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Editorial Board Member of *World Journal of Cardiology*, Wattana Leowattana, MD, MSc, PhD, Associate Professor, Senior Researcher, Staff Physician, Clinical Tropical Medicine, Mahidol University, Siriraj Hospital, Faculty of Medicine, Rachatawee 10400, Bangkok, Thailand. leowattana@yahoo.com

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Arrhythmic risk stratification in ischemic, non-ischemic and hypertrophic cardiomyopathy: A two-step multifactorial, electrophysiology study inclusive approach

Petros Arsenos, Konstantinos A Gatzoulis, Dimitrios Tsiachris, Polychronis Dilaveris, Skevos Sideris, Ilias Sotiropoulos, Stefanos Archontakis, Christos-Konstantinos Antoniou, Athanasios Kordalis, Ioannis Skiadas, Konstantinos Toutouzas, Charalambos Vlachopoulos, Dimitrios Tousoulis, Konstantinos Tsioufis

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Petros Arsenos, Konstantinos A Gatzoulis, Polychronis Dilaveris, Athanasios Kordalis, Konstantinos Toutouzas, Charalambos Vlachopoulos, Dimitrios Tousoulis, Konstantinos Tsioufis, First Department of Cardiology, National and Kapodistrian University of Athens, Hippokraton Hospital, Athens 11527, Attika, Greece

Dimitrios Tsiachris, Christos-Konstantinos Antoniou, Athens Heart Center, Athens Medical Center, Athens 15125, Attika, Greece

Skevos Sideris, Ilias Sotiropoulos, Stefanos Archontakis, Department of Cardiology, Hippokraton Hospital, Athens 11527, Attika, Greece

Ioannis Skiadas, Fifth Department of Cardiology, Hygeia Hospital, Marousi 15123, Attika, Greece

Corresponding author: Konstantinos A Gatzoulis, MD, PhD, Professor, First Department of Cardiology, National and Kapodistrian University of Athens, Hippokraton Hospital, 114 Vasilissis Sofias Avenue, Athens 11527, Attika, Greece. kgatzoul@med.uoa.gr

Abstract

Annual arrhythmic sudden cardiac death ranges from 0.6% to 4% in ischemic cardiomyopathy (ICM), 1% to 2% in non-ischemic cardiomyopathy (NICM), and 1% in hypertrophic cardiomyopathy (HCM). Towards a more effective arrhythmic risk stratification (ARS) we hereby present a two-step ARS with the usage of seven non-invasive risk factors: Late potentials presence ($\geq 2/3$ positive criteria), premature ventricular contractions ($\geq 30/h$), non-sustained ventricular tachycardia (≥ 1 episode/24 h), abnormal heart rate turbulence (onset $\geq 0\%$ and slope ≤ 2.5 ms) and reduced deceleration capacity (≤ 4.5 ms), abnormal T wave alternans ($\geq 65\mu V$), decreased heart rate variability (SDNN < 70 ms), and prolonged QT_c interval (> 440 ms in males and > 450 ms in females) which reflect the arrhythmogenic mechanisms for the selection of the intermediate arrhythmic risk patients in the first step. In the second step, these intermediate-risk patients undergo a programmed ventricular stimulation (PVS) for the detection of inducible, truly high-risk ICM and NICM patients, who will benefit from an implantable cardioverter defibrillator. For HCM patients, we also suggest the

incorporation of the PVS either for the low HCM Risk-score patients or for the patients with one traditional risk factor in order to improve the inadequate sensitivity of the former and the low specificity of the latter.

Key Words: Arrhythmic sudden cardiac death; Risk stratification; Non-invasive risk factors; Electrophysiology study; Two-step approach; Arrhythmias in cardiomyopathy

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Core Tip: An effective arrhythmic risk stratification approach based on two steps is proposed for the detection of truly high arrhythmic risk patients among ischemic and non-ischemic cardiomyopathy groups: In the first step, patients are screened for several non-invasive risk factors (NIRFs). When even one of these NIRFs is present, patients proceed to the second step, *i.e.*, an electrophysiological study with programmed ventricular stimulation. An implantable cardiac defibrillator is offered to the inducible patients. We also suggest the incorporation of an electrophysiological study in the arrhythmic risk stratification approach among low-risk groups of hypertrophic cardiomyopathy patients.

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INTRODUCTION

Arrhythmic sudden cardiac death (SCD) could potentially pose a threat to patients with ischemic[1] (ICM), non-ischemic[2] (NICM), and hypertrophic[3] (HCM) cardiomyopathy. It occurs by a sudden heart rhythm disorder caused by either an abrupt shift of the normal rhythm to ventricular tachycardia (VT), which degenerates into ventricular fibrillation (VF), or rarely by direct VF[4]. One of the common substrates for this rhythm disturbance in ICM as well as in NICM and HCM is myocardial fibrosis[5]. Arrhythmogenic fibrotic areas are ubiquitous in the post-infarcted myocardial segments in ICM[5], in the left ventricular septum or left ventricular free wall in NICM[6], and interstitially in the left ventricular wall in HCM[7]. The annual SCD rate may range from 0.6% to 4% in ICM[8,9], 1% to 2% in NICM[6] and 1% in HCM[3]. Nevertheless, patients may be protected from arrhythmic SCD thanks to Dr. Mirowski, who conceived the idea, invented and implanted the first cardioverter defibrillator (ICD) back in 1980. However, prior to an ICD implantation, an effective arrhythmic risk stratification (ARS) of a large number of patients at potential arrhythmic risk is required in order to identify those at truly high risk[9] thus, avoiding unnecessary implantations with undue exposure to complications and health system resources exhaustion.

