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Relationship Between Physical Activity and Long-Term Outcomes in Patients with Stable Coronary Artery Disease

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ABSTRACT

AIMS To ascertain the relationship between level of physical activity and outcomes and to discriminate the determinants of physical activity performance or avoidance.

METHODS CLARIFY is an international prospective registry of 32370 consecutive outpatients with stable coronary artery disease who were followed for up to 5 years. Patients were grouped according to the level and frequency of physical activity: i) sedentary (n=5223; 16.1%); ii) only light physical activity most weeks (light; n=16634; 51.4%); iii) vigorous physical activity once or twice per week (vigorous ≤2×; n=5427; 16.8%); iv) vigorous physical activity three or more times per week (vigorous >2×; n=5086; 15.7%). The primary outcome was the composite of cardiovascular death, myocardial infarction, and stroke.

RESULTS Patients performing vigorous physical activity ≤2× had the lowest risk of the primary outcome (hazard ratio [HR], 0.82; 95% confidence interval [CI], 0.71-0.93; *P* = .0031) taking the light group as reference. Engaging in more frequent exercise did not result in further outcome benefit. All-cause death, cardiovascular death, and stroke occurred less frequently in patients performing vigorous physical activity ≤2×. However, the rate of myocardial infarction was comparable between the four physical activity groups. Female sex, peripheral artery disease, diabetes, previous myocardial infarction or stroke, pulmonary disease, and body mass index all emerged as independent predictors of lower physical activity.

CONCLUSION Vigorous physical activity once or twice per week was associated with superior cardiac outcomes compared to patients performing no or a low level of physical activity in outpatients with stable coronary artery disease.

KEYWORDS stable coronary artery disease; physical activity.

Introduction

International guidelines suggest 30-60 minutes of moderate-to-vigorous intensity aerobic exercise on most, preferably all, days of the week for patients with stable coronary artery disease (SCAD).[1] This recommendation is derived from a single meta-analysis with >80% of the included studies dating back to the last century.[2] Recent observations have now challenged this dogma. A post-hoc analysis from the randomized Stabilization of Atherosclerotic Plaque by Initiation of Darapladib Therapy (STABILITY) study[3] showed that increased habitual exercise levels were associated with lower all-cause mortality and: i) the benefit was more pronounced at lower versus higher exercise levels; and ii) myocardial infarction (MI) and stroke are not reduced by exercise and are not related to its intensity or frequency. Another post-hoc analysis from the Nord-Trøndelag Health (HUNT) study showed that sustained strenuous physical activity is associated with a prognostic benefit in patients with SCAD during a long time span (30 years).[4]

Thus, it is not clear which exercise frequency and intensity are linked to the best outcome. This information is relevant for SCAD patients as they are likely to undertake less exercise due to symptoms such as angina or dyspnea and to the psychological consequences of the disease. Moreover, several other questions remain unanswered, including how to encourage SCAD patients to exercise.[5-7] Guidelines suggest that clinicians should explore practical ways to overcome barriers to exercise.[1] However, clinical and socio-economic determinants of levels of physical activity are unclear and interventions aimed at increasing physical activity levels are based on common sense or physicians' personal experience.

CLARIFY is a large international, prospective contemporary dataset describing features and long-term outcomes of patients with SCAD. The present analysis of the CLARIFY population was performed with the following aims: i) to ascertain the relationship between level of physical activity (assessed by self-response to a question at baseline) and outcomes and ii) to describe the determinants of physical activity performance or avoidance.

Methods

Study Design and Population

CLARIFY is a prospective, international, contemporary, observational, longitudinal registry of consecutive outpatients with SCAD who are receiving standard management. The rationale, design, and baseline characteristics of CLARIFY have previously been reported.[8, 9] Patients were enrolled in 45 countries in Africa, Asia, Australia, Europe, the Middle East, and North, Central, and South America, according to prespecified criteria and were followed for up to 5 years, in order to reach an epidemiologically representative population in each country.[8] Study participation did not alter usual clinical practice. CLARIFY enrolled patients with at least one of the following non-mutually exclusive criteria: documented MI >3 months before enrolment; angiographic demonstration of coronary stenosis >50%; chest pain with evidence of myocardial ischemia (stress electrocardiogram); or coronary artery bypass graft (CABG) or percutaneous coronary intervention (PCI) >3 months before enrolment. Enrollment started on November 26, 2009 and recruitment was completed on June 30, 2010. The study is in accordance with the principles in the Declaration of Helsinki and local ethical approval was obtained in all countries prior to recruitment. All patients gave written informed consent and the study is registered (ISRCTN43070564).

Data Collection

Electronic case report forms were completed at baseline and annually during the follow-up. Data quality was pursued via onsite monitoring visits, regular telephone contact with investigators, and centralized verification of the case report forms. At baseline and follow-up, data were collected on demographics, risk factors and lifestyle, medical history, physical condition and activity, vital signs, current symptoms, and current treatments. Available results of invasive and non-invasive tests were collected, although no test was mandated by the study. Clinical outcomes were recorded on a yearly basis.

Physical Activity Assessment

Physical activity was self-reported by the patients at the inclusion visit. A scale categorized the population into four groups according to the level and frequency of physical activity: i) no physical activity (sedentary); ii) only light physical activity during most weeks (light); iii) vigorous physical activity for ≥20 minutes once or twice a week (vigorous ≤2×); and iv) vigorous physical activity for ≥20 minutes three or more times per week (vigorous >2×). Vigorous activity was defined as causing shortness of breath, a rapid heart rate, and sweating. During follow-up, no further evaluation of physical activity was performed.

Outcomes

The primary outcome of the present analysis is the composite of cardiovascular death, MI, or stroke. Secondary outcomes are all-cause death and each component of the primary outcome. Patients were followed for up to 5 years. For composite outcomes, patients with more than one event were only counted once at first event. Events were not adjudicated, but all events were source-verified during audits, which were performed for 100% of the data at 5% of randomly selected sites.

