

# Clinical outcomes of discordant exercise electrocardiographic and echocardiographic findings compared with concordant findings in patients with chest pain and no history of coronary artery disease

## An observational study

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### Abstract

The aim of this study was to evaluate comparative clinical outcomes of discordant electrocardiographic (ECG) and echocardiographic (Echo) findings compared with concordant findings during treadmill exercise echocardiography in patients with chest pain and no history of coronary artery disease (CAD).

A total of 1725 consecutive patients who underwent treadmill echocardiography with chest pain and no history of CAD were screened. The patients were classified into 4 groups: ECG-/Echo- (negative ECG and Echo), ECG+/Echo- (positive ECG and negative Echo), ECG-/Echo+, and ECG+/Echo+. Concomitant CAD was determined using coronary angiography or coronary computed tomography. Major adverse cardiac events (MACEs) were defined as a composite of coronary revascularization, acute myocardial infarction, and death.

MACEs were similar between ECG-/Echo- and ECG+/Echo- groups. Compared with ECG+/Echo- group, ECG-/Echo+ group had more MACEs (adjusted hazard ratio [HR] adjusted by clinical risk factors [95% confidence interval {CI}], 3.57 [1.75–7.29],  $P < .001$ ). Compared with ECG+/Echo+ group, ECG-/Echo+ group had lower prevalence of concomitant CAD and fewer MACEs (HR, 0.49 [0.29–0.81],  $P = .006$ ).

Positive exercise Echo alone during treadmill exercise echocardiography had worse clinical outcomes than positive ECG alone, and the latter had similar outcomes to both negative ECG and Echo. Positive exercise Echo alone also had better clinical outcomes than both positive ECG and Echo. Therefore, exercise Echo findings might be superior for predicting clinical outcomes compared with exercise ECG findings. Additional consideration of ECG findings on positive exercise Echo will also facilitate better prediction of clinical outcomes.

**Abbreviations:** BMI = body mass index, BP = blood pressure, CAD = coronary artery disease, CAG = coronary angiography, cCT = coronary computed tomography, DBP = diastolic blood pressure, ECG = electrocardiography, Echo = echocardiography, HR = hazard ratio, IPTW = inverse probability of treatment weighted, MACEs = major adverse cardiac events, SBP = systolic blood pressure, WMA = wall motion abnormalities.

**Keywords:** clinical outcome, discordance, echocardiography, electrocardiography, myocardial ischemia

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## 1. Introduction

Estimation of wall motion abnormalities (WMA) on stress echocardiography is useful to diagnose<sup>[1,2]</sup> coronary artery disease (CAD). Degree of WMA has also been suggested as an excellent predictor of cardiovascular prognosis over clinical factors and exercise electrocardiography (ECG).<sup>[3–7]</sup> However, the usefulness of stress echocardiography as an initial test is being questioned because its superiority over exercise ECG has not been proven in clinical decision-making, despite its superior accuracy in stable patients with chest pain.<sup>[8,9]</sup> Currently, first choice of diagnosing CAD is an exercise ECG test.<sup>[2,10]</sup> On the other hand, the prognostic value of ST changes on exercise ECG is controversial. A previous study from Duke University Medical Center<sup>[11]</sup> showed the importance of ST change in predicting prognosis of CAD with the Duke treadmill score. Some researchers<sup>[7,12,13]</sup> have also insisted on its incremental prognostic value over clinical parameters and other image studies such as <sup>201</sup>Thallium SPECT. On contrary, other researchers have suggested that incremental prognostic value of ST changes is absent over clinical parameters<sup>[4,6,14,15]</sup> or exercise capacity has better prognostic value than ST change.<sup>[15,16]</sup> Comparative evaluation of diagnostic and prognostic values of discordant ECG and echocardiographic (Echo) findings compared with concordant ECG and Echo findings on treadmill exercise echocardiography would help identify whether exercise Echo has additional benefits over exercise ECG in clinical decision-making and whether discordant findings have different clinical outcomes. Therefore, we compared diagnostic and prognostic values according with exercise ECG and Echo findings during treadmill exercise echocardiography in patients with chest pain and no history of CAD.