Current status of arrhythmic risk stratification and its limitations

Current European[10] and American Guidelines for SCD prevention are based on previous studies[1,2] with significant inherent design limitations. For the primary prevention of SCD in post-myocardial infarction (post-MI) patients, an ICD implantation is recommended in all patients with left ventricular ejection fraction (LVEF) $\leq 35\%$ based on the MADIT II[1] study results, published 19 years ago. While 18 devices have to be implanted, to save one life during a 2-year follow-up with this strategy[11], a rather significant post-MI subpopulation demonstrating preserved left ventricular systolic function and LVEF $> 35\%$, will be still exposed to SCD with an annual prevalence of malignant arrhythmias ranging between 0.6% to 1%[8]. Similarly, according to the results of SCD-HeFT and DEFINITE[2] studies, an ICD implantation for primary prevention of SCD is recommended for NICM patients with a reduced left ventricular systolic function (LVEF $\leq 35\%$)[10]. The usage of the LVEF $\leq 35\%$ criterion for non-ischemic dilated cardiomyopathy patients' selection for ICD implantation bears two limitations: first, as the LVEF $\leq 35\%$ criterion fails to identify the truly arrhythmic risk patients, the majority of the implanted ICDs within this spectrum are not expected to be activated, and, as the recent DANISH study has shown, survival may not be improved. Secondly, in a significant proportion of NICM patients with an LVEF $> 35\%$, fatal arrhythmic events may occur[6].

In HCM, the current European guidelines recommend the HCM Risk-SCD score calculation and an ICD implantation for patients with an estimated 5-year SCD risk $> 6\%$ (Class IIa)[10]. The HCM Risk-

SCD score, as a screening tool, also has inherent limitations. Since its dawn in the development study among 2082 patients (derivation cohort) and the subsequent application in the evaluation study of 1593 patients[12] (validation cohort), 84 SCD cases occurred during follow-up. An HCM Risk-SCD score > 4% was able to detect 60 out of these 84 SCD cases (71%) but failed to detect the rest (29%, *i.e.*, one out of three patients). This limited performance of the current arrhythmic risk stratification approaches in ischemic and non-ischemic cardiomyopathy is of no surprise because of their inability to estimate the underlying arrhythmic substrate by ignoring significant information from already existing and promising non-invasive[9] and invasive electrophysiology (EP) related techniques[13,14]. MADIT II[1] and SCD-HeFT studies were endeavors for proving the post-ICD implantation survival benefit based on an oversimplistic, rather hemodynamic than EP oriented approach, in coronary artery disease (CAD) and NICM populations, in whom an increased incidence of cardiac mortality was anticipated. In HCM, the development of a multivariate scoring system[12], with the inclusion of clinical, echocardiographic, and electrocardiographic markers, although it achieved some degree of satisfactory performance among patients with several risk factors as recommended in both the European and American guidelines, it failed to detect relatively low-risk patients exhibiting one either strong or rather loose traditional risk factor, and who are still at risk for SCD[15,16]. Furthermore, there is a significant discrepancy between the European and American guidelines, with the former being more specific but less sensitive[17].

Value of the left ventricular ejection fraction in arrhythmic risk stratification and the role of the non-invasive risk factors

Arrhythmic mortality is known to have an inverse correlation with the left ventricular systolic function [9,18]. The more LVEF declines, the more mortality increases: in relatively preserved LVEF > 30% the annual mortality is 3.2%, while in diminished LVEF 21%-30% it raises to 7.7%, and in seriously depressed left ventricular systolic function (LVEF < 20%) it launches, to 9.4%[9]. This inverse correlation between left ventricular systolic function and arrhythmic event rates was known and well described before the MADIT II[1] trial. In this study design, the cutoff point of LVEF ≤ 30% was selected as an enrolment criterion for the recruitment of post-MI patients with moderate to serious heart failure and highly-expected future arrhythmic events[18]. Indeed, the main hypothesis (*i.e.*, ICDs improve survival in post-MI patients) was confirmed within the next 20 mo of follow-up. Thereafter, guideline recommendations[10] for patient selection and ICD implantation were dominated by the enrolment criteria for the CAD patients of the MADIT II study[1], *i.e.*, impaired LVEF ≤ 30% and for the NICM patients by the enrolment criteria of the SCDHeFT study, *i.e.*, diminished LVEF ≤ 35%. It must be emphasized the significant limitations of the LVEF screening tool[9] considering the calculation of left ventricular systolic function may be affected by the intra- and interobserver variability during measurements and may also be affected by the temporal variability arising from the natural evolution of the disease as well as from therapeutic interventions such as coronary artery bypass, percutaneous coronary intervention, and pharmacological treatment. Furthermore, the LVEF is more correlated with total mortality rather than with arrhythmic sudden cardiac death and it has low sensitivity, as only one-third of SCDs occur in patients with LVEF < 35%, while two-thirds of SCDs occur in patients with an LVEF > 35%.

