European Heart Journal Supplements (2021) **23** (Supplement E), E118–E122
The Heart of the Matter
doi:10.1093/eurheartj/suab105

Risk stratification in cardiomyopathies (dilated, hypertrophic, and arrhythmogenic cardiomyopathy) by cardiac magnetic resonance imaging

Marco Guglielmo and Gianluca Pontone*

Department of Cardiovascular Imaging, Centro Cardiologico Monzino, IRCCS, Milan, Italy

KEYWORDS
Cardiac magnetic resonance;
Arrhythmic risk;
Implantable cardiac-defibrillator

Cardiac magnetic resonance imaging (CMR) is a non-invasive, multiplanar, and high spatial resolution imaging technique, which represents the current gold standard for the evaluation of biventricular volumes and function. Furthermore, unlike other methods, it has the great advantage of characterizing the myocardial tissue by identifying the presence of alterations, such as oedema and focal and diffuse fibrosis. In particular, the late gadolinium enhancement technique makes it possible to identify areas of focal fibrosis that often constitute the substrate for the triggering of threatening ventricular arrhythmias at the basis of sudden cardiac death. For this reason, the use of CMR in the study of cardiomyopathies has become of primary importance, both for the differential diagnosis and for patient risk stratification. In this brief review, the ability of CMR in prognostic stratification of patients with dilated, hypertrophic, and arrhythmogenic cardiomyopathy will be analysed. In particular, the role of CMR in the prediction of arrhythmic risk and in the decision-making process for the implantation of a cardiac defibrillator will be examined.

Introduction

In recent years, cardiac magnetic resonance imaging (CMR) has acquired a progressively greater role in the evaluation of the patient with non-ischaemic cardiomyopathy (NICM). Non-invasive, multiplanar technique, which is not based on the use of ionizing radiation, CMR represents the gold standard for the evaluation of biventricular size and function through the use of cine functional sequences steady-state free precession. The latter, possessing a high-contrast resolution, allows the endocardial border to be very precisely delineated, making the calculation of ventricular volumes, mass, and ejection fraction highly reliable and reproducible. Furthermore, the ability of CMR to characterize myocardial tissue, identifying some specific patterns of pathology is useful in the differential diagnosis of the various forms of NICM as well as providing valuable elements for an accurate prognostic stratification of patients.[1] Indeed, through the classic morphological sequences in T1, T2, and T2* weighting, the late gadolinium enhancement (LGE) sequences, and the most recent parametric sequences of T1 and T2 mapping, CMR is able to recognize the presence at the tissue level of oedema, focal, and diffuse fibrosis, adipose metaplasia, and iron overload as well as providing the possibility of measuring any expansion of the extracellular volume (ECV).

CMR is also being used more and more frequently prior to the placement of an implantable cardiac-defibrillator (ICD). Indeed, even if echocardiography remains the first level test for morpho-functional cardiac evaluation, it appears, according to some evidence in the literature, to be less performing than CMR in the prognostic stratification of patients candidates for ICD.[2] The purpose of this short review is to provide an overview of the prognostic stratification with CMR of the patient affected by three different forms of NICM, dilated cardiomyopathy (DCM), hypertrophic cardiomyopathy (HCM), and arrhythmogenic cardiomyopathy (AC) with a particular focus on

*Corresponding author. Email: gianluca.pontone@cardiologicomonzino.it

the role of CMR in the decision to candidate the patient to an ICD.

Non-ischaemic dilative cardiomyopathy

Dilated cardiomyopathy is a pathological condition affecting myocardial tissue characterized by left ventricular or biventricular dilatation and dysfunction in the absence of coronary artery disease or conditions that cause volume and/or pressure overload, such as valvular, congenital, or hypertensive heart disease. In recent decades, the introduction of drug therapies, the use of implantable devices, such as ICDs, cardiac resynchronization therapy (CRT), and heart transplantation have significantly improved the survival of patients with DCM.[3]

However, the risk stratification of sudden cardiac death (SCD) in these patients continues to be ineffective. In particular, the DANISH Trial demonstrated how the implantation of ICDs in primary prevention in patients with non-ischaemic dilated cardiomyopathy (NI-DCM) does not reduce total mortality despite lowering the risk of SCD. Consequently, improving the prognostic stratification would result, in this population of subjects, in a better selection of the candidates for the implant with a significant increase in the effectiveness of electrical therapies with ICDs.[4]

