# Heart rate variability and non-linear dynamics in risk stratification

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The time-domain measures and power–spectral analysis of heart rate variability (HRV) are classic conventional methods to assess the complex regulatory system between autonomic nervous system and heart rate and are most widely used. There are abundant scientific data about the prognostic significance of the conventional measurements of HRV in patients with various conditions, particularly with myocardial infarction. Some studies have suggested that some newer measures describing non-linear dynamics of heart rate, such as fractal measures, may reveal prognostic information beyond that obtained by the conventional measures of HRV. An ideal risk indicator could specifically predict sudden arrhythmic death as the implantable cardioverter-defibrillator (ICD) therapy can prevent such events. There are numerically more sudden deaths among post-infarction patients with better preserved left ventricular function than in those with severe left ventricular dysfunction. Recent data support the concept that HRV measurements, when analyzed several weeks after acute myocardial infarction, predict life-threatening ventricular tachyarrhythmias in patients with moderately depressed left ventricular function. However, well-designed prospective randomized studies are needed to evaluate whether the ICD therapy based on the assessment of HRV alone or with other risk indicators improves the patients' prognosis. Several issues, such as the optimal target population, optimal timing of HRV measurements, optimal methods of HRV analysis, and optimal cutpoints for different HRV parameters, need clarification before the HRV analysis can be a widespread clinical tool in risk stratification.

**Keywords: heart rate, heart rate variability, non-linear methods, mortality, sudden death**

## INTRODUCTION

Heart rate variability (HRV) describes the complex regulatory system between heart rate and the autonomic nervous system. There are several methods to measure HRV (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996). The traditional statistical methods and the power–spectral analysis of HRV are classic methods to measure HRV and are most widely used. The conventional measures of HRV have been shown to provide prognostic information in several patient populations (Kleiger et al., 1987; Bigger et al., 1992, 1993; Fei et al., 1996; Zuanetti et al., 1996; Nolan et al., 1998). The conventional measures of HRV cannot reveal delicate changes in heart rate beat-to-beat dynamics. Therefore several non-linear methods for measuring heart rate dynamics have been developed (Saul et al., 1987; Goldberger, 1990b, 1996; Skinner et al., 1993; Pincus and Goldberger, 1994; Peng et al., 1995; Voss et al., 1998; Tuzcu et al., 2006; Norris et al., 2008a). Few of these newer methods of HRV, such as the fractal-like scaling property and the complexity, have been tested in well-designed studies, which have included a relevant number of patients and have had well-defined endpoints. Some of these studies have suggested that some of the non-linear measures of HRV work better than the traditional measures of HRV in predicting future adverse events in various patient groups. The physiological background of the non-linear measures of HRV is much less well understood than that

of the conventional measures of HRV. The non-linear methods of HRV assess qualitative properties rather than the magnitude of the heart rate dynamics.

Several other factors than the type of the parameter influence the prognostic value of HRV measurements. The timing of the HRV measurement after an acute myocardial infarction (AMI) has a direct influence on the prognostic significance of HRV due to substantial electrical and mechanical remodeling after AMI (Exner et al., 2007; Huikuri et al., 2009a). The prognostic value of HRV variables is also dependent on the left ventricular function and the severity of heart failure (Mäkikallio et al., 2001a, 2005). HRV parameters analyzed from short-term recordings obtained during controlled conditions yield somewhat different prognostic information than the HRV variables analyzed from long-term ambulatory 24-h recordings. It is also important to select appropriate preprocessing methods for editing premature depolarizations and irrelevant oscillations from RR interval time series in order to obtain reliable and reproducible prognostic data for clinical purposes (this is dealt in another review in the present issue). It is noteworthy that HRV parameters work prognostically differently in patients with different diseases and healthy subjects. The predictive power of HRV variables varies also depending on whether total mortality, different modes of mortality, or other adverse events are selected as endpoints. Several novel methods to describe heart rate dynamics, such as heart rate turbulence, have been developed

(Schmidt et al., 1999). Their role in risk stratification is discussed in other reviews in this issue as is the influence of exercise on heart rate dynamics.

