 weeks 'optimally' effective metformin and sulfonylurea (v) T: NR D: 52 weeks GP2: exenatide (v) Start: 5 µg bid Range: 5 - 10 µg bid T: Breakfast D: 52 weeks 'optimally' effective metformin and sulfonylurea therapy (v) T: NR D: 52 weeks	GP1 F-B: 2.9 p: <0.001 GP2 F-B: -2.5 p: <0.001 GP1-GP2: 5.4 (95% CI: 5 – 5.9) p: <0.001		GP1 11 (4.4) GP2 19 (7.5)	GP1 0 (0*) GP2 20 (8*)	
Insulin aspart 70/30 vs. insulin lispro 75/25						
Hermansen, 2002[55]	GP1: Insulin aspart 70/30 (fix) Start: 0.4 units/kg body weight T: Breakfast D: 1 day GP2: Insulin lispro 75/25 (fix) Start: 0.4 units/kg body weight T: Breakfast D: 1 day				GP1 1 (2*) GP2 0 (0*)	GP1 number of events: 1 GP2 number of events: 0

Evidence Table 6. Comparative effectiveness of premixed insulin analogues and other diabetes treatments on adverse events (continued)

Author, year	Intervention	Weight in kg, mean (SD)	Injection Site Reaction, n (%)	Total serious adverse events, n (%)	Withdrawn due to adverse events, n (%)	Other serious adverse events, n (%)
Niskanen, 2004[52]	GP1: Insulin aspart 70/30 (v) Mean: 0.65 U/kg to 0.67 U/kg T: Breakfast, dinner D: 12 weeks GP2: Insulin lispro 75/25 (v) Mean: 0.67 U/kg to 0.71 U/kg T: Breakfast, dinner D: 12 weeks		GP1 1 (1*) GP2 2 (2*)		GP1 1 (1*) GP2 1 (1*)	Resulted in death, life-threatening experience, inpatient hospitalization, persistent or significant disability/ incapacity, or congenital anomaly/birth defect GP1 11 (8*) GP2 3 (2*)
Insulin aspart 70/30 vs. insulin aspart 70/30 + oral antidiabetic agents						
Kvapil, 2006[48]	GP1: Insulin aspart 70/30 (v) Start: 0.3 U/kg/day Mean: 0.51 U/kg/day T: Breakfast, dinner D: 16 weeks GP2: Insulin aspart 70/30 (v) Start: 0.2 U/kg/day Mean: 0.3 U/kg/day T: Breakfast, dinner D: 16 weeks metformin (fix) Mean: 1660 mg daily Range: 500 - 3000 mg qd T: NR D: 16 weeks	GP1 F-B: 1.6 GP2 F-B: 0.8 GP1-GP2: 0.8 (SE 0.41) p: NS vs. GP2		GP1 total events for all groups: 5 GP2 total events for all groups: 5	GP1 1 (1*) GP2 2 (2*)	

Evidence Table 6. Comparative effectiveness of premixed insulin analogues and other diabetes treatments on adverse events (continued)

Author, year	Intervention	Weight in kg, mean (SD)	Injection Site Reaction, n (%)	Total serious adverse events, n (%)	Withdrawn due to adverse events, n (%)	Other serious adverse events, n (%)
Raz, 2005[51]	GP1: Insulin aspart 70/30 (v) Start: 0.3 U/kg/day Mean: 0.7 U/kg/day T: Breakfast, dinner D: 18 weeks GP2: Insulin aspart 70/30 (v) Start: 0.2 U/kg/day Mean: 0.5 U/kg/day T: Breakfast, dinner D: 18 weeks Pioglitazone (fix) Start: 30 mg Mean: 30 mg T: Breakfast D: 18 weeks	GP1 F-B: 2.2 GP2 F-B: 4 GP1-GP2: -2* Experienced weight gain GP1 3* (3) p: <0.05 overall GP2 7* (8)		GP1 2 (2*) GP2 0 (0*)	GP1 3 (3*) GP2 1 (1*)	Cellulitis GP1 1 (1*) GP2 0 (0*) Peripheral edema GP1 0* (0) GP2 6* (6)
Insulin lispro 75/25 vs. long-acting insulin analogues						
Cox, 2007[68]	GP1: Insulin lispro 75/25 (v) T: Breakfast, dinner D: 12 weeks metformin (unclear) T: NR D: 12 weeks GP2: Insulin glargine (v) T: Bedtime D: 12 weeks metformin (unclear) T: NR D: 12 weeks				GP1 0 (0*) GP2 0 (0*)	

Evidence Table 6. Comparative effectiveness of premixed insulin analogues and other diabetes treatments on adverse events (continued)

Author, year	Intervention	Weight in kg, mean (SD)	Injection Site Reaction, n (%)	Total serious adverse events, n (%)	Withdrawn due to adverse events, n (%)	Other serious adverse events, n (%)
Jacober, 2006[58]	GP1: Insulin lispro 75/25 (v) Mean: 0.353 IU/kg; 36.73 IU T: Breakfast, lunch D: 4 months Insulin lispro 75/25 (v) T: Dinner D: 4 months existing ODM (unclear) T: NR D: 4 months GP2: Insulin glargine (v) Mean: 0.276 IU/kg; 27.98 IU T: Bedtime D: 4 months existing ODM (unclear) T: NR D: 4 months	GP1 B: 98* F: 99.7 (18.6) p: 0.9106 F-B: 1.98 (0.44) p: <0.0001 vs. baseline GP2 B: 97* F: 99 (19.1) F-B: 1.52 (0.46) p: 0.0015 vs. baseline GP1-GP2: 0* p: 0.457 vs. GP2			GP1 0 (0*) GP2 0 (0*)	
Malone, 2004[59]	GP1: Insulin lispro 75/25 (v) Mean: 0.62 U/kg T: Breakfast, dinner D: 16 weeks Metformin (unclear) Mean: 1945 mg Range: 1500 - 2550 mg T: NR D: 16 weeks GP2: Insulin glargine (v) Mean: 0.57 U/kg T: Bedtime D: 16 weeks Metformin (unclear) Mean: 1997 mg Range: 1500 - 2550 mg T: NR D: 16 weeks	GP1 B: 91* F: 93 (18.8) p: 0.006 F-B: 2.3 (4) p: 0.006 GP2 B: 91* F: 93.1 (19.3) F-B: 1.6 (4) GP1-GP2: 0*			GP1 0 (0*) GP2 1 (1*)	Required hospitalization GP1 4 (4*) GP2 1 (1*)

Evidence Table 6. Comparative effectiveness of premixed insulin analogues and other diabetes treatments on adverse events (continued)

Author, year	Intervention	Weight in kg, mean (SD)	Injection Site Reaction, n (%)	Total serious adverse events, n (%)	Withdrawn due to adverse events, n (%)	Other serious adverse events, n (%)
Malone, 2005[60]	GP1: Insulin lispro 75/25 (v) Mean: 0.42 U/kg T: Breakfast, dinner D: 16 weeks Metformin (fix) Mean: 2128 mg Range: 1500 - 2550 mg T: NR D: 16 weeks GP2: Insulin glargine (v) Mean: 0.36 U/kg T: Bedtime D: 16 weeks Metformin (fix) Mean: 2146 mg Range: 1500 - 2550 mg T: NR D: 16 weeks	GP1 B: 77* F: 78.31 (15.13) p: 0.001 F-B: 0.82 (2.56) p: 0.001 vs. GP2 GP2 B: 77* F: 77.05 (14.38) F-B: 0.06 (2.49) GP1-GP2: 1*			GP1 1 (1*) GP2 0 (0*)	GP1 3 GP2 3

Evidence Table 6. Comparative effectiveness of premixed insulin analogues and other diabetes treatments on adverse events (continued)

