

Systematic Review: Comparative Effectiveness and Safety of Premixed Insulin Analogues in Type 2 Diabetes

Rehan Qayyum, MD; Shari Bolen, MD, MPH; Nisa Maruthur, MD, MHS; Leonard Feldman, MD; Lisa M. Wilson, ScM; Spyridon S. Marinopoulos, MD, MBA; Padmini Ranasinghe, MD, MPH; Muhammed Amer, MD; and Eric B. Bass, MD, MPH

Background: Evidence comparing premixed insulin analogues (a mixture of rapid-acting and intermediate-acting insulin analogues) with other antidiabetic agents is urgently required to guide appropriate therapy.

Purpose: To summarize the English-language literature on the effectiveness and safety of premixed insulin analogues compared with other antidiabetic agents in adults with type 2 diabetes.

Data Sources: The authors searched MEDLINE, EMBASE, CINAHL, and the Cochrane Central Register of Controlled Trials from inception to February 2008 and sought unpublished data from the U.S. Food and Drug Administration, European Medicines Agency, and industry.

Study Selection: Studies with control groups that compared premixed insulin analogues with another antidiabetic medication in adults with type 2 diabetes.

Data Extraction: 2 reviewers using standardized protocols performed serial abstraction.

Data Synthesis: Evidence from clinical trials was inconclusive for clinical outcomes, such as mortality. Therefore, the review focused on intermediate outcomes. Premixed insulin analogues were similar to premixed human insulin in decreasing fasting glucose levels, hemoglobin A_{1c} levels, and the incidence of hypoglycemia but were more effective in decreasing postprandial glucose levels (mean difference, -1.1 mmol/L; 95% CI, -1.4 to -0.7 mmol/L [-19.2 mg/dL; 95% CI, -25.9 to -12.5 mg/dL]). Compared with long-

acting insulin analogues, premixed insulin analogues were superior in decreasing postprandial glucose levels (mean difference, -1.5 mmol/L; CI, -1.9 to -1.2 mmol/L [-27.9 mg/dL; CI, -34.3 to -21.5 mg/dL]) and hemoglobin A_{1c} levels (mean difference, -0.39% [CI, -0.50% to -0.28%]) but were inferior in decreasing fasting glucose levels (mean difference, 0.7 mmol/L; CI, 0.3 to 1.0 mmol/L [12.0 mg/dL; CI, 6.0 to 18.1 mg/dL]) and were associated with a higher incidence of hypoglycemia. Compared with noninsulin antidiabetic agents, premixed insulin analogues were more effective in decreasing fasting glucose levels (mean difference, -1.1 mmol/L; CI, -1.7 to -0.6 mmol/L [-20.5 mg/dL; CI, -29.9 to -11.2 mg/dL]), postprandial glucose levels (mean difference, -2.1 mmol/L; CI, -3.4 to -0.8 mmol/L [-37.4 mg/dL; CI, -61.0 to -13.7 mg/dL]), and hemoglobin A_{1c} levels (mean difference, -0.49% [CI, -0.86% to -0.12%]) but were associated with a higher incidence of hypoglycemia.

Limitations: The literature search was restricted to studies published in English. Data on clinical outcomes were limited. The small number of studies for each comparison limited assessment of between-study heterogeneity.

Conclusion: Premixed insulin analogues provide glycemic control similar to that of premixed human insulin and may provide tighter glycemic control than long-acting insulin analogues and noninsulin antidiabetic agents.

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For author affiliations, see end of text.

According to the National Health Interview Survey, 28% of patients with type 2 diabetes are using insulin, either alone (16%) or in combination with oral antidiabetic agents (12%) (1). In the management of type 2 diabetes, the role of premixed insulin analogues relative to other insulin regimens and noninsulin antidiabetic agents is unclear. Premixed insulin analogues are derived from rapid-acting insulin analogues and consist of a mixture of a rapid-acting insulin analogue and its intermediate-acting protaminated form. Premixed insulin analogues may be a better alternative than premixed human insulin preparations for patients who wish to have a near-physiologic insulin administration regimen but want to avoid multiple daily insulin injections. In addition, they may allow patients flexible meal times, because these preparations can be administered from 15 minutes before meals to immediately after a meal. Given the increasing prevalence of type 2 diabetes (2), the number of patients who use insulin for glycemic control (1), and the importance of glycemic control in decreasing mortality and morbidity (3), it is imperative to establish the weight of evidence for the safety and effectiveness of these relatively newer insulin preparations

compared with traditional insulin preparations. Therefore, the Agency for Healthcare Research and Quality commissioned a systematic review of published studies on the comparative effectiveness and safety of all the premixed insulin analogues that are approved by the U.S. Food and Drug Administration and are available in the United States.

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Appendix Table
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CME quiz
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Context

The relative effects of premixed insulin analogues, other insulin regimens, and noninsulin antidiabetic agents for adults with type 2 diabetes are unclear.

Contribution

This systematic review of comparative trials in adults with type 2 diabetes found that premixed insulin analogues and premixed human insulin provided similar glycemic control. Premixed analogues provided tighter glycemic control and caused more hypoglycemia than long-acting insulin analogues and noninsulin antidiabetic agents.

Caution

Evidence for effects on clinical outcomes was scant and inconclusive.

Implication

We need large, long-term trials that compare premixed insulin analogues with other agents to see whether improvements in glucose control lead to improved clinical outcomes.

—The Editors

METHODS**Data Sources**

We searched MEDLINE, EMBASE, the Cochrane Central Register of Controlled Trials, and CINAHL from inception to February 2008. The complete search strategy is available at <http://effectivehealthcare.ahrq.gov/>. We also reviewed reference lists of included articles, recent issues of 13 medical journals, the U.S. Food and Drug Administration and European Medicines Agency Web sites for the premixed insulin analogues, unpublished data from premixed insulin analogue manufacturers (Eli Lilly and Company, Indianapolis, Indiana; Sanofi-Aventis, Bridgewater, New Jersey; and Novo Nordisk, Bagsvaerd, Denmark), and Web sites of public registries of clinical trials (ClinicalTrials.gov and ClinicalStudyResults.org).

Study Selection

We included studies that compared a premixed insulin analogue approved by the U.S. Food and Drug Administration as of February 2008 with any other drug for adults with type 2 diabetes and evaluated clinical outcomes (such as mortality), intermediate outcomes (such as hemoglobin A_{1c} level), or adverse events (such as hypoglycemia). We included randomized, controlled trials (RCTs); controlled clinical trials; and observational studies with control groups, regardless of their duration or sample size. However, we used data from crossover studies only for intermediate outcomes and hypoglycemia. We excluded crossover trials from the quantitative evaluation of outcomes that were either progressive (for example, retinopathy) or irreversible (for example, death). For the evaluation of hemo-

globin A_{1c}, we included crossover trials with at least 12 weeks of follow-up before and after the crossover phase. We aimed to use within-individual comparisons from crossover trials if trials had reported data in such detail, but no study did so. Because all crossover studies reported results for each intervention and no trial reported a statistically significant carryover effect, we ignored the crossover design and used reported estimates as if they came from a parallel trial. We excluded non-English-language articles, editorials, comments, letters, and abstracts.

Data Extraction and Quality Assessment

Two investigators independently reviewed the titles, abstracts, and full articles for inclusion and abstracted data by using standardized forms. We developed a study quality assessment tool based on the Jadad criteria (4), the Newcastle-Ottawa Scale (5), and questions from Agency for Healthcare Research and Quality's guide for conducting comparative effectiveness reviews (6). We adapted the evidence grading scheme recommended by the GRADE (Grading of Recommendations Assessment, Development and Evaluation) Working Group (7) to classify the strength of the body of evidence on each comparison as high, moderate, low, or insufficient.

Data Synthesis and Analysis

We conducted meta-analyses for outcomes when data were sufficient (≥ 2 trials). For intermediate outcomes (fasting glucose, postprandial glucose, and hemoglobin A_{1c} levels) and the adverse outcome of weight gain, we recorded the mean difference between groups, along with its measure of dispersion. If this was not reported, we calculated the point estimate by using the mean difference from baseline for each group. If the mean difference from baseline was not reported, we calculated this from the baseline and final values for each group. If no measure of dispersion was reported for the between-group difference, we calculated it by using the sum of the variances for the mean difference from baseline for each group. If there were no measures of dispersion for the mean difference from baseline for each group, we calculated the variance by using the standard deviation of the baseline and final values, assuming a correlation between baseline and final values of 0.5.

