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Efficacy and safety of insulin glargine 300 U/mL (Gla-300) during hospitalization and therapy intensification at discharge in patients with insufficiently controlled type 2 diabetes: results of the phase IV COBALTA trial

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ABSTRACT

Introduction This study assessed the efficacy and safety of insulin glargine 300 U/mL (Gla-300) during hospitalization and therapy intensification at discharge in insufficiently controlled people with type 2 diabetes.

Research design and methods COBALTA (for its acronym in Spanish, COntrol Basal durante la hospitalizacion y al ALTA) was a multicenter, open-label, single-arm, phase IV trial including 112 evaluable inpatients with type 2 diabetes insufficiently controlled (glycosylated hemoglobin (HbA1c) 8%–10%) with basal insulin and/or non-insulin antidiabetic drugs. Patients were treated with a basal–bolus–correction insulin regimen with Gla-300 during the hospitalization and with Gla-300 and/or non-insulin antidiabetics for 6 months after discharge. The primary endpoint was the HbA1c change from baseline to month 6 postdischarge.

Results HbA1c levels decreased from 8.8%±0.6% at baseline to 7.2%±1.1% at month 6 postdischarge (p<0.001, mean change 1.6%±1.1%). All 7-point blood glucose levels decreased from baseline to 24 hours predischarge (p≤0.001, mean changes from 25.1±66.6 to 63.0±85.4 mg/dL). Fasting plasma glucose also decreased from baseline to 24 hours predischarge (p<0.001), month 3 (p<0.001) and month 6 (p<0.001) postdischarge (mean changes 51.5±90.9, 68.2±96.0 and 77.6±86.4 mg/dL, respectively). Satisfaction was high and hyperglycemia/hypoglycemia perception was low according to the Diabetes Treatment Satisfaction Questionnaire at month 6 postdischarge. The incidence of confirmed (glucose<70 mg/dL)/severe hypoglycemia was 25.0% during hospitalization and 59.1% 6 months after discharge. No safety concerns were reported.

Conclusions Inpatient and intensification therapy at discharge with Gla-300 improved significantly glycemic control of patients with type 2 diabetes insufficiently controlled with other basal insulin and/or non-insulin antidiabetic medication, with high treatment satisfaction. Gla-300 could therefore be a treatment choice for hospital and postdischarge diabetes management.

Significance of this study

What is already known about this subject?

► Hospitalization is an opportunity to evaluate the metabolic situation of insufficiently controlled patients with type 2 diabetes and to intensify their antidiabetic treatment at discharge.

► Glargine 300 U/mL (Gla-300) is a basal insulin analog that results in more even pharmacokinetic and pharmacodynamic profiles compared with insulin glargine 100 U/mL, which translates into similar glycosylated hemoglobin (HbA1c) reductions and less hypoglycemic events with once-daily subcutaneous injections.

What are the new findings?

► The use of Gla-300 during hospitalization and therapy intensification at discharge in hospitalized people with type 2 diabetes insufficiently controlled with basal insulin and/or non-insulin antidiabetic drugs significantly improved their glycemic status, reaching HbA1c levels close to 7%, with an adequate safety profile and a high degree of treatment satisfaction 6 months after the hospital discharge.

How might these results change the focus of research or clinical practice?

► Gla-300 can be a treatment choice for hospital and postdischarge diabetes management when type 2 diabetes is insufficiently controlled with other basal insulin and/or non-insulin antidiabetic medication.

INTRODUCTION

Insulin is the antihyperglycemic treatment of choice for inpatients due to its rapid action and effectiveness to control blood glucose in most clinical situations.[1 2] Physiological insulin programs can best accomplish the

flexibility needed to achieve glycemic control in the challenging situation of hospitalized patients.[1] They mimic the one-half of daily insulin secretion that serves a basal function and one half secreted in response to intake, with regimens including basal and nutritional insulins.[1 3 4] Basal–bolus insulin therapy is proven safe and effective for type 2 hyperglycemia in the inpatient setting,[5–7] and clinical practice guidelines consider regimens with basal, prandial and correction components the preferred treatment for non-critically ill hospitalized patients.[2–4 8]

The growing evidence of the inpatient glycemic control benefits on morbimortality and associated costs[7 9] support hospitalization as an opportunity to evaluate the metabolic situation of insufficiently controlled patients and intensify their antidiabetic treatment at discharge. While prehospitalization treatment can be maintained when preadmission control is acceptable, insufficiently controlled patients will need their outpatient therapy intensification.[3 6 10–12] According to the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD), another antidiabetic drug should be administered in patients insufficiently controlled with lifestyle management and metformin.[13 14] Advancing to triple therapy is reasonable when glycemic targets are not reached after 3-month dual therapy, and basal insulin may be an alternative to add-on therapy.[13 14]