Author, year	Intervention	Weight in kg, mean (SD)	Injection Site Reaction, n (%)	Total serious adverse events, n (%)	Withdrawn due to adverse events, n (%)	Other serious adverse events, n (%)
Roach, 2006[57]	GP1: Insulin lispro 75/25 (v) Mean: 23 U (morning) and 37 U (evening) Range: 0 - 72 U (morning); 11 - 88 U (evening) T: Breakfast, dinner D: 12 weeks ODM (NR) Start: current dose T: NR D: 12 weeks Metformin (v) Start: 500 mg qd T: NR D: 12 weeks GP2: Insulin glargine (v) Mean: 44 U Range: 14 U - 100 U T: Breakfast D: 12 weeks ODM (NR) Start: current dose T: NR D: 12 weeks Metformin (v) Start: 500 mg qd T: NR D: 12 weeks	GP1 F: 103.9 (17.8) p: 0.068 GP2 F: 102.5 (17.9)			GP1 1 (3*) GP2 0 (0*)	

Evidence Table 6. Comparative effectiveness of premixed insulin analogues and other diabetes treatments on adverse events (continued)

Author, year	Intervention	Weight in kg, mean (SD)	Injection Site Reaction, n (%)	Total serious adverse events, n (%)	Withdrawn due to adverse events, n (%)	Other serious adverse events, n (%)
Insulin lispro 75/25 vs. premixed human insulins						
Coscelli, 2003[61]	GP1: Insulin lispro 75/25 (v) Mean: 38.1 Range: 12 - 72 T: Breakfast, dinner D: 12 days diet/exercise D: 12 days GP2: NPH/regular 70/30 (v) Mean: 37.3 Range: 10 - 72 T: Breakfast, dinner D: 12 days diet/exercise D: 12 days	GP1 B: 79 (13.1) F: 79.4 (12.9) p: NS vs. baseline F-B: 0* GP2 B: 80.2 (11.8) F: 80.4 (12.8) p: NS vs. baseline F-B: 0* GP1-GP2: 0*			GP1 0 (0*) GP2 0 (0*)	GP1 1 GP2 2
Hermansen, 2002[55]	GP1: Insulin lispro 75/25 (fix) Start: 0.4 units/kg body weight T: Breakfast D: 1 day GP2: NPH/regular 70/30 (fix) Start: 0.4 units/kg body weight T: Breakfast D: 1 day				GP1 0 (0*) GP2 0 (0*)	GP1 number of events: 0 GP2 number of events: 0
Herz, 2002[65]	GP1: Insulin lispro 75/25 (v) Mean: 26.1 U T: Breakfast, dinner D: 4 weeks GP2: NPH/regular 70/30 (v) Mean: 26.2 U T: Breakfast, dinner D: 4 weeks				GP1 0 (0*) GP2 0 (0*)	

Evidence Table 6. Comparative effectiveness of premixed insulin analogues and other diabetes treatments on adverse events (continued)

Author, year	Intervention	Weight in kg, mean (SD)	Injection Site Reaction, n (%)	Total serious adverse events, n (%)	Withdrawn due to adverse events, n (%)	Other serious adverse events, n (%)
Herz, 2003[13]	GP1: Insulin lispro 75/25 (v) Mean: Mean: 31.6¶ (morning) and 26.8¶ units (evening) and 32.4§ (morning) and 27.6§ units (evening) T: Breakfast, dinner D: 4 weeks GP2: NPH/regular 70/30 (v) Mean: 32.3¶ (morning) and 26.4¶ units (evening) and 33.3§ (morning) and 27.5§ units (evening) T: Breakfast, dinner D: 4 weeks				GP1 0 (0*) GP2 0 (0*)	
Malone, 2000[41]	GP1: Insulin lispro 75/25 (fix) Mean: 35.4 U (0.43U/kg) T: Breakfast D: 2 days GP2: NPH/regular 70/30 (fix) Mean: 35.4 U (0.43U/kg) T: Breakfast D: 2 days				GP1 0 (0*) GP2 0 (0*)	
Mattoo, 2003[64]	GP1: Insulin lispro 75/25 (unclear) Mean: 20U (morning), 32U (evening) T: Breakfast, dinner D: 2 weeks GP2: NPH/regular 70/30 (unclear) Mean: 20U (morning), 32U (evening) T: Breakfast, dinner D: 2 weeks	GP1 p: NS vs. baseline for all patients			GP1 0 (0*) GP2 0 (0*)	

Evidence Table 6. Comparative effectiveness of premixed insulin analogues and other diabetes treatments on adverse events (continued)

Author, year	Intervention	Weight in kg, mean (SD)	Injection Site Reaction, n (%)	Total serious adverse events, n (%)	Withdrawn due to adverse events, n (%)	Other serious adverse events, n (%)
Roach, 1999[67]	GP1: Insulin lispro 75/25 (v) Mean: 0.37 (morning) and 0.28 (evening) T: Breakfast, dinner D: 13 weeks GP2: NPH/regular 70/30 (v) Mean: 0.36 (morning) and 0.27 (evening) T: Breakfast, dinner D: 13 weeks	GP1 p: NS vs. GP2			GP1 0 (0*) GP2 0 (0*)	
Schwartz, 2006[56]	GP1: Insulin lispro 75/25 (fix) Start: 2/3 of usual daily dose Mean: 44.1 U T: Breakfast D: 1 days GP2: NPH/regular 70/30 (fix) Start: 2/3 of usual daily dose Mean: 44.1 U T: Breakfast D: 1 days		GP1 1 (5*) GP2 0 (0*)	GP1 0 (0*) GP2 0 (0*)	GP1 0 (0*) GP2 0 (0*)	
Insulin lispro 75/25 vs. oral antidiabetic agents						
Herz, 2002[66]	GP1: Insulin lispro 75/25 (v) Start: 0.3-0.5 U/kg Mean: 0.46 U/kg T: Breakfast, dinner D: 16 weeks GP2: Glyburide (fix) Start: 15 mg/day T: Breakfast, dinner D: 16 weeks	GP1 B: 78.65 (SE 1.36) p: 0.519 vs GP2 F: 79.7 (SE 1.47) p: 0.151 vs GP2 F-B: 1.02 (SE 0.35) p: <0.001 vs GP2 GP2 B: 77.34 (SE 1.53) F: 76.61 (SE 1.55) F-B: -0.85 (SE 0.18) GP1-GP2: 2*		GP1 2 (3*) GP2 1 (1*)	Liver carcinoma GP1 1 (1*) GP2 0 (0*)

Evidence Table 6. Comparative effectiveness of premixed insulin analogues and other diabetes treatments on adverse events (continued)

Author, year	Intervention	Weight in kg, mean (SD)	Injection Site Reaction, n (%)	Total serious adverse events, n (%)	Withdrawn due to adverse events, n (%)	Other serious adverse events, n (%)
Malone, 2003[62]	GP1: Insulin lispro 75/25 (v) Mean: 0.19 U/kg (morning) and 0.14 U/kg (evening) T: Breakfast, dinner D: 16 weeks Metformin (v) Mean: 1813 mg/day Range: 1500 – 2550 mg/day T: 2 to 3 times/day D: 16 weeks GP2: Metformin (v) Mean: 1968 mg/day Range: 1500 - 2550 mg/day T: 2 to 3 times/day D: 16 weeks Glibenclamide (v) Mean: 14.2 mg/day T: NR D: 16 weeks	GP1 B: 83 (15.2) F: 84 (15.1) F-B: 1* GP2 B: 81.7 (15.7) F: 82.2 (15.4) F-B: 0* GP1-GP2: 1* p: 0.33			GP1 1 (0*) GP2 2 (1*)	Treatment-emergent adverse events GP1 number of events: 7 GP2 number of events: 5
Tirgoviste, 2003[40]	GP1: Insulin lispro 75/25 (v) Start: 0.3 - 0.5 U/kg T: Breakfast, dinner D: 16 weeks GP2: glibenclamide (v) Start: 15 mg T: Breakfast, dinner D: 16 weeks	GP1 F-B: 1.32 (2.4) p: <0.001 GP2 F-B: -0.7 (2.6) GP1-GP2: 2*				