## 2. Methods

### 2.1. Study population

A total of 1725 consecutive patients who underwent treadmill exercise echocardiography with chest pain and no history of CAD between January 2007 and March 2015 at one cardiology center (Kyung Hee University Hospital at Gangdong, Seoul, Korea) were screened. Patients under 20 years old, who had a past history of myocardial infarction and percutaneous coronary intervention or cardiac artery bypass graft due to ischemic heart disease, ST-T abnormalities such as bundle branch block, ST segment depression, T wave inversion and left ventricular hypertrophy by strain pattern on baseline ECG, WMA and hypertrophic cardiomyopathy on baseline Echo, heart failure (ejection fraction of  $\leq 40\%$ ), valvular heart disease of at least moderate grade, or severe systemic diseases such as end-stage renal disease requiring dialysis and liver cirrhosis were excluded from this study. Patient with inadequate ECG artifact, such as loose leads and wandering baseline, or poor echocardiographic images were also excluded from this study. The hospital ethics committee approved this study (KHNMC IRB 2013–01-114).

### 2.2. Treadmill exercise echocardiography and interpretations

Treadmill exercise echocardiography was performed with symptom-limited treadmill exercise cessation using the standard Bruce protocol. Twelve-lead ECG, blood pressure (BP), and heart rate were monitored during exercise and recorded at each stage

and the end of exercise. After exercise, the patient was moved to the left decubitus position to assess WMA. An experienced sonographer acquired post-exercise echocardiographic images within 30 to 60 seconds after exercise. The images were digitalized and recorded. Positive exercise Echo results (Echo+) were defined as newly developed WMA after exercise. Two cardiology experts independently interpreted WMA without information of clinical data and ECG results. Wall motion score index was estimated using a 17-segment model of the left ventricle (1, normal; 2, hypokinesia; 3, akinesia; 4, dyskinesia).<sup>[17]</sup> Positive exercise ECG results (ECG+) were defined as the development of horizontal or down-sloping ST-depression in  $\geq 2$  contiguous leads during peak exercise. Exercise ECG results were blindly interpreted without information regarding clinical and Echo data. Target heart rate was calculated as 220 minus age. Work load was presented as estimated metabolic equivalents (METs) of exercise. Duke score was calculated as  $([\text{exercise time, min}] - 5) \times [\text{maximal ST-segment depression, mm}] - 4 \times [\text{angina index}]$ .<sup>[11,18]</sup> According to exercise ECG and Echo results, the patients were classified into 4 groups: ECG–/Echo–, negative ECG and Echo results (1404 patients, 81.4%); ECG+/Echo–, positive ECG and negative Echo results (192, 11.1%); ECG–/Echo+, negative ECG and positive Echo results (33, 1.9%); ECG +/Echo+, positive ECG and Echo results (96, 5.6%).

### 2.3. Coronary evaluation, CAD, and coronary revascularization

Coronary angiography (CAG) and coronary computed tomography (cCT) were selectively performed according to treadmill exercise echocardiographic results and physician decision. Concomitant CAD was defined as 50% or more stenosis of the coronary arteries on CAG or cCT. The location of diseased coronary vessels was analyzed based on American Heart Association guidelines for CAG.<sup>[19]</sup> Coronary revascularization was determined by physician discretion based on the patient's symptoms and clinical necessity.

### 2.4. Clinical characteristics and test analysis, follow-up and clinical outcomes

Clinical characteristics and test results were obtained using medical records. Typical angina was defined as exercise-associated chest discomfort, such as exertional chest pain or discomfort, and exertional dyspnea. Major adverse cardiac events (MACEs) including coronary revascularization, acute myocardial infarction, cardiac death, and death were examined through telephone interview. After development of MACEs, patients were censored in follow-up. Acute myocardial infarction was defined as significant cardiac enzyme elevation with appropriate symptoms and ECG changes.

### 2.5. Statistical analysis

Statistical analyses were performed using R software, version 3.3.1 for event-free survival analysis and SPSS for Windows, version 13.0 (SSPS Inc., Chicago, IL) for others. ECG–/Echo– group were selected by random sampling as 3 time numbers of the second most group, ECG+/Echo– and considered expected follow up loss rate of 20%. Histograms and absolute values of skewness ( $< 2$ ) and kurtosis ( $< 7$ ) of the distribution were used to estimate normality of data.<sup>[20]</sup> Continuous variables were expressed as

mean ± standard deviations (or medians and interquartile ranges in the case of variables for which the data were skewed). Categorical variables were expressed as group percentages. According to results of normality tests, analysis of variance or Kruskal-Wallis test was performed to compare continuous variables of 4 groups. Post-hoc tests used Tukey honestly significant difference if data met the assumption of homogeneity of variances, and Games Howell if data did not meet the homogeneity of variances assumption. Chi-squared test (or Fisher exact test when cell counts were <5) was used to compare categorical variables. An inverse probability of treatment weighted (IPTW) method based on propensity score was used to balance of covariates, including traditional cardiovascular risk factors between groups. To reduce the influence of outlying weights, weights were stabilized via multiplication by mean propensity score. The propensity score was obtained from a logistic regression model and was the conditional probability given a set of covariates including age, sex, hypertension, diabetes, dyslipidemia, smoking, and body mass index (BMI). A standardized difference of <0.2 after the IPTW method indicated balance of the covariates between groups (see Table, Supplementary Table 1, <http://links.lww.com/MD/D239>, which illustrates standardized differences and balance prior to and after