The severe reduction of the ejection fraction (EF) of the left ventricle ($\leq$35%) continues to represent, according to the recommendations of the European Society of Cardiology (ESC), the fundamental criterion on which the choice of ICD implantation in primary prevention is based.[5] However, this criterion is neither sensitive nor specific. Indeed, only one-fifth of patients with SCD have an EF $\leq$35%, and as many as 80% of patients with EF $\leq$35% and NI-DCM with ICD do not present at the 5-year follow-up device intervention for ventricular tachycardia or ventricular fibrillation.[6]

It is known how myocardial fibrosis and the resulting tissue inhomogeneity represent a potential substrate for the triggering of threatening ventricular arrhythmias. Several studies have proven the existence of a strong correlation between LGE, ventricular arrhythmic events, and SCD. In particular, Becker *et al.*, in a meta-analysis that included 34 studies, for a total of 4554 patients, showed that patients with DCMP-NI and LGE have a higher risk of cardiovascular mortality [odds ratio (OR) 3.40, 95% confidence interval (CI): 2.04–5.67] and ventricular arrhythmias (OR 4.52, 95% CI: 3.41–5.99) compared to patients without LGE. Importantly, the absence of LGE was associated with reverse remodelling.[7] Furthermore, even if the extension of the LGE was associated with a worse prognosis, even small amounts of LGE significantly increase the risk of events. Among other things, not only the presence but also the localization of the LGE is important in prognostic stratification. In particular, LGE at the level of the interventricular septum is more likely associated with the risk of SCD and total mortality. Finally, the risk of SCD is further increased in the presence of an association between septal and the lateral wall of the left ventricle LGE[8] (*Figure 1A*).

The DERIVATE study[9] is a large multicentre registry that evaluated the usefulness of a new risk score that combines clinical and CMR variables in predicting major arrhythmic events (MACCE) and all causes of mortality in the patient with NI-DCM. The registry included patients with chronic heart failure and an EF <50%. The score was therefore also applied to patients who did not meet the current ESC criteria for the implantation of an ICD in primary prevention. The registry included a total of 1508 patients, 1000 in the score derivation court and 508 in the validation court, followed up for a mean of over 2 years. In multivariate analysis, patient age and the presence of mid-wall LGE were independent predictors of all causes of mortality while male sex, an indexed end-diastolic volume (LVEDVi) on CMR >120.5 mL/m^2 and the presence of more of three segments with midwall fibrosis were predictors of MACCE.

Based on these data, the authors created a risk score that includes male sex, LVEDVi >120.5 mL/m^2, and the presence of $\geq$3 segments with mid-wall LGE as variables. This score makes it possible to reclassify about one-third of patients who meet the current criteria for ICD implantation in NI-DCM in primary prevention as low-risk MACCE patients. On the contrary, in 5% of patients with EF >35%, at the echocardiogram, in which an ICD according to the standard of care is not indicated, MACCEs occurred. These data seem to suggest a crucial role of CMR in selecting the patient with NI-DCM candidate for ICD but obviously will have to be confirmed by future prospective randomized trials before any implementation in the guidelines.

Hypertrophic cardiomyopathy

The risk of SCD in HCM is low overall, with an annual SCD mortality <1%. However, death from SCD may be the feared first manifestation of this condition. For this reason, it is necessary to identify criteria capable of identifying the minority of patients at high risk and reassuring the others considered to be at lower risk.[10]

Thanks to the high spatial resolution, the CMR allows characterizing in detail the phenotype of the hypertrophic patient, providing a great contribution in the differential diagnosis with other conditions, such as cardiac amyloidosis and athlete's heart.

CMR has also been shown to be able to identify areas of hypertrophy of the left ventricle that are not easily characterized by echocardiography, in particular, at the level of the apex and anterolateral wall of the left ventricle. In cases of apical hypertrophic cardiomyopathy, the presence of aneurysms, associated with an increased risk of SCD, is not frequently identified by echocardiography. On the contrary, CMR is able to identify with great accuracy the presence of apical aneurysms and associated complications, such as parietal fibrosis and the presence of intracavitary thrombi with the LGE technique. In addition, thanks to the better definition of the endocardium, the measurement with CMR of the wall thicknesses of the left ventricle is more accurate than echocardiography which tends vice versa to underestimate the measure. This results in greater identification with CMR compared to echocardiography of myocardial areas with thicknesses >30 mm, associated with a greater risk of SCD.[11]