Evidence Table 6. Comparative effectiveness of premixed insulin analogues and other diabetes treatments on adverse events (continued)

Author, year	Intervention	Weight in kg, mean (SD)	Injection Site Reaction, n (%)	Total serious adverse events, n (%)	Withdrawn due to adverse events, n (%)	Other serious adverse events, n (%)
Insulin lispro 75/25 vs. insulin lispro 50/50						
Schwartz, 2006[56]	GP1: Insulin lispro 75/25 (fix) Start: 2/3 of usual daily dose Mean: 44.1 U T: Breakfast D: 1 day GP2: Insulin lispro 50/50 (fix) Start: 2/3 of usual daily dose Mean: 43.8 U T: Breakfast D: 1 day		GP1 1 (5*) GP2 1 (4*)	NR GP1 0 (0*) GP2 0 (0*)	GP1 0 (0*) GP2 0 (0*)	
Insulin lispro 50/50 vs. long-acting insulin analogues						
Kazda, 2006[69]	GP1: Insulin lispro 50/50 (v) Start: 0.30 IU/kg/day--mean Mean: 0.59 IU/kg/day T: Breakfast, lunch, dinner D: 24 weeks GP2: Insulin glargine (v) Start: 0.16 IU/kg/day--mean Mean: 0.43 IU/kg/day T: Bedtime D: 24 weeks	GP1 F-B: 1.8 (3.4) GP2 F-B: 0.7 (3.8) GP1-GP2: 1* BMI (in kg/m2) GP1 F-B: 0.6 (1.1) p: 0.19 vs GP2 GP2 F-B: 0.2 (1.3) GP1-GP2: 1*			GP1 0 (0*) GP2 0 (0*)	
Insulin lispro 50/50 vs. rapid-acting insulin analogues						
Kazda, 2006[69]	GP1: Insulin lispro 50/50 (v) Start: 0.30 IU/kg/day--mean Mean: 0.59 IU/kg/day T: Breakfast, lunch, dinner D: 24 weeks GP2: Insulin lispro (v) Start: 0.25 IU/kg/day-mean Mean: 0.50 IU/kg/day T: Breakfast, lunch, dinner D: 24 weeks	GP1 F-B: 1.8 (3.4) GP2 F-B: 2.3 (4.3) GP1-GP2: 0* BMI (in kg/m2) GP1 F-B: 0.6 (1.1) GP2 F-B: 0.9 (1.5) GP1-GP2: 0*			GP1 0 (0*) GP2 0 (0*)	

Evidence Table 6. Comparative effectiveness of premixed insulin analogues and other diabetes treatments on adverse events (continued)

Author, year	Intervention	Weight in kg, mean (SD)	Injection Site Reaction, n (%)	Total serious adverse events, n (%)	Withdrawn due to adverse events, n (%)	Other serious adverse events, n (%)
Insulin lispro 50/50 vs. premixed human insulins						
Roach, 1999[11]	GP1: Insulin lispro 50/50 (v) Mean: 0.31 U/kg T: Breakfast D: 3 months Insulin lispro 75/25 (v) Mean: 0.26 U/kg T: Dinner D: 3 months GP2: NPH/regular 50/50 (v) Mean: 0.32 U/kg T: Breakfast D: 3 months NPH/regular 70/30 (v) Mean: 0.26 U/kg T: Dinner D: 3 months	GP1 p: NS vs. GP2			GP1 0 (0*) GP2 0 (0*)	
Schern-thaner, 2004[70]	GP1: Insulin lispro 50/50 (v) Mean: 64.6 IU T: Breakfast, lunch, dinner D: 12 weeks diet/exercise D: 12 weeks GP2: NPH/regular 70/30 (v) Mean: 61.8 IU T: Breakfast, dinner D: 12 weeks diet/exercise D: 12 weeks				GP1 0 (0*) GP2 0 (0*)	GP1 0 (0*) GP2 5 (12*)

Evidence Table 6. Comparative effectiveness of premixed insulin analogues and other diabetes treatments on adverse events (continued)

Author, year	Intervention	Weight in kg, mean (SD)	Injection Site Reaction, n (%)	Total serious adverse events, n (%)	Withdrawn due to adverse events, n (%)	Other serious adverse events, n (%)
Schwartz, 2006[56]	GP1: Insulin lispro 50/50 (fix) Start: 2/3 of usual daily dose Mean: 43.8 U T: Breakfast D: 1 day GP2: NPH/regular 70/30 (fix) Start: 2/3 of usual daily dose Mean: 44.1 U T: Breakfast D: 1 day		GP1 1 (4*) GP2 0 (0*)	NR GP1 0 (0*) GP2 0 (0*)	GP1 0 (0*) GP2 0 (0*)	
Yamada, 2007[71]	GP1: Insulin lispro 50/50 (v) Start: current dose Mean: 0.37 (start), 0.38 U/kg (end) T: twice daily D: 4 months GP2: NPH/regular 70/30 (v) Start: current dose Mean: 0.34 (start), 0.37 U/kg (end) T: twice daily D: 4 months NPH/regular 50/50 (v) Start: current dose Mean: 0.34 U/kg (start) and 0.37 U/kg (end) T: twice daily D: 4 months	BMI (in kg/m2) GP1 B: 27 (5.8) F: 27.3 (5.9) F-B: 0* p: NS vs. baseline GP2 B: 23.8 (3.4) F: 23.6 (3.6) F-B: 0* p: NS vs. baseline GP1-GP2: 0* p: NS vs. baseline			GP1 0 (0*) GP2 0 (0*)	

* Number has been imputed.

‡ One-hundred and four (36%) of the 291 participants of this trial are patients with type 1 diabetes. The remaining population has type 2 diabetes and is the same study population as Boehm 2004.[42] Only data for the Boehm 2004 study is presented because it has the longest followup.

‖ Among those who were not using thiazolidinediones.

¶ Dosing during the outpatient phase.

§ Dosing during the inpatient phase.

µg = microgram; B = baseline; bid = twice daily; BMI = body mass index; Cl = confidence interval; D = duration; F = final; F-B = mean difference from baseline; GP = group; GP1-GP2 = mean difference between the difference from baseline; IU = international unit; kg = kilogram; kg/m2 = kilogram per square meter; mg = milligram; ml = milliliter; NA = not applicable; NPH = neutral protamine Hagedorn; NR = not reported; NS = not significant; ODM = oral diabetes medicine; p = p-value; qd = once daily; SD = standard deviation; SE = standard error; T = time of day when insulin taken; U = unit; v = dosing varied

Evidence Table 7. Quality of studies comparing a premixed insulin analogue to other diabetes treatments

