Treadmill walking speed and survival prediction in men with cardiovascular disease.
A 10-year follow-up study.

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Title Treadmill walking speed and survival prediction in men with cardiovascular disease.

A 10-year follow-up study.

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ABSTRACT

Objective To determine whether the walking speed maintained during a one Km treadmill test at moderate intensity predicts survival in subjects with cardiovascular disease.

Design Population-based prospective study.

Setting Outpatients following secondary prevention in Ferrara, Italy.

Participants 1,255 male stable cardiac patients, aged 25-85 years at baseline.

Main outcome measures Walking speed maintained during a one Km treadmill test, measured at baseline and mortality over a median follow-up of 8.2 years.

Results Among 1,255 patients, 141 died, for an average annual mortality of 1.4%. Of the variables considered, the strongest predictor of all-cause mortality was walking speed (95%CI, 0.45 to 0.75, P<0.0001). Based on the average speed maintained during the test, subjects were subdivided into quartiles and mortality risk was calculated. Compared to the slower quartile (average walking speed 3.4 Km/h), the relative mortality risk decreased for the second, third, and fourth quartile (average walking speed 5.5 Km/h), with hazard ratios of 0.77 (95%CI, 0.52 to 1.13,); 0.41 (95%CI, 0.24 to 0.70); and 0.36 (95%CI, 0.19 to 0.68), respectively (P for trend <0.0001). Receiver operating curve analysis showed an area under the curve of 0.71 (P<0.0001) and the highest Youden index (0.347) for a walking speed of 4.0 Km/h.

Conclusions The average speed maintained during a one Km treadmill walking test is inversely related to survival in patients with cardiovascular disease and is a simple and useful tool for stratifying risk in patients undergoing secondary prevention.

ARTICLE SUMMARY

Article focus

- An inverse relationship between walking speed and survival is well documented in older subjects.
- The aim of this study was to determine whether walking speed predicts survival in subjects with cardiovascular disease.

Key messages

- A strong inverse association between average walking speed and mortality was observed in patients with cardiovascular disease.
- Average walking speed using the one Km test is useful for predicting survival among subjects with stable cardiovascular disease and for guiding their rehabilitation.

Strengths and limitations of this study

- The walking test used in this study measures cardiovascular function. The test is submaximal, easy to perform and allows the concurrent measurement of physiologic data..
- The study included male participants only, the results may not be generalized to women.
- Participants were excluded from the test if they were not able to walk for one Km.

INTRODUCTION

In patients with cardiovascular disease, peak oxygen consumption is utilized for assessing disease severity and for quantifying the effectiveness of rehabilitation programs.[1 2] Moreover, it is a strong independent predictor of risk of death and for estimating risk of mortality and other adverse outcomes[3].

Peak oxygen consumption is commonly determined by maximal exercise testing, but it can be difficult to carry out in some cardiac patients. For this reason, walking tests at a submaximal exercise intensity have been developed for quantifying functional capabilities of patients with cardiovascular and pulmonary disease[4], including time-based[5 6] and distance-based protocols[7-9] involving walking on the ground, treadmill or along a corridor.[10-13] Short walking tests have also been employed, but they generally do not adequately quantify aerobic fitness[14], and the optimal duration or length for these submaximal protocols has been debated[15].

Walking tests have been used to assess exercise capacity,[16-19] and to investigate outcomes in many rehabilitation programs[20]. Walking speed has been considered a "vital sign" and a surrogate of physiological function in several cohort studies among patients with cardiovascular disease.[19] Walking speed is a commonly used objective measure of the functional capabilities among older subjects, and has been demonstrated to be a strong predictor of survival[21 22]. A 3-fold higher risk of mortality in the lowest quartile of walking speed compared with the highest was reported in a recent meta-analysis.[21 23 24]

We recently developed a moderate, perceptually regulated one Km walking test for the indirect estimation of peak oxygen consumption in patients with cardiovascular disease.[25] In the current study, we addressed the association between average walking speed maintained during this one Km test and survival in a cohort of patients with stable cardiovascular disease. The average walking speed maintained during the one Km test among 1,255 patients with cardiovascular disease was determined, and all-cause mortality over 10 years of follow up was quantified.

METHODS

The study population consisted of 1,442 men, aged 25-85 years, referred by their physician for exercise testing prior to participation in an exercise-based secondary prevention program between 1997 and 2012. Women were not included in the study because of their small number. Subjects with heart failure classified as New York Heart Association class II or higher, and those who had conditions that interfered with walking ability such as neurological, musculoskeletal, or peripheral vascular conditions were also excluded.

Before the walking test, participants underwent a comprehensive clinical evaluation, including medical history, smoking status and fasting blood chemistry analyses. Weight and height were measured and used to calculate body mass index. Hypertension was defined as systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or use of antihypertensive agents.

Walking speed determination

Average walking speed was determined for each participant at the time of their baseline examination using the one Km treadmill walking test previously described.[25] Briefly, the test was carried out as follows: the subjects were instructed to select a pace that they could maintain for 10 to 20 minutes at a moderate perceived exercise intensity using the Borg 6-20 scale.[26] Subjects began the test walking on the level at 2.0 km/h, with subsequent increases of 0.3 km/h every thirty seconds up to a walking speed corresponding to a perceived exertion of 11-13 on the Borg scale. The test was then started and rate of perceived exertion acquired every two minutes, adjusting walking speed to maintain the selected moderate perceived intensity. Heart rate was monitored continuously during the test using a Polar Accurex Plus heart rate monitor (Polar Electro, Kempele, Finland). Blood pressure was monitored before and immediately after the test. The time to complete one kilometer was recorded and average walking speed calculated accordingly**.**

Mortality assessment

Participants were followed for all-cause mortality from the date of their baseline examination for up to 10 years. Subjects were flagged by the regional Health Service Registry of the Emilia-Romagna region, who provided the date of death where applicable, or by contacting relatives and personal physician to determine vital status. Time from initial evaluation to death was calculated in years.

Statistical Analysis

All-cause mortality was used as the end point for survival analysis. Differences in survival across quartiles during the follow up period were assessed using Kaplan-Meier curves. Hazard Ratios and 95% confidence intervals were estimated across quartiles using Cox proportional hazard models. Individuals in the quartile with the lowest average walking speed were considered the reference group. The models were adjusted for age. The assumption of proportionality of all variables introduced in the models was assessed through the analysis of Schoenfeld residuals. The proportional hazards assumption held for all models. To assess the discriminatory accuracy of average walking speed in estimating survival, receiver-operating-characteristics (ROC) curves were constructed and the corresponding areas under the curve were calculated. The optimal cut-off point was calculated using the Youden index (sensitivity+specificity-1).[27] The level of statistical significance was set at $P < 0.05$. Statistical analyses were performed using Medcalc 11.4 software, Mariakerke, Belgium.

RESULTS

Of the 1,442 participants who were initially considered, 187 (13%) were excluded due to the inability to complete the one Km test. The walking test was completed by the remaining 1255 subjects; average speed maintained during the one Km test was 4.3 (0.8) km/h.

The median follow-up period was 8.2 years during which a total of 141 deaths from any cause occurred, yielding an average annual mortality of 1.4%. The age-adjusted hazard ratios for death relative to average walking speed and to other clinical predictors of mortality are presented in Table 1. The best predictor of all-cause mortality was average walking speed.

On the basis of the average walking speed, the subjects were subdivided into quartiles. The baseline demographic and clinical characteristics of the study population, stratified in quartiles of average walking speed, are presented in Table 2. Significant difference between quartiles were documented for age, body mass index, ejection fraction, hypertension, family history, fasting glucose, total cholesterol, serum triglycerides, serum creatinine, medical history (excluding valvular replacement) and therapy with diuretics and statins.

Kaplan-Meier survival curves of the quartiles are presented in Figure 1. Subjects in the first quartile (average walking speed 3.4 Km/h) had a marked reduction in survival compared to subjects in quartile IV (average walking speed 5.5 Km/h). A 64 % reduction in risk of death was observed in the

quartile with highest compared to the quartiles with slower average walking speeds (Table 3). The reduction in risk was significant in quartiles III and IV vs. quartile I. The relationship between relative risk of death and average walking speed among the quartiles fit the polynomial equation $y=0.26x^2 - 2.6x + 7.2$ with an R^2 of 0.97 (Figure 2).

The strength of average walking speed in the prediction of all-cause mortality is shown in Figure 3 (area under the curve 0.71, 95% CI: 0.68-0.74, P<0.0001). The highest Youden index (0.347) was observed at a walking speed of 4.0 Km/h, corresponding to a sensitivity of 70.2 % and a specificity of 64.5%.

DISCUSSION

We observed an inverse association between average walking speed, estimated by a one Km treadmill test carried out at a perceived exertion of 11-13 on the 6-20 Borg scale, and all-cause mortality in a cohort of 1,255 patients with stable cardiovascular disease. Independent from traditional cardiovascular risk factors and clinical history, low average walking speed was associated with higher rates of mortality.

The prognostic power of average walking speed was underscored by dividing the sample into quartiles; a significant reduction in risk of death was observed among the quartiles with higher average walking speeds compared to those with lower walking speeds. Subjects with the highest walking speed exhibited a 64% overall reduction in mortality risk compared to those with the lowest walking speed. The trend for risk of death sharply increased when average walking speed decreased to below 3.4 Km/h (Figure 2), a finding similar to that reported by Stanaway et al.[22] The ability of the one Km walking test to predict mortality we observed is similar to that reported by Studensky et al[21] and by Stanaway et al[22] documenting the association between walking speed (determined by the use a short walking test of 4 to 6 meters) and survival in healthy older adults. These gait speed tests, although short, are regarded as both measures of lower extremity function and markers of physiological reserve.[19] The one Km walking test we used has the advantage of estimating cardio-respiratory function, since we have shown it can be used for the indirect evaluation of peak oxygen consumption .[25] Other tests, such as the widely-used 6 min walk test, are considered measures of

submaximal endurance and have been shown to have prognostic value; however, these tests are performed at near-maximal intensity.

STRENGTHS AND LIMITATIONS OF THE STUDY

The one Km walking test we developed is performed on treadmill and therefore allows the concurrent measurement of physiologic data including the ECG, and can be done comfortably in a standard exercise laboratory.[28] It should also be noted that while peak oxygen consumption is often considered the gold standard for cardiopulmonary function,[2] it is strongly influenced by genotype (accounting for up to 50% of its variance).[29] In contrast, walking ability closely reflects a patient's cardiovascular capabilities associated with ability to perform daily activities, and is therefore relevant for participants in cardiac rehabilitation.[2]

This study has some limitations. Although it has been demonstrated that exercise capacity is an independent predictor of mortality in women,[21] our study included male participants only; thus, the results may not be generalized to women. Participants were excluded from the test if they were not able to walk for one Km, and the results therefore may not apply to patients with markedly low exercise capacity. We did not consider social, behavioral or psychological factors that have been independently associated with reduced walking speed.[31] Finally, these results were obtained from patients with an interest in participating in a secondary prevention program. Therefore, external validation of our findings is needed.

CONCLUSIONS AND CLINICAL IMPLICATIONS

Our findings suggest that a simple and easy-to-perform one Km treadmill walking test at a moderate intensity is a useful tool for identifying mortality risk in patients with stable cardiovascular disease. In addition to its utility for stratifying risk, the test can also be used by health professionals involved in secondary prevention to assess the efficacy of exercise prescription and quantify functional changes with rehabilitation.

Footnotes

Contributors: LC, FC, GM and GG conceived and designed the study. EB, GC, FC, GG analysed the data, interpreted the results and co-wrote the paper. FT and SV analysed the data. JM discussed the results, and revised the manuscript. All authors had full access to the data and take responsibility for its integrity and the accuracy of the analysis.

Competing interests: "All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: no support from any organization for the submitted work; no financial relationships with any organization that might have an interest in the submitted work in the previous three years; and no relationship or activities that could appear to have influenced the submitted work.

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Ethical approval: This study was approved by the Emilia Romagna Health Service human research ethics committee.

Data sharing: No additional data available.

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Tables

Table 1. Age-adjusted risk of death according to clinical variables.

Variable	HR	*P* value	95 % CI
Demographics			
BMI	0.98	0.57	0.94-1.04
LV Ejection fraction (%)	0.99	0.47	0.98-1.01
Risk factor			
Current Smoking	2.24	0.02	1.12-4.47
Hypertension	1.22	0.25	0.87-1.72
Fasting glucose	1.01	0.07	0.99-1.01
Total cholesterol	0.99	0.38	0.99-1.00
HDL cholesterol	1.00	0.70	0.99-1.01
Serum tryglicerides	0.99	0.20	0.99-1.00
Family history	1.03	0.85	0.74-1.44
Serum creatinine	1.67	0.13	0.87-3.19
Medical history			
CABG	1.10	0.57	0.78-1.58
Myocardial infarction	1.1	0.6	0.74-1.63
PTCA	0.78	0.55	0.34-1.76
Valvular replacement	0.69	0.30	0.34-1.40
Other	0.77	0.72	0.19-3.12
Medications (%)			
Calcium antagonist	0.80	0.4	0.48-1.34
Aspirin	1.40	0.1	0.93-2.1
Statin	0.97	0.9	0.70-1.35
β-blocker	1.04	0.8	0.74-1.44
Diuretic	1.30	0.17	0.89-1.91
ACE inhibitor or ARB	0.88	0.47	0.64-1.23
Average walking speed	0.58	<0.0001	0.45-0.75

Data are from the Cox proportional-hazards model.

Table 2. Baseline Characteristics of the 1255 subjects by Quartile of average walking speed.

Variable	All Subjects (n=1255)	I Quartile (n=316)	II Quartile (n=313)	III Quartile (n=300)	IV Quartile (=326)	P for trend
AWS (Km/h)	4.3 (0.8)	3.4 (0.3)	4.1 (0.1)	4.6 (0.2)	5.5 (0.5)	<0.001
Demographics						
Age (yr)	61 (10)	65 (9)	63 (9)	59 (9)	57 (9)	<0.001
BMI	27.6 (3.4)	28.3 (3.7)	27.6 (3.3)	27.7 (3.2)	27.0 (3.3)	<0.001
LV ejection fraction (%)	56 (10)	53 (11)	56 (9)	57 (11)	58 (10)	0.002
Risk factor						
Current Smoking (%)	5.6	4.1	5.4	4.6	7.8	0.055
Hypertension (%)	56.6	62.3	57.8	53.3	52.8	0.008
Family history (%)	53.7	48.4	51.7	54.3	60.7	0.001
Fasting glucose (mg/dl)	107 (27)	110 (28)	110 (28)	106 (29)	105 (28)	0.03
Total cholesterol (mg/dl)	194 (42)	195 (47)	199 (43)	194 (41)	188 (39)	0.04
HDL cholesterol (mg/dl)	49 (14)	50 (16)	49 (13)	47 (14)	50 (13)	0.55
Serum tryglicerides (mg/dl)	139 (80)	147 (97)	138 (71)	143 (80)	129 (67)	0.046
Serum creatinine (mg/dl)	1.1 (0.2)	1.2 (0.3)	1.1 (0.2)	1.1 (0.2)	1.0 (0.2)	<0.001
Medical history (%)						
CABG	49.4	63.3	52.0	46.3	36.2	<0.001
Myocardial infarction	28.1	22.2	29.1	31.3	30.0	0.02
PTCA	8.7	4.7	5.7	9.0	15.3	0.001
Valvular replacement	8.9	8.2	8.9	7.6	10.4	0.4
Other	4.4	1.3	3.8	5	7.4	0.001
Medications (%)						
ACE inhibitor or ARB	53.3	57.3	54.0	50.0	68.9	0.09
Aspirin	74.6	75.9	72.8	74.3	75.1	0.9
β-blocker	59.4	57.9	63.6	60.0	55.8	0.4
Calcium antagonist	12.9	13.6	12.5	14.0	11.7	0.6
Diuretic	18.1	26.6	20.4	13.7	10.4	<0.001
Statin	52.9	50.3	49.2	52.0	60.1	0.01

Data are presented as mean (standard deviation, SD).
Abbreviations: AWS, average walking speed; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BMI, Body Mass Index; CABG, Coronary Artery Bypass Graft; LV, Left Ventricular; PTCA, Percutaneous Transluminal Coronary Angioplasty, stenting or both.

Table 3. Age adjusted relative risk of death from any cause across quartiles of average walking speed.

