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Review

Electrical Ventricular Remodeling in Dilated Cardiomyopathy

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Abstract: Ventricular arrhythmias contribute significantly to morbidity and mortality in patients with heart failure (HF). Pathomechanisms underlying arrhythmogenicity in patients with structural heart disease and impaired cardiac function include myocardial fibrosis and the remodeling of ion channels, affecting electrophysiologic properties of ventricular cardiomyocytes. The dysregulation of ion channel expression has been associated with cardiomyopathy and with the development of arrhythmias. However, the underlying molecular signaling pathways are increasingly recognized. This review summarizes clinical and cellular electrophysiologic characteristics observed in dilated cardiomyopathy (DCM) with ionic and structural alterations at the ventricular level. Furthermore, potential translational strategies and therapeutic options are highlighted.

Keywords: dilated cardiomyopathy; ion channel; remodeling; sudden cardiac death; ventricular arrhythmia

Citation: Mages, C.; Gampp, H.; Syren, P.; Rahm, A.-K.; André, F.; Frey, N.; Lugenbiel, P.; Thomas, D. Electrical Ventricular Remodeling in Dilated Cardiomyopathy. *Cells* **2021**, *10*, 2767. https://doi.org/10.3390/cells10102767

Academic Editors: Ursula Ravens, Rémi Peyronnet and Alexander E. Kalyuzhny

Received: 3 September 2021
Accepted: 12 October 2021
Published: 15 October 2021

1. Introduction: Characteristics of Ventricular Arrhythmias in Patients with Dilated Cardiomyopathy

Ventricular arrhythmias contribute significantly to morbidity and mortality in patients with cardiomyopathies. Dilated cardiomyopathy (DCM) is one major cause of progressive heart failure (HF). The disease entity summarizes a variety of heterogenous clinical subgroups [1–3]. DCM is currently defined as left ventricular or biventricular dilatation and systolic dysfunction in the absence of abnormal loading conditions or coronary artery disease sufficient to cause global cardiac impairment [4,5]. The reported prevalence is estimated between 1:250 and 1:500 [1]. One-year mortality ranges between 25 and 30%, and five-year mortality yields up to 50% [2]. Cases of sudden cardiac death (SCD) due to life-threatening ventricular arrhythmias such as ventricular tachycardia (VT) and ventricular fibrillation (VF), as well as bradyarrhythmia, are reported in up to 12% of patients and account for approximately 30% of overall mortality [2,3,6].

DCM is classified either according to the European Society of Cardiology (ESC) as genetic or non-genetic or according to the American Heart Association (AHA) as secondary or primary with genetic, acquired or mixed cause, respectively [5,7]. Primary forms of DCM primarily affect the cardiac muscle, while secondary forms are caused by systemic conditions, with a large overlap between these forms [2]. Both variants may include genetic mutations, infections, autoimmune diseases, exposure to toxins and endocrine or neuromuscular causes [3]. Channelopathies (short and long QT syndrome, Brugada syndrome and catecholaminergic polymorphic ventricular tachycardia) may also be considered cardiomyopathies because of electric myocyte dysfunction [1]. Both genetic predisposition and environmental factors play a pivotal role in the natural history of the diseases.

Pathophysiological changes in DCM include a reduction in stroke volume and in cardiac output, as well as an increase in end-diastolic pressure. Compensatory volume overload results in an increased preload, contributing to increased afterload and ultimately left ventricular elevated wall stress. Furthermore, neurohumoral activation enhances sympathetic adrenergic activity and the activation of the renin–angiotensin–aldosterone system (RAAS) [3]. Clinical manifestations of patients with DCM are heterogenous and depend on etiology, age, comorbidities and the severity of the disease. Typical clinical findings include symptoms of acute or chronic HF that range from signs of volume overload, dyspnea and fatigue, to arrhythmia manifesting as palpitations, tachycardia or cardiogenic shock.

Electrocardiographic findings are mostly unspecific and include T-wave inversion, right and left bundle branch block or atrioventricular and intraventricular conduction abnormalities [3,8]. In addition, supraventricular and ventricular arrhythmias are clinically relevant in patients with DCM [9–13]. This work will focus on ventricular arrhythmias (see Figure 1). The pathophysiology of arrhythmogenesis in DCM is incompletely understood despite its clinical and prognostic significance. Potential proarrhythmic mechanisms include changes in the conduction system through dilatation and the increased wall stress, the generation of arrhythmogenic substrates through focal fibrosis and neurohumoral activation leading to electrophysiological and structural remodeling [14]. Virtually all (>90%) DCM patients exhibit premature ventricular contractions (PVC), and non-sustained VT is found in 40–60% of patients' Holter recordings [15]. These clinical findings highlight the need to better understand genetic, epigenetic and structural changes underlying ventricular arrhythmogenesis. Mechanistic insights may serve as a basis for the development of therapies to prevent maladaptive electrical remodeling and to identify patients at risk of SCD. A systematic search through the web-based engine PubMed was conducted in order to identify all studies meeting the eligibility criteria using the search terms "dilated cardiomypathy, cardiomyopathy, DCM, arrhythmia".

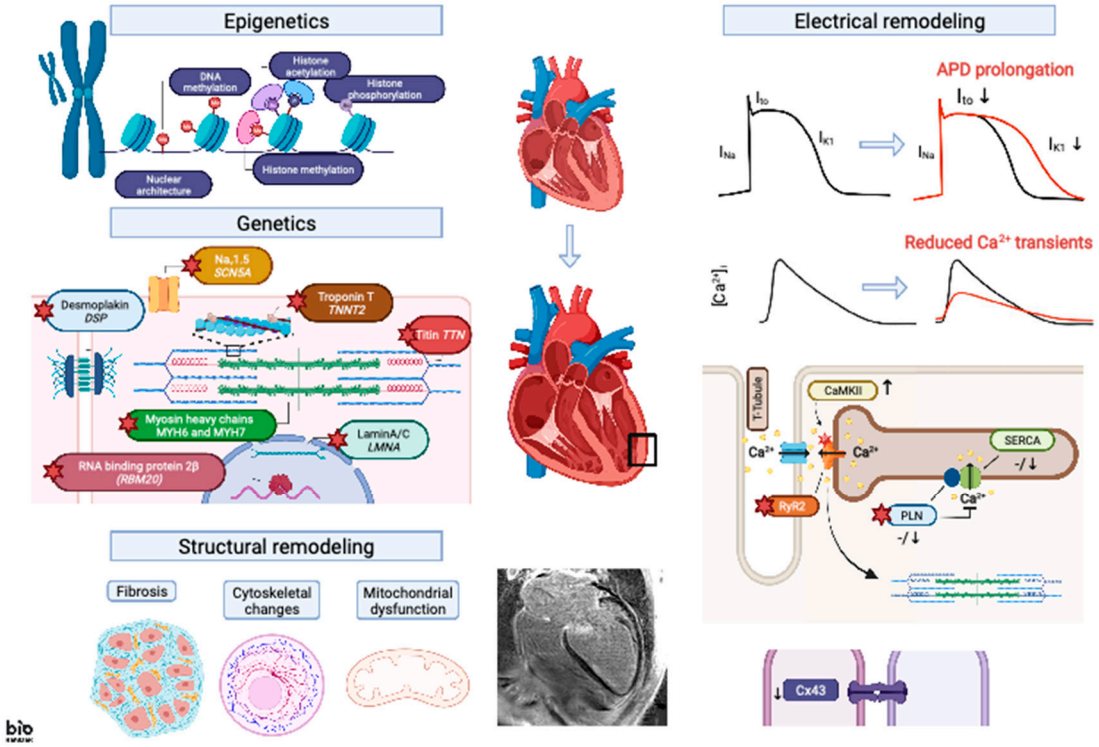

Figure 1. Graphical abstract on electrical ventricular remodeling in dilated cardiomyopathy.

2. Genetic Basis of Ventricular Arrhythmogenesis in DCM

More than 60 genes encoding for sarcomere proteins, cytoskeleton, nuclear envelope, sarcolemma, ion channels and/or intercellular junction molecules have been implicated in the pathogenesis of DCM to date [16,17]. The identification of new genes or novel mutations and variants in known genes is currently a subject of intensive research. Familiar forms of DCM with associated mutations are found in 30–40% of all patients, with titin (*TTN*) being the most prevalent (20–25% of familial DCM cases), followed by lamin A/C (*LMNA*, 5–10%) [17–19]. Genetic forms of DCM, which are typically characterized by cardiac conduction disorders and are particularly prone to malignant arrhythmias, are linked to mutations in lamin A/C (*LMNA*), cardiac sodium channel $Na_v1.5$. (*SCN5A*), filamin C (*FLNC*), desmoplakin (*DSP*), phospholamban (*PLN*) and RNA-binding motif protein 20 (*RBM20*) (see Table 1) [17,20]. The recognition of DCM with electric instability is clinically relevant as the presence of mutations may impact therapeutic management [17,21]. However, in many cases, a correlation between genotype and phenotype cannot be readily established due to incomplete penetrance and variable expression of the disease [16]. Furthermore, there is an overlap between 'arrhythmogenic DCM' and the current concept of arrhythmogenic cardiomyopathies that requires further clarification [10,22]. Direct effects of DCM-related mutations on action potential duration (APD) are not well characterized. Indeed, DCM is not characterized by a single pattern of electrophysiological changes. Although arrhythmias are commonly caused by variations in ion channels when isolated, they may also be a part of a complex manifestation of cardiomyopathy. On a cellular level, proarrhythmic defects in cardiac electrophysiology may be caused by ion channel remodeling, intercellular uncoupling, altered calcium homeostasis and changes in the extracellular matrix, each resulting or participating in dysregulated action potential duration and/or propagation [23]. For example, the defective force hypothesis proposes that genetic mutations in DCM may impair the highly organized cytoskeleton and sarcomere architecture of the cardiomyocyte, resulting in myocyte dysfunction and in arrhythmias based on structural remodeling [3,19]. Furthermore, electrophysiological defects associated with *SCN5A* gain-of-function may induce triggered activity during repolarization or diastole, whereas *SCN5A* channel loss-of-function may promote arrhythmogenesis through conduction slowing and re-entry. By contrast, pathways that cause ventricular dilatation and dysfunction associated with *SCN5A* mutations and their underlying structural defects are unclear [24].