It should also be noted that, despite the guideline recommendations for primary prevention of SCD, ICD implantation rates in patients with LVEF ≤ 35% seem to be below, both in the United States[19] and Europe[20]. Therefore, a reasonable question arouses: why does LVEF, an anatomic-functional index per se, also predicts future arrhythmic events[9]? Impaired left ventricular systolic function is the consequence of post-MI ischemia, myocardial cell necrosis, and myocardial tissue fibrosis. After the infarction of the left ventricle, both anatomic and electric remodelings are evolving. At the anatomic-functional tissue level, the fibrotic scar formation reduces the left ventricular systolic function, while at the molecular scale, the action potential is prolonged, the intracellular calcium homeostasis is affected, and the dispersion of repolarization is increased. Accumulation of connective tissue into the cellular gap junctions occurs in parallel with systemic neurohormonal activation and increased tone of the sympathetic limb of the autonomic nervous system[21]. As a consequence, the LVEF that quantifies the impaired left ventricular functionality also reflects the subsequent electrical instability, predisposing to VT/VF[9]. The more this anatomic-functional index LVEF decreases, the more it encapsulates hidden electric information occurring in electrophysiological and myocardial cell levels. This information is of some prognostic value but the LVEF criterion is raw, modest, and remote from a personalized estimation of the active presence of the arrhythmogenic mechanisms[9]. The need for effective ARS prior to an ICD implantation constitutes a great challenge; in addition to using LVEF, which is of limited sensitivity and specificity, our research group proposes that this hidden electric information should be discriminated and extracted from the impaired anatomic-functional performance of the left ventricle for personalized prognostic ARS by applying the appropriate methods[9]. Arrhythmic SCD is electric in its origin and the most appropriate ARS approach is the usage of conventional and advanced electrocardiography through recording the electric function of the myocardium and detecting the presence and activity of different arrhythmogenic mechanisms[9,22]. Conventional electrocardiographic (ECG) indices, such as late potentials from signal-averaged ECG[23], QTc interval duration[24], number of ventricular premature beats[24], and non-sustained VT episodes[24] per 24 h, as well as advanced ECG

indices such as standard deviation of normal to normal beats from heart rate variability (SDNN)[25], deceleration capacity of heart rate (DC)[26], heart rate turbulence (HRT)[27,28], and T-wave alternans (TWA)[29], may reveal this prognostic information that is related to different arrhythmogenic mechanisms[22]. The above ECG indices were named “non-invasive risk factors” (NIRFs) when applied during the first step in the PRESERVE-EF[24] study for the selection of patients who were further investigated with programmed ventricular stimulation (PVS) in the second step. The main limitation of NIRFs for SCD prediction is solely that each of these risk factors has low positive predictive accuracy by achieving low odds or hazard ratios. To support a decision for an ICD implantation with an acceptable number needed to treat, it has been advocated that a risk stratification index is required to achieve an odds ratio of 25-30. This limitation was effectively addressed in the PRESERVE-EF study[24], through the implementation of PVS in the second step which essentially augmented the performance of the total algorithm after the seven NIRFs had been investigated in the first step.

Cardiac magnetic resonance imaging

Assessment of the arrhythmogenic substrate of the myocardium can be also conducted through cardiac magnetic resonance (CMR). Magnetic resonance diagnostic imaging is based on the contrast between tissues created by the signal generated from the response of hydrogen atoms to the magnetic field. T1 relaxation is the recovery of the longitudinal net magnetization vector and T2 relaxation time is the recovery of the transverse net magnetization vector[30]. T1 mapping does not separate extracellular from cellular segments[31,32]. CMR imaging enhanced with intravenous contrast agents *e.g.*, Gadolinium-based contrast agents (GBCAs), multiplies the extracted information[33]. GBCAs cannot enter the intracellular compartment and are distributed only to the extracellular and interstitial space. After the first distribution, a progressive washout of CBCA is observed in the normal myocardium but this washout is delayed in abnormal fibrotic areas. While late gadolinium enhancement (LGE) expresses the difference between two areas, the extracellular volume (ECV) is reflecting histological changes early in the cardiomyopathies' course, independently of their cause. In CAD, the scar tissue following an acute coronary syndrome forms the arrhythmogenic substrate[34]. LGE detects focal myocardial fibrosis predisposing to arrhythmic risk[35,36]. While in the dense core of the scar the fibrotic areas are interrupted by viable fibers serving as slow conduction pathways, in the “grey zone” that surrounds the core of the scar, the hypoperfused myocardium conceals arrhythmogenic properties[37,38]. CMR by assessing and quantifying the heterogeneity of the scar and size of the border zone predicts malignant arrhythmias and appropriate ICD activations[39]. T1 mapping and ECV abnormal measurements are also correlated with an increased arrhythmic burden[40].

In NICM, both the existence and localization of LGE are independent predictors for arrhythmic SCD and hospitalization in all ranges of LVEF[6,41,42]. Septal LGE carries the worst prognosis, even if the fibrotic area is restricted, while the coexistence of septal with free wall LGE, as well as a subepicardial pattern of LGE, are all additive risk factors for fatal arrhythmias[6,41-43]. ECV reveals the early stages of the disease and represents an independent prognostic factor for cardiovascular death and appropriate ICD activations[44,45].