We pooled the results of the plasma and blood glucose levels from different studies because blood glucose measurements accurately reflect plasma glucose levels (8). For hypoglycemia, we used 2 strategies to synthesize data. If a trial reported the incidence of hypoglycemia, we calculated an odds ratio (OR) by using the incidence of hypoglycemia in each study group. If a trial did not report the incidence of hypoglycemia but reported event rates in episodes per patient per 30 days, we calculated the rate ratio by dividing the event rate in the premixed insulin analogue group by the event rate in the comparator group. If a trial reported the number of episodes in each group or reported an event rate in a form other than episodes per patient per 30 days, we converted this information into episodes per patient per

30 days. We pooled the results of individual studies by using a random-effects model. These analyses were conducted by using Comprehensive Meta-Analysis, version 2.2.046 (Biostat, Englewood, New Jersey).

For clinical outcomes, we included all studies that reported any information about clinical events (all-cause mortality and cardiovascular mortality and morbidity). All analyses followed the intention-to-treat principle. We combined results from the premixed insulin analogue group of different trials, assuming that the results were similar enough between premixed insulin analogues. In the study with 3 groups and comparing a premixed insulin analogue with 2 different insulin preparations (9), we chose the most relevant comparison to include in the meta-analyses (premixed insulin analogue vs. long-acting insulin analogue). We calculated pooled ORs and 95% CIs by using a Mantel-Haenszel fixed-effects model (with a 0.1 continuity correction) in Stata Intercooled, version 9.2 (Stata, College Station, Texas) (10, 11). For analysis of clinical outcomes, we used a fixed-effects model because it is less biased with rare event data (12). For sensitivity analyses, we used 3 meta-analytic methods: the Peto method, the Mantel-Haenszel fixed-effects model (with 0.5 and 0.01 continuity corrections), and Bayesian analysis (13). Heterogeneity among the trials was tested by using a standard chi-square test, with a significance level of 0.10 or less. We also examined inconsistency among studies by using an I^2 statistic (14); a value greater than 50% represented substantial variability.

For all outcomes, we conducted sensitivity analyses by omitting 1 study at a time. We assessed publication bias visually by examining the symmetry of funnel plots and statistically by using the Begg (15) and Egger (16) tests.

Role of the Funding Source

The Agency for Healthcare Research and Quality suggested the initial questions and provided copyright release for this manuscript but did not participate in the literature search, data analysis, or interpretation of the results.

RESULTS

Study Characteristics

The **Appendix Figure** (available at www.annals.org) shows the results of the literature search. We found 45 studies that reported at least 1 of the intermediate clinical outcomes or adverse events (**Appendix Table**, available at www.annals.org). All studies except 2 (17, 18) were RCTs. In 1 study (17), patients were enrolled consecutively and followed prospectively, and in the other study (18), data were obtained from the medical record database of a large employer. Among the RCTs, 23 were parallel-group (9, 19–40) and 20 were crossovers (41–60). The median duration of follow-up in these trials was 16 weeks (range, 1 day to 2 years).

The trials enrolled a total of 14 603 patients (median per trial, 93 patients [range, 8 to 8166 patients]). Patients had a median age of 59 years (range, 51 to 68 years), and

most were male (median, 52% [range, 16% to 92%]) (**Appendix Table**, available at www.annals.org). The study populations had a median hemoglobin A_{1c} level of 8.7% (range, 7.3% to 10.7%), a median body mass index of 29.4 kg/m² (range, 24 to 37 kg/m²), and a median duration of diabetes of 11 years (range, 4 to 16 years). Eleven trials enrolled insulin-naïve patients (9, 18, 19, 27, 29, 33, 34, 36, 38, 43, 44), 26 enrolled insulin-treated patients (23, 25, 28, 32, 34, 35, 37, 39–42, 45–55, 57–60), and 9 did not specify history of insulin treatment (17, 20–22, 24, 26, 30, 31, 56).

Study Quality and Applicability

Randomization methods were described in 17 studies (9, 20–22, 24, 27–30, 35–37, 39, 41, 44, 46, 59) and were adequate in all except 1 (20). Five trials used blinding for patients and providers (32, 41, 49, 57, 60), and 2 trials used blinding for outcome assessors (9, 28). It is difficult to achieve blinding of patients and providers because premixed insulin analogues need to be given with meals, whereas the other insulin preparations are generally given at other times or with different frequency. The funding source was the pharmaceutical industry in all studies except 2: One was funded jointly by the National Institutes of Health and Eli Lilly (56), and the other was funded by the Japan Diabetes Foundation (40). Six trials did not report their funding source (29, 38, 44, 45, 52, 60).

All but 5 studies (20, 34, 41, 47, 57) enrolled patients similar in age to the general U.S. diabetic population. Women were underrepresented in 5 trials (17, 19, 30, 35, 57), and 2 trials (27, 36) included more women than men. In most trials, the spectrum of diabetic complications and comorbid conditions among the enrolled participants was limited. All trials either excluded patients with cardiac, renal, or hepatic disease or did not report whether such patients were included, thus limiting our ability to generalize the results to these subpopulations.

Publication Bias

Using the Egger test, we found evidence of possible publication bias for the comparison between premixed insulin analogues and noninsulin antidiabetic agents and between insulin aspart 70/30 and noninsulin antidiabetic agents for fasting glucose (1-sided $P = 0.07$ and 0.05 , respectively) and for mild hypoglycemia (1-sided $P = 0.03$ and 0.07 , respectively). Not enough studies were available to assess possible bias for other comparisons.

Premixed Insulin Analogues versus Long-Acting Insulin Analogues

Premixed insulin analogues were less effective than long-acting insulin analogues (administered alone) in decreasing fasting glucose levels (pooled difference, 0.7 mmol/L; 95% CI, 0.3 to 1.0 mmol/L [12.0 mg/dL; CI, 6.0 to 18.1 mg/dL]) (**Table** and **Figures 1 to 4**). Individually, insulin lispro 75/25 and insulin lispro 50/50 were less effective than long-acting insulin in decreasing fasting

Table. Strength of the Evidence Comparing Premixed Insulin Analogues with Other Antidiabetic Agents for Intermediate Outcomes and Adverse Events

Outcome	Strength of Evidence*			
	Premixed Insulin Analogues vs. Long-Acting Insulin Analogues	Premixed Insulin Analogues vs. Premixed Human Insulin	Premixed Insulin Analogues vs. Other Insulin Regimens	Premixed Insulin Analogues vs. Noninsulin Antidiabetic Agents
Fasting glucose level	Moderate; favors long-acting insulin analogues	Moderate; suggests similar effectiveness	Low; cannot make a conclusion	Moderate; favors premixed insulin analogues
Postprandial glucose level	High; favors premixed insulin analogues	High; favors premixed insulin analogues	Low; cannot make a conclusion	Moderate; favors premixed insulin analogues
Hemoglobin A _{1c} level	High; favors premixed insulin analogues	High; suggests similar effectiveness	Low; cannot make a conclusion	Moderate; favors premixed insulin analogues
Hypoglycemia	High; favors long-acting insulin analogues	High; suggests similar effectiveness	Low; cannot make a conclusion	High; favors noninsulin antidiabetic agents
Weight	Moderate; favors long-acting insulin analogues	Moderate; suggests similar effectiveness	Low; cannot make a conclusion	Moderate; favors noninsulin antidiabetic agents
All-cause mortality, CVD mortality, and CVD morbidity	Low; cannot make a conclusion	Low; cannot make a conclusion	Low; cannot make a conclusion	Low; cannot make a conclusion

CVD = cardiovascular disease.

* The strength of evidence was defined as follows: 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.

glucose levels. Although the difference between insulin aspart 70/30 and long-acting insulin analogues was not statistically significant, the direction of the effect was in favor of the long-acting insulin analogues.

In contrast to their effect on fasting glucose levels, premixed insulin analogues were more effective than long-acting insulin analogues in decreasing postprandial glucose levels (pooled difference, -1.5 mmol/L; CI, -1.9 to -1.2 mmol/L [-27.9 mg/dL; CI, -34.3 to -21.5 mg/dL]) and hemoglobin A_{1c} levels (pooled difference, -0.39% [CI, -0.5% to -0.3%]). When compared individually with long-acting insulin analogues, all 3 premixed insulin analogues remained statistically significantly better in decreasing postprandial glucose and hemoglobin A_{1c} levels.

