Prognostic Value of Fasting Glucose Levels in Elderly Patients with Acute Coronary Syndrome

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Abstract

Background: The fasting plasma glucose (FPG) test is a predictor of complications after Acute Coronary Syndrome (ACS). However, its prognostic value is not yet fully established in different age groups.

Objective: To evaluate the role of admission fasting plasma glucose (FPG) as a predictor of 30 days after ACS, and the association of hyperglycemia with major cardiovascular events (MACE): death, reinfarction and coronary artery bypass grafting, in two different age groups (<65 year and ≥65 year-old patients).

Methods: Contemporary cohort of patients hospitalized for ACS in the Institute of Cardiology of Rio Grande do Sul (Southern Brazil). In the first 24 hours of admission, patients answered a questionnaire with clinical information and had peripheral blood collected for measurement of FPG. Patients were followed up during hospitalization and for 30 days for the presence of MACE. Statistical analyses were performed using the SPSS 15.0 with the chi-square or Fisher Exact test (categorical variables) and the Student t test (numerical variables). Multivariate analysis was performed.

Results: 580 patients were included in the study. Mean age was 61.2 (±12.3) years, with 38.6% of the patients (224) ≥65 years old, and 67.7% (393) were male. Multivariable analysis showed that, after 30 days of follow-up, only FPG (OR= 1.01, 95% CI:1.00-1.01, P= 0.001) was associated with MACE in both age groups.

Conclusion: Admission FPG was an independent predictor for MACE in the early phase of ACS. (Arq Bras Cardiol 2012;98(3):203-210)

Keywords: Acute coronary syndrome; blood glucose; age of onset; prognosis.

Introduction

The leading cause of morbidity and mortality in Brazil and worldwide are cardiovascular diseases (myocardial infarction, stroke and peripheral arterial disease)[1,2].

Aging is the most important risk factor for mortality after ACS[3-5]. In 2004, 35% of all deaths among individuals aged ≥ 65 years in the U.S. were due to ACS[3,4]. ACS mortality rates are around 2.1% for individuals under 55 years old, but around 26.3% for those older than 85 years[3,4]. Among those who survive the acute stage, the risk of mortality remains high in long-term follow-up. The prognostic score GRACE (Global Registry of Acute Coronary Events) showed that the mortality rate among individuals between 75 and 84 years old was 15% during the first year after ACS, with rates of 25% for patients ≥ 85 years old. The probability of death one year after an acute episode for 75-year-old patients was one in five, and for ≥ 85-year-old individuals it exceeded one in four[3-5].

The number of studies with samples of elderly patients large enough for reliable estimation of results is still low[6]. In the last decade, more than half of all studies with ACS patients failed to include ≥ 75-year-old individuals. This age group was present in only around 9% of large studies[7]. After 1990, the tendency to exclude older individuals from large studies decreased, but it still persists[8].

Most studies have evaluated the association between admission blood glucose levels and prognosis following ACS[9-18]. More recent publications have shown the clinical relevance of fasting glucose level in ACS[19-27]. Studies that assessed adequately fasting plasma glucose (FPG) levels in acute myocardial infarction (AMI) patients show that it is a predictor for complications after AMI, and may even be better than admission FPG to predict in-hospital and short-term mortality[19,25,27]. Another study has also shown that FPG was a good predictor of long-term mortality in non-diabetic AMI patients[19]. In some other studies, however, no association between admission FPG and adverse events after ACS was observed in long-term follow-up[28,29].

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To our knowledge, no study has evaluated the role of FPG as a predictor of progression to ACS among different age groups. This study aims to assess the association between fasting glucose levels and major cardiovascular events (death, reinfarction and surgical and/or percutaneous coronary artery bypass grafting) in patients with ACS according to age (<65 years and ≥ 65 years).

