Original article

The IMPROVE™ study – a multinational, multicentre, observational study in type 2 diabetes: results from the Italian cohort

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Abstract. *Aims:* The IMPROVE™ study evaluated the safety and effectiveness of biphasic insulin aspart 30/70 (BIAsp 30) in type 2 diabetes patients in the routine practice. Here we present the results for patients from Italy. *Methods:* Adverse events, hypoglycaemia, glycaemic control, patient treatment satisfaction and physician resource utilisation were assessed at baseline and 26 weeks. *Results:* Out of the 1371 patients enrolled, 84.1% (*n* = 1153) were receiving BIAsp 30 at baseline (in accordance with local regulations), and were included in the study. Mean HbA_{1c} reduction was −0.63% after 26 weeks ($p < 0.001$); 26.5% and 13.5% of patients reached the HbA_{1c} targets of <7% and <6.5%, respectively. Fasting and postprandial blood glucose significantly decreased; 65% of patients were using BIAsp 30 once daily and 32% twice daily at final visit. Rates of major and minor hypoglycaemic events also significantly decreased. Small weight increase was observed, and total insulin daily dose increased from 0.29 IU/kg pre-study to 0.32 IU/kg at final visit. *Conclusions:* In Italy, BIAsp 30 in the routine care improved glycaemic control and reduced hypoglycaemia; however, there was little intensification and titration. This may partly explain the relatively small improvement in glycaemic control in Italy compared with other countries in the IMPROVE™ study. (www.actabiomedica.it)

Key words: Type 2 diabetes; glycaemic control; biphasic insulin aspart; HbA_{1c}; hypoglycaemia

What's known?

Large, international, observational studies such as PRESENT and IMPROVE have shown BIAsp 30 to be effective and well tolerated when used to initiate insulin therapy, or intensify basal insulin or human premix insulin therapy in patients with type 2 diabetes. Unlike other countries in the IMPROVE study, local regulations required patients in Italy to be using BIAsp 30 prior to enrolment, and is therefore of special interest.

What's new?

In this Italian cohort of the IMPROVE study, the continued use of BIAsp 30 from baseline for 26 weeks resulted in further improvement in glycaemic control, but more aggressive dose titration may have further reduced glycaemia. The management of insulin therapy in Italy appears to be focussed on reduc-

The Italian IMPROVE™ Board wishes to thank all the Investigators involved (see Appendix)

ing the risk of hypoglycaemia rather than pursuing strict glycaemic targets.

Introduction

Diabetes mellitus is a progressive disease and, initially, the treatment of type 2 diabetes usually involves lifestyle adjustment, including diet and exercise (1). The next treatment step involves oral antidiabetic drugs (OADs) and, over time, many patients require insulin since OADs eventually fail to maintain recommended levels of glycaemic control in many cases (2, 3). Evidence suggests that it is important to initiate insulin therapy early in the disease process to minimise the risk of long-term complications (4, 5).

Many options for the beginning of insulin therapy are available; a basal insulin analogue is one of them (with or without OADs), frequently chosen for the simplicity of the regimen, often requiring only one daily injection. Another option is a premixed insulin analogue, covering basal as well as prandial insulin needs in each injection (6). With the progression of diabetes, glycaemic control may become inadequate with only basal insulin therapy, due to postprandial hyperglycaemia; hence, the need arises for rapid-acting prandial insulin (7). At this point, insulin therapy should be intensified to either basal–bolus therapy or a more intensive premixed insulin regimen. Premixed insulin analogues provide both intermediate and rapid-acting insulin, thus having the advantage of fewer daily injections than basal-bolus therapy (7). One such analogue is biphasic insulin aspart 30/70 (BIAsp 30, NovoMix® 30, Novo Nordisk, Copenhagen, Denmark), containing 30% free rapid-acting insulin aspart and 70% intermediate-acting protamine-bound aspart in each injection.

Randomised controlled trials (RCTs) have shown that initiating insulin therapy with, or switching to, BIAsp 30 can achieve better glycaemic control than basal insulin analogue therapy alone (6, 8-10). Complementing results from RCTs, observational studies provide data from large heterogeneous populations, and can demonstrate whether the benefits associated with particular treatments in RCTs translate into 'real-life' clinical practice (11-13).

