

Physical Stress Echocardiography: Prediction of Mortality and Cardiac Events in Patients with Exercise Test showing Ischemia

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Abstract

Background: Studies have demonstrated the diagnostic accuracy and prognostic value of physical stress echocardiography in coronary artery disease. However, the prediction of mortality and major cardiac events in patients with exercise test positive for myocardial ischemia is limited.

Objective: To evaluate the effectiveness of physical stress echocardiography in the prediction of mortality and major cardiac events in patients with exercise test positive for myocardial ischemia.

Methods: This is a retrospective cohort in which 866 consecutive patients with exercise test positive for myocardial ischemia, and who underwent physical stress echocardiography were studied. Patients were divided into two groups: with physical stress echocardiography negative (G1) or positive (G2) for myocardial ischemia. The endpoints analyzed were all-cause mortality and major cardiac events, defined as cardiac death and non-fatal acute myocardial infarction.

Results: G2 comprised 205 patients (23.7%). During the mean 85.6 ± 15.0 -month follow-up, there were 26 deaths, of which six were cardiac deaths, and 25 non-fatal myocardial infarction cases. The independent predictors of mortality were: age, diabetes mellitus, and positive physical stress echocardiography (hazard ratio: 2.69; 95% confidence interval: 1.20 – 6.01; $p = 0.016$). The independent predictors of major cardiac events were: age, previous coronary artery disease, positive physical stress echocardiography (hazard ratio: 2.75; 95% confidence interval: 1.15 – 6.53; $p = 0.022$) and absence of a 10% increase in ejection fraction. All-cause mortality and the incidence of major cardiac events were significantly higher in G2 ($p < 0.001$ and $p = 0.001$, respectively).

Conclusion: Physical stress echocardiography provides additional prognostic information in patients with exercise test positive for myocardial ischemia. (Arq Bras Cardiol. 2014; 103(5):418-425)

Keywords: Echocardiography; Stress/mortality; Exercise Test; Physical Exertion; Coronary Artery Disease; Myocardial Ischemia.

Introduction

Coronary artery disease (CAD) is the major cause of morbidity and mortality in Western countries¹. In Brazil, cardiovascular diseases account for more than 30% of deaths². Since new effective therapeutic options are now available, the identification of patients at a higher risk for cardiovascular events is mandatory³. Although coronary angiography remains the gold-standard for the diagnosis of CAD⁴, non-invasive techniques play a key role in the diagnosis and in the indication of invasive procedures.

Myocardial ischemia and infarction occur as a result of sequential changes known as “ischemic cascade”. Perfusion

abnormalities are followed by metabolic changes, left ventricular (LV) diastolic dysfunction, regional contraction deficit, electrocardiographic abnormalities and chest pain⁵. The ischemic cascade may be understood as a spectrum throughout which different markers of myocardial ischemia may show different sensitivity^{6,7}.

Exercise test (ET) is the noninvasive test initially recommended for the diagnosis and risk stratification of patients with suspected CAD⁸⁻¹⁰. However, the use of ET is limited in several situations such as in the presence of left bundle branch block (LBBB) or of ST-segment abnormalities in resting electrocardiogram (ECG)¹⁰, thus requiring the association of imaging methods to improve the diagnostic accuracy¹¹.

Physical stress echocardiography (PSE) has high sensitivity and specificity, and is more accurate than ECG, ET and resting echocardiography in the detection of CAD^{12,13}. LV wall motion abnormalities (WMA) detected by PSE occur earlier than angina or ST-segment abnormalities¹⁴. Additionally, PSE also has an additional value in the location and quantification of myocardial ischemia as well as in the prediction of adverse events in patients with established CAD¹⁵.

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The objective of this study was to analyze the effectiveness of PSE in predicting mortality and major cardiac events (MCE) in patients with ET showing ischemia.

Methods

Patients

A total of 866 consecutive patients referred for PSE in the Laboratory of Echocardiography of São Lucas Hospital, Aracaju (SE), after their respective physicians had detected electrocardiographic signs of myocardial ischemia on ET, were included between January 2001 and June 2010. The exclusion criteria were: ET negative for myocardial ischemia; presence of LBBB; failure to confirm ischemia by ET (repeated as PSE protocol); patient refusal to participate in the study; and failure to establish phone contact during the follow-up period.

