Arrhythmogenic right ventricular cardiomyopathy (ARVC) is a disease characterised by progressive replacement of myocytes with fibrofatty tissue. These changes create a substrate prone to ventricular arrhythmia (VA) and increased risk for sudden cardiac death (SCD). Although initially thought to affect only the right ventricle, it has since been well-recognised that left ventricular (LV) involvement is common, with a higher prevalence in specific regions of Italy (Padua, Venice). The mean age of first presentation in one large cohort study was 36 ± 14 years.4 The most common presentations included VA in 50% of patients and cardiac arrest in 11%. The median age at cardiac arrest was 25 years old. It remains an important cause of SCD in young patients, particularly athletes.3 These factors highlight the importance of early recognition and appropriate therapy in ARVC.

Many individuals diagnosed with ARVC have a family history of the disease, and it is typically transmitted through an autosomal dominant pattern.5,6 In most cases, ARVC is inherited with an autosomal dominant pattern with variable expression. Most mutations that are associated with ARVC code for desmosomal proteins. A pathogenic mutation can be found in approximately two-thirds of patients. The clinical manifestations of ARVC appear to be worse in men compared with women, and this is further discussed later in this article.

Diagnosis and Management
The diagnosis of ARVC is based on the 2010 Task Force Criteria.7 These diagnostic criteria consist of major and minor diagnostic criteria pertaining to characteristics of RV dysfunction, histopathology on endomyocardial biopsy, repolarisation and depolarisation abnormalities on ECG, history of arrhythmia in the individual, and family history of ARVC or SCD. Each category has major (2 points) and minor (1 point) criteria. A score of 4 is considered definite ARVC; 3 points is borderline ARVC; 1–2 points is possible ARVC and 0 points is not ARVC.

Accurate diagnosis based on the 2010 Task Force Criteria is the first step in ARVC management. Once the diagnosis is secured, the second step of management is determination of an individual’s risk for VA and SCD. This will help to facilitate decisions regarding ICD placement, and is a large focus of this article. The other three components of this five-step approach to ARVC management are the minimisation of ICD placement with the risk for VA and SCD in the individual patient. This article reviews the literature regarding the factors that contribute to the assessment of risk stratification in ARVC patients.

Abstract
Arrhythmogenic right ventricular cardiomyopathy (ARVC), also called arrhythmogenic right ventricular dysplasia or arrhythmogenic cardiomyopathy, is a genetic disease characterised by progressive myocyte loss with replacement by fibrofatty tissue. This structural change leads to the prominent features of ARVC of ventricular arrhythmia and increased risk for sudden cardiac death (SCD). Emphasis should be placed on determining and stratifying the patient’s risk of ventricular arrhythmia and SCD. ICDs should be used to treat the former and prevent the latter, but ICDs are not benign interventions. ICDs come with their own complications in this overall young population of patients. This article reviews the literature regarding the factors that contribute to the assessment of risk stratification in ARVC patients.

Keywords
Arrhythmogenic right ventricular cardiomyopathy, ventricular arrhythmia, risk stratification, right ventricular dysplasia, ICD, sudden cardiac death, cardiomyopathy

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therapy, prevention of disease progression; and cascade screening of family members.

Pharmacotherapy, catheter ablation, and exercise restriction are used to address the third step of ARVC management, the minimisation of ICD therapy. Pharmacotherapies include β-blockers and anti-arrhythmic drugs. β-blockers are thought to be beneficial in almost all patients with ARVC. Patients with ARVC are particularly sensitive to catecholamine effects.7 Beta-blockers not only prevent VAs, but are also a cornerstone of management in patients who have heart failure (Class of Recommendation [COR] I). In addition to β-blockers, sotalol (COR IIb) is the most commonly used anti-arrhythmic agent, followed by flecainide (COR IIb) and amiodarone (COR IIb).8–10