The results of the PRESENT observational study showed improvements in glycaemic control and hypoglycaemia rates in type 2 diabetes patients when switching from basal insulin therapy to BIAsp 30 (13). While providing important data on BIAsp 30, the PRESENT study was mainly confined to Asian countries. The IMPROVE™ study, however, is a multinational, nonrandomised, noninterventional, observational study- the largest to date-investigating the safety profile and effectiveness of BIAsp 30 in type 2 diabetes in 11 countries (14–17).

While the global results include patients from a variety of pre-study therapies, regional differences in the patient populations are present, in accordance with local regulations regarding observational studies. For example, in Italy, all patients were required to be using the test insulin prior to enrolment in the IMPROVE™ study. This country cohort is therefore different from other country cohorts reported in the global results (15), and thus of special interest.

Here, we report the safety and effectiveness results of BIAsp 30 treatment in patients with type 2 diabetes in Italy, who were prescribed BIAsp 30 therapy by their physicians in routine clinical care.

Subjects, Materials and Methods

Study design

IMPROVE™ was a multicentre, open-label, nonrandomised, 26-week observational study carried out in 11 countries: Canada, China, Greece, the Gulf Region, India, Iran, Italy, Japan, Poland, Russia and South Korea. The aim of the study was to investigate the safety profile and effectiveness of BIAsp 30 when prescribed to patients with type 2 diabetes in routine clinical practice. In this paper we report the results from the Italian cohort. The study was carried out in accordance with the Declaration of Helsinki and procedures complied with Italian local and national regulations governing observational studies. According to national Italian regulations, the study protocol was approved by the ethics committee in each single site. Data from enrolled patients were collected at three scheduled visits: baseline, follow-up and final

visit (at 0 and approximately 13 and 26 weeks, respectively).

Patients

Patients with type 2 diabetes treated with BIAsp 30 in routine care were eligible for enrolment. According to local regulation, all patients included in the observational study were required to be using BIAsp 30 prior to enrolment.

Treatment

The treatment regimen, dose and timing of BIAsp 30 injections and any concomitant medication were chosen by the treating physician. The dose was individually adjusted, and any changes in BIAsp 30 treatment were recorded at baseline and approximately 13 and 26 weeks after.

Assessments and outcome measures

Physicians used medical history and patient's diaries and recall to record the patient data, including demographics and medical history at baseline and final visit (26 weeks). The primary outcome measure was the incidence of major hypoglycaemic events reported as serious adverse drug reactions (SADRs) during the 26 weeks of BIAsp 30 therapy. The secondary outcome measures included changes in glycated haemoglobin (HbA_{1c}), fasting blood glucose (FBG), postprandial blood glucose (PPBG) after all main meals, hypoglycaemic events, insulin dose, weight and body mass index (BMI), patient treatment satisfaction and physician resource utilisation.

Major hypoglycaemia was defined as an event with severe central nervous system symptoms that could not be self-treated, with either blood glucose levels <2.8 mmol/l or symptoms that were reversed after either carbohydrate intake or glucagon or intravenous glucose administration. Any event with blood glucose levels <2.8 mmol/l that the patient could self-treat (with or without symptoms of hypoglycaemia) was classified as a minor hypoglycaemic event. Major hypoglycaemic events were recorded over 13 weeks prior to each visit and minor hypoglycaemic events over 4 weeks prior to each visit; both were calculated as events per patient per year.

Both effectiveness and safety analyses were carried out on data from all patients who supplied baseline and final visit measurements.

Statistical analyses

Comparisons of BIAsp 30 outcome measures at baseline and final visit were performed with paired t-tests for continuous variables, and with Wilcoxon signed-rank tests for discrete variables. All testing used two-sided tests with the significance level set at $\alpha = 0.05$.

Results are presented for the total cohort of patients, and also for three subgroups: patients who were prescribed BIAsp 30 only, those who used BIAsp 30 with OADs and those who used BIAsp 30 with other insulins ± OADs. Results are also presented for patients who were >65 years old, and compared with patients ≤65 years old.

