



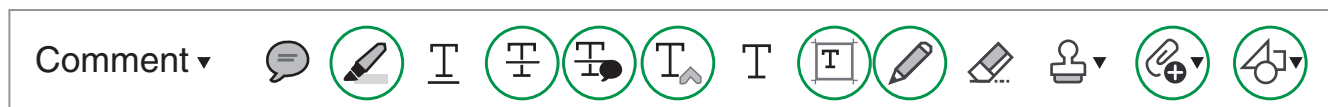
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Moderate walking speed predicts hospitalisation in hypertensive patients with cardiovascular disease

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Hypertension (HTN) is a leading risk factor for developing cardiovascular disease (CVD), and carries a major global burden of disease.¹ Blood pressure (BP) and CVD are strongly associated, with even small increments in BP leading to an increased risk of CVD.¹ The prevalence of HTN is influenced by several lifestyle factors, including smoking, diet, body mass and insufficient physical activity.² On the other hand, it is well known that healthy lifestyle changes, including increased physical activity, contribute significantly to better BP control.^{3,4} Epidemiological studies have demonstrated an inverse relationship between physical activity, cardiorespiratory fitness (CRF) and HTN.⁴ In addition, a considerable number of studies have shown significant lowering of BP through regular aerobic exercise of moderate intensity in patients with HTN.

Even though higher CRF has been associated with lower risk of future events among people with HTN,⁵⁻⁷ hypertensive patients are less physically active than normotensive people.^{5,8} The gold standard for the assessment of CRF is the direct determination of the peak oxygen uptake (VO_2peak) by measuring gas exchange during incremental and maximal exercise testing.⁹

The assessment of VO_2peak is recommended for assessing CVD severity, predicting prognosis and evaluating the efficacy of cardiac rehabilitation/secondary prevention programmes.¹⁰ When added to common risk factors, including systolic blood pressure, VO_2peak significantly improves the estimation of both short- and long-term risk for CVD mortality.¹¹⁻¹³ However, practical, financial and time constraints limit the direct determination of VO_2peak in many clinical settings.

VO_2peak has been demonstrated to be strongly associated with walking capacity in well-functioning older adults and among heart failure patients.^{14,15} Walking is the most common physical activity among adults, and is the preferred mode of exercise testing. A simple, sub-maximal 1-km treadmill walking test (1 k-TWT) has been validated for the estimation of VO_2peak among stable outpatients with CVD,^{16,17} with and without

preserved left ventricular ejection fraction.¹⁸ In addition, walking speed is a well-known indicator of health and function in aging and disease. Whether higher walking speed attenuates the risk of hospitalisation in adults with HTN is less known. Thus, we aimed to examine the association between walking speed and long-term all-cause hospitalisation in patients with HTN and CVD.

Hospitalisation was assessed in 1078 patients (male/female 867/211, age 64 ± 10 years) with HTN and CVD ($\approx 85\%$ with coronary heart disease) three years after enrolment in an exercise-based secondary prevention programme. All patients completed a baseline health examination and a 1-km treadmill walk at a moderate intensity, perceptually regulated at 11–13/20 on the Borg Scale. All-cause hospitalisation was assessed as function of the walking speed during the 1 k-TWT.

At baseline subjects were subdivided into three groups based on walking speed as follows: SLOW (2.6 ± 0.5 km/h, $n = 359$), INTERMEDIATE (3.9 ± 0.3 km/h, $n = 362$) and FAST (5.1 ± 0.5 km/h, $n = 357$). During the following three years all-cause

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hospitalisations were 182 for SLOW (50% of the sample), 160 for INTERMEDIATE (44% of the sample) and 110 for FAST (31% of the sample).

Slow walkers compared with fast walkers were significantly older (69 ± 9 vs. 59 ± 9 years), had a higher body mass index (28.0 vs. 27.2), a lower prevalence of family history for CVD (37% vs. 53%), higher serum fasting glucose (111 ± 34 vs. 106 ± 27 mg/dL), higher total cholesterol (197 ± 40 vs. 184 ± 35 mg/dL) and higher creatinine (1.19 ± 0.6 vs. 1.10 ± 0.5 mg/dL). In addition, slow walkers had significantly lower use of β -blockers and statins, and a higher use of diuretics.

Compared with the SLOW group, the fully adjusted hazard ratios for hospitalisation were 0.97 (95% confidence interval (CI) 0.75 to 1.24, $p=0.78$) for the INTERMEDIATE, and 0.63 (95% CI 0.45 to 0.88, $p < 0.001$) for the FAST groups (p for trend < 0.01). Each additional 1 km/h in walking speed resulted in a 19% reduction in overall hospitalisation (hazard ratio 0.81, 95% CI 0.71 to 0.91, $p < 0.001$). Length of hospital stay was 4186 days for SLOW (23 days per person); 2240 for INTERMEDIATE (14 days per person) and 990 days for FAST (nine days per person).