AWS quartile	AWS (km/h)	HR	95% CI	*P* Value
I	3.4 (0.3)	1.00		
II	4.1 (0.1)	0.77	0.52 - 1.13	0.18
III	4.6 (0.2)	0.41	0.24 - 0.70	0.01
IV	5.5 (0.5)	0.36	0.19 - 0.68	0.002

Data are presented as mean (standard deviation, SD).
AWS: average walking speed, HR: Hazard Ratio.

Figures

Figure 1. Survival curves of the quartiles stratified according to average walking speed.

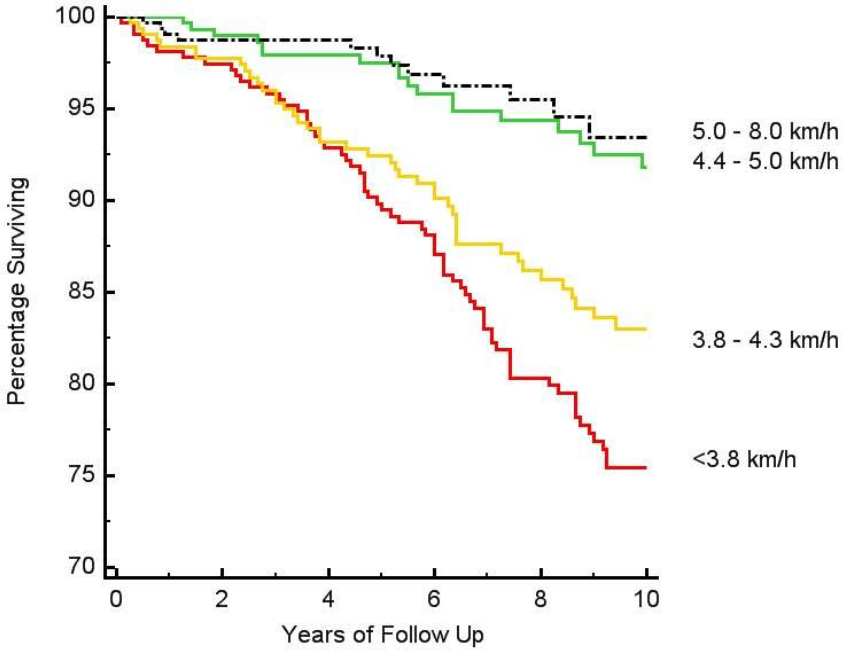


Figure 2. The polynomial relationship between quartile average walking speed and relative risk of death.

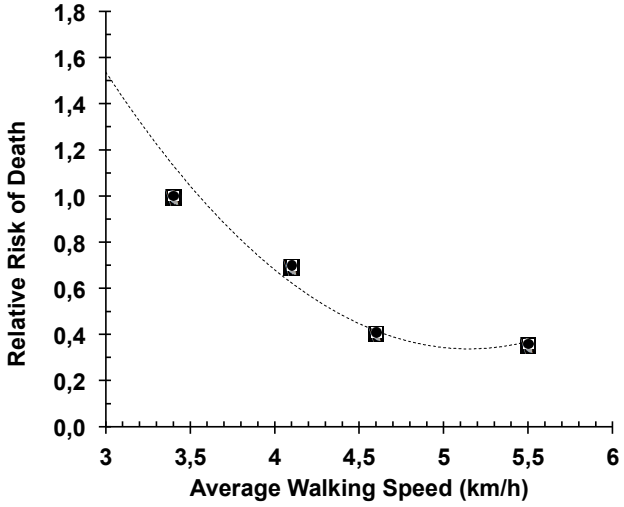
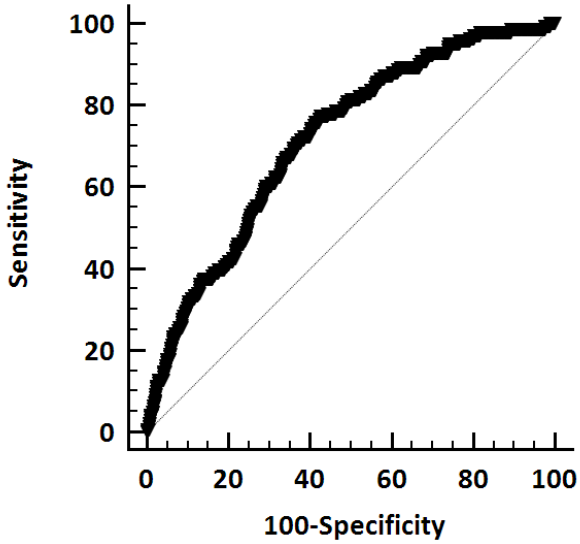


Figure 3. Receiver operating characteristic curves for estimating risk of death from any cause by

average walking speed.



STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract Page 2, line 11
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found Page 2, lines 44-48
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported Page 4, lines 29-41
Objectives	3	State specific objectives, including any prespecified hypotheses Page 4, lines 43-54
Methods		
Study design	4	Present key elements of study design early in the paper Page 5, line 3 and page 5, 49-53
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection Page 5, line 5-7
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up Page 5, lines 7-13
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable Page 5, lines 15-22
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group Page 5, lines 24-47 and page 5 lines 53-57
Bias	9	Describe any efforts to address potential sources of bias
Study size	10	Explain how the study size was arrived at Page 5, lines 3-4
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why Page 6, lines 3-5
Statistical methods	12	Page 6, lines 3-24
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed Page 6, line 28
		(b) Give reasons for non-participation at each stage Page 6, lines 28-30
Descriptive data	14*	Summarise follow-up time (eg, average and total amount) Page 6, line 34
Outcome data	15*	Report numbers of outcome events or summary measures over time Page 6, lines 34-36
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and

		their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included Page 6, lines 36-53; page 13 lines 3-44
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses Page 7, lines 11-18
Discussion		
Key results	18	Summarise key results with reference to study objectives Page 7, lines 21-30
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias Page 8, lines 24-39
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence Page 7, lines 32-57 and page 8, lines 2-5
Generalisability	21	Discuss the generalisability (external validity) of the study results Page 8, lines 43-52
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based Page 9, line 22

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

Treadmill walking speed and survival prediction in men with cardiovascular disease.
A 10-year follow-up study.

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Title Treadmill walking speed and survival prediction in men with cardiovascular disease.

A 10-year follow-up study.

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ABSTRACT

Objective To determine whether the walking speed maintained during a one Km treadmill test at moderate intensity predicts survival in subjects with cardiovascular disease.

Design Population-based prospective study.

Setting Outpatient secondary prevention program in Ferrara, Italy.

Participants 1,255 male stable cardiac patients, aged 25-85 years at baseline.

Main outcome measures Walking speed maintained during a one Km treadmill test, measured at baseline and mortality over a median follow-up of 8.2 years.

Results Among 1,255 patients, 141 died, for an average annual mortality of 1.4%. Of the variables considered, the strongest predictor of all-cause mortality was walking speed (95%CI, 0.45 to 0.75, P<0.0001). Based on the average speed maintained during the test, subjects were subdivided into quartiles and mortality risk **adjusted for confounders** was calculated. Compared to the slowest quartile (average walking speed 3.4 Km/h), the relative mortality risk decreased for the second, third, and fourth quartiles (average walking speed 5.5 Km/h), with hazard ratios of 0.73 (95%CI, 0.46 to 1.18,); 0.54 (95%CI, 0.31 to 0.95); and 0.20 (95%CI, 0.07 to 0.56), respectively (P for trend <0.0001). Receiver operating curve analysis showed an area under the curve of 0.71 (P<0.0001) and the highest Youden index (0.35) for a walking speed of 4.0 Km/h.

Conclusions The average speed maintained during a one Km treadmill walking test is inversely related to survival in patients with cardiovascular disease and is a simple and useful tool for stratifying risk in patients undergoing secondary prevention **and cardiac rehabilitation programs**.

ARTICLE SUMMARY

Article focus

- An inverse relationship between walking speed and survival is well documented in older subjects.
- The aim of this study was to determine whether walking speed predicts survival in subjects with cardiovascular disease.

Key messages

- A strong inverse association between average walking speed and mortality was observed in patients with cardiovascular disease.
- Average walking speed using the one Km test is useful for predicting survival among subjects with stable cardiovascular disease and provides an additional tool for guiding **secondary prevention and cardiac rehabilitation programs.**

Strengths and limitations of this study

- The walking test used in this study measures cardiovascular function. The test is submaximal, easy to perform and allows the concurrent measurement of physiologic data.
- The study included male participants only, and the results may not be generalized to women.
- Participants not able to walk for one Km were excluded from the study.

INTRODUCTION

In patients with cardiovascular disease, peak oxygen consumption is utilized for assessing disease severity and for quantifying the effectiveness of **secondary prevention and cardiac rehabilitation programs.**[1 2] Moreover, it is a strong independent predictor of risk of death and for estimating risk of mortality and other adverse outcomes.[3]

Peak oxygen consumption is commonly determined by maximal exercise testing, but it can be difficult to carry out in some cardiac patients. For this reason, walking tests at a submaximal exercise intensity have been developed for quantifying functional capabilities of patients with cardiovascular and pulmonary disease[4], including time-based[5 6] and distance-based protocols[7-9] involving walking on the ground, treadmill or along a corridor.[10-13] Short walking tests have also been employed, but they generally do not adequately quantify aerobic fitness[14], and the optimal duration or length for these submaximal protocols has been debated.[15]

Walking tests have been used to assess exercise capacity,[16-19] and to investigate outcomes in many rehabilitation programs.[20] Walking speed has been considered a "vital sign" and a surrogate of physiological function in several cohort studies among patients with cardiovascular disease.[19] Walking speed is a commonly used objective measure of functional capabilities among older subjects, and has been demonstrated to be a strong predictor of survival.[21 22] For example, a 3-fold higher risk of mortality in the lowest quartile of walking speed compared to the highest quartile was reported in a recent meta-analysis.[21-24] **However, less is known about the prognostic relevance of walking performance in younger individuals with cardiovascular disease, particularly for community-based programs.[25]**

We recently developed a **moderate-intensity, self-paced** one Km walking test for the indirect estimation of peak oxygen consumption in patients with cardiovascular disease **across a broad age range**.[26] In the current study, we addressed the association between average walking speed maintained during this one Km test and survival in a cohort of patients with stable cardiovascular

disease. The average walking speed maintained during the one Km test among 1,255 patients was determined, and all-cause mortality over 10 years of follow up was quantified.

METHODS

The study population consisted of 1,442 men, with stable cardiovascular disease, aged 25-85 years, referred by their physician to the Department of Rehabilitative Medicine of the University of Ferrara, Italy, for participation in an exercise-based secondary prevention program, between 1997 and 2012.

The program was guided by a cardiologist and a sports medicine doctor. A comprehensive clinical evaluation, including personal medical history, risk factor and medications was carried out. Left ventricular ejection fraction was derived from previous echocardiographic evaluations. Standard blood chemistry analyses previously performed were registered. Weight and height were measured and used to calculate body mass index.

Subjects with heart failure classified as New York Heart Association class II or higher, and those who had conditions that interfered with walking ability such as neurological, musculoskeletal, or peripheral vascular conditions were not included in the study.

127 women, aged 60 (10), average walking speed 3,9 (0,7) km/h, were considered. During the follow up period 9 (7%) of these excluded subjects died. Because of the small number of woman and events a stratified analysis according to gender was not feasible.

Walking speed determination

Average walking speed was determined for each participant at the time of their baseline examination using the one Km treadmill walking test previously described, **and developed in 178 subjects belonging to the same population of the current study.**[26] Briefly, the test was carried out as follows: the subjects were instructed to select a pace that they could maintain for 10 to 20 minutes at a moderate perceived exercise intensity using the Borg 6-20 scale.[27] Subjects began the test walking on the level at 2.0 km/h, with subsequent increases of 0.3 km/h every thirty seconds up to a walking speed

corresponding to a perceived exertion of 11-13 on the Borg scale. The test was then started and rate of perceived exertion acquired every two minutes. Walking speed was adjusted to maintain the selected moderate perceived intensity. Heart rate was monitored continuously during the test using a Polar Accurex Plus heart rate monitor (Polar Electro, Kempele, Finland). Blood pressure was monitored before and immediately after the test. The time to complete one kilometer was recorded and average walking speed calculated accordingly**.**

Mortality assessment

Participants were followed for all-cause mortality from the date of their baseline examination for up to 10 years. Subjects were flagged by the regional Health Service Registry of the Emilia-Romagna region, which provided the date of death where applicable, or by contacting relatives and personal physician to determine vital status.

Covariates

The covariates considered as potential confounders were: average walking speed, age, body mass index, left ventricular ejection fraction, current smoking, hypertension, family history, fasting glucose, total cholesterol, HDL cholesterol, serum triglycerides, serum creatinine, personal medical history (coronary artery bypass graft, myocardial infarction, percutaneous transluminal coronary angioplasty, valvular replacement and medical therapy for stable angina), and use of angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, aspirin, β-blockers, calcium antagonists, diuretics, statins and number of medications.

Statistical Analysis

All-cause mortality was used as the end point for survival analysis. Differences in survival across quartiles during the follow up period were assessed using Kaplan-Meier curves. Hazard Ratios and 95% confidence intervals were estimated across quartiles using Cox proportional hazard models. Individuals in the quartile with the lowest average walking speed were considered the reference group. The models were adjusted for **confounders significantly related to death**. The assumption of proportionality of all variables introduced in the models was assessed through the analysis of Schoenfeld residuals. The proportional hazards assumption held for all models. To assess the

discriminatory accuracy of average walking speed in estimating survival, receiver-operating-characteristics (ROC) curves were constructed and the corresponding areas under the curve were calculated. The optimal cut-off point was calculated using the Youden index (sensitivity+specificity-1).[28] The level of statistical significance was set at $P < 0.05$. Statistical analyses were performed using Medcalc 11.4 software, Mariakerke, Belgium.

RESULTS

Of the 1,442 participants who were initially included in the study, 187 (13%) were excluded due to the inability to complete the one Km test. These subjects were significantly older (70 vs. 61 years, P<0.0001), had a higher body mass index (28.4 vs. 27.6, P< 0.01), a higher prevalence of hypertension (68% vs. 57%, P=0.002), higher serum creatinine (1.7 vs. 1.1 mg/dl, P<0.001), and a lower ventricular ejection fraction (53% vs. 56%, P=0.001). In addition, those excluded had a lower use of statins (35% vs. 53%), and β-blockers (43% vs. 59%), and a higher use of diuretics (44% vs. 18%). 71 of these subjects died during the 10 years of follow up.

The one Km walking test was completed by the remaining 1255 subjects at an average speed of 4.3 (0.8) km/h. The median follow-up period was 8.2 years during which a total of 141 deaths from any cause occurred, yielding an average annual mortality of 1.4%.

Clinical and exercise-test predictors of mortality from the Cox proportional hazards model are presented in Table 1. After adjustment for age, the best predictor of an increased risk of death from any cause was average walking speed, followed by smoking status and fasting glucose.

On the basis of the average walking speed, the subjects were subdivided into quartiles. The baseline variables of the study population, stratified in quartiles of average walking speed, are presented in Table 2. Kaplan-Meier survival curves for the quartiles are presented in Figure 1. Subjects in the first quartile (average walking speed 3.4 Km/h) had a marked reduction in survival compared to subjects in the fourth quartile (average walking speed 5.5 Km/h). **Comparison between quartiles revealed significant differences in age, left ventricular ejection fraction, body mass index, smoking status, hypertension, family history, fasting glucose, total cholesterol, serum triglycerides and creatinine, medical history, number of medication, diuretics and statins use. The relative risk of**

death from any cause across quartiles adjusted for these confounders is presented in Table 3. An 80% reduction in risk of death was observed in the quartile with highest compared to the quartiles with slower average walking speeds. The reduction in risk was significant in third and fourth quartiles vs. first quartile. The relationship between relative risk of death and average walking speed among the quartiles after adjusting for confounders fit the exponential equation $y=15.6e^{-0.77x}$ ($R^2=0.95$) (Figure 2). The strength of average walking speed in the prediction of all-cause mortality is shown in Figure 3 (area under the curve 0.71, 95% CI: 0.68-0.74, P<0.0001). The highest Youden index (0.35) was observed at a walking speed of 4.0 Km/h, corresponding to a sensitivity of 70 % and a specificity of 65%.