In HCM, the presence of scar, imaged by LGE, is considered to be a strong independent predictor for ventricular arrhythmias, ventricular remodeling, all-cause mortality, and cardiac death[46]. The extent of myocardial LGE involvement has been proposed as a better risk stratifier, with cutoffs oscillating from as low as 10% to as high as 20%, with the mean value of 15% attaining wider acceptance. The pattern of LGE distribution, patchy with multiple foci or diffuse, does not carry additional risk. Nevertheless, we are not aware of whether the decision for an ICD implantation for primary protection against SCD can be exclusively made based on the cardiac MRI; the specific criteria for such a decision are unknown, and we lack prospective information relevant to the rate of appropriate defibrillator activations among all the implanted devices at follow-up time to evaluate such kind of strategy[47]. The results of the ongoing GUIDE-CMR multicenter study[48] in Australia, a study randomizing both post-MI and NICM patients with relatively preserved LVEF 35%-50% upon CMR findings to ICD *vs* ILR, may provide the initial answers to these questions. In the electrophysiology perspective, CMR characterizes the cardiac tissue and detects the substrate that may be arrhythmogenic. This is a necessary condition for arrhythmogenicity, however, it is considered insufficient. The potential arrhythmogenic function of this scar substrate with the usage of CMR solely remains unknown. In order for this predictive information to be extracted, it is necessary that non-invasive and invasive electrocardiography with VPBs, NSVT, LPs, and inducibility upon PVS in electrophysiology (EP) lab is included in the ARS. CMR may classify an extended number of patients with a scar presence[6,47], and convert all of them to ICD candidates. Following such a strategy, a large number needed to treat may not be avoided, and as it happened with the devices implanted for two decades according to the LVEF criterion, only a small portion will be appropriately activated. While mere CMR is probably insufficient to staunchly support the decision for appropriate patient selection before an ICD implantation, it represents an excellent NIRF for the first initial screening of a two-step, EP inclusive approach.

Electrophysiology study with PVS

Ventricular arrhythmias leading to SCD can be studied in the EP Lab and can be triggered or reproduced in patients prone to arrhythmia. Since 1971, when Wellens *et al*[49] introduced the PVS in

the investigation of arrhythmias, it has been known that malignant VT and VF may be triggered in the EP Lab, with the patient being fully conscious in the supine position. This triggering procedure involves an intracardiac catheter, which has been percutaneously inserted and intravenously advanced into the right ventricle, to contact the myocardium. After the external connection of the catheter to a suitable pulse generator, and the assessment of the effective refractory period of that point of the myocardium, PVS with a specific protocol follows. To increase the sensitivity and specificity of the study, the procedure is usually performed and repeated at two different sites, *i.e.*, at the apex and the right ventricle outflow tract, while NICM patients additionally receive intravenously β -agonists. Myocardial fibrosis forms the substrate for a reentrant mechanism which, during programmed ventricular stimulation with the extra stimuli addition, may be activated and generate monomorphic ventricular tachycardia. Multiple programmed ventricular stimuli may act on the triggering mechanism and they may also cause ventricular tachycardia. The laboratory result of an induced or non-induced sustained ventricular tachyarrhythmia provides unique and valuable information for the management of such patients. This information cannot be extracted through other modalities and requires patients to be subjected to this specific protocol, which in the controlled EP Lab setting, is absolutely safe. Given the importance of the question and the risk of possible future exposure to SCD, there is not a single doubt that a patient's subjection to this invasive procedure is worthwhile. Inducible sustained monomorphic VT has been repeatedly proved to be a predictor of SCD in prospective trials[50]. In contrast, the existing data for polymorphic VT or VF induction are conflicting.

Some studies conclude that the induced polymorphic VT or VF are not associated with a high risk for SCD[50,51] but this point is conflicting, as other data support the aspect that such an arrhythmic response to PVS is also of prognostic value[13,14,52].

In addition, previous studies suggest a low risk of SCD in patients with relatively preserved left ventricular systolic function and LVEF > 40%, even in the presence of inducible VT[53], however, primary protection from major arrhythmic events was recently confirmed for these patients, when the implanted ICDs with the improved two-step, EP inclusive approach in PRESERVE EF study were appropriately activated[24]. In CAD, the ARS may be discerned at three different periods, considering the time pass after the myocardial infarction (MI): (1) the early phase (first 40 d); (2) the subacute phase (40 d–6 mo after the MI); and (3) the remote phase (> 6 mo after the MI).

Acute MI phase (< 40 d): Animal studies have shown that within two weeks after MI, the substrate for reentrant ventricular arrhythmias was formed in the myocardium. In terms of pathophysiology, the experimental results justify an early post-MI PVS investigation[54].

The BEST-ICD study[55] enrolled 143 survivors with left ventricular ejection fraction \leq 35% and either frequent VPBs > 10/h or depressed SDNN < 70 ms from heart rate variability or abnormal signal-averaged ECG within a month after an acute MI. Of these, 138 were randomized, in a 2:3 ratio, to conventional strategy ($n = 59$) or PVS guided/ICD strategy ($n = 79$), with 24 ICDs implanted in the inducible patients. A nonsignificant survival benefit of this early PVS-guided strategy of ICD implantation was shown, but the study was underpowered to provide a definite conclusion for the performance of such an approach. It must be noted that this was a two-step ARS study, with the preselected patients exhibiting a combination of a depressed LVEF \leq 35% and/or three basic NIFRS, while the PVS was performed after total sample randomization.

Two observational ICD studies found that a positive response on PVS is an efficient arrhythmia predictor. In the first one[56], which included ST-elevation MI patients who had received a primary percutaneous coronary intervention, a benefit from an early ICD implantation for the patients with an impaired LVEF and positive PVS was shown, while in the second one[57], which enrolled post-MI patients with a depressed left ventricular systolic function, the PVS study effectively discriminated - in the long term - patients with a protective ICD implantation (PVS positives) from the vast majority of those at significantly lower risk of arrhythmic events without a defibrillator (PVS negatives).

