



# Addition of Insulin Aspart with Basal Insulin is Associated with Improved Glycemic Control in Indian Patients with Uncontrolled Type 2 Diabetes Mellitus: The A<sub>1</sub>chieve Observational Study

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## Abstract

Insulin aspart (IAsp) has been used in patients for more than a decade. A plethora of data is available, from clinical trials, to document its efficacy and safety and suggest that IAsp is a favorable choice to be used in a basal-bolus regimen. The A<sub>1</sub>chieve® was a non-interventional study that explored the safety and effectiveness of initiating or switching to insulin analogues in routine clinical practice in more than 60,000 patients from 28 different countries. In this manuscript, we discuss the findings from the subgroup of the Indian cohort who were treated with insulin aspart (IAsp), in addition to a basal insulin analogue (insulin detemir, IDet). In a cohort of 343, who were on IAsp + IDet, 175 (51%) were insulin naïve and 168 (49%) had been on insulin therapy earlier. Glycaemic parameters were high at baseline. Mean HbA<sub>1c</sub> was 9.3% in them and was comparable in both insulin naïve and insulin experienced groups. After 24 weeks of therapy with IAsp + basal insulin, there were reductions in HbA<sub>1c</sub> in both the insulin naïve group, (-1.6) and insulin experienced group (-1.5). Fasting plasma glucose (FPG) and postprandial plasma glucose (PPG) levels were also reduced significantly from baseline (-77 and -110 mg/dL, respectively,  $p < 0.001$ ). Overall, hypoglycaemia decreased from 0.97 (baseline) to 0.18 events/patient years (24 weeks). There was also an increase in quality of life score as evaluated by EQ-5D questionnaire. Addition of IAsp with a basal insulin in patients with poor glycaemic control leads to an improvement in glycaemic profile with no major hypoglycaemia or clinically significant weight gain along with an improvement in the quality of life in patients with type 2 diabetes.

## Introduction

The progressive nature of type 2 diabetes (T2D) over time results in the majority of people with diabetes being unable to maintain HbA<sub>1c</sub> targets on a management regimen of lifestyle changes with oral glucose-lowering drugs (OGLDs).<sup>1,2</sup> Furthermore, suboptimal glycaemic control commonly persists even in insulin users.<sup>3</sup> What is sometimes described as “clinical inertia” or “patient resistance” further results in people remaining on inappropriate therapy regimens for too long.<sup>4,6</sup> It is known that when therapies are actively titrated and increased in number, glycaemic targets are more likely to be achieved.<sup>7</sup> In practice, however, most people with T2D still experience significant periods when their HbA<sub>1c</sub> levels are well above 7.0–8.0%, increasing their risk of developing diabetes-related complications.<sup>8–10</sup>

Insulin analogues were designed to aid better glycaemic control while addressing concerns over tolerability, notably in regard of hypoglycaemia and body weight gain.<sup>11,12</sup> Their clinical benefits have been assessed in randomised controlled trials (RCTs) and observational studies.<sup>6,13–19</sup> These studies have shown that a change of therapy from OGLDs or conventional insulin preparations to insulin analogues can be associated with clinically significant improvements in efficacy measures, while being well tolerated.

It is also widely recognized that having T2DM has a negative impact on quality of life (QoL).<sup>20</sup> Having to deal with lifestyle

change, complex treatment regimens, potentially having to manage self-injection, and sometimes fear of hypoglycaemia and weight gain can contribute to poor QoL and adverse perceptions of diabetes therapies.<sup>21–23</sup> Consequently, people with T2DM and their physicians often delay starting or optimizing insulin therapy, despite the current burdens of poor glycaemic control.<sup>23–26</sup> Alongside effective glycaemic control, maintaining or improving QoL is an integral part of the successful management of diabetes because QoL improves with better glycaemic control.<sup>27</sup>

The aim of the A<sub>1</sub>chieve study was to broaden the knowledge of the clinical safety and effectiveness of insulin analogues in a large and diverse population from a globally broad variety of clinical care along with determining the effects on health-related quality of life (HRQoL) of insulin analogue therapies in people with T2DM.<sup>28,29</sup>

## Methods

### Study design and patient description

A<sub>1</sub>chieve was an international, multi-centre, open-label, non-interventional, prospective, study for 24 weeks in subjects with type 2 diabetes using insulin analogs. The study included 66,726 subjects from 30 countries across four continents (Asia, Africa, South America, and Europe). India contributed with 20,554 subjects for this study which is almost 1/3 of the total study population. According to their previous treatment options, the subjects were divided into the following groups: No therapy 1314 (6%), oral glucose lowering drugs 15509 (76%) and insulin ± oral glucose lowering drugs 3731 (18%). These