In order to evaluate if the relationship between average walking speed and mortality could be applied to different age groups, participants were divided into three age categories at baseline: <60 years [n=471, average walking speed 4.7 (0.8) km/h, 39 died], 60 to 70 years [n=434, average walking speed 4.4 (0.8) km/h, 76 died], and >70 years [n=184, average walking speed 3.9 (0.7) km/h, 62 died]. The association between average walking speed and mortality risk remained significant. The highest Youden index for the three age groups considered was 0.35 at 4.6 km/h for the <60 group; 0.32 at 4.0 km/h for the 60-70 group and 0.31 at 3.6 km/h for the >70 group.

During the second year of follow-up the average walking speed of 960 subjects was determined. Of the 835 subjects who improved their walking speed [from 4.3 (0.8) to 5.0 (0.8) km/h] 91 died while of the 125 subjects who did not improve [from 4.7 (0.9) to 4.4 (0.8) km/h] 21 died. Adjusting for age the Hazard Ratio of the subjects in which walking speed improved relative to the subjects in which walking speed did not improve was reduced to 0.51 (P=0.006).

DISCUSSION

We observed an inverse association between average walking speed, estimated by a one Km treadmill test carried out at a perceived exertion between 11-13 on the 6-20 Borg scale, and all-cause mortality

in a cohort of 1,255 patients with stable cardiovascular disease. Independent from traditional cardiovascular risk factors and clinical history, low average walking speed was associated with higher rates of mortality.

The prognostic power of average walking speed was underscored by dividing the sample into quartiles; a significant reduction in risk of death was observed among the quartiles with higher average walking speeds compared to those with lower walking speeds. Subjects with the highest walking speed **after adjusting for confounders exhibited an 80%** overall reduction in mortality risk compared to those with the lowest walking speed. **The trend for risk of death sharply increased with the decreased of average walking speed.**

These results extend the message on the health benefits of walking to patients with stable cardiovascular disease and support the concept that healthcare professionals should encourage cardiac patients to initiate and maintain a physically active lifestyle consisting of moderate walking at any age. The walking speed-related health benefits are achieved regardless of age.

The ability of the one Km walking test to predict mortality we observed is similar to that reported by Studensky et al[21] and by Stanaway et al[22] documenting the association between walking speed (determined by the use a short walking test of 4 to 6 meters) and survival in healthy older adults. These gait speed tests, although short, are regarded as both measures of lower extremity function and markers of physiological reserve.[19] The one Km walking test we used has the advantage of estimating cardio-respiratory function, since we have previously shown that it can be used for the indirect evaluation of peak oxygen consumption .[26] Other tests, such as the widely-used 6 min walk test, are considered measures of submaximal endurance and have been shown to have prognostic value; however, these tests are performed at near-maximal intensity.

Strengths and Limitations of The Study

The one Km walking test we developed is performed on a treadmill and therefore allows the concurrent measurement of physiologic data including the ECG, and can be done comfortably in a standard exercise laboratory.[29] It should also be noted that while peak oxygen consumption is often considered the gold standard for cardiopulmonary function,[2] it is strongly influenced by genotype (accounting for up to 50% of its variance).[30] **In contrast, walking ability closely reflects a patient's cardiovascular capabilities associated with the capacity to perform daily activities, and is therefore relevant for participants in secondary prevention and cardiac rehabilitation programs.[2]**

We have observed that an improvement in walking speed during follow-up in a subset of 835 patients was associated with a significant further reduction of their mortality risk. Therefore, the one km treadmill walking test offers the advantage of measuring the effectiveness of the prescribed rehabilitation programs.

This study has some limitations. **First, our findings are applicable only to men. Although it has been demonstrated that exercise capacity is an independent predictor of mortality in women, [21] exercise testing responses between men and women have been disputed. In fact, some authors shown to differ significantly[31] while others failed to demonstrate such differences.[32] Second, in our study women were 127, aged 60 (10), with an average walking speed during the test of 3,9 (0,7) km/h, and nine of them died during the follow-up period. Thus, because of the small number of woman and events a stratified analysis according to gender was not feasible. Third**, participants were excluded from the test if they were not able to walk for one Km, and the results therefore may not apply to patients with markedly low exercise capacity. **Fourth**, we did not consider social, behavioral or psychological factors that have been independently associated with reduced walking speed.[33] **Fifth**, these results were obtained from patients with an interest in participating in a secondary prevention program. Therefore, external validation of our findings is needed. **Finally, the prognostic value of walking speed determined at baseline on mortality can be modified by intervening clinical and functional changes occurring during the follow-up.**

CONCLUSIONS AND CLINICAL IMPLICATIONS

Our findings suggest that a simple and easy-to-perform one Km treadmill walking test at a moderate intensity is a useful tool for identifying mortality risk in patients with stable cardiovascular disease. In addition to its utility for stratifying risk, the test can also be used by health professionals involved in secondary prevention and cardiac rehabilitation programs to assess the efficacy of exercise prescription and to quantify functional changes regardless of age.

Footnotes

Contributors: LC, FC, GM and GG conceived and designed the study. EB, GC, FC, GG analysed the data, interpreted the results and co-wrote the paper. FT and SV analysed the data. JM discussed the results, and revised the manuscript. All authors had full access to the data and take responsibility for its integrity and the accuracy of the analysis.

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Competing interests: "All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: no support from any organization for the submitted work; no financial relationships with any organization that might have an interest in the submitted work in the previous three years; and no relationship or activities that could appear to have influenced the submitted work.

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The study protocol was approved by the ethical commission of the University of Ferrara, Italy (application number 22-13), and all subjects gave written informed consent before entering the program.

Data sharing: No additional data available.

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Tables

Table 1. Age-adjusted risk of death according to clinical variables.

Variable	HR	*P* value	95 % CI
BMI	0.98	0.57	0.94-1.04
Left ventricular ejection fraction	0.99	0.47	0.98-1.01
Risk factor			
Current Smoking	2.24	0.02	1.12-4.47
Hypertension	1.22	0.25	0.87-1.72
Family history	1.03	0.85	0.74-1.44
Fasting glucose	1.01	0.07	0.99-1.01
Total cholesterol	0.99	0.38	0.99-1.00
HDL cholesterol	1.00	0.70	0.99-1.01
Serum triglycerides	0.99	0.20	0.99-1.00
Serum creatinine	1.67	0.13	0.87-3.19
Medical history			
CABG	1.10	0.57	0.78-1.58
Myocardial infarction	1.1	0.6	0.74-1.63
PTCA	0.78	0.55	0.34-1.76
Valvular replacement	0.69	0.30	0.34-1.40
Other	0.77	0.72	0.19-3.12
Medications			
ACE inhibitor or ARB	0.88	0.47	0.64-1.23
Aspirin	1.40	0.1	0.93-2.1
β-blocker	1.04	0.8	0.74-1.44
Calcium antagonist	0.80	0.4	0.48-1.34
Diuretic	1.30	0.17	0.89-1.91
Statin	0.97	0.9	0.70-1.35
Number of medications	1.08	0.15	0.97-1.19
AWS	0.58	<0.0001	0.45-0.75

Data are from the Cox proportional-hazards model.
Abbreviations: AWS, average walking speed; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BMI, Body Mass Index; CABG, Coronary Artery Bypass Graft; LV, Left Ventricular; PTCA, Percutaneous Transluminal Coronary Angioplasty, stenting or both.

Table 2. Baseline Characteristics of the 1255 subjects by quartile of average walking speed.

Variable	All Subjects (n=1255)	I Quartile (n=316)	II Quartile (n=313)	III Quartile (n=300)	IV Quartile (=326)	P for trend
AWS (km/h) (m/sec)	 4.3 (0.8) 1.19 (0.22)	 3.4 (0.3) 0.94 (0.08)	 4.1 (0.1) 1.13 (0.02)	 4.6 (0.2) 1.27 (0.05)	 5.5 (0.5) 1.53 (0.14)	<0.001
Deaths (n)	141	68	43	18	12	<0.001
Age (yr)	61 (10)	65 (9)	63 (9)	59 (9)	57 (9)	<0.001
BMI	27.6 (3.4)	28.3 (3.7)	27.6 (3.3)	27.7 (3.2)	27.0 (3.3)	<0.001
LV ejection fraction (%)	56 (10)	53 (11)	56 (9)	57 (11)	58 (10)	0.002
Risk factor						
Current Smoking (%)	5.6	4.1	5.4	4.6	7.8	0.055
Hypertension (%)	56.6	62.3	57.8	53.3	52.8	0.008
Family history (%)	53.7	48.4	51.7	54.3	60.7	0.001
Fasting glucose (mg/dl)	107 (27)	110 (28)	110 (28)	106 (29)	105 (28)	0.03
Total cholesterol (mg/dl)	194 (42)	195 (47)	199 (43)	194 (41)	188 (39)	0.04
HDL cholesterol (mg/dl)	49 (14)	50 (16)	49 (13)	47 (14)	50 (13)	0.55
Serum triglycerides (mg/dl)	139 (80)	147 (97)	138 (71)	143 (80)	129 (67)	0.046
Serum creatinine (mg/dl)	1.1 (0.2)	1.2 (0.3)	1.1 (0.2)	1.1 (0.2)	1.0 (0.2)	<0.001
Medical history (%)						
CABG	49.4	63.3	52.0	46.3	36.2	<0.001
Myocardial infarction	28.1	22.2	29.1	31.3	30.0	0.02
PTCA	8.7	4.7	5.7	9.0	15.3	0.001
Valvular replacement	8.9	8.2	8.9	7.6	10.4	0.4
Other	4.4	1.3	3.8	5	7.4	0.001
Medications (%)						
ACE inhibitor or ARB	53.3	57.3	54.0	50.0	68.9	0.09
Aspirin	74.6	75.9	72.8	74.3	75.1	0.9
β-blocker	59.4	57.9	63.6	60.0	55.8	0.4
Calcium antagonist	12.9	13.6	12.5	14.0	11.7	0.6
Diuretic	18.1	26.6	20.4	13.7	10.4	<0.001
Statin	52.9	50.3	49.2	52.0	60.1	0.01
Number of medications	3.2	3.5	3.2	3.1	3.1	0.004

Data are presented as mean (standard deviation, SD).

Abbreviations: AWS, average walking speed; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BMI, Body Mass Index; CABG, Coronary Artery Bypass Graft; LV, Left Ventricular; PTCA, Percutaneous Transluminal Coronary Angioplasty, stenting or both.

Table 3. Full-adjusted relative risk of death from any cause according to quartiles of average walking speed.

AWS quartile	AWS (km/h)	AWS (m/s)	HR	95% CI	*P* Value
I	3.4 (0.3)	0.94 (0.08)	1.00	-	-
II	4.1 (0.1)	1.13 (0.02)	0.73	0.46 - 1.18	0.2
III	4.6 (0.2)	1.27 (0.05)	0.54	0.31 - 0.95	0.003
IV	5.5 (0.5)	1.53 (0.14)	0.20	0.07 - 0.56	0.003

Data are presented as mean (standard deviation).
AWS: average walking speed, HR: Hazard Ratio.

Figures

Figure 1. Survival curves of the quartiles stratified according to average walking speed.

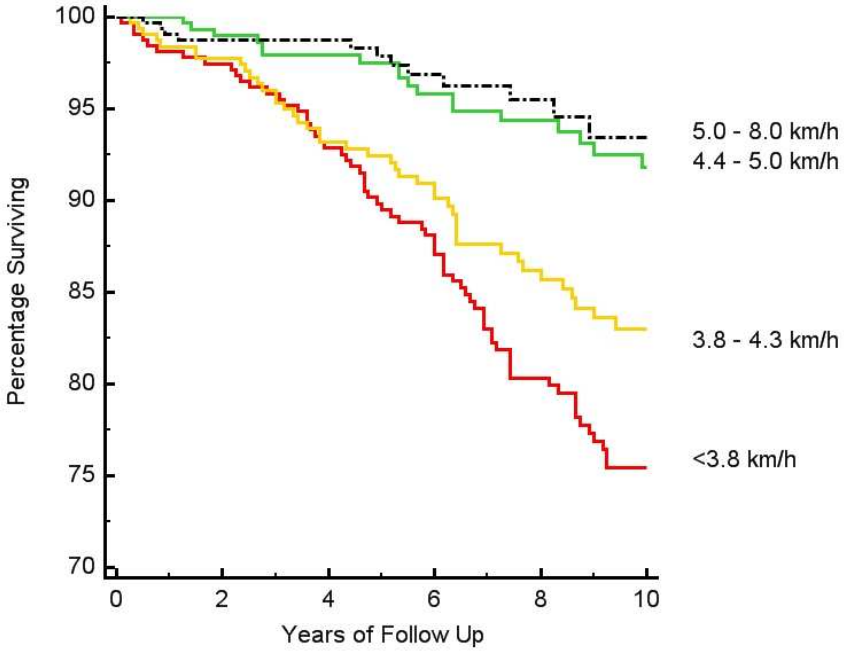


Figure 2. The exponential relationship between quartiles average walking speed and relative risk of death.

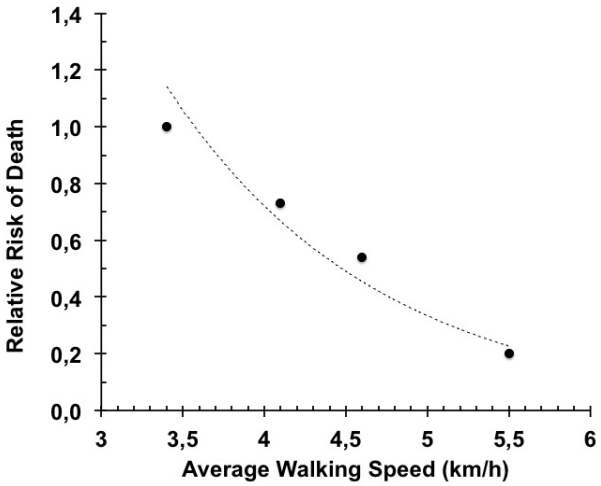
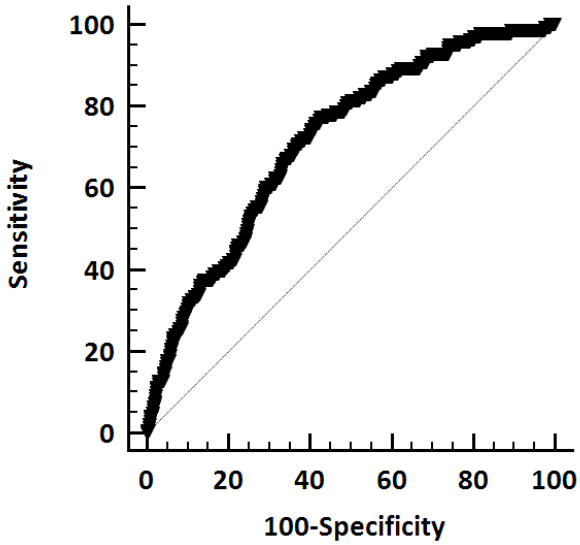


Figure 3. Receiver operating characteristic curve for estimating risk of death from any cause by average walking speed (area under the curve 0.71, 95% CI: 0.68-0.74, P<0.0001).



STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract Page 2, line 14
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found Page 2, lines 47-51
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported Page 4, lines 29-46
Objectives	3	State specific objectives, including any prespecified hypotheses Page 4, lines 52-54 and page 5 lines 3-5
Methods		
Study design	4	Present key elements of study design early in the paper Page 5, line 11
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection Page 5, lines 13-28
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up Page 5, lines 30-41
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable Page 5, lines 19-28
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group Page 5, lines 45-56 and page 6 lines 3-13 and 20-24
Bias	9	Describe any efforts to address potential sources of bias
Study size	10	Explain how the study size was arrived at Page 5, lines 11-13
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why Page 6, lines 26-41
Statistical methods	12	Page 6, lines 44-57 and page 7 lines 3-11
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed Page 7, line 15
		(b) Give reasons for non-participation at each stage Page 7, lines 15-17
Descriptive data	14*	Summarise follow-up time (eg, average and total amount) Page 7, line 32
Outcome data	15*	Report numbers of outcome events or summary measures over time Page 7, lines 32-34
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and

		their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included Page 7, lines 36-57 and page 8 lines 3-20; page 15 lines 5-33
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses Page 8, lines 15-48
Discussion		
Key results	18	Summarise key results with reference to study objectives Page 8, lines 54-57 and page 9 lines 3-7
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias Page 10, lines 28-55
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence Page 9, lines 22-36
Generalisability	21	Discuss the generalisability (external validity) of the study results Page 11, lines 5-14
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based Page 11, line 43

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

Title Treadmill walking speed and survival prediction in men with cardiovascular disease.