Table 1. Monogenetic causes of DCM particularly prone to ventricular arrhythmia.

Protein	Gene	Protein Function
Titin	*TTN*	Sarcomere structural protein
Lamin A/C	*LMNA*	Inner nuclear membrane
Cardiac sodium channel $Na_v1.5$	*SCN5A*	Cardiac sodium channel α-subunit
Filamin C	*FLNC*	Actin cytoskeleton
Desmoplakin	*DSP*	Desmosomal protein
RNA-binding motif protein 20	*RBM20*	RNA binding and splicing regulation
Phospholamban	*PLN*	Sarcoplasmic reticulum protein involved in calcium homeostasis

3. Electrical Remodeling

DCM is characterized by complex changes in electrical properties of ventricular cardiomyocytes that predispose to ventricular arrhythmias. Electrophysiological changes include the prolongation of APD by changes in repolarization, a decrease in conduction velocity and disturbed excitation–contraction (EC) coupling. At the cellular and molecular levels, alterations involve ion channels, calcium handling proteins and intercellular gap junctions. Conduction slowing may arise from reduced depolarizing current and reduced intercellular coupling by gap junctions.

3.1. APD Changes

Prolongation of the action potential is a characteristic feature of cells isolated from failing animal and human hearts, irrespective of their etiology, and has been confirmed repeatedly for DCM [25–27]. A prolonged action potential is associated with a significant delay in repolarization, which may increase susceptibility to malignant arrhythmias by mechanisms such as triggered activity or reentry. The fast depolarization of cardiomyocytes (phase 0 of the ventricular action potential) is initiated by the opening of voltage-dependent sodium channels, which are primarily composed of $Na_v1.5$. In animal models of DCM, sodium current densities did not differ from the control [28,29]. As alterations in the ion channel gene *SCN5A* are associated with DCM, there is evidence of sodium channel involvement in dilation etiology, but the mechanisms by which the disruption of sodium channel function leads to dilation remodeling remain unclear (Olson et al. 2005) [30]. *SCN5A* deficiency in a mouse model reduced membrane excitability and the resulting slowed conduction may promote arrhythmia as a result of functional block [31]. Sodium channels inactivate during repolarizing phase 1, and the transient outward potassium current (I_{to1}) formed by $K_v4.2$, $K_v4.3$ and $K_v1.4$ is activated. In a mouse model of familial DCM, I_{to} was significantly reduced in DCM cardiomyocytes before the onset of HF, and the downregulation of $K_v4.2$ was evident on the mRNA and protein level [32]. In humans, two isoforms of $K_v4.3$, $K_v4.3$-S and $K_v4.3$-L have been described, and isoform-specific remodeling was detected in failing hearts due to DCM, with increased $K_v4.3$-L and reduced $K_v4.3$-S mRNA transcript levels [33]. As this finding was also confirmed for ICM, it may be a common feature of remodeling in cardiomyopathies [34]. Ventricular cardiomyocytes exhibit an inward rectifying potassium current (I_{K1}) that contributes to phase 3 repolarization of ventricular action potentials and to the maintenance of the negative resting membrane potential. It has been shown that the late repolarization phase for DCM is slower than that for ICM, resulting in action potential prolongation [26]. In failing hearts due to underlying DCM, the expression of the inwardly rectifying potassium channels (K_{ir}) $K_{ir}2.2$ and $K_{ir}2.3$ decreased, which may account for the decreased I_{K1} current in DCM) [35].

3.2. EC Coupling

In DCM, excitation–contraction coupling is disturbed by alterations of the myocardial architecture and by expression changes of calcium-handling proteins with subsequent abnormal calcium cycling. These alterations contribute to reduced calcium transients, impaired contractility and arrhythmia. Dyads formed by the apposition of transverse (T)-tubules and junctional sarcoplasmic reticulum (jSR) are the main site for the coupling of excitation and contraction. T-tubules are invaginations of the cardiac sarcolemma with a high density of voltage-gated L-type Ca^{2+} channels (LTCC). Membrane depolarization leads to Ca^{2+} influx into the dyadic cleft via LTCC, triggering Ca^{2+} release from the SR via ryanodine receptors (RyR2), which then initiates sarcomere contraction. T-tubule remodeling is seen in many forms of HF, including DCM [36]. In DCM, there is a regional variability in the extent of T-tubule remodeling, as regions with near-normal contractility featured intact T-tubules, while regions with diminished contractility showed loss and disorganization of the T-tubule system. Furthermore, spatial re-organization occurs, with a change in T-tubule orientation from a transverse to an axial direction [37,38]. Ryanodine receptors are regulated by calcium and calcium/calmodulin dependent kinase II (CaMKII), and increased phosphorylation has been shown in patients with DCM but not in patients with ICM [39]. Increased CaMKII phosphorylation of RyR2 is suggested to play a critical role in the development of pathological diastolic SR Ca^{2+} release events (SR Ca^{2+} leaks) and the manifestation of arrhythmias [40–42].

Calcium sequestration into the sarcoplasmic reticulum (SR) lumen by the SR Ca^{2+}-ATPase (SERCA) determines the rate of cardiac relaxation and the calcium load available for following contraction. SERCA pump activity is reversibly inhibited by PLN. Studies have described decreased expression of PLN and SERCA2 mRNA levels in human failing hearts due to DCM, while other studies show controversy about a corresponding decrease

in protein levels [43–46]. Despite no significant protein level change in some studies, Ca^{2+} uptake activity and SERCA activity were shown to be significantly decreased, indicating that additional regulatory factors that have not been discovered yet may be responsible for the impaired uptake of Ca^{2+} into the SR [44]. Furthermore, genetic variants for *PLN* have been identified that may predispose to an arrhythmogenic phenotype [47,48], reflected by higher incidences of ICD therapy, premature ventricular contractions during Holter monitoring and positive family history for SCD compared with DCM patients without a *PLN* mutation [49,50]. Dominant-negative effects of *PLN* mutations on SERCA activity have been reported, resulting in decreased calcium storage and Ca^{2+} transients [51,52].

3.3. Cell–Cell Coupling

Gap junctions connect two neighboring cardiomyocytes at their intercalated discs and play a crucial role in impulse propagation across the myocardium and electrical synchronization between myocytes. Connexin 43 (Cx43) is the major connexin protein found in ventricular gap junctions and is predominantly expressed in its phosphorylated form in the healthy heart. Left ventricular tissue samples from patients with DCM showed a decrease in Cx43 expression and phosphorylation. Gap junctions were heterogeneously redistributed to the lateral cell borders of cardiomyocytes [53,54]. Gap junction remodeling appears to be associated with the presence of ventricular arrhythmia in DCM patients, as the patient group with a history of VT showed reduced and more heterogeneous distribution of Cx43 than the non-VT group [53]. In knockout mice, Cx43 deficiency correlates with slowed and dispersed impulse conduction [55,56], with significant contributions from changes in the phosphorylation status and subcellular distribution [27]. It has been suggested that the concurrent development of fibrosis is a prerequisite for conduction slowing [57]. Regional uncoupling due to gap junction remodeling is hypothesized to drive the dispersion of repolarization between transmural layers and contribute to electrophysiological heterogeneity of action potential duration [58]. Mechanisms by which dilation-induced cellular changes form a substrate for ventricular arrhythmias remain poorly understood. As DCM may arise from a variety of underlying causes and frequently presents with HF, distinguishing specific electrophysiological remodeling that can be attributed to DCM from alterations generally found in HF diseases is challenging.

4. Modulation of Epigenetic Signaling in DCM

Chromosomal alterations without changes in DNA sequence, also referred to as epigenetic changes [59,60], affect electrical remodeling in DCM [61]. Chromatin compaction via histone modifications represents one epigenetic mechanism. Typical modifications include acetylation, methylation and phosphorylation. An equilibrium of enzymes regulates the frequency of these changes. In human DCM, multiple alterations in the expression of histone methylation- [62–65], acetylation- [63,66,67] and phosphorylation- [68,69] modifying enzymes have been reported. Effects on several major pathways involved in DCM-induced electrical remodeling have been described. Histone demethylases JMJD1A, JMJD2A and JMJD2B mediate DCM-induced reactivation of atrial and brain natriuretic peptide (ANP and BNP), with reduced histone methylation in their respective promotor regions [63]. This demethylation is furthermore conveyed by increased nuclear export and reduced total expression of histone deacetylase 4 (HDAC4) [63]. While the exact effects of ANP and BNP on human cardiac electrophysiology are not fully understood due to their pleiotropic mechanism of action and high inter-species variability, relevance in this field is likely [70–72]. Some evidence points towards an AP-shortening in human ventricles, potentially due to influence on calcium and potassium channels [70,71,73,74]. In a porcine HF model, HDAC2 was downregulated in HF with increased ventricular effective refractory periods and prolonged QT intervals, potentially linked to reduced potassium channel transcripts *KCNJ2*, *KCNJ5* and *KCNH2* [67].

