

REVIEW ARTICLE

Management of patients with Arrhythmogenic Right Ventricular Cardiomyopathy in the Nordic countries

KRISTINA H. HAUGAA¹, HENNING BUNDGAARD², THOR EDVARDSEN¹,
OLE ESCHEN³, THOMAS GILLJAM⁴, JIM HANSEN⁵, HENRIK KJÆRULF JENSEN⁶,
PYOTR G. PLATONOV⁷, ANNELI SVENSSON⁸ & JESPER H. SVENDSEN⁹

¹Dept of Cardiology, Center for Cardiological Innovation, Institute for Surgical Research, Oslo University Hospital, Rikshospitalet, Oslo, Norway and University of Oslo, Oslo, Norway, ²Unit for Inherited Cardiac Diseases, The Heart Center, The National University Hospital, Rigshospitalet, Copenhagen, Denmark, ³Dept. of Cardiology, Aalborg University Hospital, Denmark, ⁴Institute of Medicine at Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden, ⁵Dept. of Cardiology, Gentofte Hospital, University of Copenhagen, Kildegårdsvej 28, 2900 Hellerup, Denmark, ⁶Dept. of Cardiology, Aarhus University Hospital, Palle Juul-Jensens Boulevard 99, 8200 Aarhus N, Denmark, ⁷Dept. of Cardiology, Lund University and Arrhythmia Clinic, Skåne University Hospital, Lund, Sweden, ⁸Department of Cardiology and Department of Medical and Health Sciences, Linköping University, Linköping, Sweden, and ⁹Dept. of Cardiology, The Heart Centre, Rigshospitalet, University of Copenhagen, and Danish National Research Foundation Centre for Cardiac Arrhythmia (DARC), Copenhagen, Denmark and Department of Clinical Medicine, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark

Abstract

Objectives. Diagnostics of patients with arrhythmogenic right ventricular cardiomyopathy (ARVC) are complex, and based on the 2010 Task Force document including different diagnostic modalities. However, recommendations for clinical management and follow-up of patients with ARVC and their relatives are sparse. This paper aims to give a practical overview of management strategies, risk stratification, and selection of appropriate therapies for patients with ARVC and their family members. **Design.** This paper summarizes follow-up and treatment strategies in ARVC patients in the Nordic countries. The author group represents cardiologists who are actively involved in the Nordic ARVC Registry which was established in 2009, and contains prospectively collected clinical data from more than 590 ARVC patients from Denmark, Norway, Sweden, and Finland. **Results.** Different approaches of management and follow-up are required in patients with definite ARVC and in genetic-mutation-positive family members. Furthermore, ARVC patients with and without implantable cardioverter defibrillators (ICDs) require different follow-up strategies. **Conclusion.** Careful follow-up is required in patients with ARVC diagnosis to evaluate the need of anti-arrhythmic therapy and ICD implantation. Mutation-positive family members should be followed regularly for detection of early disease and risk stratification of ventricular arrhythmias.

Key words: arrhythmogenic right ventricular cardiomyopathy, Ventricular arrhythmias, mutation positive family members, Management of ARVC

Introduction

Diagnostics and management of patients with arrhythmogenic right ventricular cardiomyopathy (ARVC) are challenging. The 2010 Task Force document revised the diagnostic criteria (1) to be more detailed aiming at increased specificity for detection of ARVC. The revision has also resulted in increased

complexity of the diagnostic workup and its interpretation. However, recommendations for clinical management and follow-up of patients with ARVC and their relatives are sparse.

This paper aims to give a practical overview of management strategies, risk stratification, and selection of appropriate therapies for patients with ARVC

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Correspondence: Kristina H. Haugaa, MD, PhD, Department of Cardiology, Oslo University Hospital, Rikshospitalet, PO Box 4950 Nydalen, NO-0424 Oslo, Norway. Fax: + 4723073530, Tel: + 4723071393. E-mail: Kristina.Haugaa@rr-research.no

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and their family members. In addition, we will discuss sports participation as well as pregnancy recommendations, and how to follow these patients. The author group represents cardiologists who are actively involved in the Nordic ARVC Registry, which was established in 2009 and contains prospectively collected clinical data from more than 592 ARVC patients (per August 2015) from Denmark, Norway, Sweden, and Finland (ARVC.dk).

