

ORIGINAL RESEARCH

VENTRICULAR ARRHYTHMIA

Prediction of Sudden Cardiac Death With Ultra-Short-Term Heart Rate Fluctuations



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ABSTRACT

BACKGROUND Conventional measures of heart rate variability (HRV) have shown only modest associations with sudden cardiac death (SCD). Detrended fluctuation analysis (DFA), with novel methodological developments to evaluate the short-term scaling exponent, is a potentially superior method compared to conventional HRV tools.

OBJECTIVES In this study, the authors studied the analysis of the association between DFA and SCD.

METHODS The investigators studied the predictive value of ultra-short-term heart rate fluctuations (1-minute electrocardiogram samples) with DFA at rest and during different stages of physical exertion for incident SCD among 2,794 participants undergoing clinical exercise testing in the prospective FINCAVAS (Finnish Cardiovascular Study). The novel key DFA measure, the short-scale scaling exponent computed with second-order detrending (DFA2 α_1), was the main exposure variable. SCDs were defined by American Heart Association/European Society of Cardiology criteria using death certificates with written accounts of the events.

RESULTS During a median follow-up of 8.3 years (Q1-Q3: 6.4-10.5), 83 SCDs occurred. DFA2 α_1 measured at rest (but not in exercise) associated highly significantly with the risk of SCD, with 1-SD lower values associating with a 2.4-fold (Q1-Q3: 2.0-3.0) risk ($P < 0.001$). The results persisted when adjusting for other major risk factors for SCD, including age, cardiovascular morbidities, cardiorespiratory fitness, heart rate reduction, and left ventricular ejection fraction. Associations between conventional HRV parameters (measured at any stage of exercise or at rest) and SCD were substantially weaker and statistically nonsignificant after adjusting for other risk factors.

CONCLUSIONS Ultra-short-term DFA2 α_1 , when measured at rest, is a powerful and independent predictor of SCD. The association between DFA2 α_1 and SCD is modified by physical exertion. (JACC Clin Electrophysiol. 2024;10:2010-2020) © 2024 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>).

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Manuscript received October 10, 2023; revised manuscript received April 11, 2024, accepted April 20, 2024.

The prediction of sudden cardiac death (SCD) is a formidable challenge.¹ The best (and cost-effective) gains in quality life-years are achieved specifically in patients who are at a high risk of SCD but who have an otherwise good functional capacity and low overall mortality risk. Measurable physiological variables, such as heart rate reduction (HRR) after exercise and cardiorespiratory fitness (CRF), have been associated with the risk of SCD.²⁻⁵ However, standardized measurement of HRR and CRF requires a standardized testing environment and good overall cooperation. Unfortunately, reduced CRF and HRR are also directly associated with poor functional capacity and high overall mortality.²

The recent proliferation of wearable consumer devices, such as watches and rings using photoplethysmography (and even electrocardiography when needed), has provided entirely new avenues for risk stratification for several medical conditions.⁶ These devices can easily detect atrial fibrillation and reliably measure resting heart rate and heart rate variability (HRV).⁶ Provided that the data extracted from these devices could be used for accurate risk stratification, their applicability would be unparalleled, because they provide continuously updating data over time.

HRV has been associated with heart failure, coronary artery disease, and even SCD.⁷⁻¹⁵ HRV can be determined from changes in the beat-to-beat interval over time by several conventional time-domain and frequency-domain methods.¹⁶ There are also so-called nonlinear HRV methods, such as the short-term scaling exponent α_1 of detrended fluctuation analysis (DFA), usually applied with linear (first-order) detrending (DFA1). In recent years, it has been shown that the performance of DFA can be improved by using overlapping windows for the detrending¹⁷; robust estimation of the scaling exponent with Kalman smoothers^{17,18}; higher polynomials for the detrending order, with the second-order (DFA2) often being a reasonable choice for HRV¹⁷; as well as dynamic DFA.¹⁹ The purpose of this study was to evaluate the applicability of DFA in predicting SCD in the prospective FINCAVAS (Finnish Cardiovascular Study) on patients undergoing clinical exercise testing. Furthermore, because HRV usually changes with different levels of physical exertion, regardless of the measurement method, our aim was to analyze whether the possible association changes depending on the measurement context (rest, exercise, and recovery).