Glargine 300 U/mL (Gla-300) is a second-generation basal insulin analog with a slow-release mechanism after subcutaneous injection that results in more even and prolonged pharmacokinetic and pharmacodynamic profiles compared with insulin glargine 100 U/mL (Gla-100).[15] The more gradual release of Gla-300 from the subcutaneous depot enables blood glucose to be controlled beyond 24 hours, allowing more flexibility in its once-daily injection time.[16] Moreover, the phase III EDITION program evidenced similar glycosylated hemoglobin (HbA1c) reductions that were better sustained over 12 months, along with less hypoglycemic events and weight gain with Gla-300 compared with Gla-100.[17–21] The recently published DELIVER cohort studies also supported the comparable HbA1c reduction with less hypoglycemic events after switching to Gla-300 versus other basal insulins even in older patients in the real-world setting.[22 23] As hypoglycemia, weight gain and injection burden are frequent concerns that may negatively affect the efficacy of diabetes treatments,[24–27] the lower hypoglycemia risk and weight gain after Gla-300 once-daily subcutaneous injection may facilitate treatment intensification. In addition, the absence of data on Gla-300 administration in the hospital setting and therapy intensification at discharge warrants further assessment.

We therefore assessed Gla-300 efficacy and safety during hospitalization and therapy intensification at discharge in people with type 2 diabetes insufficiently controlled with basal insulin and/or non-insulin antidiabetic drugs.

MATERIALS AND METHODS

Study design and participants

COBALTA (for its acronym in Spanish, COntrol Basal durante la hospitalizacion y al ALTA) (EudraCT number 2015-004715-20) was an open-label single-arm phase IV trial conducted at 15 Spanish hospitals (online supplementary appendix) according to the Declaration of Helsinki, good clinical practices and national regulations.

Patients meeting selection criteria were consecutively recruited between June 2016 and December 2017. Main inclusion criteria comprised type 2 diabetes insufficiently controlled (HbA1c 8%–10%) after ≥3 months of unchanged antidiabetic therapy with basal insulin and/or non-insulin antidiabetic drugs and hospitalization for an expected length of 5–14 days. Main exclusion criteria included patient hospitalization due to hyperglycemic decompensation of diabetes, being critically ill, treatment with premixed or rapid-acting insulin for ≥1 week before hospital admission, glomerular filtration rate <30 mL/minute, need of treatment intensification with rapid-acting insulin at hospital discharge. All inclusion and exclusion criteria are presented in online supplementary table 1.

The study included a first visit at hospital admission (baseline), a hospitalization period of 5–14 days throughout which patients were daily monitored, and a second study visit at discharge. Follow-up visits were scheduled at months 1, 3 and 6 postdischarge (online supplementary figure 1). A postdischarge telephone follow-up was scheduled for patients who were hospitalized for <7 days.

Study treatment

Patients started Gla-300 and prandial/correction insulin at hospital admission, and previous non-insulin therapy was discontinued. The individual insulin dose was at the investigator's discretion, but 50% had to be basal insulin and 50% rapid-acting insulin. Gla-300 was subcutaneously administered once daily at bedtime (±3 hours). Prandial insulin was administered before the main meals and at bedtime only when patients ate carbohydrates. Supplemental correction doses were administered to correct preprandial hyperglycemia. Gla-300 doses were adjusted to target fasting plasma glucose (FPG) 90–140 mg/dL and prandial/correction insulin to achieve preprandial and postprandial blood glucose 90–140 and <180 mg/dL, respectively (online supplementary table 2).

Treatment at discharge was based on the preadmission therapy and HbA1c levels (online supplementary figure 2). The Gla-300 dose was 80% of the total insulin required within the 24 hours prior to discharge. Subsequent doses were adjusted every 3–7 days, considering the median capillary blood glucose level of the previous 3 days and the ADA/EASD consensus targets[14] 80–130 mg/dL (online supplementary table 2). Non-insulin antidiabetic treatment was prescribed according to the patient's status and the investigator's criteria.

Study endpoints

The primary study endpoint was the mean HbA1c change from baseline to month 6 postdischarge.

