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Author(s): Salokari, Esko; Laukkanen, Jari; Lehtimäki, Terho; Kurl, Sudhir; Kunutsor, Setor; Zaccardi, Francesco; Viik, Jari; Lehtinen, Rami; Nikus, Kjell; Kööbi, Tiit; Turjanmaa, Väinö; Kähönen, Mika; Nieminen, Tuomo

Title: The Duke treadmill score with bicycle ergometer : Exercise capacity is the most important predictor of cardiovascular mortality

Year: 2019

Version: Published version

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Please cite the original version:

Salokari, E., Laukkanen, J., Lehtimäki, T., Kurl, S., Kunutsor, S., Zaccardi, F., Viik, J., Lehtinen, R., Nikus, K., Kööbi, T., Turjanmaa, V., Kähönen, M., & Nieminen, T. (2019). The Duke treadmill score with bicycle ergometer : Exercise capacity is the most important predictor of cardiovascular mortality. *European Journal of Preventive Cardiology*, 26(2), 199-207.
<https://doi.org/10.1177/2047487318804618>

The Duke treadmill score with bicycle ergometer: Exercise capacity is the most important predictor of cardiovascular mortality

Esko Salokari¹, Jari A Laukkanen^{2,3,4}, Terho Lehtimäki⁵,
Sudhir Kurl², Setor Kunutsor⁶, Francesco Zaccardi⁷, Jari Viik⁸,
Rami Lehtinen⁹, Kjell Nikus¹⁰, Tiit Kööbi¹¹, Väinö Turjanmaa¹²,
Mika Kähönen¹¹ and Tuomo Nieminen^{13,14}

European Journal of Preventive
Cardiology

2019, Vol. 26(2) 199–207

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Cardiology 2018



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DOI: 10.1177/2047487318804618

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Abstract

Background: The Duke treadmill score, a widely used treadmill testing tool, is a weighted index combining exercise time or capacity, maximum ST-segment deviation and exercise-induced angina. No previous studies have investigated whether the Duke treadmill score and its individual components based on bicycle exercise testing predict cardiovascular death.

Design: Two populations with a standard bicycle testing were used: 3936 patients referred for exercise testing (2371 men, age 56 ± 13 years) from the Finnish Cardiovascular Study (FINCAVAS) and a population-based sample of 2683 men (age 53 ± 5.1 years) from the Kuopio Ischaemic Heart Disease study (KIHD).

Methods: Cox regression was applied for risk prediction with cardiovascular mortality as the primary endpoint.

Results: In FINCAVAS, during a median 6.3-year (interquartile range (IQR) 4.5–8.2) follow-up period, 180 patients (4.6%) experienced cardiovascular mortality. In KIHD, 562 patients (21.0%) died from cardiovascular causes during the median follow-up of 24.1 (IQR 18.0–26.2) years. The Duke treadmill score was associated with cardiovascular mortality in both populations (FINCAVAS, adjusted hazard ratio (HR) 3.15 for highest vs. lowest Duke treadmill score tertile, 95% confidence interval (CI) 1.83–5.42, $P < 0.001$; KIHD, adjusted HR 1.71, 95% CI 1.34–2.18, $P < 0.001$). However, after progressive adjustment for the Duke treadmill score components, the score was not associated with cardiovascular mortality in either study population, as exercise capacity in metabolic equivalents of task was the dominant harbinger of poor prognosis.

Conclusions: The Duke treadmill score is associated with cardiovascular mortality among patients who have undergone bicycle exercise testing, but metabolic equivalents of task, a component of the Duke treadmill score, proved to be a superior predictor.

