

APPENDIXES

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/analog 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]))	1149

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)	1344
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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 "analog") OR (TX "Humalog"))))	299
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The Cochrane Central Register of Controlled Trials (CENTRAL)

#1 (type 2 diabetes):ti,ab,kw in Clinical Trials	654
#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. Anonymous. 1-2-3: study results and clinical application: the "Start & Stay" approach. *Journal of Diabetes Nursing* 2006;(1):3p.
No original data
2. Anonymous. The 1-2-3 study: achieving glycaemic goals in type 2 diabetes. *Journal of Diabetes Nursing* 2006;(1):1p.
No original data
3. Anonymous. Key abstract: the EUROMIX study. *Journal of Diabetes Nursing* 2005;[3].
No original data
4. Anonymous. Rapid acting insulin analogue effective in a range of body types launched. *Pharm. J.* 2005;275(7369):401.
No original data
5. Anonymous. DTB questions first-line use of insulin analogues. *Pharm. J.* 2004;273(7321):552.
No original data
6. Anonymous. Lispro, a rapid-onset insulin. *Med. Lett. Drugs Ther.* 1996;38(986):97-98.
No original data
7. Anonymous. The why and how of early intervention with insulin analogs. *Diabetes Educator* 2007;3352S-75s.
No original data
8. Anonymous. CDC Fact Book 2000/2001. Department of Health and Human Services Centers for Disease Control and Prevention, 2000 Sep (138 p)
No original data
9. Anonymous. Diabetes Overview. US Department of Health and Human Services National Institute of Diabetes and Digestive and Kidney Diseases, 2000 Sep (8 p)
No original data
10. Anonymous. Is biphasic, prandial, or basal insulin best for poorly controlled type 2 diabetes? *J Fam Pract* 2008;57(2):84.
No original data
11. Abraham M R, Al-Sharafi B A, Saavedra G A et al. Lispro in the treatment of insulin allergy. *Diabetes Care* 1999;22(11):1916-1917.
No original data
12. Akram J. Prevention of hypoglycaemia in insulin-treated patients during Ramadan: results from a multicentre study: 2. *Practical Diabetes International* 1998;15(1):S19.
Did not evaluate a premixed insulin analogue
13. 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

14. 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
15. 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* 1991;9(1):63-73.
Did not evaluate a premixed insulin analogue
16. Bolli G B, Di Marchi R D, Park G D et al. Insulin analogues and their potential in the management of diabetes mellitus. *Diabetologia* 1999;42(10):1151-1167.
No original data
17. 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
18. 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
19. 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
20. 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
21. Clements M R, Tits J, Kinsley B T et al. Improved glycaemic control of thrice-daily biphasic insulin aspart compared with twice-daily biphasic human insulin; a randomized, open-label trial in patients with type 1 or type 2 diabetes. *Diabetes Obes Metab* 2008;10(3):229-37.
Did not evaluate people with type 2 diabetes
22. 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
23. 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* 1992;15(11):1628-30.
Did not evaluate a premixed insulin analogue
24. 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

25. 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
26. 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
27. 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
28. Dunbar JM, Madden PM, Gleeson DT et al. Premixed insulin preparations in pen syringes maintain glycemic control and are preferred by patients. *Diabetes care* 1994;17(8):874-8.
Did not evaluate people with type 2 diabetes
29. Ebeling P, Tuominen J A, Koivisto V A. Insulin analogues and carcinoma of the breast. *Diabetologia* 1996;39(1):124-125.
No original data
30. 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
31. Ejlskjaer 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
32. Gale E, Del Prato S. Emerging clinical uses for insulin lispro. *Pract. Diabetes Int.* 1997;14(4 SUPPL.):S4-S10.
No original data
33. 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
34. Garg S K. New insulin analogues. *Diabetes Technol Ther* 2005;7(5):813-7.
No original data
35. 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* 1984;106(1):97-101.
Did not evaluate a premixed insulin analogue
36. 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

37. Herz M. Clinical update on Humalog Mix25 a novel pre-mixed formulation of insulin lispro and NPL. *Int J Clin Pract Suppl* 1999;1048-13; discussion 18-20.
No original data
38. Home PD, Bailey CJ, Donaldson J et al. A double-blind randomized study comparing the effects of continuing or not continuing rosiglitazone + metformin therapy when starting insulin therapy in people with Type 2 diabetes. *Diabetic medicine : a journal of the British Diabetic Association* 2007;24(6):618-25
Did not evaluate a premixed insulin analogue
39. 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
40. 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
41. Iwamoto Y, Kawamori R, Kadowaki T, et al. Clinical study on insulin lispro Mixture-25 and Mixture-50 administered twice daily in insulin requiring patients with type 1 and 2 diabetes mellitus. *Rinsho-Iyaku* 2002;18(3):395-409.
Non-English article
42. 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
43. 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
44. 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
45. 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
46. 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
47. Kitowicz A, Criswell D F. Question: is insulin glargine more effective? *J Okla State Med Assoc* 2007;100(1):26-7.
No original data

48. Kitzmiller J L, Buchbinder A, Khoury J et al. Insulin lispro and the development of proliferative diabetic retinopathy during pregnancy (multiple letter) [4]. *Am. J. Obstet. Gynecol.* 2001;185(3):774-775.
No original data
49. Kitzmiller J L, Main E, Ward B et al. Insulin lispro and the development of proliferative diabetic retinopathy during pregnancy. *Diabetes Care* 1999;22(5):874-6.
Did not evaluate a premixed insulin analogue
50. Koivisto V A. International experience with insulin lispro. *Pract. Diabetes Int.* 1998;15(1 SUPPL.):S15-S17.
No original data
51. Koivisto V A, Tuominen J A, Ebeling P. Lispro Mix25 insulin as premeal therapy in type 2 diabetic patients. *Diabetes Care* 1999;22(3):459-62.
Does not apply to a key question
52. Kokic S, Bukovic D, Radman M *et al.* Lispro insulin and metformin versus other combination in the diabetes mellitus type 2 management after secondary oral antidiabetic drug failure. *Coll Antropol* 2003; 27(1):181-7.
Did not evaluate a premixed insulin analogue
53. 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.
Did not compare a premixed insulin analogue to another antidiabetic agent
54. Levinson P D. Premixed or self-mixed insulin for elderly patients. *Ann. Intern. Med.* 1993;118(SUPPL. 3):80.
No original data
55. 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
56. Luddeke H J. Improving post-prandial control with Humalog and Humalog mixtures. *Int J Clin Pract Suppl* 2000;(112):23-8.
No original data
57. McCormack J, Bassett K. The evidence for insulin lispro. *CMAJ* 1998;159(11):1353-5.
No original data
58. 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
59. Mohn A, Marcovecchio M, Chiarelli F et al. Insulin analogues [5] (multiple letters). *New Engl. J. Med.* 2005;352(17):1822-1824.
No original data
60. Moisey R S, Jenkins R, Nagi D. The use of basal insulin (NPH) compared with pre-mixed biphasic insulin in patients with type 2 diabetes mellitus. A single centre experience. *Pract. Diabetes Int.* 2007;24(4):212-216.
Exclude other reason

61. 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
62. 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
63. Ning G, Xiang K, Gao Y, et al. Comparison of post-prandial blood glucose excursions between insulin lispro 75/25 and human insulin 70/30 in Chinese patients with type 1 or type 2 diabetes. *International Journal of Medicine* 2005;9(2):14-22.
Did not compare a premixed insulin analogue to another antidiabetic agent
64. Oosthuizen H. Insulin therapy in type 2 diabetes mellitus. *J. Endocrinol. Metab. Diabetes S. Afr.* 2003;8(3):72-78.
No original data
65. 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
66. Peragallo-Dittko V. Insulin therapy for type 2 diabetes. *Diabetes Self-Management* 2003;20(5):17.
No original data
67. Plog T. Insulin analogs plus oral antidiabetic drug therapy for older patients with type 2 diabetes. *Long-Term Care Interface* 2007; 7.
No original data
68. 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* 1983;125(Suppl 1):57-62.
Non-English article
69. Reviriego J, Herz M, Roach P, and the Humalog® Mix25 Spanish Study Group. Improved glycaemic control without increased risk of hypoglycaemia with a 25% insulin/lispro 75% NPL mixture twice daily compared with NPH twice daily in patients with type 2 diabetes. *J Appl Ther Res* 2004;4(4):3-9.
Exclude other reason
70. 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
71. 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

72. 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
73. 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
74. 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
75. 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 2B21-9.
Did not evaluate a premixed insulin analogue
76. 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
77. Swenson K, Brackenridge B. Lispro for type 2? *Diabetes Forecast* 2000;53(7):81-83.
No original data
78. Swenson K, Brackenridge B. Lispro insulin for improved glucose control in obese patient with type 2 diabetes. *Diabetes Spectrum* 1998;11(1):13-15.
No original data
79. 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
80. 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
81. 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
82. 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

83. White J R. Insulin glargine clinical trials. Clin Ther 2004;26(7):1179-81; discussion 1182-3.
No original data
84. Yamada S, Watanabe M, Funae O et al. Effect of combination therapy of a rapid-acting insulin secretagogue (glinide) with premixed insulin in type 2 diabetes mellitus. Intern Med 2007;46(23):1893-7.
Did not evaluate a premixed insulin analogue
85. 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
86. Zinman B. The pharmacokinetics of insulin analogues and pumps. Pract. Diabetes Int. 2001;18(5 SUPPL.):S3-S4.
No original data

Appendix D: Data Abstraction Forms

Previewing Only: You cannot submit data from this form



Previewing at Level 1

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

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

Yes—potentially eligible

No—not eligible

[Clear Selection](#)

Form took 0.484375 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 2

Refid: 1, Devries, J. H., Natrass, 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

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.)

QK1. 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., exenatide)
- Some combination of antidiabetic medications
- Usual care not otherwise specified

5. Comments

[Enlarge](#) [Shrink](#)

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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., Natrass, 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

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 <60 ml/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., exenatide)
- 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., Natrass, 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

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	<input type="text"/>	<input type="text"/>	<input type="checkbox"/>
8. Median	<input type="text"/>	<input type="text"/>	<input type="checkbox"/>
9. Intended duration of followup	<input type="text"/>	<input type="text"/>	<input type="checkbox"/>

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 Creation Date: Not available
Form Last Modified: Nov 9 2007 8:29AM



Previewing at Level 5

Refid: 1, Devries, J. H., Natrass, 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

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
<input type="button" value="Please Select"/>	<input type="radio"/> Fixed <input type="radio"/> Varied <input type="radio"/> Unclear Clear Selection	Starting dose _____ Mean dose _____ Lower limit of range _____ Upper limit of range _____	<input type="checkbox"/> breakfast <input type="checkbox"/> lunch <input type="checkbox"/> dinner <input type="checkbox"/> bedtime <input type="checkbox"/> other (specify:) _____ <input type="checkbox"/> not specified	days _____ weeks _____ months _____ years _____ other _____ <input type="checkbox"/> unclear
<input type="button" value="Please Select"/>	<input type="radio"/> Fixed <input type="radio"/> Varied <input type="radio"/> Unclear Clear Selection	Starting dose _____ Mean dose _____ Lower limit of range _____ Upper limit of range _____	<input type="checkbox"/> breakfast <input type="checkbox"/> lunch <input type="checkbox"/> dinner <input type="checkbox"/> bedtime <input type="checkbox"/> other (specify:) _____ <input type="checkbox"/> not specified	days _____ weeks _____ months _____ years _____ other _____ <input type="checkbox"/> unclear
<input type="checkbox"/> Diet and/or exercise	NA	NA	NA	days _____ weeks _____ months _____ years _____ other _____ <input type="checkbox"/> unclear
<input type="checkbox"/> Usual care _____	NA	NA	NA	days _____ weeks _____ months _____ years _____ other _____ <input type="checkbox"/> unclear
<input type="checkbox"/> Placebo	NA	NA	NA	days _____ weeks _____ months _____ years _____ other _____ <input type="checkbox"/> unclear

<input type="checkbox"/> Other (specify.)	<input checked="" type="radio"/> Fixed <input type="radio"/> Varied <input type="radio"/> Unclear Clear Selection	Starting dose _____ Mean dose _____ Lower limit of range _____ Upper limit of range _____	<input type="checkbox"/> breakfast <input type="checkbox"/> lunch <input type="checkbox"/> dinner <input type="checkbox"/> bedtime <input type="checkbox"/> other (specify.) _____ <input type="checkbox"/> not specified	days _____ weeks _____ months _____ years _____ other _____ <input type="checkbox"/> unclear
<input type="checkbox"/> Other (specify.)	<input checked="" type="radio"/> Fixed <input type="radio"/> Varied <input type="radio"/> Unclear Clear Selection	Starting dose _____ Mean dose _____ Lower limit of range _____ Upper limit of range _____	<input type="checkbox"/> breakfast <input type="checkbox"/> lunch <input type="checkbox"/> dinner <input type="checkbox"/> bedtime <input type="checkbox"/> other (specify.) _____ <input type="checkbox"/> not specified	days _____ weeks _____ months _____ years _____ other _____ <input type="checkbox"/> unclear
<input type="checkbox"/> Other (specify.)	<input checked="" type="radio"/> Fixed <input type="radio"/> Varied <input type="radio"/> Unclear Clear Selection	Starting dose _____ Mean dose _____ Lower limit of range _____ Upper limit of range _____	<input type="checkbox"/> breakfast <input type="checkbox"/> lunch <input type="checkbox"/> dinner <input type="checkbox"/> bedtime <input type="checkbox"/> other (specify.) _____ <input type="checkbox"/> not specified	days _____ weeks _____ months _____ years _____ other _____ <input type="checkbox"/> unclear

Please indicate the intervention used by Group 2.

Intervention	Dosing	Dose (include units)	Timing	Duration of use
Please Select	<input checked="" type="radio"/> Fixed <input type="radio"/> Varied <input type="radio"/> Unclear Clear Selection	Starting dose _____ Mean dose _____ Lower limit of range _____ Upper limit of range _____	<input type="checkbox"/> breakfast <input type="checkbox"/> lunch <input type="checkbox"/> dinner <input type="checkbox"/> bedtime <input type="checkbox"/> other (specify.) _____ <input type="checkbox"/> not specified	days _____ weeks _____ months _____ years _____ other _____ <input type="checkbox"/> unclear
Please Select	<input checked="" type="radio"/> Fixed <input type="radio"/> Varied <input type="radio"/> Unclear Clear Selection	Starting dose _____ Mean dose _____ Lower limit of range _____ Upper limit of range _____	<input type="checkbox"/> breakfast <input type="checkbox"/> lunch <input type="checkbox"/> dinner <input type="checkbox"/> bedtime <input type="checkbox"/> other (specify.) _____ <input type="checkbox"/> not specified	days _____ weeks _____ months _____ years _____ other _____ <input type="checkbox"/> unclear
<input type="checkbox"/> Diet and/or exercise	NA	NA	NA	days _____ weeks _____ months _____ years _____ other _____ <input type="checkbox"/> unclear
<input type="checkbox"/> Usual care	NA	NA	NA	days _____ weeks _____ months _____ years _____ other _____ <input type="checkbox"/> unclear
<input type="checkbox"/> Placebo	NA	NA	NA	days _____ weeks _____ months _____

				years _____
				other _____
				<input type="checkbox"/> unclear
<input type="checkbox"/> Other (specify.) _____	<input type="radio"/> Fixed <input type="radio"/> Varied <input type="radio"/> Unclear Clear Selection	Starting dose _____ Mean dose _____ Lower limit of range _____ Upper limit of range _____	<input type="checkbox"/> breakfast <input type="checkbox"/> lunch <input type="checkbox"/> dinner <input type="checkbox"/> bedtime <input type="checkbox"/> other (specify.) _____ <input type="checkbox"/> not specified	days _____ weeks _____ months _____ years _____ other _____ <input type="checkbox"/> unclear
<input type="checkbox"/> Other (specify.) _____	<input type="radio"/> Fixed <input type="radio"/> Varied <input type="radio"/> Unclear Clear Selection	Starting dose _____ Mean dose _____ Lower limit of range _____ Upper limit of range _____	<input type="checkbox"/> breakfast <input type="checkbox"/> lunch <input type="checkbox"/> dinner <input type="checkbox"/> bedtime <input type="checkbox"/> other (specify.) _____ <input type="checkbox"/> not specified	days _____ weeks _____ months _____ years _____ other _____ <input type="checkbox"/> unclear
<input type="checkbox"/> Other (specify.) _____	<input type="radio"/> Fixed <input type="radio"/> Varied <input type="radio"/> Unclear Clear Selection	Starting dose _____ Mean dose _____ Lower limit of range _____ Upper limit of range _____	<input type="checkbox"/> breakfast <input type="checkbox"/> lunch <input type="checkbox"/> dinner <input type="checkbox"/> bedtime <input type="checkbox"/> other (specify.) _____ <input type="checkbox"/> not specified	days _____ weeks _____ months _____ years _____ other _____ <input type="checkbox"/> unclear

Please indicate the intervention used by Group 3.

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

				<input type="checkbox"/> unclear
<input type="checkbox"/> Placebo	NA	NA	NA	days weeks months years other <input type="checkbox"/> unclear
<input type="checkbox"/> Other (specify:)	<input type="radio"/> Fixed <input type="radio"/> Varied <input type="radio"/> Unclear Clear Selection	Starting dose _____ Mean dose _____ Lower limit of range _____ Upper limit of range _____	<input type="checkbox"/> breakfast <input type="checkbox"/> lunch <input type="checkbox"/> dinner <input type="checkbox"/> bedtime <input type="checkbox"/> other (specify:) <input type="checkbox"/> not specified	days _____ weeks _____ months _____ years _____ other _____ <input type="checkbox"/> unclear
<input type="checkbox"/> Other (specify:)	<input type="radio"/> Fixed <input type="radio"/> Varied <input type="radio"/> Unclear Clear Selection	Starting dose _____ Mean dose _____ Lower limit of range _____ Upper limit of range _____	<input type="checkbox"/> breakfast <input type="checkbox"/> lunch <input type="checkbox"/> dinner <input type="checkbox"/> bedtime <input type="checkbox"/> other (specify:) <input type="checkbox"/> not specified	days _____ weeks _____ months _____ years _____ other _____ <input type="checkbox"/> unclear
<input type="checkbox"/> Other (specify:)	<input type="radio"/> Fixed <input type="radio"/> Varied <input type="radio"/> Unclear Clear Selection	Starting dose _____ Mean dose _____ Lower limit of range _____ Upper limit of range _____	<input type="checkbox"/> breakfast <input type="checkbox"/> lunch <input type="checkbox"/> dinner <input type="checkbox"/> bedtime <input type="checkbox"/> other (specify:) <input type="checkbox"/> not specified	days _____ weeks _____ months _____ years _____ other _____ <input type="checkbox"/> unclear

Please indicate the intervention used by Group 4.

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

<input type="checkbox"/> Usual care					<input type="checkbox"/> days <input type="checkbox"/> weeks <input type="checkbox"/> months <input type="checkbox"/> years <input type="checkbox"/> other <input type="checkbox"/> unclear
<input type="checkbox"/> Placebo	NA	NA	NA	NA	<input type="checkbox"/> days <input type="checkbox"/> weeks <input type="checkbox"/> months <input type="checkbox"/> years <input type="checkbox"/> other <input type="checkbox"/> unclear
<input type="checkbox"/> Other (specify:)	<input type="radio"/> Fixed <input type="radio"/> Varied <input type="radio"/> Unclear Clear Selection	Starting dose Mean dose Lower limit of range Upper limit of range	<input type="checkbox"/> breakfast <input type="checkbox"/> lunch <input type="checkbox"/> dinner <input type="checkbox"/> bedtime <input type="checkbox"/> other (specify:) <input type="checkbox"/> not specified	<input type="checkbox"/> days <input type="checkbox"/> weeks <input type="checkbox"/> months <input type="checkbox"/> years <input type="checkbox"/> other <input type="checkbox"/> unclear	
<input type="checkbox"/> Other (specify:)	<input type="radio"/> Fixed <input type="radio"/> Varied <input type="radio"/> Unclear Clear Selection	Starting dose Mean dose Lower limit of range Upper limit of range	<input type="checkbox"/> breakfast <input type="checkbox"/> lunch <input type="checkbox"/> dinner <input type="checkbox"/> bedtime <input type="checkbox"/> other (specify:) <input type="checkbox"/> not specified	<input type="checkbox"/> days <input type="checkbox"/> weeks <input type="checkbox"/> months <input type="checkbox"/> years <input type="checkbox"/> other <input type="checkbox"/> unclear	
<input type="checkbox"/> Other (specify:)	<input type="radio"/> Fixed <input type="radio"/> Varied <input type="radio"/> Unclear Clear Selection	Starting dose Mean dose Lower limit of range Upper limit of range	<input type="checkbox"/> breakfast <input type="checkbox"/> lunch <input type="checkbox"/> dinner <input type="checkbox"/> bedtime <input type="checkbox"/> other (specify:) <input type="checkbox"/> not specified	<input type="checkbox"/> days <input type="checkbox"/> weeks <input type="checkbox"/> months <input type="checkbox"/> years <input type="checkbox"/> other <input type="checkbox"/> unclear	

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

HbA1c

fasting glucose

other glucose measure

126. Comments

Enlarge Shrink

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

Previewing Only: You cannot submit data from this form



Previewing at Level 6

Refid: 1, Devries, J. H., Natrass, 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	<input type="text"/>				
2. Total N for enrollment	<input type="text"/>				
Age					
3. Mean age	<input type="text"/>				
4. Age range	<input type="text"/>				
5. Other age	<input type="text"/>				
6. Other age	<input type="text"/>				
7. Other age	<input type="text"/>				
8. Other age	<input type="text"/>				
Male					
9. N	<input type="text"/>				
10. %	<input type="text"/>				
Race/ethnicity					
11. African American (N)	<input type="text"/>				
12. African American (%)	<input type="text"/>				
13. Caucasian (N)	<input type="text"/>				
14. Caucasian (%)	<input type="text"/>				
15. Asian or Asian American (N)	<input type="text"/>				
16. Asian or Asian American (%)	<input type="text"/>				
17. Hispanic/Latino (N)	<input type="text"/>				
18. Hispanic/Latino (%)	<input type="text"/>				
19. Other race/ethnicity (N)	<input type="text"/>				
20. Other race/ethnicity (%)	<input type="text"/>				
21. Other race/ethnicity (N)	<input type="text"/>				
22. Other race/ethnicity (%)	<input type="text"/>				
BMI/Weight					
23. Mean BMI (kg/m ²)	<input type="text"/>				
24. Mean weight (kg)	<input type="text"/>				
25. Other weight/BMI	<input type="text"/>				
26. Other weight/BMI	<input type="text"/>				

27. Other weight/EMI
 28. Other weight/EMI

HbA1c

	Group 1	Group 2	Group 3	Group 4	Total	
29. Mean HbA1c(%)						
30. Mean HbA1 (%)						
31. Mean fasting plasma glucose	Specify unit	Group 1	Group 2	Group 3	Group 4	Total
32. Other hemoglobin	Specify other hemoglobin category	Group 1	Group 2	Group 3	Group 4	Total
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)						
37. Other duration of diabetes measures	Specify other duration of diabetes	Group 1	Group 2	Group 3	Group 4	Total

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

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

Enlarge Shrink

Thank you very much!

