Predictors of adverse outcome in a diabetic population following acute coronary syndromes [21]

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Rev Port Cardiol 2011; 30 (03): 263-275

ABSTRACT

Introduction: People with diabetes are at increased risk for heart failure (HF), major adverse cardiovascular events (MACE) and death following acute coronary syndromes (ACS). It is important to recognize the most powerful predictors of these events after an ACS as early as possible, in order to address them more aggressively. This is particularly important considering that various studies have shown that this population is undertreated in the setting of ACS.
Objectives: To characterize a diabetic population presenting with ACS and to determine independent predictors of HF, MACE and mortality on follow-up.
Methods: This was a longitudinal, observational, retrospective study including 471 consecutive diabetic patients, both previously known and newly diagnosed, hospitalized for ACS in a single center between May 2004 and December 2006. A mean 12-month follow-up was conducted. Cox regression analysis was used to determine the independent predictors of HF, MACE and mortality on follow-up, divided into different periods – 1 month, 6 months and 1 year.
Results: Of the overall diabetic population, 67.3% were male and mean age was 69±11 years. Mean glomerular filtration rate (GFR) was 62±22 ml/min and mean left ventricular

Preditores de prognóstico adverso numa população com diabetes após síndromes coronárias agudas

RESUMO

Introdução: Os doentes com diabetes apresentam elevado risco de desenvolver insuficiência cardíaca (IC), eventos cardiovasculares adversos *major* (MACE) e morte após síndromes coronárias agudas (SCA). É importante reconhecer, o mais precocemente possível, os preditores mais poderosos destes eventos após uma SCA, de forma a adoptar uma abordagem terapêutica mais agressiva. Isto é particularmente relevante considerando que vários estudos mostraram que esta população tem sido subtratada no contexto de SCA.
Objectivos: Caracterizar uma população diabética com SCA e determinar preditores independentes de IC, MACE e morte no seguimento clínico.
Métodos: Estudo longitudinal, observacional, retrospectivo incluindo 471 doentes diabéticos, com diagnóstico prévio ou recém-diagnosticados, consecutivamente hospitalizados por SCA num único centro entre Maio de 2004 e Dezembro de 2006. Foi efectuado um seguimento clínico mediano de 12 meses. A análise de regressão de Cox foi usada para determinar

Recebido para publicação: Abril de 2010 • Aceite para publicação: Outubro de 2010
Received for publication: April 2010 • Accepted for publication: October 2010

ejection fraction (LVEF) was 50%. Diagnosis on admission was ST-elevation myocardial infarction (STEMI) in 31.3%, non-ST elevation myocardial infarction (NSTEMI) in 50.1%, unstable angina (UA) in 14.3% and ACS with left bundle branch block or pacemaker in 4.2%. Cardiac catheterization was performed in 55.6% of the patients during the index hospitalization. Mortality during hospitalization and at 1 year was 6.4% and 10.4%, respectively. The one-year MACE rate was 20.4% and hospitalization for HF occurred in 10.1% of the patients. The independent predictors of HF at 1 year were blood glucose on admission >184.5 mg/dl, GFR <63.8 ml/min, LVEF <46.5% and NSTEMI, while predictors of mortality were LVEF <40.5% and Killip class on admission >I. Blood glucose on admission >130.5 mg/dl and LVEF <49.5% were independent predictors of MACE, whereas cardiac catheterization was a protective factor.

Conclusion: Following ACS diabetic patients have high rates of mortality, HF and MACE. The low rate of invasive strategy may contribute to this situation. HF during hospitalization, whether by low LVEF or Killip class >I, and higher blood glucose on admission were powerful predictors of poorer outcome. Moreover, the use of recommended cardiovascular agents and procedures were protective factors. These findings suggest that diabetic patients should not be excluded from recommended cardiovascular interventions. Efforts should be made to identify these high-risk patients as early as possible in order to manage them carefully and aggressively to improve their poor prognosis.

preditores independentes de IC, MACE e morte no seguimento clínico, descriminados por vários períodos – 1 mês, 6 meses e 1 ano.

Resultados: Cerca de 67,3% da população diabética total era do sexo masculino e a idade média foi de 69 ± 11 anos. A taxa de filtração glomerular (TFG) média foi de 62 ± 22 ml/min e a fracção de ejecção do ventrículo esquerdo (FEVE) média foi de 50%. Relativamente ao diagnóstico na admissão, o enfarte agudo do miocárdio com supradesnivelamento de ST (EAMCSST) esteve presente em 31,3%, o enfarte agudo do miocárdio sem supradesnivelamento de ST (EAMSSST) em 50,1%, a angina instável em 14,3% e *o SCA com bloqueio completo de ramo esquerdo ou pacemaker em 4.2%*. Cerca de 55,6% dos doentes foram submetidos a cateterização cardíaca durante a referida hospitalização. As taxas de mortalidade durante a hospitalização e a 1 ano foram de 6,4% e 10,4%, respectivamente. A taxa de MACE a 1 ano foi de 20,4% e a hospitalização por IC ocorreu em 10,1% dos doentes. Os preditores independentes de IC a 1 ano foram a glicemia na admissão > 184,5 mg/dl, TFG < 63,8 ml/min, FEVE < 46,5% e EAMSSST, enquanto que os preditores de mortalidade foram FEVE < 40,5% e classe de Killip na admissão >1. Uma glicémia na admissão > 130,5 mg/dl e FEVE <49,5% foram os preditores independentes de MACE, enquanto que a realização de cateterização cardíaca foi um factor protector.

