Recent Non-Invasive Parameters to Identify Subjects at High Risk of Sudden Cardiac Death

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Abstract: Cardiovascular diseases remain among the leading causes of death worldwide and sudden cardiac death (SCD) accounts for ~25% of these deaths. Despite its epidemiologic relevance, there are very few diagnostic strategies available useful to prevent SCD mainly focused on patients already affected by specific cardiovascular diseases. Unfortunately, most of these parameters exhibit poor positive predictive accuracy. Moreover, there is also a need to identify parameters to stratify the risk of SCD among otherwise healthy subjects. This review aims to provide an update on the most relevant non-invasive diagnostic features to identify patients at higher risk of developing malignant ventricular arrhythmias and SCD.

Keywords: sudden cardiac death; prognosis; ECG; cardiac magnetic resonance; genetic testing

1. Introduction

While deaths associated with cardiovascular diseases have decreased over the past several decades, these disorders remain among the leading causes of death worldwide. Sudden cardiac death (SCD) accounts for ~25% of these deaths [1,2]. Likewise, and despite its epidemiologic relevance, there are very few diagnostic strategies available that can be used to prevent SCD. Numerous parameters have been evaluated to identify those at higher risk of SCD, with a particular focus on patients already diagnosed with specific cardiovascular diseases. Unfortunately, most of these parameters exhibit poor positive predictive accuracy. Moreover, there is also a need to identify parameters to stratify the risk of SCD among otherwise healthy subjects. For these reasons, there is a critical need for new parameters that can be used to identify individuals at high risk for SCD, particularly among those who might benefit from appropriate therapeutic strategies. In this clinical setting, it should be considered the information carried by the different available diagnostic tools. A multiparametric approach, based on the use of imaging and non-imaging techniques and able to more appropriately identify those patients in whom a cardioverter defibrillator (ICD) implantation could exert the greatest beneficial effects (Figure 1).

This review aims to provide an update on the most relevant diagnostic features revealed by electrocardiography (ECG), imaging modalities, and genetic testing to identify patients at higher risk of developing malignant ventricular arrhythmias and SCD.
2. Electrocardiographic Features Associated with the Risk of Arrhythmias

ECG is an ideal tool for both diagnosis and prognostic stratification because it is non-invasive, cost-effective, and widely accessible. Currently, electrocardiographic findings used to prevent SCD are primarily those used to diagnose inherited channelopathies, such as long QT (LQTS) or Brugada (BrS) syndrome [3]. Over the last few years, several new electrocardiographic parameters have been identified that are associated with an increased risk of SCD mainly in patients with arrhythmogenic cardiomyopathies (Table 1).

Table 1. ECG findings associated with an increased arrhythmic risk.

| ECG Abnormality | Pathophysiologic Background | Clinical Setting |
|-----------------|------------------------------|------------------|
| QRSf            | Conduction delay from inhomogeneous activation of the ventricles due to myocardial scar | DCM, IDCM, HCM, BrS, LQTS, ARVD, Cardiac Sarcoidosis |
| ER ("J-waves" or "J-point elevation") | Altered ion channel function (alterations in sodium, potassium and calcium currents) | Young African men, Athletes, HCM |
| TW Inversion    | Changes during phase three of the action potential | ARVD |

BrS: Brugada syndrome; ER: early repolarization; ICM: ischemic cardiomyopathy; NICM: non-ischemic cardiomyopathy; HCM: Hypertrophic cardiomyopathy; ARVC: arrhythmogenic right ventricular cardiomyopathy; QRSf: fragmented QRS.

2.1. QRS Fragmentation

While QRS duration is consistently associated with an increase in mortality of all causes [4,5], fragmented QRS complexes (fQRS) may specifically represent conduction disarray secondary to ventricular myocardial fibrosis and/or scarring [6]. fQRS was initially defined as additional spikes in the QRS complex in the absence of bundle branch block [7]. The definition was subsequently broadened to include QRS complexes with notches in addition to those detected in the pre-existing pattern. These notches can be observed even in wide QRS complexes resulting from bundle branch block, paced rhythm, or ventricular ectopy. In the latter case, this pattern is described as a fragmented wide QRS (f-wQRS),
in contrast with the aforementioned fragmented QRS complexes of normal duration (i.e., <120 ms). An fQRS detected in a paced rhythm is known as f-pQRS [8]. A recent large meta-analysis that included 45 studies with a total enrollment of 6088 patients revealed that fragmentation of the QRS complex was independently associated with arrhythmic events, including SCD and malignant ventricular arrhythmias (odds ratio [OR], 6.73; 95% confidence interval [CI], 3.85–11.76; \( p < 0.001 \)) [9].

### 2.2. Early Repolarization (ER)

ER can be detected on an electrocardiogram by its characteristic J-point elevation of at least 1 mm in two contiguous leads. This finding can include a “notching” type appearance, i.e., a positive J-deflection inscribed within the S wave, or a “slurring”, i.e., a gradual rather than a distinct transition from the QRS to the ST segment in the inferior, lateral, or inferolateral leads [10,11]. ER was historically considered to be a benign finding. ER was observed frequently in the anterolateral leads of ECG tracings from young black male athletes and adolescents and could be accentuated by vagal tone and hypothermia [12–14]. However, recent studies have revealed that ER can be an inherited finding. Results from a study of 500 families revealed that subjects with at least one parent exhibiting an ER pattern on ECG were twice as likely to display the same variant. Family transmission is observed more frequently in subjects whose mothers have an ER pattern. Of importance, these families exhibit a comparatively high incidence of sudden death which may be linked to ER [15].

Malignant ER may predispose affected individuals to arrhythmias and fatal events due to re-entry phenomena, premature beats, and/or transmural dispersion [16]. Thus, it is important to recognize ECG characteristics that differentiate a relatively benign ER pattern from one that is malignant. Benign forms of ER include rapidly ascending ST-segments that blend with T-wave associated with a normal QT interval (QTc). By contrast, ECG tracings in which ST segments remain flat, horizontal, or descend towards the T-wave with a prolonged QTc are diagnostic of the more malignant variant of ER that has been associated with mortality due to arrhythmias in long-term follow-up [17,18]. Likewise, ER with a deflection in the R-wave (slurred pattern) descending in the terminal part of the QRS observed in tracings from at least two inferior leads (II, III, aVF) and two lateral leads (I, aVL, V4–V6) has been associated with an increased risk of idiopathic ventricular fibrillation (IVF) [19,20]. This pattern has been identified as an independent predictor of fatal arrhythmic events in patients diagnosed with Brugada syndrome (BrS) as described below [21,22].

### 2.3. Brugada Syndrome (BrS)

ECG plays a key role in the diagnosis of the rare but potentially lethal condition known as Brugada Syndrome (BrS). The diagnosis of BrS is based on the detection of one of two types of aberrant ECG patterns. A Brugada type 1 ECG pattern exhibits a prominent coved ST-segment elevation displaying a J-point amplitude or ST-elevation \( \geq 2 \) mm in more than one of the right precordial leads (V1–V3) followed by a negative symmetric T-wave. Patients with spontaneous type 1 ECG patterns are at higher risk of arrhythmic events than those displaying the drug-induced pattern [23,24]. The risk of arrhythmias in these individuals ranges from 0.81%/year in those who remain asymptomatic to 2.3%/year in symptomatic patients [25].

Recently several ECG parameters have been proposed to identify individuals at higher risk for developing these negative sequelae. QRS fragmentation (f-QRS) in precordial leads V1 and/or V2–V3 has been recognized as an independent predictor for future arrhythmias in patients diagnosed with BrS [26,27]. QRS prolongation in leads II, V2, and V6 is also associated with an increased risk of developing arrhythmic events [28].

The “aVR sign” has also been identified as a potential marker of arrhythmic risk in this syndrome. The aVR sign features an R wave \( \geq 0.3 \) mV or R/q \( \geq 0.75 \) in the aVR lead. Mechanistically, this finding might reflect a right ventricular conduction delay associated
with an increased risk of arrhythmic events in BrS patients [29]. The specific relevance of the aVR lead in these cases relates to its focus on events in the right ventricular outflow tract (RVOT); electroanatomical abnormalities at this site may predict the inducibility of ventricular fibrillation in patients diagnosed with BrS [30]. Lateral leads, including L1 and aVL, provide complementary information that focuses on depolarization and repolarization of the RVOT. Similarly, the presence of an S wave in lead I $\geq 40$ ms with amplitude $\geq 0.1$ mV and area $\geq 1$ mm$^2$ in patients with BrS strongly predicted both VF and SCD with good sensitivity albeit with low specificity [31].

Finally, a prolonged QTc, a longer interval between the peak and the end of the T-wave (Tpeak-Tend interval), a higher Tpeak-Tend/QT ratio, and a higher Tpeak-Tend dispersion in precordial leads [31–34], first-degree atrioventricular block (AVB) [35], and spontaneous atrial fibrillation (AF) [36] have all been associated with an increased risk of significant arrhythmic events.

2.4. T-Wave Morphology in Long QT Syndrome (LQTS)

LQTS is typically diagnosed on repeated 12-lead ECGs that exhibit either a QTc $\geq 480$ ms or a calculated LQTS risk score >3 in patients with a confirmed pathogenic LQTS mutation [37]. Electrocardiographic parameters have been studied in patients diagnosed with this disorder to stratify arrhythmic risk. Among these parameters, T-wave morphology may be a relevant feature with respect to the increased arrhythmic risk exhibited among patients affected by one or more of these inherited channelopathies. For example, female carriers of type 2 LQTS with abnormal T-waves had a significantly higher risk of cardiac events compared to those with normal T-wave morphology; interestingly, this association was not significant in males [38]. In these cases, T-wave morphology was evaluated in leads V5 and II and classified as normal, broad, flat, notched, or biphasic.

2.5. Electrocardiographic Markers in Arrhythmogenic Right Ventricular Dysplasia/Cardiomyopathy (ARVD/C)

A recent systematic review and meta-analysis considered the current status of electrocardiographic markers to assess risk in patients diagnosed with ARVD/C [39]. Among the conclusions reached, the presence of non-sustained VT (NSVT) and the extent of T-wave inversion (TWI) on anterior and/or inferior leads can predict the likelihood of the development of sustained ventricular arrhythmias (VAs) and SCD [40,41]. While epsilon waves may reflect the short-term risk of developing critical arrhythmias, the use of this marker is limited by its low sensitivity and specificity, and its dependence on ECG filter setting and magnification [42].

