CLINICS

RAPID COMMUNICATION

Design and baseline characteristics of a coronary heart disease prospective cohort: two-year experience from the strategy of registry of acute coronary syndrome study (ERICO study)

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OBJECTIVES: To describe the ERICO study (Strategy of Registry of Acute Coronary Syndrome), a prospective cohort to investigate the epidemiology of acute coronary syndrome.

METHODS: The ERICO study, which is being performed at a secondary general hospital in Sao Paulo, Brazil, is enrolling consecutive acute coronary syndrome patients who are 35 years old or older. The sociodemographic information, medical assessments, treatment data and blood samples are collected at admission. After 30 days, the medical history is updated, and additional blood and urinary samples are collected. In addition, a retinography, carotid intima-media thickness, heart rate variability and pulse-wave velocity are performed. Questionnaires about food frequency, physical activity, sleep apnea and depression are also applied. At six months and annually after an acute event, information is collected by telephone.

RESULTS: From February 2009 to September 2011, 738 patients with a diagnosis of an acute coronary syndrome were enrolled. Of these, 208 (28.2%) had ST-elevation myocardial infarction (STEMI), 288 (39.0%) had non-ST-elevation myocardial infarction (NSTEMI) and 242 (32.8%) had unstable angina (UA). The mean age was 62.7 years, 58.5% were men and 77.4% had 8 years or less of education. The most common cardiovascular risk factors were hypertension (76%) and sedentarism (73.4%). Only 29.2% had a prior history of coronary heart disease. Compared with the ST-elevation myocardial infarction subgroup, the unstable angina and non-ST-elevation myocardial infarction patients had higher frequencies of hypertension, diabetes, prior coronary heart disease ($p<0.001$) and dyslipidemia ($p=0.03$). Smoking was more frequent in the ST-elevation myocardial infarction patients ($p=0.006$).

CONCLUSIONS: Compared with other hospital registries, our findings revealed a higher burden of CV risk factors and less frequent prior CHD history.

KEYWORDS: Coronary Acute Syndrome; Epidemiology; Registries.

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INTRODUCTION

Acute coronary syndrome (ACS) is a major cause of mortality and morbidity worldwide. This syndrome is a broad term that includes unstable angina (UA), non-ST elevation myocardial infarction (NSTEMI) and ST elevation myocardial infarction (STEMI) (1). According to recent official data, there were 12,340 hospitalizations in the city of São Paulo during the 2011 calendar year due to angina pectoris or myocardial infarction (International Classification of Diseases – ICD I20/I21) that were reimbursed by the Brazilian National Health System, with a total 94,857 days of hospitalization (2). However, most medical facilities that assist these patients are classified as secondary care hospitals and do not provide interventional cardiac procedures. ACS registries are more frequently conducted in tertiary-care hospitals (3-4).

Hereafter, we will describe the design and baseline characteristics of the ERICO (Estratégia de Registro de

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Insuficiência Coronariana – Strategy of Registry of Acute Coronary Syndrome) study, a hospital-based cohort study of patients with ACS, which is still ongoing in a community-hospital in the city of São Paulo.

METHODS

Setting

The ERICO study was launched in February 2009 to establish a surveillance strategy for ACS and the quality of care at Hospital Universitário, Universidade de São Paulo (HU-USP). This institution is a 260-bed teaching community hospital in the borough of Butantã that had a population of 428,000 inhabitants in 2010 and a human development index of 0.716 (5-6). The frequency of patients with ACS in HU-USP is approximately one patient per day. Individuals with ACS are treated in the emergency department, the internal medicine ward or a general intensive care unit. Patients who need an interventional procedure are mostly referred to the Heart Institute at the University of São Paulo.