Author, year	Clear quest	Rand# / Rand app#	Comp gp* / Exp asc* / Out not present*	Blind	Out assess	FU long enough	Lost to FU / Desc of WD	Conc	Fund / COI	Overall quality†
Abrahamian, 2005[50]	Yes	Yes / NR	NA	No	Indep blind	Yes	< 10% / No	Partially	Pharmaceutical / Yes	Fair
Bebakar, 2007[43]	Yes	Yes / NR	NA	No	Indep blind	Yes	< 10% / Yes	Yes	Pharmaceutical / NR	Good
Boehm, 2004[42] Boehm, 2002[10]	Yes	Yes / Yes	NA	Outcome assessors	Indep blind, self report	Yes	< 10% / Yes	Yes	Pharmaceutical / Yes	Good
Christiansen, 2003[14]	No	Yes / NR	NA	Patients, providers	Indep blind	Yes	< 10% / Yes	Partially	Pharmaceutical / Yes	Fair
Coscelli, 2003[61]	Yes	Yes / NR	NA	No	Indep blind	Yes	NR / No	Yes	Pharmaceutical / NR	Fair
Cox, 2007[68]	Yes	Yes / NR	NA	No	Indep blind, self report	Yes	> 10% / No	Yes	Pharmaceutical / NR	Fair
Hermansen, 2002[55]	Yes	Yes / Yes	NA	No	Indep blind	No	< 10% / Yes	Yes	Pharmaceutical / NR	Fair
Herz, 2002[65]	Yes	Yes / NR	NA	No	Indep blind	Yes	< 10% / Yes	Yes	NR / NR	Fair
Herz, 2002[66]	Yes	Yes / NR	NA	No	Indep blind, self report	Yes	< 10% / Yes	Partially	Pharmaceutical / Yes	Poor
Herz, 2003[13]	Yes	Yes / NR	NA	No	Indep blind	Yes	> 10% / No	Yes	Pharmaceutical / NR	Fair
Holman, 2007[28]	Yes	Yes / Yes	NA	Outcome assessors	Indep blind, self report	Yes	< 10% / Yes	Yes	Pharmaceutical / Yes	Good
Jacober, 2006[58]	Yes	Yes / NR	NA	No	Indep blind, self report	Yes	> 10% / Yes	Partially	Pharmaceutical / NR	Fair
Joshi, 2005[49]	No	NA	drawn from same community / other / NA	No	Indep blind	Yes	Complete FU / Yes	Partially	Pharmaceutical / Yes	Poor
Kann, 2006[47]	Yes	Yes / Yes	NA	No	Indep blind	Yes	< 10% / Yes	Yes	Pharmaceutical / Yes	Good
Kapitza, 2004[53]	Yes	Yes / NR	NA	No	Indep blind	No	Complete FU / No	Yes	Pharmaceutical / NR	Fair
Kazda, 2006[69]	Yes	Yes / NR	NA	No	Indep blind, self report	Yes	< 10% / Yes	Yes	Pharmaceutical / Yes	Good
Kilo, 2003[16]	Yes	Yes / NR	NA	No	Indep blind, self report	Yes	< 10% / Yes	Yes	Pharmaceutical / NR	Good
Kvapil, 2006[48]	Yes	Yes / Yes	NA	No	Indep blind	Yes	< 10% / Yes	Yes	Pharmaceutical / NR	Good
Ligthelm, 2006[82]	Yes	Yes / Yes	NA	No	Indep blind, self report	Yes	< 10% / Yes	Yes	Pharmaceutical / NR	Good

Evidence Table 7. Quality of studies comparing a premixed insulin analogue to other diabetes treatments (continued)

Author, year	Clear quest	Rand# / Rand app#	Comp gp* / Exp asc* / Out not present*	Blind	Out assess	FU long enough	Lost to FU / Desc of WD	Conc	Fund / COI	Overall quality†
Malone, 2000[41] Malone, 2000[15]	Yes	Yes / NR	NA	Patients, providers	Indep blind	No	< 10% / Yes	Yes	NR / NR	Fair
Malone, 2003[62]	Yes	Yes / NR	NA	No	Indep blind, self report	Yes	Complete FU / Yes	Yes	Pharmaceutical / NR	Good
Malone, 2004[59]	Yes	Yes / Yes	NA	No	Indep blind, self report	Yes	< 10% / Yes	Yes	NR / NR	Poor
Malone, 2005[60]	Yes	Yes / NR	NA	No	Indep blind, self report	Yes	< 10% / Yes	Yes	NR / Yes	Fair
Mattoo, 2003[64]	Yes	Yes / NR	NA	No	Indep blind, self report	Yes	< 10% / No	Yes	Pharmaceutical / NR	Fair
McNally, 2007[45]	Yes	Yes / Yes	NA	Patients, providers	Indep blind, self report	Yes	< 10% / Yes	Yes	NR / Yes	Good
McSorley, 2002[12]	Yes	Yes / NR	NA	Patients, providers	Indep blind	Yes	NR/ No	Yes	Pharmaceutical / NR	Fair
Nauck, 2007[46]	Yes	Yes / Yes	NA	No	Indep blind	Yes	< 10% / Yes	Yes	Pharmaceutical / Yes	Good
Niskanen, 2004[52]	Yes	Yes / Yes	NA	No	Indep blind, self report	Yes	< 10% / Yes	Yes	Pharmaceutical / NR	Good
Raskin, 2005[36] Raskin, 2007[37] Brod, 2007[38]	Yes	Yes / Yes	NA	No	Indep blind	Yes	< 10% / Yes	Yes	Pharmaceutical / Yes	Good
Raz, 2003[54]	Yes	Yes / Yes	NA	No	Indep blind, medical record review, self report	No	< 10% / Yes	Yes	Pharmaceutical / NR	Fair
Raz, 2005[51]	Yes	Yes / NR	NA	No	Indep blind	Yes	> 10% / Yes	Yes	Pharmaceutical / Yes	Fair
Roach, 1999[67]	Yes	Yes / NR	NA	No	Indep blind, self report	Yes	< 10% / Yes	Yes	Pharmaceutical / Yes	Fair
Roach, 1999[11]	Yes	Yes / NR	NA	No	Indep blind	Yes	Complete FU / Yes	Yes	Pharmaceutical / NR	Fair
Roach, 2003[63]	Yes	Yes / NR	NA	Patients, providers	Indep blind	No	< 10% / Yes	Yes	Pharmaceutical / NR	Good
Roach, 2006[57]	Yes	Yes / NR	NA	No	Indep blind	Yes	> 10% / Yes	Yes	Pharmaceutical / Yes	Fair
Schernthaner, 2004[70]	Yes	Yes / NR	NA	No	Indep blind	Yes	< 10% / Yes	Yes	Pharmaceutical / NR	Fair
Schwartz, 2006[56]	Yes	Yes / NR	NA	Patients, providers	Indep blind	No	< 10% / Yes	Yes	Pharmaceutical / Yes	Fair

Evidence Table 7. Quality of studies comparing a premixed insulin analogue to other diabetes treatments (continued)

Author, year	Clear quest	Rand# / Rand app#	Comp gp* / Exp asc* / Out not present*	Blind	Out assess	FU long enough	Lost to FU / Desc of WD	Conc	Fund / COI	Overall quality†
Tamemoto, 2007[44]	Yes	Yes / No	NA	No	No description	Yes	< 10% / Yes	Yes	NR / NR	Poor
Tirgoviste, 2003[40] Roach, 2001[39]	Yes	Yes / Yes	NA	No	Indep blind, self report	Yes	Complete FU / Yes	Yes	NR / NR	Good
Yamada, 2007[71]	Yes	Yes / Yes	NA	No	Indep blind	Yes	NR / No	Partially	NR / NR	Fair

Questions only rated for trials.

* Questions only rated for non-randomized studies.

† Overall quality ratings were good, fair, or poor, which were defined 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 it is not sufficient 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.

