

Outpatient Insulin Therapy in Type 1 and Type 2 Diabetes Mellitus

Scientific Review

Dawn E. DeWitt, MD, MSc

Irl B. Hirsch, MD

P RIMARY CARE PHYSICIANS PROVIDE diabetes care for 39% of the 16 million patients in the United States (US) with type 1 diabetes mellitus (DM) and 82% of patients with type 2 DM.¹ The greatest change in diabetes therapy in the last decade has been the introduction of insulin analogues. Currently, 6 to 7 million Americans use human insulin or insulin analogues. The availability of the new insulin analogues makes physiologic insulin therapy realistic for many patients, because the onset and duration of the action of these analogues more closely mimic human insulin secretion, thus simplifying insulin dosing and adjustment and increasing flexibility for patients. The use of physiologic insulin replacement and continuous subcutaneous insulin infusion (CSII, or pump therapy) are increasingly popular and have become the criterion standard, with more than 200 000 patients with type 1 DM using CSII therapy worldwide.²

The American Diabetes Association recommends a hemoglobin (Hb) A_{1c} level less than 7%.³ Data from 1988-1995⁴ show that 43% of US patients had an HbA_{1c} level greater than 8.0%, 18% had poor control with an HbA_{1c} level greater than 9.5% (24% of the insulin-treated patients had poor control). More than 50% of US patients with type 1 DM

See also p 2265 and Patient Page.

Context Newer insulin therapies, including the concept of physiologic basal-prandial insulin and the availability of insulin analogues, are changing clinical diabetes care. The key to effective insulin therapy is an understanding of principles that, when implemented, can result in improved diabetes control.

Objective To systematically review the literature regarding insulin use in patients with type 1 and type 2 diabetes mellitus (DM).

Data Sources A MEDLINE search was performed to identify all English-language articles of randomized controlled trials involving insulin use in adults with type 1 or type 2 DM from January 1, 1980, to January 8, 2003. Bibliographies and experts were used to identify additional studies.

Study Selection and Data Extraction Studies were included (199 for type 1 DM and 144 for type 2 DM, and 38 from other sources) if they involved human insulins or insulin analogues, were at least 4 weeks long with at least 10 patients in each group, and glycemic control and hypoglycemia were reported. Studies of insulin-oral combination were similarly selected.

Data Synthesis Twenty-eight studies for type 1 DM, 18 for type 2 DM, and 48 for insulin-oral combination met the selection criteria. In patients with type 1 DM, physiologic replacement, with bedtime basal insulin and a mealtime rapid-acting insulin analogue, results in fewer episodes of hypoglycemia than conventional regimens. Rapid-acting insulin analogues are preferred over regular insulin in patients with type 1 DM since they improve HbA_{1c} and reduce episodes of hypoglycemia. In patients with type 2 DM, adding bedtime neutral protamine Hagedorn (isophane) insulin to oral therapy significantly improves glycemic control, especially when started early in the course of disease. Bedtime use of insulin glargine results in fewer episodes of nighttime hypoglycemia than neutral protamine Hagedorn regimens. For patients with more severe insulin deficiency, a physiologic insulin regimen should allow lower glycemic targets in the majority of patients. Adverse events associated with insulin therapy include hypoglycemia, weight gain, and worsening diabetic retinopathy if hemoglobin A_{1c} levels decrease rapidly.

Conclusions Many options for insulin therapy are now available. Physiologic insulin therapy with insulin analogues is now relatively simple to use and is associated with fewer episodes of hypoglycemia.

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Author Affiliations: Division of General Internal Medicine, Department of Medicine, University of Washington (Dr DeWitt); and Division of Metabolism, Endocrinology, and Nutrition, Department of Medicine, University of Washington, and Diabetes Care Center, University of Washington Medical Center (Dr Hirsch), Seattle.

Corresponding Author and Reprints: Dawn E. DeWitt, MD, MSc, Rural Clinical School, University of

Melbourne, PO Box 6500, Shepparton VIC 3632, Australia (e-mail: ddewitt@unimelb.edu.au).

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use only 1 to 2 insulin injections per day, a suboptimal, nonphysiologic approach to type 1 DM insulin therapy.⁵ Importantly, even many patients with type 2 DM would not achieve adequate control using twice-daily neutral protamine Hagedorn (NPH or isophane insulin).⁶

Most physicians would agree that good diabetes control, which often requires intensive insulin therapy, is desirable for patients with type 1 DM and type 2 DM. Patients receiving intensive therapy with lower HbA_{1c} levels with type 1 DM in the Diabetes Control and Complications Trial, or with type 2 DM in the United Kingdom Prospective Diabetes Study (UKPDS), had fewer, later microvascular complications.^{7,8} Interestingly, some data suggest that insulin may benefit patients with DM in other ways. For example, early insulin therapy may preserve β -cell function.^{9,10} Insulin therapy can also improve lipid metabolism¹¹⁻¹⁵ and mortality after myocardial infarction.¹⁶

With diabetes-related medical costs of \$132 billion per year (more than 12% of the US health care budget),¹⁷ many experts question whether intensive insulin therapy (approximately \$16000-30000 per quality-adjusted life years gained)¹⁷ is cost-effective. In the UKPDS, the incremental yearly cost of intensive insulin therapy for patients with type 2 DM (either with sulfonylurea [SU] agents or with insulin) was \$1866,¹⁸ while in the Kumamoto trial, multiple injection therapy for patients with type 2 DM reduced costs from \$31 525 for conventional therapy to \$30 310, by decreasing complications.¹⁹

METHODS

We searched MEDLINE for all English-language articles involving insulin use in adults with type 1 DM (n=199) or type 2 DM (n=144) between January 1, 1980, and January 8, 2003. Bibliographies and experts allowed for the identification of additional relevant abstracts (n=3) and studies (n=35). Randomized controlled trials were included (28 for type 1 DM and 18 for type 2 DM) if they compared currently available human insu-

Table 1. Currently Available Insulin Products*

Insulin†	Onset	Peak	Effective Duration, h	Cost per 10 mL per 100 U/mL‡
Rapid-acting	5-15 min	30-90 min	5	
Lispro (Humalog)				\$46
Aspart (NovoLog)				\$58
Short-acting	30-60 min	2-3 h	5-8	
Regular U100				\$25
Regular U500 (concentrated)				\$220/20 mL
Buffered regular (Velosulin)				\$55
Intermediate-acting				
Isophane insulin (NPH, Humulin N/Novolin N)	2-4 h	4-10 h	10-16	\$24-\$26
Insulin zinc (Lente, Humulin L/Novolin L)	2-4 h	4-12 h	12-18	\$24-\$26
Long-acting				
Insulin zinc extended (Ultralente, Humulin U)	6-10 h	10-16 h	18-24	\$25
Glargine (Lantus)	2-4 h§	No peak	20-24	\$46
Premixed				
70% NPH/30% regular (Humulin 70/30)	30-60 min	Dual	10-16	\$25
50% NPH/50% regular (Humulin 50/50)	30-60 min	Dual	10-16	\$46
75% NPL/25% lispro (Humalog Mix 75/25)	5-15 min	Dual	10-16	\$58
70% NP/30% aspart (NovoLog Mix)	5-15 min	Dual	10-16	\$59

Abbreviations: L, Lente; NPH, neutral protamine Hagedorn; NPL, insulin lispro protamine (neutral protamine lispro).
 *Adapted with permission from *Practical Insulin: A Handbook for Prescribing Providers*, The American Diabetes Association, 2002.¹⁶³
 †Assuming 0.1-0.2 U/kg per injection. Onset and duration vary significantly by injection site.
 ‡Prices are for comparison and may vary widely. Sources of prices are from Drugstore.com (<http://www.drugstore.com>) or retail ranges from Costco, Safeway, Rite Aid, and Walgreens.
 §Time to steady state.

lins, reported glucose measurements and/or rates of hypoglycemic episodes, and were at least 4 weeks long with at least 10 patients in each group. Using similar criteria, randomized controlled trials of insulin-oral agent combination therapy (n=48) were reviewed in detail. Studies with English-language abstracts or those using animal and human insulins were selected if they were included in previously published reviews or meta-analyses and met our other criteria.

The authors reviewed, summarized, and synthesized the data. We found the literature highly problematic because it lacked standardized medication protocols, methods, and end points. A large majority of trials were sponsored by the pharmaceutical industry. Given the paucity of evidence in some areas, we believe that expert clinical diabetes practice is far ahead of clinical trials.

RESULTS

What Are the Major Types of Insulin?

Rapid-Acting Insulin. Insulin lispro and insulin aspart do not self-aggregate in

solution as human (regular) insulin does, and these insulins are rapidly absorbed (TABLE 1). Insulin lispro differs from human insulin by an amino acid exchange of lysine and proline at positions 28 and 29. The substitution of aspartic acid for proline at position 28 created insulin aspart. Rapid-acting insulins are most appropriately injected at mealtime as “prandial” insulin (sometimes referred to as “bolus” insulin) or used in insulin pumps.

Short-Acting Insulin. Regular insulin has a delay to onset of action of 30 to 60 minutes (Table 1). Patients are instructed to inject regular insulin 20 to 30 minutes prior to meals (ie, lag time is the time between injecting insulin and eating) to match insulin availability and carbohydrate absorption. Regular insulin acts almost immediately when injected intravenously.

Intermediate-Acting Insulin. Neutral protamine Hagedorn (isophane insulin; NPH) insulin is slowly absorbed due to the addition of protamine to regular insulin (Table 1). Regular insulin bound to zinc, Lente insulin, has a slightly longer effective duration than

NPH. Lente and NPH are commonly used as twice-daily basal insulins. Neutral protamine lispro (insulin lispro protamine; NPL) and protamine crystalline (crystal) aspart, available in the United States only in premixed insulins, are functionally identical to NPH.

Long-Acting Insulin. Ultralente insulin (insulin zinc extended) is absorbed slowly in its zinc crystalline form. Insulin glargine, a modified human insulin that forms a microprecipitate in the subcutaneous tissue, is released slowly with a peakless delivery of about 20 to 24 hours in most patients (Table 1).

What Are the Major Adverse Effects of Insulin?

