Chapter 3

Sudden Death in Ischemic Heart Disease

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Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/52661

1. Introduction

Sudden cardiac death (SCD) is defined by the death from unexpected circulatory arrest, usually due to a cardiac arrhythmia occurring within one hour of the onset of symptoms [1].

It is a major health problem worldwide, with a prevalence estimated in the range of 300 000 to 350 000 cases per year in the United States [2]. Event rates in Europe are similar to those in United States [3].

Coronary heart disease (CHD) is the leading cause of SCD explaining approximately 80% of cases [4]; cardiomyopathies and primary electrical abnormalities account for most of the remainder. Approximately 50% to 70% of these deaths are related to ventricular tachyarrhythmias (ventricular fibrillation/ tachycardia) [5].

Available medical therapies, such as beta-blockers [6] or anthiarrhytmic drugs including amiodarone, failed to abolish the occurrence of SCD after a myocardial infarction (MI) [7], [8].

Implantable cardioverter defibrillators (ICD) are devices currently available capable of abort life-threatening ventricular tachyarrhythmias and therefore prevent SCD.

Although it is not possible to prevent all cases of SCD in the general population, the main issue is the identification of individuals at increased risk that may benefit from ICD implantation.

The highest risk of SCD in various heart diseases, either genetic or acquired, is related with the previous occurrence of ventricular arrhythmias [9].In secondary prevention, predominantly three randomized clinical trials have established the criteria for ICD implantation.

The antiarrhythmics versus Implantable Defibrillators (AVID) trial showed mortality reduction with ICD among survivors of ventricular fibrillation or sustained ventricular tachycar-

dia causing severe symptoms [10]. The Canadian Implantable Defibrillator Study (CIDS) trial showed a 20% relative risk reduction in mortality with ICD therapy compared to amiodarone [11], although not statistically significant. The Cardiac Arrest Study Hamburg (CASH) trial confirm, though not with a statistical level of significance, the beneficial role of ICD therapy in the treatment of cardiac arrest survivors during long-term follow-up [12].A meta-analysis of these trials showed a 28% reduction in mortality due predominantly to a reduction in arrhythmic death [13].

Thus, patients with ventricular tachyarrhythmias (VT or VF), not secondary to a transient or reversible cause, meet a Class I indication for ICD therapy. In addition, patients with syncope and significant documented VT/VF also meet indications for ICD therapy (Level of Evidence A) [14].

However it is worth noting that, in most centers, the deployment of an ICD for primary prevention far exceeds the number of devices placed for secondary prevention.

Compared to optimal medical therapy, the use of ICDs in recent trials for primary prophylaxis in CHD population was associated with a reduction in 5-year all-cause mortality of 23% to 36% and a reduction in absolute mortality of 1.5% to 3% per year.

2. Clinical parameters

Coronary disease is the main etiology of heart disease in Western countries and the major cause of heart failure and SCD.It is defined by the presence of significant coronary stenosis in a main coronary vessel or by the demonstration of previous MI.

Sudden death associated with CHD may occur in the acute context or months to years after MI. At least 50% of all SCDs due to CHD occur as a first clinical event and among subgroups of patients thought to be at relatively low risk for SCD [15].

SCD risk is associated with the conventional risk factors for coronary atherosclerosis [16] including obesity, smoking [17], genetic predisposition [18], [19], ECG pattern of LVH or LBBB, certain angiographic parameters or heart rate profile during exercise [20].

The rhythm most often recorded at the time of sudden cardiac arrest is VT or VF [21]. The pathophysiological mechanism underlying the arrhythmias can be variable and multifactorial.

Transient factors may interact with a fixed substrate that, in ischemic heart disease, is attributed to scar-based re-entry.

In chronic stage of CHD, the occurrence of SCD has an inverse relation with EF of left ventricle and, at present, this is the parameter most widely used to categorize “high risk” patients for SCD.

Other factors that have been demonstrated to contribute to the risk for SCD after MI include the presence of non-sustained ventricular tachycardia (nsVT), inducible VT by EP testing

[22] or symptomatic heart failure (HF). Premature ventricular complexes (PVC) predict an increased risk of SCD during long-term follow-up, especially if ≥ 10 PVC per hour. The presence of frequent PVCs during or after exercise has been associated with greater risk for serious cardiovascular events but not specifically SCD.

Several other parameters are considered predictors of sudden death, but all with low or moderate predictive values, whose sensitivity and specificity have not yet been studied in detail in large patient populations.

