Association of the Extent of Myocardial Ischemia with Outcomes in Patients with Suspected Coronary Artery Disease

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Abstract

Background: There is an ongoing controversy regarding the necessity of single-photon emission computed tomography (SPECT) for patients with ischemic heart diseases after the publication of the results of the ISCHEMIA trial. We aimed to evaluate the association of the extent of myocardial ischemia with outcomes in patients with suspected coronary artery disease in Japan.

Methods: From the data of 2780 patients with stable angina, who were enrolled prospectively between January 2006 and March 2008 in Japan and had undergone physician-referred non-invasive imaging tests, 1205 patients managed with SPECT were stratified by 10% myocardial ischemia. Major adverse cardiac events (MACEs), including death, myocardial infarction, hospitalization for heart failure, and late revascularization, were followed-up for 1 year.

Results: Patients with ≥10% myocardial ischemia (n=173) were older than patients with <10% myocardial ischemia (n=1032) and had a significantly higher 1-year cumulative incidence of MACEs (9.1% vs. 1.2%, P<0.0001). After adjusting for confounders, the risk of ≥10% myocardial ischemia relative to <10% myocardial ischemia for MACEs remained significant (adjusted hazard ratio [95% confidence interval], 2.40 [1.09-5.26], P=0.029).

Conclusion: The presence of ≥10% myocardial ischemia was significantly associated with the 1-year risk for MACEs in Japanese patients with suspected coronary artery disease.

Introduction

The ISCHEMIA (International Study of Comparative Health Effectiveness with Medical and Invasive Approaches) trial strikingly showed no survival benefits of an initial interventional strategy to an initial conservative strategy in patients with stable coronary artery disease (CAD)[1]. This study has important implications for the diagnostic imaging, as all patients in the study had moderate-severe ischemia based on stress testing (≥ 10% myocardial ischemia), which was determined at the enrolling site, and anatomic stenosis defined by a 50% left main coronary artery or a 70% epicardial stenosis by a coronary computed tomography (CT). Overall, 14% of the patients enrolled in the trial had moderate-severe ischemia on imaging but no significant coronary stenosis on CT[1]. There is an ongoing controversy regarding the necessity of imaging for patients with ischemic heart diseases, especially after the publication of the results of the ISCHEMIA trial.[2] Suggestions have been made that imaging may be unnecessary as it does not contribute to the development of a treatment strategy for these patients.[2]

However, it is important to note that the ISCHEMIA trial does not clarify if testing is necessary. Although false-positive single-photon emission computed tomography (SPECT) results due to attenuation artifacts were a likely factor, some patients may have had ischemia from diffuse but less significant stenosis or microvascular disease that could help explain their chest pain syndromes with an associated cardiovascular risk[3]. In fact, ischemia assessment offers the information to diagnose CAD, to

prognosticate CAD risk [4], and to refer for an intervention. The spectrum of ischemia extent has extensive established prognostic value[5–8]. Despite evidence for the necessity of non-invasive ischemia testing, the above-mentioned opinion against ischemia testing has been emerging[2]. Thus, we aimed to re-assess and confirm the association between the extent of ischemia and prognosis in patients with CAD. According to Japanese registries, the prognostic impact of ≥ 10% myocardial ischemia has not yet been elucidated. The purpose of this post hoc analysis of a subgroup of patients recruited for the Japanese Coronary-Angiography or Myocardial Imaging for Angina Pectoris Study (J-COMPASS)[9], a multicenter study in Japan, was to evaluate the association of 10% myocardial ischemia on physician-referred SPECT with outcomes in Japanese patients with suspected CAD.

Methods

Ethical statements

All methods were performed according to the principles of the Declaration of Helsinki. The study protocol was approved by the institutional review board of Kitano Hospital (approval number: P16-01-005) and each institutional review board (Appendix). All participants provided written or oral informed consent before enrolment into the study[9]. We anonymized patient records and information before commencing the analysis.

Patient and public involvement

Patients and the public were not involved in the design or conduct of the study.

Study design and population

The design and main trial results of the J-COMPASS study has already been published[9]. From 81 centers in Japan with high-end diagnostic facilities (Appendix), 2,870 consecutive patients with suspected stable angina were enrolled prospectively between January 2006 and March 2008 and followed-up. Based on the results of initial tests and other clinical findings, well-trained cardiologists determined the initial diagnostic imaging modality to be used and the treatment strategy without any pre-specified criteria. In this post hoc sub-study, we excluded patients who had undergone coronary angiography (CAG; n= 950) and CT (n=635). Thus, symptomatic patients who underwent SPECT (n=1205) as the initial diagnostic test for suspected chronic CAD were analyzed (**Figure 1**). The exclusion criteria of the original study were acute coronary syndrome at presentation or within a short period after the initial test and a history of myocardial infarction (MI) or revascularization therapy.