Clinical management of patients with definite ARVC diagnosis

ARVC is a progressive disease associated with significant risk of sudden death, and an ARVC diagnosis may therefore be associated with important consequences for affected individuals, including long-time medical follow-up. From this perspective, only patients with a “definite” diagnosis according to the 2010 Revised Task Force document (1) are considered ARVC patients. Individuals with “borderline” or “possible” ARVC, often relatives of patients with established diagnosis, are discussed in a separate section.

Currently, there is no treatment with documented effect on disease progression. Nevertheless, there is recently published evidence of the causative association between the vigorous physical activity, which is a modifiable risk factor, and more advanced ARVC phenotypes (2,3). Clinical management of ARVC patients will therefore focus on

1. Risk stratification and prevention of sudden cardiac death (SCD);
2. Management of symptomatic arrhythmias;
3. Treatment of heart failure.

Treatment strategies include medication, implantation of a cardioverter defibrillator (ICD), catheter ablation, and cardiac transplantation.

Follow-up program

Patients with ARVC should be followed clinically on a regular basis at dedicated centers, usually at tertiary hospitals. At most hospitals represented by the writing group, patients with definite ARVC are followed at least annually and half yearly for those with ICDs (Table I). In addition to symptom-driven examinations, a regular, structured follow-up of patients **without** an ICD to delineate SCD risk, ICD implantation indication, and left ventricular involvement should be conducted and include (Table I)

- Patient history focusing on possible syncope or symptoms that can be suggestive of ventricular arrhythmias.
- 12-lead ECG for assessment of progression of depolarization and repolarization abnormalities and ventricular premature complexes.
- 24-hour ambulatory ECG monitoring for documentation of ventricular arrhythmias and number of ventricular premature complexes.
- Echocardiography including careful assessment of right ventricular (RV) function by visual assessment, RV fractional area change, and RV outflow tract (RVOT) diameter in addition to left ventricular (LV) function by ejection fraction (EF).
- Cardiac magnetic resonance imaging (CMR) is generally not indicated during follow-up in patients with an established definite ARVC diagnosis. CMR is usually considered contraindicated in the patient with implanted ICD, except in those with a CMR compatible device. In patients with possible or borderline ARVC, CMR is indicated at baseline for diagnostic purposes, and repeated during follow-up to evaluate disease progression.

Table I. Intervals of follow-up in patients with definite ARVC with and without ICD, and in first-degree relatives of ARVC patients.

	Clinical assessment	ECG	SAECG	Holter monitoring	Echocardiography	CMR
<i>Definite ARVC patients</i>						
ARVC patients with ICD (visits in addition to ICD follow-ups)	1y				1–3y	not indicated
ARVC patients without ICD	(1/2)–1y	1y	1y	1y	1–3y	3–5y or when indicated
<i>Relatives > 10–15 y – genotype positive or from families without identified mutations</i>						
Asymptomatic with borderline findings	1–2y	1–2y	1–2y	1–2 y	1–2 y	5y or when indicated
Asymptomatic without any positive findings	3–5y	3–5y	3–5y	3–5y	3–5y	5y or when indicated

Full non-invasive testing; Clinical assessment, 12-lead ECG, echocardiography, 24 h Holter monitoring, late potentials and cardiac MRI. Stress testing may be considered in patients with exercise-related symptoms.

ECG: electrocardiography, SAECG: signal-averaged electrocardiography, CMR: cardiac magnetic resonance imaging, y = years.

- Exercise test may be helpful for assessment of exercise-related symptoms, exercise-induced arrhythmias, evaluation of and assessment of beta-blocker effect and, finally, to achieve an impression of physical capacity and give advice regarding level of physical activity. An external defibrillator should always be available during exercise test. The use of exercise test in ARVC patients varies from performing exercise test on a regular basis to symptom-driven use.

Patients with ARVC who have received ICDs for primary or secondary prevention of SCD do not generally need full-scale reexaminations on an annual basis, and may have follow-ups limited to clinical history, ECG, and echocardiography unless symptoms warrant additional tests (Table I).

Risk stratification and ICD treatment

The prognosis of ARVC is mainly determined by ventricular tachyarrhythmias and SCD, which highlights the importance of risk stratification in the management of patients with ARVC. Today, however, tools for risk stratification of arrhythmias in ARVC are not clearly defined. The therapeutic approach to ARVC patients who have survived cardiac arrest or have had sustained ventricular tachycardia (VT) fulfill secondary prevention criteria for ICD. In contrast, primary prevention of SCD and ICD implantation in currently asymptomatic patients with ARVC remains challenging. Most of the data on risk stratification in patients with ARVC, however, relies on retrospective studies and non-randomized trials, which in part explains the large variability in SCD risk assessment strategies applied at different clinics in Europe and overseas.