The protocol consisted of complete clinical assessment with investigation of previous symptoms such as chest pain or shortness of breath, as well as risk factors for CAD, followed by ECG and resting echocardiography. Then, the patients underwent physical exertion on a treadmill and new echocardiographic images were acquired. Clinical and demographic data, as well as the results of the stress tests were recorded in the database. The individuals were divided into two groups according to the absence (G1) or presence (G2) of myocardial ischemia on PSE.

Exercise test

After a light meal, the patients were examined and advised not to practice any excessive physical activity on the day the test was performed. The study was performed with the individuals breathing spontaneously in room air, at a constant temperature (20 to 24°C). The Bruce protocol was used to perform ET. During the test, the individuals were continuously monitored by three-lead ECG, and were encouraged to reach their peak physical exertion. ET was considered as positive for myocardial ischemia whenever ST-segment elevation or horizontal or downsloping ST-segment depression ≥ 1 mm was detected for at least 60 to 80 ms of J point¹⁰.

Physical stress echocardiography

Echocardiographic studies were performed using Packard/Phillips Hewlett SONOS 5500 equipment according to the technical specifications described by Schiller et al¹⁶. Two-dimensional echocardiographic images were obtained with the patient in the left lateral position, in the parasternal and apical acoustic windows, at rest and immediately after exercise, with simultaneous electrocardiographic recording in videocassette or digital video, and assessed by an experienced echocardiographer (level III), as recommended by the American Society of Echocardiography¹⁷. In cases of doubt, the images were analyzed by a second, equally experienced, examiner.

Wall motion was scored from 1 to 4 (1 if normal, 2 if hypokinesia, 3 if akinesia, and 4 if dyskinesia), according to a 16-segment model. The wall motion index (WMI)

was determined at rest and at peak exercise as the sum of segmental scores divided by the number of segments visualized. Left ventricular systolic function was quantified, based on WMI, as: 1 if normal; 1.1 to 1.6 if mild ventricular dysfunction; 1.61 to 2 if moderate ventricular dysfunction; and > 2 if severe ventricular dysfunction¹⁶. The difference between exercise and resting WMI was named Δ WMI; it was considered normal when equal to zero, and abnormal when different from zero. Any result showing the development of new motion abnormalities induced by exercise or worsening of a preexisting contractile deficit, that is, every Δ WMI different from zero was considered as myocardial ischemia on PSE; absence of myocardial ischemia was defined as the absence of the criteria described above, that is, Δ WMI equal to zero.

Follow-up and endpoints

Patients were followed-up by means of telephone interviews, contact with the assisting physician, or medical record review. All-cause death and MCE were considered as study endpoints; MCE were defined as cardiac death and non-fatal acute myocardial infarction (AMI).

Statistical analysis

Categorical variables were described as percentages and compared between groups using the chi-square or Fisher's exact test. Continuous variables were described as mean and standard deviation (SD), and the differences between groups were analyzed using the Student's t test or Mann-Whitney test, as appropriate. The cumulative events curves were estimated using the Kaplan-Meier method and compared using the log-rank test. To evaluate the risk factors for MCE and death, Cox regression was used, considering univariate and multivariate analyses. The variables included in the multivariate model were those with $p < 0.1$ in the univariate analysis. Differences were considered significant when $p < 0.05$. The statistical analyses were carried out using the Statistical Package for the Social Sciences (SPSS) program, version 17.0 (Chicago, IL).

The study was carried out in compliance with the ethical principles for human experimentation and the patients gave written informed consent. The study was approved by the Research and Ethics Committee of Federal University of Sergipe (CAAE 1818.0.000.107-06).

Results

Clinical characteristics of the study population

The population comprised 866 patients with ST-segment abnormalities during ET, and who underwent PSE. The patients were divided into two groups, one with 661 (76.3%) patients without ischemia on PSE (Δ WMI = 0) (G1), and the other with 205 (23.7%) patients with ischemia (Δ WMI \neq 0) (G2). In G1, the mean age of patients was 55.97 ± 11 years, and 298 (45.1%) were men; in G2, the mean age was 58.96 ± 9.83 years, and 87 (42.4%) were men. G2 patients had significantly higher BMI ($p = 0.002$), age ($p < 0.001$), and presence of suggestive chest pain

($p < 0.001$) in relation to G1; non-suggestive chest pain was more frequent in G1 ($p = 0.004$). Additionally, there were significantly more patients with hypertension ($p = 0.004$), diabetes mellitus ($p = 0.001$), dyslipidemia ($p = 0.01$), and family history of CAD ($p = 0.008$) in G2. No other significant differences were observed between the groups regarding their clinical characteristics (Table 1).

