Narrative review

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Improving the appropriateness of sudden arrhythmic death primary prevention by implantable cardioverter-defibrillator therapy in patients with low left ventricular ejection fraction. Point of view

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It is generally accepted that the current guidelines for the primary prevention of sudden arrhythmic death, which are based on ejection fraction, do not allow the optimal selection of patients with low left ventricular ejection fraction of ischemic and nonischemic etiology for implantation of a cardioverter-defibrillator. Ejection fraction alone is limited in both sensitivity and specificity. An analysis of the risk of sudden arrhythmic death with a combination of multiple tests (ejection fraction associated with one or more arrhythmic risk markers) could partially compensate for these limitations. We propose a polyparametric approach for defining the risk of sudden arrhythmic death using ejection fraction in combination with other clinical and arrhythmic risk markers (i.e. late gadolinium enhancement cardiac magnetic resonance, T-wave alternans, programmed ventricular stimulation, autonomic tone, and genetic testing) that have been validated in nonrandomized trials. In this article, we examine these approaches to identify three subsets of patients who cannot be comprehensively assessed by the current guidelines: patients with ejection fraction of 35% or less and a relatively low risk of sudden arrhythmic death despite the ejection fraction value; patients with ejection fraction of 35% or less and high competitive risk of death due to evolution of heart failure or noncardiac causes; and patients with ejection fraction between 35 and 45% with relatively high risk of sudden arrhythmic death despite the ejection fraction value.

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Introduction

The present article is partially based on the Position Paper of 'Associazione Nazionale Medici Cardiologi Ospedalieri (ANMCO)' by Disertori *et al.*,[1] issued in *Giornale Italiano di Cardiologia*, and developed on behalf of ANMCO.

The implantable cardioverter-defibrillator (ICD) is widely utilized in clinical practice, and its efficacy in reducing sudden arrhythmic death has been proven by a number of studies.[2–6] In the current international guidelines,[7–10] left ventricular ejection fraction of 35% or less is the major determinant for ICD implantation for the primary prevention of sudden arrhythmic death in patients with left ventricular dysfunction of ischemic or nonischemic etiology. In these patients, even the recent European Society of Cardiology (ESC) guidelines[10] do not suggest the use of markers of arrhythmic risk other than ejection fraction and New York Heart Association (NYHA) functional class. However, as a risk marker for sudden arrhythmic death, low ejection fraction has limited sensitivity and specificity.[11] Most patients implanted with an ICD according to the current guidelines do not actually benefit from it[3,12,13] and may suffer from side effects.[6,14,15] The randomized Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT),[3] published in 2005 and still implemented in the ICD guidelines, had a low rate of appropriate ICD therapy (5-year event rate of 21%). Moreover, in recent years improvements in drug treatment for heart failure and myocardial revascularization have reduced the incidence of sudden arrhythmic death in patients with low left ventricular ejection fraction.[16] Consequently, currently the rate of appropriate ICD therapy is even lower. In the recently published analysis of an Israeli ICD Registry including 2349 consecutive cases,[17] the rate of appropriate

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ICD shocks among primary prevention patients was 2.6% at 30 months of follow-up. Although the rates of appropriate ICD therapy vary widely depending mainly on patient selection and device programming,[4,5,17] many patients are unlikely to benefit from ICD implantation. By contrast, many patients who are at risk of sudden arrhythmic death are not identified, because the largest population of sudden arrhythmic death patients exhibit only mildly depressed ejection fraction.[18–20]

Thus, identifying patients who are at risk of sudden arrhythmic death solely based on ejection fraction appears to be an oversimplified method that does not maximize the benefit of ICD therapy. However, to improve the selection of patients for ICD therapy, two important obstacles that have barred the modification of guidelines in the last 10 years have to be overcome: the wait for new randomized trials and the search for a single marker to replace ejection fraction in sudden arrhythmic death risk stratification.

Overcoming the obstacles

The wait for new randomized trials

Current indications for ICD implantation for primary prevention of sudden arrhythmic death are based on randomized studies performed in the 2000s that showed a reduction in mortality among patients undergoing ICD implantation based mainly on ejection fraction.[21] Specifically, the inclusion criteria of the MADIT-II[2] and SCD-HeFT[3] trials have been implemented in the guidelines. No randomized studies using markers other than ejection fraction for risk stratification of sudden arrhythmic death have been published subsequently. In patients with ejection fraction of 35% or less, who are indicated for ICD therapy based on the guidelines,[7,10] the lack of subsequent randomized trials is due to both ethical and economic considerations. It is infeasible for both patients and doctors to randomize subjects who are indicated for ICD therapy according to the established guidelines to receive non-ICD implantation. Moreover, in the last few years, improvements in therapy have reduced the incidence of sudden arrhythmic death in patients with low left ventricular ejection fraction.[16] To reach statistical significance, compared with the studies performed in the 2000s, the randomization of many more patients would be necessary, and this approach would be economically infeasible.[22] Thus, in these patients, randomized trials using markers of sudden arrhythmic death other than ejection fraction are not available, not ongoing, and unlikely to be performed in the future.