A number of risk factors associated with high risk of SCD in ARVC patients have been reported. According to the guidelines endorsed by the European Heart Rhythm Association and the Heart Rhythm Society (4), the following risk factors can be used to identify individuals at increased risk of SCD, in whom ICD therapy should be considered (Class IIa, Level of evidence C):

- Presence of extensive signs of disease, including LV involvement
- Unexplained syncope when VT or ventricular fibrillation (VF) has not been excluded as the cause of syncope (5)

The definition of “extensive signs of disease” remains uncertain and leaves room for subjective interpretations. However, LV involvement appears to be a factor that aggravates the disease course. Also other risk markers for ventricular arrhythmias have

been reported, including male gender (6), proband status, documented non-sustained VT, and frequent premature ventricular contractions (PVCs; >1000 per 24 hours), (7) early onset of disease (5), and participation in competitive sports. (2,3) Syncope is generally considered an important risk factor, and appears to be a single independent predictor of ICD shocks for VF in a prospective ARVC cohort (8). However, this finding was not reproduced by others (7). Occurrence of SCD in affected relatives has been mentioned as a risk factor; however, there is little data to support that family history is a potent risk factor. ECG findings as QRS dispersion ≥ 40 ms, QT dispersion > 65 ms, and negative T wave beyond V1 have also been associated with SCD, although not confirmed (9). Imaging parameters have shown promising results for risk stratification (10), but the findings remain to be confirmed in larger studies. Recent studies have shown that specific genotype data may indicate the clinical course (11).

Each ARVC patient needs individual evaluation at every follow-up, where the risks and benefits of ICD implantation are reviewed in detail, thereby facilitating an informed decision. Complications such as perforation of transvenous ICD leads have been reported with an incidence of 1–5% in large populations (8), which is higher than that in other ICD-treated patients, and probably due to the thinner RV myocardium in patients with ARVC. Also, it can be more difficult to achieve satisfactory sensing, pacing, and defibrillation programming, and the thresholds can change with progression of the disease (8). Inappropriate shocks have been observed in 16% of ARVC patients (12). Dual-chamber ICD may reduce inappropriate ICD therapies and is recommended in ARVC patients (13). The vast majority of ventricular arrhythmias in ARVC are sustained monomorphic VT and ATP, even for rapid VT, should therefore be programmed for all patients with ARVC (12), as opposed to other arrhythmia syndromes.

Other diagnostic modalities

Coronary angiography/coronary computed tomography and RV angiography Coronary angiography by invasive techniques or by computed tomography (CT) is indicated in patients > 40 years of age with VT. An invasive coronary angiography should be performed on classical indications, including chest pain and suspicion of coronary abnormalities, and in patients with reduced LV function of uncertain origin, whereas coronary CT is a reasonable choice in patients with low probability of ischemic heart disease. Right ventricular angiography is included in 2010 TFC to assess RV morphology, but is now rarely performed due to the invasive nature.

Electrophysiological study An electrophysiological study may have diagnostic impact, but has no value to assess risk in asymptomatic ARVC family members. Inducibility of VT during invasive electrophysiological study has not been shown to be predictive for the occurrence of VT during follow-up (8).

Electrophysiological study can be indicated in ARVC patients with recurrent monomorphic VT for evaluation of VT ablation or as part of the differential diagnostic workup in patients presenting with wide QRS tachycardia with left bundle branch block morphology. In selected patients, electro-anatomical mapping can be used to demonstrate areas of diseased myocardium and help in the differential diagnosis against outflow tract tachycardia (14).

Myocardial biopsy Histological evaluation has been specified in the current 2010 Task Force criteria with focus on the quantifiable morphometric assessment of residual myocytes in biopsies taken from the RV wall. However, due to the low diagnostic yield and the potential risks, this procedure is rarely performed, and is not part of our routine diagnostic workup of patients with suspected ARVC or in relatives of ARVC patients.

Pharmacological treatment

Anti-arrhythmic treatment In ICD-treated patients with VTs, either beta-blockers or class-III anti-arrhythmic drugs (Sotalol and Amiodarone), used alone or in combination, seem to be the most effective agents although larger randomized studies are lacking (4,15–17). Amiodarone, usually used in combination with beta blockers, can be efficient in patients in whom beta-blocker medication alone has insufficient arrhythmic control. When patients remain stable on the maintenance dose of amiodarone (usually 200 mg daily) for 6 months after episodes of symptomatic arrhythmia or ICD therapy, an attempt to reduce or cease amiodarone treatment can be made. The efficacy of the anti-arrhythmic treatment is evaluated by reported symptoms and Holter monitoring may be useful. However, current available drug treatment does not protect against SCD, and medical therapy should therefore not replace ICD treatment, but supplement ICD in order to minimize ICD shocks.