Conclusão: A população com diabetes apresenta elevadas taxas de mortalidade, IC e MACE após SCA. O baixo recurso à estratégia invasiva poderá contribuir para esta situação. A IC durante a hospitalização, revelada por baixa FEVE ou classe de Killip > 1, e uma glicemia na admissão elevada foram preditores poderosos de mau prognóstico. O uso dos agentes e procedimentos cardiovasculares recomendados foram factores protectores. Estes dados sugerem que os doentes diabéticos não devem ser excluídos das intervenções cardiovasculares recomendadas e que todo o esforço deve ser

Key words
Diabetes mellitus;
Acute coronary syndromes; Prognosis

feito para identificar estes doentes de alto risco o mais precocemente possível, tratá-los cuidadosa e agressivamente de forma a melhorar o seu pobre prognóstico.

Palavras chave:
Diabetes *mellitus*; Síndromes coronárias agudas; Prognóstico

INTRODUCTION

Diabetes is widely recognized as a powerful risk factor for cardiovascular disease. People with diabetes are especially prone to acute coronary syndromes (ACS) and heart failure (HF), and cardiovascular disease is their leading cause of death [1-4]. The prevalence of diabetes is rising and recent projections point to an increase from 171 million in 2000 to 366 million worldwide by 2030 [5], with "an expected" increase in the number of diabetic patients with coronary artery disease (CAD) and HF[2, 4, 6, 7]. Despite all advances in ACS treatment, with consequent improvements in prognosis in recent decades, diabetic patients presenting with ACS remain a particularly high-risk population, with worse in-hospital [1, 8-11] and long-term [2-4, 8, 9, 11-13] outcomes. Diabetes was found to be an independent adverse prognostic factor after ACS[8, 9, 12, 13], being associated with a twofold increase in risk of death compared to their non-diabetic counterparts [12]. The development of acute HF during the index hospitalization [1, 3, 8, 10] and post-discharge [3, 11] contributes to this outcome. This poor prognosis may be explained by the inherent pathophysiology of diabetes, the extent and severity of coronary artery disease in this population, the frequency of comorbidities and also the underuse of the recommended treatments in this subgroup [1, 4, 8-10, 13]. Although some data from registries and controlled studies have shown benefits from established cardiovascular strategies, diabetic patients are usually under-represented in clinical trials [4, 10]. Despite the widespread recognition that people with diabetes are at increased risk and have a dismal prognosis following ACS, little is known regarding predictors of HF, major adverse cardiovascular events (MACE) and mortality after discharge in this population. Because of the particularly high incidence of these complications, it is important to recognize their most powerful predictors as early as possible, in order to optimize the approach. The aim of our study was to characterize a "real-world" diabetic population presenting with ACS in terms of baseline characteristics and treatment patterns, to evaluate their in-hospital and follow-up outcomes, and to determine independent predictors of HF, MACE and mortality on follow-up.

METHODS

Study design and patient population

This was a longitudinal, observational and retrospective study including 471 diabetic patients out of a total of 1329 patients consecutively admitted for ACS to a single intensive coronary care unit, between May 2004 and December 2006. Patients with both previously known and newly-diagnosed diabetes were included. Diabetes was diagnosed during hospitalization by an oral glucose tolerance test (75 g) performed on the last day of hospitalization. Patients with two-hour blood glucose ≥200 mg/dl were classified as diabetic.

A database with standardized records was used to characterize the overall diabetic population in terms of clinical and demographic characteristics, cardiovascular risk factors, ACS

type, laboratory and electrocardiographic data, evidence-based pharmacological agents (previous, at admission and at discharge) and interventional therapies. Complications during hospitalization (including ventricular fibrillation, cardiogenic shock, cardiac arrest, recurrent myocardial infarction and acute pulmonary edema), as well as length of hospital stay, were recorded.