Secondary efficacy endpoints included changes in mean 7-point blood glucose profile measurements during hospitalization and FPG levels during hospitalization and months 3 and 6 postdischarge. Safety endpoints included the incidence of confirmed or severe hypoglycemia during hospitalization and at 6-month follow-up, the number of rehospitalizations or visits to emergency room 6 months after discharge and the adverse event profile throughout the study. Confirmed hypoglycemia was any symptomatic/asymptomatic event with blood glucose of <70 mg/dL; severe hypoglycemia was any hypoglycemia requiring assistance from another person.

Other study endpoints included changes in body weight and body mass index from hospital discharge to month 6, and treatment satisfaction according to Diabetes Treatment Satisfaction Questionnaire (DTSQ) at month 6. The DTSQ is an 8-item questionnaire with six items assessing treatment satisfaction and two items assessing the perceived frequency of hyper- and hypoglycemia.[28 29] Satisfaction items were scored from 6 (very satisfied) to 0 (very dissatisfied), accounting for an overall score from 36 (very satisfied) to 0 (very dissatisfied), and the frequency of hyper/hypoglycemia from 6 (most of the time) to 0 (none of the time).

Statistical methods

A sample size of 106 patients was estimated considering the mean HbA1c reduction of 1.42%±0.05% in the EDITION 3 trial after 6 month Gla-300 treatment,[30] a bilateral alpha risk of 0.05, a precision of 0.01% and a patient loss of ≤10%.

Efficacy endpoints and treatment satisfaction were assessed in patients with ≥1 Gla-300 dose, baseline efficacy measure and follow-up visit (intention-to-treat (ITT)). Weight, body mass index and safety endpoints were analyzed in patients with ≥1 Gla-300 dose (safety population).

Changes in mean HbA1c, 7-point blood glucose, FPG, weight and body mass index were assessed using Wilcoxon or t-tests. Treatment satisfaction was analyzed using frequency distributions and mean scores. Frequency distributions were also used to assess the severe or confirmed hypoglycemia incidence—along with annualized rates—patients with ≥1 rehospitalizations/visits to emergency room and adverse events. Adverse events were coded using the Medical Dictionary for Regulatory Activities V.20.0.

Subanalyses post hoc comparing insulin-naïve versus previous basal insulin use and age <75 vs ≥75 years were performed using χ^2, Fisher, Mann-Whitney, Wilcoxon or t-tests. Odds ratios (ORs) or relative risks (RRs), 95% confidence intervals (CIs) and p values of hypoglycemia incidences and rates were also calculated.

Means are presented with standard deviation (SD); missing data were not considered in the analyses, and

a significance level of 0.05 was used. Statistical analyses were performed with the Statistical Package for the Social Sciences V.22.0 (SPSS Inc, Chicago, USA).

RESULTS

Study population

A total of 115 patients were screened from 11 internal medicine and 4 endocrinology and nutrition departments, 3 of whom were screening failures due to absence of poor control or previous treatment with premixed/rapid-acting insulin (online supplementary figure 3). The remaining 112 patients received Gla-300 and comprised the safety population (table 1 and online supplementary figure 4). Eighteen patients did not perform the 3-month study visit and were excluded from the ITT population, which finally included 94 patients.

Study treatment

At baseline, the mean Gla-300 daily dose was 18.8±11.8 U (online supplementary table 3). The Gla-300 dose increased by 23.4%±46.7% until the 24 hours prior to hospital discharge, reaching a mean of 21.4±10.9 U. The mean Gla-300 dose during the whole hospital stay (mean stay, 10.5±5.9 days) was 20.7±12.3 U. In addition, 110 (98.2%) patients received ≥1 dose of prandial insulin (mean dose, 23.6±13.7 U) and 92 (82.1%) received ≥1 dose of correction insulin (mean dose, 5.1±3.4 U). At hospital discharge, the mean Gla-300 daily dose was 38.0±19.3 U (online supplementary table 3). This dose decreased by 1.3%±50.6% from discharge to month 1 and increased by 2.6%±37.0% from months 1 to 3 and by 10.1%±50.9% from months 3 to 6, reaching 36.3±18.3 U at study end. Ninety-eight (93.3%) patients were prescribed non-insulin antidiabetic drugs at hospital, and 89 (89.9%) continued with them at month 1, 83 (89.2%) at month 3 and 84 (90.3%) at month 6 postdischarge.

No significant differences in insulin doses were observed according to insulin-naïve versus previous basal insulin use or age <75 vs ≥75 years (online supplementary table 4).