SPECT images were divided into 17 segments, each of which was scored on a 5-point scale under both stress and rest conditions (0, normal; 1, mildly reduced; 2, moderately reduced; 3, severely reduced; 4, absent) according to the American Heart Association criteria[10]. Summed stress scores (SSS) and summed rest scores were obtained by adding the scores of 17 myocardial segments. The sum of the differences between these 2 scores defined the summed difference score. The percent (%) myocardial

ischemia (100 × summed difference score [SDS]/68) was calculated and a SDS ≥7 was considered to be ≥10% myocardial ischemia[5, 11].

Outcome measures

The outcomes included major adverse cardiovascular event (MACEs), such as death, acute MI, hospitalization for heart failure, and late revascularization (>3 months) in accordance with the original and sub-studies[9, 12-14]. A 1-year follow-up was performed with an allowance of 1 month.

Statistical analysis

In this analysis, we 1) compared the baseline characteristics of patients with and without ≥10% myocardial ischemia, 2) investigated the outcomes of the two groups, and 3) investigated the prognostic implication of ≥10% myocardial ischemia stratified by stress myocardial perfusion abnormality.

Categorical variables are expressed as numbers and percentages; they were compared using the chi-square test. Continuous variables are expressed as means (standard deviation) or median and interquartile ranges. Continuous variables were compared between the two groups using Student's *t*-test. The Kaplan-Meier analysis was used to estimate the MACE rate between the revascularization and non-revascularization groups; the log-rank test was used to perform univariate comparisons. To compare risks between the revascularization and non-revascularization groups, a multivariable Cox proportional hazard model was developed for MACEs. The results are expressed as hazard ratios (HRs) and 95% confidence intervals (CIs). We selected 13 clinically relevant risk-adjusting variables as well as SDS ≥7: age ≥60 years; sex; body mass index (BMI); estimated glomerular filtration rate <60 mL/min/m^2; the presence of hypertension, dyslipidemia, diabetes, hyperuricemia, chronic obstructive pulmonary disease, and aortic aneurysms; Canadian Circulation Society class 2 or higher[15]; current smoking status; and New York Heart Association (NYHA) functional class 2 or higher[16], which are mostly consistent with that used in our previous reports (Table 1). We then analyzed the impact of SDS≥ 7 stratified by SSS.

Statistical analysis was performed by the study biostatistician using SAS 9.4 software (SAS Institute Inc., Cary, NC). All reported P values were two-tailed, and P values <0.05 were considered statistically significant.

Results

Patient characteristics

Of 1205 patients who underwent SPECT, 173 patients (14.4%) showed SDS≥7 (≥10% myocardial ischemia) and 1032 patients (85.6%) showed SDS<7 (<10% myocardial ischemia) (**Figure 1**).

Patients with ≥10% myocardial ischemia were less likely to be women (26.0% vs. 46.8%, P<0.0001) and had a greater prevalence of diabetes (48.6% vs. 24.7%, P<0.0001), hyperuricemia (8.7% vs. 4.7%, P=0.04),

and peripheral artery disease (5.8% vs. 2.1%, P=0.02); their symptoms were more severe with a higher SSS than those with <10% myocardial ischemia (n=1032, 85.6%) (**Table 1**).

Association of the extent of myocardial ischemia with outcomes

The 1-year follow-up rate was 97.6%. The 1-year cumulative incidence of MACEs was significantly higher in the ≥10% myocardial ischemia group than in the <10% myocardial ischemia group (6.9% vs. 1.8%, log-rank P<0.0001, **Figure 2**). After adjusting for confounders, the risk of MACEs was significantly higher in the ≥10% myocardial ischemia group than in the <10% myocardial ischemia group (adjusted HR [95% CI], 2.40 [1.09-5.26], P=0.029, **Table 2**). In the subgroup analysis, the impact of the ≥10% myocardial ischemia seemed to be greater on low SSS (**Table 2**)

Discussion

The main findings of this study are as follows: 1) patients with ≥ 10% myocardial ischemia had a higher risk of atherosclerosis, more severe symptoms, and higher SSS on SPECT than those without, and 2) the risk of MACEs in the ≥ 10% myocardial ischemia group remained significantly high compared to that in the <10% myocardial ischemia in Japanese patient in clinical practice.

