

# Glycemic variability in type 2 diabetes mellitus and acute coronary syndrome: liraglutide compared with insulin glargine: a pilot study

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## Abstract

**Objective:** To explore the glucagon-like peptide-1 analogue liraglutide in the hospital setting in patients with type 2 diabetes mellitus (T2DM) and acute coronary syndrome and to evaluate the safety and efficacy and its impact on hospitalization and short-term glycemic variability (GV).

**Methods:** A 12-week, open-label, prospective, randomized pilot clinical study with parallel groups that compared liraglutide (group 1) with glargine (group 2) and its impact on glycemic control and GV.

**Results:** Thirteen patients were included. During hospitalization, mean glucose was 164.75 mg/dL (standard deviation [SD] 19.94) in group 1 and 166.69 mg/dL (38.22) in group 2. GV determined by CV and SD was 20.98 (7.68) vs. 25.48 (7.19) and 34.37 (13.05) vs. 43.56 (19.53) in groups 1 and 2, respectively. Group 1 prandial insulin requirements during hospitalization were lower compared with group 2. Follow-up A1c in group 1 was 6.9% (−1.51%) and

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6.5% in group 2 ( $-1.27$ ). GV after discharge and hypoglycemia were lower in group 1 compared with group 2.

**Conclusions:** Liraglutide seems to reduce GV in the acute phase of acute coronary syndrome, and patients achieved optimal control with a low incidence of hypoglycemia. These results support the need to explore liraglutide in a larger multicenter trial.

**Trial registration:** The study was approved by the National Medical Ethics Committee of Spain. The study was registered at European Clinical Trials Database (EudraCT): 2014003298-40.

## Keywords

Glycemic variability, type 2 diabetes mellitus, acute coronary syndrome, liraglutide, GLP-1 receptor agonist, hypoglycemia

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## Introduction

Cardiovascular disease, which includes coronary artery disease, is the major cause of morbidity and mortality in patients with type 2 diabetes mellitus (T2DM). The prevalence of diabetes is high, as demonstrated by several studies, and it is frequently undiagnosed or there is a prediabetic state in patients with coronary heart disease (CHD).<sup>1,2</sup> Patients with acute coronary syndrome (ACS) and poor glucose control during hospitalization have been associated with less favorable outcomes.<sup>3</sup>

Different strategies aim to improve glucose control of diabetic and hyperglycemic patients with ACS predominantly using continuous insulin administration. The recommendations of how tight the glucose control should be to avoid the deleterious effects of hypoglycemia in these patients remains controversial.<sup>4</sup> However, hyperglycemia and hypoglycemia may affect these patients deleteriously, and this can be extended to glycemic variability (GV), which includes both downward and upward acute glucose fluctuations. GV covers predominantly two kinds of measurements: short-term GV, which is represented by both

inter-day and intra-day GV; and long-term GV, which is based on consecutive glucose determinations over a long period of time such as serial fasting plasma glucose (FPG) and postprandial glucose and usually HbA1c measurements.<sup>5,6</sup>

In the hospital, findings suggest that GV is a risk factor for both diabetic and non-diabetic patients by increasing the length of hospital stay and both short-term and long-term mortality. In patients with an ACS, a high GV during hospitalization has been associated with an increased risk in the 30 days following admission of a major cardiovascular event, intracerebral hemorrhage, and isolated cardiac valvular surgery.<sup>7-10</sup> Recently, a high GV in patients with ACS was demonstrated to be one of the most powerful predictive factors for the development of major adverse cardiac events (MACE) in patients with ACS and T2DM. In this study, GV remained the best predictor of a greater risk of midterm MACE in this population.<sup>11-13</sup> Therefore, physicians should aim to control the three main components of dysglycemia in patients with ACS and diabetes: chronic hyperglycemia, hypoglycemia, and short-term and long-term GV.

Glucagon-like peptide (GLP)-1 analogues reduce hyperglycemia without inducing hypoglycemia.<sup>14</sup> Two randomized published studies have investigated GV with GLP-1 analogues: the AWARD-4 substudy and the FLAT-SUGAR trial. Both of these studies investigated the effect of a GLP-1 analogue in combination with basal insulin on GV and glucose control. In both studies, GV was reduced in those with a combination of GLP-1, although improvement in HbA1c was similar in both therapeutic groups.<sup>15,16</sup>

The DUAL I study investigated the fluctuations in plasma glucose for the combination of liraglutide and insulin degludec (IDegLira) against its components separately. A considerably lower range of fluctuations were observed with IDegLira compared with insulin degludec alone. Additionally, GV in the liraglutide treatment arm behaved similarly compared with the cohort that received insulin degludec alone.<sup>17</sup> GV and hypoglycemia should be explored in trials with GLP-1 analogues because of its attainable impact on cardiovascular morbidity and mortality.