When anti-arrhythmic drugs fail or are not tolerated, catheter ablation becomes an important treatment option. Catheter ablation has been shown to reduce ventricular tachycardia (VT) events but does not reduce SCD risk or improve survival. Notably, a recent large study with more than 400 patients demonstrated continuing high rates of recurrence at 1 year (59%; 95% CI [44–71%]) and at 5 years (74%; 95% CI [59–84%]) despite ablation, but that overall burden of VA was reduced.11 The origin of VT is most commonly epicardial, and epicardial ablation paired with or without endocardial ablation has been shown to be safe and effective in further reducing VT events.12,13 In addition to pharmacological therapy and catheter ablation, exercise restriction is critical. We have recently reported that the tertiile of patients with ARVC who reduce their exercise to the greatest degree have a 90% lower risk of developing VA (HR 0.10; 95% CI [0.02–0.43]).14

The fourth component of ARVC management is the prevention of progression and development of heart failure. It has been well-established that ARVC is a progressive disease and that heart failure develops over time in more than 40% of patients.9 The risk of progression is addressed with pharmacological therapy (β-blockers and renin–angiotensin–aldosterone system [RAAS] blockade) and exercise restriction. Management of overt heart failure symptoms is similar to any aetiology of heart failure. Diuretics should be used for congestive symptoms, and close attention should be placed on electrolyte balances given this population’s high risk for arrhythmia. Guideline-directed medical therapy for heart failure with reduced ejection fraction including β-blockers and RAAS blockade should be initiated as appropriate.15 Cardiac transplantation is required in a significant subset of patients.15 Cardiac transplantation is generally needed more than 15 years after initial presentation and is most commonly performed due to intractable right- or left-sided heart failure.15,16

Cascade screening of family members, the fifth component of ARVC management, is discussed in the ARVC risk stratification section below.

**Arrhythmogenic Right Ventricular Cardiomyopathy Risk Stratification**

The approach to ARVC risk stratification has evolved considerably over time. A general guideline to follow is the more severe the disease, as assessed from an electrical and structural perspective, the greater the risk of sustained VA or SCD. This approach is based on a long list of risk markers that have been identified. These risk markers include: previous history of sustained VT or VF; premature ventricular contraction (PVC) frequency; non-sustained VT (NSVT); cardiac syncope; proband status and genetic testing; gender; degree of exercise restriction; and degree of myocardial involvement.

As identified in Orgeron et al., and supported by previous studies by Mazzanti et al. and Piccini et al., a history of VA predicts appropriate ICD therapy for any future VA.16–21 Corrado et al. suggested that the risk for VF is likely to be low in patients with a history of haemodynamically stable VT, but other studies have suggested that haemodynamically significant VT is still associated with an unacceptably high risk for lethal VA and SCD.22 As a result, a history of any VA is a poten risk factor. Current guidelines advise ICD implantation for all patients with ARVC who have had a previous sustained VA.23,24 However, the more critical issue concerns risk stratification in patients who have never had a sustained VA. In the following sections, we discuss some of the most important primary prevention risk markers.

**Electrical Instability**

Electrical instability is an important risk factor in ARVC risk stratification. PVC burden (more than 1,000 in 24 hours), NSVT or more invasive

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Corrado et al. 2015. Reproduced with permission from Oxford University Press.
evaluation with electrophysiology study can all quantify electrical instability. High PVC burden, NSVT and a positive electrophysiology study (defined as VT >30 seconds or haemodynamically significant VA requiring termination) all predict appropriate future ICD firing (for VT/VF). Interestingly, only high PVC burden was found to be predictive of future VF or ventricular flutter (Vfl) events. Only one study, by Corrado et al. in 2010, found that inducibility was not predictive of future appropriate therapies, and cited a positive predictive value of programmed ventricular stimulation (PVS) of 35% for any appropriate ICD therapy, and only 20% for VF/Vfl. However, given the abundance of evidence suggesting an association with VA and or appropriate ICD therapy, inducibility should be considered a marker of higher risk ARVC, along with high PVC burden and history of NSVT.

Cardiac Syncope
A history of syncope should raise suspicion for a previously unrecognised VA event. A detailed history of the syncopal event should be carried out to search for clues of cardiac origin (diaphoresis, shortness of breath, palpitations, severe injuries sustained from syncopal event). In 1989, Marcus et al. first recognised that previous syncope was associated with worse outcomes in ARVC, including arrhythmic death. Later studies confirmed this and found that syncope at first presentation was not only common but also suggestive of poor outcomes, such as SCD. One of these studies found that approximately half of patients diagnosed with ARVC after SCD had syncope prior to the event. Syncope (especially when there is a high suspicion of cardiac origin) should be considered as a significant risk factor for poor outcomes in patients with ARVC.