IPTW).<sup>[21]</sup> Survival curves were estimated with the Kaplan-Meier method. Crude hazard ratio (HR) was calculated using an unadjusted Cox proportional hazards model. Adjusted HR was calculated using an IPTW-weighted Cox proportional hazards model. Two-sided *P* values <.05 were considered as statistically significant.

### 3. Results

#### 3.1. Clinical characteristics and treadmill exercise echocardiographic results between groups

Among 1404 patients with ECG-/Echo-, 600 patients were selected by random sampling and 490 patients (82%) were finally examined through telephone interview. Telephone interview was possible in 161 (84%) of 192 patients with ECG+/Echo-, 29 (88%) of 33 patients with ECG-/Echo+, and 95 (99%) of 96 patients with ECG+/Echo+. Compared with ECG-/Echo- group, ECG+/Echo- group was older, had more hypertension and symptom of typical angina, elevated baseline and peak systolic BP (SBP), higher target heart rate achievement, and lower Duke score (Table 1). Compared with ECG-/Echo- group, ECG-/Echo+ group was older and had more diabetes, lower peak heart rate,

**Table 1**  
Clinical variables of 4 groups.

	ECG-/Echo-(G1, n=490)	ECG+/Echo-(G2, n=161)	ECG-/Echo+ (G3, n=29)	ECG+/Echo+ (G4, n=95)	<i>P</i> value	<i>P</i> value between groups			
						G1 vs G2	G1 vs G3	G2 vs G3	G3 vs G4
Clinical characteristics									
Age, yrs <sup>a</sup>	55 ± 11	58 ± 8	62 ± 10	59 ± 8	<.001	.002	.005	.188	.551
Male, n (%)	269 (55)	100 (62)	18 (62)	78 (82)	<.001	.109	.45	.997	.024
Hypertension, n (%)	185 (38)	75 (47)	12 (41)	50 (53)	.025	.047	.696	.605	.289
Diabetes, n (%)	76 (16)	34 (21)	9 (31)	27 (28)	.006	.099	.038*	.334	.786
Dyslipidemia, n (%)	96 (20)	29 (18)	3 (10)	14 (15)	.460	.659	.218	.423*	.760
Smoking, n (%)	108 (22)	33 (21)	8 (28)	27 (28)	.448	.697	.49	.403	.930
BMI, kg/m <sup>2a</sup>	25 ± 4	25 ± 3	25 ± 4	25 ± 4	.512	.963	.979	.934	.989
Typical angina	193 (39)	82 (51)	15 (52)	51 (54)	.009	.010	.188	.937	.853
TMT Echo									
b-SBP, mmHg <sup>a</sup>	115 ± 15	120 ± 17	125 ± 17	124 ± 17	<.001	.002	.803	.880	1.000
b-DBP, mmHg <sup>a</sup>	68 ± 11	70 ± 12	73 ± 12	72 ± 12	.006	.463	.136	.509	.979
b-HR, beats/min <sup>b</sup>	71 ± 12	69 ± 10	69 ± 11	68 ± 10	.125	.227	.925	.996	.965
p-SBP, mmHg <sup>a</sup>	168 ± 25	176 ± 25	172 ± 22	172 ± 24	.004	.003	1.000	1.000	1.000
p-DBP, mmHg <sup>a</sup>	77 ± 17	76 ± 16	81 ± 16	80 ± 15	.098	.975	.462	.395	.991
p-HR, beats/min <sup>b</sup>	160 ± 17	163 ± 18	148 ± 23	149 ± 20	<.001	.482	.048	.017	1.000
Target HR, % <sup>b</sup>	98 ± 10	101 ± 11	93 ± 14	92 ± 12	<.001	.005	.359	.039	.994
METS <sup>b</sup>	11.5 ± 2.3	11.7 ± 2.1	9.9 ± 3.6	10.4 ± 2.8	<.001	.872	.107	.074	.906
Duke score <sup>b</sup>	9.6 ± 2.2	-0.8 ± 5.7	7.7 ± 3.7	-7.1 ± 9	<.001	<.001	.085	<.001	<.001
WMI after exercise <sup>c</sup>	1	1	1.2 (0.8-1.5)	1.4 (0.9-1.8)	<.001	-	<.001	<.001	.796
CAG, n (%)	55 (11)	35 (22)	21 (72)	77 (81)	<.001	.002	<.001*	<.001	.317
cCT or CAG, n (%)	175 (36)	79 (49)	25 (86)	81 (85)	<.001	.003	<.001	<.001	1.000*
Characteristics of cCAD									
cCAD, n (%)	34 (19)	23 (29)	12 (48)	68 (84)	<.001	.087	.001	.082	<.001
LM, n (%)	1 (3)	0 (0)	0 (0)	8 (12)	.119*	1.000*	1.000*	-	.591*
LAD, n (%)	23 (68)	14 (61)	10 (91)	61 (90)	.007*	.757	.240*	.212*	1.000*
LCx, n (%)	16 (47)	9 (39)	5 (45)	33 (49)	.952	.651	.926*	1.000*	.850
RCA, n (%)	10 (29)	8 (35)	6 (55)	31 (46)	.328	.586	.161*	.459	.581
Numbers of diseased vessels <sup>b</sup>									
Single	23 (68)	15 (65)	4 (36)	32 (47)					
Double	6 (18)	5 (22)	4 (36)	14 (21)					
Triple	5 (9)	2 (9)	3 (27)	22 (32)					

