Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC) Externally-Led Patient-Focused Drug Development (EL-PFDD) Meeting

Meeting Date: Tuesday, June 20, 2023

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Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC) Voice of the Patient Report

The Sudden Arrhythmia Death Syndromes (SADS) Foundation exists to save the lives and support the families of children and young adults who are genetically predisposed to sudden death due to heart rhythm abnormalities. This *Voice of the Patient* report was prepared on behalf of the SADS Foundation as a summary of the input shared by families and caregivers living with arrhythmogenic right ventricular cardiomyopathy (ARVC) during an Externally-Led Patient Focused Drug Development (EL-PFDD) meeting, conducted virtually on June 20, 2023.

Authors and Collaborators: This report was prepared and submitted on behalf of SADS by Alice Lara, RN, BSN, CEO & President; Marcia Baker, MS Ed, Program Director; Anna Goodson, Communication Director; and Genevie Echols, RCIS, Family Support Director, all from the SADS Foundation, and by Chrystal Palaty, medical writer.

Consulting Partners include Larry Bauer, RN, MA, and James Valentine, Esq. and from Hyman, Phelps & McNamara, P.C.

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James Valentine, Esq. and Larry Bauer, RN, MA are employed by Hyman, Phelps & McNamara, P.C., a law firm that represents patient advocacy organizations and companies that are developing therapeutics and technologies to advance health.

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Point of Contact: Please contact Marcia Baker, MS Ed, Program Director (SADS@SADS.org) for questions related to this report.

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Thank you to the many representatives from industry, federal agencies, and physician scientists from across the world who attended our meeting and who, on a daily basis, are striving towards a better understanding of the basic and translational science. Thank you for helping to move us closer to future clinical trials. Our hope is that this meeting will encourage future research and successful new product development for people living with ARVC who urgently need better treatment options.

The SADS Foundation would like to thank the ARVC community members who took the time to attend this meeting. Thank you to our speakers, panelists, and callers for so honestly sharing how ARVC and its current treatments affect you on a day-to-day basis. This meeting would not have been possible without each of you.

Key ARVC Insights

1. **Arrhythmogenic right ventricular cardiomyopathy (ARVC) is a rare, progressive genetic disease, that can lead to heart failure and death**. Diagnosis is often unexpected and multiple family members can be affected.
2. **The most burdensome ARVC-related health effects include arrhythmias/palpitations, fatigue, anxiety/depression**, **exercise intolerance, sudden cardiac arrest, and heart failure.** Many live with a combination of these symptoms. Symptoms are interconnected; arrhythmias, palpitations and shocks cause anxiety and PTSD, which can result in more arrhythmias, palpitations, and shocks. ARVC is progressive and 49% of those living with ARVC develop heart failure.
3. **ARVC families have many worries.** They worry about other family members, especially younger adults, teens, and children who have inherited an ARVC gene variant and do not yet show symptoms. They worry about progression to heart failure, death, and sudden cardiac arrest. They worry about arrhythmias and palpitations leading to more shocks**.**
4. **ARVC impacts the entire family.** Exercise promotes progression, so exercise and participation in sports is restricted. This worsens anxiety and depression and forces many affected with ARVC to reconsider their self-identities and family roles, further contributing to the tremendous mental health burden of this disease.
5. **Despite the potentially life-threatening manifestations and daily symptoms and impacts of ARVC, there are no FDA-approved treatments that are curative or stop progression.** Individuals living with ARVC require multiple medical therapies to manage their disease, including implantable cardioverter-defibrillators (ICD) and combinations of medications. Most also use exercise moderation and lifestyle modifications to manage symptoms.
6. **Treatments and lifestyle choices improve quality of life but are accompanied by significant downsides.** ICDs cause sudden unexpected shocks, leading to major depression, anxiety, and PTSD. Side effects of beta blockers and antiarrhythmic medications impact quality of life. Some patients require multiple cardiac ablations. Some living with ARVC will eventually require a heart transplant.
7. **Individuals living with ARVC need new treatments to stop advanced heart failure, arrhythmias/palpitations, and the risk of sudden cardiac arrest.** Although even minor medication improvements would improve their quality of life, they need a disease modifying therapy such as gene therapy. Heartbreakingly, many living with ARVC recognize that it is too late for a disease modifying treatment for themselves but wish for a treatment to help others, especially for those who are still asymptomatic. They also need improved/enhanced ICD/devices, medications with fewer side effects, more ARVC education, awareness and research, and more mental health support.

Contents

ARVC Clinical Overview[1]

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is a rare, genetically determined disease. ARVC causes a progressive replacement of right ventricular myocardium with fatty and fibrous tissue, leading to the weakening of the right ventricle (RV), resulting in irregular heartbeats or ventricular arrhythmias. ARVC is referred to as an arrhythmogenic cardiomyopathy, as a left-dominant or biventricular form of the disease is also included in the ARVC disease classification.

ARVC was first described in 1982. The disease is rare, occurring in one in 5000 in the US, as compared to hypertrophic cardiomyopathy, which is one in 500. ARVC is slightly more common in men than in women, and accounts for 5% of sudden deaths in young individuals in the United States, with a slightly higher incidence in Italy.

Two-thirds of patients have a genetic variant affecting desmosome proteins which function to connect one cell to another. Affected genes include plakophilin-2 (*PKP2*), desmoplakin (*DSP*), desmoglein-2 (*DSG2*), plakoglobin (*JUP*), and desmocollin (*DSC2)*. ARVC can also involve other, non-desmosome proteins. Patients without an identified ARVC genetic variant are referred to as "gene elusive".

Having a genetic variant alone is just one factor in disease development; multiple clinical studies have demonstrated that exercise exacerbates the disease in those at risk for developing ARVC. Athletes or endurance sports participants with the gene have a much higher risk of developing heart failure over time. The identification of a genetic variant in a young person is a strong enough predictor of the disease that these individuals are recommended to prophylactically avoid competitive and endurance sports.

ARVC typically presents around the age of 29, with palpitations, syncope (fainting), sudden death, or resuscitated sudden death. Approximately 10% of ARVC patients are diagnosed after experiencing a resuscitated cardiac arrest or sudden cardiac death.[2] About 70% of those living with ARVC experience ventricular arrhythmia at least once during their lifetime. ARVC is a progressive condition with a gradual decline of right and left ventricular function and right ventricular dilation. Heart failure is a late manifestation of ARVC, usually occurring 10-20 years or more after the first symptoms develop. Half of patients develop heart failure symptoms, and some require a heart transplant.

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[1] Clinical overview was extracted from the presentations made at the June 20 ARVC EL-PFDD meeting by Dr. Hugh Calkins, Professor of Cardiology and the Director of the Electrophysiology Lab and Arrhythmia Service at Johns Hopkins, and Dr. Harikrishna Tandri, Chief of Cardiac Electrophysiology at Vanderbilt University Medical Center.
[2] Krahn AD, Wilde AAM, Calkins H, La Gerche A, Cadrin-Tourigny J, Roberts JD, et al. Arrhythmogenic Right Ventricular Cardiomyopathy. JACC: Clinical Electrophysiology. 2022;8(4):533-53.

ARVC is managed with a multi-prong approach.

(1) **Accurate diagnosis**. ARVC diagnostic criteria were updated in 2010 and include ECG T wave inversions, specifically a terminal activation delay in V1 and MRI changes. Diagnosis is confirmed through biopsy, family history and the presence of a pathogenic variant.

(2) **Stratify risk.** Patients are risk stratified for the risk of sustained ventricular tachycardia or sudden death and the need for an implantable cardioverter-defibrillator (ICD). Validated prediction models for ventricular arrhythmias are in widespread use and can be accessed at www.ARVCrisk.com.

(3) **Reduce arrhythmia burden.** In addition to an ICD, first line therapies include beta blockers, antiarrhythmic drugs. Second line treatment is radiofrequency catheter ablation. If symptoms persist, cardiac sympathetic denervation is used to sever a nerve bundle from the brain down to the heart to reduce arrhythmias.

(4) **Prevent progression of cardiomyopathy and ventricular dysfunction**. Exercise restriction is essential to reduce the risk of progression and those living with ARVC are advised not to participate in endurance or competitive sports. Approaches to potentially reduce structural progression include angiotensin converting enzymes (ACE inhibitors) and aldosterone receptor blockers (ARBs). Gene therapy is emerging as a potential approach for reducing structural progression. Although current approaches focus on the plakophilin (*PKP2*) gene, desmoplakin (*DSP*) and desmoglein-2 (*DSG2*) genes are being investigated in animal models.

(5) **Cascade family screening**. As ARVC is an inherited genetic disease, after one person is diagnosed, all first-degree family relatives need to be screened.

ARVC EL-PFDD Meeting summary

The Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC) Externally-Led Patient Focused Drug Development (EL-PFDD) was held virtually on June 20, 2023. The meeting was an important opportunity for the Sudden Arrhythmia Death Syndromes (SADS) Foundation to share patient perspectives regarding the symptoms and daily impact of ARVC, as well as current and future approaches to therapies. The meeting was cohosted by **Genevie Echols**, RCIS, Family Support Director, the SADS Foundation, and **James Valentine**, Esq. from Hyman, Phelps & McNamara, P.C.

Genevie Echols opened the meeting by welcoming all meeting attendees including the members of the US Food and Drug Administration. She introduced **Dr. Chinwe Okoro**, MD, Medical Officer, Division of Clinical Evaluation and Pharmacology/Toxicology, from the Center for Biologic Evaluation and Research, CBER at the FDA. In her opening remarks from the FDA, Dr. Okoro described how this EL-PFDD meeting will help the FDA to obtain insights from ARVC experts, the caregiver and patients living with the disease. She thanked the ARVC community for attending the meeting and sharing their personal stories, experiences, and perspectives.

Dr. Hugh Calkins, MD, Director, Johns Hopkins ARVC program presented a clinical overview of ARVC which served as a foundation for the first half of the meeting. **James Valentine** provided an overview of the meeting structure and invited all individuals living with ARVC to contribute their voices through online polling, calling in by phone, and to contribute written comments using the online portal.

Over 200 unique viewers attended the livestream, including 88 individuals living with ARVC, 22 family members, 16 parents/caregivers, 11 from the government, 18 scientists and researchers, 31 from pharmaceutical and biotechnology industries, 9 healthcare providers, five from nonprofit organizations and two consultants.

Online polling was restricted to people living with ARVC and their caregivers. The vast majority of those participating in polling were individuals living with ARVC (84%). Others included caregivers of someone living with ARVC (13%) and caregivers of someone who has died from ARVC (4%). Most were from the United States (85%), with representation from all time zones. Others were from Europe and the UK (11%), Canada and Mexico (2%), and other (2%).

Most individuals living with ARVC represented at the meeting were female (65%). The largest group of patients represented were 31-50 years of age (40%), followed by individuals aged 51-70 years (39%). Participants were asked at what age they first had ARVC symptoms and at what age they were diagnosed with ARVC; results indicate that some individuals experience symptoms years before diagnosis. Results of demographic polling are shown in **Appendix 1.**

The ARVC EL-PFDD meeting was structured around two key topics. The morning session focused on *Living with ARVC: Symptoms and Daily Impact,* and the afternoon session focused on

Perspectives on Current and Future Approaches for ARVC Treatments. The meeting agenda is in **Appendix 2**.

The morning session continued with a pre-recorded panel of individuals who shared patient and caregiver perspectives on the symptoms and daily impacts of ARVC. James Valentine moderated a discussion between individuals in a live Zoom panel as well as those who dialed in by phone, and Genevie Echols read out relevant comments entered through an online portal. Meeting panelists and callers are listed in **Appendix 3.**

After a brief break, the afternoon session commenced with an ARVC treatment overview from **Dr. Harikrishna Tandri**, MBBS, Professor of Medicine in the Division of Cardiovascular Medicine at Vanderbilt University Medical Center. A pre-recorded panel of patients and caregivers described different medications and medical treatments as well as other approaches they use to address ARVC manifestations. Again, meeting attendees had an opportunity to participate in online polling, by calling in and submitting written comments. To conclude, **Larry Bauer, RN, MA** Hyman, Phelps, & McNamara provided a summary of key points. Genevie Echols closed the meeting by thanking all of the meeting attendees.

Online polling results from Topics 1 and 2 are included in **Appendix 4**. Additional patient comments were collected through the registration portal and an online comment submission portal was open for four weeks after the meeting to include as many patient voices as possible. All submitted patient comments are included in a separate PDF document, with selected comments included in the body of this report.

The ARVC *Voice of the Patient* Report

This *Voice of the Patient* report is provided to all ARVC community supporters including the US FDA, other government agencies, regulatory authorities, medical products developers, academics, clinicians, and any other interested individuals. The input received from the EL-PFDD meeting reflects a wide range of ARVC experiences, however not all symptoms and impacts may be captured in this report.

The final report, the accompanying document containing the submitted comments and a video recording of the meeting are available on the SADS Foundation website at https://sads.org.

Follow up Adjunct Scientific Workshop

As a follow up to the EL-PFDD, the SADS Foundation hosted an Adjunct Scientific Workshop on July 20, 2023. Invited experts reflected and discussed what patients said during the EL-PFDD and provided recommendations for integrating the patient voice into future therapeutic development. The SADS Foundation website at https://sads.org includes a video recording and a summary report of the ARVC Adjunct Scientific Workshop.

Session 1 – ARVC Symptoms & Daily Impact

Patients and caregivers shared their perspectives and experiences of living with ARVC through presentations, online polling, moderated discussion and submitted comments. They described ARVC-related health effects that they experienced, impacts of ARVC on activities of daily living, and their worries and fears for the future. Several themes emerged that were not captured in online polling.