Keywords

Cardiovascular mortality, prognostic factors, stress test

Received 23 December 2017; accepted 11 September 2018

¹Department of Internal Medicine, University of Helsinki, Finland

²Institute of Public Health and Clinical Nutrition, University of Eastern Finland, Finland

³Department of Medicine, Central Finland Health Care District, Finland

⁴Faculty of Sport and Health Sciences, University of Jyväskylä, Finland

⁵Department of Clinical Chemistry, University of Tampere, Finland

⁶School of Clinical Sciences, University of Bristol, Southmead Hospital, Bristol, UK

⁷Diabetes Research Centre, Leicester General Hospital, Leicester, UK

⁸Department of Biomedical Engineering, Tampere University of Technology, Finland

⁹Department of ICT and Health Technology, Tampere University of Applied Sciences, Finland

¹⁰Faculty of Medicine and Life Sciences, University of Tampere and Heart Center, Finland

¹¹Department of Clinical Physiology, Tampere University Hospital and University of Tampere, Finland

¹²Science Centre, Pirkanmaa Hospital District, Finland

¹³Department of Internal Medicine, University of Helsinki, Finland

¹⁴South Karelia Central Hospital, Lappeenranta, Finland

Corresponding author:

Tuomo Nieminen, University of Helsinki, Internal Medicine PL 22 (Haartmaninkatu 4), 00014 Helsingin Yliopisto, Finland.

Email: tuomo.vm.nieminen@helsinki.fi

Introduction

Although other modalities have partially replaced clinical exercise test as a diagnostic tool for assessment of coronary artery disease (CAD), the test has become more vital in evaluating prognosis and focusing available treatments for high-risk patients.^{1,2} One of the most widely studied and used prognostic variables in exercise testing is the Duke treadmill score (DTS), which is a weighted index combining treadmill exercise time with standard Bruce protocol, maximum ST-segment deviation on electrocardiogram (ECG) and exercise-induced angina.³ The score was initially developed to add prognostic information to that provided by clinical data, coronary anatomy and left ventricular ejection fraction in patients with suspected CAD referred for catheterisation.³ The DTS was later also validated for patients with suspected CAD,⁴ and it is still in clinical use for risk stratification for these patients.^{5,6} Interestingly, prior studies have not properly tested whether the DTS is a superior prognostic marker in comparison with its components.

As exercise time of the Bruce protocol can be replaced with metabolic equivalents of tasks (METs), the DTS is also suitable for other exercise test protocols.⁷ In many European countries, a bicycle ergometer rather than a treadmill is the preferred testing modality. However, the prognostic value of the DTS using the standard bicycle exercise testing has not yet been investigated. Thus the purpose of this study was to assess the prognostic value of the DTS in bicycle exercise testing. Combined analysis of several parameters is commonly used to simplify risk assessment; however, the combination needs to be superior to an independent assessment of each variable. Therefore, we also compared the prognostic capability of the DTS to that of its components. We hypothesise that the DTS is a useful prognostic marker of cardiovascular death, superior to its components, in the exercise test performed with a bicycle ergometer.

Methods

Study cohorts

We used two independent data cohorts. In the Finnish Cardiovascular Study (FINCAVAS), all consecutive patients referred for an exercise test at Tampere University Hospital and willing to participate were enrolled between October 2001 and December 2008. A detailed description of the study has been published.⁸ A study population of 4178 patients (2537 men and 1641 women) was recruited. Data from a total of 3758 patients (2249 men and 1509 women) with technically successful exercise tests – including exercise

capacity and angina data as well as continuous digital ECG with ST-segment deviation and slope data – were analysed in the present study.

The main indications for exercise testing were a suspicion of CAD (47%), evaluation of work capacity (27%), evaluation of arrhythmias (26%), adequacy of CAD treatment (13%), as well as obtaining an exercise test profile prior to an invasive procedure (9%) or after myocardial infarction (MI) (7%); some patients had more than one indication. The ethics committee of Tampere University Hospital district approved the study protocol, and all patients gave informed consent as stipulated in the Declaration of Helsinki.

The other dataset was from the Kuopio Ischaemic Heart Disease (KIHD) risk factor study. This was a longitudinal population-based study designed to investigate risk factors for cardiovascular diseases, atherosclerosis and related outcomes. The baseline data consist of randomly selected 2683 men between 42 and 61 years of age living in the city of Kuopio and surrounding rural communities in eastern Finland, of which 2392 men with successful exercise test data were included in our study. The baseline examinations were conducted between March 1984 and December 1989. The KIHD study has previously been described in detail.⁹

Study flow

FINCAVAS. In FINCAVAS, written informed consent, medical history, resting and exercise ECGs and exercise systolic and diastolic blood pressure recordings were obtained, as previously described.⁸ In brief, prior to the exercise test using a bicycle ergometer, subjects lay down in the supine position for 10 minutes, and the resting ECG was digitally recorded. The Mason–Lickar 12-lead system was used. The exercise tests were intended to be maximal tests except for 7% of the tests, which evaluated the status after an MI and applied a heart rate limit of 120–130 beats/min; even those were included in the analysis.