A 10-year follow-up study.

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ABSTRACT

Objective To determine whether the walking speed maintained during a one Km treadmill test at moderate intensity predicts survival in subjects with cardiovascular disease.

Design Population-based prospective study.

Setting ~~Outpatient~~Outpatients following secondary prevention ~~program~~ in Ferrara, Italy.

Participants 1,255 male stable cardiac patients, aged 25-85 years at baseline.

Main outcome measures Walking speed maintained during a one Km treadmill test, measured at baseline and mortality over a median follow-up of 8.2 years.

Results Among 1,255 patients, 141 died, for an average annual mortality of 1.4%. Of the variables considered, the strongest predictor of all-cause mortality was walking speed (95%CI, 0.45 to 0.75, P<0.0001). Based on the average speed maintained during the test, subjects were subdivided into quartiles and mortality risk ~~adjusted for confounders~~ was calculated. Compared to the ~~slowest~~slower quartile (average walking speed 3.4 Km/h), the relative mortality risk decreased for the second, third, and fourth ~~quartiles~~quartile (average walking speed 5.5 Km/h), with hazard ratios of 0.~~73~~77 (95%CI, 0.~~46~~52 to 1.~~18~~13,); 0.~~54~~41 (95%CI, 0.~~31~~24 to 0.~~95~~70); and 0.~~20~~36 (95%CI, 0.~~07~~19 to 0.~~56~~68), respectively (P for trend <0.0001). Receiver operating curve analysis showed an area under the curve of 0.71 (P<0.0001) and the highest Youden index (0.~~35~~347) for a walking speed of 4.0 Km/h.

Conclusions The average speed maintained during a one Km treadmill walking test is inversely related to survival in patients with cardiovascular disease and is a simple and useful tool for stratifying risk in patients undergoing secondary prevention ~~and cardiac rehabilitation programs~~.

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ARTICLE SUMMARY

Article focus

- An inverse relationship between walking speed and survival is well documented in older subjects.
- The aim of this study was to determine whether walking speed predicts survival in subjects with cardiovascular disease.

Key messages

- A strong inverse association between average walking speed and mortality was observed in patients with cardiovascular disease.
- Average walking speed using the one Km test is useful for predicting survival among subjects with stable cardiovascular disease and ~~provides an additional tool~~ for guiding ~~**secondary prevention and cardiac**~~their rehabilitation ~~**programs**~~.

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Strengths and limitations of this study

- The walking test used in this study measures cardiovascular function. The test is submaximal, easy to perform and allows the concurrent measurement of physiologic data~~.~~..
- The study included male participants only, ~~and~~ the results may not be generalized to women.
- Participants were excluded from the test if they were not able to walk for one Km ~~were excluded from the study.~~.

INTRODUCTION

In patients with cardiovascular disease, peak oxygen consumption is utilized for assessing disease severity and for quantifying the effectiveness of ~~secondary prevention and cardiac~~ rehabilitation programs.[1 2] Moreover, it is a strong independent predictor of risk of death and for estimating risk of mortality and other adverse ~~outcomes.~~[3]outcomes[3].

Peak oxygen consumption is commonly determined by maximal exercise testing, but it can be difficult to carry out in some cardiac patients. For this reason, walking tests at a submaximal exercise intensity have been developed for quantifying functional capabilities of patients with cardiovascular and pulmonary disease[4], including time-based[5 6] and distance-based protocols[7-9] involving walking on the ground, treadmill or along a corridor.[10-13] Short walking tests have also been employed, but they generally do not adequately quantify aerobic fitness[14], and the optimal duration or length for these submaximal protocols has been ~~debated.~~[15]debated[15].

Walking tests have been used to assess exercise capacity,[16-19] and to investigate outcomes in many rehabilitation ~~programs.~~[20]programs[20]. Walking speed has been considered a "vital sign" and a surrogate of physiological function in several cohort studies among patients with cardiovascular disease.[19] Walking speed is a commonly used objective measure of the functional capabilities among older subjects, and has been demonstrated to be a strong predictor of ~~survival.~~[21]survival[21] [22] ~~For example, a.~~ A 3-fold higher risk of mortality in the lowest quartile of walking speed compared ~~to~~with the highest ~~quartile~~ was reported in a recent meta-analysis.[21-~~23~~ 24] ~~**However, less is known about the prognostic relevance of walking performance in younger individuals with cardiovascular disease, particularly for community-based programs.**~~[25]

We recently developed a moderate ~~**-intensity, self-paced**~~, perceptually regulated one Km walking test for the indirect estimation of peak oxygen consumption in patients with cardiovascular disease ~~**across a broad age range.**~~[26],[25] In the current study, we addressed the association between average walking speed maintained during this one Km test and survival in a cohort of patients with stable cardiovascular disease. The average walking speed maintained during the one Km test among 1,255

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patients with cardiovascular disease was determined, and all-cause mortality over 10 years of follow up was quantified.

METHODS

The study population consisted of 1,442 men, ~~with stable cardiovascular disease,~~ aged 25-85 years, referred by their physician ~~to the Department of Rehabilitative Medicine of the University of Ferrara, Italy, for~~ for exercise testing prior to participation in an exercise-based secondary prevention program, between 1997 and 2012.

~~The program was guided by a cardiologist and a sports medicine doctor. A comprehensive clinical evaluation, including personal medical history, risk factor and medications was carried out. Left ventricular ejection fraction was derived from previous echocardiographic evaluations. Standard blood chemistry analyses previously performed~~Women were ~~registered. Weight and height were measured and used to calculate body mass index.~~

not included in the study because of their small number. Subjects with heart failure classified as New York Heart Association class II or higher, and those who had conditions that interfered with walking ability such as neurological, musculoskeletal, or peripheral vascular conditions were ~~not included in the study.~~ also excluded.

~~127 women, aged 60 (10), average walking speed 3,9 (0,7) km/h, were considered. During the follow up period 9 (7%) of these excluded subjects died. Because of the small number of woman and events a stratified analysis according to gender was not feasible.~~

Before the walking test, participants underwent a comprehensive clinical evaluation, including medical history, smoking status and fasting blood chemistry analyses. Weight and height were measured and used to calculate body mass index. Hypertension was defined as systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or use of antihypertensive agents.

Walking speed determination

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Average walking speed was determined for each participant at the time of their baseline examination using the one Km treadmill walking test previously described~~, and developed in 178 subjects belonging to the same population of the current study.~~[26,25] Briefly, the test was carried out as follows: the subjects were instructed to select a pace that they could maintain for 10 to 20 minutes at a moderate perceived exercise intensity using the Borg 6-20 scale.[27,26] Subjects began the test walking on the level at 2.0 km/h, with subsequent increases of 0.3 km/h every thirty seconds up to a walking speed corresponding to a perceived exertion of 11-13 on the Borg scale. The test was then started and rate of perceived exertion acquired every two minutes~~. Walking~~, adjusting walking speed~~ was adjusted~~ to maintain the selected moderate perceived intensity. Heart rate was monitored continuously during the test using a Polar Accurex Plus heart rate monitor (Polar Electro, Kempele, Finland). Blood pressure was monitored before and immediately after the test. The time to complete one kilometer was recorded and average walking speed calculated accordingly.

Mortality assessment

Participants were followed for all-cause mortality from the date of their baseline examination for up to 10 years. Subjects were flagged by the regional Health Service Registry of the Emilia-Romagna region, ~~which~~who provided the date of death where applicable, or by contacting relatives and personal physician to determine vital status. Time from initial evaluation to death was calculated in years.

~~**Covariates**~~

~~**The covariates considered as potential confounders were: average walking speed, age, body mass index, left ventricular ejection fraction, current smoking, hypertension, family history, fasting glucose, total cholesterol, HDL cholesterol, serum triglycerides, serum creatinine, personal medical history (coronary artery bypass graft, myocardial infarction, percutaneous transluminal coronary angioplasty, valvular replacement and medical therapy for stable angina), and use of angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, aspirin, β-blockers, calcium antagonists, diuretics, statins and number of medications.**~~

Statistical Analysis

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All-cause mortality was used as the end point for survival analysis. Differences in survival across quartiles during the follow up period were assessed using Kaplan-Meier curves. Hazard Ratios and 95% confidence intervals were estimated across quartiles using Cox proportional hazard models. Individuals in the quartile with the lowest average walking speed were considered the reference group. The models were adjusted for ~~confounders significantly related to death~~age. The assumption of proportionality of all variables introduced in the models was assessed through the analysis of Schoenfeld residuals. The proportional hazards assumption held for all models. To assess the discriminatory accuracy of average walking speed in estimating survival, receiver-operating-characteristics (ROC) curves were constructed and the corresponding areas under the curve were calculated. The optimal cut-off point was calculated using the Youden index (sensitivity+specificity-1).~~2827~~ The level of statistical significance was set at $P < 0.05$. Statistical analyses were performed using Medcalc 11.4 software, Mariakerke, Belgium.

RESULTS

Of the 1,442 participants who were initially ~~included in the study~~considered, 187 (13%) were excluded due to the inability to complete the one Km test. ~~These subjects were significantly older (70 vs. 61 years, P<0.0001), had a higher body mass index (28.4 vs. 27.6, P< 0.01), a higher prevalence of hypertension (68% vs. 57%, P=0.002), higher serum creatinine (1.7 vs. 1.1 mg/dl, P<0.001), and a lower ventricular ejection fraction (53% vs. 56%, P=0.001). In addition, those excluded had a lower use of statins (35% vs. 53%), and β-blockers (43% vs. 59%), and a higher use of diuretics (44% vs. 18%). 71 of these subjects died during the 10 years of follow up.~~

The ~~one Km~~ walking test was completed by the remaining 1255 subjects ~~at an~~ average speed ~~of~~maintained during the one Km test was 4.3 (0.8) km/h.

The median follow-up period was 8.2 years during which a total of 141 deaths from any cause occurred, yielding an average annual mortality of 1.4%. The age-adjusted hazard ratios for death relative to average walking speed and to other clinical predictors of mortality are presented in Table 1.

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~~Clinical and exercise-test predictors of mortality from the Cox proportional hazards model are presented in Table 1. After adjustment for age, the~~The best predictor of ~~an increased risk of death from any~~ all-cause mortality was average walking speed~~, followed by smoking status and fasting glucose~~.

On the basis of the average walking speed, the subjects were subdivided into quartiles. The baseline ~~variables~~demographic and clinical characteristics of the study population, stratified in quartiles of average walking speed, are presented in Table 2. Significant difference between quartiles were documented for age, body mass index, ejection fraction, hypertension, family history, fasting glucose, total cholesterol, serum triglycerides, serum creatinine, medical history (excluding valvular replacement) and therapy with diuretics and statins.

Kaplan-Meier survival curves ~~for~~of the quartiles are presented in Figure 1. Subjects in the first quartile (average walking speed 3.4 Km/h) had a marked reduction in survival compared to subjects in ~~the fourth~~ quartile IV (average walking speed 5.5 Km/h). ~~Comparison between quartiles revealed significant differences in age, left ventricular ejection fraction, body mass index, smoking status, hypertension, family history, fasting glucose, total cholesterol, serum triglycerides and creatinine, medical history, number of medication, diuretics and statins use. The relative risk of death from any cause across quartiles adjusted for these confounders is presented in Table 3. An 80~~A 64 % reduction in risk of death was observed in the quartile with highest compared to the quartiles with slower average walking speeds~~.~~ (Table 3). The reduction in risk was significant in ~~third and fourth~~ quartiles III and IV vs. ~~first~~ quartile I. The relationship between relative risk of death and average walking speed among the quartiles ~~after adjusting for confounders~~ fit the ~~exponential~~polynomial equation $y=$~~$15.6e^{-0.77x}$~~$(26x^2 - 2.6x + 7.2$ with an R^2~~$= of 0.95)$~~97 (Figure 2). The strength of average walking speed in the prediction of all-cause mortality is shown in Figure 3 (area under the curve 0.71, 95% CI: 0.68-0.74, P<0.0001). The highest Youden index (0.~~35~~347) was observed at a walking speed of 4.0 Km/h, corresponding to a sensitivity of 70.2 % and a specificity of ~~65~~64.5%.

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~~In order to evaluate if the relationship between average walking speed and mortality could be applied to different age groups, participants were divided into three age categories at baseline: <60 years [n=471, average walking speed 4.7 (0.8) km/h, 39 died], 60 to 70 years [n=434, average walking speed 4.4 (0.8) km/h, 76 died], and >70 years [n=184, average walking speed 3.9 (0.7) km/h, 62 died]. The association between average walking speed and mortality risk remained significant. The highest Youden index for the three age groups considered was 0.35 at 4.6 km/h for the <60 group; 0.32 at 4.0 km/h for the 60-70 group and 0.31 at 3.6 km/h for the >70 group.~~

~~During the second year of follow-up the average walking speed of 960 subjects was determined. Of the 835 subjects who improved their walking speed [from 4.3 (0.8) to 5.0 (0.8) km/h] 91 died while of the 125 subjects who did not improve [from 4.7 (0.9) to 4.4 (0.8) km/h] 21 died. Adjusting for age the Hazard Ratio of the subjects in which walking speed improved relative to the subjects in which walking speed did not improve was reduced to 0.51 (P=0.006).~~

DISCUSSION

We observed an inverse association between average walking speed, estimated by a one Km treadmill test carried out at a perceived exertion ~~between~~of 11-13 on the 6-20 Borg scale, and all-cause mortality in a cohort of 1,255 patients with stable cardiovascular disease. Independent from traditional cardiovascular risk factors and clinical history, low average walking speed was associated with higher rates of mortality.

The prognostic power of average walking speed was underscored by dividing the sample into quartiles; a significant reduction in risk of death was observed among the quartiles with higher average walking speeds compared to those with lower walking speeds. Subjects with the highest walking speed ~~after adjusting for confounders~~ exhibited ~~an 80~~a 64% overall reduction in mortality risk compared to those with the lowest walking speed. The trend for risk of death sharply increased ~~with the decreased of~~when average walking speed~~.~~

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~~These results extend the message on the health benefits of walking~~ decreased to ~~patients with stable cardiovascular disease and support the concept~~ below 3.4 Km/h (Figure 2), a finding similar to that ~~healthcare professionals should encourage cardiac patients to initiate and maintain a physically active lifestyle consisting of moderate walking at any age. The walking speed-related health benefits are achieved regardless of age.~~ reported by Stanaway et al.[22] The ability of the one Km walking test to predict mortality we observed is similar to that reported by Studensky et al[21] and by Stanaway et al[22] documenting the association between walking speed (determined by the use a short walking test of 4 to 6 meters) and survival in healthy older adults. These gait speed tests, although short, are regarded as both measures of lower extremity function and markers of physiological reserve.[19] The one Km walking test we used has the advantage of estimating cardio-respiratory function, since we have ~~previously~~ shown ~~that~~ it can be used for the indirect evaluation of peak oxygen consumption .~~[26][25]~~ Other tests, such as the widely-used 6 min walk test, are considered measures of submaximal endurance and have been shown to have prognostic value; however, these tests are performed at near-maximal intensity.

