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Noninvasive Predictors of Malignant Arrhythmias

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Key Words
Malignant ventricular arrhythmia · Sudden cardiac death · Coronary artery disease · Brain natriuretic peptide · Biomarkers

Abstract
Background: Prediction and potential prevention of sudden cardiac death (SCD) due to malignant ventricular arrhythmia (MVA) represent an obvious unmet medical need. We estimated the prognostic relevance of numerous biomarkers associated with future MVA development in patients with coronary artery disease (CAD) over 2 years of follow-up. ***Methods:*** Patients with stable documented CAD (n = 97) with a mean age of 61 ± 10 years were prospectively enrolled in a single-center observational cohort study. Heart failure was diagnosed in 68% of the patients (NYHA class II–III). The mean left ventricular ejection fraction (LVEF) was 50 ± 13%, while 20% of patients had LVEF ≤35%. Sixty-two patients underwent myocardial revascularization during the follow-up (mean 25 ± 11 months). Clinical characteristics (age, gender, diabetes, history of coronary disease and arrhythmias, prior interventions and antecedent medications), noninvasive electrophysiological markers [microvolt T-wave alterations, signal-averaged electrocardiography, QT interval duration and alteration, and heart rate turbulence (HRT) and HR variability], laboratory indices [serum creatinine and creatinine clearance, brain natriuretic peptide (BNP), NT-proBNP, and C-reactive protein and troponin T levels] were assessed with regard to the MVA prognosis. ***Results:*** MVA was diagnosed in 11 patients during the prospective follow-up. Prior percutaneous coronary intervention ($p < 0.05$), MVA or syncope ($p < 0.05$), on-pump coronary artery bypass grafting during follow-up ($p < 0.01$), LVEF ≤47% ($p < 0.01$), a left atrium size ≥4.7 cm ($p < 0.05$), left atrium index ($p = 0.01$), filtered QRS duration ($p < 0.05$), abnormal HRT ($\chi^2 = 6.2$, $p = 0.01$) or turbulence slope ($\chi^2 = 9.5$, $p < 0.01$), BNP ≥158 pg/ml ($p < 0.01$) and NT-proBNP ≥787 pg/ml ($\chi^2 = 4.4$, $p < 0.05$) were significantly associated with MVA risk by univariate analysis. However, only prior MVA or syncope [odds ratio (OR) 11.1; 95% confidence interval (CI) 2.8–44.4; $p < 0.01$], abnormal HRT (OR 13.6; 95% CI 2.8–66.1; $p < 0.01$) and plasma BNP (OR 14.3; 95% CI 3.2–65.0; $p < 0.01$) remained independent predictors of MVA occurrence by multivariate Cox regression analysis. ***Conclusion:*** Prior syncope or MVA, HRT and elevated plasma BNP were independent MVA predictors, advocating for the prospective screening of high-risk CAD patients for potential SCD awareness.

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Introduction

Sudden cardiac death (SCD) is one of the most common causes of mortality in the Western world. In fact, in the USA alone, about 325,000–350,000 SCDs occur annually [1], representing a stunning range of 50–100 fatalities per 100,000 population [2]. According to the latest data, the SCD rate ranges from 1.4/100,000 person-years in women to up to 6.68/100,000 person-years in men [3]. In Russia, the estimated annual incidence of SCD is approximately 200,000–250,000 cases, and is probably heavily underestimated [4]. The most common cause of SCD is ventricular tachyarrhythmia due to coronary artery disease (CAD), particularly following acute coronary syndrome. Alarming data were presented in the AHA 'Heart disease and stroke statistics – a 2016 update' report, suggesting that Russia tops the mortality rate for coronary atherosclerosis, with the SCD rates several times higher than in Europe or the USA [5].

Malignant ventricular arrhythmia (MVA) is the leading cause of SCD. Ironically, despite obvious progress in emergency care over the past decade, the survival rate after MVA episodes is still woefully small, even in developed countries [6]. Currently, the most effective way of preventing SCD is by means of an implantable cardioverter-defibrillator (ICD), common in high-risk patients [7]. However, these devices, apparently, are helpful only in selected patients, usually before the first episode of MVA [2].

