Prediction of cardiovascular, cancer and non-cardiovascular non-cancer death by exercise echocardiography

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Exercise echocardiography (ExE) can predict overall and cardiovascular mortality.[1–3] ExE provides information from two sources: imaging and exercise electrocardiogram testing. However, the relative contributions of imaging and the 'exercise part' of an ExE study for prognostication of the different causes of mortality are less known. We aimed to assess the value of imaging and exercise variables of an ExE for the prediction of the different causes of death.

We studied 12,615 consecutive patients with ExE performed between 1995 and 2014. Reasons for ExE included chest pain in 72%. The Bruce protocol was mostly used (93%). Maximal exercise workload in metabolic equivalents (METs) was derived from exercise testing characteristics (slope and speed). A good functional capacity was defined as a maximal workload of 10 METs.[4] Peak treadmill imaging acquisition was performed with the patient exercising, as reported[1,2,4]

(https://www.youtube.com/watch?v=gnYRa6PoYVw). Wall motion score index and its change with exercise were calculated. Ischaemia was defined as new/worsening wall motion abnormalities (WMA) with exercise, and fixed WMAs as resting WMAs without changes with exercise. All patients gave informed consent. Follow-up was obtained by hospital databases review, death certificates and telephone interviews.

End point was cardiovascular (CV), cancer (CA) or non-cardiovascular non-cancer (NCV-NCA) death. CV death was considered in the case of cardiac death, stroke or complications from arteriosclerosis. Cardiac death was defined as death due to acute myocardial infarction, congestive heart failure, life-threatening arrhythmias or cardiac arrest. Unexpected, otherwise unexplained sudden death was considered cardiac death. NCV-NCA death included infectious diseases, neurological, pulmonary, renal failure, liver disease, multiorgan failure, non-cardiac surgery, accident/trauma, suicide, other non-cardiac; and unknown or unobtainable. CA deaths were identified by codes from the International Classification of Diseases 9th/10th revisions. Information on causes of death was provided by the local community registry (Registry of Mortality of Galicia). Continuous variables were reported as mean ± 1 standard deviation and intergroup differences assessed with analysis of variance. Univariable and multivariable associations of variables with the different causes of death were assessed. To compare the subdistribution of hazard ratios for each cause-specific mortality according to different variables, modified Cox regression hazard models were employed by the Fine–Gray method.[5] This test considers as a single cause of death both the association of the different variables with a single cause of death and the contribution of another competing event by actively maintaining subjects in the risk sets.[6] For those variables measuring related aspects, only the one with the higher C-index was included. A cause-specific C-index in the presence of competing risks was considered. The cumulative incidence in competing risk analyses was calculated using the cmprsk package of R.[7] The cause-specific C-index was computed using the C-index function from the risk Regression package of R. A two-sided p value < 0.05 was considered significant.

Table 1 summarizes the clinical and ExE characteristics of the patients according to workload. During a mean follow-up of 4.7 ± 4.8 years (interquartile range 0.1–8.0) there were 1253 CV, 670 CA and 650 NCV-NCA deaths. Different clinical characteristics predicted CV death, along with achieved METs and ExE variables. Both CA and NCV-

NCA deaths were also independently predicted by several clinical characteristics as well as for achieved METs. Imaging from ExE was not predictive of non-cardiovascular deaths.

Annualized CV deaths were triple in patients with bad versus good functional capacity (3.2% *vs*. 1.2%, $p < 0.001$). The same occurred for NCV-NCA death (1.7% *vs*. 0.6%, $p < 0.001$), whereas CA deaths were double in patients with bad functional capacity (1.5% *vs*. 0.8%, $p < 0.001$). Annualized mortality rates <1% for CA and NCV-NCA were found for patients who achieved 10 METs, independently of the imaging results; whereas annualized rates <1% for CV were found for patients who achieved 10 METs with negative imaging results. All the other subgroups had higher mortality rates for any cause (Figure 1).

Our results confirm and expand previous literature demonstrating the benefits of being fit.[1–4,8,9] However, this literature did not always investigate separately predictions for the different causes of mortality, and relatively few studies have explored the relationship between fitness and cancer. A unique advantage of ExE over other types of stress is that, apart from offering imaging of the heart during physiological standing exercise, non-imaging exercise functional parameters are also available. Imaging mainly offered prognostic information on CV mortality, whereas exercise capacity offered prognostic information related to any type of death. Patients with abnormal imaging results were at high risk of cardiovascular mortality, whereas patients with limited functional capacity were also at high risk of NCV death, independently of the imaging results. This is an important issue as patients with negative ExE results could be reassured that their risk of CV death is low, but actually this is only true in the case of good functional capacity.

