

## Conventional insulin *vs* insulin infusion therapy in acute coronary syndrome diabetic patients

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### Abstract

**AIM:** To evaluate the impact on glucose variability (GLUCV) of an nurse-implemented insulin infusion protocol when compared with a conventional insulin treatment during the day-to-day clinical activity.

**METHODS:** We enrolled 44 type 2 diabetic patients ( $n = 32$  males;  $n = 12$  females) with acute coronary syndrome (ACS) and randomly assigned to standard a subcutaneous insulin treatment ( $n = 23$ ) or a nurse-implemented continuous intravenous insulin infusion protocol ( $n = 21$ ). We utilized some parameters of GLUCV representing well-known surrogate markers of prognosis, *i.e.*, glucose standard deviation (SD), the mean daily  $\delta$  glucose (mean of daily difference between maximum and minimum glucose), and the coefficient of variation (CV) of glucose, expressed as percent glucose (SD)/glucose (mean).

cose (mean).

**RESULTS:** At the admission, first fasting blood glucose, pharmacological treatments (insulin and/or anti-diabetic drugs) prior to entering the study and basal glycated hemoglobin (HbA1c) were observed in the two groups treated with subcutaneous or intravenous insulin infusion, respectively. When compared with patients submitted to standard therapy, insulin-infused patients showed both increased first 24-h (median 6.9 mmol/L *vs* 5.7 mmol/L  $P < 0.045$ ) and overall hospitalization  $\delta$  glucose (median 10.9 mmol/L *vs* 9.3 mmol/L,  $P < 0.028$ ), with a tendency to a significant increase in first 24-h glycaemic CV (23.1% *vs* 19.6%,  $P < 0.053$ ). Severe hypoglycaemia was rare (14.3%), and it was observed only in 3 patients receiving insulin infusion therapy. HbA1c values measured during hospitalization and 3 mo after discharge did not differ in the two groups of treatment.

**CONCLUSION:** Our pilot data suggest that no real benefit in terms of GLUCV is observed when routinely managing blood glucose by insulin infusion therapy in type 2 diabetic ACS hospitalized patients in respect to conventional insulin treatment

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**Key words:** Glycaemic management; Intensive insulin therapy; Conventional insulin treatment; Acute coronary syndrome; Glucose variability

**Core tip:** In type 2 diabetic patients hospitalized for acute coronary syndrome no real benefit in terms of reduced glucose variability is observed by intensively managing blood glucose through insulin infusion therapy in respect to conventional insulin treatment

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## INTRODUCTION

It is well-known that type 2 diabetes and acute coronary syndromes (ACS) are strictly related. Also, patients with type 2 diabetes are more likely than non-diabetic subjects to experience silent or symptomatic myocardial ischaemia as the first presentation of coronary artery disease<sup>[1]</sup>.

The role of admission and fasting glucose level as best indicator of glucose metabolic state in predicting outcome in ACSs remains, however, uncertain<sup>[2-4]</sup>. Fasting glucose levels have been shown to represent a marker of adverse outcome after ST-segment elevation myocardial infarction (STEMI)<sup>[5,6]</sup> and elevated blood glucose level at admission for acute myocardial infarction (AMI) is associated with worse outcome in both non-diabetic and diabetic patients<sup>[4-7]</sup>. On the contrary, the role of high fasting glucose levels in non-STEMI ACSs is less defined. On the other hand, an increased incidence of cardiac events also in patients with a prediabetic state presenting with either STEMI or non-STEMI, compared with non-diabetic patients has been already shown<sup>[8]</sup>.

High coefficient of variation (CV) of blood glucose as an indicator of glucose variability (GLUCV) predicts increased risk of death in intensive care unit (ICU) patients<sup>[9]</sup> and represents a better discriminator of in-hospital mortality than mean blood glucose in patients with ACS<sup>[10]</sup>. In this context, epidemiological studies have also shown that beside spontaneous hypoglycaemia, treatment-induced hypoglycemia was associated with higher mortality<sup>[11]</sup>.