Hypoglycemia is the most common adverse effect of insulin therapy. In the Diabetes Control and Complications Trial (type 1 DM),²⁰ intensive therapy increased the risk of severe hypoglycemia, defined as needing the assistance of another person. Severe hypoglycemia was reported by 26% of patients with a mean of 1.9 episodes per patient per year, and 43% of episodes occurred nocturnally. In the UKPDS, patients with type 2 DM receiving insulin therapy had lower HbA_{1c} levels, but 1% to 2% more patients receiving insulin reported at least 1 episode of severe hypoglycemia per year than those patients receiving other therapies. Intensive therapy, with oral medications or insulin, has been shown to increase the risk of episodes of hypoglycemia.⁸

Generally, patients receiving insulin gain weight. As patients attempt better glycemic control, decreased glycosuria and intermittent overinsulinization can result in hypoglycemia, hunger, and increased caloric intake. In the Diabetes Control and Complications Trial, patients with type 1 DM receiving intensive insulin therapy gained 4.75 kg more than patients receiving conventional therapy during the 3.5- to 9-year study period ($P < .001$), although waist-hip ratios did not differ between groups.²¹ In the UKPDS, patients with type 2 DM receiving intensive insulin therapy gained significantly more

weight (1.4-2.3 kg) than those patients treated with SUs or metformin.⁸ Bedtime administration of NPH produces less weight gain than daytime NPH, making bedtime administration a preferred strategy when starting insulin therapy in patients with type 2 DM.^{22,23} In one study, patients gained less weight with insulin glargine than with conventional therapy with NPH.²⁴

Rapid improvement in diabetes control results in progressive worsening of retinopathy in approximately 5% of patients.²⁵⁻²⁷ Patients with proliferative retinopathy and who have an HbA_{1c} level greater than 10% are at highest risk of worsening retinopathy.²⁸ In these patients, we recommend reducing the HbA_{1c} level slowly (2% each year) with frequent ophthalmologic examinations (eg, every 6 months or for any symptoms) to ensure aggressive treatment of progressive retinopathy.

What Are the Major Issues Regarding Insulin Delivery?

When prescribing insulin for patients, important issues include insulin pharmacokinetics and compatibility, technological issues, and costs. Insulin absorption variability is the biggest confounder of efforts to mimic physiologic insulin secretion. The onset and duration of action of types of insulin vary greatly when different insulins are mixed, by injection site, and among patients.²⁹ Large doses of human insulins form an insulin depot, unpredictably prolonging the duration of action; this response is less of an issue for the insulin analogues.³⁰ Thus, patients injecting 40 U of NPH insulin into their abdominal region before breakfast may have a significantly different onset and peak of action than the same patients injecting 20 U of NPH in their thigh in the evening; mixing insulin lispro with the morning NPH dose and regular with the evening NPH dose would result in further variation. Insulin glargine may not be mixed with other insulins. Cloudy insulins, for example NPH, must be resuspended before administration, and if done improperly the insulin concentration may vary signifi-

cantly.³¹ Importantly, any strategy that increases the consistency of delivery should decrease glucose fluctuations.

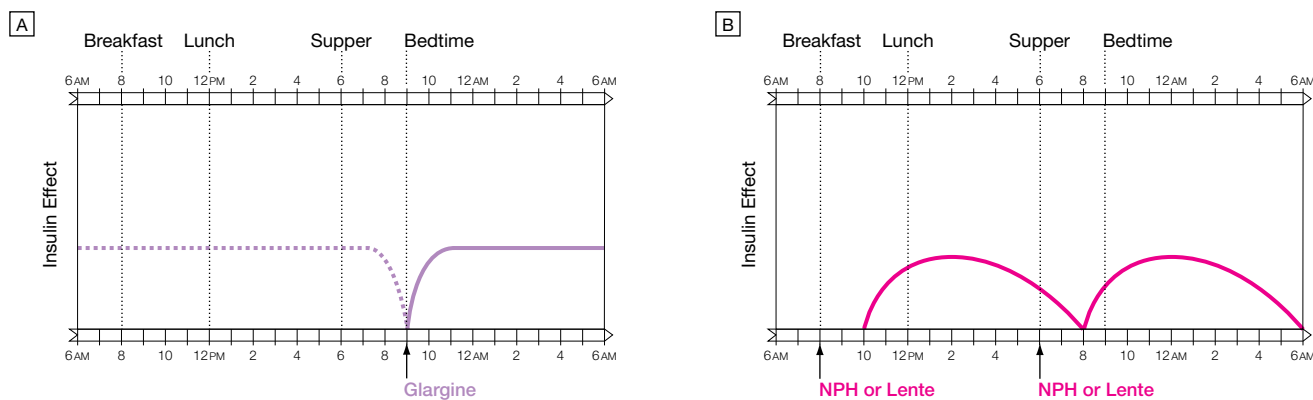
Insulin pens are convenient and may help avoid some insulin errors, but insulin cartridges for pens are more expensive than insulin in vials. Patients using insulin pumps must attend to tubing and injection site issues, must closely monitor their blood glucose level, and should have a back-up method of insulin administration.

What Are the Differences Between Physiologic and Nonphysiologic Insulin Regimens?

We refer to regimens that do not mimic normal β -cell secretion as “nonphysiologic insulin replacement” (FIGURE 1). “Physiologic insulin replacement” attempts to mimic normal insulin secretion. In general, physiologic regimens replace basal and prandial insulin (often referred to as “bolus”) separately. In our experience, physicians and patients frequently misunderstand this key difference.

Traditionally, NPH was the primary basal insulin and regular was the primary prandial insulin. However, as typically used, each provides both basal and prandial effects. In conventional twice-daily NPH and regular insulin regimens (FIGURE 2), morning regular insulin is responsible for glucose disposal for breakfast, but its effective duration of 5 to 8 hours also makes it prandial insulin at lunch. After the absorption of breakfast (carbohydrate disposal is usually complete by midmorning), the regular insulin becomes, by definition, basal insulin. The morning NPH insulin is basal insulin after breakfast and lunch absorption are complete, and becomes the primary prandial insulin for lunch. But the relatively quick onset of NPH makes it functionally a component of the breakfast prandial insulin. This regimen requires strict consistency of the timing of injections and meals. Delaying lunch frequently results in hypoglycemia, at least for many patients trying to achieve meticulous glycemic control. Because NPH and regular insulin overlap in the later part

Figure 1. Examples of Nonphysiologic Insulin Replacement



Nonphysiologic insulin replacement does not mimic normal β -cell insulin secretion. A, Once-daily, long-acting insulin glargine is released with a peakless delivery of approximately 20 to 24 hours in most patients. Glargine achieves steady state at approximately 2 hours. Dashed line indicates the effective duration of glargine continuing through the following day. B, Twice-daily, intermediate-acting neutral protamine Hagedorn (isophane insulin; NPH) and Lente (insulin zinc) are commonly used as basal insulin. Arrows indicate insulin injection.

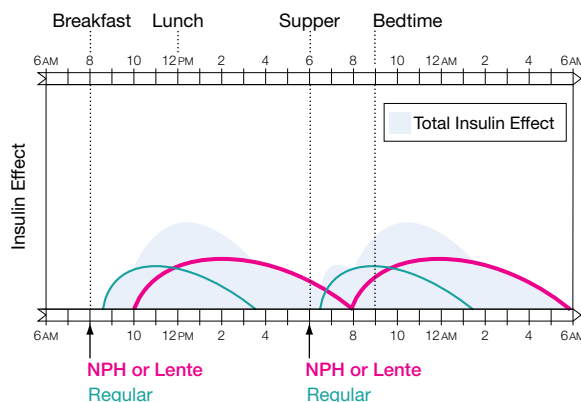
of the morning, many patients require midmorning snacks to prevent hypoglycemia (Figure 2).

Using prandial insulin for each meal (either regular insulin, insulin lispro, or insulin aspart) with separate basal insulin (NPH, Lente, Ultralente, or insulin glargine) adds flexibility to the regimen, and glargine-lispro or glargine-aspart regimens allow patients to skip meals or change mealtimes (FIGURE 3). This approach requires more injections than with conventional twice-daily physiologic regimens, but surveys show that patients with type 1 DM are injecting insulin more frequently and they prefer the dietary freedom, with education about more complex strategies for their care, rather than simplistic rules.^{1,32} In one study, 80% of patients preferred a qualitative strategy and 20% preferred a quantitative strategy to a “simple” but relatively inflexible strategy.³³ Dose adjustment is much simpler with true basal-prandial regimens (eg, glargine-lispro) than with insulins that function as both a basal and a prandial insulin (eg, NPH).

How Does the Patient Use Supplements and Adjustments?

Hyperglycemia correction is an important principle of insulin therapy. A supplement is a predetermined dose of rapid- or short-acting insulin used to

Figure 2. Example of Conventional Physiologic Insulin Regimen



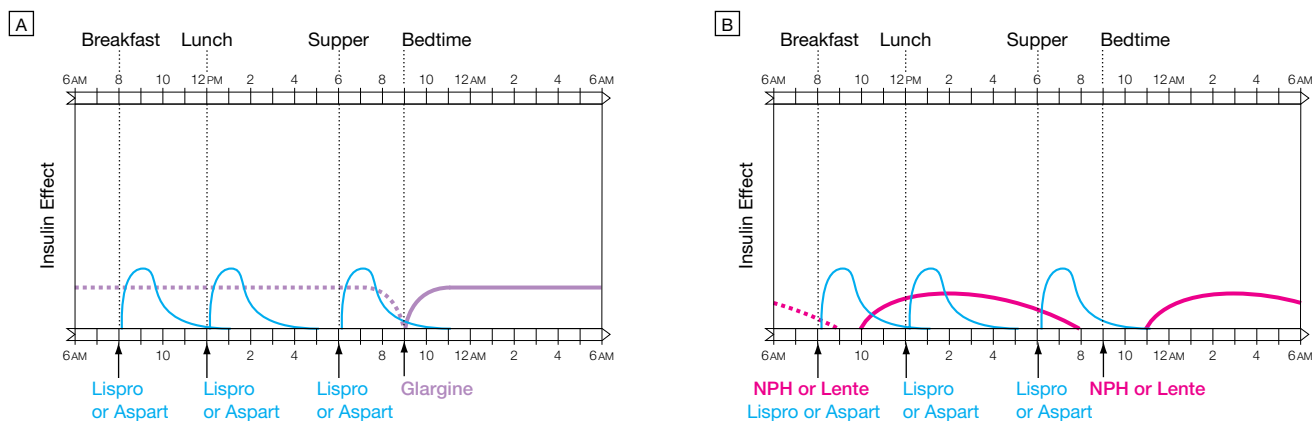
Physiologic insulin replacement with intermediate-acting neutral protamine Hagedorn (isophane insulin; NPH) or Lente (insulin zinc) and short-acting regular insulin (shown in a ratio of 70:30) attempts to mimic normal β -cell insulin secretion. Each insulin serves as both a basal and a prandial insulin. Meal timing and consistency are important for patients using this regimen. Many patients require a midmorning and bedtime snack to prevent hypoglycemia when the effect of the 2 insulins overlap at late morning and nighttime. Moving the dinnertime NPH injection to bedtime decreases the risk of nocturnal hypoglycemia. Arrows indicate insulin injection.

correct hyperglycemia. Supplements are easier to determine when basal and prandial insulins are administered separately. Supplements are usually injected with the usual prandial dose of insulin. A conservative dose for patients with type 1 DM is an additional 1 U per 50 mg/dL (2.7 mmol/L) above the target blood glucose level. For patients with type 2 DM, we recommend 1 U of supplemental insulin per 30

mg/dL (1.7 mmol/L) above the target glucose level.

