ORIGINAL ARTICLE

Heart Rate Variability Density Analysis (*Dyx*) and Prediction of Long-Term Mortality after Acute Myocardial Infarction

Rikke Mørch Jørgensen, M.D.,* Steen Z. Abildstrøm, M.D., Ph.D.,† Jacob Levitan, Dr. Scient.,‡ Roi Kobo, B.Sc.,‡ Natalia Puzanov, Ph.D.,‡ Meir Lewkowicz, Dr. Scient.,‡ Heikki Huikuri, M.D.,§ Mirja Peltola, M.Sc.,§ Jens Haarbo, M.D., Ph.D.,* and Poul Erik Bloch Thomsen, M.D., Ph.D.¶, on behalf of the Nordic ICD pilot study group

*From the *Department of Cardiology, Copenhagen University Hospital Gentofte, Denmark; †Department of Cardiology, Bispebjerg Hospital, Copenhagen, Denmark; ‡Department of Physics, Ariel University, Samaria, Israel; §Department of Internal Medicine, University of Oulu, Finland; and ¶Department of Cardiology, Aalborg University Hospital, Aalborg, Denmark*

Aims: The density HRV parameter *Dyx* is a new heart rate variability (HRV) measure based on multipole analysis of the Poincaré plot obtained from RR interval time series, deriving information from both the time and frequency domain. Preliminary results have suggested that the parameter may provide new predictive information on mortality in survivors of acute myocardial infarction (MI). This study compares the prognostic significance of *Dyx* to that of traditional linear and nonlinear measures of HRV.

Methods and results: In the Nordic ICD pilot study, patients with an acute MI were screened with 2D echocardiography and 24-hour Holter recordings. The study was designed to assess the power of several HRV measures to predict mortality. *Dyx* was tested in a subset of 206 consecutive Danish patients with analysable Holter recordings. After a median follow-up of 8.5 years 70 patients had died. Of all traditional and multipole HRV parameters, reduced *Dyx* was the most powerful predictor of all-cause mortality (HR 2.4; CI 1.5 to 3.8; $P < 0.001$). After adjustment for known risk markers, such as age, diabetes, ejection fraction, previous MI and hypertension, *Dyx* remained an independent predictor of mortality ($P = 0.02$). Reduced *Dyx* also predicted cardiovascular death ($P < 0.01$) and sudden cardiovascular death ($P = 0.05$). In Kaplan–Meier analysis, *Dyx* significantly predicted mortality in patients both with and without impaired left ventricular systolic function ($P < 0.0001$).

Conclusion: The new nonlinear HRV measure *Dyx* is a promising independent predictor of mortality in a long-term follow-up study of patients surviving a MI, irrespectively of left ventricular systolic function.

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heart rate variability; *Dyx*; multipoles; Poincaré plot; myocardial infarction

Mortality after acute MI remains substantial despite improved treatment regimens with β-blockers, statins, ACE inhibitors, and early revascularization.[1–3] There is an urgent need for improved risk-stratification, in order to determine which survivors of MI are likely to benefit from treatment with an Implantable Cardioverter Defibrillator (ICD).

Several heart rate variability (HRV) measurements have been shown to predict mortality in survivors of MI.[4–8] However, when tested prospectively in the early phase after MI,[9] they

Address for correspondence: Rikke Mørch Jørgensen, M.D., Department of Cardiology, Copenhagen University Hospital Gentofte, Sygehus Nord, Køgevej 7-13, 4000 Roskilde, Denmark. E-mail: mojo@dadlnet.dk

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have failed to show a clinical significant value in predicting arrhythmic death.

In the present study we compare a new HRV parameter *Dyx*, derived by multipole analysis, with some of the more traditional linear and nonlinear HRV methods, in order to improve risk stratification beyond estimation of left ventricular ejection fraction (LVEF).[10] The multipole method is a new HRV analysis, investigating the Poincaré plot, where RR intervals, obtained from Holter recordings, are plotted as a function of previous RR intervals.[11,12] Each data point is assigned a unit mass, and the mass density distribution within the plot is calculated, thereby computing exact measures that are essential in describing the features of the heart rate dynamics resulting from nonlinear processes, that are not easily detected by linear measures.

