Prognostic value of myocardial perfusion SPECT images in combination with the maximal heart rate at exercise testing in Japanese patients with suspected ischemic heart disease: A sub-analysis of J-ACCESS.

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Abstracts

Objectives: We assessed whether combination of summed stress scores (SSS) using exercise myocardial perfusion SPECT (Ex-SPECT) and a maximal heart rate accurately predicts cardiac events as a sub-analysis of J-ACCESS (Japanese Assessment of Cardiac Events and Survival Study by Quantitative Gated SPECT) which was conducted to evaluate the prognosis in Japanese patients with suspected ischemic heart diseases.

Methods: In J-ACCESS, 2,373 patients with suspected coronary artery disease without beta-blockers treatment underwent Ex-SPECT. These patients were categorized as following 4 groups: Group A (achieve target heart rate (THR) and SSS<4: n=631), B (not achieve THR and SSS<4: n=612), C (achieve THR and SSS≥4: n=570), and D (not achieve THR and SSS≥4: n=560). We evaluated the incidence rate of cardiac events including cardiac death, myocardial infarction, and heart failure for requiring hospital admission for 3 years.

Results: In patients with group A, B, C, and D, 9 of 631 (1.4%), 15 of 612

(2.4%), 23 of 570 (4.0%) and 30 of 560 (5.4%) patients experienced cardiac events, respectively. Although the hazard ratio of the SSS $\geq$ 4 was 2.45 ($p<0.001$) and that of the attained THR was 0.69 ($p=0.10$) in the multiple Cox regression analysis, Kaplan-Meier curves showed that the cardiac events rate was lower in the order of A, B, C and D ($p<0.001$).

Conclusions: The combination of SSS using Ex-SPECT and the maximal heart rate is the useful predictor of cardiac events in patients with suspected coronary artery disease.

Introduction

Nuclear medicine guidelines in the USA have approved prognostic evaluation with myocardial perfusion SPECT and recognize the additional value of gated studies [1]. Although the prognostic values of both normal and abnormal SPECT findings in terms of event rates per year has been described, a large-scale investigation has not been conducted in a Japanese population. Accordingly, a multicenter study was conducted to establish a Japanese database called the Japanese Assessment of Cardiac Events and Survival Study by Quantitative Gated SPECT (J-ACCESS investigation) [2, 3]. In a total of 4,629 patients with suspected coronary artery disease, gated stress/rest myocardial perfusion SPECT was performed. Then, this trial disclosed that large myocardial perfusion defects and decreased cardiac function could be predictors of high event rates in these patients [3]. Furthermore, some sub-analyses of the J-ACCESS were performed, and impressive results were reported [4-7]. Imamura et al. demonstrated that normal myocardial perfusion scan portends a benign prognosis independent from the pretest probability of coronary artery disease [4]. Momose et al. disclosed that myocardial perfusion imaging with Quantitative Gated SPECT (QGS) is the useful tool with which to guide decisions regarding therapy even among patients referred for coronary angiography [5].

Meanwhile, the variables obtained by exercise tests have not been focused on in previous sub-analyses. For example, an attenuated heart rate response to exercise has been shown to predict adverse cardiac events in the subjects with or without known cardiovascular disease [8-11]. This chronotropic incompetence has also been associated with an increased left ventricular mass, left ventricular cavity dilatation [12, 13], and carotid atherosclerosis [14]. Therefore, additional information regarding a maximal heart rate during exercise testing may improve a predictive value for cardiac events. Accordingly, we investigated whether the combination of summed stress scores (SSS) using exercise myocardial perfusion SPECT images and the heart rate at the end of exercise testing more accurately predict cardiac events as a sub-analysis of J-ACCESS.