Methods

This contemporary cohort study evaluated 580 consecutive patients who were hospitalized for ACS (unstable angina or myocardial infarction with or without ST segment elevation) at the Institute of Cardiology of Rio Grande do Sul. Among these 580 patients, 199 were selected from March 2002 to November 2002, and the other 381 patients were selected from November 2006 to January 2008, with the same methodology. The following criteria were used for diagnosis of ACS: 1) unstable angina: clinical picture, abnormal resting electrocardiogram (ST segment depression greater than 1 mm in at least two leads, or inversion of T wave) and no alteration of cardiac enzymes (creatine phosphokinase or total CK and creatine phosphokinase isoenzyme or CK-MB); 2) AMI without ST segment elevation: clinical picture, absence of ST segment elevation in resting electrocardiogram and elevated cardiac enzymes (total CK and CK-MB); and 3) AMI with ST segment depression: clinical picture, changes in resting electrocardiogram (ST segment elevation of at least 2 mm in two subsequent derivations) and elevated cardiac enzymes (total CK and CK-MB).

Patients with any type of systemic inflammatory disease (collagenosis), malignancy, HIV+ patients (as reported) or with current or recent use (less than one month) of corticosteroids or non-hormonal anti-inflammatory drugs were excluded. Due to technical problems, blood glucose levels could not be determined in three of the 583 patients initially evaluated, so the final sample was composed of 580 patients. This study was approved by the IC/FUC Committee of Ethics in Research on 01/12/06 (UP 3881).

During the first 24 hours after admission, patients signed an informed consent, which was previously approved by the Ethics Committee of the institution, and answered a questionnaire. The variables evaluated were: age, gender, skin color, weight, height (referred to by the patient) and waist circumference. The body mass index was calculated using the formula weight/height squared. Waist circumference was measured according to the guidelines established by the I Brazilian Guideline for Diagnosis and Treatment of Metabolic Syndrome, of the Brazilian Society of Cardiology[30].

Risk factors (family history of ischemic heart disease, smoking, diabetes, dyslipidemia, hypertension, physical inactivity and alcohol use), previous diseases, current medication and treatment received during hospitalization were also recorded. Patients were considered to have family history of ischemic heart disease when they had a first-degree relative younger than 55 years or 65 years (when male or female, respectively) diagnosed with coronary artery disease or other atherosclerotic disease; were defined as smokers if they had the habit of smoking, and ex-smokers if they had quit smoking at least one year earlier. Patients were considered as diabetics when they presented previous diagnosis of the disease and/or using antidiabetic drugs. The classification of systemic arterial hypertension depended on diagnosis prior to admission and/or use of antihypertensive drugs. Individuals were considered sedentary when regular physical activity (more than 3 times per week or more than 30 minutes at a time) was not reported. Dyslipidemic patients included those who had used statins and/or had LDL cholesterol >130 mg/dL and/or HDL cholesterol <40 mg/dL or <45 mg/dL (for males or females, respectively) and/or triglycerides >150 mg/dL. Individuals with body mass index ≥30 kg/m^2 were considered obese. Patients were also evaluated for regular consumption of alcoholic beverages.

After answering the questionnaire, blood samples were collected with patients in the supine position. The samples were analyzed for FPG levels, total CK and CK-MB, among other tests, at the clinical laboratory of Institute of Cardiology of Rio Grande do Sul. Blood glucose levels were measured using commercially available kits (*Boehringer Mannheim Diagnostics*). CPK and CPK-MB were also evaluated by the kinetic method.

All laboratory tests were conducted in a single sample, collected after 12 hours of fasting, within the first 24 hours of onset of coronary ischemia (determined by the clinical picture associated with enzymatic and/or electrocardiogram, as previously described).

Patients were followed up for 30 days after ACS, and major cardiovascular events, including death, reinfarction and surgical and/or percutaneous coronary artery bypass grafting were recorded. Reinfarction was defined as occurrence of at least two of the following: recurrence of initial pain lasting more than 30 minutes and/or new increase of the ST segment in the affected wall and/or new increase of enzyme levels to at least twice the previous level, if already normalized, or at least 50% the previous value while still not normalized, and surgical and/or percutaneous coronary artery bypass grafting.