If patients are using insulin supplements between meals, they must be aware of “insulin stacking.” Injecting additional short- or rapid-acting insulin 1 hour after a dose of regular and NPH insulin would result in insulin stacking and in predictable hypoglycemia within several hours because most of the previously injected insulin has not been ab-

Figure 3. Examples of Physiologic Insulin Delivery Regimen



A, Once-daily glargine with lispro or aspart (shown in a ratio of 50:50) allows patients to skip meals or change mealtimes. Insulins lispro and aspart (rapid acting) are prandial insulins and glargine (long acting) is a basal insulin. This regimen is easier to use since it has true basal and prandial insulins. Dashed line indicates the effective duration of glargine continuing through the following day. Glargine achieves steady state at approximately 2 hours. B, Intermediate-acting neutral protamine Hagedorn (isophane insulin; NPH) and Lente (insulin zinc) are basal insulins. Rapid-acting lispro and aspart insulins are prandial insulins. This regimen (shown in a ratio of 50:50) is more difficult to adjust because NPH can act as both a basal and a prandial insulin. Dashed line indicates the effective duration of NPH or Lente continuing through the following day. Arrows indicate insulin injection.

sorbed. If patients are to inject supplements less than 3 hours after a previous insulin dose, they can decrease the supplement by 50%. Patients who exercise may be required to adjust their dose of rapid-acting insulin analogues. Patients who exercise early in the postprandial period (1-3 hours) may need to decrease their dose of rapid-acting insulin by 75%, whereas patients who exercise later in the postprandial period may require a smaller or no change in dose.^{34,35}

An “adjustment” means changing the dose of any type of insulin based on a consistent pattern of blood glucose levels. For example, the adjustment for a patient receiving bedtime NPH insulin who has frequent fasting hypoglycemia would be to decrease the bedtime insulin dose. Aggressive but careful adjustments based on patients’ injection timing meal patterns and activity levels are key to excellent long-term glucose control.

Why Is It Important for Patients to Self-monitor?

While there is little controversy that all patients receiving insulin should perform self-monitoring of blood glucose tests, there is disagreement about the frequency and timing of the tests. For type 1 DM, the American Diabetes Association

suggests 3 or more tests per day.²⁹ The data are less clear for patients with insulin-requiring type 2 DM. Many type 2 DM studies exclude patients receiving insulin, lump insulin users and non-users, and were conducted before the availability of insulin analogues and improved self-monitoring of blood glucose equipment. A recent study suggests self-monitoring of blood glucose is associated with improved control in patients with type 2 DM who use the results to adjust insulin doses.³⁶

What Regimens Are Best for Patients With Type 1 DM?

Type 1, autoimmune, DM occurs in adults of all ages, including obese patients with phenotypic type 2 DM. Latent autoimmune DM (also known as LADA) of adults can be confused with type 2 DM early in diagnosis, but patients become insulinopenic relatively rapidly.³⁷

Nonphysiologic Regimens. Some newly diagnosed patients with type 1 DM or latent autoimmune DM of adults who are still producing endogenous insulin may do well receiving once- or twice-daily basal insulin injections before they progress to complete β -cell failure (Figure 1). The time to com-

plete insulin deficiency varies, but it is generally longer in adults than in children. Even with euglycemia, few physicians would recommend discontinuing insulin completely because intensive insulin therapy appears to promote β -cell preservation.^{9,10,38} Data are not available to date to compare different nonphysiologic insulin regimens in this patient population.

Physiologic Regimens (TABLE 2). In patients with severe insulin deficiency, replacement of both prandial and basal insulin components is required. In patients with type 1 DM and no endogenous insulin secretion, it is very difficult to safely reach target HbA_{1c} level (<7%) with conventional insulin therapy, twice-daily NPH, and regular insulin (as shown in Figure 2). This regimen is difficult to adjust, and it is relatively inflexible because it uses both insulin components as both a prandial and a basal insulin. Moving NPH insulin from dinnertime to bedtime was first suggested in the 1980s as a strategy to optimize this conventional regimen.³⁹ Mixed NPH and regular insulin are given before breakfast, regular insulin is injected before dinner, and NPH is given at bedtime. A recent randomized, crossover study confirmed that this bedtime

Table 2. Available Insulin Delivery Systems and the Cost of a Physiologic Regimen With Each System

Delivery System	Advantages	Disadvantages	Cost (Comparative Examples for Initial and Monthly Cost)*	
			Item	Amount
Syringe	Maximal ability to “freemix” insulin and adjust to patient needs	Multiple injections Need to carry bottles, syringes, and supplies Variable absorption depending on type of insulin and body injection site Lispro and glargine are both clear insulins and therefore difficult to distinguish, patients must read labels carefully	Insulin glargine 1000 U	\$44
			Insulin lispro 1000 U	\$46
			Syringes for 4 injections/d (120-gauge)	\$36
			Total cost per month for glargine at bedtime + lispro 3 times/d	\$126 Bedtime NPH + 3 times/d of prandial regular = \$25 + \$25 + \$36 = \$86
Pen	Convenient, less to carry Easy to distinguish between insulins by pen color/size Improves dosing accuracy Although not recommended, many use 1 needle per 24 h	For injection, approximately 30% more expensive per 1000 U than bottled insulin	Pen injector	Novopen 3 = \$29-\$32 retail
			Pen cartridges for 1000 U	NPH = \$42 Glargine = \$63 Lispro = \$63
			Total cost per month for bedtime dose with needles	NPH/prandial lispro = \$105 Glargine/lispro = \$126
			Pump: Medtronic MiniMed	\$5500/60 mo at \$92 per month (assumes pump life of 5 years)
Pump	Fewer injections Physiologic delivery with best glycemic control and fewest hypoglycemic events overall Eliminates variable injection-site absorption	Expensive Additional training needed Patient must be aware of potential technical problems	Monthly cost of tubing/reservoirs	\$150
			Insulin lispro 2000 U	\$92
			Total cost per month	\$334

Abbreviation: NPH, neutral protamine Hagedorn (isophane insulin).

*We estimated costs based on 0.9 U/kg for a 70-kg person at 63 U/d, 32 U of each per day, equals 1000 U/mo of each insulin type. Patients are told to discard their unused bottles at the end of the month if they use less insulin.

NPH strategy reduces both HbA_{1C} levels and nocturnal hypoglycemic episodes in patients with type 1 DM.⁴⁰

Overall, patients using insulin analogues (lispro, aspart, glargine) in physiologic regimens (Figure 3A), including patients with hypoglycemia unawareness, have fewer hypoglycemic episodes than patients using traditional insulins (regular and NPH).⁴¹⁻⁴⁶ Because of shorter duration of action, insulin lispro (introduced in the United States in 1996) and insulin aspart are only used as prandial insulins or in CSII programs. When patients use insulins lispro or aspart, they have fewer episodes of severe hypoglycemia and nocturnal hypoglycemia than with regular insulin.⁴⁷⁻⁵⁰ (eTABLE 1^{42-44,46,50-72} and eTABLE 2^{12,24,27,41,53-67,72-83}; tables are published online at <http://www.jama.com>). Lag time depends on the onset of action of the prandial insulin used (eg, 30 minutes for regular insulin and none for insulin lispro or aspart). An inadequate lag time results in postprandial hyperglycemia and in later risk of hypoglycemia. Patient compliance with the recommended 30-minute lag time for regular insulin is 30% to 70% (pa-

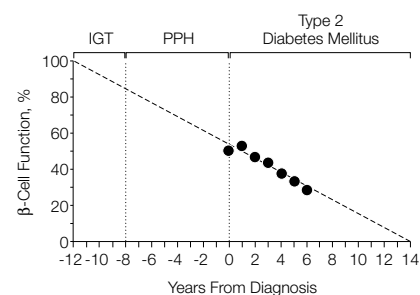
tients inject insulin closer to or at meal-time.^{84,85} The lack of required lag time for rapid-acting insulins and improved matching of action with carbohydrate absorption explain their clinical advantage (Figure 3).

Data on regimens using rapid-acting analogues with basal NPH are mixed (Figure 3B). Improvements in HbA_{1C} levels have not been seen when analogues are given with basal NPH provided once or twice daily, because the improvement in postprandial hyperglycemia seen with the rapid-acting analogues is negated by higher preprandial and overnight glycemia (compared with regular insulin). One study using small doses of NPH given with insulin lispro before each meal and at bedtime, to better control basal needs between meals, showed decreased HbA_{1C} levels and episodes of hypoglycemia.⁶² However, in a recent study of patients with type 1 DM receiving NPH basal insulin (1-2 injections per day) with prandial lispro, adding an additional injection of NPH at lunchtime in an attempt to give smoother basal control resulted in 6.9 more episodes of severe hypoglycemia per patient-year (P = .007).⁸⁶ Ultralente, which is longer

acting than NPH or Lente, was developed to improve basal insulin delivery. However, twice-daily Ultralente, as compared with Lente, mildly improves fasting glucose levels but increases episodes of hypoglycemia.⁸⁷

Insulin glargine became available in the United States in 2001. Theoretically, this peakless, long-acting basal insulin analogue should reduce hypoglycemia and improve glycemic control.⁸⁸ In actuality, reductions in episodes of hypoglycemia, especially nocturnal hypoglycemia, occur consistently whereas reductions in HbA_{1C} levels have been more difficult to achieve (eTables 1 and 2; tables are published online at <http://www.jama.com>). A large multicenter trial of patients with type 1 DM using insulin glargine with prandial regular insulin showed no change in HbA_{1C} levels, although 25% fewer hypoglycemic episodes were noted.⁴² When insulin lispro was used as the prandial insulin, no differences in HbA_{1C} levels or hypoglycemic episodes were observed, but patients receiving glargine gained slightly less weight.⁶³ When glargine and lispro were compared with NPH and regular insulin in adoles-

Figure 4. Progressive Decline in β -Cell Function and Insulin Secretion in Type 2 Diabetes Mellitus



Data show 50% of normal β -cell function at diagnosis of type 2 diabetes mellitus (year 0) and a steady decline up to 6 years following diagnosis. Clinically, most patients have had prediabetes (impaired glucose tolerance [IGT] and postprandial hyperglycemia [PPH]) for some time before clinical diagnosis of type 2 diabetes mellitus. Dotted line shows the extrapolation of β -cell function before and after diagnosis of diabetes. Adapted with permission from *Diabetes Reviews*¹³³ based on data from the United Kingdom Prospective Diabetes Study.⁹²

cents, results of HbA_{1C} levels were similar, but the glargine-lispro regimen produced fewer hypoglycemic episodes.⁶¹ However, in a population with a lower baseline HbA_{1C} level (7.1%), substituting insulin glargine for NPH, with prandial insulin lispro, decreased hypoglycemic episodes and HbA_{1C} levels.⁸⁹

It may be that the main impact of physiologic insulin regimens and insulin glargine in particular is that the separation of prandial and basal components improves our understanding of insulin use, simplifies dosing adjustments, and allows patients more flexibility in meal timing. With a distinctly different basal insulin component (glargine or pump therapy), patients need approximately half of their insulin as basal insulin. When initiating a basal-prandial regimen, patients should decrease the calculated 50% basal insulin dose by 20% to avoid hypoglycemia. Using this calculation, one third of patients are receiving the correct dose, one third need more, and one third need less basal insulin.⁹⁰

When Should Insulin Be Used in Type 2 DM?

