**Name of Journal:** *World Journal of Cardiology*

**Manuscript NO:** 65958

**Manuscript Type:** REVIEW

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

Arsenos P *et al*. Arrhythmic risk stratification with a two-step 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

**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, Hippokration 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, Hippokration Hospital, Athens 11527, Attika, Greece

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

**Author contributions:** Arsenos P and Gatzoulis KA wrote the article; Dilaveris P, Kordalis A, Tsiachris D, Antoniou CK, Sideris S, Sotiropoulos I, Archontakis S and Skiadas I made critical revisions related to the important intellectual content of the manuscript; Toutouzas K, Vlachopoulos C, Tousoulis D, Tsioufis K and Gatzoulis KA approved the final manuscript for publication.

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

**Received:** March 18, 2021

**Revised:** October 28, 2021

**Accepted:** **February 23, 2022**

**Published online:**

**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 (≥ 2/3 positive criteria), premature ventricular contractions (≥ 30/h), non-sustained ventricular tachycardia (≥ 1episode/24 h), abnormal heart rate turbulence (onset ≥ 0% and slope ≤ 2.5 ms) and reduced deceleration capacity (≤ 4.5 ms), abnormal T wave alternans (≥ 65μV), decreased heart rate variability (SDNN < 70ms), and prolonged QTc 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 ICD. 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

Arsenos P, Gatzoulis KA, Tsiachris D, Dilaveris P, Sideris S, Sotiropoulos I, Archontakis S, Antoniou CK, Kordalis A, Skiadas I, Toutouzas K, Vlachopoulos C, Tousoulis D, Tsioufis K. Arrhythmic risk stratification in ischemic, non-ischemic and hypertrophic cardiomyopathy: a two-step multifactorial, electrophysiology study inclusive approach. *World J Cardiol* 2022; In press

**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.

**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) ≤ 35% based on the MADIT II[1] studyresults, 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-HeFTand DEFINITE[2] studies, an ICD implantation for primary prevention of SCD is recommended for NICM patients with a reduced left ventricular systolic function (LVEF ≤ 35%)[10]. The usage of the LVEF ≤ 35% criterion for non-ischemic dilated cardiomyopathy patients’ selection for ICD implantation bears two limitations: first, as the LVEF ≤ 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 DANISHstudy 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-HeFTstudies 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 beforethe 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 dominatedby 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 SCDHeFTstudy, *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 arousing 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 limp 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 ventriclefor 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].

Ιn 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-CMRmulticenter 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 b-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 where 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 ≤ 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 ≤ 35% and/or three basic NIRFS, 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 IRISand DINAMITstudies, 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 DINAMITstudies 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 ≤ 40% and randomizes them to either PVS-guided early ICD implantation or a control standard care arm.

**Subacute and remote phases after MI phase (≥ 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 trialin 2009, investigated 312 post-MI phase patients with a mean LVEF of 31% ± 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 guidelinesthat 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 Hippocration 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.

**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] applyingan 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 (VPBsand 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 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.

**CONCLUSION**

Τhe 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.

**REFERENCES**

1 **Moss AJ**, Zareba W, Hall WJ, Klein H, Wilber DJ, Cannom DS, Daubert JP, Higgins SL, Brown MW, Andrews ML; 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 [PMID: 11907286 DOI: 10.1056/NEJMoa013474]

2 **Kadish A**, Dyer A, Daubert JP, Quigg R, Estes NA, Anderson KP, Calkins H, Hoch D, Goldberger J, Shalaby A, Sanders WE, Schaechter A, Levine JH; Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation (DEFINITE) Investigators. Prophylactic defibrillator implantation in patients with nonischemic dilated cardiomyopathy. *N Engl J Med* 2004; **350**: 2151-2158 [PMID: 15152060 DOI: 10.1056/NEJMoa033088]

3 **Elliott PM**, Gimeno JR, Thaman R, Shah J, Ward D, Dickie S, Tome Esteban MT, McKenna WJ. Historical trends in reported survival rates in patients with hypertrophic cardiomyopathy. *Heart* 2006; **92**: 785-791 [PMID: 16216855 DOI: 10.1136/hrt.2005.068577]

4 **Bayés de Luna A**, Coumel P, Leclercq JF. Ambulatory sudden cardiac death: mechanisms of production of fatal arrhythmia on the basis of data from 157 cases. *Am Heart J* 1989; **117**: 151-159 [PMID: 2911968 DOI: 10.1016/0002-8703(89)90670-4]