In addition to the previous data, GLP-1 analogues have demonstrated superiority in cardiovascular outcomes.<sup>18</sup> Preclinical and clinical studies have shown that GLP-1 analogues exhibit a cardioprotective effect.<sup>12,18</sup> Thus, we consider that it is relevant to explore the use of a GLP-1 analogue such as liraglutide in a hospital setting for patients with ACS and T2DM to evaluate its safety and efficacy as well as its impact in the hospital setting, short-term GV, and hypoglycemic events.

## Patients and methods

### Study design

This was a 12-week, open-label, prospective, randomized pilot clinical study with parallel groups to evaluate the use of liraglutide and its impact on glycemic control in T2DM

patients with ACS in the hospital setting and in the short-term as an outpatient.

Patients interrupted their treatment for diabetes and were randomized 1:1 into two groups without matching by clinical characteristics. Group 1 was treated with liraglutide at an initial dose of 0.6 mg/day that was increased after 7 days to 1.2 mg/day subcutaneously. Group 2 was treated with insulin glargine at an initial dose of 0.25 U/kg/day subcutaneously. Patients who were >70 years old and/or with creatinine levels >2 mg/dL started with a 0.15-UI/kg/day dose. Patients within this group were initiated using a total daily insulin dose of 0.5 U/kg/day, which was divided as 50% glargine insulin (0.25 U/kg/day) as a basal insulin dose and the other 50% (0.25 U/kg/day) divided into prandial insulin doses. The insulin dose was adjusted to maintain basal glucose between 100 and 140 mg/dL.

In both groups, additional corrections with prandial insulin aspart were made when patients required it to maintain a prandial glucose level of <140 mg/dL and a postprandial glucose level of <180 mg/dL. Therapeutic failure was considered when the mean daily glucose level was >240 mg/dL or two consecutive measures were >240 mg/dL. In this case, patients started with a basal-bolus regimen with a daily insulin dose of 0.5 UI/kg/day divided as 50% glargine insulin (0.25 UI/kg/day) and 50% prandial insulin aspart.

The total length of the study period was 12 weeks. All subjects voluntarily participated during this study. All subjects provided written informed consent. The study was approved by the National Medical Ethics Committee of Spain. The study was registered at European Clinical Trials Database (EudraCT): 2014-003298-40.

### Study population

We consecutively studied T2DM patients with ACS at the Department of

Cardiology and Intensive Medical Unit of University and Politècnic Hospital La Fe of Valencia. The inclusion criteria were as follows: (i) T2DM patients 18 to 80 years old who were hospitalized with a diagnosis of ACS with a glucose measure before admission or at randomization  $<400$  mg/dL; (ii) T2DM patients treated with diet, noninsulin agents in various combinations, or a day insulin regimen with a dose  $<0.7$  UI/kg/day; and (iii) patients who provided informed consent. Exclusion criteria included the following: (i) Patients with glucose levels before admission or randomization  $>400$  mg/dL; (ii) patients with hyperglycemia and HbA1c  $<6.5\%$  at admission; (iii) patients with a history of diabetic ketoacidosis; (iv) patients with a history of pancreatitis or active disease in bile ducts; (v) patients with kidney failure (glomerular filtration rate  $<30$  mL/minute) or liver failure; (vi) pregnancy, lactation, or females of a reproductive age without contraceptive methods; (vii) mental disturbance; (viii) untreated thyroid disease or clinically unstable; (ix) untreated adrenal disease or clinically unstable; or (x) patients with diseases such as kidney, liver, or thyroid disease, based on the technical specifications of the drugs that were investigated.

Fifty-four consecutive patients were evaluated, among whom 13 were eligible, and these patients were randomized and included into the study. The Consort diagram is shown in Figure 1.

### Endpoints

The aim of this pilot study was to explore the safety and efficacy of liraglutide in a hospital setting for glycemic control, as defined by short-term GV, and outpatient glycemic control, as defined by long-term GV (12 weeks after starting treatment), as well as the incidence of hypoglycemic events.

### Study protocol

At the beginning of the study, a complete history including the demographic data, pathological history, cardiovascular risk factors, and diabetic history was taken, and a full examination of each patient was performed. At study entry, a complete blood analysis, which included a glucometabolic profile as well as oxidative stress markers was taken. During hospital admission, all patients were equipped with a continuous glucose monitoring system (CGMS) (iPRO2, Medtronic, Minneapolis, MN, USA) based on the availability, and their glucose levels were monitored for 7 consecutive days. Patients checked their blood glucose level with using a self-monitoring blood glucose (SMBG) device (Ascensia, Contour XT, Ascensia Diabetes, Basel, Switzerland) at least four times per day.

Patients were discharged based on their randomized treatment (group 1 or 2) after a complete educational program. Each week, a physician contacted the patient to discuss and optimize their blood glucose control. In the telephone contacts, treatment compliance, adverse reactions, weight, blood pressure, and the four daily SMBG results were evaluated.

