ORIGINAL MANUSCRIPT

Intensive Glycemic Control in Patients with Acute Myocardial Infarction: Diabetes Time Duration Counts!

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Abstract

Background: Cardiovascular disease (CVD) is the leading cause of death in patients with diabetes. The presence of type 2 diabetes mellitus (T2DM) puts the patients with and without history of myocardial infarction at risk for significant cardiovascular risk.
Objective: To evaluate the prognostic impact of the time of duration and metabolic control of T2DM in a population hospitalized for acute coronary syndrome.
Methods: Retrospective study of 731 consecutive patients admitted for acute coronary syndrome from May 2007 to August 2013. Patients were stratified into: Group 1 (n=297) with known diabetes mellitus (DM) (prior to hospitalization) and hemoglobin A1c (HbA1c) <6.5%; Group 2 (n=383) with known DM and HbA1c ≥6.5%; Group 3 (n=39), with recently diagnosed DM (during hospitalization) and HbA1c <6.5% and Group 4 (n=12) recently diagnosed with DM and HbA1c ≥6.5%. The primary endpoint was death from all causes (cardiovascular and non-cardiovascular) at one year, and the secondary endpoint at two years of follow-up.
Results: The distribution by sex and age was similar in both groups. In-hospital mortality was also higher in Group 2 (4.4%). Mortality from all causes over one year was higher in Groups 1 (8.3%) and 4 (8.3%), and at two years was higher in Group 1 (9.8%). Group 3 had better prognosis.
Conclusion: Of the data presented, the authors consider that the diabetes time of duration is important to decide the therapy and adjust the target of metabolic control of patients with ACS.

Keywords: Diabetes mellitus; Myocardial infarction; Blood glucose

Introduction

Cardiovascular disease (CVD) is the leading cause of death in patients with diabetes. Patients with acute myocardial infarction (AMI), previously diagnosed with diabetes mellitus (DM), have worse short-term prognosis than those without diabetes.

Despite major advances in the diagnosis and treatment of cardiovascular disease and, specifically, in the treatment of acute coronary syndrome (ACS) with incredible impact on morbidity and mortality of AMI, type 2 diabetes mellitus (T2DM) also puts patients with and without history of myocardial infarction at significant cardiovascular risk[1,2]. The presence of diabetes doubles the risk adjusted for age for cardiovascular disease in men and triples it in women, according to the Framingham study, and remained as an independent risk factor, even after adjustment for age, hypertension, smoking, hyperlipidemia and left ventricular hypertrophy[3,4].

Hyperglycemia on admission is a predictor of poor outcome in diabetic and non-diabetic patients, and the

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ABBREVIATIONS AND ACRONYMS

- *ACS – acute coronary syndrome*
- *AMI – acute myocardial infarction*
- *DM – diabetes mellitus*
- *LBBB – left bundle branch block*
- *LVEF – left ventricular ejection fraction*
- *T2DM – type 2 diabetes mellitus*

role of an intensive glycemic control in ACS adjustment has been discussed[5]. The latest European guidelines on AMI with ST segment elevation suggest a "strict but not too strict" control of glucose to prevent hypoglycemia (blood glucose levels ≤198 mg/dL) and the American College of Cardiology/American Heart Association guidelines suggest the maintenance of blood glucose levels <180 mg/dL, regardless of a previous diagnosis of diabetes mellitus[6,7].

Another interesting question is: what is the real influence of diabetes duration on the occurrence of cardiovascular events? In some studies, the diabetes mellitus time of duration was a powerful independent risk factor for cardiovascular mortality, but this statement needs further study to be confirmed. The objectives of this study were to quantify the impact of prognosis of type 2 diabetes mellitus duration time in a population hospitalized for ACS and evaluate how metabolic control influences the prognosis of this specific population.

Methods

Retrospective observational study involving 731 consecutive patients (690 with known T2DM and 41 diagnosed during the hospital stay) admitted for ACS (33.2% with AMI with ST-segment elevation, 62.9% with AMI without ST-segment elevation, 3.8% with new or supposedly new left bundle branch block (LBBB) in a single coronary care unit from May 2007 to August 2013.