Different noninvasive exams that allow quantification of ischemia (cardiac SPECT) [23], characterization of longitudinal strain abnormalities (echocardiography) [24] or MI scar (Cardiac Magnetic Resonance) [25], T wave alternant (ECG) or the presence and extent of sympathetic denervation(cardiac ^{123}I-MIBG imaging) were used in order to improve risk stratification of sudden death in ischemic cardiomyopathy [26], [27].

3. Primary prevention trials

To date, seven multicenter studies were essential for defining the criteria and timing for ICD implantation in ischemic heart disease: Multicenter Automatic Defibrillator Implantation Trial (MADIT [28]), Coronary Artery Bypass Graft Patch (CABG-Patch) [29], Multicenter Unsustained Tachycardia Trial (MUSTT) [30], MADIT II [31], Defibrillators In Acute Myocardial Infarction Trial (DINAMIT) [32], Sudden Cardiac Death in Heart Failure (SCD-HeFT)[8] and Immediate Risk Stratification Improves Survival (IRIS) [33].

Low LV ejection fraction (up to 30 to 40%) was the inclusion criterion similar in all of these studies.

Specific criteria in each of the studies were the presence of non sustained ventricular tachycardia and electrophysiological study showing inducible VT (MADIT and MUSTT), recent coronary revascularization and abnormal signal-averaged ECG (CABG-Patch), recent MI (DINAMIT, IRIS) and heart failure (SCD-HeFT).

Based on these trials, the American College of Cardiology, American Heart Association and the European Society of Cardiology guidelines recommend the implementation of ICDs in all patients with an ejection fraction inferior or equal to 30%, as well as patients with EF less than 35% with heart failure New York Heart Association (NYHA) class II or III. ICD can be considered in postinfarction patients with EF to 40% who have sustained ventricular arrhythmias inducible during electrophysiology study [14].

As a rule, ICD implantation is not indicated in patients recovering from an acute MI (less than 40 days) or CABG surgery (within 90 days) or in patients with NYHA class IV.

The Number needed to treat (NNT) of ICD implantation in quite different between the trials depending on the severity of the patients evaluated and varied between 4 in MUSTT and 14 in SCD-HeFT [34].

There is still a controversy regarding the effect of Cardiac Resynchronization Therapy (CRT) on the risk of ventricular tachyarrhythmias, specially in patients at higher risk of heart failure [36].Some studies suggested that epicardial activation in CRT may cause dispersion of depolarization and prolongation of QT interval [37].

Recently, MADIT-CRT trial showed an inverse association between reverse remodeling and the risk of subsequent ventricular tachyarrhythmias: in high responders to resynchronization therapy (defined as ≥25% reduction in LVESD), there was a 55% lower risk of arrhythmias at 1-year post-implantation.

It seems that reverse remodeling had a dual effect of both heart failure and arrhythmia risk reduction [38].

4. ECG measurements

Classically, the presence of Left Bundle Branch Block (LBBB) was considered of major prognostic importance, associated with the occurrence of sudden death in patients with ischemic heart disease. This was based on earlier studies, most of them performed before the era of percutaneous coronary revascularization [39].

In more recent investigations, especially those resulting from secondary analyses of MUSTT and MADIT-II trials, it has become clear that QRS prolongation is related with mortality after MI, although the magnitude of the relationship between abnormal intraventricular conduction and SCD in CHD remains unclear [40].

In an analysis of MUSTT trial, the authors noted that patients with LBBB had lower ejection fractions and higher incidence of symptomatic heart failure, suggesting that the increase in overall mortality was probably due to a sicker population [41].

In the MADIT-II cohort with prolonged QRS its duration (QRSd) was found to be an independent predictor of SCD in medically managed patients (HR 2.12) but not in ICD-treated patients (HR 0.77).This was attributed to the fact that ICD-treated MADIT II patients died predominantly of non-sudden HF, and QRSd would not predict HF mortality [42]

In the cardiac resynchronization therapy trial (MADIT-CRT), CRT dramatically reduces the progression of HF in patients with a low ejection fraction and a wide QRS complex. QRS duration and morphology was considered an important prognostic factor indicating more advanced cardiac pathology [43].

Other electrocardiographic parameters in which the prognostic value was evaluated were T-wave alternant (MTWA), the signal-averaged ECG (SAECG) and QT parameters and dynamics [44].

One of the parameters with more consistent results was MTWA. TWA consist of a fluctuation of the amplitude or morphology of the T wave every other beat assessed during exercise testing or atria pacing [45].