Glycemic control

The primary endpoint analysis revealed that mean HbA1c levels significantly decreased from 8.8%±0.6% at baseline to 7.2%±1.1% at month 6 (p<0.001), representing a mean change of 1.6%±1.1% (figure 1A and online supplementary table 5). The decline was evident from month 3 (p<0.001), with a mean variation of 1.6%±1.2% (figure 1A and online supplementary table 5). Although insulin-naïve versus previous basal insulin use showed a higher HbA1c decrease from baseline to month 3 (1.9±1.2 vs 1.3±1.1%, p=0.025), no significant differences were observed at month 6 nor in the <75 and ≥75 years of subanalyses (online supplementary figure 5).

Glucose levels in all 7-point measurements significantly decreased from baseline to 24 hours pre-discharge (p≤0.001), with mean changes from 25.1±66.6 mg/dL prebreakfast to 63.0±85.4 mg/dL postlunch (figure 2

Table 1 Baseline patient characteristics (N=112)

Characteristics	Value
Age (years)	
Mean±SD	72.3±10.8
<75 years, n (%)	65 (58.0)
≥75 years, n (%)	47 (42.0)
Male, n (%)	68 (60.7)
Caucasian, n (%)	110 (98.2)
Weight (kg), mean±SD	80.1±16.6
Body mass index (kg/m^2), mean±SD	30.1±5.9
Renal function, mean±SD	
Creatinine (mg/dL)	1.1±0.4
GFR (mL/min)	75.4±32.4
Diabetes duration (years), mean±SD	10.9±7.9
Previous insulin treatment, n (%)	
Previous basal insulin	57 (50.9)
Insulin-naïve	55 (49.1)
Non-insulin treatment schedule, n (%)	
Monotherapy	45 (45.5)
Dual therapy	42 (42.4)
Triple therapy or more	11 (11.1)
GLP-1 receptor analogue monotherapy	1 (1.0)
HbA1c (%), mean±SD	8.9±0.7
FPG (mg/dL), mean±SD	205.4±83.9
7-point capillary blood glucose profile (mg/dL), mean±SD	
Prebreakfast	182.0±65.6*
Postbreakfast	237.0±80.1†
Prelunch	222.7±72.2‡
Postlunch	236.6±78.0§
Predinner	232.5±79.3‡
Postdinner	227.0±82.4¶
Bedtime	208.1±80.5**

*Missing data, n=7.
†Missing data, n=26.
‡Missing data, n=3.
§Missing data, n=20.
¶Missing data, n=21.
**Missing data, n=14.
FPG, fasting plasma glucose; GFR, glomerular filtration rate according to the MDRD-4 equation; GLP-1, glucagon-like peptide-1; HbA1c, glycosylated hemoglobin.
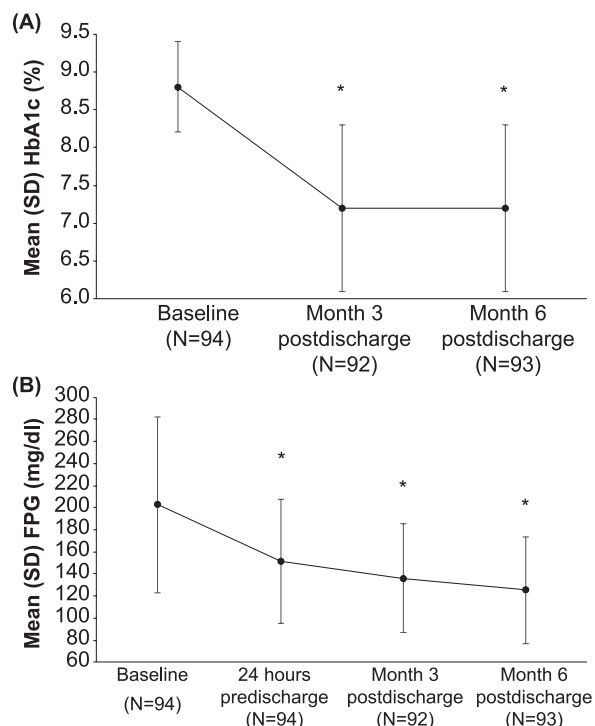

Figure 1 HbA1c levels (A) and FPG levels (B) during the study. *P≤0.001 vs baseline. FPG, fasting plasma glucose; HbA1c, glycosylated hemoglobin.

Decreasing blood glucose levels of the 7-point profile and FPG were evidenced regardless of previous basal insulin treatment and age (online supplementary figure 5). However, a greater change was observed before breakfast in insulin-naïve versus previous basal insulin use (48.5±73.5 vs 4.2±52.3 mg/dL, p=0.003) and age <75 vs ≥75 years (39.6±68.2 vs 5.5±59.9 mg/dL, p=0.019), and also before meal in insulin-naïve versus previous basal insulin use (59.3±67.5 vs 29.2±71.1 mg/dL, p=0.038). No significant differences between groups were observed in FPG levels (online supplementary figure 5).

