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Utility of Graded Exercise Tolerance Tests for Prediction of Cardiovascular Mortality in Old Age: The Rancho Bernardo Study

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Abstract

Background—Exercise electrocardiography in asymptomatic adults has been criticized because of relatively poor accuracy predicting future heart disease risk, but studies may have been too short. We investigated if integrated analysis of graded exercise tolerance tests (GXT) predicted long-term coronary heart disease (CHD) and all-cause mortality among community-dwelling older adults.

Methods and Results—From 1972 - 1974, 1789 adult residents of a predominantly Caucasian, middle- to upper-middle-class southern California community participated in a clinical evaluation that included a GXT; 52.4% (N=939) of those who had baseline GXT were followed to 2010—up to 36 years—for vital status, CHD and all-cause mortality. Multiply adjusted hazard ratios of an abnormal graded GXT were 1.65 (95% CI 0.78-3.49) and 1.56 (95% CI 1.15-2.11) for CHD and

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all-cause mortality, respectively. An integrated analysis hazard ratio was calculated based on the following GXT findings: significant ST change, inability to achieve target heart rate [THR], abnormal heart rate recovery [HRR], and chronotropic incompetency [ChI]. Compared to those with 0 or 1 abnormality, participants with 2 or more positive findings had significantly higher CHD (HR 2.18) and all-cause (HR 1.92) mortality. Participants with 3 or more positive findings showed even higher hazard ratios--CHD (HR 6.16) and all-cause (HR 2.49) mortality. When adjusted for any of 3 Framingham risk models, the integrated electrocardiographic model correlated well with CHD and all-cause mortality.

Conclusions—An integrated analysis of electrocardiographic and non-electrocardiographic measures of GXT is useful in predicting long-term CHD and all-cause mortality in an asymptomatic middle-aged population.

Keywords

Cardiovascular disease; Chronotropic Incompetency; GXT (graded exercise tolerance test); Heart Rate Recovery; ST Segment Change; Target Heart Rate

1. Introduction

Cardiovascular disease is one of the leading causes of death in the world. Given the increasing population age, assessing long-term risk of cardiovascular disease from mid-life to old age may be useful for prevention (1). While the overall death rate from cardiovascular disease has declined in both sexes in the United States(2), heart disease still causes more than one-third of all deaths, and more than half these deaths occur in women (52.8% (459,096 in 2004)(3).

The graded exercise tolerance test (GXT) has been useful for diagnosing clinical coronary heart disease (CHD); it is simple to administer, inexpensive, and safe(1, 4). The test remains widely available, with more data supporting its diagnostic and prognostic utility than newer, more expensive methods(1). For example in middle-aged men who had elevated levels of heart disease risk factors at baseline, an abnormal GXT was associated with at least a 3.5-fold increased risk of coronary death in the 1980s (5-8) In presumably healthy asymptomatic people, however, clinical usefulness of a GXT has been questioned because of its low prevalence (5), and screening with resting or exercise ECG in adults especially at low risk for CHD is not supported by the U.S. Preventive Services Task Force.(9). More specific systems to predict the long-term risk for cardiovascular events should be further evaluated.

The objectives of the present report were to evaluate the predictive value of an integrated analysis of electrocardiographic and non-electrocardiographic measures of GXT for long-term all-cause and CHD risk in older, asymptomatic community-dwelling adults followed for up to 36 years, and to assess the independent predictive value of this integrated analysis in the context of baseline CVD risk factors prior to widespread use of lipid-lowering and effective blood pressure medicines.

2. Methods

2.1 Study participants

Between 1972 and 1974, adults >20 years old from a predominantly Caucasian, middle- to upper-middle-class community (Rancho Bernardo, a suburb of San Diego) participated in Visit 1, when a brief heart disease risk factor survey was completed as part of a Lipid Research Clinics Prevalence Study. Participants were invited to return for Visit 2 within 100 days if they met one or more of the following criteria: (1) 15% random sample of all Visit 1 participants, (2) those whose Visit 1 fasting plasma cholesterol levels met or exceeded the following age-specific cut points: 240 mg/dl for ages 30 to 39, 260 mg/dl for ages 40 to 49, and 280 mg/dl for ages 50+, (3) those whose Visit 1 fasting plasma triglyceride levels exceeded the following age-specific cut points: 250 mg/dl for ages 30 to 39, and 300 mg/dl for ages 40+, (4) individuals with borderline elevations in cholesterol and/or triglyceride levels before Visit 1, and (5) individuals who indicated at Visit 1 that they were currently taking cholestyramine, colestipol, clofibrate, nicotinic acid, or other lipid-lowering drugs. These Visit 2 returnees are the subjects of the current study.