[Save to finish later](#) [Submit Data](#)

Form took 0.5 seconds to render
 Form Creation Date: Not available
 Form Last Modified: Oct 25 2007 10:03AM

Previewing Only: You cannot submit data from this form



Previewing at Level 7

Ref: 1, Davies, J. H., Nafrass, 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 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-DT9Q)
- 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 logit 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. <input type="radio"/> days <input type="radio"/> weeks <input type="radio"/> months <input type="radio"/> years <input type="radio"/> person-years <input type="radio"/> Other (specify) _____ <input type="radio"/> not applicable Clear Selection	P-value
Group 1	<input type="text"/>	# with 1 or more events: % with 1 or more events: Specify other numerator type: Specify other numerator value:	<input type="text"/>	<input type="text"/>
Group 2	<input type="text"/>	# with 1 or more events: % with 1 or more events: Specify other numerator type: Specify other numerator value:	<input type="text"/>	<input type="text"/>
Group 3	<input type="text"/>	# with 1 or more events: % with 1 or more events: Specify other numerator type: Specify other numerator value:	<input type="text"/>	<input type="text"/>
Group 4	<input type="text"/>	# with 1 or more events: % with 1 or more events: Specify other numerator type: Specify other numerator value:	<input type="text"/>	<input type="text"/>

MEASURE OF ASSOCIATION FOR COMPARISON OF OUTCOME BETWEEN STUDY GROUPS

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

BASELINE MEASURES OF OUTCOME

Point Estimate <input type="radio"/> Mean <input type="radio"/> Median	Measure of Variability <input type="radio"/> SE <input type="radio"/> SD	95% CI <input type="radio"/> IQR Clear Selection	N for analysis	P-value
<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>

	<input type="radio"/> Other (specify): Clear Selection	<input type="radio"/> 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 <input type="radio"/> Mean <input type="radio"/> Median <input type="radio"/> Other (specify): Clear Selection	Measure of Variability <input type="radio"/> SE <input type="radio"/> SD <input type="radio"/> Other (specify): Clear Selection	<input type="radio"/> 95% CI <input type="radio"/> 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 <input type="radio"/> Mean <input type="radio"/> Median <input type="radio"/> Other (specify): Clear Selection	Measure of Variability <input type="radio"/> SE <input type="radio"/> SD <input type="radio"/> Other (specify): Clear Selection	<input type="radio"/> 95% CI <input type="radio"/> 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 <input type="radio"/> Mean <input type="radio"/> Median <input type="radio"/> Other (specify): Clear Selection	Measure of Variability <input type="radio"/> SE <input type="radio"/> SD <input type="radio"/> Other (specify): Clear Selection	<input type="radio"/> 95% CI <input type="radio"/> 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 _____ 

- Results are not adjusted
- Not applicable (i.e., RCT)

148. Comments

[Enlarge](#) [Shrink](#)

Form took 0.53125 seconds to render
 Form Creation Date: Sep 17, 2007, 12:47PM
 Form Last Modified: Oct 31, 2007, 9:47AM

Previewing Only: You cannot submit data from this form



Previewing at Level 27

Refid: 1, Devries, J. H., Natrass, 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 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](#)

Form took 0.15625 seconds to render
Form Creation Date: Not available
Form Last Modified: Nov 7 2007 1:32PM

Previewing Only: You cannot submit data from this form



Previewing at Level 2B

Refid: 1, Devries, J. H., Natrass, 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

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 <input type="checkbox"/> Inpatient/hospital <input type="checkbox"/> Outpatient clinics <input type="checkbox"/> Subspecialty clinics <input type="checkbox"/> Community <input type="checkbox"/> Other <input type="checkbox"/> Not reported	2. University affiliation <input type="checkbox"/> University affiliated <input type="checkbox"/> Non-university affiliated <input type="checkbox"/> 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:

[Enlarge](#) [Shrink](#)

Form took 0.109375 seconds to render
Form Creation Date: Oct 12 2007 9:11AM
Form Last Modified: Nov 8 2007 11:19AM

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)

	Fasting 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:	11	2	2	9	2	10
Number of studies						
Range of sample sizes	20-469	107-473	145	25-177	93-403	49-597
Quality and consistency of evidence:	High	High	Moderate	High	High	High
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)?						
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.

E-1

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 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:	8	3	1	7	1	8
Number of studies						
Range of sample sizes	20-469	106-474	374	25-187	394	49-501
Quality and consistency of evidence:	High	High	Moderate	High	High	High
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)?						
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)	Moderate	Moderate	Moderate	Moderate	Moderate	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 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:	9	1	1	11	2	10
Number of studies						
Range of sample sizes	20-315	107	374	23-177	140-403	143-597
Quality and consistency of evidence:	High	High	Moderate	High	High	High
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)?						
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	NA	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)?	-1	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	0	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.	1	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	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)

	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:	10	2	2	8	2	9
Number of studies						
Range of sample sizes	20-469	107-473	145-374	25-177	140-143	49-597
Quality and consistency of evidence:	High	High	Moderate	High	High	high
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)?						
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:	9	2	1	7	2	6
Number of studies						
Range of sample sizes	20-708	159-708	145	40-177	140-403	129-597
Quality and consistency of evidence:	High	High	Low	High	High	High
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)?						
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:	11	2	2	16	2	10
Number of studies						
Range of sample sizes	20-708	159-708	145-374	13-187	140-403	49-597
Quality and consistency of evidence:	High	High	Moderate	High	High	High
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)?						
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:	10	2	2	7	2	10
Number of studies						
Total number of patients studied	20-469	98-473	145-374	30-151	93-403	49-597
Quality and consistency of evidence:	High	High	Medium	High	High	High
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)?						
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, 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.

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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 (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 comparisons	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:	2	1	2	0	3
Number of studies					
Total number of patients studied	456	501	368	NA	530
Quality and consistency of evidence:	High	High	High	NA	High
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)?					
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.

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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 (continued)

	Nephropathy	
	Premixed vs. long-acting insulin analogues or oral agents	Other comparisons
Quantity of evidence: Number of studies	3	0
Total number of patients studied	1223	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)	-1	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:	3	1	0	1	0	2
Number of studies						
Total range in number of patients studied	45 to 708	159	NA	160	NA	451
Quality and consistency of evidence:	High	High	NA	High	NA	High
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)?						
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	-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	-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 ⁵³	Austria	Parallel-arms, randomized controlled trial	Intended duration: 24 weeks	A1c < 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 ⁴⁶	Western Pacific	Parallel-arms, randomized controlled trial	Intended duration: 24 weeks	Age < 18 years, any liver disease, any kidney disease, A1c < 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	A1c ≤ 8.5% FPG ≤ 7 mmol/L (126 mg/dL)
Boehm, 2004 ⁴⁵ Boehm, 2002 ^{9*}	United Kingdom, Germany, Ireland	Parallel-arms, randomized controlled trial	Intended duration: 104 weeks	Age < 18 years, A1c > 11%, no T2DM, BMI > 35 kg/m ² , duration of diabetes < 2 years	NR
Christiansen, 2003 ¹³	9 countries	Parallel-arms, randomized controlled trial	Intended duration: 16 weeks	Age < 18 years, A1c > 11%, no T2DM, BMI > 35 kg/m ² , insulin doses ≥ 1.8 IU/kg/day, history of serious late diabetic complications or other serious disease	NR
Coscelli, 2003 ⁶⁷	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, A1c > 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 ⁷⁴	United States	Cross-over, randomized controlled trial, no washout period	Intended duration: 24 weeks	A1c < 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, A1c ≥ 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

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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 ¹ Croatia	Cross-over, randomized controlled trial, no washout period	Intended duration: 4 weeks	Age < 38 and > 69 years, A1c ≥ 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 (126 mg/dL) 2-hr PPG < 10.0 mmol/L (180 mg/dL)
Herz, 2002 ² 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, A1c < 1.2 fold ULN at visit 1, FBG < 7.8 mmol/L (140 mg/dL) 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 agents 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 (126 mg/dL) (encouraged by the study investigators but targets were at the discretion of the physician) 2 hour PPG < 10 mmol/L (180 mg/dL)
Herz, 2003 ¹² South Africa	Cross-over, randomized controlled trial, no washout period	Intended duration: 4 weeks	Age < 40 and > 70 years, A1c > 10%, no T2DM, BMI > 35 kg/m ² , not treated with human insulin 30/70 twice daily, have not practiced self-monitoring of BG for at least 3 months, usually injected human insulin 30-45 minutes before meals, being treated with OA agents, systemic glucocorticoids, or insulin doses > 2.0 U/kg/day	FPG < 7.0 mmol/L (126 mg/dL) 2-hr PPG < 10 mmol/L (180 mg/dL)
Hirao, 2008 ⁶¹ Japan	Parallel-arms, randomized controlled trial	Intended duration: 6 months	A1c < 8%, soft drink ketoacidosis	A1c < 7%
Holman, 2007 ³² 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, A1c < 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)	A1c 6.5% FPG 72 - 99 mg/dL PPG 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
Jacober, 2006 ⁵⁴	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, A1c < 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 ⁵²	India	Prospective study	Intended duration: 12 weeks	No T2DM	A1c < 7% but was up to the individual clinician to titrate
Kann, 2006 ⁵⁰	Austria, Czech Republic, Germany, Hungary, Poland, Slovakia, Slovenia	Parallel-arms, randomized controlled trial	Intended duration: 26 weeks	A1c ≤ 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 (90 – 144 mg/dL) for both groups 90-min PPG 5 - 10 mmol/L (90 – 180 mg/dL) for BIAsp group
Kapitza, 2004 ^{5b}	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 (180 mg/dL)
Kazda, 2006 ⁶	Germany	Parallel-arms, randomized controlled trial	Intended duration: 24 weeks	Age < 30 or > 75 years, A1c < 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 (126 mg/dL) for insulin glargine 2-hr PPG < 10 mmol/L (180 mg/dL) for lispro groups
Kilo, 2003 ¹⁵	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, A1c < 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 - 26 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 ⁵¹	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 (90 – 144 mg/dL); evening insulin aspart 70/30 dose adjusted to target post-dinner, nighttime, and pre-breakfast blood glucose of 5 – 8 mmol/L (90 – 144 mg/dL)
Malone, 2000 ⁴⁴ Malone, 2000 ¹⁴	Canada	Cross-over, randomized controlled trial, washout period: 3-11 days	Intended duration: 1 day	Age < 38 and > 74 years, A1c > 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 ⁶⁸	14 countries	Parallel-arms, randomized controlled trial	Mean: 16 weeks	Age < 35 and > 75 years, A1c < 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 ⁶⁵	United States	Cross-over, randomized controlled trial, no washout period	Intended duration: 16 weeks	Age < 30 and > 80 years, history of insulin treatment, A1c < 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 - 126 mg/dL 2-hr PPG 144 - 180 mg/dL
Malone, 2005 ⁶⁶	Spain and France	Cross-over, randomized controlled trial, no washout period	Intended duration: 16 weeks	Age < 30 and > 75 years, A1c < 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 ⁷⁰	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 ⁴⁸	United Kingdom	Cross-over, randomized controlled trial, no washout period	Intended duration: 16 weeks	A1c \geq 9.5%, no T2DM, BMI \geq 40 kg/m ² , not treated with insulin for at least 6 months	FPG 5 - 7 mmol/L (90 - 126 mg/dL) Preprandial glucose 5 - 7 mmol/L (90 - 126 mg/dL)
McSorley, 2002 ¹¹	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 ⁴⁹	13 countries	Parallel-arms, randomized controlled trial	Intended duration: 52 weeks	Age < 30 and > 75 years, A1c < 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 ⁵⁵	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, A1c > 12%, no T2DM, BMI > 35 kg/m ² , did not require insulin for the past 6 months, insulin dose \geq 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 - 8.0 mmol/L (90 - 144 mg/dL) Postprandial BG (1-3 hours after a meal) 5.0 - 10.0 mmol/L (90 - 180 mg/dL)
Raskin, 2005 ³⁹ Raskin, 2007 ⁴⁰ Brod, 2007 ⁴¹	United States	Parallel-arms, randomized controlled trial	Intended duration: 28 weeks	Age < 18 and > 75 years, history of insulin treatment, A1c < 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
Raskin, 2007 ⁶⁰	United States	Parallel-arms, randomized controlled trial	Intended duration: 34 weeks	Age < 18 years, history of insulin treatment, A1c < 7.5 and > 12, no T2DM, BMI > 42 kg/m ² , not treated with 2 OA agents for at least 6 months	FPG 4.4 - 6.1 mmol/L (79.2 - 109.8 mg/dL)
Raz, 2003 ⁵⁷	Israel	Parallel-arms, randomized controlled trial	Intended duration: 6 weeks	Age < 30 years, any liver disease, history of CVD, history of insulin treatment, A1c \leq 8 and \geq 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 - 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 ⁵⁴	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, A1c < 7.4 and > 14.7%, no T2DM, BMI > 40kg/m ² , no treatment with SU 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 (90 – 180 mg/dL) for insulin aspart 70/30 PPG 5-8 mmol/L (90 -180 mg/dL) for insulin aspart 70/30
Roach, 1999 ⁷³	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, A1c > 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 ¹⁰	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, A1c > 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 (140 mg/dL) 2-hr PPG ≤ 10 mmol/L (180 mg/dL)
Roach, 2003 ⁵⁹	India	Cross-over, randomized controlled trial, no washout period	Intended duration: 8 weeks	Age < 25 and > 75 years, A1c > 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 ⁶³	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, A1c < 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 (108 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
Robbins, 2007 ⁷⁹	United States, Australia, Greece, the Netherlands, Poland, and Puerto Rico	Parallel-arms, randomized controlled trial	Intended duration: 24 weeks	Age < 35 and > 75 years, any liver disease, any kidney disease, A1c < 6.5 and > 11, no T2DM, had a clinically unacceptable level of LDL cholesterol determined by investigator's opinion, not currently using metformin and/or a sulfonylurea with a stable dose of 0 to 2 daily insulin injections for at least 3 months, receiving continuous SC insulin infusions, ≥ 3 daily insulin injections or a total daily insulin dose > 2.0 U/kg, change in the type or dose of lipid-altering medications or TZD use up to 3 months prior to study start, fasting triglyceride levels > 4.5 mmol/L (81 mg/dL), pregnant women or women not using an effective method of contraception	FPG < 120 mg/dL (6.7 mmol/L) 2-hr PPG < 144 mg/dL (8.0 mmol/L) for insulin lispro 50/50 group only
Rosenstock, 2008 ⁸⁰	United States, Puerto Rico	Parallel-arms, randomized controlled trial	Intended duration: 24 weeks	Age < 30 and > 75 years, any liver disease, any kidney disease, history of CVD, A1c < 7.5 and > 12%, no T2DM, BMI > 45 kg/m ² , not taking insulin glargine for at least 90 days in combination with OA agents as monotherapy, dual therapy, or triple therapy, history of scheduled mealtime insulin use or more than one episode of severe hypoglycemia within the prior 6 months, total daily insulin dose > 2.0 U/kg	FPG < 110 mg/dL (6.1 mmol/L)
Scherthaner, 2004 ⁷⁷	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, A1c > 11%, no T2DM, BMI > 40 kg/m ² , no severe diabetic complications	NR
Schwartz, 2006 ⁶²	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, A1c ≥ 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
Sun, 2007 ⁷⁵	United States	Retrospective cohort study	Intended duration: 18 months	History of insulin treatment, no T2DM, no initiation or less than 3-month use of insulin therapy with either once-daily insulin glargine, twice-daily premixed insulin analogue, or twice-daily premixed human insulin, without switching to another insulin regimen during the observation period, multiple A1c records before and after insulin initiation, taking twice-daily premixed insulin aspart 70/30	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
Tamemoto, 2007 ⁴⁷	Japan	Parallel-arms, randomized controlled trial	Intended duration: 24 weeks	Age < 40 or > 75 years, A1c < 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	A1c < 7% FPG < 120 mg/dL
Tirgoviste, 2003 ⁴³ Roach, 2001 ⁴²	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, A1c ≤ 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 (140 mg/dL), PPG ≤ 10 mmol/L (180 mg/dL), 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
Ushakova, 2007 ⁵⁹	Russia	Parallel-arms, randomized controlled trial	Intended duration: 8 weeks titration; 8 weeks maintenance	Age < 40 and > 70 years, any liver disease, any kidney disease, history of CVD, history of insulin treatment, retinopathy, A1c < 8%, no T2DM, BMI > 35.0 kg/m ² , was not treated with at least 1 OA agents for at least 6 months, recurrent major hypoglycemia, using medication known to interfere with glucose metabolism, pregnant or breastfeeding women	FPG: 79.2 - 126 mg/dL (4.4 - 7.0 mmol/L) PPG: 79.2 - 162 mg/dL (4.4 - 9.0 mmol/L)
Yamada, 2007 ⁷⁸	Japan	Parallel-arms, randomized controlled trial	Intended duration: 4 months	Any liver disease, any kidney disease, history of CVD, retinopathy, A1c ≤ 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 2002⁹ was patients with either type 1 or type 2 diabetes. The type 2 diabetic population was the same study population used for Boehm 2004.⁴⁵ The study duration was 12 weeks.

A1c = Hemoglobin A1c; 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; 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 A1c in % Mean FBG in mg/dL#	Mean duration of diabetes in years	Previous treatment, n (%)
Abrahamian, 2005 ⁵³	Insulin aspart 70/30, 89	62.6	46* (52)	NR	BMI: 28	A1c: 9.8	12.7	Insulin naive: No
	NPH/regular 70/30, 88	62.3	31* (35)	NR	BMI: 28.3	A1c: 9.85	9.5	Insulin naive: No
Bebakar, 2007 ⁴⁶	Insulin aspart 70/30 + OA agents, 128	55	48 (92)	NR	BMI: 26.2	A1c: 8.6	4.4	Insulin naive: Yes OA agents: 128 (100)
	OA agents, 63	52.7	41 (69)	NR	BMI: 25.4	A1c: 8.5	4.3	Insulin naive: Yes OA agents: 63 (100)
Boehm, 2004 ⁴⁵	Insulin aspart 70/30, 58	62.8	32 (55*)	NR	BMI: 29.1	A1c: 8.11	15.5	Insulin naive: No
Boehm, 2002 ^{9†}	NPH/regular 70/30, 67	62.6	34 (51*)	NR	BMI: 27.2	A1c: 8.21	12.9	Insulin naive: No
Christiansen, 2003 ¹³	Insulin aspart 70/30, 201	59.3	94* (47)	NR	BMI: 28	A1c: 8.8	9.2	Insulin: 66 (33) OA agents: 78 (39)
	NPH insulin, 202	59.6	101* (50)	NR	BMI: 28.4	A1c: 8.8	10.5	Insulin and OA agents: 55 (27) Insulin: 66 (33) OA agents: 75 (37) Insulin and OA agents: 59 (29)
Coscelli, 2003 ⁶⁷	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 ⁷⁴	Total, 45	52.6	NR	NR	BMI: 35.08	NR	11.9	Insulin naive: NR OA agents: 45 (100)
Hermansen, 2002 ⁵⁸	Total, 61	60.1	40 (66*)	NR	BMI: 27.3	A1c: 8.3	11.6	Insulin naive: No Insulin: 61* (100)
Herz, 2002 ⁷¹	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 ⁷²	Insulin lispro 75/25, 71	68.1	37 (52.1)	NR	BMI: 28	A1c: 9.82	11.4	Insulin naive: No
	Glyburide, 72	67.7	32 (44.4)	NR	BMI: 27.8	A1c: 9.9	12.4	Insulin naive: No

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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/m ² Mean weight in kg	Mean A1c in % Mean FBG in mg/dL#	Mean duration of diabetes in years	Previous treatment, n (%)
Herz, 2003 ¹²	Insulin lispro 75/25, 13	54.8	10 (77*)	NR	BMI: 29.2	A1c: 7.81	NR	Insulin naive: No Insulin: 13* (100)
	NPH/regular 70/30, 12	53.6	7 (58*)	NR	BMI: 29.3	A1c: 7.6	NR	Insulin naive: No Insulin: 12* (100)
Hirao, 2008 ⁶¹	Insulin aspart 70/30, 80	58.5	47 (59*)	NR	BMI: 23.7 Weight: 62.5	A1c: 10.5	9.5	Insulin naive: No OA agents: 41 (51*)
	Insulin aspart + NPH insulin, 80	57.9	49 (61*)	NR	BMI: 23.7 Weight: 62.1	A1c: 10.7	12.2	Insulin naive: No OA agents: 39 (49*)
Holman, 2007 ³²	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	A1c: 8.6 FBG: 175	9 median (IQR: 6 - 12)	Insulin naive: Yes OA agents: 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	A1c: 8.6 FBG: 173	9 median (IQR: 6 - 14)	Insulin naive: Yes OA agents: 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	A1c: 8.4 FBG: 171	9 median (IQR: 6 - 12)	Insulin naive: Yes OA agents: 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	A1c: 8.5 FBG: 173	9 median (IQR: 6 - 13)	Insulin naive: Yes OA agents: 672 (95*)
Jacobson, 2006 ⁶⁴	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	A1c: 9.21	8.4	Insulin naive: Yes OA agents: 60 (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/m ² Mean weight in kg	Mean A1c in % Mean FBG in mg/dL#	Mean duration of diabetes in years	Previous treatment, n (%)
Joshi, 2005 ⁵²	Insulin aspart 70/30, 114	52.41	76 (67*)	NR	Weight: 70.4	A1c: 8.79 FBG: 186.59	9.53	Insulin naive: NR Insulin: 62 (54.39) OA agents: 102 (89.47)
	Insulin aspart + insulin glargine, 31	51.1	24 (77*)	NR	Weight: 69.63	A1c: 8.53 FBG: 190.23	11.98	Insulin naive: NR Insulin: 21 (67.74) OA agents: 25 (80.65)
Kann, 2006 ⁵⁰	Insulin aspart 70/30 + metformin, 128	61.5	69 (54*)	NR	BMI: 29.9 Weight: 84.2	A1c: 9.21	10.3	Insulin naive: NR
	Insulin glargine + glimepiride, 127	61	62 (49*)	NR	BMI: 30.6 Weight: 86.6	A1c: 8.9	10.2	Insulin naive: NR
Kapitza, 2004 ^{5b}	Total, 31	57	21 (68*)	NR	BMI: 29	A1c: 8.7	12	Insulin naive: No Insulin: 31* (100)
Kazda, 2006 ⁷⁶	Insulin lispro 50/50, 54	58.7	32 (59*)	NR	BMI: 31	A1c: 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	A1c: 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	A1c: 8.1 FBG: 172.8	5.5	Insulin naive: No Insulin: 0 in last 3 months
Kilo, 2003 ¹⁵	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	A1c: 9.5 FBG: 241.8	10.4	Insulin naive: Yes Insulin: 0 (0) OA agents: 46 (100) Insulin and OA agents: 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	A1c: 9.5 FBG: 242.7	10.7	Insulin naive: Yes Insulin: 0 (0) OA agents: 47 (100) Insulin and OA agents: 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	A1c: 9.3 FBG: 227.2	8.4	Insulin naive: Yes Insulin: 0 (0) OA agents: 47 (100) Insulin and OA agents: 0 (0)

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/m ² Mean weight in kg	Mean A1c in % Mean FBG in mg/dL#	Mean duration of diabetes in years	Previous treatment, n (%)
Kvapil, 2006 ⁵¹	Insulin aspart 70/30, 107	55.2	50 (47*)	NR	BMI: 30.9 Weight: 87.3	A1c: 9.6	8.2	Insulin naive: NR
	Insulin aspart 70/30 + metformin, 108	56.4	53 (49*)	NR	BMI: 30.4 Weight: 85.1	A1c: 9.3	6.7	Insulin naive: NR
	Metformin + glibenclamide, 114	58.1	52 (46*)	NR	BMI: 30.5 Weight: 84	A1c: 9.4	8.1	Insulin naive: NR
Malone, 2000 ⁴⁴ Malone, 2000 ¹⁴	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)
Malone, 2003 ⁶⁸	Insulin lispro 75/25 + metformin, 296	58	169 (57)	C: 263 (88.9) H: 22 (7.4) Other: 9 (3) African: 2 (0.7)	BMI: 29.8 Weight: 83	A1c: 9.17	8	Insulin naive: NR OA agents: 296 (100)
	Glibenclamide + metformin, 301	59	146 (49)	C: 268 (89) H: 18 (6) Other: 12 (4) African: 3 (1)	BMI: 29.6 Weight: 81.7	A1c: 9.27	7.4	Insulin naive: NR OA agents: 301 (100)
Malone, 2004 ⁶⁵	Insulin lispro 75/25 + metformin, 52	54.5 (32.3 - 79.1)	33 (63.5)	NR	BMI: 30.1 Weight: 88.5	A1c: 8.7 FBG: 150.2	8.1	Insulin naive: Yes OA agents: 52 (100)
	Insulin glargine + metformin, 53	55.3 (35.5 - 75.1)	33 (62.3)	NR	BMI: 31.7 Weight: 94.4	A1c: 8.7 FBG: 155.3	9.8	Insulin naive: Yes OA agents: 53 (100)
Malone, 2005 ⁶⁶	Insulin lispro 75/25 + metformin, 50	59.18	25 (50)	NR	BMI: 29.41 Weight: 77.82	A1c: 8.5 FBG: 155.34	13.52	Insulin naive: No Insulin: 50* (100) OA agents: 26 (52*)
	Insulin glargine + metformin, 47	59.63	18 (38)	NR	BMI: 29.64 Weight: 77.21	A1c: 8.48 FBG: 147.78	11.9	Insulin naive: No Insulin: 47* (100) OA agents: 28 (60*)