b-DBP = baseline diastolic blood pressure, b-HR = baseline heart rate, BMI = body mass index, b-SBP = baseline systolic blood pressure, CAG = coronary angiography, cCAD = concomitant coronary artery disease, cCT = coronary computed tomography, LAD = left anterior descending artery, LCx = left circumflex artery, LM = left main, MET = metabolic equivalent of tasks, p-DBP = peak diastolic blood pressure, p-HR = peak heart rate, p-SBP = peak systolic blood pressure, RCA = right coronary artery, TMT Echo = treadmill exercise echocardiography, WMI = wall motion score index.

<sup>a</sup> *P* values based on Tukey post-hoc test.

<sup>b</sup> *P* values based on Games-Howell post-hoc test.

<sup>c</sup> Kruskal-Wallis test.

\* Fisher exact test.

and higher wall motion score index (WMI) after exercise (Table 1). Compared with ECG+/Echo- group, ECG-/Echo+ group had lower peak heart rate and target heart rate achievement, and higher Duke score and WMI after exercise (Table 1). Compared with ECG-/Echo+ group, ECG+/Echo+ group had more men and lower Duke score (Table 1).

### 3.2. Follow up and clinical outcomes compared between groups

Among a total of 775 patients, 112 events (mean follow up,  $4.1 \pm 2.5$  years) were observed (see Table, Supplementary Table 2, <http://links.lww.com/MD/D239>, which illustrates distribution of MACEs): 22 events (4.5%) in ECG-/Echo- group; 16 events (9.9%) in ECG+/Echo- group; 11 events (37.9%) in ECG-/Echo+ group; 63 events (66.3%) in ECG+/Echo+ group. Among these, 108 (96%) events were coronary revascularization. Compared with ECG-/Echo- group, ECG+/Echo- group underwent coronary evaluation more frequently, but did not have significantly higher prevalence of concomitant CAD (Table 1) or more MACEs on both unadjusted analyses and analyses adjusted by cardiovascular risk factors (Table 2, Fig. 1A). Compared with ECG-/Echo- group, ECG-/Echo+ group underwent coronary evaluation more frequently, had higher prevalence of concomitant CAD (Table 1), and more MACEs (Table 2, Fig. 1B). Compared with ECG+/Echo- group, ECG-/Echo+ group underwent coronary evaluation more frequently, had more MACEs (Table 2, Fig. 1C), and did not have significantly higher prevalence of concomitant CAD (Table 1). Compared with ECG-/Echo+ group, ECG+/Echo+ group had higher prevalence of concomitant CAD (Table 1) and more MACEs (Table 2, Fig. 1D), but did not have significantly higher WMI after exercise (Table 1).

Determinants of MACEs were older age, male sex, hypertension, diabetes, current smoker, typical angina, lower work load, and existent WMA on univariate analysis. On multivariate analysis showed determinants of MACEs were hypertension, typical angina, and existent WMA (Table 3).