Heart failure treatment In ARVC patients with LV involvement and reduced LV function, standard heart failure treatment is indicated (18). In asymptomatic patients with LVEF < 45%, medication with angiotensin-converting enzyme (ACE) inhibitors/angiotensin receptor blockers can be initialized and in ARVC patients with symptoms of heart failure the

addition of beta-blockers, spironolactone, ivabradine, and in some cases loop diuretics is indicated. Cardiac resynchronization therapy (CRT) may be indicated in rare cases. In patients with isolated RV dysfunction, heart failure treatment can be considered, although no data exist on the effectiveness of this treatment on RV function. Heart transplantation is the final therapeutic option in case of end-stage heart failure or untreatable ventricular arrhythmias.

Catheter ablation therapy

Catheter ablation is an option for treatment in ARVC patients with VTs resistant to drug therapy or when anti-arrhythmic drug use is limited by side effects. Due to the progressive nature of the underlying disease, catheter ablation should not be considered as curative treatment in ARVC patients. Although one recent study has suggested that patients with preserved LV function presenting with monomorphic VT, including those with ARVC, can be safely managed with catheter ablation without ICD backup (19), we currently consider ablation as an adjunct to ICD therapy. Catheter ablation of VT in ARVC is challenging, due to the predominantly epicardial, diffuse distribution of the disease⁴². Mapping and ablation can either target “mappable” monomorphic VTs or target areas of potentially arrhythmogenic diseased myocardium characterized electrophysiologically by areas of fragmented or late potentials surrounding scar areas (“substrate elimination”). Using extensive endo- and epicardial ablation strategies to eliminate inducible VT/and or substrate elimination, often in multiple procedures, recent studies have reported mid-term (1–3 years) freedom from VF/VT recurrences from 64 to 88% and long-term (4–5 years) freedom from 45 to 50% (20–22). Thus, in a substantial number of patients, even those with a considerable VT/ICD therapy burden and non-monomorphic VT, long-term freedom from arrhythmia can be achieved with catheter ablation. We currently consider catheter ablation in ARVC patients on optimal anti-arrhythmic drug therapy with recurrent appropriate ICD shocks, symptomatic VT/PVCs, or PVCs suspected of causing impairment of LV function.

Key points

- ARVC is a progressive disease with significant risk of sudden death
- ARVC patients with definite diagnosis without ICD should be followed clinically at least annually
- High-risk patients should be offered an ICD
- Risk assessment and clinical examinations include patient history, 12-lead ECG, signal-averaged ECG, 24-hour ambulatory ECG

monitoring, echocardiography, CMR, and often an exercise test

- An echocardiographic study includes (RV) function, RV fractional area change, RVOT diameter, and LVEF
- Risk factors for ventricular arrhythmias: extensive signs of disease including LV dysfunction, early onset of disease, unexplained syncope, frequent PVCs, non-sustained VT, and participation in competitive sports
- Anti-arrhythmic treatment includes beta-blockers and/or class-III anti-arrhythmic drugs
- Catheter ablation should be considered in recurrent appropriate ICD shocks on optimal medical treatment
- Standard heart failure treatment is indicated in reduced LV function and is possibly indicated in reduced RV function

Clinical management of relatives

Work-up and follow-up programs

Clinical as well as genetic screening should be preceded by careful information of the relative about the rationale for and expected outcome of screening, as well as information on potential legal aspects of screening. The genetic counseling can be provided either by the cardiologist or by a clinical geneticist. First-degree relatives of patients with a definite ARVC diagnosis are offered genetic and clinical screening (cascade screening) (Table I).

When a disease-causing mutation is identified in the proband, testing for that specific mutation in the relatives can be used to identify relatives at risk (genetic cascade screening). The asymptomatic relative should be genetically tested for the specific family mutation, and await the result before clinical workup is commenced. Follow-up is offered in those with a disease-causing mutation, whereas follow-up is ceased in relatives without it. On this basis, genetic testing is offered to the proband from a family where one or more relatives may benefit from the potential finding of a disease-causing mutation. The genetic screening of young relatives may be offered from the age of 10 to 15 years. ARVC-related symptoms before this age are uncommon. In the Nordic ARVC Registry, only 6 (2%) of 257 patients with definite ARVC diagnosis had first ARVC symptom before the age of 15 years. However, although family history does not appear to be a key indicator of adverse events in ARVC (23), it seems prudent to offer genetic screening in the earlier part of this age range in families with ARVC-related events during early adolescence, in response to the parents' preferences.