A positive MTWA determined an approximately 2.5-fold higher risk of cardiac death and life-threatening arrhythmia and showed a very high negative predictive value both in ischemic [46] and no ischemic patients . According to guidelines, it is a recommendation class IIa the use of TWA to improve the diagnosis and risk stratification of patients with ventricular arrhythmias [14].

In a small study in patients post-MI and EF less than or equal to 30%, microvolt TWA was better than QRS duration at identifying a high-risk group and also a low-risk group unlikely to benefit from ICD therapy [47].

SAECG permits the identification of low-amplitude signals (microvolt level) at the end of the QRS complex referred to as late potentials. These indicate regions of abnormal myocardium with slow conduction believed to serve as markers of the substrate for reentrant ventricular tachyarrhythmias [48]. It has a high negative predictive value but its value is lower after coronary revascularization. [49]

5. Autonomic variables

The main variables studied included the autonomic heart rate variability (HRV)/turbulence and the baroreceptor sensitivity.

HRV corresponds to a beat-to-beat variance in cardiac cycle length resulting from the sympatho-vagal influence on the sinus node. HRV is a term that encompasses a large number of different measures derived from 24-h Holter recordings.

In general, if such measures are extremely low, it is considered that there is autonomic dysfunction and this has been shown to independently predict the risk of SCD in post-infarct patients [50].

Methods based on non-linear dynamics and HR turbulence seams to provide better prognostic information than the traditional ones [51], [52].

Several studies have evaluated the prognostic value of heart rate variability in patients with ischemic heart disease [53]. In the randomized defibrillator in AMI trial (DYNAMIT), which used reduced SDNN combined with reduced left ventricular ejection fraction measured early (within 2weeks) after AMI as an inclusion criterion, there was no mortality benefit from ICD therapy in these presumably high risk patients [32].

On the contrary, in the cardiac arrhythmias and risk stratification after myocardial infarction (CARISMA) study, reduced HR variability measured at 6weeks after AMI, particularly the very-low frequency spectral component, was a powerful index in predicting arrhythmic events. The REFINE trial (Risk estimation after infarction, non-invasive evaluation) confirmed that HRV and HR turbulence yield more powerful prognostic information for arrhythmic events when measured later (6–10weeks) after AMI [54].

Despite these promising results, further prospective studies are needed to determine the usefulness of these parameters in clinical practice.

Reduced baroreflex sensivity, a quantitative index of primarily vagal reflexes, evaluated by the phenylephrine method or by a non-invasive measurement [55], is also useful in assessing the risk of SCD [56, 57].

6. Autonomic imaging

There is evidence that regional and global sympathetic denervation could predispose to ventricular arrhythmias in post-MI patients. The denervated but viable myocardium could be hyperresponsive to circulating catecholamines [58, 59].

Using imaging methods for the evaluation of the sympathetic system in vivo, in human and animal models, such as [12[3]I-mIBG cardiac imaging, it has been reported that the mismatch between sympathetic innervation and perfusion could be associated with increased risk of ventricular arrhythmias.

The extent of sympathetic denervation measured at 4-Hour delayed ^{123}I-mIBG SPECT imaging has been correlated with inducibility of ventricular arrhythmias in electrophysiological testing [60]. In another study including patients with advanced heart failure, late [12[3]I-MIBG SPECT defect score was also an independent predictor for ventricular arrhythmias causing appropriate ICD therapy (primary end point) as well as the composite of appropriate ICD therapy or cardiac death (secondary end point) [27]

More studies are required to determine the role of autonomic imaging in post-MI patients, possibly detailing their correlation with CMR findings.

7. Electrophysiological testing

Patients after MI have the highest induction rates in electrophysiological study and the presence of ejection fraction less than 40% and asymptomatic NSVT is associated with a inducibility of 20-40% [22], [61].

Programmed ventricular stimulation identifies most patients at risk for sustained monomorphic ventricular tachycardia associated with reentrant circuits that result of the healing process after infarction [22].

Electrophysiological study was required in MADIT, MUSTT, BEST–ICD [62], but not in MADIT –II and SCD-HeFt trials.

Based on these trials, electrophysiological testing is not required before ICD implantation. It is recommended (class I) for diagnostic evaluation of symptoms suggestive of tachyarrhythmias, to guide VT ablation and for differential diagnosis of a wide-QRS-complex tachycardias of unclear mechanism [14].

Electrophysiological study is also reasonable for risk stratification in patients with NSVT, and LVEF equal or less than 40% (Class IIa). Inducibility of VT in patients with NSVT is as-

sociated with a high risk for VT/FV and the characteristics of NSVT could not predict the inducibility [63].