Three out of four positive ET did not show ischemia on PSE, i.e., approximately 75% of the study patients were better analyzed.

Hemodynamic and echocardiographic measurements

G2 showed a significantly lower peak heart rate (HR) ($p < 0.001$), higher resting WMA ($p = 0.036$), higher exercise WMI and higher Δ WMI ($p < 0.001$). In relation to the other hemodynamic and echocardiographic parameters, there were no significant differences between G1 and G2 (Table 2).

Follow-up and endpoints

During the mean 85.6 ± 15.0 -month follow-up, there were 26 all-cause death, of which seven in G1 (sudden death, sepsis, stroke, airway obstruction and neoplasia), and 19 in G2 (kidney failure, sepsis, pancreatitis and neoplasia); additionally, there were 31 MCE (one cardiac death and five AMI in G1, and five cardiac deaths and 20 AMI in G2). As regards overall mortality, in the univariate analysis the significant variables were: age ≥ 60 years ($p < 0.001$), diabetes mellitus ($p = 0.001$), resting WMA ($p = 0.003$), positive PSE ($p = 0.001$) and left ventricular mass index (LVMI; $p < 0.001$).

As regards MCE, the significant variables in univariate analysis were: male gender ($p = 0.044$), age ≥ 60 years ($p < 0.001$), typical chest pain ($p = 0.030$), atypical chest pain ($p = 0.017$),

diabetes mellitus ($p = 0.005$), dyslipidemia ($p = 0.019$), previous CAD ($p < 0.001$), resting WMA ($p < 0.001$), positive PSE ($p < 0.001$), LV ejection fraction (LVEF; $p < 0.001$), LVMI ($p = 0.006$) and Δ WMI ($p = 0.042$). (Table 3). In the multivariate analysis, the independent predictors of mortality were age ≥ 60 years, and positive PSE. The independent predictors of MCE were age ≥ 60 years, previous CAD, positive PSE, and absence of a 10% increase in EF (Tables 4 and 5).

For MCE, there was a significant difference between groups G1 vs. G2, with $p = 0.022$. For overall mortality, there was also a significant difference between groups G1 vs. G2, with $p = 0.016$.

Mortality and MCE curves are shown in Figures 1 and 2, respectively.

Discussion

This study has demonstrated that PSE is an independent predictor of death and MCE in patients with ET showing ischemia. The independent predictors of mortality after multivariate analysis were: age ≥ 60 years, diabetes mellitus, and positive PSE. Predictors of MCE were age ≥ 60 years and previous CAD. Several studies have demonstrated the clinical characteristics described above as well-established risk factors for CAD¹⁸⁻²¹ and as predictors of adverse events in patients with stable or suspected angina or established CAD²²⁻²⁴. Our results corroborate these previous findings.

Echocardiographic findings have the ability to demonstrate pathophysiological changes resulting from myocardial ischemia in earlier phases and are, therefore, more sensitive than clinical results and ECG changes²⁵. In this study, we found an important association of suggestive pain in patients with myocardial ischemia on PSE and on MCE.

Table 1 – Clinical characteristics of patients with and without myocardial ischemia on physical stress echocardiography