### 3.3. Angiographic results in patients with negative ECG and positive exercise Echo

Angiographic data of 21 patients with ECG-/Echo+ were available (Table 4). Nine patients (Number 1–9) had concomitant CAD and 7 underwent on-site coronary revascularization (Number 1–7), of whom 1 (Number 7) had a lesion on the small coronary vessels. Twelve patients had minimal or normal

coronary lesions (Number 10–21). In ECG-/Echo+ group, patients with concomitant CAD complained of more frequent typical angina than patients without concomitant CAD (data not shown; 75% vs 31%,  $P=.027$ ).

## 4. Discussion

This study demonstrates that compared with positive exercise ECG alone, positive Echo alone was associated with increased rate of MACEs. Compared with both negative ECG and Echo, positive ECG alone also had similar rate of MACEs. In addition, positive exercise Echo alone was associated with lower prevalence of CAD and decreased rate of MACEs than both positive ECG and Echo.

### 4.1. Clinical outcomes in patients with negative exercise Echo results

There was no significant difference in concomitant CAD prevalence between ECG-/Echo- and ECG+/Echo- groups in our study. However, coronary evaluation was performed in only 39% of patients with negative exercise Echo results and more frequently in ECG+/Echo- group (49% vs 36%,  $P=.003$ ), and concomitant CAD was identified more frequently in ECG+/Echo- group than in ECG-/Echo- group (29% vs 19%) although the difference was not statistically significant ( $P=.087$ ). Therefore, present study cannot confirm whether ECG+/Echo- group compared with ECG-/Echo- group had more CAD or not. It requires further evaluation using a prospective study design.

There was no difference in MACE between ECG-/Echo- and ECG+/Echo- groups. It is an important finding regardless of unclear identification of concomitant CAD, which is consistent with those of several previous studies in which patients with a negative stress Echo result had benign prognosis regardless of stress ECG results.<sup>[3,15,22]</sup>

### 4.2. Clinical outcomes in patients with positive exercise echo results

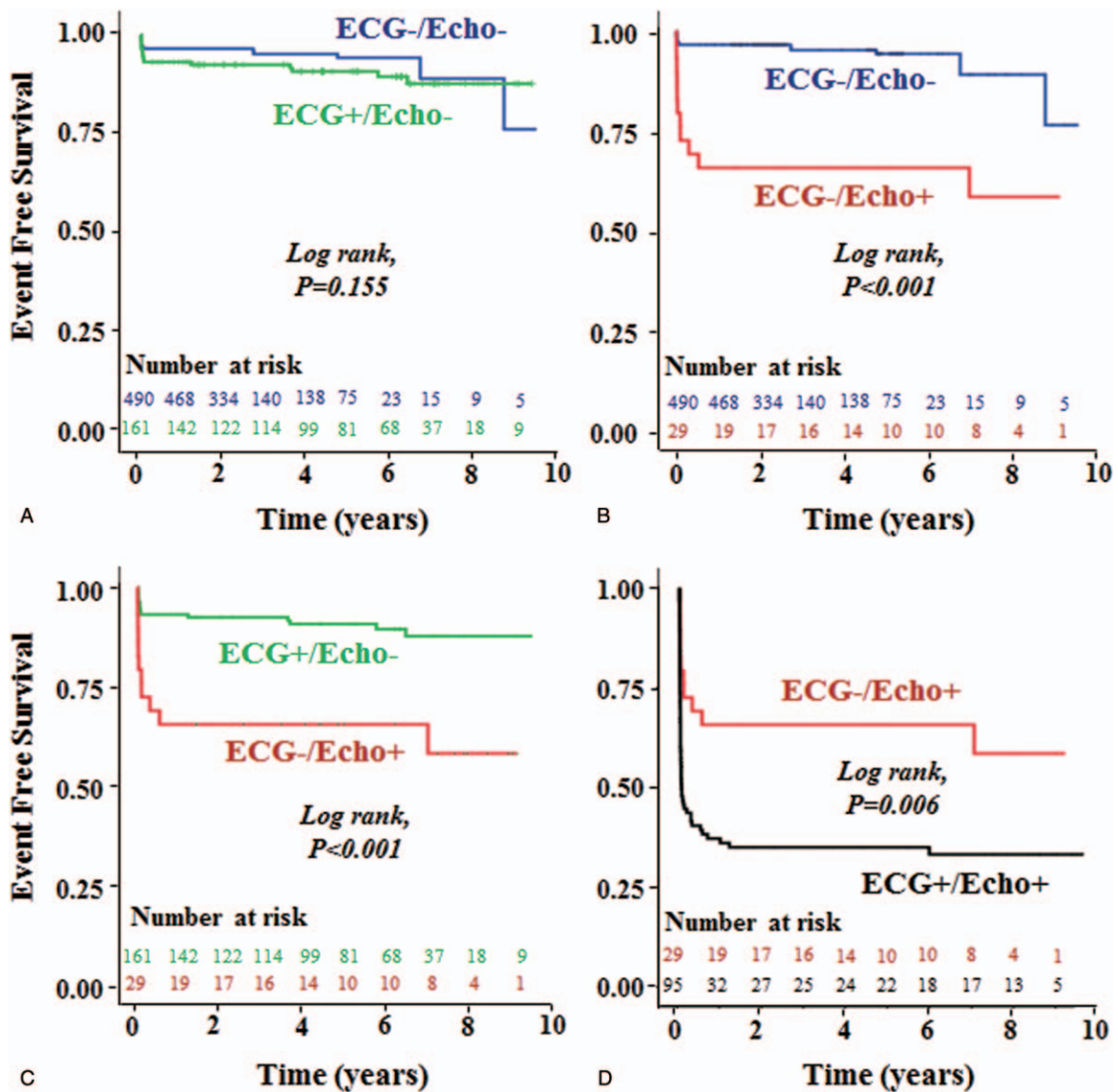
Compared with patients with ECG+/Echo-, patients with ECG-/Echo+ underwent more coronary evaluation and had more MACEs in our study, but they did not have significantly more concomitant CAD. The lack of significant concomitant CAD between 2 groups might be due to the small sample size of ECG-/Echo+ group and fewer coronary evaluation of ECG+/Echo- groups (48% vs 29% in ECG-/Echo+ and ECG+/Echo-, respectively,  $P=.082$ ). In fact, the diagnostic accuracy for