Patients older than 18 with knowledge or with diagnosis of type 2 diabetes mellitus were included in the study. Patients without hemoglobin A1c (HbA1c) measured or type 1 diabetes mellitus were excluded. Readmissions to the same coronary care unit were not considered for statistical analysis.

Diagnosis of ACS was based on clinical, electrocardiographic and analytical criteria, according to the instructions available at the time of hospital admission.

The sample population (n=731) was stratified into four groups: Group 1 (n=297) - known T2DM and hemoglobin A1c (HbA1c) <6.5%; Group 2 (n=383) - known T2DM and HbA1c ≥6.5%; Group 3 (n=39) T2DM newly diagnosed and HbA1c <6.5%; and Group 4 (n=12) T2DM newly diagnosed and HbA1c ≥6.5%.

Clinical, analytical and demographic data were retrospectively collected, using the computer software used in the coronary care unit. Since the data are systematically recorded for all patients, no data was missing for the parameters analyzed. Hemoglobin A1c was obtained on the first day and oral glucose tolerance test was measured on the third or fourth day after admission.

All patients underwent standard echocardiographic evaluation and coronary angiography and percutaneous coronary intervention, if indicated according to the instructions available at the time.

Follow-up was conducted by personal interview at the clinic, reviewing hospital records, by telephone and review of official mortality records.

This study has been approved by the Research Ethics Committee of the institution (no number).

The primary endpoint was death from all causes (cardiovascular or non-cardiovascular) in the first year of follow-up; and the secondary endpoint was death from all causes over two years of follow-up.

Statistical analysis

Continuous variables were normally distributed and assessed using the Shapiro-Wilk test, and expressed as means±standard deviations, and those with asymmetric distribution were expressed as medians (semiquartiles). Dichotomous variables were expressed as frequencies (percentages).

To compare data between the groups studied, analysis of variance was used for continuous data and the chi-square test (Fisher, as appropriate) for dichotomous data.

All variables with a significant value (p≤0.10) were tested for mortality using the multivariate Cox-regression testing. Variables with significant relevance between the groups in the univariate analysis (age, type of ACS, heart rate, Killip class on admission, left ventricular function, maximum troponin, minimum hemoglobin and previous use of acetylsalicylic acid, beta blockers and statins) were

included in the model to adjust the final analysis for all possible confounding factors. Kaplan-Meyer survival curves were constructed and compared using the log-rank test.

The entire analysis was performed using SPSS for Windows, version 16.0 (SPSS Inc.; Chicago, Illinois, USA). In this study, $p \leq 0.05$ was considered statistically significant.

Results

The baseline characteristics of the patients are listed in Table 1. Distribution by sex and age was similar between groups.

The groups studied (Group 1, Group 2, Group 3 and Group 4) were hospitalized with the following diagnoses: AMI with ST segment elevation (31.3%; 34.5%; 35.9%; 33.3%, respectively, from Group 1 to 4, with no significant difference); AMI without ST segment elevation (64.3%; 62.7%; 53.8%; 66.7%, respectively, from Group 1 to 4, with no significant difference); and LBBB (4.4%; 2.9%; 10.3%; 0.0%, respectively, from Group 1 to 4, with no significant difference).

The prevalence of cardiovascular risk factors was similar between the groups, except for high blood pressure, which was more prevalent in Group 1 (88.1%; 86.5%; 63.9%; 81.8%; $p<0.001$, respectively, from Group 1 to 4).

Group 4 had more three-vessel coronary artery disease compared to the other groups, even though it did not reach statistical significance (31.7%; 31.6%; 7.1%; 37.5%; respectively, from Group 1 to 4).