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/m ² Mean weight in kg	Mean A1c in % Mean FBG in mg/dL#	Mean duration of diabetes in years	Previous treatment, n (%)
Mattoo, 2003 ⁷⁰	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 ⁴⁸	Insulin aspart 70/30, 80	61.8	49 (61*)	NR	BMI: 29.7 Weight: 83.3	A1c: 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	A1c: 7.5	12.1	Insulin naive: No Insulin: 80 (100)
	Total, 160	62.3	112 (70*)	NR	BMI: 30.1 Weight: 86.2	A1c: 7.5	11.8	Insulin naive: No Insulin: 160 (100)
McSorley, 2002 ¹¹	Total, 13	64	8 (62*)	NR	BMI: 28.1	A1c: 7.7	13	Insulin naive: No Insulin: 13* (100)
Nauck, 2007 ⁴⁹	Insulin aspart 70/30 + metformin + sulfonylurea, 248	58	126.5 (51)	NR	BMI: 30.2 Weight: 83.4	A1c: 8.6 FBG: 203.4	10	Insulin naive: NR OA agents: 248 (100)
	Exenatide + metformin + sulfonylurea, 253	59	118.9 (47)	NR	BMI: 30.6 Weight: 85.5	A1c: 8.6 FBG: 198	9.8	Insulin naive: NR OA agents: 253 (100)
Niskanen, 2004 ⁵⁵	Total, 133	62.3	79 (59*)	NR	BMI: 28.1	A1c: 8.5	12.1	Insulin naive: No Insulin: 133* (100)
Raskin, 2005 ³⁹ Brod, 2007 ⁴¹	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	A1c: 9.7 FBG: 252 A1c > 8.5% at baseline, n (%): 10.2 (89)	9.5	Insulin naive: Yes OA agents: 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	A1c: 9.8 FBG: 243 A1c > 8.5% at baseline, n (%): 10.1 (99)	8.9	Insulin naive: Yes OA agents: 116 (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/m ² Mean weight in kg	Mean A1c in % Mean FBG in mg/dL#	Mean duration of diabetes in years	Previous treatment, n (%)
Raskin, 2007 ^{40‡}	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	A1c: 9.9 FBG: 255.6	NR	Insulin naive: Yes Insulin: 0 (0) OA agents: 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	A1c: 9.9 FBG: 239.4	NR	Insulin naive: Yes Insulin: 0 (0) OA agents: 78 (100)
Raskin, 2007 ⁶⁰	Insulin aspart 70/30, 102	53.4	46 (45*)	AA: 12* (12) C: 53* (52) Asian: 3* (3) H: 34* (33) Other: 0*(0)	BMI: 32.4	A1c: 8.1	9.2	Insulin naive: Yes Insulin: 0 (0) OA agents: 102 (100)
	Metformin and pioglitazone, 98	54.2	38 (39*)	AA: 10* (10) C: 43* (44) Asian: 4* (4) H: 36* (37) Other: 5*(5)	BMI: 33.4	A1c: 8.1	8.3	Insulin naive: Yes Insulin: 0 (0) OA agents: 98 (100)
Raz, 2003 ⁵⁷	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	A1c: 9.9 FBG: 259.8 Serum fructosamine: 398 µmol/L	10.9	Insulin naive: NR OA agents: 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	A1c: 10.3 FBG: 265.2 Serum fructosamine: 409.2 µmol/L	10.3	Insulin naive: NR OA agents: 23 (100%)
Raz, 2005 ⁵⁴	Insulin aspart 70/30, 97	55.2	63 (65)	NR	BMI: 29.5	A1c: 9.5	10	Insulin naive: NR OA agents: 97* (100)
	Insulin aspart 70/30 + pioglitazone, 93	56.7	49 (53)	NR	BMI: 29.4	A1c: 9.6	9.2	Insulin naive: NR OA agents: 93* (100)
	Glibenclamide + pioglitazone, 91	55.8	56 (62)	NR	BMI: 29.5	A1c: 9.4	9.9	Insulin naive: NR OA agents: 91* (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/m ² Mean weight in kg	Mean A1c in % Mean FBG in mg/dL#	Mean duration of diabetes in years	Previous treatment, n (%)
Roach, 1999 ⁷³	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 ¹⁰	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 ⁶⁹	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 ⁶³	Total, 20	53.5	10 (50)	AA: 4* (20) C: 16* (80)	BMI: 36.7 Weight: 108	A1c: 8.4	NR	Insulin naive: No
Robbins, 2007 ⁷⁹	Insulin lispro 50/50 + metformin, 157	57.4	79 (50.3)	AA: 9 (5.7) C: 102 (65) Asian: 22 (14) H: 24 (15.3)	BMI: 32.1 Weight: 89.1	A1c: 7.8	11.3	Insulin naive: No Insulin: 125 (79.6)
	Insulin glargine + metformin, 158	58.1	78 (49.4)	AA: 9 (5.7) C: 100 (63.3) Asian: 23 (14.6) H: 26 (16.4)	BMI: 32 Weight: 88.1	A1c: 7.8	12.5	Insulin naive: No Insulin: 123 (77.8)
Rosenstock, 2008 ⁸⁰	Insulin lispro 50/50, 187	55.4	99 (53)	AA: 25 (13.4) C: 103 (55.1) H: 49 (26.2) Other: 10 (5.3)	BMI: 34.1 Weight: 99.1	A1c: 8.83 FBG: 171.81	10.9	Insulin naive: No Insulin: 187 (100) Insulin and OA agents: 185 (98.9)
	Insulin glargine + insulin lispro, 187	54	98 (52)	AA: 18 (9.6) C: 102 (54.6) H: 53 (28.3) Other: 14 (7.5)	BMI: 34.8 Weight: 99.8	A1c: 8.89 FBG: 181.48	11.2	Insulin naive: No Insulin: 187 (100) Insulin and OA agents: 184 (98.5)
Scherntaner, 2004 ⁷⁷	Insulin lispro 50/50, 18	66.1	3 (17*)	NR	BMI: 29.5	A1c: 8.3	16.2	Insulin naive: No Insulin: 18* (100)
	NPH/regular 70/30, 17	67.8	5 (29*)	NR	BMI: 28.8	A1c: 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)

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/m ² Mean weight in kg	Mean A1c in % Mean FBG in mg/dL#	Mean duration of diabetes in years	Previous treatment, n (%)
Schwartz, 2006 ⁶²	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	A1c: 8.1 FBG: 158.7	NR	Insulin naive: No Insulin: 23 (100)
Sun, 2007 ⁷⁵	Insulin lispro 75/25, 895	62.8	439* (49.1)	AA: 161* (17.5) C: 268* (30.1) H: 63* (6.8)	Weight: 93.9	A1c: 8.6	20.5	Insulin naive: Yes
	Insulin glargine, 3624	58.4	1740* (48.5)	AA: 362* (10.3) C: 906* (25.2) H: 72* (2.4)	Weight: 93.3	A1c: 8.6	24.7	Insulin naive: Yes
	NPH/regular 70/30, 3647	65.7	1641* (44.7)	AA: 584* (16.5) C: 1204* (32.6) H: 73* (1.6)	Weight: 92.3	A1c: 8.4	18.3	Insulin naive: Yes
Tamemoto, 2007 ⁴⁷	Insulin aspart 70/30, 14	55.9	6 (54)	NR	BMI: 23.9	A1c: 9.13 FBG: 183.3	9.8	Insulin naive: NR OA agents: 14 (100)
	Insulin glargine, 20	61.7	13 (68)	NR	BMI: 25.5	A1c: 8.45 FBG: 184.1	10.4	Insulin naive: NR OA agents: 19 (100)
Tirgoviste, 2003 ⁴³	Insulin lispro 75/25, 85	58.7	30 (35*)	NR	BMI: 26.8 Weight: 74.1	A1c: 9.85 FBG: 208.8	10.3	Insulin naive: Yes OA agents: 85 (100)
Roach, 2001 ⁴²	Glibenclamide, 87	60.3	31 (36*)	NR	BMI: 27.6 Weight: 75.8	A1c: 10.07 FBG: 219.6	10.2	Insulin naive: Yes OA agents: 87 (100)
	Total, 172	59.5	61 (35*)	NR	Weight: 75	NR	10.2	Insulin naive: Yes OA agents: 172 (100)
Ushakova, 2007 ⁵⁹	Insulin aspart 70/30 TID, 104	58	17 (16.3)	NR	BMI: 29.8 Weight: 79.3	A1c: 10.4	9.9	Insulin naive: Yes OA agents: 104 (100)
	Insulin aspart 70/30 BID + metformin, 100	58.4	27 (27)	NR	BMI: 29.2 Weight: 78.4	A1c: 10.4	8.4	Insulin naive: Yes OA agents: 100 (100)
	OA agents, 104	58.4	21 (20.2)	NR	BMI: 29.3 Weight: 78	A1c: 10.1	8.3	Insulin naive: Yes OA agents: 104 (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/m ² Mean weight in kg	Mean A1c in % Mean FBG in mg/dL#	Mean duration of diabetes in years	Previous treatment, n (%)
Yamada, 2007 ⁷⁸	Insulin lispro 50/50, 15	66	12 (80*)	NR	BMI: 27	A1c: 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	A1c: 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 2002⁹ was patients with either type 1 or type 2 diabetes. The type 2 diabetic population was the same study population used for Boehm 2004.⁴⁵

‡Raskin 2007⁴⁰ was conducted among a subpopulation of Raskin 2005³⁹ who were not using thiazolidinediones.

µmol/L = micromole per liter; A1c = hemoglobinA1c; AA = African American; BMI = body mass index; BID = twice daily; C = Caucasian; dL = deciliter; FPG = fasting blood glucose; H = Hispanic; IQR = interquartile range; kg = kilogram; kg/m² = kilogram per square meter; mg/dL = milligram per deciliter; NPH = neutral protamine Hagedorn; NR = not reported; OA = oral antidiabetic medication; TID = thrice daily

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#	A1c in %#	Quality of life#
Insulin aspart 70/30 vs. long-acting insulin analogues							
Holman, 2007 ³²	GP1: Insulin aspart 70/30 (v) Start: 16 median IU/day Range: 10 – 26 IU/day T: bid D: 1 year Usual care D: 1 year GP2: Insulin detemir (v) Start: 16 median IU/day Range: 10 – 24 IU/day 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)

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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#	A1c in %#	Quality of life#
Kann, 2006 ⁵⁰	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	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*	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 A1c < 7%, n (%) GP1 42* (33.1) p: 0.2711 GP2 33* (26.2)	
	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	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*					

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#	A1c in %#	Quality of life#
Raskin, 2005 ^{39,40}	GP1: Insulin aspart 70/30 (v) Start: 10 or 12 U T: Breakfast, dinner D: Unclear	GP1 F: 118.75 [†] p: <0.05	90-min PPG - after breakfast (mg/dL) GP1 F: 153.125 [†] p: NS	GP1 F: 120.31 [†] p: <0.05	90-min PPG - after dinner (mg/dL) GP1 F: 135.5 [†] p: <0.05	GP1 B: 10* F: 6.91 (1.17) p: <0.01	
	Metformin (v) Range: 1500 – 2550 mg/day T: NR D: Unclear	GP1 F: 122.4 [†] p: NS	GP2 F: 168.75 [†]	GP1 F: 129.6 [†] p: NS	GP2 F: 171.88 [†]	GP2 F: 127.62 (40.68) p: 0.0008	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: Insulin glargine (v) Start: 10-12 U T: Bedtime D: Unclear	Fasting plasma glucose (time not specified) (mg/dL) GP1 B: 252 (67.4)	F: 172.8 [†]		Dinner postprandial glucose increment (mg/dL) GP1-GP2 : 19.386 [†] p: 0.003	GP1-GP2: -1* GP1 F: 7.4 (1.3) F-B: -2.46 (1.6)	
	Metformin (v) Range: 1500 - 2550 mg/day T: NR D: Unclear	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*				A1c < 7.0%, n (%) GP1 71.3* (66†) p: <0.001 GP2 45.6* (40†) GP1 (65) p: 0.003 GP2 (41)	
						A1c ≤ 6.5%, n (%) 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#	A1c in %#	Quality of life#
Tamemoto, 2007 ⁴⁷	<p>GP1: Insulin aspart 70/30 (v) Start: 10-16 U/day Mean: 26.7 U T: Breakfast, dinner D: 6 months Continued OA agents (NR) T: NR D: 6 months</p> <p>GP2: Insulin glargine (v) Start: 6-8 U/day T: NR D: 6 months Continued OA agents (NR) T: NR D: 6 months</p>	<p>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</p>	<p>PPG (time not specified) (mg/dL) GP1 F-B: -68 (63) p: <0.001 vs. GP2 GP2 F-B: -83 (54) GP1-GP2: 15*</p>	<p>GP1 F: 113.04 Median GP2 F: 128.52 Median</p>	<p>GP1 F-B: -1.2 (1.06) p: 0.49 GP2 F-B: -0.95 (0.84) GP1-GP2: 0*</p> <p>A1c < 7%, n (%) GP1 1 (9.1) p: NS GP2 6 (31.6)</p>	<p>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)</p> <p>Glycated hemoglobin ≤ 7.0% GP1 98 (41.7) p: 0.08 vs. GP2 GP2 116 (48.7)</p>	
Insulin aspart 70/30 vs. rapid-acting insulin analogues							
Holman, 2007 ³²	<p>GP1: Insulin aspart 70/30 (v) Start: 16 median IU/day Range: 10 – 26 IU/day T: bid D: 1 year Usual care D: 1 year</p> <p>GP2: Insulin aspart (v) Start: 18 median IU/day Range: 9 – 24 IU/day T: Breakfast, lunch, dinner D: 1 year Usual care D: 1 year</p>	<p>GP1 F-B: -45 (56) p: <0.001 vs. GP2 GP2 F-B: -23 (49) GP1-GP2: -22*</p>	<p>GP1 F: 113.04 Median GP2 F: 128.52 Median</p>	<p>GP1 F: 113.04 Median GP2 F: 128.52 Median</p>	<p>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*</p>	<p>GP1 F: 0.76 (95% CI: 0.73 – 0.8) p: overall 0.48 GP2 F: 0.76 (95% CI: 0.73 – 0.79)</p>	

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#	A1c in %#	Quality of life#
Insulin aspart 70/30 vs. rapid-acting with long-acting insulin analogues							
Joshi, 2005 ⁵²	GP1: Insulin aspart 70/30 (v) Mean: 40.19 U/day T: bid D: 12 weeks	GP1 B: 186.59 (47.35) F: 114.83 (18.68) F-B: -72* p: <0.0001	PPG (time not specified) (mg/dL) GP1 B: 287.29 (58.4) F: 171.54 (28.75) F-B: -115* p: <0.0001			GP1 B: 8.79 (1.13) F: 7.2 (0.83) F-B: -1.58 p: <0.0001	
	GP2: Insulin aspart (v) Mean: 28.26 U/day T: Before every meal D: 12 weeks	GP2 B: 190.23 (55.63) F: 110.61 (16.79) F-B: -79* p: <0.0001	GP2 B: 281.42 (68.76) F: 177.52 (24.72) F-B: -103* p: <0.0001			GP2 B: 8.53 (1.22) F: 7.37 (0.83) F-B: -1.16 p: <0.0001	
	Insulin glargine (v) Mean: 24.52 U/day T: Bedtime D: 12 weeks	GP1-GP2: 7*	F-B: -12*			GP1-GP2: -1* p: <0.05	
						A1c < 7%, n (%) GP1 52* (45.61) GP2 10* (32.26)	
Insulin aspart 70/30 vs. premixed human insulins							
Abraha-mian, 2005 ⁵³	GP1: Insulin aspart 70/30 (v) Mean: 0.49 U/kg (start), 0.61 U/kg (end) T: Breakfast, lunch, 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†)	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†)	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	
	GP2: NPH/regular 70/30 (v) Mean: 0.46 U/kg (start), 0.59 U/kg (end) T: Breakfast, dinner D: 24 weeks		90-min PPG increment - after breakfast (mg/dL) F: p: 0.0572 vs. GP2 (favoring GP1)		90-min PPG increment - after dinner (mg/dL) F: p: 0.4096		

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#	A1c in %#	Quality of life#
Boehm, 2004 ^{9,45,‡}	GP1: Insulin aspart 70/30 (v) Start: 0.57 U/kg T: Breakfast, dinner D: 24 months	GP1 B: 151.2 F: 160.56 (SE 5.04) F-B: 10*	90-min PPG - after breakfast (mg/dL) GP1 B: 212.4 F: 187.2 (SE 6.66) F-B: -25*		90-min PPG - after dinner (mg/dL) GP1 B: 181.8 F: 165.96 (SE 5.94) F-B: -16*	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	
	GP2: NPH/regular 70/30 (v) Start: 0.57 U/Kg T: Breakfast, dinner D: 24 months	GP2 B: 149.4 F: 148.32 (SE 4.86) F-B: -1* GP1-GP2: 12.06 (95% CI: -0.9 – 25.2) p: NS	GP2 B: 212.4 F: 205.2 (SE 6.48) F-B: -7* GP1-GP2: -18.18 (95% CI: -35.46 – -0.9) p: <0.05		GP2 B: 187.2 F: 183.6 (SE 5.76) F-B: -3* GP1-GP2: -18.54 (95% CI: -34.02 – -3.24) p: <0.02		
Herman-sen, 2002 ⁵⁸	GP1: Insulin aspart 70/30 (fix) Start: 0.4 U/kg T: Breakfast D: 1 day		GP1 F: 13.9 [†] GP2 F: 15.0 [†]				
	GP2: NPH/regular 70/30 (fix) Start: 0.4 U/kg T: Breakfast D: 1 day		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 ⁵⁶	GP1: Insulin aspart 70/30 (NA) T: Breakfast (15 min after) D: 1 day		2-hr PPG increment - after breakfast (mg/dL) GP1 F: 52.2 [†]				
	GP2: NPH/regular 70/30 (NA) T: Breakfast (15 min before) D: 1 day		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#	A1c in %#	Quality of life#
Kapitza, 2004 ⁵⁶	GP1: Insulin aspart 70/30 (NA) T: Breakfast (15 min after) D: 1 day		2-hr PPG increment - after breakfast (mg/dL) GP1 F: 52.2 [†]				
	GP2: NPH/regular 70/30 (NA) T: Breakfast (right before) D: 1 day		GP2 F: 81 [†]				
Kapitza, 2004 ⁵⁶	GP1: Insulin aspart 70/30 (NA) T: Breakfast (right before) D: 1 day		2-hr PPG increment - after breakfast (mg/dL) GP1 F: 81 [†]				
	GP2: NPH/regular 70/30 (NA) T: Breakfast (15 min before) D: 1 day		GP2 F: 91.8 [†]				
Kapitza, 2004 ⁵⁶	GP1: Insulin aspart 70/30 (NA) T: Breakfast (right before) D: 1 day		2-hr PPG increment - after breakfast (mg/dL) GP1 F: 81 [†]				
	GP2: NPH/regular 70/30 (NA) T: Breakfast (right before) D: 1 day		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#	A1c in %#	Quality of life#
Kilo, 2003 ¹⁵	GP1: Insulin aspart 70/30 (v) Start: 0.16 U/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	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†) 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†) 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*	
	GP2: NPH/regular 70/30 (v) Start: 0.16 U/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						
McNally, 2007 ⁴⁸	GP1: Insulin aspart 70/30 (v) Start: 100 U/mL Mean: 68.8 U Range: 6 - 238.7 U 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
	GP2: NPH/regular 70/30 (v) Start: 100 U/mL Mean: 66.6 U Range: 11.3 – 240 U T: Breakfast, dinner D: 16 weeks						

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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#	A1c in %#	Quality of life#
Insulin aspart 70/30 vs. intermediate-acting human insulins							
Christiansen, 2003 ¹³	<p>GP1: Insulin aspart 70/30 (v)</p> <p>Start: insulin naïve: 8 - 16 U/day; taking NPH prior to trial: pretrial dose</p> <p>T: Breakfast, dinner</p> <p>D: 16 weeks</p> <p>GP2: NPH insulin (v)</p> <p>Start: insulin naïve: 8 - 16 U/day; taking NPH prior to trial: pretrial dose</p> <p>T: Breakfast, dinner</p> <p>D: 16 weeks</p>	<p>GP1</p> <p>F-B: -25.2</p> <p>GP2</p> <p>F-B: -27</p> <p>GP1-GP2: 2*</p>				<p>GP1</p> <p>F-B: 0.67</p> <p>p: <0.0001 vs. baseline</p> <p>GP2</p> <p>F-B: 0.61</p> <p>p: <0.0001 vs. baseline</p> <p>GP1-GP2: 0*</p>	
Kilo, 2003 ¹⁵	<p>GP1: Insulin aspart 70/30 (v)</p> <p>Start: 0.16 U/day</p> <p>Mean: 26 U/day</p> <p>T: Dinner</p> <p>D: 12 weeks</p> <p>Metformin (fix)</p> <p>Mean: about 2200 mg</p> <p>Range: 500 - 2550 mg</p> <p>T: 1-3 times/day</p> <p>D: 4 weeks run-in, then 12 weeks</p> <p>GP2: NPH insulin (v)</p> <p>Start: 0.16 U/day</p> <p>Mean: 28 U/day</p> <p>T: Bedtime</p> <p>D: 12 weeks</p> <p>Metformin (fix)</p> <p>Mean: about 2200 mg</p> <p>Range: 500 - 2550 mg</p> <p>T: 1-3 times/day</p> <p>D: 4 weeks run-in, then 12 weeks</p>	<p>GP1</p> <p>F-B: -75 (72.3)</p> <p>GP2</p> <p>F-B: -91 (72)</p> <p>GP1-GP2: 16*</p>	<p>GP1</p> <p>B: 265† (±SE 5-10†)</p> <p>F: 190† (±SE 5-10†)</p> <p>F-B: -75</p> <p>GP2</p> <p>B: 266† (±SE 5-10†)</p> <p>F: 180† (±SE 5-10†)</p> <p>F-B: -86</p> <p>GP1-GP2: 11</p>		<p>GP1</p> <p>B: 250† (±SE 5-10†)</p> <p>F: 165† (±SE 5-10†)</p> <p>F-B: -85</p> <p>GP2</p> <p>B: 240† (±SE 5-10†)</p> <p>F: 190† (±SE 5-10†)</p> <p>F-B: -50</p> <p>GP1-GP2: -35</p>	<p>GP1</p> <p>F-B: -1.3 (SE 0.2†)</p> <p>GP2</p> <p>F-B: -1.2 (SE 0.2†)</p> <p>GP1-GP2: 0*</p>	

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#	A1c in %#	Quality of life#
Insulin aspart 70/30 vs. oral antidiabetic agents							
Bebakar, 2007 ⁴⁶	<p>GP1: Insulin aspart 70/30 (v) Start: 0.2 U/kg Range: 0.16 U/kg (qd group) - 0.43 U/kg (bid group) T: once or twice daily D: 24 weeks</p> <p>GP2: OA agents (v) T: NR D: 24 weeks</p>	<p>GP1 F-B: -39.6 (54) p: <0.005 vs. GP2 GP2 F-B: -9 (48.24) GP1-GP2: -31*</p> <p>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*</p>	<p>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*</p>	<p>GP1 F-B: -36.72 (69.66) p: <0.005 vs. GP2 GP2 F-B: 1.44 (61.92) GP1-GP2: -38*</p>	<p>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*</p>	<p>GP1 F-B: -1.16 (1.01) p: <0.005 vs. GP2 GP2 F-B: -0.58 (0.95) GP1-GP2: 0*</p> <p>A1c < 7%, n (%) GP1 32* (25) GP2 8* (12)</p>	
E-39 Kvapil, 2006 ⁵¹	<p>GP1: Insulin aspart 70/30 (v) Start: 0.3 U/kg Mean: 0.51 U/kg T: Breakfast, dinner D: 16 weeks</p> <p>GP2: Metformin (fix) Mean: 1660 mg daily Range: 500 - 3000 mg T: NR D: 16 weeks</p> <p>Glibenclamide (v) Start: 1.75 mg Mean: 2.33 (start), 6.58 mg daily (end) T: once or twice daily D: 16 weeks</p>	<p>GP1-GP2: -0.18 (SE 4.86) p: NS</p>	<p>90-min PPG - after breakfast (mg/dL) GP1-GP2: -5.22 (SE 7.2) p: NS</p>	<p>GP1-GP2: 10.26 (SE 6.12) p: NS</p>	<p>90-min PPG - after dinner (mg/dL) GP1-GP2: 2.7 (SE 6.66) p: NS</p>	<p>GP1-GP2: 0.2 (SE 0.15) p: NS</p>	