The sample size was calculated using the PEPI software (Programs for Epidemiologists) version 4.0, based on a study of Duarte et al[20]. The minimum sample size required to achieve a power of 90%, a significance level of 5%, an average standard deviation of 65 mg/dL glucose in each group (with and without major cardiovascular events) and a difference of 24.9 mg/dL between the means, was determined as a minimum of 149 patients in each group, totaling 298 patients.

The statistical analysis was performed with the SPSS software, version 15.0. Numerical variables were described as mean and standard deviation. Categorical variables were described as absolute and relative frequencies. Chi-square or Fisher Exact test was used for categorical variables and the Student *t* test was used for numerical variables. Fasting plasma glucose levels were analyzed as a continuous variable.

Initially, results obtained during the two different collection periods (2002 and 2006-2008) were compared. Since no significant differences were observed between them, especially in relation to the description of the sample, we chose to present the unified results.

The variables with p values <0.10 in the bivariate analysis were included in a logistic regression model to assess the role of FPG as an independent predictor of clinical outcomes. $p \leq 0.05$ was considered to be statistically significant.

Models for bivariate and multivariate logistic regression were used to calculate the odds ratio (OR).

The effect of the interactions of the variables included in the logistic regression model with age was evaluated.

Results

The mean age of the 580 patients evaluated was 61.2 (± 12.3) years, 38.6% (224) were aged ≥ 65 years, and 67.7% (393) were male.

The analysis of the distribution of ACS types showed that 65.3% (379) of the patients were hospitalized for AMI with ST segment elevation, with the highest frequency for extensive anterior AMI (98 patients, 25.9%), followed by AMI without ST segment elevation (103 patients, 17.7%) and unstable angina (98 patients, 16.9%).

In this sample, 79.6% (462) of the patients were sedentary, 68.3% (396) were hypertensive, 46.9% (272) were dyslipidemic, 41.5% (241) had a family history for ischemic heart disease, 40% (232) smoked, 23.8% (138) were diabetic, 20.3% (118) drank alcohol regularly and 20% (116) were obese. Among the 580 patients, 3.1% (18) could not be followed-up for 30 days, and were considered as losses. These patients were later contacted by telephone, or had their medical records reviewed, for verification of events.

During the 30 days of follow-up, 49.8% (289) of the patients had at least one of the outcomes (death, reinfarction, coronary artery bypass grafting, arrhythmia with hemodynamic instability, heart failure or new onset of angina after admission) and 14.8 % (86) experienced one of the major cardiovascular events (death, reinfarction or coronary artery bypass grafting). The incidence of reinfarction was 4.1% (24), of percutaneous and/or surgical coronary artery bypass grafting was 5.3% (31), of heart failure 23.1% (134), of arrhythmias with hemodynamic instability was 16.5 % (96), and the incidence of a new episode of angina after admission was 25.2% (146). The 30-day mortality was 6.4% (37). The average Δ t value was 10 hours.

Sixty-three percent (368) of the patients underwent primary angioplasty with stent placement, and 18.6% (108) received medical treatment alone.

The clinical characteristics of patients according to age groups are described in Table 1.

A significantly higher frequency of females (p<0.001), history of prior cerebrovascular accident (CVA) (p<0.001), heart failure (p=0.004), renal failure (p=0.011), hypertension (p=0.002), as well as greater use of oral anticoagulants (p=0.005), nitrate (p<0.001), beta-blockers (p=0.037), antiplatelet aggregant (p=0.010) and digital (p=0.006) was observed aged 65 years and over. This same group showed significantly lower frequencies of AMI with ST segment elevation (p=0.013), alcohol consumption (p<0.001), obesity (p<0.001), family history of ischemic heart disease (p=0.001) and smoking (p<0.001).

Analysis of outcomes (Table 2) showed that patients aged ≥ 65 years had a significantly higher proportion of combined events (p<0.001), death (p<0.001) and heart failure (p<0,001), and significantly lower frequencies of coronary artery bypass grafting procedures (p=0.014).

After adjusting for variables with P value <0.10 in the bivariate analysis (FPG, type of ACS, age, prior hypertension, previous stroke and previous renal failure), only fasting plasma glucose OR 1.005 (IC 95% 1.002-1.009; p<0.001) remained associated with major cardiovascular events in 30-day follow-up. The risk of major cardiovascular events was 1% higher for every unit (mg/dL) of elevation of fasting blood glucose levels (p<0.001). These data are presented in Table 3.