Blind = blinding; Clear quest = clearly stated study questions or objectives; COI = conflict of interest; Comp gp = selection of comparison group; Conc = conclusions reflective of results; Desc of WD = description of withdrawals; Exp asc = ascertainment of exposure; FU = followup; Fund = funding source; Indep blind = independent blind assessment; NA = not applicable; NR = not reported; Out assess = outcome assessment; Out not present = demonstration that outcome was not present at study start; Rand = randomized; Rand app = randomization scheme appropriate

Evidence Table 8. Applicability of studies comparing a premixed insulin analogue to other diabetes treatments

Author, year	Pop source/ % enrolled / Run-in periods excluding >10%	Demographically representative	Illness severity representative	Dose, schedule, or route of administration reflective of current practice	Interventions or monitoring reflective of current practice	Comparison best alternative / Adequate dose, interval, schedule	Clinical outcomes measured / adverse events reported	Standards of care different from US
Abrahamian, 2005[50]	NR / ≥50% / No	Sex: Yes Age: Yes Race/ethnicity: No: assumed mostly Caucasian	Yes	Yes for only 2 of the 3	No: monitoring of blood glucose occurred 7 times/day	Yes / Yes	No / No	No
Bebakar, 2007[43]	NR / ≥50% / Yes	Sex: No: Western Pacific Age: NR Race/ethnicity: No: Western Pacific countries	No: insulin naive	Yes for all 3	Yes	Yes / NR	Yes / No	Yes
Boehm, 2004[42] Boehm, 2002[10]	NR / ≥50% / No	Sex: Yes Age: Yes Race/ethnicity: NR	Yes	Yes for all 3	Yes	Yes / Yes	Yes / Yes	No
Christiansen, 2003[14]	NR / NR / No	Sex: Yes Age: Yes Race/ethnicity: No: different from US racial and ethic make-up	Yes	Yes for all 3	No: monitoring too frequent	Yes / Yes	No / Yes	Yes
Coscelli, 2003[61]	Subspecialty clinics / NR / No	Sex: Yes Age: Yes Race/ethnicity: No: 100% Caucasian	No: excluded patients with diabetic complications; must have been taking insulin; average duration of diabetes was 14 years	Yes for all 3	Yes	Yes / Yes	No / Yes	No
Cox, 2007[68]	NR / ≥50% / NA	Sex: NR Age: Yes Race/ethnicity: No:	No: no early diabetics	Yes for all 3	NA	Yes / Yes	No / Adverse outcomes not reported	No

Evidence Table 8. Applicability of studies comparing a premixed insulin analogue to other diabetes treatments (continued)

Author, year	Pop source/ % enrolled / Run-in periods excluding >10%	Demographically representative	Illness severity representative	Dose, schedule, or route of administration reflective of current practice	Interventions or monitoring reflective of current practice	Comparison best alternative / Adequate dose, interval, schedule	Clinical outcomes measured / adverse events reported	Standards of care different from US
Hermansen, 2002[55]	NR / ≥50% / NA	Sex: Yes Age: Yes Race/ethnicity: NR	No: subjects needed to have been on insulin and insulin dose < 1.4 U/kg, excluded those with diabetes complications	Yes for all 3	No: patients were given a single dose of insulin and a standard meal and then monitored for 5 hours afterwards	Yes / Yes	No / Yes	No
Herz, 2002[65]	NR / NR / No	Sex: Yes Age: Yes Race/ethnicity: NR	No: all participants were currently taking insulin	Yes for all 3	No: patients were hospitalized for a few days while they performed an exercise test	Yes / Yes	No / Yes	No
Herz, 2002[66]	Subspecialty clinics / ≥50% / No	Sex: Yes Age: No: subjects 60 to 80 years old Race/ethnicity: NR	No: excluded those with new diagnosis of type 2 diabetes	Yes for all 3	Yes	No: compared to glyburide when patients were already on maximum dose of glyburide / Yes	No / No	No
Herz, 2003[13]	NR / NR / No	Sex: Yes Age: Yes Race/ethnicity: NR	No: all respondents have been taking insulins, none were currently taking an OAM	Yes for all 3	No: investigators telephoned patients at least once weekly	Yes / Yes	No / Yes	No
Holman, 2007[28]	Clinical centers / ≥50% / NA	Sex: Yes Age: Yes Race/ethnicity: No: over 90% Caucasian	No: patients were insulin naive	Yes for all 3	Yes	Yes / Yes	No / Yes	No

Evidence Table 8. Applicability of studies comparing a premixed insulin analogue to other diabetes treatments (continued)

Author, year	Pop source/ % enrolled / Run-in periods excluding >10%	Demographically representative	Illness severity representative	Dose, schedule, or route of administration reflective of current practice	Interventions or monitoring reflective of current practice	Comparison best alternative / Adequate dose, interval, schedule	Clinical outcomes measured / adverse events reported	Standards of care different from US
Jacober, 2006[58]	NR / ≥50% / NA	Sex: Yes Age: Yes Race/ethnicity: No: study contained more Caucasians and fewer African Americans and Mexican Americans	No: study likely excluded newly diagnosed and those with comorbidities	Yes for all 3	Yes	Yes / Yes	No / Yes	No
Joshi, 2005[49]	Outpatient clinics, subspecialty clinics / ≥50% / NA	Sex: No: 67 to 77% male per group Age: Yes Race/ethnicity: No: all from India	Yes	Yes for all 3	Yes	Yes / Yes	No / Yes	No
Kann, 2006[47]	NR / NR / No	Sex: Yes Age: NR Race/ethnicity: NR	No: Male and female insulin-naive patients	Yes for all 3	Yes	Yes / Yes	Yes / Yes	Yes
Kapitza, 2004[53]	NR / NR / NA	Sex: Yes Age: Yes Race/ethnicity: NR	No: participants had to have been on insulin for at least 6 months	Yes for only 1 of the 3	NA	Yes / Yes	No / Adverse outcomes not reported	No
Kazda, 2006[69]	NR / ≥50% / No	Sex: Yes Age: Yes Race/ethnicity: No: assumed mostly Caucasian	No: included those who have a longer duration of diabetes	Yes for all 3	Yes	No: would usually add glargine to OAM as opposed to give it alone / Yes	No / Yes	No
Kilo, 2003[16]	NR / ≥50% / No	Sex: Yes Age: Yes Race/ethnicity: Yes	Yes	Yes for all 3	No: 8-point glucose profile measurement is not used in clinical practice	Yes / Yes	No / Yes	No
Kvapil, 2006[48]	NR / ≥50% / No	Sex: Yes Age: Yes Race/ethnicity: No: assumed mostly Caucasian	No: treatment naive patients not included	Yes for all 3	Yes	Yes / Yes	No / Yes	No

Evidence Table 8. Applicability of studies comparing a premixed insulin analogue to other diabetes treatments (continued)

Author, year	Pop source/ % enrolled / Run-in periods excluding >10%	Demographically representative	Illness severity representative	Dose, schedule, or route of administration reflective of current practice	Interventions or monitoring reflective of current practice	Comparison best alternative / Adequate dose, interval, schedule	Clinical outcomes measured / adverse events reported	Standards of care different from US
Ligthelm, 2006[82]	NR / ≥50% / No	Sex: Yes Age: Yes Race/ethnicity: No: predominantly Caucasian with an Asian minority	No: only patients who previously used insulin	Yes for all 3	No: interventions and monitoring likely too frequent	No: better alternatives are available / Yes	No / Yes	No
Malone, 2000[41] Malone, 2000[15]	NR / NR / No	Sex: Yes Age: Yes Race/ethnicity: NR	No: all patients needed to be on insulin	Yes for all 3	No: patients were monitored in house and had frequent blood glucose measurements	Yes / Yes	No / Yes	No
Malone, 2003[62]	NR / ≥50% / No	Sex: Yes Age: NR Race/ethnicity: No: 90% Caucasian, 2% African American, 7% Hispanic	No:	Yes for all 3	No: there was intense titration of dosing and patients visits every 4 weeks for 16 weeks	Yes / Yes	No / Yes	No
Malone, 2004[59]	NR / ≥50% / No	Sex: Yes Age: Yes Race/ethnicity: NR	No: patients were insulin naive and had to be poorly controlled on an OAM for at least 30 days	Yes for all 3	Yes	Yes / Yes	No / Yes	No
Malone, 2005[60]	NR / NR / Yes	Sex: Yes Age: Yes Race/ethnicity: NR	No: all had previously taken insulin	Yes for all 3	Yes	Yes / Yes	No / Yes	No
Mattoo, 2003[64]	NR / NR / No	Sex: Yes Age: Yes Race/ethnicity: NR	No: participants had to be taking insulin for at least 6 months	Yes for only 1 of the 3	Yes	Yes / Yes	No / Yes	No