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#	A1c in %#	Quality of life#
Kvapil, 2006 ⁵¹	<p>GP1: Insulin aspart 70/30 (v) Start: 0.2 U/kg Mean: 0.3 U/kg T: Breakfast, dinner D: 16 weeks Metformin (fix) Mean: 1660 mg daily Range: 500 - 3000 mg T: NR D: 16 weeks</p> <p>GP2: Metformin (fix) Mean: 1660 mg daily Range: 500 - 3000 mg T: NR D: 16 weeks</p> <p>Glibenclamide (v) Start: 1.75 mg Mean: 2.33 (start), 6.58 mg daily (end) T: once or twice daily D: 16 weeks</p>	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	

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#	A1c in %#	Quality of life#
Raskin, 2007 ⁶⁰	GP1: Insulin aspart 70/30 (v) Start: 6 U bid Mean: 0.6 U/kg/day T: Breakfast, dinner D: 34 weeks Metformin (fix) Mean: 2446 mg T: NR D: 34 weeks Pioglitazone (fix) Mean: 32.5 mg T: NR D: 34 weeks GP2: Metformin (fix) Mean: 2439 mg T: NR D: Unclear Pioglitazone (fix) Mean: 31.7 T: NR D: Unclear	GP1 B: 173.16 (39.78) p: NS F: 129.78 (50.04) p: < 0.001 F-B: -44.1 (49.86) p: < 0.001 GP2 B: 163.26 (35.46) F: 162.18 (40.86) F-B: 1.08 (43.56) GP1-GP2: -45* Met target FBG values of 79.2 – 109.8 mg/dL (4.4 - 6.1 mmol/L) GP1 34* (37) GP2 2* (2)	GP1 B: 167.4† (SE 7.2†) F: 124.2 † (SE 3.6†) p: < 0.05 F-B: 43 GP2 B: 178.2† (SE 7.2 †) F: 156.6 † (SE 7.2 †) F-B: 22 GP1-GP2: 21*	GP1 B: 8* F: 6.5 (1) p: < 0.0001 F-B: -1.5 (1.1) p: <0.05 vs. baseline; < 0.0001 vs. GP2 GP2 B: 8* F: 7.8 (1.2) F-B: -0.2 (0.9) p: <0.05 vs. baseline GP1-GP2: -2* A1c < 7.0%, n (%) GP1 71* (76) p: < 0.001 GP2 21* (24) A1c ≤ 6.5%, n (%) GP155 (59†) p: < 0.001 GP2 10 (11†)			

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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#	A1c in %#	Quality of life#
Raz, 2003 ⁵⁷	<p>GP1: Insulin aspart 70/30 (v) Start: 6 - 8 U bid T: Breakfast, dinner D: 6 weeks</p> <p>Rosiglitazone (fix) Start: 4 mg T: Breakfast D: 6 weeks</p> <p>GP2: Glibenclamide (fix) Range: 7.5 – 15 mg T: Dinner D: 6 weeks</p> <p>Rosiglitazone (fix) Start: 4 mg T: Breakfast D: 6 weeks</p>	<p>GP1 F-B: 58 p: NS vs. GP2 GP2 F-B: 34.2 GP1-GP2: 24*</p> <p>GP2 F: 169 (65) F-B: -2 p: NS GP1-GP2: -14*</p>	<p>PPG (time not specified) (mg/dL) GP1 F-B: 80.6 GP2 F-B: 52.9 GP1-GP2: 28*</p> <p>90-min PPG - after breakfast (mg/dL) GP1 F: 196.2[†] GP2 F: 223.2[†]</p>	<p>GP1 F-B: 36.2 p: NS vs. GP2 GP2 F-B: 43.3 GP1-GP2: -7*</p> <p>90-min PPG - after dinner (mg/dL) GP1 F: 199.8[†] GP2 F: 212.4[†]</p> <p>90-min PPG increment - after dinner (mg/dL) GP1-GP2: -8.1 (8.46) p: NS</p>	<p>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*</p> <p>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*</p>		
Raz, 2005 ⁵⁴	<p>GP1: Insulin aspart 70/30 (v) Start: 0.3 U/kg Mean: 0.7 U/kg T: Breakfast, dinner D: 18 weeks</p> <p>GP2: Glibenclamide (v) Start: 5 to 10 mg Mean: 14 mg T: Breakfast D: 18 weeks</p> <p>Pioglitazone (fix) Start: 30 mg Mean: 30 mg T: Breakfast D: 18 weeks</p>	<p>GP1 B: 178* F: 162[†] F-B: -16 p: NS GP2 B: 171* F: 169 (65) F-B: -2 p: NS GP1-GP2: -14*</p>	<p>90-min PPG - after breakfast (mg/dL) GP1 F: 196.2[†] GP2 F: 223.2[†]</p>	<p>90-min PPG - after dinner (mg/dL) GP1 F: 199.8[†] GP2 F: 212.4[†]</p> <p>90-min PPG increment - after dinner (mg/dL) GP1-GP2: -8.1 (8.46) p: NS</p>	<p>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*</p>		

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#	A1c in %#	Quality of life#
Raz, 2005 ⁵⁴	<p>GP1: Insulin aspart 70/30 (v) Start: 0.2 U/kg Mean: 0.5 U/kg T: Breakfast, dinner D: 18 weeks</p> <p>Pioglitazone (fix) Start: 30 mg Mean: 30 mg T: Breakfast D: 18 weeks</p> <p>GP2: Glibenclamide (v) Start: 5 to 10 mg Mean: 14 mg T: Breakfast D: 18 weeks</p> <p>Pioglitazone (fix) Start: 30 mg Mean: 30 mg T: Breakfast D: 18 weeks</p>	<p>GP1 B: 184* F: 153 (45) p: 0.012 vs GP2 F-B: -31 p: NS</p> <p>GP2 B: 171* F: 169 (65) F-B: -2 p: NS GP1-GP2: -29*</p>	<p>90-min PPG - after breakfast (mg/dL) GP1 F: 178.2[†] GP2 F: 223.2[†]</p>		<p>90-min PPG increment - after dinner (mg/dL) F: 178.2[†] GP2 F: 212.4[†] GP1-GP2: -12.96 (8.64) p: NS</p>	<p>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</p>	

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#	A1c in %#	Quality of life#
Ushakova, 2007 ⁵⁹	GP1: Insulin aspart 70/30 (v) Start: 0.3 - 0.5 U/kg Mean: 55.5 U T: bid for 2 weeks, then tid D: 16 weeks GP2: Continuation of OA agents (v) T: NR D: 16 weeks	GP1 B: 235.8† F: 163.8† F-B: 72 GP2 B: 225† F: 171† F-B: 54 GP1-GP2: 18*		GP1 B: 261† F: 156.6† F-B: 105 GP2 B: 243† F: 178.2† F-B: 65 GP1-GP2: 40*		GP1 F-B: -2.9 (1.5) p: < 0.001 vs. GP2 GP2 F-B: -2.1 (1.4) GP1-GP2: -0.65 (95% CI: -0.958 – -0.337) p: <0.001 vs. GP2 A1c ≤ 7.0%, n (%) GP1 42 (42) p: 0.012 GP2 27 (26.2) A1c after 3-month extension GP1 F: 7.2 (1.2) A1c ≤ 7.0% after 3-month extension, n (%) GP1 22 (51.2)	Diabetes Health Profile GP1 F-B: p: <0.001 vs. baseline GP2 F-B: p; <0.001 vs. baseline

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#	A1c in %#	Quality of life#
Ushakova, 2007 ⁵⁹	<p>GP1: Insulin aspart 70/30 (v) Start: 0.3 - 0.5 U/kg Mean: 44.8 U T: Breakfast, dinner D: 16 weeks metformin (varied) Start: 500 mg qd or bid or 850 mg qd T: NR D: 14 weeks (started after 2 weeks)</p> <p>GP2: Continuation of OA agents (v) T: NR D: 16 weeks</p>	<p>GP1 B: 234† F: 160.2† F-B: 74 GP2 B: 225† F: 171† F-B: 54 GP1-GP2: 20*</p>		<p>GP1 B: 252† F: 172.8† F-B: 80 GP2 B: 243† F: 178.2† F-B: 65 GP1-GP2: 15*</p>		<p>GP1 F-B: -3 (1.6) p: < 0.001 vs. GP2 GP2 F-B: -2.1 (1.4) GP1-GP2: -0.85 vs (95% CI: -1.163 – -0.537) p: <0.001</p> <p>A1c ≤ 7.0%, n (%) GP1 45 (45) p: 0.002 GP2 27 (26.2)</p> <p>A1c after 3-month extension GP1 F: 7.2 (1.4)</p> <p>A1c ≤ 7.0% after 3-month extension, n (%) GP1 23 (54.8)</p>	<p>Diabetes Health Profile GP1 F-B: p: <0.001 vs. baseline GP2 F-B: p; <0.001 vs. baseline</p>

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#	A1c in %#	Quality of life#
Insulin aspart 70/30 vs. exenatide							
Nauck, 2007 ⁴⁹	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 A1c ≤ 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#	A1c in %#	Quality of life#
Insulin aspart 70/30 vs. insulin lispro 75/25							
Hermansen, 2002 ⁵⁸	GP1: Insulin aspart 70/30 (fix) Start: 0.4 U/kg T: Breakfast D: 1 day		GP1 F: 13.9 [†] GP2 F: 14.5 [†]				
	GP2: Insulin lispro 75/25 (fix) Start: 0.4 U/kg T: Breakfast D: 1 day		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 ⁵⁵	GP1: Insulin aspart 70/30 (v) Mean: 0.65 to 0.67 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#	A1c in %#	Quality of life#
Insulin aspart 70/30 vs. insulin aspart 70/30 + oral antidiabetic agents							
Kvapil, 2006 ⁵¹	<p>GP1: Insulin aspart 70/30 (v) Start: 0.3 U/kg Mean: 0.51 U/kg T: Breakfast, dinner D: 16 weeks</p> <p>GP2: Insulin aspart 70/30 (v) Start: 0.2 U/kg Mean: 0.3 U/kg T: Breakfast, dinner D: 16 weeks Metformin (fix) Mean: 1660 mg daily Range: 500 - 3000 mg T: NR D: 16 weeks</p>	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	
E-48 Raz, 2005 ⁵⁴	<p>GP1: Insulin aspart 70/30 (v) Start: 0.3 U/kg Mean: 0.7 U/kg T: Breakfast, dinner D: 18 weeks</p> <p>GP2: Insulin aspart 70/30 (v) Start: 0.2 U/kg Mean: 0.5 U/kg T: Breakfast, dinner D: 18 weeks Pioglitazone (fix) Start: 30 mg Mean: 30 mg T: Breakfast D: 18 weeks</p>	<p>GP1 B: 178* F: 162[†] F-B: -16 p: NS</p> <p>GP2 B: 184* F: 153 (45) F-B: -31 p: NS GP1-GP2: 15*</p>	<p>90-min PPG - after breakfast (mg/dL) GP1 F: 196.2[†]</p> <p>GP2 F: 178.2[†]</p>		<p>90-min PPG - after dinner (mg/dL) GP1 F: 199.8[†] GP2 F: 178.2[†]</p> <p>90-min PPG increment - after dinner (mg/dL) GP1-GP2: 4.86 (8.46) p: NS</p>	<p>GP1 B: 9.5 (1.3) F: 9 (1.3) F-B: -0.5 p: NS</p> <p>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</p>	

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#	A1c in %#	Quality of life#
Ushakova, 2007 ⁵⁹	<p>GP1: Insulin aspart 70/30 (v) Start: 0.3 - 0.5 U/kg Mean: 55.5 U T: bid for 2 weeks, then tid D: 16 weeks</p> <p>GP2: Insulin aspart 70/30 (v) Start: 0.3 - 0.5 U/kg Mean: 44.8 U T: Breakfast, dinner D: 16 weeks</p> <p>Metformin (v) Start: 500 mg qd or bid or 850 mg qd T: NR D: 14 weeks (started after 2 weeks)</p>	<p>GP1 B: 235.8 † F: 163.8 † F-B: 72</p> <p>GP2 B: 234 † F: 160.2 † F-B: 74 GP1-GP2: -2*</p>	<p>GP1 B: 261 † F: 156.6 † F-B: 105</p> <p>GP2 B: 252 † F: 172.8 † F-B: 80 GP1-GP2: 25*</p>	<p>GP1 B: 261 † F: 156.6 † F-B: 105</p> <p>GP2 B: 252 † F: 172.8 † F-B: 80 GP1-GP2: 25*</p>	<p>GP1 F-B: -2.9 (1.5)</p> <p>GP2 F-B: -3 (1.6)</p> <p>GP1-GP2: 0.20 (95% CI: -0.108–0.514)</p> <p>A1c ≤ 7.0%, n (%)</p> <p>GP1 42 (42) p: 0.012</p> <p>GP2 45 (45) p: 0.002</p> <p>A1c after 3-month extension</p> <p>GP1 F: 7.2 (1.2)</p> <p>GP2 F: 7.2 (1.4)</p> <p>A1c ≤ 7.0% after 3-month extension, n (%)</p> <p>GP1 22 (51.2)</p> <p>GP2 23 (54.8)</p>	<p>Diabetes Health Profile GP1 F-B: p: <0.001 vs. baseline</p> <p>GP2 F-B: p: <0.001 vs. baseline</p>	

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#	A1c in %#	Quality of life#
Insulin aspart 70/30 vs. rapid-acting insulin analogues with intermediate-acting human insulin							
Hirao, 2008 ⁶¹	GP1: Insulin aspart 70/30 (NR) T: BID D: 6 months					GP1 B: 10.2 (2.1) F: 7.6 (1.3) p: NS F-B: -2.5	
	GP2: Insulin aspart (NR) T: TID D: 6 months NPH insulin (unclear) T: Optional multiple daily injections D: 6 months					GP2 B: 10.4 (2) F: 7.8 (1.8) F-B: -2.5 GP1-GP2: 0*	
						A1c < 7.0%, n (%) GP1 (32.1) p: NS GP2 (32.8)	
						A1c < 6.5%, n (%) GP1 (17.9) GP2 (16.4)	

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#	A1c in %#	Quality of life#
Insulin lispro 75/25 vs. long-acting insulin analogues							
Cox, 2007 ⁷⁴	GP1: Insulin lispro 75/25 (v) T: Breakfast, dinner D: 12 weeks Metformin (NR) 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#	A1c in %#	Quality of life#
Jacobson, 2006 ⁶⁴	GP1: Insulin lispro 50/50 (v) Mean: 0.353 IU/kg; 36.73 IU T: Breakfast, lunch D: 4 months	GP1 F: 130† (25†) p: NS	GP1 F: 153.5 (35.6) p: 0.0034	GP1 F: 123.1 (36.1) p: 0.0205	GP1 F: 145.4 (38.2) p: 0.0066	Overall results GP1 B: 8* F: 7.08 (0.11) p: 0.003	
	Insulin lispro 75/25 (v) T: Dinner D: 4 months Existing OA agents (NR) T: NR D: 4 months	GP2 F: 125† (15†)	GP2 F: 172.1 (35)	GP2 F: 139 (41.9)	GP2 F: 161.9 (42.3)	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*	
	GP2: Insulin glargine (v) Mean: 0.276 IU/kg; 27.98 IU T: Bedtime D: 4 months Existing OA agents (NR) T: NR D: 4 months					1 st per. results GP1 F: 6.97 (0.62†) GP2 F: 7.32 (0.93†)	
						2 nd per. results GP1 F: 7.22 (0.77†) GP2 F: 7.33 (0.92†)	
						A1c ≤ 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#	A1c in %#	Quality of life#
Malone, 2004 ⁶⁵	GP1: Insulin lispro 75/25 (v)	GP1	GP1		GP1	GP1	
	Mean: 0.62 U/kg	B: 150*	F: 156.4 (43.6)		F: 164.8 (42.5)	B: 8.7 (1.3)	
	T: Breakfast, dinner	F: 139.3 (36.6)	p: 0.012		p: <0.001	F: 7.4 (1.1)	
	D: 16 weeks	p: <0.001	GP2		GP2	p: 0.002	
	Metformin (NR)	F-B: -11.3 (44.5)	F: 171.1 (44.9)		F: 193.8 (51)	F-B: -1.32 (1.01)	
	Mean: 1945 mg	p: 0.001 vs. GP2				p: 0.003 vs. GP2;	
	Range: 1500 - 2550 mg	GP2	Met target 2-hr		Met target 2-hr	<0.001 vs.	
	T: NR	B: 153*	PPG of 144 to 180		PPG of 144 to 180	baseline	
	D: 16 weeks	F: 123.9 (34.9)	mg/dL, n (%)		mg/dL, n (%)	GP2	
		F-B: -29 (47.4)	GP1		GP1	B: 8.7 (1.3)	
	GP2: Insulin glargine (v)	GP1-GP2: 18*	55 (80)		50 (72)	F: 7.8 (1.1)	
	Mean: 0.57 U/kg		p: 0.036		p: <0.001	F-B: -0.93 (0.89)	
	T: Bedtime	Met target FBG of	GP2		GP2	p: <0.001 vs.	
	D: 16 weeks	90 to 126 mg/dL, n	43 (63)		29 (43)	baseline	
	Metformin (NR)	(%)				GP1-GP2: 0*	
	Mean: 1997 mg	GP1					
	Range: 1500 - 2550 mg	31 (45)				A1c ≤ 7.0%, n (%)	
	T: NR	p: 0.019				GP1	
	D: 16 weeks	GP2				30 (42)	
		44 (65)				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#	A1c in %#	Quality of life#
Malone, 2005 ⁶⁶	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* A1c ≤ 7.0%, n (%) GP1 (30) p: 0.002 GP2 (12) A1c ≤ 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#	A1c in %#	Quality of life#
Roach, 2006 ⁶³	<p>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 OA agents (NR) Start: Current dose T: NR D: 12 weeks Metformin (v) Start: 500 mg qd T: NR D: 12 weeks</p> <p>GP2: Insulin glargine (v) Mean: 44 U Range: 14 - 100 U T: Breakfast D: 12 weeks OA agents (NR) Start: Current dose T: NR D: 12 weeks Metformin (v) Start: 500 mg qd T: NR D: 12 weeks</p>	<p>GP1 F: 104.4 (20.16) p: 0.649 GP2 F: 99 (38.52)</p>	<p>GP1 F: 187.2 (43.2) p: 0.551 GP2 F: 180 (37.8)</p>	<p>GP1 F: 91.8 (17.1) p: 0.141 GP2 F: 100.8 (25.38)</p>	<p>GP1 F: 144 (39.24) p: 0.005 GP2 F: 176.4 (36)</p>	<p>GP1 F: 6.9 (0.52) p: 0.035 GP2 F: 7.3 (0.81)</p>	
Sun, 2007 ⁷⁵	<p>GP1: Insulin lispro 75/25 (NR) T: bid D: 18 months</p> <p>GP2: Insulin glargine (NR) T: qd D: 18 months</p>					<p>GP1 B: 8.6 (3.7) F: 8* F-B: -0.87 GP2 B: 8.6 (3.5) F: 8* F-B: -0.71 GP1-GP2: -0.16 p: <0.05</p>	

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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#	A1c in %#	Quality of life#
Insulin lispro 75/25 vs. premixed human insulins							
Coscelli, 2003 ⁶⁷	GP1: Insulin lispro 75/25 (v) Mean: 38.1 Range: 12 - 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: 12.2 (48.01) p: <0.05 GP2 F: 35.5 (36.92)		
	GP2: NPH/regular 70/30 (v) Mean: 37.3 Range: 10 - 72 T: Breakfast, dinner D: 12 days Diet/exercise D: 12 days		2-hr PPG excursion GP1 F: 2.4 (48.9) p: 0.08 GP2 F: 17.9 (41.43)				
E-56 Hermansen, 2002 ⁵⁸	GP1: Insulin lispro 75/25 (fix) Start: 0.4 U/kg T: Breakfast D: 1 day		GP1 F: 14.5 [†] GP2 F: 15.0 [†]				
	GP2: NPH/regular 70/30 (fix) Start: 0.4 U/kg T: Breakfast D: 1 day		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#	A1c in %#	Quality of life#
Herz, 2002 ⁷¹	GP1: Insulin lispro 75/25 (v) Mean: 26.1 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 ¹²	GP1: Insulin lispro 75/25 (v) Mean: 31.6 [¶] (morning) and 26.8 [¶] U (evening) and 32.4 [§] (morning) and 27.6 [§] U (evening) T: Breakfast, dinner D: 4 weeks	GP1 F: 117 [†] GP2 F: 117 [†]	GP1 F: 223.2 [†] GP2 F: 259.2 [†]	GP1 F: 135 [†] GP2 F: 135 [†]	GP1 F: 181.8 [†] GP2 F: 201.6 [†]		
	GP2: NPH/regular 70/30 (v) Mean: 32.3 [¶] (morning), 26.4 [¶] U (evening) and 33.3 [§] (morning), 27.5 [§] U (evening) T: Breakfast, dinner D: 4 weeks		2-hr PPG excursion GP1 F: 99 (SE 6.12) p: 0.002 GP2 F: 129.6 (SE 6.12)		2-hr PPG excursion GP1 F: 43.2 (SE 4.86) p: 0.018 GP2 F: 61.2 (SE 4.86)		
Malone, 2000 ⁴⁴	GP1: Insulin lispro 75/25 (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)				
	GP2: NPH/regular 70/30 (fix) Mean: 35.4 U (0.43 U/kg) T: Breakfast D: 2 days		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#	A1c in %#	Quality of life#
Mattoo, 2003 ⁷⁰	GP1: Insulin lispro 75/25 (NR) 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)	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)		
	GP2: NPH/regular 70/30 (NR) Mean: 20 U (morning), 32 U (evening) T: Breakfast, dinner D: 2 weeks		2-hr PPG excursion GP1 F: 48.6 (57.6) p: 0.397 GP2 F: 54 (55.8)		2-hr PPG excursion GP1 F: 61.2 (52.2) p: 0.007 GP2 F: 72 (57.6)		
Roach, 1999 ⁷³	GP1: Insulin lispro 75/25 (v) Mean: 0.37 (morning), 0.28 U/kg (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	
	GP2: NPH/regular 70/30 (v) Mean: 0.36 (morning), 0.27 (evening) T: Breakfast, dinner D: 13 weeks						
Schwartz, 2006 ⁶²	GP1: Insulin lispro 75/25 (fix) Start: 2/3 of 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				
	GP2: NPH/regular 70/30 (fix) Start: 2/3 of usual daily dose Mean: 44.1 U T: Breakfast D: 1 day						

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#	A1c in %#	Quality of life#
Sun, 2007 ⁷⁵	GP1: Insulin lispro 75/25 (NR) T: bid D: 18 months					GP1 B: 8.6 (3.7) F: 8* F-B: -0.87	
	GP2: NPH/regular 70/30 (unclear) T: bid D: 18 months					GP2 B: 8.4 (3.9) F: 7* F-B: -0.75 GP1-GP2: -0.16 p: <0.05	
Insulin lispro 75/25 vs. oral antidiabetic agents							
Herz, 2002 ⁷²	GP1: Insulin lispro 75/25 (v) Start: 0.3 - 0.5 U/kg Mean: 0.46 U/kg 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	GP1 B: 255.6 (SE 9) p: 0.621 vs. GP2 F: 174.96 (SE 6.66) p: <0.001 vs. GP2	GP1 B: 222.48 (SE 8.82) p: 0.216 vs. GP2 F: 175.68 (SE 5.94) p: 0.120 vs. GP2	GP1 B: 241.2 (SE 9.54) p: 0.711 vs. GP2 F: 181.98 (SE 6.84) p: <0.001 vs. GP2	GP1 B: 9.82 (1.51) F: 8.64 (SE 0.17) p: <0.001 vs. GP2 0.18) p: 0.001 vs. GP2	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
	GP2: Glyburide (fix) Start: 15 mg/day T: Breakfast, dinner D: 16 weeks	GP2 F-B: -52.74 (SE 5.94) p: <0.001 vs. GP2	GP2 F-B: -80.82 (SE 9) p: <0.001 vs. GP2	GP2 F-B: -47.34 (SE 7.92) p: 0.002 vs. GP2	GP2 F-B: -58.86 (SE 8.82) 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*	Willingness to continue treatment GP1 (92) p: 0.041 GP2 (79)
		GP2 B: 187.74 (SE 4.68) F: 176.76 (SE 5.22) F-B: -8.82 (SE 5.04) GP1-GP2: -44*	GP2 B: 261.18 (SE 7.02) F: 236.52 (SE 7.02) F-B: -22.5 (SE 7.02) GP1-GP2: -59*	GP2 B: 207.18 (SE 8.64) F: 189.9 (SE 7.02) F-B: -14.76 (SE 6.48) GP1-GP2: -32*	GP2 B: 245.88 (SE 8.28) F: 227.52 (SE 7.56) F-B: -14.94 (SE 7.56) GP1-GP2: -44*		