During the past two decades the number of publications dealing with HRV has exploded reaching at least over 14,000 at the moment. The present review is focusing on some of these studies, of which the majority have relevant number of patients and well-defined endpoints, and which elucidate the value of conventional and non-linear methods of HRV in risk assessment.

## HEART RATE VARIABILITY IN RISK EVALUATION

### CLASSIC STUDIES APPLYING CONVENTIONAL METHODS OF HEART RATE VARIABILITY ANALYSIS

The prognostic significance of the conventional measures of HRV in post-AMI patients is well established. Schneider and Costiloe (1965) first proposed that HRV is reduced in patients with AMI and is associated with adverse prognosis. Wolf et al. (1978) found a significantly lower in-hospital mortality rate among the patients with AMI, who had more pronounced sinus arrhythmia. Kleiger et al. (1987) published the cornerstone study, where they showed that decreased HRV measured by the SD of all normal-to-normal RR-intervals (SDNN) analyzed from 24-h electrocardiographic recordings predicts mortality in post-infarction patients. The combination of reduced HRV and the occurrence of late potentials was found to have a sensitivity of 58%, a positive predictive accuracy of 33%, and a relative risk of 18.5 for arrhythmic events in post-AMI patients (Farrell et al., 1991). In the study by Cripps et al. (1991), which included 177 patients after AMI, the relative risk of sudden death or symptomatic sustained ventricular tachycardia during a median follow-up of 16 months was found to be seven times greater in those with low baseline values of the triangular index of HRV. In another study, after adjustment for relevant clinical risk markers, the total, ultralow-frequency and very-low-frequency powers of HRV remained a significant and powerful predictor of mortality after AMI (Bigger et al., 1992). In 433 survivors of first AMI, Odemuyiwa et al. (1994) observed that HRV was an independent predictor of sudden death and total cardiac mortality only during the first 6 months of follow-up. The results of the study including 226 consecutive patients with AMI confirmed the previous observations concerning the association between decreased HRV and mortality after AMI and suggested the importance of disturbance in sympathovagal regulation unrelated to left ventricular function or infarct location as a mechanism of high-risk (Vaishnav et al., 1994). Reduced HRV has been found to be related to both arrhythmic and non-arrhythmic death in post-AMI patients (Hartikainen et al., 1996). Fei et al. (1996) showed in their study including 700 consecutive patients after AMI that although the predictive accuracy of SDNN analyzed from 5-min short-term RR interval data for 1-year total cardiac mortality was lower than that of the HRV index analyzed from 24-h period, the SDNN short-term data could be used in preselection of high-risk patients. Bigger et al. (1993) studied the predictive value of the power–spectral measures of HRV obtained from short from 2 to 15 min electrocardiographic recordings in 715 post-AMI patients. They concluded that the power–spectral measures of HRV obtained from short recordings are remarkably similar to those obtained from 24-h recordings and predict

all-cause mortality and sudden cardiac death. Zuanetti et al. (1996) evaluated the predictive value of several time-domain measures of HRV for total and cardiovascular mortality in 567 patients with AMI, who were treated with thrombolytic therapy and followed up for 1000 days. They concluded that time-domain indexes of HRV retain their independent prognostic significance even in post-AMI patients of all ages treated with fibrinolysis. Heart rate and HRV analyzed from predischarge 24-h electrocardiographic recordings were found to be more powerful predictors of mortality than ejection fraction in post-AMI patients in the study by Copie et al. (1996). Disturbed autonomic modulation of heart rate seems to be specifically related to susceptibility to ventricular fibrillation, but not to stable monomorphic ventricular tachycardia, suggesting that autonomic influences modify the presentation of malignant ventricular tachyarrhythmia after previous myocardial infarction (Perkiömäki et al., 1997).

The analysis of HRV can give an insight into various pathophysiological processes including the progression of focal coronary atherosclerosis (Huikuri et al., 1999a) and the angiographic severity of coronary artery disease (Hayano et al., 1990). Patients with coronary artery disease may have decreased vagal activity (Airaksinen et al., 1987) and abnormal circadian rhythm of HRV (Huikuri et al., 1994). Furthermore, ischemia may be preceded by increased sympathetic tone (Bernardi et al., 1988).