At 12 weeks after hospital admission, the patient attended the outpatient clinic, where a complete history and full examination of each patient was performed as well as a complete blood analysis.

### Continuous glucose monitoring

During hospital admission, all patients were equipped with a CGMS (iPRO2, Medtronic) and were monitored for 7 consecutive days. A CGMS sensor was inserted into the subcutaneous abdominal fat tissue and calibrated in accordance with the standard Medtronic iPRO2 operating guidelines. During CGMS monitoring, patients

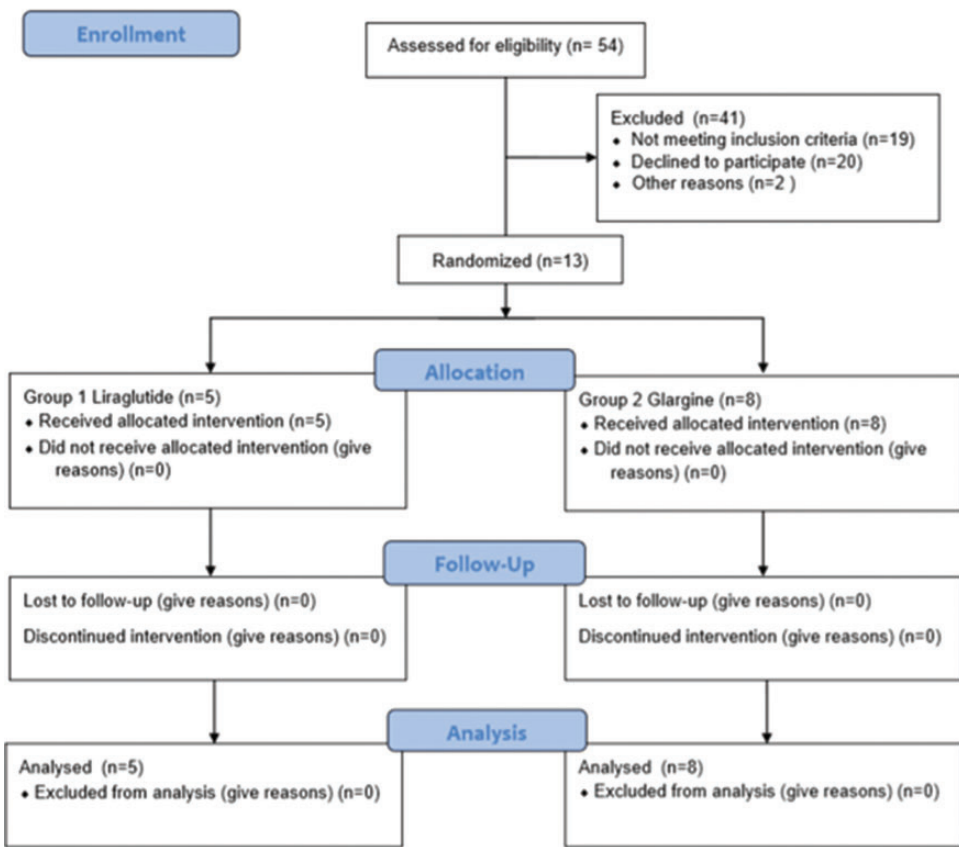


Figure 1. Consort flow diagram.

checked their blood glucose level using a SMBG device (Ascensia, Contour XT) at least four times per day. After monitoring for 7 days, the recorded data were downloaded into a personal computer for analysis of the glucose profile and glucose excursion parameters using iPRO2 Solutions software (Medtronic).

After downloading the recorded data, indices of GV were analyzed based on the data from the previous 48 hours, as follows: standard deviation (SD), coefficient of variability (CV), mean amplitude glucose excursions (MAGE), mean of daily differences (MODD), and low blood glucose index (LBGI).<sup>19</sup>

### Statistical analysis

Data were summarized using the mean (standard deviation) and median (1st, 3rd quartile) for continuous variables, and the relative and absolute frequencies for categorical variables. Differences between both treatment groups for the different GV measures were assessed using the Mann–Whitney–Wilcoxon test. The association between long-term glucose levels and treatment groups taking into account at different times of the day, and these data were assessed by adjusting a linear mixed model, which included an interaction between treatment groups and times of the day and a random intercept for each individual.

All statistical analyses were performed using R (version 3.5.3) and R packages lme4 (version 1.1-21) (R Foundation for Statistical Computing, Vienna, Austria, <https://www.R-project.org/>), and GlyCulator2.0.<sup>20</sup>  $P < 0.05$  was considered to be significant.

## Results

### Patient characteristics

There were 13 patients enrolled into the study, 5 patients in the liraglutide group and 8 patients in the glargine group. Patient characteristics at inclusion in the study (before) and after 12 weeks (after) are presented in Table 1. The mean age was 59.5 years, and 92% of the patients were male.