~~Strengths and Limitations of The Study~~

STRENGTHS AND LIMITATIONS OF THE STUDY

The one Km walking test we developed is performed on ~~a~~ treadmill and therefore allows the concurrent measurement of physiologic data including the ECG, and can be done comfortably in a standard exercise laboratory.~~[29][28]~~ It should also be noted that while peak oxygen consumption is often considered the gold standard for cardiopulmonary function,[2] it is strongly influenced by genotype (accounting for up to 50% of its variance).~~[30][29]~~ In contrast, walking ability closely reflects a patient's cardiovascular capabilities associated with ~~the capacity~~ability to perform daily activities, and is therefore relevant for participants in ~~secondary prevention and~~ cardiac rehabilitation ~~programs~~.[2]

~~We have observed that an improvement in walking speed during follow-up in a subset of 835 patients was associated with a significant further reduction of their mortality risk. Therefore,~~

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~~the one km treadmill walking test offers the advantage of measuring the effectiveness of the prescribed rehabilitation programs.~~

This study has some limitations.~~ First, our findings are applicable only to men.~~ Although it has been demonstrated that exercise capacity is an independent predictor of mortality in women,[21] ~~exercise testing responses between men and women have been disputed. In fact, some authors shown to differ significantly[31] while others failed to demonstrate such differences.[32] Second, in our study women were 127, aged 60 (10), with an average walking speed during the test of 3,9 (0,7) km/h, and nine of them died during the follow-up period. Thus, because of the small number of woman and events a stratified analysis according to gender was not feasible. Third,~~ ~~participants~~our study included male participants only; thus, the results may not be generalized to women. Participants were excluded from the test if they were not able to walk for one Km, and the results therefore may not apply to patients with markedly low exercise capacity. ~~Fourth, we~~We did not consider social, behavioral or psychological factors that have been independently associated with reduced walking speed.[33] ~~Fifth~~[31] Finally, these results were obtained from patients with an interest in participating in a secondary prevention program. Therefore, external validation of our findings is needed. ~~Finally, the prognostic value of walking speed determined at baseline on mortality can be modified by intervening clinical and functional changes occurring during the follow-up.~~

CONCLUSIONS AND CLINICAL IMPLICATIONS

Our findings suggest that a simple and easy-to-perform one Km treadmill walking test at a moderate intensity is a useful tool for identifying mortality risk in patients with stable cardiovascular disease. In addition to its utility for stratifying risk, the test can also be used by health professionals involved in secondary prevention ~~and cardiac rehabilitation programs~~ to assess the efficacy of exercise prescription and ~~to~~ quantify functional changes ~~regardless of age~~with rehabilitation.

Footnotes

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Contributors: LC, FC, GM and GG conceived and designed the study. EB, GC, FC, GG analysed the data, interpreted the results and co-wrote the paper. FT and SV analysed the data. JM discussed the results, and revised the manuscript. All authors had full access to the data and take responsibility for its integrity and the accuracy of the analysis.

~~We wish to acknowledge Dr. Franco Guerzoni, and Dr. Nicola Napoli for their invaluable work over the years in data collection, management, and retrieval.~~

Competing interests: "All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: no support from any organization for the submitted work; no financial relationships with any organization that might have an interest in the submitted work in the previous three years; and no relationship or activities that could appear to have influenced the submitted work.

Funding: No external funding sources were used for this study.

~~The study protocol was approved by the ethical commission of the University of Ferrara, Italy (application number 22-13), and all subjects gave written informed consent before entering the program.~~

Ethical approval: This study was approved by the Emilia Romagna Health Service human research ethics committee.

Data sharing: No additional data available.

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Tables

Table 1. Age-adjusted risk of death according to clinical variables.

Variable	HR	*P* value	95 % CI
Demographics			
BMI	0.98	0.57	0.94-1.04
~~Left ventricular ejection~~LV Ejection fraction (%)	0.99	0.47	0.98-1.01
Risk factor			
Current Smoking	2.24	0.02	1.12-4.47
Hypertension	1.22	0.25	0.87-1.72
~~Family history~~	~~1.03~~	~~0.85~~	~~0.74-1.44~~
Fasting glucose	1.01	0.07	0.99-1.01
Total cholesterol	0.99	0.38	0.99-1.00
HDL cholesterol	1.00	0.70	0.99-1.01
Serum ~~triglycerides~~ trygliceride	0.99	0.20	0.99-1.00
Family history	1.03	0.85	0.74-1.44
Serum creatinine	1.67	0.13	0.87-3.19
Medical history			
CABG	1.10	0.57	0.78-1.58
Myocardial infarction	1.1	0.6	0.74-1.63
PTCA	0.78	0.55	0.34-1.76
Valvular replacement	0.69	0.30	0.34-1.40
Other	0.77	0.72	0.19-3.12
Medications (%)			
~~ACE inhibitor or ARB~~	~~0.88~~	~~0.47~~	~~0.64-1.23~~
~~Aspirin~~	~~1.40~~	~~0.1~~	~~0.93-2.1~~
~~β-blocker~~	~~1.04~~	~~0.8~~	~~0.74-1.44~~
Calcium antagonist	0.80	0.4	0.48-1.34
Aspirin	1.40	0.1	0.93-2.1
Statin	0.97	0.9	0.70-1.35
β-blocker	1.04	0.8	0.74-1.44
Diuretic	1.30	0.17	0.89-1.91
ACE inhibitor or ARB~~Statin~~	0.9788	0.947	0.7064-1.3523
~~Number of medications~~	~~1.08~~	~~0.15~~	~~0.97-1.19~~
~~AWS~~ **Average walking speed**	0.58	<0.0001	0.45-0.75

Data are from the Cox proportional-hazards model.

~~Abbreviations: AWS, average walking speed; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BMI, Body Mass Index; CABG, Coronary Artery Bypass Graft; LV, Left Ventricular; PTCA, Percutaneous Transluminal Coronary Angioplasty, stenting or both.~~

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Table 2. Baseline Characteristics of the 1255 subjects by ~~quartile~~Quartile of average walking speed.

Variable	All Subjects (n=1255)	I Quartile (n=316)	II Quartile (n=313)	III Quartile (n=300)	IV Quartile (=326)	P for trend
AWS						
~~(km~~(Km/h) ~~(m/sec)~~	4.3 (0.8) ~~1.19 (0.22)~~	3.4 (0.3) ~~0.94 (0.08)~~	4.1 (0.1) ~~1.13 (0.02)~~	4.6 (0.2) ~~1.27 (0.05)~~	5.5 (0.5) ~~1.53 (0.14)~~	<0.001
~~Deaths (n)~~	~~141~~	~~68~~	~~43~~	~~18~~	~~12~~	~~<0.001~~
Demographics						
Age (yr)	61 (10)	65 (9)	63 (9)	59 (9)	57 (9)	<0.001
BMI	27.6 (3.4)	28.3 (3.7)	27.6 (3.3)	27.7 (3.2)	27.0 (3.3)	<0.001
LV ejection fraction (%)	56 (10)	53 (11)	56 (9)	57 (11)	58 (10)	0.002
Risk factor						
Current Smoking (%)	5.6	4.1	5.4	4.6	7.8	0.055
Hypertension (%)	56.6	62.3	57.8	53.3	52.8	0.008
Family history (%)	53.7	48.4	51.7	54.3	60.7	0.001
Fasting glucose (mg/dl)	107 (27)	110 (28)	110 (28)	106 (29)	105 (28)	0.03
Total cholesterol (mg/dl)	194 (42)	195 (47)	199 (43)	194 (41)	188 (39)	0.04
HDL cholesterol (mg/dl)	49 (14)	50 (16)	49 (13)	47 (14)	50 (13)	0.55
Serum ~~triglycerides~~tryglicerides (mg/dl)	139 (80)	147 (97)	138 (71)	143 (80)	129 (67)	0.046
Serum creatinine (mg/dl)	1.1 (0.2)	1.2 (0.3)	1.1 (0.2)	1.1 (0.2)	1.0 (0.2)	<0.001
Medical history (%)						
CABG	49.4	63.3	52.0	46.3	36.2	<0.001

~~4~~

Myocardial infarction	28.1	22.2	29.1	31.3	30.0	0.02
PTCA	8.7	4.7	5.7	9.0	15.3	0.001
Valvular replacement	8.9	8.2	8.9	7.6	10.4	0.4
Other	4.4	1.3	3.8	5	7.4	0.001
Medications (%)						
ACE inhibitor or ARB	53.3	57.3	54.0	50.0	68.9	0.09
Aspirin	74.6	75.9	72.8	74.3	75.1	0.9
β-blocker	59.4	57.9	63.6	60.0	55.8	0.4
Calcium antagonist	12.9	13.6	12.5	14.0	11.7	0.6
Diuretic	18.1	26.6	20.4	13.7	10.4	<0.001
Statin	52.9	50.3	49.2	52.0	60.1	0.01
~~Number of medications~~	~~3.2~~	~~3.5~~	~~3.2~~	~~3.1~~	~~3.1~~	~~0.004~~

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Data are presented as mean (standard deviation, SD).
Abbreviations: AWS, average walking speed; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BMI, Body Mass Index; CABG, Coronary Artery Bypass Graft; LV, Left Ventricular; PTCA, Percutaneous Transluminal Coronary Angioplasty, stenting or both.

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Table 3. ~~Full~~ Age adjusted relative risk of death from any cause ~~according to~~across quartiles of average walking speed.

AWS quartile	AWS (km/h)	~~AWS (m/s)~~	HR		95% CI	*P* Value
I	3.4 (0.3)	~~0.94 (0.08)~~	1.00		-	-
II	4.1 (0.1)		~~1.13 (~~0.~~02)~~77	~~0.73~~	0.~~46~~52 - 1.~~18~~13	0.~~2~~18
III	4.6 (0.2)		~~1.27 (~~0.~~05)~~41	~~0.54~~	0.~~31~~24 - 0.~~95~~70	0.~~003~~01
IV	5.5 (0.5)		~~1.53 (~~0.~~14)~~36	~~0.20~~	0.~~07~~19 - 0.~~56~~68	0.~~003~~002

Data are presented as mean (standard deviation, SD).
AWS: average walking speed, HR: Hazard Ratio.

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Figures

Figure 1. Survival curves of the quartiles stratified according to average walking speed.

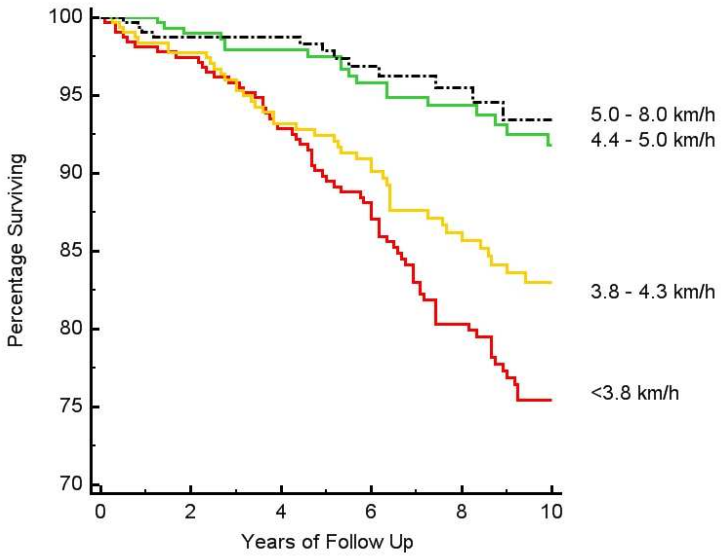
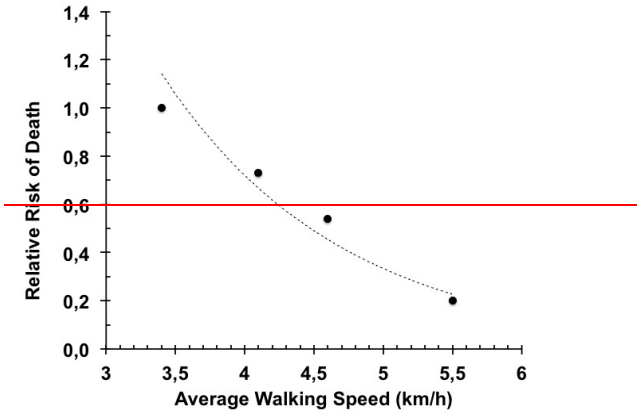


Figure 2. The ~~exponential~~polynomial relationship between ~~quartiles~~quartile average walking speed and relative risk of death.



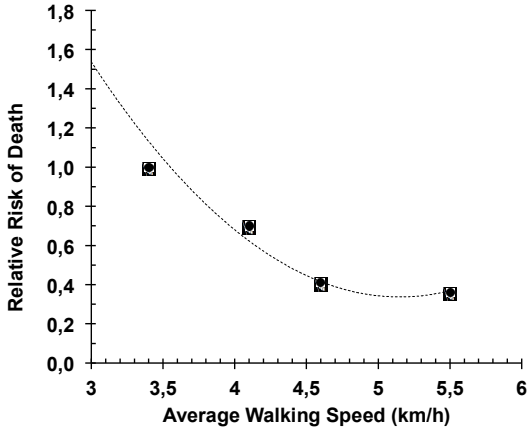
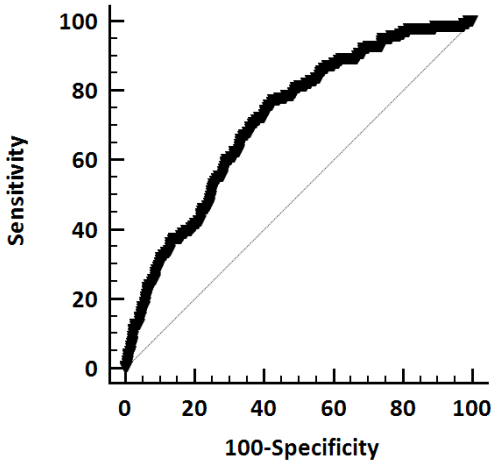


Figure 3. Receiver operating characteristic ~~curve~~curves for estimating risk of death from any cause by average walking speed ~~(area under the curve 0.71, 95% CI: 0.68-0.74, P<0.0001).~~.



Treadmill walking speed and survival prediction in men with cardiovascular disease.
A 10-year follow-up study.

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Keywords:	walking speed , survival, cardiac patients

Title Treadmill walking speed and survival prediction in men with cardiovascular disease.

A 10-year follow-up study.

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ABSTRACT

Objective To determine whether the walking speed maintained during a one Km treadmill test at moderate intensity predicts survival in subjects with cardiovascular disease.

Design Population-based prospective study.

Setting Outpatient secondary prevention program in Ferrara, Italy.

Participants 1,255 male stable cardiac patients, aged 25-85 years at baseline.

Main outcome measures Walking speed maintained during a one Km treadmill test, measured at baseline and mortality over a median follow-up of 8.2 years.

Results Among 1,255 patients, 141 died, for an average annual mortality of 1.4%. Of the variables considered, the strongest predictor of all-cause mortality was walking speed (95%CI, 0.45 to 0.75, P<0.0001). Based on the average speed maintained during the test, subjects were subdivided into quartiles and mortality risk adjusted for confounders was calculated. Compared to the slowest quartile (average walking speed 3.4 Km/h), the relative mortality risk decreased for the second, third, and fourth quartiles (average walking speed 5.5 Km/h), with hazard ratios of 0.73 (95%CI, 0.46 to 1.18,); 0.54 (95%CI, 0.31 to 0.95); and 0.20 (95%CI, 0.07 to 0.56), respectively (P for trend <0.0001). Receiver operating curve analysis showed an area under the curve of 0.71 (P<0.0001) and the highest Youden index (0.35) for a walking speed of 4.0 Km/h.

Conclusions The average speed maintained during a one Km treadmill walking test is inversely related to survival in patients with cardiovascular disease and is a simple and useful tool for stratifying risk in patients undergoing secondary prevention and cardiac rehabilitation programs.

ARTICLE SUMMARY

Article focus

- An inverse relationship between walking speed and survival is well documented in older subjects.
- The aim of this study was to determine whether walking speed predicts survival in subjects with cardiovascular disease.

Key messages

- A strong inverse association between average walking speed and mortality was observed in patients with cardiovascular disease.
- Average walking speed using the one Km test is useful for predicting survival among subjects with stable cardiovascular disease and provides an additional tool for guiding secondary prevention and cardiac rehabilitation programs.

Strengths and limitations of this study

- The walking test used in this study measures cardiovascular function. The test is submaximal, easy to perform and allows the concurrent measurement of physiologic data.
- The study included male participants only, and the results may not be generalized to women.
- Participants not able to walk for one Km were excluded from the study.