Verification of the prognostic value of 10% myocardial ischemia in Japan

There is evidence for the role of SPECT in predicting cardiac event rate, most of which showed that the semi-quantitative assessment of SSS or SDS was well associated with the cardiac event rate[4-8]. Prognostic impact of the ≥ 10% myocardial ischemia has been reported in Western countries with therapeutic implication[6, 17] or cost effectiveness[18]. In a previous multi-center study in Japan, Nishimura et al. showed the incremental prognostic value of SSS in patients who underwent SPECT for suspected CAD[7]. From the same registry, Momose et al. described SDS as a prognostic factor in patients who underwent SPECT and subsequent CAG[8]. Currently, evaluating the 10% myocardial ischemic cut-off is an issue when deploying the results of the ISCHEMIA trial in clinical practice. In the present study, we described the patient characteristics with the ≥ 10% myocardial ischemia in Japan and verified that the prognostic implication of this cut-off is applied to Japanese patient. Patients with moderate to severe myocardial ischemia had more severe symptoms that may be relieved by revascularization and should be treated carefully in the risk control.

Role of SPECT in the post ISCHEMIA era

There was no difference in the outcomes on comparing SPECT and coronary CT as an initial strategy[9, 14, 19]. However, anatomic testing as an initial strategy has been consistently associated with increased invasive catheterization and revascularization[9, 20, 21]. Although the benefit of revascularization was not shown in the COURAGE (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation) trial[22] ,the ISCHEMIA trial[1], and patients with diabetes[23], to diagnosing chest pain is an important role of SPECT with functional testing. These two randomized controlled trials and ORBITA (Objective

Randomized Blinded Investigation with Optimal Medical Therapy of Angioplasty in Stable Angina) trial[24] suggest that the demonstration of ischemia may be critically important when selecting patients who will experience symptomatic relief after revascularization. Only the presence of angina and anatomic stenosis is insufficient to identify a population for whom revascularization can improve the quality of life[24]. Therefore, identification of patients who may have symptomatic benefit from revascularization is an important role for ischemia imaging. The present study clearly showed that the risk of MACEs in the ≥ 10% myocardial ischemia group was significantly higher than that in the <10% myocardial ischemia group, consistently with previous studies[6, 25]. Thus, risk-stratification is another important role for ischemia imaging. Microvascular dysfunction and diffuse stenotic lesions in coronary artery disease can lead to stress-induced myocardial perfusion abnormalities and are recognized as an important cause of chest pain linked to the prognosis. These abnormalities cannot be diagnosed with anatomic testing[3]. The therapeutic goal and treatment strategy for patients with ≥10% myocardial ischemia as identified by SPECT need to be considered when we deploy the results of randomized controlled trials in clinical practice; however, SPECT may still remain the main diagnostic tool to assess patients with suspected CAD in the post ISCHEMIA era[2].

Limitations

First, information about the criteria for the selection of diagnostic modalities, obstructive coronary disease in subsequent CAG, and the completeness of revascularization was not collected and analyzed because the cohort was enrolled between January 2006 and March 2008, and this was before the widespread use of fractional flow reserve in Japan. Second, semi-quantitative scoring for SPECT was not performed by an interpretation committee but in each institution, which may limit the reliability of scoring results, although all centers had state-of-the-art diagnostic facilities. Third, because of a 1-year follow-up, the event rate was so low that the statistical analysis was limited. Fourth, we did not include the therapeutic factors in the outcome analyses for two reasons: 1) to clearly show the prognostic implication of the diagnostic process and 2) to consider the neutral results of the randomized controlled trials comparing the treatment strategies[1, 22, 24]. Finally, there might be several sources of bias that could not be corrected despite our statistical treatment due to the observational study design.

Conclusion

The presence of ≥10% myocardial ischemia was significantly associated with a 1-year risk for MACEs in Japanese patients with suspected CAD.

Declarations

Author contributions

Kato T had full access to all data in the study, and takes responsibility for the integrity of the data and accuracy of the data analysis.

Study concept and design: T. K., M. M.

Acquisition, analysis, or interpretation of data: T. K., M. M., Y. U., M. N., N., M., S. H., T. Y., T. N., E. S., M. I., and N. T.