Patients with ejection fraction higher than 35% are not indicated for ICD therapy based on the current guidelines,[7,10] and thus, these patients do not have ethical contraindications for inclusion in randomized trials. However, randomized trials are lacking even in this subset of patients. The DETERMINE trial[23] randomized post-infarction patients with left ventricular ejection fraction higher than 35% and a left ventricular infarct mass higher than 10% to ICD or optimal medical therapy and assessed the included subjects using late gadolinium enhancement cardiac magnetic resonance (LGE-CMR) imaging with the primary endpoint of total mortality. However, this trial was stopped due to the low level of enrolment. There is only one ongoing study (REFINE-ICD; ClinicalTrial.gov Identifier NCT00673842) that is expected to randomize 1400 survivors of myocardial infarction with an ejection fraction between 36 and 50%, a positive microvolt T-wave alternans (TWA) test, and impaired heart rate turbulence (HRT) to receive ICD or optimal medical therapy with the primary outcomes of cardiac death and resuscitated cardiac arrest. However, the conclusion of the REFINE-ICD trial is not expected within the next few years.

Although randomized trials are the best analysis tools and are often advocated[10,20,24] it is unlikely that they will be performed to address this issue in the near future. Thus, other research options to improve the selection of patients for ICD therapy should be adopted. For example, in the 2014 ESC guidelines on the diagnosis and management of hypertrophic cardiomyopathy,[25] the majority of recommendations are based on observational cohort studies.

The polyparametric approach

Because of the complexity of the substrates that underlie sudden arrhythmic death, it is very unlikely for a single test to achieve significantly better predictive accuracy than ejection fraction. To overcome this limitation, a combination of markers could be used, combining ejection fraction evaluation with tests that investigate different arrhythmic mechanisms. Encouraging observational data on this topic obtained using multiple techniques already exists.[26–28] For instance, Buxton *et al.*[27] conducted a study of 674 patients with ischemic heart disease to correlate 25 prognostic variables with total and arrhythmic mortality. Patients with ejection fraction greater than 30% in the presence of other arrhythmic risk factors had a higher risk of sudden arrhythmic death than patients with ejection fraction of 30% or less and no other arrhythmic risk factors. Similar results were reported by Klem *et al.*,[29] who combined ejection fraction with myocardial scar assessment by LGE-CMR. Recently, Merchant *et al.*[30] conducted a multisite study of 3335 patients and showed significant improvement in sudden arrhythmic death risk prediction with a multimarker strategy employing ejection fraction, presence of ischemic heart disease, and TWA test result. The use of ejection fraction and TWA variables alone resulted in C-index values of 0.637 and 0.716, respectively, both significantly lower than the C-index of the multivariate model (0.817).

This finding suggests that a polyparametric approach is likely to predict the risk of sudden arrhythmic death more accurately than any individual risk marker. Therefore, it

seems that a more promising option to improve sudden arrhythmic death risk stratification may be to evaluate the available data from nonrandomized studies that used a polyparametric approach to determine sudden arrhythmic death risk.

Sudden arrhythmic death risk stratification by polyparametric approaches in patients with low left ventricular ejection fraction

We propose the hypothesis that a polyparametric approach, applied if possible to the majority of patients before ICD implantation, would better define the risk of sudden arrhythmic death than any individual risk marker. In particular, the polyparametric approach could be useful to identify three subsets of patients with low left ventricular ejection fraction who cannot be thoroughly analyzed by the current guidelines.[7,10] We examined polyparametric approaches using ejection fraction in combination with other clinical and arrhythmic risk markers that have been validated in nonrandomized trials.

Patients with ejection fraction 35% or less and a relatively low risk of sudden arrhythmic death

Patients with an ejection fraction of 35% or less are indicated for ICD implantation for primary prevention of sudden arrhythmic death according to the current guidelines.[7,10] However, this patient subset is a heterogeneous group, with widely varying levels of sudden arrhythmic death risk. To date, the most useful techniques for identifying those at relatively low risk of sudden arrhythmic death seem to be LGE-CMR and the TWA test.