Patients and Methods

The principal design of the J-ACCESS study has been described [2, 3]. In brief, a total of 4,629 consecutive patients were registered at 117 hospitals. The patients underwent stress and rest myocardial perfusion SPECT using 99mTc-tetrofosmin and quantitative gated SPECT with QGS software (Cedars Sinai Medical Center, CA, US) and were followed up for 3 years. Quantitative gated SPECT data were analyzed using QGS software and a standard processing method. The SPECT images were divided into 20 segments, and visual perfusion of 99mTc-tetrofosmin uptake in each segment was scored as follows: 0, normal; 1, mildly reduced; 2, moderately reduced; 3, severely reduced and 4, absent [15, 16]. SSS and summed rest scores (SRS) were calculated based on the stress and rest findings. The severity of myocardial perfusion defects was defined with four grades of category (0, I, II and III) using summed scores: normal (score 0-3) and mildly (4-8), moderately (9-13) or severely (≥14) abnormal, respectively [15, 17].

In patients who underwent sign- and symptom-limited exercise testing, their heart rates were continuously monitored with a twelve-lead ECG. Patients were encouraged to reach 85% of maximal age-predicted heart rate (target heart rate; THR) or more. The exercise was terminated when subjects reached the THR or had the following signs and/or symptoms: chest pain, dyspnea, leg fatigue, hypertension (systolic blood pressure > 230 mmHg), hypotension, faintness, significant ST-T change and dangerous arrhythmia.

There were a total of 4,031 patients analyzed in the main J-ACCESS trial. Patients who underwent pharmacological stress testing or took β blockades were excluded from the present analysis. Since the other 8 patients were excluded because of missing data on exercise tests, the final prognostic findings were derived from the remaining 2,373 patients (Fig 1). For the analysis, patients were divided into following 4 groups. Group A was consisted of 631 patients who achieved their THR with SSS < 4, Group

B was consisted of 612 patients who failed to achieve their THR with SSS < 4, Group C was consisted of 570 patients who achieved the THR with their SSS ≥ 4, and Group D was consisted of 560 patients who failed to achieve their THR with SSS ≥ 4. Clinical characteristics of these patients group were shown in Table 1. We evaluated the occurrence of major cardiac events (cardiac death, non-fatal myocardial infarction, and heart failure for requiring hospital admission) for 3 years as previously reported.

Data are expressed as averages +/- standard deviation (SD) of continuous variables. Differences in baseline characteristics among groups were tested with the ANOVA to continuous variables and the chi-square test to categorical variables. The incidence proportions were calculated using the Kaplan-Meier method and compared with a log-rank test. The hazard ratio and 95% confidence intervals (CI) were also estimated using the multiple Cox regression analysis adjusted by SSS, attained THR, left ventricular ejection fraction, and diabetes mellitus. Statistical significance was defined as $P < 0.05$.

Results

Among 2,373 patients followed up for 3 years, a total of 94 (4.0 %) patients developed major cardiac events that comprised 28 cardiac deaths, 33 non-fatal myocardial infarctions and 33 hospital admission for heart failures. In patients with the group A, B, C, and D, 9 of 631 (1.4%), 15 of 612 (2.4%), 23 of 570 (4.0%) and 30 of 560 (5.4%) patients experienced major cardiac events, respectively. Furthermore, 2 of 631 (0.3%), 4 of 612 (0.7%), 6 of 570 (1.1%), and 16 of 560 (2.9%) patients experienced cardiac deaths, and 6 of 631 (1.0%), 7 of 612 (1.1%), 9 of 570 (1.6%), and 11 of 560 (2.0%) patients experienced non-fatal myocardial infarctions, and 2 of 631 (0.3%), 5 of 612 (0.8%), 13 of 570 (2.3%), and 13 of 560 (2.3%) patients experienced heart failures requiring hospital admission, respectively (Fig 2). As shown in Fig 3, Kaplan-Meier curves for major cardiac events revealed that the major cardiac events rate for 3 years was lower in the order of A, B, C and D ($p<0.001$). In the multiple Cox regression analysis, the hazard ratio of the SSS $\geq$ 4 was 2.45 (CI: 1.51 to 3.97, $p<0.001$) and that of the attained THR was 0.69 (CI: 0.44 to 1.08, $p=0.10$).