Weight and body mass index

No significant changes from hospital discharge to month 6 postdischarge were evidenced in patients' weight

and online supplementary table 5). Similarly, FPG levels significantly decreased during hospitalization (p<0.001), with a mean variation of 51.5±90.9 mg/dL from baseline to 24 hours predischarge (figure 1B and online supplementary table 5). Significant decreases were also observed at months 3 (p<0.001) and 6 (p<0.001) postdischarge, with mean changes of 68.2±96.0 mg/dL and 77.6±86.4 mg/dL, respectively (figure 1B and online supplementary table 5).
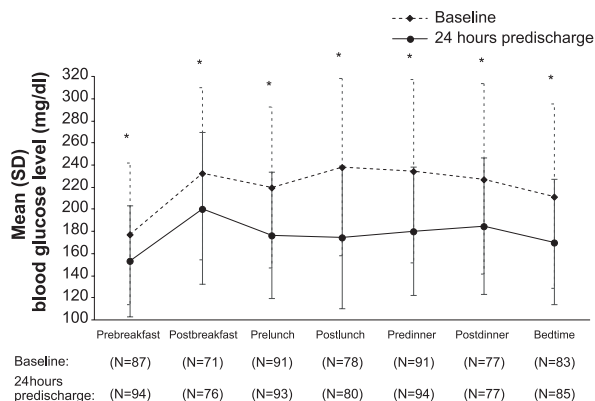

Figure 2 Seven-point blood glucose profile at baseline and 24 hours predischarge. *P≤0.001 vs baseline.

Table 2 Hypoglycemia during hospitalization and after hospital discharge

Type of hypoglycemia	During hospitalization (N=112)			Month 6 postdischarge (N=93)		
	n (%)	Mean±SD*	Rate†	n (%)	Mean±SD*	Rate†
Overall confirmed‡ or severe hypoglycemia	28 (25.0)	2.2±1.4	20.3	55 (59.1)	8.0±10.1	9.2
Asymptomatic confirmed‡ hypoglycemia	21 (18.8)	1.7±0.7	11.6	49 (52.7)	6.9±7.4	7.2
Symptomatic confirmed‡ hypoglycemia	12 (10.7)	1.3±0.6	5.0	21 (22.6)	3.0±3.1	1.3
Severe hypoglycemia	4 (3.6)	1.8±1.0	2.3	4 (4.3)	2.3±1.3	0.2
Nocturnal hypoglycemia	2 (1.8)	1.5±0.7	0.1	1 (1.1)	24.0±NA	0.5
Severe nocturnal hypoglycemia	1 (0.9)	1.0±NA	0.3	1 (1.1)	4.0±NA	0.1

*The mean number of hypoglycemic events was calculated over the number of patients with each type of hypoglycemia.
†Hypoglycemic episodes per person-year was calculated as Σ number of hypoglycemias/Σ time (years).
‡Confirmed: glucose<70 mg/dL.
NA, not applicable.

(78.2±14.3 vs 78.2±14.7 kg, p=0.467) and body mass index (29.3±4.6 vs 29.1±4.4 kg/m², p=0.710).

Subanalyses according to insulin-naïve versus previous basal insulin use and age <75 vs ≥75 years showed neither significant variations nor differences between groups (data not shown).

Hyperglycemia and hypoglycemia
Hyperglycemia
Three (2.7%) of the 112 included patients experienced symptoms of hyperglycemia during their hospitalization. In addition, 5 (5.4%) of the 93 patients with data available at month 6 reported having experienced hyperglycemia symptoms after discharge.

Anytime hypoglycemia
Twenty-eight (25.0%) patients exhibited ≥1 confirmed or severe hypoglycemia during hospitalization and 55 (59.1%) within the 6-month postdischarge follow-up, mostly asymptomatic (table 2). The rate of confirmed or severe hypoglycemia 6 months postdischarge was 9.2 episodes/person-year (table 2). Only one was reported as a serious adverse event.

Only one confirmed or severe hypoglycemia (according to ADA guidelines) was reported as a serious adverse event (ie, an adverse event that met at least one of the following conditions: resulted in death, was life-threating, required inpatient hospitalization or caused prolongation of existing hospitalization, resulted in persistent or significant disability/incapacity, caused a congenital anomaly/birth defect, and/or prolonged an existing hospitalization, was considered an important medical event or was a suspected transmission of an infectious agent).