Late gadolinium enhancement cardiac magnetic resonance

Ventricular fibrosis plays an important role in the genesis of ventricular arrhythmias in patients with low left ventricular ejection fraction.[31] Fibrotic tissue may constitute a substrate for ventricular arrhythmias, where the slow and heterogeneous conduction associated with fibrosis may favor the instauration of re-entrant circuits, increasing the vulnerability to ventricular tachycardia or ventricular fibrillation.[32,33] Thus, the assessment of ventricular fibrosis by LGE-CMR imaging has recently been suggested as a candidate marker for sudden arrhythmic death risk stratification. Numerous studies have shown that LGE is a powerful predictor of ventricular tachyarrhythmic events both in ischemic and nonischemic cardiomyopathy patients and in patients with moderately to severely depressed ejection fraction.[29,34–53]

Table 1 outlines 19 studies[29,34–51] (2692 patients) in which it was possible to identify an arrhythmic endpoint. All studies reported a statistically significant correlation between the presence or extent of ventricular fibrosis assessed with LGE-CMR and arrhythmic events. Moreover, in many of these studies, the negative predictive value (NPV) for sudden arrhythmic death was very high (>95%) when the single evaluation of ejection fraction was added to the evaluation of fibrosis by LGE-CMR. The largest study was published by Gulati *et al.*,[42] who prospectively followed 472 patients with nonischemic cardiomyopathy for a median of 5.3 years. They found that the presence of midwall fibrosis was correlated with the occurrence of ventricular tachyarrhythmic events [adjusted hazard ratio (HR) 4.61; 95% confidence interval (CI): 2.75–7.74]. The combination of ventricular fibrosis with ejection fraction significantly improved risk reclassification for the arrhythmic end point (net reclassification improvement 0.29; 95% CI: 0.11–0.48). These data were also confirmed in two meta-analyses. In the meta-analysis of 1063 patients (572 with coronary artery disease and 491 with nonischemic cardiomyopathy) by Scott *et al.*,[52] a greater extent of fibrosis as assessed by LGE-CMR was strongly associated with the occurrence of ventricular arrhythmias, with a relative risk of 4.33 (95% CI: 2.98–6.29). In the group of patients with implanted ICD, the relative risk increased to 6.22 (95% CI: 2.41–16.05). The meta-analysis of Kuruvilla *et al.*,[53] which included 1488 patients with nonischemic cardiomyopathy, found that patients with fibrosis had an annualized risk of arrhythmic events of 6% compared with 1.2% in patients without fibrosis ($P < 0.001$), with an odds ratio of 5.32 (95% CI: 3.45–8.20).

Ventricular fibrosis was present in approximately 40% of patients with nonischemic cardiomyopathy, predominantly located within the myocardial wall (midwall fibrosis).[53] By contrast, fibrosis was present in almost all ischemic cardiomyopathy patients, with a common pattern of core dense fibrosis within a heterogeneous periinfarct zone (or gray zone) characterized by both viable and nonviable myocardium.[52] In nonischemic cardiomyopathy patients, the presence/absence of fibrosis and midwall fibrosis were most widely used as indicators to differentiate patients at high versus low risk of arrhythmic events. In ischemic cardiomyopathy patients the problem is more complex: the majority of studies analyzing total LGE or gray zone extent reported a statistically significant dose-response effect for arrhythmic risk. The larger and more heterogeneous the scar was, the higher the probability of ventricular arrhythmias during follow-up. In the absence a definite cut-off value, the presence of a large versus small extent of ventricular fibrosis has been generally used as an indicator to differentiate patients at high versus low risk of arrhythmic events. However, different studies on this topic have applied a variety of analysis methods and diagnostic thresholds. Therefore, standardization of LGE-CMR could be of great importance to aid in the practical implementation of the LGE test for the stratification of ventricular arrhythmic risk.

T-wave alternans

The association of TWA with the risk of sudden arrhythmic death in ischemic and nonischemic cardiomyopathy

Table 1 Studies on late gadolinium enhancement cardiac magnetic resonance testing for arrhythmic risk stratification in patients with with low left ventricular ejection fraction of ischemic and nonischemic etiology