Discussion

ACC/AHA/ASNC guidelines for the clinical use of cardiac radionuclide imaging indicate that cardiac nuclear tests are best applied for risk stratification in patients with a clinically intermediate risk of a subsequent cardiac event [1]. Since many of the major determinations of prognosis in ischemic heart disease can be assessed by measurements of stress-induced perfusion and function, normal stress perfusion SPECT results are consistently predictive of a less than 1 % annual risk of cardiac death or myocardial infarction [1]. Especially, the annual rates of cardiac events were significantly lower in Japan than in the western countries. The original J-ACCESS trial identified 0.5% of hard cardiac events per year for Japanese patients with normal SSS. Moreover, SSS category was only one valuable index obtained by perfusion images as a significant predictor for cardiac events by the Cox multivariate analysis [3]. Ischemic changes of ECG during exercise testing, however, were not a significant predictor for major cardiac events [3].

Otherwise, it has been well known that chronotropic incompetence, which is defined as the failure to achieve 85% of the maximal age-predicted heart rate during the exercise test, is an independent predictor for cardiovascular events [18-20]. Then we focused on this phenomenon in the present study, and the enrolled patients were classified into 4 groups such as the normal heart rate response or not, and the normal perfusion images or not. But, the underlying mechanism of an attenuated heart rate response to exercise has not been clarified. Since the maximal heart rate reflects exercise tolerance, failure to achieve the THR may combine with physical unfitness. Myers studied a total of 6,213 consecutive men referred for treadmill exercise testing [21]. Patients, who died during a follow-up period, had a lower maximal heart rate, lower maximal systolic and diastolic blood pressure, and lower exercise capacity [21]. The abnormal contraction of an ischemic ventricle may stimulate ventricular mechanoreceptors and thereby increase vagal activation, which tends to oppose a sympathetically-mediated increase in heart rate. Other proposed explanations include abnormal cardiovascular autonomic control [22-24], such as β receptor down-regulation in sinus node caused by a chronically-heightened sympathetic activation and reduced carotid baroreflex sensitivity [24]. In addition, a recent research indicated that impaired chronotropic response associated with endothelial dysfunction and enhanced systemic inflammation [22]. These findings may partly explain the mechanism of chronotropic incompetence as a predictor of cardiovascular risks.

In patients with cardiac death, a significant difference was observed between group C and D. On the other hand, this tendency was not observed in patients with myocardial infarction or cardiac failure. Incidence of heart failure of group C and D was significantly higher than that of group A.

Because the higher SSS (group C and D: SSS $\geq$ 4) reflected their low cardiac function and severe ischemia compared with those of group A or B (SSS $<$ 4), the higher incidence of heart failure may occur in group C and D. Furthermore, serial angiographic studies indicated that coronary occlusion and acute myocardial infarction most frequently evolved from mild to moderate stenoses [25-27]. Accordingly, myocardial perfusion SPECT images with the exercise test, which are useful to detect moderate or severe coronary stenoses, may be not able to predict the onset of acute myocardial infarction accurately. Moreover, although chronotropic incompetence itself was not an independent predictor for cardiac events in this sub-analysis, other variables reflecting exercise tolerance precisely such as the anaerobic threshold or maximal oxygen consumption instead of the maximal heart rate may predict for cardiac events.

In this sub-analysis, however, it should be noticed that the high-risk group of cardiac death (group D) could be identified by the combination of the SSS and the maximal heart rate. Since the combination of the SSS obtained by exercise myocardial perfusion SPECT images and the maximal heart rate during exercise test may reflect the cardiac ischemia and function from different viewpoints, this classification and combination may predict cardiovascular events more accurately.

Limitations

Several limitations in the present study should be noted. First, since this analysis was post-hoc and patients who underwent pharmachological stress testing and took β blockades were excluded, this study population and number of cardiovascular events may not be enough to analyze the influence of SSS and THR on these events. Although we failed to clarify that chronotropic incompetence itself was an independent predictor for the major cardiac events, it may be caused by this reason. But, it should be noted that the combination of the data obtained from high-tech examinations such as the SSS of SPECT images with low-tech examinations such as the maximal heart rate of the exercise testing contributed to improve the predictive capability of the cardiac events.

Second, evaluation of all SPECT images at a core center was not practically feasible. Then, SSS was scored at the participating institute. Although, the staffs of image interpretation were repeatedly trained, reduction of inter-institute variation may not be absolutely enough. In addition, although a 20-segment model was used to score SSS or SRS, this can be converted to the 17-segment model that is currently recommended [16].