Currently, some evidence suggests that certain indices may serve as predictors of SCD, including noninvasive parameters of cardiac electrical instability, biomarkers of inflammation, myocardial damage and overload and certain imaging variables [8]. However, current guidelines acknowledge only prior myocardial infarction (MI) that has occurred at least 6 weeks earlier and heart failure [left-ventricular ejection fraction (LVEF) ≤35%; NYHA class II–III, after ≥3 months on optimal medical treatment] as the 2 established predictors of SCD (class I, level of evidence A) [3, 9]. Despite the fact that an ICD reduces mortality in patients with a low LVEF [10, 11], the search for better predictive biomarkers is still underway. Finding such predictors represents an utmost priority and an urgent medical need [12].

Methods

Patients

The study was designed as a prospective, single-center observational cohort assessment. It included 108 consecutive CAD patients admitted to the Bakoulev Center for Cardiovascular Surgery, Moscow, Russia, from 2009 to 2011. The study design was approved by the ethics committee, and all patients provided a written informed consent. Inclusion criteria were: coronary heart disease as documented by coronary angiography performed during the previous ≤2 years and regular contact with the clinic for follow-up visits. Exclusion criteria were: acute coronary syndromes, congenital heart disease, severe acquired valvular disease, ventricular preexcitation syndromes, congenital long/short QT syndromes or acquired prolongation of QT interval (>500 ms on standard ECG).

Follow-Up and End Points

Follow-up information was obtained via telephone or hospital visits at least every 6 months. The combined end point was defined as the development of MVA including SCD, successful resuscitation, ICD discharge or transient syncope. In the case of death, the cause was verified by autopsy. All patients underwent standard echocardiography with measurement of LV end-systolic and end-diastolic dimension and volume, LVEF, mitral regurgitation, regional myocardial contractility and left atrium size. In the event of out-of-hospital death, detailed information about the circumstances of the death was collected from the relatives. SCD was defined as a nontraumatic, unexpected death within 1 h of acute symptoms without prior worsening [3]. Autopsy, confirming the cardiac reason for the death was performed in several cases.

24-Hour Ambulatory ECG

The analysis included episodes of transient syncope without ECG registration that occurred with witnesses. All enrolled patients underwent 24-hour ambulatory ECG with 3- and 12-lead monitors (ASTROCARD, Meditech, Moscow, Russia). Heart rate turbulence (HRT) was calculated using ECGs containing 3–5 consecutive sinus RR intervals prior to a ventricular premature beat (VPB) and 15–20 RR intervals following a VPB. The following RR intervals were excluded: <300 ms, >2,000 ms and when there was a difference of >200 ms between the preceding sinus intervals or >20% of the average of 5 consecutive sinus intervals. VPB was appropriate for analysis if it exhibited a minimum prematurity of 20% of the RR interval or a post-extra-systole interval of at least 20% longer than the mean RR interval. Turbulence onset (TO), reflecting the initial phase of sinus rhythm acceleration, and turbulence slope (TS), representing the compensatory deceleration phase, were also estimated and analyzed. TO was defined according to the formula:

$$TO = [(RR_1 + RR_2) - (RR_2' + RR_1')]/(RR_2' + RR_1') \times 100,$$

where RR_2' and RR_1' represent the 2 RR intervals before VPB and RR_1 and RR_2 represent the first 2 RR intervals following VPB. TS was defined as the maximum positive slope of a regression line assessed over any 5 consecutive RR intervals after a VPB. Measurements of HRT were estimated automatically for every VPB and were presented as an average value with a standard deviation (SD) for day, night and 24-hour periods. TO ≥0% and/or TS ≤2.5 ms/RR interval were defined as abnormal [13]. In addition to HRT, the following measurements were made: microvolt T-wave alternans (MTWA), high-resolution ECG variables [late ventricular potentials, filtered QRS (fQRS) duration, high-frequency low-amplitude (HFLA) signal and filtered P-wave duration (fP)], corrected QT interval and its circadian dynamics and HR variability with SD of normal-normal (NN) RR intervals (SDNN), SD of average NN intervals (SDANN) and proportion of NN50 (pNN50). MTWA was

defined as positive when present for at least 1 min with an HR <110 bpm, alternan amplitude ≥1.9 μV and alternan ratio (signal-to-noise ratio) – K-score ≥3 in the vector magnitude lead, any orthogonal lead or 2 consecutive standard leads (MTWA+). TWA was defined as being negative if the criteria for a positive test were not registered while the HR was ≥80 bpm (TWA–). All other cases of MTWA were considered indeterminate. Both negative and indeterminate results were defined as nonnegative [14]. The following values of high-resolution ECG variables were considered abnormal: fQRS >114 ms, HFLA >38 ms and root mean square <20 μV [15]. Daily mean corrected QT duration was estimated automatically for each lead. The relation of the QT interval and RR interval is described using a linear regression formula:

$$QT = \beta + \alpha \times RR,$$

where the coefficient α reflects the slope of a graph of the linear regression. Two parameters were included this analysis: the highest coefficient α of all leads (α max) and the difference between the maximum and minimum α values (Dα), which reflects the severity of the spatial dispersion of the RR interval dependence on the QT interval. Both parameters were calculated separately for the day and night periods [14].