Carpeggiani et al. found that imaging obtained mostly from pharmacological stress echocardiography could predict any kind of death.[10] Thus, the results were similar to ours in terms of prediction of CV death, but were not for the prediction of CA death. The authors partially attributed their ability to predict CA deaths to downstream radioactive procedures for coronary artery disease suspicion.

Although imaging resulted useful for predicting CV death in our investigation, we observed that the ‘exercise part’ of an ExE study predicts not only CV death, but death due to CA or other causes. The accomplishment of stage 4 of the Bruce protocol (velocity 6.8 km/h, treadmill inclination 16%) is equivalent to a functional capacity of 10 METs.

Other exercises equivalent to 10 METs are running at 10.4 km/h, bicycling at 22–26 km/h or walking very fast up four flights of stairs. Physical activity has a positive effect on blood pressure and lipids and therefore in the cardiovascular system, it reduces inflammation and improves the body's response to tumours. Our results add to common knowledge about the benefits of being fit for longevity.

In conclusion, the 'exercise part' of an ExE study predicts not only CV death, but also CA or NCV-NCA death. Fit patients, based on the achievement of 10 METs during exercise testing, have less chance of death from any cause.

Author contribution

JP and ABM contributed to the conception and design of the work. JP, ABM, CBC, SP and FB contributed to the data acquisition, analysis and interpretation of results for the work. JP, ABM, CBC and JMVR critically revised the manuscript. All authors gave final approval and agree to be accountable for all aspects of work ensuring integrity and accuracy.

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Table 1.Clinical baseline characteristics, exercise testing results and exercise echocardiography findings in the 12,615 patients classified according to the achieved workload.

	<7 METs	7–9.9 METs	≥10 METs	
	n = 2201	*n* = 4097	*n* = 6317	*p* value
Clinical characteristics				
Male, n (%)	1169 (53.1)	2183 (53.3)	4549 (72)	<0.001
Age, years	69 ± 10	66 ± 10	58 ± 12	<0.001
Current smokers, n (%)	475 (21.6)	821 (20)	1772 (28.1)	<0.001
Diabetes, n (%)	643 (29.2)	915 (22.3)	835 (13.2)	<0.001
Hypertension, n (%)	1443 (65.6)	2470 (60.3)	2742 (43.4)	<0.001
Hypercholesterolaemia, n (%)	1059 (48.1)	2096 (51.2)	2893 (45.8)	<0.001
History of CAD, n (%)	717 (32.6)	1259 (30.7)	1961 (31)	0.3
Typical angina, n (%)	297 (13.5)	438 (10.7)	403 (6.3)	<0.001
Atrial fibrillation, n (%)	246 (11.1)	251 (6.1)	127 (2)	<0.001
Abnormal resting ECG, n (%)	695 (31.6)	1105 (27)	1231 (19.5)	<0.001
Medications				
Beta-blockers, n (%)[a]	224 (10.2)	396 (9.7)	622 (9.8)	0.81
ACEIs/ARAIIs, n (%)	990 (45)	1609 (39.3)	1827 (28.9)	<0.001
Calcioantagonists, n (%)	322 (14.6)	435 (10.7)	464 (7.3)	<0.001
Nitrates, n (%)	723 (32.8)	1071 (26.1)	1264 (20)	<0.001
Digoxine, n (%)	97 (4.4)	105 (2.6)	88 (1.4)	<0.001
Diuretics, n (%)	276 (12.5)	302 (7.4)	236 (3.7)	<0.001
Exercise testing				
Rate–pressure product, beats/min × 10 (3)				
Rest	11.2 ± 3.0	10.8 ± 2.7	10.0 ± 2.4	<0.001
Peak	21.0 ± 5.9	23.7 ± 5.9	26.4 ± 5,4	<0.001
% Achieved of the maximal age-predicted heart rate	89 ± 16	93 ± 13	95 ± 10	<0.001
Angina during the test, n (%)	556 (25.3)	847 (20.6)	713 (11.3)	<0.001
Positive ECG, n (%)	414 (18.8)	750 (18.3)	899 (14.2)	<0.001
Positive exercise testing, n (%)[b]	774 (35.2)	1262 (30.8)	1359 (21.5)	<0.001
ExE				
Resting wall motion abnormalities, n (%)	729 (33.1)	1035 (25.3)	1305 (20.7)	<0.001
Ischaemia, n (%)	904 (41.1)	1396 (34.1)	1564 (24.8)	<0.001