An invasive strategy was defined as cardiac catheterization performed during the first 72 hours of the index hospitalization, on either an urgent or a non-urgent basis, followed by percutaneous coronary revascularization when indicated and possible. Patients presenting with ST-elevation myocardial infarction (STEMI) at our center underwent primary angioplasty; only those patients who were, at presentation, outside the therapeutic window and had no clinical or electrocardiographic signs of ischemia were excluded. Generally, these patients also underwent early cardiac catheterization (first 72 hours) during the index hospitalization. Complete revascularization was defined as the successful percutaneous revascularization of all significant coronary lesions (≥75%) detected in the main epicardial vessels.

Left ventricular ejection fraction was calculated by echocardiography, using Simpson's biplane method.

A mean 12-month follow-up was conducted by telephone interview or personal communication. Rehospitalization for HF management, unplanned revascularization or death were recorded. HF during follow-up was defined as hospitalization for signs and symptoms of HF. MACE was defined as the combined result of cardiovascular death, non-fatal myocardial infarction, re-admission for unstable angina (UA) or unplanned non-urgent percutaneous coronary intervention (PCI), which excludes PCI in the setting of a new ACS, at 1 month, 6 months and 1 year. The investigation was conducted according to the principles outlined in the Declaration of Helsinki.

Statistical analysis

Statistical analyses were performed using SPSS version 13. Results are expressed as mean ± standard deviation or quartiles for continuous variables and as frequencies and percentages for categorical variables. The frequencies of categorical variables in the two groups were compared by the chi-square test or Fisher's exact test. Continuous variables were compared by the two-tailed Student's t test or the Mann-Whitney test. Independent predictors of HF, MACE and mortality after ACS were identified by multivariable Cox regression analysis using the forward method of variable selection (with a likelihood ratio test). Predetermined clinically significant variables were entered into the model: age, gender, cardiovascular history (hypertension, dyslipidemia, smoking status, previous stroke, previous myocardial infarction, PCI, coronary artery bypass graft surgery, peripheral vascular and cerebrovascular disease); previous medication with aspirin, clopidogrel, angiotensin-converting enzyme inhibitors (ACEIs), beta-blockers, calcium channel blockers, statins and nitrates; total and LDL cholesterol; troponin and CK-MB; heart rate and Killip class on admission; body mass index; electrocardiographic data (normal, left bundle branch block [LBBB], atrial fibrillation [AF], sinus rhythm); type of ACS (STEMI, non-ST elevation myocardial infarction [NSTEMI] or UA); LVEF, GFR, admission blood glucose, cardiac catheterization, medical treatment during the initial 24 hours of hospitalization (aspirin, clopidogrel, nitrates, beta-blockers, ACEIs, calcium channel blockers, statins) and medical treatment at discharge (aspirin, clopidogrel, beta-blockers, statins and ACEIs). Discrimination and calibration were evaluated by the area under the receiver operating characteristic curve and the Hosmer-Lemeshow goodness-of-fit test, respectively. The Kaplan-Meier method was used for cumulative survival analysis for each studied endpoint.

A p value of <0.05 was considered statistically significant.

RESULTS

Baseline characteristics

Diabetes, both previously known and newly

diagnosed, was present in 35.4% of the cases hospitalized for ACS in the study period, stndy period, being previously known in 81.7% of these cases, and diagnosed for the first time during hospitalization in the remaining 18.3%. Of the total diabetic population 67.3% were male and mean age was 69.0±11.0 years. Hypertension and dyslipidemia were present in 80.5% and 80.7%, respectively, and 12.1% were current smokers. Previously known CAD was present in 64.5%, 21.8% had previous myocardial infarction; 9.6% and 7.4% had undergone percutaneous and surgical coronary revascularization, respectively, while 4.0% had previously known HF, 7.9% previous stroke and 5.3% peripheral arterial disease. Diagnosis on admission was STEMI in 31.3%, NSTEMI in 50.1%, UA in 14.3% and ACS with left bundle branch block or pacemaker in 4.2% (*Table I*). Of the total diabetic population, 20.2% were previously on insulin and 42.6% on oral hypoglycemic agents (*Table IV*).

Comparing the group undergoing a conservative strategy with those undergoing an invasive approach in terms of baseline characteristics, we found that the former included a higher proportion of women and the subjects were older and had a longer known diabetes duration and a higher prevalence of heart and renal failure (*Table II*).

Table I. **Baseline characteristics**

Total number of patients	471
Demographic data	
Male (%)	67.3
Mean age (years) (SD)	69.0±11.0
Type of ACS (%)	
ST-elevation myocardial infarction	31.3
Non-ST elevation myocardial infarction	50.1
Unstable angina	14.3
Left bundle branch block / pacemaker	4.2
Cardiovascular risk factors (%)	
Previously known diabetes	81.7
Newly diagnosed diabetes	18.3
Hypertension	80.5
Dyslipidemia	80.7
Smoking status	12.1
Stress / sedentary lifestyle	14.9
Family history of coronary artery disease	11.0
Cardiovascular history (%)	
Myocardial infarction	21.8
Coronary artery disease	64.5
Percutaneous coronary intervention	9.6
Coronary artery bypass grafting	7.4
Stroke	7.9
Heart failure	4.0
Peripheral vascular disease	5.3

SD: standard deviation

Hemodynamic, electrocardiographic and laboratory data

Regarding hemodynamic data on admission, about 20.6% of the patients presented with Killip class >1 and most had TIMI scores between 2 and 4. Mean heart rate on admission was 80.0±16.0 bpm. On the baseline ECG, LBBB was present in 6.8% of cases and AF in 9.3%.