Nocturnal hypoglycemia
Two (1.8%) patients reported nocturnal hypoglycemia during hospitalization and another (1.1%) after discharge (table 2). The rate of nocturnal hypoglycemia during the 6 months postdischarge was 0.5 episodes/person-year (table 2).

Severe hypoglycemia
Four (3.6%) patients reported severe hypoglycemia during hospitalization and four (4.3%) after discharge (table 2). Moreover, one (0.9%) patient reported severe nocturnal hypoglycemia during hospitalization and another (1.1%) 6 months postdischarge (table 2). The rates of severe hypoglycemia and severe nocturnal hypoglycemia 6 months postdischarge were 0.2 and 0.1 episodes/person-year, respectively (table 2).

Hyperglycemia and hypoglycemia subanalyses
When hypoglycemia was analyzed according to insulin-naïve versus previous basal insulin use, no significant differences were found in hypoglycemia incidence during hospitalization or after discharge. With regard to hypoglycemia rates during hospitalization, there was a higher risk of asymptomatic hypoglycemia in insulin-naïve patients (RR=2.32, 95% CI 1.08 to 5.42, p=0.029) and symptomatic hypoglycemia in those with previous basal insulin (RR=0.23, 95% CI 0.04 to 0.86, p=0.025). After hospital discharge, patients with previous basal insulin also showed a higher risk of confirmed or severe hypoglycemia (RR=0.48, 95% CI 0.39 to 0.59, p<0.001) and asymptomatic hypoglycemia (RR=0.48, 95% CI 0.37 to 0.60, p<0.001) rates. Subanalyses according to age showed that patients aged ≥75 years had a higher risk of confirmed or severe hypoglycemia incidence (OR=0.29, 95% CI 0.11 to 0.78, p=0.008) during hospitalization, without significant differences after discharge. With regard to hypoglycemia rates, there was a higher risk of confirmed or severe hypoglycemia (RR 0.26, 95% CI 0.14 to 0.47, p<0.001) and asymptomatic hypoglycemia (RR=0.33, 95% CI 0.15 to 0.69, p=0.002) during hospitalization in patients aged ≥75 years. A higher risk of asymptomatic hypoglycemia rate was also evidenced in patients aged ≥75 years after discharge (RR=0.72, 95% CI 0.58 to 0.89, p=0.003).

Rehospitalizations and visits to emergency rooms
Forty-five (40.2%) patients reported 64 visits to emergency rooms and 46 rehospitalizations. The main reasons for emergency room visits (frequency ≥5%) were acute complications (n=15, 23.4%) and acute bronchitis (n=7, 10.9%); only one (1.6%) was related to hypoglycemia. The main reasons for

Table 3 DTSQ scores (N=91)

Item	n (%) 0	1	2	3	4	5	6	Mean±SD
Satisfaction with current treatment	0 (0.0)	1 (1.1)	0 (0.0)	5 (5.5)	11 (12.1)	18 (19.8)	56 (61.5)	5.3±1.0
Perceived frequency of hyperglycemia	27 (29.7)	22 (24.2)	16 (17.6)	8 (8.8)	10 (11.0)	5 (5.5)	3 (3.3)	1.8±1.7
Perceived frequency of hypoglycemia	32 (35.2)	28 (30.8)	12 (13.2)	8 (8.8)	6 (6.6)	5 (5.5)	0 (0.0)	1.4±1.5
Treatment convenience	0 (0.0)	0 (0.0)	2 (2.2)	4 (4.4)	17 (18.7)	25 (27.5)	43 (47.3)	5.1±1.0
Treatment flexibility	1 (1.1)	2 (2.2)	3 (3.3)	10 (11.0)	19 (20.9)	28 (30.8)	28 (30.8)	4.6±1.3
Satisfaction with diabetes understanding	0 (0.0)	0 (0.0)	1 (1.1)	15 (16.5)	11 (12.1)	26 (28.6)	38 (41.8)	4.9±1.1
Recommendation of this treatment	0 (0.0)	0 (0.0)	0 (0.0)	5 (5.5)	4 (4.4)	24 (26.4)	58 (63.7)	5.5±0.8
Satisfaction with continuing this treatment	0 (0.0)	0 (0.0)	0 (0.0)	5 (5.5)	6 (6.6)	21 (23.1)	59 (64.8)	5.5±0.8
Total score								31.0±4.5

DTSQ score 0–36, higher scores reflecting higher satisfaction.
DTSQ, Diabetes Treatment Satisfaction Questionnaire.

rehospitalization (frequency ≥5%) were cardiovascular disease (n=16, 34.8%) and infection (n=10, 21.7%); no rehospitalization was associated with treatment.