METHODS

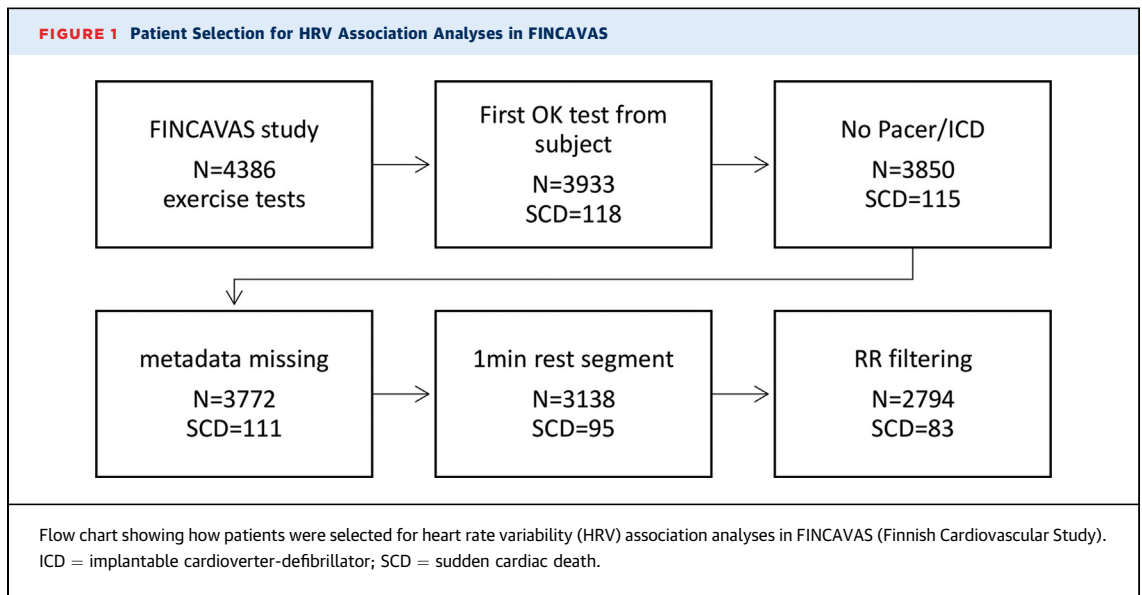
The study sample of the prospective clinical FINCAVAS study comprises all willing consecutive patients between October 2001 and December 2008 undergoing clinical exercise testing at Tampere University Hospital. The major indications for referral to the test included: suspicion of coronary artery disease, evaluation of drug therapy efficacy, preinterventional assessment, evaluation of arrhythmia, evaluation after myocardial infarction, and evaluation of work capacity. The Ethics Committee of the Tampere University Hospital District approved the study protocol, and all patients gave written informed consent. The study adheres to the Declaration of Helsinki. Details of the study including full description of phenotype data collection are presented in the [Supplemental Appendix](#) and have been published earlier in more detail.²⁰

PATIENT SELECTION FOR THE ANALYSIS. During the trial, 3,933 patients performed a combined 4,386 exercise tests. Only the first technically successful exercise test was considered for each patient as the baseline event in this study so that each patient contributed to the follow-up only once. A technically successful exercise test was defined as a test with a reliably measured heart rate and electrocardiogram (ECG). Patients with pacemakers, those without fully available metadata on pre-existing significant comorbidities, as well as patients without a minimum of 1 minute of resting heart rate (ECG) data were excluded. After these exclusions, 3,138 patients were available for consideration in the HRV analysis of which 344 patients were removed after data filtering in which unusual RR intervals caused by ectopic beats and/or falsely detected R peaks were removed from the time series before the analysis (detailed in the [Supplemental Methods](#)) ([Figure 1](#)). The full a priori defined patient selection process for the analysis in the present study is presented in [Figure 1](#).

MEASUREMENT OF HRV. HRV was measured using time-domain and frequency-domain methods, Poincaré plots, and DFA from 1-minute segments of the resting phase, the beginning of exercise, maximal exercise, and the recovery phase (see [Supplemental Appendix](#) for method descriptions and [Supplemental Table 1](#) for variable listing).¹⁶ For DFA calculations, we used the conventional short-scale

ABBREVIATIONS AND ACRONYMS

CRF = cardiorespiratory fitness
DFA = detrended fluctuation analysis
DFA1 = first-order detrended fluctuation analysis
DFA1 α_1 = short-term scaling exponent of detrended fluctuation analysis with a polynomial detrending order of 1
ECG = electrocardiogram
HRR = heart rate reduction
HRV = heart rate variability
LVEF = left ventricular ejection fraction
SCD = sudden cardiac death



scaling exponent α_1 (scales 4-16)²¹ with maximally overlapping windows for better statistical properties¹⁷ and the detrending orders 1 and 2. Using maximally overlapping windows and a higher detrending order has been previously shown to improve the detection of patients with long QT syndrome.²² In addition, scale-dependent DFA,¹⁹ where the scaling exponent α is determined as a function of the scale, was used in sensitivity analyses to provide further information on the short-scale properties of the data. Thus, we also consider the scale-dependent DFA exponent $\alpha(s)$.

MAIN EXPOSURE VARIABLES. The main exposure variables in this study were DFA1 α_1 , which denotes a short-term scaling exponent of DFA with a polynomial detrending order of 1, and DFA2 α_1 , denoting a short-term scaling exponent of DFA with a polynomial detrending order of 2. Secondary exposure variables included other conventionally determined HRV measures and other significant values measured during clinical exercise testing, such as CRF, HRR, and resting heart rate.

ENDPOINT DEFINITION AND ADJUDICATION. The primary endpoint of this study was SCD, as defined by the American Heart Association/European Society of Cardiology criteria as a sudden and unexpected death owing to a cardiac cause (without any evidence or other probable cause) and occurring within approximately 1 hour from the onset of symptoms or,

if the death was not witnessed, in a person who has last been seen symptomless within 24 hours of the death.^{23,24} Patients who were witnessed to experience sudden ventricular fibrillation and hemodynamic collapse (direct cardiac cause) within 1 hour of any symptom onset but who were successfully resuscitated by a bystander and/or medical personnel were also included to the group of patients suffering an SCD. For the endpoint adjudication of SCD among patients who died, written death certificates outlining the circumstances of the deaths and specific causes of death (based on the 10th revision of the International Classification of Diseases) were received from the Causes of Death Register maintained by Statistics Finland. To identify patients who otherwise would have suffered an SCD but were successfully resuscitated, written medical records with detailed accounts of the events were reviewed. Loss to follow-up for the main endpoint data was 0%. The autopsy rate was 46% for all deaths in the FINCAVAS study.^{2,25} The adjudication committee for the definition of the cause of death comprised physicians who all reviewed the death certificates and written medical records blinded to the exercise test results. All uncertain cases were discussed until a consensus was achieved.²

STATISTICAL ANALYSIS. The association between HRV measures and SCD was tested with Fine-Gray model for calculating subdistribution hazard estimates, which account for censoring because of deaths

TABLE 1 Population Characteristics of Patients Undergoing Exercise Testing in FINCAVAS and With Applicable Data for HRV Analysis