Figure 3: Comparison of 2015 International Task Force Consensus Statement Model to ARVCrisk.com Model

Impact of potential 5-year VA risk thresholds for ICD implantation calculated using the new arrhythmogenic right ventricular cardiomyopathy risk model (ARVCrisk.com) versus the International Task Force consensus statement model (on the far right). The solid blue represents patients in the model who have an ICD but who are predicted to never sustain a VA event. The solid black triangle represents the number of ICDs required to achieve protection of one patient from VA. All = ICDs implanted in all patients; none = ICDs implanted in no patients; VA = ventricular arrhythmia. Source: Cadrin-Tourigny et al. 2019. Reproduced with permission from Oxford University Press.

Genetic Testing and Proband Status
ARVC is a disease of desmosomal dysfunction. Eighty per cent of patients have a single copy mutation of the plakophilin-2 (PKP2) gene, but the less common mutation of the desmoplakin gene is associated with significantly higher rates of SCD. Importantly, the rate of first life-threatening arrhythmic event (LAE) in one study was found to be greatest between the ages of 21 and 40 years, measured at 4.0 per 100 person years. This suggests that children in families with ARVC should be screened for these mutations in the teenage years, prior to this period of increased LAE risk. Patients with more than one identified mutation are at an even higher risk for not only earlier onset of symptoms, but also for SCD and VA. The importance of
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A recent study by Gasperetti et al. reinforced these findings by showing a reduction in PVC burden through "detraining" of athletes with ARVC. However, there was no improvement in RV ejection fraction (RVEF) with exercise restriction.46 An additional study by Maupain et al. further supported exercise restriction by finding an increased VA risk in those who exercised more than 6 hours per week.25 All of these findings together suggest that exercise restriction alone is not sufficient to avoid ICD placement, but it should be strongly recommended to patients with ARVC to reduce VA events. Accordingly, the current 2019 Heart Rhythm Society (HRS) Guidelines for ARVC Management recommend that those with ARVC should avoid competitive exercise and high-intensity endurance exercise.10 Exercise intensity is expressed using metabolic equivalents (METs). Low-MET activities such as yoga and walking for pleasure should be considered safe, and even encouraged. However, more intense exercises, such as running, swimming and sports, should be avoided given the deleterious effects of exercise.20 Unwillingness to restrict exercise should be considered during risk stratification and decision-making regarding ICD placement.

Degree of myocardial involvement should be assessed as well. Extensive RV involvement, defined as RVEF ≤45% or ≥2 areas of regional dysfunction, is predictive of appropriate ICD therapy.41 Greater RV dysfunction as measured on echocardiogram is associated with an overall increase in major adverse cardiovascular events (MACEs), with VA unsurprisingly being the most common MACE.42 In addition to RV involvement, LV involvement in ARVC is becoming well-recognised. Akdis et al. found that higher levels of testosterone in men and lower levels of oestrogen in women were both associated with higher rates of major arrhythmic cardiovascular events in patients with ARVC.37 The underlying pathophysiology is thought to be due to testosterone promoting apoptosis and lipogenesis, while oestrogen inhibits these effects. This possibly explains why regular exercise, which is thought to lower oestrogen levels, is associated with worse outcomes in ARVC.38 Additionally, these findings may provide an explanation for the rare occurrence of ARVC before pubertal years.

Figure 4: Prediction of Life-threatening Ventricular Arrhythmia and Any Sustained Ventricular Arrhythmia