Theme: An ARVC diagnosis is often unexpected. Many individuals diagnosed with ARVC are young, healthy and extremely athletic. Some have had no prior symptoms before their first episode, and many endure an extended diagnosis.

> *"I was an elite athlete at 20 years old and collapsed while I was competing as a rower for my university."* - Heather, living with ARVC for over 30 years
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> *"My first symptom that I had any problem with my heart was sudden cardiac arrest when I was 41. And fortunately, my neighbor, who's an anesthesiologist, was able to perform CPR and I actually survived."* - Susan, heart transplant recipient (*DSP* variant)
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> *"It wasn't until my sudden cardiac arrest three years ago in San Francisco when my ARVC presented itself. I was out with friends at a San Francisco speakeasy having fun and enjoying conversation where I lost consciousness for a moment. I experienced a sharp pain in my chest and thought, 'huh, that was weird'. …Still feeling the pain in my chest, I went to sleep thinking that everything would be fine until the next morning, I realized that something might be wrong."* - Julia, 31-years-old, living with ARVC

Theme: ARVC can affect multiple family members. Many were only diagnosed with ARVC after the death of a parent or sibling. Genetic testing permits children to be identified before the first ARVC symptoms appear.

> After Adam's wife Jackie died of a sudden cardiac arrest, both of their sons, *"tested positive for the DSP genetic mutation, known to be associated with ARVC. …Both of Jackie's siblings and three out of four of her nieces and nephews were also found to be gene positive. With seven living members of our family now genetically diagnosed and with ages ranging from seven to 45, the importance of unique patient focused treatment was obvious."* - Adam, husband of a wife who died at the age of 31, and father of two sons with ARVC (*DSP* variant)
>
> *"After my brother was diagnosed with ARVC (DSP positive) I underwent testing to find out if I had the same genetic mutation. Not only do I have the gene, but I went ahead and passed it on to all three of my children… 11 months, 3 years, and 6 years old."* - Paula, 33 years old, living with ARVC (*DSP* variant)

Tracy's daughter, *"was diagnosed with this disease at 10 years old. She had no symptoms, but she was PKP2 gene positive and had a strong family history of ARVC. Pediatric cardiologists followed her closely. They did MRIs at five and 10 years old and found significant changes to her heart structure enough for a formal diagnosis. She now has a defibrillator implanted and has started on beta blockers to hopefully slow the progression of the disease*." - Tracy, 46-year-old, living with ARVC (*PKP2* variant)

Theme: ARVC is a progressive disease that leads to heart failure and can result in death.

Those with ARVC live with fear, worry and feelings of hopelessness.

"It's the continued progression of the disease that breaks you." - Sean, living with ARVC

"My symptoms have gotten worse by the years, by the days, by the hours, by the minute." - Nelson, 51-year-old living with ARVC (*PKP2* variant)

"I am most frustrated by how ARVC is so inconsistent and there is no way to predict how it will progress. Despite limiting physical activity, following all of the meds and even an experimental surgery, my disease progressed to needing a transplant." - Maudi, heart transplant recipient

POLL Q1 & Q2

Arrhythmias/palpitations, fatigue and anxiety/depression are the most burdensome ARVC-related health effects.

Meeting attendees participating in online polling first selected all of the ARVC-related health effects that they experience, then selected the top three most burdensome. Most patients experience many health effects; each individual selected an average of 5.9 different symptoms. Poll question results are shown in **Appendix 4, Q1 and Q2** and illustrated below with selected patient quotes.

Arrhythmias and palpitations

Most individuals living with ARVC experience arrhythmias and palpitations, and these were selected as the most burdensome symptoms. Patients experience arrhythmias, tachycardia, and premature ventricular contractions (PVCs) in response to exercise, stress, anxiety, and sometimes, in response to nothing at all. Unfortunately, these events trigger anxiety, further worsening the condition. For those with an implantable cardioverter-defibrillator (ICD), arrhythmias can lead to both appropriate and inappropriate shocks.

"Last year, a seven-day Holter monitor showed I was experiencing 12,000 PVCs a day, a number that had doubled in the four years since my last monitor. I was so accustomed to the feeling of PVCs, my heart jumping in my chest in an immediate sense of anxiety during things like important work meetings, while sitting in traffic during rush hour or even as I was vacuuming the house. PVCs make me uncomfortably aware of my heart,

which often triggers more PVCs, a vicious cycle that is exasperated during times of stress, anxiety, and even dehydration." - Courtney, 29 years old, living with ARVC, sibling of a brother who died at age 17 from ARVC

"I had a sudden ventricular tachycardia storm out of the clear blue sky at age 47 in April of 2020 while standing at my kitchen counter. Over the course of a few hours, I had to be shocked in the hospital three times and put on several IV antiarrhythmic [medications] before my heart regained a normal rhythm." - Christy, living with ARVC (*DSP* variant)

"The arrhythmias often go hand in hand with anxiety surrounding our condition. One tends to precipitate the other. So that's definitely a struggle with ARVC and those of us who live with this because it's hard to know which comes first. You're having lots of palpitations and arrhythmia that can stir some anxiety for whatever reason, whether that's ICD, shocks, et cetera. And then being worked up and having that adrenaline really precipitates more arrhythmias." - Regina, diagnosed with ARVC eight years ago

Fatigue

Fatigue is experienced by three-quarters of those with ARVC and selected as the second most bothersome ARVC-related health effect. Fatigue can also be a medication side effect.

"The symptoms that affected me the most are the fatigue and arrhythmias. The symptoms of ARVC have a snowball effect with each effect causing a ripple in other aspects of your life. For me, it starts with the lack of energy and onset of fatigue. The fatigue has led to depression, social anxiety, weight gain, and has worked its way into every corner of my life, both physically and mentally." - Julia, 31-years-old, living with ARVC

"The fatigue caused by the heart failure from ARVC impacts my life the most. On my worst days, I struggle to do normal household tasks such as doing the laundry or vacuuming. But even on good days, I am limited by how far I can walk and have a limited ability to go upstairs and inclines. I can't do the things I most want to do. …I'm sure some of my fatigue and weakness comes from the medications I am taking." - Michelle, living with ALVC (*DSP* variant)

"I fatigue very easily just from kneeling down or standing up. Doing the littlest things, like walking exhausts me. At time, for no reason, or just standing will trigger PVCs, a weakness that fills my entire body, and I have to immediately lay on the sofa for days. I cannot even pick up my guitar and play for more than five minutes as my weakness and anxiety kicks in." - Nelson, 51-year-old living with ARVC (*PKP2* variant)

Anxiety or depression

Anxiety and depression are among the most frequently experienced ARVC-related health effects and are one of the most burdensome. The high levels of anxiety and depression

experienced by those diagnosed with ARVC emerged as a major EL-PFDD meeting insight. Many live in a state of "high alert" or are afraid to even move, lest they trigger more arrhythmias and shocks.

> *"The anxiety is very real when you're lying in bed, and you think you're safe in bed, and you can feel your heart rate accelerating and pounding. It's terrifying."*- Heather, living with ARVC for over 30 years

> *"From an emotional standpoint or psychological standpoint, it's a difficult disease to deal with. I liken it to walking in a minefield every day. You know something's going to happen. You don't know when and you don't know how severe it's going to be, but it's going to happen. Picture living with that every day."* - Darin, living with ARVC for 28 years

> *"I was very depressed for the first 18 months. I would say I'm now just under 'very depressed'. …I used to have a lot of confidence in my physical abilities, but now I am scared to try things."* - Michelle, living with ALVC (*DSP* variant)

In addition to anxiety and depression, many experience PTSD after sudden cardiac arrest, ICD shocks and VT storms.

> *"The mental health component is really important. …I had 30 shocks from my device, six one day, and then 25 a couple days later. And it took me about three years to mentally recover from that. I think the first year after I was in a despondent funk for about a year, and I would not even want to get up to go to the bathroom. I would try to get up as infrequently as possible. Taking a shower was like an act of God. It was a really, really, really horrible year."* - Alex, living with ARVC

> *"I even had what are considered phantom shocks in my sleep. Phantom shocks are when your body thinks you have had a shock because of the trauma your brain experiences from previous shocks. Sometimes the mental struggles are just as real and hard as the physical ones."* - Jason, 38 years old, living with ARVC

> "*The thing that has surprised me the most about this disease has been the mental hardships it has brought. … The anxiety, the PTSD, worry, insomnia. Driving, talking, even closing my eyes sometimes all suddenly became issues for me. …This device, diagnosis, and the effects of them have had a significant impact on my life, and assurances from doctors, nurses, and loved ones couldn't fix this."* - Jeff, 57-year-old living with ARVC

Exercise intolerance

Many individuals living with ARVC were athletic and extremely fit yet are no longer able to tolerate exercise. Unfortunately, when first diagnosed, some were instructed to exercise.

> *"[After COVID], it was deemed safe to start playing team sports again. But soon I began passing out playing soccer, having to sit down mid-point while playing ultimate frisbee, and I simply stopped getting stronger on my bike as my boyfriend got faster and faster with every ride we went on together."* – Jenny D., 48 years old, living with ARVC

> *"I ignored the symptoms for years and just carried on. ... When cycling uphill or running, I was always the slowest, on the flat I was able to keep up. Uphill, the air was simply scarce."* - Katja, living with ARVC (*DSG2* variant)

> Marsha was formerly an Ironman Triathlete. *"I was an active person for years and then suddenly started becoming light-headed, short of breath, and things just escalated."* - Marsha, living with ARVC (gene elusive)

Sudden cardiac arrest

During the EL-PFDD meeting, 28% of poll respondents reported having experienced a sudden cardiac arrest. For some, a sudden cardiac arrest is the first ARVC symptom experienced.

> *"I don't remember anything of the day of my cardiac arrest. I was literally on my way to work. I had my eight-year-old son in the backseat of the car. And the last thing I said to my nanny, because I had three kids, was 'I'm running late'. And little did I know that I would never make it to work that day or ever again. … it was a major life-altering thing that happened to me. But I'm so grateful that I actually survived because as we heard before, not everyone survives."* - Susan, heart transplant recipient (*DSP* variant)

> *"I had collapsed …my friend who recognized the symptoms of cardiac arrest made a coordinated effort to get me to the hospital. My heart rate was 236 beats per minute, and I was defibrillated twice after doctors tried other solutions to slow my heart rate down. My ICD was put in a day later after meeting the criteria and officially being diagnosed with ARVC."* - Julia, 31-years-old, living with ARVC

Many described the tragedy of a sudden cardiac arrest resulting in the death of a child, a sibling, a spouse or a parent.

> "*My vibrant loving 17-year-old brother collapsed during football practice from sudden cardiac arrest. Jake died on the field that day. He had no prior symptoms, and we had no family history of heart disease. I was away at college when I got the phone call, and my heart was broken."* - Courtney, 29 years old, living with ARVC, sibling of a brother who died at age 17 from ARVC

"My high school sweetheart and wife of seven years, Jackie and I were side by side on the outfield of a recreational softball game. When I last looked over at Jackie on this hot humid day, she was slumped in a pile on the turf. Despite being at her side in less than 30 seconds and despite a fellow player and trained firefighter administering CPR in less than 90 seconds, Jackie's first and only cardiac arrest had just robbed her of her last breath in that moment." - Adam, husband of a wife who died at the age of 31, and father of two sons with ARVC (*DSP* variant)

Other ARVC-related health effects selected in the polls

These include **light-headedness, dizziness and fainting**, **shortness of breath**, **weight loss or gain**, **chest pain or pressure**, **fluid retention/swelling in the legs** and **persistent cough**. Some of these health effects are ARVC-related, and others are caused by medications and treatments.

"The ARVC symptoms that impact me the most are fatigue, dizziness, weakness, shortness of breath with exertion, and rapid heart rate during periods of exertion or standing." - Alexa, 25-year-old living with ARVC (*DSP* variant)

"Recently, as a result of medication, I've had trouble breathing and going up the stairs. I feel like I'm going to die and can't keep up. It's very scary and I'm traumatized." - Allison, living with ARVC

"I used to engage in daily sports activities, but I have had to completely stop exercising. This change has led to a weight gain of approximately 45 pounds, causing significant unhappiness. My son expresses constant concern about the possibility of my demise, while my daughter intervenes if she believes I am pushing myself too hard. Navigating this disease feels like walking on eggshells." - Leigh, living with ARVC (*PKP2* variant)

"The swelling in my face and legs really didn't do much to boost a teenage girl's self-esteem. The medication challenges and changes to manage disease progression and fluid balance was also a struggle." - Joelle, aged 18, heart transplant recipient

Other ARVC-related health effects not included in the polls

Individuals living with ARVC described advanced heart failure requiring a **heart transplant**, ICD-related symptoms including **head pressure** and **superior vena cava syndrome**, **nausea**, **discomfort**, **leaky heart valves**, **low ejection fraction**, **hypoxic or anoxic brain injury**.

"If tachycardia is a loud, dramatic, roaring monster that rears its head at unpredictable times, heart failure is a quiet, slow caterpillar moving down a progressive path. This caterpillar has taken things from me as it moves along the path. The slow progression requires a constant process of accepting new limitations and adapting my life over and over again." - Tracy, 46-year-old, living with ARVC (*PKP2* variant)

"I have had complications related to my ICD leads narrowing my vessels. and have something called superior vena cava syndrome. … I get facial fullness, dizziness, and headaches as a result of bending over and lying flat." - Regina, living with ARVC

"Greg felt his ICD activate, called 911 himself, then passed out while on the phone. Despite his ICD attempting to restart his heart 30 times, the muscle did not respond on its own. In the hour that it took paramedics to reach Greg in his apartment to report vital signs and to get his heart pumping again, he had endured a severe anoxic brain injury. … Having recently turned 25, Greg now lives in a long-term care facility and is minimally responsive on his best days, requiring staff to perform all of his basic needs." - Adam, husband of a wife who died at the age of 31, and father of two sons with ARVC (*DSP* variant)

POLL Q3

ARVC is characterized by worry, especially for family members with the gene variant. Worries about progression to advanced heart failure, shortened lifespan and sudden cardiac arrest topped the poll results.