Statistical Analysis

Baseline characteristics are presented using descriptive statistics with mean (standard deviation [SD]) or median (quartiles 1 and 3) for continuous variables, and number of observed values (%) for categorical variables. Baseline values were compared between the four physical activity level groups using analysis of variance (ANOVA) or Kruskal-Wallis tests for continuous variables, depending on the distribution of the data, and $\chi 2$ tests for categorical variables. Univariate Cox proportional-hazards models were used to provide hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) to evaluate the relationship between each of the baseline variables and the primary outcome. Variables that were significant at the 10% level (probability value <0.1) from the univariate analyses were allowed to enter into a stepwise model. The stepwise model then

entered or removed variables from this reduced list based on a significance level of 5% (probability value <0.05). A final multivariable model was then obtained for the primary outcome using the statistically significant independent predictors from the resultant stepwise model. Models for each of the secondary outcomes were also obtained using these statistically significant independent predictors. Determinants of physical activity as a binary variable (vigorous activity [≤2× or >2×] compared to sedentary or light) were identified via multivariable logistic regression analyses, generating odds ratios (ORs) and corresponding 95% CIs for the effect of each baseline variable on the outcome of interest. Statistical analysis was performed at the Robertson Centre for Biostatistics at the University of Glasgow, UK using the statistical program SAS (version 9.3).

Results

For the present analysis, the study population comprised 32 370 subjects with available information regarding level of physical activity at baseline (98.0% of those enrolled) (eFigure 1). The largest group was the light physical activity group (n = 16 634, 51.4%), while the other three groups had a comparable number of patients (sedentary: n = 5223 [16.1%]; vigorous ≤2×: n = 5427 [16.8%]; vigorous >2×: n = 5086 [15.7%]). As expected, baseline demographics, risk factors, lifestyle, medical history, vital signs, symptoms, measurements, and medications were different in the four groups (Table 1 and eTables 1 and 2). In particular, sedentary patients and those undertaking only light physical activity were older; had higher body mass indexes (BMIs); higher prevalence of diabetes, peripheral artery disease (PAD), and current smoking, had worse symptoms as indicated by New York Heart Association (NYHA) classes; and had lower mean left ventricular ejection fractions (LVEFs) compared to those who undertook vigorous physical activity (≤2× or >2× each week) (Table 1).

Kaplan-Meier Plots of Primary and Secondary Outcomes

The primary outcome (cardiovascular death, MI, or stroke) occurred in 2807 patients (8.6%). A

Kaplan-Meier plot of time to first event of the composite primary outcome shows that this was most likely to occur among sedentary patients, followed by those undertaking only light activity, then those undertaking vigorous activity >2× (Figure 1). Kaplan-Meier plots for all-cause death, MI, cardiovascular death, and stroke showed similar trends, although this was least pronounced for MI (eFigures 2-5).

Univariate Analysis

Univariate analysis identified multiple risk factors, most notably estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2 (HR, 4.12; 95% CI, 3.28-5.17, eGFR 60-89.99 mL/min/1.73m^2 as reference), hospitalization for congestive heart failure (CHF) (HR, 2.95; 95% CI, 2.62-3.31), age ≥75 years (HR, 2.73; 95% CI, 2.48-2.99, age <65 years as reference), and combined CHF and NYHA class III (HR, 2.55; 95% CI, 2.16-3.01, no CHF as reference) (eTable 3). Patients performing vigorous physical activity ≤2× or >2× experienced a lower risk of the primary outcome than patients performing light physical activity (≤2×: HR, 0.70; 95% CI, 0.62-0.79; >2×: HR, 0.71; 95% CI, 0.62-0.80), while sedentary patients had a higher risk of the primary outcome (HR, 1.58; 95% CI, 1.44-1.73).

Multivariable Analysis

Physical activity remained a predictor of the primary outcome after multivariable stepwise regression (Table 2, Figure 2). Patients performing vigorous physical activity ≤2× had the best outcome (HR, 0.82; 95% CI, 0.71-0.93). Engaging in more frequent exercise was not associated with further benefit, with no difference between the outcomes of the vigorous >2× group versus the light activity group (HR, 0.94; 95% CI, 0.82-1.07). Sedentary patients had the highest risk of the primary outcome (HR, 1.31; 95% CI, 1.18-1.46; Table 2, Figure 2).

Secondary Outcomes

All secondary outcomes were evaluated in a model adjusting for multivariable analysis predictors (Figure 2). Patients who performed vigorous physical activity ≤2× had a lower risk of some of the secondary outcomes compared to the light physical activity group (all-cause death: HR, 0.81; 95% CI, 0.70-0.94; cardiovascular death: HR, 0.79; 95% CI, 0.65-0.96; stroke: HR, 0.74; 95% CI, 0.56-0.98). However, the risk of MI was comparable between the four groups (Figure 2).

Logistic Regression Analysis of Physical Activity Determinants

Logistic regression analysis identified multiple correlates of physical activity (eTable 4), of which the most significant determinants are presented in Figure 3. Correlates of lower physical activity included race/ethnicity (Chinese, Latin American), not working full time, smoking, and various comorbidities (e.g. CHF, angina, PAD, diabetes, chronic obstructive pulmonary disease [COPD]/asthma). Correlates of higher physical activity included race/ethnicity (Japanese/Korean), male, higher education, moderate alcohol consumption, family history of coronary artery disease, and dyslipidemia.

Discussion

There are five main observations derived from the present study. Firstly, in SCAD patients, performing some exercise is associated with a beneficial outcome in terms of all-cause mortality, cardiovascular mortality, myocardial infarction, and stroke. Secondly, by different levels of exercise, vigorous physical activity once or twice a week is associated with lower cardiovascular and all-cause mortality at 5 years. Thirdly, the risk of MI is not associated with exercise, irrespective of levels. Fourthly, Chinese race/ethnicity, female sex, less education, not working full time, CHF, COPD/asthma, diabetes, and smoking appear among the main determinants for avoiding physical activity. Lastly, the relationship between level of activity and outcome is not linear, i.e. although vigorous activity ≤2× is associated with superior outcomes to light activity, and light activity is associated with superior outcomes to sedentary, a higher frequency of vigorous physical

activity was not associated with greater clinical benefit.