**Table 2**  
Cox proportional hazard models for unadjusted and adjusted<sup>a</sup> hazard ratio (HR) of MACEs between groups.

	Unadjusted HR (95% CI), <i>P</i> value	Adjusted HR (95% CI), <i>P</i> value
Compared to ECG-/Echo-		
HR of ECG+/Echo-	1.62 (0.83–3.19), <i>P</i> =.158	1.24 (0.63–2.44), <i>P</i> =.524
HR of ECG-/Echo+	7.08 (3.30–15.18), <i>P</i> <.001	6.15 (3.19–11.87), <i>P</i> <.001
Compared to ECG+/Echo-		
HR of ECG-/Echo+	4.36 (2.02–9.40), <i>P</i> <.001	3.57 (1.75–7.29), <i>P</i> <.001
Compared to ECG-/Echo+		
HR of ECG+/Echo+	2.38 (1.25–4.53), <i>P</i> =.008	2.05 (1.23–3.42), <i>P</i> =.006

CI=confidence interval, HR=hazard ratio, MACEs=major adverse cardiac events.

<sup>a</sup>Using inverse probability of treatment weighted method given a set of covariates including age, sex, hypertension, diabetes, dyslipidemia, smoking, and body mass index.



**Figure 1.** Survival curves for MACEs between groups: A, curve between groups with ECG-/Echo- and ECG+/Echo-; B, curve between groups with ECG-/Echo- and ECG-/Echo+; C, curve between groups with ECG+/Echo- and ECG-/Echo+; D, curve between groups with ECG-/Echo+ and ECG+/Echo+. MACE= major adverse cardiac events.

CAD on exercise ECG test is known to be inferior to exercise Echo.<sup>[8,9]</sup> Our previous report also showed that exercise ECG and Echo accuracy for CAD was 64% (sensitivity 67%, specificity 60%) and 72% (sensitivity 68%, specificity 78%), respectively.<sup>[23]</sup> This finding suggests that exercise Echo findings are more closely associated with prognosis than exercise ECG findings, and may be more useful for detecting significant CAD that requires coronary intervention or aggressive medical support at least.

Compared with patients with ECG+/Echo+, patients with ECG-/Echo+ had less CAD and fewer MACEs, but did not have significantly lower WMI after exercise or fewer diseased vessels number. Southard et al<sup>[9]</sup> demonstrated that only 6 patients among 22 patients with ECG-/Echo+ and exercise capacity of  $\geq 6$  minutes had significant CAD. All of these patients had lesions on the small coronary vessels or CAD with grafted or collateralized vessels. Thus, they asserted that exercise ECG in patients with suspected CAD is preferred to stress Echo test if patients have

baseline normal ECG and can adequately exercise. Our study results are similar to theirs in that patients with significant CAD were small in group of ECG-/Echo+ and 3 patients had lesions on small or distal coronary vessels. However, 4 patients had lesions on large coronary vessels, and 2 patients had subtotal occluded large vessels with insufficient collateral flow. Among these, only 1 patient had exercise capacity of  $< 6$  minutes (Table 4, Number 3). Therefore, exercise echocardiographic test has additional benefits compared with exercise ECG, and ECG-/Echo+ findings should not be regarded as negative because they are associated with more MACEs, which might be missed on an exercise ECG test.