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#	A1c in %#	Quality of life#
Malone, 2003 ⁶⁸	GP1: Insulin lispro 75/25 (v)	GP1	GP1			Test meal patients	
	Mean: 0.19 (morning), 0.14 U/kg (evening)	B: 239.4 (68.22)	B: 252 (+/- SE 246.6 - 257.4)			GP1	
	T: Breakfast, dinner	F: 156.06 Median (60.48)	F: 147.6 (+/- SE 145.8 - 151.2)			B: 9.64 (1.6)	
	D: 16 weeks	F-B: -83*	F-B: -104*			F: 7.29 (1.12)	
	Metformin (v)	GP2	GP2			p: 0.192 vs. GP2	
	Mean: 1813 mg/day	B: 233.82 (68.04)	GP2			F-B: -3*	
	Range: 1500 - 2550 mg/day	F: 169.74 Median (61.02)	B: 259.2 (+/- SE 252 - 273.6)			GP2	
	T: 2 to 3 times/day	F-B: -64*	F: 190.8 (+/- SE 185.4 - 199.8)			B: 9.78 (1.83)	
	D: 16 weeks	GP1-GP2: -19* p: 0.173	F-B: -68*			F: 7.53 (1.27)	
	GP2: Metformin (v)		GP1-GP2: -36*			F-B: -2*	
Mean: 1968 mg/day			2-hr PPG (time not specified) (mg/dL)			All patients	
Range: 1500 - 2550 mg/day			GP1			GP1	
T: 2 to 3 times/day			F-B: -124.02 (84.42) p: 0.007			B: 9.17 (1.5)	
D: 16 weeks			GP2			F: 7.29 (1.00)	
Glibenclamide (v)			F-B: -68.94 (84.96)			p: 0.661 vs. GP2	
Mean: 14.2 mg/day			GP1-GP2: -55*			F-B: -1.87 (1.35)	
T: NR						p: <0.001	
D: 16 weeks			2-hr PPG excursion (time not specified) (mg/dL)			GP2	
			GP1			B: 9.27 (1.55)	
			F-B: -40.86 (69.66) p: 0.009			F: 7.33 (1.14)	
			GP2			F-B: -1.98 (1.28)	
			F-B: -3.96 (35.82)			p: <0.001	
			GP1-GP2: -37*			GP1-GP2: 0*	
						A1c < 7.0%, (%)	
						GP1	
						(40)	
						GP2	
						(41)	
						A1c < 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#	A1c in %#	Quality of life#
Tirgoviste, 2003 ⁴³	GP1: Insulin lispro 75/25 (v) Start: 0.3 - 0.5 U/kg T: Breakfast, dinner D: 16 weeks	GP1 B: 221* F: 171 F-B: -50.4 p: <0.01	GP1 B: 279* F: 187.2 F-B: -91.8 p: <0.001	GP1 B: 233* F: 192.6 F-B: -39.6 p: <0.05	GP1 B: 272* F: 192.6 F-B: -79.2 p: <0.001	GP1 B: 9* F: 8.5 (1.3) p: 0.001 F-B: -1.4 p: 0.004	
	GP2: Glibenclamide (v) Start: 15 mg T: Breakfast, dinner D: 16 weeks	GP2 B: 209* F: 189 F-B: -19.8 GP1-GP2: -30*	GP2 B: 265* F: 234 F-B: -30.6 GP1-GP2: -61*	GP2 B: 219* F: 205.2 F-B: -14.4 GP1-GP2: -26*	GP2 B: 261* F: 234 F-B: -27 GP1-GP2: -52*	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 ⁶⁹	GP1: Insulin lispro 75/25 (v) Mean: 31.3 (morning), 27.6 U (evening) T: Breakfast, 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)			GP1 F: 8.14 (SE 1.07) p: 0.919 GP2 F: 8.14 (SE 1.14)	
	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		2-hr PPG excursion GP1 F: 63 (SE 5.04) p: <0.001 GP2 F: 25.2 (SE 5.04)				
Schwartz, 2006 ⁶²	GP1: Insulin lispro 75/25 (fix) Start: 2/3 of usual daily dose Mean: 44.1 U T: Breakfast D: 1 day		GP1 F: 198 (67.5) p: <0.05 GP2 F: 159 (52.3) p: <0.05				
	GP2: Insulin lispro 50/50 (fix) Start: 2/3 of usual daily dose Mean: 43.8 U T: Breakfast D: 1 day						

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#	A1c in %#	Quality of life#
Insulin lispro 50/50 vs. long-acting insulin analogues							
Kazda, 2006 ⁷⁶	GP1: Insulin lispro 50/50 (v) Start: 0.30 IU/kg Mean: 0.59 IU/kg T: Breakfast, lunch, dinner D: 24 weeks	GP1 B: 167.4 (37.8) F: 151* F-B: -16.2 (32.4) p: <0.001 vs. GP2	GP1 B: 214.2 (50.4) F: 164* F-B: -50.4 (52.2) p: 0.43 vs. GP2	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*	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 (non validated): proportion with high or very high treatment satisfaction GP1 B: 18.5% F: 63% GP2 B: 26.4% F: 50.9%
	GP2: Insulin glargine (v) Start: 0.16 IU/kg Mean: 0.43 IU/kg T: Bedtime D: 24 weeks	GP2 B: 172.8 (43.2) F: 126* F-B: -46.8 (43.2) GP1-GP2: 31*	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*	GP2 B: 174.06 [†] (SE 5.4 [†]) F: 159.12 [†] (SE 7.56 [†]) F-B: -14.94* GP1-GP2: -7.56*	GP2 B: 208.44 [†] (SE 7.38 [†]) F: 207 [†] (SE 7.38 [†]) F-B: -1.44* GP1-GP2: -46.62*	GP2 B: 8.1 (1.3) F: 8* F-B: -0.3 (1.1) GP1-GP2: -1* A1c < 7%, n (%) GP1 29* (59.3) GP2 12* (24.5)	

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#	A1c in %#	Quality of life#
Robbins, 2007 ⁷⁹	GP1: Insulin lispro 50/50 (v) Mean: 0.7 U/kg T: Breakfast, lunch, dinner D: 24 weeks Metformin (fix) Mean: 1641 mg T: bid D: 24 weeks	GP1 B: 152† (95% CI: 146† – 158†) F: 146 (33) p: < 0.001 vs GP2 F-B: 6 GP2 B: 148† (95% CI: 143† – 153†) F: 118 (29) F-B: 30 GP1-GP2: -24*	GP1 B: 183† (95% CI: 177† – 191†) F: 156 (39) p: 0.03 vs. GP2 F-B: 27 GP2 B: 180† (95% CI: 174† – 186†) F: 166 (46) F-B: 14 GP1-GP2: 13*	GP1 B: 168† (95% CI: 161† – 174†) F: 149 (36) p: 0.04 vs GP2 F-B: 19 GP2 B: 170† (95% CI: 163† – 177†) F: 160 (50) F-B: 10 GP1-GP2: 9*	GP1 B: 183† (95% CI: 174† – 190†) F: 157 (40) p: <0.001 vs GP2 F-B: 26 GP2 B: 183† (95% CI: 176† – 191†) F: 193 (57) F-B: -10 GP1-GP2: 36*	GP1 B: 7.8 (0.9) p: F: 7.1 (0.9) p: <0.001 vs. GP2 F-B: -0.7 (0.9) p: <0.001 vs GP2 GP2 B: 7.8 (1) F: 7.5 (1) F-B: -0.4 (0.9) GP1-GP2: -1*	
	GP2: Insulin glargine (v) Mean: 0.6 U/kg T: Bedtime D: 24 weeks Metformin (fix) Mean: 1636 mg T: bid D: 24 weeks	GP2 F: 118 (29) F-B: 30 GP1-GP2: -24*	GP2 F: 166 (46) F-B: 14 GP1-GP2: 13*	GP2 F: 160 (50) F-B: 10 GP1-GP2: 9*	GP2 F: 193 (57) F-B: -10 GP1-GP2: 36*	A1c ≤ 7.0%, n (%) GP1 85 (56.3) p: 0.005 vs GP2 GP2 58 (39.7) F-B: -8 (50) p: < 0.001 vs. GP2 GP2 46 (30.5) p: 0.001 vs GP2 GP2 21 (14.4)	

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#	A1c in %#	Quality of life#
Insulin lispro 50/50 vs. rapid-acting insulin analogues							
Kazda, 2006 ⁷⁶	GP1: Insulin lispro 50/50 (v) Start: 0.30 IU/kg mean Mean: 0.59 IU/kg T: Breakfast, lunch, dinner D: 24 weeks	GP1 B: 167.4 (37.8) F: 151* F-B: -16.2 (32.4)	GP1 B: 214.2 (50.4) F: 164* F-B: -50.4 (52.2)	GP1 B: 166.5 [†] (SE 5.4 [†]) F: 144 [†] (SE 7.56 [†]) F-B: -22.5*	GP1 B: 198 [†] (SE 5.94 [†]) F: 149.94 [†] (SE 5.94 [†]) F-B: -48.06*	GP1 B: 8.1 (1.2) F: 7* F-B: -1.2 (1.1)	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%
	GP2: Insulin lispro (v) Start: 0.25 IU/kg mean Mean: 0.50 IU/kg T: Breakfast, lunch, dinner D: 24 weeks	GP2 B: 176.4 (50.4) F: 160* F-B: -16.2 (39.6) GP1-GP2: 0*	GP2 B: 205.2 (61.2) F: 151* F-B: -54 (63) GP1-GP2: 4*	GP2 B: 169.38 [†] (SE 5.4 [†]) F: 145.44 [†] (SE 7.56 [†]) F-B: -23.94* GP1-GP2: -1.44	GP2 F-B: -64.26* GP1-GP2: 16.2	GP2 B: 8.2 (1.2) F: 7* F-B: -1.1 (1.1) GP1-GP2: 0* A1c < 7%, n (%) GP1 29* (59.3) GP2 20* (40.4)	

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#	A1c in %#	Quality of life#
Insulin lispro 50/50 vs. rapid-acting with long-acting insulin analogues							
Rosenstock, 2008 ⁸⁰	<p>GP1: Insulin lispro 50/50 (v) Start: Insulin glargine dose at entry (52.5 U) Mean: 123 U T: Breakfast, lunch, dinner D: 24 weeks</p> <p>Insulin lispro 75/25 (v) Start: Allowed to switch evening dose to insulin lispro 75/25 T: Dinner D: Unclear</p> <p>GP2: Insulin glargine (v) Start: 50% of insulin glargine dose at entry (54.9 U) Mean: 70 U T: Bedtime D: 24 weeks</p> <p>Insulin lispro (v) Start: 50% of insulin glargine dose at entry divided in 3 equal doses (54.9 U) Mean: 76 U T: Breakfast, Lunch, dinner D: 24 weeks</p>	<p>GP1 F: 159 (55) p: 0.013</p> <p>GP2 F: 147 (43)</p>	<p>GP1 F: 174 (56) p: 0.002</p> <p>GP2 F: 155 (53)</p>	<p>GP1 B: 208† F: 144† p: > 0.05 vs. GP2</p> <p>F-B: 64</p> <p>GP2 B: 212† F: 150† F-B: 62 GP1-GP2: 2*</p>	<p>GP1 B: 8.8 (1) p: 0.598 F: 6.95 F-B: -1.87 p: 0.021</p> <p>GP2 B: 8.9 (1.1) F: 6.78 F-B: -2.09 GP1-GP2: 0.22 (90% CI: 0.07 – 0.38)</p> <p>A1c < 7.5%, n (%)</p> <p>GP1 (82)</p> <p>GP2 (83)</p> <p>A1c < 7.0%, n (%)</p> <p>GP1 81 (54) p: < 0.05</p> <p>GP2 101 (69)</p> <p>A1c < 6.5%, n (%)</p> <p>GP1 53 (35) p: < 0.05</p> <p>GP2 74 (50)</p> <p>A1c < 6.0%, n (%)</p> <p>GP1 (12.5†)</p> <p>GP2 (12.5†)</p>		

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#	A1c in %#	Quality of life#
Insulin lispro 50/50 vs. premixed human insulins							
Roach, 1999 ¹⁰	GP1: Insulin lispro 50/50 (v) Mean: 0.31 U/kg T: Breakfast D: 3 months	GP1 F: 160.38 p: NS	GP1 F: 150.3 p: <0.001	GP1 F: 171 p: 0.01	GP1 F: 179.28 p: NS	GP1 F: 7.73 p: 0.371	
	Insulin lispro 75/25 (v) Mean: 0.26 U/kg T: Dinner D: 3 months	GP2 F: 162.18	GP2 F: 182.16	F: 166.68	GP2 F: 188.64	GP2 F: 7.66	
	GP2: NPH/regular 50/50 (v) Mean: 0.32 U/kg T: Breakfast D: 3 months		2-hr PPG excursion GP1 F: -10.44 p: <0.001		2-hr PPG excursion GP1 F: 6.48 p: NS		
	NPH/regular 70/30 (v) Mean: 0.26 U/kg T: Dinner D: 3 months		GP2 F: 21.42		GP2 F: 21.96		

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#	A1c in %#	Quality of life#
Schern- thaler, 2004 ⁷⁷	GP1: Insulin lispro 50/50 (v) Mean: 64.6 IU T: Breakfast, lunch, 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	GP1 B: 198* F: 189.8 (SE 10.2) F-B: -8.3 (SE 11) p: 0.456 vs. baseline GP2	GP1 B: 192* F: 174.8 (SE 7.3) F-B: -17.3 (SE 9.6) p: 0.079 vs. baseline GP2	GP1 B: 209* F: 166.3 (SE 7.2) F-B: -42.8 (SE 10) p: <0.001 vs. baseline GP2	GP1 B: 9* F: 7.6 (SE 1.1) F-B: -0.8 (SE 1.1) p: <0.001 vs. baseline GP2	
	GP2: NPH/regular 70/30 (v) Mean: 61.8 IU T: Breakfast, dinner D: 12 weeks Diet/exercise D: 12 weeks	B: 154* F: 147.4 (SE 6.3) F-B: -7 (SE 8) p: 0.387 vs. baseline GP1-GP2: 30* p: <0.001	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	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	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	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	
			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		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		
Schwartz, 2006 ⁶²	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 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#	A1c in %#	Quality of life#
Yamada, 2007 ⁷⁸	GP1: Insulin lispro 50/50 (v) Start: Current dose Mean: 0.37 (start), 0.38 U/kg (end) T: bid D: 4 months	GP1 B: 130.3 (50.7) F: 158.5 (63.4) F-B: 28* p: NS vs. baseline				GP1 B: 7.59 (0.44) F: 7.24 (0.49) F-B: -1* p: <0.05 vs. baseline	
	GP2: NPH/regular 70/30 (v) Start: current dose Mean: 0.34 (start), 0.37 U/kg (end) T: bid D: 4 months	GP2 B: 141.8 (51.9) F: 136.4 (47.2) F-B: -6* p: NS vs. baseline GP1-GP2: 34* p: NS				GP2 B: 7.33 (0.58) F: 7.29 (0.65) F-B: 0* p: NS vs. baseline GP1-GP2: -1* p: <0.05	
	NPH/regular 50/50 (v) Start: current dose Mean: 0.34 (start), 0.37 U/kg (end) T: bid D: 4 months						

Numbers are mean (SD) unless otherwise specified.

* Number has been imputed.

† Number has been estimated from a figure.

‖ Among those who were 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 2004.⁴⁵ 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.

µg = microgram; A1c = Hemoglobin A1c; 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; 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; OA = oral antidiabetic; 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; tid = thrice daily; 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 ³²	<p>GP1: Insulin aspart 70/30 (v) Start: 16 median IU/day Range: 10 – 26 IU/day T: bid D: 1 year Usual care D: 1 year</p> <p>GP2: Insulin detemir (v) Start: 16 median IU/day Range: 10 – 24 IU/day T: Bedtime, twice if required D: 1 year Usual care D: 1 year</p>		<p>Grade 2: symptoms and BG < 56 mg/dL GP1 Median number of events/patient-year: 3.9 (IQR 1.0 - 9.0) p: 0.01 GP2 Median number of events/patient-year: 0 (IQR 0 - 2.0)</p>	<p>Grade 3: third party assistance required GP1 11 (4.7) p: overall 0.20 Median number of events/patient-year: 0 p: overall 0.10 GP2 4 (1.7) Median number of events/patient-year: 0</p>			<p>Grades 1, 2, or 3 GP1 216 (91.9) p: overall < 0.001 GP2 173 (73.9)</p>
E-69 Kann, 2006 ⁵⁰	<p>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</p> <p>GP2: Insulin glargine (v) Start: 0.2 U/kg qd Mean: 0.3 U/kg T: preferred time (constant through study) D: Glimepiride (v) Start: 1 mg daily or current dose T: Breakfast D: 26 weeks</p>	<p>Treat self, PG < 55.8 mg/dL (3.1 mmol/L) GP1 26* (20.3) p: 0.0124 GP2 11* (9)</p>	<p>Unable to treat self GP1 1 (1*) GP2 1 (1*) Hypoglycemic coma GP1 2 (1.6) GP2 0 (0)</p>	<p>% mild episodes that occurred in daytime GP1 GP2 number (%) of events: 61 (77) GP2 number (%) of events: 25 (71)</p>	<p>Symptoms only GP1 14* (10.6) GP2 9* (6.6)</p>		

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 ^{39,40}	<p>GP1: Insulin aspart 70/30 (v) Start: 10 or 12 U/day T: Breakfast, dinner D: Unclear Metformin (v) Range: 1500 – 2550 mg/day T: NR D: Unclear</p> <p>GP2: Insulin glargine (v) Start: 10-12 U/day T: Bedtime D: Unclear Metformin (v) Range: 1500 – 2550 mg/day T: NR D: Unclear</p>	<p>PG < 56 mg/dL with or without symptoms, self-treated GP1 46.4* (43) event rate: 3.4/patient-year p: < 0.05</p> <p>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</p>		<p>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)</p>		<p>Mild or serious between 11pm and 8am GP1 19.8* (25) p: 0.021 GP2 7.8* (10)</p>	<p>Symptoms but PG ≥ 56 mg/dL GP1 event rate: 9.8/patient-year p: < 0.05 GP2 event rate: 4.7/patient-year</p> <p>Reported hypoglycemic event GP1 54 (68) p: 0.0013 GP2 33 (42)</p>
Tame-moto, 2007 ⁴⁷	<p>GP1: Insulin aspart 70/30 (v) Start: 10 - 16 U/day Mean: 26.7 U T: Breakfast, dinner D: 6 months Continued OA agents (NR) T: NR D: 6 months</p> <p>GP2: Insulin glargine (v) Start: 6 - 8 U/day T: NR D: 6 months Continued OA agents (NR) T: NR D: 6 months</p>						<p>From self-monitored blood glucose data, < 70 mg/dL GP1 2 (50*) number of events: 11 GP2 4 (57*) number of events: 43</p> <p>Self-reported events GP1 4 (80*) GP2 6 (55*)</p>

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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 ³²	<p>GP1: Insulin aspart 70/30 (v) Start: 16 median IU/day Range: 10 – 26 IU/day T: bid D: 1 year Usual care D: 1 year</p> <p>GP2: Insulin aspart (v) Start: 18 median IU/day Range: 9 – 24 IU/day T: Breakfast, lunch, dinner, D: 1 year Usual care D: 1 year</p>		<p>Grade 2: symptoms and BG < 56 mg/dL GP1 Median number of events/patient-year: 3.9 (IQR 1.0-9.0) p: 0.002</p> <p>GP2 Median number of events/patient-year: 8.0 (IQR 2.9-17.7)</p>	<p>Grade 3: third party assistance required GP1 11 (4.7) p: overall 0.20</p> <p>Median number of events/patient-year: 0 GP2 16 (6.7) Median number of events/patient-year: 0</p>			<p>Grades 1, 2, or 3 GP1 216 (91.9) p: 0.08 GP2 229 (96.2)</p>
Insulin aspart 70/30 vs. rapid-acting with long-acting insulin analogues							
Joshi, 2005 ⁵²	<p>GP1: Insulin aspart 70/30 (v) Mean: 40.19 U/day T: bid D: 12 weeks</p> <p>GP2: Insulin aspart (v) Mean: 28.26 U/day at 12 weeks T: tid D: 12 weeks</p> <p>Insulin glargine (v) Mean: 24.52 U/day T: Bedtime D: 12 weeks</p>	<p>BS < 50 mg/dL but self managed GP1 19* (16.7) p: < 0.05 vs GP2 GP2 18* (58.06)</p>	<p>Requiring 3rd party assistance GP1 0 (0) GP2 0 (0)</p>				

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 insulin							
Abramian, 2005 ⁵³	GP1: Insulin aspart 70/30 (v) Mean: 0.49 (start), 0.61 U/kg (end) T: Breakfast, lunch, dinner D: 24 weeks GP2: NPH/regular 70/30 (v) Mean: 0.46 (start), 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 p: NS	
Boehm, 2004 ⁴⁵ Boehm, 2002 ^{9‡}	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			
Hermansen, 2002 ⁵⁸	GP1: Insulin aspart 70/30 (fix) Start: 0.4 U/kg T: Breakfast D: 1 day GP2: NPH/regular 70/30 (fix) Start: 0.4 U/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

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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 ¹⁵	<p>GP1: Insulin aspart 70/30 (v) Start: 0.16 U/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</p> <p>GP2: NPH/regular 70/30 (v) Start: 0.16 U/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</p>	<p>Symptoms with BS < 50 mg/dL but not requiring third party assistance GP1 11 (24) GP2 9 (19)</p>		<p>BS < 50 mg/dL with severe CNS symptoms and required third party assistance GP1 0 (0*) GP2 0 (0*)</p>		<p>Between midnight and 6 am GP1 7 (15) GP2 11 (23)</p>	<p>Symptoms only GP1 13 (28) GP2 11 (23)</p> <p>Any (reported symptoms or BS < 50 mg/dL) GP1 20 (43) p: overall 0.245 GP2 15 (32)</p>

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 ⁴⁸	GP1: Insulin aspart 70/30 (v) Start: 100 U/mL Mean: 68.8 U Range: 6 - 238.7 U 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))		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)	< 45 mg/dL (2.5 mmol/L) recorded by CGMS between 0000 - 0600 h GP1 18* (25) p: 0.039 GP2 28* (37)	< 45 mg/dL (2.5 mmol/L) recorded by CGMS at any time GP1 32* (46) p: 0.28 GP2 40* (54)
	GP2: NPH/regular 70/30 (v) Start: 100 U/mL Mean: 66.6 U Range: 11.3 - 240 U T: Breakfast, dinner D: 16 weeks	GP1 63* (90) GP2 65* (84)			< 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	< 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	< 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
					Daytime self-reported rates p: NS	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)	Total self-reported rates 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 ¹¹	GP1: Insulin aspart 70/30 (NR) T: Breakfast, dinner D: 2 weeks GP2: NPH/regular 70/30 (NR) 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 ¹³	GP1: Insulin aspart 70/30 (v) Start: insulin naive = 8 - 16 U/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 U/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 ¹⁵	<p>GP1: Insulin aspart 70/30 (v) Start: 0.16 U/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</p> <p>GP2: NPH insulin (v) Start: 0.16 U/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</p>	<p>Symptoms with BS < 50 mg/dL but not requiring third party assistance GP1 11 (24) GP2 6 (13)</p>		<p>BS < 50 mg/dL with severe CNS symptoms and required third party assistance GP1 0 (0*) GP2 0 (0*)</p>		<p>Between midnight and 6 am GP1 7 (15) GP2 11 (23)</p>	<p>Symptoms only GP1 13 (28) GP2 10 (21)</p> <p>Any (reported symptoms or BS < 50 mg/dL) GP1 20 (43) p: overall 0.245 GP2 13 (28)</p>
Insulin aspart 70/30 vs. oral antidiabetic agents							
Bebakar, 2007 ⁴⁶	<p>GP1: Insulin aspart 70/30 (v) Start: 0.2 U/kg/day Range: 0.16 U/kg (qd) - 0.43 U/kg (bid) T: once or twice daily D: 24 weeks</p> <p>GP2: OA agents (v) T: NR D: 24 weeks</p>	<p>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</p>		<p>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</p>			<p>Mild and severe GP1 178 (54) p: < 0.005 GP2 46 (30)</p>