Biochemical Markers

Venous blood samples for laboratory indices were drawn by sterile venipuncture into EDTA tubes before echocardiography after 10 min of supine rest. Blood samples were immediately centrifuged for 15 min at 3,000 rpm. Separated plasma samples were processed for brain natriuretic peptide (BNP) measurements by immunoassay using ARCHITECT i1000SR analyzer (Abbott, Skokie, Ill., USA). Creatinine and C-reactive protein were assessed by turbidimetric method using the IMMAGE 800 analyzer (Beckman Coulter, Fullerton, Calif., USA) and NT-proBNP and troponin T with the Elecsys 2010 analyzer (Roche Hitachi, Rotkreuz, Switzerland). Creatinine clearance was calculated applying the MDRD formula.

Statistical Analysis

Continuous variables are shown as mean ± SD and for categorical data, frequencies and percentages were used. The difference between 2 groups for continuous variables was assessed with the Student t test and the Mann-Whitney U test was used for nonparametric variables. Differences between groups were analyzed for statistical significance with the χ^2 test with the Yates correction for continuity or the Fisher exact test for small samples. $p < 0.05$ was considered statistically significant. The odds ratio (OR), hazard ratio (HR) of MVA and 95% confidence interval (CI) were calculated according to standard formulas. Receiver operating characteristic (ROC) curve analysis was performed to determine the cutoff values for continuous variables. The quality of the chosen model was evaluated depending on the area under the curve (AUC): 0.9–1.0 (excellent), 0.8–0.9 (very good), 0.7–0.8 (good), 0.6–0.7 (average) and <0.6 (unsatisfactory). Survival curves for all variables significantly associated with end points were analyzed using the Kaplan-Meier method and the log-rank test was applied for significance. All variables significantly associated with arrhythmic events according to univariate analysis were included in the multivariate Cox regression analysis to identify independent predictors. All analyses were carried out with SPSS v21.0 (SPSS, Chicago, Ill., USA).

Table 1. Demographics, clinical characteristics, interventions and outcomes dependent on MVA development

Parameters	MVA (n = 11)	No MVA (n = 86)	p value
Age, years	62.0±9.6	60.6±13.5	0.68
Females	2 (18)	10 (12)	0.59
Prior MI	8 (73)	61 (71)	0.90
Prior MVA or syncope	5 (45)	8 (9)	0.02*
Angina class	2.1±1.2	2.2±1.3	0.82
Heart failure, NYHA class	1.7±1.2	2.2±1.1	0.62
Permanent atrial fibrillation	4 (36)	12 (14)	0.14
Left bundle-branch block	3 (27)	22 (26)	0.91
Diabetes mellitus	3 (27)	14 (16)	0.43
Medication/prior myocardial revascularization			
Amiodarone	5 (45)	16 (19)	0.09
Other antiarrhythmic agents	1 (9)	2 (2)	0.45
Beta-blockers	8 (73)	63 (73)	0.97
ACE inhibitors	7 (64)	56 (65)	0.92
Diuretics	7 (64)	28 (33)	0.053
Spironolactone	2 (18)	33 (38)	0.12
Statins	6 (55)	60 (70)	0.34
Prior CABG	2 (18)	10 (12)	0.59
Prior PCI	6 (55)	18 (21)	0.034*
Myocardial revascularization during follow-up			
On-pump CABG	0 (0)	11 (13)	<0.001*
Off-pump CABG	2 (18)	17 (20)	0.90
PCI	1 (9)	24 (28)	0.06
Outcomes			
Stent thrombosis	1 (9)	1 (1)	0.62
Syncope	2 (18)	0 (0)	
Total mortality	6 (55)	9 (10)	0.005*
Cardiovascular mortality	6 (55)	2 (2)	<0.01*
Sudden cardiac death	3 (27)	0 (0)	

Values are expressed as n (%) or mean ± SD. * $p < 0.05$.