Consecutive patients with an acute MI screened for the Nordic Implantable Cardioverter-Defibrillator Pilot Study (Nordic ICD pilot study),[13,14] were Holter-monitored for 24 hours, and data were analyzed by the multipole method. The predictive value of the new HRV parameter *Dyx* was compared to that of well-known clinical risk factors as well as traditional HRV measures.

METHODS

Population

The Nordic ICD pilot study ($n = 697$) was conducted in five Nordic hospitals from 1996 to 1998 and was designed to assess the power to predict mortality of several HRV measurements and left ventricular systolic function in patients surviving acute MI. The results have been reported previously.[13,14]

Patients admitted to hospital with an enzyme verified acute MI, were screened consecutively, and enrolled in the study within the first 7 days post-MI. Patients who died before discharge or had coronary artery bypass surgery (CABG) performed before measurements were excluded from the analyses. Patients were followed for 2 years, with telephone calls at 6, 12, and 24 months after the acute MI. In the present substudy, we performed a long-term follow-up with regard to mortality in the Danish subset of patients ($n = 303$).

Echocardiography

Left ventricular systolic function was measured with 2D echocardiography at day 2–7 post-MI. Measures of LVEF were based on wall motion index scoring as previously described.[15,16]

Holter Recordings

Holter recordings were performed using an ambulatory 2-channel ECG recorder (Polar Electro Co. Ltd., Kempele, Finland)[17] with an RR interval sampling frequency of 1000 Hz for 24 hours. The Holter recordings were performed between day 5 and 14. The data were edited manually as previously described.[18,19] HRV analyses were performed on RR interval data including only sinus beats. RR intervals longer than 2500 ms and technical artifacts were excluded. Recordings with less than 18 hours of data or less than 85% of qualified sinus beats were excluded.

For multipole analyses, RR intervals from the entire recording period were plotted against the preceding RR interval in a Poincaré plot after detrending.

Reasons for not obtaining or excluding Holter recordings were technical failure in 21 patients, atrial fibrillation (or other nonsinus rhythm) in nine patients and CABG prior to discharge in eight patients. A group of 16 patients died or were discharged prior to recording and 9 patients refused to participate. In 34 patients the reason for not obtaining a Holter recording was unaccounted for.

Time Domain Analyses of HRV

The standard deviation of all normal-to-normal RR intervals (SDNN) was computed as standard time domain measures from the entire recording period and analyses were performed as recommended by the task force.[20]

Detrended Fluctuation Analysis

The detrended fluctuation analysis (DFA) technique was used to quantify the fractal scaling properties of short-term RR interval time series (α_1). The root-mean-square fluctuation of integrated and detrended time series is measured at different observation windows and plotted against the size of the observation window on a log–log scale. Details of this method have been described elsewhere.[5,21]

Poincaré Dimension

SD12 is described as an intermediate term nonlinear HRV measure derived from the Poincaré plot of RR interval time series.[4,22–25] SD12 is the ratio between length (SD2) and width (SD1) of an imaginary ellipse fitted to the Poincaré plot with the center in the average RR interval.

The length (*L*) of the plot is considered a measure of overall variability and is calculated by $L = 2$ SDRR. The width (*W*) of the plot is considered to be a measure of short-term variability and correlate highly with high frequency (HF) spectral power. Width can be calculated by $W = \sqrt{2}$ SDSD (standard deviation of successive differences).