The initial workload of 20–30 W was increased stepwise by 10–30 W every minute based on patient characteristics. ECGs were digitally recorded at 500 Hz with the CardioSoft exercise system (version 4.14; GE Healthcare, Freiburg, Germany). The reasons for termination of the test were chest pain (5.7%), dyspnoea (12.8%), fatigue (61.6%), ECG changes (1.4%), blood pressure changes (1.5%) or other reasons (11.5%). The objective exercise levels as defined by the supervising physician were maximal in 76.4%, almost maximal in 18.7%, reasonable in 3.1% and poor in 0.6% of the tests.

KIHD. In the KIHD study, the patients underwent a maximal symptom-limited exercise tolerance test using an electrically braked cycle ergometer with increase in

the workload of 20 W/minute. Maximal exercise capacity was calculated from $\text{VO}_{2\text{max}}$, which was defined as the highest value or the plateau of directly measured oxygen consumption using a respiratory gas analyser (Mijnhardt and Medical Graphics, Minneapolis, MN, USA). ECG was recorded continuously with the Kone 620 electrocardiograph (Kone, Turku, Finland). ECG was printed at 30 second intervals during exercise and at least 5 minutes of recovery while the subject was sitting on the bicycle.^{9,10}

The Duke treadmill score

FINCAVAS. The DTS was calculated as follows: exercise time – ($5 \times \text{max ST-segment depression}$) – ($4 \times \text{Angina index}$). The exercise time in minutes was approximated from the maximal METs using a linear approach derived from the scientific statement of the American Heart Association regarding exercise standards for testing and training.⁷ The following equation was used: exercise time = $(\text{METs} - 1)/1.044$. METs were estimated on the standardised basis of maximum workload and patient weight, with 1 MET being equivalent to 3.5 ml oxygen uptake/kg/min.

The original DTS used maximal ST-segment deviation – whether depression or elevation – compared to the resting phase from the lead with the most deviation.³ We took into account only the maximal net ST-segment depression (STD) because non-diagnostic ST-segment elevation is rather common in healthy people due to early repolarisation. ST-segments were analysed with modified CASE/CardioSoft software (V.1.84; GE Healthcare, Freiburg, Germany). The software also calculates the ST slope on the basis of the current median complex, measured over an interval from the J point to the 1/8 of the average R-R interval (a maximum of 80 ms). This definition of slope takes into account the correlation between heart rate and repolarisation time, avoiding the effects of the T wave.¹¹ The STD and slope were calculated for the end of the resting phase and for each minute of the exercise and recovery. Possible ST-segment deviation at the resting phase was extracted from the values during the exercise and recovery to assess the difference caused by the exercise. If the simultaneous ST-segment slope was at least 0.5 mV/s, the depression was set to zero, as up-sloping STD, whether rapid or slow, might be associated with an increased risk of future coronary events, but is not predictive for the presence of myocardial ischaemia in the general population.¹² The maximal STD in all the leads except aVR was used in the analysis. If the maximal STD was less than 1 mm, it was set to zero, as it is not considered pathological. Values greater than 5 mm ($n=34$) were excluded from the data because they were most likely due to measurement error.

The angina index has values of 0 (no exercise induced ischaemic chest pain), 1 (non-exercise-limiting angina) and 2 (exercise-limiting angina). To create the angina index variable, we had to merge original FINCAVAS variables. If the patient had no pain or atypical pain during the exercise, the angina index has the value 0. If the patient did not report possible angina, but the clinician estimated the post-test probability for CAD to be low, we also set the angina index value to 0. If the patient had experienced typical angina during the exercise, the angina index was 1 and if angina was the reason for ending the test, the index was 2.

KIHD. Exercise time was calculated from the METs as above.