Variables	G1 n = 661 (76.3%)	G2 n = 205 (23.7%)	p value
Male gender, n (%)	298 (45.1)	87 (42.4)	0.506
Age, years	55.97 \pm 10.58	58.96 \pm 9.83	0.001
BMI, kg/m ²	27.13 \pm 4.05	28.14 \pm 4.30	0.002
Suggestive chest pain, n (%)	25 (3.8)	53 (26.0)	0.001
Non-suggestive chest pain, n (%)	391 (59.3)	98 (48.0)	0.004
Obesity, n (%)	137 (21.2)	53 (26.1)	0.141
Hypertension, n (%)	341 (51.7)	129 (63.2)	0.004
Diabetes mellitus, n (%)	76 (11.5)	42 (20.6)	0.001
Dyslipidemia, n (%)	428 (64.8)	152 (74.5)	0.001
Smoker, n (%)	34 (5.2)	15 (7.4)	0.235
Family history of CAD, n (%)	361 (54.7)	133 (65.2)	0.008
Previous diagnosis of CAD, n (%)	75 (11.3)	31 (15.1)	0.150
Use of betablocker, n (%)	121 (18.4)	49 (23.9)	0.081
Use of calcium antagonist, n (%)	34 (5.2)	16 (7.8)	0.152

G1: Patients without myocardial ischemia; G2: Patients with myocardial ischemia; BMI: body mass index; CAD: coronary artery disease.

Table 2 – Hemodynamic and echocardiographic findings in patients without (G1) and with ischemia (G2) on physical stress echocardiography

Variables	G1 n = 661 (76.3%)	G2 n = 205 (23.7%)	p value
SBP, mmHg			
Resting	127.65 ± 13.12	130.44 ± 13.36	0.080
Peak	187.72 ± 20.16	187.82 ± 21.20	0.950
DBP, mmHg			
Resting	84.10 ± 14.31	83.55 ± 12.57	0.626
Peak	87.26 ± 9.21	88.02 ± 9.40	0.304
HR, bpm			
Resting	77.35 ± 13.80	76.58 ± 12.82	0.478
Peak	157.36 ± 18.02	147.23 ± 18.68	< 0.001
Arrhythmia, n (%)	147 (22.2)	59 (28.8)	0.055
WMA, n (%)	84 (12.7)	38 (18.5)	0.036
EF (%)	0.66 ± 0.06	0.66 ± 0.06	0.165
WMI			
Resting	1.03 ± 0.15	1.04 ± 0.12	0.800
Exercise	1.03 ± 0.15	1.17 ± 0.18	< 0.001
Δ WMI	0.0 ± 0.0	0.35 ± 0.13	< 0.001

SBP: systolic blood pressure; DBP: diastolic blood pressure; HR: heart rate; WMA: wall motion abnormalities; EF: ejection fraction; WMI: wall motion index; Δ WMI: difference between resting and exercise wall motion indexes.

As regards the echocardiographic findings, a significant presence of resting WMA, greater stress WMI and high Δ WMI were observed in G2. The results associated with overall mortality were resting WMA, positive PSE, and high LVMI. Those associated with endpoints were resting WMA, positive PSE, low EF, high LVMI and Δ WMI. After multivariate analysis, positive PSE remained as an independent predictor of mortality; and positive PSE and low EF, as predictive of MCE. Even patients showing WMA only at rest had an increased risk of MCE and death in this study. This finding is also described in a recent study with 333 patients in which Schlett et al²⁶ observed that the 2-year cumulative probability of MCE increased in patients with resting WMA with coronary stenosis (relative risk – RR = 62.4%; log-rank $p < 0.0001$), as well as in those with resting WMA without stenosis (RR = 15%; log-rank $p < 0.0001$).

LVMI was also relevant in patients with myocardial ischemia on PSE and multivariate analysis. The risk of MCE was represented by Δ WMI. Our results are consistent with those of a cohort of 5798 patients with known or suspected CAD, which demonstrated that Δ WMI had a significant prognostic value for MCE²⁷. Δ WMI is known to be associated not only with a higher risk of adverse events, but also with mortality²⁷.

In a Spanish cohort of 4004 patients, 16.7% had myocardial ischemia on PSE, and Δ WMI was an independent predictor of mortality and MCE²⁸. However, this was not observed in relation to mortality, in our study. This can be explained by the adequate use of medical treatment with drugs that decrease mortality.

Additionally, the univariate analysis demonstrated that a positive PSE was associated with risk of death and MCE, and remained an independent predictor of both after multivariate analysis. Several studies have analyzed the value of PSE as predictive of mortality and MCE²⁸⁻³¹. This study corroborates the prognostic importance of PSE, already established in the literature.