INTRODUCTION

In patients with cardiovascular disease, peak oxygen consumption is utilized for assessing disease severity and for quantifying the effectiveness of secondary prevention and cardiac rehabilitation programs.[1 2] Moreover, it is a strong independent predictor of risk of death and for estimating risk of mortality and other adverse outcomes.[3]

Peak oxygen consumption is commonly determined by maximal exercise testing, but it can be difficult to carry out in some cardiac patients. For this reason, walking tests at a submaximal exercise intensity have been developed for quantifying functional capabilities of patients with cardiovascular and pulmonary disease[4], including time-based[5 6] and distance-based protocols[7-9] involving walking on the ground, treadmill or along a corridor.[10-13] Short walking tests have also been employed, but they generally do not adequately quantify aerobic fitness[14], and the optimal duration or length for these submaximal protocols has been debated.[15]

Walking tests have been used to assess exercise capacity,[16-19] and to investigate outcomes in many rehabilitation programs.[20] Walking speed has been considered a "vital sign" and a surrogate of physiological function in several cohort studies among patients with cardiovascular disease.[19] Walking speed is a commonly used objective measure of functional capabilities among older subjects, and has been demonstrated to be a strong predictor of survival.[21 22] For example, a 3-fold higher risk of mortality in the lowest quartile of walking speed compared to the highest quartile was reported in a recent meta-analysis.[21-24] However, less is known about the prognostic relevance of walking performance in younger individuals with cardiovascular disease, particularly for community-based programs.[25]

We recently developed a moderate-intensity, self-paced one Km walking test for the indirect estimation of peak oxygen consumption in patients with cardiovascular disease across a broad age range.[26] In the current study, we addressed the association between average walking speed maintained during this one Km test and survival in a cohort of patients with stable cardiovascular

disease. The average walking speed maintained during the one Km test among 1,255 patients was determined, and all-cause mortality over 10 years of follow up was quantified.

METHODS

The study population consisted of 1,442 men, with stable cardiovascular disease, aged 25-85 years, referred by their physician to the Department of Rehabilitative Medicine of the University of Ferrara, Italy, for participation in an exercise-based secondary prevention program, between 1997 and 2012. The program was guided by a cardiologist and a sports medicine doctor. A comprehensive clinical evaluation, including personal medical history, risk factor and medications was carried out. Left ventricular ejection fraction was derived from previous echocardiographic evaluations. Standard blood chemistry analyses previously performed were registered. Weight and height were measured and used to calculate body mass index.

Subjects with heart failure classified as New York Heart Association class II or higher, and those who had conditions that interfered with walking ability such as neurological, musculoskeletal, or peripheral vascular conditions were not included in the study.

127 women, aged 60 (10), average walking speed 3,9 (0,7) km/h, were considered. During the follow up period 9 (7%) of these excluded subjects died. Because of the small number of woman and events a stratified analysis according to gender was not feasible.

Walking speed determination

Average walking speed was determined for each participant at the time of their baseline examination using the one Km treadmill walking test previously described, and developed in 178 subjects belonging to the same population of the current study.[26] Briefly, the test was carried out as follows: the subjects were instructed to select a pace that they could maintain for 10 to 20 minutes at a moderate perceived exercise intensity using the Borg 6-20 scale.[27] Subjects began the test walking on the level at 2.0 km/h, with subsequent increases of 0.3 km/h every thirty seconds up to a walking speed corresponding to a perceived exertion of 11-13 on the Borg scale. The test was then started and rate of

perceived exertion acquired every two minutes. Walking speed was adjusted to maintain the selected moderate perceived intensity. Heart rate was monitored continuously during the test using a Polar Accurex Plus heart rate monitor (Polar Electro, Kempele, Finland). Blood pressure was monitored before and immediately after the test. The time to complete one kilometer was recorded and average walking speed calculated accordingly.

Mortality assessment

Participants were followed for all-cause mortality from the date of their baseline examination for up to 10 years. Subjects were flagged by the regional Health Service Registry of the Emilia-Romagna region, which provided the date of death where applicable, or by contacting relatives and personal physician to determine vital status.

Covariates

The covariates considered as potential confounders were: average walking speed, age, body mass index, left ventricular ejection fraction, current smoking, hypertension, family history, fasting glucose, total cholesterol, HDL cholesterol, serum triglycerides, serum creatinine, personal medical history (coronary artery bypass graft, myocardial infarction, percutaneous transluminal coronary angioplasty, valvular replacement and medical therapy for stable angina), and use of angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, aspirin, β-blockers, calcium antagonists, diuretics, statins and number of medications.

Statistical Analysis

All-cause mortality was used as the end point for survival analysis. Differences in survival across quartiles during the follow up period were assessed using Kaplan-Meier curves. Hazard Ratios and 95% confidence intervals were estimated across quartiles using Cox proportional hazard models. Individuals in the quartile with the lowest average walking speed were considered the reference group. The models were adjusted for confounders significantly related to death. The assumption of proportionality of all variables introduced in the models was assessed through the analysis of Schoenfeld residuals. The proportional hazards assumption held for all models. To assess the discriminatory accuracy of average walking speed in estimating survival, receiver-operating-

characteristics (ROC) curves were constructed and the corresponding areas under the curve were calculated. The optimal cut-off point was calculated using the Youden index (sensitivity+specificity-1).[28] The level of statistical significance was set at $P < 0.05$. Statistical analyses were performed using Medcalc 11.4 software, Mariakerke, Belgium.

RESULTS

Of the 1,442 participants who were initially included in the study, 187 (13%) were excluded due to the inability to complete the one Km test. These subjects were significantly older (70 vs. 61 years, $P<0.0001$), had a higher body mass index (28.4 vs. 27.6, $P< 0.01$), a higher prevalence of hypertension (68% vs. 57%, $P=0.002$), higher serum creatinine (1.7 vs. 1.1 mg/dl, $P<0.001$), and a lower ventricular ejection fraction (53% vs. 56%, $P=0.001$). In addition, those excluded had a lower use of statins (35% vs. 53%), and β-blockers (43% vs. 59%), and a higher use of diuretics (44% vs. 18%). 71 of these subjects died during the 10 years of follow up.

The one Km walking test was completed by the remaining 1255 subjects at an average speed of 4.3 (0.8) km/h. The median follow-up period was 8.2 years during which a total of 141 deaths from any cause occurred, yielding an average annual mortality of 1.4%.

The baseline variables of the study population, stratified in quartiles of average walking speed, are presented in Table 1.

Clinical and exercise-test predictors of mortality from the Cox proportional hazards model are presented in Table 2. After adjustment for age, the best predictor of an increased risk of death from any cause was average walking speed, followed by smoking status and fasting glucose.

On the basis of the average walking speed, the subjects were subdivided into quartiles. Kaplan-Meier survival curves for the quartiles are presented in Figure 1. Subjects in the first quartile (average walking speed 3.4 Km/h) had a marked reduction in survival compared to subjects in the fourth quartile (average walking speed 5.5 Km/h). Comparison between quartiles revealed significant differences in age, left ventricular ejection fraction, body mass index, smoking status, hypertension, family history, fasting glucose, total cholesterol, serum triglycerides and creatinine, medical history, number of medication, diuretics and statins use. The relative risk of death from any cause across quartiles

adjusted for these confounders is presented in Table 3. An 80% reduction in risk of death was observed in the quartile with highest compared to the quartiles with slower average walking speeds. The reduction in risk was significant in third and fourth quartiles vs. first quartile. The relationship between relative risk of death and average walking speed among the quartiles after adjusting for confounders fit the exponential equation $y=15.6e^{-0.77x}$ ($R^2=0.95$) (Figure 2). The strength of average walking speed in the prediction of all-cause mortality is shown in Figure 3 (area under the curve 0.71, 95% CI: 0.68-0.74, P<0.0001). The highest Youden index (0.35) was observed at a walking speed of 4.0 Km/h, corresponding to a sensitivity of 70 % and a specificity of 65%.

In order to evaluate if the relationship between average walking speed and mortality could be applied to different age groups, participants were divided into three age categories at baseline: <60 years [n=471, average walking speed 4.7 (0.8) km/h, 39 died], 60 to 70 years [n=434, average walking speed 4.4 (0.8) km/h, 76 died], and >70 years [n=184, average walking speed 3.9 (0.7) km/h, 62 died]. The association between average walking speed and mortality risk remained significant. The highest Youden index for the three age groups considered was 0.35 at 4.6 km/h for the <60 group; 0.32 at 4.0 km/h for the 60-70 group and 0.31 at 3.6 km/h for the >70 group.

During the second year of follow-up the average walking speed of 960 subjects was determined. Of the 835 subjects who improved their walking speed [from 4.3 (0.8) to 5.0 (0.8) km/h] 91 died while of the 125 subjects who did not improve [from 4.7 (0.9) to 4.4 (0.8) km/h] 21 died. Adjusting for age the Hazard Ratio of the subjects in which walking speed improved relative to the subjects in which walking speed did not improve was reduced to 0.51 (P=0.006).

DISCUSSION

We observed an inverse association between average walking speed, estimated by a one Km treadmill test carried out at a perceived exertion between 11-13 on the 6-20 Borg scale, and all-cause mortality in a cohort of 1,255 patients with stable cardiovascular disease. Independent from traditional

cardiovascular risk factors and clinical history, low average walking speed was associated with higher rates of mortality.

The prognostic power of average walking speed was underscored by dividing the sample into quartiles; a significant reduction in risk of death was observed among the quartiles with higher average walking speeds compared to those with lower walking speeds. Subjects with the highest walking speed after adjusting for confounders exhibited an 80% overall reduction in mortality risk compared to those with the lowest walking speed. The trend for risk of death sharply increased with the decreased of average walking speed.

These results extend the message on the health benefits of walking to patients with stable cardiovascular disease and support the concept that healthcare professionals should encourage cardiac patients to initiate and maintain a physically active lifestyle consisting of moderate walking at any age. The walking speed-related health benefits are achieved regardless of age.

The ability of the one Km walking test to predict mortality we observed is similar to that reported by Studensky et al[21] and by Stanaway et al[22] documenting the association between walking speed (determined by the use a short walking test of 4 to 6 meters) and survival in healthy older adults. These gait speed tests, although short, are regarded as both measures of lower extremity function and markers of physiological reserve.[19] The one Km walking test we used has the advantage of estimating cardio-respiratory function, since we have previously shown that it can be used for the indirect evaluation of peak oxygen consumption .[26] Other tests, such as the widely-used 6 min walk test, are considered measures of submaximal endurance and have been shown to have prognostic value; however, these tests are performed at near-maximal intensity.

Strengths and Limitations of The Study

The one Km walking test we developed is performed on a treadmill and therefore allows the concurrent measurement of physiologic data including the ECG, and can be done comfortably in a standard exercise laboratory.[29] It should also be noted that while peak oxygen consumption is often

considered the gold standard for cardiopulmonary function,[2] it is strongly influenced by genotype (accounting for up to 50% of its variance).[30] In contrast, walking ability closely reflects a patient's cardiovascular capabilities associated with the capacity to perform daily activities, and is therefore relevant for participants in secondary prevention and cardiac rehabilitation programs.[2]

We have observed that an improvement in walking speed during follow-up in a subset of 835 patients was associated with a significant further reduction of their mortality risk. Therefore, the one km treadmill walking test offers the advantage of measuring the effectiveness of the prescribed rehabilitation programs.

This study has some limitations. First, our findings are applicable only to men. Although it has been demonstrated that exercise capacity is an independent predictor of mortality in women, [21] exercise testing responses between men and women have been disputed. In fact, some authors shown to differ significantly[31] while others failed to demonstrate such differences.[32] Second, in our study women were 127, aged 60 (10), with an average walking speed during the test of 3,9 (0,7) km/h, and nine of them died during the follow-up period. Thus, because of the small number of woman and events a stratified analysis according to gender was not feasible. Third, participants were excluded from the test if they were not able to walk for one Km, and the results therefore may not apply to patients with markedly low exercise capacity. Fourth, we did not consider social, behavioral or psychological factors that have been independently associated with reduced walking speed.[33] Fifth, these results were obtained from patients with an interest in participating in a secondary prevention program. Therefore, external validation of our findings is needed. Finally, the prognostic value of walking speed determined at baseline on mortality can be modified by intervening clinical and functional changes occurring during the follow-up.

CONCLUSIONS AND CLINICAL IMPLICATIONS

Our findings suggest that a simple and easy-to-perform one Km treadmill walking test at a moderate intensity is a useful tool for identifying mortality risk in patients with stable cardiovascular disease. In addition to its utility for stratifying risk, the test can also be used by health professionals involved in

secondary prevention and cardiac rehabilitation programs to assess the efficacy of exercise prescription and to quantify functional changes regardless of age.

Footnotes

Contributors: LC, FC, GM and GG conceived and designed the study. EB, GC, FC, GG analysed the data, interpreted the results and co-wrote the paper. FT and SV analysed the data. JM discussed the results, and revised the manuscript. All authors had full access to the data and take responsibility for its integrity and the accuracy of the analysis.

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Competing interests: "All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: no support from any organization for the submitted work; no financial relationships with any organization that might have an interest in the submitted work in the previous three years; and no relationship or activities that could appear to have influenced the submitted work.

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The study protocol was approved by the ethical commission of the University of Ferrara, Italy (application number 22-13), and all subjects gave written informed consent before entering the program.

Data sharing: No additional data available.

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Tables

Table 1. Baseline Characteristics of the 1255 subjects by quartile of average walking speed.

Variable	All Subjects (n=1255)	I Quartile (n=316)	II Quartile (n=313)	III Quartile (n=300)	IV Quartile (=326)	P for trend
AWS (km/h) (m/sec)	4.3 (0.8) 1.19 (0.22)	3.4 (0.3) 0.94 (0.08)	4.1 (0.1) 1.13 (0.02)	4.6 (0.2) 1.27 (0.05)	5.5 (0.5) 1.53 (0.14)	<0.001
Deaths (n)	141	68	43	18	12	<0.001
Age (yr)	61 (10)	65 (9)	63 (9)	59 (9)	57 (9)	<0.001
Risk factor						
BMI	27.6 (3.4)	28.3 (3.7)	27.6 (3.3)	27.7 (3.2)	27.0 (3.3)	<0.001
LV ejection fraction (%)	56 (10)	53 (11)	56 (9)	57 (11)	58 (10)	0.002
Family history (%)	53.7	48.4	51.7	54.3	60.7	0.001
Fasting glucose (mg/dl)	107 (27)	110 (28)	110 (28)	106 (29)	105 (28)	0.03
Total cholesterol (mg/dl)	194 (42)	195 (47)	199 (43)	194 (41)	188 (39)	0.04
HDL cholesterol (mg/dl)	49 (14)	50 (16)	49 (13)	47 (14)	50 (13)	0.55
Serum triglycerides (mg/dl)	139 (80)	147 (97)	138 (71)	143 (80)	129 (67)	0.046
Serum creatinine (mg/dl)	1.1 (0.2)	1.2 (0.3)	1.1 (0.2)	1.1 (0.2)	1.0 (0.2)	<0.001
Medical history (%)						
CABG	49.4	63.3	52.0	46.3	36.2	<0.001
Myocardial infarction	28.1	22.2	29.1	31.3	30.0	0.02
PTCA	8.7	4.7	5.7	9.0	15.3	0.001
Valvular replacement	8.9	8.2	8.9	7.6	10.4	0.4
Other	4.4	1.3	3.8	5	7.4	0.001
Medications (%)						
ACE inhibitor or ARB	53.3	57.3	54.0	50.0	68.9	0.09
Aspirin	74.6	75.9	72.8	74.3	75.1	0.9
β-blocker	59.4	57.9	63.6	60.0	55.8	0.4
Calcium antagonist	12.9	13.6	12.5	14.0	11.7	0.6
Diuretic	18.1	26.6	20.4	13.7	10.4	<0.001
Statin	52.9	50.3	49.2	52.0	60.1	0.01
Number of medications	3.2	3.5	3.2	3.1	3.1	0.004

Data are presented as mean (standard deviation, SD).
Abbreviations: AWS, average walking speed; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BMI, Body Mass Index; CABG, Coronary Artery Bypass Graft; LV, Left Ventricular; PTCA, Percutaneous Transluminal Coronary Angioplasty, stenting or both.

Table 2. Age-adjusted risk of death according to clinical variables.