These worries contribute to the heavy ARVC mental health burden. Meeting attendees used online polling to indicate what worries them most about their condition in the future. Poll results are shown in **Appendix 4, Q3** and the top worries are listed below and illustrated with patient quotes.

Worries about family members with an ARVC gene variant. This worry was not captured in online polling, but was a key theme reiterated throughout the EL-PFDD meeting. ARVC families worry about when their asymptomatic children will start experiencing symptoms. They worry whether to prophylactically treat asymptomatic family members or to wait until after they symptoms emerge. Some worry about passing a gene variant to future children while others feel guilty for already having done so. Those who are gene elusive worry whether their children will be correctly diagnosed and treated. Only a few of the many patient comments are represented below.

"*While my child has no evidence of disease yet, we live in a state of anxiety that one day, symptoms will appear. We have been advised to limit our child's involvement in sports and notify schools/camps/caregivers of the risk of arrhythmia/sudden cardiac death to ensure that CPR and use of an AED is the go-to for any emergencies*." - Andrea, living with ALVC and mother of a child with the *DSP* variant

"I have three children, and this is a genetic disease, and two of them have the same DSP mutation that I did. …They're going to be monitored by a cardiologist annually for the

rest of their life. But I worry about that. I don't want them to have to go through what I've gone through. I mean, this disease is awful." - Susan, heart transplant recipient (*DSP* variant)

"*At present, none of the four younger members of the family have ICDs, each not showing enough evidence to warrant the procedure and treatment, at least according to the doctors. This part is tough, finding the balance between protecting our kids and allowing them to live as normal lives as possible, it can be excruciating*." - Adam, husband of a wife who died at the age of 31, and father of two sons with ARVC (*DSP* variant)

Worries about progression to advanced heart failure

The top worry selected by individuals living with ARVC is the worry about progressing to advanced heart failure. Patients worry about declining heart function, diminishing physical capabilities, treatments failing, becoming a burden on their loved ones, and eventually requiring a heart transplant. Even those with stable disease worry about progression.

"I fear that the heart failure will get worse (it's currently LVEF 35%) and that I will need a transplant some day." - Michelle, living with ALVC (*DSP* variant)

"I constantly worry about the current treatments that I'm on failing and becoming a burden to my husband, kids, and aging parents. - Jennifer C., living with ARVC (gene elusive)

"Shocks, pills, ablations, heart failure, heart transplant are the things I have to look forward to now; things I think about at night and the moment I wake up." – Ryan, living with ARVC

Worries about a shortened lifespan

The second most selected worry of those with ARVC is **a shortened lifespan**. Some described fears of not living long enough to see their children grow up.

"*When I was diagnosed, I was 20 years old and I was told by my electrophysiologist, 'You are on the cutting edge of mortality,' which means there wasn't many people that were much older than me that had lived.* - Heather, living with ARVC for over 30 years

"*Currently my biggest fears are shortened lifespan. I mean, the average age that someone lives with a heart transplant is 10 years. I'm almost four years in. Don't really like to think of it that way. Hope I'm going to be one of those that last 20 plus years."* - Susan, heart transplant recipient (*DSP* variant)

"Will I see my kids graduate from high school, college? See them get married and have kids? If I'm still around with grandkids, will I even trust myself to hold them safely?" - Jennifer C., living with ARVC (gene elusive)

Worries about a sudden cardiac arrest

Some with ARVC experienced a sudden cardiac arrest, so it is not surprising that this was a top worry selected in the polls. Some fear that they will die in front of their children.

> *"My daughter died of a sudden cardiac death in 2011 at the age of 14. … It is impossible to describe how great my fear of losing another child is. That's why I desperately hope that a therapy for ARVC will finally be found so that I don't have to experience this fate for the second time. No family should ever have to experience losing a child and even more other family members."* - Ruth, mother of a daughter who passed away from ARVC and a son with the *DSP* variant

> *"I am afraid that I will go into cardiac arrest in front of my kids and how that will affect them, especially if I don't survive. I really worry my kids also have ARVC and how that could affect them physically and emotionally."* - Sarah, living with ARVC

> *"Some of my fears are going into cardiac arrest when no one is around or triggering an ICD shock from overexertion."* - Julia, 31-years-old, living with ARVC

Worries about arrhythmias/palpitations and ICD shocks

The worry about experiencing arrhythmias or heart palpitations is accompanied by the worry about receiving ICD shocks.

> "*I find myself constantly checking my pulse. My Garmin watch rarely leaves my body. I must be aware of any type of physical exertion. Sometimes going up two flights of stairs with a laundry basket makes me sit down and worry about my heart. I'm not a big worrier. I don't believe it helps, but since diagnosis, I have found myself to be worrying about real or imaginary flutters in my heart.*"- Jason, 38 years old, living with ARVC

> *"I have watched my brother struggle the past few years with many hospital stays, several ICD shocks, trial and error with medication, cardiac ablation, and now PTSD from all the shocks. He lives in fear of doing anything that could cause a shock, so he stays home every day and doesn't do anything. That's no way to live."* - Paula, 33 years old, living with ARVC (*DSP* variant)

> *"I've been shocked by my ICD a dozen times. My ICD is constantly on my mind. I wonder when my ICD will go off again. I think about my ICD when I'm driving. I think about my ICD when I'm out and about. I worry about my ICD going off and having to go to the emergency room. I bought this Apple Watch so I can monitor my heart rhythm and rate at any time. Heart disease and my ICD affect my life in many ways."* - Jeff, 57-year-old living with ARVC

Other worries selected in the polls relate to worsening ARVC symptoms

The other worries selected in the polls all reflect disease progression and the worsening of ARVC related symptoms, described in the previous section. These include worries about

exercise intolerance, **fatigue**, **weight loss or gain**, **shortness of breath**, **light-headedness/dizziness/fainting** and **chest pain or pressure**.

Other worries not captured in the polls

Many of those living with ARVC selected "other" worries in the poll, and these fell into two general categories: **worries about family members**, a major meeting theme described at the beginning of this section and **worries about devices**. In addition to worries about ICD shocks, individuals living with ARVC worry whether their ICD will work when required and the number of devices they will need during their lifetime.

> *"A genuine fear for the future; what if my ICD doesn't work? What if I'm by myself or not near my phone?"* - Jennifer B., living with ARVC

> *"Looking ahead, the average life expectancy for healthy women in our country, is well into seventies and even beyond. I think about 'how many devices am I going to need?' and 'what are the complications related to device-related issues?' …We're facing these device changes every five to 15 years. And so that's something that I kind of keep in my mind, because with each procedure comes risks."* - Regina, diagnosed with ARVC eight years ago

POLL Q4

ARVC impacts the entire family. Exercising and participating in sports are particularly affected, forcing many to reconsider their self-identity and family roles.

Using online polling meeting attendees selected the top three activities that were most important to them, that they were NOT able to participate in, to the degree they would like, due to ARVC. The results of these poll questions are shown in **Appendix 4, Q4** and described with patient quotes below. A theme emerged that was not captured in online polling.

Theme: ARVC impacts the entire family. Many individuals living with ARVC are unable to interact as much as they want with their children and other family members due to exercise restrictions, fatigue, and medication side effects. Some have had to alter their family planning.

> *"Impact to family: They are under constant stress, worrying about me. Their lives are frequently disrupted by my medical needs, office visits, tests, and emergencies that result in abrupt hospitalizations. My withdrawal, reclusiveness, depression, anxiety, and irritability negatively impact their lives on a daily basis."* - Gary, living with ARVC

> *"The fatigue… affects the play time that I can enjoy with my kids, one of whom also has the same gene mutation."* - Sumant, living with ARVC

"*ARVC took my ability to have a second child, which I've accepted, but it still breaks my heart. Telling my only child, 'I don't have the energy to do that'. I am not the mother I want to be, but I am proud of the mother I am despite my limitations."* - Tracy, 46-year-old, living with ARVC (*PKP2* variant)

Exercising and participation in sports

Exercising and **participating in sports** were the top two most impacted activities selected in the polls. Many individuals living with ARVC used to be competitive athletes and now high intensity sports are no longer permitted as they can cause disease progression. They mentioned missing competitive cycling, mountain biking, running, competing in marathons and triathlons, martial arts, baseball, basketball, tennis, hiking, rock climbing, canyoneering, backpacking, kayaking, competitive swimming, and figure skating. For many, exercise was their top stress management or type 1 diabetes management tool. ARVC forced many athletes to reconsider their self-identity.

"My ARVC diagnosis came during the summer of 2017. Not only was I a four-sport athlete with my goal set very high in the figure skating world, I also participated in volleyball, basketball, and track and field. That year, I qualified for my first figure skating national showcase and was not able to participate due to the rapid progression of my disease." - Joelle, aged 18 and living with ARVC

"Imagine losing your favorite hobbies. Mine were long distance running, mountain biking, and being a volunteer firefighter. Notice how I said 'were'; those were unexpectedly taken from me during the summer of 2020 when I was diagnosed with ARVC. I used to think I was one of the healthiest people I knew, running marathons and participating in stair climbs with full firefighting gear on." - Jason, 38 years old, living with ARVC

"My passion was cycling. …I was diagnosed at age 49, so I'm fortunate that [ARVC] wasn't discovered until later in life, so I got to live a full life until then. …I lived and breathed cycling, in particular mountain biking, so that was my favorite thing to do. … Yes, I can go out and do an e-bike ride, but it's just not the same. It doesn't bring me the joy that I had before." - Kathy, diagnosed at age 49 with ARVC

"I've lost my body— the vessel in which I played and explored and enjoyed the world within. I realize that all along I foolishly expected that all my exercise and good habits (food, sleep, sobriety) entitled me to a healthy mobile fully engaged lifetime." – Jenny D., 48 years old, living with ARVC

Social interaction and participation

ARVC interferes in social interaction and participation. Depression, fatigue, risks of physical exertion, and anxieties about COVID infection limits socializing, play, participation in social events, parties, dinners, concerts and sporting events.

> *"I don't like going into crowds of people. When there are a lot of people around it makes me nervous because I don't want to get sick on top of whatever's going on."* - Melanie, living with ARVC for one year (*PKP2* variant)

> *"It's hard to explain to my son that I can't chase him or play soccer or lacrosse with him and breaks my heart every time he asks."* - Jason, 38 years old, living with ARVC

> *"In addition to the inability to physically participate in activities the loss of friendships has impacted me greatly. I have/had very active friends and because I cannot join in, I have been left out of many occasions. This has devasted me and made my mental health problems so much worse. I now spend most of my time alone with my husband who has been a godsend."* - Elizabeth, living with ARVC

> *"My wife, who enjoys socializing with others, is frequently unhappy with the negative impact to our social life resulting from my ever-increasing reclusiveness. Also, she worries when she observes my periods of very low energy and exhaustion."* - Gary, living with ARVC

Traveling outside my home area

Many are afraid to go on vacation or travel far away from their health care teams who understand their condition. After traumatizing events, some are afraid of even leaving their own neighborhoods.

> Shelly's husband loves to travel. *"He likes to go away, and unplug, and be out in the wilderness. He's an outdoor person. And I'm not comfortable doing that. So, there are a lot of compromises in terms of our travel."* - Shelly, diagnosed with ARVC at age 62

> "*I feel like if I am traveling or outside of my comfort of my own hospitals, of my own home, that people, physicians won't know the condition that I have and that could perhaps prevent appropriate and effective care. I fear for the uncertainty*." - Cassidy, 20 years old, living arrhythmogenic left ventricular cardiomyopathy (ALVC)

> *Jennifer experienced a VT storm when she was walking her dog. "I was by myself and had left my phone at home and didn't think anything of it as I was only going to be gone 10-15 minutes. … It was a terrifying experience. My husband and kids now walk our dogs*

and walking in the neighborhood is still an anxiety-inducing experience." - Jennifer B., living with ARVC

Performing my job

Many had to change or leave jobs because they could no longer meet physical requirements, their condition was considered a liability, or because they can no longer work alone.

> *"Firefighting was a major component of who I am, but now my gear has been passed down and the comradery is gone. Although my electrophysiologist signed off on a light duty version of being a firefighter - helping with training, rehab for firefighters, basic station duties - some of the officers at my local department thought it too much of a liability to simply have me around. I was forced to give up just one more thing that I loved dearly."* - Jason, 38 years old, living with ARVC

> *"I am a captain in the Air Force and can no longer look forward to being a Major (gaining rank). I am now restricted to serving only 20 years, which is just two years away and then I will have to navigate a new career way earlier than I ever expected."* - Leigh, living with ARVC (*PKP2* variant)

> *"I am an environmental biologist, so my job has changed considerably because I can't go out in the field by myself. … I can't really do the thing that I went to school for. … It's a really disheartening thing."* - Alex, living with ARVC

Attending school/work

Many have had to change employment or education plans after diagnosis. This can ultimately impact financial security. Younger patients are cautioned against high stress careers.

