Selection of patients eligible for implantable cardioverter defibrillator: beyond left ventricular ejection fraction

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KEYWORDS
Implantable cardioverter defibrillator; Cardiomyopathy; Arrhythmic risk

The selection of patients eligible for implantable cardioverter defibrillator (ICD), in primary prevention, is a critical moment in the management of the patients with cardiomyopathies as it needs a right balance of the patients’ arrhythmic risk and the risks related to the implantation, as well as the device costs. Several data indicate that left ventricular ejection fraction alone is not a sufficient criterion for a proper identification of patients who could benefit most from ICD. Numerous findings show that genetic analysis and characterization of myocardial fibrosis with magnetic resonance imaging allow an important improvement of this process.

Background

The selection of patients eligible for implantable cardioverter defibrillator (ICD), in primary prevention, is a critical moment in the management of the patients with cardiomyopathies because it needs an adequate balance of the patient’s arrhythmic risk and the non-trivial risks related to the implantation (peri-procedural complications, infectious and electrical problems), as well as the relevant costs of the device. In recent years, several tools have been proposed to improve the patient’s selection process, with different evidence in the different kinds of cardiomyopathy.

Patients’ selection in ischaemic dilated cardiomyopathy

In ischaemic dilated cardiomyopathy (IDCM) patients, large evidence supports the high arrhythmic risk in the presence of low (≤35%) left ventricular ejection fraction (LVEF), based on the strong correlation between the extent of scar and LVEF decrease. These data represent the base of the class I indication (level of evidence A) for ICD in patients with IDCM, according to international guidelines.1,2

Recently, to differentiate, in patients with reduced LVEF, the risk of arrhythmic and non-arrhythmic death, Younis et al.3 suggested two scores, based on clinical variables, to define the likelihood of ICD benefit; the scores were developed on the populations included in the four Multicentre Automatic Defibrillator Implantation Trials, including mainly patients with IDCM. Patients with the greatest benefit were those classified as at high risk of arrhythmic death and at low risk of non-arrhythmic death; moreover, the ICD benefit decreased in patients at high risk of non-arrhythmic death.3 The usefulness of LVEF alone to stratify arrhythmic risk in patients with IDCM has been further challenged, because many patients with LVEF >35% experience sudden cardiac death (SCD). In these patients, inducible sustained monomorphic ventricular tachycardia by programmed electrical stimulation could justify ICD.2 In addition, magnetic resonance imaging (MRI) studies showed that the quantification of the so-called ‘grey-zone’ (GZ), the area surrounding myocardial fibrosis (identified by late-gadolinium enhancement, LGE), allows a more accurate identification of patients who will experience SCD, compared to LVEF.3 Furthermore, in the multivariate analysis,
the extent of the GZ showed an additive predictive power for arrhythmic events compared to LVEF. Particularly, in patients with LVEF > 35%, the GZ identified a group of patients at high arrhythmic risk, who were not properly stratified by LVEF alone. The mechanism underlying the arrhythmogenicity of GZ could be the mixture of viable and non-viable myocardium which would create a heterogeneity of potentials and electrical instability. If this data will be confirmed in randomized studies, the application of this parameter, in addition to the evaluation of LVEF, could be useful in clinical practice to allow ICD implantation even in patients who are currently excluded according to guidelines.

**Patients’ selection in non-ischaemic dilated cardiomyopathy**

The benefit of ICD for primary prevention of SCD in patients with non-ischaemic dilated cardiomyopathy (NIDCM) and LVEF ≤ 35% has been challenged by the results of the Danish Study to Assess the Efficacy of ICD in Patients with Non-ischaemic Systolic Heart Failure on Mortality (DANISH) trial, enrolling only patients with NIDCM and failing to show a reduction in total mortality. This disappointing result may be explained by the low arrhythmic risk of the study population which was well treated with mortality-reducing strategies such as ACE inhibitors, beta-blockers, aldosterone receptor antagonists, and cardiac resynchronization (58% of cases). Indeed, the incidence of SCD in the DANISH trial was very low (1.8 events per 100 patient/year in the placebo group and 0.9 events per 100 patient/year in the treated group). Given such a low arrhythmic risk, it is unlikely that the ICD could significantly reduce all-cause mortality. The low incidence of SCD in patients with NIDCM is in line with two recent studies that showed a significant reduction in SCD in patients enrolled in randomized clinical trials over a time range of 20 years and in a cohort of patients included in the Trieste Register of Cardiomyopathies over a 40-years interval. Considering the DANISH results, the last update of the European Society of Cardiology Guidelines for the Treatment of Ventricular Arrhythmias and the Prevention of SCD downgraded from I to IIa the indication to ICD in patients with NIDCM. Therefore, it appears clear that patients’ selection based only on LVEF is insufficient, and it is necessary to improve patients’ selection, with the aim of identifying those at higher risk of SCD, who are most likely to benefit from ICD implantation. In fact, many patients that received ICD in accordance with the guidelines do not receive appropriate shocks and remain exposed to the risks associated with the procedure. On the other hand, registry data show that up to 80% of out-of-hospital cardiac arrest cases occur in patients with EF > 35%, indicating that the greatest benefit of ICD is achievable in patients not properly stratified by LVEF.