Over the last years, glycaemic management in critical care patients has dramatically changed. Emerging evidence seems to indicate that intensive blood glucose control by intravenous insulin infusion may significantly reduce morbidity and mortality in hyperglycaemic patients admitted to ICU<sup>[1]</sup>. Furthermore, some evidence suggests that diabetic patients with ACS might benefit by intravenous insulin infusion<sup>[12,13]</sup>. For the above reasons, the European Society of Cardiology/European Association for the Study of Diabetes recommends blood glucose control by intensive insulin treatment (Class I recommendation) in patients with AMI (Class II, level of evidence B)<sup>[14]</sup>. Some schemes of insulin infusion therapy have been proposed for critically ill patients<sup>[15-22]</sup>; however, among the nurse-implemented insulin infusion protocols available none was specifically tested in patients with ACS during the day-to-day clinical activity of a coronary care unit<sup>[21]</sup>.

Aim of the present pilot study was to compare the impact on GLUCV of a nurse-implemented insulin infusion therapy and conventional insulin treatment for management of diabetic patients affected by ACS in a day-to-day in-hospital clinical activity. In order to avoid potential bias in studied population we decided to enrol only type

2 diabetic patients by considering that type 2 diabetes comprises 90% of people with diabetes in Europe.

## MATERIALS AND METHODS

### Ethics

This work has been carried out in accordance with the Declaration of Helsinki (2000) of the World Medical Association. Informed consent was obtained from all patients and the study was approved by the institutional review board of the Hospital.

### Patients

All type 2 diabetic patients admitted to the Heart Department of Fondazione CNR/Regione Toscana G. Monasterio from January 2013 to July 2013 with a diagnosis of ACS (*i.e.*, STEMI, non-STEMI or unstable angina) and confirmed by electrocardiographic changes consistent with ACS, increased biochemical markers of cardiac necrosis and/or documented coronary artery disease were potentially eligible.

Additional inclusion criteria were: (1) age 18-80 years; (2) history of diabetes; (3) admission glucose level > 180 mg/dL (*i.e.*, 10 mmol/L); and (4) glycated hemoglobin (HbA1c) > 6.2%.

Exclusion criteria were: (1) stage of chronic kidney disease >3; (2) severe chronic liver, autoimmune diseases; (3) active neoplastic disease; and (4) treatment with corticosteroids.

We enrolled 44 patients, 32 males, 12 females, randomly assigned to standard multidose subcutaneous insulin treatment ( $n = 23$ ) or continuous insulin infusion protocol (see below) for the first one-three days followed by standard subcutaneous multidose insulin treatment.

### Methods

We adopted the nurse-implemented continuous intravenous insulin infusion protocol as proposed by Avanzini *et al.*<sup>[21]</sup> developed also to drive the optimal transition to subsequent subcutaneous insulin therapy<sup>[22]</sup>, with little modifications. In particular targeting glycemic values were 120-180 mg/dL (*i.e.*, 6.6-10 mmol/L) instead of 100-139 mg/dL (*i.e.*, 5.5-7.7 mmol/L), and infusion treatment was stopped in presence of glycemic values below 120 mg/dL (*i.e.*, 6.7 mmol/L) instead of 100 mg/dL (*i.e.*, 5.5 mmol/L).

To facilitate acceptance, during year 2012 all nurses involved in the study were previously trained by a week-long series of 1-h in-service training sessions and all experienced very good compliance with the infusion protocol at the time of the study.

The frequency of blood glucose determinations was guided by the infusion protocol as previously suggested<sup>[21]</sup>; usually blood samples were withdrawn every 2 h during day-time and every three hours during night-time. Blood glucose was checked at fixed times (*i.e.*, 07:00 am; 10:00 am; 12:00 am; 04:00 am; 06:00 pm; 10:00 pm) in the case of subcutaneous insulin treatment.