In the KIHD study, maximal ST-segment deviation from the baseline during exercise was recorded from the leads V5 and aVF and the maximal value for ST-segment deviation was used in the analyses. ST-segment elevations were excluded, as well as depressions less than 1 mm and greater than 5 mm. The ECGs were also coded manually by an experienced cardiologist, giving a variable for ischaemia values from 0 to 3, 0 meaning no ischaemia and 1–3 indicating the severity of ischaemia. We factored in this variable so that our variable for the maximal STD of the DTS would be as close to that we used in the FINCAVAS population. If the ischaemia variable had a value of 0, the maximal STD variable was set to 0, and if the ischaemia variable had values 1–3, the maximal STD variable was constituted as above. This way we approximated that the final ST-variable takes into account the slope of the ST-segment.

If the patient had no angina, the DTS angina index has a value 0, and if a patient had exercise-limiting angina, the angina index has a value of 2. Non-limiting angina was not taken into account in the original study setting. The DTS was constituted as above from FINCAVAS.

Originally, if the overall DTS is at least 5, the patient is considered as ‘low risk’, a score between –11 and 5 denotes ‘moderate risk’, and a score of –11 or less indicates ‘high risk’.³ Because only a limited number of patients were classified as belonging to the high-risk DTS category, we also divided the DTS into equal tertiles taking account the whole population from two cohorts.

Definition of comorbidities

The presence of CAD (no/yes) was taken from the medical records and questionnaire (previous MI, angina pectoris, revascularisation, and/or use of nitroglycerin). Diabetes (no/yes) was defined as having a clinical diagnosis and regular treatment with diet or medications.

In the KIH D study, fasting plasma glucose of 7.0 mmol/l or greater was an additional criterium. Smoking (no/yes) was defined as daily smoking (FINCAVAS) or smoking within the past 30 days (KIH D). The use of β -blockers was defined as regular use (no/yes). Some of the regular β -blocker users within FINCAVAS were advised to pause the drug 3 days before the test; those patients were classified in the 'no' category.

Ascertainment of follow-up events

Death certificates based on the 9th or 10th revision of the International Classification of Diseases (ICD-10) were received from the causes of death register maintained by Statistics Finland;^{8,13} the data source has been validated.¹⁴ The reviewers of death certificates were blinded to events and test results. The deaths were classified as cardiovascular when the ICD-10 code was I00–I79. Cardiovascular mortality was the primary endpoint and all-cause mortality the secondary endpoint. In FINCAVAS, the autopsy rate was 46% for all deaths and 57% for patients who succumbed to cardiovascular death. In the KIH D study the autopsy rate was 80% for all deaths.

Statistical analysis

Differences between patient and exercise test characteristics according to the DTS in tertiles were compared using one-way analysis of variance, Kruskal–Wallis test or chi-square test as appropriate.

The usefulness of the DTS in assessing the prognosis was tested with a Cox proportional hazards model. Covariates included age, sex, body mass index (BMI), a diagnosed CAD, smoking status, β -blocker usage and diabetes. The components of the DTS (STD, angina index and performance in METs) were added to an additional model with other covariates. The DTS was entered as the original version categorised into three parts (low risk, moderate risk and high risk) and as a three-category version with tertiles.

Statistical analyses were performed using the SPSS release 23.0 for Mac (SPSS Inc., Chicago, IL, USA). All statistical tests were two-tailed and used an alpha level of 0.05.

Results

Patient characteristics are given in Table 1. Within the original DTS categorisation, 3.5% of patients of the FINCAVAS population were classified as being in high, 52% in moderate and 40% in low risk. In the KIH D study population, only 1.6% were classified as high, 31.4% as moderate and 67.0% as low-risk

patients. In our new categorisation a DTS over 6.7 belongs to the lowest risk tertile, scores from 3.0 to 6.7 to the middle tertile and scores below 3.0 to the highest risk tertile.

FINCAVAS

The age of the population was 56 ± 13 years. Death from any cause or from cardiovascular causes was recorded in 404 (10.3%) and 180 (4.6%) patients, respectively, over the median follow-up period of 6.3 years (interquartile range (IQR) 4.5–8.2).