The Multipole Method

The multipole method has been described in detail elsewhere.[11,12] Briefly, the multipole HRV analysis is a new way of investigating the Poincaré Plot from complex time series. We interpret the Poincaré Plot as a two dimensional body, where each data point in the plot is assigned a unit mass, in order to describe the total mass distribution within the plot (Figs. 1A and 1B). The measures obtained from this kind of analyses bear intrinsic time dependence due to the very construction of the plot as opposed to linear measures, SDNN which does not include any time ordering (shuffling the RR intervals lead to the same value for SDNN). As a result the multipole method, as do other Poincaré plot indices, derives information from both the time and frequency domains as well as reflecting increased randomness in the RR interval time series. From the detrended RR time series we calculated different multipoles; quadrupoles, octupoles, and hexadecapoles, and from the latter we derived the new HRV parameter *Dyx*. Quadrupoles (*Qxx* and *Qyy*) describe the overall distribution of data points in the Poincaré Plot, that is, the shape of the plot. Octupoles (*Txxx*) measures the skewness of data points within the plot. Hexadecapoles are used to describe the peak (kurtosis) of the RR interval distribution curve along the axes of the plot. The density ratio *Dyx* is derived from the kurtosis and calculates the ratio between the peak-density on the *y*-axis (*dy*) and the *x*-axis (*dx*), respectively.

Endpoints

Endpoints were all-cause mortality, cardiovascular death and sudden cardiovascular death. All deaths were classified using information from death certificates, hospital records and/or autopsy reports.

At first, death was classified as cardiovascular or due to other conditions. If the documentation was inadequate or unclear, the cause of death was classified as unknown.

Second, cardiovascular death was classified as sudden or nonsudden. Death was defined as sudden or presumed arrhythmic, if it was (1) witnessed death occurring within 60 minutes of onset or worsening of symptoms; (2) death during sleep, in the absence of preexisting symptoms when the patient was known to have been alive within 12 hours prior to the recorded time of death; (3) death during attempted resuscitation; (4) death after a period of coma, following resuscitated cardiac arrest.[26,27]

Statistical Analyses

All HRV parameters and clinical data were used as explanatory variables in univariable comparisons, performed with the chi-square test for categorical variables and Wilcoxon rank-sum for continuous variables. Cox proportional hazards regression analysis was used to assess the association between different risk predictors and mortality using SAS for Windows version 9.1. For all continuous risk variables the cutoff points were chosen as the value defining the high-risk tertile. Each variable was tested, first univariately and then retested with adjustment for known risk factors in the Cox regression model. All variables that entered the multivariable regression analysis were tested for interactions with the multipole parameters. Prognostic power of the HRV parameters were assessed by plotting sensitivity and 1-specificity as ROC curves, quantifying the area under the curve (AUC) as the integral. Differences in AUC were tested with nonparametric tests.

P values ≤ 0.05 were considered significant. Kaplan–Meier estimates of the cumulative survival from baseline to death and log-rank analysis to compare survival curves for the dichotomized HRV variables were performed. Correlations between