The present study, with its global geographic scope, confirms a non-linear relationship between the frequency and intensity of physical activity and a lower risk of adverse clinical outcomes. However, the relationship between optimal intensity and frequency of physical activity and outcomes in patients with SCAD is complex and controversial. Also, the risk of an adverse clinical outcome is greater in SCAD patients who are also more likely to have exercise-limiting symptoms.

Among heart attack survivors, strenuous physical activity (running >50 km per week) has been associated with an excess risk of cardiovascular mortality not related to the traditional cardiovascular risk factors.[10] In fact, strenuous exercise in SCAD patients elicits instant and general inflammation, as well as procoagulant activity and platelet and endothelial activation,[11, 12] thus increasing cardiovascular risks such as MI[13] or sudden death.[14] On the other hand, in the STABILITY trial, SCAD patients who performed physical activity volumes below current recommendations also had a lower mortality risk than sedentary patients.[3, 15]

A reverse J-shaped association of physical activity with prognosis among patients with SCAD has also been observed in terms of physical activity frequency. In the KAROLA study, both inactive and daily active patients had increased hazards of mortality compared to the reference group of patients who were active 2-4 times per week.[16] A similar finding has been observed in a recent meta-analysis on the effect of physical activity in a general population of older people (≥60 years, n = 22 709).[17] Meta-regressions on mortality showed that exercise 2-3 times per week appeared to be the optimal frequency of exercise.[17]

Studies that have investigated physical activity changes over time have shown that the difference in mortality is greater when increasing activity at lower levels of habitual exercise, and less pronounced when increasing activity at higher levels of exercise,[3] supporting the concept that the association between physical activity level and outcome in SCAD patients is not linear.[15]

Our data show that vigorous physical activity with moderate frequency (once or twice per

week) was associated with the lowest risk of all-cause and cardiovascular death, while those who undertake vigorous physical activity more frequently had a mortality rate comparable to those with light activity. Thus, the goal with SCAD patients should be to promote sustainable physical activity and reduce the number of sedentary patients, rather than achieving the highest possible frequency of vigorous physical activity. Another important finding is that even achieving a lower level of physical activity (only light physical activity most weeks) is related to a prognostic benefit when compared to no physical activity. Thus, the message for SCAD patients and healthcare professionals should be that it is paramount to perform even light physical activity rather than be sedentary, and that non-strenuous physical activity (≥20 minutes of vigorous physical activity once or twice per week) is associated with the best outcome. This goal is theoretically achievable for most SCAD patients, but was only reached in a third of the CLARIFY population. Patients should also be advised that a higher frequency of physical activity does not appear to be related to greater benefit.

The mechanism for cardiovascular and non-cardiovascular mortality reduction secondary to physical activity is still unclear. In the STABILITY study,[3] reduction of cardiovascular death was independent from prevention of MI or stroke. Our analysis failed to show a reduction in MI, but stroke was reduced. This is the first documentation of physical activity-related stroke reduction in a large SCAD population. Previous studies in the general population have reported an association between increased physical activity and reduced occurrence of either ischemic or hemorrhagic stroke, in both men and women.[18-23]

In our study, approximately half of the patients were in the light physical activity group. This is not surprising, as SCAD patients are likely to be cautious about exercising or limited by their symptoms. However, most SCAD patients who report low physical activity are not significantly limited by symptoms and, when symptoms are limiting, they are generally non-specific symptoms such as shortness of breath, fatigue, and weakness.[24] Equally, SCAD patients who participate in rehabilitation programs are generally not symptom-limited, and are usually younger

men with less comorbidities.[25]

After adjustment for confounders in the STABILITY population, older age, male sex, and obesity were associated with lower physical activity.[26] We performed a broader characterization of the physical activity determinants. Ethnicity significantly impacted on the level of physical activity, with Japanese/South Korean or South Asian origin being associated with higher levels of physical activity, Chinese or Latin American origin with lower. This could be related to the higher income in some countries than in other countries, leading to more awareness that a sedentary lifestyle is a risk factor for CAD. In line with this, lack of full-time employment, and lower level of education are also correlated with lower levels of exercise.

In contrast with the STABILITY study,[26] our analysis shows that being female is strongly associated with a lower level of physical activity, indicating that women are less frequently enrolled in cardiac rehabilitation programs and have less intensive lifestyle counseling.[25]

Comorbidities (e.g. PAD, diabetes) and the severity of cardiovascular disease (i.e. congestive heart failure, Canadian Cardiovascular Society and NYHA class, and previous MI or stroke), smoking, and higher BMI were also associated with a lower level of exercise. Thus, patients "at risk" for not exercising (i.e. women and complex patients with comorbidities) can be readily identified and should be targeted for further intervention, counseling, or rehabilitation in order to achieve at least a light physical activity level. In fact, in the STABILITY population, more complex patients had a greater benefit from a physically active lifestyle.[15]

Limitations

There are some limitations to be acknowledged. First, physical activity levels were collected by questionnaires, which can overestimate activity and have poor agreement with objective measurement of physical activity.[27] In particular, the definition of vigorous was subjective and information regarding volume of endurance and strength training is lacking. In addition, physical activity level was self-reported at baseline. Thus, we did not capture the impact of changes in the

level of activity during the 5-year follow-up. Further, we could not ascertain whether the level of physical activity was sustained during follow-up, and studies have suggested that sustained physical activity confers the largest cardiovascular prognostic benefits in patients with CAD.[4, 10] We did not collect information regarding participation to rehabilitation program that could have been prognostically impactful. Lastly, although we corrected for baseline characteristics in the multivariable analysis, there may have been unmeasured confounders, and differences in prognosis according to level of physical activity could be related to reverse causality, being patients with lowest physical activity older patients, with a high risk profile and less ideally medically treated.