Terminal activation duration (TAD) is measured from the nadir of the S wave to the end of all depolarization deflections; prolonged TAD is defined as a duration of $\geq 55$ ms in any of the V1–V3 leads in the absence of complete right bundle branch block. Of note, TAD prolongation was the only ECG abnormality detected in four family members (of seven) who carried a genetic variant associated with ARVD/C. These findings suggest that TAD may be used as a means for early recognition of at-risk individuals [43].

3. Echocardiographic Markers for Arrhythmias

Echocardiography is the first and the most commonly used cardiac imaging technique. Compared to cardiac magnetic resonance and cardiac computed tomography, echocardiography is an inexpensive, rapid, and readily available imaging modality. Echocardiographic imaging of patients with ventricular arrhythmias facilitates the identification (or exclusion) of structural heart disease. Furthermore, echocardiography performed in patients who are exercising or responding to pharmacological stress can be applied to a selected group of patients with VAs triggered by ischemia [1,37].

Currently, left ventricular ejection fraction (LVEF) is the main echocardiographic parameter used to stratify the risk of SCD. Current guidelines recommend an implantable cardioverterdefibrillator (ICD) for patients who present with a low LVEF [44]. However,
SCD frequently occurs in the absence of reduced LVEF. In the community-based Oregon Sudden Unexpected Death Study, almost half of all cases of SCD (48%) were individuals who had normal LVEFs (55%), with less than a third exhibiting severely reduced LV systolic function [45]. Furthermore, results from several studies revealed that less than a third of the recipients with LVEF ≤35% received effective therapeutic benefit from an ICD, while subject to the well-known complications of this device [46].

Evaluation of additional risk factors revealed by echocardiography might help to identify patients at higher risk of SCD. Considering the widespread availability of this imaging modality, a larger understanding of these potential risk factors could have a substantial impact on the health and well-being of the general population [47]. Newly identified echocardiographic parameters have been proposed that may offer a more accurate evaluation of ventricular function and a more effective means to prevent SCD (Table 2). However, the clinical utility of these markers needs to be examined in randomized clinical trials.

Table 2. Echocardiographic parameters associated with an increased risk of malignant ventricular arrhythmias.

| Echocardiography | Pathophysiologic Background | Clinical Setting | Information |
|------------------|-------------------------------|------------------|-------------|
| LVEF             | Left ventricular systolic function | ICM, NICM, Myocarditis, ARVC, LVNC | Severe LV systolic dysfunction, of any cause, identified by measuring the LVEF, is associated with an increased risk of SCD (LVEF < 35%) |
| LV GLS/RLS       | Measure of LV systolic function (indirect reflector of myocardial fibrosis/scar) | ICM, NICM, HCM | GLS is associated with SCD, appropriate ICD therapy and VA |
| Mechanical dispersion | Slow and heterogeneous electrical conduction of the LV myocardium (indirect reflector of myocardial fibrosis/scar) | ICM, NICM, HCM, ARVC | Predictor of VA in patients with moderate and severe LV systolic dysfunction (despite the etiology of LV dysfunction) and in HCM patients. Predictor of VT/VF (in patients with ARVC) |
| LV wall thickness | Left ventricular hypertrophy | HCM, Myocarditis | Independent predictor of SCD |
| RVEF, RV diameter, regional RV akinesia, dyskinesia or aneurism | RV remodeling and dysfunction | ARVC | Correlated with more frequent sustained ventricular arrhythmias and ICD appropriate shocks |

CMR: cardiac magnetic resonance; LV: left ventricular; GLS/RLS: left ventricular global longitudinal strain/regional longitudinal strain; ICD: implantable cardioverter defibrillator; ICM: ischemic cardiomyopathy; NICM: non-ischemic cardiomyopathy; HCM: Hypertrophic cardiomyopathy; ARVC: arrhythmogenic right ventricular cardiomyopathy; LVNC: left ventricular noncompaction; RV: right ventricular; RVEF: right ventricular ejection fraction; SCD: sudden cardiac death.

3.1. Left Ventricular Hypertrophy (LVH)

Increased left ventricular (LV) mass is associated with an increased risk of SCD in the general population [48,49]. LVH is associated with abnormal interstitial remodeling which can impair electrical conduction and promote Vas [50]. In the Framingham Heart Study, increased LV mass and hypertrophy as assessed by echocardiogram, were independently associated with SCD after accounting for other known risk factors [51]. LVH, defined as LV mass (adjusted for height) >143 g/m² in men and >102 g/m² in women, was associated with a 116% increase in the risk of SCD. Estimates revealed that each 50 g/m² incremental increase in LV mass was associated with an additional 45% increase in the risk of SCD.
during a mean follow-up of 10.3 years. The increased risk of SCD associated with LVH is also observed among patients diagnosed with ischemic cardiomyopathy [52].

3.2. Global and Segmental Longitudinal Strain

Several new echocardiographic parameters reflecting myocardial function have been developed in recent years. Among these are speckle tracking echocardiography (STE) which provides information on myocardial deformation by linking electrical activity to specific anatomical structures. Active myocardial deformation (strain) is assessed by tracking ultrasound markers (speckles). The analysis focuses on LV longitudinal strain and presents a value for global longitudinal strain (GLS). GLS has been independently associated with SCD, appropriate ICD therapy, and VA in patients diagnosed with ischemic cardiomyopathy, cardiac systemic sclerosis, and in patients who have undergone repair of tetralogy of Fallot. Detection of impaired segmental longitudinal strain in the peri-infarct zone is also independently associated with an increased risk of the need for ICD therapy to treat either VF or VT [53].

The transitional zone between necrotic and healthy tissue may play an important role in the pathophysiology of VAs and SCD. Mixed scar and viable tissue in peri-infarct areas represent a potential substrate for electrical re-entry and lower values of longitudinal strain on STE. Thus, detection of lower levels of longitudinal strain specifically in peri-infarct zones will help to identify subjects at increased risk for VF and VT [53,54]. Overall, reductions in parameters that reflect regional longitudinal myocardial deformation may provide incremental prognostic information beyond that provided by clinical and conventional echocardiographic risk factors regardless of whether the origins of the cardiomyopathy were ischemic or non-ischemic [55,56].

3.3. Mechanical Dispersion

STE can also be used to measure the time to peak of longitudinal strain and a calculation of LV mechanical dispersion (LVMD). Mechanical dispersion reflects the heterogeneity of myocardial contraction as a product of electrical alterations and tissue abnormalities. High levels of LV mechanical dispersion suggest the presence of slow and heterogeneous electrical conduction of the LV myocardium (e.g., secondary to scar tissue). After a myocardial infarction, the combination of LV GLS and LVMD may suggest the need for an ICD, even in patients with an LVEF >35% [57]. Moreover, an LVMD ≥ 75 ms may be an independent predictor of SCD and malignant VAs regardless of an ischemic etiology, even in patients with LVEF > 35% [58]. Measurements of LVMD and LV GLS of hypertrophic segments may prove to be a useful tool to also stratify the risk of SCD among patients diagnosed with hypertrophic cardiomyopathy [59,60] and mitral valve prolapse [61]. Finally, STE can also be used to identify abnormalities of right ventricular (RV) function. Both RV GLS and RVMD are associated with malignant VAs [62,63].

4. Cardiac Magnetic Resonance (CMR)

CMR provides the most complete evaluation of a patient’s cardiac status with good temporal and spatial resolution that facilitates the quantitative assessment of chamber size, myocardial wall thicknesses, ventricular function and mass, and segmental function, as well as the identification of anomalous coronary arteries. CMR can be used to diagnose myocarditis, amyloidosis, sarcoidosis, Chagas disease, Fabry disease, LV non-compaction cardiomyopathy (LVNC), hemochromatosis, and arrhythmogenic cardiomyopathy.

Numerous studies have considered the relevance of CMR for the study of arrhythmogenic factors that might predict SCD (Table 3, Figure 2). In particular, techniques including late gadolinium enhancement (LGE), T1 mapping, and T2 mapping, as well as those that evaluate extracellular volume can be used to identify structural changes, storage, infiltration, inflammation, fibrosis, and scarring.
Table 3. Imaging parameters associated with an increased risk of malignant arrhythmias.

| CMR       | Pathophysiologic Background          | Clinical Setting                                              | Information                                      |
|-----------|--------------------------------------|---------------------------------------------------------------|--------------------------------------------------|
| LGE       | Fibrosis                             | ICM, NICM HCM, Myocarditis ARVC, LVNC Mitral valve prolapse   | Independent predictor for VA and SCD             |
| T1 and ECV| Tissue edema and diffuse fibrosis    | ICM, NICM HCM, Myocarditis                                   | Higher native T1 values associated with VA       |
| T2        | Myocardial edema                     | Myocarditis                                                   | Abnormal T2 mapping is involved in predicting major adverse events including cardiac death |
| LVEF      | Left ventricular systolic function   | ICM, NICM HCM, Myocarditis ARVC LVNC                         | LV systolic dysfunction is associated with an increased risk of SCD |
| RVEF      | Right ventricular systolic function  | ARVDC                                                         | Overall increase in VA in RV dysfunction         |
| Strain Imaging and MD | Myocardial deformation and function | ICM, NICM                                                     | Impaired strain associated with SCD             |

CMR: cardiac magnetic resonance; LGE: late Gadolinium enhancement; ICM: ischemic cardiomyopathy; NICM: non-ischemic cardiomyopathy; HCM: hypertrophic cardiomyopathy; ARVC: arrhythmogenic right ventricular cardiomyopathy; LVNC: left ventricular noncompaction; RVEF: right ventricular ejection fraction.

Figure 2. In the left panel T2-STIR (a) and PSIR-TFE (b) sequences showing increased signal predominantly subepicardial patchy of the left ventricular wall due to necrosis of acute myocarditis. In the right panel sequence T1-TSE and T1-Fat Sat (c) showing multiple areas of adipose infiltration with mesocardial and subepicardial distribution of the left ventricle walls, (d) extended subepicardial signal hyperintensity in PSIR sequences for the study of “Late Gadolinium Enhancement” indicative of fibrosis for Left Dominant Arrhythmogenic Dysplasia.