Concerning laboratory data, mean GFR and blood glucose on admission were, respectively, 62.2±22.3 ml/min and 169.0 (132.7-224.3) mg/dl. Mean LVEF was 50.0±11%. Table III presents details of hemodynamic, electrocardiographic and laboratory parameters in this population.

Catheterization laboratory results and treatment patterns

Coronary angiography was performed in 55.6% of the patients, but only 46.7% actually underwent complete revascularization. Among these, stents were used in 65.9% and drug-eluting stents were the choice in 71.9%. Of those who underwent coronary angiography, 29.7% did not undergo PCI. Of these, 19% underwent coronary artery bypass graft surgery after discharge. Details of coronary lesions and interventions are shown in Table IV.

Table V describes the medical treatment used during the first 24 hours of hospitalization and at discharge.

All patients presenting with blood glucose >180 mg/dl on admission underwent intensive insulin perfusion to obtain target blood glucose between 90-140 mg/dl, in accordance with the protocol in use in our coronary care unit [17]. The remaining patients were treated with low doses of short-acting insulin, according to blood glucose values determined at two-hour intervals.

In-hospital outcomes

The mean length of stay was 6.0±4.0 days. About a third of the patients reached Killip class >I during hospital stay. The rate of pre-

Table II. **Baseline characteristics – comparison between groups according to the selected strategy**

	Invasive strategy	Conservative strategy	p
Total number of patients	262	209	-
Demographic data			
Male (%)	73.7	59.3	0.001
Mean age (years) (SD)	66.0±10.0	73.0±9.0	<0.001
Type of ACS (%)			
ST-elevation myocardial infarction	42.2	17.8	<0.001
Non-ST elevation myocardial infarction	37.5	65.8	<0.001
Unstable angina	16.3	11.9	0.179
Left bundle branch block / pacemaker	4.0	4.5	0.804
Cardiovascular risk factors (%)			
Previously known diabetes	77.9	85.6	0.031
Newly diagnosed diabetes	22.1	14.4	0.031
Hypertension	79.2	82.1	0.476
Dyslipidemia	79.2	82.6	0.373
Smoking status	15.6	7.7	0.009
Cardiovascular history (%)			
Myocardial infarction	80.8	74.4	0.120
Coronary artery disease	63.4	66.0	0.547
Percutaneous coronary intervention	12.1	6.3	0.042
Coronary artery bypass grafting	5.9	9.3	0.163
Stroke	6.9	9.1	0.365
Heart failure	1.4	8.0	0.029
Peripheral vascular disease	3.8	7.2	0.103
Glomerular filtration rate (ml/min) (P25-P75)	68.4 (55.6-81.9)	56.3 (41.1-72.1)	<0.001

SD: standard deviation

Table III. **Hemodynamic, electrocardiographic and laboratory data**

Hemodynamic data	
Heart rate, (bpm) (SD)	80.0±16.0
Systolic blood pressure (mmHg) (SD)	141.0±26.0
Diastolic blood pressure (mmHg) (SD)	73.0±14.0
Killip class I at admission (%)	79.4
Killip class II at admission (%)	17.8
Killip class III at admission (%)	1.5
Killip class IV at admission (%)	1.3
Left ventricular ejection fraction (%) (SD)	50.0±11.0
Electrocardiographic data (%)	
Normal	22.7
Sinus rhythm	85.6
Atrial fibrillation	9.3
Left bundle branch block	6.8
Laboratory parameters (P25-P75)	
Peak troponin I (ng/ml)	10.2 (2.3-32.0)
Peak CK-MB mass (ng/ml)	29.9 (7.0-116.7)
Triglycerides (ng/ml)	149.0 (107.0-205.0)
LDL cholesterol (ng/ml)	123.0 (99.0-147.0)
HDL cholesterol (ng/ml)	40.0 (35.0-47.0)
HbA1c (%)	6.5 (6.0-8.2)
GFR (ml/min)	62.0 (42.0-84.0)
Admission blood glucose (mg/dl)	169.0 (132.8-224.3)
BMI (kg/m²) (SD)	28.6±5.3

Hb: hemoglobin; GFR: glomerular filtration rate; BMI: body mass index; SD: standard derivation

specified in-hospital complications was 8.3% and mortality was 6.4% (*Table VI*).