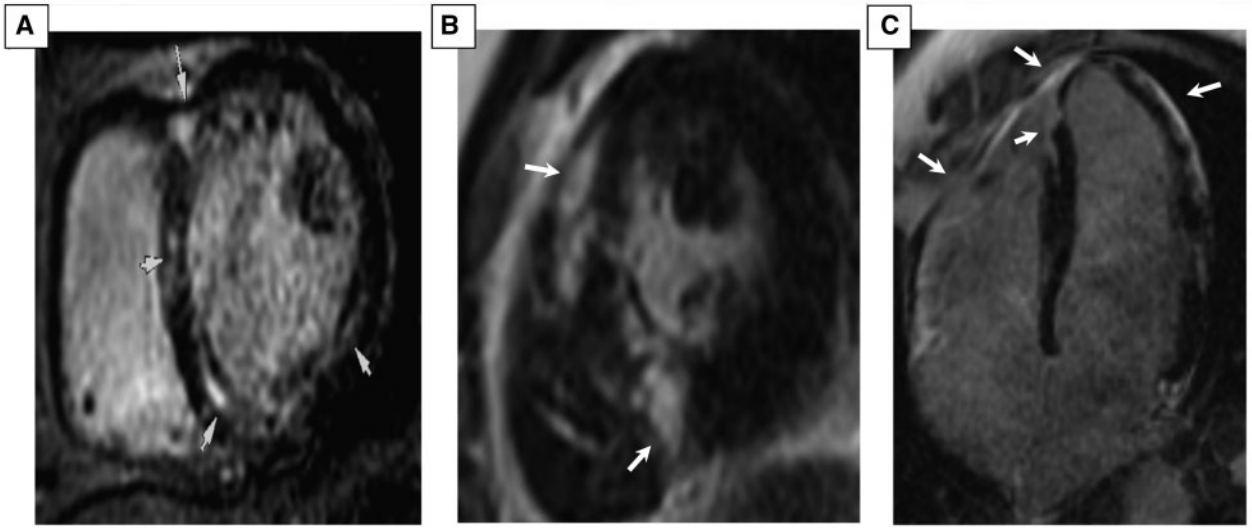

Figure 1 MRI images showing LGE in patients with cardiomyopathies: (*A*) NI-DCMP with areas of LGE at the level of the interventricular septum and inferolateral wall (arrows); (*B*) HCMP with large areas of interventricular septal LGE (arrows); (*C*) AC with LGE involving both ventricles (arrows). AC, arrhythmogenic cardiomyopathy; CMR, cardiac magnetic resonance; LGE, late gadolinium enhancement; NI-DCMP, non-ischaemic dilated cardiomyopathy.

However, the presence of LGE alone is not sufficient to stratify HCM patients at risk for SCD. In fact, about 50% of patients with HCM present with LGE, and it is, therefore, crucial to quantify its extent, which in this context represents a much more powerful marker of arrhythmic risk than the mere presence of LGE. In particular, the presence of an extension of LGE greater than 15% of the myocardial mass is associated with two times greater risk of SCD.[12] Similarly, more recently, Mentias *et al.*[13] demonstrated a 3-fold increased risk of SCD in patients with obstructive HCM in the presence of an LGE >15%.

Based on this evidence, the American College of Cardiology (ACC), American Heart Association (AA) guidelines added CMR with evaluation of the extension of the LGE in the decision to implant an ICD in the patient with HCM in grey cases in which it is not possible to classify the patient's risk based on clinical, echocardiographic and electrocardiographic data only.[14]

Less abundant than LGE, the literature data on prognostic evaluation with the T1-mapping technique suggest, in particular, a role of the ECV as an additional risk marker.[15] Avanesov *et al.*,[16] in a study of 73 patients with HCM, showed that ECV is a better predictor of SCD than LGE. Furthermore, according to the authors, the ECV associated with the HCM-SCD risk score, currently suggested by the ESC guidelines for the decision to implant an ICD in this patient group, significantly improves the accuracy of patient identification with HCM to experience ventricular syncope and arrhythmias.

