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Original article

# Basal insulin or premix analogue therapy in type 2 diabetes patients ☆

Philip R. Raskin [a,*], Priscilla A. Hollander [b], Andrew Lewin [c], Robert A. Gabbay [d], Bruce Bode [e], Alan J. Garber [f]
on behalf of the INITIATE Study Group

[a] UT Southwestern Medical Center at Dallas, 5323 Harry Hines Blvd, Dallas, TX, 75390–8858, USA
[b] Baylor University Medical Center, 3600 Gaston Ave, Wadley Tower Suite 656, Dallas, TX 75246, USA
[c] National Research Institute, 2010 Wilshire Blvd, Suite 302, Los Angeles, CA 90057, USA
[d] Penn State Diabetes Center, Penn State College of Medicine, 500 University Drive, H044, Hershey, PA 17033, USA
[e] Atlanta Diabetes Association, Endocrinology and Diabetes, 77 Collier Road, NW, Suite 2080, Atlanta, GA 340309, USA
[f] Departments of Medicine, Biochemistry and Molecular Biology and Molecular and Cellular Biology, Baylor College of Medicine Faculty Center, Suite 1000, 1709 Dryden Road, BCM 620, Houston, TX 77030, USA

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**Abstract**

*Background:* We sought to compare the safety and efficacy of biphasic insulin aspart 30 (BIAsp 30) given twice daily with once-daily insulin glargine in patients with type 2 diabetes beginning insulin therapy and who did not use thiazolidinediones, which are contraindicated with insulin in the European Union, in a subpopulation ($N$=157) of the INITIATE study.
*Methods:* At baseline, $HbA_{1c}$ was ≥8.0% on ≥1000 mg/day metformin alone or in combination with other oral antidiabetic drugs (OADs; e.g. sulphonylurea or alpha-glucosidase inhibitors). Metformin was adjusted up to 2550 mg/day and other OADs were discontinued. Starting insulin doses were subsequently adjusted weekly for 26 weeks by algorithm-directed titration.
*Results:* The proportion of patients achieving a $HbA_{1c}$ below 7.0% at 28 weeks was greater with BIAsp 30 than with insulin glargine (65% vs 41%, $P$=0.003). The mean reduction in $HbA_{1c}$ was greater for BIAsp 30 than for insulin glargine: −2.89±1.6% vs −2.46±1.6%, respectively ($P$=0.035). Postprandial glucose increments were lower for the BIAsp 30 group after breakfast ($P$=0.003) and dinner ($P$=0.033); post-lunch values were not significantly different. No major hypoglycemic episodes were recorded. Nocturnal hypoglycemia was reported by 25% of subjects in the BIAsp 30 group and by 10% in the insulin glargine group ($P$=0.021). Weight gain was 5.6±4.6 and 3.0±4.3 kg ($P$=0.0004) for BIAsp 30 and insulin glargine, respectively.
*Conclusions:* BIAsp 30, given twice daily in combination with metformin, was more effective than insulin glargine, given once daily in combination with metformin, at controlling blood glucose in insulin-naïve patients with type 2 diabetes, but was associated with increased weight gain and minor hypoglycemic events.


*Keywords:* Type 2 diabetes mellitus; Hypoglycemic agents; Clinical protocols; Insulin analogs

## 1. Introduction

Insulin is typically initiated in type 2 diabetes in one of two ways–injection of a basal insulin OD or BID [1,2], or premixed insulin (analog or human) BID [3]–and usually in addition to a patient's prior oral antidiabetic drugs (OADs). Although there is no consensus about the optimal strategy for initiating insulin therapy, the International Diabetes Federation (IDF) recommends several different regimens, including

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* Corresponding author. Tel.: +1 214 648 2017; fax: +1 214 648 4854.
*E-mail address:* Philip.Raskin@UTSouthwestern.edu (P.R. Raskin).

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a basal insulin once daily, twice-daily premixed insulin, or a multi-injection (basal-bolus) regimen. A twice-daily premixed insulin was advocated by the IDF, particularly for patients with elevated $HbA_{1c}$ [4]. The American Association of Clinical Endocrinologists' (AACE) guidelines recommend premixed insulin analogs for patients with $HbA_{1c}$ above 7.0 [5]. By comparison, for those with $HbA_{1c}$ above 10.0%, the only two recommended options are basal-bolus therapy or premixed insulin analogs [5].