Case definition

Myocardial infarction (MI) was defined by the presence of symptoms consistent with cardiac ischemia within 24 hours of hospital presentation and troponin I levels above the 99th percentile with a test-specific coefficient of variation $<10\%$ (1,7). STEMI was defined by the presence of criteria for MI plus one of the following: (a) persistent ST segment elevation of ≥ 1 mm in two contiguous electrocardiographic leads or (b) the presence of a new or presumably new left bundle branch block. NSTEMI was defined by the presence of criteria for MI but not for STEMI. The UA diagnosis required the presence of symptoms consistent with cardiac ischemia 24 hours prior to hospital admission, absence of MI criteria and at least one of the following: (a) history of coronary heart disease (CHD); (b) positive coronary disease stratification test (invasive or non-invasive); (c) transient ST segment changes ≥ 0.5 mm in two contiguous leads, new T-wave inversion of ≥ 1 mm and/or pseudonormalization of previously inverted T waves; (d) troponin I >0.4 ng/ml (which guarantees a troponin I level above the 99th percentile regardless of the utilized kit); or (e) diagnostic concordance of two independent doctors.

Study protocol

All individuals with suspected ACS are invited to participate in our study. Data regarding sociodemographics, main cardiovascular risk factors (hypertension, diabetes, obesity, dyslipidemia, smoking, familial and personal history of CHD, physical inactivity, cocaine use and menopause), medications and a questionnaire for depressive symptoms (Patient Health Questionnaire-PHQ9) are obtained by trained interviewers (8). Three physicians are responsible for the review of all medical charts, for asking participants about all necessary information at hospital admission and for ordering electrocardiograms, laboratory tests (troponin I, MB-creatine kinase, serum glucose, total cholesterol, HDL/LDL-cholesterol, triglycerides and total blood cell count) and in-hospital medical treatment. All participants are asked permission for the storage of blood samples in the HU-USP biobank for further evaluation.

30-day follow-up

Participants are reevaluated by a physician 30 days after the event. Additional data on cardiovascular risk stratification, such as urgent or scheduled percutaneous coronary transluminal angioplasty (PTCA) and/or coronary artery bypass graft surgery (CABG), echocardiogram findings and information about medications are obtained. Questionnaires regarding depressive symptoms (PHQ-9) (8), food-frequency (9), physical activity (10,11), sexual activity and sleep apnea (Berlin questionnaire) (12) are also administered by trained interviewers.

Tests for serum creatinine, fasting blood glucose, oral glucose tolerance test, hepatic enzymes, cholesterol levels and microalbuminuria are conducted. Additionally, a more detailed evaluation of the cardiovascular system, including pulse-wave velocity, heart rate variability, carotid artery intima-media thickness and retinography is performed. A new blood sample for biobank storage is obtained.

For those participants who are unable to attend the 30-day consultation, information about their cardiovascular evaluation and vital status is obtained by phone.

Long-term follow-up

Six months and annually after the index event, all participants are contacted by phone to update information about their vital status, cardiovascular history, medications, depressive symptoms, physical activity and sleep apnea.

Outcomes

Relevant outcomes include the occurrence of: (a) new chest pain, (b) confirmed new ACS event, (c) cardiac revascularization via either PTCA or CABG (not due to the index event), (d) stroke and (e) all-cause and cardiovascular deaths. Each identified event is adjudicated using predefined international criteria (1,7). Vital status is complemented periodically by a hot-pursuit strategy. We routinely check the state death index to look for missing participants. Death certificates are obtained whenever possible.

Statistical Analysis

The subjects are classified into three subgroups according to the ACS subtype. Categorical variables are presented as proportions and are compared using Chi-square/Fisher's exact tests. Continuous variables are presented as means (standard deviations) and are compared using one-way ANOVA, with the Bonferroni post-hoc test for multiple comparisons. The statistical analyses are performed with SPSS version 16.0.

RESULTS

From February 2009 to September 2011, 738 patients diagnosed with ACS were enrolled. Of those, 208 (28.2%) had STEMI, 288 (39.0%) had NSTEMI and 242 (32.8%) had UA (Table 1). The mean age was 62.7 years, 58.5% were men and 77.4% had ≤ 8 years of education. The most common primary cardiovascular risk factors were hypertension (76.0%) and physical inactivity (73.4%). Only 29.2% had a prior history of CHD. Compared with the STEMI subgroup, the UA and NSTEMI patients had higher frequencies of hypertension, diabetes, prior CHD and dyslipidemia. Current smoking was more frequent in the STEMI patients. Furthermore, based on the telephone follow-up, our one-year case-fatality rate for all-cause deaths was 12.1% (89 fatal events/738 ACS cases).