Table 1
Characteristics of the population studied

	Group 1 (%)	Group 2 (%)	Group 3 (%)	Group 4 (%)	p-value
Male sex	67.0	64.8	82.1	41.7	NS
Age in years (mean±SD)	71.0±11.0	69.0±11.0	68.0±12.0	69.0±10.0	NS
Family history	7.1	7.0	7.7	8.3	NS
Hypertension	88.1	86.5	63.9	81.8	<0.001
Dyslipidemia	89.1	89.1	70.4	83.3	NS
Smoking	7.7	7.8	12.8	25.0	NS
History of coronary artery disease	7.3	7.4	7.7	8.3	NS
History of ACTP	18.9	12.4	16.2	0.0	NS
History of CABG	6.2	6.7	12.8	0.0	NS
Coronary artery with no lesions.	12.6	9.3	17.9	12.5	NS
Three-vessel disease	31.7	31.6	7.1	37.5	NS
Aspirin	47.5	43.3	54.2	50.0	NS
Beta-blockers	35.0	27.8	33.3	37.5	NS
ACEI/ARB	43.3	50.7	45.8	37.5	NS
Statins	53.3	50.4	45.8	50.0	NS
Oral antidiabetic drugs	49.6	43.7	0.0	25.0	<0.001
Insulin	18.3	36.3	0.0	0.0	<0.001

ACEI – angiotensin-conversion enzyme inhibitor; ARA – angiotensin receptor blocker; CABG – coronary artery bypass grafting; PTCA – percutaneous transluminal coronary angioplasty; SD – standard deviation

The mean hospital stay (in days) was higher in Groups 2 and 4 (5.0±3.0; 7.0±4.0; 6.0±3.0; 7.0±3.0; p<0.001, respectively, from Group 1 to 4).

The average HbA1c level at admission was 5.4±0.8% in Group 1; 8.2±1.2% in Group 2; 5.8±0.3% in Group 3 and 7.2±1.0% in Group 4 (p<0.001). Creatinine on admission, hemoglobin levels and peak troponin I were similar between the groups (Table 2). Left ventricular ejection fraction (LVEF) assessed by echocardiography was also similar between the groups. With respect to cholesterol levels, LDL levels were higher in Group 4 (108.0±36.0 mg/dL; 119.0±38 mg/dL; 127.0±39.0 mg/dL; 132.0±52.0 mg/dL; p<0.001, respectively, from Group 1 to 4).

During the hospital stay (Table 3), Groups 1 and 2 were further treated with clopidogrel (92.3%; 90.1%; 70.9%; 66.7%; p<0.001, respectively, from Group 1 to 4) and less treated with glycoprotein IIb/IIIa (17.2%; 32.6%; 69.2%; 75%; p<0.001, respectively, from Group 1 to 4). After discharge, angiotensin-converting enzyme blockers/angiotensin receptor blockers were more often prescribed in Group 3 (65.0%; 77.3%; 94.9%; 66.7%; p<0.001, respectively, from Group 1 to 4).

Overall in-hospital mortality (Figure 1) was estimated at 3.8%; it was higher in Group 2 (3.4%; 4.4%; 2.6%; 0.0%; not statistically significant, respectively, from Group 1 to 4).

Mortality from all causes at one year of follow-up was higher in Groups 1 and 4 (8.3%; 4.5%; 5.4%; 8.3%; respectively, from Group 1 to 4), without statistical significance in the Kaplan-Meier analysis, log rank p=0.351) (Figure 2).

Figure 3 shows the two-year follow-up mortality (secondary endpoint), which remained high in Group 1 (9.8%) compared to the others: 8.3%; 5.4%; 8.3%, respectively, from Group 2 to 4, without statistical significance in Kaplan-Meier, log rank p=0.547).