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patients were prescribed basal insulin detemir (Levemir, Novo Nordisk, Denmark), bolus insulin aspart (NovoRapid, Novo Nordisk, Denmark) or biphasic insulin aspart 30 (NovoMix 30, NovoNordisk, Denmark), alone or in combination, to evaluate their clinical safety and effectiveness in routine clinical practice in India. These insulin therapies were prescribed by a physician in the course of normal clinical practice according to the requirement by the subjects.<sup>28</sup>

This subgroup analyses had a total of 343 subjects included to the basal + NovoRapid ± oral glucose treatment arm which

included 175 subjects from the oral glucose lowering drug group and 168 from insulin ± oral glucose lowering drugs group.

**Primary and secondary outcomes**

The primary objective of this study was to evaluate the clinical safety of the insulin analogues by the incidence of serious adverse drug reactions (SADRs) These included major hypoglycaemic episodes which were considered related to the study insulin between baseline and the final visit. The secondary safety assessments were the change in number of hypoglycaemic episodes, nocturnal hypoglycaemic, adverse drug reactions (ADRs) events 24 weeks from baseline. Major hypoglycaemic events were defined as events with severe central nervous system symptoms, consistent with hypoglycaemia, for which the person was unable to self-treat and accompanied by plasma glucose <3.1 mmol/L or 56 mg/dL, or reversal of symptoms after either food intake or glucagon or intravenous glucose administration. Minor hypoglycaemia was any event, with or without symptoms of hypoglycaemia, with a plasma glucose reading below 3.1 mmol/L or 56 mg/dL that the participant was able to self treat. Nocturnal hypoglycaemia was defined as a symptomatic event consistent with hypoglycaemia that occurred during sleep between bedtime after the evening insulin injection and before getting up in the morning<sup>28</sup>.

The efficacy parameters were analyzed by assessing the changes in HbA1c, fasting plasma glucose (FPG), postprandial plasma glucose (PPG), body weight, along with quality of life between baseline and visit at 24 week.<sup>28</sup>

HRQoL was measured using the EQ-5D questionnaire<sup>30</sup> at baseline and after 24 weeks of therapy with insulin analogues. This questionnaire is a descriptive system of HRQoL states consisting of five dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression). This EQ-5D VAS score ranges from 0 (worst imaginable health) to 100 (best imaginable health).<sup>29</sup>

**Statistical analysis**

For hypoglycaemia change from baseline, the percentage

**Table 1 : Baseline characteristics of Indian cohort**

	Total	No therapy	OGLD alone	Insulin ± OGLD
N	20554	1314	15509	3731
Percent of total	-	6.4	75.4	18.2
Sex M/F (%)	62.8/37.2	56.9/43.1	62.7/37.3	65.5/34.5
Age (years)	51.8 (10.1)	54.6 (12.6)	50.8 (9.5)	55.3 (10.5)
Weight (kg)	68.9 (10.5)	63.4 (8.4)	69.1 (10.2)	69.9 (12.1)
BMI (kg/m <sup>2</sup> )	26.3 (3.7)	28.4 (4.9)	26.1 (3.4)	26.5 (4.3)
Diabetes duration (yr)	6.3 (4.6)	2.2 (4.8)	5.7 (3.8)	9.9 (5.5)
HbA <sub>1c</sub> (%)	9.3 (1.4)	9.3 (1.3)	9.3 (1.3)	9.2 (1.5)

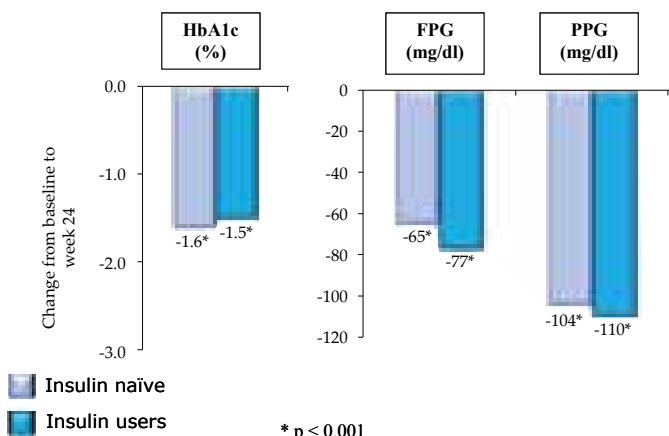
**Table 2: Baseline characteristics of subjects in this subgroup analysis**