Nuclear CaMKII with relevance in electromechanical coupling and calcium handling [75] regulates chromatin accessibility via histone phosphorylation [68,69] and influ-

ences the nuclear export of HDAC4, -5 and -9 [76–79]. Bromodomain-containing protein 4 (BRD4), important for the recognition of histone acetylation sites, leads to the formation of super-enhancers with enrichment at calcium-handling gene loci [80]. Histone methylation-induced expressional changes in structural proteins such as cell adhesion molecules [81] and dystrophin [62] were reported in human DCM and show effects on AP duration [82]. Further epigenetic alterations in DCM include direct DNA methylation [83–86], changes in the higher order of chromatin [87] and interactions with the nuclear membrane. Lamin A/C mutations cause diminished conduction velocity, reduce action potential duration and I_{Na} current and downregulate $Na_V1.5$ channel expression by the binding of lamin to the promotor region of *SCN5A* [88]. Furthermore, some definitions of epigenetics include non-coding RNAs [89] as well, with several reported alterations in DCM [61].

Several clinically used HDAC inhibitors exert QT interval-prolonging effects [90–93]. QT prolongation is likely caused by (epi-)genetic regulation and not induced by direct pharmacological interaction [94], which underlines the electrophysiological relevance of epigenetic modulation in the electrical remodeling in DCM and its therapeutic potential.

5. Structural Remodeling

Structural remodeling in DCM is accompanied to a variable extent by ventricular fibrosis and scar formation that can promote arrhythmia by re-entry mechanisms. Myocardial fibrosis on a cellular level is caused by increased myofibroblast activity and the deposition of extracellular matrix proteins. Various cell types and proteins are involved in these processes, and depending on the genetic causes and pathophysiology of fibrogenesis, disease progression may vary. DCM induced by sarcomere protein mutations most commonly involves myosin and troponin, causing cardiomyocytes' degeneration and interstitial fibrosis [95]. The most common form of familial DCM caused by truncating titin mutations disturbs mitochondrial energetic metabolism and alters the cytoskeleton, thereby leading to cardiomyocyte dysfunction and inflammation and finally to myocardial fibrosis [96]. In patients with lamin A/C mutations, increased production of fibronectin, syndecans and nidogens and TGF-ß activation has been reported, with pronounced influence on cardiac electrophysiology [97].

From a clinical perspective, fibrosis has been suggested as a prognostic marker [98–101]. Currently, the main detection methods for myocardial fibrosis rely on cardiovascular magnetic resonance (CMR) with late gadolinium enhancement (LGE) and mapping techniques as the non-invasive gold standard for the identification and the quantification of myocardial fibrosis (see Figure 2). While LGE is ideal for the detection of focal fibrosis, native T1 mapping and extracellular volume (ECV) quantification using gadolinium contrast agent are more suitable for the detection of diffuse fibrosis and may therefore better detect early stages of DCM [102].

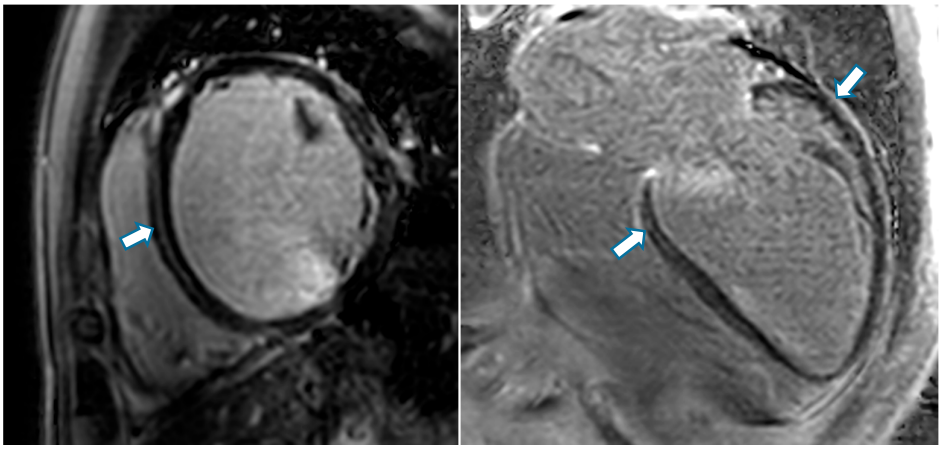

Figure 2. Cardiovascular magnetic resonance (late gadolinium enhancement sequences) shows subepicardial late gadolinium enhancement (white arrows) in axial (left) and longitudinal view (right).

In most patients with sustained and hemodynamically not tolerated VT, MRI is limited by artifacts from implanted ICDs for secondary prevention, and although scar detection and ECV imaging by cardiac CT are possible, data are still scarce compared to CMR, and it is not performed in clinical routine [103,104]. Endomyocardial biopsy is used in selected cases in clinical routine, and serum markers are under evaluation in clinical studies [105]. The analysis of LGE patterns render the identification of patients with non-ischemic causes possible, as those patients show non-ischemic patterns including mid-wall/sub-epicardial or patchy distribution, in contrast to ischemic patterns in cardiomyopathies [106].

Fibrosis itself has been identified as a risk factor for mortality in DCM patients as the presence of LGE has been associated with increased VT occurrence and with overall mortality [107,108]. In addition, the complexity and extent of myocardial scars have been associated with VT incidence and mortality [109,110]. The computer-based modeling of reentry circuits in individual patients may help to identify patients at risk for arrhythmia and support the planning of catheter ablation strategies [111].

6. Translational Perspective and Conclusions

The individualized risk prediction and treatment of patients with DCM remain challenging. The optimal pharmacological treatment according to current guideline recommendations forms the basis of DCM therapy [9,112]. Yet, the current treatment of HF in DCM does not differ from general HF management and effects of disease-modifying drugs on ionic and structural alterations in DCM are less well characterized.

In antiarrhythmic therapy, potential reversible causes need to be excluded first (such as the existence/progress of coronary artery disease, changes in electrolytes or proarrhythmic drugs). Secondly, the severity and treatment options of the arrhythmia itself (PVC vs. VT/VF), as well as the need for additional device therapy such as ICD therapy, need to be addressed [10]. Antiarrhythmic drugs in DCM are mostly limited to class III compounds acting through action potential prolongation. Antiarrhythmic treatment should also consider using secondary antiarrhythmic effects of not primarily antiarrhythmic drugs such as sacubitril/valsartan [113]. Furthermore, only recently a potential antiarrhythmic effect of the sodium-glucose cotransporter 2 inhibitor dapagliflozin has been reported [114]. Recently, the Defibrillator Implantation in Patients with Nonischemic Systolic Heart Failure Trial (DANISH-Trial) found no long-term benefit of prophylactic ICD implantation among a heterogenic cohort of patients with non-ischemic HF [115]. Therefore, it appears relevant to identify DCM patients with the highest risk of SCD. The 'arrhythmic risk stratification in nonischemic dilated cardiomyopathy' trial (ReCONSIDER) aims at evaluating a two-step model including non-invasive risk factors and electrophysiology data for risk stratification in DCM [116].

Some ECG features could be clues of specific DCM subtypes, as certain disease-causing genes are associated with characteristic ECG abnormalities and indeed point toward particularly aggressive forms [8]. Currently, genetic testing is not part of routine patient care in DCM because of high cost and relatively low yield, but might be considered in patients suspected to have arrhythmogenic cardiomyopathy involving *LMNA*, *PLN* or *FLNC* mutations [10]. A genetic test is generally performed in an index patient with either a clinical diagnosis that fulfills the clinical criteria for the disease in question or when there is at least a reasonable indication for the presence of that specific disorder [10]. Emerging data suggest that genetic information may allow for gene-specific, more personalized therapeutic strategies. In an individualized medical approach, it is therefore relevant to evaluate every patient individually.

The focus in risk stratification is shifting towards optimized characterization of the underlying etiology of DCM and the development of multi-parametric models [117]. Advanced SCD risk stratification could include the underlying DCM pathology or family history for ventricular arrhythmias, clinical presentation, results of cardiac MRI, echocardiography and ECG. Recently, sex- and age-based differences in the natural history of DCM have been reported [118]. Lower baseline left ventricular ejection fraction (LVEF), higher

New York Heart Association (NYHA) class (III–VI), significant mitral regurgitation, the presence of left bundle branch block and higher natriuretic peptide levels are predictors of adverse outcomes [119].

In the case of refractory VT, catheter ablation should be considered depending on the suspected arrhythmogenic substrate and scar evaluation to reduce VT/VF burden [9]. Integrating imaging-based ablation strategies and computational modeling may improve ablation strategies, ICD risk prediction and outcome [111,120]. In the future, the multimodal characterization of patients is expected to provide the basis for optimized, personalized antiarrhythmic DCM management.

Funding: This work was supported in part by research grants from the University of Heidelberg, Faculty of Medicine (Postdoctoral Fellowships to P.L. and A.-K.R.), from the German Cardiac Society (Fellowships to A.-K.R. and P.L., Otto-Hess-Promotionsstipendium to P.S.), from the Elisabeth und Rudolf-Hirsch Stiftung für Medizinische Forschung (to A-.K.R.), from the Ernst und Berta Grimmke-Stiftung (to P.L.), from the German Heart Foundation/German Foundation of Heart Research (F/08/14 to D.T., Fellowship to A.-K.R.), from the German Internal Medicine Society (Clinician-Scientist-Program to A.-K.R.), from the Joachim Siebeneicher Foundation (to D.T.), from the Deutsche Forschungsgemeinschaft (German Research Foundation; TH 1120/8-1 to D.T.) and from the Ministry of Science, Research and the Arts Baden-Wuerttemberg (Sonderlinie Medizin to D.T.).