It is noteworthy that the HRV counterparts of autonomic drives are very different in patients with heart failure and in normal subjects (van de Borne et al., 1997). However, there are a lot of publications, which show that HRV is decreased in patients with congestive heart failure (Saul et al., 1988; Casolo et al., 1989, 1991; Kienzle et al., 1992; Nolan et al., 1992; Mortara et al., 1994). Saul et al. (1988) observed decreased vagal, but relatively well preserved sympathetic modulation of heart rate in patients with chronic stable congestive heart failure. On the contrary, reduction of all spectral components of HRV were found in patients with congestive heart failure in the study by Casolo et al. (1991). Brouwer et al. (1996) observed in 95 patients with mild to moderate heart failure that abnormal Poincare plots were independent predictors of all-cause and sudden cardiac death.

Hypertensive patients have been found to have increased low-frequency components and reduced high-frequency components of HRV (Guzetti et al., 1988). On the other hand, lower values of low- and high-frequency power of HRV were observed in hypertensive patients with left ventricular hypertrophy than in controls, while ultralow- and very-low-frequency components were similar in the groups (Petretta et al., 1995). Left ventricular hypertrophy is a well known risk indicator, and HRV has been shown to be inversely related to left ventricular mass index (Mandawat et al., 1994, 1995; Petretta et al., 1995). However, not all studies have confirmed this finding (Perkiömäki et al., 1996).

Disturbances in cardiac autonomic regulation assessed by HRV have been observed in several other conditions. Patients with diabetic neuropathy have decreased HRV (Wheeler and Watkins, 1973; Pfeifer et al., 1982; Smith, 1982). A reduced HRV in patients with diabetes still yields long-term prognostic information (Wheeler et al., 2002). In post-AMI patients the association between decreased HRV and long-term mortality has been observed to be at least as strong in diabetic patients as in

non-diabetic patients (Whang and Bigger, 2003). However, there are also some data to suggest that including patients with diabetes decreases the association between HRV and mortality after AMI (Stein et al., 2004). The measurement of HRV offers also prognostic information in an elderly population beyond that provided by the assessment of conventional risk factors (Tsuji et al., 1994). Patients with chronic renal failure (Axelrod et al., 1987; Cloarec-Blanchard et al., 1992) have decreased HRV. Patients with different neurological conditions, such as Parkinsonism (Kuroiwa et al., 1983), multiple sclerosis (Neubauer and Gundersen, 1978), and quadriplegia (Inoue et al., 1990), have also been observed to have reduced HRV. Decreased HRV has been found in heart transplant recipients, but allograft rejection may lead to increased HRV (Sands et al., 1989).

## STUDIES APPLYING NON-LINEAR METHODS OF HEART RATE VARIABILITY AND NEWER STUDIES

The fractal measures are the non-linear measures of HRV, whose prognostic significance has most widely been assessed in clinical studies including relevant number of patients and using well-defined endpoints. The fractal measures of HRV analysis have been shown to provide incremental prognostic information compared with the conventional measures of heart rate fluctuations. A basic feature of a fractal system is scale-invariance, i.e., same features repeat themselves on different measurement scales (Goldberger, 1996). Healthy subjects´ erratic fluctuations of sinus rhythm have fractal-like characteristics (Denton et al., 1990; Goldberger, 1990a).