**4.3. Additional parameters for predicting MACEs in treadmill exercise echocardiography**

Exercise Echo can estimate exercise capacity as well as WMA. Work load during exercise testing has often been suggested as a

**Table 3**  
**Predictors of MACEs (Cox proportional hazard models for unadjusted and adjusted HR).**

	HR (95% CI), P value		
	Unadjusted HR	Adjusted HR (model 1)	Adjusted HR (model 2)
Age	1.1 (1.0–1.1), <.001	1.0 (1.0–1.1), .103	1.0 (1.0–1.0), .460
Male	2.2 (1.4–3.5), <.001	2.3 (1.4–3.7), .001	1.4 (0.9–2.3), .194
Hypertension	2.0 (1.3–2.8), <.001	1.5 (1.0–2.3), .031	1.7 (1.2–2.5), .007
Diabetes	2.1 (1.4–3.1), <.001	1.4 (0.9–2.2), .095	1.3 (0.9–2.2), .176
Smoking	1.6 (1.1–2.3), .029	1.3 (0.9–2.1), .214	1.4 (0.9–2.2), .176
Typical angina	1.9 (1.3–2.7), .001	1.7 (1.1–2.4), .010	1.5 (1.0–2.2), .041
METs	0.8 (0.8–0.9), <.001	0.9 (0.8–0.9), .001	0.9 (0.9–1.0), .083
WMA	13.6 (9.1–20.1), <.001	-	10.1 (6.6–15.5), <.001

CI=confidence interval, HR=hazard ratio, MACEs=major adverse cardiac events, MET=metabolic equivalent of tasks, WMA=wall motion score index.

prognostic marker that is superior to ST change on exercise ECG. Many studies also showed that exercise capacity is an independent predictor of the risk of cardiac events and death.<sup>[15,16,24,25]</sup> Al-Mallah et al<sup>[15]</sup> suggested that patients with negative exercise Echo results and good exercise capacity had excellent long-term clinical outcomes. In our study, patients with negative exercise Echo results had better exercise capacity than patients with positive exercise Echo results (some data not shown in results; exercise capacity in group with ECG+/Echo+ compared with that in groups with ECG-/Echo- or ECG+/Echo- was lower [ $P<.001$ , respectively]) and better exercise capacity was associated with fewer MACEs. However, the power as a predictor of exercise capacity rapidly declined in a model adjusted by existent WMA. Therefore, exercise-induced transient

myocardial dysfunction in patients with positive exercise Echo might provoke exercise intolerance, which is associated with more MACEs.

We also showed the usefulness of ECG findings in patients with positive exercise Echo. Previous studies<sup>[3,4,6,13,15,22]</sup> suggested that the clinical outcomes of positive exercise ECG in patients with negative exercise Echo were not different from those of negative ECG. Our result is not opposite to their studies because our suggestion is limited as usefulness of ECG findings in patients with positive exercise Echo, and it is a unique finding. In addition, our results showed that typical angina was associated with more MACEs. Especially, the existence or absence of typical angina might be the most useful for clinical decision-making in ECG-/Echo+ group. Indeed, patients with concomitant CAD

**Table 4**  
**Angiographic data of patients with ECG-/Echo+.**

No	Age/Sex	Symptoms	Coronary angiography	Character	MACEs
1	50/M	CP (typical)	70% LAD ostial stenosis, total occlusion of mid LAD, 70% mid RCA stenosis, 100% distal RCA stenosis (bridging collateral flow)		
2	68/F	CP (atypical)	80% mid LAD stenosis, 80% diagonal ostial stenosis		
3	79/M	DOE	90% mid LAD stenosis, 50% distal LCx stenosis		
4	51/M	CP (typical)	80% proximal LAD stenosis		
5	61/M	CP (typical)	60% mid LAD stenosis, subtotal occlusion in proximal RCA (TIMI 1) with collateral flow from LCx (grade II)	With collaterals	Existent (+)
6	71/F	CP (typical)	Subtotal occlusion of mid LAD (TIMI 2) with collateral flow from RCA (grade II)		
7	52/F	CP (typical)	Subtotal occlusion (2.5 mm sized) of distal LAD, subtotal occlusion of distal PD, 60% PL stenosis	small vessels	
8	68/F	DOE	60% mid RCA stenosis, 60% PD stenosis, 60% mid LCx stenosis		
9	77/F	CP (typical)	50% mid LAD stenosis, 80% diagonal stenosis, 80% distal LCx stenosis, 80% PL stenosis	Small vessels	
10	64/F	CP (typical)	Minimal coronary lesion or normal		
11	57/F	CP (typical)	Minimal coronary lesion or normal		
12	70/M	DOE	Minimal coronary lesion or normal		
13	64/M	DOE	Minimal coronary lesion or normal		Absent (-)
14	51/M	CP (atypical)	Minimal change and spasm of proximal RCA		
15	50/M	CP (atypical)	Under-developed LCx		
16	62/M	CP (atypical)	Under-developed LCx and big diagonal		
17	53/M	CP (atypical)	Minimal coronary lesion or normal		
18	51/M	CP (atypical)	Minimal coronary lesion or normal		
19	52/M	CP (atypical)	Minimal coronary lesion or normal		
20	55/F	CP (atypical)	Minimal coronary lesion or normal		
21	65/F	CP (atypical)	Minimal coronary lesion or normal		