Evidence Table 8. Applicability of studies comparing a premixed insulin analogue to other diabetes treatments (continued)

Author, year	Pop source/ % enrolled / Run-in periods excluding >10%	Demographically representative	Illness severity representative	Dose, schedule, or route of administration reflective of current practice	Interventions or monitoring reflective of current practice	Comparison best alternative / Adequate dose, interval, schedule	Clinical outcomes measured / adverse events reported	Standards of care different from US
McNally, 2007[45]	NR / ≥50% / No	Sex: Yes Age: No: Mean age of population is 62 with a standard deviation of 9 years. Study is unlikely capturing the younger (<44 years) diabetic population Race/ethnicity: NR	No: All respondents have been pretreated on insulin for at least 6 months	Yes for all 3	Yes	Yes / Yes	No / No	No
McSorley, 2002[12]	NR / NR / No	Sex: Yes Age: Yes Race/ethnicity: NR	No: participants had to be diagnosed with diabetes for at least 1 year	Yes for all 3	No: there was a sampling period where standard meals were provided for the participants	Yes / Yes	No / Yes	No
Nauck, 2007[46]	Outpatient clinics / ≥50% / No	Sex: Yes Age: Yes Race/ethnicity: NR	No: suboptimal blood sugar control	Yes for all 3	Yes	No: comparator is a new drug that is not being used often / Yes	Yes / Yes	Yes
Niskanen, 2004[52]	NR / ≥50% / No	Sex: Yes Age: Yes Race/ethnicity: NR	No: included only patients who had been receiving insulin	Yes for all 3	Yes	Yes / Yes	No / Yes	No
Raskin, 2005[36] Raskin, 2007[37] Brod, 2007[38]	NR / NR / Yes	Sex: Yes Age: NR Race/ethnicity: Yes	No: insulin naive patients	Yes for all 3	Yes	Yes / Yes	No / Yes	No

Evidence Table 8. Applicability of studies comparing a premixed insulin analogue to other diabetes treatments (continued)

Author, year	Pop source/ % enrolled / Run-in periods excluding >10%	Demographically representative	Illness severity representative	Dose, schedule, or route of administration reflective of current practice	Interventions or monitoring reflective of current practice	Comparison best alternative / Adequate dose, interval, schedule	Clinical outcomes measured / adverse events reported	Standards of care different from US
Raz, 2003[54]	Outpatient clinics / NR / No	Sex: No: this was done in Israel Age: Yes Race/ethnicity: No: 82% Caucasian	No: insulin naive patients	Yes for all 3	Yes	No / No: Insulin dose was adjusted while gliben-clamide and rosiglitazone doses were not adjusted	No / Yes	No
Raz, 2005[51]	NR / ≥50% / No	Sex: Yes Age: Yes Race/ethnicity: NR	No: excluded those with serious complications or disease	Yes for all 3	Yes	Yes / Yes	No / Yes	No
Roach, 1999[67]	NR / NR / No	Sex: Yes Age: Yes Race/ethnicity: NR	No: excluded those not taking insulin and those with diabetic complications	Yes for all 3	Yes	Yes / Yes	No / Yes	No
Roach, 1999[11]	NR / NR / No	Sex: Yes Age: Yes Race/ethnicity: NR	No: participants must have been on insulin and could not have had any diabetes complications	Yes for all 3	Yes	Yes / Yes	No / Yes	No
Roach, 2003[63]	NR / NR / No	Sex: Yes Age: Yes Race/ethnicity: No: population was 100% Western Asian (Indian)	No: all had to have been taking insulin; excluded respondents taking OAMs	Yes for all 3	Yes	Yes / Yes	No / Yes	Yes
Roach, 2006[57]	NR / NR / No	Sex: Yes Age: Yes Race/ethnicity: No: 80% Caucasian and 20% African American; no Hispanics were included	No: needed to be on an OAM or insulin for at least 3 months	Yes for all 3	Yes	Yes / Yes	No / Yes	No

Evidence Table 8. Applicability of studies comparing a premixed insulin analogue to other diabetes treatments (continued)

Author, year	Pop source/ % enrolled / Run-in periods excluding >10%	Demographically representative	Illness severity representative	Dose, schedule, or route of administration reflective of current practice	Interventions or monitoring reflective of current practice	Comparison best alternative / Adequate dose, interval, schedule	Clinical outcomes measured / adverse events reported	Standards of care different from US
Scherntha-ner, 2004[70]	NR / NR / No	Sex: No: there were fewer males (23%) enrolled in the study Age: No: Average age is 67 with standard deviation of 8.4 years. Unlikely capturing younger diabetics (e.g., <50 years of age) Race/ethnicity: NR	No: excluded respondents with severe diabetic complications; average time on insulin was over 5 years	Yes for all 3	Yes	Yes / Yes	No / Yes	No
Schwartz, 2006[56]	Subspecialty clinics / ≥50% / NA	Sex: No: 74% of the population was male Age: No: mean age of the population was 61 with a standard deviation of 10; study unlikely captured younger diabetics Race/ethnicity: No: The study population had fewer blacks and more Hispanics	No: only diabetics already on insulin were enrolled	No for all three	NA	Yes / Yes	No / No	Yes
Tamemoto, 2007[44]	Outpatient clinics / NR / No	Sex: Yes Age: No: this was done in Japan Race/ethnicity: No: assumed 100% Japanese	No: had diabetes for at least 1 year	Yes for all 3	Yes	Yes / Yes	No / Yes	No
Tirgoviste, 2003[40] Roach, 2001[39]	NR / NR / No	Sex: Yes Age: NR Race/ethnicity: NR	No: only patients needing 1 OAM	Yes for all 3	No: There were 5 visits in 12 weeks. Dose adjustments for insulin were made every 2-3 days.	No: OAM dose could not increase / No: could not increase the OAM dose	No / Yes	Yes

Evidence Table 8. Applicability of studies comparing a premixed insulin analogue to other diabetes treatments (continued)

Author, year	Pop source/ % enrolled / Run-in periods excluding >10%	Demographically representative	Illness severity representative	Dose, schedule, or route of administration reflective of current practice	Interventions or monitoring reflective of current practice	Comparison best alternative / Adequate dose, interval, schedule	Clinical outcomes measured / adverse events reported	Standards of care different from US
Yamada, 2007[71]	NR / NR / NA	Sex: No: mostly male Age: Yes Race/ethnicity: No: assumed mostly Japanese	No: excluded insulin naive patients and those with severe comorbidity	Yes for all 3	Yes	Yes / Yes	No / Yes	No

kg = kilogram; NA = not applicable; NR = not reported; OAM = oral antidiabetic medication; Pop source = population source; U = units; US = United States

Evidence Table 9. Comparative effectiveness of premixed insulin analogues and other diabetes treatments on clinical outcomes