This same type of statistical analysis showed that, when the sample was stratified according to age, only FPG remained significantly associated with major cardiovascular events in 30-day follow-up, in both groups. The risk of major cardiovascular events was 1% higher for every unit (mg/dL) of elevation of fasting blood glucose levels (p=0.001), for patients <65 years (p=0.018) as well as for those aged ≥ 65 years (P=0.026). These data are presented in Table 4. When the FPG levels were increased in 10 mg/dL, the risk of major cardiovascular events was 5% higher for both age groups (p=0.026).

No interaction was observed between age and incidence of FPG (p=0.477), CVA (p=0.683), ACS type (p=0.090), hypertension (p=0.882), and renal failure (p=0.678). Regardless of age, patients with major cardiovascular events had higher average FPG levels, as shown in Figure 1.

When age was analyzed as a continuous variable, only FPG levels (OR 1,005; CI 95% 1,002-1,009; p<0.001) and (OR=2.16; CI 95% 1.03-4.52) remained associated with major cardiovascular events in 30-day follow-up, for the entire group of patients (data not shown).

As the research was conducted in different periods (2002 and 2006/2008), it is important to observe that no differences were observed in the proportion of major cardiovascular events in the two periods (χ^2=0.00, p=0.999). In 2002, 14.6% (29/199) of the patients had major cardiovascular events, whereas during the period between 2006 and 2008 this outcome was seen in 15% (57/381) of the patients.

When patients were categorized as diabetic and non-diabetic, the same type of statistical analysis showed that, FPG levels associated with major cardiovascular events only for the non-diabetic group non-diabetic group (OR 1,01; CI 95% 1,00-1,01). None of the other variables were associated with major cardiovascular events.

Table 1 - General characteristics of the sample according to different age groups

General characteristics	< 65 years (n = 356)	≥ 65 years (n = 224)	p
Gender (%)			
Female	95 (26.7)	92 (41.1)	< 0.001
Male	261 (73.3)	132 (58.9)	
Diagnosis n (%)			
UA/AMI without elevation	109 (30.6)	92 (41.1)	0.013
ST elevation AMI	247 (69.4)	132 (52.9)	
Previous diseases n (%)			
Carotid	2 (0.6)	6 (2.7)	0.078
AMI	72 (20.2)	59 (26.3)	0.107
PVD	23 (6.5)	24 (10.7)	0.095
CVA	15 (4.2)	28 (12.5)	< 0.001
DM	88 (24.7)	50 (22.3)	0.575
HF	6 (1.7)	15 (6.7)	0.004
RF	4 (1.1)	11 (4.9)	0.011
Risk factors n (%)			
SAH	226 (63.5)	170 (75.9)	0.002
Alcohol	101 (28.4)	17 (7.6)	< 0.001
Dyslipidemia	167 (46.9)	105 (46.9)	1.000
Obesity	90 (25.3)	26 (11.5)	< 0.001
FH	168 (47.2)	73 (32.6)	0.001
Smoking	182 (51.1)	50 (22.3)	< 0.001
Sedentary	277 (73.8)	185 (82.6)	0.198
Prev Med n (%)			
ACEI	130 (36.5)	91 (40.6)	0.366
Statin	61 (17.1)	43 (19.2)	0.604
Diuretic	62 (17.4)	54 (24.1)	0.060
Anticoagulant	1 (0.3)	8 (3.6)	0.005
Oral anti-diabetic	48 (13.5)	24 (10.7)	0.386
Insulin	11 (3.1)	4 (1.8)	0.484
Nitrate	53 (14.9)	61 (27.2)	< 0.001
Beta-blocker	92 (25.8)	77 (34.4)	0.037
APA	124 (34.8)	103 (46)	0.010
Digital	4 (1.1)	12 (5.4)	0.006

** Pearson chi-square test; UA - unstable angina; AMI without elevation - acute myocardial infarction without ST segment elevation; ST segment elevation AMI - acute myocardial infarction with ST-segment elevation; AMI - acute myocardial infarction, PVD - peripheral vascular disease; CVA - cerebrovascular accident; DM - diabetes mellitus; HF - heart failure; RF - renal failure; SAH - systemic arterial hypertension; FH - family history; ACEI - angiotensin converting enzyme inhibitor; APA - antiplatelet aggregant.*

Discussion

This cohort study showed that admission FPG levels of patients who were hospitalized for ACS was a predictor for major cardiovascular events in 30-day follow-up, regardless of age.