At Visit 1, plasma lipids, lipoproteins, and glucose levels were measured after a requested 12-hour fast. Height and weight were measured with the participant wearing light clothing and no shoes. Blood pressure was measured after a 5-min. rest in a seated position. Medical history and behavioral characteristics were determined by interview using a structured questionnaire. Participants were asked about current cigarette smoking, number and type of alcoholic beverages consumed in the past week, and current vigorous physical activity at least three times per week. Modified ATP-III criteria were used to define metabolic syndrome, which consists of three or more of the following; 1) Fasting plasma glucose concentration ≥ 110 mg/dl; 2) Blood pressure $\geq 130/85$ mmHg; 3) Fasting triglyceride concentration ≥ 150 mg/dl; 4) HDL cholesterol concentration < 35 mg/dl in men or < 39 mg/dl in women; 5) BMI > 30 kg/m² (10, 11).

All participants gave written informed consent. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the University of California, San Diego Human Subjects Protections Program.

2.2 Electrocardiographic measure

A submaximal treadmill exercise tolerance test using a modified Bruce protocol was administered to participants judged by a cardiologist to be able to perform the test safely (12); exclusions included Aortic Stenosis, Congestive Heart Failure, Hypertension, R-on-T type PVCs, Ventricular Tachycardia, Parasystolic Focus, Atrial Flutter, Congenital Heart Disease, Second Reschedule Required, Other. The GXT consisted of a series of seven 3-min stages in which the speed and inclination were increased stepwise and during which the electrocardiogram was monitored continually for heart rate and voltage changes. The exercise test was terminated for any of the following reasons; 1) Subjective response: the subject was unwilling or unable to continue exercise; 2) Development of potential hazards to the subject (e.g., ventricular arrhythmia); 3) Attainment of near-maximal exercise: exercise was stopped if the subject attained age-predicted target heart rate and maintained it for one

minute, if the subject maintained it until the end of the ongoing exercise stage, or if subject's heart rate exceeded target heart rate by 8 beats/min, whichever occurred first (12, 13). A test was considered to be positive if 1) ST depression or elevation of 1 mm or more was recorded by the visual coders, 2) the ST integral fell by at least 10 diV-sec from its resting value to a value of 10 gV-sec or less, or 3) the ST integral rose by at least 10 gV-sec from its resting value.

Three non-electrocardiographic measures were defined as following: 1) An abnormal heart rate recovery (HRR) was defined as decrease of <22 bpm after 2 min of recovery(14). 2) Chronotropic incompetence (ChI) was defined as the inability to achieve 80% of heart rate reserve, using a standard equation to define the percentage heart rate reserve [(maximal heart rate-resting heart rate)/ (174-0.54 × age) - (resting heart rate) × 100](15). 3) When 90% of maximal heart rate predicted for subject's age was attained, the target heart rate was considered achieved(14).

2.3 Ascertainment of death

Vital status of >99% of the cohort was determined annually to 2010 with a mean of 24.11±10.58 years of follow up and a maximum of 36 years. Death certificates were obtained for all decedents and coded for cause of death by a certified nosologist using the ninth revision of the “International Classification of Diseases, Adapted” (ICDA-9). Deaths due to coronary heart disease (CHD) were coded separately and included coronary death, MI, coronary insufficiency, and angina (ICD-9 codes 410-414). There were 1171 deaths, including 256 CHD deaths.

2.4 Statistical Analysis

Data were analyzed using the SAS statistical package (SAS institute, Chicago, Illinois).

Rates of death were calculated by dividing the number of cases occurring during the study period by the number of person-years over the period. Proportional hazards regression analysis was performed to obtain multivariate-adjusted hazard ratios of deaths of those who have abnormal test results obtained during the GXT versus normal test results. Hazard ratios were adjusted for age by decade, sex, cholesterol level, history of diabetes, and smoking.