In conclusion, the walking speed maintained during a moderate 1-km walk was inversely related to all-cause hospitalisation in patients with HTN and CVD. The higher the baseline walking speed, the lower the relative risk of hospitalisation, and the shorter the length of hospital stay. These findings provide further support to the prognostic relevance of walking speed in outpatients with CVD.^{19,20}

Declaration of Conflicting Interests

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References

- Pazoki R, Dehghan A, Evangelou E, et al. Genetic predisposition to high blood pressure and lifestyle factors: Associations with midlife blood pressure levels and cardiovascular events. *Circulation* 2017; DOI: 10.1161/CIRCULATIONAHA.117.030898 [AQ1].
- Kokkinos P, Manolis A, Pittaras A, et al. Exercise capacity and mortality in hypertensive men with and without additional risk factors. *Hypertension* 2009; 53: 494–499.
- Grimm Jr RH, Grandits GA, Cutler JA, et al. Relationships of quality-of-life measures to long-term lifestyle and drug treatment in the Treatment of Mild Hypertension Study. *Arch Intern Med* 1997; 157: 638–648.
- 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the prevention, detection, evaluation, and management of high blood pressure in adults. *J Am Coll Cardiol* 2017; DOI: 10.1016/j.jacc.2017.11.006 [AQ2] [AQ3].
- Sharman JE, La Gerche A and Coombes JS. Exercise and cardiovascular risk in patients with hypertension. *Am J Hypertens* 2015; 28: 147–158.
- Faselis C, Doumas M, Pittaras A, et al. Exercise capacity and all-cause mortality in male veterans with hypertension aged ≥ 70 years. *Hypertension* 2014; 64: 30–35.
- Berry JD, Willis B, Gupta S, et al. Lifetime risks for cardiovascular disease mortality by cardiorespiratory fitness levels measured at ages 45, 55, and 65 years in men: The Cooper Center Longitudinal Study. *J Am Coll Cardiol* 2011; 57: 1604–1610.
- Churilla JR and Ford ES. Comparing physical activity patterns of hypertensive and nonhypertensive US adults. *Am J Hypertens* 2010; 23: 987–993.
- Arena R, Myers J, Williams A, et al. Assessment of functional capacity in clinical and research settings: A Scientific Statement from the American Heart Association Committee on Exercise, Rehabilitation, and Prevention of the Council on Clinical Cardiology and the Council on Cardiovascular Nursing. *Circulation* 2007; 116: 329–343.
- Balady GJ, Arena R, Sietsema K, et al. Clinician's guide to cardiopulmonary exercise testing in adults: A Scientific Statement from the American Heart Association. *Circulation* 2010; 122: 191–225.
- Gupta S, Rohatgi A, Ayers CR, et al. Cardiorespiratory fitness and classification of risk of cardiovascular disease mortality. *Circulation* 2011; 123: 1377–1383.
- Israel A, Kivity S, Sidi Y, et al. Use of exercise capacity to improve SCORE risk prediction model in asymptomatic adults. *Eur Heart J* 2016; 37: 2300–2306.
- Myers J, Nead KT, Chang P, et al. Improved reclassification of mortality risk by assessment of physical activity in patients referred for exercise testing. *Am J Med* 2015; 128: 396–402.
- Simonsick EM, Fan E and Fleg JL. Estimating cardiorespiratory fitness in well-functioning older adults: Treadmill validation of the long distance corridor walk. *J Am Geriatr Soc* 2006; 54: 127–132.
- Piotrowicz E, Zielinski T, Bodalski R, et al. Home-based telemonitored Nordic walking training is well accepted, safe, and effective and has high adherence among heart failure patients, including those with cardiovascular implantable electronic devices: A randomized controlled study. *Eur J Prev Cardiol* 2015; 22: 1368–1377.
- Chiaranda G, Myers J, Mazzoni G, et al. Peak oxygen uptake prediction from a moderate, perceptually regulated, 1-km treadmill walk in male cardiac patients. *J Cardiopulm Rehabil Prev* 2012; 32: 262–269.
- Grazzi G, Chiaranda G, Myers J, et al. Outdoor reproducibility of a 1-km treadmill-walking test to predict peak oxygen consumption in cardiac outpatients. *J Cardiopulm Rehab Prev* 2017; 37: 347–349.

18. Mandini S, Grazzi G, Mazzoni G, et al. A moderate 1-km treadmill walk predicts mortality in men with mid-range left ventricular dysfunction. *Eur J Prev Cardiol* 2017; 15: 1670–1672.
19. Kamiya K, Hamazaki N, Matsue Y, et al. Gait speed has comparable prognostic capability to six-minute walk distance in older patients with cardiovascular disease. *Eur J Prev Cardiol* 2018; 25: 212–219.
20. Granacher U and Voller H. Gait speed is not magic, but is prognostically important in older patients. *Eur J Prev Cardiol* 2018; 25: 209–211.