Author, year	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Nephropathy, n (%)
Insulin aspart 70/30 vs. long-acting insulin analogues					
Holman, 2007[28]	GP1: Insulin aspart 70/30 (v) Start: 16 median Range: 10 - 26 T: bid D: 1 year Usual care D: 1 year GP2: Insulin detemir (v) Start: 16 median Range: 10 - 24 T: Bedtime, twice if required D: 1 years Usual care D: 1 year	GP1 3 (1*) GP2 0 (0*)	Myocardial infarction GP1 3 (1*) GP2 0 (0*)		Change in plasma creatinine GP1 F-B: 0.05 (0.09) p: 0.008 vs. GP2 GP2 F-B: 0.02 (0.11) GP1-GP2: 0* Median change in ratio of albumin to creatinine GP1 F-B: -0.9 Median (IQR: -8 – 9.7) p: overall 0.07 GP2 F-B: -1.8 Median (IQR: -10.6 – 2.7) GP1-GP2: 1*
Kann, 2006[47]	GP1: Insulin aspart 70/30 (v) Start: 0.1 U/kg bid Mean: 0.4 U/kg T: Breakfast, dinner D: 26 weeks metformin (v) Start: 500 mg bid or current dose T: Breakfast, dinner D: 26 weeks GP2: Insulin glargine (v) Start: 0.2U/kg qday Mean: 0.39U/kg T: preferred time D: 26 weeks glimepiride (v) Start: 1 mg daily or current dose T: Breakfast D: 26 weeks			Peripheral vascular disorder GP1 1 (0.8) GP2 0 (0) Cardiac failure GP1 0 (0) GP2 1 (0.8)	

Evidence Table 9. Comparative effectiveness of premixed insulin analogues and other diabetes treatments on clinical outcomes (continued)

Author, year	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Nephropathy, n (%)
Insulin aspart 70/30 vs. rapid-acting insulin analogues					
Holman, 2007[28]	GP1: Insulin aspart 70/30 (v) Start: 16 median Range: 10 - 26 T: bid D: 1 year Usual care D: 1 year GP2: Insulin aspart (v) Start: 18 median Range: 9 - 24 T: Breakfast, lunch, dinner D: 1 year Usual care D: 1 year	GP1 3 (1*) GP2 1 (0*)	Myocardial infarction GP1 3 (1*) GP2 1 (0*)		Change in plasma creatinine GP1 F-B: 0.05 (0.09) p: 0.62 vs. GP2 GP2 F-B: 0.05 (0.12) GP1-GP2: 0* Median change in ratio of albumin to creatinine GP1 F-B: -0.9 Median (IQR: -8 – 9.7) p: overall 0.07 GP2 F-B: -0.9 Median (IQR: -12.4 – 6.2) GP1-GP2: 0*
Insulin aspart 70/30 vs. premixed human insulins					
Boehm, 2004[42]	GP1: Insulin aspart 70/30 (v) Start: 0.57 U/kg T: Breakfast, dinner D: 24 months GP2: NPH/regular 70/30 (v) Start: 0.57 U/Kg T: Breakfast, dinner D: 24 months	GP1 3 (5*) GP2 1 (2*)	Cardiac failure GP1 1 (2*) GP2 0 (0*)	Cardiovascular adverse events GP1 15 (26) events: 19 GP2 17 (25) events: 19	
Hermansen, 2002[55]	GP1: Insulin aspart 70/30 (fix) Start: 0.4 units/kg T: Breakfast D: 1 day GP2: NPH/regular 70/30 (fix) Start: 0.4 units/kg T: Breakfast D: 1 day			Transient ischemic attack GP1 1 (2*) GP2 0 (0)	

Evidence Table 9. Comparative effectiveness of premixed insulin analogues and other diabetes treatments on clinical outcomes (continued)

Author, year	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Nephropathy, n (%)
Insulin aspart 70/30 vs. oral antidiabetic agents					
Kvapil, 2006[48]	GP1: Insulin aspart 70/30 (v) Start: 0.3 U/kg/day Mean: 0.51 U/kg/day T: Breakfast, dinner D: 16 weeks GP2: metformin (fix) Mean: 1660 mg daily Range: 500 - 3000 mg qd T: NR D: 16 weeks glibencamide (v) Start: 1.75 mg Mean: 2.33 (start) and 6.58 mg (end) T: once or twice daily D: 16 weeks	GP1 0 (0*) GP2 0 (0*)	Myocardial infarction GP1 0 (0*) GP2 0 (0*)		
Kvapil, 2006[48]	GP1: Insulin aspart 70/30 (v) Start: 0.2 U/kg/day Mean: 0.3 U/kg/day T: Breakfast, dinner D: 16 weeks metformin (fix) Mean: 1660 mg daily Range: 500 - 3000 mg qd T: NR D: 16 weeks GP2: metformin (fix) Mean: 1660 mg daily Range: 500 - 3000 mg qd T: NR D: 16 weeks glibencamide (v) Start: 1.75 mg Mean: 2.33 mg qd (start) and 6.58 mg (end) T: once or twice daily D: 16 weeks	GP1 1 (1*) GP2 0 (0*)	Myocardial infarction GP1 1 (1*) GP2 0 (0*)		

Evidence Table 9. Comparative effectiveness of premixed insulin analogues and other diabetes treatments on clinical outcomes (continued)

Author, year	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Nephropathy, n (%)
Raz, 2003[54]	GP1: Insulin aspart 70/30 (v) Start: 6 - 8 U bid T: Breakfast, dinner D: 6 weeks rosiglitazone (fix) Start: 4 mg T: Breakfast D: 6 weeks GP2: glibenclamide (fix) Range: 7.5 – 15 mg T: Dinner D: 6 weeks rosiglitazone (fix) Start: 4 mg T: Breakfast D: 6 weeks			Non-fatal myocardial infarction GP1 1 (4*) GP2 0 (0*)	
Raz, 2005[51]	GP1: Insulin aspart 70/30 (v) Start: 0.3 U/kg per day Mean: 0.7 U/kg/day T: Breakfast, dinner D: 18 weeks GP2: Glibenclamide (v) Start: 5 to 10 mg Mean: 14 mg T: Breakfast D: 18 weeks Pioglitazone (fix) Start: 30 mg Mean: 30 mg T: Breakfast D: 18 weeks			Non-fatal myocardial infarction GP1 1 (1*) GP2 0 (0*)	

Evidence Table 9. Comparative effectiveness of premixed insulin analogues and other diabetes treatments on clinical outcomes (continued)

Author, year	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Nephropathy, n (%)
Raz, 2005[51]	GP1: Insulin aspart 70/30 (v) Start: 0.2 U/kg per day Mean: 0.5 U/kg/day T: Breakfast, dinner D: 18 weeks Pioglitazone (fix) Start: 30 mg Mean: 30 mg T: Breakfast D: 18 weeks GP2: Glibenclamide (v) Start: 5 to 10 mg Mean: 14 mg T: Breakfast D: 18 weeks Pioglitazone (fix) Start: 30 mg Mean: 30 mg T: Breakfast D: 18 weeks			Non-fatal myocardial infarction GP1 0 (0*) GP2 0 (0*)	
Insulin aspart 70/30 vs. exenatide					
Nauck, 2007[46]	GP1: Insulin aspart 70/30 (v) Start: 15.7 U/day Mean: 24.4 U/day T: Breakfast, dinner D: 52 weeks 'optimally' effective metformin and sulfonylurea therapy (v) T: NR D: 52 weeks GP2: exenatide (v) Start: 5 µg bid Range: 5 - 10 µg bid T: Breakfast D: 52 weeks 'optimally' effective metformin and sulfonylurea therapy (v) T: NR D: 52 weeks	GP1 1 (0.4) GP2 2 (0.8)		Unspecified cardiac disorder adverse events GP1 5 (2*) GP2 10 (4*)	

Evidence Table 9. Comparative effectiveness of premixed insulin analogues and other diabetes treatments on clinical outcomes (continued)