	All Patients (N= 2,794)
Age, y	55.4 ± 12.8
Male	59.2
History of stroke	5.6
Diabetic	15.0
History of atrial fibrillation	15.9
History of myocardial infarction	26.6
Use of beta-blockers	55.2
Left ventricular ejection fraction, %	64.9 ± 14.5 ^a
Cardiorespiratory fitness, METs ^a	7.7 ± 2.9

Values are mean ± SD or percentage of total. ^aData available for 70.3% (n = 1,964 of 2,794).
 FINCAVAS = Finnish Cardiovascular Study; HRV = heart rate variability; METs = metabolic equivalents.

to other causes. Time scale in the analysis was the duration of the follow-up. All continuous variables except age were standardized to zero mean and unit variance, meaning that the HR of these measures corresponds to the risk change related to a 1-SD change in the given measure, whereas the HR for age corresponds to the risk increase in age. Proportionality assumptions were visually checked using scaled Schoenfeld residuals and formally confirmed with adding interaction term with time to the model. Only diabetes broke the assumptions with a *P* value of < 0.05.

Preliminary screening for the association between the main exposure variable (and conventional HRV parameters) and SCD was performed by analyzing the association using data obtained from different stages of the exercise testing (beginning of exercise, during maximal exercise, and recovery phase). This screening was further supplemented by dynamic DFA,¹⁹ which allows for the evaluation of the magnitude of the association as a function of scale used to determine the DFA and heart rate (in which phase of the exercise testing the measurement is performed).¹⁹ In effect, HRs for the dynamic DFA scaling exponent α were calculated as a function of both relative heart rate and dynamic DFA scale, which showed the highest association at the lowest heart rates and short scales, with significant variation between different phases of the entire exercise test (Supplemental Figure 1).

Multivariable analysis of factors associating with SCD included measures with *P* values of <0.05 in the univariable analysis. However, DFA1 α_1 was excluded

from the analysis because it is highly correlated with DFA2 α_1 but consistently showed a weaker association with SCD (and did not persist as significant when DFA2 α_1 was included in the analysis). Both root mean square of successive RR differences (RMSSD) and percentage of successive RR intervals that differ by more than 50 ms (pRR50) are calculated from successive RR interval differences, and they are also highly correlated. Only RMSSD was tested in the multivariable analysis because pRR50 is not reasonably measurable during exercise (there are no intervals with an over 50-millisecond difference during high heart rates). Sensitivity analyses were also performed by including only patients with 5-minute resting ECG available for different HRV parameter estimation and after stratification of the study sample by indications for exercise testing. Heterogeneity for associations across indication groups was tested using inverse variance method (*I*²) because many patients had >1 indication for exercise testing. For the numerical analysis, we employed Python (lifelines, pandas, numpy, matplotlib, seaborn, scikit-learn libraries). The association curves were calculated with the R rms package and subdistribution hazard models with the R cmprisk package (R Foundation).

DATA AVAILABILITY STATEMENT. The data are available in fully anonymized form for research purposes pending the approval of the study monitoring board.

RESULTS

At baseline, the mean age of participants was 55.4 ±12.8 years, and 59.2% of the study sample were men. The general characteristics are presented in Table 1. The mean follow-up time was 8.3 years (Q1-Q3: 6.4-10.5 years), during which 77 patients suffered a SCD, 6 additional patients suffered an SCD-equivalent event but were successfully resuscitated (coded as SCDs), and 378 patients died. SCDs accounted for 20.4% of all deaths.

DFA2 α_1 AND THE RISK OF SCD. After the preliminary screening, resting-phase DFA2 α_1 was observed to show the most evident association with SCD, with a clear inverse association (lower values indicating a higher risk of SCD) (see Supplemental Figure 1 and Supplemental Table 2 for preliminary screening results). This association became nonsignificant when approaching maximal levels of exertion. The patients suffering an SCD had the lowest recorded mean value for resting DFA2 α_1 when compared to the patients who

TABLE 2 Absolute Values of Different HRV Parameters (Measured From Ultra-short 1-minute Segments at Rest Before Exercise) Stratified by the Outcome During Follow-up

	Alive	Other Death	SCD	P value	
				SCD vs Alive	SCD vs Other Death
Mean RR	830.8 ± 162.2	851.8 ± 158.4	870.6 ± 181.9	0.052	0.393
SD RR	37.7 ± 28.1	38.0 ± 44.1	39.2 ± 44.1	0.750	0.824
CV RR	4.6 ± 3.6	4.5 ± 5.5	4.7 ± 5.3	0.847	0.793
RMSSD	28.6 ± 40.3	40.1 ± 65.2	44.1 ± 63.1	0.029	0.610
pRR20	29.1 ± 22.6	26.9 ± 29.5	31.7 ± 30.1	0.445	0.198
pRR50	8.1 ± 15.8	12.7 ± 25.7	14.7 ± 24.6	0.018	0.505
SD2 RR	59.2 ± 33.9	52.8 ± 45.3	53.3 ± 44.2	0.228	0.931
SD1/SD2 RR	0.3 ± 0.2	0.4 ± 0.4	0.5 ± 0.3	<0.001	0.081
DFA1 α_1	1.3 ± 0.3	1.2 ± 0.4	1.1 ± 0.4	<0.001	0.017
DFA2 α_1	1.5 ± 0.4	1.2 ± 0.4	1.1 ± 0.4	<0.001	0.019
log LF	-2.0 ± 1.4	-2.1 ± 1.6	-2.2 ± 1.8	0.314	0.930
log HF	-1.6 ± 1.3	-1.7 ± 1.6	-1.8 ± 1.7	0.316	0.924
LF/HF	0.4 ± 0.1	0.4 ± 0.1	0.4 ± 0.1	0.051	0.241

Values are mean ± SD. ^aSignificance for comparison between SCD victims and patients who were alive at the end of the follow-up. ^bSignificance for comparison between SCD victims and patients who died of other causes.