Arrhythmogenic cardiomyopathy

Arrhythmogenic cardiomyopathy is a hereditary cardiomyopathy characterized by the presence of ventricular arrhythmias and an increased risk of SCD.[17,18] It is therefore not surprising that once the diagnosis of AC is made, the most important clinical decision to make is whether or not the affected patient needs an ICD. This is a crucial decision because AC is a disease that often affects young people, and SCD can be the first manifestation. On the other hand, the decision to implant an ICD must consider the possible complications of the intervention in the short and long term. According to the literature, the main factors that appear related to the risk of SCD in these patients are history of ventricular arrhythmias and in particular of sustained ventricular tachycardia, the extent of cardiac structural anomalies, a recent syncope episode, young age, male sex, genetic abnormalities, and intense physical exercise. In 2015, a consensus document was published regarding the indication for ICD implantation in patients with AC which divided the patients into three groups: (i) high-risk patients in which implantation of the defibrillator is indicated: history of cardiac arrest or sustained ventricular tachycardia and people with severe left or right ventricular dysfunction; (ii) patients with intermediate-risk in whom the implant is reasonable, who have at least one of the following conditions: syncope, non-sustained ventricular tachycardia or moderate dysfunction of the right or left ventricle; and (iii) low-risk patients in whom ICD implantation should be considered especially in the presence of multiple risk factors but not systematically performed: subjects with frequent ventricular ectopic beats, ventricular tachycardia induced by the electrophysiological study, male sex, genetic alterations, young age, inversion of T waves.[17] More recently, an arrhythmogenic right ventricle cardiomyopathy (ARVC) risk score has been proposed to guide the choice of ICD implantation decision based on age, gender, recent syncope, history of non-sustained ventricular tachycardia, number of ventricular ectopic ventricular beats in 24 h, number of leads with inverted T waves and right ventricular ejection fraction.[19]

Gold-standard method for the evaluation of biventricular size and function, in addition to allowing the characterization of myocardial tissue, CMR has become the reference

method for the assessment of the patient with suspected AC (*Figure 1C*).

According to the criteria of the 2010 task force, still widely used for the diagnosis of the disease, AC is defined based on major and minor criteria, based on electrocardiographic, arrhythmic, morphological, histopathological, clinical, and genetic findings. In particular, the criteria for imaging diagnosis provide for the identification of regional or global alterations in the function of the right ventricle, associated or not with anomalies of the left ventricle.[20]

However, it is now known that AC is a condition that can present with isolated anomalies in the right or left ventricle or with biventricular involvement with a predominance of one or the other ventricle. Furthermore, the absence of an assessment of tissue characterization findings on CMR represents an important limitation of the criteria proposed in 2010. To overcome these limitations, the Padua criteria for the diagnosis of AC were proposed in 2020, which include the assessment of the LGE in CMR to identify fibroadipose infiltration of both ventricles.[21]

Recently, Aquaro *et al.*[22] have shown that the forms of AC in which there is a prevalent involvement of the left ventricle on CMR with systolic dysfunction and/or fibroadipose infiltration, often demonstrated with the presence of LGE, are those with a worse prognosis than the biventricular forms or in which there is an isolated right ventricle involvement, with increased risk of SCD, aborted cardiac arrest and appropriate ICD interventions. Based on these data, the authors always suggest ICD implantation in the case of involvement of the left ventricle. The study also confirmed the crucial role of CMR in characterizing the phenotype of AC, confirming the high negative predictive risk of CMR in AC.

Conclusions

CMR is a non-invasive imaging method that allows an accurate morpho-functional cardiac evaluation with the possibility of characterizing myocardial tissue, identifying and quantifying the fibrosis that constitutes the substrate on which ventricular arrhythmias responsible for SCD are triggered. According to the data in the literature, CMR plays an additional role in the prognostic evaluation of patients with cardiomyopathies. If this role is confirmed by future randomized trials, CMR could acquire a crucial role in the selection of the candidate patient for the implantation of an ICD.

Conflict of interest: none declared.