Furthermore, a negative PVS predicted survival in the absence of an ICD implantation[56]. Despite the negative results produced by IRIS and DINAMIT studies, whose design failed to detect the truly early post-MI high arrhythmic risk patients and, thus, failed to prove a survival benefit for the ICD recipients', consequently withholding such patients from an ICD implantation with a class III recommendation[10], the arrhythmic SCD risk in early post-MI phase exists and this is well known and described. The acknowledgment of this risk explains the paradox: while guidelines that are based on the IRIS and DINAMIT studies reject ICD implantation in early post-MI patients with a Class III recommendation[10], the same guidelines, propose screening these early post-MI patients at potential arrhythmic risk with PVS with a Class IIb recommendation. This specific clinical issue questioning the most appropriate ARS strategy is under investigation by the PROTECT-ICD trial[58], which recruits early post-MI patients with LVEF \leq 40% and randomizes them to either PVS-guided early ICD implantation or a control standard care arm.

Subacute and remote phases after MI phase (\geq 40 d): Data for the utility of PVS in remote phases after an MI comes from both randomized and observational studies. MADIT I study, 1996, included 196 post-MI patients at increased risk for ventricular tachyarrhythmias. Enrollment was focused on patients fulfilling the inclusion criteria of LVEF < 35%, non-sustained VT, and the inducibility of VT in PVS.

These patients were randomly assigned to receive either an implanted defibrillator ($n = 95$) or conventional medical therapy ($n = 101$). A 54% reduction in overall mortality was observed for the ICD treatment arm with a 27-mo follow-up. The MUSTT study[59], 1999, investigated a population at relatively increased arrhythmic risk consisting of patients with a prior MI, LVEF% < 40%, and non-sustained VT that was inducible in PVS ($n = 704$). After randomization, 351 of them were assigned to EP-guided therapy and 353 were assigned to no antiarrhythmic therapy. The five-year estimates of the incidence of the primary endpoint of cardiac arrest or death from arrhythmia were 25% for the EP guided therapy receivers and 32% for the patients assigned to no antiarrhythmic therapy with a relative risk: 0.73, representing a 27% risk reduction. In this study, a combination of LVEF<40% and inducibility in the PVS resulted in a greater reduction in mortality than the one observed in the MADIT II trial[1], which used the LVEF as the sole criterion for selecting patients for ICD implantation. These two randomized trials have demonstrated the utility of PVS in combination with a reduced LVEF and other variables in the appropriate selection of the candidates before an ICD implantation. MADIT II study[1] in 2002, extended the prophylactic use of an ICD to a broader post-MI patients spectrum under a less arrhythmic risk compared to the MUSST[59] population with an LVEF < 30% as the only pre-implantation criterion. In the MADIT II trial[1], a PVS was not considered necessary for the initial study. These 1232 post-MI patients with significant heart failure were randomly assigned in a 3:2 ratio to receive either an ICD ($n = 742$) or conventional medical therapy ($n = 490$). An improvement in survival was observed in the ICD group during an average follow-up of 20 mo with a 0.69 hazard ratio. Although a PVS was not an inclusion criterion for patient selection in the initial study, its performance was examined in a MADIT II sub-study[51] and inducibility was found to be related to subsequent ICD-detected arrhythmias. In that study, while an inducible monomorphic VT predicted future arrhythmic episodes, the induction of polymorphic VT or VF appeared less relevant. These data were retrospectively acquired, with many study-centers contributing only 2–4 cases and without having used a standardized PVS protocol. On the other hand, high PVS predictive accuracy was consistently shown when the EP study was performed in dedicated centers in the context of single-center studies, using standardized protocols[13,14,52]. The prospective observational Cardiac Arrhythmias and Risk Stratification After Acute Myocardial Infarction - CARISMA trial in 2009, investigated 312 post-MI phase patients with a mean LVEF of $31\% \pm 6\%$ with application of NIRFs (Heart rate variability/turbulence, ambient arrhythmias, signal-averaged electrocardiogram, T-wave alternans) and PVS, applying the NIRFs and the PVS rather independently in a parallel screening than in a two-step sequential approach. Induction of sustained monomorphic VT predicted the future occurrence of VT/VF (adjusted HR = 4.8, $P = 0.003$).

PVS in NICM and HCM

In NICM, the role of PVS has been disputed[60] for years. However, this view was recently challenged by a prospective study of 157 NICM patients[13,61,62], who were evaluated with PVS for primary prevention; during long-term follow-up, appropriate ICD intervention or SCD occurred significantly more frequently among PVS positive NICM patients. This PVS-guided approach was incorporated for the first time in current ESC guidelines[10], albeit at a class IIb recommendation. In HCM, the ESC guidelines[10] for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death, following ESC HCM guidelines that are based on an expert opinion level of evidence, do not recommend a PVS for ARS. However, recent results[15] support its use in a study that investigated 203 HCM patients with ≥ 1 NIRFs who were submitted to PVS and received an ICD. During a median follow-up period of 60 mo, the primary endpoint was observed in 20 patients, of whom 19 were inducible in a procedure that was proven safe and they had an ICD implanted. Inducibility at PVS predicted SCD or appropriate device therapy while non-inducibility was associated with prolonged event-free survival. The addition of an EP/PVS risk estimation[15], among HCM patients demonstrating one traditional risk factor, may improve the frequently observed rather poor performance[15,63] of either the American or the European guidelines in this subgroup of HCM patients. Considering the time course for the evolution of research in the field of SCD ARS, one could say that data from previous studies have now dried up, leaving significant gaps in the management of such patients[60], gaps that we do not know if and how they will be filled in by methods such as MRI [17] or Virtual PVS[64] in the future. Nevertheless, the latest results published[24] describe a two-step SCD ARS strategy: in the first step of this strategy, if the included bloodless non-invasive ECG markers (NIRFs) are positive, we proceed with the second step of PVS for the patient selection before an ICD implantation. Similar results based on a two-step, EP inclusive approach, were documented in patients across the entire spectrum of ischemic and organic cardiomyopathy, in post-MI patients with preserved LVEF[24], in patients with heart failure and moderately impaired left ventricular systolic function[65], in NICM[13], and HCM[15] patients, noteworthy with correct ICDs activation of the devices implanted. This strategy has been applied in sudden cardiac death ARS by the First Department of Cardiology and EP Lab, National and Kapodistrian University of Athens at Hippocraton Hospital of Athens, Attica, Greece[66], over the last twenty years, thus contributing to the final decision for the appropriate patient selection for ICD implantation across all the ICM[24,65] and NICM[13] and HCM[15] patients' spectrum.