| Number at risk | Time (years) |
|----------------|--------------|
| **A** | **B** |
| LTVA | Any sustained VA |
| No prior event | 0.00 | 0.00 |
| Prior LTVA or unstable VT | 0.25 | 0.25 |
| Prior stable VT | 0.50 | 0.50 |
| Number at risk | 0.75 | 0.75 |
| 206 112 69 49 32 24 18 12 9 | 109 76 48 33 23 15 104 77 59 | 129 57 36 20 13 7 7 6 4 |
| 206 175 146 119 95 76 58 45 32 | 129 104 77 59 48 33 30 23 15 | 109 86 66 49 39 32 24 16 9 |
| 206 175 146 119 95 76 58 45 32 | 129 104 77 59 48 33 30 23 15 | 109 86 66 49 39 32 24 16 9 |
| p=0.43 | p<0.0001 |
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According to the 2015 International Task Force (ITF) consensus statement, Class I indications for ICD placement include a history of sustained VT or VF, severe RV dysfunction (fractional area change ≤17% or RVEF ≤35%), and severe LV dysfunction (LVEF ≤35%; Figure 1). However, this ITF consensus statement is less clear regarding ICD placement for primary prevention in ARVC patients. The ITF consensus statement provides Class IIa indications for when ICD placement should be considered in patients with ≥1 major risk factor, such as a history of syncope, NSVT, moderate RV dysfunction (RV fractional area change between 24% and 17% or RVEF 36–40%), moderate LV dysfunction (LVEF 36–45%) or biventricular dysfunction. Class IIb indications for when ICD placement may be considered include T wave inversion in ≥3 precordial leads, male sex, inducibility on electrophysiological study, and proband status. These guidelines lack clarity regarding ICD placement for primary prevention in ARVC patients.

A paper by Cadrin-Tourigny et al. in 2019 attempted to provide more clarity regarding primary prevention ICD placement by creating an ARVC risk calculator (which can be found at http://www.arvcrisk.com). This risk calculator uses age at diagnosis, number of T wave inversions, maximum 24-hour PVC count, history of NSVT, and RVEF to provide a predicted risk of sustained VA. Compared with the 2015 ITF algorithm, which treats ARVC risk as high, intermediate or low, the more recent ARVC risk calculator treats VA risk as a continuum. This new algorithm showed similar levels of benefit and protection from ICD placement at a much lower rate of ICD placement (20.6% fewer ICD implantations compared with the ITF algorithm; Figures 2 and 3). Another study comparing this new ARVC risk score with both the ITF and HRS guidelines found that an ARVC risk score >10% had the greatest net benefit compared with the guidelines. This new model provides the physician with a tool with which to quantify an individual patient’s risk and which can supplement clinical judgement during ICD placement decision-making. It is worth mentioning that this new model may underestimate non-classical forms of ARVC, such as biventricular or left dominant forms. Notably, this risk calculator also does not include inducibility on PVS, which is one of the discussed risk factors in the present article. Future ARVC risk calculators may include this to provide even more robust models regarding ARVC risk.

**Figure 5: Protection Rates When Using Life-threatening Ventricular Arrhythmia to Determine ICD Placement**

The resulting protection rate at various rates of ICD placement based on a model that looks specifically at LTVA, instead of any ventricular arrhythmia. The red bar demonstrates patients with an ICD who are predicted to sustain an LTVA. The blue bar represents those with an ICD and who are not predicted to sustain an LTVA. The dashed red bar represents patients who are without an ICD and who will be unprotected from a predicted LTVA. All = ICDs implanted in all patients; none = ICDs implanted in no patients; LTVA = life-threatening ventricular arrhythmia. Source: Cadrin-Tourigny et al. 2021. Reproduced with permission from Wolters Kluwer Health.
An even more recent study by Cadrin-Tourigny et al. specifically investigated predictive factors of life-threatening VTs (LTVs) to serve as a closer surrogate marker for SCD risk. That study did not find that prior sustained VA predicted LTVA, but that younger age, male sex, PVC count and number of leads with T wave inversion were predictive of LTVA. However, that study did reinforce the predictive value of any previous sustained VA event (Figure 4). That study also equips clinicians with more data for shared decision-making regarding ICD placement by providing more objective measures of risk and protection rates (Figure 5). It may not be unreasonable to forgo ICD placement in those deemed high risk for complications, or in low-risk patients who are hesitant to have an ICD placed. Regardless of these data, current ARVC guidelines recommend ICD placement as secondary prevention in patients with a history of any VA.

**Conclusion**

Risk stratification should be carried out immediately when a diagnosis of ARVC is made. Risk factors predictive of VA and SCD include age of onset, male sex, specific genetic mutation, cardiac syncpe, history of VA, degree of myocardial involvement, electrical instability, and exercise restriction. An individualised risk assessment is required to weigh the risks and benefits in the important decision of whether or not to proceed with ICD placement.