Although premixed insulin analogues were effective in decreasing postprandial glucose and hemoglobin A_{1c} levels, they may increase the incidence of hypoglycemia (severity not specified) (OR, 2.0 [CI, 1.3 to 3.0]) and the amount of weight gain (pooled difference, 2.0 kg [CI, 1.1 to 3.0 kg]) to a greater extent than the long-acting insulin analogues. Insulin aspart 70/30 was associated with a higher incidence of hypoglycemia (severity not specified) and minor hypoglycemia and statistically significantly more weight gain (pooled difference, 2.5 kg [CI, 1.6 to 3.4 kg]). Although the incidence of hypoglycemia was neither consistent nor statistically significant across all trials, the direction of the individual study effect sizes suggested that both insulin lispro 75/25 and insulin lispro 50/50 may increase the incidence of hypoglycemia compared with long-acting insulin analogues. In 2 studies, use of insulin lispro 50/50 resulted in greater weight gain than did long-acting insulin analogues; this difference was statistically significant in only 1 study. None of the studies reported the comparative effects

of insulin lispro 75/25 and long-acting insulin analogues on weight change.

Premixed Insulin Analogues versus Premixed Human Insulin

We found 16 studies that compared premixed insulin analogues with premixed human insulin (Table and Figures 1 to 4). The pooled analysis suggested that premixed insulin analogues may be less effective than premixed human insulin in decreasing the fasting glucose level (pooled difference, 0.2 mmol/L; CI, -0.1 to 0.6 mmol/L [4.3 mg/dL; CI, -1.5 to 10.2 mg/dL]), but this difference was not statistically significant. However, these analogues were more effective in decreasing postprandial glucose levels (pooled difference, -1.1 mmol/L; CI, -1.4 to -0.7 mmol/L [-19.2 mg/dL; CI, -25.9 to -12.5 mg/dL]). Premixed insulin analogues were similar to premixed human insulin in decreasing hemoglobin A_{1c} levels (pooled difference, -0.05% [CI, -0.14% to 0.04%]). Insulin aspart 70/30 was less effective than, and insulin lispro 75/25 and 50/50 were similar to, premixed human insulin in decreasing fasting glucose levels. All 3 premixed insulin analogues were more effective than premixed human insulin in decreasing postprandial glucose levels. None of the premixed insulin preparations was better than premixed human insulin in decreasing hemoglobin A_{1c} levels.

Premixed insulin analogues, as a group or individually, were similar to premixed human insulin in the incidence of major and minor hypoglycemia (ORs, 0.6 [CI, 0.2 to 1.3] and 1.0 [CI, 0.6 to 1.5], respectively). Similarly, insulin aspart 70/30 and insulin lispro 50/50 were similar to premixed human insulin in weight gain (28, 35).

Premixed Insulin Analogues versus Other Insulin Regimens

We found 2 studies that compared a premixed insulin analogue with a rapid-acting insulin analogue (9, 23), 2 studies that compared a premixed insulin analogue with a combination regimen of long-acting and rapid-acting insulin analogues (17, 39), 2 studies that compared a premixed insulin analogue with an intermediate-acting insulin (32, 33), and 1 study that compared a premixed insulin analogue with a combination of rapid-acting insulin analogues and intermediate-acting human insulin (40). Because data were sparse, we cannot draw firm conclusions about these comparisons.

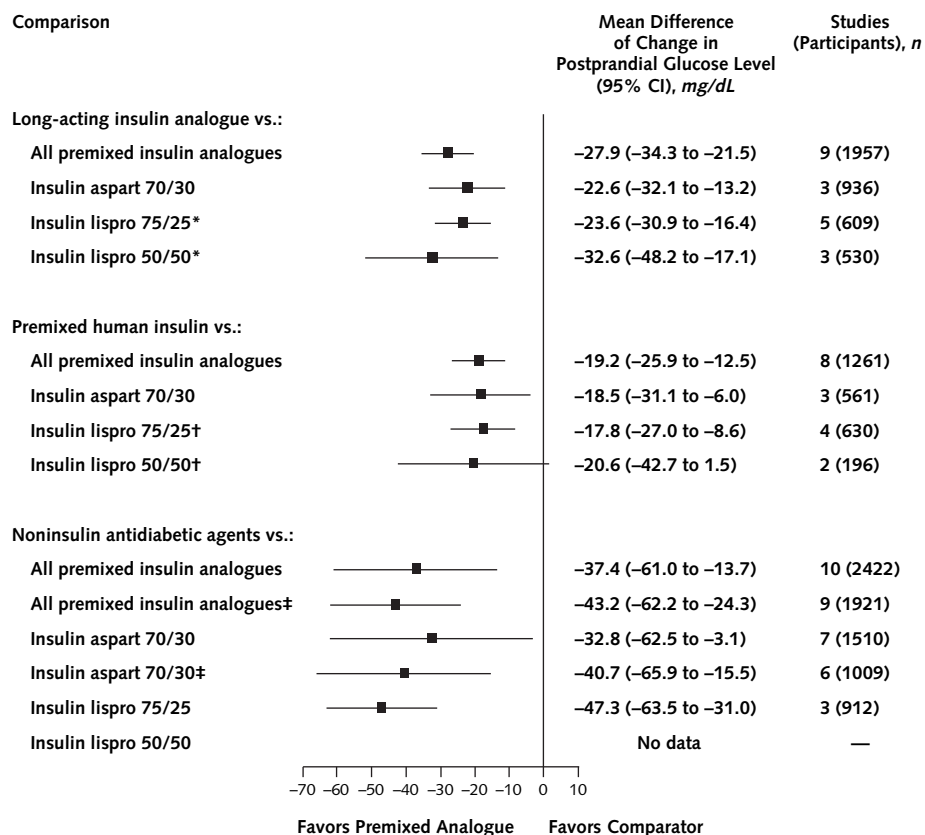
Premixed Insulin Analogues versus Noninsulin Antidiabetic Agents

Ten studies compared premixed insulin analogues with noninsulin antidiabetic agents (Table and Figures 1 to 4). Premixed insulin analogues were more effective than noninsulin antidiabetic agents in decreasing fasting glucose

levels (pooled difference, -1.1 mmol/L; CI, -1.7 to -0.6 mmol/L [-20.5 mg/dL; CI, -29.9 to -11.2 mg/dL]), postprandial glucose levels (pooled difference, -2.1 mmol/L; CI -3.4 to -0.8 mmol/L [-37.4 mg/dL; CI, -61.0 to -13.7 mg/dL]), and hemoglobin A_{1c} levels (pooled difference, -0.5% [CI, -0.9% to -0.1%]). These results did not change after we excluded the only study that compared premixed insulin analogue (insulin aspart 70/30) with exenatide. Insulin aspart 70/30 was more effective than noninsulin antidiabetic agents in decreasing fasting glucose, postprandial glucose, and hemoglobin A_{1c} levels. However, when only oral antidiabetic agents were kept in the meta-analysis, the pooled results for hemoglobin A_{1c} were no longer statistically significant. Insulin lispro 75/25 was also more effective than oral antidiabetic agents in decreasing fasting glucose, postprandial glucose, and hemoglobin A_{1c} levels, although the latter effect did not reach statistical significance.

Premixed insulin analogues were associated with an

Figure 1. Weighted mean difference of change in postprandial glucose level with premixed insulin analogues versus other antidiabetic agents.