8. Echocardiographic parameters

The echocardiogram is a fundamental exam for the identification of candidates for ICD implantation. Although an LVEF of <40% is commonly used for stratification of patients at risk for ventricular arrhythmias, it does not allow accurate discrimination of patients with or without sudden arrhythmic death. Moreover, sudden arrhythmic death also occurs in patients with an LVEF of ≥40% [64].

The technical advances in echocardiography will probably allow exploring the appraisal value of new variables beyond the ejection fraction of the left ventricle in the risk stratification.

In a unicenter study a greater involvement of peri-infarct zone longitudinal strain was independently associated with an increased risk of having an appropriate ICD therapy on follow-up. In such study the odds of dying in a patient with a peri-infarct zone strain value of -6% was approximately 11.5 times that of a patient with a peri-infarct zone strain value of -17% [65].

9. Cardiac magnetic resonance

Cardiac MRI allows characterization of cardiac morphology in patients with poor echo cardiographic window and provides an estimate of the location and amount of intramyocardial fibrosis.

The presence of myocardial scar or fibrosis as measured by delayed enhancement after administration of gadolinium has been recently associated with post-infarct arrhythmic death [66], [67] suggesting that contrast-enhanced MRI may enable better risk stratification for ICD implantation among patients with prior MI compared with traditional variables such as LVEF and NYHA class.

Roes S et al identified infarct tissue heterogeneity on contrast-enhanced MRI as a strong predictor of spontaneous ventricular arrhythmia in ICD therapy recipients [68]. In a more recent study from a tertiary center which included the monitoring of 52 patients, it was identified a relationship between the transmurality of infarction and the occurrence of spontaneous ventricular arrhythmias in patients with chronic ischemic cardiopathy [69].

10. Conclusion

Ischemic heart disease is the heart disease in which most often there is indication for an ICD implantation. However, after placed, these devices are used in a minority of patients in the context of primary prevention.

Left ventricular dysfunction remains the most robust parameter in the decision to implant an ICD. All therapeutic measures that can accelerate or improve myocardial reperfusion by contributing to the preservation of ventricular function are undoubtedly the best strategies to reduce costs associated with ICDs.

In recent years numerous studies have been performed using non-invasive methods for diagnosis of autonomic dysfunction or anatomic-functional abnormalities but it remains a need for a proper validation of predictors of arrhythmic death.

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References

[1] Buxton AE, Calkins H, Callans DJ, DiMarco JP, Fisher JD, Greene HL, et al. ACC/AHA/HRS 2006 key data elements and definitions for electrophysiological studies and procedures: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Data Standards (ACC/AHA/HRS Writing Committee to Develop Data Standards on Electrophysiology). Circulation. 2006; 114(23): 2534-70.

[2] Jimenez RA, Myerburg RJ. Sudden cardiac death. Magnitude of the problem, substrate/trigger interaction, and populations at high risk. Cardiol Clin. 1993; 11(1): 1-9.

[3] Priori SG, Aliot E, Blomstrom-Lundqvist C, Bossaert L, Breithardt G, Brugada P, et al. Update of the guidelines on sudden cardiac death of the European Society of Cardiology. Eur Heart J. 2003; 24(1): 13-5.

[4] Barbour DJ, Warnes CA, Roberts WC. Cardiac findings associated with sudden death secondary to atherosclerotic coronary artery disease: comparison of patients with and those without previous angina pectoris and/or healed myocardial infarction. Circulation. 1987; 75(3 Pt 2): II9-11.

[5] Goldberger JJ, Cain ME, Hohnloser SH, Kadish AH, Knight BP, Lauer MS, et al. American Heart Association/American College of Cardiology Foundation/Heart Rhythm Society scientific statement on noninvasive risk stratification techniques for identifying patients at risk for sudden cardiac death: a scientific statement from the American Heart Association Council on Clinical Cardiology Committee on Electro-

cardiography and Arrhythmias and Council on Epidemiology and Prevention. Circulation. 2008; 118(14): 1497-518.

[6] Hjalmarson A. Effects of beta blockade on sudden cardiac death during acute myocardial infarction and the postinfarction period. Am J Cardiol. 1997; 80(9B): 35J-9J.

[7] Waldo AL, Camm AJ, deRuyter H, Friedman PL, MacNeil DJ, Pauls JF, et al. Effect of d-sotalol on mortality in patients with left ventricular dysfunction after recent and remote myocardial infarction. The SWORD Investigators. Survival With Oral d-Sotalol. Lancet. 1996; 348(9019): 7-12.