CV RR = coefficient of variation, defined as standard deviation divided by mean value; DFA1 α_1 = first-order detrended fluctuation analysis with scaling exponent; HF = high frequency; HRV = heart rate variability; LF = low frequency; pRR20 = percentage of successive RR intervals that differ by more than 20 ms; RMSSD = root mean square of successive differences; RR = RR interval; SCD = sudden cardiac death; SD1 = poincaré plot standard deviation perpendicular the line of identity; SD2 = poincaré plot standard deviation along the line of identity; SD1/SD2 RR = ratio of SD1-to-SD2.

TABLE 3 Univariable Analysis of Risk Factors for SCD in the FINCAVAS Study Calculated by Fine-Gray Analysis Accounting for Competing Events Due to Other Deaths

Features	HR	96% CI	P Value
Mean RR	1.24	0.98-1.56	0.067
SD RR	1.05	0.82-1.35	0.701
CV RR	1.03	0.80-1.34	0.792
RMSSD	1.19	1.07-1.34	0.002
pRR20	1.13	0.88-1.44	0.347
pRR50	1.27	1.09-1.48	0.002
SD2 RR	0.86	0.62-1.19	0.038
SD1/SD2 RR	1.36	1.25-1.48	<0.001
DFA1 α_1	0.56	0.48-0.65	<0.001
DFA2 α_1	0.41	0.33-0.50	<0.001
log LF	0.89	0.69-1.15	0.376
log HF	0.89	0.68-1.16	0.381
LF/HF	0.86	0.75-0.998	0.027
HRR	0.62	0.52-0.75	<0.001
CRF, METs	0.53	0.41-0.70	<0.001
Age, y	1.03	1.01-1.04	0.003
Female	0.44	0.27-0.74	0.002
Use of beta blockers	3.23	1.88-5.58	<0.001
History of stroke	1.96	0.99-3.89	0.055
Prevalent diabetes (any)	2.69	1.71-4.24	<0.001
Prevalent atrial fibrillation	2.02	1.26-3.26	0.004
History of myocardial infarction	4.98	3.18-8.81	<0.001

CRF = cardiorespiratory fitness; HRR = heart rate reduction; other abbreviations as in Tables 1 and 2.

died of other causes ($P = 0.019$) or to those who were alive at the end of the follow-up ($P < 0.001$) (Table 2).

Before any adjustments, a 1-SD higher resting DFA2 α_1 corresponded with an HR of 0.41 for SCD (95% CI: 0.33-0.50, $P < 0.001$) (Table 3). Inversely, this corresponds to a 2.4 (95% CI: 2.0-3.0) times higher risk for a 1-SD lower DFA2 α_1 value in among these patients. DFA1 α_1 computed with linear detrending, which is highly correlated with DFA2 α_1 , showed a similar but weaker association with SCD (Tables 2 and 3). In the multivariable analysis, adjusted with the significant risk factors for SCD in univariable analysis (age, sex, use of beta-blockers, history of stroke, diabetes, atrial fibrillation, history of myocardial infarction, CRF and HRR), the association between DFA2 α_1 and SCD remained highly significant (HR: 0.45; 95% CI: 0.31-0.65; $P < 0.001$) (Table 4). This association persisted despite adjusting for left ventricular ejection fraction (LVEF) (HR: 0.39; 95% CI: 0.25-0.61; $P < 0.001$ when LVEF was included in the model as a continuous variable; and HR: 0.41; 95% CI: 0.26-0.62; $P < 0.001$ when LVEF was included in the model as a dichotomous variable, with stratification by LVEF value of 35%). The unadjusted association curve depicting the SCD risk associated with different values of DFA2 α_1 is presented in Figure 2. The main finding is presented in the Central Illustration.

In univariable analyses, only a few of the conventional HRV parameters associated significantly with the risk of SCD during the resting phase (Tables 2 and 3). Some of the conventional HRV parameters also showed significant and stronger associations with SCD in the univariable analyses when they were measured during the recovery phase or during the final stages of the exercise (Supplemental Table 2). However, none of these HRV parameters remained as significant risk factors for SCD when the analyses were adjusted for other risk factors, and none of them showed similar association magnitudes to that of DFA2 α_1 (Supplemental Tables 2 and 3).

In sensitivity analyses, we also repeated the analysis by measuring same HRV variables in resting ECG but among patients with at least 2 minutes or 5 minutes of recorded resting ECG with no apparent changes in the results (Supplemental Tables 4 and 5). Furthermore, limiting analyses to only cases with true fatal SCD ($n = 77$) did not change the results in any significant manner (data not shown). When the association between DFA2 α_1 and SCD was analyzed separately by stratifying the study sample by indication for exercise testing (individual patients could have >1 indication), no indication of significant

heterogeneity in the association magnitude was observed ($I^2 = 12.3\%$; $P = 0.337$ for heterogeneity in meta-analysis of coefficients) (Supplemental Table 6).

DFA2 α_1 AND SCD IN DIFFERENT SUBGROUPS OF PATIENTS. Several subgroupings were performed to screen for potentially significant interactions between DFA2 α_1 and other SCD risk factors. At baseline, resting-phase DFA2 α_1 associated significantly with several cardiovascular risk factors (Figure 3). The association between resting-phase DFA2 α_1 and SCD after stratification by these risk factors is presented in Figure 4. According to interaction testing, the association was not significantly altered by sex, the use of beta-blockers, history of stroke, diabetes, atrial fibrillation, history of myocardial infarction or by CRF ($P > 0.05$ for all) (Figure 4).