As a three-category variable with the cut points from the original treadmill studies, the DTS (highest vs. lowest group) was highly predictive of both cardiovascular death (HR 2.26, 95% CI 1.48–3.45, $P < 0.001$) and all-cause mortality (HR 1.70, 95% CI 1.31–2.22, $P < 0.001$) when adjusting for other covariates. However, the prognostic signal of the DTS disappeared entirely when the model was also adjusted with the three components of the DTS (METs, angina index and maximal STD): HR for cardiovascular death was 1.10 (95% CI 0.63–1.92, $P = 0.740$). Importantly, exercise capacity in METs was the only DTS component with a statistically significant HR (0.77, 95% CI 0.70–0.85, $P < 0.001$) in this fully adjusted model.

The results were similar for the DTS divided into equal tertiles: the DTS was predictive of cardiovascular death (HR 3.15, 95% CI 1.83–5.43, $P < 0.001$) and all-cause death (HR 2.08, 95% CI 1.49–2.90, $P < 0.001$). However, when adjusted with the three individual components, the DTS was not predictive of cardiovascular death and, again, METs was the sole component linked with prognosis, as shown in Table 2 and Figure 1.

KIH D

The age of the KIH D study population was 53 ± 5.1 years. A total of 1200 deaths (44.7%) occurred from any cause and 562 (21.0%) from cardiovascular causes over the median follow-up period of 24.1 years (IQR 18.0–26.2 years).

As a traditional three-category variable and adjusted with covariates, the DTS was predictive of cardiovascular death and all-cause mortality when comparing the lowest with the highest group (HR 1.52, 95% CI 1.25–1.85, $P < 0.001$ and 1.37, 95% CI 1.20–1.56, $P < 0.001$, respectively). When also adjusted with all three components of the DTS, the three-categorical DTS was not associated with cardiovascular death (HR 1.11, 95% CI 0.83–1.49, $P = 0.48$). Of the three individual components, only exercise capacity in METs was related to the risk of cardiovascular death (HR 0.85, 95% CI 0.79–0.90, $P < 0.001$).

Table 1. Patient and exercise test characteristics of both cohorts according to the DTS risk tertiles.

FINCAVAS										KIHD																					
DTS										DTS																					
Lowest risk tertile (n = 1209)					Middle risk tertile (n = 1024)					Highest risk tertile (n = 1525)					Lowest risk tertile (n = 1158)					Middle risk tertile (n = 704)					Highest risk tertile (n = 530)					P value	
Mean	SD				Mean	SD				Mean	SD				Mean	SD				Mean	SD				Mean	SD					
Age (years)	50.3	12.6			57.9	11.7				59.1	12.7				51.6	5.3				54.0	4.5				54.1	4.6				<0.001	
BMI (kg/m ²)	26.5	4.1			28.4	4.7				27.7	4.7				26.2	3.0				28.1	3.9				26.5	3.1				<0.001	
METs	10.0	2.2			6.8	2.2				6.3	2.7				10.0	1.6				7.0	1.7				7.9	2.3				<0.001	
	Median	IQR			Median	IQR				Median	IQR				Median	IQR				Median	IQR				Median	IQR					
STD (mm)	0.0	0.0–0.0	0.0		0.0	0.0–0.0	0.0		1.3	0.0–1.9	1.3				0.0	0.0–0.0	0.0		0.0	0.0–0.0	0.0				1.6	1.3–2.1	1.6			<0.001	
	n (%)				n (%)				n (%)						n (%)				n (%)						n (%)						
Angina index	3 (0.2%)				23 (2.2%)				122 (8.0%)						0 (0.0%)				0 (0.0%)						86 (16.2%)						<0.001
Women	0 (0.0%)				3 (0.3%)				216 (14.2%)						0 (0.0%)				0 (0.0%)						86 (16.2%)						<0.001
	448 (37.1%)				446 (43.6%)				615 (40.3%)						151 (13.0%)				229 (32.5%)						194 (36.6%)						<0.001
CAD	219 (18.1%)				129 (12.8%)				564 (37.0%)						88 (7.6%)				183 (26.0%)						140 (26.4%)						<0.001
β-Blocker	471 (39.0%)				628 (61.3%)				1011 (66.3%)						35 (3.0%)				46 (6.5%)						42 (7.9%)						<0.001
Diabetes	92 (7.8%)				129 (12.8%)				205 (13.8%)						340 (29.4%)				258 (36.6%)						163 (30.9%)						0.004
Smoking	278 (23.0%)				251 (24.5%)				319 (20.9%)						0.095																
Prior MI	152 (12.6%)				216 (21.1%)				344 (22.6%)						<0.001																

SD: standard deviation; DTS: Duke treadmill score; METs: metabolic equivalents of tasks; STD: = maximal ischaemic ST-segment depression during exercise; CAD: diagnosed coronary artery disease; MI: myocardial infarction.