If no mutation is identified or if an identified mutation is not clearly pathogenic, genetic testing of the relatives is not indicated.

Relatives with a disease-causing mutation and first-degree relatives of mutation negative index patients are offered clinical workup including clinical assessment, 12-lead ECG, signal-averaged ECG, echocardiography, 24-h Holter monitoring, and CMR imaging (Table I). The imaging modality chosen for follow-up depends on availability and local expertise. CMR is the best tool for evaluating structural changes and should be preferred if high-quality CMR is accessible (24). Exercise test to assess physical capacity and exercise-induced arrhythmias may be considered in ARVC relatives with exercise-related symptoms. If a relative fulfills definite diagnostic criteria, further management strategy would be the same as for a patient with ARVC (see above).

In relatives with borderline or possible diagnostic criteria, the individual is offered repeated non-invasive testing with 1–2-year intervals (Table I) depending on age. Asymptomatic relatives without any positive findings are offered follow-up with age-dependent intervals after initial full non-invasive screening. Yearly follow-ups should be considered in physically very active children and adolescents. Follow-up intervals may be increased to every second year after the age of 25 years or when the family member has been followed with stable conditions for a reasonable period (3–5 years). All relatives are instructed to seek acute medical attention if symptoms develop. In asymptomatic relatives without any positive findings, one may consider ceasing follow-up from the age of 60 years. However, 16/257 (6%) of definite ARVC patients in the Nordic ARVC Registry had first symptom at >60 years of age, indicating late-age penetrance with ventricular arrhythmias or atrial fibrillation.

Risk stratification

Prophylactic ICD implantation in asymptomatic relatives, with no or minimal manifestations of the disease or in healthy mutation-positive relatives is currently not recommended. These individuals are now identified at a much earlier stage of disease than earlier stage due to the implementation of family screening, routine use of genetic testing, and improved cardiac imaging. Risk assessments in relatives follow the same recommendations as for ARVC patients (see 2.2).

Pharmacological treatment

No data exist supporting the effects of primary prophylactic medical therapy on ARVC progression or arrhythmic complications in asymptomatic

mutation-positive relatives.¹⁷ There are few studies evaluating treatment strategies in asymptomatic patients with mild RV alterations and no evidence of arrhythmia. Beta-blockers might be reasonable to recommend reducing catecholaminergic-induced arrhythmia (16,25). In family members with no abnormal findings on any tests, we do not normally prescribe beta-blockers, but have a low threshold to start if any signs of abnormal test results are found. Whether medication with ACE inhibitors may be protective is unknown, and is subject of investigation (25). We practice a low threshold for ACE inhibitors if any reduction in LV function is observed.

Key points

- A disease-causing mutation is identified in about 40–60% of index patients
- First-degree relatives of mutation-positive patients should be offered genetic counseling and genetic testing for the family mutation
- First-degree relatives of mutation-negative patients with definite ARVC should be offered clinical screening
- Clinical or genetic screening of first-degree children can start from the age of 10 to 15 years
- Prophylactic ICD implantation in asymptomatic relatives or minimal clinical findings is not recommended

Pregnancy

Genetic counseling should be performed in ARVC patients and their partners when planning a pregnancy, delineating the dominant inheritance mode with variable penetrance in ARVC. In women with ARVC, increased circulatory demand during pregnancy and delivery may in theory precipitate disease progression and trigger symptoms, that is, ventricular arrhythmias. Larger studies of pregnancy in ARVC women are lacking, but case reports have indicated that pregnancy in ARVC is generally well tolerated (26,27). In severe ARVC cases, a moderate risk of disease progression and arrhythmia has been observed from the last trimester until 2–3 months post-partum (26,28). In women with RV failure including significant LV involvement, larger studies are lacking, but pregnancy may impose additional risks that need to be addressed at pre-pregnancy counseling (29). How repeated pregnancies influence on RV size and function as well as worsening of symptoms is not known. Pregnancy in women with ARVC needs to be addressed by a multidisciplinary team involving cardiologists, obstetricians, and anesthesiologists at a tertiary center. During pregnancy we advocate clinical workup at 3 and 7 months of gestation, as well as at 2–3 months post-partum, including 12-lead ECG, 24-h Holter

monitoring and echocardiography (26), and additional visits if symptoms occur. Anti-arrhythmic medication should be continued throughout pregnancy, but may be altered if there are contraindications (26,28). Beta-blocker medication is generally well tolerated, and flecainide medication may also be maintained during pregnancy. Amiodarone is usually regarded as contraindicated during pregnancy due to teratogenicity and high rates of abnormal thyroid function in the newborn (29).