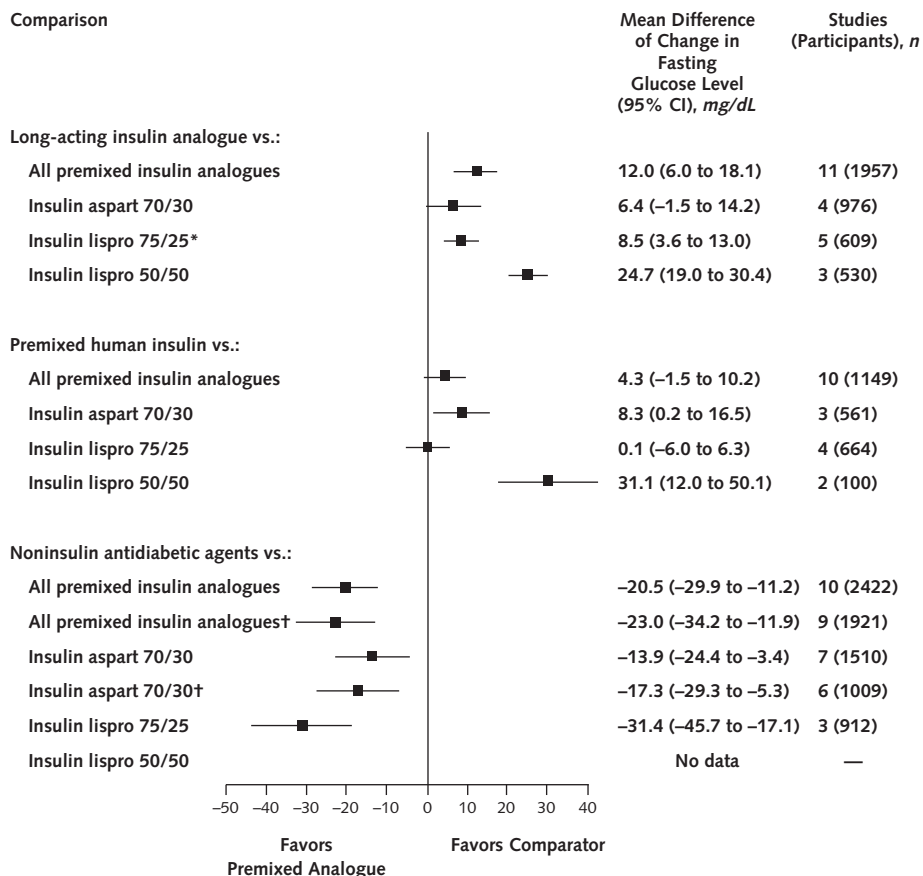
Error bars represent 95% CIs. To convert glucose values to mmol/L, multiply by 0.0555.

* Pooled results include those of a study (43) that administered insulin lispro 50/50 in the morning and afternoon and insulin lispro 75/25 in the evening.

† Pooled results include those of a study (55) that administered insulin lispro 50/50 in the morning and insulin lispro 75/25 in the evening.

‡ Reference 21 was excluded.

Figure 2. Weighted mean difference of change in fasting glucose level with premixed insulin analogues versus other antidiabetic agents.



Error bars represent 95% CIs. To convert glucose values to mmol/L, multiply by 0.0555.

* Pooled results include those of a study (43) that administered insulin lispro 50/50 in the morning and afternoon and insulin lispro 75/25 in the evening.

† Reference 21 was excluded.

increased risk for minor hypoglycemia (OR, 4.6 [CI, 2.0 to 10.6]) and weight gain (pooled difference, 2.3 kg [CI, 0.8 to 3.9 kg]) compared with noninsulin antidiabetic agents, but these classes of agents did not differ in risk for major hypoglycemia (OR, 1.0 [CI, 0.3 to 3.4]). Patients receiving insulin aspart 70/30 had a higher incidence of minor hypoglycemia and symptom-only hypoglycemia and experienced greater weight gain than did those receiving oral antidiabetic agents. Patients receiving exenatide lost weight, in contrast to the weight gain experienced by patients receiving premixed insulin analogues. Insulin lispro 75/25 was associated with a higher rate (measured as episodes per patient per 30 days) of overall hypoglycemia (rate ratio, 4.86 [CI, 0.5 to 49.5]) and greater weight gain (pooled mean difference, 1.88 kg [CI, 1.35 to 2.41 kg]) compared with oral antidiabetic agents. No studies compared insulin lispro 50/50 with oral antidiabetic agents.

Premixed Insulin Analogues versus Other Antidiabetic Medications: Clinical Outcomes

We found 16 studies that evaluated clinical outcomes (Table and Figure 5). Eleven studies were parallel-group RCTs (9, 21, 22, 24, 26, 28, 30, 31, 37, 38, 40), and 5 were crossover RCTs. Two studies reported 1 death but did not state in which group the event occurred (29, 49). No statistically significant differences were found between premixed insulin analogues and their comparators in terms of all-cause mortality, cardiovascular mortality, or cardiovascular morbidity. A suggestion of harm was seen in the pooled ORs for all-cause mortality, cardiovascular mortality, and the combined outcome of cardiovascular morbidity and all-cause mortality when premixed insulin analogues were compared with other antidiabetic medications, but these point estimates were based on few absolute events in only some studies in which clinical outcomes were not

the primary end points. Insufficient or no evidence was found on microvascular outcomes.

No statistically significant heterogeneity was found in these studies, with I^2 statistics less than 50% for all analyses. Sensitivity analyses using different meta-analytic techniques did not markedly affect the results, although less conservative techniques, such as the Peto method, reached borderline statistical significance for potential harm comparing premixed insulin analogues with active comparators.

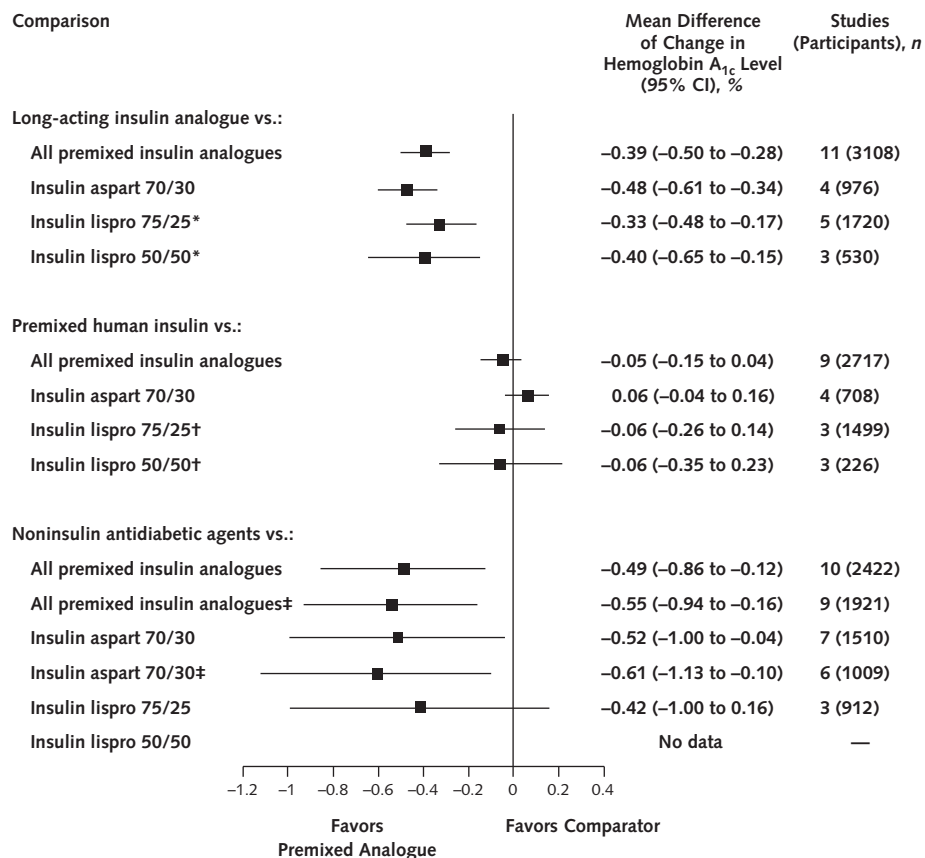
DISCUSSION

The ultimate goal of treatment of diabetes mellitus is improvement in clinical outcomes, particularly microvascular and macrovascular complications and death. We found no studies that were specifically designed to evaluate these clinical outcomes. All studies were designed to evaluate intermediate outcomes (such as hemoglobin A_{1c}, fast-

ing glucose, and postprandial glucose levels), although some studies reported clinical outcomes as adverse events. Because data on clinical outcomes were sparse, estimates of the comparative efficacy of premixed insulin analogues with other insulin preparations and noninsulin antidiabetic agents were inconclusive. Although pooled data suggested the possibility of worse clinical outcomes with premixed insulin analogues than with other antidiabetic medications, the data were too weak to support a firm conclusion about such a possibility. Because evidence on clinical outcomes was lacking, we evaluated the effects of premixed insulin analogues on intermediate outcomes. Although not ideal, these outcomes are commonly used clinically to optimize glycemic control and are known to predict clinical outcomes.

For intermediate outcomes, we found that premixed insulin analogues were similar to premixed human insulin in decreasing fasting glucose and hemoglobin A_{1c} levels but were more effective in decreasing the postprandial glucose

Figure 3. Weighted mean difference of change in hemoglobin A_{1c} level with premixed insulin analogues versus other antidiabetic agents.