Results

Patients

The demographics, major clinical characteristics, interventions and major outcomes of the study groups dependent on MVA are presented in table 1. There were a few differences between groups including significantly more prior malignant arrhythmias in the MVA group and more frequent percutaneous coronary interventions (PCIs) during the follow-up. However, the most prevalent feature distinguishing MVA prognosis was the lack of on-pump coronary artery bypass grafting (CABG) in the MVA group so prominent in the cohort with favorable outcomes. Most patients (61%) developed heart fail-

Table 2. Laboratory biomarkers

Marker	MVA (n = 11)	No MVA (n = 86)	p value
Echocardiography			
LVED size, cm	6.3±1.2	5.9±0.9	0.11
LVED size/BSA, cm/m^2	3.1±0.5	3.0±0.5	0.35
LVED volume, ml	194.5±72.1	168.6±59.5	0.19
LVED volume/BSA, ml/m^2	96.3±37.7	85.0±30.8	0.27
LVEF, %	42.7±13.0	50.9±13.0	0.053
LVEF ≤35%	4 (36)	15 (17)	0.226
LA size, cm	5.2±1.2	4.5±0.6	0.002*
LA size/BSA, cm/m^2	2.6±0.8	2.3±0.3	0.013*
Mitral regurgitation, degrees	1.6±0.7	1.3±0.6	0.115
Holter monitoring			
Mean HR, bpm	72.2±15.5	66.5±8.8	0.07
High-grade VPB (3–4 beats)[a]	8 (73)	44 (51)	0.14
Noninvasive electrophysiology			
Positive MTWA	4 (36)	36 (42)	0.73
Negative MTWA	2 (18)	27 (31)	0.30
Indeterminate MTWA	2 (18)	7 (8)	0.26
Mean corrected QT interval, ms	434.6±57.5	414.1±44.0	0.20
Late ventricular potentials	6 (55)	26 (30)	0.13
fQRS duration, ms	152.0±45.7	124.8±34.7	0.033*
SDNN, ms	114.9±32.5	126.9±36.6	0.75
Abnormal TO	4 (36)	18 (21)	0.31
Abnormal TS	3 (27)	3 (4)	0.08
Abnormal HRT	2 (18)	2 (2)	0.18
Biochemistry			
Creatinine, μmol/l	110.8±33.5	103.5±31.8	0.55
Creatinine clearance, ml/min/1.73 m^2	69.8±27.2	72.7±18.0	0.68
BNP, pg/ml	1,013.7±617.8	180.8±267.8	<0.001*
NT-proBNP, pg/ml	3,058.0±1,614.2	833.9±565.5	0.003*
C-reactive protein, mg/dl	0.6±0.7	0.6±0.9	0.70
Troponin T >0.01 ng/ml	2 (18)	11 (13)	0.66

Values are expressed as n (%) or mean ± SD. * $p < 0.05$. BSA = Body surface area; ED = end-diastolic; LA = left atrium. [a] According to Lown and Wolf [16].

ure (NYHA II–III). The mean LVEF was 50 ± 13% and 20% of patients had LVEF ≤35%. Use of amiodarone, spironlactone and persistent atrial fibrillation were more common in the MVA group, although these differences did not reach significance (table 1). Among prior interventions, PCI, but not CABG, was associated with a higher risk for MVA. In contrast, on-pump CABG during follow-up did not occur in the MVA group.

As expected, hard outcomes were rare. However, cardiovascular and total mortality were significantly more prevalent in patients with MVA. During the follow-up, 15/97 patients died. Cardiac mortality was reported in 8 patients, 3 of whom died suddenly without prior worsening. Importantly, the mortality in the MVA group was as high as 55%. The other causes of death were bleeding (n = 2), mesenteric thrombosis (n = 1) and acute heart failure (n = 1) or were unknown (n = 3). The cumulative distribution of laboratory indices dependent on MVA occurrence is presented in table 2. According to the 24-hour ambulatory ECG monitoring at enrollment, 54% of the patients had high-grade VPB as classified by Lown and Wolf [16]. The MTWA test was positive in 41%, negative in 30% and undetermined in 29%. Late ventricular potentials were observed in 33% of cases. Pathological HRT (i.e.