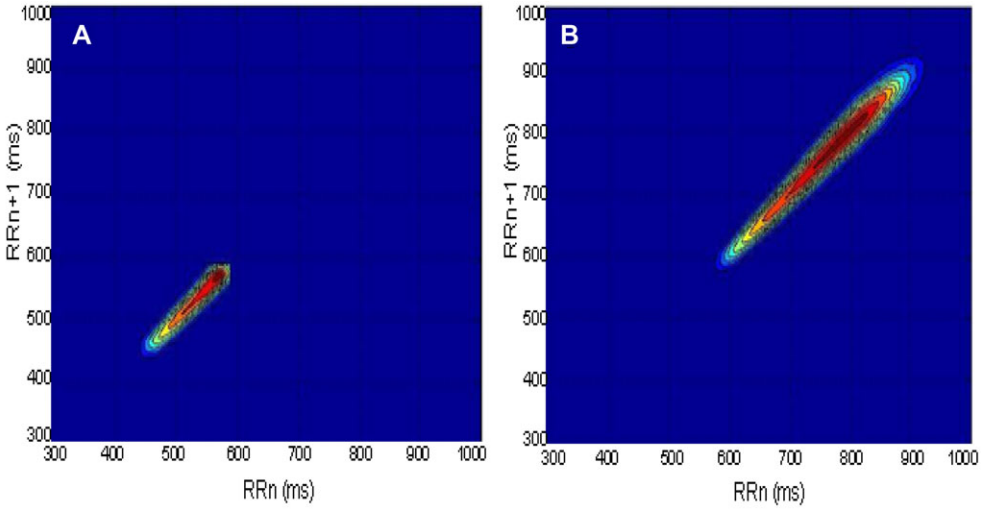

Figure 1. Poincaré plots of RR intervals from two study patients suffering acute MI. (A) Patient who suffered cardiovascular death. LVEF 24%, *Dyx* 1.79. (B) Long-term survivor. LVEF 9% *Dyx* 5.12.

all HRV variables were tested and expressed as Pearson's correlation coefficients. Positive and negative predictive values for all HRV variables were analyzed, considering the decreasing number of endpoints in each subgroup.

RESULTS

In the Nordic ICD pilot study a total of 303 Danish patients were included and 206 of these had an analyzable Holter recording. After a median follow-up period of 8 (0–9.3) years, 70 patients had died; 41 (59%) deaths were classified as nonsudden cardiovascular deaths, 17 (24%) as sudden cardiovascular death, and 12 (17%) as noncardiovascular death. Fourteen patients received a prophylactic ICD according to protocol.

Baseline characteristics (Table 1) for patients who died and remained alive reveals that patients who died during follow-up were significantly older, had lower LVEF and more often diabetes.

Both Mean RR interval, α_1 and the multipole HRV parameters showed significant differences in patients that died during follow-up as compared to those who stayed alive. (Table 2).

Univariable Analyses

In Cox regression analyses (Table 3) the demographic variables; age, diabetes, previous MI and low LVEF predicted all-cause mortality. Cardiovascular death was predicted by age, diabetes and low LVEF and the 17 sudden cardiovascular deaths were predicted only by history of hypertension and low LVEF.

Among the tested HRV variables, all multipole parameters significantly predicted all-cause mortality. Most powerful was *Dyx* with hazard ratio (HR) 2.4 and 95% confidence interval (CI) 1.5–3.8 (P = 0.0003). Neither SDNN, α_1 nor the Poincaré index SD12 reached statistical significance. Cardiovascular death was predicted by *Qyy*, *Qxx*, and *Dyx*. Finally there was a trend toward predicting sudden cardiovascular death for *Dyx* with a P value of 0.05, whereas all other tested HRV parameters failed.

In Kaplan–Meier survival analysis (Figs. 2A–C) Dyx predicted a significant difference in survival rates for all-cause mortality (P = 0.0002), cardiovascular death (P = 0.001) and for sudden cardiovascular death (P = 0.03).

When the follow-up period was dichotomized at 5 years, *Dyx* still predicted all-cause mortality.

Multivariable Analyses

When adjusting for known clinical risk variables (Table 3), *Dyx* was the only HRV parameter that continued to hold independent predictive information on both all-cause mortality (HR 1.9 CI 1.1–3.5) and cardiovascular death (HR 2.1 CI 1.0–4.5). HR for *Dyx* predicting sudden cardiovascular death was 2.7 (CI 0.7–8.3), but did not reach statistical significance. There were no interactions between *Dyx* and other variables entered in

Table 1. Baseline Clinical Variables for Patients Dead or Alive, after a Median Follow-Up of 8.5 Years

	All Patients (n = 206)	Alive (n = 136)	Dead (n = 70)
Male sex	149 (72%)	102 (75%)	47 (67%)
Age (years)	62 (54–69)	61 (52–66)	68 (61–71)§
LVEF (%)	48 (36–54)	51 (42–57)	42 (33–51)§
NYHA III-IV	6 (3%)	3 (2%)	3 (4.5%)
Hypertension	53 (26%)	30 (23%)	23 (33%)
Diabetes mellitus	24 (12%)	8 (6%)	16 (23%)§
Previous MI	45 (22%)	25 (18%)	20 (29%)
Q-wave MI	103 (53%)	65 (50%)	38 (57%)
Anterior MI	81 (43%)	57 (45%)	24 (39%)
Thrombolytic therapy	98 (49%)	67 (50%)	31 (45%)
β-blockers	106 (52%)	77 (58%)	29 (42%)*
ACE inhibitors	69 (34%)	36 (27%)	33 (48%)+