Conclusions

Vigorous physical activity performed once or twice per week was associated with substantially lower cardiovascular and all-cause mortality compared to patients performing no or a low level of physical activity. However, more frequent vigorous activity was not associated with superior outcomes.

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REFERENCES

1. Montalescot G, Sechtem U, Achenbach S, et al. 2013 ESC guidelines on the management of stable coronary artery disease: the Task Force on the management of stable coronary artery disease of the European Society of Cardiology. *Eur Heart J* 2013; 34: 2949-3003. DOI: 10.1093/eurheartj/eht296.

2. Taylor RS, Brown A, Ebrahim S, et al. Exercise-based rehabilitation for patients with coronary heart disease: systematic review and meta-analysis of randomized controlled trials. *Am J Med* 2004; 116: 682-692. DOI: 10.1016/j.amjmed.2004.01.009.

3. Stewart RAH, Held C, Hadziosmanovic N, et al. Physical Activity and Mortality in Patients With Stable Coronary Heart Disease. *J Am Coll Cardiol* 2017; 70: 1689-1700. DOI: 10.1016/j.jacc.2017.08.017.

4. Moholdt T, Lavie CJ and Nauman J. Sustained Physical Activity, Not Weight Loss, Associated With Improved Survival in Coronary Heart Disease. *J Am Coll Cardiol* 2018; 71: 1094-1101. DOI: 10.1016/j.jacc.2018.01.011.

5. Aragam KG, Moscucci M, Smith DE, et al. Trends and disparities in referral to cardiac rehabilitation after percutaneous coronary intervention. *Am Heart J* 2011; 161: 544-551 e542. DOI: 10.1016/j.ahj.2010.11.016.

6. Golwala H, Pandey A, Ju C, et al. Temporal Trends and Factors Associated With Cardiac Rehabilitation Referral Among Patients Hospitalized With Heart Failure: Findings From Get With The Guidelines-Heart Failure Registry. *J Am Coll Cardiol* 2015; 66: 917-926. DOI: 10.1016/j.jacc.2015.06.1089.

7. Brown TM, Hernandez AF, Bittner V, et al. Predictors of cardiac rehabilitation referral in coronary artery disease patients: findings from the American Heart Association's Get With The Guidelines Program. *J Am Coll Cardiol* 2009; 54: 515-521. DOI: 10.1016/j.jacc.2009.02.080.

8. Steg PG, Ferrari R, Ford I, et al. Heart rate and use of beta-blockers in stable outpatients with coronary artery disease. *PLoS One* 2012; 7: e36284. DOI: 10.1371/journal.pone.0036284.

9. Steg PG, Greenlaw N, Tardif JC, et al. Women and men with stable coronary artery disease have similar clinical outcomes: insights from the international prospective CLARIFY registry. *Eur Heart J* 2012; 33: 2831-2840. DOI: 10.1093/eurheartj/ehs289.

10. Williams PT and Thompson PD. Increased cardiovascular disease mortality associated with excessive exercise in heart attack survivors. *Mayo Clin Proc* 2014; 89: 1187-1194. DOI: 10.1016/j.mayocp.2014.05.006.

11. Cwikiel J, Seljeflot I, Berge E, et al. Pro-coagulant activity during exercise testing in patients with coronary artery disease. *Thromb J* 2017; 15: 3. DOI: 10.1186/s12959-016-0127-8.

12. Cwikiel J, Seljeflot I, Berge E, et al. Effect of strenuous exercise on mediators of inflammation in patients with coronary artery disease. *Cytokine* 2018; 105: 17-22. DOI: 10.1016/j.cyto.2018.02.006.

13. Mittleman MA, Maclure M, Tofler GH, et al. Triggering of acute myocardial infarction by heavy physical exertion. Protection against triggering by regular exertion. Determinants of Myocardial Infarction Onset Study Investigators. *N Engl J Med* 1993; 329: 1677-1683. DOI: 10.1056/NEJM199312023292301.

14. Albert CM, Mittleman MA, Chae CU, et al. Triggering of sudden death from cardiac causes by vigorous exertion. *N Engl J Med* 2000; 343: 1355-1361. DOI: 10.1056/NEJM200011093431902.

15. Eijsvogels TMH and Maessen MFH. Exercise for Coronary Heart Disease Patients: Little Is Good, More Is Better, Vigorous Is Best. *J Am Coll Cardiol* 2017; 70: 1701-1703. DOI: 10.1016/j.jacc.2017.08.016.

16. Mons U, Hahmann H and Brenner H. A reverse J-shaped association of leisure time physical activity with prognosis in patients with stable coronary heart disease: evidence from a large cohort with repeated measurements. *Heart* 2014; 100: 1043-1049. DOI: 10.1136/heartjnl-2013-305242.

17. de Souto Barreto P, Rolland Y, Vellas B, et al. Association of Long-term Exercise Training With Risk of Falls, Fractures, Hospitalizations, and Mortality in Older Adults: A Systematic

Review and Meta-analysis. *JAMA Intern Med* 2018: [Epub ahead of print]. DOI: 10.1001/jamainternmed.2018.5406.

18. Abbott RD, Rodriguez BL, Burchfiel CM, et al. Physical activity in older middle-aged men and reduced risk of stroke: the Honolulu Heart Program. *Am J Epidemiol* 1994; 139: 881-893.

19. Hu FB, Stampfer MJ, Colditz GA, et al. Physical activity and risk of stroke in women. *JAMA* 2000; 283: 2961-2967.

20. Sattelmair JR, Kurth T, Buring JE, et al. Physical activity and risk of stroke in women. *Stroke* 2010; 41: 1243-1250. DOI: 10.1161/STROKEAHA.110.584300.

21. Sacco RL, Gan R, Boden-Albala B, et al. Leisure-time physical activity and ischemic stroke risk: the Northern Manhattan Stroke Study. *Stroke* 1998; 29: 380-387.