5 **Disertori M**, Masè M, Ravelli F. Myocardial fibrosis predicts ventricular tachyarrhythmias. *Trends Cardiovasc Med* 2017; **27**: 363-372 [PMID: 28262437 DOI: 10.1016/j.tcm.2017.01.011]

6 **Halliday BP**, Gulati A, Ali A, Guha K, Newsome S, Arzanauskaite M, Vassiliou VS, Lota A, Izgi C, Tayal U, Khalique Z, Stirrat C, Auger D, Pareek N, Ismail TF, Rosen SD, Vazir A, Alpendurada F, Gregson J, Frenneaux MP, Cowie MR, Cleland JGF, Cook SA, Pennell DJ, Prasad SK. Association Between Midwall Late Gadolinium Enhancement and Sudden Cardiac Death in Patients With Dilated Cardiomyopathy and Mild and Moderate Left Ventricular Systolic Dysfunction. *Circulation* 2017; **135**: 2106-2115 [PMID: 28351901 DOI: 10.1161/CIRCULATIONAHA.116.026910]

7 **Maron MS**. Clinical utility of cardiovascular magnetic resonance in hypertrophic cardiomyopathy. *J Cardiovasc Magn Reson* 2012; **14**: 13 [PMID: 22296938 DOI: 10.1186/1532-429X-14-13]

8 **Ikeda T**, Yoshino H, Sugi K, Tanno K, Shimizu H, Watanabe J, Kasamaki Y, Yoshida A, Kato T. Predictive value of microvolt T-wave alternans for sudden cardiac death in patients with preserved cardiac function after acute myocardial infarction: results of a collaborative cohort study. *J Am Coll Cardiol* 2006; **48**: 2268-2274 [PMID: 17161258 DOI: 10.1016/j.jacc.2006.06.075]

9 **Arsenos P**, Gatzoulis K, Dilaveris P, Manis G, Tsiachris D, Archontakis S, Vouliotis AI, Sideris S, Stefanadis C. Arrhythmic sudden cardiac death: substrate, mechanisms and current risk stratification strategies for the post-myocardial infarction patient. *Hellenic J Cardiol* 2013; **54**: 301-315 [PMID: 23912922]

10 **Priori SG**, Blomström-Lundqvist C, Mazzanti A, Blom N, Borggrefe M, Camm J, Elliott PM, Fitzsimons D, Hatala R, Hindricks G, Kirchhof P, Kjeldsen K, Kuck KH, Hernandez-Madrid A, Nikolaou N, Norekvål TM, Spaulding C, Van Veldhuisen DJ; ESC Scientific Document Group . 2015 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: The Task Force for the Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death of the European Society of Cardiology (ESC). Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC). *Eur Heart J* 2015; **36**: 2793-2867 [PMID: 26320108 DOI: 10.1093/eurheartj/ehv316]

11 **Ezekowitz JA**, Armstrong PW, McAlister FA. Implantable cardioverter defibrillators in primary and secondary prevention: a systematic review of randomized, controlled trials. *Ann Intern Med* 2003; **138**: 445-452 [PMID: 12639076 DOI: 10.7326/0003-4819-138-6-200303180-00007]

12 **O'Mahony C**, Jichi F, Pavlou M, Monserrat L, Anastasakis A, Rapezzi C, Biagini E, Gimeno JR, Limongelli G, McKenna WJ, Omar RZ, Elliott PM; Hypertrophic Cardiomyopathy Outcomes Investigators. A novel clinical risk prediction model for sudden cardiac death in hypertrophic cardiomyopathy (HCM risk-SCD). *Eur Heart J* 2014; **35**: 2010-2020 [PMID: 24126876 DOI: 10.1093/eurheartj/eht439]

13 **Gatzoulis KA**, Vouliotis AI, Tsiachris D, Salourou M, Archontakis S, Dilaveris P, Gialernios T, Arsenos P, Karystinos G, Sideris S, Kallikazaros I, Stefanadis C. Primary prevention of sudden cardiac death in a nonischemic dilated cardiomyopathy population: reappraisal of the role of programmed ventricular stimulation. *Circ Arrhythm Electrophysiol* 2013; **6**: 504-512 [PMID: 23588627 DOI: 10.1161/CIRCEP.113.000216]