Post-discharge outcomes

Follow-up was possible in 424 patients, representing 90% of the total population.

MACE and mortality rates at 1-year follow-up were, respectively, 20.4% and 10.4%. Of the overall population 10.1% were hospitalized for HF. Follow-up event rates in the different periods considered are listed in Table VI. Figures 1 and 2 represent the Kaplan-Meier curves for survival and MACE-free survival at 1-year follow-up.

Predictors of poor outcome on follow-up

Patient characteristics were evaluated to identify predictors of mortality, MACE and

Table IV. **Catheterization laboratory data (%)**

Catheterization during hospitalization	55.6
Normal coronary anatomy	12.6
1-vessel disease	38.2
2-vessel disease	20.2
3-vessel disease	28.2
Complete revascularization	46.7
Partial revascularization	23.6
No revascularization	29.7
Stenting	65.9
Drug-eluting stent	71.9
Number of stents per patient	
1	63.8%
2	26.2%
3	7.4%
4	0.7%
5	2.0%

Table V. **Pharmacological treatment**

	Previous treatment	Medication in first 24 hours	Medication at discharge
Aspirin (%)	40.1	96.4	89.4
Enoxaparin (%)	-	96.2	-
Clopidogrel (%)	16.4	75.8	48.2
GP IIb/IIIa (%)	-	57.3	-
Beta-blockers (%)	22.1	78.6	78.6
ACEIs (%)	45.4	93.2	89.0
Statins (%)	32.2	97.0	95.8
Diuretics (%)	27.8	38.2	MD
Nitrates (%)	22.7	40.8	MD
Ezetimibe (%)	MD	8.9	8.9
OHA (%)	42.0	32.0	MD
Insulin (%)	21.5	76.3	MD

GP IIb/IIIa: glycoprotein IIb/IIIa inhibitors; ACEIs: angiotensin-converting enzyme inhibitors; OHA: oral hypoglycemic agents; ND: no data.
MD: missing data.

Table VI. **Endpoints In-hospital and on follow-up**

In-hospital complication rate (%)	8.3
In-hospital mortality rate (%)	6.4
Mortality at 30 days (%)	3.1
Mortality at 6 months (%)	7.5
Mortality at 1 year (%)	10.4
MACE at 30 days (%)	7.2
MACE at 6 months (%)	16.3
MACE at 1 year (%)	20.4
Heart failure - 1 year (%)	10.1

MACE: major adverse cardiovascular events

HF development after an ACS. In multivariate Cox regression analysis, the main independent predictors of HF at one year were blood glucose on admission >184.5 mg/dl (OR 3.64), GFR <63.8 ml/min (OR 3.65), LVEF <46.5% (OR 2.7) and NSTEMI (OR 2.86). Independent predictors of mortality at one year were LVEF <40.5% (OR 3.53) and Killip class >I (OR 3.55) and independent predictors of MACE at one year were blood glucose on admission >130.5 mg/dl (OR 2.61) and LVEF <49.5% (OR 1.83). An invasive strategy was a protective factor against MACE (OR 0.53). The predictors of mortality, MACE and HF for the different follow-up periods considered are listed in Tables VII and VIII.

DISCUSSION

Data from recent registries in Europe show that diabetes prevalence among ACS patients is increasing, presently ranging from 29 to 35% [12]. This is in agreement with our results, in which diabetic patients represent 35.4% of the total ACS population, and is also comparable to that observed in the CRUSADE registry [10]. As previously reported by other authors [4], undiagnosed diabetes was present in a significant proportion of our population. Diabetic patients are at particularly high risk for cardiovascular events, as several studies and registries have shown. GRACE[1] and CRUSADE [10] revealed increased in-hospital mortality compared with non-diabetics. The Euro Heart Survey on Diabetes and the Heart and the OASIS registry also reported, respectively, increased 1 and 2-year mortality in diabetic patients with various presentations of coronary disease [16, 17]. In fact, some studies have revealed that this mortality may be as high as 7-18% at 30 days, 15-34% after 1 year, and up to 43% after 5 years [4]. Although diabetes status was not among the inclusion criteria in the GRACE risk prediction tool, it was included in the TIMI risk scores [12]. In our diabetic population the 1-year mortality rate was 10.4%; although still high, this value is slightly lower than those previously reported.