Age and LVEF presented by the median (25th and 75th percentile). P values calculated with chi-square test for categorical variables and Wilcoxon rank-sum for continuous variables. *P < 0.05, +P < 0.01, §P < 0.001 for differences between patients alive and dead.
NYHA = New York Heart Association class; MI = myocardial infarction.

Table 2. Baseline HRV Variables for Patients Alive and Dead, and AUC

	All Patients (n = 206)	Alive (n = 136)	Dead (n = 70)	AUC (n = 206)
Traditional HRV				
Mean RR ms	801 (740; 927)	852 (746; 952)	785+ (731; 839)	0.61
SDNN ms	91 (65; 108)	92 (67; 110)	89 (64; 105)	0.54
α_1	0.95 (0.89–1.05)	0.97 (0.89–1.07)	0.92* (0.86–1.0)	0.61
SD12	0.16 (0.12–0.19)	0.15 (0.13–0.19)	0.16 (0.12–0.20)	0.49
Multipole HRV				
Qxx ms^2	3783 (2355–8052)	4207 (2670–9116)	3357+ (1765–6052)	0.61
Qyy ms^2	−1670 (−3642; −993)	−1888 (−4209; −1147)	−1443+ (−2868; −777)	0.61
Txxx ms^3/10^3	−144 (−775; 2)	−240 (−838; −21)	−61+ (−380; 24)	0.62
Dyx	3.1 (2.5; 3.7)	3.2 (2.7; 3.7)	2.8+ (2.3; 3.5)	0.63

All values presented as median value (25th; 75th percentile). P values calculated by Wilcoxon rank-sum.
*P < 0.05, +P < 0.01 for differences between survival and all-cause mortality. α_1 = scaling exponent analyzed by detrended fluctuation analysis; SD12 = Poincaré dimension SD1/SD2; *Qyy* and *Qxx* = quadrupole moments on *x*- and *y*-axis = respectively; *Txxx* = octupole moment on *x*-axis; *Dyx* = density ratio *Dy*/*Dyx*; AUC = area under receiver operating characteristics curve.

the multivariable model. *Dyx* was significantly correlated to all HRV variables although the correlations were weak, with an r^2 value of 0.38 between *Dyx* and α_1 being the strongest.

Additional Analyses

In ROC analysis, *Dyx* had the largest AUC of 0.63 (P < 0.0001), but was not significantly better than the other HRV parameters (Table 2).

When dichotomized according to the high risk tertile, the positive (PPV) and negative predictive (NPV) value of *Dyx* in predicting all-cause mortality was 50% and 75%, respectively. For cardiovascular death PPV was 31% and NPV 86%. Regarding sudden cardiovascular death *Dyx* reached a PPV of 13% and a NPV of 94%.

The predictive value of LVEF in combination with *Dyx* is illustrated in Kaplan–Meier analysis. Patients were divided in two groups based on LVEF and the predictive value of *Dyx* was tested in each group. Reduced values of *Dyx* (≤2.77) predicted a significant increased risk of death in each group and the analysis identified a high risk group of patients with the combination of reduced *Dyx* and depressed LVEF, a group with intermediate risk as well as a low risk group with the combination of preserved LVEF and normal *Dyx* (Fig. 2D).