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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 ⁵¹	GP1: Insulin aspart 70/30 (v) Start: 0.3 U/kg Mean: 0.51 U/kg T: Breakfast, dinner D: 16 weeks	Symptoms confirmed by BG < 50.4 mg/dL (2.8 mmol/l), handled by patient; asymptomatic BG < 50.4 mg/dL		Required assistance, BG < 50.4 mg/dL (2.8 mmol/l), need for food or IV glucose			Total hypoglycemic events (includes minor and symptomatic only) GP1 event rate: 0.037/patient-week
	GP2: Metformin (fix) Mean: 1660 mg daily Range: 500 - 3000 mg qd T: NR D: 16 weeks Glibenclamide (v) Start: 1.75 mg Mean: 2.33 (start), 6.58 mg (end) T: once or twice daily	GP1 10 (9*) number of events: 20 GP2 9 (8*) number of events: 28		GP1 0 (0*) GP2 0 (0*)			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
Kvapil, 2006 ⁵¹	GP1: Insulin aspart 70/30 (v) Start: 0.2 U/kg Mean: 0.3 U/kg T: Breakfast, dinner D: 16 weeks	Symptoms confirmed by BG < 50.4 mg/dL (2.8 mmol/l), handled by patient; asymptomatic BG < 50.4 mg/dL		Required assistance, BG < 50.4 mg/dL (2.8 mmol/l), need for food or IV glucose			Symptoms without confirmatory BG GP1 22 (20*) number of events: 44 GP2 23 (20*) number of events: 43
	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 Glibenclamide (v) Start: 1.75 mg Mean: 2.33 (start), 6.58 mg daily (end) T: once or twice daily D: 16 weeks	GP1 13 (12*) number of events: 23 GP2 9 (8*) number of events: 28		GP1 0 (0*) GP2 0 (0*)			Total hypoglycemic events (includes minor and symptomatic only) GP1 event rate: 0.039/patient-week GP2 event rate: 0.04/patient-week

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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, 2003 ⁵⁷	<p>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</p> <p>GP2: Glibenclamide (fix) Range: 7.5 – 15 mg T: Dinner D: 6 weeks Rosiglitazone (fix) Start: 4 mg T: Breakfast D: 6 weeks</p>	<p>BG < 50 mg/dL handled by self GP1 event rate: 1.8/year p: 0.03 GP2 event rate: 0/year</p>					<p>Minor episodes with symptoms but no blood sugars GP1 event rate: 5.3/year p: <0.01 vs. GP2 GP2 event rate: 0/year</p>
E-78 Raz, 2005 ⁵⁴	<p>GP1: Insulin aspart 70/30 (v) Start: 0.3 U/kg Mean: 0.7 U/kg T: Breakfast, dinner D: 18 weeks</p> <p>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</p>	<p>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</p>		<p>BG < 50 mg/dL or requiring third party assistance GP1 0 (0*) GP2 0 (0*)</p>		<p>Midnight to 6 am GP1 number of events: 8 GP2 number of events: 0</p>	<p>All hypoglycemic episodes - symptoms or BG < 50 mg/dL GP1 event rate: 0.132/patient-week GP2 event rate: 0.032/patient-week</p>

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 ⁵⁴	<p>GP1: Insulin aspart 70/30 (v) Start: 0.2 U/kg Mean: 0.5 U/kg T: Breakfast, dinner D: 18 weeks Pioglitazone (fix) Start: 30 mg Mean: 30 mg T: Breakfast D: 18 weeks</p> <p>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</p>	<p>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</p>	<p>BG < 50 mg/dL or requiring third party assistance GP1 0 (0*) GP2 0 (0*)</p>	<p>BG < 50 mg/dL or requiring third party assistance GP1 0 (0*) GP2 0 (0*)</p>	<p>Midnight to 6 am GP1 number of events: 0 GP2 number of events: 0</p>	<p>All hypoglycemic episodes - symptoms or BG < 50 mg/dL GP1 event rate: 0.083/patient-week GP2 event rate: 0.032/patient-week</p>	
Usha-kova, 2007 ⁵⁹	<p>GP1: Insulin aspart 70/30 (v) Start: 0.3 - 0.5 U/kg Mean: 55.5 U T: bid for 2 weeks, then tid D: 16 weeks</p> <p>GP2: Continuation of OA agents (v) T: NR D: 16 weeks</p>	<p>BG < 55.8 mg/dL (3.1 mmol/L), with or without symptoms, and handled by patient GP1 4 (4*) GP2 1 (1*)</p>	<p>BG < 55.8 mg/dL (3.1 mmol/L) and required 3rd party help or symptoms reversed after intake of food, glucagon, or IV glucose GP1 0 (0*) GP2 0 (0*)</p>	<p>Symptoms only GP1 28 (27.5) GP2 4 (3.8)</p> <p>Overall hypoglycemia GP1 Event rate: 0.73/ person-year GP2 Event rate: 0.69/person-year</p>			

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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 ⁴⁹	<p>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</p> <p>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</p>			<p>Severe, not further defined GP1 0 (0) GP2 0 (0)</p>	<p>Not further defined GP1 Event rate: 4.4/patient-year p: NS GP2 Event rate: 4.1/patient-year</p>	<p>Nocturnal, not further defined GP1 25 (62) event rate: 1.1/patient-year p: NS GP2 44 (17) event rate: 0.6/patient-year</p>	<p>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</p>
Insulin aspart 70/30 vs. insulin lispro 75/25							
Herman- sen, 2002 ⁵⁸	<p>GP1: Insulin aspart 70/30 (fix) Start: 0.4 U/kg T: Breakfast D: 1 day</p> <p>GP2: Insulin lispro 75/25 (fix) Start: 0.4 U/kg T: Breakfast D: 1 day</p>			<p>Requiring third-party assistance GP1 number of events: 2 GP2 number of events: 5</p>			<p>Overall hypoglycemia rates (not specified) GP1 number of events: 23 GP2 number of events: 19</p>

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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 (%)
Niskanen, 2004 ⁵⁵	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 ⁵¹	GP1: Insulin aspart 70/30 (v) Start: 0.3 U/kg Mean: 0.51 U/kg T: Breakfast, dinner D: 16 weeks GP2: Insulin aspart 70/30 (v) Start: 0.2 U/kg Mean: 0.3 U/kg 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 ⁵⁴	<p>GP1: Insulin aspart 70/30 (v) Start: 0.3 U/kg Mean: 0.7 U/kg T: Breakfast, dinner D: 18 weeks</p> <p>GP2: Insulin aspart 70/30 (v) Start: 0.2 U/kg Mean: 0.5 U/kg T: Breakfast, dinner D: 18 weeks</p> <p>Pioglitazone (fix) Start: 30 mg Mean: 30 mg T: Breakfast D: 18 weeks</p>	<p>BG < 50 mg/dL but did not require third party assistance GP1 15 (15) number of events: 47</p> <p>GP2 11 (12) number of events: 15</p>		<p>BG < 50 mg/dL or requiring third party assistance GP1 0 (0*) GP2 0 (0*)</p>		<p>Midnight to 6 am GP1 number of events: 8 GP2 number of events: 0</p>	<p>All hypoglycemic episodes - symptoms or BG < 50 mg/dL GP1 Event rate: 0.132/patient-week GP2 Event rate: 0.083/patient-week</p>
E-82 Usha-kova, 2007 ⁵⁹	<p>GP1: Insulin aspart 70/30 (v) Start: 0.3 - 0.5 U/kg Mean: 55.5 U T: bid for 2 weeks, then tid D: 16 weeks</p> <p>GP2: Insulin aspart 70/30 (v) Start: 0.3 - 0.5 U/kg Mean: 44.8 U T: Breakfast, dinner D: 16 weeks</p> <p>Metformin (v) Start: 500 mg qd or bid or 850 mg qd T: NR D: 14 weeks (started after 2 weeks)</p>	<p>BG < 55.8 mg/dL (3.1 mmol/L), with or without symptoms, and handled by patient GP1 4 (4*) GP2 9 (9*)</p>		<p>BG < 55.8 mg/dL (3.1 mmol/L) and required 3rd party help or symptoms reversed after intake of food, glucagon, or IV glucose GP1 0 (0*) GP2 0 (0*)</p>		<p>Symptoms only GP1 28 (27.5) p: NS vs. GP2 GP2 28 (28)</p> <p>Overall hypoglycemia GP1 event rate: 0.73/ person-year p: NS vs. GP2 GP2 event rate: 0.69/ person-year</p>	

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 with intermediate-acting human insulin							
Hirao, 2008 ⁶¹	GP1: Insulin aspart 70/30 (NR) T: bid D: 6 months			Major hypoglycemia, not further defined GP1 0 (0)			
	GP2: Insulin aspart (NR) T: tid D: 6 months NPH insulin (NR) T: Optional multiple daily injections D: 6 months			GP2 0 (0)			
Insulin lispro 75/25 vs. long-acting insulin analogues							
Cox, 2007 ⁷⁴	GP1: Insulin lispro 75/25 (v) T: Breakfast, dinner D: 12 weeks Metformin (NR) T: NR D: 12 weeks			Severe, not defined GP1 0 (0*)			Symptoms or BG < 63 md/dL (3.5 mmol/L) GP1 p: NS
	GP2: Insulin glargine (v) T: Bedtime D: 12 weeks Metformin (NR) T: NR D: 12 weeks			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 (%)
Jacober, 2006 ⁶⁴	<p>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</p> <p>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</p>			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 42* (72.2) p: 0.033 Event rate: 3.98/patient/30 days (SD: 4.74) GP2 56* (94.8) Event rate: 2.57/patient/30 days (SD: 3.22)
E-84 Malone, 2004 ⁶⁵	<p>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</p> <p>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</p>			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 ⁶⁶	<p>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</p> <p>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</p>			<p>Not defined GP1 0 (0*) GP2 0 (0*)</p>	<p>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)</p>	<p>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)</p>	<p>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)</p>

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 ⁶³	<p>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 OA agents (NR) Start: current dose T: NR D: 12 weeks Metformin (v) Start: 500 mg qd T: NR D: 12 weeks</p> <p>GP2: Insulin glargine (v) Mean: 44 U Range: 14 U - 100 U T: Breakfast D: 12 weeks OA agents (NR) Start: current dose T: NR D: 12 weeks Metformin (v) Start: 500 mg qd T: NR D: 12 weeks</p>	<p>Self reported BG < 63 mg/dL (3.5 mmol/L) or symptoms GP1 3 (15*) GP2 2 (10*)</p>		<p>Not defined GP1 0 (0*) GP2 0 (0*)</p>	<p>PG < 63 mg/dL (3.5 mmol/L) GP1 0 (0*) GP2 1 (5*)</p>	<p>PG < 63 mg/dL (3.5 mmol/L) GP1 8 (40*) GP2 2 (10*)</p>	<p>PG < 63 mg/dL (3.5 mmol/L) GP1 8 (40*) GP2 3 (15*)</p>

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 ⁶⁷	<p>GP1: Insulin lispro 75/25 (v) Mean: 38.1 Range: 12 - 72 T: Breakfast, dinner D: 12 days Diet/exercise D: 12 days</p> <p>GP2: NPH/regular 70/30 (v) Mean: 37.3 Range: 10 - 72 T: Breakfast, dinner D: 12 days Diet/exercise D: 12 days</p>						Not defined GP1 p: NS vs. GP2
Herman- sen, 2002 ⁵⁸	<p>GP1: Insulin lispro 75/25 (fix) Start: 0.4 U/kg T: Breakfast D: 1 day</p> <p>GP2: NPH/regular 70/30 (fix) Start: 0.4 U/kg T: Breakfast D: 1 day</p>			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

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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 ⁷¹	<p>GP1: Insulin lispro 75/25 (v) Mean: 26.1 U T: Breakfast, dinner D: 4 weeks</p> <p>GP2: NPH/regular 70/30 (v) Mean: 26.2 U T: Breakfast, dinner D: 4 weeks</p>						<p>Symptoms or BG < 54 mg/dL (3.0 mmol/L)[¶] GP1 Event rate: 0.7/patient/30 days (SE = 0.2) p: 0.042</p> <p>GP2 Event rate: 1.2/patient/30 days (SE = 0.3)</p> <p>Symptoms or BG < 54 mg/dL (3.0 mmol/L)[§] GP1 Event rate: 0.9/patient/30 days (SE = 0.2) p: 0.569</p> <p>GP2 Event rate: 0.9/patient/30 days (SE = 0.1)</p>

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 ¹²	<p>GP1: Insulin lispro 75/25 (v) Mean: 31.6 (morning)¶ and 26.8 U (evening)¶ and 32.4 (morning)§ and 27.6 U (evening)§ T: Breakfast, dinner D: 4 weeks</p> <p>GP2: NPH/regular 70/30 (v) Mean: 32.3 (morning)¶ and 26.4 U (evening)¶ and 33.3 (morning)§ and 27.5 U (evening)§ T: Breakfast, dinner D: 4 weeks</p>						<p>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)</p> <p>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)</p>

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 ⁴⁴	<p>GP1: Insulin lispro 75/25 (fix) Mean: 35.4 U (0.43 U/kg) T: Breakfast D: 2 days</p> <p>GP2: NPH/regular 70/30 (fix) Mean: 35.4 U (0.43 U/kg) T: Breakfast D: 2 days</p>						<p>BG < 63 mg/dL (3.5 mmol/L) or symptoms occurring between lunch and dinner</p> <p>GP1 number of events: 3</p> <p>GP2 number of events: 5</p> <p>BG < 63 mg/dL (3.5 mmol/L) or symptoms</p> <p>GP1 number of events: 7</p> <p>GP2 number of events: 10</p> <p>BG < 63 mg/dL (3.5 mmol/L) or symptoms occurring within 4 hours of test meal</p> <p>GP1 number of events: 5</p> <p>GP2 number of events: 8</p>

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 ⁷⁰	<p>GP1: Insulin lispro 75/25 (NR) Mean: 20 (morning), 32 U (evening) T: Breakfast, dinner D: 2 weeks</p> <p>GP2: NPH/regular 70/30 (NR) Mean: 20 (morning), 32 U (evening) T: Breakfast, dinner D: 2 weeks</p>						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 ⁷³	<p>GP1: Insulin lispro 75/25 (v) Mean: 0.37 (morning), 0.28 (evening) U/kg T: Breakfast, dinner D: 13 weeks</p> <p>GP2: NPH/regular 70/30 (v) Mean: 0.36 (morning), 0.27 (evening) U/kg T: Breakfast, dinner D: 13 weeks</p>			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 ⁶²	<p>GP1: Insulin lispro 75/25 (fix) Start: 2/3 of usual daily dose Mean: 44.1 U T: Breakfast D: 1 day</p> <p>GP2: NPH/regular 70/30 (fix) Start: 2/3 of usual daily dose Mean: 44.1 U T: Breakfast D: 1 day</p>	GP1 0 (0*) GP2 1 (5*)					

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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 ⁷²	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: 0.17 episodes/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 ⁶⁸	<p>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</p> <p>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</p>			<p>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*</p>		<p>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*</p> <p>Symptoms or BG < 63 mg/dL (3.5 mmol/L) occurring after bedtime GP1 (1) GP2 (5)</p>	<p>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*</p>
Tirgo-viste, 2003 ⁴³	<p>GP1: Insulin lispro 75/25 (v) Start: 0.3 - 0.5 U/kg T: Breakfast, dinner D: 16 weeks</p> <p>GP2: Glibenclamide (v) Start: 15 mg T: Breakfast, dinner D: 16 weeks</p>						<p>Symptoms and/or BG < 54 mg/dL (3.0 mmol/L) GP1 38 (44.7) p: 0.001 GP2 9 (10.3)</p>

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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 ⁶⁹	<p>GP1: Insulin lispro 75/25 (v) Mean: 31.3 (morning), 27.6 U (evening) T: Breakfast, dinner D: 8 weeks</p> <p>GP2: Insulin lispro 50/50 (v) Mean: 31.5 U T: Breakfast D: 8 weeks</p> <p>Insulin lispro 75/25 (v) Mean: 27.9 U T: Dinner D: 8 weeks</p>			<p>Required third party assistance</p> <p>GP1 0* (0)</p> <p>GP2 0* (0)</p>			<p>Symptoms</p> <p>GP1 28* (26.1) p: 0.078</p> <p>number of events: 65 p: 0.681</p> <p>GP2 34* (32.4) number of events: 68</p>
Schwartz, 2006 ⁶²	<p>GP1: Insulin lispro 75/25 (fix) Start: 2/3 of usual daily dose Mean: 44.1 U T: Breakfast D: 1 day</p> <p>GP2: Insulin lispro 50/50 (fix) Start: 2/3 of usual daily dose Mean: 43.8 U T: Breakfast D: 1 day</p>	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 ⁷⁶	<p>GP1: Insulin lispro 50/50 (v) Start: 0.30 IU/kg mean Mean: 0.59 IU/kg T: Breakfast, lunch, dinner D: 24 weeks</p> <p>GP2: Insulin glargine (v) Start: 0.16 IU/kg mean Mean: 0.43 IU/kg T: Bedtime D: 24 weeks</p>			<p>Not defined GP1 0 (0) GP2 0 (0)</p>			<p>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</p>
Robbins, 2007 ⁷⁹	<p>GP1: Insulin lispro 50/50 (v) Mean: 0.7 U/kg T: Breakfast, lunch, dinner D: 24 weeks Metformin (fix) Mean: 1641 mg T: bid D: 24 weeks</p> <p>GP2: Insulin glargine (v) Mean: 0.6 U/kg T: Bedtime D: 24 weeks Metformin (fix) Mean: 1636 mg T: bid D: 24 weeks</p>			<p>Required 3rd party assistance and BG < 50 mg/dL (2.9 mmol/L) or prompt recovery GP1 3 (1.9) number of events: 8 p: NS GP2 2 (1.3) number of events: 4</p>		<p>Episodes occurring after bedtime and before awakening GP1 Event rate: 0.2/30 patient-days (SD = 0.7) p: 0.30 vs GP2 GP2 Event rate: 0.3/30 patient-days (SD = 0.6) s</p>	<p>Overall (signs or symptoms or BG < 63 mg/dL (3.5 mmol/L)) GP1 81 (51.9) Event rate: 0.8/30 patient-days (SD = 1.4) p: 0.07 for event rate vs GP2 GP2 77 (48.4) Event rate: 0.5/30 patient-days (SD = 1.0)</p>
Insulin lispro 50/50 vs. rapid-acting insulin analogues							
Kazda, 2006 ⁷⁶	<p>GP1: Insulin lispro 50/50 (v) Start: 0.30 IU/kg mean Mean: 0.59 IU/kg T: Breakfast, lunch, dinner D: 24 weeks</p> <p>GP2: Insulin lispro (v) Start: 0.25 IU/kg mean Mean: 0.50 IU/kg T: Breakfast, lunch, dinner D: 24 weeks</p>			<p>Not defined GP1 0 (0) GP2 0 (0)</p>			<p>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</p>

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. rapid-acting with long-acting insulin analogues								
Rosenstock, 2008 ⁶⁰	<p>GP1: Insulin lispro 50/50 (v) Start: Insulin glargine dose at entry (52.5 U) Mean: 123 U T: Breakfast, lunch, dinner D: 24 weeks Insulin lispro 75/25 (v) Start: allowed to switch evening dose to insulin lispro 75/25 T: Dinner D: Unclear</p> <p>GP2: Insulin glargine (v) Start: 50% of insulin glargine dose at entry (54.9 U) Mean: 70 U T: Bedtime D: 24 weeks Insulin lispro (v) Start: 50% of insulin glargine dose at entry divided in 3 equal doses (54.9 U) Mean: 76 U T: Breakfast, lunch, dinner D: 24 weeks</p>			<p>Required 3rd party assistance GP1 6 (3.21) p: 0.751 Event rate: 0.1/patient-year (SD = 0.65) p: 0.266 GP2 4 (2.14) Event rate: 0.05/patient-year (SD = 0.31)</p>			<p>Nocturnal (not further defined) GP1 109 (58.29) p: 1 Event rate: 4.78/patient-year (SD = 7.15) p: 0.139 GP2 110 (58.82) Event rate: 6.17/patient-year (SD = 10.68)</p>	<p>BG < 72 mg/dL (4.0 mmol/L) GP1 165 (88.24) p: 1 Event rate: 46.5/patient-year (SD = 48) p: 0.747 GP2 165 (88.24) Event rate: 44.95/patient-year (SD = 46.8) BG < 60 mg/dL (3.3 mmol/L) GP1 148 (79.14) p: 0.898 Event rate: 20.75/patient-year (SD = 26.86) p: 0.574 GP2 150 (80.21) Event rate: 19.26/patient-year (SD = 24.51) BG < 50 mg/dL (2.8 mmol/L) GP1 104 (55.61) p: 0.294 Event rate: 7.34/patient-year (SD = 12.88) p: 0.23 GP2 115 (61.5) Event rate: 5.93/patient-year (SD = 9.92)</p>

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 insulin							
Roach, 1999 ¹⁰	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 Event rate: 0.3/3 patient-months (SD: 1.0) p: 0.199 GP2 Event rate: 0.6/3 patient-months (SD: 1.4)	Symptoms or BG < 54 mg/dL (3.0 mmol/L) GP1 25* (40) p: NS GP2 23* (37)
E-97 Scherthaner, 2004 ⁷⁷	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 ⁶²	GP1: Insulin lispro 50/50 (fix) Start: 2/3 of usual daily dose Mean: 43.8 U T: Breakfast D: 1 day	GP1 0 (0*)		GP2 1 (5*)			
	GP2: NPH/regular 70/30 (fix) Start: 2/3 of usual daily dose Mean: 44.1 U T: Breakfast D: 1 day						
E-98 Yamada, 2007 ⁷⁸	GP1: Insulin lispro 50/50 (v) Start: current dose Mean: 0.37 (start), 0.38 U/kg (end) T: twice daily D: 4 months			Requiring third party assistance GP1 0 (0*) GP2 0 (0*)			
	E-99 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), 0.37 U/kg (end) T: twice daily D: 4 months						

* 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 2004.⁴⁵ 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.