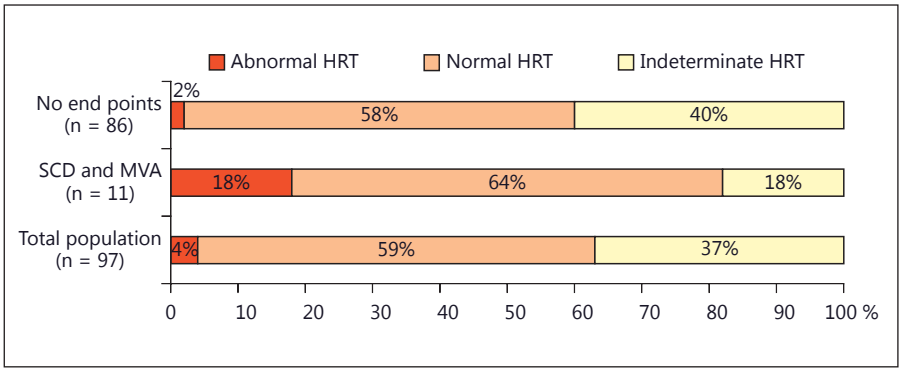

Fig. 1. Outcome distribution of HRT measurements.

a combination of pathological TO and TS) was reported in 4% of patients. In 23% of the cases, TO was different from the normal values (table 2). It should be noted that the HRT test was successfully performed in only 64% of patients. In the remaining patients, the calculations were limited by the presence of permanent atrial fibrillation, pacemaker rhythm or VPB absence (fig. 1).

Predictors of Arrhythmic Events during Follow-Up

According to univariate analysis, the following markers were significantly associated with MVA during follow-up: a history of malignant arrhythmias or syncope ($p = 0.02$), prior PCI ($p = 0.03$), LVEF ≤47% ($p = 0.01$), left atrium size ≥4.7 cm ($p = 0.03$), left atrium index ($p = 0.01$), fQRS duration ($p = 0.03$), HRT ($p = 0.01$), abnormal TS ($p = 0.002$), BNP ≥158 pg/ml ($p = 0.003$) and NT-proBNP ≥787 pg/ml ($p = 0.04$). The details are outlined in table 2. The MTWA test, HRT, late ventricular potentials, QT interval duration and circadian dynamics as well as most biochemical indices (creatinine clearance and levels of creatinine, C-reactive protein and troponin T) had no significant predictive value for MVA development. According to the multivariate Cox analysis, the remaining independent predictors of malignant arrhythmic events were an abnormal HRT test ($p = 0.01$) and a plasma BNP level ≥158 pg/ml ($p = 0.01$).

Discussion

The search for reliable predictors for MVA with a high SCD risk required the identification of suitable candidates for ICD therapy and the implementation of new, affordable, noninvasive diagnostic tools. The utilization of ICD therapy for SCD prevention is well justified by randomized evidence yielded from several large randomized trials (e.g. AVID, CASH and CIDS) [16]. In our study, patients who had prior malignant arrhythmia or syncope also exhibited a high risk of repeated life-threatening arrhythmias. Since all our patients underwent ICD intervention for secondary SCD prevention, previous ICD per se was associated with the very high rate for second MVA development (OR 39.1; 95% CI 5.0–304.7; $p < 0.0001$). Besides previous episodes of MVA and syncope, we identified 2 independent predictors of catastrophic arrhythmic events: an abnormal HRT and an elevation of plasma BNP to ≥158 pg/ml. The prognostic model which includes at least one of these predictors has sufficient negative predictive value to identify patients at low risk of MVA. The HRT effectively reflects HR disturbances as a response to blood pressure fluctuations. The normal VPB followed by dramatic shortening of RR intervals (the first 2–4 beats after VPB) is probably due to a decrease in blood pressure, following further RR gradual extension for the next 5–20 cardiac cycles. Our data are in agreement with the results of contemporary trials, suggesting that abnormal HRT impacts cardiac mortality and life-threatening arrhythmias in post-MI patients [15]. The significance of abnormal HRT among the other factors of autonomic dysfunction, such as baroreceptor sensitivity or HR variability in patients with recent MI (<28 days), has been shown in the ATRAMI study (Autonomic Tone and Reflexes after Myocardial Infarction) [13, 16]. In fact, TS and its combination with TO significantly increase the risk of fatal and nonfatal MVA (RR: 4.1 and 6.9, respectively; $p < 0.0001$ for both).