Variable	HR	*P* value	95 % CI
BMI	0.98	0.57	0.94-1.04
Left ventricular ejection fraction	0.99	0.47	0.98-1.01
Risk factor			
Current Smoking	2.24	0.02	1.12-4.47
Hypertension	1.22	0.25	0.87-1.72
Family history	1.03	0.85	0.74-1.44
Fasting glucose	1.01	0.07	0.99-1.01
Total cholesterol	0.99	0.38	0.99-1.00
HDL cholesterol	1.00	0.70	0.99-1.01
Serum triglycerides	0.99	0.20	0.99-1.00
Serum creatinine	1.67	0.13	0.87-3.19
Medical history			
CABG	1.10	0.57	0.78-1.58
Myocardial infarction	1.1	0.6	0.74-1.63
PTCA	0.78	0.55	0.34-1.76
Valvular replacement	0.69	0.30	0.34-1.40
Other	0.77	0.72	0.19-3.12
Medications			
ACE inhibitor or ARB	0.88	0.47	0.64-1.23
Aspirin	1.40	0.1	0.93-2.1
β-blocker	1.04	0.8	0.74-1.44
Calcium antagonist	0.80	0.4	0.48-1.34
Diuretic	1.30	0.17	0.89-1.91
Statin	0.97	0.9	0.70-1.35
Number of medications	1.08	0.15	0.97-1.19
AWS	0.58	<0.0001	0.45-0.75

Data are from the Cox proportional-hazards model.
Abbreviations: AWS, average walking speed; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BMI, Body Mass Index; CABG, Coronary Artery Bypass Graft; LV, Left Ventricular; PTCA, Percutaneous Transluminal Coronary Angioplasty, stenting or both.

Table 3. Full-adjusted relative risk of death from any cause according to quartiles of average walking speed.

AWS quartile	AWS (km/h)	AWS (m/s)	HR	95% CI	*P* Value
I	3.4 (0.3)	0.94 (0.08)	1.00	-	-
II	4.1 (0.1)	1.13 (0.02)	0.73	0.46 - 1.18	0.2
III	4.6 (0.2)	1.27 (0.05)	0.54	0.31 - 0.95	0.003
IV	5.5 (0.5)	1.53 (0.14)	0.20	0.07 - 0.56	0.003

Data are presented as mean (standard deviation).
AWS: average walking speed, HR: Hazard Ratio.

Figures

Figure 1. Survival curves of the quartiles stratified according to average walking speed.

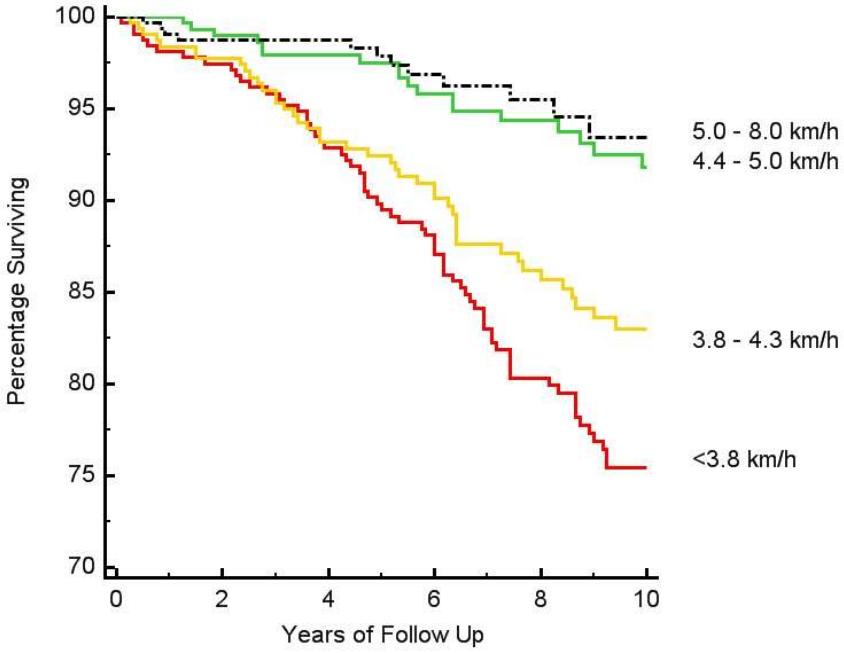


Figure 2. The exponential relationship between quartiles average walking speed and relative risk of death.

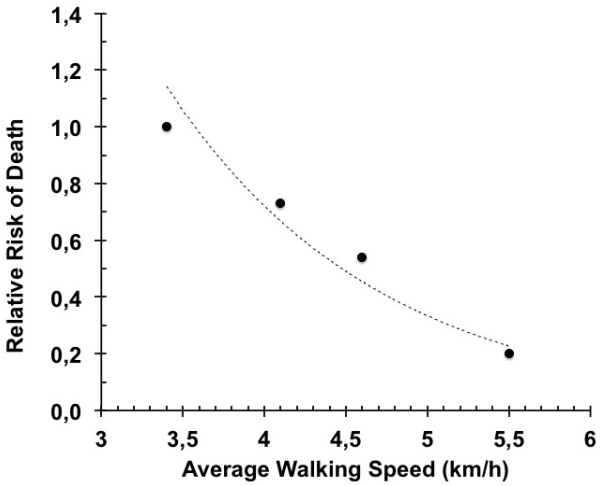
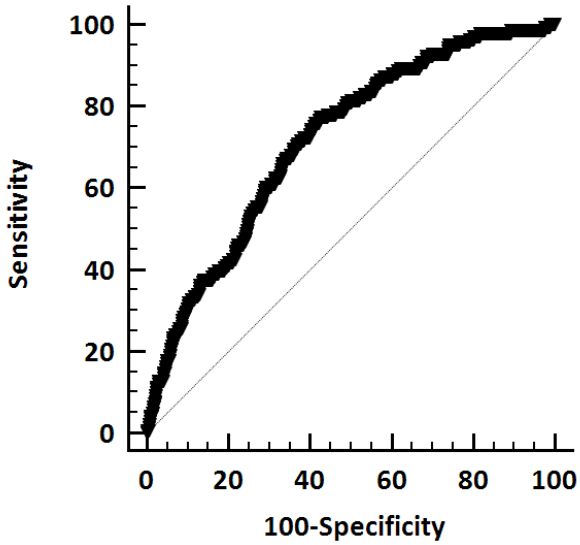


Figure 3. Receiver operating characteristic curve for estimating risk of death from any cause by average walking speed (area under the curve 0.71, 95% CI: 0.68-0.74, P<0.0001).



Title Treadmill walking speed and survival prediction in men with cardiovascular disease.

A 10-year follow-up study.

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ABSTRACT

Objective To determine whether the walking speed maintained during a one Km treadmill test at moderate intensity predicts survival in subjects with cardiovascular disease.

Design Population-based prospective study.

Setting Outpatient secondary prevention program in Ferrara, Italy.

Participants 1,255 male stable cardiac patients, aged 25-85 years at baseline.

Main outcome measures Walking speed maintained during a one Km treadmill test, measured at baseline and mortality over a median follow-up of 8.2 years.

Results Among 1,255 patients, 141 died, for an average annual mortality of 1.4%. Of the variables considered, the strongest predictor of all-cause mortality was walking speed (95%CI, 0.45 to 0.75, P<0.0001). Based on the average speed maintained during the test, subjects were subdivided into quartiles and mortality risk **adjusted for confounders** was calculated. Compared to the slowest quartile (average walking speed 3.4 Km/h), the relative mortality risk decreased for the second, third, and fourth quartiles (average walking speed 5.5 Km/h), with hazard ratios of 0.73 (95%CI, 0.46 to 1.18,); 0.54 (95%CI, 0.31 to 0.95); and 0.20 (95%CI, 0.07 to 0.56), respectively (P for trend <0.0001). Receiver operating curve analysis showed an area under the curve of 0.71 (P<0.0001) and the highest Youden index (0.35) for a walking speed of 4.0 Km/h.

Conclusions The average speed maintained during a one Km treadmill walking test is inversely related to survival in patients with cardiovascular disease and is a simple and useful tool for stratifying risk in patients undergoing secondary prevention **and cardiac rehabilitation programs**.

ARTICLE SUMMARY

Article focus

- An inverse relationship between walking speed and survival is well documented in older subjects.
- The aim of this study was to determine whether walking speed predicts survival in subjects with cardiovascular disease.

Key messages

- A strong inverse association between average walking speed and mortality was observed in patients with cardiovascular disease.
- Average walking speed using the one Km test is useful for predicting survival among subjects with stable cardiovascular disease and provides an additional tool for guiding **secondary prevention and cardiac rehabilitation programs.**

Strengths and limitations of this study

- The walking test used in this study measures cardiovascular function. The test is submaximal, easy to perform and allows the concurrent measurement of physiologic data.
- The study included male participants only, and the results may not be generalized to women.
- Participants not able to walk for one Km were excluded from the study.

INTRODUCTION

In patients with cardiovascular disease, peak oxygen consumption is utilized for assessing disease severity and for quantifying the effectiveness of **secondary prevention and cardiac rehabilitation programs.**[1 2] Moreover, it is a strong independent predictor of risk of death and for estimating risk of mortality and other adverse outcomes.[3]

Peak oxygen consumption is commonly determined by maximal exercise testing, but it can be difficult to carry out in some cardiac patients. For this reason, walking tests at a submaximal exercise intensity have been developed for quantifying functional capabilities of patients with cardiovascular and pulmonary disease[4], including time-based[5 6] and distance-based protocols[7-9] involving walking on the ground, treadmill or along a corridor.[10-13] Short walking tests have also been employed, but they generally do not adequately quantify aerobic fitness[14], and the optimal duration or length for these submaximal protocols has been debated.[15]

Walking tests have been used to assess exercise capacity,[16-19] and to investigate outcomes in many rehabilitation programs.[20] Walking speed has been considered a "vital sign" and a surrogate of physiological function in several cohort studies among patients with cardiovascular disease.[19] Walking speed is a commonly used objective measure of functional capabilities among older subjects, and has been demonstrated to be a strong predictor of survival.[21 22] For example, a 3-fold higher risk of mortality in the lowest quartile of walking speed compared to the highest quartile was reported in a recent meta-analysis.[21-24] **However, less is known about the prognostic relevance of walking performance in younger individuals with cardiovascular disease, particularly for community-based programs.[25]**

We recently developed a **moderate-intensity, self-paced** one Km walking test for the indirect estimation of peak oxygen consumption in patients with cardiovascular disease **across a broad age range**.[26] In the current study, we addressed the association between average walking speed maintained during this one Km test and survival in a cohort of patients with stable cardiovascular

disease. The average walking speed maintained during the one Km test among 1,255 patients was determined, and all-cause mortality over 10 years of follow up was quantified.

METHODS

The study population consisted of 1,442 men, with stable cardiovascular disease, aged 25-85 years, referred by their physician to the Department of Rehabilitative Medicine of the University of Ferrara, Italy, for participation in an exercise-based secondary prevention program, between 1997 and 2012.

The program was guided by a cardiologist and a sports medicine doctor. A comprehensive clinical evaluation, including personal medical history, risk factor and medications was carried out. Left ventricular ejection fraction was derived from previous echocardiographic evaluations. Standard blood chemistry analyses previously performed were registered. Weight and height were measured and used to calculate body mass index.

Subjects with heart failure classified as New York Heart Association class II or higher, and those who had conditions that interfered with walking ability such as neurological, musculoskeletal, or peripheral vascular conditions were not included in the study.

127 women, aged 60 (10), average walking speed 3,9 (0,7) km/h, were considered. During the follow up period 9 (7%) of these excluded subjects died. Because of the small number of woman and events a stratified analysis according to gender was not feasible.

Walking speed determination

Average walking speed was determined for each participant at the time of their baseline examination using the one Km treadmill walking test previously described, **and developed in 178 subjects belonging to the same population of the current study.**[26] Briefly, the test was carried out as follows: the subjects were instructed to select a pace that they could maintain for 10 to 20 minutes at a moderate perceived exercise intensity using the Borg 6-20 scale.[27] Subjects began the test walking on the level at 2.0 km/h, with subsequent increases of 0.3 km/h every thirty seconds up to a walking speed

corresponding to a perceived exertion of 11-13 on the Borg scale. The test was then started and rate of perceived exertion acquired every two minutes. Walking speed was adjusted to maintain the selected moderate perceived intensity. Heart rate was monitored continuously during the test using a Polar Accurex Plus heart rate monitor (Polar Electro, Kempele, Finland). Blood pressure was monitored before and immediately after the test. The time to complete one kilometer was recorded and average walking speed calculated accordingly.

Mortality assessment

Participants were followed for all-cause mortality from the date of their baseline examination for up to 10 years. Subjects were flagged by the regional Health Service Registry of the Emilia-Romagna region, which provided the date of death where applicable, or by contacting relatives and personal physician to determine vital status.

Covariates

The covariates considered as potential confounders were: average walking speed, age, body mass index, left ventricular ejection fraction, current smoking, hypertension, family history, fasting glucose, total cholesterol, HDL cholesterol, serum triglycerides, serum creatinine, personal medical history (coronary artery bypass graft, myocardial infarction, percutaneous transluminal coronary angioplasty, valvular replacement and medical therapy for stable angina), and use of angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, aspirin, β-blockers, calcium antagonists, diuretics, statins and number of medications.

Statistical Analysis

All-cause mortality was used as the end point for survival analysis. Differences in survival across quartiles during the follow up period were assessed using Kaplan-Meier curves. Hazard Ratios and 95% confidence intervals were estimated across quartiles using Cox proportional hazard models. Individuals in the quartile with the lowest average walking speed were considered the reference group. The models were adjusted for **confounders significantly related to death**. The assumption of proportionality of all variables introduced in the models was assessed through the analysis of Schoenfeld residuals. The proportional hazards assumption held for all models. To assess the

discriminatory accuracy of average walking speed in estimating survival, receiver-operating-characteristics (ROC) curves were constructed and the corresponding areas under the curve were calculated. The optimal cut-off point was calculated using the Youden index (sensitivity+specificity-1).[28] The level of statistical significance was set at $P < 0.05$. Statistical analyses were performed using Medcalc 11.4 software, Mariakerke, Belgium.

RESULTS

Of the 1,442 participants who were initially included in the study, 187 (13%) were excluded due to the inability to complete the one Km test. These subjects were significantly older (70 vs. 61 years, P<0.0001), had a higher body mass index (28.4 vs. 27.6, P< 0.01), a higher prevalence of hypertension (68% vs. 57%, P=0.002), higher serum creatinine (1.7 vs. 1.1 mg/dl, P<0.001), and a lower ventricular ejection fraction (53% vs. 56%, P=0.001). In addition, those excluded had a lower use of statins (35% vs. 53%), and β-blockers (43% vs. 59%), and a higher use of diuretics (44% vs. 18%). 71 of these subjects died during the 10 years of follow up.

The one Km walking test was completed by the remaining 1255 subjects at an average speed of 4.3 (0.8) km/h. The median follow-up period was 8.2 years during which a total of 141 deaths from any cause occurred, yielding an average annual mortality of 1.4%.

The baseline variables of the study population, stratified in quartiles of average walking speed, are presented in Table 1.

Clinical and exercise-test predictors of mortality from the Cox proportional hazards model are presented in Table 2. After adjustment for age, the best predictor of an increased risk of death from any cause was average walking speed, followed by smoking status and fasting glucose.

On the basis of the average walking speed, the subjects were subdivided into quartiles. Kaplan-Meier survival curves for the quartiles are presented in Figure 1. Subjects in the first quartile (average walking speed 3.4 Km/h) had a marked reduction in survival compared to subjects in the fourth quartile (average walking speed 5.5 Km/h). **Comparison between quartiles revealed significant differences in age, left ventricular ejection fraction, body mass index, smoking status, hypertension, family history, fasting glucose, total cholesterol, serum triglycerides and**

creatinine, medical history, number of medication, diuretics and statins use. The relative risk of death from any cause across quartiles adjusted for these confounders is presented in Table 3. An 80% reduction in risk of death was observed in the quartile with highest compared to the quartiles with slower average walking speeds. The reduction in risk was significant in third and fourth quartiles vs. first quartile. The relationship between relative risk of death and average walking speed among the quartiles after adjusting for confounders fit the exponential equation $y=15.6e^{-0.77x}$ ($R^2=0.95$) (Figure 2). The strength of average walking speed in the prediction of all-cause mortality is shown in Figure 3 (area under the curve 0.71, 95% CI: 0.68-0.74, P<0.0001). The highest Youden index (0.35) was observed at a walking speed of 4.0 Km/h, corresponding to a sensitivity of 70 % and a specificity of 65%.