The use of tests for prognostic purposes is based on the premise that patients identified as having a high risk for adverse events may undergo more invasive interventions aimed at changing the natural history of the disease, thus reducing the risk of events^{32,33}. Randomized clinical studies have demonstrated that drug therapies and coronary revascularization may reduce mortality in certain groups of patients³⁴. Clinical studies using drug therapy have shown a reduction in the rates of cardiac death and of fatal and non-fatal myocardial infarction³⁵. During the study, we observed that a significant proportion of patients with ET positive for myocardial ischemia did not show ischemia on PSE. Three in every four patients with positive ET did not show ischemia on PSE, i.e., approximately 75% of the study patients were better analyzed. Additionally, the 25% with a positive PSE were those who were actually at an increased risk of adverse cardiac events, thus confirming the importance of the prognostic assessment of PSE.

The limitation of this study was the failure to compare the results found in the population with those of the population with an ET negative for myocardial ischemia.

Table 3 – Univariate analysis of predictors of mortality and major cardiac events (MCE)

Variables	Overall mortality		MCE	
	RR (IC95%)	p value	RR (IC 5%)	p value
Male gender	0.80 (0.36-1.77)	0.586	2.10 (1.02-4.33)	0.044
Age (≥ 60 years)	8.32 (2.90-24.14)	< 0.001	5.18 (2.23-12.03)	< 0.001
Suggestive chest pain	2.01 (0.69-5.85)	0.200	2.68 (1.10-6.56)	0.030
Non-suggestive chest pain	0.55 (0.25-1.20)	0.130	0.41 (0.20-0.85)	0.017
Obesity	0.14 (0.02-1.03)	0.053	1.25 (0.56-2.79)	0.591
Hypertension	1.70 (0.75-3.80)	0.203	1.79 (0.84-3.81)	0.129
Diabetes mellitus	4.00 (1.82-8.83)	0.001	2.99 (1.40-6.35)	0.005
Dyslipidemia	0.96 (0.43-2.14)	0.911	3.51 (1.23-10.03)	0.019
Smoking	1.27 (0.30-5.37)	0.748	0.49 (0.07-3.63)	0.489
Previous diagnosis of CAD	2.16 (0.87-5.39)	0.098	7.47 (3.69-15.13)	< 0.001
Hypertension (peak exercise)	0.42 (0.10-1.76)	0.232	0.72 (0.25-2.05)	0.534
Arrhythmia	2.01 (0.92-4.43)	0.083	1.34 (0.62-2.90)	0.464
Resting WMA	3.40 (1.52-7.63)	0.003	6.26 (3.09-12.67)	< 0.001
Positive PSE	3.67 (1.66-8.12)	0.001	5.10 (2.39-10.90)	< 0.001
10% increase in EF	0.67 (0.41-1.12)	0.127	0.41 (0.27-0.61)	< 0.001
10g/m increase in LVMI	1.39 (1.17-1.64)	< 0.001	1.27 (1.07-1.50)	0.006
Abnormal ΔWMI	1.65 (0.72-3.82)	0.240	2.16 (1.03-4.53)	0.042

RR: relative risk; 95%CI: 95% confidence interval; CAD: coronary artery disease; WMA: wall motion abnormalities; PSE: physical stress echocardiography; EF: ejection fraction; LVMI: left ventricular mass index; ΔWMI: Difference between resting and exercise wall motion index.

Table 4 – Multivariate analysis of predictors of overall mortality

Variables	RR (95%CI)	p value
Age ≥ 60 years	6.61 (2.25-19.4)	0.001
Diabetes mellitus	2.37 (1.06-5.31)	0.035
Positive PSE	2.69 (1.20-6.01)	0.016

RR: relative risk; 95%CI: 95% confidence interval; PSE: physical stress echocardiography.

The sample size, follow-up period (approximately 9 years), and the fact that the study was carried out in only one study center are considered favorable factors. The most important contribution of this study was to show that in every four positive ET, only one showed PSE positive for myocardial ischemia, which, in fact, provides a better stratification of this population at a low and intermediate risk for CAD, thus preventing the unnecessary use of invasive tests.

Conclusion

Physical stress echocardiography allows for a more accurate identification of patients at a higher risk of developing adverse cardiac events during the progression of coronary artery disease, thus providing important prognostic information for the clinical practice.