Table 2. Cox regression survival analysis of the DTS as tertiles, its components and covariates, cardiovascular-mortality as an endpoint.

	FINCAVAS				KIHD			
	HR	95% CI		P value	HR	95% CI		P value
		Lower	Upper			Lower	Upper	
DTS (3rd vs. 1st tertile)	1.149	0.604	2.185	0.672	0.900	0.677	1.195	0.466
METs	0.799	0.726	0.88	<0.001	0.821	0.767	0.879	<0.001
STD	1.042	0.869	1.251	0.656	1.209	1.012	1.444	0.036
Angina	0.757	0.571	1.003	0.053	1.057	0.863	1.295	0.592
Age	1.034	1.018	1.05	<0.001	1.068	1.044	1.094	<0.001
Sex	2.929	1.985	4.323	<0.001				
BMI	0.999	0.964	1.035	0.965	1.058	1.029	1.087	<0.001
CAD	0.952	0.69	1.313	0.763	1.403	1.138	1.731	0.002
β -Blocker	1.387	0.935	2.057	0.104	1.379	1.109	1.715	0.004
Diabetes	1.216	0.823	1.796	0.327	2.018	1.509	2.700	<0.001
Smoking	1.183	0.832	1.681	0.349	2.199	1.823	2.652	<0.001

HR: hazard ratio; DTS: Duke treadmill score; METs: metabolic equivalents of tasks; STD: maximal ischaemic ST-segment depression during exercise; Angina: non-limiting (FINCAVAS) and limiting (FINCAVAS and KIHD) angina during exercise; BMI: body mass index; CAD: diagnosed coronary artery disease.

When divided into equal tertiles, the DTS was predictive of cardiovascular death (adjusted HR 1.43, 95% CI 1.13–1.80, $P=0.003$) and all-cause death (HR 1.43, 95% CI 1.22–1.66, $P<0.000$). However, when all components of the DTS were included in the multivariable model, only METs and maximal STD were statistically significant, as shown in Table 2 and Figure 1.

Discussion

Our findings demonstrate that the DTS based on the bicycle ergometer test is consistently predictive of fatal cardiovascular and all-cause mortality. The DTS was predictive of cardiovascular death in both populations as an original three-category variable. However, exercise capacity alone proved to be a superior predictor of outcomes in comparison to the DTS. One unit increment in exercise capacity (METs) was related to a 17–20% lower risk of cardiovascular mortality. From the other two DTS components, the angina index was not predictive of cardiovascular death in either population; however, maximal STD was statistically significant in the KIHD study population. The results are unequivocal in demonstrating that the DTS does not provide any prognostic information independent of its components.

This is the first study to assess the prognostic value of the DTS with the standard bicycle ergometer. A previous study with a limited number of participants ($n=211$) was conducted to compare the bicycle ergometer in the supine position and the treadmill test when

assessing the value of the DTS.¹⁵ The use of the supine bicycle ergometer instead of the treadmill led to a lower maximal workload and METs level.¹⁵ This was a reason that patients got lower DTS results and thus they were mostly classified into higher risk categories.

There are several possible explanations as to why BMI, smoking status and diabetes were associated with outcome in the KIHD study but not in FINCAVAS patients. First, the study populations were quite different. In the FINCAVAS cohort, patients were referred for an exercise test due to clinical reasons, whereas in the KIHD study, participants were a randomly selected population-based sample of men. The KIHD study included middle-aged men based on a genetically and ethnically homogeneous population from eastern Finland, an area previously known for its high prevalence and incidence of cardiometabolic diseases. In addition, it is possible that the assessment methods of baseline characteristics and risk factors influenced the observed findings. Finally, the KIHD study data had an essentially longer follow-up than the other dataset, granting the risk factors more time to cause clinical events and cardiovascular mortality.