4.1. Late Gadolinium Enhancement

LGE detected 15 min after collection of contrast-enhanced CMR sequences can be used to identify patients with both ischemic and non-ischemic dilated cardiomyopathy who are at increased risk of developing malignant Vas [64–67]. The association between LGE and an arrhythmic endpoint was presented in studies in patients with LVEFs < 35% but may also be applicable in patients with a mean LVEF >35% [68]. LGE detected in patients diagnosed with myocarditis suggests an increased risk of SCD regardless of LVEF [69–71].
Various LGE features are relevant for arrhythmic risk stratification (e.g., findings documenting its extension, localization, and size of the border zone). While risk is increased under conditions in which LGE exceeds to include more than 5% of LV mass, detection of LGE may be relevant even at lower percentages [72,73]. There are only a few studies that have examined the association of total LGE with arrhythmic risk in patients diagnosed with chronic myocarditis. In these studies, the size of the scar was directly associated with the probability of manifesting VAs [74]. Anterior and septal as well as mid-wall LGE locations have been associated with arrhythmic events in patients with non-ischemic cardiomyopathy [75,76]. The area surrounding the region of LGE, known as the “border zone”, consists of viable and nonviable myocytes separated by scar/fibrotic tissue involved in the development of arrhythmias [77,78]. The characteristics of the border zone can predict the inducibility of VT on electrophysiological studies (EPSs), the need for appropriate ICD therapy, and the likelihood of SCD, all independently of the LVEF [79–83]. LGE could also be useful in patients diagnosed with hypertrophic cardiomyopathy (HCM); replacement fibrosis that is commonly detected in these patients has been associated with an adverse prognosis [84,85].

CMR plays an important role in the differential diagnosis of HCM versus athlete’s heart. This modality can be used to measure LV wall thickness and detect LV hypertrophy that was not detected on echocardiography. A diagnosis of athlete’s heart can be made in patients who decondition over time in association with regression in cardiac wall thickness >2 mm. By contrast, a diagnosis of HCM is suggested in cases in which the hypertrophy remains unchanged. Likewise, LGE and a focal area of LV hypertrophy that remains unchanged following deconditioning also support a diagnosis of HCM. LV remodeling associated with a diagnosis of athlete’s heart typically does not result in focal areas of myocardial scarring, especially in younger individuals. However, although the detection of LGE on contrast-enhanced CMR favors the diagnosis of HCM, the absence of LGE cannot be used to exclude HCM, as this finding has been reported in only half of patients with this clinical diagnosis.

LGE assessments are limited by their semi-quantitative nature and the fact that they can provide only an estimate of irreversible myocardial damage. The methods used to detect and report LGE have not been standardized. Furthermore, LGE may be a dynamic parameter. For example, the expansion of the extracellular volume at early timepoints after cardiac injury leads to an increased volume of gadolinium distribution; as such, this finding reflects not only the fibrosis at this stage but also the interstitium. Finally, CMR is not widely available and impaired renal function is a relative contraindication for the administration of gadolinium-based contrast agents.

4.2. Mapping Techniques and Extracellular Volume

T1 and T2 mapping methods provide a quantitative approach to the assessment of cardiac tissue and reflect the magnetic properties of cardiac muscle based on its composition. T1 values are increased by tissue edema and fibrosis and are reduced by lipid (e.g., Anderson-Fabry disease) and iron overload. T1 mapping also detects diffuse fibrosis associated with both ischemic cardiomyopathy and NICM and has been explored as an independent predictor of sustained VT and the need for appropriate ICD therapy [86]. Unlike LGE, native T1 values are frequently abnormal in diffuse diseases of the myocardium and thus can provide insights into the etiology and pathogenesis of NICM. A T1 map may highlight focal areas of edema such as those accompanying acute myocarditis, acute myocardial infarction, or Takotsubo cardiomyopathy. LGE can be used to evaluate ECV, even if the role of this value in determining the risk of SCD risk remains to be evaluated. Postcontrast T1 mapping techniques combined with measurements of native T1 and hematocrit provide an estimation of the ECV [87]. Myocardial fibrosis identified by ECV measurements may be associated with hospitalization and death secondary to heart failure (HF) [88]. The ECV is also elevated in regions of chronic infarction. The main advantage of T1 mapping over LGE for the stratification of the risk of arrhythmias is the possibility
of using this modality to identify diffuse myocardial fibrosis in the setting of NICM [89]. The evaluation of pre-contrast (native) and post-contrast T1 mapping images can identify diffuse myocardial fibrosis that remains undetectable by LGE [90,91].

T2-weighted sequences identify and provide a quantitative assessment of myocardial edema. There are several technical limitations to this method, including its non-standardized assessment. However, initial data suggest that an abnormal T2 mapping can be used to predict major adverse events including SCD and the need for cardiac transplantation and/or implantation of a ventricular assist device.

4.3. Feature Tracking (FT)

FT is a recently developed postprocessing tool that can be applied to CMR to acquire information on strain parameters regardless of contrast agent. One recent study revealed that measurements of LV GLS and RV-global radial strain can be used to predict outcomes in patients diagnosed with ischemic cardiomyopathy with an LVEF > 35%. This information might assist with decision making regarding ICD use in patients with ischemic cardiomyopathy with a mild or moderately reduced EF [92].

4.4. CMR in Mitral Valve Prolapse

Mitral valve prolapse (MVP) is rarely associated with SCD. In addition to the aforementioned echocardiographic parameters, CMR may also elucidate features that reflect an increased risk of malignant arrhythmias. Myocardial fibrosis associated with arrhythmias as detected by LGE [93] is mainly found at the LV posteromedial papillary muscle or the level of the inferobasal wall [94,95]. Subclinical diffuse ventricular fibrosis (which may be a precursor of focal fibrosis in MVP or a different disease in which fibrotic markers undergo up-regulation) may be a marker for early identification of patients at risk of SCD [96]. Disjunction of the mitral annulus (i.e., detachment of the root of the annulus from the ventricular myocardium located at the base of the posterior leaflet) is a pro-arrhythmogenic event [97]. Finally, LGE findings may be used to predict future adverse cardiac events associated with this finding in other clinical settings such as sarcoidosis [98–102].

5. Genetic Testing

The number of genetic defects that have been associated with the pathogenesis of inherited cardiomyopathy has been increasing. Moreover, the ongoing development of new techniques for rapid evaluation of the human genome suggests that genetic analysis will be even more relevant in future clinical practice. Recent advances in DNA sequencing technologies have made it possible to explore large numbers of disease genes simultaneously as mutational analysis proceeds much more rapidly and at a reduced cost. These new methods, collectively known as next-generation sequencing (NGS), represent a major advance in our ability to identify causative mutations in families affected by genetic disorders [103,104]. The second relevant aspect concerning the progress of genetic testing to prevent SCD is the association between specific genetic polymorphisms and aberrancies with malignant VAs. As shown in Table 4, genetic mutations have been identified that are associated with an increased risk of VAs in patients diagnosed with cardiomyopathy [105]. More than one hundred specific genes identified in patients with dilated cardiomyopathy (DCM) have been evaluated [106–108]; some of these were strongly associated with both DCM and specific electrical phenotypes [109]. Mutations in the gene encoding the nuclear structural protein lamin a/c (LMNA) have been identified as among the leading causes of an increased risk of arrhythmias in patients diagnosed with DCM [110]. Mutations in LMNA have also been implicated in several distinct phenotypes of familial cardiomyopathy and a high incidence (46%) of SCD [111,112]. Based on these data, both European and American guidelines suggest that ICDs might be provided to patients with LMNA mutations with other risk factors, including non-sustained VT, LVEF < 45%, non-missense mutations, and male sex, even in the absence of severe LV dysfunction. DCM patients with variants in the gene encoding the critical muscle protein, titin (TTN) were also at an increased risk of
Vas [113,114]. Likewise, mutations in the gene encoding the sodium voltage-gated channel alpha subunit 5 (SCN5A) correlated with the development of supraventricular arrhythmias (86%), sick sinus syndrome (33%), AF (60%), VT (33%), and conduction disease (60%) also in patients diagnosed with DCM [115,116]. Analogously, patients with DCM and mutations in the gene encoding filamin C (FLNC) also have a notably high incidence of VA and SCD [117,118].

| Inherited Cardiomyopathy | Genes Associated with SCD | Protein Encoded          |
|--------------------------|--------------------------|--------------------------|
| DCM                      | TTN                      | Titin                    |
|                          | LMNA                     | Lamin A/C                |
|                          | FLNC                     | Filamin C                |
|                          | SCN5A                    | Sodium voltage-gated channel alpha subunit 5 |
| HCM                      | MYH7                     | B-Myosin Heavy Chain 7   |
|                          | MYBP3C                   | Myosin-Binding Protein C 3 |
| BrS                      | SCN5A                    | Nav1.5—Cardiac sodium channel α subunit |
| ARVD                     | PLN R14del               | Phospholamban            |
|                          | LMNA                     | Lamin A/C                |
|                          | SCN5A                    | Sodium voltage-gated channel alpha subunit 5 |
|                          | RBM20                    | RNA binding motif protein 20 |
|                          | TMEM43                   | Transmembrane Protein 43 |
| LQTS                     | SCN5A                    | Nav1.5—Cardiac sodium channel α subunit |

SCD: sudden cardiac death; BrS: Brugada Syndrome; DCM: dilated cardiomyopathy; HCM: hypertrophic cardiomyopathy; LQTS: long QT syndrome; ARVD: arrhythmogenic ventricular dysplasia.

Genetic variants have also been identified to be associated with malignant arrhythmias in other cardiomyopathies. For example, mutations in numerous genes encoding sarcomere proteins have been identified in patients diagnosed with HCM [119]. Among these is the Val606Met mutation in the cardiac beta-myosin heavy chain that was identified in a patient cohort diagnosed with familial HCM. This specific mutation has been associated with a high risk of SCD at a young age [120]. Similarly, mutation in the gene encoding cardiac myosin-binding protein C (MyBP-C) has been reported in patients with HCM and substantial hypertrophy and has been associated with a moderate incidence of SCD; by contrast, the Arg820Gly mutation has been associated with end-stage HCM [121].