**Clinical Perspective**

- Arrhythmogenic right ventricular cardiomyopathy (ARVC) management consists of a 5-step approach that includes accurate diagnosis, determination of the need for ICD placement, minimisation of ICD therapy, prevention of disease progression and cascade screening of family members.
- ARVC risk stratification is determined by age at presentation, male sex, proband status, history of ventricular arrhythmia, history of cardiac syncpe, frequency of premature ventricular contractions and non-sustained ventricular tachycardia, degree of myocardial involvement and exercise plans.
- ARVC risk calculators provide more objective measures of risk stratification and can supplement clinical judgment when weighing the risks and benefits of ICD placement.
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- **Arrhythmic risk in arrhythmogenic right ventricular cardiomyopathy:** a systematic review and meta-analysis. *Heart Rhythm* 2018;15:1097–1107. https://doi.org/10.1016/j.hrthm.2018.01.031; PMID: 29408436.

- **Clinical profile and long-term follow-up of 37 families with arrhythmogenic right ventricular cardiomyopathy.** *J Am Coll Cardiol* 2000;36:2226–33. https://doi.org/10.1016/S0735-1097(00)00957-9; PMID: 1127465.

- **Compound and digenic heterozygosity predicts lifetime arrhythmic outcome and sudden cardiac death in desmosomal gene-related arrhythmogenic right ventricular cardiomyopathy.** *Circ Cardiovasc Genet* 2013;6:533–42. https://doi.org/10.1161/CIRCGENETICS.113.000288; PMID: 24070718.

- **Sex hormones affect outcome in arrhythmogenic right ventricular cardiomyopathy/dysplasia: from a stem-cell derived cardiomyocyte-based model to clinical biomarkers of disease outcome.** *Eur Heart J* 2017;38:1498–1508. https://doi.org/10.1093/eurheartj/ehx011; PMID: 28329361.

- **The effects of aerobic exercise on estrogen metabolism in healthy premenopausal women.** *Cancer Epidemiol Biomarkers Prev* 2013;22:756–64. https://doi.org/10.1158/1055-9965.EPI-12-1325; PMID: 23652373.

- **Age-related penetrance and arrhythmic risk in arrhythmogenic right ventricular dysplasia/cardiomyopathy-associated desmosomal mutation carriers.** *J Am Coll Cardiol* 2013;62:1290–7. https://doi.org/10.1016/j.jacc.2013.06.033; PMID: 23878885.

- **Novel risk calculator performance in athletes with arrhythmogenic right ventricular cardiomyopathy.** *Heart Rhythm* 2020;17:1251–8. https://doi.org/10.1016/j.hrthm.2020.03.007; PMID: 32200046.

- **Comparison of different prediction models for the indication of implanted cardioverter defibrillator in patients with arrhythmogenic right ventricular cardiomyopathy.** *ESC Heart Fail* 2020;7:4080–8. https://doi.org/10.1002/ehf2.133019; PMID: 32556295.

- **A new prediction model for ventricular arrhythmias in arrhythmogenic right ventricular cardiomyopathy.** *Eur Heart J* 2018;40:3650–8. https://doi.org/10.1093/eurheartj/ehy369; PMID: 30915475.

- **Comparison of functional right ventricular parameters in arrhythmogenic right ventricular cardiomyopathy/dysplasia based on signal averaged electrocardiograms.** *Int J Cardiol* 2014;174:628–33. https://doi.org/10.1016/j.ijcard.2014.04.169; PMID: 24820746.

- **Prognostic value of magnetic resonance phenotype in patients with arrhythmogenic right ventricular cardiomyopathy.** *J Am Coll Cardiol* 2020;75:2753–65. https://doi.org/10.1016/j.jacc.2020.04.023; PMID: 32498802.

- **Comparison of different prediction models for the indication of implanted cardioverter defibrillator in patients with arrhythmogenic right ventricular cardiomyopathy.** *ESC Heart Fail* 2020;7:4080–8. https://doi.org/10.1002/ehf2.133019; PMID: 32556295.