Current guidelines for management of ACS [12] include special considerations for diabetic patients. Several studies [11, 12, 18, 19], but not all [20, 21], have shown survival benefits from intensive insulin infusion protocols in diabetic ACS patients. European and American guidelines [4, 12, 22, 23] advocate tight glycemic control as soon as possible, if necessary with insulin infusion, in patients presenting with high glucose levels

Table VII. **Independent predictors of mortality on follow-up**

	OR	CI	p
Mortality at 30 days			
LVEF <39.5%	15.45	3.05-78.35	0.001
BMI <29.7 kg/m²	0.10	0.02-0.57	0.009
Statins during hospitalization	0.06	0.01-0.63	0.019
Mortality at 6 months			
LVEF <40.5%	3.27	1.30-8.27	0.012
Heart rate >101.5 bpm	3.96	1.57-10.03	0.004
Killip class >I	3.67	1.51-8.89	0.004
Mortality at 1 year			
LVEF <40.5%	3.53	1.69-7.40	0.001
Killip class >I	3.55	1.70-7.40	0.001
MACE at 30 days			
Female	0.34	0.13-0.92	0.033
Invasive strategy	0.43	0.21-0.90	0.026
MACE at 6 months			
Previous medication with statins	0.34	0.14-0.82	0.016
Invasive strategy	0.51	0.26-0.98	0.044
LVEF <51.5%	1.84	0.94-3.58	0.075
MACE at 1 year			
Invasive strategy	0.53	0.31-0.91	0.021
Admission blood glucose >130.5 mg/dl	2.61	1.11-6.10	0.027
LVEF <49.5%	1.83	1.07-3.14	0.028
Heart failure at 1 year			
Admission blood glucose >184.5 mg/dl	3.64	(1.65-8.06)	0.001
GFR <63.8 ml/min	3.65	(1.70-7.83)	0.001
LVEF <46.5%	2.7	(1.14-6.37)	0.023
NSTEMI	2.86	(1.23-6.60)	0.014

CI: 95% confidence interval; BMI: body mass index; LVEF: left ventricular ejection fraction; GFR: glomerular filtration rate; NSTEMI: non-ST elevation myocardial infarction.

(serum glucose >180 mg/dl). Although the target glucose levels are not well defined, a reasonable goal was considered to be near-normal blood glucose (90-140 mg/dl). "Nevertheless, recent studies have drawn attention to the inherent risks of hypoglycemia in these high-risk subjects, leading to the proposal of more moderate glycemic levels."

Some reports have shown an additional protective role for the recommended cardiovascular drugs in this population. Although a major specific secondary prevention trial has not yet been conducted in a diabetic population, subgroup analysis from statins trials showed similar benefits to non-diabetics in coronary event reduction; these drugs are therefore recommended for all diabetic patients with cardiovascular disease, regardless of lipid profile[4]. Similar results have been found with ACEI trials, leading to their indication in this context[4]. Beta-blockers have been shown to reduce mortality and new coronary events, supporting their recommendation in tåhis setting[4]. However, beta-blockers have often been withheld[4] due to concerns over potential deterioration of metabolic control and blunting of hypoglycemia awareness and response[9, 13]. Finally, the addition of clopidogrel to aspirin is also proposed as a result of studies that have proved its benefit[4]. Regarding medical therapy and the international guidelines, we noticed in our population a low rate of prescription of the main cardiovascular drugs, particularly clopidogrel and beta-blockers, although we have no information on potential contraindications that could have limited their use. Explanations for the low rate of prescription of antiplatelet therapy may be the existence of gastrointestinal disease or the possibility of bleeding complications during hospitalization or in the future due to double antiplatelet therapy in an elderly and renally impaired population. The use of statins was a protective factor for the incidence of MACE at 6 months and mortality at 30 days, an observation in agreement with the studies referred to above, highlighting the importance of optimized medical treatment. It