14 **Gatzoulis KA**, Tsiachris D, Dilaveris P, Archontakis S, Arsenos P, Vouliotis A, Sideris S, Trantalis G, Kartsagoulis E, Kallikazaros I, Stefanadis C. Implantable cardioverter defibrillator therapy activation for high risk patients with relatively well preserved left ventricular ejection fraction. Does it really work? *Int J Cardiol* 2013; **167**: 1360-1365 [PMID: 22534047 DOI: 10.1016/j.ijcard.2012.04.005]

15 **Gatzoulis KA**, Georgopoulos S, Antoniou CK, Anastasakis A, Dilaveris P, Arsenos P, Sideris S, Tsiachris D, Archontakis S, Sotiropoulos E, Theopistou A, Skiadas I, Kallikazaros I, Stefanadis C, Tousoulis D. Programmed ventricular stimulation predicts arrhythmic events and survival in hypertrophic cardiomyopathy. *Int J Cardiol* 2018; **254**: 175-181 [PMID: 29407088 DOI: 10.1016/j.ijcard.2017.10.033]

16 **Monfredi O**, Calkins H. Was a mistake made when programmed electrical stimulation was eliminated as a sudden death risk marker in hypertrophic cardiomyopathy? *Int J Cardiol* 2018; **254**: 238-239 [PMID: 29407097 DOI: 10.1016/j.ijcard.2017.12.019]

17 **Kariki O**, Antoniou CK, Mavrogeni S, Gatzoulis KA. Updating the Risk Stratification for Sudden Cardiac Death in Cardiomyopathies: The Evolving Role of Cardiac Magnetic Resonance Imaging. An Approach for the Electrophysiologist. *Diagnostics (Basel)* 2020; **10** [PMID: 32751773 DOI: 10.3390/diagnostics10080541]

18 **Myerburg RJ**, Kessler KM, Castellanos A. Sudden cardiac death: epidemiology, transient risk, and intervention assessment. *Ann Intern Med* 1993; **119**: 1187-1197 [PMID: 8239250 DOI: 10.7326/0003-4819-119-12-199312150-00006]

19 **Pillarisetti J**, Emert M, Biria M, Chotia R, Guda R, Bommana S, Pimentel R, Vacek J, Raghuveer D, Berenbom L, Dawn B, Lakkireddy D. Under-Utilization of Implantable Cardioverter Defibrillators in Patients with Heart Failure - The Current State of Sudden Cardiac Death Prophylaxis. *Indian Pacing Electrophysiol J* 2015; **15**: 20-29 [PMID: 25852239 DOI: 10.1016/S0972-6292(16)30838-5]

20 **European Society of Cardiology. The EHRA White Book,** 10th Edition. Available from: https://www.escardio.org/Sub-specialty-communities/European-Heart-Rhythm-Association-(EHRA)/Research-and-Publications/ The-EHRA-White-Books

21 **Rubart M**, Zipes DP. Mechanisms of sudden cardiac death. *J Clin Invest* 2005; **115**: 2305-2315 [PMID: 16138184 DOI: 10.1172/JCI26381]

22 **Qu Z**, Weiss JN. Mechanisms of ventricular arrhythmias: from molecular fluctuations to electrical turbulence. *Annu Rev Physiol* 2015; **77**: 29-55 [PMID: 25340965 DOI: 10.1146/annurev-physiol-021014-071622]

23 **Gatzoulis KA**, Arsenos P, Trachanas K, Dilaveris P, Antoniou C, Tsiachris D, Sideris S, Kolettis TM, Tousoulis D. Signal-averaged electrocardiography: Past, present, and future. *J Arrhythm* 2018; **34**: 222-229 [PMID: 29951136 DOI: 10.1002/joa3.12062]

24 **Gatzoulis KA**, Tsiachris D, Arsenos P, Antoniou CK, Dilaveris P, Sideris S, Kanoupakis E, Simantirakis E, Korantzopoulos P, Goudevenos I, Flevari P, Iliodromitis E, Sideris A, Vassilikos V, Fragakis N, Trachanas K, Vernardos M, Konstantinou I, Tsimos K, Xenogiannis I, Vlachos K, Saplaouras A, Triantafyllou K, Kallikazaros I, Tousoulis D. Arrhythmic risk stratification in post-myocardial infarction patients with preserved ejection fraction: the PRESERVE EF study. *Eur Heart J* 2019; **40**: 2940-2949 [PMID: 31049557 DOI: 10.1093/eurheartj/ehz260]