	Total	OGLD alone	Insulin ± OGLD
N	343	175	168
Percent of total	-	51	49
Sex M/F (%)	58.6/41.4	61.1/38.9	56/44
Age (years)	52.9	51.8 (10.3)	54.0 (11.1)
Weight (kg)	71.8	70.7 (14.1)	72.9 (14.2)
BMI (kg/m <sup>2</sup> )	27.5	27.1 (4.9)	27.8 (4.7)
Diabetes duration (yr)	9.2	7.0 (4.6)	11.3 (6.7)
HbA1c (%)	9.3	9.3 (1.4)	9.2 (1.3)

**Table 3: Hypoglycaemic events at baseline and 24 weeks for patients treated with basal insulin + insulin aspart (Novorapid) ± OADs, by baseline insulin status**

	Major Hypoglycemia (events/patient year)		Minor Hypoglycemia (events/patient year)		Nocturnal Hypoglycemia (events/patient year)	
	Insulin naïve	Insulin experienced	Insulin naïve	Insulin experienced	Insulin naïve	Insulin experienced
Baseline	0.07	0.7	0.89	4.02	0.07	1.39
24 weeks	0.0	0.0	0.18	0.52*	0.0	0.0*

\* p < 0.001.



**Fig. 1 : Change in glycemic parameters from baseline**

**Table 4 : Change in body weight**

	All	Insulin-naïve	Insulin-experienced
N	252	135	117
Baseline (kg)	71.8	71.5	72.1
Week 24 (kg)	71.5	71.1	71.8
Change from baseline (kg)	-0.3	-0.4	-0.3

of people reporting at least one event was analyzed using Fisher’s exact test. Change from baseline HbA1c, FPG, PPG and blood lipids was analyzed using an analysis of covariance (ANCOVA) model with baseline characteristics as covariates. Health related quality of life analyses were performed for people who completed the EQ-5D questionnaire at both baseline and 24 weeks. Change from baseline in HRQoL with the EQ-5D

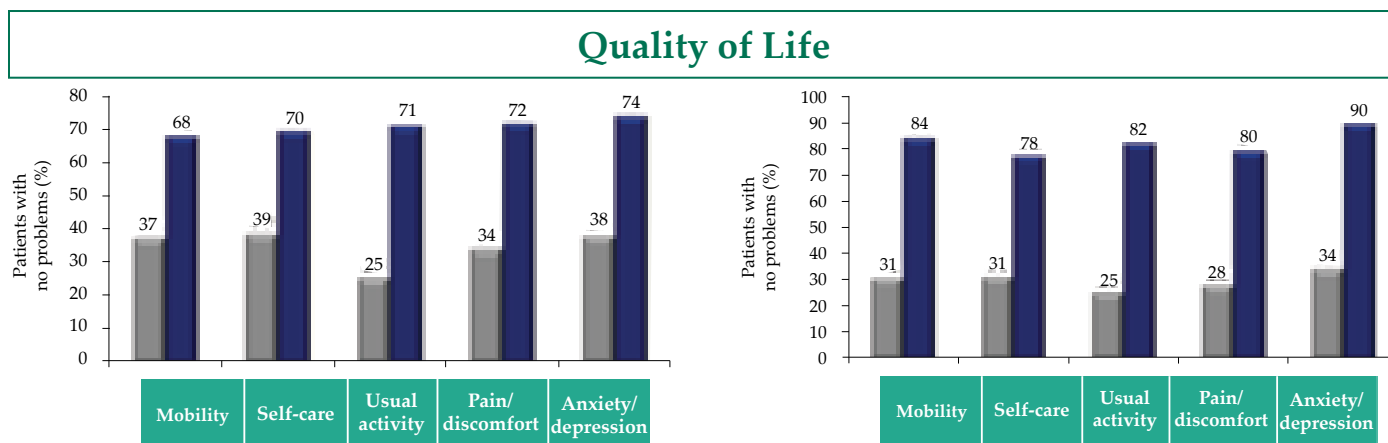


Fig. 2 : Self-rated health in insulin-naïve patients

VAS as a continuous variable was analyzed with the Wilcoxon signed-rank test.<sup>28</sup>

All data were analyzed by Novo Nordisk using SAS (Version 9.1.3).