To contribute equally to statistical analysis, blood

**Table 1** Main clinical characteristics of study population

	Total <i>n</i> = 44	Conventional insulin treatment <i>n</i> = 23	Infusion insulin treatment <i>n</i> = 21	<i>P</i> value
Gender (M)	72.7	69.6	76.2	0.622
Age (yr)	68.2 ± 11.5	69.6 ± 12.0	66.6 ± 11.0	0.397
BMI	29 (26; 31) <sup>o</sup>	28 (26; 32)	29 (26; 30)	0.867
Urea mg/dL	46.7 ± 20.7	46.3 ± 15.5	47.2 ± 25.6	0.880
Creatinine mg/dL	1.0 ± 0.3	1.0 ± 0.4	1.0 ± 0.2	0.341
Basal glycated haemoglobin (%)	8.3 ± 1.8	8.1 ± 1.8	8.5 ± 1.9	0.459
First fasting glycaemia (mmol/L)	9.1 (7.4; 12.1)	9.4 (8.3; 10.9)	8.8 (6.9; 12.3)	0.435
Admission glycaemia (mmol/L)	12.0 (10.3; 13.8)	11.4 (10.0; 13.2)	13.0 (10.8; 17.1)	0.205
Glycated haemoglobin after 3 mo from discharge (%)	8.1 ± 1.0	8.0 ± 1.1	8.3 ± 0.6	0.575
% Patients with new diagnosis of diabetes	13.6	13	14.3	1.000
% Patients under insulin treatment before admittance	26.3	26.3	26.3	1.000
% Patients with previous AMI	18.8	17.7	20.0	1.000
Length of in-hospital stay (d)	8 (7; 10)	8 (7; 10)	9 (7; 12)	0.368
% Patients with STEMI	45.5	34.8	57.1	0.137
% Patients with non-STEMI	47.7	56.5	38.1	0.222
% Patients with in-hospital major complications <sup>1</sup>	18.2	8.7	28.6	0.088
% Diabetic patients under dietetic treatment only	15.9	8.7	23.8	0.232
% Diabetic patients under oral antidiabetic drugs	45.5	52.2	38.1	0.382
% Patients under insulin treatment <sup>1</sup>	20.5	21.7	19.1	1.000

<sup>o</sup>Interquartile ranges (25<sup>th</sup>, 75<sup>th</sup> percentile) values reported in brackets; <sup>1</sup>Major complications include re-infarction, malignant arrhythmias, death. M: Males; BMI: Body mass index; AMI: Acute myocardial infarction; STEMI: ST-segment elevation myocardial infarction.

glucose levels utilized to determine GLUCV parameters (see below) were based only on measurements obtained at the same timetables in the two mentioned protocols (*i.e.*, 07:00 am; 10:00 am; 12:00 am; 04:00 am; 06:00 pm; 10:00 pm).

Blood glucose levels were measured by a standard hospital glucose meter which was calibrated daily.

### Assessment of glucose variability

GLUCV was assessed according to Brunner *et al.*<sup>[23]</sup> using three statistical indicators calculated for the three periods of interest *i.e.*: (1) during the first 24 h; (2) during the whole hospitalization; and (3) during the pre-discharge day. The first indicator was represented by standard deviation (SD), the second by mean daily  $\delta$  glucose, assessed as the mean of daily difference between maximum and minimum glucose, and the third indicator was the CV of glucose, express as percent [glucose (SD)/glucose (mean) (%)].

### Statistical analysis

Continuous variables were expressed as mean ± SD or median (25<sup>th</sup>, 75<sup>th</sup> percentiles) and categorical variables were expressed as percentage. Student Independent *t*-test or Wilcoxon test was used as appropriate to compare continuous and ordinal variable differences between patients. Due to the small number of patients analyzed, the Wilcoxon test is preferred to the *t*-test for comparison of the indices of GLUCV between groups. Comparison between categorical variables was performed by  $\chi^2$  test or by Fisher exact test (if an expected cell count was 5). All statistical tests were evaluated with the use of 2-tailed 95%CI, and tests with *P*-value < 0.05 were considered significant. All analyses were performed using Stata, version 10.2.

## RESULTS

Baseline characteristics of the 44 studied patients are reported in Table 1. Similar admission, first fasting blood glucose, pharmacological treatments (insulin and/or anti-diabetic drugs) prior to entering the study and basal HbA1c were observed in the two groups treated with subcutaneous or intravenous insulin infusion, respectively. Also, glycaemic control did not differ after three months from discharge between the two groups, as documented by superimposable HbA1c values (Table 1).