Table 5 – Multivariate analysis of predictors of major cardiac events

Variables	RR (95%CI)	p value
Age ≥ 60 years	4.39 (1.77-10.9)	0.014
Previous CAD	2.85 (1.27-6.38)	0.011
Positive PSE	2.75 (1.15-6.53)	0.022
EF (10% increase)	0.56 (0.37-0.85)	0.007

RR: relative risk; 95%CI: 95% confidence interval; CAD: coronary artery disease; PSE: physical stress echocardiography; EF: ejection fraction

Author contributions

Conception and design of the research: Araujo ACP, Calasans FR, Pinto IMF, Oliveira JLM; Acquisition of data: Araujo ACP, Santos BFO, Calasans FR, Melo LD, Andrade SM, Tavares IS, Oliveira JLM; Analysis and interpretation of the data: Araujo ACP, Santos BFO, Calasans FR, Pinto IMF, Oliveira DP, Melo LD, Andrade SM, Tavares IS, Sousa ACS, Oliveira JLM; Statistical analysis: Araujo ACP, Calasans FR, Oliveira DP, Tavares IS, Sousa ACS, Oliveira JLM; Writing of the manuscript: Araujo ACP, Santos BFO, Calasans FR, Melo LD, Andrade SM, Tavares IS; Critical revision of the manuscript for intellectual content: Calasans FR, Pinto IMF, Oliveira DP, Tavares IS, Sousa ACS, Oliveira JLM.