DISCUSSION

The main finding of this long-term follow-up study was that the HRV parameter *Dyx*, independently predicted all-cause and cardiovascular

Table 3. Predictors of Mortality: Results of Univariable and Multivariable Analyses

	All-Cause Mortality		Cardiovascular Death		Sudden Cardiovascular Death	
	HR (95% CI)	**P**	**HR (95% CI)**	**P**	**HR (95% CI)**	**P**
Univariable analyses						
Traditional HRV						
Mean RR ≤ 761 ms	1.5 (0.9–2.4)	NS	1.7 (0.9–3.2)	0.09	1.9 (0.7–5.0)	NS
SDNN ≤ 77 ms	1.1 (0.6–1.7)	NS	1.3 (0.7–2.4)	NS	1.1 (0.4–3.0)	NS
SD12 ≥ 0.18	0.9 (0.6–1.6)	NS	0.5 (0.3–1.2)	NS	1.1 (0.4–2.9)	NS
α_1 ≤ 0.91	1.6 (1.0–2.5)	0.06	1.3 (0.7–2.5)	NS	1.1 (0.4–3.0)	NS
Multipole HRV						
Qyy ≥ −1209 ms^2	1.7 (1.1–2.7)	0.03	2.4 (1.3–4.4)	<.01	2.0 (0.8–5.1)	NS
Qxx < 2798 ms^2	1.7 (1.0–2.7)	0.03	2.3 (1.3–4.3)	<.01	1.5 (0.6–4.0)	NS
Txxx ≥ −35 ms^3/10^3	1.8 (1.1–2.9)	0.02	1.7 (0.9–3.2)	0.08	0.9 (0.3–2.6)	NS
Dyx ≤ 2.77	2.4 (1.5–3.8)	<.001	2.7 (1.5–5.0)	<.01	2.6 (1.0–6.7)	0.05
Multivariable analyses						
Multipole HRV						
Qyy ≥ −1209 ms^2	1.1 (0.6–1.9)	NS	1.5 (0.7–3.1)	NS	1.7 (0.6–5.2)	NS
Qxx < 2798 ms^2	1.0 (0.6–1.9)	NS	1.4 (0.7–3.0)	NS	1.2 (0.4–3.8)	NS
Txxx ≥ −35 ms^3/10^3	1.1 (0.6–1.9)	NS	1.0 (0.5–2.1)	NS	0.6 (0.2–1.9)	NS
Dyx ≤ 2.77	1.9 (1.1–3.5)	0.02	2.1 (1.0–4.5)	0.05	2.7 (0.7–8.3)	0.09

All values obtained by Cox regression analyses after dichotomization. Variables that reached P values ≤0.05 in univariable analyses entered a multivariable model with adjustment for age, diabetes, ejection fraction, previous MI, hypertension and medication. NS, P values >0.1; HR = Hazard Ratio; CI = confidence interval. Abbreviations for HRV parameters as in Table 2.

mortality in a population of post-MI patients with both depressed and preserved LVEF. Furthermore, *Dyx* distinguished between a high and a low-risk group of patients when calculating cumulative mortality rates for sudden cardiovascular death.

Several studies have investigated the Poincaré plot of RR interval time series.[4,22,24,28] It is well established that there is a strong correlation between standard time and frequency domain measurements and Poincaré indices. SDNN correlates with the length of the Poincaré plot along the line of identity, describing the overall RR interval variability or total spectral power and this again correlates to our new measures *Qyy* and *Qxx*. The width of the plot measured on the axes vertically to the line of identity is correlated to rMSSD and HF power, describing short-term variability attributed to parasympathetic tone.

Increased SD12 (SD1/SD2) has been shown to predict mortality in post-MI patients.[24,29] *Dyx* compares to SD12 in the sense that it calculates a ratio between measures along the short (*Dx*) and the long (*Dy*) axes of the Poincaré plot. *Dyx* describes the skewness in densities within the plot and thereby reflects the incresased randomness in the RR inteval time series and integrates measures of both vagal and sympathetic activation. Presumably *Dyx* performs better than SD12 because it is more accurate to calculate exact densities than standard deviations when describing the individual specific features of the plot, making the measure less susceptible to clusters of rare RR intervals and more descriptive of the predominant RR interval lengths. We suggest that *Dyx* should be considered a new, important nonlinear HRV measure of altered sympathovagal balance and increased randomness of the RR intervals. However, further and larger prospective studies are needed to confirm this hypothesis.