In patients submitted to intravenous infusion insulin therapy transition to subcutaneous insulin treatment was, on average, obtained after 3.5 ± 1.5 d.

The effectiveness of the two therapeutic protocols (*i.e.*, infusion *vs* conventional insulin treatment) was assessed with regard to values of several relevant parameters of GLUCV (Tables 2 and 3 and Figure 1). Notwithstanding increased staff's efforts and increased number of glycaemic determinations, patients receiving insulin infusion therapy showed both first 24-h and overall hospitalization increased GLUCV  $\delta$  associated with a tendency to a significant increase in first 24-h glycaemic CV (*P* = 0.059). Importantly, severe hypoglycemia (*i.e.*, with glycaemic values < 50 mg/dL) was extremely rare (14.3%), but it was observed only in patients receiving insulin infusion therapy (Table 2).

All data, taken as whole, suggest that no improvement is observed in glucose management in day-to-day clinical activity by intensive insulin infusion protocol in diabetic type 2 patients with ACS when compared to standard subcutaneous insulin treatment.

## DISCUSSION

An alteration of glucose metabolism which includes

**Table 2** Hypo and hyperglycaemic states in patients treated with conventional insulin or insulin-infused protocol

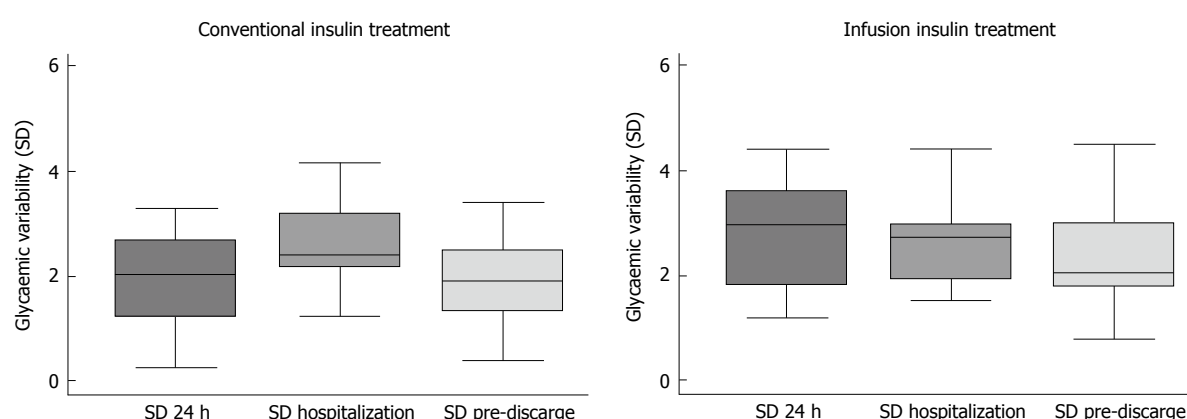
	Total <i>n</i> = 44	Conventional insulin treatment <i>n</i> = 23	Infusion insulin treatment <i>n</i> = 21	<i>P</i> value
% Patients with glycaemic values > 11.1 mmol/L (at least one determination)	100.0	100.0	100.0	-
% Patients with glycaemic values 7.77-11.1 mmol/L (at least one determination)	100.0	100.0	100.0	-
% Patients with glycaemic values 5.55-7.72 mmol/L (at least one determination)	90.9	95.7	85.7	0.335
% Patients with glycaemic values < 5.55 mmol/L (at least one determination)	45.5	39.1	52.4	0.378
% Patients with severe hypoglycaemia (i.e., glucose < 2.77 mmol/L)	6.8	0.0	14.3	0.100
% Patients with more than 5 glycaemic values > 13.88 mmol/L	22.7	21.7	23.8	0.870
% Patients with more than two glycaemic values > 16.66 mmol/L	13.6	8.7	19.1	0.403
Average number of glycaemic values evaluated	30.8 ± 12.5	23.4 ± 9.0	31.0 ± 10.8	<i>P</i> < 0.001
Number of glycaemic values evaluated	1356 (6; 56) <sup>o</sup>	538 (6; 38)	818 (12; 56)	

<sup>o</sup>Interquartile ranges (25<sup>th</sup>; 75<sup>th</sup> percentile) values reported in brackets.