### Glucose control in hospital setting:

#### Short term GV

During hospital admission 12 of the patients were equipped with a CGMS and were monitored for 7 consecutive days.

Glucose variables are presented in Table 2 and Figure 2.

The average prandial insulin requirements for both groups to maintain glucose levels in the hospital setting were different and varied throughout the hospital stay (Table 3), with the liraglutide group patients requiring lower doses compared with those in the glargine group ( $p = 0.046$ ).

Hypoglycemia (glucose  $< 70$  mg/dL) in the hospital setting were infrequent, and there were only two events in group 2 (glargine) and none in group 1 (liraglutide). No severe hypoglycemia events occurred (glucose  $< 60$  mg/dL) in the hospital setting.

### Glucose control in the outpatient setting: Long term GV (12 weeks)

Glycemic control was evaluated using A1c and long-term GV using the CV and SD from the SMBG (Table 4 and Figure 3). The average SMBG per patient was  $336 \pm 12$  mg/dL over 12 weeks. Both groups achieved optimal glucometabolic control at the 12-week follow-up, with an average

**Table 1.** Patients characteristics at admission and after 12 weeks.

	Group 1. Liraglutide n = 5		Group 2. Glargine n = 8	
Age (years)	53.8 (7.3)		65.2 (3.5)	
Duration of diabetes (years)	9.2 (3.5)		15 (1.2)	
Type of ACS	AMI	UAP	AMI	UAP
	4	1	5	3
Peak TnT levels (ng/L) (N 0–14 ng/L)	2,032.6 (313)		1,070.5 (512)	
Treatment for ACS	PCI	CABG	PCI	CABG
	4	1	6	2
Glucose (mg/dL)	Before (baseline)	After (12 weeks)	Before (baseline)	After (12 weeks)
	196.6 (13.4)	129 (8.7)	165.3 (12)	122 (14.3)
HbA1c (%)	8.48 (0.67)	6.9 (0.3)	7.8 (0.83)	6.5 (0.45)
Weight (kg)	88.8 (4.6)	87.5 (2.4)	81 (5.3)	83.8 (3.2)
BMI (kg/m <sup>2</sup> )	29.46 (1.2)	28.6 (0.8)	27.9 (1.3)	29 (0.56)
Waist circumference (cm)	103.6 (2.3)	99.8 (1.6)	109 (2.3)	108.3 (1.4)

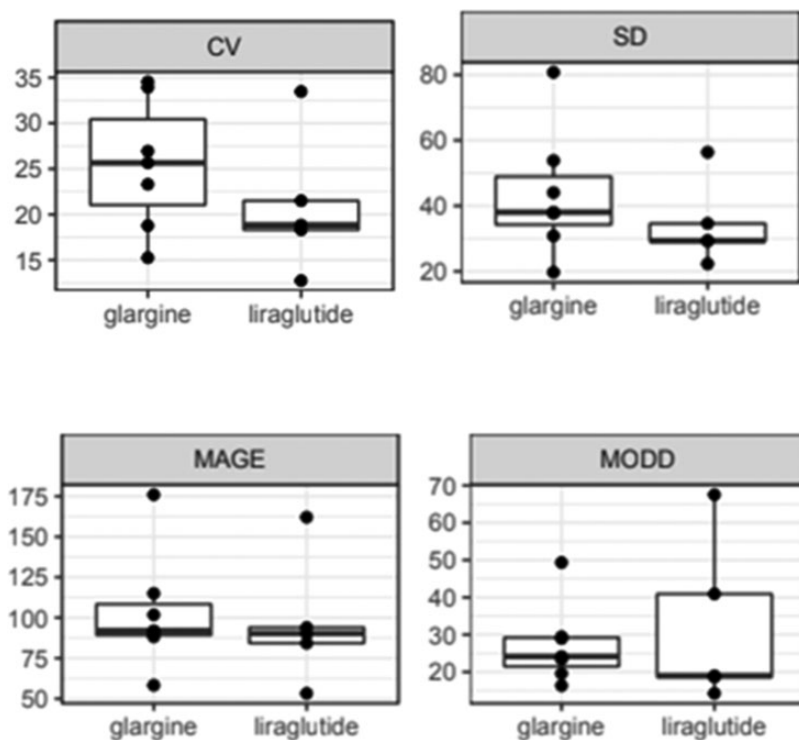
ACS, acute coronary syndrome; AMI, acute myocardial infarction; UAP, unstable angina pectoris; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; BMI, body mass index; TnT, Troponin T; BMI, body mass index.