22. Lee CD, Folsom AR and Blair SN. Physical activity and stroke risk: a meta-analysis. *Stroke* 2003; 34: 2475-2481. DOI: 10.1161/01.STR.0000091843.02517.9D.

23. Wendel-Vos GC, Schuit AJ, Feskens EJ, et al. Physical activity and stroke. A meta-analysis of observational data. *Int J Epidemiol* 2004; 33: 787-798. DOI: 10.1093/ije/dyh168.

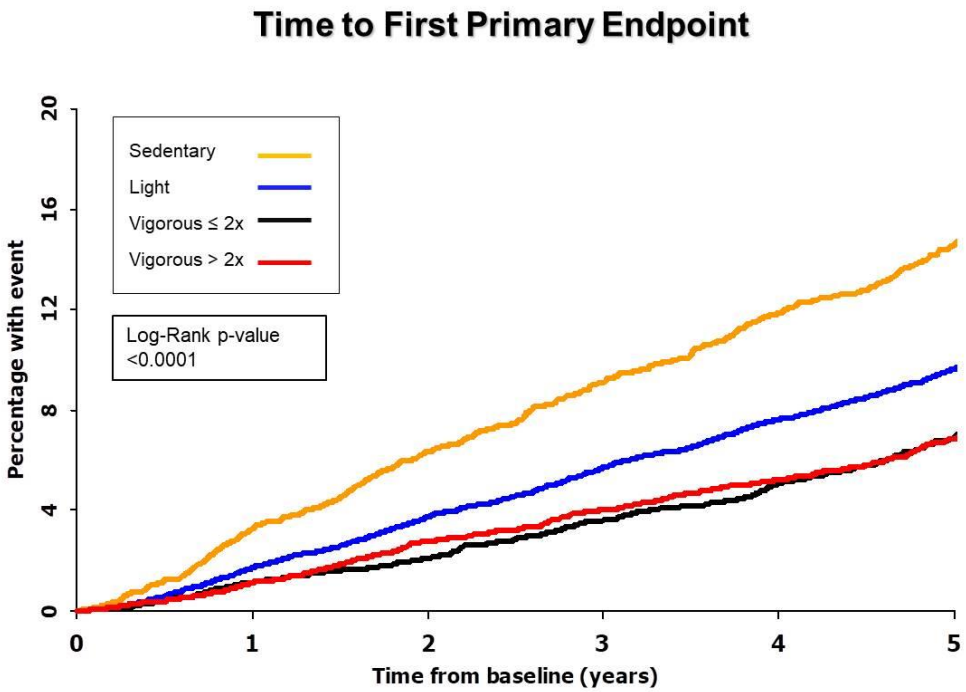
24. Brewer LC, Svatikova A and Mulvagh SL. The Challenges of Prevention, Diagnosis and Treatment of Ischemic Heart Disease in Women. *Cardiovasc Drugs Ther* 2015; 29: 355-368. DOI: 10.1007/s10557-015-6607-4.

25. McMahon SR, Ades PA and Thompson PD. The role of cardiac rehabilitation in patients with heart disease. *Trends Cardiovasc Med* 2017; 27: 420-425. DOI: 10.1016/j.tcm.2017.02.005.

26. Stewart R, Held C, Brown R, et al. Physical activity in patients with stable coronary heart disease: an international perspective. *Eur Heart J* 2013; 34: 3286-3293. DOI: 10.1093/eurheartj/eht258.

27. Dyrstad SM, Hansen BH, Holme IM, et al. Comparison of self-reported versus accelerometer-measured physical activity. *Med Sci Sports Exerc* 2014; 46: 99-106. DOI: 10.1249/MSS.0b013e3182a0595f.

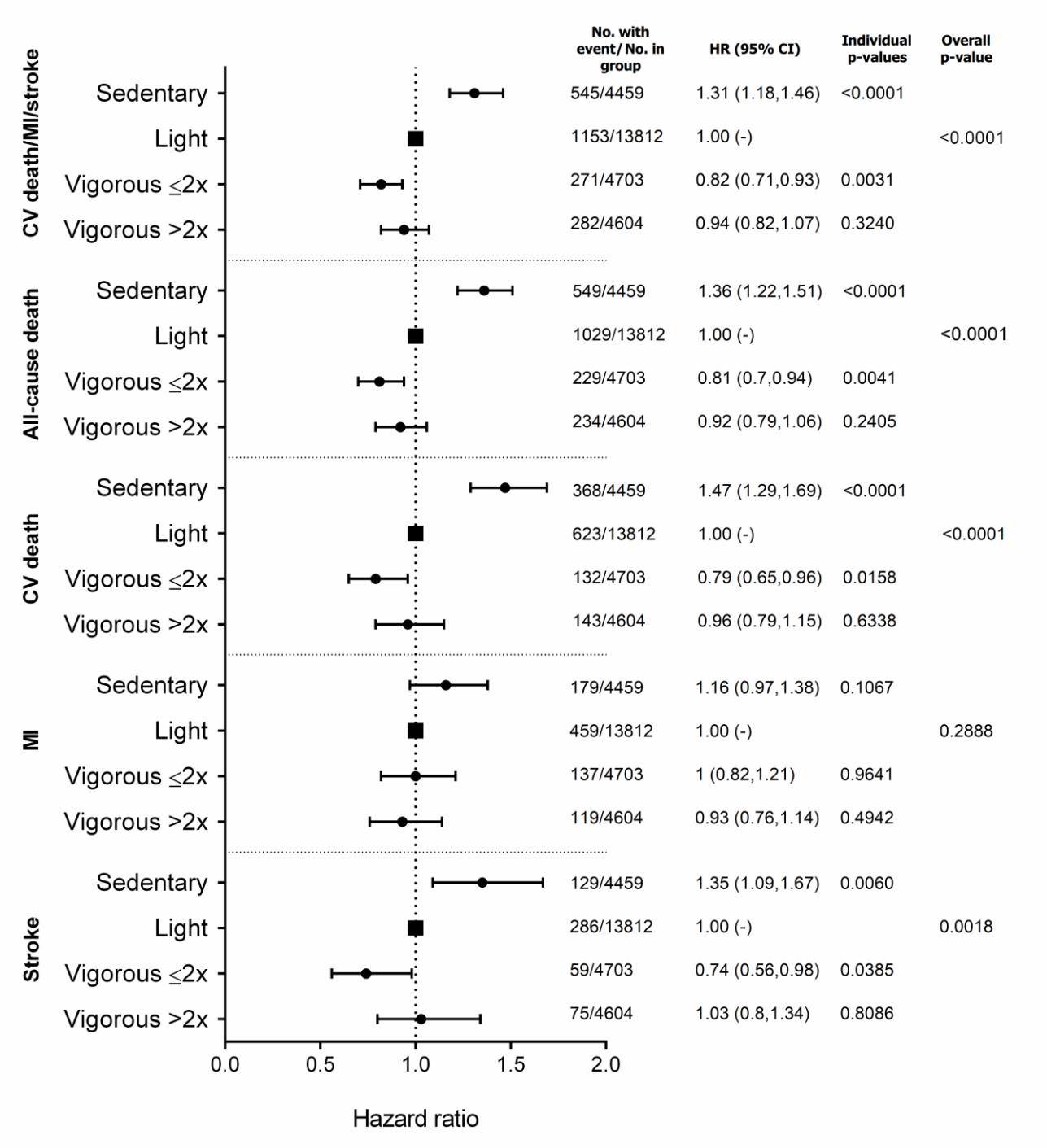
Figure 1. Kaplan-Meier Plot of Time to First Primary Endpoint, by Physical Activity Level