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Conflicts of Interest: A.K.R. reports educational support from Boston Scientific, Johnson & Johnson, Abbott and Medtronic. D.T. reports receiving lecture fees/honoraria from Bayer Vital, Boehringer Ingelheim Pharma, Bristol-Myers Squibb, Daiichi Sankyo, Medtronic, Pfizer Pharma, Sanofi-Aventis, St. Jude Medical and ZOLL CMS. P.L. reports receiving lecture fees from Bayer Vital and Pfizer Pharma and educational support from Boston Scientific and Johnson & Johnson. The remaining authors have reported that they have no relationships relevant to the content of this paper to disclose.

References

1. McKenna, W.J.; Maron, B.J.; Thiene, G. Classification, Epidemiology, and Global Burden of Cardiomyopathies. *Circ. Res.* **2017**, *121*, 722–730. [CrossRef] [PubMed]
2. Weintraub, R.G.; Semsarian, C.; Macdonald, P. Dilated Cardiomyopathy. *Lancet* **2017**, *390*, 400–414. [CrossRef]
3. Schultheiss, H.-P.; Fairweather, D.; Caforio, A.L.P.; Escher, F.; Hershberger, R.E.; Lipshultz, S.E.; Liu, P.P.; Matsumori, A.; Mazzanti, A.; McMurray, J.; et al. Dilated Cardiomyopathy. *Nat. Rev. Dis. Primers* **2019**, *5*, 32. [CrossRef] [PubMed]
4. Elliott, P.; Andersson, B.; Arbustini, E.; Bilinska, Z.; Cecchi, F.; Charron, P.; Dubourg, O.; Kühl, U.; Maisch, B.; McKenna, W.J.; et al. Classification of the Cardiomyopathies: A Position Statement from the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases. *Eur. Heart J.* **2008**, *29*, 270–276. [CrossRef] [PubMed]
5. Pinto, Y.M.; Elliott, P.M.; Arbustini, E.; Adler, Y.; Anastasakis, A.; Böhm, M.; Duboc, D.; Gimeno, J.; de Groote, P.; Imazio, M.; 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. Heart J.* **2016**, *37*, 1850–1858. [CrossRef]
6. Dec, G.W.; Fuster, V. Idiopathic Dilated Cardiomyopathy. *N. Engl. J. Med.* **1994**, *331*, 1564–1575. [CrossRef]
7. Maron, B.J.; Towbin, J.A.; Thiene, G.; Antzelevitch, C.; Corrado, D.; Arnett, D.; Moss, A.J.; Seidman, C.E.; Young, J.B.; American Heart Association; et al. Contemporary Definitions and Classification of the Cardiomyopathies: An American Heart Association Scientific Statement from the Council on Clinical Cardiology, Heart Failure and Transplantation Committee; Quality of Care and Outcomes Research and Functional Genomics and Translational Biology Interdisciplinary Working Groups; and Council on Epidemiology and Prevention. *Circulation* **2006**, *113*, 1807–1816. [CrossRef] [PubMed]
8. Finocchiaro, G.; Merlo, M.; Sheikh, N.; De Angelis, G.; Papadakis, M.; Olivotto, I.; Rapezzi, C.; Carr-White, G.; Sharma, S.; Mestroni, L.; et al. The Electrocardiogram in the Diagnosis and Management of Patients with Dilated Cardiomyopathy. *Eur. J. Heart Fail.* **2020**, *22*, 1097–1107. [CrossRef]
9. Priori, S.G.; Blomström-Lundqvist, C.; Mazzanti, A.; Blom, N.; Borggrefe, M.; Camm, J.; Elliott, P.M.; Fitzsimons, 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. [CrossRef]

10. Towbin, J.A.; McKenna, W.J.; Abrams, D.J.; Ackerman, M.J.; Calkins, H.; Darrieux, F.C.C.; Daubert, J.P.; de Chillou, C.; DePasquale, E.C.; Desai, M.Y.; et al. 2019 HRS Expert Consensus Statement on Evaluation, Risk Stratification, and Management of Arrhythmogenic Cardiomyopathy. *Heart Rhythm* **2019**, *16*, e301–e372. [CrossRef]
11. Brugada, J.; Katritsis, D.G.; Arbelo, E.; Arribas, F.; Bax, J.J.; Blomström-Lundqvist, C.; Calkins, H.; Corrado, D.; Deftereos, S.G.; Diller, G.-P.; et al. 2019 ESC Guidelines for the Management of Patients with Supraventricular TachycardiaThe Task Force for the Management of Patients with Supraventricular Tachycardia of the European Society of Cardiology (ESC). *Eur. Heart J.* **2020**, *41*, 655–720. [CrossRef]
12. Hindricks, G.; Potpara, T.; Dagres, N.; Arbelo, E.; Bax, J.J.; Blomström-Lundqvist, C.; Boriani, G.; Castella, M.; Dan, G.-A.; Dilaveris, P.E.; et al. 2020 ESC Guidelines for the Diagnosis and Management of Atrial Fibrillation Developed in Collaboration with the European Association for Cardio-Thoracic Surgery (EACTS): The Task Force for the Diagnosis and Management of Atrial Fibrillation of the European Society of Cardiology (ESC) Developed with the Special Contribution of the European Heart Rhythm Association (EHRA) of the ESC. *Eur. Heart J.* **2021**, *42*, 373–498. [CrossRef]
13. Nuzzi, V.; Cannatà, A.; Manca, P.; Castrichini, M.; Barbati, G.; Aleksova, A.; Fabris, E.; Zecchin, M.; Merlo, M.; Boriani, G.; et al. Atrial Fibrillation in Dilated Cardiomyopathy: Outcome Prediction from an Observational Registry. *Int. J. Cardiol.* **2021**, *323*, 140–147. [CrossRef]
14. Towbin, J.A.; Lorts, A. Arrhythmias and Dilated Cardiomyopathy. *J. Am. Coll. Cardiol.* **2011**, *57*, 2169–2171. [CrossRef] [PubMed]
15. Liuba, I.; Marchlinski, F.E. The Substrate and Ablation of Ventricular Tachycardia in Patients with Nonischemic Cardiomyopathy. *Circ. J.* **2013**, *77*, 1957–1966. [CrossRef] [PubMed]
16. Bondue, A.; Arbustini, E.; Bianco, A.; Ciccarelli, M.; Dawson, D.; De Rosa, M.; Hamdani, N.; Hilfiker-Kleiner, D.; Meder, B.; Leite-Moreira, A.F.; et al. Complex Roads from Genotype to Phenotype in Dilated Cardiomyopathy: Scientific Update from the Working Group of Myocardial Function of the European Society of Cardiology. *Cardiovasc. Res.* **2018**, *114*, 1287–1303. [CrossRef] [PubMed]
17. Peters, S.; Kumar, S.; Elliott, P.; Kalman, J.M.; Fatkin, D. Arrhythmic Genotypes in Familial Dilated Cardiomyopathy: Implications for Genetic Testing and Clinical Management. *Heart Lung Circ.* **2019**, *28*, 31–38. [CrossRef] [PubMed]
18. Watkins, H.; Ashrafian, H.; Redwood, C. Inherited Cardiomyopathies. *N. Engl. J. Med.* **2011**, *364*, 1643–1656. [CrossRef] [PubMed]
19. Hershberger, R.E.; Hedges, D.J.; Morales, A. Dilated Cardiomyopathy: The Complexity of a Diverse Genetic Architecture. *Nat. Rev. Cardiol.* **2013**, *10*, 531–547. [CrossRef]
20. Zegkos, T.; Panagiotidis, T.; Parcharidou, D.; Efthimiadis, G. Emerging Concepts in Arrhythmogenic Dilated Cardiomyopathy. *Heart Fail. Rev.* **2020**, *4*, 1219–1229. [CrossRef]
21. Spezzacatene, A.; Sinagra, G.; Merlo, M.; Barbati, G.; Graw, S.L.; Brun, F.; Slavov, D.; Di Lenarda, A.; Salcedo, E.E.; Towbin, J.A.; et al. Arrhythmogenic Phenotype in Dilated Cardiomyopathy: Natural History and Predictors of Life-Threatening Arrhythmias. *J. Am. Heart Assoc.* **2015**, *4*, e002149. [CrossRef]
22. Corrado, D.; Perazzolo Marra, M.; Zorzi, A.; Beffagna, G.; Cipriani, A.; Lazzari, M.D.; Migliore, F.; Pilichou, K.; Rampazzo, A.; Rigato, I.; et al. Diagnosis of Arrhythmogenic Cardiomyopathy: The Padua Criteria. *Int. J. Cardiol.* **2020**, *319*, 106–114. [CrossRef] [PubMed]
23. Coronel, R.; Wilders, R.; Verkerk, A.O.; Wiegerinck, R.F.; Benoist, D.; Bernus, O. Electrophysiological Changes in Heart Failure and Their Implications for Arrhythmogenesis. *Biochim. Biophys. Acta* **2013**, *1832*, 2432–2441. [CrossRef] [PubMed]
24. Wilde, A.A.M.; Amin, A.S. Clinical Spectrum of SCN5A Mutations: Long QT Syndrome, Brugada Syndrome, and Cardiomyopathy. *JACC Clin. Electrophysiol.* **2018**, *4*, 569–579. [CrossRef] [PubMed]
25. Beuckelmann, D.J.; Näbauer, M.; Erdmann, E. Intracellular Calcium Handling in Isolated Ventricular Myocytes from Patients with Terminal Heart Failure. *Circulation* **1992**, *85*, 1046–1055. [CrossRef]
26. Koumi, S.; Backer, C.L.; Arentzen, C.E. Characterization of Inwardly Rectifying K+ Channel in Human Cardiac Myocytes. Alterations in Channel Behavior in Myocytes Isolated from Patients with Idiopathic Dilated Cardiomyopathy. *Circulation* **1995**, *92*, 164–174. [CrossRef] [PubMed]
27. Akar, F.G.; Nass, R.D.; Hahn, S.; Cingolani, E.; Shah, M.; Hesketh, G.G.; DiSilvestre, D.; Tunin, R.S.; Kass, D.A.; Tomaselli, G.F. Dynamic Changes in Conduction Velocity and Gap Junction Properties during Development of Pacing-Induced Heart Failure. *Am. J. Physiol. Heart Circ. Physiol.* **2007**, *293*, H1223–H1230. [CrossRef] [PubMed]
28. Akar, F.G.; Spragg, D.D.; Tunin, R.S.; Kass, D.A.; Tomaselli, G.F. Mechanisms Underlying Conduction Slowing and Arrhythmogenesis in Nonischemic Dilated Cardiomyopathy. *Circ. Res.* **2004**, *95*, 717–725. [CrossRef]
29. Wiegerinck, R.F.; Verkerk, A.O.; Belterman, C.N.; van Veen, T.A.B.; Baartscheer, A.; Opthof, T.; Wilders, R.; de Bakker, J.M.T.; Coronel, R. Larger Cell Size in Rabbits With Heart Failure Increases Myocardial Conduction Velocity and QRS Duration. *Circulation* **2006**, *113*, 806–813. [CrossRef] [PubMed]
30. Olson, T.M.; Michels, V.V.; Ballew, J.D.; Reyna, S.P.; Karst, M.L.; Herron, K.J.; Horton, S.C.; Rodeheffer, R.J.; Anderson, J.L. Sodium Channel Mutations and Susceptibility to Heart Failure and Atrial Fibrillation. *JAMA* **2005**, *293*, 447–454. [CrossRef]
31. Papadatos, G.A.; Wallerstein, P.M.R.; Head, C.E.G.; Ratcliff, R.; Brady, P.A.; Benndorf, K.; Saumarez, R.C.; Trezise, A.E.O.; Huang, C.L.-H.; Vandenberg, J.I.; et al. Slowed Conduction and Ventricular Tachycardia after Targeted Disruption of the Cardiac Sodium Channel Gene Scn5a. *Proc. Natl. Acad. Sci. USA* **2002**, *99*, 6210–6215. [CrossRef]