Table 1 - Baseline characteristics of ERICO patients according to the diagnosis at discharge.

Characteristics	Diagnosis at discharge				
	Non-ST-segment elevation myocardial infarction (n = 288)	ST-segment elevation myocardial infarction (n = 208)	Unstable angina (n = 242)	Total (n = 738)	*p*-value
Mean age (years) (±SD)	65.3 (±13.3)	59.2(±13.2)	62.7(±12.5)	62.7(±13.2)	<0.001
Age strata (%)					<0.001
≤45	15 (5.2)	26 (12.5)	16 (6.6)	57 (7.7)	
46-55	48 (16.7)	51 (24.5)	53(21.9)	152 (20.6)	
56-65	79 (27.4)	70 (33.7)	66 (27.3)	215 (29.1)	
66-75	70(24.3)	34 (16.3)	60 (24.8)	164 (22.2)	
>75	76 (26.4)	27 (13.0)	47 (19.4)	150 (20.3)	
Gender (%)					0.054
Male	167(58.0)	135 (64.9)	130 (53.7)	432 (58.5)	
Female	121 (42.0)	73 (35.1)	112 (46.3)	306 (41.5)	
Race (%)					0.004
White	207 (71.9)	151 (72.6)	149 (61.6)	507 (68.7)	
Mixed	55 (19.1)	51 (24.5)	77 (31.8)	183 (24.8)	
Black	22 (7.6)	5 (2.4)	15 (6.2)	42 (5.7)	
Asiatic	4 (1.4)	1 (0.5)	1 (0.4)	6 (0.8)	
Years of Education (%)					0.44
Illiterate	41(14.3)	24 (11.7)	41(16.9)	106 (14.4)	
1-7	186 (64.8)	129 (62.6)	148 (61.20)	463(63.0)	
>8	60 (20.9)	53 (25.7)	53 (21.9)	166 (22.6)	
Marital status (%)					0.01
Single	31 (10.8)	37 (17.9)	36 (14.9)	31 (14.2)	
Married	173 (60.5)	138 (66.7)	139 (57.7)	450 (61.3)	
Divorced	26 (9.1)	13 (6.3)	21 (8.7)	60 (8.2)	
Widowed	56 (19.6)	19 (9.2)	45 (18.7)	120 (16.3)	
Prior CHD (%)	64 (24.9)	30 (15.8)	98 (46.7)	192 (29.2)	<0.001
Cardiovascular risk factors* (%)					
Family history of premature CHD **	68 (26.1)	51 (27.6)	69 (30.8)	188 (28.1)	0.50
Hypertension *	219 (77.4)	123 (61.5)	206 (86.6)	548 (76.0)	<0.001
Diabetes mellitus *	131 (46.1)	57 (28.6)	96 (41.4)	284 (39.7)	<0.001
Smoking status *					0.006
Never	91 (34.3)	53 (26.8)	80 (36.5)	224 (32.8)	
Past	93 (35.1)	69 (34.8)	91 (41.6)	253 (37.1)	
Current	81(30.6)	76 (38.4)	48 (21.9)	205 (30.1)	
Dyslipidemia *	141(55.3)	81(48.2)	124 (62.0)	346 (55.5)	0.03
Sedentarism (%)	206 (75.7)	134 (70.5)	157 (73.0)	497 (73.4)	0.45

Some proportions might not add up to 100% due to rounding.
*All cardiovascular risk factors were based on previous medical history.
**Family history of premature coronary heart disease was defined as coronary heart disease in a first-degree male relative before age 55 or in a first-degree female relative before age 65.