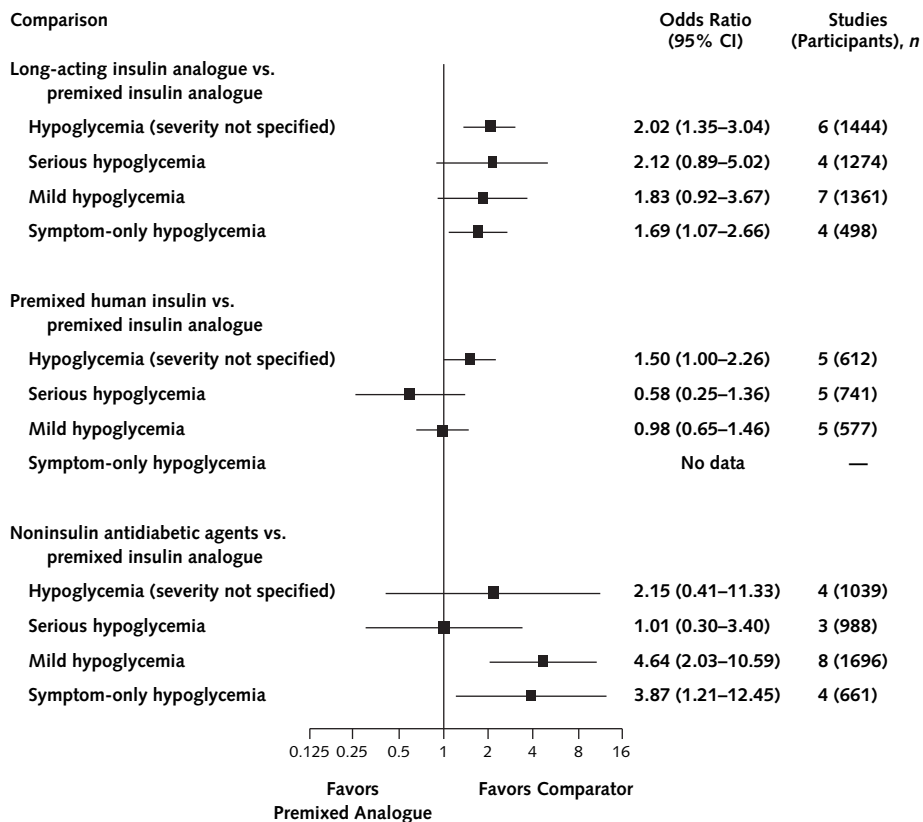
Error bars represent 95% CIs.

* Pooled results include those of a study (43) that administered insulin lispro 50/50 in the morning and afternoon and insulin lispro 75/25 in the evening.

† Pooled results include those of a study (55) that administered insulin lispro 50/50 in the morning and insulin lispro 75/25 in the evening.

‡ Reference 21 was excluded.

Figure 4. Incidence of unclassified hypoglycemia, serious hypoglycemia, mild hypoglycemia, and symptom-only hypoglycemia with premixed insulin analogues versus other antidiabetic agents.

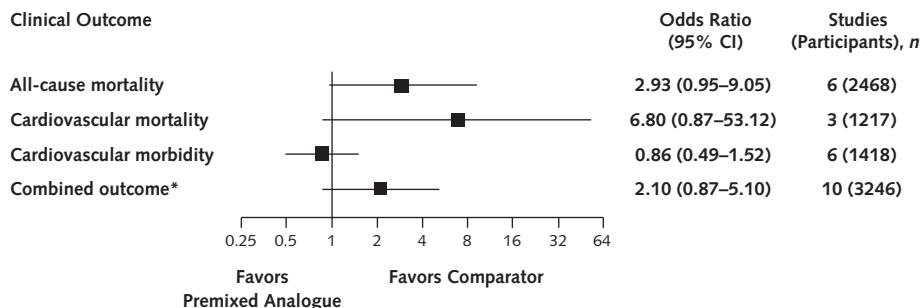


Error bars represent 95% CIs.

level. Premixed insulin analogues seemed to be better than long-acting insulin analogues and noninsulin antidiabetic agents in decreasing hemoglobin A_{1c} and postprandial glucose levels. Premixed insulin analogues seemed to be less effective than long-acting insulin analogues but more effective than oral antidiabetic agents in decreasing fasting glucose levels. Control of fasting and postprandial glucose lev-

els in diabetic patients is important to bring and keep the hemoglobin A_{1c} level within the desired range (61). The hemoglobin A_{1c} value is the standard of care for monitoring long-term glycemic control because it reflects both fasting and postprandial glucose control (62). A lower hemoglobin A_{1c} value is associated with a decrease in diabetic complications, such as retinopathy, nephropathy, and neu-

Figure 5. Incidence of clinical outcomes with premixed insulin analogues versus other antidiabetic agents.



Error bars represent 95% CIs.

* Combined outcome includes all-cause mortality and cardiovascular morbidity.

ropathy (3, 63), whereas cardiovascular complications of diabetes, such as coronary heart disease, stroke, cardiovascular mortality, sudden cardiac death, and all-cause mortality, are closely related to fasting and postprandial glucose levels (64–68). Whether the observed effectiveness of premixed insulin analogues in decreasing fasting and postprandial hyperglycemia translates into decreased mortality and morbidity remains unclear.

An important clinical consideration in the treatment of diabetic patients is to strike a balance between optimal glycemic control and treatment-associated side effects, such as hypoglycemia and weight gain. This consideration is particularly important, as more recent data suggest that intensive glycemic control (a target hemoglobin A_{1c} level <6%) may be associated with poorer clinical outcomes compared with standard glycemic control (69, 70). Premixed insulin analogues were more likely than noninsulin antidiabetic agents and long-acting insulin analogues to cause hypoglycemia, whereas the incidence of hypoglycemia was similar between premixed insulin analogues and other insulin preparations. Data demonstrated a trade-off between tighter glucose control and more hypoglycemic events. This was evident in comparisons between the premixed insulin analogues and the long-acting insulin analogues or noninsulin antidiabetic agents, where the premixed insulin analogues decreased hemoglobin A_{1c} level more effectively at the expense of an increased incidence of hypoglycemia. A similar trade-off was seen between tighter glycemic control and treatment-associated weight gain, although the paucity of data limited our evaluation of change in weight to only 1 of the premixed insulin analogues: insulin aspart 70/30.

For individual premixed insulin preparations, the number of comparative studies and the strength of evidence varied, thereby affecting the precision of estimates of the direction and magnitude of effect size. Study design characteristics may, at least in part, explain the differences between premixed insulin analogues and premixed human insulin and long-acting insulin analogues. For example, late administration (<30 minutes before meals) of premixed human insulin preparations may be responsible for the observed benefit of the premixed insulin analogues over the premixed human insulin preparations in lowering postprandial glucose levels, because fewer than half of the studies (25, 28, 33, 47, 48, 51, 55, 71) administered human insulin at least 30 minutes before meals. Although premixed insulin analogues seem to be better than long-acting insulin analogues in decreasing the hemoglobin A_{1c} level, this finding may reflect that the total daily dose of the long-acting insulin analogue was lower than that of premixed insulin analogue in several studies (20, 22, 23, 27, 42–45, 72). Similarly, in several studies, the dose of premixed insulin analogues was titrated to achieve optimal glycemic control, but the dose of oral antidiabetic agents was kept constant. This difference in dosing of the drugs

may be responsible for the observed benefit of premixed insulin analogue preparations (24, 30, 34, 36, 38).

Our study has limitations, many of which are due to the constraints of limited reporting of data in the trials. Several studies presented blood glucose data in figures only, and we abstracted data from these figures when possible. Crossover studies did not report data in a manner that could be used in a quantitative synthesis without some assumptions being made. These assumptions may have affected the quantitative synthesis of the evidence. We could not explore heterogeneity because relatively few studies were available for each comparison. We addressed this limitation by using a random-effects model for all analyses of intermediate outcomes, regardless of the presence or absence of statistical heterogeneity. The small number of studies also precluded us from fully assessing the potential for publication bias.

Because most of the studies excluded patients with diabetic complications or other comorbid conditions, our findings cannot be generalized to all diabetic patients. Moreover, because follow-up was short in most studies, we cannot draw conclusions about the long-term comparative effectiveness of premixed insulin analogues. Finally, because we limited our search to English-language articles, we may have missed some studies published in other languages.

In conclusion, premixed insulin analogues provide glycemic control similar to that of premixed human insulin and may provide better glycemic control than long-acting insulin analogues and noninsulin antidiabetic agents, but data on clinical outcomes are very limited. Studies with longer follow-up are needed to determine whether the effects observed early in treatment are sustainable long-term. Moreover, given that improvement in intermediate clinical outcomes may not always result in improvement in clinical outcomes, studies specifically designed to evaluate clinical outcomes are needed.