[8] Mark DB, Nelson CL, Anstrom KJ, Al-Khatib SM, Tsiatis AA, Cowper PA, et al. Cost-effectiveness of defibrillator therapy or amiodarone in chronic stable heart failure: results from the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT). Circulation. 2006; 114(2): 135-42.

[9] Weaver WD, Cobb LA, Hallstrom AP, Fahrenbruch C, Copass MK, Ray R. Factors influencing survival after out-of-hospital cardiac arrest. J Am Coll Cardiol. 1986; 7(4): 752-7.

[10] A comparison of antiarrhythmic-drug therapy with implantable defibrillators in patients resuscitated from near-fatal ventricular arrhythmias. The Antiarrhythmics versus Implantable Defibrillators (AVID) Investigators. N Engl J Med. 1997; 337(22): 1576-83.

[11] Connolly SJ, Gent M, Roberts RS, Dorian P, Roy D, Sheldon RS, et al. Canadian implantable defibrillator study (CIDS) : a randomized trial of the implantable cardioverter defibrillator against amiodarone. Circulation. 2000; 101(11): 1297-302.

[12] Kuck KH, Cappato R, Siebels J, Ruppel R. Randomized comparison of antiarrhythmic drug therapy with implantable defibrillators in patients resuscitated from cardiac arrest : the Cardiac Arrest Study Hamburg (CASH). Circulation. 2000; 102(7): 748-54.

[13] Connolly SJ, Hallstrom AP, Cappato R, Schron EB, Kuck KH, Zipes DP, et al. Meta-analysis of the implantable cardioverter defibrillator secondary prevention trials. AVID, CASH and CIDS studies. Antiarrhythmics vs Implantable Defibrillator study. Cardiac Arrest Study Hamburg . Canadian Implantable Defibrillator Study. Eur Heart J. 2000; 21(24): 2071-8.

[14] Zipes DP, Camm AJ, Borggrefe M, Buxton AE, Chaitman B, Fromer 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 (Writing Committee to Develop Guidelines for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death). J Am Coll Cardiol. 2006; 48(5): e247-346.

[15] Myerburg RJ. Sudden cardiac death: exploring the limits of our knowledge. J Cardiovasc Electrophysiol. 2001; 12(3): 369-81.

[16] Holmes DR, Jr., Davis K, Gersh BJ, Mock MB, Pettinger MB. Risk factor profiles of patients with sudden cardiac death and death from other cardiac causes: a report from the Coronary Artery Surgery Study (CASS). J Am Coll Cardiol. 1989; 13(3): 524-30.

[17] Kannel WB, Thomas HE, Jr. Sudden coronary death: the Framingham Study. Ann N Y Acad Sci. 1982; 382: 3-21.

[18] Snapir A, Mikkelsson J, Perola M, Penttila A, Scheinin M, Karhunen PJ. Variation in the alpha2B-adrenoceptor gene as a risk factor for prehospital fatal myocardial infarction and sudden cardiac death. J Am Coll Cardiol. 2003; 41(2): 190-4.

[19] Friedlander Y, Siscovick DS, Weinmann S, Austin MA, Psaty BM, Lemaitre RN, et al. Family history as a risk factor for primary cardiac arrest. Circulation. 1998; 97(2): 155-60.

[20] Jouven X, Empana JP, Schwartz PJ, Desnos M, Courbon D, Ducimetiere P. Heart-rate profile during exercise as a predictor of sudden death. N Engl J Med. 2005; 352(19): 1951-8.

[21] Luu M, Stevenson WG, Stevenson LW, Baron K, Walden J. Diverse mechanisms of unexpected cardiac arrest in advanced heart failure. Circulation. 1989; 80(6): 1675-80.

[22] Buxton AE, Lee KL, DiCarlo L, Gold MR, Greer GS, Prystowsky EN, et al. Electrophysiologic testing to identify patients with coronary artery disease who are at risk for sudden death. Multicenter Unsustained Tachycardia Trial Investigators. N Engl J Med. 2000; 342(26): 1937-45.

[23] Piccini JP, Horton JR, Shaw LK, Al-Khatib SM, Lee KL, Iskandrian AE, et al. Single-photon emission computed tomography myocardial perfusion defects are associated with an increased risk of all-cause death, cardiovascular death, and sudden cardiac death. Circ Cardiovasc Imaging. 2008; 1(3): 180-8.

[24] Yan GH, Wang M, Yiu KH, Lau CP, Zhi G, Lee SW, et al. Subclinical left ventricular dysfunction revealed by circumferential 2D strain imaging in patients with coronary artery disease and fragmented QRS complex. Heart Rhythm. 2012; 9(6): 928-35.