> *"ARVC took away my ability to work after going to school for many years and earning a master's degree. … With the loss of my ability to work, ARVC has taken my financial stability."* - Tracy, 46-year-old, living with ARVC (PKP2 variant)

> "*I've been told by countless physicians and people with ARVC that entering the medical field as a physician is not probably the best career choice for me, but this is something that I've dreamed about doing since I was younger."* - Cassidy, 20 years old, living arrhythmogenic left ventricular cardiomyopathy (ALVC)

> *"I can't hold a job due to side effects; I've lost many jobs. Even talking to people on the phone works me up. Friendships are impacted, I got divorced, I can't function. My parents take care of me. I'm afraid to be alone."* - Allison, living with ARVC

Being sexually active

Impacts on sexual activity were not discussed during the meeting, however marriage break-ups and the loss of friendships are just some of the relationship impacts of ARVC.

> *"ARVC has taken a toll on my relationships in my life. It's difficult for people to understand how sick I am because I look healthy. My 13-year marriage dissolved due to my ex-husband's inability to accept my heart failure and limitations. I'm not a reliable friend to make plans with because I may have to cancel if I'm too tired. Watching me slowly deteriorate is hard on those who love me."* - Tracy, 46-year-old, living with ARVC (*PKP2* variant)

Walking

With ARVC, even walking can be a challenge.

> *"I'm a pretty normal, healthy-looking 57-year-old man, but my body hides secrets that very few around me know about. I walk slow. I go up steps or hills even slower. I tire easily. I can't run anymore. I can't play most sports anymore. I can't really help family or friends move anymore. I constantly check my heart rate with my Apple Watch. I sometimes have insomnia. I suffer from anxiety that I've never known before."* - Jeff, 57-year-old living with ARVC
>
> *"Just walking up my driveway gets me very winded thanks to all the medications that I am on. I can't fully enjoy activities with my kids because I worry it's too hot out or it's too much walking (especially if in a hilly area). … I can't keep up with the walking pace of some of my coworkers and have to ask them to slow down."* - Jennifer C., living with ARVC (gene elusive)

Other impacts

Other impacts mentioned throughout the meeting and in comments include **interference with all activities of daily living** including chores, and **interference with sleep**.

> *"Housework is only possible to a limited extent and heavy work such as cleaning windows is hardly possible and EVERYTHING requires many breaks. What used to be possible in a few hours now takes several days and the activities have to be well thought out, planned and coordinated. In some cases, nausea and vomiting occur."* - Katja, living with ARVC (*DSG2* variant)
>
> *"I do not climb ladders, stand at the top of stairs, or any other situation where there is potential to lose balance and fall due to light-headedness or syncope. For the same reason, I limit the amount of driving by myself and with my family."* - Gary, living with ARVC

When Tracy could no longer work, *"I found other things to occupy my time, including reading, crafting, and cooking. I set a goal and read 100 books in 2013. Today I no longer read books because of brain fog from medications and heart failure fatigue makes it difficult to focus. I now listen to audiobooks."* Tracy, 46-year-old, living with ARVC (*PKP2* variant)

"When I experience arrhythmias at night I have difficulty to sleep, when I experience them in the day, I feel fatigued and have to lay down. I lose sometimes whole days like this for lack of sleep and fatigue." - Luise, living with ARVC

Session 2 – ARVC Current and Future Treatment Approaches

Through online polling, moderated discussion and submitted comments, patients and caregivers described all the different medical treatments used to manage ARVC-related symptoms, as well as non-medical approaches. They described the most significant drawbacks associated with each approach and articulated their hopes for a future ideal ARVC treatments.

POLL Q5

Individuals living with ARVC require multiple medical therapies to manage their disease, yet none are curative or stop the progression. All have significant side effects.

Using online polling, individuals living with ARVC indicated all the medical therapies that they had used in the past five years. Most require a combination of medications and medical approaches to manage their ARVC; each respondent selected an average of four types of medications that they have used. Results are in **Appendix 4, Q5** and described below with patient comments. A theme emerged that was not captured in online polling.

Theme: ARVC medication side effects are significant. Medication side effects have a negative impact on quality-of-life for many. Some felt that their side-effects were dismissed.

> *"There are not really any great options without any side effects. You're having to pick the lesser of two evils on that weighted scale."* - Courtney, 29 years old, living with ARVC, sibling of a brother who died at age 17 from ARVC

> *"These side effects and after effects were terrible to live with from a quality-of-life perspective, and yet they were easily treatable once identified. They had simply been overlooked."* - Jennifer A., 58 years old, living with ARVC

Implantable cardiac defibrillator (ICD or S-ICD)

Most poll respondents indicated that they or their loved one with ARVC has or had an ICD or subcutaneous ICD (S-ICD) surgically implanted.

> *"I was diagnosed with the same disease that took my brother's life despite having no symptoms. And within two months, I received my first subcutaneous defibrillator, a surgery that gave me three incisions along my chest and inside, and a device that could thrust an agonizing shock into my heart at any given time."* - Courtney, 29 years old, living with ARVC, sibling of a brother who died at age 17 from ARVC

> "*On a beautiful Sunday morning in the spring of 2010, while I was out for a long-distance run, I collapsed. At the age of 44, my strong and healthy heart had gone into a ventricular tachycardia recorded at 285 beats per minute. Moments after I arrived at the hospital, a code blue was called. Multiple defibrillations, two emergency transfers, six*

days in a series of cardiac procedures later, I was diagnosed with ARVC and received an implantable cardioverter defibrillator." - Jennifer A., 58 years old, living with ARVC

ICD downsides: shocks, surgery, nerve damage, superior vena cava narrowing and hard decisions to implant in younger patients. Although ICDs can be lifesaving, patients experience PTSD from previous shocks, and anxiety and worry about future shocks. ICD complications, malfunctions, and replacements necessitate additional surgical procedures. Side effects can include permanent nerve damage or narrowing of the blood vessels (superior vena cava syndrome). Because of these side effects, the decision to implant an ICD in a young person is very difficult.

"*Months after I was all healed up from my [ablation and ICD] surgery, I attempted to cut up a tree with a chainsaw which is something I rather enjoy doing. I could feel the arrhythmia develop and I quickly shut off the saw and set it down. As my son came up to check on me, the shock went off and it felt like someone kicked me in the chest. A very painful hit that took a few days to get over physically, but months mentally."* - Jason, 38 years old, living with ARVC

"I had a VT storm in August 2021 that caused me to get shocked 10 times in 26 minutes. The experience was horrific. The physical pain is immense yet momentary, but as others have noted, the psychological trauma is lasting. Even today, two years later, I still regularly have phantom shocks in my sleep and have recurring nightmares about getting shocked, as well as recurring anxiety in my daily life which I've never had before." - Samer living with ARVC

"I'm thankful I have my ICD, but I hate getting shocked. I've had seven ICD replacements; one recall, two bad leads. I've got a lead that's been cut and capped, so they basically left it in because the risk of removing it was very high." - Darin, living with ARVC for the 28 years

Beta blockers (ex. metoprolol, bisoprolol, atenolol, carvedilol, nadolol)

Beta-blockers are a first line therapy for ARVC patients and were selected by most poll respondents. These medications work by blocking the cardiac beta receptors (for adrenalin) to reduce adrenaline-derived ventricular arrhythmias or neurologically driven ventricular arrhythmias. Beta blocker downsides: medication efficacy varies from one patient to another, efficacy diminishes with time, the medication can be poorly tolerated, and side effects can limit compliance. Those with low blood pressure may be unable to take these medications.

"Each of the seven members of the family are currently being treated with medicine based on their own unique progression of the condition. In all, potassium, magnesium,

bisoprolol and metoprolol have all been used to manage Greg's risk. Ben has been exclusively on bisoprolol since his diagnosis four years ago with slight changes to the dosing along the way." - Adam, father of two sons with ARVC (*DSP* variant)

"[After trying an antiarrhythmic medication] I was switched to metoprolol, and although that worked well for a while, it did not control my arrhythmias even as they increased the dosage after previous episodes." - Christy, living with ARVC (*DSP* variant)

"My younger son also experienced medication side effects including light-headedness and tiredness, which made getting him to stay on medication very difficult, particularly during the high school years." - Jennifer A., 58 years old, living with ARVC

"Atenolol contributes to fatigue, exhaustion, lowers blood pressure, and bradycardia." - Gary, living with ARVC

Antiarrhythmic medications (ex. flecainide, sotalol, amiodarone, mexiletine)

Antiarrhythmic medications block various types of receptor channels in the heart to reduce arrhythmias and palpitations. Antiarrhythmic downsides: flecainide can induce new arrhythmias in patients with significant structural disease, can cause side effects such as blurry vision and shortness of breath, and is contraindicated in those who want to start a family. The other medications can cause side effects, especially amiodarone, which can potentially cause thyroid, liver, and kidney toxicity.

"I tried a trial with the antiarrhythmic flecainide, which ironically made my PVCs worse. Very frustrating when a medication that is supposed to help that, would make it worse." - Lizzie, living with ARVC (gene elusive)

"I've been on sotalol probably most of the time I've had ARVC. I was on mexiletine for a while until I had that VT storm. I was able to come off the mexiletine, which is great because it caused me an ulcer." - Darin, living with ARVC for the 28 years

"I start every morning with a dose of heart medication and end every night with two more doses. Both of my medications cause symptoms like fatigue and dizziness, and one even impacts my vision. I have to be conscious about blood draws to gauge potential impacts on my kidneys and liver. And one medication [flecainide] is unsuitable for pregnancy. So careful family planning is also important. The side effects and possible long-term implications of these medications are panic-inducing at times." - Courtney, 29 years old, living with ARVC, sibling of a brother who died at age 17 from ARVC

Ablation to treat arrhythmias

Half of the poll respondents have had an ablation procedure to treat arrhythmias. Ablation downsides: surgical complications including pericarditis and fluid build up around the heart, and many individuals had to have the procedure repeated multiple times. Others described experiencing a reduced ejection fraction as a result of their ablation.

> *"An ablation procedure I received in 2015 transformed my disease progression. I was living with the daily trials of an advancing ARVC symptoms where thousands of daily PVCs and random and seemingly unprovoked VT - both sustained and nonsustained - presented challenges that I was barely able to manage emotionally and physically. The ablation reduced the PVC load to a near normal number for even a non-ARVC subject and my sustained VT have vanished with nonsustained VT only appearing a few times a year."* - Chris, living with ARVC

> *"I've had nine ablations, both endo and epicardial. The worst ablation I've had, both at once, which was seven-hour surgery. I almost died during the surgery because my vitals plummeted and I went into atrial fibrillation because of this procedure just a month later, and had to start taking a new medication. …My last ablation was just a month ago, and although it went well, I know that in just a few months, it will, very likely I will need another surgery to try to manage my arrhythmias."* - Nelson, 51-year-old living with ARVC (*PKP2* variant)

ACE inhibitors (ex. lisinopril and enalapril)

Many individuals living with ARVC described taking ACE inhibitors to treat heart failure, but some experience side effects including fatigue, dizziness and light-headedness, especially those with already low blood pressure.

> "*I take a blood pressure medicine to slow the progression and I have cut out most sports or activities that raise my heart rate, except occasionally playing tag with my kids because they need their mom to be normal sometimes."* - Sarah, living with ARVC

> *"While I am grateful there are medications that exist, being on most of them have trade offs. I have low blood pressure and am limited on what beta blockers and ACE inhibitors I can take and deal with fatigue and dizziness."* - Andrea, living with ALVC (*DSP* variant) and mother of a gene-positive child

Blood thinners (ex. warfarin [Coumadin], apixaban [Eliquis], rivaroxaban [Xarelto])

Although many are prescribed blood thinners, these are accompanied by side effects including potential bruising and bleeding.

> *"Warfarin was added to the regimen and led to weekly blood draws. Figure skating and blood thinner do not work well together, so protecting my head from falls was another*

downer, and my protective helmet added a piece of equipment." - Joelle, aged 18, heart transplant recipient

"The rivaroxaban prevents use of NSAIDS and promotes my fear of playing sports due to potential injury as well as auto accidents." - Gary, living with ARVC

Heart transplant

Heart transplant is currently the ultimate treatment for ARVC and heart failure. Less than 10% of poll respondents have experienced a heart transplant, and since donor hearts are rare, not all will have this life-saving option available for them. Even with a successful transplant, a transplanted heart has an average lifespan of 10 years, patients still require medications including anti-rejection medications, and a transplant cannot alleviate the PTSD from years of progressive heart failure.

"I received an ICD at diagnosis in 2006, followed by starting beta blockers a year later. Then I would go on to try at least five different beta blockers over the years, received many ICD shocks, had multiple ablations, a bilateral sympathectomy, and yet I still continued to develop severe heart failure. The most recent treatment option was a last resort, a heart transplant at the beginning of 2023." - Maudi, heart transplant recipient

Joelle received a new heart at the age of 14. *"Many people have asked, 'What does it feel like to receive a new heart?' While it is indescribable, I can now say that when I fall asleep at night, I can now hear a normal beating heart."* Joelle described downsides*. "I am just balancing another lifestyle after transplant. I still have daily medications interrupting my day, checkups every six months, and I have new precautions to deal with. I can't eat some of the foods I love. I have mouth sores from medications."* - Joelle, aged 18, heart transplant recipient

"*Two years ago, … I was evaluated for heart transplant. My antibodies are unusually high and my body chemistry will outright reject 93% of the available hearts. So, my wait for a heart match is currently long and hard. I'm still working on accepting and adapting to this fact. As discouraging as the sounds, I am determined to find my perfect heart match and have a successful transplant."* - Tracy, 46-year-old, living with ARVC (*PKP2* variant)

Cardiac sympathetic denervation

Thoracoscopic surgery is used to sever the nerve bundle from the brain to the heart to reduce arrhythmias in ARVC patients who have failed catheter ablation. Downsides include surgical complications, pain, and the risk of drooping eyelids (Horner syndrome).