From Evidence-based Practice Center, Johns Hopkins University, Baltimore, Maryland.

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Requests for Single Reprints: Rehan Qayyum, MD, Johns Hopkins Hospital, Hospitalist Program, 600 North Wolfe Street, Park 307-A, Baltimore, MD 21287; e-mail, rqayyum@jhmi.edu.

Current author addresses are available at www.annals.org.

References

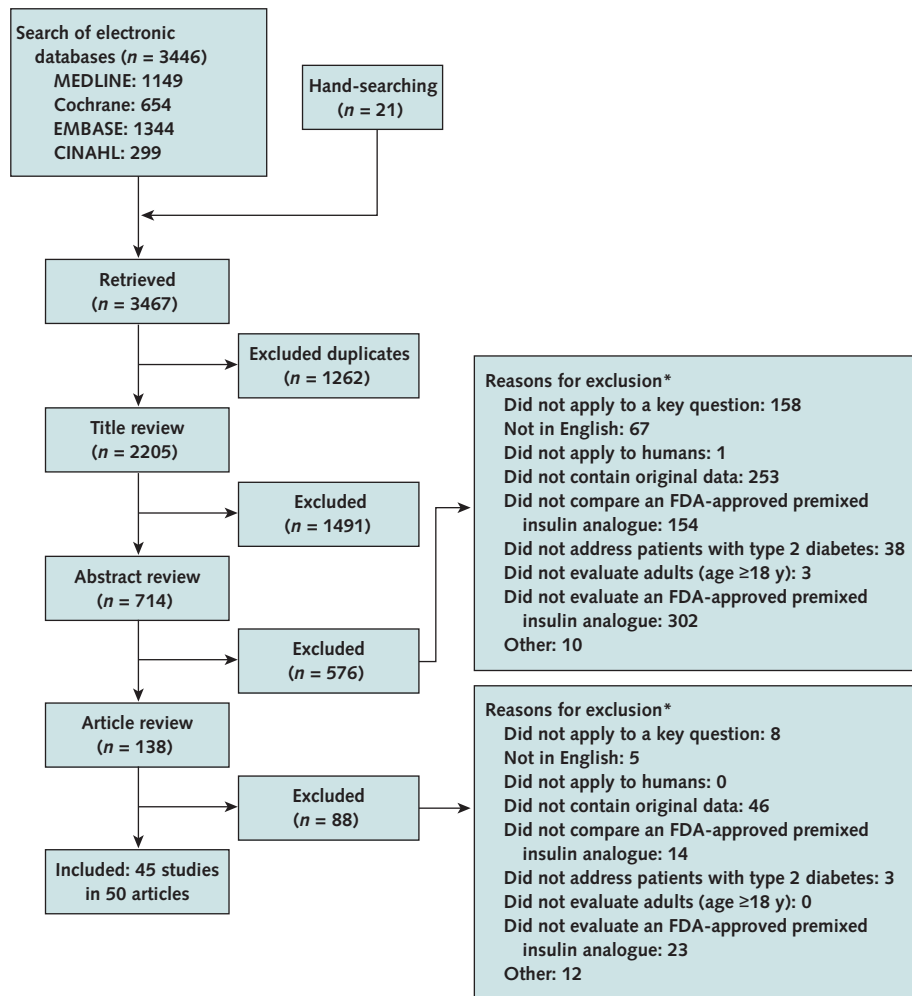
- Centers for Disease Control and Prevention. National diabetes fact sheet: general information and national estimates on diabetes in the United States, 2005. Atlanta: Department of Health and Human Services, Centers for Disease Control and Prevention; 2005.
- Gregg EW, Cadwell BL, Cheng YJ, Cowie CC, Williams DE, Geiss L, et al. Trends in the prevalence and ratio of diagnosed to undiagnosed diabetes according to obesity levels in the U.S. *Diabetes Care*. 2004;27:2806-12. [PMID: 15562189]
- Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. *Lancet*. 1998;352:837-53. [PMID: 9742976]
- Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials*. 1996;17:1-12. [PMID: 8721797]
- Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Losos M, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. 2007. Accessed at www.ohri.ca/programs/clinical_epidemiology/oxford.htm on 4 August 2008.
- Agency for Healthcare Research and Quality. Methods Reference Guide for Effectiveness and Comparative Effectiveness Reviews. Rockville, MD: Agency for Healthcare Research and Quality; 2007. Accessed at http://effectivehealthcare.ahrq.gov/repFiles/2007_10DraftMethodsGuide.pdf on 4 August 2008.
- Atkins D, Best D, Briss PA, Eccles M, Falck-Ytter Y, Flottorp S, et al. GRADE Working Group. Grading quality of evidence and strength of recommendations. *BMJ*. 2004;328:1490. [PMID: 15205295].
- Saudek CD, Derr RL, Kalyani RR. Assessing glycemia in diabetes using self-monitoring blood glucose and hemoglobin A1c. *JAMA*. 2006;295:1688-97. [PMID: 16609091]
- Holman RR, Thorne KI, Farmer AJ, Davies MJ, Keenan JF, Paul S, Levy C. 4-T Study Group. Addition of biphasic, prandial, or basal insulin to oral therapy in type 2 diabetes. *N Engl J Med*. 2007;357:1716-30. [PMID: 17890232]
- Mantel N, Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. *J Natl Cancer Inst*. 1959;22:719-48. [PMID: 13655060]
- Robins J, Greenland S, Breslow NE. A general estimator for the variance of the Mantel-Haenszel odds ratio. *Am J Epidemiol*. 1986;124:719-23. [PMID: 3766505]
- Bradburn MJ, Deeks JJ, Berlin JA, Russell Localio A. Much ado about nothing: a comparison of the performance of meta-analytical methods with rare events. *Stat Med*. 2007;26:53-77. [PMID: 16596572]
- Yusuf S, Peto R, Lewis J, Collins R, Sleight P. Beta blockade during and after myocardial infarction: an overview of the randomized trials. *Prog Cardiovasc Dis*. 1985;27:335-71. [PMID: 2858114]
- Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ*. 2003;327:557-60. [PMID: 12958120]
- Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. *Biometrics*. 1994;50:1088-101. [PMID: 7786990]
- Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ*. 1997;315:629-34. [PMID: 9310563]
- Joshi SR, Kalra S, Badgandi M, Rao YS, Chawla M. Designer insulins regimens in clinical practice—pilot multicenter Indian study. *J Assoc Physicians India*. 2005;53:775-9. [PMID: 16334621]
- Sun P, Wang R, Jacober S. The effectiveness of insulin initiation regimens in patients with type 2 diabetes mellitus: a large national medical records review study comparing a basal insulin analogue to premixed insulin. *Curr Med Res Opin*. 2007;23:3017-23. [PMID: 17961295]
- Bebakar WM, Chow CC, Kadir KA, Suwanwalakorn S, Vaz JA, Bech OM. BIAsp-3021 Study Group. Adding biphasic insulin aspart 30 once or twice daily is more efficacious than optimizing oral antidiabetic treatment in patients with type 2 diabetes. *Diabetes Obes Metab*. 2007;9:724-32. [PMID: 17593237]
- Tamemoto H, Ikoma A, Saitoh T, Ishikawa SE, Kawakami M. Comparison of once-daily glargine plus sulfonylurea with twice-daily 70/30 aspart premix in insulin-naïve Japanese patients with diabetes. *Diabetes Technol Ther*. 2007;9:246-53. [PMID: 17561795]
- Nauck MA, Duran S, Kim D, Johns D, Northrup J, Festa A, et al. A comparison of twice-daily exenatide and biphasic insulin aspart in patients with type 2 diabetes who were suboptimally controlled with sulfonylurea and metformin: a non-inferiority study. *Diabetologia*. 2007;50:259-67. [PMID: 17160407]