References

1. Patel AR, Kramer CM. Role of cardiac magnetic resonance in the diagnosis and prognosis of nonischemic cardiomyopathy. *JACC Cardiovasc Imaging* 2017;**10**:1180–1193.
2. Pontone G, Guaricci AI, Andreini D, Solbiati A, Guglielmo M, Mushtaq S, Baggiano A, Beltrama V, Fusini L, Rota C, Segurini C, Conte E, Gripari P, Dello Russo A, Moltrasio M, Tundo F, Lombardi F, Muscogiuri G, Lorenzoni V, Tondo C, Agostoni P, Bartorelli AL, Pepi M. Prognostic benefit of cardiac magnetic resonance over transthoracic echocardiography for the assessment of ischemic and nonischemic dilated cardiomyopathy patients referred for the evaluation of primary prevention implantable cardioverter-defibrillator therapy. *Circ Cardiovasc Imaging* 2016;**9**:e004956.
3. Castelli G, Fornaro A, Ciaccheri M, Dolara A, Troiani V, Tomberli B, Olivotto I, Gensini GF. Improving survival rates of patients with idiopathic dilated cardiomyopathy in Tuscany over 3 decades: impact of evidence-based management. *Circ Heart Fail* 2013;**6**:913–921.
4. Køber L, Thune JJ, Nielsen JC, Haarbo J, Videbæk L, Korup E, Jensen G, Hildebrandt P, Steffensen FH, Bruun NE, Eiskjær H, Brandes A, Thøgersen AM, Gustafsson F, Egstrup K, Videbæk R, Hassager C, Svendsen JH, Høfsten DE, Torp-Pedersen C, Pehrson S; DANISH Investigators. Defibrillator implantation in patients with nonischemic systolic heart failure. *N Engl J Med* 2016;**375**:1221–1230.
5. Priori SG, Blomström-Lundqvist C, Mazzanti A, Blom N, Borggrefe M, Camm J, Elliott PM, Fitzsimons D, Hatala R, Hindricks G, Kirchhof P, Kjeldsen K, Kuck K-H, Hernandez-Madrid A, Nikolaou N, Norekvål TM, Spaulding C, Van Veldhuisen DJ; ESC Scientific Document Group. 2015 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: the task force for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death of the European Society of Cardiology (ESC). Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC). *Eur Heart J* 2015;**36**:2793–2867.
6. Pathak RK, Sanders P, Deo R. Primary prevention implantable cardioverter-defibrillator and opportunities for sudden cardiac death risk assessment in non-ischaemic cardiomyopathy. *Eur Heart J* 2018;**39**:2859–2866.
7. Becker MAJ, Cornel JH, van de Ven PM, van Rossum AC, Allaart CP, Germans T. The prognostic value of late gadolinium-enhanced cardiac magnetic resonance imaging in nonischemic dilated cardiomyopathy: a review and meta-analysis. *JACC Cardiovasc Imaging* 2018;**11**:1274–1284.
8. Halliday BP, Baksi AJ, Gulati A, Ali A, Newsome S, Izgi C, Arzanauskaite M, Lota A, Tayal U, Vassiliou VS, Gregson J, Alpendurada F, Frenneaux MP, Cook SA, Cleland JGF, Pennell DJ, Prasad SK. Outcome in dilated cardiomyopathy related to the extent, location, and pattern of late gadolinium enhancement. *JACC Cardiovasc Imaging* 2019;**12**:1645–1655.
9. Guaricci AI, Masci PG, Muscogiuri G, et al. CarDiac magnEtic Resonance for prophylactic Implantable-cardioVerter defibrillAtor ThErapy in Non-Ischaemic dilated CardioMyopathy: an international Registry. *Europace* 2021;**23**:1072–1083.
10. Maron BJ, Rowin EJ, Casey SA, Lesser JR, Garberich RF, McGriff DM, Maron MS. Hypertrophic cardiomyopathy in children, adolescents, and young adults associated with low cardiovascular mortality with contemporary management strategies. *Circulation* 2016;**133**:62–73.
11. Tower-Rader A, Kramer CM, Neubauer S, Nagueh SF, Desai MY. Multimodality imaging in hypertrophic cardiomyopathy for risk stratification. *Circ Cardiovasc Imaging* 2020;**13**:e009026.
12. Chan RH, Maron BJ, Olivotto I, Pencina MJ, Assenza GE, Haas T, Lesser JR, Gruner C, Crean AM, Rakowski H, Udelson JE, Rowin E, Lombardi M, Cecchi F, Tomberli B, Spirito P, Formisano F, Biagini E, Rapezzi C, De Cecco CN, Autore C, Cook EF, Hong SN, Gibson CM, Manning WJ, Appelbaum E, Maron MS. 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.
13. Mentias A, Raeisi-Giglou P, Smedira NG, Feng K, Sato K, Wazni O, Kanj M, Flamm SD, Thamilarasan M, Popovic ZB, Lever HM, Desai MY. Late gadolinium enhancement in patients with hypertrophic cardiomyopathy and preserved systolic function. *JACC* 2018;**72**:857–870.
14. Ommen SR, Mital S, Burke MA, et al. 2020 AHA/ACC guideline for the diagnosis and treatment of patients with hypertrophic cardiomyopathy: executive summary: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation* 2020;**142**:e533–e557.
15. Baggiano A, Torto AD, Guglielmo M, et al. Role of CMR mapping techniques in cardiac hypertrophic phenotype. *Diagnostics (Basel)* 2020;**10**:770.
16. Avanesov M, Münch J, Weinrich J, Well L, Säring D, Stehning C, Tahir E, Bohnen S, Radunski UK, Muellerleile K, Adam G, Patten M, Lund G. Prediction prediction of the estimated 5-year risk of sudden cardiac death and syncope or non-sustained ventricular tachycardia in patients with hypertrophic cardiomyopathy using late gadolinium