In contrast to findings in previous studies,[5,6,24,30] neither SDNN, α_1 nor SD12 could show independent predictive value in the present substudy. There may be several reasons for this controversy. Mainly there could be a power problem, considering that the danish population only consists of 206 patients of the 697 patients included in the original study. In the main study[13] both traditional and nonlinear measures predicted all-cause mortality, with α_1 being the strongest. The Holter editing did not differ between the main-study and the present substudy, only cutoff values for bad prognosis and follow-up time. In previous studies cutoff values have often changed according to optimized values from different populations. The present study is the first study to test the HRV parameters

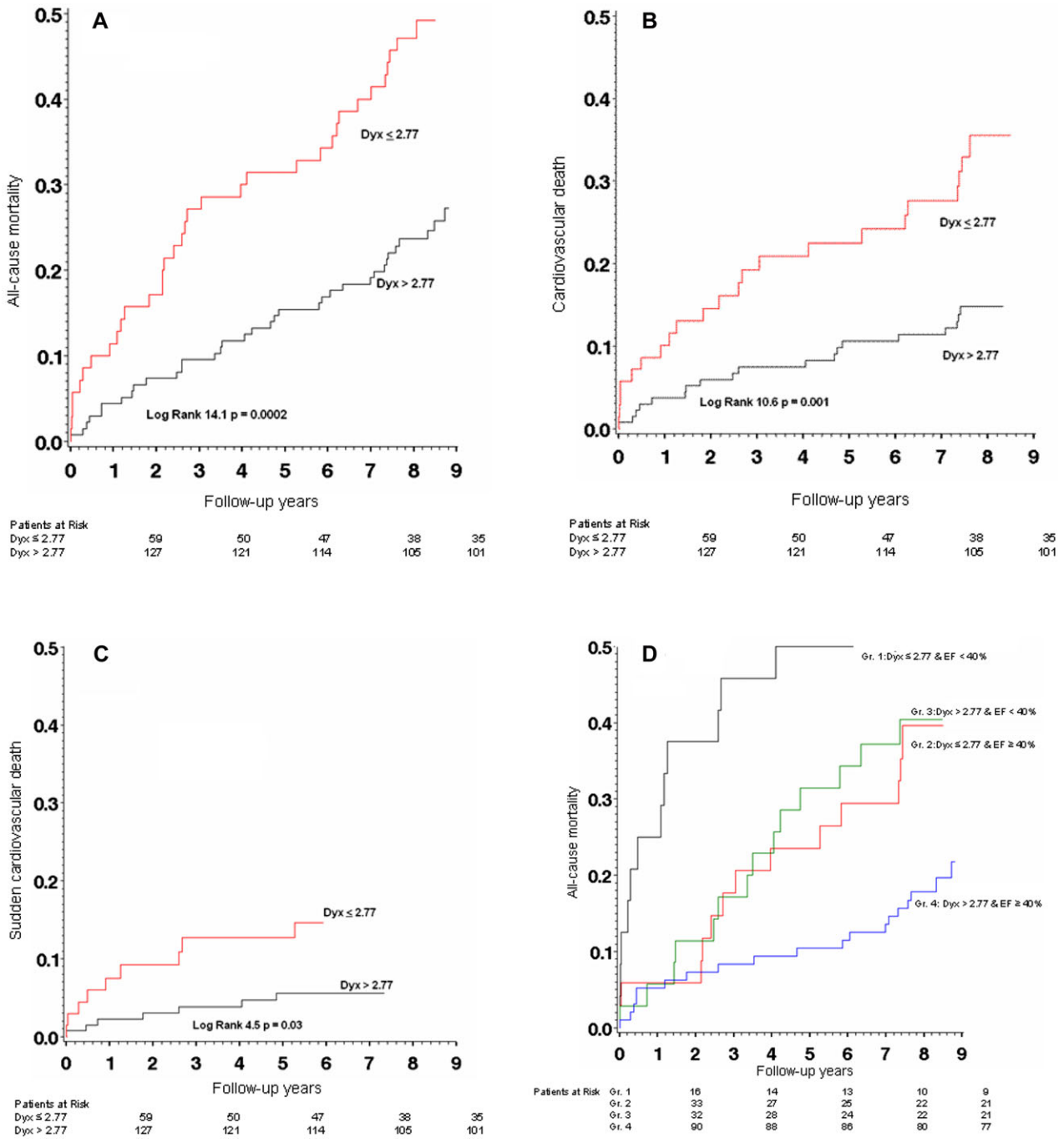

Figure 2. A. Kaplan–Meier curve for *Dyx* and all-cause mortality. (B) Kaplan–Meier curve for *Dyx* and cardiovascular death. (C) Kaplan–Meier curve for *Dyx* and sudden cardiovascular death. (D) Kaplan–Meier curve for combinations of *Dyx* and LVEF, and all-cause mortality.

Dyx, *Qxx*, *Qyy*, and *Txxx* and for this reason we dichotomized all continuous variables according to high-risk tertiles for a relevant comparison and this increased the cutoff values for traditional HRV parameters significantly, and might in itself explain the insignificant findings.

The Danish subset of patients had less diabetes (12%) and less hypertension (26%) than seen in

most post-MI studies. Left ventricular systolic function was not an inclusion criterion in this study and mean LVEF was 48%, whereas most studies addressing risk prediction have studied populations with LVEF of less than 30%–40%[2,5,9,31] and only 3% where in NYHA class III-IV all together describing a population with a lower risk of cardiac mortality than in the typical post-MI population. Most previous studies[2,5,6,13] had follow-up periods of 2–4 years, where the present study had a very long follow-up period of almost 10 years, in which many changes occur in a post-MI population, that is, left ventricular remodelling,[32,33] progressing heart failure together with age-related changes in autonomic tone[34,35] and mortality risk. We have earlier tested *Dyx* in a normal population of 106 healthy subjects (not published), and found the mean value of *Dyx* to be 3.72 showing only a minor overlap with post-MI patients. In the present study *Dyx* was able to distinguish between groups of patients with very high risk, intermediate and very low risk of death when combined with LVEF.