32. Suzuki, T.; Shioya, T.; Murayama, T.; Sugihara, M.; Odagiri, F.; Nakazato, Y.; Nishizawa, H.; Chugun, A.; Sakurai, T.; Daida, H.; et al. Multistep Ion Channel Remodeling and Lethal Arrhythmia Precede Heart Failure in a Mouse Model of Inherited Dilated Cardiomyopathy. *PLoS ONE* **2012**, *7*, e35353. [CrossRef]
33. Radicke, S.; Cotella, D.; Graf, E.M.; Banse, U.; Jost, N.; Varró, A.; Tseng, G.-N.; Ravens, U.; Wettwer, E. Functional Modulation of the Transient Outward Current Ito by KCNE Beta-Subunits and Regional Distribution in Human Non-Failing and Failing Hearts. *Cardiovasc. Res.* **2006**, *71*, 695–703. [CrossRef] [PubMed]
34. Rahm, A.-K.; Müller, M.E.; Gramlich, D.; Lugenbiel, P.; Uludag, E.; Rivinius, R.; Ullrich, N.D.; Schmack, B.; Ruhparwar, A.; Heimberger, T.; et al. Inhibition of Cardiac Kv4.3 (Ito) Channel Isoforms by Class I Antiarrhythmic Drugs Lidocaine and Mexiletine. *Eur. J. Pharmacol.* **2020**, *880*, 173159. [CrossRef]
35. Szuts, V.; Ménesi, D.; Varga-Orvos, Z.; Zvara, Á.; Houshmand, N.; Bitay, M.; Bogáts, G.; Virág, L.; Baczkó, I.; Szalontai, B.; et al. Altered Expression of Genes for Kir Ion Channels in Dilated Cardiomyopathy. *Can. J. Physiol. Pharmacol.* **2013**, *91*, 648–656. [CrossRef]
36. Guo, A.; Zhang, C.; Wei, S.; Chen, B.; Song, L.-S. Emerging Mechanisms of T-Tubule Remodelling in Heart Failure. *Cardiovasc. Res.* **2013**, *98*, 204–215. [CrossRef] [PubMed]
37. Crossman, D.J.; Ruygrok, P.N.; Ruygrok, P.R.; Soeller, C.; Cannell, M.B. Changes in the Organization of Excitation-Contraction Coupling Structures in Failing Human Heart. *PLoS ONE* **2011**, *6*, e17901. [CrossRef]
38. Zhang, H.-B.; Li, R.-C.; Xu, M.; Xu, S.-M.; Lai, Y.-S.; Wu, H.-D.; Xie, X.-J.; Gao, W.; Ye, H.; Zhang, Y.-Y.; et al. Ultrastructural Uncoupling between T-Tubules and Sarcoplasmic Reticulum in Human Heart Failure. *Cardiovasc. Res.* **2013**, *98*, 269–276. [CrossRef]
39. Respress, J.L.; van Oort, R.J.; Li, N.; Rolim, N.; Dixit, S.S.; de Almeida, A.; Voigt, N.; Lawrence, W.S.; Skapura, D.G.; Skårdal, K.; et al. Role of RyR2 Phosphorylation at S2814 during Heart Failure Progression. *Circ. Res.* **2012**, *110*, 1474–1483. [CrossRef]
40. Maier, L.S.; Zhang, T.; Chen, L.; DeSantiago, J.; Brown, J.H.; Bers, D.M. Transgenic CaMKIIdeltaC Overexpression Uniquely Alters Cardiac Myocyte Ca^{2+} Handling: Reduced SR Ca^{2+} Load and Activated SR Ca^{2+} Release. *Circ. Res.* **2003**, *92*, 904–911. [CrossRef] [PubMed]
41. Fischer, T.H.; Maier, L.S.; Sossalla, S. The Ryanodine Receptor Leak: How a Tattered Receptor Plunges the Failing Heart into Crisis. *Heart Fail. Rev.* **2013**, *18*, 475–483. [CrossRef]
42. Van Oort, R.J.; McCauley, M.D.; Dixit, S.S.; Pereira, L.; Yang, Y.; Respress, J.L.; Wang, Q.; De Almeida, A.C.; Skapura, D.G.; Anderson, M.E.; et al. Ryanodine Receptor Phosphorylation by Calcium/Calmodulin-Dependent Protein Kinase II Promotes Life-Threatening Ventricular Arrhythmias in Mice with Heart Failure. *Circulation* **2010**, *122*, 2669–2679. [CrossRef] [PubMed]
43. Meyer, M.; Schillinger, W.; Pieske, B.; Holubarsch, C.; Heilmann, C.; Posival, H.; Kuwajima, G.; Mikoshiba, K.; Just, H.; Hasenfuss, G. Alterations of Sarcoplasmic Reticulum Proteins in Failing Human Dilated Cardiomyopathy. *Circulation* **1995**, *92*, 778–784. [CrossRef] [PubMed]
44. Schwinger, R.H.; Böhm, M.; Schmidt, U.; Karczewski, P.; Bavendiek, U.; Flesch, M.; Krause, E.G.; Erdmann, E. Unchanged Protein Levels of SERCA II and Phospholamban but Reduced Ca^{2+} Uptake and Ca(2+)-ATPase Activity of Cardiac Sarcoplasmic Reticulum from Dilated Cardiomyopathy Patients Compared with Patients with Nonfailing Hearts. *Circulation* **1995**, *92*, 3220–3228. [CrossRef]
45. Kubo, H.; Margulies, K.B.; Piacentino, V.; Gaughan, J.P.; Houser, S.R. Patients with End-Stage Congestive Heart Failure Treated with Beta-Adrenergic Receptor Antagonists Have Improved Ventricular Myocyte Calcium Regulatory Protein Abundance. *Circulation* **2001**, *104*, 1012–1018. [CrossRef]
46. Haghighi, K.; Kolokathis, F.; Pater, L.; Lynch, R.A.; Asahi, M.; Gramolini, A.O.; Fan, G.-C.; Tsiapras, D.; Hahn, H.S.; Adamopoulos, S.; et al. Human Phospholamban Null Results in Lethal Dilated Cardiomyopathy Revealing a Critical Difference between Mouse and Human. *J. Clin. Investig.* **2003**, *111*, 869–876. [CrossRef] [PubMed]
47. Posch, M.G.; Perrot, A.; Geier, C.; Boldt, L.-H.; Schmidt, G.; Lehmkuhl, H.B.; Hetzer, R.; Dietz, R.; Gutberlet, M.; Haverkamp, W.; et al. Genetic Deletion of Arginine 14 in Phospholamban Causes Dilated Cardiomyopathy with Attenuated Electrocardiographic R Amplitudes. *Heart Rhythm* **2009**, *6*, 480–486. [CrossRef]
48. Young, H.S.; Ceholski, D.K.; Trieber, C.A. Deception in Simplicity: Hereditary Phospholamban Mutations in Dilated Cardiomyopathy. *Biochem. Cell Biol.* **2015**, *93*, 1–7. [CrossRef] [PubMed]
49. Hof, I.E.; van der Heijden, J.F.; Kranias, E.G.; Sanoudou, D.; de Boer, R.A.; van Tintelen, J.P.; van der Zwaag, P.A.; Doevendans, P.A. Prevalence and Cardiac Phenotype of Patients with a Phospholamban Mutation. *Neth. Heart J.* **2019**, *27*, 64–69. [CrossRef]
50. Van der Zwaag, P.A.; van Rijsingen, I.A.W.; Asimaki, A.; Jongbloed, J.D.H.; van Veldhuisen, D.J.; Wiesfeld, A.C.P.; Cox, M.G.P.J.; van Lochem, L.T.; de Boer, R.A.; Hofstra, R.M.W.; et al. Phospholamban R14del Mutation in Patients Diagnosed with Dilated Cardiomyopathy or Arrhythmogenic Right Ventricular Cardiomyopathy: Evidence Supporting the Concept of Arrhythmogenic Cardiomyopathy. *Eur. J. Heart Fail.* **2012**, *14*, 1199–1207. [CrossRef]
51. Schmitt, J.P.; Kamisago, M.; Asahi, M.; Li, G.H.; Ahmad, F.; Mende, U.; Kranias, E.G.; MacLennan, D.H.; Seidman, J.G.; Seidman, C.E. Dilated Cardiomyopathy and Heart Failure Caused by a Mutation in Phospholamban. *Science* **2003**, *299*, 1410–1413. [CrossRef] [PubMed]
52. Liu, G.-S.; Morales, A.; Vafiadaki, E.; Lam, C.K.; Cai, W.-F.; Haghighi, K.; Adly, G.; Hershberger, R.E.; Kranias, E.G. A Novel Human R25C-Phospholamban Mutation Is Associated with Super-Inhibition of Calcium Cycling and Ventricular Arrhythmia. *Cardiovasc. Res.* **2015**, *107*, 164–174. [CrossRef] [PubMed]