Table 2
Laboratory and imaging characteristics

	Group 1 (mean±SD)	Group 2 (mean±SD)	Group 3 (mean±SD)	Group 4 (mean±SD)	p-value
Minimum hemoglobin (g/dL)	11.1±2.0	11.2±1.9	11.8±1.9	12.4±1.5	NS
Creatinine on admission (mg/dL)	1.5±1.4	1.5±1.3	1.6±1.8	1.3±0.4	NS
Peak troponin I (ng/mL)	35.8±65.4	36.4±63.3	32.7±39.8	30.1±44.3	NS
Total cholesterol (mg/dL)	163.0±44.0	180.0±56.0	189.0±50.0	187.0±71.0	<0.001
LDL (mg/dL)	108.0±36.0	119.0±38.0	127.0±39.0	132.0±52.0	<0.001
HDL (mg/dL)	40.0±11.0	40.0±11.0	45.0±11.0	38.0±10.0	NS
HbA1c (%)	5.4±0.8	8.2±1.4	5.8±0.3	7.2±1.0	<0.001
LVEF (%)	49.0±12.0	47.0±12.0	47.0±10.0	54.0±8.0	NS

HbA1c – glycated hemoglobin; HDL – high-density lipoprotein cholesterol; LDL – low-density lipoprotein cholesterol; LVEF – left ventricular ejection fraction; SD – standard deviation

Table 3
Medications used during hospitalization

Medications	Group 1 (%)	Group 2 (%)	Group 3 (%)	Group 4 (%)	p-value
Aspirin	94.9	96.3	94.9	100	NS
Clopidogrel	92.3	90.1	76.9	66.7	<0.001
Inhibitors of glycoprotein IIb/IIIa	17.2	32.6	69.2	75	<0.001
Beta-blockers	86.2	87.7	82.1	75	NS
ACEI/ARB	86.2	92.4	94.9	91.7	NS
Statin	98.0	97.9	97.4	100.0	NS

ACEI – angiotensin-conversion enzyme inhibitor; ARB – angiotensin receptor blocker