General differences between treadmill and standard bicycle ergometer exercise testing have been studied earlier, and patients seem to get 10–20% lower maximal METs if they are not accustomed to cycling,¹⁶ possibly because muscle fatigue prevents them from reaching their $\text{VO}_{2\text{max}}$.

When the DTS was originally developed for treadmill exercise testing, ST-deviation was the most

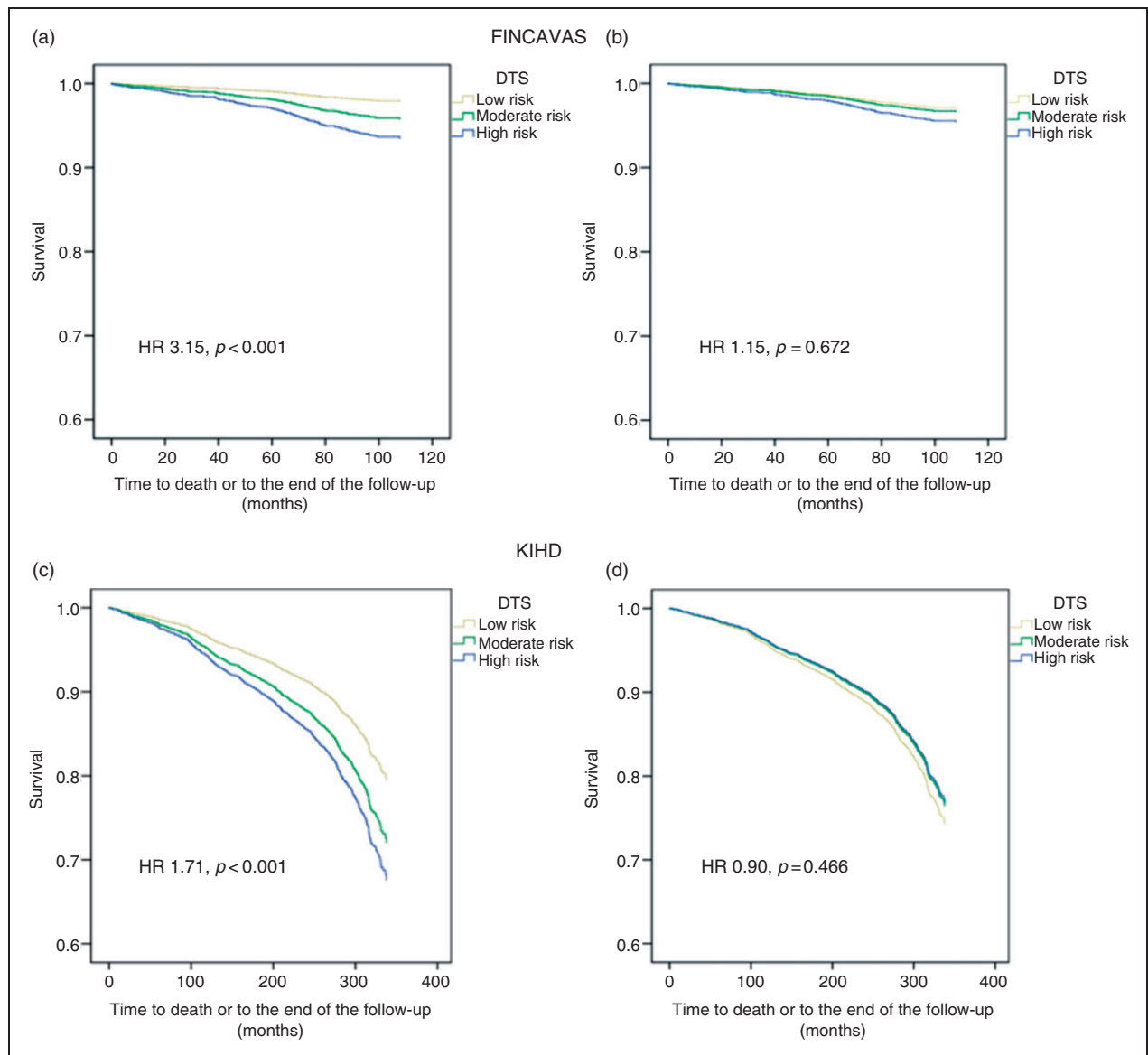


Figure 1. Adjusted Cox regression survival analysis according to Duke treadmill score risk tertiles in both cohorts, cardiovascular mortality as an endpoint; (a) and (c) without the components of the DTS; (b) and (d) with the components.