53. Kitamura, H.; Ohnishi, Y.; Yoshida, A.; Okajima, K.; Azumi, H.; Ishida, A.; Galeano, E.J.; Kubo, S.; Hayashi, Y.; Itoh, H.; et al. Heterogeneous Loss of Connexin43 Protein in Nonischemic Dilated Cardiomyopathy with Ventricular Tachycardia. *J. Cardiovasc. Electrophysiol.* **2002**, *13*, 865–870. [CrossRef]
54. Salameh, A.; Krautblatter, S.; Karl, S.; Blanke, K.; Gomez, D.R.; Dhein, S.; Pfeiffer, D.; Janousek, J. The Signal Transduction Cascade Regulating the Expression of the Gap Junction Protein Connexin43 by β-Adrenoceptors. *Br. J. Pharmacol.* **2009**, *158*, 198–208. [CrossRef]
55. Guerrero, P.A.; Schuessler, R.B.; Davis, L.M.; Beyer, E.C.; Johnson, C.M.; Yamada, K.A.; Saffitz, J.E. Slow Ventricular Conduction in Mice Heterozygous for a Connexin43 Null Mutation. *J. Clin. Investig.* **1997**, *99*, 1991–1998. [CrossRef]
56. Van Rijen, H.V.M.; Eckardt, D.; Degen, J.; Theis, M.; Ott, T.; Willecke, K.; Jongsma, H.J.; Opthof, T.; de Bakker, J.M.T. Slow Conduction and Enhanced Anisotropy Increase the Propensity for Ventricular Tachyarrhythmias in Adult Mice with Induced Deletion of Connexin43. *Circulation* **2004**, *109*, 1048–1055. [CrossRef]
57. Jansen, J.A.; van Veen, T.A.B.; de Jong, S.; van der Nagel, R.; van Stuijvenberg, L.; Driessen, H.; Labzowski, R.; Oefner, C.M.; Bosch, A.A.; Nguyen, T.Q.; et al. Reduced Cx43 Expression Triggers Increased Fibrosis Due to Enhanced Fibroblast Activity. *Circ. Arrhythm. Electrophysiol.* **2012**, *5*, 380–390. [CrossRef]
58. Poelzing, S.; Rosenbaum, D.S. Altered Connexin43 Expression Produces Arrhythmia Substrate in Heart Failure. *Am. J. Physiol. Heart Circ. Physiol.* **2004**, *287*, H1762–H1770. [CrossRef]
59. Waddington, C.H. The Epigenotype. *Endeavour* **1942**, *1942*, 18–20. [CrossRef]
60. Berger, S.L.; Kouzarides, T.; Shiekhattar, R.; Shilatifard, A. An Operational Definition of Epigenetics. *Genes Dev.* **2009**, *23*, 781–783. [CrossRef] [PubMed]
61. Yu, J.; Zeng, C.; Wang, Y. Epigenetics in Dilated Cardiomyopathy. *Curr. Opin. Cardiol.* **2019**, *34*, 260–269. [CrossRef] [PubMed]
62. Nguyen, A.T.; Xiao, B.; Neppl, R.L.; Kallin, E.M.; Li, J.; Chen, T.; Wang, D.-Z.; Xiao, X.; Zhang, Y. DOT1L Regulates Dystrophin Expression and Is Critical for Cardiac Function. *Genes Dev.* **2011**, *25*, 263–274. [CrossRef]
63. Hohl, M.; Wagner, M.; Reil, J.-C.; Müller, S.-A.; Tauchnitz, M.; Zimmer, A.M.; Lehmann, L.H.; Thiel, G.; Böhm, M.; Backs, J.; et al. HDAC4 Controls Histone Methylation in Response to Elevated Cardiac Load. *J. Clin. Investig.* **2013**, *123*, 1359–1370. [CrossRef]
64. Ito, E.; Miyagawa, S.; Fukushima, S.; Yoshikawa, Y.; Saito, S.; Saito, T.; Harada, A.; Takeda, M.; Kashiyama, N.; Nakamura, Y.; et al. Histone Modification Is Correlated With Reverse Left Ventricular Remodeling in Nonischemic Dilated Cardiomyopathy. *Ann. Thorac. Surg.* **2017**, *104*, 1531–1539. [CrossRef]
65. Jiang, D.-S.; Yi, X.; Li, R.; Su, Y.-S.; Wang, J.; Chen, M.-L.; Liu, L.-G.; Hu, M.; Cheng, C.; Zheng, P.; et al. The Histone Methyltransferase Mixed Lineage Leukemia (MLL) 3 May Play a Potential Role on Clinical Dilated Cardiomyopathy. *Mol. Med.* **2017**, *23*, 196–203. [CrossRef]
66. Montgomery, R.L.; Davis, C.A.; Potthoff, M.J.; Haberland, M.; Fielitz, J.; Qi, X.; Hill, J.A.; Richardson, J.A.; Olson, E.N. Histone Deacetylases 1 and 2 Redundantly Regulate Cardiac Morphogenesis, Growth, and Contractility. *Genes Dev.* **2007**, *21*, 1790–1802. [CrossRef]
67. Syren, P.; Rahm, A.-K.; Schweizer, P.A.; Bruehl, C.; Katus, H.A.; Frey, N.; Thomas, D.; Lugenbiel, P. Histone Deacetylase 2-Dependent Ventricular Electrical Remodeling in a Porcine Model of Early Heart Failure. *Life Sci.* **2021**, *281*, 119769. [CrossRef] [PubMed]
68. Awad, S.; Kunhi, M.; Little, G.H.; Bai, Y.; An, W.; Bers, D.; Kedes, L.; Poizat, C. Nuclear CaMKII Enhances Histone H3 Phosphorylation and Remodels Chromatin during Cardiac Hypertrophy. *Nucleic Acids Res.* **2013**, *41*, 7656–7672. [CrossRef]
69. Awad, S.; Al-Haffar, K.M.A.; Marashly, Q.; Quijada, P.; Kunhi, M.; Al-Yacoub, N.; Wade, F.S.; Mohammed, S.F.; Al-Dayel, F.; Sutherland, G.; et al. Control of Histone H3 Phosphorylation by CaMKIIδ in Response to Haemodynamic Cardiac Stress. *J. Pathol.* **2015**, *235*, 606–618. [CrossRef] [PubMed]
70. Perrin, M.J.; Gollob, M.H. The Role of Atrial Natriuretic Peptide in Modulating Cardiac Electrophysiology. *Heart Rhythm* **2012**, *9*, 610–615. [CrossRef] [PubMed]
71. Moghtadaei, M.; Polina, I.; Rose, R.A. Electrophysiological Effects of Natriuretic Peptides in the Heart Are Mediated by Multiple Receptor Subtypes. *Prog. Biophys. Mol. Biol.* **2016**, *120*, 37–49. [CrossRef] [PubMed]
72. Goetze, J.P.; Bruneau, B.G.; Ramos, H.R.; Ogawa, T.; Bold, M.K.; Bold, A.J. Cardiac Natriuretic Peptides. *Nat. Rev. Cardiol.* **2020**, *17*, 698–717. [CrossRef]
73. Miao, L.; Wang, M.; Yin, W.-X.; Yuan, Q.; Chen, Y.-X.; Fleischmann, B.; Hescheler, J.; Ji, G. Atrial Natriuretic Peptide Regulates Ca Channel in Early Developmental Cardiomyocytes. *PLoS ONE* **2010**, *5*, e8847. [CrossRef]
74. Burley, D.S.; Cox, C.D.; Zhang, J.; Wann, K.T.; Baxter, G.F. Natriuretic Peptides Modulate ATP-Sensitive K(+) Channels in Rat Ventricular Cardiomyocytes. *Basic Res. Cardiol.* **2014**, *109*, 402. [CrossRef] [PubMed]
75. Stull, J.T.; Manning, D.R.; High, C.W.; Blumenthal, D.K. Phosphorylation of Contractile Proteins in Heart and Skeletal Muscle. *Fed. Proc.* **1980**, *39*, 1552–1557. [PubMed]
76. McKinsey, T.A.; Zhang, C.L.; Lu, J.; Olson, E.N. Signal-Dependent Nuclear Export of a Histone Deacetylase Regulates Muscle Differentiation. *Nature* **2000**, *408*, 106–111. [CrossRef]
77. Backs, J.; Song, K.; Bezprozvannaya, S.; Chang, S.; Olson, E.N. CaM Kinase II Selectively Signals to Histone Deacetylase 4 during Cardiomyocyte Hypertrophy. *J. Clin. Investig.* **2006**, *116*, 1853–1864. [CrossRef]