Available data suggest that patients diagnosed with ARVC with multiple mutations in desmosomal genes are likely to have a more severe phenotype and an increased lifetime risk of malignant arrhythmias and SCD; interestingly, healthy carriers of this gene are considered to be at low risk for this outcome. The current International Task Force recommendations stratify patients with ARVC into high-, intermediate-, and low-risk groups as a basis for guiding decisions regarding ICD implantation [122–124]. In the case of ARVD, pathogenic mutations represent one variable of many that have been linked to the more severe progression of the disease; mutational data can be included together with several other well-defined variables to create an appropriate risk stratification model and to improve the evaluation of the overall risk of SCD [125].

Subunit alpha of voltage-gated sodium channel 5A plays an important role in cardiac myocyte depolarization. Pathologic mutations in this gene were first reported in 1995 and were originally associated with electrical cardiac pathologies, including LQTS [126], BrS [127], and Lenegre’s disease [128]. This mutation has also been reported in small cohorts of patients diagnosed with DCM [129], ARVC [130], and LVNC [131]. All patients in these cohorts have a higher risk of both supraventricular arrhythmias (SVAs) and VAs;
consideration for ICDs has already been recommended although this issue is not addressed in the current guidelines [132]. Finally, mutations in CPVT1 which encode the cardiac ryanodine receptor (RyR2) have been identified in patients with autosomal dominant for catecholaminergic polymorphic ventricular tachycardia (CPVT). The autosomal recessive form, which is less common, results from mutations in the gene encoding cardiac calsequestrin 2 (CASQ2) [133,134]. It will be critical to assess the role of these mutations as there are very few risk factors available to provide prognostic information in patients diagnosed with CPVT [135,136].

Targeted genetic analysis of ion channels (i.e., RYR2, KCNQ1, KCNH2, and SCN5A) should be considered to establish the probable cause of death in patients with SCD of unclear etiology as well as to facilitate the identification of relatives who are potentially at risk [137]. With this information, family screening of first-degree relatives could represent an effective strategy to prevent SCD [138]. Targeted molecular screening in first-degree relatives might also be considered when there is the suspicion of the presence of an inheritable disease in family members. On the other hand, genetic screening of large panels of genes should not be performed without clinical clues for a specific disease or pathology. In most cases, only a fraction of potentially affected family members undergo screening, in part due to the lack of appropriate infrastructure but also secondary to the levels of anxiety and distress that may result from a positive finding [139]. Decisions regarding the need to proceed with genetic testing should be based on the clinical value that genetic information might provide to the care of individual patients and their families. In most cases, genetic testing is not necessary to establish a diagnosis. The main point of genetic testing in this field currently is to facilitate screening of family members who might carry hereditary heart diseases and to identify cases of subclinical disease that might require medical surveillance. In some circumstances, genetic tests can help establish a diagnosis in cases of equivocal clinical presentations. However, it is critical to bear in mind that genetic information requires careful interpretation and is frequently inconclusive. Considering the low prevalence of hereditary arrhythmic syndromes, clinical evaluation and decisions relating to the usefulness of genetic tests should be carried out by physicians with dedicated and specific skills [140]. The term “personalized medicine” was recently introduced to refer to the integration of clinical, molecular, and environmental markers associated with the risk of developing a specific disease. At present, clinical genetics can play a role in defining a personalized approach to the prevention of SCD via the integration of clinical, environmental, and molecular data [141].

6. Conclusions

Cardiac disease can lead to SCD via various etiologies that converge on a final pathway that ultimately leads to fatal VAs. While there are no models for the prediction of SCD risk among those in the general population, there are numerous studies that describe individual risk factors for patients diagnosed with cardiac disease. Identification and treatment of these underlying conditions and determining how to optimize cardiac function remain essential parameters in the ongoing effort to prevent SCD. Secondary and primary prevention are best achieved by ICD implantation. In this setting, there is the clinical need to identify patients in whom ICD implantation may be more beneficial. On the basis of a systematic review of the literature, this review summarized the parameters derived from different non-invasive techniques which can be used to support risk-stratification strategies in patients. The goal was to provide an update useful in the routine clinical practice, which focused on the parameters derived from the more easily accessible tests, such as ECG and echocardiography, to more advanced ones, such as CMR and genetic testing.

The goal for the future is to move forward from population-based management to personalized therapeutic strategies. To this end, risk stratification algorithms based on findings from epidemiological studies that evaluate traditional cardiovascular risk factors, lifestyle, and dietary habits, as well as imaging, biological markers, and genetic variants alone or in combination may aid in the identification of susceptible subgroups within a
given population. Improvements in epidemiological studies, experimental investigations, and clinical trials will be essential to achieve strategies aimed at reducing the incidence and lethality of SCD across the entire population.

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References
1. Al-Khatib, S.M.; Stevenson, W.G.; Ackerman, M.J.; Al Bryant, W.J.; Callans, D.J.; Curtis, A.B.; Deal, B.J.; Dickfeld, T.; Field, M.E.; Fonarow, G.C.; et al. 2017 AHA/ACC/HRS Guideline for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. Circulation 2018, 138, 210–271.
2. Mendis, S.; Puska, P.; Norrving, B. Global Atlas on Cardiovascular Disease Prevention and Control; World Health Organization: Geneva, Switzerland, 2011.
3. Abdelghani, S.A.; Rosenthal, T.M.; Morin, D.P. Surface Electrocardiogram Predictors of Sudden Cardiac Arrest. Ochsner J. 2016, 16, 280–289. [PubMed]
4. Hathaway, W.R.; Peterson, E.D.; Wagner, G.S.; Granger, C.B.; Zabel, K.M.; Pieper, K.S.; Clark, K.A.; Woodlief, L.H.; Califf, R.M. Prognostic significance of the initial electrocardiogram in patients with acute myocardial infarction. GUSTO-I Investigators. Global Utilization of Streptokinase and t-PA for Occluded Coronary Arteries. JAMA 1998, 279, 387–391. [CrossRef] [PubMed]
5. Petrina, M.; Goodman, S.G.; Eagle, K.A. The 12-lead electrocardiogram as a predictive tool of mortality after acute myocardial infarction: Current status in an era of revascularization and reperfusion. Am. Heart J. 2006, 152, 11–18. [CrossRef] [PubMed]
6. Flowers, N.C.; Horan, L.G.; Thomas, J.R.; Tolleson, W.J. The anatomic basis for high-frequency components in the electrocardiogram. Circulation 1969, 39, 531–539. [PubMed]
7. Das, M.K.; Khan, B.; Jacob, S.; Kumar, A.; Mahenthiran, J. Significance of a fragmented QRS complex versus a Q wave in patients with coronary artery disease. Circulation 2006, 113, 2495–2501. [CrossRef] [PubMed]
8. Das, M.K.; Suradi, H.; Maskoun, W.; Michael, M.A.; Shen, C.; Peng, J.; Dandamudi, G.; Mahenthiran, J. Fragmented wide QRS on a 12-lead ECG: A sign of myocardial scar and poor prognosis. Circ. Arrhythm. Electrophysiol. 2008, 1, 258–268. [CrossRef] [PubMed]
9. Goldberger, J.J.; SubaÈius, H.; Patel, T.; Cunnane, R.; Kadish, A.H. Sudden cardiac death risk stratification in patients with nonspecific dilated cardiomyopathy. J. Am. Coll. Cardiol. 2014, 63, 1879–1889. [CrossRef] [PubMed]
10. Haïssaguerre, M.; Derval, N.; Sacher, F.; Jesel, L.; Deisenhofer, I.; de Roy, L.; Pasquier, J.L.; Nogami, A.; Babuty, D.; Yli-Mayry, S.; et al. Sudden cardiac arrest associated with early repolarization. N. Engl. J. Med. 2008, 358, 2016–2023. [CrossRef]
11. Rizzo, C.; Monitillo, F.; Iacovello, M. 12-lead electrocardiogram features of arrhythmic risk: A focus on early repolarization. World J. Cardiol. 2016, 8, 447–455. [CrossRef] [PubMed]
12. Junttila, M.J.; Sager, S.J.; Freiser, M.; McGonagle, S.; Castellanos, A.; Myerburg, R.J. Inferolateral early repolarization in athletes. J. Inter. Card. Electrophysiol. 2011, 31, 33–38. [CrossRef] [PubMed]
13. Higgins, J.P. Normal resting electrocardiographic variants in young athletes. Phys. Sportsmed. 2008, 36, 69–75. [CrossRef] [PubMed]
14. Osborn, J.J. Experimental hypothermia; respiratory and blood pH changes in relation to cardiac function. Am. J. Physiol. 1953, 175, 389–398. [CrossRef] [PubMed]
15. Reinhard, W.; Kaess, B.M.; Debic, R.; Nelson, C.P.; Stark, K.; Tobin, M.D.; Macfarlane, P.W.; Tomaszewski, M.; Samani, N.J.; Hengstenberg, C. Heritability of early repolarization: A population-based study. Circ. Cardiovasc. Genet. 2011, 4, 134–138. [CrossRef] [PubMed]
16. Yan, G.X.; Antzelevitch, C. Cellular basis for the Brugada syndrome and other mechanisms of arrhythmogenesis associated with ST-segment elevation. Circulation 1999, 100, 1660–1666. [CrossRef] [PubMed]
17. Tikkkanen, J.T.; Anttonen, O.; Junttila, M.J.; Aro, A.L.; Kerola, T.; Rissanen, H.A.; Reunanen, A.; Huikuri, H.V. Long-term outcome associated with early repolarization on electrocardiography. N. Engl. J. Med. 2009, 361, 2529–2537. [CrossRef] [PubMed]
18. Tikkkanen, J.T.; Junttila, M.J.; Anttonen, O.; Aro, A.L.; Luttimen, S.; Kerola, T.; Sager, S.J.; Rissanen, H.A.; Myerburg, R.J.; Reunanen, A.; et al. Early repolarization: Electrocardiographic phenotypes associated with favorable long-term outcome. Circulation 2011, 123, 2666–2673. [CrossRef] [PubMed]
19. Rosso, R.; Adler, A.; Halkin, A.; Viskin, S. Risk of sudden death among young individuals with J waves and early repolarization: Putting the evidence into perspective. *Heart Rhythm* 2011, 8, 923–929. [CrossRef] [PubMed]