Table 1 Abnormal values and connection of every non-invasive risk factors with the arrhythmogenic mechanisms

Non-invasive risk factors	Abnormal values	Mechanisms
SAECG, LPs	2/3 positive criteria	Fibrotic areas, slow conduction, reentry
QTc	≥ 440 ms (δ), ≥ 450 ms (\varnothing)	Prolonged repolarization, EAD, DAD
TWA	≥ 65 μ V (2-channels)	APD and Ca ²⁺ alternans, steep APDR and CVR, steep FSRCR
VPBs	$\geq 30/24$ h	Automaticity (Ca ²⁺ oscillations), reentry
NSVT	≥ 1 episode/24 h	Automaticity (Ca ²⁺ oscillations), reentry
SDNN/HRV	≤ 75 ms	Enhanced sympathetic tone, autonomic imbalance
DC/HRT	DC ≤ 4.5 ms HRT onset $\geq 0\%$ HRT slope ≤ 2.5 ms	Vagal and sympathetic ANS dysfunction

ANS: Autonomic nervous system; APD: Action potential duration; APDR: Action potential duration restitution; CVR: Conduction velocity restitution; DAD: Delayed afterdepolarization; DC: Deceleration capacity from heart rate dynamics; EAD: Early afterdepolarization; FSRCR: Fractional sarcoplasmic reticulum Ca²⁺ release; HRT: Heart rate turbulence; LPs: Late potentials from signal-averaged electrocardiogram; NSVT: Non-sustained ventricular tachycardia; QTc: Corrected according to Fridericia formula QT interval; SAECG: Signal-averaged electrocardiogram; SDNN: Standard deviation of normal to normal beats from heart rate variability analysis; TWA: T wave alternans; VPBs: Ventricular premature beats.

TWO-STEP, NON-INVASIVE RISK FACTORS ELECTROPHYSIOLOGY STUDY INCLUSIVE, RISK STRATIFICATION ALGORITHM

Initially, the concept of the two-step multifactorial, EP inclusive approach had been successfully introduced for the risk stratification and management of post-MI patients, incorporating NIRFs such as heart rate variability, LVEF, late potentials, and complex ventricular arrhythmias[67,68]. Indeed, such studies identified a high-risk group of post-MI patients, predominantly among those with reduced LVEF that are usually offered an ICD, based on current guidelines. This strategy was further refined and improved in the PRESERVE EF study[24] applying an accurate algorithm with multiple advanced ECG markers[9] that reflect the presence and activity of diverse arrhythmic mechanisms to detect high-risk post-MI patients after a limited myocardial injury without any evidence of ongoing myocardial ischemia or significant left ventricular dysfunction. In the first step, the advanced form of the algorithm [24] determined the presence of seven NIRFs, while in its simplified, yet equally effective form[65], it appears to be working well even in the simple presence of only three fundamental NIRFs. Upon detecting the presence of at least one of the NIRFs, patients are referred for PVS. The advantage of ARS using multiple NIRFs during the first step is that they reflect the presence and activity of multiple different arrhythmogenic mechanisms, such as fibrotic areas with late conduction properties predisposing for re-entry (SAECG late potentials)[23], prolonged action potential repolarization duration (QTc)[24], electrical instability with T wave alternations during repolarization (TWA)[29], increased sympathetic tone (SDNN)[25], decreased parasympathetic tone (DC[26] and HRT[27,28]), triggered activity on a substrate that predisposes to and maintains ventricular arrhythmias (VPBs and NSVT)[24]. The pathophysiological connection for every NIRF with the arrhythmogenic mechanisms[22] is presented in Table 1, while its prevalence in the total sample, in the truly high-risk group that was detected after the two-step, EP inclusive approach, and in the 9 patient subgroup with SCD equivalent major arrhythmic events during a 32 mo of follow-up, as investigated in the PRESERVE EF study[24], are presented in Table 2. The results of the implementation of this two-step risk stratification strategy were described in this study in 575 post-MI, relatively not aged (mean age = 57 years) with preserved left ventricular systolic function (LVEF = 50.8%) patients. In this study, 9 major arrhythmic events (MAEs) were observed during a 32 mo follow-up. The MAE prevalence in the total sample of 575 patients was 1.5%. The implementation of the first step of the algorithm determined an intermediate risk subpopulation of 204 patients out of 575 patients in total, with at least one NIRF present. In this intermediate-risk subpopulation with positive NIRFs, who were risk-stratified using the first step, the MAE prevalence increased from 1.5% to 4.4%. When this subpopulation underwent PVS as per the second step, 41 out of 152 patients developed arrhythmia (out of the 204 patients of the intermediate-risk group who gave their informed consent to participate in the EP study). This third group of 41 PVS-positive patients represented the subpopulation at actual high risk with the MAE prevalence accounting for 22% (Figure 1). It is realistically feasible that by this approach, out of the general population of the ischemic, the NICM and the HCM patients, the subpopulation at actual high risk for SCD who could undergo ICD implantation can be defined in 2 steps, whereas the rest of the patients can safely be excluded from implantation[24,60,69]. This approach will be tested in NICM patients in the