25 **Kleiger RE**, Miller JP, Bigger JT Jr, Moss AJ. Decreased heart rate variability and its association with increased mortality after acute myocardial infarction. *Am J Cardiol* 1987; **59**: 256-262 [PMID: 3812275 DOI: 10.1016/0002-9149(87)90795-8]

26 **Bauer A**, Kantelhardt JW, Barthel P, Schneider R, Mäkikallio T, Ulm K, Hnatkova K, Schömig A, Huikuri H, Bunde A, Malik M, Schmidt G. Deceleration capacity of heart rate as a predictor of mortality after myocardial infarction: cohort study. *Lancet* 2006; **367**: 1674-1681 [PMID: 16714188 DOI: 10.1016/S0140-6736(06)68735-7]

27 **Schmidt G**, Malik M, Barthel P, Schneider R, Ulm K, Rolnitzky L, Camm AJ, Bigger JT Jr, Schömig A. Heart-rate turbulence after ventricular premature beats as a predictor of mortality after acute myocardial infarction. *Lancet* 1999; **353**: 1390-1396 [PMID: 10227219 DOI: 10.1016/S0140-6736(98)08428-1]

28 **Bauer A**, Barthel P, Müller A, Ulm K, Huikuri H, Malik M, Schmidt G. Risk prediction by heart rate turbulence and deceleration capacity in postinfarction patients with preserved left ventricular function retrospective analysis of 4 independent trials. *J Electrocardiol* 2009; **42**: 597-601 [PMID: 19853731 DOI: 10.1016/j.jelectrocard.2009.07.013]

29 **Verrier RL**, Nearing BD, La Rovere MT, Pinna GD, Mittleman MA, Bigger JT Jr, Schwartz PJ; ATRAMI Investigators. Ambulatory electrocardiogram-based tracking of T wave alternans in postmyocardial infarction patients to assess risk of cardiac arrest or arrhythmic death. *J Cardiovasc Electrophysiol* 2003; **14**: 705-711 [PMID: 12930249 DOI: 10.1046/j.1540-8167.2003.03118.x]

30 **Kwong R.Y. Cardiovascular Magnetic Resonance Imaging; Humana Press Inc.: Totowa,** NJ, USA, 2008.

31 **Mavrogeni S**, Apostolou D, Argyriou P, Velitsista S, Papa L, Efentakis S, Vernardos E, Kanoupaki M, Kanoupakis G, Manginas A. T1 and T2 Mapping in Cardiology: "Mapping the Obscure Object of Desire". *Cardiology* 2017; **138**: 207-217 [PMID: 28813699 DOI: 10.1159/000478901]

32 **Moon JC**, Messroghli DR, Kellman P, Piechnik SK, Robson MD, Ugander M, Gatehouse PD, Arai AE, Friedrich MG, Neubauer S, Schulz-Menger J, Schelbert EB; Society for Cardiovascular Magnetic Resonance Imaging; Cardiovascular Magnetic Resonance Working Group of the European Society of Cardiology. Myocardial T1 mapping and extracellular volume quantification: a Society for Cardiovascular Magnetic Resonance (SCMR) and CMR Working Group of the European Society of Cardiology consensus statement. *J Cardiovasc Magn Reson* 2013; **15**: 92 [PMID: 24124732 DOI: 10.1186/1532-429X-15-92]

33 **Xiao YD**, Paudel R, Liu J, Ma C, Zhang ZS, Zhou SK. MRI contrast agents: Classification and application (Review). *Int J Mol Med* 2016; **38**: 1319-1326 [PMID: 27666161 DOI: 10.3892/ijmm.2016.2744]

34 **Moran JM**, Kehoe RF, Loeb JM, Lichtenthal PR, Sanders JH Jr, Michaelis LL. Extended endocardial resection for the treatment of ventricular tachycardia and ventricular fibrillation. *Ann Thorac Surg* 1982; **34**: 538-552 [PMID: 7138122 DOI: 10.1016/s0003-4975(10)63001-9]

35 **Zhang Y**, Guallar E, Weiss RG, Stillabower M, Gerstenblith G, Tomaselli GF, Wu KC. Associations between scar characteristics by cardiac magnetic resonance and changes in left ventricular ejection fraction in primary prevention defibrillator recipients. *Heart Rhythm* 2016; **13**: 1661-1666 [PMID: 27108939 DOI: 10.1016/j.hrthm.2016.04.013]