Power-law HRV analysis is as a qualitative measure of the power spectrum in the region of the ultralow- and very-low-frequency bands obtained from long-term recordings. A plot of spectral power and frequency on bi-logarithmic scale shows linear portion between $10^{-4}$ and $10^{-2}$ Hz, and the slope of this relationship reflects long-term fractal-like scaling characteristics of HRV (Saul et al., 1987). Healthy subjects have power-law exponent values around $-1$ (Saul et al., 1987; Bigger et al., 1996), and the value of this slope has been observed to decrease with advancing age (Pikkujämsä et al., 1999). The finding that denervated hearts have a substantially steeper power-law slope emphasizes the important role of the autonomic nervous system in determining the steepness of the slope (Bigger et al., 1996). A steep power-law slope has been shown to be a better predictor of all-cause mortality or arrhythmic death than the traditional power–spectral bands in post-AMI patients (Bigger et al., 1996), and a better predictor of mortality than the traditional measurements of HRV in the elderly (Huikuri et al., 1998).
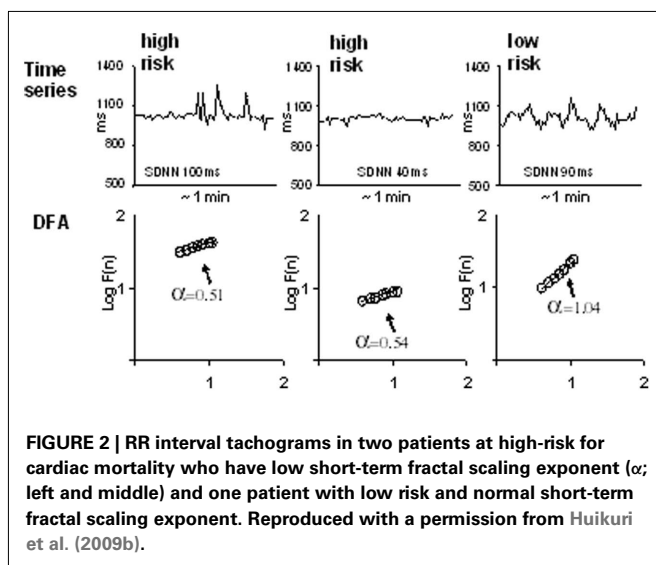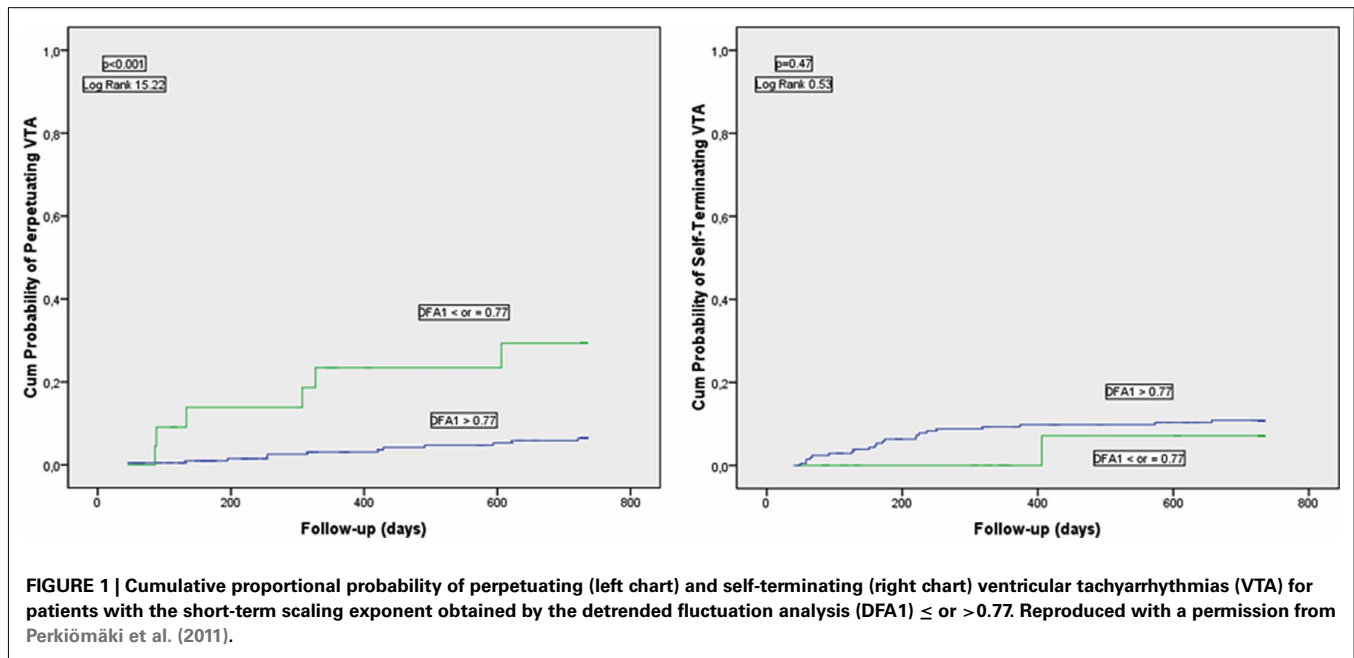
Detrended fluctuation analysis (DFA) quantifies intrinsic fractal-like correlation properties of dynamic systems (Peng et al., 1994). Peng et al. (1995) have described the details of this method. Briefly, the RR interval variability in relation to a local trend is analyzed in observation windows of different sizes in preprocessed and integrated RR interval time series. The RR interval variability is shown on a log–log scale as a function of the observation window size. In the presence of scaling, this relationship has a linear portion. The short-term scaling exponent (DFA1; for window sizes <11 beats) describes short-term scaling properties, and the intermediate-term scaling exponent (DFA2; for window sizes