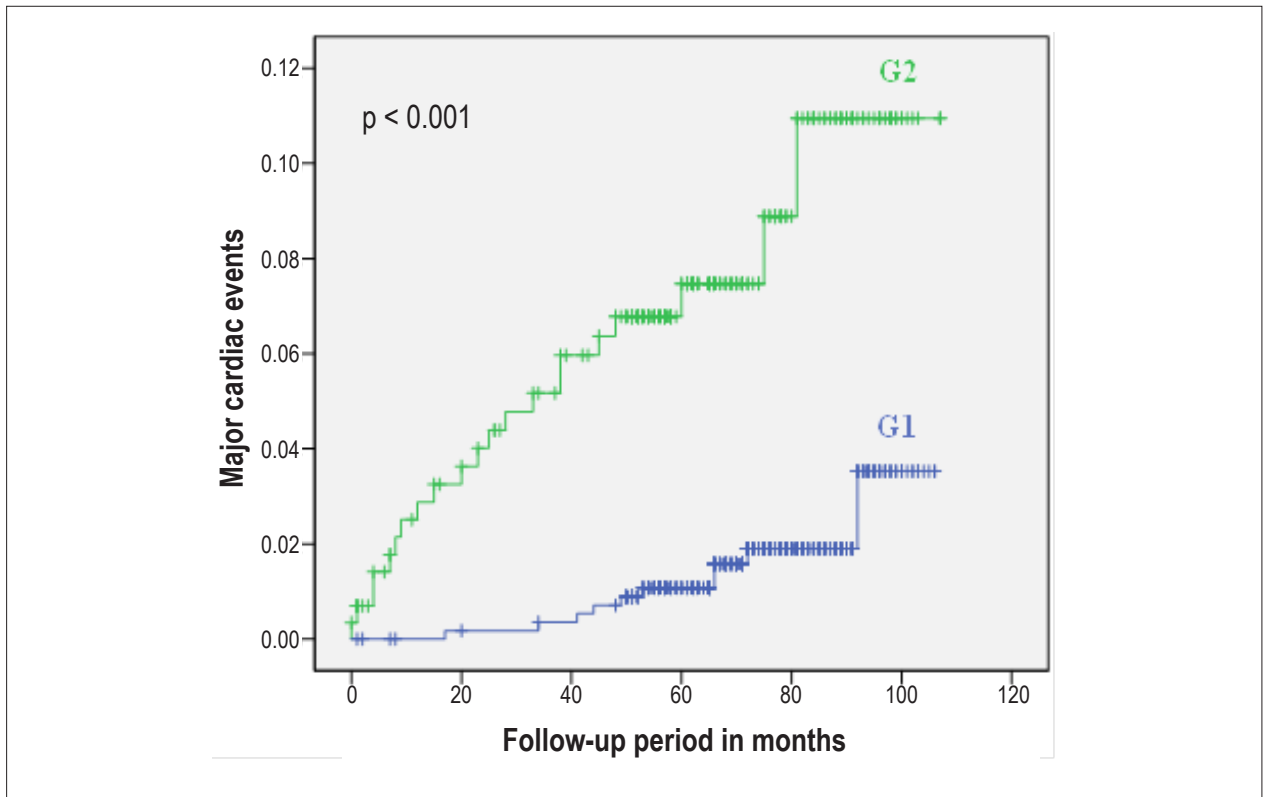


Figure 1 – Relative risk for major cardiac events of 5.0 (95% confidence interval: 2.37-10.78).

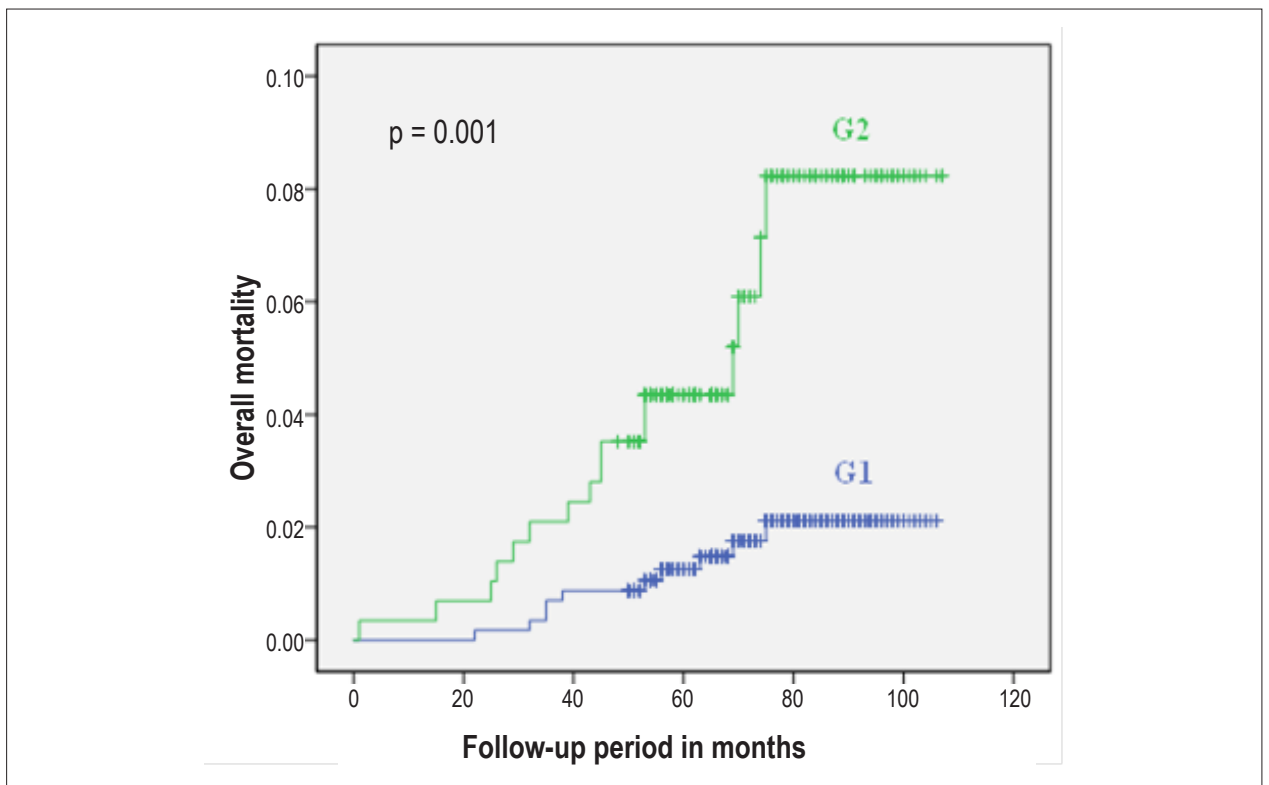


Figure 2 – All-cause death. Relative risk of death of 3.6 (95% confidence interval: 1.65 – 8.06).

Potential Conflict of Interest

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

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Study Association

This study is not associated with any thesis or dissertation work.

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