powerful prognostic variable, and adding angina and exercise time increased prognostic power.³ Exercise capacity (METs) has been repeatedly validated to be the single most powerful prognostic marker predicting cardiovascular mortality^{17–20} and major cardiovascular events.²¹ The American Heart Association recently made a statement that cardiorespiratory fitness should be assessed routinely in clinical practice.²² In a previous study, classic cardiovascular risk factors including diabetes, hypertension, obesity and smoking, were linked to decreased exercise capacity.²³ In a cohort of middle-aged men with more than 40 years of follow-up, low exercise capacity led to increased overall mortality rates, independent of smoking, blood pressure and

serum cholesterol.²⁴ A large longitudinal study of Swedish adolescent men found that poor exercise capacity was also associated with a greater risk of incident heart failure.²⁵ These examples outline the independent prognostic importance of exercise capacity. In contrast, the prognostic significance of ST-deviation and angina is still unclear, despite the fact that the diagnostic power of both ST-segment changes and angina is well established.^{26–29}

The relative importance of each of the DTS components probably depends largely on the population. The study population from which the DTS was initially derived had a high probability of CAD, confirmed by consequent coronary catheterisation, whereas most

of the later studies have consisted of patients referred for exercise testing because of a milder suspicion of CAD. This could partially explain the shift of the best prognostic marker from ST-deviation to exercise capacity.

Whether combining the three components into the DTS yields additional prognostic information in comparison to using the components separately has not been well explored. Previously, using multivariable analyses in assessing the prognosis of patients has enhanced the prognostic power compared to analysing independent variables other than the DTS components.^{19,30,31} In these studies, the analysed variables were heart rate recovery, T-wave alternans and METs. This supplementary prognostic information may have been due to the different pathophysiological bases assessed by different variables. In the DTS, there are two variables indicating myocardial ischaemia which may not be helpful.

The strength of this study is the usage of two independent large prospective datasets and the assessment of a comprehensive range of potential covariates. The follow-up of the KIHd study is particularly long; however, the study is limited by the absence of female participants. Data on angina that did not limit exercise was not considered in the original KIHd study setting. The strengths of FINCAVAS are a large population and electronically saved beat-to-beat ECG data. Measuring exercise capacity as METs may have its weaknesses regarding patients' age and fat-free mass.^{32–34} Neither study takes into account the changes in patient characteristics and treatment during the follow-up period. There can be residual confounders affecting cardiovascular mortality in addition to covariates, which we accounted for. Naturally, we cannot draw causal inferences from observational studies.

In conclusion, the DTS seemed to be predictive of cardiovascular death for patients who underwent bicycle exercise testing in two different populations. However, when adjusted with its components, the predictive power of the DTS disappeared, as exercise capacity proved to be a superior predictor of fatal cardiovascular outcomes. More studies are needed to confirm our findings using bicycle exercise testing. Measuring and categorising exercise capacities should be further cultivated. Future research should also concentrate on developing more accurate multivariable prognostic scores which take into account more versatile underlying pathophysiological bases.

Author contribution

ES, TN and JAL contributed to the conception and design of the work. All authors contributed to the acquisition, analysis, or interpretation of data for the work. ES drafted the manuscript. All authors critically revised the manuscript.

All authors gave final approval and agree to be accountable for all aspects of the work ensuring integrity and accuracy.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: the Finnish Cardiovascular Study (FINCAVAS) has been financially supported by the competitive research funding of Tampere University Hospital (Grants X51001), the Finnish Cultural Foundation, the Finnish Foundation for Cardiovascular Research (TL), the Emil Aaltonen Foundation (TL), Finland, and the Tampere Tuberculosis Foundation and by the Academy of Finland (grant 286284 for TL).

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