>11 beats) longer term scaling properties of the signal. Healthy middle-aged subjects have the short-term scaling exponent values somewhat over or around 1 (Pikkujämsä et al., 2001). The values of the short-term scaling exponent are determined by a complex interplay of the parasympathetic and sympathetic autonomic nervous system. Concomitant activation of both vagal and sympathetic outflow has been shown to decrease the short-term fractal scaling exponent resulting in a random heart rate behavior (Tulppo et al., 2005). The physiological background of the short-term scaling exponent has been discussed in detail elsewhere (Huikuri et al., 2009b). Healthy elderly subjects may have changes in the fractal correlation properties of heart rate dynamics (Iyengar et al., 1996; Pikkujämsä et al., 1999), and the short-term scaling exponent has also been observed to predict cardiac death in the elderly (Mäkikallio et al., 2001b).

There is some evidence that the short-term fractal-like scaling properties of heart rate dynamics analyzed by the DFA technique can yield prognostic information beyond that obtained by the conventional measures of HRV. Studies in post-AMI patients have suggested that decreased short-term scaling exponent is a better predictor of mortality than the conventional measurements of HRV (Mäkikallio et al., 1999a; Huikuri et al., 2000) and that decreased short-term scaling exponent values are associated with vulnerability to ventricular tachycardia (Mäkikallio et al., 1997), ventricular fibrillation (Mäkikallio et al., 1999b), arrhythmic death, and non-arrhythmic cardiac death (Huikuri et al., 2000). The prognostic value of the short-term scaling exponent has also been shown in a general post-AMI population without a marked left ventricular dysfunction and high proportion of patients on beta-blocking medication (Tapanainen et al., 2002). Fractal HRV has been observed to retain its prognostic value even when the vast majority of the patients were taking beta-blockers after AMI (Jokinen et al., 2003). Among the autonomic risk markers, the short-term scaling exponent has been found to be the strongest predictor of recurrent non-fatal coronary events after AMI (Perkiömäki et al., 2008). Disturbed cardiac autonomic regulation represented by reduced values of the short-term scaling exponent has been found to predict perpetuating ventricular tachyarrhythmias, but not self-terminating ventricular tachyarrhythmias in post-AMI patients with moderate left ventricular dysfunction suggesting that perpetuating and self-terminating ventricular tachyarrhythmias may have differences in factors, which modify arrhythmias (Perkiömäki et al., 2011; **Figure 1**). **Figure 2** shows two typical cases of RR interval behavior in high-risk patients with low short-term fractal scaling exponent and one case with normal fractal scaling exponent.