Conclusion

The maximal heart rate obtained by exercise testing combined with SSS using exercise myocardial SPECT is the useful predictor of cardiac events in patients with suspected coronary artery disease.

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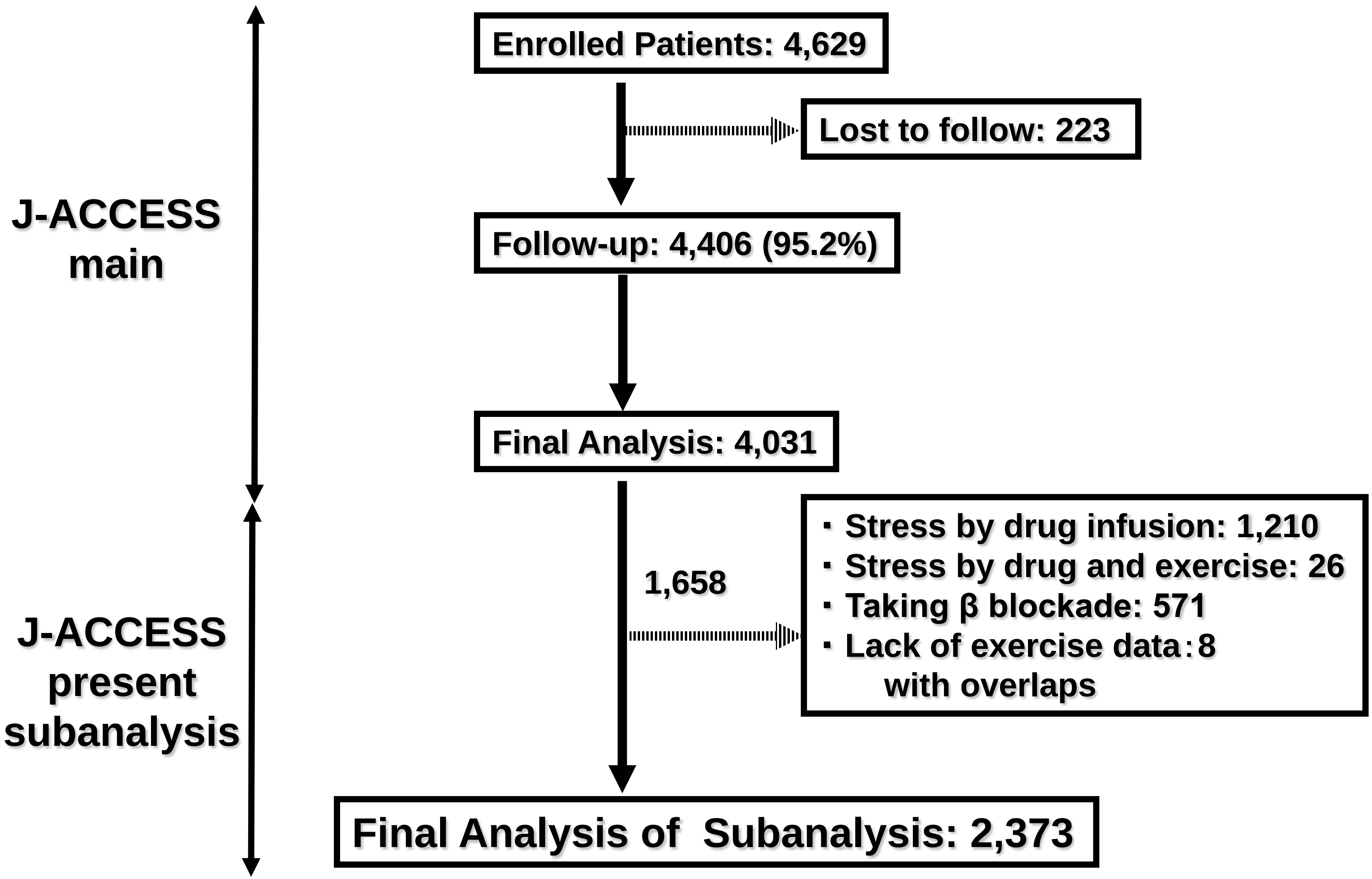
Figure Legends