Subanalyses according to insulin-naïve versus previous basal insulin use and age <75 vs ≥75 years showed no significant differences (data not shown).

Adverse events

Eighty-four (75.0%) patients reported 286 adverse events, with urinary tract infections and hypoglycemia being the most frequent (online supplementary table 6). Adverse events were serious in 37 (33.0%) patients, led to treatment discontinuation in 10 (8.9%) and were fatal in 8 (7.1%).

Subanalyses according to insulin-naïve versus previous basal insulin use and age <75 vs ≥75 years showed no significant differences in the number of adverse events per patient, action taken, resolution and relationship with Gla-300 (data not shown).

Patient-reported outcomes

Ninety-one patients completed the DTSQ at month 6 postdischarge (table 3). Patient responses showed a low perception of hyperglycemia/hypoglycemia and high satisfaction regarding the different items of the questionnaire (total score, 31.0±4.5).

Similar results were observed when data were analyzed according to insulin-naïve versus previous basal insulin use and age <75 vs ≥75 years (online supplementary table 7). Significant differences were only evidenced when comparing mean scores of satisfaction with continuing treatment and diabetes understanding, showing higher satisfaction with continuing treatment in patients with previous basal insulin (5.7±0.6 vs 5.2±1.0, p=0.011) and with diabetes understanding in those aged <75 years (5.1±1.1 vs 4.7±1.1, p=0.044) (data not shown).

The DTSQ covers eight items with regard to the diabetes treatment over the past weeks and measures overall satisfaction, convenience, flexibility, understanding of diabetes, willingness to recommend current treatment to others and willingness to continue the current treatment. Each item is rated on a 7-point Likert scale with a score ranging from 0 (ie, very dissatisfied) to 6 (ie, very satisfied). DTSQ items 2 and 3 assess glycemic control rather than satisfaction (perceived hyperglycemia and perceived hypoglycemia). These items are rated differently: 0 reflects 'never' and 6 reflects 'most of the time'. All scores, except those from DTSQ items 2 and 3, are added up to produce a DTSQ total score (range 0–36). Higher scores on the DTSQ total score indicate higher treatment satisfaction, and lower scores indicate lower treatment satisfaction.

DISCUSSION

This study assessed the efficacy and safety of insulin Gla-300 during hospitalization and therapy intensification at discharge in people with type 2 diabetes insufficiently controlled with basal insulin and/or non-insulin antidiabetic drugs. It was mostly conducted in general internal medicine wards, which have a relevant role in diabetes management and often includes more clinically compromised patients,[31] and demonstrated that using basal–bolus regimens with Gla-300 as basal insulin is effective during the hospital stay. The study results also indicate that restarting oral agents in combination with 80% of hospital daily insulin dose as Gla-300 at discharge is an effective strategy for therapy intensification when admission HbA1c ranges between 8% and 10% (1.6% HbA1c reduction at months 3 and 6 postdischarge). These findings support using Gla-300 for type 2 diabetes management of inpatients and offer an algorithm

to guide discharge therapy in those insufficiently controlled with basal insulin and/or non-insulin antidiabetic drugs.

Insulin therapy is the most appropriate method for controlling glycemia in the hospital, but its higher risk of hypoglycemia is a barrier to achieving glycemic goals. Basal–bolus insulin regimen with reduction or withdrawal of boluses in people who are not eating regularly is the preferred method for achieving and maintaining glucose control in non-critically ill inpatients.[6 8 32–36] Because of their flatter pharmacodynamic profile (a much lower peak of action and prolonged duration), once-daily administration and lower perceived hypoglycemia risk (particularly nocturnal hypoglycemia),[37] neutral protamine Hagedorn insulin has been largely supplanted by basal insulin Gla-100. Gla-300 is a second-generation basal insulin analog with prolonged pharmacokinetic and pharmacodynamic profiles compared with Gla-100,[15] allowing more flexible once-daily injections,[16] and similar glycemic control with less hypoglycemic events and weight gain than Gla-100.[17–23] However, information on Gla-300 administration in the hospital setting is limited to a small study.[38] In our study, the Gla-300 basal–bolus regimen resulted in a reduction in blood glucose from admission to discharge with an incidence of hypoglycemia of 25%, which are in the range (1% and 42%) observed in other studies conducted in non-critical patients, depending on the objectives of glycemic control, treatment received and hypoglycemia definition.[6 32 33 36 39–41] There were few events of severe hypoglycemia (4 of 112 patients), and only 2 (1.8%) patients presented nocturnal hypoglycemia during hospitalization. This low frequency of nocturnal hypoglycemia was also observed in a small study with Gla-300 versus Gla-100.[38] Previous studies in the outpatient setting with large sample sizes have also shown that the risk of hypoglycemia, particularly nocturnal, is lower with Gla-300 than Gla-100.[17–19 42 43] Therefore, the Gla-300 basal-bolus regimen improves glycemic status, with low frequency of hyperglycemia and nocturnal hypoglycemia in adult inpatients with type 2 diabetes. These benefits were achieved regardless of previous basal insulin treatment and age, with a manageable safety profile even in more fragile patients as those aged >75 years.