**Table 2.** GV variables during hospitalization.

GV variable	Group 1 Mean (SD) Median (1st, 3rd Q) (n = 5)	Group 2 Mean (SD) Median (1st, 3rd Q) (n = 7)	p-value
Mean	164.75 (19.94) 168.42 (155.51, 174.84)	166.69 (38.22) 161.7 (139.03, 181.99)	0.76
Median	158.8 (21.26) 153 (151,173)	159.29 (32.46) 157 (136.5, 174)	1
SD	34.37 (13.05) 29.31 (29.29, 34.58)	43.56 (19.53) 38.04 (34.26, 48.92)	0.34
CV	20.98 (7.68) 18.85 (18.32, 21.5)	25.48 (7.19) 25.65 (21.04, 30.43)	0.27
M100	208.06 (53.06) 216.95 (184.86, 239.2)	211.07 (80.5) 208.37 (159.25, 248)	0.88
MAGE	96.75 (39.89) 90.26 (84.26, 93.95)	103.08 (36.46) 91.97 (89.27, 108.4)	0.53

GV, glycemic variability; SD, standard deviation; CV, coefficient of variation; MAGE, mean amplitude glucose excursions.



**Figure 2.** Box-plot diagrams of GV variables during hospitalization. GV, glycemic variability.

**Table 3.** Insulin requirements during hospitalization.

	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6
Group 1 (Liraglutide; mg/day)	4	4.4	3.4	6.8	4	1.6
Group 2 (Glargine; U/day)	7	8	9.14	9.28	8.42	8

**Table 4.** GV variables after 12 weeks of follow-up.

GV variable	Group 1 Mean (SD) Median (1st, 3rd Q) (n = 5)	Group 2 Mean (SD) Median (1st, 3rd Q) (n = 8)
Mean (mg/dL)	146.14 (17.09) 139.85 (138.32, 150.85)	142.65 (17.37) 145.37 (135.6, 149.89)
Median (mg/dL)	143.6 (18.19) 138 (132, 150)	137.81 (16.07) 138 (129.75, 146)
SD (mg/dL)	28.6 (7.89) 24.11 (23.33, 35.91)	40.38 (12.09) 42.62 (32.3, 48.38)
CV (%)	19 (4) 19 (15, 22)	28 (6) 29 (23, 33)
A1c (%)	6.9 (0.85) 6.65 (6.35, 7.2)	6.49 (0.92) 6.2 (5.75, 7.05)

SD, standard deviation; CV, coefficient of variation; GV, glycemic variability.

A1c in group 1 of 6.9%, while that in group 2 was 6.5%. A1c levels in group 1 decreased (-1.51) compared with the A1c basal values ( $p < 0.001$ ) and that in group 2 decreased by -1.271 compared with baseline ( $p = 0.045$ ). Basal A1c was also higher in the liraglutide group (8.48% vs. 7.8%) compared with the glargine group. Mean glucose measured by SMBG was 142.59 (1.11) mg/dL in group 1 and 135.64 (1.12) mg/dL, which was not significant. However, GV that was assessed using SD and CV showed differences between the groups. SD in group 1 was 28.6 (7.89) mg/dL while that in group 2 was 40.38 (12.09), and CV in group 1 was 19 (4)%, while that in group 2 was 28 (6)%.

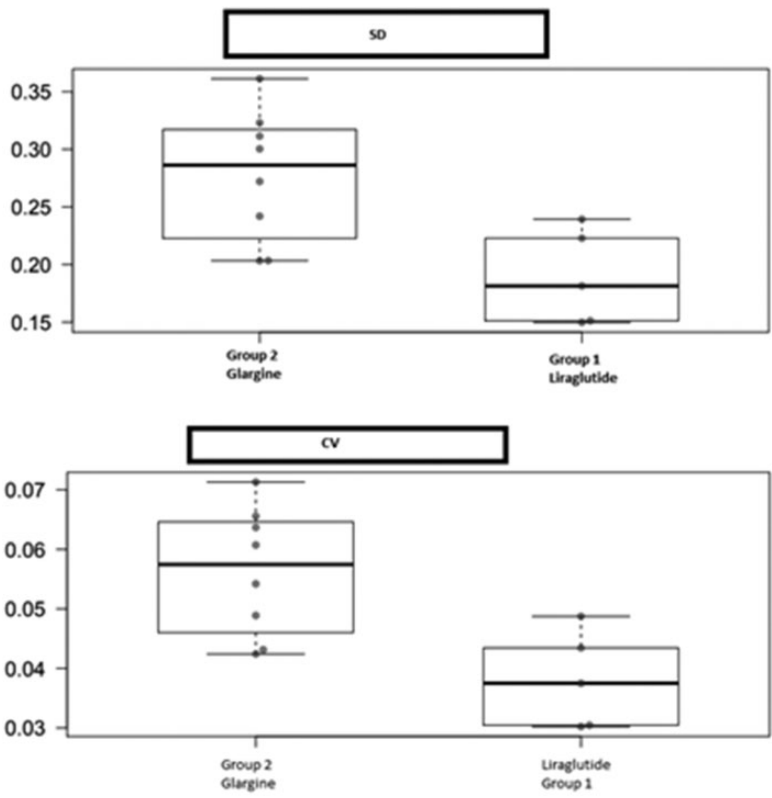
GV did not show a normal distribution, and thus, it was compared using a logarithmic scale. When measured, GV by SD and CV showed a statistically significant difference that favored liraglutide treatment, which resulted in less GV during the 12-week follow-up in group 1 compared with

group 2 ( $p = 0.019$ ). Prandial insulin requirements were similar in both groups; group 1 required 0.9 U/day and glargine group required 2.2 U/day, which was not significantly different.