In the past, different non-invasive parameters such as non-sustained ventricular tachycardias (VT), t-wave alternance, late potentials, heart rate variability, and assessment of sympathetic innervation with the SPECT-123I-MIBG method have been used for SCD risk stratification in patients with NIDCM but with conflicting and disappointing results.

**Role of MRI**

In recent years, numerous retrospective and prospective studies have shown that 30-40% of patients with NIDCM have a variable degree of fibrosis, identified by LGE on MRI. Typically, the LGE pattern in NIDCM has a sub-epicardial, mid-wall, or patchy distribution, not congruent with coronary artery distribution. This parameter was found to be an independent predictor of SCD. Actually, in the meta-analysis by Becker et al., LGE was associated with an OR of 4.52 for arrhythmic events (VT, ventricular fibrillation, appropriate ICD shocks, and SCD). Gutman et al. showed, in a cohort of patients with NIDCM and EF ≥ 35%, that ICD reduced mortality only in patients with LGE, but not in those without LGE. Currently, the Randomized Controlled, Multicentre Trial of Cardiac Magnetic Resonance Guidance of Implantable Cardioverter Defibrillator Implantation in Non-ischaemic Dilated Cardiomyopathy (NCT04558723) is enrolling patients with NIDCM, EF ≤ 35% and evidence of LGE randomized to optimal medical therapy or ICD. The purpose of the study is to evaluate whether, in the presence of LGE, ICD reduces mortality compared with medical therapy. Furthermore, the meta-analysis by Di Marco et al., on 2948 patients with LVEF between 20 and 43%, showed that the presence of fibrosis remained a powerful predictor of VT or SCD regardless of LVEF. The predictive value of LGE for fatal arrhythmic events was confirmed in a study by Halliday et al. that demonstrated the presence and localization of LGE in the inter-ventricular septum and/or the free wall of the LV were better predictors of arrhythmic events than the extension and distribution pattern of LGE, even after correction for LVEF. The same authors prospectively followed about 400 patients with NIDCM and EF > 40% and demonstrated that LGE was associated with an OR of 9.2 for the combined end-point of SCD or resuscitated cardiac arrest, compared to the absence of LGE. Finally, in a recent paper, Di Marco et al. proposed an algorithm based on LVEF and LGE for the definition of three risk categories. In patients with EF > 35%, the presence of LGE configured an intermediate-high risk of SCD (about 3%/year) which could justify ICD. This hypothesis is currently being evaluated in the Cardiac Magnetic Resonance GUIDEd Management of Mild-moderate Left Ventricular Systolic Dysfunction (CMR-GUIDE, NCT01918215) randomized trial, which is enrolling patients with LGE in at least two segments and LVEF between 36 and 50%, treated with ICD.

Cardiac MRI could improve risk stratification also by T1 mapping and extracellular volume (ECV) assessment, allowing quantification of diffuse fibrosis, even in the absence of LGE. In a multicentre study of 637 patients with NIDCM, T1 mapping, and ECV were strong predictors of total mortality and heart failure. Moreover, other data suggest that T1 mapping could be useful to predict arrhythmic events, regardless of LGE. Although these
data are extremely promising, more robust evidence is needed, as well as greater standardization of the method, before these parameters can be realistically implemented in the decision-making process.

Role of genetics
NIDCM includes heterogeneous clinical conditions due to very different etiopathogenetic mechanisms (inflammatory, toxic, environmental, genetics, nutritional deficiencies), some of which being still unknown (in the idiopathic form). A genetic basis has been recognized in 25-55% of NIDCM cases, with more than 50 genes involved; therefore, the most recent guidelines recommend (Class IB) genetic testing in these patients. The most frequent genetic alterations are those involving the titin gene. Although these changes are generally associated with a good prognosis, some evidence indicates that the coexistence of mid-wall LGE exposes these patients to a greater arrhythmic risk. A certainly less frequent genetic alteration (8-10% of patients with NIDCM), but with a very high risk of SCD, is that of the Lamin A/C gene. Recently, a risk calculator was developed (https://lchina-risk-vta.fr/) to predict life-threatening VT. A 5-year risk ≥10% in association with a manifest cardiac phenotype (LVEF < 50%, non-sustained VT or conduction delay) represent a criterion for ICD (class IIa) in the most recent international guidelines. It should be noted that even in these patients the presence of LGE contributes to increasing the risk of SCD. In addition, a truncating mutation in the filamin C gene has been associated with a very high risk of even fatal arrhythmias. Typically, a unique ‘ring-like’ pattern of sub-epicardial LGE has been described in these patients. Based on the high arrhythmic risk of carriers of the mutation, a recent consensus document recommended the prophylactic implantation of ICD in patients with LVEF < 45%. Two other genes increases arrhythmic risk are RBM20 and the phospholamban and therefore should be included in the genetic analysis.