Most patients with type 2 DM will eventually need insulin. Insulin therapy was started in patients with type 2 DM with

a mean HbA_{1C} level of 10.4% in the United States,⁹¹ and the UKPDS⁹² showed that β -cell failure is progressive; 50% of normal β -cell function at diagnosis with a steady decline following diagnosis (FIGURE 4). Concomitantly, 53% of patients with type 2 DM initially treated with SUs required insulin therapy by 6 years, and almost 80% required insulin by 9 years.^{93,94} Although we may be diagnosing DM earlier and thus altering this time frame, physicians should consider starting insulin therapy in patients whose HbA_{1C} level approaches 8% despite optimal oral therapy.

Improved glycemic control delays or prevents complications in patients with type 2 DM,^{8,95,96} although patients often need an insulin dosage of greater than 100 U/d to achieve glycemic control.⁹⁴ Patients with type 2 DM often resist physician recommendations to start insulin therapy, partly because of misperceptions that starting insulin means the patient and physician have failed. Several unmasked studies suggest that switching from oral agents to the use of insulin in patients with type 2 DM improves treatment satisfaction, general well being, and quality of life, especially if patients previously had poor glycemic control.^{22,75,79,97} When choosing an insulin regimen, the benefits of intensive therapy must be tempered by cost and ease of regimen. In general, treatment satisfaction is better with simpler regimens. Patients allocated to strict control (fasting plasma glucose level <117 mg/dL [6.5 mmol/L]) or less strict control (fasting plasma glucose level <153 mg/dL [8.5 mmol/L]) for 1 year reported improved mood and general well being if their HbA_{1C} level decreased 1% or more, but strict targets increased perceived treatment burden.⁹⁸ It has been shown that patients prefer insulin glargine to NPH,⁶⁶ twice-daily NPH to Ultralente, and insulin pen administration or pre-mixed insulin to free-mixed insulin administered with syringes.⁹⁹⁻¹⁰³

What Is the Best Regimen for Patients With Type 2 DM?

Combination Oral Agent/Insulin Therapy. When using bedtime basal in-

sulin (NPH or glargine), continuing 1 or 2 daytime oral medications is reasonable (eTABLE 3^{6,8,15,94,97,104-132,134-146}; table is published online at <http://www.jama.com>). Metformin with insulin results in similar metabolic control, less weight gain, lower insulin doses, and fewer hypoglycemic episodes than insulin alone or insulin/SU therapy.* Thus, metformin and insulin may be the best combination for the majority of patients with type 2 DM who do not have contraindications. However, it should be emphasized that the goal is the target HbA_{1C} level, not lower insulin dose. Patients who must discontinue metformin because of increasing plasma creatinine levels should have their insulin dose increased 20% to 36% to maintain glycemic control.¹⁴⁷

Combining SUs with insulin lowers insulin doses (25%-50%) with less weight gain, but increases cost.† Sulfonylureas increase endogenous insulin secretion (C-peptide) early in the disease process. Improvement of HbA_{1C} with SU use in the UKPDS was in patients whose HbA_{1C} levels were well below 10%.⁹³ As insulin production declines and HbA_{1C} levels approach 10%, the combination of insulin and SUs eventually becomes ineffective.¹⁴⁹

Insulin secretagogues include the SUs and the glinides. Glinides are functionally short-acting SUs and may improve prandial control with or without basal insulin. Not enough data are available to date to endorse their use,¹⁵⁰ especially given their cost, although they may be beneficial in patients with hypoglycemia or who skip meals.

Although thiazolidinediones (TZDs) are effective insulin sensitizers, combined TZD/insulin therapy has been problematic, and TZDs are expensive. Troglitazone was taken off the market due to liver failure, but one randomized trial comparing intensive insulin monotherapy vs insulin with either metformin or troglitazone showed that all therapies lowered HbA_{1C} levels effectively.¹⁵¹ Patients gained about 4.4 kg while receiv-

*References 97, 113, 114, 119, 120, 140, 144.

†References 105, 110, 119, 123-125, 127, 148.

ing insulin or insulin/troglitazone, but only 0.5 kg while receiving insulin/metformin. Troglitazone significantly reduced the dose of insulin but caused the same rate of hypoglycemic episodes as insulin (2 per month), while patients receiving insulin/metformin reported no hypoglycemia. Pioglitazone and rosiglitazone should not be used with patients in New York Heart Association (NYHA) class III or IV heart failure, and patients' liver function must be monitored. Significant weight gain, pulmonary edema, and heart failure are increasingly associated with TZDs.¹⁵² Given these issues, combination TZD/insulin therapy should be used with caution.

Insulin Therapy. The goals of insulin therapy in both type 1 and type 2 DM are to reach the target HbA_{1C} level with a low rate of hypoglycemic episodes and the least amount of weight gain (eTable 2; table is published online at <http://www.jama.com>). However, goals must be individualized since older patients with type 2 DM and with no complications may not benefit from intensive therapy. When starting insulin therapy in patients continuing daytime insulin secretagogues or metformin, with an HbA_{1C} level less than 9.5% to 10%, bedtime basal insulin therapy is effective, convenient, and produces less weight gain.^{22,23,73} Compared with NPH, basal insulin glargine is associated with 25% fewer nocturnal hypoglycemic episodes, better postdinner control, and slightly less weight gain at twice the cost.^{24,41} Both NPH and glargine are easily adjusted based on fasting blood glucose levels. Once-daily Ultralente insulin produces more hypoglycemic episodes than twice-daily NPH despite a higher HbA_{1C} level.⁷⁵ If nocturnal hypoglycemia is an issue and glargine is not an option, prandial lispro with SU lowers HbA_{1C} levels with fewer hypoglycemic episodes than NPH with SU.¹⁴⁶

With progressive β -cell exhaustion, patients will be more successful in achieving glycemic control with progressively more physiologic regimens. Premixed insulins, given twice daily, (70% NPH/30% regular [70N/30R],

70% NP [neutral protamine]/30% aspart [A] [BIAsp], and 75% NPL/25% lispro [L]) are convenient but no prandial insulin is given for lunchtime. BIAsp improves postbreakfast/dinner blood glucose levels, but not HbA_{1C} levels, and decreases severe hypoglycemic episodes by 50% when compared with 70N/30R. Patients who are uncontrolled (ie, not achieving glycemic control) receiving premixed insulin regimens can often achieve control at the same insulin dose by adding lunchtime prandial insulin and by decreasing the morning insulin accordingly. Prandial insulin lispro is associated with fewer episodes of nocturnal hypoglycemia than regular insulin.⁸² Another trial of lispro vs regular, with twice-daily basal Lente or Ultralente, showed a lower HbA_{1C} level with lispro at similar insulin doses.⁶⁷ Prandial therapy with lispro vs bedtime therapy with NPH lowers HbA_{1C} levels without additional hyperglycemia.⁸¹ Importantly, patients with type 2 DM may require large insulin doses (>1 U/kg) to reach an HbA_{1C} level less than 7%.^{6,153,154}

What Are the Advantages of Insulin Pump Therapy?

Patients with type 1 DM receiving CSII therapy show more improvement in HbA_{1C} levels than patients receiving intensive multiple injection therapy¹⁵⁵; but it remains to be seen whether CSII will reduce the risk of microvascular complications. Compared with multiple injection therapy, CSII reduces hypoglycemic events up to 74%.¹⁵⁵ Intensive insulin therapy reduces costs by decreasing complications; and a study of CSII vs multiple injection therapy in peripartum patients with type 1 DM shows equal costs, but patients preferred pump therapy.¹⁵⁶

An external pump is programmed to deliver individualized basal rates of short- or rapid-acting insulin (usually 0.5-1.5 U/h). Since patients receiving CSII need less insulin, it has been recommended to decrease the total daily dose by 20% to 30% and then use 50% of that reduced dose as basal insulin.² Prandial (bolus) insulin is given by manual activation.

Rapid-acting insulins have been shown to be superior to regular insulin in a CSII program because of improved prandial control.^{52,70}

The main indications for pump use in patients with type 2 DM without significant C-peptide secretion are severe hypoglycemia and wide fluctuations of glucose levels.^{27,80} However, physiologic regimens with insulin glargine and lispro or aspart probably offer the same benefits at lower cost, albeit with more injections.

What Other Approaches Improve Outcomes or Reduce Costs?

While the practice of diabetes care is now increasingly precise, the complexities of care and compliance issues are overwhelming for many physicians. Improving systems of diabetes care may improve glycemic control compared with standard care as shown by (1) frequent insulin dose adjustment by nurse educators via telephone lowered the HbA_{1C} level from 9.4% to 7.8% (0.3% more than standard care)¹⁵⁷; (2) "telecare" (transmitted data and telephone advice) improved HbA_{1C} levels 1% (vs 1.2%) and saved patients considerable travel time¹⁵⁸; and (3) using computer decision models for adjustments of insulin doses lowered HbA_{1C} levels approximately 12% and decreased the rate of hypoglycemic episodes by 50% per week.^{159,160}

COMMENT

An HbA_{1C} level less than 7% consistently reduces microvascular complications and is now the goal for most patients. Limited data suggest that reducing complications also reduces costs. A team approach with diabetes educators may be more effective at reducing complications at a similar cost. The lack of resources for efficient team care is a major barrier to diabetes care, especially in the primary care community.