DISCUSSION

Here, we describe the design and baseline characteristics of a prospective cohort of patients with an ACS event assisted at a community hospital, with the main objective of identifying prognostic factors associated with early and late case-fatality and survival. At the baseline, a low proportion of ERICO participants had previous ACS events (29.2%). This result contrasted with the findings of: the GRACE (the Global Strategy of Acute Coronary Events) study, which included individuals with ACS events from 184 centers, most located in high-income countries; the multi-center Gulf registry of acute coronary events (Gulf RACE) study conducted in Middle Eastern countries; and the data of the tertiary center-based study in Brazil in which 47.6% of individuals diagnosed with ACS had previous coronary disease (13). We may speculate that these differences occurred because patients with previous ACS events are more prone to seek specialized centers in the case of a new event.

The frequencies of the cardiovascular risk factors vary across registries. Compared with the GRACE registry, the ERICO participants have high frequencies of cardiovascular risk factors (14,15). A possible reason that explains these differences is the low number of individuals with prior CHD in this cohort, which could be associated with a high frequency of cardiovascular risk factors, as lifestyle changes are more frequent in people with a previous ACS events. The comparison with the Gulf RACE participants revealed a high proportion of current smokers, which is most likely associated with the cultural lifestyle in Middle Eastern countries (16).

There are two large studies of ACS patients in Brazil, both with methodological differences compared with ERICO. The BRACE study is a multi-center study designed to evaluate regional differences regarding the use of effective in-hospital treatments of patients with ACS (17). The second study is the Brazilian arm of INTERHEART, an international case-control study designed to ascertain the impact of conventional and emerging cardiovascular risk factors on acute MI (18).

The ERICO study has several characteristics that distinguish it from other registries in Brazil. First, it evaluates prognostic factors at the emergency room and 30 days after

the event to verify the best time for the association of appropriate factors with late outcomes. Second, each participant in the study has multiple biological samples stored in liquid nitrogen, which can be used for future nested case-control studies addressing new prognostic factors. We intend to evaluate biomarkers associated with the nitration of proteins, such as nitrotyrosine and myeloperoxidase, and biomarkers involved with monocyte/macrophage activation, such as the monocyte chemoattractant protein 1 (MCP1), ILβ1 and netrin-1, in samples collected at hospital admission and after 30 days and determine the relationships of these biomarkers with long-term prognosis. In addition, DNA and RNA markers will be investigated with respect to their predictive accuracy for incident events and will be incorporated into clinical prediction models calibrated for the Brazilian population. Third, the number of exposures included in the study is high. In addition to common cardiovascular risk factors, we are exploring inflammatory biomarkers, DNA extraction, psychosocial factors, diet evaluation via a food-frequency questionnaire, carotid intima-media thickness, pulse-wave velocity, heart rate variability and retinography. Although this is a single-center study, which may not be representative of all of the diversity of the Brazilian population, ERICO can add new information about prognostic factors in ACS related to early and late outcomes in a community hospital, which is an underrepresented scenario for ACS studies.

AUTHOR CONTRIBUTIONS

Goulart AC conceived and designed the study, was responsible for the data acquisition, analysis and interpretation, drafting of the manuscript, critical revision of the manuscript for important intellectual content, statistical analysis, administrative and technical support, and study supervision. Santos IS conceived and designed the study, was responsible for the data acquisition, analysis and interpretation, drafting of the manuscript, critical revision of the manuscript for important intellectual content, statistical analysis and study supervision. Sitnik D was responsible for the data acquisition and critical revision of the manuscript for important intellectual content. Staniak HL conceived and designed the study, was responsible for the data acquisition, analysis and interpretation and critical revision of the manuscript for important intellectual content. Fedeli LM was responsible for the data acquisition, analysis and interpretation and critical revision of the manuscript for important intellectual content. Pastore CA and Samesima N performed the analysis and interpretation of data (ECG) and critical revision of the manuscript for important intellectual content. Bittencourt MS conceived and designed the study and was responsible for the critical revision of the manuscript for important intellectual content. Pereira AC conceived and designed the study and was responsible for the data analysis and interpretation and critical revision of the manuscript for important intellectual content. Lotufo PA and Benseñor IM obtained the funding, conceived and designed the study and were responsible for the critical revision of the manuscript for important intellectual content, statistical analysis, administrative and technical support, study supervision.

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