Patients at risk

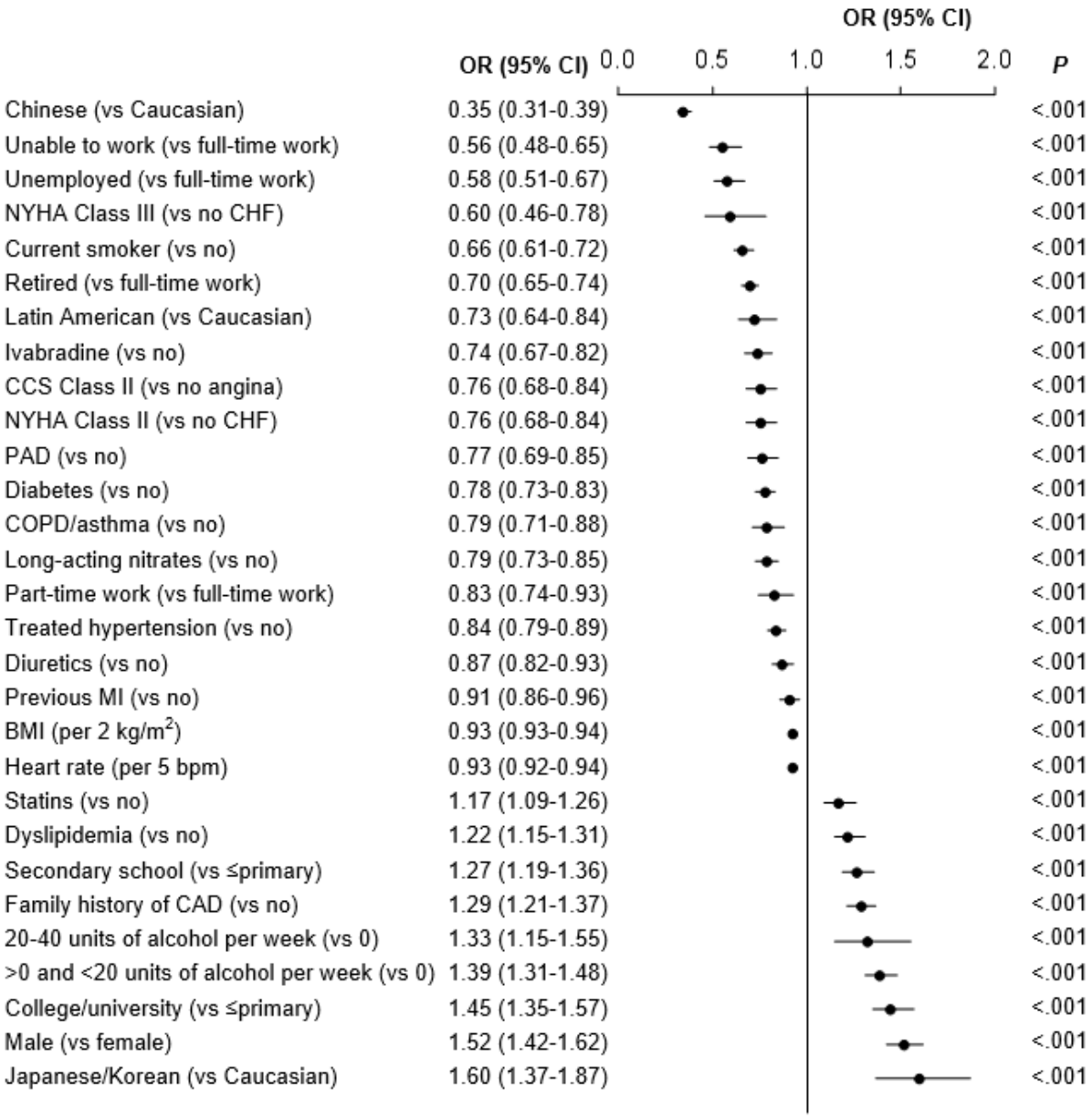
Sedentary	5223	4901	4477	4068	3582	2074
Light	16634	16031	15087	14028	12785	8108
Vigorous ≤ 2x	5427	5280	5029	4681	4178	2573
Vigorous > 2x	5086	4941	4681	4381	3922	2405

Figure 2. Primary and Secondary Endpoint Hazard Ratios According to Physical Activity Level after Multivariable Stepwise Regression Analysis



Abbreviations: CI, confidence interval; CV, cardiovascular; HR, hazard ratio; MI, myocardial infarction.