For adjustment with classic Framingham risk factors, 3 different Framingham risk models were used--Framingham risk score to predict 10-year general cardiovascular disease, revised Framingham risk score for 10-year general cardiovascular disease risk, and Framingham risk score to predict 10-year coronary heart disease (16, 17). All participants were categorized into four groups by each 10-year risk; very low, low, moderate, and high risk(17). The 10-year risk was adjusted to analyze the predictive value of integrated analysis of electrocardiographic and non-electrocardiographic measures of GXT.

3. Results

3.1 Baseline Data

The baseline characteristics of participants are provided in Table 1. From the original cohort of 1789 participants, 939 completed a GXT (mean age 55.44±0.5, 497 were women); 219

(23.4%) were current smokers, 378 (40.3%) were daily drinkers, 193 (20.6%) had metabolic syndrome; only 154 (16.6%) had a family history of CVD; 2 lacked a record for ST segment change.

3.2 Electrocardiographic and non-electrocardiographic measures

The GXT test showed ST segment changes in 60 (6.4%) participants. Overall, about half (489) achieved their target heart rate (THR) during the test with mean duration of 5.94 ± 2.95 min; 448 participants were unable to achieve their THR, 298 because of heart-related symptoms, 98 because of leg pain or weakness, and 57 for miscellaneous other reasons. Only 22 participants did not have their heart rate decrease 22 beats/min at 2 min after GXT (abnormal HRR); and chronotropic incompetency (ChI) was detected in 64 participants.

In Cox proportional hazards models, positive GXT by ST criteria was independently associated with all-cause mortality (HR 1.56, 95% CI 1.15-2.11) but marginally CHD mortality (HR 1.65, 95% CI 0.78-3.49) and after adjusting for age, sex, cholesterol level, diabetic, current cigarette smoking, systolic blood pressure and exercise capacity.

Inability to achieve THR was associated with CHD mortality (adjusted HR 1.74, 95% CI 1.02-2.97) and all-cause mortality (HR 1.45, 95% CI 1.18-1.79) (Table 2). Even in subjects without ST segment abnormalities, inability to achieve THR was significantly associated with higher all-cause (adjusted HR 1.46, 95% CI 1.17-1.82) and CHD mortality (adjusted HR 1.72, 95% CI 1.00-2.99) (Table 3).

Abnormal HRR was associated with CHD mortality (adjusted HR 3.04, 95% CI 1.23-7.49) and all-cause mortality (HR 2.30, 95% CI 1.47-3.60). And ChI was associated with all-cause mortality (HR 1.24, 95% CI 0.92-1.66) but not CHD mortality (adjusted HR 1.42, 95% CI 0.70-2.89). Although ChI showed a tendency to increased risk for CHD mortality, this association did not reach statistical significance, possibly because of the low number of positive findings (Table 2).

3.3 Integrated analysis of electrocardiographic and non-electrocardiographic measures

The number of positive findings among these 4 measures (ST change, inability to achieve THR, abnormal HRR, and ChI, defined as "GXT score in table 4) was closely related to higher all-cause and CHD mortality. Two or more abnormal findings predicted a 2.18 -fold higher risk for CHD mortality and 1.92 for all-cause mortality. Three or more positive findings were associated with a 6.16-fold higher risk for CHD mortality and 2.49-fold for all-cause mortality (Table 4). ChI might have similar pathogenesis with inability to achieve target heart rate; we performed a separate analysis applying only three measures excluding ChI and similar results were obtained (data not shown).

After adjusting for measured previous Framingham cardiovascular risk factors, we observed a similar trend for CHD and all-cause mortality.

4. Discussion

The current well-characterized, population-based and long-term follow up study demonstrates that an integrated analysis of electrocardiographic and non-electrocardiographic measures obtained during the exercise test was useful to predict long-term all-cause and CHD mortality in the Rancho Bernardo cohort. The higher number of abnormal findings was well correlated with increased risk for CHD and all-cause mortality. Participants with three or more abnormal findings had more than a 6.16-fold increased risk for CHD mortality compared to those without abnormal findings. After accounting for different Framingham risk scoring models, our integrated analysis showed linear correlation with CHD and all-cause mortality. Even in populations without significant ST segment change during GXT, this integrated analysis was useful to predict CHD mortality risk. Our study also clearly shows that not only ST segment change but also other parameters provide useful information in predicting future CV risk, and that this integrated analysis could augment Framingham risk scoring models in predicting long-term CHD and all-cause mortality.