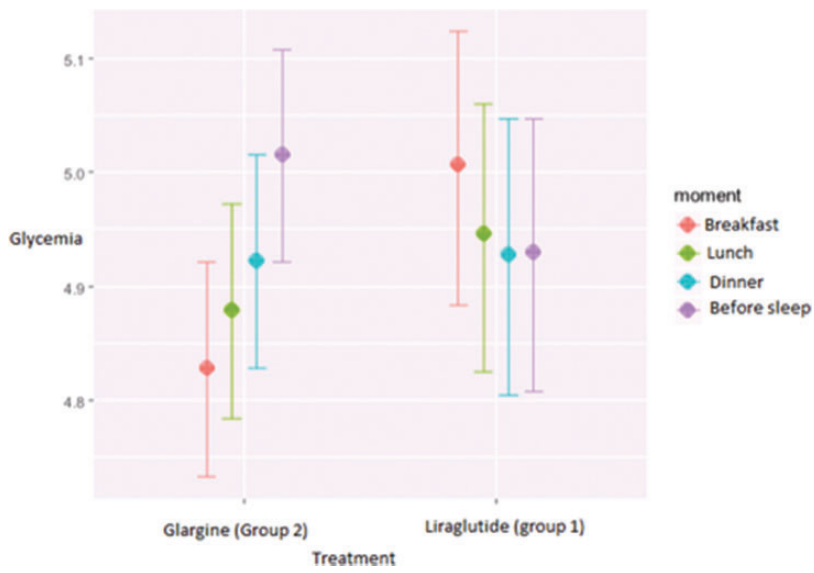
SMBG data were analyzed to see if there were differences at different times of the day. Mostly, the differences that were observed were in the trend of glucose values throughout the day. In group 2 (glargine), blood glucose was lower at breakfast time and it increased progressively throughout the day, while in group 1 (liraglutide), breakfast blood glucose levels were the highest of the day and they decreased but remained constant throughout the day. These trends that were observed throughout the day were significantly different ( $p < 0.001$ ) Figure 4 (logarithmic scale).

Hypoglycemia (glucose  $< 70$  mg/dL) during follow-up was infrequent. Overall, there were 17 episodes of hypoglycemia.

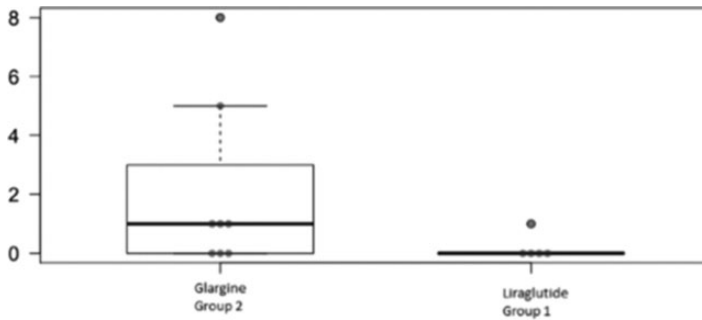




**Figure 3.** Box-plot diagrams of GV variables after the 12 week follow-up. GV, glycemic variability.



**Figure 4.** Glycemic trends throughout the day.



**Figure 5.** Hypoglycemic episodes during follow-up.

Group 2 had 16 episodes and group 1 had 1 episode, which was significantly different ( $p = 0.065$ ; Figure 5).

During follow-up, all of the treatments were well tolerated and none of the patients had secondary effects that made them stop either of the two treatments that were evaluated. Only one patient in group 1 had nausea during follow-up and her treatment dose had to be decreased. Regarding cardiac safety, only one patient had a myocardial infarction recurrence during follow-up (group 2).