Figure 3. Most Significant Determinants of Physical Activity as a Binary Variable (Vigorous Activity [≤2× or >2×] Compared to Sedentary or Light) after Multivariable Logistic Regression Analysis



Abbreviations: BMI, body mass index; CAD, coronary artery disease; CCS, Canadian Cardiovascular Society; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; MI, myocardial infarction; NYHA, New York Heart Association; PAD: peripheral artery disease.

Table 1. Baseline Clinical and Socio-Economic Features by Weekly Physical Activity

Information	**All (n = 32 370)**	**Sedentary (n = 5223)**	**Light (n = 16 634)**	**Vigorous ≤2× (n = 5427)**	**Vigorous >2× (n = 5086)**	***P* Value**
Male, No. (%)	25 107 (77.6)	3540 (67.8)	12 620 (75.9)	4562 (84.1)	4385 (86.2)	<.0001
Age, mean (SD), years	64.2 (10.5)	66.5 (10.9)	64.5 (10.4)	62.5 (10.2)	62.5 (10.1)	<.0001
Race/ethnicity, No. (%)						<.0001
Caucasian	20 945 (64.7)	3054 (58.5)	10 962 (65.9)	3702 (68.2)	3227 (63.4)	
South Asian	2415 (7.5)	355 (6.8)	1217 (7.3)	356 (6.6)	487 (9.6)	
Chinese	2740 (8.5)	362 (6.9)	1972 (11.9)	197 (3.6)	209 (4.1)	
Japanese/Korean	1035 (3.2)	237 (4.5)	345 (2.1)	205 (3.8)	248 (4.9)	
Latin American	1568 (4.8)	475 (9.1)	668 (4.0)	191 (3.5)	234 (4.6)	
Black/African	337 (1.0)	67 (1.3)	155 (0.9)	60 (1.1)	55 (1.1)	
Unknown	3330 (10.3)	673 (12.9)	1315 (7.9)	716 (13.2)	626 (12.3)	
Employment, No. (%)						<.0001
Full-time	7894 (24.4)	857 (16.4)	3543 (21.3)	1795 (33.1)	1699 (33.4)	
Part-time	2249 (6.9)	256 (4.9)	1203 (7.2)	444 (8.2)	346 (6.8)	
Unable to work	1265 (3.9)	257 (4.9)	716 (4.3)	145 (2.7)	147 (2.9)	
Unemployed	1831 (5.7)	586 (11.2)	838 (5.0)	222 (4.1)	185 (3.6)	
Retired	17 916 (55.4)	2949 (56.5)	9723 (58.5)	2695 (49.7)	2549 (50.1)	
Other	1213 (3.7)	318 (6.1)	609 (3.7)	126 (2.3)	160 (3.1)	
Level of education, No. (%)						<.0001
≤Primary	8571 (26.5)	2191 (41.9)	4173 (25.1)	1155 (21.3)	1052 (20.7)	

Secondary	15 033 (46.4)	2099 (40.2)	7986 (48.0)	2571 (47.4)	2377 (46.7)	
College/ university	8764 (27.1)	933 (17.9)	4473 (26.9)	1701 (31.3)	1657 (32.6)	
Family history of CAD, No. (%)	9214 (28.5)	1288 (24.7)	4518 (27.2)	1733 (31.9)	1675 (32.9)	<.0001
Treated hypertension, No. (%)	22 987 (71.0)	4010 (76.8)	12 105 (72.8)	3638 (67.0)	3234 (63.6)	<.0001
Diabetes, No. (%)	9390 (29.0)	2033 (38.9)	4937 (29.7)	1247 (23.0)	1173 (23.1)	<.0001
Dyslipidemia, No. (%)	24 253 (74.9)	3711 (71.1)	12 396 (74.5)	4188 (77.2)	3958 (77.8)	<.0001
PAD, No. (%)	3203 (9.9)	660 (12.6)	1732 (10.4)	440 (8.1)	371 (7.3)	<.0001
Smoking status, No. (%)						<.0001
Current	4039 (12.5)	784 (15.0)	2119 (12.7)	661 (12.2)	475 (9.3)	
Former	14 967 (46.2)	2004 (38.4)	7511 (45.2)	2675 (49.3)	2777 (54.6)	
Never	13 364 (41.3)	2435 (46.6)	7004 (42.1)	2091 (38.5)	1834 (36.1)	
MI, No. (%)	19 398 (59.9)	3008 (57.6)	10 195 (61.3)	3216 (59.3)	2979 (58.6)	<.0001
PCI, No. (%)	18 954 (58.6)	3057 (58.5)	9401 (56.5)	3297 (60.8)	3199 (62.9)	<.0001
CABG, No. (%)	7628 (23.6)	1201 (23.0)	3837 (23.1)	1306 (24.1)	1284 (25.2)	.0076
Stroke	1301 (4.0)	306 (5.9)	711 (4.3)	165 (3.0)	119 (2.3)	<.0001
TIA, No. (%)	993 (3.1)	210 (4.0)	510 (3.1)	153 (2.8)	120 (2.4)	<.0001
Hospitalization for CHF, No. (%)	1512 (4.7)	365 (7.0)	842 (5.1)	173 (3.2)	132 (2.6)	<.0001