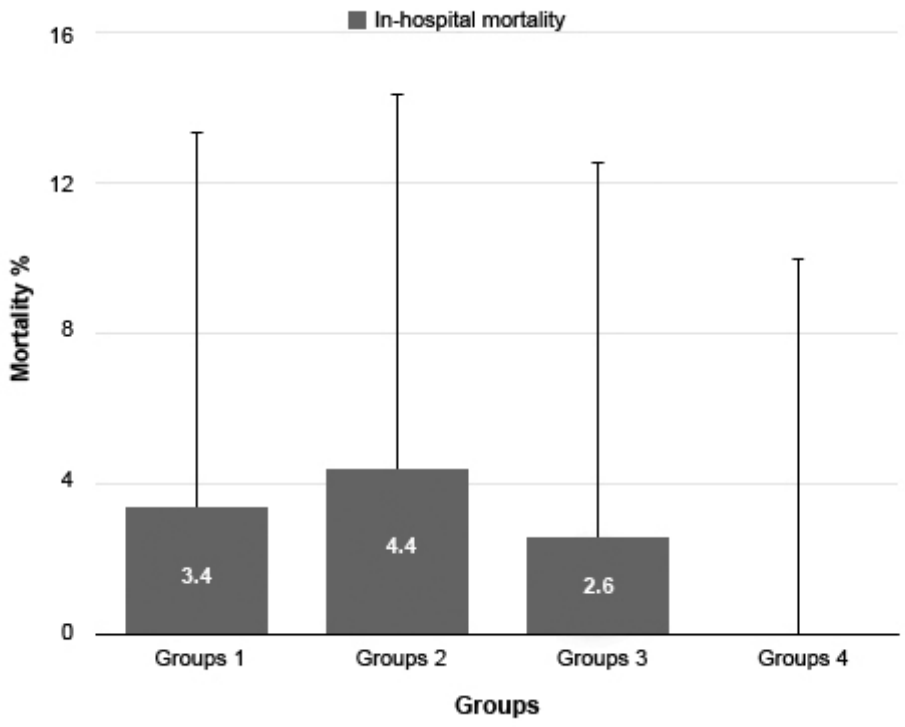

Figure 1
In-hospital mortality (%) of the patients studied

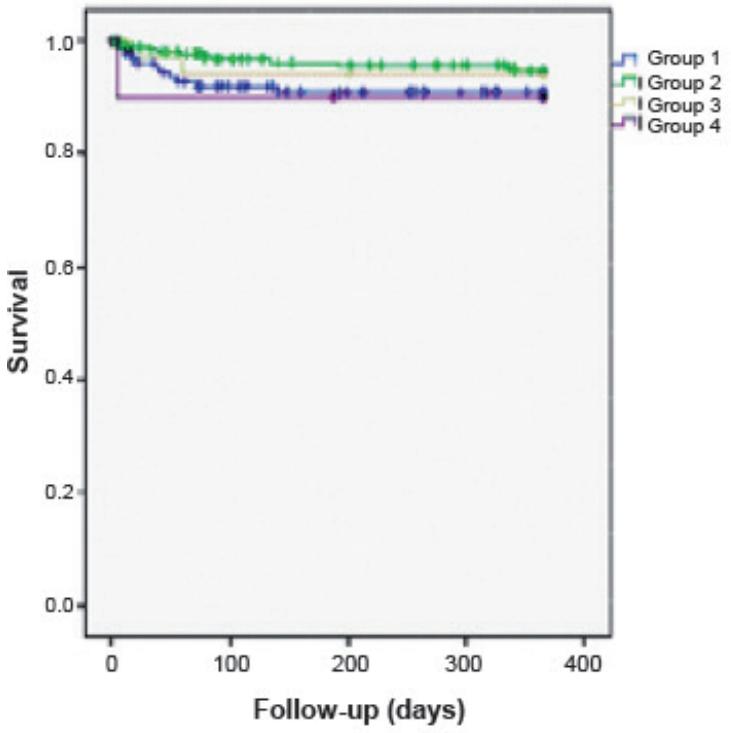

Figure 2
Kaplan-Meier analysis: all-cause mortality over one year of follow-up

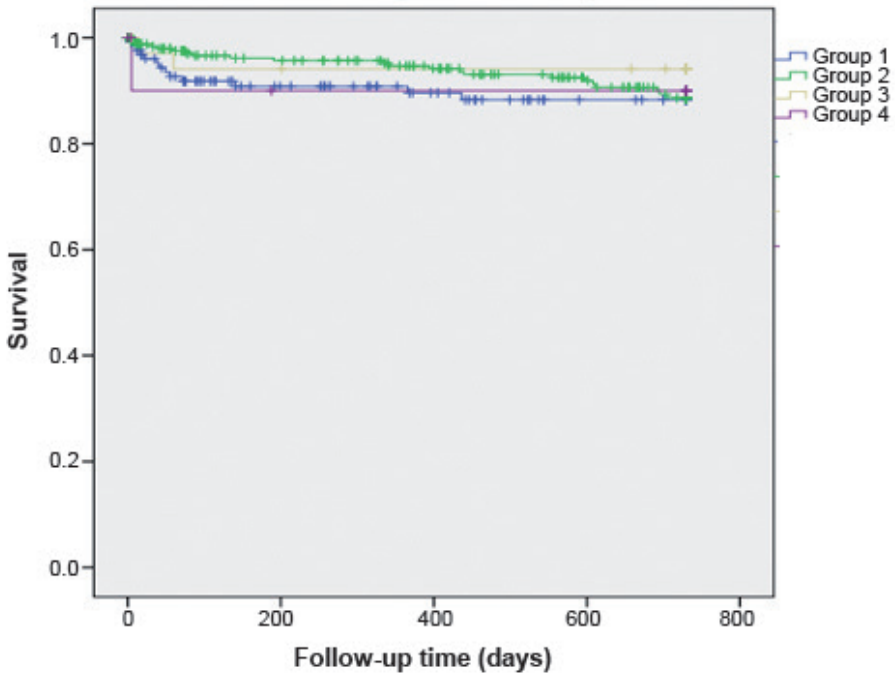

Figure 3
Kaplan-Meier analysis: all-cause mortality over two years of follow-up

Discussion

This population-based study emphasizes the magnitude of DM as an important risk factor for cardiovascular mortality.