**Table 3** Main glucose variability parameters measured in patients treated with conventional insulin or insulin-infused therapy

	Total <i>n</i> = 44	Conventional insulin treatment <i>n</i> = 23	Infusion insulin treatment <i>n</i> = 21	<i>P</i> value
Median of glycaemic values				
Glycaemic values (first 24 h) mmol/L	10.3 (9.0; 12.1) <sup>o</sup>	10.1 (8.6; 11.6)	10.3 (9.2; 12.1)	0.716
Glycaemic values (overall hospitalization) mmol/L	10.2 (8.8; 11.5)	9.8 (8.7; 10.7)	10.6 (9.1; 11.5)	0.366
Glycaemic values (pre-discharge) mmol/L	9.3 (8.6; 10.2)	9.1 (8.5; 9.9)	9.4 (8.6; 11.4)	0.331
Median of glycaemic values variability (δ)				
Variability of glycaemic values (first 24 h)	6.2 (4.5; 9.5)	5.7 (2.9; 7.5)	6.9 (5.5; 10.2)	0.045
Variability of glycaemic values (overall hospitalization)	9.9 (8.1; 13.1)	9.3 (7.3; 10.9)	10.9 (9.2; 14.3)	0.028
Variability of glycaemic values (pre-discharge)	5.2 (3.6; 6.1)	4.3 (2.9; 6.1)	5.3 (4.3; 6.8)	0.236
Median of glycaemic variability (Coefficient of Variation)				
Glycaemic Coefficient of Variation (first 24 h)	21.4% (15.7%; 31.2%)	19.6% (12.6%; 29.6%)	23.1% (20.7%; 33.1%)	0.059
Glycaemic Coefficient of Variation (overall hospitalization)	25.3% (20.7%; 28.5%)	27.1% (20.7%; 30.1%)	24.9% (21.7%; 27.1%)	0.518
Glycaemic Coefficient of Variation (pre-discharge)	23.1% (17.0%; 28.5%)	23.1% (14.8%; 26.4%)	23.4% (17.9%; 29.1%)	0.466

<sup>o</sup>Interquartile ranges (25<sup>th</sup>; 75<sup>th</sup> percentile) values reported in brackets.

**Figure 1** Standard deviation of glycaemic levels determined in patients treated with conventional insulin or insulin infused therapy.

a prediabetic state is frequently observed during acute cardiac events<sup>[2,5,8,11,22,24,25]</sup>. Furthermore, diabetic patients show an increased mortality and morbidity after both AMI and ACS in general when compared with non-diabetic patients<sup>[8]</sup>. Also, the relationship of high blood glucose with risk of death or poor outcome after AMI is

present for both diabetic and non-diabetic patients<sup>[4,26]</sup>.

A large meta-analysis<sup>[27]</sup> clearly indicated that new hyperglycaemia *per se* in presence of AMI represents a strong prognostic predictor of short and long-term mortality and progression toward heart failure in both diabetic and non-diabetic patients.



On the other hand, worse outcome in diabetic patients with ACS has not been improved by progressive diffusion of new, more efficacious pharmacological cardiac treatments and interventional procedures thus suggesting the hyperglycemia and glucose toxicity playing a critical role on adverse prognosis in ACS.

Serum GLUCV and in particular SD/CV of glycaemic values measured during the first days after acute events including ACS has been demonstrated to represent a good prognostic biomarker of increased death rate<sup>[28]</sup>.

It has been also reported that the relationship between mean serum GLUCV and mortality is described by a “U-shaped” curve, with lower and higher GLUCV values associated with higher death rate<sup>[9]</sup>. This suggests that preventing both hypo and hyperglycemic states may be an important therapeutical target to minimize changes in GLUCV.