Premixed insulins offer the advantage of being a more physiological treatment regimen, able to address prandial, as well as fasting, insulin requirements with one single injection, unlike basal insulins, which primarily address fasting glucose. There is mounting evidence that it is important to control all aspects of the glucose triad — $HbA_{1c}$, fasting glucose, and postprandial glucose. In a large observational study [6], impaired 2-h glucose tolerance was associated with increased mortality from cardiovascular disease, coronary heart disease, and all causes in people not yet diagnosed with diabetes as well as among those with known diabetes [6]. Although not yet confirmed by prospective intervention trials, as recently reviewed by several authors, numerous observational studies have demonstrated that improved control of postprandial glucose is statistically associated with a significantly decreased risk of macrovascular [7–10] and microvascular [11] complications of diabetes. Thus, it could be argued that premixed analog insulins, by virtue of their ability to control postprandial glucose, may offer significant prognostic advantages over basal insulin for patients with type 2 diabetes. Indeed, four clinical trials have provided data supporting the use of premixed analog insulins as an alternative to basal insulin [12–15]. All four trials demonstrated improved glycemic control using premixed analog insulins vs insulin glargine.

In the INITIATE trial [14], one of the four trials mentioned above, approximately one-third ($N=76$) of the study participants continued their pre-trial use of thiazolidinediones (TZDs) after initiation of insulin treatment. [Due to lack of a US indication for the TZD rosiglitazone (Avandia®, GlaxoSmithKline, Philadelphia, PA) at the time of the study, patients who had used that drug were switched to pioglitazone (Actos®, Takeda Pharmaceuticals, Lincolnshire, IL) instead.] Use of TZDs in combination with insulin has to be considered carefully. TZDs are excellent insulin sensitizers that enhance the glucose-lowering effect of both endogenous and exogenous insulin and have been shown to improve clinical outcomes [16–18]. However, the use of TZDs in combination with insulin is contraindicated in the European Union [19] for reasons described below. Thus, findings from those patients not using TZDs in the INTIATE trial (presented here) will better enable physicians in the European Union to apply those results to their patients.

The European Medicines Agency has not approved the use of TZDs with insulin because, when used as monotherapy, TZDs can cause fluid retention in up to 5% of patients [20,21], possibly via effects on renal sodium reabsorption [22]. Consequently, TZDs may magnify the natural edematogenic properties of insulin when used together (~5% incidence of edema with insulin alone compared with ~15% when combined with TZDs) [20]. Indeed, clinical studies have indicated that TZD-related edema can, either on its own or via exacerbating pre-existing conditions, result in congestive heart failure in some patients [23,24]. Congestive heart failure as a result of treatment-associated edema has been reported to occur at a frequency of 0.3–0.6% in patients on oral combination therapy and to increase to about 2.5% when rosiglitazone is combined with insulin [25].

Hence, in the European Union, TZDs are approved only for oral combination or monotherapy in type 2 diabetes [19]. The UK National Institute for Clinical Excellence has also continued to exclude TZD combination therapy with insulin from licensed use [24]. By contrast, in the US, TZDs are approved for use with insulin, with certain precautions. Specifically, they may be prescribed for asymptomatic or mildly symptomatic patients with stable New York State Heart Association class I or class II heart failure, but they are not recommended for class III or IV disease [21,26].

Given the finding that 66% of insulin-naïve patients using BIAsp 30 plus metformin achieved a target $HbA_{1c}$ below 7.0%, with or without a TZD, in the INITIATE trial [14], the question of whether similar outcomes can be achieved for type 2 patients not taking TZDs is of great relevance. Although similar reductions in $HbA_{1c}$ were previously reported for the two subgroups using and not using TZDs in the original INITIATE study [14], detailed breakdowns of secondary efficacy endpoints and safety were not provided. Those results for the subpopulation not using TZDs are presented here.

## 2. Research design and methods

Details of the trial design of the full study have previously been reported and are reproduced here in brief [14]. This was a 28-week, randomized, open-label, parallel group, treat-to-target trial in patients with type 2 diabetes conducted at 25 centers in the US. For inclusion, subjects had to be insulin-naïve, 18–75 years old, have a BMI<40 kg/m$^2$ and a body weight <125 kg (275 lbs), a $HbA_{1c} \geq 8\%$, and to have been previously treated with metformin≥1000 mg/day, as a single agent or in OAD combination therapy, for at least 3 months before the trial. Patients were randomized to receive either twice-daily BIAsp 30 (NovoMix 30®, NovoLog® Mix 70/30 in the US, Novo Nordisk, Bagsvaerd, Denmark), which is a single-peak, premixed analog insulin, before breakfast and dinner, or once-daily insulin glargine (Lantus®, Sanofi-Aventis, Bridgewater, NJ), 12 U given at bedtime, with stratification according to TZD use. Thus, similar numbers of patients using TZDs were included in each arm of the parent trial.