- Kann PH, Wascher T, Zackova V, Moeller J, Medding J, Szocs A, et al. Starting insulin therapy in type 2 diabetes: twice-daily biphasic insulin Aspart 30 plus metformin versus once-daily insulin glargine plus glibenclamide. *Exp Clin Endocrinol Diabetes*. 2006;114:527-32. [PMID: 17115351]
- Kazda C, Hülstrunk H, Helsberg K, Langer F, Forst T, Hanefeld M. Prandial insulin substitution with insulin lispro or insulin lispro mid mixture vs. basal therapy with insulin glargine: a randomized controlled trial in patients with type 2 diabetes beginning insulin therapy. *J Diabetes Complications*. 2006;20:145-52. [PMID: 16632233]
- Kvapil M, Swatko A, Hilberg C, Shestakova M. Biphasic insulin aspart 30 plus metformin: an effective combination in type 2 diabetes. *Diabetes Obes Metab*. 2006;8:39-48. [PMID: 16367881]
- Abrahamian H, Ludvik B, Scherthaner G, Prager R, Zellenka U, Knudsen L, et al. Improvement of glucose tolerance in type 2 diabetic patients: traditional vs. modern insulin regimens (results from the Austrian Biaspart Study). *Horm Metab Res*. 2005;37:684-9. [PMID: 16308837]
- Raz I, Stranks S, Filipczak R, Joshi P, Lertoft B, Rastam J, et al. Efficacy and safety of biphasic insulin aspart 30 combined with pioglitazone in type 2 diabetes poorly controlled on glibenclamide (glyburide) monotherapy or combination therapy: an 18-week, randomized, open-label study. *Clin Ther*. 2005;27:1432-43. [PMID: 16291416]
- Raskin P, Allen E, Hollander P, Lewin A, Gabbay RA, Hu P, et al. INI-TIATE Study Group. Initiating insulin therapy in type 2 Diabetes: a comparison of biphasic and basal insulin analogs. *Diabetes Care*. 2005;28:260-5. [PMID: 1567776]
- Boehm BO, Vaz JA, Brøndsted L, Home PD. Long-term efficacy and safety of biphasic insulin aspart in patients with type 2 diabetes. *Eur J Intern Med*. 2004;15:496-502. [PMID: 15668084]
- Tirgoviște CI, Străchinariu R, Farcașiu E, Milicevic Z, Teodorescu G. Humalog Mix 25 in patients with type 2 diabetes which do not achieve acceptable glycemic control with oral agents: results from a phase III, randomized, parallel study. *Rom J Intern Med*. 2003;41:153-62. [PMID: 15526500]
- Raz I, Mouritzen U, Vaz J, Hershkovitz T, Wainstein J, Harman-Boehm I. Addition of biphasic insulin aspart 30 to rosiglitazone in type 2 diabetes mellitus that is poorly controlled with glibenclamide monotherapy. *Clin Ther*. 2003;25:3109-23. [PMID: 14749149]
- Malone JK, Beattie SD, Campaigne BN, Johnson PA, Howard AS, Milicevic Z. Therapy after single oral agent failure: adding a second oral agent or an insulin mixture? *Diabetes Res Clin Pract*. 2003;62:187-95. [PMID: 14625133]
- Christiansen JS, Vaz JA, Metelko Z, Bogoev M, Dedov I. Twice daily biphasic insulin aspart improves postprandial glycaemic control more effectively than twice daily NPH insulin, with low risk of hypoglycaemia, in patients with type 2 diabetes. *Diabetes Obes Metab*. 2003;5:446-54. [PMID: 14617231]
- Kilo C, Meztis N, Jain R, Mersey J, McGill J, Raskin P. Starting patients with type 2 diabetes on insulin therapy using once-daily injections of biphasic insulin aspart 70/30, biphasic human insulin 70/30, or NPH insulin in combination with metformin. *J Diabetes Complications*. 2003;17:307-13. [PMID: 14583174]
- Herz M, Sun B, Milicevic Z, Erickson P, Fövönyi J, Grzywa M, et al. Comparative efficacy of preprandial or postprandial Humalog Mix75/25 versus glyburide in patients 60 to 80 years of age with type 2 diabetes mellitus. *Clin Ther*. 2002;24:73-86. [PMID: 11833837]
- Yamada S, Watanabe M, Kitaoka A, Shiono K, Atsuda K, Tsukamoto Y, et al. Switching from premixed human insulin to premixed insulin lispro: a prospective study comparing the effects on glucose control and quality of life. *Intern Med*. 2007;46:1513-7. [PMID: 17878636]
- Ushakova O, Sokolovskaya V, Morozova A, Valeeva F, Zanozina O, Sazonova O, et al. Comparison of biphasic insulin aspart 30 given three times daily or twice daily in combination with metformin versus oral antidiabetic drugs alone in patients with poorly controlled type 2 diabetes: a 16-week, randomized, open-label, parallel-group trial conducted in Russia. *Clin Ther*. 2007;29:2374-84. [PMID: 18158078]
- Robbins DC, Beisswenger PJ, Ceriello A, Goldberg RB, Moses RG, Pagkalos EM, et al. Mealtime 50/50 basal + prandial insulin analogue mixture with a basal insulin analogue, both plus metformin, in the achievement of target HbA1c and pre- and postprandial blood glucose levels in patients with type 2 diabetes: a multinational, 24-week, randomized, open-label, parallel-group comparison. *Clin Ther*. 2007;29:2349-64. [PMID: 18158076]
- Raskin P, Matfin G, Schwartz SL, Chaykin L, Chu PL, Braceras R, et al.