SCALE-DEPENDENT DFA AND THE RISK OF SCD IN SENSITIVITY ANALYSIS. The short-scale scaling exponent of DFA, conventionally determined for 4-16 consecutive RR intervals, may not be the optimal scale to capture the physiological differences between the subgroups. DFA can be further improved by calculating the scale-dependent $\alpha(s)$ as a derivative of the logarithmic fluctuation function¹⁹ by employing maximally overlapping windows for each scale. The optimal scale for DFA2 $\alpha(s)$ was found to be in the range of 7-9, with HR estimates of <0.4 and the narrowest associated CIs (Supplemental Figure 2).

DISCUSSION

The results of the present study reveal a robust association between SCD and a novel nonlinear HRV method (DFA2 α_1). In a prospective cohort of patients undergoing clinical exercise testing, we observed that 1-SD lower DFA2 α_1 at rest before the exercise is associated with a ~2.4 times higher risk of SCD. This association persisted despite adjusting for other major predictors of SCD (including LVEF) and was similar in all subgroup analyses (See Central Illustration). Conventional HRV parameters showed only weak nominal associations with SCD.

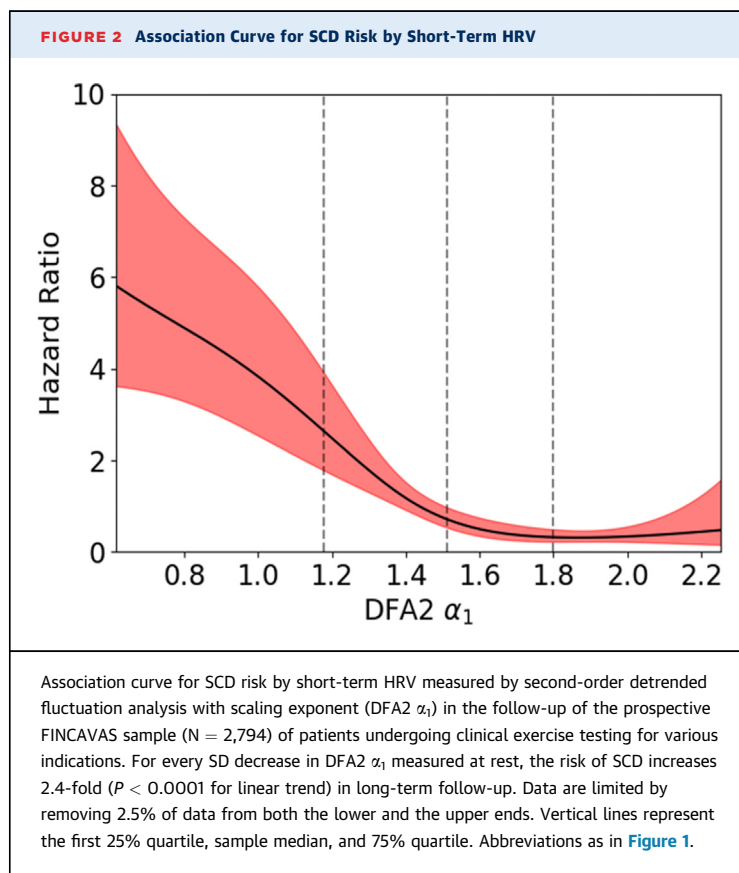
Different conventional measures of HRV determined from 24-hour Holter recordings have been previously linked with SCD or arrhythmic death in small series of myocardial infarction survivors and patients with heart failure treated in the 1980s and 1990s.¹⁰⁻¹⁵ In line with this, the observations of the ARTEMIS (The Innovation to Reduce Cardiovascular Complications of Diabetes at the Intersection) study have shown that conventional HRV measures, and DFA1 α_1 , are associated with the risk of SCD and