20. Rosso, R.; Kogan, E.; Belhassen, B.; Rozovski, U.; Scheinman, M.M.; Zeltser, D.; Halkin, A.; Steinvil, A.; Heller, K.; Glikson, M.; et al. J-point elevation in survivors of primary ventricular fibrillation and matched control subjects: Incidence and clinical significance. *J. Am. Coll. Cardiol.* 2008, 52, 1231–1238. [CrossRef]

21. Sarcozy, A.; Chierchia, G.B.; Paparella, G.; Boussy, T.; De Asmundis, C.; Roos, M.; Henkens, S.; Kaufman, L.; Buyl, R.; Brugada, R.; et al. Inferior and lateral electrocardiographic repolarization abnormalities in Brugada syndrome. *Circ. Arrhythm. Electrophysiol.* 2009, 2, 154–161. [CrossRef]

22. Kawata, H.; Morita, H.; Yamada, Y.; Noda, T.; Satomi, K.; Aiba, T.; Isobe, M.; Nagase, S.; Nakamura, K.; Fukushima Kusano, K.; et al. Prognostic significance of early repolarization in inferolateral leads in Brugada patients with documented ventricular fibrillation: A novel risk factor for Brugada syndrome with ventricular fibrillation. *Heart Rhythm* 2013, 10, 1161–1168. [CrossRef] [PubMed]

23. Bayoumy, A.; Gong, M.Q.; Christen Li, K.H.; Wong, S.H.; Wu, W.K.; Li, G.P.; Bazoukis, G.; Letsas, K.P.; Wong, W.T.; Xia, Y.L.; et al. Spontaneous type 1 pattern, ventricular arrhythmias and sudden cardiac death in Brugada syndrome: An updated systematic review and meta-analysis. *J. Geriatr. Cardiol.* 2017, 14, 639–643. [PubMed]

24. Shi, S.; Barajas-Martinez, H.; Liu, T.; Sun, Y.; Yang, B.; Huang, C.; Hu, D. Prevalence of spontaneous Brugada ECG pattern recorded at standard intercostal leads: A meta-analysis. *Int. J. Cardiol.* 2017, 254, 151–156. [CrossRef] [PubMed]

25. Probst, V.; Veltmann, C.; Eckardt, L.; Meregalli, P.G.; Gaita, F.; Tan, H.L.; Babuty, D.; Sacher, F.; Giustetto, C.; Schulze-Bahr, E.; et al. Long-term prognosis of patients diagnosed with Brugada syndrome: Results from the FINGER Brugada Syndrome Registry. *Circulation* 2010, 121, 635–643. [CrossRef] [PubMed]

26. Priori, S.G.; Gasparini, M.; Napolitano, C.; Della Bella, P.; Ottonelli, A.G.; Sassone, B.; Giordano, P.; Pappone, C.; Mascoli, G.; Rossetti, G.; et al. Risk stratification in Brugada syndrome: Results of the PRELUDE (PRogrammed ELeCTrical StimulatiOn predicts ventricular EnuRcency) registry. *J. Am. Coll. Cardiol.* 2012, 59, 37–45. [CrossRef] [PubMed]

27. Meng, L.; Letsas, K.P.; Baranchuk, A.; Shao, Q.; Tse, G.; Zhang, N.; Zhang, Z.; Hu, D.; Li, G.; Liu, T. Meta-analysis of fragmented QRS as an electrocardiographic predictor for arrhythmic events in patients with Brugada syndrome. *Front. Physiol.* 2017, 8, 678. [CrossRef] [PubMed]

28. Ohkubo, K.; Watanabe, I.; Okumura, Y.; Ashino, S.; Kofune, M.; Nagashima, K.; Kofune, T.; Nakai, T.; Kunimoto, S.; Kasamaki, Y.; et al. Prolonged QRS duration in lead V2 and risk of life-threatening ventricular arrhythmia in patients with Brugada syndrome. *Int. Heart J.* 2011, 52, 98–102. [CrossRef] [PubMed]

29. BabaBigi, M.A.; Aslani, A.; Shahrzad, S. aVR sign as a risk factor for life-threatening arrhythmic events in patients with Brugada syndrome. *Heart Rhythm* 2007, 4, 1009–1012. [CrossRef] [PubMed]

30. Letsas, K.P.; Efremidis, M.; Asvestas, D.; Vlachos, K.; Georgopoulos, S.; Tse, G.; Liu, T.; Bazoukis, G.; Sideris, A.; Baranchuk, A.; et al. Right ventricular outflow tract electroanatomical abnormalities predict ventricular fibrillation inducibility in Brugada syndrome. *Circ. Arrhythm. Electrophysiol.* 2018, 11, e005928. [CrossRef] [PubMed]

31. Calò, L.; Giustetto, C.; Martino, A.; Sciarrà, L.; Cerrato, N.; Marziali, M.; Rauzino, G.; Carlino, G.; de Ruvo, E.; Guerra, F.; et al. New Electrocardiographic Marker of Sudden Death in Brugada Syndrome: The S-Wave in Lead I. *J. Am. Coll. Cardiol.* 2016, 67, 1427–1440. [CrossRef] [PubMed]

32. Castro Hevia, J.; Antzelevitch, C.; TornésBárzaga, F.; Dorantes Sánchez, M.; DotorcósBalea, F.; Zayas Molina, R.; Quiñones Pérez, M.A.; Fayad Rodríguez, Y. Tpeak-tend and Tpeak-tend dispersion as risk factors for ventricular tachycardia/ventricular fibrillation in patients with the Brugada syndrome. *J. Am. Coll. Cardiol.* 2006, 47, 1828–1834. [CrossRef] [PubMed]

33. Maury, P.; Sacher, F.; Pourraud, J.B.; Pasquié, J.L.; Raczka, F.; Bongard, V.; Duparc, A.; Mondoly, P.; Sadron, M.; Chatel, S.; et al. Increased Tpeak-Tend interval is highly and independently related to arrhythmic events in Brugada syndrome. *Heart Rhythm* 2015, 12, 2469–2476. [CrossRef] [PubMed]

34. Zumhagen, S.; Zeidler, E.M.; Stallmeyer, B.; Ernsting, M.; Eckardt, L.; Schulze-Bahr, E. Tpeak-Tend interval and Tpeak-Tend/QT ratio in patients with Brugada syndrome. *Europace* 2016, 18, 1866–1872. [PubMed]

35. Migliore, F.; Testolina, M.; Zorzi, A.; Bertaglia, E.; Silvano, M.; Leoni, L.; Bellin, A.; Basso, C.; Thiene, G.; Allocca, G.; et al. First-degree atrioventricular block on basal electrocardiogram predicts future arrhythmic events in patients with Brugada syndrome: A long-term follow-up study from the Veneto region of Northeastern Italy. *Europace* 2019, 21, 322–331. [CrossRef]

36. Morita, H.; Watanabe, A.; Kawada, S.; Miyamoto, M.; Morimoto, Y.; Nakagawa, K.; Nishii, N.; Nakamura, K.; Ito, H. Identification of electrocardiographic risk markers for the initial and recurrent episodes of ventricular fibrillation in patients with Brugada syndrome. *J. Cardiovasc. Electrophysiol.* 2018, 29, 107–114. [CrossRef] [PubMed]

37. Priori, S.G.; Blomstrom-Lundqvist, C. 2015 European Society of Cardiology Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death summarized by co-chairs. *Eur. Heart J.* 2015, 36, 2757–2759. [CrossRef] [PubMed]

38. Platonov, P.G.; McNitt, S.; Polonsky, B.; Rosero, S.Z.; Kutyifa, V.; Huang, A.; Moss, A.J.; Zareba, W. Risk Stratification of Type 2 Long-QT Syndrome Mutation Carriers With Normal QTc Interval: The Value of Sex, T-Wave Morphology, and Mutation Type. *Circ. Arrhythm. Electrophysiol.* 2018, 11, e005918. [CrossRef]

39. Bosman, L.P.; Sammari, A.; James, C.A.; Cadrin-Tourigny, J.; Calkins, H.; van Tintelen, J.P.; Hauer, R.N.W.; Asselbergs, F.W.; TeRiel, L.S.J.M. Predicting arrhythmic risk in arrhythmogenic right ventricular cardiomyopathy: A systematic review and meta-analysis. *Heart Rhythm* 2018, 15, 1097–1107. [CrossRef]
40. Corrado, D.; Wichter, T.; Link, M.S.; Hauer, R.; Marchlinski, F.; Anastasakis, A.; Bauce, B.; Basso, C.; Brunckhorst, C.; Tsatsopoulou, A.; et al. Treatment of arrhythmogenic right ventricular cardiomyopathy/dysplasia: An international task force consensus statement. *Eur. Heart J.* 2015, 36, 3227–3237. [CrossRef] [PubMed]

41. Orgeron, G.M.; Te Riele, A.; Tichnell, C.; Wang, W.; Murray, B.; Bhonsale, A.; Judge, D.P.; Kamel, I.R.; Zimmerman, S.L.; Tandri, H.; et al. Performance of the 2015 International Task Force Consensus Statement Risk Stratification Algorithm for Implantable Cardioverter-Defibrillator Placement in Arrhythmogenic Right Ventricular Dysplasia/Cardiomyopathy. *Circ. Arrhythm. Electrophysiol.* 2018, 11, e005993. [CrossRef] [PubMed]

42. Platonov, P.G.; Calkins, H.; Hauer, R.N.; Corrado, D.; Svendsen, J.H.; Wichter, T.; Biernacka, E.K.; Saguner, A.M.; TeRiele, A.S.; Zareba, W. High interobserver variability in the assessment of epsilon waves: Implications for diagnosis of arrhythmogenic right ventricular cardiomyopathy/dysplasia. *Heart Rhythm* 2016, 13, 208–216. [CrossRef] [PubMed]

43. Cox, M.G.; van der Zwaag, P.A.; van der Werf, C.; van der Smagt, J.J.; Noorman, M.; Bluijzen, Z.A.; Wiesfeld, A.C.; Volders, P.G.; van Langen, I.M.; Atsma, D.E.; et al. Arrhythmogenic right ventricular dysplasia/cardioangiopathy: Pathogenic desmosome mutations in index-patients predict outcome of family screening: Dutch arrhythmogenic right ventricular dysplasia/cardioangiopathy genotype-phenotype follow-up study. *Circulation* 2011, 123, 2690–2700. [CrossRef] [PubMed]