Fig 1: The enrolled patients to the present subanalysis of J-ACCESS

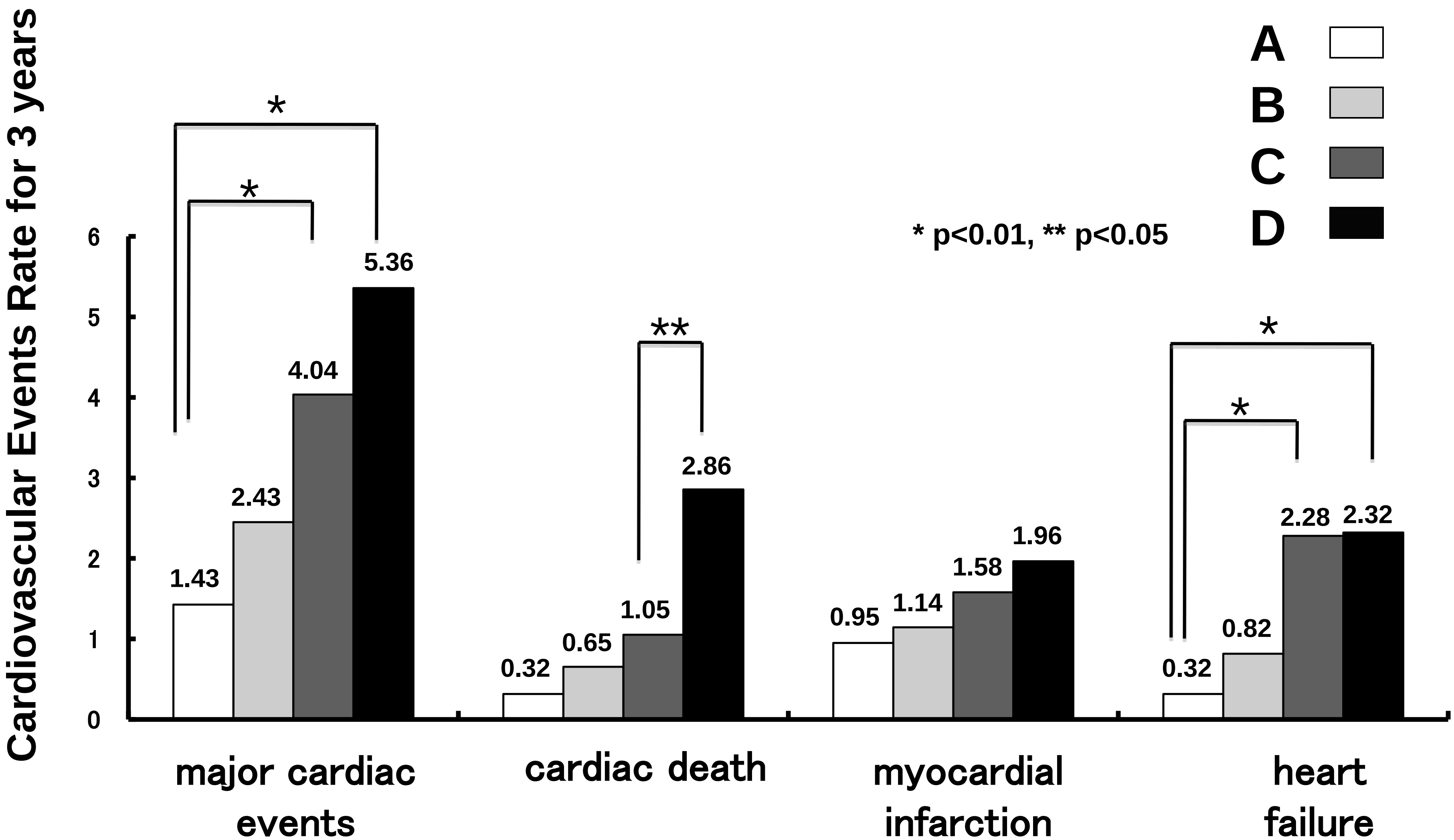
Table 1: Characteristics of participating patients in the present subanalysis of J-ACCESS. Group A: attained their target heart rate (THR) and their summed stress score (SSS) < 4, Group B: not achieved their THR and their SSS < 4, Group C: attained their THR and their their SSS ≥ 4, and Group D: not achieved their THR and their SSS ≥ 4.