Results

Patients

A total of 1371 patients were enrolled in the study. However, deviations from the protocol were present, since not all patients were using BIAsp 30 prior to the study: 68 patients were insulin-naïve and 150 were using other insulins. These patients did not fulfil the protocol criteria for inclusion and therefore were excluded from the analyses. A total of 1153 patient were included in the study; demographics are shown in Table 1.

Out of the 1153 patients included in the study, 60.7% (n = 700) were using BIAsp 30 with other insulins ± OADs, 31.6% (n = 364) were using BIAsp 30 with OADs, and 7.7% (n = 89) were using only BIAsp 30. In addition, 581 patients were >65 years old.

Many patients reported diabetic complications at baseline: 50% had signs of microvascular complications (33% retinopathy, 18% diabetic nephropathy, 18% peripheral neuropathy, 2% autonomic neuropathy), and 37% showed macrovascular complications

Table 1. Patient baseline demographics

	Total BIAsp 30 cohort	BIAsp 30 only	BIAsp 30 + OAD	BIAsp 30 + insulin ± OAD
Number enrolled	1153	89	364	700
Age, mean ± SD (years)	66.2 ± 10.0	68.1 ± 11.2	66.3 ± 9.7	65.9 ± 9.9
Gender, male/female (%)	53/47	52/48	51/49	53/47
Weight, mean ± SD (kg)	76.7 ± 14.3	78.0 ± 15.2	77.5 ± 15.1	76.1 ± 13.8
BMI, mean ± SD (kg/m^2)	29.0 ± 4.9	29.1 ± 4.6	29.1 ± 5.2	28.8 ± 4.8
Diabetes duration, mean ± SD (years)	15.2 ± 9.1	13.1 ± 9.6	15.3 ± 8.4	15.4 ± 9.3
HbA_{1c}, mean ± SD (%)	8.3 ± 1.5	8.1 ± 1.4	8.4 ± 1.5	8.3 ± 1.6

BIAsp 30, biphasic insulin aspart 30/70; HbA_{1c}, glycated haemoglobin; OAD, oral antidiabetic drug; SD, standard deviation

(16% peripheral vascular disease, 25% coronary heart disease, 5% stroke).

Safety

Over the study period, three (0.3%) patients reported three SADRs (all hypoglycaemia), 15 pts. (1.3%) reported 18 adverse drug reactions, 20 pts. (1.7%) reported 21 severe adverse events, and 32 pts. (2.8%) reported at least one adverse event (in total, 40 adverse events were reported, 19 of which were hypoglycaemia). The rate of major hypoglycaemic events significantly decreased from 0.182 events per patient per year at baseline to 0.009 events per patient per year at final visit ($p < 0.001$). Major hypoglycaemia decreased for all subgroups, although the most pronounced reduction was observed in the BIAsp 30 + insulin ± OADs group (Fig. 1a). Minor hypoglycaemic events also decreased from 7.02 to 4.75 events per patient per year for the total cohort ($p < 0.001$), with the largest reduction in the BIAsp 30 only group (Fig. 1b). No significant differences were observed in the rate of major or minor hypoglycaemia between patients who were >65 and ≤65 years old.

Effectiveness

The total BIAsp 30 cohort and all pre-study therapy subgroups showed improvements in glycaemic control from baseline to final visit. HbA_{1c}, FBG and PPBG concentrations following breakfast, lunch and dinner significantly improved after 26 weeks of BIAsp 30 treatment (Table 2). The mean HbA_{1c} reduction was 0.63%, FBG reduction was 0.94 mmol/L, and mean PPBG reduction after breakfast was 0.99 mmol/L. Furthermore, 26.5% of patients achieved the HbA_{1c} target of <7%, and 13.5% achieved the HbA_{1c} target of 6.5%. The changes in HbA_{1c} were similar for patients for all pre-study subgroups (Table 2). There were no differences between patients >65 and ≤65 years old in mean HbA_{1c} reduction and mean PPBG reductions after all three main meals (NS). The only significant difference found at final visit was in mean FBG: patients >65 years old experienced slightly greater FBG reduction than patients ≤65 years old (−1.23 vs. −0.91 mmol/L, respectively; $p < 0.01$).