Studies	Patients, *n*	AE, *n*	Arrhythmic end point	F-U (months)	Ejection fraction (%)	LGE-CMR patterns	Univariate analysis: HR (95% CI)	Multivariate analysis: HR (95% CI)	*P*
Studies with only ischemic cardiomyopathy patients									
Roes *et al.* (2009)[34]	91	18	ICD therapy[a]	9	28	Gray zone extent per 10-g increase	1.56 (1.19–2.06)	1.49 (1.01–2.20)	0.04
Scott *et al.* (2011)[35]	64	19	ICD therapy[a]	19	30	Transmural LGE segments, n	1.40 (1.15–1.70)	1.48 (1.18–1.84)	0.001
Alexandre *et al.* (2013)[36]	66	14	ICD therapy[a]	42	23	LGE extent per 1-g increase	1.08 (104–1.12)	3.15 (1.35–7.33)	<0.001
Demirel *et al.* (2014)[37]	94	34	ICD therapy[a], ventricular tachycardia	65	32	Peri- to core-infarct mass ratio % increase	2.03 (1.18–3.48)	2.01 (1.17–3.44)	0.01
Zeidan-Shwiri *et al.* (2015)[38]	43	28	ICD therapy[a]	30	27	Gray zone extent per 1 g increase	1.25 (1.08–1.44)	2.09 (1.14–3.85)	0.0018
Studies with only nonischemic cardiomyopathy patients									
Assomull *et al.* (2006)[39]	101	7	Sudden death, ventricular tachycardia[b]	22	36	Midwall LGE presence	5.2 (1.0–26.9)	5.9 (1.1–32.2)	0.04
Iles *et al.* (2011)[40]	61	9	ICD therapy[a]	19	25	LGE presence	25.8 (1.4–466.0)[c]	NR	<0.01
Leyva *et al.* (2012)[41]	97	3	Sudden death	35	22	Midwall LGE presence	31.0 (1.5–627.8)[c]	NR	0.0029
Gulati *et al.* (2013)[42]	472	65	ICD therapy, sudden death, aSD[b]	64	37	Midwall LGE presence	5.24 (3.15–8.72)	4.61 (2.75–7.74)	<0.001
Neilan *et al.* (2013)[43]	162	37	ICD therapy[a], sudden death[b]	29	26	LGE presence	14 (4.39–45.65)	NR	<0.0001
Perazzolo *et al.* (2014)[44]	137	22	ICD therapy[a], ventricular tachycardia / fibrillation, sudden death	36	32	LGE presence	4.17 (1.56–11.2)	3.8 (1.3–10.4)	0.01
Masci *et al.* (2014)[45]	228	8	ICD therapy, aSD	23	43	LGE presence	8.31 (1.66–41.55)	NR	0.01
Chimura *et al.* (2015)[46]	175	24	ICD therapy[a], ventricular tachycardia / fibrillation	61	28	Both septal and lateral midwall LGE presence	27.6 (7.18–106.3)	23.1 (2.88–184.9)	0.003
Piers *et al.* (2015)[47]	87	28	Ventricular tachycardia / fibrillation	45	29	Core extent per 10-g increase	2.38 (1.34–4.22)	NR	0.003
Studies with mixed ischemic and nonischemic cardiomyopathy patients									
Fernandez-Armenta *et al.* (2012)[48]	78 (41/37)[d]	9	ICD therapy[a]	25	22	LGE extent per 1% increase	1.09 (1.05–1.14)	1.1 (1.06–1.15)	<0.01
Gao *et al.* (2012)[49]	124 (59/65)[d]	18	ICD therapy[a], sudden death, aSD	21	26	LGE extent per 10-g increase	1.40 (1.21–1.62)	1.38 (1.18–1.62)	<0.001
Klem *et al.* (2012)[29]	137 (73/64)[d]	25	ICD therapy, MI[b]	24	35	LGE >5%	4.76 (1.65–13.7)	4.59 (1.79–11.8)	0.004
Mordi *et al.* (2014)[50]	157 (61/96)[d]	20	ICD therapy[a,b]	31	28	LGE extent per 1% increase	1.06 (1.04–1.09)	1.04 (1.01–1.07)	0.004
Almehmadi *et al.* (2014)[51]	318 (149/169)[d]	49	ICD therapy[a], sudden death, aSD	16	33	Midwall LGE presence	2.7 (1.5–5.0)	2.4 (1.2–4.6)	0.01

Only studies with evidence of a statistical analysis of the arrhythmic endpoint have been reported. AE, arrhythmic events; aSD, aborted sudden death; CI, confidence interval; CMR, cardiac magnetic resonance; F-U, mean follow-up; HR, hazard ratio; LGE, late gadolinium enhancement; NR, not reported. [a]Including antitachycardia pacing. [b]Secondary endpoint. [c]Odds ratio (95% CI). [d]Ischemic/nonischemic cardiomyopathy patients.

patients is likely related to the ability of TWA to provide a quantitative assessment of the temporal and spatial heterogeneity of repolarization, which facilitates the occurrence of ventricular arrhythmias.[54] The clinical utility of TWA in sudden arrhythmic death risk stratification was confirmed by numerous studies in patients with both chronic ischemic and nonischemic cardiomyopathy.[30,55–63] In contrast to many studies with positive results on the utility of TWA in sudden arrhythmic death risk stratification, other studies have reported negative findings, such as the subanalysis of the SCD-HeFT study and the MASTER study.[64,65] The negative results of these studies could be related in part to their methodology, because in both studies β-blocker therapy was discontinued before the test. The meta-analysis by Chan *et al.*[66] highlighted the importance of TWA testing without discontinuing β-blocker therapy: NPV of the test with respect to sudden arrhythmic death was 98% in patients studied on a β-blocker and decreased to 91% in those studied after β-blocker discontinuation.

The Consensus Guideline by the International Society for Holter and Noninvasive Electrocardiology,[54] published in 2011, stated that TWA provides valuable information regarding the risk of cardiovascular mortality and sudden arrhythmic death beyond that of standard clinical variables for cardiovascular diseases. In a recent multicenter study of 2883 patients with ischemic and nonischemic cardiomyopathy by Merchant *et al.*,[60] the annualized risk of sudden arrhythmic death was 0.4% in patients with a negative TWA test result (0.9% in the subgroup of 1004 patients with ejection fraction $\leq$35%). Moreover, all meta-analyses[66–71] have confirmed the predictive value of TWA with respect to ventricular arrhythmic events with a high NPV, thus allowing the identification of patients with a relatively low risk of sudden arrhythmic death (Table 2).