Heart failure patients show loss of fractal organization in heart rate dynamics (Peng et al., 1995), and this is associated with the risk of death (Ho et al., 1997). Reduced short-term scaling exponent is more closely related to the risk of mortality in patients with less severe than in those with more advanced heart failure (Mäkikallio et al., 2001a). The short-term scaling exponent has also been shown to predict long-term risk for heart failure hospitalization after AMI (Perkiömäki et al., 2010).

The spontaneous onset of atrial fibrillation in patients without a structural heart disease is preceded by altered short-term fractal-like scaling properties of HRV (Vikman et al., 1999), and the short-term scaling exponent changes toward more random direction in

**FIGURE 1 | Cumulative proportional probability of perpetuating (left chart) and self-terminating (right chart) ventricular tachyarrhythmias (VTA) for patients with the short-term scaling exponent obtained by the detrended fluctuation analysis (DFA1) ≤ or >0.77. Reproduced with a permission from Perkiömäki et al. (2011).**



**FIGURE 2 | RR interval tachograms in two patients at high-risk for cardiac mortality who have low short-term fractal scaling exponent (α; left and middle) and one patient with low risk and normal short-term fractal scaling exponent. Reproduced with a permission from Huikuri et al. (2009b).**

ectopic tachycardia reflecting disturbances in autonomic regulation or in ectopic atrial pacemakers (Huikuri et al., 1999b).

Some of the non-linear measures of HRV, such as the short-term scaling exponent, have some advantages over the conventional measures of HRV considering risk stratification purposes. These advantages include: less dependency on heart rate, less inter-individual and intra-individual variation (Perkiömäki et al., 2001c; Pikkujämsä et al., 2001; Maestri et al., 2007), smaller relative changes of individual values over time after AMI (Perkiömäki et al., 2001c), and relatively good comparability of individual values between long-term and short-term electrocardiographic recordings (Perkiömäki et al., 2001b).

The cardiac arrhythmias and risk stratification after acute myocardial infarction (CARISMA) study included patients, who

had left ventricular ejection fraction ≤40% measured from 3 to 21 days after AMI. Several HRV measures, when analyzed from 24-h ECGs recorded at 6 weeks after the AMI, predicted the primary endpoint of ventricular fibrillation or symptomatic sustained ventricular tachycardia. However, the short-term scaling exponent was the only HRV measure, when analyzed from 24-h ECGs recorded at 1 week after the AMI, which significantly predicted the primary endpoint. It is noteworthy that the arrhythmic endpoint events were objectively detected using implantable loop recorders in the CARISMA study (Huikuri et al., 2009a), whereas in most of the previous studies arrhythmic events/sudden arrhythmic cardiac death have been evaluated on clinical basis. In the recent non-invasive risk assessment early after a myocardial infarction (REFINE) study (Exner et al., 2007), which included post-AMI patients with somewhat better preserved left ventricular function than the CARISMA study, HRV measured from 10 to 14 weeks after the AMI tended to predict the primary endpoint of cardiac death or resuscitated cardiac arrest, but had no association with the primary endpoint when measured from 2 to 4 weeks after the AMI. These notions underline the importance of timing for measurement of HRV after AMI.

The data on the prognostic significance of the complexity measures of HRV are limited (Huikuri et al., 2009b). Decreased multiscale entropy of heart rate has been observed to predict mortality in trauma patients (Norris et al., 2008a,b). There has been shown to be association with reduced complexity in heart rate dynamics and postoperative complications after vascular surgery (Fleisher et al., 1993). Decreased complexity in heart rate behavior measured by approximate entropy has been found to precede spontaneous episodes of atrial fibrillation in patients without structural heart disease (Vikman et al., 1999) and in patients after coronary artery bypass surgery (Hogue et al., 1998). Furthermore, the complexity of heart rate dynamics has been observed to reduce during 1 year follow-up after coronary artery bypass operation (Laitio et al., 2006).