Patients with type 1 DM almost always require multiple injections to attain an HbA_{1C} level less than 7%. Physiologic basal-prandial regimens are easier to use and adjust and cause fewer episodes of hypoglycemia. They also provide patients with more flexibility, and

studies on patient satisfaction support their use. However, insulin analogues cost 50% more than human insulins.

Patients with type 2 DM who still secrete endogenous insulin often do well receiving oral agents. The choice of oral agent depends largely on adverse effects and cost.¹⁶¹ Oral agents alone lower HbA_{1c} levels 1% to 2%. Adding bedtime insulin, usually NPH, to oral agents is the standard approach to starting insulin therapy. Although insulin may be added to any approved oral agent, metformin does not cause weight gain and may offer additional cardioprotection¹⁶² and thus is our first choice for use with insulin in patients without contraindications. Oral agents lower the required insulin dose. When patients with type 2 DM become insulin deficient, the principles of insulin use are the same as for patients with type 1 DM. Importantly, patients with type 2 DM often require large insulin doses, for example, 1 to 2 U/kg per day, and the use of lower doses in clinical practice is a common barrier to effective diabetes control.

Finally, treatment goals and intensity of insulin therapy must be individualized since young patients may benefit the most from intensive therapy and even expensive therapies may be cost-effective, while older patients without complications may not benefit as much from intensive therapy with its attendant risks.

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Table 1. Randomized Controlled Trials of Standard Human Insulins vs Currently Available Insulin Analogues in Type 1 Diabetes Mellitus

Source	No. of Patients	Study Length*	Treatment Arms†	Main Outcomes (Glucose Reported as mg/dL)‡
Crossover Trials				
Pfutzner et al, ⁴⁴ 1996	107	3 mo	Lispro/NPH vs regular/NPH	No difference in HbA _{1c} levels between groups but fewer hypoglycemic events with lispro (absolute RR, 6%; <i>P</i> = .008)
Daniels et al, ⁵¹ 1997	20	3 mo	Lispro vs regular with basal NPH, NPL, or Ultralente	No differences in HbA _{1c} levels or hypoglycemia between groups
Zinman et al, ⁵² 1997	30	3 mo	Lispro vs regular in CSII	Double-blind trial HbA _{1c} levels lower with lispro (<i>P</i> = .0041) Lispro lowered PPBG levels after all meals (breakfast, <i>P</i> = .006; lunch, <i>P</i> = .049; dinner, <i>P</i> = .03) No difference in hypoglycemia between groups
Vignati et al, ⁵³ 1997	379	2 mo	Twice-daily NPH/prandial regular vs lispro	Treatment to target FPG level <140 and PPPG level <160 Lispro lowered PPBG levels (breakfast, <i>P</i> <.001; dinner, <i>P</i> <.056) No difference in HbA _{1c} levels or hypoglycemia between groups
Del Sindaco et al, ⁵⁴ 1998	69	3 mo	Lispro/bedtime NPH vs regular/bedtime NPH	Group 1, lispro with bedtime NPH showed no difference in HbA _{1c} levels but an increase in hypoglycemic episodes (<i>P</i> <.05) Group 2, lispro with NPH 3-4 times/d showed a decrease in HbA _{1c} levels with no increase in hypoglycemic events Group 3, regular at meals with no lag time with bedtime NPH showed no change in HbA _{1c} levels or hypoglycemic episodes Group 4, regular with a lag time of 10-40 minutes with bedtime NPH showed higher HbA _{1c} levels without lag time (group 3) but with an increase in hypoglycemic events with longer lag times
Home et al, ⁵⁵ 1998	90 men	4 wk	Aspart/bedtime NPH vs regular/bedtime NPH	No changes in fructosamine levels (short HbA _{1c} equivalent) Aspart improved PPG control after lunch and dinner (<i>P</i> <.05) Regular lowered nighttime glucose levels (<i>P</i> <.01) Severe hypoglycemic episodes decreased with aspart (absolute RR, 38%; <i>P</i> <.002)
Melki et al, ⁵⁶ 1998	39	3 mo	Lispro vs regular in CSII	HbA _{1c} levels were lower with lispro (<i>P</i> = .01) PPBG levels were lower with lispro (<i>P</i> <.001) as were SDs of all BG levels (<i>P</i> <.02) No differences in hypoglycemic events between groups 95% of patients chose to continue lispro
Colombel et al, ⁵⁷ 1999	25	3 mo	Lispro/NPH vs regular/NPH	Variability in BG levels was lower with lispro (<i>P</i> <.01) but no change in HbA _{1c} levels Less severe hypoglycemic events were observed with lispro (<i>P</i> = .048; absolute RR, 45%)
Renner et al, ⁵⁸ 1999	113	4 mo	Lispro vs regular in CSII	HbA _{1c} levels were significantly better (<i>P</i> = .02) and PPBG levels better after all meals (<i>P</i> <.001) with lispro No difference in hypoglycemic events between groups Patient satisfaction was higher with lispro
Gale, ⁵⁹ 2000	93	12 wk	Lispro/bedtime NPH vs regular/bedtime NPH	No difference in HbA _{1c} levels between groups Decrease in nocturnal hypoglycemic episodes with lispro (absolute RR, 44%; <i>P</i> <.001) Increase in hypoglycemic episodes with lispro between 6 AM and noon (absolute RI, 12%; <i>P</i> = .03)
Annucci et al, ⁶⁰ 2001	85	3 mo	Regular/NPH vs lispro/NPH	Basal NPH at evening with prandial regular or lispro NPH could be added at breakfast and lunch if necessary Number of injections was kept constant: 42% of patients injected 3 times/d and 58% of patients injected 4 times/d FBG and preprandial BG levels were similar PPBG levels improved with insulin lispro at all 3 meals (<i>P</i> = .003) HbA _{1c} levels improved with lispro (8.1% vs 8.3%; <i>P</i> <.05) No difference in hypoglycemia between groups Better rate of patient acceptance of lispro (<i>P</i> <.001)
Ferguson et al, ⁴⁶ 2001	33	24 wk	Lispro/NPH vs regular/NPH	Patients with known hypoglycemia unawareness who had HbA _{1c} levels of approximately 9%, and 55% of patients had 1 or more severe hypoglycemic episodes Fewer severe hypoglycemic episodes with lispro (55% vs 84%; <i>P</i> = .09; absolute RR = 20%)
Raskin et al, ⁴³ 2001	58	12 wk; 2-way	Lispro vs buffered regular in CSII	Open-label study Lower HbA _{1c} levels with lispro (<i>P</i> = .004) FPG levels were the same but PPBG levels at 1 hour (<i>P</i> = .012) and 2 hours (<i>P</i> = .001) were lower with lispro No difference in hypoglycemia between groups
Murphy et al, ⁶¹ 2002	25	16 wk	Lispro/glargine vs regular/bedtime NPH	Glargine produced lower FBG levels (144 vs 166; <i>P</i> <.0001) and lower PPBG levels (<i>P</i> <.005) Nocturnal hypoglycemic events were less with glargine (<i>P</i> <.05) HbA _{1c} levels were lower (8.7% vs 9.1%; not significant) despite lower insulin doses (1.16 vs 1.26 U/kg; <i>P</i> <.005) with glargine and lispro

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Table 1. Randomized Controlled Trials of Standard Insulins (NPH and Regular) vs Currently Available Insulin Analogues in Type 1 Diabetes Mellitus (cont)

Source	No. of Patients	Study Length*	Treatment Arms	Main Outcomes (Glucose Reported as mg/dL)
Parallel Trials				
Lalli et al, ⁶² 1999	56	1 y	Lispro/bedtime NPH vs regular/bedtime NPH	Lispro taken at meals; regular taken at meals with 10-40 minute lag time Small doses of basal NPH at mealtime with lispro In lispro group, mean BG levels were lower ($P < .05$), HbA _{1c} levels were lower ($P < .002$), less frequent hypoglycemic episodes (absolute RR, 22%; $P < .05$)
Raskin et al, ⁶³ 2000	619	16 wk	Prandial lispro/glargine vs prandial lispro/NPH	Decreased FBG levels ($P = .001$); more people in glargine (30%) than in NPH (17%) group reached FBG target level ($n = 119$) No differences in HbA _{1c} levels or hypoglycemia between groups Weight gain of 0.54 kg in NPH group vs 0.12 kg in glargine ($P = .034$) group
Rosenstock et al, ⁶⁴ 2000	256	4 wk	Prandial regular/glargine vs prandial regular/NPH	FPG levels decreased by 40 for glargine compared with NPH Glargine was superior to NPH in reducing FPG levels in patients previously receiving twice-daily NPH but not in those previously taking bedtime NPH
Ratner et al, ⁴² 2000	534	28 wk	Prandial regular/glargine vs prandial regular/NPH	No changes in HbA _{1c} levels but a significant reduction in FPG levels with glargine ($P = .0145$) Fewer hypoglycemic episodes (absolute RR, 27%; $P = .02$) and fewer nocturnal hypoglycemic episodes (absolute RR, 22%; $P = .01$) with glargine
Pieber et al, ⁶⁵ 2000	333	4 wk	Prandial regular/glargine vs prandial regular/NPH	FPG and FBG levels were lower ($P < .005$) with glargine Glargine lowered HbA _{1c} levels ($P = .03$) and decreased frequency of nocturnal hypoglycemic episodes (36% vs 55%; absolute RR, 19%; $P = .004$, significant compared with once- but not twice-daily NPH)
Home et al, ⁵⁰ 2000	1070	6 mo	Aspart/NPH vs regular/NPH	Aspart reduced HbA _{1c} levels (0.12%; 95% CI, 0.03-0.22; $P < .02$) Lower PPBG levels ($P < .01$) but higher preprandial levels before breakfast and dinner ($P < .01$) Patient satisfaction better with aspart ($P < .001$) Fewer nocturnal hypoglycemic events (absolute RR, 15%; $P < .05$) with aspart Absolute RR for severe hypoglycemic events was 9% for aspart
Witthaus et al, ⁶⁶ 2001	517	28 wk	Glargine/prandial regular vs NPH/prandial regular	Quality-of-life questionnaires showed glargine significantly improved treatment satisfaction with lower perceived frequency of hypoglycemic episodes ($P = .002$) No difference in psychological well being between groups
Roach et al, ⁶⁷ 2001	166 (102 type 1 DM; 64 type 2 DM)	12 mo	Freemix 75% NPL/25% lispro vs freemix NPH/regular	BG levels were lower with lispro/NPL 2 hours after breakfast ($P = .001$), before lunch ($P = .016$), 2 hours after evening meal ($P < .001$), and at bedtime ($P = .001$) at end point No differences in HbA _{1c} levels between groups Authors of Scientific Review note that physicians and patients were allowed to adjust insulin freely after 3 months with NPH, regular, or lispro, making this study difficult to interpret
Tamas et al, ⁶⁸ 2001	423	3 mo	Aspart/NPH vs regular/NPH	HbA _{1c} levels were lower with aspart ($P < .05$) and PPBG levels were lower after breakfast ($P < .001$) and dinner ($P < .01$) No difference in hypoglycemia between groups Patient(s) satisfaction for perceived hypoglycemia was improved with aspart ($P = .005$) and patients perceived increased flexibility ($P = .002$)
Tsui et al, ⁶⁹ 2001	27	9 mo	Lispro with basal NPH vs lispro in CSII	No difference in HbA _{1c} levels, in hypoglycemia, and in quality-of-life scores between groups
Bode and Strange, ⁷⁰ 2001	29	7 wk	Aspart vs regular in CSII	Open-label study for aspart ($n = 19$) vs buffered regular ($n = 10$) insulin No differences in HbA _{1c} levels between groups Fewer hypoglycemic events with aspart (absolute RR, 6%)
Roach et al, ⁶⁷ 2001	102	12 mo	Freemix lispro/NPL vs regular/NPH	Lower BG levels at multiple points for the freemix lispro group HbA _{1c} levels lower with NPL/L (7.54% vs 7.2%; $P = .02$) with similar insulin doses No difference in hypoglycemia between groups
Rossetti et al, ⁷¹ 2002	51	3 mo	Once-daily glargine/lispro vs 4 times/d NPH/lispro	Mean BG level was lower with glargine vs NPH (134 vs 149; $P < .05$) HbA _{1c} levels decreased with glargine (-0.4% to 6.5%; $P < .05$ vs NPH) Use of glargine increased basal and decreased prandial insulin vs NPH ($P < .05$) Fewer mild hypoglycemic events with glargine (approximately 7.9 vs 12.2 events per patient per month; absolute RR, 21%; $P < .05$) No significant difference between dinner or bedtime glargine
Boehm et al, ⁷² 2002	104	12 wk	Twice-daily 70% protamine aspart/30% aspart (BIAsp) vs twice-daily 70% NPH/30% regular	BIAsp lowered all CBG levels (postbreakfast, prelunch, postdinner, and bedtime were lower by approximately 18, $P < .05$) HbA _{1c} level was 0.1% lower (not significant) with 0.3 U/kg (0.65 vs 0.62 U/kg) mean increase insulin total dose per day in the BIAsp group ($P < .01$) but no weight gain Severe hypoglycemic episodes were reduced by 50% (14 vs 30) in the BIAsp group