Weight

Mean weight slightly increased from baseline to final visit (+0.5 kg; $p < 0.001$) (Table 2). BMI also slightly increased from 29.0 kg/m^2 at baseline to 29.2 kg/m^2 at final visit (+0.20 kg/m^2, $p < 0.001$), but these changes may not be considered as clinically significant.

BIAsp 30 dose and injection frequency

The total insulin daily dose increased by only 0.03 IU/kg, from 0.29 IU/kg pre-study to 0.32 IU/kg at final visit. At baseline, the majority of patients (68.3%) were using BIAsp 30 once daily (OD), 30.0% twice daily (BID), and 1.6% three-times daily (TID). After 26 weeks, most patients (65.1%) were still using BIAsp 30 OD, 31.9% BID and 3.0% TID.

Patient satisfaction

The overall treatment satisfaction score significantly increased from 69.6 at baseline to 71.6 at final

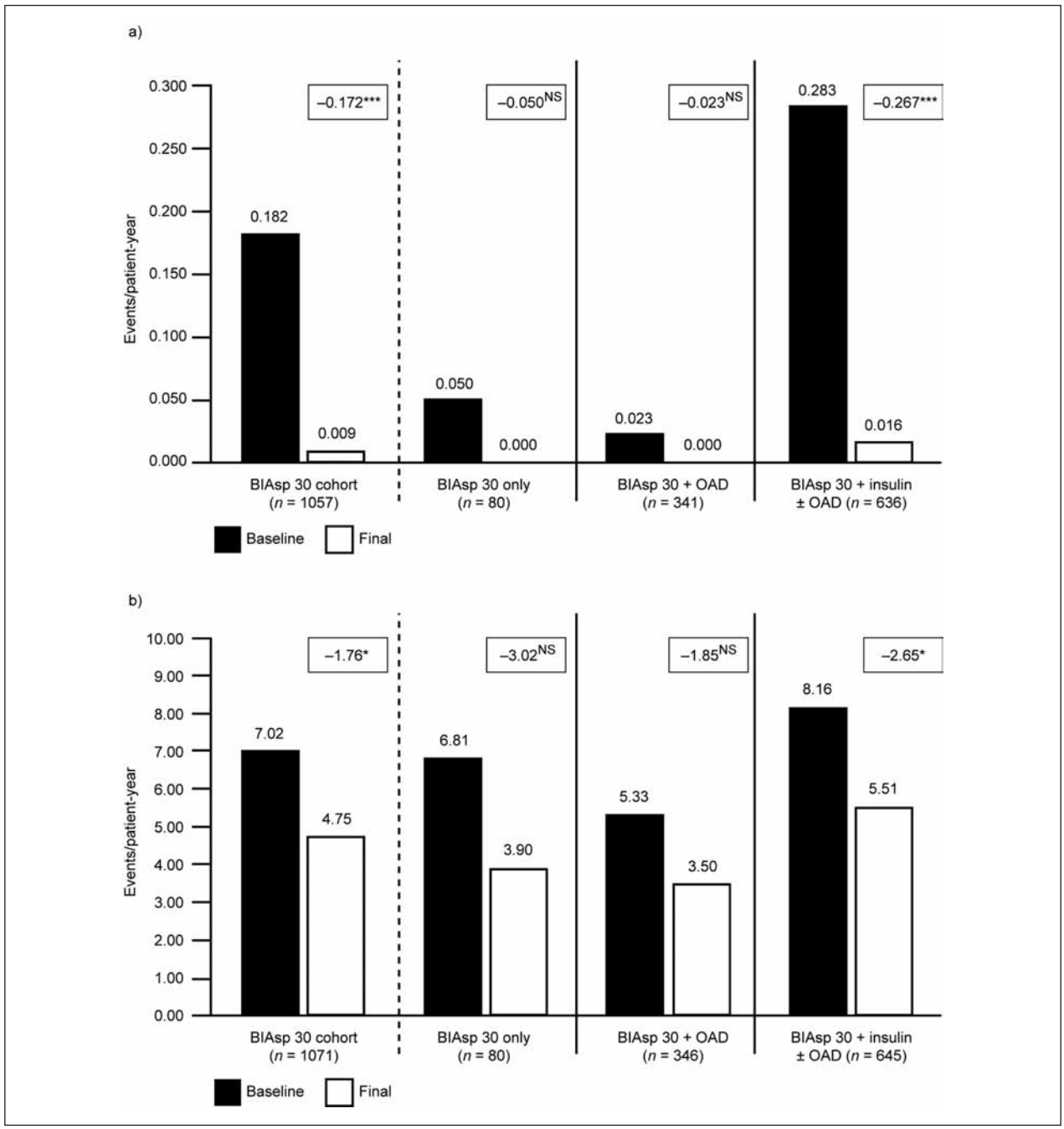

Figure 1. Reduction in a) major and b) minor hypoglycaemia rates after 26 weeks

visit ($p < 0.001$). The scores for relief of burden and relief of symptoms increased but not significantly, but the efficacy score increased by 4 points, from 60.2 to 64.2 ($p < 0.001$).

Physician resource utilisation

The majority of physicians (66%) found it 'very easy' or 'easy' to teach patients to monitor blood glu-

Table 2. Change from baseline in effectiveness parameters when using BIAsp 30 for 6 months

Outcome measure	Total BIAsp 30 cohort (n = 915)	BIAsp 30 only (n = 73)	BIAsp 30 + OAD (n = 307)	BIAsp 30 + insulin ± OAD (n = 535)
HbA_{1c} (%)				
Baseline	8.28 ± 1.47	8.17 ± 1.40	8.38 ± 1.45	8.24 ± 1.50