Several other trials (REFINE, CARISMA and ISAR-Risk) observed the recovery of the autonomic regulation of HR after MI and also demonstrated the prognostic value of HRT in life-threatening arrhythmic events during long-term follow-up after MI [17–20]. Also, in agreement with the index report, some strong evidence has suggest-

ed that T-wave alterations (based on the modified moving average method, MMA-TWA) and HRT were both independent predictors of cardiac mortality and fatal arrhythmic events in post-MI patients [21, 22]. Thus, the adverse effects of derangements in autonomic heart rhythm regulation in post-MI patients represent a real threat [23]. Importantly, 68% of the patients in our report experienced prior MI. This fact explains the limited role of other heart rhythm autonomic control indices such as circadian HR and QT interval variability regarding prognosis in our study. However, HRT had a definite impact on MVA development according to the multivariate Cox regression analysis ($p < 0.01$).

We also tried to identify the best suitable biochemical markers to distinguish future MVA risks in order to target potential SCD prevention. Among the variety of markers, only BNP holds predictive value for MVA development. Importantly, BNP is the most explored neurohumoral marker consistently linked to the prediction of serious arrhythmic events. According to a large meta-analysis of >4,500 patients, elevated levels of BNP were associated with SCD risks in a wide range of MVA patients [24]. The elevation of BNP in patients without an ICD predicts a 4-fold increase in the risk of SCD and a >4.5-fold increase in the case of concomitant CAD. In patients with an ICD, an elevated BNP predicts a 2-fold increase in the risk of appropriate shocks. In another meta-analysis of 6 studies which included 3,543 patients, the cut-off values of natriuretic peptides for MVA and SCD prediction varied greatly across studies: from 187 to 265 pg/ml for BNP and from 130 to 4,500 pg/ml for NT-proBNP [24]. This clearly indicates that BNP is a more reproducible marker and also corresponds well with our study. Finally, in another report on 94 patients with ischemic LV dysfunction following ICD therapy, elevated BNP was the only independent predictor of MVA during the 3.5-year follow-up [25].

Our study has several limitations. The patients were not randomized, and the individual duration of follow-up was different. A relatively small sample size, the clinical heterogeneity of the patients and the low event rate reduced the power of the potential predictors of sudden cardiac death. We included patients with persistent or paroxysmal atrial fibrillation, right or left bundle-branch block disturbance and implanted pacemakers (including paced rhythm). The Holter monitoring data were analyzed without additional quantification of HRT, HR variability, QT interval dynamics and high-resolution ECG variables, and the results of the MTWA test were considered indeterminate. Finally, not all causes of death were well documented or clearly identified.

We conclude that, during the 2-year follow-up, there were 3 independent predictors of MVA in stable CAD patients, namely: prior malignant arrhythmias or syncope, HRT and a plasma BNP ≥158 pg/ml. These predictors are important for SCD prevention. Patients with at least one of these biomarkers exhibited an increased risk of malignant arrhythmias, regardless of LVEF, the main risk stratification factor according to the current guidelines. All these easy-to-use, low-cost and noninvasive tests could improve the risk stratification for ICD candidate selection and potentially improve the prevention of SCD.

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References

1 Zipes DG, Camm AJ, Borggrefe M, et al: ACC/AHA/ESC 2006 guidelines for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. A report of the American College of Cardiology/American Heart Association Task Force and the European Society of Cardiology Committee for Practice Guidelines. Circulation 2006;114:e385–e484.

2 Fishman GI, Chugh SS, DiMarco JP, Albert, et al: Sudden cardiac death prediction and prevention: report from a National Heart, Lung, and Blood Institute and Heart Rhythm Society Workshop. Circulation 2010;122:2335–2348.

3 Priori SG, Blomström-Lundqvist C, Mazzanti A, et al: 2015 ESC guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. Eur Heart J 2015;36:2793–2867.

4 Revishvili AS, Ardashev AV, Bojcov SA, et al: Clinical Recommendations for Electrophysiologic Studies, Catheter Ablation and the Use of Implantable Antiarrhythmic Devices. Moscow, MAKS Press, 2013, p 596.

5 Mozaffarian D, Benjamin EJ, Go AS, et al: Heart disease and stroke statistics – 2016 update: a report from the American Heart Association. Circulation 2016;133:447–454.

6 Nichol G, Thomas E, Callaway CW, et al: Regional variation in out-of-hospital cardiac arrest incidence and outcome. JAMA 2008;300:1423–1431.