Table 2 Prevalence of non-invasive risk factors in the total sample, in the truly high-risk group, detected after the two-step, electrophysiology inclusive approach, and in patients with major arrhythmic events during a 32-mo follow-up, as investigated in the PRESERVE EF study[24]

NIRF	Prevalence in the total preserve-EF study (n = 577)	Prevalence in the high-risk group (n = 41)	Prevalence in 9 MAE/SCD patients
LPs (%)	13.8	51.2	78 (7/9)
NSVT (%)	8.6	46.3	66 (6/9)
QTc (%)	13.6	36.6	55 (5/9)
VPBs (%)	10.8	39	33 (3/9)
TWA (%)	6.8	24.4	11 (1/9)
SDNN (%)	2.8	9.8	0 (0/9)
HRT and DC (%)	2.8	9.8	0 (0/9)

DC: Deceleration capacity from heart rate dynamics; HRT: Heart rate turbulence from heart rate dynamics; LPs: Late potentials from signal-averaged electrocardiogram; MAE: Major arrhythmic event; NIRF: Non-invasive risk factor; NSVT: Non-sustained ventricular tachycardia; QTc: Corrected according to Fridericia formula QT interval; SDNN: Standard deviation of normal to normal beats from heart rate variability analysis; TWA: T wave alternans; VPBs: Ventricular premature beats.

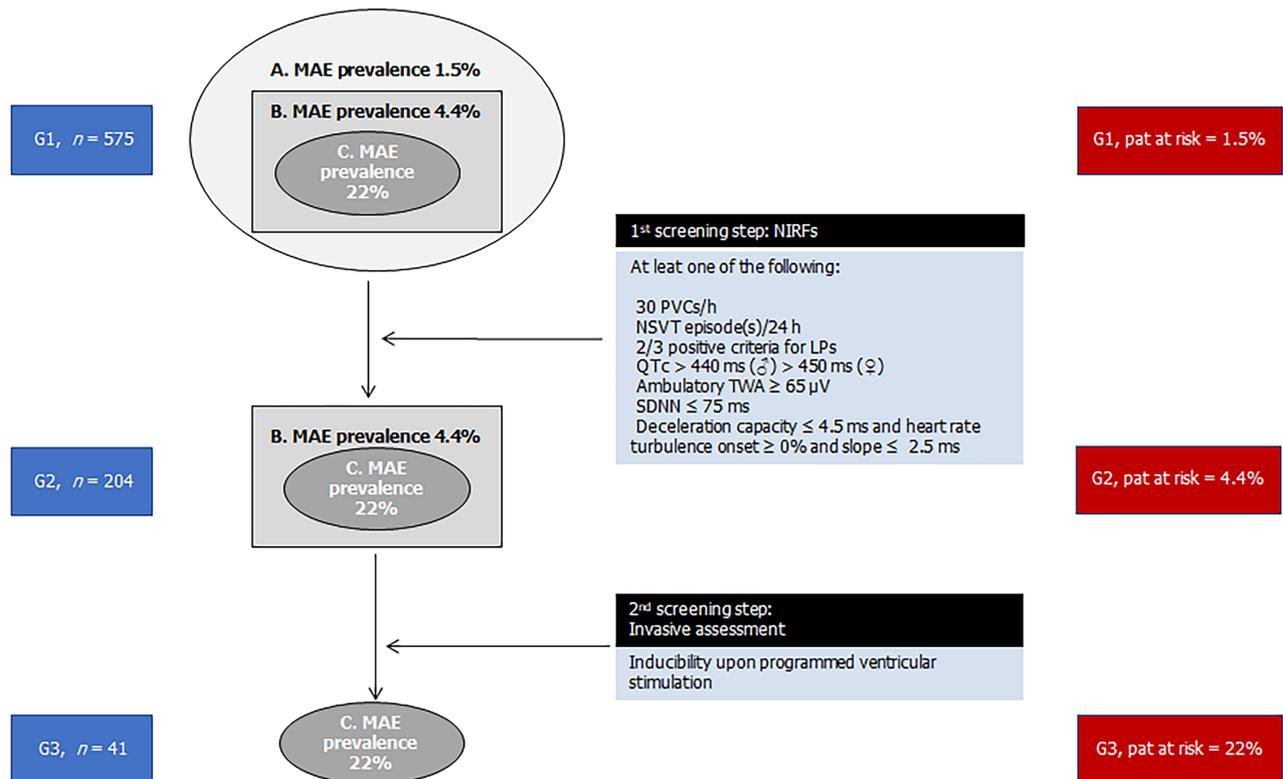


Figure 1 The PRESERVE EF[24] study's two-step arrhythmic risk stratification algorithm. In the total sample of patients the estimated prevalence of major arrhythmic events (MAE) during the 32-mo follow-up was 1.5%. Implementation of the algorithm with the detection of the NIRFs in the first step determines the intermediate-risk subpopulation, with the MAE prevalence accounting for 4.4%. In the second step, the Programmed Ventricular Stimulation determines the actual high-risk subpopulation, with a prevalence reaching 22%. Of the 37 patients with implantable cardioverter defibrillator, there were 9 true activations during the 32-mo follow-up. Neither sudden cardiac death(SCD) nor inappropriate ICD activations were observed during follow-up. (Modified with permission from EHJ[24]).

ReCONSIDER study[70]. An overview of a two-step, non-invasive, EP inclusive ARS approach, for ICM, NICM, and HCM is depicted in Figure 2.