36 **Scott PA**, Rosengarten JA, Curzen NP, Morgan JM. Late gadolinium enhancement cardiac magnetic resonance imaging for the prediction of ventricular tachyarrhythmic events: a meta-analysis. *Eur J Heart Fail* 2013; **15**: 1019-1027 [PMID: 23558217 DOI: 10.1093/eurjhf/hft053]

37 **Martin R**, Maury P, Bisceglia C, Wong T, Estner H, Meyer C, Dallet C, Martin CA, Shi R, Takigawa M, Rollin A, Frontera A, Thompson N, Kitamura T, Vlachos K, Wolf M, Cheniti G, Duchâteau J, Massoulié G, Pambrun T, Denis A, Derval N, Hocini M, Della Bella P, Haïssaguerre M, Jaïs P, Dubois R, Sacher F. Characteristics of Scar-Related Ventricular Tachycardia Circuits Using Ultra-High-Density Mapping: A Multi-Center Study. *Circ Arrhythm Electrophysiol* 2018; **11**: e006569 [PMID: 30354406 DOI: 10.1161/CIRCEP.118.006569]

38 **Fenoglio JJ Jr**, Pham TD, Harken AH, Horowitz LN, Josephson ME, Wit AL. Recurrent sustained ventricular tachycardia: structure and ultrastructure of subendocardial regions in which tachycardia originates. *Circulation* 1983; **68**: 518-533 [PMID: 6223722 DOI: 10.1161/01.cir.68.3.518]

39 **Roes SD**, Borleffs CJ, van der Geest RJ, Westenberg JJ, Marsan NA, Kaandorp TA, Reiber JH, Zeppenfeld K, Lamb HJ, de Roos A, Schalij MJ, Bax JJ. 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**: 183-190 [PMID: 19808591 DOI: 10.1161/CIRCIMAGING.108.826529]

40 **Chen Z**, Sohal M, Voigt T, Sammut E, Tobon-Gomez C, Child N, Jackson T, Shetty A, Bostock J, Cooklin M, O'Neill M, Wright M, Murgatroyd F, Gill J, Carr-White G, Chiribiri A, Schaeffter T, Razavi R, Rinaldi CA. Myocardial tissue characterization by cardiac magnetic resonance imaging using T1 mapping predicts ventricular arrhythmia in ischemic and non-ischemic cardiomyopathy patients with implantable cardioverter-defibrillators. *Heart Rhythm* 2015; **12**: 792-801 [PMID: 25533585 DOI: 10.1016/j.hrthm.2014.12.020]

41 **Becker MAJ**, Cornel JH, van de Ven PM, van Rossum AC, Allaart CP, Germans T. The Prognostic Value of Late Gadolinium-Enhanced Cardiac Magnetic Resonance Imaging in Nonischemic Dilated Cardiomyopathy: A Review and Meta-Analysis. *JACC Cardiovasc Imaging* 2018; **11**: 1274-1284 [PMID: 29680351 DOI: 10.1016/j.jcmg.2018.03.006]

42 **Di Marco A**, Anguera I, Schmitt M, Klem I, Neilan TG, White JA, Sramko M, Masci PG, Barison A, Mckenna P, Mordi I, Haugaa KH, Leyva F, Rodriguez Capitán J, Satoh H, Nabeta T, Dallaglio PD, Campbell NG, Sabaté X, Cequier Á. Late Gadolinium Enhancement and the Risk for Ventricular Arrhythmias or Sudden Death in Dilated Cardiomyopathy: Systematic Review and Meta-Analysis. *JACC Heart Fail* 2017; **5**: 28-38 [PMID: 28017348 DOI: 10.1016/j.jchf.2016.09.017]

43 **Halliday BP**, Baksi AJ, Gulati A, Ali A, Newsome S, Izgi C, Arzanauskaite M, Lota A, Tayal U, Vassiliou VS, Gregson J, Alpendurada F, Frenneaux MP, Cook SA, Cleland JGF, Pennell DJ, Prasad SK. Outcome in Dilated Cardiomyopathy Related to the Extent, Location, and Pattern of Late Gadolinium Enhancement. *JACC Cardiovasc Imaging* 2019; **12**: 1645-1655 [PMID: 30219397 DOI: 10.1016/j.jcmg.2018.07.015]

44 **aus dem Siepen F**, Buss SJ, Messroghli D, Andre F, Lossnitzer D, Seitz S, Keller M, Schnabel PA, Giannitsis E, Korosoglou G, Katus HA, Steen H. T1 mapping in dilated cardiomyopathy with cardiac magnetic resonance: quantification of diffuse myocardial fibrosis and comparison with endomyocardial biopsy. *Eur Heart J Cardiovasc Imaging* 2015; **16**: 210-216 [PMID: 25246502 DOI: 10.1093/ehjci/jeu183]