To our knowledge, this is the first paper to show the predictive value of integrated analysis of electrocardiographic and non-electrocardiographic measures for long-term cardiovascular mortality in a healthy, older, community-dwelling population.

A high proportion (89%) of our cohort exercised regularly 3+ times per week and had mean values of lipid profile within normal range. These are the two important factors that may be related to low CHD deaths. Therefore we conclude that this upper-middle-class cohort with health insurance had a healthy life style, which may have caused such favorable differences in CVD outcomes.

Our data demonstrate that both electrocardiographic measures and non-electrocardiographic measures are strong predictors for long-term cardiovascular mortality after up to 36 years of follow up. In contrast to previous studies evaluating the usefulness of exercise testing that have either excluded women(7) or included only small groups of women(6, 18), the present findings showed that an integrated analysis of exercise tolerance tests was useful in both women and men.

The positive rate of GXT was about 6% in alignment with previous reports(7), and this low positivity might be why the practicality of this test is in question. ST depression during the exercise and delayed recovery of ST segment after exercise were considered important surrogate markers to predict future CV risk. The result of the present study suggests that a positive GXT finding can be predictive of long-term all-cause and CHD mortality. The abnormal GXT was associated with a 1.45-fold increased risk of all-cause mortality and a 1.65-fold increased risk of CHD mortality up to 36 years after baseline (mean 24.11 ± 10.58 years). The marginal significance for CHD mortality may be related to small number of subjects (n=8) with positive ST change.

Inability to achieve target heart rate (THR) was associated with 1.45- and 1.74-fold increased risk for all-cause and CHD mortality, respectively. Reasons for inability to complete the test were attributed to heart-related symptoms, or leg pain, weakness, or other

reasons. Our results suggest that not only definite cardiac symptoms but also these other reasons for terminating the test should be carefully evaluated. Initially we assumed that only participants with cardiac problems that caused termination of the test might have higher risk for CVD and CHD mortality. However, our statistical analyses showed that all-cause and CHD mortality risks were increased regardless of reason to terminate the test; and from a clinical point of view, the need to closely monitor such patients as well, not only those with cardiac problems.

Interestingly, inability to achieve target heart rate was strongly associated with more than 1.72-fold higher risk for CHD mortality in GXT negative subjects. Traditionally, the ability to reach target heart rate was used as a signal of sufficient cardiac loading during the treadmill exercise test. However, our data suggest inability to reach THR is a useful marker for predicting long-term cardiovascular risk.

In addition, abnormal HRR and ChI were associated with higher all-cause and CHD mortality, respectively, although with marginal significance in ChI. It is probable that a small number of participants with positive findings precluded reaching statistical significance.

These observations confirm previous reports that ChI is a good predictor of cardiac death and all-cause mortality(19), and abnormal HRR provides prognostic information for global mortality(20). Myers and colleagues reported that patients exhibiting both ChI and abnormal HRR have more than a four-fold risk of cardiovascular mortality(15). An additional observation from this study was that these non-electrocardiographic measures were associated with increased risk for all-cause and CHD mortality in participants without significant ST segment changes in ECG. This is important because the simple application of heart rate during and after exercise may provide powerful information regarding future risk of cardiovascular mortality.

The mechanisms that have been proposed to explain the inability to achieve THR and ChI are 1) underlying autonomic nervous system imbalance; 2) reduced myocardial viability; and 3) attenuated protective response to permit greater myocardial perfusion in the presence of narrowed coronary arteries (21, 22). The ability of heart rate to recover following exercise is related to the capacity of the cardiovascular system to reverse autonomic nervous system and baroreceptor adaptations that occur during exercise, often termed vagal reactivation (23, 24).

4.1 Study Limitations

A limitation of this study is that death certificates were used to define cause of death, which may raise questions on validity of our data. Also, because we did not assess the concordance of exercise test outcomes with a concurrent “standard” measurement of the status of coronary arteries with coronary angiography, false positive cases cannot be excluded. However, even with such limitations, our study provides good evidence that integrated analysis of electrocardiographic and non-electrocardiographic measures of GXT can assess the correlation with CHD mortality long-term (up to 36 years). In addition, this correlation

was observed in subjects without significant ST segment changes at GXT test, which suggests the potential value of GXT in asymptomatic subjects in long-term prognosis.