44. McDonagh, T.A.; Metra, M.; Adamo, M.; Gardner, R.S.; Baumbach, A.; Böhm, M.; Burri, H.; Butler, J.; Čelutkien˙e, J.; et al. Regional therapy in hypertrophic cardiomyopathy patients. *J. Clin. Med.* 2019, 8, 1151. [CrossRef]

45. Stecker, E.C.; Vickers, C.; Waltz, J.; Socoteanu, C.; John, B.T.; Mariani, R.; McAnulty, J.H.; Gunson, K.; Jui, J.; Chugh, S.S. Increased left ventricular mass and hypertrophy are associated with increased risk for sudden death. *J. Am. Coll. Cardiol.* 2010, 56, 1454–1459. [CrossRef] [PubMed]

46. Reinier, K.; Dervan, C.; Singh, T.; Uy-Evanado, A.; Lai, S.; Gunson, K.; Jui, J.; Chugh, S.S. Increased left ventricular mass and decreased left ventricular systolic function have independent pathways to ventricular arrhythmogenesis in coronary artery disease. *Heart Rhythm* 2011, 8, 1177–1182. [CrossRef] [PubMed]

47. Ng, A.C.; Bertini, M.; Borleffs, C.J.; Delgado, V.; Boersma, E.; Piers, S.R.; Thijssen, J.; Nucifora, G.; Shanks, M.; Ewe, S.H.; et al. Predictors of death and occurrence of appropriate defibrillator therapies in patients with ischemic cardiomyopathy. *Am. J. Cardiol.* 2010, 106, 1566–1573. [CrossRef] [PubMed]

48. Ersbøll, M.; Valeur, N.; Andersen, M.J.; Mogensen, U.M.; Vinther, M.; Svendsen, J.H.; Møller, J.E.; Kisslo, J.; Velazquez, E.J.; Hassager, C.; et al. Early echocardiographic deformation analysis for the prediction of sudden cardiac death and life-threatening arrhythmias after myocardial infarction. *JACC Cardiovasc. Imaging* 2013, 6, 851–860. [CrossRef] [PubMed]

49. Biering-Sørensen, T.; Knappe, D.; Pouleur, A.C.; Claggett, B.; Wang, P.J.; Moss, A.J.; Solomon, S.D.; Kutyifa, V. Regional Longitudinal Deformation Improves Prediction of Ventricular Tachyarrhythmias in Patients With Heart Failure With Reduced Ejection Fraction: A MADIT-CRT Substudy (Multicenter Automatic Defibrillator Implantation Trial-Cardiac Resynchronization Therapy). *Circ. Cardiovasc. Imaging* 2017, 10, e005906. [PubMed]

50. Wu, T.J.; Ong, J.J.; Hwang, C.; Lee, J.J.; Fishbein, M.C.; Czer, L.; Trento, A.; Blanche, C.; Kass, R.M.; Mandel, W.J.; et al. Characteristics of wave fronts during ventricular fibrillation in human hearts with dilated cardiomyopathy: Role of increased fibrosis in the generation of reentry. *J. Am. Coll. Cardiol.* 1998, 32, 187–196. [CrossRef]

51. Haugaa, K.H.; Grenne, B.L.; Eek, C.H.; Ersbøll, M.; Valeur, N.; Svendsen, J.H.; Florian, A.; Sjøli, B.; Brunvand, H.; Køber, L.; et al. Strain echocardiography improves risk prediction of ventricular arrhythmias after myocardial infarction. *JACC Cardiovasc. Imaging* 2013, 6, 841–850. [CrossRef] [PubMed]

52. Perry, R.; Patil, S.; Marx, C.; Horsfall, M.; Chew, D.P.; Sree Raman, K.; Daril, N.D.M.; Tiver, K.; Joseph, M.X.; Ganesan, A.N.; et al. Advanced Echocardiographic Imaging for Prediction of SCD in Moderate and Severe LV Systolic Function. *JACC Cardiovasc. Imaging* 2020, 13, 604–612. [CrossRef] [PubMed]

53. Debonnaire, P.; Thijssen, J.; Leong, D.P.; Joyce, E.; Katsanos, S.; Hoogslag, G.E.; Schallj, M.J.; Atsma, D.E.; Bax, J.J.; Delgado, V.; et al. Global longitudinal strain and left atrial volume index improve prediction of appropriate implantable cardioverter defibrillator therapy in hypertrophic cardiomyopathy patients. *Int. J. Cardiovasc. Imaging* 2014, 30, 549–558. [CrossRef] [PubMed]
60. Haland, T.F.; Almaas, VM.; Hasselberg, N.E.; Saberiak, J.; Leren, I.S.; Hopp, E.; Edvardsen, T.; Haugaa, K.H. Strain echocardiography is related to fibrosis and ventricular arrhythmias in hypertrophic cardiomyopathy. *Eur. Heart J. Cardiovasc. Imaging* **2016**, *17*, 613–621. [CrossRef] [PubMed]

61. Ermakov, S.; Gulhar, R.; Lim, L.; Bibby, D.; Fang, Q.; Nah, G.; Abraham, T.P.; Schiller, N.B.; Delling, F.N. Left ventricular mechanical dispersion predicts arrhythmic risk in mitral valve prolapse. *Heart* **2019**, *105*, 1063–1069. [CrossRef]

62. Alizade, E.; Yesin, M.; Tabacki, M.M.; Avci, A.; Bulut, M.; Acar, G.; Şimşek, Z.; İzci, S.; Baruçu, S.; Pala, S. Utility of speckle tracking echocardiography imaging in patients with asymptomatic and symptomatic arrhythmic right ventricular cardiomyopathy. *Echocardiography* **2016**, *33*, 1683–1688. [CrossRef] [PubMed]

63. Sarvari, S.I.; Haugaa, K.H.; Anfinsen, O.G.; Leren, T.P.; Smiseth, O.A.; Kongsgaard, E.; Amlie, J.P.; Edvardsen, T. Right ventricular mechanical dispersion is related to malignant arrhythmias: A study of patients with arrhythmogenic right ventricular cardiomyopathy and subclinical right ventricular dysfunction. *Eur. Heart J.* **2011**, *32*, 1089–1096. [CrossRef] [PubMed]

64. Gulati, A.; Jabbour, A.; Ismail, T.F.; Guha, K.; Khwaja, J.; Raza, S.; Morarji, K.; Brown, T.D.; Ismail, N.A.; Dweck, M.R.; et al. Association of fibrosis with mortality and sudden cardiac death in patients with nonischemic dilated cardiomyopathy. *JAMA* **2013**, *309*, 896–908. [CrossRef] [PubMed]

65. Disertori, M.; Rigoni, M.; Pace, N.; Casolo, G.; Masè, M.; Gonzini, L.; Lucci, D.; Nollo, G.; Ravelli, F. Myocardial Fibrosis Assessment by LGE Is a Powerful Predictor of Ventricular Tachyarrhythmias in Ischemic and Nonischemic LV Dysfunction: A Meta-Analysis. *JACC Cardiovasc. Imaging* **2016**, *9*, 1046–1055. [CrossRef] [PubMed]

66. Halliday, B.P.; Gulati, A.; Ali, A.; Guha, K.; Newsome, S.; Arzanauskaitė, M.; Vassiliou, VS.; Lota, A.; Izza, C.; Tayal, U.; et al. 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. [CrossRef] [PubMed]

67. Di Marco, A.; Anguera, I.; Schmitt, M.; Klem, I.; Neilan, T.G.; White, J.A.; Sramko, M.; Masci, P.G.; Barison, A.; Mckenna, P.; et al. Late Gadolinium Enhancement and the Risk for Ventricular Arrhythmias or Sudden Death in Dilated Cardiomyopathy: Systematic Review and Meta-Analysis. *JACC Cardiovasc. Imaging* **2017**, *5*, 28–38. [CrossRef] [PubMed]

68. Piers, S.R.; Everaerts, K.; van der Geest, R.J.; Hazebroek, M.R.; Siebelink, H.M.; Pison, L.A.; Schalij, M.J.; Bekkers, S.C.; Heymans, S.; Zeppenfeld, K. Myocardial scar predicts monomorphic ventricular tachycardia but not polymorphic ventricular tachycardia or ventricular fibrillation in dilated cardiomyopathic heart. *Heart Rhythm* **2015**, *12*, 2106–2114. [CrossRef] [PubMed]

69. Assomull, R.G.; Prasad, S.K.; Lyne, J.; Smith, G.; Burman, E.D.; Khan, M.; Sheppard, M.N.; Poole-Wilson, P.A.; Pennell, D.J. Cardiovascular magnetic resonance imaging is associated with ventricular tachyarrhythmia in patients with ischemic cardiomyopathy. *J. Cardiovasc. Magn. Reson.* **2012**, *14*, 24. [CrossRef] [PubMed]

70. Grani, C.; Eichhorn, C.; Biere, L.; Murthy, V.L.; Agarwal, V.; Kaneko, K.; Cuddy, S.; Aghayev, A.; Steigner, M.; Blankstein, R.; et al. Prognostic Value of Cardiac Magnetic Resonance Tissue Characterization in Risk Stratifying Patients With Suspected Myocarditis. *J. Am. Coll. Cardiol.* **2017**, *70*, 1964–1976. [CrossRef] [PubMed]

71. Cheong, B.Y.; Muthupillai, R.; Wilson, J.M.; Sung, A.; Huber, S.; Amin, S.; Elayda, M.A.; Lee, V.V.; Flamm, S.D. Prognostic significance of delayed-enhancement cardiac magnetic resonance imaging: Survival of 857 patients with and without left ventricular dysfunction. *Circulation* **2009**, *120*, 2069–2076. [CrossRef] [PubMed]

72. Klem, I.; Weinsaft, J.W.; Bahnsen, T.D.; Hegland, D.; Kim, H.W.; Hayes, B.; Parker, M.A.; Judd, R.M.; Kim, R.J. Assessment of myocardial scarring improves risk stratification in patients evaluated for cardiac defibrillator implantation. *J. Am. Coll. Cardiol.* **2012**, *60*, 408–420. [CrossRef] [PubMed]