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

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; OA = oral antidiabetic; 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; tid = thrice daily; U = unit; v = dosing varied

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 ³⁹	GP1: Insulin aspart 70/30 (v) Start: 10 or 12 U	GP1 F-B: 5.4 (4.8)		GP1 4 (5)	GP1 4 (3*)	
Raskin, 2007 ⁴⁰	T: Breakfast, dinner D: Unclear Metformin (v) Range: 1500 – 2550 mg/day T: NR D: Unclear GP2: Insulin glargine (v) Start: 10-12 U/day T: Bedtime D: Unclear Metformin (v) Range: 1500 - 2550 mg/day T: NR D: Unclear	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*		GP2 5 (6)	GP2 1 (1*) GP1 3 (4*) GP2 0 (0*)	
Tamemoto, 2007 ⁴⁷	GP1: Insulin aspart 70/30 (v) Start: 10 - 16 U/day Mean: 26.7 U T: Breakfast, dinner D: 6 months Continued OA agents (NR) T: NR D: 6 months GP2: Insulin glargine (v) Start: 6 - 8 U/day T: NR D: 6 (expected) months Continued OA agents (NR) 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*)	

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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 ³²	GP1: Insulin aspart 70/30 (v) Start: 16 median IU/day Range: 10 – 26 IU/day T: bid 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)
	GP2: Insulin aspart (v) Start: 18 median IU/day Range: 9 – 24 IU/day T: Breakfast, lunch, dinner D: 1 year Usual care D: 1 year					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 ³²	GP1: Insulin aspart 70/30 (v) Mean: 40.19 U/day T: bid D: 12 weeks	GP1 B: 70.4 (12.18) F: 70.61 (11.23) F-B: 1* p: NS vs. baseline		GP1 0 (0*) GP2 0 (0*)	GP1 0 (0*) GP2 0 (0*)	
	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	GP2 B: 69.63 (10.31) F: 69.68 (9.58) F-B: 0* p: NS vs. baseline GP1-GP2: 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. premixed human insulins						
Abrahamian, 2005 ⁵³	GP1: Insulin aspart 70/30 (v) Mean: 0.49 (start), 0.61 U/kg (end) T: Breakfast, lunch, dinner D: 24 weeks			GP1 number of events: 16	GP1 3 (3*) GP2 0 (0*)	
	GP2: NPH/regular 70/30 (v) Mean: 0.46 (start), 0.59 U/kg (end) T: Breakfast, dinner D: 24 weeks			GP2 number of events: 15		
Boehm, 2004 ⁴⁵	GP1: Insulin aspart 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			GP1 5 (6*) GP2 6 (6*)	
Boehm, 2002 ^{9†}	GP2: NPH/regular 70/30 (v) Start: 0.57 U/kg T: Breakfast, dinner D: 24 months	GP2 F-B: 2 (SE 0.69) GP1-GP2: -2*				
Hermansen, 2002 ⁵⁸	GP1: Insulin aspart 70/30 (fix) Start: 0.4 U/kg T: Breakfast D: 1 day				GP1 1 (2*) GP2 0 (0*)	GP1 number of events: 1 GP2 number of events: 0
	GP2: NPH/regular 70/30 (fix) Start: 0.4 U/kg T: Breakfast D: 1 day					
Kapitza, 2004 ⁵⁶	GP1: Insulin aspart 70/30 (NA) T: Breakfast D: 1 day				GP1 0 (0*) GP2 0 (0*)	
	GP2: NPH/regular 70/30 (NA) T: Breakfast D: 1 day					

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 ¹⁵	GP1: Insulin aspart 70/30 (v) Start: 0.16 U/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	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*)
	GP2: NPH/regular 70/30 (v) Start: 0.16 U/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					
McNally, 2007 ⁴⁸	GP1: Insulin aspart 70/30 (v) Start: 100 U/mL Mean: 68.8 U Range: 6 - 238.7 T: Breakfast, dinner D: 16 weeks GP2: NPH/regular 70/30 (v) Start: 100 U/mL Mean: 66.6 U Range: 11.3 - 240 U 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 ¹¹	GP1: Insulin aspart 70/30 (NR) T: Breakfast, dinner D: 2 weeks				GP1 0 (0*) GP2 0 (0*)	GP1 0 (0*) GP2 0 (0*)
	GP2: NPH/regular 70/30 (NR) T: Breakfast, dinner D: 2 weeks					
Insulin aspart 70/30 vs. intermediate-acting human insulin						
Christiansen, 2003 ¹³	GP1: Insulin aspart 70/30 (v) Start: insulin naïve: 8 - 16 U/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*)
	GP2: NPH insulin (v) Start: insulin naïve: 8 - 16 U/day; taking NPH prior to trial: pretrial dose T: Breakfast, dinner D: 16 weeks					

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 ¹⁵	GP1: Insulin aspart 70/30 (v) Start: 0.16 U/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	GP1 F-B: 0.7 p: 0.251 overall 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*)
	GP2: NPH insulin (v) Start: 0.16 U/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					
Insulin aspart 70/30 vs. oral antidiabetic agents						
Bebakar, 2007 ⁴⁶	GP1: Insulin aspart 70/30 (v) Start: 0.2 U/kg/day Range: 0.16 U/kg (qd) - 0.43 U/kg (bid) T: Once or twice daily 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*)	
	GP2: OA agents (v) T: NR D: 24 weeks					

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 ⁵¹	GP1: Insulin aspart 70/30 (v) Start: 0.3 U/kg/day Mean: 0.51 U/kg/day T: Breakfast, dinner D: 16 weeks	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*)	
	GP2: Metformin (fix) Mean: 1660 mg Range: 500 - 3000 mg qd T: NR D: 16 weeks Glibenclamide (v) Start: 1.75 mg Mean: 2.33 (start), 6.58 mg (end) T: once or twice daily D: 16 weeks					
E-107 Kvapil, 2006 ⁵¹	GP1: Insulin aspart 70/30 (v) Start: 0.2 U/kg/day Mean: 0.3 U/kg/day T: Breakfast, dinner D: 16 weeks	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*)	
	GP2: Metformin (fix) Mean: 1660 mg daily Range: 500 - 3000 mg qd T: NR D: 16 weeks Glibenclamide (v) Start: 1.75 mg Mean: 2.33 (start), 6.58 mg (end) T: once or twice daily D: 16 weeks					

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 ⁵⁷	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	GP1 F-B: 0.23 p: NS vs. GP2 GP2 F-B: 0.03 GP1-GP2: 0*			GP1 0 (0*) GP2 0 (0*)	
	GP2: Glibenclamide (fix) Range: 7.5 – 15 mg T: Dinner D: 6 weeks Rosiglitazone (fix) Start: 4 mg T: Breakfast D: 6 weeks					
Raz, 2005 ⁵⁴	GP1: Insulin aspart 70/30 (v) Start: 0.3 U/kg/day Mean: 0.7 U/kg/day T: Breakfast, dinner D: 18 weeks	GP1 F-B: 2.2 GP2 F-B: 2.2 GP1-GP2: 0*		GP1 2 (2*) GP2 0 (0*)	GP1 3 (3*) GP2 2 (2*)	Cellulitis GP1 1 (1*) GP2 0 (0*)
	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	Experienced weight gain GP1 3* (3) p: < 0.05 overall GP2 2* (2)				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 ⁵⁴	GP1: Insulin aspart 70/30 (v)	GP1		GP1	GP1	Cellulitis
	Start: 0.2 U/kg/day	F-B: 4		0 (0*)	1 (1*)	GP1
	Mean: 0.5 U/kg/day	GP2		GP2	GP2	0 (0*)
	T: Breakfast, dinner	F-B: 2.2		0 (0*)	2 (2*)	GP2
	D: 18 weeks	GP1-GP2: 2*				0 (0*)
	Pioglitazone (fix)	Experienced weight gain				Peripheral edema
	Start: 30 mg	GP1				GP1
	Mean: 30 mg	7* (8)				6* (6)
	T: Breakfast	p: < 0.05 overall				GP2
	D: 18 weeks	GP2				1* (1)
GP2: Glibenclamide (v)	2* (2)					
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						

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, 2007 ⁶⁰	<p>GP1: Insulin aspart 70/30 (v) Start: 6 U bid Mean: 0.6 U/kg/day T: Breakfast, dinner D: 34 weeks Metformin (fixed) Mean: 2446 mg T: NR D: 34 weeks Pioglitazone (fixed) Mean: 32.5 mg T: NR D: 34 weeks</p> <p>GP2: Metformin (fixed) Mean: 2439 mg T: NR D: Unclear Pioglitazone (fixed) Mean: 31.7 T: NR D: Unclear</p>				<p>GP1 3 (2.9) GP2 4 (4.1)</p>	<p>Peripheral edema GP1 8* (9) GP2 11* (12)</p>
Ushakova, 2007 ⁵⁹	<p>GP1: Insulin aspart 70/30 (v) Start: 0.3 - 0.5 U/kg Mean: 55.5 U T: bid for 2 weeks, then tid D: 16 weeks</p> <p>GP2: Continuation of OA agents (v) T: NR D: 16 weeks</p>			<p>GP1 0 (0*) GP2 0 (0*)</p>	<p>GP1 1 (1*) GP2 1 (1*)</p>	

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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 (%)
Ushakova, 2007 ⁵⁹	<p>GP1: Insulin aspart 70/30 (v) Start: 0.3 - 0.5 U/kg Mean: 44.8 U T: Breakfast, dinner D: 16 weeks Metformin (v) Start: 500 mg qd or bid or 850 mg qd T: NR D: 14 weeks (started after 2 weeks)</p> <p>GP2: Continuation of OA agents (v) T: NR D: 16 weeks</p>			<p>GP1 0 (0*) GP2 0 (0*)</p>	<p>GP1 1 (1*) GP2 1 (1*)</p>	
Insulin aspart 70/30 vs. exenatide						
Nauck, 2007 ⁴⁹	<p>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</p> <p>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</p>	<p>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</p>		<p>GP1 11 (4.4) GP2 19 (7.5)</p>	<p>GP1 0 (0*) GP2 20 (8*)</p>	

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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. insulin lispro 75/25						
Hermansen, 2002 ⁵⁸	GP1: Insulin aspart 70/30 (fix) Start: 0.4 U/kg T: Breakfast D: 1 day GP2: Insulin lispro 75/25 (fix) Start: 0.4 U/kg T: Breakfast D: 1 day				GP1 1 (2*) GP2 0 (0*)	GP1 number of events: 1 GP2 number of events: 0
Niskanen, 2004 ⁵⁵	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		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 ⁵¹	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		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*)	

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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 ⁵	GP1: Insulin aspart 70/30 (v) Start: 0.3 U/kg/day Mean: 0.7 U/kg/day T: Breakfast, dinner D: 18 weeks ⁴	GP1 F-B: 2.2 GP2 F-B: 4 GP1-GP2: -2*		GP1 2 (2*) GP2 0 (0*)	GP1 3 (3*) GP2 1 (1*)	Cellulitis GP1 1 (1*) GP2 0 (0*)
	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	Experienced weight gain GP1 3* (3) p: < 0.05 overall GP2 7* (8)				Peripheral edema GP1 0* (0) GP2 6* (6)
E-113 Ushakova, 2007 ⁵⁹	GP1: Insulin aspart 70/30 (v) Start: 0.3 - 0.5 U/kg Mean: 55.5 U T: bid for 2 weeks, then tid D: 16 weeks			GP1 0 (0*) GP2 0 (0*)	GP1 1 (1*) GP2 1 (1*)	
	GP2: Insulin aspart 70/30 (v) Start: 0.3 - 0.5 U/kg Mean: 44.8 U T: Breakfast, dinner D: 16 weeks Metformin (varied) Start: 500 mg qd or bid or 850 mg qd T: NR D: 14 weeks (started after 2 weeks)					

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 70/30 vs. rapid-acting insulin analogue with intermediate-acting human insulin						
Hirao, 2008 ⁶¹	GP1: Insulin aspart 70/30 (NR) T: bid D: 6 months	GP1 B: 23.8 (4.1) p: NS F: 25.2 (4)				
	GP2: Insulin aspart (NR) T: tid D: 6 months NPH insulin (NR) T: Optional multiple daily injections D: 6 months	p: < 0.0001 vs. baseline; NS vs. GP2 F-B: 1.47 (1.82) p: 0.013 vs. GP2 GP2 B: 24 (4.2) F: 24.8 (4.5) p: < 0.0001 vs. baseline F-B: 0.69 (1.04) GP1-GP2: 0*				
Insulin lispro 75/25 vs. long-acting insulin analogues						
Cox, 2007 ⁷⁴	GP1: Insulin lispro 75/25 (v) T: Breakfast, dinner D: 12 weeks Metformin (NR) T: NR D: 12 weeks				GP1 0 (0*) GP2 0 (0*)	
	GP2: Insulin glargine (v) T: Bedtime D: 12 weeks Metformin (NR) T: NR D: 12 weeks					

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 (%)
Jacobson, 2006 ⁶⁴	GP1: Insulin lispro 75/25 (v) Mean: 0.353 IU/kg; 36.73 IU T: Breakfast, lunch D: 4 months	GP1 B: 98* F: 99.7 (18.6) p: 0.9106			GP1 0 (0*) GP2 0 (0*)	
	Insulin lispro 75/25 (v) T: Dinner D: 4 months Existing OA agents (NR) T: NR D: 4 months	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				
Malone, 2004 ⁶⁵	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	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 0 (0*) GP2 1 (1*)	Required hospitalization GP1 4 (4*) GP2 1 (1*)
	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-GP2: 0*				

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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 ⁶⁶	GP1: Insulin lispro 75/25 (v) Mean: 0.42 U/kg T: Breakfast, dinner D: 16 weeks	GP1 B: 77* F: 78.31 (15.13) p: 0.001			GP1 1 (1*) GP2 0 (0*)	GP1 3 GP2 3
	Metformin (fix) Mean: 2128 mg Range: 1500 - 2550 mg T: NR D: 16 weeks	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*				
	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					

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 ⁶³	<p>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 OA agents (NR) Start: Current dose T: NR D: 12 weeks Metformin (v) Start: 500 mg qd T: NR D: 12 weeks</p> <p>GP2: Insulin glargine (v) Mean: 44 U Range: 14 U - 100 U T: Breakfast D: 12 weeks OA agents (NR) Start: Current dose T: NR D: 12 weeks Metformin (v) Start: 500 mg qd T: NR D: 12 weeks</p>	<p>GP1 F: 103.9 (17.8) p: 0.068 GP2 F: 102.5 (17.9)</p>			<p>GP1 1 (3*) GP2 0 (0*)</p>	

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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 ⁶⁷	GP1: Insulin lispro 75/25 (v) Mean: 38.1 U/l Range: 12 – 72 U/l T: Breakfast, dinner D: 12 days Diet/exercise D: 12 days GP2: NPH/regular 70/30 (v) Mean: 37.3 U/l Range: 10 – 72 U/l 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
E-118 Hermansen, 2002 ⁵⁸	GP1: Insulin lispro 75/25 (fix) Start: 0.4 U/kg T: Breakfast D: 1 day GP2: NPH/regular 70/30 (fix) Start: 0.4 U/kg T: Breakfast D: 1 day				GP1 0 (0*) GP2 0 (0*)	GP1 number of events: 0 GP2 number of events: 0
Herz, 2002 ⁷¹	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 ¹²	GP1: Insulin lispro 75/25 (v) Mean: Mean: 31.6 [¶] (morning) and 26.8 [¶] U (evening) and 32.4 [§] (morning) and 27.6 [§] U (evening) T: Breakfast, dinner D: 4 weeks				GP1 0 (0*) GP2 0 (0*)	
	GP2: NPH/regular 70/30 (v) Mean: 32.3 [¶] (morning) and 26.4 [¶] U (evening) and 33.3 [§] (morning) and 27.5 [§] U (evening) T: Breakfast, dinner D: 4 weeks					
Malone, 2000 ⁴⁴	GP1: Insulin lispro 75/25 (fix) Mean: 35.4 U (0.43 U/kg) T: Breakfast D: 2 days				GP1 0 (0*) GP2 0 (0*)	
	GP2: NPH/regular 70/30 (fix) Mean: 35.4 U (0.43 U/kg) T: Breakfast D: 2 days					
Mattoo, 2003 ⁷⁰	GP1: Insulin lispro 75/25 (NR) Mean: 20 U (morning), 32 U (evening) T: Breakfast, dinner D: 2 weeks	GP1 p: NS vs. baseline for all patients			GP1 0 (0*) GP2 0 (0*)	
	GP2: NPH/regular 70/30 (NR) Mean: 20 U (morning), 32 U (evening) T: Breakfast, dinner D: 2 weeks					

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 ⁷³	<p>GP1: Insulin lispro 75/25 (v) Mean: 0.37 (morning), 0.28 U/kg (evening) T: Breakfast, dinner D: 13 weeks</p> <p>GP2: NPH/regular 70/30 (v) Mean: 0.36 (morning), 0.27 U/kg (evening) T: Breakfast, dinner D: 13 weeks</p>	<p>GP1 p: NS vs. GP2</p>			<p>GP1 0 (0*) GP2 0 (0*)</p>	
Schwartz, 2006 ⁶²	<p>GP1: Insulin lispro 75/25 (fix) Start: 2/3 of usual daily dose Mean: 44.1 U T: Breakfast D: 1 day</p> <p>GP2: NPH/regular 70/30 (fix) Start: 2/3 of usual daily dose Mean: 44.1 U T: Breakfast D: 1 day</p>		<p>GP1 1 (5*) GP2 0 (0*)</p>	<p>GP1 0 (0*) GP2 0 (0*)</p>	<p>GP1 0 (0*) GP2 0 (0*)</p>	
Insulin lispro 75/25 vs. oral antidiabetic agents						
Herz, 2002 ⁷²	<p>GP1: Insulin lispro 75/25 (v) Start: 0.3 - 0.5 U/kg Mean: 0.46 U/kg T: Breakfast, dinner D: 16 weeks</p> <p>GP2: Glyburide (fix) Start: 15 mg/day T: Breakfast, dinner D: 16 weeks</p>	<p>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> <p>GP2 p: < 0.001 vs GP2 B: 77.34 (SE 1.53) F: 76.61 (SE 1.55) F-B: -0.85 (SE 0.18) GP1-GP2: 2*</p>			<p>GP1 2 (3*) GP2 1 (1*)</p>	<p>Liver carcinoma GP1 1 (1*) GP2 0 (0*)</p>

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 ⁶⁸	<p>GP1: Insulin lispro 75/25 (v) Mean: 0.19 (morning), 0.14 U/kg (evening) T: Breakfast, dinner D: 16 weeks</p> <p>Metformin (v) Mean: 1813 mg/day Range: 1500 – 2550 mg/day T: 2 to 3 times/day D: 16 weeks</p> <p>GP2: Metformin (v) Mean: 1968 mg/day Range: 1500 - 2550 mg/day T: 2 to 3 times/day D: 16 weeks</p> <p>Glibenclamide (v) Mean: 14.2 mg/day T: NR D: 16 weeks</p>	<p>GP1 B: 83 (15.2) F: 84 (15.1) F-B: 1*</p> <p>GP2 B: 81.7 (15.7) F: 82.2 (15.4) F-B: 0*</p> <p>GP1-GP2: 1* p: 0.33</p>		<p>GP1 1 (0*) GP2 2 (1*)</p>	<p>Treatment-emergent adverse events GP1 number of events: 7 GP2 number of events: 5</p>	
Tirgoviste, 2003 ⁴³	<p>GP1: Insulin lispro 75/25 (v) Start: 0.3 - 0.5 U/kg T: Breakfast, dinner D: 16 weeks</p> <p>GP2: Glibenclamide (v) Start: 15 mg T: Breakfast, dinner D: 16 weeks</p>	<p>GP1 F-B: 1.32 (2.4) p: < 0.001</p> <p>GP2 F-B: -0.7 (2.6) GP1-GP2: 2*</p>				

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 ⁶²	GP1: Insulin lispro 75/25 (fix) Start: 2/3 of usual daily dose Mean: 44.1 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*)	
	GP2: Insulin lispro 50/50 (fix) Start: 2/3 of usual daily dose Mean: 43.8 U T: Breakfast D: 1 day					
Insulin lispro 50/50 vs. long-acting insulin analogues						
Kazda, 2006 ⁷⁶	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		GP1 F-B: 1.8 (3.4) GP2 F-B: 0.7 (3.8) GP1-GP2: 1*		GP1 0 (0*) GP2 0 (0*)	
	GP2: Insulin glargine (v) Start: 0.16 IU/kg/day--mean Mean: 0.43 IU/kg/day T: Bedtime D: 24 weeks	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*				

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 (%)
Robbins, 2007 ⁷⁹	GP1: Insulin lispro 50/50 (v) Mean: 0.7 U/kg T: Breakfast, lunch, dinner D: 24 weeks Metformin (fixed) Mean: 1641 mg T: bid D: 24 weeks	GP1 B: 89.1 (20.4) F: 90 (20.5) p: < 0.001 vs. GP2 F-B: 1.2 (3.2) p: < 0.001 vs. GP2	GP2	GP1 N and % of events: 11 (7%) p: NS GP2 N and % of events: 5 (3.2%)	GP1 5 (3.2) GP2 1 (0.6)	
	GP2: Insulin glargine (v) Mean: 0.6 U/kg T: Bedtime D: 24 weeks Metformin (fixed) Mean: 1636 mg T: bid D: 24 weeks	F-B: -0.5 (2.8) GP1-GP2: 1*				
Insulin lispro 50/50 vs. rapid-acting insulin analogues						
Kazda, 2006 ⁷⁶	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	GP1 F-B: 1.8 (3.4) GP2 F-B: 2.3 (4.3) GP1-GP2: 0*			GP1 0 (0*) GP2 0 (0*)	
	GP2: Insulin lispro (v) Start: 0.25 IU/kg/day-mean Mean: 0.50 IU/kg/day T: Breakfast, lunch, dinner D: 24 weeks	BMI (in kg/m ²) GP1 F-B: 0.6 (1.1) GP2 F-B: 0.9 (1.5) GP1-GP2: 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. rapid-acting with long-acting insulin analogues						
Rosenstock, 2008 ⁸⁰	<p>GP1: Insulin lispro 50/50 (v) Start: Insulin glargine dose at entry (52.5 U) Mean: 123 U T: Breakfast, lunch, dinner D: 24 weeks</p> <p>Insulin lispro 75/25 (v) Start: Allowed to switch evening dose to insulin lispro 75/25 T: Dinner D: Unclear</p> <p>GP2: Insulin glargine (v) Start: 50% of insulin glargine dose at entry (54.9 U) Mean: 70 U T: Bedtime D: 24 weeks</p> <p>Insulin lispro (v) Start: 50% of insulin glargine dose at entry divided in 3 equal doses (54.9 U) Mean: 76 U T: Breakfast, Lunch, dinner D: 24 weeks</p>			<p>GP1 6 (3.2) number of events: 9 p: 0.600 for incidence</p> <p>GP2 9 (4.8) number of events: 13</p>		

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 ¹⁰	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*)	
Schernthaner, 2004 ⁷⁷	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*)

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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 ⁶²	GP1: Insulin lispro 50/50 (fix) Start: 2/3 of usual daily dose Mean: 43.8 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*)	
	GP2: NPH/regular 70/30 (fix) Start: 2/3 of usual daily dose Mean: 44.1 U T: Breakfast D: 1 day					
Yamada, 2007 ⁷⁸	GP1: Insulin lispro 50/50 (v) Start: current dose Mean: 0.37 (start), 0.38 U/kg (end) T: bid D: 4 months	BMI (in kg/m2) GP1 B: 27 (5.8) F: 27.3 (5.9) F-B: 0* p: NS vs. baseline			GP1 0 (0*) GP2 0 (0*)	
	GP2: NPH/regular 70/30 (v) Start: current dose Mean: 0.34 (start), 0.37 U/kg (end) T: bid D: 4 months NPH/regular 50/50 (v) Start: current dose Mean: 0.34 (start), 0.37 U/kg (end) T: bid D: 4 months	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				

* Number has been imputed.

|| Among those who were 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 2004.⁴⁵ 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.