Synthesis

A subset of patients has a relatively low risk of sudden arrhythmic death despite having an ejection fraction of 35% or less (approximately 1–2% annualized risk of sudden arrhythmic death), who could be identified by LGE-CMR or TWA tests (Figs 1 and 2). In these patients, the appropriateness of ICD implantation could be discussed because of their lower chance to gain a meaningful benefit from ICD therapy, in spite of the exposition to its side effects.

Patients with ejection fraction 35% or less and high competitive risk of death due to evolution of heart failure or noncardiac causes

Among patients with low left ventricular ejection fraction, a subset has a high risk of death due to heart failure evolution or noncardiac conditions. Existing guidelines do not recommend ICD implantation in patients with NYHA functional class IV, high 1-year total mortality, or relevant comorbidities.[7,10] However, these criteria seem too generic to identify patients who are 'too sick' for ICD implantation. Therefore, a polyparametric approach was suggested to develop some risk prediction scores for total mortality. Prognostic scores allow an objective evaluation of patient risk, but for several reasons (historical cohorts with different treatments, heterogeneous methodological approach, case selection) lack optimal discriminatory power and calibration in real-world applications.[72] Nevertheless, increasing age, comorbidity burden, and life expectancy should be taken into account in the decision-making process for ICD implantation. The frequent finding of 1-year mortality greater than 20–25% in elderly patients with multiple comorbidities, with a proportion of sudden arrhythmic death usually <20–25%, is a convincing illustration of the general lack of efficacy of ICD implantation in this cohort of patients.[72–75]

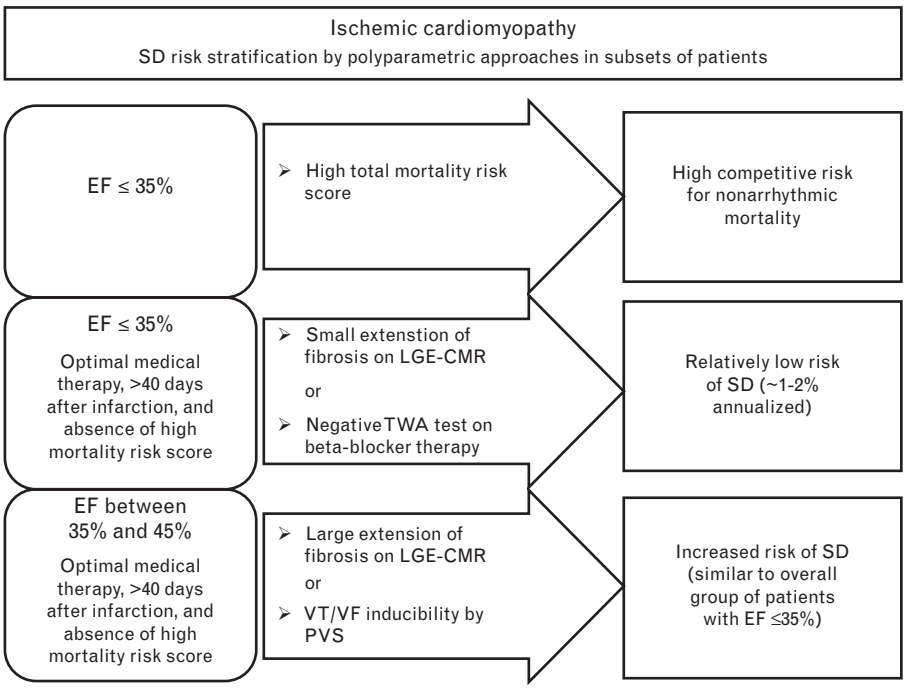
The MADIT-II trial provided a classic example of this subset of patients: a posthoc analysis of the presence or absence of five risk factors associated with ejection fraction (NYHA class >II, age >70 years, blood urea nitrogen >26 mg/dl, QRS duration >0.120 s, and atrial fibrillation)

Table 2 Meta-analyses on microvolt T-wave alternans testing for arrhythmic risk stratification in patients with with low left ventricular ejection fraction of ischemic and nonischemic etiology

Meta-analysis	Studies, *n*	Patients, *n*	Relative risk (95% CI)	*P*	NPV (%)
Studies with only ischemic cardiomyopathy patients					
Chen *et al.* (2013)[70]	7	3385	1.65 (1.32–2.07)	<0.001	NR
Studies with only nonischemic cardiomyopathy patients					
Golberger *et al.* (2014)[71]	12	1631	3.25 (2.04–5.16)	<0.001	97
Studies with mixed ischemic and nonischemic cardiomyopathy patients					
Gehi *et al.* (2005)[67]	19	2608	3.77 (2.39–5.55)	NR	97
Chan *et al.* (2010)[66]	9	3939	1.95 (1.29–2.96)	0.002	NR
Calò *et al.* (2011)[68]	15	5681	2.40 (1.54–3.74)	NR	95
Gupta *et al.* (2012)[69]	20	5945	3.68 (2.23–6.07)	NR	96
Studies in which β-blockers were administered					
Chan *et al.* (2010)[66]	4	1277	5.39 (2.68–10.84)	<0.001	98
Studies in which β-blockers were withheld					
Chan *et al.* (2010)[66]	5	2662	1.40 (1.06–1.84)	0.02	91

CI, confidence interval; NPV, negative predictive value; NR, not reported.