73. Kwong, R.Y.; Chan, A.K.; Brown, K.A.; Chan, C.W.; Reynolds, H.G.; Tsang, S.; Davis, R.B. Impact of unrecognized myocardial scar detected by cardiac magnetic resonance imaging on event-free survival in patients presenting with signs or symptoms of coronary artery disease. *Circulation* **2006**, *113*, 2733–2740. [CrossRef] [PubMed]

74. Grün, S.; Schummen, J.; Greulich, S.; Wagner, A.; Schneider, S.; Bruder, O.; Kispert, E.M.; Hill, S.; Ong, P.; Klingel, K.; et al. Long-term follow-up of biopsy-proven viral myocarditis: Predictors of mortality and incomplete recovery. *J. Am. Coll. Cardiol.* **2012**, *59*, 1604–1615. [CrossRef] [PubMed]

75. Aquaro, G.D.; Perfetti, M.; Canasta, G.; Monti, L.; Dellegrottaglie, S.; Moro, C.; Pepe, A.; Todiere, G.; Lanzillo, C.; Scatteia, A.; et al. Cardiac MR With Late Gadolinium Enhancement in Acute Myocarditis With Preserved Systolic Function: ITAMY Study. *J. Am. Coll. Cardiol.* **2017**, *70*, 1977–1987. [CrossRef] [PubMed]

76. Halliday, B.P.; Baksí, A.J.; Gulati, A.; Ali, A.; Newsome, S.; Izza, C.; Arzanauskaitė, M.; Lota, A.; Tayal, U.; Vassiliou, V.S.; et al. Outcome in Dilated Cardiomyopathy Related to the Extent, Location, and Pattern of Late Gadolinium Enhancement. *JACC Cardiovasc. Imaging* **2019**, *12*, 1645–1655. [CrossRef] [PubMed]

77. Schuleri, K.H.; Centola, M.; Evers, K.S.; Zviman, A.; Evers, R.; Lima, J.A.; Lardo, A.C. Cardiovascular magnetic resonance characterization of peri-infarct zone remodeling following myocardial infarction. *J. Cardiovasc. Magn. Reson.* **2012**, *14*, 24. [CrossRef] [PubMed]

78. Demirel, F.; Adiyaman, A.; Timmer, J.R.; Dambrik, J.H.; Kok, M.; Boeve, W.J.; Elvan, A. Myocardial scar characteristics based on cardiac magnetic resonance imaging is associated with ventricular tachyarrhythmia in patients with ischemic cardiomyopathy. *Int. J. Cardiol.* **2014**, *177*, 392–399. [CrossRef] [PubMed]
79. Kwon, D.H.; Halley, C.M.; Carrigan, T.P.; Zyseke, V.; Popovic, Z.B.; Setser, R.; Schoenhagen, P.; Starling, R.C.; Flamm, S.D.; Desai, M.Y. Extent of left ventricular scar predicts outcomes in ischemic cardiomyopathy patients with significantly reduced systolic function: A delayed hyperenhancement cardiac magnetic resonance study. JACC Cardiovasc. Imaging 2009, 2, 34–44. [CrossRef] [PubMed]

80. Gao, P.; Yee, R.; Gula, L.; Krahn, A.D.; Skanes, A.; Leong-Sit, P.; Klein, G.J.; Stirrat, J.; Fine, N.; Pallaveshi, L.; et al. Prediction of arrhythmic events and dilated cardiomyopathy patients referred for implantable cardiac defibrillator: Evaluation of multiple scar quantification measures for late gadolinium enhancement magnetic resonance imaging. Circ. Cardiovasc. Imaging 2012, 5, 448–456. [CrossRef] [PubMed]

81. Schmidt, A.; Azevedo, C.F.; Cheng, A.; Gupta, S.N.; Bluemke, D.A.; Fof, T.K.; Gerstenblith, G.; Weiss, R.G.; Marbán, E.; Tomaselli, G.F.; et al. Infarct tissue heterogeneity by magnetic resonance imaging identifies enhanced cardiac arrhythmia susceptibility in patients with left ventricular dysfunction. Circulation 2007, 115, 2006–2014. [CrossRef] [PubMed]

82. Jablonowski, R.; Chaudhry, U.; van der Pals, J.; Engblom, H.; Arshed, H.; Heiberg, E.; Wu, K.C.; Borgquist, R.; Carlsson, M. Cardiovascular Magnetic Resonance to Predict Appropriate Implantable Cardioverter Defibrillator Therapy in Ischemic and Nonischemic Cardiomyopathy Patients Using Late Gadolinium Enhancement Border Zone: Comparison of Four Analysis Methods. Circ. Cardiovasc. Imaging 2017, 10, e006105. [CrossRef] [PubMed]

83. Yan, A.T.; Shayne, A.J.; Brown, K.A.; Gupta, S.N.; Chan, C.W.; Loo, T.M.; Di Carli, M.F.; Reynolds, H.G.; Stevenson, W.G.; Kwong, R.Y. Characterization of the peri-infarct zone by contrast-enhanced cardiac magnetic resonance imaging is a powerful predictor of post-myocardial infarction mortality. Circulation 2006, 114, 32–39. [CrossRef] [PubMed]

84. Moon, J.C.; Reed, E.; Sheppard, M.N.; Elkingston, A.G.; Ho, S.Y.; Burke, M.; Petrou, M.; Pennell, D.J. The histologic basis of late gadolinium enhancement cardiac magnetic resonance in hypertrophic cardiomyopathy. J. Am. Coll. Cardiol. 2004, 43, 2250–2256. [CrossRef] [PubMed]

85. Chan, R.H.; Maron, B.J.; Olivetto, I.; Pencina, M.J.; Assenza, G.E.; Haas, T.; Lesser, J.R.; Gruner, C.; Crean, A.M.; Rakowski, H.; et al. Prognostic value of quantitative contrast-enhanced cardiovascular magnetic resonance for the evaluation of sudden death risk in patients with hypertrophic cardiomyopathy. Circulation 2014, 130, 484–495. [CrossRef] [PubMed]

86. Chen, Z.; Sohal, M.; Voigt, T.; Sammut, E.; Tobon-Gomez, C.; Child, N.; Jackson, T.; Shetty, A.; Bostock, J.; Cooklin, M.; et al. 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. [CrossRef] [PubMed]

87. Flett, A.S.; Hayward, M.P.; Ashworth, M.T.; Hansen, M.S.; Taylor, A.M.; Elliott, P.M.; McGregor, C.; Moon, J.C. Equilibrium contrast cardiovascular magnetic resonance for the measurement of diffuse myocardial fibrosis: Preliminary validation in humans. Circulation 2010, 122, 138–144. [CrossRef] [PubMed]

88. Spieker, M.; Haberkorn, S.; Gastl, M.; Behm, P.; Katsianos, S.; Horn, P.; Jacoby, C.; Schnackenburg, B.; Reinecke, P.; Kelm, M.; et al. Abnormal T2 mapping cardiovascular magnetic resonance correlates with adverse clinical outcome in patients with suspected acute myocarditis. J. Cardiovasc. Magn. Reson. 2017, 19, 38. [CrossRef] [PubMed]

89. Haaf, P.; Garg, P.; Messroghli, D.R.; Broadbent, D.A.; Greenwood, J.P.; Plein, S. Cardiac T1 Mapping and Extracellular Volume (ECV) in clinical practice: A comprehensive review. J. Cardiovasc. Magn. Reson. 2016, 18, 39. [CrossRef] [PubMed]

90. Messroghli, D.R.; Moon, J.C.; Ferreira, V.M.; Grosse-Wortmann, L.; He, T.; Kellman, P.; Mascherbauer, J.; Nezafat, R.; Salerno, M.; Schelbert, E.B.; et al. Clinical recommendations for cardiovascular magnetic resonance mapping of T1, T2, T2* and extracellular volume: A consensus statement by the Society for Cardiovascular Magnetic Resonance (SCMR) endorsed by the European Association for Cardiovascular Imaging (EACVI). J. Cardiovasc. Magn. Reson. 2017, 19, 75. [PubMed]

91. Leyva, F.; Zegard, A.; Acquaye, E.; Gubran, C.; Taylor, R.; Foley, P.W.X.; Umar, F.; Patel, K.; Panting, J.; Marshall, H.; et al. Outcomes of Cardiac Resynchronization Therapy With or without Defibrillation in Patients with Nonischemic Cardiomyopathy. J. Am. Coll. Cardiol. 2017, 70, 1216–1227. [CrossRef]

92. Overhoff, D.; Ansari, U.; Hohnbeck, A.; Tüümän, E.; Rudic, B.; Kuschyk, J.; Lossnitzer, D.; Baumann, S.; Froelich, M.F.; Waldeck, S.; et al. Prediction of cardiac events by non-contrast magnetic resonance feature tracking in patients with ischaemic cardiomyopathy. ESC Heart Fail. 2022, 9, 574–584. [CrossRef] [PubMed]

93. Miller, M.A.; Dukkipati, S.R.; Turagam, M.; Liao, S.L.; Adams, D.H.; Reddy, V.Y. Arrhythmic Mitral Valve Prolapse: JACC Review Topic of the Week. J. Am. Coll. Cardiol. 2018, 72, 2904–2914. [CrossRef] [PubMed]

94. Basso, C.; Perazzolo Marra, M.; Rizzo, S.; De Lazzari, M.; Giorgi, B.; Cipriani, A.; Frigo, A.C.; Rigato, I.; Migliore, F.; Pilichou, K.; et al. Arrhythmic Mitral Valve Prolapse and Sudden Cardiac Death. Circulation 2015, 132, 556–566. [CrossRef] [PubMed]

95. Syed, F.F.; Ackerman, M.J.; McLeod, C.J.; Kapa, S.; Mulpuru, S.K.; Sriram, C.S.; Cannon, B.C.; Asirvatham, S.J.; Noseworthy, P.A. Sites of Successful Ventricular Fibrillation Ablation in Bileaflet Mitral Valve Prolapse Syndrome. Circ. Arrhythm. Electrophysiol. 2016, 9, e004005. [CrossRef] [PubMed]

96. Bui, A.H.; Roujol, S.; Foppa, M.; Kissinger, K.V.; Goddu, B.; Hauser, T.H.; Zimetbaum, P.J.; Ngo, L.H.; Manning, W.J.; Nezafat, R.; et al. Diffuse myocardial fibrosis in patients with mitral valve prolapse and ventricular arrhythmia. Heart 2017, 103, 204–209. [CrossRef]
97. Perazzolo Marra, M.; Basso, C.; De Lazzari, M.; Rizzo, S.; Cipriani, A.; Giorgi, B.; Lacognata, C.; Rigato, I.; Migliore, F.; Pilichou, K.; et al. Morphofunctional Abnormalities of Mitral Annulus and Arrhythmic Mitral Valve Prolapse. Circ. Cardiovasc. Imaging 2016, 9, e005300. [CrossRef] [PubMed]

98. Nadel, J.; Lancefield, T.; Voskoboinik, A.; Taylor, A.J. Late gadolinium enhancement identified with cardiac magnetic resonance imaging in sarcoidosis patients is associated with long-term ventricular arrhythmia and sudden cardiac death. EurHeart J. Cardiovasc. Imaging 2015, 16, 634–641.