## USEFULNESS OF HEART RATE VARIABILITY IN CLINICAL DECISION MAKING AND FUTURE PERSPECTIVES

Despite a large body of evidence documenting the predictive value of various HRV indices, none of these methods are in widespread clinical use at the moment. If patients would be risk stratified to a therapy based on a HRV measurement, the therapy should improve the patients' outcome. Therefore it should be evaluated in well-designed prospective randomized studies, whether the selection of the patients to the therapy based on potentially useful HRV measurements improves the prognosis. An ideal risk stratifier should specifically predict sudden arrhythmic death as an implantable cardioverter-defibrillator (ICD) therapy is effective in preventing such events. The patients with severely depressed left ventricular function are at highest risk for life-threatening ventricular arrhythmias (Huikuri et al., 2001), however, it has been found that HRV measurements work prognostically better in patients with more preserved left ventricular function (Mäkikallio et al., 2005) than in those with more severe left ventricular dysfunction. Additionally, there is evidence to support the concept that disturbed HRV predicts cardiac death in general and not specifically sudden arrhythmic death in patients with severe left ventricular dysfunction (Perkiömäki et al., 2001a; Zareba et al., 2003). On the other hand, there are numerically more sudden deaths among lower risk post-AMI patients with better preserved left ventricular function (Huikuri et al., 2001). Furthermore, as described above the results of the CARISMA study show that measures of HRV analyzed from electrocardiographic recordings obtained several weeks after AMI predict life-threatening ventricular tachyarrhythmias in post-AMI patients with moderately depressed left ventricular function (Huikuri et al., 2009a). Taken together, the post-AMI patients with moderate/mild left ventricular dysfunction would be the best target population for future prospective studies aiming to assess whether an intervention based on the assessment of HRV improves the outcome. In the CARISMA study, according to the receiver operator characteristics curve analysis, e.g., the short-term scaling exponent analyzed from 24-h ECGs recorded at 6 weeks after the AMI had the area under the curve of order of 0.75 for predicting life-threatening ventricular tachyarrhythmias. This can be considered potentially useful accuracy for risk stratification purposes. However, the accuracy of this level does not simultaneously allow both an excellent specificity and sensitivity for any selected cutpoint. Therefore it would be important to try to find additional good risk markers, which could in combination with HRV measurements increase the accuracy in predicting sudden arrhythmic death. This is particularly important, if ICD therapy is considered based on this risk stratification strategy as ICD implantation and therapy suffer from potential complications and discomfort and are relatively expensive. Severely depressed left ventricular function is considered to be a sufficient risk indicator for prophylactic ICD implantation in post-AMI patients with acceptable numbers needed to treat values for getting a benefit (Moss et al., 2002; Bardy et al., 2005). However, most of the post-AMI patients with better preserved left ventricular function at high-risk for sudden arrhythmic death do not get a primary prophylactic ICD therapy. Taken together, it would therefore be justified to consider to apply a cutpoint with compromised sensitivity of a HRV measurement to get high specificity, high positive predictive accuracy, and a low number needed to treat value in future prospective randomized prophylactic ICD studies in post-AMI patients with moderate/mild left ventricular dysfunction.

Despite many advancements, the analysis of HRV is still far from routine clinical use. Before it can be a useful tool for clinicians, at least the following questions need clarification: what would be the optimal timing for HRV analysis after AMI? What would be the optimal target population for the use of HRV analysis as a risk stratifier? What method(s) should be used for HRV analysis in clinical settings? What would be the optimal preprocessing method for editing premature depolarizations for different HRV parameters in different clinical settings? What would be the recommendable cutpoints of selected HRV measurements for risk stratification purposes in different cardiac conditions for different endpoints, in a same cardiac condition with different degree of left ventricular dysfunction and heart failure, and in different age and gender groups? What would be a recommendable length of ECG recording? Under what kind of conditions should the ECG recordings be done? What is the accuracy of selected HRV measures in predicting different adverse events in different cardiac conditions? What would be the expected benefits of HRV analysis to patients' further evaluation and treatment? What would be the number needed to treat value, e.g., to get benefit from ICD therapy? Could the HRV analysis be used in the patients' follow-up, etc.? Hopefully, after further developments and standardization the HRV analysis alone or with other risk indicators will soon serve as a useful tool for risk stratification.

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**Conflict of Interest Statement:** The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.