



Top Stories: Clinical Electrophysiology

Top stories on arrhythmogenic (right ventricular?) cardiomyopathy

Alessio Gasperetti, MD, PhD, Hugh Calkins, MD, FHRS

(Heart Rhythm 2025;22:872–873) © 2024 Heart Rhythm Society. All rights are reserved, including those for text and data mining, AI training, and similar technologies.

The switch from a phenotypic to a gene first approach to diagnosis and management of arrhythmogenic cardiomyopathy

For the past several decades, research on arrhythmogenic right ventricular (RV) cardiomyopathy has focused on describing the clinical features, genetic underpinnings, and natural history of patients with this condition. Crucial to the field were the initial diagnostic criteria proposed in 1994 and later revised in 2010. As the genetic basis of arrhythmogenic right ventricular cardiomyopathy (ARVC) was discovered, it became clear that the clinical spectrum of ARVC was broad and that the previous “one size fits all” approach to the diagnosis of ARVC did not work. We now recognize that the many genetic subtypes of ARVC have different clinical features, arrhythmia risks, and natural histories. For this reason, the field of arrhythmogenic (not only RV anymore) cardiomyopathy (ACM) has undergone a profound shift toward a genotype-centered approach. This new gene-first approach to diagnosis and management of ARVC was the focus of a large (>100 participants) international conference of ACM experts in Zurich organized by Professor Firat Duru. The first publication we have chosen is a review article describing the new “gene first” approach.¹ Based on the Zurich conference a larger publication of gene-specific guidelines for managing ACM is expected by the end of 2025.

Characterizing desmoplakin cardiomyopathy

The perfect example of a gene-specific approach to ACM is given by the desmoplakin (*DSP*) gene. Pathogenic/likely pathogenic (P/LP) variants in *DSP* are associated with the development of an ACM phenotype whose unique characteristics were not fully appreciated in the past, as those patients were often diluted as part of larger, multigenotype ACM cohorts. A large, gene-specific, multicenter network leveraged data from 800 patients with *DSP* P/LP variants to describe this left ventricular (LV) predominant form of ACM, here shown at high risk of

ventricular arrhythmias (VA) and heart failure (HF) episodes.² Female patients were reported at higher risk of VAs, in contrast with most of other forms of ACMs in which male patients are at higher risk. A strong association of this genotype with episodes of myocarditis was reported, as well as their prognostic value, as a significant worsening in outcomes after the occurrence of these episodes was observed (2.3x and 5-fold increases in VA and HF episodes). These findings show how gene-uniform cohorts can enhance our understanding of individual characteristics and the natural history of different forms of ACM.

Characterizing desmin-related ACM

A similar gene-first characterization effort was recently pursued for the desmin (*DES*)-associated ACM phenotype. In the largest cohort available to date, the characteristics of 87 patients with *DES*-related ACM were described.³ These patients developed an LV-dominant ACM with high familial penetrance, frequent ring-like LV scarring, and a substantial VA burden. This phenotype presented similar phenotypical characteristics to lamin A/C (*LMNA*)-associated cardiomyopathy, albeit with distinct gene-specific risk factors, as the association of female sex with improved outcomes (not seen in *LMNA*-ACM). These data again reinforce the importance of genetic testing of patients with ACM, as very similar phenotypes can have different risk factors and prognoses, depending on the genetic substrate.

Gene-specific risk stratification: tailor algorithms for implantable cardioverter defibrillator insertion in different genotypes

Current guideline-recommended VA risk-stratification tools (ie, the ARVC Risk Score) have been shown to underperform in patients with specific genotypes (ie, *DSP*, desmoglein/desmocollin). The *DSP* Risk Score is a gene-specific risk-stratification algorithm meant to help clinicians gather reliable estimates for patients specifically carrying *DSP* P/LP variants.

From the Division of Cardiology, Department of Medicine, Johns Hopkins University, Baltimore, Maryland.

<https://doi.org/10.1016/j.hrthm.2024.12.024>

1547-5271/\$-see front matter © 2024 Heart Rhythm Society. All rights are reserved, including those for text and data mining, AI training, and similar technologies.

Developed and internally validated using 471 DSP P/LP variant carriers without any previous VA episodes, this novel risk score integrating 4 major risk factors (female sex, previous nonsustained ventricular tachycardia, 24-Holter arrhythmia-burden, and moderate-to-severe RV dysfunction) performed well in this cohort (C statistic 0.782).⁴ This study represents a clear example of how a genotype-first approach leads to the development of more precise and tailored instruments for informing clinical care.

Acting on a gene-specific etiology: the promises of gene therapy

The main promise of a gene-first approach is represented by the hope of a gene-specific etiologic therapy to correct the DNA variant leading to the clinical ACM phenotype. In-human results for ACM gene therapies are yet to come (with several studies actively enrolling in phase 1 and 2 stages). Previous studies in murine models demonstrated the efficacy of gene therapy for plakophilin-2-associated disease through a viral vector. In a recent study, the use of adeno-associated virus vector of serotype rh.74 (AAVrh.74) led to a complete restoration of *PKP2* expression in a cardiac-specific knockout mouse model, preventing RV dilation, arresting LV functional decline, and mitigating VA burden.⁵ These results offer a clear

example of how a gene-first approach to ACM will help guide treatment.

Funding Sources: None.

Disclosures: Dr Calkins is a consultant to Abbott, Medtronic, and Boston Scientific. The Johns Hopkins ARVC Program receives research support for Lexeo and Tenaya Inc. Dr Gasperetti has no conflicts of interest to disclose.

Address reprint requests and correspondence: Dr Hugh Calkins, Sheikh Zayed Tower 7125R, 1800 Orleans Street, Baltimore MD 21287-0409. E-mail address: hcalkins@jhmi.edu

References

1. Muller SA, Bertoli G, Wang J, et al. Arrhythmogenic cardiomyopathy: towards genotype based diagnoses and management. *J Cardiovasc Electrophysiol* 2024; Available at: <https://doi.org/10.1111/jce.16519>.
2. Gasperetti A, Carrick R, Protonotarios A, et al. Clinical features and outcomes of 800 patients harboring desmoplakin pathogenic variants. *Eur Heart J* 2024;ehaes571.
3. Bermudez-Jimenez FJ, Protonotarios A, García-Hernández S, et al. Phenotype and clinical outcomes in desmin-related arrhythmogenic cardiomyopathy. *JACC Clin Electrophysiol* 2024;10:1178–1190.
4. Carrick RT, Gasperetti A, Protonotarios A, et al. A novel tool for arrhythmic risk stratification in desmoplakin gene variant carriers. *Eur Heart J* 2024; ehae409.
5. Van Opbergen CJM, Narayanan B, Sacramento CB, et al. AAV-mediated delivery of plakophilin-2a arrests progression of arrhythmogenic right ventricular cardiomyopathy in murine hearts: preclinical evidence supporting gene therapy in humans. *Circ Genom Precis Med* 2024;17:e004305.