99. Ichinose, A.; Otani, H.; Iikawa, M.; Takase, K.; Saito, H.; Shimokawa, H.; Takahashi, S. MRI of cardiac sarcoidosis: Basal and subepicardial localization of myocardial lesions and their effect on left ventricular function. AJR 2008, 191, 862–869. [CrossRef]

100. Crawford, T.; Mueller, G.; Sarsam, S.; Prasitdumrong, H.; Chaityn, N.; Gu, X.; Schuller, J.; Kron, J.; Nour, K.A.; Cheng, A.; et al. Magnetic resonance imaging for identifying patients with cardiac sarcoidosis and preserved or mildly reduced left ventricular function at risk of ventricular arrhythmias. Circ. Arrhythm. Electrophysiol. 2014, 7, 1109–1115. [CrossRef] [PubMed]

101. Patel, A.R.; Klein, M.R.; Chandra, S.; Spencer, K.T.; Decara, J.M.; Lang, R.M.; Burke, M.C.; Arrhythmia, E.R.; Hogarth, D.K.; Archer, S.L.; et al. Myocardial damage in patients with sarcoidosis and preserved left ventricular systolic function: An observational study. Eur. J. Heart Fail. 2011, 13, 1231–1237. [CrossRef]

102. Smedema, J.P.; van Geuns, R.J.; Ainslie, G.; Ector, J.; Heidbuchel, H.; Crijsen, H. Right ventricular involvement in cardiac sarcoidosis demonstrated with cardiac magnetic resonance. ESC Heart Fail. 2017, 4, 533–544. [CrossRef] [PubMed]

103. Sikkema-Raddatz, B.; Johansson, L.F.; de Boer, E.N.; Almomani, R.; Boven, G.L.; van den Berg, M.P.; van Spaendonck-Zwarts, K.Y.; van Tintelen, J.P.; Sijmons, R.H.; Jongbloed, J.D.; et al. Targeted next-generation sequencing can replace Sanger sequencing in clinical diagnostics. Hum. Mutat. 2014, 35, 1034–1042. [CrossRef] [PubMed]

104. Fokstuen, S.; Makrythanasis, P.; Nikolaev, S.; Santoni, F.; Robyr, D.; Munoz, A.; Bevillard, J.; Farinelli, L.; Iseli, C.; Antonarakis, S.E.; et al. Multiplex targeted high-throughput sequencing for Mendelian cardiac disorders. Clin. Genet. 2014, 85, 365–370. [CrossRef] [PubMed]

105. Osman, J.; Tan, S.C.; Lee, P.Y.; Low, T.Y.; Jamal, R. Sudden Cardiac Death (SCD)—Risk stratification and prediction with molecular biomarkers. J. Biomed. Sci. 2019, 26, 39. [CrossRef] [PubMed]

106. Mazzarotto, F.; Tayal, U.; Buchan, R.J.; Midwinter, W.; Wilk, A.; Whiffin, N.; Govind, R.; Mazaika, E.; de Marvao, A.; Dawes, T.J.W.; et al. Reevaluating the Genetic Contribution of Monogenic Dilated Cardiomyopathy. Circulation 2020, 141, 387–398. [CrossRef] [PubMed]

107. Pinto, Y.M.; Elliott, P.M.; Arbustini, E.; Adler, Y.; Anastasakis, A.; Böhm, M.; Duboc, D.; Gimeno, J.; de Groote, P.; van Tintelen, J.P.; Sijmons, R.H.; Jongbloed, J.D.; et al. Proposal for a revised definition of dilated cardiomyopathy, hypokinetic non-dilated cardiomyopathy, and its implications for clinical practice: A position statement of the ESC working group on myocardial and pericardial diseases. Eur. J. Heart Fail. 2016, 18, 1850–1858. [CrossRef] [PubMed]

108. Dal Ferro, M.; Severini, G.M.; Gigli, M.; Mestroni, L.; Sinagra, G. Genetics of Dilated Cardiomyopathy: Current Knowledge and Future Perspectives. In Dilated Cardiomyopathy: From Genetics to Clinical Management; Springer: Cham, Switzerland, 2019.

109. Verdonschot, J.A.J.; Hazebroek, M.R.; Krapels, I.P.C.; Henkens, M.T.H.M.; Raafs, A.; Wang, P.; Merken, J.J.; Claes, G.R.F.; Vanhoutte, E.K.; van den Wijngaard, A.; et al. Implications of Genetic Testing in Dilated Cardiomyopathy. Circ. Genomic Precis. Med. 2020, 13, 476–487. [CrossRef] [PubMed]

110. Pasotti, M.; Klersy, C.; Pilotto, A.; Marziliano, N.; R apezzi, C.; Serio, A.; Mannarino, S.; Gambarin, F.; Favalli, V.; Grasso, M.; et al. Long-term outcome and risk stratification in dilated cardiomyopathies. J. Am. Coll. Cardiol. 2008, 52, 1250–1260. [CrossRef] [PubMed]

111. Bécane, H.M.; Bonne, G.; Varouarn, S.; Muchir, A.; Ortega, V.; Hammouda, E.H.; Utzibereza, J.A.; Lavergne, T.; Fardeau, M.; Eynard, B.; et al. High incidence of sudden death with conduction system and myocardial disease due to lamin A and C gene mutation. Pacing Clin. Electrophysiol. 2000, 23, 1661–1666. [CrossRef] [PubMed]

112. Van Berlo, J.H.; de Voogt, W.G.; van der Kooi, A.J.; van Tintelen, J.P.; Bonne, G.; Yao, R.B.; Duboc, D.; Rosenbacker, T.; Heidbüchel, H.; de Visser, M.; et al. Meta-analysis of clinical characteristics of 299 carriers of LMNA gene mutations: Do lamin A/C mutations portend a high risk of sudden death? J. Mol. Med. 2005, 83, 79–83. [CrossRef]

113. Verdonschot, J.A.J.; Hazebroek, M.R.; Derks, K.W.J.; van den Wijngaard, A.; Merken, J.J.; Claes, G.R.F.; Vanhoutte, E.K.; van den Wijngaard, A.; et al. Titin cardiomyopathy leads to altered mitochondrial energetics, increased fibrosis and long-term life-threatening arrhythmias. Eur. Heart J. 2018, 39, 864–873. [CrossRef] [PubMed]

114. Parikh, V.N.; Caleshu, C.; Reuter, C.; Lazzeroni, L.C.; Ingles, J.; Garcia, J.; McCaleb, K.; Adesiyun, T.; Sedaghat-Hamedani, F.; Jiménez-Jáimez, J.; Hidalgo-Olivares, V.M.; et al. Truncating FLNC mutations are associated with high-risk dilated and Arrhythmogenic cardiomyopathies. J. Am. Coll. Cardiol. 2016, 68, 2440–2451. [CrossRef] [PubMed]

115. Vérondoschot, J.A.J.; Hazebroek, M.R.; Derks, K.W.J.; Barandiaran, A.; van den Wijngaard, A.; et al. Meta-analysis of clinical characteristics of 299 carriers of LMNA gene mutations: Do lamin A/C mutations portend a high risk of sudden death? J. Mol. Med. 2005, 83, 79–83. [CrossRef] [PubMed]

116. McNeil, W.P.; Sinagra, G.; Taylor, M.R.; Di Lenarda, A.; Ferguson, D.A.; Salcedo, E.E.; Slavov, D.; Zhu, X.; Caldwell, J.H.; Mestroni, L. SCN5A mutations associate with arrhythmogenic dilated cardiomyopathy and commonly localize to the voltage-sensing mechanism. J. Am. Coll. Cardiol. 2011, 57, 2160–2168. [CrossRef] [PubMed]

117. Zecchin, M.; Muser, D.; Vitali-Serdoz, L.; Buiatti, A.; Morgera, T. Arrhythmias in Dilated Cardiomyopathy: Diagnosis and Treatment. In From Genetics to Clinical Management; Springer: Cham, Switzerland, 2019.

118. Ortiz-Genga, M.F.; Cuenca, S.; Dal Ferro, M.; Zorio, E.; Salgado-Araña, R.; Climent, V.; Padró-Barthe, L.; Duro-Aguado, I.; Jiménez-Jáimez, J.; Hidalgo-Olivares, V.M.; et al. Truncating FLNC mutations are associated with high-risk dilated and Arrhythmogenic cardiomyopathies. J. Am. Coll. Cardiol. 2016, 68, 2440–2451. [CrossRef] [PubMed]
139. Ormondroyd, E.; Oates, S.; Parker, M.; Blair, E.; Watkins, H. Pre-symptomatic genetic testing for inherited cardiac conditions: A qualitative exploration of psychosocial and ethical implications. *Eur. J. Hum. Genet.* 2014, 22, 88–93. [CrossRef] [PubMed]

140. Priori, S.G.; Blomström-Lundqvist, C.; Mazzanti, A.; Blom, N.; Borggrefe, M.; Camm, J.; Elliott, P.M.; Fitzsimores, D.; Hatala, R.; Hindricks, G.; et al. 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. [PubMed]

141. Priori, S.G. Genetic testing to predict sudden cardiac death: Current perspectives and future goals. *Indian Heart J.* 2014, 66, S58–S60. [CrossRef] [PubMed]