Although an early publication from the Lipid Research Clinic Mortality Follow-up Study (the Rancho Bernardo Study)(7) does list hypertension as an exclusion criterion for GXT, our data set does include some participants who had used hypertension medication among those who had a GXT. Most cardiologists do not recommend GXT for those with uncontrolled (or malignant) hypertension, but some people with controlled hypertension can complete a GXT safely, as they did in the Rancho Bernardo Study. To avoid any related bias, systolic blood pressure was adjusted for all analysis.

In addition, because a high proportion (89%) of our cohort exercised regularly 3+times per week and had mean values of lipid profile within normal range, this cohort study of upper-middle-class participants with healthy life style may not represent the general population.

5. Conclusions

This is the first study to demonstrate the clinical usefulness of integrated analysis of electrocardiographic and non-electrocardiographic measures to predict long-term all-cause and CHD mortality up to 36 years in older adults. Our study suggests that this simple exercise test can be used to assess and refine prognosis, particularly when non-electrocardiographic measures are assessed in conjunction with ST segment changes in ECG.

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Highlights

1. Integrated analyses of GXT predicted long-term all-cause and CHD mortality.
2. 937 community-dwelling adults underwent GXT test and were followed up to 36 years.
3. Participants with 2 positive findings had 2.18-fold higher risk for CHD mortality.
4. Participants with 3 positive findings had 6.13-fold higher risk for CHD mortality.

Table 1

Baseline characteristics of study population.

	Total population (n=1789)	Subjects completed GXT (n= 939)	p-value ¹
	Mean (SE)	Mean (SE)	
Age	57.8 (0.4)	55.4 (0.5)	<0.001
Body mass index	25.0 (0.1)	25.0 (0.1)	0.96
Cardiovascular Risk Factors			
Total Cholesterol, mg/dL	233.4 (1.0)	228.3 (1.4)	0.004
Triglycerides, mg/dL	148.2 (2.5)	142.2 (3.4)	0.17
HDL, mg/dL	57.7 (0.5)	58.1 (0.6)	0.59
LDL, mg/dL	157.3 (1.0)	152.3 (1.3)	0.002
SBP, mmHg	151.6 (0.5)	147.9 (0.6)	<0.001
DBP, mmHg	100.2 (0.2)	99.2 (0.3)	0.007
Fasting plasma glucose, mg/dL	100.7 (0.5)	99.6 (0.6)	0.17
	N(%)	N(%)	p-value ²
	959 (53.6)	497 (53.0)	0.80
Lifestyle Parameters			
Current Smoker (yes)	406 (22.7)	219 (23.4)	0.70
Daily Alcohol Drinker (yes)	694 (38.8)	378 (40.3)	0.46
Regular Exercise (3+ times per week)	149 (89.2)	114 (89.1)	1.00
Co-morbidities			
Family History of CVD	291 (16.5)	154 (16.6)	0.96
Diabetes	103 (5.8)	43 (4.6)	0.21
Metabolic Syndrome (Modified WHO)	406 (22.7)	193 (20.6)	0.22
Medication History			
Dyslipidemia	125 (7.0)	74 (7.9)	0.39
Diabetes	41 (2.3)	16 (1.7)	0.40
Hypertension	269 (15.0)	109 (11.6)	0.014
Diuretics	133 (8.1)	48 (5.1)	0.017
Arrhythmia	38 (2.1)	8 (0.9)	0.018

Categorical variables are reported as number (percentages) and continuous variables as mean (standard deviation). CVD (cardiovascular disease), CHD (coronary heart disease), BMI (body mass index), HDL (high-density lipoprotein), LDL (low-density lipoprotein), SBP (systolic blood pressure), DBP (diastolic blood pressure)

¹ Student's T-test

² Fisher's exact test

Table 2

Hazard ratios (95% confidence intervals) of abnormal results in graded exercise tolerance test for mortality from all cause and coronary heart disease among participants who underwent GXT test and with result for ST segment change (N=937)

	N of cohort	N of all deaths	HR (95% CI) ⁴	N of CHD deaths	HR (95% CI) ⁴
Significant ST change					
Negative	877	507	1.00	85	1.00
Positive ¹	60	49	1.56 (1.15-2.11)	8	1.65 (0.78-3.49)
Target heart rate(THR)					
Achieved	489	185	1.00	24	1.00
Not achieved	448	371	1.45 (1.18-1.79)	69	1.74 (1.02-2.97)
Heart rate recovery (HRR)					
Normal	913	532	1.00	87	1.00
Abnormal ²	22	22	2.30 (1.47-3.60)	6	3.04 (1.23-7.49)
Chronotropic incompetency (ChI)					
Negative	872	495	1.00	82	1.00
Positive ³	64	60	1.24 (0.92-1.66)	11	1.42 (0.70-2.89)

¹ A test was considered to be positive if (1) ST depression or elevation of 1 mm or more was recorded by the visual coders, (2) the ST integral fell by at least 10 diV-sec from its resting value to a value of 10 gV-sec or less, or (3) the ST integral rose by at least 10 gV-sec from its resting value.