[25] Scott PA, Morgan JM, Carroll N, Murday DC, Roberts PR, Peebles CR, et al. The extent of left ventricular scar quantified by late gadolinium enhancement MRI is associated with spontaneous ventricular arrhythmias in patients with coronary artery disease and implantable cardioverter-defibrillators. Circ Arrhythm Electrophysiol. 2011; 4(3): 324-30.

[26] Nishisato K, Hashimoto A, Nakata T, Doi T, Yamamoto H, Nagahara D, et al. Impaired cardiac sympathetic innervation and myocardial perfusion are related to lethal arrhythmia: quantification of cardiac tracers in patients with ICDs. J Nucl Med. 2010; 51(8): 1241-9.

[27] Boogers MJ, Borleffs CJ, Henneman MM, van Bommel RJ, van Ramshorst J, Boersma E, et al. Cardiac sympathetic denervation assessed with 123-iodine metaiodobenzylguanidine imaging predicts ventricular arrhythmias in implantable cardioverter-defibrillator patients. J Am Coll Cardiol. 2010; 55(24): 2769-77.

[28] Moss AJ, Hall WJ, Cannom DS, Daubert JP, Higgins SL, Klein H, et al. Improved survival with an implanted defibrillator in patients with coronary disease at high risk for ventricular arrhythmia. Multicenter Automatic Defibrillator Implantation Trial Investigators. N Engl J Med. 1996; 335(26): 1933-40.

[29] Bigger JT, Jr. Prophylactic use of implanted cardiac defibrillators in patients at high risk for ventricular arrhythmias after coronary-artery bypass graft surgery. Coronary Artery Bypass Graft (CABG) Patch Trial Investigators. N Engl J Med. 1997; 337(22): 1569-75.

[30] Lee KL, Hafley G, Fisher JD, Gold MR, Prystowsky EN, Talajic M, et al. Effect of implantable defibrillators on arrhythmic events and mortality in the multicenter unsustained tachycardia trial. Circulation. 2002; 106(2): 233-8.

[31] Moss AJ, Zareba W, Hall WJ, Klein H, Wilber DJ, Cannom DS, et al. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. N Engl J Med. 2002; 346(12): 877-83.

[32] Hohnloser SH, Kuck KH, Dorian P, Roberts RS, Hampton JR, Hatala R, et al. Prophylactic use of an implantable cardioverter-defibrillator after acute myocardial infarction. N Engl J Med. 2004; 351(24): 2481-8.

[33] Steinbeck G, Andresen D, Seidl K, Brachmann J, Hoffmann E, Wojciechowski D, et al. Defibrillator implantation early after myocardial infarction. N Engl J Med. 2009; 361(15): 1427-36.

[34] Mountantonakis SE, Hutchinson MD. Indications for implantable cardioverter-defibrillator placement in ischemic cardiomyopathy and after myocardial infarction. Curr Heart Fail Rep. 2011; 8(4): 252-9.

[35] Goldenberg I, Gillespie J, Moss AJ, Hall WJ, Klein H, McNitt S, et al. Long-term benefit of primary prevention with an implantable cardioverter-defibrillator: an extended 8-year follow-up study of the Multicenter Automatic Defibrillator Implantation Trial II. Circulation. 2010; 122(13): 1265-71.

[36] Barsheshet A, Moss AJ, Huang DT, McNitt S, Zareba W, Goldenberg I. Applicability of a risk score for prediction of the long-term (8-year) benefit of the implantable cardioverter-defibrillator. J Am Coll Cardiol. 2012; 59(23): 2075-9.

[37] Medina-Ravell VA, Lankipalli RS, Yan GX, Antzelevitch C, Medina-Malpica NA, Medina-Malpica OA, et al. Effect of epicardial or biventricular pacing to prolong QT interval and increase transmural dispersion of repolarization: does resynchronization therapy pose a risk for patients predisposed to long QT or torsade de pointes? Circulation. 2003; 107(5): 740-6.

[38] Barsheshet A, Wang PJ, Moss AJ, Solomon SD, Al-Ahmad A, McNitt S, et al. Reverse remodeling and the risk of ventricular tachyarrhythmias in the MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial-Cardiac Resynchronization Therapy). J Am Coll Cardiol. 2011; 57(24): 2416-23.

[39] Brilakis ES, Wright RS, Kopecky SL, Reeder GS, Williams BA, Miller WL. Bundle branch block as a predictor of long-term survival after acute myocardial infarction. Am J Cardiol, 2001; 88:205–209.