Drafting of the manuscript: T. K.

Critical revision of the manuscript for important intellectual content: T. K., M. M., Y. U.,, M. N., N., M., S. H., T. Y., T. N., E. S., M. I., and N. T.

Statistical analysis: Y. U.

Administrative, technical, or material support: E. S., and N. T.

Study supervision: N. T.

Competing interest

The author(s) declare no competing interests.

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None.

Data availability

All data relevant to the study are included in the article or uploaded as supplementary information.

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Tables

Table 1
Patient population

	≥ 10% myocardium ischemia (SDS ≥ 7) (n = 173, 14.4%)		< 10% myocardium ischemia (SDS < 7) (n = 1032, 85.6%)		p value
Age	66.1	10.5	66.2	10.6	0.95
Age > = 60 years old*	127	73.4%	738	71.5%	0.65
Women*	45	26.0%	483	46.8%	< .0001
BMI (kg/m^2) || *	24.1	3.3	23.8	3.6	0.38
Systolic Bp (mmHg)	138.8	18.1	137.5	20.3	0.44
Diastolic Bp (mmHg)	77.3	11.8	78.4	12.3	0.27
Smoking*	46	26.6%	203	19.7%	0.04
Hypertension*	103	59.5%	576	55.8%	0.41
Dyslipidemia*	91	52.6%	441	42.7%	0.02
Diabetes*	84	48.6%	255	24.7%	< .0001
Hyperuricemia*	15	8.7%	49	4.7%	0.04
Familial history of CAD	18	10.4%	124	12.0%	0.61
Cerebrovascular disease	14	8.1%	91	8.8%	0.88
Peripheral artery disease	10	5.8%	22	2.1%	0.02
Atrial fibrillation	8	4.6%	41	4.0%	0.68
COPD*	2	1.2%	11	1.1%	1.00
Disease of aorta*	3	1.7%	23	2.2%	1.00
Malignancy	7	4.0%	22	2.1%	0.17

Values are expressed as number (%) or mean (SD).

P values were calculated using a chi-square test for categorical variables; continuous variables are expressed as means (standard deviation [SD]). Continuous variables were compared using the Student's t-test between two groups.

|| Body mass index was calculated as weight in kilograms divided by height in meters squared.

* Potential risk-adjusting variables selected for Cox proportional hazard models. CCS was adjusted for Class 2 or more, and NYHA functional class was adjusted for II or more.

BP = blood pressure, BMI = body mass index, CAD = coronary artery disease, COPD = chronic obstructive pulmonary disease, eGFR = estimated glomerular filtration rate, CCS = Canadian Circulation Society, NYHA = New York Heart Association, SPECT = single photon emission computed tomography, SSS = summed stress score, SDS = summed difference score.

		≥ 10% myocardium ischemia (SDS ≥ 7) (n = 173, 14.4%)		< 10% myocardium ischemia (SDS < 7) (n = 1032, 85.6%)		p value
eGFR(mL/min/1.73 m^2)*		70.3	23.7	73.2	31.0	0.24
SSS	SSS: 0 ~ 7	6	3.5%	958	92.8%	< .0001
	SSS: 8 ~ 11	38	22.0%	36	3.5%	
	SSS: 12~	129	74.6%	38	3.7%	
CCS*	Class1	106	61.3%	833	80.7%	< .0001
	Class2	60	34.7%	190	18.4%	
	Class3	7	4.0%	6	0.6%	
	Class4	0	0.0%	3	0.3%	
NYHA*	I	137	79.2%	970	94.0%	< .0001
	II	34	19.7%	59	5.7%	
	III	2	1.2%	3	0.3%	
	IV	0	0.0%	0	0.0%	

Values are expressed as number (%) or mean (SD).

P values were calculated using a chi-square test for categorical variables; continuous variables are expressed as means (standard deviation [SD]). Continuous variables were compared using the Student's t-test between two groups.