(-) = without MACEs, (+) = with MACEs, CP = chest pain, DOE = dyspnea on exertion, F = female, initial = chief complained symptoms on initial visit, LAD = left anterior descending artery, LCx = left circumflex artery, M = male, MACEs = major adverse cardiac events, PD = posterior descending branch, PL = posterolateral branch, RCA = right coronary artery, TIMI = thrombolysis in myocardial infarction, TMT = symptoms to cause termination of treadmill test.

complained of more frequent typical angina than patients without CAD in ECG-/Echo+ group. Therefore, patients with positive exercise Echo alone and atypical angina might be better supported medically to relieve symptoms and modify cardiovascular risks than be immediately managed by coronary intervention.

#### 4.4. Limitations

First, this study was a cohort study in routine clinical practice settings. Therefore, clinical decisions differed according to attending physicians, including performing a CAG and/or cCT, considering of ECG results, and prescribing medications. Second, we did not examine all patients with ECG-/Echo-, which is over 80% of all patients. When comparing 2 groups, statistical power does not get increased if the number of one group is much smaller than that of the other group, no matter how large the other group might be.<sup>[26]</sup> Therefore, we randomly selected 600 patients with ECG-/Echo- to be 3 times the population of the second largest group (ECG+/Echo-) and considered a follow up loss rate of 20%. We then used a propensity score weighting method to minimize selection bias and adjust traditional risk factors. Third, there were few myocardial infarction and death events in present study, thus we could not clearly confirm whether exercise Echo results predict hard cardiovascular events including myocardial infarction and death. A similar previous report by Mahenthiran et al<sup>[31]</sup> showed that a composite of myocardial infarction and cardiac death was rate of about 4% during  $2.8 \pm 0.9$  years and positive Echo result was associated with hard cardiovascular events. However, the study analyzed exercise and dobutamine stress Echo together, which made inclusion of more fragile or older people (age,  $60 \pm 12$  years) possible. Our study only included patients who can get exercise Echo. Another recent report by Park et al<sup>[6]</sup> showed lower MACE (0.1%) with no cardiac death and myocardial infarction of 4 patients (0.13%) than ours (1%). We suggest that the development of preventive medicines such as early management of patients with cardiovascular risk factors might have lowered future hard cardiovascular events. In addition, myocardial infarction and death events might have been observed more rarely because patients who underwent coronary revascularization as development of MACEs were censored in follow-up. Fourth, ECG-/Echo+ findings were observed in only 27 patients (1.7%) among a total of 1725 patients. In fact, this deviation in patient composition is similar to that of other previous studies although there are differences to a greater or lesser degree.<sup>[3,6,15]</sup> Therefore, some statistical power associated with ECG-/Echo+ results might be observed lower than real power. Fifth, concomitant CAD between groups of ECG-/Echo- and ECG+/Echo- and between groups of ECG +/Echo- and ECG-/Echo+ was not certainly compared because coronary evaluation was performed less in patients with negative exercise Echo results.

#### 5. Conclusions

Compared with positive exercise ECG alone, positive exercise Echo alone was associated with increased rate of MACEs. Positive ECG alone had similar MACEs compared with both negative ECG and Echo. Compared with both positive ECG and Echo, positive exercise Echo alone was associated with lower prevalence of CAD and decreased MACE rate. Thus, exercise Echo findings may be a better predictor for clinical outcomes than

exercise ECG findings. However, in patients with positive exercise Echo results, exercise ECG findings should be considered together with Echo findings for improved decision-making associated with coronary intervention and prediction of prognosis.

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