ICD indications should optimally be reassessed before pregnancy. Arrhythmias during pregnancy may warrant ICD implantation. ICD discharge and external electrical cardioversion in case of VT is generally well tolerated by the fetus (28).

In female ARVC patients without arrhythmias or abnormal contractile function, vaginal delivery is preferred. In cases with symptomatic ARVC, a cesarean section during epidural anesthesia is advocated (26). Telemetry monitoring during delivery should be continued in 24 hours post-partum. In cases with maternal anti-arrhythmic medication, the child should be transferred to the neonatal unit for 24-h observation.

Key points

- Genetic counseling should be offered in the planning of a pregnancy
- Anti-arrhythmic medication without evidence of teratogenicity should be continued throughout pregnancy if there are no contraindications
- Amiodarone should be avoided during pregnancy
- A cesarean section in epidural anesthesia is advocated in symptomatic patients

Sports participation

Increasing evidence indicates an important link between exercise and the development and outcomes of ARVC (2,3,30). Athletic activity includes acute volume overload and increased wall stress of the myocardium, in particular in the right ventricle. Observational studies of patients with ARVC or at risk of ARVC have reported that high cumulated athletic activity is associated with earlier onset of disease and higher incidence of ventricular arrhythmias (2,3). A recent study indicated that exercise test may reveal latent electrical substrate for arrhythmias in a subset of ARVC subjects which was not present in healthy individuals (31).

Current guidelines recommend patients with overt ARVC to refrain from competitive sports (32,33). We recommend ARVC patients to restrict from competitive sports, while patients with less severe disease may continue recreational sports as

part of a healthy life style. However, patients are instructed not to exercise at maximum capacity and to be aware of symptoms occurring during activity due to the risk of exercise-induced ventricular arrhythmias.

Currently, no restrictions apply for healthy ARVC mutation-positive relatives in American recommendations (34), while European sports recommendations warrant only recreational sports in these subjects (35). However, a recent report indicated that cardiac function was lower in ARVC mutation-positive relatives with a history of athletic activity (2). We inform ARVC relatives about the sparse guidelines for athletic activity, but that there is a possibility of accelerated and aggravated disease progression by high intensity and repeated athletic activity. The threshold for “safe” weekly activity is unknown and no threshold value may exist. These recommendations need to be balanced with quality-of-life considerations and should be evaluated on an individual basis.

Key points

- There is an important link between exercise and outcomes in ARVC
- Vigorous athletic activity is associated with earlier onset of disease and higher incidence of ventricular arrhythmias
- We recommend ARVC patients to restrict from competitive sports, but patients with less severe disease and asymptomatic mutation-positive family members may continue recreational sports

Cardiomyopathy Clinics

Several arrhythmia syndromes and cardiomyopathies share common features in inheritance and workup, which has facilitated the concept of cardiomyopathy clinic, that is, clinics dedicated to evaluate and follow-up of patients with inherited cardiomyopathies and their relatives. The general management, including family screening and genetic counseling, is optimally organized in multidisciplinary teams including cardiologists, geneticists, pediatricians, pathologists, and specialized nurses. Furthermore, the presence of a multidisciplinary team for pregnancy and delivery is important. Optimal imaging services including high-standard echocardiographic facilities and CMR imaging services in addition to an invasive electrophysiological laboratory should be available. The cardiomyopathy clinic should have easy access to genetic testing and expert counseling. The clinic should ideally follow national or international guidelines for diagnostic workup of patients with suspected ARVC and their relatives. It is recommended that ARVC patients, and their first-degree

relatives as well as patients with suspected of ARVC are followed at such centers. The follow-up of low-risk individuals may be organized to take place at smaller units in collaboration with the specialized cardiomyopathy clinic.

Key points

- We recommend that all ARVC patients, their first-degree relatives and patients with suspected ARVC are followed at cardiomyopathy clinics
- The clinic is optimally organized in multidisciplinary teams including cardiologists, geneticists, pediatricians, pathologists, and specialized nurses, and should have easy access to genetic testing
- Imaging facilities include echocardiography and CMR

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