A multicenter observational study on the management of hyperglycemia in patients with acute coronary syndrome

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Abstract *Aim:* To assess the prevalence, risk and management of hyperglycemia in patients with acute coronary syndrome (ACS).

Methods and Results: Design: a multicenter prospective observational study of a representative sample of patients with ACS consecutively admitted to intensive cardiac care units (ICCU).

Setting: 31 out of 61 ICCUs in Lombardy, the most heavily populated Italian region.

From May 2009 to April 2010 1260 patients (69.4% male; mean age 68 ± 13 years) were included in the study: 301 (23.9%) were known diabetic patients (D) and 265 (21.0%) had hyperglycemia (H) (blood glucose >180 mg/dL) at hospital admission, 174 with a history of diabetes (D+H+) and 91 without (D−H+). On the first day after admission intravenous insulin infusion was prescribed to 72 D+H+ (41.4%) and 10 D−H+ (11.0%), according to different protocols. Approximately one third of D+H+ patients (59) and one fifth (17) of D−H+ maintained mean blood glucose higher than 180 mg/dL during the first day in the ICCU.

Patients with diabetes or hyperglycemia had a higher incidence of major adverse cardiovascular events or death in hospital. However, at multivariable analysis neither diabetes nor blood glucose at admission was associated with a poor prognosis whereas mean blood glucose on the first day was an independent negative prognostic predictor (OR 1.010, 95% CI 1.002−1.018, p = 0.016).

Conclusion: Hyperglycemia is frequent in patients with ACS and is independently associated with a poor in-hospital prognosis if it persists in first day. Unfortunately, however, this condition is still poorly treated, with far from optimal blood glucose control.

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[1] See Appendix.

Introduction

Diabetes mellitus is a major risk factor for coronary artery disease and is therefore often present in patients with acute coronary syndrome (ACS) [1–6]. Observational studies have documented a higher risk of fatal and non-fatal complications in diabetic patients with ACS, although multivariable analyses do not always confirm the independent prognostic significance of diabetes in the short period, when taking account of other confounding variables such as other cardiovascular risk factors and diseases or the under-use of recommended treatment [2–6]. Hyperglycemia in diabetic and non-diabetic patients with ACS is also frequent as a patho-physiological reaction to stress [7–11]. Observational studies have suggested that high blood glucose (BG) levels at the onset of an ACS are a negative prognostic factor in diabetic and even more in non-diabetic patients [7–11]. Hyperglycemia in the early period after hospital admission is an additional unfavorable factor, often more important than hyperglycemia at admission [10–19]. Hypoglycemia at admission for ACS and immediately afterwards is also associated with unfavorable outcomes [15,20].

In the 1990s the DIGAMI study showed the benefit of intensive insulin treatment in patients with acute myocardial infarction (MI) and BG ≥ 200 mg/dL at hospital admission [21]. The goal of DIGAMI was to keep BG during the acute phase within the range of 125–180 mg/dL by intravenous (i.v.) insulin infusion. Despite the promising results, none of the subsequent studies [22–24] aimed at confirming the advantage of glucose control in the acute phase of an ACS and defining the optimal glycemic range have reached conclusive results. In the absence of evidence from controlled clinical trials, clinical guidelines, while recognizing the importance of controlling BG in ACS, do not clearly and uniformly define the therapeutic strategies and the BG target range [25–29].

With this uncertainty about the therapeutic approach for patients with ACS and hyperglycemia we planned a prospective observational study in a large sample of patients with ACS admitted to intensive cardiac care units (ICCU) to describe:

1) the prevalence of diabetes and hyperglycemia, the type of pharmacological and nutritional treatment and BG control during the acute phase;
2) the incidence of mortality and major adverse cardiovascular events (MACE) in hospital in relation to the presence of diabetes and BG at admission and in the first 24 h.

The findings of this study should help in planning an *ad hoc* interventional study to determine the benefits and risks of treatment for hyperglycemia in ACS patients.

Methods

GLICINE-SPIDER (Gruppo **L**ombardo per lo studio dell'**i**pergli**c**emia **n**elle **s**indromi coro**n**ariche acut**e** − **S**tudio osservazionale **p**rospettico sulla gestione dell'**i**perglicemia in corso di sin**d**rom**e** co**r**onarica acuta) is a prospective observational, multicenter study on the management of diabetes and/or hyperglycemia in patients with ACS admitted to ICCU. All the 61 ICCUs in the Lombardy Region, the most heavily populated region in Italy, were invited to participate. Eligible patients were women or men of any age consecutively admitted to the ICCU for ACS, with written informed consent to participate in this study.

Demographic characteristics, cardiovascular risk factors, clinical history and laboratory variables were collected at hospital admission. The diagnosis of diabetes was self-reported. BG was checked in all patients at admission. After admission BG was measured according to local practice and all the measurements in the first 24 h were recorded. Medical and interventional therapies, MACE and in-hospital mortality were also recorded.

Statistical methods

Each ICCU was asked to admit 40 patients and the expected study population was 1300−1400 patients. The sample size was calculated considering that the expected proportion of diabetes or hyperglycemia among patients with ACS would be one third [2–11] and the expected mortality of diabetic patients in hospital would be about 5% [2–11].

A sample of 450 patients with diabetes or hyperglycemia would show up the assumed incidence with good precision ($\pm 0.2\%$) with the 95% confidence interval approach. Sample size was calculated by the algorithm described by Yamane to obtain the prevalence/incidence [30].

Descriptive data are expressed as numbers (percentages) for categorical data and as means (SD) or median (interquartile range) for continuous variables, as appropriate.

Main analyses were done on the whole case-list and on four subgroups of patients, identified on the basis of their history of diabetes and hyperglycemia at admission (BG > 180 mg/dL): patients with known diabetes and hyperglycemia (D+H+), patients with known diabetes and no hyperglycemia (D+H−), patients with hyperglycemia but no history of diabetes (D−H+), and patients with no history of diabetes and no hyperglycemia (D−H−). The distribution of baseline characteristics between these four subgroups was investigated with the Chi-square test for categorical variables; continuous variables were compared by analysis of variance or by the nonparametric Kruskal−Wallis test for non-normally distributed data.

We calculated mean BG in the first 24 h as the arithmetic average of all BG measurements in each patient in the 24 h after admission, excluding the admission BG. The number of hypoglycemic episodes (BG < 70 mg/dL) and severe ones (BG < 40 mg/dL) during the first 24 h was recorded.

The combined end-point was the composite of in-hospital death or MACE defined as heart failure (HF), atrial fibrillation (AF), sustained ventricular tachycardia or