Fig. 1



Sudden arrhythmic death risk stratification in patients with ischemic cardiomyopathy. The risk of sudden arrhythmic death was stratified according to ejection fraction, total mortality risk score, and the results of specific tests: late gadolinium enhancement cardiac magnetic resonance imaging (LGE-CMR) or the T-wave alternans (TWA) test in patients with ejection fraction of 35% or less, and LGE-CMR or programmed ventricular stimulation (PVS) in patients with ejection fraction between 35 and 45%. In ischemic cardiomyopathy, LGE is present in almost all patients; negative and positive LGE-CMR results are related to the presence of a small and large extent of ventricular fibrosis, respectively. The TWA test is considered negative only if it is performed under β-blocker therapy. The PVS test is considered positive if sustained ventricular tachycardia or ventricular fibrillation is inducible. EF, ejection fraction; LGE-CMR, late gadolinium enhancement cardiac magnetic resonance imaging; PVS, programmed ventricular stimulation; SD, sudden arrhythmic death; TWA, T-wave alternans; VF, ventricular fibrillation; VT, ventricular tachycardia.

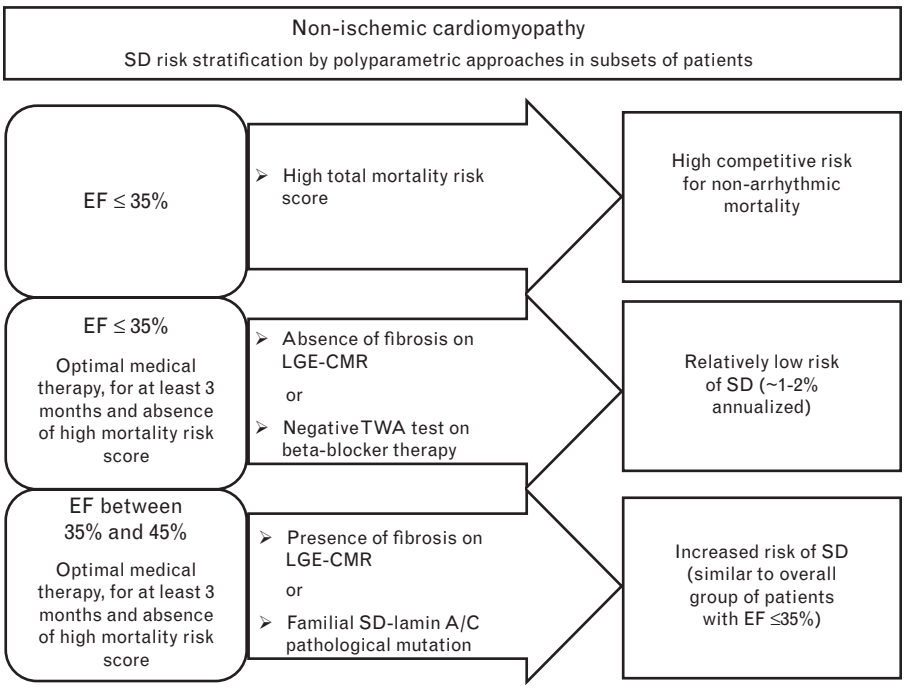
demonstrated that it was possible to identify patients with largely different mortality risk. In patients with a score of at least 3 using this polyparametric approach, no benefit of ICD implantation was observed, even over a prolonged follow-up period of up to 8 years.[74]

Many other scores reflecting risk of death have been developed.[73,75–80] Levy *et al.*[73] applied the Seattle Heart Failure Model score, previously tested in patients with heart failure, to patients of the SCD-HeFT trial. They found that patients with an annual risk of death more than 20% did not receive any benefit from ICD implantation. Recently, Zhang *et al.*[78] performed the prospective PROSE-ICD trial in a population of 1189 patients and validated a score based on six clinical parameters (age ≥75 years, NYHA class III/IV, atrial fibrillation, glomerular filtration rate <30 ml/min, diabetes, and use of diuretics) in addition to three biomarkers (tumour necrosis factor α receptor II, pro–brain natriuretic peptide and cardiac troponin T), which allowed the identification of patients with a high probability of early total mortality [area under the curve for prediction of 1-year mortality 0.82 (95% CI: 0.76–0.88)] but not of sudden arrhythmic death. Thus, the score was able to identify patients with a low probability of receiving a benefit from ICD therapy (those with a score >4) with high accuracy. Senni *et al.*[77] validated another score in a cohort of 6274 patients with heart failure treated at 24 European Departments of Cardiology and Internal Medicine. In this study, in addition to age and severity of heart failure (blood pressure, NYHA class, and ejection fraction), the presence of aortic stenosis, atrial fibrillation, prescription of validated drugs for heart failure, and a number of comorbidities were combined to form the prognostic score. In patients identified by the score with an annualized mortality risk of at least 20%, the efficacy of ICD therapy was not clear.