enhancement and extracellular volume CMR. *Eur Radiol* 2017;**27**: 5136–5145.
17. Corrado D, Basso C, Judge DP. Arrhythmogenic cardiomyopathy. *Circulation Res* 2017;**121**:784–802.
18. Sommariva E, Brambilla S, Carbucicchio C, Gambini E, Meraviglia V, Dello Russo A, Farina FM, Casella M, Catto V, Pontone G, Chiesa M, Stadiotti I, Cogliati E, Paolin A, Ouali Alami N, Preziuso C, d'Amati G, Colombo GI, Rossini A, Capogrossi MC, Tondo C, Pompilio G. Cardiac mesenchymal stromal cells are a source of adipocytes in arrhythmogenic cardiomyopathy. *Eur Heart J* 2016;**37**:1835–1846.
19. Cadrin-Tourigny J, Bosman LP, Nozza A, Wang W, Tadros R, Bhonsale A, Bourfiss M, Fortier A, Lie ØH, Saguner AM, Svensson A, Andorin A, Tichnell C, Murray B, Zeppenfeld K, van den Berg MP, Asselbergs FW, Wilde AAM, Krahn AD, Talajic M, Rivard L, Chelko S, Zimmerman SL, Kamel IR, Crosson JE, Judge DP, Yap S-C, van der Heijden JF, Tandri H, Jongbloed JDH, Guertin M-C, van Tintelen JP, Platonov PG, Duru F, Haugaa KH, Khairy P, Hauer RNW, Calkins H, Te Riele ASJM, James CA. A new prediction model for ventricular arrhythmias in arrhythmogenic right ventricular cardiomyopathy. *Eur Heart J* 2019;**40**:1850–1858.
20. Marcus FI, McKenna WJ, Sherrill D, Basso C, Bauce B, Bluemke DA, Calkins H, Corrado D, Cox MGPJ, Daubert JP, Fontaine G, Gear K, Hauer R, Nava A, Picard MH, Protonotarios N, Saffitz JE, Sanborn DMY, Steinberg JS, Tandri H, Thiene G, Towbin JA, Tsatsopoulou A, Wichter T, Zareba W. Diagnosis diagnosis of arrhythmogenic right ventricular cardiomyopathy/dysplasia: proposed modification of the Task Force Criteria. *Eur Heart J* 2010;**31**:806–814.
21. Corrado D, Perazzolo Marra M, Zorzi A, Beffagna G, Cipriani A, Lazzari MD, Migliore F, Pilichou K, Rampazzo A, Rigato I, Rizzo S, Thiene G, Anastasakis A, Asimaki A, Bucciarelli-Ducci C, Haugaa KH, Marchlinski FE, Mazzanti A, McKenna WJ, Pantazis A, Pelliccia A, Schmied C, Sharma S, Wichter T, Bauce B, Basso C. Diagnosis of arrhythmogenic cardiomyopathy: the Padua criteria. *Intern J Cardiol* 2020;**319**:106–114.
22. Aquaro GD, De Luca A, Cappelletto C, Raimondi F, Bianco F, Botto N, Lesizza P, Grigoratos C, Minati M, Dell'Omodarme M, Pingitore A, Stolfo D, Ferro MD, Merlo M, Di Bella G, Sinagra G. Prognostic value of magnetic resonance phenotype in patients with arrhythmogenic right ventricular cardiomyopathy. *JACC* 2020;**75**:2753–2765.