[40] Brenyo A, Zareba W. Prognostic significance of QRS duration and morphology. Cardiol J. 2011; 18(1): 8-17.

[41] Zimetbaum PJ, Buxton AE, Batsford W, Fisher JD, Hafley GE, Lee KL, et al. Electrocardiographic predictors of arrhythmic death and total mortality in the multicenter unsustained tachycardia trial. Circulation. 2004; 110(7): 766-9.

[42] Dhar R, Alsheikh-Ali AA, Estes NA, 3rd, Moss AJ, Zareba W, Daubert JP, et al. Association of prolonged QRS duration with ventricular tachyarrhythmias and sudden cardiac death in the Multicenter Automatic Defibrillator Implantation Trial II (MADIT-II). Heart Rhythm. 2008; 5(6): 807-13.

[43] Goldenberg I, Moss AJ, Hall WJ, Foster E, Goldberger JJ, Santucci P, et al. Predictors of response to cardiac resynchronization therapy in the Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy (MADIT-CRT). Circulation. 2011; 124(14): 1527-36.

[44] Jensen BT, Abildstrom SZ, Larroude CE, Agner E, Torp-Pedersen C, Nyvad O, et al. QT dynamics in risk stratification after myocardial infarction. Heart Rhythm. 2005; 2(4): 357-64.

[45] Ikeda T, Saito H, Tanno K, Shimizu H, Watanabe J, Ohnishi Y, et al. T-wave alternans as a predictor for sudden cardiac death after myocardial infarction. Am J Cardiol. 2002; 89(1): 79-82.

[46] Chow T, Kereiakes DJ, Bartone C, Booth T, Schloss EJ, Waller T, et al. Prognostic utility of microvolt T-wave alternans in risk stratification of patients with ischemic cardiomyopathy. J Am Coll Cardiol. 2006; 47(9): 1820-7.

[47] Bloomfield DM, Steinman RC, Namerow PB, Parides M, Davidenko J, Kaufman ES, et al. Microvolt T-wave alternans distinguishes between patients likely and patients not likely to benefit from implanted cardiac defibrillator therapy: a solution to the Multicenter Automatic Defibrillator Implantation Trial (MADIT) II conundrum. Circulation. 2004; 110(14): 1885-9.

[48] Steinberg JS, Prystowsky E, Freedman RA, Moreno F, Katz R, Kron J, et al. Use of the signal-averaged electrocardiogram for predicting inducible ventricular tachycardia in patients with unexplained syncope: relation to clinical variables in a multivariate analysis. J Am Coll Cardiol. 1994; 23(1): 99-106.

[49] Cook JR, Flack JE, Gregory CA, Deaton DW, Rousou JA, Engelman RM. Influence of the preoperative signal-averaged electrocardiogram on left ventricular function after coronary artery bypass graft surgery in patients with left ventricular dysfunction. The CABG Patch Trial. Am J Cardiol. 1998; 82(3): 285-9.

[50] Zuanetti G, Neilson JM, Latini R, Santoro E, Maggioni AP, Ewing DJ. Prognostic significance of heart rate variability in post-myocardial infarction patients in the fibrinolytic era. The GISSI-2 results. Gruppo Italiano per lo Studio della Sopravvivenza nell' Infarto Miocardico. Circulation. 1996; 94(3): 432-6.

[51] Bauer A, Malik M, Schmidt G, Barthel P, Bonnemeier H, Cygankiewicz I, et al. Heart rate turbulence: standards of measurement, physiological interpretation, and clinical use: International Society for Holter and Noninvasive Electrophysiology Consensus. J Am Coll Cardiol. 2008; 52(17): 1353-65.

[52] Perkiomaki JS, Jokinen V, Tapanainen J, Airaksinen KE, Huikuri HV. Autonomic markers as predictors of nonfatal acute coronary events after myocardial infarction. Ann Noninvasive Electrocardiol. 2008; 13(2): 120-9.

[53] Huikuri HV, Stein PK. Clinical application of heart rate variability after acute myocardial infarction. Front Physiol. 2012; 3: 41.

[54] Huikuri HV, Exner DV, Kavanagh KM, Aggarwal SG, Mitchell LB, Messier MD, et al. 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(2): 229-35.

[55] Pinna GD, La Rovere MT, Maestri R, Mortara A, Bigger JT, Schwartz PJ. Comparison between invasive and non-invasive measurements of baroreflex sensitivity; implications for studies on risk stratification after a myocardial infarction. Eur Heart J. 2000; 21(18): 1522-9.