Investigating a smaller sample of patients (n=199), we have previously reported a statistically significant association between high-sensitivity C-reactive protein (hs-CRP) and high FPG levels and in-hospital events (re-infarction, angina pectoris, heart failure, ventricular fibrillation and death) after ACS[20]. A recently published study evaluated 13,526 patients from the Global Registry of Acute Coronary

Table 2 - Incidence of outcomes according to age group

Outcome	< 65 years (n = 356)	≥ 65 years (n = 224)	p
Major CV events	45 (12.6%)	41 (18.3%)	0.080
Combined events	152 (42.7%)	137 (61.2%)	< 0.001
Death	8 (2.2%)	29 (12.9%)	< 0.001
Reinfarction	13 (3.7%)	11 (4.9%)	0.598
Coronary artery bypass grafting	26 (7.3%)	5 (2.2%)	0.014
HF	49 (13.8%)	85 (37.9%)	< 0.001
Arrhythmia	50 (14%)	46 (20.5%)	0.053
Angina	86 (24.2%)	60 (26.8%)	0.541

Major CV events - major cardiovascular events (death, reinfarction and coronary artery bypass grafting); Combined events - major CV events and/or heart failure, arrhythmia or new episode of angina after hospitalization; HF - heart failure.

Table 3 - Predictors of major cardiovascular events in 30 day follow-up (multivariate analysis)

Variable	OR	95% CI	p
Fasting glucose level	1,005	1.002-1.009	0.001
Type of ACS (AMI with elevation)	1.28	0.75-2.17	0.354
Age group (≥ 65 years)	0.72	0.44-1.17	0.189
Prior SAH	0.65	0.37-1.15	0.141
Previous CVA	0.74	0.22-1.96	0.410
Prior RF	0.40	0.12-1.32	0.135

OR - Odds ratio; CI - confidence interval; ACS type - type of acute coronary syndrome; AMI with elevation - acute myocardial infarction with ST segment elevation; SAH - systemic arterial hypertension; CVA - cerebrovascular accident; RF - renal failure.

Events (GRACE) and showed that, after adjusting for the variables of the GRACE score, higher levels of FPG levels were associated with higher mortality rates during hospitalization as well as six months after ACS (AMI with or without ST segment elevation and unstable angina).

Whereas most studies investigate the role of admission blood glucose levels as a predictor for complications after AMI[9-18], we have analyzed the role of FPG as a predictor of outcome after ACS. Other reports indicate the probable superiority of fasting glucose level as a predictor of outcome after ACS. Vivas D et al assessed 547 patients who were hospitalized for ACS, and observed that fasting glucose level was more important than admission glucose level as a predictor of death and reinfarction during hospitalization. The superiority of fasting glucose level as compared to admission glucose level in predicting adverse events after ACS may be explained by different factors. Modifications in circadian rhythms and in the period since the last meal could affect admission blood glucose values,

Table 4 - Predictors of major CV events in 30 day follow-up as compared with age (multivariate analysis)

Variables	OR	95% CI	p
<65 years			
Fasting glucose level	1.005	1.002-1.009	0.018
Type ACS (AMI with elevation)	0.87	0.42-1.76	0.700
Prior SAH	0.66	0.32-1.37	0.268
Previous CVA	0.33	0.10-1.07	0.670
Prior RF	0.39	0.03-4.12	0.440
≥ 65 years			
Fasting glucose level	1.01	1.00-1.01	0.026
Type ACS (AMI with elevation)	1.94	0.88-4.25	0.097
Prior SAH	0.65	0.26-1.65	0.372
Previous CVA	0.53	0.20-1.42	0.212
Prior RF	0.42	0.10-1.74	0.235