Abnormal ExE, n (%)	1212 (55.1)	1856 (45.3)	2244 (35.5)	<0.001
Wall motion score index				
Rest	1.19 ± 0.34	1.12 ± 0.26	1.08 ± 0.21	<0.001
Peak	1.37 ± 0.43	1.26 ± 0.36	1.15 ± 0.27	<0.001
Left ventricular ejection fraction, %				
Rest	55 ± 11	57 ± 90	59 ± 7	<0.001
Peak exercise	55 ± 15	61 ± 13	65 ± 10	<0.001

[a] The day of the ExE.

[b] Defined as either symptoms or ischaemic ECG changes during testing.

MET: metabolic equivalent; CAD: coronary artery disease; ECG: electrocardiogram; ExE: exercise echocardiography; ACEI: angiotensin-converting enzyme inhibitor; ARAII: angiotensin II receptor antagonist.

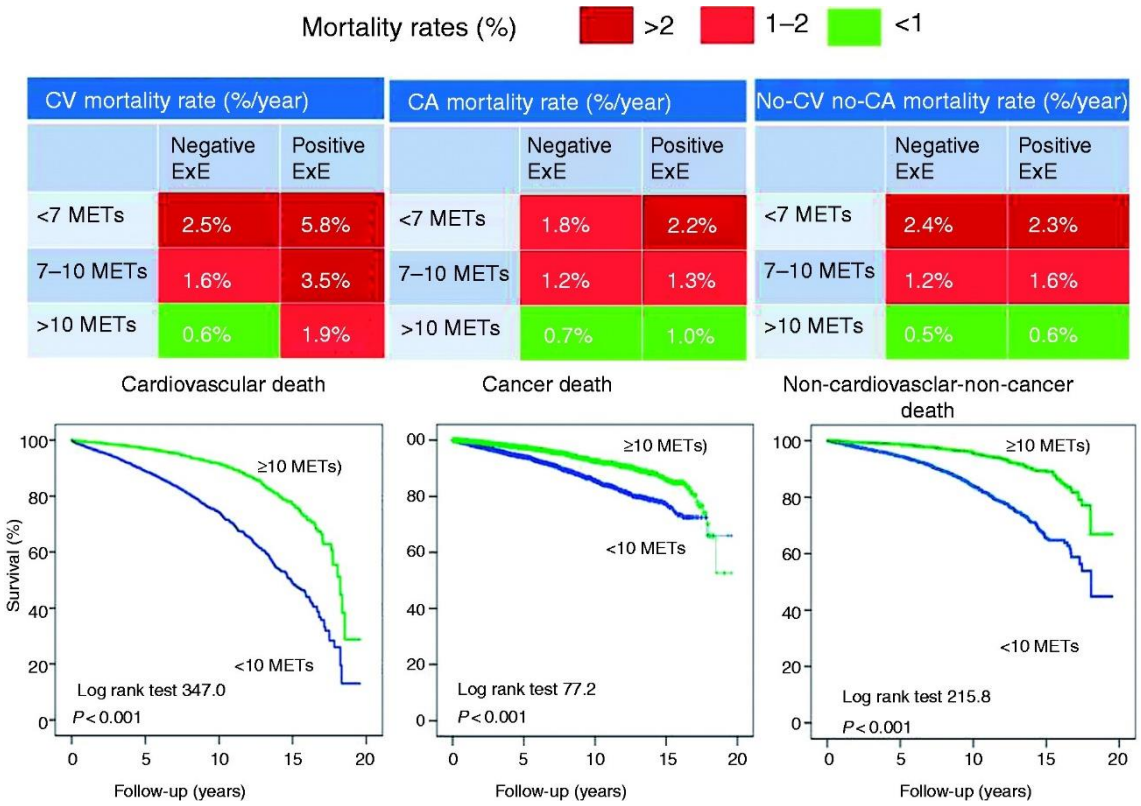

Figure 1. Mortality rates according to the different causes of death, functional capacity and imaging (on the top), and cardiovascular, cancer, and non-cardiovascular non-cancer death curves for patients with good (≥10 METs) and bad functional capacity (<10 METs) (on the bottom).

CV: cardiovascular; CA: cancer; ExE: exercise echocardiography; MET: metabolic equivalent