"A bilateral sympathectomy is when the doctors knock out both of your lungs on both sides of your body, cut out and remove a big piece of your nerve to reduce the heart's electrical activity. The pain after the particular surgery was excruciating. It took me a year to recover, and even to this day I have side effects, including droopy eye, or ptosis, heavy sweating, back pain, scars all over my body. Despite the suffering, it does not fix the root cause of the problem or the arrhythmia." - Nelson, 51-year-old living with ARVC (*PKP2* variant)

"*As Nelson spoke about, it is not a surgery to be taken lightly. It has a number of side effects afterwards. I've had the back pain. I have had drooping eyelid, which I just actually had another surgery recently to correct. On the positive side, I have had no further VT storms or shocks or registered VT on my ICD since that procedure."* Jennifer B., living with ARVC

"I had the bilateral sympathectomy and it eliminated the VT burden, drastically reducing my dependence on high doses of beta blockers … and it also reduced the number of shocks I received. However, I sustained a severe post op injury, damaging my brachial plexus due to my arm being hyperextended during surgery, … I still have limited use of my right hand and severe nerve pain. Unfortunately, this experimental surgery didn't help the advanced heart failure I had already developed, and I still ended up needing a transplant." - Maudi, heart transplant recipient

Other medication or other medical therapy

A small proportion of individuals selected **experimental medications as part of a clinical trial** as a poll response, yet no one discussed this during the meeting. A quarter of poll respondents indicated that they had tried other medications or medical therapies, including combination formulations, heart failure medications, and monitoring.

Other medications, especially combination formulations. These include immune-suppressants, allergy medications, anti-depressants, blood pressure medications, diuretics as well as heart failure medications/diuretics and diuretic/blood pressure medication/beta-blockers combinations, some of which had significant side effects. Some patients just avoid contraindicated medications.

"I am on an immunosuppressant to prevent flares of myocarditis associated with the DSP gene mutation, but that puts me at increased risk for infection." - Andrea, living with ALVC (*DSP* variant) and mother of a gene-positive child

"Spring seems to be a trigger for increased PVCs and VT for me and suspecting that it's allergies, I include Zyrtec to my medications in the spring. …Anxiety has also been a trigger, so I've been managing that with Zoloft." - Jennifer C., living with ARVC (gene elusive)

"I do not take any non-essential medications, such as NSAIDs, azythromycin, and other drugs that are known to prolong the QT interval or invoke cardiac dysrhythmias." - Gary, living with ARVC

Heart failure medications. Many individuals require medications such as milrinone, sacubitril/ valsartan to maintain cardiac function. These can include side effects such as liver toxicity.

Joelle received a heart failure medication prior to her transplant. "*I was told this drug is my rocket fuel, and it was required for me to be listed higher on the transplant list. In the words of my cardiologist, 'she's on a trajectory to death'."* - Joelle, aged 18, heart transplant recipient

Monitoring. This includes the CardioMEMS, a small paperclip size device that measures the blood volume as well as ongoing monitoring for asymptomatic teens/young adults using Loop or Holter monitors. Many mentioned using Garmin or Apple watches to monitor their heart rates.

POLL Q6

Exercise moderation is the top non-medical approach to manage ARVC symptoms, but most try many different approaches.

Using online polling, individuals living with ARVC indicated what they were doing to help manage ARVC symptoms besides medications and medical treatments. Each respondent selected an average of 5.5 response options. Poll results are shown in **Appendix 4, Q6** and described below.

Exercise moderation

Exercise moderation is the top approach for non-medical ARVC symptom management. This approach is particularly challenging for individuals who were extremely athletic and even competitive athletes before their diagnoses.

"I attempt to manage my condition and symptoms by staying hydrated, avoiding physical activity and overexerting myself and/or by shortening the duration of the given activity." - Gary, living with ARVC

"Exercise reduction has been a very difficult "treatment" plan to follow as a former endurance athlete." - Lizzie, living with ARVC (gene elusive)

"Upon diagnosis, I got a dog, and so we do all kinds of fun things together. So I can still walk, I can do light hikes and things like that, but you don't understand… my passion was cycling. I lived and breathed it. So, having that taken away from me was just a punch in the gut." - Kathy, diagnosed at age 49 with ARVC

Avoiding caffeine, reducing or eliminating alcohol use, and dietary changes/hydration

Many have made lifestyle and dietary changes to protect their hearts, to manage symptoms and to lose weight.

> *"I restrict my diet e.g. eliminate caffeine, alcohol, chocolate, etc. I obtain an adequate amount of sleep and try to reduce stress through mindfulness. When ill, I have to treat fevers more aggressively than I otherwise would."* - Gary, living with ARVC

> *"I cut alcohol to make sure I wasn't giving my heart more than it could handle, and I will never forget being told, 'I wish you were drinking so we could have fun again'."* Julia has no regrets about this decision. *"I knew that what I was experiencing was impactful, required my intention, and in reality made sure that I was putting my health first."* - Julia, 31-years-old, living with ARVC

> *"Hydration has also been a big thing for me. Making sure that I get enough electrolytes in a day has really been useful."* - Melanie, living with ARVC for one year (*PKP2* variant)

Self-education or peer support

Many patients rely on continuing education and participation in ARVC-specific support groups to alleviate the anxiety and depression associated with the disease, to overcome a sense of denial and to accept their diagnosis, and to manage self expectations. Several emphasized the importance of finding the right support group.

> *"Only time, and help from my ARVC, and SADS support groups, and my support team have got me to the place I am today."* - Jeff, 57-year-old living with ARVC

> For Michael, support groups are, *"the driver that's really helped our family navigate a lot of the tragedy that's happened. … I was in denial. I didn't want to believe I had [ARVC]. …Those support groups and talking to people in all these different stages in the spectrum of how ARVC is affecting them has been really helpful, and it's been really helpful for my mental state."* - Michael, living with ARVC

> "*Before I found the SADS Foundation, there were a few other support groups, but many of them, really were focusing in on the negatives. …The more I kept on hearing about that, the more that started to build anxiety with myself, more worry. At one point, I stepped away from that and then I just felt, "Okay, well, I probably have to do this on my own, or with the support of my family*." - Allen, living with ARVC, on the transplant list

Modification/accommodation at home/work/school

Many choose to work less or adjust what they did at home.

"I used to manage up to 15 employees and had a very [ambitious] career before the diagnosis. … I made changes to reduce my workload and reduce management only two employees." - Sumant, living with ARVC

"Over the last couple of years, I have transitioned to a less critical role which has affected my career progression." - Sam, living with ARVC

"I finished my master's degree. It took me four years instead of two years, but I was able to finish it." - Alex, living with ARVC

"I actually recently just had a major career change and because of the stress of just my position working in medicine, have had to step away from that a bit." - Regina, diagnosed with ARVC eight years ago

Counseling/therapy/stress management, meditation or mindfulness/spiritual practice

Individuals living with ARVC find it difficult to maintain a stress-free lifestyle with this disease. They maintain a positive mindset, find acceptance, slow down, spend time in nature, get more sleep, are more aware about how they feel and decline to participate if they are feeling poor.

"I've dramatically changed my lifestyle, which has been no small task, and it's still an ongoing process, but I'm learning to find just a lot of beauty and enjoy the different things in life. …Often times it's a big struggle, not being able to do what I want to do and resume the life that gave me joy previously." - Valerie, living with ARVC (*DSP* variant)

"I had to go through extreme therapy [to help cope with the sudden cardiac arrest and shocks]. I actually did EMDR [Eye Movement Desensitization and Reprocessing] …, and that helped me tremendously. But it's a kind of therapy for people that have been in Iraq or been in war, but to deal with PTSD." - Susan, heart transplant recipient (*DSP* variant)

For Heather, *"grit, fortitude, persistence, positive mental attitude"* are all necessary. *"I would say, the number one thing has got to be a positive mental attitude, because there are so many things that come at us. … We can't live just like the normal population."* - Heather, living with ARVC for over 30 years

Other approaches

In the polls, many indicated that they used **weight maintenance** to manage ARVC symptoms, but there were few quotes. One participant described how **activism** helps their family manage.

"We have a family website. My brother-in-law rode across Canada to raise money and awareness and connect people around ARVC. It was his wife - my sister - who passed away. It helps you deal with everything that is surrounding the thoughts that you have

about what could happen, and worrying about your kids, and what happened with my nephew." - Michael, living with ARVC

POLL Q7

Most individuals felt that their treatments and lifestyle choices improved their quality of life, however these approaches only help manage symptoms but are not curative.

Individuals living with ARVC used online polling to respond to the question, "In general, how much have these treatments and lifestyle choices helped improve your quality of life?" Poll responses are in **Appendix 4, Q7,** and described below with patient quotes.

Very significant benefit

A small number of individuals felt that their medical treatments and lifestyle changes had "very significant benefits" on their ARVC-related symptoms, however many endured multiple procedures and treatments to reach this point.

> Julie's journey included an endo-epi ablation, replacement of her ICD with an S-ICD and a venoplasty. *"Remarkably, my PVC burden is less than 1% a day now, I have not had any VT in 2.5 years. I now live a fairly normal life. I exercise, work, take care of a million chores around my property."* - Julie, diagnosed at age 50 with ARVC

> "*I had an endo and an epi-ablation done, and that lowered my PVC burden. It also stopped the VT storms. …I feel much better now, and I'm going on eight years with being shock free*." - Darin, living with ARVC for the 28 years

> *"I saw a significant reduction in frequency of NSVT [non-sustained ventricular tachycardia] episodes after discontinuing exercise. Eliminating alcohol helps avoid undesirable symptoms that would otherwise occur after consuming it. …Recently, symptomatic ventricular ectopy had increased to the point of heart failure and stroke which required an endocardial and epicardial ablation. … The ablation in 2019 successfully reduced my PVC burden from 37% down to 2%."* - Gary, living with ARVC

Helped a lot

Almost a quarter of individuals indicated that their treatments and lifestyle changes had helped a lot. Even so, many worry about diminishing efficacy or future side effects.

> *"Currently, flecainide and metoprolol combined with an epi/endo ablation has kept me stable for the last few years, but I'm aware that the drugs may lose effectiveness or start to affect my liver at some point."* - Jennifer C., living with ARVC (gene elusive)

> *"Within one week of starting a new antiarrhythmic, my PVC count went down [from 12,000 a day] to 700 per day, and I can feel a noticeable difference in my heart. …You*

don't always realize how bad a moment is with your heart or that you're not feeling well until you feel better." - Courtney, 29 years old, living with ARVC, sibling of a brother who died at age 17 from ARVC

Helped somewhat

Over half of individuals indicated that their treatments had helped somewhat. Some qualified this by saying "they are working for now" and by pointing out that treatments and lifestyle changes don't stop disease progression.

> *"My current treatments are working for me right now. I know that part of this disease is that treatments (medication, ablations, ICD, etc) only last for a short time before another storm of symptoms starts up again."* - Annelese, living with ARVC (*PKP2* variant)

> *"Current treatments haven't stopped my progression of the disease, so quality of life has declined regardless of the treatments. I am alive though and I have treatments to thank for that. But my life is severely limited and continues to add new limitations every few months. I need a heart transplant."* - Tracy, living with ARVC (*PKP2* variant)

Not sure if they've helped or No benefit at all

A small number of individuals indicated that they were not sure if their treatments and lifestyle helped or offered no benefit at all.

> *"Six months after the ablation, my heart function has not improved. I did not even know reduced ejection fraction was a risk of that procedure. I am now on three of the four classes of heart failure medicines and a lower dose of flecainide. I have low blood pressure and I still feel dizzy, lightheaded, and off balance a lot of the time."* - Christy, living with ARVC (*DSP* variant)

> *"I've tried beta blockers, ace inhibitors, Entresto, Furosemide, Farxiga, and had an ICD placed since being diagnosed. All of the medications have had negative side effects with very little benefit, if any. … The medications make me fatigued, dizzy, brain fogged, nauseous, and overall very ill."* - Alexa, 25-year-old living with ARVC (*DSP* variant)

POLL Q8

The ARVC community would like a new medication to stop advanced heart failure, arrhythmias/ palpitations and the risk of sudden cardiac arrest.

Considering their current health status, individuals living with ARVC used online polling to select the top 3 symptoms that most want a future medication or treatment to address. Although stopping advanced heart failure, arrhythmias/palpitations and risk of sudden cardiac arrest were the top three poll responses, the community selected almost all poll responses available. Poll responses are in **Appendix 4, Q8**, and illustrated with patient quotes below. Several themes emerged during meeting discussion which were not captured in online polling.

Theme: Patients want even minor medication improvements that would enhance their quality of life.

> *"I would love nothing more than for there to be a medication that actually makes me feel better instead of just making me feel worse!"* - Alexa, 25-year-old living with ARVC (*DSP* variant)

> *"[If you asked this question] Ten years ago, I would have said that I wanted to dance. But now I just want to be able to live my life. To go to the grocery store, to complete a pregnancy safely, to function day to day without any issues, to feel good. To go to the mall by myself, even."* - Allison, living with ARVC

> *"It's a long-term curse to see your health slowly deteriorate, and I'm helpless to do anything about it. A treatment or cure could be a miracle for people with this disease. It would provide a new lease on life and potentially save millions by avoiding the procedures and medical care that comes with heart failure."* - Jason, 53 years old, living with ARVC

Theme: Although many living with ARVC recognize that they are unlikely to benefit from new treatments, they want effective treatments for others living with ARVC.