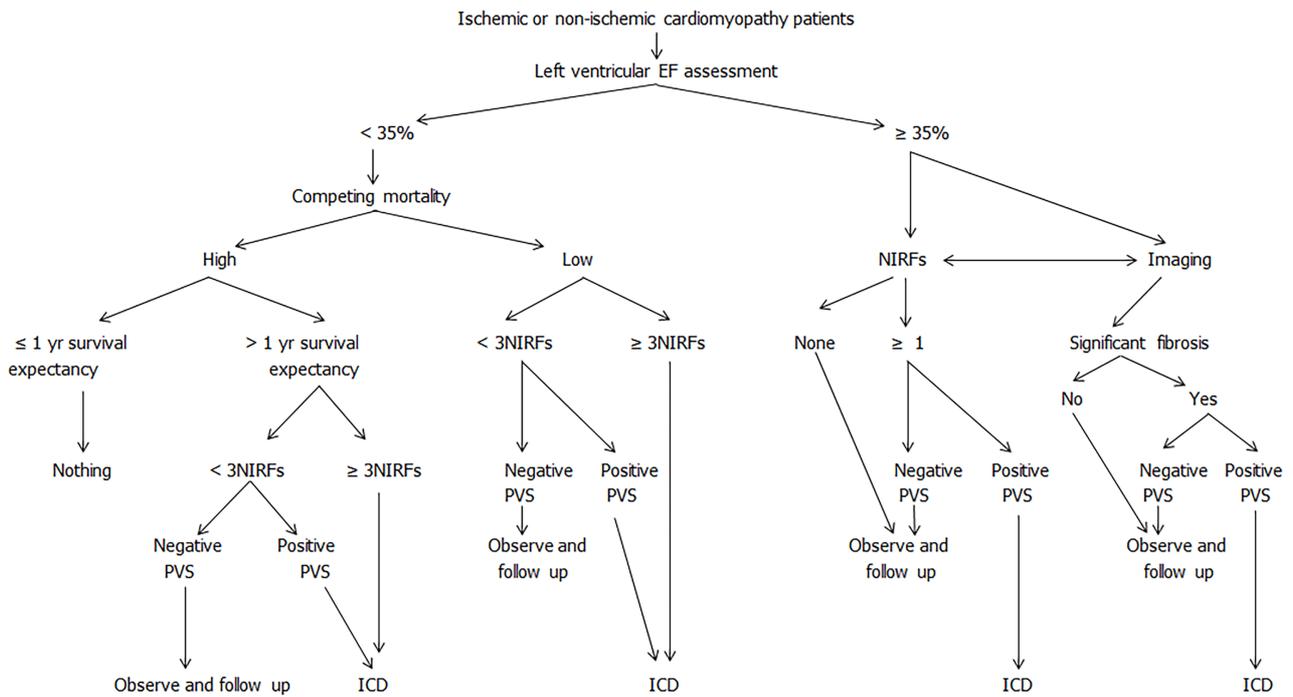


Figure 2 Emerging new sudden cardiac death risk stratification paradigm. It is based on newer evidence, incorporating competing mortality assessments, as well as non-invasive and invasive tests. Non-invasive tests are performed before programmed ventricular stimulation (PVS) to assess the likelihood of functional circuit formation. PVS is pivotal in determining the potential for arrhythmia sustainability and guiding treatment, especially in intermediate and low-risk patients. “Observe and Follow-up” involves repeating tests for NIRF annually and PVS every 3–5 yr. NIRFs (noninvasive ECG risk factors) including the presence of late potentials ($\geq 2/3$ criteria), frequent premature ventricular contractions ($\geq 30/h$), non-sustained VT ($\geq 1/24$ h), abnormal heart rate turbulence (onset $\geq 0\%$ and slope $\leq 2.5ms$) and reduced deceleration capacity (≤ 4.5 ms), positive T wave alternans ($\geq 65 \mu V$), decreased heart rate variability (SDNN $< 70ms$), prolonged QT_c interval (> 440 ms in males and > 450 ms in females). (Modified after permission from ANE[60]).

CONCLUSION

The arrhythmic risk stratification for SCD in Ischemic, Non-Ischemic, and Hypertrophic cardiomyopathy for ICD implantation patient selection may be improved with the proposed two-step algorithm. This broad spectrum of patients shares arrhythmogenic mechanisms. Appropriate screening of all these patients with basic and advanced electrocardiographic indices in the first step may detect the subpopulation of intermediate SCD risk. When this subpopulation is subjected to programmed ventricular stimulation in the second step, the truly high SCD risk patients may be detected and effectively protected with an ICD.

FOOTNOTES

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Country/Territory of origin: Greece

ORCID number: Petros Arsenos 0000-0003-4426-8407; Konstantinos A Gatzoulis 0000-0002-6628-0303; Dimitrios Tsiachris 0000-0003-4531-9712; Polychronis Dilaveris 0000-0003-0399-4111; Skevos Sideris 0000-0003-3165-224X; Ilias Sotiropoulos 0000-0001-7272-9042; Stefanos Archontakis 0000-0001-6905-5788; Christos-Konstantinos Antoniou 0000-0003-4861-2404;

Athanasios Kordalis 0000-0003-4093-4601; Ioannis Skiadas 0000-0002-4964-0266; Konstantinos Toutouzas 0000-0001-9099-1554; Charalambos Vlachopoulos 0000-0002-9904-3558; Dimitrios Tousoulis 0000-0001-7492-4984; Konstantinos Tsioufis 0000-0002-7636-6725.

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