78. Wu, X.; Zhang, T.; Bossuyt, J.; Li, X.; McKinsey, T.A.; Dedman, J.R.; Olson, E.N.; Chen, J.; Brown, J.H.; Bers, D.M. Local InsP3-Dependent Perinuclear Ca^{2+} Signaling in Cardiac Myocyte Excitation-Transcription Coupling. *J. Clin. Investig.* **2006**, *116*, 675–682. [CrossRef]
79. Ago, T.; Liu, T.; Zhai, P.; Chen, W.; Li, H.; Molkentin, J.D.; Vatner, S.F.; Sadoshima, J. A Redox-Dependent Pathway for Regulating Class II HDACs and Cardiac Hypertrophy. *Cell* **2008**, *133*, 978–993. [CrossRef]
80. Kim, S.Y.; Zhang, X.; Schiattarella, G.G.; Altamirano, F.; Ramos, T.A.R.; French, K.M.; Jiang, N.; Szweda, P.A.; Evers, B.M.; May, H.I.; et al. Epigenetic Reader BRD4 (Bromodomain-Containing Protein 4) Governs Nucleus-Encoded Mitochondrial Transcriptome to Regulate Cardiac Function. *Circulation* **2020**, *142*, 2356–2370. [CrossRef] [PubMed]
81. Chen, G.; Wang, X.; Zhang, Y.; Ru, X.; Zhou, L.; Tian, Y. H3K9 Histone Methyltransferase G9a Ameliorates Dilated Cardiomyopathy via the Downregulation of Cell Adhesion Molecules. *Mol. Med. Rep.* **2015**, *11*, 3872–3879. [CrossRef]
82. Koenig, X.; Rubi, L.; Obermair, G.J.; Cervenka, R.; Dang, X.B.; Lukacs, P.; Kummer, S.; Bittner, R.E.; Kubista, H.; Todt, H.; et al. Enhanced Currents through L-Type Calcium Channels in Cardiomyocytes Disturb the Electrophysiology of the Dystrophic Heart. *Am. J. Physiol. Heart Circ. Physiol.* **2014**, *306*, H564–H573. [CrossRef]
83. Haas, J.; Frese, K.S.; Park, Y.J.; Keller, A.; Vogel, B.; Lindroth, A.M.; Weichenhan, D.; Franke, J.; Fischer, S.; Bauer, A.; et al. Alterations in Cardiac DNA Methylation in Human Dilated Cardiomyopathy. *EMBO Mol. Med.* **2013**, *5*, 413–429. [CrossRef]
84. Jo, B.-S.; Koh, I.-U.; Bae, J.-B.; Yu, H.-Y.; Jeon, E.-S.; Lee, H.-Y.; Kim, J.-J.; Choi, M.; Choi, S.S. Methylome Analysis Reveals Alterations in DNA Methylation in the Regulatory Regions of Left Ventricle Development Genes in Human Dilated Cardiomyopathy. *Genomics* **2016**, *108*, 84–92. [CrossRef]
85. Meder, B.; Haas, J.; Sedaghat-Hamedani, F.; Kayvanpour, E.; Frese, K.; Lai, A.; Nietsch, R.; Scheiner, C.; Mester, S.; Bordalo, D.M.; et al. Epigenome-Wide Association Study Identifies Cardiac Gene Patterning and a Novel Class of Biomarkers for Heart Failure. *Circulation* **2017**, *136*, 1528–1544. [CrossRef]
86. Gi, W.-T.; Haas, J.; Sedaghat-Hamedani, F.; Kayvanpour, E.; Tappu, R.; Lehmann, D.H.; Shirvani Samani, O.; Wisdom, M.; Keller, A.; Katus, H.A.; et al. Epigenetic Regulation of Alternative MRNA Splicing in Dilated Cardiomyopathy. *J. Clin. Med.* **2020**, *9*, 1499. [CrossRef] [PubMed]
87. Rosa-Garrido, M.; Chapski, D.J.; Schmitt, A.D.; Kimball, T.H.; Karbassi, E.; Monte, E.; Balderas, E.; Pellegrini, M.; Shih, T.-T.; Soehalim, E.; et al. High-Resolution Mapping of Chromatin Conformation in Cardiac Myocytes Reveals Structural Remodeling of the Epigenome in Heart Failure. *Circulation* **2017**, *136*, 1613–1625. [CrossRef] [PubMed]
88. Salvarani, N.; Crasto, S.; Miragoli, M.; Bertero, A.; Paulis, M.; Kunderfranco, P.; Serio, S.; Forni, A.; Lucarelli, C.; Dal Ferro, M.; et al. The K219T-Lamin Mutation Induces Conduction Defects through Epigenetic Inhibition of SCN5A in Human Cardiac Laminopathy. *Nat. Commun.* **2019**, *10*, 2267. [CrossRef] [PubMed]
89. Skinner, M.K.; Manikkam, M.; Guerrero-Bosagna, C. Epigenetic Transgenerational Actions of Environmental Factors in Disease Etiology. *Trends Endocrinol. Metab.* **2010**, *21*, 214–222. [CrossRef]
90. Shah, M.H.; Binkley, P.; Chan, K.; Xiao, J.; Arbogast, D.; Collamore, M.; Farra, Y.; Young, D.; Grever, M. Cardiotoxicity of Histone Deacetylase Inhibitor Depsipeptide in Patients with Metastatic Neuroendocrine Tumors. *Clin. Cancer Res.* **2006**, *12*, 3997–4003. [CrossRef]
91. Olsen, E.A.; Kim, Y.H.; Kuzel, T.M.; Pacheco, T.R.; Foss, F.M.; Parker, S.; Frankel, S.R.; Chen, C.; Ricker, J.L.; Arduino, J.M.; et al. Phase IIb Multicenter Trial of Vorinostat in Patients with Persistent, Progressive, or Treatment Refractory Cutaneous T-Cell Lymphoma. *J. Clin. Oncol.* **2007**, *25*, 3109–3115. [CrossRef] [PubMed]
92. Shi, Y.; Dong, M.; Hong, X.; Zhang, W.; Feng, J.; Zhu, J.; Yu, L.; Ke, X.; Huang, H.; Shen, Z.; et al. Results from a Multicenter, Open-Label, Pivotal Phase II Study of Chidamide in Relapsed or Refractory Peripheral T-Cell Lymphoma. *Ann. Oncol.* **2015**, *26*, 1766–1771. [CrossRef] [PubMed]
93. Shah, R.R. Safety and Tolerability of Histone Deacetylase (HDAC) Inhibitors in Oncology. *Drug Saf.* **2019**, *42*, 235–245. [CrossRef] [PubMed]
94. Spence, S.; Deurinck, M.; Ju, H.; Traebert, M.; McLean, L.; Marlowe, J.; Emotte, C.; Tritto, E.; Tseng, M.; Shultz, M.; et al. Histone Deacetylase Inhibitors Prolong Cardiac Repolarization through Transcriptional Mechanisms. *Toxicol. Sci.* **2016**, *153*, 39–54. [CrossRef]
95. Morita, H.; Seidman, J.; Seidman, C.E. Genetic Causes of Human Heart Failure. *J. Clin. Investig.* **2005**, *115*, 518–526. [CrossRef]
96. Verdonschot, J.A.J.; Hazebroek, M.R.; Derks, K.W.J.; Barandiarán Aizpurua, A.; Merken, J.J.; Wang, P.; Bierau, J.; van den Wijngaard, A.; Schalla, S.M.; Abdul Hamid, M.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]
97. Chatzifrangkeskou, M.; Le Dour, C.; Wu, W.; Morrow, J.P.; Joseph, L.C.; Beuvin, M.; Sera, F.; Homma, S.; Vignier, N.; Mougenot, N.; et al. ERK1/2 Directly Acts on CTGF/CCN2 Expression to Mediate Myocardial Fibrosis in Cardiomyopathy Caused by Mutations in the Lamin A/C Gene. *Hum. Mol. Genet.* **2016**, *25*, 2220–2233. [CrossRef]
98. Lehrke, S.; Lossnitzer, D.; Schöb, M.; Steen, H.; Merten, C.; Kemmling, H.; Pribe, R.; Ehlermann, P.; Zugck, C.; Korosoglou, G.; et al. Use of Cardiovascular Magnetic Resonance for Risk Stratification in Chronic Heart Failure: Prognostic Value of Late Gadolinium Enhancement in Patients with Non-Ischaemic Dilated Cardiomyopathy. *Heart* **2011**, *97*, 727–732. [CrossRef]
99. Gulati, A.; Jabbour, A.; Ismail, T.F.; Guha, K.; Khwaja, J.; Raza, S.; Morarji, K.; Brown, T.D.H.; 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]