² When 90% of maximal heart rate predicted for subject's age was attained, it was defined as the target heart rate was achieved

³ Abnormal heart rate recovery (HRR) was defined as a decrease of <22bpm after 2 min of recovery.

⁴ Chronotropic incompetency (ChI) was defined as the inability to achieve 80% of heart rate reserve, using the regression equation [(maximal heart rate-resting heart rate) / (174-0.54 × age)-(resting heart rate) ×100].

⁴ Adjusted for age, sex, cholesterol levels, history of diabetes, current cigarette smoking, systolic blood pressure, and exercise capacity (metabolic equivalents)

Hazard ratios (95% confidence intervals) for mortality from all cause and coronary heart disease among participants without significant ST segment changes (N=877)¹

Table 3

	N of cohort (N=877)	N of all deaths (N=507)	HR (95% CI) ²	N of CHD deaths (N=85)	HR (95% CI) ²
Target heart rate (THR)					
Achieved ²	477	177	1.00	24	1.00
Not achieved	500	330	1.46 (1.17-1.82)	61	1.72 (1.00-2.99)
Heart rate recovery (HRR)					
Normal	857	485	1.00	81	1.00
Abnormal ³	20	20	2.15 (1.35-3.44)	4	2.25 (0.77-6.57)
Chronotropic incompetency (ChI)					
Negative	817	449	1.00	76	1.00
Positive ⁴	60	57	1.28 (0.94-1.73)	9	1.25 (0.58-2.72)

¹ A test was considered to be positive if (1) ST depression or elevation of 1 mm or more was recorded by the visual coders, (2) the ST integral fell by at least 10 diV-sec from its resting value to a value of 10 gV-sec or less, or (3) the ST integral rose by at least 10 gV-sec from its resting value.

² When 90% of maximal heart rate predicted for subject's age was attained, it was defined as the target heart rate was achieved

³ Abnormal heart rate recovery (HRR) was defined as a decrease of <22bpm after 2 min of recovery.

⁴ Chronotropic incompetency (ChI) was defined as the inability to achieve 80% of heart rate reserve, using the regression equation [(maximal heart rate-resting heart rate) / (174-0.54 × age)-(resting heart rate) × 100]

⁵ Adjusted for age, sex, cholesterol levels, history of diabetes, current cigarette smoking, systolic blood pressure, and exercise capacity (metabolic equivalents)

Table 4
Hazard ratios (95% confidence intervals) of integrated analysis of electrocardiographic and non-electrocardiographic measures for mortality from all cause and coronary heart disease

GXT score ¹	N of cohort (M=934)	N of all deaths (N=553)	HR (95% CI) ^{2,3}	HR (95% CI) ^{2,3}	N of cohort	N of CHD deaths	HR (95% CI) ^{2,3}	HR (95% CI) ^{2,3}
0	475	175	1.00	1.00	451	24	1.00	1.00
1	347	276	1.44 (1.16-1.79)	1.44 (1.15-1.79)	278	51	1.59 (0.92-2.76)	1.54 (0.89-2.66)
2	94	85	1.84 (1.37-2.49)	1.92 (1.44-2.56)	66	12	1.76 (0.81-3.79)	2.18 (1.08-4.42)
3-4	18	17	2.49 (1.47-4.24)		14	6	6.16 (2.16-17.56)	

¹ GXT score means the number of abnormal Graded Exercise tolerance test findings such as significant ST change, abnormal HRR, inability to achieve target heart rate (THR), and Chronotropic incompetency (ChI)

² Adjusted for age, sex, cholesterol levels, history of diabetes, current cigarette smoking, systolic blood pressure, and exercise capacity (metabolic equivalents)

³ The HRs (95% CIs) were persistent after adjusted for previous CVDrisk scores