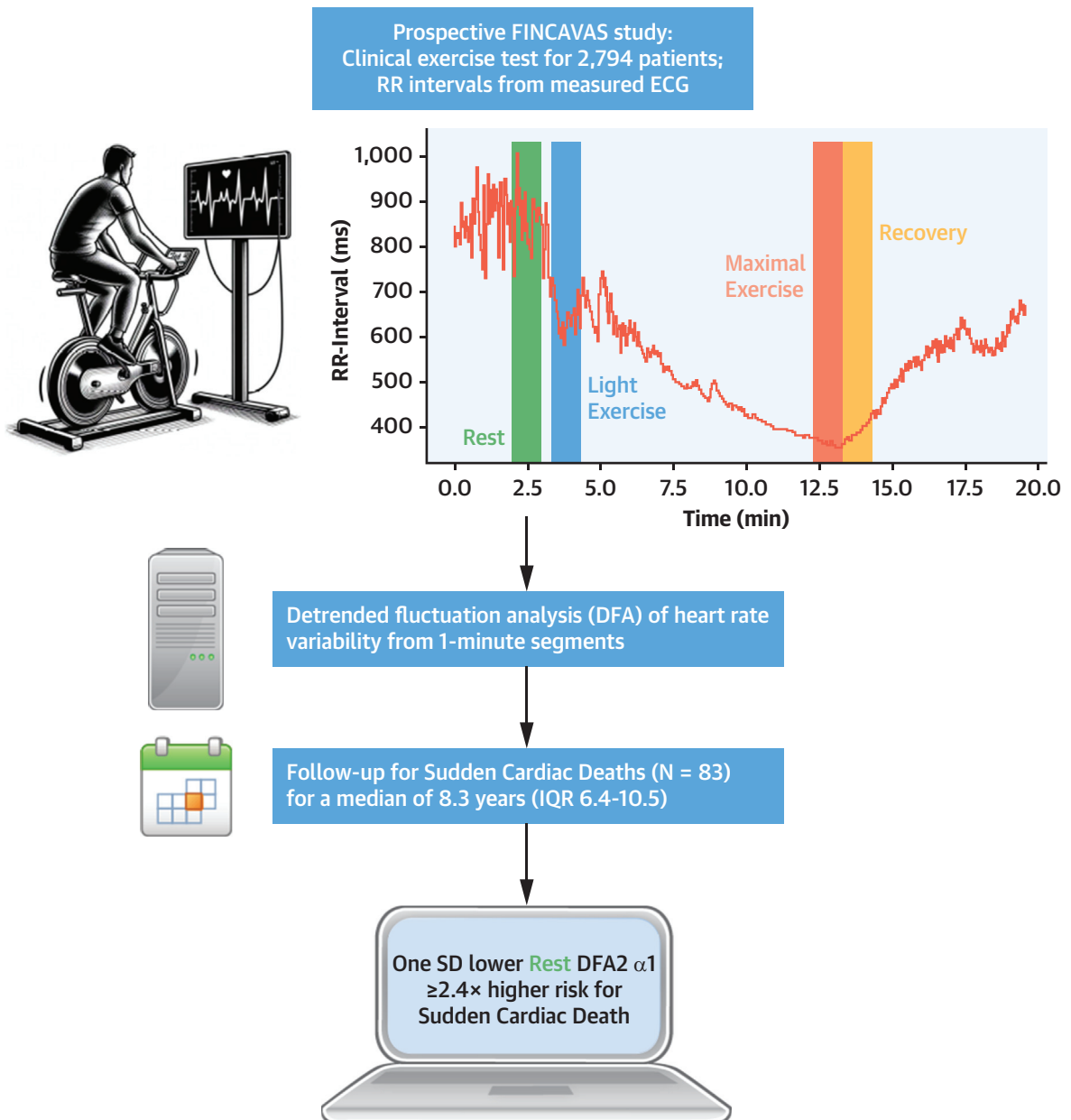
TABLE 4 Multivariable Analysis of Risk Factors for SCD in FINCAVAS Calculated by Fine-Gray Analysis Accounting for Competing Events Due to Other Deaths

Features	HR	95% CI	Sig
Mean RR	1.04	0.84-1.29	0.716
RMSSD	0.96	0.80-1.15	0.663
SD1/SD2 RR	0.95	0.77-1.17	0.643
DFA2 α_1	0.45	0.31-0.65	<0.001
HRR	0.83	0.65-1.06	0.127
CRF, METs	0.73	0.53-1.0	0.059
Age, y	0.98	0.96-1.00	0.017
Female	0.61	0.35-1.10	0.096
Use of beta-blockers	1.06	0.57-1.96	0.855
History of stroke	1.00	0.48-2.08	0.995
Prevalent diabetes (any)	1.35	0.83-2.21	0.224
Prevalent atrial fibrillation	1.51	0.91-2.53	0.113
History of myocardial infarction	3.13	1.86-5.26	<0.001

Abbreviations as in Tables 1-3.

sudden cardiac arrest among patients with angiographically verified coronary artery disease.⁹ The association between SCD and DFA1 α_1 has later been indirectly replicated using data from the SCD-HeFT (Sudden Cardiac Death in Heart Failure Trial), in which DFA1 α_1 was seen to associate with the



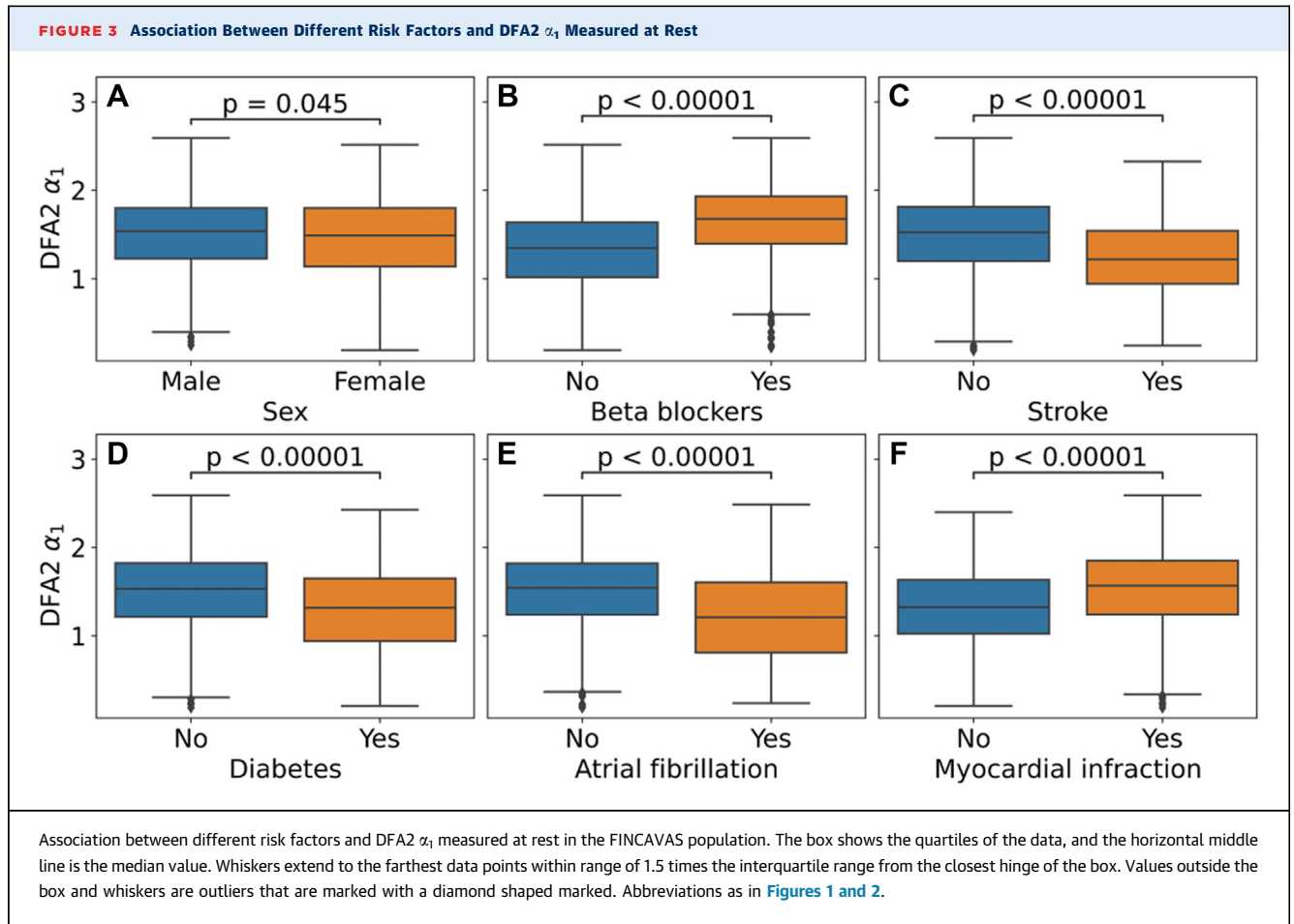
CENTRAL ILLUSTRATION Association Between Long-Term Sudden Cardiac Death and Heart Rate Variability, Measured in Different Stages of Exercise Testing