Final visit	7.66 ± 1.21	7.79 ± 1.30	7.70 ± 1.26	7.61 ± 1.17
Change from baseline	–0.63 ± 1.37***	–0.38 ± 1.24*	–0.68 ± 1.29**	–0.63 ± 1.43**
Patients reaching				
HbA_{1c} <6.5% (%)	13.5	10.7	14.2	13.4
HbA_{1c} <7.0% (%)	26.5	30.7	25.2	26.7
FBG (mmol/l)				
Baseline	9.29 ± 2.68	8.75 ±2.59	9.11 ± 2.60	9.47 ± 2.73
Final visit	8.35 ± 2.24	8.25 ± 2.07	8.19 ± 2.15	8.45 ± 2.31
Change from baseline	–0.94 ± 2.67**	–0.50 ± 2.83NS	–0.91 ± 2.52**	–1.02 ± 2.73**
PPBG breakfast (mmol/l)				
Baseline	9.41 ± 2.86	9.50 ± 2.86	9.73 ± 3.04	9.26 ± 2.76
Final visit	8.43 ± 2.05	8.61 ± 2.21	8.56 ± 1.92	8.35 ± 2.11
Change from baseline	–0.99 ± 3.05**	–0.89 ± 2.91NS	–1.17 ± 3.19**	–0.90 ± 3.00**
PPBG lunch (mmol/l)				
Baseline	9.74 ± 2.89	10.14 ± 2.47	10.41 ± 3.12	9.30 ± 2.73
Final visit	9.08 ± 2.29	9.51 ± 2.47	9.62 ± 2.58	8.71 ± 2.01
Change from baseline	–0.66 ± 2.97**	–0.63 ± 2.63NS	–0.79 ± 3.52*	–0.59 ± 2.67**
PPBG dinner (mmol/l)				
Baseline	9.83 ± 2.64	9.19 ± 2.86	10.01 ± 2.76	9.79 ± 2.55
Final visit	8.87 ± 2.07	9.55 ± 2.48	8.96 ± 2.20	8.75 ± 1.94
Change from baseline	–0.96 ± 2.71**	0.36 ± 2.83NS	–1.05 ± 2.93**	–1.04 ± 2.53**
BIAsp 30 daily dose (IU/kg)				
Pre-study	0.29 ± 0.16	0.34 ± 0.17	0.27 ± 0.17	0.29 ± 0.15
Final visit	0.32 ± 0.18	0.39 ± 0.20	0.31 ± 0.17	0.32 ± 0.17
Change from baseline	0.03 ± 0.13	0.05 ± 0.15	0.04 ± 0.13	0.03 ± 0.12
Weight (kg)				
Baseline	76.80 ± 14.31	78.63 ± 15.39	77.46 ± 14.52	76.21 ± 14.03
Final visit	77.30 ± 14.32	79.50 ± 15.40	77.72 ± 14.37	76.80 ± 14.14
Change from baseline	0.50 ± 3.16**	0.86 ± 3.38*	0.25 ± 3.10NS	0.58 ± 3.16**