Because hypoglycaemia, hyperglycaemia and high GLUCV are associated with an increased risk of death, an intensive insulin treatment has been proposed as a better strategy than conventional treatment to ameliorate glycaemic control immediately after the acute cardiac event and, consequently patient's prognosis<sup>[1]</sup>. Data so far reported are somewhat contrasting<sup>[1,29,30]</sup>; actually, although the DIGAMI study<sup>[12]</sup> demonstrated the superiority of intravenous insulin infusion when compared with standard care in reducing early and long-term mortality in diabetic AMI patients, the later DIGAMI 2 study did not confirm previous results<sup>[31]</sup>. Also, a major risk of intensive insulin treatment is the greater appearance of hypoglycaemic episodes which are mainly related to diabetes life span, frequency of previous hypoglycaemic attacks and pre-existing coronary artery disease<sup>[29,30]</sup> with worsening of prognosis and prolongation of in-hospital stay. Several insulin-infused operational protocols to be adopted in ICUs have been proposed so far<sup>[15-22]</sup> but no specific guidelines with validate protocols in day-to-day clinical practice and definite glycaemic target values have been provided. Furthermore, an additional concern is represented by a recurrence of hyperglycaemic states during the transition from intravenous to subcutaneous treatment regimen.

With the above premises, in our pilot study we evaluated the superiority of an intensive, nurse-implemented insulin treatment for treating type 2 diabetic patients with ACS in a clinical practice setting. We utilized GLUCV parameters as well-established surrogate markers of early and long-term outcome in ACS patients<sup>[30]</sup>. Our preliminary results indicate that GLUCV as represented by SD of blood glucose levels and glucose  $\delta$  variation does not improve by intensive *in* insulin treatment when compared to conventional approach. A concurrent clear disadvantage is represented by both higher personnel efforts and costs related to the significant increase in number of blood glucose determinations in the case of an insulin-infused protocol.

We do not have definite explanations for our find-

ings. Among the possible causes we may recognize an increased difficulty in: (1) managing the infusion protocol, also by well-trained and compliant nurses, when compared with conventional insulin therapy, in a day-to-day clinical practice of a cardiac ICU; (2) managing the infusion protocol in feeding patients as in the case of ACS; and (3) managing the transition to conventional insulin treatment.

In conclusion our pilot study suggests that no benefit in terms of GLUCV is observed by early insulin infusion therapy in type 2 diabetic ACS in-patients in respect to conventional treatment in a day-to-day clinical practice. Further studies in larger populations and with a longer follow-up are, however, necessary to confirm these preliminary results.

## COMMENTS

### Background

Glycaemic management in severely ill acute patients is a critical issue and in-hospital glucose variability (GLUCV) represents a good prognostic predictor. Emerging evidence suggests that diabetic patients hospitalized for acute coronary syndrome (ACS) may benefit intensive blood glucose control.

### Research frontiers

Some nurse-implemented insulin infusion protocols have been proposed for patients affected by ACS but none was specifically tested in patients during the day-to-day clinical activity. In their pilot study they compared for the first time the impact on GLUCV of a nurse-implemented insulin infusion protocol with a conventional insulin treatment in a group of 44 type 2 diabetic patients with acute coronary syndrome.

### Innovations and breakthroughs

Over the last years, glycaemic management in critical care patients has dramatically changed. Emerging evidence seems to indicate that intensive blood glucose control by intravenous insulin infusion may significantly reduce morbidity and mortality in hyperglycaemic patients admitted to intensive care units. Some evidence suggests that diabetic patients with ACS might benefit by intravenous insulin infusion.

### Applications

The results of the present pilot study may represent a stimulus to further studies on large populations of diabetic patients with ACS to define the better strategy for glycaemic control during hospitalization.

### Terminology

GLUCV was assessed by using three statistical indicators calculated for the three periods of interest during hospitalization: (1) during the first 24 h; (2) during the whole hospitalization; and (3) during the pre-discharge day. The first indicator was represented by glucose standard deviation (SD), the second by mean daily  $\delta$  glucose, assessed as the mean of daily difference between maximum and minimum glucose, and the third indicator was the coefficient of variation of glucose, express as percent (%) glucose (SD)/glucose (mean).

### Peer review

The present manuscript deals with a very interesting topic: comparison between intravenous insulin therapy and conventional insulin treatment. The main criticism arises from the reduced number of participants as the authors point.

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