Synthesis

Determining what risk score to use and what cut-off points should be applied is challenging. Nevertheless, it would be useful to obtain a score of total mortality (better defined by a multidisciplinary group) in the majority of patients prior to ICD implantation for primary prevention of sudden arrhythmic death, and possibly discuss the appropriateness of ICD therapy in those with a high score for nonarrhythmic death (Figs 1 and 2).

Fig. 2



Sudden arrhythmic death risk stratification in patients with nonischemic cardiomyopathy. The risk of sudden arrhythmic death was stratified according to ejection fraction, risk score of total mortality, and the results of specific tests: late gadolinium enhancement cardiac magnetic resonance imaging (LGE-CMR) or the T-wave alternans (TWA) test in patients with ejection fraction of 35% or less, and LGE-CMR in patients with ejection fraction between 35 and 45%. In nonischemic cardiomyopathy, negative and positive LGE-CMR results are defined as the absence and presence of LGE, respectively. The TWA test is considered negative only if it is performed under β-blocker therapy. A genetic test is proposed in cases of familial dilated cardiomyopathy, in particular for the identification of a family history of sudden arrhythmic death and for the identification of a pathological mutation in lamin A/C, which both select patients at high risk of sudden arrhythmic death, even in the presence of only a moderately impaired ejection fraction. EF, ejection fraction; LGE-CMR, late gadolinium enhancement cardiac magnetic resonance imaging; SD, sudden arrhythmic death; TWA, T-wave alternans.

Patients with ejection fraction between 35 and 45% and a relatively high risk of sudden arrhythmic death

Patients with an ejection fraction between 35 and 45% do not have an indication for ICD implantation for primary prevention of sudden arrhythmic death according to the current guidelines.[7,10] However, this patient subset is also a heterogeneous group, with largely different levels of sudden arrhythmic death risk. To date, the most useful techniques for identifying patients at relatively high risk of sudden arrhythmic death seem to be LGE-CMR, programmed ventricular stimulation (PVS), autonomic tone, and genetic testing.

Late gadolinium enhancement cardiac magnetic resonance

Based on the data previously reported in the text and Table 1, nonischemic cardiomyopathy patients with the presence of ventricular fibrosis confirmed by LGE-CMR and ischemic cardiomyopathy patients with a large fibrotic area could represent a subset of patients at relatively high risk of sudden arrhythmic death, despite having an ejection fraction between 35 and 45%.

Programmed ventricular stimulation

In patients with postinfarction cardiomyopathy, the inducibility of ventricular tachyarrhythmias by PVS seems to be related to the presence of a reentry circuit.[81,82] Based on the results of the MUSTT trial[83,84] and subsequent studies,[58,85,86] the predictive ability of PVS with respect to sudden arrhythmic death was particularly high in patients with an ejection fraction between 30 and 40%. The ACCF/AHA/HRS 2012 guidelines for device-based treatment of cardiac rhythm abnormalities[7] recommend ICD implantation (Class I recommendation, level of evidence B) in chronic postinfarction patients with an ejection fraction of 40% or less, nonsustained ventricular tachycardia, and inducibility of sustained ventricular tachyarrhythmias by PVS. Unfortunately, the clinical use of PVS is progressively declining.[86]

Autonomic tone

Numerous clinical observations and experimental studies have shown that alterations in the autonomic nervous system and in particular sympathetic activation and

reduced vagal modulation have an important proarrhythmic effect and may facilitate the onset of ventricular tachycardia/fibrillation, in particular in ischemic heart disease.[20,87] Even in the investigation of autonomic tone, the usefulness of the combination of more tests has been confirmed in several studies.[88–91] In the REFINE study,[88] 322 patients with ischemic heart disease were studied at different intervals from infarction (2–4 weeks and 10–14 weeks). In the analysis carried out at 10–14 weeks after infarction, the predictive value of depressed HRT (HR 2.91; 95% CI: 1.13–7.48) increased if the test was associated with an abnormal TWA test (HR 4.18; 95% CI: 2.06–8.32) with respect to a combined endpoint of cardiac death and arrhythmic events. The further addition of ejection fraction of less than 50% increased the HR to 6.22 (95% CI: 2.88–13.42). The ongoing REFINE-ICD study described above was designed on the basis of these results.