Abbreviations: BG, blood glucose; BIAsp, biphasic insulin aspart; CI, confidence interval; CSII, continuous subcutaneous insulin infusion; DM, diabetes mellitus; FBG, fasting (whole) blood glucose (usually capillary blood glucose); FPG, fasting plasma glucose; Hb, hemoglobin; NPH, isophane insulin (neutral protamine Hagedorn); NPL, insulin lispro protamine (neutral protamine lispro); PP, postprandial; RR, risk reduction; RI, risk increase.

SI conversion factor: for glucose, to convert mg/dL to mmol/L, multiply by 0.0555.

*Crossover study time is months in each arm.

†Ultralente is insulin zinc extended.

‡Authors of Scientific Review comment on study interpretation: When regular insulin vs lispro or aspart insulin is used with NPH as a basal/prandial insulin, NPH confuses the ability to separate outcomes by insulin type and essentially flaws these studies.

Table 2. Randomized Controlled Trials Comparing Insulin Regimens in Type 2 Diabetes Mellitus

Source	No. of Patients	Study Length*	Treatment Arms†	Main Outcomes (Glucose Reported as mg/dL)
Crossover Trials				
Seigler et al, ⁷³ 1992	12	4 mo	Morning vs bedtime NPH	FPG levels better with bedtime insulin ($P < .001$) Mean HbA _{1c} levels better with bedtime NPH (6.2% vs 5.8%; $P < .05$) with no difference in insulin dose
Groop et al, ⁷⁴ 1992	24	3 mo	Morning NPH vs bedtime NPH	Glibenclamide control, and continued in both arms Similar treatment effects and no difference in HbA _{1c} levels between groups Bedtime NPH led to lower FBG levels ($P < .01$) and NPH at morning led to lower evening BG levels ($P < .01$)
Vignati et al, ⁵³ 1997	328	2 mo	Twice daily NPH/premeal regular vs NPH/lispro	Treatment to target FPG level < 140 and PPPG level < 160 Lispro lowered PPBG levels (breakfast, $P < .001$ and dinner, $P < .056$) No difference in HbA _{1c} levels or episodes of hypoglycemia between groups
Taylor et al, ⁷⁵ 2000	79	6 mo	Once-daily Ultralente vs twice-daily NPH	HbA _{1c} levels lower with NPH use (-9.0% vs -9.7% ; $P < .01$) More severe hypoglycemic episodes with Ultralente ($P < .01$) Quality of life improved in both groups but improved more with NPH ($P < .001$)
Parallel Trials				
Tindall et al, ⁷⁶ 1988	22	6 mo	Humulin-Zn vs Neulente	Older patients (aged 48-88 y) HbA _{1c} levels improved significantly from baseline (13.2% to 10.6% with Humulin-Zn and to 11.2% with Neulente) vs 46 patients who continued taking oral agents Fewer hypoglycemic episodes in the Neulente group (4 vs 46) 6 Humulin-Zn patients and 1 Neulente patient required short-acting insulin to overcome high PPBG levels
Paterson et al, ⁷⁷ 1991	35	14 wk	Basal Ultralente vs prandial regular	Evening Ultralente vs 3 premeal regular insulin injections with 15-minute lag time HbA _{1c} levels improved (from 12.5% to 10.7% for basal and from 12.0% to 9.5% for prandial) FPG levels did not differ between groups and insulin dose was higher in prandial regular group (44 vs 27 U, $P < .005$) No difference in frequency or severity of hypoglycemic episodes between groups Weight gain was 2.7 kg in prandial regular group
Jennings et al, ²⁷ 1991	20	4 mo	CSII regular vs twice-daily NPH/regular	8 of 10 CSII patients had HbA _{1c} levels $< 10.1\%$ vs 3 of 10 taking NPH/regular Weight gain, hypoglycemia, and insulin dose were similar between groups
Soneru et al, ⁷⁸ 1993	29	12-wk parallel and 6-wk insulin only	Glyburide and either morning or bedtime Lente then morning Lente vs bedtime Lente	Insulin adjusted to FPG target during 12-week combined, then glyburide stopped and insulin doses adjusted FPG levels same with morning or evening insulin with or without glyburide with FPG levels less than baseline ($P < .02$) No difference in HbA _{1c} levels and no change in lipid levels More hypoglycemic reactions with morning insulin (1.4 vs 0.4; $P < .025$) Weight gain of 3.0 kg during combination phase and did not increase during the insulin phase only
Taylor et al, ⁷⁹ 1994	21	6 mo	Twice-daily intermediate-acting insulin vs prandial regular	HbA _{1c} levels improved similarly between groups PP control better with regular insulin use and FBG levels better with intermediate-acting insulin
Landstedt-Hallin et al, ¹² 1995	80	16 wk	Glibenclamide/bedtime NPH vs glibenclamide/premeal regular	FBG levels were lower in NPH group (-115 vs -50 ; $P < .001$) HbA _{1c} levels and insulin doses were similar between groups Both insulin regimens lowered total cholesterol and triglyceride levels compared with baseline (all $P < .05$) Weight gain in regular insulin group was greater than NPH group (3.4 vs 1.9 kg; $P < .002$)
Saudek et al, ⁸⁰ 1996	121	1 y	IIP vs MDI	HbA _{1c} levels improved similarly in both groups IIP reduced BG fluctuations and reduced mild hypoglycemic episodes by 68% ($P < .001$) IIP produced no weight gain and had better quality of life ($P = .03$)
Bastyr et al, ⁸¹ 2000‡	135	3 mo	Glyburide with either prandial lispro vs NPH bedtime vs MET	HbA _{1c} levels for all groups lower than baseline ($P < .001$), but lispro group (7.68%) was lower than NPH group (8.51%; $P = .003$) and MET group (8.31%; $P = .025$) FPG levels in NPH group (153) were lower than lispro group (190; $P = .001$) and MET group (174; $P = .029$) 2-Hour PPBG level in lispro group (196) was lower than NPH group (220; $P = .052$) and MET group (229; $P = .009$) No difference in hypoglycemic episodes between both groups ($P = .16$) More weight gain in insulin group than MET group ($P < .01$) and more in NPH group than lispro group ($P = .051$)

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eTable 2. Randomized Controlled Trials Comparing Insulin Regimens in Type 2 Diabetes Mellitus (cont)

Source	No. of Patients	Study Length*	Treatment Arms	Main Outcomes (Glucose Reported as mg/dL)
Parallel Trials (cont)				
Bastyr et al, ⁸² 2000	365	12 mo	Basal NPH or Ultralente with either prandial regular vs lispro	Trend toward more nocturnal hypoglycemic episodes with regular (RR, 1.3; $P = .07$) and less nocturnal hypoglycemic episodes in a subset of 195 North American patients (RR = 1.6; $P < .01$) than with lispro More hypoglycemic episodes with Ultralente basal (RR = 1.5; $P = .02$) than with NPH
Yki-Jarvinen et al, ⁴¹ 2000	426	12 mo	Bedtime NPH vs glargine	Oral agents continued Treatment to target FBG level of 120 HbA _{1c} levels improved in both groups (8.2% vs 8.3%; $P < .001$) Fewer nocturnal hypoglycemic episodes with glargine (9.9% vs 24%; $P < .02$) Lower postdinner CBG levels with glargine (178 vs 193; $P < .02$)
Roach et al, ⁶⁷ 2001	64	12 mo	Freemix lispro/NPL vs regular/NPH	Lower BG levels at multiple points Lispro/NPH lowered HbA _{1c} levels by 0.4%: 7.54% ($P = .02$) with similar insulin doses No difference in hypoglycemia between groups Authors of Scientific Review note that NPL is not sold separately but it is functionally identical to NPH
Rosenstock et al, ²⁴ 2001	518	28 wk	Glargine bedtime vs once- or twice-daily NPH	Dose adjustment to FBG target level <120 63% took prandial regular insulin Both arms reduced HbA _{1c} levels (-0.41 to -0.59%, with HbA _{1c} level approximately 8.5%; $P < .001$) and FBG level ($P < .001$) vs baseline Less nocturnal hypoglycemic episodes (26.5% vs 35.5%; $P = .014$) and weight gain (0.4 vs 1.4 kg; $P < .007$) with glargine
Fritsche et al, ⁸³ 2002	695	24 wk	Glimepiride with morning glargine or bedtime glargine or bedtime NPH	Insulin titrated to FBG target level <101 HbA _{1c} level improved in all groups vs baseline (morning glargine, -1.29% vs bedtime glargine, -1.01%; $P = .009$) More achieved HbA _{1c} level <8% with morning (58%; $P = .002$) or bedtime glargine (54%; $P = .046$) than NPH (44%) Lowest rate of hypoglycemic episodes with morning glargine vs NPH (17% vs 38%; $P = .001$) Authors of Scientific Review note that doses not specified; morning vs evening glargine may differ based on actual amount of insulin available for meals and timing of hypoglycemia
Boehm et al, ⁷² 2002	187	12 wk	Twice-daily 70% protamine aspart/30% aspart (BIAsp) vs twice-daily 70% NPH/30% regular	BIAsp lowered all BG levels (postbreakfast, prelunch, postdinner, bedtime) with a mean approximately 18 Severe hypoglycemic episodes were reduced by 50% (6 vs 12) in the BIAsp group