OR - Odds ratio; CI - confidence interval; ACS type - type of acute coronary syndrome; AMI with elevation - acute myocardial infarction with ST segment elevation; SAH - systemic arterial hypertension; CVA - cerebrovascular accident; RF- renal failure.

but not fasting plasma glucose levels, which may thus represent in a more appropriate way the actual metabolic state of the patient. Moreover, in patients presenting a very unfavorable clinical course during the first hours after ACS, a growing increase in FPG could reflect a worsening of the metabolic state and would usually be associated with more severe situations[27, 31-33].

One important factor to consider in the present study is that, different from most of the large studies, it includes a significant number of elderly patients (almost 40% of the sample were aged ≥65 years). Information on elderly individuals is generally inferred from data obtained in studies with younger individuals, which may lessen their significance. The inclusion in this study of a considerable number of elderly patients aimed at investigating a possible influence of age on this association. In a retrospective study including a large number of elderly people (141,680), only the role of admission blood glucose level as a predictor of adverse events after AMI was investigated[14]. An association was observed between admission glucose level and mortality after AMI in both 30-day and one year follow-up, especially for patients with no history of diabetes mellitus. However, to our knowledge this is the first study to assess the prognostic value of fasting glucose levels after ACS in a sample with a representative number of elderly patients.

Alterations in the glucose metabolism are frequently observed in cases of ACS. Verges et al[26], in a recent report, showed that 25% of a cohort of 2,353 AMI patients had impaired fasting glucose, between 100-126 mg/dL. Furthermore, they demonstrated that glucose levels between 110-126 mg/dL were an important predictor for