Fig 2: Cardiovascular events rate in each categorized group. Group A: attained their target heart rate (THR) and their summed stress score (SSS) < 4, Group B: not achieved their THR and their SSS < 4, Group C: attained their THR and their their SSS ≥ 4, and Group D: not achieved their THR and their SSS ≥ 4.

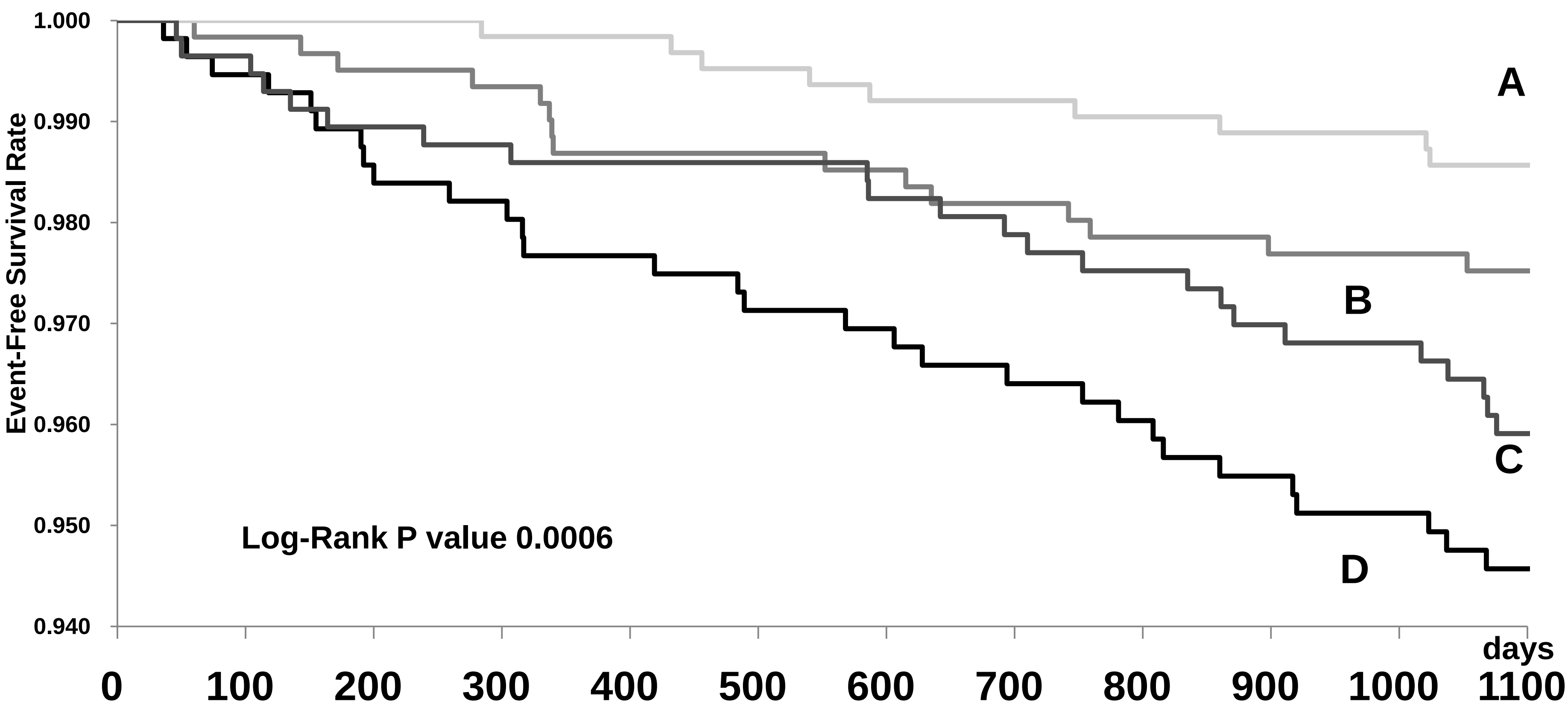
Fig 3: Kaplan-Meier estimates for major cardiac events (cardiac death, non-fatal myocardial infarction, and heart failure required to hospitalization) according to classification by the SSS and the maximal heart rate during exercise testing. Group A: attained their target heart rate (THR) and their summed stress score (SSS) < 4, Group B: not achieved their THR and their SSS < 4, Group C: attained their THR and their their SSS ≥ 4, and Group D: not achieved their THR and their SSS ≥ 4.