> *"Hope is a hard thing to hold onto, so I routinely tell myself that gene therapies may be on board for next gen ARVC patients, but not me. I need to find my happiness and purpose in what remains mine today. But I dream of running and chasing and feeling powerful and helpful and capable again."* – Jenny D., 48 years old, living with ARVC

> *"My hope is that even if this can't be cured, that the disease progression can one day be stopped so my children won't have to go through any of this."* - Paula, 33 years old, living with ARVC (*DSP* variant)

> "*I look at my kids every day and think, '*Please, let's do something about this.*'"* - Michael, living with ARVC

Prevent advanced heart failure, arrhythmias/palpitations, risk of sudden death and mortality

Preventing advanced heart failure was the top choice of a future medication for ARVC in the poll, followed by **reduction in arrhythmias/palpitations, reducing the risks of sudden death and mortality.** This would ultimately help to **avoid/delay ICD/transplant/other treatment**.

> *"Anything that can improve heart function. I know a lot of things that we have right now are designed to slow the progression or remove some of the symptoms of the disease, but are there other treatments that can improve some of the heart functions so that we*

can regain some of our abilities? Or go from where we're at to just a higher functioning state?" - Jason, 53 years old, living with ARVC

"I would love the chance at a normal life for both me and my daughter, and I hope that new medications and treatments can be quickly developed to completely prevent dangerous arrhythmias and the progression of heart failure in our lifetime." - Christy, living with ARVC (*DSP* variant)

"Short of a cure, a medication that could definitively halt progression of heart deterioration / scarring of tissue would be very promising to someone like myself who struggles with the psychological aspects of disease progression." - Valerie, living with ARVC

Addressing other symptoms selected in the polls

Patients selected many other symptoms that they need new medications to address, including **exercise intolerance**, **light-headedness/dizziness/fainting**, **weight loss or gain**, **chest pain or pressure** and **fluid retention.**

Other treatment wishes for the future

Other treatment goals that the ARVC community identified include **gene therapy/editing**, **improved/enhanced ICD/devices, less medication side effects, more ARVC education**, **awareness and research**, **more mental health support**. These are described with selected quotes below. The community also asked for more affordable medications, medications with a greater duration of effect, and better surgery.

Gene therapy/editing. The ARVC community would benefit greatly from a therapy to stop disease progression and to even prevent symptoms.

"*We need something that is as close to a cure as possible, and I think that's gene editing, and I think we're on the right track. I think people will be very willing to take those risks to [try the treatment] for the greater good. … I want a better future for my nieces, and for everyone. That's the direction we have to go."* - Heather, living with ARVC for over 30 years

"I hope that soon gene therapy will be available to make this world a better place for all the generations that live with this disease and the future ones that will come." - Nebojsa, living with ARVC (*PKP2* variant)

"Once the PKP2 gene therapies are fully FDA approved I will be first in line for this treatment. Stopping progression is everything for me." - Chris, living with ARVC

Those with other gene variants, including DSP and gene elusive, want gene therapy for themselves and their families as well.

"I'm really hoping there is some kind of gene therapy to help people like me with a DSP mutation. I attended a seminar last year discussing the gene therapy they're working on for PKP2 and would love if they could use similar technology for DSP. I don't care if the damage can't be reversed on my heart, but I would love if further progression could be stopped" - Alexa, 25-year-old living with ARVC (*DSP* variant)

"I am hopeful that more treatment options will come, but also that gene therapy/other innovations will come to prevent disease progression for myself and my child." - Andrea, living with ALVC (*DSP* variant) and mother of a gene-positive child

"There has been a lot of talk of gene therapy helping current and future ARVC patients, but I am a gene elusive exercise induced ARVC patient and there hasn't been a lot of talk about how this will help us. As 50% of people diagnosed are gene elusive I am curious how gene therapy will work if you don't have a gene for it." - Lizzie, living with ARVC (gene elusive)

Improved/enhanced ICD/devices. The community wants leadless devices with additional functionality, and most importantly, without the painful shocks of the current models.

"As of now, no fully leadless devices that pace both chambers as well as provide shocks exist, but I remain hopeful this will be on the horizon for those like myself who have had device related complications!" - Regina, living with ARVC

"The ICD shock itself is one of the most challenging and traumatic symptoms of ARVC. We are all desperate for less traumatic methods of cardioversion. It feels like I got this ICD put in me without even knowing the nightmare that I was about to inherit, and I know other ARVC patients feel this way." - Samer, living with ARVC

"I would like to see something like a subcutaneous ICD that actually does brady pacing as well as ATP, because I do have sick sinus syndrome from the sotalol. My heart rate normally is around 50 and I'm being paced for bradycardia if it goes below 50." - Darin, living with ARVC for the 28 years

Less medication side effects.

I would love nothing more than for there to be a medication that actually makes me feel better instead of just making me feel worse!" - Alexa, 25-year-old living with ARVC (*DSP* variant)

"The medications come with harsh side effects and the mental fortitude it takes to deal with such a disease is not well understood in the overall medical community." - Sean, living with ARVC

"By anticipating and intervening in the side effects of medication and the aftereffects of therapeutic technologies, we can simultaneously support patient well-being while treating a disease like ARVC." - Jennifer A., 58 years old, living with ARVC

More ARVC-specific education, awareness, and research. The ARVC community wants to ensure that those living with ARVC receive an earlier diagnosis, better access to experts, unambiguous treatment guidelines both for adults as well as children. Those living with DSP variant want more attention drawn to their condition.

"*If the gene is activated in younger people, research and education HAS to start ASAP because the public needs to be aware that this is a real threat to young athletes. CPR only keeps the blood pumping, but the AED is what shocks the heart back in the rhythm. The AED is what brought Myles back to life (three times to be exact)."* - Americ, living with ARVC and parent of three children (*PKP2* variant)

"For me, the ideal treatment is early diagnosis and education of patients and their families. …Cardiologists in private practice and general practitioners should be better informed about the disease in order to avoid unnecessary diagnostic errors or waiting times and thus the uncertainties of the patients. In addition, close cooperation with centres should be sought, as well as a change in policy on organ donation." - Katja, living with ARVC (*DSG2* variant)

"I have a lot of anxiety and worry about the future and the uncertainty of this condition overall, especially having the DSP gene affected. There's a lot less information about left-sided cardiomyopathy. And it's challenging to be in the minority of a condition that's already so rare." - Cassidy, 20 years old, living arrhythmogenic left ventricular cardiomyopathy (ALVC)

Additional mental health support for the ARVC community. As emphasized throughout this report, ARVC is accompanied with significant anxiety, depression, and trauma.

Psychological and social counseling should be provided right from the start." - Katja, living with ARVC (*DSG2* variant)

"The mental health arena for those of us that are suffering from this disease is unique in many ways. I don't think there are enough good choices out there for mental health support. …My hope is that there will be more of that kind of care available to us that can help us such as EMDR and other modalities." - Shelly, diagnosed with ARVC at age 62

Incorporating Patient Input into a Benefit-Risk Assessment Framework

> *"No parent, no grandparent, no sibling, no spouse should ever have to fear what my family continues to endure. We all need things to change, and we need it to change now from the bottom of our collective hearts, as fragile as they may be."* - Adam, husband of a wife who died at the age of 31, and father of two sons with ARVC (DSP variant)

The ARVC EL-PFDD meeting helped to increase the understanding of how arrhythmogenic cardiomyopathy impact patients and their loved ones. The meeting also reinforced the urgent need for effective therapeutics for this disorder. **Table 1** speaks to the challenge of having a lifelong (albeit with a potentially shortened lifespan) disease burden that patients living with ARVC endure. It serves as the proposed introductory framework for the Analysis of Condition and Current Treatment Option to be adapted and incorporated in the FDA's Benefit-Risk Assessment. This may enable a more comprehensive understanding of these disorders for key reviewers in the FDA Centers and Divisions who would be evaluating new treatments for ARVC. The data resulting from this meeting may help inform the development of ARVC-specific, clinically meaningful endpoints for current and future clinical trials, as well as encourage researchers and industry to investigate better treatment.

The information presented captures the perspectives of patients and families living with ARVC presented at the June 20, 2023 EL-PFDD. The collective hope of ARVC families is that this meeting will encourage future research and successful new product development for people living with ARVC who urgently need treatment options. Note that the information in this sample framework is likely to evolve over time.

TABLE 1: Benefit-Risk Table for ARVC

	EVIDENCE AND UNCERTAINTIES	CONCLUSIONS AND REASONS
ANALYSIS OF CONDITION/ IMPACTS ON ACTIVITIES OF DAILY LIVING	**Arrhythmogenic right ventricular cardiomyopathy (ARVC) is a rare, progressive genetic disease, that can lead to heart failure and death**. Diagnosis is often unexpected and multiple family members can be affected. **The most burdensome ARVC-related health effects include arrhythmias/ palpitations, fatigue, anxiety/ depression**, **exercise intolerance, sudden cardiac arrest, and heart failure.** Many live with a combination of these symptoms. Symptoms are interconnected; arrhythmias, palpitations and shocks cause anxiety and PTSD, which can result in more arrhythmias, palpitations, and shocks. ARVC is progressive and 49% of those living with ARVC develop heart failure.	**ARVC families have many worries.** They worry about other family members, especially younger adults, teens, and children who have inherited an ARVC gene variant and do not yet show symptoms. They worry about progression to heart failure, death, and sudden cardiac arrest. They worry about arrhythmias and palpitations leading to more shocks**.** **ARVC has broad impacts.** Exercise promotes progression, so exercise and participation in sports is restricted. This worsens anxiety and depression and forces many affected with ARVC to reconsider their self-identities and family roles, further contributing to the tremendous mental health burden of this disease.
CURRENT TREATMENT OPTIONS/ PROSPECTS FOR FUTURE TREATMENTS	**Despite the potentially life-threatening manifestations and daily symptoms of ARVC, there are no FDA-approved treatments that are curative or stop progression.** Individuals living with ARVC require multiple medical therapies to manage their disease, including implantable cardioverter-defibrillators (ICD) and combinations of medications. Most also use exercise moderation and lifestyle modifications to manage symptoms. **Treatments and lifestyle choices improved their quality of life but are accompanied by significant downsides.** ICDs cause sudden unexpected shocks, leading to major depression, anxiety, and PTSD. Side effects of beta blockers and antiarrhythmic medications impact quality of life. Some patients require multiple cardiac ablations. Some will eventually require a heart transplant.	**Individuals living with ARVC need a medication to stop advanced heart failure, arrhythmias/palpitations, and the risk of sudden cardiac arrest.** Although even minor medication improvements would improve their quality of life, they want a disease modifying therapy such as gene therapy. Heartbreakingly, many living with ARVC recognize that they have progressed too far for a disease modifying treatment to help them but wish for a treatment to help others, especially for those who are still asymptomatic. They also need improved/enhanced ICD/devices, less medication side effects, more ARVC education, awareness and research, more mental health support.
	See the Voice of the Patient report for a more detailed narrative.	

Appendix 1: Demographic polling

The graphs below include patients, parents and caregivers who chose to participate in online polling at the June 20, 2023 meeting. The number of individuals who responded to each polling question is shown below the X axis (N=x).

While the response rates for these polling questions is not considered scientific data, it provides a snapshot of those who participated in the ARVC EL-PFDD meeting. Note that meeting demographics are dynamic and may have changed as more individuals joined the meeting.

Appendix 2: June 20, 2023 EL-PFDD Meeting Agenda

10:00 am- 10:05 am	Welcome
	Genevie Echols, RCIS, Family Support Director, the SADS Foundation
10:05 am-10:15 am	FDA Opening Remarks
	Chinwe Okoro, MD, FDA
10:15 am-10:30 am	ARVC Clinical Overview
	Hugh Calkins, MD, Director, Johns Hopkins ARVC Program
10:30 am-10:35 am	Introduction and Meeting Overview
	James Valentine, JD, Hyman, Phelps & McNamara, PC, Meeting Moderator
10:35 am-10:45 am	Demographic Polling

Session 1 – Living with ARVC: Symptoms and Daily Impact

10:45 am-11:10 am	Patient/Caregiver Panel 1 – Five patient/caregiver panelists
11:10 am-12:30 pm	Audience polling & moderated discussion - Five patient/caregiver discussion starters, telephone call ins, written comments.
12:30 pm- 1:00 pm	Lunch

Session 2 – Perspectives on Current and Future Approaches for ARVC Treatments

1:00 pm-1:10 pm	ARVC Clinical Treatment Overview
	Harikrishna Tandri, MBBS, Professor of Medicine, Vanderbilt University
1:10 pm-1:35 pm	Patient/Caregiver Panel 2 – Five patient/caregiver panelists
1:35 pm-2:40 pm	Audience polling & moderated discussion - Five patient/caregiver discussion starters, telephone call ins, written comments.
2:40 pm-2:50 pm	Summary Remarks
	Larry Bauer, RN, MA, Sr Regulatory Drug Expert, HPM
2:50 pm- 3:00 pm	Closing Remarks
	Genevie Echols, RCIS, Family Support Director, the SADS Foundation

Appendix 3: Panelists and Callers

Session 1 Pre-recorded Panel

- Courtney, 29 years old, living with ARVC, sibling of a brother who died at age 17 from ARVC
- Tracy, 46 years old, living with ARVC (*PKP2* variant), and mother of a teenaged girl diagnosed with ARVC
- Jason, 38 years old, living with ARVC
- Julia, 31 years old, living with ARVC
- Adam, husband of a wife who died at the age of 31, father of two sons with ARVC (*DSP* variant)

Session 1 Discussion starters

- Cassidy, 20 years old, living with ALVC, (*DSP* variant)
- Susan, heart transplant recipient (*DSP* variant)
- Regina, diagnosed with ARVC eight years ago
- Shelly, diagnosed with ARCV at 62 years

Session 1 Callers

- Alex, living with ARVC
- Kathy, diagnosed with ARVC at 49 years

Session 2 Pre-recorded Panel

- Joelle, 18 years old, heart transplant recipient
- Jennifer A., 58 years old, living with ARVC
- Jeff, 57 years old, living with ARVC
- Nelson, 51 years old, living with ARVC (*PKP2* variant)
- Christy, living with ARVC (*DSP* variant)