Abbreviations: BG, blood glucose; BIAsp, biphasic insulin aspart; CSII, continuous subcutaneous insulin infusion; FBG, fasting blood glucose; Hb, hemoglobin; IIP, implantable insulin pump; MDI, multiple daily (insulin) injections; MET, metformin; NPH, isophane insulin (neutral protamine Hagedorn); NPL, insulin lispro protamine (neutral protamine lispro); PP, postprandial; RR, relative risk.

SI conversion factor: for glucose, to convert mg/dL to mmol/L, multiply by 0.0555.

*Crossover study time is time in each arm.

†Ultralente is insulin zinc extended and Lente is insulin zinc.

‡Study also included an oral agent arm but this study is not included in eTable 3.

Table 3. Randomized Controlled Trials of Combination Therapy With Available Oral Agents and Human or Animal Insulin

Source	No. of Patients	Study Length	Treatment Arms*	Outcomes (Glucose Reported as mg/dL)†
Crossover Trials				
Groop et al, ¹⁰⁴ 1984	13	2 mo	Insulin/glibenclamide vs insulin/placebo	Insulin and glibenclamide lowered FPG levels ($P = .026$) and increased C-peptide levels ($P = .037$) vs placebo
Groop et al, ¹⁰⁵ 1985	13	8 wk	Insulin/glibenclamide vs insulin/placebo	Combination therapy lowered FBG levels ($P < .001$) and HbA _{1c} levels ($P < .05$), and increased C-peptide levels ($P < .01$) No difference in insulin dose, weight gain, or lipid levels between groups
Samanta et al, ¹⁰⁶ 1987	20	3 mo	NPH/regular vs tolbutamide	Insulin lowered PPBG levels (139 vs 157; $P < .05$) and HbA _{1c} levels (6.6% vs 7.8%; $P < .05$) more than with SU C-peptide levels improved after insulin therapy ($P < .05$)
Schade et al, ¹⁰⁷ 1987	16	16 wk	Once- or twice-daily insulin (NPH or Lente) and either glyburide or placebo	Insulin dose could only be decreased HbA _{1c} levels were lower with SU therapy (10.2% vs 10.9%; $P < .05$) with lower insulin dose (53.5 vs 54.9 U; $P < .05$) Similar weight gain between groups
Kitabchi et al, ¹⁰⁸ 1987	12	3 mo	NPH vs NPH/tolbutamide	As C-peptide levels increased to 70% ($P < .02$) with similar glucose controls, combined therapy lowered insulin dose 23% (0.69 vs 0.89 U/kg; $P < .002$) and triglyceride levels (142 vs 181 mg/dL) ($P < .05$)
Holman et al, ¹⁰⁹ 1987	15	8-wk multiple crossover trial	Control (SU) vs SU/MET, or Ultralente, or SU/Ultralente, or Ultralente/regular	HbA _{1c} level for control SU was 10.7% HbA _{1c} level for Ultralente was 10.1% ($P = .002$) HbA _{1c} level for SU and Ultralente was 9.5% ($P < .001$) HbA _{1c} level for Ultralente and regular was 9.4% ($P = .001$) SU and Ultralente showed no improvement over Ultralente alone, but less insulin was used (25 vs 40 U; $P = .001$)
Stenman et al, ¹¹⁰ 1988	15	4 mo	Insulin/glibenclamide vs insulin/placebo	Insulin and SU lowered HbA _{1c} levels (8.3% vs 9.1%; $P < .001$) and FPG levels (133 vs 164; $P < .05$) with lower insulin dose (-10 U; $P < .001$), but with increased frequency of hypoglycemia ($P < .01$) and at a 30% to 50% higher cost
Woffenbittel et al, ¹⁵ 1989	13	6 mo	Insulin vs SU	HbA _{1c} levels lower with insulin vs SU (9.5% vs 11.0%; $P < .05$) Insulin produced greater weight gain (4.2 vs 1.1 kg; $P < .05$) HDL levels higher and triglyceride levels lower with insulin ($P < .05$)
Lewitt et al, ¹¹¹ 1989	31	12 wk	Insulin/glyburide vs insulin/placebo	Insulin and glyburide improved HbA _{1c} levels from 9.9% to 9.1% ($P < .001$) Responders had higher C-peptide levels and shorter duration of disease predicted response to SU
Riddle et al, ¹¹² 1989	20	4 mo	Bedtime insulin/glyburide vs insulin/placebo	FPG levels ($P < .01$) and HbA _{1c} levels (9.8% vs 10.6%; $P < .01$) improved in the SU group More weight gain insulin and glyburide therapy
Vigneri et al, ¹¹³ 1991	12	8 wk	Glyburide/bedtime NPH vs glyburide/MET	PPBG levels were lower with MET (196 vs 249; $P < .05$) Increase in weight gain with NPH (2 kg; $P < .005$) No difference in FPG or HbA _{1c} levels between groups
Trischitta et al, ¹¹⁴ 1992	16	8 wk	Glyburide/bedtime NPH vs glyburide/MET	NPH dose fixed at 0.2 U/kg No difference in HbA _{1c} levels between groups PPPG level of 239 for NPH vs 203 for MET ($P < .05$) More weight gain with NPH (1.9 kg; $P < .01$)
Ravnik-Oblak and Mrevlje, ¹¹⁵ 1995	27	3-mo crossover + 1 y	NPH/regular/glibenclamide vs NPH/regular/placebo	3-Month crossover trial with a then continuation of the more successful therapy for 1 year SU lowered HbA _{1c} levels (7.0% vs 7.9%; $P < .05$) and insulin dose (0.39 vs 0.62 U/kg; $P < .05$) SU better in 2/3 of patients and remained effective at 1 year if continued
Feinglos et al, ¹¹⁶ 1998	37	30 mo	Insulin (NPH with or without regular) and placebo vs insulin/glipizide	HbA _{1c} levels lower in insulin and glipizide group (9.8% vs 11.4%; $P < .008$) Insulin dose was lower with glipizide (69 vs 87 U; $P < .005$)
Robinson et al, ¹¹⁷ 1998	19 + 14	12 wk	Insulin/MET vs insulin/placebo	2 Crossover studies with 19 with 1 g of MET and 14 with 1 to 2.5 g of MET HbA _{1c} and FPG levels improved (1.6%-2.4%; $P < .003$) Lower triglycerides and LDL levels ($P < .032$) in MET group
Lopez-Alvarenga et al, ¹¹⁸ 1999	29	3 mo	Placebo vs acarbose vs bedtime NPH	All subjects already taking SUs Acarbose improved FPG levels ($P = .05$) but not HbA _{1c} levels Bedtime NPH (mean dose 19 U) decreased FPG and HbA _{1c} levels ($P < .01$)
Fritsche et al, ¹¹⁹ 2000	13	10 wk	MDI/MET vs MDI/placebo	Intensive MDI modeled on the Diabetes Control and Complications Trial Since goals were by SMBG, MET did not lower HbA _{1c} levels but did decrease insulin dose by 30%
Ponssen et al, ¹²⁰ 2000	31	5 mo	Insulin/MET vs insulin/placebo	Significantly reduced insulin dose (-9 U; $P < .001$), HbA _{1c} levels ($-0.7%$; $P = .005$), and total cholesterol levels (-7 mg/dL; $P = .005$)

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Table 3. Randomized Controlled Trials of Combination Therapy With Available Oral Agents and Human or Animal Insulin (cont)