Values are mean (± SD).
*p < 0.05;**p < 0.001; NS = not significant.
BIAsp 30, biphasic insulin aspart 30/70; HbA_{1c}, glycated haemoglobin; NS, not significant; PPBG, postprandial blood glucose

cose, and 52% replied that it took <10 min; 67% were 'very confident' or 'confident' in patients' ability to monitor blood glucose. Furthermore, 73% of physicians found it 'very easy' or 'easy' to teach patients to inject BIAsp 30, and 71% needed <10 min. Overall, 70% were 'very confident' or 'confident' in patients' ability to inject BIAsp 30.

Discussion

These results from the Italian cohort show that BIAsp 30 improved glycaemic control over 26 weeks and was well tolerated. The HbA_{1c} reduction in this population was not as great as observed in other countries reported in the IMPROVE™ global results (15),

possibly due to the Italian cohort receiving BIAsp 30 for some time prior to enrolment in the study. It is much more difficult to lower HbA_{1c} from a baseline of 8.3% than from >9.0%, which was the baseline value for the majority of other countries (15). This aside, the lack of BIAsp 30 intensification may also have been a contributing factor for the modest HbA_{1c} reduction of 0.63% after 26 weeks of therapy. Over this period, the dose only increased on average by 0.03 IU/kg, and the proportion of patients receiving BIAsp 30 OD (almost two out of three patients) was almost the same at baseline and at the end of the study. This suggests that, despite relatively poor control, the number of daily injections was not increased. The treating physicians may have been reluctant to intensify BIAsp 30 therapy because of fear of hypoglycaemia. Although many RCTs show an increase in minor hypoglycaemia with BIAsp 30, major and nocturnal hypoglycaemia are usually shown to decrease in frequency when compared with human insulin (18-20). Physicians may therefore have been over-cautious.

As well as HbA_{1c}, FBG and PPBG at all three daily meals significantly improved in the Italian cohort, but the improvements were also fairly modest when compared with other countries in the IMPROVE™ study, probably for similar reasons to those above outlined. Thus, if more aggressive titration and intensification had been implemented, greater glycaemic control may have been achieved and more than one out of four patients may have reached the HbA_{1c} target of <7%.

Since patients in the Italian cohort were already on BIAsp 30 treatment at the start of the study, one would not expect huge changes in the frequency of hypoglycaemia - minor or major. Interestingly, what the results have shown is a significant decrease in major and minor hypoglycaemia, which is contrary to results from RCTs comparing BIAsp 30 with human insulin (18-21). However, these results are consistent with what was observed in the global IMPROVE™ cohort in patients coming from insulin ± OADs (although BIAsp 30 was not included), or indeed from the PRESENT study main cohort - another large observational study of BIAsp 30 (15,22). The rate of major hypoglycaemia dropped by ~90% and minor by ~50% in the IMPROVE™ global results of patients from insulin ± OADs, although the reduction was smaller in the Italian cohort for minor hypoglycaemia (~30% reduction). This unexpected improvement in hypoglycaemia may be due to the conservative dose titration and lack of intensification of BIAsp 30 therapy. While glycaemic control does not benefit from this approach to dosing, the benefit is seen in hypoglycaemia.

Regarding the elderly patient group, apart from FBG, no significant differences in effectiveness and safety measures between patients >65 and ≤65 years old were observed, suggesting that BIAsp 30 can be effectively used in patients >65 years old. Interestingly, greater mean FBG reductions were observed in patients >65 years than in patients ≤65 years old.