Hernesniemi JA, et al. *JACC Clin Electrophysiol.* 2024;10(9):2010-2020.

The association between long-term sudden cardiac death and heart rate variability and measured by nonlinear second-order detrended fluctuation analysis with scaling exponent (DFA2 α_1) in different stages of the exercise testing with strongest (and inverse) association observed for DFA2 α_1 values measured at rest. ECG = electrocardiography; FINCAVAS = Finnish Cardiovascular Study.

incidence of ventricular arrhythmias requiring implantable cardioverter-defibrillator shocks.²⁶ In the ARTEMIS study, the magnitudes of the associations were modest at best, with estimated adjusted risk

increases ranging from 15% to 27%, corresponding to 1-SD changes in HRV parameter values (most of these linear associations were not statistically significant).⁹ These results are almost exactly in line with the

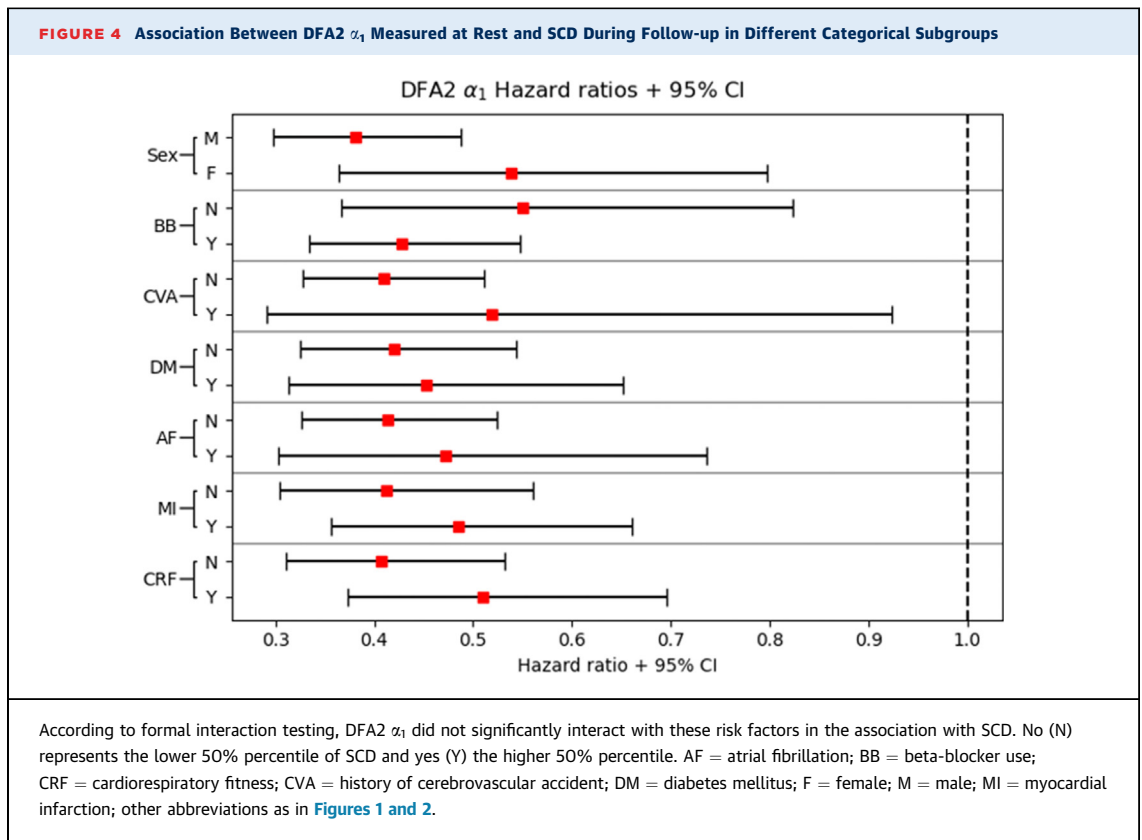


results of the large general population-based ARIC (Atherosclerosis Risk in Communities) study in which similar changes in conventional HRV measures were associated with an adjusted 16% 27% increased risk of SCD.⁸ Due to the modest overall quantity of positive findings and magnitude of the observed associations, these conventional HRV parameters have not been incorporated into clinical use.