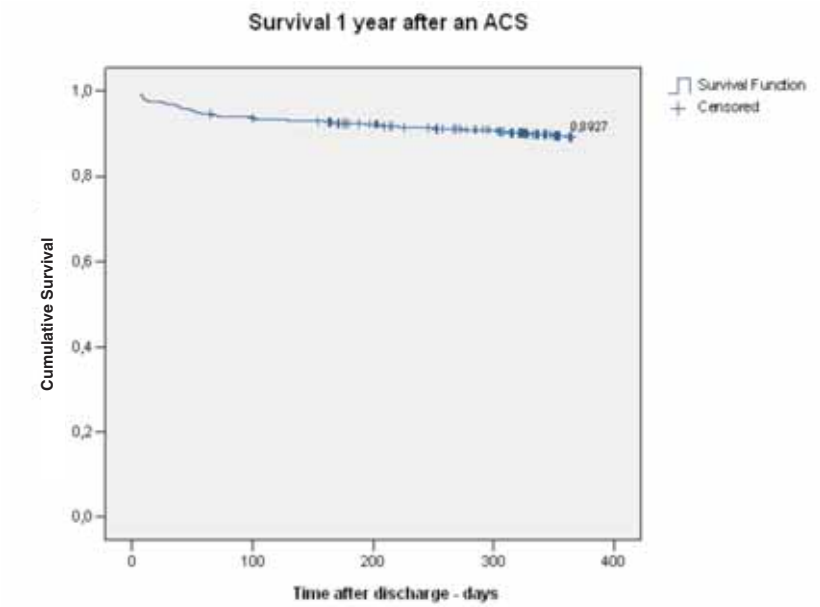

Figure 1. Kaplan-Meier curve for 1-year survival

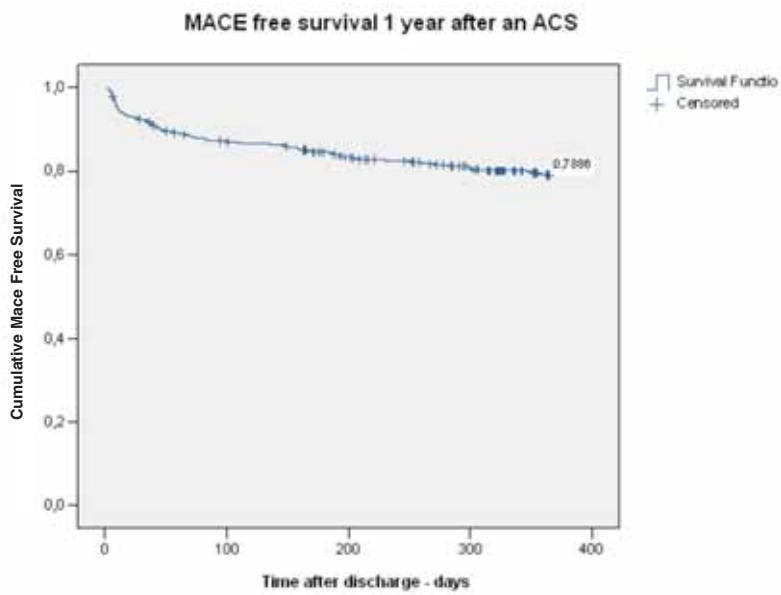

Figure 2. Kaplan-Meier curve for 1-year MACE-free survival

is, therefore, reasonable to assume that the prognosis of this diabetic population may be further improved by more frequent utilization of the recommended cardiovascular treatments.

Despite the considerable improvements in ACS treatment in recent years and the current international recommendations for this high-risk population, several registries and studies have shown that, similarly to our results, this population has paradoxically been undertreated, benefiting less frequently from medical and revascularization procedures, which could partly account for their worse prognosis [1, 4, 8-10, 12, 13]. Several studies have shown that there is actually no reason to expect an increased rate of side-effects in people with diabetes, although most information comes from subgroup analy-

sis of larger trials and not from specific trials involving diabetic populations [4]. Nonetheless, comparison of the results of Euro Heart Survey ACS I with Euro Heart Survey ACS II points towards a positive temporal trend in this context [8, 24].

Similarly to previous registries, in terms of the international guidelines, in our diabetic population we found lower-than-expected rates of revascularization procedures. A possible explanation for this undertreatment (and also the rate of conservative strategy in some of our patients presenting with STEMI) could be delayed diagnosis of ACS due to atypical presenting symptoms which narrowed the therapeutic window for some interventions. Another possible reason is that people with diabetes are thought to be more vulnerable and considered to have a relative contraindication for some treatments [4]. Diabetic patients frequently have several comorbidities, which may contraindicate some of the recommended treatments such as revascularization procedures. In our population, patients undergoing a conservative strategy were older and had lower GFR, which may have contributed to this therapeutic option. Furthermore, we have no information on patient preferences that may have influenced some decisions regarding invasive interventions. We can speculate that, due to the above-mentioned baseline characteristics and due to longer known diabetes duration, patients undergoing a conservative strategy may have a similar or even higher rate of significant coronary disease, compared to patients undergoing an invasive approach. Moreover, we should take into account that an invasive strategy was a protective factor against the incidence of MACE in all follow-up periods considered, which is in agreement with previous results concerning its benefits [4, 12]. These findings highlight the need to put into practice the international guidelines in order to improve the prognosis of this population.

A significant proportion of our diabetic population had previous known CAD and some were known to have CAD not suitable for revascularization. This, in addition to the fact that some patients had normal coronary anatomy, could partially explain the low rate of revascularization in the index hospitalization. The rate of CABG was even lower, probably because most patients underwent PCI in the context of STEMI. Among the remainder, PCI was the procedure of choice in our department if the coronary lesions were suitable. There is an ongoing controversy regarding the optimal approach for coronary revascularization in diabetic patients. Although some studies have shown a less favorable prognosis with PCI, they were not conducted in the era of modern stents, and some of them involved stable CAD patients [4, 12]. The availability of newer stents and adjuvant antithrombotic therapy has improved the angiographic success of PCI in diabetic patients, even those with multivessel disease. In fact, some recent studies using these more modern revascularization approaches did not confirm earlier reports regarding mortality, although it appeared that diabetic patients more often had further revascularization procedures in the PCI arm [4, 12]. Further studies are therefore needed to determine the optimal revascularization strategy in diabetic patients.