Session 2 Discussion starters

- Heather, living with ARVC for over 30 years
- Michael, living with ARVC
- Allen, living with ARVC, on the transplant list
- Darin, living with ARVC for 28 years
- Melanie, living with ARVC for one year (*PKP2* variant)

Session 2 Callers

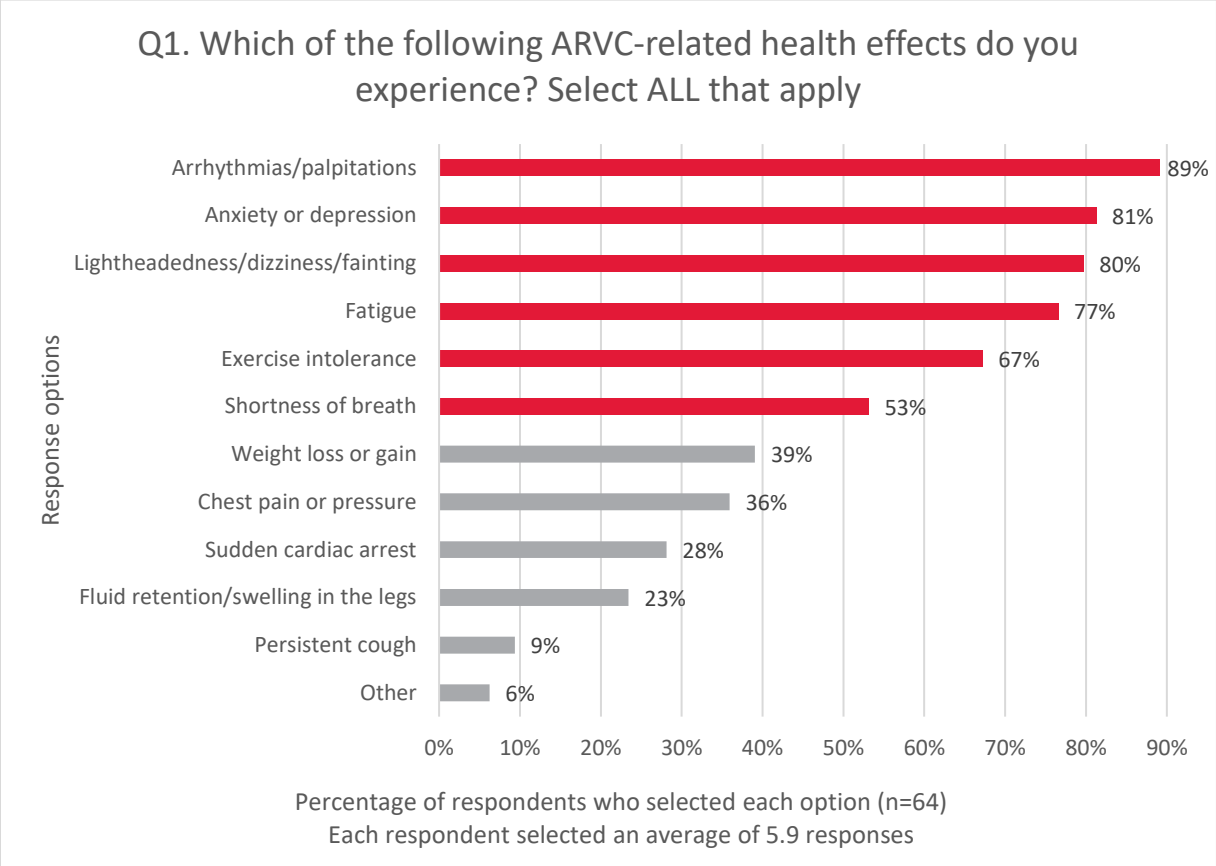
- Jennifer B., living with ARVC
- Courtney, 29 years old, living with ARVC, sibling of a brother who died at age 17 from ARVC
- Jason, 53 years old, living with ARVC
- Robin, living with ARVC and a caregiver of four children with a gene variant

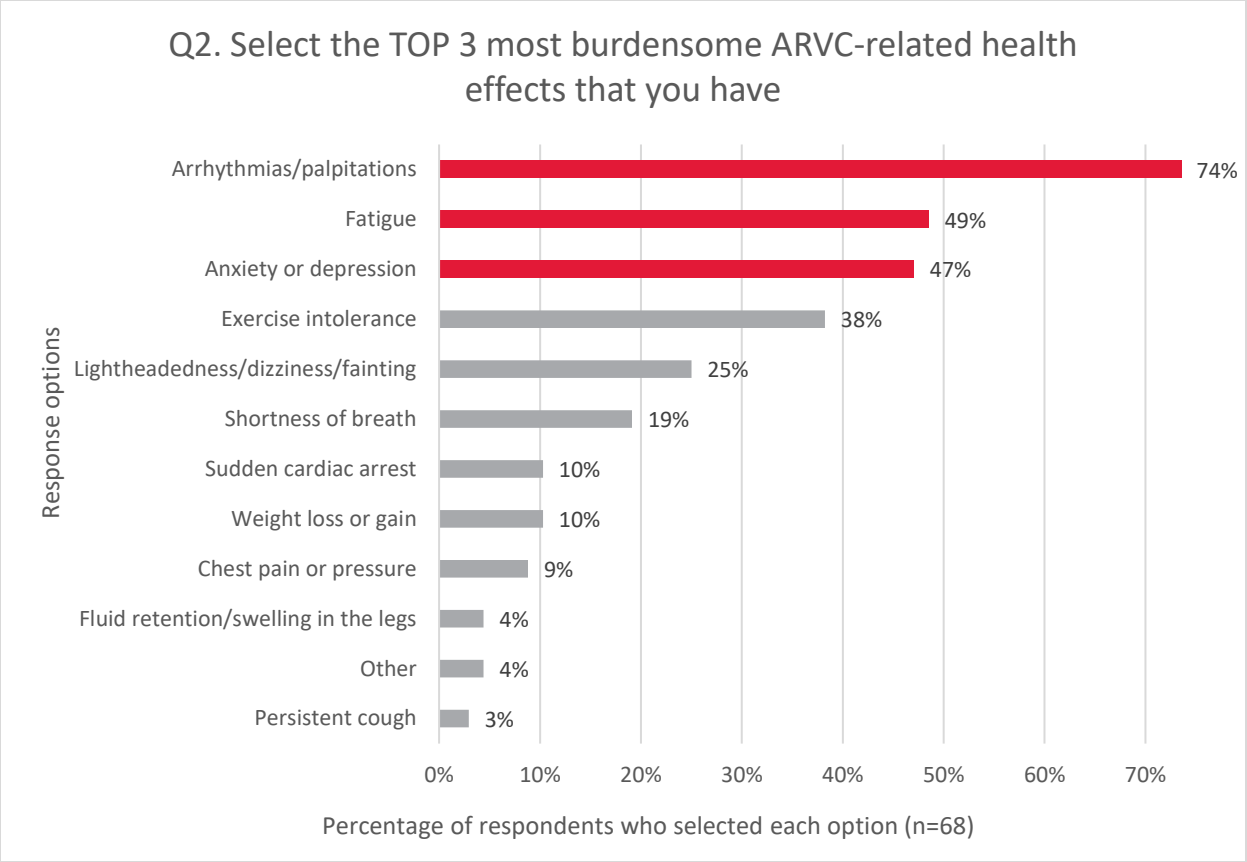
Appendix 4: Online Poll Results

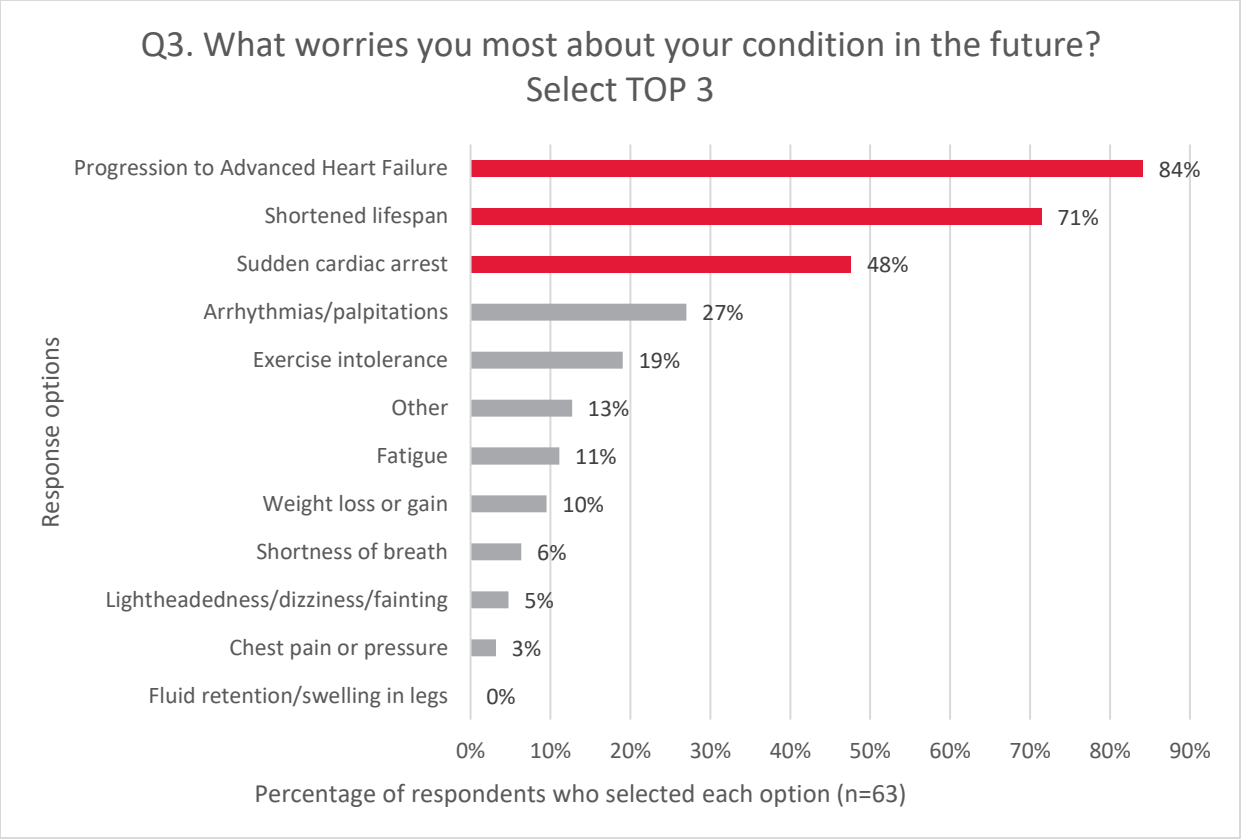
The graphs below include patients, parents and caregivers who chose to participate in online polling. The number of individuals who responded to each polling question is shown below the X axis (N=x).

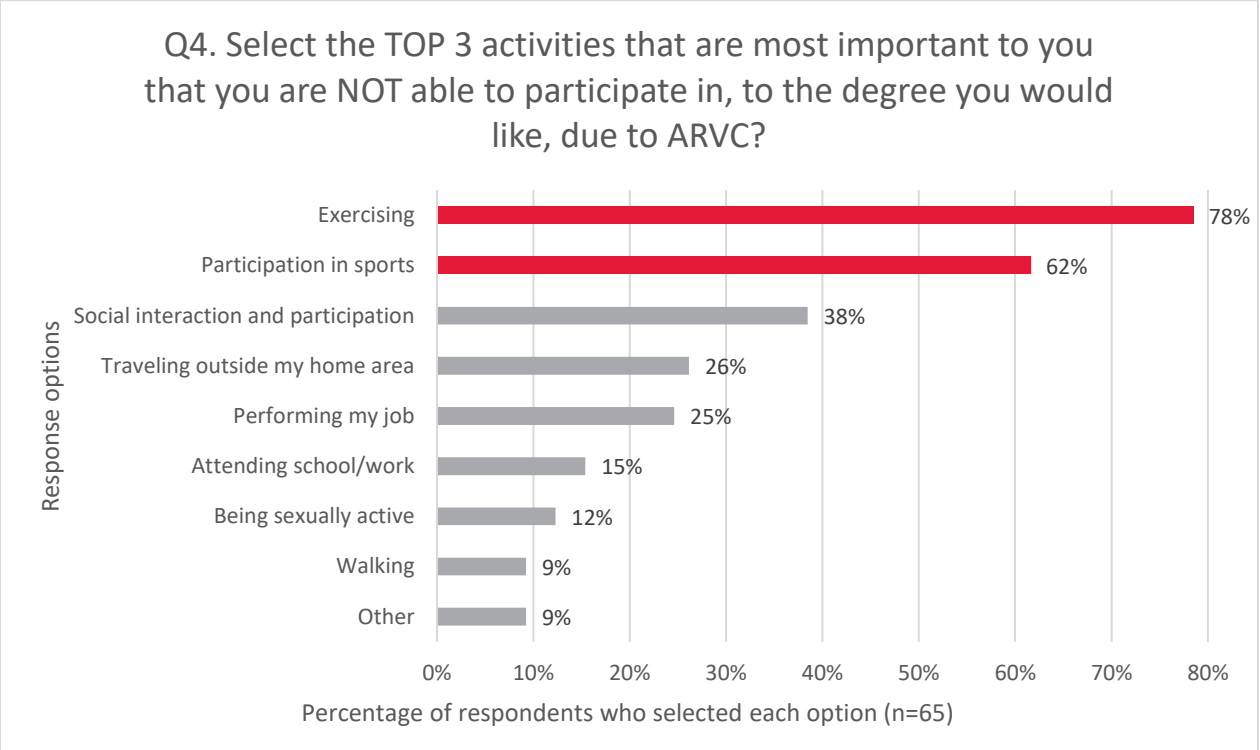
The responses for these polling questions are not considered scientific data. These are intended to complement the patient comments made during and after the meeting.