As expected, in-hospital mortality was higher in Group 2 (4.4%), which included patients with known type 2 diabetes mellitus and worse glycemic control. The dysmetabolism effects on the cardiovascular system have been studied over the years[8,9]. It has been recently demonstrated that hyperglycemia could increase infarct size, inducing cardiac myocyte death (apoptosis) or exaggerate ischemia - repercussion of cell damage and consequent reduction in collateral coronary blood flow[10]. In this analysis, Group 2 had the highest peak value of troponin I (35.8±65.4; 36.4±63.3; 32.7±39.8; 30.1±44.3; without statistical significance, respectively, from Group 1 to 4) during the hospital stay, which also helps explain the higher in-hospital mortality occurred.

Considering the data presented, the following questions were asked: Should we treat all diabetic patients in the same way? Glycemic control should be strict for everyone? The answer seems to be no!

Three major randomized trials have shown no benefit in reducing cardiovascular events in diabetic patients at high cardiovascular risk under intensive glycemic control[11-14]. Evidence suggests that the potential benefits or dangers of intensive glycemic control depend on the presence or absence of significant atherosclerotic disease and DM duration[15,16].

Patients newly diagnosed with diabetes without significant cardiovascular disease and long life expectancy are good candidates for the establishment of intensive hypoglycemic therapy aiming at HbA1c values close to normal. On the other hand, diabetics with long evolution, with micro and/or macro-vascular complications and limited life expectancy should be subject to less strict metabolic control (target HbA1c between 7-7.5%)[17,18].

Analyzing the data presented in this study, Group 1 (known T2DM and hemoglobin A1c (HbA1c) <6.5%) had worse prognosis at one year (primary endpoint) and at two years (secondary endpoint). On the other hand, mortality was significantly lower in Group 3 (5.4%). This confirms the potential danger of high glycemic control in patients with established disease, and the benefits of intensive glycemic control at the time of diagnosis of DM[19].

Another reason for the better results found in Group 3 can be attributed to increased use of angiotensin-converting enzyme blockers (ACE)/angiotensin receptor blockers after hospital discharge (65.0%; 77.3%; 94.9%; 66.7%; p<0.001, respectively, from Group 1 to 4). There is growing evidence that aspirin, statins, ACE inhibitors and reduce cardiac death in such patients.

Two studies of prevention: HOPE (Heart Outcomes Prevention Evaluation) using ACE inhibitor in heart patients, and the LIFE (Losartan Intervention For Endpoint reduction in hypertension) using angiotensin II receptor blockers in hypertensive patients with proven left ventricular hypertrophy on electrocardiogram demonstrated to decrease the incidence of cardiovascular events in this high-risk population[20,21].

The growing number of DM in developed countries and the cardiovascular consequences related to it, in the diabetic population, deserve intensive risk reduction strategies in both primary and secondary prevention. Recommendations of observational and intervention studies specifically focused on diabetic populations may help physicians apply the guidelines and appropriate treatment in order to achieve the main goals of cardiovascular disease prevention[22].

Limitations

This is a retrospective study based on the records of a single center. The evaluation of post-discharge death was performed by reviewing medical records and phone interview with relatives, which contributed to the rate of patients lost during follow-up.

The primary and secondary endpoints were death from any cause. A significant number of patients died out of the hospital and the causes of death could not be assessed accurately. Some of the items of clinical history and previous risk factors were based on patient report (not always completely reliable). Despite all these aspects, the results can be extrapolated to other ACS populations, as the demographic and clinical data are

in line with those reported in the most published ACS records.

Conclusion

Patients with known T2DM and smaller HbA1c had long-term prognosis similar to those with newly diagnosed T2DM with worse metabolic control. Considering this data, it can be said that the diabetes duration is important to decide the therapy and the goal of metabolic control.

Patients newly diagnosed with T2DM should have tighter glycemic control than those with known T2DM.

Potential Conflicts of Interest

This study has no relevant conflicts of interest.

Sources of Funding

This study had no external funding sources.

Academic Association

This study is not associated with any graduate programs.

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