In patients with moderately depressed ejection fraction, reduced HRT (especially when combined with a positive TWA test) appears to identify a subgroup of patients at relatively high risk of sudden arrhythmic death. However, it may be appropriate to await the results of the randomized REFINE-ICD trial before using HRT for the evaluation of possible ICD implantation.

Genetic testing

The combination of ejection fraction with genetic analysis can also contribute to sudden arrhythmic death risk stratification.[92,93] Both familial history and genotyping may aid in diagnostic and prognostic classification in patients with familial dilated cardiomyopathy, particularly for the identification of a family history of sudden arrhythmic death[8,94] and the identification of a pathological mutation in lamin A/C,[95–98] which both indicate patients at high risk of sudden arrhythmic death even in the presence of only a moderately depressed ejection fraction (Fig. 2). In the recent ESC guidelines,[10] an ICD should be considered (Class IIa recommendation, level of evidence B) in patients with dilated cardiomyopathy, a confirmed disease-causing lamin A/C mutation, and clinical risk factors (nonsustained ventricular tachycardia, ejection fraction <45%, male sex, and nonmissense mutations).

Synthesis

Despite having an ejection fraction between 35 and 45%, a subset of patients has a relatively high risk of sudden arrhythmic death similar to the overall group of patients with ejection fraction of 35 or less and could be identified by LGE-CMR in cases of both ischemic and nonischemic cardiomyopathy, and by PVS in ischemic cardiomyopathy (Figs 1 and 2). Moreover, the combination of ejection fraction with genetic testing in nonischemic cardiomyopathy patients could contribute to identifying those with a relatively high risk of sudden arrhythmic death. In patients with a relatively high arrhythmic risk, ICD therapy could be critically evaluated.

Clinical considerations

In the described subsets of patients, until a more thorough evaluation method is included in the guidelines for sudden arrhythmic death risk stratification, the choice of ICD therapy could be critically evaluated using a polyparametric analysis, as outlined above. The conclusions and uncertainties resulting from the polyparametric analysis could be discussed with the patient to allow a truly 'informed' consensus. The emerging concept of 'sharing the work' or 'healthcare co-production,' which involves discussion between the patient and doctor, could be used in ICD therapy decisions.

In addition, it is important to recognize the side effects of ICD implantation, which are not trivial. In a recently published registry of patients who underwent ICD ($n = 1729$) or CRT-D ($n = 1326$),[6] the 12-year cumulative incidence of adverse events was 20% (95% CI: 18–22%) for inappropriate shock, 6% (95% CI: 5–8%) for device-related infection, and 17% (95% CI: 14–21%) for lead failure. In the Danish registry,[14] complications following implantable electronic device treatment were more frequent than generally acknowledged: at 6 months, major complications occurred in 5.6% (95% CI: 5.0–6.1%) of patients, and any complication (major and minor) in 9.5% (95% CI: 8.7–10.2%). Both patient- (particularly female, age, and underweight) and procedure-related predictors (complexity and annual center volume of procedures) may identify patients at particularly high risk of complications.[14] This information should be taken into account when establishing individual patient treatment plans, but it is not included in our algorithm, which is mainly aimed at arrhythmic risk stratification. Recently a pooled analysis of IDE study and EFFORTLESS Registry provided evidence for the safety and efficacy of the totally subcutaneous implantable defibrillator.[99] This technological innovation, that is less affected by transvenous technology-related complications, will help address some of the current problems regarding ICD therapy, but it is unlikely to significantly affect clinical indications. In addition, ICD is an expensive device that requires frequent follow-up monitoring. Although not all data are in agreement,[100] ICD implantation following the current guidelines is considered cost-effective.[101] However, if a more complex strategy of sudden arrhythmic death risk stratification could improve the appropriateness of ICD implantation, it would lead to a further significant advantage in both cost/benefit and risk/benefit ratios. The modest increase in costs due to a polyparametric approach to risk stratification would be largely outweighed by the improvement in the appropriateness of ICD implantation.

Finally, it should be recognized that the definition of risk is not static but, rather, continues to change over

time, necessitating periodic reassessment to determine significant variations in the patient's clinical status. No single arrhythmic risk stratification test should be considered permanently valid. However, the exact timing of the periodic reassessment of such tests is not known and will be varying according to not only the clinical aspects of the patient but also the complexity, availability, biological impact, and economic costs of the method used.

This point-of-view article does not intend to question actual guidelines for sudden arrhythmic death risk stratification, but rather to highlight the potential additive value of a new polyparametric approach to the risk stratification of specific groups of patients with low left ventricular ejection fraction, supported by highly significant published data derived from nonrandomized studies. We believe that this working hypothesis to aid in the decision-making process could be appropriate and implemented in the future. In the absence of randomized trials, the polyparametric approach could be further investigated by prospective trials, high-quality registries, and eventually by the new system of performing registry-based randomized trials that may be another alternative to obtaining high-quality clinical data at lower cost.[102]

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