7 Bockeria LA, Revishvili AS, Neminushhij NM, et al: Implantable cardioverter-defibrillators: indications and long-term results of clinical application in patients with life-threatening arrhythmias. Ann Arithm 2005;1:51–57.

8 Gromova OI, Aleksandrova SA, Makarenko VN, Golukhova EZ: Contemporary predictors of life-threatening arrhythmias (in Russian). Creative Cardiol 2012;2:30–46.

9 Epstein AE, Di Marco JP, Ellenbogen KA, et al: 2012 ACCF/AHA/HRS focused update incorporated into the ACCF/AHA/HRS 2008 guidelines for device-based therapy of cardiac rhythm abnormalities. A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and Heart Rhythm Society. J Am Coll Cardiol 2013;61:e6–e75.

10 Moss AJ, Hall WJ, Cannom DS, et al; Multicenter Automatic Defibrillator Implantation Trial Investigators: Improved survival with an implanted defibrillator in patients with coronary disease at high risk for ventricular arrhythmia. N Engl J Med 1996;335:1933–1940.

11 Moss AJ, Zareba W, Hall WJ, et al; Multicenter Automatic Defibrillator Implantation Trial II Investigators: Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. N Engl J Med 2002;346:877–883.

12 Bardy GH, Lee KL, Mark DB, et al; SCD-HeFT Investigators: Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. N Engl J Med 2005;352:225–237.

13 Ghuran A, Reid F, La Rovere MT, et al: Heart rate turbulence-based predictors of fatal and nonfatal cardiac arrest (the Autonomic Tone and Reflexes after Myocardial Infarction Substudy). Am J Cardiol 2002;89:184–190.

14 Myerburg RJ, Interian A, Simmons J, Castellanos A: Sudden cardiac death; in Zipes DP (ed): Cardiac Electrophysiology: From Cell to Bedside, ed 4. Philadelphia, WB Saunders, 2004, pp 720–731.

15 La Rovere MT, Bigger JT Jr, Marcus FI, et al: Baroreflex sensitivity and heart-rate variability in prediction of total cardiac mortality after myocardial infarction. ATRAMI (Autonomic Tone and Reflexes after Myocardial Infarction) Investigators. Lancet 1998;351:478–484.

16 Bethge KP: Classification of arrythmias. J Cardiovasc Pharmacol 1991;17(suppl 6):S13–S19.

17 Bauer A, Barthel P, Schneider R: Improved Stratification of Autonomic Regulation for risk prediction in post-infarction patients with preserved left ventricular function (ISAR-Risk). Eur Heart J 2009;30:576–583.

18 Exner DV, Kavanagh KM, Slawnych MP: Noninvasive risk assessment early after a myocardial infarction: the REFINE study. J Am Coll Cardiol 2007;50:2275–2284.

19 Huikuri HV, Exner DV; CARISMA and REFINE Investigators: Attenuated recovery of heart rate turbulence early after myocardial infarction identifies patients at high risk for fatal or near-fatal arrhythmic events. Heart Rhythm 2010;7:229–235.

20 La Rovere MT, Pinna GD: Baroreflex sensitivity and heart rate variability in the identification of patient of risk for life-threatening arrhythmias: implications for clinical trials. Circulation 2001;103:2072–2077.

21 Hoshida K, Miwa Y, Miyakoshi M, et al: Simultaneous assessment of T-wave alternans and heart rate turbulence on Holter electrocardiograms as predictors for serious cardiac events in patients after myocardial infarction. Circ J 2013;77:432–438.

22 Maeda S, Nishizaki M, Yamawake N, et al: Ambulatory ECG-based T-wave alternans and heart rate turbulence predict high risk of arrhythmic events in patients with old myocardial infarction. Circ J 2009;73:2223–2228.

23 Rubart M, Zipes DP: Mechanisms of sudden cardiac death. J Clin Invest 2005;115:2305–2315.

24 Scott PA, Barry J, Roberts PR, et al: Brain natriuretic peptide for the prediction of sudden cardiac death and ventricular arrhythmias: a meta-analysis. Eur J Heart Fail 2009;11:958–966.

25 Galante O, Zahger D, Wagshal A, et al: Brain natriuretic peptide (BNP) level predicts long term ventricular arrhythmias in patients with moderate to severe left ventricular dysfunction. Harefuah 2012;151:20–23.