In patients with remote myocardial infarction and depressed left ventricular function the effect of prophylactic ICD implantation is well established.[36,37] However, implantation rates still vary significantly from one country to another, due to the combination of limited finances and inadequate risk stratification. It is in this regard very interesting that reduced *Dyx* in combination with low LVEF was able to predict a high-risk group of patients which might be likely to benefit from ICD implantation, but also a low-risk group in which ICD implantation might not be beneficial. Since reduced *Dyx* also demonstrated a high negative predictive value for sudden cardiovascular death, it could prove to be an important risk-factor in determining which post-MI patient should or should not be treated with a prophylactic ICD, and which patient are in intermediate risk and need further evaluation.

LIMITATIONS

There are several limitations to the study, the modest sample size ($n = 303$) being the most important. However, patients were well characterized and screened consecutively.

Because of the findings in the main study, where α_1 surpassed the traditional frequency measures and also predicted mortality in patients without significantly depressed LVEF, we chose not to include frequency measures in this study, which might have shown significant predictive value, even though other traditional measures did not.

According to the protocol prophylactic ICD was implanted in 14 patients within the first 30 days after the index infarction. This presents a bias since the ICD might have reduced arrhythmic mortality.[36,37]

Dyx was tested during long-term follow-up and it is obvious that the treament regimens for MI and progressing heart failure have changed considerably since the data were collected. In our study population only 52% were treated with β-blockers at the time of inclusion and 49% were treated with thrombolytic therapy during the acute phase of the index MI. Thus the results of this study have to be validated in a large scale prospective study in post-MI patients treated according to current guidelines.

CONCLUSION

The new nonlinear HRV parameter *Dyx*, measured in the first 2 weeks after an acute myocardial infarction, is a promising independent predictor of mortality in a long term follow-up study, irrespectively of left ventricular systolic function.

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