J-ACCESS main
Enrolled Patients: 4,629
Lost to follow: 223
Follow-up: 4,406 (95.2%)
Final Analysis: 4,031
J-ACCESS present subanalysis
1,658
・Stress by drug infusion: 1,210
・Stress by drug and exercise: 26
・Taking β blockade: 571
・Lack of exercise data：8
with overlaps
Final Analysis of Subanalysis: 2,373

		A (n=631)	B (n=612)	C (n=570)	D (n=560)	P value
age		65±10	64±11	66±9	64±11	0.0007
gender	male (%)	325 (51.5)	371 (60.6)	437 (76.7)	444 (79.2)	<0.0001
BMI	kg/m^2	23.5±3.1	23.7±3.2	23.5±3.0	24.0±3.1	0.5845
past history of myocardial infarction	yes (%)	49 (7.8)	50 (8.2)	253 (44.4)	274 (48.9)	<0.0001
	no (%)	579 (91.7)	555 (90.7)	311 (54.6)	278 (49.7)	
	unknown (%)	3 (0.5)	7 (1.1)	6 (1.0)	8 (1.4)	
diabetes mellitus	yes (%)	131 (20.8)	160(26.1)	170(29.8)	189(33.8)	<0.0001
	no (%)	492 (77.9)	442(72.3)	390(68.4)	367(65.5)	
	unknown (%)	8 (1.3)	10 (1.6)	10 (1.8)	4 (0.7)	
hypertension	yes (%)	289 (45.8)	302(49.4)	277(48.6)	286(51.1)	0.364
	no (%)	335 (53.1)	308(50.3)	288(50.5)	270(48.2)	
	unknown (%)	7 (1.1)	2 (0.3)	5 (0.9)	4 (0.7)	
hyperlipidemia	yes (%)	258 (40.9)	252(41.2)	257(45.1)	299(53.4)	<0.0001
	no (%)	356 (56.4)	349(57.0)	301(52.8)	257(45.9)	
	unknown (%)	17 (2.7)	11 (1.8)	12 (2.1)	4 (0.7)	
previous coronary revascularization	yes (%)	132 (20.9)	153(25.0)	244(42.8)	253(45.2)	<0.0001
	no (%)	499 (79.1)	458(74.8)	322(56.5)	303(54.1)	
	unknown (%)	0 (0.0)	1 (0.2)	4 (0.7)	4 (0.7)	
abnormal ECG at rest	yes (%)	282 (44.7)	275(44.9)	371(65.0)	361(64.5)	<0.0001
	no (%)	323 (51.2)	311(50.9)	173(30.4)	171(30.5)	
	unknown (%)	26 (4.1)	26 (4.2)	26 (4.6)	28 (5.0)	
Ischemic change in exercise testing	yes (%)	167 (26.5)	148(24.2)	130(22.8)	134(23.9)	0.828
	no (%)	158 (25.0)	157(25.7)	138(24.2)	128(22.8)	
	unknown (%)	306 (48.5)	307 (50.1)	302 (53.0)	298 (53.2)	



Cardiovascular Events Rate for 3 years
A
B
C
D
* p<0.01, ** p<0.05
0
1
2
3
4
5
6
1.43
2.43
4.04
5.36
0.32
0.65
1.05
2.86
0.95
1.14
1.58
1.96
0.32
0.82
2.28
2.32
*
*
**
*
*
major cardiac events
cardiac death
myocardial infarction
heart failure



A	631	630	630	629	629	627	624	624	621	619	619	613
B	612	610	608	605	598	597	594	591	588	584	581	579
C	570	567	560	559	555	555	552	548	546	541	540	532
D	560	557	550	546	543	538	535	528	525	520	518	513