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Table 2
Clinical outcomes of patients and subgroup analysis

	≥ 10% myocardium ischemia: SDS ≥ 7	< 10% myocardium ischemia: SDS < 7	Unadjusted			Adjusted		
	N of patients with event/N of patients at risk	N of patients with event/N of patients at risk	HR	95%CI	P value	HR	95%CI	P value
Entire	12 (6.9%)	19 (1.8%)	3.86	1.87–7.94	0.0003	2.40	1.09–5.26	0.029
Subgroup analysis stratified by SSS								
SSS 0–7	1/6 (16.9%)	16/958 (1.7%)	10.9	1.44-82.0	0.02	n/a		
SSS 8–11	1/38 (2.6%)	2/36 (0.6%)	0.47	0.04–5.17	0.54	n/a		
SSS 12-	10/129 (7.7%)	1/38 (2.6%)	3.04	0.39–23.7	0.29	n/a		

HR = hazard ratio, CI = confidence interval, SSS = summed stress score, SDS = summed difference score, n/a = not available,

Figures

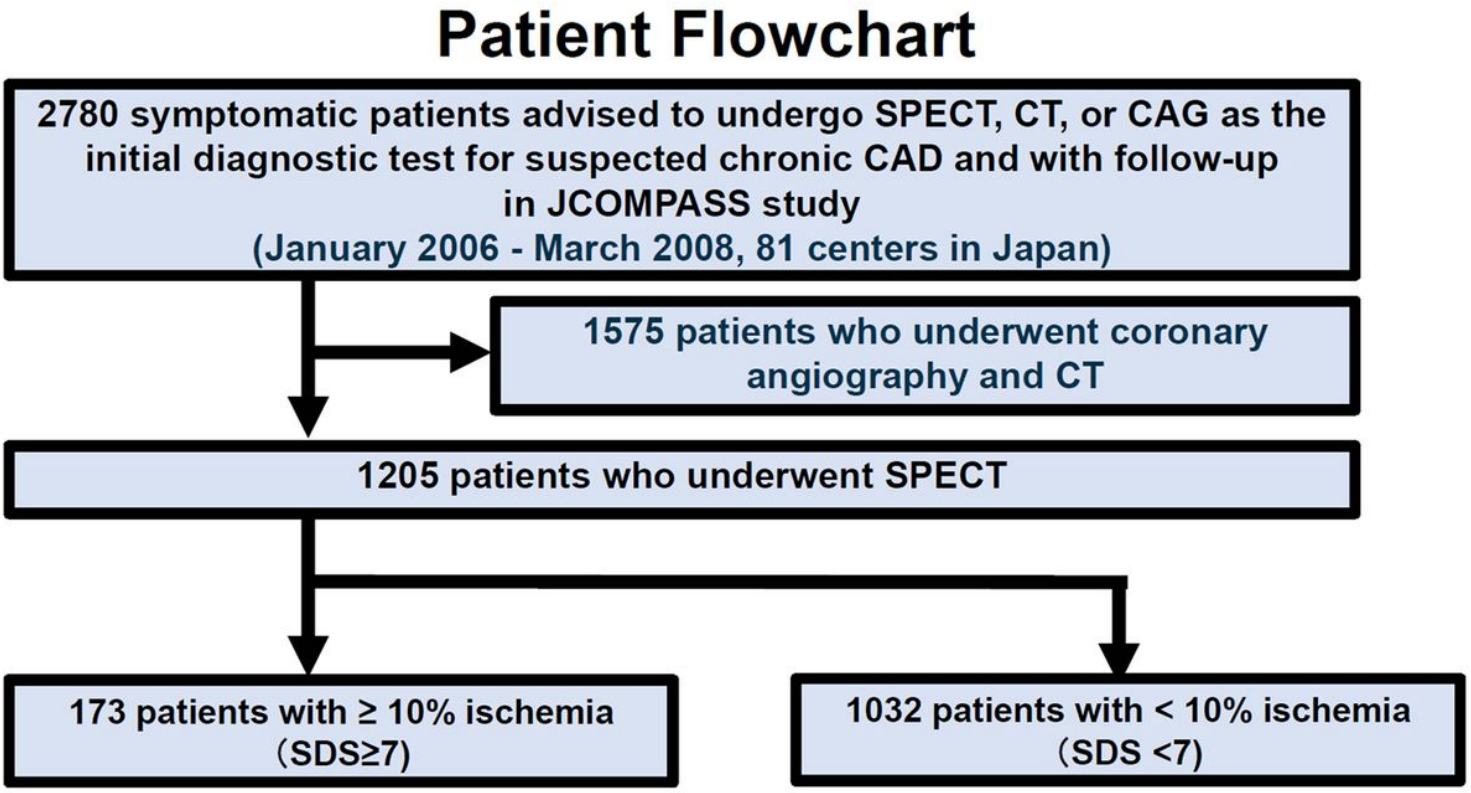

Figure 1

Patient flowchart. SPECT= single photon emission computed tomography, CT=computed tomography, CAG=coronary angiography, J-COMPASS= Japanese Coronary-Angiography or Myocardial Imaging for Angina Pectoris Study, SDS=summed difference scores. ≥10% myocardial ischemia was defined as SDS ≥7.