45 **Barison A**, Del Torto A, Chiappino S, Aquaro GD, Todiere G, Vergaro G, Passino C, Lombardi M, Emdin M, Masci PG. Prognostic significance of myocardial extracellular volume fraction in nonischaemic dilated cardiomyopathy. *J Cardiovasc Med (Hagerstown)* 2015; **16**: 681-687 [PMID: 26090916 DOI: 10.2459/JCM.0000000000000275]

46 **Adabag AS**, Maron BJ, Appelbaum E, Harrigan CJ, Buros JL, Gibson CM, Lesser JR, Hanna CA, Udelson JE, Manning WJ, Maron MS. Occurrence and frequency of arrhythmias in hypertrophic cardiomyopathy in relation to delayed enhancement on cardiovascular magnetic resonance. *J Am Coll Cardiol* 2008; **51**: 1369-1374 [PMID: 18387438 DOI: 10.1016/j.jacc.2007.11.071]

47 **Zegard A**, Okafor O, de Bono J, Kalla M, Lencioni M, Marshall H, Hudsmith L, Qiu T, Steeds R, Stegemann B, Leyva F. Myocardial Fibrosis as a Predictor of Sudden Death in Patients With Coronary Artery Disease. *J Am Coll Cardiol* 2021; **77**: 29-41 [PMID: 33413938 DOI: 10.1016/j.jacc.2020.10.046]

48 **Selvanayagam JB**, Hartshorne T, Billot L, Grover S, Hillis GS, Jung W, Krum H, Prasad S, McGavigan AD. Cardiovascular magnetic resonance-GUIDEd management of mild to moderate left ventricular systolic dysfunction (CMR GUIDE): Study protocol for a randomized controlled trial. *Ann Noninvasive Electrocardiol* 2017; **22** [PMID: 28117536 DOI: 10.1111/anec.12420]

49 **Wellens HJ**, Brugada P, Stevenson WG. Programmed electrical stimulation of the heart in patients with life-threatening ventricular arrhythmias: what is the significance of induced arrhythmias and what is the correct stimulation protocol? *Circulation* 1985; **72**: 1-7 [PMID: 4006120 DOI: 10.1161/01.cir.72.1.1]

50 **Bourke JP**, Richards DA, Ross DL, McGuire MA, Uther JB. Does the induction of ventricular flutter or fibrillation at electrophysiologic testing after myocardial infarction have any prognostic significance? *Am J Cardiol* 1995; **75**: 431-435 [PMID: 7863984 DOI: 10.1016/s0002-9149(99)80576-1]

51 **Daubert JP**, Zareba W, Hall WJ, Schuger C, Corsello A, Leon AR, Andrews ML, McNitt S, Huang DT, Moss AJ; MADIT II Study Investigators. Predictive value of ventricular arrhythmia inducibility for subsequent ventricular tachycardia or ventricular fibrillation in Multicenter Automatic Defibrillator Implantation Trial (MADIT) II patients. *J Am Coll Cardiol* 2006; **47**: 98-107 [PMID: 16386671 DOI: 10.1016/j.jacc.2005.08.049]

52 **De Ferrari GM**, Rordorf R, Frattini F, Petracci B, De Filippo P, Landolina M. Predictive value of programmed ventricular stimulation in patients with ischaemic cardiomyopathy: implications for the selection of candidates for an implantable defibrillator. *Europace* 2007; **9**: 1151-1157 [PMID: 17947251 DOI: 10.1093/europace/eum230]

53 **Buxton AE**, Marchlinski FE, Waxman HL, Flores BT, Cassidy DM, Josephson ME. Prognostic factors in nonsustained ventricular tachycardia. *Am J Cardiol* 1984; **53**: 1275-1279 [PMID: 6711427 DOI: 10.1016/0002-9149(84)90078-x]

54 **Kontonika M**, Barka E, Roumpi M, La Rocca V, Lekkas P, Daskalopoulos EP, Vilaeti AD, Baltogiannis GG, Vlahos AP, Agathopoulos S, Kolettis TM. Prolonged intra-myocardial growth hormone administration ameliorates post-infarction electrophysiologic remodeling in rats. *Growth Factors* 2017; **35**: 1-11 [PMID: 28264596 DOI: 10.1080/08977194.2017.1297432]