µg = microgram; B = baseline; bid = twice daily; BMI = body mass index; CI = 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; OA = oral antidiabetic; p = p-value; qd = once daily; SD = standard deviation; SE = standard error; T = time of day when insulin taken; tid = thrice daily; U = unit; U/l = units per liter; 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 ⁵³	Yes	Yes / NR	NA	No	Indep blind	Yes	< 10% / No	Partially	Pharmaceutical / Yes	Fair
Bebakar, 2007 ⁴⁶	Yes	Yes / NR	NA	No	Indep blind	Yes	< 10% / Yes	Yes	Pharmaceutical / NR	Good
Boehm, 2004 ⁴⁵ Boehm, 2002 ⁹	Yes	Yes / Yes	NA	Outcome assessors	Indep blind, self report	Yes	< 10% / Yes	Yes	Pharmaceutical / Yes	Good
Christiansen, 2003 ¹³	No	Yes / NR	NA	Patients, providers	Indep blind	Yes	< 10% / Yes	Partially	Pharmaceutical / Yes	Fair
Coscelli, 2003 ⁶⁷	Yes	Yes / NR	NA	No	Indep blind	Yes	NR / No	Yes	Pharmaceutical / NR	Fair
Cox, 2007 ⁷⁴	Yes	Yes / NR	NA	No	Indep blind, self report	Yes	> 10% / No	Yes	Pharmaceutical / NR	Fair
Hermansen, 2002 ⁵⁸	Yes	Yes / Yes	NA	No	Indep blind	No	< 10% / Yes	Yes	Pharmaceutical / NR	Fair
Herz, 2002 ⁷¹	Yes	Yes / NR	NA	No	Indep blind	Yes	< 10% / Yes	Yes	NR / NR	Fair
Herz, 2002 ⁷²	Yes	Yes / NR	NA	No	Indep blind, self report	Yes	< 10% / Yes	Partially	Pharmaceutical / Yes	Poor
Herz, 2003 ¹²	Yes	Yes / NR	NA	No	Indep blind	Yes	> 10% / No	Yes	Pharmaceutical / NR	Fair
Hirao, 2008 ⁶¹	Yes	Yes / NR	NA	No	Indep blind	Yes	> 10% / Yes	Yes	Non-pharmaceutical / No	Fair
Holman, 2007 ³²	Yes	Yes / Yes	NA	Outcome assessors	Indep blind, self report	Yes	< 10% / Yes	Yes	Pharmaceutical / Yes	Good
Jacober, 2006 ⁶⁴	Yes	Yes / NR	NA	No	Indep blind, self report	Yes	> 10% / Yes	Partially	Pharmaceutical / NR	Fair
Joshi, 2005 ⁵²	No	NA	Drawn from same community / other / NA	No	Indep blind	Yes	Complete FU / Yes	Partially	Pharmaceutical / Yes	Poor
Kann, 2006 ⁵⁰	Yes	Yes / Yes	NA	No	Indep blind	Yes	< 10% / Yes	Yes	Pharmaceutical / Yes	Good
Kapitza, 2004 ⁵⁶	Yes	Yes / NR	NA	No	Indep blind	No	Complete FU / No	Yes	Pharmaceutical / NR	Fair
Kazda, 2006 ⁷⁶	Yes	Yes / NR	NA	No	Indep blind, self report	Yes	< 10% / Yes	Yes	Pharmaceutical / Yes	Good
Kilo, 2003 ¹⁵	Yes	Yes / NR	NA	No	Indep blind, self report	Yes	< 10% / Yes	Yes	Pharmaceutical / NR	Good
Kvapil, 2006 ⁵¹	Yes	Yes / Yes	NA	No	Indep blind	Yes	< 10% / Yes	Yes	Pharmaceutical / NR	Good
Ligthelm, 2006 ⁸³	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 ⁴⁴ Malone, 2000 ¹⁴	Yes	Yes / NR	NA	Patients, providers	Indep blind	No	< 10% / Yes	Yes	NR / NR	Fair
Malone, 2003 ⁶⁸	Yes	Yes / NR	NA	No	Indep blind, self report	Yes	Complete FU / Yes	Yes	Pharmaceutical / NR	Good
Malone, 2004 ⁶⁵	Yes	Yes / Yes	NA	No	Indep blind, self report	Yes	< 10% / Yes	Yes	NR / NR	Poor
Malone, 2005 ⁶⁶	Yes	Yes / NR	NA	No	Indep blind, self report	Yes	< 10% / Yes	Yes	NR / Yes	Fair
Mattoo, 2003 ⁷⁰	Yes	Yes / NR	NA	No	Indep blind, self report	Yes	< 10% / No	Yes	Pharmaceutical / NR	Fair
McNally, 2007 ⁴⁸	Yes	Yes / Yes	NA	Patients, providers	Indep blind, self report	Yes	< 10% / Yes	Yes	NR / Yes	Good
McSorley, 2002 ¹¹	Yes	Yes / NR	NA	Patients, providers	Indep blind	Yes	NR / No	Yes	Pharmaceutical / NR	Fair
Nauck, 2007 ⁴⁹	Yes	Yes / Yes	NA	No	Indep blind	Yes	< 10% / Yes	Yes	Pharmaceutical / Yes	Good
Niskanen, 2004 ⁵⁵	Yes	Yes / Yes	NA	No	Indep blind, self report	Yes	< 10% / Yes	Yes	Pharmaceutical / NR	Good
Raskin, 2005 ³⁹ Raskin, 2007 ⁴⁰ Brod, 2007 ⁴¹	Yes	Yes / Yes	NA	No	Indep blind	Yes	< 10% / Yes	Yes	Pharmaceutical / Yes	Good
Raskin, 2007 ⁶⁰	No	Yes / NR	NA	No	Indep blind	Yes	< 10% / Yes	Yes	NR / No	Fair
Raz, 2003 ⁵⁷	Yes	Yes / Yes	NA	No	Indep blind, medical record review, self report	No	< 10% / Yes	Yes	Pharmaceutical / NR	Fair
Raz, 2005 ⁵⁴	Yes	Yes / NR	NA	No	Indep blind	Yes	> 10% / Yes	Yes	Pharmaceutical / Yes	Fair
Roach, 1999 ⁷³	Yes	Yes / NR	NA	No	Indep blind, self report	Yes	< 10% / Yes	Yes	Pharmaceutical / Yes	Fair
Roach, 1999 ¹⁰	Yes	Yes / NR	NA	No	Indep blind	Yes	Complete FU / Yes	Yes	Pharmaceutical / NR	Fair
Roach, 2003 ⁶⁹	Yes	Yes / NR	NA	Patients, providers	Indep blind	No	< 10% / Yes	Yes	Pharmaceutical / NR	Good
Roach, 2006 ⁶³	Yes	Yes / NR	NA	No	Indep blind	Yes	> 10% / Yes	Yes	Pharmaceutical / Yes	Fair
Robbins, 2007 ⁷⁹	Yes	Yes / Yes	NA	No	Indep blind	Yes	< 10% / Yes	Yes	Pharmaceutical / Yes	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†
Scherthaner, 2004 ⁷⁷	Yes	Yes / NR	NA	No	Indep blind	Yes	< 10% / Yes	Yes	Pharmaceutical / NR	Fair
Rosenstock, 2008 ⁸⁰	Yes	Yes / Yes	NA	No	Indep blind	Yes	> 10% / Yes	Yes	Pharmaceutical / Yes	Good
Schwartz, 2006 ⁶²	Yes	Yes / NR	NA	Patients, providers	Indep blind	No	< 10% / Yes	Yes	Pharmaceutical / Yes	Fair
Tamemoto, 2007 ⁴⁷	Yes	Yes / No	NA	No	No description	Yes	< 10% / Yes	Yes	NR / NR	Poor
Tirgoviste, 2003 ⁴³ Roach, 2001 ⁴²	Yes	Yes / Yes	NA	No	Indep blind, self report	Yes	Complete FU / Yes	Yes	NR / NR	Good
Sun, 2007 ⁷⁵	Yes	NA	Drawn from the same community / secure record / NA	No	Medical record review	Yes	> 10% / No	Yes	Pharmaceutical / Yes	Fair
Ushakova, 2007 ⁵⁹	Yes	Yes / Yes	NA	No	Indep blind	Yes	< 10% / Yes	Yes	Pharmaceutical / No	Good
Yamada, 2007 ⁷⁸	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 ⁵³	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 ⁴⁶	NR / ≥50% / Yes	Sex: Yes Age: NR Race/ethnicity: No: Western Pacific countries	No: insulin naive	Yes for all 3	Yes	Yes / NR	Yes / No	Yes
Boehm, 2004 ⁴⁵ Boehm, 2002 ⁹	NR / ≥50% / No	Sex: Yes Age: Yes Race/ethnicity: NR	Yes	Yes for all 3	Yes	Yes / Yes	Yes / Yes	No
Christiansen, 2003 ¹³	NR / NR / No	Sex: Yes Age: Yes Race/ethnicity: No: different from US racial and ethnic make-up	Yes	Yes for all 3	No: monitoring too frequent	Yes / Yes	No / Yes	Yes
Coscelli, 2003 ⁶⁷	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 ⁷⁴	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

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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 ⁵⁸	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 ⁷¹	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 ⁷²	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 ¹²	NR / NR / No	Sex: Yes Age: Yes Race/ethnicity: NR	No: all respondents have been taking insulins, none were currently taking an OA agent	Yes for all 3	No: investigators telephoned patients at least once weekly	Yes / Yes	No / Yes	No
Hirao, 2008 ⁶¹	Clinics and hospitals affiliated with JDDM / NR / NA	Sex: Yes Age: NR Race/ethnicity: No: Japanese study	Yes	Yes for all 3	Yes	Yes / Yes	Yes / Yes	Yes
Holman, 2007 ³²	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 ⁶⁴	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 ⁵²	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 ⁵⁰	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 ⁵⁶	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 ⁷⁶	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 OA agents as opposed to give it alone / Yes	No / Yes	No
Kilo, 2003 ¹⁵	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 ⁵¹	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 ⁶³	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 ⁴⁴ Malone, 2000 ¹⁴	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 ⁶⁸	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 patient visits every 4 weeks for 16 weeks	Yes / Yes	No / Yes	No
Malone, 2004 ⁶⁵	NR / ≥50% / No	Sex: Yes Age: Yes Race/ethnicity: NR	No: patients were insulin naive and had to be poorly controlled on an OA agent for at least 30 days	Yes for all 3	Yes	Yes / Yes	No / Yes	No
Malone, 2005 ⁶⁶	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 ⁷⁰	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
McNally, 2007 ⁴⁸	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

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
McSorley, 2002 ¹¹	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 ⁴⁹	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 ⁵⁵	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 ³⁹ Raskin, 2007 ⁴⁰ Brod, 2007 ⁴¹	NR / NR / Yes	Sex: Yes Age: NR Race/ethnicity: Yes	No: insulin naive patients	Yes for all 3	Yes	Yes / Yes	No / Yes	No
Raskin, 2007 ⁶⁰	NR / ≥50% / Yes	Sex: Yes Age: Yes Race/ethnicity: Yes	No: insulin naive patients were enrolled	Yes for all 3	Yes	No: comparison is placebo, technically / No: comparison is technically placebo	No / Yes	No
Raz, 2003 ⁵⁷	Outpatient clinics / NR / No	Sex: Yes Age: Yes Race/ethnicity: No: 82% Caucasian	No: insulin naive patients	Yes for all 3	Yes	No / No: insulin dose was adjusted while glibenclamide and rosiglitazone doses were not adjusted	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, 2005 ⁵⁴	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 ⁷³	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 ¹⁰	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 ⁶⁹	NR / NR / No	Sex: Yes Age: Yes Race/ethnicity: No: 100% Western Asian (Indian)	No: all had to have been taking insulin; excluded respondents taking OA agents	Yes for all 3	Yes	Yes / Yes	No / Yes	Yes
Roach, 2006 ⁶³	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 OA agent or insulin for at least 3 months	Yes for all 3	Yes	Yes / Yes	No / Yes	No
Robbins, 2007 ⁷⁹	NR / ≥50% / No	Sex: Yes Age: Yes Race/ethnicity: No: only 6% African American and 22% were Asian but rest were representative (i.e. Caucasian and Hispanic numbers representative)	No: did not include those with renal or liver complications	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
Rosenstock, 2008 ⁸⁰	NR / >=50% / NA	Sex: Yes Age: NR Race/ethnicity: Yes	No: only those already receiving insulin	Yes for all 3	No: blood glucose was checked much more often: patients met with physicians much more often	Yes / Yes	No / Yes	No
Scherthaler, 2004 ⁷⁷	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 ⁶²	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
Sun, 2007 ⁷⁵	NR / NR / NA	Sex: Yes Age: Yes Race/ethnicity: Yes	No: insulin naive	Yes for all 3	Yes	Yes / Yes	No / Adverse outcomes not reported	No
Tamemoto, 2007 ⁴⁷	Outpatient clinics / NR / No	Sex: Yes Age: Yes Race/ethnicity: No: assumed 100% Japanese	No: had diabetes for at least 1 year	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
Tirgoviste, 2003 ⁴³ Roach, 2001 ⁴²	NR / NR / No	Sex: Yes Age: NR Race/ethnicity: NR	No: only patients needing 1 OA agent	Yes for all 3	No: there were 5 visits in 12 weeks. Dose adjustments for insulin were made every 2-3 days.	No: OA agent dose could not increase / No: could not increase the OA agent dose	No / Yes	Yes
Ushakova, 2007 ⁵⁹	NR / >=50% / NR	Sex: No: majority of respondents were female Age: Yes Race/ethnicity: No: likely majority Caucasian	No: those treated with insulin or with diabetes-related complications were excluded	Yes for all 3	Yes	Yes / Yes	No / Yes	Yes
Yamada, 2007 ⁷⁸	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; OA = oral antidiabetic; 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 ³²	GP1: Insulin aspart 70/30 (v) Start: 16 median IU/day Range: 10 – 26 IU/day T: bid D: 1 year Usual care D: 1 year	GP1 3 (1*) GP2 0 (0*)	Myocardial infarction GP1 3 (1*) GP2 0 (0*)		Change in plasma creatinine, mean (SD) GP1 F-B: 0.05 (0.09) p: 0.008 vs. GP2 GP2 F-B: 0.02 (0.11) GP1-GP2: 0*
	GP2: Insulin detemir (v) Start: 16 median IU/day Range: 10 – 24 IU/day T: Bedtime, twice if required D: 1 years Usual care D: 1 year				Change in ratio of albumin to creatinine, median (IQR) GP1 F-B: -0.9 (-8 – 9.7) p: overall 0.07 GP2 F-B: -1.8 (-10.6 – 2.7) GP1-GP2: 1*
Kann, 2006 ⁵⁰	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			Peripheral vascular disorder GP1 1 (0.8) GP2 0 (0)	
	GP2: Insulin glargine (v) Start: 0.2 U/kg qday Mean: 0.39 U/kg T: preferred time D: 26 weeks Glimepiride (v) Start: 1 mg daily or current dose T: Breakfast D: 26 weeks			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 ³²	GP1: Insulin aspart 70/30 (v) Start: 16 median IU/day Range: 10 – 26 IU/day T: bid 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, mean (SD) GP1 F-B: 0.05 (0.09) p: 0.62 vs. GP2 GP2 F-B: 0.05 (0.12) GP1-GP2: 0*
	GP2: Insulin aspart (v) Start: 18 median IU/day Range: 9 – 24 IU/day T: Breakfast, lunch, dinner D: 1 year Usual care D: 1 year				Change in ratio of albumin to creatinine, median (IQR) GP1 F-B: -0.9 (-8 – 9.7) p: overall 0.07 GP2 F-B: -0.9 (-12.4 – 6.2) GP1-GP2: 0*
Insulin aspart 70/30 vs. premixed human insulins					
Boehm, 2004 ⁴⁵	GP1: Insulin aspart 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	
	GP2: NPH/regular 70/30 (v) Start: 0.57 U/Kg T: Breakfast, dinner D: 24 months				
Hermansen, 2002 ⁵⁸	GP1: Insulin aspart 70/30 (fix) Start: 0.4 U/kg T: Breakfast D: 1 day			Transient ischemic attack GP1 1 (2*) GP2 0 (0)	
	GP2: NPH/regular 70/30 (fix) Start: 0.4 U/kg T: Breakfast D: 1 day				

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 ⁵¹	GP1: Insulin aspart 70/30 (v) Start: 0.3 U/kg/day Mean: 0.51 U/kg/day T: Breakfast, dinner D: 16 weeks	GP1 0 (0*) GP2 0 (0*)	Myocardial infarction GP1 0 (0*) GP2 0 (0*)		
	GP2: Metformin (fix) Mean: 1660 mg daily Range: 500 - 3000 mg qd T: NR D: 16 weeks Glibenclamide (v) Start: 1.75 mg Mean: 2.33 (start), 6.58 mg (end) T: once or twice daily D: 16 weeks				
E-140 Kvapil, 2006 ⁵¹	GP1: Insulin aspart 70/30 (v) Start: 0.2 U/kg/day Mean: 0.3 U/kg/day T: Breakfast, dinner D: 16 weeks	GP1 1 (1*) GP2 0 (0*)	Myocardial infarction GP1 1 (1*) GP2 0 (0*)		
	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 Glibenclamide (v) Start: 1.75 mg Mean: 2.33 (start), 6.58 mg (end) T: once or twice daily D: 16 weeks				

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 (%)
Raskin, 2007 ⁶⁰	<p>GP1: Insulin aspart 70/30 (v) Start: 6 U bid Mean: 0.6 U/kg/day T: Breakfast, dinner D: 34 weeks Metformin (fix) Mean: 2446 mg T: NR D: 34 weeks Pioglitazone (fix) Mean: 32.5 mg T: NR D: 34 weeks</p> <p>GP2: metformin (fix) Mean: 2439 mg T: NR D: Unclear Pioglitazone (fix) Mean: 31.7 T: NR D: Unclear</p>			<p>Withdrawn due to arrhythmia, angina pectoris, and coronary artery disease GP1 1 (1*) GP2 2 (2*)</p>	<p>Withdrawn due to increased blood creatinine GP1 1 (1*) GP2 0 (0*)</p>
Raz, 2003 ⁵⁷	<p>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</p> <p>GP2: Glibenclamide (fix) Range: 7.5 – 15 mg T: Dinner D: 6 weeks Rosiglitazone (fix) Start: 4 mg T: Breakfast D: 6 weeks</p>			<p>Non-fatal myocardial infarction GP1 1 (4*) GP2 0 (0*)</p>	

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 ⁵⁴	GP1: Insulin aspart 70/30 (v) Start: 0.3 U/kg/day Mean: 0.7 U/kg/day T: Breakfast, dinner D: 18 weeks			Non-fatal myocardial infarction GP1 1 (1*) GP2 0 (0*)	
	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				
Raz, 2005 ⁵⁴	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			Non-fatal myocardial infarction GP1 0 (0*) GP2 0 (0*)	
	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				

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. exenatide					
Nauck, 2007 ⁴⁹	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	GP1 1 (0.4) GP2 2 (0.8)		Unspecified cardiac disorder adverse events GP1 5 (2*) GP2 10 (4*)	
	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				
Insulin aspart 70/30 vs. insulin lispro 75/25					
Hermansen, 2002 ⁵⁸	GP1: Insulin aspart 70/30 (fix) Start: 0.4 U/kg T: Breakfast D: 1 day			Transient ischemic attack GP1 1 (2*) GP2 0 (0)	
	GP2: Insulin lispro 75/25 (fix) Start: 0.4 U/kg T: Breakfast D: 1 day				
Niskanen, 2004 ⁵⁵	GP1: Insulin aspart 70/30 (v) Mean: 0.65 U/kg to 0.67 U/kg T: Breakfast, dinner D: 12 weeks	GP1 0 (0*) GP2 1 (1*)	Myocardial infarction GP1 0 (0*) GP2 1 (1*)		
	GP2: Insulin lispro 75/25 (v) Mean: 0.67 U/kg to 0.71 U/kg T: Breakfast, dinner D: 12 weeks				

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 aspart 70/30 + oral antidiabetic agents					
Kvapil, 2006 ⁵¹	GP1: Insulin aspart 70/30 (v) Start: 0.3 U/kg/day Mean: 0.51 U/kg/day T: Breakfast, dinner D: 16 weeks	GP1 0 (0*) GP2 1 (1*)	Myocardial infarction GP1 0 (0*) GP2 1 (1*)		
	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				
Raz, 2005 ⁵⁴	GP1: Insulin aspart 70/30 (v) Start: 0.3 U/kg/day Mean: 0.7 U/kg/day T: Breakfast, dinner D: 18 weeks			Non-fatal myocardial infarction GP1 1 (1*) GP2 0 (0*)	
	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				

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 analogue with intermediate-acting human insulin					
Hirao, 2008 ⁶¹	GP1: Insulin aspart 70/30 (NR) T: bid D: 6 months	GP1 1 (1*) GP2 0 (0*)			
	GP2: Insulin aspart (NR) T: tid D: 6 months NPH insulin (NR) T: Optional multiple daily injections D: 6 months				
Insulin lispro 75/25 vs. long-acting insulin analogues					
Malone, 2004 ⁶⁵	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			Congestive heart failure GP1 1 (1*) GP2 0 (0*)	
	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				

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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 ⁶⁶	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	GP1 1 (1*)	Myocardial infarction GP1 1 (1*)		
	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	GP2 1 (1*)	GP2 0 (0*)		
Insulin lispro 75/25 vs. premixed human insulins					
Hermansen, 2002 ⁵⁸	GP1: Insulin lispro 75/25 (fix) Start: 0.4 U/kg T: Breakfast D: 1 day			Transient ischemic attack GP1 0 (0)	
	GP2: NPH/regular 70/30 (fix) Start: 0.4 U/kg T: Breakfast D: 1 day			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 ⁶⁸	GP1: Insulin lispro 75/25 (v) Mean: 0.19 (morning), 0.14 U/kg (evening) T: Breakfast, dinner D: 16 weeks	GP1 1 (0*)			
	Metformin (v) Mean: 1813 mg/day Range: 1500 – 2550 mg/day T: 2 to 3 divided doses with meals D: 16 weeks	GP2 0 (0*)			
	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				
Insulin lispro 50/50 vs. premixed human insulins					
Schern- thaler, 2004 ⁷⁷	GP1: Insulin lispro 50/50 (v) Mean: 64.6 IU T: Breakfast, lunch, dinner D: 12 weeks	GP1 0 (0*)			
	Diet/exercise D: 12 weeks	GP2 1 (2*)			
	GP2: NPH/regular 70/30 (v) Mean: 61.8 IU T: Breakfast, dinner D: 12 weeks				
	Diet/exercise D: 12 weeks				

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 50/50 vs. long-acting insulin analogues					
Robbins, 2007 ⁷⁹	GP1: Insulin lispro 50/50 (v) Mean: 0.7 U/kg T: Breakfast, lunch, dinner D: 24 weeks Metformin (fixed) Mean : 1641 mg T: bid D: 24 weeks GP2: Insulin glargine (v) Mean: 0.6 U/kg T: Bedtime D: 24 weeks Metformin (fixed) Mean: 1636 mg T: bid D: 24 weeks				Withdrew due to renal insufficiency GP1 0 (0) GP2 1 (0.6)

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; tid = thrice daily; 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 = 6 studies)		
Bayesian	6.00	0.32 to 237.4
Mantel-Haenszel (0.5 cont corr)	2.39	0.87 to 6.59
Mantel-Haenszel (0.1 cont corr)	2.93	0.95 to 9.05
Mantel-Haenszel (0.01 cont corr)	3.10	0.97 to 9.91
Peto	3.05	1.04 to 8.93
Cardiovascular disease mortality (n = 3 studies)		
Bayesian	-*	-*
Mantel-Haenszel (0.5 cont corr)	3.80	0.76 to 18.98
Mantel-Haenszel (0.1 cont corr)	6.80	0.87 to 53.12
Mantel-Haenszel (0.01 cont corr)	8.56	0.92 to 79.55
Peto	6.60	1.23 to 35.47
Cardiovascular disease morbidity (n = 6 studies)		
Bayesian	0.89	0.33 to 3.05
Mantel-Haenszel (0.5 cont corr)	0.85	0.49 to 1.49
Mantel-Haenszel (0.1 cont corr)	0.86	0.49 to 1.52
Mantel-Haenszel (0.01 cont corr)	0.86	0.49 to 1.52
Peto	0.86	0.49 to 1.52
Combined outcome of mortality and cardiovascular disease morbidity (n = 10 studies)		
Bayesian	3.36	0.96 to 16.82
Mantel-Haenszel (0.5 cont corr)	1.78	0.80 to 3.96
Mantel-Haenszel (0.1 cont corr)	2.10	0.87 to 5.10
Mantel-Haenszel (0.01 cont corr)	2.21	0.89 to 5.49
Peto	2.20	0.92 to 5.27

*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

Evidence Table 11. Grading of the body of evidence of the effects of premixed insulin analogues in patients taking oral antidiabetic agents

	Intermediate outcomes					
	A1c	Fasting glucose	Pre-dinner glucose	2-hour postprandial glucose after breakfast	2-hour postprandial glucose after dinner	Quality of life
Quantity of evidence: Number of studies	3	3	3	3	3	1
Range of sample sizes	281-329	281-329	281-329	281-329	281-329	308
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	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)?	-1	-1	-1	-1	-1	-1
Were data imprecise or sparse? (-1) (i.e. lack of data or very wide confidence intervals that may change conclusions)	-1	-1	-1	-1	-1	-1
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)	Low	Low	Low	Low	Low	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; very low = any estimate of effect is very uncertain.

Evidence Table 11. Grading of the body of evidence of the effects of premixed insulin analogues in patients taking oral antidiabetic agents (continued)

	Safety/adverse events and clinical outcomes					
	Hypoglycemia	Weight change	All-cause mortality	CVD mortality	CVD morbidity	Nephropathy
Quantity of evidence: Number of studies	3	3	1	1	2	0
Range of sample sizes	281-329	281-329	329	329	281-329	0
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	High	High	0
Did the studies have serious (-1) or very serious (-2) limitations in quality? (Enter 0 if none)	0	0	-1	-1	-1	0
Did the studies have important inconsistency? (-1)	0	-1	0	0	-1	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	-1	-1	-1	-1	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	-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)	Low	Low	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.