Asthma/COPD, No. (%)	2393 (7.4)	536 (10.3)	1288 (7.7)	324 (6.0)	245 (4.8)	<.0001
BMI, mean (SD), kg/m^2	27.9 (4.6)	28.6 (5.3)	27.9 (4.7)	27.6 (4.0)	27.3 (3.9)	<.0001
SBP, mean (SD), mmHg	131.1 (16.7)	131.6 (17.2)	131.6 (16.9)	130.5 (16.1)	129.4 (16.0)	<.0001
DBP, mean (SD), mmHg	77.3 (10.0)	76.8 (10.2)	77.5 (10.1)	77.6 (9.6)	76.7 (9.8)	<.0001
Heart rate by ECG, mean (SD), bpm	67.1 (11.4)	68.9 (12.1)	67.8 (11.4)	66.0 (11.0)	64.6 (10.8)	<.0001
CCS Class, No. (%)						<.0001
Class I	2051 (28.6)	227 (21.7)	1132 (26.3)	377 (33.8)	315 (44.6)	
Class II	3812 (53.2)	577 (55.2)	2345 (54.5)	578 (51.9)	312 (44.2)	
Class III	1225 (17.1)	221 (21.1)	779 (18.1)	155 (13.9)	70 (9.9)	
Class IV	78 (1.1)	21 (2.0)	44 (1.0)	4 (0.4)	9 (1.3)	
NYHA Class, No. (%)						<.0001
Class II	4098 (83.6)	541 (74.2)	2589 (84.0)	650 (88.3)	318 (90.1)	
Class III	803 (16.4)	188 (25.8)	494 (16.0)	86 (11.7)	35 (9.9)	
LVEF, mean (SD), %	56.1 (11.1)	54.4 (11.9)	55.8 (11.1)	56.9 (10.3)	57.9 (10.6)	<.0001

Abbreviations: BMI, body mass index; CABG, coronary artery bypass graft; CAD, coronary artery disease; CCS, Canadian Cardiovascular Society; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; DBP, diastolic blood pressure; ECG, electrocardiogram; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NYHA, New York Heart Association; PAD, peripheral artery disease; PCI, percutaneous coronary intervention; SBP, systolic blood pressure; SD, standard deviation; TIA, transient ischemic attack.

Table 2. Multivariable Analysis of Predictors of the Composite Primary Endpoint

	HR (95% CI)	Overall and (Individual) *P* Values[a]
Physical activity (vs light)		<.001
Sedentary	1.31 (1.18-1.46)	(<.001)
Vigorous ≤2×	0.82 (0.71-0.93)	(.003)
Vigorous >2×	0.94 (0.82-1.07)	(.324)
Race/Ethnicity (vs Caucasian)		<.001
South Asian	1.01 (0.84-1.20)	(.947)
Chinese	0.87 (0.73-1.02)	(.086)
Japanese/Korean	0.67 (0.48-0.94)	(.018)
Latin American	1.19 (0.98-1.44)	(.075)
Black/African	1.75 (1.23-2.47)	(.002)
Unknown	0.95 (0.79-1.14)	(.595)
Employment (vs full-time)		<.001
Part-time	1.16 (0.94-1.44)	(.177)
Unable to work	1.46 (1.16-1.83)	(.001)
Unemployed	1.232 (0.99-1.53)	(.062)
Retired	1.36 (1.18-1.57)	(<.001)
Other	1.12 (0.86-1.46)	(.412)
Diabetes (vs no)	1.25 (1.15-1.37)	<.001
PAD (vs no)	1.27 (1.13-1.43)	<.001
Smoking status (vs never)		<.001
Current	1.59 (1.38-1.82)	(<.001)
Former	1.29 (1.17-1.42)	(<.001)

Hospitalization for CHF (vs no)	1.49 (1.29-1.74)	<.001
Asthma/COPD (vs no)	1.17 (1.02-1.34)	.023
MI (vs no)	1.28 (1.17-1.40)	<.001
Stroke (vs no)	1.72 (1.47-2.00)	<.001
DBP (per 10 mmHg)	0.95 (0.90-0.99)	.032
Hemoglobin (vs 8-8.99 mmol/L)		<.001
<8 mmol/L	1.22 (1.08-1.38)	(.002)
9-9.99 mmol/L	0.98 (0.86-1.11)	(.736)
>10 mmol/L	1.29 (1.05-1.59)	(.017)
Missing	0.95 (0.83-1.08)	(.406)
SBP (per 10 mmHg)	1.045 (1.014-1.076)	.004
Age (vs <65 years)		<.001
65-74 years	1.33 (1.18-1.49)	(<.001)
≥75 years	2.06 (1.81-2.36)	(<.001)
Combined angina and CCS class (vs no angina)		.003
Class I	1.26 (1.07-1.49)	(.005)
Class II	1.06 (0.92-1.21)	(.437)
Class III/IV	1.34 (1.09-1.65)	(.006)
Aspirin (vs no)	0.76 (0.68-0.85)	<.001
Combined CHF and NYHA class (vs no CHF)		.003
Class II	1.24 (1.09-1.41)	(<.001)
Class III	1.19 (0.94-1.50)	(.146)
eGFR group vs 60-89.99 mL/min/1.73 m^2		<.001
<30 mL/min/1.73 m^2	1.92 (1.46-2.53)	(<.001)
30-44.99 mL/min/1.73 m^2	1.49 (1.25-1.77)	(<.001)

45-59.99 mL/min/1.73 m^2	1.21 (1.06-1.37)	(.006)
≥90 mL/min/1.73 m^2	1.00 (0.87-1.15)	(.994)
Missing	1.14 (0.99-1.31)	(.077)
Heart rate (per 2 bpm)	1.03 (1.01-1.05)	.004
LVEF (vs 40-50%)		<.001
<40%	1.29 (1.10-1.51)	(.002)
>50%	0.72 (0.64-0.81)	(<.001
Missing	0.89 (0.78-1.01)	(.064)
Vessel disease (vs 0)		<.001
1	1.01 (0.79-1.29)	(.919)
≥2	1.30 (1.03-1.65)	(.030)

Abbreviations: CCS, Canadian Cardiovascular Society; CHF, congestive heart failure; CI, confidence interval; COPD, chronic obstructive pulmonary disease; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HR, hazard ratio; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NYHA, New York Heart Association; PAD, peripheral artery disease; SBP, systolic blood pressure.