Source	No. of Patients	Study Length	Treatment Arms	Outcomes (Glucose Reported as mg/dL)
Parallel Trials				
Osei et al, ¹²¹ 1984	22	16 wk	Insulin/glyburide vs insulin/placebo	Combination therapy decreased FBG levels (252 vs 286; $P < .05$) and HbA _{1c} levels (9.62% vs 10.92%; $P < .05$) vs placebo and increased C-peptide levels ($P < .05$) vs baseline No difference in results of lipid levels or glucose tolerance tests between groups
Falko and Osei, ¹²² 1985	22	16 wk	Fixed dose insulin/glyburide or insulin/placebo	FBG ($P < .01$) and HbA _{1c} ($P < .05$) levels decreased with glyburide C-peptide levels were higher in responders than nonresponders (5 vs 4; $P < .01$) No difference in lipid levels between groups
Quatraro et al, ¹²³ 1986	30	1 y	Insulin vs insulin/glicazide	Combined therapy lowered HbA _{1c} levels (8.7% vs 9.0%; $P < .05$), FPG levels (152 vs 165; $P < .05$), and insulin dose (40%) 2 Nonresponders were excluded
Mauerhoff et al, ¹²⁴ 1986	22	16 wk	Insulin/glibenclamide vs insulin/placebo	Decreased FPG (179 to 147; $P < .02$) and triglyceride ($P < .05$) levels in SU group vs baseline Increased hypoglycemic episodes (107 vs 25) despite an 8% to 10% insulin dose reduction (0.5 to 0.45 U/kg; $P < .02$), weight gain (1.3 kg; $P < .02$), and C-peptide levels ($P < .02$) in SU group
Gutniak et al, ¹²⁵ 1987	20	325 d	NPH/regular/glyburide vs NPH/regular/placebo	HbA _{1c} levels improved in both groups Decreased insulin dose (63 to 35 U; $P < .001$) for glyburide in insulin and SU group Weight gain was greater with SU use vs control (6.0 kg; $P < .005$ vs baseline, vs 2.9 kg [not significant])
Reich et al, ¹²⁶ 1987	20	4 mo	Insulin/glyburide vs glyburide/placebo	Patients hospitalized to add SU or placebo with resultant decrease in insulin dose, then HbA _{1c} levels worsened from 9.9% to 10.9% in placebo group
Bachmann et al, ¹²⁷ 1988	68	24 wk	Glibenclamide/insulin vs insulin	Goal PPBG target level < 220 attained by 75% in both groups No difference in FBG and HbA _{1c} levels or hypoglycemia between groups Insulin dose decreased with SU (20 vs 35 U)
Casner ¹²⁸ 1988	64	12 mo	NPH/regular/SU vs NPH/regular/placebo	HbA _{1c} levels lowered with SU at 3 months (11% to 10%; $P < .05$) but increased at 12 months (13%) C-peptide levels increased ($P < .05$) at 3 months then decreased 42% of patients responded to SU Responder insulin dose of 39 U/d vs 79 U/d at a cost increase of 50% for responders No difference in weight gain between groups
Lawrence and Abreira, ¹²⁹ 1988	20	16 wk	Insulin/glyburide vs insulin/placebo	Glyburide decreased HbA _{1c} levels ($P < .05$), then HbA _{1c} levels increased with placebo (9.9%-10.9%), but remained unchanged (8.9%) in SU group
Lins et al, ¹³⁰ 1988	20	12 wk	Insulin/glibenclamide vs insulin/placebo	SU improved HbA _{1c} levels from 8.3% to 7.0% and reduced insulin dose by 30%
Klein, ¹³¹ 1991	50	12 mo	Glibenclamide/MET vs glibenclamide/insulin	Insulin dose 12 to 40 U No difference in HbA _{1c} or PPG or lipid levels between groups Treatment "failures" (inadequate control) were withdrawn from analysis Insulin type not specified Authors of Scientific Review note that the study design is questionable
Groop and Widen, ¹³² 1991	36	6 mo	Twice-daily intermediate/regular insulin vs glibenclamide/MET vs 6 wk 3 times/d intermediate/regular insulin, then back to SU	All arms showed decrease in FPG and HbA _{1c} levels by 30% Insulin 3 times/d lowered CBG levels but return to SU alone brought CBG levels back to baseline level Insulin produced a weight gain of 5 kg No change in lipid levels between groups Insulin not specified (authors acknowledge Nordisk)
Yki-Jarvinen et al, ²² 1992	153	3 mo	Morning NPH/SU vs evening NPH/SU vs 2 times/d 70/30 vs MIT vs SU only	Insulin lowered HbA _{1c} levels ($P < .001$) and improved patient well being vs SU ($P < .001$) Less weight gain in evening insulin group only ($P < .05$)
Riddle et al, ¹³⁴ 1992	21	16 wk	Predinner 70% NPH/30% regular and glyburide vs predinner 70% NPH/30% regular	SU lowered HbA _{1c} levels (-1.3% vs -0.8%; $P < .05$), FBG levels ($P < .05$), despite lower insulin dose (50 U vs 101 U; $P < .01$) Similar weight gain between groups
Chiasson et al, ¹³⁵ 1994	354	1 y	Acarbose and either diet, MET, SU, or insulin	HbA _{1c} levels improved compared with placebo in all groups (all $P < .01$) No change in FBG or lipid levels among groups
Shank et al, ¹³⁶ 1995	30	1 y	1. SU; 2. SU vs bedtime NPH+SU vs bedtime NPH; 3. and 4. titrated NPH	4-Phase study FPG and HbA _{1c} levels best controlled with bedtime NPH and SU (all $P < .05$) Weight gain correlated with decreased glycosuria (vs SU) levels Lipid levels improved significantly with insulin vs SU and as glucose control improved

(continued)

Table 3. Randomized Controlled Trials of Combination Therapy With Available Oral Agents and Human or Animal Insulin (cont)

Source	No. of Patients	Study Length	Treatment Arms	Outcomes (Glucose Reported as mg/dL)
Parallel Trials (cont)				
Clauson et al, ¹³⁷ 1996	39	1 y	Bedtime NPH/glibenclamide vs MDI	Nonobese patients (BMI approximately 25.6 kg/m ²) HbA _{1c} levels better at 6 months in MIT (6.8% vs 8.2%; <i>P</i> < .001) but not at 12 months (7.5% vs 7.8%; not significant) More weight gain with MIT (5.6 vs 3.3 kg; <i>P</i> = .06) No change in lipid levels in both groups
Chow et al, ⁹⁷ 1995	53	6 mo	Bedtime NPH/SU or bedtime NPH/MET vs twice-daily 70% N/30% regular	Control improved in both groups, no difference in FBG or HbA _{1c} levels Combined therapy had decrease in insulin dose (15 vs 57 U; <i>P</i> < .0001) and weight gain (<i>P</i> < .005) Triglyceride levels lower (<i>P</i> < .02) and well being and quality of life better with insulin only (<i>P</i> < .05)
Wolfenbuttel et al, ¹³⁸ 1996	95	6 mo	Twice-daily 70% NPH/30% regular vs bedtime NPH/glibenclamide vs twice-daily NPH/glibenclamide	HbA _{1c} levels improved in all groups HbA _{1c} levels < 8% in 8 insulin and SU patients; 11 taking bedtime NPH and SU; 15 taking twice-daily 70 NPH/30 regular Mean NPH dose of 34 U in 70 NPH/30 regular group vs 23 U for once-daily NPH group Significantly more patients had HbA _{1c} levels > 9% while taking morning NPH and SU No difference in weight gain or hypoglycemia between groups
Colwell, ¹³⁹ 1996	153	27 mo	Once- or twice-daily insulin vs intensive treatment: (1) bedtime insulin; (2) add daytime glipizide; (3) twice-daily insulin no SU; (4) MDI	In intensive group (36% of patients taking MDI), HbA _{1c} levels decreased 2.1% with mean insulin dose of 100 U Near maximal HbA _{1c} levels decrease occurred at bedtime insulin and glipizide stage
Abraira et al, ⁵ 1998	153	27 mo	Bedtime insulin vs bedtime insulin/morning glipizide vs twice-daily insulin vs MDI	4-Phase trial with intensive patients' goal HbA _{1c} levels < 7.3% HbA _{1c} levels for bedtime insulin of -1.4%, bedtime insulin and glipizide of -1.9%, twice-daily no better, and MDI of -2.4% MDI significantly increased hypoglycemic events and insulin dose
Relimpio et al, ¹⁴¹ 1998	47	4 mo	Insulin vs insulin/MET	Maximum dose MET or 20% increase from baseline insulin dose Weight gain with insulin vs insulin and MET (1.2 vs 0.3 kg) Significantly better HbA _{1c} levels (-1.9% vs -0.03%; <i>P</i> < .01) and total cholesterol and LDL levels (<i>P</i> < .01)
Niazi and Muzaffar, ¹⁵⁵ 1998	36	20 wk	Insulin vs MET/glibenclamide	20 to 40 U of bedtime NPH vs MET and glibenclamide Similar reduction in BG levels between groups 50% of insulin group (<i>n</i> = 9) dropped out
Kelley et al, ¹⁴² 1998	145	24 wk	Insulin/acarbose vs insulin/placebo	HbA _{1c} levels reduced from approximately 8.7% by 0.58% (<i>P</i> < .001) more than placebo Despite more gastrointestinal tract adverse effects (acarbose), no difference in drop-out rates between groups
Riddle and Schneider, ¹⁴³ 1998	145	24 wk	Supper premix 70% NPH/30% regular/glimepiride vs premix 70% NPH/30% regular/placebo	Treated to target FPG level < 140 HbA _{1c} (7.7%) and FPG levels (137-138) equivalent at end of study Lower insulin dose in SU group (49 vs 78 U/d; <i>P</i> < .001) No differences in hypoglycemia, weight gain, or lipid levels between groups
UKPDS 33 et al, ⁹ 1998	3867	10 y	Intensive (SU or insulin) vs diet	Intensive (insulin or SU) decreased HbA _{1c} levels (7.0% vs 7.9%) and complications (12%), and increased frequency of severe hypoglycemic episodes by 3% and weight gain (insulin, 4.0 kg vs SUs, < 2.6 kg)
Yki-Jarvinen et al, ¹⁴⁴ 1999	96	1 y	Bedtime NPH and either SU and placebo; MET and placebo; SU and MET; or morning NPH	Less weight gain in NPH and MET (0.9 kg; <i>P</i> < .001 vs 3.6-4.6 kg for all other groups) Lower HbA _{1c} levels in NPH and MET (<i>P</i> < .05) and fewer episodes of hypoglycemia (<i>P</i> < .05)
Aviles-Santa et al, ¹⁴⁵ 1999	43	24 wk	Insulin/MET vs insulin/placebo	MET lowered HbA _{1c} levels (2.5% vs 1.6%; <i>P</i> = 0.04) and insulin dose (29%; <i>P</i> < .002); and less weight gain (0.5 vs 3.2 kg; <i>P</i> = .07)
Bastyr et al, ¹⁴⁶ 1999	423	2 mo	Prandial lispro/SU vs SU/bedtime NPH vs prandial lispro/bedtime NPH	HbA _{1c} levels lower with lispro and SU vs NPH and SU (-1.21 vs -1.40; <i>P</i> = .003) and both lower than baseline (<i>P</i> < .001) FBG levels lowest for NPH and SU (<i>P</i> < .001) Lowest frequency of nocturnal hypoglycemic episodes in lispro and SU (<i>P</i> = .004)
Turner, ⁹⁴ 1999	4075	9 y	Diet vs insulin vs SU vs MET	HbA _{1c} levels < 7%: diet group, 9%; insulin group, 28%; SU group, 24%; MET group, 18% FPG levels < 140: diet group, 8%; insulin group, 42%; SU group, 24%; MET group, 13% MET patients were obese Progressive need for multiple therapies: 50% at 3 years; 75% at 9 years

Abbreviations: BG, blood glucose; FBG, fasting blood glucose; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MDI, multiple daily injections; MET, metformin; NPH, isophane insulin (neutral protamine Hagedorn); PP, postprandial; SMBG, self-monitored blood glucose; SU, sulfonylurea.

SI conversion factors: for glucose, to convert mg/dL to mmol/L, multiply by 0.0555; for cholesterol, to convert mg/mL to mmol/L, multiply by 0.0259.

*Ultralente is insulin zinc extended.

†Authors of Scientific Review note that troglitazone data have not been included since it has been taken off the US market. Many trials with oral insulin do not specify insulin regimens or concomitant insulin adjustment protocols during the trial making it difficult to interpret reported outcomes.