## Discussion

### Importance of glucose variability

A1c levels have recently been the dominant parameter that is used to assess glycemic control. However, A1c has certain limitations. Glycemic goals that focus uniquely on lowering A1c might end in unbalanced treatments, which could potentially increase the risk of hypoglycemia; high GV has been related to this risk.<sup>21</sup>

GV is becoming a vital metric to consider when assessing glycemic control in clinical practice. GV can show inter-day and intra-day variations, which can increase both glycemic swings and hypoglycemia risk. Additionally, a reduction in GV has been strongly correlated with reductions in

both hyperglycemic and hypoglycemic episodes.<sup>10,22,23</sup> The link between GV and the development of severe hypoglycemia and ultimately mortality was recently shown in the DEVOTE trial.<sup>24</sup> However, even in non-diabetic patients or recently diagnosed diabetic patients with optimal metabolic control, GV has also been associated with an increase in markers of endothelial and cardiovascular damage.<sup>25</sup> Some studies have shown that an elevated GV, especially those in the highest GV quartile, was significantly associated with short-term cardiovascular composite outcomes. This associated risk was described in both hyperglycemic and normoglycemic groups.<sup>10</sup>

Although it remains controversial, some proof has suggested that GV, particularly within the hyperglycemic range, is associated with a higher risk of macro and microvascular complications that are linked to changes in glucose levels, endothelial dysfunction, and changes in oxidative stress.<sup>26</sup> The development of complications such as cardiovascular autonomic neuropathy, diabetic peripheral neuropathy, and stroke were also shown to have a potential association with GV.<sup>27</sup>

### Importance of glucose variability and ACS

An increased risk of complications and mortality in diabetic patients has been

reported to be associated with GV. Several studies have shown that a high GV that is noted at subsequent visits increases the chance of all-cause mortality and cardiovascular disease in T2DM patients independently from A1c values and mean plasma glucose levels.<sup>10</sup>

Specifically, GV has also been explored in patients with ACS. Other studies have shown the potential risk of GV in patients with T2DM and ACS. The degree of left ventricular remodeling that is measured with cardiac MRI in patients with an acute myocardial infarction showed a significant association with a high GV.<sup>28</sup> In patients with T2DM and AMI, GV predicts mortality, with an increased risk that is observed in those patients who have an increased GV at subsequent visits. GV has also been shown to have a significant connection with plaque vulnerability. Recently, GV (determined by MAGE) was also shown to predict the prognosis in patients with T2DM and ACS, and it was shown to be probably the strongest independent predictive factor for midterm MACE in patients with diabetes and ACS. Therefore, it seems that whereas A1c represents only long-term glucose dysregulation, elevated GV also adds information about stress and poor health status.<sup>11</sup>

### *GLP-1 receptor agonists and glucose variability*

Postprandial glucose levels have shown a direct association with the development of cardiovascular risk factors. The beneficial effect of several therapeutic agents may be a result of their impact over postprandial glucose, such as that observed with GLP-1 receptor agonists (RAs). Both sodium glucose cotransporter 2 inhibitors and GLP-1 RAs have demonstrated significant improvements in GV.<sup>29</sup> However, trials such as FLAT-SUGAR, AWARD 4, or DUAL 1 showed the probable positive

effect of GLP RAs and GV.<sup>15–17</sup> Specifically, some studies that were performed with liraglutide and CSII show that liraglutide was superior to CSII monotherapy by improving GV and glycemic control and by decreasing oxidative stress markers.<sup>30</sup>

### *Liraglutide and glucose variability in patients with ACS*

To the best of our knowledge, this is the first trial that introduces liraglutide in the acute phase of an ACS as the main treatment for blood glucose control during hospitalization. Recently, Gerbaud et al.<sup>11</sup> highlighted the importance of performing studies that explore the effect of reducing the short-term GV in the acute phase of myocardial infarction. This trial captured SMBG profiles and CGM to more precisely characterize fluctuations in daily glucose levels, thereby allowing a more in-depth evaluation of diabetes treatment. These data provide further evidence of the complementary effects of liraglutide in glucose control and safety in a hospital setting.

During hospitalization both groups were able to maintain glucose values within the target range (140–180 mg/dL). Mean glucose values in group 1 (liraglutide) were 164 mg/dL and those of group 2 (glargine) were 166 mg/dL. Group 1 patients had less GV, as measured by the CV, SD, and MAGE, compared with those of group 2 patients, although this difference was not statistically significant.

This control was achieved using a sub-optimal dose of liraglutide (0.6 mg/daily) compared with a standard dosage of insulin glargine (0.25 UI/kg/day). Moreover, the use of prandial insulin was required less often in the liraglutide group to obtain a glucose levels within the target range ( $p=0.046$ ). Additionally, while prandial insulin requirements in group 2 were stable throughout the hospital stay, there

was a tendency for a lower insulin requirement in group 1.

After 12 weeks of follow-up, optimal glucometabolic control ( $A1c < 7\%$ ) was achieved in both groups. The liraglutide group had an  $A1c$  of 6.9% ( $p = 0.045$ ) and glargine had an  $A1c$  of 6.5% ( $p < 0.001$ ). Basal  $A1c$  was also higher in the liraglutide group compared with the glargine group. However, GV that was assessed using SD and CV showed differences between the groups. Therefore, patients in group 1 had less GV compared with those in group 2 ( $p = 0.019$ ). CV has been described as the preferred amplitude measure. CV (SD divided by the mean glucose) is a parameter that is related to the mean blood glucose level, and this makes it easier to explain hypoglycemic swings.<sup>5</sup>

The present study demonstrates that although different treatments for diabetes may reduce  $A1c$  to the same extent, their effectiveness in reducing GV can differ considerably. Additionally, patients treated with liraglutide had higher glucose values at breakfast, but throughout the day, the glucose values decreased and became lower compared with those of insulin glargine ( $p < 0.001$ ).