In order to evaluate if the relationship between average walking speed and mortality could be applied to different age groups, participants were divided into three age categories at baseline: <60 years [n=471, average walking speed 4.7 (0.8) km/h, 39 died], 60 to 70 years [n=434, average walking speed 4.4 (0.8) km/h, 76 died], and >70 years [n=184, average walking speed 3.9 (0.7) km/h, 62 died]. The association between average walking speed and mortality risk remained significant. The highest Youden index for the three age groups considered was 0.35 at 4.6 km/h for the <60 group; 0.32 at 4.0 km/h for the 60-70 group and 0.31 at 3.6 km/h for the >70 group.

During the second year of follow-up the average walking speed of 960 subjects was determined. Of the 835 subjects who improved their walking speed [from 4.3 (0.8) to 5.0 (0.8) km/h] 91 died while of the 125 subjects who did not improve [from 4.7 (0.9) to 4.4 (0.8) km/h] 21 died. Adjusting for age the Hazard Ratio of the subjects in which walking speed improved relative to the subjects in which walking speed did not improve was reduced to 0.51 (P=0.006).

DISCUSSION

We observed an inverse association between average walking speed, estimated by a one Km treadmill test carried out at a perceived exertion between 11-13 on the 6-20 Borg scale, and all-cause mortality in a cohort of 1,255 patients with stable cardiovascular disease. Independent from traditional cardiovascular risk factors and clinical history, low average walking speed was associated with higher rates of mortality.

The prognostic power of average walking speed was underscored by dividing the sample into quartiles; a significant reduction in risk of death was observed among the quartiles with higher average walking speeds compared to those with lower walking speeds. Subjects with the highest walking speed **after adjusting for confounders exhibited an 80%** overall reduction in mortality risk compared to those with the lowest walking speed. **The trend for risk of death sharply increased with the decreased of average walking speed.**

These results extend the message on the health benefits of walking to patients with stable cardiovascular disease and support the concept that healthcare professionals should encourage cardiac patients to initiate and maintain a physically active lifestyle consisting of moderate walking at any age. The walking speed-related health benefits are achieved regardless of age.

The ability of the one Km walking test to predict mortality we observed is similar to that reported by Studensky et al[21] and by Stanaway et al[22] documenting the association between walking speed (determined by the use a short walking test of 4 to 6 meters) and survival in healthy older adults. These gait speed tests, although short, are regarded as both measures of lower extremity function and markers of physiological reserve.[19] The one Km walking test we used has the advantage of estimating cardio-respiratory function, since we have previously shown that it can be used for the indirect evaluation of peak oxygen consumption .[26] Other tests, such as the widely-used 6 min walk test, are considered measures of submaximal endurance and have been shown to have prognostic value; however, these tests are performed at near-maximal intensity.

Strengths and Limitations of The Study

The one Km walking test we developed is performed on a treadmill and therefore allows the concurrent measurement of physiologic data including the ECG, and can be done comfortably in a standard exercise laboratory.[29] It should also be noted that while peak oxygen consumption is often considered the gold standard for cardiopulmonary function,[2] it is strongly influenced by genotype (accounting for up to 50% of its variance).[30] **In contrast, walking ability closely reflects a patient's cardiovascular capabilities associated with the capacity to perform daily activities, and is therefore relevant for participants in secondary prevention and cardiac rehabilitation programs.[2]**

We have observed that an improvement in walking speed during follow-up in a subset of 835 patients was associated with a significant further reduction of their mortality risk. Therefore, the one km treadmill walking test offers the advantage of measuring the effectiveness of the prescribed rehabilitation programs.

This study has some limitations. **First, our findings are applicable only to men. Although it has been demonstrated that exercise capacity is an independent predictor of mortality in women, [21] exercise testing responses between men and women have been disputed. In fact, some authors shown to differ significantly[31] while others failed to demonstrate such differences.[32] Second, in our study women were 127, aged 60 (10), with an average walking speed during the test of 3,9 (0,7) km/h, and nine of them died during the follow-up period. Thus, because of the small number of woman and events a stratified analysis according to gender was not feasible. Third**, participants were excluded from the test if they were not able to walk for one Km, and the results therefore may not apply to patients with markedly low exercise capacity. **Fourth**, we did not consider social, behavioral or psychological factors that have been independently associated with reduced walking speed.[33] **Fifth**, these results were obtained from patients with an interest in participating in a secondary prevention program. Therefore, external validation of our findings is needed. **Finally, the prognostic value of walking speed determined at baseline on mortality can be modified by intervening clinical and functional changes occurring during the follow-up.**

CONCLUSIONS AND CLINICAL IMPLICATIONS

Our findings suggest that a simple and easy-to-perform one Km treadmill walking test at a moderate intensity is a useful tool for identifying mortality risk in patients with stable cardiovascular disease. In addition to its utility for stratifying risk, the test can also be used by health professionals involved in secondary prevention and cardiac rehabilitation programs to assess the efficacy of exercise prescription and to quantify functional changes regardless of age.

Footnotes

Contributors: LC, FC, GM and GG conceived and designed the study. EB, GC, FC, GG analysed the data, interpreted the results and co-wrote the paper. FT and SV analysed the data. JM discussed the results, and revised the manuscript. All authors had full access to the data and take responsibility for its integrity and the accuracy of the analysis.

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Competing interests: "All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: no support from any organization for the submitted work; no financial relationships with any organization that might have an interest in the submitted work in the previous three years; and no relationship or activities that could appear to have influenced the submitted work.

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The study protocol was approved by the ethical commission of the University of Ferrara, Italy (application number 22-13), and all subjects gave written informed consent before entering the program.

Data sharing: No additional data available.

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Tables

Table 1. Baseline Characteristics of the 1255 subjects by quartile of average walking speed.

Variable	All Subjects (n=1255)	I Quartile (n=316)	II Quartile (n=313)	III Quartile (n=300)	IV Quartile (=326)	P for trend
AWS (km/h) (m/sec)	 4.3 (0.8) 1.19 (0.22)	 3.4 (0.3) 0.94 (0.08)	 4.1 (0.1) 1.13 (0.02)	 4.6 (0.2) 1.27 (0.05)	 5.5 (0.5) 1.53 (0.14)	<0.001
Deaths (n)	141	68	43	18	12	<0.001
Age (yr)	61 (10)	65 (9)	63 (9)	59 (9)	57 (9)	<0.001
BMI	27.6 (3.4)	28.3 (3.7)	27.6 (3.3)	27.7 (3.2)	27.0 (3.3)	<0.001
LV ejection fraction (%)	56 (10)	53 (11)	56 (9)	57 (11)	58 (10)	0.002
Risk factor						
Current Smoking (%)	5.6	4.1	5.4	4.6	7.8	0.055
Hypertension (%)	56.6	62.3	57.8	53.3	52.8	0.008
Family history (%)	53.7	48.4	51.7	54.3	60.7	0.001
Fasting glucose (mg/dl)	107 (27)	110 (28)	110 (28)	106 (29)	105 (28)	0.03
Total cholesterol (mg/dl)	194 (42)	195 (47)	199 (43)	194 (41)	188 (39)	0.04
HDL cholesterol (mg/dl)	49 (14)	50 (16)	49 (13)	47 (14)	50 (13)	0.55
Serum triglycerides (mg/dl)	139 (80)	147 (97)	138 (71)	143 (80)	129 (67)	0.046
Serum creatinine (mg/dl)	1.1 (0.2)	1.2 (0.3)	1.1 (0.2)	1.1 (0.2)	1.0 (0.2)	<0.001
Medical history (%)						
CABG	49.4	63.3	52.0	46.3	36.2	<0.001
Myocardial infarction	28.1	22.2	29.1	31.3	30.0	0.02
PTCA	8.7	4.7	5.7	9.0	15.3	0.001
Valvular replacement	8.9	8.2	8.9	7.6	10.4	0.4
Other	4.4	1.3	3.8	5	7.4	0.001
Medications (%)						
ACE inhibitor or ARB	53.3	57.3	54.0	50.0	68.9	0.09
Aspirin	74.6	75.9	72.8	74.3	75.1	0.9
β-blocker	59.4	57.9	63.6	60.0	55.8	0.4
Calcium antagonist	12.9	13.6	12.5	14.0	11.7	0.6
Diuretic	18.1	26.6	20.4	13.7	10.4	<0.001
Statin	52.9	50.3	49.2	52.0	60.1	0.01
Number of medications	3.2	3.5	3.2	3.1	3.1	0.004

Data are presented as mean (standard deviation, SD).

Abbreviations: AWS, average walking speed; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BMI, Body Mass Index; CABG, Coronary Artery Bypass Graft; LV, Left Ventricular; PTCA, Percutaneous Transluminal Coronary Angioplasty, stenting or both.

Table 2. Age-adjusted risk of death according to clinical variables.

Variable	HR	*P* value	95 % CI
BMI	0.98	0.57	0.94-1.04
Left ventricular ejection fraction	0.99	0.47	0.98-1.01
Risk factor			
Current Smoking	2.24	0.02	1.12-4.47
Hypertension	1.22	0.25	0.87-1.72
Family history	1.03	0.85	0.74-1.44
Fasting glucose	1.01	0.07	0.99-1.01
Total cholesterol	0.99	0.38	0.99-1.00
HDL cholesterol	1.00	0.70	0.99-1.01
Serum triglycerides	0.99	0.20	0.99-1.00
Serum creatinine	1.67	0.13	0.87-3.19
Medical history			
CABG	1.10	0.57	0.78-1.58
Myocardial infarction	1.1	0.6	0.74-1.63
PTCA	0.78	0.55	0.34-1.76
Valvular replacement	0.69	0.30	0.34-1.40
Other	0.77	0.72	0.19-3.12
Medications			
ACE inhibitor or ARB	0.88	0.47	0.64-1.23
Aspirin	1.40	0.1	0.93-2.1
β-blocker	1.04	0.8	0.74-1.44
Calcium antagonist	0.80	0.4	0.48-1.34
Diuretic	1.30	0.17	0.89-1.91
Statin	0.97	0.9	0.70-1.35
Number of medications	1.08	0.15	0.97-1.19
AWS	0.58	<0.0001	0.45-0.75

Data are from the Cox proportional-hazards model.
Abbreviations: AWS, average walking speed; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BMI, Body Mass Index; CABG, Coronary Artery Bypass Graft; LV, Left Ventricular; PTCA, Percutaneous Transluminal Coronary Angioplasty, stenting or both.

Table 3. Full-adjusted relative risk of death from any cause according to quartiles of average walking speed.

AWS quartile	AWS (km/h)	AWS (m/s)	HR	95% CI	*P* Value
I	3.4 (0.3)	0.94 (0.08)	1.00	-	-
II	4.1 (0.1)	1.13 (0.02)	0.73	0.46 - 1.18	0.2
III	4.6 (0.2)	1.27 (0.05)	0.54	0.31 - 0.95	0.003
IV	5.5 (0.5)	1.53 (0.14)	0.20	0.07 - 0.56	0.003

Data are presented as mean (standard deviation).
AWS: average walking speed, HR: Hazard Ratio.

Figures

Figure 1. Survival curves of the quartiles stratified according to average walking speed.

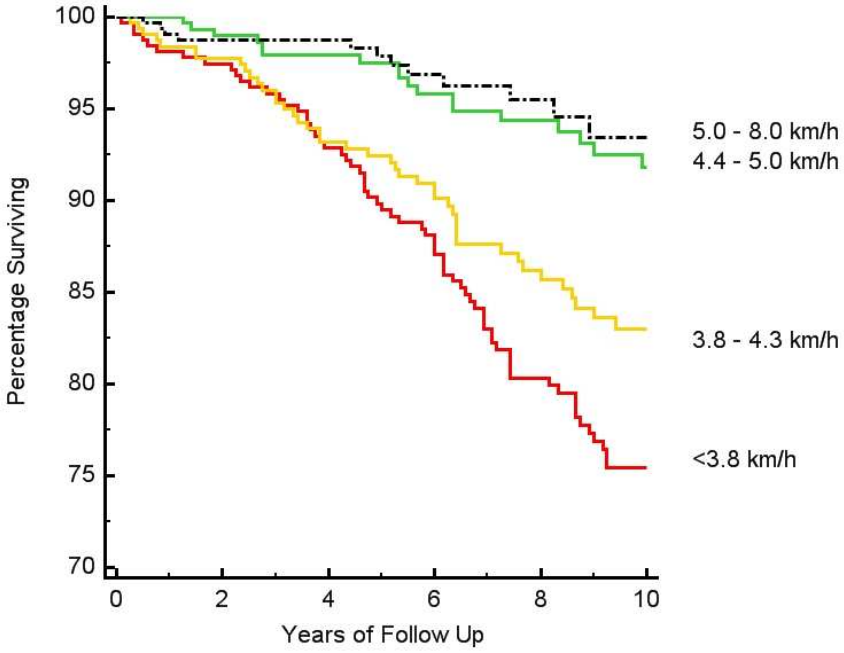


Figure 2. The exponential relationship between quartiles average walking speed and relative risk of death.

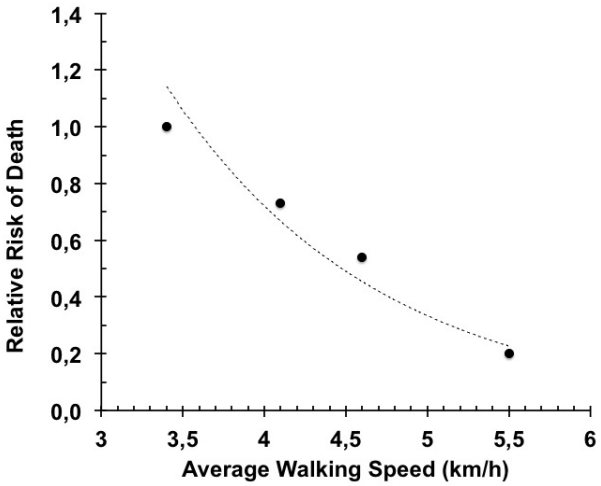
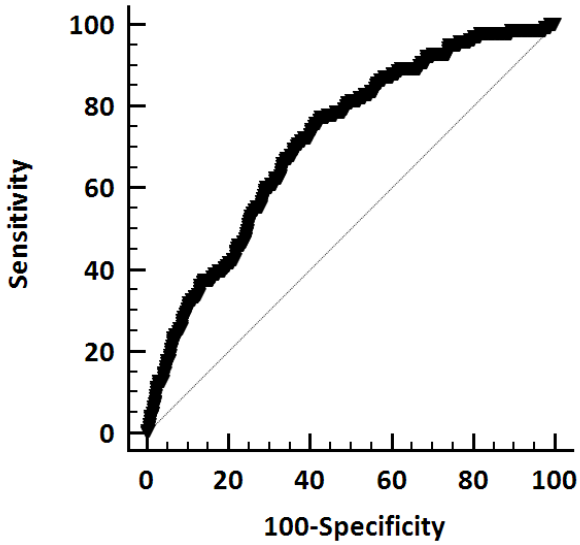


Figure 3. Receiver operating characteristic curve for estimating risk of death from any cause by average walking speed (area under the curve 0.71, 95% CI: 0.68-0.74, P<0.0001).



STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract Page 2, line 14
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found Page 2, lines 47-51
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported Page 4, lines 29-46
Objectives	3	State specific objectives, including any prespecified hypotheses Page 4, lines 52-54 and page 5 lines 3-5
Methods		
Study design	4	Present key elements of study design early in the paper Page 5, line 11
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection Page 5, lines 13-28
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up Page 5, lines 30-41
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable Page 5, lines 19-28
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group Page 5, lines 45-56 and page 6 lines 3-13 and 20-24
Bias	9	Describe any efforts to address potential sources of bias
Study size	10	Explain how the study size was arrived at Page 5, lines 11-13
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why Page 6, lines 26-41
Statistical methods	12	Page 6, lines 44-57 and page 7 lines 3-11
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed Page 7, line 15
		(b) Give reasons for non-participation at each stage Page 7, lines 15-17
Descriptive data	14*	Summarise follow-up time (eg, average and total amount) Page 7, line 32
Outcome data	15*	Report numbers of outcome events or summary measures over time Page 7, lines 32-34
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and

		their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included Page 7, lines 36-57 and page 8 lines 3-20; page 15 lines 5-33
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses Page 8, lines 15-48
Discussion		
Key results	18	Summarise key results with reference to study objectives Page 8, lines 54-57 and page 9 lines 3-7
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias Page 10, lines 28-55
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence Page 9, lines 22-36
Generalisability	21	Discuss the generalisability (external validity) of the study results Page 11, lines 5-14
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based Page 11, line 43

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.