Author, year	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Nephropathy, n (%)
Insulin aspart 70/30 vs. insulin lispro 75/25					
Hermansen, 2002[55]	GP1: Insulin aspart 70/30 (fix) Start: 0.4 units/kg T: Breakfast D: 1 day GP2: Insulin lispro 75/25 (fix) Start: 0.4 units/kg T: Breakfast D: 1 day			Transient ischemic attack GP1 1 (2*) GP2 0 (0)	
Niskanen, 2004[52]	GP1: Insulin aspart 70/30 (v) Mean: 0.65 U/kg to 0.67 U/kg T: Breakfast, dinner D: 12 weeks GP2: Insulin lispro 75/25 (v) Mean: 0.67 U/kg to 0.71 U/kg T: Breakfast, dinner D: 12 weeks	GP1 0 (0*) GP2 1 (1*)	Myocardial infarction GP1 0 (0*) GP2 1 (1*)		
Insulin aspart 70/30 vs. insulin aspart 70/30 + oral antidiabetic agents					
Kvapil, 2006[48]	GP1: Insulin aspart 70/30 (v) Start: 0.3 U/kg/day Mean: 0.51 U/kg/day T: Breakfast, dinner D: 16 weeks GP2: Insulin aspart 70/30 (v) Start: 0.2 U/kg/day Mean: 0.3 U/kg/day T: Breakfast, dinner D: 16 weeks metformin (fix) Mean: 1660 mg daily Range: 500 - 3000 mg qd T: NR D: 16 weeks	GP1 0 (0*) GP2 1 (1*)	Myocardial infarction GP1 0 (0*) GP2 1 (1*)		

Evidence Table 9. Comparative effectiveness of premixed insulin analogues and other diabetes treatments on clinical outcomes (continued)

Author, year	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Nephropathy, n (%)
Raz, 2005[51]	GP1: Insulin aspart 70/30 (v) Start: 0.3 U/kg per day Mean: 0.7 U/kg/day T: Breakfast, dinner D: 18 weeks GP2: Insulin aspart 70/30 (v) Start: 0.2 U/kg per day Mean: 0.5 U/kg/day T: Breakfast, dinner D: 18 weeks Pioglitazone (fix) Start: 30 mg Mean: 30 mg T: Breakfast D: 18 weeks			Non-fatal myocardial infarction GP1 1 (1*) GP2 0 (0*)	
Insulin lispro 75/25 vs. long-acting insulin analogues					
Malone, 2004[59]	GP1: Insulin lispro 75/25 (v) Mean: 0.62 U/kg T: Breakfast, dinner D: 16 weeks Metformin (NR) Mean: 1945 mg Range: 1500 - 2550 mg T: NR D: 16 weeks GP2: Insulin glargine (v) Mean: 0.57 U/kg T: Bedtime D: 16 weeks Metformin (NR) Mean: 1997 mg Range: 1500 - 2550 mg T: NR D: 16 weeks			Congestive heart failure GP1 1 (1*) GP2 0 (0*)	

Evidence Table 9. Comparative effectiveness of premixed insulin analogues and other diabetes treatments on clinical outcomes (continued)

Author, year	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Nephropathy, n (%)
Malone, 2005[60]	GP1: Insulin lispro 75/25 (v) Mean: 0.42 U/kg T: Breakfast, dinner D: 16 weeks Metformin (fix) Mean: 2128 mg Range: 1500 - 2550 mg T: NR D: 16 weeks GP2: Insulin glargine (v) Mean: 0.36 U/kg T: Bedtime D: 16 weeks Metformin (fix) Mean: 2146 mg Range: 1500 - 2550 mg T: NR D: 16 weeks	GP1 1 (1*) GP2 1 (1*)	Myocardial infarction GP1 1 (1*) GP2 0 (0*)		
Insulin lispro 75/25 vs. premixed human insulins					
Hermansen, 2002[55]	GP1: Insulin lispro 75/25 (fix) Start: 0.4 units/kg T: Breakfast D: 1 day GP2: NPH/regular 70/30 (fix) Start: 0.4 units/kg T: Breakfast D: 1 day			Transient ischemic attack GP1 0 (0) GP2 0 (0)	

Evidence Table 9. Comparative effectiveness of premixed insulin analogues and other diabetes treatments on clinical outcomes (continued)

Author, year	Intervention	Overall mortality, n (%)	CVD mortality, n (%)	CVD morbidity, n (%)	Nephropathy, n (%)
Insulin lispro 75/25 vs. oral antidiabetic agents					
Malone, 2003[62]	GP1: Insulin lispro 75/25 (v) Mean: 0.19 U/kg (morning) and 0.14 U/kg (evening) T: Breakfast, dinner D: 16 weeks Metformin (v) Mean: 1813 mg/day Range: 1500 – 2550 mg/day T: 2 to 3 divided doses with meals D: 16 weeks GP2: Metformin (v) Mean: 1968 mg/day Range: 1500 – 2550 mg/day T: 2 to 3 divided doses with meals D: 16 weeks Glibenclamide (v) Mean: 14.2 mg/day T: NR D: 16 weeks	GP1 1 (0*) GP2 0 (0*)			
Insulin lispro 50/50 vs. premixed human insulins					
Schern-thaner, 2004[70]	GP1: Insulin lispro 50/50 (v) Mean: 64.6 IU T: Breakfast, lunch, dinner D: 12 weeks diet/exercise D: 12 weeks GP2: NPH/regular 70/30 (v) Mean: 61.8 IU T: Breakfast, dinner D: 12 weeks diet/exercise D: 12 weeks	GP1 0 (0*) GP2 1 (2*)			

µg = microgram; bid = twice daily; CVD = cardiovascular disease; D = duration; F-B = mean difference from baseline; fix = fixed dosing; GP = group; GP1-GP2 = mean difference between the difference from baseline; IQR = interquartile range; IU = international unit; kg = kilogram; mg = milligram; NPH = neutral protamine Hagedorn; NR = not reported; p = p-value; qd = once daily; T = time of day when insulin taken; U = unit; v = dose varied

Evidence Table 10. Pooled estimates of effect for clinical outcomes using different meta-analytic techniques

Outcomes and meta-analytic methods	Pooled estimates (odds ratio)	95% CI
All-cause mortality (n = 5 studies)		
Bayesian	3.74	0.69 to 38.87
Mantel-Haenszel (0.5 cont corr)	2.29	0.76 to 6.95
Mantel-Haenszel (0.1 cont corr)	2.90	0.81 to 10.30
Mantel-Haenszel (0.01 cont corr)	3.11	0.83 to 11.61
Peto	2.81	0.90 to 8.81
Cardiovascular disease mortality (n = 3 studies)		
Bayesian	-*	-*
Mantel-Haenszel (0.5 cont corr)	3.86	0.66 to 22.70
Mantel-Haenszel (0.1 cont corr)	15.82	0.41 to 615.58
Mantel-Haenszel (0.01 cont corr)	-*	-*
Peto	7.06	1.20 to 41.56
Cardiovascular disease morbidity (n = 5 studies)		
Bayesian	0.98	0.32 to 4.77
Mantel-Haenszel (0.5 cont corr)	0.88	0.50 to 1.57
Mantel-Haenszel (0.1 cont corr)	0.89	0.50 to 1.60
Mantel-Haenszel (0.01 cont corr)	0.89	0.50 to 1.61
Peto	0.89	0.50 to 1.60
Combined outcome of mortality and cardiovascular disease morbidity (n = 8 studies)		
Bayesian	3.51	0.90 to 23.33
Mantel-Haenszel (0.5 cont corr)	2.05	0.81 to 5.20
Mantel-Haenszel (0.1 cont corr)	2.71	0.98 to 8.07
Mantel-Haenszel (0.01 cont corr)	2.96	0.94 to 9.30
Peto	2.66	0.99 to 7.18

*Unable to calculate due to scarcity of data (i.e., no convergence of the Markov Chain Monte Carlo model or confidence intervals were so wide, results did not make sense to report).
CI = confidence interval, cont corr = continuity correction, n = number