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 δglucose (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.
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.[11] developed also to drive the optimal transition to subsequent subcutaneous insulin therapy,[22] 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,[21] 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
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.[23] 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 δ 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 (25th; 75th 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 χ² 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 δ 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

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

|                          | Total  | Convensional insulin treatment | Infusion insulin treatment | P 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) | 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 glycemia (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   |
| **Lenght 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** | 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 anti diabetic drugs** | 45.5 | 52.2                         | 38.1                   | 0.382   |
| **% Patients under insulin treatment** | 20.5 | 21.7                         | 19.1                    | 1.000   |

*[Interquartile ranges (25th; 75th percentile) values reported in brackets; Major complications include re-infarction, malignant arrhythmias, death. M: Males; BMI: Body mass index; AMI: Acute myocardial infarction; STEMI: ST-segment elevation myocardial infarction.]*
A large meta-analysis 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.

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

|                     | Total n = 44 | Conventional insulin treatment n = 23 | Infusion insulin treatment n = 21 | P 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 | P < 0.001 |
| Number of glycaemic values evaluated | 1356 (6; 56)† | 538 (6; 38) | 818 (12; 56) | |

†Interquartile ranges (25th; 75th percentile) values reported in brackets.

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

|                     | Total n = 44 | Conventional insulin treatment n = 23 | Infusion insulin treatment n = 21 | P value |
|---------------------|--------------|--------------------------------------|-----------------------------------|---------|
| Median of glycaemic values Glycaemic values (first 24 h) mmol/L | 10.3 (9.0; 12.1)† | 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%; 31.1%) | 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 |

†Interquartile ranges (25th; 75th 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. Furthermore, diabetic patients show an increased mortality and morbidity after both AMI and ACS in general when compared with non-diabetic patients. 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.

Arvia C et al. Insulin treatment in ACS 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 glycemic values measured during the first days after acute events including ACS has been demonstrated to represent a good prognostic biomarker of increased death rate[29].

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[9]. This suggests that preventing both hypo and hyperglycemic states may be an important therapeutic target to minimize changes in GLUCV.

Because hypoglycemia, hyperglycemia 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 glycemic control immediately after the acute cardiac event and, consequently patient’s prognosis[1]. Data so far reported are somewhat contrasting[1,29,30]; actually, although the DIGAMI study[13] 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[31]. Also, a major risk of intensive insulin treatment is the greater appearance of hypoglycemic episodes which are mainly related to diabetes life span, frequency of previous hypoglycemic attacks and pre-existing coronary artery disease[8,25,30] 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[15-22] but no specific guidelines with validate protocols in day-to-day clinical practice. Our preliminary results indicate that GLUCV as represented by SD of blood glucose levels and glucose δ variation does not improve by intensive 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 findings. 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.

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