## Results

### Study participants

The baseline characteristics of participants for the entire Indian cohort by prestudy therapy (insulin-naïve or insulin users) are given in Table 1. Of the 20,554 patients enrolled, all 20,554 (100%) were exposed and constituted the full analysis set and the safety analysis set. Data is presented as mean (SD).

The baseline characteristics of participants in this subgroup analysis are given in Table 2.

### Hypoglycemia

Hypoglycemia was analyzed for major, nocturnal and overall events per patient year. In the insulin-naïve population reported rates of overall hypoglycaemia decreased from 0.97 to 0.18 events/person-year, whereas the prior insulin users cohort, reported a significantly decreased rate from 4.72 to 0.52 events/patient year ( $p < 0.0001$ ).

Table 3 summarizes the hypoglycemic events at baseline and 24 weeks.

### Efficacy Parameters

#### Glycemic Parameters

Blood glucose control improved markedly between baseline and 24 weeks (Figure 1). HbA1c: -1.6% and -1.5%, FPG: -65 and -77 mg/dl and PPG: -104 and -110 mg/dl in insulin-naïve and insulin-experienced patients, respectively. These differences from baseline were statistically significantly ( $p < 0.001$ ).

#### Body weight

The mean body weight change over 24 weeks was neither statistically significant, nor clinically relevant (Table 4).

## Discussion

The results from the Achieve non-interventional observational study found that beginning therapy with the insulin analogues detemir with aspart in routine clinical practice was associated with marked improvements in average blood glucose levels (as measured by HbA1c), without evident tolerability or safety issues in the short term. Given that increase in hypoglycaemia was not a problem, and body weight was essentially unchanged,

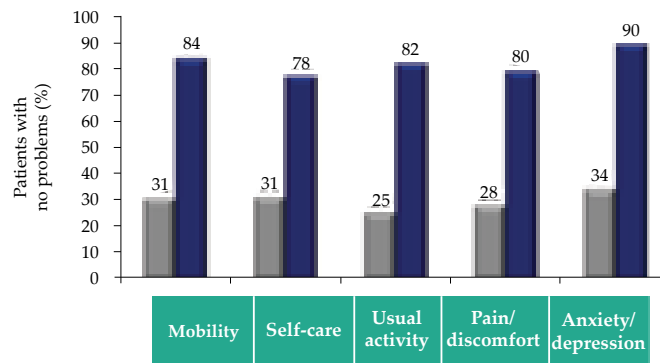


Fig. 3 : Self-rated health in insulin users

an improvement in HbA1c of 1.5-1.6% is note-worthy. Although the reductions in HbA1c were large, the proportion of people achieving a target level of  $< 7.0\%$  was disappointing, reflecting the very poor blood glucose control at baseline, the short duration of follow-up and the limited titration of insulin doses over the 6 months of study.

The HbA1c data is supported by the large and consistent reductions in FPG and PPG control.

The fact that there was no weight gain suggests that physicians advised lifestyle modifications which was adhered to by the participants, or else weight gain in 6 months (with such significant improvements in glycaemic parameters) would be expected to be around 4 kg,<sup>31</sup> due to amelioration of urinary glycosuria and glucose concentration driven glucose metabolism.<sup>32</sup>

Overall, the improvement in glycaemic parameters, following 24 weeks of use of detemir + aspart, was associated with a low incidence of hypoglycaemia. While improvements in glycaemic control are usually associated with an increased risk of hypoglycaemia,<sup>33</sup> the Indian sub-group analysis from this study reported a decrease in the rate of all hypoglycaemic episodes from 2.8 events/person-year at baseline to 0.34 events/person-year in the 24 weeks before the end of the study. The reduction in the reported relative event rate was also seen for minor hypoglycaemic episodes. Explanations for these findings may be better self-management behaviors, including more consistent eating patterns as a result of patient education given at the time of starting insulin analogues, although the possibility that investigator recording of hypoglycaemic events differed in some way at 24 weeks from that at baseline cannot be excluded.

In addition, people starting insulin with, or switching to, insulin detemir + insulin aspart, experienced significantly increased overall HRQoL, with significant improvements across all five components.

In summary, in people whose HbA1c suggests that the diabetes management has been neglected, starting an detemir + aspart (whether in a current insulin user or not) appears to provide an opportunity for improvements in self-management and metabolic control, independently of the type of insulin begun.

Morover, starting these insulin products was not associated with any tolerability or safety problem, notably of hypoglycaemia or body weight, which, in turn, led to an improvement in the QoL parameters.

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