Numerous factors regarding the pathophysiology of diabetes may contribute to this poorer outcome, such as hyperglycemia-induced toxicity with consequent vascular damage and impaired collateral vessel formation [9], endothelial dysfunction, increased platelet activity [3], decreased vasodilatory reserve and fibrinolysis, elevated platelet aggregability [4] and autonomic neuropathy [1, 4, 10, 11], the latter potentially being responsible for ventricular arrhythmias[1]. Specific aspects of this condition, such as the occurrence of widespread and diffuse coronary artery disease, small vessel disease and diabetic cardiomyopathy [4, 9, 13], may also play an important role. Diabetic patients have more comorbid conditions, including renal dysfunction, hypertension, prior HF and myocardial infarction, obesity, stroke and vascular disease, further contributing to their dismal prognosis [3, 4, 12]. As previously stated, our diabetic population had a high prevalence of car-

diovascular risk factors and comorbidities, and notably, they had also a high prevalence of previous CAD.

Diabetic patients are also at increased risk for developing HF both during hospitalization [1, 8, 9] and after discharge[8, 9]. HF in these patients has a complex and multifactorial etiology that results from a constellation of pathophysiologic processes. It has been traditionally attributed to the concurrent presence of ischemic or hypertensive heart disease [6]. However, diabetic cardiomyopathy, a distinct entity that has been described as myocardial dysfunction that occurs independently of CAD or hypertension, adds to HF development in this population; as a consequence, both diastolic and systolic dysfunction may occur [1, 7]; some antidiabetic drugs have also been implicated [1]. Not only are diabetes and HF often associated; this association carries an extremely adverse outcome, with substantially higher mortality and recurrent hospitalization, especially in patients with ischemic cardiomyopathy [6].

Several studies in ACS populations have shown that the incidence of HF is a strong predictor of subsequent mortality [4, 12, 15]. In our population, systolic dysfunction was, in fact, the most powerful predictor of adverse outcome, leading to HF, MACE and death after discharge in all follow-up periods considered. Furthermore, Killip class >I, reflecting HF on admission, with either systolic or diastolic dysfunction, was a potent predictor of mortality. This implies that every effort should be made to treat these patients carefully and as early as possible, particularly with reperfusion strategies and drugs that have been demonstrated to improve HF prognosis.

NSTEMI was another predictor of HF in follow-up, reflecting the lower use of an invasive strategy in this type of ACS compared with STEMI.

The median HbA1c value was not very high, possibly indicating acceptable blood glucose levels in the weeks before admission. However, some authors [23] propose that a high admission glucose level could reflect the degree of glycemic control in the outpatient setting, which could explain the link between outpatient glycemic control and outcomes in the inpatient population. Higher blood glucose on admission was an independent predictor of HF (above 184 mg/dl) and MACE at one year (above 130 mg/dl). This was in agreement with previous studies indicating that admission blood glucose levels in diabetic ACS patients were an independent risk factor of poor outcome in both the short and long term [4, 12, 20, 26-30]. It also shows the importance of the recommended measures to lower high blood glucose values as soon as possible, as was the practice in our center.

LIMITATIONS

It was not possible in our database to differentiate types of diabetes and no information was available regarding the known duration of the disease.

It was also not possible to identify the timing of cardiac catheterization during the index hospitalization. We have no information about possible patient preferences, which may have influenced some decisions regarding the actual choice of procedures, particularly invasive interventions. In the same way, we have no data regarding possible bleeding complications or contraindications to the prescribed medications, which could be relevant to the interpretation of the prescription rates.

We also have no data regarding hypoglycemic agents prescribed at discharge and during follow-up, and we could not obtain information on diabetes control in the 12-month follow-up, both of which constitute an important limitation of our study.

There were no data regarding the occurrence of elective percutaneous revascularization procedures after discharge, which could have affected the results. However, it is important to note that in the majority of our patients, when indicated and when lesions suitable for revascularization were present, the procedure took place during the first hospitalization, minimizing potential bias.

It was not possible to obtain information regarding follow-up in 10% of the population, which we recognize to be a limitation of our study.

Finally, this was an observational and non-randomized study, with the inherent limitations.

CONCLUSION

Diabetes is common among ACS patients and these patients have a high incidence of MACE, HF and mortality at 1-year follow-up. This poor outcome could be partially explained by the relatively low utilization of the recommended cardiovascular agents and revascularization procedures. An invasive strategy and statins were protective factors, while systolic dysfunction, high Killip class and high blood glucose were the most consistent predictors of worse prognosis. These data show that more extensive use of established treatments may have the potential to improve the picture of diabetic patients presenting with ACS. Diabetes should be more carefully considered in the risk stratification of ACS patients. Our results also highlight the need for research to identify effective strategies to manage ACS in this high-risk population.

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