- Addition of biphasic insulin aspart 30 to optimized metformin and pioglitazone treatment of type 2 diabetes mellitus: The ACTION Study (Achieving Control Through Insulin plus Oral ageNts). *Diabetes Obes Metab*. 2007. [PMID: 17941873]
39. Rosenstock J, Ahmann AJ, Colon G, Scism-Bacon J, Jiang H, Martin S. Advancing insulin therapy in type 2 diabetes previously treated with glargine plus oral agents: prandial premixed (insulin lispro protamine suspension/lispro) versus basal/bolus (glargine/lispro) therapy. *Diabetes Care*. 2008;31:20-5. [PMID: 17934150]
40. Hirao K, Arai K, Yamauchi M, Takagi H, Kobayashi M. Japan Diabetes Clinical Data Management Study Group. Six-month multicentric, open-label, randomized trial of twice-daily injections of biphasic insulin aspart 30 versus multiple daily injections of insulin aspart in Japanese type 2 diabetic patients (JDDM 11). *Diabetes Res Clin Pract*. 2008;79:171-6. [PMID: 17919762]
41. McNally PG, Dean JD, Morris AD, Wilkinson PD, Compion G, Heller SR. Using continuous glucose monitoring to measure the frequency of low glucose values when using biphasic insulin aspart 30 compared with biphasic human insulin 30: a double-blind crossover study in individuals with type 2 diabetes. *Diabetes Care*. 2007;30:1044-8. [PMID: 17277042]
42. Roach P, Malone JK. Comparison of insulin lispro mixture 25/75 with insulin glargine during a 24-h standardized test-meal period in patients with Type 2 diabetes. *Diabet Med*. 2006;23:743-9. [PMID: 16842478]
43. Jacober SJ, Scism-Bacon JL, Zagar AJ. A comparison of intensive mixture therapy with basal insulin therapy in insulin-naïve patients with type 2 diabetes receiving oral antidiabetes agents. *Diabetes Obes Metab*. 2006;8:448-55. [PMID: 16776752]
44. Malone JK, Kerr LF, Campaigne BN, Sachson RA, Holcombe JH. Lispro Mixture-Glargine Study Group. Combined therapy with insulin lispro Mix 75/25 plus metformin or insulin glargine plus metformin: a 16-week, randomized, open-label, crossover study in patients with type 2 diabetes beginning insulin therapy. *Clin Ther*. 2004;26:2034-44. [PMID: 15823767]
45. Malone JK, Bai S, Campaigne BN, Reviriego J, Augendre-Ferrante B. Twice-daily pre-mixed insulin rather than basal insulin therapy alone results in better overall glycaemic control in patients with Type 2 diabetes. *Diabet Med*. 2005;22:374-81. [PMID: 15787659]
46. Niskanen L, Jensen LE, Råstam J, Nygaard-Pedersen L, Erichsen K, Vora JP. Randomized, multinational, open-label, 2-period, crossover comparison of biphasic insulin aspart 30 and biphasic insulin lispro 25 and pen devices in adult patients with type 2 diabetes mellitus. *Clin Ther*. 2004;26:531-40. [PMID: 15189750]
47. Scherthaner G, Kopp HP, Ristic S, Muzyka B, Peter L, Mitteregger G. Metabolic control in patients with type 2 diabetes using Humalog Mix50 injected three times daily: crossover comparison with human insulin 30/70. *Horm Metab Res*. 2004;36:188-93. [PMID: 15057674]
48. Coscelli C, Iacobellis G, Calderini C, Carleo R, Gobbo M, Di Mario U, et al. Importance of premeal injection time in insulin therapy: Humalog Mix25 is convenient for improved post-prandial glycaemic control in type 2 diabetic patients with Italian dietary habits. *Acta Diabetol*. 2003;40:187-92. [PMID: 14740279]
49. Roach P, Arora V, Campaigne BN, Mattoo V, Rangwala S. India Mix25/Mix50 Study Group. Humalog Mix50 before carbohydrate-rich meals in type 2 diabetes mellitus. *Diabetes Obes Metab*. 2003;5:311-6. [PMID: 12940868]
50. Herz M, Arora V, Campaigne BN, Scholtz HE, Potgieter MA, Mollentze W. Humalog Mix25 improves 24-hour plasma glucose profiles compared with the human insulin mixture 30/70 in patients with type 2 diabetes mellitus. *S Afr Med J*. 2003;93:219-23. [PMID: 12768948]
51. Mattoo V, Milicevic Z, Malone JK, Schwarzenhofer M, Ekangaki A, Levitt LK, et al. Ramadan Study Group. A comparison of insulin lispro Mix25 and human insulin 30/70 in the treatment of type 2 diabetes during Ramadan. *Diabetes Res Clin Pract*. 2003;59:137-43. [PMID: 12560163]
52. Herz M, Profozic V, Arora V, Smircic-Duvnjak L, Kovacevic I, Boras J, et al. Effects of a fixed mixture of 25% insulin lispro and 75% NPL on plasma glucose during and after moderate physical exercise in patients with type 2 diabetes. *Curr Med Res Opin*. 2002;18:188-93. [PMID: 12201618]
53. McSorley PT, Bell PM, Jacobsen LV, Kristensen A, Lindholm A. Twice-daily biphasic insulin aspart 30 versus biphasic human insulin 30: a double-blind crossover study in adults with type 2 diabetes mellitus. *Clin Ther*. 2002;24:530-9. [PMID: 12017398]
54. Roach P, Yue L, Arora V. Improved postprandial glycaemic control during treatment with Humalog Mix25, a novel protamine-based insulin lispro formulation. Humalog Mix25 Study Group. *Diabetes Care*. 1999;22:1258-61. [PMID: 10480767]
55. Roach P, Trautmann M, Arora V, Sun B, Anderson JH Jr. Improved postprandial blood glucose control and reduced nocturnal hypoglycemia during treatment with two novel insulin lispro-protamine formulations, insulin lispro mix25 and insulin lispro mix50. Mix50 Study Group. *Clin Ther*. 1999;21:523-34. [PMID: 10321421]
56. Cox DJ, McCall A, Kovatchev B, Sarwat S, Ilag LL, Tan MH. Effects of blood glucose rate of changes on perceived mood and cognitive symptoms in insulin-treated type 2 diabetes. *Diabetes Care*. 2007;30:2001-2. [PMID: 17473060]
57. Schwartz S, Zagar AJ, Althouse SK, Pinaire JA, Holcombe JH. A single-center, randomized, double-blind, three-way crossover study examining postchallenge glucose responses to human insulin 70/30 and insulin lispro fixed mixtures 75/25 and 50/50 in patients with type 2 diabetes mellitus. *Clin Ther*. 2006;28:1649-57. [PMID: 17157120]
58. Kapitza C, Rave K, Ostrowski K, Heise T, Heinemann L. Reduced postprandial glycaemic excursion with biphasic insulin Aspart 30 injected immediately before a meal [Letter]. *Diabet Med*. 2004;21:500-1. [PMID: 15089801]
59. Hermansen K, Colombo M, Storgaard H, Østergaard A, Kølendorf K, Madsbad S. Improved postprandial glycaemic control with biphasic insulin aspart relative to biphasic insulin lispro and biphasic human insulin in patients with type 2 diabetes. *Diabetes Care*. 2002;25:883-8. [PMID: 11978685]
60. Malone JK, Woodworth JR, Arora V, Yang H, Campaigne BN, Hallé JP, et al. Improved postprandial glycaemic control with Humalog Mix75/25 after a standard test meal in patients with type 2 diabetes mellitus. *Clin Ther*. 2000;22:222-30. [PMID: 10743981]
61. Monnier L, Colette C, Monnier L, Colette C. Contributions of fasting and postprandial glucose to hemoglobin A_{1c}. *Endocr Pract*. 2006;12 Suppl 1:42-6. [PMID: 16627379]
62. American Diabetes Association. Standards of medical care in diabetes—2008. *Diabetes Care*. 2008;31 Suppl 1:S12-54. [PMID: 18165335]
63. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). UK Prospective Diabetes Study (UKPDS) Group. *Lancet*. 1998;352:854-65. [PMID: 9742977]
64. Lowe LP, Liu K, Greenland P, Metzger BE, Dyer AR, Stamler J. Diabetes, asymptomatic hyperglycemia, and 22-year mortality in black and white men. The Chicago Heart Association Detection Project in Industry Study. *Diabetes Care*. 1997;20:163-9. [PMID: 9118765]
65. Orenca AJ, Daviglus ML, Dyer AR, Walsh M, Greenland P, Stamler J. One-hour postload plasma glucose and risks of fatal coronary heart disease and stroke among nondiabetic men and women: the Chicago Heart Association Detection Project in Industry (CHA) Study. *J Clin Epidemiol*. 1997;50:1369-76. [PMID: 9449940]
66. de Vegt F, Dekker JM, Ruhé HG, Stehouwer CD, Nijpels G, Bouter LM, et al. Hyperglycaemia is associated with all-cause and cardiovascular mortality in the Hoorn population: the Hoorn Study. *Diabetologia*. 1999;42:926-31. [PMID: 10491751]
67. Curb JD, Rodriguez BL, Burchfiel CM, Abbott RD, Chiu D, Yano K. Sudden death, impaired glucose tolerance, and diabetes in Japanese American men. *Circulation*. 1995;91:2591-5. [PMID: 7743621]
68. Boden-Albala B, Cammack S, Chong J, Wang C, Wright C, Rundek T, et al. Diabetes, fasting glucose levels, and risk of ischemic stroke and vascular events: findings from the Northern Manhattan Study (NOMAS). *Diabetes Care*. 2008;31:1132-7. [PMID: 18339972]
69. Gerstein HC, Miller ME, Byington RP, Goff DC Jr, Bigger JT, Buse JB, et al. Action to Control Cardiovascular Risk in Diabetes Study Group. Effects of intensive glucose lowering in type 2 diabetes. *N Engl J Med*. 2008;358:2545-59. [PMID: 18539917]
70. Treggiari MM, Karir V, Yanez ND, Weiss NS, Daniel S, Deem SA. Intensive insulin therapy and mortality in critically ill patients. *Crit Care*. 2008;12:R29. [PMID: 18312617]
71. White JR Jr. Insulin glargine clinical trials [Letter]. *Clin Ther*. 2004;26:1179-81; discussion 1182-3. [PMID: 15336483]
72. Raskin PR, Hollander PA, Lewin A, Gabbay RA, Bode B, Garber AJ, on behalf of the INITIATE Study Group. Basal insulin or premix analogue therapy in type 2 diabetes patients. *Eur J Intern Med*. 2007;18:56-62. [PMID: 17223044]

Current Author Addresses: Dr. Qayyum: Johns Hopkins Hospital, Hospitalist Program, 600 North Wolfe Street, Park 307-A, Baltimore, MD 21287.
 Dr. Bolen: 2024 East Monument Street, Suite 2-600, Baltimore, MD 21205.
 Dr. Maruthur: 2024 East Monument Street, Suite 2-500, Baltimore, MD 21205.
 Drs. Feldman, Ranasinghe, and Amer: Johns Hopkins Hospital, Hospitalist Program, 600 North Wolfe Street, Park 307, Baltimore, MD 21287.

Ms. Wilson: Johns Hopkins Evidence-based Practice Center, 1830 East Monument Street, Room 8064, Baltimore, MD 21287.
 Dr. Marinopoulos: Johns Hopkins Outpatient Center Practice, 601 North Caroline Street, Suite 7143, Baltimore, MD 21287.
 Dr. Bass: Johns Hopkins Evidence-based Practice Center, 1830 East Monument Street, Room 8068, Baltimore, MD 21287.

Appendix Figure. Study flow diagram.



FDA = U.S. Food and Drug Administration.

* The total may exceed the number in the corresponding box because articles could be excluded for more than 1 reason at this level.