Poll responses selected by more than 50% of poll respondents are shown in **red**.

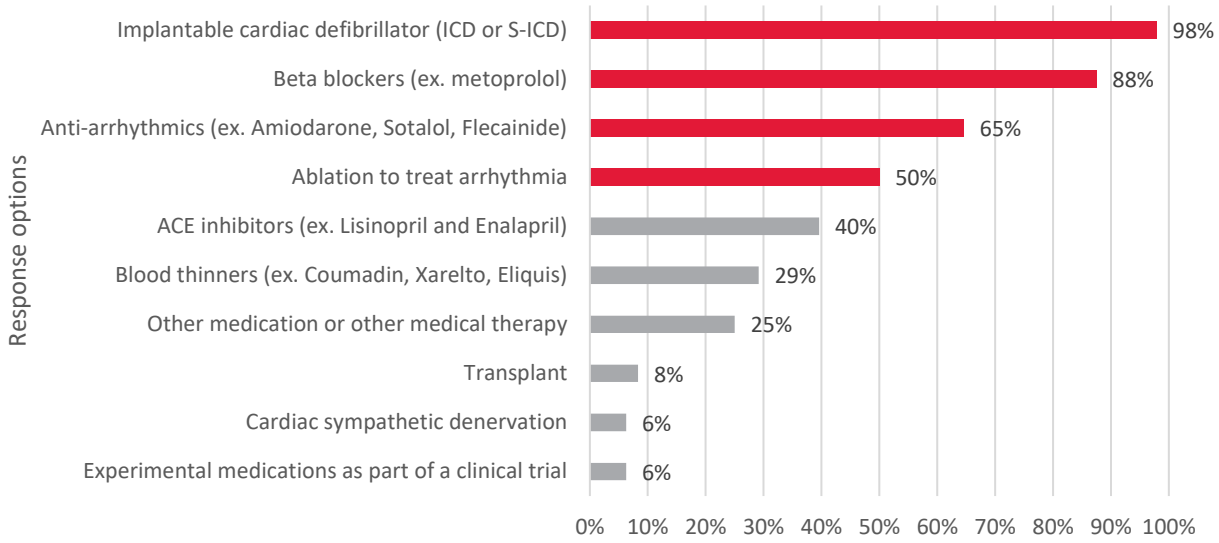



Q2. Select the TOP 3 most burdensome ARVC-related health effects that you have
Response options
Arrhythmias/palpitations
Fatigue
Anxiety or depression
Exercise intolerance
Lightheadedness/dizziness/fainting
Shortness of breath
Sudden cardiac arrest
Weight loss or gain
Chest pain or pressure
Fluid retention/swelling in the legs
Other
Persistent cough
74%
49%
47%
38%
25%
19%
10%
10%
9%
4%
4%
3%
0%
10%
20%
30%
40%
50%
60%
70%
Percentage of respondents who selected each option (n=68)


Q3. What worries you most about your condition in the future? Select TOP 3
Response options
Progression to Advanced Heart Failure
Shortened lifespan
Sudden cardiac arrest
Arrhythmias/palpitations
Exercise intolerance
Other
Fatigue
Weight loss or gain
Shortness of breath
Lightheadedness/dizziness/fainting
Chest pain or pressure
Fluid retention/swelling in legs
84%
71%
48%
27%
19%
13%
11%
10%
6%
5%
3%
0%
0% 10% 20% 30% 40% 50% 60% 70% 80% 90%
Percentage of respondents who selected each option (n=63)

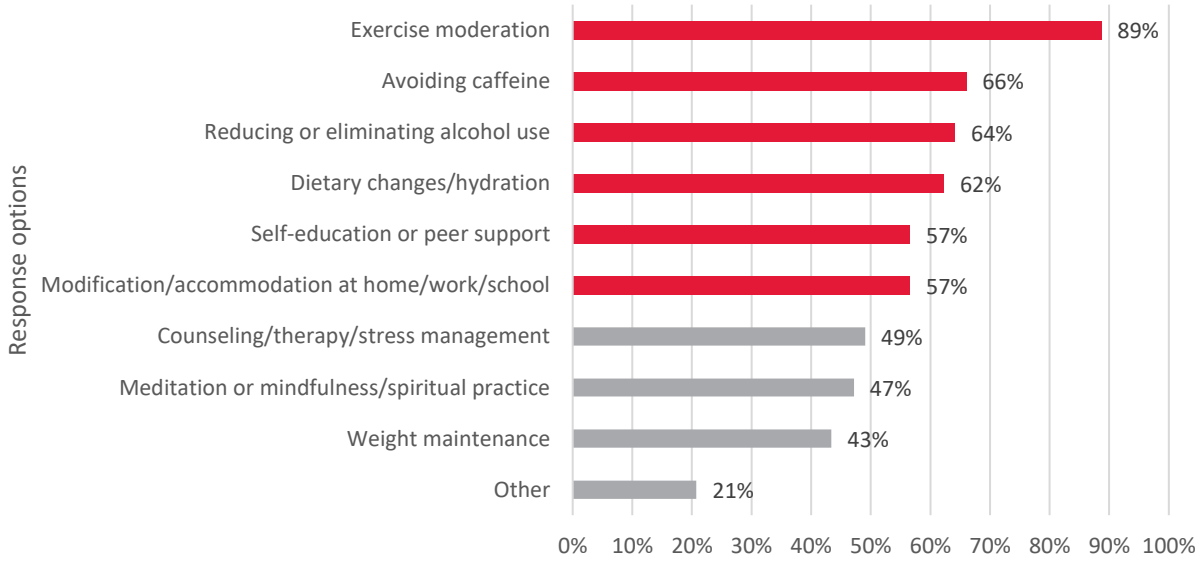

Q4. Select the TOP 3 activities that are most important to you that you are NOT able to participate in, to the degree you would like, due to ARVC?
Response options
Exercising
Participation in sports
Social interaction and participation
Traveling outside my home area
Performing my job
Attending school/work
Being sexually active
Walking
Other
78%
62%
38%
26%
25%
15%
12%
9%
9%
0% 10% 20% 30% 40% 50% 60% 70% 80%
Percentage of respondents who selected each option (n=65)

Q5: What medical therapies have you used in the past 5 years? Select ALL that apply

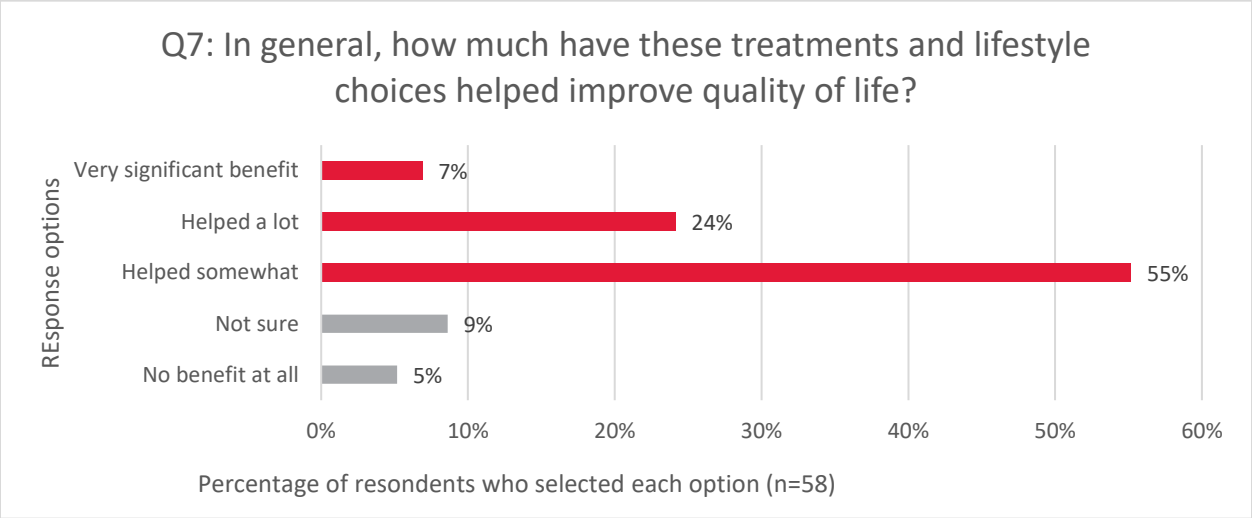


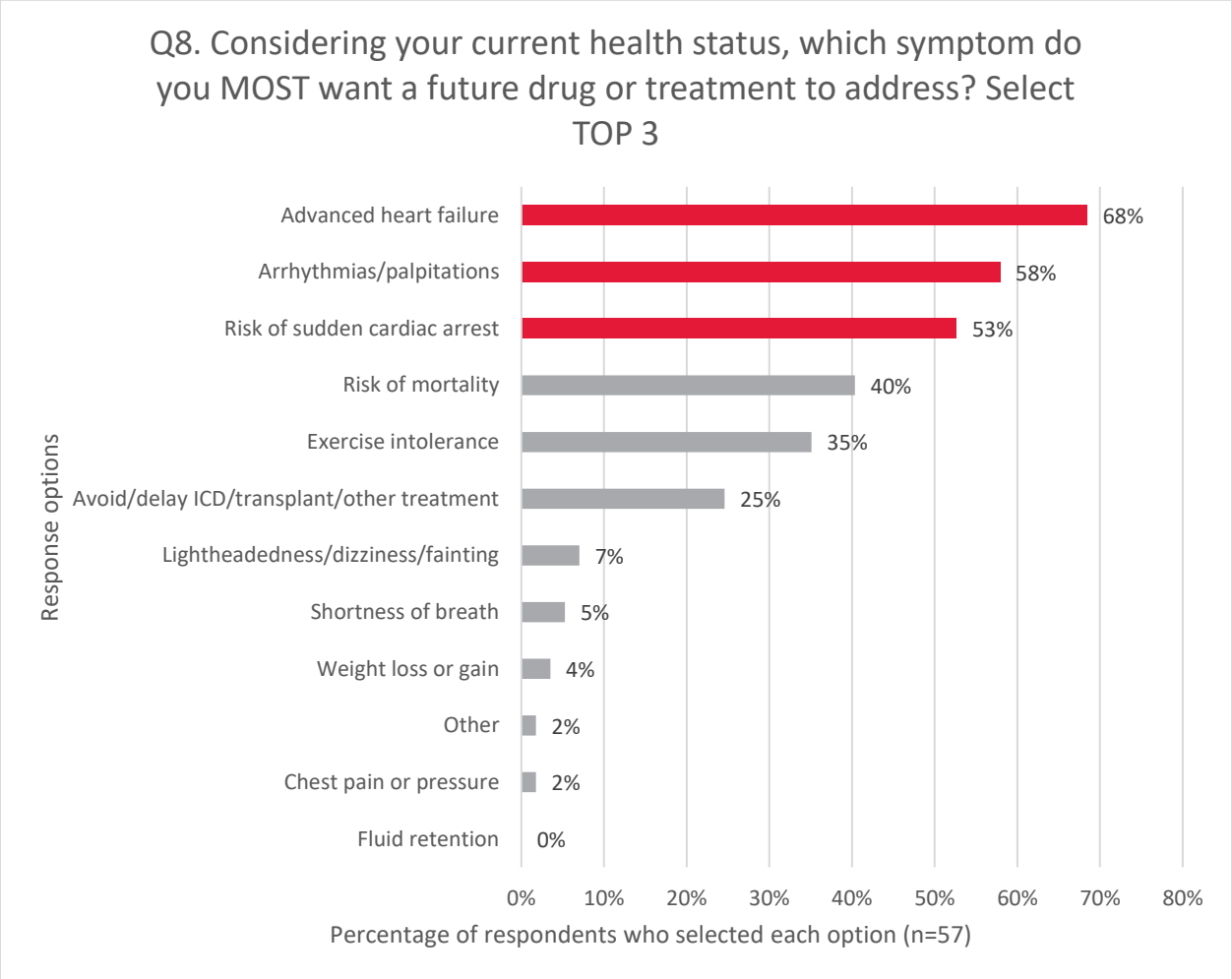
Percentage of respondents who selected ealch option (n=48)
Each respondent selected an average of 4 response options

Q6: Besides medications and treatments, what are you currently doing to help manage ARVC symptoms? Select ALL that apply



Percentage of respondents who selected each option (n=53)
Each respondent selected an average of 5.5 response options


Q7: In general, how much have these treatments and lifestyle choices helped improve quality of life?
REsponse options
Very significant benefit
Helped a lot
Helped somewhat
Not sure
No benefit at all
7%
24%
55%
9%
5%
0%
10%
20%
30%
40%
50%
60%
Percentage of resondents who selected each option (n=58)


Q8. Considering your current health status, which symptom do you MOST want a future drug or treatment to address? Select TOP 3
Response options
Advanced heart failure
Arrhythmias/palpitations
Risk of sudden cardiac arrest
Risk of mortality
Exercise intolerance
Avoid/delay ICD/transplant/other treatment
Lightheadedness/dizziness/fainting
Shortness of breath
Weight loss or gain
Other
Chest pain or pressure
Fluid retention
68%
58%
53%
40%
35%
25%
7%
5%
4%
2%
2%
0%
0%
10%
20%
30%
40%
50%
60%
70%
80%
Percentage of respondents who selected each option (n=57)