Based on these considerations, the decision-making process in the patient with NIDCM to candidate to ICD should be integrated with information regarding LGE, family history, and/or genetic analysis. Particularly, in the presence of EF ≤ 35%, the absence of LGE and the lack of family history of NIDCM/SCD could reclassify the patient into a lower risk category and avoid ICD implantation. On the other hand, in the case of EF > 35–<50%, the presence of LGE and/or a positive family history/genetics, could define a higher risk profile and justify ICD.

Patients’ selection in arrhythmogenic cardiomyopathy
ACM is the new designation of arrhythmogenic right ventricle cardiomyopathy (ARVC) following the observation that the fibro-adipose replacement, characteristic of the disease, can involve the LV simultaneously or even exclusively. This observation was possible thanks to various histopathological findings and numerous clinical studies that used MRI to evaluate the RV more accurately and allowed identification of kinetic alterations, adipose infiltration, and LGE also in the LV. ACM is caused by pathogenic mutations in desmosomal and non-desmosomal genes (less frequently) and genetic testing is a major criterion for diagnosis. Particularly, some gene alterations (desmoglobin2, desmoplakin) are more often associated with LV involvement and a greater arrhythmic risk. According to the criteria proposed by the Task Force of 2010, the defined diagnosis of ARVC is supported in the presence of major and minor criteria represented by electrocardiographic, histopathological, anamnestic, genetics, and morpho-functional parameters. However, these criteria appear to be limited as they refer exclusively to the RV. On the other hand, the new Padova Criteria have also included in the diagnostic criteria the electrocardiographic and MRI signs indicative of LV involvement, allowing the diagnosis of all the phenotypic variants of ACM. SCD represents a possible clinical manifestation (and sometimes even the first) of ACM, often with onset at an early age. Therefore, the stratification of the arrhythmic risk of these patients, and family members, is relevant for primary prevention ICD implantation. Traditionally, clinical, electrocardiographic, functional, and morphological parameters related to right ventricle have been used in the assessment of arrhythmic risk, which categorized patients into three levels of low (<1%/year), intermediate (1-10%/year) and high risk (>10%/year) proposed by the 2015 consensus document of the International Task Force and in the ‘5-years ARVC risk score’. However, recently Aquaro et al. demonstrated that the presence of LV involvement (at MRI) is associated with an increased risk of SCD compared to right-ventricular forms, with an additive prognostic value compared to the ‘5-years ARVC risk score’. Actually, in patients with LV involvement, the actual risk of SCD was underestimated by about 30% by the ‘5-years ARVC risk score’. According to this observation, the authors suggest that an ICD is also implanted in patients with a prevalent or exclusive LV involvement, as this finding is associated with an arrhythmic risk >15%, classifying patients into the category defined at high risk by the International Task Force. Although these results seem very appealing, further confirmation is needed before being implemented in clinical practice.

Patients’ selection in hypertrophic cardiomyopathy
Although the risk of SCD in HCM is low (<1%/year), SCD can be the first devastating manifestation of cardiomyopathy. Therefore, it is necessary to achieve criteria that can properly identify the rare high-risk patients and discriminate them from that at low risk. The presence of single or multiple pathogenic/likely pathogenic mutations in sarcomeric genes has been associated with a higher arrhythmic risk. The European Society of Cardiology has proposed, for the arrhythmic risk stratification in these patients, the HCM Risk-SCD score which is based on seven variables (age, family history of SCD,
unjustified syncope, outflow obstruction, maximum LV thickness, left atrium diameter, non-sustained VT). This score defines the risk of SCD at 5 years as follows: <4%: low, >4 < 6%: intermediate and >6%: high); however, the score’s sensitivity is very low. In recent years, large evidence supports the use of LGE for identification of patient with HCM at higher risk of SCD. In patients with HCM, the finding of fibrosis with MRI is very common (up to 70% of cases), with the characteristic patchy pattern, particularly at the insertion of the RV and in the most hypertrophic segments. Therefore, the presence of LGE alone is not an adequate criterion for patient stratification and growing evidence shows that a better predictor of prognosis is the presence of a substantial amount of fibrosis (LGE). Indeed, several studies have showed that the presence of a LGE > 15% of the cardiac mass increases the risk of SCD up to three-fold. According to these data, this most recent update of the international guidelines included the evaluation of the extension of the LGE in the work-up of HCM patients. This parameter appears particularly critical for the choice of ICD implantation in patients who fall within the so-called ‘grey area’, in which the classic criteria are unsatisfactory.

Conclusions

The selection of the patient to be treated in primary prevention with ICD is a critical moment in the management of the patients with cardiomyopathies and needs a right balance between arrhythmic risk on the one hand and risks related to device implantation and costs on the other. Growing evidence indicates that LVEF alone is not a sufficient criterion for proper identification of patients who benefit most from ICD. Genetic analysis and MRI seem to be extremely useful tools to improve this process and should be performed in every individual patient with a cardiomyopathy to obtain a multiparametric estimate of SCD risk.

Conflict of interest: None declared.

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