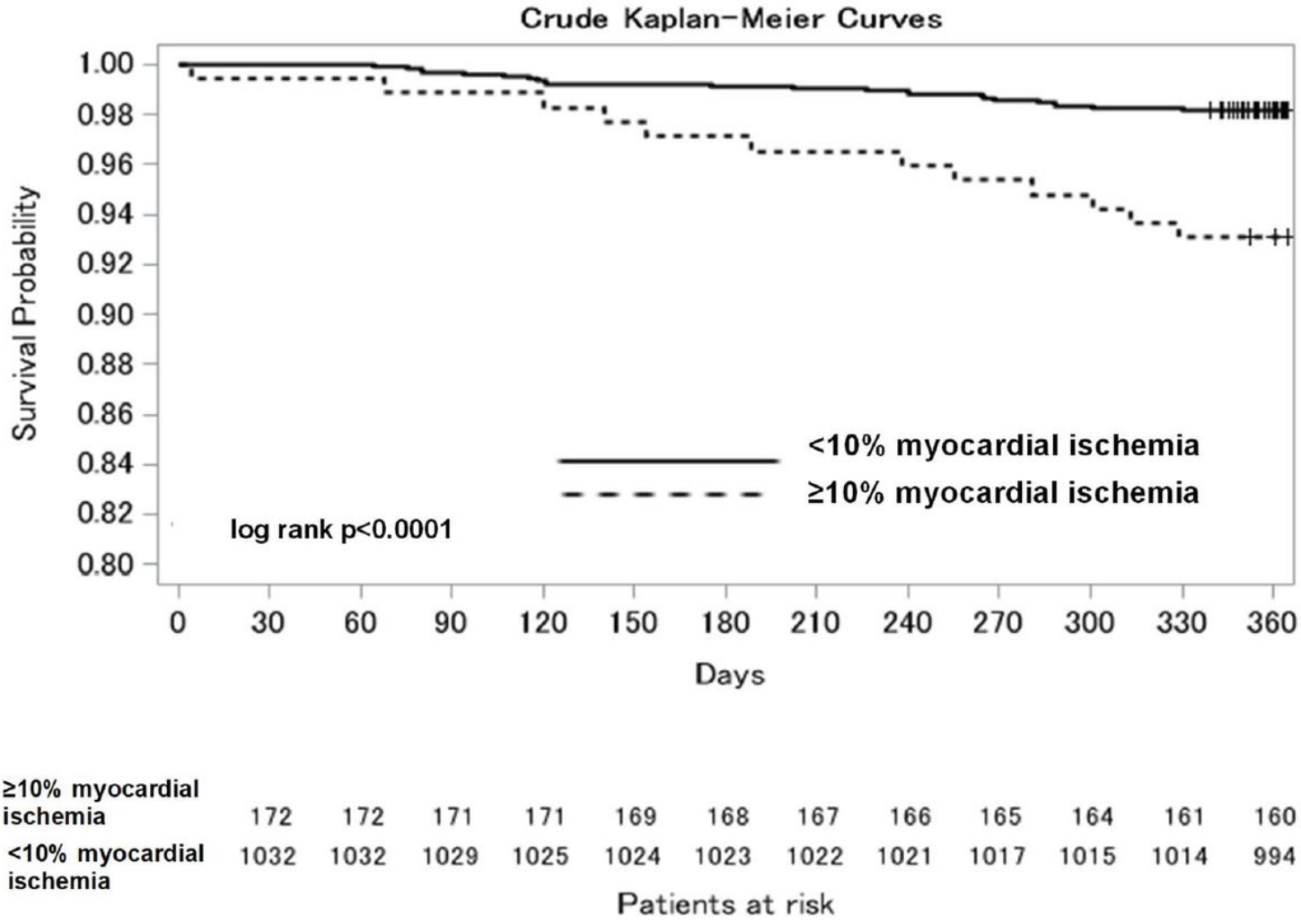

Figure 2

Crude Kaplan-Meier curve for major adverse cardiovascular events (MACEs) MACEs were defined as death, acute myocardial infarction, heart failure hospitalization, and late revascularization (>3 months).

Supplementary Files

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- Appendix.docx