55 **Raviele A**, Bongiorni MG, Brignole M, Cappato R, Capucci A, Gaita F, Gulizia M, Mangiameli S, Montenero AS, Pedretti RF, Uriarte JA, Sermasi S, Nisam S; BEST + ICD Trial Investigators. 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**: 327-337 [PMID: 16028343 DOI: 10.1016/j.eupc.2005.03.003]

56 **Zaman S**, Sivagangabalan G, Narayan A, Thiagalingam A, Ross DL, Kovoor P. Outcomes of early risk stratification and targeted implantable cardioverter-defibrillator implantation after ST-elevation myocardial infarction treated with primary percutaneous coronary intervention. *Circulation* 2009; **120**: 194-200 [PMID: 19581496 DOI: 10.1161/CIRCULATIONAHA.108.836791]

57 **Kumar S**, Sivagangabalan G, Zaman S, West EB, Narayan A, Thiagalingam A, Kovoor P. Electrophysiology-guided defibrillator implantation early after ST-elevation myocardial infarction. *Heart Rhythm* 2010; **7**: 1589-1597 [PMID: 20650333 DOI: 10.1016/j.hrthm.2010.07.019]

58 **Zaman S**, Taylor AJ, Stiles M, Chow C, Kovoor P. Programmed Ventricular Stimulation to Risk Stratify for Early Cardioverter-Defibrillator Implantation to Prevent Tachyarrhythmias following Acute Myocardial Infarction (PROTECT-ICD): Trial Protocol, Background and Significance. *Heart Lung Circ* 2016; **25**: 1055-1062 [PMID: 27522511 DOI: 10.1016/j.hlc.2016.04.007]

59 **Buxton AE**, Lee KL, Fisher JD, Josephson ME, Prystowsky EN, Hafley G. A randomized study of the prevention of sudden death in patients with coronary artery disease. Multicenter Unsustained Tachycardia Trial Investigators. *N Engl J Med* 1999; **341**: 1882-1890 [PMID: 10601507 DOI: 10.1056/NEJM199912163412503]

60 **Gatzoulis KA**, Sideris A, Kanoupakis E, Sideris S, Nikolaou N, Antoniou CK, Kolettis TM. Arrhythmic risk stratification in heart failure: Time for the next step? *Ann Noninvasive Electrocardiol* 2017; **22** [PMID: 28252256 DOI: 10.1111/anec.12430]

61 **Dilaveris P**, Antoniou CK, Gatzoulis KA. Arrhythmic risk stratification in non-ischemic dilated cardiomyopathy: Where do we stand after DANISH? *Trends Cardiovasc Med* 2017; **27**: 542-555 [PMID: 28709811 DOI: 10.1016/j.tcm.2017.06.003]

62 **Mitrani RD**, Goldberger JJ. Editorial Commentary: Where do we stand after DANISH? It's tough to make predictions, especially about the future. *Trends Cardiovasc Med* 2017; **27**: 556-557 [PMID: 28709813 DOI: 10.1016/j.tcm.2017.06.014]

63 **Mattos BPE**, Scolari FL, Garbin HI. Discrepancy between International Guidelines on the Criteria for Primary Prevention of Sudden Cardiac Death in Hypertrophic Cardiomyopathy. *Arq Bras Cardiol* 2020; **115**: 197-204 [PMID: 32876184 DOI: 10.36660/abc.20190161]

64 **Arevalo HJ**, Vadakkumpadan F, Guallar E, Jebb A, Malamas P, Wu KC, Trayanova NA. Arrhythmia risk stratification of patients after myocardial infarction using personalized heart models. *Nat Commun* 2016; **7**: 11437 [PMID: 27164184 DOI: 10.1038/ncomms11437]

65 **Arsenos P**, Gatzoulis KA, Doundoulakis I, Dilaveris P, Antoniou CK, Stergios S, Sideris S, Ilias S, Tousoulis D. Arrhythmic risk stratification in heart failure mid-range ejection fraction patients with a non-invasive guiding to programmed ventricular stimulation two-step approach. *J Arrhythm* 2020; **36**: 890-898 [PMID: 33024466 DOI: 10.1002/joa3.12416]

66 **Tousoulis D**. CardioAthena Meeting 2018, Greece. *Eur Heart J* 2018; **39**: 2123-2125 [PMID: 29905814 DOI: 10.1093/eurheartj/ehy260]