Hospital admission can be an useful time to intensify antidiabetic treatment at discharge and improve long-term glycemic control in people with diabetes, but this is a clearly deficient area and clinical inertia is a major factor that contributes to inadequate management at the time of hospital discharge.[44–46] Evaluating the best strategies to establish treatment at discharge may help to ensure a safe and effective transfer to the community. According to the ADA/EASD consensus, basal insulin may be considered an alternative to add-on therapy in patients insufficiently controlled with dual non-insulin therapy[13 14] and adding basal insulin is the most frequent change in treatment from admission to discharge in patients with uncontrolled diabetes.[6 11 12 47]

In the present study, we focused on a subgroup of people with type 2 diabetes with poor control (HbA1c 8%–10%) after ≥3 months of unchanged antidiabetic therapy with basal insulin and/or non-insulin antidiabetic drugs and used a more ambitious approach to calculate initial Gla-300 dose than previous studies focused on hospital discharge, in which the initial dose was generally estimated as 50%–80% of the baseline dose during hospitalization.[6 11 12] In patients with oral agents with/without insulin prior to admission who were discharged with oral agents plus basal insulin Gla-100, Umpierrez et al[11] calculated glargine doses at discharge as 50% of total hospital daily insulin dose during hospitalization when admission HbA1c was 7%–9% and 80% when it was >9%. They observed an HbA1c reduction from 9.2% to 7.5% 12 weeks after discharge and ≥1 episode of hypoglycemia in 30% of patients. Our strategy improved HbA1c by 1.6% with an acceptable rate of hypoglycemia, an adequate safety profile and high treatment satisfaction during the 6-month study period. The rate of overall hypoglycemia (9.2 episodes/person-year) observed in our study is lower than the incidence rates (18.8 events/person-years) of symptomatic hypoglycemia reported in patients treated with insulin in the Hypos-1 Study[48] and within the range (0.286–16.4 episodes/patient-year) of people with type 2 diabetes receiving basal–oral regimens in randomized controlled trials.[49] The event rate of hypoglycemia was also similar to the BRIGHT trial with Gla-300 and insulin degludec-100 (9.3 and 10.8 events/patient-year, respectively) in insulin-naïve patients with uncontrolled long-standing type 2 diabetes on multiple oral antihyperglycemic drugs and similar diabetes duration and HbA1c.[50] In addition, the lower risk of hypoglycemia evidenced in our study in insulin-naïve patients versus previous basal insulin users agree with the hypoglycemia rates evidenced in the EDITION 3 and EDITION 2 trials in insulin-naïve patients (6.4 episodes/patient-year) and previous basal insulin users (11.6 episodes/patient-year) receiving Gla-300, respectively.[17 30] Finally, the 6-month persistence of discharge insulin dose, absence of rehospitalizations associated with treatment, low perception of hyperglycemia/hypoglycemia and high-treatment satisfaction reinforce the effectiveness of this approach to calculate initial Gla-300 dose.

We acknowledge that the study has certain limitations that should be considered when interpreting its findings, including the lack of a control group and its open-label nature. However, this study provides valuable information on the inpatient and postdischarge type 2 diabetes management that warrant further assessment in controlled trials and observational studies. Our post hoc analyses also includes relevant data in people aged >75 years and in both insulin-naïve and insulin-experienced people.

In conclusion, the use of Gla-300 during hospitalization and therapy intensification at discharge in hospitalized adults with type 2 diabetes insufficiently controlled with basal insulin and/or non-insulin antidiabetic drugs significantly improved their glycemic status, reaching HbA1c levels close to 7% with an adequate safety profile and a high treatment satisfaction. Gla-300 could therefore

be considered a treatment choice for inpatient and post-discharge diabetes management. Further studies are needed to confirm the effects of this algorithm of treatment for clinical practice.

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