Changes in weight and BMI, although significant, were small and probably not clinically significant. These results are consistent with those from other countries and the global IMPROVE™ results (15), and indeed the PRESENT study results, in which weight changed by −0.1 to 0.5 kg, regardless of prior therapy (22).

Patients' scores for treatment satisfaction changed only slightly from baseline to the end of the study, as expected, due to patients already having been receiving BIAsp 30 at the baseline visit. However, the small significant increase that was observed in this score was no doubt helped by the ease of learning to monitor blood glucose and inject BIAsp 30, as indicated by physician responses in the resource utilisation questionnaire results.

Conclusions

The continued use of BIAsp 30 from baseline, for 26 weeks, resulted in further improvements in glycaemic control in the Italian cohort of the IMPROVE™ study. Moreover, BIAsp 30 was well tolerated and resulted in significant reductions in major and minor hypoglycaemia. It can be speculated that, if dose titration had been more aggressive and the number of daily injections had increased in patients who were not achieving target during the observation period, the mean level of glycaemic control may have been improved even further. Our findings highlight that the current management of insulin therapy in Italy mainly aims to avoid any risk of hypoglycaemia rather than pursuing strict metabolic control.

Appendix

Italian IMPROVE™ investigators

Name	City	Name	City
M Agrusta	Cava dei Tirreni	D Mannino	Reggio Calabria
A Aiello A	Martina Franca	G Maolo	Macerata
U Amelia	Nocera Inferiore	T Marcone	Foggia
P Auletta	Frattamaggiore	N Marin	Castelfranco Veneto
D Barbaro	Livorno	V Mastrilli	Volla
G Bargero	Casale Monferrato	C Mattiuzzo	Tivoli
G Bax	Padova	F Micale	Maglie
D Belladonna	Todi	S Mongelli	Bari
E Bosi	Milano	V Montani	Atri
A Bossi	Treviglio	M Nizzoli	Forlì
G Camarda	Caltagirone	M Nuzzo	Lecce
R Candido	Trieste	E Orsi	Milano
L Carmina	Nola	V Paciotti	Avezzano
A Cattaneo	Genova	M Parillo	Caserta
C Cazzalini	Crema	P Pata	Messina
F Cervellino	Venosa	G Perugi	Viterbo
A Ciavarella	Bologna	E Picchio	Perugia
M Comoglio	Moncalieri	G Pipicelli	Soverato
M Contin	Mirano	P Pippo	Avellino
G D'Alessandro	Castellammare di Stabia	V Provenzano	Partinico
S Davì	Susa	L Puccio	Catanzaro
P De Cata	Pavia	F Ragonese	Messina
P Desenzani	Montichiari	E Rastelli	Riccione
M Di Mauro	Catania	M Rizzo	Palermo
C Dradi	Cesena	A Rocca	Cinisello Balsamo
G Fatati	Terni	G Romano	Castelnuovo
M Fetonti	Roma	M Rossi	Grosseto
P Foglini	Fermo	G Saitta	Messina
F Frigato	Mestre	M Sancandi	Palmanova
A Gallo	Dolo	E Santilli	Frascati
R Gelisio	Portogruaro	V Schirò	Palermo
S Gialdino	Castrovillari	G Scifo	Augusta
O Giampietro	Pisa	T Sorrentino	Ottaviano
A Gigante	Nuoro	I Testa	Ancona
M Giuliano	Roma	G Testori	Milano
A Granata	Caltanissetta	B Tizio	Eboli
F Gregorio	Fabriano	G Tonolo	Olbia
A Guberti	Fidenza	G Torchio	Paderno
L Improta	Sant'Agnello	MS Trabacca	Genova
A Lanzilli	Avellino	V Vassallo	Noto
G Leccia	Aversa	M Vasta	Urbino
C Leotta	Catania	S Verga	Palermo
C Lieto	Nola	L Vincis	Sirai
A Lo Presti	Marsala	A Volpi	Montebelluna
G Magro	Cuneo	D Zavaroni	Piacenza
A Maioli	Potenza		

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