67 **Pedretti R**, Etro MD, Laporta A, Sarzi Braga S, Carù B. Prediction of late arrhythmic events after acute myocardial infarction from combined use of noninvasive prognostic variables and inducibility of sustained monomorphic ventricular tachycardia. *Am J Cardiol* 1993; **71**: 1131-1141 [PMID: 8480637 DOI: 10.1016/0002-9149(93)90635-p]

68 **Schmitt C**, Barthel P, Ndrepepa G, Schreieck J, Plewan A, Schömig A, Schmidt G. Value of programmed ventricular stimulation for prophylactic internal cardioverter-defibrillator implantation in postinfarction patients preselected by noninvasive risk stratifiers. *J Am Coll Cardiol* 2001; **37**: 1901-1907 [PMID: 11401129 DOI: 10.1016/s0735-1097(01)01246-3]

69 **Xenogiannis I**, Gatzoulis KA, Flevari P, Ikonomidis I, Iliodromitis E, Trachanas K, Vlachos K, Arsenos P, Tsiachris D, Tousoulis D, Brilakis ES, Alexopoulos D. Temporal changes of noninvasive electrocardiographic risk factors for sudden cardiac death in post-myocardial infarction patients with preserved ejection fraction: Insights from the PRESERVE-EF study. *Ann Noninvasive Electrocardiol* 2020; **25**: e12701 [PMID: 31605453 DOI: 10.1111/anec.12701]

70 **Gatzoulis KA**, Dilaveris P, Arsenos P, Tsiachris D, Antoniou CK, Sideris S, Kolettis T, Kanoupakis E, Sideris A, Flevari P, Vassilikos V, Kappos K, Maounis T, Katsivas A, Kotsakis A, Karvounis H, Kossyvakis C, Leventopoulos G, Kalpakos D, Tousoulis D; ReCONSIDER study Investigators. Arrhythmic risk stratification in nonischemic dilated cardiomyopathy: The ReCONSIDER study design - A two-step, multifactorial, electrophysiology-inclusive approach. *Hellenic J Cardiol* 2021; **62**: 169-172 [PMID: 32330568 DOI: 10.1016/j.hjc.2020.03.008]

**Footnotes**

**Conflict-of-interest statement:** Authors declare no conflict of interests for this article. PRESERVE EF is a physician-initiated study that received unrestricted funding by Medtronic Hellas SA.

**Open-Access:** This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution-Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/Licenses/by-nc/4.0/

**Provenance and peer review:** Invited article; Externally peer reviewed.

**Peer-review model**: Single blind

**Peer-review started:** March 18, 2021

**First decision:** September 29, 2021

**Article in press:**

**Specialty type:** Cardiac and cardiovascular systems

**Country/Territory of origin:** Greece

**Peer-review report’s scientific quality classification**

Grade A (Excellent): 0

Grade B (Very good): 0

Grade C (Good): C

Grade D (Fair): 0

Grade E (Poor): 0

**P-Reviewer:** Purevjav E **S-Editor:** Ma YJ **L-Editor:** A **P-Editor:** Ma YJ

**Figure Legends**



**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 ICD, there were 9 true activations during the 32-mo follow-up. Neither SCD nor inappropriate ICD activations were observed during follow-up. (Modified with permission from EHJ[24]).



**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 (≥ 2/3 criteria), frequent premature ventricular contractions (≥ 30/h), non-sustained VT (≥ 1/24 h), abnormal heart rate turbulence (onset ≥ 0% and slope ≤ 2.5ms) and reduced deceleration capacity (≤ 4.5 ms), positive T wave alternans (≥ 65 μV), decreased heart rate variability (SDNN < 70ms), prolonged QTc interval (> 440 ms in males and > 450 ms in females). (Modified after permission from ANE[60]).

**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 (♂), ≥ 450 ms (♀) | Prolonged repolarization, EAD, DAD |
| TWA | ≥ 65 μV (2-channels) | APD and Ca2+ alternans, steep APDR and CVR, steep FSRCR |
| VPBs | ≥ 30/24 h | Automaticity (Ca2+oscillations), reentry |
| NSVT | ≥ 1 episode/24 h | Automaticity (Ca2+oscillations), reentry |
| SDNN/HRV | ≤ 75 ms | Enhanced sympathetic tone, autonomic imbalance |
| DC/HRT | DC ≤ 4.5 ms | Vagal and sympathetic ANS dysfunction |
| HRt onset ≥ 0% |
| HRT slope ≤ 2.5ms |

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.

**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.