Comparing the results of the present study to previous observations, a distinct difference can be seen. In terms of relative risk, the association between resting-phase ultra-short-term DFA2 α_1 and SCD is very strong compared to the previous findings on the association between SCD and the conventional HRV parameters—also including DFA1 α_1 . Besides the possibility of a novel method (DFA2 α_1) being a comparatively superior predictor of SCD, differences in study protocols and populations and study samples of patients are likely to explain some of the discrepancies. Usually, as was done in the ARTEMIS study and in all previous post-myocardial infarction studies, HRV parameters were measured using the

entire 24-hour recording.^{9,11,13-15} Confounding may be caused by the fact that HRV can vary greatly within even the standard 24-hour cycle, depending on changes in physical activity, sleep quantity and quality, and the level of emotional stress. In the present study—using dynamic DFA¹⁹ as a preliminary screening method—we observed major changes in the association between DFA2 α_1 and SCD depending on the measurement phase (rest, exercise, recovery) and the scale (number of consecutive RR intervals), with the strongest association observed with the conventionally used short scale. Similarly, the weaker associations between conventional HRV parameters and SCD also seemed context specific.

The observations made in the present FINCAVAS study sample have clear implications. Evaluating possible SCD risk, the use of DFA2 α_1 as a method enables the utilization of simple (and short-interval) resting measurements instead of resorting to exercise testing. Furthermore, exercise and the associated movement artifacts usually have a higher probability of resulting in poor signal quality and confounding



the HRV measurement. Our observations may facilitate clinical practice and enable the use of wearable devices through, for example, photoplethysmography. Accelerometers in wearable consumer devices can easily distinguish between the states of physical activity and rest and perform the measurement when applicable.²⁷ Unfortunately, in our data set, we did not have Holter data available, which would have allowed for a longer dynamic (time-dependent) analysis with dynamic DFA and more extensive testing for association between conventional HRV parameters and SCD. However, according to our sensitivity analyses, using standard 5-minute segments for conventional HRV measures or for DFA did not result in any significant change in the results.

In this proof-of-concept study, we applied clear a priori-defined criteria for data filtering to use only the best possible data for determining the HRV parameters. This step resulted in approximately 11% ($n = 344$) of otherwise eligible patients being excluded from the study (including 13% of incident SCD cases). In data filtering, patients with ECG recordings containing too many extrasystoles of ectopic origin owing to any cause are usually excluded.

In real life, when estimating HRV by any method, this would not be a problem, because continuous data can be easily acquired with any mobile application of a medical device, given that the measurement is extended slightly longer than in normal exercise testing. Unfortunately, we are unable to compare the data filtering protocols between our study and most previous ones because they have not been routinely published. Generally, in studies using 24-hour Holter data, filtering may be a less significant issue if a sufficient number of RR intervals in continuous segments are available for the analysis from the entire recording.

STUDY LIMITATIONS. Our results are not directly applicable to the general population because all the patients in the FINCAVAS study were assigned to undergo clinical exercise testing due to clinical indications. Therefore, this association should be replicable in other studies (and other study samples) with comparable data on the incidence of SCD. Conversely, the inherent strength of the present study is that we were also able to test the association across all relevant subgroups of patients. Conventional HRV parameters and DFA2 α_1 are highly associated with age, the use of beta-blockers, diabetes,

and the presence of atrial fibrillation, and stratification along these parameters is pivotal when assessing the applicability of any HRV parameter. Importantly, our results also show that the association between DFA and SCD is independent of CRF, which is highly associated with not only the risk of SCD but also with overall prognosis and functional capacity. According to our results, DFA also associates with the risk of SCD among patients with average or good CRF—a group of patients who are specifically ideal for targeted interventions to prevent SCD.

CONCLUSIONS

The results of this prospective study of consecutive patients undergoing clinical exercise testing demonstrate that a novel method of measuring HRV—acquired from an only 1-minute ECG signal—is a very robust predictor of SCD regardless of CRF, LVEF, or clinically significant risk factors for SCD.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

FINCAVAS has been financially supported by the Competitive Research Funding of Tampere University Hospital (grants 9M048 and 9N035); the Finnish Cultural Foundation; the Finnish Foundation for Cardiovascular Research (to T.L.); the Emil Aaltonen Foundation; the Tampere Tuberculosis Foundation, EU Horizon 2020 (grants 755320 for TAXINOMISIS and 848146 for To Aition); and the Academy of

Finland (grant 322098). Additional funding has been also granted by Business Finland, R2B Funding 2022-23 (to E.R). The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE 1: Ultra-short-term HRV can be measured by conventional or by nonlinear method by DFA in different stages of clinical exercise testing even from 1-minute time intervals.

COMPETENCY IN MEDICAL KNOWLEDGE 2: DFA measuring HRV at rest is a powerful predictor of long-term SCD risk. Measuring HRV during exercise does not seem to yield stronger associations between HRV and SCD.

TRANSLATIONAL OUTLOOK: DFA identified as a potential risk marker for SCD is easy to measure from continuous ECG recordings or even from data collected by mobile devices using photoplethysmography. Given the large magnitude of the association, this risk marker could prove very useful in identifying high-risk individuals in interventional studies aimed to decrease mortality due to SCD.

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KEY WORDS detrended fluctuation analysis, exercise testing, heart rate variability, sudden cardiac death

APPENDIX For supplemental methods, references, figures, and tables, please see the online version of this paper.