100. Barison, A.; Del Torto, A.; Chiappino, S.; Aquaro, G.D.; Todiere, G.; Vergaro, G.; Passino, C.; Lombardi, M.; Emdin, M.; Masci, P.G. Prognostic Significance of Myocardial Extracellular Volume Fraction in Nonischaemic Dilated Cardiomyopathy. *J. Cardiovasc. Med.* **2015**, *16*, 681–687. [CrossRef] [PubMed]
101. Puntmann, V.O.; Carr-White, G.; Jabbour, A.; Yu, C.-Y.; Gebker, R.; Kelle, S.; Hinojar, R.; Doltra, A.; Varma, N.; Child, N.; et al. T1-Mapping and Outcome in Nonischemic Cardiomyopathy: All-Cause Mortality and Heart Failure. *JACC Cardiovasc. Imaging* **2016**, *9*, 40–50. [CrossRef] [PubMed]
102. Aus dem Siepen, F.; Buss, S.J.; Messroghli, D.; Andre, F.; Lossnitzer, D.; Seitz, S.; Keller, M.; Schnabel, P.A.; Giannitsis, E.; Korosoglou, G.; et al. T1 Mapping in Dilated Cardiomyopathy with Cardiac Magnetic Resonance: Quantification of Diffuse Myocardial Fibrosis and Comparison with Endomyocardial Biopsy. *Eur. Heart J. Cardiovasc. Imaging* **2015**, *16*, 210–216. [CrossRef] [PubMed]
103. Bello, D.; Kipper, S.; Valderrábano, M.; Shivkumar, K. Catheter Ablation of Ventricular Tachycardia Guided by Contrast-Enhanced Cardiac Computed Tomography. *Heart Rhythm* **2004**, *1*, 490–492. [CrossRef] [PubMed]
104. Crean, A.M.; Spears, D.A.; Suszko, A.M.; Chauhan, V.S. High-Resolution 3D Scar Imaging Using a Novel Late Iodine Enhancement Multidetector CT Protocol to Guide Ventricular Tachycardia Catheter Ablation. *J. Cardiovasc. Electrophysiol.* **2013**, *24*, 708–710. [CrossRef] [PubMed]
105. Liu, T.; Song, D.; Dong, J.; Zhu, P.; Liu, J.; Liu, W.; Ma, X.; Zhao, L.; Ling, S. Current Understanding of the Pathophysiology of Myocardial Fibrosis and Its Quantitative Assessment in Heart Failure. *Front. Physiol.* **2017**, *8*, 238. [CrossRef]
106. Mitropoulou, P.; Georgiopoulos, G.; Figliozzi, S.; Klettas, D.; Nicoli, F.; Masci, P.G. Multi-Modality Imaging in Dilated Cardiomyopathy: With a Focus on the Role of Cardiac Magnetic Resonance. *Front. Cardiovasc. Med.* **2020**, *7*, 97. [CrossRef] [PubMed]
107. 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 Heart Fail.* **2017**, *5*, 28–38. [CrossRef]
108. Elming, M.B.; Hammer-Hansen, S.; Voges, I.; Nyktari, E.; Raja, A.A.; Svendsen, J.H.; Pehrson, S.; Signorovitch, J.; Køber, L.; Prasad, S.K.; et al. Myocardial Fibrosis and the Effect of Primary Prophylactic Defibrillator Implantation in Patients with Non-Ischemic Systolic Heart Failure-DANISH-MRI. *Am. Heart J.* **2020**, *221*, 165–176. [CrossRef]
109. Pedretti, S.; Vargiu, S.; Baroni, M.; Dellegrottaglie, S.; Lanzarin, B.; Roghi, A.; Milazzo, A.; Quattrocchi, G.; Lunati, M.; Pedrotti, P. Complexity of Scar and Ventricular Arrhythmias in Dilated Cardiomyopathy of Any Etiology: Long-Term Data from the SCARFEAR (Cardiovascular Magnetic Resonance Predictors of Appropriate Implantable Cardioverter-Defibrillator Therapy Delivery) Registry. *Clin. Cardiol.* **2018**, *41*, 494–501. [CrossRef]
110. Klem, I.; Klein, M.; Khan, M.; Yang, E.Y.; Nabi, F.; Ivanov, A.; Bhatti, L.; Hayes, B.; Graviss, E.A.; Nguyen, D.T.; et al. Relationship of LVEF and Myocardial Scar to Long-Term Mortality Risk and Mode of Death in Patients With Nonischemic Cardiomyopathy. *Circulation* **2021**, *143*, 1343–1358. [CrossRef]
111. Balaban, G.; Halliday, B.P.; Porter, B.; Bai, W.; Nygård, S.; Owen, R.; Hatipoglu, S.; Ferreira, N.D.; Izgi, C.; Tayal, U.; et al. Late-Gadolinium Enhancement Interface Area and Electrophysiological Simulations Predict Arrhythmic Events in Patients With Nonischemic Dilated Cardiomyopathy. *JACC Clin. Electrophysiol.* **2021**, *7*, 238–249. [CrossRef] [PubMed]
112. McDonagh, T.A.; Metra, M.; Adamo, M.; Gardner, R.S.; Baumbach, A.; Böhm, M.; Burri, H.; Butler, J.; Čelutkienė, J.; Chioncel, O.; et al. 2021 ESC Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure. *Eur. Heart J.* **2021**, *42*, 3599–3726. [CrossRef] [PubMed]
113. De Diego, C.; González-Torres, L.; Núñez, J.M.; Centurión Inda, R.; Martin-Langerwerf, D.A.; Sangio, A.D.; Chochowski, P.; Casasnovas, P.; Blazquéz, J.C.; Almendral, J. Effects of Angiotensin-Neprilysin Inhibition Compared to Angiotensin Inhibition on Ventricular Arrhythmias in Reduced Ejection Fraction Patients under Continuous Remote Monitoring of Implantable Defibrillator Devices. *Heart Rhythm* **2018**, *15*, 395–402. [CrossRef]
114. Curtain, J.P.; Docherty, K.F.; Jhund, P.S.; Petrie, M.C.; Inzucchi, S.E.; Køber, L.; Kosiborod, M.N.; Martinez, F.A.; Ponikowski, P.; Sabatine, M.S.; et al. Effect of Dapagliflozin on Ventricular Arrhythmias, Resuscitated Cardiac Arrest, or Sudden Death in DAPA-HF. *Eur. Heart J.* **2021**, *42*, 3727–3738. [CrossRef]
115. Køber, L.; Thune, J.J.; Nielsen, J.C.; Haarbo, J.; Videbæk, L.; Korup, E.; Jensen, G.; Hildebrandt, P.; Steffensen, F.H.; Bruun, N.E.; et al. Defibrillator Implantation in Patients with Nonischemic Systolic Heart Failure. *N. Engl. J. Med.* **2016**, *375*, 1221–1230. [CrossRef]
116. Gatzoulis, K.A.; Dilaveris, P.; Arsenos, P.; Tsiachris, D.; Antoniou, C.-K.; Sideris, S.; Kolettis, T.; Kanoupakis, E.; Sideris, A.; Flevari, P.; et al. Arrhythmic Risk Stratification in Nonischemic Dilated Cardiomyopathy: The ReCONSIDER Study Design-A Two-Step, Multifactorial, Electrophysiology-Inclusive Approach. *Hell. J. Cardiol.* **2021**, *62*, 169–172. [CrossRef]
117. Akhtar, M.; Elliott, P.M. Risk Stratification for Sudden Cardiac Death in Non-Ischaemic Dilated Cardiomyopathy. *Curr. Cardiol. Rep.* **2019**, *21*, 155. [CrossRef] [PubMed]
118. Halliday, B.P.; Gulati, A.; Ali, A.; Newsome, S.; Lota, A.; Tayal, U.; Vassiliou, V.S.; Arzanauskaite, M.; Izgi, C.; Krishnathasan, K.; et al. Sex- and Age-Based Differences in the Natural History and Outcome of Dilated Cardiomyopathy. *Eur. J. Heart Fail.* **2018**, *20*, 1392–1400. [CrossRef]

119. Seferović, P.M.; Polovina, M.; Bauersachs, J.; Arad, M.; Gal, T.B.; Lund, L.H.; Felix, S.B.; Arbustini, E.; Caforio, A.L.P.; Farmakis, D.; et al. Heart Failure in Cardiomyopathies: A Position Paper from the Heart Failure Association of the European Society of Cardiology. *Eur. J. Heart Fail.* **2019**, *21*, 553–576. [CrossRef] [PubMed]
120. Siontis, K.C.; Kim, H.M.; Sharaf Dabbagh, G.; Latchamsetty, R.; Stojanovska, J.; Jongnarangsin, K.; Morady, F.; Bogun, F.M. Association of Preprocedural Cardiac Magnetic Resonance Imaging with Outcomes of Ventricular Tachycardia Ablation in Patients with Idiopathic Dilated Cardiomyopathy. *Heart Rhythm* **2017**, *14*, 1487–1493. [CrossRef] [PubMed]