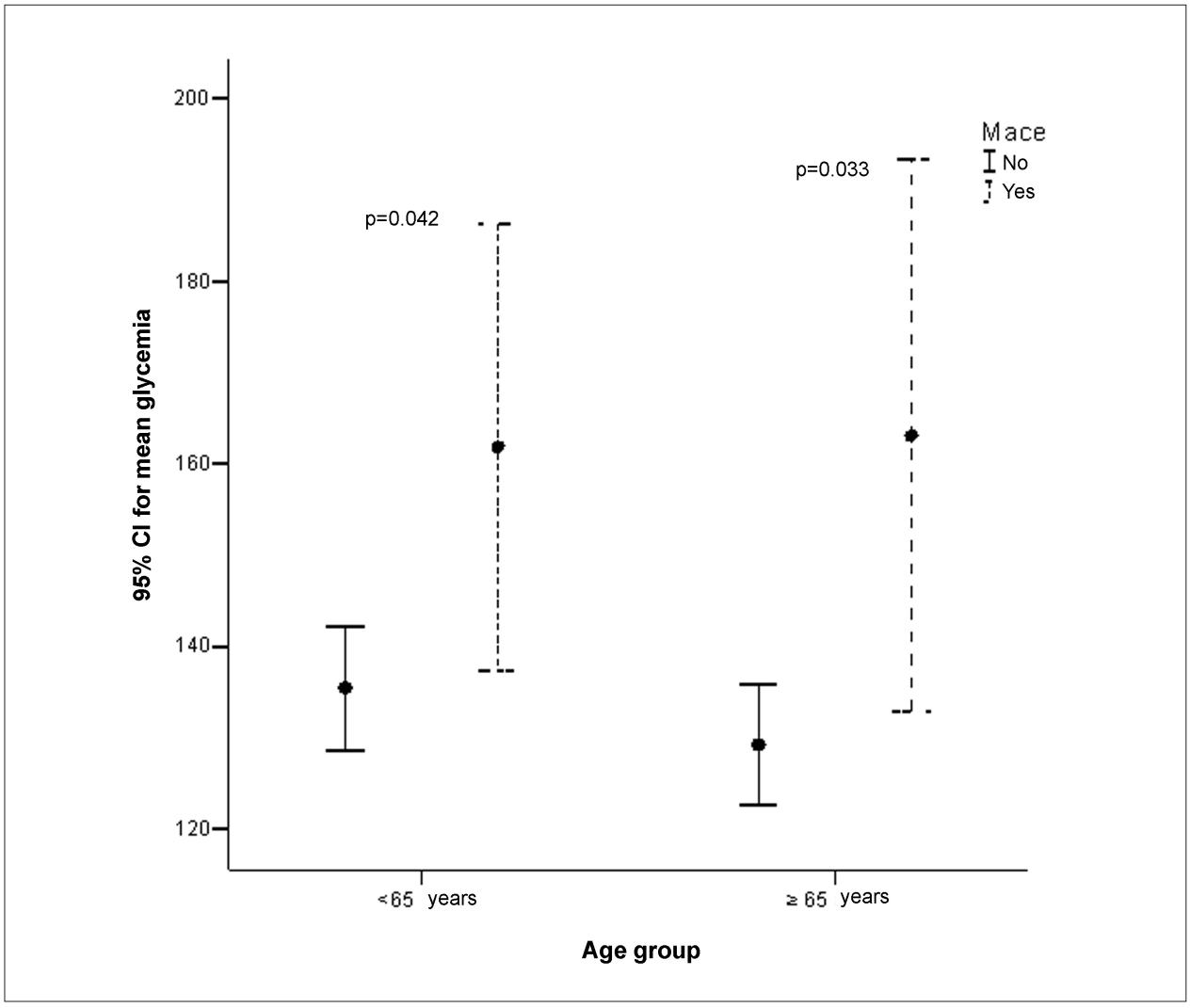

Figure 1 - *Average fasting glucose (mg/dL) and presence or absence of major cardiovascular events in each age group (CI: 95%).*

the onset of severe congestive heart failure after myocardial infarction and cardiovascular mortality in 30 days, even with adjustment for possible confounding factors[26]. Therefore, the identification of prognostic factors for the ACS is of great importance, allowing closer monitoring and treatment of patients with increased risk of adverse events, possibly improving survival rates. Furthermore, FPG represents a marker of good applicability, since it is easy to determine and has low cost.

Some questions about the association between FPG and mortality rate and/or complications after ACS remain to be answered. The exact values or ranges of blood glucose values that represent a higher risk for adverse events are not known. Another question is whether hyperglycemia would be a direct mediator of increased mortality and complication rates or just a marker of greater disease severity. What would be the most suitable methods for its determination? How should it be monitored? Would there be clinical benefits related to a reduction of blood glucose levels? Which targets should be set? Since hyperglycemia seems to have greater impact on non-diabetics, would the type of intervention and glucose values representing greater risk for complications after ACS differ between diabetic and non-diabetic patients? [31-33].

In a recent publication, Kosiborod[32] reviewed the results of several studies and suggested that admission glucose levels indicating a higher risk of short-term mortality should be higher than 110-120 mg/dL for non-diabetics and 200 mg/dL for diabetics. The American Heart Association (AHA) guidelines recommend intensive glycemic control for critically ill patients presenting blood glucose >180 mg/dL at admission for AMI[31]. Recent studies are highlighting the importance of persistent hyperglycemia, as assessed through frequent evaluations of blood glucose, as a predictor of complications after AMI[34]. These observations, however, should be confirmed in clinical trials[34].

Most studies have assessed only mortality after AMI. This study included the investigation of complications occurred after episodes of unstable angina. Clinical outcomes assessed were of great relevance and interest. Moreover, not only mortality, but also other important outcomes such as re-infarction and coronary artery bypass grafting, were evaluated. Although the follow-up period was only 30 days, we observed a significant frequency of complications, represented by almost half of the sample (49.8%).

Another aspect to consider in the present study is the rigor of the methodology, with sample collection after a 12-hour fast for all patients and a period of at most 24 hours of onset of ACS.

Conclusion

This study demonstrated that admission fasting blood glucose levels of patients who were hospitalized for ACS is an independent predictor of major cardiovascular events in 30-day follow-up, in both age groups.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

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