[56] La Rovere MT, Pinna GD, Hohnloser SH, Marcus FI, Mortara A, Nohara R, et al. Baroreflex sensitivity and heart rate variability in the identification of patients at risk for life-threatening arrhythmias: implications for clinical trials. Circulation. 2001; 103(16): 2072-7.

[57] Farrell TG, Odemuyiwa O, Bashir Y, Cripps TR, Malik M, Ward DE, et al. Prognostic value of baroreflex sensitivity testing after acute myocardial infarction. Br Heart J. 1992; 67(2): 129-37.

[58] Podrid PJ, Fuchs T, Candinas R. Role of the sympathetic nervous system in the genesis of ventricular arrhythmia. Circulation. 1990; 82(2 Suppl): I103-13.

[59] Kammerling JJ, Green FJ, Watanabe AM, Inoue H, Barber MJ, Henry DP, et al. Denervation supersensitivity of refractoriness in noninfarcted areas apical to transmural myocardial infarction. Circulation. 1987; 76(2): 383-93.

[60] Bax JJ, Kraft O, Buxton AE, Fjeld JG, Parizek P, Agostini D, et al. 123 I-mIBG scintigraphy to predict inducibility of ventricular arrhythmias on cardiac electrophysiology

testing: a prospective multicenter pilot study. Circ Cardiovasc Imaging. 2008; 1(2): 131-40.

[61] Swerdlow CD, Bardy GH, McAnulty J, Kron J, Lee JT, Graham E, et al. Determinants of induced sustained arrhythmias in survivors of out-of-hospital ventricular fibrillation. Circulation. 1987; 76(5): 1053-60.

[62] Raviele A, Bongiorni MG, Brignole M, Cappato R, Capucci A, Gaita F, et al. Early EPS/ICD strategy in survivors of acute myocardial infarction with severe left ventricular dysfunction on optimal beta-blocker treatment. The BEta-blocker STrategy plus ICD trial. Europace. 2005; 7(4): 327-37.

[63] Buxton AE, Lee KL, DiCarlo L, Echt DS, Fisher JD, Greer GS, et al. Nonsustained ventricular tachycardia in coronary artery disease: relation to inducible sustained ventricular tachycardia. MUSTT Investigators. Ann Intern Med. 1996; 125(1): 35-9.

[64] Goldberger JJ, Cain ME, Hohnloser SH, Kadish AH, Knight BP, Lauer MS, et al. American Heart Association/American College of Cardiology Foundation/Heart Rhythm Society Scientific Statement on Noninvasive Risk Stratification Techniques for Identifying Patients at Risk for Sudden Cardiac Death. A scientific statement from the American Heart Association Council on Clinical Cardiology Committee on Electrocardiography and Arrhythmias and Council on Epidemiology and Prevention. J Am Coll Cardiol. 2008; 52(14): 1179-99.

[65] Ng AC, Bertini M, Borleffs CJ, Delgado V, Boersma E, Piers SR, et al. Predictors of death and occurrence of appropriate implantable defibrillator therapies in patients with ischemic cardiomyopathy. Am J Cardiol. 2010; 106(11): 1566-73.

[66] Klem I, Weinsaft JW, Bahnson TD, Hegland D, Kim HW, Hayes B, et al. Assessment of myocardial scarring improves risk stratification in patients evaluated for cardiac defibrillator implantation. J Am Coll Cardiol. 2012; 60(5): 408-20.

[67] Gao P, Yee R, Gula L, Krahn AD, Skanes A, Leong-Sit P, et al. Prediction of arrhythmic events in ischemic and dilated cardiomyopathy patients referred for implantable cardiac defibrillator: evaluation of multiple scar quantification measures for late gadolinium enhancement magnetic resonance imaging. Circ Cardiovasc Imaging. 2012; 5(4): 448-56.

[68] Roes SD, Borleffs CJ, van der Geest RJ, Westenberg JJ, Marsan NA, Kaandorp TA, et al. Infarct tissue heterogeneity assessed with contrast-enhanced MRI predicts spontaneous ventricular arrhythmia in patients with ischemic cardiomyopathy and implantable cardioverter-defibrillator. Circ Cardiovasc Imaging. 2009; 2(3): 183-90.

[69] Boye P, Abdel-Aty H, Zacharzowsky U, Bohl S, Schwenke C, van der Geest RJ, et al. Prediction of life-threatening arrhythmic events in patients with chronic myocardial infarction by contrast-enhanced CMR. JACC Cardiovasc Imaging. 2011; 4(8): 871-9.