### *Hypoglycemia during hospitalization*

Hypoglycemia during hospitalization increases the mortality rate, possibly because of adrenergic stimulation, increased apoptosis, increased myocardial ischemia, and impaired metabolism. The major problem for intensive blood glucose control remains in the recognition of hypoglycemia. The American Diabetes Association and the American College of Endocrinology suggest frequent blood glucose measurements during treatment and an adequate carbohydrate consumption as the cornerstone of its prevention.

Recent European Society of Cardiology guidelines from 2008 suggest that target

glucose levels should be between 90 and 140 mg/dL in hospitalized diabetic patients with an ST-elevation myocardial infarction (MI). Blood glucose levels between 80 and 90 mg/dL should be avoided in the hospital setting. Additionally, the American Heart Association statement from 2018 recommends considering intensive glucose control in patients with a glycemia level above 180 mg/dL.<sup>31,32</sup> However, how strictly the glucose levels should be managed to avoid deleterious effects of hypoglycemia in patients with ACS remains controversial.

### *Liraglutide GV and hypoglycemia*

The Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial was stopped prematurely after 3.5 years of follow-up because of an increase in deaths (22% more) in patients who had intensive treatment for hypoglycemia. This, along with other evidence created worry among the diabetes community that cardiovascular events, both fatal and non-fatal, could be increased because of hypoglycemia. There is evidence to support that hypoglycemia causes sympathoadrenal activation, low-grade inflammation, and endothelial function impairment, and thereby contributes to cardiac events; spontaneous hypoglycemia, particularly at night, has been related to an increased risk of arrhythmia; and low  $A1c$  levels added to hypoglycemia have been associated with an increase in the risk of death in diabetic patients who were hospitalized for MI.<sup>21</sup> However, when GV is higher, the risk of hypoglycemia is also higher.

CV has been postulated as the best variable with which to assess GV that is associated with hypoglycemia. In our study, we observed a low incidence of hypoglycemia, only two hypoglycemia events during hospitalization, and 17 hypoglycemia events during outpatient follow-up. This is probably because of intensive glucose control and

nurse training in the hospital. However, among all the episodes that were observed in the trial, only one took place in the liraglutide group during outpatient follow-up, and the rest of these events occurred in the glargine group, with two of them occurring during an acute ACS.

### **Clinical implications**

Recent publications have established the importance of GV in patients with ACS and T2DM. T2DM treatment reduces A1c levels and glycemic fluctuations, which are desirable. Based on the current pilot study's results, there is the potential for liraglutide to be used in the hospital setting in patients with ACS. Liraglutide offers similar metabolic control, measured by A1c, compared with glargine, but liraglutide significantly reduces glycemic fluctuations in the short-term after an ACS (12 weeks) and potentially also during the first hours in a hospital setting. Thus, patients with liraglutide had also fewer hypoglycemic episodes during hospitalization and in the following 12 weeks along with fewer requirements of prandial insulin. However, liraglutide benefits are also added to the known metabolic effects such as weight loss.

The LEADER trial showed liraglutide's superiority in terms of cardiovascular safety. Those who were patients treated with liraglutide had a lower risk of presenting with the primary outcome, and a lower risk of cardiovascular death, death from any cause, and microvascular complications. These findings should support the possibility of conducting multicenter clinical trials to introduce the use of GLP-1 in the hospital setting for patients with ACS.

### **Study limitations**

The present study had some limitations. First, it was a small pilot trial that was conducted at a single center. Recruitment was

difficult because among the 54 patients who were evaluated, only 13 signed an informed consent form. In addition, this was an exploratory study that should be expanded to confirm the VG findings, which are scarce, but should be explored. Starting liraglutide in the hospital and dose escalation to ensure tolerance supports using the dose low and possibly explains the absence of differences during hospitalization. Furthermore, basal differences between both groups were observed because the randomized patients were not matched based on clinical characteristics. Patients should be matched in the following trials to assure group homogeneity.

### **Conclusions**

Liraglutide seems to reduce GV in the acute phase of ACS in T2DM patients with optimal metabolic control and a low incidence of hypoglycemia compared with insulin glargine. These treatments, which reduce GV, should be explored in multicentric trials to introduce their use in a hospital setting, especially in the acute phase of a major cardiovascular event.

### **Declarations and conflicts of interest**

The authors declare that there is no conflict of interest.

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